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Challenges with risk mitigation in academic drug discovery: finding the best solution

Anuradha Roy

High Throughput Screening laboratory, University of Kansas, Lawrence, KS, USA

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Probe discovery; drug discovery; academia-pharma; high throughput screening

1. Introduction

A drug discovery program is initiated once a druggable target is unraveled through either academic research or from clinical observations [1]. Academic research is all-encompassing and covers a wide range of research areas and investigates various aspects of a target or pathway of interest. The research is not driven by any return on investment or its failure to adapt to established investigational platforms. Pharma-driven research, on the other hand, is a more profit driven focus on targets and diseases affecting large population groups. Pharma-academia collaborations surfaced in the last decade as a means to alleviate issues arising from low returns anticipated from high corporate R&D budgets and patent expirations. Overall, the pharma-academia collaboration is complementary and mutually beneficial [2], with the successful and innovative early-stage academic discovery projects finding their way for further development in spin-off biotechnology companies or big Pharma, for the more complex and time-and costintensive late-stage drug development involving clinical trials.

The National Institutes of Health (NIH) initiatives like the Molecular Libraries Program [3] that were set up to accelerate academic small molecule screening campaigns provided not only chemical compounds for mechanistic studies but also enabled access to excellent assay development guidelines and funding opportunities for academic scientists who are interested in probe and drug discovery. As the specialized screening centers setup under the Molecular Libraries Screening Center Network, transitioned to the production phase, the vast majority of nonprofit universities and institutes supported establishment of academic screening centers that vary in their capabilities and infrastructures. The academic Drug Discovery consortium [4] has listed around 150 drug discovery centers/ programs that operate across United States, Europe, and Australia. The academic discovery, chemical biology, and informatics programs have contributed greatly toward expanding the boundaries of target

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identification, discovering novel chemistries and expanding the chemical space, as well as have contributed greatly to the development of novel algorithms for data integration and analysis [5,6] There has also been a significant contribution toward approvals for marketed drugs in strong Pharma-academia collaborations. Given the large numbers of basic researchers with years of expertise in diverse areas of research, a disproportionately small number of targets and probes have made it from bench to bedside. The challenges lie in the expectations and pressures of academic responsibilities, limited funding, and lack of comprehensive institutional programs to guide the researchers in taking their innovative targets and research to significant drug discovery milestones.

1.1. Early drug discovery in academia

The early discovery process in majority of the academic programs is initiated with target identification validation and development and optimization of a target-dependent assay. The assay is used to screen randomized or focused libraries of organic compounds, natural products, or peptides. The hit molecules from a screening campaign are developed and characterized further for potency, efficacy, and selectivity with limited medicinal chemistry intervention [7]. The process of probe or tool discovery is limited in scope, meets smaller milestones, and requires much less resources than the full spectrum of drug discovery and development. The process leads to identification of molecules that modulate the target being studied with high potency (either <0.1 μM in a biochemical assay or up to 10 μM in a cell-based assay). The probes are derived from limited chemical optimization or analoging and are selected for reasonable selectivity (>50–100-fold difference in activity against targets from same or relevant distinct functional or structural classes. When funding or expertise is available, the probes are also characterized for aqueous solubility, cytochrome inhibition, stability to liver enzymes, or animal model studies. The probe molecules can serve as tools to study target modulation in homeostasis or disease or to study signaling pathways. When the path of drug discovery is pursued, in many cases, the probes with novel scaffolds and good characteristics can serve as starting points for lead discovery, in which the scaffolds are subjected to extensive chemical optimization for further improvement of potencies (from nM to pM range), broad target activity profiling, improvement of therapeutic windows, target engagement, and physicochemical properties. Lead development also involves applying highly stringent selection filters for chemical properties, adsorption, metabolism, *in vivo* availability, and efficacy in animal models. Extensive preclinical datasets are acquired for developing the leads further as candidates for clinical investigation and development. The process of lead optimization and late-stage drug discovery process is both time-and cost-intensive and requires concerted efforts from highly skilled multidisciplinary teams and remain outside the scope of majority of the academic drug discovery programs. There are some notable exceptions to this generalization as few academic scientists have successfully established biotechs for advancing the discoveries from their academic research. The Molecular Libraries Initiative (MLI) lists successful identification of ~350 high-quality probe molecules against various biological targets that fit the probe criterion [6] and several of which are being advanced further for drug development. In addition to the probes discovered through the MLI initiative, academic centers have also contributed to identification of chemical scaffolds that modulate varied targets selectively and with high potency. The process of probe discovery is well suited for academic timelines and limited

