From Discovery to the Clinic

Steering the Innovation Pipeline from Research Discovery to Therapeutics

Guidance for Researchers Navigating the Innovation Pipeline from Research Discovery to Therapeutic Drug

Key messages:

- *It is never too early to reach out to the facilities within **TIA's Small Molecules Capability** for advice on making the transition from research to development.*
- *Early engagement with TIA or one of the facilities will enable you to leverage their significant expertise and expedite your translation to clinical development.*
- *Understanding the process and the fact that you don't have to do it all yourself will maximise the chances of success.*

More accessible means to screen diverse chemical libraries in a high-throughput setting, as well as advances in assay technology, has accelerated early stage discovery of hit compounds.

Typically, academic researchers identify new visions or paradigms into the pathways of a disease process which, after validation via *in vitro* or *in vivo* models, permits subsequent investigators to design a pipeline that will lead to the development of a medicine to prevent or control the disease process.

Commercialisation is the route that transforms ideas and technologies into medicines that can be used in clinical practice.

This document outlines key points on the drug discovery and development journey and provides an overview of the necessary processes to successfully translate science from laboratory to patient.

TIA's **Small Molecules Capability** is a network of research infrastructures in Australia with expertise in progression of early-stage discoveries through to preclinical development. They include:

- Compounds Australia (CA), Griffith University
- A network of 10 high-throughput screening centres across the nation that may be accessed through TIA's Pipeline Accelerator voucher system
- Australian Translational Medicinal Chemistry Facility (ATMCF), Monash University
- Centre for Drug Candidate Optimisaton (CDCO), Monash University
- Centre for Integrated Preclinical Drug Development (CIPDD), University of Queensland

Our Mission

Therapeutic Innovation Australia Ltd (TIA) enables and accelerates the translation of research discovery along the therapeutic development pipeline by ensuring world class research infrastructure facilities are accessible to the Australian translational research community. We partner with leading national research infrastructure facilities across three capabilities, Small Molecules, Biologics & Vaccines and Cell & Gene Therapies, to deliver world-class research infrastructure across Australia.

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Early engagement with TIA or one of the facilities will enable you to leverage their significant expertise and network to expedite your research through clinical translation.

"Drug Discovery and Development 101"

Drug discovery and development is an expensive process with high costs for research and development (R&D). It can take between 10-15 years to develop a single new drug/molecule from the time of discovery to when it is available for treatment of patients. For every 5-10,000 small molecules screened and investigated that entered the development pipeline, ultimately only 1 attained approval as a therapeutic, with the total cost for R&D for each drug likely to be in the range of $1 - $2 billion. This amount includes the cost of the many failed programs and so it is most helpful to come to a brief understanding of the drug discovery and development process and its challenges.

Drug Discovery and Development in the 21st Century

The modern drug discovery and development pipeline may be summarised by the key stages below and summarised in Figure 1.

