PLANTING THE SEED FOR SPEED

iBio's commercial-scale biotherapeutics manufacturing facility built speed and flexibility into every step – from initial design and construction to daily operations

By Karen Langhauser, Chief Content Director

YOU PROBABLY won't find a lot of presidents of successful contract manufacturing organizations gleefully operating the forklift inside the manufacturing plant, but Barry Holtz is no ordinary leader — which is quite fitting because iBio is no ordinary biopharma facility.

"Anyone can build monuments," says Dr. Holtz. "But the fun comes in seeing them in action — being the one to push that green button. Building systems that work is the greatest reward."

The iBio facility is a testament to what can be accomplished when efficiency is built into the design from the start. Formerly operated by Caliber Biotherapeutics, the Bryan, Texas, facility was designed, constructed and fully functional in less than 18 months from groundbreaking. The facility boasts meticulous design considerations ranging from concepts as simplistic as locating parking lights across the street to avoid insect infestation to the sophistication of an automated, multilevel growing environment that uses proprietary LED lighting.

The 139,000-square-foot building, conveniently located in the "bio-corridor" abutting the campus of Texas A&M University, was developed with funding from the Defense Advanced Research Projects Agency (DARPA) as part of the Blue Angel project. The Blue Angel project focused on new ways to produce large amounts of high-quality, vaccine-grade protein in less than three months in response to emerging biological threats. iBio's proprietary plant-made pharmaceutical technology was licensed to Caliber for the project, which demonstrated successful use of the technology on a commercial scale.

In January 2016, iBio, together with investors Eastern Capital Limited, purchased the Caliber facility and formed iBio CMO — a contract manufacturing organization for the development, scale-up and large-scale manufacturing of biologicals.

This summer, the U.S. FDA granted Orphan Drug Designation to iBio's lead investigational biotherapeutic product, iBio-CFB03, for the treatment of systemic sclerosis. Additionally, iBio recently announced the successful application of its plant-based technologies to achieve the first milestone in its commercial development agreement with AzarGen Biotechnologies for the development and manufacture of an improved surfactant protein for the treatment of neonatal respiratory distress syndrome (RDS).

THE TECHNOLOGY

iBio's primary research, development and manufacturing system employs vacuum-infiltrated *Nicotiana benthamiana* plants — tobacco relatives indigenous to Australia — grown in a fully contained, hydroponic system for transient expression of recombinant proteins. In plain English, once the plants have been infiltrated with agrobacteria, the bacteria hijacks the protein-making functions of the plant and the plant leaves replace a traditional bioreactor, becoming a "protein factory." The plant biomass is then harvested and the resulting extract is purified through a downstream process similar to what you'd see in a typical biopharma facility. (See sidebar)

The iBio CDMO facility can grow over 4 million plants hydroponically as "in process inventory" and can deliver over 300 kilograms of finished therapeutic protein per year if run at full capacity. Technology transfer and scale-up is vastly simplified because the need to adapt cell lines to the scale of the bioreactor is eliminated in the plant-based process. Simplification also equates to customer cost-savings. As a CDMO using proprietary plant-made biopharmaceutical development and manufacturing technologies, iBio can take a potential protein

Each G-CON POD is served by its own independently controlled, redundant HVAC system.

into commercialization faster and more cost-effectively than traditional CDMOs. A recent, in-depth, technoeconomic peer-reviewed paper reported the cost of goods for a monoclonal antibody was estimated at $160 /gram at a yearly production rate of 300 kg per year. Economical production at this smaller scale is difficult in CHO. And yet, the great majority of mAbs coming forward have smaller total production requirements, between 10-120 kg.

SMART DESIGN

The building was designed in a parametric building information management (BIM) and estimation model using advanced three-dimensional, computer-aided-design (CAD) systems. The BIM process involves creating digital representations of the physical and functional characteristics of the facility. Several sophisticated software systems, such as D-Profiler (a parametric 3D CAD-based estimating tool), Revit object-based 3D CAD design system, Navisworks for 'in silico' design conflict resolution and Synchro Design timeline planning were utilized.

This "virtual construction" allowed the design team to work out design problems and inefficiencies prior to actual construction. The 3-D design software enabled the team to visualize concepts and simulate how the designs would perform.

COLLABORATIVE DESIGN

The manufacturing facility project was design-build. Design-build, often seen as a faster, more cost-effective alternative to traditional design-bid-build methods, enables the design-build team to work under a single contract with the project owner to provide design and construction services. "One entity, one contract, one unified flow of work from initial concept through completion — thereby re-integrating the roles of designer and constructor," explains the Design-Build Institute of America.