resources. Further lead discovery processes that require extensive resources and expertise are not always available for many academic institutions and universities. As a result, despite several significant contributions to the area of early drug discovery, the academic drug discovery still faces challenges that curtail its overall success in commercialization.

2. Challenges with risk mitigation

Time and cost are two major challenges in academic drug discovery. Unlike the pharmaceutical companies or biotechnology companies, where the time, labor, and cash investment is solely focused on following the established drug discovery workflow, an academic investigator with interest in drug discovery process faces struggles to balance and prioritize time and money for the final measure of academic productivity. The preponderance of academic and administrative responsibilities, teaching students, and guiding laboratory research leaves faculty with very limited time to devote to expediting drug discovery stages, interacting with technology transfer or learn about advancing their technology or innovative findings. There is also an absolute pressure to publish research findings. The number of publications reflects productivity and is required by the students to graduate and by the faculty to apply for tenure. Over and above, the publications increase the chances of obtaining highly competitive extramural grant funding, which is critical for survival in academia. The pressure to publish and teach is a measure of research productivity not only in the US universities but also in the European university control agencies like the British Research Excellence Framework [8], the French Evaluation Agency for Research and Higher Education [9], and Italian National Agency for University and Research Systems Evaluations (ANVUR) [10] that periodically evaluate institutions for teaching and research productivity (number, quality of published books, research articles, impact, and potential of research). Interestingly, the ANVUR has recruited Elsevier Scopus, an abstract and citation database of peer-reviewed scientific literature, for the review and assessment for their national research funding initiative.

It is important to emphasize that it is not any lack of interest, but the academic responsibilities and priorities that slow down the process of early discovery. Academic drug discovery has to conform to meeting shorter milestones that allow the investigator to fulfil other obligations. The urgency to publish may sometimes lead to bias and over interpretation of data, as well as selective reporting of positive results. Experimental design may preclude statistically relevant sampling sizes, or managing and reporting replicate variability. In many low-throughput wet bench studies, an assay performed in only three to six wells may not be truly reflective of the suitability of the assay for high-throughput screening, which requires statistical analysis of values across rows and columns from whole plates in day-to-day and plate-to-plate experiments. Data interpretation issues can also arise from experiments for studying compound selectivity at a single or 2–3 concentrations as the % inhibition or agonist response at up to 3 concentrations is insufficient to clearly establish the selectivity window. A complete 8–10 concentration dose-response study is required to unambiguously evaluate the shape of curves, and subjecting them to appropriate mathematical treatments such as the four parametric analyses to define IC50 values. Additionally, the issues in rigor and reproducibility surfaces when the published data on novel targets cannot be repeated in drug discovery programs in both academia and industry. Lab-to-lab differences in basic