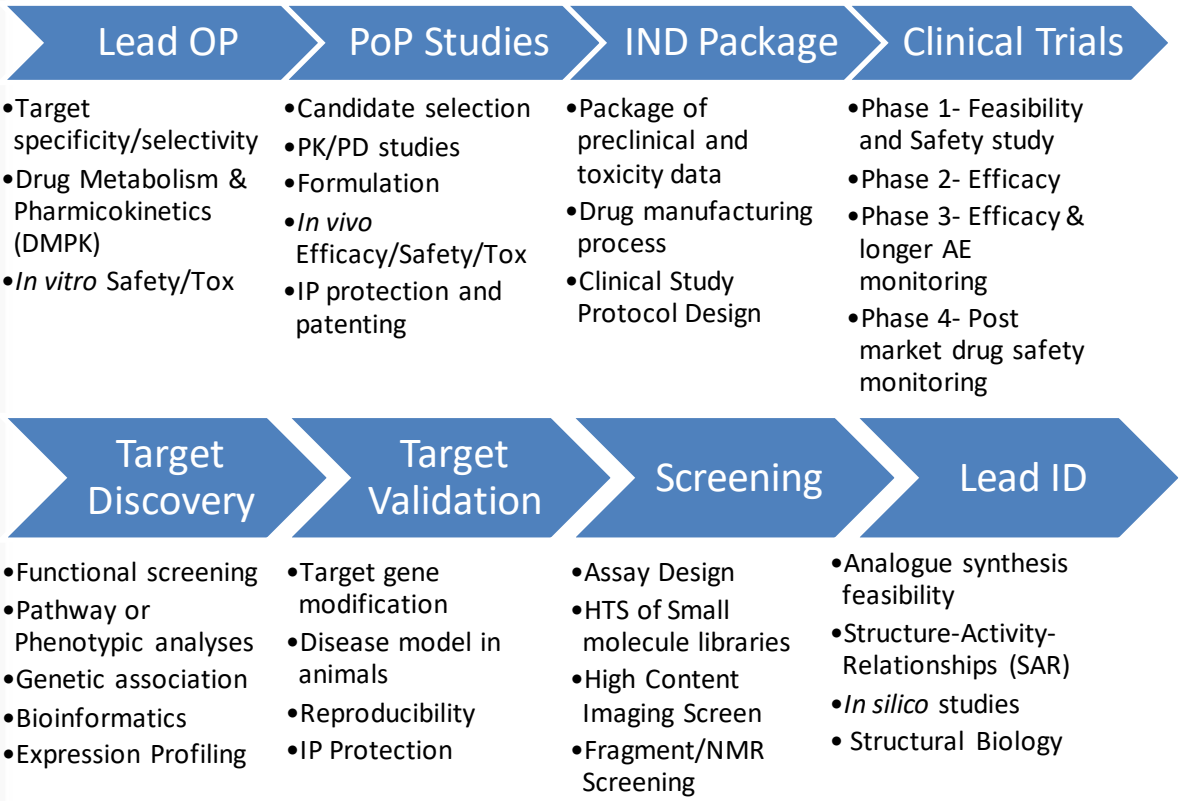

Figure 1: Stages and Process involved in Modern Drug Discovery and Development

Modern drug discovery employs techniques that enable the identification of the biological origin of a disease and in most instances, the potential targets for therapeutic intervention. **Target Discovery** is the process of identifying targets that are differentially expressed in the diseased and normal states. The process usually involves genomic and/or proteomic techniques. Typical techniques include genome wide association studies,

expression(mRNA/protein) profiling, phenotypic/pathway analysis, functional screening (knock out or knock down of target gene) and more recently, bioinformatic data mining (genomic cohorts). An ideal target should aim to be able to produce a drug that is efficacious, safe, has commercialisation potential (IP protection and patenting) and exceeds current clinical practice (standard of care/competition). These factors are loosely termed whether a target is "druggable" by the pharmaceutical industry.

The next stage called **Target Validation** is where one demonstrates that the molecular target of a small molecule has a functional role in the disease phenotype that you are targeting. Ideally the set of target validation data obtained in this process demonstrates reproducible evidence that manipulation of the target gene levels; either by genetic methods (siRNA, CRISPR), cellular assays and/or in animals, antibodies, peptides and/or tool molecules (not drug-like).

Once a therapeutic target has been validated, **High-Throughput Screening** (HTS) of small molecule libraries may be performed and has been proven a very effective technology for the identification of compounds that interact with your target, typically called "hits" from a screen. Advances in robotic automation of assay procedures such as pipetting and assay format miniaturisation to extreme high densities in microtitre plates have greatly reduced the time required for the initial drug screening and hit-to-lead (HtL) screening periods. Typically, the target of interest may be screened using fluorescent read outs of receptor (GPCR)-binding, enzymatic (kinase) reactions or ion channel (Ca^{2+}) flux to name just a few of the common types. Recently, many groups have used cell-based assays allowing high-content imaging of cellular features and functions to monitor live cell responses during HTS.

https://www.therapeuticinnovation.com.au/small-molecules

How can TIA's SMOL Network help? Please go to the above link for further information on how TIA can put you in touch with the right HTS facility.

