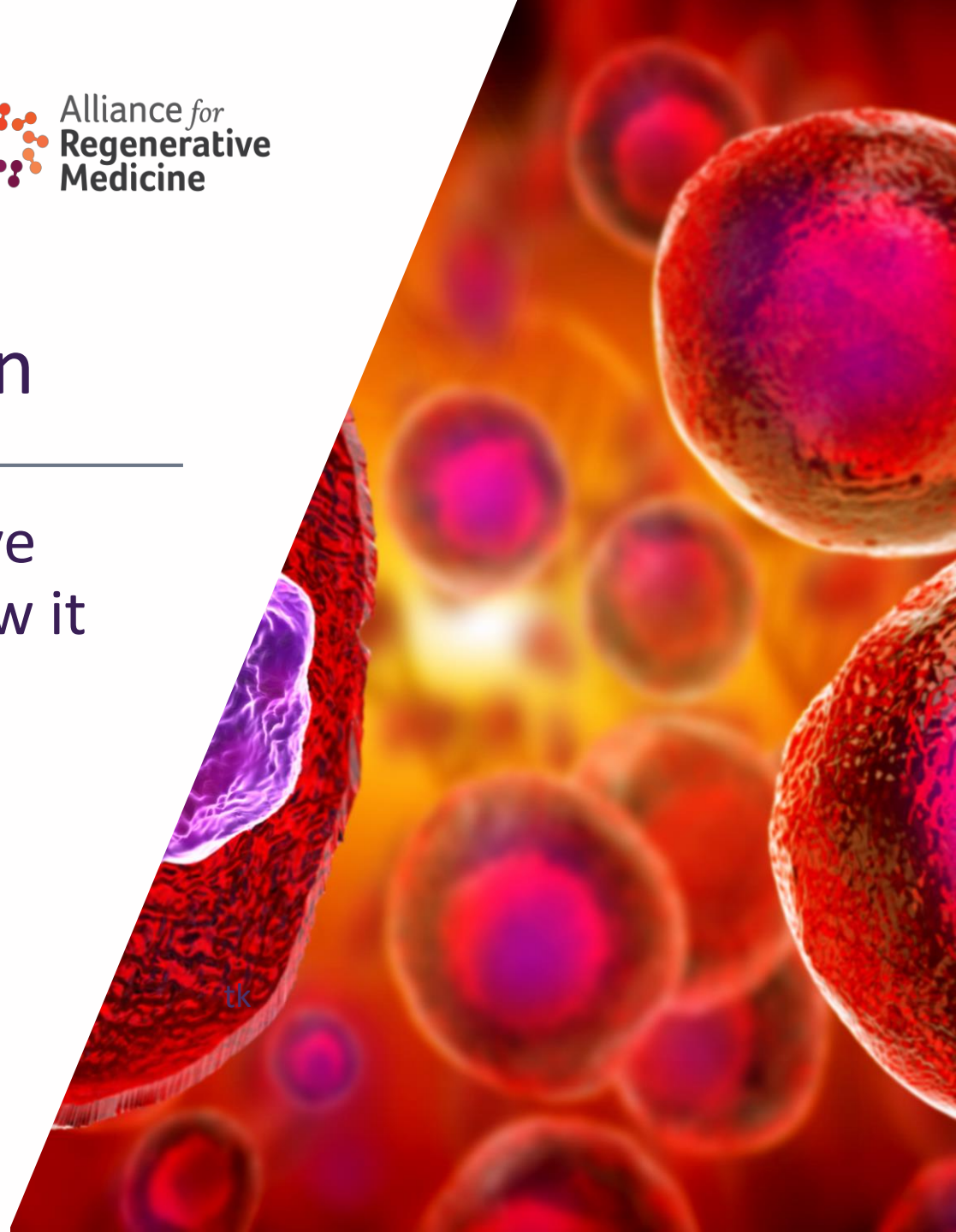


RMAT Designation

Impact on Regenerative
Medicine Sector & How it
Compares with Other
Accelerated Approval
Programs



Agenda

RMAT primer

Introductions

RMAT designation and ARM

Accelerated approval designations

Experience with RMAT

Q&A

RMAT primer



Patricia Reilly
Vice President,
Alliances and Product Unification
Pharma Intelligence



Regenerative Medicine Advanced Therapy (RMAT)

21st Century Cures Act passed by Congress on December 2016

This Act contains several provisions aimed at expediting approval of advanced therapy products, including a designated pathway for regenerative advanced therapies.

