

COVER STORY

**DRUG HUNTERS**

Foundations and government agencies are relying on the expertise of CROs to develop innovative leads at resource-poor research ventures.

BRIDGING THE GAP

As big pharma exits early-stage drug development, contract research firms are serving the **NONPROFIT AND GOVERNMENT INSTITUTIONS** that are taking it on

RICK MULLIN, C&EN NORTHEAST NEWS BUREAU

CONTRACT RESEARCH organizations, or CROs, have a natural tendency to bridge gaps in the landscape of pharmaceutical R&D. As laboratories for hire, CROs have emerged as vital agents in screening compounds, developing synthetic routes, and supporting clinical trials. They provide expertise and infrastructure to virtual drug companies, small biotech firms, and even big pharmaceutical makers that lack necessary resources.

Increasingly, though, the research conducted by CROs is being funded by nonprofit foundations and government agencies. The trend reflects a tectonic shift

in how drugs are discovered in the pharmaceutical industry. For Western CROs, which are benefiting most from the trend, the new business is helping to offset contracts lost to competitors based in India and China.

Traditional funders of drug discovery are retrenching, explains Walter H. Moos, vice president of the Biosciences Division of SRI International, a nonprofit research institute and CRO. Venture capital for early-stage drug discovery has been declining since the recession. Major drug companies have become increasingly risk averse, committing to acquire compounds only in later stages of development. And the traditional

commercial support for projects crossing the so-called valley of death—the early stretch of the long drug development process—has all but evaporated.

“But nature abhors a vacuum,” Moos says. Nontraditional support is rushing into the space, and governments are doing more of the research that was traditionally the domain of commercial entities. One example is the National Institutes of Health’s Roadmap, now called the Common Fund, which was started in 2006 to support drug discovery and development. The agency’s newly launched National Center for Advancing Translational Sciences (NCATS)



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is another program supporting early-stage drug development.

And foundations are going beyond their traditional grant-making role to call the shots on drug discovery projects. The Cystic Fibrosis Foundation and the Michael J. Fox Foundation, which targets Parkinson's disease, are two examples of nonprofits focused on specific diseases.

OTHER ORGANIZATIONS have a broader focus. "The Bill & Melinda Gates Foundation is the gorilla in the room," Moos says. The founder of Microsoft, once criticized for amassing Rockefeller-scale wealth without an established charitable venture, has launched the largest foundation supporting drug research, with an asset trust endowment of \$36 billion and the support of investor Warren Buffett.

With names like Fox, Gates, and Buffett at the vanguard, other foundations have recruited Hollywood and media celebrities who bring money to bear on the search for

new cures. Yet while these foundations have new ideas and the funding to pursue them, they don't have an established research infrastructure.



Buckley



Ribeill

CRO executives say their companies are bridging that gap. One such firm is Albany Molecular Research Inc., which recently announced a five-year contract with NIH and the National Institute of Neurological Disorders & Stroke (NINDS) for chemistry and

other services to support neurotherapy drug development. Thomas E. D'Ambra, AMRI's chief executive officer, sees three trends creating the opportunity for CROs to work with nonprofits and the government.

"Nonprofits have taken a more venture-based approach to their funding," he says. "Where in the past they may have funded academic research looking into the basis of some of these diseases, they are now actually funding drug discovery and full development in some cases."

The Cystic Fibrosis Foundation and the CHDI Foundation, which focuses on therapies for Huntington's disease, are among the most active nonprofits, says D'Ambra, whose company has conducted research for both. Last year AMRI announced a five-year expansion of a contract

begun in 2009 with CHDI to provide chemistry- and biology-based drug discovery and compound library production services.

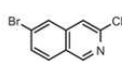
D'Ambra points to a similar evolution of NIH funding from basic science to applied research on product development. The neurotherapy research program, he says, has been launched on the base of longer-standing programs, including the agency's Molecular Libraries Program under which NIH set up screening facilities and acquired compound collections that it makes available to academic researchers.

For that project, NIH hired Compound Focus, a compound library management firm that was recently acquired by the German CRO Evotec. In addition to its NIH contract, Evotec is working with Harvard University and the Howard Hughes Medical Institute on a diabetes therapy, and also with the CHDI Foundation on a treatment for Huntington's disease.

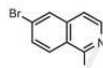
MORE RECENTLY, D'Ambra says, drug companies have turned to academic labs to support research, often as they are making big cutbacks in their own R&D capabilities. Companies such as Pfizer and Merck & Co. have announced programs to significantly increase discovery and development partnerships with academic centers, D'Ambra says. Much of the work will involve research in molecular biology and will likely generate more business for CROs.

