THERAPEUTICS DEVELOPMENT

Leveraging Crowdsourcing to Facilitate the Discovery of New Medicines

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Gloomy predictions about the future of pharma have forced the industry to investigate alternative models of drug discovery. Public-private partnerships (PPPs) have the potential to revitalize the discovery and development of first-in-class therapeutics. The new PPP Arch2POCM hopes to foster biomedical innovation through precompetitive validation of pioneer therapeutic targets for human diseases. In this meeting report, we capture insights garnered from the April 2011 Arch2POCM conference.

INTRODUCTION

> *When useful knowledge exists in companies of all sizes and also in universities, non-profits and individual minds, it makes sense to orient your innovation efforts to accessing, building upon and integrating that external knowledge into useful products and services.*
>
> —Henry Chesbrough, author of *Open Innovation: The New Imperative for Creating and Profiting from Technology*

Science selects for the opinionated and the critical. But when it comes to drug development, almost everyone agrees that it takes too long, costs too much, and is too unpredictable. In 2010, the pharmaceutical and biotechnology industries spent more than $100 billion and generated only 21 U.S. Food and Drug Administration–approved new chemical entities (NCEs). Driven by patent cliffs (*1*, *2*) and dismal forecasts of future growth (*3*), the global pharmaceutical industry has begun to invest in alternative models of drug discovery, such as public-private partnerships (PPPs), to reinvigorate the development of new molecular entities (NMEs) for unmet medical needs. PPP objectives tend to focus on the creation of new tools and methods to support faster and more cost-effective drug development, rather than pharmaceutical drug discovery and development itself (*4*), in large part because of challenges in managing future intellectual property (IP) rights (*5*, *6*). One nascent PPP, Arch2POCM (*7*), was formed with the following question in mind: What would happen to pharmaceutical productivity and biomedical research innovation if an open access (or precompetitive) (*7*, *8*) PPP was created to discover and clinically validate pioneer targets for human diseases? Here, we outline insights from the recent Arch2POCM conference held in April 2011.

Fig. 1. Leveraging the collective brain trust. [CREDIT: iStockPhoto.com]

GLOBAL NETWORKING

The name Arch2POCM was derived from the terms archipelago (Arch)—a distributed network of entities (here, diverse biomedical professionals)—and proof of clinical mechanism (POCM)—the goal of the group's pursuit. To achieve POCM, the PPP scientists will demonstrate in a Phase II setting that the mechanism of the selected disease target can be safely and usefully modulated. Members of the archipelago—pharmaceutical organizations; E.U., U.S., and Canadian regulatory and funding agencies; academic institutions; patient advocacy groups; and contract research organizations—gathered to discuss the value proposition and structure needed to launch a precompetitive (*8*) drug-development PPP (*9*). As a means to facilitate more complete and rapid knowledge sharing, these potential stakeholders pondered ways in which they might participate in new drug discovery and development approaches that focus on high-risk, high-opportunity disease targets without pursuing patents. Data generated by Arch2POCM scientists and clinicians would be made publicly available, all without patent claims. The rapid publication of data showing that proper inhibition of a disease target does not modulate the corresponding disease is valuable for patients, academics, and others conducting drug discovery: These so-called negative POCM results would maximize patient safety by reducing the number of clinical

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studies designed to test such therapeutic targets. Neurologist Edvokia Anagnostou of the Bloorview Research Institute, an expert on the neuro-psychopharmacology of autism, commented, "The field of autism is ripe for any initiative that places an emphasis on knowledge generation and de-emphasizes the focus on capturing IP. We understand so little about autism, but potential new molecular targets are now being identified, the community is engaged, and several networks of basic [and] clinical researchers are now well positioned to participate in an effort such as Arch2POCM."

The open access model could also provide significant economic return to industry. With an open access format, POCM is no longer a redundant proprietary effort conducted by numerous companies on the same therapeutic target, but instead is pursued in the public domain; in such a setting, cost-avoidance models for negative POCM studies highlight savings to the global pharmaceutical industry of up to $12.5 billion annually (*10*). Positive POCM studies demonstrating that an Arch2POCM test compound can safely and usefully modulate the selected disease target would also benefit Arch2POCM partner companies: Both the Arch2POCM investigational new drug (IND) filings and the Arch2POCM test compounds are valuable assets, because clinically validated pioneer targets are associated with a higher likelihood of success than are non-validated ones. The commercial development of the validated Arch2POCM test compound has the potential for a strong positive return on investment. Arch2POCM pharmaceutical partners would be offered the opportunity to purchase the Arch2POCM test compound and corresponding proprietary IND database, which is required to enable subsequent clinical development. Although the Arch2POCM test compound would not have patent protection to generate market exclusivity, data exclusivity periods that currently apply to all small-molecule development candidates (United States, 5 years; Japan, 6 years; European Union, 8 years) would provide sufficient return on investment in most therapeutic areas. A second benefit of positive POCM studies is that all pharmaceutical companies would have the opportunity to develop their own proprietary molecules to create new and effective first-in-class therapeutics.

