Regenerative Medicine: Regulatory, Legal, and Compliance Challenges for Cell and Gene Therapies

Bonus Session: A Primer on Regenerative Medicine Science and Recent Breakthroughs

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Heather C. Hatcher, PhD
Regulatory Scientist, Womble Bond Dickinson (US) LLP
Collin Stabler, PhD
Senior Associate, Exponent, Inc.
Moderated by:
Barbara A. Binzak Blumenfeld, PhD, MA, Esq.
Shareholder, Buchanan Ingersoll & Rooney PC

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Learning Objectives

- Key Terms Defined
- Regenerative Medicine vs “Traditional” Therapies
  - FDA-Approved Cell and Gene Therapies
  - Common Technologies
  - Emerging Technologies

Key Terms Defined

Key Terms: Regenerative Medicine

- Regenerative Medicine Therapy*
  - A **cell therapy**, **therapeutic tissue engineering product**, **human cell and tissue product**, or **any combination product using such therapies or products**
  - *For RMAT purposes*, FDA interprets this term to include certain **human gene therapies** and **xenogeneic cell products**
  - *For RMAT purposes*, does not include 361 HCT/Ps

Prometheus by Nicolas-Sébastien Adam, 1762 (Louvre)

*As defined in 21st Century Cures Act for RMAT Designation

Key Terms: Cell Therapy

- **Cell Therapy:** Administering living cells to a human to treat
- **Autologous:** Implantation, transplantation, infusion, or transfer of human cells or tissue back into the individual from whom the cells or tissue were removed
- **Allogeneic:** Use of human cells or tissue that is not autologous; *i.e.*, using cells or tissue from one or more individuals in a different individual

Key Terms: Tissue Engineering

- **Tissue Engineering:** Combining scaffolds, cells, and biologically active molecules into functional tissues with the goal of assembling functional constructs that restore, maintain, or improve damaged tissues or whole organs
- **Additive Manufacturing (*i.e.*, 3D Printing):** Process that builds an object by sequentially building 2D layers and joining each to the layer below

NIH/National Institute of Biomedical Engineering and Bioengineering

FDA, Guidance for Industry and FDA Staff, “Technical Considerations for Additive Manufactured Medical Devices” (2017)

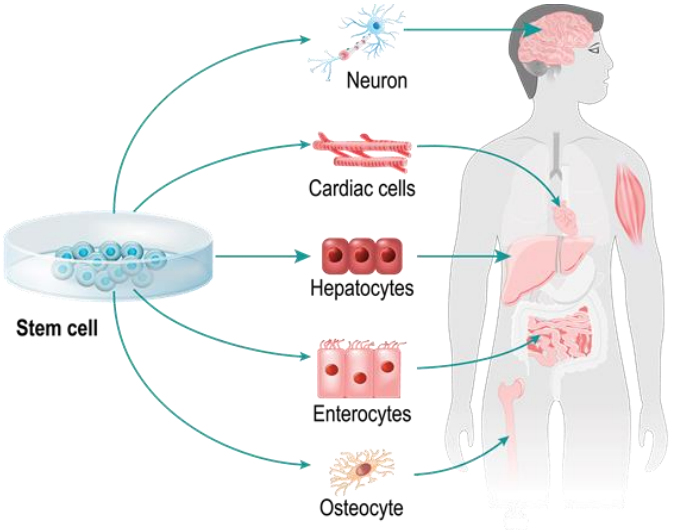
Key Terms: HCT/Ps

- **Human cell, tissue, and cellular and tissue-based product (HCT/P):** Articles containing or consisting of human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient
- **Homologous Use:** Repair, reconstruction, replacement, or supplementation of a recipient's cells or tissues with an HCT/P that performs the same basic function(s) in recipient as in donor
- **Minimal Manipulation:** For *structural tissues*, processing that does not alter the original relevant characteristics of the tissue (*i.e.*, utility to reconstruct, repair, or replace); for cells or *nonstructural tissues*, processing that does not alter the relevant biological characteristics of cells or tissues