Applies to:

- Cell therapies,
- Therapeutic tissue engineering products,
- Human cell and tissue products,
- Any combination product using such therapies or products.

Qualifications:

- Drugs are intended to treat or cure serious, life-threatening conditions.
- Preliminary clinical evidence indicates the drug has the potential to address unmet medical needs.

Benefits:

- Eligibility for increased and earlier interactions with the FDA, similar to those available to sponsors of breakthrough-designated therapies.
- Eligibility for priority review and accelerated approval.

Regulatory pathways are providing incentives for gene therapy development

EMA's ATMP	FDA's RMAT
<ul style="list-style-type: none">• Gene therapies• Somatic-cell therapies that contain cells or tissues• Tissue-engineered medicines• Combined ATMPs (one or more devices integrated with the medicine)	<ul style="list-style-type: none">• Cell therapy• Therapeutic tissue engineering product• Human cell and tissue product• Any combination product using such therapies or products• Gene therapies*
<p>*Inclusion is planned as part of FDA's commitment to fully implement the RMAT pathway. ATMP = advanced therapy medicinal product; EMA = European Medicines Agency; FDA = Food and Drug Administration; RMAT = regenerative medicine advanced therapy</p>	

Gene therapy, including genetically modified cells, would qualify if it leads to a durable modification of cells or tissues, per FDA draft guidance published November 2017

2017 RMAT Designations

COMPANY	PRODUCT	INDICATION
Asterias Biotherapeutics	AST-OPC1	Spinal Cord Injury (SCI)
Athersys	MultiStem	Ischemic Stroke
Bluebird Bio	LentiGlobin	Severe Sickle Cell Disease
Cellvation Inc. (Fortress Biotech Co.)	CEVA101	Traumatic Brain Injury (TBI)
Humacyte, Inc	Humacyl	Vascular Access for Hemodialysis
Enzyvant	RVT-802	DiGeorge Syndrome
jCyte	jCell	Retinitis Pigmentosa (RP)
Juno Therapeutics	JCAR017	Lymphoma (large B cell NHL)
Kiadis Pharma	ATIR101	Leukemia
Mallinckrodt Pharmaceuticals	Stratagraft	Thermal Burns
Mesoblast, Ltd.	MPC-150-IM	Heart Failure
Vericel Corporation	Ixmyelocel-T	Dilated Cardiomyopathy

2018 RMAT Designations

COMPANY	PRODUCT	INDICATION
Abeona Therapeutics	EB-101	Recessive RDEB
Abeona Therapeutics	ABO-102	Sanfilippo Syndrome Type A (MPS IIIA)
Capricor Therapeutics	CAP-1001	Duchenne muscular dystrophy (DMD)
MiMedx Group	AmnioFix® Injectable	Osteoarthritis (OA) of the knee

- Abeona is the only company with two RMAT-designated products and both are gene therapies.

Current RMAT figures :

- 20 designations granted- 16 publicly disclosed
- 64 requests received
- 33 requests denied

Introductions



Amanda Micklus, Moderator
Principal Analyst
Pharma Intelligence



Michael Werner
Co-founder & Senior Policy Counsel
Alliance for Regenerative Medicine



Tim Miller
President & Chief Scientific Officer
Abeona Therapeutics



Kevin Healy
Global Regulatory Lead
Roivant Sciences, Inc.
Representing Enzyvant Therapeutics



Gil Van Bokkelen
Chief Executive Officer
Athersys

RMAT Designation

Michael Werner

Senior Policy Counsel, Alliance for Regenerative Medicine

June 13, 2018

ARM leads meetings w/ OCTGT (now OTAT) to discuss ways to support sector

Publication of 21st Century Cures Act Section 3033 – “Accelerated Approval for regenerative advanced therapies”

21st Century Cures Act Passes

ARM advocates for gene therapies to qualify, FDA confirms

19 approved RMAT Designations to date;

2015

OCTGT becomes OTAT
May 2016

Nov 25, 2016

Dec 2016

Fall 2017

Current

July 2016

Feb 2017

Spring 2018

ARM meets with FDA, Congress to discuss ways to support development of regenerative medicine while maintaining FDA’s existing safety & efficacy standards

ARM hosts RMAT Webinar w/ Dr. Wilson Bryan

FDA announces disease-specific guidances for gene therapies



Regenerative Medicine Advanced Therapy (RMAT) Designation, creates a program for designation of regenerative medicine advanced therapies.



