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FEATURE ARTICLE
Bringing a Regenerative Medicine Product to Market: Contract Manufacturing Organizations Improve Probability of Success

WHAT'S INSIDE:

In This Issue

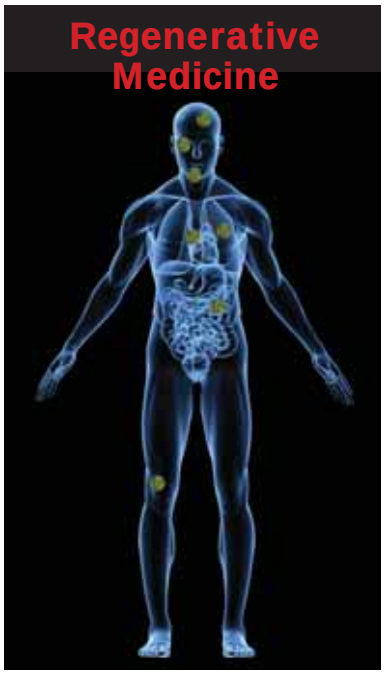

Photo Credit: Front Cover Image courtesy of Lonza Bioservices.

WEB RESOURCES

www.aabb.org | *American Association of Blood Banks*
www.celltherapy.org | *International Society for Cellular Therapy*
www.asbmt.org | *American Society for Blood and Marrow Transplantation*
www.ishrs.org | *International Society of Hair Restoration Surgery*
www.alliancerm.org | *Allliance for Regenerative Medicine*
www.bestcollaborative.org | *BEST Collaborative*
www.regenerativemedicinefoundation.org | *Regenerative Medicine Foundation*
www.phacilitate.co.uk/pages/cgtherapy/index.html | *Phacilitate*

UPCOMING EVENTS

Phacilitate Cell & Gene Therapy Forum *www.phacilitate.co.uk/pages/cgtherapy/index.html*	Washington, DC	Jan 24-26, 2011
ASBMT 2011 BMT Tandem Meetings *www.asbmt.org*	Honolulu, HI	Feb 17-21, 2011
17th Annual ISCT Meeting *www.celltherapysociety.org/index.php/meetings-events/isct-2011-annual-meeting*	Rotterdam, NL	May 18-21, 2011

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EDITOR'S CORNER

Mike Rice, Chairman & CEO, BioLife Solutions, Inc.

Happy New Year to our readers of BioPreservation Today®,

I'm writing to you from the Phacilitate Cell & Gene Therapy Forum 2011 in Washington, DC. 2011 marks the fifth consecutive year that BioLife has exhibited and supported this key scientific and business development conference. To coincide with Phacilitate's focus on the development and commercialization of novel cell gene, and tissue-based clinical products and therapies, this issue of BioPreservation Today (BPT) includes corporate profiles of several leading cell and gene therapy contract manufacturing organizations (CMO).

Those of us that have been in the regenerative medicine space for a while will recognize the familiar and trusted names of Cell Therapies Party, Ltd, Lonza, PharmaCell, and Progenitor Cell Therapy. New participants in this space are encouraged to consider the cost, quality, and schedule benefits that may be realized by outsourcing the production of your clinical product to one of these established CMOs.

Regarding our participation in the dynamic and high-growth regenerative medicine market, I'm happy to report that in 2010, our biopreservation media products were incorporated into the manufacturing and delivery processes of several new developmental stage regenerative medicine products. We estimate that our products are incorporated into 40 – 50 regenerative medicine products currently in the pre-clinical or clinical trial stage of development. 2010 revenue from this segment grew 34% from 2009, and accounted for about 31% of total 2010 revenue.

For those readers attending Phacilitate this year, please stop by our corporate exhibit. Also, feel free to visit our newly updated website at www.biolifesolutions.com. Thank you for your interest in our products.

Best regards,

Mike

CELL THERAPIES DELIVERS CLINICAL TRIAL AND COMMERCIAL SOLUTIONS

by Ray Wood, Managing Director

While the number of companies involved in cell therapies is growing, there are few organisations capable of delivering the combination of skills and expertise needed to translate such therapies into clinical practice. Contract manufacturers in the cell and tissue space must have an ability to understand and work with both the commercial imperatives and a complex regulatory environment.