Key Terms: HCT/Ps

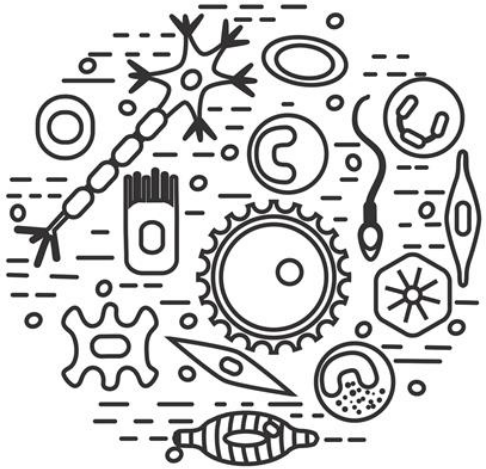
351 HCT/Ps

- HCT/P regulated under PHS Act § 351 as a biologic
- Requires FDA pre-approval (BLA)



361 HCT/Ps

- HCT/P regulated under PHS Act § 361 and 21 C.F.R. Part 1271
- Does not require FDA pre-approval



Key Terms: Combination Product

- **Combination Product:** Product comprised of two or more regulated components physically, chemically, or otherwise combined or mixed and produced as a single entity; or two or more products packaged together
  - Must be drug/device; drug/biologic; device/biologic; or drug/device/biologic
- **Examples—combination products with biologic primary mode of action:**
  - Cellular transplant for diabetes treatment
  - Autologous cellular product and delivery device
  - Autologous cells and scaffold for organ replacement

FDA, "RFD Jurisdictional Decisions"

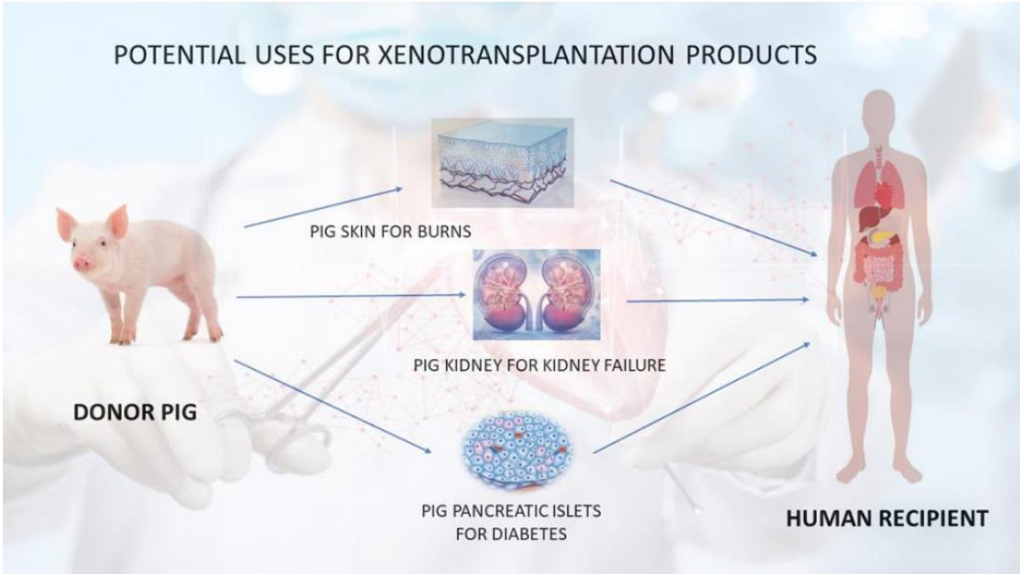
21 C.F.R. § 3.2(e)

Key Terms: Gene Therapy

- **Gene Therapy:** Products that mediate their effects by transcription or translation of transferred genetic material or by specifically altering host (human) genetic sequences
- **Examples:**
  - Nucleic acids (*e.g.,* plasmids, *in vitro* transcribed ribonucleic acid (RNA))
  - Genetically modified microorganisms (*e.g.,* viruses, bacteria, fungi)
  - Engineered site-specific nucleases used for human genome editing
  - *Ex vivo* genetically modified human cells

Key Terms: Xenotransplantation

- **Xenotransplantation:** Transplantation, implantation, or infusion into a human recipient of live cells, tissues, or organs from a nonhuman animal; or human body fluids, cells, tissues, or organs that have had *ex vivo* contact with live nonhuman animal cells, tissues, or organs



https://www.fda.gov/vaccines-blood-biologics/xenotransplantation

Thank You!

