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DRUG DISCOVERY

A helping hand

The pharmaceutical industry is increasingly turning to academics to tackle the early stages of drug discovery.

BY TRISHA GURA

When neuroscientist Mark Zylka launched his laboratory at the University of North Carolina (UNC) in Chapel Hill six years ago, he was not thinking about synthesizing chemicals. He was focusing on trying to identify the molecules expressed by pain neurons and how they function. But then he discovered a pain-relieving pathway that might be targeted with a chemical: an adenosine receptor stimulator, or agonist. Unfortunately, drug developers had previously tested such agonists and found that they had serious cardiovascular side effects, such as slowed heart rate and blockages in the impulse that regulates heartbeat. Zylka had an idea about how to modify the agonist's structure to avoid these side effects. But to do that, he needed medicinal chemistry experience, something his neuroscience training had not provided.

So he found a collaborator, Stephen Frye, who in 2007 had been recruited from the nearby research facility of drug firm GlaxoSmithKline (GSK) in Research Triangle Park, North Carolina, to direct a new Center for Integrative Chemical Biology and Drug Discovery at UNC. Frye found a way to synthesize the modified agonist, which Zylka then used to gather preliminary data that showed that the agonist could mitigate pain without cardiovascular side effects. Together, the pair netted a grant from the US National Institutes of Health (NIH) in Bethesda, Maryland. Now Zylka, with Frye's help, is learning drug-discovery skills on the fly. "It is very different from academic research," he says.

Zylka is one of a new breed of researchers who are staying in academia but moving into drug discovery, which has long been considered the domain of industry. "Before I die, I would love to directly identify something that would ultimately be used to treat a disease in humans," says Zylka. "But there is a big separation between what basic scientists do and what drug companies want. I felt it was important to try to bridge that gap."

It is a tall order — and a great opportunity. Industry has increasingly pulled out of the earliest stages of drug development, deeming them too risky and expensive. At the same time, "there has been an absolute deluge of new discoveries of the fundamental basis of disease", says Christopher Austin, director of the National Center for Advancing Translational Sciences (NCATS) at the NIH. "We are talking about the past 50 years of NIH-funded mechanistic science."

This accumulation of data that could be used to formulate new therapies has driven large-scale, national efforts to give academia a more industrial focus. For example, the NIH launched the US$576-million NCATS less than a year ago to speed up the development of new therapeutics in academic settings (see *Nature* **481,** 128; 2012). At the same time, industry has stepped into academic territory, setting up drug-discovery collaborations with scientists working in basic research as well as joint industrial–academic fellowships for postdocs. These opportunities are blurring the lines between academia and industry, and, increasingly, ambitious academics can learn how to translate bench work into real-world applications by stepping into industry, at least temporarily. "This is something that is learned by doing," says Torsten Hoffmann, chair of the Roche Postdoc Fellowship (RPF) Program at the pharmaceutical company Roche in Basel, Switzerland.

NEW APPROACH

In the United States, the process of drug discovery typically occurs in three stages. First, researchers identify a biochemical pathway involved in the disease of interest. Second, cell and molecular biologists develop assays based on that pathway to screen libraries of small molecules for potential drugs. And third, geneticists create cell and animal models to validate drug targeting. Then, as the drug moves into development, teams of experts are assembled to run clinical trials and deal with regulatory agencies. The process also often entails other steps, such as formulating drug candidates to optimize delivery and doing ▶

toxicology studies. But for academics, the endpoint might be quite early in the process; identifying a molecule that biotechnology companies can develop further, for example, or, if a biotech partner cannot be found, launching a start-up company to take the work to early clinical trials.

Increasingly, scientists can learn these kinds of skills within academia. As a result of consolidation and programme cuts, "some very, very good people have left pharma to go to academic institutions", says Austin. They are starting up translational medicine programmes to teach aspects of drug discovery.

Right now, says Austin, there is "a robust network" of more than 60 academic centres and programmes in the United States (http://addconsortium.org) with precisely this goal. The idea, says Austin, is not to replicate the work of industry, but rather to sort through the academic pile-up of ideas, to identify the most promising and make them attractive to potential industrial partners.

