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SCCTSI SOUTHERN CALIFORNIA CLINICAL AND TRANSLATIONAL SCIENCE INSTITUTE
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USC Mann Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences
Department of Regulatory and Quality Sciences

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DK Kim International Center for Regulatory Science

REGISTER NOW!

Regulatory Science Symposium

Innovations in Regenerative Medicine Products

Friday, October 20, 2023 | 9AM - 4:30 PM PST | Online via Zoom

Agenda

9:00 AM PDT	**Introduction** Eunjoo Pacifici, PharmD, PhD *USC Mann, SC-CTSI I Chair & Associate Professor, Dept. of Reg. & Quality Sciences* *Associate Director, DK Kim International Center for Regulatory Science*
9:30 AM PDT	**Regulatory Aspects of Cell Therapy and Regenerative Medicine** Nancy Pire-Smerkanich, DRSc *USC Mann Assistant Professor, Dept. of Reg. & Quality Sciences*
10:30 AM PDT	**Break**
10:45 AM PDT	**Translational Approach and Use of Stem Cells for Arthritis and Cartilage Restoration** Denis Evseenko, MD, PhD *Vice Chair for Research, J. Harold and Edna La Briola Endowed Chair | Professor of Orthopaedic Surgery | Stem Cell Biology and Regenerative Medicine, Keck School of Medicine, USC*
12:00 PM PDT	**Lunch**
1:00 PM PDT	**Cell Therapy Manufacturing** Mohamed Abou-El-Enein, MD, PhD, MSPH *Associate Professor of Medicine (Clinical Scholar), Pediatrics, and Stem Cell Biology & Regenerative Medicine | Executive Director, Joint USC/CHLA Cell Therapy Program*
2:00 PM PDT	**The Marriage of Ophthalmology and Bioengineering** Mark Humayun, MD, PhD *Director, Institute for Biomedical Therapeutics | Co-Director USC Roski Eye Institute | Director of Sensory Science Initiatives*
3:00 PM PDT	**Break**
3:15 PM PDT	**Target Identification for Gene Therapy** Robert Pacifici, PhD *Chief Scientific Officer, CHDI, Inc.*
4:15 PM PDT	**Wrap-Up** Eunjoo Pacifici, PharmD, PhD

Fall 2023 Regulatory Science Symposium

Innovations in Regenerative Medicine Products

Speaker Bios

Eunjoo Pacifici, PharmD, PhD

Chair and Associate Professor of Regulatory and Quality Sciences

Associate Director, D. K. Kim International Center for Regulatory Science

Phone: (323) 442-1975

Email: epacific@usc.edu

Biography

Dr. Eunjoo Pacifici received her BS in Biochemistry from University of California at Los Angeles followed by PharmD and PhD in Toxicology from University of Southern California. She conducted her graduate research in the laboratory of Dr. Alex Sevanian in the Institute for Toxicology at USC where she studied the mechanism of oxidative damage and repair in endothelial cell membrane. After receiving her graduate degrees, Dr. Pacifici worked at Amgen and gained experience in conducting clinical research with special focus on Asia Pacific and Latin America region. She initially worked in the clinical development group managing U.S. investigational sites and central laboratories and then went on to work in the Asia Pacific/ Latin America group interfacing with local clinical and regulatory staff in Japan, People's Republic of China, Taiwan, and Mexico. She represented regional clinical and regulatory views on therapeutic product development teams and led satellite task forces in order to align local efforts with U.S. activities. Her additional professional experiences include community pharmacy practice in various settings and clinical pharmacy practice at the Hospital of the Good Samaritan in Los Angeles. Dr. Pacifici currently serves as the Chair and Associate Professor of the Department of Regulatory and Quality Sciences and Associate Director of DK Kim International Center for Regulatory Science at University of Southern California working to provide the next generation of regulatory scientists with knowledge, tools, and skills to expedite the development of innovative, safe, and effective biomedical products.

Nancy Pire-Smerkanich, DRSc, MS

Assistant Professor of Regulatory and Quality Sciences

Associate Director, Regulatory Knowledge and Support

Phone: (323) 442-4822

Email: piresmer@usc.edu

Biography

Dr. Nancy Pire-Smerkanich received her faculty appointment after successfully completing her Doctoral Dissertation on “Benefits Risk Frameworks – Implementation in Industry” in 2015. In addition to teaching in courses related to drug development and clinical trials, she continues to provide regulatory guidance to industry peers. Nancy brings many years of practical regulatory knowledge and experience to academia where she participated in all regulatory aspects of product development, having served as Regulatory Liaison, US Agent, and Global Regulatory Lead across all therapeutic areas. Known for her dedication to education and mentoring across industry, Nancy continues to be recognized for her ability to provide accurate, relevant and dynamic instruction on both the technical and strategic aspects of global regulatory affairs and for her service to professional organizations such as the Drug Information Association (DIA) and The Organization for Professionals in Regulatory Affairs (TOPRA).

Mohamed Abou-el-Enein, MD, PhD, MSPH

Associate Professor of Medicine (Clinical Scholar), Pediatrics, and Stem Cell Biology & Regenerative Medicine

Executive Director, Joint USC/CHLA Cell Therapy Program

Email: Mohamed.Abouelenein@med.usc.edu

Biography

Dr. Abou-el-Enein is an Associate Professor of Clinical Medicine (Oncology), Pediatrics, and Stem Cell Biology & Regenerative Medicine at USC Keck School of Medicine and serves as the Executive Director of the Joint USC/CHLA Cell Therapy Program. He is also a member of the Norris Comprehensive Cancer Center.

He is also the Director of the cGMP Core facility at CHLA and the new unit at USC. Dr. Abou-el-Enein is a nationally and internationally recognized expert in planning and executing clinical development programs, designing and operating academic GMP facilities, and in translating cell and gene therapy products from preclinical stage to clinical applications. He has over 11 years of experience in clinical research and regulatory affairs and has successfully brought several cell-based therapies to early phase clinical trials.

Dr. Abou-el-Enein obtained his Bachelor of Medicine and Surgery (MBBCh) degree from Mansoura University in Egypt in 2005. In 2014, he completed a Masters of Pharmaceutical Sciences and Technologies from the University of Strasburg in France, a Clinical Research Diploma from Harvard Medical School, and a PhD in the Economics of Manufacturing Clinical-Grade Advanced Therapy Medicinal Products from Charité Medical University in Berlin. He obtained an MPH from the London School of Hygiene and Tropical Medicine and a Master in Manufacturing of Advanced Therapy Medicinal Products from the University of Granada in Spain in 2020.

Abou-el-Enein served as Head of the Clinical Development Platform and Head of Translational Research Unit at the BIH Center for Regenerative Therapies and Berlin Center for Advanced Therapies, respectively, both at the Charité Medical University in Berlin. Abou-el- Enein is one of the inaugural Lawrence Goldstein Policy Fellows of the ISSCR, associate Editor-in- Chief of Molecular Therapy – Methods and Clinical Development, served as regional secretary of the International Society of cell and gene therapy as well as on several other organizations and committees.

He has been recognized with multiple honors and awards, including the Max-Rubner Prize for Innovation and the Global Eisenhower Fellowship. His publications reflect global leadership in translational development of cell and gene therapy products in top-tier journals such as Cell Stem Cell, BMJ, Lancet Oncology, Molecular Therapy, Nature Biotechnology, Nature Reviews Clinical Oncology

Dr. Abou-el-Enein is a strong advocate for equitable access to safe and effective medical innovations. He is committed to addressing the risk associated with the global rise of clinics marketing unproven stem cell interventions.

Mark S. Humayun, MD, PhD

Professor of Ophthalmology

Cornelius J. Pings Chair in Biomedical Sciences

Director, USC Ginsberg Institute for Biomedical Therapeutics

Co-Director USC Roski Eye Institute

Email: humayun@usc.edu

Biography

Dr. Mark S. Humayun is an ophthalmologist, engineer, scientist and inventor and the only ophthalmologist ever to be elected a member of both U.S. National Academies of Medicine and Engineering. He is a university professor with joint appointments at the Keck School of Medicine of USC and the USC Viterbi School of Engineering.

U.S. President Barack Obama named Dr. Humayun a recipient of the National Medal of Technology and Innovation in December 2015. The award recognizes "those who have made lasting contributions to America's competitiveness and quality of life and helped strengthen the Nation's technological workforce."

Dr. Humayun co-invented the Argus Series retina implants, which are manufactured by Second Sight, and are intended to restore sight to the blind. The Argus Series implants were named by Time Magazine among the top 10 inventions of 2013.

He has more than 125 issued patents, and is a member of the National Academy of Inventors.

Denis Evseenko

Vice Chair for Research, J. Harold and Edna La Briola Endowed Chair

Professor of Orthopaedic Surgery,
Stem Cell Biology and Regenerative Medicine,
Keck School of Medicine, USC

Email: evseenko@usc.edu

Biography

Dr. Denis Evseenko is currently a Professor of Orthopaedic Surgery, Stem Cell Research and Regenerative Medicine at USC. Dr Evseenko was trained in both medicine and molecular pharmacology. His research focuses on the development of novel translational stem cell and small molecule-based approaches for prevention of arthritis and restoration of damaged articular cartilage. Dr. Evseenko has been involved in translational research for over 10 years and is the author of numerous peer-reviewed research articles, presentations and patents.

Robert Pacifici, PhD

Chief Scientific Officer, CHDI Foundation

Email: robert.pacifici@chdifoundation.org

Biography

Dr. Robert Pacifici is the Chief Scientific Officer of CHDI Foundation, a private, not-for-profit research organization that works with an international network of scientists to accelerate therapeutics development for Huntington's disease. Previously he was the Site Director and Chief Scientific Officer at the Research Triangle Park Laboratories of Eli Lilly and Company. There he oversaw the company's global screening and quantitative-biology efforts. Prior to joining Lilly, Pacifici was Vice President of Discovery Technologies at Xencor, a privately held biotechnology company that applied rational design principles to the development of protein therapeutics. At Amgen for nearly ten

years, Pacifici held positions of increasing responsibilities including leadership for their automation, high throughput screening, and information technologies groups.

He received a BS in Biochemistry from the University of Massachusetts, Amherst, and a PhD in Biochemistry from the University of Southern California.

Outside of CHDI, Robert currently participates in several external boards and advisory committees including: An adjunct appointment at the University of Southern California's (USC) Department of Molecular Pharmacology and Toxicology; USC Board of Supervisors of the International Center for Regulatory Science; Council member for National Institutes of Health/National Institute of Neurological Disorders and Stroke (NIH/NINDS) from 2011 util 2014; Panel of Experts for National Center for Advancing Translational Sciences (NCATS) at NIH, in the NIH Center for Translational Therapeutics (NCTT). This division is home to two programs that seek to advance promising therapeutic agents through late-stage preclinical development: Therapeutics for Rare and Neglected Diseases (TRND), and Bridging Interventional Development Gaps (BrIDGs); Chair, Working Group for the NINDS Anticonvulsant Screening Program; Member, Spinal Muscular Atrophy Foundation Scientific Advisory Board; Member, DART Rx, Scientific Advisory Board.

Robert has previously served on: Chair, NIH/NINDS Spinal Muscular Atrophy Project's Scientific Steering Committee; Advisor, Marigold Foundation for Myotonic Dystrophy; Advisor, Cooperative International Neuromuscular Group (CINRG) the clinical research arm of the Duchenne Muscular Dystrophy Research Center (DMDRC) and the Center for Genetic Medicine Research at the Children's National Medical Center (CNMC); Member, Science Advisory Board for Edison Pharmaceuticals; Member, TREAT ALS Steering Committee; Member, Pathogenesis of Facioscapulohumeral Muscular Dystrophy advisory board.

He also serves in the non-scientific capacity of Board Member with the Asia America Symphony Association. Robert, his wife Eunjoo, and his two children Sarina and Noah, live in Palos Verdes Estates, California. Robert is an avid amateur road-cyclist and a classic BMW enthusiast.

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Regulatory Science Symposium: Innovations in Regenerative Medicine Products

Eunjoo Pacifici, PharmD, PhD
Chair and Associate Professor, Regulatory and Quality Sciences
Associate Director, DK Kim International Center for Regulatory Science

October 20, 2023

Welcome, All!

HYBRID EVENT:

- In-person students (RSCI 606/MPTX 521-Emerging Technologies)
- Online Attendees from Clinical & Translational Science Consortia and Guests

Questions are welcome at the end of each presentation!

In-person attendees please raise your hand and wait for the microphone

Online attendees please use the “Chat” feature and your question will be read by our virtual moderator

SC CTSI Clinical Research Support (CRS)

A single stop for accessing all services an investigator and research team needs to develop, activate, conduct, and report results for human subject research studies.

Contact
Ari Padilla, MBA
Program Manager, Clinical Research Support

Contact Information:
crs@sc-ctsi.org

Services

- Clinical research coordinators for hire
- Research navigation
- Recruitment support
- Budget preparation support

Clinical Trials Unit (CTU)

- Skilled research and nursing staff
- Services to support highly-complex human subjects research studies
- Specimen processing lab

Voucher Program

- Awards up to $3,000 to generate new data for development of clinical and/or community research projects

Clinical Trial Quality Training Series

- Module 1: **Monitoring** of a Clinical Trial Site + Ch.4 Addendum Remote Monitoring
- Module 2: **Auditing** of a Clinical Research Site
- Module 3: Site Readiness for **FDA Inspection (Launching 2024)**

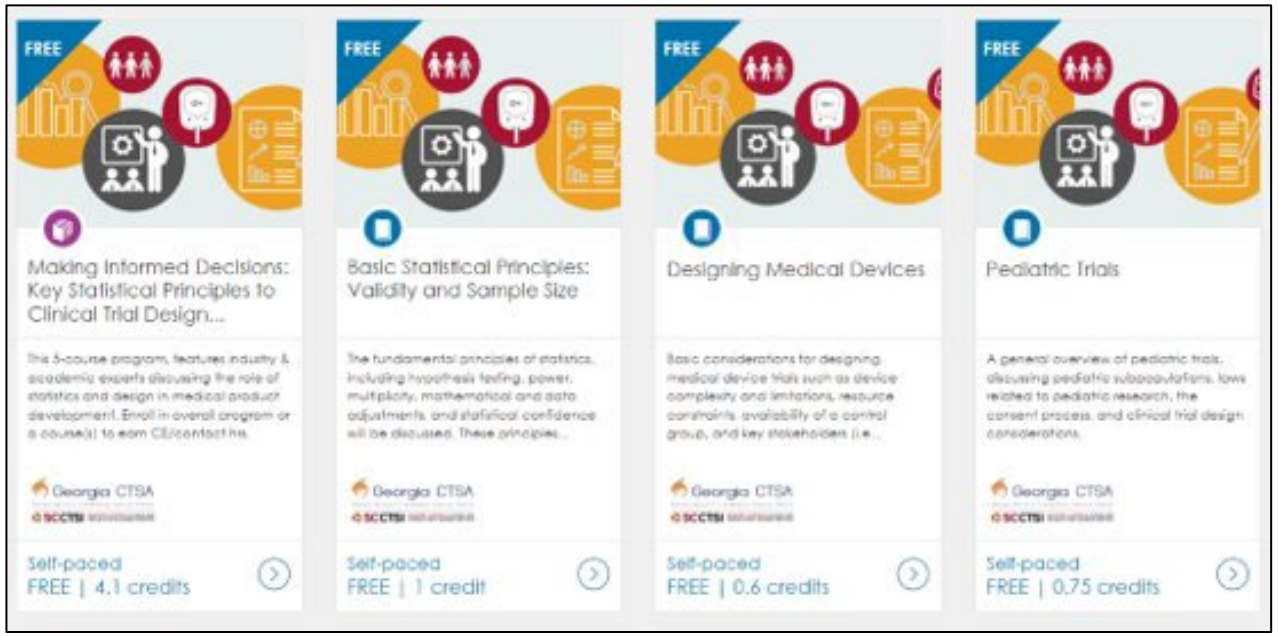
Access this free resource:

1. Go to: http://uscregsci.remote-learner.net
2. Sign In/Create a new account
   For new accounts, open your email and confirm
3. Select the module and click “Enroll Me”

Georgia CTSA and SC CTSI: Online Course Catalog

Earn CE credits for clinical research professionals with self-paced modules

- Registration provides unlimited access to all courses and programs in the Online Course Catalog
- Free, high quality certificate programs for clinical research professionals at novice to expert levels of experience.
- Obtain CE / contact hours can be used to meet renewal requirements for certifications, annual reviews, and advancement.
- To get started: https://twd.ce.emorynursingexperience.com/



Web Portal

In Development

- One-stop shop for regulatory resources
- Streamline translation of IITs to treatment

UP-23-00757

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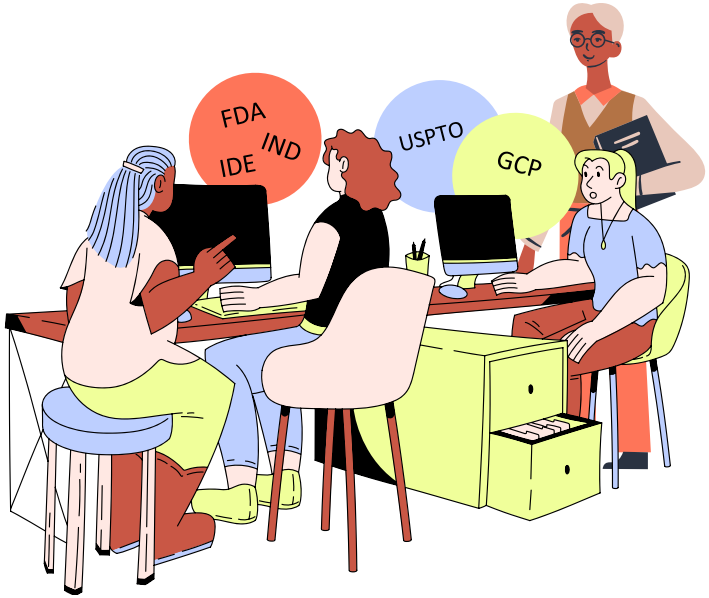
Regulatory Knowledge & Support

Calling all Researchers and Investigators

Help us understand your challenges in obtaining regulatory resources to advance your research

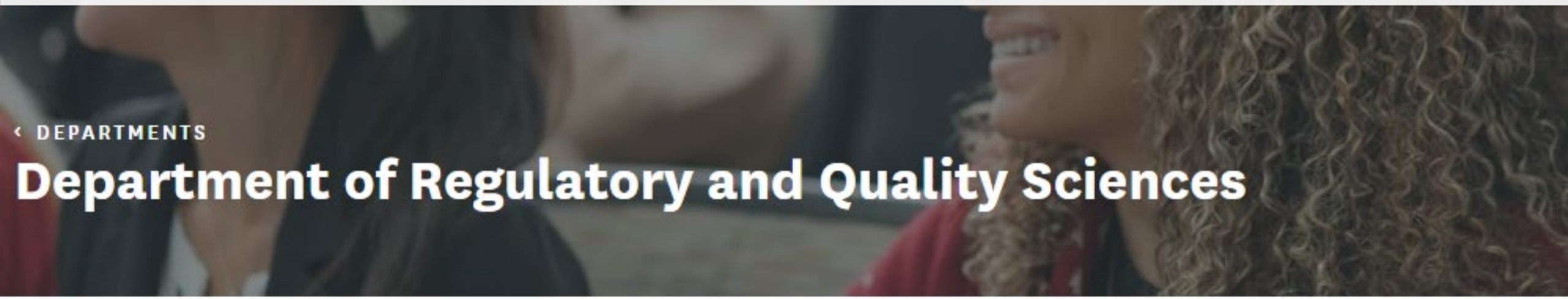


Who can participate?

- Clinical research professional
- Work in an academic institution
- ≥ 18 years old

Survey responses will be used in the creation of an interactive web portal.

Find us on our website: https://regulatory.usc.edu/



Department of Regulatory & Quality Sciences

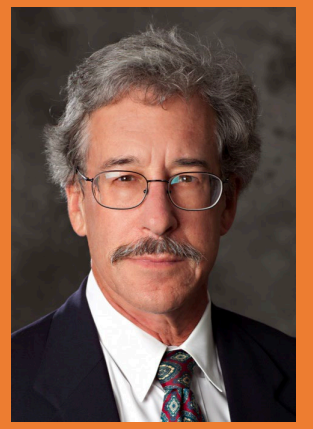
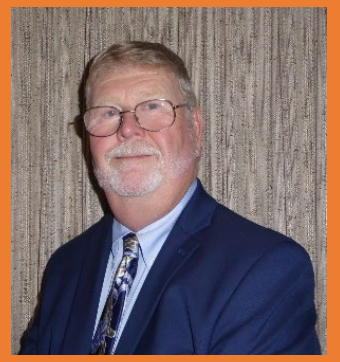
Advancing the Profession

One of the first programs in this dynamic arena, the Department of Regulatory and Quality Sciences remains a global leader in producing professionals with the knowledge and skills to manage regulated biomedical products worldwide. This rapidly growing and increasingly global field encompasses every aspect of pharmaceutical and medical device development, quality assurance and clinical trials oversight—helping shepherd life-improving and often lifesaving advances to the marketplace.




Faculty

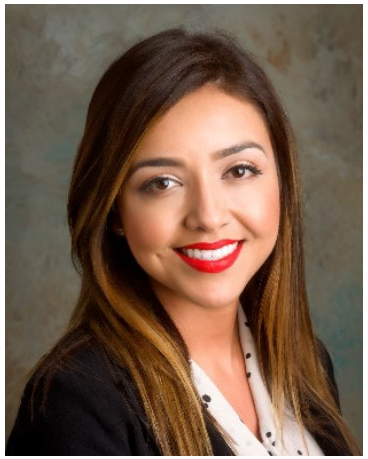
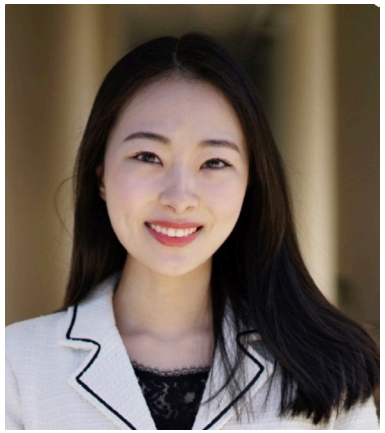


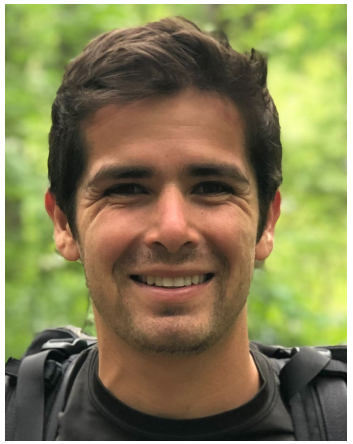









Our staff

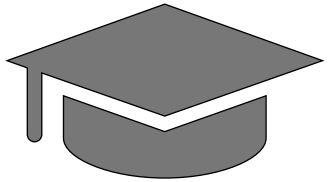



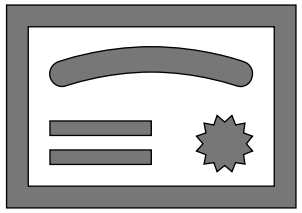







Degree Programs





Six Graduate Streams

- DRSC
- MS Regulatory Science
- MS Regulatory Management
- MS Management of Drug Development
- MS Medical Product Quality
- **MS Clinical Trial Management (COMING Fall 2024)**

Certificate Programs

- Food safety
- Regulatory Science
- Early Drug Development
- Clinical Design and Management
- Patient and Product Safety

Nancy Smerkanich
DRSc, MS

Assistant Professor
Department of Regulatory and Quality Sciences

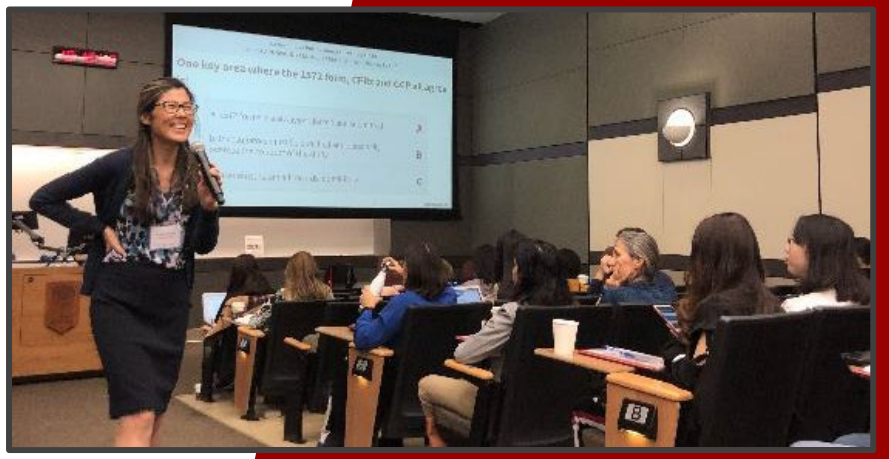
piresmer@usc.edu

MS in Clinical Trial Management

Desirae Hernandez, MPA
Program Manager,
Department of Regulatory and Quality Sciences
Email: desiraeh@usc.edu

Regulatory Science Symposiums

- **2015 -** Clinical Trial Hurdles
- **2016 Spring** - Clinical Trial Startup
- **2016 Fall** - Monitoring and Auditing
- **2017 Spring** - Clinical Trials in Special Populations
- **2017 Fall** - Clinical Trials in the Era of Emerging Technologies and Treatments
- **2018 Spring** - Regulatory Aspects of Clinical Trial Design
- **2018 Fall** - Pharmacovigilance and Safety Reporting
- **2019 Spring** - Patient-Centered Drug Development and Real-World Evidence/Data
- **2019 Summer** - Clinical Trials with Medical Devices
- **2019 Fall** - Legal Aspects of Conducting Clinical Trials
- **2020 Spring** - Quality by Design in Clinical Trials
- **2020 Fall –** Diversity in Clinical Trials in the Time of COVID-19
- **2021 Spring** – Clinical Research Career Pathways (half-day)
- **2021 Spring** – Principles of Global Clinical Research for Medical Devices
- **2021 Fall** – Innovation to Translation: Role of Genomics in Medical Product Development
- **2022 Spring** – Make Informed Decisions: Key Statistical Principles to Clinical Trial Design
- **2022 Fall** – Emerging Technologies – The Digital World
- **2023 Spring** - Study Designs for Clinical Trials – Types and Trends
- **2023 Fall –** Innovations in Regenerative Medicine Products



We have hosted 18 symposiums!

Today's Program: Innovations in Regenerative Medicine Products

9:00 AM PDT	**Introduction** Eunjoo Pacifici, PharmD, PhD
9:30 AM PDT	**Regulatory Aspects of Cell Therapy and Regenerative Medicine** Nancy Pire-Smerkanich, DRSc
10:30 AM PDT	**Break**
10:45 AM PDT	**Translational Approach and Use of Stem Cells for Arthritis and Cartilage Restoration** Denis Evseenko, MD, PhD
12:00 PM PDT	**Lunch**
1:00 PM PDT	**Cell Therapy Manufacturing** Mohamed Abou-El-Enein, MD, PhD, MSPH
2:00 PM PDT	**The Marriage of Ophthalmology and Bioengineering** Mark Humayun, MD, PhD
3:00 PM PDT	**Break**
3:15 PM PDT	**Target Identification for Gene Therapy** Robert Pacifici, PhD
4:15 PM PDT	**Wrap-Up** Eunjoo Pacifici, PharmD, PhD

Before the end of today's symposium, you will receive a link to take the program evaluation.

Please complete the program evaluation to receive an electronic certificate of completion by **Friday, November 3**.

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Thank You!

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USC Mann
Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences
Department of Regulatory and Quality Sciences

regulatory.usc.edu
Phone: (323) 442-3521
Email: regsci@usc.edu
Instagram: @epacifici_uscregsci
Facebook: @RegSci

Regulatory Aspects of Cell Therapy and Regenerative Medicine

Nancy Pire-Smerkanich, DRSc, MS

University of Southern California • Children's Hospital Los Angeles
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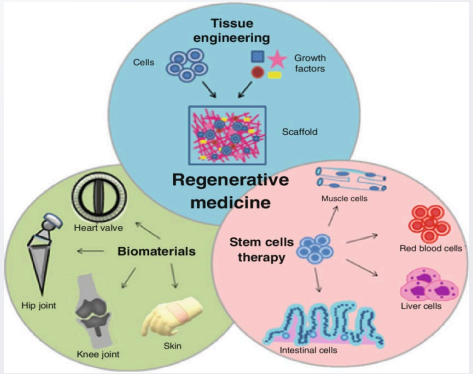
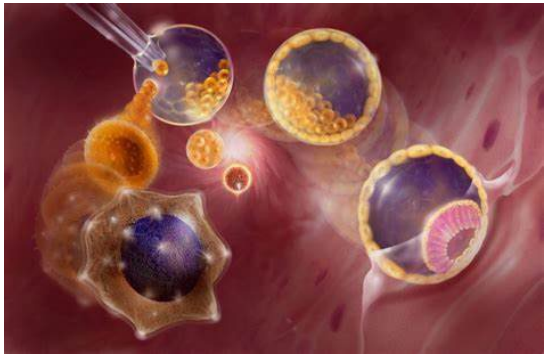
Agenda

1. Definitions
2. FDA Oversight
3. Regenerative Medicine
4. Expedited Development



Definitions

Cell Therapy- involves the transfer of cells with relevant/desired function into the patient.



Gene therapy - involves the transfer of genetic material in a carrier or vector and the uptake of the gene into targeted cells.

Definitions

Regenerative Medicine - refers to a general approach to restore, replace, or recreate cells, tissues, or organs to treat or mitigate disease.

- Involves using stem cells, engineered biomaterials, gene editing, and other technologies

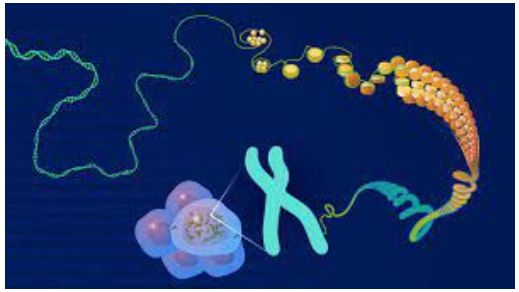
Definitions

NOTE:

Cell and Gene Therapies are Biologics!

There are some protocols that use both gene and cell therapy

For example: stem cells are isolated from the patient, genetically modified in culture to express a new gene, typically using a viral vector, expanded to sufficient numbers and then returned to the patient.



Small Molecule (Drug) vs Large Molecule (Biologic)

Drugs:

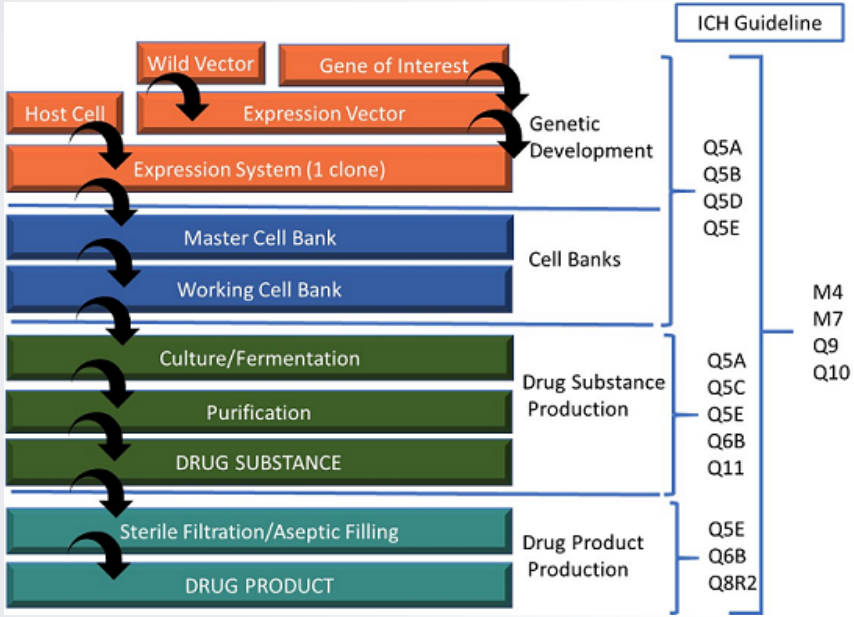
- Simple, well defined, independent of manufacturing process
- Produced by chemical synthesis
- Predictable chemical process
- Identical copy can be made
- Easy to characterize completely
- Stable
- Mostly non-immunogenic

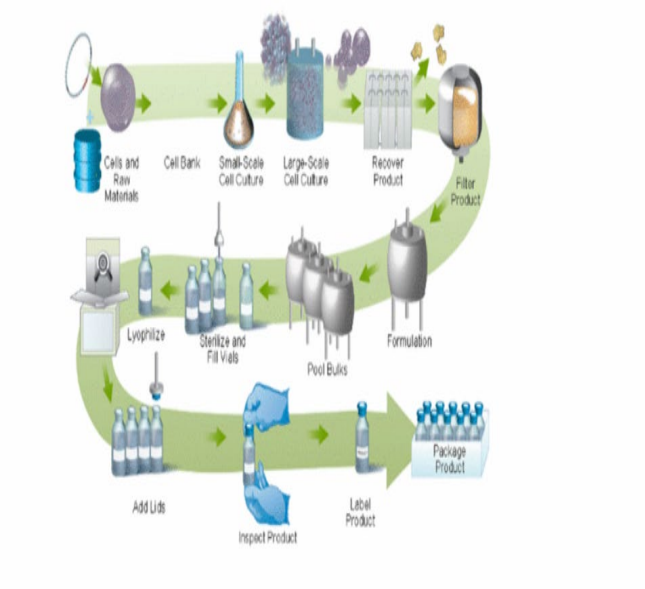
Biologics

- Complex (heterogeneous), defined by the exact manufacturing process
- Produced in living cell culture
- Difficult to control from starting material to final API
- Impossible to ensure identical copy
- Cannot be characterized completely (e.g., molecular composition and heterogenicity)
- Unstable, sensitive to external conditions

The process is the product!

Biologic Products Depend on Process





Regulations

Regenerative medicine therapies (RMTs) are defined in section 506 (g) (8) of the Food Drug & Cosmetic Act except for those regulated solely under section 361 of the Public Health Service Act (42 U.S.C. 264) and Title 21 of the Code of Federal Regulations Part 1271 (21 CFR Part 1271)123.

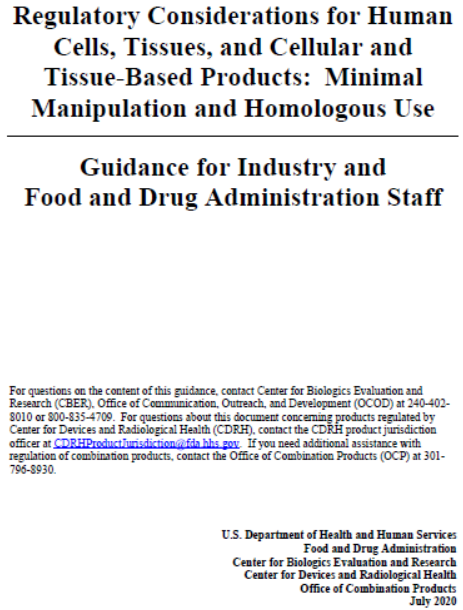
Translation:

Section 361 are the regulations to control communicable diseases (e.g., Covid)

Part 1271 established donor-eligibility, current good tissue practice (GTP), and other procedures to prevent the introduction, transmission, and spread of communicable diseases by HCT/P's

Human Cells, Tissues, and cellular and tissue-based Products(HCT/P)

- Those products that are regulated under 21CFR1271
  - Human cells or tissues that are intended for implantation, transplantation, infusion, or transfer into a human recipient
  - Examples: Bone, ligament, skin, dura matter, heart valve, cornea, semen, reproductive tissue, epithelial cells on a synthetic matrix, and hematopoietic stem/progenitor cells from peripheral and cord blood



Regulatory Considerations for Human Cells, Tissues, and Cellular and Tissue-Based Products: Minimal Manipulation and Homologous Use

Guidance for Industry and Food and Drug Administration Staff

For questions on the content of this guidance, contact Center for Biologics Evaluation and Research (CBER), Office of Communication, Outreach, and Development (OCOD) at 240-402-8010 or 800-835-4709. For questions about this document concerning products regulated by Center for Devices and Radiological Health (CDRH), contact the CDRH product jurisdiction officer at CDRHProductJurisdiction@fda.hhs.gov. If you need additional assistance with regulation of combination products, contact the Office of Combination Products (OCP) at 301-796-8930.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
Center for Devices and Radiological Health
Office of Combination Products
July 2020

Regulations for Cell Therapies

- In addition to 21CFR1271 for GTP these products may have to follow these regulations as part of development:
- 21CFR 312 for Investigational New Drug Applications
- 21CFR 600/610 for Biologics Establishment and Biologic Product Standards
- 21 CFR 210 and 211 for Good Manufacturing Practices

FDA Oversight

CDER (Drugs and Therapeutic proteins)
CBER (Vaccines, Blood & Biologics)
Medical Devices
Office of Combination Products
Other Offices:
- Food
- Radiation-Emitting Products
- Animal & Veterinary
- Cosmetics
- Tobacco

FDA Oversight/CBER

- Several “Offices” within CBER
- CBER Regulates blood and blood products, vaccines, tissue and tissue products, and cellular and gene therapies.
- Current Structure:
    - Office of Therapeutic Products (OTP)
    - A designated “Super Office” since 9/2022
    - Formerly known as the Office of Tissues and Advanced Therapies (OTAT)
    - Increase review capabilities and enhance expertise on new cell and gene therapies.

Guidance for Industry

- 32 Guidance documents since 2007 (1 from 1998)
- Some focusing on therapeutic area (i.e., cancer)
- Some of regulatory requirements (i.e., IND or BLA)
- Many on the requirements/role of manufacturing
- Testing and use of viral vectors
- Most recent guidance (July 2023) on "Manufacturing Changes and Comparability for Human Cellular and Gene Therapy Products", Draft still out for comment

OTP Regulated Products

Gene Therapies

- **Gene editing**
- **Ex vivo genetically modified cells**
- **Non-viral vectors** (e.g., plasmids)
- **Replication-deficient viral vectors** (e.g., adenovirus, adeno-associated virus, lentivirus)
- **Replication-competent viral vectors** (e.g., measles, adenovirus, vaccinia)
- **Microbial vectors** (e.g., *Listeria*, *Salmonella*)

Stem Cells/Stem Cell-Derived

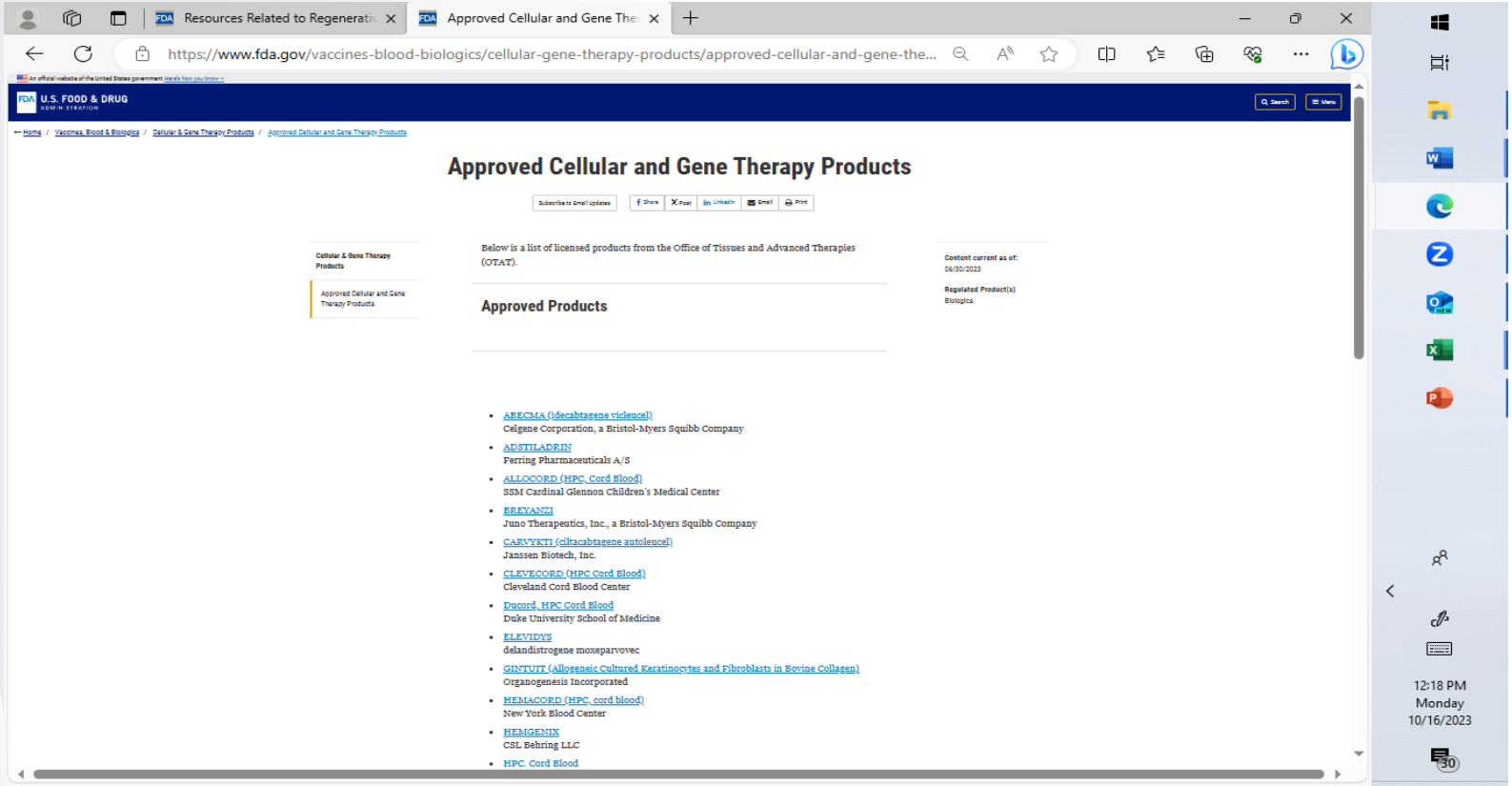
- **Adult** (e.g., hematopoietic, neural, cardiac, adipose, mesenchymal)
- **Perinatal** (e.g., placental, umbilical cord blood)
- **Fetal** (e.g., neural)
- **Embryonic**
- **Induced pluripotent stem cells** (iPSCs)

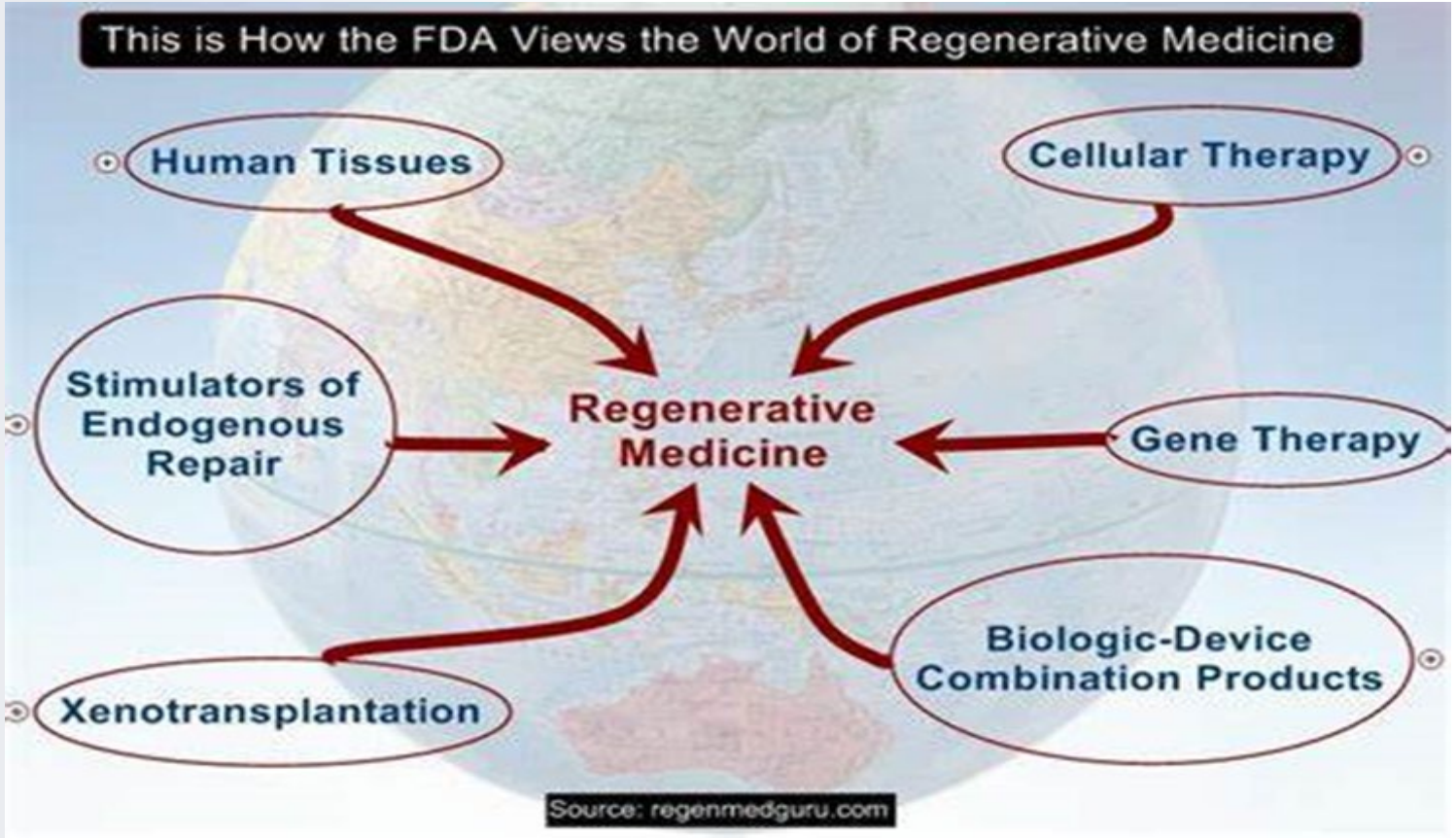
- **Tissues**
- **Blood- and plasma-derived products**
  - Coagulation factors
  - Fibrin sealants
  - Fibrinogen
  - Thrombin
  - Plasminogen
  - Immune globulins
  - Anti-toxins
  - Venom antisera for scorpions, snakes, and spiders