Barbara A Binzak Blumenfeld, PhD, MA, Esq.
Shareholder, Buchanan Ingersoll & Rooney PC
1700 K Street NW, Suite 300
Washington, DC 20006
P | 202.452.7906
E | barbara.binzak@bipc.com

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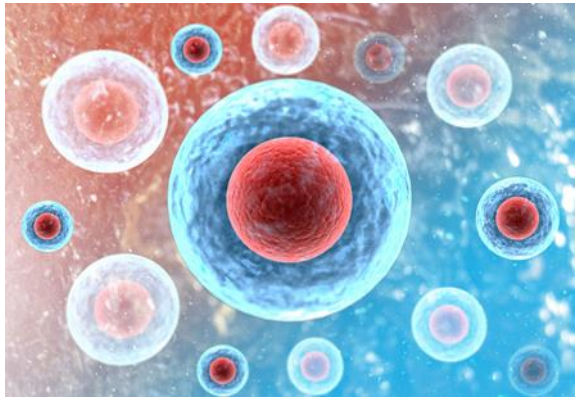
Regenerative Medicine vs. Traditional Therapies

Regenerative Medicine vs “Traditional” Therapies

Cells, genes, tissues, or combo products

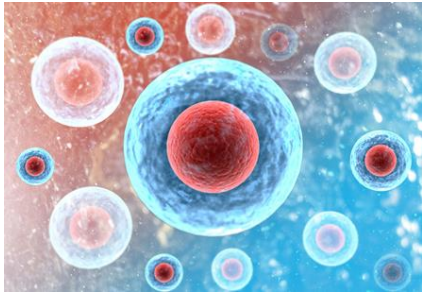
- Derived from patient or donor
- Immediate use or expanded in culture
- Repair, replace and restore function
- Potentially curative



Prescription, generic and OTC drugs

- Chemically-defined API
- Taken regularly to manage a disease or condition
- Pass through the body

Cell Therapies



FDA Approved (OTAT)[1]

CAR-T:

ABECMA – Celgene
BREYANZI – Juno Therapeutics
KYMRIAH – Novartis
TECARTUS – Kite Pharma
YESCARTA – Kite Pharma

HPC:

ALLOCORD – SSM Cardinal Glennon CMC
CLEVECORD – Cleveland Cord Blood Center
DUCORD – Duke USM
HEMACORD – New York Blood Center
HPC – Clinimmune Labs
HPC – MD Anderson Cord Blood Bank
HPC – LifeSouth Community Blood Centers
HPC – Bloodworks

Autologous Fibroblasts:

Azficel-T – Fibrocell Technologies

Immunotherapy:

PROVENGE – Dendreon

Up & Coming

OUS CAR-T Approvals[2]:

APCEDEN – Apac Biotech (India)
Immuncell-LC - GC PHARMA (S. Korea)

OUS Immunotherapy Approvals[2]:

CreaVax RCC - JW CREAGENE (S. Korea; PBMC-derived dendriditc cells)

Novel CAR-T targets:

B cell maturation antigen (BCMA)

Induced Pluripotent Stem Cells

1– *licensed products from the Office of Tissues and Advanced Therapies (OTAT). https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Last accessed: 6/7/2021*

2 – *Alliance for Regenerative Medicine. https://alliancerm.org/available-products/. Last accessed: 6/7/2021*

Cell Therapies

Up & Coming

OUS Cell Therapy Product Approvals[2]:

Alofisel – TIGENIX (EU Marketing Authorization; adipose derived)
Cartistem – MEDIPOST (S. Korea; Cord Blood derived)
Cellgram-AMI – FCB PHARMICELL (S. Korea; Bone Marrow derived)
Cupistem – ANTEROGEN (S. Korea; adipose derived)
CureSkin – S. BIOMEDICS (S. Korea; Dermal derived)
Holoclar – CHIESI FARMACEUTICI (EMA; Limbal derived)
Kaloderm – TEGO SCIENCES (S. Korea; Dermal derived)
KeraHeal – BIOSOLUTIONS (S. Korea; Dermal derived)
Neuronata-r – CORESTEM (S. Korea; Bone Marrow derived)
Queencell – ANTEROGEN (S. Korea; Bone Marrow derived)
Rosmir – TEGO SCIENCE (S. Korea)
Stemirac – NIPRO CORP (Japan)
Stempeucel – STEMPEUTICS RESEARCH PVT (India)
TEMCELL – JCR PHARMACEUTICALS (Japan, Canada, New Zealand)

