



Minding the Drug Development Gap

| VISION | *Accelerator models can ease the often difficult transition between academia and industry* | By Edward Spack

Twenty-five years after the enactment of the Bayh-Dole Act, scientists and administrators in academia who are interested in moving bench discoveries to the clinic are learning what travelers in London's subway system already know: It's important to "mind the gap." Some technology transfer offices are struggling to support patent prosecution costs, and they face difficult decisions for maintaining their intellectual property. Fewer licenses mean fewer transfers of discoveries across the development gap to commercial chaperones. University entrepreneurs who want to commercialize their own discoveries are finding startup funds and development partners scarce. The gap can seem insurmountable.

As funding models have changed, many groups are developing new models to support reengineering the translational R&D pipeline. Building a traditional "brick and mortar" incubator facility is unlikely to provide enough monetary support and expertise for most startup companies. Furthermore, not all discoveries merit building a company around them. That's where new accelerator models come in.

TRANSLATING THE INDUSTRY ALPHABET Part of the challenge of translating bench science to the bedside lies in the different sets of expertise that academia's "Eureka!" and industry's "Good Laboratory Practice" require. Novelty is paramount in academia: It is rewarded with grants, lab space, and tenure. However, the path to the clinic requires a transition from novelty to a documented set of activities carefully prescribed by the US Food and Drug Administration.

To the academic researcher, the path to an Investigational New Drug (IND) application is strewn with an unfamiliar alphabet: GLP for good laboratory practice, CMC for chemistry, manufacturing, and control, and many others. Many labs are not equipped to perform and document GLP studies, and the CMC and safety activities integral to an IND submission require specialized training. In addition, universities often lack expertise in US and international regulatory requirements for studies in humans. Discovery and development require different skills, and perhaps more importantly they require different temperaments. This often contributes to a communications gap. As a result, promising leads may stall while other compounds may receive far more attention than their insolubility or toxicity merit.

This communication gap is compounded by a growing funding gap. Traditionally, the National Institutes of Health has funded both the discovery and clinical sides of drug development through mechanisms such as RO1s and the General Clinical Research Centers. Pre-IND studies, including formulation, pharmacokinetics, and tox-

icology, are not traditionally supported by NIH funding. There are exceptions, however, including Small Business Innovative Research and Small Business Technology Transfer grants for fledgling businesses, and the National Cancer Institute Rapid Access to Interventional Development program. In recent years, the NIH Road Map initiative and several requests for applications from individual NIH institutes have emphasized translational components.

In some cases, researchers have found that study sections for these grants penalize proposals that are not novel, even though the development steps, by their nature, are standardized. For example, if a multiyear NIH cooperative-agreement program seeks to transition a discovery from bench to clinic, the study section should not penalize a proposal for a toxicity testing protocol that is "insufficiently innovative" when the protocol follows FDA guidelines. In a time of tightening budgets, some question whether the NIH should play a role in translational development. The NIH has a mission and a unique position to bridge the development gap, but it should not bear the financial burden alone. By establishing additional public-private funding initiatives, NIH can attract other stakeholders, including pharma and private disease-focused foundations, to participate in solutions that address their common clients: the many patients with unmet medical needs.

In the 1980s and 1990s, the venture capital sector played a large role in funding very early-stage companies and chaperoning the development of new compounds and technologies discovered in university labs. A series of events changed this funding model in 2000-2001. Concerns over company valuations, commercializing the genome, and terrorism all contributed to a downturn in funding. In addition, the long timelines and growing costs of drug development caused increasing concerns about liquidity and exit strategies for early-stage investors. As a result, many investors shifted the majority of their funding focus to companies with drugs in Phase II and Phase III clinical trials. Startup companies have struggled for seed and early-stage funding in this new environment, and many established biotech companies shifted their focus to the later stages of their development pipeline. This shift in investment strategy had several consequences for academic translation. Even as the NIH budget grew, universities saw that the number of invention disclosures and patents kept pace with research funding, but the number of licensed patents flattened or declined.

UNIVERSITIES ADAPT Some institutions are establishing funds or importing personnel from biotech and building an infra-

structure on campus to support pilot translational projects. Others are forming partnerships to fill gaps in funding and expertise. SRI International, a nonprofit R&D organization based in Menlo Park, Calif., has initiated several recent partnerships with universities – including Stanford University, University of Arizona, and several University of California campuses – to develop collaborative responses to current challenges in translational development. Founded in 1946 as Stanford Research Institute, the organization became independent of Stanford in 1970 and changed its name to SRI International. SRI continues its commitment to the original charter by making a difference in the world through basic and applied research, research services, technology development, and commercialization of its innovations. Today, SRI conducts client-sponsored R&D in policy, information/computing sciences, physical sciences, engineering systems, and biosciences.