- **Functionally mature/differentiated cells** (e.g., retinal pigment epithelial cells, pancreatic islets, chondrocytes, keratinocytes)
- **Therapeutic vaccines and other antigen-specific active immunotherapies**
- **Combination products**
  - Engineered tissues/organs
- **Devices**
- **Products for xenotransplantation**

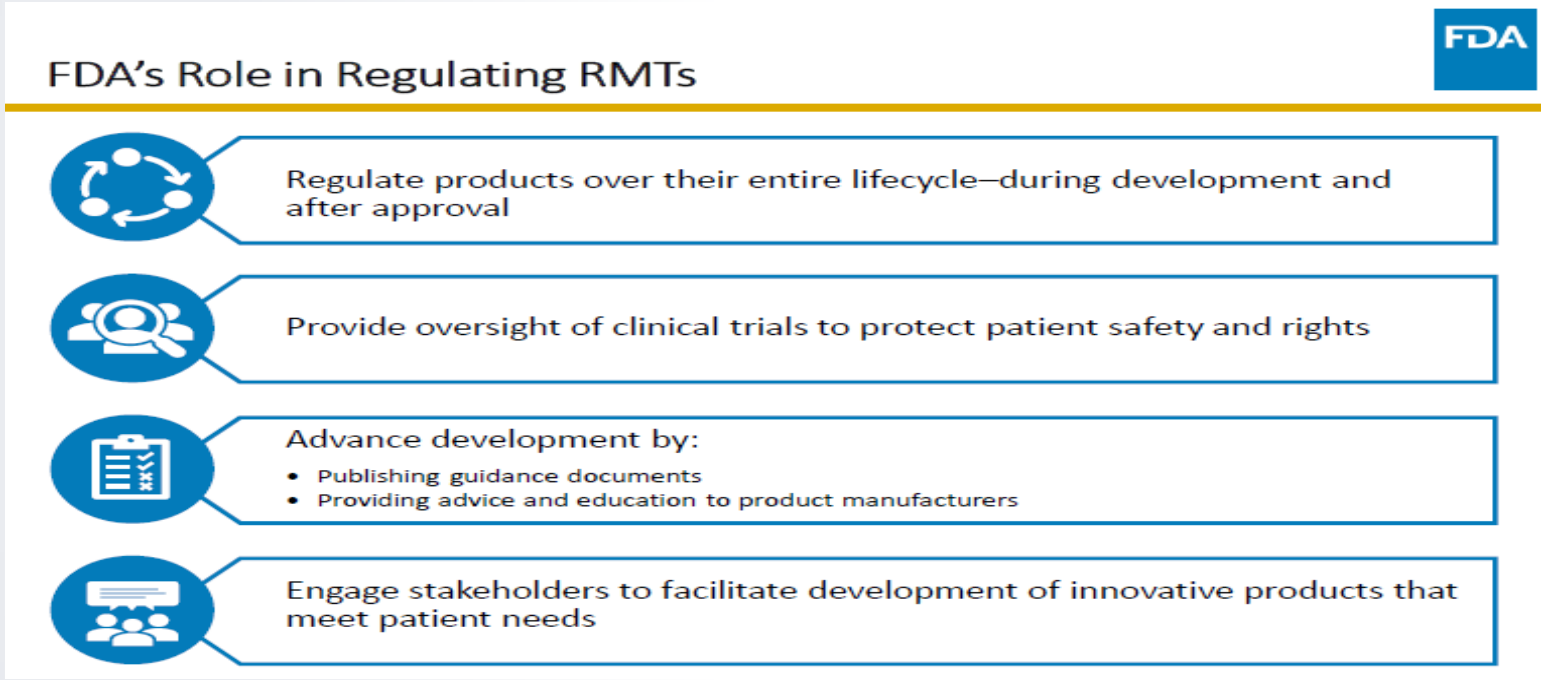
Office of Therapeutic Products (OTP)

Approved Cellular and Gene Therapy Products | FDA




This is How the FDA Views the World of Regenerative Medicine
Human Tissues
Cellular Therapy
Stimulators of Endogenous Repair
Regenerative Medicine
Gene Therapy
Biologic-Device Combination Products
Xenotransplantation
Source: regenmedguru.com

Regenerative Medicine 101



Regenerative Medicine 101

Advancing Development: Today, Tomorrow & Beyond

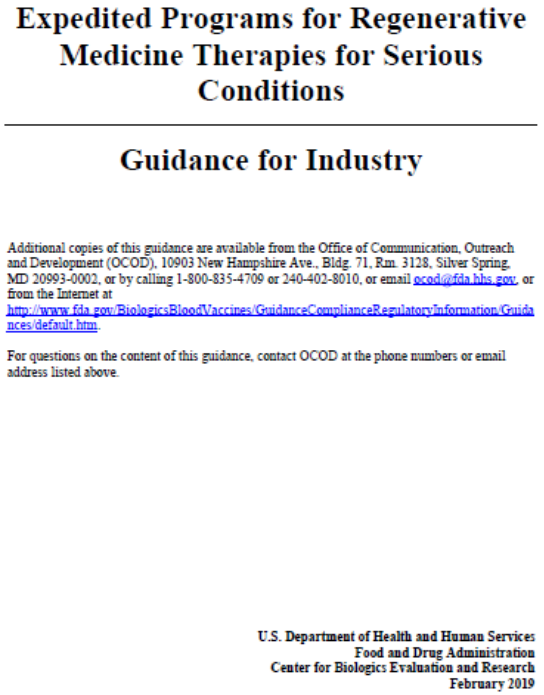
- Gene and cell therapies hold great promise for patients with difficult diseases and few treatment options
- 900+ investigational new drug (IND) applications for ongoing clinical studies for gene and cell therapy treatments
- Gene therapy has great potential for patients with rare diseases:
  - An estimated 80% of rare diseases are caused by a single-gene defect
- New: Bespoke Gene Therapy Consortium (BGTC)
  - Partnership between National Institutes of Health (NIH), FDA, pharmaceutical companies and nonprofit organizations
  - Goal: Accelerate development of gene therapies for the 30 million people in the United States who suffer from a rare disease

RMAT

- Legislatively established as part of the 21st Century Cures Act to facilitate the development and review of certain RMTs (Ref: Section 3033)
- How to qualify:
  - The product has to be a regenerative medicine therapy (see definition)
  - The product must be intended to treat, modify, reverse, or cure a serious or life-threatening disease or condition;
  - There needs to be preliminary clinical evidence that indicates that the product has the potential to address unmet medical needs for that disease or condition

RMAT Designation

- The request for RMAT designation must be made either concurrently with submission of an Investigational New Drug application (IND) or as an amendment to an existing IND.
- FDA/CBER will not grant a RMAT designation if an IND is on hold or is placed on hold during the designation review



Expedited Programs for Regenerative Medicine Therapies for Serious Conditions

Guidance for Industry

Additional copies of this guidance are available from the Office of Communication, Outreach and Development (OCOD), 10903 New Hampshire Ave., Bldg. 71, Rm. 3128, Silver Spring, MD 20993-0002, or by calling 1-800-835-4709 or 240-402-8010, or email ocod@fda.hhs.gov, or from the Internet at http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/default.htm.

For questions on the content of this guidance, contact OCOD at the phone numbers or email address listed above.

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Biologics Evaluation and Research
February 2019

RMAT Designation

- Same benefits as Fast Track and Breakthrough Therapy Designation including early interactions w/FDA
- 91 Designations so far (230 requests as of Jun 30, 2023)
- Designated products are eligible as appropriate for priority review and accelerated approval *
- Expanded range of options for fulfilling post approval requirements of accelerated approval *

**See Peter Marks quote*

Use of Expedited Programs

Many of the Biologic License Applications (BLA) have had success with expedited programs and faster, smoother reviews

- Orphan product designation and approval
- Priority review
- Accelerated approval
- Fast track
- Breakthrough therapy
- Most recent program - Regenerative Medicine Advanced Therapies (RMAT) from 21st Century Cures Act in December 2016 – 1st designation submission came in 1 day after Act was signed into law

Early Communication with CBER/OTP

- From FDA Guidance

- Pre-preIND, now referred to as Interact, meetings
  - Non-binding, informal scientific discussions between CBER/OTP nonclinical review disciplines (P/T & CMC) and the sponsor: INTERACT-CBER@fda.hhs.gov
  - Initial targeted discussion of specific issues
- Pre-IND meetings
  - Non-binding, but formal between FDA and sponsor (minutes generated)
  - Sponsor should provide summary data and sound scientific principles to support use of a specific product in a specific patient population

FDA and Sponsor Interactions to Expedite Development

INitial Targeted Engagement for Regulatory Advice on CBER producTs (INTERACT)*

- Early interaction with sponsors and replaced the pre-pre-IND meeting process across the Center regarding preclinical, manufacturing and, clinical development plans
- Approximately 30% of requests are granted

FDA and Sponsor Interactions to Expedite Development

CBER Advanced Technology Team (CATT)**

- Interactive mechanism for discussion of advanced technologies or platforms needed for development of CBER-regulated biologics products; CATT allows access to early and ongoing interactions with CBER before filing of a regulatory submission
- Primary focus on platforms for manufacturing

*https://www.fda.gov/BiologicsBloodVaccines/ResourcesforYou/Industry/ucm611501.htm
**https://www.fda.gov/vaccines-blood-biologics/industry-biologics/cber-advanced-technologies-team-catt

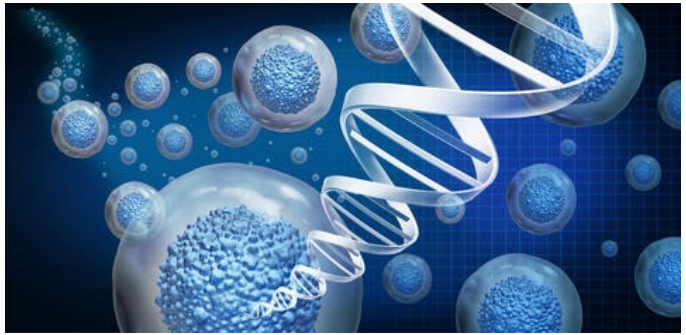
CBER RMAT Approvals = 5

Data as of June 30, 2023

Application Number	Submission Type and Number	Proprietary Name	Established Name	Applicant	Approval Date	Use
BLA 125720	ORIGINAL-1	ROCTAVIAN	valoctocogene roxaparvovec-rvox	Biomarin Pharmaceutical, Inc.	29-Jun-2023	For the treatment of adults with severe hemophilia A (congenital factor VIII deficiency with factor VIII activity <1 IU/dL) without pre-existing antibodies to adeno-associated virus serotype 5 (AAV5) detected by an FDA approved test.
BLA 125774	ORIGINAL-1	VYJUVEK	beremagene geperpavec-svdt	Krystal Biotech, Inc.	19-May-2023	Treatment of wounds in patients 6 months of age and older with dystrophic epidermolysis bullosa with mutation(s) in the collagen type VII alpha 1 chain (COL7A1) gene.
BLA 125685	ORIGINAL-1	RETHYMIC	Allogeneic processed Thymus Tissue	Enzyvant Therapeutics GmbH	08-Oct-2021	Immune reconstitution in pediatric patients with congenital athymia.
BLA 125730	ORIGINAL-1	StrataGraft	Allogeneic Keratinocyte Cell Line (NIKS), Seeded on Rat Collagen (BD) Conditioned with Human Dermal Fibroblasts (Clonetics)	Stratatech Corporation	15-Jun-2021	Indicated to promote durable wound closure & regenerative healing in the treatment of adult patients with debrided thermal burns that contain intact dermal elements, and for which surgical intervention is clinically indicated.
BLA 125714	ORIGINAL-1	BREYANZI	lisocabtagene maraleucel	Juno Therapeutics, a Celgene Company	05-Feb-2021	Treatment of adult patients with relapsed or refractory (R/R) large B-cell lymphoma after at least two prior therapies.

* RMAT designation was enacted in the 21st Century Cures Act on December 13, 2016.

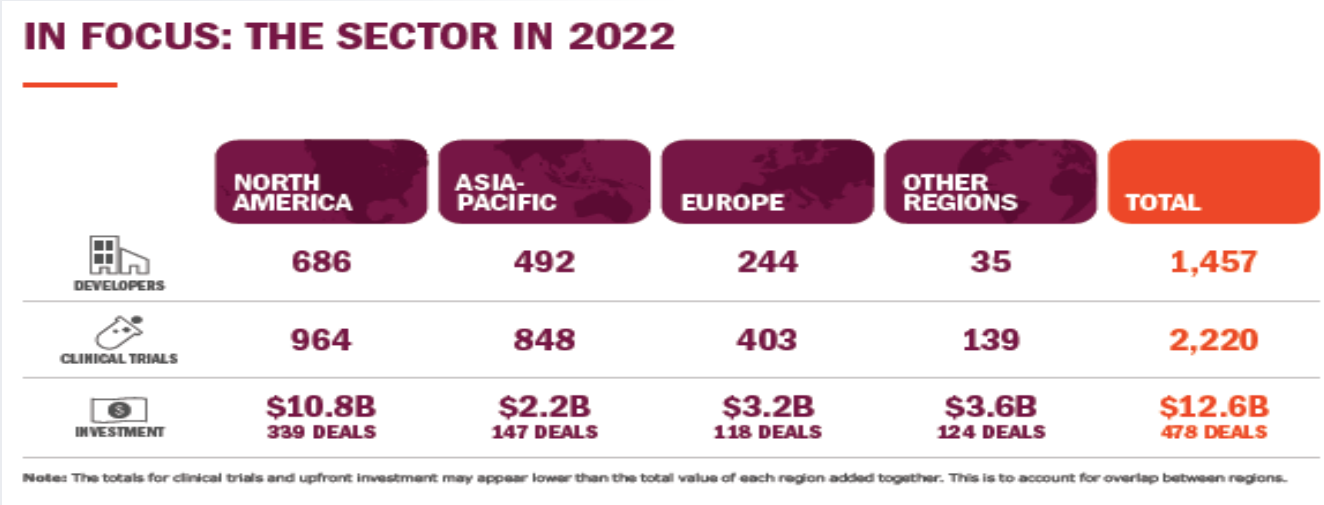
Content current as of:
07/21/2023



CBER Regenerative Medicine Advanced Therapy (RMAT) Approvals | FDA

Regenerative Medicine Globally

From the Alliance for Regenerative Medicine



IN FOCUS: THE SECTOR IN 2022

	NORTH AMERICA	ASIA-PACIFIC	EUROPE	OTHER REGIONS	TOTAL
DEVELOPERS	686	492	244	35	1,457
CLINICAL TRIALS	964	848	403	139	2,220
INVESTMENT	$10.8B 339 DEALS	$2.2B 147 DEALS	$3.2B 118 DEALS	$3.6B 124 DEALS	$12.6B 478 DEALS

Note: The totals for clinical trials and upfront investment may appear lower than the total value of each region added together. This is to account for overlap between regions.

Regenerative Medicine Globally

APPROVED THERAPIES IN 2022

NEW THERAPIES APPROVED

Carvykti (CAR-T)
LEGEND BIOTECH & JANSSEN - US AND EU

Roctavian (Gene Therapy)
BIOMARIN PHARMACEUTICAL - EU

Upstaza (Gene Therapy)
PTC THERAPEUTICS - EU

Hemgenix (Gene Therapy)
UNIQURE AND CSL BEHRING - US

Adstiladrin (Gene Therapy)
FERRING PHARMACEUTICALS - US

Ebvallo (Cell Therapy)
ATARA BIOTHERAPEUTICS - EU

THERAPIES APPROVED IN NEW GEOGRAPHIES OR NEW INDICATIONS

Breyanzi (CAR-T)
BRISTOL-MYERS SQUIBB - US AND EU

Kymriah (CAR-T)
NOVARTIS - US

Yescarta (CAR-T)
KITE PHARMA (GILEAD) - US AND EU

Zynteglo (Gene Therapy)
BLUEBIRD BIO INC. - US

Skysona (Gene Therapy)
BLUEBIRD BIO INC. - US

Regenerative Medicine Pipeline

POSSIBLE REGULATORY DECISIONS IN 2023

UNITED STATES

AFAMI-CEL (CELL THERAPY) *Adaptimmune Therapeutics* Advanced synovial sarcoma	**BB1111 (GENE THERAPY)** *bluebird bio* Sickle cell disease	**B-VEC (GENE THERAPY)** *Krystal Bio* Dystrophic epidermolysis bullosa	**CTX001 (GENE EDITING THERAPY)** *Vertex Pharmaceuticals & CRISPR Therapeutics* Sickle cell disease, ß-thalassemia
HPC CORD BLOOD (CELL THERAPY) *StemCyte* Unrelated donor hematopoietic progenitor cell transplantation	**LIFILEUCEL (CELL THERAPY)** *Iovance* Metastatic melanoma	**OMIDUBICEL (CELL THERAPY)** *Gamida Cell* Hematological malignancies	**REMESTEMCEL-L (CELL THERAPY)** *Mesoblast* Steroid-refractory Acute Graft Versus Host Disease
ROCTAVIAN (GENE THERAPY) *BioMarin Pharmaceutical* Hemophilia A	**SRP-9001 (GENE THERAPY)** *Sarepta Therapeutics* Duchenne muscular dystrophy	**TAB-CEL (CELL THERAPY)** *Atara Biotherapeutics* Epstein-barr virus associated post transplant lymphoproliferative disorder (EBV-PTLD)	

Recent comments from FDA/CBER

"Use of novel endpoints and clinical trial designs, manufacturing process standardization, enhanced communication with regulatory authorities, and global regulatory convergence together could go a long way toward facilitating the availability of these potentially life-saving treatments. The facilitation of advances in each of these areas could combine to allow those populations both large and small affected by addressable conditions to derive the potential benefits of gene therapy"

Peter Marks,
Director CBER
Full article: Enhancing gene therapy regulatory interactions (tandfonline.com)

Cell and Gene Therapy Resources - US

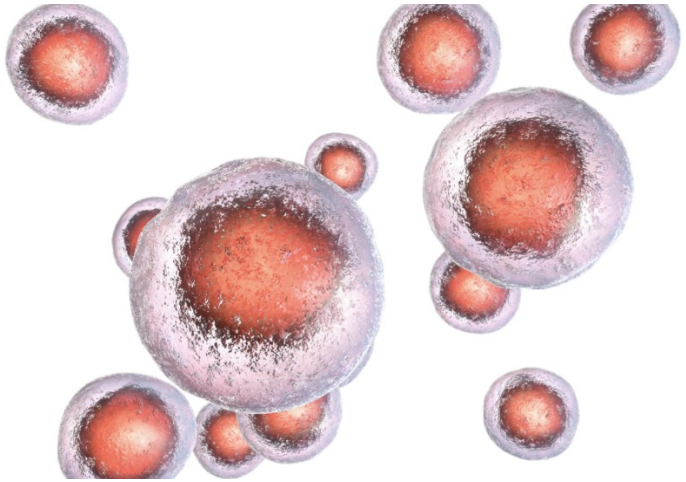
Center for Biologics Evaluation and Research (CBER) | FDA

Cellular Therapy Products | FDA

Cellular & Gene Therapy Guidances | FDA

Cellular, Tissue, and Gene Therapies Advisory Committee October 31, 2023 Meeting Announcement - 10/31/2023 | FDA

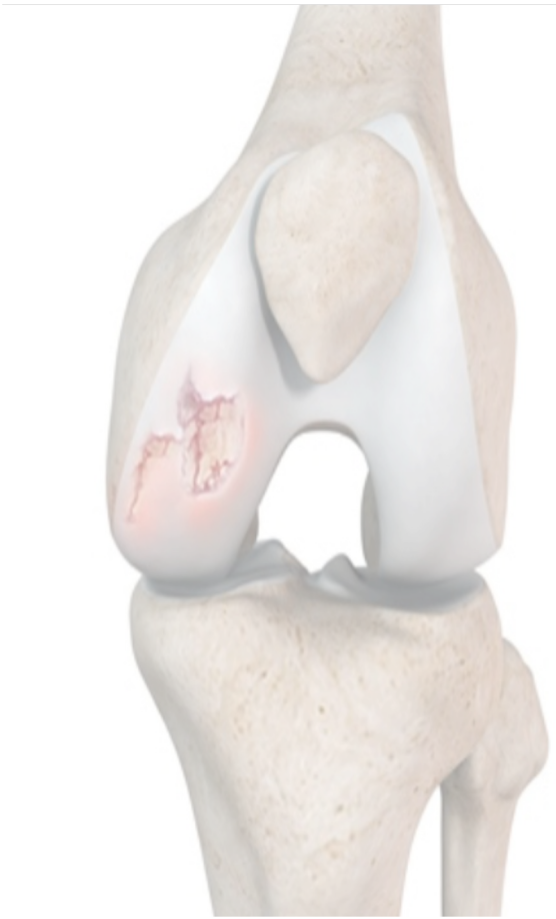
Translational Approach and Use of Stem Cells for Arthritis and Articular Cartilage Restoration



Denis A Evseenko MD., PhD

Vice Chair for Research, J. Harold and Edna La Briola Endowed Chair,
Professor of Orthopaedic Surgery,
Stem Cell Biology and Regenerative Medicine,
Keck School of Medicine, USC

USC, October 20, 2023



Keck School of Medicine of USC

USC Stem Cell

Conflict of interest disclosure

Co-founder, consultant and significant shareholder of:

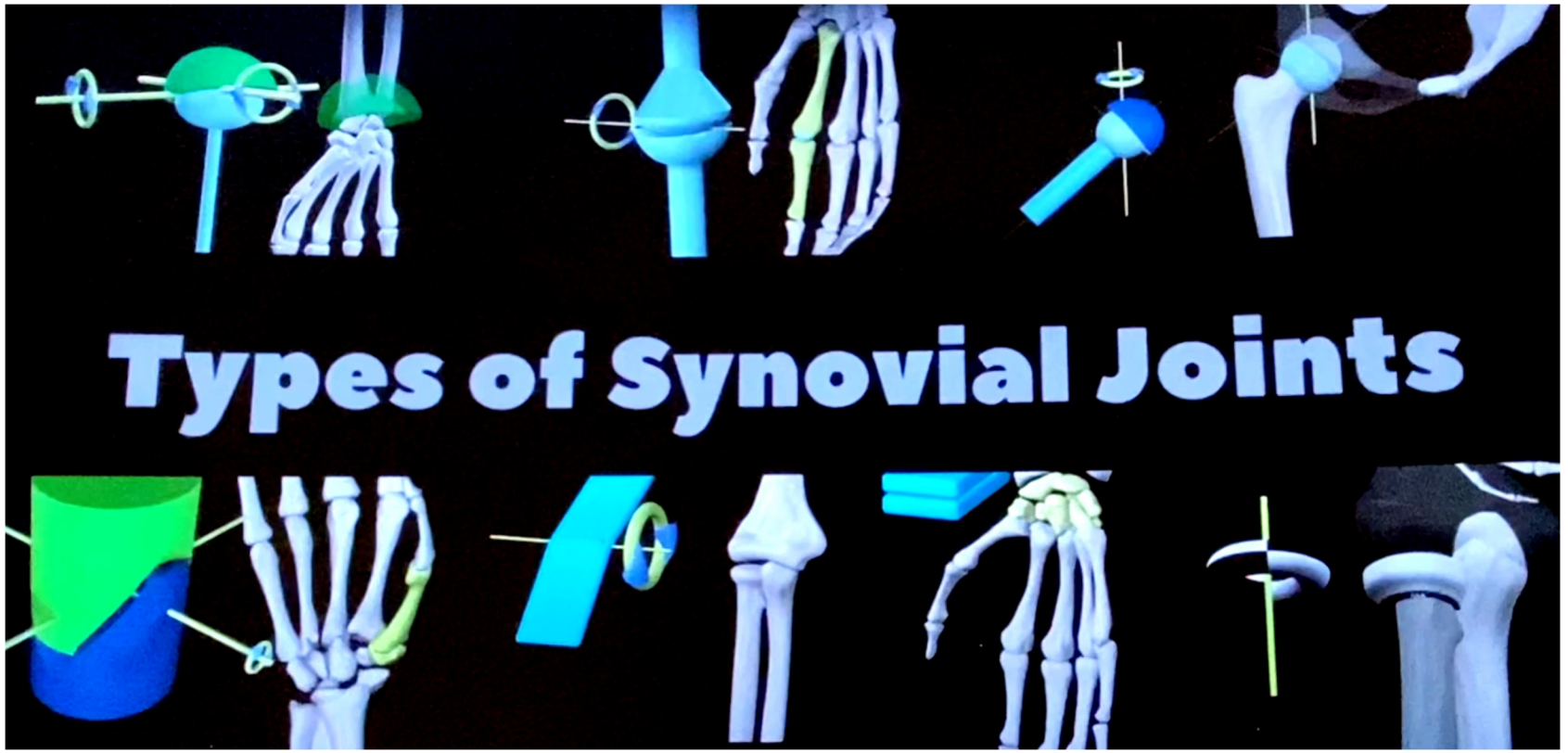
Plurocart - cartilage repair

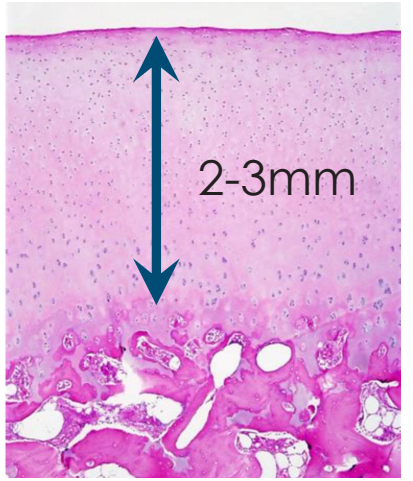
CARTHRONIX - osteoarthritis and fibrotic diseases

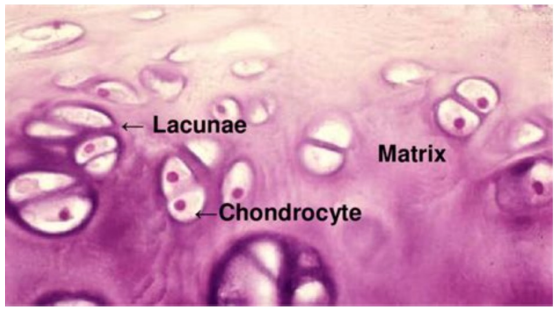
REPARRIS - solutions for healthy aging

Synovial joints

Synovial joint: a structure where bones connect for the purpose of moving body parts
Human adult has ~ 206 named bones and 250 joints (one bone can be part of more than 1 joint)
6 different types of synovial joints: Ball-and-Socket Joints, Condyloid Joints, Gliding Joints, Hinge Joints, Pivot Joints, Saddle Joints

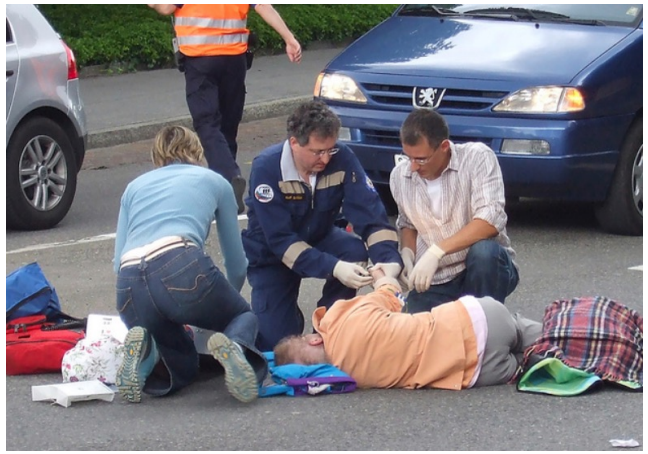


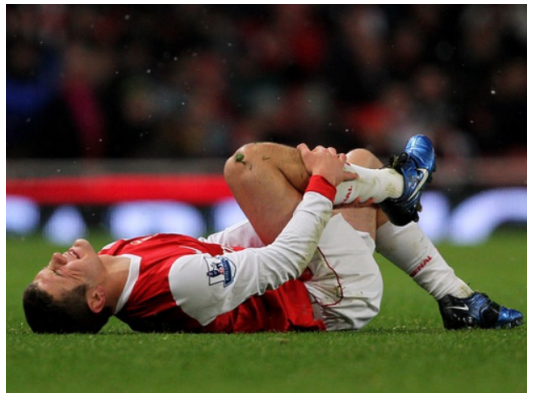




Benefits and the cost: Diseases of synovial joints

Injuries



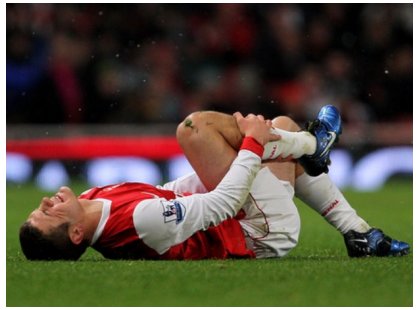


Arthritis

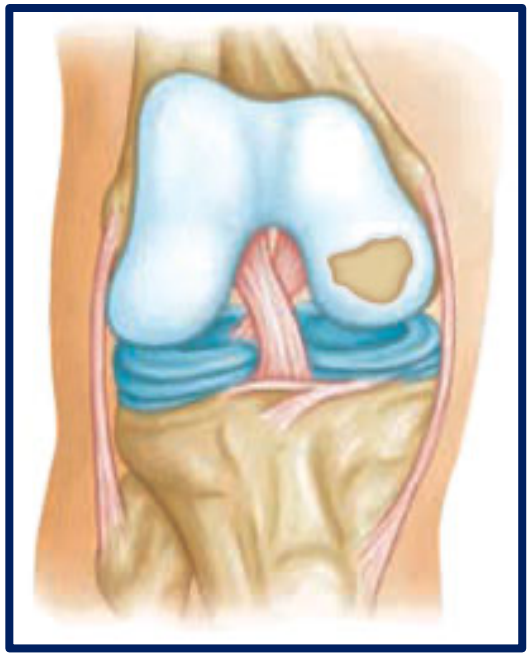
Osteoarthritis #1

Cartilage lesions
Autoimmune diseases
Cristalophathy (e.g. gout)
Infectious diseases (septic arthritis)

Focal cartilage lesions



Focal femoral defect, knee



- Usually young patients, no comorbidities
- No spontaneous regeneration of articular cartilage in adult (no or minimal number of progenitors, no vascularization)
- If not treated usually progresses to osteoarthritis

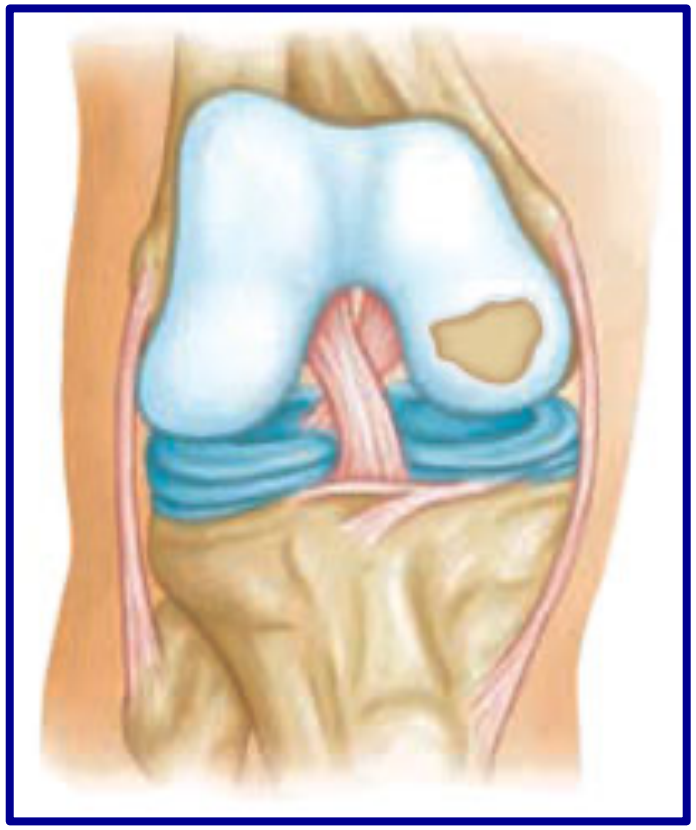
Ideal situation for the "Replace" approach:
local defect, invasive procedures are unlikely to cause any serious adverse events, healthy young patients

Focal cartilage lesions often predispose to osteoarthritis

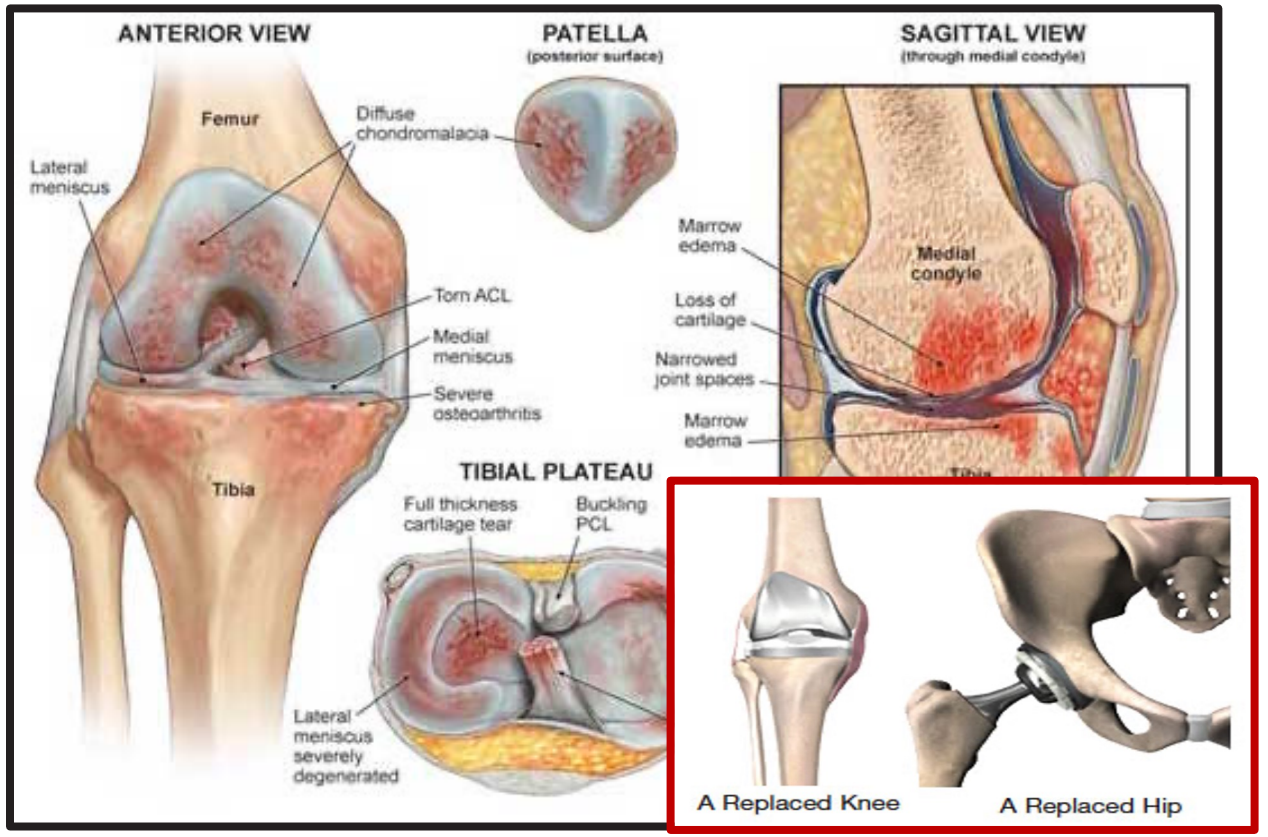
10 % of adult Californians have focal articular cartilage lesions

The lab has small molecule-based solutions RCGD family of drugs for this stage but not cells – too late

Focal defect



Degenerative Joint Disease/Osteoarthritis

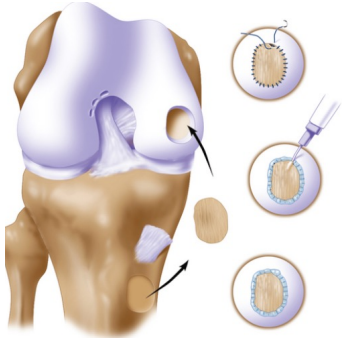


Articular cartilage defects do not regenerate in adult

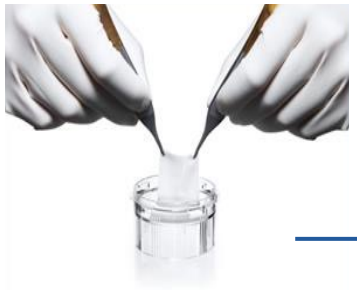
Current cell-based strategies have limitations

Autologous Chondrocyte Implantation

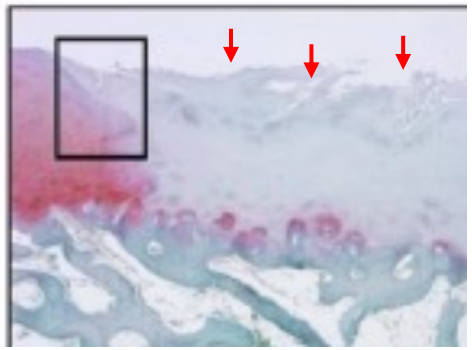
ACI



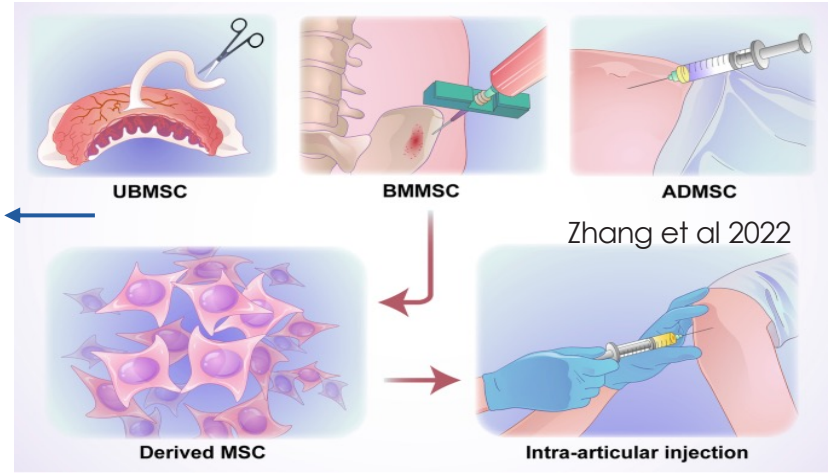
MACI®



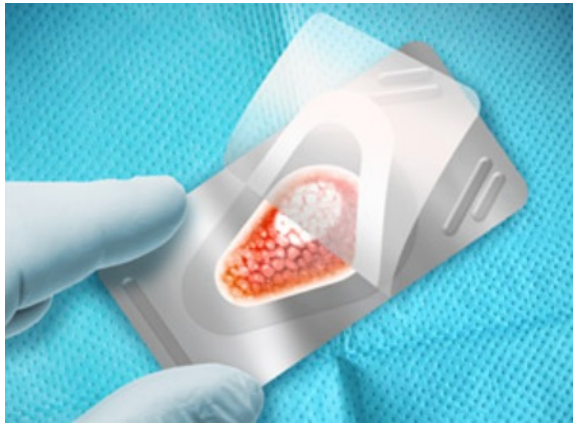
Typical outcome:
Disorganized fibrocartilage



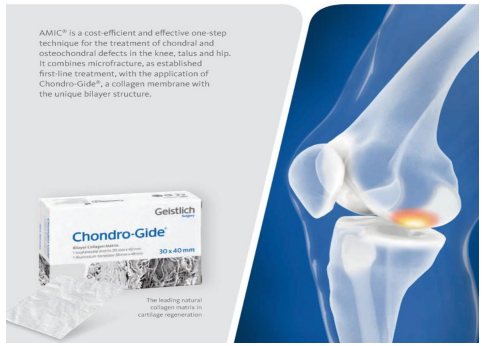
Injections of mesenchymal cells



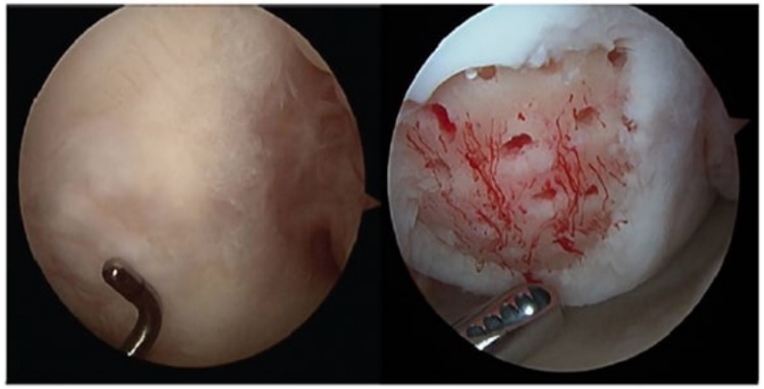
De Novo®



Amic®



Microfracture



Autologous chondrocytes - what is missing?

- Very limited number of cells are usually obtained, ex vivo expansion results in a significant loss of the chondrogenic potential

Investigations & Diagnostics

Morphological Assessment of MACI Grafts in Patients with Revision Surgery and Total Joint Arthroplasty

CARTILAGE
2021, Vol. 13(Suppl 1) 526S–539S
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DOI: 10.1177/1947603519890754
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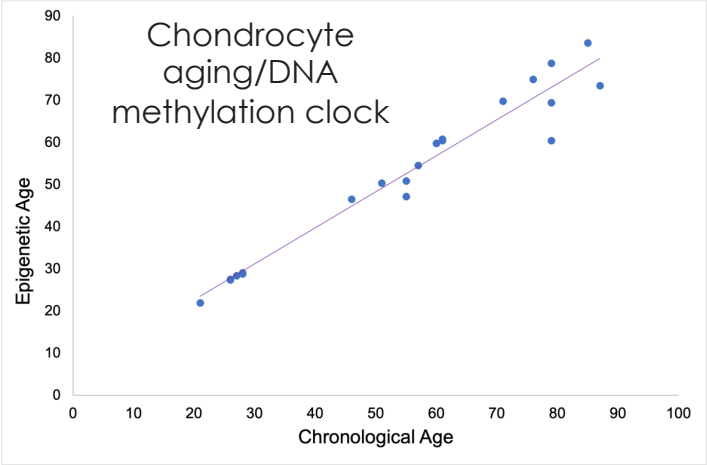
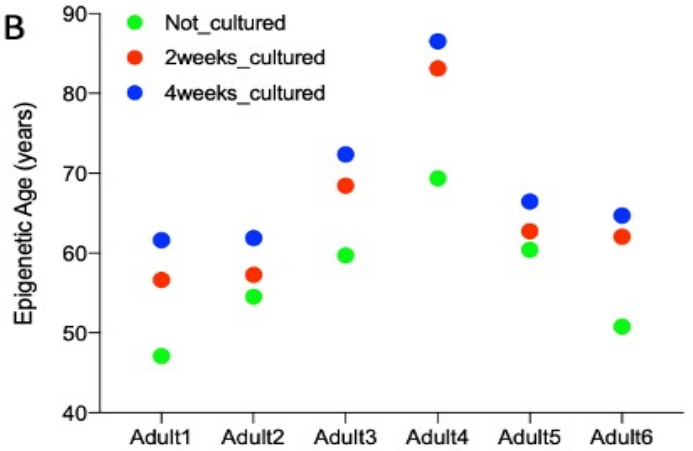
SAGE

Aswin Beck[1], David Wood[1], Christopher J. Vertullo[2], Jay Ebert[3], Greg Janes[4], Martin Sullivan[5], and Ming-Hao Zheng[1]



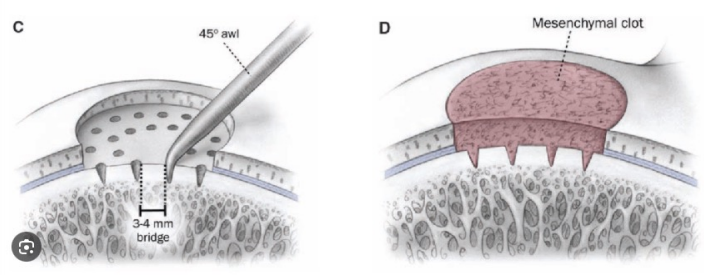
Clinically beneficial, but: "Histologically, the predominant tissue was of fibrocartilaginous nature".

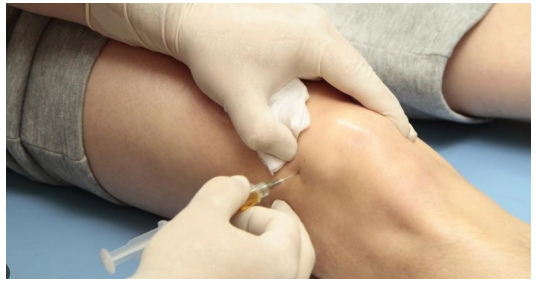
- Phenomenon of accelerated aging ex vivo – NOT "dedifferentiation" during expansion



Sarkar et al, Evseenko; *Aging Cell 2023*

MSCs, local or injected systemically- what is missing?





- **Microfracture: local cells migrate into the defect but form fibrocartilage**

- **Injected MSCs - these cell types do not show engraftment and long-term functional integration** (may be transient positive effects on microenvironment, inflammation, pain etc)

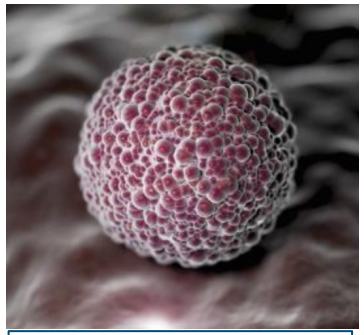
- There is no definitive evidence to date that mesenchymal stromal cells/MSCs of any origin can make proper articular cartilage tissue in vivo.

- **Reason:** lack of the intrinsic potential or a critical inducive signal is missing.

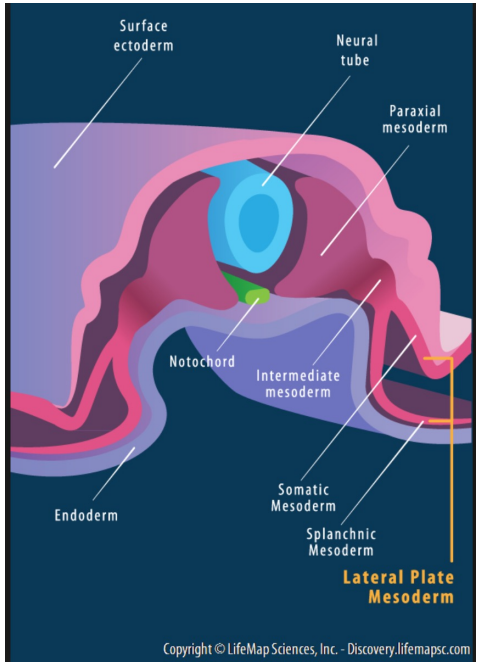
Specification of articular cartilage cells in humans

Can we reproduce it in the dish?

