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# BioPreservation Today®

BioLife Solutions®
BIOPRESERVATION TOOLS FOR REGENERATIVE MEDICINE

Volume 9 - Issue 1 | Winter 2019

## FEATURE ARTICLE:

### BIOLIFE CUSTOMERS CONTINUE PATH TOWARDS COMMERCIALIZATION

## WHAT'S INSIDE

# IN THIS ISSUE



## WEB RESOURCES

**alliancerm.org** | Alliance for Regenerative Medicine

**aabb.org** | American Association of Blood Banks

**bestcollaborative.org** | BEST Collaborative

**bioinformant.com** | BioInformant

**biolifesolutions.com/evidence** | BioLife Solutions Cryopreservation and Hypothermic Storage Evidence

**celltherapysociety.org** | International Society for Cellular Therapy

**fiercebiotech.com** | FierceBiotech

**insights.bio** | Cell & Gene Therapy Insights

**ishrs.org** | International Society of Hair Restoration Surgery

**lifesciences.knect365.com** | KNect365 Life Sciences

**phacilitate.co.uk** | Phacilitate

**regmedfoundation.org** | Regenerative Medicine Foundation

**regmednet.com** | RegMedNet

## UPCOMING EVENTS

**ECI Advancing Manufacture of Cell and Gene therapies VI**
27-31 January 2019
Coronado, CA

**Perinatal Stem Cell Society Annual Meeting**
28 February – 01 March 2019
Salt Lake City, UT

**PDA Annual Meeting**
11-15 March 2019
San Diego, CA

**ISCT Annual Meeting**
29 May – 01 June 2019
Melbourne, Australia

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# EDITOR'S CORNER

**Mike Rice, President & CEO, BioLife Solutions, Inc.**

## Greetings from Phacilitate: Leaders World 2019 in Miami

Customers, partners, and friends of BioLife Solutions; we extend a warm Miami welcome to Phacilitate: World Leaders and The World Stem Cell Summit. We're honored and proud to support "the world's largest advanced therapies partnering event" in several ways. We kick off Day 1, with the co-sponsored Supply Chain session, **Extending Shelf Life and Minimizing Logistics Challenges in Starting Materials for Clinical and Commercial Development**. As a co-presenter in this session, BioLife's Aby J. Mathew, PhD will address key considerations for ***Biopreservation Best Practices for Source Material Stability and Cell/Tissue Manufacturing***. We also look forward to session presentations from our valued industry partners, HemaCare's Dominic Clarke, PhD, and Thomas Heathman of HCATS. Please read Dr. Clarke's summary of the presentation topics in this edition of BioPreservation Today. In a related article, Dr. Mathew's ***Ask the Scientists*** column addresses a question often posed by cell and gene therapists: "Is it possible to increase stability of apheresis/leukapheresis cell products?"

BioLife Solutions had a remarkable year in 2018. Our feature article *BioLife Customers Continue on a Path Toward Commercialization* highlights the notable growth in Regenerative Medicine over the past year, and what that means for our company and the industry as a whole.

BioLife's scientific team continues to be recognized as biopreservation key influencers in Regenerative Medicine Advanced Therapies (RMAT). *BioLife Solutions Scientists Partner with the Parenteral Drug Association to Advance Biopreservation Best Practices,* by Brian J. Hawkins, PhD, et al., summarizes activities focused on The Cryopreservation Standards Project, as well as our leadership role in the newly formed PDA Pacific Northwest Chapter.

We also provide exciting updates on our biologistics partners, SAVSU Technologies; their latest Smart Shippers, the new and expanded state-of-the art facilities, and the addition of European business development personnel.

Members of BioLife's scientific, executive and business development teams will be available throughout the conference at our biopreservation exhibit in Booth 301, and around the BioLife Solutions sponsored Coffee Break Station located near our booth.

Thank you for your continued interest in BioLife Solutions and our mission to bring Biopreservation Best Practices and Tools to our industry.

Best regards,

Mike

BOOTH #301

# Biolife Solutions Scientists Partner With The Parenteral Drug Association To Advance Biopreservation Best Practices

**Brian J. Hawkins, PhD, Alireza Abazari, PhD, Aby J. Mathew, PhD**

Regenerative Medicine Advanced Therapy (RMAT) was defined by the U.S. 21st Century Cures Act of 2016, and refers to a class of biologics that includes cell therapies, tissue-engineered products, human cell and tissue products, gene therapies, and combination products in which the primary mode of action is conveyed by the biological product component[1]. Although complicated and expensive to develop and manufacture, RMATs have shown great promise in the treatment of once incurable diseases such as cancer. Consequently, the Alliance for Regenerative Medicine reports that there are 892 regenerative medicine companies worldwide conducting 1003 active RMAT clinical trials[2]. Of these trials, 330 are in Phase I, 580 are in Phase II, and 93 are in Phase III; all of which require a high degree of coordination between product developers, contract manufacturing organizations, tools and service providers, clinical centers, and regulatory bodies. To foster coordination between these diverse groups and accelerate RMAT commercialization, there is an increasing effort by a number of professional organizations to develop standards and best practices that can harmonize RMAT development and accelerate the time needed to translate these promising therapies from the bench to the bedside. Examples of such organizations include the Parenteral Drug Association (PDA), Standards Coordinating Body (SCB), and National Institute of Standards and Technology (NIST). As the leading developer, manufacturer, and supplier of GMP-manufactured biopreservation media to the cell therapy and regenerative medicine field, BioLife Solutions® has for years been advancing the concept of Biopreservation Best Practices[3,4]. BioLife scientists are active participants in these organizations and are taking a lead role in the development of standards and best practices that can be utilized by both academic and industry partners.

Biopreservation refers to the processes required to maintain the health and function of biologics outside the body, as well as suppress the degradation of these biologic materials to ensure post-preservation return to function[5]. Biopreservation Best Practices in turn define the most accepted and effective means to incorporate optimized biopreservation protocols into the manufacture and commercialization of biologic-based therapies. The rapid clinical adoption of RMATs has outpaced the incorporation of Biopreservation Best Practices in many cell/tissue manufacturing methods, especially where First-to-Market may be prioritized over Best-in-Class. The commercialization of RMATs has therefore progressed with some potential risks, as groups look to individually define and incorporate non-optimized biopreservation protocols without appropriate guidance with regards to biopreservation, quality, and regulatory expertise. To educate and advance Biopreservation Best Practices, BioLife scientists over the past few years have cultivated discussions with the PDA, which is the leading global facilitator of science, technology and regulatory information for parenteral (i.e. non-orally delivered) pharmaceuticals and biologics. The BioLife/PDA relationship was initiated in 2015, and furthered through invited presentations at PDA events such as PDA Europe Advanced Therapy Medicinal Products from 2016-2018, a poster and video presentation at the 2018 PDA Annual Meeting (https://www.pda.org/pda-letter-portal/multimedia/videos), publication of 'Cell Viability after Cryopreservation' in the PDA Letter, conference planning for the PDA Cell and Gene Therapy Meeting from 2016-2019, and most recently in a leadership role within the newly established PDA Pacific Northwest Chapter (https://www.pda.org/chapters/north-america/pacific-northwest/chapter-officers).

Recognizing BioLife's participation within the RMAT community and the important role of biopreservation in the RMAT product lifecycle, the PDA requested that BioLife take the lead in developing a standard for how cells should be frozen for clinical manufacturing and application. The PDA standard 02-201x, Cryopreservation of Cells for Use in Cell Therapies and Regenerative Medicine Manufacturing, specifically aims to: 1) Address the challenges associated with maintaining viable recovery and functionality of cellular therapies and tissue products; 2) Discuss the benefits and considerations of low-temperature biopreservation; 3) Outline Biopreservation Best Practices for users; And 4) Propose considerations for incorporating Biopreservation Best Practices into a GMP cell therapy product. More information on the PDA's standards efforts can be found at: https://www.pda.org/scientific-and-regulatory-affairs/pda-ansi. Following approval by PDA leadership, 02-201x will be submitted to the American National Standards Institute (ANSI) for approval as an accepted standard document. The Cryopreservation Standards project, led by BioLife scientists, will commence in early 2019 and should take approximately 18-24 months to complete.

