RESEARCH TECHNIQUES MADE SIMPLE

Research Techniques Made Simple: An Introduction to Drug Discovery for Dermatology

Mark Bell¹, Lauren Webster² and Andrew Woodland¹

This article aims to provide an overview of drug discovery with a focus on application within dermatology. The term “drug” can be used to describe a wide variety of agents, including small molecules, cell therapies, and antibodies, which may be dosed intravenously, orally, topically, or by other routes of administration. We summarize the economics and risks involved in drug discovery. Understanding the needs of patients and clinicians through use of a target product profile before initiating drug discovery can reduce time and effort spent developing a poor or unneeded drug. For small molecule drug discovery, a chemical starting point is then required. We present four options for finding a chemical starting point for drug discovery projects: screening libraries of compounds or modifying, reformulating, or repositioning a known drug. Examples of each technique’s use in dermatology are provided. We also describe the subsequent steps involved in discovery of a new drug. To help interested readers, we provide information on how to engage with academic drug discovery centers or industrial partners.

INTRODUCTION

Drug discovery is a complex, slow, risky and expensive process (Figure 1). It is estimated that it takes, on average, around 10–15 years and $1.8 billion of investment for each new drug launched (Paul et al., 2010). Only around one in 24 projects successfully deliver a drug, with many failures occurring toward the end of the process in expensive Phase II and Phase III clinical trials. As a result, drug discovery is dominated by the cost of failure (Figure 1) (Paul et al., 2010).

The pharmaceutical industry delivered many new valuable therapies for dermatology between the 1950s and 1990s (Benedek, 2011). Dermatology then experienced a hiatus,
with most therapeutic innovation focusing on the optimization of dosage or delivery vehicles, rather than the discovery of new medicines (Humphries et al., 2016). Today, however, dermatology is attracting record levels of investment, with 28 new approvals in the last 5 years for drugs treating skin disease (Table 1) (CenterWatch, 2019).

**TYPES OF DRUGS FOR DERMATOLOGY**

Discovering a drug for dermatology is in most ways identical to any other indication. A drug treating a dermatological condition may be an oral, topical, or injectable low-molecular-weight small molecule (usually 200–600 Da). Alternatively, it may be a biological agent such as an antibody, silencing RNA, peptide replacement, or cell therapy. Each type of drug has advantages and disadvantages that must be considered during development. Similarly, the discovery and development of different classes of drug will require the input of specialist experts in drug design, manufacture, and clinical development.

The complexity of drug development means that no one person can discover a drug. Interested parties are therefore encouraged to seek out collaborators or partners who can complement their skill sets.

**CENTERS OF EXCELLENCE**

In the last 10 years, there has been a large increase in the number of not-for-profit drug discovery facilities. The Academic Drug Discovery Consortium lists 149 centers worldwide (Academic Drug Discovery Consortium, 2018). These centers typically work on a wide range of targets and diseases, although some focus on specific therapeutic areas. The centers can offer a range of capabilities, allowing them to collaboratively run early- to mid-stage projects.

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**Figure 1. An overview of the drug discovery process.** The numbers for success rate, projects per launch, total cost, and cost of capital were taken from a well-accepted economic model of drug discovery (Paul et al., 2010). Success rate refers to the proportion of projects successfully progressing to the next stage of development. The cumulative success rate allows calculation of the number of projects required at each stage to deliver one new drug launch, on average (No. of projects per launch). Total cost refers to the cumulative cost of all projects required at a given stage of development to deliver one drug launch. The costs include the cost of capital (11%) that accounts for the lost opportunity cost of developing a drug compared with a comparable investment. ID, identification; No., number.
There are, however, few centers that are capable of progressing projects through all stages of a drug discovery process, although these do exist and are increasing in number (Frye et al., 2011; Tralau-Stewart et al., 2014). Most pharmaceutical companies describe on their websites how they engage with academic or clinical partners. Examples of dermatology-focused companies include Almirall, LEO Pharma, Galderma-Nestlé Skin Health, Pierre Fabre, GSK-Stiefel, and Maruho Co. Ltd. This list is not exhaustive and there are many other companies (small and large) with an interest in dermatology.

