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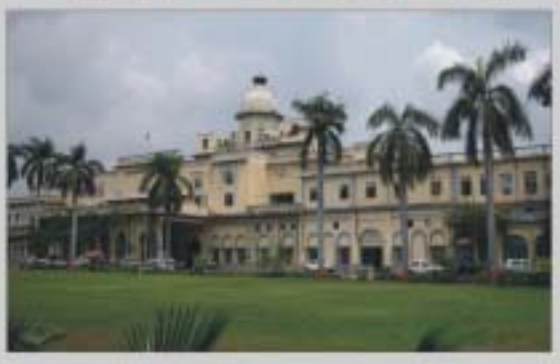

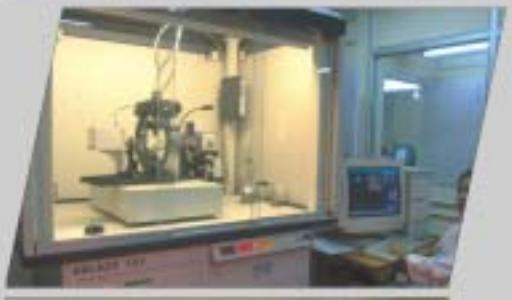

वार्षिक प्रतिवेदन
ANNUAL REPORT
2005-06

CDRI
LUCKNOW

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FROM THE DIRECTOR'S DESK

The year under review (2005-2006) precedes the closing year (2006-2007) of the tenth five-year plan, and the year 2006-2007 is indeed drawing closer. The tenth plan is very important for the institute because during this period major efforts and reforms concerning infrastructure development, engagement of fresh blood in frontier disciplines, introduction of quality systems, and creation of a new state-of-the-art-facility to house the future CDRI have been undertaken; all these efforts comprised capacity and capability building necessary to compete and achieve under the new global R&D and business environment.

The year 2005-2006 has been a significant milestone of the current plan offering an opportunity to review progress, alert against the set targets well in advance, and overcome the shortcomings. While I am satisfied at the progress made during the year on most fronts by the institute, the progress made for creation of the institute's new campus has been slow. Undoubtedly creation of the new facility is indeed an onerous task needing support and execution at different levels. The most important silver lining in the whole project is its approval on 16 June, 2005, by the Cabinet Committee on Economic Affairs.

The global drug research scenario is fast changing, and the institute has to make-up with the challenges on all fronts, say choices of problem disease areas and projects based on the current and future needs, regular upgradation of infrastructure and its judicious utilization, expert manpower development and their replenishment, benchmarking of business processes to international levels and quality certifications, adoption of best management practices, creation of appropriate authorities at institute level for IT/ regulatory compliances / quality compliance, knowledge management, etc. We are alive to these needs!

During the year, the institute effectively utilized the infrastructure and facilities created earlier, such as, those for generation of chemical libraries and in vitro screening of compounds and natural products. During the last few years new technology has been successfully applied at this institute to generate new molecular targets, in vitro test systems and libraries of compounds. The concept of drug research at CDRI now stands changed and it is totally in line with the current global thinking. The quality of operating procedures in areas requiring regulatory clearances are world class and we are gearing to apply for quality certifications in the near future.

On the business development front we have made very good progress during the year in

licensing, contract services, collaborations, and S&T services. The institute licensed to industry a PCR based tuberculosis diagnostic kit and technology for vegetable capsules for commercialization.

Over the years institute has developed a rich library of compounds and natural products which

are a valuable resource for drug screening programme conducted in collaboration with any

organization working on common areas of interest. The institute's recent collaboration for screening of our collection of compounds and natural products against leishmania and Trypanosoma brucei with the Geneva based organization, Drugs for Neglected Diseases Initiative (DNDi) are culmination of this potential.

A collaboration with the leading antimalarials producing company, Ipca, has been funded by

DST for optimization and development of second generation of antimalarials and back-up molecules identified at CDRI. The other industrial activities include contract toxicity evaluation of export-oriented products of an Ayurvedic company. Besides an advisory consultancy assignment was entered into in the area of structural and molecular genomics with inputs from computational biology and HTS.

The institute has collaborated with another company for the development and commercialization of two novel plant derived fractions, which possess combined activities of an anti-hyperglycemic and an anti-hyperlipidemic. The objective of collaboration includes delineation of the mechanism of action studies. Three synthetic molecules with significant anti-hyperglycemic and an anti-hyperlipidemic activity are open for collaboration-cum-licensing.

During the year there are several important developments on the research front. To examine clinical application of Arteether against P.falciparum infection in children, trials were conducted at five cities, and no side effects were observed. Trials on other products, namely, Picroliv, CT-1, Compound 80/574 progressed well. The marine drug CDR-134D123 (anti-hyperglycemic) completed Phase-1 single dose tolerance studies in 31 volunteers. Some leads selected earlier, namely the marine anti-hyperglycemic-cum-anti-hyperlipidemic, synthetic anti-osteoporotic and plant-derived anti-osteogenic also made progress.

During the year, 14 libraries of a total of 6559 compounds were developed. The entire existing libraries of compounds were screened against M.tuberculosis H37Ra, and selected hits were screened against M.tuberculosis H37Rv; active compounds are being pursued further for in vivo screening. Collaborative project with Dabur for screening of CDRI compounds against anti-cancer cell lines progressed well. The institute's X-ray crystallography facility was successfully utilized to solve structures of 25 compounds. Under the NMITLI project, work is continued on development of inhalable microparticles containing anti-TB drugs.

The measurable R&D performance indicators in terms of publications and patents reflect good performance during the year. There is definite improvement in the quality of research papers (about 207) published in high impact journals, and the average impact factor was 2.3. A total of 34 patents were filed, including 14 patents in India and 20 abroad, including 5 PCT applications.

During the last few years the human resource front has made rapid progress, and we have now reached more or less the required critical mass of scientists in frontier areas, and it is a matter of some satisfaction. But losing our trained scientist to industry, though unavoidable, is a matter of concern, and it is also a pleasant loss, seeing our scientists productively engaged in the industry. The institute participated in various activities and efforts to promote science awareness. In order to educate the small and medium pharma enterprises in Uttar Pradesh about the necessity of implementing GMP norms, a conference of all stakeholders was arranged.

The institute continued to live to the nation's expectations by fulfilling the elements of its mission.

(C. M. Gupta)

Director

SIGNIFICANT ACHIEVEMENTS

SIGNIFICANT ACHIEVEMENTS

During the year 2005-06, the Institute made steady progress on all fronts. A closer liaison and across the table discussions with pharma industry was given a top priority and this approach has paid rich dividends in terms of establishing contacts and maintaining our scientific creditability with Indian and international pharma companies. Given below are salient achievements made by CDRI during the period of report.

1. Business Development and Contract Research

During the year, Institute licensed two CDRI products for the manufacture and marketing. The Institute also signed several agreements with pharmaceutical companies with a view to involve the industry at the stage of confirmation of the efficacy of the lead molecules and immediately after evaluation of their safety profile in lower animals in New Drug Discovery and Development program. The details are given below:

(i) A laboratory process know-how for the preparation of specific DNA probes and oligonucleotides primers were developed and licensed to Biotron Health Care Ltd., Mumbai for manufacturing and marketing the **PCR Based Tuberculosis Diagnostic Kit.**

(ii) On Technology Day (May 11, 2005), the Institute licensed the process know-how for the preparation of **Vegetable Capsules** to Strides Arcolab. Ltd., Bangalore, one of the largest manufacturers of soft Gelatin Capsules in India.

(iii) There is no drug available in the market, which controls the blood sugar as well as lipid level in the area of diabetes and associated hyperlipidemia. CDRI has identified two marine fractions namely **CDR-134F194** and **CDR-267F018** having significant anti-hyperglycemic and anti-hyperlipidemic activity. In order to add the commercial value of these fractions, CDRI has collaborated with Connexios Life Sciences, Bangalore for further studies through its pathway biology-based drug discovery platform and ascribe molecular modes of action of these products. Both parties have tied up jointly to develop the product for manufacturing and marketing. Three synthetic molecules namely S-001-469, S-002-853, and S-002-857 have significant anti-hyperglycemic and anti-hyperlipidemic activity. Negotiations are in progress for joint development of these products. The data is being evaluated by a number of companies for commercial and research venture with CDRI.

(iv) In the area of osteoporosis, number of industries are approaching for collaboration with CDRI towards its synthetic molecule 99-373 as anti-resorptive (anti-osteoporosis) agent and a plant based product **NP-1** as an anti-osteogenic (bone forming) agent. The data is being evaluated under secrecy agreement and is expected to finalize shortly.

(v) A material transfer agreement has been executed with Drugs for Neglected Diseases initiative (DNDi), Geneva for *in vitro* and *in vivo* screening of 5 compounds for antileishmanial activity from the Institute's chemical library.

(vi) A Memorandum of Understanding was also signed with DNDi, Geneva for training of CDRI scientist at DNDi identified institute to undertake *in vitro* screening of Institute's compounds against human African Tripanosomiasis. A CDRI scientist has been deputed to DNDi for setting up suitable screening model in CDRI after getting the above training.

(vii) The toxicity testing of one of the export oriented products of Maharishi Ayurved Pvt. Ltd., Noida has been undertaken under sponsored project with CDRI.

(viii) With a view to develop the second generation of antimalarials and back ups molecules, the institute collaborated with IPCA, Mumbai under DST funded project (CDRI-IPCA-DST) for optimization of new antimalarial leads identified at this Institute.

(ix) A general advisory consultancy agreement was executed with Connexios Life Sciences, Bangalore for consultancy in the area of structural and molecular biology which integrates computational and high throughput screening in its new drug discovery and development programmes.

2. Modernization of Infrastructure Facilities

During the year of report, following new facilities were added in the Sophisticated Analytical Instrument Facility Division:

(i) **Open Access LC-MS**: A Thermo Electron Advantage MAX Ion Trap LC-MS has been installed and is functional. This facility can record ESI and APCI and MS^n mass spectra of samples automatically.

(ii) **FT-NMR Open System**: A new Bruker Avance 300 MHz FT NMR spectrometer has been installed. The system has a 120 sample autosampler with capability to record ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra.

(iii) **FT-NMR with HR MAS**:- A new Bruker 400 MHz FT NMR spectrometer with H R MAS and multinuclear inverse probe head has been commissioned. It has aH R M A S Dual probe head accessory.

3. Progress in R&D Programs

3.1 Clinical Studies

Post marketing surveillance studies on CONSAP (contraceptive cream) were initiated and a six-month program was discussed for product acceptability. Multicentric clinical trials with Arteether (blood schizontocidal) were conducted for efficacy in children suffering from *P. falciparum* malaria. Clinical trials were initiated at Dibrugarh, Rourkela, Jabalpur, Jodhpur and Guwahati and no side were effects observed during the study. Compound 80-53 (antirelapse antimalarial), requested by Seth G.S. Medical College, Mumbai was supplied in 8g. quantity through Scientist In-charge, Pharmaceutics for undertaking study to evaluate its use as a gametocytocidal agent. With regard to Picroliv (hepatoprotective), clinical trials in patients of tuberculosis receiving MDT and in patients suffering from alcoholic cirrhosis are in progress at Seth G.S. Medical College, T.N. Medical College, Mumbai and KGMU, Lucknow. Studies related to antidiabetic agent CT-1 and compound 80-574 (hypolipidemic) are progressing well. Phase I single dose tolerance double blind studies with CDR-134D123 (antihyperglycemic) were completed in 31 healthy human volunteers.

3.2 Pharmacokinetic Studies

Plasma protein binding studies on 4 antimalarial compounds viz. 97-78, 99-357, 99-408 and 99-411 were carried out by charcoal adsorption method where as *in situ* absorption studies on 3 antimalarial compounds viz. 99-357, 99-408 and 99-411 were carried out. *In vitro* metabolic studies on 97-78 revealed that the compound metabolized into 97-63 on incubation with rat liver S-9 fraction. A sensitive, selected and validated HPLC-MS/MS assay was developed for rapid estimation of 97-78 in rat plasma. Preclinical PK studies on this compound were carried out in rats and monkeys. PK studies on 99-373 (anti-osteoporotic) revealed the presence of 2 metabolites in Sprague Dawley rats serum. Pharmacokinetic studies on 80-574 (anti-hyperlipidemic) and 3 antidiabetic compounds S-001-469, S-002-853, S-002-857 and herbal preparations viz. Picroliv (hepatoprotective) and Herbal Medicament (for prevention and cure of cerebral stroke) continued during the year.

3.3 Toxicity Studies

A total of eight compounds were tested for systemic toxicity, two for genotoxic potential and one for teratogenic potential. Experimental toxicology work (expression studies using microarrays, rat whole embryo culture, short-term bioassays for carcinogenicity testing and CFU-GM assay for haematotoxicity) has involved short-term training of 20 candidates during this period.

4. Progress in R&D Project Areas

During the year 2005, a total of 1342 new synthetic compounds and 14 libraries consisting of 6559 compounds were prepared while the Botany Division collected 35 new terrestrial plants and 17 marine flora/fauna samples.

4.1 Biological Screening

The entire chemical library of the Institute was subjected to high-throughput screening against *M. tuberculosis* $H_{37}R_a$ and selected 'hits' were further screened against *M. tuberculosis* $H_{37}R_v$. Active compounds were short listed and subjected to *in vivo* screening. Further work on these compounds, including lead optimization, is in progress. The project on cancer drug development is in progress in collaboration with Dabur. All the compounds of the chemical library were screened against five cancer (pancreas, ovary, prostate, breast, colon) and one normal (fibroblast) cell lines. Hit molecules, belonging to 4 chemical classes, were short-listed for chemistry-based lead optimization.

4.2 CNS/CVS & Other Disorders

Studies related to antistroke agents included herbal medicament which was shown to produce neuroprotective effect on cerebral ischemia and mild anti-inflammatory activity. Around 158 synthetic compounds were screened against collagen and adrenaline induced thrombosis and several compounds exhibited 40% or more protection against collagen induced thrombosis, which was better than the protection offered by Aspirin. Fifteen synthetic compounds, 530 extracts from CSIR co-ordinated project, and 44 plant extracts were tested for their effect on BP and heart rate and four compounds exhibited appreciable lowering in BP in anaesthetized rats. Molecular studies related to differential regulation of neurotrophins gene expression by focal cerebral

ischemia in rat brain indicate that BDNF, NT-3, NT-4 and NGF gene expressions increased at 12 hours and returned to the basal level at 24 hours of reperfusion injury. Seven synthetic compounds and 86 extracts from CSIR co-ordinated project were tested for anti-dementia activity and the leads from active moieties are being followed up. Several samples were tested for CNS, memory, anti-depressant, antioxidant and anti-inflammatory activities. Significant effects were observed in 4 samples on anti-nociceptive activity and 2 samples on anti-dementia activity. One sample showed significant antioxidant profile. A synthetic compound S-002-853 was identified as lipid lowering agent. Dose response studies were conducted and was found active at 12.5 mg/kg dose using pair fed group as control. 24 Compounds were tested for appetite suppressant activity in rats and two were found active. The ethanolic extract of CDR-134F234 was found to be effective against CRU, ASP, AL, PL and HST induced gastric and duodenal ulcer. It has significantly reduced the acid secretion along with enhancing mucin secretion.

4.3 Filariasis

5 Synthetic compounds, 18 new plant extracts and over 2300 extracts under CSIR coordinated project were evaluated for their antifilarial potential. Active ones are being followed up for confirmation of activity. Immunoprophylactic studies with recombinant myosin and paramyosin of *B. malayi* adult female worms are continuing. Studies related to isolation of *S. cervi* antigen equivalent to filarial circulating antigen suggest that parasite proteins present in the circulation of infected host play an important role in defining nature and mechanism of action of these molecules. Biochemical and molecular studies continued this year also. *S. cervi* acetyl choline esterase monoclonal antibodies were raised, isolated, identified and selected for further studies based on high and consistent reactivity. Studies on octopamine and serotonin receptors in filariids by fluorescent microscopy suggest localization of these receptors in intestinal mucosa of adult *B. malayi*.

4.4 Leishmania

Primary biological screening of several synthetic compounds, plant and marine extracts was carried out and the active ones are being evaluated further for confirmation of activity. Four compounds exhibited moderate activity in the *in vivo* hamster model. Repeat experiments with these compounds are in progress for confirmation of activity. Studies related to identification of TH1 specific proteins for immunoprophylaxis exhibited good lymphoproliferative response and NO production in cured hamsters. Work on cloning and expression of serine hydroxymethyl transferase, pteridine reductase, trypanothione reductase, dipeptidase carboxy peptidase etc. continued during the year. An ACE inhibitor, catopril, was shown to inhibit LdDCP enzyme activity as well as promastigote growth suggesting thereby that this newly identified DCP could serve as a drug target in Leishmania. Analysis of genomic microarray data in relation to antimony resistant field isolates led to identification of important biochemical pathways for use as drug targets.

4.5 Malaria

A total of 455 new synthetic compounds, 85 marine extracts and 2800 of natural origin, under CSIR coordinated network were screened *in vitro* against *P. falciparum*. Several materials exhibited activity at varying concentrations and promising ones are being followed up. Based

upon the leads obtained from *in vitro P. falciparum* results, a total of 44 synthetic compounds and 35 plant extracts were screened against *P. yoelii in vivo*. None of them were found to have appreciable activity. Regulatory developmental studies with 97-78 are under way. Immunological studies in malaria are progressing well. Efforts have been made to produce monoclonal antibodies against the conformational and linear epitopes of *P. vivax* MSP1 antigen. Studies related to molecular biology of malaria are also underway. Analysis of replication within the apicoplast of *P. falciparum* revealed the presence of partial and full length constructs of 2 proteins-GyrA and GyrB which have been cloned and expressed. Nearly 800 hundred samples from large families were collected for single nucleotide polymorphism analysis of TNF-α as well as 6 genes that are implicated in adhesion of *P. falciparum*. Initial results indicate subpopulation specific variation in polymorphic allele frequencies.

4.6 Microbial Infections

Two genes of *V. cholerae*, Vc0973 and Vc0974 were isolated and their interaction was confirmed. Vc0974 was cloned, expressed in *E. coli* and recombinant protein was purified. In tuberculosis, work is in progress in various areas viz. identification of genes of *M. fortuitum* involved in virulence, knockout mutant generation and its role in pathogenesis, human T-cell responses against *M. tuberculosis* membrane antigens, etc. Cloning and expression of *M. tuberculosis* genes, three *rpf* genes were amplified from genomic DNA and a promoter library of $H_{37}R_V$ was constructed. Studies on molecular mechanisms involved in the intercellular survival of mycobacterium suggest that protein kinases play a pivotal role in regulating and coordinating metabolism and gene expression.

Out of the 9 compounds tested *in vitro* against HIV-RT, 4 showed promising activity. Studies related to fungal infections continued this year also. Five new monoclonal antibodies were raised and identified against *A. fumigatus* and *C. albicans* cell wall antigens respectively. PCR products have been sequenced and identified.

4.7 Natural Products

During the year of report, collection, identification and documentation of 35 terrestrial plants and 17 marine flora/fauna were completed. Follow-up studies with several plants continued. Plants 3200, 4659, 1703, 4574, CDR-267, CDR-134F194, CDR-324 and CDR-150 were perused further for Antihyperglycemic/Antidyslipidemic activities. Synthetic modifications of pure and active compounds have been carried out in several plants. Regulatory pharmacology and toxicity studies of CDR-134F194 are progressing well. Antiulcerogenic activity was confirmed in the ethanolic extract of plant 38. Pure compounds from this plant viz. K099, K114, K116, K117 and K171 were found to be effective in reverting the alteration induced in acute and chronic unpredictable stress model. Eleven compounds have been isolated from 2659 with promising memory enhancing activity. From the plant 4604, compounds of various classes such as flavonoid glycosides, pterocarpanoids, lipids, glycolipids and alkaloids have been isolated and identified from the 4604 whole plant. Aminoglucosyl glycerolipid is reported here for the first time. Its structure has been elucidated by spectroscopic and degradation studies. This novel compound exhibited *in-vitro* antileishmanial and immunomodulatory activities. Chemical modifications of solanesol (antidiabetic), lupeol, neoandrographolide (antimalarials) and coumarins e.g. psoralin,

isopsoralin and seselin (antithrombotic) are continuing. Isolation and transformation of aromatic turmeron, a constituent of herbal medicament and synthetic analogues of aromatic turmeron were prepared for antistroke activity.

4.8 Newer Approaches in Drug Discovery and Design

Crystallization and X-ray intensity data collection and data processing of 26 compounds were performed out of which structures of 25 compounds were solved. The structure analyses of around 10 heterocyclic compounds revealed unusual N-N bond formation and double-cyclisation for some compounds. In our attempts to develop target specific new antidiabetic agents, designing, synthesis and bio-evaluation of peptidomimetics was carried out. All the compounds were evaluated for their ability to inhibit protein tyrosine phosphatase 1B activity *in vitro* using a commercially available kit based assay system. PNP is used as positive control. Some of the new compounds have shown ~90% inhibition at 100 μM concentration. Further work on the synthesis and bioassay is in progress. During this period 45 thiazolidinone analogues were synthesized and evaluated for HIV-RT inhibitory activity. The *in vitro* HIV-RT evaluation of these compounds through colorimetric enzyme based immunoassay showed that some of the compounds exhibited 50-95% inhibition at 100 μg/ml. In order to overcome the ever-growing problem of acquired resistance of erythromycin derivatives, synthesis of newer analogues was completed and evaluated for their *in vitro* antibacterial activity against several strains of *S aureus*, *E.coli* and *K. pneumoneae*. The compounds exhibited MIC between 0.2-6.5 μg/ml.

4.9 Reproductive Health Research

Nine synthetic compounds were screened for anti-osteoporotic screening with no significant activity. Molecular mechanism and the transcriptional activation of estrogen receptor studies related to osteoclastogenesis of 99-373 were carried out. 19 Synthetic compounds and 7 plant extracts were screened for cytotoxic/antiproliferative activity *in vitro*. 6 Materials had LC_{50} ≤ twice that of tamoxifen. Experiments are in progress in relation to establishment of estrogenicity profile of promising lead molecules in mammary and endometrial carcinoma cell lines. A new class of substituted phenanthrene derivatives, with basic amino side chains, exhibited significant antiproliferative activity (IC_{50} 3.53 – 22.25 μM). Five synthetic compounds and 39 extracts of natural product including marine flora and fauna were tested for anti-implantation-cum-early post-implantation interceptive activity in adult female Sprague-Dawley rats when administered on days 1-5/1-7 *post-coitum* by the oral route, but were found to be inactive. In follow-up studies, MEC of six previously active compounds has been determined. Out of the 31 synthetic compounds evaluated for spermicidal activity *in vitro* by Sander-Cramer assay using liquefied human semen, 8 compounds were found to be active. However, none of the 33 natural products tested using 'Spot test' exhibited any detectable spermicidal activity *in vitro*. Stability studies performed with medicated condoms coated with the herbal spermicide (*Sapindus* saponins) indicated that the product was stable up to one year of manufacture. This study is being performed in collaboration with M/S Hindustan Latex Limited, Chennai. Twenty-eight synthetic compounds and 15 natural products were screened for anti-*Trichomonas* activity using *in vitro* susceptibility assay. Metranidazole was used as reference standard. Of these, 11 synthetic compounds and 6 natural products have been found to be active in preliminary screening. Anti-*Trichomonas* activity of CONSAP cream was studied in detail and preliminary scanning electron microscopic studies

have indicated that treatment of parasites with the saponins decreased their phagocytic ability, which complements well with the observed decrease in hemolytic activity of parasites after saponin treatment.

4.10 Technology Development

4.10.1 Chemical Technology

Process for 97-78 (antimalarial) has been optimized on pilot scale. Technology development of three generic drugs has been undertaken based on their patent expiry and market profile. These drugs include Simavastatin (hypolipidemic), Sertraline hydrochloride and Paroxetine hydrochloride (antidepressants). Further work is in progress.

4.10.2 Fermentation Technology

Isolation and screening of microbial cultures with antibacterial and antifungal activity was continued with considerable success. A very potent antibacterial strain, isolated during the study was taxonomically characterized as *Streptomyces halstedii*. The culture produced more than one active compound. One of the active compounds was extracted, purified and chemically characterized as actinomycin D. Fermentation aspects of optimum actinomycin production conditions were studied. Work on other microbial cultures showing antifungal or antibacterial activity is in progress. Purification of an antibacterial glycopeptide antibiotic and SDS-PAGE analysis of the active crude has demonstrated the presence of a major 65 KD peptide band. Kojic acid producing fungal culture was isolated from the soil samples. Fermentation parameters and downstream processing are being optimized to achieve maximum yield.

4.10.3 Pharmaceutical Technology

Under the NMITLI project, inhalable microparticles containing two anti-TB drugs were taken up for product development and methods for quality assurance, stability studies and pharmacokinetic analysis were developed and validated. Experiments for delivery systems for testosterone, GLP-1 and cyclosporine are progressing well. Inclusion complex of 80-574 with β-cyclodextrin and/or hydroxypropyl-β-cyclodextrin were evaluated for solubility, dissolution rate and transport. Studies related to quality control included 6 compounds for which HPLC methods were validated.

5. Publications and Patents

During the year, the Institute published over 200 research papers in national and international periodicals and contributed several papers and posters in national and international seminars/symposia and conferences. The success of Institute's innovative approaches is well reflected in filing and grant of 15 patents of which 6 were Indian and 9 foreign.

6. Administrative Reforms

Local area network of all the computers of the Institute became operational with effect from April 1, 2005. In order to increase the efficiency and transparency of procurement process, new software, ComPASS, was co-developed with Tata Consultancy Services and successfully implemented w.e.f. 1.4.05. Mr. Sudhir Kumar, Joint Secretary, Government of India formally launched it on July 15, 2005 at the Institute.

A Combinatorial Chemistry Unit was created out of the Medicinal & Process Chemistry Division.

The DST funded project on establishment of GLP Compliant National Facility for Regulatory Pharmacology and Toxicology has given impetus to up gradation of facilities and setting up of new units in the Institute. In this connection, Quality Assurance Unit, Central Archives and Employees' Health Checkup Units have been set up in the Institute. Organizational Structures, Floor Plans with Demarcation of GLP Areas, Pest Control Procedures, Formats for Study Protocols and SOPs and a list of about 600 SOPs have been finalized.

In accordance with the introduction of Government of India's Right to Information Act – 2005, Dr. Zaka Imam and Dr. A.K. Goel were nominated as Public Information Officer and Assistant Public Information Officer respectively. Dr. K.P. Madhusudanan was designated as Appellate Authority under Section 19(1) of the Act. The Act became fully operational from 12.10.05 and the Institute geared itself to implement it in true sprit. Queries received under this head were promptly attended to.

In order to resolve individual grievances of the Institute employees, a Local Grievance Committee was constituted under the chairmanship of Dr. Chandan Singh.

7. Technical Services Provided

Sophisticated Analytical Instruments Facility (SAIF) and **National Laboratory Animal Center** continued to provide their services to the scientists, academia, industrial units, etc. SAIF analysed over 9600 external and 18700 internal samples for various spectral analyses. Eighty-seven samples were analysed under electron and cofocal microscopy from external users. Collaborative research projects with in association with several scientific organizations continued. Under the national project on "Development of Potential Drugs from Ocean", publication of quarterly bulletin **Ocean Drugs Alert** continued and all the 4 issues were published. Special emphasis was given on international patents in the area of marine drugs/pharmaceuticals. Documentation and Library Services Division continued to publish current awareness bulletins viz. **Drugs & Pharmaceuticals – Industry Highlights** and **Drugs & Pharmaceuticals – R&D Highlights**.

CDRI provided digital designing facility of exhibition display panels to NBRI, CIMAP, ITRC and CSIR. A total of 90 panels, including 6 in Hindi, were prepared for CSIR Foundation Day Celebrations (held at Lucknow) and for Indian Science Congress, Ahmedabad.

8. Human Resource Development

CSIR launched a scheme of providing training to the laboratory scientists in business development activities. Under this scheme, Mr. N.S. Rana and Mr. Vinay Tripathi attended a "CSIR – WIPO Workshop on Negotiating Technology Licensing Agreements" held at India Habitat Centre, New Delhi from 4-8 July 2005.

Further, the Institute continued to participate in DST sponsored **Kishore Vaigyanik Protsahan Yojna**. This program is meant to attract students in science, medicine and engineering subjects and adopt them as their careers in research. Interviews of 87 students were conducted from 20-23 December 2005.

During the year of report, the Institute organized the **CSIR Program on Youth for Leadership in Science (CPYLS)** on 27 – 28 December 2005. In this 2 day program, 9 meritorious students of Uttar Pradesh participated. They were exposed to latest techniques being employed in drug research by way of exposure to experiments, laboratory visits, use of various instruments and holding lectures followed by discussions with our scientists.

Several students completed their research work and submitted their theses. During the year, 21 students were awarded Ph.D. degree while MD/MS degrees were awarded to 6 students from various universities/medical colleges. 17 Students have submitted their theses and their Ph.D. degrees are likely to be awarded shortly.

9. Seminars / Symposia / Lectures / Exhibitions

The Institute celebrated its **54th Foundation Day** on 17.2.2005. During the day, **Mellanby Memorial Oration** was delivered by Dr. Sandip K. Basu, Director, National Institute of Immunology, New Delhi. The topic of his lecture was **Chasing Ehrlich's Dream: Receptor-mediated Manipulations of Macrophage Metabolism.** During the day, 2 facilities viz. **Computational Biology & Bioinformatics Facility** and **NMR Facility for Macro-molecular Structures** were inaugurated by Dr. M.K. Bhan, Secretary, DBT. Prof. M. Bhandari, Vice Chancellor, KGMU, released 2 publications, viz. **CDRI Annual Report 2004-05** and **Major Facilities & Capabilities.** Besides, several national and foreign dignitaries visited the Institute on various occasions.

National Science Day was celebrated on 28th February 2005 wherein college students and faculty members participated in several events. Prof. Mohan Raizada, University of Florida, USA, delivered the **9th Dr. C.R. Krishna Murti Memorial Oration** on March 9, 2005 entitled **Is Gene Therapy for Hypertension Possible?** Prof. Ajoy Ghatak, Emeritus Professor, Physics Department, IIT, Delhi delivered the **Dr. Biren Roy Memorial Lecture** on the topic **The Amazing Story of the Optical Fiber** on 26.4.2005.

A conference **Small and Medium Pharma Enterprises in Uttar Pradesh: Challenges and Prospects** was organized on 19-20 September 2005 in collaboration with SIDBI. Several participants from small and medium pharmaceutical industries participated in the event and the Institute played a proactive role in helping UP pharma SME's to take up the challenges, now being faced by them due to introduction of new Schedule M of the Drugs & Cosmetics Act 1945. Mr. N. Balasubramanian, Chairman & Managing Director, SIDBI graced the occasion by being the chief guest.

Likewise the previous years, **CSIR Foundation Day Celebrations** were held on 26th September 2005. All the Lucknow based 4 CSIR laboratories jointly organized the function at Scientific Convention Centre, Lucknow. A roving exhibition on major achievements of Lucknow CSIR laboratories was organized and it remained open for public upto 30th September 2005. Dr. Deepak Pental, Vice Chancellor, Delhi University delivered his lecture **Molecular Biology and Precision Breeding of Crops**. Members of the Institute staff, completing 25 years of their service, were awarded certificates and wristwatches.

A Bioethics symposium **Protecting Human Participants in Clinical Research** was organized on 14th October 2005. The aim of the meeting was to create awareness among the

human volunteers about the latest trends being employed for development of new drugs at a greater pace.

The 74th Annual Meeting of **Society of Biological Chemists (India)** was organized at the Institute from November 7 to 10, 2005. During the meet, a half-day international symposium **Emerging Trends in Drug Discovery** also took place. Deliberations in it covered scientific strategies and promising techniques that are currently being employed worldwide to accelerate drug discovery efforts. Besides, a number of dignitaries visited the Institute and shared their experiences with our scientists, details thereof are given in respective section of this publication.

10. Training Programs Conducted

CSIR has implemented a scheme **Towards Excellence in Science for an Innovative India** for promoting interaction of science students with CSIR labs and thereby nurturing a cadre of most brilliant and gifted youths to take up science as a career. Under this scheme, in order to improve the overall standard of science education and learning capabilities of students in selected government schools and colleges, a program **Training and Motivation of School / College Faculty and Students** was organized on 14th and 15th February 2005. Several students and teachers from three colleges of Lucknow, viz. Jubilee Inter College, Husainabad Inter College and Government Girl's Inter College participated in this event. The program comprised of distinguished lectures, visit to laboratories, exposure to experiments related to drug research, personal discussions with scientists and use of sophisticated instruments. Selected students from all the three adopted colleges were invited to visit the major facilities of the Institute and had closer interaction with bench level scientists on 28th February 2005. About 65 students and teachers visited different laboratories.

Documentation & Library Services Division organized a 3 day workshop on **E-Journals** from 5-7 August 2005 wherein hands on training of the techniques of the e-journal browsing and searching was imparted to information personnel of five CSIR laboratories of the region (viz. CDRI, ITRC, NBRI, CIMAP and RRL, Bhopal).

The Sophisticated Analytical Instrument Facility organized a **Brainstorming Session – Direct Analysis in Real Time Mass Spectrometry** on 26th August 2005 to discuss the latest techniques being employed in this area.

11. Honors and Awards

Several scientists received recognition for their outstanding and meritorious achievements during the year. Dr. C.M. Gupta received 4 honors viz. **Panjab University Pharmaceutical Science Oration 2004; Platinum Jubilee Lecture Award from Indian Science Congress, Ahmedabad; Prof. V. Ramakrishna Memorial Lecture Award** from IIT, Delhi and **Gujral – Bhargava Memorial Oration Award** from KGMU, Lucknow. Drs. Anup Kumar Misra and Atul Kumar received the **CSIR Young Scientist Award-2005** in Chemical Sciences. Dr. (Mrs.) Ranjana Srivastava received 2 awards during the year of report viz. **CSIR New Idea Fund Award** and **Best Poster Award** for her paper on "Production of Antibodies Against Intact Microfilariae of *S. cervi*" at 17th National Congress of Parasitology, Dibrugarh. Dr. Ram Raghubir was elected as Vice President, Indian Pharmacological Society 2005. Dr. Gautam Palit received the **Dr. D.N. Prasad Memorial Oration Award** and gold medal from Indian Council of Medical

Research. Dr. C. Nath was the recipient of **Prof. G. Achari Oration Award** 2005 by Indian Pharmacological Society. Ms. Sushma Chaubey was conferred upon the **Young Scientist Award** on her paper "Translation within the *Plasmodium falciparum* Apicoplast". Ms. Prachi Bhargava and Ms. Ritu Malik too were awarded for their research papers, details thereof are given in the respective section of this report.

12. Sports and Cultural/Miscellaneous Activities

The Institute continued to participate in several activities related to sports and cultural events. 37th Shanti Swaroop Bhatnagar Memorial Tournament (SSBMT) was organized from 17 – 20 February 2005 where over 300 participants from 32 laboratories of CSIR participated in several indoor/outdoor games. Its inaugural ceremony was presided over by former Indian cricket captain Mr. Kapil Dev. For the first time in the history of SSBMT, the cricket team of CDRI became the National Cricket Champion (CSIR) for the year 2005 by defeating National Chemical Laboratory, Pune by 5 wickets.

In order to promote Hindi in official working, a two-week **Hindi *Pakhwara* 2005** was organized during 14th September 2005 to 28th September 2005. Several events like essay competitions, drafting/noting/translation/typing, songs, dance, dramas, *hasya musharaya*, recitation and extempore speeches were presented. Likewise the previous years, Lord Sri Vishwakarma Puja took place on 17th September 2005. During the year, CSIR Foundation Day was celebrated on 26th September 2005 wherein besides scientific activities, prizes and cash awards were given to children, winning several competitions, by the first lady of the Institute, Mrs. Savita Gupta. Three students, who got admission in IIM/IIT, were awarded the CSIR Foundation Studentship of Rs. 1000/= per month on the occasion.

In pursuance of Central Vigilance Commission's instructions, **Vigilance Awareness Week** was observed from 7th to 11th November 2005. On this occasion, Dr. Ram Lal, Additional Director General, Vigilance Commission U.P. delivered a lecture **Vigilance Awareness**. Likewise the previous years, ***Kaumi Ekata* Week** was observed from 19th to 25th November 2005. All staff members took a pledge on 21st November 2005 for maintaining communal harmony and national integrity.

In order to help the earthquake victims of Jammu and Kashmir, several staff members donated their one-day salary in the Prime Minister's Relief Fund.

PROGRESS IN RESEARCH PROJECTS

REGULATORY STUDIES

1. CLINICAL TRIALS & PHARMACOKINETIC STUDIES

Coordinator: Dr. O.P. Asthana

Clinical studies on candidate drugs continued this year. A total of 7 candidate drugs were undertaken for different phases of clinical studies. Pharmacokinetic studies were undertaken on 13 candidate drugs. This section covers progress in studies carried on different drugs.

1.1 CONSAP (Contraceptive Cream)

Post marketing surveillance program was initiated on June 17, 2004 at Chennai. Hindustan Latex Limited (HLL) organized a meet of lady doctors at Chennai where presentations were made by experts from HLL, Business and Industrial Research Division (BIRD) of IMRB International and CDRI to give a brief profile of the product CONSAP Cream (NOVARY). Proforma has been developed for PMS study. Project roll out schedule was also presented. HLL and IMRB decided to go for product acceptability study before initiating large-scale PMS study. In this connection a meeting with Gynecologists at Cochin and Chennai was organized in March 2005 and was attended by 30-40 doctors for a discussion on CONSAP as contraceptive. A six months plan was discussed for product acceptability. Further response from HLL, BIRD & IMRB is awaited.

1.2 Arteether (Blood schizontocidal agent)

Multicentric clinical trials were conducted for efficacy in children suffering from *P. falciparum* malaria. Clinical trials were initiated at Dibrugarh, Rourkela, Jabalpur, Jodhpur and Guwahati. One more centre CRPF Base Hospital, Guwahati has been included and clinical trials in collaboration with MRC, Sonapur is in progress.

1.2.1 Center-wise clinical trial status

(a) Assam Medical College, Dibrugarh

So far 7 cases of *P. falciparum* malaria were treated and results are encouraging. Further reports are awaited.

(b) IGH, Rourkela

- Total 72 cases are enrolled for this study and so far 45 case-sheets have been received.
- 43 Cases have completed the study (age range 1.3 to 14 years; body weight range 7.3-49.5 kg).
- Number of cases dropped out or LAMA – 2.
- Results of this study demonstrated rapid clearance of parasitemia, early fever clearance and low recrudescence/reappearance of parasite in PBS. In majority of cases, a complete cure was achieved and no side effects were observed during the study.

(c) Medical College/CRPF Base Hospital, Guwahati/MRC, Sonapur

So far, 25 cases of *P. falciparum* malaria have been successfully treated with Arteether. Injection was well tolerated, no side effects were reported. Completed case record forms are awaited for detailed data analysis.

(d) Jabalpur Center (Medical College/RMRC)

Trial is in progress and so far 10 patients are enrolled in the study. 8 completed the trial, 1 showed recrudescence in the 4th week, 9 showed encouraging results with regard to FCT and PCT. Study is in progress.

(e) Jodhpur Center (Medical College)

So far 20 cases are included in the study. Trials have been completed in 20 cases and response is encouraging.

Until now, 103 children suffering from *P. falciparum* malaria have been included in the multicentric clinical trial and study is in progress.

1.3 Compound 80/53 (Antirelapse antimalarial)

Compound 80/53, requested by CPU, Seth G.S. Medical College, Mumbai was supplied in 8 g. quantity through Scientist In-charge, Pharmaceutics for undertaking study to evaluate its use as a gametocytocidal agent.

1.4 Picroliv (Hepatoprotective agent)

1.4.1 Evaluation of hepatoprotective effects of Picroliv in patients with alcoholic cirrhosis

So far a total of 36 patients were screened, 16 patients have been recruited in the study. Eight patients completed the study period of 6 months. Trial is in progress in 3 cases. 3 Patients were withdrawn due to non-compliance of protocol, 4 cases dropped out and 1 patient expired during the study.

1.4.2 Evaluation of hepatoprotective effects of Picroliv in patients on AKT

A total of 259 tuberculosis patients were screened and dialogued, out of which 142 have enrolled for the study so far. Sixty-one patients have completed the study period of 6 months. Forty-five patients are on going. Thirty-six patients have dropped out. Five patients absconded and 21 refused to continue the treatment. None of the patients has developed hepatotoxicity till now.

