Pharmacology skills for drug discovery

Why is pharmacology important?

Pharmacology, the science underlying the interaction between chemicals and living systems, emerged as a distinct discipline allied to medicine in the mid-19th century, when the basic principles of physiology and chemistry provided a framework for understanding how therapeutic drugs act. As a discipline, it grew out of the need to understand and improve therapeutics, and this remains its main focus.

Rational drug design, based on pharmacological principles, began in the early 20th century, and accelerated rapidly from the mid-20th century onwards, with essential contributions from pharmacologists. The majority of currently used drugs, which have steadily transformed medical practice, have come from applying pharmacological thinking to the drug discovery process. Life-changing innovations include antihypertensive drugs, antibiotics, antiviral drugs, antipsychotic drugs, surgical anaesthetics and oral contraceptives. Illnesses that were previously untreatable are now routinely and successfully treated. Transplant surgery only became possible following the discovery of a new class of immunosuppressant drugs. This revolution in ideas about how to invent and test new medicines could not have happened without pharmacologists, such as James Black, George Hitchings and many others.

There remain many areas of unmet medical need (e.g. Alzheimer's disease, stroke, cancer, obesity) for which we still lack effective treatments, so it is vital that the expertise needed for drug discovery is sustained.

The human genome and its ramifications are providing much new information about disease mechanisms and possible new therapeutic approaches, providing the basis for new drug discovery projects – presaging a second revolution in the view of many biomedical scientists – in which pharmacologists will play an essential role.

What do pharmacologists contribute?

Understanding drug action at all levels, ranging from molecular to clinical, defines the broad yet distinctive scope of pharmacology. What matters to the individual patient is the beneficial effect of the drug on symptoms, disabilities and survival, balanced against its unwanted effects. The pharmacologist needs to understand drug action across all levels of biological organisation, from the molecules (drug targets) with which drug molecules interact chemically, through the cellular and physiological effects that this interaction produces, and the way in which these effects influence the disease process, culminating with the expected impact on patient care. Both basic and clinical pharmacologists play an essential role in any drug discovery team.

What are the special skills of a pharmacologist in drug discovery?

1. Basic pharmacologists (Table 1)

Quantitative Pharmacology

Knowledge of the interaction between drug molecules and targets is a key pharmacological skill. Molecular biological approaches have greatly increased our knowledge of the structure and function of drug targets, such as receptors, enzymes and transport molecules, revealing diversity far greater than had been realised. Molecular pharmacologists command the experimental approaches to analyse the action of novel substances (e.g. candidate drugs) in terms of this target diversity. Analytical pharmacologists apply rigorous quantitative methods to characterise, in terms of potency and specificity, the action of novel compounds. An ability to apply an analytical, mathematical approach (including regression, curve fitting and the appropriate statistical methods) is a core skill. Knowledge of how drugs influence cellular functions (e.g. cell division, contractility, secretion, neural transmission, gene expression), is also essential in order to analyse drug action at this level.

Systems Pharmacology/in vivo pharmacology

Understanding the experimental approaches for analysing drug action at the level of whole organs (e.g. heart, liver, kidney) and systems (e.g. Central Nervous System, Cardiovascular System, Gastrointestinal System, Respiratory System, Immune/Inflammatory System, Endocrine System) is a core pharmacological skill that requires an understanding of both the interactions between systems and the systems' response to drugs. Such methods commonly involve measurements on whole animals, free-moving or anaesthetised, which require specialised training and qualification in order to gain a personal licence under the Animals (Scientific Procedures) Act.

Disease modelling

Modelling human disease in experimental animals is the responsibility of the pharmacologist. It requires both an understanding of the aetiology and treatment of human disease and a detailed knowledge of disease models (their mechanistic basis, response to standard drugs and relevance to the human condition). Animal models often provide insight into likely readouts of the functional effect or therapeutic response to a drug (biomarkers). Usually it is the pharmacologist who quantifies biomarker changes and makes recommendations on their likely translation to the clinic

Statistical Methods

The ethical use of animals requires a strong grasp of the principles of experimental design, particularly in the case of modelling human disease in animals. Balancing the need to test a hypothesis *in vivo* with the requirement to minimise the numbers of animals studied usually falls to the project pharmacologist, and requires an intimate understanding of the normal distribution, parametric and non-parametric statistics, tests of significance and power calculations.

Pharmacokinetics and pharmacokinetic/pharmacodynamic (PK/PD) relationships

It is impossible to fully understand the action of a drug unless the relationship between drug exposure and effect has been reasonably well described. Pharmacologists are

responsible for defining the pharmacodynamics of a drug in vivo, but must also have a working knowledge of absorption, distribution, metabolism and excretion (ADME) of drugs in animals and humans, understand the use of drug and metabolite measurements to quantitate these processes, and relate them to the magnitude and time-course of the actions of the drug.

Safety Pharmacology

The broad systems understanding of the pharmacologist is required for rational prediction of the likely 'on-target' effects of novel compounds, the definition of likely 'off-target' beneficial and adverse effects and testing for their occurrence in experimental models. Predicting and testing for likely drug interactions, both pharmacodynamic and pharmacokinetic, also falls into the pharmacologist's remit. It is usually the pharmacologist who is responsible for dosing novel drugs to animals, determining their tolerability (often by observational skills) and contextualising their effects by reference to the pharmacology of the drug and the model system used. In practice, an understanding of the pharmacological differences between synthetic chemicals and biopharmaceuticals is essential.

