Indian Initiative for generic and novel bioactive molecules
Indian scenario:

Largest number of USFDA approved plants outside US - 61 as compared to 22 in China

Meets entire need of formulations, caters to 70% of the bulk drugs

Ranks 4th in pharma production in volume
Ranks 13th in pharma production in value.
S & T Infrastructural Competence for drug discovery & process development

- Strong Chemical Technology base
- Photochemistry & Natural product based drug development
- Combinatorial synthesis
- Structural biology
- Computer aided drug design
- Proteomics
- High / Medium throughput screening
- Electron & confocal microscopy
- Biomaterial design and development
- Safety evaluation of natural & genetically engineered drugs
- Infectious disease research (in vitro & in vivo)
- International type culture collection for microbes
- Bioprocess and enzyme technology centers
- Biochemical engineering research & process development centers
- Medicinal plant gene banks
- State-of-the-art Instrumentation.
CSIR Contribution

Playing significant role in identifying drug molecules relevant to global and Indian markets

New synthetic routes and process engineering

Screening for novel lead molecules for diseases relevant to Indian and global markets

Prospecting and harnessing biodiversity for unique and affordable drugs
<table>
<thead>
<tr>
<th>Discipline</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Scientists</td>
<td>5223</td>
</tr>
<tr>
<td>Chemical Sciences</td>
<td>24.54%</td>
</tr>
<tr>
<td>Biological Sciences</td>
<td>20.39%</td>
</tr>
<tr>
<td>Engineering Sciences</td>
<td>34.13%</td>
</tr>
<tr>
<td>Physical sciences</td>
<td>9.91%</td>
</tr>
<tr>
<td>Earth Sciences</td>
<td>5.82%</td>
</tr>
<tr>
<td>Mathematical Sciences</td>
<td>2.98%</td>
</tr>
<tr>
<td>Information technology</td>
<td>1.26%</td>
</tr>
<tr>
<td>Others</td>
<td>0.91%</td>
</tr>
</tbody>
</table>
Cost effective Processes for Generics

- CSIR institutes possess the core-competence to provide competitive technologies for off patent drugs

- Technologies for chiral drug intermediates and bulk drugs of high value

- New cost effective, environment friendly, catalytic processes for drugs
Examples:
Processes for the production of drugs & drug intermediates:

Ciprofloxacin, Losartran-K, Doxazocin, L-ephedrine, Dextroprooxyphene, Artemether, Cetrizine, Amlodipine, Naltrexone, Pyrazinamide, Mefloquine, Naproxine, Paroxetine etc.
Examples of Drug Synthesis Processes Transferred to Industry

Cardiovascular
1. Amlodipine : Crosland Ltd
2. Atorvastatin : USV Ltd

Malaria
2. Mefloquine : CIPLA

Antihistamine

Antidepressant
1. Venalafaxine : Cadila
2. Fluoxetine : Crosland Ltd

Anti-psychotic
1. Olanzapine : CIPLA

Vitamin B6 : Commercialized by Lupin Lab.
Vitamin H : Vetcare, Bangalore (Biotin)
Anti-AIDS Drugs (NCL contribution)

• Philosophy:

• Help Indian companies to make available all the anti-AIDS drugs in the country at a low cost for a common man
Processes Developed:
Zidovudine, Stavudine Lamivudine, Abacavir, Nevirapine:

- Prevents transfer of HIV virus from AIDS mother to the Child (63% success)

Efavirenz: Non-Nucleosidic Reverse Transcriptase Inhibitor

Calanolide:
1. Natural product from Calophyllum Sp.
2. Available in small quantities in Nature
3. Developing an economically viable synthetic Process
TOTAL SYNTHESIS OF CAMPTOTHECIN & RELATED COMPOUNDS
<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Licensee</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centchroman (Saheli)</td>
<td>Once a week oral contraceptive</td>
<td>Hindustan latex Ltd</td>
</tr>
<tr>
<td></td>
<td>selective estrogen receptor modulator.</td>
<td></td>
</tr>
<tr>
<td>Centchroman</td>
<td>Drug for the treatment of dysfunctional</td>
<td>Torrent Pharmaceuticals</td>
</tr>
<tr>
<td></td>
<td>uterine bleeding.</td>
<td></td>
</tr>
<tr>
<td>Arteether</td>
<td>Antimalarial drug MDR &amp; cerebral malaria.</td>
<td>Themis Medicare Ltd.</td>
</tr>
<tr>
<td>Elubaquin / Aablaquin</td>
<td>For relapsing Malaria</td>
<td>Nicholas Piramal India Ltd.</td>
</tr>
</tbody>
</table>
Products Currently in Pipeline

