

POLICY

Bench-to-Bench Bottlenecks in Translation

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Transfer of biopharmaceutical inventions between firms has bottlenecks in upstream development that suggests a role for repurposing mechanisms well before the clinical trials stage.

The policy community has embraced and implemented cross-cutting approaches designed to enhance the translation of fundamental scientific discoveries through clinical trials—from bench to bedside (1). National Center for Advancing Translational Sciences (NCATS) initiatives tend to complement, rather than substitute for, fundamental research and thus address mid-to-downstream translational bottlenecks. For example, the New Therapeutics Program (NTP) focuses on repurposing of molecules that have already undergone substantial development or clinical testing by the pharmaceutical industry (www.ncats.nih.gov/research/reengineering/rescue-repurpose/therapeutic-uses/therapeutic-uses.html). Indeed, much of the discussion in the pharmaceutical industry has focused on high failure rates in phase III clinical trials (2).

Here, we dissect a different branch of the therapeutics development pathway in which inventions move between firms for development in disease categories not specified or envisioned in the original patent or license. Our analysis of patented university inventions licensed to biotechnology firms revealed bottlenecks that suggest that initiatives to speed translation are needed much earlier in the process: the point at which academic science meets drug development. On the basis of these findings, we highlight the role of university scientists in biomedical translation.

BENCH-TO-BENCH

Drug development efforts frequently are derived from discoveries made in university laboratories and licensed to biotechnology firms (3). We constructed a database of 835 patents in 342 university licenses with biotech firms (“first-license”) and followed the patents to document whether they were

subsequently sublicensed to another firm (“second-license”) for testing in a new disease category (Fig. 1A and supplementary materials). This switch effectively resets the development timeline so that much of the time spent on bench-to-bedside translation actually occurs during the “bench-to-bench” part of a nonlinear translational pathway.

To examine upstream development processes when products are yet to be defined, we used a measure of translational success other than regulatory approval by exploiting the fact that biotech firms rarely have capabilities that span the entire value chain from invention to marketing. In this environment, successful commercialization typically requires a second-license at some stage (4). Thus, a natural measure of success that can be observed before product launch, or even clinical trials, is whether a patent proceeds to a second-license. Technologies are sublicensed for many reasons, including progress in development, a change in focus of the initial licensee, or discovery that an invention has potential in a focal area beyond the interests or capabilities of the first licensee. Further, as suggested in our interviews with industry scientists, second-licenses might follow failure of the technology for its original intended use. In all cases, however, a second-license indicates that another business entity continues to view the technology as viable and potentially profitable.

Of the 835 inventions, 27% appeared in a second license and thus were considered to be successful. Because we could not observe efforts internal to first licensees, it remains unknown whether or not the other 73% are now undergoing successful development. The average time between invention and first-license was 66 months, and the average time between first- and second-license was 42 months. This time span for the upstream phase of the translation process is substantial, given that the average time from discovery to approval of new drugs (including biologics) by the U.S. Food and Drug Administration (FDA) is 156 months (1).

Of the first-licenses that list a stage of development, 92% were either at the discovery or lead molecule stages (the earliest two stages, respectively), with only 6% listed in clinical trials. Among the second-licenses, only 22% were in clinical trials or beyond.

If a first-license was in a discovery stage, then more than 70% of the second-licenses were still in discovery, and just over 14% were in clinical trials or beyond. When a first-license stage was lead molecule, 20% of the second-licenses in our sample were at the clinical trials stage or beyond, and for another 20%, the lead molecules had regressed back to the discovery stage.

NEW DISEASE INDICATIONS

However, second-licenses in the discovery stage might not indicate a lack of progress in the development of an invention. Instead, development might have revealed potential uses for the invention outside the areas of interest or capabilities of the first licensee, such as for entirely new disease indications. The disease categories indicated in our licenses spanned 20 distinct disease indications (table S3), with individual licenses including up to five indications. These categories were broad and included, for example, cancer, cardiovascular, central nervous system (CNS), and infectious diseases.

