POLICY

Opening Up to Precompetitive Collaboration

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In order to enhance biomedical research and development efficiency and innovation, nontraditional research collaborations have emerged that feature the sharing of information, resources, and capabilities. Although many of these so-called precompetitive collaborations are in the field of oncology, the lessons they offer are broadly applicable to other subfields of translational medicine.

Spending on biomedical research in the public and private sectors in the United States has topped $100 billion per year (*1*); yet despite this heavy investment and great strides in scientific understanding, the impact of these resources on human health lags far behind. Pharmaceutical research and development (R&D) productivity (as reflected by the number of new drug approvals per year) remains stagnant or worse (*2*), underscoring the limitations of the traditional target-driven approach to drug development, which is essentially an exercise in trial and error. It is now estimated to cost $1.8 billion or more to develop a new drug, with much of the investment consumed by the failure of putative therapeutics at late stages of development (*3*). In addition, there is considerable duplication of efforts in research devoted to providing the basic biological insights that are needed for successful drug design. As a result, prodigious biomedical research spending to date has failed to produce a fundamental understanding of disease that could enable a more judicious approach to therapeutic development. The biomedical enterprise is broken. This crisis must be solved by radical change.

In order to increase biomedical R&D efficiency and innovation, new models for research collaboration have emerged in recent years that feature the sharing of information, resources, and capabilities across traditional organizational boundaries (*4*–*7*). Many of these new precompetitive approaches—concerted efforts among competitors during the earlier stages of product development—have been pioneered in oncology (for example, the I-SPY-2 trial) (*8*); however, their lessons have broad applicability to other areas of biomedicine and offer a viable alternative to the traditional, proprietary model of R&D.

To examine the role of precompetitive collaboration in biomedical and oncology research, the National Cancer Policy Forum of the Institute of Medicine (IOM) sponsored a workshop in February 2010 titled "Extending the Spectrum of Precompetitive Collaboration in Oncology Research." The IOM commissioned the biomedical research strategy consulting firm AltshulerGray to analyze the range of precompetitive collaboration models and their applications. More than 50 biomedical research partnerships and consortia were examined for specific goals, participants, and organizational structure in order to identify and define the landscape of precompetitive collaboration. The findings from that investigation and the resulting framework, informed further by the workshop discussion, are presented here.

GOALS OF PRECOMPETITIVE COLLABORATION

At a high level, the precompetitive collaborations examined in the workshop share the same motivation: They were designed to focus on a shared challenge that could not be readily met by a single individual or organization. Rising to the challenge was essential for enhancing scientific knowledge and productivity. In analyzing these precompetitive efforts, four broad goals were identified that encompass all steps along the R&D value chain.

Developing standards and infrastructure. The primary purpose of these initiatives is to develop mutual standards to facilitate data sharing or to create shared infrastructure and research tools to improve process efficiency. Efforts within the biomedical community are leading to the creation of standards for data annotation, analysis platforms, and contract language.

Data generation and aggregation. New technologies are enabling high-throughput data generation at an unprecedented rate. No one organization has the scale to create and maintain this deluge of data on its own. Through collaboration, organizations can pool the financial and human resources necessary to undertake these large-scale projects. This category is exemplified by the Human Genome Project as well as by emerging platforms such as Sage Bionetworks (*9*).

Knowledge creation. These precompetitive collaborations leverage existing standards and infrastructure and build upon aggregated data sets to generate new scientific knowledge. Research areas of particular interest in the creation of shared knowledge are biomarker discovery and disease-model development. Because these types of knowledge are costly to generate, essential for progress, and not immediately monetizable, collaborators are increasingly willing to create these resources in a precompetitive space.

Product development. Although there are fewer examples of collaboration at the product-development end of the R&D value chain, the number is growing owing to a sense of frustration with the pace of the traditional, closed model of drug development. Increasing numbers of patient advocacy groups are seeking to expedite disease cures by offering research funding in exchange for open data sharing among participants. In addition, industry collaborators have begun to explore opportunities for partnering on late-stage drug development.

COLLABORATION PARTICIPANTS AND STRUCTURE

Players in the precompetitive space include academic and industry scientists, government entities, foundations, and patient advocacy groups, or the public at large. Collaborators can participate both in the execution of a project and as beneficiaries of its outputs. For the examples surveyed, par-

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ticipation in both of these dimensions was either completely open to all collaborators or limited to a predetermined set of collaborators, as illustrated in Fig. 1.