CDRI compound 80/574
(a lipid lowering compound)
Phase III A clinical trials
(licenced to Cadila Pharma)

CDRI compound 97/78
an antimalarial drug
(licenced to IPCA)

CDRI COMPOUND 99/373
antiosteoporosis activity Toxicity studies in rodents

CDRI compounds S-002-853 and S-002-857
antidiabetic-cum-antidyslipidemic activity
Herbals

Picroliv
(hepatoprotective) Phase III clinical trials (Duphar Pharma)

CT-1
(antidiabetic) Phase II clinical trials (Nicholas Piramal)

Herbal medicament
(anti-cerebral stroke) Toxicity studies
(Themis Medicare)

CDR-134 F194 & CDR-267 F018
(antidiabetic and anti-dyslipidemic)
Toxicity studies (Not yet licenced)
NEW DRUGS FROM THE OCEAN
NOVEL CHEMICAL LEADS AS DRUGS AND PHARMACOLOGICAL TOOLS

INSTITUTES INVOLVED
- CSMCRI
- IICT
- NIO
- RRL(Bah)
- CDRI
- Biotech., Chennai
- Bharathidasan Univ
- Andhra Univ. (2 depts.)
- PGI (Basic Med. Sci), Kolkata

Deliverables:

New Investigative Natural Drugs

- Antihyperglycemic Agent: Ph-I Clinical trial in progress
- Antihyperlipidaemic Agent: Safety studies in monkeys initiated

MARINE ORGANISMS IDENTIFIED FOR FOLLOW-UP STUDIES

Discovery Groups:

- Antihyperglycaemic: 7
- Antihyperlipidaemic: 4
- Spermicidal: 2
- Antibacterial & Antifungal: 3
Drivers from Indian perspective

GOLDEN TRIANGLE APPROACH

Traditional Knowledge
Modern Science
Modern Medicine
Drug Discovery and Development Process

Expensive, time consuming, numerous bottlenecks

Target Identification → Lead Identification → Lead Optimization → Preclinical Studies → Clinical Trials → Drug to Market

Economical, time sparing, least bottlenecks

Reverse Pharmacology

Phase IV → RELEVANT SCIENCE → Animal Pharmacology → Drug Development → Clinical Trials Phase III & I → Safety study → Drug to Global Market → Drug to Market

Traditional wisdom
New Botanicals under Clinical trials using Reverse Pharmacology approach

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Indication</th>
</tr>
</thead>
<tbody>
<tr>
<td>M-97</td>
<td>Hepato-protective</td>
</tr>
<tr>
<td>NMHPT</td>
<td>Hepato-curative</td>
</tr>
<tr>
<td>RRLJCD-SFE</td>
<td>Anti-Psoriasis</td>
</tr>
<tr>
<td>NMITLI-DM-FN</td>
<td>Type II Diabetes</td>
</tr>
<tr>
<td>NMITLI-OA-JP</td>
<td>Osteo-arthritis</td>
</tr>
<tr>
<td>RRLJ0125-F09</td>
<td>Anti-Hepatocellular carcinoma</td>
</tr>
<tr>
<td>AP9CD</td>
<td>Breast Cancer</td>
</tr>
</tbody>
</table>
### NMITLI Programme

**Deliverables:** 3 NDAs

**Targets**

<table>
<thead>
<tr>
<th>Diabetes mellitus</th>
<th>Hepatitis</th>
<th>Arthritis</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Insulin sensitisation</td>
<td>• Cytoprotective</td>
<td>• Pain relief</td>
</tr>
<tr>
<td>• Dyslipidemia</td>
<td>• Hydrocholeretic</td>
<td>• Anti-inflammatory</td>
</tr>
<tr>
<td>• Complications</td>
<td>• Antifibrotic</td>
<td>• Chondroprotective</td>
</tr>
<tr>
<td>• P.C.O.S.</td>
<td>• Immunomodulation</td>
<td>• TNF - ( \infty )</td>
</tr>
<tr>
<td>• Oxidant damage</td>
<td>• N.A.S.H.</td>
<td>• Sarcopenia</td>
</tr>
<tr>
<td>• New leads</td>
<td>• Antiviral</td>
<td>• Q.O.L.</td>
</tr>
</tbody>
</table>
Response of acute viral Hepatitis patients (n=9) treated with NMITLI hepatoprotective formulation on Serum bilirubin levels