"The kind of science that you use for drug discovery is a bit different from typical basic science."

An academic who has discovered a disease-relevant target can contact one of these centres and apply to spend a year or more there, learning, for example, how to develop an assay that could be scaled up and used to identify promising drug compounds. "The kind of science that you use for drug discovery is a bit different from typical basic science," says Marcie Glicksman, co-director of the Laboratory for Drug Discovery in Neurodegeneration at Harvard Medical School in Boston, Massachusetts, one of the 60 centres in the consortium.

Rather than making a breakthrough, publishing it and then moving on to the next project, as is typical in academic research, drug discovery involves creating procedures and assays that can be scaled up to high-throughput levels, with particular attention paid to reproducibility and standardization.

"You have a different level of quality control," says Richard Boucher, co-principal investigator of translational research at UNC, "and also an element of documentation that you don't have in a research lab. You are trying to continually make your measurement with better technology, more efficiently, faster."

Garret FitzGerald, a pharmacologist and director of the Institute for Translational Medicine and Therapeutics at the University of Pennsylvania in Philadelphia, and his colleagues have formalized drug-discovery training with a three-year master's programme for postdoctoral fellows or instructors at the early faculty stage. FitzGerald says that the idea is to recruit candidates with a PhD or medical doctorate in a specific discipline — for example, cell biology — and make them proficient in drug discovery and development. A small percentage would then stay in the translational centres, working as the next generation of trainers.

As at conventional large 'centres of clinical pharmacology', the training is project-based and, at the end, the trainees go back to their disciplines "with value added", FitzGerald says. "That should enhance their ability to be funded, and transform their departments."

INDUSTRIAL STRENGTH

One possible criticism of these centres and of academia-focused translational science programmes is that some are run by academics without industrial drug-discovery expertise. "Everybody claims that they are doing translation," says Rajesh Ranganathan, director of the Office of Translational Research at the US National Institute of Neurological Disorders and Stroke (NINDS) in Bethesda, Maryland. But he argues that only a small percentage of academics making that claim understand the process and have the resources to actually discover and develop a drug.

Thus, the best training involves establishing industry ties and working either in industry or with industrial scientists, says Ranganathan. "Get into a laboratory in an industrial setting and work on a project, take it forward. Do that for three, four years, whatever it might take," he says. "Then you are in a position to move into situations where you can parlay that into a broader job in translation."

One way to move into translational research is through postdoctoral fellowships sponsored by companies such as Roche, the Novartis Institute for Biomedical Research headquartered in Cambridge, Massachusetts, or Genentech, headquartered in South San Francisco, California. The fellowships pair academic postdocs with both industrial scientists and academic mentors to work on creative projects

Erick Carreira says synthetic chemists need to include drug discovery in their skills repertoire.

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Rajesh Ranganathan says that getting industrial experience in drug discovery is key for academics.

that would not normally be pursued by industry (see *Nature* **461,** 554–555; 2009).

The programmes aim to address one of the main concerns about industrial research, which was "getting more and more entangled in engineered research where everything was milestones and very short-sighted", says Klaus Müller, a medicinal chemist at Roche. To keep from "drying out", companies such as Roche recruit top scientists, promote cutting-edge science and encourage publication. At the same time, postdocs in company programmes have industry resources at their disposal, and gain experience in drug discovery

But an element of caution is needed, says Ranganathan, who worked at Novartis and set up the company's postdoctoral fellow programme before moving to the NINDS. "Make sure that such a programme is not a reward structure for internal scientists." Otherwise academic postdocs act as a "pair of hands for those people who are already successful in the company", he says, rather than as well-mentored trainees and achievers of scientific renown for themselves.

A PRODIGIOUS PARTNER

Academia–industry collaborations can be a way to both gain drug-discovery expertise and advance a project. Organic chemist Erick Carreira, at the Swiss Federal Institute of Technology in Zurich (ETHZ), followed that path when he began to collaborate with scientists at Roche. Before he came to Switzerland from the United States, his group was synthesizing new molecules and testing them through standard chemical means, such as measuring boiling and melting points or solubility. He never thought about designing drugs.