1.4.3 Evaluation of hepatoprotective effects of Picroliv in patients of tuberculosis on MDT

Department of Pulmonary Medicine, KGMU, Lucknow has initiated clinical trials of Picroliv in patients with tuberculosis receiving MDT. Studies initiated in April 2005. During the year, 133 patients were registered in the trial of which 13 completed the study. Now 58 patients are continuing in the study. During the trial 1 patient expired and 51 cases dropped out. Trial is in progress.

1.5 CT-1 (Antidiabetic)

Exploratory double blind clinical trials were concluded at KGMU, Lucknow under the supervision of Prof. C.G. Agarwal. A total of 150 patients were screened, 105 enrolled in this study and total of 55 patients (22 on placebo and 33 on CT-1) completed the trial as per protocol. Clinical trial data, alongwith protocol, have been presented by clinicians from KGMU, Lucknow before experts from Nicholas Piramal India Limited (NPIL). Inputs from NPIL were again discussed with Prof. C.G. Agarwal, Head, Medicine Department, KGMU, and his comments and views regarding future action plans have been conveyed to NPIL for further action plan. Reply is awaited.

1.6 Compound 80/574 (Hypolipidemic)

Phase III multicentric trial protocol and case record form was presented/discussed in the investigators meeting. Suggestions of the investigators were incorporated in the minutes of the meeting and accordingly protocol and CRF was modified. Phase III clinical trials in patients of hyperlipidemia have been initiated at SGPGI and KGMU, Lucknow. PGIMER, Chandigarh has also initiated the trial. Very soon Seth G.S. Medical College, Mumbai is also going to initiate clinical trials.

1.7 CDR-134D123 (Antihyperglycemic)

Phases I single dose tolerance studies (double blind) were completed in 31 healthy human volunteers at a dose of 0.5 to 7.5 g. Data compilation has been done. Phase I multiple dose tolerance studies are to be undertaken at Seth G.S. Medical College and KEM Hospital, Mumbai. Coded sachets for double blind clinical trial, alongwith case record forms, have been sent.

1.8 Pharmacokinetic and metabolic studies of synthetic compounds

1.8.1 97-78, 99-357, 99-408 and 99-411 (Antimalarial)

1.8.1.1 *In situ* absorption

In situ absorption studies of 99-357, 99-408 and 99-411 were carried out in male Sprague Dawley rats using intestinal re-circulation technique.

1.8.1.2 Plasma protein binding

Plasma protein binding studies of compounds 99-357, 99-408 and 99-411 were carried in rat plasma and that of 97-78 was carried out in monkey plasma.

1.8.1.3 *In-vitro* metabolic study

In vitro metabolic study of 97-78 was carried out with rat liver S-9 fraction. Inhibition experiments were performed with 7 substrates to characterize CYP isoform involved with metabolism.

1.8.1.4 97-78 Method development

A sensitive, selective and validated HPLC-MS-MS assay was developed for the rapid estimation of compound 97-78 in rat plasma by quantitatively converting it to 97-63 with a linearity range of 1.56– 400 ng/ml. Inter and intra day accuracy and precision were well within acceptable limits.

1.8.1.5 PK studies with 97-78 (racemate) in rats

Preclinical PK studies of compound 97-78 were carried out in male and female SD rats after oral administration at 47 mg/kg dose level.

1.8.1.6 PK studies with 97-78 (racemate) in monkeys

Intravenous pharmacokinetic studies were carried out at 2 mg/kg dose levels.

1.8.1.7 PK studies with 97-78 (enantiomer-A & -B) in monkeys

Pharmacokinetic studies of enantiomer A and B of 97-78 after oral (20 mg/kg) and intravenous (2 mg/kg) administration were carried out in male rhesus monkeys.

1.8.2 99-373 (Anti-osteoporotic)

PK studies were carried out at 10 mg/kg single oral dose in Sprague Dawley Rats. *In-vitro* metabolic studies were performed with liver S-9 fraction.

1.8.3 80-574 (Anti-hyperlipidemic)

1.8.3.1 Method development

A simultaneous bioanalytical assay method was developed and validated in rat/rabbit plasma by HPLC-MS-MS including six putative metabolites. The method was validated in terms of accuracy, precision, absolute recovery, freeze thaw stability and dry residue stability. The accuracy and precision were found to be well within the acceptable limits and analytes were found to be stable after three f-t cycles.

1.8.3.2 In vitro studies

Stability studies were conducted in simulated gastric fluid and simulated intestinal fluid. *In situ* permeability studies were performed using intestinal re-circulation technique. *In vitro* metabolic studies were performed with rat liver S-9 fraction.

1.8.3.3 PK studies in rats

Single dose pharmacokinetic studies of compound 80-574 were carried out in male SD rats after oral (72 mg/kg) and i.v. (1 mg/kg) administration. PK studies were also carried out in male SD rats by i.m. route (10 mg/kg).

1.8.4 S-001-469, S-002-853 and S-002-857 (Anatidiabetic)

1.8.4.1 Method development

A simultaneous bioanalytical assay method was developed and validated in rat plasma by HPLC-UV using sample pooling technique for rapid generation of pharmacokinetic data. The method was validated in terms of accuracy, precision, absolute recovery, freeze thaw stability and dry residue stability. The accuracy and precision were found to be well within the acceptable limits and analytes were found to be stable after three f-t cycles.

1.8.4.2 *In vitro* studies

Stability studies of S-001-469, S-002-853 and S-002-857 were carried out in Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF). *In situ* permeability studies were performed using intestinal re-circulation technique.

1.8.5 Centchroman-metformin interaction studies

Effect of centchroman on pharmacokinetics of metformin was investigated in female Sprague-Dawley rats at a single oral dose of 70 mg/kg oral of metformin and 1.5 mg/kg of centchroman.

1.8.6 α-, β-Arteether

Clinical pharmacokinetic studies were carried out after multiple (150 mg x 3 days) by intramuscular route in three more male volunteers. The pharmacokinetics correlated well with earlier data generated in 6 volunteers humans (total n = 9). Briefly the pharmacokinetics of the

isomers of arteether was different with the β isomer showing significantly longer elimination half life and mean residence time as compared to the α isomer. Plasma accumulation of α arteether was moderate while that of β arteether was significantly higher.

1.9 Pharmacokinetic studies of herbal preparations

1.9.1 Picroliv

1.9.1.1 SGF and SIF stability

Stability studies of Picroside-I and Kutkoside were performed in Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF).

1.9.1.2 *In-situ* absorption of Picroside-I and Kutcoside

In-situ absorption studies were conducted in male Wistar rats using intestinal re-circulation technique.

1.9.2 Turmeric oil (herbal medicament)

PK studies of the herbal medicament were conducted at 500 mg/kg single dose and 125 mg/kg single dose by oral route of administration in male SD rats.

Multiple dose (125 mg/kg) PK studies, wherein 4 oral doses were administered on four consecutive days (τ = 24 h), were conducted in male SD rats.

2. PRECLINICAL SAFETY EVALUATION AND REGULATORY TOXICITY

Coordinator: Dr. Sudhir Srivastava

The studies carried out under this project had two major objectives:

I. Toxicological profiling of candidate drugs according to internationally accepted methods for studying local, systemic, reproductive and genetic toxicity, and

II. Deployment of alternative test systems that will reduce, refine or replace the use of animals in toxicity testing, and provide vital information on safety/mechanism of toxicity/ metabolism of drugs.

2.1 Toxicity Studies of Candidate Drugs

2.2 Experimental Toxicology Work

2.3 Other Studies

2.1 Toxicity Studies of Candidate Drugs

A total of eight compounds have been tested for systemic toxicity, two for genotoxic potential and one for teratogenic potential.

2.2 Experimental Toxicology Work

Experimental toxicology work (Expression Studies using Microarrays, Rat Whole Embryo Culture, Short-term Bioassays for Carcinogenicity Testing and CFU-GM Assay for Haematotoxicity) has involved short-term training of 20 candidates during this period.

2.3 Other Studies

(a) Efforts have been initiated for the establishment of following activities in the Division:

- Immunotoxicity Testing
- Phototoxicity Testing
- Profiling of Blood Coagulation Parameters
- INH-Induced Toxicity in HepG2 Cells (ROS Mediated)
- G-3-PDH & AP2: Biomarkers for Evaluating the Efficacy of PPAR-Gamma Agonist Activity
- Cytochrome P450 Isoform Profiling for Selection of Appropriate Species for Toxicity Testing
- Assessment of Genetic Predisposition to Breast Cancer in Indian Women.

(b) Two new externally funded toxicity-testing projects have been initiated:

- Systemic toxicity studies of from Cholesterol Lowering Herbal Preparation Maharishi Ayurveda Products Limited, New Delhi
- Pre-Clinical Studies of Lysostaphin Cream Formulation from Bharat Biotech, Hyderabad (NMITLI Project, CSIR, New Delhi).

PROJECT AREA STUDIES

1. AREA: BIOLOGICAL SCREENING

Coordinator: Dr. Sudhir K. Sinha

The main objectives of this project area are: (a) high-throughput screening and (b) development of new screening models. In addition, this project also covers screening of the anti-tuberculosis and anti-cancer molecules produced by the Institute.

1.1 Tuberculosis

1.2 Cancer

1.3 High-throughput Screening of Botanicals for the Identification of Skin and Hair Bioactives

1.1 Tuberculosis

1.1.1 Screening

Institute's entire chemical library of over 15,000 molecules was subjected to high-throughput screening against *M. tuberculosis* $H_{37}R_a$. The selected 'hits' were further screened against *M. tuberculosis* $H_{37}R_v$. 10 Molecules, with a minimum inhibitory concentration (MIC) of 3 μg/ ml or less, were short listed as probable leads. These molecules did also not show any *in vitro* cytotoxicity against Vero cells. All selected molecules have been subjected to *in vivo* screening using the mouse model of tuberculosis. When administered orally for 28 days at a daily dose of 100 mg/kg body weight, one of the molecules showed an early indication of protection against infection, which is being confirmed. Four molecules did not show any protection, whereas 2 molecules showed systemic toxicity leading to early death of animals. Results on 3 other molecules are awaited.

1.1.2 Chemical modifications

Poor gastric stability, water solubility and oral bioavailability of some of the *in vitro* active molecules were major concerns, limiting their *in vivo* activity profiles. Presently, the chemistry-based lead optimization effort is going on with the view to enhance the bioavailability of these molecules.

1.1.3 Development of new screening models

Efforts have been directed towards development of new *ex vivo* and *in vivo* models for evaluation of compounds for anti-TB activity. The following models are under advanced stages of development.

1.1.3.1 Mouse bone marrow macrophage as *ex vivo* model for TB and latent TB

This model mimics growth environment in the natural TB infection. It demonstrates penetration by candidate molecule of host cell membrane and the phagocytic vacuole, penetration of *M. tuberculosis* within the vacuole and the ability to reach the desired drug target within the bacterial cells. In addition, this also serves as a model for 'hypoxia induced' latent TB infection, since tissue concentration of oxygen is considerably less than that in the ambient air. Many 'latency marker' proteins of the pathogen are known to get expressed during its intracellular growth phase.

1.1.3.2 'Cornell mouse model' for persistent TB

One of the problems in treatment of tuberculosis is development of 'persisters' against the currently used chemotherapy. These persister bacteria get activated and start multiplying in patients, once the treatment is stopped. Cornell mouse model is a model for screening of molecules against persistent TB. In this model, the mice intravenously infected with *M. tuberculosis* are treated for 12 weeks with the 'first line' anti-TB drugs isoniazid and pyrazinamide. The animals become culture negative at the end of treatment. After 3 more months without treatment, one third of the animals relapse with culture positive spleens and lungs.

1.2 Cancer

The project on cancer drug development is being pursued in collaboration with the industrial partner Dabur, and is jointly funded by DST and Dabur.

After high-throughput screening of the entire chemical library of CDRI against five cancer (pancreas, ovary, prostate, breast, colon) and one normal (fibroblast) cell lines, 43 'hit' molecules belonging to 4 chemical classes were short listed for chemistry-based lead optimization. 71 New compounds or analogs of selected 'hit' molecules were synthesized at CDRI and submitted for advanced screening (using 8 cancer cell lines- lung, leukemia and oral; in addition to the above mentioned 5) at Dabur. Eight molecules have so far been selected, showing single (against one cancer type), limited (against 2-4 cancer types) or a broad spectrum of specificities.

Poor solubility of some of the compounds in aqueous medium was a concern, prior to initiating the *in vivo* efficacy experiments in mice. This problem is being addressed through synthesis of suitable analogs of the selected lead molecules.

1.3 High-throughput screening of botanicals for the identification of skin and hair bio-actives

The HTS laboratory of CDRI has been selected as a partner lab in this CSIR - Procter & Gamble joint project funded by P&G, USA. The lab will do screening assays for the target enzymes Cycloxygenase (COX)-1 and -2, using plant materials provided by other partner CSIR Institutes. P&G have transferred the technology for these assays to CDRI's HTS lab. 36 Samples have so far been screened using COX assays.

2: AREA: CARDIOVASCULAR CENTRAL NERVOUS SYSTEM & OTHER DISORDERS

Coordinator: Dr. Ram Raghubir

The research activity pursued under the above project includes design, synthesis and development of new drugs for various diseases of Cardiovascular System (stroke, thrombosis & hypertension), Central Nervous System (dementia & stress) and other disorders (diabetes, lipid disorders, impaired wounds, inflammation, allergy including asthma & ulcers). The project area also covers regulatory pharmacological studies of the drug candidates. Development of suitable better and predictable screening models for evaluation of plant extracts, fractions and synthetic compounds. Besides, this neurochemical and molecular investigations are also persuaded for analyzing the possible mechanism(s) of action of newer drugs. Developing new target based assays is prime concern, which may eventually help in the development of new target based drugs.

2.1 Cardiovascular System

2.2 Central Nervous System

2.3 Any Other Disorders

2.4 Safety Pharmacological Studies

2.1 CARDIOVASCULAR SYSTEM

2.1.1 Development of Anti-stroke agents

Herbal Medicament produced a dose dependent neuroprotective effect on cerebral ischemia /reperfusion injury induced by MCAO in rats. Pretreatment of rats with low dose (125 mg/kg po) of HM for 5 days produced significant neuroprotective effect. Thus HM is not only curative but also has significant preventive effect as well. HM also produced mild anti-inflammatory activity.

A total of 9 compounds have also been screened at a dose of 100 μM for anti-TNF activity using whole blood assay and ELISA. Compounds S-004-1470, S-004-1471, S-004-1478 showed 53 %, 43 % and 42 % TNF inhibitory activity. Standard compound Pentoxifylline (10 mM) showed 56 % activity.

2.1.2 Anti-thrombotic activity of test compounds

Compounds were tested at the dose of 30 μM/kg against collagen and adrenaline induced thrombosis (n=158). Among them several compounds exhibited 40% or more protection against collagen induced thrombosis, which was better than the protection offered by Aspirin. In addition various alcohol extracts of natural substances were tested among them Amla extract, when administered for 10 days at a dose of 100 mg/kg, offered appreciable protection against thrombosis in mice. An interesting lead from a CDR fraction was also identified during this period.

2.1.3 $FeCl_3$ induced thrombosis in rats

Along with standard drugs Heparin, Warfarin, Aspirin and Ticlopidine, CDRI compounds S-000-20, S-002-329 and S-002-333 were evaluated in this model. Anti-coagulant drugs offered maximal protection, while aspirin was not effective in this model. CDRI compounds offered nominal yet significant protection, which was comparable but better than Ticlopidine.

2.1.4 Inhibition of platelet aggregation by analogues of compound 99-353

All the six compounds submitted inhibited ADP induced platelet aggregation, while all were less effective against arachidonic acid and PMA induced aggregation. All of these compounds exhibited better profile (*in vitro*) than 99-353 but they were not more active than 99-353 in mice against collagen and adrenaline induced thrombosis.

2.1.5 Model of thrombosis in hamsters

Hamsters similar to mice were found to develop intravascular thrombosis when challenged with a mixture of collagen-epinephrine. It was also observed that the incidence time to occlusion was not significantly different in the normolipidemic and hyperlipidemic hamsters. Warfarin was also found to prevent ferric chloride induced thrombosis in hamsters. CDRI compounds were also evaluated in this model.

2.1.6 Anti-hypertensive activity

2.1.6.1 CDRI compounds

Fifteen compounds were tested for their effect on BP and heart rate at 5,10 and 25 mg/kg; among these four compounds exhibited appreciable lowering in BP in anaesthetized rats.

2.1.6.2 CSIR coordinated samples

A total of 530 extracts were bio-evaluated for antihypertensive activity in SHR. Two new leads have been obtained. The detailed work on already identified lead molecule is in progress for product development.

2.1.6.3 Plant extracts

A total of 44 plant extracts have been evaluated for antihypertensive activity in anaesthetized rats on polygraph. None of the substance tested showed any promising effect.

2.1.6.4 Establishment of Telemetry system for assessing cardiovascular effects in conscious hypertensive rats

Telemetry system for recording cardiovascular parameters in conscious normotensive/ hypertensive rats has been established. Blood pressure, ECG and core temperature of rats were continuously monitored using biotelemetry system and data has been collected using ART Dataquest software on a computer. Effects of clinically used antihypertensive agents atenolol, enalapril and amlodipine have been studied to validate the system.

2.1.7 Basic studies in CVS

2.1.7.1 Expression of PARP following cerebral ischemia/reperfusion in diabetic rats

STZ induced diabetic male S.D. rats (270±20g) were subjected to MCAO. The degree of neurological deficit was more pronounced in diabetic as compared to control rats. Blood GSH level was reduced with significant elevation of MDA level in diabetic animals. The cytochrome c release was significantly higher in hyperglycemic as compared to control at each time point of I/R. However it was lower at 6.0 hr as compared to 3.0 hr of reperfusion. This is the indicative of the mitochondrial dysfunction owing to oxidative stress produced by I/R. Similar pattern of expression was seen with PARP-1. An increase in PARP-1 expression at early time point seems to be due to DNA damage, however the expression at late hours may be due to the cleavage by caspase-3. Thus the propensity of molecular changes seen in the affected brain regions of the diabetic MCAO rats clearly reflects the severity of stroke as compared to normal subjects.

2.1.7.2 Nature of cell death in cerebral ischemia reperfusion injury

Focal cerebral ischemia was induced in male Sprague-Dawley rats (260±10g) by occluding middle cerebral artery. This led to the activation of cell death cascade both necrosis and or apoptosis, which resulted in loss of functional and structural integrity of cells. The percentage of population of necrotic and apoptotic cells following I/R injury was examined using single cell suspension of brain parts (striatum, hippocampus, frontal cortex and parietal cortex) followed by analysis in a flow cytometer using PI and FITC to quantitate necrotic and apoptotic population. The results showed highest apoptotic percentage (42%) of cells in the hippocampus followed by 30% and 33% in the frontal and parietal cortex and least 21% in the striatum. The necrotic cell population was maximum in case of hippocampus and it varied between 4-6% in other brain regions. It seems the nature and mode of cell death in various parts of the brain depends solely on severity of ischemic insult and network of circulation to these brain areas.

2.1.7.3 Neuroprotective effect of calcineurin inhibitor on cerebral ischemia/reperfusion injury

The dephosphorylation processes of target proteins are critical to the reversible regulation of intracellular signal transduction system during ischemia. The present study was designed to delineate the role of a Ca^{2+}/CaM dependent Ser/Thr protein phosphatase i.e. calcineurin (PP2B) in cerebral ischemia due to its abundant and specific localization in the brain. The calcineurin (CaN) expression and neuroprotective effect of an immunosuppressant drug, FK-506 on I/R injury was assessed in 2/24 hr I/R injury induced by MCAO in rats. Oxidative stress due to I/R caused lipid peroxidation resulting into elevated MDA and a significant depletion in the GSH levels. However, there was no significant alteration in the CaN expression but FK-506 pretreatment offered significant neuroprotection as the ND, MDA and GSH levels returned near to basal level possibly due to inhibition of CaN activity. Thus the results demonstrate a clear distinction between the expression and activity of CaN in cerebral stroke.

2.1.7.4 Studies on the role of endoplasmic reticulum stress following cerebral ischemia

An evidence, indicate that endoplasmic reticulum (ER) stress occurs during I/R injury, which activates various cell signaling pathways responsible for brain damage. The I/R (2/24hr) caused significant neurological deficit. The rats showing ND score of >6 on a 10 point scale were used in the follow up studies. Reduced Blood GSH levels with significant elevation of serum MDA levels indicated oxidative stress resulting into neuronal loss as revealed by TTC staining.

Further, the expression level GRP78 (ER specific stress marker) in cytosol and procaspase12 (ER specific apoptotic molecule) in microsomal fraction were found to be elevated in cortex (37% & 34%), striatum (25%and 23%) and hippocampus (75%, 18%) respectively. However, decreased expression level of Bcl-2 (an antiapoptotic molecule) was found in microsomal fraction of cortex (20%) and striatum (10%) but in hippocampus, an elevated level (50%) following I/R injury. Interestingly, the cytochrome c level was increased by 20% in the microsomal fraction as compared to cytosol.

Thus, it appears that altered expression of GRP78 and procaspase12 indicated I/R induced ER stress signaling, an initiation of apoptotic pathway. Down regulation of Bcl-2 further supports the above notion. Furthermore, cytochrome c released from mitochondria may play a stimulatory role in ER induced apoptotic signaling.

2.1.7.5 Differential regulation of neurotrophins gene expression by focal cerebral ischemia/ reperfusion injury in rat brain

We have investigated the cerebral ischemia/reperfusion (I/R)-induced alteration in the neurotrophins mRNA level in different brain regions at selected time points of I/R. The ischemia of 1hr followed by reperfusion for 12/24hr. Plasma GSH was reduced to 54% and 47% whereas serum MDA was elevated to 75% and 74%, respectively. There was a 66% reduction in the SOD levels in striatum at 24hr as compared to sham indicative of oxidative stress. The histochemical studies of the affected brain regions showed an infarcted area and swollen neurons with apoptotic bodies on H & E staining. Further, the TUNEL-positive cells (TUNEL staining) were found in

large number at 12hr post-reperfusion in striatum and cortex but not in hippocampus as compared to 24hr of reperfusion.

Molecular studies showed that BDNF, NT-3, NT-4 and NGF gene expressions were found to be increased at 12hr, which returned to the basal level at 24hr of reperfusion injury in cortex, striatum and hippocampus but NGF remained unaffected in the striatum.

2.1.7.6 Studies on the NOS immunocytochemistry in the neutrophils

Nitric oxide (NO) modulates diverse functions of neutrophils (PMNs), but localization of nitric oxide synthase (NOS) and identification of its interacting proteins remain the least defined. The ongoing study discerned subcellular distribution of NOS and caveolin-1, a prominent NOS interacting protein in rat PMNs. Localization of NOS was explored by confocal and immunogold electron microscopy, while its activity was assessed by L-(^{3}H) arginine and 4,5- diaminofluorescein diacetate (DAF-2DA). RT-PCR using NOS primers and Western blotting (WB) demonstrated presence of neuronal (nNOS) and inducible (iNOS) NOS in PMNs. Immunocytochemical studies exhibited distribution of nNOS and iNOS in cytoplasm and nucleus, while L-(^{3}H) citrulline formation and DAF fluorescence confirmed NOS activity in both fractions. NOS activity positively correlated with calmodulin (CaM) concentration in both the fractions. nNOS and iNOS colocalized with caveolin-1 as evidenced by immunocytochemical and immunoprecipitation (IP) studies. The results provide evidence of nNOS and iNOS presence in the nuclear compartment and suggest NOS interaction with caveolin-1 in rat PMNs.

2.1.7.7 Effect of NO and peroxynitrite (ONOO) donor, SIN-1 on PMNs free radical generation

PMNs free radical generation as assessed by DCF (which reacts with H_2O_2, HOCl, ONOO, NO_2Cl) or DHE (which reacts with O_2^-) was evaluated in the presence of potassium channel blockers (Iberiotoxin, Paxilline, Glybenclamide) and opener (NS1619). The large conductance potassium channel modulators showed alteration in DCF response, while DHE response was not altered. The results obtained suggest that intracellular potassium support free radical generation in the PMNs. The possibility of involvement of degranulation in nitric oxide induced free radical generation was also studied by using kinase inhibitors, cytoskeleton inhibitors, calcium chelators. The PKC inhibitor (Staurosporine) and PKG inhibitor (KT5823) significantly inhibited free radical generation by NO, ONOO, and fMLP. The neutrophil response was also reduced in the presence of PD98059, U-0126 (ERK1/2 & MEK inhibitor), KT5720 (PKA inhibitor). It suggests that NO possibly mediated response by stimulating PKC, PKG as well as PKA and MEK1/2. NO mediated increase in the DCF fluorescence in potassium channel activity was observed. Further studies will help in delineating the network of the signaling molecules.

2.1.7.8 Studies on effect of ascorbic acid on NO generation from scorbutic guinea pig PMNs

Biopterin (BH_4) content in neutrophils was obtained from scorbutic guinea pigs measured 1 and 2 weeks following ascorbic acid deficiency was reduced significantly. The ascorbic acid content in plasma and neutrophils correlated with the decreased trend of BH_4 content among the scorbutics. NOS activity in neutrophils obtained from scorbutic animals was also reduced significantly. NOS activity though augmented *in vitro* in the presence of ascorbate and biopterin

but the reduction in NOS activity in the scorbutic guinea pig was still measurable. Generation of superoxide radical and free radical in scorbutic guinea pig showed attenuation.

Flow cytometry study on the influence of ascorbic acid on phagocytic activity in neutrophils was also conducted in rat and guinea pig neutrophils. Ascorbate profoundly influenced the apoptotic activity in neutrophils following phagocytosis ensuring effective resolution of inflammation by clearing the apoptotic neutrophils from both rats and guinea pigs. There was an augmentation of phagocytic activity following administration of ascorbic acid 1mM, but ascorbic acid at a concentration of 300μM failed to elicit such response. Further studies will help in understanding the mechanism involved in ascorbic acid mediated modulation of PMNs responses and apoptosis.

2.2 CENTRAL NERVOUS SYSTEM

2. 2.1 Anti-dementia

Synthetic compounds (7) were tested on scopolamine induced dementia in passive avoidance test in mice. 4 compounds showed significant activity. Daily administration of Gugulipid in mice showed significantly less latency time as compared to control in Morris water maze test, which indicates memory enhancing potential of gugulipid.

86 Samples were tested for anti-dementia activity under CSIR-Coordinated programme (COR-023). 2 New samples were found active. Among samples of discovery groups NBR and AM20 series samples were tested on streptozotocin models for post-treatment effect. The AM20 samples were effective on this model. Standardized extract of July 05 collection from NBR and fresh samples from FNCM were tested and found active.

2.2.2 Anti-depression

32 samples under CSIR-Coordinated program were tested and none was found to be active.

2.2.3 Anti-anxiety activity

Under CSIR Coordinated program, 69 compounds were screened for anti anxiety activity using Elevated Plus Maze test in mice and 4 compounds showed promising activity.

2.2.4 NMTILI project (*Withania somnifera*)

15 Samples were tested for CNS, memory, anti-depressant, antioxidant and anti-inflammatory activities. Significant effects were showed by 4 samples on anti-nociceptive activity and 2 samples on anti-dementia activity. One sample showed significant antioxidant profile.

2.2.5 Basic Studies in CNS

2.2.5.1 Role of insulin in learning and memory in rodents

Recently the presence of insulin and its receptors have been demonstrated in the brain areas including hippocampus, which is a center brain site, involved in regulation of learning and memory functions. The results of our earlier studies with scopolamine model in passive avoidance test indicated that brain insulin might be playing a protective role in learning and memory functions. Streptozotocin (25 μg, i.c. on 1st and 3rd day, passive avoidance test on 14th day) induced dementia

on single trial passive avoidance test in mice was standardized. Insulin (0.1 unit/kg, ip) was effective in streptozotocin induced dementia model. Streptozotocin model of dementia in rat has been standardized. Streptozotocin (250 μg, i.c.v on 1st and 3rd day) resulted into deficit in learning and memory functions in Morris water maze test after 14th day without affecting blood glucose level. Donepezil an anti-dementic drug successfully inhibited streptozotocin induced deficit. Streptozotocin caused significant decrease in glutathione in different brain areas particularly in hippocampus.

2.2.5.2 Pharmacological and biochemical correlate on different nature of stresses

Rats were subjected to acute, chronic unpredictable and chronic stress varying in time and stressor intensity. The effect of perturbed neurotransmitters on free radical homeostasis was observed. Acute stress (AS) significantly increased dopamine (DA), 5-hydroxy tryptamine (5-HT) and reduced the levels of noradrenaline (NA) in all the brain regions without affecting the free radical homeostasis. Chronic unpredictable stress (CUS) significantly depleted the neurotransmitters and also a considerable oxidative load was observed as reflected by increase in lipid peroxidation, glutathione peroxidase (GPX) with simultaneous depletion of super- oxide dismutase (SOD), catalase (CAT) and glutathione. Frontal cortex (FC), hippocampus (HP) were significantly affected compared to hypothalamus (HT) by the increased oxidative load during CUS. The change in the brain free radical homeostasis is well correlated with decreased plasma total anti-oxidant capacity (TAC). In chronic stress model the response of neurotransmitters was normalized in HP and HT regions and a decrease of NA and DA was observed whereas the glutathione concentration was increased in all the brain regions studied. There are no considerable changes in lipid per oxidation and anti-oxidant defense enzymes in all the brain regions. This study suggested the role of severe and prolonged neurotransmitter perturbations during stressful conditions in free radical mediated damage.

2.2.5.3 Study on role of central histaminergic system in depressive disorder

L-Histidine (LH) a precursor of histamine attenuated the effect of amphetamine hyperactivity, which was blocked by H1 and H3 receptor antagonists, whereas LH potentiated the effect of amphetamine on chronic treatment. LH treatment for 21 days resulted in decrease of plasma corticosterone in depressed animals. In addition, LH treatment lead to significant increase in cytosolic glucocorticoid receptor density in cortex and hippocampus regions of the brain. Further activation of central histaminergic system elevated the levels of neurotransmitters in cortex and hippocampus regions of the brain. However, H3 receptor expression is unaltered in all region of the brain.

2.3 OTHER DISORDERS

2.3.1 Anti-hyperglycemic Activity

Efficacy doses of S-002-853, S-002-857 and S-001-469 were determined to be around 67.1, 158 and 108 μmole/kg, respectively, compared to gold standard metformin i.e. 125 μmole/kg in sucrose challenged low dosed streptozotocin- induced diabetic rats. Anti-hyperglycemic, anti-hyperinsulinemic and anti-dyslipidemic activity of S-002-853 and S-002-857 were evaluated in mild, moderate and severe hyperglycaemic db/db mice at 100 mg/kg dose. Results showed that both the compounds were capable of declining the blood glucose with tendency of declining

total plasma triglycerides, cholesterol and LDL-cholesterol profiles and raising the HDL-cholesterol ratio. These compounds were also found to lower the plasma insulin levels in hyperinsulinemic db/db mice. In MTT cytotoxicity assay using 3T3 L1 (pre adipocytes) and L-6 (muscle) cell lines these compounds were devoid of any cytotoxic signs upto 10 μM.

2.3.2 Anti-dyslipidemic Activity

S-002-853 is identified as lipid lowering agent. Dose response studies were conducted and was found active at 12.5 mg/kg dose using pair fed group as control. Compound did not show any adverse effect or lipid lowering effect in normal diet fed animals. Dose response studies were conducted on compound S-002-857 and S-002-469 identified as an active compound at 100 mg/kg dose.

2.3.3 Development of anti-inflammatory agents

A total of 92 compounds, 25 plant extracts and 24 samples have been evaluated for anti-inflammatory activity in carraginin induced paw oedema model in rats. Plant extract 4032 F011 showed 48.5% AI activity at 100mg/kg po dose. Ibuprofen 100 mg/kg p.o. used as standard drug showed. 61.5% activity.

2.3.4 Appetite suppressant activity

24 compounds were tested on scheduled fed rat and two were found active.

2.3.5 Anti-ulcer activity

The anti-ulcer activity of WGI76P was studied against cold restraint stress (CRU), aspirin (ASP), alcohol (AL), pyloric ligation (PL) and chronic acetic acid induced ulcer models in rodents and histamine induced (HST) induced duodenal ulcer model in guinea pigs and was compared with standard drugs omperazole and sucralfate. It showed significant anti-ulcer activity against all acute and chronic ulcer models. Among the various batches, batch N0. 18 showed a very significant anti-ulcer activity. It also increased mucin secretion. Further, ICB 014 P04 A002 and F006 showed significant anti ulcer activity against all acute models and F006 is more effective whereas F007 is not showing significant anti ulcer activity.

Anti-ulcerogenic and ulcer healing properties of plant extract 38C002/4483 was evaluated and found that 38C002/4483, decreased the incidence of ulcers and also enhanced the healing of ulcers. Therefore, 38C002/4483 seems to be curative and prophylactic peptic ulcer. Compound 4484/C002, F005, F010 and K016 showed significant anti-ulcer activity against different ulcer models and K016 is most effective. The antiulcer activity was also found in 4627A001.

The ethanolic extract of CDR-134F-234 was found to be effective against CRU, ASP, AL, PL and HST induced gastric and duodenal ulcers. It has significantly reduced the acid secretion along with enhancing mucin secretion.

2.3.6 Anti-histaminic activity

Anti-histaminic activity of 22 compounds was evaluated using GPI assay. The graded doses of four test compound produced significant blockade of histamine induced ileal contraction. The anti-histaminic activity was though significant but was relatively less than reference drug cetrizet.

2.3.7 Basic studies in other disorders

2.3.7.1 Studies on inflammatory mediators - Studies of tumor necrosis factor (TNFα) and nitric oxide (NO) in macrophages

Experiments on peritoneal macrophages and macrophage cell line J774A showed TNFα released from lipopolysaccharides (LPS) stimulated macrophages was significantly decreased on inhibition of NO synthesis. L-NAME, an inhibitor of NOS, reduced the TNFα release from stimulated macrophages at a level comparable with that of reduction in NO release. Similarly pentoxifyllin, an inhibitor of TNF synthesis, also decreased the release of NO at a level comparable with the reduction in TNF release. More interestingly, the release of both TNFα and NO from stimulated macrophages was also found to be inhibited by NSAIDs treatment (celecoxib, indomethacin and Curcumin), indicating the role of prostaglandin's in mediating increased release of both TNFα and NO from macrophages.

2.3.7.2 Cyclo-oxygenase-2 expression and prostaglandin E_2 production in experimental chronic gastric ulcer healing

Cyclooxygenase-2 (COX-2) plays a major role in normal as well as drug mediated ulcer healing. A compative study on expression profile of COX-2 protein, mRNA, prostaglandin E_2 (PGE_2) levels and myeloperoxidase activity in acetic acid induced chronic gastric ulcer model in rats treated with anti-ulcer drugs as omeprazole, ranitidine, sucralfate, misoprostol was carried out. Specific COX-2 inhibitor, celecoxib delayed gastric ulcer healing. Thus it may be concluded that induction of COX-2 expression leading to higher level of prostaglandin appears to be an important contributing factor in drug-mediated ulcer healing apart from the respective mechanisms of different drugs.

2.3.7.3 Role of PPAR-ã receptors in gastric ulcer healing

PPAR-γ a nuclear receptor has been recently identified for its anti-ulcer activity. Preliminary studies showed that the effects of pioglitazone, a PPAR-γ agonist, healed the gastric ulcers in acetic acid induced chronic ulcer model. Antagonist treatment with BADGE has also established the involvement of this nuclear receptor in effective ulcer healing. Further localization of PPAR-γ in gastric tissue is being carried out with Western blot analysis.

2.4 SAFETY PHARMACOLOGICAL STUDIES

The essential safety pharmacological studies of following candidate drugs were carried out as per Appendix III of Schedule Y gazette dated 20th January 2005.

1. Compound 97/78 - anti-malarial
2. Compound 99/373 - anti-osteoporotic
3. Fraction 194 - anti-diabetic cum anti-dyslipidemic
4. Fraction 018 - anti-diabetic cum anti-dyslipidemic
5. DRF –7295 - anti-cancer
6. DONDR-012 - anti-cancer

The single dose toxicity of the four institute compounds was undertaken and all of them presented a high therapeutic window. Graded doses of test compounds, accelerating to ten times of efficacy dose, were administered by the intended routes. Cardiovascular effects (BP, HR) in anaesthetised rats and also in non-anaesthetised SHR by telemetry was done. The gross behavioural effects were also under taken in mice with 3-4 doses. The respiratory effects (rate, amplitude) BP, HR were also assessed in anaesthetized rabbits.

In general all the candidate drugs even with maximal dose were found safe on all the observed parameters of the cardiovascular, CNS and respiratory systems being necessary elements of safety pharmacological studies.

3. AREA: FILARIASIS

Coordinator: Dr. Shailja Bhattacharya

Lymphatic filariasis has been and still is a major public health problem in India. The disease though is not fatal, but in chronic state is disabling and a cause of social stigma. Development of a macrofilaricide and/or female worm sterilizing agent is today's urgent need.

The project is being pursued with the objective to develop orally active macrofilaricides and female worm sterilizing agents, to define biochemical and immunological functions of parasites and host, to utilize genomic information in the identification of molecular targets for *in vitro* screening and rational design of potential antifilarials and also to understand pathogenesis of the disease.

3.1 Development of New Antifilarial Agents

3.2 Basic Studies

3.3 Biochemical and Molecular Studies.

3.1 Development of new antifilarial agents

3.1.1 Screening of synthetic and natural products *in vitro* and *in vivo*

3.1.1.1 Synthetic compounds

Two compounds received from VCRC, Pondicherry, for evaluation of antifilarial activity exhibited that VCRC PF-210 had *in vitro* adulticidal efficacy upto a lowest concentration of 3.17 μM when tested at two fold dilutions starting from 200 μM to 0.18 μM concentration. However, in the i*n vivo* experiments, this compound was found to be toxic at the dose of 50 mg/kg i.p. x 5 days when given to infected mastomys bringing about mortality of all the treated animals. It appears that the *in vitro* antifilarial activity could be the result of high toxicity of the compound. In the repeat experiment, a low dose of 6 mg/kg i.p. x 5 days was also found toxic. Another compound, VCRC PF-19 showed neither microfilaricidal efficacy nor any embryostatic effect. However, this compound exerted macrofilaricidal action. Repeat experiment is underway to confirm these results.

3.1.1.2 Natural products

18 New plant extracts were tested *in vivo* against *B. malayi* in *Mastomys coucha*. All the extracts were found inactive. Further, 63 marine products belonging to NIT, ICAR and CDR group were tested *in vitro* against adult female *B. malayi*. 5 Extracts were found to be active at 62.5 μg/ml concentration in one experiment. Repeat testing is in progress to confirm these results.

3.1.1.3 CSIR Co-ordinated project

During the period of report, more than 2300 samples were screened *in vitro* against *B. malayi* adult worms. None was active *in vitro*.

3.1.2 Follow up studies

Micro emulsion formulation of albendazole was found to possess *B. malayi* adult female sterilizing potential. Pure albendazole and commercially available tablet of the same were ineffective. Further, activity of extracts of original and repeat collection from CSIR Co-ordinated Project were confirmed *in vitro* and i*n vivo* studies are in progress.

3.2 Basic studies

3.2.1 Immunological studies

3.2.1.1 Immunoprophylactic studies with recombinant myosin and paramyosin of *B. malayi* adult female worms

Groups of *Mastomys coucha* were immunized with recombinant myosin and paramyosin. Five groups of male mastomys each consisting of 5 animals were included in the immunization study using each protein. Three immunizing doses were given subcutaneously on days 0, 15 and 23. First dose contained FCA while the subsequent ones had FIA. Animals have been challenged with ~100 infective larvae of *B. malayi* subcutaneously in the back region. The animals are under incubation period and periodic collection of their blood is being done for assaying immune parameters.

