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PERSPECTIVES

The Alabama Drug Discovery Alliance: A Collaborative Partnership to Facilitate Academic Drug Discovery

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ABSTRACT The Alabama Drug Discovery Alliance is a collaboration between the University of Alabama at Birmingham and Southern Research Institute that aims to support the discovery and development of therapeutic molecules that address an unmet medical need. The alliance builds on the expertise present at both institutions and has the dedicated commitment of their respective technology transfer and intellectual property offices to guide any commercial opportunities that may arise from the supported efforts. Although most projects involve high throughput screening, projects at any stage in the drug discovery and development pathway are eligible for support. Irrespective of the target and stage of any project, well-functioning interdisciplinary teams are crucial to a project's progress. These teams consist of investigators with a wide variety of expertise from both institutions to contribute to the program's success.

KEY WORDS academic drug discovery · Alabama · University of Alabama at Birmingham · high throughput screening · Southern Research Institute

ABBREVIATIONS

ADDA	Alabama Drug Discovery Alliance
CCC	Comprehensive Cancer Center
CCTS	Center for Clinical and Translational Science
FDA	Food and Drug Administration
HTS	high throughput screening
IP	intellectual property
SR	Southern Research Institute
UAB	University of Alabama at Birmingham

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INTRODUCTION

With pharmaceutical companies increasingly looking for druggable, promising targets as well as promising compounds to in-license, drug discovery in academia, research institutes and small biotechnology companies will become an increasingly important source of new therapeutics in the future. In fact, although the exact numbers differ, depending on the definition of the origin of a drug, it has been estimated that universities and biotechnology companies already account for about a quarter of all new drugs and about half of scientifically innovative drugs approved by the FDA, in particular those that address unmet medical needs (1,2). It is well-documented that the pharmaceutical industry's productivity has been declining, for which several explanations have been offered, including increasing costs, institutional environments that are not conducive to creativity and innovation, pressures from shareholders that are not compatible with the long-term view that is necessary in drug discovery and development, and a shift from research and development to marketing, with a historical, although changing, focus on potential blockbuster drugs (3–5). Because of the high-risk nature of the basic research that is needed to support innovative drug discovery, pharmaceutical companies are reluctant to invest, but academia is a natural fit for these types of

investigations (6), making partnerships between academia and industry a logical proposition. However, these partnerships are not always straightforward, due to a variety of reasons. For example, there is a disconnect between what the pharmaceutical industry and academia consider a validated target and a promising lead compound. For instance, publication of a new protein target and its role in disease in a high impact journal would be considered a great achievement in the academic world, whereas the pharmaceutical industry would consider it no more than a good start, with the ultimate validation being the existence of an effective, tolerated drug that manipulates its target in humans (7). In addition, if a compound demonstrates efficacy in an animal model of disease, an academician might consider it a promising lead compound, whereas a pharmaceutical company will examine the safety profile of the new compound, its composition of matter, the patent landscape for the intended indication and the potential market size, among others. These views lead to differences of opinion about the value of a novel target or compound, complicating negotiations between a university's technology transfer office and a potential pharmaceutical partner (8). A related problem is the academic investigator's need to rapidly publish to be considered for promotion, tenure and grant applications, whereas pharmaceutical companies would want to wait to disclose similar data in order to ensure a strong patent position. In addition, it is uncommon for academic investigators to have access to the knowledge and resources needed to bridge the gap between an interesting laboratory finding and a novel lead compound for the treatment of disease, so that (pre-)clinical proof of concept can be achieved (9). These reasons, in combination with the increased emphasis at the National Institutes of Health on translational science, prompted an increasing number of academic institutions to create drug discovery programs, using a variety of funding sources, infrastructure and operational procedures. The idea behind most, if not all, of these programs is to 'de-risk' the basic findings of the academic investigator and develop a molecule to a stage in the discovery and development pipeline that is mature enough to attract interest and investment of pharmaceutical partners. We herein describe one such drug discovery program, entitled the Alabama Drug Discovery Alliance (ADDA), which is a collaboration between the University of Alabama at Birmingham (UAB) and Southern Research Institute (SR), also located in Birmingham, Alabama. In addition to being an academic drug discovery program, it serves as an example of a public-private partnership, as SR is a not-for-profit organization that conducts basic and applied research in the areas of preclinical drug discovery and vaccine and drug development. We will discuss the infrastructure and operations we have put in place to ensure transparency, trust and productivity for selected drug discovery projects.