The PDA Cryopreservation Standards brings together diverse individuals from industry, regulatory bodies, academia, and professional organizations. One such organization is the SCB, whose participation in the Cryopreservation Standards project will help ensure consensus among a range of stakeholders across the RMAT community. As a representative of

the PDA and in partnership with the SCB, BioLife scientists will be discussing Biopreservation Best Practices at two separate events in 2019. First, BioLife scientists will be participating as both a speaker and panel subject expert in a workshop entitled, "Realizing the Benefit of 21st Century Cures through Standards Development: A workshop convened by FDA, NIST, SCT, and NEXIGHT Group," that will be held on the NIST campus in Rockville, Maryland on January 14-15 (https://www.standardscoordinatingbody.org/jan2019-standards-workshop-event-page). On the heels of the NIST workshop, and in recognition of their leadership in Biopreservation Best Practices, BioLife scientists will represent the PDA and SCB and present an update on the Cryopreservation Standards at the 2019 International Society for Cell and Gene Therapy (ISCT) Annual Meeting in Melbourne, Australia. These opportunities represent a unique opportunity to disseminate the strong BioLife/PDA relationship to the cell therapy and regenerative community, as well as communicate the upcoming Cryopreservation Standards Project to relevant academic and industry stakeholders. In total, the aggregate number of these activities illustrates the strong partnership of BioLife scientists with the PDA, the recognized expertise of BioLife scientists in the cell therapy and regenerative medicine space, and reinforces the growing recognition of the importance of Biopreservation Best Practices in RMAT commercialization and clinical adoption. It is the aim of BioLife Solutions scientists to continue their scientific outreach mission to the PDA and other leading organizations in the hope of accelerating RMAT development and helping bring these truly innovative therapies to patients in need.

References

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## Extending Shelf Life and Minimizing Logistics Challenges in Starting Materials for Clinical and Commercial Development

**Dominic Clarke, PhD, Global Head of Cell Therapy, HemaCare Corporation**

The cell and gene therapy (CGT) industry is experiencing tremendous translational and clinical success which has enabled commercial realization. This success has also paved the way for a wealth of new companies and clinical trials targeting further advancement in the treatment of life-threatening disease[1, 2]. Although positioned for continued success, the industry must now address new challenges, as recently highlighted as part of the ISCT 2018 commercialization signature series[3]. A key challenge to the increase in clinical product development is the availability to manage the incoming clinical material and subsequent manufacturing capacity. One of the most critical components for any cellular therapy for both development and clinical application is the starting material. The limited availability and overall product stability place a premium on supply chain and logistics to enable greater access and ensure the highest quality can be achieved[4].

A number of factors influence the starting material (e.g. apheresis) quality and that quality subsequently impacts each of the downstream steps. Once the material is collected (whether clinically or from a donor), the product needs to be delivered to a processing facility which may be the sponsor's production site, or a contracted manufacturer (CMO) for process development or further manufacturing. Much like CGT final products relied previously on being delivered fresh until stability and logistics became a challenge, the same is true of most starting material products to date. Under current practice, starting material (development and clinical) is collected from the donor or patient when they are available - a time which is not always known. Logistics to transport the material need to be arranged and processing facilities such as the sponsor's manufacturing site or contracted CMO need to have personnel and space available to accept the material. Because these products are typically requested to be provided fresh, they need to be transported and processed quickly (a time that can range from hours to days depending on the location) to minimize loss of cell viability and function[5]. This current model and practice can most certainly impact quality, but it also places a significant strain on manufacturing site flexibility, personnel, and capacity. Furthermore, the overall quality of the cell therapy starting material is compromised – especially if delays occur.

Over the past few years, the CGT industry has placed a strong emphasis on the supply chain and logistics of the final therapeutic product. As many of these clinical products are manufactured at a remote facility and then transported long distances to a recipient awaiting trea ent, cold chain and cryopreservation have become common practice to provide extended stability and preserve the critical quality

*Continued from page 5*

attributes of the product[5]. Fresh products ultimately have a limited shelf-life as biological material viability declines over time as has been described at length in the literature[6 - 8]. For starting materials, receiving and processing "fresh" product 24 to even 48 hours post-collection is currently common practice. Cell loss is accepted, but delays in obtaining and receiving the product are also common and the impact to the stability can be significant as depicted in the illustration (Figure 1). Extending the stability of the starting material through cryopreservation or hypothermic storage offer alternatives to traditional industry practice for starting materials. Including a hypothermic storage medium such as HypoThermosol® at the point of collection could extend the stability window by days depending on the product, whereas cryopreservation offers indefinite stability (Figure 1). Initial collaborative studies performed demonstrate the efficacy and potential to extend the stability window. The details of this approach are the focal point of the joint session with HemaCare, HCATS and BioLife Solutions at the Phacilitate Leaders World 2019 Summit. While a number of factors need to be considered when choosing the most appropriate biopreservation option (material availability, logistics, desired cell model or quality attribute, etc.), extending stability of the starting material can help to alleviate some of the logistics constraints faced by the manufacturer in addition to preserving the material quality and reducing downstream processing variability.

As more products are developed, and clinical trials increase, the current model for managing the starting material will need to evolve in an effort to support growth of the cell and gene therapy industry. Without a quality starting material, the development of a critical, life-saving CGT product can be severely compromised before it even begins. Evaluating methods to offer extended stability can potentially transform current practice while enabling improved product quality and availability.

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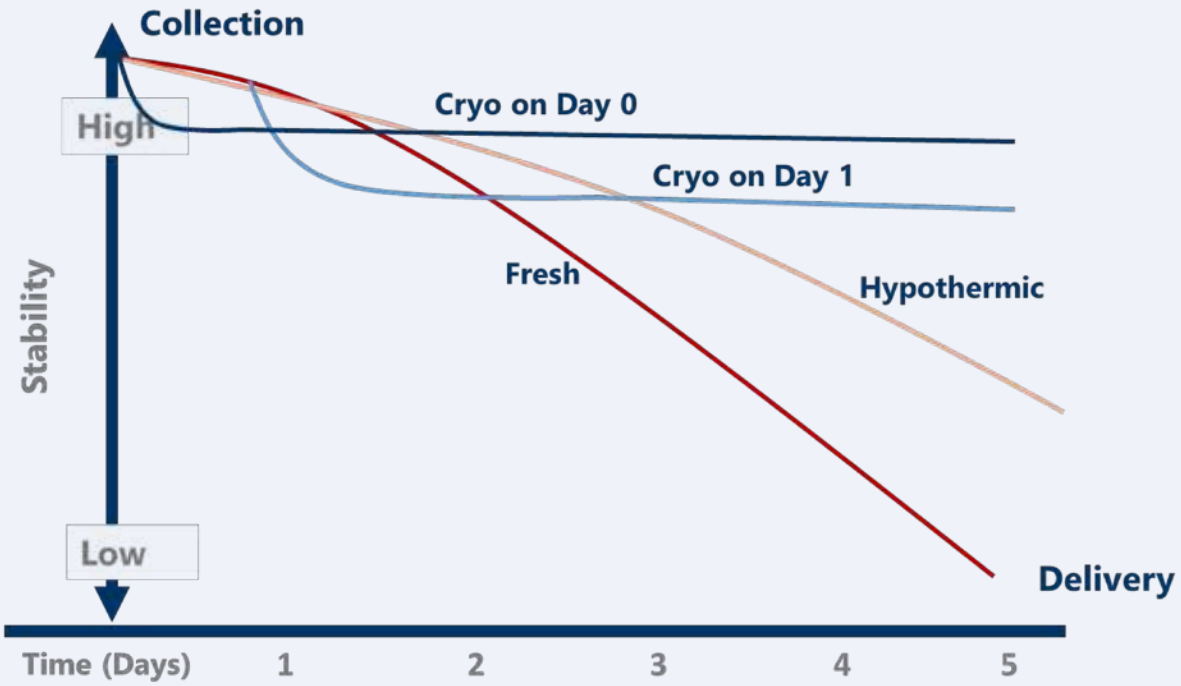
Figure 1: Stability Impact on Starting Material Quality