protocols of technical execution, cell maintenance, mycoplasma evaluation, passages in culture, compound handling, etc. can also add to the problem of data replication. Effect of passage number on assay read-outs is shown in reference [1], where a change in fold activation of gamma globin promoter was observed with the passage number of bone morphogenetic cells (BMC). The high-throughput screening with the BMC required using cells in the same passage number for each batch of compound screening that led to identification of hit compounds that effectively induced expression of gammaglobin promoter in human primary erythroid progenitor cells [11]. In another case, the luminescence read-outs from a mycoplasma-infected cancer cell line was found to vary up to 8-fold with passages in culture. After removal of mycoplasma using plasmocin/puromycin treatment, the passage-dependent luminescence read variability was eliminated. In such instances, the early discovery programs do not progress far when target validation or reporter activity or read-outs do not reproduce in the hands of screening labs [12,13] or the robustness is affected by an assay that reports data from impurities in enzyme preparations, substrate contaminants, and mixed cell subpopulations exhibiting a positive phenotype or reporter expression. Likewise, it is also risky to rely on data that reports activities from compounds that have not been evaluated for its purity at every stage of its reacquisition via new synthesis or from commercial vendors. If the activity is associated with an impurity or degradation product or some chemical modification, any analoging based on assumed scaffold will go nowhere. Small-molecule fragments that are identified from fragment-based screens via Nuclear Magnetic Resonance (NMR) or Surface Plasmon Resonance (SPR) binding assays also need to be supported by highly involved medicinal chemistry optimizations to increase their potencies and show appropriate target modulation in a biologically relevant assay.

The establishment of high-throughput screening laboratories across numerous academic campuses has enabled access to compound libraries for academic screening projects that are normally not affordable for individual academic labs. The number of compounds in the library collections that can be screened for an academic project can vary depending on availability of reagents and funding. The compounds identified from small screens are flagged for chemical liabilities and promiscuity, reactivity or instability by the cheminformatics filters. While there is an increasing emphasis from editorial boards and grant guidelines on deemphasizing compounds that are chemical liabilities (PAINS and other reactive species) [14], the need to publish to justify investment of money, time and labor can sometimes override all advice from experts. Unfortunately, some reactive PAINS scaffolds behave like specific and true hits and make perfect sense to a biologist, who will try to publish the data. The issues are also compounded when only the positive aspects of compound characterization are published. This presents a biased picture of what appears to be a promising hit, but one that will ultimately be culled in the rigorous hit to lead optimization phase of the discovery processes.

Investment of limited academic dollars into cost-intensive early discovery screens is a major issue encountered in academic settings. In many instances, gaps exist in knowledge and understanding of what comprises an innovative target for drug discovery, what defines target validation, and makes a target druggable [15]. Thus, finding a chemical scaffold or a peptidomimetic that binds in silico to a predicted protein model alone does not validate the

target unless other experiments are performed to show functional modulation in a disease model. The complexity, cross-talks, multiple interactions, and protein complexes in biological systems may sometimes preclude precise and selective definition for target functionality. While phenotypic screens with no prior knowledge of target have been reported to result in several first-inclass drugs, it is essential that both the investigator, who has expansive knowledge of his biology, and the early discovery experts with knowledge of compound attrition workflows contribute collaboratively toward developing secondary and selectivity assays that will help fine-tune hit selection process. This collaboration can help define the questions that need to be explored from drug discovery perspective and the best possible way to unambiguously arrive at solutions for moving the project forward.

The assays developed within the High Throughput Screening (HTS) labs or transferred to screening laboratory are miniaturized and rigorously tested for reproducibility, signal to background windows, low-, medium-, and high-signal variability across rows and columns of assay plates run at least thrice within a day and over 3 days at the minimum. A robust and reliable signal readout is critical for screening process for primary hit identification and the follow-up analoging processes. The challenges arise when the reagents are limiting or when the academic budgets preclude purchase of bulk assay specific reagents required for all quality control and screening campaigns. Cost considerations can also sometimes negatively impact use of more innovative screening technologies such as use of physiologically relevant three-dimensional cell culture systems [16] for large screening projects. In addition, the stringent growth requirements of some academic infectious diseases projects may prove impractical for screening in acceptable established Society for Biochemical Screening (SBS) plate formats and may prove labor-intensive in terms of obtaining acceptable signal to background ratios or modifying some heterogeneous assays with large number of steps to alternative platform technology-based homogeneous formats, without disrupting the biology being addressed.

