aptuit

aptuit.com

DRUG DISCOVERY IN THE 21st CENTURY

HOW TO SAVE TIME, MONEY AND RESOURCES WHILE INCREASING YOUR CHANCES OF SUCCESS

CONTENTS

aptuit

1. INTRODUCTION

The primary aim of most research teams performing drug discovery is to make a significant positive difference to the management and quality of life of patients suffering from diseases where there is a clear unmet clinical need. The discovery process, if such a thing really exists, is scientifically challenging, typically takes several years to reach candidate selection, is notoriously difficult to navigate and manage, and devours R&D budgets. Small and virtual companies are particularly vulnerable to the vagaries and expectations of the investor market with regular resourcing gaps and strict financial constraints to deliver on time and to budget.

Given the high risk of failure, it is not surprising to note that very few commercial companies receive a financial return on their shareholders' original investment. However, the rewards for success can be huge both clinically and financially. History shows, and numerous industry reports reveal, that the vast majority of drug discovery programs fail to produce novel compounds that make it to market. It is therefore totally logical to have a well-planned and executed discovery process to help 'kill-quick' no hope projects, and focus on improving the translation of testing into humans, therefore reducing late-stage attrition and facilitating rapid and successful preclinical and clinical development.

The financial headaches of continued high attrition rates, particularly in late stage clinical development, are forcing R&D organizations to radically re-think the discovery model and look at significantly improving the translational aspects of target validation, target engagement and target response. On the positive side success rates have improved in recent years,[1] with the implementation of 'fast to fail' models[2] and various iterations of the three pillars of survival.[3] These drivers are making many companies and research teams abandon traditional linear discovery processes focused on internal knowledge and capabilities in favor of new models based on effective outsourcing, external collaborations and new types business relationship. These relationships can be between pharma companies, academia, charities biotechs and even contract research companies (CRO).

In this new paradigm a truly streamlined and effective process is often challenging to maintain and many 'new' process owners or decision makers have limited drug discovery expertise. Academic and virtual organizations tend to utilize external expertise from a myriad of consultants and numerous research organizations.

To help, here we provide an overview of the various dynamic stages of the drug discovery process, as well as advice on the key factors to consider at each stage to increase your chances of success.

We hope you will enjoy this e-book, it's not rocket science, but we hope it makes you re-think the road ahead. For more information on building an efficient and effective drug discovery pipeline, please contact our team at discovery@aptuit.com.

2. DRUG DISCOVERY STARTS WITH FINDING FUNDING

WHAT ARE THE OPTIONS FOR DRUG DISCOVERY FUNDING?

Developing a new drug from concept through to the launch of a finished product is a complex process that is estimated to cost in excess of $1 billion.[4] It's therefore easy to see why pharmaceutical organizations are looking to share risks and as a consequence principal investors at each stage of the R&D process are emerging. Securing adequate funding for early stage drug discovery continues however to be challenging, often with a level of complexity that can make it feel like navigating a minefield.

As a result, the diversity of financing options available to biotech companies is increasing. There a number of funding options available, including:

- Government
- Not-for-profit organizations
- Venture capital
- Large Pharma
- Patient foundations

Government funding initiatives, such as Horizon 2020 and Innovate UK, provide grants to businesses and research organizations to drive science and technology innovation, including drug discovery and in particular personalized medicine.[5] Typically government funding initiatives will have various funding 'competitions' throughout the year focusing on different sectors and industries, such as the development of vaccines and then use of synthetic biology to develop novel materials. These 'competitions' can provide a valuable opportunity to increase the likelihood of receiving funding by tying your program to the theme or aim of the 'competition'.

Not for profit organizations, for example the Wellcome Trust and the National Institutes of Health, continue to form a pillar of funding for early stage drug discovery. Venture capital firms are another traditional method of financing drug discovery programs for biotech, which tend to take into account the need to develop new drugs (rather than the drive to make improvements to existing drugs) when investing.[6]

In recent years, large pharma has also been exploring additional ways to invest in emerging biotech companies, which simultaneously expands its access to attractive early-stage drugs for in-licensing. Another way large pharma is helping fund drug discovery is via academic collaborations, such as GSK's Discovery Partnerships with Academia (DPAc) program. These initiatives see the researchers work with a team of GSK scientists in GSK labs, with access to their facilities, experts and often even their compound libraries.

2. DRUG DISCOVERY STARTS WITH FINDING FUNDING

KEY POINTS

It is also worth noting that university Technology Transfer Offices (TTO) play a different, yet central, role in the biotech industry when it comes to funding. In the US, the Bayh-Dole Act gave universities the right to a significant stake in the technology's economics for conducting technology transfer out of publicly funded research. This model has also been largely adopted in Europe, with similar legislations in place that see the TTOs acting as gatekeepers between academia and industry. The main aim of the TTOs is to enable the transfer and translation of academic discoveries into practical tools, processes and technologies that can be commercialized and used to bring new medicines to patients. However, there is some feeling in the pharmaceutical industry that the former scientists that tend to staff TTOs often lack significant industry experience.[7] Therefore, in some cases it may be necessary to round out the 'commercialization team' by bringing in additional supporting players. Contract Research Organizations (CROs), for example, can help fill the gap of industry knowledge and help with best practices in successfully getting a potential drug to market, as many scientists in these organizations have many years of experience working with (and within) large pharma.

WHAT ARE THE DIFFERENCES IN FUNDING SOURCING?

Although the five main types of funding organizations are standard globally, there are some key differences between territories. For example, in the US much more capital is invested in life sciences than in Europe, and the European venture capital market is not as developed, meaning there are many more venture capital opportunities in America.[8] Funding also varies across therapeutic areas. Rare disease funding has seen a large increase over the past decade in terms of both dollars raised and number of companies funded, while threefold more venture dollars were raised by companies working on drug improvements centered around previously approved pain drugs than for novel drug R&D in Alzheimer's Disease.[9] Patient Foundations, such as the Michael J. Fox Foundation, CHDI Foundation and ALS Association, help fill funding gaps for their respective diseases, with the common aim to accelerate breakthroughs that will make a difference to patients. This can be through increasing the speed of development of treatments that can slow, stop or even reverse the progression of diseases, the development of more effective medications, and the creation of therapies that can address or avoid the debilitating side effects caused by currently available drugs.

2. DRUG DISCOVERY STARTS WITH FINDING FUNDING

These foundations tend to look to form partnerships with groups performing promising research in their disease area of interest, and make a commitment to find resources and support, whether they be financial, scientific or practical. When seeking support from such organizations, we recommend you look to their websites for the types of projects they are interested in, where you can also find indications as to the level of data you may need to present in order to be considered.

INCREASE YOUR CHANCES OF SECURING FUNDING FOR YOUR DRUG DISCOVERY PROGRAM

To increase your chances of securing funding, investigate which organizations and institutions are looking to fund programs similar to the one you are conducting. It is also important to find out how comprehensive your data package needs to be to present to the potential investors, and ensure you correctly and fully fill out any application forms. Securing investment from a company or organization is a one-shot opportunity; if your proposal fails once, it is unlikely to be looked at again, even if you re-submit with additional information.