*Note: This figure is intended as a general illustration only to demonstrate the idea on how stability can be impacted. Specific trends will vary based on the cell model system and impacting conditions.*

# BioLife Customers Continue Path Towards Commercialization

**Todd Berard, Vice President of Marketing, BioLife Solutions, Inc.**

The year 2018 saw whirlwind changes, with increased financial investments, steady clinical progress, and significant milestones achieved in the growing and evolving cell and gene therapy industry. BioLife customers and non-customers alike continued down the path toward commercialization, with the first two CAR T based therapies finally reaching the market. Both Kite Pharma and Novartis received approval of their respective CD 19 CAR T cellular therapies, in addition to Spark Therapeutics receiving approval for their adeno-associated virus vector gene therapy to treat biallelic RPE65 mutation-associated retinal dystrophy; and in Asia, BioLife customer Kolon TissueGene received approval of Invossa for knee osteoarthritis in South Korea.

With the industry moving ahead so rapidly, we are pleased to provide this summary of key activities and milestones achieved by some of our customers and non-customer "industry influencers". Customers of BioLife are noted where applicable, and disclosure is permitted.

In October of 2017, the US Food and Drug Administration (FDA) approved the second chimeric antigen receptor T-cell therapy in the form of Yescarta (axicabtagene ciloleucel), developed by Kite.

Then Gilead Sciences bought Kite Pharma in 2018 for $11.9 billion (€10.2 billion). Since then, Kite has slowly been working through the scaling challenges of their business. Gilead stated that in October of last year they now have 60 different centers certified to administer their CAR-T therapy Yescarta; with plans to add more as further indications are approved.

Yescarta is made by isolating peripheral blood mononuclear cells – including T-cells – from the patient's white blood cells, and then sending them to Kite's manufacturing facilities for proliferation and transduction with a retroviral vector. Once the CAR sequence is introduced into the patient's T cells, they are grown in cell culture bags, washed, frozen in CryoStor, and sent back to a clinical center to be administered back into the patient.

Kite's 43,500 ft manufacturing plant in El Segundo, California has capacity to treat up to 5,000 patients a year. As demand for Yescarta grows, Gilead has had to ramp up the number of certified administration centers. "In terms of the sales trajectory, the first part of launching Yescarta has been to certify all these different centers," Gilead's CEO John Milligan said at the Morgan Stanley 16th Annual Global Healthcare Conference. "This was a market that had never been tested before as a commercial market and there is quite a bit of work that went into getting centers up and running." Currently, he told investors, there are 60 centers that have been certified and are able to prescribe Yescarta to treat hematologic cancers (Yescarta is approved to treat patients with relapsed or refractory diffuse large B-cell lymphoma and primary mediastinal large B-cell lymphoma). But as further indications get approved, the number of centers will have to increase, he added.


Figure 1: BioLife's Key Customers

The firm is also involved in Phase IIb studies for patients with refractory large B-cell lymphoma after conventional therapy failure for a proposes label expansion, while studies are currently underway in indolent mantle cell lymphoma, BCMA and myeloma.

While Milligan did not divulge a target number of administration centers, a 10-Q filing submitted to the SEC last year puts a target of as many as 90 centers. "To ensure that any apheresis center is prepared to ship cells to our manufacturing facilities, we plan to conduct quality certifications of each apheresis center," the filing states. "Accordingly, we plan to target 70-90 key transplant and

lymphoma centers."

And speaking at the Cell Therapy Manufacturing & Gene Therapy Congress in Amsterdam last December, Prentice Curry, VP of Quality and Compliance at Kite said the firm spends a great deal of time with the hospitals and clinics involved. "They need to understand the therapies, they need to understand how to administer the therapies, they need to understand even basic things like the control of the frozen bag of cells," she told attendees.

Yescarta® (axicabtagene ciloleucel), which was launched in the United States in October 2017, generated $75 million in sales during the third quarter of 2018.

Kite utilizes CryoStor® in the manufacture of Yescarta and other clinical trials.

Bellicum Pharmaceuticals, Inc. (NASDAQ:BLCM) is a leader in developing novel, controllable cellular immunotherapies for cancers and orphan inherited blood disorders. In December 2018 Bellicum Reported Safety Results and Promising Activity of Its Controlled CAR-T Candidate BPX-601 in Patients with Advanced Pancreatic Cancer in Part 1 of a Phase 1/2 dose-escalation study in patients with advanced, metastatic pancreatic cancer expressing PSCA (prostate stem cell antigen). BPX-601 is a novel GoCAR-T® cell candidate incorporating Bellicum's co-activation domain, iMC, designed to boost T cell proliferation and persistence via administration of rimiducid. Data were reviewed during an oral presentation at the European Society for Medical Oncology Immuno-Oncology Congress (ESMO-IO) held in Geneva, Switzerland from December 13-16 2018.

"These initial results in advanced pancreatic cancer suggest that having greater control over the expansion and persistence of therapeutic cells may provide unique treatment benefits. We have observed promising initial clinical activity with BPX-601 in patients with one of the most challenging solid tumors, where there is a critical need for better treatments," commented Carlos R. Becerra, M.D., lead study investigator and oncologist and medical director of the Innovative Clinical Trials Center at Baylor University Medical Center at Dallas. "I am looking forward to the next phase of our study, which allows for a standard lymphodepletion regimen and administration of multiple doses of rimiducid to further increase the expansion and persistence of BPX-601 cells and the potential for greater impact against pancreatic and other tumor types."

A total of 12 patients with advanced metastatic pancreatic cancer expressing PSCA were treated with escalating doses of BPX-601 cells in a 3+3 design. Nine of 12 patients received a single dose of rimiducid following BPX-601 treatment to evaluate its effect on cell expansion and persistence. Patients in the study received a reduced conditioning regimen consisting of cyclophosphamide only.

## Interim Results:

- The administration of BPX-601 without rimiducid resulted in limited expansion of cells, but the cells did not persist;
- A single dose of rimiducid seven days following BPX-601 administration resulted in significant expansion of cells (three-fold to 20-fold) in four patients in spite of a reduced conditioning regimen;
- BPX-601 cells persisted longer than three weeks in three patients after a single dose of rimiducid
- Increases in key cytokine levels were observed in patients receiving higher doses of BPX-601 cells and rimiducid
- Four of six efficacy-evaluable patients treated with BPX-601 and a single dose of rimiducid had stable disease, with two patients demonstrating tumor shrinkage greater than 20 percent
- No cytokine release syndrome or neurotoxicity of any grade was reported
- The most frequently observed AEs were consistent with those experienced by advanced cancer patients undergoing cytotoxic chemotherapy or other cancer immunotherapies
- Patients continue to be evaluated in the study

"These results provide the first clinical evidence suggesting that our GoCAR-T technology drives expansion and persistence of therapeutic T cells in patients," said Rick Fair, President & CEO of Bellicum Pharmaceuticals. "We are excited about BPX-601 and the broader application of our technology intended to improve the safety and efficacy of cell therapies. With these promising results, we're preparing to begin Part 2 of the BPX-601 study, adding patients with prostate and gastric cancers, allowing multiple doses of rimiducid and a more complete conditioning regimen. We're looking forward to reporting updated results in 2019."

BioLife entered into a ten-year supply agreement with Bellicum Pharmaceuticals for CryoStor® Use in Their Cellular Immunotherapies.