Response of acute viral Hepatitis patients (n=9) treated with NMITLI hepatoprotective formulation on SGOT levels

Response of acute viral Hepatitis patients (n=9) treated with NMITLI hepatoprotective formulation on SGPT levels
New concept based on TK (Ayurveda)

New Drug formulations

Dose Reduction by 50 – 80%

Reduction in:
• Dose related toxicity
• Cost

Bioenhancers

Transformed into a Product (Anti TB drug formulation)

Final approval of DCG (I) for marketing permission

Anti-infective
Anti-cancer
Anti-hypertensives

Drug Activity Modifiers

Dose Reduction by 50 – 80%
BIO RESOURCES

PLANTS | HERBAL PREPs | BACTERIA & FUNGI

TRADITIONAL WISDOM

AYURVEDA (AVS) | UNANI (CCRUM) | SIDDHA (INCOPS)

MODERN SCIENCE & TECHNIQUES

CHEMISTRY | BIOLOGY | STATISTICS

ANTICIPATED OUTPUTS

NEW BIOENHANCERS

INVESTIGATIVE NEW DRUGS (IND)

ENTIRELY NEW HERBALS

SERVICES TO ISM

Resource Management
Standardization
Agrotechnologies
Automation
Product Safety
COORDINATED EXTRACTION AND ISOLATION ACTIVITY

PLANTS
(RRL, J)

CSMCRI  IICB  NBRI  RRL, Jt  RRL, Tvm
CIMAP  IHBT  NCL  RRL(Bh)  RRL(Bl)

Fungi & Microbes
(IMTECH)

CIMAP  IHBT  RRL, Jm
NIO

Selection of Niches Areas

Isolation & Extraction

Coding

Distribution

Bioassay

Lead Identification
BIOLOGICAL SCREENING
DISEASE SELECTION

DEGENERATIVES
METABOLIC DISORDERS
CNS
TROPICAL
INFECTIVES
OTHERS

IN VITRO SCREENING

NBRI
CDRI
CIMAP
IICT
IICB
ITRC
RRL,J

ALZHEIMER
ATHEROSCLEROSIS
BACTERIAL
CANCER
DEPRESSION
DIABETICS
FILARIASIS
FUNGAL
GASTRIC ULCER
HEPATITIS
HYPERTENSION
IMMUNOMO-DEFICIENCIES
INFLAMMATION
LEISHMANIA
MALARIA
MEMORY REDUCTION
NEURO DISORDERS (3)
PARKINSONIAN
OBJECTIVES

- DEVELOP NEW FORMULATIONS OR NCEs
- STRUCTURE OPTIMIZATION
- FAST TRACK SCREENS
- MULTIDISCIPLINARY

DISCOVERY GROUP FORMATION

- PHYTOCHEMISTRY
- SYN.ORG. CHEMISTRY
- MODELLING
- PHARMACOLOGY

59 Discovery Groups in 13 Institutes
Herbal Therapeutics
Expected Deliverable:

Antigastric ulcer IND (Botanical)

Ap76p (Batch 31)
- Six constituents
- All the constituents are necessary

Active against different models
- Cold restraint induced ulcer test
- Asprin induced ulcer
- Histamine induced ulcer
- Pyloric ligation
- Ethanol induced ulcer
- Active against *H. pylori* (in vitro)

✓ Equal or better than Omeprazole
✓ Acts by multiple mechanisms
✓ Only one drug is required
✓ Presently combination of three drugs are used in Allopathic
✓ Nontoxic (LD50 = >2200 mg/kg)
Anticancer (Colon, Cervix, Breast)

AVS → AP9a → AP9cd (Mix 3 Compounds)

- Active in vitro
- Active in vivo
- Non-toxic
- US Patent (6649650 dt. 18.11.03)
- PCT & Indian patent filed
- Agreement with a Company for development
Liver Cancer

(Hepatocellular carcinoma)

Model: Hepatitis B Virus

Disease causing gene

Breeding

HCC HCC NO HCC

RJM 0125 P04 A003 F009 (K001 & K002)
CSIR Agenda

- New Drug discovery
- Cost effective generic drugs
- New 6 bioenhancer based formulations
- New standardized botanicals
- New standardized traditional knowledge based drugs
Thanks for your patience

Please visit us at

www.rrljammu.org
www.herbalnet.org
www.csir.res.in