The appropriateness of an animal model for the disease being addressed has always been questioned regardless of their use in academia or industry. While cheaper animal models are still utilized extensively in academia, the problem lies in when the basic unmodified scaffolds are administered to the animal models. The rush to an outcome very often leads to failure if the compound is not characterized for its toxicity, bioavailability, and limited Pharmacokinetic/ Pharmacodynamic (PK/PD) studies. Chemists use in silico characterization of compounds early to guide Structure-Activity Relationship (SAR), but the in silico approach is not entirely predictive of the behavior in animal model systems. There is much optimism that the use of Patient-Derived Xenografts (PDX) mice-derived cell lines [17] or new models generated using CRISPR-Cas technology will provide more clinically relevant datasets in early discovery

3. Risk mitigation solutions

Many academic screening laboratories have hired industry-trained drug discovery scientists to apply industry best practices to academic operations and streamline workflows toward more productive outcomes. Mitigation of academic discovery projects can be effectively controlled when industry-trained scientists spend time to educate and communicate with the

academic investigators about the complexity of discovery process, and provide a realistic take on timelines and robustness to arrive at a probe molecule that meets all specificity, potency, and selectivity requirements. Equally important is the need to inform clients and collaborators that the target being pursued may not always lead to a viable hit especially for intractable targets or complex biological processes that are modulated by various factors. With that being said, it is also imperative that the drug discovery experts learn details, complexities of a research project from the investigators who are experts in their biology.

The early intervention of assay development and screening labs also helps control day-to-day reproducibility and signal-to -noise ratios. The assay can be modified or reformatted early if it does not interfere with the biology of the pathway or the target being studied. The academia is well versed with Z' factors, but in many cases, the distribution of controls is not reproducible between the screening lab and the client lab. The academic labs can be encouraged to provide raw instrument data files and repeat data sets from day-to-day execution of the assay for unbiased evaluation. When the research material is costly and limiting, and there is reluctance to dedicate resources on extensive reproducibility experiments, a limited version of inter-and intra-plate signals is usually set up to strike a balance between available resources and for reasonable interpretation of variability and reproducibility.

Increasingly, there is emphasis from grant funding agencies and academic journals in addressing authentication of biological and chemical reagents and submission of detailed protocols and data files. The need to authenticate starting cell lines, working with mycoplasma-free cells, avoiding cross-contaminations, cannot be overemphasized. The early intervention of screening labs in assay development in basic research lab is very productive as this can save both time and labor especially when stable cell lines are being generated to interrogate a signaling pathway or for modeling disease setting. The screening group can bring into focus the importance of performing mycoplasma tests to preserve the characteristics of the cell line being modified. The imaging-based assays need to be more quantitative and transferring a cell line where only 10% or less of the cells express reporters like Green Fluorescent Protein (GFP) should be discouraged. Some cell lines like the bone morphogenetic progenitor cell populations should be optimized for the effect of the passage numbers on reporters.

It takes a village to execute drug discovery programs. Universities and institutes benefit from setting up infrastructures not only for the basic siRNA, peptide, biologics, or small molecule screening facilities, but also by providing resources and capabilities to translate innovative early discovery research for therapeutics and diagnostics. At the University of Kansas, multidisciplinary executive steering committees composed of investigator(s) and industry-trained HTS, medicinal chemistry and ADME/formulation expertise, clinicians from relevant disease areas, and late-stage drug discovery experts meet every month to evaluate and guide early target discovery projects and participate in defining project objectives, key decision points, and detailed project plans. The team evaluates the research projects presented by the investigators; suggestions are made to address any deficiencies in target validation or disease relevance, or in analoging or improving bioavailability or formulations of available probe molecules or proposing combination therapies with known clinical