We documented substantial changes in disease indications from the first- to second-license. Indeed, only 19% of the patent-license pairs showed no change in disease indication (Fig. 1B). For a large number of cases (44%), none of the first-license indications remained in the second-license. Of the remaining cases, 28% added indications and 9% added and subtracted indications in the second-license. Focusing on the four most prevalent disease indications (Fig. 1C) showed the frequency with which the indication was listed in the first- or second-license or both. Of these, the CNS disease category was the only one that was listed in both the first- and second-licenses of more than half of the patent-license pairs. In contrast, indications for cancer and infectious diseases were commonly found only in second-licenses.

An example is a set of eight patents (priority dates between 1975 and 1987) licensed (first-licenses) by the Massachusetts Institute of Technology (MIT) to the company Advanced Tissue Science in 1992 for dermatologic applications, and the stage of development was “lead molecule.” In 1993, MIT licensed (first-license) four of those patents

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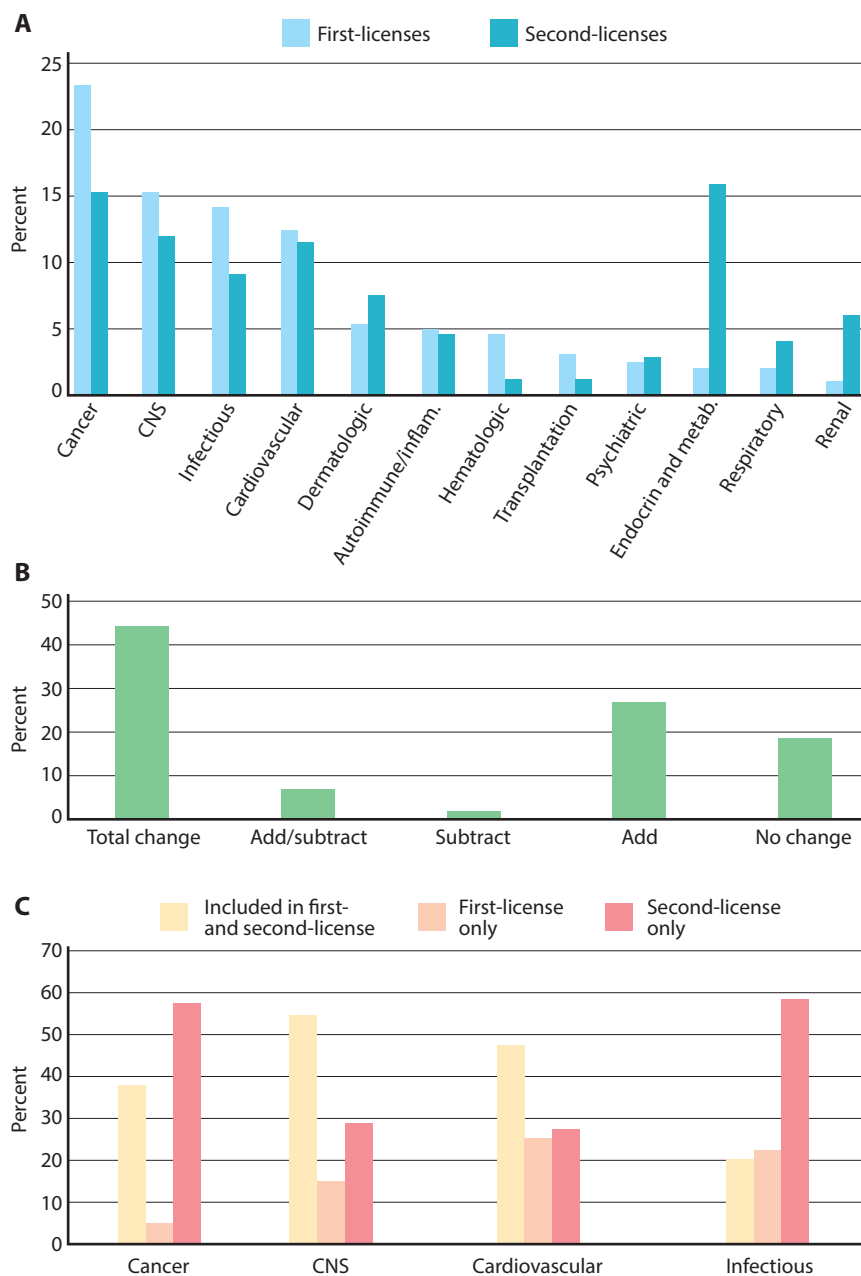