One company that brings both world-best research and science together with astute commercial operations is Cell Therapies Pty Ltd, a Melbourne based organisation that has successfully delivered a range of services to clients from around the world.

Raymond Wood, Managing Director of Cell Therapies says, "The key to the Company's success is its attention to the needs of researchers and clinicians in combination with the commercial imperatives of bringing a new therapy to market. Clients require a multidisciplinary resource that can absorb and master the technical aspects and simultaneously provide services that facilitate and synchronise with the commercial imperatives of the business."

"We are often required to execute manufacturing for a clinical trial while advising on and developing functionally closed or automated processes for later stage trials or standard of care products. Cell Therapies is novel in that we are a standalone small company attached to an academic research centre (Peter MacCallum Cancer Centre)." Mr Wood said.

"The services we offer range from project planning through complex cGMP compliant manufacturing of cells and tissue to fully-integrated execution of clinical trials. We deliver our client's requirements under a combination of regulatory oversight from the Australian Therapeutic Goods Administration (TGA), US Food and Drug Administration (FDA) or the European Medicines Agency (EMEA)," he added.

The Company offers a range of competitive advantages to its cell therapy customers, including:

- Cost effective turn-key solutions for contract cGMP manufacturing
- Integrated clinical, research and manufacturing resources
- Navigation of the international regulatory framework leading to standard of care reimbursed treatments
- Proven capacity to work with GMO products
- Support for Pre-clinical through to Phase III trials
- Delivery of standard of care products.
- Five fully equipped and staffed clean rooms
- Project control from apheresis through production to cryo-preservation
- Advanced diagnostic imaging (PET/CT, SPECT/CT, 3T MRI), including cell tracking

Dr. Dominic Wall, Chief Scientific Officer of Cell Therapies explains: "Management of the regulatory interface is our focus. Our ability to efficiently translate the client's research to cGMP compliant documentation and produce the necessary validation data is key to our success."

To gain a better understanding of the range of services and capabilities offered by Cell Therapies, recent collaborations

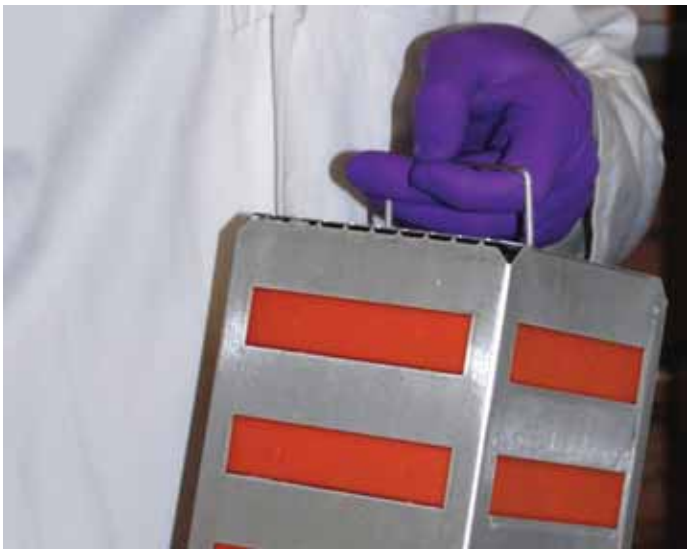
with local and international partners include:

- Long-time client Mesoblast Limited is committed to the commercialisation of proprietary adult stem cells, Mesenchymal Precursor Cells (MPC). Mesoblast has utilised Cell Therapies to manage the migration of its research into the cGMP environment, into the clinic for clinical trials and beyond through to a manufacturing license from the TGA.

- Professor Silviu Itescu, Executive Director of Mesoblast, said that "Cell Therapies has provided us with best practice services related to cGMP compliance and manufacturing. We continue to out source our requirements to them because of their first-rate expertise at an international level, attention to detail and on-time delivery."

- On behalf of Orthogen Australia, a division of Orthogen AG, Cell Therapies receives, processes and cultures autologous chondrocytes combined with a collagen matrix for implantation in patients with a focal defect in their articulating joints. "It's rare to find one company that can provide the range and depth of services required to deliver in such a heavily regulated industry" said Robert Anderson, Managing Director of Orthogen Australia.