Fortunately, there are experts available to help with this process. Contracting a consultant who specializes in securing funding for drug discovery can be a wise investment. Alternatively, CROs are often happy to take on this consulting role and tend to have teams of researchers who have valuable experience working in large Pharma.

Before committing to funding, you should closely consider the conditions attached to the agreement. Venture capital institutes will invest in companies in exchange for equity, usually around 15–20 %, while big pharma investments often have clauses around downstream commercialization (e.g. that they have the first right to develop and sell the drug resulting from the drug discovery program). Grants from government organizations typically don't have such restrictions, but they rarely cover the entire cost of the drug discovery process, so selecting your funding source is definitely a complex choice based on evaluating the pros and cons in each unique case.

Furthermore, government grants are often only released in stages, with milestones needing to be achieved before the next portion of money is released. This can also be true of not-for-profit organizations, however they also tend to require that the money is paid back in the future.

Each investment will be considered on an individual basis and will contain its own set of clauses. It is crucial to be aware of your responsibility to investors when you sign the contract.

2. DRUG DISCOVERY STARTS WITH FINDING FUNDING

HOW TO MAKE THE BEST USE OF YOUR FUNDING

Once your funding is secured, it is important to make the best use of it. Of course, your options depend on the level of finance obtained. Potentially you could set-up a development company, create a new in-house department, or outsource. If you choose to use third parties, it is important to ensure you keep at least some core competencies and expertise within the company, using them to fill in resourcing gaps and provide additional advice where needed.

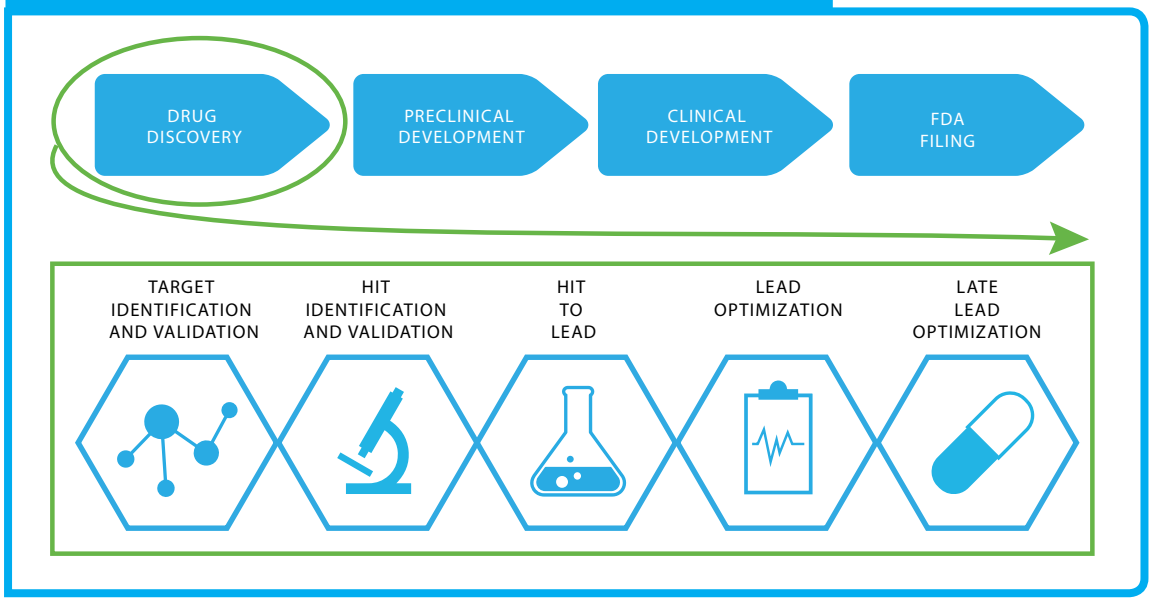
There are positives and negatives to all these options and the best option will depend upon the circumstances of individual companies. Starting a separate company provides both flexibility and control as the company is ultimately under the leadership of the parent company. Creating an in-house department can help fill resource gaps, but if you have a limited internal infrastructure then no matter how many staff you employ, a blockage in the pipeline will remain. Outsourcing is also an option that should be considered. CROs, particularly those that offer a comprehensive range of services, can be valuable to work with. One advantage of CROs is that they can often push work through quicker, helping to reduce the overall timeline of your drug development process.

3. AN INTRODUCTION TO THE DRUG DISCOVERY PROCESS

The drug discovery process is the cornerstone of the pharmaceutical industry. It is the process that encompasses early stages of research, from target discovery and validation right through to the identification and partial validation of a drug candidate or lead compound. During lead discovery, a thorough search is performed to find a small, drug-like molecule or biological therapeutic candidate, the likes of which can be progressed into later stages such as preclinical and clinical trials. Well thought-out and thorough analysis at this early stage will help reduce risks and increase the chances of success throughout the drug development pipeline.

Drug discovery is a diverse practice that takes place across multiple sectors including academic institutions, biotech companies and large pharmaceutical corporations. Until recently, there has been little collaboration between these sectors. However, with the development of new technologies and breakthroughs in genetics, proteomics and other big data studies, there has been an increase in translational research and collaborative work approaches, a change that could continue to alter the landscape of drug discovery. The following chapters of this ebook will explore the stages of the drug discovery process.

Figure 1: Overview of the complete process undertaken to bring a drug to market, and the stages involved in the first step – the drug discovery process.



STEP ONE – TARGET IDENTIFICATION AND VALIDATION

One of the most important steps in developing a new drug is target identification and validation. The target is the naturally existing cellular or modular structure that appears to have an important role in a particular disease pathway and will be targeted by the drug that will subsequently be developed.

A good target needs to be efficacious, safe, meet clinical needs and be accessible by the drug module.[10] Typically, drug molecules, whether large biomolecules or smaller molecules, elicit a biological response upon binding to the target, such as antibodies binding with proteins to block and prevent protein-protein interactions. Once you have identified your target, good validation is essential in increasing confidence in the relationship between the target and disease, and allows you to explore whether the target will be responsive to the development of novel medicines designed to elicit a specific therapeutic result.

THE SYSTEMATIC APPROACH OF TARGET VALIDATION

Target validation should be a continuous process throughout your drug discovery program, as it lets you understand if and how your lead candidates are performing. Validation techniques range from *in vitro* and *in silico* methods through to the use of whole animal models and continue into drug development where Phase III clinical trials are the ultimate test.

