# Academic Drug Discovery: Current Status and Prospects

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## Abstract

***Introduction***. The contraction in pharmaceutical drug discovery operations in the past decade has been counter-balanced by a significant rise in the number of academic drug discovery groups. In addition, pharmaceutical companies that used to operate in completely independent, vertically-integrated operations for drug discovery are now collaborating more with each other, and with academic groups. We are in a new era of drug discovery.

***Areas Covered***. This review provides an overview of the current status of academic drug discovery groups, their achievements and the challenges they face,, together with perspectives on ways to achieve improved outcomes.

***Expert Opinion***. Academic groups have made important contributions to drug discovery, from its earliest days and continue to do so today. However, modern drug discovery and development is exceedingly complex, and has high failure rates, principally because human biology is complex and poorly understood. Academic drug discovery groups need to play to their strengths and not just copy what has gone before. However, there are lessons to be learnt from the experiences of the industrial drug discoverers and four areas are highlighted for attention: (i) increased validation of targets, (ii) elimination of false hits from HTS, (iii) increasing the quality of molecular probes and (iv) investing in a high quality informatics infrastructure.

**Keywords**: academic, drug discovery, high throughput screening, HTS, molecular probes, pan-assay interference compounds (PAINS)

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## 1. Introduction.

The past ten years (2005 to 2015) have witnessed a significant contraction in drug discovery operations by large pharmaceutical companies that for decades were the main source of new small molecule drugs. A recent review cites 137 companies having produced at least one new molecular entity (NME) approved by the Food and Drug Administration (FDA) [1]. Of these 137, only 62 remain active and independent, with 54 of the companies disappearing in the past ten years [1]. Mergers and acquisitions in the industry have accounted for a number of these losses with, for instance, Pfizer having successively acquired Warner Lambert, Pharmacia and then Wyeth in addition to several other smaller companies. The impact of mergers and acquisitions on the productivity of the industry has been the subject of some debate. Productivity as measured by the number of NMEs approved by the FDA per year fell from a high of 53 in 1996 to a low of 15 in 2010, which is a staggering loss [2]. Some seasoned observers have attributed at least part of this loss to the negative impact of mergers and acquisitions on the productivity of the companies involved [3,4].

The main reason for the decline in drug discovery productivity has been the significant rise in attrition (project failure) in Phase II and Phase II clinical trials, principally due to the drugs being tested having insufficient efficacy or safety [5].

High attrition has been particularly associated with the pursuit of novel targets lacking clinical validation, and with the non-optimal execution of clinical trials [6]. Recent progression rates from Phase II to Phase III have been below 20% on average [7] i.e. attrition in Phase II of > 80%. Combined with Phase III attrition of ca. 50% [7], this makes for an unacceptably high rate of failure for candidate drugs in the development process.

Increasingly, the remaining pharmaceutical companies are collaborating and networking much more extensively to produce new products, in contrast to ten years ago, when the predominant model was of a vertically integrated organisation that tackled most aspects of drug research and development in-house [8]. This new focus on collaboration and networking includes the participation of pharmaceutical companies, biotechnology companies and academic groups in public-private partnerships (PPPs) [9] such as the Innovative Medicines Initiative (IMI) in Europe [10]. IMI is the world's largest public-private partnership in the life sciences with a budget of Euro 3.3 billion for 2014-2024, of which Euro 1.6 billion derives from the European Union and Euro 1.4 billion derives from the European pharmaceutical industry. The aim of IMI is to develop next generation medicines and treatments through partnerships between companies, universities and small- and medium-sized enterprises (SMEs). It thus represents an excellent example of the new collaborative model of drug discovery between academia and the pharmaceutical industry, plus other partners. There are currently 50 ongoing projects listed on the IMI web site. This new model of operating is attractive to European pharmaceutical companies as pre-competitive areas can be pursued in IMI in a collective fashion, in close

partnership with academic and SME centres of excellence, and with shared risks and costs.

Encouragingly for the industry and for the patients who rely on the improved drugs being developed, the productivity in terms of NME output has improved over the past four years with 24, 33, 25 and 30 NMEs being approved by the FDA in 2011, 2012, 2013 and 2014 respectively, a significant improvement upon the nadir of 15 NMEs in 2010 [2]. Academic groups are now key players in this new, revitalized drug discovery environment.