HISTORICAL BACKGROUND

Over the past three decades SR and UAB have collaborated on many different one-off projects, each with different goals, management processes and IP agreements. In 2006, discussions between the institutions were expanded toward a more formal collaborative coordinated programmatic effort, though the discussion of a collaborative drug discovery initiative or possibility of even a joint drug discovery center had been discussed for many years. In 2007, a formal plan for the ADDA concept was developed such that the two institutions implemented infrastructure, operating procedures and an IP agreement to manage the collaboration. Pilot projects provided both organizations actual examples of the hurdles that required attention. For example, it became clear that help was required for collaborative team management, in particular with respect to communication between the two institutions. This led to the hiring of a dedicated Research Project Director, who serves as the liaison between UAB and SR. In addition, a proper oversight structure for the overall program needed to be put in place, comprised of both scientific and IP expertise, which could aid in balancing the need to publish results *versus* the goal of developing and protecting IP. This need for oversight led to the establishment of the ADDA Advisory Board, which consists of UAB and SR senior leadership, including technology transfer officers.

Benchmarks of the ADDA's success include new grants awarded to UAB and/or SR based on the data generated in the pilot projects, new patents and new drugs. As touched upon in the Introduction, academic investigators are judged for promotion and tenure decisions in large part by the number of publications and awarded grants. This could potentially conflict with the commercial goals of the program, for which one would want to delay disclosure (and thus patent applications) to extend the patent life as long as possible. Since the ADDA is still in its infancy, such conflicts have not arisen yet, though these kind of decisions will heavily depend on the individual project, potential funding avenues and career stage and needs of the Principal Investigator.

INSTITUTIONAL ENVIRONMENT

The ADDA builds on the existing infrastructure and expertise at UAB and SR to drive the academic drug discovery engine; a website was developed to highlight the resources at both institutions and guide interested investigators to appropriate collaborators (10). ADDA funds pilot projects from investigators at either institution that address an unmet medical need. Therapeutic areas of interest include, but are not limited to, oncology, neurodegenerative disorders and

infectious diseases. UAB's strength in basic biomedical research as well as clinical trial expertise complements SR's expertise in drug discovery and pre-clinical development. SR has a long and successful track record in drug discovery, including seven FDA-approved drugs as well as more than 20 new chemical entities placed in clinical trials. (11,12)

Within UAB, the School of Medicine, the Comprehensive Cancer Center (CCC) and the Center for Clinical and Translational Science ((CCTS) UAB's Center for Translational Science Award from the National Institutes of Health) monetarily contributed to the ADDA's inception and continue to contribute funding to award two-year pilot grants for drug discovery projects. In addition, resources are available in the Department of Chemistry, Center for Neurodegeneration and Experimental Therapeutics and Center for Biophysical Sciences and Engineering to aid with pilot project funding or knowledge and technologies relevant to the drug discovery process.

The bulk of submitted and funded project applications require HTS assay development for targets identified by academic investigators, although projects at other stages of the drug discovery pipeline are accepted as well. For the HTS-assay development projects, the UAB-provided funds are directed towards the actual assay development in the lead investigator's laboratory; the actual screen itself and some medicinal chemistry follow-up are funded by SR. Within SR, the High Throughput Screening (HTS) Center in the Drug Discovery Division facilitates the scaling of laboratory assays to high throughput format in the initial stages of the pilot projects. Importantly, scientists from both institutions work side by side to develop the high throughput screening assay. This Center also ultimately performs the actual screen, usually with a library of approximately 100,000 compounds. When an assay is adequately mature for screening, medicinal chemists' input aids in library choice. Several commercial and proprietary compound libraries are available at SR; it currently has a collection of *ca.* 800,000 compounds obtained from 1) over 40 years of in-house medicinal chemistry, 2) a collection of non-commercial compounds obtained from international collaborators, 3) the NIH Molecular Libraries collection, and 4) commercial suppliers, including Chembridge and Enamine.

ADDA OPERATIONS

Project Identification

Drug discovery projects are identified by a Request for Applications that is circulated at both institutions, twice annually. Submitted proposals are peer-reviewed by a team of scientists from UAB to SR for scientific validity of the target, the drug discovery approach and the expertise of the investigator. If HTS is proposed, the head of the HTS Center at SR reviews the proposal for feasibility from a screening perspective. In addition, licensing associates from the UAB Research Foundation and SR's Intellectual Property office assess the commercial opportunities for the assay, the target, or newly developed compounds. All these reviews are combined, blinded and examined by the ADDA Advisory Board. This Advisory Board determines which projects get funded, based on scientific merit, commercial potential and the overall project portfolio.