A systematic approach to target validation is essential. The approach you undertake also depends on the therapeutic area you are interested in, as the screen cascade will need to be tailored accordingly. However, you are generally looking to answer biological questions that help create full confidence in the role of the target in the disease (or, that allow you to dismiss it early on if it is not involved as originally believed). The following questions are examples of the thought process you may go through when undertaking systematic target validation:

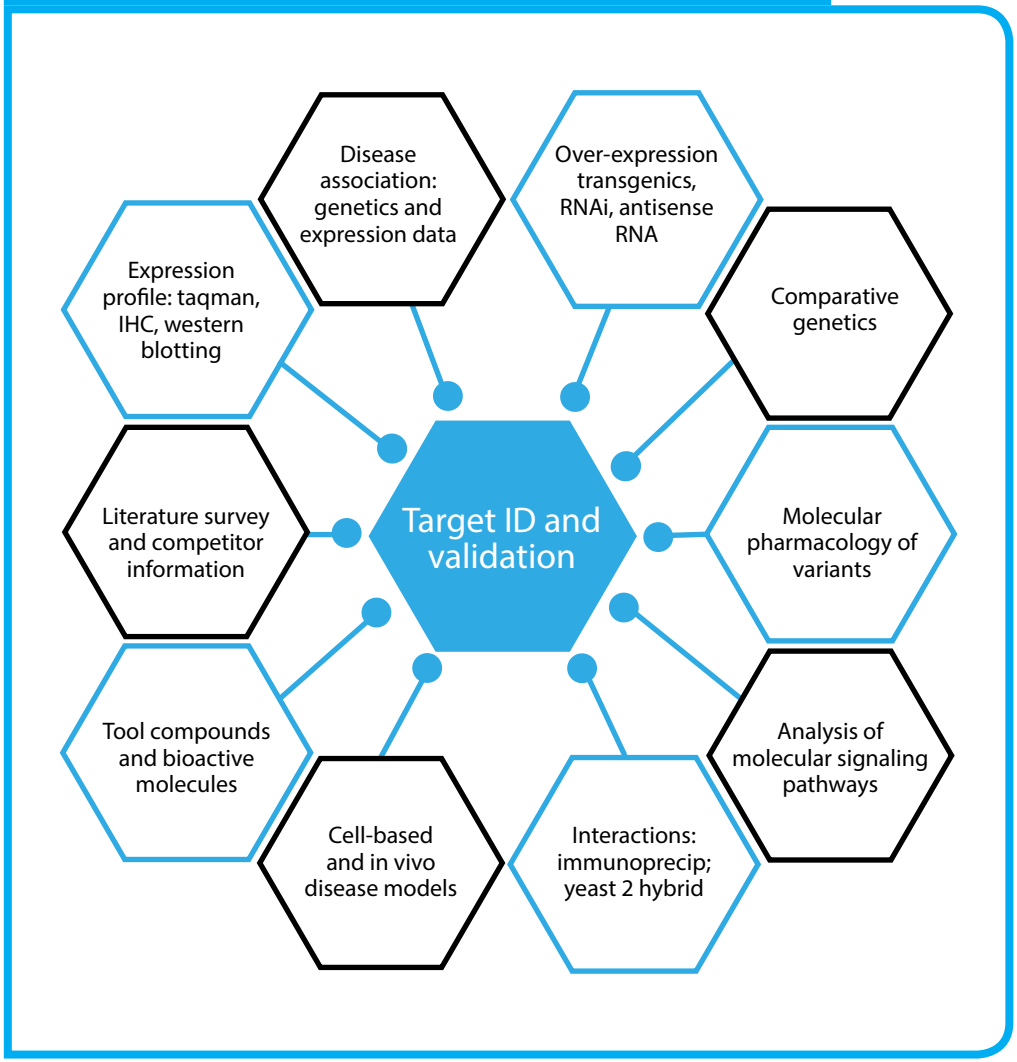
- Disease association:
  - Are there any genetic links to the disease?
  - Are expression data in any disease samples available?
- Comparative genomics:
  - Are there any available data that can be used to assess the complete genome sequences in different species?
- Preclinical evidence in key cells:
  - Are there any expression data available for key cells?
  - Are any cell signaling data available?

- Preclinical evidence in intact systems:
  - Are there any available data from transgenic animals?
  - Are there any data available from *in vivo* disease models?
  - Are any post-drug treatment data available?
- Literature survey and competitor information:
  - How much research data and information has already been published about the target?
  - Is there any information available to suggest that your competitors are also working on this target (e.g. press releases, conference abstracts, their websites etc.)?

REMEMBER TO USE MULTI-VALIDATION

As part of your systematic approach, you should use multi-validation to increase your confidence in the observed outcomes. This can include determining the structure-activity relationship of different lead analogues, generating a drug-resistant mutant of the presumed target, overexpression, and monitoring the known signaling systems downstream of the target.[11] Figure 2 provides a snap-shot of some of the techniques you may use.

Figure 2:
Possible methods you may conduct during target identification and validation.



• Back to Contents

3. AN INTRODUCTION TO THE DRUG DISCOVERY PROCESS

The techniques and methods you use will vary depending on the therapeutic area you are exploring and the information already available. For example, the antisense technique can be very powerful and uses RNA-like chemically modified oligonucleotides, which are made to be complimentary to a target mRNA molecule. Although the effects of the antisense oligonucleotides are reversible (unlike the gene knockout approach) they have very limited bioavailability and cause problems due to non-specific activity, which can be significant in some cases. As another example, monoclonal antibodies are more time-consuming to produce, but they interact with a larger region of the target so allow for better discrimination between even closely related targets.

Where the data isn't pre-existing, whole animal studies may be attractive. However, these are extremely costly so for early stages of the drug discovery process would generally be an unwise investment and therefore tend to be avoided until later stage validation.

A carefully considered, systematic and multi-validated approach throughout your drug discovery process is essential in ensuring confidence in your target an increasing your chances of conducting a successful drug discovery program.

STEP TWO – HIT IDENTIFICATION AND VALIDATION

Following target validation, compound screening assays are developed as part of the hit identification, hit validation and lead discovery phases of the drug discovery process.[10] 'Hit' molecules can mean slightly different things to different researches, but in this ebook, we refer to hit identification as the process of identifying small molecules with the desired activity against the identified targets. Hits can be identified through one or more approaches, which can depend on the target and what, if any, previous knowledge exists.[12]

HIGH THROUGHPUT SCREENING

There are a number of methods used to identify hit molecules. High throughput screening (HTS) is the process of screening an entire compound or candidate library directly against the target. This method is popular as it allows the assaying of a large number of potential molecules against the chosen targets.[10] Molecules that have little or no effect against the targets can quickly be dropped from further investigation and a portfolio of hits can be quickly built-up. As a general rule, large Pharma will run large compound banks, however CROs and academia will usually run smaller, more focussed compound banks, which may help to reduce costs.

USING A KNOWLEDGE-BASED APPROACH

If existing knowledge on the identified target is available, it should be analyzed and assessed. Depending on the level of information and data available, it may prove to be unjustifiable to invest in the 'chance factor' that is involved when you run HTS. Alternatively, you can use any existing materials to help focus a screen, potentially reducing cost, or aid the development of a virtual screen (see below).

VITRUAL SCREENING

There is a push to try and provide coverage across a wide chemical space using computer assisted analysis to reduce the number of compounds screened, and potentially cut costs. Such virtual screening can provide the starting chemical structures for a focused screen, without the need to physically screen a large, expensive compound library screen. Another advantage of virtual screening is that it can also be used to look for novel patent space around existing compound structures.