Who is allowed to directly contribute? A collaboration is more likely to be open if there are low barriers to entry, if the problem benefits from the broadest set of perspectives, or if the desire for maximizing input outweighs the need for careful quality control. On the other hand, a collaboration is more likely to be limited if there are substantial barriers to entry (for example, costly equipment or an advanced level of expertise needed) or a high degree of coordination and quality control are required.

Who is allowed to directly access the outputs? Collaborators were found to be more willing to share their data the further the output is from commercialization, if public access to the information enables continuous development (for example, software), or if openness propels the efforts of a broad community of researchers (for example, genomic information). On the other hand, outputs are more likely to be limited if they are closer to commercialization, if proprietary intellectual property is involved, or if collaborators wish to protect their investments against free riders—those who use more than their fair share of a resource.

EIGHT MODELS OF PRECOMPETITIVE COLLABORATION

Using the goals and participation structures defined above, a map was created to determine where along these axes the surveyed collaborations fell. Eight distinct models of precompetitive collaboration in biomedicine were identified (Fig. 2).

(i) Open-source initiatives. These partnerships are aimed at building collaborative platforms, infrastructure, and standards to create fully open networks for innovation. To date, this model has been primarily used in software development, the classic example being Linux. Within biomedicine, initiatives such as BioPerl, BioJava, and BioPython have engaged volunteer communities to create open-source software tools for biological computation (*10*, *11*). More recently, open-source collaborations have emerged further down the biomedical R&D value chain. Sage Bionetworks is developing an open platform for investigating disease models, whereas Pink Army Cooperative is testing a community-based approach to developing individualized therapies for breast cancer, opening its entire R&D process to all contributors.

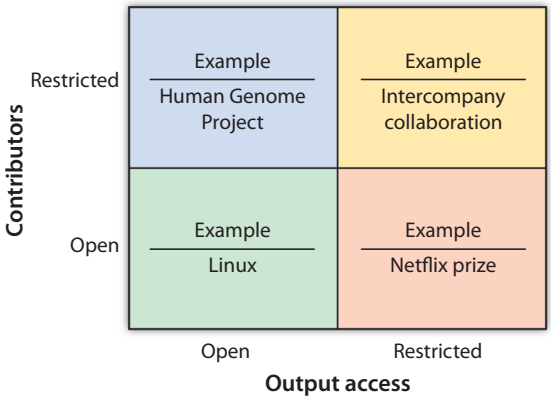

Fig. 1. Precompetitive participants. Collaborations and consortia can be open or restricted both in terms of those who directly contribute (for example, scientifically) (Contributors) versus those who will directly access the outputs (Output access), suggesting four potential combinations: restricted/open (blue); restricted/restricted (tan); open/open (green); and open/restricted (salmon).

(ii) Industry consortia for R&D process innovation. These alliances within industry are aimed at improving noncompetitive aspects of the R&D process that have hitherto been developed redundantly and in parallel. Outside biomedicine, a prominent example is Sematech, a consortium of semiconductor manufacturers that banded together to develop shared technologies to create greater efficiency in the manufacturing process. Within biomedicine, the CEO Roundtable on Cancer's Life Sciences Consortium's first project, START, has created a standardized set of clinical trials contracts in order to streamline the negotiation process. In addition, the Pistoia Alliance, a consortium of major pharmaceutical companies and other partners, is developing common data standards and ontologies for the drug-discovery workflow.

(iii) Discovery-enabling consortia. These consortia of academic and/or industry participants provide critical mass to generate the scale of data needed for innovation—a scale not easily achieved by any one participant alone. Although not immediately monetizable, these data warehouses are critical to future scientific discovery. Contribution is generally limited because of the cost of participation (for example, expensive equipment) and the need for coordination and quality control. Access to outputs may be open or limited, largely depending on the nature of the aggregated data and the motivations of the collaboration (for example, a desire to keep the data in the public domain). The Human Genome Project exemplifies this model.

(iv) Public-private consortia for knowledge creation. These are collaborations between industry and academia designed to create upstream knowledge that has no immediate market potential but is critical to enabling future downstream innovation. These efforts are farther along the research value chain than discovery-enabling consortia because they seek to leverage the data warehouses created in that model and exploit them to create new preproduct innovation. Current efforts to jointly develop and qualify biomarkers (such as the Biomarkers Consortium) and to identify DNA variants to predict drug-related serious adverse events (such as the Serious Adverse Event Consortium) reside in this category.