BIOMEDICINE MEDLEY

In the course of a spirited debate about the Arch2POCM value proposition for participants and benefits for patients, industry, and academics, the group arrived at an important insight best framed by Abraxis Senior Vice President Dr. Lex VanDerPloeg: The most significant benefit of a precompetitive drug development model may be "its ability to catalyze a simultaneous massively parallel crowdsourced search for POCM without PPP funding."

"Crowdsourcing" is a term more often associated with the open source software industry than with pharmaceutical drug development: It is the act of outsourcing tasks traditionally performed by an employee to an undefined, large group of people or community (a "crowd"). The term has become popular as shorthand for the leveraging of mass collaboration to achieve business goals and to lower barriers to innovation (*5*). The precompetitive Arch2POCM approach differs fundamentally from the current model of drug discovery and development; compounds intended to test the clinical attributes of a pioneer therapeutic target would be generated with no IP filed and with no target indication, efficacy, or safety requirements to uphold. By making these clinically characterized probes available to all researchers and without restriction on use, Arch2POCM will seed independently funded, crowdsourced experimental medicine studies in academic labs and pharmaceutical companies. These studies would provide clinical information about the pioneer targets in many indications. In this way, Arch2POCM's workflow would enable a "cultivated crowd" (scientists) to identify novel applications for test molecules that impact clinical outcomes.

If crowdsourced drug discovery and clinical POCM were operational, might some of today's drug development issues have been significantly ameliorated? Gleevec (imatinib), a highly successful drug that is currently approved for nine indications, represents a prime example of a drug whose wider uses emerged only after appearing on the market for the treatment of chronic myelogenous leukemia. It is now understood that Gleevec acts on not one but three different tyrosine kinases. Had Gleevec or a related molecule been an Arch2POCM test compound freely available to all for precompetitive research, its multiple activities would likely have been recognized sooner, providing pharmaceutical companies with an opportunity to accelerate and optimize further development. The Gleevec example showcases how Arch2POCM's precompetitive model could catalyze experimental medicine by efficiently defining the safety and efficacy parameters of a given NCE and, in so doing, accelerate drug development.

Given the highly proprietary, risk-averse culture of drug development, it is ironic to consider that the pharmaceutical industry may benefit most from a paradigm shift to a model such as that of Arch2POCM in which discovery and early clinical information are openly shared. To get started, however, some key questions must be addressed: Will Arch2POCM's structure and objectives provide sufficient incentives to all of the anchor groups to garner an initial commitment? Will potential pharma partners invest in an Arch2POCM model with unrestricted information sharing? How much small-molecule optimization is necessary to provide a clear Phase II POCM readout? Will placing the data in the public domain stimulate the global research community in ways that promote drug discovery as well as expand and accelerate development?

Dr. Paul Chapman, Head of Takeda's Pharmaceutical Research Division, remarked that the meeting "ended with great enthusiasm and a sense that there is a way forward. In particular, I was very excited about the opportunities generated by crowdsourcing clinical trials. In neuroscience, for example, we are often faced with very difficult decisions about which, of several unmet medical needs, to address first with a good compound for a novel target. Precompetitive crowdsourcing would mean that we could get multiple shots on multiple goals. This way, when we invest limited resources in a competitive compound, we can understand how to align our compound with the most promising unmet medical need."

In July, the Arch2POCM group will convene industry and academic leaders to craft disease-specific proposals around oncology and central nervous system (CNS) targets: Both are therapeutic areas with high unmet medical need, a perceived abundance of targets to de-risk, a multitude of potential indications that could be investigated by the "crowd," and the feasibility to achieve POCM in Phase II. Within the CNS arena, Arch2POCM will focus on autism and schizophrenia: Both are high-risk, high-opportunity diseases that are in the public spotlight and are well suited to Arch2POCM's crowdsourced approach, which will advance broad scientific understanding and clinical benefit more significantly than what could be achieved within a single company. With disease area objectives and planning defined, Arch2POCM leaders in concert with the therapeutic area strategic design teams will define the critical details of leadership, organizational, and decision-making

structures. If a working consortium of industry and academic scientists, policy makers, and funding agencies can be engaged, Arch2POCM will launch operation early in 2012. Recognizing that "… the world is becoming too fast, too complex, and too networked for any company to have all the answers inside" (*9*), Arch2POCM's open access PPP for drug discovery and POCM could establish a modern sustainable model for linking fundamental discovery to development and application, validating pioneer therapeutic targets, and creating innovative state-of-the-art medicines.

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11. **Competing interests:** T.C.N. is an employee of Ambrx Inc., La Jolla, CA.

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