Generally, virtual screening can be divided into two different categories – ligand-based and structure-based, depending on the availability of crystal structure complexes containing the protein and the molecules of interest for that particular target. Common examples of virtual screening can be found in Table 1.

Table 1:
Common examples of ligand-based and structure-based virtual screening techniques.

Structure based	Ligand Based
Virtual screening using high throughput docking	Virtual screening using pharmacophores
Virtual screening using shape, pharmacophoric features derived from crystal structure complexes	Virtual screening based on fingerprint descriptors

The ideal approach to hit identification would be to conduct knowledge-based, virtual screening and HTS where possible. However, budget, time and informational constraints often mean this is not possible. The method, or combination of methods, you choose to progress with could have implications further down the drug discovery pipeline, so it is important to make the best possible choices.

To help reduce risk and give you the best chances of success, consider consulting with an expert in hit identification and validation. Those based in CROs often have experience of working in large pharma and are able to process many projects within a short timescale utilizing their valuable knowledge. Consultants who specialize in hit identification and validation will also be able to assess the materials you have available and your research data to date and make recommendations with how to proceed.

"consider consulting with an expert in hit identification and validation"

HIT VALIDATION

After you have found your initial hits there are various options to further expand and validate them. Hit validation investigates whether the identified hits have the potential to be further developed into compounds that have properties suitable for clinical use.

3. AN INTRODUCTION TO THE DRUG DISCOVERY PROCESS

The triage process of validation is essential. From the screening processes in hit identification, you will likely be left with many possible hits that you will need to reduce, confirm and group into series. The first process of validation is to conduct hit expansion.[10] This can be by buying in commercially available compounds or by synthesizing more small sets of hit analogs.

Buying commercially available compounds where possible can be advantageous due to the time saved when compared to synthesizing analogs. Of course, it is not always possible to purchase commercial compounds that meet your requirements, but before you even consider synthesis, you should find out what is available first.

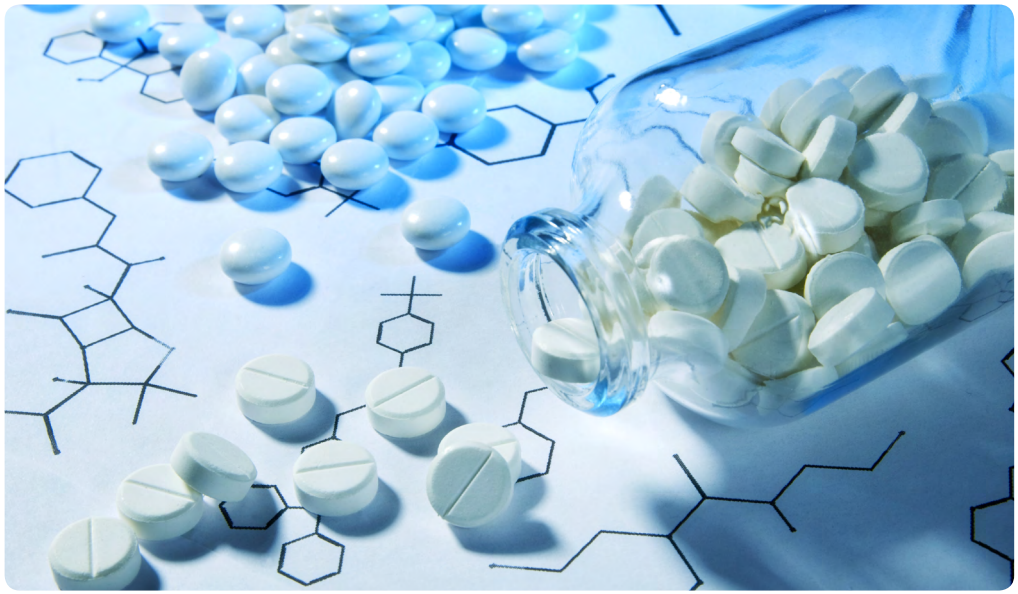
A number of other activities also need to be conducted in order for you to select the most suitable hits to take forward to the hit-to-lead phase of the drug discovery process:

- The affinity and selectivity for the target of the hits should be confirmed.
- The hit series should not have activity against undesired targets, for example a related family member of the target molecule.
- The hits should be absent of obviously undesirable chemical features.
- The chemical tractability and developability of the molecules needs to be considered, such as their physico-chemical characteristics (which would ideally allow them to be studied in cellular and *in vivo* assays). This means that in order to progress, molecules need to be:
  - Reasonably soluble
  - Able to be absorbed by the body
  - Metabolically stable
- To ensure your hit series meet the criteria you need, you will typically look to solubility, permeability, metabolic stability, bioactivations and the pharmacokinetics and pharmacodynamics properties.

The decision as to which methods are used during the hit identification and validation process can have consequences for success later in lead optimization and clinical development. Due to the escalation of downstream costs, there has been an increased focus on making this stage of drug discovery as well-planned and comprehensive as possible.[13] Flexible, fast and cost-effective strategies are crucial to meeting the demands of producing high-content lead series with improved chances of clinical success. Where appropriate, expert advice (in the form of CROs or even consultants) could prove to be particularly valuable.

STEP THREE – MOVING FROM HIT TO LEAD

Through hit identification and validation, you will have selected a number of hit series to take forward. At this point during the drug discovery process, the aim is to refine each hit series to try and produce more potent and selective compounds, i.e. those which possess pharmacokinetic (PK) properties that allow their efficacy *in vivo* to be investigated. After chemical exploration it is likely that some hit series will fail. This could be due to a particular characteristic (e.g. the hit series could have poor metabolic selectivity that cannot be solved without strongly compromising a favorable property, such as the activity of the compound).



KEY POINTS

The importance of structural diversity

To increase the chances of success during the hit-to-lead stage, you should focus on and investigate multiple hit series that are structurally different. By selecting structurally distinctive series, it is unlikely they will have the same chemico-physical properties and will therefore have different pharmacokinetic (PK) profiles. This means it would be unusual for the hit series to fail for the same reasons, as you will be able to employ unique manipulations suitable to the individual PK profiles of each to try and solve their undesirable characteristics.

During this stage, medicinal and computational chemists try to understand how to modify the chemical structure to increase activity and improve other properties of the compounds, such as selectivity, absorption, distribution, metabolism and excretion (otherwise known as the ADME properties).[11] If there is inadequacy in some parameters, it is possible they could be corrected. Compounds that meet the basic criteria, or that can be easily adapted to, are taken further *in vivo* studies.

3. AN INTRODUCTION TO THE DRUG DISCOVERY PROCESS

Primary and secondary assays are typically used to try and improve the synthesized analogs within the hit series via structure-activity relationships. Structure-activity relationship (SAR) investigations around each core compound structure are conducted to establish characteristics such as, the magnitude of activity and the selectivity of each compound. It is important to carry out this process systematically; you should use any existing background information to focus the investigations.[10] For instance, if the structural information of the target is known, you should consider structure-based drug design techniques, such as nuclear magnetic resonance (NMR) and X-ray crystallography, to help develop a more efficient SAR strategy, faster and more efficiently.

