Research techniques made simple

Bell, Mark; Webster, Lauren; Woodland, Andrew

Published in:
Journal of Investigative Dermatology

DOI:
10.1016/j.jid.2019.07.699

Publication date:
2019

Licence:
CC BY-NC-ND

Document Version
Peer reviewed version

Research techniques made simple: An introduction to drug discovery for dermatology

Mark Bell[1]; Postdoctoral research fellow. The Drug Discovery Unit, University of Dundee, Nethergate, Dundee, United Kingdom, DD1 4HN. E-mail: m.u.bell@dundee.ac.uk.

Lauren Webster[2]; Postdoctoral research fellow. Wellcome Centre for Anti-Infectives Research, School of Life Sciences, University of Dundee, Dow Street, Dundee, DDI 5EH. E-mail: l.a.webster@dundee.ac.uk.

Andrew Woodland[1]; subject matter expert. The Drug Discovery Unit, University of Dundee, Nethergate, Dundee, United Kingdom, DD1 4HN. Telephone: +44 1382386453. E-mail: awoodland@dundee.ac.uk

Short title: An introduction to drug discovery for dermatology

Key words: Drug Development, Methods/Tools/Techniques

Abbreviations used: Target product profile (TPP), high throughput screening (HTS), lead optimisation (LO), ribonucleic acid (RNA), phosphodiesterase 4 (PDE4), Janus kinase (JAK), histone deacetylase (HDAC) and new chemical entity (NCE).

Author Accepted Manuscript Bell, M, Webster, L & Woodland, A 2019, 'Research techniques made simple: An introduction to drug discovery for dermatology', Journal of Investigative Dermatology. Available via DOI: 10.1016/j.jid.2019.07.699

Abstract

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 (TPP) prior to 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 re-positioning 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 centres or industrial partners.

Key points

- Drug Discovery is expensive, time consuming and risky. To discover a drug, it is estimated that on average 24 projects must be started, at a total cost of around $1.8 billion over 10-15 years.
- Drugs may be small molecules or biological therapies and may be designed for application through a range of routes of administration.
- Before starting a project the acceptable success criteria are defined in a target product profile (TPP).
- The process of discovering a drug can be broken down into a series of stages. Hit identification, hit to lead and lead optimisation describe progress towards inventing a potential drug (discovery); pre-clinical development, Phase I-III clinical trials and registration are stages of drug evaluation and approval (development).

- There are a number of approaches to the discovery of a small molecule drug, each with their advantages: screening, fast-follower, repositioning and re-formulation.

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 1 in 25 projects successfully deliver a drug, with many failures occurring towards the end of the process in expensive Phase 2 and Phase 3 clinical trials. As a result, drug discovery is dominated by the cost of failure (Paul *et al.*, 2010), **Figure 1**.

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 optimisation 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 (CenterWatch, 2019), **Table 1**.

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 Daltons). 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.

Centres 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 centres worldwide (Academic Drug Discovery Consortium, 2018). These centres typically work on a wide range of targets and diseases, although some focus on specific therapeutic areas. The centres can offer a range of capabilities, allowing them to collaboratively run early to mid-stage projects.

There are however few centres 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 web sites 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 must first carefully consider 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 organisations publish their TPPs, which can serve as useful templates (Drugs for neglected diseases initiative 2018).

A TPP consists of a series of questions, which 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 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:

1. 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 (HTS). 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 optimised in a phase called Hit to Lead. An iterative design-make-test approach is employed, where the chemical structure is altered to optimise 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. They may however 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 Optimisation (LO).

In LO, multi-parametric optimisation 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. Lead optimisation 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 (Pre-clinical development), to assess safety prior to initiating human trials (Phase 1).

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 (PDE4) (O'Donnell, 2004) and (PDE4) Janus kinase (JAK) inhibitors (Hutmacher, 2008) were initially evaluated in clinical trials of non-skin diseases, before their use in dermatology was explored. Screening approaches to drug discovery have therefore been comparatively rare in dermatology.