2 – *Alliance for Regenerative Medicine. https://alliancerm.org/available-products/. Last accessed: 6/7/2021*

Gene Therapies

FDA Approved (OTAT)[1]

Adeno-Associated Virus (AAV) vector-based:

LUXTURNA – Spark Therapeutics

ZOLGENSMA – AveXis

Other:

IMLYGIC (genetically modified herpes simplex virus type 1) – BioVex

Up & Coming

OUS Approvals[2]:

Collatagene – Anges (Japan)

Gendicine – Shenzen Sibiono Genentech (China)

Libmeldy – Orchard Therapeutics (EMA)

Strimvelis – GSK (EMA)

Zynteglo – Bluebird Bio (EMA)

TALENs:

Transcription activator-like effector nucleases (TALENs)

CRISPR:

Clustered regularly interspaced short palindromic repeats (CRISPR)

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2 – *Alliance for Regenerative Medicine. https://alliancerm.org/available-products/. Last accessed: 6/7/2021*

TEMPs & Tissue-Derived Products

FDA Approved (OTAT)[1]

Cells & "Matrix":

GINTUIT (Allogeneic Cultured Keratinocytes and Fibroblasts in Bovine Collagen) – Organogenesis

MACI (Autologous Cultured Chondrocytes on a Porcine Collagen Membrane) – Vericel

Other:

RYPLAZIM (plasma-derived glu-pasminogen) – Prometic Biotherapeutics

FDA Approved (CDRH)[2]

Cells & "Matrix":

GAURIX (platelet-rich plasma gel) – Nuo Therapeutics

APLIGRAF (skin substitute) – Organogenesis, Inc. & Novartis Ag

CARDIOCEL – Admedus

DERMAGRAFT – Organogenesis

EPICEL – Vericel

Omnigraft – INTEGRA

Transcyte – ORGANOGENESIS

Up & Coming

OUS Approvals[2]:

KeraHeal-Allo – BIOSOLUTIONS (hydrogel-type allogeneic keratinocyte)

Spherox – CO.DON AG (spheroids of human autologous chondrocytes)

Heart Sheet – TERUMO BCT (skeletal myoblast preparation; Japan)

Holloderm – TEGO SCIENCES (S. Korea)

Hyalograft 3D – CHA BIO&DIOSTECH CO LTD (S. Korea)

JACC – J-TEC (Japan)

JACE – J-TEC (Japan)

Novocart 3D – AESCULAP BIOLOGICS (EMA)

Ortho-ACI – ORTHOCELL (Australia)

Ossron (India, S. Korea)

ReGenerCel – AVITA MEDICAL (EMA)

ReNovaCell – AVITA MEDICAL (EMA)

Vergenix FG – COLLPLANT (EMA)

Vergenix-STR – COLLPLANT (EMA)

1- *licensed products from the Office of Tissues and Advanced Therapies (OTAT). https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products. Last accessed: 6/7/2021*

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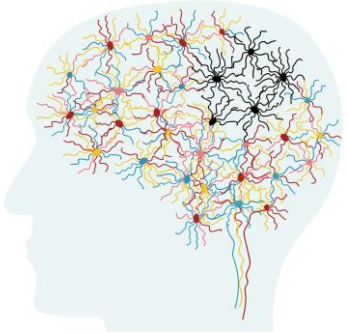
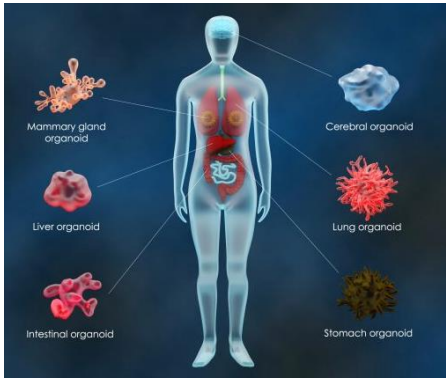
Regenerative Medicine Costs