**2. Academic Drug Discovery: Background and Current Status**

Academic drug discovery has a long and distinguished history that goes back at least to the discovery of penicillin by Alexander Fleming at St Mary's Hospital, London in 1928 and the subsequent production, purification and isolation of the drug by the group including Sir Ernst Chain, Howard Florey and Norman Heatley at the Dunn School of Pathology, Oxford University in 1940 [11]. This was a major life-saving discovery that had an immediate effect on the treatment of wounded combatants in the 2nd World War, and has continued to save millions of lives ever since. The later discovery of the 6-aminopenicillanic acid nucleus of penicillin [12] and the subsequent development of a host of semi-synthetic penicillins by Beecham Pharmaceuticals [13] and others ushered in the modern era of antibiotic treatment. Since that time a large number of drugs on the market have had their origins in academic research [14]. A recent analysis showed that of 483 NMEs approved by the FDA in the period 1990 to 2007, 64 (13%) were discovered, at least in part, by public sector research institutes

(PSRIs) that include universities, research hospitals, non-profit research institutes and federal laboratories in the USA [15].

In recent years, investment into academic drug discovery has increased significantly. A 2011 review of academic small molecule drug discovery groups in the USA revealed the existence of 78 active drug discovery groups working across a wide range of therapeutic areas. Hit generation was 45% from high throughput screening (HTS), and 20% from screening of focused compound sets, over a wide variety of target types [16]. Of significance was the fact that 49% of the targets being investigated were unique institutional discoveries with little validation whilst a further 27% had significant pre-clinical i.e. animal validation but no clinical (human) evidence of validation. Given the lack of success in conventional pharmaceutical R&D with unvalidated targets (see Section 1 above) it seems unlikely that the academic groups will have any more success and we can therefore predict significant attrition in the portfolios of these groups.

Approximately 60% of projects reported in this survey were in the early stages of discovery up to hit optimisation with only 2% of projects at the Investigational New Drug (IND) application stage or beyond [16]. 72% of the US academic drug discovery centres had hit to lead chemistry capability and 65% had HTS, whilst only 51% and 42% had *in vivo* efficacy biology and drug metabolism/ pharmacokinetics capabilities respectively. Lack of funding for the centres was cited as a major concern [16].

The Academic Drug Discovery Consortium ($aD_2c$) [17] is a new organisation based in the USA that aims to build a collaborative network of academic drug discovery centres. It has a web site [18] that now (9th April 2015) lists 124 registered drug discovery centres or programs, 106 of which are in the USA. A complementary view can be obtained from the website of the Society for Laboratory Automation and Screening (slas) [19] that as of 8th April 2015 listed 105 academic screening centres (Figure 1). The differences between the aD2c and slas numbers are due to differences in the registrations/affiliations of the centres. The striking thing about the figures is the sheer scale of the modern academic drug discovery operation with well over 100 centres operating worldwide, the vast majority of which are in the USA. This predominance of operations in the USA was caused by the stimulus of the National Institute of Health's Molecular Libraries Initiative and then boosted by funding for clinical or translational projects from the NIH (CTSA Program) and from the National Cancer Institute. Even though some of these funding streams are no longer available,[20] the legacy of the funding in terms of established screening centres remains, and has been supported by further NIH programs in 'Blueprint for Neuroscience', drug repurposing and the druggable genome.