Although D'Ambra emphasizes that doing research for NIH is nothing new at AMRI, the company he started in 1991, he says the latest contract reflects an increase in the government agency's commitment

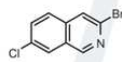
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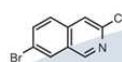
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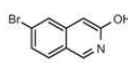
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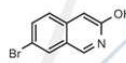
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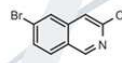
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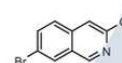
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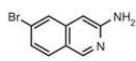
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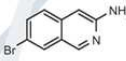
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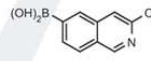
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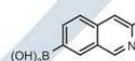
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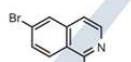
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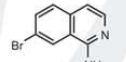
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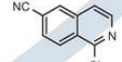
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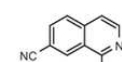
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Pure and (not so) simple

to pursuing breakthroughs in drug development. "Our original work with NINDS was specific to a therapeutic target," he says. "The new contract is broad, encompassing an entire therapeutic area."

George Buckley, business development manager for Domainex, a U.K.-based CRO, says nonprofit-funded research is picking up with his firm as well. "We've done a lot of work over the last five years or so on projects funded through the Wellcome Trust," he says. The British charitable foundation employs CROs to advance the development of drug targets discovered in academic labs.

"They like to have experienced drug hunters," Buckley says. While some universities have adequate medicinal chemistry resources to advance drug development, many need support from commercial labs such as CROs.

Domainex, which has operated as a CRO since the 2001 merger with NCE Discovery, a medicinal chemistry company, offers drug discovery services ranging from cloning of proteins and protein purification to medicinal chemistry. Many of its initial contracts were with academic labs funded by drug companies. This began to change with Wellcome's 2005 launch of the Seeding Drug Discovery initiative, a program aimed at funding research that drug companies were backing away from. It was started with \$142 million in funding and recently won a new commitment of \$171 million from Wellcome.

Domainex is currently working with the University of London and the University of Manchester on an asthma therapy, providing lead optimization services for a research program at St. George's Hospital. The project is funded by Wellcome. Now two years into the agreement, the partners have patented a drug candidate, Buckley says.

Cambridge Major Laboratories is also working on a project funded by Wellcome. The Wisconsin-based firm's facility in Weert, the Netherlands, is providing medicinal chemistry synthesis, solid-state studies, and manufacturing services to Summit, an Oxford, England, biotech firm working on an antibiotic for the hospital "superbug" *Clostridium difficile*.

Overall, customer inquiries involving nonprofit funding have increased significantly in recent months, says Roger

McDonald, Cambridge Major's European business development director, and are "at least a third higher this year." Some of the work is cofunded by nonprofits and big pharma, he says.

Cambridge Major has been retained by two large European research centers to provide initial assessments of the chemistry required to develop drugs in a range of therapeutic areas.

WORK ON RARE and neglected diseases has also generated contracts between nonprofits and CROs. The Drugs for Neglected Diseases Initiative (DNDi), created by the humanitarian group Doctors Without Borders, calls on CROs such as Scynexis, a Research Triangle Park, N.C.-based firm that has been working with DNDi on human

African trypanosomiasis, or sleeping sickness, since 2006.

"Organizations like DNDi are pure virtual organizations, subcontracting for early discoveries across the planet," says Scynexis CEO Yves Ribeill. "They are asking for the availability of compounds and screening the most likely potential drugs. They are working with universities, biotechs, and large pharmas." And, like any virtual drug company, DNDi is working with CROs.

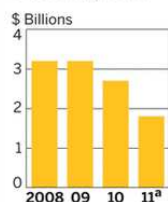
Ribeill sees DNDi's approach as a model that even the big drug companies will

adopt for discovery and early-stage development. "These groups are advanced compared to the big pharma companies," he says. "This idea that you can manage a project by finding the best target and taking the work to the most competent CRO in the West or the East is what we will soon see adopted at big pharma."

NovAlix, a drug discovery services firm launched 10 years ago in Strasbourg, France, recently landed a contract with the Jérôme Lejeune Foundation, a Paris-based organization named after a geneticist who specialized in Down syndrome. NovAlix' medicinal chemists and structural biologists will help develop small-molecule inhibitors of cystathionine- β -synthase for the treatment of trisomy 21, a genetic variant of Down syndrome.

Other than the Pasteur Institute, not many French foundations fund drug research, says NovAlix President Stephan

RECEDING CAPITAL Venture financing for U.S. therapeutics firms is trending down.



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Jenn. Still, a few small groups such as the Jérôme Lejeune Foundation, which supports research on genetically based mental impairments such as fragile X syndrome and cri du chat syndrome, are coming forward with work for contract research firms.

Unlike many of his counterparts, Jenn does not connect the rise in nonprofit funding of drug discovery to a drop in venture funding. Nor does he see research for nonprofits as a necessary haven for Western CROs as drug companies outsource more research to India and China. He says service contracts are starting to come back to the U.S. and Europe.