In 2017, the US Food and Drug Administration (FDA) granted Kiadis Pharma N.V.'s ATIR101 the Regenerative Medicine Advanced Therapy (RMAT) designation. Similar to a Breakthrough Therapy designation, RMAT status allows companies developing regenerative medicine therapies to interact with the FDA more frequently, and RMAT-designated products may be eligible for priority review and accelerated approval. As part of its RMAT status, Kiadis Pharma is benefitting from productive interactions with the US FDA, including a recent meeting.

The Company's ongoing Phase 3 clinical study intends to enroll 250 patients at leading transplant centers globally. The Company has now enrolled 22 patients and has 14 sites open in 7 countries. Kiadis Pharma expected to have over 20 sites open by the end of 2018, including several US sites. An interim analysis of the Phase 3 study is expected in the second half of 2020.

Arthur Lahr, CEO of Kiadis Pharma, commented: "We are pleased with our continued clinical and regulatory progress and remain on track for the initial commercial launch of ATIR101 in a first EU country in the second half of 2019. We are confident that we can address the remaining questions from EMA, allowing for a CHMP

opinion in the first half of 2019. The FDA granting the RMAT status is a clear validation of the importance of ATIR101 and has resulted in productive interactions with the US FDA. We are very pleased with progress made in our Phase 3 clinical trial to date. We are again a step closer to bringing ATIR101 to patients."

Kiadis Pharma N.V. (Euronext Amsterdam and Brussels: KDS), a clinical-stage biopharmaceutical company, then recently announced a regulatory and clinical update for ATIR101. Following recent meetings of the Committee for Advanced Therapies (CAT) and the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA), Kiadis Pharma received a Day 180 second List of Outstanding Issues relating to its marketing authorization application (MAA) for ATIR101. Kiadis Pharma has completed its evaluation of these remaining Day 180 questions. Addressing the questions will require additional analyses of existing clinical data. As expected, no new experimental or new clinical data needs to be generated. EMA has accepted the Company's request for the time needed to respond to the remaining questions. As a result, the timing of the expected CHMP opinion has moved from the fourth quarter of 2018 into the first half of 2019. Following potential EU approval, which typically follows a positive CHMP Opinion within 67 days, Kiadis Pharma intends to commercially launch ATIR101 in a first EU member state in the second half of 2019, which is unchanged versus previous guidance.

Kiadis Utilizes BioLife Solutions HypoThermosol® to Improve Viability and Shelf Life of Donor Leukocytes in Clinical Trial of ATIR101™ T Cell Therapy for Blood Cancers.

KOLON TISSUEGENE

Kolon TissueGene, Inc., is an advanced cell therapies company headquartered in South Korea that saw approval of its first-in-class cell and gene therapy; targeting knee osteoarthritis (OA). Kolon TissueGene's lead product, Invossa, is an allogeneic cell and gene therapy. The Company is conducting Phase III clinical trials in the U.S. under a Special Protocol Assessment (SPA) agreement reached with the U.S. Food and Drug Administration.

On November 21, 2018, they announced that it has dosed its first patient in its pivotal US Phase III clinical trials for Invossa. "This is an exciting step for Kolon TissueGene as we progress towards providing key clinical benefits for patients of this debilitating disease with this novel cell and gene therapy for knee osteoarthritis," stated Mr. Woosok Lee, President and CEO of Kolon TissueGene. The pivotal phase III trials for US approval of Invossa will enroll close to 1,020 patients in approximately 60 clinical sites across the United States. The trial investigators include orthopedic surgeons, rheumatologists and pain specialists. During the trial, the company will assess pain and function endpoints as well as MRI, X-Ray and liquid biomarkers.

In addition to demonstrating significant improvements in pain relief and function, the trials are designed to show structural benefits, including a delay in disease progression, and if successful could achieve a Disease Modifying Osteoarthritis Drug or "DMOAD" label claim. Such an indication by the FDA would be a first for any osteoarthritis drug approved in the US.

Invossa currently is frozen in BioLife's best in class cGMP CryoStor freeze media.

PROMETHERA BIOSCIENCES

Promethera Biosciences Announces Investment by ITOCHU Corporation and a Broad Strategic Collaboration to Access the Asian Markets.

On January 2, 2019, Promethera Biosciences SA, a global innovator in cell-based medicines and liver diseases, announced a strategic investment of EUR10 million by ITOCHU Corporation, one of the biggest Japan-based business conglomerate with global presence and networks with annual revenues of more than JPY 5.5 trillion (approximately EUR 44 billion). ITOCHU Corporation is the first lead investor in Promethera's Series D round, which the company expects to close in Q1 2019. Following the transaction, Mr. Tajio Enoki, Manager, Medical Business Team, Chemicals Division, Energy & Chemicals Company, ITOCHU Corporation will join Promethera's Board of Directors as a Director.

In addition to the first tranche of the Series D round secured, Promethera has recently raised EUR 14.6 million through the issuance of convertible bonds to existing and new investors bringing the total amount raised in by the company to date to more than EUR 90 million.

Beyond the investment, ITOCHU intends to support Promethera to advance Promethera's product and business development strategy in Asia. The scope of the relationship includes R&D support for Promethera's HepaStem development program in Acute on Chronic Liver Failure (ACLF), Non-Alcoholic Steatohepatitis (NASH) and Urea Cycle Disorder (UCD) in selected Asian markets.

"We are very honored to have ITOCHU Corporation a premier Japanese conglomerate with a strong outreach to the wider Asian hemisphere, come in as the first lead investor in our next fundraising effort. The Series D round, which we expect to close early this year, and the commitment by our existing and new shareholders participating in the recent automatically convertible bond offering will further strengthen our financial resources to drive and accelerate the HepaStem program in ACLF and NASH," commented John Tchelingerian, PhD, President and CEO of Promethera Biosciences SA (Group).

"With HepaStem at the core of our relationship with ITOCHU, we expect to make important progress in our plan to develop the world's first cell-based treatment for severe chronic and acute liver diseases as a tangible alternative to liver transplantation," added Prof Etienne Sokal, CSMO and founder of Promethera.

"We are delighted and honored to have the opportunity to invest in Promethera's Series D round in addition to collaborating in business development. We are focusing on regenerative medicine and cell therapy in both autologous and allogenic. We are sure Promethera's technology addresses unmet medical needs in liver disease globally," said Mr. Tajio Enoki, Manager, Medical Business Team, Chemicals Division, Energy & Chemicals

Company, ITOCHU Corporation.

HepaStem consists of liver-derived Mesenchymal Stem Cells that are obtained from ethically healthy donated human organs and expanded in the lab. The product candidate is currently being evaluated in a Phase 2a clinical trial in the indication ACLF with safety and initial efficacy results expected to be available early 2019. The initiation of clinical trials in NASH is expected for 2019.

BioLife Solutions' CryoStor® Embedded in Manufacturing Process for Promethera Biosciences HepaStem Cell-Based Treatment for Liver Disorders.

Celyad

Celyad is a clinical-stage biopharmaceutical company focused on the development of specialized CAR-T cell-based therapies. The company utilizes its expertise in cell engineering to target cancer. Celyad's Natural Killer Receptor based T-Cell (NKR-T) platform has the potential to treat a broad range of solid and hematologic tumors. Its lead oncology candidate, CYAD-01 (CAR-T NKG2D), is being evaluated in the THINK open-label Phase I study to assess the safety & clinical activity of multiple administrations of autologous CAR-T NKR-2 cells in 7 refractory cancers. Celyad is also advancing a robust immuno-oncology pipeline that includes CYAD-02 (Celyad's allogeneic platform), CYAD-03 (CAR-T B7H6), CYAD-04 (CAR-T NKp30) and CYAD-05 (CAR-T NKG2Dβ), all at pre-clinical stage. Celyad was founded in 2007 and is based in Mont-Saint-Guibert, Belgium, and Boston, Massachusetts. Celyad's American Depository Shares are listed on NASDAQ Global Market, all under the ticker symbol CYAD.

