

# Platform Technologies in Regenerative Medicine: Maximizing the Technology Early in the Process

By Barbara A. Nelsen, Ph.D.

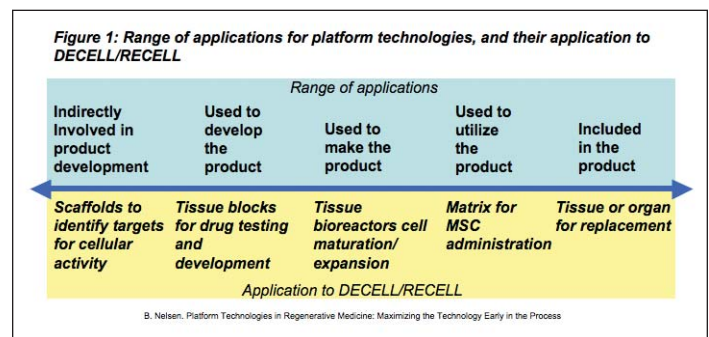
**P**latform technologies have far-reaching breadth and utility. They can enable multiple applications within one industry or be influential across many. If the magnitude of change is significant enough, for example as in the discovery of recombinant DNA or stem cells, entirely new industries may be created. The platform, quite literally, serves as a springboard for the technology to foster a new industry or create a paradigm shift in an existing one.

## Origin of Platform Technologies and the Path to Commercialization

Platform technologies often originate in the university setting; and, as a result, it is the university technology transfer office's job to recognize the platform's potential and determine the best strategy for commercialization. While enormously exciting and with seemingly unlimited potential (though sometimes without focus), the platform is an early development stage in the commercialization process. This makes it difficult for technology transfer organizations to create a commercialization strategy that develops the technology as broadly as possible for all applications, while maximizing the return on investment for the University.

The roadmap described in this article illustrates how the University of Minnesota designed a commercialization plan, i.e. the licensing strategy, for the DECELL/RECELL platform technology developed by Dr. Doris Taylor and Dr. Harald Ott.<sup>1,2</sup> The breadth of this technology ranges from use as a research tool in the life sciences industry to assisting the creation of a bio-identical organ for transplantation (Figure 1). In fact, by eliminating the need to create a tissue or organ from scratch, this platform technology enables a paradigm shift for the regenerative medicine industry.

Figure 1



## Key Lessons for Successful Commercialization: Selected Case Studies

Case studies of other university-discovered platform technologies were examined to find key lessons for successful commercialization. When results from these case studies were combined with due diligence on the DECELL/RECELL platform technology, a strategy to optimize the commercial potential of this technology emerged. The three key elements of this strategy are:

- 1) To be aggressive in pursuing patent claims that creates barriers to entry, while focusing on market applications with the highest commercial value;
- 2) To develop a mechanism to stimulate use in the academic market, as secondary market adoption relies on the validation and expansion of uses created by researchers; and
- 3) To design a licensing structure that promotes development in as many fields of use as possible, where revenue is linked to milestones obtained during the life of the patent.

## Case Studies from Other Universities

As part of developing a plan for the DECELL/RECELL platform technology, commercialization strategies utilized by other

universities were examined. Specifically, recombinant DNA, RNAi, and early stem cell licensing activities and outcomes were reviewed in order to develop a best practices guide for commercialization of platform technologies discovered in an academic institution.

## rDNA (Stanford University)

Stanford paved the way for other university technology transfer offices with the development of their licensing strategy for the Cohen-Boyer recombinant DNA patents that were issued in 1980.<sup>3</sup> The Bayh-Dole Act had just been enacted, giving universities and not inventors ownership and licensing authority for new inventions generated from Federal Funding.<sup>4</sup>

Recombinant DNA had been in the public domain for wide usage since publication of the initial discovery in 1973.<sup>5</sup> In fact, start-up companies such as Genentech, Amgen, and Chiron were already using the technology to develop products. For example, Genentech had proven they had the ability to use rDNA to produce human insulin as early as 1978, two years prior to the issuance of the patent.<sup>6</sup> To avoid infringement, these companies represented a ready licensee base for the technology.