One of the potential disadvantages of small molecule HTS is that the small molecule libraries themselves may lack diversity and thus address a limited range of biological targets. Many publications have claimed that 70% of approved small molecule drugs target only four human biological target types (33 % GPCR, 18% ion channels, 16% nuclear receptors and 3% act on kinases). This may be due to the fact that many early versions of these small molecule libraries were based on strict compliance with "drug-like structures" consisting of certain physicochemical boundaries and properties (known as Lipinski's rule of 5"). However, with the advent of better structure-ligand based computer-guided approaches and other, more intelligent algorithms, larger libraries (>500k small molecules) may now be used for HTS of a biological target that can be completed within days (ultraHTS) as opposed to months somewhat negating the need for more focussed libraries.

https://www.griffith.edu.au/griffith-sciences/compounds-australia

How can TIA's SMOL Network help? Please go to the above link for further information on Compounds Australia library and compound logistics capabilities.

It is important to note that at the conclusion of the screening phase, you will not have a small molecule drug that is ready for preclinical or clinical testing – this is just the start of the drug development journey.

Lead Identification describes once the many hits have been whittled down to a few a chemical leads that have been found to be synthetically stable, feasible and drug-like in primary and secondary screens with reasonable affinity, specificity and selectivity for the target of interest. Hits from the HTS campaigns form the basis for the Lead Identification phase where those small molecules that have been demonstrated to be reproducibly active against the biological target and where this activity can be titrated to obtain concentration-dependent responses (determination of IC50 or Ki). Structure-activity-relationships (SAR) can begin to be defined and evidence of early selectivity against other similar biological target classes or family members with preliminary favourable toxicity, drug metabolism and pharmicokinetic (DMPK) properties. In addition, further knowledge such as binding measured with nuclear magnetic resonance (NMR) and/or mass-spectrometry or even the crystal structure of the binding interaction is ideal but not always attainable at this early period.

https://www.monash.edu/atmcf

How can TIA's SMOL Network help? Please go to the above link for further information on the Australian Translational Medicinal Chemistry Facility capabilities and how they can help you build new leads and new IP.

Lead Optimisation describes the process by which lead molecules are whittled down to a few drug candidates that are identified post-screening and HtL. For a small molecule to be considered a drug-like candidate, it should bind and inhibit the biological target in a specific and selective manner but moreover, it should also have suitable physicochemical properties. Favourable *in vitro* metabolism and a pharmacokinetic profile including suitable absorption, distribution, metabolism and excretion (ADME), preferably with high oral bioavailability and plasma protein binding < 90%. Before undertaking *in vivo* efficacy and toxicity studies, it is important to develop a stable formulation for the intended dosing route *in vivo*. Furthermore, low toxicity in screens such as for cellular cytotoxicity, hERG ion channel cardiotoxicity and Ames mutagenicity tests, needs to be demonstrated. Concurrently, a patent search should be instigated to ensure one has the freedom to operate in developing IP.

https://www.monash.edu/pharm/research/areas/optimisation

How can TIA's SMOL Network help? Please go to the above link for further information on the Centre for Drug Candidate Optimisation capabilities and how they can help you improve your compound design, selection and progression to drug candidates.

The definition of **Proof-of-Principle (PoP) Studies** varies depending on the reference point as compared from academia to that of industry, but in this document, it is specifically referring to the key preclinical trials performed in the drug development process to evaluate a drug's safety and efficacy in animal species. These preclinical studies are designed to determine the pharmacology and toxicology parameters of a drug: Pharmacokinetic and pharmacodynamic measures deal with desired pharmacological effects of a drug in animal models whilst toxicology is aimed at identifying unwanted or undesirable effects. Preclinical efficacy studies are essential to evaluate the efficacy and adverse effects in the therapeutic dose range. The duration of action is likely underpinned by the half-life of the drug in the animal model which in turn will inform design of an Investigational New Drug (IND)-enabling toxicology/safety pharmacology program, the data from which are essential for gaining regulatory approval.

https://biomedical-sciences.uq.edu.au/research/research-groups/centre-integrated-preclinical-drug-development

How TIA's SMOL Network can help? Please go to the above link for further information on the Centre for Integrated Drug Preclinical Drug Development capabilities and how they can help you determine your drug candidate's efficacy in rodent models of human disease under GLP conditions.