Project Portfolio

The current portfolio consists of 14 projects, nine of which are focused on oncology, two on Parkinson's disease, and one each on HIV, ischemia/reperfusion injury, and diabetes. Historically, oncology, neurodegenerative disorders and infectious diseases are areas of focus and strength, both at UAB and SR; this fact is reflected in the ADDA portfolio. As mentioned above, however, drug discovery projects in any therapeutic area are eligible for funding, as long as there is sufficient expertise available on either campus. Of the 14 projects, 12 focus or have focused on HTS assay development: three screens have been completed or are in the process of being completed, four assays will be ready for HTS within this calendar year, and five other assays are in the initial stages of development. The other two projects focus on target identification and determination of a target's crystal structure, respectively. There has been one additional project funded, which evaluated the *in vivo* effects of newly developed alkaloid compounds in xenograft tumor models. After determination of the maximum tolerated dose upon repeat administration and preliminary pharmacokinetic analysis, a therapeutic study in tumor-bearing mice was initiated. Since tumor size was not sufficiently reduced according to previously defined parameters, the project was terminated.

Project Teams

Importantly, all funded projects have a team built around them that consists of various experts in either the subject matter or a particular technology. The teams formally meet quarterly, with meetings facilitated by the Research Project Director; members come from both institutions, and teams typically consist of experts in HTS and HTS assay development, medicinal chemistry, pharmacology, cell biology and/or virology, pathology and clinical care. Such a team approach is especially important for academic drug discovery, since most researchers are experts in the biology or biochemistry of the target that they have identified or are studying; they are not experts in how to develop an HTS assay or even in how the drug discovery process works in general (13).

After an HTS assay has been developed and screened, the HTS informatics group ranks hits for follow-up dose-response screening, after which the confirmed hits are evaluated by SR's medicinal and computational chemists for interesting scaffolds. Importantly, secondary and tertiary assays need to have been identified and put in place before HTS commences; this ensures a timely progression from hit confirmation to lead identification, ideally while confirming the mechanism(s) of action. These secondary and tertiary assays tend to be available in the PI's laboratory, although sometimes additional project team members need to be recruited to ensure that the infrastructure and expertise are available to confirm the hits' activity in biologically relevant assays. For example, one of the initial pilot projects was submitted by an investigator with expertise in crystallography. Although one of the initial project goals was to obtain a high-resolution crystal structure of the target, follow-up studies in cell culture and animal models required the addition of team members with expertise in cell biology, pharmacology and pathology.

In general, a key aspect of the ADDA is to focus the pilot projects on the critical path to drug discovery, thus maximizing the impact of the limited funds. Extensive follow-up assays are generally beyond the scope of ADDA's pilot grants, but investigators are encouraged to apply for external federal and non-federal funding to facilitate further lead optimization, molecular modeling, preliminary pharmacokinetic studies, animal efficacy studies, and other preclinical development. Of course, use of proprietary data in grant applications needs to be approved by both parties, allowing time for (provisional) patent applications, if needed. Alternatively, partnering with pharmaceutical companies who have an interest in the target and/or compounds is a desirable option. To encourage and facilitate this commercial development, UAB's technology transfer office (the UAB Research Foundation) and SR's Intellectual Property office are both intimately involved in the ADDA and kept abreast of all drug discovery projects. The agreement between UAB and SR ensures that information and materials can flow freely between institutions and protects IP.

The participation of technology transfer officers on the project team not only ensures timely disclosure of inventions to the respective proper institutional bodies, but it also contributes to the education of all team members about the IP process. Such education is needed, since some investigators fail to recognize the importance of IP and laws associated with protection, thereby jeopardizing commercialization of the drug to be developed (7). In addition, as noted in the Introduction, there are some investigators who overestimate the value of their inventions, illustrating the difference of opinion as to when a target is considered validated (7). In both cases, educating the research community and facilitating communication between scientists and IP personnel can prevent or ameliorate these problems.