Table 1: Core and Aligned Skills for Basic Pharmacologists

	Core	Aligned
Quantitative Pharmacology	Technical Skills GPCRs, enzymes & other targets Concentration/dilution calculations Regression & curve fitting	Mathematical skills Analytical skills
In vivo Pharmacology	Experimental Design, dose calculations Ethics/NC3Rs & working with ASPA (1986) Animal handling/technical skills	
Pharmacology of key body systems	Central Nervous System; Cardiovascular System; Gastrointestinal System; Respiratory System; Immune/Inflammatory System; Endocrine System	Specialist systems understanding (e.g. Immunology)
Disease modelling	Animal handling/technical skills Experimental readouts and biomarkers Knowledge of human disease; current therapies & standard drugs; genetics of disease Target validation	Specialist disease understanding (e.g. Alzheimer's disease)
Statistics	Normal Distribution Parametric and non-parametric statistics Tests of significance Power calculations	
PK/PD relationships	Pharmacokinetics Quantitative pharmacodynamics Bioanalysis	Clinical pharmacology
Safety Pharmacology	Rational prediction of on-target and off-target effects. Therapeutic window Dose ranging tolerability studies Drug specificity & non-specific effects	Toxicology

2. Clinical pharmacologists

Clinical Pharmacology

Knowledge of human pharmacology, and an understanding the relationship between the desired and undesired actions of a drug, is a key guiding principle in drug development, and the responsibility of the clinical pharmacologist. The fundamental contribution of the clinical pharmacologist is an understanding of the exposure (dose) effect relationship. Effects can be beneficial or adverse and vary between different tissues of the body. It is the sum of these that determines the benefit/risk proposition for any medicine. The clinical pharmacologist must consider how the drug is to be given (both the dose and route of administration) in order to optimise the balance of benefit to risk. Different patient populations may have very different profiles and these must be explored in order to be able to recommend the right dosing regimen. Finally, the clinical pharmacologist must consider how the dosing regimen needs to be adjusted to take account of other medicines a patient may be taking, or how kidney or liver disease might affect clearance of the drug.

Translational Medicine and Disease Pathophysiology

Understanding of disease mechanisms, current therapies and areas of unmet medical need in a particular indication is an essential skill of the clinical pharmacologist, as is the extrapolation from preclinical studies (e.g. animal models of disease) to the human condition. These translational skills are relevant to many of the other core skills, which are contextualised by an understanding of the relevant pathophysiology.

Experimental Medicine

Medicines are typically registered based on results from large-scale clinical trials. In early development, however, the objective is to gain an understanding of how the candidate medicine affects the disease process. This is often addressed in small-scale, intensive studies in patients with the clinical condition – known as experimental medicine. Modelling and simulation have become key features of these types of study providing a more integrated approach to understanding PK/PD relationships, and require a mix of mathematical and biological skills.

Systems Biology and Biological Sciences

For the clinical pharmacologist, an understanding of the systems underlying the (often complex) drug response in normal subjects and patients requires an understanding of human systems biology and a knowledge of the underlying processes driving both human disease and the pharmacology of drug effect. As most current drugs are pluripotent, the integration of *in vitro* and *in vivo* animal model data is essential for the prediction of the likely effects of a drug in man. Redundancy is common in biological systems and it is vital to understand whether the pathway under evaluation will really influence pathophysiology. Similarly, a beneficial impact in one tissue may be adverse in another and this needs to be considered early in development.

Pharmacogenomics and other ‘omics’ technologies

Basic understanding of modern ‘omics’ technologies, particularly genomics, are playing an increasingly important role in drug discovery and development. Pharmacogenomics

concerns the link, now increasingly recognised as important for 'personalised medicine', between the genetic make-up of an individual and his/her response to a drug. Increasingly, familiarity with database technology and 'data mining' techniques (i.e. bioinformatics) are becoming key requirements of the clinical pharmacologist. In the end, the clinical pharmacologist will be key in integrating information on environmental factors (e.g diet), disease sub-phenotypes based on molecular stratification and host genomic (and other omic) factors in order for us to realise the promise of personalised medicine.

Core and Aligned Skills for Clinical Pharmacologists

	Core	Aligned
Drug and disease mechanisms	Critical evaluation of literature relevant to CPT including basic pharmacology, toxicology and phase I, II, III and IV clinical trials and meta-analyses. Use of knowledge of mechanisms of drug action to extrapolate likely effect of new drugs, doses and combinations Anticipate (and hence minimise), detect, manage, report and analyse adverse drug reactions (ADRs). Identify means to investigate these effects in humans	Computational/ systems biology Drug safety and pharmacovigiliance Experimental/translationalmedicine
PK PD	Understand the determinants of exposure response relationships and means to investigate them in humans Use pharmacological principles to devise, or advise on, appropriate dosing regimens Identify patient characteristics that have the potential to alter PK/PD effects of the drug	Clinical Pharmacokinetics
Therapeutics	Prescribe rationally in individual patients Advise on cases of overdose or poisoning Anticipate (and hence minimise), detect, manage, report possible drug prescription or administration errors Identify the potential for an means to manage interactions between treatments and disease conditions	Patient safety Personalised medicine (sometimes also termed precision medicine) Medicines Management. Heath Technology Assessment Creation of treatment guidelines