**INITIATING A NEW DRUG DISCOVERY PROJECT: DEFINING SUCCESS**

Before commencing drug discovery, a project first must consider carefully what patient and healthcare professionals need in a new product. This information is usually gathered in the form of a target product profile (TPP) (Table 2). The TPP is a strategic document that defines the required development outcome. Project teams work back from the TPP to define the success criteria for each stage of the project (Figure 1). TPPs are rarely published by companies, as they are considered to be commercially sensitive. However, some not-for-profit organizations publish their TPPs, which can serve as useful templates (Drugs for Neglected Diseases Initiative, 2018).

A TPP consists of a series of questions that focus on what is acceptable rather than on desirable traits. For instance, which patient populations are in need of a new therapeutic? Must the drug be taken as a tablet, an injection, or a topical agent? Similarly, what level of clinical benefit is required to replace or supplement the standard of care?

**INITIATING A NEW DRUG DISCOVERY PROJECT: FINDING A STARTING POINT**

Having defined success criteria with a TPP, the team must then decide where the project will find a chemical or biological starting point. For small molecule drug discovery there are four main options.

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**Table 1. FDA Drug Approvals for Dermatology, 2014–2018**

<table>
<thead>
<tr>
<th>2014</th>
<th>2015</th>
<th>2016</th>
<th>2017</th>
<th>2018</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dalvance for acute bacterial skin infections</td>
<td>Cosentyx for plaque psoriasis</td>
<td>Ameluz for actinic keratosis</td>
<td>Baxdela for the treatment of acute bacterial skin and skin structure infections</td>
<td>Cimzia for moderate-to-severe plaque psoriasis</td>
</tr>
<tr>
<td>Jubia 10% topical gel for onychomycosis of the toenails</td>
<td>Entilmar for psoriasis</td>
<td>Eucrisa ointment for atopic dermatitis</td>
<td>Dupixent for atopic dermatitis</td>
<td>Illunya for plaque psoriasis</td>
</tr>
<tr>
<td>Keydinon for onychomycosis of the toenails</td>
<td>Kybella for submental fat</td>
<td>Taltz for plaque psoriasis</td>
<td>Eskata for seborrhoeic keratosis</td>
<td>Ltiyba for cutaneous squamous cell carcinoma</td>
</tr>
<tr>
<td>Oritrect for acute bacterial skin and skin structure infections</td>
<td>Odomzo for locally advanced basal cell carcinoma</td>
<td>Imbruvica for chronic graft-versus-host disease</td>
<td>Nuzyra for acute bacterial skin and skin structure infections</td>
<td></td>
</tr>
<tr>
<td>Otezla for moderate to severe plaque psoriasis</td>
<td>Rhofo for facial erythema associated with rosacea</td>
<td>Qibrez for primary axillary hyperhidrosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sivestros for acute bacterial skin and skin structure infections</td>
<td>Siliq for plaque psoriasis</td>
<td>Selysara for moderate to severe acne vulgaris</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soolantra cream, 1% for inflammatory lesions of rosacea</td>
<td>Tremfya for moderate-to-severe plaque psoriasis</td>
<td></td>
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</tbody>
</table>
| Abbreviation: FDA, Food and Drug Administration. The table does not include systemic treatments for metastatic cancers of skin origin or cancers of skin origin with high metastatic potential such as melanoma. Libtayo is approved for locally advanced squamous cell carcinoma as well as metastatic squamous cell carcinoma and is therefore included.

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**Table 2. A List of Common Questions in a TPP**

<table>
<thead>
<tr>
<th>Topics</th>
<th>Objectives</th>
</tr>
</thead>
<tbody>
<tr>
<td>Indications</td>
<td>Disease of study</td>
</tr>
<tr>
<td>Populations</td>
<td>Which patient population does the TPP refer to?</td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td>What are the weaknesses in the current treatments? What is required to supplant or supplement current treatments?</td>
</tr>
<tr>
<td>Safety and tolerability</td>
<td>Are any side effects acceptable? If so, what level of, and what form of, side effects would be tolerated in the patient population?</td>
</tr>
<tr>
<td>Stability</td>
<td>How long and in what state can the therapy be stored? Is refrigeration acceptable?</td>
</tr>
<tr>
<td>Route of administration</td>
<td>Which routes of administration are acceptable for the indication/patient population?</td>
</tr>
<tr>
<td>Dosing frequency</td>
<td>How often and how long is treatment acceptable for the patient population, when considering requirements for cure or maintenance of disease remission?</td>
</tr>
<tr>
<td>Cost</td>
<td>What cost would the target patient population (or payer organization) tolerate for a new treatment?</td>
</tr>
</tbody>
</table>

