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BY WILLIAM LOONEY

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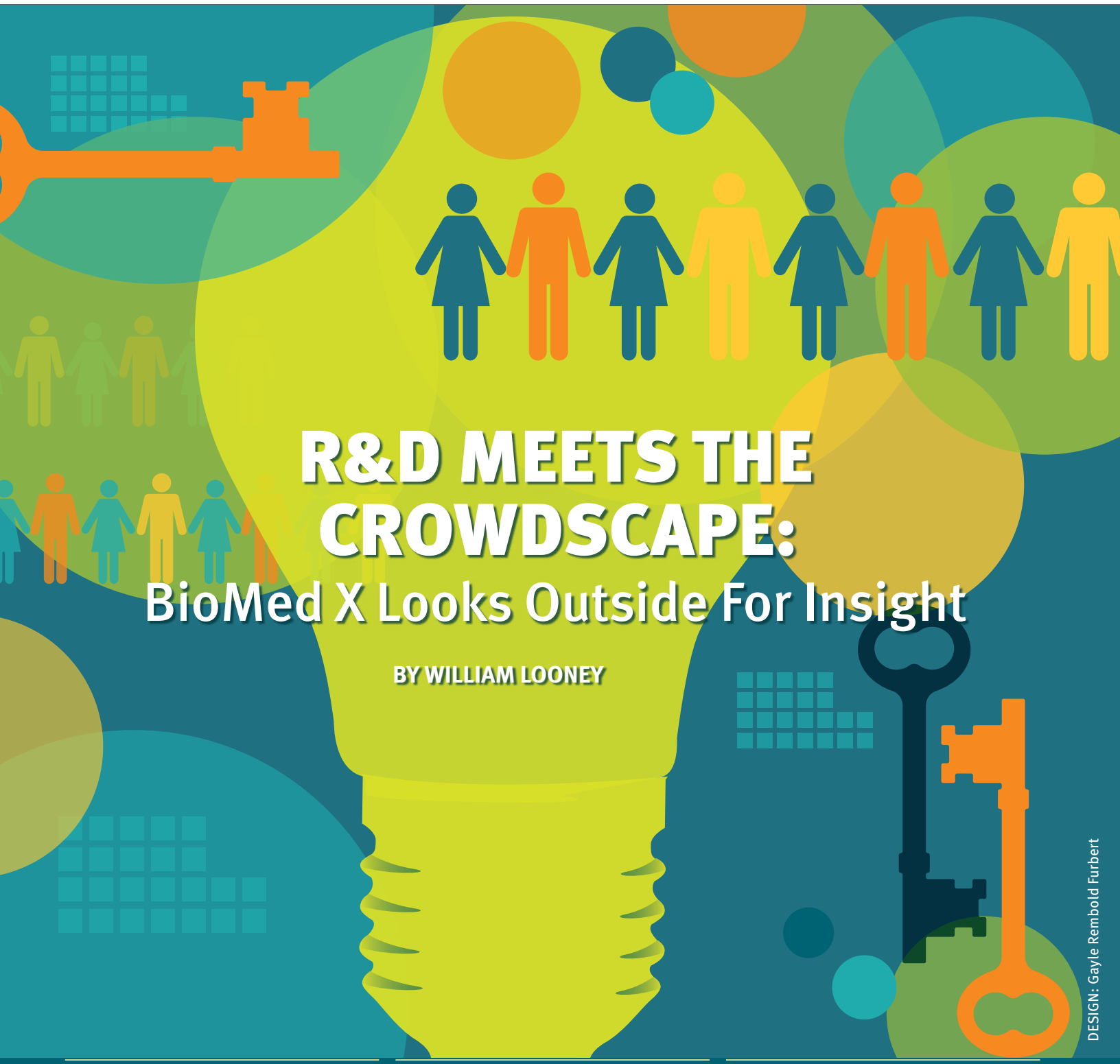

R&D MEETS THE CROWDSCAPE:

BioMed X Looks Outside For Insight

BY WILLIAM LOONEY

DESIGN: Gayle Rembold Furbert

Germany's BioMed X "outcubator" is investing in the wisdom of the science crowd to redeploy the cognitive division of labor in preclinical research. The goal is to consistently deliver novel druggable targets that matter to markets, payers and patients.