3.2.1.2 Characterization of inflammation modulating molecules of *B. malayi* adult worms

(a) BmAFII fraction

Sensitization of *M. coucha* with BmAFII (Sephadex G-200 eluted fraction of *B. malayi* adult worm extract) and subsequent exposure to *B. malayi* L3 resulted into >84% lesser establishment of adult worms. Microfilaraemia was significantly suppressed in these animals as compared to controls. L3 exposure in sensitized animals resulted in to enhanced IgG, CMI, IFN-γ responses and NO release. The findings show that BmAFII has molecules that protect the host and adversely affect the establishment of challenged infection. Further fractionation of BmAFII is underway**.**

(b) Nitrocellulose (NC) bound BmA antigens

Of the various NCP bound fractions of *B. malayi* adult extract, three fractions viz. B8, B11 and B12 (~45-48, ~33-38 and ~28-33kDa, respectively) were observed to possess NO release stimulating potential. *In vivo* results revealed that the fractions were immunosuppressive in nature as evidenced by the suppressed CMI and strong IL-10 release stimulating potential. Study on the effect of these molecules on parasite survival is in progress. Another fraction (B6), which appeared to possess highest proinflammatory (TNF-α, IL-1β and IL-6) response was further fractionated by SDS-PAGE and one sub fraction (~59-63 kDA) was identified to show strong TNF-α release stimulating potential. Characterization of the effective fraction by 2-D gel electrophoresis is underway.

3.2.1.3 Isolation of *S. cervi* antigen equivalent to filarial circulating antigen

Characterization of parasite proteins present in the circulation of infected host or in the excretory-secretory products of filarial parasites is important to define the exact nature and role of these molecules. We have monoclonal antibodies against the filarial circulating antigen and trying to isolate *S. cervi* antigens equivalent to filarial circulating antigen using these Mabs. The somatic extract from *S. cervi* adults was prepared, subjected to heat treatment and the supernatant obtained was fractionated using DEAE Sephacel column. The fractions showing high reactivity with filarial Mab (detecting the filarial circulating antigen) were pooled and this pooled antigen fraction was further purified on Sephacryl S500 column. The pool column fraction obtained just after the void volume showed high reactivity with Mab and would be further purified to produce polyclonal antibodies.

3.3 Biochemical and molecular studies

3.3.1 Over expression and purification of recombinant myosin and paramyosin of adult *B. malayi*

Paramyosin and myosin were over expressed and purified by Ni-NTA column. Protein in bulk was produced and purified which was sufficient in quantity for initiating immunization experiments. The recombinant proteins were confirmed in western blots by reaction with human bancroftian sera, hyperimmune rabbit serum, anti-HIS antibody and mastomys antisera raised against purified recombinant proteins.

3.3.2 Acetyl cholinesterase

3.3.2.1 Isolation and characterization of isoenzymic forms of *S. cervi* acetyl choline esterase

In our earlier studies we have purified the filarial parasite AchE using a combination of gel filtration, ion exchange and affinity columns and the purified enzyme showed two isoenzymic forms on native PAGE. In order to separate the two forms, the partially purified *S. cervi* AchE (ScAchE), obtained by column chromatography was further purified. After electrophoresis, histochemical activity staining identified the AchE bands and two isoforms were isolated from PAGE strips by electro elution. The eluted enzyme was tested for substrate specificity and the inhibitor sensitivity. Both the isoforms of enzyme were found to be true AchE as both preferentially utilized Acetylthiocholine Iodide (ATI) as substrate while about 20% activity was obtained with Butyrylthiocholine Iodide (BTI). The host enzyme showed 40% activity with ATI and 60% with BTI. The enzyme activity of two isoforms of the parasite was strongly inhibited by the true AchE inhibitor BW284C51 and not by iso-OMPA (butyrylthiocholine esterase inhibitor). This was also analysed by histochemical staining of enzyme activity on native PAGE. BW284C51 inhibited the enzyme activity as no AchE bands were observed on staining, while iso-OMPA had no effect on the enzyme activity or staining of AchE bands.

3.3.2.2 Monoclonal antibody against gel eluted *S. cervi* acetylcholine esterase

Six Balb/c mice were immunized with gel eluted parasite AchE and all the mice showed high antibody titer. The spleen cells from the immunized mouse were fused with Sp2/0 myeloma cells and plated on HAT selection medium. The culture supernatants from 6 wells were found positive for anti-ScAchE antibody and cloned by limiting dilution in 96-well plates. Seven clones were finally selected, recloned and established in culture. The *S. cervi* AchE monoclonal antibodies (Mabs) produced by these clones were isotyped and three Mabs was were found to be IgG1 isotype, three were IgG2a and one IgG2b. One of each isotype Mabs selected for further studies based on high and consistent reactivity with *S. cervi* AchE. All the three Mabs showed reactivity with *B. malayi* antigen in ELISA and Dot ELISA. The epitope mapping revealed that all the three Mabs were directed against different epitopes. Out of these three Mabs, one was directed against the catalytic site as it inhibited the activity of parasite AchE. These Mabs were produced in ascites and will be used for characterization of parasite AchE.

3.3.2.3 Polyclonal antibody against electric eel AchE

A rabbit was immunized with electric eel AchE (EeAchE, commercial preparation) by intramuscular injection of 20 μg of EeAchE emulsified in FCA. Second injection was given after 1 month, while the subsequent ones on further 15 days intervals. Rabbits were bled one week after each injection starting from the 2nd dose. ELISA showed increasing antibody titre upto sixth immunizing dose reaching plateau thereafter. This antibody will be used for parasite AchE characterization.

3.3.3 Localization of octopamine and its receptor in filariids by fluorescent microscopy

Both octopamine as well as serotonin receptors were localized in intestinal mucosa of adult *B. malayi*. Studies with *A. viteae* adult parasites are underway.

4. Area: LEISHMANIASIS

Coordinator: Dr. Anuradha Dubey

Visceral Leishmaniasis (VL) is a chronic and infectious disease which often becomes epidemic and leads to a heavy loss of human lives in many parts of the world, including India. In the face of new challenges of drug resistance, treatment failures, occurrence of relapses and convergence of HIV related VL cases; there is an urgent need to search for new and better alternatives of chemotherapy.

Our program, therefore, envisages screening of synthetic compounds as well as extracts from plants and marine sources for antileishmanial activity, development of diagnostic kit of high specificity and sensitivity, studies in molecular mechanism of virulence and drug resistance and search for newer specific biochemical and molecular targets.

4.1 Development of New Antileishmanial Agents

4.2 Development of Screening Models

4.3 Basic Studies

4.4 Genomic Microarray Analysis.

4.1 Development of new antileishmanial agents

4.1.1 Screening against *L. donovani*

4.1.1.1 Against promastigotes (*in vitro*)

(a) Synthetic compounds

Two hundred thirteen synthetic compounds were tested for their anti-promastigote activity by Luciferase assay. At 10 µg/ml concentration, 104 synthetic compounds were found active (criteria for selecting active compounds were those exhibiting 80-100% inhibition). Of these, 31compounds showed activity up to 5 µg/ml concentration, 9 compounds at 2 µg/ml concentration, 2 compounds at 1 µg/ml, 4 at 500 ng/ml concentration, 3 at 250 ng/ml concentration and 1 compound at 50 ng/ml concentration.

(b) Natural products

29 Plant extracts (crude as well as pure) were screened *in vitro* against promastigotes by FACS (with GFP tagged promastigotes) at the concentration of 100 µg/ml for their antileishmanial activity, none were found active. Out of the 47 DOD extracts, only one extract, NIT-157A001 has shown 99% activity at 50µg/ml concentration by luciferase assay.

4.1.1.2 Against amastigotes in macrophages (*in vitro*)

(a) Synthetic compounds

91 Compounds were tested against amastigotes at 10 µg/ml concentration. Amongst them, 23 compounds were found active (80-100% inhibition in parasite multiplication). Eleven compounds showed activity up to 5 µg/ml concentration and 3 compounds at 2 µg/ml concentration.

(b) Natural products

Of the 29 plant extracts and marine products screened *in vitro* against GFP tagged amastigotes within macrophages at the concentration of 100 µg/ml for their antileishmanial activity by FACS, none were found active.

4.1.1.3 Against *L. donovani* in hamster (i*n vivo*)

(a) Synthetic compounds

Thirty-five compounds were evaluated *in vivo*. Of these, 4 compounds have shown 72-85% inhibition in parasite multiplication on day 7 post treatment in first trial. Same number of compounds exhibited medium activity (45-65% inhibition). Repeat trials with active compounds are underway.

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Out of the 37 plant extracts screened *in vivo* at the dose of 500 mg/kg x 5, none were found active.

4.2 Development of screening models - transgenic (Green Fluorescent Protein & luciferase) tagged parasites for HTS & hamster model

4.2.1 Green Fluorescent Protein

To achieve the aim of constructing *Leishmania* lines that strongly and stably express GFP without any drug pressure, efforts are being made for stable integration of the GFP-reporter gene into the genome of *L. donovani* at ribosomal RNA gene downstream of promoter site. These parasites will be employed for developing *in vivo* animal model of drug screening and also for developing 96-microplate screening assay for high throughput screening of new molecules.

4.2.2 Luciferase

Stable cell lines expressing luciferase gene using four *L. donovani* field isolates (two responsive and two non-responsive to SAG) were established and tested for their sensitivity to antimony under *in vitro* condition. Luciferase tagged *L. donovani* strain Dd8 cells was used to determine IC_{50} of standard drugs in macrophage-amastigote system. The cell line (LDd-Luc 8) is in use for regular *in vitro* and semi *in vivo* screening of antileishmanials.

4.2.3 Combination therapy in Stibanate (Sbv) resistant experimental models of visceral leishmaniasis with Picroliv (*Picrorhiza kurrooa*)

Two Sb^V resistant strains (2039 & 2041) have shown refractoriness to Sb^V therapy at 40 mg /kgx5 i.p. dose level. Picroliv was administered (10 mg/kg x 12 days, p.o.) with SSG (40 mg/kg x 5 i.p.) in hamsters having well-established infection. The results demonstrated that although Picroliv *per se* has no activity, but its co-application enhances the activity of SSG in 2039 strain from 67% to 98% and in 2041 strain from 51% to 89% on day 7 post treatment. The difference in activity was statistically significant. Further dose optimization of Picroliv in combination with SSG is under progress.

4.3 Basic studies

4.3.1 Identification of TH1 specific proteins for immunoprophylaxis

F2 proteins from soluble leishmania proteins ranging from 68 to 97.4 kDa were further fractionated by Prep Cell into 7 fractions. Out of these, 4 had exhibited considerably good lymphoproliferative response and NO production in cured hamsters. These will further be evaluated against cured Leishmania patients. Further work on 2D characterization of F2 proteins will validate the antigenicity of these identified proteins for potential candidate vaccines.

4.3.2 Biochemical and molecular mechanism of drug resistance

4.3.2.1 Studies on signal transduction

The identified gene PG1, to be involved in drug resistance in antimonial resistant clinical isolates of Leishmania, has been overexpressed in *E. coli*. Antibodies raised against it recognized the corresponding polypeptide in promastigotes by Western blotting. This gene is on chromosome 18 and Southern hybridization experiments confirm that it is a single copy gene.

4.3.2.2 Drug efflux studies in SAG resistant isolates

Resistance mechanisms developed by the parasites are often ingenious and novel. The mechanisms of resistance as identified by functional studies and flow cytometry suggested the presence of two type of efflux pumps in clinical isolates. Characterization of these pumps is still underway.

4.3.3 Studies on thiol levels

More *L. donovani* field isolates responsive and non-responsive to SAG were evaluated for their total thiol levels. The sensitive isolates exhibited significant lower levels of thiols as compared to sensitive ones. Further, there was significant decrease in thiol levels of field isolates (both resistant and sensitive) in presence of BSO and BCNU which affects the sensitivity and viability of the parasite.

4.3.4 Cloning and expression of enzymes / proteins

4.3.4.1 Serine hydroxymethyl transferase (SHMT)

Serine hydroxymethyltransferase (SHMT) is a PLP dependent enzyme that catalyses the interconversion of serine to glycine with tetrahydrofolate serving as the one carbon acceptor. This enzyme is component of thymidylate cycle. The SHMT activity has been described in number of trypanosomatids but the enzyme has not been overexpressed and purified. Earlier we have reported the cloning, over-expression and localization of SHMT.

Biophysical and biochemical characterization of recombinant SHMT is under way. Enzyme kinetic studies were carried with recombinant SHMT. Km and V_{max} of *Leishmania donovani* SHMT substrates were determined and found comparable to the SHMT from other sources. In order to understand the mechanism of ligand binding and the interaction between the substrates and lSHMT, a three-dimensional (3D) homology model of lSHMT based on the x-ray crystallographic structure of the human cytosolic SHMT (hSHMT) (PDB code 1BJ4) was made The overall stereochemical quality of the lSHMT was assessed against the published hSHMT structure solved by x-ray crystallography. Starting with this model, a flexible substrate docking study is performed and comparison between the substrate binding to our model and that of crystallographic hSHMT revealed some key differences in substrate interaction that could be exploited for rational design of selective inhibitors against lSHMT.

4.3.4.2 Pteridine reductase

The enzyme, which is an attractive drug target for antifolate chemotherapy, has been overexpressed and purified. Crystallization of the recombinant enzyme has been done. An HTS assay employing this target enzyme has been developed. Structure based drug design is underway for identification of inhibitors.

4.3.4.3 Trypanothione reductase

Biophysical properties of *Leishmania donovani* recombinant trypanothione reductase (rLdTR) were studied. The enzyme was found stable up to 60^0C with maximum enzymatic activity at pH 7.5. Further, a 96 well micro-method was developed for the screening of antileishmanial compounds using recombinant LdTR. Standard drugs as well as 20 newly synthesized

antileishmanial compounds of pyrimidine series were screened using this method. Among them, once again only melarson oxide and trivalent antimony significantly inhibited the recombinant enzyme.

4.3.4.4 Dipeptidase Carboxy Peptidase (DCP)

Dipeptidylcarboxypeptidae of *L. donovani* is cloned and characterized. It belongs to M3 type metallopeptidase family. Southern hybridization studies revealed that more than one copy of the gene is present in genome. The gene is expressed in *E. coli*. Western blot analysis revealed increased expression of the gene in amastigote stage of parasite. The recombinant LdTR has enzyme activity and cleaves Hip-His-Leu, a substrate for mammalian peptidyl dipeptidase A, also known as angiotensin converting enzyme (ACE). Further, captopril, an ACE specific inhibitor was able to inhibit significantly both the LdDCP enzyme activity as well as promastigote growth, therefore, strongly suggests that this newly identified DCP could serve as drug target in *Leishmania.*

4.3.5 Characterization of actin network

Actin network is indispensable for the survival of any eukaryotic organism. Leishmania has long been assumed to have no role and presence of actin in it. Our recent report for the presence of abundant actin in Leishmania has uncovered the facts regarding an essential element in these parasites. This study includes elaborate analyses of actin network and its role in Leishmania parasites. Many regulatory/actin binding proteins that alter network composition, stability and functional parameters for the cell have been planned to analyze in order to explore function of actin network in Leishmania parasites.

After the analysis of coronin actin interaction in filamentous structures of actin, various deletion mutants have been created to characterize different functional motifs and their roles in actin filament interaction. Mutants are transfected in *Leishmania donovani* and are currently being selected against G-418. One of the cloned actin related proteins (ARPs) was analyzed with regard to its distribution where it appeared to be present selectively in the kinetoplast and nucleus of the *Leishmania* promastigotes by immuno-fluorescence. This ARP was then cloned in pXG-GFP vector and the construct was transfected in *Leishmania*. Transfectants again showed nuclear presence of this GFP-fusion product. Actin depolymerizing protein (ADF / cofilin) which is responsible to alter actin dynamics was cloned as GFP-fusion product and over-expressed in *Leishmania*. Transfectants were analysed by various ways that showed remarkably increased chemo-taxis whereas rate of invasion in macrophage was found to be decreased. Filamentous structures of actin present in ADF/cofilin over-expressing cells were also found to decrease remarkably. One of the two myosins present in the *Leishmania* genome has been cloned and over-expressed in *E.coli*. Antibodies have been raised and made mono-specific by affinity chromatography. Initial immunolocalization of myosin has showed very specific localization in the basal region of flagella.

4.4 Genomic microarray analysis

4.4.1 Gene expression in antimony resistant field isolates

Analysis of microarray data resulted in identification of important biochemical pathways for use as drug targets viz. ADP/ATP translocase, long chain fatty acyl Co-A ligase and dynein. Southern blotting and transcripts have done detection of the endogenous copy of these genes for the genes detected by northern blotting.

4.4.2 Identification of stage specific genes using genomic micro array

Complete coding sequence of four genomic clones, which exhibited constant upregulated expression in amastigote stage of parasite, were PCR amplified and cloned in pGMT vector.

4.4.3 Identification and molecular characterization of Proteophosphoglycans on promastigotes and amastigotes of *L. donovani*

Proteophosphoglycans (PPGs) are mucin-like glycoproteins of *Leishmania* that are found as membrane bound and also as secretary forms. Confocal microscopy, flow cytometry and western blotting studies in promastigotes and amastigotes of drug sensitive (Dd8, 2001& 2093) and drug resistant (2039, 2041 & 2087) strains as well as atypical avirulent strain (UR6) of *L. donovani* using anti-PPG antibody, revealed that PPG is differentially expressed in both sodium stibogluconate sensitive as well as resistant Indian clinical isolates of *L. donovani*. Isolation of PPG from culture supernatants has been done and now elucidation of its possible function as well as its molecular characterization is underway.

4.4.4 Sequence Characterize Amplified Region (SCAR) marker for the diagnosis of SAG resistant *L. donovani* field isolates

Sequence characterized amplified region (SCAR) primers have been developed to distinguish SAG sensitive and resistance strains of *L. donovani* field isolates. To test the efficacy of the SCAR marker 7 coded samples corresponding to drug sensitive and resistance strains were taken. On decoding it was proved that this marker amplifies the 756-bp fragment in resistant strain thus differentiating between the field isolates of *L. donovani.* SCAR primers will help in deciding the mode of chemotherapy to the patients suffering from visceral Leishmaniasis and in the diagnosis of disease in symptomatic and non-symptomatic population.

5. AREA: MALARIA

Coordinator: Dr. S.K. Puri

Malaria is a major health problem in many tropical countries, including India. Inspite of tremendous gains witnessed in biomedical research during 20th century, infectious diseases like malaria continue to provide barriers to the global health community. The global problem of malaria is largely due to the emergence of parasite resistance to limited armamentarium of antimalarial drugs. The progress in our understanding of mechanism of action and resistance to traditional drugs, the emergence of artemisinins as one of the most important antimalarial class and determination of the genome sequence of malaria parasite promise a more optimistic future for antimalaria drug development. The focus of our research programme is aimed towards development of novel, orally effective chemotherapeutic agents for treatment of drug resistant malaria; exploration of suitable drug combinations with available agents; characterization of enzyme markers for drug resistant parasites; and validation of novel parasite-specific drug targets as a result of an improved understanding of the parasite biology.

5.1 Chemotherapy of Malaria

5.2 Immunology of Malaria

5.3 Biochemistry of Malaria

5.4 Molecular Biology of Malaria

5.1 Chemotherapy of malaria

5.1.1 Synthesis and screening

Novel synthetic moieties comprising 600 compounds representing several prototypes viz. peroxides, piperazines, pyrozoloquinolines, pyrazolotriazines, pyrimidines, indoles, β carbolines, chalcones, thiazolidinones, lupeole derivatives, and urea derivatives were synthesized during the year for evaluation against *in vitro* or *in vivo* experimental malaria models. In addition, 113 extracts/fractions from natural sources were prepared and evaluated for antimalarial activity.

5.1.1.1 Screening against *P. falciparum in vitro*

A total of 455 new synthetic compounds were screened against *Plasmodium falciparum* (strain NF 54 / 3D7) *in vitro* at various concentrations ranging between 100 ng/ml to 50 μg/ml. The screening protocol employed incubation of ring stage parasites with designated concentrations of the test agent for 36-40 hours under defined environment *in vitro*. The moieties exhibiting total parasite maturation inhibition at < 2 μg/ml were identified for evaluation against *in vivo* models. Screening of several urea derivative compounds yielded 8 novel moieties with MIC in the range of ≤ 1 μg/ml. Several new compounds representing pyrazolotriazine, pyrimidine and related folate metabolism inhibitors have also been identified. SAR studies with thiazolidinone and guanidine analogues have also resulted in selection of a few novel analogues inhibiting parasite maturation at below 1μg/ml concentration. Evaluation of 85 samples representing marine fauna against *in vitro* model did not yield any promising lead. In addition, nearly 2800 samples of natural origin were evaluated under a CSIR coordinated network program and 8 plant extracts, showing schizont maturation inhibition at 10 μg/ml concentration, were identified for follow up studies.

5.1.1.2 Screening against *Plasmodium yoelii* (N-67) Swiss mice model

Based on leads from *in vitro P. falciparum* screening results, a total of 44 synthetic compounds, representing five different prototypes, were evaluated against chloroquine resistant *P.yoelii* (strain N-67) Swiss mice model employing 50mg/kg (i.p.) x 4 days regimen. Though none of these agents provided total clearance of parasites, some of the compounds exhibiting above 80% parasite clearance were selected for further optimization. A total of 35 plant extracts at 500 mg/kg x 4 days p.o. were also evaluated against the same model. None of these agents showed any promising activity.

5.1.1.3 Screening against *Plasmodium yoelii* (MDR) Swiss mice model

Lead optimization studies with synthetic peroxide generating derivatives were continued and 120 new compounds were screened at 96 mg/kgx4 days, both p.o. and i.m.routes, against multi-drug resistant model *P. yoelii* in Swiss mice. Several of the active compounds were also evaluated at lower doses. Two new orally active saturated trioxanes and three aminofunctionalised trioxanes showing curative efficacy in a 24 mg/kg x 4 days regimen were identified as the promising lead for follow up studies.

5.1.1.4 Follow up studies with compound 97-78

Synthetic endoperoxide compound 97-78 had been recorded earlier to exhibit curative activity against *P. yoelii* - Swiss mice and *P.cynomolgi* rhesus monkey models. The compound is currently undergoing regulatory developmental studies. With a view to compare the efficacy profile of 97-78 racemic mixture *vis a vis* its enantiomers, limited trials were conducted against both rodent and simian models. The results, as demonstrated by the respective curative dose and the parasite clearance time against established infections, have shown that the racemic mixture and two enantiomers possess equipotent antimalarial activity.

5.1.1.5 Combination chemotherapy

Our earlier studies have established that concurrent administration of arteether (i.m.) with sulfadoxine and pyrimethamine in fixed dose combination (S:P:: 20:1) (p.o.) exhibit marked potentiaion in their antimalarial response. During our further studies, we have initiated studies with combination of mefloquine and arteether / aresunate against *P.yoelii* (MDR) - Swiss mice model. Our preliminary results suggest that mefloquine produces better additive response with arteether as compared to artesunate. Combination studies with arteether and an antifungal agent ketoconazole (cytochrome P_{450} inhibitor) have also shown strong additive potential against the rodent model.

5.1.1.6 Arteether resistant rodent malaria model

A strain of rodent malaria parasite *P. vinckei* showing experimentally induced (>12 fold) stable resistance to arteether was reported previously. Studies have been initiated for biochemical and molecular characterization of resistance. In our attempts to understand the mechanism by which malarial parasites become resistant to arteether, a comparative estimation on status of anti-oxidant enzymes in parasite preparations from sensitive and resistant lines is being evaluated, since generation of carbon centered free radicals is believed to be involved in antimalarial action of this class of compounds. Our initial studies have shown a marked increase in the levels of glutathione reductase in resistant parasites. In addition, the SDS-PAGE analysis of parasite proteins from the two preparations has shown occurrence of an additional 37 Kd band in preparations from the resistant parasites. Immunochemical analysis of this protein is proposed to be undertaken.

5.2 Immunology of malaria

5.2.1 Monoclonal antibodies against *P. vivax* MSP-1 antigen

Plasmodium vivax has been recognized as the second most important malaria parasite of human in South East Asia including India. A major problem with testing of *P. vivax* vaccines is that there is no *in vitro* culture system and the *in vivo* method requires highly specialized monkey model. *Plasmodium cynomolgi bastianelli*, a parasite of rhesus monkeys, has a clinical course of infection much like *P. vivax* infection in humans and we have evaluated the *P. cynomolgi* rhesus monkey model for testing the protective potential of *P. vivax* MSP1-42 kD antigen. Monkeys immunized with *vivax* and *cynomolgi* MSP1-42 kD antigens showed significant reduction in parasite burden. As the protective epitopes of MSP1 antigens are known to be conformational, the monoclonal antibodies against these conformational epitopes of malaria MSP1 antigen would be helpful in evaluating the protective efficacy of malaria vaccine preparations. Efforts have

been made to produce monoclonal antibodies against the conformational and linear epitopes of *P. vivax* MSP1 antigen. Mice were immunized with *P. vivax* MSP1 antigen and the spleen cells from immunized mouse, showing high ELISA antibody titers with both conformational and linear epitopes of *P. vivax* MSP1 antigen were used for fusion with myeloma cells. Limiting dilution cloned the hybridomas showing high and consistent ELISA reactivity. Twenty hybridoma clones secreting monoclonal antibodies against *P. vivax* MSP-1 antigen were produced and established *in vitro* culture and cryopreserved. Six of these monoclonal antibodies are directed towards the conformational epitope and fourteen are against the linear epitope of MSP1 antigen. Nine monoclonal antibodies showed reactivity with both *P. vivax* and *P. cynomolgi* MSP-1 antigen while eleven showed specificity to *P. vivax* MSP1 antigen. Out of eleven *P. vivax* specific monoclonals, three are against conformational and eight against linear epitopes. Among nine *P. vivax* and *P. cynomolgi* cross-reactive monoclonal antibodies, three are against conformational and six are against linear epitopes. Out of five Moabs produced against *P. cynomolgi* MSP-1 antigen, two monoclonals antibodies are *P. cynomolgi* specific and three showed reactivity with both *P. cynomolgi* and *P. vivax* MSP1 antigens. Out of two *P. cynomolgi* specific monoclonals, one is against conformational epitope and other against linear epitope. Other three monoclonals (cross-reactive *P. cynomolgi* and *P. vivax* MSP1) are against the conformational epitopes.

5.3 Biochemistry of malaria

5.3.1 Molecular characterization of a putative choline kinase from the human malaria parasite *Plasmodium falciparum*

Generation of phosphocholine by choline kinase is important for phosphatidylcholine biosynthesis via Kennedy pathway and phosphatidylcholine biosynthesis is essential for intra-erythrocytic growth of malaria parasite. Inhibition of choline kinase is postulated to inhibit parasite membrane biosynthesis during the growth of intra-erythrocytic parasite stages and hence may serve as a target for antimalarial chemotherapy. A putative gene (Gene ID PF14_0020) in chromosome 14, having highest sequence homology with choline kinase has been identified by BLAST searches from *P. falciparum* genome sequence database. This gene has been PCR amplified, cloned, over-expressed and characterized. RT-PCR studies indicated the expression of PfCK in both trophozoite and schizont stage but not in the ring stage. It was found to be cytosolic protein as evidenced by western immunoblotting using anti-PfCK and subsequent confocal microscopy. A model structure of PfCK was constructed based on the crystal structure of choline kinase of *C. elegans* to see structural homology and finally the modeled structure was experimentally validated by CD analysis of the purified protein. Since choline kinase plays a vital role for growth and multiplication of *P. falciparum* during intra-erythrocytic stages, this well characterized PfCK would be exploited for the screening of new choline kinase inhibitors to evaluate their antimalarial activity.

5.4 Molecular biology of malaria

5.4.1 Analysis of replication, within the apicoplast of *Plasmodium falciparum*

The previous studies had identified replication *ori* of *P. falciparum* plDNA within the inverted repeat region of the circular 35kb molecule. Subsequent analysis indicated the presence of multiple initiation sites within each inverted repeat segment with differential activation of

these ori indicated by competitive PCR analysis. In order to identify proteins required for initiation and progression of plDNA replication, a two-pronged approach has been adopted. The first deals with analysis of DNA-protein interactions at selected ori regions in the plDNA IR while the second approaches the problem by looking at putative replication enzymes encoded by *P. falciparum* nuclear genome. Initial identification and characterization of a DNA-binding protein has been carried out by EMSAs. Two specific DNA-protein complexes were detected with a 198bp *ori* probe. Determination of the Kd value of the complexes indicated that the proteins bound the DNA probe with high affinity. Competition with minor and major groove binding compounds indicated that the protein(s) interact with the minor groove of the DNA double helix. Peptide mass analysis of the proteins identified a few candidate genes from the *P. falciparum* genome database. Further analysis of these genes is underway. As a follow up of the second approach, partial and full-length constructs of two proteins-GyrA and GyrB (gyraseA & B assemble as a hoterotetramer to relieve positive supercoils in front of the replication fork) have been cloned and expressed. The proteins are predicted to carry targeting sequences for import into the apicoplast. Purified antibodies raised against GyrA and GyrB recognize specific protein bands of the sizes expected from cleaved and uncleaved proteins in the parasite lysate. Full length GyrB (~116kDa), expressed as a soluble protein in *E. coli* has been purified to about 90% homogeneity. The recombinant protein exhibits ATPase activity *in vitro*.

Available crystal structures of *E. coli* gyrase A and B domains (65kDa GyrA and 42 kDa GyrB domain) were used to model corresponding regions of the *P. falciparum* proteins. The *P. falciparum* GyrA protein modeled very well on the *E. coli* template. Assembly of the GyrA dimer revealed that tyrosine residues (at position 122) were positioned correctly in order to interact with the broken 5' end of each DNA strand to form the cleavable complex. Additionally, an Asp87 residue that is required for quinolone binding is conserved in the *Plasmodium* counterpart. The *Plasmodium* GyrB also exhibits extensive homology with the *E. coli* protein in the ATPase as well as C-terminal regions. There are, however, two large intervening segments in the parasite protein that do not exhibit homology to *E. coli* GyrB. The ~42 kDa GyrB model of the ATPase domain (with the loops excluded) showed near-perfect alignment with *E.coli* GyrB, Lysine (aa103) as well as other residues required for ATP hydrolysis in *E. coli* were conserved in the dimer as were the aa required for novobiocin binding.

5.4.2 Predictive medicine using repeat and single nucleotide polymorphisms

Eight hundred samples covering large families and closely related groups have been collected for SNP analysis of TNF-α as well as six genes that are implicated in adhesion of *P.falciparum* infected RBCs. Sequencing of samples from the discovery panel (DSNP) has been carried out for all genes and several novel SNPs in these genes have been identified. SNP validation of both novel and reported SNPs is currently underway in the Sequenom mode. The validation panel comprises a total of 1600 samples representing 42 Indian subpopulations. Sequenom SNP data has been generated for three SNPs (of TNF- α and ICAM-1). Initial results indicate subpopulation-specific variation in polymorphic allele frequencies.

6. AREA: MICROBIAL INFECTIONS

Coordinator: Dr. Ranjana Srivastava

The objective of the project area cover the development of vaccines for cholera and tuberculosis, development of rapid molecular screens for drug screening, screening of synthetic compounds and natural products for antituberculosis, antifungal and antibacterial activity, development of diagnostics for tuberculosis infection, construction of mycobacterial vectors, novel antigens and drug targets, basic studies on mycobacterial, bacterial and HIV proteins and virulence genes.

6.1 Cholera

The two genes of *V. cholerae*, Vc0973 and Vc0974 constituting an operon and involved in a probable two component signal transduction system has been confirmed by bacterial two hybrid system demonstrating interaction between two proteins. Mutation in Vc0973 affects colonization of *V. cholerae* in rabbit intestine. Vc0974 has been cloned, expressed in *E. coli* and recombinant protein purified for structure and function elucidation.

6.2 Tuberculosis

6.2.1 Drug targets validation: knockout mutant generation and role in pathogenesis

The knockout mutant of *lpd*A in *M. tuberculosis* generated by antisense approach showed reduced pathogenicity in mice confirmed by tissue bacillary load and histopathology of lungs. The role of the protein in oxidative stress has been demonstrated.

6.2.2 Cloning and expression of *M. tuberculosis* genes coding for rapid suscitation factors (rpf): identification of receptors for Rpf on dormant cells

Rapid suscitation factors (Rpf) have been reported to resuscitate the dormant mycobacteria. Out of five genes (rpf A-E) identified in *M. tuberculosis*, three *rpf* genes have been cloned and confirmed by nucleotide sequencing. The gene encoding RpfE has been cloned in pET vector and over expressed in soluble fraction in *E. coli*.

6.2.3 Identification of mycobacterial genes activated during infection in murine macrophages and physiological stress/ latency

A promoter library of H37Rv constructed in promoterless *gfp-kan* vector was electroporated into BCG strain. The library was infected in macrophages to select fluorescent and kanamycin resistant clones. The genes thus identified were confirmed by RT-PCR of RNA derived from mycobacterial clones infected in macrophages. The cloning of genes is in progress.

The same library was subjected to hypoxia in which mycobacteria remain viable but with arrested replication. By fluorescence and kanamycin resistance, the surviving clones were selected and sequenced to reveal the identity of genes. Three of the selected clones include *icl*, α-crystallin and *nar*X genes. Cloning of genes is in progress.

6.2.4 Identification of genes of *M. fortuitum* involved in virulence

In vivo screening in murine infection model led to isolation of two Transposon insertion mutants of *M. fortuitum*, attenuated in pathogenesis. The behaviour of two mutants suggested that the insertion mutation affected the ability of the mutant to persist in kidney. The ORF disrupted by Tn insertion was sequenced and showed homology to Rv3291c, a probable transcriptional regulatory factor of *M. tuberculosis*. The ^{1}H NMR of the PCA extract showed distinctive differences in various metabolites in the two mutants and WT strain.

6.2.5 Human T-cell responses against *M. tuberculosis* membrane antigens

6.2.5.1 Immunogenic membrane associated proteins of *Mycobacterium tuberculosis*

The membrane associated ribosomal protein RpIE was identified as potent immunogen through membrane proteomics and human T cell activation assays. The gene encoding RplE was

cloned, overexpressed and purified in soluble form. The purified protein was used for T cell activation assays (DNA synthesis and gamma interferon production) using blood samples from health BCG vaccinated individuals who were also exposed to tuberculosis. PHA was used a mitogen (positive control for the assays) and *M. tuberculosis* membrane and cytosol were used for comparative evaluation of response to the single protein RpIE. All study subjects showed a significant T cell response to RplE both in terms of thymidine uptake and IFNγ production.

6.2.5.2 Biology of interaction between human macrophages and *Mycobacterium tuberculosis*

The project is aimed at elucidating the factors working at the level of macrophage *M. tuberculosis* interaction which could determine the course of infection leading to either clinically covert or latent disease in a TB endemic population such as India. Preliminary flow cytometry data on health BCG vaccinated and TB-exposed donors showed differences in nitiric oxide and hydrogen peroxide production by macrophages in response to phagocytosis of live and heat-killed *M. tuberculosis*. For study of trafficking events through confocal microscopy, Cyto-9 labeled mycobacteria were found to show more stable and strong fluorescence than the FITC labeled mycobacteria. Phalloidin-FITC could be used as a probe to distinguish resting from active macrophages by monitoring the mobilization of cytoskeletal actin. Entry of mycobacteria through Fc gamma receptor was established by colocalization of Cyto-9 labeled microbes and Cy5 labeled antibody against human Fc gamma receptor type-2 Mycobacteria could also be colocalized with rab5 (early phagosome marker) and LAMP-2, Cathepsin-D and Lysotracker Red (lysosome and phagolysosome markers).

6.2.5.3 Studies on interaction of mycobacterial Eis and HspX with macrophages

Rv246c of *Mycobacterium tuberculosis* reported to enhance intracellular survival of *M. smegmatis* within macrophages was analysed for its biological role and was found to play a role in modulation of immune response. Eis inhibited the ConA mediated T-cell proliferation. The production of IL4, IL10, TNFα and IFNγ by Eis treated PBMC was checked. There is a marked decrease in IL4 and TNFα production by Eis treated PBMCs while the secretion of IL10 and INFγ is more.

Modulation of immune response by Eis predicts that Eis might be playing a role in immune signaling. Therefore, effect of Eis on STAT, ERK1/2 and pSTAT in PBMc was checked through immuno-blotting. Interestingly, Eis was found to affect the expression of STAT, ERK1/2 and pSTAT.

Eis, reported to be secretory protein, has two very strong hydrophobic domains between 1 to 120 amino acids. Hydrophobic domains have been deleted serially and in combination to study the role of these domains in secretion.

6.2.5.4 Molecular mechanisms involved in the intracellular survival of mycobacteria: characterization of PKC isoforms

Protein kinases (PK) play pivotal role in regulating and coordinating aspects of metabolism, gene expression and switching on and off of PK is crucial for its function as its catalytic activities. Comparative PKC isoform specific studies between pathogenic and non pathogenic mycobacterial strains along with the study on the involvement of macrophage and mycobacterial specific protein

kinases during infection has been initiated to study the involvement of macrophage and mycobacterial specific protein kinases during infection.

6.2.5.6 Reconstruction and evaluation of a novel drug screen system against *M. tuberculosis* FASII pathway in a non-pathogenic mycobacterial strain (*M. aurum*)

Using the upstream DNA sequence of *M.tb* kas operon and *E.coli lac* Z gene, a transgenic *M. aurum* strain has been constructed which senses the disruption of FASII elongation pathway and responds by upregulating the *lac*Z expression. The increasing presence of *lac*Z gene product after the treatment of microbe was demonstrated with control drug isoniazid (INH), which is known to disrupt the FASII elongation pathway.

6.3 Viral infections

6.3.1 Standardization of *in vitro* assay system for screening herbal or synthetic compounds against HIV-RT

From nine compounds selected based on *in vtiro* anti-HIV-I RT activity, four compounds showed anti-HIV-I activity against HIV-I III B strain and Indian - HIV Clade C virus.

6.3.2 To develop a mammalian two hybrid system for screening inhibitors of interaction between HIV-1 Nef and cellular PACS-1 protein

The HIV-1 Nef mediated down regulation of cell surface MHC-I molecule to the trans Golgi network enables HIV-1 to escape immune surveillance. MHC-I down regulation is initiated by the binding of the Nef acidic cluster ^{62}EEEE^{65} to PACS/ AP-1 cellular protein. PACS-1 gene has been cloned in mammalian two-hybrid vector.

6.4 Fungal infections

6.4.1 *In vitro* and *in vivo* evaluation of compounds

A total of 571 (synthetic 236, marine 275 and plants 60) compounds/extracts were evaluated for *in vitro* antifungal and antibacterial activity. None were found to have appreciable activity.

6.4.2 Molecular diagnosis of fungal infections

The DNA samples from human cases of lung infection (3) and mycotic keratitis (8) were successfully identified by PCR using the primer pair ITS1 and ITS2. Single stranded conformation polymorphism (SSCP) of restriction profile of the amplified large subunit of fungal rRNA was successfully used to identify fungi (47 fungal isolates, and 3 clinical samples) at genus and species level.

6.4.3 Monoclonal antibodies

(a) *Aspergillus fumigatus*

Three new mAbs (B, 7 and 3) were identified against *A. fumigatus* cell wall antigens. The isotype of these mAbs was found to be mAb B=IgG1, mAb 7 and 3 = IgM. The cDNA of mAb B (IgG1) was amplified using IgG specific primers. The PCR product has been sequenced and identified as Kappa light chain of IgG.

(b) ***Candida albicans***

Two monoclonal antibodies were produced against cell wall antigens of *C. albicans* designated as NE5 and F3SP. The protein for the mAb NE5 was identified as Glyceraldehyde-3-phosphate dehydrogenase (GADPH) by MALDI-TOF and database search. The cDNA of this mAb was amplified using IgM specific primers. The PCR product has been sequenced and identified as Kappa light chain of IgM.

7. AREA: NATURAL PRODUCTS

Coordinator: Dr. Chandan Singh

Chemical and pharmacological investigation of Indian medicinal plants and marine flora /fauna for isolation of active constituents to obtain new therapeutic agents.

7.1 Drugs from Medicinal Plants

7.2 Modification of Natural Products

7.3 General Screening of Terrestrial Plants and Mflora/Fauna for Antihyperglycaemic/ Antidyslipidemic Activities.

7.1 Drugs from medicinal plants

7.1.1 Collection, identification and documentation of 35 terrestrial plants and 17 marine flora/ fauna were completed.

7.1.2 Antihyperglycaemic/ antidyslipidemic activities

7.1.2.1 Plant 3200

Earlier K011 and K027 were isolated as the active constituents of this plant and 24 new analogues of K027 have been synthesized.

