Positioned for Success: Building a Biological Product Using a High-Value Preclinical Plan

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Today's biotechnology executive charged with the development of a novel biological product is faced with producing scientific validation, innovation and ongoing forward progress on an aggressive timeline and a limited budget. The natural response to this challenge is to focus preclinical discovery and development on getting to the clinic as quickly as possible. Yet this tactic often drives the development process past one of the most influential factors for success, the preclinical research plan. This white paper will explore several ways a high-value preclinical research strategy can enable a company to progress with greater overall speed and efficiency, reduce development risk, and overcome road blocks in the development of novel biological products.

Biological products are biologics that contain a biological component such as cells or structures that influence cell behavior. Biological products include cell and tissue transplants, cellular therapeutics and products from tissue engineering. By their nature, they encompass multiple biological aspects and often, structural components as well, creating a unique series of challenges.

Gathering the skills needed to implement a high-value preclinical research and development plan is well worth the effort and will provide both time and cost savings. The old adage "pay now or pay later" applies. At the end of the day, regulators will expect answers to key questions and the clinical response will be an even tougher task master. Having to fill in missing science or re-engineer even a portion of a product strategy or process after you have begun clinical testing is not only costly, but also difficult to do. Weaknesses in strategy tend to escalate and second chances are rare. A high-value preclinical plan ensures that the company puts its best foot forward.

Why a Preclinical Plan Matters

In 2000, Time Magazine[1] named tissue engineering the hottest job in biomedical research for the new millennium. Today, few will argue that applications of stem cell biology and regenerative medicine are still eagerly anticipated. As pharmaceutical and biotechnology companies struggle to maintain a robust pipeline, biologics are seen as an important factor for their future. However only a few large pharmaceutical (Novartis, Johnson & Johnson, Baxter Healthcare), biotechnology (Genzyme BioSurgery) and device companies (Smith and Nephew) have

[1] Time Magazine, May 15, 2000

been involved in the biological products space with limited success. This area of biotechnology continues to rely on the smaller, entrepreneurial biotechnology company for innovation and advance.

Virtually every company is faced with the problem of strategic allocation of finite resources. Ian MacMillan of the Wharton School argues that strategic allocation is a key task of entrepreneurship[2]. According to Burns of the Wharton School and Sammut of Burrill & Company[3], even larger pharmaceutical and biotechnology companies are focusing on a smaller number of projects and therapeutic areas, recognizing the benefit of smaller, multidisciplinary groups and the value of integration.

The need for multi-disciplinary innovation

Biological products present multi-disciplinary problems and often require convergence of multiple disciplines and technologies, each requiring a sufficient level of sophistication and expertise. Both the range of disciplines and the breadth of knowledge required within each has significantly expanded. Burns and Sammut argue that firms using multiple technologies to make their products need to have knowledge "in excess of what they need for what they produce."

Biological products are in many ways poster-children for the need for sophisticated multi-disciplinary integration of science and engineering innovation. Biological product firms therefore need a way to enable necessary innovation while keeping costs and head count under control.

The need for skillful applied science

Pharmaceutical industry veteran Jon Northrup writes: "[In applied research] there is no research just for the sake of understanding unless that understanding can be applied to creating or finding a drug candidate. It is called research because it is so risky, and it is very different than academic research…Discovery also differs from development in that discovery is about creating the molecule, and development is about creating the knowledge and processes around the molecule to make it a pharmaceutical product."[4]. **Northrup views lead discovery in pharmaceutical research as the major bottleneck in the discovery research process which suffers from a need for greater "*in vivo* and *in vitro* connectivity."**

[2] McGrath and MacMillan The Entrepreneurial Mindset. 2000, Harvard Business School Press.

[3] Burns and Sammut, *Healtcare Innovation Across Sectors: Convergences and Divergences* in: The Business of Healthcare Innovation, LR Burns, ed. 2005 Cambridge Univ. Press.

[4] Northrup,*The Pharmaceutical Sector* in: The Business of Healthcare Innovation, LR Burns, ed. 2005 Cambridge Univ. Press.

While Northrup is referring to the challenges of drug development, the same challenges are true for biological product discovery and development. The *in vitro* to *in vivo* connectivity is just as important although approached differently. While biological understanding has made great strides in target identification and molecular and genetic characterization, the biological systems that one is working with in biological products are still extremely complex. **There is a need to rapidly identify and deal with core issues.**

The need for rapid targeting

According to Northrup, key levers of productivity in pharmaceutical research are moving in the wrong direction and "anything that can be done to test the research hypothesis as quickly and as early as possible has tremendous cost savings." Based on the paucity of new biological product approvals over the last decade, this problem is echoed in the biological products segment of the biotechnology industry as well. Northrup contends that **a "higher biological understanding" is needed for better and quicker choices in pharmaceutical development, the same can be said for biological products**.

