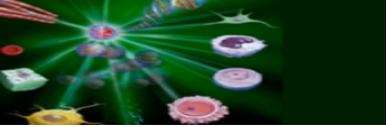


Regenerative medicine

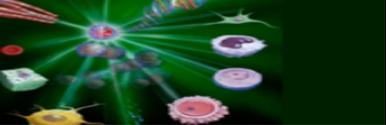
Mahendra Rao Director
NIH CRM





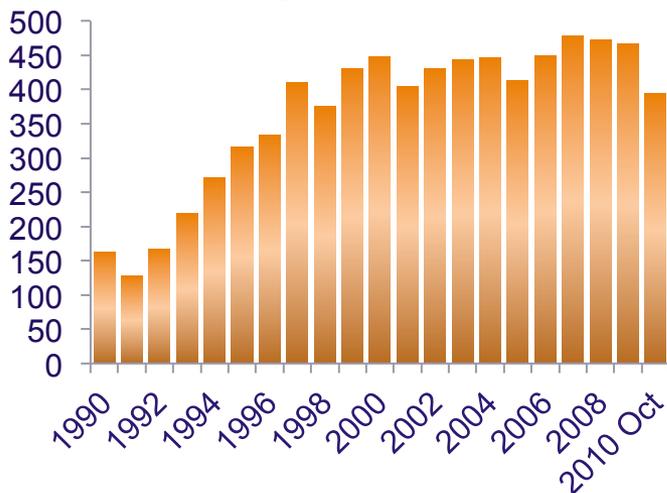
What is Regenerative Medicine?

- Regenerative Medicine is the "process of replacing or regenerating human cells, tissues or organs to restore or establish normal function". It refers to a group of biomedical approaches to clinical therapies that may involve the use of stem cells.
 - Grow organs in vitro
 - Mobilize endogenous repair processes
 - Tissue engineering
 - Personalized Medicine