2. 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. These projects start in the LO phase, skipping the early stages and saving time and effort. Fast followers often aim to deliver improved selectivity and safety profiles. In dermatology an oral drug may be re-designed and optimised for use as a topical therapy.

The JAK inhibitors are promising therapies under investigation for use in dermatology. Tofacitinib was the first JAK inhibitor to be approved (Cotter *et al.*, 2018). Ruxolitinib and baricitinib, which are being evaluated in clinical trials may be considered to be fast followers as they contain many structural features present in tofacitinib, **Figure 2 (Cotter *et al.***, 2018). Fast followers will often have altered clinical profiles, as even small changes to a drug’s chemical structure can lead to large

differences in selectivity or other properties. This is especially evident when the fast follower is designed for use in a new route of administration, for instance, topical vs oral.

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 metabolised. 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 metabolised, **Figure 2**. In a phase 2 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 re-positioning or re-formulation 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.

3. Repositioning

The quickest approach to drug discovery is the repurposing or repositioning of existing drugs (Michael J. Barratt, 2012). While only approximately 10 percent of new chemical entity (NCE) applications obtain market approval, it is estimated that nearly 30 percent 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 leprosy patients (Teo *et al.*, 2002), **Figure 2**. By avoiding treatment of pregnant mothers the primary side effect (birth defects) is avoided. A recent study of the topical pharmacokinetics of tofacitinib (Purohit 2019) illustrates a general observation that topical application of a drug to BSA of <30% rarely leads to systemic drug concentration sufficient to lead to side effects. Repositioning can therefore be a particularly effective strategy in dermatology.

4. 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 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 prior to human clinical trials.

A recent example of re-formulation is valsartan (Abadir *et al.*, 2018). Valsartan is an approved therapy for the management of blood pressure, **Figure 2**. In pre-clinical 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 diabetic patients (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.

Funding

This article was written by staff supported under funding from Scottish Enterprise [PS730566-In4Derm] and a Wellcome Trust Centre Award [203134/Z/16/Z].

Acknowledgements

The authors recognize Kevin Read, PhD for his expertise, contribution and oversight during the preparation of this manuscript.

Author contributions

AW supervised the preparation of the article. AW and MB conceived of the article. AW, MB and LW wrote and edited the draft article. AW and MB produced tables and visual aids.

Conflict of interest

The authors state no conflict of interest.

Questions

1. According to a published estimate how much does it cost to discover a drug?
    A. $94 million
    B. $0.9 billion
    C. $1.8 billion
    D. $3.0 billion
2. What is a good approach to finding a hit (chemical starting point) for a novel drug target?
    A. High throughput screening
    B. Repositioning
    C. Fast follower
    D. Reformulation

3. What is the primary deliverable of the Lead Optimisation stage of the drug discovery process

    A. A lead with activity in animal models

    B. A preclinical candidate

    C. An approved drug

    D. A clinical candidate

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

    A. It is more expensive

    B. It is less likely to succeed

    C. Intellectual property protection can be challenging

    D. It requires additional technical expertise

5. How many new projects are required to deliver 1 new drug?

    A. 24

    B. 1

    C. 10

    D. 12

Answers

1. C: 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. A: 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. B: The lead optimisation phase leads to the discovery of a pre-clinical candidate (the prospective drug). The prospective drug is then named a clinical candidate once it has passed pre-clinical development.
4. C: 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. A: Most drug discovery projects fail and it requires around 24 new projects to deliver 1 drug approval on average.

1.

References

Abadir P, Hosseini S, Faghih M, Ansari A, Lay F, Smith B, et al. Topical Reformulation of Valsartan for Treatment of Chronic Diabetic Wounds. J Invest Dermatol 2018; 138(2):434-443.

Acadmic Drug Discovery Consortium (ADDC). http://addconsortium.org/index.php (accessed 2018-09-04).

Benedek TG, History of the development of corticosteroid therapy. Clin Exp Rheumatol 2011; 29(5 Suppl 68):S5-12.

