Small (molecule) thinking in academia

By Joanne Kotz, Senior Editor

A team at **The University of North Carolina at Chapel Hill** has analyzed the status of small molecule drug discovery in academia in the U.S. and documented a large jump over the last six years, with the number of dedicated centers more than doubling during that period.[1] The result has been an uptick in commercial activity at these centers, including new company formation and collaborations or licensing deals with biopharmas. Although some of these efforts have led to drug leads, the biggest potential impact of academic drug discovery may be in the generation of research compounds for pharmacological validation of new targets.

Going forward, key challenges include funding academia's drug discovery effort and overcoming potential valuation disconnects between academia and industry.

"The biotech revolution—recombinant protein and antibodies as drugs—was driven from academics into industry," according to Stephen Frye, a senior author of the academic drug discovery analysis and director of the Center for Integrative Chemical Biology and Drug Discovery at the **UNC Eshelman School of Pharmacy**.

"A similar phenomenon is happening on the chemistry side, but in reverse," added Frye, who was previously worldwide VP of discovery medicinal chemistry at **GlaxoSmithKline plc**.

"The expertise in small molecule drug discovery that has traditionally resided in industry is being integrated into academia. The result is that you've brought what industry is good at and juxtaposed it with innovative targets and disease-specific knowledge," both of which are areas of strength for academia, he said.

To quantify how the increased focus on academic small molecule drug discovery has played out to date, Frye and Rudolph Juliano, associate dean for research and graduate education at the UNC Eshelman School of Pharmacy, teamed up with colleagues at UNC's Odum Institute for Research in Social Science to survey academic drug discovery centers.

The team identified 78 small molecule–focused drug discovery centers at universities or nonprofit research organizations in the U.S. Of those, 56 responded to a survey seeking information on facilities, capabilities, funding, targets and pipeline. The results of the survey were published in *Nature Reviews Drug Discovery*.

Two-thirds of responding drug discovery centers said they have high throughput screening infrastructure and hit-to-lead medicinal chemistry expertise, while only half have *in vivo* efficacy capabilities. Less than half have facilities for metabolism and pharmacokinetic studies.

According to the published survey results, 50% of the small molecule drug discovery efforts at the centers are focused on "innovative targets based on unique discoveries or expertise residing within [the affiliated] institution with little validation evidence in the literature."

The disease indications being explored at the academic centers correlate with industry activity, with cancer, neurological diseases and infectious diseases topping both lists (*see* **Figure 1, "Academic drug discovery by the numbers"**).