Celyad recently announced that it is accelerating its clinical development strategy for AML and MDS and provided updates on clinical candidates CYAD-01 and CYAD-101 with key upcoming milestones for 2019.

"We made progress in 2018 with our CAR-T clinical programs and we believe the Company is poised to achieve a number of important milestones in 2019," noted Dr. Christian Homsy, CEO of Celyad. "We continue to be encouraged by the clinical data observed with CYAD-01 for the treatment of hematological indications. As a result, we are prioritizing the clinical development program of CYAD-01 for the treatment of relapsed or refractory acute myeloid leukemia or myelodysplastic syndrome towards Phase 2 trials."

Building upon its 2018 accomplishments, the Company intends to achieve the following key milestones over the next 12 months:

- Report additional data from the Phase I dose-escalation THINK trial for CYAD-01 in r/r AML or MDS patients, including initial data from the schedule optimization portion of the trial;
- Complete enrollment for and report initial data from the Phase I dose-escalation DEPLETHINK trial evaluating CYAD-01 with preconditioning chemotherapy in r/r AML or MDS patients;
- Accelerate the development strategy and refine the regulatory pathway plan for CYAD-01 for the treatment of r/r AML or MDS patients, including the initiation of a Phase 2 clinical trial;
- Present in vivo preclinical data for our proprietary non-gene edited allogeneic shRNA platform and progress towards an Investigational New Drug (IND) application for the program; and
- Further evaluate the potential for next-generation autologous and allogeneic NKG2D-based CAR-T therapies in the treatment of solid tumors.

## Clinical Update for CYAD-01 in Hematological Malignancies

Celyad's lead clinical candidate, CYAD-01, is currently being evaluated in multiple clinical trials for the treatment of patients with hematological malignancies, including r/r AML and MDS.

### THINK Phase I Trial:

- In December 2018 at the 60th Annual American Society of Hematology meeting, Celyad reported an encouraging objective response rate in r/r AML patients of 38% (three out of eight) from the THINK Phase I trial, evaluating CYAD-01 without preconditioning chemotherapy.
- Preliminary data for the last two patients enrolled and treated at dose level 3 show one patient with relapsing MDS with refractory anemia with excess blasts achieved a marrow complete response after two injections of CYAD-01, while the second patient with r/r AML experienced disease stabilization after the first cycle of CYAD-01. Both patients plan to receive a second (consolidation) cycle of therapy.
- Additional results from the THINK Phase I trial are expected to be announced during the first half of 2019.

Dr. Frédéric Lehmann, Vice President of Clinical Development and Medical Affairs at Celyad, commented, "Current clinical data for the last two patients treated at dose level 3 of the THINK trial provide additional support for the further development of CYAD-01 as a potential treatment of r/r AML and MDS and our decision to rapidly identify the best clinical path forward for the investigational therapy."

### DEPLETHINK Phase I Trial

- In December 2018, Celyad reported initial data from Cohort I of the trial, in which the administration of CYAD-01 following the preconditioning regimen of cyclophosphamide and fludarabine was well-tolerated, with no dose-limiting toxicity or treatment-related grade 3 or above adverse events observed. Based on these preliminary safety data from Cohort I, enrollment has been initiated in Cohort 2 of the trial. Preliminary data from the DEPLETHINK Phase I trial are expected in mid-2019.

### EPITHINK Phase I Trial

- Based on the data generated to date for CYAD-01 from the THINK trial and the recent update in the treatment landscape for newly diagnosed AML patients, the Company has put the EPITHINK trial on hold to focus its efforts on the development of CYAD-01 for the treatment of r/r AML patients. Celyad plans to reassess the opportunity for

CYAD-01 in newly diagnosed AML patients after the optimal treatment design for the therapy is determined. The EPITHINK Phase 1 dose-escalation trial planned to assess the administration of CYAD-01 concurrently with 5-azacytidine in treatment-naïve and/or elderly AML patients ineligible for intensive treatment.

### Solid Tumor Clinical Program Update

- In November 2018 at the Society for Immunotherapy of Cancer 33rd Annual Meeting, the Company reported an interim analysis from the Phase 1 dose-escalation SHRINK trial evaluating the safety and activity of CYAD-01 administered concurrently with FOLFOX chemotherapy (a combination of 5-fluorouracil, leucovorin and oxaliplatin) in patients with metastatic colorectal cancer (mCRC). Follow-up assessment of patients based on response evaluation criteria in solid tumors (RECIST) from dose level 1 of the trial confirmed one patient achieved a partial response and two patients experienced disease stabilization. Full data from the SHRINK Phase 1 trial are expected in 2019.
- In December 2018, Celyad initiated the alloSHRINK trial evaluating the non-gene edited allogeneic CAR-T therapy, CYAD-101, administered concurrently with FOLFOX chemotherapy in the treatment of patients with unresectable mCRC. To date, no relevant treatment related toxicity has been observed in the first subject enrolled in the trial. Topline data from alloSHRINK trial are expected in the second half of 2019.

BioLife's CryoStor clinical grade cell freeze media is incorporated into Celyad's manufacturing process for its Natural Killer Receptor based T-Cell (NKR-T) platform.

Adaptimmune
TRANSFORMING T CELL THERAPY

Adaptimmune Therapeutics plc (Nasdaq: ADAP), a leader in T-cell therapy to treat cancer, announced this year that the Safety Review Committee (SRC) has endorsed dose escalation in the ongoing ADP-A2AFP (AFP) study in patients with hepatocellular carcinoma (liver cancer) to the second dose cohort. The SRC has also endorsed moving to the expansion phase of the ADP-A2M10 (MAGE-A10) lung cancer study.

Across both studies, most adverse events have been consistent with those typically experienced by cancer patients undergoing cytotoxic chemotherapy or other cancer immunotherapies with no evidence of alloreactivity or toxicity related to off-target binding.

In the ADP-A2AFP study, two patients have received 100 million transduced SPEAR T-cells targeting AFP in the first dose cohort, and there was no evidence of hepatotoxicity. The SRC endorsed dose escalation after evaluating the first two patients and taking into consideration the benefit:risk profile observed across programs in Cohort 1.

In the ADP-A2M10 lung cancer study, ten patients have been treated in the first three cohorts (up to six billion transduced cells), and the expansion phase will allow for doses of up to ten billion transduced cells (range 1.2 to 10 billion).

"We are pleased that the SRC has endorsed moving to the expansion phase of the ADP-A2M10 lung cancer study. Additionally, our ADP-A2AFP study has progressed to the next dose level of 1 billion transduced cells. Importantly, we did not observe liver toxicity in the two patients treated at a dose of 100 million transduced cells. In our other studies, we continue to enroll in the expansion phases and, as we previously have said, we are on track to report our next clinical data by May this year," said Rafael Amado, Adaptimmune's President of Research & Development.

BioLife Solutions maintains a Supply Agreement with Adaptimmune for CryoStor® Use in their SPEAR T-Cell Platform. Our Proprietary Clinical Grade Cell Freeze Media Enables Long-Term Storage and Distribution of T-Cells.

IOVANCE
BIOTHERAPEUTICS

BioLife customer Iovance Biotherapeutics, Inc. (Nasdaq:IOVA) is a cutting edge biotechnology company developing novel cancer immunotherapies based on tumor-infiltrating lymphocyte (TIL) technology. In 2018, they raised more capital via an initial Public Offering (IPO) in October, raising almost $220 million. Iovance intends to use the proceeds to fund the expansion of its organization to support the potential commercial launch of lifileucel, to fund its commercial manufacturing capabilities and facilities, and to fund its ongoing clinical trials for its current product candidates. These include it's on-going Phase 2 clinical trials of LN-144, TIL for the treatment of metastatic melanoma and LN-145, TIL for the treatment of cervical and head and neck cancers. Funds will also be used to fund its planned clinical trials for its current product candidates, including its ongoing Phase 2 clinical trial of LN-145 for the treatment of non-small cell lung cancer (or NSCLC) in collaboration with MedImmune, and its ongoing Phase 2 clinical trials of LN-145 as an early-line therapy alone or in combination with pembrolizumab in melanoma, head and neck cancer, and NSCLC, and for other general corporate purposes. All of this with the hope for a possible BLA in 2020.