As basic research adapts to the downstream practicalities of translational medicine, more must be done to retain scientists capable of working productively in both settings.

So what? An open crowdsourcing model requires commitments to strategic discipline and operational efficiency so that the next wave of innovations is also market relevant and commercially feasible – BioMed X is a leading global advocate for this approach, but additional examples of this interdisciplinary form of biopharma engagement are needed.

IT IS A CLICHÉ TO SAY THAT PHARMA SCIENCE LOVES TO COLLABORATE – THE HARD THING IS THAT LEAKY DECISION FRAMEWORK BY WHICH GOOD IDEAS DO NOT GET EXECUTED.

Solving hard problems in biopharma usually starts like this: expert teams of specialists develop a research premise, test it in a carefully-defined cohort of patients and then validate the results using standard randomized methodologies. Failure rates are high because, at heart, drug research remains a messy exercise in improvisation. That is because we still do not know the basics of how nature uses physics to make the biology that determines individual health status.

Given the sheer number of variables in disease causation, an extended interdisciplinary approach to preclinical research may offer the best leads against today's biggest challenges in medicine. And while there is no single model that works perfectly in translating different streams of knowledge into useful innovations, the one that appears to have the most staying power due to its economy and lower risk is crowdsourcing.

Described as an "open door to the global brain," crowdsourcing first took root in the software and high tech business. The concept has evolved a bit differently within the tightly regulated world of biopharma. What crowdsourcing really means in drug R&D is mobilizing external research talent around a specific project arranged between a company and an early-stage "incubator" facility, which is in turn associated with a major academic research institute. "It is actually very grounded and results-oriented, with the added advantage of being able to generate novel science at a lower cost than doing it in-house," Dr. Ken Kaitin, Director of the Tufts University Center for the Study of Drug Development (TCSDD), told *In Vivo*.

Science Of Silos

Crowd science also appeals as a remedy for declining productivity in the biopharma pipeline, particularly for big companies with high fixed costs for R&D. Pharmaprojects' *Pharma R&D Review 2019* found that new drugs introduced by the top 25 companies in sales dropped from 18.3% of the total in 2011 to 11% in 2018; among the top 10 revenue leaders the figure was 6.45%, down from 13.2% in 2011. Small companies with one or two marketed products have leapt ahead, with portfolios bolstered by the fresh talent recruited from the endless downsizing of big pharma. Redressing this gap is a priority for the drug majors and the crowdsourced research model is touted as one solution: it replicates the freedom and flexibility of these smaller start-up enterprises without the constraints of a permanent fixed tie to one organization.

Accompanying the rise of the crowd-based model is a steep decline in funding and career opportunities in public academic research. Experienced clinicians with lab experience are being displaced and are more willing to taking assignments in the private-sector. The problem, noted Kaitin, is the difficulty in melding two different work cultures. "Integration and execution skills are the missing link in partnerships between industry and academe and can only be joined through active mentorship by the research sponsor. To work, crowd science cannot proceed *ad hoc*; having a tight decision infrastructure up and running from the start is essential to succeeding in the race to turn an idea into a product, one that fulfills a market need, beyond nice to know."

One Company's Claim To The Crowd

To explore trends and current practice in biopharma crowdsourcing, *In Vivo* spoke with a prominent leader in the space: Germany's **BioMed X Innovation Center**, established in August 2013 by some well-connected researchers in the city of Heidelberg, home to not only a world-class university and medical school, but the German Cancer Research Center (DKFZ), a public foundation; the European Molecular Biology Lab (EMBL), an

EU intergovernmental organization supported by the 28 member states; as well as 20 other local organizations focused on disease and drug research. In total, the University of Heidelberg community hosts more than 15,000 people engaged in biotech and medicine, with an additional boost from the 16,000 students enrolled in the medical school and other life science disciplines.