Fig. 1. On second thought. (A) Percentage of first-licenses and second-licenses, for patent/license pairs across a variety of disease indications. (B) Changes in disease indications from first- to second-licenses for patent/license pairs. Total change, different disease; add, new disease indications added; subtract, disease indications eliminated. (C) Percent of first-licenses, second-licenses, or both (for patents on potential therapies) that were directed toward cancer or CNS, cardiovascular, or infectious diseases. "Included in first- and second-license," disease indication listed in first and second license; "first-license only," disease indication listed only in first-license; "second-license only," disease indication listed only in second-license.

to another company, Integra Life Science, for dermatologic applications, but the stage of development of the license was "discovery." In 1996, MIT licensed (first-license) to the company Reprogenesis the same four patents licensed to Advanced Tissue Science

but not licensed to Integra Life Science. The stage of development was "lead molecule," and the disease categories were genitourinary and gynecological disease and organ transplantation. The eight patents licensed to Advanced Tissue Science were sublicensed

(second-licenses) in 1996 to yet another company, Smith and Nephew, for phase III clinical trials and the disease categories endocrinological, metabolic, and dermatological diseases. Then in 2001, Advance Tissue Science sublicensed (second-licenses) seven of the eight patents to Medtronic in the stage "lead molecule" for disease categories endocrinological and metabolic, cardiovascular, and CNS diseases.

There are other examples of new disease indications unearthed during clinical trials (such as occurred with the erectile dysfunction drug Viagra, which was originally being tested as a cardiovascular drug and, during clinical trials, was also shown to treat erectile dysfunction) or after a drug has been approved (for example, Propecia, which was approved for treatment of an enlarged prostate and was later found to treat male-pattern baldness). But our data reveal substantial changes much earlier in development. Small, narrowly focused biotechnology firms typically conduct early-stage (upstream) translation. For discovery of new disease indications to occur at these stages, the first licensee must be able to appreciate the new potential and be capable of identifying potential licensees across broad disease categories. Our interviews with scientists in biotechnology firms suggest that such diverse knowledge is rarely found in small, specialized groups of scientists.

During the earliest stages of study and experimentation, it is highly unlikely that an academic laboratory or institution can identify all the relevant disease categories an invention may serve. Moreover, firms carefully guard information about their upstream research programs, including their failures, so that information asymmetries abound. In this environment, finding a second licensee takes time and might not occur in the presence of these information asymmetries. Such bottlenecks suggest the need for strategic mechanisms to facilitate new research directions for inventions in the early stages of translation.

INVENTOR INCENTIVES

Our data also address the participation of academic scientists in translational research. Much of the discussion of academic scientists' involvement in translation has focused on incentives for clinical faculty to conduct translational research (5). We examined a different translational incentive issue: the involvement of university faculty inventors of the patents in our database.

Previous studies have shown that inventor participation is critical for the successful development of university inventions (6). Thus, license contracts are often designed specifically to secure inventor participation.

In order to assess inventor effort, we examined a larger sample of 948 first-licenses. Twelve percent of the contracts contained clauses that required inventor effort in the development of the technology, whereas 34% included research funding for the inventor's lab, and 43% include milestone payments. Only 38% of licenses did not include one or more of these incentives.