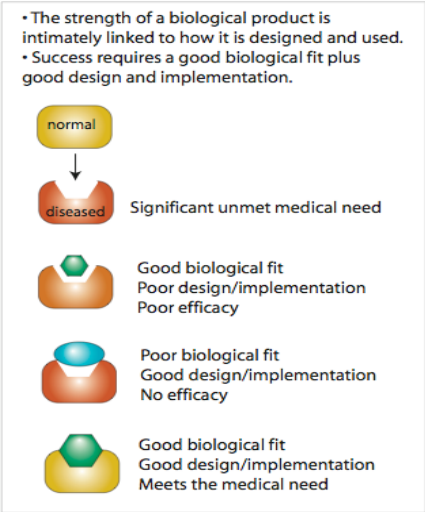
The goal of higher biological understanding is also important for efficient biological product research, however most biotechnology companies engaged in biological product research and development do not have multiple candidate products in their pipeline but rather a core technology with the possibility of multiple applications. So the "fast fail" approach to increasing efficiency must be modified to a rapid targeting approach to include not only the ability to rapidly assess the feasibility of a product approach but also understand how a technology might be used in its best way. **Biological understanding must also be used to determine a technology's best use as rapidly as possible.**

One of the first tissue engineering products and cell therapies was Apligraf®[5] a skin construct. While the most obvious and first indication tested was in severe burns, it had limitations in being able to act as a skin graft under extreme inflammatory conditions. While the first generation product later demonstrated some benefit when used as a temporary covering or in conjunction with meshed autograft to alleviate scarring, the use of the product in this indication alone might have been considered insufficient to justify continued development and production based soly on a burn application. However, it was known that skin grafts promoted healing of hard to heal wounds suggesting at least three potential clinical indications for the product[6]. Apligraf went on to gain approval in two chronic wound indications, which represent significantly larger markets than severe burns and where the product's efficacy was competitive and filled an unmet medical need, as the first generation

[5] Apligraf is a trademark of Novartis Pharmaceuticals. Apligraf is a product of Organogenesis Inc.

[6] Diabetic ulcers, venous ulcers and decubitus ulcers (pressure sores)

product. **Biological technology companies are challenged with finding the best biological fit for what they can provide that also makes market sense.**



Product targets have been a special challenge for biological products. On one hand, companies have suffered from being unable to move their potential applications beyond a niche market or boutique applications. Example of current boutique applications are Tengion's autologous bladder construct currently in Phase II clinical trials and Epicel, autologous epidermal sheet grafts produced as a life-saving treatment for severe burn patients from Genzyme Biosurgery which was first applied to patients in the early 1980s but only received formal FDA BLA approval in 2007. A significant hurdle to the approval of this technology was the use of xenogeneic mouse feeder cells in the culture process – a method first developed in 1975. Whether Genzyme could have developed a comparable transplant without the use of mouse feeder cells and achieved approval sooner could be debated but business considerations such as the cost of development for a severe burn indication and the securing of new patent rights would not have been insignificant.

While some product approaches may evolve slowly in part due to business reasons, business reasons can also push technologies into clinical applications where the biological rationale is still undeveloped and therefore a higher risk. One example of this is the interest in the use of bone marrow-derived mesenchymal stem cells for the abrogation of auto-immunity and inflammation. In this case, experimental observations *in vitro* and limited animal experimentation suggest that suppressive cytokines and possibly other suppressive factors are produced when MSC encounter immune cells. It has been postulated that this reaction could serve as a way of modulating immune disorders from Graft versus Host Disease to diabetes. However, it has been reported that infused MSC tend to localize in capillary beds, particularly in the lungs in the experimental animals. The biological relevance of the suppressive effect in nature is still in question and it appears other cell types may also have the same effect, including more common fibroblasts as well as parenchymal cells like the epidermal cell (based on data reported a decade ago).[7] Another example, somewhat related, is the use of bone marrow fractions and mesenchymal stem cells to improve repair of cardiac muscle. A common denominator in these high risk applications is the use of stem cells. Part of the latitude to pursue these aggressive applications comes from the drive to show utility in stem cell applications. If one were to use dermal fibroblasts for the same indication, the product might appear far less appealing and of questionable risk, yet the biology would likely have many similarities.