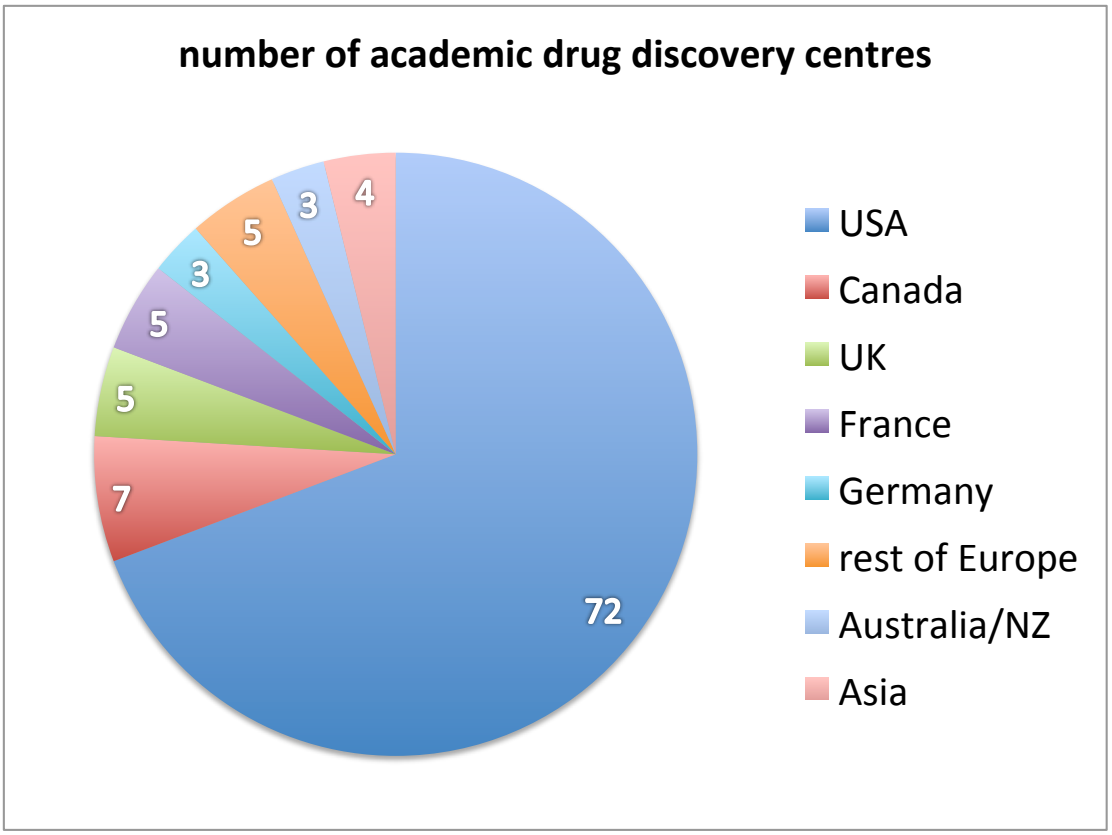


Figure 1: the geographical distribution of academic drug discovery centres in the world from information retrieved in April 2015 from the website of the Society for Laboratory Automation and Screening (slas) [19].

A major new player in this arena is the European Lead Factory (ELF), a partnership of 30 international pharmaceutical companies, universities and institutions, jointly funded by the IMI and pharmaceutical partners [21]. Seven pharmaceutical companies initially contributed a total of ca. 300,000 compounds from their screening files to the Joint European Compound Library (JECL) [22]. The library now comprises 353,000 compounds, including 27,000 newly-synthesised compounds, a further 28,000 to be added, and a plan to grow it to 500,000 compounds [23]. A key advantage of the ELF is the quality of the screening library, derived as it is from pharmaceutical compound files and new

compounds synthesised to exacting criteria. Screening has already started with 43 qualified hit lists (QHLs) produced so far, of which 28 are for European pharmaceutical companies' (EFPIA) targets, and the remaining 15 for public targets derived from crowd-sourced target idea. Projects are starting to go into the hit-to-lead stage with structure-based drug-design support and the application of in vivo ADME/Tox studies. The ELF is accepting ideas for new compound libraries and assays on its web site. A further major European operation may also emerge shortly: a new project called EU-Openscreen, involving 12 European countries, is planning to establish a European infrastructure of open screening for chemical biology in 2016 [24].

A review of the status of UK academic drug discovery has also appeared recently [25]. In total contrast to the US, most of the 38 respondents to this UK survey were in single discipline academic groups with just 5 in a multidisciplinary drug discovery centre and with no group reporting HTS capability (defined as ability to screen at least 100,000 compounds), although 16 of the groups reported low throughput screening facilities. On the other hand, the target types and therapeutic areas tackled by the UK drug discovery groups were quite similar to those of the US academic groups. As would be expected from the lack of HTS facilities, hit identification in the UK centres was principally from phenotypic screening (28%), computational design (28%), focused set screening (20%) and fragment screening (13%) rather than HTS (9%). A clear view of the UK project pipeline is not yet available. Funding is equally a concern to the UK groups and funding expiration has already led to the closure of one UK Drug Discovery Centre [26].