7.1.2.2 Plants 4659 and 1703

The active compound K009 has been estimated by HPTLC method. Plants 4659 and 1703 contain 1.42% and 1.06% of active principle K009 respectively.

7.1.2.3 Plant 4574

Ethanolic extract (C003) and three fractions (F004 to F006) were evaluated for antidyslipidemic activity. From the active chloroform fraction (F004), three compounds (K017 to K019) were isolated. K017 and K019 showed antidyslipidemic activity. Five derivatives of K017 and K019 are under evaluation.

7.1.2.4 CDR-267

Three batches of CDR-267F018 were evaluated for antidyslipidemic activity. All the batches showed same activity profile. CDR-267F018 is in the preclinical phase of development. It has been found safe in regulatory pharmacology and toxicity studies. Earlier 6 compounds were isolated and characterized. During this period 1 more compound was isolated.

7.1.2.5 CDR-134F194

CDR-134F194, which is in the preclinical phase, is currently undergoing regulatory pharmacology and toxicity studies.

7.1.2.6 CDR-324

Ethanolic extract (A001) showed promising activity in SLM and STZ-S models at 250 mg/kg dose. Five fractions F003-F007 are under evaluation.

7.1.2.7 CDR-150

Antidiabetic activity was reconfirmed in the extracts C003 and C004 prepared from the repeat collections. Fractionation of F005 to F008 is under evaluation.

7.1.3 Antistress activity

7.1.3.1 Plant 38

Antiulcerogenic activity of EtOH extract of 38 was studied against cold restraint, asprin, alcohol, pyloric ligation induced gastric ulcer models in rats and histamine induced duodenal ulcer in guinea pig, and ulcer healing activity in acetic acid induced chronic ulcer model. We found that EtOH extract decreased the incidence of ulcer and also enhanced the healing of ulcers. Therefore, it possesses potent antiulcerogenic as well as healing properties. 12 Compounds have

been isolated from n-BuOH active fraction and 1 from chloroform fraction. Pure compounds K099, K114, K116, K117 and K171 were found to be effective in reverting the alteration induced in acute and chronic unpredictable stress model.

7.1.3.2 Plant 2659

Evaluation of antistress and anti-oxidant activity of 2659 in plasma and brain regions of rats subjected to chronic unpredictable stress in rats. Ethanolic extract (200 mg/kg, p.o.) has normalized the stress-induced alterations, reduced lipid peroxidation and changes in antioxidant enzymes in plasma and different areas of brain. 11 Compounds have been isolated from butanol fraction. The plant 2659 has also shown promising memory enhancing activity in Morris Water Maze Test model. Pure compounds K014, K015 and K019 reverted the alteration induced in acute and chronic unpredictable stress model.

7.1.3.3 Plant 4627

Ethanolic extract was studied against different ulcer models and it showed significant antiulcer activity and significantly increased the mucus secretion.

7.1.4 Antiparasitic activity

7.1.4.1 Plant 4604

Nineteen compounds of various classes such as flavonoid glycosides, pterocarpanoids, lipids, glycolipids and alkaloids have been isolated and identified from the 4604 whole plant. Aminoglucosyl glycerolipid is reported here for the first time. Its structure has been elucidated by spectroscopic and degradation studies. This novel compound exhibited *in-vitro* antileishmanial and immunomodulatory activities as it enhanced Nitric Oxide (NO) production and provided resistance against infection established in peritoneal macrophages by the protozoan parasite *Leishmania donovani*. Another known compound glycosphingolipid (cerebroside) was found to possess significant *in-vitro* antileishmanial and immunomodulatory activities against the same parasite. Other compounds were found inactive.

7.1.4.2 Plant 4658

Two prenylated chalcones isolated from this plant have shown antimalarial activity *in-vitro* against *P. falsiparum* at the concentration of 2 μg/ml. New analogues have been synthesized are under evaluation.

7.1.5 Anti-osteoporotic activity

Extracts and fractions from five plants 1020, 4404, 4455, 4617 and 4627 were evaluated. Only ethanolic extract and *n*-butanol fraction of plant 1020 showed promising osteogenic activity. 14 Compounds have been isolated from n-butanol fraction.

7.1.6 Anticancer activity

7.1.6.1 Plant 4539

5 Compounds were isolated and out of these one compound (K056) showed *in-vivo* antibreast cancer activity at the dose of 10 mg/kg.

7.1.7 Analgesic activity

7.1.7.1 Plant 4406

Three compounds have been isolated from roots of plant 4406. Activity of these compounds is under evaluation.

7.1.8 Antithrombotic activity

7.1.8.1 CDR-148

Crude extract (A001) showed promising antithrombotic activity. The activity was localized in three fractions (F006, F007 and F009). Chromatography of fraction F006 afforded compound K011, which showed marginal activity.

7.2 Modification of natural products

Transformation activities with regard to solanesol (antidiabetic), lupeol, neoandrographolide (antimalarials) and coumarins e.g. psoralin, isopsoralin and seselin (antithrombotic) are continuing. Isolation and transformation of aromatic turmeron, a constituent of herbal medicament and synthetic analogues of aromatic turmeron were prepared for antistroke activity.

7.3 General screening of terrestrial plants and marine flora / fauna for antihyperglycaemic / antidyslipidemic activities

38 New plant extracts were evaluated in sucrose-loaded rats. Six extracts 4643, 4650, 4655, 4665, 4676 and 4699 showed significant improvement on glucose tolerance of the normal rats post glucose load.

57 Marine samples were evaluated in sucrose-loaded rats and six extracts viz. CDR-150C003, CDR-150C004, CDR-333A002, NIO-799B002, NIO-780A001 and NIO-781A001 showed significant improvement on glucose tolerance of the normal rats post glucose load. One marine fraction CDR-181F004 and two marine extracts CDR-324A001 and CDR-325A001 also showed significant antihyperglycemic activity in this model in the repeat collection. Out of a total of 7 marine extracts/fractions evaluated in STZ-induced diabetic rats, only one extract CDR-324A001 showed mild antihyperglycemic activity.

18 New plant extracts were evaluated at 500 mg/kg dose in dyslipidemic hamster model six samples 4652, 4655, 4657, 4659, 4664 and 4667 were found to be active.

8. AREA: NEWER APPROACHES IN DRUG DESIGN AND DISCOVERY

Coordinator: Dr. S. B. Katti

The project area envisages exploring and exploiting emerging technologies like x-ray crystallography, structural biology and in-silico design towards lead generation and optimization of drug like molecules. Structural studies on small and macromolecules and identification of druggable targets.

8.1 Structural Function Studies of Proteins, Antimicrobial peptides and Design of Peptide Inhibitor

8.2 Synthesis of Combinatorial Libraries

8.3 Novel Methodologies for Peptide Design and Synthesis

8.4 X-ray Crystallographic Studies

8.5 Studies on Protein Folding

8.6 Structural Genomics of *Mycobacterium tuberculosis* Proteins Using NMR Spectroscopy

8.7 Drug Target Development Using *in-silico* Biology.

8.1 Structural function studies of proteins, antimicrobial peptides and design of peptide inhibitor

8.1.1 Structure-Function studies of membrane-associated proteins and polypeptides

Majority of the antimicrobial peptides cause damage to the microbial cell membrane and thereby destroy their cellular integrity within a short time. Therefore, to develop resistance against these peptides will be difficult for bacteria. However, one of the barriers for converting an antimicrobial peptide into a drug is that majority of them have toxic effects against normal human cells. In this context we are investigating the structure-function relationships in some of the naturally occurring antimicrobial peptides with a goal to identify important elements in these molecules, involved with the antimicrobial and toxic activities. At the same time using the knowledge obtained from our own work on the naturally occurring molecules, we are designing novel antimicrobial peptides with reduced toxicity.

In order to design antimicrobial peptides and a control over their toxicity, several amphipathic peptides have been designed on the basis of leucine zipper motif sequence and characterized structurally and functionally. The first one was a leucine zipper peptide (LZP) and in others leucine residues at ‘a’ and/or ‘d’ position were substituted by single or double alanine. The LZP exhibited appreciable antibacterial activity and moderate toxicity. Although the substitution of leucine by alanine at ‘a’ and/or ‘d’ position had a little effect on the antibacterial activity, it progressively reduced the hemolytic activity of LZP against the human red blood cells. Transmission electron microscopic studied showed that the LZP, and the single and double alanine substituted analogs inflicted a similar damage to *E. coli* cells. In order to understand the molecular basis of similar antibacterial but contrasting toxic activities of these of LZP and its analogs, peptide-induced permeability of different kinds of lipid vesicles, secondary structures of the peptides in aqueous and membrane environments, localization of the peptides onto the lipid vesicles and human red blood cells and the peptides’ self-association properties in aqueous buffer were studied. Further, we have designed and synthesized several analogs of a bovine antimicrobial peptide BMAP-27. Studies on Phospholipid membrane interaction of peptides derived from the conserved segments of voltage gated potassium channels.

8.1.2 Studies on phospholipid membrane interaction of peptides derived from the conserved segments of voltage gated potassium channels

Potassium channels are a class of membrane proteins, found virtually in all cell types in most of the organisms that play an important role in many physiological functions such as neuronal signaling, immune cell activation, cardiovascular functions and muscle contraction. Several genetic diseases like cardiovascular arrhythmia, deafness, epilepsy, and diabetes are believed to be caused by the disruption of the potassium channel genes. However, very little is known about the membrane-interaction and membrane-assembly of most of these channel proteins. Presently we are working on the S6 segment of KvAP potassium channel. We have identified an important structural element in this segment, which is also conserved in several other potassium channels. With a goal to characterize the possible role of this motif, a wild type and several mutated peptides have been designed and synthesized.

8.2 Synthesis of combinatorial libraries

8.2.1 'Second-generation' substrates for the Pictet-Spengler reaction

Based on our new concept for Pictet-Spengler reaction involving an aryl amine attached to an activated heterocyclic ring, we extended the strategy to pyrazoles and thiazoles as substrates. The studies led to formation of pyrazolo- and thiazolo-quinolines in high yields and purities. The substrates underwent Pictet-Spengler reaction with aldehydes having both electron-donating and -withdrawing groups. This is in contrast to the traditional Pictet-Spengler reaction, where aliphatic amine derived substrate fail to undergo cyclization with aldehydes having electron-donating group.

8.2.2 Solid-phase synthesis of 2-aminoquinazolinone derivatives

A versatile solid-phase method for the synthesis of various substituted 2-amino-4(3H)-quinazolinones with two- and three-point diversity is described. The synthesis commenced with the generation of polymer bound *S*-methylisothiourea followed by N-acylation with different substituted *o*-nitrobenzoic acid. Finally reduction of the nitro group triggered intramolecular cyclization via formation of guanidine to afford 2-amino- 4(3H)-quinazolinone and its derivatives in high yields and purities.

8.2.3 Unprecedented $SnCl_2$ mediated reductive cyclization of nitro arenes via *N-N* bond formation

A mild, efficient and one-pot protocol for the reductive cyclization of nitro-aryl substrates using $SnCl_2$ has been developed. In our effort directed towards the reduction of the nitro group of 1-(2-nitrophenyl)-3,4-dihydroisoquinoline using $SnCl_2.2H_2O$, we observed formation of an unusual side product with a molecular weight of 280 daltons in 3% isolated yield along with the corresponding amine in 85% isolated yield. Subjecting the byproduct to NMR and X-ray analysis revealed that an intramolecular reductive cyclization via *N-N* bond formation had occurred resulting in a novel hetero system 2,3-dimethoxy-5,6-dihydro-indazolo[3,2-*a*]isoquinoline. The mechanistic course of the reaction suggests involvement of hydroxylamine intermediate leading to an intramolecular cyclization via *N-N* bond formation. The generality of the method has been demonstrated by using two nitro-aryl substrates derived from dihydro-isoquinolines and β-carbolines. The reductive cyclizations led to the formation of indazoles in high yields and purities.

8.3 Novel methodologies for peptide design and synthesis

8.3.1 Peptidomimetics as selective inhibitors of Protein Tyrosine Phosphatase 1B (PTP-1B) for the development of anti-diabetic agents

Diabetes mellitus is a major and growing public health problem throughout the world. The available treatment is inadequate and therefore there is an urgent need to develop target specific new therapeutic agents. In type II diabetes that is a major form of diabetes, tissues develop resistance to the actions of insulin even though the insulin receptors in these tissues are structurally normal and are in near normal abundance.

One strategy to combat the insulin resistance therapeutically may be to maintain insulin receptors (IRs) in the active tyrosine-phosphorylated form by inhibiting enzymes that catalyze IR dephosphorylation. It has been shown that Protein tyrosine phosphatase 1B attenuates insulin

signaling by catalyzing dephosphorylation of insulin receptors (IR) and is an attractive target of potential new drugs for treating the insulin resistance that is central to type II diabetes. In recent literature, there are reports describing various inhibitors to PTP1B and among them peptidomimetic derived from CCK-8 are found to possess potent inhibitory activity. A dipeptide, Boc Phe-Tyr(O-Mal)-NH-C5H11 with malonyl substitution was quite active. However, this compound has poor cellular uptake hence could not exhibit promising *in vivo* activity.

Taking lead from the above dipeptide, we have designed a few peptidomimetics and evaluated their inhibitory activity. For the design of new peptidomimetic, major considerations are: (i) development of novel phosphate surrogates for improved potency and selectivity (ii) incorporation of peptide bond surrogates for better half life and (iii) optimization of lipophilicity for improved cellular uptake. The compounds were synthesized using the chemistry already developed and standardized in our lab. We have synthesized 21 new compounds during this period. All the compounds were evaluated for their ability to inhibit protein tyrosine phosphatase 1 B *in vitro* using a commercially available kit based assay system. PNP is used as positive control. Some of the new compounds have shown 90% inhibition at 100 M concentration. Further work on the synthesis and bioassay is in progress.

8.3.2 HIV-RT inhibitors (NNRTs)

Viral enzymes are the prime targets in search for effective drugs for the treatment of HIV/AIDS. One such essential enzyme is human immunodeficiency virus type - 1 reverse trascriptase (HIV-1 RT), which enables integration of viral genetic information into the host genome. Non-nucleoside reverse transcriptase inhibitors (NNRTI's) *inter alia* have been extensively investigated and several NNRTI's have been approved by the FDA and are clinically used. Unfortunately the virus rapidly develops resistance to the existing drugs through mutation. Therefore, it is imperative to look for new chemical entities having broad-spectrum HIV-RT inhibitory activity. 4-Thiazolidinone scaffold is one of the NNRTI, which inhibits HIV-RT evaluation of these compound through colorimetric enzyme based immunoassay showed that some of the compounds exhibited 50-95% inhibition at 100 μg/ml. While in the MT-4 cell based assay ten compounds had the EC_{50} in the range 0.38-1.63 μg/ml. Further, our attempt in co-relating the derived electronic descriptors from MOE with the HIV-RT inhibitory activity resulted in some statistically significant QSAR models with good predictive ability. Apart from the importance of hydrophobicity and compact structural features, the study indicated the role of charged molecular surface areas in the inhibitory activity. Flexible docking simulations and 3D-QSAR analyses were performed on 4-thiazolidinones. A good correlation between the binding free energies and the experimentally observed inhibitory activities suggest that the identified binding conformations of these inhibitors are reliable.

8.3.3 Synthesis of erythromycin derivatives as antibacterial agents

Erythromycin has been in clinical use for several decades for the treatment of upper and lower respiratory track infection. Several semi synthetic derivatives have been reported in the literature with improved activity against erythromycin resistant pathogens. However, the ever-growing problem of acquired resistance is yet to be resolved. Therefore, there is a need to develop new chemical entities, which are effective against resistant pathogens. Towards this objective, several new erythromycin derivatives have been envisaged. During this period, 11 new compounds

have been completed and evaluated for their *in vitro* antibacterial activity against several strains of *S. aureus, E. coli* and *K. pneumoneae*. The compounds exhibited MIC between 0.2-6.5μg/ml.

8.4 X-ray crystallographic studies

8.4.1 Small molecule X-ray crysrtal structure

Crystallization, X ray intensity data collection and data processing of 26 compounds were performed out of which structures of 25 compounds were solved. Structure analyses of six pyrazolo pyrimidine compounds showed the presence of both the intra & inter-molecule interactions of the types, π ….π C-H…..π, S…. Ar and S …S. The chemical structures of six triaryls, telphenyls and pentaphenyls were confirmed through the X ray crystallographic studies. The crystal packing of pentaryl showed a novel N…. interaction. The X ray structures of these compounds further revealed the presence of a network of strong intermolecular H-bonding of the types C-H…. N, N-H…O and C-H……π. The structure analyses of around 10 heterocyclic compounds revealed unusual N-N bond formation and double cyclisation for some compounds.

8.4.2 Macromolecule X-ray crystal structure

A vigorous program to elucidate the crystal of proteins implicated, as being important for the persistent stage of tuberculosis is a major activity of this project area. Towards this objective a dozen proteins were cloned and expressed. Three promising proteins including a feast/famine regulator and lysine-e-amino transferase were purified, crystallized and structure elucidation is in progress.

During this period we have solved the crystal structures of a NAD+ ligase from Mtb complexed to its cofactor AMP. We are also in the process of carrying out *in silico* screening of the structure against a select in-house database to identify novel inhibitors of the protein and so far have identified glycosyl ureides and amines as novel classes of specific inhibitory compounds. Co-crystal structure studies with the identified inhibitor have been initiated.

Crystal structure of Lysine-e-amino transferase has been solved and refined in its internal and external aldimine forms and insights into the mechanism are being garnered through structural analysis. Heavy atom derivatives are being prepared for the feast/famine regulator.

8.5 Studies on protein folding

8.5.1 Structural and functional features of the *Streptococcus pyogenes* bacteriophage hyaluronate lyases

Hyaluronate lyases are class of endoglucosamidase enzymes of considerable complexity and heterogeneity whose primary function is to degrade the hyaluronan. Among hyaluronate lyases, the bacteriophage-associated enzymes are unique as they have the smallest molecular mass and have no amino acid sequence homology with bacterial hyaluronate lyases. In spite of such unique properties no information on structural properties of bacteriophage hyaluronte lyases is known.

The *Streptococcus pyogenes*, bacteriophage 10403 and H4489A contain gene *hylP2* and *hylP* respectively, that encodes for the protein hyaluronidase in these organisms. The *hylP2* and *hylP*-proteins were cloned, over expressed and purified to homogeneity. The recombinant *hylP2*

and *hylP* proteins exist as homo-trimer of molecular mass of about 111 and 120 kDa respectively, under physiological conditions. This is the first report of a hyaluronate lyase having an oligomeric structure. Limited proteolysis and GdmCl denaturation studies demonstrated that the N-terminal region of the *hylP2* protein is flexible whereas, the C-terminal portion has a compact conformation. We were able to isolate a functionally active C-terminal fragment (S128-K337) of *hylP2* protein, which was stabilized in trimeric configuration. Structural and functional studies on isolated domain demonstrated that the active site of the *hylP2* protein is present in the C-terminal portion of the enzyme and this domain is also responsible for the stabilization of the trimeric conformation of the *hylP2* protein. Detailed comparative functional studies with full-length protein and C-terminal domain demonstrated that the N-terminal portion of the enzyme modulates the enzymatic activity of C-terminal domain and is also responsible for specificity of enzyme for polysaccharide substrate.

8.5.2 Independent folding/unfolding domains of *Streptococcus agalactiae* hyaluronate lyase and their role in modulating the functional activity of the enzyme

Streptococcus agalactiae hyaluronate lyase degrades hyaluronan and chondroitin sulfate into unsaturated polysaccharide. The native functional enzyme is about 111 kDa. However, on *in vivo* expression of the full-length gene, a truncated enzyme of molecular mass 92 kDa (rSagHL) is obtained. The thermal and guanidine hydrochloride denaturation studies indicate that the rSagHL consists of three domains with different thermal stability and guanidine hydrochloride sensitivity. On limited proteolysis of the rSagHL, at defined GdmCl concentrations, single protein fragment either corresponding to SagHL2 (83 kDa; rSagHL-I) and α-domain (43 kDa) is obtained. These individual fragment/domain and the C-terminal domain of the rSagHL were cloned, over expressed and purified. Comparative stability studies using these fragments/domains demonstrated that they are independent folding/unfolding units of the enzymes. The isolated catalytic α domain, showed enzymatic activity independent of other two domains (max of about 10%). Comparative studies with the rSagHL and rSgHL2 demonstrated that the BI domain of the enzyme does not take part in functional activity. The isolated catalytic and the C-terminal domain interact strongly with each other and on *in vitro* incubation an enzymatically active complex of these is stabilized which showed significantly enhanced (maximum about 59%) activity as compared to the catalytic domain alone suggesting a supporting role of C-terminal-βII domain in modulating the enzymatic activity of the catalytic domain. These results for the first time provide a direct demonstration of the role of different domains of the *Streptococcus agalactiae* hyaluronate lyase in modulating functional activity of the enzyme.

8.6 Structural genomics of M*ycobacterium tuberculosis* proteins using NMR spectroscopy

8.6.1 Studies on peptidyl tRNA hydrolase

The major achievements during January-December 2005 were the installation of 600 MHz NMR spectrometer and probes, including the triple nuclear inverse cryoprobe. This is the first cryoprobe of M/s Varian AG Germany in the country. The Biopack suite of pulse programs for protein and RNA structure determination have been compiled and tested on several protein samples. In addition, saturation transfers difference NMR (STD-NMR) and water LOGSY experiments have been set up on standard samples. These experiments can be used for screening of ligands for unlabeled proteins.

Sequential assignment of peptidyl tRNA hydrolase (Rv 1014c, 1912 residues, PTH) is in the final stages. 168 Backbone residues have been assigned out of a total of 179 assignable residues. Assignment of side chains is in progress. Paralleyl, refinement of NMR struture of PTH is being carried out. Enzyme activity *M. tuberculosis* PTH was characterized *in vitro*. In addition, complementation of *M. tuberculosis* pth gene into E coli pth Ts mutant AA 7852 could support at non-permissive temperature of 42 C, demonstrating that *M. tuberculosis* pth was constitutively active.

Characterization of thermodynamic and biochemical stabilities of ESAT-6 and CFP-10 of *M. tuberculosis* has been completed. Complex formation between CFP-10 and several minutes of ESAT-6 was also studied, during this period. Structural characterization of Rv0603, a secretary protein of *M. tuberculosis*, was initiated.

8.7 Drug target development using in-silico biology

The major achievements during January-December 2005 were the establishment of the high performance computing facility with SGI Graphics octane workstations, SGI Origin 300 and Altix 350 computer servers, SGI Total performance 9100 (TP100) high performance fiber channel storage array, and the software packages like Accelrys (InsightII & Cerius2), Tripos (Sybyl & Unity), for computer-aided drug design, bio-molecular modeling & simulation and storage, management and mining of genetic, biological, chemical data and information. The facility provides integrated environment for informatics systems, computational chemistry and molecular modeling to facilitate and enhance drug design and discovery.

Three-dimensional models of proteins from *Mycobacterium tuberculosis* (chorismate synthase), *Plasmodium falciparum* (chorismate synthase, DNA gyrase) and *Leishmania donovani* (SHMT, dipeptidylcarboxipeptidse) with their substrates and cofactor has been build using homology modeling, docking and molecular dynamics tools. These studies provide a structural framework on which the design of specific inhibitors may be based. Also, three-dimensional searchable small molecule databases of approximately 15 lakh compounds for *in-silico* screening has been developed using small molecules from various sources. These databases are being used for virtual screening to identify and design lead compounds against different therapeutically relevant protein drug targets.

Structure-based investigations and CoMFA and CoMSIA 3D-QSAR studies were done on Diaryloxy methano phenanthrene analogues as Anti-tuberculosis Agents and 4-thiazolidinones as potent HIV-1 RT inhibitors and results provide clear guidelines and reasonably good activity predictions for novel inhibitors design.

9. AREA: REPRODUCTIVE HEALTH RESEARCH

Coordinator: Dr. Man Mohan Singh

Design and synthesize novel molecules / isolate from natural sources and bioevaluate them for generating new leads and to develop them as female or male contraceptives, spermicides with anti-HIV / anti-STI properties, agents for the management of post-menopausal osteoporosis and other endocrine disorders; evaluate traditional remedies for fertility regulation and endocrine disorders; understand the mode of action of promising agents and undertake basic research to generate new knowledge on male and female reproductive endocrinology relevant to fertility regulation.

9.1 Development of Antiosteoporosis Agents

9.2 Development of Antiproliferative Agents

9.3 Development of Anti-implantation and Early Post-implantation Interceptive Agents

9.4 Development of Contraceptives for the Male and Spermicides

9.5 Development of Anti-STI Agents

9.6 Development of Agents for the Management of Benign Prostatic Hyperplasia.

9.1 Development of antiosteoporosis agents

With the continuing demographic shift in population towards a more aged society, age-related diseases including osteoporosis have emerged as major public health problem. Normal ageing is associated with loss of bone mineral density and disruption in balance of bone turnover rate and changes in crystalline properties of bone mineral deposits. Marked age-related changes in bone mass, bone strength and trabecular structure may begin in women after menopause and this loss in men may also occur after 60 years of age. Alteration in calcium metabolism with ageing has been attributed to a variety of different and highly interdependent mechanisms including inherent functional changes in bone cells and, at least in part, to a combination of hormonal and nutritional factors that impairs regulation of calcium homeostasis. Osteoporosis accompanying menopause and other estrogen deficiency states represent a major cause of morbidity and mortality in women world-over. This is due to estrogen-deficiency induced increased generation and function of bone resorbing cells or osteoclasts, which perforate bone trabeculae and reduce their strength resulting in increased fracture risk. In comparison, age related osteoporosis is accompanied by decrease in bone formation due to decreased generation and function of bone forming cells or the osteoblasts. Hormone/estrogen replacement therapy, though highly effective in preventing bone loss following menopause, is known to be associated with increased risk of endometrial hyperplasia and carcinoma, cancer breast and thromboembolic diseases, in addition to other estrogen-related health hazards. Selective Estrogen Receptor Modulators, by virtue of their tissue selective pharmacology, have generated considerable interest as potential alternative to HRT/ ERT for the prevention and therapeutic treatment of estrogen-deficiency (including post-menopausal) osteoporosis in women. Pertinently, raloxifene, reported to mimic effects of estrogen in bone and cardiovascular system and exhibit estrogen antagonistic effect in endometrial tissue, has recently been reported to increase incidence of hot flashes, deep vein thrombosis, pulmonary embolism and leg cramps similar to that associated with use of Hormone Replacement Therapy. It also induces weak, but significant, uterotrophic response with significant increase in uterine dry weight and height, mitotic activity, vacuolization and degeneration of uterine luminal epithelial cells and number of endometrial glands in immature and ovariectomized rats and a potent estrogenic effect on hypothalamo-pituitary-ovarian axis. Of the other marketed anti-resorbing agents, bisphosphonates are associated with upper gastrointestinal disturbances, esophagitis and oesophageal ulcers and erosions, while calcitonin has been reported to cause nasal dryness, soreness, irritation and epitasis.

Currently, the only agents reported to promote bone formation include parathyroid hormone (PTH) and fluoride. It has, however, been shown that increase in cancellous bone formed during treatment with PTH is associated with loss of cortical bone. This occurs because of calcium withdrawal from cortical bones is used for mineralization of cancellous bone mass. Moreover, PTH may be anabolic or catabolic, depending on dose, duration and timing of treatment, method of administration and certain other factors. Its anabolic effect depends upon its intermittent administration and maintenance of optimal concentration for a very short time. Elevated levels of PTH for even 2 h might produce hypercalcaemia and osteoclast stimulated bone loss. Like PTH, fluoride treatment has also been reported to increase trabecular bone while reducing cortical bone, such that the bone mass formed at one site is at the expense of bone lost from another site.

Strict monitoring is also required during the fluoride therapy, since at higher doses it may increase fracture risk due to improper mineralization and loss of elasticity of fluoride bones. Moreover, reports of inability of fluoride to reduce vertebral fractures are also available. Another side effect associated with sodium fluoride treatment is the gastrointestinal irritation causing nausea, vomiting, pain and diarrhea. Osteoarticular pain, particularly of the lower extremities, is another major side effect of fluoride use. Fluoride treatment is not a common therapy in osteoporosis management. It has also not been approved by FDA for the treatment of post-menopausal osteoporosis. In view of this, there appears to be an urgent need to develop safe and effective anti-resorbing as well as osteogenic agents for human use and welfare.

9.1.1 Screening

Nine synthetic compounds were tested *in vitro* for antiresorptive activity using ^{45}Ca labeled chick fetal bone culture assay, but were found to be inactive with T/C ratio of >0.8 in preliminary testing.

9.1.2 Follow-up studies: Compound 99-373

9.1.2.1 Molecular mechanism of osteoclastogenesis

Compound 99-373 inhibited osteoclastogenesis. Decreased expression of c-src, is reported to play an important role in polarization of osteoclasts and maintenance of their resorptive capacity. The expression of TRAP and Cathepsin K gene, known to play an important role during osteoclast differentiation, was seen only in differentiated cells. Dysfunctional status of osteoclasts due to reduced expression of c-src was confirmed by reduced expression of integrins at the protein level.

9.1.2.2 Transcriptional activation of estrogen receptors α and β

Estrogen receptors (ER) α and β were cloned and expressed in mammalian cells. i.e., COS-1 cells. Expressed receptors were characterized for estradiol binding activity and estradiol-induced transcriptional activity. Using transcriptional activation of both the ER isoforms under the influence of SERMs, as assessed by luciferase reporter construct containing ERE consensus sequences, 7-hydroxy centchroman showed potent estrogen antagonistic activity for ERα than for ERβ. Compound 99-373, a potent anti-resorptive agent, also suppressed transactivation of estrogen receptors although it does not bind to ERs. This effect of 99-373 appears to be due to down regulation of ERs induced via different pathway.

9.1.2.3 Pharmacokinetic studies

In pre-clinical pharmacokinetic studies undertaken in adult Sprague Dawley rats treated with a single 10 mg/kg oral dose of compound 99-373, the compound exhibited multiple C_{max} and low systemic bioavailability. Two metabolites were identified in serum. *In vitro* metabolic studies with liver S-9 fraction revealed that it was metabolised fast and two metabolites, as identified *in vivo*, were obtained.

9.1.3 Effect of ormeloxifene on ovariectomy induced bone resorption, osteoclast differentiation and apoptosis and TGF β-3 expression

Effect of ormeloxifene, a multifunctional selective estrogen receptor modulator (SERM) on prevention of ovariectomy-induced bone resorption in retired breeder female rats,

osteoclastogenesis using bone marrow cells from adult Balb/c mice cultured in presence of M-CSF and RANKL, osteoclast apoptosis using terminal deoxynucleotidyl transferase Fragment End Labeling and TGFβ-3 expression were investigated. Raloxifene, a benzothiophene reported to mimic effects of estrogen in the bone, and estradiol were used for comparison. Ormeloxifene significantly inhibited osteoclastogenesis as evidenced by lower number of TRAP-positive osteoclasts in bone marrow cultures and caused apoptosis of osteoclasts. The effect was almost equivalent to that observed in presence of estradiol-17β. Raloxifene, though inhibited osteoclastogenesis at much lower concentrations, failed to cause apoptosis of osteoclasts at any of the concentrations used. While ormeloxifene, raloxifene and ethynylestradiol significantly prevented ovariectomy-induced bone loss *in vivo* in retired breeder female rats, prevention of ovariectomy-induced decrease in BMD and trabecular network of proximal tibia, calcium and phosphorus levels in femur and tibia and prevention of ovariectomy-induced down regulation of TGFβ-3 expression in lumbar vertebrae was of lower order in raloxifene- than ormeloxifene- or ethynylestradiol-supplemented females. Both the SERMs, however, produced considerable estrogenic effects at the uterine level as evidenced by increase in weight, total and endometrial area and luminal epithelial cell height; the effect being generally greater in raloxifene- than ormeloxifene-treated rats. Findings demonstrate that inhibition of estrogen-deficiency osteoporosis by ormeloxifene, as in case of estradiol, was mediated *via* inhibition of osteoclastogenesis, apoptosis of osteoclasts and up-regulation of TGFβ-3 expression. Raloxifene, though effective in inhibiting osteoclastogenesis *in vitro* at much lower concentrations, was not only less potent in preventing ovariectomy-induced bone loss in retired breeder female rats *in vivo* but also appeared to have a different mechanism of action than ormeloxifene and estradiol.

9. 2 Development of antiproliferative agents

9.2.1 Screening

Nineteen synthetic compounds and seven natural products were evaluated for cytotoxic/ antiproliferative activity in MCF-7 cells *in vitro* using Sulforhodamine-B(SRB) assay. Of these, 5 synthetic compounds and one natural product showed promising activity in preliminary testing with $LC_{50} \leq$ twice that of tamoxifen.

9.2.2 Estrogenicity profile of promising lead molecules in mammary and endometrial carcinoma cell lines

This study was aimed to compare the effect of promising lead molecules on estrogen receptor (ER) responsive genes in mammary (MCF-7) and endometrial (Ishikawa) carcinoma cell lines using tamoxifen and raloxifene as reference standards. Using MCF-7 cell line, maximum expression of all the three ER responsive genes i.e., CAT-D, cMyc and IGF-1 were observed in estradiol treated cultures. In comparison, raloxifene, tamoxifen as well as centchroman exhibited ER antagonistic response. These results are complementary with those observed by Shang and Brown (Shang Y and Brown M. Molecular determinants for the tissue specificity of SERMs. Science 295, 2465-2468, 2002). In studies on Ishikawa cell line, while tamoxifen acted as an estrogen agonist with expression levels of all ER responsive genes almost comparable to that of estradiol treated samples thus implicating it in endometrial cancer, no such agonistic effect was observed in raloxifene or centchroman treated cultures.

9.2.3 Substituted phenanthrenes with basic amino side chains: A new series of anti-breast cancer agents

In the course of search for new anti-breast cancer agents, substituted phenanthrenes with basic amino side chains were synthesized and some of them showed remarkable antiproliferative activity against ER-positive MCF-7 cell line with IC_{50} in the range of 3.53–22.25 mM. One of the compounds showed anticancer activity in 7,12-dimethylbenz[a]anthracene (DMBA) induced hormone-dependent mammary tumor in rat and the activity was comparable to that shown by tamoxifen.

9.2.4 Development of anti-cancer breast agents: Use of non-invasive imaging technique

Studies involving use of non-invasive imaging technique for detection and accurate measurement of growth curve of the tumor and change in growth pattern and complete regression of tumor and establishment of breast cancer cell lines based on their estrogen dependency, aggressiveness etc. have been initiated. Preliminary studies demonstrate induction of mammary tumour in rats within two weeks following single dose of DMBA.

9.3 Development of anti-implantation and early post-implantation interceptive agents

9.3.1 Screening

Five synthetic compounds and 39 extracts of natural products including marine flora and fauna were tested for anti-implantation-cum-early post-implantation interceptive activity in adult female Sprague-Dawley rats when administered on days 1-5/1-7 *post-coitum* by the oral route, but were found to be inactive. In follow-up studies, MEC of six previously active compounds has been determined.

9.3.2 Relative Binding Affinity (RBA) to estrogen receptors

A total of 10 synthetic compounds synthesized as possible estrogen receptor modulators were evaluated for their relative binding affinity to uterine estrogen receptors using *in vitro* competitive binding assay. Of these, 2 compounds showed RBA of <0.1%, 4 compounds showed RBA of 0.1%, 1 compounds showed RBA of 1%, while the remaining 3 compounds were found to be inactive with RBA of <0.001% of estradiol-17β.

9.3.3 Expression of estrogen receptor α in ovariectomized rat uterus under the influence of SERM

In order to analyse the estrogen receptor α mediated action of ormeloxifene, the expression of ERα was studied using immunohistochemical technique. The results revealed that estradiol treatment to ovariectomized rats up-regulated its expression level significantly, whereas in ormeloxifene treated rats, the expression levels were of low order. In rats co-administered with estradiol and ormeloxifene, the level was increased as compared to ovariectomized control rats. Interestingly, the expression was low in nuclear compartment than that of the cytoplasm of luminal epithelial cells. This suggests that ormeloxifene antagonised estrogen action via inhibiting nuclear localization of estrogen receptors α functional in the uterus.

9.3.4 Demonstration of uterine receptivity *in vitro* using rat epithelial cells and blastocyst co-culture

Uterine receptivity is a polarity dependent specialized function of uterine epithelial cells. An *in vitro* model to demonstrate the receptivity of uterine epithelial cells isolated from stage specific (non-pregnant/pregnant) Sprague-Dawley rats has been developed. Receptivity of the cells in culture was tested by blastocyst adhesion assay. The uterine epithelial cells were polarized on extracellular matrix coated petri dishes. Their polarity was validated by responsiveness to exogenously administered estradiol-17β. Uterine epithelial cells isolated from nonpregnant and day 3 post-coitum rats when polarized in culture behaved like cells *in utero* by exhibiting non-receptivity, while cells isolated on day 4 post-coitum exhibited receptivity. These *in vitro* results were validated *in vivo* by inducing decidual cell reaction. The findings demonstrate that the receptivity of uterine epithelial cells was mandatory for mimicking the process of implantation *in vitro*.

9.3.5 Contraceptive and hormonal properties of stem bark of *Dysoxylum binectariferum* in rat and docking analysis of Rohitukine, the alkaloid isolated from active chloroform soluble fraction

Post-coital oral administration of ethanolic extract of stem bark of *Dysoxylum binectariferum* intercepted pregnancy in Sprague-Dawley rats. On fractionation, the activity was localized primarily in the chloroform soluble fraction. At sub-contraceptive doses, most of the implantations showed signs of resorption. Chromatography of this fraction yielded the active alkaloid, Rohitukine. In immature rat bioassay, while the active chloroform fraction was found to be devoid of any estrogen agonistic or antagonistic properties even up to twice its contraceptive dose, mild uterotrophic effect without induction of premature opening of vagina or cornification of vaginal epithelium was observed following once daily administration of Rohitukine. Rohitukine with almost similar molecular size (Mol. wt. 305) as 17β-estradiol appears to fit ideally into the hydrophobic pocket of estrogen receptor. While it does not appear to simultaneously interact with all the three salient aminoacids GLU353, ARG394 and HIS524 as estradiol to elicit frank estrogenic response, different conformations of the ligand or its metabolite(s) might acquire geometry with phenolic groups at C-3', C-5 and C-7 positions disposed in a fashion to interact with the active site(s) to stimulate estrogen receptor, which might be responsible for its contraceptive and/or weak uterotrophic effects. Absence of basic side chain directed towards antiestrogen binding site (ASP351) on the receptor appears to be responsible for lack of any estrogen antagonistic activity. Structural modification of this ligand might enhance its anti-implantation/estrogen antagonistic activity.

9.4 Contraceptives for the male and spermicides

9.4.1 Screening for spermicidal activity

Out of the 31 synthetic compounds evaluated for spermicidal activity *in vitro* by Sander-Cramer assay using liquefied human semen, 8 compounds were found to be active. However, none of the 33 natural products tested using 'Spot test' exhibited any detectable spermicidal activity *in vitro*.

9.4.2 Medicated condoms

Stability studies performed with medicated condoms coated with the herbal spermicide (*Sapindus* saponins) indicated that the product was stable up to one year of manufacture. This study is being performed in collaboration with M/s. Hindustan Latex Limited, Chennai.

9.5 Development of anti-STI agents

9.5.1 Screening

Twenty-eight synthetic compounds and 15 natural products were screened for anti-*Trichomonas* activity using *in vitro* susceptibility assay. Metranidazole was used as reference standard. Of these, 11 synthetic compounds and 6 natural products have been found to be active in preliminary screening.