The project design team was led by Beck Architecture, with preconstruction and construction teams from Beck Group. The design group also included EEA Engineering (mechanical and process) and a team from G-CON Manufacturing — the makers of autonomous, cleanroom

IBIO PLANT-BASED TECHNOLOGY: HOW IT WORKS

1. iBio scientists engineer vectors containing the target sequence within a viral replicon.
2. The vector is transferred to an Agrobacterium host that efficiently introduces target DNA to the plant cell nucleus.
3. The viral replicon directs the production of large amounts of target-specific messenger RNA in plant cells, which is translated into protein by the plant's own machinery for several days.
4. Once the plants have been infiltrated with agrobacteria, the viral sequences of the launch vectors, along with the cloned target sequences, are massively amplified through the action of virally encoded enzymes. Translation of these recombinant viral vector mRNAs can result in the accumulation of gram quantities of target protein per kilogram of fresh plant tissue in less than a week.
5. The plants accumulate high levels of target protein in their leaf and stem tissue. This expression of recombinant protein is termed "transient" expression because the target gene sequence is expressed as protein for a fixed period of time, and the foreign genes are not incorporated into the plant chromosome to result in the creation of transgenic plants.
6. The plant biomass is harvested, homogenized and clarified to produce an extract containing the protein of interest. Proteins are further purified as required using conventional separation and chromatography steps.

PODs. Beck Architecture was the owner of the BIM model. The design group worked directly with the mechanical and electrical contractors, Britt Rice Electric and Garrett Mechanical, who were also familiar with Revit.

During the build, the lead architect, lead mechanical engineer, CAD specialists in Revit, Navisworks, and Synchro were onsite as was the iBio QA team and Barry Holtz himself. This onsite collaboration, according to Holtz, allowed the team to "process change orders in hours instead of days and design many of the systems 'on the fly' — including the proprietary lighting (which was being developed during the build) and the laminar flow wall optimization. "The design-build process, combined with the skill of the team and direct participation of the owners, allowed this technical achievement to be made real and operational in record time," reflected Bryan Jones, principal and lead architect, The Beck Group.

BUILDING IN PROCESS EFFICIENCY

The facility's vertically designed, space-efficient grow rooms feature 14 levels of racks of *N. benthamiana* plants growing under iBio's proprietary LED lights. Due to the 40-foot height of the ceilings and the need for plants to be maintained at uniform temperatures, the grow rooms had to be constructed as horizontal laminar airflow rooms — in fact, the facility boasts the two largest laminar flow systems in the world. The growing rooms circulate very large volumes of air with low temperature differentials over the 100 feet between the walls and can maintain a temperature differential of less than +/- 2 degrees F.

EEA Consulting Engineers were enlisted to assist in the construction of perforated plate supply and return air plenum walls on each side of the grow rooms. Computational Flow Dynamics (CFD) modeling, which uses computational software to visualize how gas flows, was used to design specific perforation patterns and prove the concept would work prior to installation in the field.

iBio jointly designed its own custom LED-based lighting array fixture with an LED lighting provider. LED lighting provides multiple advantages over standard fluorescent lighting. Most importantly, it enables higher environmental temperature uniformity at a much lower energy input.

The facility's novel LED lighting system has proven to reduce germination and pre-infiltration growth time from 6 weeks to 5 weeks, as well as reduce energy costs. "A photon is a terrible thing to waste," jokes Holtz, as he points out that the LED lighting provides 166 percent more photic energy on plants than conventional lighting, for 66 percent of the energy cost.

All downstream processing occurs in G-CON's groundbreaking GMP manufacturing POD technology.

Higher environmental temperature uniformity is achieved with LED lights, at a much lower energy input. Lights are also low voltage and waterproof.

The completely self-contained units, which are equipped with air bearings that enable them to be easily moved into place, provided a truly flexible, cost-effective approach to construction. The POD shells were transported to the iBio site by flatbed truck and moved in and connected to the building in only a matter of hours.

The PODs provide iBio with "ultimate flexibility," says Holtz, enabling rapid reconfiguration of the downstream processes without disruption of the ongoing operations in the facility. The PODs offer a complete control system, utilizing Rockwell ControlLogix programmable logic controllers. Each POD is served by its own independently controlled redundant heating, ventilating and air conditioning system. The PODs recapture and reuse heated and cooled air from their hosting facility for enhanced energy efficiency.

HANDS-ON APPROACH

Under the careful supervision of Holtz and his team, every detail of the facility was scrutinized, optimized and customized. "In this business, your hands need to be connected to your head," says Holtz. Coming from a world-renowned pioneer in plant-made pharmaceuticals who also got behind the wheel of the bulldozer during groundbreaking, this sentiment couldn't be more believable.

The resulting execution of an 18-month build is a shining example of design innovation, rapid facilities systems integration and highly efficient construction management — with the added bonus of the ability to develop medical countermeasures to rapidly respond to biothreats and outbreaks.