Included in the 21st Century Cures Act (passed Dec 2016)

- For the first time in the U.S., a specific RM / AT technology product designation.
- Optimizes FDA's approval pathways for RM / AT products – similar to FDA's Breakthrough Therapy designation, or other expedited approval programs.
- Maintains the FDA's high approval standards for product safety and efficacy.

Product sponsor benefits:

- Guaranteed interactions with the FDA.
- Eligibility for priority review and accelerated approval.
- Flexibility in the number of clinical sites used and the possibility to use patient registry data and other sources of “real-world” evidence for post-approval studies (pending FDA approval).

What does it do?

1. Protects patients by maintaining the FDA's high safety and efficacy standards.
2. Provides product developers with the necessary regulatory clarity via details and specific examples of how these regulations will apply to specific product types.

Why is it needed?

1. Industry needed further clarity on how FDA planned to regulate RM products, and which kinds of products required regulatory approval.
2. Other nations (incl UK, Japan, Canada), recognizing the immense value of these products, have established special RM regulatory provisions. The U.S. could fall behind its economic competitors if it did not take specific steps to support the field.



Accelerated Approval Pathways

Expedited Review Pathways: Fast Track & Breakthrough Therapy



Definition/Use

- Facilitates the development and expedites review of drugs for serious conditions that fill an unmet medical need based on nonclinical or clinical evidence

Benefits

- Actions to facilitate development and expedite review (e.g. frequent interactions w/ FDA; rolling review)
- Eligible for priority review if supported by clinical data submitted



- Facilitates the development and expedites review of drugs for serious conditions which demonstrate substantial improvement on clinically significant endpoint(s) over available therapy based on preliminary clinical evidence
- Breakthrough requires a higher level of evidence than fast track

Fast Track benefits, plus:

- Intensive FDA guidance on efficient drug development
- Organizational commitment to involve senior management in facilitating the development program

Source: FDA guidance, "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions" (draft); "Expedited Programs for Serious Conditions – Drugs and Biologics" (final)

Expedited Review Pathways: Accelerated Approval & Priority Review



Definition/Use

- Applies to settings where disease course is long, and extended period would be required to measure the intended clinical benefit
- Available only for products that generally provide a meaningful therapeutic benefit over existing treatments

Benefits

- Enables approval of drugs for serious conditions that fill an unmet medical need based on surrogate endpoint likely to predict clinical benefit, or on clinical endpoint that can be measured earlier than irreversible morbidity or mortality



- Granted to products intended to treat serious conditions, and, if approved, represent a significant improvement in safety or effectiveness of the treatment of the condition

- Ensures FDA will take action on an application within six months of receipt
- Priority review may be granted to products with fast track, breakthrough, or RMAT designation

Source: FDA guidance, "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions" (draft); "Expedited Programs for Serious Conditions – Drugs and Biologics" (final)

How does RMAT compare?

Regenerative Medicine Advanced Therapy (RMAT)

Definition/Use

- Special status pathway to foster development and approval of regenerative medicines that treat, modify, reverse, or cure a serious or life-threatening disease or condition, based on preliminary clinical evidence

Benefits

Breakthrough Therapy benefits, plus:

- Early interactions with FDA to discuss potential surrogate or intermediate endpoints to support accelerated approval; regulatory interactions to be more focused on manufacturing issues
- Potential ways to support accelerated approval and satisfy post-approval requirements
- Eligibility for other expedited pathways

Source: FDA guidance, “Expedited Programs for Regenerative Medicine Therapies for Serious Conditions” (draft); “Expedited Programs for Serious Conditions – Drugs and Biologics” (final)