CBMG
Cellular Biomedicine Group

BioLife customer Cellular Biomedicine Group, Inc. (NASDAQ: CBMG) develops proprietary cell therapies for the treatment of cancer and degenerative diseases. The company conducts immuno-oncology and stem cell clinical trials in China using products from its integrated GMP laboratory. CBMG has GMP facilities in China, consisting of twelve independent cell production lines, all designed and managed according to both China and U.S. GMP standards. CBMG recently commenced two Phase I human clinical trials in China using CAR-T to treat relapsed/refractory CD19+ B-cell Acute Lymphoblastic Leukemia (ALL) and Refractory Diffuse Large B-cell Lymphoma (DLBCL) as well as an ongoing Phase I trial in China for AlloJoin ™ (CBMG's "Off-the-Shelf" Allogeneic Human Adipose-derived Mesenchymal Stem Cell) for the treatment of Knee Osteoarthritis (KOA). CBMG was also recently awarded $2.29 million from the California Institute for Regenerative Medicine (CIRM) to support pre-clinical studies of AlloJoin™ for Knee Osteoarthritis in the United States.

CBMG uses BioLife's CryoStor® in their Clinical Trial of AlloJoin™, and have been in the news recently when they announced they

entered into a strategic licensing and collaboration agreement with Novartis to manufacture and supply the CAR-T cell therapy Kymriah® in China.

The future of CAR-T is off the shelf, according to Cellectis CEO André Choulika. Allogeneic CAR-T therapy, which uses donor T cells, has the potential to clear the hurdles that come with autologous CAR-T, which uses a patient's own T cells. Those challenges include the cost, complexity and time-consuming nature of autologous treatments, as well as distribution and market access. Some patients can't benefit from autologous CAR-T because they don't have enough T cells or T cells of good enough quality to make those treatments.

"With off-the-shelf CAR-T, you don't ask patients to provide part of the raw materials for their treatment," Choulika said at the J.P. Morgan Healthcare Conference. And the allogeneic approach could expand the reach of CAR-T treatments beyond certain indications, namely those in which patients don't need that particular tissue to survive.

Take the blood cancers for which CAR-T therapies have already been approved—two different forms of B-cell lymphoma. If the CAR-T cells remain in the body for a long time, "that's OK," Choulika said. "The patient can survive without B cells." They're not as harmless if they persist in the body and their target is expressed on a different type of cell. "If the target is expressed on myeloid progenitor cells … the patient cannot rebuild blood, even red blood cells," Choulika said. "You don't want the CAR to stay there forever, so it doesn't really make sense to make an autologous CAR."

Founded nearly 20 years ago as a gene-editing company, Cellectis found validation—and "a bit of cash"—in a deal with Servier in 2014. "[It] was a really difficult decision for us … If we'd had the same amount of cash [in 2014] that we have today, I wouldn't have licensed any of our targets to anyone," Choulika said.

But at the time, the autologous treatments Kymriah and Yescarta hadn't been approved and no one really believed in allogeneic CAR-Ts, Choulika said. So, the company licensed out its lead asset, UCART19, to gain some credibility and to be able to move it forward. Later in 2014, Cellectis licensed another 14 assets to Pfizer.

Between them, Cellectis, Servier and Pfizer had programs with 31 targets, though some of the disease areas overlap. Working in the same indications doesn't necessarily spell out competition, though. Combining these treatments could make them more effective, reducing relapse in patients. Four years later, in 2018, Pfizer spun out its CAR-T portfolio, the assets finding their way to Arie Belldegrun and David Chang's Allogene. It was a good decision, Choulika said. "We are excited to be working with very experienced people such as Belldegrun and Chang … It's great for UCART19 that has been licensed from Servier to Allogene and it's good for us because we benefit from this experience that the Allogene team had in past in our current development."

Choulika sees autologous CAR-T therapies as something to be used in a hospital setting, like a bone marrow transplant, with off-the-shelf versions being the way forward. He also sees the technology being applied to not just T cells, but other immune cells, such as natural killer cells, to tackle other diseases, expanding its utility from liquid cancers into solid tumors and then into other areas, such as autoimmune diseases.

NantCell and its founder Dr. Patrick Soon-Shiong announced that Celgene has completed its crossover investment in NantCell. Dr. Soon-Shiong then planned on introducing the company at the 37th Annual JP Morgan Healthcare Conference at the Westin St. Francis Hotel, San Francisco on Monday, January 7th at 8:30am.

NantCell is a privately held immunotherapy company, whose goal is to employ a broad portfolio of biological molecules that will enable it to develop a cancer vaccine to combat multiple tumor types without the use of high-dose chemotherapy. NantCell has one of the most comprehensive late stage clinical pipelines of an integrated platform of immunotherapy technologies addressing both the innate (activated macrophage and natural killer cell) and the adaptive immune system (dendritic, CD4 and CD8 killer T cells). Currently the company is actively enrolling patients for registration trials in 15 indications.

On December 19, 2018, Celgene completed a crossover funding round of $30 million in NantCell at a $4 billion valuation, bringing its overall investment in the company to $105 million with a 2.8% ownership in the company. This follows the May 2015 Celgene initial investment of $75 million in NantCell. "We have partnered with Dr. Soon-Shiong and his mission to change the course of cancer from the very beginning," said Mark Alles, Chairman and CEO of Celgene. "From his invention of Abraxane, to acquiring his company in 2010, to launching this protein nanoparticle drug as the backbone of immunotherapy to its current blockbuster status, and now to supporting his vision at NantCell of developing a chemo free cancer vaccine utilizing the body's own immune system. Celgene invested in NantCell since its inception in 2015 and we are excited to extend this partnership today with the significant clinical progress he has made in developing cytokines and bispecific proteins in the ongoing quest to conquer this disease," said Alles. Celgene announced on January 3, 2018 that it would be acquired by Bristol-Myers Squibb for $74 billion.

"To our knowledge," said Soon-Shiong, "there is no other biotech or large pharma company with NantCell's broad pipeline of bispecific and trispecific fusion cytokine proteins, peptides, mRNA, monoclonal antibodies, neoepitope and tumor associated vaccine delivery and cell therapy products, all in clinical phase of development, across multiple indications, for the treatment of cancer and infectious disease. We are very pleased with Celgene's continued investment in the company and our shared vision of developing a chemotherapy free cancer vaccine."

"With the clinical advances of the technology platforms across multiple tumor types at NantCell, the company is now poised to integrate the technologies developed at the two early stage immunotherapy public companies, NantHealth and NantKwest," said Dr. Soon-Shiong, founder of all three companies. "The

adenovirus and yeast vector delivery systems in NantCell compliments the tumor associated antigen and neoepitope discovery engine (GPS Cancer™) developed by NantHealth, enabling the subcutaneous delivery of the neoepitopes to enable the recruitment of T cells that target only expressed cancer mutations. The bispecific fusion cytokine proteins of NantCell stimulates the patient's autologous primary NK and T cells, thereby supplementing the off-the-shelf, cryopreserved haNK cells developed by NantKwest. Collectively the immunotherapy platforms in NantCell, NantHealth and NantKwest serve as a comprehensive path to the development of a cancer vaccine," said Soon-Shiong.