Given the combination of enabled technology and existing company use, Stanford utilized a licensing strategy that included: non-exclusive licenses; incentives for taking a license early; graduated royalty rates based on fields of use; and tiered upfront and minimum payments based on entity size. Not only did this approach facilitate the creation of a range of products from research tools to therapeutics, but it gave rise to a whole host of new companies, thus effectively creating the biotechnology industry. Ultimately, Stanford licensed this platform technology to over 450 companies, generating \$255 million in revenue for the university.<sup>7</sup>

### Key Lessons Learned

- 1) Platform technology that is “ready to use” will have fast, broad adoption;
- 2) Creating a few standard agreements is an effective mechanism to reduce the time and cost to execute transactions, allowing a high volume of licensees; and
- 3) Incentives for early licensing accelerate the use of the platform.

## RNAi – The Fire Mello patent (Carnegie Institution/U Mass Medical School)

The mechanism for interfering with messenger RNA to suppress gene expression was discovered by Fire and Mello in 1998.<sup>8</sup> While a huge leap forward in terms of controlling cellular activity, the technology as described in the original patent had significant commercial limitations. First, the patent claims only to RNA molecules of 25 nucleotides or more in length, and it could be worked around with shorter sequences.<sup>9</sup> Secondly, this larger size can apparently cause immunogenic responses, thus limiting therapeutic applications.

The Carnegie Institution followed Stanford’s model of making the intellectual property broadly available to interested commercial entities through standard, non-exclusive, licenses. This was an

effective strategy as it lessened the potential impact of weak IP by encouraging compliance through ease of licensing. Additionally, this minimized the administrative burden of the approximately 50 licenses executed to date.<sup>10</sup>

## The Tuschl patents (Max Planck Institute)

Four researchers (Tuschl, Sharp, Zamore, and Bartel) overcame the initial patent’s commercial limitations by showing that smaller RNAi molecules avoid immune reactions while still disabling mRNA.<sup>11,12</sup> This work led to two new patents generally referred to as Tuschl I and Tuschl II covering both modified and unmodified short interfering RNA (siRNA) molecules, 19 to 25 nucleotides long.<sup>13</sup> In addition, Tuschl II was the first patent that had strong claims enabling the technology for mammalian, i.e. valuable therapeutic, use. Max Planck’s Tuschl II patent, unlike the preceding examples, is licensed *exclusively* to the biopharmaceutical company Alnylam for use in therapeutic products.

What is noteworthy about this example is that despite the exclusive nature of the license, the Alnylam agreement met the research institute’s mission to broadly develop its technology. This was accomplished through Alnylam’s business model that relies on strategic partnering for the development of therapeutic applications outside the company’s internal focus. The question remains as to whether this will provide a good ROI to Max Planck. Given the finite lifespan of the original IP and the long cycle for therapeutic product development, royalties from products are a long-term proposition. As a result, this licensing strategy will provide a good ROI to the institution if sizable upfront and milestone payments associated with strategic alliances, and development, are incorporated into the terms of the agreement.

### Key Lessons Learned

- 1) Realistic assessment of breadth, strength and commercial application of patents is critical;
- 2) A non-exclusive licensing strategy encourages broad development (standardization) and compliance, and likely may be an appropriate strategy in situations for IP with critical limitations in utility, or in high value applications; and
- 3) An exclusive licensing strategy may deliver the desired outcome of broad development and financial return if the terms are written to either incent or mandate the licensee to sub-license the technology, and payments occur within the anticipated life of the patent.

## Stem Cells (Wisconsin Alumni Research Foundation)

In the mid-1990s Dr. James Thomson and coworkers made a breakthrough discovery when they isolated and cultured primate and human embryonic stem cells at the University of Wisconsin-Madison. The Wisconsin Alumni Research Foundation (WARF) followed Stanford’s Cohen-Boyer licensing strategy (i.e. a few standard, non-exclusives with the exception of an exclusive license with Geron for six fields of use). Geron, incorporated in 1990 and in

business since 1992, was one of the first start-up companies in the regenerative medicine industry.

While Geron has advanced the technology by becoming the first company to receive FDA clearance to begin a clinical trial employing an embryonic stem cell-based therapy, several significant fields of use they had licensed went undeveloped. Ultimately, WARF recovered the additional three fields of use in order to ensure effective commercialization per the requirements outlined in Bayh-Dole.<sup>14</sup>

For most universities this delay would represent a significant loss of revenue given the life of the patent, but given WARF's extensive IP portfolio in stem cells, this is unlikely to be a problem. The past three years have seen a dramatic increase in licensing activity by WARF to large pharmaceutical companies in addition to start-up and boutique companies.<sup>15, 16</sup> It can be argued that the more significant impact of sequestering the stem cell technology has been a delay in the development of the regenerative medicine industry as a whole.

