Making the case for precompetitive clinical development

By Chris Cain, Staff Writer

The **Structural Genomics Consortium** and **Sage Bionetworks** are spearheading an effort to build a precompetitive, pharma-backed public-private partnership to optimize the clinical validation of new therapeutic targets. By removing IP and data-access restrictions, the group hopes to create an environment that will eliminate redundant discovery programs and reduce the overall cost of R&D.

A newly established public-private partnership called the Archipelago to Proof of Clinical Mechanism (Arch2POCM) hopes to improve the efficiency and lower the costs of drug development by generating a portfolio of small molecules that hit new therapeutic targets and by carrying out early clinical work—up to Phase II clinical trials.

Both the discovery and the trials would happen in a precompetitive environment.

“In 1999, everyone accepted the human gene sequence as precompetitive. In 2003, protein structures were precompetitive. In 2009, small molecule probes became precompetitive. Now what we are proposing is that Phase II clinical proof of mechanism for novel targets be considered precompetitive,” said Chas Bountra, chief scientist of the Structural Genomics Consortium (SGC) and one of the leaders of Arch2POCM.

Founded in 2004 to decrease duplication in protein structure discovery, SGC operates out of the **University of Oxford**, **University of Toronto** and **Karolinska Institute** and includes academic and industry members.

SGC has teamed up with Sage Bionetworks to organize Arch2POCM. Sage is a nonprofit foundation that is developing a computational platform to share and analyze genomic information in an open-access environment to build network models of disease.

According to Stephen Friend, president, cofounder and director of Sage Bionetworks, the IP-free, open-sharing environment is a core tenet of Arch2POCM. “This is what separates it from all other partnerships,” he said. “We want proof of clinical mechanism; we are not trying to develop IP around a molecule.”

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All compounds generated through Arch2POCM thus would be IP free and would be available to any investigator outside the partnership. All data generated by Arch2POCM also would be published and shared online.

According to the organizers, the lack of IP should not be a roadblock to participation. The value to companies would come from reducing the cost of validation for promising therapeutic targets that could then form the basis for proprietary internal drug development.

The partnership plans to recruit public agencies and four to six pharmaceutical companies to provide the tens of millions of dollars necessary to fund development from discovery through Phase II.¹

To do so, the partners need to have a persuasive business plan, which they plan to begin sharing with potential participants later this year.

Making the case

Bountra, who was VP and head of biology at **GlaxoSmithKline plc** before joining the SGC, made the economic case for transforming drug discovery.

“Globally, the industry is spending \$160 billion a year on R&D and only getting 3–5 novel drugs targeting pioneer mechanisms per year. The R&D cost per new molecule isn’t going to go down, so we need to reduce duplication and become more efficient,” he told *SciBX*.

Kevan Shokat, chair of cellular and molecular pharmacology at the **University of California, San Francisco**, professor of chemistry at **University of California, Berkeley** and an investigator at the **Howard Hughes Medical Institute**, told *SciBX* the ability to choose the right mol-

ecule to move into the clinic—without having to worry about any IP constraints—could be a key to Arch2POCM’s success.

Although the small molecule space is “theoretically unbelievably large, clinically good small molecules with the right size and structure can keep bumping into other people’s patents,” he said.

Thus, Shokat said, “a company pursuing a small molecule series may find a good structure that is potent or has positive pharmacological properties, but then the company scientists have to back away for IP reasons.”

Polly Murphy, VP of business development and R&D at **Pfizer Inc.**, concurred. “The way IP free is useful from where I sit is that you don’t have to negotiate everything that happens. If you take out the need to over-negotiate, it enables a facile working environment.”

Bountra pointed to SGC as a model for precompetitive collaboration between academia and industry in the area of small molecules.

He noted that GSK, Pfizer, **Novartis AG** and **Eli Lilly and Co.** have contributed medicinal chemists—paid for by the companies—to develop chemical probes with the consortium.

Importantly, there is no IP. All compounds resulting from this SGC project are placed into the public domain. The benefit to the companies is leveraging public funding and academic resources to learn more about how to target new areas of science, such as epigenetics.

Building the roadmap

Bountra believes the natural next step is to extend precompetitive discovery to the clinic.

Thus, the primary goal of Arch2POCM is to validate the clinical potential of new targets by developing and testing small molecule probes.

This will entail developing at least three structurally distinct small molecules per target. At least two of those compounds would be expected to progress into Phase I and Phase II studies, said Friend.

Friend admits there is always ambiguity in clinical trial results, but argues that “if you throw two strikes down the center where you hit the target with full occupancy and inhibition and have no effect *in vivo*, I’d argue it’s foolish to do it a third time.”

By pooling resources to go after many high-risk targets, pharmaceutical companies could hedge their bets against failure.

Friend, who formerly was SVP and head of oncology at **Merck & Co. Inc.**, emphasized that companies would have access to data being generated by investigators and would have freedom to operate in generating their own compounds to use in any indications they wish to pursue.