Dr. Christian Tidona, founder and current managing director of BioMed X, trained as a biologist and led several private biotech start-ups in the area before entering the economic development field as director of the regional Rhine Neckar Biotech Cluster (BioRN) and more recently as co-founder of Health Axis Europe, a government-backed initiative to promote the "cluster" development model around several leading university-based research centers of excellence: Heidelberg, Leuven in Belgium, Maastricht in the Netherlands, and Copenhagen in Denmark.

Tidona started by tackling that unmet need in biopharma R&D: how to tap into the global reserve of academic brainpower in a more structured way, with insights that can be applied directly to a viable research target. "The big problem we saw in crowdsourcing approaches at the time was that the big companies were good at collecting ideas but faltered in turning the inputs into projects that mesh with the decision culture and could be implemented in-house," said Tidona. "Typically, there was much difficulty in turning a contributed thesis into a commercial target, which led many executives to discount externalization as an asset in innovating R&D."

Channeling The Creatives

This was the conceptual flaw that BioMed X strives to fix. The unfiltered aggregation of novel ideas had to be redressed with some process guardrails that facilitate actionable outcomes. It starts with BioMed X signing on with a pharma company to jointly identify a tough preclinical research challenge that the company wants to solve. Only after that does the action move to the crowd, through a worldwide online call for original RFP's to address the challenge. BioMed X commonly receives several hundred RFP's, from 70 or more countries, all of which are reviewed with the company. Researchers associated with 15 to 17 of the most promising ones are selected to attend, at BioMed X's expense, a week-long "innovation boot camp" in Heidelberg. The individual candidates are arranged in five competing groups and combine their ideas into project proposals to solve the research challenge. Each group gets to pitch to a jury composed of senior R&D management of the sponsor company, after which the winning team gets a research grant to address the challenge. The grant covers four years of salaried residence for the team in Heidelberg, including access to the entire local network of scientists and its world-class physical plant.

"We are a proving ground for recruitment of the next generation of life scientists."

Christian Tidona
BioMed X

An interesting theme here is that each candidate arrives as an individual and becomes part of a team only during this week of discovery. The model allows BioMed X and the sponsors to assess team dynamics and observe how well the groups do in combining their ideas to move things forward.

"The way big pharma has traditionally looked for the brightest stars outside the private sector is like trying to find a needle in a haystack," Tidona continued. "Our global crowdsourcing approach makes the needle – unheralded young academic scientists and their ideas – come to us. We can crowdsource the best people in the various disciplines and put them to work for four years in one of the strongest biomedical research hubs in Europe." Time and a generous research budget allow these researchers full reign to unleash their creativity on a specific problem that matters to a dominant player in the industry.

BioMed X serves a larger purpose in advancing translational medicine: where basic research is redirected toward the commercialization of small molecules and biologics that matter to patients. Data is essential to this mix, but business and academia are two solitudes when it comes to using it. Academic and public research institutions generate data with an eye to getting written up in high-profile professional journals, while big pharma needs huge stores of data obtained over long periods to obtain a marketing license. That's a completely different data set, at costs that run into the tens, even hundreds of millions of

