KRISHNA TEJA PHARMACY COLLEGE

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VARIOUS APPROACHES TO DRUG DISCOVERY

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INTRODUCTION

- **Drug development** is the process of bringing a new pharmaceutical drug to the market once a lead compound has been identified through the process of drug discovery. It includes pre-clinical research on microorganisms and animals, filing for regulatory status, such as via the United States Food and Drug Administration for an investigational new drug to initiate clinical trials on humans, and may include the step of obtaining regulatory approval with a new drug application to market the drug.

- New chemical entities (NCEs, also known as new molecular entities or NMEs) are compounds that emerge from the process of drug discovery. These have promising activity against a particular biological target that is important in disease. However, little is known about the safety, toxicity, pharmacokinetics, and metabolism of this NCE in humans. It is the function of drug development to assess all of these parameters prior to human clinical trials.

- In addition, drug development must establish the physicochemical properties of the NCE: its chemical makeup, stability, and solubility. Manufacturers must optimize the process they use to make the chemical so they can scale up from a medicinal chemist producing milligrams, to manufacturing on the kilogram and ton scale. They further examine the product for suitability to package as capsules, tablets, aerosol, intramuscular injectable, subcutaneous injectable, or intravenous formulations. Together, these processes are known in preclinical development as *chemistry, manufacturing, and control* (CMC).

INTRODUCTION

- The various approaches to drug discovery include

1. Pharmacological
2. Toxicological
3. IND application
4. Drug characterization
5. Dosage form

- STEPS 1 and 2 constitute the PRECLINICAL STUDIES

PRECLINICAL TRIALS

- **Preclinical trial -** a laboratory test of a new drug or a new medical device, usually done on animal subjects, to see if the hoped-for treatment really works and if it is safe to test on humans.

PHARMACOLOGICAL APPPROACHES TO DRUG DISCOVERY

- Pharmacology as an academic principle can be loosely defined as the study of effects of chemical substances on living systems.
- This definition is so broad that it encompasses all the aspects of drug discovery, ranging from details of interaction between drug molecule and its target to consequences of placing the drug in the market

Components of pharmacological evaluation

1.Selectivity testing.

2. Pharmacological profiling.

3.Testing in animal models of disease.

4.Safety pharmacology.

SELECTIVITY TESTING

- The selectivity testing mainly involves 2 main stages:

1. **Screening for selectivity**
2. **Binding assays.**

Screening for selectivity

- The selectivity of a compound for a chosen molecular target needs to be assessed because it determines the **potency of the drug**.
- A selected compound may bind to molecular targets that are related or unrelated to the chosen molecular target thereby causing unwanted side effects.

Binding assays

- The aim of carrying out binding assays is **to determine the dissociation constant of the test compound as a measure of affinity to the receptor.**
- These assays are generally done with membrane preparations made from intact tissues or receptor expressing cell lines.
- In most cases the assay measures the ability of the test compound to inhibit the binding of a high affinity radioligand which selectively combines with the receptor in question.

PHARMACOLOGICAL PROFILING

- *Pharmacological profiling refers to determining the pharmacodynamic effects of a new compound. Either on:*

1. ***In vitro models:*** *Cell lines or isolated tissues.*
2. ***In vivo models****: Normal animals, animal models of disease*.*

The aim of pharmacological profiling is to answer the following questions:

- Does the molecular and cellular effects measured in screening assays actually give rise to the predicted pharmacological effects in intact tissues and whole animals?
- Does the compound produce effects in intact tissues or whole animals not associated with actions on its principle molecular target?

- Is there a correspondence between potency of the drug at molecular level, tissue level and the whole animal level.
- Do in vivo duration of action match up with the pharmacokinetic properties of the drug.
- What happens if the drug is continuously or repeatedly given to an animal over a course of days or weeks. Does it loose its effectiveness or reveal effects not seen on acute administration and whether there is any rebound after effect when it is stopped.

In vitro profiling

- In vitro profiling involves the studies on isolated tissues.
- This technique is extremely versatile and applicable to studies on smooth muscle* as well as cardiac and striated muscle, secretory epithelia, endocrine glands, brain slices, liver slices.
- In most cases tissue is obtained from a freshly killed or anaesthetized animal and suspended in warmed oxygenated physiological fluid solution.