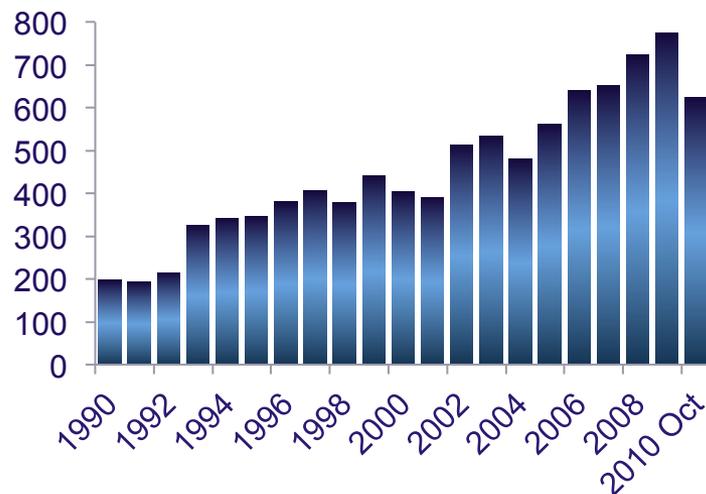


Number of Publications trends are different among Cell Therapy tissues

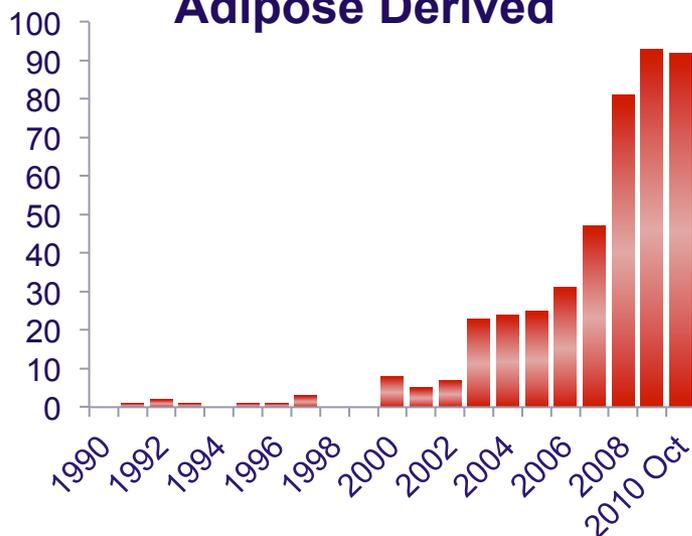
Peripheral Blood



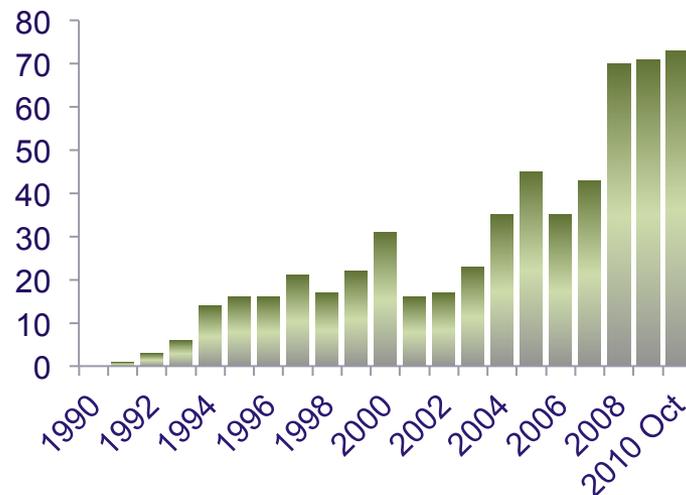
Bone Marrow

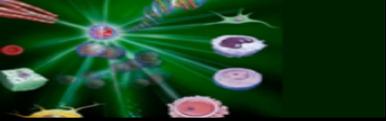


Adipose Derived

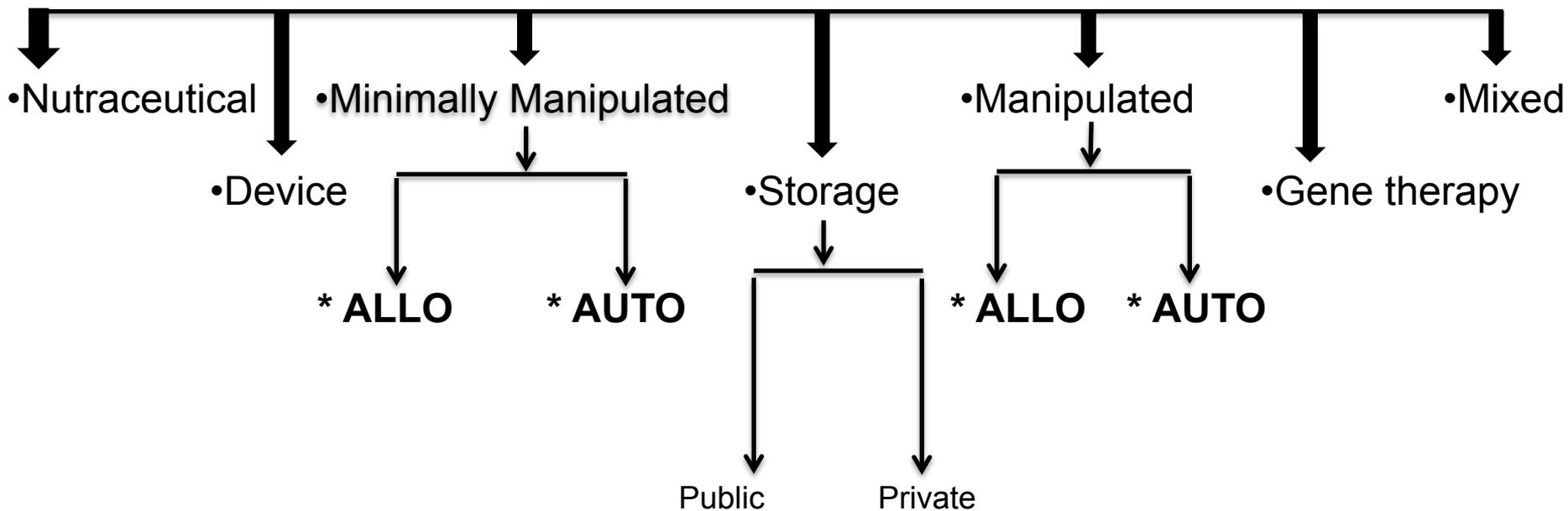


Umbilical Cord

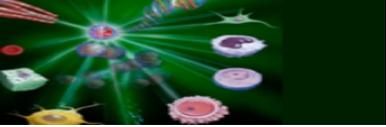




The Field of Regenerative Medicine



- Stemkine
- Nuvasive
- NYCBC
- Athersys
- Aastrom
- Pluristem
- Fibrocell
- Dendreon
- Tengion
- Lentigen
- Cytori
- Artecell
- Organogenesis
- Atherix
- CBR
- Genzyme
- Horizon
- Wake Forest
- Stem cell Inc
- Neural Stem
- Mesoblast
- Q Therapeutics



STEM-KINE



- *Stem-Kine is not a drug. Rather it is a food supplement that increases the number of circulating stem cells through a proprietary combination of ingredients that cause the release of stem cells from their source, the bone marrow.*

Stem-Kine was developed by stem-cell scientists and has been validated in peer-reviewed publications by leading researchers in the field.