Arch2POCM thus would primarily be a precompetitive launching pad to generate leads for pharma companies to pursue their own discovery and development.

To ensure that any clinically viable compounds could be developed despite a lack of IP protection, the partnership would retain possession of a compound’s IND package. This package would contain small bits of otherwise undisclosed information that would be necessary to get regulatory approval of the compound based on the data.

Arch2POCM would auction the package to the highest private-partner bidder, with the proceeds going back into a separate research fund.

“Since there’s no IP on the molecule, others could take the molecule as well, but they would have to redo all the preclinical, Phase I and Phase II work,” Bountra told *SciBX*. “We’ve spoken to people at Pfizer and GSK about whether they’d take such a molecule, and they’ve said yes.”

Seeking ROI

The key task for Arch2POCM is to demonstrate that the partnership will provide a return on investment (ROI) for the tens of millions of dollars it is seeking from industry annually. Sage Bionetwork’s best estimates are that going from discovery to proof of clinical mechanism will take seven to eight years—a long time before the concept could prove its worth.

Although Arch2POCM has not yet started signing up pharma partners, members of industry who spoke to *SciBX* see potential for a return.

“The ROI may be less obvious by traditional measurements, but I am convinced it will be there,” said Paul Chapman, general manager of the Pharmaceutical Research Division at **Takeda Pharmaceutical Co. Ltd.** “Industry may be overvaluing some of its IP that is really more obstructive than productive.”

Joseph Bolen, CSO of Takeda’s **Millennium Pharmaceuticals Inc.** subsidiary, also did not see an IP issue.

“The IP-free nature of the plan is not a showstopper from my perspective,” he said. “Open data access will allow for any of the participants to independently decide to launch their own drug discovery projects for the target, thereby generating new chemical matter that would be proprietary.”

“Each company has to ask how much they spend in this discovery space,” said Pfizer’s Murphy. “If five companies diverted money to this consortium, you would be spending 20 cents on the dollar, and if you could efficiently leverage that money, it would be a really well-spent dollar.”

Core decisions remain to be made on the content of Arch2POCM, but neurology and oncology are emerging as broad disease areas of interest. In particular, Friend noted cancer metabolism as an oncology area with potential, while Bountra noted schizophrenia and autism as neurology areas.

A third disease area is still under consideration, with the possibility that a disease foundation will step in to sponsor research in a specific indication.

Although there was consensus that every funder would have a say in what targets would be nominated to pursue, a remaining logistical question is how funding proposals will be solicited and evaluated.

Indeed, when asked about the major challenges facing Arch2POCM, members of academia and industry pointed to the difficulties of finding compounds able to demonstrate clinical mechanism for a target—a task that requires finding the right people to synthesize and test the compounds.

“The most difficult thing is going to be creating the molecules that will allow proof of clinical mechanism,” said Takeda’s Chapman. “A combination of repurposed molecules and a few new key molecules may, however, get the momentum going that will engage broader participation in the early discovery component of this effort.”

Shokat said it can be difficult to separate proof of clinical mechanism from the effects of a specific compound. He cited Pfizer’s torcetrapib cholesteryl ester transfer protein (CETP) inhibitor as an example in which a compound’s failure could inaccurately lead to suspicions about the clinical viability of its target. Merck recently demonstrated positive early stage data from its anacetrapib CETP inhibitor, suggesting Pfizer’s data may have been compound specific.²

An early proof of concept will be essential for a potential long-term project such as Arch2POCM.

“The biggest challenge for this enterprise is to demonstrate that the model will yield a level of innovation that can not be easily duplicated by other approaches,” said Bolen. “This means that focusing on fewer therapeutic areas with some near-term, clear, notable achievement would be highly persuasive,” he said.

The next milestone for Arch2POCM is in September, when Friend expects to have ready a draft business plan to share with potential industry and public funders. He said he is working to identify four to six companies that are “ready to roll up their sleeves” and engage in a series of meetings to help contribute to the design of the plan over the next few months, with the goal of starting the first projects in 2012.

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2. Flanagan, M. *BioCentury* 17(51), A12–A14; Nov. 22, 2010

COMPANIES AND INSTITUTIONS MENTIONED

Eli Lilly and Co. (NYSE:LLY), Indianapolis, Ind.
GlaxoSmithKline plc (LSE:GSK; NYSE:GSK), London, U.K.
Howard Hughes Medical Institute, Chevy Chase, Md.
Karolinska Institute, Stockholm, Sweden
Merck & Co. Inc. (NYSE:MRK), Whitehouse Station, N.J.
Millennium Pharmaceuticals Inc. (NASDAQ:MLNM), Cambridge, Mass.
Novartis AG (NYSE:NVS; SIX:NOVN), Basel, Switzerland
Pfizer Inc. (NYSE:PFE), New York, N.Y.
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