RMAT vs. BTM

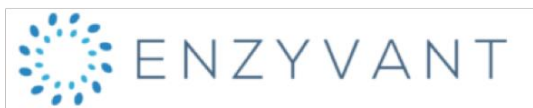
	Breakthrough Therapy Designation (BTM)	Regenerative Medicine Advanced Therapy (RMAT)
Use of preliminary clinical evidence to support designation	✓	✓
Use of preliminary non-clinical evidence to support filing	✗	✗
Frequent interactions with FDA for discussions e.g. study design, extent of safety data required to support approval, dose-response concerns, and use of biomarkers	✓	✓
Eligible for priority review	✓	✓
Eligible for accelerated approval	✓	✓
Restricted to regenerative medicines	✗	✓
Show substantial improvement on clinically significant endpoint(s) over available therapy	✓	✗
Early interactions with FDA to discuss and determine potential surrogate or intermediate endpoints in support of accelerated approval	✗	✓
Regulatory interactions with FDA should be more focused around manufacturing issues	✗	✓

Source: FDA guidance, "Expedited Programs for Regenerative Medicine Therapies for Serious Conditions" (draft); "Expedited Programs for Serious Conditions – Drugs and Biologics" (final)

Experience with RMAT

Experience with RMAT – Discussion Topics

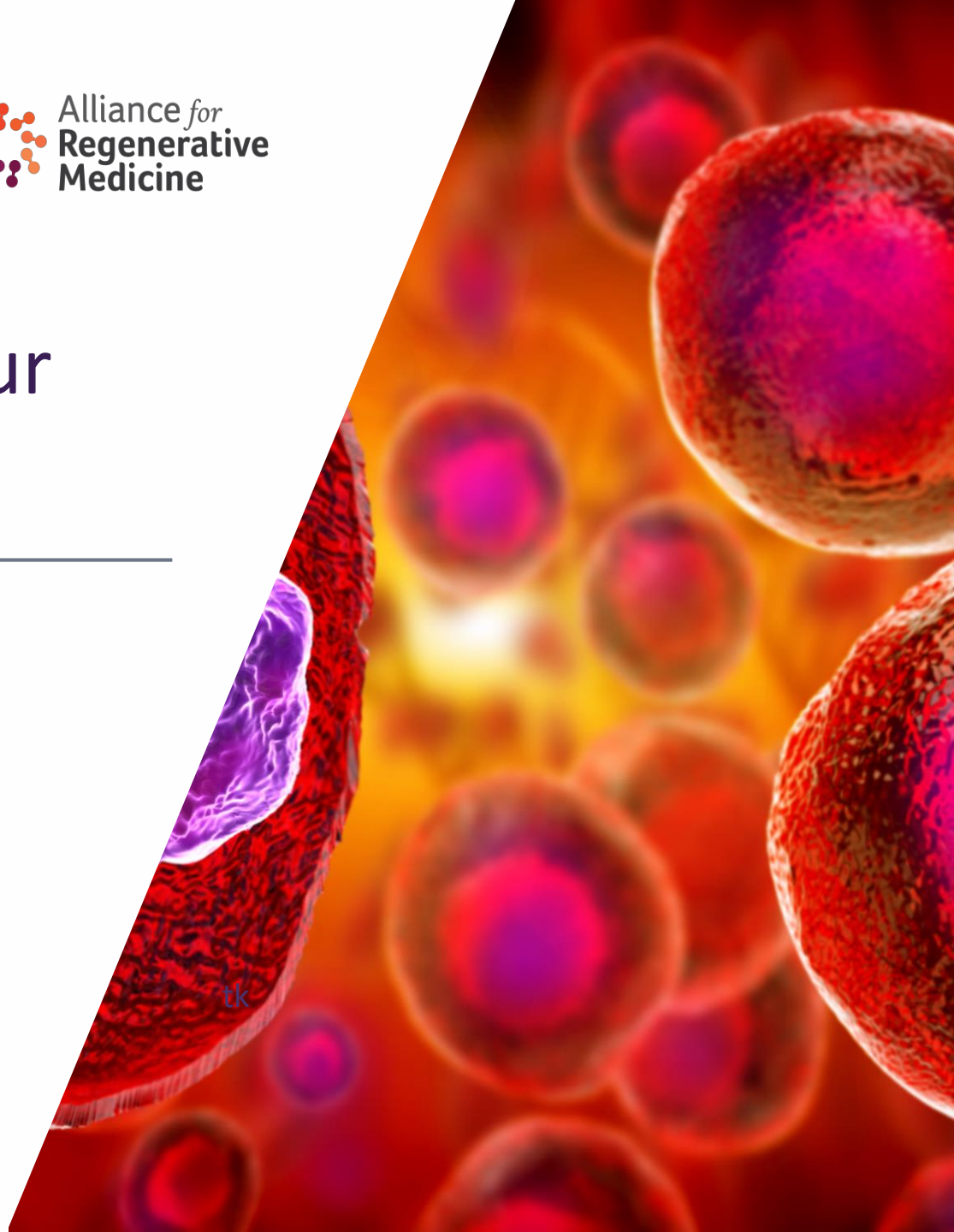
- **Context setting** – Program status / what had we done prior to RMAT?
- **Evaluation of our results vs. designation criteria** – Do we think our program qualifies and why?
- **RMAT vs. BTM** – What is the strategy of securing one over the other, or securing both?
- **Assessment of potential benefits** – RMAT designation provides an opportunity for additional engagement with FDA on multiple fronts.
- **Process of engagement, review process and outcome** – Conveying a focused and concise summary of relevant data and results to FDA for their consideration.
- **Recommendations for others considering RMAT pathway** – Lessons learned and what to avoid.