Specifically, NantCell has 28 unique molecules in its preclinical pipeline consisting of fusion proteins, mRNA, cytokines and monoclonal antibodies including checkpoints and novel cytokine fusion proteins, six of which are IND ready with anticipated filings in 2019. The company has developed a novel proprietary library of fully human single chain variable fragment antibodies (ScFv) with a diversity greater than 1012. This library has yielded fully human monoclonal antibodies with high affinity target binding and is being incorporated into chimeric antigen receptor (CAR) in both off-the-shelf NK cell lines as well as autologous primary NK and T cells for the development of novel cell therapy products. To enable intracellular uptake of both DNA and mRNA, NantCell has also developed novel methods of scalable electroporation enabling high viability and high expression of the desired genes in NK92 cell line, and in primary NK and T cells. In addition, NantCell has developed an automated method of a fully closed system for manufacturing targeted NK cell lines, primary NK and T cells (GMP in the box).

2019 has barely begun, but the activity so far promises more rapid progress and change in our industry. Last year, Novartis and Kite (a Gilead Company) broke innovative new ground with a new payment method for their CAR T therapies – paying only if they work. Already, at the JP Morgan Healthcare conference in early January, BlueBird Bio announced another groundbreaking pricing model for their gene replacement therapy for LentiGlobin, with annual payments contingent on continued effectiveness over time; possibly a five year "installment plan" – based on the drug's effectiveness. Some reports say pricing could reach as high as $2.1 million per patient. Coupled with Novartis's strategy of insurers only paying for durability and efficacy; we should continue to see an evolving payment system evolve from both the manufacturers, reimbursement, and the insurance side – a critical component of our industry's success.

As we continue into the New Year, scaling and commercialization problems will of course still persist – whether they are manufacturing, cold chain visibility and tracking, biopreservation, or final dose yield – but, as always BioLife will be standing by to help support with any relevant issues – including process optimization, yield improvements, Biopreservation Best Practices, or regulatory body support for the uniqueness of our gold standard biopreservation products.

## ASK THE SCIENTISTS

**Aby J. Mathew, PhD – Senior Vice President & Chief Technology Officer, BioLife Solutions Inc.**

Ask The Scientists is intended to be a multi-channel resource that links prospective and current customers to our scientific support team via the avenues of print (BioPreservation Today), direct website link (BioLifeSolutions.com/Evidence), and direct email channels. We welcome your questions and feedback and value the unparalleled direct communications and relationships that have led to HypoThermosol® and CryoStor® being incorporated into several hundred customer clinical applications. For more information or if you have a question for the BioLife Solutions scientific team, please submit your questions at http://www.biolifesolutions.com/ask-the-scientists. Here are some examples of representative customer questions, and our feedback:

### *Is it possible to increase stability of apheresis/ leukapheresis cell products?*

With the increased development and regulatory/marketing approvals of cell immunotherapies, there has been greater recognition of the starting material variability, and potential cell product manufacturing impact vulnerability from the starting material quality. The clinical and industry interest on the topic of apheresis/leukapheresis material quality has generated discussions in various circles regarding gaps in the methods, and development of best practices for starting material collection, processing and biopreservation. A representative discussion has been provided by Juliano et al.[1]

Promising commercial development of cell therapies from apheresis/leukapheresis starting material, some of which have encountered disappointing post-commercial manufacturing variability issues[2]. This has also increased scrutiny on potential variability stresses in the cell therapy manufacturing workflow from source material to patient administration. With the diseased patient starting material as a major source of variability in autologous cell therapies, and increased time and distance between starting material collection and manufacturing activities, additive workflow stresses that exacerbate that initial variability between collection and culture expansion/activation are only further detrimental.

BioLife Solutions scientists have been engaged with a number of leading cell immunotherapy developers to increase stability, and reduce variability, of source material apheresis/leukapheresis material. For several years, we have raised discussions

regarding starting material quality, and were encouraged by early recognition of potential variabilities amongst clinical centers[3]. We have been issued a patent on Whole Blood Collection[4]. The recognition that time and temperature impacted the isolated cells from apheresis and bone marrow further reinforced the recognition of a biopreservation/stability gap that might be improved with Biopreservation Best Practices methods optimization.

In the subsequent development years for commercial cell immunotherapies, several collection service providers and industry partners began evaluating cryopreservation of the apheresis/leukapheresis starting material with CryoStor CS10, as well as non-frozen hypothermic storage with HypoThermosol FRS. Collection service providers HemaCare and Key Biologics have been leaders in working with cell therapy manufacturers, and sharing their knowledge and positive feedback of BioLife's intracellular-like biopreservation media.

Current methods for cryopreserving apheresis/leukapheresis might involve just adding 100% DMSO and/or using a freezing protocol that had been developed for isolated hematopoietic stem cells for transplant. Current methods for non-frozen apheresis/leukapheresis storage might involve storage as-is, and at temperatures that could be room temperature, variable ambient, or 2-8°C. In contrast, methods modifications with our customers specific to increasing stability of apheresis/leukapheresis starting materials has focused on adding intracellular-like biopreservation media at a 1:1 ratio to the collected cellular product. Those that target a cryopreserved starting material would add CryoStor CS10 (and store/ship frozen), and those that target a non-frozen starting material would add HypoThermosol FRS (and store/ship at 2-8°C). The cryopreservation method optimization may also entail protocol modifications to pre-freeze handling, controlled rate freezer steps specific to the use model, and thawing methods. We believe biopreservation of starting materials for Regenerative Medicine and patient-derived testing models will continue to gain recognition as a risk point for potential improvement. Our scientific team at BioLife Solutions, Inc. welcomes the opportunity to further this discussion topic.

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**Aby J. Mathew, PhD – Senior Vice President & Chief Technology Officer, BioLife Solutions Inc.**

Dr. Mathew was part of the founding team of BioLife Solutions, Inc., and is a co-developer of BioLife's biopreservation media solutions. He is a co-inventor on multiple issued and pending patents related to methods, devices, and formulations for the preservation of cells, tissues, and organs. He holds a Ph.D. in Biological Sciences within the Biochemistry, Cell and Molecular Biology Program from Binghamton University and a B.S. in Microbiology from Cornell University. Dr. Mathew has been researching low temperature biopreservation since 1994, and his studies contributed to the development of BioLife's current commercial HypoThermosol® and CryoStor® product platforms and intellectual property foundation. Dr. Mathew was part of the scientific team that linked cell death via apoptosis (programmed cell death) to exposure to hypothermic and/or freezing temperatures. These discoveries were integral to the development of BioLife's intracellular-like biopreservation media, and also contributed to improvements in cryosurgical ablation of cancer. Dr. Mathew was BioLife's first Director of Manufacturing, established BioLife's initial Quality system, and has been Senior Vice President & Chief Technology Officer since February 2011. From January 2007 through February 2011, Dr. Mathew served as Senior Scientist, Director of Strategic Relations, and Senior Director of Strategic Relations. From June 2003 through January 2007, Dr. Mathew served as Director of Manufacturing. From September 2000 through June 2003, Dr. Mathew served as Clinical Accounts Manager and Director of Hypothermic Preservation for Cryomedical Sciences/BioLife Solutions. Dr. Mathew is currently active in, or previously a member of, AABB (formerly the American Association of Blood Banks), BEST (the Biomedical Excellence for Safer Transfusion collaborative), the International Society for Cell Therapy (ISCT), the Alliance for Regenerative Medicine (ARM), Tissue Engineering & Regenerative Medicine International Society (TERMIS), Society for Cryobiology, Standards Coordinating Body (SCB), International Society for Biological and Environmental Repositories (ISBER), American Society for Cell Biology, and the Society for In Vitro Biology. Dr. Mathew is a member of: the Board of Directors, and Advisory Panel, of the Parent's Guide to Cord Blood Foundation, the Scientific Advisory Board of HemaCare Corporation, the founding Board of Directors of the Cord Blood Association, the NIST-AMTech National Cell Manufacturing Consortium, the California Institute for Regenerative Medicine (CIRM) Clinical Advisory Panel, the Business Advisory Board of RoosterBio Inc., and the Scientific Advisory Board of SAVSU Technologies. Dr. Mathew has obtained UCLA Corporate Governance Program Certification.