(v) Prizes. Prizes can be sponsored by companies that wish to solve internal R&D problems or by foundations that seek to further a mission. By offering cash prizes, these challenges receive a broad and diverse pool of innovative solutions from the public. Although employed in other knowledge sectors for some time (*12*), the use of prizes as a viable innovation platform within biomedicine is a recent phenomenon (*13*, *14*). InnoCentive, a Web-based company that evolved from an internal Eli Lilly effort, offers a prize-matchmaking service, posting industry challenges online and soliciting solutions from the public. The X PRIZE Foundation has established the Archon X PRIZE for Genomics to be awarded to the first team to develop technology that can sequence 100 human genomes in 10 days or fewer for $10,000 or less per genome.

(vi) Innovation incubators/insourcing. Insourcing links industry sponsors with academic or startup entrepreneurs to bring sponsored research in-house for a more extended and collaborative relationship. The result is a win-win for both partners. Companies can fill their pipelines with creative capital they might not otherwise be able to access, while entrepreneurial partners benefit from the resources and organizational expertise of the host company. Both parties benefit by sharing risks and rewards. Biogen Idec's Innovation Incubator (bi^3) is one such example, established to fill a gap between the

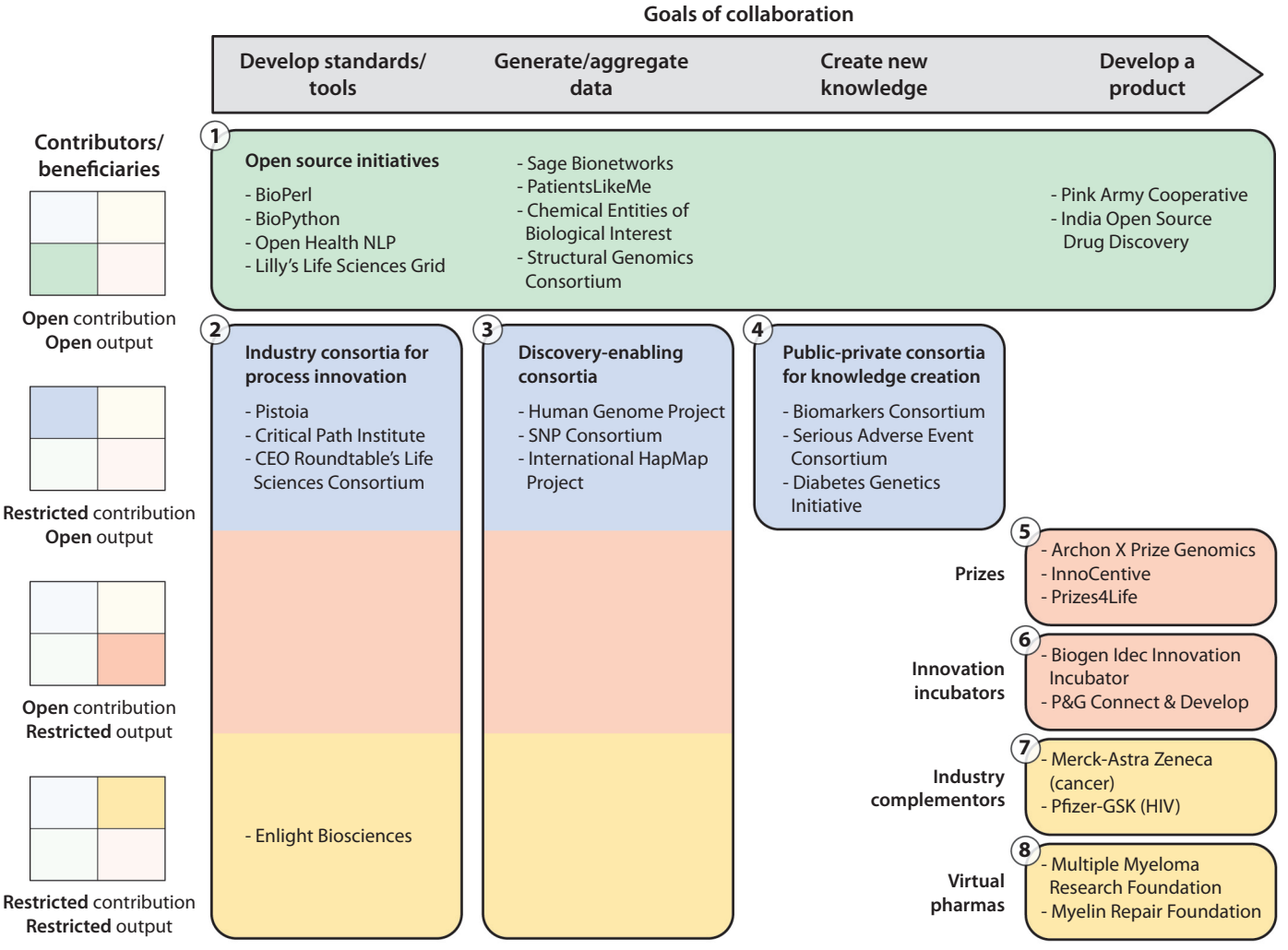

Fig. 2. Mapping precompetitive collaborations. In mapping goals versus participants, eight models of precompetitive collaboration emerged (please see text for details). The four broad goals listed across the top of the figure encompass all steps along the R&D value chain. The color-coding of the types of collaborations (open or restricted contributors and output access) defined in Fig. 1 is used here at the left. Open Health NLP, Open Health Natural Language Processing; GSK, GlaxoSmithKline; P&G, Procter and Gamble.

company's early-stage sponsored research and the late-stage investments of its venture capital arm. To date, the initiative has incubated three companies, each with the goal of producing viable drug candidates within 2 to 3 years (*15*).

(vii) Industry complementor relationships. These are relationships between businesses for which the market value of what they can provide together is greater than the sum of what they could provide separately. Pharmaceutical companies may find that by combining certain assets they can unlock value in dormant intellectual property or increase the value of their active drug portfolios. The clinical trials partnership between Merck and AstraZeneca exemplifies the value that these kinds of liaisons can create. This partnership was designed to perform joint clinical trials in cancer patients to test Merck's and AstraZeneca's inhibitors of the mitogen-activated protein kinase/extracellular signal–regulated kinase (MEK) and the Akt serine/threonine protein kinase, respectively (*16*). By jointly testing drugs that target complementary growth factor signaling pathways, the two companies hope to demonstrate that this novel combination can produce a greater response than either drug alone. As this example illustrates, both inputs and outputs tend to be limited to small groups of participants because the research is close to market and involves protected intellectual property.