Most biological product research is not dealing with a "black box" but rather something that lies between empiricism, the "put it in and see what

[7] An extended bibliography may be found at http://www.parenteaubc.com/supplementaryinfo.html.

it does" approach used for years in the design and testing of traditional medical devices, and an hypothesis-driven approach where the technology, tools and information are focused on piecing together clues to identify a target and eventually a product. Northup contends that lack of biological understanding results in lower output and higher variability in pharmaceutical research. **In biological products development, lack of biological understanding or rather, failure to position a technology to achieve its best biological fit, leads to the increased risk of ineffective or marginally effective products, inability to meet regulatory scrutiny, and decreased output from the industry as a whole.**

The need for innovative, science-linked design and development

Biological products face unique challenges in design and delivery. They are not pills and will often require specialized methods of delivery or application. Even with proper targeting, product design can be a significant factor in determining product acceptance. Use of the product must meet physician and patient needs. Innovative engineering in this area is also very competitive and windows of opportunity can close rapidly making time to market an important factor in development innovation.

Biological products face a challenge of meeting the need of the product and the patient. For example, while research clinicians have developed several promising tissue engineering applications, few have translated into commercial products. Access to boutique services is very limited, usually confined to a specific clinical group or hospital. Methodology can also be complex. An autologous, cell-produced vascular shunt now in clinical trials (Cytograft), currently has an extremely long processing time, which will need significant refinement to achieve effective commercialization.

Even currently marketed products have challenges: The standard application procedures for the use of chondrocytes for cartilage repair require an open surgical procedure where the trend in today's joint surgery is arthroscopic. The world's leading cell therapy, the Apligraf® skin construct, still employs just in time manufacturing even though cryopreservation technology was developed over a decade ago. Boutique application, unrefined methodology, and slow adoption of innovation, both from a manufacturing and end user perspective, can create a potential barrier to acceptance and limit the rate of adoption.

While limitations of early products may be seen as an acceptable aspect of pioneering products, next generation offerings are unlikely to have that luxury. **A preclinical plan formulated in 2007 should address issues of use and delivery up front.**

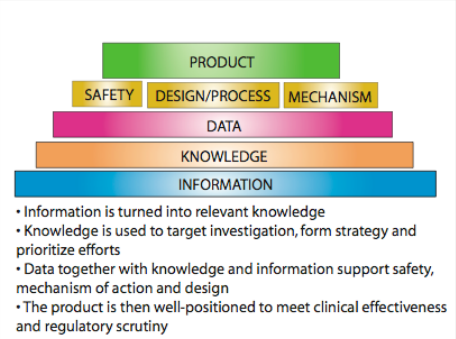
The response and activity of biological products is intimately linked to its design. For example, there is a biological impact linked to the

decision to design a skin construct with an epidermis, with a cornified epidermis or with a cornified epidermis that exhibits barrier function. These parameters are not only related to process but translate directly to how they are used by the physician and their biological response and interaction with the patient. Likewise, deciding to implant pancreatic islet precursors will result in significantly different scientific and medical considerations versus a decision to implant mature islet clusters, even though the cell source may be the same. The technical, medical and regulatory burden will be different depending on the strategy chosen. **A preclinical plan should involve the weighing of options to find the strongest biologically-justified strategy based on the technology available, the technical ability for innovation, and awareness of competitive risk.**

The ultimate medical and commercial success of biological products is dependent on both an efficient discovery *and* development strategy prior to entry into the clinic. The high-value preclinical plan is one that lays the foundation for success, absence of a well-designed preclinical plan can create weaknesses in product design, lead to poor choice of clinical target and protocol design or failure to pass regulatory muster. It also leaves a door open for the competition.

Building the high-value preclinical plan

The Preclinical Research Phase



Northrup describes this phase in pharmaceutical research as the pharmaceutical discovery phase. In biological products it represents research that is conducted to gain insight that will directly contribute to strategic decisions regarding technology application, product design, and product parameters. This portion of the research plan lays the foundation for scientific rationale and safety.

Plan for success

Acquire a clear vision of the road ahead learn from history, benchmark biological information gathered from basic science and disease-related research, and assimilate the information into relevant knowledge pertinent to applied research. This foundation can then be used to identify major questions that are important to specific technology and product goals. A preclinical plan can then be formulated to find the answers.[8]

[8] Our white paper: *Reducing Risk in Bioscience Development: Closing the Information to Knowledge Gap* discusses the importance of closing the gap in greater detail and covers ways even small companies can create a broad base of what we view as *foundational knowledge* for the preclinical plan.