Advantages

- The concentration-effect relationship can be accurately measured.
- The design of the experiments are highly flexible allowing measurement of:
- Onset and recovery of drug effects.
- Measurements of synergy and antagonism by other compounds.

Disadvantages

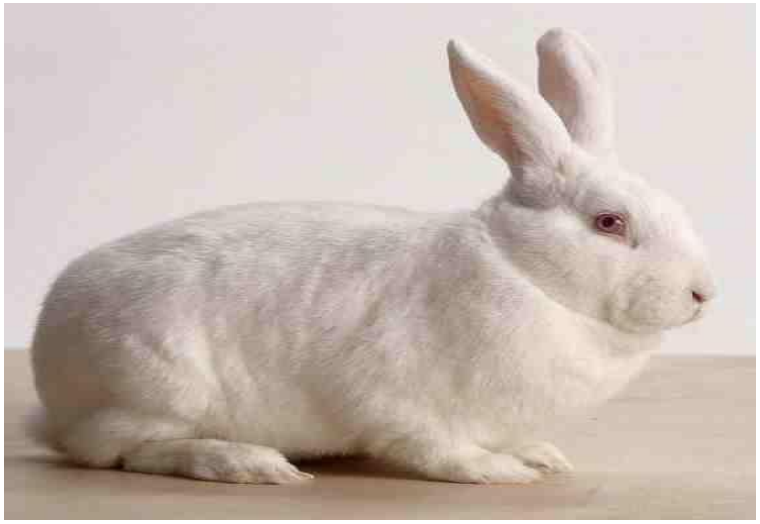
- The tissues normally have to be obtained from small laboratory animals, rather than humans or other primates.
- The preparations rarely survive for more than a day, so only short experiments are feasible.

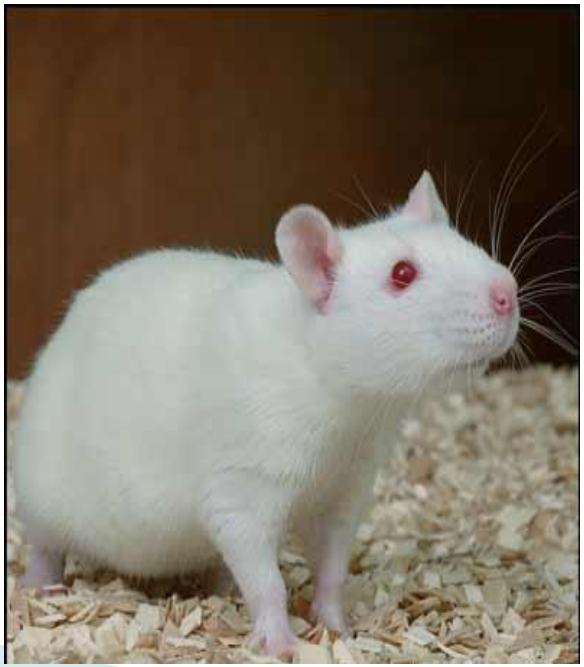
In vivo profiling

- In vivo profiling involves the testing on normal animal models.
- These methods are time consuming and very expensive.
- They can be done on larger animals.
- A particularly important role of in vivo experiments is to evaluate the effects of long term drug administration on intact organism.

SPECIES DIFFERENCES

- It is important to take species differences into account at all stages of pharmacological profiling.
- The same target in different species will generally differ in its pharmacological specificity.
- The growing use of transgenic animal models will undoubtedly lead to an increase in animal experimentation





- Here there involves the use of animal models with the human disease for which the drug has been prepared.
- There tests are done to answer a crucial question to whether the physiological effects result in a therapeutic benefit.
- Despite the range of diversity of animal models from humans these tests will provide a valuable link to the chain of evidence.