standard of care. Industry-trained project managers define timelines with go/ no-go decision points and deliverables are tracked to help the principal investigator identify and mitigate potential risks. Project managers along with the team also try to identify funding sources for innovative research projects through disease philanthropy, non-profit organizations, or through the university or department pilot grant funding programs. Financial support for generating pilot data for diverse early discovery projects is critical for testing feasibility and providing proof of concept data. The seeding support for a new target segways into applying for more substantial NIH funding through Program Announcements (PA), RFAs (Request for Application) or RFP (request for proposal) funding. With guidance from drug discovery experts and consultants, SBIR and STTR grants are also submitted for more advanced projects. A small initial investment from university/institutes in financially supporting viable and innovative targets or potent and selective probe development/PK/PD studies goes a long way and promises good returns in terms of bringing dollars back for the facilities and administration costs for the universities, and ultimately, in few cases, receive returns from sale of patents or royalties from commercialized technology. Albeit slow, the process of applying for funding from NIH or dedicated disease societies or donors or applying general endowment funds at various stages of the early discovery process are the only available paths for supporting the process on academic campuses. The big pharma has also invested into academic early discovery processes across some university campuses in the hope of identifying novel targets for some diseases. With high-quality leads or probes that are good starting points for preclinical development, biotech spin-offs can be set up in university incubators or the university technology and translational transfer offices along with the drug discovery team can leverage collaborations with Pharma for late-stage development processes. While larger well-endowed universities can support larger operations, smaller universities, despite their limited budgets, can be encouraged to expand the ability of technology transfer offices to identify innovation and financially support all viable patent applications in order to improve chances of commercialization. While the overall goals of academia and pharma are divergent, the pharma’s requisite to establish exclusivity via patents is sometimes achieved by publishing papers around scaf-folds that are less potent than the one patented for further discovery development.

4. Conclusions

The freedom of academic pursuit across wide areas of biology holds high potential of unraveling innovative technologies and novel targets in disease settings. Despite pharma interests being guided by ultimate financial goals of profitability to its investors and board members, an inflow of previously untapped targets from academia for late-stage drug discovery into Pharma is mutually rewarding and beneficial. Quality control and expert guidance at all stages of early discovery in academia at both institutional and individual levels with Pharma-experienced leadership can help minimize risks and expedite transition of projects from bench to bedside.

5. Expert opinion

In summary, the academic mission and commercialization of research were always considered antithetical and required conquering mental barriers through fostering of

entrepreneurial spirit. Increased funding from agencies for probe discovery and chemical biology also helped to realign basic research interests with that of the pharma-driven drug discovery. While the traditional drug discovery is cost-and time-intensive and can take over 15 years to reach significant milestones, academic probe discovery was found to be much more practical end point of translational research. The innovative targets or viable compound leads discovered in academia could then feed the industry pipelines for further development. For the drug discovery process to be implemented in academia, the entire process of pharma-defined drug discovery process is dissected into shorter well-defined milestones which include target validation, defining druggability, pilot screening, and limited medicinal chemistry optimization of hits to arrive at a scaffold that meets thedefinition ofa probe.The identified chemical or probe is used by the investigator to study relevant biology and a dataset is generated that can be published and grants can be submitted for larger HTS or focused in silico screening campaigns or for more extensive medicinal chemistry optimization and animal model studies. The probe serves as a tool for further validating the target and dissecting its mechanism of action. The goal of probe discovery is well within the reach of the academic researchers. The much shorter development time for the drug repurposing campaigns designed to find new uses for the Food and Drug Administration (FDA)-approved drugs are also well suited for academic timelines and are also being pursued extensively especially by both basic and clinical researchers. Nonetheless, compared with industry, the time taken in academia, for presenting a target or an assay for probe discovery or postscreening assays takes much longer. In academic labs, post-doctoral researchers and graduate students who have been hired for wet bench experiments work and learn as they chug along a project. Therefore, there is hesitation in allocating limited dollars for paying resident drug discovery expertise for executing steps that a postdoctoral researcher can theoretically perform in the investigator’s laboratory. While the investigator team is indisputably an expert in their biology, the drug or probe discovery programs can lose direction if left unguided with no involvement of drug discovery experts. While the investigators who prefer to work in silos have the opportunity to learn from numerous publications and NIH guidelines on all stages of drug discovery process [18], the process and interpretation are more impactful and productive, when the basic research investigators utilize decades of experience of drug discovery teams.

