The Focus is on Patients at the University of Pittsburgh Cancer Institute Immunologic Monitoring and Cellular Products Laboratory:

Interview with Lisa Butterfield, PhD, Director

Kara Wacker, MBA, RAC, Director of Operations
Foundation for the Accreditation of Cellular Therapy
Omaha, NE USA

FACT is interviewing personnel at facilities FACT-accredited for more than minimal manipulation processing activities to share their knowledge and experience with members of ISCT. We were pleased to first talk with Lisa Butterfield, PhD, the Director of the Immunologic Monitoring and Cellular Products Laboratory (IMCPL) of the University of Pittsburgh Cancer Institute. She explained the benefits of her facility and its FACT accreditation in terms that resonate with those passionate about bringing cell therapies to the bedside: patients are the priority and the clinical mindset brings results.

IMCPL’s Unique Structure Supports Translational Research
The IMCPL facility is comprised of three laboratories. One is the Immunologic Monitoring Laboratory, which consists of about 10 people performing blood and tumor banking and immune assays for patients on immunotherapy vaccine trials and other biologic and small molecule inhibitor trials. The Tissue Procurement Facility focuses on tissue banking in support of clinical trials. The Cellular Product Laboratory focuses on personalized medicine and investigator-initiated trials. This laboratory has three cleanrooms and is staffed by approximately nine people.
The University of Pittsburgh has a long history of developing dendritic cell-based vaccines produced with patients’ monocytes derived from leukapheresis products. This is the IMCPL’s main area of focus. Each trial is unique based on the targeted cancer, the antigens used to promote anti-tumor effects, and the type of dendritic cell (DC) cultured.

The IMCPL also collaborates with external companies on unique stem cell- or tumor-based cellular products. The facility provides a direct service and tracks, stores, processes, manufactures, formulates, and releases these products based on the external companies’ Standard Operating Procedures (SOPs). When asked how the university made the decision to run these products through the IMCPL versus the pharmacy, Dr. Butterfield explained that the facility can provide liquid nitrogen storage and has the expertise to handle a wide variety of cellular products. The pharmacy does have freezers and, from a chemistry standpoint, can formulate a variety of products, but the IMCPL can provide many more services specific to cells. The facility has been able to handle everything the external companies have needed. These include endotoxin and mycoplasma testing and cell surface phenotyping by flow cytometry. They can also confirm that products produce certain cytokines by saving supernatant and undertaking cytokine and chemokine assays.

A Champion of Clinically-Oriented Researchers

Dr. Butterfield believes the IMCPL is attractive to clinically-oriented researchers. “Our researchers want to bring their intellectual property and scientific endeavors out of the laboratory and into the clinic using specialized facilities. IMCPL can take products out of the research lab and into the GMP context of appropriate mediums, assays, and release testing.” The facility’s support structure not only assists researchers with developing aspects of clinical protocols, but assists with the Chemistry, Manufacture and Controls (CMC) section of INDs. “At IMCPL, researchers do not have to reinvent the wheel. That is very important and draws a lot of translational researchers to our facility.”

IMCPL supports researchers’ grant applicants and much of the work is funded by the National Cancer Institute (NCI). The facility helps develop necessary SOPs and budgets, and provides assurance to funding organizations about the feasibility and quality of the research based on their centralized facility and accreditations. “That goes a long way towards obtaining grant funding. Reviewers can see we are accredited and know they can remove that from their list of concerns and focus on the scientific ones.” The fact that the facility, although it is a research-based laboratory, was able to meet the rigor of FACT accreditation helps with grant applications and institutional support. “That is absolutely a benefit of FACT accreditation.”

Collecting outcome and safety information is unquestionably an important and sometimes difficult aspect of clinical trials. At the University of Pittsburgh, Dr. Butterfield or another member of the IMCPL attends monthly clinic and safety meetings of the disease-specific programs they serve. This ensures communication between the clinic and the lab flows clearly and smoothly. When participating in multi-center trials, the IMCPL produces only those products that will be administered to University of Pittsburgh patients to minimize liability and provide confidence that it will receive outcome and safety data.
Bringing Hope to Patients with Melanoma

Melanoma is a difficult cancer to treat, and patients with Stage IV melanoma have little hope for survival. Dr. Butterfield is hoping to change that with a melanoma cancer vaccine. She is the IND sponsor of a trial using a replication-deficient adenovirus to genetically engineer the patient’s autologous DCs to produce melanoma antigens. The second patient has just been enrolled.

To create the vaccine, patients first undergo a three-hour leukapheresis procedure. The lymphocytes and monocytes are banked, and a portion of the monocytes are cultured in CellSTACK® flasks for six days with GM-CSF and IL-4 to produce DCs. Those cells are matured with interferon gamma and LPS for 24 hours and transduced with a replication-deficient adenoviral vector that encodes 3 full-length melanoma tumor antigens, Tyrosinase, MART-1, and MAGE-A6, resulting in DCs that produce high levels of all three proteins. The approach of using full-length sequences allows the presentation of restricted class I and class II epitopes by DCs from any HLA-type patient and recognition by both CD4 helper and CD8 cytotoxic T cells and activation of Natural Killer (NK) cells.

Patients are given three vaccine cycles, and all three doses can be manufactured at one time. The first vaccine can be delivered to the patient fresh or cryopreserved. The other two are cryopreserved, then thawed and administered at two-week intervals. For Dr. Butterfield’s trial, the patients are going to be randomized to receive one month of high dose interferon alpha as a boost, versus observation.

The scientific question is, “Can we not only activate multiple CD8 and CD4 cytotoxic and helper T cells to directly attack the cancer cells that produce those tumor antigens, but can we also promote spreading of the immune response to a broad array of antigens?”