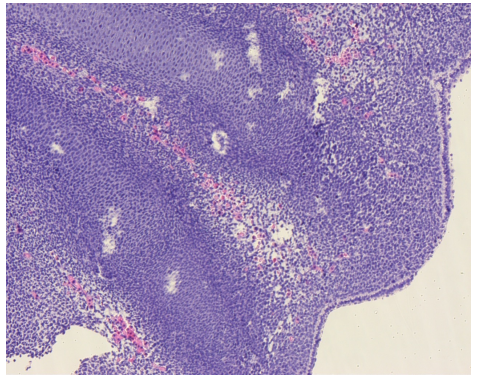
Morula | 21 day | 4-6 weeks | After 7-8 weeks | Postnatal articular cartilage



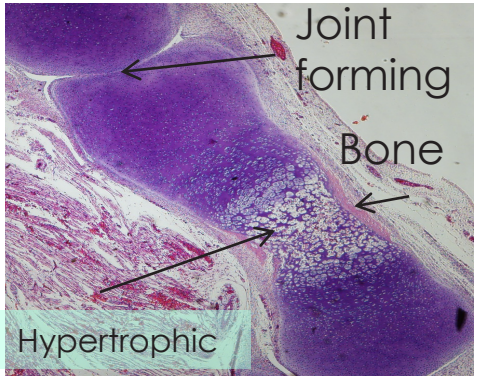
Pluripotent stem cells



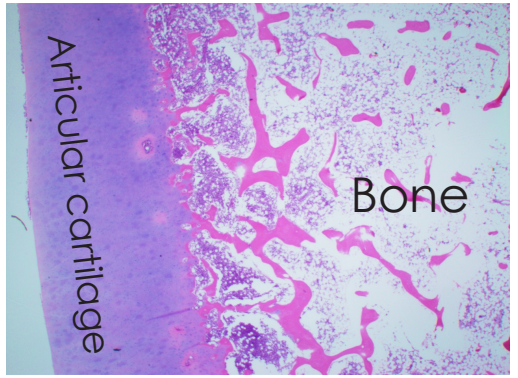
Gastrulation: germ layer specification, mesoderm induction



Multipotent skeletal progenitors committed to pre-chondrocytes



Functional specification of chondrocytes



Stable articular cartilage

Definitive mesenchymal cartilage progenitors capable of making joint articular cartilage

Embryonic and induced pluripotent stem cells

Ongoing clinical trials with PSC-derived products

NK (iPSC-derived) cell-based cancer immunotherapy

Age-Related Macular Degeneration (AMD)

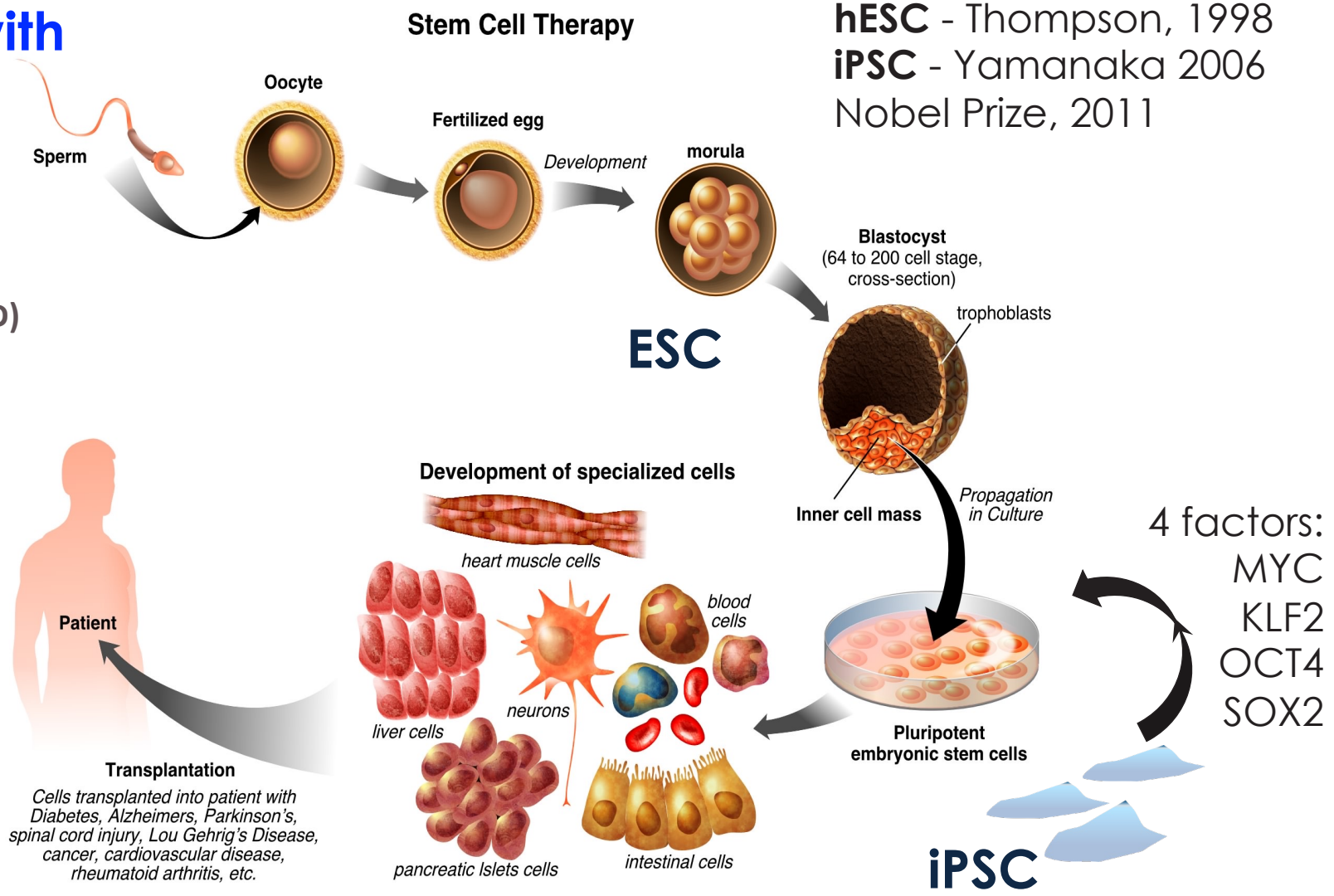
Steroid-resistant acute graft versus host disease/GvHD

Amyotrophic Lateral Sclerosis (ALS)

Parkinson's disease

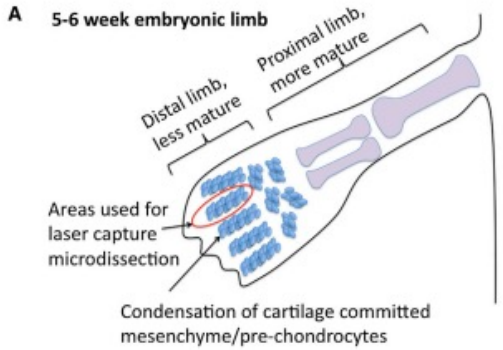
Heart failure

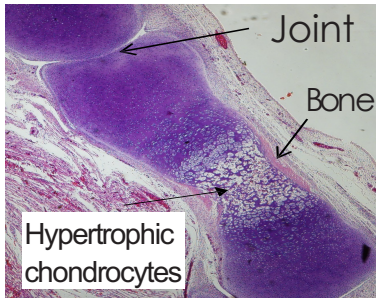
Projected: Plurocart® 2024

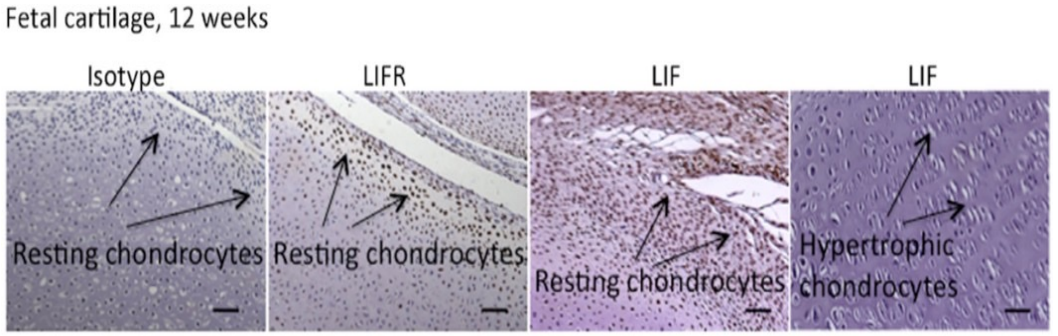


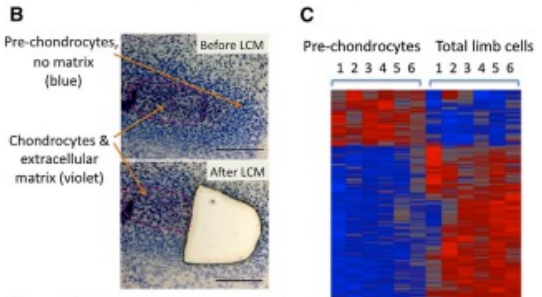
hESC - Thompson, 1998
iPSC - Yamanaka 2006
Nobel Prize, 2011

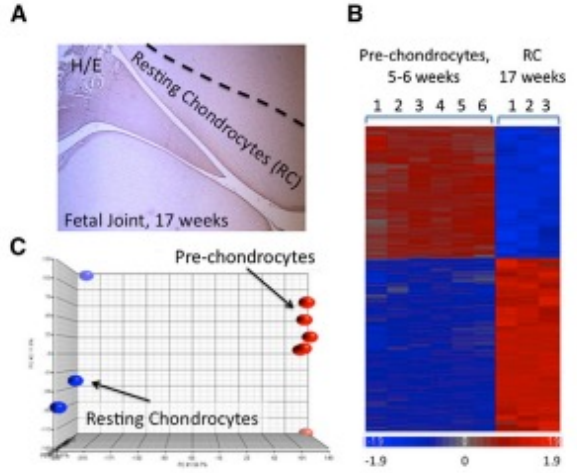
Developmental chondrogenesis - inspired technology







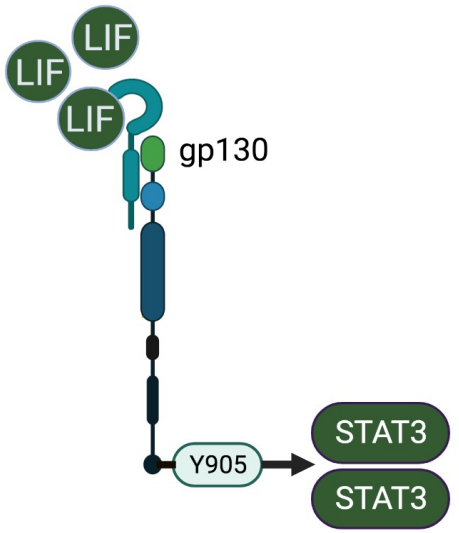


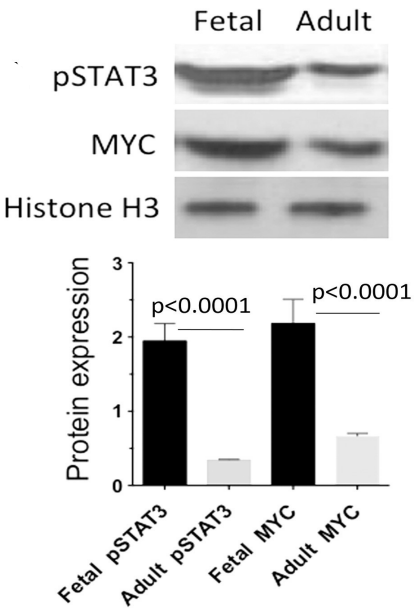


	BMP6	3.56×10^{-5}	−20.7
	TGFB2	1.01×10^{-7}	−37.2
#1	*LIF*	2.28×10^{-9}	−76.8

LIF/gp130/STAT3 in human development

"Inflammation like"

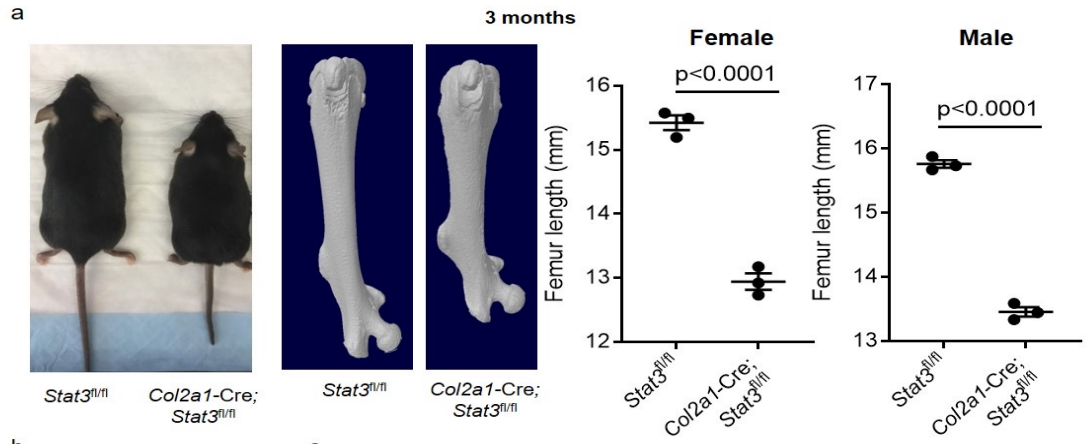


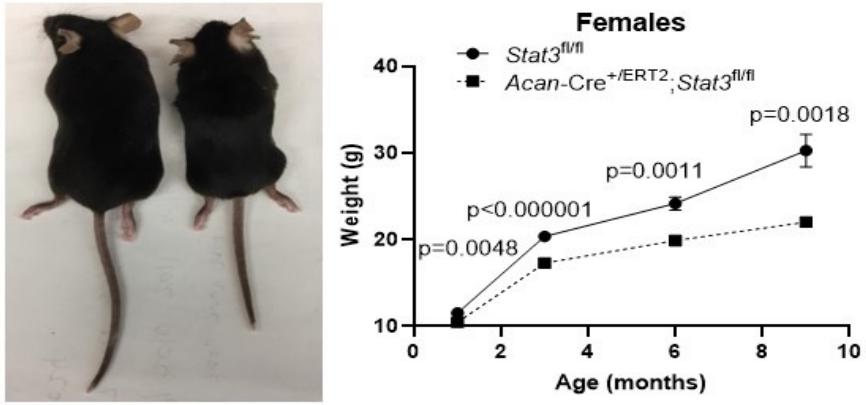


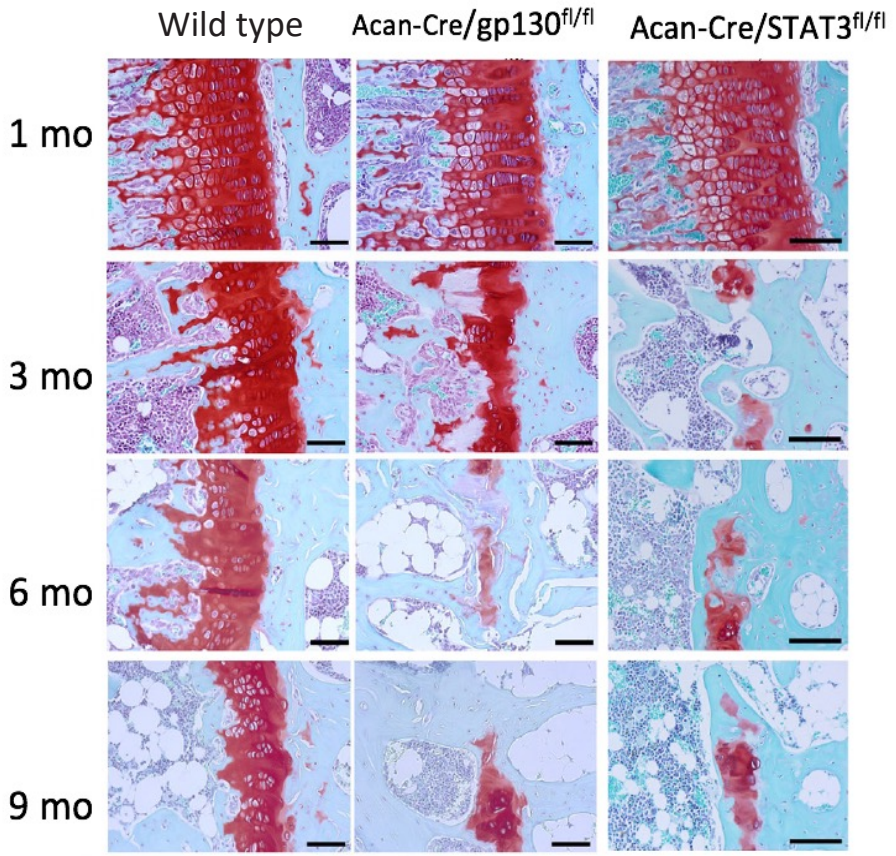
Wu et al., 2013; Shkhyan et al. 2018

Lifr/gp130/Stat3 in stem cells and development: maintenance of stemness, proliferation, survival

Fetal or neonatal ablation of Lifr, gp130 or Stat3 results in short stature and premature loss of skeletal progenitors in mice







Liu et al, Evseenko; *Comm Bio 2022*

10+ years of work: articular chondrocytes from embryonic stem cells. PLUROCART® technology

Evseenko et al., 2010

PNAS

Mapping the first stages of mesoderm commitment during differentiation of human embryonic stem cells

Denis Evseenko[a], Yuhua Zhu[a], Katja Schenke-Layland[b], Jeffrey Kuo[a], Brooke Latour[a], Shundi Ge[a], Jessica Scholes[a], Gautam Dravid[a], Xinmin Li[a], W. Robb MacLellan[b], and Gay M. Crooks[a,1]

[a]Department of Pathology and Laboratory Medicine, and Broad Stem Cell Research Center and [b]Cardiovascular Research Laboratory, David Geffen School of Medicine, University of California, Los Angeles, CA 90095

Edited* by Owen N. Witte, Howard Hughes Medical Institute, UCLA, Los Angeles, CA, and approved June 25, 2010 (received for review February 19, 2010)

Wu et al., 2013

Stem Cell Reports

Article

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Human Developmental Chondrogenesis as a Basis for Engineering Chondrocytes from Pluripotent Stem Cells

Ling Wu,[1,9] Carolina Bluguermann,[1,8,9] Levon Kyupelyan,[1] Brooke Latour,[2] Stephanie Gonzalez,[1] Saumya Shah,[1] Zoran Galic,[3] Sundi Ge,[2] Yuhua Zhu,[2] Frank A. Petrigliano,[1] Ali Nsair,[3,7] Santiago G. Miriuka,[8] Xinmin Li,[2] Karen M. Lyons,[1,6] Gay M. Crooks,[2,3,5] David R. McAllister,[1] Ben Van Handel,[4] John S. Adams,[1,3,5] and Denis Evseenko[1,3,5,*]

nature COMMUNICATIONS

Article | OPEN | Published: 07 September 2018

Mapping molecular landmarks of human skeletal ontogeny and pluripotent stem cell-derived articular chondrocytes

Ferguson et al., 2018

Gabriel B. Ferguson, Ben Van Handel, Maxwell Bay, Petko Fiziev, Tonis Org, Siyoung Lee, Ruzanna Shkhyan, Nicholas W. Banks, Mila Scheinberg, Ling Wu, Biagio Saitta, Joseph Elphingstone, A. Noelle Larson, Scott M. Riester, April D. Pyle, Nicholas M. Bernthal, Hanna KA Mikkola, Jason Ernst, Andre J. van Wijnen, Michael Bonaguidi & Denis Evseenko

Nature Communications **9**, Article number: 3634 (2018) | Download Citation

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Petrigliano et al 2021

Article | Open Access | Published: 23 November 2021

Long-term repair of porcine articular cartilage using cryopreservable, clinically compatible human embryonic stem cell-derived chondrocytes

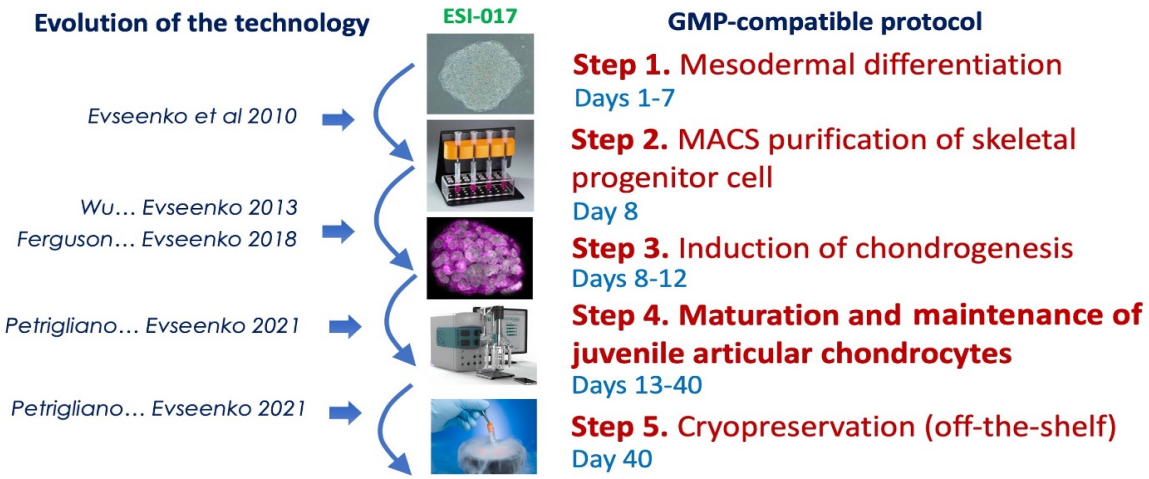
Frank A. Petrigliano, Nancy Q. Liu, ... Denis Evseenko + Show authors

npj Regenerative Medicine **6**, Article number: 77 (2021) | Cite this article

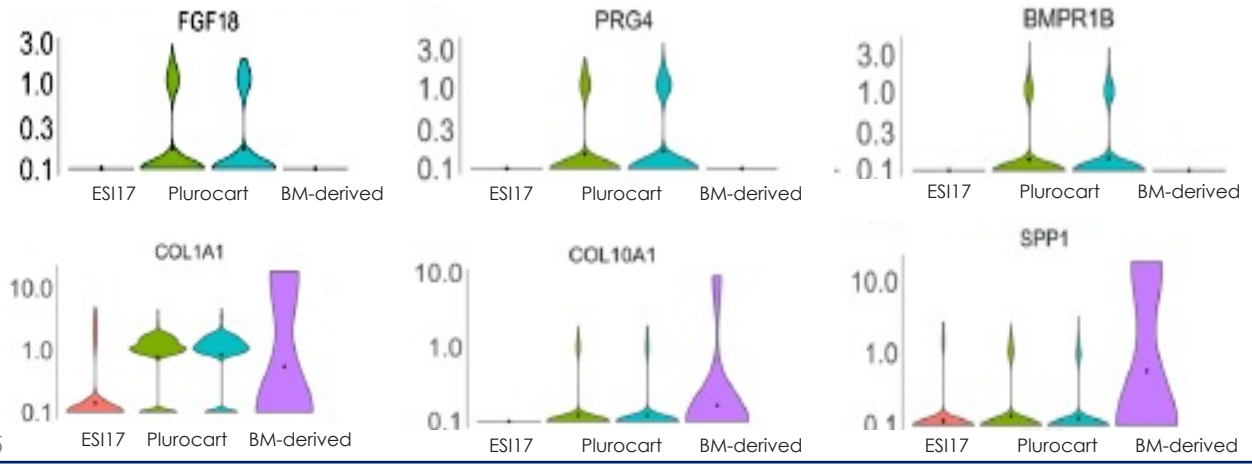
2230 Accesses | **79** Altmetric | Metrics

Clinical grade, embryonic stem cell line ESI17-derived immature articular chondrocyte

Purity and articular chondrocyte identity, expression profile is similar to primary human fetal cells

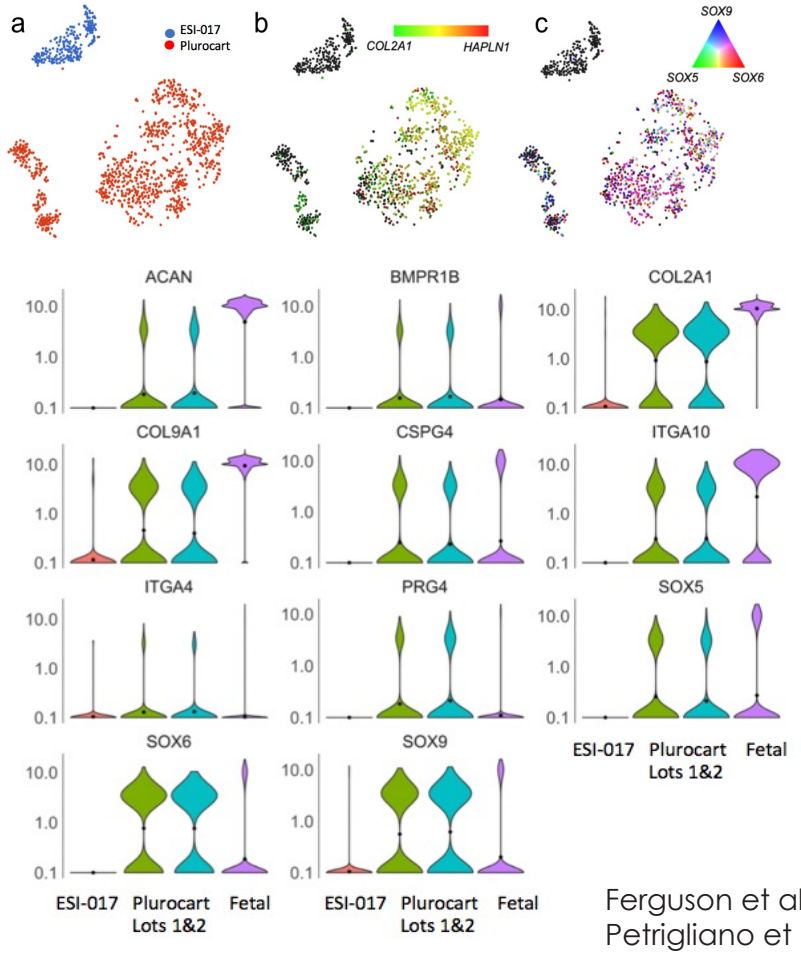


PSC-derived chondrocytes vs BM MSC-derived chondrocytes



PSC-derived vs fetal human chondrocytes

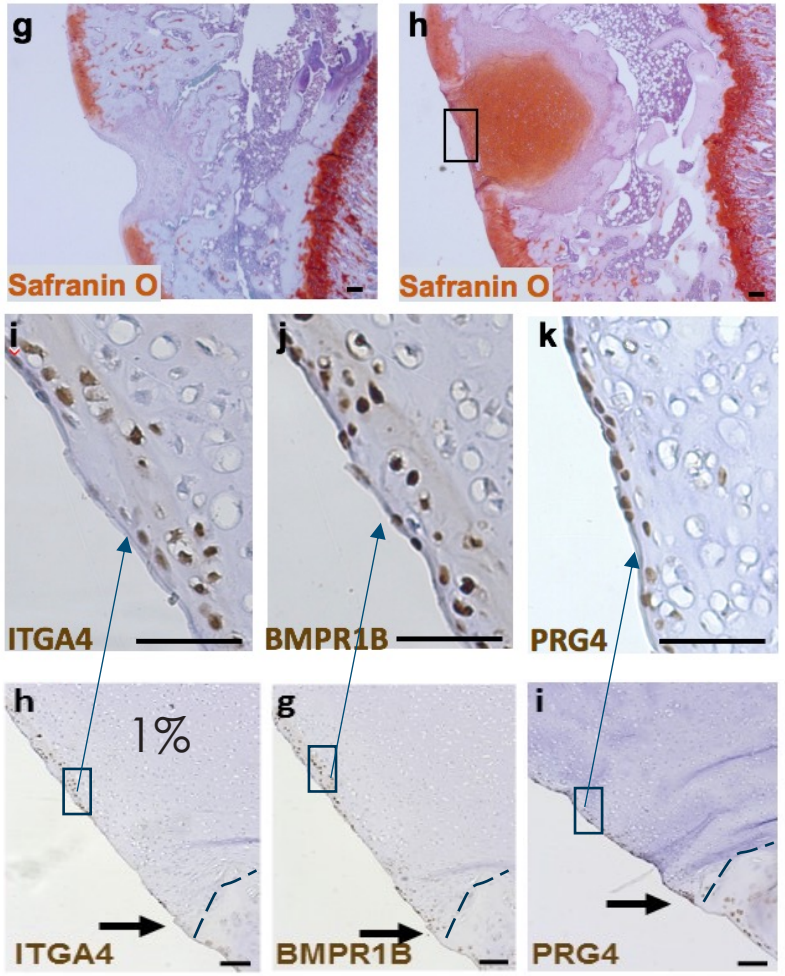
97% of PSC-derived chondrocytes express SOX 5/6/9 and Collagen 2;
Articular cartilage markers: PRG4, FGF18, BMPR1B

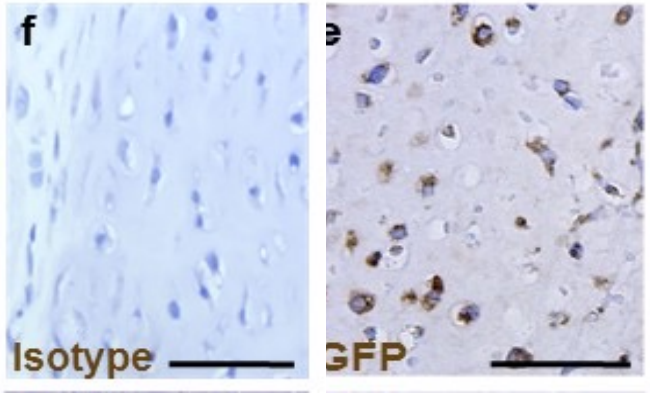


Ferguson et al 2018
Petrigliano et al 2021

Proof-of-concept assessment of embryonic stem cell-derived Immature articular chondrocytes in vivo

Miniimplants integrate and spontaneously form the superficial positive for PRG4/lubricin, ITGA4 and BMPR1B



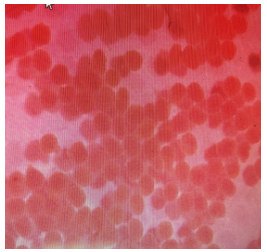


Ferguson et al; *Nat Comm 2018*

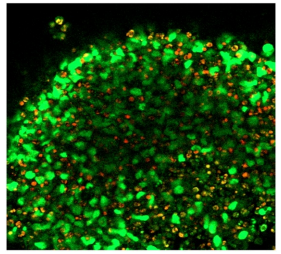
Development of the ESC-derived cell formulations for articular cartilage repair in a clinically relevant model

Formulation 1: PSC-derived chondrospheres

Cryopreserved chondrospheres

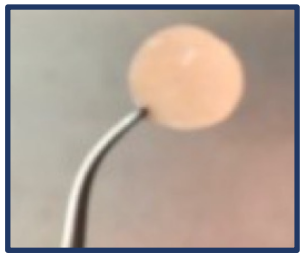


70%+ viability

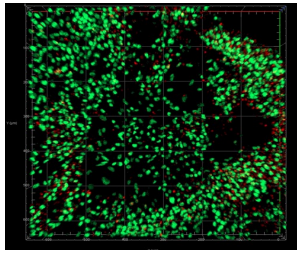


Formulation 2: collagen membrane with PSC-derived chondrocytes

Cryopreserved membranes



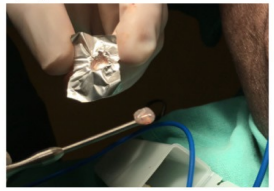
80%+ viability



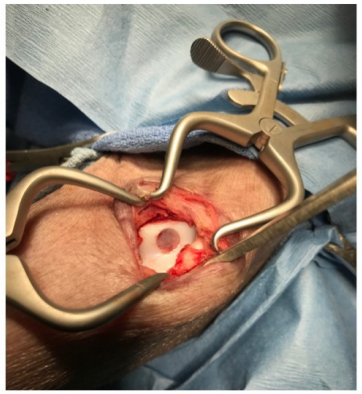
6 mm critical size defect in the load-bearing condyle region, knee joint, Yucatan minipig

Sterile foil templates for plug formation

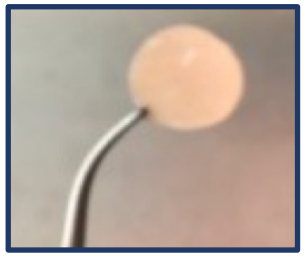
Formed plug is transferred with a fine spatula



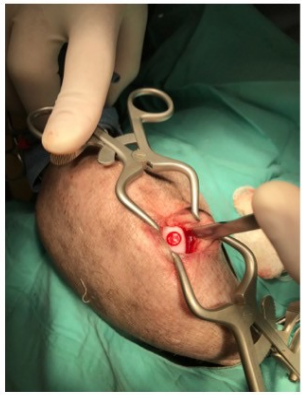
Plug with cells implanted in pig cartilage defect



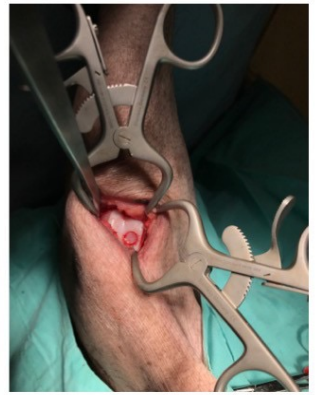
6 mm disc with cells



Focal 6-mm lesion in knee cartilage



Fixing membrane with a fibrin glue



Petrigliano et al., 2021; *NPG Regenerative Medicine*

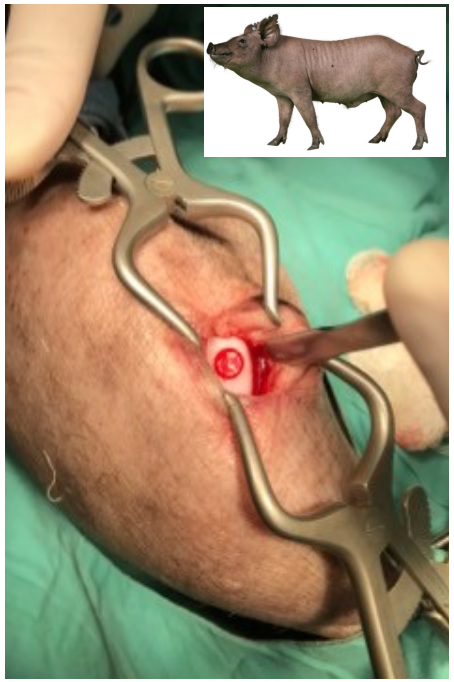
Analysis at 6 months post-transplantation

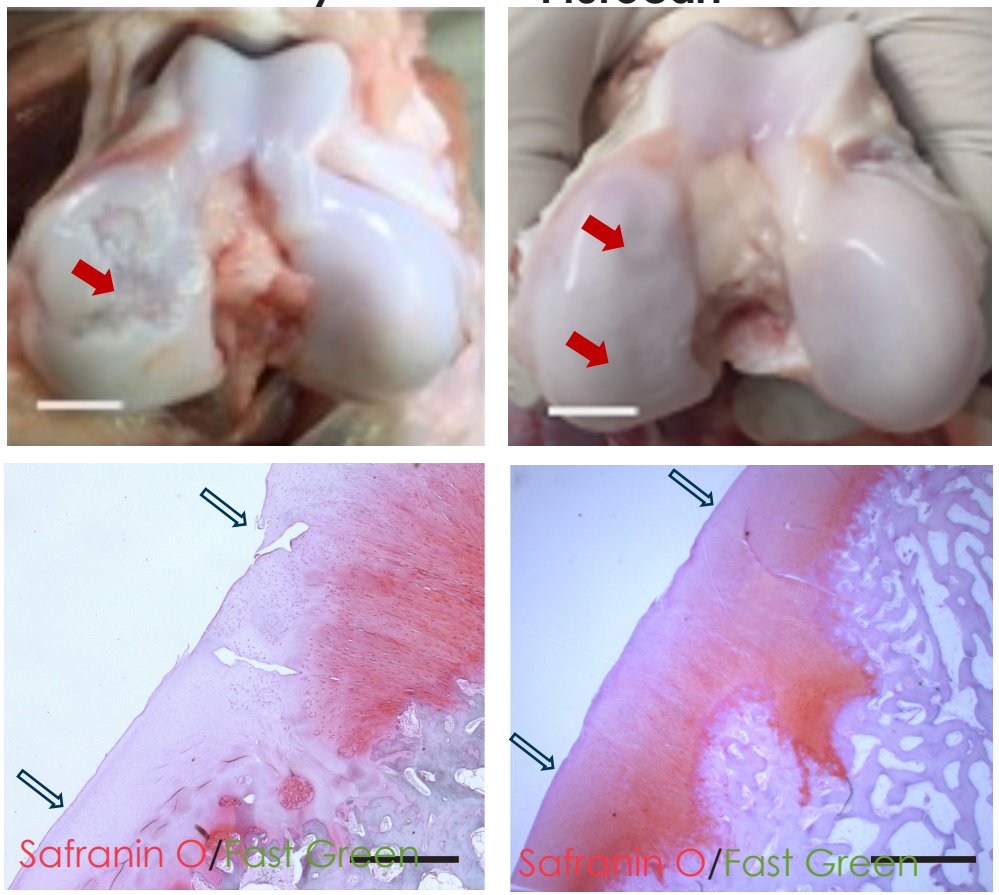
Structural outcomes: hyaline cartilage

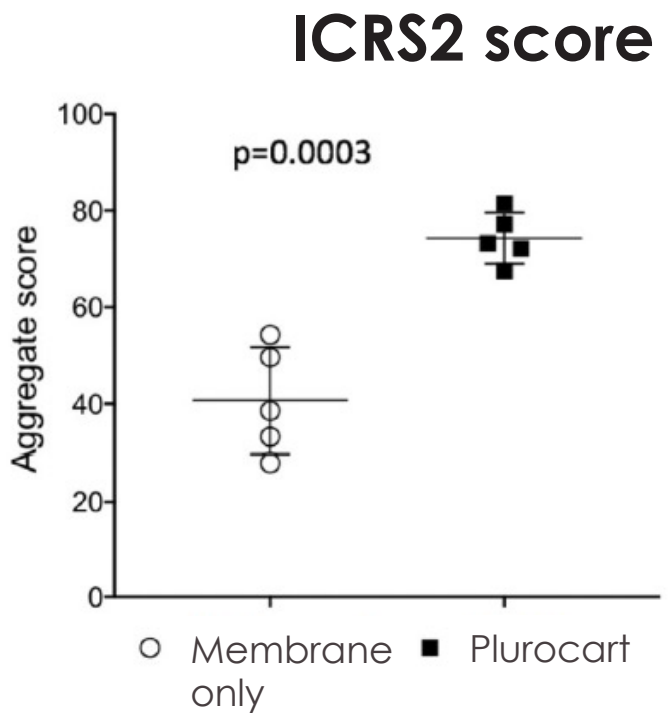
Plurocart: collagen membrane with PSC-derived chondrocytes

5 pigs per group; 2 defects, 6 mm; analysis at 6 months

Yucatan minipig





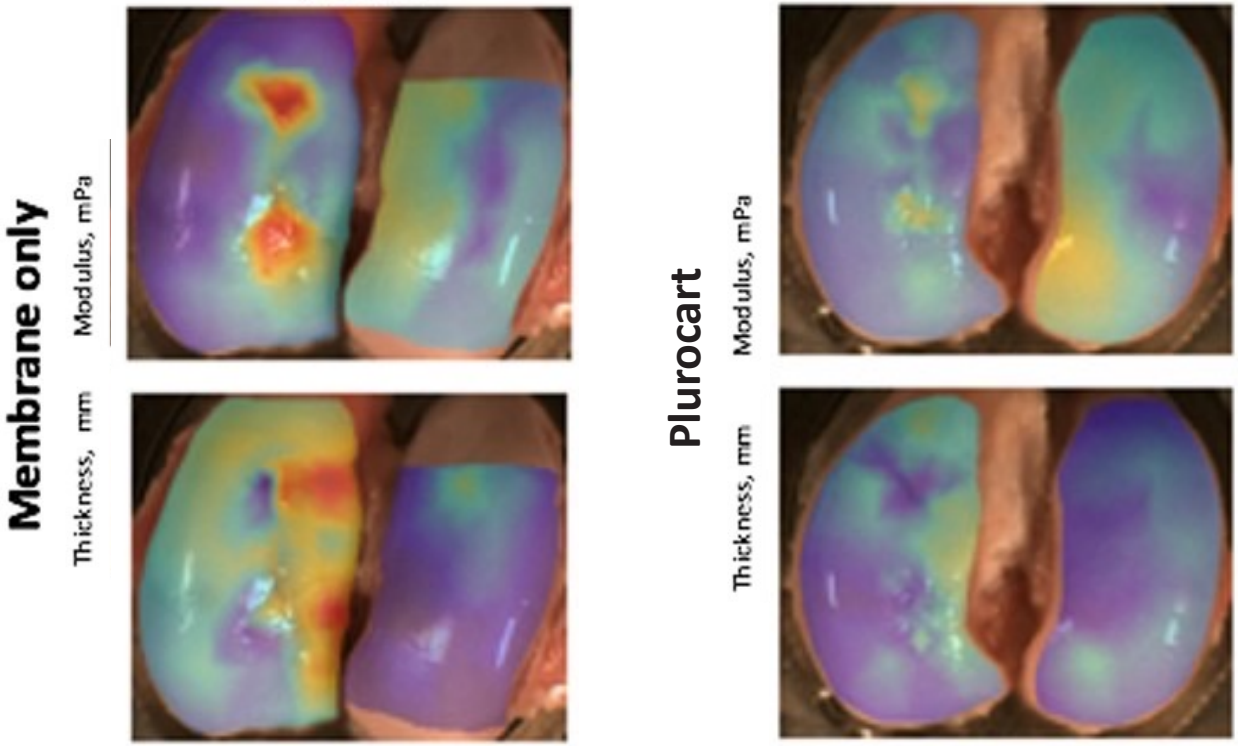


Petrigliano et al., 2021; *NPG Regenerative Medicine*

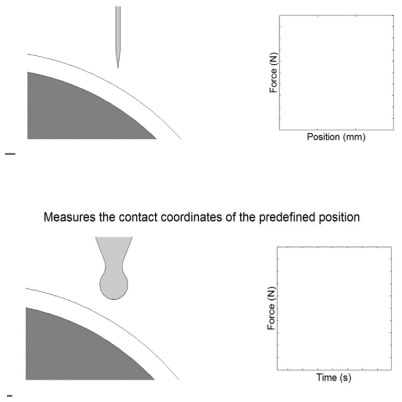
Analysis at 6 months post-transplantation

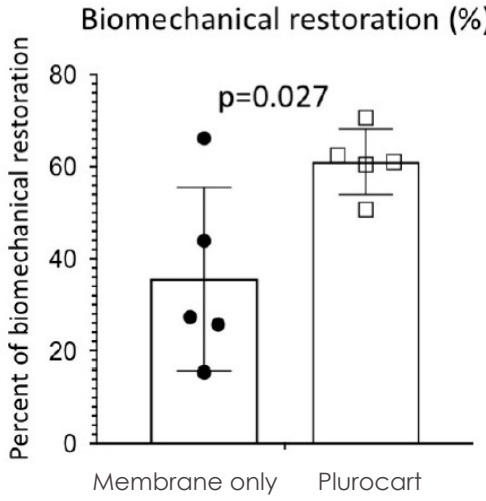
Biomechanical outcomes: functionally competent tissue

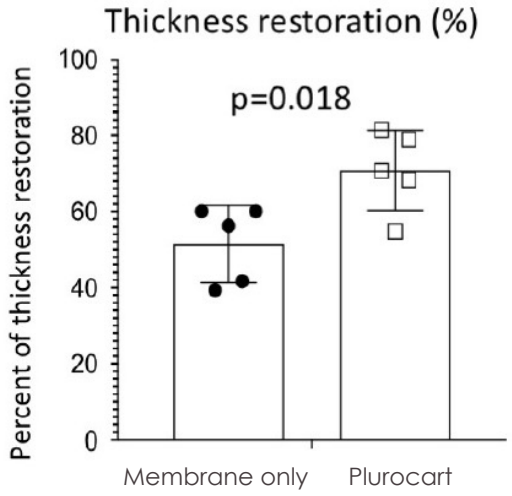
ESC-derived chondrocytes elicit biomechanically superior articular cartilage repair



Heat maps depicting scanning indentation and thickness of femoral condyles generated using Mach-1 bioindentor







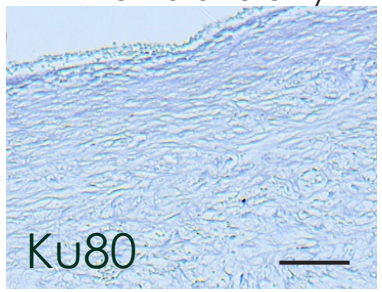
Petrigliano et al., 2021; *NPG Regenerative Medicine*

Analysis at 6 months post-transplantation

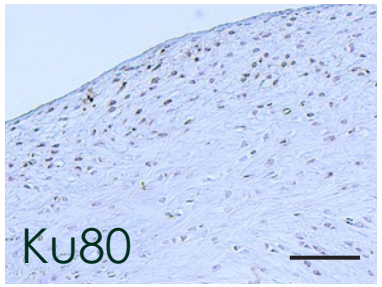
Implanted cells show long-term engraftment and survival in vivo

1-month post-implantation:

Membrane only

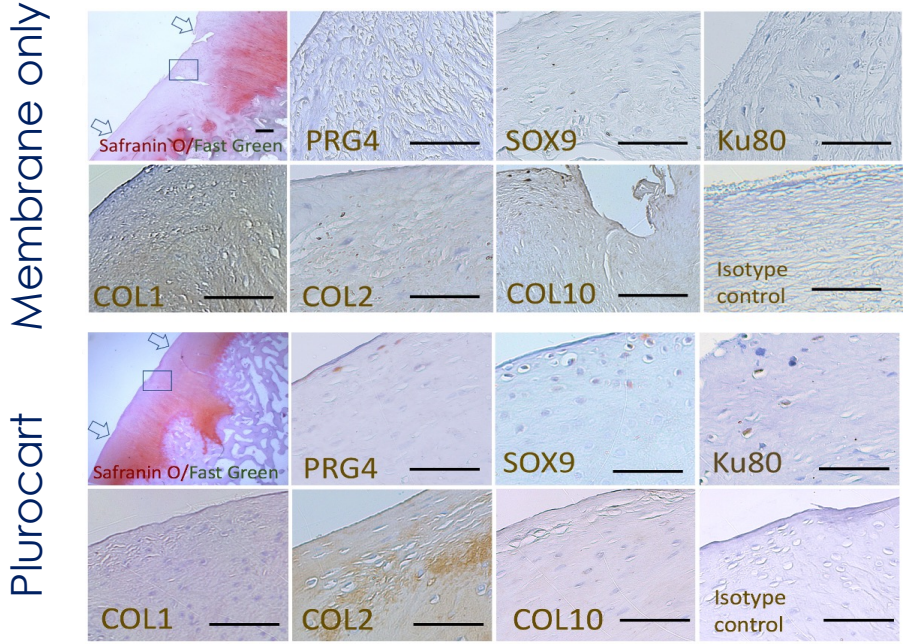


Plurocart



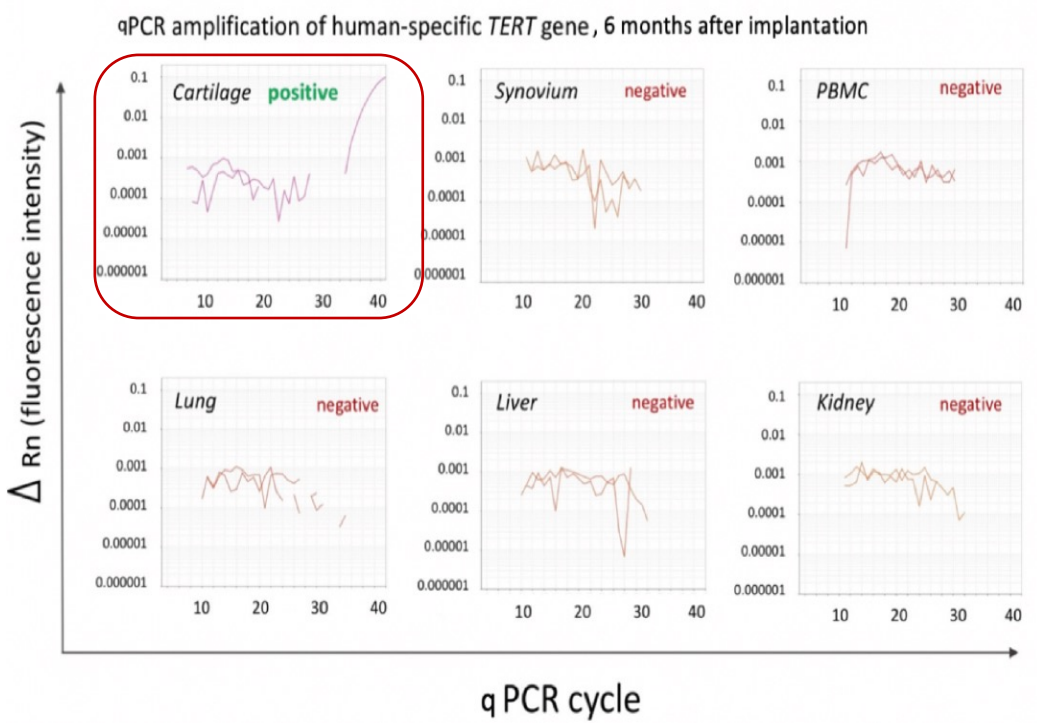
~30% - human cells Ku80 positive

6 months post –post-implantation:



Human-specific PCR for TERT gene

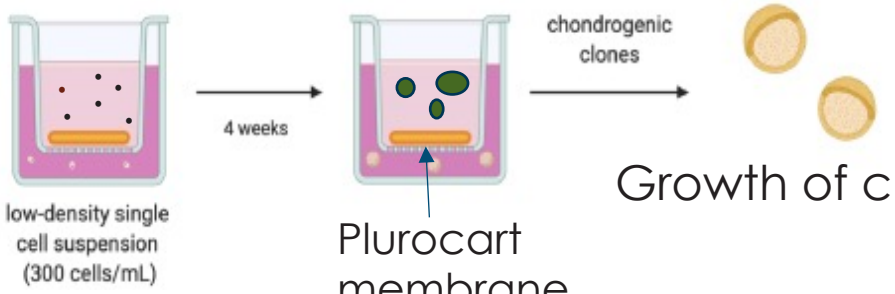
6 months post-implantation:



Petrigliano et al., 2021; *NPG Regenerative Medicine*

ESC-derived immature chondrocytes secrete BMPs and support clonal expansion of endogenous cartilage cells

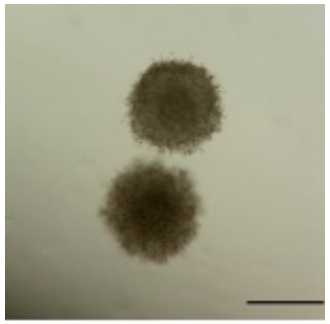
Single endogenous articular chondrocytes from the recipient

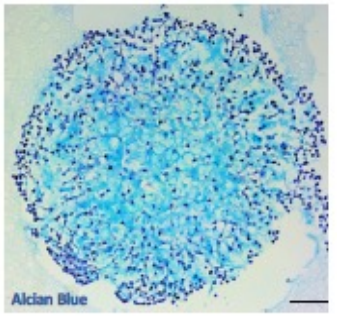


Growth of chondrogenic clones

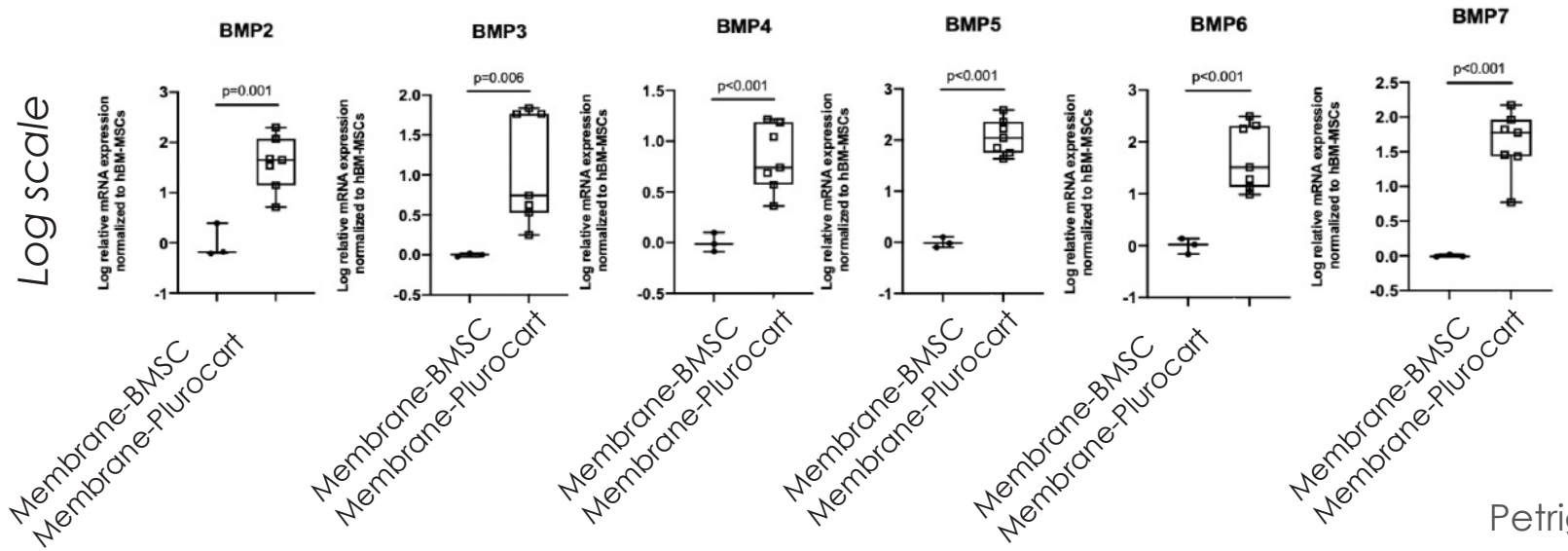
Endogenous articular chondrocytes

Clone from a single cartilage cell





ESC derived immature chondrocytes express ~100-fold higher levels of BMPs than BMSCs



Petrigliano et al., 2021; *NPG Regenerative Medicine*

Plurocart: off-the-shelf allogeneic ESC-derived chondrocytes

Meeting Information Package
FDA

Sponsor Name
DENIS EVSEENKO, MD, PHD
UNIVERSITY OF SOUTHERN CALIFORNIA
LOS ANGELES, CA

Cell Therapy Name
PLUROCART

Application or PASTN Number
PS005048

Date of Meeting
10/24/2019

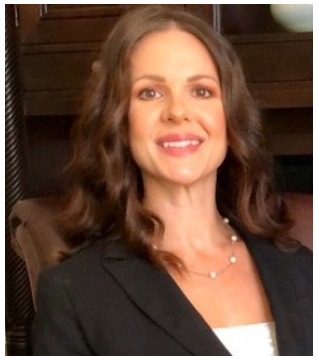
Plurocart implant

- **Allogeneic product**
- **Cell source:** Pluripotent Stem Cell (PSC) line ESI-017-derived juvenile articular chondrocytes, 500,000 viable cells per CM^2
- **Final product formulation:** Cryopreserved vial
- **Device or drug component (s):** Cells on a clinical grade collagen membrane
- **One step, minimally invasive procedure**

Plurocart program Team

Frank Petrigliano, MD
Clinical co-PI,
CIRM corresponding PI,
USC

Denis Evseenko MD, PhD
Research co-PI,
USC



Program manager,
Angela Donato, PhD
IQVIA

Shawna Jackman, PhD
GLP Safety Lead
CRL

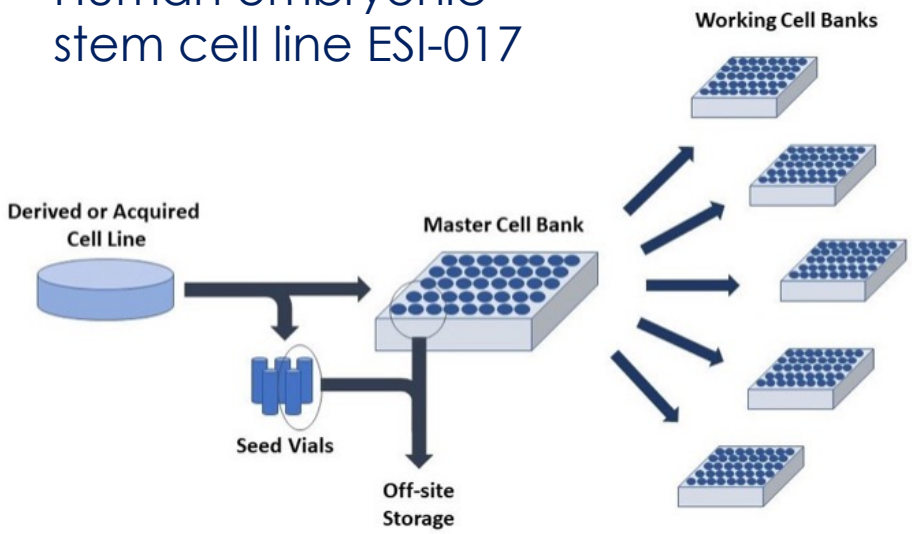
Vincent Chen, PhD
GMP Manufacturing Lead
City of Hope

Josh Lee,
Tech Transfer Lead
USC

Manufacturing and controls (GMP)

Production and release of Master and Working Cell banks

Human embryonic stem cell line ESI-017

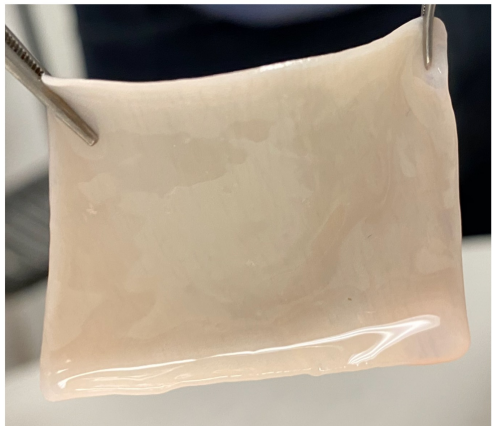


MCB (300 vials) Release testing

Assay	Result
Karyotype	Normal
Percentage of OCT4+ cells (FACS)	>80%
Percentage of SSEA4+ cells (FACS)	>80%
Mycoplasmastasis	Negative
Mycoplasma	Negative
In Vivo: Suckling and Adult Mice, Guinea Pigs, Embry. Hen Eggs	Negative
MAP: Mouse Antibody Production Test	Negative
28-day In Vitro Virus Assay GMP, 3 Cell Lines	Negative
Bovine 9CFR In Vitro Assay for 9 Viruses	Negative
Porcine Mod. 9CFR In Vitro Viruses Assay, PT-1 Cells	Negative
Retrovirus Detection by PERT	Negative
Sterility	Negative
Certificate of Analysis Detection of 14 Viruses by Real Time Polymerase Chain Reaction Assays (Human Panel I)	Negative
Adeno-Associated Virus (AAV) Serotypes 1, 2, 3, 3B, 4 and 6 by PCR	Negative

Manufacturing and controls (GMP)

Technology Transfer & manufacturing of the Plurocart implants for Phase 1 Clinical Trial under GMP standards



Allogeneic, off-the-shelf

Cryopreserved

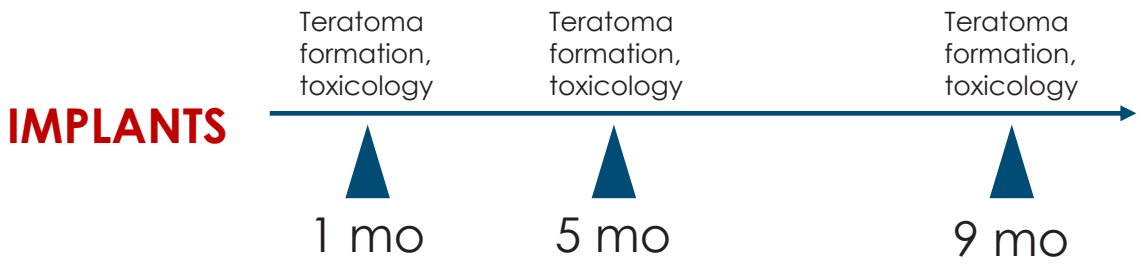
Final Product release testing

Assay	Result
Residual undifferentiated cells (quantitative RT-PCR for the pluripotency genes POU5F1 and LIN28b genes).	Relative expression (per cm^2 of the membrane with cells) lower than the expression levels in 5,000 undifferentiated ESI-017 cells
Chondrogenic activity (Taqman PCR for COL2A1 and SOX9 (potency 1)	The levels of COL2A1 gene 10-fold or higher and the levels of SOX9 gene 5-fold higherthan the levels in undifferentiated ESI-017
Viability (potency 2)	500,000 viable cells per cm^2
Mycoplasmastasis	Negative
Mycoplasma	Negative
28-day In Vitro Virus Assay GMP, 3 CellLines	Negative
Sterility	Negative
B&F	Negative
Endotoxin	< 10 EU/mL

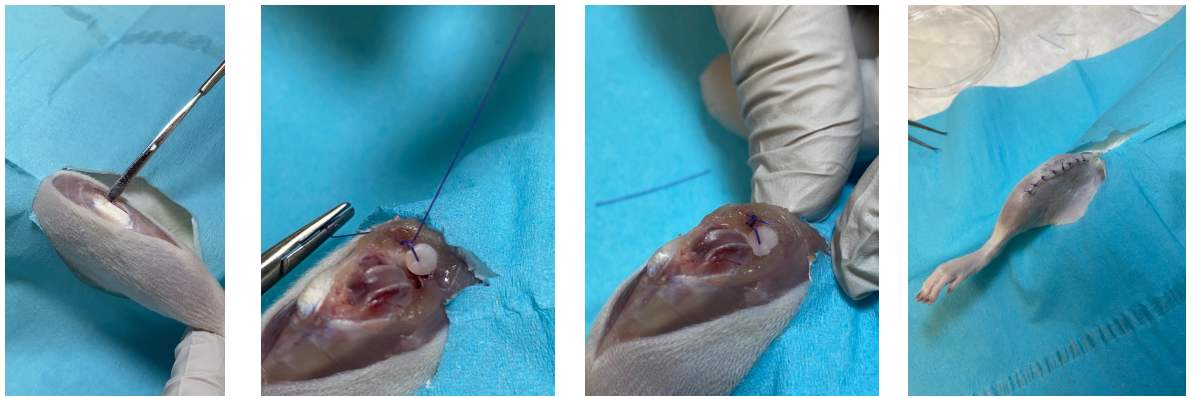
FDA requested GLP safety studies

Assessment of tumorigenicity and adverse events in vivo

Group	Dosage Level	Number of Rats	
		Males	Females
1[a]	Negative Control	15	15
2[a]	Maximum Feasible Dose	30	30
3[b]	Positive Control Cells	5	5
4[b]	1% Spiked Control	5	5
5[b,c]	0.1% Spiked Control	5	5



4 mm Plurocart implant, knee joint in rat



Current stage 1, 5 mo analyzed:

- teratomas: 40% positive in control group (undifferentiated ESI-17 cells)
- no teratomas, no side effects in test article groups (test article=Plurocart)
- ectopic human cartilage in the site of implantation in 70% of rats in test article group

An open-label Phase 1 study (first-in-man) to investigate the safety of Plurocart for the treatment of adults with single full-thickness cartilage defects of the knee

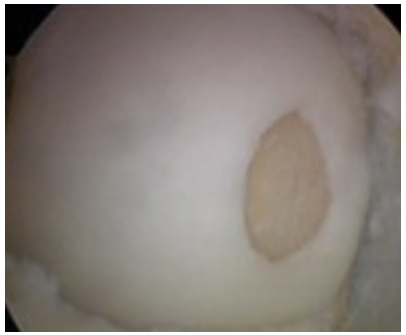
Primary objectives: Safety evaluation of Plurocart as measured via adverse event monitoring.

Secondary objectives: Clinical evaluation of Plurocart as measured via 1) patient-reported and knee-related quality of life and symptoms, and 2) MRI. Time of observation: 24 months.

Dose escalation (3-fold) strategy is based on the defect size:

Minimally invasive, one stage surgery

Small defect



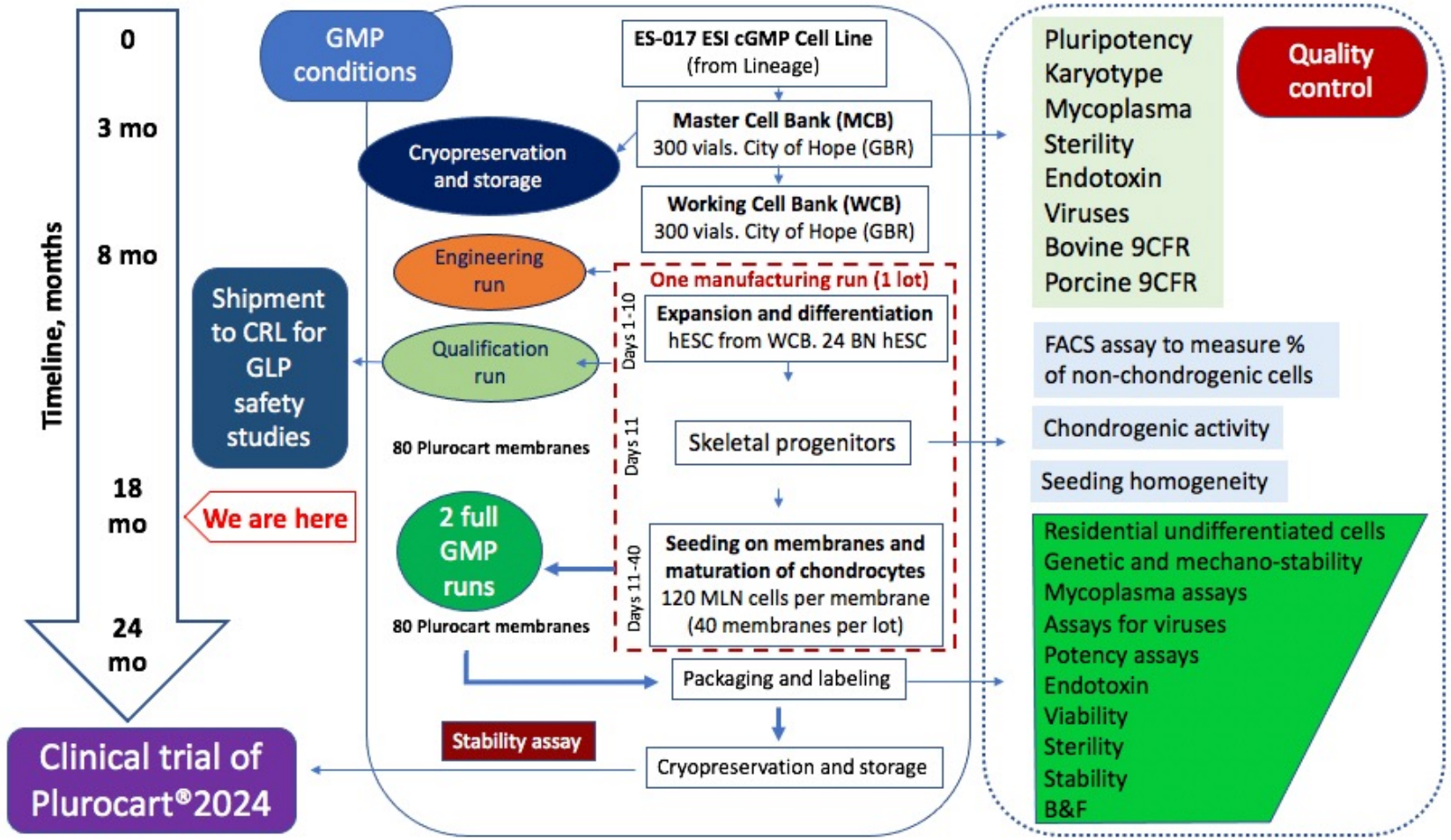
Area range 1-4 cm^2; average area 2 cm^2

Large defect

Area range 4-8 cm^2; average area 6 cm^2

2022: Clinical Award from CIRM

Current status: GMP-grade manufacturing of **Plurocart (GMP manufacturing of 80 human implants)** for a Phase 1clinical trial: 2 cm^2 and 8 cm^2 focal lesions in the knee cartilage



CIRM CALIFORNIA INSTITUTE FOR REGENERATIVE MEDICINE
The State Stem Cell Agency

Summary

1. Systematic analysis of human developmental chondrogenesis defined critical parameters for large-scale manufacturing of functional juvenile articular articular chondrocytes from human PSC

2. Plurocart – is a new generation bioimplant

- Allogeneic off-the-shelf product
- Made from "real" stem cells
- Long-term cell engraftment in vivo (> 6 months)
- Generation of functional hyaline articular cartilage in pivotal long-term studies in large animals
- One-stage surgical procedure, surgeon-friendly
- Low cost
- Cons: ES - ethical concerns; regulatory, safety in humans is not completely clear, never tested in human patients


THE WALL STREET JOURNAL.

A Knee or Hip 'Replacement' Without Surgery? It's on the Horizon

With better drugs and stem-cell therapies, researchers hope to repair cartilage—or prevent damage—before osteoarthritis sets in or an operation is needed

3. "First-in-man" Phase 1 trial of Plurocart for small (2 cm^2) and large (up to 8 cm^2) cartilage lesions is scheduled at USC for 2024-2025 (12-16 patients).

Acknowledgements

Large animal studies: Mark Hurtig, DVM (Guelph, Canada)

Mouse genetic studies: Karen Lyons, PhD (UCLA)

Epigenetic clocks: Steve Horvath PhD; Jason Ernst, PhD (UCLA)

Key clinical collaborators:

Frank A. Petrigliano, MD (USC)
Jay R. Lieberman, MD (USC)

CROs: Charles River Labs, IQVIA
GMP production: City of Hope

Evseenko Lab at USC:

Nancy Q. Liu, MD (STAT3 in skeletal development)
Josh Lee (key PSC work)
Jade Tassey (PSC work)
Arijita Sarkar, PhD (STAT3 and DNA methylation)
Other lab members: Ling Wu, PhD, Gabriel Ferguson, PhD; Xinxiu Li, Jade Tassey, Youngjoo Li, Ruzanna Shkhyan, Jenny Magallanes)

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NIH R01AG058624
DOD: W81XWH-18-1-0511
NIH-NIDCR C_DOCTOR AWARD
CIRM: BBV, TRAN and CLIN Awards

CAR T-Cell Therapy:

Navigating the Development Challenges

Mohamed Abou-el-Enein, MD, PhD, MSPH
Executive Director, USC/CHLA Cell Therapy Program
Director, USC/CHLA cGMP Facility
Associate Professor of Clinical Medicine (Oncology), Pediatrics, and Stem Cell Biology & Regenerative Medicine

October 20, 2023

Regulatory Science Symposium

USC University of Southern California

Children's Hospital LOS ANGELES

Disclaimer

The mention of specific commercial products, equipment, instruments, and materials in this presentation does not constitute an endorsement or recommendation. Nor should it be interpreted as an assertion that these are the best products available for the intended purpose.

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Agenda

- Introduction to CAR T cell therapy and its clinical applications in hematological malignancies
- Addressing key challenges in developing CAR T cell therapy:
  - Limited long-term outcome data
  - Difficulty in comparing CAR T cell therapies to standard care for cost-effectiveness analysis
  - Complex manufacturing process and potential solutions
- Translational infrastructure required for cell therapy development

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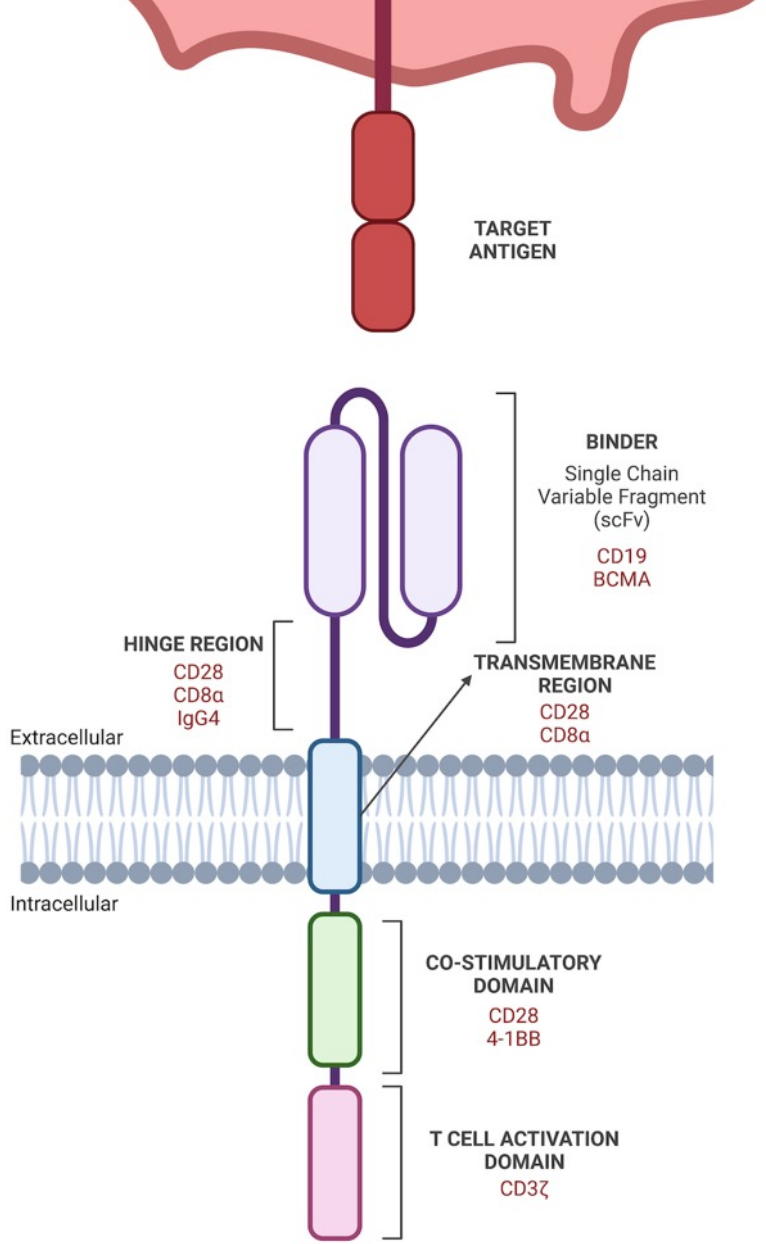
Principles of CAR T cells

- **CAR T cells:** Personalized immunotherapy using patient's own T cells, genetically engineered to target specific tumor antigens for cancer treatment.

- **Chimeric Antigen Receptor (CAR) Structure:**

➢ **Binder**: Ensures antigen recognition, specificity, and affinity
➢ **Hinge region**: Provides flexibility and maintains optimal distance to the target
➢ **Transmembrane Region**: Contributes to receptor stability and function
➢ **Co-stimulatory Domain**: Augments T cell function, metabolism, and persistence
➢ **T cell activation domain**: Facilitates downstream T cell activation and functional responses



Second Generation CAR Structure

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Principles of CAR T cells

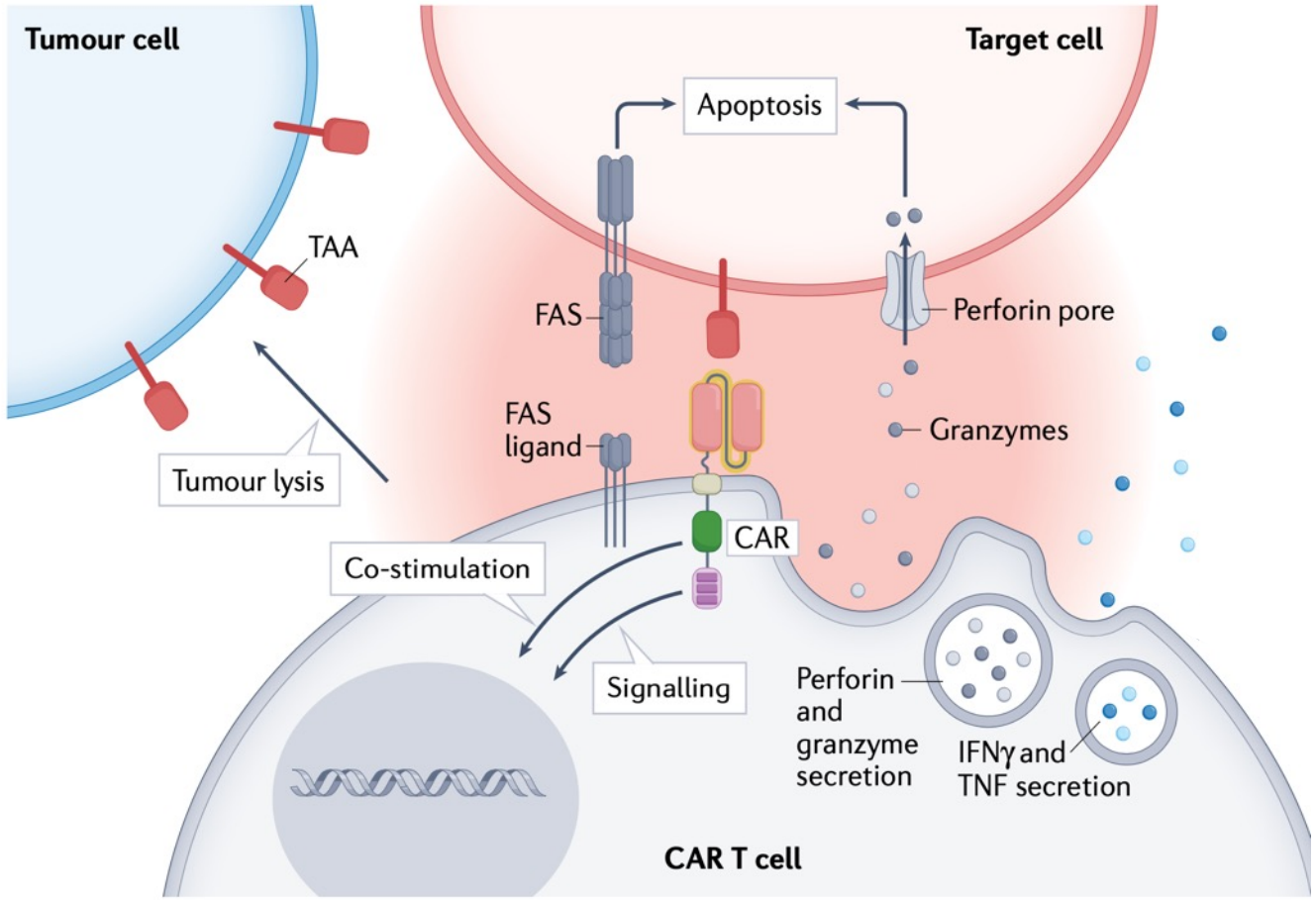
CAR T Cell Killing Mechanism:

- Recognize Tumor-Associated Antigen (TAA)
- Form Immune Synapse with Target Cell
- Release Cytotoxic Granules
- Induce Target Cell Apoptosis
- Trigger Cytokine Release & Immune Activation

➢ **Main target**: **CD19**, specifically expressed on B-cells

➢ Remarkable success in hematological B-cell malignancies as a **third line** of treatment in **Lymphoma** and **Leukemia**

➢ Recently approved CAR T-cells targeting **BCMA for Multiple Myeloma**



Flugel et al. Nat. Rev. Clin. Oncol. 2022

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FDA Approved CAR T cells

2017

KYMRIAH® (tisagenlecleucel) Suspension for IV infusion → Acute lymphoblastic leukemia (ALL) (B-cell precursor); Large B-cell lymphoma (LBCL); Follicular lymphoma (FL)

YESCARTA® (axicabtagene ciloleucel) Suspension for IV infusion → Large B-cell lymphoma (LBCL); Follicular lymphoma (FL)

2020

TECARTUS™ (brexucabtagene autoleucel) Suspension for IV infusion → Mantle cell lymphoma; Acute lymphoblastic leukemia (ALL) (B-cell precursor)

2021

Breyanzi® (lisocabtagene maraleucel) SUSPENSION FOR IV INFUSION → Large B-cell lymphoma (LBCL)

Abecma™ (idecabtagene vicleucel) SUSPENSION FOR IV INFUSION → Multiple Myeloma (MM)

2022

CARVYKTI™ (ciltacabtagene autoleucel) Suspension for IV Infusion → Multiple Myeloma (MM)

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Approval restricted to patient populations and treatment line

The Value of CAR T Cell Therapy

- Primary obstacle for first-line therapy adoption: **High cost of CAR T-cell therapy**
- **Price Range**: **$373,000** to **$475,000** for a single dose
- **List price** does NOT cover hospitalization, pre- and post-treatment, or side effect management. Overall cost ranges from **$500,000** to **$1 million**.
- **The Medicare reimbursement via MS-DRG 018** doesn't cover the full costs and services (average national reimbursement rate of **$239,933**)

ASCO, CAR T Policy Brief (2019)

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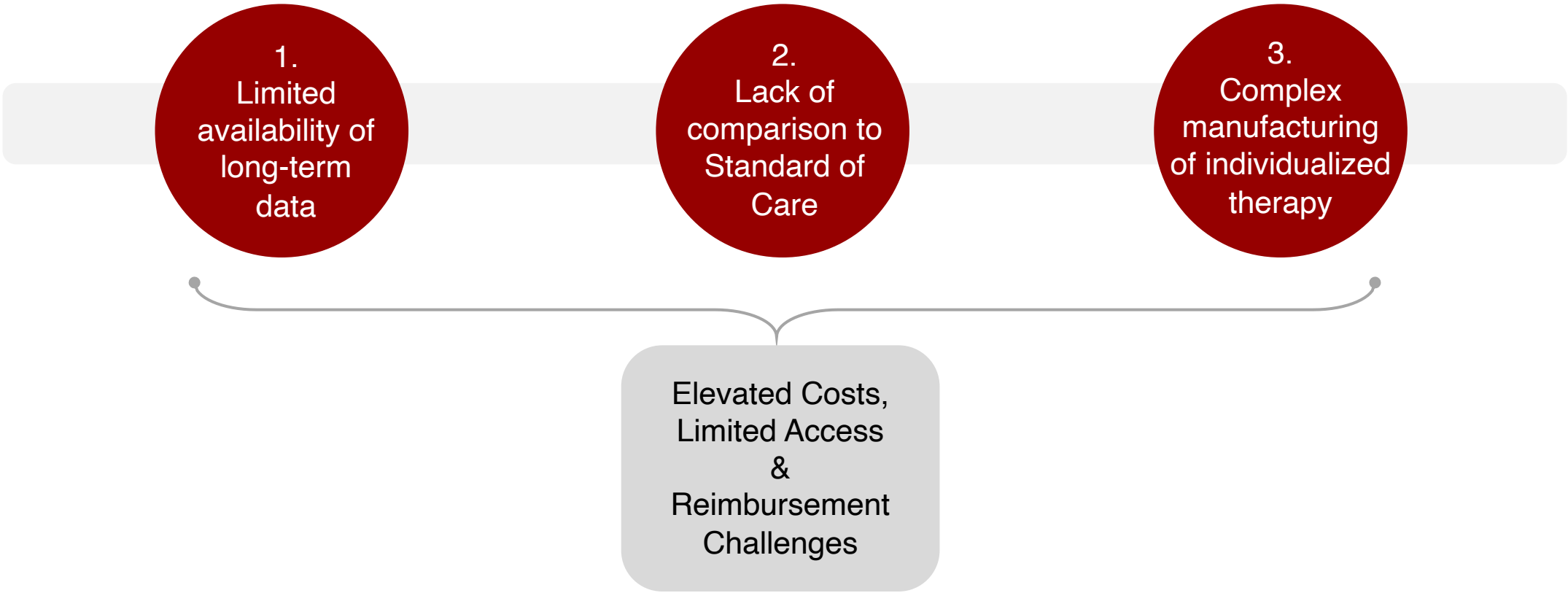
Roadblocks to CAR T cell Therapy Adoption



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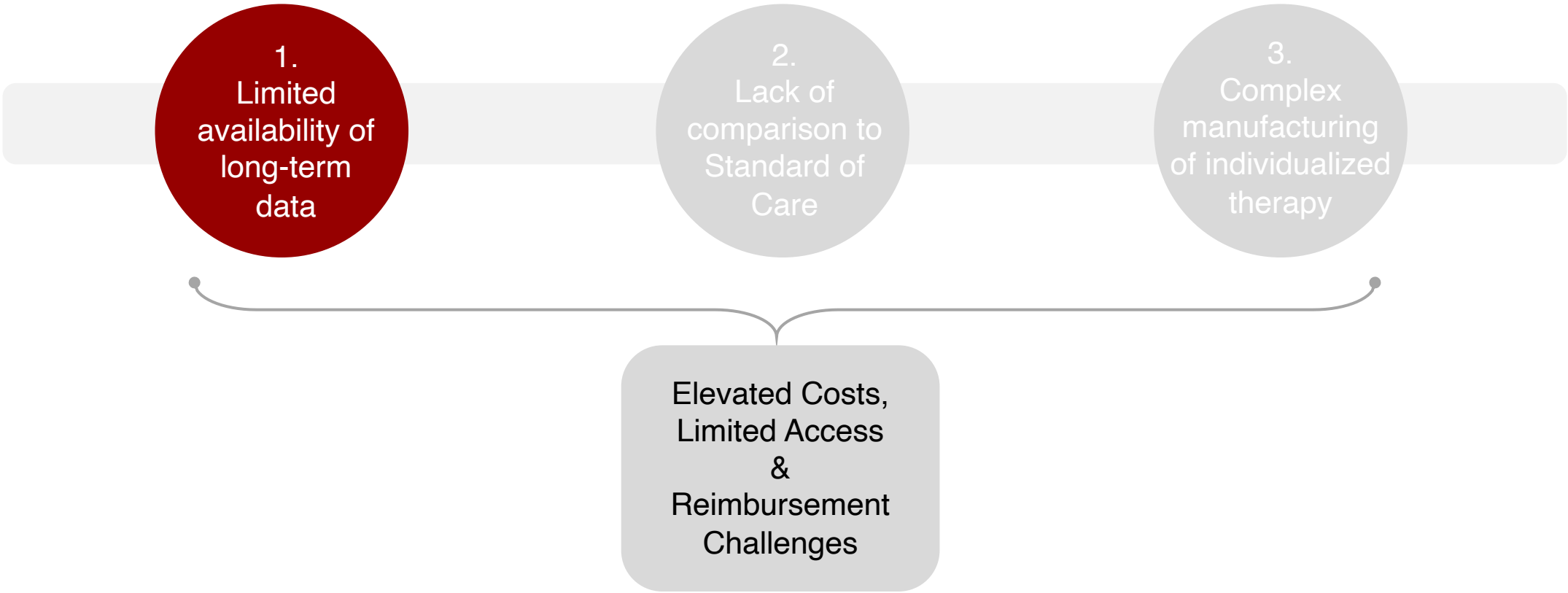
Roadblocks to CAR T cell Therapy Adoption



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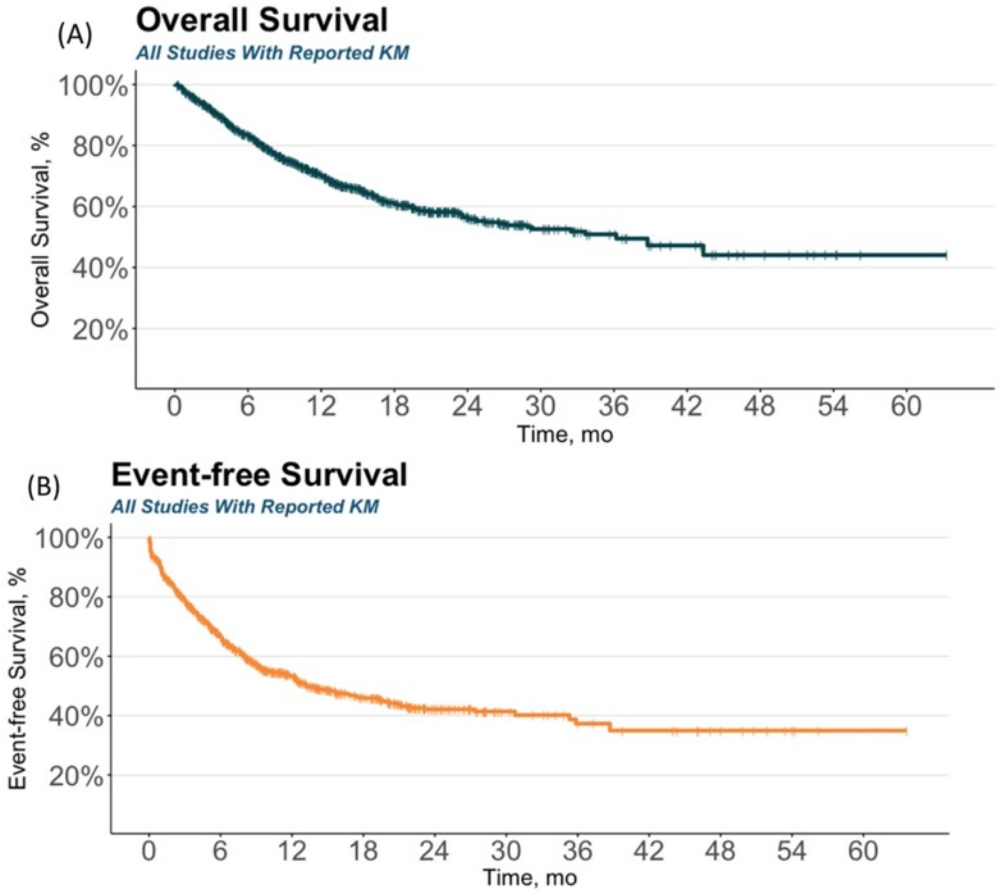
Long-Term Outcomes: Meta-Analysis

Leukemia (B-ALL)

- Analyzed 38 reports of **2,134 patients with relapsed/refractory (r/r) B-ALL**
- 5-year overall survival was 44.1%.
- Cytokine release syndrome was reported in 83% of patients and neurotoxicity in 30%.
- Only 4 of 38 studies reported information on participant race/ethnicity.
- African Americans and Asians represented at 6.2% and 4.3%, respectively.
- **Typical 5-year survival: 20%. With CAR T cells: 44.1%, showing long-term benefits.**