One constraint WARF encountered was the highly political nature of this groundbreaking technology. United States law imposed during George W. Bush's presidency limited the use of federal funding to both make and use human stem cells. WiCell, a wholly owned subsidiary of WARF, emerged to support stem cell development and enable ESC technology in basic research applications in this adverse funding and regulatory environment.

## Key Lessons Learned

For an early technology in an emerging industry:

- 1) Smaller commercial entities such as start-ups and development boutiques need exclusivity to obtain funding, but often lack the resources to develop broadly;
- 2) Compulsory development should be part of any license;
- 3) Fields-of-use should be carved out to drive broad development; and
- 4) Expansion of applications and market opportunities takes active management. It is important to create mechanisms to broaden use and applications through basic research.

## Coupling Broad Technology Adoption with Return on Investment: Suggested "Best Practices"

From the key learnings gained through these case studies, the following best practices can be applied to a University's mission of coupling broad adoption of the technology with maximizing return on investment.

1. **Patents Should Be Written With Commercially Valuable Claims In Mind To Garner Highest Value**
  - Patents should cover key features of the invention as it is likely to be used in commercial applications.
  - Aim for the greatest breadth and strength in claims as possible.
2. **Academic Researchers Enable The Technology And Expand Its Market Applications**
  - Activate use through licensing in the academic tools market.

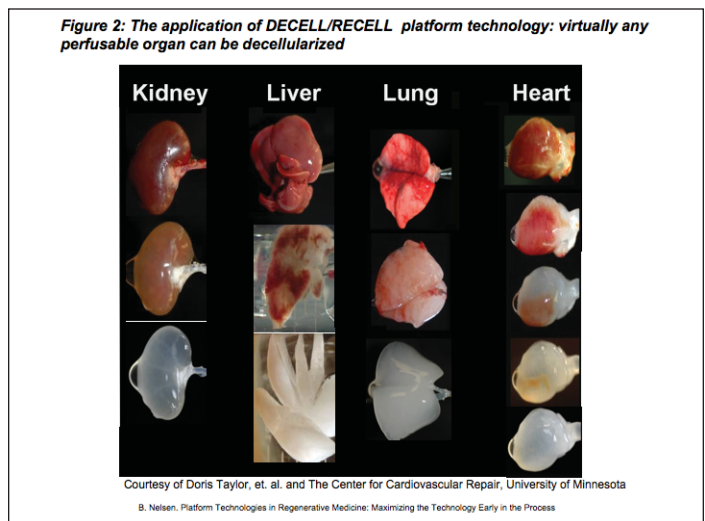
Expanding applications and market opportunities for a new technology in an emerging industry takes active management on the part of a University.

- Consider how to broaden use and applications through basic research if a commercial partner for these activities is not readily available.
3. **Focus Effort On Value That Can Be Realized During The Life Of The Patent**
    - Look to license in markets with near-term products.
    - Focus licensing terms on milestones in markets with long development cycles, such as therapeutics where a product comes to market at the end of the university's patent life. For therapeutics in an emerging industry, this likely comes from upfront and developmental milestones, rather than royalties.
    - Limit exclusive licenses to narrow usage claims if possible. Value can be lost if a large number of uses are licensed to only one entity that only has the capacity, capability, or interest of pursuing a subset of these uses.
    - Make compulsory development part of any license when broad fields of use are exclusive (developmental and financial milestones).
    - Include "claw back" clauses to recover languishing fields of use to get them developed within the life of the patent.

## Paradigm Shift in Regenerative Medicine: The University of Minnesota's DECELL/RECELL Platform Technology

In 2006, Dr. Doris Taylor and colleagues at the University of Minnesota reported in *Nature Medicine* the ability to recreate a beating heart using a proprietary perfusion-based decellularization technique together with reintroduction of primary neonatal cardiomyocytes.<sup>17</sup> Dr. Taylor's lab also demonstrated the perfusion-based DECELL/RECELL platform's ability to create whole organ and tissue scaffolds in a wide variety of organs and species.<sup>18</sup> (Figure 2) Broadly, the platform encompasses a method to decellularize and recellularize whole or partial organs and tissues.