The Bioscience Division of SRI conducts discovery research and has collaborated with US and international pharmaceutical companies to bring several drugs to FDA approval and clinical use. SRI Biosciences also includes a preclinical contract-research organization (CRO) that provides a full spectrum of preclinical support services including analytical methods, toxicology, regulatory compliance, and IND assembly to commercial clients. SRI also has a long-standing CRO relationship with the NIH, holding all or part of 13 major NIH preclinical contracts. Recently, SRI teamed with the NIH Translational Core Services Committee to provide preclinical development plans for the NIH RAID Pilot Program (nihroadmap.nih.gov/raid). This program, modeled after the NCI RAID program, provides guidance and contract services for researchers seeking translational development of small-molecule therapeutics.

In response to the widening translation gap, SRI formed the PharmaSTART consortium in August 2003 with Stanford, and the University of California at Berkeley, San Diego, and San Francisco. The consortium involves deans and the heads of technology transfer from each of the universities to coordinate collaborative approaches to translational development within and between the participating institutions and thereby accelerating the translation of breakthrough new drugs from discovery into clinical use. SRI provides preclinical development plans for selected university projects, providing an outline to IND steps that includes a timeline and approximate costs. These plans are incorporated into startup business plans, licensing summaries, and translational grant proposals.

The biggest challenge remaining is to find funding sources dedicated to preclinical activities rather than discovery or clinical trials. To meet this challenge, SRI provides guidance on government and private funding sources and has partnered with academic researchers to apply for translational grants. SRI is establishing similar relationships with other universities and clusters of research institutions.

The PharmaSTART consortium focuses on preclinical translation. A recent collaboration between SRI, the FDA, and the University of Arizona resulted in the formation of the Critical Path Institute (C-Path) to revolutionize the broader translation pathway from discovery to drug approval. Headquartered in Tucson, the home of one of the top schools of pharmacy and academic medical centers in the country, C-Path is initiating pilot programs with major pharmaceutical companies to validate new biomarkers and to test other strategies to accelerate drug development. C-Path will also establish educational programs in regulatory requirements, an expertise often under-represented in academia.

MOVING FORWARD Several lessons have emerged from our experiences in establishing PharmaSTART and C-PATH and from our conversations with other emerging models:

1. Begin Translation Early. Many research projects that come to us are too early for IND-enabling preclinical studies and need advice on selecting a viable lead candidate. Several quick and relatively inexpensive tests (e.g., maximum tolerated dose, solubility, bioavail-

ability) can help guide this decision. It is also prudent to begin the transition from the discovery with the end in mind, so early consultation with clinical and regulatory advisors is a good investment.

2. Share the Funding Burden. In response to the current funding climate, more public-private partnerships must fill the gap left by the migration of venture capital. Private, disease-focused foundations have a mission to translate the discoveries they fund to the clinic and for their patients. Biotech and large pharmaceutical companies rely on academic discoveries to fill part of their pipeline. Public-private funding by all stakeholders is needed to fill the translational funding gap.

3. Adapt Virtual Incubator or Accelerator Models. Many academic groups are testing alternative incubator models, sometimes termed accelerators, that provide discoveries and fledgling companies with more than laboratory and office space. These accelerators, such as the Accelerator Corporation in Seattle, often select projects screened by a panel of scientific and industry experts, and may provide supplemental regulatory, development, and/or management expertise. Accelerator Corporation in Seattle is one of a diverse and growing set of such innovation models. Many of these steps can be accomplished virtually, drawing on supplemental consultants and contract labs to delay the development of a fully integrated company until the technology is validated in the clinic. Because not every discovery has the potential to support a company, some institutions are considering establishing holding companies that develop a project to IND or through early-phase clinical trial, then establishing a stronger company or licensing out the more valuable technology. This may winnow out the false leads and bring a discovery to the point of funding by venture capital or licensing by an established company. If this mechanism could establish a sufficient royalty stream from successful projects, it could become self-sustaining.

Many gaps remain in the translation from research bench to patient bedside. Some are based on changing funding patterns; others arise from fundamental differences in the requirements of each step, and require a certain amount of translating between very different groups of specialists. Many new models address these challenges, yet no one solution is likely to apply universally. Unfortunately, it may take a pipeline crisis to spur changes needed to chaperone discoveries through the critical steps of preclinical development. In the face of unmet and emerging medical needs and rising costs of drug development, collaborations between academia and industry are a matter of life and death. ☒



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