PK-PD and Toxicology Division.

Overview

The primary focus is to provide support to the ongoing drug discovery program of the institute in the areas of Pharmacokinetics, ADME and Toxicology and generate preclinical data.

Mission and Goal

- Development of validated protocols for HPLC/LC-MS/Q-Tof in terms of recovery, presicision, accuracy and reproducibility.
- PK studies of new chemical entities
- Absorption (A), distribution (D), Metabolism (M), Elimination (E) and protein binding profile
- Safety pharmacology
- Photobiology
- Mode of action studies
- Stability studies

Competencies

- Pharmacokinetics
- Bioavailability/ Bioequivalence studies
- ADME Studies
- Phase I Studies
- Preparation of Pre-clinical/ Phase –I Dossiers
- *In vitro* toxicology and mechanistic studies
- *In vivo* toxicology (as per OECD guidelines)
- Safety pharmacological and stability studies

Facilities

■ Pharmacokinetics and General Instrumentation

- Shimadzu HPLC system (Class VP series)
- Thermofinningan HPLC System (Spectra Series)
- Waters LC/MS System –Q ToF (Synapt)
- Thermo Multiscan Spectrum Elisa Reader
- Perkin-Elmer LS 50B Well plate Spectroflurometer
- Perkin-Elmer LS 55 Spectroflurometer
- Shimadzu UV-1601 PC-Spectrophotometer
- Climacell Stability chamber

■ Cell culture facility.

- *In vitro* primary rat/mice hepatocyte culture.
- Human skin fibroblast cell cultures (HS-68).
- Human hepatoma cell cultures (HepG2, HuH-7, Hep3B).
- Mice transformed liver cells (AML-12).

■ Clinical Biochemistry lab facility

Clinical Biochemistry lab facility for studying clinical blood biochemistry parameters. The instruments available are

- Automated Blood Analyzer (Chem-7, ERBA, India)
- Automated Hematological Analyzer (Kamineni Life Sciences, USA)

■ **Safety Pharmacology lab facility**

- Main Instrumentation.
- Multichannel Polygraph (Expermentia, Hungry)
- Telemetry System (DSI, USA)
- Radial Arm Maze (Coulbourn, USA)
- Non Invasive Blood Pressure System (Kent Scientific, USA)
- Double chamber Plethysmograph (Buxco, UK)
- Isolated Organ Bath (Bio-Pack System, USA)
- Hot plate Analgesiometer (Ugo basile, Italy)
- Telethermometer (TSE, Germany)

Current Research

Pharmacokinetics/ Safety Pharmacology/ Toxicology/ Stability studies of new drug candidates

Competence and infrastructure is available to carry out PK/ Safety Pharmacology/ Toxicological/ and Stability studies for in-house as well as sponsored new chemical entites under the drug discovery programme. Several high-end HPLC/ LC-MS and Q-ToF systems are being used for method development and PK profiling. Toxicological studies (both in vitro/ in vivo) are being carried out using cell culture and other whole-animal bioassays.

Identification and Development of Natural Products as Drug Bioavailability Enhancers

Many clinically important drugs are not optimally utilized. If systemic availability of a drug averages 20%, for example, then 80% of a dose is wasted. For drugs that are expensive to produce, wasting 80% of the material may not be acceptable. There is a need to search for alternative drug forms having better action profile in terms of systemic availability and efficacy. The reformulated drug regimen are envisaged to utilize the potential synergy of the natural product bioenhancers to optimize the drug profile and also to improve therapy.

Essentially, the practice of Ayurvedic therapeutics has provided the important clues regarding the synergic action of medicinal entities. One of the most common features of traditional therapies is the use of multi-herb compositions containing certain plants which have been suggested to produce synergy and that remains as one of the hallmarks of such indigenous drugs. Bioevaluation of several herbal products from these plants has revealed the mechanism of a number of molecules acting together in an additive, synergistic or antagonistic manner to modify a biological response.

During the last 20 years Indian Institute of Integrative Medicine, Jammu has developed a novel concept of using natural products as bioenhancers into developing commercially viable entities. One of the foremost of such group of herbals which provided the initial proof of concept was ‘Trikatu’- which is repetitively used as an essential part of about 70% Ayurvedic prescriptions. `Trikatu’ contains three herbs in equal proportions: Piper longum, Piper nigrum and Zingiber officinalis. In various experimental studies `trikatu’ enhanced the bioavaibaility of selected drugs. Subsequently, this activity was found to remain localized in piperine, an active alkaloid present in peppers. Using piperine in combination, a 55% reduced dose regimen of anti-TB drugs was developed. This reduced dose formulation has undergone Phased Clinical Trials, and its marketing permission under the brand name `Resorin’ has been obtained by Cadila Pharma.

Development of Natural Products as Modulators of CYP 3A4 / P-glycoprotein

CYP 450 3A4/ P-glycoprotein are widely understood as major regulators of oral drug bioavailability. Several in vitro and in situ experimental models have been established to assess the mechanism of putative bioenhancers on the absorption/ permeability and metabolism which influence the systemic availability of a chemical entity under investigation.

Development of Agents against Chronic Disorders.

Liver protective agents: A mechanistic understanding has been developed for drug/ chemical induced chronic liver dysfunction. Progressive pathological features including fibrosis due to various hepatotoxicants and anti-tubercular drugs have been investigated by in vitro and in vivo protocols for liver function. A model for chemically induced hepatocarcinoigenesis has been developed. The liver protective action of several herbal as well as natural/ synthetic molecules is being investigated.

Anti-allergic/ anti-asthmatic agents:

Various investigative bioassays have been optimized to determine the protective effect of natural/ synthetic agents against experimentally induced allergy/ asthma. Protocols for anti-histaminic, anti-inflammatory and bronchodilatory activities are being used for the development of anti-allergic/ anti-asthmatic agents.

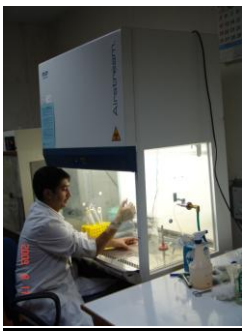
UV -irradiation induced photo-aging in human skin cells and its prevention by products from natural/synthetic sources.

A facility to investigate the protective role of new chemical entities (synthetic/ natural) against UV –induced photoageing has been established. Protocols for the use of human skin fibroblast cells line have been established and are being used for the evaluation of new test materials.

Pharmacokinetics lab

Toxicology/Pharmacology Lab

Photobiology Lab.



Cell Culture Lab