Figure 2



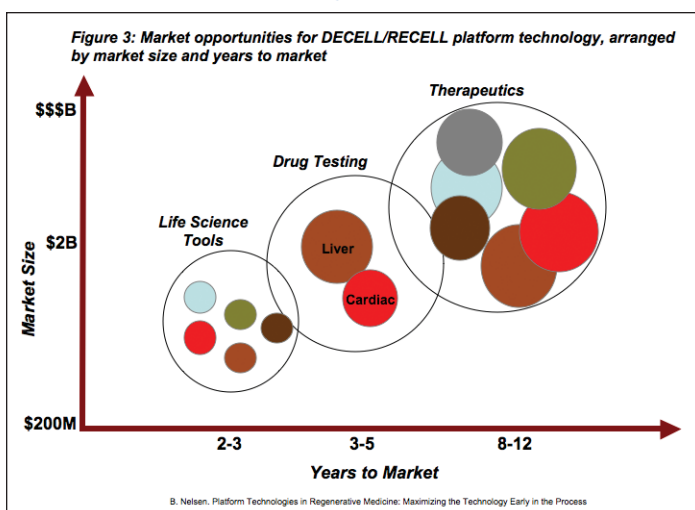
This proprietary technology removes all cellular constituents while retaining the extracellular matrix and its biologic cues, organ 3-D structure and geometry, and vascular conduits, and simply needs recellularization in order to be functional. This is a paradigm shift. No longer does an artificial tissue or organ need to be synthesized from scratch, with each section built independently and then assembled into a 3D form that performs to specific physical and biological requirements. This represents an exponential reduction in the time and cost associated with creating an organ or tissue replacement.

The University of Minnesota began the commercial strategy for this technology by applying the three key lessons learned from other universities' experiences:

## 1. Patents Should Be Written With Commercially Valuable Claims In Mind To Garner Highest Value

Though active, in-depth management of intellectual property at a university is unusual, in the case of platform technologies it is absolutely essential. In the case of the DECELL/RECELL platform, both in-house and outside patent counsel were utilized in order to file the broadest, strongest, highest-value patents obtainable. An extensive prior art search was performed prior to filing. An outside consultant from the regenerative medicine industry was hired to provide recommendations about the technology and its potential value to industry. A "wish list" of desired claims was created and laboratory notebooks mined for the enabling data. Additional studies were completed, proving out additional capabilities considered commercially valuable. An Innovation Grant from the Vice President for Research provided financial support for these activities. The University of Minnesota took the RNAi example to heart by active management of the patent portfolio for this platform, ensuring substantiation of claims for commercial applications in multiple markets, including highly valuable therapeutic applications.

Figure 3



There are three distinct market opportunities for the DECELL/RECELL platform technology (Figure 3): tools for life sciences research; tools for drug discovery, development and testing; and therapeutics for regenerative medicine.

## 2. Academic Researchers Enable the Technology and Expand Market Applications

In what types of research would retention of 3D architecture and cues in a tissue scaffold be useful? A clear value for this technology as a research tool was expressed by Carl Schrott, Director of Marketing for Regenerative Medicine and Research Cell Culture at Sigma-Aldrich, who said that it is increasingly important to design cell culture assays that closely mimic the behavior of cells in living tissues.

The extracellular matrix (ECM or scaffold) market is very small but critical. Specific advantages to the 3D biological scaffold include:

- Good intermediate between in vitro and in vivo
- Anatomically correctness
- Essential for basic stem cell differentiation and cancer cell research
- Offers significant improvements over current techniques, for example, longer in vitro cell lifespans than 2D models

In fact, while small in terms of current revenue, this market is critical for expanding fields of use through novel discoveries by primary researchers. In this market, naked scaffold alone is a piece of the product. This market application is best developed in collaboration with established vendors already providing systems and components (e.g. plates, bioreactors, media, cells) to this industry. It is interesting to note that WARF achieved this objective with their stem cell technology through the creation of the non-profit organization WiCell.

## 3. Focus Effort On Value That Can Be Realized During The Life Of The Patent

In contrast to the life sciences market, the drug development testing market is large and growing. The ADME/tox market is currently estimated to be worth \$3 billion and is growing rapidly, and drug toxicity testing makes up about half of this.<sup>19</sup> *In vitro* and *in silico* segments are growing at greater than 20% annually, and the *in silico* segment alone is expected to reach \$1B by 2012.<sup>20</sup>

Hepatotoxicity is the most common reason for non-approval or drug withdrawal by the FDA.<sup>21</sup> Hepatocytes grown on dishes quickly lose their mature phenotype, leading to a loss of normal function and predictive behavior.<sup>22</sup> Given that normal, hepatic function depends in part on an organ's 3-D structure, a test bed designed using the DECELL/RECELL platform potentially creates a model that provides for predictive *in silico* analysis.