However, these incentive mechanisms might have the unintended consequence of diverting the attention of academic scientists away from basic research and toward clinical development (7, 8). Not only is there the real possibility of diversion of faculty effort, but licenses also frequently include terms that impede the dissemination of knowledge. For example, in the 948 first-licenses we examined, 60% included, in some form, the right of the firm to delay publication. When the time of delay was specified, the median number of days was 60, and the mean was 91 days. Several licenses allowed delays as long as 18 months.

BENCH BOTTLENECKS

This analysis of early-stage biomedical translation suggests that stakeholders need to design policies and initiatives that enhance early translation by more efficiently driving more inventions into multiple disease pipelines. High failure rates in drug development are often discussed in terms of technical and market hurdles to downstream translation within a given disease category. Implicit in the discussion is a linear model of translation, long criticized by innovation researchers (9). The prevalence in our data of second-licenses for disease categories not specified in the first-license suggests a process that is anything but linear. The bench-to-bench licenses we observed suggest horizontal linkages that are hard to find in the absence of some type of upstream research clearinghouse.

One option might be the formation of an open-source translational research database that complements clinicaltrials.gov. Patents and licenses for fundamental biomedical research believed to be destined for

eventual therapeutic use initially would be logged into this database. If the knowledge advances to clinical trials, the data entry would be cross-referenced in clinicaltrials.gov. Translational research "failures" that do not enter clinical trials would remain in the early-phase database but not appear in clinicaltrials.gov. Reporting into the database could be required by journals and for any research that receives federal funding, and FDA could make reporting a requirement for any molecule that a firm intends to take into clinical trials. This would induce firms, both domestic and foreign, to report their findings early. Similar to reporting requirements for clinical trials, civil monetary penalties could also be enforced. Such an initiative would provide clarity on which areas of research and disease indications are pursued by specific scientists and institutions and help to diminish the information asymmetries that exist in early-phase translational research.

In order to make compliance with such a clearinghouse more palatable, it could be coupled with legislation similar to the Orphan Drug Act for repurposed molecules. That is, repurposed molecules (even those repurposed upstream) often have little or no patent protection from generic entry, which hinders their economic viability to a firm. An act that extends tax credits for new clinical trials and expands market exclusivity to seven years for a specific new indication could garner industry attention. The overarching goal of these actions would be to minimize the cost of repurposing while creating a viable market opportunity.

Last, the inventor incentive terms of the contracts we analyzed show that biotech firms consider the active involvement of basic scientists to be important in their research. This suggests that discovery-stage biomedical research might be best conducted by basic scientists who are trained, for example, in human physiology and pathophysiology. To conduct reproducible research ready for translation, basic scientists can consult with clinically focused faculty in translational centers on essential components of preclinical research, such as blinding, randomization, and statistical analysis.

The uncertainty associated with early-stage translation research pinpoints what we consider to be an underappreciated cost

of the current focus by funders and other stakeholders on late-stage translation—namely, the opportunity cost of basic science that is repeated, postponed, or never performed. The repetition of costly failed experiments arises largely from information asymmetries. A database that is devoted to early-stage translational research and that documents its outcomes has implications about how funding for early translational research could be appropriated.

SUPPLEMENTARY MATERIALS

www.sciencetranslationalmedicine.org/cgi/content/full/6/250/250fs32/DC1

Introduction, data sources, methods

Table S1. Stage of therapeutic development.

Table S2. Stage of therapeutic development for patents in both first- and second-licenses.

Table S3. Disease category.

Table S4. Percent of first- and second-licenses excluding blank.

Table S5. Disease indications in second-licenses when first-licenses listed cancer.

Table S6. Second-licenses that list cancer; source of first-licenses.

Table S7. First-licenses that list CNS diseases; disease indications in second-licenses.

Table S8. Second-licenses that list CNS diseases and the source of first licenses.

Appendix

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