- Goods & Manufacturing[1]
  - **$500,000** to **$1 million**
- Research & Development[2]
  - **$19.3 million** (investment between Newark and CIRM –NSCs for Alzheimer's disease)
  - **$24 million** (US Space & Naval Warfare Systems Center & WFIRM –advancing tissue organoids)
- Patient per treatment[3]
  - **$373k** (Kite Pharm/Gilead's Yescarta)
  - **$475k** (Novartis' Kymriah)
  - **Over $2 million** (Novartis' Zolgensma)





[1] https://www.cellandgene.com/doc/breaking-down-pricing-of-cell-gene-therapies-0001
[2] https://www.rdtaxsavers.com/articles/Regenerative-Medicine
[3] https://theactuarymagazine.org/gene-and-cell-therapies/

Themed Section: Curative Therapies Value Health 2019; 22(6):621-6

Estimating the Clinical Pipeline of Cell and Gene Therapies and Their Potential Economic Impact on the US Healthcare System

Casey Quinn, PhD,* Colin Young, PhD, Jonathan Thomas, BSc, Mark Trusheim, MSc, and the MIT NEWDIGS FoCUS Writing Group

Center for Biomedical Innovation, Massachusetts Institute of Technology, Cambridge, Massachusetts, USA.

Figure 2. Predicted cumulative product launches, 2018-2030.

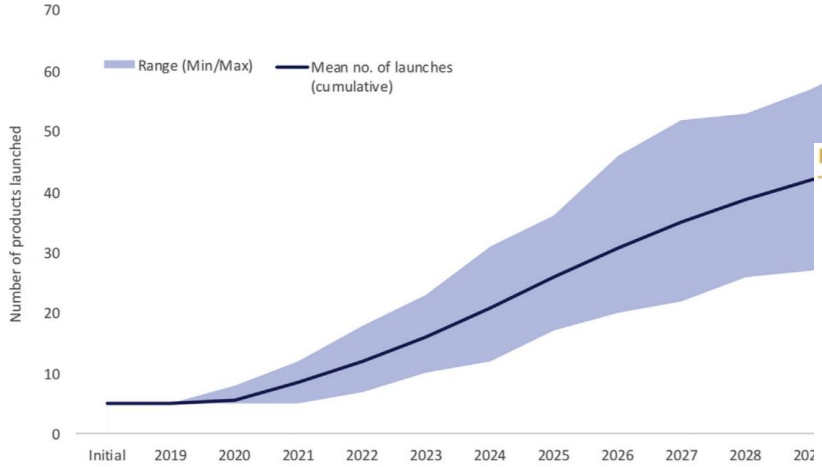
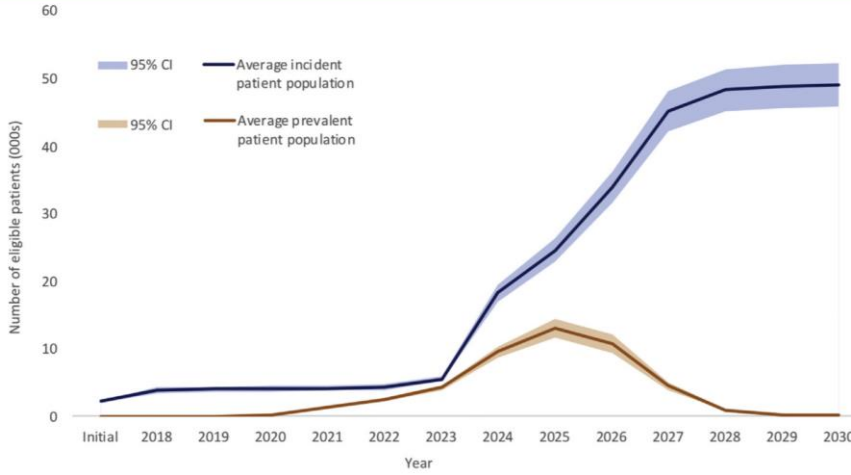


Figure 3. Predicted annual treated patient numbers, 2018-2030.

