Altogen Labs

Provider of Preclinical Research Services (GLP/non-GLP) for Drug Discovery
Efficacy and Pharm/Tox IND contract research studies (clients worldwide)
100+ Xenograft Models (validated in-house) and IND-enabling Toxicology studies
100% IP belongs to client, experienced IACUC-regulated barrier facility

In Vivo Pharmacology/ Toxicology

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Toxicology Studies

- Toxicology studies can be focused on the acute toxicological effects of a single large dose of a substance, as well as long-term studies focused on researching subchronic and chronic effects.
- A subchronic toxicology study can include repeatedly administering small doses of the substance in question over a period of up to 90 days.
- Chronic studies, on the other hand, can study the toxic effects of the experimental substance for months to years

Toxicology studies are pivotal for a transition to phase I clinical trials

What's the Purpose of Toxicology Testing?

- Preclinical toxicology studies are required to establish the toxicological profiles of new drug candidates prior to administration to humans, and to extend the known profiles of existing drugs (e.g., new indications, new formulations, new routes of administration, etc.). Preclinical studies used for direct extrapolation to human safety should be conducted according to GLP.

- The studies vary in length (e.g., acute, sub-chronic, chronic) depending on the length of dosing in the clinical trial they are supporting and the stage of development of the test article (IND, NDA, BLA, etc.).

Types of Toxicology Testing?

- *Acute toxicology* studies focus on the toxicological effects following a single large dose of the substance of interest.
- *Sub-chronic toxicology* studies include repeated small dosages of the test substance over a period of time up to 90 days.
- *Chronic toxicology* studies focus on the long term effects of the test substance over periods of months to years.

In Vivo Toxicology Service (Mouse, Rat)

- Preclinical *in vivo* toxicology is the study of toxic effects of chemical substances based on statistical and quantitative analysis. They assess the onset, severity, and duration of toxic effects, their dose dependency and degree of reversibility or irreversibility).

- At Altogen Labs, toxicology studies can include acute, sub-chronic and chronic toxicity tests via several routes of exposure (e.g., oral, intravenous, intramuscular, topical, etc.).

- The Study designs are flexible and can be customized to the client-specific projects. All testing complies with applicable Good Manufacturing Practice (GMP) and Good Laboratory Practice (GLP) regulations as needed.

- The variation in time and amount of test substance in taken by the subject helps create dose response curves to determine thresholds of biological activity associated with the test substance as well as levels of toxicity.
- Identification of potential toxicological side effects is very important to the advance of INDs to phase 1 clinical trial. Such side effects can have an impact on the future health of the subject, its progeny, and overall survival rate.
- Potential side effects can be detrimental to the immune system, the integrity of the DNA and the functionality of vital organs.
- Hence additional tests can be run to study sensitivity, irritation, mutagenic and/or carcinogenic properties, reproductive toxicity and immuno-toxicity.

- Another focal point is the route of administration of INDs. The ability of a drug to reach its target in a living system can unintentionally be deterred by immune system mechanisms, metabolic processes, and similarly natural mechanisms. Then the INDs are no longer directly targeting the desired cells but are faced with a living biological system in which their target is one of many. As a result, various drug administration routes are explored to determine toxicity and benefits.
- Evaluation of drug administration routes should anticipate clinical results and optimize beneficial efficacy.
- Thus the study should determine a safe and effective procedure for administration, as well as dosage for the drug to prevent any adverse affects.

- In vivo toxicology studies are also required to establish the toxicological profiles of materials that may pose a significant human health risk via environmental exposure
- Implications of the above these studies can lead to phase 1 clinical trial INDs if they show promising results and minimal toxicological, carcinogenic and mutagenic effects.
- Studies focusing on pharmacodynamics, pharmacokinetics and ADME processes also contribute greatly to the INDs application.
- Refer the link for more details on FDA application for INDs:
- http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/default.htm

Our Services

- Acute toxicity
- Sub chronic toxicity
- Chronic toxicity
- Pharmacokinetics
- *In vitro* permeation studies
- *In vivo* absorption studies
- Irritation and sensitization
- Immunotoxicity
- Reproductive toxicity
- Pharmacology

Standard Acute Toxicity Study

Objectives:

- 1. To determine the Median Lethal Dose (LD50) after a single dose administered through one or more routes, one of which is the intended route of administration in humans
- 2. To determine Maximum Tolerated Dose (MTD) and No Observable Effect Level (NOEL)
- 3. To identify potential target organs for toxicity, determine reversibility of toxicity, and identify parameters for clinical monitoring
- 4. To help select doses for repeated-dose toxicity tests

Duration: A few days to 2 weeks after a single dose

Parameters:

- 1. Mortality
- 2. Clinical pathology
- 3. Gross necropsy
- 4. Weight change
- 5. Signs of toxicity

Standard Sub-chronic Toxicity

Objectives:

- 1. To establish a “no observable effect level" (NOEL)
- 2. To characterize dose-response relationships following repeated doses
- 3. To identify and characterize specific organs affected after repeated administration
- 4. To help select doses for repeated-dose toxicity tests.

Duration: Commonly 90 days

Dose Administration: 4 or more doses given by the same routes as previous toxicity tests

Parameters:

1. Mortality
2. Histopathology and pathology
3. Weight change
4. Clinical Pathology
5. Signs of toxicity

Standard Chronic Toxicity

Objectives:

1. To characterize dose-response relationships following repeated doses.
2. To identify and characterize specific organs affected after repeated administration.
3. To evaluate the cumulative toxicity of chemicals.
4. To assess carcinogenic potential.