Exhibit 1
BioMed X Crowdsourcing Project Summary

TOPIC	THERAPEUTIC AREA	PHARMA SPONSOR	START DATE	END DATE	STATUS	IP TO SPONSOR
Metabolism and Signaling in Cancer	Oncology	Merck Group	8/1/2013	7/31/2017	completed	No
Selective Kinase Inhibitors	Oncology	Merck Group	8/1/2013	7/31/2016	completed	Yes
Immunosuppressive Microenvironment of Tumors	Oncology	Merck Group	3/1/2014	2/28/2018	completed	Yes
Epigenetics and COPD	Respiratory	Boehringer-Ingelheim	11/1/2015		ongoing	Yes
Nanomaterial-based Biosensors	Diagnostics	Roche	10/1/2015		ongoing	Yes
Tau-mediated Neurodegeneration in AZ	CNS	AbbVie	11/1/2015		ongoing	
Brain Microcircuits in Psychiatric Diseases	CNS	Boehringer-Ingelheim	8/1/2016		ongoing	
Oral Biofilm Disruption	Consumer Care	J&J Consumer	8/1/2016	7/31/2018	completed	Yes
DNA Damage in Cancer	Oncology	Merck Group	11/1/2016		ongoing	
Pathogen-Mediated Modulation of Innate Immunity	Immunology	Boehringer-Ingelheim	11/1/2017		ongoing	
RNA Splicing in Cancer	Oncology	Merck Group	2/1/2018		ongoing	
Rapid Identification of Auto-Antigens in Autoimmune Disease	Immunology	Janssen Pharmaceuticals	8/1/2018		ongoing	
Early Intervention in Psychiatric Disease	CNS	Boehringer-Ingelheim	Q4 2019		Call for application completed	
Intestinal Epithelial Barrier in Autoimmune diseases	Immunology	Merck Group	Q4 2019		Call for application ongoing	

dollars per therapy –at a much higher burden of risk. "In a standard bilateral collaboration, you get lots of interesting findings but what the academic partner might trumpet as a validated new drug target – because the data can be published – won't pass muster with pharma. It faces regulatory hurdles where validation requires a deeper data dive along with proof of reproducibility on the safety and efficacy of the target," Tidona said.

Project Reports

On the financial side, BioMed X is a private incubator registered in Germany as a limited liability company. It relies on income from an annual research fee covering costs for the seven staff members, physical plant and the research teams that execute the sponsors projects. These expenses are covered by the sponsor in the form of an annual project fee. At the end of the project, the sponsor has first rights to secure full ownership of the IP rights to the workstream – i.e. no future milestone or royalty payments, as is common in direct bilateral academic-industry collaborations. In return, BioMedX gets a pre-negotiated "success fee" paid by the sponsor. If the sponsor chooses to pass on the IP, then those rights are retained by BioMed X. "Transfer of IP rights to the sponsor is a very tangible marker of the practicality of our model," noted Tidona. He reports that BioMed X's first and leading big pharma partner, Merck Group KGaA, has acquired IP rights to two of the three projects it has completed to date; three others with the company are currently underway.

In the nearly six years since the launch of BioMed X, multi-platform research projects have been initiated with five big pharma, including, in addition to Merck, **AbbVie Inc.**; **Boehringer-Ingelheim GmbH**; **Janssen R&D LLC** and **J&J Consumer Health Inc.**, and **Roche Diagnostics GmbH** (*see Exhibit 1*). Most projects have a common objective: to explore a completely new field of potential drug targets; identify the most promising, within the bounds of the research protocol; and then validating these targets through *in vitro* and *in vivo* models, which, in the

best case scenario, will trigger a full-fledged drug discovery program at the sponsoring company.

"Basically, our partners look to us when they want to do something different, that could be seen as too disruptive were it initiated in-house," said Tidona. "In our first project with Boehringer-Ingelheim, we were asked to examine possible connections between epigenetics and chronic obstructive pulmonary disease (COPD). While the company was heavily invested in COPD, it did not have an active research program on epigenetics. Over four years, we succeeded in identifying several epigenetic targets that could be applied to reverse the pathology of COPD in a novel, meaningful way. It provided the independent perspective that Boehringer wanted and was also cost-effective in deciding how much resources the company wanted to devote to this new area."