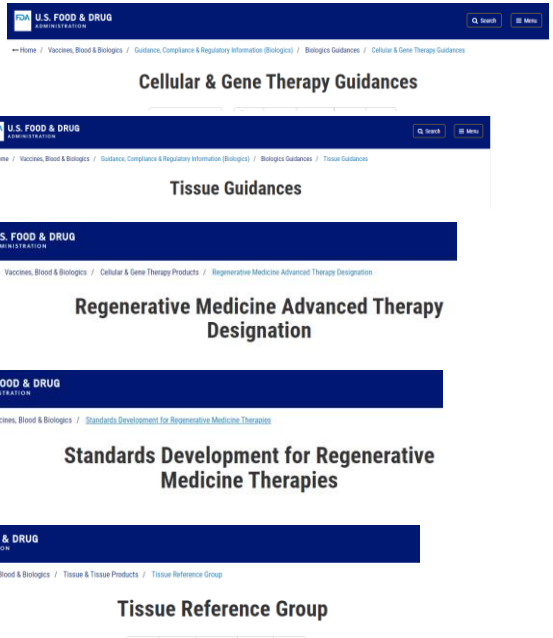


CI indicates confidence interval.

https://www.valueinhealthjournal.com/article/S1098-3015(19)30188-3/pdf

FDA Regulations & Guidance

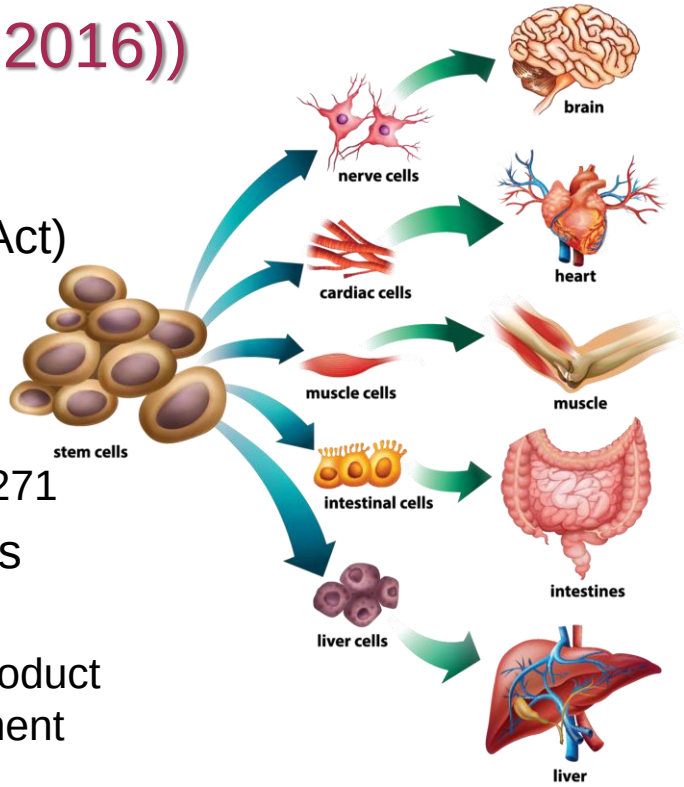
- Title 21 -Code of Federal Regulations (CFR)
  - Drugs: 21 CFR Parts 200-299, 300-369
  - Biologics: 21 CFR Parts 600-680
  - Devices: 21 CFR Parts 800-898
  - Human Cells, Tissues, & Cellular & Tissue-Based Products: 21 CFR Parts 1270/1271
  - Informed Consent/Institutional Review Boards: 21 CFR Parts 50/56
  - Good Laboratory Practice for Nonclinical Laboratory Studies: 21 CFR Part 58
  - Good Guidance Practices: 21 CFR Part 10
    - 2019 -FDA refined CMC guidance for RM & indication-specific guidances for gene therapy development