Instead, Jenn says the increase in work with nonprofits stems from the growth in innovation taking place at universities and start-up pharma companies. He also credits increased funding from foundations that have a commitment to cures, increasingly promising drug development programs, and money to invest.

And the new research opportunities are well received, according to Jenn. "It is a more peaceful relationship working with foundations," he says. "You have to deliver,

"Nonprofits have taken a more venture-based approach to their funding."

but when I talk to the scientists, they are happy. There are none of the pressures or the financial metrics that you have with drug companies. It is all about the science."

MANY FOUNDATIONS have come to the same conclusion. They are taking a more activist approach to early-stage drug development. They are providing funding for CROs to bring scientific expertise to bear on behalf of fund recipients that lack technical resources.

The Michael J. Fox Foundation spent its first five years as a traditional grant-making organization, soliciting bids from academic labs or biotech firms and awarding funding, says Mark Frasier, director of research programs. "In the last three to four years, we've recognized a unique opportunity for us to complement the investigator-initiated projects with more foundation-staff-directed projects," Frasier explains.

The foundation has become more directly involved in research, lining up CROs to provide drug development and pharmacogenetics services to academic and small commercial research organizations.

The Fox Foundation has a scientific research staff of seven Ph.D. medicinal scientists and one M.D., double what it had five years ago. But the foundation, based in New York City, has no research facilities of its own. The staffers work as project managers directly with CROs.

P. Jeffrey Conn, director of the Vanderbilt Center for Neuroscience Drug Discovery at Vanderbilt University Medical Center in Nashville, joined the Fox Foundation's advisory board eight years ago after leaving a research position at Merck. "They wanted to take a more deliberate approach," Conn says. "The conversation started back then, but it ramped up recently."

The foundation came to recognize the funding and resource gaps that needed to be filled at academic and start-up drug company labs, Conn says. "A lot of foundations and universities were very naïve as to what was required," he says. "When they understood what was required, they realized that they did not have the resources in-house. Their use of CROs is a good sign."

Conn himself is employing CROs at the Vanderbilt center, which is recognized as one of the most self-sufficient academic pharmaceutical R&D organizations in the world. Although it is fully equipped to do medicinal chemistry, it has been using outside firms for spot work in pharmacokinetics and compound screening, Conn says.

Like the Fox Foundation, the Wellcome Trust aims to fund lead optimization and other early-stage drug development efforts in commercial and academic settings, according to Ted Bianco, director of both technology transfer and the Seeding Drug Discovery initiative.

Wellcome is interested in cultivating CROs as expert resources for its clients, Bianco notes, but it does not yet deal directly with service firms on most projects. "Interestingly, they come in primarily as a service to the people who succeed in securing funds," Bianco says. "But I think there will be a trend toward CROs approaching us directly."

NIH, meanwhile, is outsourcing re-

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search to CROs. Rebecca Farkas, program director for NINDS's Office of Translational Research, says NIH and its constituent institutes are doing this partly to bridge funding gaps elsewhere in the research world. But more important, the institute is building on the scientific advances of the past decade, particularly in neuroscience.

"In the last 10 years there has been an increase in knowledge about mechanisms of disease that affect the nervous system, opening up targets for new drugs," she says. And NIH staffers understand that the academic and small business research communities lack adequate resources to pursue drug development. "Most universities do not have the medicinal chemistry facilities that allow doing chemical optimization with the power you would see at a large pharmaceutical company."

NINDS's Spinal Muscular Atrophy Project, Farkas explains, established a kind of virtual pharmaceutical model supported by a series of service contracts, including

the initial contract for medicinal chemistry with AMRI. "The program has been successful in getting to IND studies," she says, referring to the Food & Drug Admin-



Farkas



Fraser

istration's Investigational New Drug Application, "and we've decided to expand it to a general approach that will include any disease that affects the nervous system."

The agency's Blueprint for Neuroscience Research, encompassing 16 NIH institutes

and research centers, is using a similar virtual pharma approach. Several CROs have been awarded contracts to support research. In addition to AMRI, SRI International and Southern Research Institute have been hired to perform drug metabolism and pharmacokinetics screening and other services. "We have solicited applications from small business and academic researchers around the country," Farkas says. "Successful applicants will be plugged into the network."

The agency's support of early-stage drug development, Farkas says, may reflect a permanent realignment in the field of drug discovery and development as big pharma embraces a streamlined business model. Shifts in the industry, she says, will affect where NIH targets support along the drug discovery and development continuum.

"Our commitment to doing therapeutics development is here to stay," Farkas says. "Research aimed at improving public health is our mission." ■

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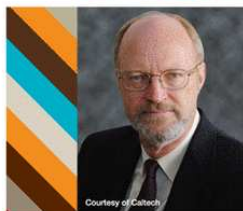
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