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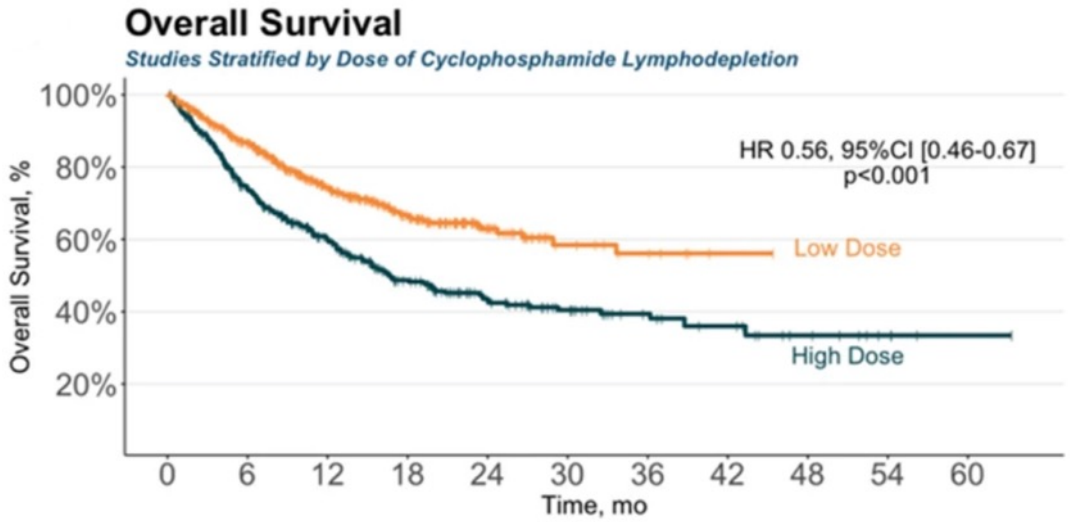
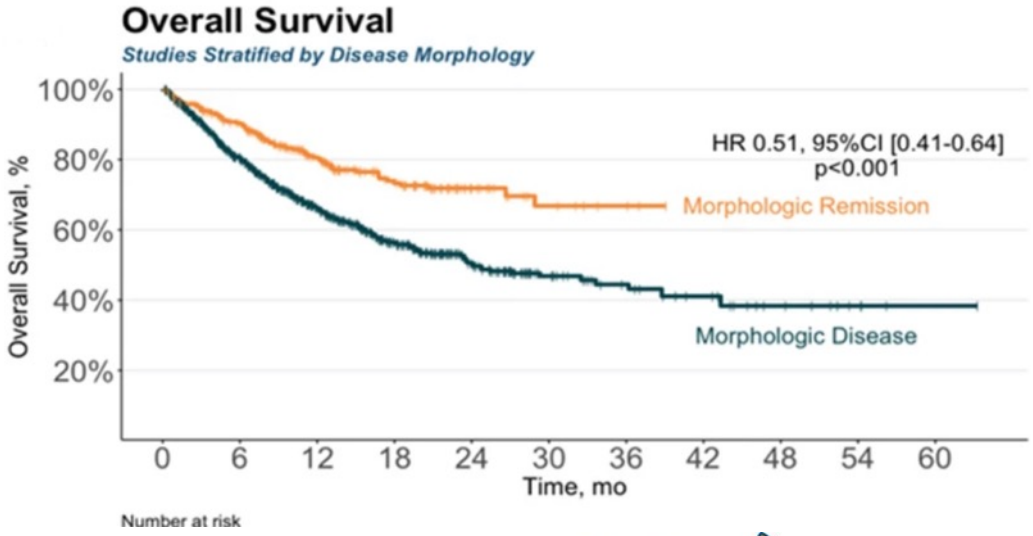
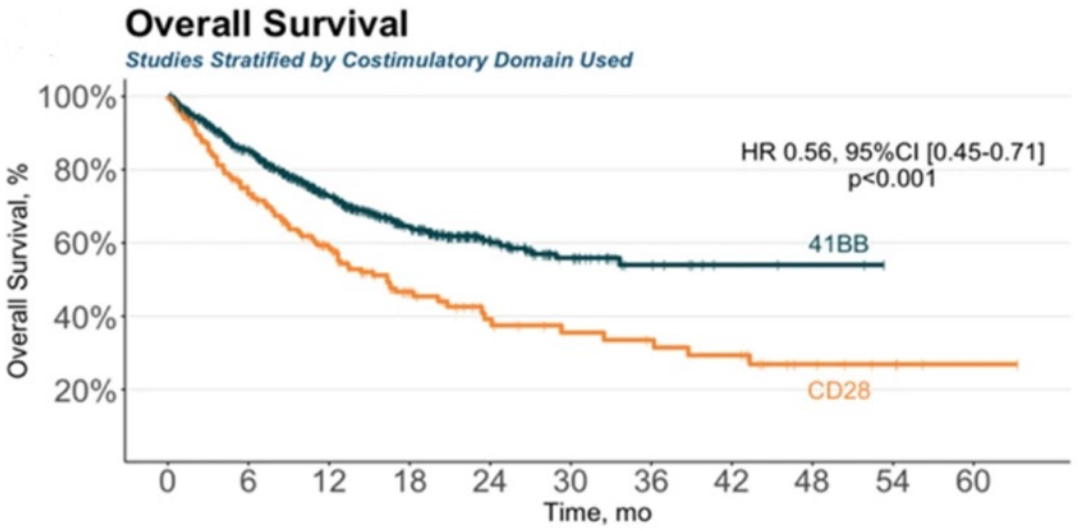
Elsallab et al. (2023), Cancer Gene Therapy

Long-Term Outcomes: Meta-Analysis

- **Lower survival features:**
- Patients with morphologic disease prior to treatment
- CD28 domain lower persistence & less sustained response
- Lymphodepletion: High-dose of cyclophosphamide







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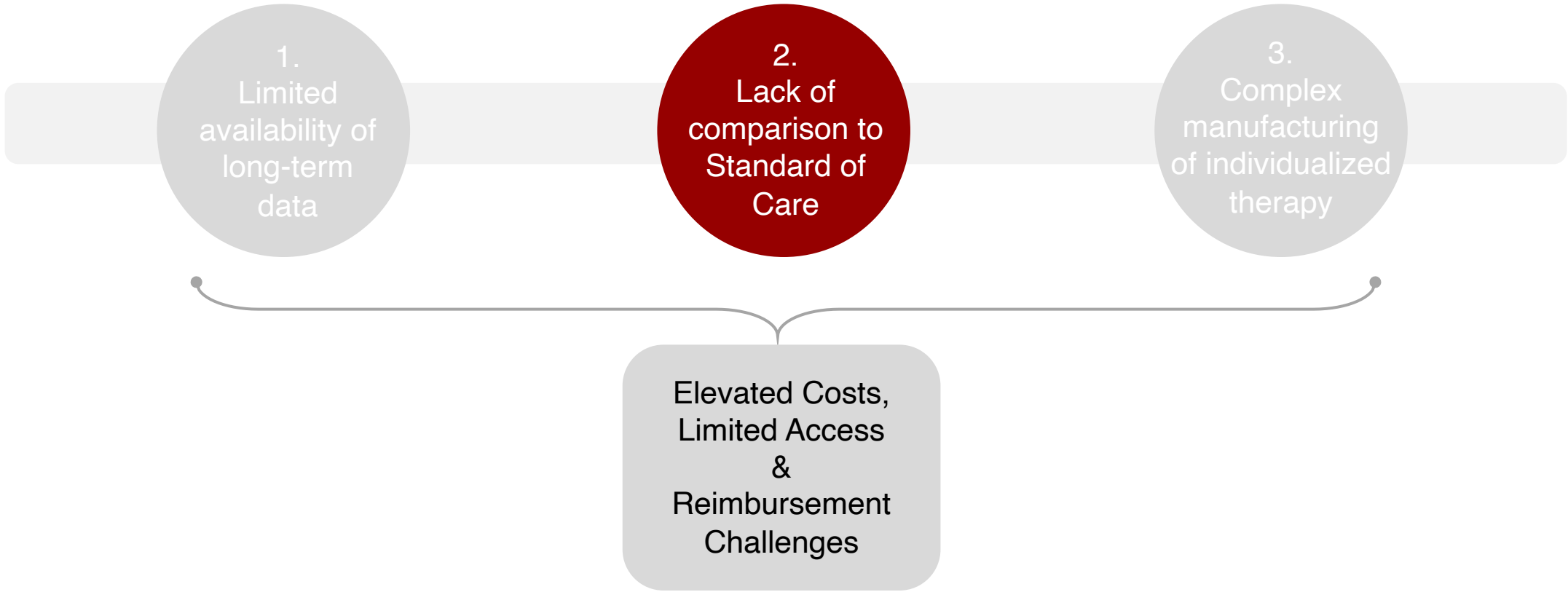
Elsallab et al. (2023), Cancer Gene Therapy

Roadblocks to CAR T cell Therapy Adoption



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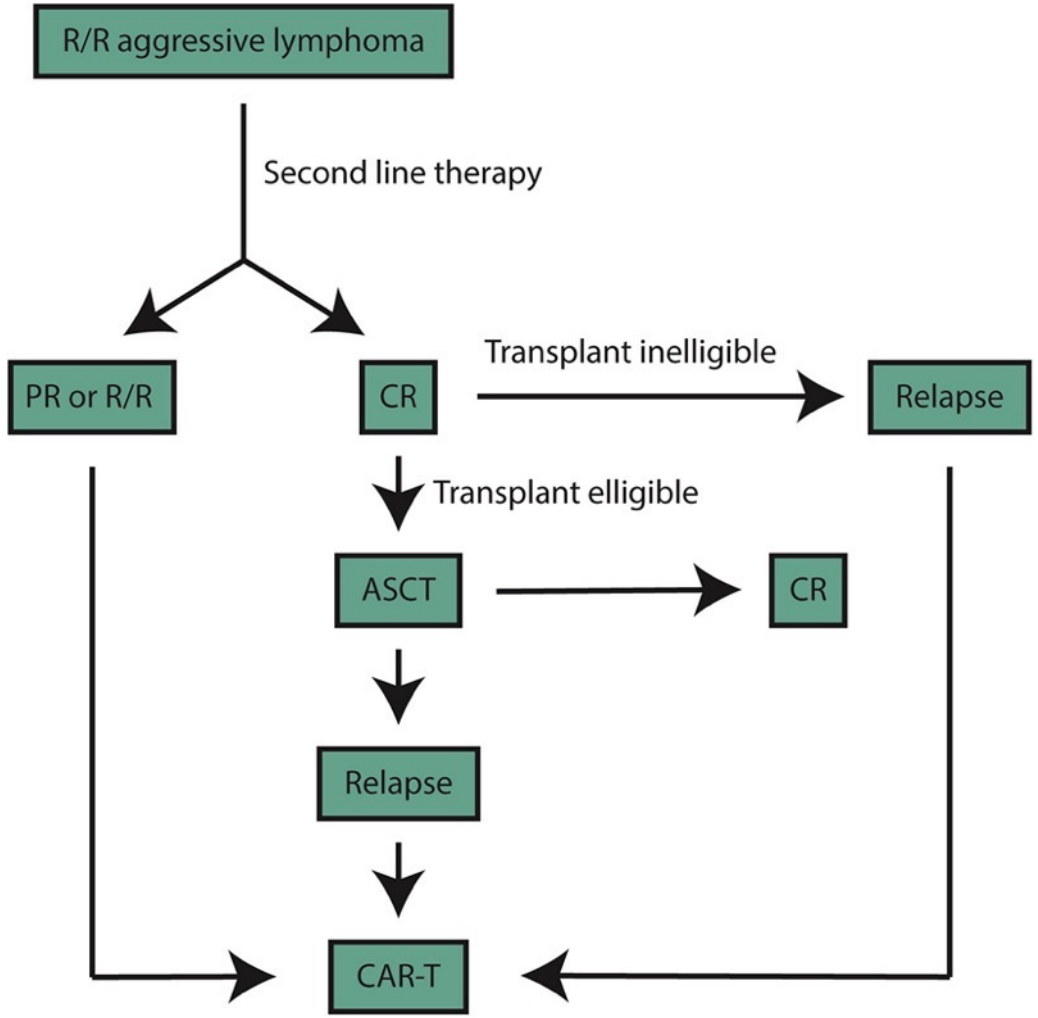
CAR T vs. Standard Care: Cost-Effectiveness

Cost-effectiveness analyses are vital for therapy **acceptance by health insurance providers**

Assessing CAR T-cell therapy faces challenges:

- ✓ Limited randomized studies for direct comparison to standard care (3rd line)
- ✓ Reliance on historical data
- ✓ Variability in bridging therapies and lymphodepletion approaches

As CAR T-cell therapies move towards earlier lines (2nd and 1st) of treatment, **cost-effectiveness analysis becomes more feasible.**



Leick et al. (2021), Molecular Therapy

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CAR T vs. Standard Care: Cost-Effectiveness

Large B-cell Lymphoma

- Evaluated CAR T-cell therapies as **2nd-line or 3rd-line treatment for r/r DLBCL**
- ➢ Axicabtagene ciloleucel (2nd-line) and tisagenlecleucel (3rd-line or later) were **cost-effective at $150,000/QALY**
- ➢ Tisagenlecleucel (2nd-line): dominated by standard care
- ➢ Clinical outcomes (ZUMA-7 and BELINDA) align with cost-effectiveness
- **Despite survival benefits and cost-effectiveness, CAR T remains expensive.**

Analysis perspectives	Incremental Costs, $[a]	Incremental QALYs	ICER per QALY, $[a]
Base case			
Health care sector perspectives			
Axicabtagene ciloleucel (2L)	59 754	0.60	99 101
Standard care	NA	NA	NA
Tisagenlecleucel (2L)	37 803	−0.02	Dominated[b]
Standard care	NA	NA	NA
Tisagenlecleucel (≥3L)	271 399	2.14	126 593
Standard care	NA	NA	NA
Societal perspectives			
Axicabtagene ciloleucel (2L)	59 076	0.60	97 977
Standard care	NA	NA	NA
Tisagenlecleucel (2L)	39 480	−0.02	Dominated[b]
Standard care	NA	NA	NA
Tisagenlecleucel (≥3L)	274 442	2.14	128 012
Standard care	NA	NA	NA

Choe et al. (2022), JAMA Network

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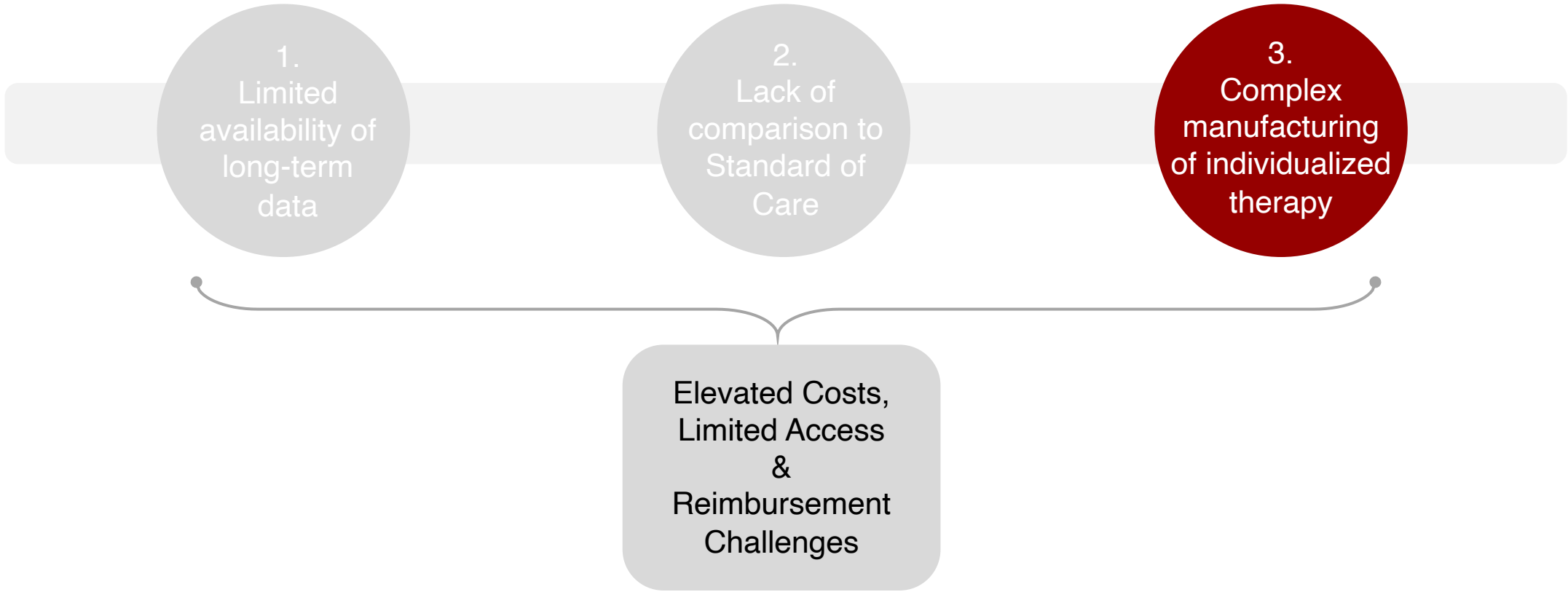
Roadblocks to CAR T cell Therapy Adoption



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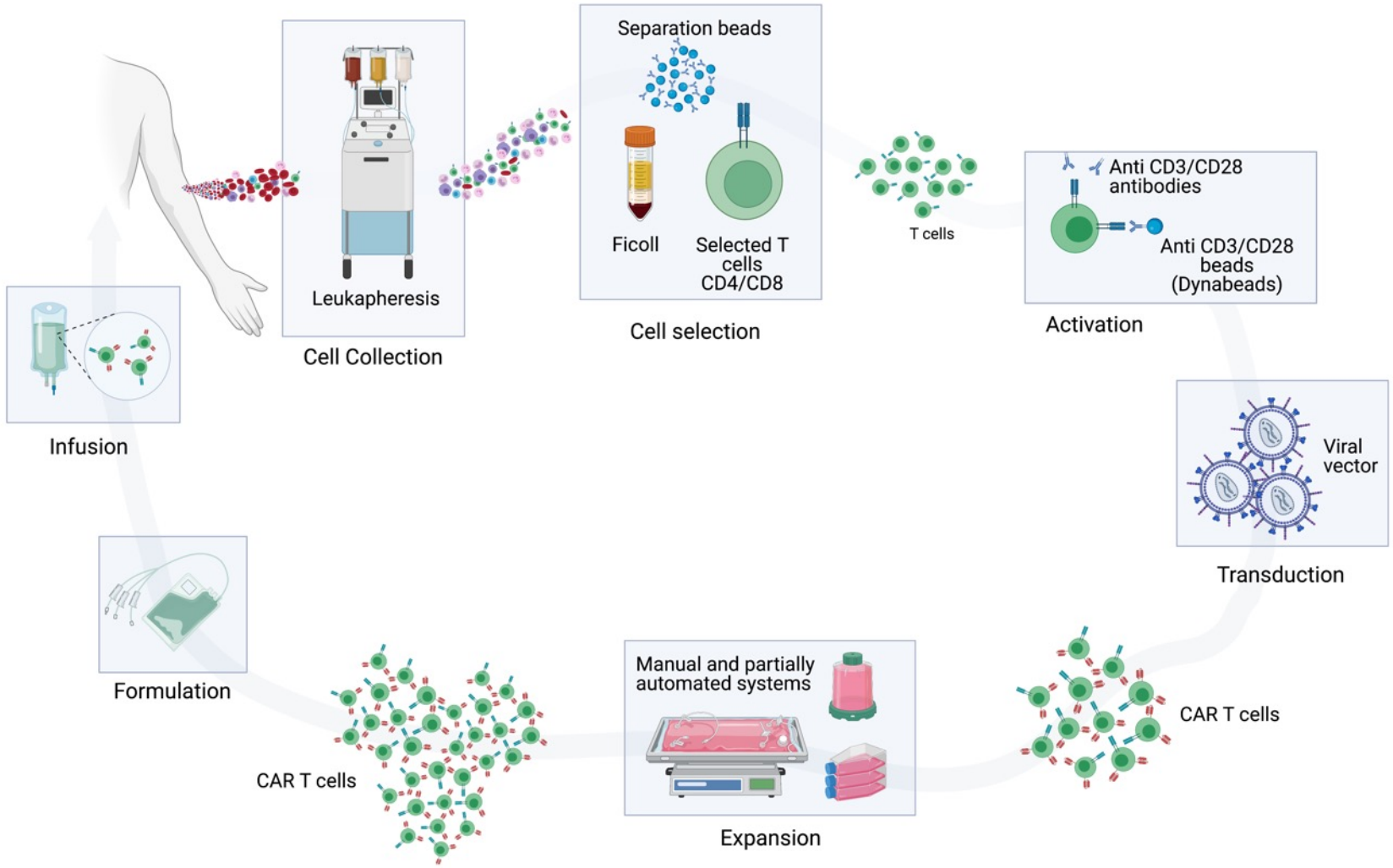
CAR T Cell Manufacturing



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Abou-el-Enein et. al. (2021), Blood Cancer Discov

Cell Therapy Manufacturing: Overcoming Challenges

CHALLENGE	RESPONSE
Expensive cGMP Facilities add to the overall cost of therapy	**Shorten manufacturing times and personnel involvement**
Open processes increase contamination risks and may result in operator errors, leading to significant manufacturing delays	**Implement automated/closed** systems to enhance workflow efficiency and shorten manufacturing time
Autologous cells of poor quality may add complexity and variability to the process, leading to production failures	Develop **allogeneic cell therapies** to enable large-scale production, catering to a broader range of patients
Viral vectors for genetic delivery pose safety concerns and high costs	**Develop & optimize non-viral delivery** for improved safety & efficiency

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1-Cell Therapy Manufacturing: What is cGMP?

Highly controlled and clean environment

Periodic maintenance of premises & equipment

Specialized Personnel

Quality Management System

Identifying deviations, investigating causes, & taking actions

Operationally independent quality control (QC) system

Rigorous product testing under set acceptance criteria

Traceability of starting materials, raw materials and final products

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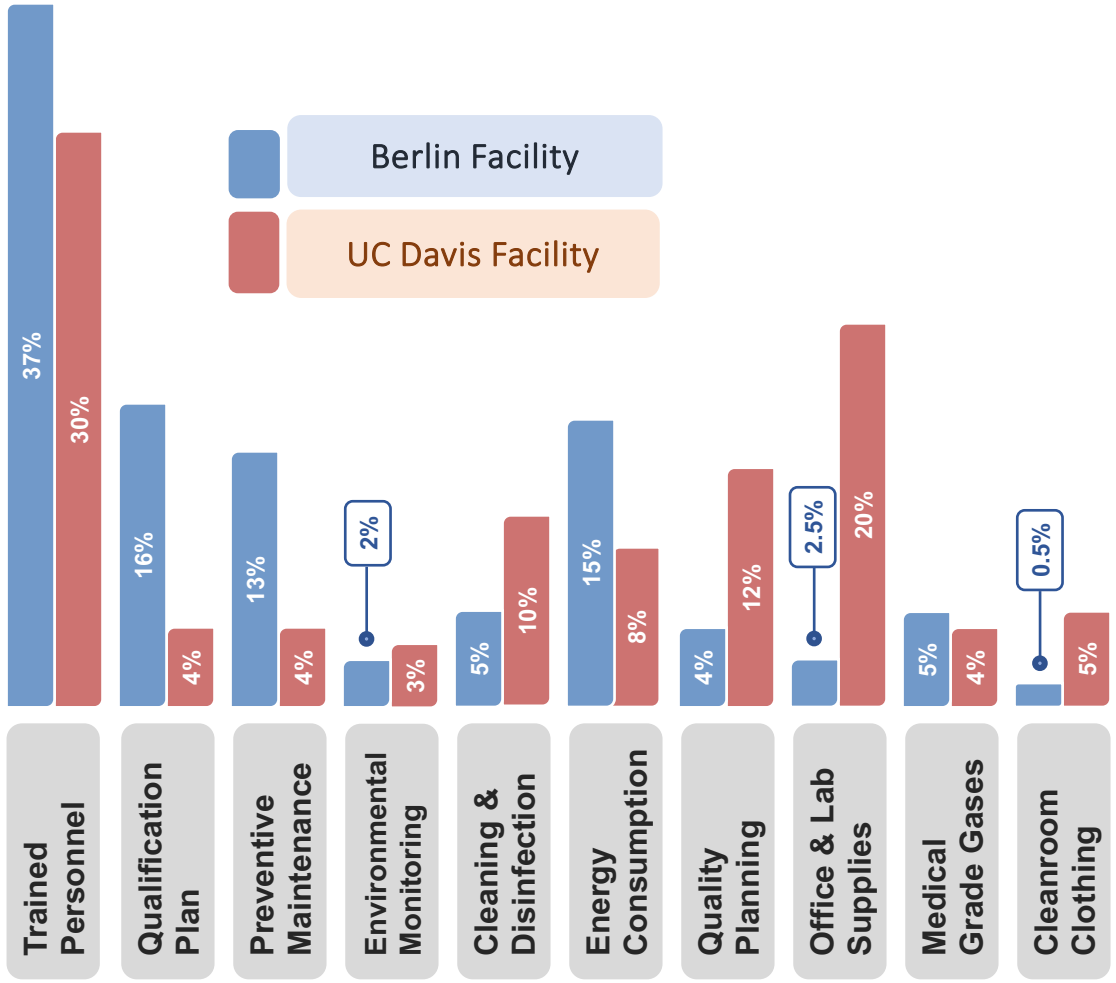
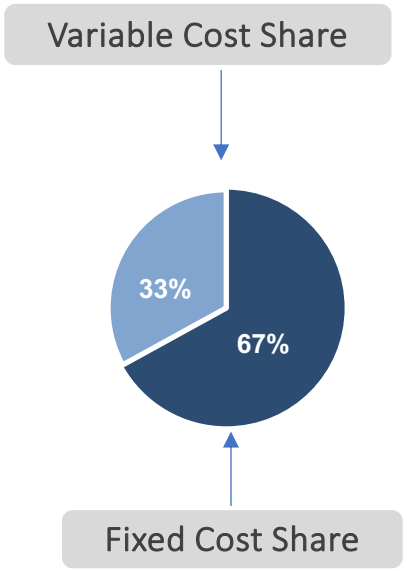
1-Cell Therapy Manufacturing: cGMP costs





Abou-el-Enein *et al.*, Cytotherapy 2013

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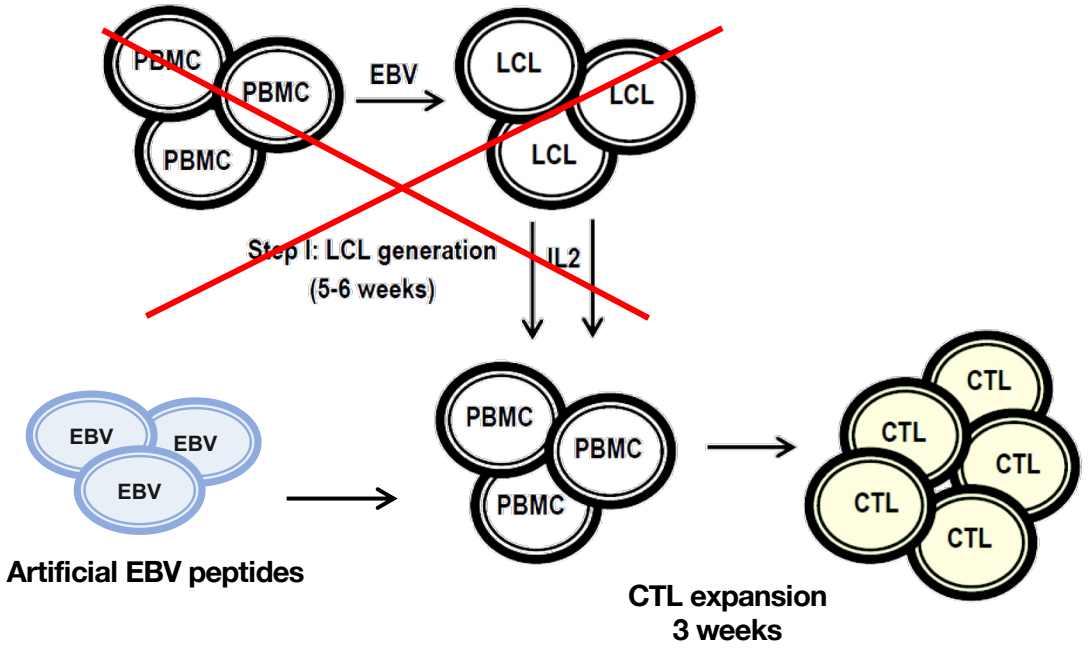
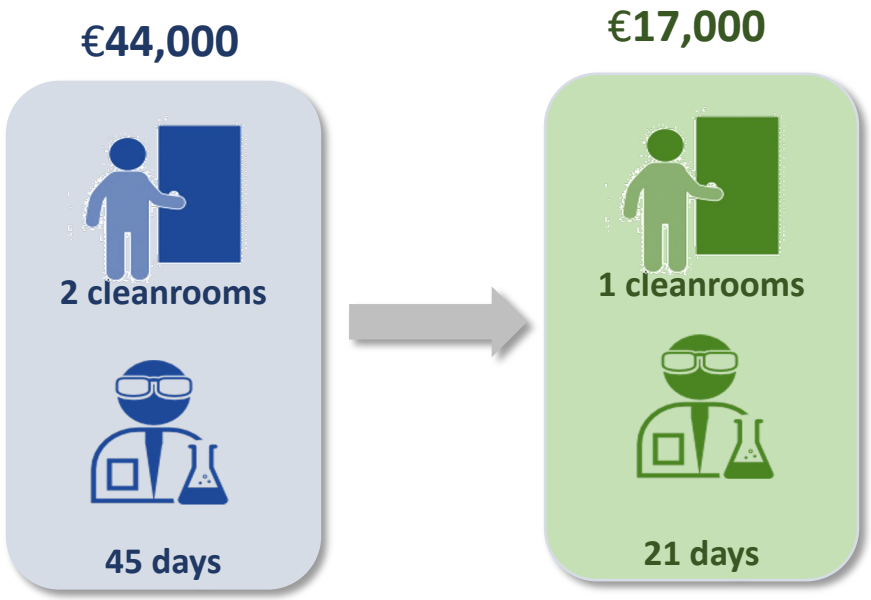
1-Cell Therapy Manufacturing: cGMP costs

Cost estimation and optimization of EBV-specific T cell therapy

- Optimized manufacturing process (protein-spanning peptide pool)
- Shorter manufacturing duration and reduce cleanroom use





EBV = Epstein-Barr virus
LCL = Lymphoblastoid Cell Lines

Abou-el-Enein M, *et. al.* Cytotherapy. 2013

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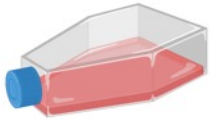
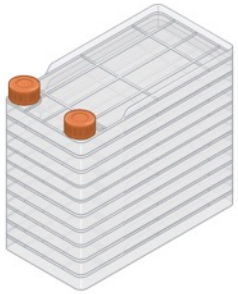
2-Cell Therapy Manufacturing: Closing the Process



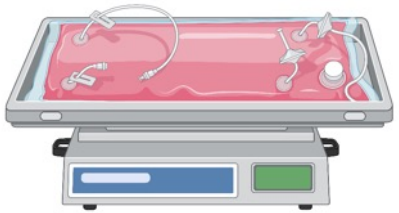


Flasks **Cell stacks**

- ❑ Open systems
- ❑ Labor intensive (manual)
- ❑ Stringent cleanroom requirements

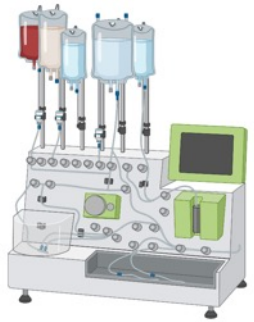
G-Rex

- ❑ Open & semi-closed
- ❑ High number of operator interventions
- ❑ Additional instruments required



Bioreactors

- ❑ Semi-closed
- ❑ Less operator interventions
- ❑ Additional instruments required



CliniMACS Prodigy

- ❑ Functionally closed/automated
- ❑ Minimal operator interventions
- ❑ Less stringent cleanroom requirement

Open/Manual → **Closed/automated**

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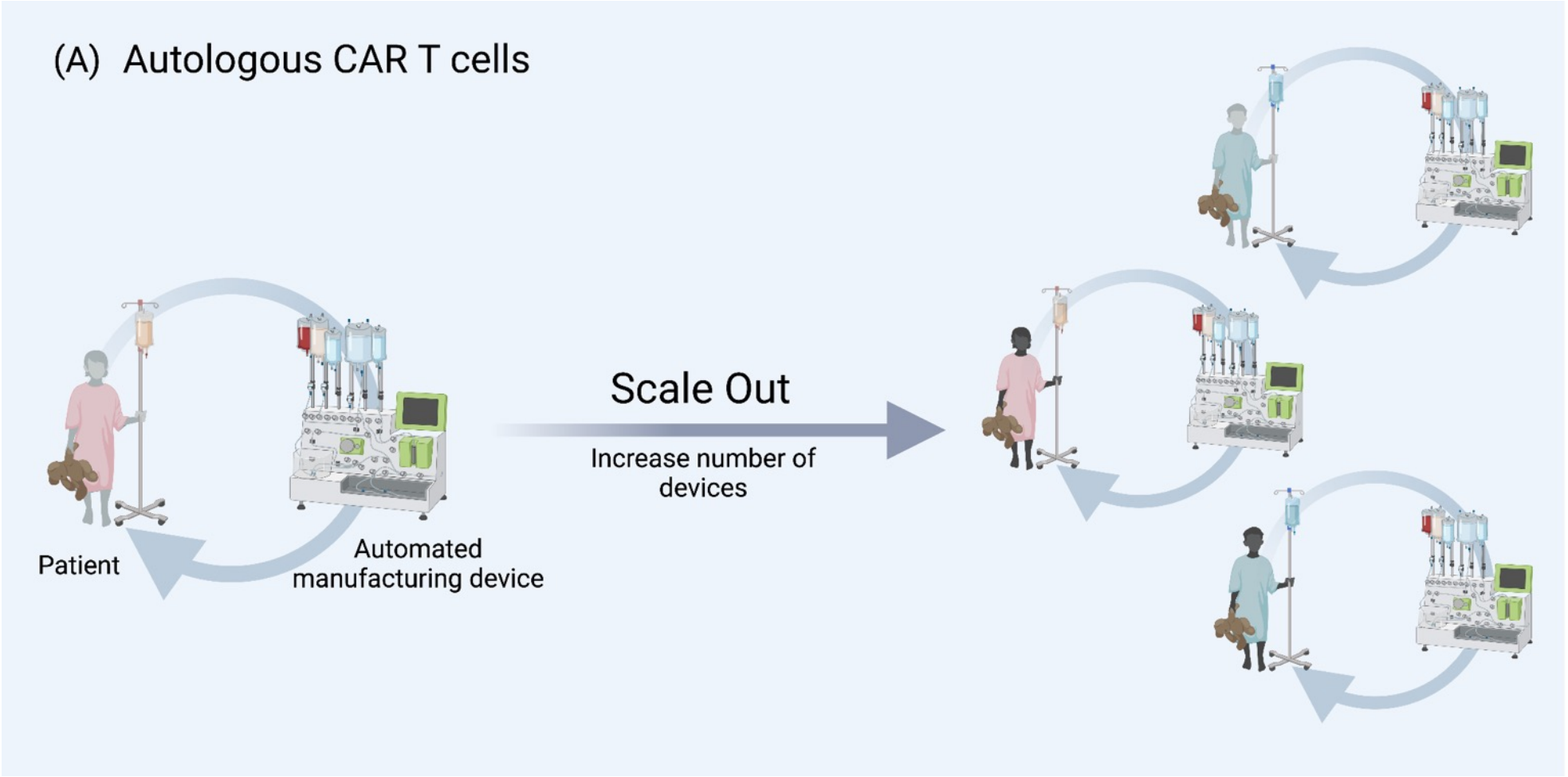
2-Cell Therapy Manufacturing: Closing the Process



Abou-el-Enein et. al. Blood Cancer Discov., 01 September 2021

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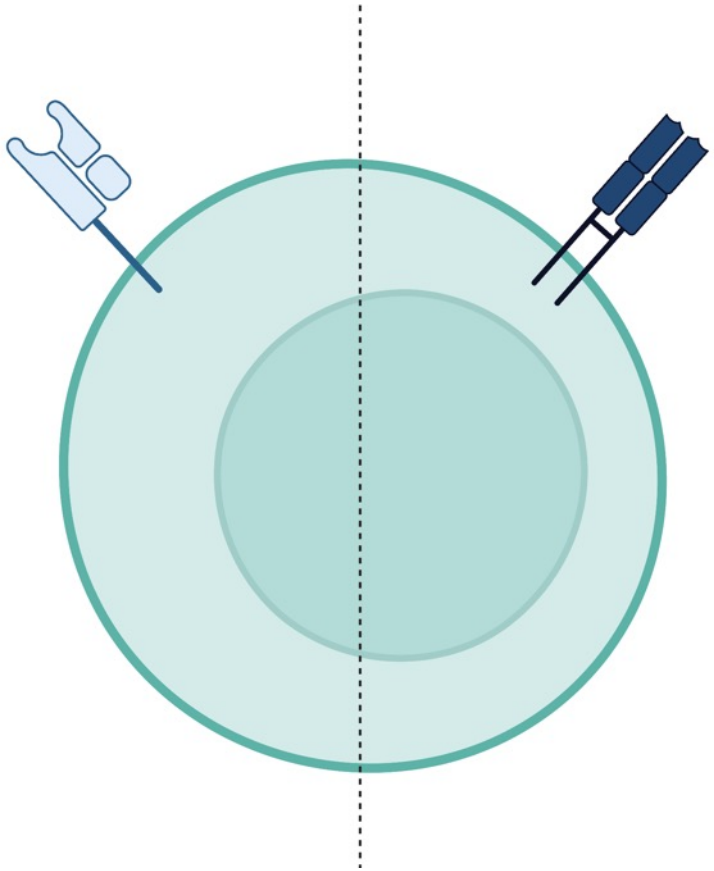
3-Cell Therapy Manufacturing: Autologous to allogeneic

	AUTOLOGOUS CELLS	ALLOGENEIC CELLS
Origin	- Own Patient	- Healthy Donor
Variability	- High	- Low
Availability	- Limited	- On demand
Quality of SM	- Low	- High
Batch Size	- Reduced	- Large scale
Risks	- Malignant cell transduction	- Alloreactivity & GvHD
Benefits	- Low immunogenicity	- Standardization & scaling



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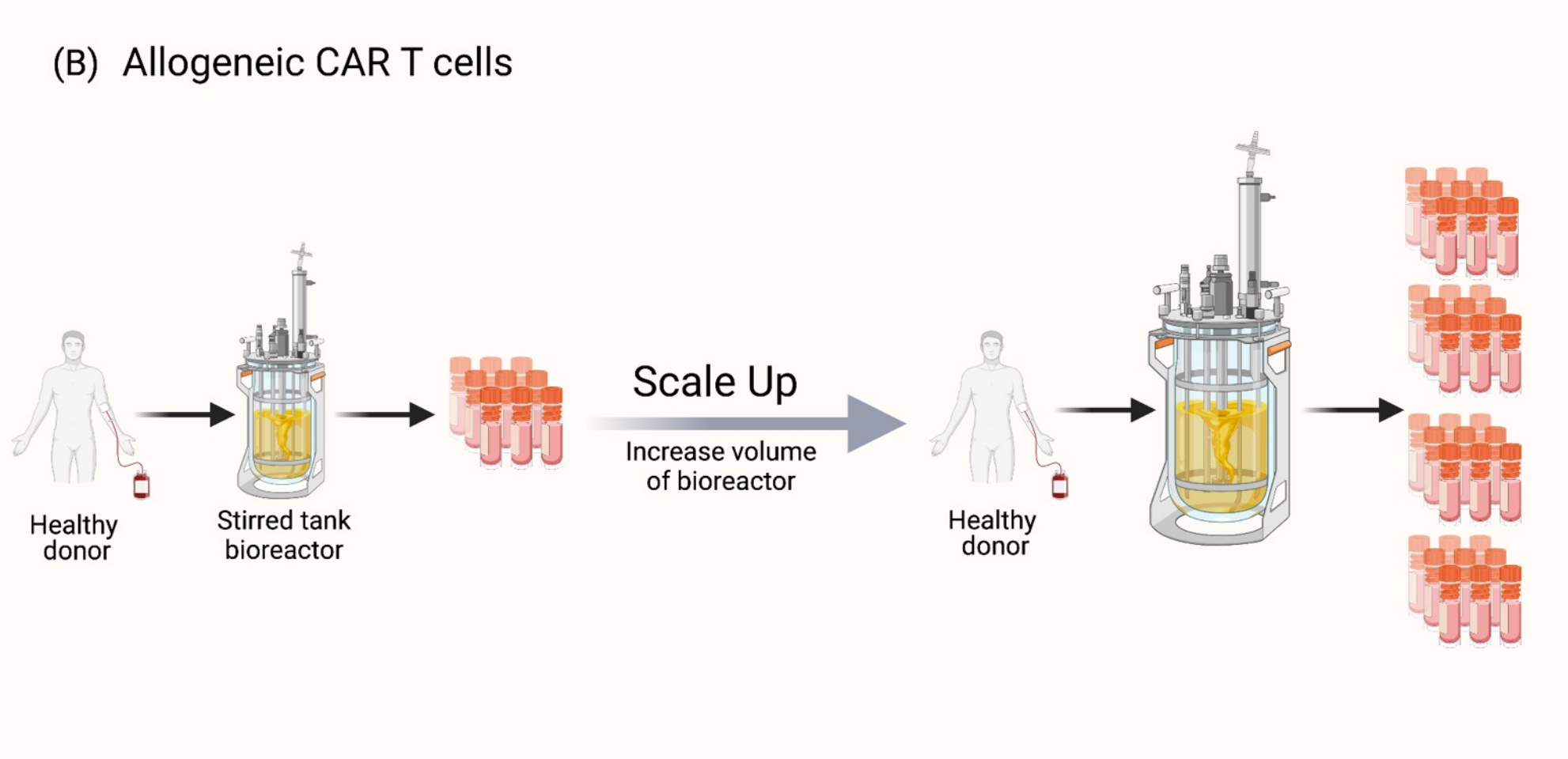
3-Cell Therapy Manufacturing: Autologous to allogeneic



Abou-el-Enein et. al. Blood Cancer Discov., 01 September 2021

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4-Cell Therapy Manufacturing: Viral to non-viral

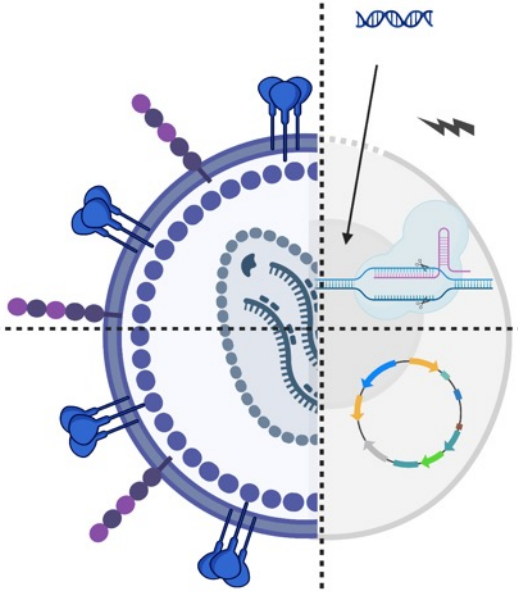
VIRAL VECTORS

Advantages

- High transduction efficiency
- Specific delivery to target cells
- Widely used

Disadvantages

- Pre-existing immunity
- High cost and complex production
- Limited scalability
- Low packaging capacity



NON-VIRAL VECTORS

Advantages

- Low immunogenicity
- Low cost
- Scalable
- High packaging capacity
- Enable multiplex editing

Disadvantages

- Low transfection efficiency
- Low cell viability
- Need for cell sorting post-engineering
- Limited experience

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USC/CHLA Cell Therapy Program

- Launched in 2021 with investment from **Keck School of Medicine (KSOM) of USC, Keck Medicine (KM) of USC, and Children's Hospital Los Angeles (CHLA).**

- Create a mature ecosystem for **clinical translation of cell and gene therapy** research.

- Provide comprehensive support; from **strategic planning and training to product manufacturing and quality testing**.

The centerpiece is a state-of-the-art **cGMP facility**

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Cell Therapy Manufacturing: Capabilities

- Serves a **diverse range of clients**, both internal and external.
- Supports **all stages of clinical trials**, from pre-clinical to Phase I, II, and III.
- Offers more than just CDMO services, providing **strategic, regulatory, and scientific support**.

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USC/CHLA Cell Therapy Program: cGMP

Opened January 24, 2023.

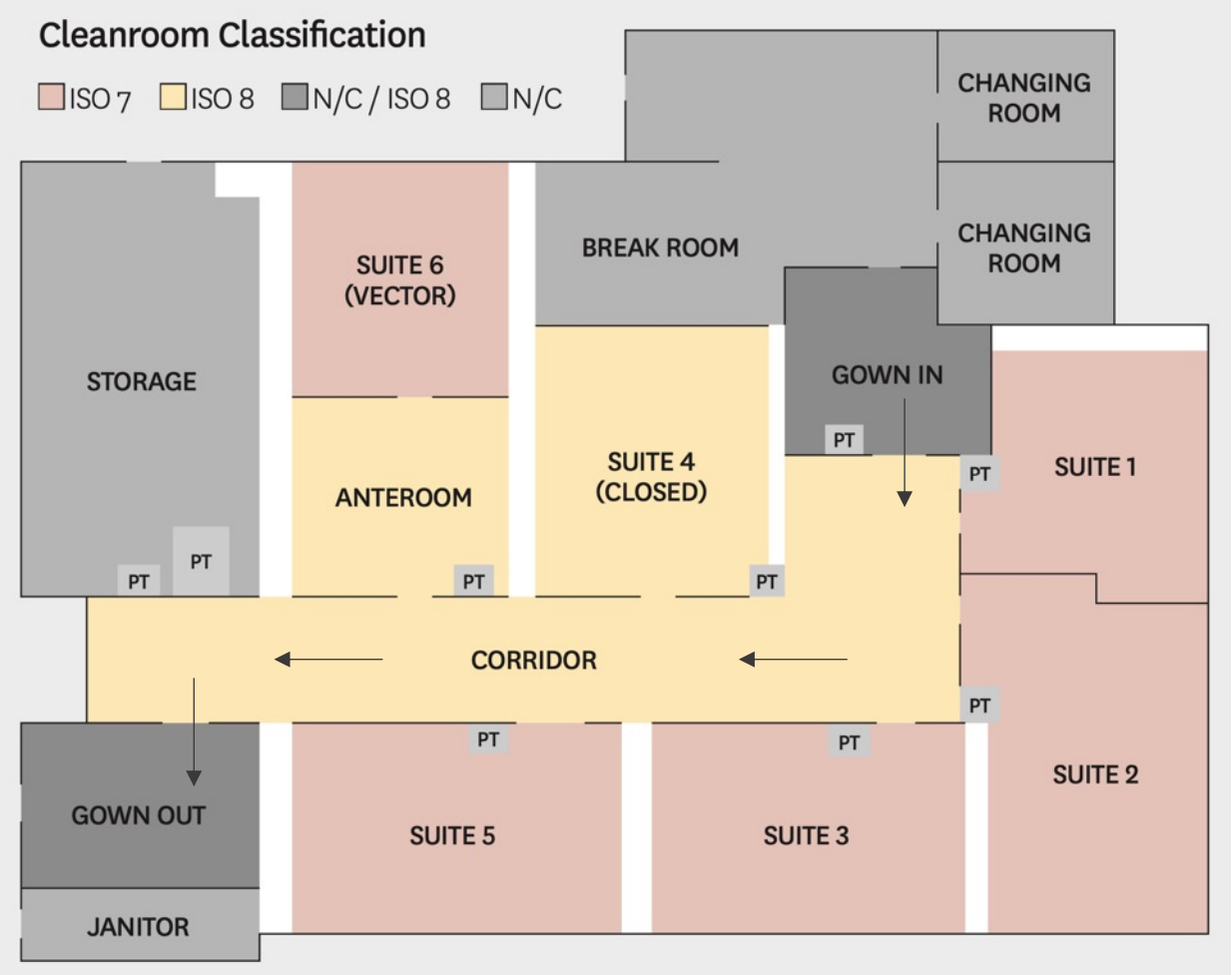
The cGMP facility spans 3,184 sf and has:

- Four ISO-7 cleanrooms for product manufacturing
- One ISO-7 cleanroom for **vector** manufacturing
- One ISO-8 for **closed system** manufacturing

Supporting infrastructure:

- Quality Control (QC) lab
- Process Development (PD) lab
- Vector Engineering lab

Maximum capacity: **Approx. 200** patient products per year.