Stem-Kine contains all natural ingredients and has no reported side effects.

Stem-Kine is a food supplement only. It is not evaluated by the FDA and it is not intended to cure, treat or prevent any disease or condition.



StemCello



International Stem Cell Institute
Medicine of the Future...TODAY
800.609.7795

Stem Cell Breakthrough
Adipose Stem Cell Ther

Newest Procedure is Now Available
In North America



기적을 만드는 Blue Science

BRTCTAB

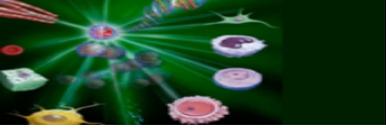
세포과학
흔적을 지우다

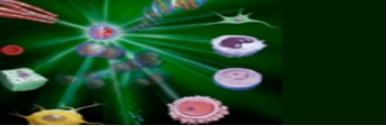
안티에이징을 위한
놀라운 Stem Cell과학
BRTC MEDI STEM Series

식물의 성장호르몬을 담은
메디스텝 복합체스가 피부 깊숙한 곳까지
스며들어 주름 완화, 탄력 향상 등의
피부 손상과 노후를 막고 피부 본연의
복원 시스템을 강화시켜 보다
어린 피부로 만들어 드립니다.



Face and Hand transplant





Tracheal transplant

Abingdon man first in the U.S. to get synthetic trachea transplant: 30-year-old credits surgery in Sweden with saving his life from rare cancer

|By Andrea K. Walker, The Baltimore Sun

Doctors in America told Chris Lyles a cancerous tumor on his windpipe was inoperable, but he and his family wouldn't take no for an answer.

They wrote surgeons all over the world, pleading for someone to take his case. Then during an Internet search, Lyles' brother-in-law stumbled upon a doctor in who recently implanted a synthetic trachea in a man in Eritrea.



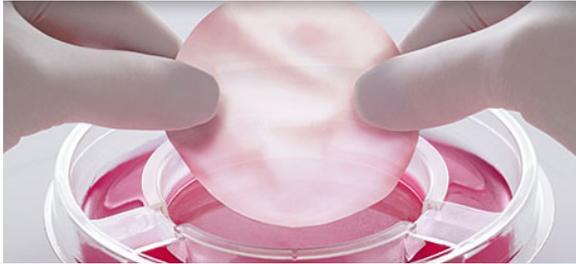
The windpipe, or trachea, made from minuscule plastic fibers and covered in stem cells taken from the man's bone marrow was implanted in November 2011.



