Changing the Paradigm of Cancer Drug Discovery and Development with Plants

An exploration of how iBio's new Drug Discovery Center is using the *FastPharming* System® to reduce costs and bring more therapeutic candidates into the clinic

FastPharming®

It is no secret to scientists working in oncology that cancer is a vexing and incredibly diverse disease. Although there are more than 100 documented cancer types,[1] there are likely many more.

The array of cancers requires oncologists to have plenty of therapeutic tools available for the fight, and iBio is committed to continually pushing the boundaries, ultimately expanding therapeutic options for patients. iBio's Chief Scientific Officer, Martin Brenner, DVM, Ph.D.; Chief Operating Officer, Randy Maddux; and oncology pipeline advisor, Steven King, took a break from their work building iBio's oncology pipeline and opening the iBio Drug Discovery Center in San Diego, California, to discuss how they are recruiting creative scientific talent, pioneering new approaches, and leveraging iBio's *FastPharming* System to deliver additional therapeutic options to the market.

Martin Brenner, Randy Maddux, and **Steven King,** iBio

Q: Why is the *FastPharming* System so well-suited for the discovery, development, and manufacturing of oncology therapeutics?

Martin: As we know, monoclonal antibodies are a critical component in the cancer immunotherapy toolbox. Plants can make an extensive range of proteins, and the *Nicotiana benthamiana* plants we use in our ***FastPharming* System** express antibodies particularly well. We have been able to make virtually any antibody that has been handed to us. Other systems have difficulty expressing some antibodies and sometimes cannot express them at all.

Q: I've heard concerns about plants producing proteins with glycosylation patterns different from those of humans—basically creating allergic reactions in humans. Is this a problem?

Martin: Glycosylation of biopharmaceuticals has a pivotal role in their safety and efficacy

by modulating a wide range of drug properties, including immunogenicity, half-life, and effector functions. From a regulatory perspective, human-compatible and consistent glycosylation is required for a safe and efficacious drug product. Controlling glycosylation has been a long-standing challenge that requires a detailed understanding of the pathways in mammalian cell culture processes.[2]

We can control glycosylation patterns very effectively in our *FastPharming* System® by using our ***Glycaneering* Technology™**. This allows us to grow plants that add or remove specific sugars, and we have very robust analytical capabilities to demonstrate uniformity.

As noted above, uniformity is often crucial in drug discovery, and, as I said, we can deliver that. However, when working in some therapeutic areas—like immuno-oncology—we sometimes want those antibodies to be a little foreign in a certain place. We want them to look different than the body's own antibodies so that they attract an immune response that is guided against the targeted cells.

This is precisely the strategy we are taking with the new candidate we just added to our **oncology pipeline, IBIO-101**. We are changing the antibodies so that the warheads—where the molecule binds to the regulatory T cells (T_{reg}) —are like a human antibody, but we've removed a specific sugar to enable the patient's immune system to recognize IBIO-101 as a foreign molecule and kill the attached T_{reg} cell. Without these immunosuppressive T_{reg} cells, the tumor cells can no longer hide from the immune system and will be vulnerable for clearance.

Many great therapeutic possibilities don't move forward because proof-of-concept studies consume too much time and money, leaving few resources available to produce product for toxicology studies and later-stage development work. By using the *FastPharming* System® and leveraging the expertise of our scientific team, we can advance programs more quickly—for less money—leaving resources to advance the asset along its development path.
–Martin Brenner

Q: Discovery and development speed are critical for any therapeutic area; oncology certainly being no exception. How does *FastPharming* expedite discovery and development timelines?

Martin: When you start a discovery process, you have an idea of what your target looks like, but you conduct a screening campaign and ultimately identify specific antibody sequences. Hundreds of molecules will present as potential candidates. The challenge becomes quickly producing these candidates so that you can evaluate them.

Producing the candidates can take quite some time in mammalian or other protein expression systems, so organizations typically have to prioritize and sequentially express such "hits." They'll produce the first ten possibilities, then the next ten, and so on.

In contrast, *FastPharming* allows us to make and further analyze basically everything that comes from our screening efforts in parallel, which saves time and resources and allows for more opportunities that could ultimately increase the odds of finding successful molecules.

Randy: *FastPharming* presents developers with an option: either be restricted by the time constraints of other protein expression systems or produce large numbers of potential antibody candidates in different plants simultaneously.

For instance, to produce product for further assessment using other protein expression systems, you typically use a small volume scale-down system such as the Ambr® Bioreactor, which is intended to emulate cell culture production at greater than thousand-liter scales. While this technology significantly improves cell culture development throughput, it remains limited to 24 or fewer simultaneous experiments.