Thank you for your attention

Questions?

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Appendix





ENZYVANT

Kevin Healy, PhD
Head of Regulatory Affairs

June 13, 2018

Enzyvant Overview

Enzyvant was formed in 2016 and is privately funded by Roivant Sciences to develop **innovative therapies for rare diseases** with significant unmet medical needs

We have a particular focus on **fatal pediatric conditions**

At present we have **two therapies in development:**
RVT-801 for Farber disease and RVT-802 for Complete DiGeorge Anomaly

We plan to file for regulatory approval of RVT-802 **later this year**

RVT-802 has **RMAT designation**, Breakthrough Therapy designation, as well as Orphan Drug and Pediatric Rare Disease Designations

About Complete DiGeorge Anomaly

Complete DiGeorge Anomaly (cDGA) refers to the 1% of DiGeorge syndrome patients¹ who **completely lack a thymus**²

- This represents approximately **10-20 live births per year** in the US*

cDGA patients are athymic at birth and have a profound deficiency of circulating T-cells³, resulting in **primary immunodeficiency**

Athymia is **detected by T-cell deficiency** observed in newborn screening³⁻⁵

With supportive care alone, **almost all cDGA infants die by the age of 2** due to infections²

1. Ryan AK, Goodship JA, Wilson DI, Philip N, Levy A, Seidel H, et al. J Med Genet 1997;34: 798-804.

2. Markert ML, Hummell DS, Rosenblatt HM, Schiff SE, Harville TO, Williams LW, et al. J Pediatr. 1998; 132(1):15-21

3. Markert ML, Devlin BH, Alexieff MJ, Li J, McCarthy EA, Gup-ton SE, et al. Blood. 2007; 109(10):4539-47.

4. Markert ML, Devlin BH, McCarthy EA. Clin Immunol. 2010;135(2):236-46.

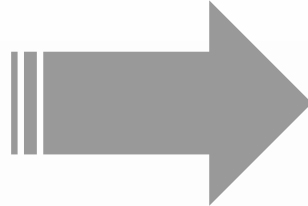
5. Davies EG, Cheung M, Gilmour K, Maimaris J, Curry J, Furmanski A et al. J Allergy Clin Immunol. 2017 140(6):1660-1670

6. Fomin AB, Pastorino AC, Kim CA, Pereira AC, Carneiro-Sampaio M, Abe Jacob CM. Clinics. 2010;65(9):865-869.

RVT-802: FROM INVESTIGATIONAL MEDICINE TO BLA



Duke University
Medical Center



- Treatment of cDGA patients with cultured thymus (RVT-802) was pioneered by Dr. Louise Markert (Duke) in 1990s
- Published data show a significant survival benefit following treatment
- No FDA-approved treatments for cDGA
- Today tissue processing takes place at Duke's cGMP facility
- BLA submission being planned for later this year, in collaboration with Duke
- FDA has awarded RVT-802 Regenerative Medicine Advanced Therapy Designation and other designations – supported extensive FDA interactions