(Kenneth K. Lam, Baltimore Sun) January 13, 2012

Cell therapy overview

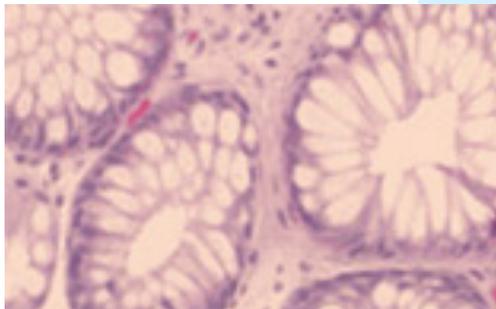
Tissue



Organogenesis - Apligraf

- Diabetic & venous ulcers
- Launched 2000
- 2007 revenue - \$60m

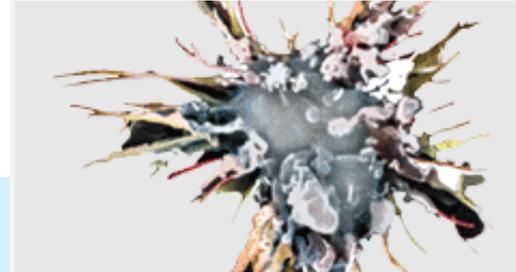
Stem cells



Osiris - Prochymal

- GvHD
- Phase III underway
- Potential 2012 launch

Immunotherapy



Dendreon - Provenge

- Prostate cancer
- Pivotal trial on-going
- BLA enabling results 2009

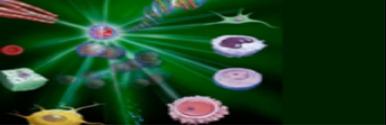
Cord blood



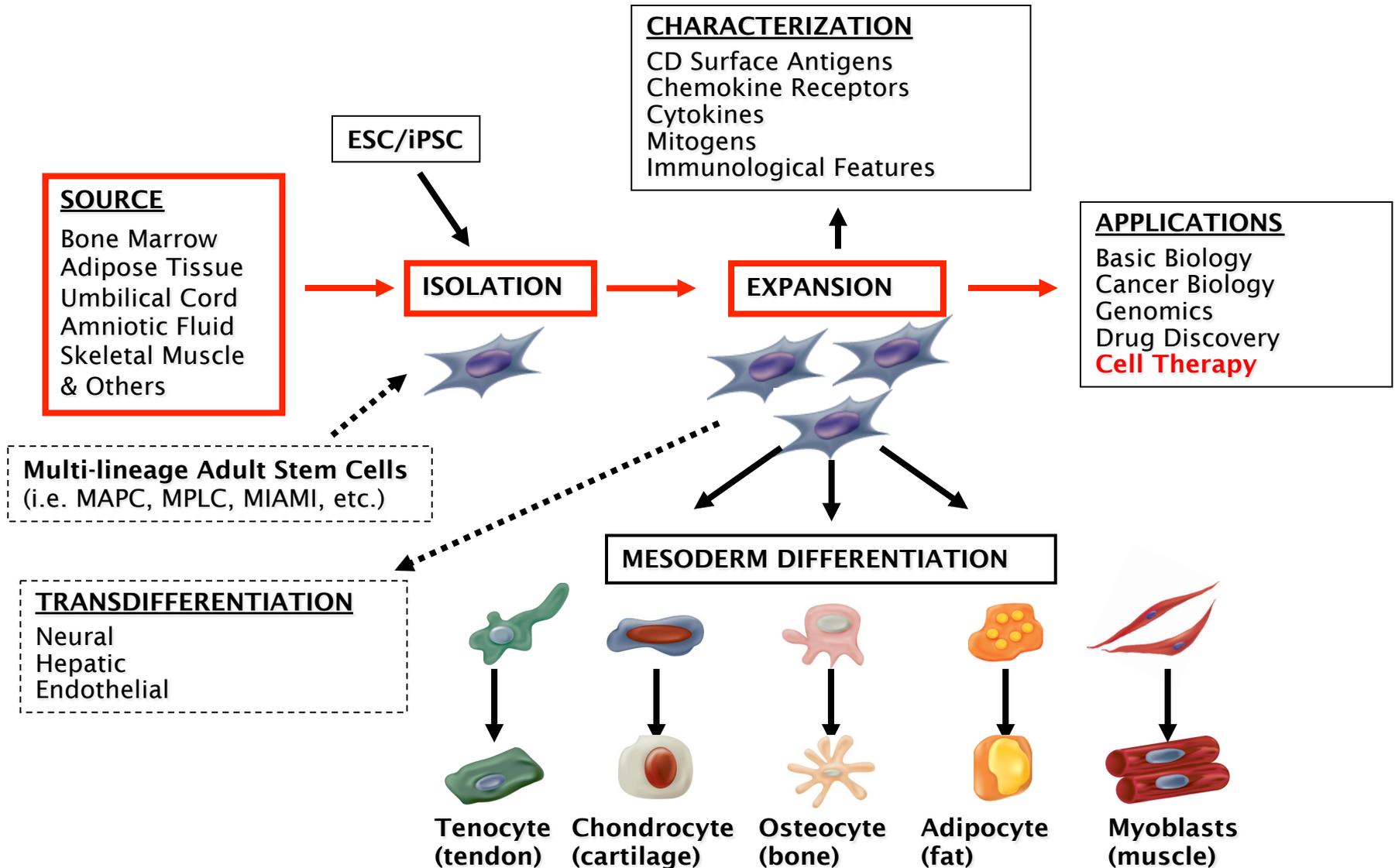
Viacell - Viacord

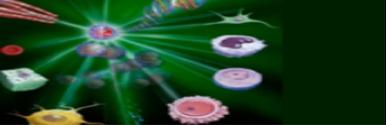
- Bone marrow alternate for leukemia
- Service launched 2000
- 2007 revenue - \$60m