CenterWatch. https://www.centerwatch.com/drug-information/fda-approved-drugs/therapeutic-area/3/dermatology (accessed 2019-01-07)

Cotter DG, Schairer D, Eichenfield L, Emerging therapies for atopic dermatitis: JAK inhibitors. Journal of the American Academy of Dermatology 2018; 78(3 Suppl 1):S53-S62.

Drugs for neglected diseases initiative (DNDi), Target Product Profiles (TPP). https://www.dndi.org/diseases-projects/target-product-profiles/ (accessed 2018-10-16).

Duvic M, Guitart J, Huen A, Porcu P, LeBoeuf NR, Skolnik J, et al., Anti-pruritic properties of remetinostat (SHAPE), a topical histone deacetylase inhibitor (HDACi); data from a randomized phase 2 study in patients with stage IA-IIA mycosis fungoides. J Invest Dermatol 2018; 138:S103-S103.

Frye S, Crosby M, Edwards T, Juliano R, US academic drug discovery. Nature reviews Drug discovery 2011; 10(6):409-410.

Humphries B, Kaplan R, Alves M, The Role of Entrepreneurial Leadership and Innovation in the Future of Therapeutic Dermatology. J Invest Dermatol 2016; 136(12):2330-2333.

Hutmacher MM, Krishnaswami S, Kowalski KG, Exposure–response modeling using latent variables for the efficacy of a JAK3 inhibitor administered to rheumatoid arthritis patients. J. Pharmacokinet. Pharmacodyn. 2008; 35:139–57.

Kaiser J, Biomedicine. NIH's secondhand shop for tried-and-tested drugs. Science 2011; 332(6037):1492.

McBride W. 1961. Thalidomide and congenital malformations. Lancet 1:358

Michael JB, Donald EF, editors. Drug Repositioning: Bringing New Life to Shelved Assets and Existing Drugs. New Jersey: Wiley; 2012.

O'Donnell JM, Zhang HT, Antidepressant effects of inhibitors of cAMP phosphodiesterase (PDE4). Trends Pharmacol. Sci. 2004; 25(3):158-63.

Paul SM, Mytelka DS, Dunwiddie CT, Persinger CC, Munos BH, Lindborg SR, et al., How to improve R&D productivity: the pharmaceutical industry's grand challenge. Nature reviews. Drug discovery 2010; 9(3):203-214.

Purohit VS, Ports WC, Wang C, Riley S, Systemic Tofacitinib Concentrations in Adult Patients With Atopic Dermatitis Treated With 2% Tofacitinib Ointment and Application to Pediatric Study Planning. J Clin Pharmacol. 2019, 59(6):811-820.

Smith RB, Repositioned drugs: integrating intellectual property and regulatory strategies. Drug Discovery Today: Therapeutic Strategies 2011; 8(3-4):131-137.

Tralau-Stewart C, Low CM, Marlin N, UK academic drug discovery. Nature reviews Drug discovery 2014; 13:15-16.

Teo S, Resztak KE, Scheffler MA, Kook KA, Zeldis JB, Stirling DI, et al., Thalidomide in the treatment of leprosy. Microbes and infection 2002, 4(11):1193-1202.

Tables

Table 1: FDA drug approvals for dermatology 2014-2018. 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 SCC as well as metastatic SCC and is therefore included.

2014	2015	2016	2017	2018
Dalvance for acute bacterial skin and skin structure infections	Cosentyx for plaque psoriasis	Ameluz for actinic keratosis	Baxdela for the treatment of acute bacterial skin and skin structure infections	Cimzia for moderate-to-severe plaque psoriasis
Jublia 10% topical gel for onychomycosis of the toenails	Enstilar for psoriasis	Eucrisa ointment for atopic dermatitis	Dupixent for atopic dermatitis	Ilumya for plaque psoriasis
Kerydin for onychomycosis of the toenails	Kybella for submental fat	Taltz for plaque psoriasis	Eskata for seborrheic keratosis	Libtayo for cutaneous squamous cell carcinoma
Orbactiv for acute bacterial skin and skin structure infections	Odomzo for locally advanced basal cell carcinoma		Imbruvica for chronic graft-versus-host disease	Nuzyra for acute bacterial skin and skin structure infections
Otezla for moderate to severe plaque psoriasis			Rhofade for facial erythema associated with rosacea	Qbrexza for primary axillary hyperhidrosis
Sivextro for acute bacterial skin and			Siliq for plaque psoriasis	Seysara for moderate to

skin structure infections				severe acne vulgaris
Soolantra cream, 1% for inflammatory lesions of rosacea			Tremfya for moderate-to-severe plaque psoriasis	
			Xepi for impetigo	