Central to the concept of this facility is the principle that basic research findings should be translated to patient care as quickly as possible



- Martin Rogers, Director of Prima BioMed Ltd, said, "The company has been associated with Cell Therapies over an extended period, "providing processing for our Phase IIb IND trial and developing our functionally-closed cGMP manufacturing process." Mr Rogers said.

Mr Wood said "We provide clients with a fully-accredited, focused business unit that is able to negotiate and execute all aspects of the cell and tissue market. We are one of the few groups in the world with the range and depth of experience needed to deliver in this field."

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Cell Therapies

LONZA BIOSERVICES

by Phil Vanek, Head of Innovation and Business Development

Introduction

Although the commercial history of cell therapy is not as extensive as the broader biotherapeutic market, a number of parallels can be drawn between the two. In the early 1980's it was clear to many scientists that commercially manufactured therapeutic grade antibodies could have a significant benefit if used as ligand-mimetic agonists or antagonists of important signaling pathways. The problem was that, at the time, production of commercial scale (kilogram) amounts was unfathomable. Yields of milligram-per-liter of culture were the norm, and current levels of 10 plus grams per liter were pure science fiction. It was through the vision of biotherapeutic pioneers that the challenges of yield, delivery, and commercially viable cost of goods (COGs) were ultimately realized.

Fast forward almost 30 years, and the emerging stem cell therapeutic market faces similar challenges. Two therapeutic paradigms, autologous (patient specific) and allogeneic (patient independent) are jockeying for favor in a largely untested market. Each approach brings unique challenges and potential benefits.

Autologous therapies are less likely to be rejected by the patient since the starting material is derived from one's own tissue, however, there are few manufacturing economies of scale. Therefore, all contributing production costs, in particular testing costs, have a tremendous impact on total cost. A high manufacturing cost ultimately impacts the viability of this therapeutic approach, thus limiting it to indications with very high lifetime associated costs. Other challenges for autologous therapies include chain of custody logistics, processing proximity to patient for fresh, un-cryopreserved products, and relatively high per-patient processing costs.

Allogeneic therapies can be manufactured with a favorable cost of goods, however, persistent therapies need to overcome the challenge of patient rejection. Many allogeneic cell therapies have a transient but clearly beneficial effect in the body, and thereby may overcome the rejection issues in this way.

For allogeneic cellular therapies, the COGs is driven by production scale, with cGMP facilities overhead and labor driving costs at small scale production, while media and other raw materials drive costs at scale up. Another significant challenge is that comparability must be proven between products grown at all scales – something that can be difficult to assess without effective potency bioassays, and often overlooked by early stage companies focusing on clinical trials.

A further consideration that must be appreciated is the regulatory "friendliness" of either approach in the region of commercialization. Regulatory guidance is developing along with the cell therapy field, and companies may find one approach more accepted than the other in certain regions of the world.

Process Development with Lonza

Lonza is the market leader in human primary cells and media, and our broad experience with ethically sourcing tissues for research and therapeutic applications is exceptional. With over 60 years experience in culturing mammalian cells (both cell lines and primary sourced cells), our process development group can provide a considerable advantage in developing regulatory-friendly scalable processes for your cell therapeutic that can help mitigate commercial risk.

When working with Lonza, your process will be carefully evaluated to assess the commercial scalability of the process, and to reduce the manufacturing cost of goods over the long run. Our process development scientists will meet with you early in the process and remain engaged during the technical transfer onward for consultation.

A commercially viable strategy typically involves closing down the culture system to reduce contamination risk during manipulation, and identifying manufacturing lot sizes appropriate to the scale of production needed to support commercial volumes. As mentioned earlier, raw materials quickly become the primary cost driver at scale production.

To further reduce costs, the process development group can customize a chemically defined culture media and work to reduce (or eliminate) serum to provide a more therapeutically friendly culture process.

Our process development function operates an independent R&D group whose charter is to invent and/or implement technologies that efficiently scale up both upstream and downstream processes to give our clients every competitive advantage in the commercialization of their product. This group has implemented scale up culture processes including 40-layer robotically manipulated cell culture vessels, alternative culture approaches, and downstream volume reduction with simultaneous residuals removal. These proprietary approaches are available to each of our clients.

A final step in process optimization involves product formulation and packaging. Our process development group has worked with clients to improve the clinical appropriateness of packaging, and to deliver a stabilized product with extended shelf life.