Investigators should be prepared to maximise the protection of their intellectual property (IP) through filing for patents (see below) once data from PoP experiments evidently supports their application. The definition of IP is "an intangible asset that is the product of human knowledge and ideas that may have commercial value." A patent is granted by government and yields its owner exclusive rights to the idea or invention for a limited period of time. In drug development this period is commonly based on US law and comprises of 20 years of protection from others making, using or selling your idea/invention. Drug candidates that have a longer patent exclusivity period remaining when first-in-human (FIH) studies are started will more likely have higher inherent commercialisation value when external pharma partners or investors evaluate the potential strength and value of the investigator's IP.

Once ready to consider putting together an **IND package** for submission to the US FDA, it is also very important not to overlook the feasibility and cost of manufacture of high-quality, clinical grade material for these studies, often referred to as "Chemistry, Manufacturing and Controls (CMC), and one of the most common points of failure of drug development.

An IND application must typically include the following package:

- All data generated to date including preclinical pharmacokinetic/pharmacodynamic (PK/PD) and toxicity (safety and tolerability) study data
- CMC/drug manufacturing details (API formulation, dosing regimen and route of administration)
- Clinical research protocol and design for proposed studies
- Information about the investigators and sponsors of the proposed studies

Once the developers of a drug have consulted investigators/clinical research organisations for the design of Phase1 **Clinical Trials**, trials are conducted for the first time in healthy human subjects with the intention to

answer specific questions about safety and pharmacokinetics. Once Phase 1 clinical trials are complete and there are no untoward safety or PK concerns, the drug will be progressed to Phase 2a proof-of-concept clinical trials in the target patient population.

What about Intellectual Property and Know-How?

If an investigator has a new discovery/invention in relation to a potential IND application whilst putting together initial proof of principle data, they will usually need to disclose it to their employer (academia or industry), consistent with the obligations of an employment contract that have clauses governing IP policies. You must know who owns or has claim to IP associated with the potential product. Collectively this is known as your **"freedom-to-operate"**.

Most universities and research institutes have a technology transfer and/or commercialisation office and you should approach them as early as possible for them to guide you through the process of developing a successful IP strategy. If a discovery shows promise, the organization's technology transfer/commercialisation team will perform a patent search to help file a new patent application with the appropriate government IP office.

Within academic research institutions, discoveries or inventions that stem from research sponsored by federal government grants often lead to IP that is owned by the institutions themselves despite being created by their investigators. However, legislative changes decades ago have created incentives for academic research institutions to commercialise the IP through licensing to encourage the sharing of the fruits of the IP with its inventors. Consequently, it is in the best interests of the academic research institution that patent protection and licensing of IP have become a significant part of their operations.

Thus, it is important for the investigator to **not make any public disclosures of the research findings** that may impair the ability to obtain patent protection for their discovery. Such public disclosures include seminars, papers, conference abstract submissions and posters, any presentation that is outside of the bounds of the investigator's own research team. Any public disclosure will be assessed by patent examiners as "prior-art", leading to the probable rejection of claims sought to be granted.

Furthermore, the premature publishing of a patent without any drug candidate structures within the field of drug discovery and development, may lead to great difficulty in obtaining patent protection later on when the drug candidate has been fully characterised due to prior-art having previously been established by the earlier patent publication. With the help and guidance of experts within technology transfer and/or commercialisation teams either within academia or industry, it is possible to both publish one's research and commercialise it with stepwise, careful IP management strategies.

Further information/ Contacts

If you would like to discuss next steps in your product development, then please contact Dr John Parisot, the scientific liaison and business development manager at TIA who will be able to guide you through the initial stages: j.parisot@therapeuticinnovation.com.au

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