9.5.2 Anti-*Trichomonas* activity of CONSAP

Trichomoniasis is an important sexually transmitted disease (STD) caused by the protozoan *Trichomonas vaginalis* and has been associated with increased HIV incidence. Classical treatment involves drugs of nitroimidazole family, which are toxic and are associated side effects. Moreover, resistance to these classical drugs is on the increase, thus emphasizing the need for development of effective novel anti-*Trichomonas* agents. Saponins, a component of the herbal local contraceptive CONSAP, exhibit *in vitro* spermicidal activity at a concentration of 0.05%. Using *in vitro* susceptibility assay, the minimum lethal concentration of *Sapindus* saponins for *Trichomonas vaginalis* (0.005%) was found to be ten-folds lower than that of its effective spermicidal concentration (0.05%). *T. vaginalis* adheres to cervical epithelial cells through adhesins and cysteine proteinases. Using cytoadherence assay, saponins were found to inhibit the ability of parasites to adhere to HeLa cells by ~50%. Substrate gel electrophoresis analysis has shown that 2-hour treatment of parasites with the saponins decreases proteolytic activity of the parasite's cysteine proteinases. Hemolytic activity of the parasites was also diminished on treatment with the saponins for 3 hours. Saponins at the concentration of 0.005% significantly reduced expression level of parasite specific genes TvCP2 and AP65. Saponins also inhibited the host immune evasion effect of *T. vaginalis,* as evidenced by consistent up-regulation of IL-8 up to six hours in HeLa cells incubated with the saponin treated parasites. Preliminary scanning electron microscopic studies have indicated that treatment of parasites with the saponins decreased their phagocytic ability, which complements well with the observed decrease in hemolytic activity of parasites after saponin treatment.

9.5.3 Spermicidal and anti-*Trichomonas* activities of certain SSRI antidepressants

This study investigated spermicidal and anti-*Trichomonas* activities of certain SSRI antidepressants with a view to generate new leads for development of dual-function spermicidal contraceptives, which is an urgent global need. Fluoxetine, Sertraline and Fluvoxamine exhibited both spermicidal and anti-*Trichomonas* activities *in vitro,* whereas Paroxetine and Citalopram showed only the spermicidal activity. Fluoxetine exhibited better activity profile than the other antidepressant drugs with its spermicidal and anti-*Trichomonas* activities being comparable to the OTC contraceptive Nonoxynol-9. The non-detergent nature of Fluoxetine and a much superior spermicidal ED_{50} value may add considerably to its merit as a candidate for microbicidal

contraceptive. Thus, the antidepressants exhibiting both spermicidal and antitrichomonas activities might provide useful lead for the development of novel, dual-function spermicidal contraceptives.

9.6 Development of agents for the management of Benign Prostatic Hyperplasia

Benign Prostatic Hyperplasia (BPH) affects a large fraction of human male population at the age of 50 years and more. Under this area of Reproductive Health research introduced during this year, in an *in vivo* assay using 5α-reductase inhibitor Finasteride effectively reduced the prostate size of rats in which BPH was induced by giving exogenous testosterone injections. Anti-estrogens had a synergistic effect with finasteride in reducing prostate size though they were ineffective *per se*. α-Adrenergic receptor blocker tamsulosin was also effective in BPH management. Caspase-3 activity was used as an early marker for assessing prostatic response to different treatment regimens in rats. A variety of new structures/natural products are being explored to identify suitable leads for drug development.

10. AREA: TECHNOLOGY DEVELOPMENT

Co-ordinator : Dr. Vinod Bihari

Development of appropriate technology for production of Institute's candidate drugs, generic drugs, their intermediates and biochemicals.

The development of commercially viable technology of drugs and their intermediates is one of the key activities in the launching of new drugs. An appropriate environment friendly technology is the only solution to successful commercialization of a new and generic drug compatible with international standards, viz. ISO 9000 and ISO 14000. Development of know-how of drugs through sponsored as well as collaborative projects, has been the regular activity of Technology Development area.

10.1 Sub Area: Fermentation Technology

Co-ordinator: Dr. Vinod Bihari

10.2 Sub Area: Chemical Technology

Co-ordinator: Dr. Chandan Singh

10.3 Sub Area: Pharmaceutical Technology

Co-ordinator: Dr. Satyawan Singh

10.1 Sub Area: Chemical Technology

10.1.1 Compound 97-78 (Antimalarial)

The process has been optimized on pilot scale.

10.1.2 Generic Drugs

Technology development of the following three generic drugs has been undertaken based on their patent expiry and market profile:

10.1.2.1 Simavastatin (Hypolipidaemic)

Simvastatin was prepared from Lovastatin in 6 steps. Lovastatin on annulation with a secondary amine gave corresponding amide which on metallation and subsequent alkylation afforded Simvastatin amide. The hydrolysis of amide followed by lactonization yielded Simvastatin. All the steps have been carried out on bench scale. Scaling up and optimization of the process is under progress.

10.1.2.2 Sertraline Hydrochloride (Antidepressant)

A novel 5-step synthetic route was envisaged with a view to use a much cheaper catalyst as resolving agent. All the steps have been carried out on bench scale.

10.1.2.3 Paroxetine Hydrochloride (Antidepressant)

An 11-step new synthetic strategy has been envisaged with an objective to avoid the usage of Lithium aluminium hydride (LAH). LAH being highly pyrophoric is very hazardous for large-scale synthesis. First 6 steps of the synthesis have been carried out.

10.2 Sub area: Fermentation Technology

10.2.1 Screening of microbial cultures for biologically active compounds

Biodiversity is the most successful source for providing biologically active molecules of greater chemical/ structural diversity and offer opportunity for finding novel drug lead compounds that are active against wide range of targets. Microorganisms, isolated from diverse natural sources, are extremely important for this purpose as more and more strains are being isolated that produce amazing array of valuable products. Antibiotics are the best known group of microbial secondary metabolites and with the spread of multiple drug resistance among the infectious microbes search for novel antibiotics acting on new targets has become very essential. Keeping in view the above fact, isolation and screening of microbial cultures with antibacterial and antifungal activity was continued with considerable success. A very potent antibacterial strain, isolated during the study was taxonomically characterized as *Streptomyces halstedii* by MTCC, IMT Chandigarh. The culture produced more than one active compound. One of the active compounds was extracted, purified and chemically characterized as actinomycin D. Fermentation aspects of optimum actinomycin production conditions were studied. Product formation was statistically optimized by identifying different medium ingredients with the help of initial screening method of Plakett-Burman Surface Response Methodology (RSM) and about three folds increase in antibiotic yield was achieved. This strain is not reported to produce actinomycins. Work on other microbial cultures showing antifungal or antibacterial activity is in progress. Purification of an antibacterial

glycopeptide antibiotic and SDS-PAGE analysis of the active crude has demonstrated the presence of a major 63 KD peptide band. Purification and structure elucidation of the antibiotic is in progress.

10.2.2 Biotransformation

Biocatalytic transformation of various synthetic/natural compounds may improve and or induce biological activities. Microbial hydroxylations have been frequently employed to achieve the functioning of non-activated saturated carbon atoms.11-α hydroxylation of 80-574 compound was achieved using a strain of *Aspergillus ochraceus*. 7-Keto and 7,11 dihydroxy derivatives were also produced in small quantities as by-products. The process has been standardized at shake flask level. All the three products were supplied to the Divisions of Pharmacokinetics and Medicinal & Process Chemistry for evaluation.

10.2.3 Production of Kojic acid

Kojic acid producing fungal culture was isolated from the soil samples. Fermentation parameters and downstream processing are being optimized to achieve maximum yield.

10.2.4 Biocatalysis

Microbial cells are frequently used as biocatalysts to accomplish various chemical/ biochemical biotransformation reactions in better-controlled conditions in more specific manners. Biocatalysts are immobilized and used in bioreactors to enhance the efficacy of biotechnological processes for several cycles.

10.2.4.1 Hydrolysis of Lactose

Yeast, *Kluyveromysis lactis* was applied for hydrolytic conversion of lactose to glucose, with free and immobilized cells under various biotransformation conditions. Various concentrations of lactose, the substrate, in combination with varying amounts of biocatalysts were tried and the yield of glucose was optimized. Attempts were made to isolate and purify the enzyme galactosidase from the sonicated cells.

10.2.4.2 L-phenylacetyl carbinol (L-PAC) production

L-PAC of higher purity was produced by trying various carbon sources other than molasses as quality of molasses is not consistent with all the available batches. Free and immobilized cells of the yeast *Saccharomyces cerevisiae* were applied for the biotransformation of benzaldehyde to produce PAC.

10.2.5 Culture maintenance

Preservation and regular maintenance of production and test microorganisms was done and potency and purity of the cultures were checked at regular frequency as scheduled.

10.3 Sub area: Pharmaceutical Technology

10.3.1 Development of drug delivery systems

10.3.1.1 Biodegradable microparticles of antitubercular drugs

Inhalable microparticles containing two anti-TB drugs were taken up for product development under NMITLI during the previous reporting period. This exercise continued, taking up issues of process optimization, shelf stability, aerosol characterization, dose uniformity and bioavailability in guinea pigs. Dose delivery, from an inhalation apparatus, designed and fabricated in-house, was correlated with industry-standard equipment available at ITRC, Gheru. Methods for routine quality assurance, stability studies and pharmacokinetic analysis were developed and validated.

10.3.1.2 Delivery system for testosterone

The mathematical model of the circadian rhythms of gonadotropin-releasing hormone, luteinizing hormone and testosterone reported in the previous reporting period was optimized. Transdermal testosterone delivery systems were prepared in the lab for pulsatile drug release. *In silico* superposition of these profiles on the model was observed to disrupt rhythmicity. New equations were introduced in the computational model to account for observed delay in testosterone concentrations reaching pre-intervention levels.

10.3.1.3 Delivery of Glucagon-like Peptide-1 (GLP-1)

Experiments were initiated on a micro- or nano-particulate delivery system for the management of both type 1 and type 2 diabetes, incorporating GLP-1.

10.3.1.4 Delivery system for cyclosporine

Novel surfactant vesicles bearing cyclosporine have been prepared. Stability studies in different bile salt solutions (1-10mM) revealed that all Spans (20, 40, 80) vesicles except Span 60 turned into micelles when exposed to 10mM of Na deoxycholate. Unlike native vesicles, the stability was further enhanced when bile salt (Na deoxycholate) was incorporated as integral component of the vesicles. These vesicles were subjected to absorption studies using everted intestine sac method. The permeation flux of cyclosporine was increased up to three times in case of vesicles modified with Na deoxycholate compared to unmodified ones. The study revealed that this formulation could provide improved absorption that is not dependent on bile flow in the GI tract like available formulations.

10.3.2 Studies on effect of cyclodextrin on the permeation of compound 80-574

Inclusion complex of 80-574 with β-cyclodextrin and/or hydroxy-propyl-β-cyclodextrin were prepared. The complexes were evaluated for solubility, dissolution rate and transport through artificial lipophilic membranes and intestinal everted sac. Phase solubility studies indicated that the solubility of the compound was improved by formation of complexes with β-CD and HP-β-CD. The transport of drug across lipophilic membrane and intestinal everted sac was increased by complexation.

10.3.3 Quality control and stability studies

Validated HPLC methods for the compounds 99-259, S-001-469, S-002-329, S-002-333, S-002-853 and S-004-1032 with base line separation of the starting materials and intermediates without any interfering peaks, were developed.

RESEARCH OUTPUT & OTHER ACTIVITIES

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Bioorganic & Medicinal Chemistry Letters, 15, 5324-8.

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III. PATENTS

Patents Filed in India	14
Patents Filed Abroad	20
Patents Granted in India	06
Patents Granted Abroad	09

V

1 **Patent Appl. No.:** 0394DEL2004 **Filing Date:** 08/03/2004
Title: **One pot synthesis of carbamate esters using Mitsunobu's reagent**
Inventors: Devdutt Chaturvedi & Suprabhat Ray
Supporting Staff: Vasi Ahmed

2 **Patent Appl. No.:** 0431NF2004/IN **Filing Date:** 19/11/2004
Title: **Novel N^1, N^n-diglycosylated diaminoalanes useful in chemotherapy of tubercular infections**
Inventors: Rama Pati Tripathi, Vinod Kumar Tiwari, Neetu Tewari, Ranjana Srivastava, Anil Srivastava, Vinita Chaturvedi, Kishore Kumar Srivastava, Sudhir Sinha & Brahm Shankar Srivastava
Supporting Staff: Vinod Kumar Maurya

3 **Patent Appl. No.:** 01258DELNP2005 **Filing Date:** 31/03/2005
Title: **2-Alkyl aryl sulfonyl-1,2,3,4 tetrahydro-9H-pyrido[3,4-b] indole-3-carboxylic acid esters and amides as antithrombic agents**
Inventors: Stuti Gaur, Zeeshan Fatima, Anshuman Dixit, Zahid Ali, William Rasican Surin, Kapil Kapoor, Kanta Bhutani, Mohd. Saleem Ansari, Madhu Dikshit & Anil Kumar Saxena
Supporting Staff: Arimardan Singh Kushwaha & Dayanand Vishwakarma

4 **Patent Appl. No.:** 0703DEL2005 **Filing Date:** 31/03/2005
Title: **Novel N-substituted dihydrobenzothiepino dihydrobenzoxepino and tetrahydro benzocyclohepta indoles as selective estrogen receptor modulators**
Inventors: Kanchan Hajela, Ashok Kumar Jha, Man Mohan Singh, Girish Kumar Jain, Anil Kumar Balapure, Anila Dwivedy, Bharat Agarwal & P.S.R.Murthy
Supporting Staff: Vasi Ahmed, Govind Kesari, Mohini Chabara & Ramesh Sharma

5 **Patent Appl. No.:** 01282DELNP2005 **Filing Date:** 31/03/2005
Title: **Novel amino functionalized 1,2,4-trioxanes useful as antimalarials and a process of preparation thereof**
Inventors: Chandan Singh, Heetika Malik & Sunil Kumar Puri
Supporting Staff: Shashi Rastogi, Akhilesh Kumar Srivastava & Kamlesh Kumar Singh

6 **Patent Appl. No.:** 01289DELNP2005 **Filing Date:** 31/03/2005
Title: **Synergistic combination kits of α,β-arteether and sulfadoxin-pyrimethamine for the treatment of severe/ multidrug resistant and cerebral malaria**
Inventors: Renu Tripathi, Sunil Kumar Puri, Jagdishwar Sahai Srivastava, Satyawan Singh, Onkar Prasad Asthana & Anil Kumar Dwivedi

7 **Patent Appl. No.:** 01278DELNP2005 **Filing Date:** 31/03/2005
Title: **Substituted carbamic acid quinolin-6-yl esters as acetylcholinesterase inhibitors**
Inventors: Neeraj Shakya, Zeeshan Fatima, Chandishwar Nath & Anil Kumar Saxena
Supporting Staff: Zahid Ali & Bishambhar Nath

8 **Patent Appl. No.:** 2460DEL2005 **Filing Date:** 12/09/2005
Title: **Novel-[(4 -diphenylmetyl)- piperazin-1-yl]-3-aryloxypropan-2-ol**
Inventors: Kalpana Bhandari & Ram Raghubir
Supporting Staff: Anoop Kumar Srivastava & Tarun Lata Seth

9 **Patent Appl. No.:** 2463DEL2005 **Filing Date:** 12/09/2005
Title: **A process for the preparation of novel 1-[(4-diphenylmetyl)-piperazin-1-yl]-3-aryloxypropan-2-ol**
Inventors: Kalpana Bhandari & Ram Raghubir
Supporting Staff: Anoop Kumar Srivastava & Tarun Lata Seth

10 **Patent Appl. No.:** 2464DEL2005 **Filing Date:** 12/09/2005
Title: **A process for the isolation of the standardized anti-diabiatic and antidislipidemic fraction from the fruits of mangrove plant and its use as an antidiabetic drug**
Inventors: Vijai Laxmi, Ajet Saxena, Rajesh Kumar, Arvind Kumar Srivastava, Preeti Tiwari, Deepak Raina, Brijendra Saxena, Rajesh Kumar, Poonam Gupta, Thadigoppula Narender, Brijendra Kumar Tripathi, Anju Puri, Ramesh Chander, Mahendra Nath Srivastava, Sudhir Srivastava, Ram Raghubir, Raghwendra Pal & Satyawan Singh

Supporting Staff: Hriday Ram Misra, Suresh Chandra, Naveen Prakash Misra, Mukesh Srivastava, Teeka Ram, R.R.Gupta, Ganesh Shankar Sonkar, Subhash Chandra Tripathi, Raja Krishna Puroshottam, Ganga Ram Bhatt, Radhey Krishna, Madhury Chaudhary, J.P.Chaturvedi & Suresh Yadav

11 **Patent Appl. No.:** 1760DEL2004 **Filing Date:** 15/09/2005
Title: ***Mycobacterium tuberculosis* specific DNA fragments, a set of oligonucleotide primers and a kit thereof useful for rapid diagnosis of *Mycobacterium tuberculosis* infection in clinical samples**
Inventors: Ranjana Srivastava, Deepak Kumar & Brahm Shanker Srivastava

12 **Patent Appl. No.:** 2026DEL2004 **Filing Date:** 07/10/2005
Title: **Oxy substituted flavones as antihyperglycemic and antidyslipidemic agents**
Inventors: Ram Pratap, Mavurapu Satyanarayan, Chandeshwar Nath, Ram Raghubir, Ashok Kumar Khanna, Anju Puri, Ramesh Chander, Priti Tiwari, Brajendra Kumar Tripathi & Arvind Kumar Srivastava

13 **Patent Appl. No.:** 2724DEL2005 **Filing Date:** 10/10/2005
Title: **Oxy substituted chalcones as antihyperglycemic and antidyslipidemic agents**
Inventors: Ram Pratap, Mavurapu Satyanarayan, Chandeshwar Nath, Ram Raghubir, Ashok Kumar Khanna, Anju Puri, Ramesh Chander, Priti Tiwari, Brajendra Kumar Tripathi & Arvind Kumar Srivastava

14 **Patent Appl. No.:** 0248NF2004/IN **Filing Date:** 18/11/2005
Title: **Heterologus expression of trypanothione reductase from *Leishmania donovani* in a prokaryotic system**
Inventors: Neena Goyal & Mukul Kumar Mittal

Patents Filed Abroad

1 **US Patent Appl. No.:** 10/811296 **Filing Date:** 26/03/2004
Title: **N-aryloxypropanolyl-N'-phenethyl-urea**
Inventors: Kalpana Bhandari, Shipra Srivastava & Chandeshwar Nath
Supporting Staff: Anoop Kumar Srivastava, Ram Pati Maurya & Vishwabhar Nath

2 **US Patent Appl. No.:** 11/018923 **Filing Date:** 22/12/2004
Title: **Oxy substituted chalcones as antihyperglycemic and antidyslipidemic agents**
Inventors: Ram Pratap, Mavurapu Satyanarayan, Chandeshwar Nath, Ram Raghubir, Ashok Kumar Khanna, Anju Puri, Ramesh Chander, Priti Tiwari, Brajendra Kumar Tripathi & Arvind Kumar Srivastava

3 **US Patent Appl. No.:** 0447NF2004/US **Filing Date:** 23/12/2004
Title: **Synergistic combination kits of α, β-arteether and sulfadoxin-pyrimethamine for the treatment of severe/ multidrug resistant and cerebral malaria**
Inventors: Renu Tripathi, Sunil Kumar Puri, Jagdishwar Sahai Srivastava, Satyawan Singh, Onkar Prasad Asthana & Anil Kumar Dwivedi
Supporting Staff: Shashi Rastogi, Akhilesh Kumar Srivastava & Kamlesh Kumar Singh

4 **US Patent Appl. No.:** 0437NF2004/US **Filing Date:** 23/12/2004
Title: **Novel amino functionalized 1,2,4-trioxanes useful as antimalarials and a process of preparation thereof**
Inventors: Chandan Singh, Heetika Malik & Sunil Kumar Puri

5 **US Patent Appl. No.:** 0495NF2004/US **Filing Date:** 24/12/2004
Title: **Substituted carbamic acid quinoln-6-yl esters as acetylcholinesterase inhibitors**
Inventors: Neeraj Shakya, Zeeshan Fatima, Chandishwar Nath & Anil Kumar Saxena
Supporting Staff: Zahid Ali & Bishambhar Nath

6 **PCT Patent Appl. No.:** PCT/IN04/00427 **Filing Date:** 28/12/2004
Title: **Substituted carbamic acid quinoln-6-yl esters as acetylcholinesterase inhibitors**
Inventors: Neeraj Shakya, Zeeshan Fatima, Chandishwar Nath & Anil Kumar Saxena
Supporting Staff: Zahid Ali & Bishambhar Nath

7 **PCT Patent Appl. No.:** PCT/IN04/00426 **Filing Date:** 28/12/2004
Title: **Synergistic combination kits of α, β-arteether and sulfadoxin-pyrimethamine for the treatment of severe/ multidrug resistant and cerebral malaria**
Inventors: Renu Tripathi, Sunil Kumar Puri, Jagdishwar Sahai Srivastava, Satyawan Singh, Onkar Prasad Asthana & Anil Kumar Dwivedi

8 **US Patent Appl. No.:** 11/052,833 **Filing Date:** 09/02/2005
Title: **Oxy substituted flavones as antihyperglycemic and antidyslipidemic agents**
Inventors: Ram Pratap, Mavurapu Satyanarayan, Chandeshwar Nath, Ram Raghubir, Ashok Kumar Khanna, Anju Puri, Ramesh Chander, Priti Tiwari, Brajendra Kumar Tripathi & Arvind Kumar Srivastava

9 **PCT Patent Appl. No.:** PCT/IN05/00081 **Filing Date:** 15/03/2005
Title: **Novel N-substituted dihydrobenzothiepino dihydrobenzoxepino and tetrahydro benzocyclohepta indoles as selective estrogen receptor modulators**
Inventors: Kanchan Hajela, Ashok Kumar Jha, Man Mohan Singh, Girish Kumar Jain,Anil Kumar Balapure, Anila Dwivedy, Bharat Agarwal & P.S.R.Murthy
Supporting Staff: Vasi Ahmed, Govind Kesari, Mohini Chabara & Ramesh Sharma

10 **US Patent Appl. No.:** 11/089907 **Filing Date:** 25/03/2005
Title: **Novel N-substituted dihydrobenzothiepino dihydrobenzoxepino and tetrahydro benzocyclohepta indoles as selective estrogen receptor modulators**
Inventors: Kanchan Hajela, Ashok Kumar Jha, Man Mohan Singh, Girish Kumar Jain, Anil Kumar Balapure, Anila Dwivedy, Bharat Agarwal & P.S.R.Murthy
Supporting Staff: Vasi Ahmed, Govind Kesari, Mohini Chabara & Ramesh Sharma

11 **PCT Pat. Appl. No.:** PCT/IB05/01069 **Filing Date:** 13/04/2005
Title: **Oxy substituted flavones as antihyperglycemic and antidyslipidemic agents**
Inventors: Ram Pratap, Mavurapu Satyanarayan, Chandeshwar Nath, Ram Raghubir, Ashok Kumar Khanna, Anju Puri, Ramesh Chander, Priti Tiwari, Brajendra Kumar Tripathi & Arvind Kumar Srivastava

12 **Canada Patent Appl. No.:** 0345NF2001/CA **Filing Date:** 04/07/2005
Title: **An improved process for the synthesis of Guggulsterones: a pharmacologically active constituent of Gugulipid**
Inventors: Ram Pratap, Dharmendra Pratap Singh, Raghvendra Pal & Satyawan Singh

13 **British Pat. Appl. No.:** 0514808.5 **Filing Date:** 20/07/2005
Title: **An improved process for the synthesis of Guggulsterones: a pharmacologically active constituent of Gugulipid**
Inventors: Ram Pratap , Dharmendra Pratap Singh, Raghvendra Pal & Satyawan Singh

14 **PCT Patent Appl. No.:** PCT/IB04/03864 **Filing Date:** 23/11/04
Title: **Heterologus expression of trypanothione reductase from *Leishmania donovani* in a prokaryotic system**
Inventors: Neena Goyal & Mukul Kumar Mittal

15 **Sri lanka Patent Appl. No.:** 0390NF2001/LK **Filing Date:** 11/06/2004
Title: **Herbal medicaments for treatment of neurocerebrovascular disorders**
Inventors: Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna
Supporting Staff: Jharna Arun & Madhuri Chaudhary

16 **Estonia Patent Appl. No.:** 0390NF2001/EE **Filing Date:** 09/07/2004
Title: **Herbal medicaments for treatment of neurocerebrovascular disorders**
Inventors: Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna
Supporting Staff: Jharna Arun & Madhuri Chaudhary

17 **China Patent Appl. No.:** 0390NF2001/CN **Filing Date:** 13/07/2004
Title: **Herbal medicaments for treatment of neurocerebrovascular disorders**
Inventors: Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna
Supporting Staff: Jharna Arun & Madhuri Chaudhary

18 **Eurasian Patent Appl. No.:** 200400807 **Filing Date:** 13/07/2004
Title: **Herbal medicaments for treatment of neurocerebrovascular disorders**
Inventors: Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna
Supporting Staff: Jharna Arun & Madhuri Chaudhary

19 **Canadian Patent Appl. No.:** 0390NF2001/CA **Filing Date:** 10/06/2004
Title: **Herbal medicaments for treatment of neurocerebrovascular disorders**
Inventors: Madhur Ray, Raghwendra Pal, Satyawan Singh & Nandoo Mal Khanna
Supporting Staff: Jharna Arun & Madhuri Chaudhary

20 **Patent Appl. No.:** 0495NF2001/MM **Filing Date:** 20/07/2004
Title: **Novel 6-[(cycloalkylphenyl) vinyl] -1,2,4-trioxanes useful as antimalarial agents**
Inventors: Chandan Singh, Pallvi Tiwari & Sunil Kumar Puri
Supporting Staff: Shashi Rastogi & Akhilesh Kumar Srivastav

Patents Granted In India

1 **Patent No.:** 192291 **Grant Date:** 11/01/2005
Patent Appl. No.: 0620DEL2001 **Filing Date:** 29/05/2001
Title: **A process for the preparation of novel 4-alkyl-7-o-(acetamid-2-yl)-2H-1-benzopyran-2-ones useful as inhibitors of helminthic and protozoan DNA topoisomerases**
Inventors: Rama Pati Tripathi, Jitendra Kumar Saxena, Onkar Prasad Shukla, Subhash Chandra, Puvada Kalpana Murthy, Shailja Bhattacharya, Kamal Kamboj, Anil Kumar Dwivedi, Ranjeet Kumar Chatterjee, Satyawan Singh, Vishwa Mohan Lal Srivastava, Anil Kumar Rastogi & Amiya Prasad Bhaduri

2 **Patent No.:** 191660 **Grant Date:** 30/08/2005
Patent Appl. No.: 0211DEL2000 **Filing Date:** 09/03/2000
Title: **A process for the preparation of novel ether derivatives of dihydroartemisinin**
Inventors: Chandan Singh, Rani Kanchan & Sunil Kumar Puri

3 **Patent No.:** 192852 **Grant Date:** 09/09/2005
Patent Appl. No.: 0047DEL2001 **Filing Date:** 19/01/2001
Title: **A process for the preparation of novel 4-alkyl-7-o-alkanoyl-2H-1-benzopyran-2-ones useful as inhibitors of helminthic and protozoan DNA topoisomerases**
Inventors: Rama Pati Tripathi, Jitendra Kumar Saxena, Onkar Prasad Shukla, Subhash Chandra, Puvada Kalpana Murthy, Shailja Bhattacharya, Kamal Kamboj, Anil Kumar Dwivedi, Ranjeet Kumar Chatterjee, Satyawan Singh, Vishwa Mohan Lal Srivastava, Anil Kumar Rastogi & Amiya Prasad Bhaduri

4 **Patent No.:** 192853 **Grant Date:** 09/09/2005
Patent Appl. No.: 0048DEL2001 **Filing Date:** 19/01/2001
Title: **A process for the preparation of noval alkyl- 3 -amino -3-glycosylited propanoates and corresponding propionic acid useful as inhibitors of helminthic and protozoan DNA topoisomerases**

Inventors: Rama Pati Tripathi, Jitendra Kumar Saxena, Onkar Prasad Shukla, Subhash Chandra, Puvada Kalpana Murthy, Shailja Bhattacharya, Kamal Kamboj, Anil Kumar Dwivedi, Ranjeet Kumar Chatterjee, Satyawan Singh, Vishwa Mohan Lal Srivastava, Anil Kumar Rastogi & Amiya Prasad Bhaduri

5 **Patent No.:** 192822 **Grant Date:** 09/09/2005
Patent Appl. No.: 1206DEL2001 **Filing Date:** 29/11/2001
Title: **A process for the preparation of noval 1-arylalkyl -5-oxo-proline carboxamides useful as thrombin inhibitors**
Inventors: Dinesh Kumar Dikshit, Madhu Dikshit, Stuti Srivastava & Prashant Sharma
Supporting Staff: M.S. Ansari & Kanta Bhutani

6 **Patent No.:** 192802 **Grant Date:** 14/10/2005
Patent Appl. No.: 0437DEL1995 **Filing Date:** 04/07/1995
Title: **A process for the synthesis of novel (3S) -2 substituted -1,2,3,4-tetrahydro-9H-pyrido (3,4-b) indole-3-carboxylic acids as potential anti-C.C.K. agents**
Inventors: Ravish Chandra Tripathi, Anil Kumar Saxena & Ram Raghubir

Patents Granted Abroad

1 **Viet Nam Pat. No.:** 4230 **Grant Date:** 13/04/2004
Patent Appl. No.: S20000281 **Filing Date:** 31/03/2000
Title: **Substituted 1,2,4-trioxanes as antimalarial agents and a process of producing the substituted 1,2,4-trioxanes**
Inventors: Chandan Singh & Sunil Kumar Puri

2 **US Pat. No.:** 6737438 **Grant Date:** 18/05/2004
Patent Appl. No.: 10/113,205 **Filing Date:** 28/03/2002
Title: **Substituted 1,2,4-trioxanes useful as antimalarial agents and a process for the preparation thereof**
Inventors: Chandan Singh, Pallvi Tiwari & Sunil Kumar Puri
Supporting Staff: Shashi Rastogi & Akhilesh Kumar Srivastava

3 **US Pat. No.:** 6740639 **Grant Date:** 25/05/2004
Patent Appl. No.: 09/537088 **Filing Date:** 29/03/2000
Title: **Inclusion complexes of a high potent opioid peptide, pharmaceutical compositions and method of treatment**
Inventors: Anil Kumar Dwivedi, Madhu Khanna, Wahajul Haq, Ram Raghubir, Sudhir Srivastava, Puvvada Sri Ramchandra Murthy, Onkar Prasad Asthana, Jagdishwar Sahay Srivastava & Satyawan Singh

4	**Slovenia Pat. No.:**	0084585	**Grant Date:**	30/09/2004
	Patent Appl. No.:	200001862.2	**Filing Date:**	31/03/2000
	Title:	**Substituted 1,2,4-trioxanes as antimalarial agents and a process of producing the substituted 1,2,4-trioxanes**		
	Inventors:	Chandan Singh & Sunil Kumar Puri		
5	**South African Pat. No.:**	2003/2453	**Grant Date:**	27/10/2004
	Patent Appl. No.:	2003/2453	**Filing Date:**	28/03/2003
	Title:	**Substituted 1,2,4-trioxanes useful as antimalarial agents and a process for the preparation thereof**		
	Inventors:	Chandan Singh, Pallvi Tiwari & Sunil Kumar Puri		
	Supporting Staff:	Shashi Rastogi & Akhilesh Kumar Srivastava		
6	**US Pat. No.:**	6875758	**Grant Date:**	05/04/2005
	Patent Appl. No.:	10/385936 DIV	**Filing Date:**	14/03/2003
	Title:	**Method of treating hyperlipidemic and hyperglycemic conditions in mammals using pregnadienols and pregnadienones**		
	Inventors:	Ram Pratap, Ram Chandra Gupta, Ramesh Chander & Ashok Kumar Khanna		
7	**China Pat. No.:**	CN 1197568 C	**Grant Date:**	20/04/2005
	Patent Appl. No.:	99104738.9	**Filing Date:**	30/03/1999
	Title:	**Formulation of dihydroartemisinin for the control of wide spectrum of malaria**		
	Inventors:	Dharm Chand Jain, Rajendra Singh Bhakuni, Ram Prakash Sharma & Guru Prakash Dutta		
8	**US Pat. No.:**	6896901	**Grant Date:**	24/05/2005
	Patent Appl. No.:	09/742424	**Filing Date:**	22/12/2000
	Title:	**Method of treating a cognitive memory dysfunction using Gugulipid**		
	Inventors:	Ram Pratap, Ram Chandra Gupta, Ramesh Chander & Ashok Kumar Khanna		
9	**US Pat. No.:**	6962945	**Grant Date:**	08/11/2005
	Patent Appl. No.:	10/811296	**Filing Date:**	26/03/2004
	Title:	**N-aryloxypropanolyl-N'-phenethyl-urea**		
	Inventors:	Kalpana Bhandari, Shipra Srivastava & Chandeshwar Nath		

IV. PAPERS PRESENTED IN CONFERENCES

2005

Conference on Molecular Basis of Diseases, Chennai (8-9 January)

Identification of SAG (Sodium Antimony Gluconate) resistant and sensitive strain *Leishmania donovani* field isolate by sequence characterized amplified region marker. R. Vatsyayan, A. Dixit, A. Tripathi, P. Bhargava & U. Roy.

9th National Conference on Bioactive Heterocycles and Drug Discovery Paradigm, Rajkot (8-10 January)

A convenient regiospecific synthesis of substituted 1,3,4,6,6a, 11b, 12,12a-octahydro-2H, 7H-pyrazino-[2',1':6,1] pyrido (3,4-b) indoles. J. Rao, R. Chakrabarty, R. Roy, A. Mishra & A.K. Saxena.

Biomarkers of bone turnover and the risk of tooth loss and edentulism in post-menopausal Indian women. A. Makker, R. Kaur, G.K. Jain, S. Chandra, & M.M. Singh.

Effect of raloxifene on osteoclastogenesis and expression of marker genes. S. Kumar, R. Trivedi & M.M. Singh.

Evaluation of antispermatogenic activity of mineralo-herbal preparation in adult male Sprague-Dawley rats. S.R. Srivastava, S. Kesarwani & M.M. Singh.

Liposomised lipopeptide : Immunomodulatory activity and immunoprophyctic efficacy against *P. berghei* infection. A. Puri & W. Haq.

Permeability studies of new antimalarial trioxane derivative CDRI compound No. 97–78 in presence of cyclodextrins. A.K. Dwivedi, S. Srivastav, C. Singh & S. Singh.

Post- coital interceptive activity of *Wrightia tinctoria* in rat. G. Keshri, D.K. Kulshreshtha & M.M. Singh

Synthesis of 2,4,6 trisubstituted pyrimidine derivatives as a new class of antifilarial topoisomerases II inhibitors. S.B. Katiyar, I. Bansal, J.K. Saxena & P.M.S. Chauhan.

Synthesis of some new pyrazole derivatives. R. Saxena & S. Batra.

Threshold boundaries for osteoporosis in rats. M. Srivastava, S.K. Mandal, S. Sengupta, M. Arshad & M.M. Singh.

4th Indo-US Workshop on Mathematical Chemistry, Pune University, Pune (8-12 January)

QSAR and molecular modeling studies of substituted tropane analogs as dopamine transporter ligands. A. Chattopadhyay, A. Dixit & A.K. Saxena.

Evaluation of binary QSAR models derived from LUDI and MOE scoring functions for structure based virtual screening. P. Prathipati & A.K. Saxena.

International Conference on "Antioxidants & Free Radicals in Health-Nutrition & Radio-protectors & 4th Annual Conference of Society for Free Radical Research in India, Banglore (9-12 January)

Role of nitric oxide in the experimental models of Parkinson's disease. S. Singh & M. Dikshit.

Silver Jubilee Symposium on Ethnobotany in the New Millennium, NBRI, Lucknow (12-14 January)

Importance of Indian ethnobotanical knowledge for searching new pharmaceuticals. D.K. Mishra & K.R. Arya.

Some notable ethnomedicines of Tharu tribe in Uttaranchal. K.R. Arya & D.K. Mishra.

34th Annual Conference of Indian Pharmacological Society, Kolkata (14-16 January)

Effect of gemfibrozoid on muscle glycogen metabolism in dyslipidemic hamster model. M.K. Khan, R. Saxena, A. Puri, A.K. Khanna, R. Chandra & J.K. Saxena.

Search for antileishmanial agents from plant and marine resources. A. Dube & N. Singh.

Disparate inferences from cytotoxicity data and flow results with novel antineoplastic agent centchroman vis-s-vis MCF-7/MDA MB 231 cells. A.K. Balapure, S. Srivastava & R. Sharma

Role of potassium channels in NO mediated free radical generation from rat Polymorphonuclear leucocytes. S. Patel & M. Dikshit.

Lipid lowering of 5-arylidine thiazolidine-2-4 dione-3acetic acid ester derivative. A.K. Khanna, B.A. Bhatt, D.P. Sahu, R. Chandra & J.K. Saxena.

21st International Conference on Magnetic Resonance in Biological Systems (ICMRBS), Hyderabad (16-21 January)

Proton NMR analysis and identification of predictive metabolite-descriptors for the differentiation of unresponsive and responsive strains in *Leishmania donovani*. A. Subramanian, M. Srivasatava, U. Roy, A.K. Rastogi, S.K. Mandal & Raja Roy.

Proton MR CSF analysis and a new software as predictors for the differentiation of meningitis in children. A. Subramanian, A. Gupta, S. Saxena, A. Gupta, R. Kumar, A. Nigam, R. Kumar, S.K. Mandal & Raja Roy.

Cholesterol esters and Ceramide in human intracranial tuberculomas. S. Subramanian, B.S. Joshi & Raja Roy.

A novel intramolecular rearrangement investigated by NMR leading to the synthesis of biheterocyclic indole-benzoimidazole derivatives on solid phase. A.D. Roy, B. Kundu & Raja Roy.

Aminoquinazolines to imidazoquinazolines: Mechanism of cyclisation via structure elucidation leading to transamidation in solid phase. R.K. Grover, S. Sharma, B. Kundu & Raja Roy.

XXIX All India Cell Biology Conference and Symposium on gene to Genome Environment and Chemical Interaction, Lucknow (18-20January)

Differetial regulation of neurotrophins gene expression by focal cerebral ischemia/reperfusion injury in rat brain. R. Sharma & R. Raghubir.

Expression of PARP following cerebral ischemia/reperfusion in diabetic rats. P. Tripathi, S.L. Mehta & R. Raghubir.

Studies on the role of endoplasmic reticulum stress following cerebral ischemia. N.V. Parasuja & R. Raghubir.

57th Annual National Conference of Indian Psychiatric Society, PGIMER, Chandigarh (29 January- 1 February)

Ethics of placebo controlled trials in psychotropic drug research. J. S. Srivastava.

National Workshop on Non-Invasive Measurement of Peripheral Blood Flow and Cardiac Output, KGMU, Lucknow (1-19 February)

Non-invasive assessment of cardiac output in rats by impedance cardiography. K. Kapoor.

XXIII Symposium on Reproductive Biology and Comparative Endocrinology, Kolkata, (7-9 February)

Expression of estrogen receptor and α and β during pre-implantation period in rat uterus. C.S. Blesson, S. Awasthi & A. Dwivedi.

6th Controlled Release Society International Symposium on Advances in Technology and Business Potential of New Drug Delivery Systems (18-19 February)

Insights offered by a mathematical model of the hypothalamus pituitary testicular axis on transdermal testerone delivery for male contraception. R. Malik, A. Mishra, V.S. Venkatesh & S. Tondwal.

7th International Symposium on Vector and Vector Borne Disease, Punjab University, Patiala (18-20 February)

Effect of filarial infection on the progression of experimental *Leishmania donovani* infection in hamsters. P.K. Murthy, S. Dixit, R. Gaur & S. Gupta.

International Symposium on Infectious Diseases, Lucknow (23-25 February)

Saponins: Potential as contraceptive microbicide. P. Tiwari, D.Singh, K. Mitra & M.M. Singh

International Conference on Drug Discovery: Prospective and Challenges, CDRI, Lucknow (24-26 February)

Enhanced dose dependent lipolytic activity of WY14643 in dyslipidimic diabetic hamster. G. Bhatia, A. Puri, R. Chandra, A.K. Khanna, J.K. Saxena, R. Pal & A.K. Saxena.

Micorarrary of *Leishmania donovani*: A role in drug discovery and development. N. Goyal.

Indo-Australian Conference on Biotechnology in Infectious Diseases, Manipal, (1-3 March)

A DNA binding peptide from combinatorial libraries exhibit synergy against *Candida albicans* strains with known antifungals. A.K. Chaturvedi, M. Kumar, A. Kavishwar, A.P. Kesarwani, B. Kundu & P.K. Shukla.