- CBER regulates cellular & gene therapy products

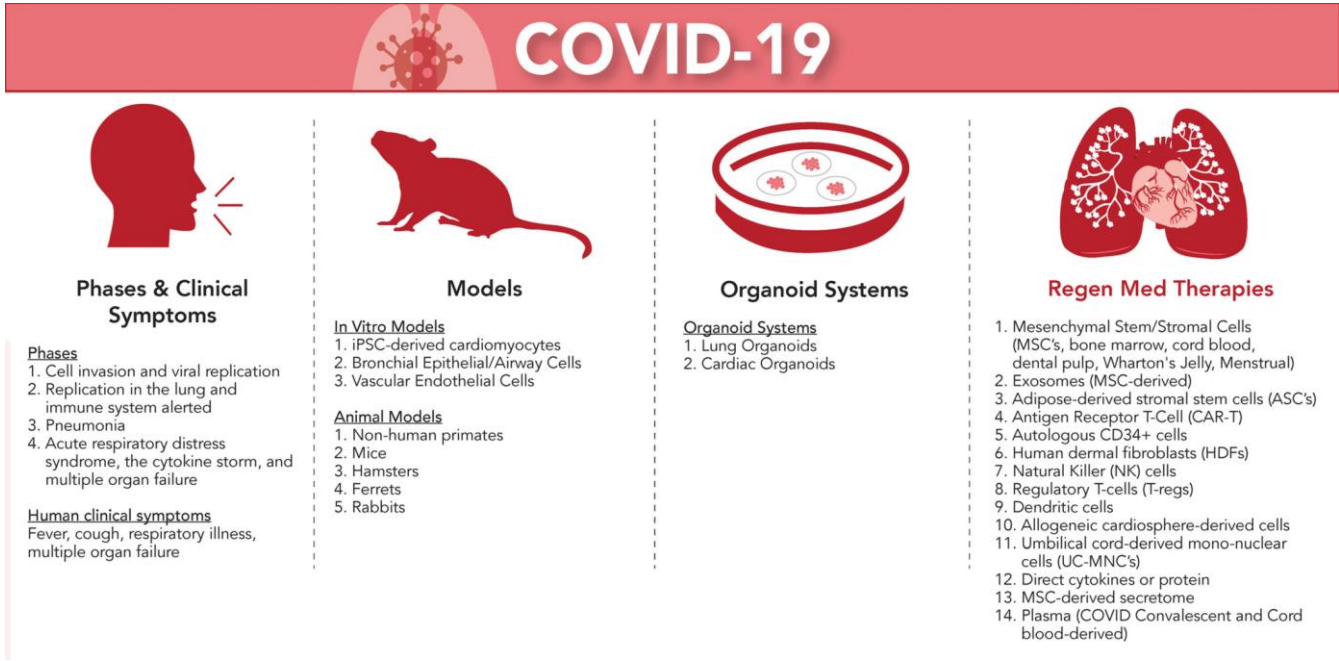
RMAT Designation
(§3033 of 21st Century Cures Act (Dec. 2016))

- **Criteria**
- Regenerative medicine therapy (§506(g) of FD&C Act)
  - Allogeneic & autologous cell therapies
  - Therapeutic tissue engineering product
  - Human cell & tissue product, or combo
    - not regulated under §361 PHSA and 21 CFR §1271
- Potential to address unmet medical need for serious condition
  - Preliminary clinical evidence generated using the product that the sponsor intends to use for clinical development
- Breyanzi® -1st therapy with RMAT (Feb. 2021)



Impact of COVID-19

- Coronavirus Treatment Acceleration Program (CTAP)
- RM resources to address COVID-19 (at right)



STEM CELLS Translational Medicine, 27 August 2020, DOI: (10.1002/sctm.20-0245)

Key Challenges

- **Complex manufacturing process for cell & gene therapies**
- **Need for CMC regulatory clarity & flexibility**
- **Supply chain interruptions**

Thank You!

Collin T. Stabler, PhD
Senior Associate, Exponent, Inc.
3440 Market Street, Suite 600
Philadelphia, PA 19104
Phone: 215.594.8931
Email: cstabler@exponent.com

Heather C. Hatcher, PhD
Regulatory Scientist, Womble Bond Dickinson (US) LLP
One West 4th Street
Winston-Salem, NC 27101
Phone: 336.728.7114
Email: heather.hatcher@wbd-us.com

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