"During the hit to lead phase of the drug discovery process, it is important not to focus too much on the *in vitro* activity of your compounds. It will be the compound with the most balanced set of properties that will have the highest chances of success, and not the most active."

Animal models are later used to validate the activity of the compounds in *in vivo* disease models, in pharmacodynamics (PD) and PK modelling, and in preclinical toxicity studies. The criteria needed to take a compound through to *in vivo* studies can vary depending on the project. In academic environments, there may only be funds for a predefined number of the expensive animal model tests, whereas in large pharma, numerous compounds may be profiled within the in-house drug metabolism pharmacokinetics (DMPK) departments. The best performing compounds will be taken forward as leads and undergo optimization to improve on any deficiencies in the structure.

Your hit-to-lead process should be carefully thought out and have a developed strategy. This phase can end up being a bottle neck within the drug discovery process and be costly and time consuming if not planned well.

STEP FOUR – LEAD OPTIMIZATION

Once high quality leads have been selected, they are taken through to lead optimization. In this stage of the drug discovery process, the aim is to produce a preclinical drug candidate by maintaining the desired and favorable properties in the lead compounds, while improving on the deficiencies in their structures. Points of your investigation may include solving questions such as, "does your compound metabolize in the right area of the body to be effective on your target?", and "does the metabolite have any side effects that are a cause for concern?" The resulting analogs should deliver improved potency, reduced off-target effects and the required physiochemical and metabolic properties.

CONTINUING TO REDUCE THE CHANCES OF LATE STAGE FAILURE

Lead optimization is one of the most time consuming aspects of drug discovery, but it is extremely important that the highest standards are maintained while the structure of the leads and its characteristics are defined.[10] One of the main challenges of this stage is to prevent timelines from extending while ensuring the candidate selected for development is of the highest quality, thereby minimizing the likelihood of a costly late-stage fail.

Lead optimization can vary depending on the therapeutic area due to structure differences of the target. The key is to develop a translational lead optimization process that is tailored to what you are trying to achieve. The process should provide detailed characterization of lead compound series and lead biologics, including data related to toxicity, efficacy, stability and bioavailability.

TAILORING YOUR APPROACH

Each project will have a slightly different characterization approach. In general, however, the molecules need to be examined to establish the pharmacokinetic and pharmacodynamics (PK/PD) in validated disease models. This allows you to demonstrate correct target engagement and define the therapeutic index over limiting observations from safety assessment studies. Repeat dosing PK studies and metabolic profiling should also be conducted at this stage to provide information on drug-induced metabolism.[14] Once you know details such as the fraction of the drug administered that enters systemic circulation upon dosing, the apparent volume of plasma the dose dissolved in, and the estimate of the dose required in humans, you can start PK optimization.

BUILD AN ONGOING PROCESS

Some compounds at this stage may have met the initial goals of the lead optimization phase and are ready for final characterization in late lead optimization before being declared as preclinical candidates. However, the discovery process does not stop here, as ideally you should synthetically explore more compounds to produce potential back up molecules in case the compounds undergoing late lead optimization or further preclinical and clinical characterization fail.[10] This continuous process is also strategically beneficial in terms of looking for follow-up series if the candidate is a success.

USING AN INTEGRATED APPROACH

An integrated approach to lead optimization is the best approach, ideally combining the expertise of specialists in computational chemistry, medicinal chemistry, drug metabolism, *in vivo* models and efficacy models. An integrated process not only helps reduce timelines, but also improves the probability of developing a candidate that can go through to late lead optimization, active pharmaceutical ingredient (API) development, and continue into further preclinical and clinical studies. Given the obvious complexity this can introduce, not to mention the variety of expertise required, it is not unusual for biotechs to outsource lead optimization. If you are looking to a third party, it is crucial you understand their capabilities, as not all CROs will be able to deliver a fully integrated approach.

STEP FIVE – LATE LEAD OPTIMIZATION

The importance of late lead optimization before continuing on to preclinical and clinical studies is often underestimated. This stage takes the molecules that successfully underwent lead optimization and further investigates pharmacological safety, formulation drug metabolism and pharmacokinetics (DMPK), as well as the factors that will be important during production scale-up. If this stage is overlooked, problems in efficacy, pharmacokinetics and safety are more likely to occur later in drug development. At the end of late lead optimization, the goal is to deliver a molecule suitable for initial formulations development and clinical testing.

SAFEFTY OPTIMIZATION

Safety optimization is a key part of late lead optimization; it is critical if a lead is to make any headway into the clinic.[10] The aims here are to identify and progress the leads with the best overall drug safety profile, remove the most toxic leads from the portfolio to reduce clinical attrition due to toxicity, and establish a well-characterized hazard and translational risk profile to enable further *in vivo* tests and effective clinical trial design.

Any toxic side effects observed can often be classified as undesired, expected, desired excessive effects, undesired expected, and poor predictability effects.[12] In addition to toxicity, leads also need to be examined for genotoxicity by tests such as the Ames test and using *in vivo* models. If the Ames test shows the lead is mutagenic, it is usually rejected at this stage and is unlikely to be further tested in animals, let alone used in humans.[10]

DMPK INVESTIGATIONS AND API SCALE UP

The additional DMPK investigations in late lead optimization will further analyze at least the five essential properties of the drug candidate: potency, bioavailability, duration, safety and pharmaceutical acceptability. Other important properties, such as selectivity and dose-proportionality, are also likely to be considered. Exactly which tests are undertaken will rely on the therapeutic area of your leads and target. Here, the suitability of the lead for API development is also investigated; for instance, will your lead have adequate aqueous solubility and is there a reasonable synthetic pathway available that will generate a product with good chemical stability? It is very important to establish these parameters so a developable lead is taken through to drug development. If the lead

fails to meet at least the minimum acceptance criteria for the five essential properties highlighted above, it is highly unlikely to succeed.

The compounds that successfully make it through late lead optimization are usually then declared as candidates for early clinical trials. All the information gathered throughout lead optimization and late lead optimization, along with toxicological and chemical manufacture and control considerations, will form the basis of a regulatory submission to allow human administration to begin.[10]

To ensure you have the correct data necessary, tailor your late lead optimization strategy so it is specific for your target and lead, as legislation varies depending on therapeutic area. To prevent any time delays in completing your data package, it is worth speaking to a CRO or consultant who has expertise in integrate drug discovery.

WHAT DO YOU NEED FOR SUCCESSFUL LATE LEAD OPTIMIZATION?

Successful late lead optimization relies on the integrated use of a variety of technologies and models that achieve levels of qualification and validation that delivers confidence in results.[15] Multidisciplinary teams that co-exist within the same facility with access to *in silico*, *in vitro* and *in vivo* technologies are the ideal for late lead optimization. This should ensure an efficient strategy is developed to help advance the lead towards pre-clinical development. If you do not have the internal resource in terms of instrumentation or man-power, consider outsourcing the entirety of your lead optimization and late lead optimization phases.