In contrast, each of our plants is a bioreactor in the *FastPharming* System. As such, it is possible to infiltrate each plant with a different sequence, theoretically allowing you to produce an almost unlimited number of drug candidates.

By producing many candidates concurrently, we significantly increase the chances of identifying a molecule having the desired characteristics. And by the way, when we have that molecule identified, we don't have to worry about whether or not we've successfully emulated large-scale manufacturing conditions. That's because, while in R&D, we've already produced protein in our large-scale bioreactor — our plants. So, when we need large-scale quantities of protein, we just plant more of our green bioreactors.

Q: What about discovery and development costs working within the *FastPharming* System compared with cell culture-based systems?

Steve: Within a cell culture-based system, it generally requires at least ten months* to make a cell line and create a cell bank for each target. However, when working in the *FastPharming* System, we have the ability to move more quickly because we don't have to make a stable cell line for every product candidate. We simply refine the *FastPharming* vector through rapid synthesis and transfect the plants—it takes about seven weeks to produce proteins for further analysis, with no cell line engineering required. This approach represents not only tremendous time savings but also significantly reduced development costs, given that the process doesn't have to be scaled up to produce more material for clinical trials; we just grow more plants.

Randy: It all comes down to *FastPharming*'s ability to do transient transfection versus having to stably transfect mammalian, insect, bacterial, or other types of cells.

Q: It seems as though *FastPharming* provides an ideal framework for the scientists working in the iBio Drug Discovery Center, as well as for other biotechs that might partner with iBio. Is this the case?

Martin: We're hiring top scientific talent for our Drug Discovery Center. Moreover, we're

thinking about the team as an assembly of scientific entrepreneurs. We are recruiting scientists who dream of starting their own biotech and understand the impact of moving a project forward because patients are waiting. Then, we give them the freedom and latitude to create and discover.

Our decisions are purely data driven. The outcome of every experiment triggers an assessment to determine if a program is viable and should be rapidly advanced or if our efforts need to be re-focused. This allows our team of entrepreneurial scientists to take accountability for their programs and rapidly move the most promising ones forward into IND-enabling studies.

We also offer an excellent resource for other biotechs in early development. Many great therapeutic possibilities don't move forward because proof-of-concept studies consume too much time and money, leaving few resources available to produce product for toxicology studies and later-stage development work. By using the *FastPharming* System® and leveraging the expertise of our scientific team, we can advance programs more quickly—for less money—leaving resources to advance the asset along its development path.

Whether a molecule comes from the result of our team's discovery and development work or that of a client or partner, our driving mission is to take more shots on goal. Ultimately, we use the resources available to explore as many promising therapeutic candidates as possible.

Q: Some cancers have very small patient populations. Do you view *FastPharming* and the iBio Drug Discovery Center playing a role in helping to develop therapies for rare forms of cancer?

Randy: While numerous factors would need to fall into place, and there are several obstacles to address, I believe iBio can play a role in developing and manufacturing medicines for very small patient populations.

I envision the possibility of working with leading cancer centers or pioneering oncologists who can conduct investigator-sponsored trials, with the proper safety measures in place, of course. We anticipate the *FastPharming* system can produce drug candidates of human-use quality much more quickly than other protein expression platforms, making medicines that are right-sized for a given patient population much more feasible.

There would need to be some rethinking of regulatory constructs, clinical oversight, and institutional review board approaches, and, obviously, these changes will take time. However, the speed, versatility, and economy that *FastPharming* delivers makes serving very small patient populations a practical possibility.

The speed and economic feasibility of serving very small patient populations is exciting, as these patients don't have time to wait for therapeutics developed and manufactured with the platforms being utilized today. If successful, we could help save a lot of lives, and the thought of iBio playing a role is exciting.

Q: Combination therapeutics are obviously commonplace within the oncology space. Are iBio and *FastPharming* well-positioned to play a key role in offering combination cancer therapies?

Steve: Absolutely, improving treatment options for cancer patients is all about combining standard of care with new approaches. Even with the recent breakthroughs in immuno-oncology, it is still only the minority of patients that receive the biggest benefit. The versatility and speed of the *FastPharming* System make it possible to generate a number of candidates very quickly for screening, and once a lead is selected, moving the candidate forward can be equally fast, which is a real strategic advantage for iBio and its partners.

Q: IBIO-101 is a recent addition to your oncology pipeline. What makes this product competitive with an anti-CD25 candidate such as Roche's, and how does this product play into the company's overall drug discovery and development model?