Monitoring the Process

Throughout process development, your scientists work closely with the Lonza Bioservices group to identify, develop, and implement an effective set of biological assays so that your final product specifications are well defined and measurable. Bioservices provides extensive raw materials validation testing services to assure that each batch of your product has the highest probability of meeting rigid final product specifications.

This team is well equipped with state-of-the art facilities and equipment, including flow cytometers, validated plate readers, fluorescence microscopes, plus laboratory support equipment, all meeting requirements for cGMP and GLP compliant experimental approaches. Using design of experiment (DoE) approaches, the group can help extend the working range or increase the sensitivity of existing assays. It can also design and perform a variety of stability and formulation studies to support your process.

These assays become critical to managing the process improvements, as they form the foundation for evaluating and confirming product comparability whenever changes are introduced.

The Bioservices group also has additional capabilities to support the production of master cell banks, including in vivo testing for inapparent viruses, tumorigenicity, and general safety.

Manufacturing

Whether you are entering an early phase clinical trial or readying for a regulatory inspecition prior to commercial launch, partnering with Lonza can help assure your success. On a global level, we have experience with regulatory agencies throughout the world. Our regulatory group can advise on approaches that will best support product launch of a regulated product and our cell therapy team works closely with our clients to help avoid surprises throughout the process.

As the largest cell therapy contract manufacturer, we continually expand and upgrade our manufacturing facilities. We currently run seven cGMP compliant (ISO Class 7) suites in Walkersville, MD (a suburb of Washington, DC), and are mid-way through a commercial expansion that will add an additional 9,000 square feet of regulated space. An additional suite is classified to run at ISO Class 5 to meet the more stringent EU regulations, yet still take advantage of our cost efficient work force and our extensive US-based tissue procurement capabilities. These facilities are supported by both quality and regulatory groups to provide full-service support to each of our clients. With the existing infrastructure, we can support multiple clients with production scales ranging from a few million cells to several hundred billion cells, with lot sizes upwards of 8 billion cells per product run. As we implement new technologies, and bring the new facilities on-line, these scales will continue to grow.

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PHARMACELL BV
MAASTRICHT (THE NETHERLANDS)

by Alexander Vos, CEO

PharmaCell operates a state-of-the-art **cGMP-Licenced** facility for human cell and tissue culturing located centrally in Europe. We are the CMO of choice to leading biotech companies in the field of cell therapy and regenerative medicine and are one of very few companies in Europe to hold an official licence as a **Registered Tissue Establishment**.

Our facilities include 250 square meters of clean room, classes A, B, C and D. (Classes 100 / 10,000 / 100,000), 180 square meters of R&D and QC laboratories including cryopreservation area, and a further 180 square meters dedicated to warehouse and office space. PharmaCell has a strategic focus on cell therapy and regenerative medicine. Over the course of our history we have supported several US- as well as European based development companies with our expertise in production and logistics for their innovative therapies in several early as well as late stage clinical trials.

PharmaCell offers **fully integrated solutions for autologous and allogeneic cell and tissue therapies,** with established competencies that cover the full range of preclinical and clinical services for cell based biopharmaceuticals and therapies, including cell line development, cell banking, cell line characterization, process development and scale-up, custom cGMP manufacturing, lot release, stability testing and final product formulation and fill & finish. In addition we offer regulatory support and QP services. PharmaCell offers storage and distribution of

All our customers have a single point of contact for the management of their project.

Clinical Trial Materials including cell products and tissues and can also coordinate all logistics for autologous cell and tissue therapies throughout the European Union and into North America. All our customers have a single point of contact for the management of their project.

PharmaCell is located in the Biopartner Center in Maastricht the Netherlands. Strategically **located within one hour of major international airports** such as Brussels and Dusseldorf, as well as close to a hub of one of the major international courier companies in Liege (Belgium). Close cooperation with Maastricht University and the associated Academic Hospital gives PharmaCell the unique capability to provide support and/or partnership to R&D companies to bring new products from the lab into the clinic.

PharmaCell is also **actively engaged in Research & Development work**, both on behalf of some of its customers as well as in research consortia together with Universities, Academic Hospitals and other (bio)tech companies. The **BioMedical Materials program (BMM)** is a public private partnership, which aims to further strengthen the world-leading position of the Netherlands in the field of biomedical materials and applications. BMM is an initiative of leading Dutch industrial players such as Philips and DSM, SMEs and independent research institutions. PharmaCell participates in the SMARTCATE and BIOKID programs within BMM, respectively focused on the development of cellular regenerative approaches to cardiomyopathy and kidney dialysis.