Abbreviation: TPP, target product profile.
Screening

For novel biological targets where there are no known drugs, the project will need to find a small molecule starting point for the project that is called a hit. The most common screening method is high throughput screening. This involves the testing of thousands to millions of diverse chemical compounds either directly against the drug target biochemically (target-based screening) or in a cellular system (phenotypic screening). Active hits should be carefully assessed to ensure that they are true positives.

The hit is then optimized in a phase called hit to lead. An iterative design-make-test approach is employed, where the chemical structure is altered to optimize activity, selectivity, and physical properties. The resulting leads are tested to determine their pharmacokinetic profile and tolerability in animals. If the leads are predicted to be safe and effective, they are then tested in animal models of disease. However, they may be evaluated in cellular or ex vivo models when no suitable animal model exists. If a lead is active in the animal model, and assuming the project has not identified other significant issues, it then progresses into a phase called lead optimization (LO).

In LO, multiparametric optimization is conducted to find the optimal balance of properties, including the drug’s physical characteristics and biological activity as well as the pharmacokinetic and safety profile. LO can be a lengthy process that involves large teams of chemists as well as expensive assays and experiments, including employing cellular and animal models of drug exposure, safety, and efficacy. If successful, LO culminates in the declaration of a preclinical candidate. At this point, the molecular structure of the drug is no longer altered; the drug has been discovered. It will then progress through manufacturing process development and regulatory toxicity testing (preclinical development), to assess safety before initiating human trials (Phase I).

Typically, it is easiest to obtain a patent position in a project that starts from a library screen. However, it is the most time consuming, complex, and expensive approach to drug development. It is important to highlight that historically dermatology has not been the initial focus of drug discovery efforts on novel biological targets. For example, phosphodiesterase 4 (O’Donnell and Zhang, 2004) and Janus kinase (JAK) inhibitors (Hutmacher et al., 2008) were initially evaluated in clinical trials of non-skin diseases before their use in dermatology was explored. Screening approaches to drug discovery therefore have been comparatively rare in dermatology.

Fast follower

The observation of Nobel laureate Sir James Black that “the most fruitful basis for the discovery of a new drug is to start with an old drug” is still true today. This maxim can be applied to repositioning, reformulation, and fast follower approaches to drug discovery, all of which enable researchers to deliver effective therapies to patients in the shortest possible time.

The fast follower approach starts with a known drug that is altered with the aim of delivering an improved therapeutic profile.
The fast follower approach is well suited to the discovery of topical soft drugs. Soft drugs are stable and active when locally applied to skin but on entering the blood are rapidly metabolized. Remetinostat is a recently discovered soft drug topical histone deacetylase (HDAC) inhibitor that contains a commonly used HDAC binding motif but incorporates ester soft drug groups that are rapidly metabolized (Figure 2). In a phase II trial for the treatment of mycosis fungoides, 40% of patients treated twice daily with 1% remetinostat gel achieved a confirmed response but lacked the side effects associated with systemic HDAC inhibitors (Duvic et al., 2018).

A key benefit of a fast follower approach over repositioning or reformulation is that it enables composition of matter patents to be filed covering the intellectual property associated with the new drug. This protects the interests of the drug discovery companies or investors who must pay for expensive clinical trials.

Repositioning
The quickest approach to drug discovery is the repurposing or repositioning of existing drugs (Barratt and Frail, 2012). Although only approximately 10% of new chemical entity applications obtain market approval, it is estimated that nearly 30% of repurposed drugs do so, providing a significant incentive for finding ways to repurpose existing drugs (Kaiser, 2011).