A glimpse of laboratory animals' health status within a conventionally managed husbandry practices with emphasis on zoonoses from guinea pigs. D. Hansda & P.Y. Guru.

Comparative pathogenicity of Salmonella spp. In Mongolian gerbil and human in association with other bacteria. S.C. Nigam & P.Y. Guru.

Early diagnosis of keratomycosis through single stranded conformation polymorphism targeting internal transcribed spacer region: experimental evidence. M. Kumar, A. Kavishwar, A.K. Chaturvedi, G.B. shivakeshava & P.K. Shukla

Proteome analysis of immunogenic proteins of *Candida albicans* during vaginal candidiasis. A. Kavishwar, M. Kumar, A.K. Chaturvedi, G.B. Shivakeshava & P.K. Shukla.

International Training and Research in Emerging Infectious Diseases, Asian Regional Workshop, New Delhi (8-11March)

Immunostimulatory cellular responses of cured Leishmania infected patients and hamsters against soluble antigenic fractions of recent clinical isolate of *Leishmania donovani*. R. Garg, P. Tripathi, S.K. Gupta, S. Sundar, S. Naik & A. Dube.

SCAR marker for the identification of SAG resistant *Leishmania donovani* field isolates. R. Vatsyayan & U. Roy.

3rd World Congress on Leishmaniasis, Palermo, Terrasini Sicily, Italy (10-15 April)

A screen for genes involved in sodium antimony gluconate resistance in *Leishmania donovani* clinical isolates by DNA microarray. N. Goyal, R. Duncan, Ashutosh, S. Sunder & H.L. Nakhasi.

Antimony resistance mechanisms in clinical isolates of *Leishmaniasis donovani*. N. Singh.

Application of *Leishmania donovani* cell lines expressing luciferase reporter gene in semi *in vivo* drug screening. S. Gupta, Ashutosh, Ramesh & N. Goyal.

Drug resistance in field isolates of *L. donovani* is associated with amplification of PGPA and increased thiol levels. N. Goyal, M.K. Mittal, Ashutosh, S. Gupta, G.K. Jain & S. Sunder.

Identification of lead compounds targeting pteridine reductase 1 for antifolate chemotherapy in *Leishmania donovani* .P. Kumar, R. Ravishanker, M.I. Siddiqi & N. Singh.

Immunization against experimental Visceral Leishmaniasis with fraction of adult *Brugia malayi* extracts in hamsters. S. Gupta, S. Dixit, R.L. Gaur, Ramesh & P.K. Murthy

Immunodetection of proteophosphoglycans (PPGs) in sodium stibogluconate (SSG) sensitive and resistant strains of *Leishmania donovani*. M. Samant, A. Sahastrabuddhe, N. Singh, E. Handman & A. Dube.

Leishmania donovani SHMT- putative drug target? R. Vatsyayan, P.K. Roy & U. Roy.

13th International Society for Magnetic Resonance in Medicine (ISMRM) Meeting, Miami, Florida, USA (7-13 May)

Proton MR and a new software as predictors for the differentiation of meningitis in children. A. Subramanian, A. Gupta, S. Saxena, A. Gupta, R. Kumar, A. Nigam, R. Kumar, S.K. Mandal & Raja Roy.

Conference on Bioinfromatics by Computer Society of India (CONMICRO 2005), Lucknow (14-16 May)

Single nucleotide polymorphism databases. A.K. Mitra, S. Singh & S. K. Rath.

8th Congress fuer Infektionskrankheiten und Tropenmedizin. Hamburg, Germany (9-11 June)

Design and Synthesis of new antihistamines as malarial choloroquin resistance reversal agents. M. Saxena, R. Chakravarty, S. Gaur, R. Raghubir, S.K. Puri & A.K. Saxena.

Premises & Promises for Research &Therapeutics, New Delhi (18-21 September)

Comparison of serum-free rabbit Endometrium explant culture withMCF-7/MDA MB 231 cells in estrogen and antiestrogen responsiveness: Morphological, cytological and apoptosis deduced evidences Stem Cells. A.K. Balapurs, S. Srivastava & R. Sharma.

Graduate Students Meet (Trends in Life Sciences), ACTREC, Mumbai (24 September)

Inhalable microparticles containing anti-tubercular drugs alter macrophage cytokine secretion in mice infected with *Mycobacterium tuberculosis* H37Ra. P. Muttil, R. Sharma, A.B. Yadav & A. Mishra.

IBC's International Conference & Exhibition on Drug Discovery to Clinical trials: Global Partnering and New Science, Mumbai (5-7 October)

An overview of discovery to development of pharmaceutical drugs in India. Z. Imam.

12th National Magnetic Resonance Society Meeting, RRL, Jammu (8-11 October)

A quantitative study of various metabolites in different types of breast tumors by NMR: A multivariate analysis. A. Pandey, P. Ramakant, S. Kumar, M. Srivastava and R.Roy.

Adaptability of the stored grain pest sitophilus oryzae to different cereal crops: metabolite profile study by Nuclear Magnetic Resonance. A. Pandey & R.Roy.

Clinical assessment of benign and malignant breast disorders by metabolic profiles of serum using 1H Nuclear Magnetic Resonance spectroscopy. A. Gupta, M Srivastava, P. Ramakant, S. Kumar, P. Sinha, G.A.N. Gowda, R. Roy, M. Bhandari & C.L. Khetrapal

IMCE-2005, Lucknow University, Lucknow (22 October)

Stereoselective Synthesis of allylic amines from acetyl derivatives of Baylis-Hillman adducts. R. Pathak & S. Batra.

17th National Congress on Parasitology, Dibrugarh, Assam (24-26 October)

Antifilarial activity of novel formulations of albendazole against experimental brugian filariasis. P.K. Murthy, R.L. Gaur, S. Dixit, M. Sahoo, M. Khanna & S. Singh.

Antifilarial and immunomodulatory activity of *Piper betle* L. S. Shakya, A. Dangi, S. Tewari, N. Kumar & S. Misra-Bhattacharya.

Antileishmanial profile of Nitrogen heterocycles. A. Agarwal, Ramesh, Ashutosh, Nishi, N. Goyal, P.M.S. Chauhan & S. Gupta.

Bioevaluation of novel aryl substituted terpenyl pyrimidines against *Leishmania donovani*. Ramesh, N. Chandra, S. Pandey, S.N.Suryawanshi & S.Gupta.

Bioluminescent *Leishmania donovani*: Use in Drug screening. Ashutosh, Ravinder, Ramesh, S. Gupta & N. Goyal.

Homology modeling and substrate binding study of *Leishmania donovani* Serine hydroxymethyltransferase. R. Vatsyayan, P. Bhargava, A. Kumar, Moh. I. Siddiqi & U.Roy.

Implication of intracellular glutathione and its related enzymes in resistance to antimalarial drug arteether. R. Chandra, J.K. Saxena & S.K. Puri.

In vitro and *in vivo* antileishmanial efficacy of *Piper betle* Linn (Betle vine). against *Leishmania donovani*. N. Singh, S. Tiwari, M. Samant, A. Kumar, N. Kumar & A. Dube.

In vitro cultivation of *Plasmodium falciparum* in modified media supplemented with various animal sera. K. Srivastava, S. Singh, P. Singh and S.K. Puri.

Isolation and characterization of diagnostic filarial antigens from *Setaria cervi*. A. Tandon, D.C. Kaushal & N.A. Kaushal.

Isolation of molecular forms of *Setaria cervi* acetylcholinesterase by preparative PAGE and their characterization. S.K. Singh, D.C. Kaushal & N.A. Kaushal.

Production of antibodies against intact microfilariae of *Setaria cervi*. A. Kalani, N.A. Kaushal & D.C. Kaushal. Ramesh, N. Chandra, S. Pandey, S.N. Suryawanshi & S. Gupta.

National Symposium on Plant Science Research in India: Challenges & Prospects, BSI, Northern Circle, Dehradun (24-26 October)

Research on efficacy of plant based drugs; some important issues. K.R. Arya & S.C. Agarwal.

International Symposium on Emerging Trends in Drug Discovery, CDRI, Lucknow (7-10 November)

16-Dehydropregnenolone: An approach towards enhancing oral bioavailability. R.S. Bhatta, S. Sabrinath, A.K. Khanna, R. Chandra, J.K. Saxena & G.K. Jain.

Lovastatin reduces ovariectiomy induced increased bone turnover in rats. Satyawan B. Jadhava, S. Sabrinath, P.S.N. Murthy, M.M. Singh & G.K. Jain.

74th Annual Meeting of Society of Biological Chemists (India), CDRI, Lucknow (7-10 November)

Antioxidant and lipid lowering activity of *Anthocephalus indicus* (Kadam). V. Kumar, M.M. Khan, A.K. Khanna, R. Chandra, K. Jawed, J.K. Saxena, S. Singh & R.K. Singh.

Anti-Resorptive activity and prevention of ovariectomy-induced osteoporosis in retired breeder female Sprague Dawley rats by raloxifene. T. De, R. Trivedi, K Kumar & M.M. Singh.

Bioluminiscent *Leishmania donovani* field isolates: Application in Highthroughput Screening of antileishmanial compounds. Ravinder, Ashutosh, Ramesh, S. Gupta & N. Goyal.

Cloning expression and characterization of dipeptidylcarboxypeptidase of *Leishmania donovani*. M.S. Beg, R. Duncan, S.Pandiyan, A. Debrabant, H.L. Nakhasi & N. Goyal.

Cloning, Sequencing and expression of buffalo Gonadotropin releasing Hormone Receptor (GnRH-R). R. Konwar & A.K Srivastava.

Comparative study of the organization of fabD operon in *M. tuberculosis* and nonpathogenic strrain of *M.aurum*. N. Gupta, T.K. Bansal, G. Prabha & B.N. Singh.

Cytokine release-stimulating potential of *Brugia malayi* adult worm molecules and their effect on host's mast cells. M. Sahoo, S. Dixit, R.L. Gaur, P.S.R. Murthy & P.K. Murthy.

Differential expression of Mycobacterial Promoters in viable non replicating persistant state. A. Saxena, R. Srivastava & B.S. Srivastava.

Enhancement of saquanvir solubility, dissolution and absorption using solid dispersions made of gelucire 44/14. V. Prasad, V. Jain, P.R. Mishra & R. Pal.

Estrogen responsive gene expression by centchroman in mammary carcinoma cell line. R. Saxena, D. Singh & M.M. Singh.

In vitro antileishmanial efficacy of 4-thiazolidinones. D. Pandey, Nishi, T. Srivastava, W. Haq, S.B. Katti, N. Goyal & S. Gupta.

Possible mode of action of Pyronaridine, Berinil and Camptothecin for their antimalarial activity against drug resistant malaria. R. Tripathi.

Role of potassium in peroxynitrite mediated free radical generation from rat neutrophils. S. Patel, S. Kumar & M. Dikshit.

Synthesis of Chromenochalcones and evaluation of their *in vitro* antileishmanial activity. T. Narender, Khaliq, Sweta, Nishi, N. Goyal & S. Gupta.

Trypanothione reductase of Leishmania donovani: Expression, purification and characterization of recombinant enzyme. S. Rai & N. Goyal.

Tumor necrosis factor and caspase in response to soluble or microparticle-incorporated drugs in *Mycobacterium tuberculosis* infection. A. B. Yadav R. Sharma, P. Muttil & A. Mishra.

Vitamin D receptor- gene variants of Fok-I, Taq-I and Apa-I polymorphisms in calcium oxalate urolithiasis. H.K. Bid, P.K. Manchanda & R.D. Mittal.

32nd Annual Conference of Indian Immunology Society, PGI, Chandigarh, (24-27 November)

Antigen recognition pattern of sera of *Brugia malayi* infected *Mastomy coucha* treated with diethylcarbamazine or albendazole and re-exposed to infection. R.L.Gaur, S.Dixit, M.A.Khan, M.K.Sahoo & P.K.Murthy.

Cellular responses of cured *Leishmania donovani* infected hamster against cysteine proteinases and recombinant gp 63 of *L. major.* S.K.Gupta, R.Garg & A. Dube.

Cloning expression and purification of heavy chain myosin of adult *B. malayi*. S. Vedi, S.K. Verma, I. Bansal, J.K. Saxena & S. Misra-Bhattacharya.

Combination therapy in Stibanate resistant experimental models of Visceral Leishmaniasis (Kala-azar) with Picroliv (*Picrorhiza kurrooa*) and Sodium stibogluconate (SSG). S. Gupta & Nishi.

Depletion of endosymbiont bacteria *Wolbachia* from filarial parasite *(Brugia malayi)* by free and liposomized tetracycline: Effect on the parasitological, immunological and inflammatory responses of the rodent host, *Mastomys coucha*. S. Shakya, P. Bajpai, S. Vedi, A. Dangi, M. Owais & S. Misra-Bhattacharya.

Immune responses of *Mastomys coucha* immunized with BmAFII fraction of *Brugia malayi* adult extract and exposed to infection. S. Dixit, R.L. Gaur, M. Sahoo, P.S.R. Murthy & P.K. Murthy.

Immune status of *Plasmodium yoelii* infected and artemether treated mouse. R. Sahu, U. Singh, L.M. Tripathi & S.K. Puri.

Immunostimulatory activity of loganin based dipeptide. A. Bhardwaj, R. Sahu, W. Haq, K. Raj, L.M. Tripathi & A. Puri.

Immunostimulatory cellular responses of cured Leishmania infected hamster against soluble exogenous antigens (SEAgs) of clinical isolate of *Leishmania donovani*. M. Samant, R. Garg, S. Gupta & A. Puri.

Leishmania donovani in hamsters: Effect of senescence in the disease progression and immunopathological responses. N. Singh & A. Dube.

Molecular characterization of acetylcholinesterase from filarial parasites. N. A. Kaushal, S.K. Singh & D. C. Kaushal

Monoclonal antibodies against merozoite surface protein 1 of *Plasmodium vivax*. D.C. Kaushal & N. A. Kaushal.

International Workshop on Molecular Physiology Intracellular Calcium Signaling, Pune (29 November - 4 December)

Effect of a potential anti-resorptive compound on osteoclastogenesis . R. Trivedi, S. Kumar, T. De & M.M. Singh.

57th Indian Pharmaceutical Congress, Hyderabad (2-4 December)

Amphiphilogels as vehicles for topical delivery as a bioactives. V. Prasad, N. Kumar & P.R. Mishra.

Assay method for quality control and stability studies of a new antihyperlipidemic agent 3-β-hydroxypregna-5, 16-dien-20-one. A.K. Dwivedi, N. Kumari, J. Madan, A.K. Mishra, R. Pratap & S. Singh.

Effect of antidepressant on blood glucose level and immobility time in alloxan induced diabetic mice. V. Prasad, V. Jain & P.R. Mishra.

Genetic algorithm based wavelength selection in PLS-regression for estimation of Rifampicin and Isoniazid in pharmaceutical formulation. J. Madan, S. Sethy, A.K. Dwivedi & S. Singh.

HPTLC method for analysis of Guggulsterone in formulation Guggulresin extract. V. Jain, V. Prasad, S.B. Kasture & R. Pal.

Ion pairing RP-HPLC method for estimation of simvastatin and its hydrolytic degradation product β-hydroxy acid. J. Madan, V. Thakkar, A.K. Dwivedi & S. Singh.

Studies of the inclusion complexes of a new anti-hyperlipidemic with cyclodextrins. A.K. Dwivedi, N. Kumari, J. Madan & S. Singh.

National Academy of Sciences India, Platinum Juilee Session, Pondichery University (8-9 December)

Dimensional protein maps of *Brugia malayi* adult and microfilarial antigens. B.P. Mohanty, S. Bhattacharya & S.K. Kar.

Annual Meeting of Indian Academy of Neurosciences and Symposium on Emerging Trends in Neurosciences, NIMHANS, Banglore (11-14 December)

Metabolic role of corticosterone and Glucocorticoid receptor expression during stress full conditions. K. Naila & G. Palit.

Modulation of caspase-3 activity by nitric oxide in experimental models of Parkinson,s disease. S. Singh & M. Dikshit.

Nature of cell death in cerebral ischemia/reperfusion injury. N. Manhas & R. Raghubir.

Neuroprotectine effect of calcineurin inhibitor on cerebral ischemia reperfusion injury. A. Gusain, T.K. Patro & R. Raghubir.

Nitric oxide in migraine. R. Shukla & M. Dikshit.

38th Annual Conference of Indian Pharmacological Society, Chennai (28-30 December)

Novel Bioactives from the Oceans. R. Raghubir.

2006

Silver Jubilee Symposium on Ethnobotany in the New Millennium, NBRI, Lucknow (12-14 January)

Some notable ethnomedicines of Tharu tribe in Uttaranchal. K.R. Arya & D.K. Mishra.

Importance of Indian ethnobotanical knowledge for searching new pharmaceuticals. D.K. Mishra & K.R. Arya.

V. INTER-AGENCY LINKAGES

1. Grant-in-aid projects

Antifertility Research Program	Ministry of Health & Family Welfare, Govt. of India
Development of National Laboratory Animal Centre	Department of Biotechnology, Govt. of India
Sophisticated Analytical Instrument Facility	Department of Science & Technology, Govt. of India
National Project on Development of Potential Drugs from the Ocean	Department of Ocean Development, Govt. of India

2. Sponsored projects

Development of National Laboratory Animal Centre-X FYP	Department of Biotechnology, Govt. of India
Development of Adaptogenic and Immuno-modulatory Agents from Indian Medicinal Plants	-do-
Effect of Modulation of Ionic Interactions on The Protein Stability and Function and (Ii) Optimization of Conditions for Generating an Efficient Refolding System for Complex Multimeric Proteins Using Additives, Mainly Trehalose or Slats	-do-
Development of Antiosteoporotic Agents from Indian Medicinal Plants	-do-
Genome Microarray Analysis of Differential Gene Expression in Antimony Resistance Kala-azar Field Isolates	-do-
An Approach Towards Exploration of Mechanism of Drug Non-responsiveness to SbV in Field Isolates of *Leishmania donovani*	-do-
Role of rapid suscitation promoting factors (Rpf) in wake up of dormancy in *Mycobacterium tuberculosis*	-do-

Leishmania Target Antigens from Promastigotes and Amastigotes: Identification on Experimental Visceral Leishmaniasis	-do-
Solution Structure of *M. tuberculosis*, *E. coli* and *H. sapiens* Peptidyl-tRNA Hydrolase by NMR Spectroscopy	-do-
Characterization of Secreted Antigens of Infective Larvae and Adult *Brugia malayi* Parasites which Induce Strong Thi Responses in Truly Infection Free Individuals Residing in Bancroftian Filariasis Endemic Area	Department of Science & Technology, Govt. of India
Design and Synthesis of C-glycoside Mimics of Anti-inflammatory Agents	-do-
Design and Development of Tissue Selective Antiestrogens	-do-
Studies on the Chemistry of Baylis - Hilman Reaction of Substituted Isoxazolecarboxaldehydes	-do-
Studies on the Modulation of Neutrophil Free Radical Generation and Nitro Oxide Synthesis by Calcium, Reactive Nitro and Oxygen Species	-do-
Investigation on the Structure Function Relationship of a Novel *E. coli* Toxin Hemolysis E, a Potential Virulent Factor	-do-
Identification and Characterization of Stage Specific Gene(s) of *Leishmania donovani* Using Genomic Microarray	-do-
Study of Non-replicating Persistent Mycobacteria and Identification of Genes Expression During Latency	-do-
Establishing National Facility for Regulatory Pharmacology and Toxicology	-do-
Characterization of Extracted Amyloid from Human Medullary Carcinoma of Thyroid	-do- (SERC Fast Track)

Design and Synthesis of PPAR-α, γ Modulators as Antihyperglycemic α	-do- (SERC Fast Track)
Computer Aided Drug Design and Synthesis of Arntihistamines (H)	-do- (Women Scientist Scheme)
Synthesis of Some Heterocyclic Compounds Containing Amidoalkyl Groups for Their Antiviral and Antifungal Activities	-do- (Women Scientist Scheme)
Osteoporosis in Indian Women and Men: Diagnosis Using Bone Mineral Density and Biochemical Markers of Bone Turnover	-do- (Women Scientist Scheme)
Genome wide Approaches to Assess the Involvement of Cyp1A1 Polymorphism in Indian Breast Cancer Patients and the Effect of Resveratol on Cyclophosphamide Induced Gene Expression Profile of MCF-7 Cell	-do-(Women Scientist Scheme)
Identification and Development of Novel Anticancer Agents	DST/DABUR (DRF)
Lead optimization and Development of New Orally Active Antimalarial Peroxides	DST/IPCA LAB
Plasmodium falciparum Apicoplast ORF470: Investigation of Structure-Function Relationship	Indian Council of Medical Research, New Delhi
Factors Affecting Susceptibility/Resistance on the Host to Hepatic Amoebiasis	-do-
Development of New Antimalarial Agents Based on Leads from Natural Products	-do-
Pharmacokientic Studies of Herbal Medicines	-do-
Search for the Cell Wall and Membrane Protein(s) of *Candida albicans* to be Used as Target Molecule	-do-
Investigations into Replication and Transcription of the *Plasmodium falciapum* Apicoplast Genome	Council of Scientific and Industrial Research, New Delhi
Sending a Wake Up Call to Dormant Cells of *Mycobacterium tuberculosis:* Identification of Signal Proteins and Receptors	-do- (New Idea Fund)

Synthesis and Biological Evaluation of Solanesol Derivatives as Novel Bioactive Substances	Indian Council of Agricultural Research, New Delhi
Biotoxins and other Bioactive Substances from the Marine Organisms	-do-
Identification of *Mycobacterium tuberculosis* Genes Expressed *in vivo* / *ex-in vivo* and their Relevance in Drug Development	IFCPAR Indo-French
Latent *M. tuberculosis*: Therapeutic Component	NMITLI
Development of Versatile, Portable Software for Bioinfomatics	-do-
Development of Novel Biotech Therapeutic Molecule Lysostaphin	do-
Evaluation of Latent *Mycobacterium tuberculosis,* New Targets, Drug Delivery Systems Bioenhances and Therapeutics. Expression and Evaluation of Lipoamide Dehydrogenase and Isocitrate Lyase Genes of *M. tuberculosis*	-do-
Development of Oral Herbal Formulation for Treatment of Psoriasis: A Clinical and Scientific Challenge	-do-
Development of biodegradable micro-particles containing anti-tubercular drug for delivery of dry powder inhalation (DPI)	-do-
P3 Facility for Carrying Out Target Validation for *M. tuberculosis* Strain H37Rv Pharmacological and Genomic Investigations	-do-
On *Wthania somnifera* – An Indian Medicinal Plant	-do-
Improved genome annonation through a combination of machine learning and experimental methods: *Plasmodium falciparum* as a case study	-do-
Mode of action of Artemisinin based antimalarial drug	UPCST

VI. R & D / TECHNICAL FACILITIES & SERVICES

1. Sophisticated Analytical Instrument Facility

The division is well equipped with latest and modern sophisticated instruments. Following new facilities were added:

(i) Open Access LC-MS: A Thermo Electron Advantage MAX Ion Trap LC-MS has been installed and is functional. This facility can record ESI and APCI and MS^n mass spectra of samples automatically.

(ii) FT-NMR Open System: A new Bruker Avance 300 MHz FT NMR spectrometer has been installed. The system has a 120-sample autosampler with capability to record ^{1}H, ^{13}C, ^{19}F and ^{31}P NMR spectra.

(iii) FT-NMR with HR MAS: A new Bruker 400 MHz FT NMR spectrometer with HR MAS and multinuclear inverse probe head has been commissioned. It has a HRMAS Dual probe head accessory.

During the year, over 9600 external and 18700 internal samples were analysed by using the facility. There were 540 external users and 260 internal users. Eighty-seven samples were analysed under electron and confocal microscopy from external users.

The Instrumentation Division continued to provide repair, maintenance and upkeep facilities of sophisticated analytical, biomedical electronic and laboratory instruments to all Divisions/Sections of the Institute. In cases of non-availability of imported components, equivalent indigenous substitutes were installed to ensure the smooth functioning of instrument. Specifications and technical evaluations were also prepared for procurement of new equipments for other organizations e.g. Animal Husbandry and Parag Dairy.

2. Biological screening of outside samples

The Institute has a large number of *in vitro* and *in vivo* screening models for biological screening. These facilities were extended to R&D institutions, Universities and industrial organizations on payment basis.

3. Digital designing of panels

CDRI provided digital designing facility of exhibition display panels to NBRI, CIMAP, ITRC and CSIR and a total of 90 panels, including 6 in Hindi, were prepared for CSIR Foundation Day Celebrations (held at Lucknow) and for Indian Science Congress, Ahmedabad.

4. National Laboratory Animal Centre

Laboratory Animals (comprising of 33 different strains of 8 rodent species, including 13 inbred strains of mice, 4 inbred strains of rat, 2 inbred strains of hamster, 2 strains of lagomorphs) were maintained. They were regularly supplied within the institute as well as to more than 20 different CPCSEA registered research organizations including Government, Private,

Pharmaceutical companies, Universities etc. throughout India. These animals comprised of 15 different species of mice, rats, hamsters, guinea pigs, rabbits, mastomys, gerbil, cotton rats and monkeys. This year, four new strains, two transgenic mouse strains, APOe and APOb, one specific disease mouse model NOD and a spontaneously hypertensive model of Rat (SHR) have been acquired and successfully bred.

Isolation of DNA, preparation of PCR product and analysis of RAPD and micro-satellite markers of different strains of laboratory animals has been also standardized. Cross species micro-satellite in mastomys, Golden hamster, white hamster and cotton rats were developed. DNA studies have also been done for cloning and molecular characterization of pathogenic *Salmonella species*, *Staphylococus sp.*, *Sterptococous sp*. and *E. coli*. Specific primers for identifying APOe and APOb transgenic animals have also been developed.

GMP (Grinder, Mixer & Pelletizer) plant has been installed and the manufacturing of pelleted feed for laboratory animals using several different formulae has been started. This, thus, also fulfills the GLP norms of providing certified pellet diet of known composition. Enhanced animal growth and better breeding performance has been observed in animals, which were maintained on indigenously manufactured feeds. Further compliance to better hygiene was also obtained by newly deployed monitoring of animal colonies through CCTV and audio video recording.

More than 22 cell lines, derived from human as well as animals were maintained, cryopreserved and several flasks/cultures were supplied to various researchers working in different projects in this institute and other research organizations including pharmaceutical companies.

5. Documentation & Library Services

The Institute's library has a collection of 21500 books, 64680 bound volumes and 267 subscribed periodicals. During the year, the division organized a 3-day workshop from 5-7 August 2005 on E-journals. The workshop was first in the series of workshops of the CSIR E-journal consortium. Participants from CDRI, ITRC, CIMAP, NBRI and RRL, Bhopal were provided hand on training of the techniques of the e-journal browsing and searching. Scientists from NISCAIR, New Delhi presented the on-line monitoring and complaint lodging system to the participants. All the activities of Library are completely computerized and confirm to the norms of e-governance. Publication of periodicals viz. **Drugs and Pharmaceuticals - Industry Highlights** (monthly), **Drugs and Pharmaceuticals - Current R&D Highlights** and **Ocean Drugs Alert** (quarterly) were carried out on regular basis. Subscribers and peers largely appreciated the contents of these publications. Library manages, updates and maintains the Website of the Institute.

VII. HUMAN RESOURCE DEVELOPMENT

1. Ph.D. Programme

1.1 Following students were awarded the Ph.D. degree

Name	University	Title/Guide
Amogh Sahasrabuddhe	JNU, New Delhi	Characterization of actin microfilament system in Leishmania / Dr. CM Gupta
Anant Narayan Bhatt	Ram Manohar Lohia Avadh University, Faizabad	Characterization of folding/unfolding pathways and independent folding domains of serinehyhydroxy methyltransferase from *subtilis* and *Bacillus stearothermophilus* / Dr. Vinod Bhakuni
Deepak Rai	Kolkata	Biochemical and behavioural changes involved in stress response/ Dr. G. Palit.
Divya Singh	JNU, New Delhi	Analysis of replication and transcription of the 35Kb Apicoplast genome of *Plasmodium falciparum* / Dr. Saman Habib
Heetika	JNU, New Delhi	Synthesis of potential antimalarial agents/ Dr. Chandan Singh
Kavita Arora	Delhi	Glutamate cysteine ligase and glutathione reductase in filarial worms and malarial parasites in relation to their chemotherapy/ Dr. A.K. Srivastava
Manish Banerjee	Lucknow	Studies on biochemical and immunological mediators in experimental inflammation / Dr. Rakesh Shukla
Neetu Tiwari	Ram Manohar Lohia Avadh University, Faizabad	Synthetic studies in glycohybrid molecules: Development of new class of antitubercular agents/Dr. RP Tripathi
Preeti Ojha	Ram Manohar Lohia Avadh University, Faizabad	Studies on mechanism of action of CDRI 84-35 (1-formyl-4-dichloracetyl piperazine), a potent antispermatogenic agent in rats/ Dr. J.D. Dhar & Dr. Gopal Gupta

Rajendra Pal Singh Parti	Jadavpur University, Kolkata	Isolation of virulence determinant(s) of *Mycobacterium fortuitum*/Dr. BS Srivatava
Ramesh Chandra	Ram Manohar Lohia Avadh University, Faizabad	Synthetic studies in carbohydrate molecular diversity : Development of antiparasitic agents/ Dr. R.P. Tripathi
Ravendra Garg	Indore	Prophylactic studies with immunostimulatory proteins of *Leishmania donovani* against experimental visceral Leishmaniasis/ Dr. Anuradha Dube
S. Sabrinath	JNU, New Delhi	Pharmacokinetics of α-, β-arteether, a highly effective anti-malarial drug/Dr. R.C. Gupta
Sandeep K. Srivastava	JNU, New Delhi	Structural studies on NaD^+-dependent DNA ligase (R_v3014c) from *Mycobacterium tuberculosis*/ Dr. R. Ravishankar
Sandeep Kumar Misra	JNU, New Delhi	Characterization of folding intermediates of methylene tetrahydrofolate reductase from *E. coli* / Dr. Vinod Bhakuni
Sapna Gupta	Aligarh	An investigation of glutathione metabolism and potential modifiers of glutathione metabolism in adult filarae/Dr. A.K. Srivastava
Shikha Sharma	Delhi	Antiresorptive activity of certain selective estrogen receptor modulators and their effect on bone turnover in osteogenic rats/ Dr. M.M. Singh
Surojit Sengupta	Ram Manohar Lohia Avadh University, Faizabad	Evaluation of antiresorptive activity of certain selective estrogen receptor modulator and their effect on estrogen receptor expression and bone turnover in osteopenic rats/Dr. MM Singh
V.G.M. Reddy	Ram Manohar Lohia Avadh University, Faizabad	Purification and characterization of DNA topoisomerase II of filarial parasites and its utilization as target for antifilarial compounds/ Dr. J.K. Saxena

Vipul Kumar	JNU, New Delhi	Pharmacokinetics of sulphur mustard decontaminant CC-2 and drug inteaction studies on Centchroman in rats/Dr. RC Gupta
Vishal Trivedi	JNU, New Delhi	Structural studies ion the catalytic mechanism of serine hydroxymethyl transferase from *B. strearothermophylus*/Dr. PR Maulik

1.2 Following students have submitted their thesis for the award of Ph.D. degree

Amit Prakash Kesarwani	Ram Manohar Lohia Avadh University, Faizabad	Design and synthesis of combinatorial libraries of small organic molecules for the identification of biodynamic agents/Dr. B Kundu
Amol Kavishwar	JNU, New Delhi	Proteome-wide generation of monoclonal antibodies against cell wall proteins of *Candida albicans* and their use as immunotherapeutics/ Dr. PK Shukla
Anu Agarwal	BR Ambedkar University, Agra	Synthesis of possible anti-infective agents and their combinatorial chemistry /Dr. PMS Chauhan
Atul Gupta	BR Ambedkar University, Agra	Synthesis of potential estrogens antagonists/ Dr. S Ray
Bashir Ahmed Bhatt	JNU, New Delhi	Synthesis of novel antidiabetic and hypolipidemic agents/Dr. DP Sahu
Diksha Katiyar	Ram Manohar Lohia Avadh University, Faizabad	Synthetic studies in heterocyclic and sugar derivatives: Development of potential chemotherapeutic agents/ Dr. RP Tripathi
Diptesh Sil	BR Ambedkar University, Agra	Synthesis of insulin sensitizers as antihyperglycemic agents/ Dr. VJ Ram
Mukul K Mittal	Aligarh Muslim University, Aligarh	Biochemical and molecular characterization of drug resistance in *Leishmania donovani*/ Dr. Neena Goyal
Pervez Ahmad	Lucknow	Design and synthesis of novel agents for antidiabetic and related metabolic disorders Dr. Atul Kumar

Philip Prathipati	JNU, New Delhi	Computer aided drug design: 3D QSAR and molecular modeling studies on β_3AP agonists and α_1AR antagonists/Dr. AK Saxena
Poonam Dharmani	Bundelkhand University, Jhansi	A study on the role of cyclooxygenase-2 in healing of gastric ulcer in rodents/ Dr. Gautam Palit
PS Narayana Murthy	BR Ambedkar University, Agra	Modulation of bone turnover rate *in vitro and in vivo* evaluation of agents for antiosteoporosis activity/Dr. MM Singh
Ram Sagar	BR Ambedkar University, Agra	Studies on phytochemicals from Indian medicinal plants and synthesis of biodynamic monosaccharide derivatives/ Dr. AK Shaw
Rashmi Saini	JNU, New Delhi	Studies on nitric oxide synthase and associated proteins in the regulation of blood cell functions/ Dr. Madhu Dikshit
Sanjay Babu Katiyar	BR Ambedkar University, Agra	Synthesis of possible antimalarial, antifilarial agents and their combinatorial chemistry/ Dr. PMS Chauhan
Sarita Chaturvedi	JNU,	Structural and functional characterization of serine hydroxymethyltransferase from *Mycobacterium* sp./ Dr. Vinod Bhakuni
Tumul Srivastava	Ram Manohar Lohia Avadh University, Faizabad	Design and synthesis of thiazolidine derivatives as antifungal agents/Dr. SB Katti

2. MD/MS Programme

Dr. Arshad Ahmad	KGMU, Lucknow	Study of serum ALT, AST, bilirubin, TGT, ^{1}HNMR estimated glutamine and other metabolites in various surgical hepatic disorders, especially liver trauma/Dr. Raja Roy
Dr. Jayanth Agarwal	KGMU, Lucknow	A study of antioxidant enzymes in serum and tonsillectomised tissue of patients with chronic tonsilitis/Dr. Gautam Palit
Dr. Pooja Ramakant	KGMU, Lucknow	Nuclear magnetic resonance spectroscopic changes in benign and malignant breast tissue/ Dr. Raja Roy

Dr. Rolly Shrivastava	KGMU, Lucknow	Influence of pH of various vehicles used with calcium hydroxide for intracanal medication/ Dr. J.K. Saxena.
Dr. Shivlal Sharma	KGMU, Lucknow	Effect of chlorhexidine and other mouthwashes on the levels of pro-inflammatory cytokines in gingivitis/Dr. Gautam Palit
Dr. U.P. Verma	KG Dental University, Lucknow	A comparative study of the mechanism of action of various mouthwashes on cultured human gingival fibroblasts through FACS analysis: an *in vitro* analysis/Dr. A.K. Balapure

3. Training to sponsored personnel

Under this programme, the Institute conducted the "Advance Technology Training Programme", for scientists and technical persons, mainly from industry; training to foreigners under bilateral cooperation with different countries and international agencies; training to sponsored students from academic institutions and ad-hoc short-term training for academia and industry.

3.1 International training

Long term/short term training was provided to the following person:

U.K.

Mr. Varun Gopala Krishnan — Microbiology
School of Contemporary Science
University of ABERTAY
Dandee (U.K.)

3.2 Training under cooperation with Indian universities

Under the training program PS-II, 19 students from Birla Institute of Technology and Science (BITS), Pilani were provided six months training on monthly stipend.

3.3 Training under cooperation with sister laboratories

One scientist from CCMB, Hyderabad was trained at CDRI in the field of breeding and maintenance of laboratory animals.

3.4 Adhoc training

Following industry and academia sponsored personnel were trained in Parasitology, SAIF, Molecular & Structural Biology and Microbiology divisions of the Institute.

Dr. Mrs. Madhuri Singhal
Govt. M.I.B.P.G. Girls College,
Bhopal

Dr. Praveen Singh
Indian Veterinary Research Institute
Izatnagar

Mr. Ashish Kumar Pandey
National Thermal Power Corporation
Vindhyanagar, (M.P.)

Dr. Meher Rizvi
Jawaharlal Nehru Medical College
Aligarh.