(viii) Virtual pharma companies. Frustrated by the slow pace of the current pharmaceutical model, a vanguard of foundations and patient advocacy organizations is establishing virtual entities intended to stitch together the necessary capabilities to expedite the path from discovery to cure (*17*), with a particular focus on neglected and rare diseases (*18*–*21*). Examples of this growing community can be found in the work of the Multiple Myeloma Foundation, the Michael J. Fox Foundation for Parkinson's Research, the Myelin Repair Foundation, and the Cystic Fibrosis Foundation. Rather than sponsor various independent researchers on an ad hoc basis, these foundations are playing active roles in defining

the research agenda, coordinating research efforts, and aggregating outputs to truly leverage their investments. Insofar as they seek to radically streamline pharmaceutical R&D in order to develop lower-cost therapies for underserved markets, these new entities may represent a potentially disruptive innovation to traditional pharmaceutical industry competitors (*22*).

CHALLENGES AND OPPORTUNITY

Each of the eight models has its unique challenges. It remains to be seen whether a fully open-source approach (model 1) can be translated beyond software to biomedical R&D, given the higher barriers to participation and intellectual property concerns. Individual companies seeking to insource innovation (models 5 and 6) must be prepared for the challenge of integrating outside ideas into their own innovation engines. Virtual pharmaceutical companies (model 8) have yet to prove they can drive the full R&D process from discovery to the clinic.

The ability of these models to substantially enhance industry-wide productivity will depend on the willingness of direct competitors to join forces by sharing proprietary information, R&D capabilities, and other resources (*23*)—whether for process improvement (model 2), data generation (model 3), knowledge creation (model 4), or complementary drug development (model 7). These models will require a clear alignment of participants' goals and active project management (*24, 25*). An even greater challenge will be fostering the necessary level of trust between participating competitors; in some cases, these efforts may be facilitated by third parties serving as matchmakers or independent arbiters of proprietary information. For more of these kinds of activities to flourish, structural barriers will need to be tackled, including unrealistic, outmoded, and conflicting expectations of intellectual property and incentive structures that inhibit collaboration.

Despite these challenges, the opportunity is great. The examples cited above affirm that by being open to novel alliances, competitors and other stakeholders can successfully work together on efforts that can substantially boost efficiency and spur innovation. The crisis in the biomedical enterprise should not force a retrenchment in R&D; rather, precompetitive collaboration should be actively deployed as a tool for creating and unlocking value, in both economic and human terms, and as a critical driver for reinvigorating the biomedical enterprise.

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