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Children's Hospital Los Angeles

cGMP CIRM Network

cGMP CIRM Network $2M (2024-2025)

- Implemented **eQMS** to boost efficiency and reduce errors in manufacturing.
- **Optimized and scaled cell therapy manufacturing** workflow for network-wide use.
- Developed **in-house viral vector production**.
- Launched cell therapy training, focusing on talent from diverse backgrounds.
- **Forged key partnerships** with academia and industry leaders.

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CIRM
CALIFORNIA'S STEM CELL AGENCY

CIRM Alpha Clinic

USC+CHLA CIRM Alpha Clinic $8M (2023-2027)

- Translational Infrastructure
- Education & Training
- Community Engagement
- CIRM Network Collaborations

Facilitate the translation of novel cell and gene therapies to patients in California and beyond.

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Children's Hospital LOS ANGELES

CIRM
CALIFORNIA'S STEM CELL AGENCY

USC+CHLA CIRM Alpha Clinic

Director:
Tom Buchanan

Associate Director:
Mohamed Abou-el-Enein

Site PI at CHLA:
Alan Wayne

CIRM Network Liaison:
Juliane Glaeser

Core Competencies I Offerings:

- cGMP manufacturing and process development
- Workforce Training: 4-unit course on cell and gene therapy development
- Clinical Trial Quality Training: Three-part series on study monitoring and site inspections
- Vision diseases expertise
- Musculoskeletal diseases expertise
- Craniofacial & Dental disease expertise
- Pediatric diseases expertise
- Community engagement: Support network partners with community outreach strategies.

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CIRM CALIFORNIA'S STEM CELL AGENCY

Summary

- CAR T-cell therapy has shown remarkable success in treating hematological B-cell malignancies and is moving towards earlier lines of treatment.
- High costs and reimbursement challenges limit their broad adoption
- Addressing challenges such as complex manufacturing can help reduce costs & improve accessibility.
- Automation, allogeneic cell therapies, and non-viral gene delivery methods are being developed to overcome manufacturing challenges.
- Translational infrastructure and manufacturing technologies are critical to advance therapy development and increase access to patients.

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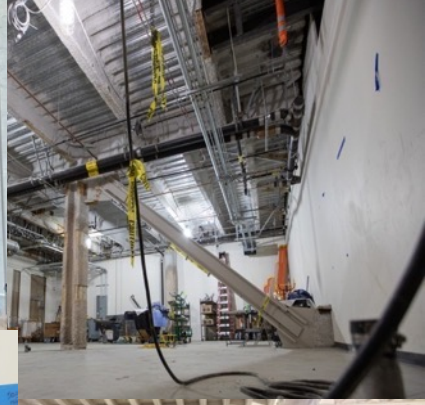
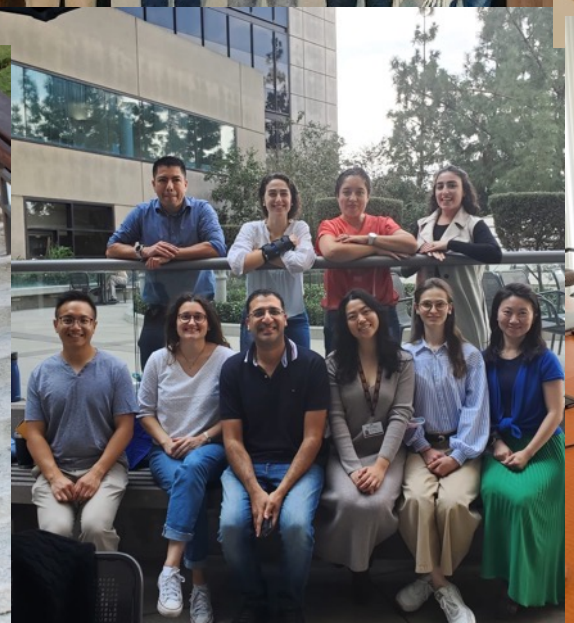
CURE


cGMP







Acknowledgment

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Allan Wayne
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Cort Brinkerhoff
Brenda Zaragoza-Dorado

Norris Comprehensive Cancer Center

Caryn Lerman
Christopher Loertscher
Patti Goldberger
and many more colleagues….

CAR T-Cell Therapy:

Navigating the Development Challenges

Thank you!

Dr. Mohamed Abou-el-Enein
mabouele@usc.edu

Follow us on LinkedIn & Twitter: USC/CHLA Cell Therapy Program

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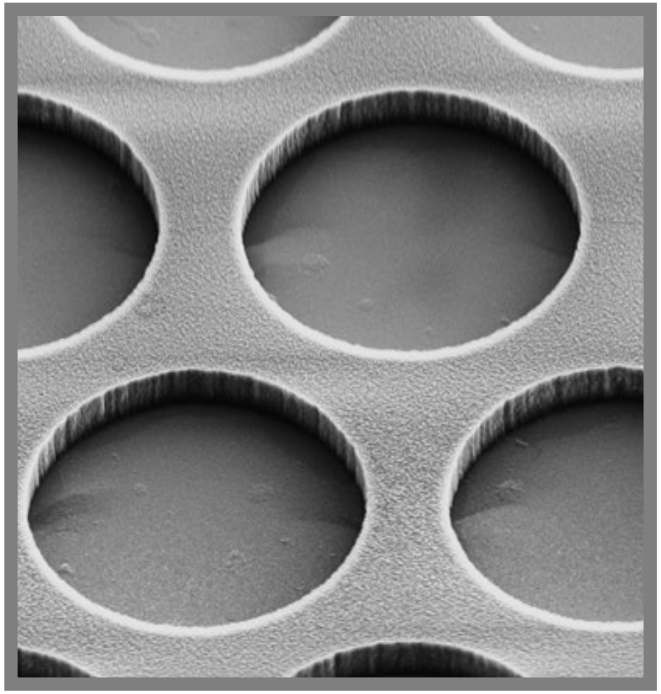
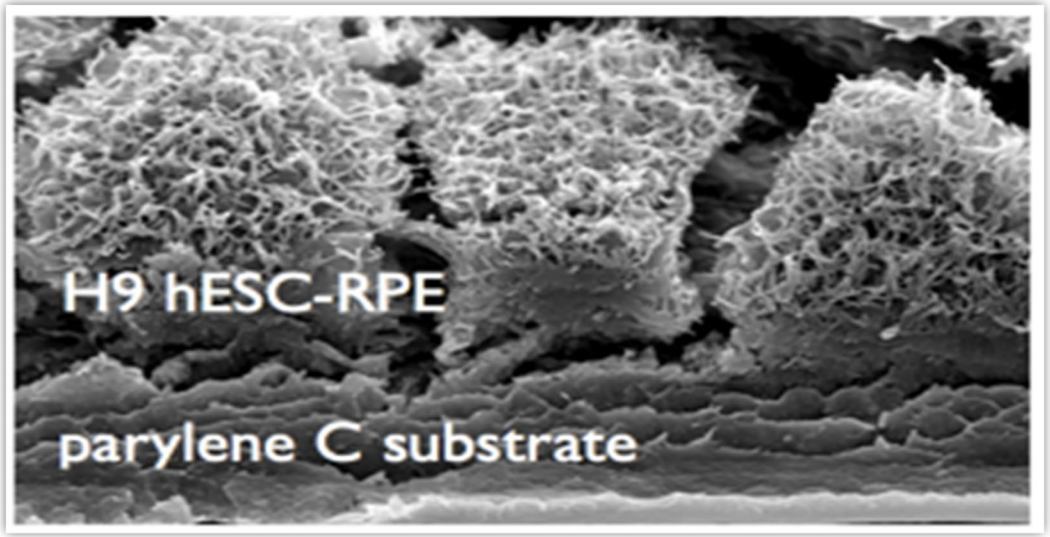
Stem Cell Implant: *For Restoring Sight to the Blind*
Phase 1/2A Results in Geographic Atrophy

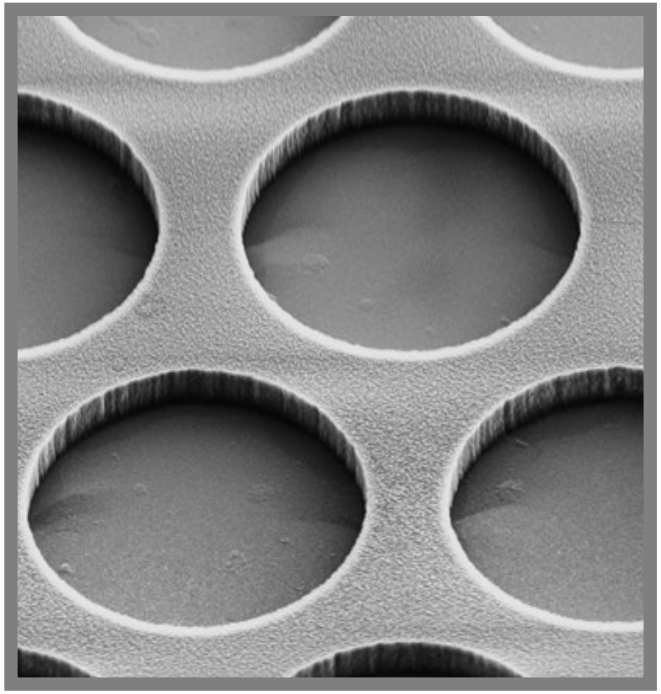


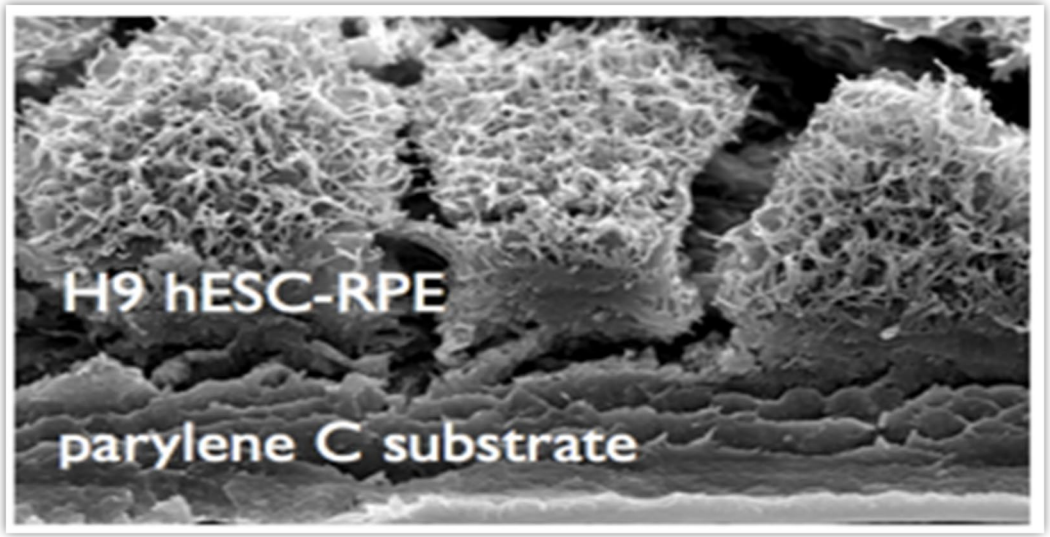


Mark S. Humayun, MD, PhD

Cornelius Pings Chair in Biomedical Sciences
Professor of Ophthalmology and Biomedical Engineering
Director USC Ginsburg Institute for Biomedical Therapeutics
Co-Director USC Roski Eye Institute

Marriage of Ophthalmology & Bioengineering





Mark S. Humayun, MD, PhD

Cornelius Pings Chair in Biomedical Sciences
Professor of Ophthalmology and Biomedical Engineering
Director USC Ginsburg Institute for Biomedical Therapeutics
Co-Director USC Roski Eye Institute

Impact of Blindness

Macular Degeneration

- **Macular Degeneration**
  - 196M living with macular degeneration in 2020
  - Expected 288 million by 2040
    - *The Lancet. Volume 2, No. 2, e106–e116, February 2014*
- **Global Cost of Visual Impairment due to Age-Related Macular Degeneration**
  - ~$300 billion
  - $255 billion in direct health care costs
    - Investigative Ophthalmology & Visual Science April 2011, Vol.52, 5543

288MM

&

$300B

Eye and Retina

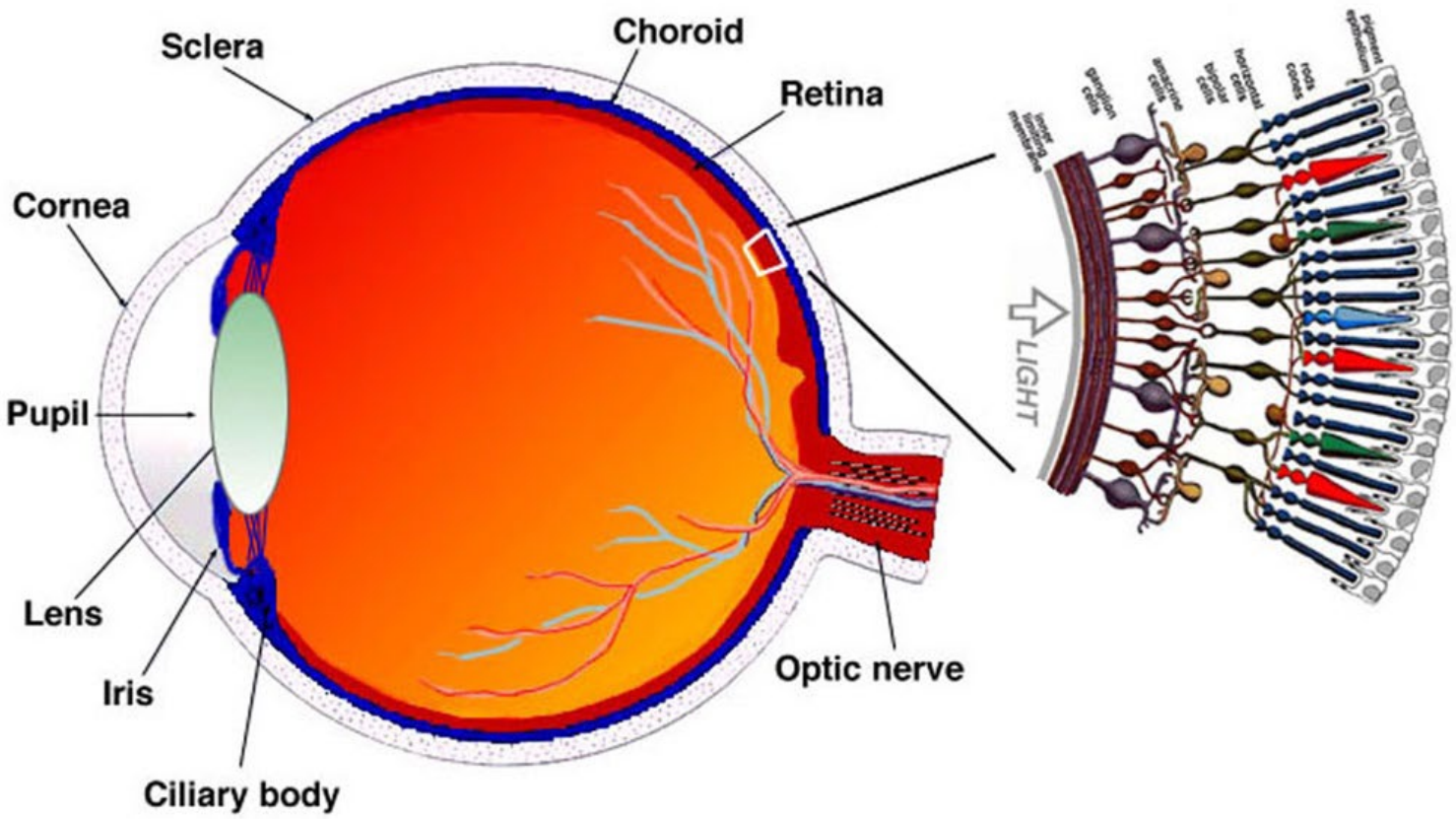
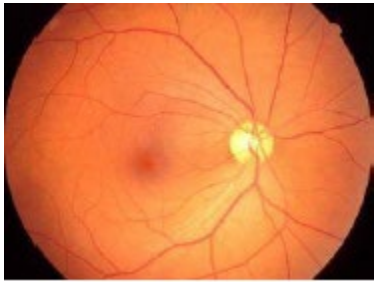


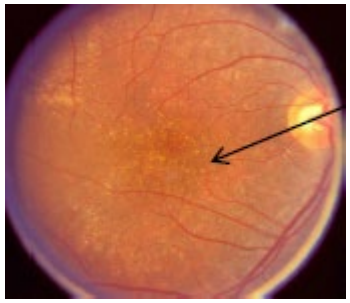
Fig. 1.1. A drawing of a section through the human eye with a schematic enlargement of the retina.

Age-Related Macular Degeneration (AMD)

Normal

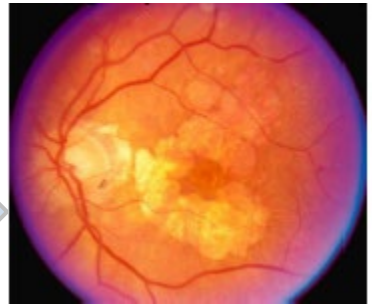


Early AMD

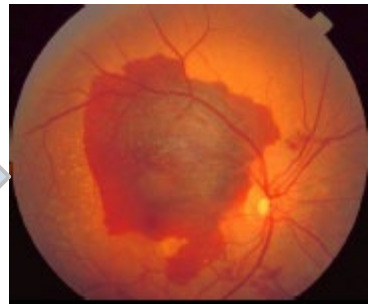


- Dysfunction of retinal pigmented epithelium (RPE)
- **Degeneration of Bruch's membrane**
- Accumulation of drusen

Advanced AMD



Dry (atrophic) AMD
80-90%



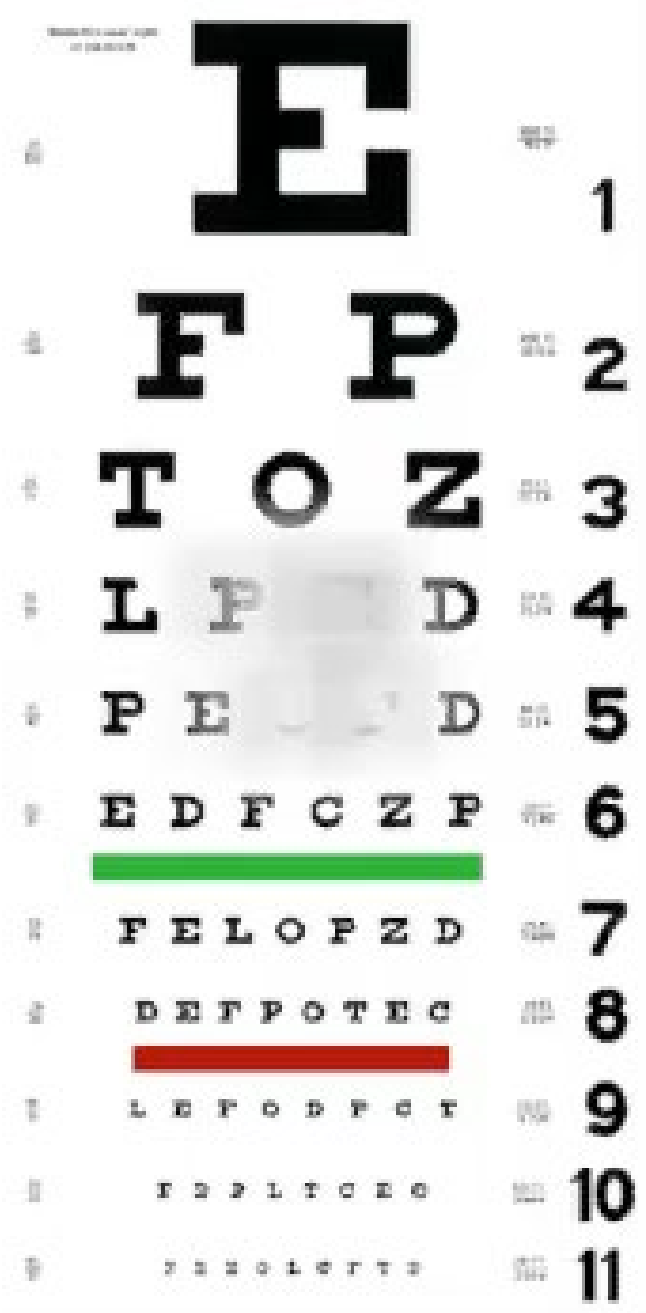
- Progressive Loss of RPE and photoreceptors
- Loss of Vision

Wet (exudative) AMD
10-20%

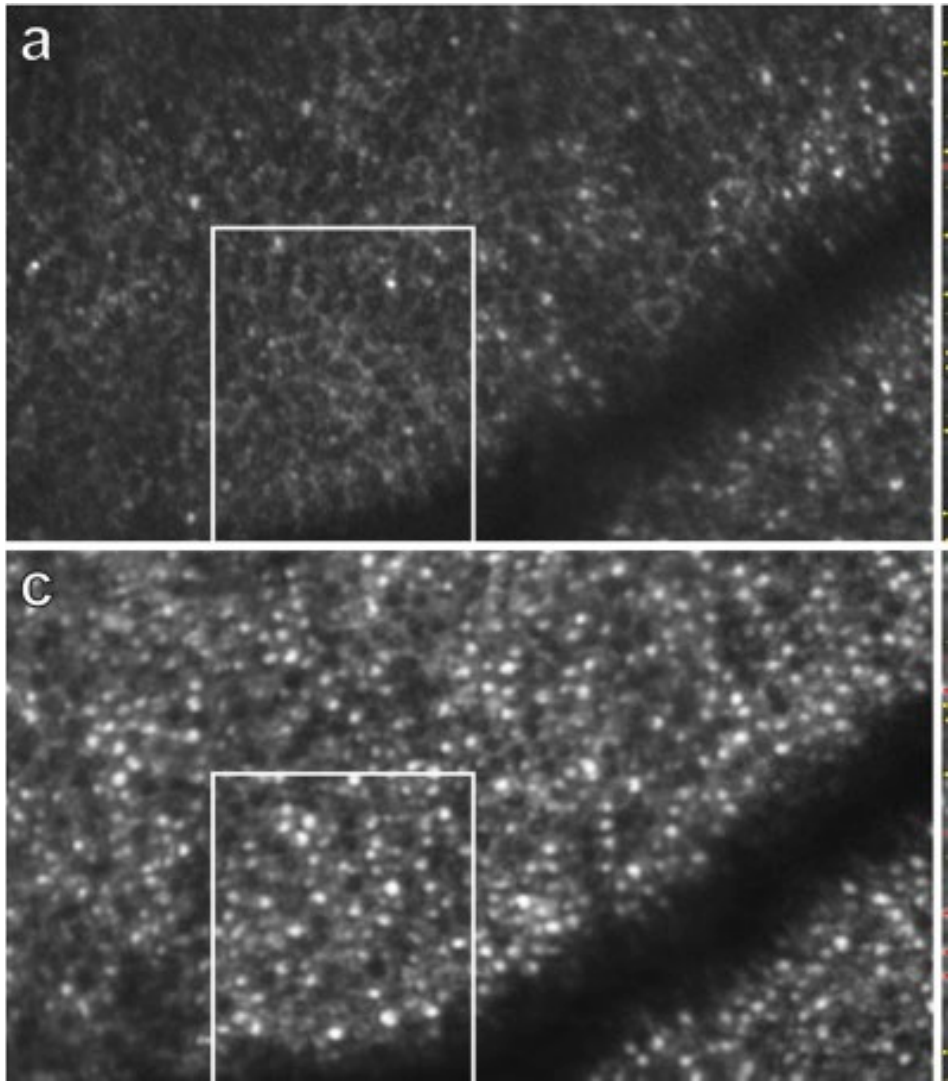
The Case for Using Stem Cells to Treat Blindness

Age-Related Macular Degeneration (AMD)

- **AMD Leads to photoreceptor (rods and cones) function loss**
  - Anti-VEGF (vascular endothelial growth factor) for wet AMD
- **Bioengineered stem cell derived implant**
  - Proposes to re-establish host photoreceptor function
  - May not require a neuronal transplant



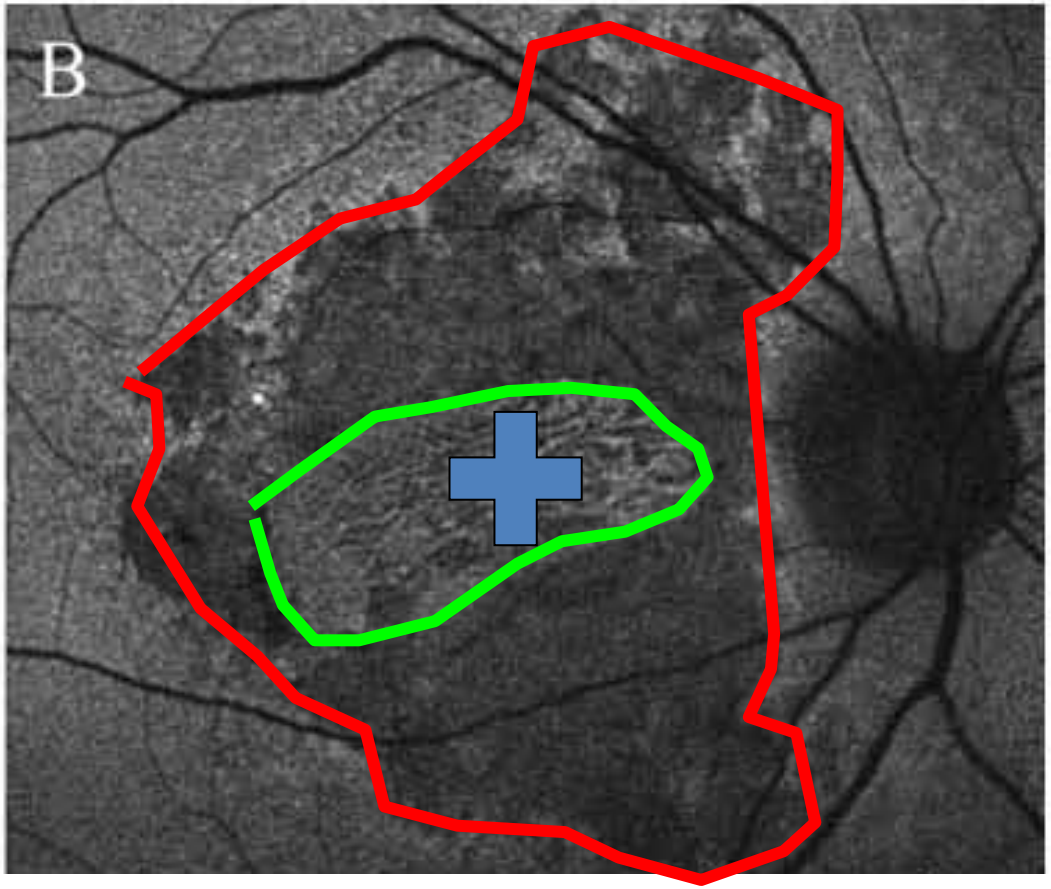
Damaged Cones:
Capable of Generating New Outer Segments



- Imaging with an adaptive optics scanning laser ophthalmoscope (AOSLO) showed depletion of cone outer segments in the affected retina
- A year later visual function had improved, with shrinkage of the enlarged blind spot
- AOSLO imaging ***showed repopulation of cone outer segments***, although not returned to normal

Sci Rep. 2015; 5: 12364

Visual Acuity Improvement after Autologous RPE Transplant



Evidence for heath of retina and choriocapillaris
High complication rate (up to 45%)

Types of Stem Cells

Types of Stem Cells

Pluripotent: Can give rise to most cell types

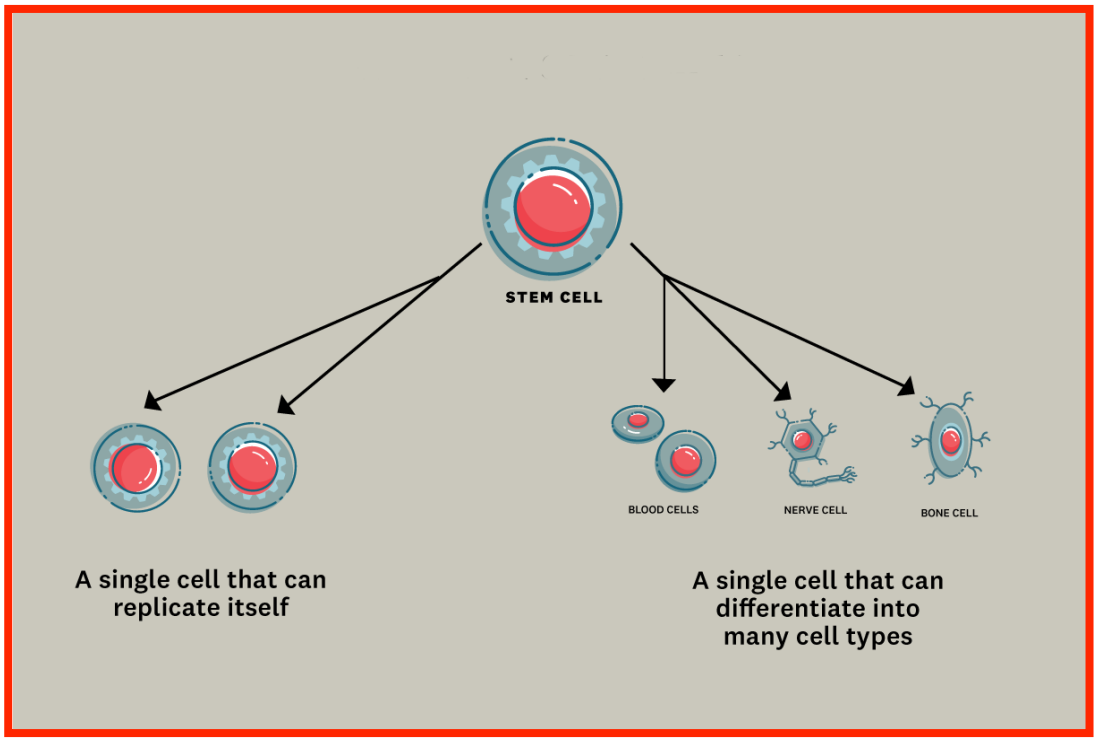
- Embryonic Stem Cells
- Induced Pluripotent Stem Cells

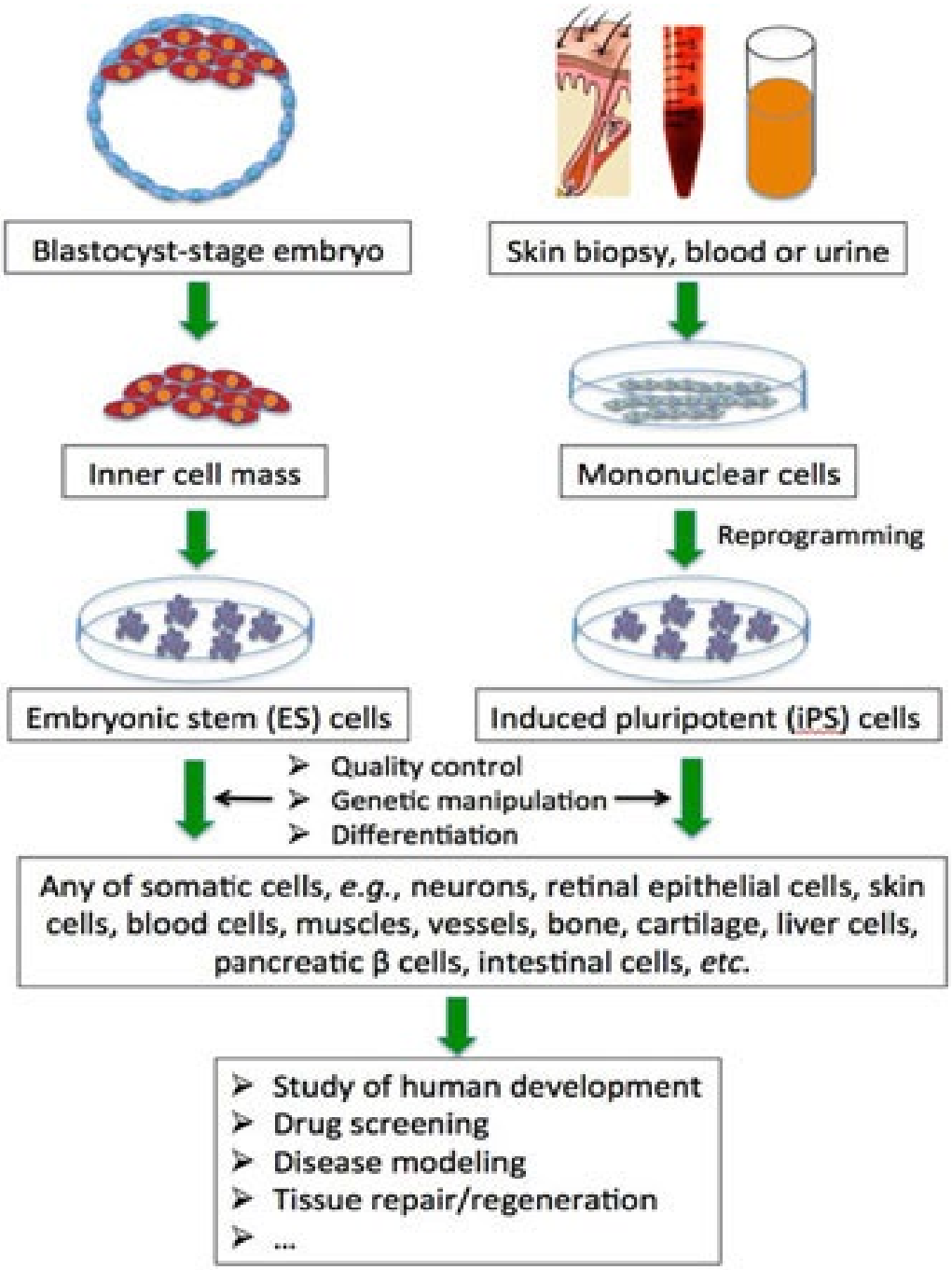
Multipotent: Can give rise to a few cell types

- Adult Stem Cells: fat, bone marrow
- Perinatal Stem Cells: amniotic fluid, umbilical cord blood

Caution

- Stem cells derived from autologous fat has led to blindness when injected into the eye of patients with AMD
- Risk of Tumor formation and rejection





Yamanaka Factors-
group of protein transcriptional factors (Nobel Prize)

Oct4, Sox2, Klf4, Myc

Stem Cell Suspension or Sheet

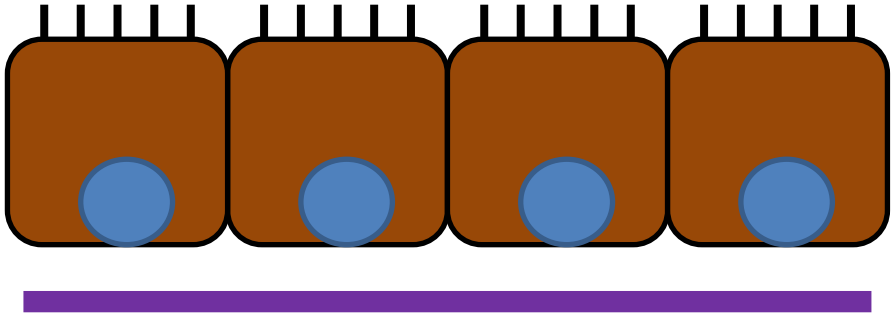
Cell-Based Therapies for AMD

Therapy	Developer	Status of Product
Suspension hESC-derived RPE Cells	Lineage Cell Therapeutics/ Genentech	Phase 1/2a Clinical Trial in GA
Suspension hESC-derived RPE Cells	Astellas (Formerly Ocata)	Phase 1/2a Clinical Trial in GA
Polarized hESC-derived RPE Cells on a Biodegradable Scaffold	University College London	Phase 1/2a Clinical Trial in Wet AMD
Polarized Autologous iPSC-derived RPE Cells on a Biodegradable Scaffold	National Eye Institute	Phase 1/2a Clinical Trial in GA
Suspension Adult RPE Progenitor Cells	LuxaBio; Neural Stem Cell Institute	Phase 1/2a Clinical Trial in GA
iPSC-Derived RPE Cells on an Amniotic Membrane	I-Stem	Phase 1/2a Clinical Trial in GA
Autologous and Haploidentical iPSC-derived RPE Cells in Suspension or on Sheets	Riken Institute, Kobe Eye Center	Pilot Clinical Trials in GA and Wet AMD
Suspension Autologous iPSC-derived RPE Cells	UCLA	Preclinical Development
iPSC-derived RPE Cells in a Fibrin Gel	Seeing Medicine	Preclinical Development

Stem Cell Derived RPE Patch:

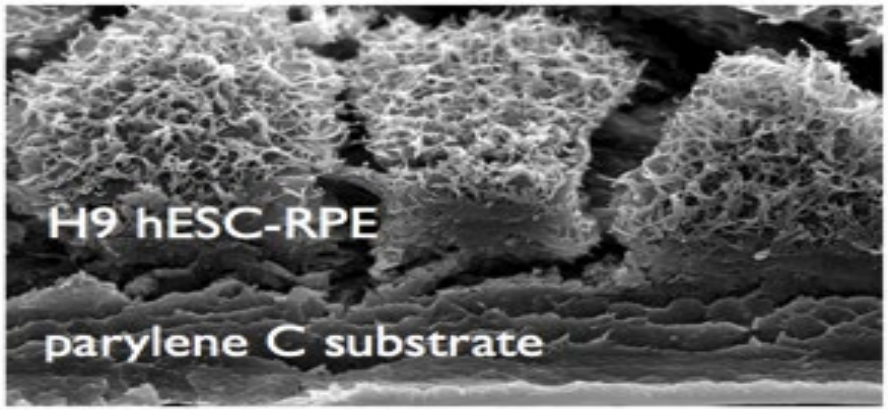
Addresses Need for Polarized Monolayer on Basement Membrane

Manufactured by Regenerative Patch Technologies, LLC



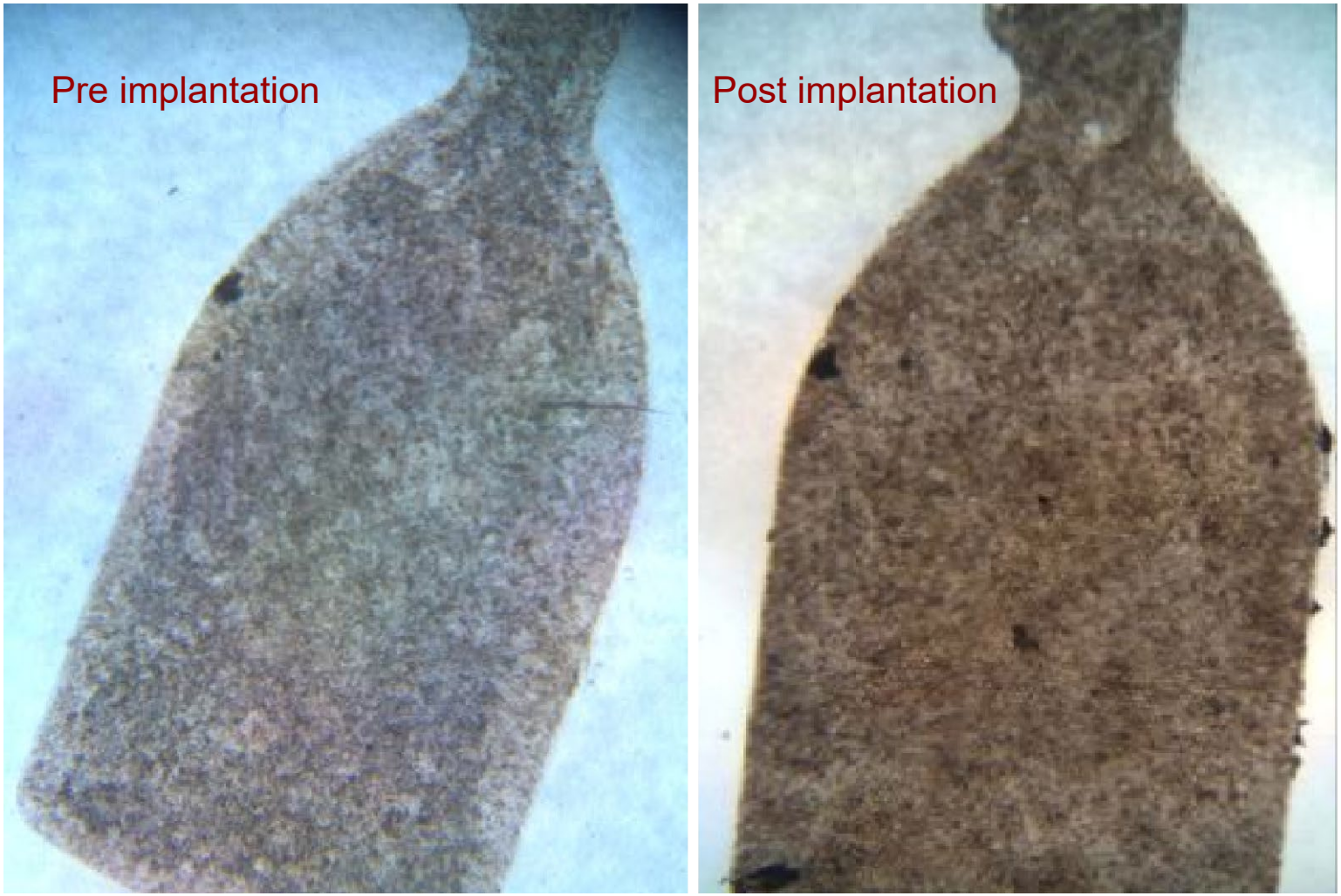
RPE Cells

Parylene Substrate



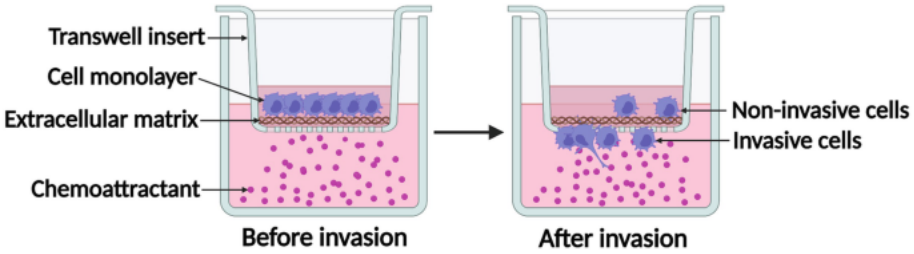
Implant Size compared to a penny (dia 19mm)

No Loss of Cells from Implant Due to Insertion Tool

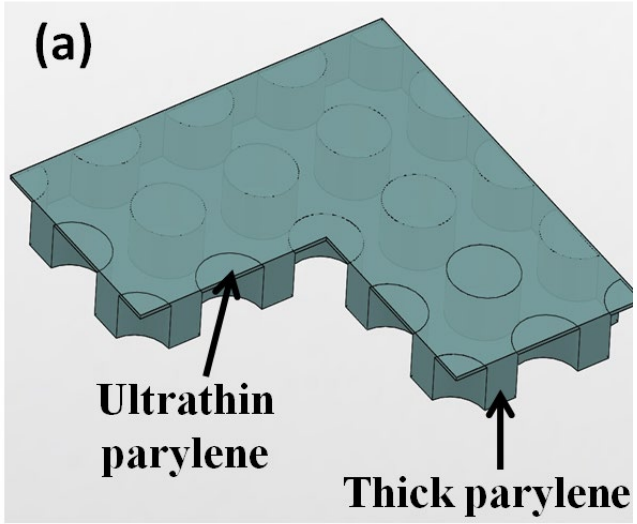


Synthetic Non-Porous Biomimetic Membrane

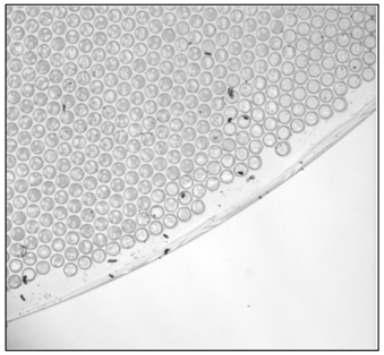
Cells Migrate Across Pores

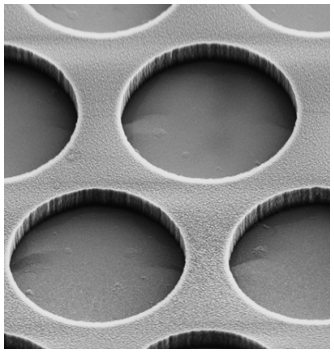


Solution: Non-Porous Membrane

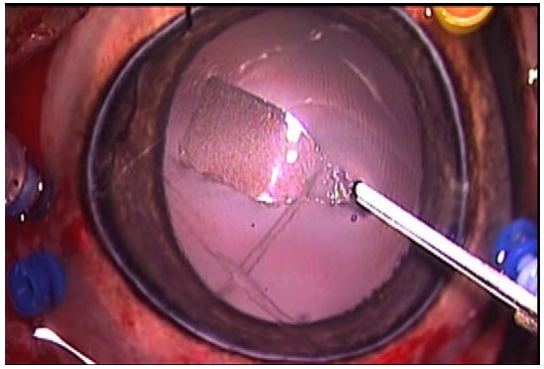


- Thick parylene mesh (6µm) provides mechanical support for surgical handling
- Ultrathin parylene membrane (0.4µm) provides diffusion of nutrients