3.5 Following university sponsored students were imparted training

A.P.S. University, Rewa	Sarita Rao Rajiv Kumar SondhiyaVarun Kumar Shukla	Molecular & Structural Biology Biochemistry Molecular & Structural Biology
Allahabad Agricultural University, Allahabad	Kavita Singh Akanksha Singh Krishan Mohan Rai Ankita Srivastava Meenakshi Verma Vijayta Gupta	Laboratory AnimalsParasitology Toxicology Endocrinology Biochemistry Parasitology
Allahabad University, Allahabad	Arun Kumar Ruchna Verma	Endocrinology Toxicology
AMITY Institute of Biotechnology, New Delhi	Isha Madan	Microbiology
Atal Bihari Vajpayee Institute of Information Technology & Management, Gwalior	Amit Shukla	Medicinal & Process Chemistry
Birla Institute of Medical Research, Gujarat	Shweta Singh	Biochemistry

Birla Institute of Technology, Mesra, Ranchi	Manish Sinha	Medicinal & Process Chemistry
	Gaurav Lodhi	Medicinal & Process Chemistry
	Satyajit Sakhardande	Medicinal & Process Chemistry
	Manish Sinha	Medicinal & Process Chemistry
	Satyajit Sakhardande	Medicinal & Process Chemistry
	Sriguru Bandana	Medicinal & Process Chemistry
Banaras Hindu University, Varanasi Banesthali	Nikhil Sachdeva	Medicinal & Process Chemistry
	Supriya Jaggi	Medicinal & Process Chemistry
	Garima Dwivedi	Pharmacology
Vidyapeeth, Rajasthan		
Bramhanand College, Kanpur	Anuj Tripathi	Biochemistry
Boston Collage, Gwalior	Rahul Solanki	Drug Target Discovery &
	Anamika Tripathi	DevelopmentMicrobiologyDrug Target
	Rahul Solanki	Discovery & Development
Bundelkhand University, Jhansi	V. K. Srivastava	Medicinal & Process Chemistry
	Sonali Singh	Molecular & Structural Biology
	Abhishek Bhargava	Molecular & Parasitology
	Aditi Gautam	Molecular & Structural Biology
	Alhar Alam	Drug Target Discovery & Development
	Anshu Mishra	Microbiology
	Archana Shankhdhar	Molecular & Structural Biology
	Bhavana Gangwar	Fermentation Technology
	Gaurav Singh	Laboratory Animals
	Himanshu Singh	Fermentation Technology
	Kalpana Katiyar	Biochemistry
	Manish Gupta	Biochemistry
	Manish Kumar Maurya	Toxicology
	Mitali Roy Chowdhary	Parasitology
	Neha Tiwari	Molecular & Structural Biology
	Poonam Yadav	Endocrinology
	Priti Singh	Laboratory Animals
	Puja Verma	Endocrinology
	Puspendra Kumar	Toxicology
	Rahul Kumar	Molecular & Structural Biology
	Rahul Yadav	Toxicology

	Ruchi Singh Thakur	Parasitology
	Shalni Agarwal	Biochemistry
	Shilpa Chakravorty	Biochemistry
	Umang Srivastava	Endocrinology
	Usha Kumari	Medicinal & Process Chemistry
	Vandana	Laboratory Animals
	Reshu Srivastava	Molecular & Structural Biology
	Saurabh Pratap Singh	Drug Target Discovery & Development
C. S. J .M. University, Kanpur	Amita Tripathi	Toxicology
	Khushbu Dixit	Fermentation Technology
	Navrose Kaur	Pharmaceutics
	Anand Prerna	Fermentation Technology
	Pushpan Jain	Fermentation Technology
	Akansha Saxena	Molecular & Structural Biology
	Alok Kumar	Biochemistry
	Ankur Srivastava	Molecular & Structural Biology
	Anshi Shukla	Microbiology
	Arti Gupta	Laboratory Animals
	Barkha Singhal	Parasitology
	Jeevan Jyoti	Biochemistry
	Namita Verma	Fermentation Technology
	Puneet Kacker	Molecular & Structural Biology
	Rachita Khanna	Molecular & Structural Biology
	Roop Trivedi	Parasitology
	Shikha Baiswar	Biochemistry
	Deepti Nigam	Molecular & Structural Biology
	Sarah Abbas	Biochemistry
Career College, Bhopal	Neetu Srivastava	Biochemistry
	Prashant M. Srivastava	Biochemistry
Ch. Charan Singh University, Meerut	Ashish Pathak	Molecular & Structural Biology
	Manmohan Singh	Parasitology
	Upendra Singh	Parasitology
	Sharad Verma	Endocrinology
	Shubhda Khanduri	Molecular & Structural Biology
College of Pharmaceutical Science, Berhampur	Bramhanand Dubey	Pharmacokinetic
	Sumant Singh Ajay	Toxicology

College of Life Sciences, Gwalior	Ankit Porwal	Pharmacology
	Geetanjali Bakshi	Parasitology
	Magresh Kumar Singh	Parasitology
	Neha Joshi	Parasitology
	Neha Saxena	Biochemistry
	Nitin Dwivedi	Parasitology
	Ramesh Mohan	Biochemistry
	Aswani Kumar	Parasitology
D.A.V. College, Muzaffarnagar	Neha Rehan	Biochemistry
D.A.V. College, Kanpur	Ishrat Husain	Biochemistry
	Anshita Srivastava	Toxicology
D.D.U. Gorakhpur University, Gorakhpur	Vishalokcchi Ashok	Toxicology
	Mani Kapoor	Fermentation Technology
	Shambhavi Mishra	Parasitology
Dayanand Girls College, Kanpur	Mina Kohli	Medicinal & Process Chemistry
Dev Sanskrit Vishwavidyalya, Hardwar	Abishree Tripathi	Medicinal & Process Chemistry
Devi Ahilya Vishwavidyalaya, Indore	Sandeep Karmarker	Medicinal & Process Chemistry
	Devendra Pal Singh	Medicinal & Process Chemistry
	Hasim Ahmed	Medicinal & Process Chemistry
	Jitendra Kumar Daryari	Medicinal & Process Chemistry
	Manish Dixit	Medicinal & Process Chemistry
	Veena Kumari	Medicinal & Process Chemistry
Dolphin P.G. Institute of Bio-Medical & Nero-Science, Dehradun	Binish Jawed	Toxicology
Doon P.G. College of Agriculture Science, Dehradun	Sapna Katiyar	Fermentation Technology
	Sarita Bharitya	Pharmacology
	Sweety Chauhan	Toxicology
	Vijay Kumar Singh	Pharmacology
	Huma Naz	Fermentation Technology
	Ankit Chaudhary	Fermentation Technology

Dr. B.R. Ambedkar University, Agra	Nandni Nath	Toxicology
Dr. D.Y. Patil Institute, Mumbai	Nimish R Subhedar	Drug Target Discovery & Development
	Niranjana S. Verma	Parasitology
	Rahul Kumar	Endocrinology
	Sanat S. Mishra	Medicinal & Process Chemistry
	Shewta S. Naik	Medicinal & Process Chemistry
	Vivek Yadav	Endocrinology
	Rajkumar Mishra	Molecular & Structural Biology
Dr. H.S. Gour University, Sagar	Divya Pandey	Biochemistry
	Govind Rajan	Toxicology
Dr. Zakir Hussain Institute, Patna	Anjala Kumari	Molecular & Structural Biology
	Priyanka Jain	Molecular & Structural Biology
Guru Nanak Khalsa College, Haryana	Neha Mittal	Medicinal & Process Chemistry
	Shailly Sagoo	Medicinal & Process Chemistry
	Sonia Verma	Medicinal & Process Chemistry
Gurukul Kangri University, Hardwar	Yatendra Verma	Medicinal & Process Chemistry
Gyan Vihar College of P.G. Studies, Jaipur	Ila Sharma	Biochemistry
	Nidhi Sharma	Biochemistry
	Rajesh Kumar Sharma	Fermentation Technology
H.N.B. Garhwal University, Srinagar, Garhwal	Abhishek Trigunaite	Parasitology
I.I.M.T. Medical College & Hospital, Agra	Ashish Bansal	Fermentation Technology
	Nand Kishore	Fermentation Technology
	Gaurav Awasthi	Fermentation Technology
Indira Gandhi Open University, Lucknow	Virandra Thapa	Documentation & Library Services
Institute of Applied Medicine & Research, Ghaziabad	Ajay Mishra	Parasitology
	Tanu Farque Ahmed	Molecular & Structural Biology
	Aarti Saxena	Parasitology
	Amrita Srivastava	Biochemistry
	Sunanda Singh	Biochemistry

Institute of Foreign Trade & Management, Moradabad	Mukesh Kumar Kanojya	Pharmaceutics
Jamia Hamdard University, New Delhi	Ariz Akhtar	Toxicology
	Kamal Kishore	Molecular & Structural Biology
	Raj Kumari	SAIF
Janta College, Bakewar, Etawah	Arpana Singh	Parasitology
	Meenu Agarwal	Microbiology
	Priyanka Gupta	Parasitology
	Jyoti Agrawal	Microbiology
	Rajnikant Shukla	Parasitology
Jiwaji University, Gwalior	Pankaj Tiwari	Pharmacology
K.S.R. College, Truchengode	Dency Oommen	Medicinal & Process Chemistry
Kanya Gurukula Mahavidyalya, Hardwar	Deepika Mishra	Fermentation. Technology
	Shikha Chaurasia	Microbiology
	Shubhangi	Fermentation Technology
Kumaun University, Nainital	Manjari Dwivedi	Fermentation Technology
	Seema Singh	Microbiology
Kurukshetra University, Kurukshetra	Suchi Srivastava	Laboratory Animals
Lucknow University, Lucknow	Deepa Deswal	Biochemistry
	Poorti Srivastava	Biochemistry
M. G. Chitrakoot Gramoday Vishwavidalaya, Chitrakoot	Priyanka Gupta	Medicinal & Process Chemistry
	Shaifali Singh	Medicinal & Process Chemistry
M.B. Khalsa College, Indore	Saurabh Soni	Parasitology
Mahatma Gandhi Institute of Applied Science, Jaipur	Neha Agarwal	Fermentation Technology

Mojhrigarani Institute Sciences & Technology, Rayagada	J. Anuradha	Fermentation Technology
	Tapsi Verma	Fermentation Technology
Manipal College of Pharmaceutical Science, Manipal	Anil Kumar Verma	Medicinal & Process Chemistry
	Ankur	Medicinal & Process Chemistry
	Ashok K. Srivastava	Medicinal & Process Chemistry
	Parul Gupta	Pharmacokinetics
	Ravi Mishra	Medicinal & Process Chemistry
	Shailendra P. Singh	Pharmacology
	Shakti Deep Pachauri	Medicinal & Process Chemistry
	Sunyana Jain	Medicinal & Process Chemistry
	T. Santosh Kumar	Pharmacology
	Lalit Kumar	Medicinal & Process Chemistry
	Sandeep Arora	Medicinal & Process Chemistry
Mata Gujri Mahila Mahavidyalaya, Jabalpur	Vartika Pradhan	Microbiology
Meerut Institute of Engineering & Technology, Meerut	Ratan Kumar Sharma	Fermentation Technology
National Institute of Pharmaceutical Education & Research, Mohali	Sumali Kapoor	Molecular & Structural Biology
	Yaqoot Fatima	Toxicology
Northern India Engineering College, Lucknow	Amit Verma	Medicinal & Process chemistry
	Archana Awasthi	Medicinal & Process Chemistry
	Harish K. Midha	Medicinal & Process Chemistry
	Krishna C. Chaurasia	Medicinal & Process Chemistry
	Manas	Medicinal & Process Chemistry
	Neelam Mishra	Medicinal & Process Chemistry
	Shom P. Kushwaha	Medicinal & Process Chemistry
	Smriti Sharma	Medicinal & Process Chemistry
	Sudhir Sharma	Medicinal & Process
	Neha Mathur	Chemistry Pharmacokinetics
Patna University, Patna	Priyatma	Medicinal & Process Chemistry
R.T.M. Nagpur University, Nagpur	Sanjay G. Wadodkar	Pharmacokinetics

Rai University, New Delhi	Lubna Faruqui Shafali Mehra	Drug Target Discovery & Development Fermentation Technology
Rajiv Gandhi Prouduogiki Vishwavidyalaya, Bhopal	Manoj Raghuvansi Bhawana Chaurasia Pratima Katiyar Sarita Chaurasia	Laboratory Animals Pharmaceutics Medicinal & Process Chemistry Medicinal & Process Chemistry
Dr. R.M.L. Avadh University, Faizabad	Rachna Singh	Fermentation Technology
Sambalpur University, Orrisa	Minarbha Patel	Microbiology
Seedling Academy, Jaipur	Monika Sharma Swati Yadav	Fermentation Technology Fermentation Technology
Shri B.M.N. University, Rohtak	Pravin Kumar MauryaVipin Kumar Agarwal	Medicinal & Process ChemistryPharmaceutics
Shri Baba Mast Nath University, Raipur	Neeraj Kumar Vikrant Silky Sethy	Pharmaceutics Pharmaceutics Pharmaceutics
Shri G. S. Institute of Technology & Science, Indore	Satyakam Singh	Medicinal & Process Chemistry
SS Institute of Advanced Studies & Research, Sardar Shahar, Rajasthan	Kalpana Singh	Microbiology
Subash Chandra Bose College, Gwalior	Saurabh Srivastava	Parasitology
T. John College, Bangalore	Manavi Chatterjee	Pharmaceutics
T.M. Bhagalpur University, Bhagalpur	Priyanka Shweta Singh	Laboratory Animals Endocrinology
Thapar Institute of Engineering & Technology, Patiala	Suraj Kumar Yadav	Toxicology

University of Hyderabad, Hyderabad	Avantika	Fermentation Technology
University of Rajasthan, Jaipur	Kumar S. Verma	Parasitology
	Nidhi Chaudhary	Endocrinology
Uttranchal Institute of Technology, Almora	Neelofar Mirza	Biochemistry
	Shilpee Mishra	Biochemistry
V.B.S. Purvanchal University, Jaunpur	Upendra Yadav	Toxicology
	Pradeep K. Bhaskar	Laboratory Animals
	Sada Shiv	Biochemistry
	Shailendra Dwivedi	Molecular & Structural Biology
	Shobha Tiwari	Drug Target Discovery & Development
Vellore Institute of Technology, Vellore	Neha Bhardwaj	Medicinal & Process Chemistry
	Nehal Begga	Medicinal & Process Chemistry
	Prem Prakash	Medicinal & Process Chemistry
	Punyatoya Patnaik	Medicinal & Process Chemistry
	Rameshwar Sahu	Molecular & Structural Biology
	T. Sundara Pandian	Medicinal & Process Chemistry
	Vivek Yadav	Biochemistry
Vinayaka Mission Research Foundation, Deemed University, Salem	Mohit Makkar	Medicinal & Process chemistry
Women's College, Jamshedpur	Partibha Mishra	
	Rupali Sani	ToxicologyPharmacology

Dr. C.M. Gupta	Resurgence of medicinal herbs in new drug discovery;	Indian Science Congress Ahmedabad, (04.01.05)
	Challenges and opportunities to Indian drugs and pharmaceutical sector in current economic scenario;	Ahmedabad, (11.02.05)
	Could India emerge as a global pharma leader by 2019;	Chandigarh, (25.02.05)
	India's march towards pill revolution;	IIT, Delhi (20.04.05)
	Drug discovery and development: Present and future;	Taj Hotel, Lucknow, (23.03.05)
	A journey through actin cytoskeleton network from mammalian cells to trypanosomatid parasites;	CDRI, Lucknow, (07.11.05)
	Resurgence of natural products in drug discovery: Current international status and priority of CDRI.	KGMU, Lucknow (03.12.05)
Dr. K. P. Madhusudanan	Application of GLC and GC-MS in the analysis of PAHs and pesticides.	ITRC, Lucknow (19.10.05)
Dr. O.P. Asthana	Need & relevance of post marketing surveillance – Phase IV study;	KGMU, Lucknow (23.08.05)
	Drug development; an Indian perspective : Achievements of CDRI.	Biotech Park, Lucknow (22.11.05) CDRI, Lucknow (28.12.05)
Dr. Chandan Singh	Antimalarial peroxides: Synthetic substitutes of artemisinin derivatives;	Mumbai, (19.09.05)
	Antimalarial 1,2,4-trioxanes.	Dibrugarh, Assam (24.10.05)

Dr. A.K. Saxena	Bioinformatics in drug discovery;	Biotech Park, Lucknow (6.12.05)
	Basics of principles and methodologies of 2D & 3D QSAR-Part I;	Biotech Park, Lucknow (6.12.05)
	Basics of principles and methodologies of 2D & 3D QSAR-Part II;	Biotech Park, Lucknow (6.12.05)
	The evolution of molecular recognition and the concurrent innovations in drug discovery research;	Saurashtra University, Rajkot (8.01.05)
	The current scenario of *in silico* drug discovery research;	Pune University, Pune (8.01.05)
	Basics and applications of 2D & 3D QSAR studies in antihistamines H1;	Ahmedabad, (11.02.05)
	Current scenario in drug discovery research;	Indian Habitat Center New Dehli, (12.02.05)
	Futuristic trends in drug development and research;	BHU, Varanasi (5.03.05)
	3D QSAR and its applications;	NIPER, Chandigarh (16.04.05)
	QSAR and global regulatory programs;	Mumbai, (25.04.05)
	Computer aided molecular modeling studies in anti-tubercular agent: pyrazinamid analogues;	Hamburg, Germany (11.06.05)
	Substituted piperazines and related molecules in rational drug design;	Rostock, Germany (14.06.05)
	Collection and preparation of molecular databases for virtual screening;	Shanghai, China (1.11.05)
	Basics concepts, methodologies and application of 2D and 3D QSARs- A case study of antihistamines (H1).	CDFD, Hyderabad (11.11.05)

Dr. Ranjana Srivastava	Identification of new drug targets of *mycobacterium tuberculosis*;	DBT-ICGEB (21.05.05)
	Search for new targets;	INSA, New Delhi (28.04.05)
	Exploring new drug targets in Tuberculosis: Identification of *M. tuberculosis* genes induced *in vivo* by IVIAT approach.	IIT, Kgaragpur (February, 05)
Dr. B. S. Srivastava	Finding genes of *Mycobacterium tuberculosis* required for survival in viable non replicating state and infected macrophages;	DBT-ICGEB (21.05.05)
	Transposons and its use as tool in identification of virulence genes of pathogenic bacteria;	BHU, Varanasi (24.01.05)
	Genetic engineering and recombinant therapeutics;	BHU, Varanasi (25.01.05)
Dr. Ram Raghubir	Novel pharmaceuticals from the ocean;	New Delhi, (25.11.05)
	Novel bioactives from the oceans;	Chennai,(30.12.05)
	Highlights of DOD project: Drugs from sea.	New Delhi, (21.11.05)
Dr. Sudhir Srivastava	Toxicity testing of candidate drugs;	IT College, Lucknow (23.09.05)
	Approach and design of toxicity studies: regulatory considerations;	CDRI, Lucknow
	An overview of special toxicity studies;	CDRI, Lucknow
	Toxicity testing of bio-pharmaceuticals;	CDRI, Lucknow
	Inspection of resources, including test items and test systems;	NOIDA (19.09.05)
	GLP compliance of test facilities;	ITRC, Lucknow (14.01.05)

	Repeat-dose toxicity studies;	New Delhi (24.10.05)
	Histopathological evaluations in toxicity studies;	New Delhi (24.10.05)
	Pathophysiological basis of toxicity.	New Delhi (24.10.05)
Dr. B. Kundu	Solid phase strategies for the design and synthesis of small organic molecules of biological interest;	Mumbai, (28.12.05)
	Impact of combinatorial technologies on medicinal chemistry;	CDRI, Lucknow (21.10.05)
	Combinatorial chemistry in the 21st century drug discovery laboratory;	BHU, Varanasi (7.03.05)
	Solid phase synthesis and characterization of chemical libraries.	MGPG College, Gorakhpur (10.01.05)
Dr. Raja Roy	A proton magnetic resonance cerebrospinal fluid analysis based software as predictor for the differentiation of meningitis in children;	Ahmedabad (6.01.05)
	Applications of multi-pulse NMR techniques in the research field of bio-sciences;	Jamia Hamdard (9.2.05)
	T_1 and T_2 relaxation;	NEHU, Shillong (23.05.05)
	Introduction to fMRI;	NEHU, Shillong (24.05.05)
	Practical aspects of NMR spectra;	NEHU, Shillong (24.05.05)
	Applications of NMR chemistry leading to biological applications;	NEHU, Shillong (27.05.05)
	Contrast agents and molecular imaging;	NEHU, Shillong (1.06.05)

	Unlimited potential of NMR spectroscopy in chemistry and biomedicine.	RRL, Jammu (8.10.05)
Dr. D. C. Kaushal	Developments of vaccine and diagnostics.	CDRI, Lucknow
	Immunology and diagnosis of malaria	CDRI, Lucknow
	Generation of knockout mutants	CDRI, Lucknow
Dr. Uma Roy	*Leishmania donovani* SHMT - putative drug target?	Sicily, Italy (10-15.04.05)
Dr. J. K. Saxena	Identification of new chemotherapeutic targets for design and synthesis of antifilarial agents.	Rajkot (10.01.05)
Dr. Anuradha Dubey	Search for antileishmanial agents from plant and marine resources;	IPMER, Kolkata, (16.01.05)
	Screening of some indigenous plant and marine extracts for their antileishmanial activity.	IPMER, Kolkata, (16.01.05)
Dr. Sanjay Batra	Exploration of Baylis-Hillman reaction in the domain of heterocyclic synthesis: our experiences;	IICT, Hyderabad (23.10.05)
	Combichem technologies: past, present and future;	Taj Residency, Lucknow (14 & 15.05.05)
	Automation in combinatorial chemistry;	CDRI, Lucknow (13.05.05)
	Venture for rapid access to new chemical architectures;	Torrent Research Centre, Gandhinagar (11.01.05)
	Interesting results of hydrogenation studies of Baylis-Hillman derivatives of substituted isoxazolecarbaldehydes;	Rajkot, (08-10.01.05)
	Venture for rapid access to new chemical architectures.	Noida, (06.01.05)

Dr. B. N. Singh	ESTs and functional genomics	Biotech Park, Lucknow
	An approach to bioinformatics and its usefulness in human molecular genetics;	Gwalior, (February, 05)
	Gene expression analysis using in silico methods and high throughput approaches;	Jiwaji University,Gwalior (November, 05)
	Genomics drives approaches to antimicrobial drug discovery.	GBPAU&T, Pantnagar (December, 05)
Dr. J. S. Srivastava	International research ethics;Rational use of drugs.	CDRI, Lucknow (14.10.05) Lucknow (3.06.05)
Dr. Sudhir Sinha	Central Drug Research Institute: A profile;	IICT, Hyderabad (13.01.05)
	Role of high-throughput screening in drug discovery;	NIPER, Mohali (28.02.05)
	Drug target: Brief overview;	INSA, New Delhi (28.04.05)
	Proteomic approach for identification of new drug targets in *Mycobacterium tuberculosis;*	ICGEB, New Delhi (21.05.05)
	CDRI initiatives in the development of anti-TB compounds;	Mumbai (21.09.05) ICGEB,
	Drug development at CDRI;	New Delhi (13.10.05)
	Proteomics as a tool for identification of novel vaccine candidates and drug targets in *Mycobacterium tuberculosis*;	CDRI, Lucknow (10.11.05)
	Mycobacterial protein antigens: Relevance in immunomodulation.	Agra, (14.11.05)
Dr. Ritu Raj Konwar	Total RNA isolation and RT-PCR technique.	IVRI, Izatnagar (5.11.05)

Dr. Neelo Singh	DNA microarray as a screening tool to genes associated with drug unresponsiveness in k*ala azar* (*visceral leishmaniasis*) field isolates;	Kolkata (16.01.05)
	Pteridine reductase 1 (PTRI) as a target for antifolate chemotherapy in *Leishmania donovani*;	IPMER, Kolkata (09.02.05)
	Efflux pump mediated resistance in *Leishmania donvani* clinical isolates.	Goa, (10.12.05)
Dr. Charu Sharma	Destination UP - Biotechnology opportunities;	Biotech Park, Lucknow (23.03.05)
	Microbial pathogenesis of *Mycobacterium tuberculosis* and host response;	ICGEB, New Delhi (21.05.05)
	Building of biological databases;	Biotech Park, Lucknow (18.08.05)
	Genomics and proteomics approaches for drug development;	Biotech Park, Lucknow (22.11.05)
	Recent techniques in gene cloning DNA analysis and functional genomics.	CIMAP, Lucknow (06.12.05)
Dr. G.K. Jain	Pharmacokinetics of Artemisinin derivatives: An overview.	Mumbai (21.09.05)
Dr. Shailja Bhattacharya	Know your parasites and the diseases they cause.	Central School, Lucknow (15.09.05)
Dr. Madhu Dikshit	Flow cytometry: A powerful technique to evaluate potential drug molecules and their toxicity;	ITRC, Lucknow, (1.12.05)
	Flow cytometric evaluation of free radical generation from neutrophils: An exploration;	ITRC, Lucknow, (1.12.05)
	Neutrophil functions and ascorbic acid: An exploration;	Banglore, (09.1.05)

	Nitric oxide synthase localization and modulation of polymorhonuclear leukocytes functions by nitric oxide;	Kolkatta, (14.1.05)
	Oxidative burst and free radical monitoring;	Chandigarh, (16.2.05)
	Nitric oxide - Neutrophils - free radical generation: Marker for pathological conditions?	Kolkata,(25.11.05)
Dr. Kapil Kapoor	Non-invasive assessment of cardiac output in rats by impedance cardiography.	KGMU, Lucknow (01-19.2.05)
Dr. Chandishwar Nath	Effect of aging on passive avoidance learning and brain acetylcholinesterase activity in rat;	Kolkatta, (14.1.05)
	Brain acetylcholinesterase activity in learning and memory functions.	Gwalior
Dr. Gautam Palit	Peptic ulcer disease - evaluation of an anti-ulcer compound from preclinical to clinical stage;	Aligarh, (14.2.05)
	Evolution of anti-ulcer compound from preclinical to clinical stage;	Kolkata, (28.4.05)
	Plant based therapeutic approach for adverse physiological and psychological implications of stress response;	Kolkata, (4.08.05)
	A noble concern: Development of anti-gastric ulcer drug.	Bhavnagar(11.11.05)
Dr. K.G. Raghu	Ion channel and its importance in drug discovery;	Ahmedabad, (3.05.05)
	Ion channel as a potential target for drug development.	Tiruchirapilli,(24.02.05)

Dr. B. N. Singh	ESTs and Functional Genomics;	Biotech Park, Lucknow (February 05)
	An approach to bioinformatics and its usefulness in Human Molecular genetics;	Jiwaji University, Gwalior(November 05)
	Gene expression analysis using in silico methods and high throughput approaches;	Pantnagar (Dec. 05)
	Genomics driven approaches to antimicrobial drug discovery.	BHU, Varanasi, (17.3.05)
Dr. Rakesh Shukla	Biochemical and immunological mediators of inflammation: An update; Role of cytokines in inflammation.	DIPSAR, New Delhi, (25.11.05)
Dr. P.Y. Guru	Application of GLP and CPCSA guidelines in test system: characterization, maintenance and usage for non-clinical safety studies;	ITRC, Lucknow (14.01.05)
	Animals in drug research;	CDRI, Lucknow (02.09.05)
	Animal ethics and regulations;	CDRI, Lucknow (30.09.05)
	Wonders of life sciences.	CDRI, Lucknow (27.12.05)
Dr. R. K. Singh	Mechanism of toxicity;	Lucknow (September 05)
	Reproductive toxicity;	Lucknow (September 05)
	Hepatotoxicity;	Lucknow (September 05)
	Cardiovascular toxicity;	Lucknow (September 05)
	Nephrotoxicity;	Lucknow (September 05)
	Cardiovascular toxicity;	IIT, Kharagpur (25.05.05)
	Thrombophilia;	IIT, Kharagpur (25.05.05)

	Disseminated intravascular coagulation.	IIT, Kharagpur (25.05.05)
Dr. S.K. Rath	SNP resources for genetic disorders;	Biotech Park, Lucknow (11.01.05)
	Importance of SNP database;	Biotech Park, Lucknow (17.08.05)
	Pharmacogenomics and new drug development;	Biotech Park, Lucknow (23.11.05)
	Importance of SNPs and their application.	CIMAP, Lucknow (08.12.05)
Dr. Sharad Sharma	Key features of different types of toxicity studies.	CDRI, Lucknow
Dr. Neeraj Sinha	Assays for detection of apoptosis in fishes – DNA ladder assay and 3' –OH end labeling assay;	NBFGR, Lucknow (28.02.05)
	How our body works;	CMS, Lucknow (12.09.05)
	Good laboratory practice – practical aspects	CDRI, Lucknow
	Testing for reproductive toxicity of candidate drugs.	CDRI, Lucknow
Vinay Tripathi	Management of IP: CDRI experiences	Lucknow (5.10.05)

IX. DISTINGUISHED VISITORS / LECTURES

Dr. Simon Croft **Director** **DNDi** **Geneva.**	"Drug Development for Leishmaniasis: Advances, Problems and New Directions." (7.2.05)
Mr. Sanjay Mohan **Director** **Secondary Education** **Government of Uttar Pradesh** **Lucknow.**	Chief Guest in CSIR Scheme on Faculty Training and Motivation & Adoption of Schools/Colleges. (14.2.05)
Prof. R.P. Singh **Vice Chancellor** **University of Lucknow** **Lucknow**	Presidential Address in CSIR Scheme on Faculty Training and Motivation & Adoption of Schools/Colleges. (14.2.05)
Dr. Sandip K. Basu **Director** **National Institute of Immunology** **New Delhi.**	*30th Mellanby Memorial Oration* "Chasing Ehrlich's Dream: Receptor Mediated Manipulations of Macrophage Metabolism". (17.2.05)
Dr. M.K. Bhan **Secretary** **Department of Biotechnology** **New Delhi**	Chief Guest in 54th Annual Day Celebrations. (17.2.05)
Prof. Mahendra Bhandari **Vice Chancellor** **King George's Medical University** **Lucknow**	Presidential Address in 54th Annual Day Celebrations. (17.2.05)
Prof. Mohan Raizada **University of Florida** **USA**	*9th Dr. C.R. Krishna Murti Memorial Oration*" Is Gene Therapy for Hypertension Possible?" (9.3.05)
Dr. Hemant Majumdar **Deputy Director** **IICB** **Kolkata**	"A Tale of Two Sub-units of *Leishmania donovani* Topoisomerase I: A Living Bridge in Eukaryotic Evolution" (6.4.05)

Prof. Ajoy Ghatak **Emeritus Professor** **Physics Department** **Indian Institute of Technology** **New Delhi**	*Dr. Biren Roy Memorial Lecture* "The Amazing Story of the Optical Fiber". (26.4.05)
Dr. Scott Leppanen **Stratagene** **USA**	"Real Time PCR and its Applications". (25.5.05)
Dr. Rajeev K. Agarwal **National Institute of Health** **USA**	"Transgenic Animals: Natural and Therapeutic Regulation of Autoimmunity to Retinal Antigens". (5.7.05)
Prof. Samir Bhattacharya **Department of Zoology** **Visva-Bharati** **Santiniketan**	*8th Dr. B. Mukerji Memorial Lecture* "Free Fatty Acid Induced Insulin Resistance and Diabetes Type 2: Understanding of the Underlying Mechanism and Need for New Therapy". (6.7.05)
Dr. Vivek Kumar Garg **Senior Consultant** **Lucknow Cancer Institute** **Lucknow**	"Myth and Facts of Cancer". (19.7.05)
Dr. Akihiko Kusai **JEOL** **Japan**	"Mass Spectrometry in Open Air With DART Techniques & Applications". (26.8.05)
Mr. N. Balasubramanian **Chairman & Managing Director** **Small Industries Development** **Bank of India** **Lucknow**	Chief Guest in the Conference "Small and Medium Pharma Enterprises in Uttar Pradesh: Challenges and Prospects". (19.9.05)
Mr. Atul Kumar Gupta **Industrial Development** **Commissioner Uttar Pradesh** **Lucknow**	Presidential Address in the Conference "Small and Medium Pharma Enterprises in Uttar Pradesh: Challenges and Prospects". (19.9.05)
Mr. Vir Saxena **Secretary** **UP Drug Manufacturers Association** **Lucknow**	"Problems of SME vis-à-vis New Schedule M". (19.9.05)

Mr. Satguru Prasad **Drug Controller** **Uttar Pradesh** **Lucknow**	"Revised Schedule M – A Need of Hour to Meet International Challenges and Prospects". (19.9.05)
Dr. Rajesh Maheshwari **Accreditation Officer** **Dept. of Science & Technology** **New Delhi**	"Calibration in Laboratory Practice for Quality Assurance". (19.9.05)
Dr. (Mrs.) Sunita Kumar **Deputy Director (Chem.)** **Office of the Development Commissioner** **Small Scale Industry** **New Delhi**	"Government Facilities for Small Scale Industry Sector". (20.9.05)
Dr. Deepak Pental **Vice Chancellor** **University of Delhi** **Delhi**	"Molecular Biology and Precision Breeding of Crops". (26.9.05)
Dr. A. Upadhyaya **Dept. of Materials & Metallurgical Engineering** **Indian Institute of Technology** **Kanpur**	"Advances in Particulate Materials". (21.10.05)
Dr. Ram Lal **Additional Director General** **Vigilance Commission, U.P.**	"Vigilance Awareness". (21.11.05)
Dr. Raj K. Singh **President & Chief Scientific Officer** **Vivo Biosciences Inc.** **Bormingham** **USA**	"New Human Bioassay Platform for Preclinical Research and Drug Discovery: IIU Biogel Assay Technology". (12.12.05)
Dr. (Ms.) Pooja Jain **Assistant Professor** **Institute of Molecular Medicine & Infectious Disease** **University College of Medicine, Philadelphia** **USA**	"Retroviral Oncoprotein Tax and the Development of Anti-HIV Microbicidal Agents". (23.12.05)

X. MEMBERSHIP OF COMMITTEES / BOARDS

Dr. C.M. Gupta

Member, Scientific Advisory Committee of *Drugs for Neglected Diseases initiative (DNDi)*, Geneva;

Chairman, Joint National Committee for Biochemistry & Molecular Biology and Microbiological Science;

Chairman, DBT Reconstituted Review Committee on Genetic Manipulation;

Chairman, DST Expert Committee on Pharmaceutical Research & Development Support Fund;

Chairman, Committee of Ministry of Chemicals & Fertilizers for Granting Exemption from Price Control under DPCO, 95;

Chairman, Scientific Advisory Committee of Tuberculosis Research Centre (ICMR), Chennai;

Chairman, Scientific Advisory Committee of National Institute for Research in Reproductive Health (ICMR), Mumbai;

Member, ASSOCHAM Pharmaceuticals Committee;

Member, FICCI Pharmaceuticals Committee;

Member, CII National Pharmaceutical Committee;

Member, Medical Biotechnology Development Board of DBT;

Member, Promotions and Assessment Committee of Indian Institute of Science, Bangalore;

Member, Drug Development Promotion Board, Govt. of India;

Member, ICMR Scientific Advisory Board;

Member, Governing Body of National Centre for Cell Science;

Member, Scientific Advisory Committee of AIDS Research Institute (ICMR), Pune;

Member, Scientific Advisory Committee of National Center for Cell Science, Pune;

Member, Scientific Advisory Committee of National Institute of Immunology, New Delhi;

Member, DBT Biotechnology Research and Promotion Committee;

Member, Academic Council of Jawaharlal Nehru University, New Delhi;

Member, Governing Body of Institute of Clinical Research, Dehradun & Mumbai;

	Member, Drugs Technical Advisory Board; Govt. of India;
	Member, Board of Directors of Bharat Immunologicals & Biologicals Corporation Ltd.;
	Member, DST Project Advisory Committee in the Area of Health Sciences.
Dr. B.S. Srivastava	Member, Research Council, IMTECH, Chandigarh;
	Member, Animal Sciences and Biotechnology Research Committee, HRD, CSIR, New Delhi;
	Member, Ethics Committee, SGPGI, Lucknow;
	Member, Research Degree Committee in Biochemistry, CSJM Kanpur University;
	Member, Research Degree Committee in Biotechnology, GND University, Amritsar;
	Member, Biotechnology Task Force, UPCST, Lucknow;
	Member, Special Committee of School of Environmental Sciences, New Delhi.
Dr. Vinod Bihari	Member, Board of Studies for Biotechnology Programme, B.I.T., Ranchi;
	Member, Board of Studies for M.Sc. (Biotechnology), V.B.S. Purvanchal University, Jaunpur;
	Member, Board of Studies for M.Tech. in Biochemical Engineering, I.T., B.H.U., Varanasi;
	Member, Core Group on Biotechnology, Council of Science & Technology, U.P., Lucknow;
	Member, Adhoc Expert Committee for Project Evaluation of TDB (2003);
	Member, Management Council of NBRI, Lucknow (2003 - 2005);
	Member, Screening cum Technical Evaluation Committee for National DSIR R&D Awards (2003);
	Member, Board of Studies, Post Graduate Programme in Applied Microbiology, V.B.S., Purvanchal University, Jaunpur, (2003);
	Member, Board of Studies, B. Tech. (Biotechnology) Programme, Himachal Pradesh University, Shimla, (2003);
	Member, Board of Studies for Microbiology, RML Avadh University, Faizabad, (2003);
	Chairman, Expert Committee for Biotechnology, Council of Science & Technology, U.P., Lucknow.

Dr. K. P. Madhusudanan	Member, Editorial Board, Journal of Mass Spectrometry, John Wiley & Sons, UK.
Dr. O.P. Asthana	Member, Scientific Advisory Committee of NLAC, National Institute of Nutrition, Hyderabad;
	Member, Panel of Project Reviewers, UPCST;
	Member, Panel of Project Reviewers, DST;
	Member, Panel of Referees, Indian Journal of Biotechnology;
	Member, Selection Committee, CDRI, Lucknow;
	Member, Selection Committee, NEERI, Nagpur;
	Member, Selection Committee, ITRC, Lucknow;
	Chairman, Selection Committee, CEERI, Pilani;
	Invited Faculty Member, Institute of Clinical Research (India), New Delhi.
Dr. Zaka Imam	Member, Editorial Board, CDRI Annual Report 2005-06;
	Member, Editorial Board, International Journal of Health Technology & Management, Inter Science Enterprises Ltd., UK.
Dr. A.K. Saxena	Member, Board of International Charitable Foundations (Scientific Partnership) Co-ordinating Board, Russia;
	Member, Editorial Board, International Journal Medicinal Chemistry Research;
	Member, Board of Directors, American Bibliography Inc. USA;
	UGC Nominee, Advisory Committee, Special Assistance Programme, Department of Chemistry, Saurastra University, Rajkot;
	UGC Nominee, Advisory Committee, Special Assistance Programme, Department of Chemistry, A. P. S University, Rewa;
	Patent Evaluator for Current Drugs Ltd., U.K.;
	Secretary, QSAR Society of India;
	Member, American Chemical Society, USA;
	Life Member, Indian Chemical Society;
	Life Member, Indian Association of Medicinal Chemists;
	Life Member, UP Association for Science and Technology Advancement.
Dr. S.C. Agarwal	Member, Governing Body, Institute of Ethnobiology, Jiwaji University, Gwalior;
	Member, Editorial Board, Ocean Drugs Alert Bulletin, CDRI, Lucknow.

Dr. Ranjana Srivastava	Member , IBSC, ITRC, Lucknow; Member, Doctoral Committee, SGPGI, Lucknow
Dr. Satyawan Singh	Member, Drug Panel for New Drugs Manufacturing Licenses, Directorate of Medical & Health Services, U.P., Lucknow; Member, Expert Panel for Inclusion of Plant Based and Herbal Drugs in Indian Pharmacopoeia, New Delhi; Member, Ecomark Technical Committee, Central Pollution Control Board, Ministry of Environment & Forests, New Delhi.
Dr. Sudhir Srivastava	Life Member, National Academy of Sciences, Allahabad, India; Life Member, Society of Toxicology, India; Life Member, Indian Medical Association; Fellow, German Academic Exchange Service, Bonn, Germany; Member, Home Grown Technology (HGT) Project Activity Monitoring Committee of TIFAC, DST, New Delhi; Member, Histochemical Society, Washington; Life Member, UP Association of Science and Technology.
Dr. P.K. Roy	Chief Editor, Drugs and Pharmaceuticals - Industry Highlights, CDRI, Lucknow ; Chief Editor, Drugs and Pharmaceuticals - Current R&D Highlights, CDRI, Lucknow ; Chairman, Lucknow Special Libraries Consortium, CDRI, Lucknow.
Dr. R. K. Sharma	Member, Editorial Board, Ocean Drugs Alert, CDRI, Lucknow.
Dr. Ram Raghubir	Secretary, Indian Pharmacological Society (Lucknow Branch); Member, Doctoral Committee, SGPGIMS, Lucknow, IVRI, Izatnagar; Chairman, Ocean Drug Alert, CDRI, Lucknow ; Member, Editorial Board, Drugs & Pharmaceuticals, Current R & D Highlights ; Member, Editorial Board, Indian Journal of Pharmacology.
Dr. Ashim Ghatak	Member, Adjudicating Committee, Indian Pharmacology Society for Awards & Orations – 2004-05; Member, Assessment Committee, NML, Jamshedpur ; Elected Secretary General, Indian Society of Hypertension 2004-06.

Dr. Sudhir Sinha	Coordinator, CSIR Networked Project "Molecular Biology of Selected Pathogens for Developing Drug Targets".
Dr. G. Bhatia	Member, Indian Society of Atherosclerosis.
Dr. R.K. Singh	Life Member, Society of Toxicology, India; Life Member, National Academy of Sciences, Allahabad; Life Member, Asian Society of Andrology; Life Member, All India Society of Intellectuals.
Dr. S.K. Rath	Member, C.S.I.R Committee for Use of Alternative Animal Models, CSIR Co-ordinated Project ; Member of Expert Committee for Genotoxicity of RISU at ICMR; Member, Doctoral Committee, ITRC, Lucknow; Member, Institutional Animal Ethics Committee, University of Allahabad; Life Member, ADNAI.
Dr. Sharad Sharma	Member, Core Committee of National GLP Compliance Monitoring Authority.
Dr. Neeraj Sinha	Life Member, Society of Toxicology, India; Life Member, ISCA; Life Member, Laboratory Animal Science Association of India; Life Member, Indian Society of Cell Biology; Life Member, National Academy of Science, Allahabad.
Dr. P.Y. Guru	Livestock Feeds Sectional Committee of Bureau of Indian Standards (Fad-5), New Delhi; Livestock Husbandry Equipment's and Systems. Sectional Committee of Bureau of Indian Standards (Fad-60), New Delhi; Member, Core Group for Designating Primate Breeding Facility of IRR, Mumbai at Sasunawghar, Thane District, (Maharashtra); Institutional Animal Ethics Committee, ITRC, Lucknow; Member, Institutional Animal Ethics Committee, Homeopathic Drug Research Institute (HDRI), Lucknow;

	Member, Institutional Animal Ethics Committee, Era's Medical College, Lucknow;
	Member, Institutional Animal Ethics Committee, Central Institute of Medicinal and Aromatic Plants (CIMAP), Lucknow;
	Faculty Member, CDRI-JNU Course on Biotechnology and Drug Development;
	CPCSEA Nominee in IAEC of Indian Animal Supplier, Lucknow;
	CPCSEA Nominee in IAEC of development of Biotechnology, Lucknow University, Lucknow;
	CPCSEA Nominee in IAEC of Jawaharlal Nehru Medical College, Aligarh Muslim University, Aligarh;
	CPCSEA Nominee in IAEC of IVRI Mukteshwar Campus, Distt. Nainital;
	CPCSEA Nominee in IAEC of Biological Products Institute, Directorate of Animal Husbandry, Badshahbagh, Lucknow.
Dr. Vinod Bhakuni	Member, DST, PAC;
	Member, DBT, Post Doctoral Committee;
	Joint Secretary, Indian Society of Chemists and Biologists.
Dr. A.K. Balapure	Member, Executive Committee, Indian Pharmacological Society.
Dr. G.K. Jain	Life Member, UP Association for Advancement of Science & Technology;
	Life Member, Indian Pharmaceutical Association;
	Member, "Official Side of the Local Council of CSIR" for Adoption of Central Civil Services Rules, 1993 & for Establishment of Joint Consultative machinery.
Dr. A.K. Dwivedi	Member, Expert Committee, Dr. B.R. Ambedkar University, Agra;
	Life Member, UP Association for Advancement of Science & Technology;
	Life Member, Indian Pharmaceutical Association;
	Member, Expert Committee, Kakatiya University, Warangal.
Dr. R.C. Tripathi	Member, Editorial Board, CDRI Annual Report-2005-06;
	Member, Research Board of Advisors, American Bibliographical Institute.