Table 2: A list of common questions in a TPP

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

Figure legends

Figure 1: An overview of the drug discovery process. The numbers (No.) for "Success rate", "No. projects per launch", "Total cost ($m)" and cost of capital were taken from a well-accepted economic model of drug discovery (Paul *et al.*, 2010)."Success rate" refers to the proportion of projects successfully progressing to the next stage of development. The cumulative success rate allows calculation of the number (No.) of projects required at each stage, in order to deliver one new drug launch, on average: "No. projects per launch". "Total cost ($m)" refers to the cumulative cost of all projects required at a given stage of development, in order 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.

Figure 2: An illustration of the fast follower approach. Many JAK inhibitors contain common features (blue), while other elements differ (black) with the aim of delivering an improved therapeutic profile for a targeted patient population. Remetinostat contains a common HDAC binding motif (blue) but incorporates metabolically labile esters (red).

Figures

Figure 1

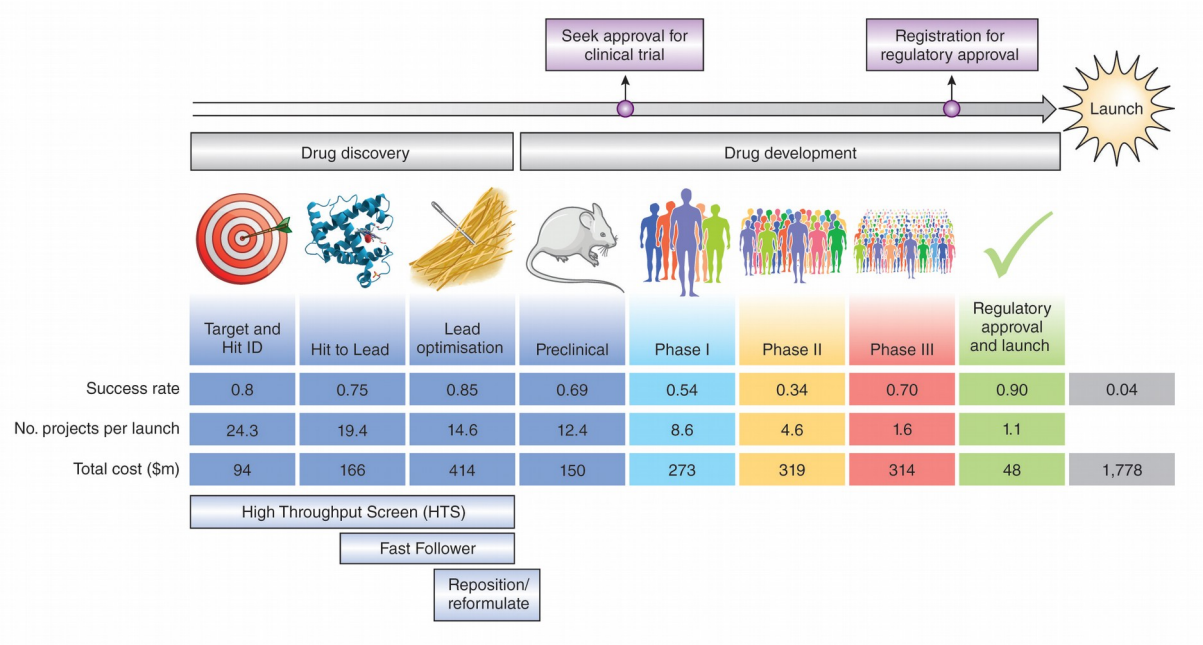

Figure 2