Even with restricted funding at many universities, investment at institutional level for such programs is also critical for providing continuous and valuable insight and guidance for academic faculty in taking their targets all the way from bench to marketed drugs. The university-supported infrastructure for drug discovery and translational therapeutics includes early-and late-stagedrug discovery teams that comprise of experts with diverse and complementary specializations, that are critical in keeping the project focused and mitigating risks in academic drug discovery programs. The drug discovery services and collaborations should also be made available at a reasonable cost to the investigator. It is also important to mention that exceptions exist especially in well-funded universities and institutes where a number of academic laboratories that routinely implement comprehensive early and preclinical drug discovery research programs. The importance of patenting innovative research and expanding the academic focus to commercialization strategies hold potential to bring in revenue for both the researcher and the university. When the specialized

drug discovery expertise for medicinal chemistry, absorption, distribution, metabolism, and excretion (ADME), or *in vivo* models is unsustainable financially, collaborations are often established with other academics harboring the required expertise.

Pharmaceutical drug discovery programs have long been characterized with high R&D budgets and focusing on targets and diseases that are financially sound. Analysis of high failure rates in clinical trial candidates as well as recalled drugs has exposed the importance of characterizing a target comprehensively and in an unbiased manner. Issues with published data reproducibility during target validation phase have recently raised questions about biased interpretations. Implementing robustness, rigor, and reproducibility in basic research and reporting statistically significant outcomes is critical not only for advancement of scientific tenets but for the development of novel therapeutics. The basic research data will ultimately have a major impact on clinical outcomes and diagnostics, in the current era of big data mining that is being pursued to create models for treatments in personalized medicine or pharmacogenomics-defined patient populations. The 150 academic screening centers listed in the addconsortium.org are not created equal and have different support infrastructures. While several screening centers partner effectively with industry, employ diverse expertise, and are very well-funded, the vast majority of screening centers have far more limited capabilities, infrastructure, and personnel resources, and may have all or some or none of the university support for salaries/lab maintenance. In a perfect world, the success of an academic screening center should be defined by how many of the hit compounds reach clinical trials or how many new industry partnerships evolve and materialize. In reality, on an average, the quantifiable output of academic translational research is the fact that majority of the projects that go through early discovery process also result in generation of datasets that are publishable and serve as starting points for larger grant submissions. Screening centers are effectively expanding the scope of basic research across various fields of study. Regardless of whether the incoming project is supported by federal/state funds, philanthropy, industry partnerships, disease foundations, university resources, or the fact that the tenured and well-funded research faculty may not face as many challenges as a junior faculty, the goal of developing drugs that reach clinical trials is still a major challenge. Lack of a strong medicinal chemistry and preclinical pharmacology support is one of the many factors that limit the scope of academic drug discovery. Probe discovery indisputably is the preferred path followed for academic translation programs. Having said that, academic pursuit of chemical biology has also resulted in numerous patents [19] and several small start-up drug development companies like Jnana Therapeutics and Takeda California Inc. were founded by academic scientists based on their laboratory research.