This will make project management much easier and likely result in an overall cost saving, while also reducing the time required to complete this phase.

> **"Multidisciplinary teams that co-exist within the same facility with access to *in silico*, *in vitro* and *in vivo* technologies are the ideal for late lead optimization."**

As this stage is critical for your lead going forward to drug development, it's also worth considering CROs that also offer API development, as teams within the same facility will be able to work together more effectively and efficiently to ensure that only the leads most likely to succeed are taken forward.

4. WHAT ARE YOUR OPTIONS AFTER LATE LEAD OPTIMIZATION?

When you have a lead that has successfully undergone late lead optimization, you have several options on how to proceed. For example, you could look to further develop, market and sell your product yourself, look to partner with large pharma to take it to market, or license your new candidate for further development via strategic partners. Whichever route you choose; you need to be sure that any financial investors will receive a return on their investment that is in line with the agreement you entered into at the very beginning of your drug discovery process.

SELLING YOUR OPTIMIZED LEAD

The simplest and easiest option is to use the data you've collected for the lead throughout your drug discovery program to create an attractive package to sell the compound, usually to a large pharmaceutical company with the expertise and resources to push it through clinical trials and to take it to market. Selling the compound now would make a smaller return than if it was taken through to proof of concept, however that can be costly, so available resources and funds have to be taken into account.

More often than not, when selling to large pharma or other potential suitors, you have one opportunity to present your data and secure a deal, therefore you have to make sure your data package is comprehensive and well presented. There are consultants who specialize in this area and many CROs will also provide assistance when preparing data packages, drawing on many years of experience working in large pharma.

DEVELOPING YOUR OPTIMIZED LEAD YOURSELF

If the lead is taken through to proof of concept under your direct control, more options are available in terms of partnerships, starting your own company, securing funding from venture capitalists (VC) and selling to large pharma, where you will be able to demand a higher price due to the additional value gained. However, getting to proof of concept can be costly. This involves taking the lead forward as a drug candidate and progressing through Phase I of clinical trials – the safety phase. These trials typically include small numbers of around 20 to 100 healthy volunteers and/or patients with diseases or conditions that have been identified as being likely to respond to treatment.[16] The Phase I study can last for several months, as the safety of the drug candidate is determined. Many factors are investigated, such as interactions with other drugs, the tolerated dose range and the identification of side effects, along with the detection of early evidence of effectiveness if the drug candidate is being tested in patients.[17]

The proof of concept process is usually further validated during Phase II, during which the drug candidate is tested for its efficacy and its safety further evaluated in patients with the disease specifically targeted by the new medication.[17] Phase II trials can

4. WHAT ARE YOUR OPTIONS AFTER LATE LEAD OPTIMIZATION?

last for several months or a few years, and involve a much larger patient base of several hundred people. The studies in this phase help determine the correct dosage, common short-term side effects and the best treatment schedule to be used in Phase III trials. This normally begins with Phase IIa where the proof of concept is ultimately confirmed. This demonstrates that the drug candidate interacted with its target when administered to patients, and altered the disease as it was intended to do. Phase IIb trials take the proof of concept further by looking at factors such as a wider range of dosages or different disease states.[17]

While the returns of taking the candidate through this process are larger, conducting Phase I and Phase IIa trials is a time consuming and costly process. Applications for additional funding can be made for you to progress your lead to candidate and attain proof of concept and beyond, but you need to determine if you have the necessary internal resources and expertise. Alternatively, you could seek partners to help progress your candidate, who may be able to provide financial, technical and practical support (see below).

LARGE PHARMA PARTNERSHIPS

It's easy to imagine why large pharma are keen to purchase or license in compounds that have already reached the proof of concept stage, due to the additional value added and reduced levels of risk for the company to take it forward (after all, only one in 10 candidates reach the market after entering clinical trials). Pharmaceutical companies are also becoming more reliant on licensing products from biotechs to fill their pipelines.[18]

However, competition is fierce, so it's important to present what large pharma are looking for – comprehensive data that backs up and supports the drug candidate and puts the approach in context. Large pharmaceutical companies are not looking for the perfect candidate but they are looking for the candidates that offer the best potential, so the data should openly present any areas of weakness that might have an impact later in development.[18]

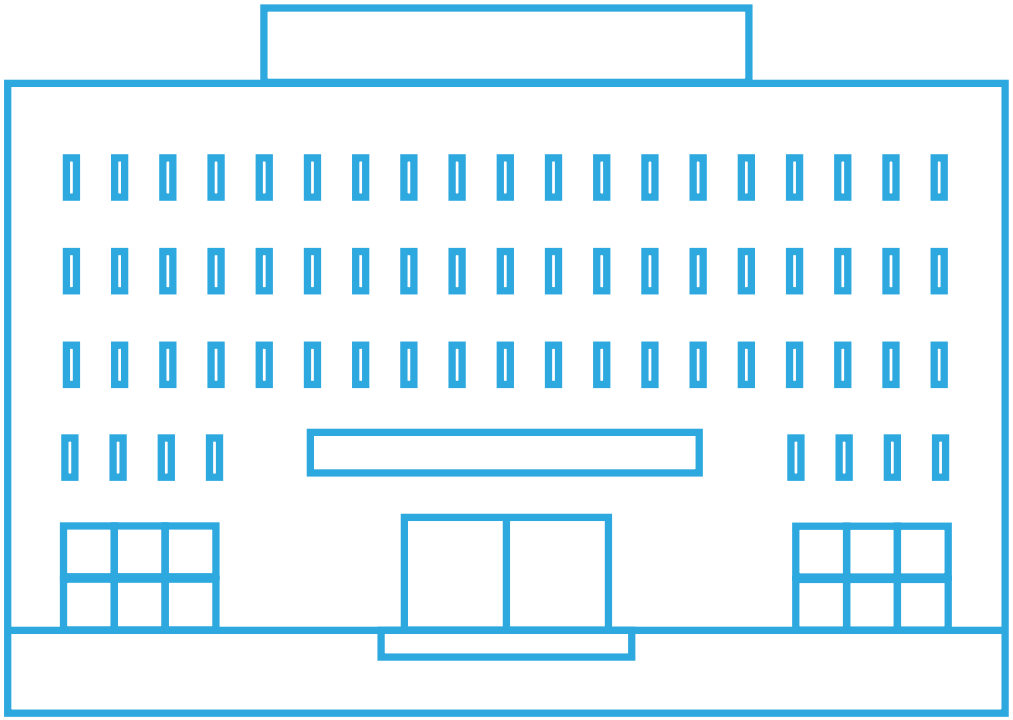
One of the toughest challenges in gaining a deal with large pharma can be as simple as approaching the right person within the organization. Well established CROs who have strong connections with large pharma will have the right network to put you in touch with the most relevant people in the industry.

"Well established CROs who have strong connections with large pharma will have the right network to put you in touch with the most relevant people in the industry."