A comprehensive global review of academic screening centres was recently completed by HTStec. Whilst this review was envisaged as a resource that would enable the identification of centres with particular facilities, a useful review of the report has been published [27]. Out of 150 academic or non-profit screening centres identified, 55 participated with 60% in the USA and 34% in Europe. The review covers the staffing, funding, activities, screening libraries, application areas, target types, assay types and future investment areas.

**3. Challenges for Academic Drug Discovery**

Current challenges for academic drug discovery are in three main areas: (i) funding stream continuity, (ii), cultural and organizational adaptation and (iii) technical/expertise.

The funding challenge is straightforward: drug discovery is an expensive business even at the pre-clinical stage with the net present value of a high quality lead at ca $1 to 3 MM. Most academic groups would not contemplate operating in the clinical arena, as their business plans tend to focus on forming spin-out companies and/or out-licensing promising drug candidates, or even drug leads, to pharmaceutical or biotechnology companies, who have larger resources available for the characterization of the candidate and its pursuit into clinical development. However, hit discovery, hit-to-lead biology and chemistry studies are themselves expensive and require funding over extended periods of time [28] which creates difficulties in an academic environment.

The cultural and organizational challenge is also significant [26]. Traditional drug discovery groups in industry had a strong, team-based focus with goals associated with the generation of intellectual property and the discovery and development of leads, and then drug candidates, of sufficient quality to enter human clinical trials. Academic groups by contrast have historically had an ethos driven by more personal goals and high impact publications that can drive research grant success. Given the complexity of drug discovery and the number of different people required to contribute different skills to this endeavour at different times over a long period, there have been concerns that academic drug discovery would not be effective [16,25,29]. There have been many cases where these barriers have been overcome in an academic setting however. One notable example being the foundation of a string of drug discovery companies: Syrrx, MemRx, Receptos and RuiYi, all emerging from pioneering work on structural biology from the group of Ray Stevens at The Scripps Research Institute, California USA.

A recent review proposes an array of strategies for academic drug discovery operations to overcome organizational and cultural issues [30]. These proposals include: establishing a culture of collaboration and playing to academic strengths rather than trying to replicate what the remaining drug discovery industry does well.

The technical/expertise challenge has manifested itself in a number of ways. There have been critiques of the quality of hit discovery in academic drug discovery groups, especially concerning the number of pan-assay interference

compounds (PAINS) that have unfortunately been reported as good starting points for drug discovery or as tools [31,32]. There are hundreds of PAINS compound classes that can aggregate, are coloured, fluoresce, exhibit non-specific binding, or simply be so reactive that they produce false-positive results across a wide variety of HTS assays. In addition, false-positive results are frequently found due to impurities in compound samples and re-synthesis of the supposed 'hit' results in no activity. In industrial settings significant effort has been made to eliminate these false positives. For instance, the HTS operation at Pfizer Global R & D used a detergent at low concentration in screening wells [33] to avoid compound aggregation [34]. Most large industrial HTS centres would also deploy file filters to prevent PAINS and other undesirable compounds from entering the screening file in the first place, and for instance, the Pfizer HTS operation had 540 substructure-specific filters in place for this purpose [35]. Much information is now available in the literature [36,37], so hopefully, this problem will soon be eradicated.

It is also important to validate hit compound quality. As an example, every HTS hit at Pfizer was retested to confirm its activity prior to multiple-concentration $IC_{50}$ or $EC_{50}$ measurement. At this stage, a quality control (QC) check of the sample would be made by on-line LC-UV-ELSD-MS (liquid chromatography – ultraviolet spectroscopy – evaporative light scattering – mass spectrometry) [35] so that the purity (UV profile), identity (MS) and quantity (ELSD) of the material in the sample could be confirmed. Other organisations have taken the approach of performing QC checks on the entire screening file but this is a major undertaking [38]. Failure to perform QC checks at the hit stage will lead to

resource wastage downstream, chasing compound activity that vanishes. However, it should be noted that occasionally, impurities can be chased down and turned to good use. Merck Research Laboratories reported [39] the isolation and structure elucidation of a 1% impurity in a renal outer medullary potassium channel (ROMK or $K_{ir}1.1$) HTS hit. Even though this hit impurity presented twin toxicophores it was turned into a useful lead. It should also be noted that relying solely on mass spectrometry rather than nuclear magnetic resonance spectroscopy or X-ray crystallography can lead to mistakes in structure identification, such as occurred recently with the oncology drug TIC10; mistakes are embarrassing, time-wasting and potentially very costly [40].