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References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Roy A Early probe and drug discovery in academia: a minireview.High Throughput 2018 Feb 9;7(1):4 PubMed PMID: ; PubMed Central PMCID: PMC5876530. eng. [PubMed: 29485615] • This is a general interest articles for providing information on the general probe discovery process and establishing expectations for academic PIs who want to step into the arena of early drug discovery.
2. Palmer M, Chaguturu R. Academia-pharma partnerships for novel drug discovery: essential or nice to have? Expert Opin Drug Discov. 2017 6;12(6):537–540. PubMed PMID: ; eng. [PubMed: 28394189]
3. Austin CP, Brady LS, Insel TR, et al. NIH molecular libraries initiative. Science (New York, NY). 2004 11 12;306(5699):1138–1139. PubMed PMID: 15542455; eng.
4. Slusher BS, Conn PJ, Frye S, et al. Bringing together the academic drug discovery community. Nat Rev Drug Discov. 2013 11;12 (11):811–812. PubMed PMID: ; PubMed Central PMCID: PMCPMC4076044. eng. [PubMed: 24172316]
5. Huryn DM, Resnick LO, Wipf P. Contributions of academic laboratories to the discovery and development of chemical biology tools. J Med Chem. 2013 9 26;56(18):7161–7176. PubMed PMID: ; PubMed Central PMCID: PMCPMC3785552. eng. [PubMed: 23672690]
6. Schreiber SL, Kotz JD, Li M, et al. Advancing biological understanding and therapeutics discovery with small-molecule probes. Cell. 2015 6 4;161(6):1252–1265. PubMed PMID: ; PubMed Central PMCID: PMCPMC4564295. eng. [PubMed: 26046436] •• The article provides a comprehensive review of the application of high quality probe molecules towards mechanistic studies.
7. Workman P, Collins I. Probing the probes: fitness factors for small molecule tools. Chem Biol. 2010 6 25;17(6):561–577. PubMed PMID: ; PubMed Central PMCID: PMCPMC2905514. eng. [PubMed: 20609406] •• Provides detailed information on probe selection criterion.
8. What is the REF? [Internet]. 2017 [cited 2018 Nov 26]. Available from: https://www.ref.ac.uk/about/whatref/
9. Chevaillier T Evaluation in French higher education: history, policy and debates. 2013 p. 8 [cited 2018 Nov 26]. Available from: www.scuolademocratica.it/en/wpcontent/uploads/2013/05/1_2013-Chevaillier.pdf
10. Turri M The new Italian agency for the evaluation of the university system (ANVUR): a need for governance or legitimacy? Qual Higher Educ. 2014 1 2;20(1):64–82.
11. Peterson KR, Costa FC, Fedosyuk H, et al. A cell-based high-throughput screen for novel chemical inducers of fetal hemoglobin for treatment of hemoglobinopathies. PLoS One. 2014;9(9): e107006 PubMed PMID: ; PubMed Central PMCID: PMCPMC4165891. eng. [PubMed: 25225870]
12. Frye SV, Arkin MR, Arrowsmith CH, et al. Tackling reproducibility in academic preclinical drug discovery [Comment]. Nat Rev Drug Discov. 2015;14:733. [PubMed: 26388229]
13. Dolgin E Drug discoverers chart path to tackling data irreproducibility. Nat Rev Drug Discov. 2014 12 1 online;13:875. [PubMed: 25435205]
14. Baell JB, Nissink JWM. Seven year itch: Pan-Assay Interference Compounds (PAINS) in 2017—Utility and limitations. ACS Chem Biol. 2018 1 19;13(1):36–44. [PubMed: 29202222] •• Oulines issues with chemical libabilities and use of filters to weed out chemically intractable hits from compound screening.
15. Wyatt PG, Gilbert IH, Read KD, et al. Target validation: linking target and chemical properties to desired product profile. Curr Top Med Chem. 2011;11(10):1275–1283. PubMed PMID: ; PubMed Central PMCID: PMCPMC3182078. eng. [PubMed: 21401506] •• The article provides information on predefining a target product profile for assessment and prioritization of targets that maximize chances of success.
16. Kyffin JA, Sharma P, Leedale J, et al. Impact of cell types and culture methods on the functionality of in vitro liver systems - A review of cell systems for hepatotoxicity assessment. Toxicol In Vitro. 2018 4;48:262–275. PubMed PMID: 29408671; eng. [PubMed: 29408671]

17. Lai Y, Wei X, Lin S, et al. Current status and perspectives of patient-derived xenograft models in cancer research. J Hematol Oncol. 2017 5 12;10(1):106. PubMed PMID: 28499452; PubMed Central PMCID: PMCPMC5427553. eng. [PubMed: 28499452]

18. Strovel J, Sittampalam S, Coussens NP, et al. Early drug discovery and development guidelines: for academic researchers, collaborators, and start-up companies In: Sittampalam GSCoussens NPBrimacombe Ket al., editors. Assay guidance manual. Bethesda (MD): Eli Lilly & Company and the National Center for Advancing Translational Sciences; 2004:1–41 •• The article describes all the parameters required for developing and optimizing an assay that can be used for compound screening.

19. Huggett B, Paisner K. Top 20 translational researchers of 2017. Nat Biotechnol. 2018 9 6 online; 36:798. [PubMed: 30188525]