4. WHAT ARE YOUR OPTIONS AFTER LATE LEAD OPTIMIZATION?

STARTING YOUR OWN COMPANY

Some biotechs decide to start drug development companies that take the drug candidate through the entire clinical trials process. To do this, you need to secure enough funds to register the company and comply to any applicable legislation requirements that are relevant to the territories in which you are based and plan to operate. Of course, there are also many other start-up costs to consider, including property, staff, instruments and consumables.



If the drug candidate is eventually successfully taken to market, this can be a very profitable business venture. However, you should not underestimate the large element of risk associated with starting a drug development company, with the majority of drug candidates failing to make it to market.

If you are unsure which is the best route for you to take – selling your optimized lead, partnering with large pharma, or creating a development company – talk to experts in the industry. They should be able to give you good feedback on the best route ahead for your particular circum.

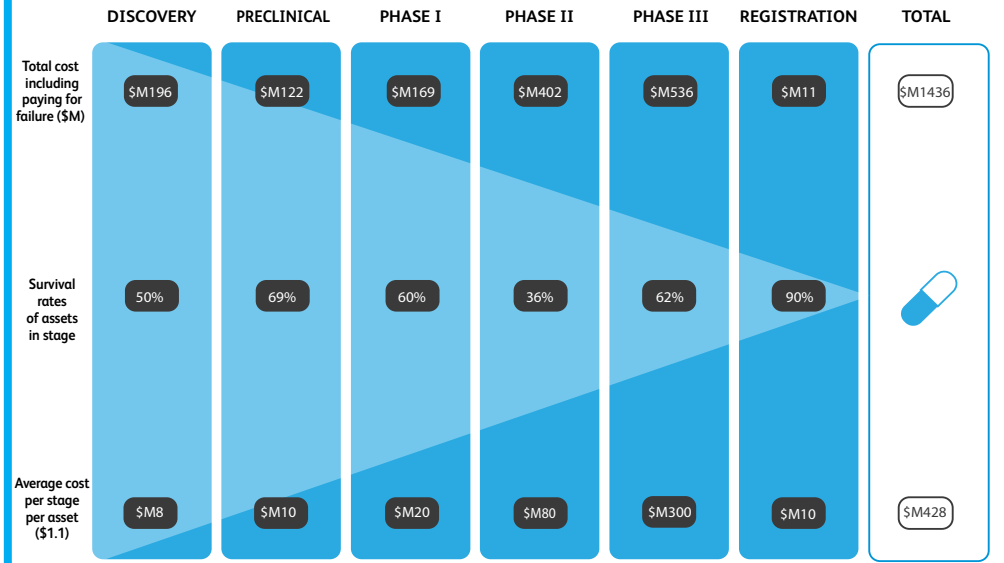
5. COST VALUE VS VALUE IN DRUG DISCOVERY

Developing a new drug from concept to the launch of a finished product is a complex and expensive process that is estimated to cost in excess of $1 billion.[10] Drug discovery is recognized as one of the most financially risky endeavors in all of science due to the high rate of failures, which are thought to account for around 75 percent of the total research and development costs.[19] Despite the failures being costly and disappointing, they still contribute to the body of knowledge on disease processes. However, the impact that failures can have on smaller biotechs (which can only usually afford to invest in a handful of promising projects) can be damning.

So how can you ensure the best chances of success? Firstly, the quantity versus quality of hit and lead compounds generated can have a big impact on the overall cost of a drug discovery project. Focus should always be on quality, not quantity, as the more hits and leads generated, the higher the cost – what's more, if the quality is poor, the risk of failure is also higher.

It is much more effective to take fewer, higher quality compounds through to the later stages of your process. Many biotechs outsource to reduce cost, but doing this can sometimes also increase the risk of failure, as you have less direct control over the project. Additionally, the tendency to focus on reducing costs by outsourcing different sections of the drug discovery process to various CROs and academia laboratories, rather than focusing on the quality of the hits and leads further increases risk. To help, we've put together a figure that puts these risk factors in context, by showing how quality financially impacts on the progression of the drug discovery and development process (Figure 3).

Figure 3:
How quality financially impacts on the progression of the drug discovery process.



• Back to Contents

5. COST VALUE VS VALUE IN DRUG DISCOVERY

The concept of the total cost versus the value created also impacts on the options you look to for outsourcing. For example, there is an overall trend that CROs in the US and Europe tend to be more expensive and slower than their counterparts in China and Japan. This can make CROs in these areas more attractive. However, there is usually increased risks associated with this approach, including the likelihood of failure, as these CROs often focus on high throughput at low cost, rather than the quality of the hit and lead molecules produced.[10] Additionally, there can be legislation variances between the territories, making it even more important for biotechs to take proactive action to identify and mitigate any risks before contracting a CRO or other third party organization.

"CROs, on the other hand, are focused on getting things done, often in a shorter time than internal teams can achieve."

That being said, carefully considered outsourcing is often more cost effective than undertaking the work internally, primarily due to a variety of underappreciated 'hidden costs', such as:

- Wages
- Employer tax
- Pensions
- Consumables
- Energy bills
- Costs of property
- Staff training costs

KEY POINTS

The timeline of a project can also have an impact on the overall cost, as the longer the timeline, the higher the cost of the total process. Large pharma may offer services for free, on the expectation or commitment that they will be involved if a compound of interest is produced. However, they work to long timelines that would have a knock on effect of the rest of the process and potentially result in higher total costs. CROs, on the other hand, are focused on getting things done, often in a shorter time than internal teams can achieve. This is because the experts in CROs will process many projects in one year so have the experience and resources available to progress through the drug discovery process much faster and without as many mistakes and unexpected delays.

6. HOW CAN YOU OVERCOME YOUR DRUG DISCOVERY RESOURCING GAPS?

Completing the drug discovery process requires significant and diverse expertise, resources and infrastructure. The majority of biotechs and organizations involved in drug discovery do not have the bandwidth to complete the full process internally. So how can resourcing gaps be successfully overcome?

There are various collaboration opportunities with different types of organizations. A collaboration could be on a basic level e.g. using another company's assays. Ely Lilly, for example, will run your compounds through their assays if there is an agreement to collaborate on any interesting hits, as do many other large pharma companies. Alternatively, you can look to work more closely with other organizations such as CROs and academic groups.

ACADEMIC GROUPS

Academic groups generally offer academic excellence and have deep knowledge in specific biological and technical areas. However, they can lack the industry experience necessary to consider the factors that will impact on downstream parts of the development process. However, the value they can add to a drug discovery program should not be underestimated, with many offering new approaches and an alternative organizational culture for drug discovery.[20]

Furthermore, while large pharma and biotechs will continue to be the major sources of new drugs, there is a recognized need for academia to be more directly involved in the translation of fundamental science into new therapeutic drugs and approaches.[21] This, combined with the increasing levels of available grants, has seen university and government labs becoming increasingly credible, consistent players in early drug discovery.

CROs and PROs

CROs offer another choice when looking to collaborate with another organization. It is worth noting that there are two main different types of CROs. 'Traditional' CROs often take on projects that are well-defined and potentially a 'one-off', perhaps with no repeat business, even for the same activity that was outsourced. However, in recent years, as patient foundations and academic research teams have become more active in translational medicine, some CROs have evolved into dedicated centers that combine academic excellence with industry expertise.