Duration: Varies from 6 months to 2 years or up to 10% of species' lifespan.

Dose Administration: At least 3 doses given by the same routes as previous toxicity tests; the lowest producing no apparent toxicity and the highest producing toxicity but less than or equal to 10% mortality.

Standard Pharmacokinetics

Objective: Evaluate the bioavailability, tissue distribution, active metabolite formation, and elimination of test materials
Duration: >48h
Dose Administration: Various
Parameters:
1. AUC (Area Under Curve)
2. Cmax (max concentration in blood)
3. Tmax (Time Cmax is reached)

Standard In vitro Permeation Studies

Objective: To study the effect of test materials on skin metabolism, or the effect of skin metabolism on xenobiotics

Duration: <48 hours

Parameters: Evaporation rate, Quantitation of deposition in different skin layers, Degree of percutaneous penetration

Standard In Vivo Absorption Studies

Objective: To study percutaneous absorption of drugs or environmental contaminants.
Duration: 48 - 72 hours
Parameters: Absorption rate (quantitation in blood, urine, and tissue samples)

Standard Irritation and Sensitization

Objective: To determine the potential of a test material to provoke ocular irritation, dermal irritation, or sensitization
Duration: Irritation – 1h to 3 weeks after a single topical or corneal administration. Sensitization – intra-dermal or topical induction doses followed by topical challenges with a non-irritating dose (6 - 8 weeks total)
Dose Administration:

1. Single patch administration
2. Multiple doses over 2 - 4 weeks
3. Topical (epicutaneous), intra-dermal, or corneal

Parameters:

1. Degree of pruritus, erythema, edema, papules, and vesicles
2. Corneal irritation, swelling, or injury
3. Microscopic integrity of corneal endothelium and other features of the eye like conjunctive, lens, or anterior portion of vitreous humor)

Standard Immunotoxicity

Objective: To determine the potential of a test material to induce immune suppression or immune enhancement.
Duration/Dosage: As explained earlier in sub-chronic and chronic exposure.
Parameters:

- Level I - Hematology, Histopathology, Quantity of T- and B-cells (cellularity of lymphoid organs), Blastogenesis (mitogen responsiveness; mixed lymphocyte reaction), Quantitation and function of NK cells, Macrophage function, Cytokine production.
- Level II - Kinetics of antibody production to T-dependent antigens, Quantity of IgM/IgG- producing cells, Delayed hypersensitivity responses to known sensitizers, Immune response to infectious agents and transplantable tumors.

Standard Reproductive Toxicity

Objectives: To determine potential adverse effects of a test material on mammalian gametogenesis, fetal organogenesis, delivery, lactation, neonatal survival, vitality and development.

Duration: Varies depending upon end points

- **Segment I** - Preconception, Treatment during gametogenesis, before mating; pregnant females treated throughout gestation, parturition, until weaning.
- **Segment II** - Pre-implanation, Treatment during gestation.
- **Segment III** - Perinatal to Postnatal, Treatment through at least 15 days of gestation and 21 days of lactation.
- **All Segments** - Data collection and evaluation are often done through two or more generations.

Dosage: As explained earlier in sub-chronic and chronic exposure.

Parameters: Preconception, Mating behavior, Pre-implantation and fertilization rates, Integrity and quantity of sperm and egg cells, Post Conception, Maternal weight gain, Time from conception to delivery, Litter size, Number of corpora lutea and implanted fetuses, Fetal mortality and viability, Placental weight, Pup weight and crown-rump length, Postnatal, Problems at parturition, Maternal-newborn relationship; maternal ability to rear young, Postnatal growth; time of occurrence of developmental landmarks, 21-day survival of young, Functional parameters after 21 days

Standard Safety Pharmacology

Objectives: To evaluate the effects of INDs on the function of all vital organ systems. These effects must be evaluated before human exposure. Safety tests in animal systems are often preceded by in vitro tests to evaluate biological and pharmacological activity at the cellular level. But standard safety pharmacology studies are not generally required for biotechnology-derived products. These studies define expected and unexpected pharmacological effects of the test material, especially on parameters associated with desired clinical activity.
Duration- Variable - depending on the test system
Test System/Animal System - *In Vivo*: pharmacologically relevant species. *In Vitro*: cell lines derived from relevant animal species.
Dose Administration- Variable
Parameters:
In Vivo: Respiratory (lungs and bronchi), Gastrointestinal and hepatic (esophagus, stomach, intestines, liver), Renal (kidney), Cardiovascular (heart and blood vessels), Blood, Endocrine (thyroid and other endocrine glands), Nervous/neurobehavioral (CNS and behavior).
In Vitro: Biological activity at the cellular level may be assessed in terms of: Receptor occupancy and affinity, Binding and transport kinetics, Production and or secretion of specific proteins in response to test material, and other pharmacological effects on cellular function.

Additional Services

- Generation of stable cell lines and cell banking services
- A-to-Z RNA interference services
- Cell Biology services including in house/custom cell lines, cell based assay development and antibody production
- Molecular biology services including gene synthesis, vector construction, sub cloning and expression.
- Xenograft mice services
- Microorganism identification (bacteria ID) services

Contact Us

- 100% IP rights belong to the client. A-to-Z RNA interference services
- For an immediate project quotation please contact us at info@altogenlabs.com or call Altogen Labs technical support at 512-433-6177. Please note that experimental details will help us provide an accurate price quote and timeline estimate.

View our complete catalog of services and how we can participate in the success of your pre-clinical research at altogenlabs.com

Contact us to discuss details, timeline estimates, and price!