Failure to address the hit quality issues mentioned above has led to the concern that 'pollution' of the drug discovery literature has occurred, with false claims as to the attributes of hit compounds leading others who are unaware to pursue false avenues of research [31,32,37]. With the exception of the hit QC checks, the quality precautions are either easily implemented computationally, or require modest additional checking of compatibility of low-level compound detergents with the integrity of the HTS assay: it is recommended that these steps be taken. However, these precautions are just of importance for the hit identification stage of drug discovery. All elements of the complex drug discovery process from target selection through to lead or candidate identification require the concerted application of the skills and expertise of a variety of scientists from disciplines including biology, biochemistry, chemistry, computational chemistry, bioinformatics, medicine, and patents. It is no mean feat to coordinate all of these activities to generate a successful drug discovery project outcome and a recent

review by Walters et al seeks to provide guidance across this whole area and thus mitigate risk in academic drug discovery [30]. Many of the recommendations would be well known to seasoned industrial drug discoverers and it is welcome that many of these scientists, displaced from contracting pharmaceutical organisations are now working in academic drug discovery centres. The advent of bodies such as the Academic Drug Discovery Consortium (aD2c, [18]) is also welcome as it is fostering networking between centres, and closer interactions between biotechnology and pharmaceutical companies and the academic centres.

**4. Outputs from Academic Drug Discovery Groups.**

The 2011 article by Stevens et al is a seminal review of the contribution of public sector research institutions to drug discovery and development [15]. However, this review does not address the productivity of the large number of academic centres specifically set up in the past decade (2005 to 2015) to tackle drug discovery. No such data is available from the aD2c [18] at this time either. The web page of the Molecular Libraries Program [41,42] contains a link to its Probe Reports but the summary spreadsheet information appears not to have been updated since 2011.

A review of five molecular probes that were generated for the following projects: reactive oxygen species (ROS) sensors, GPR30 agonists and antagonists, CB2 agonists, HSP70 modulators and β–amyloid PET imaging agents, provides a useful insight into these projects and their achievements [20]. Impressively, the $^{18}F$ analogue of one of the β–amyloid PET imaging probes developed by the

University of Pittsburgh Medical Center has now successfully completed Phase III clinical trials and is marketed by GE Healthcare [43]. In addition to this success, a sphingosine-1-phosphate receptor 1 (S1P1) agonist probe project from The Scripps Research Institute has been further developed by TSRI and Receptos and the candidate RPC1063 has now reported efficacy in Phase II clinical trial for relapsing multiple sclerosis, with Phase III studies continuing [44].

The clinical successes documented above are very welcome and it would be excellent if umbrella organisations such as aD2c could provide regular updates on the broad impact of academic drug discovery. One analysis of the early 2004 to 2008 output of molecular probes from the pilot Molecular Libraries Screening Network (MLSCN) phase of the NIH Molecular Libraries Program (MLP) concluded that 25% of the 64 probes produced were of low confidence, a further 25% of medium confidence, with 50% of high confidence in terms of the overall quality of a molecular probe and its potential to assist lead discovery [45]. With the increased hurdles for declaration of a molecular probe introduced in the production phase, (the Molecular Libraries Probe Production Centers Network (MLPCN)) it was anticipated that the later probes would score better.

**5. New Approaches and the Future of Academic Drug Discovery**

In the face of the challenges presented by drug discovery, academic researchers are looking for new approaches. One such approach, that has a long history in the pharmaceutical industry, is that of indications discovery, also known as drug repurposing [46], where new clinical indications are found for existing drugs.