These CROs, sometimes referred to as PROs (Partner Research Organizations), usually conduct research over a longer term, establishing relationships with the companies they are working with. Drug discovery will always be risky and unpredictable with various problems to solve as they arise. CROs that work in partnership with

the biotechs who are outsourcing to them will provide valuable intellectual input when needed and will work to solve these problems, as they are inherently interested and invested in the long term goals and objectives of the project. Another additional benefit of these PROs is the tendency for them to be more structured, with a project manager who oversees and tracks the whole project (which can be important, especially when weaving in and out experts from the different multidisciplinary teams needed to execute a successful drug discovery program).

CHOOSING THE RIGHT PARTNER

It is important that each biotech choses the right collaborator for them, whether it be an academic group, large pharma, a CRO or PRO, and only commits to a contract that both parties are happy with to help avoid any frustrations and disagreements further into the process. To make sure you chose the right organization for you, research the options, speak to various companies and if possible, speak to members of the team who would be leading on your project to establish whether you could have a positive working experience with them.

“Another additional benefit of these PROs is the tendency for them to be more structured, with a project manager who oversees and tracks the whole project (which can be important, especially when weaving in and out experts from the different multidisciplinary teams needed to execute a successful drug discovery program).”

7. START DISCOVERING. MAKE A DIFFERENCE.

The drug discovery process can seem daunting. In many ways, it is. The process is long, with no definite timelines or pathways, and your scientists will have to effectively react to many unknown factors throughout. It also cannot be denied that the vast majority of hit compounds and leads do not make it to market. When combined with the high financial risks and remote chance of any financial return, many may question why biotechs are established in the first place!

However, the answer is simple. Every project has the aim and opportunity to improve the quality of life for patients of a disease or condition, for which there is an unmet clinical need. This can bring significant financial and societal rewards when the process is successful.

At Aptuit, our mission is to enable scientists to make a difference by successfully conducting a drug discovery process with as a few complications, hold-ups and challenges as possible. Our diverse range of experts have many years of discovery experience in large pharma and a strong track record of delivery. As such, we are able to assist clients with a comprehensive offering of services spanning the whole discovery process, from target discovery and validation through to the final confirmation of a viable and high quality preclinical candidate. Contact us to learn more about how our team can help put together a customized packages of activities tailored to your requirements.

CLICK HERE
TO FIND OUT HOW APTUIT CAN HELP YOU

8. REFERENCES

1. Nature Reviews Drug Discovery, 2007.
2. How to improve R&D productivity: the pharmaceutical industry's grand challenge, Nature Reviews Drug Discovery, Macmillan Publishers Limited, 2010.
3. Drug development for CNS disorders: strategies for balancing risk and reducing attrition, Nature Reviews Drug Discovery, Macmillan Publishers Limited, 2014.
4. Institute of Medicine (US) Forum on Drug Discovery, Development, and Translation. Washington (DC): National Academies Press (US); 2009. http://www.ncbi.nlm.nih.gov/books/NBK50972/
5. Innovate UK https://connect.innovateuk.org/web/stratified-medicines-innovation-platform
6. Top Venture Capital Firms. FierceBiotech. 2016. http://www.fiercebiotech.com/special-reports/top-venture-capital-firms
7. Moving from academia to successful biotech: optimizing tech transfer. 2016. https://lifescivc.com/2016/04/biotech-startup-optimization-engaging-academic-tech-transfer/
8. The financing of biopharmaceutical product development in Europe. European Commission. 2009. https://www.biocity.co.uk/file-manager/Group/reports2009/2009-12-06-eu-bio-pharma-financing.pdf
9. Thomas D, Wessel C. Venture Funding of Therapeutic Innovation. A comprehensive look at a decade of venture cfunding of drug R&D. https://www.bio.org/sites/default/files/BIO-White-paper-FINAL.PDF
10. Hughes, JP et al. "Principles of Early Drug Discovery." British Journal of Pharmacology 162.6 (2011): 1239–1249. PMC. Web. 6 May 2016. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3058157/.
11. "Target validation". Nature.com Web 6 May 2016 http://www.nature.com/subjects/tar-get-validation.
12. Nature Reviews Drug Discovery 2, 369-378 (May 2003). Web. May 2016. http://www.nature.com/nrd/journal/v2/n5/full/nrd1086.html
13. "Hit and lead generation" Nature. Web. 6 May 2016. http://www.nature.com/nrd/journal/v2/n5/full/nrd1086.html
14. Cheng, K.-C., Korfmacher, W. A., White, R. E., and Njoroge, F. G. (2007). Lead Optimization in Discovery Drug Metabolism and Pharmacokinetics/Case study: The Hepatitis C Virus (HCV) Protease Inhibitor SCH 503034. Perspectives in Medicinal Chemistry, 1, 1–9. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2754917/
15. Donna M. Dambach*, Dinah Misner, Mathew Brock, Aaron Fullerton, William Proctor, Jonathan Maher, Dong Lee,Kevin Ford, and Dolores Diaz. Department of Safety Assessment, Genentech, Inc., 1 DNA Way, South San Francisco, California 94080, United States. Chem. Res. Toxicol., 2016, 29 (4), pp 452–472. Web 12 May 2016. http://pubs.acs.org/doi/abs/10.1021/acs.chemrestox.5b00396?journalCode=crtoec
16. Institute of Medicine (US) Committee on Conflict of Interest in Medical Research, Education, and Practice; Lo B, Field MJ, editors. Conflict of Interest in Medical Research, Education, and Practice. Washington (DC): National Academies Press (US); 2009. E, The Pathway from Idea to Regulatory Approval: Examples for Drug Development. Web 17 May 2016. http://www.ncbi.nlm.nih.gov/books/NBK22930/
17. Australian Government National Health and Medical Research Council Department of Industry, Innovation and Science. Web 17 May 2016. https://www.australianclinicaltrials.gov.au/what-clinical-trial/phases-clinical-trials
18. Howard K. "As big pharmas fall over each other to proclaim themselves the 'partner of choice' for biotechs, there are still some lessons the younger sibling can learn" Bioentrepreneur. Web 17 May 2016. http://www.nature.com/bioent/2004/040901/full/bioent826.html
19. Lee, G. and Misciattelli, N. "Compliance risks to consider when outsourcing clinical research to CROs in Chine". Pharmaceutical Compliance Monitor. Web 18 May 2016. http://www.pharmacompliancemonitor.com/compliance-risks-to-consider-when-outsourcing-clinical-research-to-cros-in-china/2537/
20. Frearson, J., & Wyatt, P. (2010). Drug Discovery in Academia- the third way? Expert Opinion on Drug Discovery, 5(10), 909–19. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2948567/
21. Drug discovery through industry-academic partnerships. Gray NSNat Chem Biol. 2006 Dec; 2(12):649-53. http://www.ncbi.nlm.nih.gov/pubmed/17108976

aptuit

aptuit.com