Waisman Biomanufacturing

Experience cGMP Quality with Waisman Biomanufacturing

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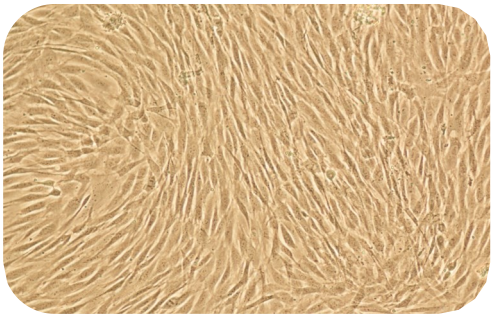
MSCs Enter Clinical Trials for Lung Transplant Rejection

A lung transplant is a last-resort option for the treatment of severe lung disease due to risk of rejection and limited donor availability. Following lung transplants, the most significant limitation of long-term patient survival is the development of bronchiolitis obliterans syndrome (BOS). There is near 100% mortality if the patient develops treatment refractory (grade 3) BOS and does not qualify for a second transplant. BOS is a type of airflow obstruction measured by a loss of forced expiratory volume (FEV1) greater than 20% for three or more consecutive weeks and not attributed to any known causes, such as infection or acute rejection. According to the International Society for Heart and Lung Transplant (ISHLT) registry, 48 percent of allograft recipients develop BOS after five years and 76 percent after 10 years. Currently, the most common treatment, intravenous corticosteroids, has not demonstrated a high-level of success in treating grade 3 BOS, so a more effective alternative therapeutic approach is needed.

With support from the National Heart, Lung, Blood Institute's (NHLBI) Production Assistance for Cellular Therapies (PACT) program, Dr. Abba Zubair and colleagues at the Mayo Clinic of Florida partnered with Waisman Biomanufacturing (WB) and other University of Wisconsin collaborators to conduct the necessary translational research and IND-enabling animal studies which would allow them to move into early stage clinical trials with the goal of treating BOS. The study was largely driven by results from a bleomycin mouse lung injury model study, which demonstrated the ability for Mesenchymal Stromal Cells (MSCs) to infiltrate and engraft in the injured lung (Ortiz et al., 2003).



Bone-Marrow Derived MSCs

This study also showed significant reduction in bleomycin-induced inflammation and paved the way for further evaluation of MSCs as a therapeutic treatment for lung injury.

To translate these early findings and perform the required safety studies,

(continued on page 2)

Staff Highlight: Cell Therapy Team

The UW PACT team includes Diana Drier, who coordinated the efforts of scientists from across the University of Wisconsin-Madison including Neehar Bhatia and Connor Lyons (manufacturing), and Laurie Larson (QC) at Waisman Biomanufacturing (WB). Additional expertise was provided by partners at the Carbone Cancer Center Flow Center including Debra Bloom (Peiman Hematti's lab) for immunopotency assay development and Dagna Scheerar who performs flow cytometry assays on MSCs and other products. The team also included John Centanni, regulatory support, and Kari Thostenson, fiscal program management.

The Zubair project was initiated as part of the PACT program in 2011. With the goal of producing large numbers of MSCs required for patient dosing and manufacturing a consistently high quality product from lot to lot, the team faced several challenges. Some of these hurdles included evaluating culture medium to optimize cell expansion and minimize variability while also establishing a large scale culture format that was cGMP compliant. WB also developed final product release testing assays for both the identification of MSCs and assessment of their biological activity.