PharmaCell is the only commercial company in The Netherlands to hold an official license as Registered Tissue Establishment.

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PharmaCell

PROGENITOR CELL THERAPY

by Robert Preti, President & Chief Scientific Officer

Progenitor Cell Therapy (PCT) is an internationally recognized commercial Client-oriented service company, with a long-term commitment to the development, manufacturing and commercialization of effective cell therapies, as the emerging paradigm for the treatment of disease.

PCT offers its Clients cost-effective turnkey service solutions for consulting and regulatory support, GLP/GTP/cGMP-compliant product development and manufacturing services, as well as storage, distribution and logistics support, with the goal of establishing a tailor-made service platform providing the Client with four core benefits:

- Cell therapy-specific focus and unmatched expertise
- Maximal financial value
- Operational leverage and control over product development
- Overall risk mitigation throughout the development and commercialization process

With state-of-the-art manufacturing facilities located in Allendale, NJ, and Mountain View, CA, PCT maintains a California Drug Manufacturing License for the conduct of clinical trial manufacture and distribution of cell-based products, is registered with the FDA as a Human Cellular or Tissue-based Product (HCT/P) facility, and maintains current Good Manufacturing Practice (cGMP) compliant Quality Systems. Founded in 1997, PCT's Management and Scientific Team have well over 200 years of combined experience in cell therapy, including:

PRODUCT QUALITY
COST SAVINGS
REGULATORY COMPLIANCE
EXPERIENCE

- The design, construction, validation and operation of cGMP facilities for the manufacture of cell-based products from pilot-scale to commercial-scale
- Servicing of over 100 clients with projects involving over 20 different types of cell-based products, including:
  - The research, development, manufacture and delivery of cells and cell:matrix combinations for implantation/infusion
  - The research, development, manufacture and delivery of gene modified cells (retroviral, adenoviral, lentiviral and plasmid transfected)
  - Scale-up of manufacturing processes from culture dish to bioreactor, including development of the Wave bioreactor as a platform for cGMP manufacture
  - Characterization and potency of cell-based products
  - Development, validation and implementation of assays and specifications for the in-process, lot release and stability QC testing of cell-based

products and reagents used for the production thereof
- Performance of over 30,000 cell therapy procedures, approximately 5,000 of which have been used for treatment of patients
- Research, development and customer support of devices commonly used for cell therapy such as Isolex CD34 Cell Selection System, CliniMACS, ELUTRA, and the CytoMate Cell Washer Device
- Interaction with regulatory agencies and participation in over 50 regulatory filings for cell-based products in both the US (FDA) and Europe (EMEA), including writing of specific submission sections such as Chemistry Manufacturing and Controls (CMC), as well as compilation and management of entire Investigational New Drug (IND) submissions and implementation of clinical trials thereafter; this regulatory experience involves the development of biologics as well as devices and reagents applicable to manufacture of cell therapy products
- Numerous patents, abstracts and peer-reviewed publications related to cell and gene therapy products
- The start-up, funding and operation of new company ventures in cell-based therapy, cord blood banking and adult stem cell banking
- Participation by Dr. Pecora and Dr. Preti in the founding and operation of the International Society for Cellular Therapy (ISCT) and the associated US accrediting Federation for Accreditation of Cell Therapy (FACT) and European Joint Accreditation Committee of the International Society for Cellular Therapy (JACIE)
- Establishment of proven and audited in-house and Client-specific Quality Systems, encompassing:
  - Maintenance of overall quality systems compliant with current Good Manufacturing
  - Practice (cGMP), Good Laboratory Practices (GLP), and Good Tissue Practice (GTP)
  - Maintenance of a California Drug Manufacturing License for the conduct of clinical trial manufacture and distribution of cell-based products
  - Maintenance of a registered HCT/P facility status
  - Incorporation of validation considerations into all pertinent project areas

In summary, PCT's unique and wide-ranging experience spans the entire spectrum of cell therapy product development from research to processing and manufacturing, and from regulatory and quality compliance to clinical application.