# Welcome to the Latest News about Savsu Technologies at Phacilitate!

**Michael Weaver, Product Development Manager, BioLife Solutions Inc.**


Our partner Savsu is proud also to be a sponsor of the Phacilitate Leaders World/World Stem Cell Summit. We have lots of news to share including:

- Two new additions to the evo product line making their debut at Phacilitate
- Introduction of industry veterans Monica Egli and Andreas Giger who will help them strengthen our service to Savsu customers in Europe
- The new home base in Albuquerque

## Introducing the new DV-7 evo Smart Shipper.

The DV-7 is designed to fit the realities of clinical site handling. Approximately half the size and weight of the DV-10, the DV-7 offers seven-day static performance compared to the DV-10's ten day static performance. The DV-7 delivers increased payload capacity and performance over the DV-4. True to the evo family of Smart Shippers, the DV-7 features:

- Automatic data collection
- Compatibility with evo.is data communication to the cloud and GPS tracking
- Compact size
- Easy pack-out and payload extraction

## Introducing the new ACS evo 2-8°C Smart Shipper.

The ACS evo 2-8°C is a high performing shipper designed for the transport of apheresis collections that need to be stored and maintained at 2-8°C. The ACS evo captures the collection leg of the journey nicely, complimenting the DV line of shippers designed for transporting cryopreserved product. Not limited to apheresis collections, any fresh products that need to be shipped at 2-8°C are good candidates for use in this shipper. The ACS evo 2-8°C features:

- 16+ days performance facilitating on site storage prior to return
- Automatic data collection
- Compatibility with evo.is data communication to the cloud and GPS tracking
- Compact size
- Easy pack-out and payload extraction

## Introducing Monica Egli and Andreas Giger; Savsu's European Representatives.

Monica Egli, Egsa Tech GmbH Business Development in the Cold Chain, is well versed in business development and sales for diverse products within the cold chain. Monica is based in Zürich, Switzerland. Also based in Zürich is cold chain sales and marketing expert Andreas Giger. Monica and Andreas look forward to collaborating with European customers to address their specific requirements relating to evo shippers integrated with evo.is cloud-based software.

## New Home Base in Albuquerque.

We're excited SAVSU has moved into a new Albuquerque, New Mexico home office, dedicated to serving our customers. They are now located at 4209 Balloon Park Rd. NE. Visitors welcome!

The new facility provides double the space for technical design and testing labs and provides for Quality process expansion. They have added new robotic fabrication equipment to enhance manufacturing and prototyping. Testing labs are equipped with new, state-of-the-art thermal test chambers and advanced validation equipment. The new testing labs increase the capacity of bespoke testing services and outbound unit validation testing. Larger meeting rooms increase client training capacity. They have developed new, comprehensive, customer training sessions also to provide hands-on solutions consultations. Lastly, the expanded office space augments our already excellent Customer Service, Fulfillment, and Software Support services.

If you are reading this during Phacilitate, please visit SAVSU at Booth 804. If not, please let us know the next time you are in Albuquerque. We will be happy to give you the grand tour!

# Explore BioLife's Solutions Evidence Library

**Michael Weaver, Product Development Manager, BioLife Solutions Inc.**

At BioLife Solutions, our scientists have been pioneering biopreservation best practices for more than 20 years. Navigate to our webpage at www.BioLifeSolutions.com and you will find tabs leading to "Evidence" and "Ask the Scientists."

## Evidence Library

BioLife has assembled an Evidence library containing presentations, journal articles, abstracts, and posters citing CryoStor® and HypoThermosol®, authored by ourselves and our customers. Our Evidence library is accessible online, searchable by author, title and keywords, and can be used as a tool by anyone searching for relevant information. Searches, for example, relating to cell lines, disease indications, cell processing, design and development will return publications citing the authors' experience and expertise with the subject as well as their specific use of our Biopreservation reagents with research and development, pre-clinical and clinical applications.

To illustrate, a search using "PDX" will return several journal articles on the topic of patient-derived xenografts including the paper authored by Marissa Mattar and coauthors at the Antitumor Assessment Core Facility, Molecular Pharmacology Program, Memorial Sloan Kettering Cancer Center, New York, reporting their experience establishing the patient-derived xenograft (PDX) core laboratory at MSKCC:

Mattar, M., McCarthy, C. R., Kulick, A. R., Qeriqi, B., Guzman, S., de Stanchina, E. Establishing and Maintaining an Extensive Library of Patient-Derived Xenograft Models. Frontiers in Oncology 2018, 8 (Article 19): 1-18. doi:10.3389/fonc.2018.00019.

Patient-derived xenograft models can augment drug discovery programs and impact the way in vivo studies are designed and conducted. Mattar et al. have made a detailed examination of the complex processes involved for establishing a PDX Core Laboratory serving a large academic center. The authors have divided the article into six main topics including regulatory needs, tumor sample collection, sample processing and propagation, modeling, data base management, and use of PDX in pre-clinical studies. Each topic provides information constituting "best practices" guidance for the associated processes. Within the topic of sample collection, in the authors' experience, patient surgical and biopsy samples collected in HypoThermosol "helps preserve tumor cell viability for up to 48 h, and is the preferred medium for shipment of patient samples to and from other institutions, or for preservation of samples collected late at night or over the weekend." Within the topic of sample processing, the group reports bone marrow and whole blood containing leukemic cells or circulating tumor cells were frozen in CryoStor CS10.

It is important to keep in mind that best practices apply to every step within processes. Success at every step matters as processes roll up and contribute to success of the project overall.

The following published research from the Johns Hopkins University School of Medicine in a university/industry collaboration with MaxCyte, Inc., citation and link available in BioLife's Evidence library, illustrates a "best practices" approach to translational research.

Hung, C., Xu, X., Li, L., Ma, Y., Jin, Q., Viley, A., Allen, C., Natarajan, P., Shivakumar, R., Peshwa, M.V. and Emens, L.A. (2018). Development of Anti-Human Mesothelin-Targeted Chimeric Antigen Receptor Messenger RNA–Transfected Peripheral Blood Lymphocytes for Ovarian Cancer Therapy. Human Gene Therapy, 29(5), 614-625. doi:10.1089/hum.2017.080

Chien-Fu Hung et al. describe development of a method to transfect peripheral blood lymphocytes with messenger RNA coding for anti-human mesothelin-targeted chimeric antigen receptor. According to the authors, the method is "cGMP and regulatory compliant, automated, closed system, resulting in a consistent, high-quality product in a practical time frame and at reasonable cost."

CARMA-hMeso cells were evaluated in vitro for their ability to recognize and lyse mesothelin-bearing tumor cells, and in vivo to inhibit tumor growth in a murine model of ovarian cancer.

Hung et al. demonstrated multiple aliquots of CARMA-hMeso cells can be manufactured within several hours of receipt of the leukapheresis unit. The authors demonstrated no significant differences between non-cryopreserved product and CARMA-hMeso cryopreserved in CryoStor CS10 in terms of viability, transfection efficiency, cell phenotype and capability to kill mesothelin-expressing tumor cells in vitro. The authors' summary states, "Together, these in vitro and animal studies support the evaluation of i.p. CARMA-hMeso cells as a treatment for patients with platinum-resistant ovarian cancer."

## Ask the Scientists

The article by Hung et al. is a reminder that the goal of best practices is to achieve a successful result. There are many steps within the Biopreservation process that impact your degree of success. Whether your processes are underperforming or you want to confirm you are on the best path, you may want to consider consulting Biopreservation experts. The "Ask the Scientists" webpage on BioLife's website is a great resource to receive the individual attention and expert advice you need. Provide your contact information and a brief message outlining your question and we will get back to you.

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