"It was truly a team effort and well worth the hard work as recent feedback from Dr. Zubair following his first patient infusions has been positive. It's especially rewarding to be a part of a group that can directly impact the lives of people suffering from debilitating or potentially fatal diseases."
– Diana Drier

Recent and Upcoming Conference Attendance

World Stem Cell Summit December 3-5, 2014 San Antonio, TX	**Phacilitate Bioleaders Forum** January 26-28, 2015 Washington, D.C.	**Wisconsin Stem Cell Symposium** April 15, 2015 Madison, WI
Attendees will learn about the latest in translational research while building new relationships at small group events. worldstemcellsummit.com	The Bioleaders Forums brings together experts from the pharma, vaccines and biotech communities "to deliver the ultimate in strategic knowledge exchange and networking through flawless, personalized service." www.bioleaders-forum.com	Brings together leading researchers who are working in the areas of limb development and regeneration and stem cells and tissue engineering. http://www.btci.org/stemcell/default.html

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Have a festive holiday and a wonderful New Year!

the PACT animal study team, consisting of Marlowe Eldridge, Rudolf Braun, Jill Koch, Eric Schmuck, and John Centanni, first designed an updated rat lung injury model using multi-dose intratracheal bleomycin administration. This design was intended to mimic BOS grade 2 and 3 with both acute and long-term endpoints. These studies also provided the data to support clinical dosing.

In parallel, Waisman developed manufacturing processes and Quality Control methods for large scale human bone marrow-derived MSCs. The process begins by collecting human bone marrow from donors by following the 21CFR1271 subpart C for donor eligibility criteria. Bone marrow is collected, washed, and processed to isolate MSCs which are expanded to a low-passage Master Cell Bank (MCB). Vials from the P=2 MCB are further expanded in Cell Factories prior to cell harvest and cryopreservation for use in the clinical trial. WB also manufactured several MSC MCBs from different donors to support other programs and to gain an understanding of donor-to-donor variability. These banks also allowed the development of QC methods to support clinical investigation. Standard tests for human cell identity, sterility, and other safety measures were well established and new methods for MSC identity by flow cytometry were developed. Additional potency assays to support the proposed immunomodulatory mechanism of action were also developed.

Cell culture manufacturing specialists

Waisman Biomanufacturing also manufactured the clinical-grade MSC product for Dr. Zubair's clinical trial and provided CMC support for Dr. Zubair's IND application. After receiving IRB and FDA approval, Dr. Abba Zubair and his collaborators at the Mayo Clinic in Florida initiated a Phase 1 human clinical trial for BOS following lung transplant in November 2014. The study administers the MSC product via intravenous infusion. To date, two patients have been treated out of the 9 planned for the Phase 1 study. We look forward to following the clinical study as it progresses and extending our collaboration and capabilities to other investigational uses.

The Waisman team has been very supportive and a key partner. They ensure we continue to achieve our research goals by supporting our IND application and manufacturing the clinical grade stem cells needed for our clinical trials. Without the knowledge and experience of the Waisman team we would not have made any progress in obtaining our IND approval from the FDA and initiating the clinical trials. We look forward to continuing our great partnership.

—Dr. Abba Zubair

References:

Ortiz, LA, et al. (2003). PNAS. 100 (14) 8407-8411.

MSC and Cell Therapy Services

Waisman Biomanufacturing (WB) has established processes for the production of cGMP bone-marrow derived mesenchymal stromal cells (MSCs). Partnering with WB grants access to our established manufacturing processes, QC methods, and established cell banks. WB's platform manufacturing process and custom QC methods include surrogate potency assays for immunosuppression, or custom assay development based on your clinical needs. These platform and custom services are part of a comprehensive support program offered at Waisman Biomanufacturing. Contact us to find out if our services are right for you.

Other cell therapy services include:

- Derivation or isolation of new human and other mammalian cell lines
- Culture, expansion, and harvesting of cells for use in clinical trials
- Cell banking and characterization
- Complete QC testing including cytogenetics
- Full cGMP documentation and support

Recap of Fall PACT Webinar

On September 25th, WB Director Derek Hei, Ph.D. participated in the PACT webinar *Challenges and Problem-Solving in Cell therapy Product Development*. Dr. Hei shared several key challenges faced in cell therapy product development that were discussed in more detail in relation to a Natural Killer-based cell therapy product for pediatric neuroblastoma:

- Autologous vs. allogeneic cell therapeutics
- Manufacturing costs – cost of goods, Quality Control testing, cleanroom facility time
- Scale-up vs. scale-out
- Patient/donor variability and impact on manufacturing processes

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