But shortly after joining the ETHZ 15 years ago, Carreira became a consultant with Roche; together, he and Roche scientists came up with a wild, "scribbled-on-a-napkin" idea. What if they introduced a new kind of chemical unit into potential drugs to help them to work better?

The idea was to hunt outside the usual 'chemical space', searching for all the possible molecules of a given class, to look for structures with properties deemed 'useful' in the drug-discovery process. Müller identified a new class of synthetic chemicals called oxetanes as an under-explored area, and Carreira began modelling ways to substitute oxetanes for common functional groups already used in drug discovery. Normally, industrial scientists would consider such an idea too "odd, too risky and unlikely to succeed", says Müller, who is secretary of the RPF Program. But for academics such as Carreira and his team, the project was perfect.

Roche backed the idea, supporting a synthetic-chemistry student, Georg Wuitschik, to work with Carreira, Müller and others to usher oxetanes into drug discovery. The results paid off, and the scientists published what became known as the oxetane concept (G. Wuitschik *et al. J. Med. Chem.* **53,** 3227–3246; 2010). It rapidly took hold in the drug-discovery community, offering potentially new ways to modify drugs. "This is really a gold mine," says Müller.

Meanwhile, Carreira, in collaboration with Roche, is coaching chemistry students, postdocs and others who are interested in drug design. "The requirements of someone now coming out of graduate school in synthetic chemistry have changed," he says. "Given the current job climate, a graduate student or postdoc needs to be fully conversant not only with the methods of chemical synthesis — how to make molecules — but also how to make novel chemicals with a pivotal role in the next generation of smart drugs."

For Zylka, working with an industry veteran who had returned to academia was key. Before coming to UNC, Frye, as head of GSK's discovery medicinal-chemistry group, had steered three drugs either to market or late-stage clinical trials. His team offers the best of both worlds, Zylka believes: the creativity and freedom of an academic lab and the wisdom and experience of an industrial mentor.

Those in academia who can take advantage of such industry ties and drug-discovery resources have a shot at a grand pay-off, and a new career path — if they dare to be bold, enterprising and an "expert at one discipline but knowledgeable about the other translational disciplines", says Austin.

"The scientific ecosystem has evolved to a place where rapid advances will happen," he adds. "And basic scientists can actually make that happen without going to a company. This is absolutely revolutionary." ■

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CITATION

Data standards urged

The academic community needs better curation and authorship standards for data, according to a committee of the US National Academies. In *For Attribution — Developing Data Attribution and Citation Practices and Standards*, published on 19 November, the Board on Research Data and Information (BRDI) presents views from experts in data curation across all scientific disciplines. It says that scientific data — such as measurements and images — should be made available for scrutiny online or through an archive or repository, and that researchers should be given full credit for their efforts in creating those data. The report notes that some scientific associations, including the American Geophysical Union, endorse giving the same importance to the publication of scientific data as to the publication of papers.

Data citation, the committee says, gives authors proper credit, makes them accountable and helps to make science reproducible. Although it offers no formal recommendations, the report suggests that digital object identifiers similar to those used for research papers would provide a permanent online address for data sets and allow the data to be cited formally.

"People are using other people's data more often, so they need a way to cite and attribute sources," says Paul Uhlir, the committee rapporteur and director of the BRDI. "Up to now, there has been no convention for it. That's really behind the whole rise in calls for data citation and attribution standards — it's an infrastructure issue. Those people need credit."

The report notes that questions remain regarding how to decide which data are curated, who would pay to maintain data in repositories or archives and who would peer review data and how.

Uhlir says that how often a researcher's data are cited is likely to become an important career metric. The report suggests that it could be incorporated into tenure decisions, as paper citations and journal impact factors are now.

For Attribution is the first of several expected publications on the subject. The BRDI will contribute to a report to be released next year by the international Committee on Data for Science and Technology (CODATA), part of the International Council for Science in Paris on current practices in data curation and authorship. A final report from CODATA presenting best practices and recommendations is expected by 2014.