As with any team-based approach in an academic environment, several challenges need to be met to ensure functionality, including member participation and team productivity. An important challenge is to build trust between participating volunteer team members, especially those from different institutions. Transparency and clear communication are instrumental in this regard; these are facilitated by the Research Project Director, who keeps track of all projects, clarifies expectations and often translates between and among the various experts on the team. An informal survey of investigators as well as participating team members illustrated that along with participation of senior leadership, the research project team structure and the participation and guidance of the Research Project Director are instrumental in moving these academic drug discovery efforts forward. Such types of interdisciplinary project managers/scientists will become more in demand as translational efforts in academia continue to grow (9,14,15).

ONGOING CHALLENGES

With the ADDA about to enter its third year of existence, several structural challenges are emerging that are not unique to this drug discovery program. The first main problem is the lack of resources for medicinal chemistry efforts, once hits have been identified. To go from hit to lead requires significant time and money, which cannot be covered by our modest pilot funding. Traditionally, funding from NIH resources for chemistry has been scarce; however, institutes such as NINDS have appropriated new Medicinal Chemistry for Neurotherapeutics contracts for fiscal year 2010, recognizing that "the need for medicinal chemistry in the NIH community has grown in recent years as non-drug compounds with therapeutic potential have been identified in many disease areas." As noted above, another way forward is to partner with commercial entities; in this regard, UAB and SR are participants in a joint venture with Jubilant Life Sciences, which was initiated in the fall of 2009. The premise of the joint venture is to enhance development capabilities by leveraging resources of all three parties while developing joint IP. This joint venture, called UniTria Pharmaceuticals, will focus on leveraging the collective enabling technologies for drug discovery, in areas of oncology, metabolic disease and infectious disease, with the goal of accelerating the development of innovative therapies. Key focus areas of UniTria Pharmaceuticals include

- selecting the most promising biological targets for unmet medical need, discovered by biomedical researchers at UAB, SR and Jubilant;
- developing new molecules around these targets through discovery and development activities performed at UAB, SR and Jubilant;
- using early research data to secure funding to create new research jobs;
- developing drugs through preclinical, phase 1 and early phase 2 clinical trials to maximize value to potential licensees, securing partnerships with the pharmaceutical industry; and
- licensing drugs to the pharmaceutical industry.

The joint venture is owned and invested in by all three parties, ensuring that both academic and commercial interests are represented in the decision-making processes on project selection and implementation. Within the limits of available funding, UniTria intends to invest sufficient resources to get a compound to clinical trials. The first projects are currently being selected for acceptance into the JV, and progress in the next few years will determine the success of this approach.

In the same vein, partnerships with additional commercial entities for individual projects are certainly encouraged, which again illustrates the importance of early and frequent involvement of IP licensing associates in the project team meetings.

Another major challenge that we anticipated and indeed encountered is the need for educating the academic community about the drug discovery process. Many investigators are, understandably, naïve about what it takes to go from bench to bedside, beyond the initial identification of hit compounds in a primary screen. This lack of understanding is being remedied at the graduate level with courses on drug discovery in UAB's Howard Hughes 'Med into Grad' Program as well as the general UAB Graduate Biomedical Sciences program; both programs interface with SR for faculty lecturers and internships. However, to educate the current generation of biomedical researchers, the ADDA organizes symposia and invites external speakers to present seminars that highlight various aspects of the drug discovery pipeline; these events are generally well-attended, illustrating the interest of the faculty body in translational research. In addition, an educational course is currently under development that is open to scientists from any level at either institution. Together with the visible success of the drug discovery projects in the ADDA portfolio, we hope to stimulate further education and interest in academic drug discovery.

The ADDA is only one of many academic drug discovery programs that have been established in the United States in recent years; listings of these programs can be found in other publications (16,17), although a comprehensive review of their activities and organization is lacking to date, and is beyond the scope of this article. However, the ADDA is clearly unique in its collaborative model between UAB and SR, as compared to universities that have started internal drug discovery centers and acquired the associated HTS equipment, compound libraries and expertise. The contributions of the long-term success and expertise in drug discovery at SR and the basic biology and clinical strength at UAB provide this partnership with the means to have a significant impact in new drug discovery and development. All academic drug discovery programs vary greatly with respect to, for example, infrastructure, intellectual and financial support and disease focus areas. Nonetheless, the challenges mentioned above are relevant for all these programs; it would be beneficial to have a conversation on an international level to exchange best practices and solutions to some of these hurdles to successful academic drug discovery.

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