Dr. J.K. Saxena	Member, B.Tech. Expert Committee, IIT, Roorkee; Member, Agriculture Research Service Examination Board, 2005; Member, Expert Committee of M.Sc. Examination in Biochemistry, Lucknow University, Lucknow; Member, Expert Committee of Biotechnology, BHU, Varanasi; Member, Expert Committee, IVRI, Izatnagar.
Dr. Uma Roy	Member, Expert of Research Degree Committee, Chhatrapati Shauji Maharaj University, Kanpur.
Dr. Neena Goyal	Member, Doctoral Committee, ITRC, Lucknow.
Dr. V. K. Bajpai	Member, Editorial Board, E.M.S.I. Bulletin, Kanpur.
Mr. Janki Prasad	Associate Member, Institution of Engineers (India); Member, Indian Institute of Chemical Engineers, Kolkata.
Dr. Gautam Panda	Member, UP Association for Science and Technology, UP, India; Member, Chemical Research Society of India, Bangalore, India.
Dr. P.K. Shukla	Joint Secretary, International Society of Applied Biology, India; Member, Editorial Board, Asian Journal of Biochemistry, Academic Journals Inc, USA.
Dr. Kumkum Srivasatava	Life Member, The Society of Biological Chemists, India, Bangalore.
Dr. A. K. Srivastava	Member, Infectious Diseases Biology, Department of Biotechnology, Government of India, New Delhi.
Mr. S.M. Rajendran	Member, Executive Council of Ethnobotanists, NBRI, Lucknow; Member Organizing Committee Silver Jubilee Symposium on Ethnobotany in the New Millennium, NBRI, Lucknow.
Dr. M. Dikshit	Member, Editorial Board, Indian Journal of Pharmacology; Member, Editorial Board, National Academy of Sciences, India; Member, Editorial Board, Drugs & Pharmaceutical Industry Highlights; Member, Doctoral Committee, SGPGIMS & ITRC, Lucknow.

Dr. C. Nath	Member, Animal Ethics Committee, ITRC; Member, Selection Committee, ITRC.
Dr. Gautam Palit	Member, Project Review Committee Department of Scientific & Industrial Research (DSIR), DST, New Delhi; Member, Advisory Committee for the Seminar & Clinical Research-Practice and Prospects, Kolkata; Member, Scientist's Assessment Committee, RRL, Jammu; Member, Internal Review Committee, ITRC, Lucknow; Member, Task Force Committee, CSIR Coordinated Programme on Bioactive Substances from Plant Sources (Anti-ulcer group); Member, Board of Examinees, Jadavpur University, Kolkata.
Dr. Rakesh Shukla	Vice President, Indian Pharmacological Society 2004; Treasurer, Indian Society of Hypertension 2003-2006; Course Co-ordinator, CDRI-JNU Ph.D. Programme; Reviewer, Indian Journal of Pharmacology.
Dr. A.K. Srivastava	Life Member, UP Association of Science and Technology; Life Member, Indian Society of Parasitology; Member, Animal House Working Committee, CDRI, Lucknow.
Dr. D. Hansda	Life Member, Indian Association of Veterinary Microbiologists, Immunologists and Specialists in Infectious Diseases; Life Member, W.B. Veterinary Council under Veterinary Council of India (V.C.I.).
Dr. A.K. Goel	Executive Editor, Ocean Drugs Alert Bulletin, CDRI, Lucknow; Executive Editor, CDRI Annual Report 2005-06.
Dr. Rajendra Prasad	Life Member, UP Association for Advancement of Science & Technology; Member, Editorial Board, CDRI Annual Report 2005-06.
Dr. V.G.M. Nair	Member, Editorial Board, CDRI Annual Report 2005-06.
Mr. Vinay Tripathi	Member, Editorial Board, Ocean Drugs Alert Bulletin, CDRI, Lucknow; Member, Editorial Board, CDRI Annual Report 2005-06.
Dr. D.N. Upadhyay	Life Member, Society for Advancement of Electrochemical Science & Technology; Member, Editorial Board, CDRI Annual Report 2005-06.

Dr. C.M. Gupta	***Geneva, Switzerland,*** To attend the SAC meeting of drugs for Neglected Diseases Initiative (DnDi).(2-5 April 2005).
Dr. J. S. Srivastava	***South Africa***, To attend International MHSc (Bioethics) Graduate Workshop.(19-22 July 2005).
Dr. Y.S. Prabhakar	***Germany***, To attend CSIR-DAAD Exchange Programme. (1 April-28 June 2005).
Dr. A. K. Saxena	***Germany,*** To attend the 8th Congress fur Infektionskrankheiten and Treopenmedizin. (9-11 June 2005); ***Germany,*** To deliver an invited lecture at University of Rostock, Institute of Chemistry.(14 June 2005); ***Germany,*** Resumption of AVH fellowship to work on "Quantitative Structure-activity Relationships Studies in 2-Phenylimidazo[1,2-a] Pyridine-3-Carboxylic Acid Derivatives Using Artificial Neural Networks (ANN)".(14 March - 13 April 2005); ***China,*** To deliver an invited lecture in 3rd International Symposium on "Computational Methods in Toxicology and Pharmacology Integrity Alternate Resources".(29 October - 1 November 2005).
Dr. Neena Goyal	***Italy,*** To participate in Third World Congress on Leishmaniasis.(10-15 April 2005).
Dr. Neelo Singh	***Italy,*** To participate in Third World Congress on Leishmaniasis.(10-15 April 2005).
Dr. A. N. Gaikwad	***USA,*** To discus collaborative opportunities between Procter and Gamble and learn some of assay technologies. (26 March - 2 April 2005).
Dr. Sudhir Srivastava	***Geneva, Switzerland,*** To participate in the meeting for finalization of the WHO publication "Quality Practices in Basic Biomedical Research".(25 – 26 January 2005). ***Ghana***, To attend refresher course for Good Laboratory Practice trainers.(7-12 August 2005).
Dr. Vinod Bhakuni	***France***, To attend 15th ESBA International Biophysics Congress. (27 August-1 September 2005).
Dr. (Mrs.) Saman Habib	***Germany,*** To attend Indo-German Workshop on Recent Advances in Global Research in Infectious Diseases. (16 -18 June 2005).
Dr. Jawahar Lal	***Germany,*** To attend INSA-Bilateral Exchange Programme. (14 September to 14 December 2005).
Dr. Renu Tripathi	***U.K.,*** To attend DNDi Sponsored Training "*In Vitro* Assay of Drugs against *Trypanosoma* b*rucel.* (7 November - 7 December 2005).

XII. HONOURS & AWARDS

Several scientists of this Institute received Honours and awards for their outstanding performance/contributions in their fields.

Dr. C.M. Gupta	2004 Panjab University Pharmaceutical Science Oration, Panjab University, Chandigarh (2005);
	Platinum Jubilee Lecture Award from Indian Science Congress, Ahmedabad (2005);
	Prof. V. Ramakrishna Memorial Lecture Award from Indian Institute of Technology, Delhi (2005);
	Gujral – Bhargava Memorial Oration Award from KGMU, Lucknow (2005).
Dr. (Ms.) Ranjana Srivastava	CSIR New Idea Fund;
	Best Poster Award for Paper on "Production of Antibodies Against Intact Microfilariae of *S. cervi*" at 17th National Congress of Parasitology, Dibrugarh (22.10.05 to 26.10.05).
Dr. Ram Raghubir	Elected as Vice President, Indian Pharmacological Society 2005.
Dr. G. Palit	Dr. D.N. Prasad Memorial Oration Award and Gold Medal, by Indian Council of Medical Research.
Dr. C. Nath	Prof. G. Achari Oration Award 2005 by Indian Pharmacological Society.
Dr. Atul Goel	Young Scientist Award 2005 by Council of Science and Technology, Govt. of Uttar Pradesh, Lucknow.
Dr. Anup Kumar Misra	CSIR Young Scientist Award-2005 in Chemical Sciences.
Ms. Prachi Bhargava	Best Poster Award for Paper on "Homology Modeling and Substrate Binding Study of *Leishmania donovani* Serine Hydroxymethyltransferase" at 17th National Congress of Parasitology, Dibrugarh (22.10.05 to 26.10.05).
Ms. Ritu Malik	Best Paper Award for Paper "Insights Offered by Amathetical Model of the Hypothalamus Pituitary Testicular Axis on Transdermal Testerone Delivery for Male Conreaception" at 6th Controlled Release Society International Symposium at Mumbai (18.2.05 to 19.2.05).
Ms. Sushma Chaubey	Young Scientist Award on paper Translation within the *Plasmodium falciparum* Apicoplast.

XIII. BUDGET

2005-06 (Sanctioned Estimates)*

	Heads		(Rs in Lakhs)
(a)	***Recurring***		
	Pay & Allowances		1464.200
	Contingencies		152.200
	HRD		4.000
	Maintenance		88.000
	Staff Quarter Maintenance		9.000
	Chemicals & Consumables		80.000
		Sub-Total	**1797.400**
(b)	***Capital***		
	Works & Services		6.500
	Equipments and Office Equipments		160.000
	Furniture and Fittings		2.000
	Library Books & Journals		140.000
		Sub-Total	**308.500**
(c)	**Network Projects**		**687.357**

*Including Network Projects

2004-05 (Actual Expenditure)#

	Heads		(Rs in Lakhs)
(a)	***Recurring***		
	Pay & Allowances		1487.867
	Contingencies		190.026
	HRD		4.170
	Maintenance		125.231
	Staff Quarter Maintenance		17.049
	Chemicals & Consumables		330.733
		Sub-Total	**2155.076**
(b)	***Capital***		
	Works & Services		19.690
	Equipments		354.152
	Furniture and Fittings		2.377
	Library Books & Journals		190.126
	Vehicles		0.144
		Sub-Total	**566.489**
(c)	**Network Projects**		**1180.807**
		Grand Total	**3902.372**

#Including Network Projects, LRF and C/F 2003-04.

XIV. RESEARCH COUNCIL

(2005 - 06)

Chairman

Prof. N.K. Ganguly
Director General
Indian Council of Medical Research
Ansari Nagar, New Delhi - 110 029.

Members

Dr. Sudarshan K. Arora
President R & D
Lupin Ltd. (Research Park)
46 A / 47 A, Village Nande, Taluka Mulshi, Pune.

Dr. Sandeep K. Basu
Director
National Institute of Immunology
Aruna Asaf Ali Marg
New Delhi - 110 067.

Dr. A. Surolia
Department of Molecular Biophysics Unit
Indian Institute of Science
Bangalore - 560 012.

Dr. M.G. Deo
Visiting Professor
School of Health Sciences
University of Pune
C-13, Kubera Gulshan Apartment, D.P. Road, Aundh
Pune - 411 007.

Prof. S.K. Brahmachari
Director
Institute of Genomics and Integrative Biology
University Campus, Mall Road
New Delhi - 110 007.

Dr. M.D. Nair
Former Vice President, SPIC Pharmaceuticals
A-11 Sagarika No. 15, 3rd Seaward Road
Valmiki Nagar, Thiruvanmiyur
Chennai - 600 041.

Secretary
Department of Biotechnology
Block 2, CGO Complex
Lodi Road, New Delhi - 110 003.

Dr. Y.K. Gupta
Former Director
Industrial Toxicology Research Centre
Lucknow - 226 001.

Dr. C.M. Gupta
Director
Central Drug Research Institute
Lucknow - 226 001.

Dr. O.P. Agarwal
Council of Scientific & Industrial Research
Rafi Marg
New Delhi - 110 001.

Secretary
Dr. S.B. Katti
Scientist F
Central Drug Research Institute
Lucknow - 226 001.

XV. MANAGEMENT COUNCIL

(1.7.2003 to 30.6.2005)

Chairman
Director
Central Drug Research Institute
Lucknow.

Members
K.P. Madhusudanan
CDRI.

Dr. M.M. Singh
CDRI.

Dr. Vinod Bhakuni
CDRI.

Dr. Neena Goyal
CDRI.

Mr. A.H. Ansari
CDRI.

Dr. S.P.S. Khanuja
Director
CIMAP.

Dr. Zaka Imam
CDRI.

Sr. Finance & Accounts Officer
CDRI.

Member - Secretary
Controller of Administration
CDRI.

XVI. THE STAFF

Director
C.M. Gupta, M.Sc., Ph.D. (Agra), FNA, FASc., FNASc.

R & D DIVISIONS / UNITS

BIOCHEMISTRY

Scientist Group IV(4)
J.K. Saxena, M.Sc. (Lucknow), Ph.D. (Kanpur), *In-Charge*
Uma Roy, M.Sc., Ph.D. (Kanpur)
A.K. Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)
Gitika Bhatia, M.Sc., Ph.D. (Agra) (MOH & FW Scheme)

Scientists Group IV(3)
Neena Goyal, M.Sc.(Lucknow), Ph.D. (Agra)

Scientists Group IV(2)
P.K.S. Visen, M.Sc. (Meerut), Ph.D. (Kanpur)
Anju Puri, M.Sc. (Kanpur), Ph.D. (Lucknow)

Scientist Group IV(1)
A.K. Tamrakar, M.Sc. (Gwalior)

Scientists Group III(6)
S.M. Kaul, M.Sc. (Lucknow), Ph.D. (Kanpur)
M.M. Khan, M.Sc., Ph.D. (Kanpur)

Scientist Group III(5)
A.K. Khanna, M.Sc. (Lucknow), Ph.D. (Kanpur)

BOTANY

Scientist Group IV(5)
S.C. Agarwal, M.Sc., Ph.D. (Lucknow), *In-charge*

Scientists Group IV(3)
M.N. Srivastava, M.Sc. (Kanpur), Ph.D. (Lucknow)
S.M. Rajendran, M.Sc. (Madurai Kamraj)

Scientists Group IV(1)
K.R. Arya, M.Sc. (Kumaon), Ph.D. (Kanpur)
D.K. Mishra, M.Sc. (Vidyasagar), Ph.D. (Pune)

CLINICAL & EXPERIMENTAL MEDICINE

Scientists Group IV(5)
O.P. Asthana, M.B.B.S., D.C.H., M.D. (Lucknow), FNASc., *In-Charge*
S.P.S. Gaur, M.B.B.S., M.D. (Lucknow)
A. Ghatak, M.B.B.S., M.D. (Lucknow), FICP
J.S. Srivastava, M.B.B.S., M.D. (Lucknow), D.M. (Chandigarh)

Scientist Group III(6)
A.K. Nigam, M.Sc. (Kanpur)

Scientist Group III(5)
O.S. Tiwari, M.Sc. (Lucknow), Ph.D. (Faizabad)

DRUG TARGET DISCOVERY AND DEVELOPMENT

Scientist Group IV(4)
Sudhir K. Sinha, M.Sc. (Lucknow), Ph.D. (Kanpur), *In-Charge*

Scientist Group IV(3)
Neeloo Singh, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(2)
Charu Sharma, M.Sc.(Lucknow), Ph.D. (Chandigarh)
Uday Bandyopadhyay, M.Sc. (Kolkata), Ph.D. (Jadavpur)

Scientist Group IV(1)
Anil N. Gaikwad, M.S.(Pharm.) (NIPER, Chandigarh)

Scientist Group III(5)
S.L. Verma, B.Sc.

ENDOCRINOLOGY

Scientist Group IV(5)
M.M. Singh, M.Sc., Ph.D., D.Sc. (Lucknow), FNASc *In-Charge*

Scientists Group IV(4)
B. Malaviya, M.Sc., Ph.D. (Banaras) [Retired on 30.6.04]
Archana Srivastav, M.Sc., Ph.D. (Lucknow)
Govind Keshri, M.Sc. (Lucknow), Ph.D. (Agra)

Scientists Group IV(3)
Anila Dwivedi, M.Sc. (Lucknow), Ph.D. (Kanpur)
Gopal Gupta, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(2)
F.W. Bansode, M.Sc. (Nagpur), Ph.D. (Udaipur)
Shobha R. Srivastava, M.Sc. (Bombay)

Scientists Group IV(1)
Divya Singh, M.Sc. (Lucknow)
Ritu Trivedi, M.Sc., Ph.D. (SGPGI)
Hemant Kumar Bid, M.Sc. (Avadh)
Konwar Rituraj, M.V.Sc., Ph.D. (IVRI)

Scientists Group III(6)
Rukmani Agarwal, B.Sc.
P.K. Dasgupta, B.Sc.

Scientists Group III(4)
J.P. Maikhuri, M.Sc. (Garhwal), Ph.D. (Jamia Hamdard)
Mohini Chhabra, B.Sc., CLSc.

Scientists Group III(3)
Shakti Kitchlu, M.Sc. (Kanpur)
Balvir Singh, M.Sc. (Rohilkhand)

FERMENTATION TECHNOLOGY

Scientist Group IV(6)
Vinod Bihari, M.Tech. (Kanpur), Ph.D. (I.I.T., Delhi), *In-Charge*

Scientists Group IV(4)
A.K. Misra, M.Tech., Ph.D. (Kanpur)
C.K.M. Tripathi, M.Sc., Ph.D. (BHU)
Banani Sur, M.Sc., Ph.D. (Utkal)

Scientist Group IV(3)
P.K. Shukla, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientist Group III(6)
A.K. Joshi, M.Sc. (Kumaon)

Scientists Group III(5)
Shyamendra Mehrotra, B.Sc.
Bikram Banerjee, B.Sc.

Scientists Group III(4)
M.K. Srivastava, M.Sc. (Sagar)
Malkhan Singh, B.Sc.
M. Prakash, Dip. Mech. Engg
Agney Lal, B.Sc.

MEDICINAL AND PROCESS CHEMISTRY DIVISION

Scientists Group IV(5)
Chandan Singh, M.Sc. (Kurukshetra), Ph.D. (Pune) *(In-Charge)*
A.K. Saxena, M.Sc., Ph.D. (Meerut)
D.P. Sahu, M.E. (Chem. Engg.) (S.I.T., USA), Ph.D., (IIT, Kharagpur)
D.K. Dikshit, M.Sc., Ph.D. (Lucknow)
Kanwal Raj, M.Sc., Ph.D. (Lucknow)
S.B. Katti, M. Pharm., Ph.D. (Mysore)
Bijoy Kundu, M.Sc., Ph.D. (Kanpur)
Ram Pratap, M.Sc., Ph.D. (BHU)
K.C. Agarwal, M.Sc., Ph.D. (Lucknow)

Scientists Group IV(4)
S.N. Suryawanshi, M.Sc., Ph.D. (Pune)
Kamlakar Avasthi, M.Sc., Ph.D. (Lucknow)
V.K. Sharma, M.Sc. (Jabalpur), Ph.D. (Faizabad)
Kalpana Bhandari, M.Sc., Ph.D. (Lucknow)
Rakesh Maurya, M.Sc., Ph.D. (Varanasi)
Vijai Lakshmi, M.Sc., Ph.D. (Allahabad)
Kanchan Hajela, M.Sc., Ph.D. (Lucknow)
R.P. Tripathi, M.Sc. (Gorakhpur), M. Phil, Ph.D. (Delhi)
W. Haq, M.Sc., Ph.D. (Lucknow)
Y.S. Prabhakar, M.Sc. (Vishakhapatnam), Ph.D. (Pilani)
Arun K. Shaw, M.Sc., Ph.D. (Calcutta)

Scientists Group IV(3)
V.L. Sharma, M.Sc., Ph.D. (Lucknow)
P.M.S. Chauhan, M.Sc., Ph.D. (Agra)
Pradeep Kumar, M.Sc. (Kanpur)
Atul Kumar, M.Sc., Ph.D. (Lucknow)

Scientists Group IV(2)
Sanjay Batra, M.Sc., Ph.D. (Meerut)
Anup K. Misra, M.Sc. (Calcutta), Ph.D. (Jadavpur)
Atul Goel, M.Sc., Ph.D. (Lucknow)
Gautam Panda, M.Sc. (IIT, Khargpur), Ph.D. (Hyderabad)
T.G. Narender, M.Sc., Ph.D. (Kakatiya University)
Sashidhara K.V., M.Sc. (MS Univ.), Ph.D. (Avadh)
Balaram Mukhyopadhyaya, M.Sc. (Burdwan), Ph.D. (Jadhavapur)

Scientists Group IV(1)
Prem Prakash Yadav, M.Sc. (Allahabad), Ph.D. (Avadh)
Vijay Kumar Goel, M.Sc. (Meerut), Ph.D. (AIIMS)

Scientists Group III(6)
A.H. Ansari, B.Sc.
R.K. Asthana, M.Sc. (Agra)
S.P. Vishnoi, M.Sc., Ph.D. (Meerut)

Scientists Group III(5)
A.K. Srivastava, B.Sc.
Janki Prasad, M. Tech. (BHU)
S.C. Tripathi
Keshav Prasad, AMIE, M. Tech. (BHU)
Suresh Chandra, B.Sc.
S.P.S. Bhandari, M.Sc., Ph.D. (Avadh)

Scientists Group III(4)
A.K. Mandwal, M.Sc., Ph.D. (Avadh)
S.K. Kakaji, B.Sc.
Vasi Ahmed, B.Sc.
P.N. Rai, Dip. Mech. Engg.
Zahid Ali, B.Sc., L.LB
Pramod Kumar, M.Sc. (Bundelkhand)
Deepali Pandey, B.Sc.
Tara Rawat, B.Sc.

Scientist Group III(3)
A.S. Kushwaha, B.Sc.

MICROBIOLOGY

Scientist Group IV(5)
Ranjana Srivastava, M.Sc., Ph.D. (Kanpur), *In-Charge*

Scientist Group IV(6)
B.S. Srivastava, M.Sc., Ph.D. (Banaras) [Retired on 31/5/2005]

Scientist Group IV(4)
D.C. Kaushal, M.Sc. (Pantnagar), Ph.D. (Kanpur)

Scientist Group IV(3)
K.K. Srivastava, M.Sc., Ph.D. (Kanpur)

Scientist Group III(7)
M.Kazim, M.Sc., Ph.D. (Lucknow)

Scientist Group IV(2)
B.N. Singh, M.Sc., Ph.D. (BHU)

Scientist Group III (6)
A.P. Singh, M.Sc. (Lucknow)
M. N. Joshi, M.Sc., Ph.D. (Agra)

Scientists Group III (5)
Reeta Singh, M.Sc., Ph.D. (Kanpur)

MOLECULAR & STRUCTURAL BIOLOGY DIVISION

Scientists Group IV(4)
Vinod Bhakuni, M.Sc., Ph.D. (Lucknow), FASc, FNASc, *In-Charge*
P.R. Moulick, M.Sc., Ph.D. (Calcutta)

Scientists Group IV(3)
Ashish Arora, M.Sc. (Jaipur), Ph.D. (PU, Chandigarh)
R. Ravishankar, M.Sc., Ph.D. (IISC, Bangalore)
Saman Habib, M.Sc. (Delhi), Ph.D. (NII)

Scientists Group IV(2)
Jimut Ghosh, M.Sc., Ph.D. (Kalyani, Calcutta)
Siddiqi Mohammad Imran, M.Sc., Ph.D.(AIIMS)

Scientists Group IV(1)
Amogh A. Sahasrabuddhe, M.Sc. (Kanpur)
Sohail Akhtar, M.Sc. (Calicut), Ph.D. (JNU)
Philip Prathipati, M.Sc. (Pondicherry)

Scientists Group III(4)
R.K. Srivastava, B.Sc.
J.P. Srivastava, B.Sc., LL.B.

PARASITOLOGY

Scientists Group IV(5)
S.K. Puri, M.Sc., Ph.D. (Punjab), *In-charge*
Shailja Bhattacharya, M.Sc., Ph.D. (Kanpur)
Aruna Kapil, M.Sc., Ph.D. (Lucknow) (Retired on 31/01/2006)
P.K. Murthy, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(4)
L.M. Tripathi, M.Sc. (Kumaon), Ph.D. (Awadh)
Anuradha Dubey, M.Sc. (Lucknow), Ph.D. (Kanpur)
Suman Gupta, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(3)
N.A. Kaushal M.Sc. (Lucknow), Ph.D. (Kanpur)
Renu Tripathi, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(2)
Kumkum Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)
S. Rajakumar, M.Sc. (Madras)

Scientist Group III(6)
A. Islam, B.Sc. [Retired on 31/7/2005]

Scientist Group III(5)
A.K. Saxena, M.Sc. (Lucknow) [Retired on 30/6/2005]

Scientist Group III(4)
A.K. Roy, M.Sc. (Kanpur)

Scientist Group III(3)
R.N. Lal, M.Sc. (Agra)

PHARMACEUTICS

Scientist Group IV(5)
Satyawan Singh, M.Pharm., Ph.D. (Banaras), *In-Charge*

Scientists Group IV(4)
Raghwendra Pal, M.Sc., Ph.D. (Lucknow)
A.K. Dwivedi, M.Sc., Ph.D. (Agra)
Madhu Khanna, M.Sc., Ph.D. (Kanpur) (Retired on 31/01/2006)

Scientist Group IV(3)
Prem Prakash, M. Pharm. (BHU)

Scientists Group IV(2)
Amit Misra, M. Pharm. (Delhi), Ph.D. (JNU)
Prabhat Ranjan Mishra, M.Pharm., Ph.D. (Sagar)
Manish Kumar Chourasia, M.Pharm. (Sagar).

Scientist Group III(5)
Madhuri Choudhary, M.Sc. (Lucknow)

PHARMACOKINETICS & METABOLISM

Scientist Group IV(4)
G.K. Jain, M.Sc. (Rewa), Ph.D. (Kanpur), *In-Charge*

Scientists Group IV(3)
S.K. Singh, M.Sc. (Patna), Ph.D. (IIT, Kanpur)
Jawahar Lal, M. Pharm., Ph.D. (BHU)

Scientist Group IV(2)
Pratima Srivastava, M.Sc. (Lucknow), Ph.D. (Kanpur)

Scientists Group IV(1)
S. Sabrinath, M. Pharm. (Pilani) (Resigned on 30/11/2005)
Nitin Mehrotra, M. Pharm., Ph.D. (BITS, Pilani) [Resigned on 16/6/2005]

Scientist Group III(5)
S.K. Pandey, M.Sc. (Kanpur)

PHARMACOLOGY

Scientists Group IV(5)
Ram Raghubir, M.V.Sc., Ph.D. (Agra), *In-Charge*
G. Palit, M.B.B.S., M.D. (Lucknow), (*Unit In-charge, Neuropharmacology Unit*)
C. Nath, M.B.B.S., M.D. (Lucknow), (*Neuropharmacology Unit*)

Scientists Group IV(4)
Rakesh Shukla, M.Sc., Ph.D. (Lucknow)
Madhu Dikshit, M.Sc., Ph.D. (Kanpur) *(Unit In-charge, Cardiovasular Pharmacology Unit)*
M. Ray, M.Sc., Ph.D. (Lucknow)

Scientist Group IV(3)
Amar Nath, M.Sc. (Lucknow)

Scientists Group IV(2)
K.G. Raghu, M.Sc. (Calicut), Ph.D. (Saurashtra)
Kapil Kapoor, M.B.B.S., M.D. (Lucknow), Ph.D. (The Netherlands),
(Cardiovasular Pharmacology Unit)

Scientist Group IV(1)
Vijay Kumar Kuchibolta, M. Pharma. (Andhra)

Scientists Group III(6)
G.P. Singh, M.Sc. (Kanpur)
Urmila Sharma, B.Sc.
M.S. Ansari, B.Sc.

Scientist Group III(5)
Kanta Bhutani, M.Sc. (Kanpur)

Scientists Group III(4)
T.L. Seth, B.Sc.
Jharna Arun, B.Sc.
V.S. Nigam, B.Sc. (MOH Scheme)
M.L. Bhatnagar, B.Sc.
C.P. Pandey, M.Sc. (Chandigarh)

TOXICOLOGY

Scientist Group IV(5)
Sudhir Srivastava, M.B.B.S., M.D. (Lucknow), *In-charge*

Scientist Group IV(4)
Neeraj Sinha, M.Sc., Ph.D., D.Sc. (Kanpur)

Scientists Group IV(3)
P.S.R. Murthy, M.Sc. (Nagpur), Ph.D. (Kanpur)
Sharad Sharma, M.B.B.S., M.D. (Kanpur)

Scientists Group IV(2)
S.K. Rath, M.Sc. (Utkal), Ph.D. (BHU)
R.K. Singh, M.Sc., Ph.D. (Lucknow)
R.K. Tripathi, M.Sc., Ph.D. (Kanpur)

Scientist Group IV(1)
Smrati Bhaduria, M.Sc. (Jiwaji)

Scientists Group III(6)
S.K. Mathur, M.Sc. (Lucknow), B.M.S.
S.K. Srivastava, M.Sc. (Bombay)

Scientists Group III(4)
P.K. Agnihotri, M.Sc. (Lucknow), Ph.D. (Kanpur)
S. M. Verma, B.Sc.
Sadan Kumar, M.Sc. (Bihar)

ANTITUBERCULAR SCREENING UNIT

Scientists Group IV(3)
Anil Srivastava, M.Sc., Ph.D. (Kanpur)
Vinita Chaturvedi, M.Sc., Ph.D. (Agra)

Scientist Group IV(1)
Y.K. Manju, M.Sc. (Calicut)

CLINICAL PHARMACOLOGY UNIT (CDRI), SETH G.S. MEDICAL COLLEGE, MUMBAI

Scientist Group IV(2)
N.K. Desai, M.Sc., Ph.D. (Bombay)

TECHNICAL INFRASTRUCTURE DIVISIONS / SECTIONS

ACADEMIC AFFAIRS UNIT

Scientist Group IV(4)
Alka Singh, M.Sc., Ph.D. (Rajasthan)

Scientist Group IV(3)
Sheela Ghoshal, M.Sc. (Burdwan), Ph.D. (Kanpur)

BIOMETRY AND STATISTICS

Scientist Group IV(5)
S.K. Mandal, M.Sc., B.Ed. (Utkal), Ph.D. (Lucknow), (Retired on 30.11.05)

Scientist Group IV(4)
M. Abbas, M.Sc. (IIT, Kanpur) , Ph.D. (IIT, Bombay) *In-Charge*

Scientist Group III(5)
Mukesh Srivastava, M.Sc. (Lucknow), Ph.D.(Kanpur), Dip. Material Management

CSIR DISPENSARY

Medical Officers Group III(7)
K.K. Arora, M.B.B.S., M.D., *In-Charge*
D.K. Bhateja, M.B.B.S., M.D.

Medical Officer Group III(6)
Asha Negi, M.B.B.S., M.D.

DOCUMENTATION & LIBRARY

Scientists Group IV(5)
P.K. Roy, M.Sc., Ph.D. (Gauhati), *In-Charge*
R.K. Sharma, M.Sc., Ph.D. (Agra)

Scientists Group IV(4)
A.K. Srivastava, B. Tech. (Bangalore)
N.N. Mehrotra, M.Sc. (Pantnagar), Ph.D. (AIIMS, New Delhi)
Sheela Tandon, M.Sc., Ph.D. (Agra)
S.K. Mallik, M.A. (JNU), B.L.Isc. (IGNOU)
Shyamala Saxena, M.Sc. (Tirupati), B.L.Sc. (Lucknow)

Scientist Group III(6)
Seema Mehrotra, M.Sc. (Lucknow)

Scientist Group III(5)
V.K. Vohra, B.Sc.

Scientists Group III(4)
W.F. Rahman, B.Sc. (Hons.), M.A. (Rohailkhand), B.L.Isc, (IGNOU)
A.K. Verma, B.Sc., M.A. (Eco.), L.L.B, Dip. Comp. Sc. (Lucknow)
J.A. Zaidi, M.Sc. (Aligarh), B.L.Isc. (IGNOU)
Sanjay Kumar, B.Sc., M.L.ISc (IGNOU)

DRAWING AND PHOTOMICROGRAPHY

Scientist Group III(6)
Ali Kausar, B.F.A. (Lucknow), *In-Charge*

Scientist Group III(5)
G.C. Gupta, B.Sc.

Scientists Group III(3)
R.M. Pathak, B.F.A. (Comm. Arts)
R.N.S. Londhe, GD Art (Comm.), Art Teachers Dip.

INSTRUMENTATION

Scientist Group IV(5)
Ravinder Singh, B.E. (Allahabad)

Scientist Group IV(4)
Sharwan Kumar, B.E. (Roorkee), F.I.E. [Retired on 30/6/2005]

Scientist Group IV(3)
N.K. Agarwala, M.Sc. (Calcutta)

Scientist Group III(6)
Usha Kapil, I.Sc., Dip Electronic Engg.

LABORATORY ANIMALS DIVISION

Scientists Group IV(4)
P.Y. Guru, M.Sc. (Indore)
A.K. Balapure, M.Sc., Ph.D. (Lucknow)
D.S. Upadhyaya, M.V.Sc. (Pantnagar), Ph.D. (Izatnagar)

Scientist Group IV(3)
A.K. Srivastava, M.Sc., Ph.D. (Lucknow)

Scientist Group IV(1)
Hansda Dhananjoy, M.V.Sc. (Izatnagar)

Scientists Group III(6)
Sidheshwar Gupta, B.Sc.
S.C. Nigam, M.Sc., Ph.D. (Kanpur)

Scientist Group III(5)
S.N.A. Rizvi, M.Sc. (Lucknow)

Scientists Group III(4)
Ramesh Sharma, M.Sc., Ph.D. (Kanpur)
A.K. Bhargava, B.Sc.
Karunesh Rai, M.Sc. (Lucknow)
B. Maity, M.Sc. (Kanpur), Ph.D. (Izatnagar)

SOPHISTICATED ANALYTICAL INSTRUMENT FACILITY

Scientist Group IV(6)
K.P. Madhusudanan, M.Sc., Ph.D. (Kerala), FNASc, *In-Charge*

Scientist Group IV(5)
V.K. Bajpai, M.Sc., Ph.D. (Kanpur)

Scientists Group IV(4)
G.R. Bhatt, M.Sc. (Meerut)
Raja Roy, M.Sc. (Lucknow), Ph.D. (Meerut), FNASc

Scientists Group IV(3)
S.M. Gupta, M.Sc. (Allahabad) [Voluntary Retirement on 1/1/2006]
Brijesh Kumar, M.Sc. Ph.D. (Awadh)

Scientists Group IV(1)
Sanjeev Kanojiya, M.Sc. (Jabalpur)
Ankita Pandey, M.Sc.(Kanpur), M.Phil. (Delhi)
Mitra Kalyan, M.Sc. (Calcutta)

Scientist Group III(6)
Prakash Narain, M.Sc. (Lucknow)

Scientists Group III(5)
Abha Arya, B.Sc., B.Ed. (Kumaun)
H.M. Gauniyal, M.Sc. (Garhwal)
A.L. Vishwakarma, M.Sc. (Kanpur)
Rakesh Khanna, B.Sc., A.I.C. (Calcutta)
A. Vohra, B.Sc., M.A. (Lucknow)

Scientists Group III(4)
A.K. Sinha, M.Sc. (Kanpur)
A.K. Sircar, B.Sc., B.A. (Lucknow)

Scientists Group III(3)
Sunil Kumar, B.Sc. (Lucknow)
R.K. Purushottam, B.Sc. (Lucknow)

TECHNICAL INFORMATION, INDUSTRIAL LIAISON & PLANNING

Scientist Group IV(5)
Zaka Imam, M.Sc., M.Phil., Ph.D. (Aligarh), *In-Charge*

Scientists Group IV(4)
A.K. Goel, M.Sc., Ph.D. (Lucknow)
Rajendra Prasad, M.Sc., Ph.D. (Lucknow)
V.G. Mohanan Nair, M.Sc. (Kerala), Ph.D. (Kurukshetra)
Vinay Tripathi, M.Sc., M.B.A. (AMU), P.G. Dip. in S&T (Pilani)

Scientists Group IV(3)
N.S. Rana, M.Sc. (Kumoun)
D.N. Upadhyay, M.Sc., Ph.D. (Gorakhpur)
R.C. Tripathi, M.Sc. (Kanpur), Ph.D. (Lucknow)

Scientist Group IV(1)
Anand P. Kulkarni, M.Sc. (Karnataka)

Scientist Group III(6)
Shri Ram, B.Sc., LL.B.

LABORATORY ENGINEERING SERVICES

Superintending Engineer
Parvez Mahmood, B.Sc. Engineering (Civil)

Assistant Executive Engineers
Manoj Kumar, B.Sc. Engineering (Civil)
Kamal Jain, B.E. (Electrical), MBA (Marketing)

Technical Officer Group III(4)
A. Dayal, Diploma (Mechanical)

HOUSE - KEEPING

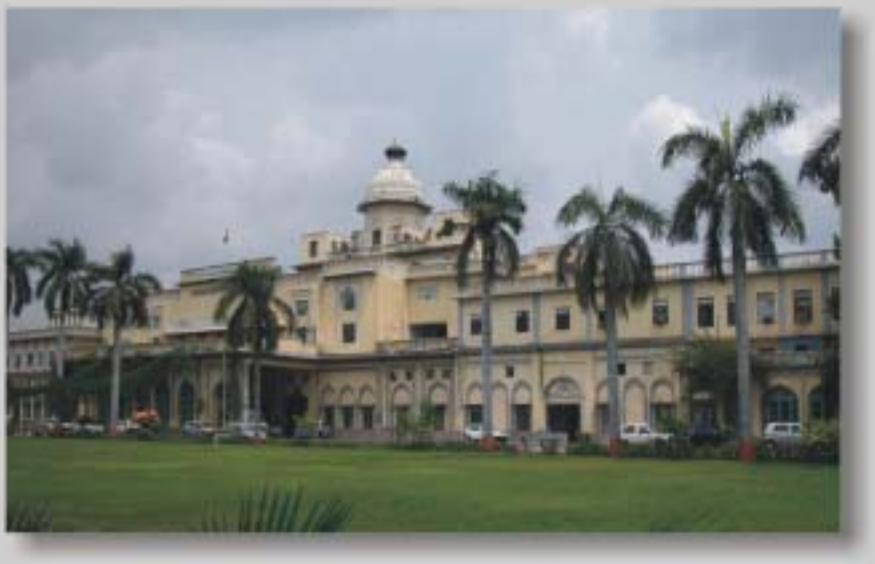
B.D. Vashisth, M.A., *Controller of Administration*
O.P. Dhawan, *Administrative Officer*
B.S. Rajput, B.A., *Administrative Officer [Transferred on 24/10/2005]*
U.S. Rawat, *Controller of Finance & Accounts*
S.C. Shukla, M.Sc. (Kanpur), *Finance & Accounts Officer*

Gopal Chand, *Store & Purchase Officer*
Raza Hussain, *Section Officer (G)*
Krishna Kumar, *Section Officer (G)*
K.K. Verma, M.A., LL.B., *Section Officer (G)*
Madhuranjan Pandey, *Section Officer (G)*
Biranchi Sarang, *Section Officer (G)*
I.B. Dixit, M. Sc. (Lucknow), *Section Officer (F&A)*
Ankeshwar Misra, *Section Officer (F&A)*
A. K. Chauhan, *Section Officer (F&A)*
S.P. Singh, M.A., *Section Officer (Store & Purchase)*
Shekhar Sarkar, *Section Officer (Store & Purchase)*
Prasanjeet Mitra, *Section Officer (Store & Purchase)*

Senior Hindi Officer
V.N. Tiwari, M.A., Ph.D. (BHU)

Senior Security Officer
R.S. Deswal, B.Sc., LL.B.

Private Secretaries
G.M. Nair
H.K. Khulve
G.M. Dayal, B.Sc., D.P.A.
K.L. Gupta, B.A.



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