

THERAPEUTICS DISCOVERY

The Precompetitive Space: Time to Move the Yardsticks

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Industry, government, patient advocacy groups, public funders, and academic thought leaders met in Toronto, Canada, to set into motion an initiative that addresses some of the scientific and organizational challenges of modern therapeutics discovery. What emerged from the meeting was a public-private partnership that seeks to establish proof of clinical mechanism (POCM) for selected “pioneer” disease targets using lead compounds—all accomplished in the precompetitive space. The group will reconvene in April 2011 to create a business plan that specifies the generation of two positive POCM results per year.

2011 may become known as the year in which “out-of-the-box thinking” transformed into “out-of-the-box doing” in the realm of therapeutics discovery—that is, if the bold conclusions that emerged from the February 2011 Summit in Toronto, Canada, are enacted (1) (Fig. 1). At this meeting, 43 key thought leaders from industry, government, patient advocacy groups, public funding agencies, and academia addressed the following dilemmas: From where will tomorrow’s breakthrough therapeutics come?

How much will these drugs cost, and how will prices be managed? With the pharmaceutical industry projected to lose control of more than 10 megamedicines this year, representing annual sales of >\$50 billion, the incentives to solve problems facing the industry have never been higher.

Attendees at the Toronto Summit gathered to consider whether the core of the research and development engine could be kickstarted by the creation of a public-private partnership (PPP) that focuses on high-risk, high-opportunity disease targets and operates in an open-access format to identify molecules that explore proof of clinical mechanism (POCM) for the selected target and disease. The PPP would consist of a distributed network, or

archipelago, of experts funded by industry, public funding agencies, and private foundations and would engage patients, clinicians, and scientists from academia, industry, and regulatory agencies as active co-participants. The name ARCH2POCM has been coined for the PPP. “ARCH” refers to the archipelago but also references the PPP’s four key constituent groups: academicians, regulators, citizens, and the health industry.

The summit opened with a sobering discussion of what might be done to alter the



Fig. 1. A chess piece moved forward. Toronto may be remembered as the site where “daring ideas” about therapeutics discovery were set into motion to “start a winning game” (3).

ever-increasing costs and time span of drug development, particularly in light of the 90% attrition rate that the so-called pioneer targets (2) experience during phase II trials (the first point at which POCM is evaluated in humans). All attendees agreed that attempts to model human biology and pharmacology in a preclinical setting will always have

their limits; but with a precompetitive drug discovery effort in place, it should be possible to rapidly disseminate negative POCM information in order to protect patient safety and minimize the costly redundancy of having multiple pharmaceutical companies pursuing the same disease targets in isolation of one another.

From this mutual starting point, Summit participants agreed that bold ideas, not pilot programs, are needed to meet the challenges that today’s pharmaceutical industry faces. And everyone concurred that ARCH2POCM must be structured such that all resulting data are made publicly available with no intellectual property (IP) generated through the POCM stage; such an open-access model would unleash truly translational, mechanism-based research and would foster rapid clinical validation of pioneer targets in a manner that (i) maximizes patient safety and (ii) rapidly informs the drug-development industry about those targets for which POCM has been successfully demonstrated.

In this setting, the results of both negative and positive POCM studies have value. Negative POCM information can reduce the redundancy of drug-development costs and time spent by multiple investigators on drug

targets destined to fail; positive POCM data can be leveraged by the pharmaceutical industry for the development of effective first-in-class therapeutics. The combined contributions from multiple funding sources should enable the discovery of a larger cache of unvalidated targets than could be prosecuted by any single company or institution. This open-access, integrated effort to validate disease mechanisms and therapeutic targets has the potential to increase return on investment for ARCH2POCM and the industry as a whole because it will allow pharmaceutical companies to focus their efforts on developing proprietary new medical entities to clinically validated targets.

Having aligned around the urgency to turn discussions into action, summit participants considered ARCH2POCM from the perspectives of its constituent groups. In order to encourage investment in an open-access clinical-validation model of drug development, the group needed to identify the

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expectations of, risks to, and opportunities for each stakeholder. Some of the findings were not surprising. Pharmaceutical industry colleagues emphasized the importance of their participating in target selection, of minimizing costs, and of having unfettered access to the results of ARCH2POCM trials. Representatives of public funding agencies, such as the Canadian Institutes of Health Research, were drawn to the ARCH2POCM model because it enables experimental medicine studies and has the potential to alter the current ecosystem of clinical trial duplication, thereby protecting the public from being treated with clinical candidate molecules for targets that are destined to fail. Academicians found the ARCH2POCM model attractive because of the potential to build bridges between academic scientists and valuable industry resources, and said that they would be willing to forgo any IP in exchange for the opportunity to further their science and to test their ideas in the interest of patients. However, these academic scientists also acknowledged the challenge of incentivizing the best universities to participate in the ARCH2POCM model without the enticement of a built-in revenue opportunity from licensing the IP of its scientists. For some, the reward of participating in a novel and speedy approach to moving innovative targets toward providing benefits directly to patients was seen as reason enough to become engaged in the initiative.

Surprising to all, however, were the opportunities for regulatory scientists to collaborate with ARCH2POCM. Scientists from the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA) who attended the Summit described changing regulatory environments and their desire to participate in and facilitate such precompetitive endeavors aimed at bringing new medicines to patients. As an example, the FDA is transforming large amounts of legacy clinical trial data into electronic form for sharing with industry, the public, and consortiums such as ARCH2POCM; furthermore, partnerships are already underway to conduct in-depth and wide-ranging analyses of clinical trial data in order to gain insights that will help to improve research designs and methods of analysis. With regulatory scientists and policy-makers serving as key participants in ARCH2POCM, a nascent dialogue has begun about the potential regulatory and legal collaborations that might motivate the pharmaceutical industry to commit to the ARCH2POCM model.

The summit ended with fertile beginnings in mind. First, the group committed to the selection of three therapeutic areas on which to focus. Second, a team is in the process of building a business plan grounded on disease-specific cost models and ARCH2POCM's strategic objective to achieve a steady-state capability to generate two positive POCM trial results

per year. Industry-endorsed strategies for commercializing the rare ARCH2POCM-derived molecules that appear to be effective have been developed. ARCH2POCM founders and key advisors will assemble again in April 2011 at the inaugural meeting of ARCH2POCM on the campus of the University of California, San Francisco. There, founders and key advisors will team up with scientists (including clinicians) who are potentially interested in joining ARCH2POCM as subject-matter experts and “doers.” With resolve that the time for a revolution has come, the April meeting will take the next steps toward turning thought into action.

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3. From Johann Wolfgang von Goethe, “Daring ideas are like chessmen moved forward; they may be beaten, but they may start a winning game.”
4. **Competing interests:** T.N. is an employee of Ambrx, Inc., La Jolla, CA.

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