Randy: In the first stages of our development process, we can evaluate interesting targets and apply our *Glycaneering*™ Technology to create molecules with improved glycosylation patterns, including afucosylation for greater ADCC. In the case of our lead oncology candidate, IBIO-101, CD25 is a well-validated target. There are published papers on this target, and now we're deploying our own top-notch scientific team with the goal of advancing the therapeutic's path to market. Previous CD25-targeting attempts proved ineffective because these approaches also depleted effector T cells (T_{effs}), which are critical for killing cancer cells. IBIO-101 improves upon this approach because it is designed to selectively remove regulatory T cells (T_{regs}) while allowing T_{eff} cells to do what they do best—eliminate cancerous cells.

> Cell culture–based systems don't allow developers to move fast enough— they are just too limiting—and exploring the number of therapeutic possibilities needing evaluation is simply too expensive. New protein expression platforms must be utilized to provide patients with needed solutions, and the *FastPharming* System® is exceptionally good at producing antibodies.
> **–Randy Maddux**

Martin: Drug discovery and drug development are risky pursuits, and efforts fail about 90% of the time. iBio is using novel technologies that allow us to flexibly pursue targets in a manner that is both faster and less expensive. We're looking for well-validated opportunities, ideally where others have established clinical proof of concept. This allows us to leverage blueprints other developers have created, learning from their mistakes, which should shorten our path to a clinical proof of concept even more.

Q: Do you have any closing thoughts?

Martin: As the scientific community continues to discover new ways cancers evade treatment, developers must quickly respond. Additionally, there are plenty of known mechanisms requiring more therapeutic options. The iBio Drug Discovery Center is in an exciting position to advance therapeutics to the market quickly.

Randy: Cell culture–based systems don't allow developers to move fast enough—they are just too limiting—and exploring the number of therapeutic possibilities needing evaluation is simply too expensive. New protein expression platforms must be utilized to provide patients with needed solutions, and the *FastPharming* System® is exceptionally good at producing antibodies.

Also, I believe the biotech industry needs to be concerned about the substantial carbon footprint contribution of single-use cell culture systems. One study concluded that the biologics industry is significantly more emission-intensive than the automotive industry,[3] and people are looking more seriously at sustainable solutions like *FastPharming* than ever before.

Steve: The iBio Drug Discovery Center is exciting because it brings together top-notch scientists, interesting oncology targets, and *FastPharming*'s ability to rapidly express antibodies and other proteins. Oncology is a diverse disease that requires the ability to rapidly adapt, select, and advance, which is the strength of the *FastPharming* System. ■

REFERENCES:

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* Mammalian cell culture timelines given above are for illustrative purposes only based upon competitive data from publicly available sources. Actual timelines may vary.

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Dr. Brenner, iBio's Chief Scientific Officer, has a strong track record of success heading drug discovery and development teams at several of the world's leading pharmaceutical companies, including AstraZeneca, Eli Lilly and Company, Pfizer Inc., and Merck Research Laboratories. Most recently, Dr. Brenner served as the CSO at Pfenex Inc., where he established and advanced a pipeline of biologics programs in oncology and metabolic diseases. Previously, Dr. Brenner served as the CSO at Recursion Pharmaceuticals, Inc., a company focused on accelerating drug discovery by integrating technological innovations across biology, chemistry, automation, machine learning and engineering.

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Mr. Maddux, iBio's Chief Operating Officer, has more than 25 years of global biologics drug development and manufacturing, business development, and relationship management experience. During his career, he has served in key roles supporting the licensure and commercial launch of several biopharmaceutical products. Before joining iBio in December 2020, Mr. Maddux was SVP and Chief Manufacturing Officer at Aptevo Therapeutics. Previously, he was VP and Site Director at GlaxoSmithKline, where he led the largest biopharmaceutical development and manufacturing site within the GSK manufacturing network and was instrumental in launching a successful contract development and manufacturing (CDMO) services business.

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Steven King
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Steven King, an advisor to iBio, has over 20 years of experience in advancing novel biologics for the treatment of cancer from discovery through late-stage clinical development, including cGMP manufacturing operations to support clinical and commercial products. His experience includes over 17 years serving as president, CEO, and board member of publicly traded biotechnology companies, including Peregrine Pharmaceuticals, Avid Bioservices, Oncotelic, and Mosaic IE. His passion is to help patients suffering from cancer and other life-threatening diseases through the development of novel production platforms and biologics that will improve and extend their quality of life.

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