TYPES OF ANIMAL MODEL

Animal models of disease can be broadly classified into

1. Acute physiological and pharmacological models
2. Chronic physiological and pharmacological models
3. Genetic models

Acute physiological and pharmacological model

- These models are intended to mimic certain aspects of the clinical disorder. The examples are:
- Seizures induced by electrical stimulation of brain as a model of epilepsy
- The hot plate for analgesic drugs as a model of pain.
- Histamine induced bronchoconstriction as a model of asthma.

Chronic physiological and pharmacological model

- These models involve the use of drugs or physical interventions to induce an ongoing abnormality similar to clinical condition. The examples are:
- The use of alloxan to inhibit insulin secretion as a model of TYPE I diabetes mellitus.
- Self administration of opiates, nicotine or other drugs as a model of drug dependence.

Genetic animals

- These are transgenic animals produced by deletion or over expression of specific genes to show abnormalities resembling the human disease.
- The development of transgenic technology has allowed inbred strains to be produced with the gene abnormality to be present throughout the animals life.
- More recent developments allow more control over timing and location of the transgenic effect.

VALIDITY CRITERIA IN CONTEXT TO ANIMAL TESTING

An animal model produced in a lab can never exactly replicate a spontaneous human disease state so certain validity criteria have been set up, they are:

1. ***Face validity***
2. ***Construct validity***
3. ***Predictive validity***

1. FACE VALIDITY:

   This validity refers to the accuracy with which the model reproduces the phenomena(symptoms, clinical signs and pathological changes) characterizing the disease.

2. CONSTRUCT VALIDITY:

   This refers to the theoretical rational with which the model is based i.e. the extent to which the etiology of the human disease is reflected in the model.

3. PREDICTIVE VALIDITY:

- This validity refers to the extent to which the effect of manipulations(e.g. drug treatment) in the model is predictive of effects in the human disorder.
- This is the most important of the 3 as it is most directly relevant to the issue of predicting therapeutic efficacy.

SAFETY PHARMACOLOGY

- Safety pharmacology is the evaluation and study of potentially life threatening pharmacological effects of a potential drug which is unrelated to the desired therapeutic effect and therefore may present a hazard.
- These tests are conducted at doses not too much in excess of the intended clinical dose.

- Safety pharmacology seeks to identify unanticipated effects of new drugs on major organ function(i.e. secondary pharmacological effects).
- It is aimed at detecting possible undesirable or dangerous effects of exposure of the drug in therapeutic doses.
- The emphasis is on acute effects produced by single-dose administration rather than effects on chronic exposure as in toxicological studies.

TYPE	PHYSIOLOGIAL SYSTEM	TESTS
CORE BATTERY	*CENTRAL NERVOUS SYSTEM*	Observations on conscious animals
		•Motor activity
		•Behavioral changes
		•Coordination
		•Reflex responses
		•Body temperatures
	CARDIVASCULAR SYSTEM	On anaesthetized animals
		•Blood pressure
		•Heart rate
		•ECG CHANGES
		Tests for delayed ventricular repolarisation
	RESPIRATORY SYSTEM	Anaesthetized and conscious
		•Respiratory rate
		•Tidal volume
		•Arterial oxygen saturation

TYPE	PHYSIOLOGIC SYSTEMS	TESTS
FOLLOW- UP TESTS	*CENTRAL NERVOUS SYSTEM*	•Tests on learning and speech
		•More complex tests for changes in behavior and motor function.
		•Tests for visibility and auditory function
	CARDIOVASCULAR SYSTEM	•cardiac output
		•Ventricular contractility
		•Vascular resistance
		•Regular blood flow
	RESPIRATORY SYSTEM	•Airway resistance and complince
		•Pulmonary arterial pressure
		•Blood gases

TYPE	PHYSIOLOGIC SYSTEM	TESTS
SUPPLEMENTARY TESTS	*RENAL FUNCTION*	•Urine volume, Osmolality, PH, •Proteinuria
		•Blood Urea/Creatinine
		•Fluid/Electrolyte balance
	AUTONOMIC NERVOUS SYSTEM	•C.V.S, Gastrointestinal and respiratory system responses to agonists and stimulation of autonomic nerves.
	GASTROINTESTINAL SYSTEM	•Gastric secretion
		•Gastric PH
		•Intestinal motility
		•Gastrointestinal transit time

THANK YOU