Look for *in vivo* and *in vitro* connectivity

The common denominators of biological response apply to the biological component of the product as well as the response of the recipient. They are rooted in native biological processes involved in tissue regulation. Being able to characterize the product will not only be necessary from a regulatory perspective, but it helps establish its *biological fit* with either the clinical target or a process that one must control to be successful. Here are the basics:

1. Injury
2. Inflammation
3. Regeneration
4. Repair
5. Maintenance/Stable function

Knowledge of the fundamentals in each of these processes can serve as road maps to characterizing changes in the cellular component before inclusion in the process, during the process and in the final product. It can target the strongest clinical application for your technology, provided you have the knowledge and understanding of normal and possibly pathological processes in the recipient and where the biological product you are constructing fits among these processes.

Ask and answer the tough questions

Invite scientific, medical, and marketing questions. The company knows its technology the best. By honestly listing the questions one should ask and preparing a way to address them, you are already far ahead in planning for your regulatory submission and product success.

Focus is particularly important at this phase. This phase is one of the most likely to be overlooked even though it will translate to a substantial reduction of risk. Many simply avoid the tough questions. Some do not see it as an option, fearing a negative answer could translate into harm to the company. **No one likes to "be told" that something is not worth doing or is not feasible. However, the earlier tough questions are asked, the more likely the chance that something good can come from it. Avoidance can set up a program for failure when it might have succeeded.**

Do not expect a scientific advisory board to put a company's feet to the fire or its investors, as they will often not know enough. But be assured that the regulators will. The regulators expectations are that you will provide answers to these questions where possible. The earlier issues can be faced, the less costly and risky your development plan will be. Adjusting the course of a dingy requires less energy than adjusting course of an ocean liner. It can also be done more rapidly.

Here are three hypothetical situations and what might be considered a fundamental question related either to safety, product design or mechanism of action:

Situation:The product strategy is to use cells derived from an individual other than the recipient.

Question: How will the recipient's immune system react to donor cells from a different individual? Will there be a safety concern?

Comment: Start with no assumptions. The degree of allogenicity should be established before your reach the clinic or decide to incorporate immune suppression in your clinical protocol. You may find you do not have to.

Situation: The goal of the therapeutic is to establish new pancreatic islet tissue using stem cells as the starting cell source.

Question: Should one focus on injecting large numbers of stem cells with the possible need for companion biologics to foster islet development or should one put resources to developing methods to mature islets *in vitro* for islet transplantation?

Comment: Be sure that the biological connection of your cells with the desired biological goal is well established through a combination of *in vitro* and *in vivo* experiments. If the information is not available in the scientific literature, you must create it. Demonstration that islet development using these cells follows normal developmental processes provides insight and practical and safety benefits. Use of *in vivo* implantation of cells at different stages can determine what works best for the product design and delivery as well as its biological establishment. By doing the preclinical work to answer the question in this way, the company is then well-positioned to understand what establishing mature islets will take, *in vitro* or *in vivo*, and you will be a long way toward having the option of providing islets if that is what is necessary to achieve treatment reproducibility and clinical robustness. Remember too, that islet transplants are the "gold standard" in this case, offering regulatory advantages as well.

Situation: The company has patented technology around a sorted cell population derived from connective tissue. The company wishes to tap into the growing interest in cells as drugs with a focus on inflammatory modulation.

Question: Is there evidence that stromal cells ever serve this function *in vivo*, such as during tumor progression, chronic inflammation, or wound repair?

Comment: Drawing parallels with natural processes is not only highly informative but provides an important link to establishing insight for both mechanism of action, feasibility, and a rationale for safety. If that link can be made, it provides evidence that one is not chasing a red herring or a non-homologous application that will be up against significant safety and efficacy hurdles.

The Preclinical Development Phase

The preclinical development phase deals with setting component and process parameters. This will be highly dependent on the type of technology and application. It is important that the design enable the biological goals that have been determined during the preclinical research phase. Every component and parameter of the process should be scientifically justified, either through assimilation of data and information or direct experimentation.

Ideally, possible clinical targets have been part of the team vision during the preclinical research phase. The research phase determines the strongest options. It is important to maintain a dialog between internal customers or members of the team that represent manufacturing, clinical and regulatory and marketing functions so that everyone buys in to the road ahead which will steadily increase in cost and commitment of resources. The best scientific use may not be the best commercial use, the most desirable business target may have serious regulatory and efficacy considerations, or the most desirable method of delivery may create substantial engineering hurdles. In other words, compromise and balance are needed to define the final product during this phase. A high-value preclinical research phase should provide the answers that clarify the technical options allowing the company to accurately assess its product and commercial options. The preclinical development phase can then focus on bringing together aspects of process and delivery that will make it a strong commercial product. The strategy for medical success begins at the preclinical research phase, but the strategy for commercial success is now the focus. The preclinical research data, if sufficiently developed, now serve as the foundation to set process parameters and define the final product for clinical testing.