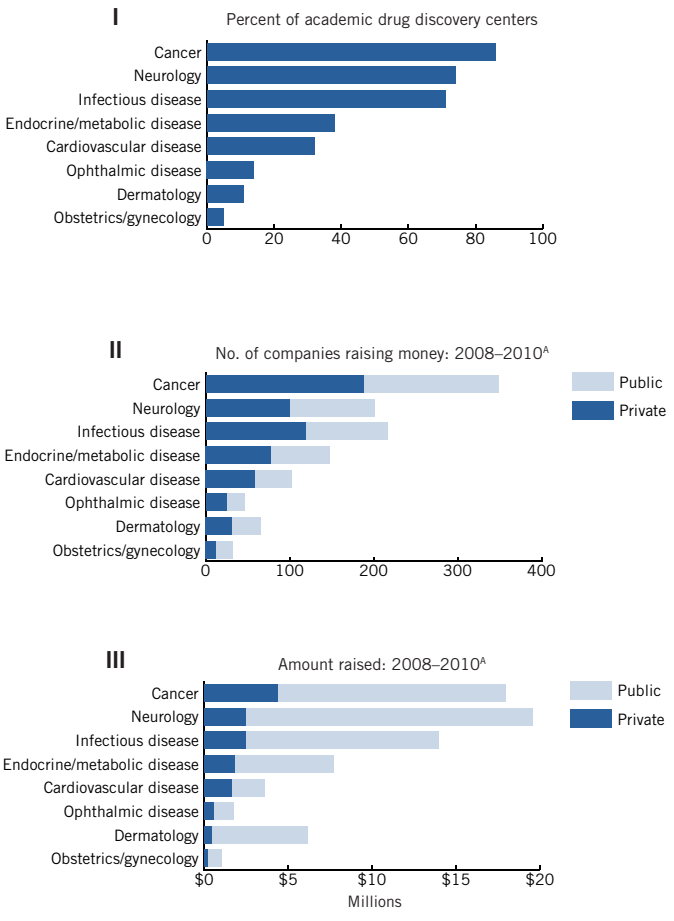

Figure 1. Academic drug discovery by the numbers. Academic drug discovery centers (**I**) as well as private and public biotechs, as determined by both the number of companies raising money (**II**) and money raised (**III**), are largely focused in the areas of cancer, infectious disease and neurology.

Sources: BCIQ: BioCentury Online Intelligence; Frye, S. et al. Nat. Rev. Drug Disc. ***10****, 409–410 (2011)*

[A]Data on money raised and number of companies raising money includes some double-counting or triple-counting of financings as certain companies are working in more than one disease area.

The aligned areas of therapeutic focus clearly have translated into deals. Marina Crosby, a coauthor on the study and a graduate student at the Odum Institute at the time, told *SciBX* that since the date of founding, the responding centers collectively have filed at least 380 patents and licensed around 95 compounds to industry.

At **Harvard University**, "we have seen an overall increase in deal flow, and a significant portion of that can be attributed to having a stronger IP package as a result of compound discovery and medchem efforts," said Curtis Keith, CSO of the Technology Development Accelerator Fund at the Harvard Office of Technology Development. "To date, small biotechs and new companies have been primary recipients."

A case in point is **Proteostasis Therapeutics Inc.**, which exclusively licensed two previously unknown ubiquitin-proteasome targets and associated small molecule compounds from Harvard in April.

According to Walter Newman, head of external innovation at Proteostasis, having small molecules against the target was a plus. "If the molecule has warts and you know you would never work with the chemical series, it would be less interesting. That wasn't the case here—the molecules figured into the deal for us," he said.

Harvard's first screening facility was set up in 1998. University faculty now has access to additional screening centers, including one at the **Broad Institute of MIT and Harvard**.

Similarly, **The Scripps Research Institute** also has seen an increase in commercial interest as a result of its screening and drug discovery capabilities, said Scott Forrest, director of business and technology development in the Scripps Office of Technology Development.

Scripps has a Molecular Screening Center and a Translational Research Institute. Both were founded in 2005 and are located on the **Scripps Florida** campus.

"We have the ability to interrogate a pathway pharmacologically and then to develop early leads. This is attractive especially to small- and medium-sized companies," said Forrest. "A few years into our screening effort, we have a track record that includes one clinical candidate."

That compound, the sphingosine-1-phosphate receptor 1 (S1PR1; S1P1; EDG1) agonist RPC1063, was licensed to **Receptos Inc.** in June 2009 and started Phase I studies in multiple sclerosis (MS) in January 2011.

Tooling up

Despite the handful of deals for small molecules on the cusp of clinical development, the biggest potential impact of academic drug discovery may be in the generation of research-grade compounds that can help startups further validate new targets.

"University researchers tend to focus on highly innovative biology and novel disease mechanisms, and the result of that is that our targets are usually at an early stage of validation from an industry perspective. Historically it has been challenging for universities to generate significant commercial interest in their disease targets for that reason," said Keith. "In recent years, however, we've seen that significantly greater interest is gained by having compounds that function as probes of those targets."

"At the end of the day, it's not typically the initial chemical matter that plagues a startup spinning out of academia. Instead it's the validity of the initial biologic hypothesis and whether the biology is relevant to disease."
—Bruce Booth, Atlas Venture

Proteostasis' Newman agreed that these 'tool compounds' can "bridge the gap between genetic proof of concept and pharmacological proof of concept," which can significantly increase industry interest.

"Typically, having more chemical matter wouldn't make that much difference to us," said Doug Cole, general partner at **Flagship Ventures**. However, for some new targets, "a tool compound can be critical for demonstrating that the problem is amenable to a small molecule approach," he added.