Confidential

EXTENSIVE FDA INTERACTIONS FOLLOWING RMAT DESIGNATION

- RMAT designation April 2017
- Multiple face-to-face FDA meetings to discuss BLA preparation
 - Pre-BLA and other Type B meetings
- Several formal teleconferences
 - Guidance on clinical and CMC portions of BLA
- Quick feedback from FDA RPM: Collaborative relationship

KEY TAKEAWAYS

- Strong and supportive interactions with FDA since granting of RMAT designation
- However, RMAT designation has significant overlap with BTM, so it is not easy to disaggregate the effect of each one individually
- That said, we believe the RMAT designation has been important in setting the tone with CBER/OTAT and that the cadence of communication has been outstanding
- One of the primary distinctions between RMAT and BTM, the use of accelerated approval, is not as relevant in our case given the survival data being used to demonstrate efficacy

(NASDAQ: ATHX)



Our Focus: Development of best in class regenerative medicine therapies for areas of substantial unmet medical need

*Neurological, Cardiovascular, Inflammatory & Immune and Other Indications
with an Emphasis in the Critical Care Segment*

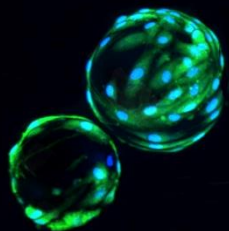




Product Profile

MULTISTEM® CELL THERAPY

Allogeneic “Off the shelf” Cell Therapy



Based on Proprietary MAPC Technology

Off the shelf administration with no tissue matching or immune suppression required

Promotes Healing and Tissue Repair

Works through multiple mechanisms of action

Given Systemically or Locally

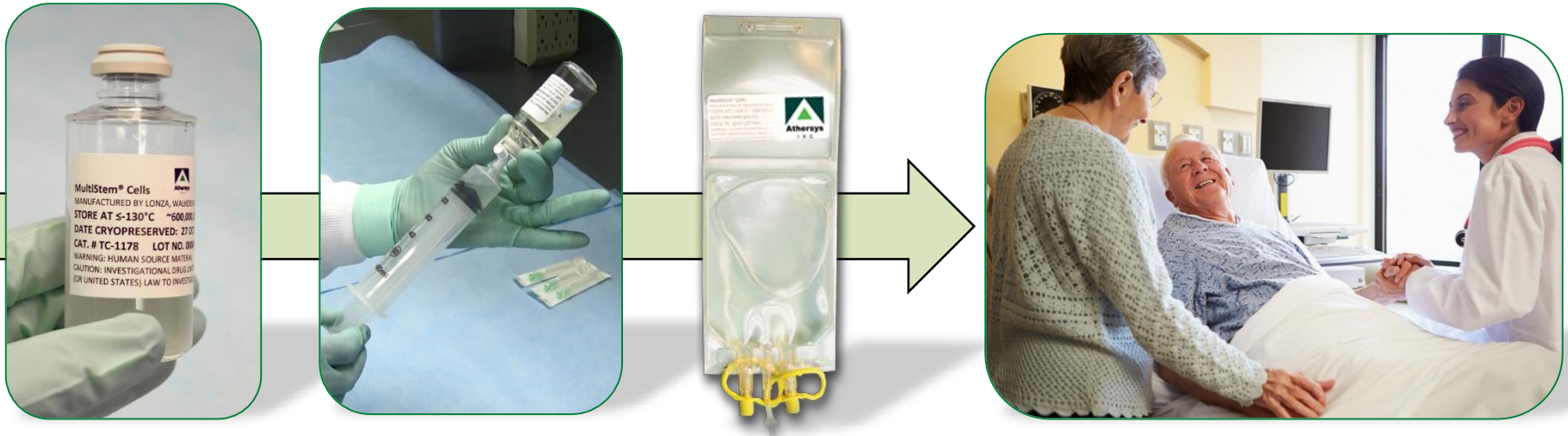
IV, catheter, injection, matrix/implant

Long Storage Life and High Production Yield

> 7 years of stability data, w/ potential yield of millions of doses from each donor bank

*Multiple Clinical Stage Programs – Most Advanced = Phase 3 for Ischemic Stroke
(Multiple Designations Including: RMAT, Fast Track, SPA and Sakigake)*

Practical: Simple to Prepare & Easy to Administer



Hospital Pharmacy to Patient in < 1 hour