Adding weight to your rationale

The foundational data to support scientific rationale and safety begins to build through the insight gained during the preclinical research phase. Once the process and product have been defined, preclinical research is then used to gain further insight into mechanism and safety. These data continue to target fundamental questions that could not be addressed earlier and strengthen the basis for a regulatory submission. Innovative use of *in vitro* assays can be particularly informative even at this phase, and the *in vitro* to *in vivo* connectivity continues by creating a synergistic use of *in vitro* and *in vivo* investigation.

Even though appropriate animal models may be lacking, relevant answers may still be possible by combining *in vivo* observations with *in vitro* analysis. For example, there is a lack of animal models that model a chronic human wound making the direct *in vivo* preclinical testing of skin constructs for wound healing of questionable relevance. However, by modeling an injury response in the construct *in vitro*, demonstrating through cytokine and growth factor modulation that the response

parallels what is known about normal healing *in vivo* and then engrafting onto athymic mice to demonstrate that the skin construct also undergoes these changes upon engraftment, a connection of the construct to wound healing is made *sans* a relevant *in vivo* wound healing model. Demonstration that the construct is able to respond normally to injury is the most powerful aspect of these data, derived *in vitro.*

Experimentation *in vitro* is much less costly and *in vitro* mechanistic studies can often be more informative than *in vivo* testing. The two are at their highest value when they are combined. **An investment in *in vitro* assay development is an enabling aspect to efficient preclinical development and the strength of the overall preclinical data package.**

The first instinct may be to rapidly advance to preclinical animal testing to provide proof of principle and evidence for probable efficacy. However, with biological products, *in vitro* experimentation and characterization is as, or more valuable, particularly when it can be connected to knowledge derived from *human* biology and pathology. *In vivo* data then forms an additional functional connection but is no longer relied upon to provide mechanistic validation on its own. This partnership translates into more relevant interpretation of both *in vitro* and *in vivo* findings and reduced risk.

Conclusion

This white paper has explored how preclinical research and development planning can positively impact scientific, technical, clinical and business decisions. The preclinical plan creates a platform for success that continues to contribute to the core value of the product and the company. The insight gained from preclinical research often establishes the understanding and expertise that creates future innovation and product opportunities. Data from a strong preclinical plan is like money in the bank for a small company. However implementation of a high value preclinical plan requires:

- The conversion of information to useful knowledge
- Efficient and accurate assimilation and interpretation of biological data
- Skill in applied bioscience
- Expertise in multiple areas involving both biology and engineering
- An innovative approach to using *in vitro* and *in vivo* methodology
- A multi-functional team willing to take an informed team approach to product development

Gather as much information and input early in the process. Be sure your team is aware of what is developing in other bioscience areas that may shed light on the use of your technology or pose a threat.

Work to purge any potential for naiveté due to lack of experience. Be sure your team is skilled in applied science and clear on the differences between applied science and academic research. Make an effort to train on the job or ideally, make training and coaching available to the staff before they are faced with the challenge. Having to learn applied bioscience by trial and error adds risk that doesn't need to exist.

Gather competitive information and up to date science from academic founders and experts on your scientific advisory board but be sure that your strategy is based on expertise in applied science. Ideally, any advisors or consultants used have demonstrated success in bioscience development. They should also demonstrate a commitment to achieving the company goals - if you are off target, you need experts willing to tell you. Issues should always be accompanied by suggested solutions.

This white paper has presented several arguments why a high-value preclinical plan is important to the success of biological products. Our firm produces a monthly open access e-zine, *The Best of Bioscience Letter* dedicated to the translation of bioscience at the forefront (www.bestofbioscience.com) that continues the dialogue as well as two podcasts that offer tips, training and straight talk about the practical challenges of applied bioscience:

- *The Applied Biologist*
- *Paths for Progress in Bioscience.*

Both podcasts are available on iTunes or through our websites.

Our scientific management consulting practice is particularly well suited to help clients in the development of biological products. If you find that bringing our expertise in-house is an option that you would like to explore, you can reach Dr. Nancy Parenteau or Dr. Janet Hardin-Young at (617) 275-8845. You can learn more about our experience and consulting practice by visiting www.parenteaubc.com.

Our firm also provides several informational and educational options for clients looking to close the information to knowledge gap and wishing to implement a biological process-based approach to their data analysis. PBC Paths for Progress Reports™ are analytical reports available on selected topics in bioscience. PBC analytical reports may also be commissioned to address the specific needs of the client.

To download a bibliography and further suggesting reading go to http://www.parenteaubc.com/supplementaryinfo.html.
Additional white papers are available online.