The NIH-Industry New Therapeutic Uses Pilot Program: Demonstrating the Power of Crowdsourcing

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It has been 2 years since the National Center for Advancing Translational Sciences (NCATS) announced its intent to test a new strategy for establishing collaborations between pharmaceutical companies and academic partners to repurpose company agents (new molecular entities and biologics) that were phase 2a-ready, but had not been approved by the Food and Drug Administration (FDA) for licensure. The new strategy would use template agreements to allow an academic institution and pharmaceutical company to quickly reach an agreement about the terms of the collaboration. In May 2012, NCATS posted template collaborative research agreements and template confidential disclosure agreements for use by collaborating academic institutions and the pilot program's first three pharmaceutical company partners, AstraZeneca, Eli Lilly and Company, and Pfizer. At the same time, NCATS published a request for information to get feedback on the template agreements. The initial response from academic institutions on the template agreements was not one of overwhelming enthusiasm. Although collaborations between academic institutions and pharmaceutical companies have been going on for years, the willingness of academic institutions to use template agreements that the NIH had drafted with pharmaceutical companies remained to be seen.

A little more than a month later, five more companies—AbbVie (formerly Abbott); Bristol-Myers Squibb Company; GlaxoSmithKline; Janssen Research & Development, LLC; and Sanofi—had joined the effort, and NCATS made a limited amount of company-provided information about each agent, along with the funding opportunity announcements (FOAs), publicly available on its website. The objective at that stage was to provide sufficient information about each agent to enable researchers to decide whether any of the agents might be a candidate therapeutic for their disease of interest based on a high-level view of the safety profile, duration of previous

trials, and the original indication for which the agent had been developed. The scope of the pilot limited investigators to using the agents in their original formulation and with short periods of support (2–3 years) to complete phase 1b and 2a clinical trials. Modification of the agents was not an option.

With only a 2-month lead time between release of the agent information and the preapplication deadline, investigators from institutions across the country submitted almost 160 preapplications for a wide array of diseases. NCATS used external experts familiar with the mechanisms of action, the diseases, and drug development to evaluate the ideas proposed for new uses of the agents in the preapplications. Only after evaluation and NIH selection of the top preapplications and those of high program priority did investigators have their first direct contact with the companies to discuss their ideas and get more information on the agents. And it was the first time that the companies got a glimpse of the ideas from prospective academic partners for their agents.

At that point, the confidential disclosure agreements were executed and data shared in both directions so that the two parties could decide whether an application requesting funding for the academic research team should be submitted to the NIH. To be accepted for review and funding consideration, an application had to contain a letter of support from the pharmaceutical company stating that the agent and associated data needed for filing an investigational new drug application would be provided if the NIH made an award. To provide such a letter, companies presumably needed to have a collaborative research agreement in place. The template agreements served their intended purpose. Applications complete with letters of support from the companies were submitted and reviewed; 6 months after applications were submitted, NIH issued awards.

Unlike many of its sister institutes and centers, NCATS does not focus on a disease or organ system, which puts the center in the advantageous position of being able to support a wide range of projects with the strongest links between indications with unmet medical needs and the agents' mechanisms of action. As a result, the supported pilot projects cover a broad swath of medicine: Alzheimer's disease,

alcohol dependence, nicotine dependence, schizophrenia, calcific aortic valve stenosis, peripheral artery disease, and two rare diseases—lymphangioleiomyomatosis (LAM) and Duchenne muscular dystrophy.

The rationale behind crowdsourcing (publicly advertising these well-developed pharmaceutical assets) to repurpose investigational drugs was to tap a much broader community of scientists for new therapeutic use ideas for these industry-held agents. By definition, NCATS expected that the proposed new therapeutic uses would differ from the indications originally investigated by the pharmaceutical company. What wasn't expected was the extent to which this occurred. Examination of the nearly 160 preapplications showed that 15 of the 16 compounds that received 5 or more applications had at least 3 diverse indications proposed. We see this diversity reflected among our awards. The Alzheimer's disease study and the LAM study are both investigating an AstraZeneca Src tyrosine kinase inhibitor originally developed for cancer treatment.¹⁻⁴ Although this kind of complete shift in therapeutic indication is somewhat expected and is the very premise of repurposing, the extent to which this occurred—at least three different ideas in addition to the original indication(s) investigated by the pharmaceutical company—was rather remarkable and speaks to the power of using a crowdsourcing strategy for repurposing.

It will be a few years before we know what the success rate is of phase 2a clinical trials established using this strategy, but enthusiasm in the academic community and in the pharmaceutical industry is high. Harnessing that enthusiasm, in May 2014, NCATS issued a new set of FOAs for the New Therapeutic Uses program. This time, several NIH institutes and the FDA Office of Orphan Product Development joined the effort. Also new this round is an FOA for pediatric indications. Based on the experiences in the pilot, NIH institutes and the pharmaceutical companies recognized that with an additional year of support, investigators could conduct FDA-required juvenile toxicity studies. As a result, 12 agents have been listed for pediatric indication consideration. As in the pilot, NCATS required each pharmaceutical company to offer at least three agents to participate in the program. Holding the bar even

higher, NCATS also required that new agents be listed; agents could not have been listed for the pilot. The only exception was that agents from the pilot could be posted for pediatric indications because those indications were not encouraged in the pilot.

With some agents in this round targeting completely new mechanisms of action, we expect to see fresh ideas from the research community and anticipate diverse hypotheses for the agents as was seen in the pilot. Awards from this new round of the program will be made in summer 2015, and we will soon begin seeing preclinical study results from the projects awarded in the pilot.

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Abbreviations Used

NCATS = National Center for Advancing Translational Sciences
 FDA = Food and Drug Administration
 FOAs = funding opportunity announcements