Discovering a new use for an existing drug has some clear advantages. In general, the safety, efficacy, and toxicity of the existing drug has been studied extensively. Repurposed drugs do however require some exposure to the drug discovery process to check that the drug is effective in disease relevant models of the proposed indication.

As the chemical structure of the drug is not novel, composition of matter patents are not an option; however, other approaches to gaining a commercially viable product may be possible, such as filing a use patent or seeking regulatory protection (Smith, 2011).

A fascinating example for dermatology is the repurposing of thalidomide, a drug previously used as a sedative that had the adverse effect of causing thousands of birth defects (McBride, 1961). In 1998, thalidomide was approved as a new treatment for erythema nodosum leprosum, a painful skin condition arising in patients with leprosy (Figure 2) (Teo et al., 2002). By avoiding treatment of pregnant mothers, the primary side effect (birth defects) is avoided. A recent study of the topical pharmacokinetics of tofacitinib (Purohit et al., 2019) illustrates a general observation that topical application of a drug to a body surface area of <30% rarely leads to a systemic drug concentration sufficient to lead to side effects. Repositioning can therefore be a particularly effective strategy in dermatology.

Reformulation
Reformulation is a subcategory of repositioning that is common in dermatology. It is often used when it is desirable to reposition an existing drug for use in a dermatological condition, but the existing drug has been designed for use in a new route of administration, for instance, topical versus oral.

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formulated for oral use (Abadir et al., 2018). It is also used to combine two effective agents into one formulation to simplify treatment regimens or to provide an optimal dosage for improved efficacy. The reformulation of oral drugs for topical use still requires development of a safe and patient-friendly formulation and testing in animal models to assess the safety and efficacy of the new formulation before human clinical trials.

A recent example of reformulation is valsartan (Abadir et al., 2018). Valsartan is an approved therapy for the management of blood pressure (Figure 2). In preclinical studies, 1% valsartan gel accelerated wound closure in mice and porcine models, and the approach may provide a valuable new therapy for the treatment of chronic wounds in patients with diabetes (Abadir et al., 2018).

**SUMMARY**

In the authors’ experience, the most effective drug discovery projects involve a wide range of stakeholders. We hope that in this article we have provided an outline of why drug discovery matters, what’s involved, and how you, the reader, can contribute to the development of meaningful new therapies for patients.

**ORCIDs**

Mark Bell: https://orcid.org/0000-0002-8166-0208

Lauren Webster: https://orcid.org/0000-0001-5192-7584

Andrew Woodland: https://orcid.org/0000-0003-2571-2699

**CONFLICT OF INTEREST**

The authors state no conflict of interest.

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**AUTHOR CONTRIBUTIONS**

Conceptualization: AW, MB; Supervision: AW; Writing - Original Draft Preparation: AW, MB, LW; Writing - Review and Editing: AW, MB, LW.

**SUPPLEMENTARY MATERIAL**

Supplementary material is linked to this paper. Teaching slides are available as supplementary material.

**REFERENCES**


DETAILED ANSWERS

1. According to a published estimate, how much does it cost to discover a drug?

Answer: C. $1.8 billion.

The cost of drug discovery is estimated as being around $1.8 billion. This cost includes the cost of failure and accounts for the cost of investing in projects that may take more than a decade to deliver a new medicine.

2. What is a good approach to finding a hit (chemical starting point) for a novel drug target?

Answer: A. High throughput screening.

Unless there are published examples of prototype or approved drugs, then the only option for a new project is to screen (test) a library of potential drugs to find the starting point (hit) for the project.

3. What is the primary deliverable of the lead optimization stage of the drug discovery process?

Answer: B. A preclinical candidate.

The lead optimization phase leads to the discovery of a preclinical candidate (the prospective drug). The prospective drug is then named a clinical candidate once it has passed preclinical development.

4. What is the main weakness in a repositioning project relative to other approaches?

Answer: C. Intellectual property protection can be challenging.

Repositioning is an attractive approach but it can be challenging to protect the intellectual property, as the drug itself is already known and the use may have been suggested in the literature, thus preventing patent protection.

5. How many new projects are required to deliver one new drug?

Answer: A. 24.

Most drug discovery projects fail and it requires around 24 new projects to deliver one drug approval on average.