In addition to specific therapy indications, BioMed X engages with companies on platform technologies and in related areas like diagnostics and materials engineering. "One of our most interesting collaborations has been with Roche, which asked us to envision a biosensor model that could incorporate sophisticated nanomaterials technology into a simple, compact and accessible diagnostic for use by physicians at the point of care. With Roche, we recruited an international team of young biomedical and nanomaterials experts who built a prototype device that was disposable, measures a variety of analytes, and could basically be read out by a personal cell phone. The Roche Diagnostics division acquired the IP package for the model, which has potential as a completely new diagnostics platform for the company. It's one of our biggest successes."

Tidona said BioMed X owed a debt to its neighbors at the Merck Group, noting that a senior executive there, vice president for innovation, Dr. Ulrich Betz, was a crucial early proponent of the crowdsourcing approach. It proved similar to Merck's Innovation Cup, a program for young academic researchers who also compete in teams for cash prizes to help advance the pipeline. To date, Merck has funded six separate BioMed X projects, mostly on challenges in the oncology space like DNA damage repair and tumor suppression.

In an interview, Betz said he coined a new term to describe the BioMed X model. "I dubbed it the 'outcubator' because it combines the creative informality of academia with the structure and discipline of a corporate R&D enterprise." Merck insisted on guidelines to ensure the company sponsor would not lose touch with the science during the four-year timeline of a typical BioMed X project. "I put forward a requirement that the sponsor appoint one of its own senior researchers to mentor the project; he or she is expected to convene at least one progress update a month with the team." Betz also insists geographic proximity has been a success factor in Merck's relationship with BioMed X, noting that the entire Heidelberg life sciences ecosystem is only a 45-minute drive from the company HQ in Darmstadt. "Human contacts are important; it's hard to complete a crowdsourcing project all virtually," he said.

One other distinctive aspect of BioMed X is its corporate research sponsors are comfortable about using the model to extend their gaze into other therapeutic areas. Examples include Merck's venture from cancer into auto-immune disorders, and Boehringer-Ingelheim's efforts beyond respiratory diseases to include novel approaches to treatment of patients with psychiatric conditions, especially adolescents. Tidona contends it's because his incubator doesn't have the restrictions commonly found in big pharma organizations, which make it difficult to take a risk and do something whimsical without fear of distraction – or censure. "Obviously we work hard to win, but I like to describe us as a 'sandbox' that softens the interface between academia and industry, combining the best of two distinct worlds. The continuing progress of BioMed X into new areas of inquiry shows that big pharma is finally opening up and embracing this new concept of seeding innovation from non-traditional sources."

Messaging The C-Suite

What is next for BioMed X? Clearly, Tidona sees himself as an advocate with designs that extend beyond just delivering R&D leaders a contracting service. Asked if he has a simple message for the C-suite, he emphasized how institutions like BioMed X can help solve the looming shortage of human capital to improve big pharma's productivity and keep operating margins in line with costs. "We are a proving ground for recruitment of the next generation of life scientists," Tidona said. "Our recruits get four years of exposure to the risk and benefits of commercially-oriented research, which stretches their learning curve to the point that most want to make the transition from pure science to the practical side, in industry. Noting that 80% of the fellows that finish their four-year stint at BioMed X move into jobs in big pharma and biotech, Tidona summarizes it this way: "our science leads not just to translational medicine, but to translational skills, writ large."

Another asset BioMed X brings to big pharma is independence. The attractiveness of an open innovation model focused on the cross-pollination of ideas would be lost if pharma companies found their innovation projects were conducted under a structure owned and controlled by a rival competitor, or even an academic institution committed to expanding its own IP portfolio. "We occupy a special position at the interface between academia and industry," Tidona said.

One option that BioMed X is avoiding – at least for the time being – is raising more capital by testing the VC market or going public. Tidona likes being a private entrepreneur and wants to maintain a pace of stable growth. The goal is to attract a more diverse array of mid-sized and smaller sponsors, as well as foundations and patient advocacy group, in addition to the big pharma firms.

IV124242

Comments:
Email the author: *William.Looney@Informa.com*