The advantage of developing a hepatoscreen using a scaffold, lobe, or slice of a liver created with the platform technology is that the resulting hepatocytes will behave as they do in the body. In addition, as new patient subset-specific ES or IPS cells are isolated, they can be used to further expand the product line of unique, *in silico* systems to test drugs and chemicals for their toxicity potential in a patient-specific manner.<sup>23</sup>

Two key factors make this an attractive market to license into. First, time to market for these products is near-term, providing



revenue to the university for a substantial period of the life of the patent. Second, the synergies and similarities of product specifications (e.g. scaffold slice, multiwall dish, cell loading, cells owned by others) between this application and the Life Sciences tools market suggest potential licensing partners with a presence in both fields that can leverage their capabilities in product and specification development, manufacturing, and distribution. Presumably these companies could bring products in both fields to market more efficiently and effectively than companies with fewer capabilities that only operate in either the tools or testing space.

The value proposition of the DECELL/RECELL platform technology applied to regenerative medicine is readily understandable. It is easy to envision bio-identical new hearts, kidneys, and livers, or even just a valve, patch, or vessel. Rather than starting from scratch to create a necessary part, as has been the case historically within the tissue engineering field, this technology provides a significant head start. The “naked” organ, completely 3D-correct and with intact vasculature, simply needs the correct assortment of cells loaded back into the organ to produce function. Of course, this is not as simple as it sounds, at least at the level of a whole organ – kidney cells have 26 distinct cell types.<sup>24</sup>

However, there are much simpler, near-term therapeutic products that can be envisioned. For example, “naked” 3D vascularized scaffold alone could be used for soft tissue repair such as breast reconstruction. Recellularized patches for cardiac repair are another simple application.

While there is interest today from big pharmaceutical companies to take a non-exclusive license for tools, test beds, and model systems for drug discovery and development, therapeutic development will more likely come from start-up companies in the regenerative medicine industry or existing companies that see the value of the platform technology to expand their product offering in biomaterials.

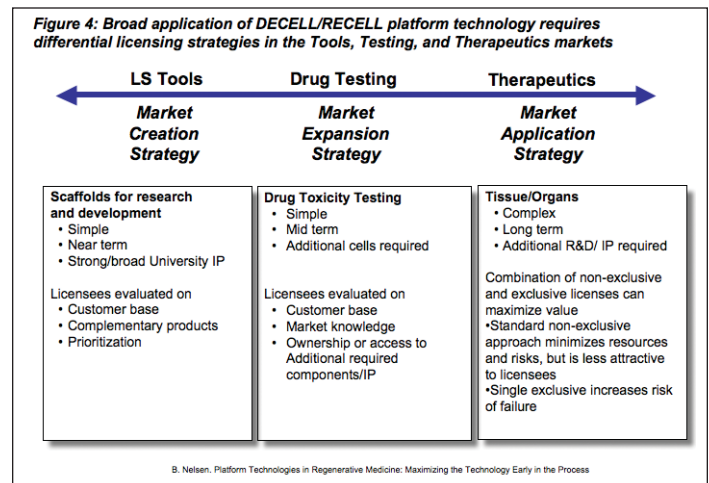
Given that no single company can possibly exploit all therapeutic possibilities, value can be lost if a large number of uses are licensed to only one entity that only has the capacity, capability, or interest of pursuing a subset of these uses. Here exclusive licensing should be narrow when possible, include compulsory development when broad, and focus on development and financial milestones as the primary sources of revenue payment to the university, not royalties.

## Conclusion

Platform technologies are both an opportunity and challenge. This is particularly true when they are discovered in an academic setting where the basic research performed may not support the most commercially relevant patent claims nor provide mechanisms for extension of patent life.

Given these limitations, the best course of action relies on three

Figure 4



primary objectives. First, be aggressive in pursuing patent claims that create barriers to entry. Focus on market applications with the highest commercial value. Next, develop a mechanism to feed use in the academic market. Secondary market adoption relies on the validation and expansion of uses created by researchers. Last, design a licensing structure to force development in as many fields of use as possible. Revenue must be linked to milestones obtained during the life of the patent. (Figure 4)

Following these guidelines develops the technology as broadly as possible, while maximizing the return on investment.

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