The main advantage of indications discovery is that the mechanism of action of the drug is usually well understood and that its safety is assured by the fact that it is an approved agent already on the market, or in late stage clinical trials. Issues may well arise however in gaining intellectual property for a new indication if the discoverer of the latter is not the owner of the composition of matter or formulation patents. The poster child for indications discovery is the human PDE5 inhibitor sildenafil. It is well known that the male erectile dysfunction indication for sildenafil was discovered in the clinic during testing of the drug as an anti-angina agent. What is less well known is that the same compound and same mechanism of action has been repurposed twice by Pfizer and the compound is now also marketed as Revatio® for pulmonary hypertension [47].

A review of multi-year, multi-project, academic drug repurposing operations by Oprea et al revealed: (i) the achievement of a pilot clinical trial of the non-steroidal anti-inflammatory drug ketorolac for ovarian cancer, on the basis of its newly discovered ability to inhibit Rho family GTPases, and (ii) a second, pilot, serial biopsy study of patients with head and neck squamous cell carcinoma, evaluating the potentiation of cis-platin treatment with raltegravir (an HIV-integrase inhibitor drug), which was discovered to have metnase inhibitory properties by virtual screening [48].

In other examples, the University of Bristol and Astra Zeneca are collaborating on a project to repurpose zibotentan (AZD4054), a selective endothelin-A receptor antagonist that failed a phase III ENTHUSE monotherapy study for the

treatment of non-metastatic prostate cancer, for a new indication in Alzheimer's disease (AD) [49]. AstraZeneca are also collaborating with Yale University to repurpose saracatinib (AZD0530), a Src tyrosine kinase inhibitor, as a treatment for AD, on the basis of its Fyn kinase inhibitory properties [50]. A phase 1b trial in AD patients has been successful and a phase IIa study is underway [51].

On a different tack, other authors have proposed a systems drug discovery approach, in which the physiological status of organ slice cultures are quantitatively assessed using high content screening and metabonomics [52]. This proposal is part of a reaction against modern, reductionist, mechanism-based drug discovery and moving towards a more holistic systems biology approach in which technologies such as metabonomics [53] may play a part in a wide range of drug discovery and development activities [54].

## 6. Expert Opinion

Progress in the establishment of academic drug discovery has been rapid over the past ten years. Large investments have been made, especially in the USA. Impacts in terms of the initiation of clinical studies are starting to emerge. It is also apparent that many academic groups are facing the same challenges met by their industrial predecessors a decade or more ago. Whilst the academic drug discovery centres must necessarily pursue a different path to the industrial operations, it is clear that paying more attention to: (i) validation of targets, (ii) elimination of false hits from HTS, (iii) increasing the quality of molecular probes and (iv) investing in a universal, high quality informatics infrastructure for the deposition and dissemination of the data these activities, will all increase return

on the investments in this area. A systematic and coherent publication and data deposition policy for screening data, such as that established at ChEMBL [55,56] would be very beneficial. Success of the old-style pharmaceutical and biotechnology company operations was relatively easy to gauge: most companies' pipelines were on their web sites and analyses of drug registrations were regularly published and analysed. Academic drug discovery quite rightly, does not have the same commercial focus. Nevertheless, it would be beneficial if an umbrella organisation like the Academic Drug Discovery Consortium (aD2c) were able to synthesise, analyse and promote the collective successes and impact in this critical era. At this point in time, the jury is still out on whether academic groups will make a greater success of screening-based drug discovery than their industrial predecessors did. Time will tell, and with so many important diseases requiring improved therapies, the patients out there are relying on their success.

**Highlights Box**

1. academic drug discovery has emerged as a significant force in the past decade to complement pharmaceutical industry efforts in this area, that have been shrinking in the same time period
2. the vast majority of academic drug discovery centres are in the USA, where the NIH Molecular Libraries Program gave a huge boost to this sector
3. significant products in terms of molecular probes, leads and some drugs have started to emerge from these operations
4. concerns have been expressed about the low quality of some hit lists and probes produced by academic groups

5. cultural and organisational challenges exist for some academic groups in engaging in drug discovery, given the large expenditure of resources in people and money required over extended period of time
6. new models of international partnership and collaboration between academia, research institutes and industry are emerging, especially in Europe, that bode well for improved future productivity

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