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Progenitor™ Cell Therapy, LLC

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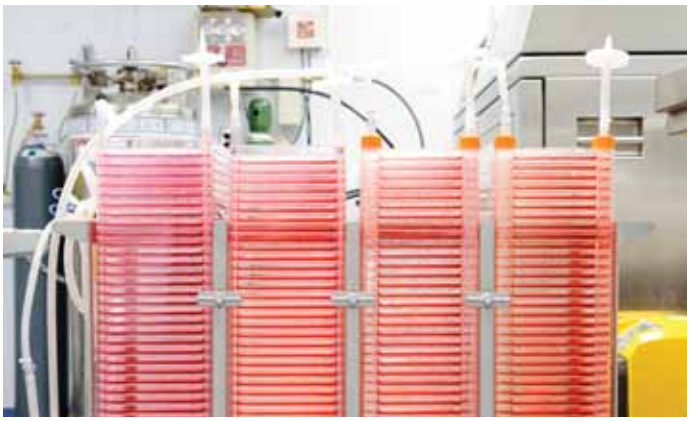
To support our European clients, we have additional cGMP production facilities in Verviers, Belgium, approximately 1 hour East of Brussels by car. This facility is ideally suited to support early phase allogeneic manufacturing as well as autologous therapy manufacturing, due to its close proximity to most of Europe by air.

More recently announced, our expansion into Lonza's Tuas footprint in Singapore will provide additional cGMP cell expansion space, regulatory support, and distribution capabilities for the first time to the region. This latest expansion will bring our manufacturing capability to a truly global level, servicing the U.S., Europe and broader Asia Pacific markets.



Each facility is designed to accommodate the different needs of each client's process. Suites can be custom configured to allow client-specific equipment to be installed, depending on any particular process requirements. This flexibility is engineered into the design of our facilities, so suites can be reconfigured to meet client-specific needs in a very short amount of time.

Each of our facilities has an extensive capacity to manufacture cell culture media under cGMP conditions. The proximity of the media production to the cell manufacturing suites eliminates high media shipping costs, and assures cost efficient, yet still customizable capabilities for each client.

Technical Transfer

The cell therapy manufacturing capability is further supported by technical program managers, each fully trained and experienced in the cell therapy production process. Some of our program managers have previously worked in the cell manufacturing suites, or supported other functions within the Cell Therapy business, and they bring this experience to your project team. The program managers can anticipate your project needs, and with consultation of the process development scientists, can help clear the path for a successful product launch.

During early discussions with prospective clients, the program managers join the evaluation team, and begin to prepare for efficient process transfer. They can make recommendations to facilitate the process transfer and to complete all tech transfer steps quickly and cost effectively.

On a continuing basis, the program manager serves as the key point of contact with the client project team, and helps with the timely delivery of every step of the process.

Distribution

Lonza's global advantage stems from our operating in over 40 countries. Our geographic proximity and regional familiarity helps eliminate cross-border logistical and cultural challenges. We can support clinical site distribution to the US and countries throughout Europe and Asia to support clinical trials regionally. We have experience distributing high quality cell products to most countries of the world and have an exceptional track record in doing so on time and on budget. Our Cell Therapy distribution capabilities continue to evolve with the market demand, so that we can be ready to distribute your commercial product at launch.

Conclusion

Our dedicated cell therapy team can help you avoid many of the pitfalls associated with cell therapy manufacturing scale up, down-stream processing, packaging and distribution. With world-class support and global services, Lonza can meet your cell therapy process design, manufacturing and logistical needs. Our ongoing passion is to deliver tomorrows processes, today.

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Lonza

BioLife Solutions develops and markets patented hypothermic storage/transport and cryopreservation media products for cells, tissues, and organs. BioLife's proprietary HypoThermosol®, CryoStor® and BloodStor® platform of biopreservation media products are marketed to academic research institutions, hospitals, and commercial companies involved in cell therapy, tissue engineering, cord blood banking, drug discovery, and toxicology testing. BioLife products are serum-free and protein-free, fully defined, and formulated to reduce preservation-induced, delayed-onset cell damage and death. BioLife's enabling technology provides research and clinical organizations significant improvement in post-preservation cell and tissue and viability and function.

BioLife Solutions
POWERING THE PRESERVATION SCIENCES