"I haven't noticed a step change in the number of licensable programs, but there are certainly examples where the chemical substrate is far more advanced than it would have been otherwise," said Bruce Booth, a partner at **Atlas Venture**. "The convergence of interesting biology and good chemical substrate is often catalytic for the creation of a startup."

He added: "A lot more academic investigators have access to chemical matter because of these screening and hit-to-lead capabilities, which enables further target validation and *in vivo* proof of principle. It's certainly a big positive to have at the very least some tool compounds to help validate targets and pathways before starting a new company."

Booth expects small molecules discovered in academia will have a positive, albeit modest, effect on pace of new company formation but should help advance the quality of the startups being formed.

"At the end of the day, it's not typically the initial chemical matter that plagues a startup spinning out of academia. Instead it's the validity of the initial biologic hypothesis and whether the biology is relevant to disease," said Booth.

Cole also believed that small molecules discovered in academia will likely have a more modest effect on new company formation than factors such as target validation and the availability of a tractable clinical development path. "If you make the assumption that the target is fundamentally druggable, then chemistry *per se* is not, in most cases, the rate-limiting step," agreed Cole.

Show me the money

Whether a university's small molecule is a research tool or a therapeutic lead, a major challenge for academic drug discovery is still finding money to fund the endeavor.

In the published survey, 40% of center funding comes from federal grants and 5% from for-profit organizations. The median annual operating expenses for all responding centers was $1.4 million, with the top 10% averaging $33 million.

In the survey, 68% of respondents cited insufficient or unstable funding as the number one obstacle to success.

"We are not set up to routinely get to a clinical candidate" despite having the infrastructure and capability, said Frye. "You can't do this on an RO1 grant—it's just not possible."

For RO1 grants, the main funding framework at the **NIH**, special justification is required for funding over $250,000 per year.

Frye said targeted federal funding that is distinct from research grants is one alternative for advancing the later stages of academic drug discovery.

He said his center has received two contracts from the **National Cancer Institute** totaling $2.4 million, with additional milestone-dependent funding possible, to develop drug leads against targets identified at UNC. The first is to target c-mer proto-oncogene tyrosine kinase (MERTK) for childhood acute lymphoblastic leukemia (ALL). The second is to tackle isocitrate dehydrogenase 1 (IDH1) for glioblastoma multiforme (GBM).

Harvard's Accelerator Fund is testing an alternative approach. Money from the fund, which was created in 2007 with private donations, is awarded to investigators through a grant-selection process to conduct projects that could help bridge the gap between academic research and commercialization. Keith told *SciBX* that Accelerator Fund money can be used for a range of translational activities depending on the project, including accessing CRO-based medicinal chemistry to optimize compounds and using consultants with drug discovery expertise.

"To the extent that we still encounter initial skepticism that our compounds will be the starting points for the drugs themselves, the support provided by the Accelerator Fund has been instrumental in helping us to overcome such obstacles," said Keith.

Public-private collaborations

Collaborations between academic drug discovery centers and industry are perhaps the most promising approach to overcoming the funding gap.

"The biggest impact we feel is the ability to collaborate early. We are seeing an uptick in early collaborations," said Scripps' Forrest. "Knowing that we can deliver a molecule that is ready for preclinical development has opened us up to types of collaborations that we didn't have before."

For instance, if a small biotech company collaborates with the Scripps screening center, the company can avoid acquiring in-house screening and medicinal chemistry, he said.

Forrest cited **Envoy Therapeutics Inc.** as an example. The company was formed in 2009 based on a technology out of **The Rockefeller University** for identifying the proteins expressed by a specific cell type in a complex tissue, such as the brain. However, Envoy based itself in Jupiter, Fla., to facilitate a screening and lead discovery collaboration with Scripps Florida, said Forrest.

Envoy's recent deals with **Merck & Co. Inc.** and **Takeda Pharmaceutical Co. Ltd.** highlight the success of the collaboration, he added.

Envoy announced a diabetes and obesity collaboration with Merck on undisclosed terms in January 2010, with the first milestone payment received in December that year.

In October 2010, the company entered into a collaboration with Takeda for schizophrenia for an upfront payment of $3 million, as well as research funding and potential milestones.

Pharmas are also beginning to take notice.