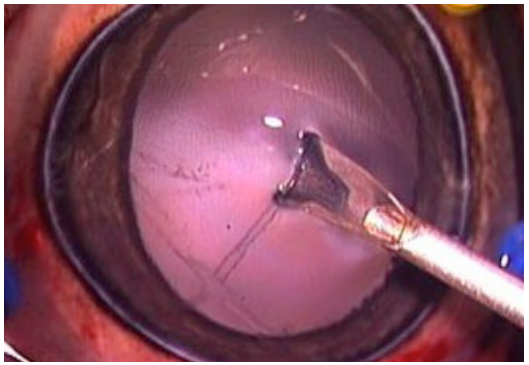


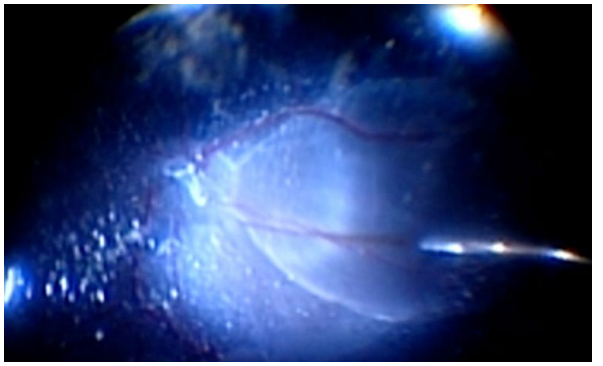


CPCB-RPE1 Implantation Procedure

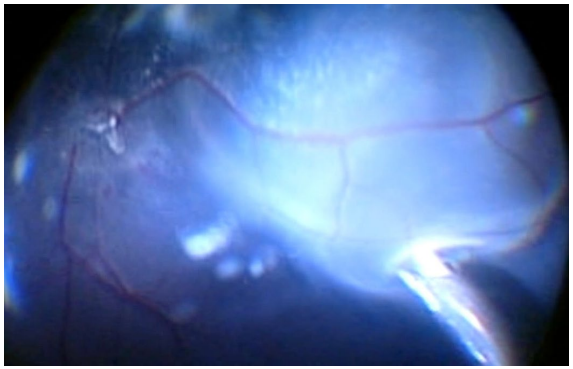


Loading of Implant

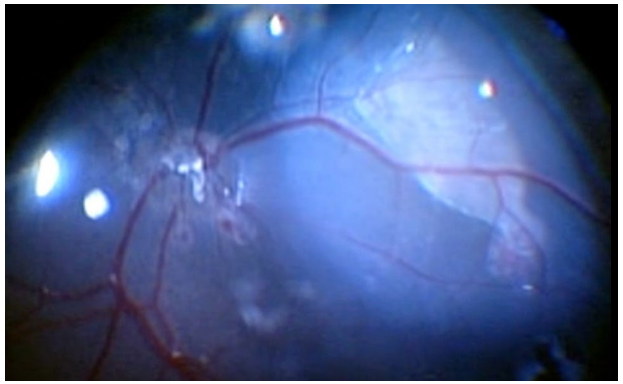




Subretinal Infusion



Subretinal implantation



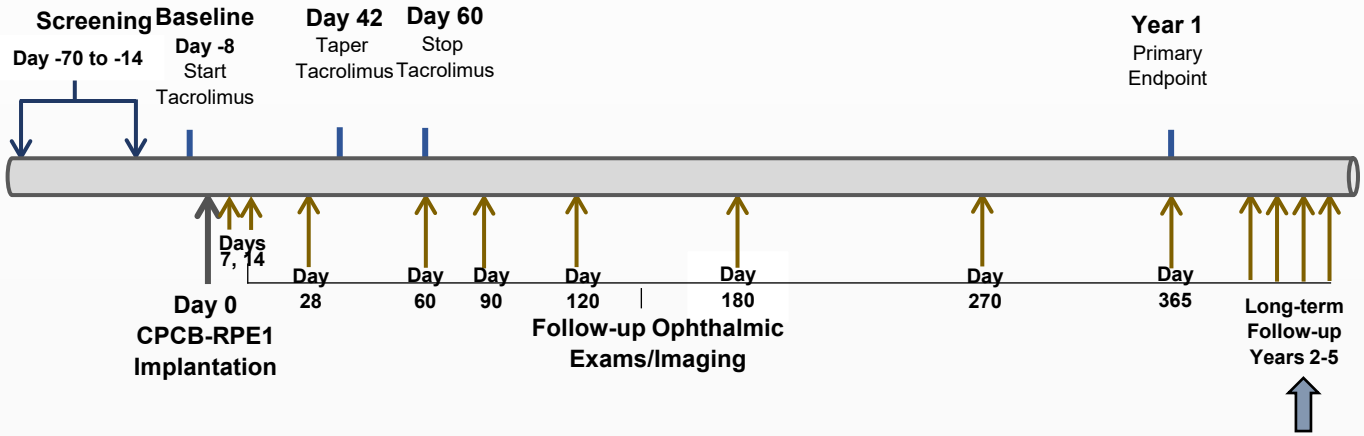
Subretinal position of Implant

First in Human Studies

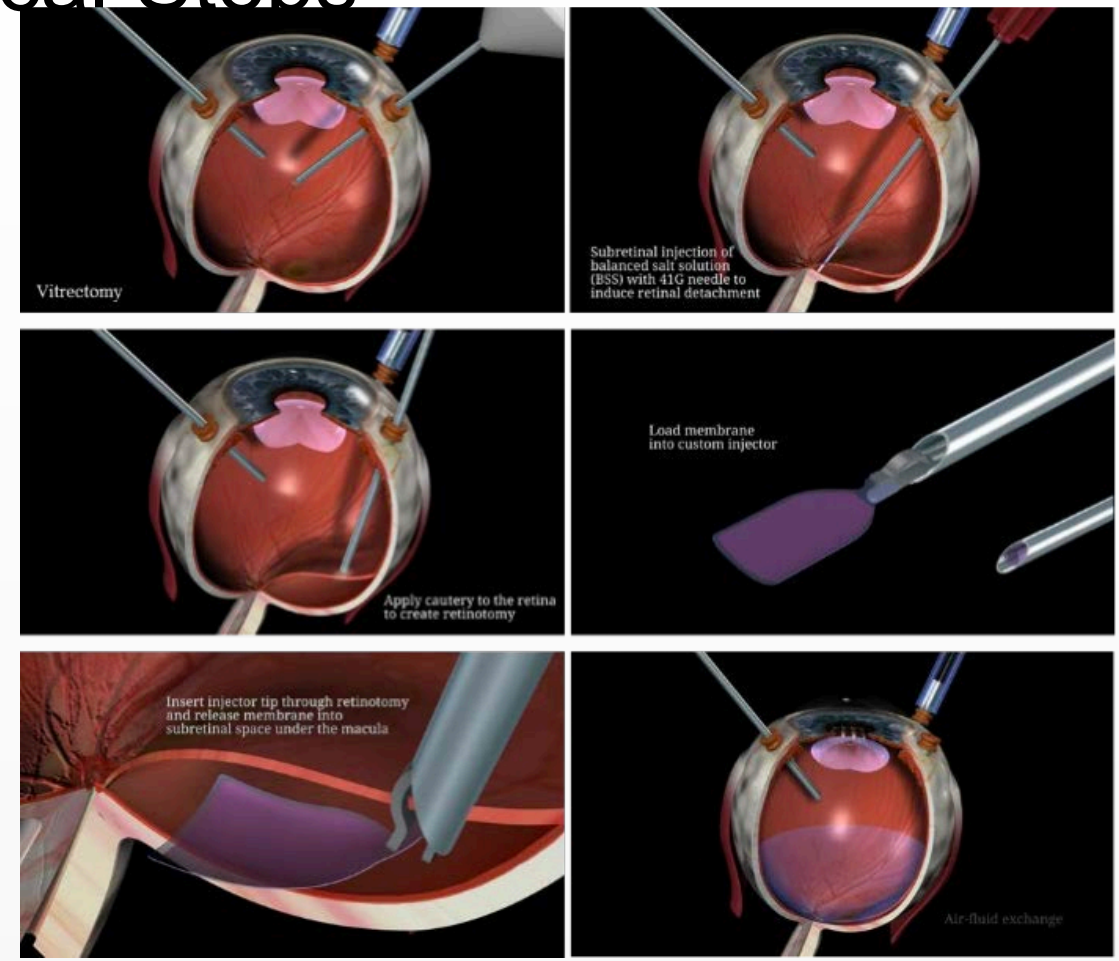
Phase 1/2a Clinical Trial Design: Summary

Study Design and Population	**Single Arm Open Label Study in Subjects with Advanced, Dry Age-related Macular Degeneration with Significant Geographic Atrophy Involving the Central Fovea**
Number of Subjects	20 (2 Cohorts of 10 Patients Each) Male or Female Subjects from 55 to 85 Years of Age
CPCB-RPE1 Implant Delivery	Pars Plana Vitrectomy with Implant to Subretinal Space
Dose	One Implant
Primary Endpoint	Test the Safety and Tolerability of CPCB-RPE1 at 1 Year Post Implantation
Secondary Endpoint	Assess Visual Acuity, Visual Field and Retinal Function After CPCB-RPE1 Administration
Exploratory Endpoints	Change in Area of Geographic Atrophy, Contrast Sensitivity
Subject Follow-up	Ophthalmic Exams up to 5 Years; Long-term Follow-up for Additional 10 Years
Major Inclusion Criteria	Geographic Atrophy, 1St Cohort Visual Acuity ≤20/200; 2nd Cohort 20/80 to >20/400
Major Exclusion Criteria	No Other Retinal Disease but Dry AMD; No History of Retinal Detachment; No History of Glaucoma or Diabetes Mellitus / Diabetic Retinopathy (except mild)

RPT-14-01: Clinical Study Scheme

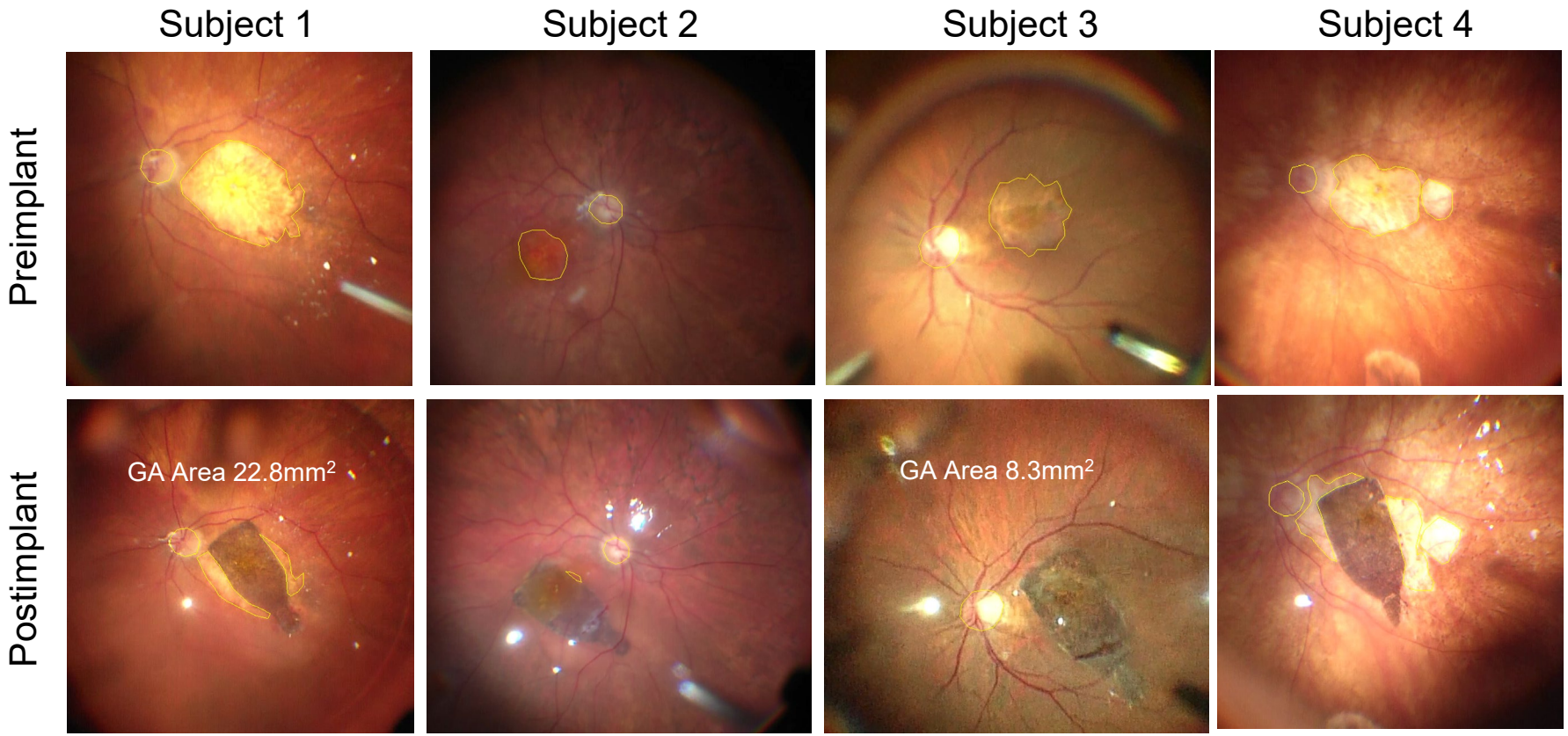


Surgical Steps



Published in Ophthalmology, Volume 127, Issue 4, April 2020, Pages 436-441

Intraoperative Surgical Placement

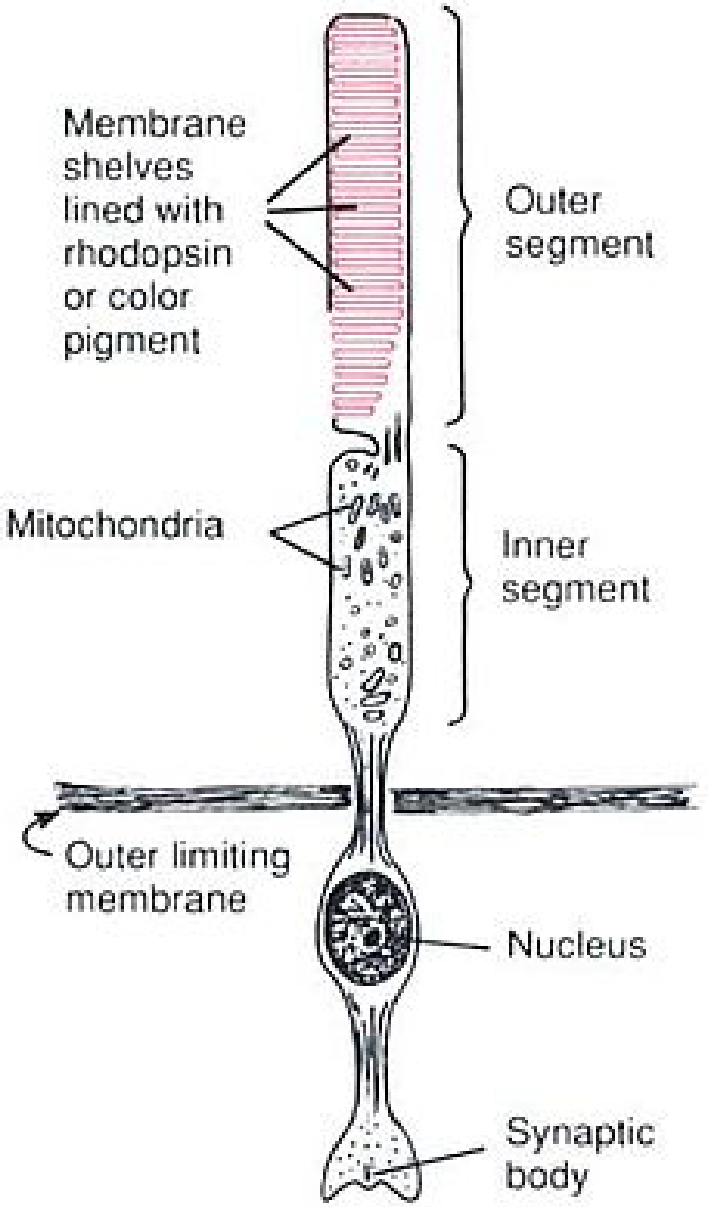


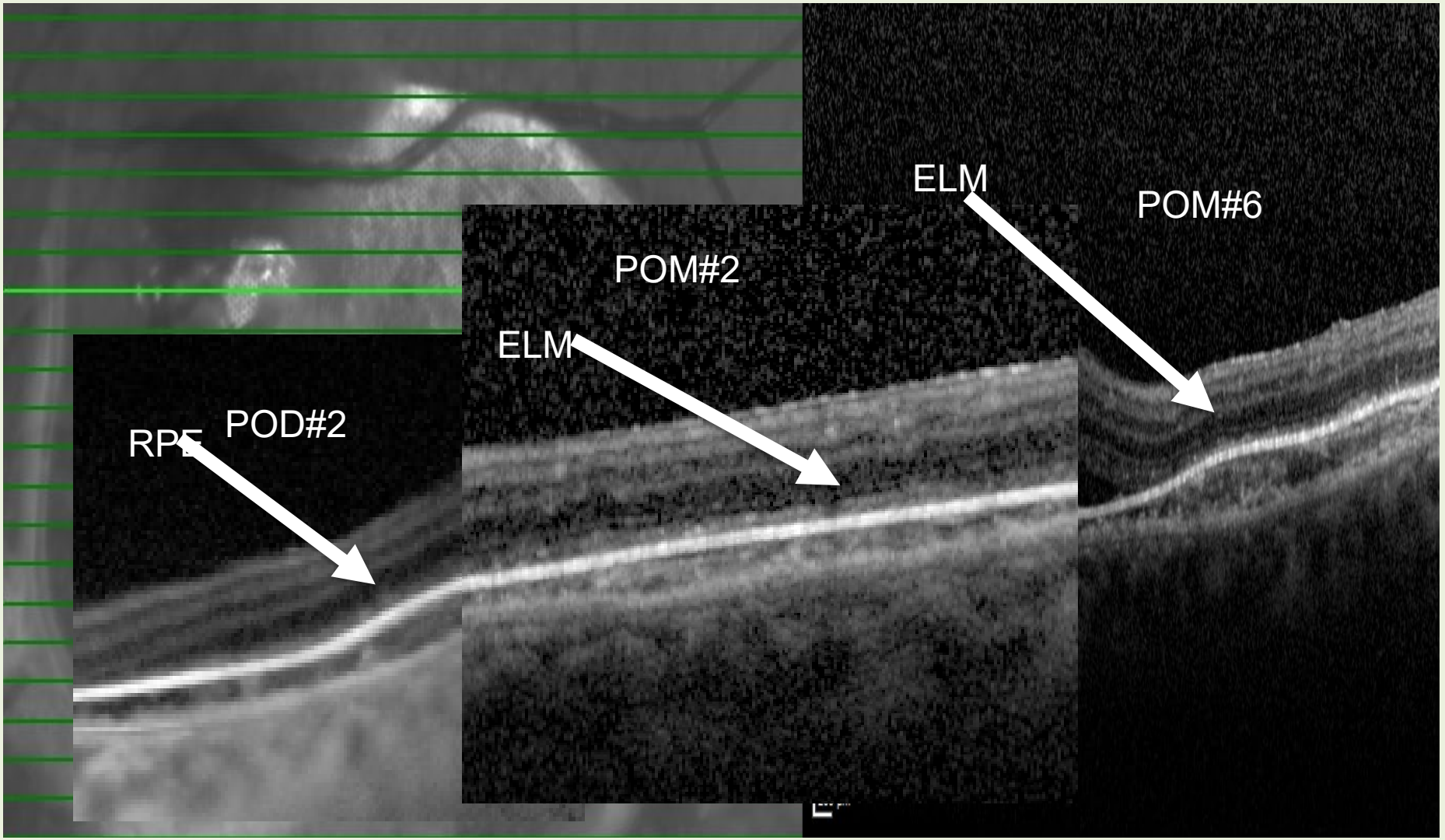
Median GA Size = 13.8 mm^2;

Median coverage by Implant = 87% ; ~ 22mm^2

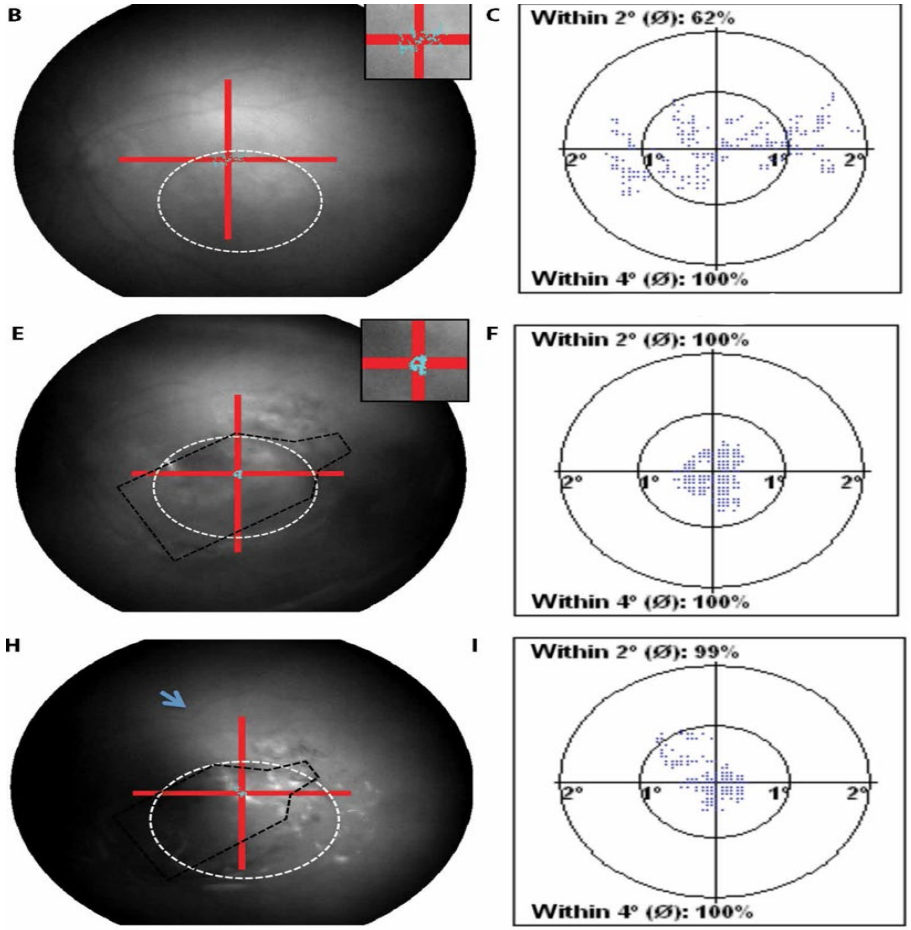
Published in *Ophthalmol Retina*. 2020; 4(3): 264–273

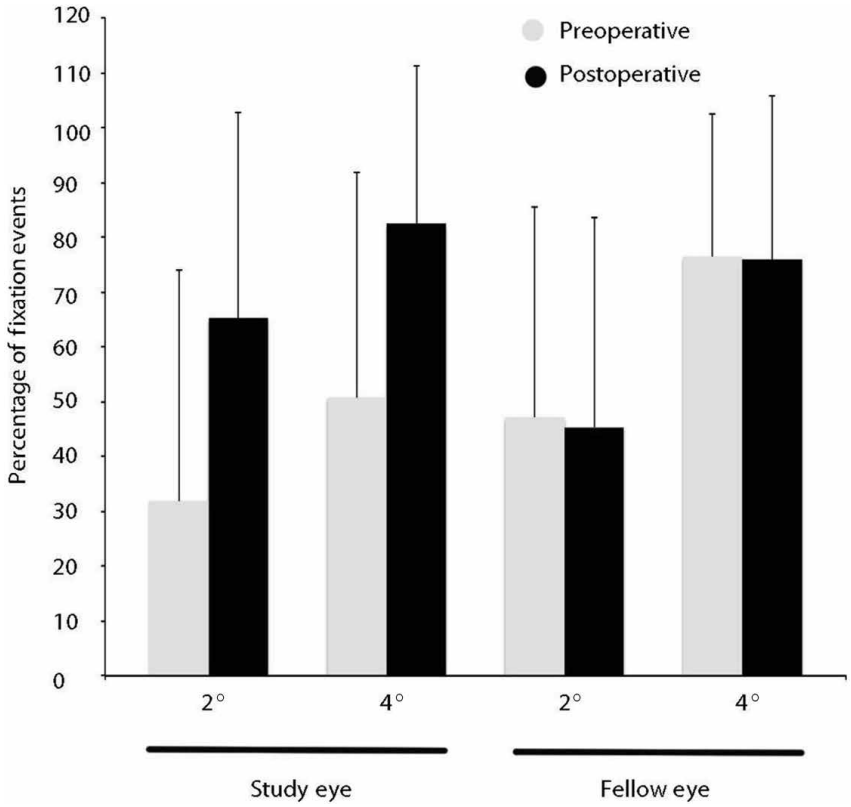
Dormant Photoreceptors




ELM
POM#6
POM#2
ELM
POD#2

Improved Fixation

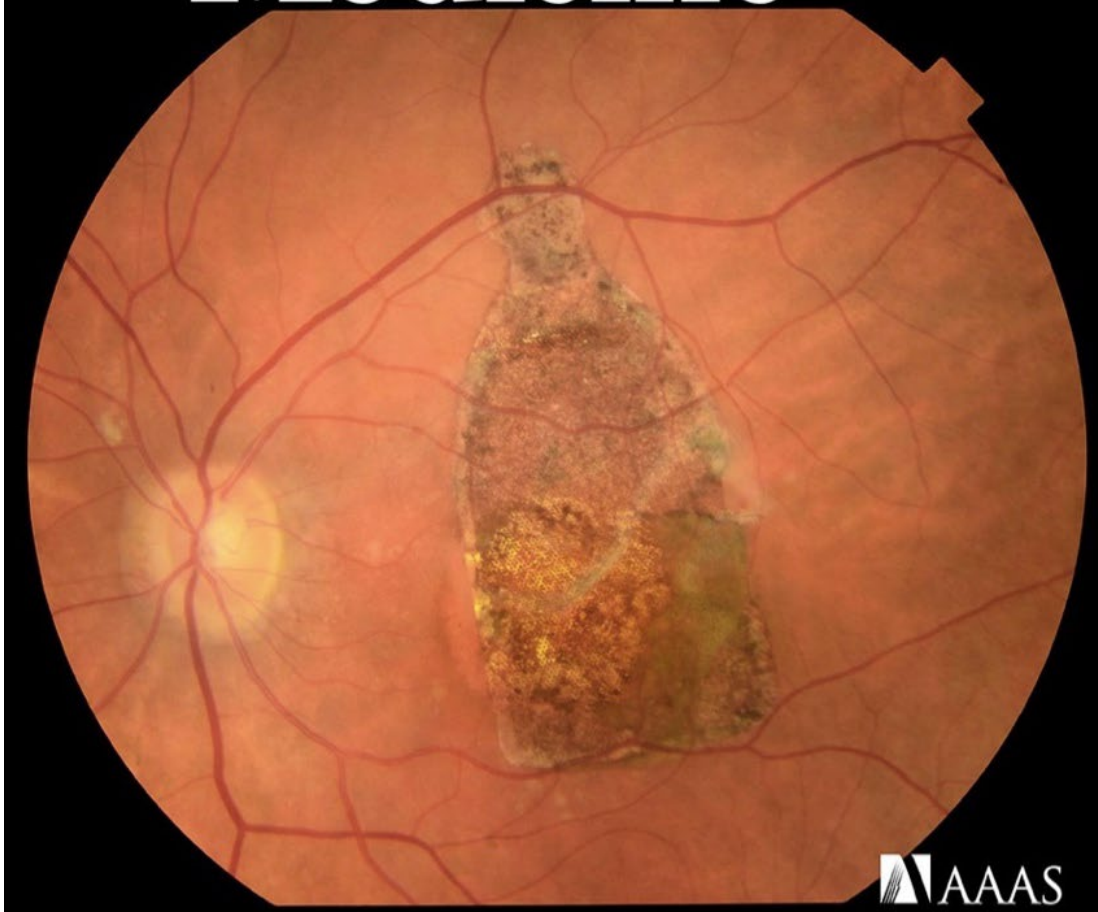




Use deep learning algorithms that are predicative of better outcomes

4 APRIL 2018

Science Translational Medicine

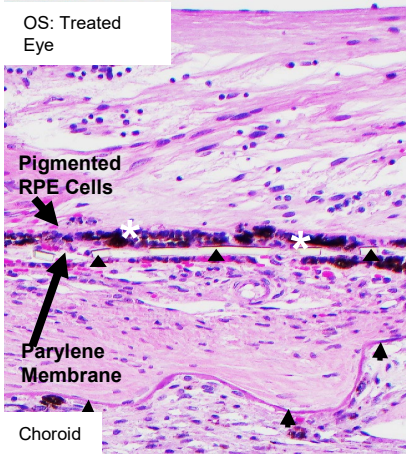


AAAS

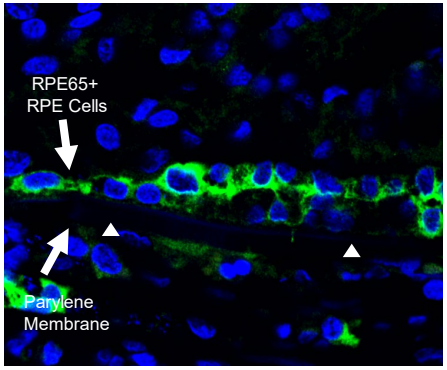
No Immune Rejection

The Transplanted RPE Cells are Polarized, Express Visual Function Proteins with Evidence of Phagocytic Activity

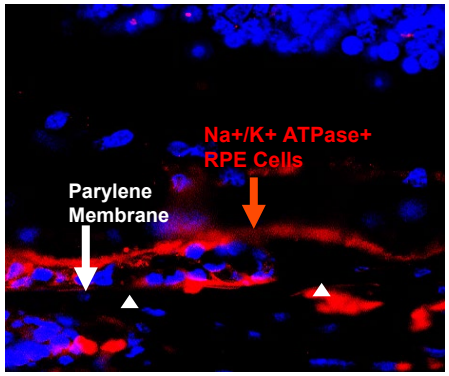
Histological sections through the implant at >2 Years post-administration in deceased subject 125



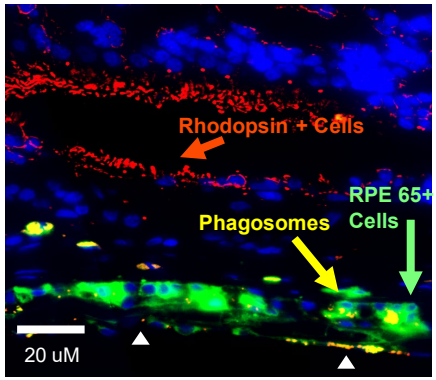
- Pigmented **RPE Cells Survive** on the Parylene Membrane at Least 2 Years



- Implanted RPE Cells **Express RPE65,** a Visual Function Protein



- Implanted RPE Cells Have Apical Expression of Na+/K+ATPase, Suggesting **Polarized Mature Function**.



- Spared Rhodopsin + Rosettes Over Implant
- **Presence of Phagosomes** Suggests Functional Integration of Implant RPE Cells

14/16 mismatched alleles; only 1 subject developed “weak antibody response Mean fluorescence intensity between 1000-3000 ; 97- 99 HLA Class I and II

Published in Stem Cell Reports, Vol 17, pp 448-458, March 2022

Substantial and Sustained Improvement of Vision

Changes in BCVA as of Latest Follow-up (mean 34, median 36, range 12-48 mos)

27% (4/15) Subjects Improved 7-15 Letters in treated eyes

% Subjects With	Treated Eye % (n/15 Implanted Subjects)	Untreated Eye % (n/15 Implanted Subjects)
% Subjects with **Improved** BCVA (>5 Letter Gain)	27% (4/15)	0% (0/15)
% Subjects with **Improved** (>5 Letter Gain) or Stable BCVA (+/- 5 Letters from Baseline)	60% (9/15)	20% (3/15)
% Subjects with **Worse** BCVA (>5 Letter Loss)	40% (6/15)	80% (12/15)

80 % (12/15) Subjects Lost 8-21 Letters In untreated eyes

Published in TVST – Special Issue Vol 10, No 10, 2021

One-Year Follow-Up in a Phase 1/2a Clinical Trial of an Allogeneic RPE Cell Bioengineered Implant for Advanced Dry Age-Related Macular Degeneration

Summary

Summary

- Pluripotent stem cells (hESC, and iPSC) are in early clinical trials to address the unmet medical need of blindness

- CPCB (our) Team performed the **largest Phase 1 clinical trial** of stem cell implant to date showing unprecedented improvement in vision in patients with AMD

- Retina and Eye an ideal location for development of cell-based therapies
  - Relatively immune privileged (potentially requiring local immune suppression)
  - Easy surgical access
  - Allows structural and functional testing using optical instruments
  - Relatively small number of cells required

- **Starting Phase 2B trial across US with stem cell implant to restore vision in macular degeneration patients**

Stem Cell Team

USC/UCSB Team

Mark Humayun, USC
Dennis Clegg, UCSB
Biju Thomas, USC
Sunny Lee, USC
Dimitri Pollalis, USC
Debbie Mitra, USC

Clinical Investigators

Amir Kashani
Firas Rahhal
Robert Avery
Sanford Chen
Clement Chan
Neal Palejwala

RPT Team

Jane Lebkowski
Britney Pennington
Linc Johnson
Mohamed Faynus
Vignesh Nadar
April Ingram
Jeff Bailey

Leap Biomedical

Juan Gonzalez
Del White

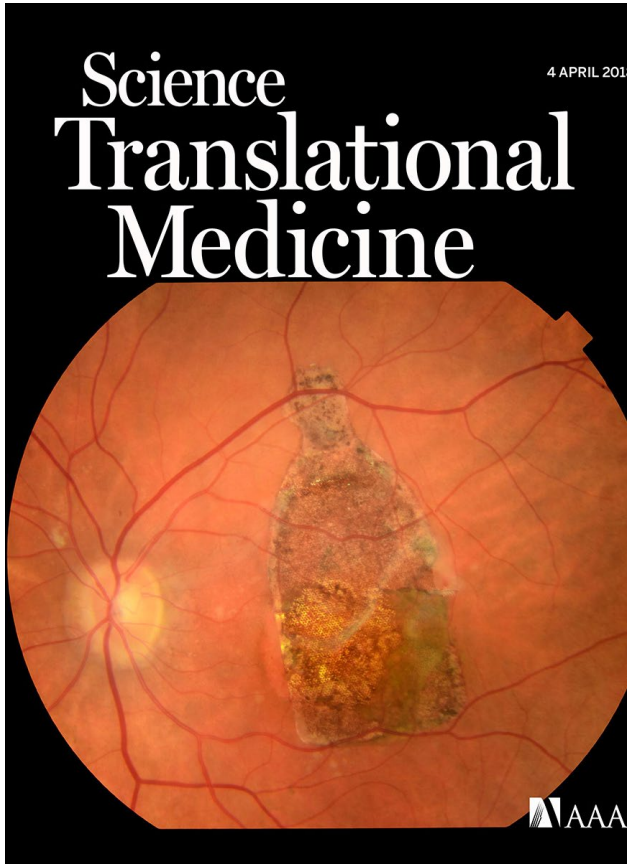
DMC
Medical Monitor
Sigi Caron

City of Hope

Joseph Gold
David Hsu
Yasmine Shad
Stephen Lin
Wei Dang
Larry Couture

CIRM
CALIFORNIA'S STEM CELL AGENCY

Santen



CHDI
Accelerating therapeutic development for Huntington's disease

USC University of Southern California

SC CTSI Symposium: Innovations in Regenerative Medicine Products

Target Identification for Gene Therapy

Robert E. Pacifici, Ph.D.

Chief Scientific Officer

CHDI Foundation, Inc/ CHDI Management, Inc.

USC Health Science Campus, in the Center for Health Professions

October 20th, 2023 2:45 pm to 4:30 pm

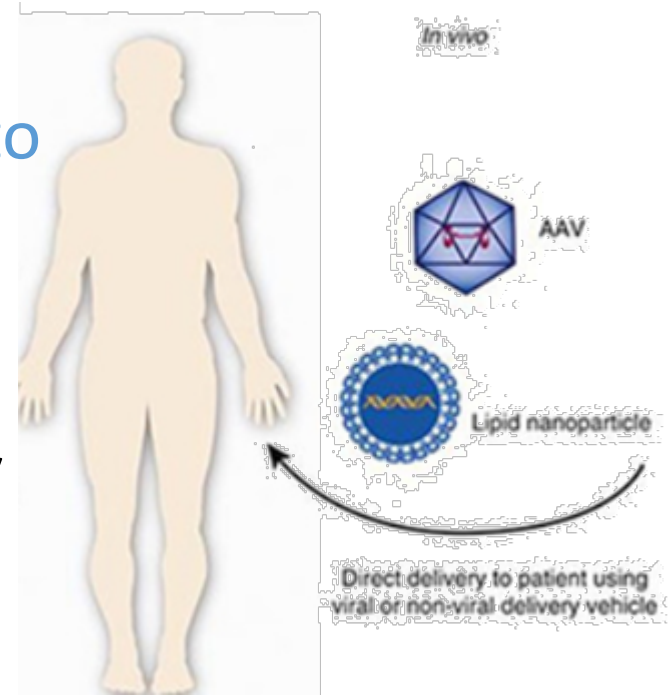
Outline for this Presentation

- **Gene Therapy**: A promising new therapeutic modality!
- **Schematic**: What are the necessary components?
- **Target Product Profile**: Specifications for safety and efficacy
- **Huntington's Disease**: An unmet medical need caused by a single gene
- **Illustrative Programs**: The HD gene therapy portfolio
- **Take aways**: Closing remarks and some thoughts for the future

Gene Therapy: FDA Website's Description

- Human gene therapy seeks to modify or manipulate the expression of a gene or to alter the biological properties of living cells for therapeutic use.

- Gene therapy is a technique that modifies a person's genes to treat or cure disease. Gene therapies can work by several mechanisms:
  - Replacing a disease-causing gene with a healthy copy of the gene
  - Inactivating a disease-causing gene that is not functioning properly
  - Introducing a new or modified gene into the body to help treat a disease



- Gene therapy products are being studied to treat diseases including cancer and various genetic disorders.

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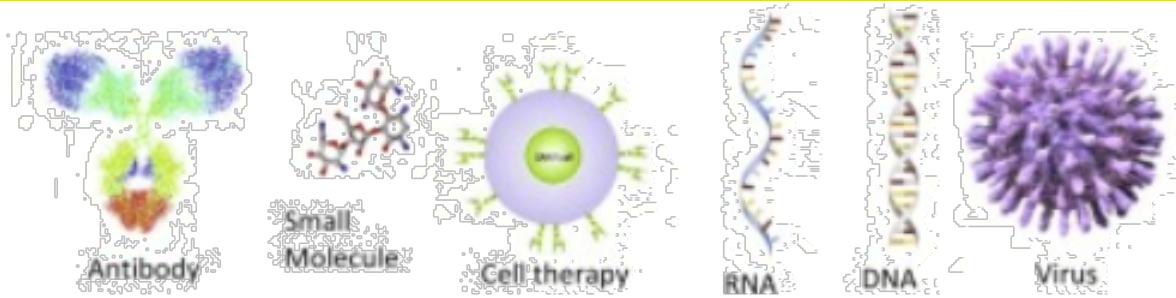
Why do we need another “therapeutic modality”?



- Each type of drug has unique pro’s & con’s
  - Small molecules
    - Low cost of goods, orally bioavailable
    - Limited target tractability, chronic administration
  - Gene Therapy
    - All genetic targets are accessible with exquisite selectivity, “one and done” dosing paradigm
    - Limited distribution, difficult and costly API, limited safety data
- It works! FDA approved therapies include:
  - Beta thalassemia gene therapy (Zynteglo®)
  - Retinal disorder gene therapy (Luxturna™)
  - Cerebral adrenoleukodystrophy gene therapy (SKYSONA®)
  - Spinal muscular atrophy gene therapy (Zolgensma®)
  - CAR T-cell therapy (KYMRIAH™) for leukemia and lymphoma

Schematic: What are the elements of a gene therapy “drug”

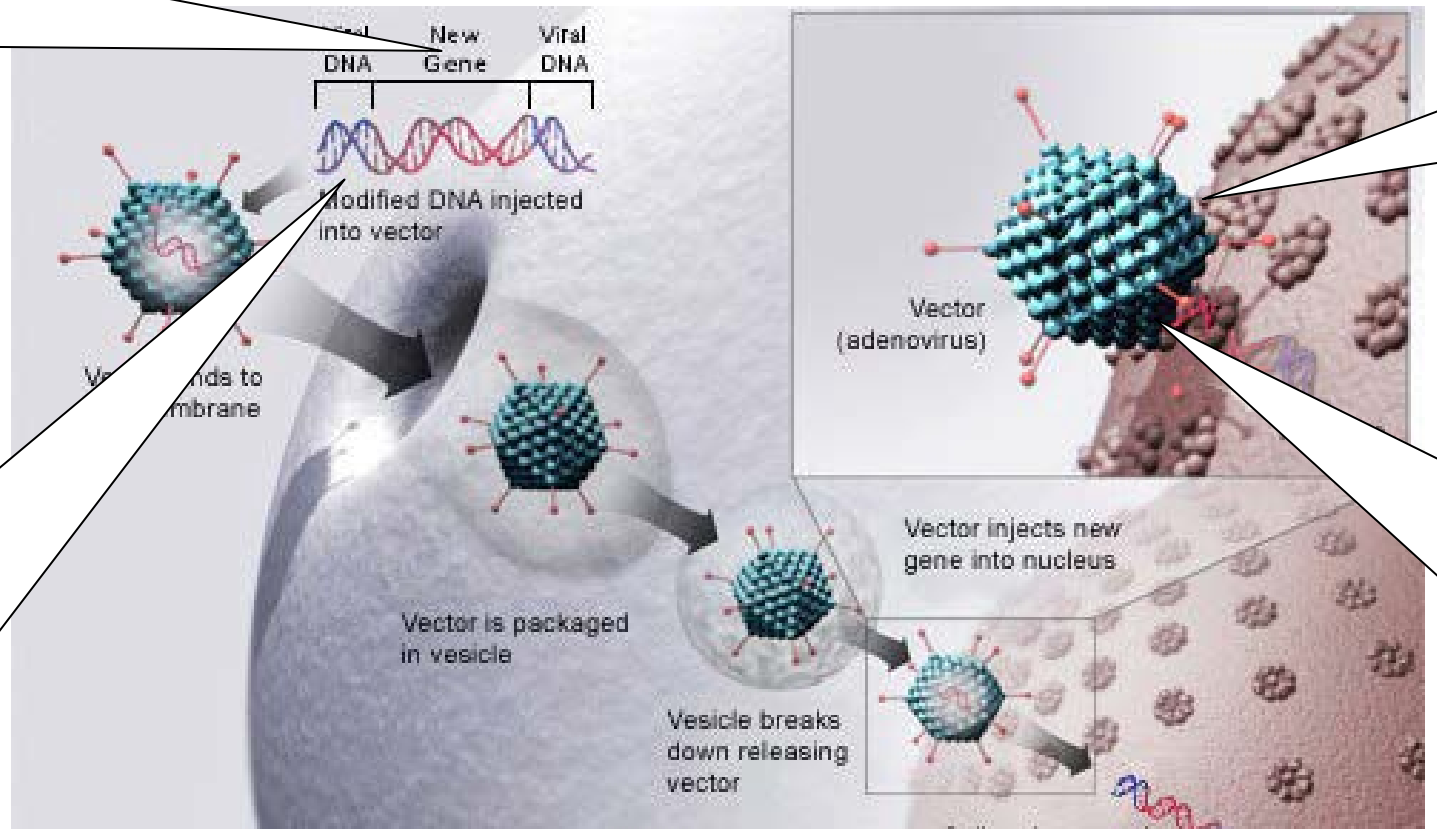
Payload

Genetic material to be delivered
DNA: cDNA,ASO
RNA: siRNA, miRNA

Flanking sequences

Promoter
Strength: how much
Type: cell specificity
Regulatable: On / Off

Viral and modifications for stability
Viral LTRs
Caps and non-natural nucleotides



Vector

Virus: AAV, Lenti
Novel: LNP, VLP
Carrier: cholesterol

Viral (sero)Type

Human safety data
Immunogenicity
Size of payload
Distribution:
Macroscopic
Cellular tropism

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Target Product Profile: Specifications for safety and efficacy

- Target Validation
  - Which gene(s) is/are associated with the disease?