The clinical question encapsulates what so many researchers are working towards: “Can we help Stage IV melanoma patients, no matter what they have been pre-treated with or their HLA type, with this vaccine and cause tumor regression and increase overall survival?”

A Direct Effect of a Controlled Facility, Qualified Researchers, and Accreditation

Despite the IMCPL’s readiness to initiate the trial for this vaccine, it faced a significant challenge when the NCI pulled funding for the national gene vector lab and the Rapid Access to Investigational Drugs (RAID) program. “There was no longer any NCI-supported service to make the recombinant vector for our trial despite what had existed when we got the funding,” Dr. Butterfield explained. “We had funding for our trial and no funding to produce this virus at clinical grade.”

The IMCPL’s response was to present the Food and Drug Administration (FDA) with compelling evidence of their qualifications to produce the viral vector: an exceptional facility with fully-accredited cleanrooms and processes. The FDA worked with the IMCPL and suggested the most critical steps to produce the virus. Their advice was that if the facility was thoughtful about this production and it is clean and safe with all the appropriate release testing, then it does not have to be produced in GMP-grade virus production; if it comes close enough, it can be used for ex vivo transduction of autologous cellular products. “With the FDA input and our accredited facilities, we were able to deal with the limited support we were going to have from the other NCI sources and get this to the clinic anyway.”
IMCPL’s Experience with the FACT Accreditation Process and the Resulting Benefits

Dr. Butterfield felt that the FACT accreditation process went smoothly at her facility. “We were seeking our first FACT accreditation and as with every new inspection there were a couple of unexpected things.” The facility was only inspected once for its initial accreditation and had minimal information to submit afterwards to verify compliance with the FACT Standards. “We had great support from FACT in terms of preparation, and we also have a Quality Assurance Manager external to the laboratory, Debe Griffin. She is very informed and helped us organize our team to prepare.” People were given tasks such as labeling requirements and SOP updates. Everyone worked as a team to achieve the accreditation. Most of the laboratory personnel come from clinical laboratories and had no worries about documentation, sign-off, and controls. “It was a nice process and we are really pleased to be a part of the FACT team and have the benefit of the high-end certification of our processes.”

In addition to the benefits of FACT accreditation for grant applications and FDA confidence discussed previously, the accreditation has also helped the IMCPL’s relationship with the University of Pittsburgh Cancer Institute. The Institute acknowledged the facility’s ability to gain a rigorous accreditation in a research-oriented environment, and was very supportive of the effort. The accreditation has in turn helped the IMCPL provide support to clinical investigators who wish to participate in trials from inside and outside the institution. “It’s really a win-win.”

Dr. Butterfield offered her thoughts on why researchers should desire FACT accreditation and be comfortable with their ability to continue progress on their studies. “Number one is patient safety and number two is controlling every variable we can control to produce the best quality products,” she said. “I don’t think any of the FACT requirements have hindered our ability to innovate and to bring new studies to the clinic at all.” In fact, she thinks FACT accreditation is a selling point for staff employed by the facility. “What I think personnel enjoy in this laboratory is the ability to do different things every day, to learn new techniques, to bring new things to the clinic, and to know they are doing those things in the best, highest quality, and safest way possible.”

This philosophy of excellence and motivation is no doubt driven by Dr. Butterfield’s leadership. We appreciate her willingness to further influence the field by allowing us to highlight her facility’s achievements with the ISCT membership, and look forward to her future success for the benefit of patients.

About Lisa Butterfield, PhD, Director

Dr. Butterfield began her graduate work in gene therapy and obtained a PhD in molecular biology at the University of California Los Angeles (UCLA) in 1993. Through her studies, she learned about molecular cloning and sequencing and RNA and DNA analysis. Her first postdoctoral work was in cellular immunology, in which she used techniques learned through her education to study immunological subsets, particularly NK cells. In 1995, she began her second postdoctoral study in cancer gene therapy. This remains the focus of her career.
After 17 years at UCLA, Dr. Butterfield sought an independent research position and landed at the University of Pittsburgh. In 2003, she chose to start her own laboratory at the University of Pittsburgh in part because the IMCPL existed under the founding director, Theresa Whiteside, PhD. Dr. Butterfield was initially a user of the IMCPL. She gained experience in immunologic monitoring and, after a term as associate director, became the director of the IMCPL. Today, her research laboratory seeks new immunotherapy biomarkers and therapies, and IMCPL produces those vaccines and other cellular products for the University of Pittsburgh.

About the Immunologic Monitoring and Cellular Products Laboratory

The University of Pittsburgh Cancer Institute (UPCI) Immunologic Monitoring and Cellular Products Laboratory (IMCPL) is responsible for therapeutic cell product generation, serial monitoring of immunologic functions in patients with cancer who are treated with biologic therapies, and banking of blood and tissues for patients on clinical protocols. The IMCPL plays a critical role in supporting novel investigator-initiated immunotherapy trials at UPCI. For a complete list of the IMCPL’s extensive services, visit http://www.upci.upmc.edu/imcpl.

This project used the UPCI IMCPL that is supported in part by award P30CA047904.

About FACT

FACT is committed to high quality patient care and laboratory practice in cellular therapies and regenerative medicine. The non-profit organization promotes improvement and progress by establishing minimum standards, providing education, and inspecting and accrediting programs worldwide. Expert inspectors and the comprehensive accreditation program verify programs provide high quality cellular products and help to achieve desirable outcomes for patients. Since 2007, FACT accreditation has been used in determining the U.S. News & World Report rankings of cancer centers for the “America’s Best Hospitals” and “America’s Best Children’s Hospitals” lists.