"We are looking more and more into early stage opportunities and, on the drug discovery side, we are interested in working directly with academics if they have any novel targets, disease-relevant assays for screening or novel molecules," said Sridar Natesan, scientific site head and head of external innovation and partnering at **Sanofi**.

The licensing option always exists, but "sharing the IP and co-developing the molecule is a new model we are considering," said Natesan.

UNC's Frye said collaborating with pharma is a potential approach being considered in his center for developing lead molecules and clinical candidates—but that new models for collaboration that are simplified, involve joint risk sharing and a collaborative approach need to be explored.

Alternatively, the Archipelago to Proof of Clinical Mechanism (Arch-2POCM) initiative being championed by the **Structural Genomics Consortium** and **Sage Bionetworks**[2] may be one IP-free mechanism for building a public-private interface, said Frye. This new paradigm could work well with the increasing drug discovery activity in academia, he added.

Coming to consensus

One challenge in negotiating deal terms is the naïveté about valuations at some academic institutions.

"We spend time with the business development team combing conferences, websites and small biotechs constantly looking for molecules of interest against the targets and therapeutic areas we care about. In the last two years, we've increasingly landed on molecules worked on by academic groups," said Michael Varney, SVP of small molecule drug discovery at **Roche**'s **Genentech Inc.** unit.

He said the company has had at least one case in which "we tried, but the molecule was overvalued on the academic side, and we did not come to an agreement."

In contrast, Genentech partnered with the Small Molecule Discovery Center at the **University of California, San Francisco** last year to discover and develop neurodegenerative disease drug candidates. The 2-year deal with an optional third year is worth up to $13 million.

In this case, an investigator at UCSF "had a lead molecule and some expertise in a target type of interest, and we built a collaboration around that," said Varney. "At UCSF they were willing to negotiate a business arrangement that was fair to both sides."

"Putting the right value on early stage compound programs at tech transfer offices is a tough thing to do, and there is a tendency to overestimate the value," added Sanofi's Natesan.

He said this is less likely to be a major hurdle going forward as industry-academic interactions around small molecules increase.

"The academic tech transfer side has less experience in dealing with small molecules compared with biological targets and so there is a bit of an educational process going on," echoed Varney, adding that he expects more reasonable valuations to emerge as more of these deals are done.

Kotz, J. *SciBX* 4(22); doi:10.1038/scibx.2011.617
Published online June 2, 2011

REFERENCES

1. Frye, S. *et al. Nat. Rev. Drug Disc.*; published online June 1, 2011; doi:10.1038/nrd3462
Contact: Stephen Frye, The University of North Carolina at Chapel Hill, Chapel Hill, N.C.
e-mail: svfrye@email.unc.edu
Contact: Rudolph Juliano, same affiliation as above
e-mail: arjay@med.unc.edu
2. Cain, C. *SciBX* **4**(20); published online May 19, 2011; doi:10.1038/scibx.2011.562

COMPANIES AND INSTITUTIONS MENTIONED

Atlas Venture, Cambridge, Mass.
Broad Institute of MIT and Harvard, Cambridge, Mass.
Envoy Therapeutics Inc., Jupiter, Fla.
Genentech Inc., South San Francisco, Calif.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Flagship Ventures, Cambridge, Mass.
Harvard University, Cambridge, Mass.
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
National Cancer Institute, Bethesda, Md.
National Institutes of Health, Bethesda, Md.
Proteostasis Therapeutics Inc., Cambridge, Mass.
Receptos Inc., San Diego, Calif.
Roche (SIX:ROG; OTCQX:RHHBY), Basel, Switzerland
The Rockefeller University, New York, N.Y.
Sage Bionetworks, Seattle, Wash.
Sanofi (Euronext:SAN; NYSE:SNY), Paris, France
Scripps Florida, Jupiter, Fla.
The Scripps Research Institute, La Jolla, Calif.
Structural Genomics Consortium, Oxford, U.K.
Takeda Pharmaceutical Co. Ltd. (Tokyo:4502), Osaka, Japan
UNC Eshelman School of Pharmacy, Chapel Hill, N.C.
University of California, San Francisco, Calif.
The University of North Carolina at Chapel Hill, Chapel Hill, N.C.