- Desired Pharmacology
  - More of the gene product: enzyme replacement therapy
  - Less: Gene silencing
  - Different: Exon skipping, gene editing
- Biodistribution
  - Which organ(s)
  - What cell-type(s)
- Route of administration
  - Ex-vivo cellular treatment followed by re-implantation
  - Peripheral administration (liver “sink”)
  - Central administration: intrathecal/CSF, intraparenchymal, stereotaxic, convection enhancement, retrograde transport
- Safety: Risk benefit of “irreversible” treatment
  - When to treat prevention/too early versus reversal/too late

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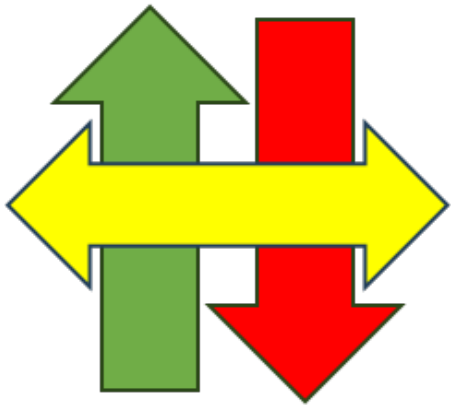

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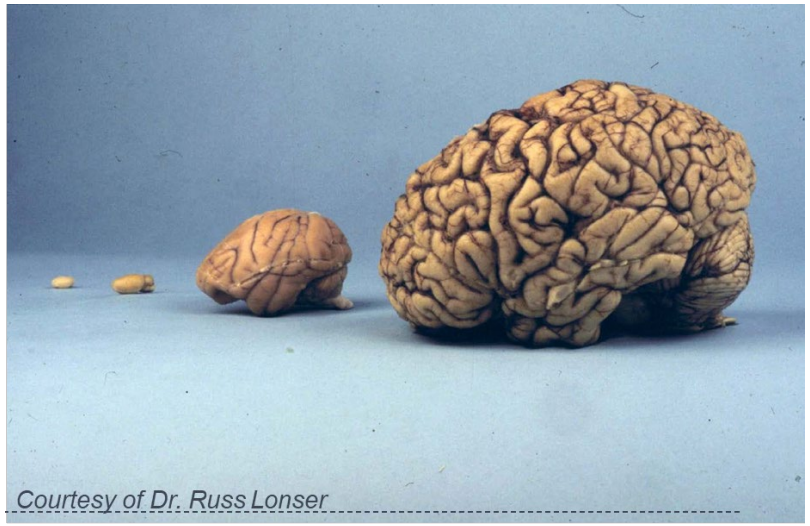

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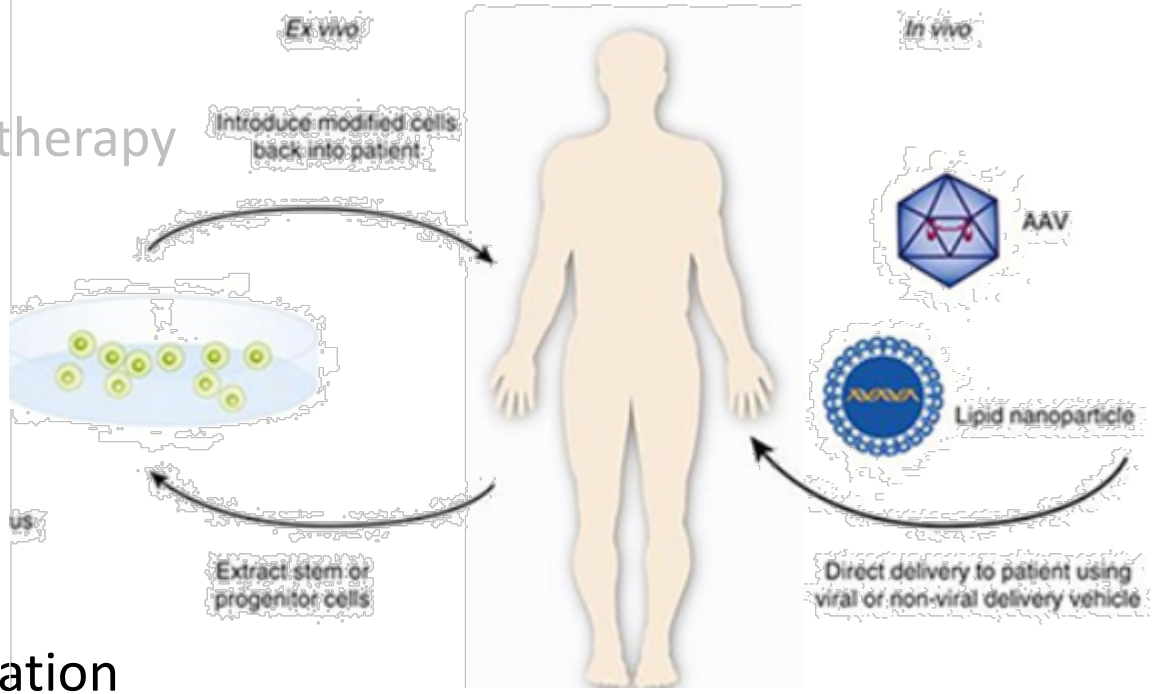

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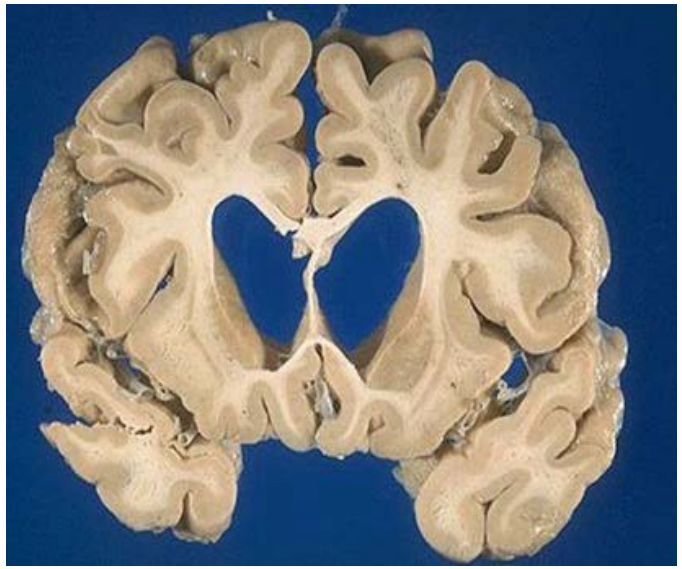

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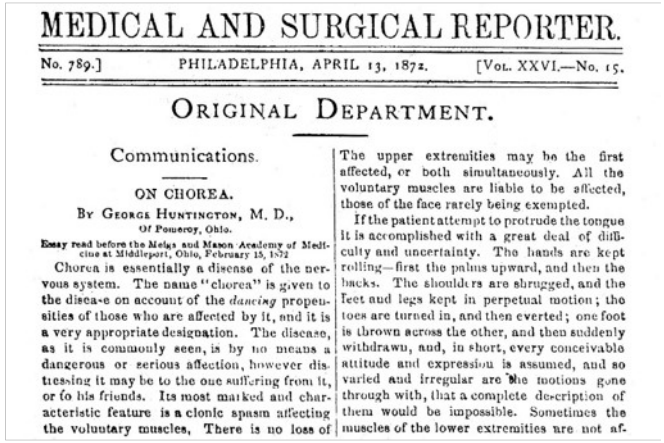
Huntington's Disease: What I work on & a good example!



MEDICAL AND SURGICAL REPORTER.

No. 789.] PHILADELPHIA, APRIL 13, 1872. [Vol. XXVI.—No. 15.

ORIGINAL DEPARTMENT.

Communications.

ON CHOREA.

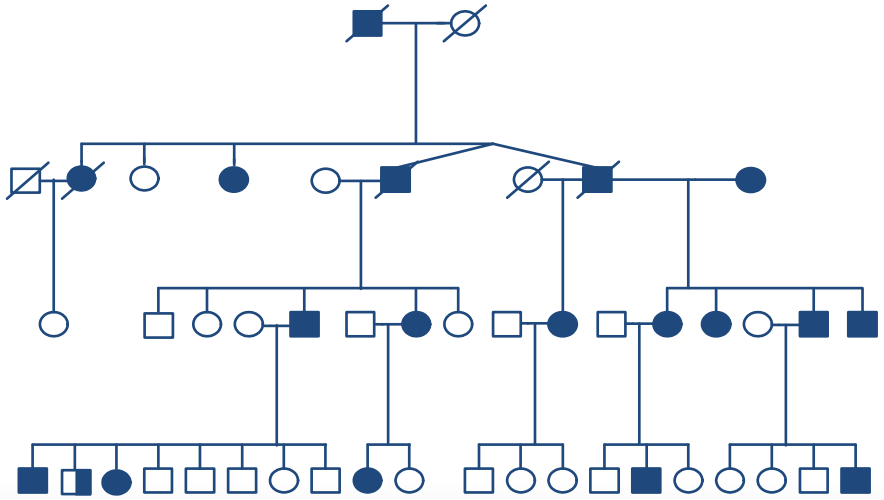
By George Huntington, M. D.,
Of Pomeroy, Ohio.

Essay read before the Meigs and Mason Academy of Medicine at Middleport, Ohio, February 15, 1872

Chorea is essentially a disease of the nervous system. The name "chorea" is given to the disease on account of the *dancing* propensities of those who are affected by it, and it is a very appropriate designation. The disease, as it is commonly seen, is by no means a dangerous or serious affection, however distressing it may be to the one suffering from it, or to his friends. Its most marked and characteristic feature is a clonic spasm affecting the voluntary muscles. There is no loss of

The upper extremities may be the first affected, or both simultaneously. All the voluntary muscles are liable to be affected, those of the face rarely being exempted.

If the patient attempt to protrude the tongue it is accomplished with a great deal of difficulty and uncertainty. The hands are kept rolling—first the palms upward, and then the backs. The shoulders are shrugged, and the feet and legs kept in perpetual motion; the toes are turned in, and then everted; one foot is thrown across the other, and then suddenly withdrawn, and, in short, every conceivable attitude and expression is assumed, and so varied and irregular are the motions gone through with, that a complete description of them would be impossible. Sometimes the muscles of the lower extremities are not af-



- George Huntington
  - Family doctor on Long Island
- Publishes his one and only paper in 1872
  - Describes the movement disorder as chorea
- HD is a hereditary disease
  - It runs in families
  - You don't "catch" it
  - You are not possessed by demons
- Autosomal dominant
  - Males and females have same chance
  - No "recessive" carriers
  - Children have a 50:50 chance

The Hunt Begins to Clone the Causal Gene

Short Arm of Chromosome 4 (4p16.3)

A polymorphic DNA marker genetically linked to Huntington's disease

James F. Gusella*, Nancy S. Wexler†‖, P. Michael Conneally†, Susan L. Naylor§, Mary Anne Anderson*, Rudolph E. Tanzi*, Paul C. Watkins*¶, Kathleen Ottina*, Margaret R. Wallace‡, Alan Y. Sakaguchi§, Anne B. Young‖, Ira Shoulson†, Ernesto Bonilla‖ & Joseph B. Martin*

*Neurology Department and Genetics Unit, Massachusetts General Hospital and Harvard Medical School, Boston, Massachusetts 02114, USA
† Hereditary Disease Foundation, 9701 Wilshire Blvd, Beverley Hills, California 90212, USA
‡ Department of Medical Genetics, Indiana University Medical Center, Indianapolis, Indiana 46223, USA
§ Department of Human Genetics, Roswell Park Memorial Institute, Buffalo, New York 14263, USA
‖ Venezuela Collaborative Huntington's Disease Project*

- Monogenic with 100% penetrance
  - Everyone that has the "bad" gene will get HD
  - Everyone that gets HD has the "bad" gene
- Relatively rare disease (1:10,000)
  - Meets with orphan designation
  - Familial link allows ID of concentrated cohorts
  - Second disease gene to be positionally cloned
- Linkage analysis finds the marker in 1983
- Full gene sequence in 1993

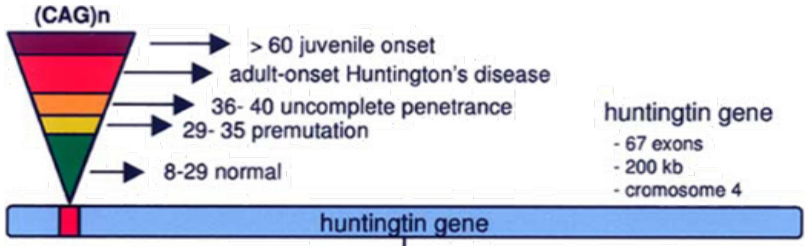
Cell Vol. 72, 971–983, March 26, 1993, Copyright © 1993 by Cell Press

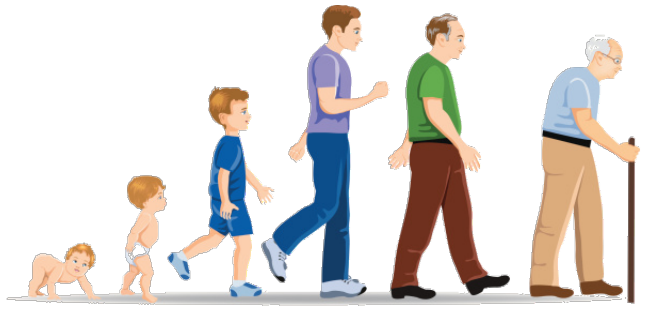
A Novel Gene Containing a Trinucleotide Repeat That Is Expanded and Unstable on Huntington's Disease Chromosomes

The Huntington's Disease Collaborative Research Group*

Big deal, you know the gene…so what?

- Huntington's disease isn't caused by a point mutation
  - Polymorphic expansion of $(CAG)_n$
  - Trinucleotide repeat or poly glutamine disorder
  - (Still) unknown function
  - Probably gain of tox versus loss of function
    - Heterozygotes (Dx and KO), Homozygotes
- Enables genetic testing (diagnostic)
  - Predict who is going to get it
  - Estimate age of onset





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  - Predict who is going to get it
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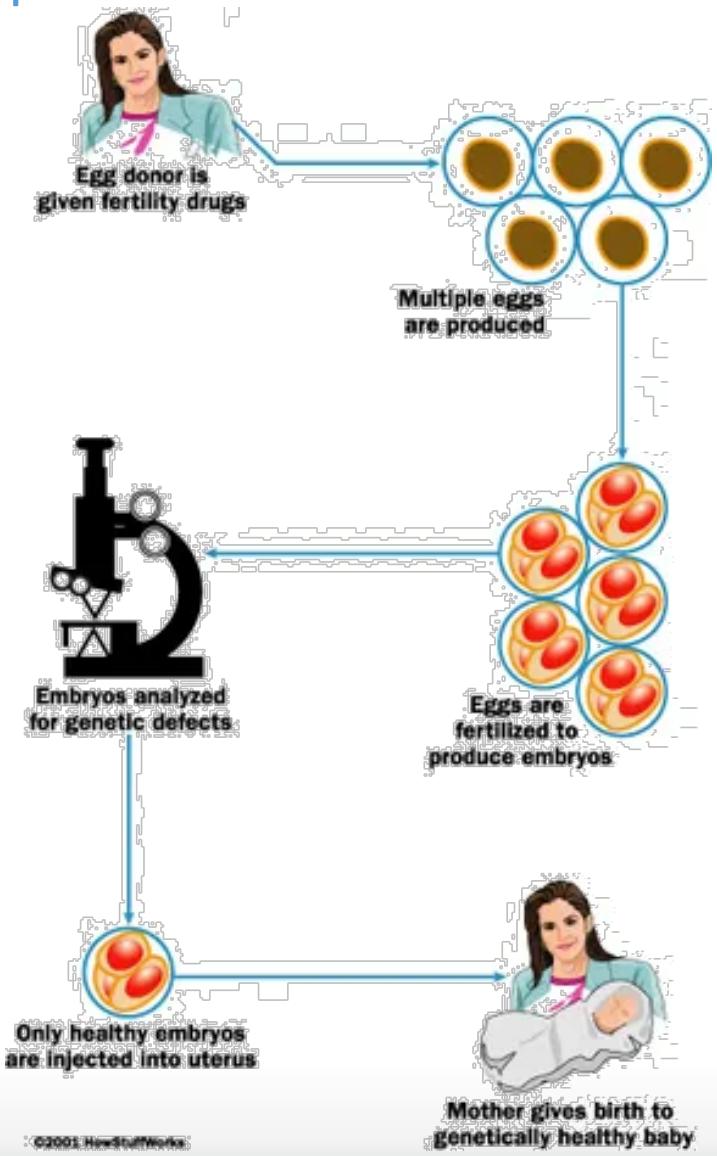
- You can do family planning
  - Do I want to take a 50% risk?
  - Pre-Implantation Genetic Diagnosis



SC CTSI

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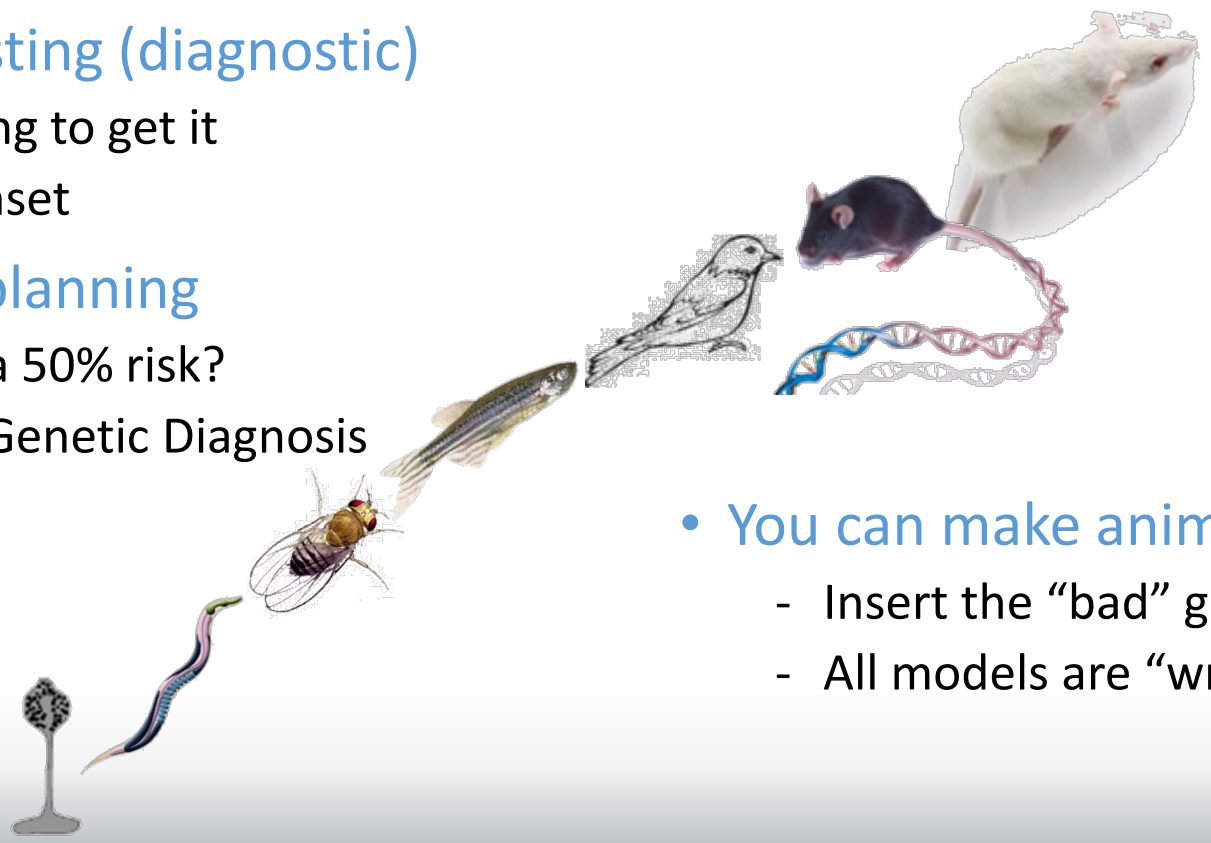

- You can make animal models of HD
  - Insert the "bad" gene
  - All models are "wrong", some are "useful"

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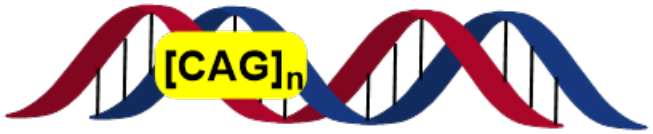
Directly enable discovery of HTT lowering drugs



- *AAV-ZFP*
- *CRISPR-Cas9*
- *Small molecule transcription blocker*

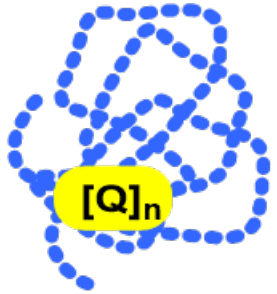
Transcription

- *AAV-miRNA*
- *ASO*
- *siRNAs*
- *Small molecule translation blocker*

IONIS PHARMACEUTICALS

UC San Diego

Translation



- *Degradation enhancers*

Aggregation

Neuron

Article

Cell PRESS

Sustained Therapeutic Reversal of Huntington's Disease by Transient Repression of Huntingtin Synthesis

Holly B. Kordasiewicz,[1] Lisa M. Stanek,[2] Edward V. Wancewicz,[3] Curt Mazur,[3] Melissa M. McAlonis,[1] Kimberly A. Pytel,[1] Jonathan W. Artates,[1] Andreas Weiss,[4] Seng H. Cheng,[2] Lamya S. Shihabuddin,[2] Gene Hung,[3] C. Frank Bennett,[3] and Don W. Cleveland[1,*]

[1]Ludwig Institute for Cancer Research and Department of Cellular and Molecular Medicine, University of California at San Diego, 9500 Gilman Drive, La Jolla, CA 92093, USA

[2]Genzyme Corporation, 49 New York Avenue, Framingham, MA 01760, USA

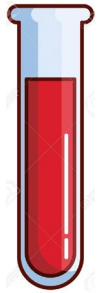
[3]Isis Pharmaceuticals, 2588 Gazelle Court, Carlsbad, CA 92010, USA

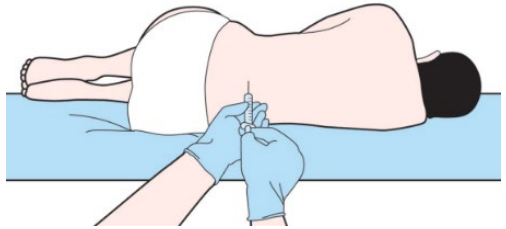
[4]Novartis Institutes for BioMedical Research, CH-4002 Basel, Switzerland

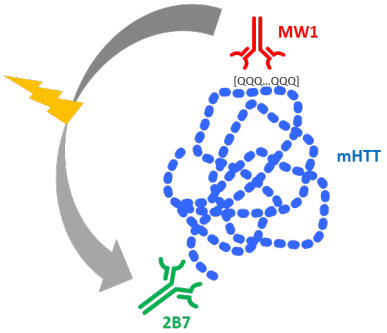
*Correspondence: dcleveland@ucsd.edu

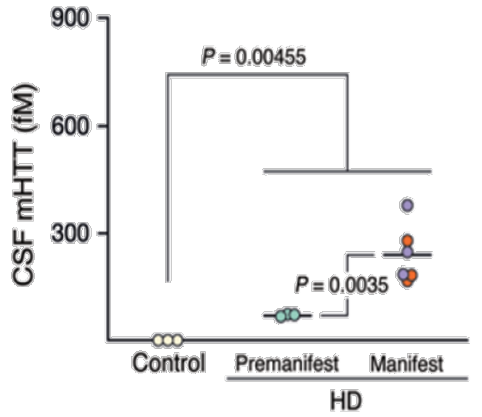
DOI 10.1016/j.neuron.2012.05.009

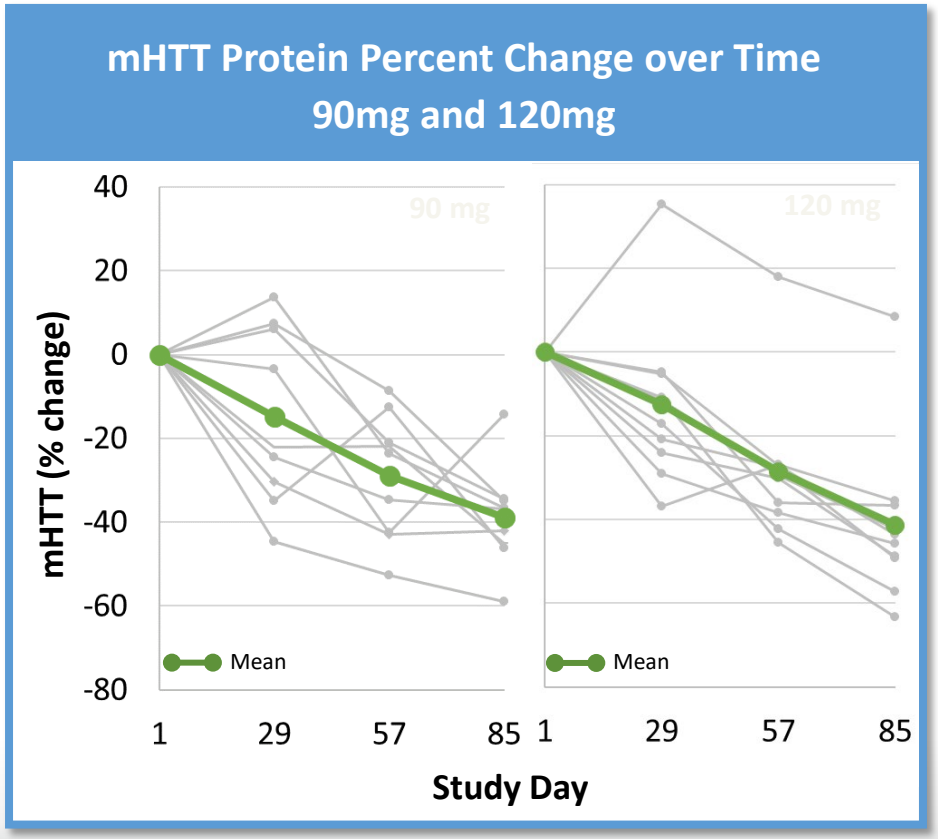
Development of pharmacodynamic biomarkers











From 2018 HDSA Annual Convention

Genentech
A Member of the Roche Group

Roche

16 September 2018

Update on RG6042 (formerly known as IONIS-HTT$_{Rx}$) Huntington's disease global development programme: Two clinical studies to begin by end of 2018

WAVE™ LIFE SCIENCES

Allele specific!

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Huntington's Disease Gene Therapy Portfolio

Organization	Therapeutic Approach Category	Therapeutic MOA	Therapeutic Modality	Current Therapeutic Stage (or most recently completed)	Therapeutic Name
Affinia Therapeutics	HTT lowering	Gene therapy, AAV	Gene therapy	Preclinical	tbd
AskBio	Other	24-OH-Cholesterol, AAV-Cyp46A1	Gene therapy	Phase 2	AB-1001 (BV-101)
NeuExcell Therapeutics	Other	AAV-delivered transcription factors to convert reactive astrocytes into neurons	Gene therapy	Preclinical	NXL-002
Passage Bio	HTT lowering	Gene therapy, AAV	Gene therapy	Preclinical	tbd
SOLA BioSciences	HTT lowering	Chaperone-based mHTT targeted gene therapy, AAV (JUMP70 cassette)	Gene therapy	Preclinical	SOL-175
Spark (Roche acquisition)	HTT lowering	HTT lowering, AAV-miRNA	Gene therapy	Preclinical	tbd
Takeda (Shire/Sangamo acquisition)	HTT lowering	HTT lowering, AAV-ZFP	Gene therapy	Preclinical	TAK-686
uniQure BV	HTT lowering	Gene therapy, AAV-miRNA	Gene therapy	Phase 2	AMT-130
VectorY Therapeutics	HTT lowering	HTT lowering, AAV-mAb	Gene therapy	Preclinical	tbd
Voyager Therapeutics	HTT lowering	mHTT and MSH3 KD, AAV-miRNA	Gene therapy	Preclinical	tbd
Vybion	HTT lowering	Intrabody	Gene therapy	Preclinical	INT41

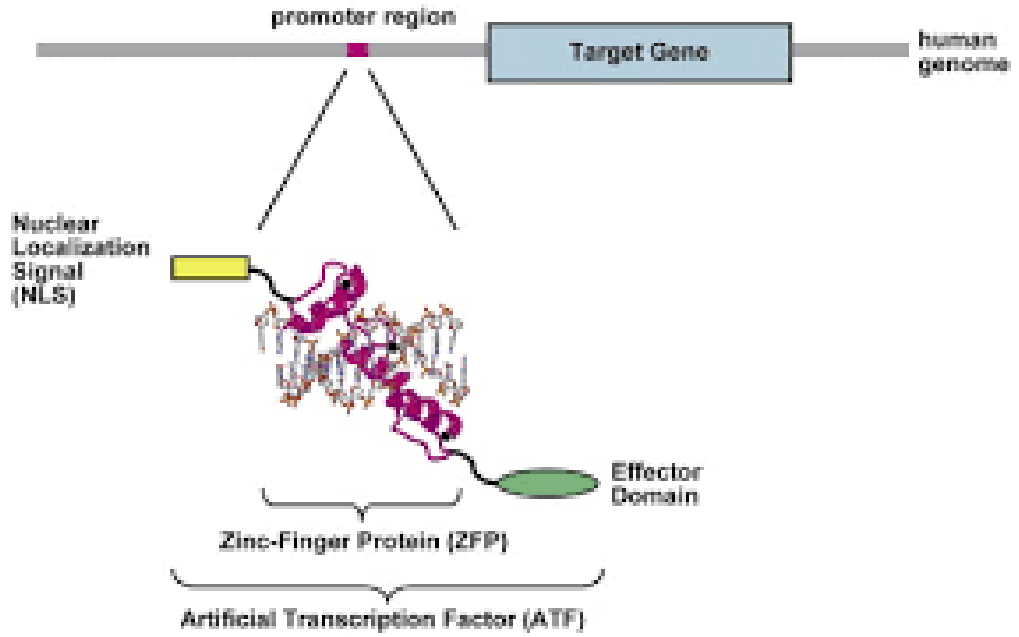
Takeda

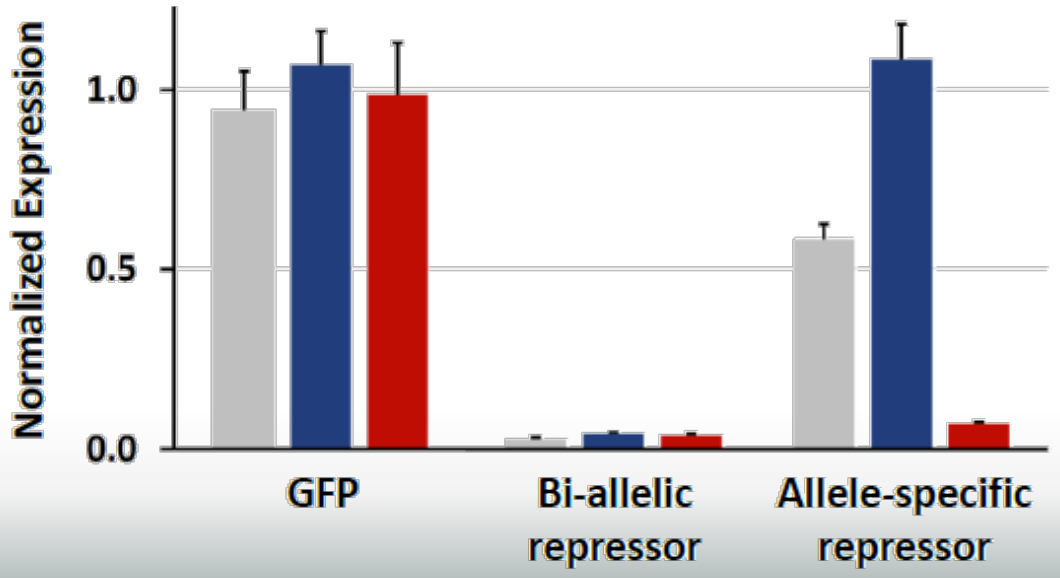
uniQure

voyager THERAPEUTICS

Illustrative Example 1: Takeda's TAK-686

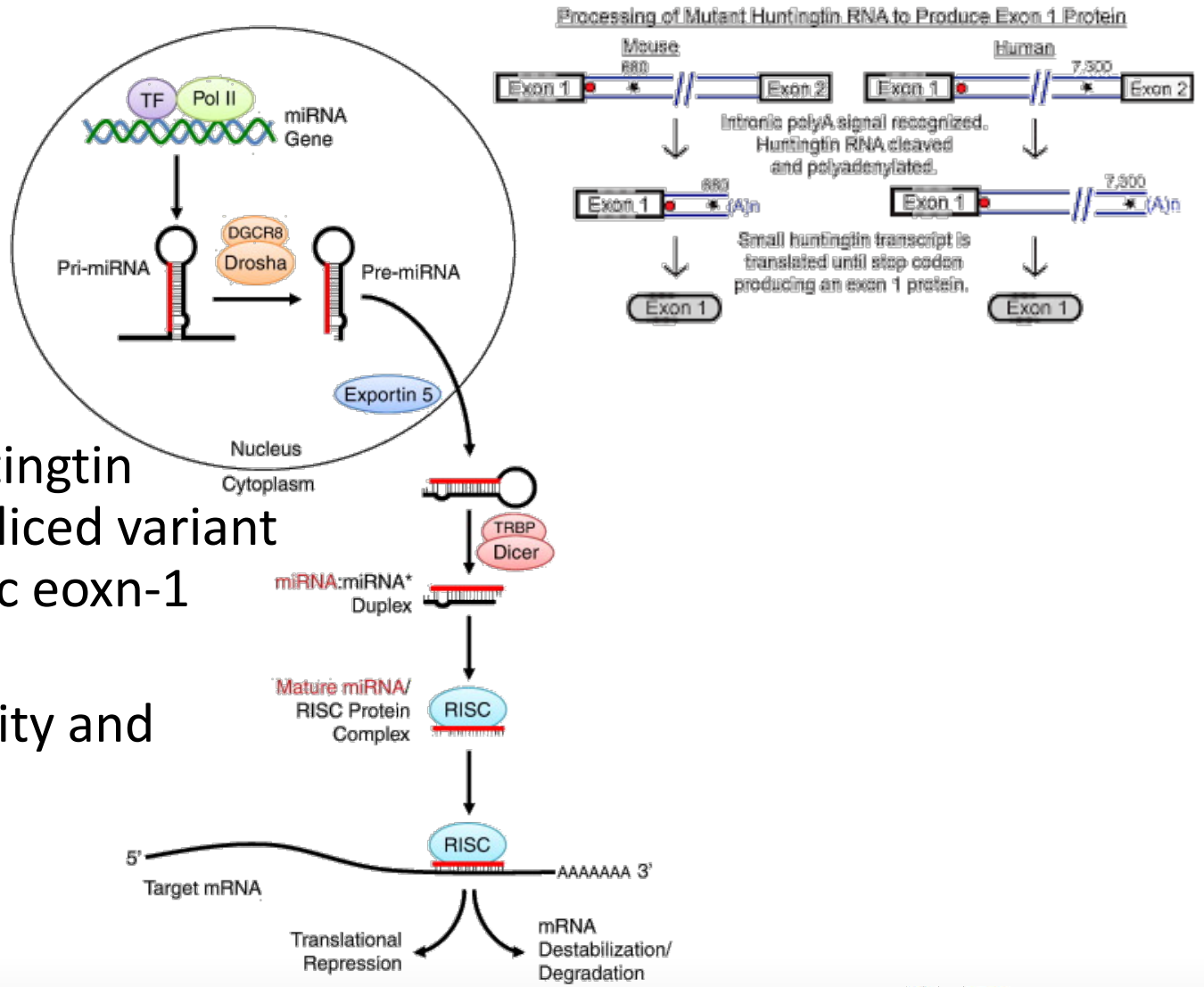
- Vector: Adeno Associated Virus
- Target: mutant Huntingtin
- Payload: Zinc finger repressor
- Stage: Preclinical
- What's cool:
  - Non-natural engineered chimeric zinc finger protein
  - Selectively binds to the mutant gene and uses a KRAB repressor to lower only mutant huntingtin protein
  - Most proximal target in "central dogma"





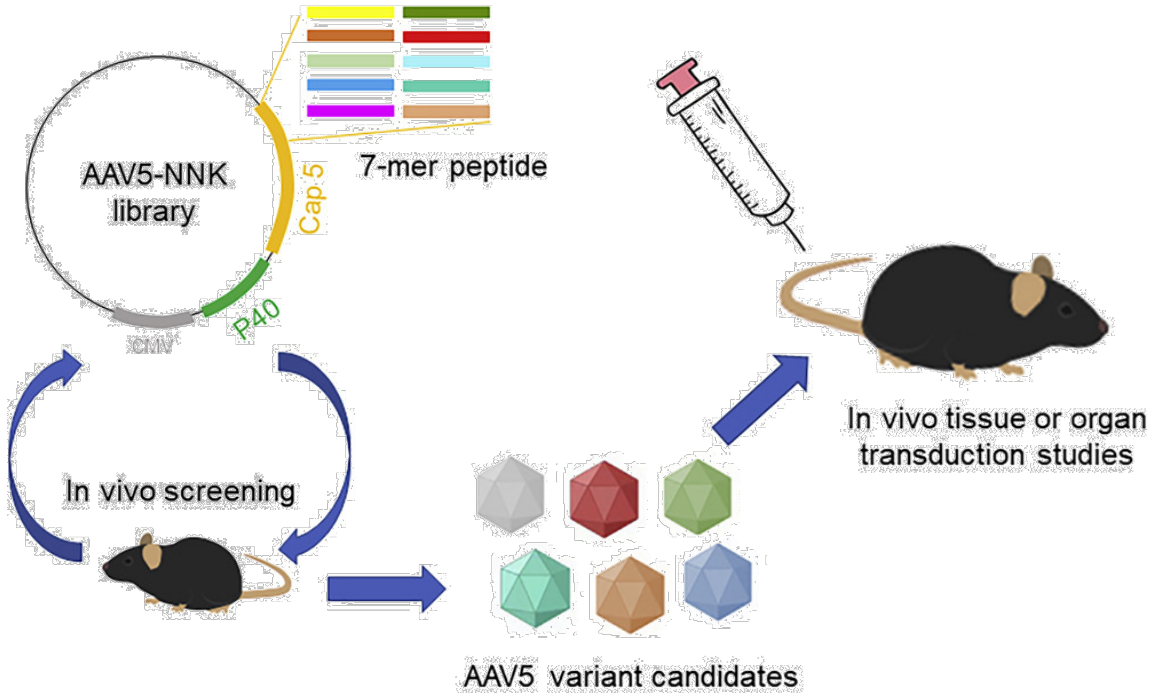
Illustrative Example 2: uniQure's AMT-130

- Vector: Adeno Associated Virus - 5
- Target: Huntingtin exon-1a
- Payload: miRNA
- Stage: Phase 2
- What's cool:
  - Artificial micro-RNA that silences huntingtin expression, including an aberrantly spliced variant that produces a potentially highly toxic eoxn-1 protein fragment.
  - Demonstrated human safety/tolerability and pharmacodynamic effect



Illustrative Example 3: Voyager

- Vector: Novel AAV
- Target: mHTT & MSH3
- Payload: siRNA
- Stage: Preclinical
- What's cool:
  - Used recursive directed evolution to engineer a new viral capsid that can be administered peripherally but shows excellent central distribution.
  - Bi-cistronic construct that simultaneously targets both mHTT and another gene (MSH3) believed to play a role in regulating the rate of somatic (CAG)n expansion



voyager THERAPEUTICS

A Few Take Aways

- Despite initial difficulties gene therapy remains an important therapeutic modality
  - Including the tragic death of Jesse Gelsinger in 1999
- There are hundreds of unmet medical needs for which the genetic basis is known and are candidates for gene therapy
  - Including Huntington's disease!
- Significant advances in viral capsids promise
  - Improved safety profiles
  - More facile routes of delivery
  - Precise special and temporal targeting
- Large (and evolving) array of payloads
  - Expression, silencing, editing
- Several challenges remain to be tackled
  - "GMP" manufacturing of API
  - Durability

Thank You!

Robert Pacifici
+1.310.342.5507
robert.pacifici@chdifoundation.org

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Thank You!

SC CTSI | www.sc-ctsi.org Phone: (323) 442-4032 Email: info@sc-ctsi.org Twitter: @SoCalCTSI

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USC Mann
Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences
Department of Regulatory and Quality Sciences

USC Mann
Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences
DK Kim International Center for Regulatory Science

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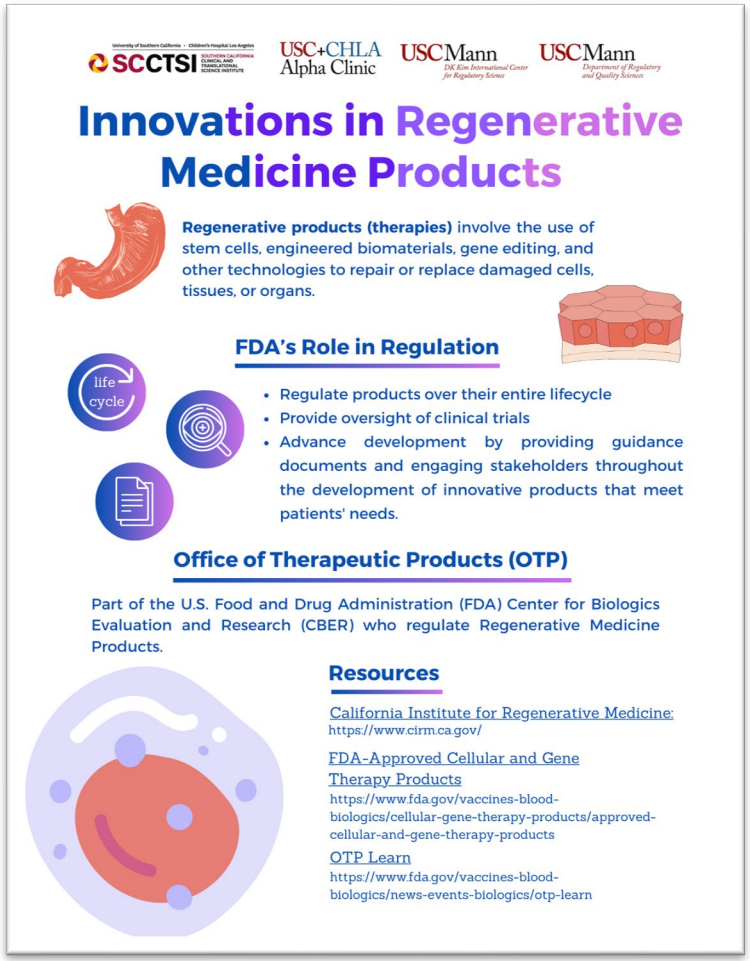
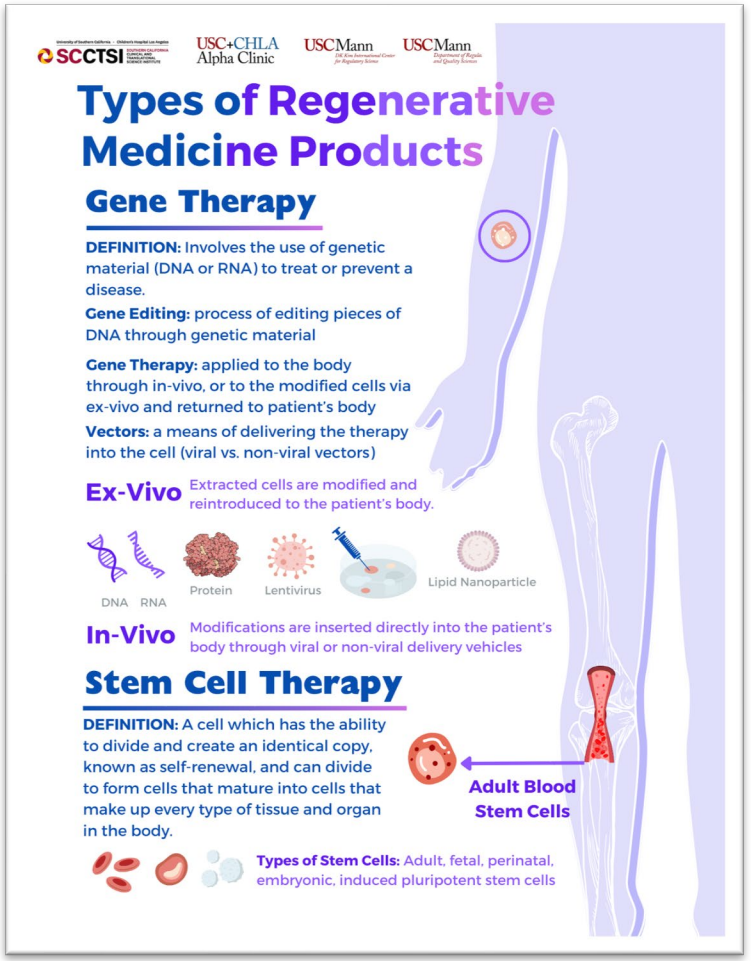
Regulatory Science Symposium: Innovations in Regenerative Medicine Products

Eunjoo Pacifici, PharmD, PhD
Chair and Associate Professor, Regulatory and Quality Sciences
Associate Director, DK Kim International Center for Regulatory Science

October 20, 2023

Symposium Resource





Before the end of today's symposium, you will receive a link to take the program evaluation.

Please complete the program evaluation to receive an electronic certificate of completion by **Friday, November 3**.

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www.sc-ctsi.org
Phone: (323) 442-4032
Email: info@sc-ctsi.org
Instagram: @socalctsi
Twitter: @SoCalCTSI

USC Mann
Alfred E. Mann School of Pharmacy and Pharmaceutical Sciences
Department of Regulatory and Quality Sciences

regulatory.usc.edu
Phone: (323) 442-3521
Email: regsci@usc.edu
Instagram: @epacifici_uscregsci
Facebook: @RegSci

University of Southern California · Children's Hospital Los Angeles
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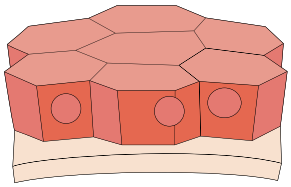
Innovations in Regenerative Medicine Products

Regenerative products (therapies) involve the use of stem cells, engineered biomaterials, gene editing, and other technologies to repair or replace damaged cells, tissues, or organs.



FDA's Role in Regulation

- Regulate products over their entire lifecycle
- Provide oversight of clinical trials
- Advance development by providing guidance documents and engaging stakeholders throughout the development of innovative products that meet patients' needs

Office of Therapeutic Products (OTP)

Part of the U.S. Food and Drug Administration (FDA) Center for Biologics Evaluation and Research (CBER) who regulate Regenerative Medicine Products

Resources

California Institute for Regenerative Medicine
https://www.cirm.ca.gov/

FDA-Approved Cellular and Gene Therapy Products
https://www.fda.gov/vaccines-blood-biologics/cellular-gene-therapy-products/approved-cellular-and-gene-therapy-products

OTP Learn
https://www.fda.gov/vaccines-blood-biologics/news-events-biologics/otp-learn

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Types of Regenerative Medicine Products

Gene Therapy

DEFINITION: Involves the use of genetic material (DNA or RNA) to treat or prevent a disease

Gene Editing: process of editing pieces of DNA through genetic material

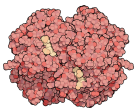
Gene Therapy: applied to the body through in-vivo, or to the modified cells via ex-vivo and returned to patient's body

Vectors: a means of delivering the therapy into the cell (viral vs. non-viral vectors)

Ex-Vivo

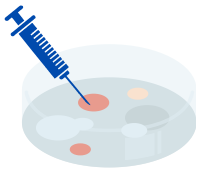
Extracted cells are modified and reintroduced to the patient's body

DNA RNA



Protein

Lentivirus



Lipid Nanoparticle

In-Vivo

Modifications are inserted directly into the patient's body through viral or non-viral delivery vehicles

Stem Cell Therapy

DEFINITION: A cell which has the ability to divide and create an identical copy, known as self-renewal, and can divide to form cells that mature into cells that make up every type of tissue and organ in the body

Adult Blood Stem Cells

Types of Stem Cells: Adult, fetal, perinatal, embryonic, induced pluripotent stem cells