Cell Therapy



Mesenchymal Stem Cells

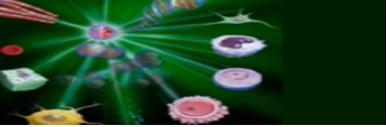




Regenerative Medicine Stock Index

ASTM	\$3.08	-0.05 133%	-1.6% -31%	2,423,038	89%	\$87.0M
				No Alerts/News		
ATHX	\$2.58	-0.07 11%	-2.6% -35%	57,494	55%	\$48.8M
	-			1 Alert (0 News) – View		
BTX	\$8.86	-0.16 120%	-1.8% -11%	183,860	55%	\$421.7M
	-			No Alerts/News		
CUR	\$2.27	+0.16 33%	+7.6% -35%	349,666	220%	\$105.4M
	-			1 Alert (0 News) – View		
CYTX	\$5.65	+0.10 79%	+1.8% -41%	288,959	62%	\$285.3M
	-			1 Alert (0 News) – View		
GERN	\$5.23	-0.01 20%	-0.2% -19%	871,087	30%	\$536.5M
	-			No Alerts/News		
ISCO	\$1.95	+0.02 144%	+1.0% -30%	71,792	15%	\$141.2M
	-			1 Alert (0 News) – View		
KOOL	\$3.61	-0.06 652%	-1.6% -9%	120,711	60%	\$50.6M
	-			No Alerts/News		
NBS	\$1.51	+0.01 37%	+0.7% -57%	173,775	57%	\$86.9M
	-			1 Alert (0 News) – View		
OPXA	\$2.16	-0.10 112%	-4.4% -30%	193,543	38%	\$39.8M
	-			1 Alert (0 News) – View		
OSIR	\$7.42	+0.36 38%	+5.1% -20%	108,993	111%	\$243.3M
	-			No Alerts/News		
PSTI	\$2.72	-0.13 189%	-4.6% -8%	704,546	173%	\$71.5M
	-			1 Alert (0 News) – View		
STEM	\$1.02		+0.02 +2.0%	1,235,734	74%	\$129.5M

And we have crimmminal activity



NATURE NEWS BLOG

American scientist arrested in stem-cell clinic sting

29 Dec 2011 | 16:22 GMT | Posted by Ewen Callaway | Category: Uncategorized

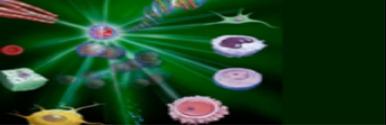
An American university scientist was arrested on 27 December, accused of supplying stem cells for use in unapproved therapies.

The US Department of Justice says Vincent Dammai, a researcher at the Medical University of South Carolina (MUSC) in Charleston, supplied the stem cells without the approval of his university or of the US Food and Drug Administration. Two other men, Francisco Morales of Brownsville, Texas, and Alberto Ramon, of Del Rio, Texas, were also arrested this week as part of the case. A fourth man, Lawrence Stowe of Dallas, Texas, has been charged and a warrant is out for his arrest, according to an FBI press release.

Many academic scientists have spoken out against unproven stem cell therapies (see Stem-cell scientists grapple with clinic). However, a 2011 opinion paper by Zubin Master, of the University of Alberta, Edmonton, Canada, and David Resnik, of the US National Institute of Environmental Health Sciences in Research Triangle Park, North Carolina, contends that many private stem cell clinics rely on scientists in the field who unknowingly supply cell lines, growth media and other reagents needed to harness stem cells.



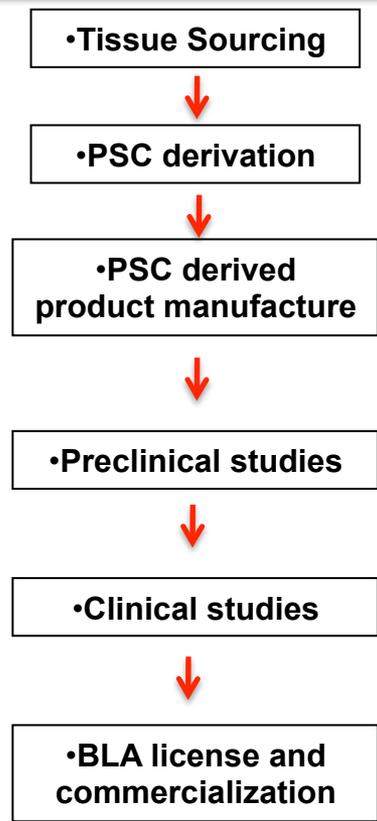
Cell Based therapy

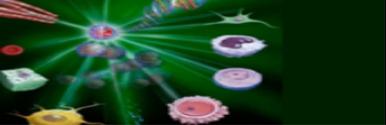


- 1: The Cosmeceutical Industry**
- 2: More than 250 Stem cell related trials**
- 3: Medical Tourism**
- 4: Some adult stem cell products introduced**
- 5: At least two pluripotent stem cell IND's approved**
- 6: More than 20 MSC companies and a similar number of neural therapy companies**
- 7: Larger Pharma companies making investments in cell therapy companies**
- 8: Several clinical translational centers set up at various Universities worldwide**

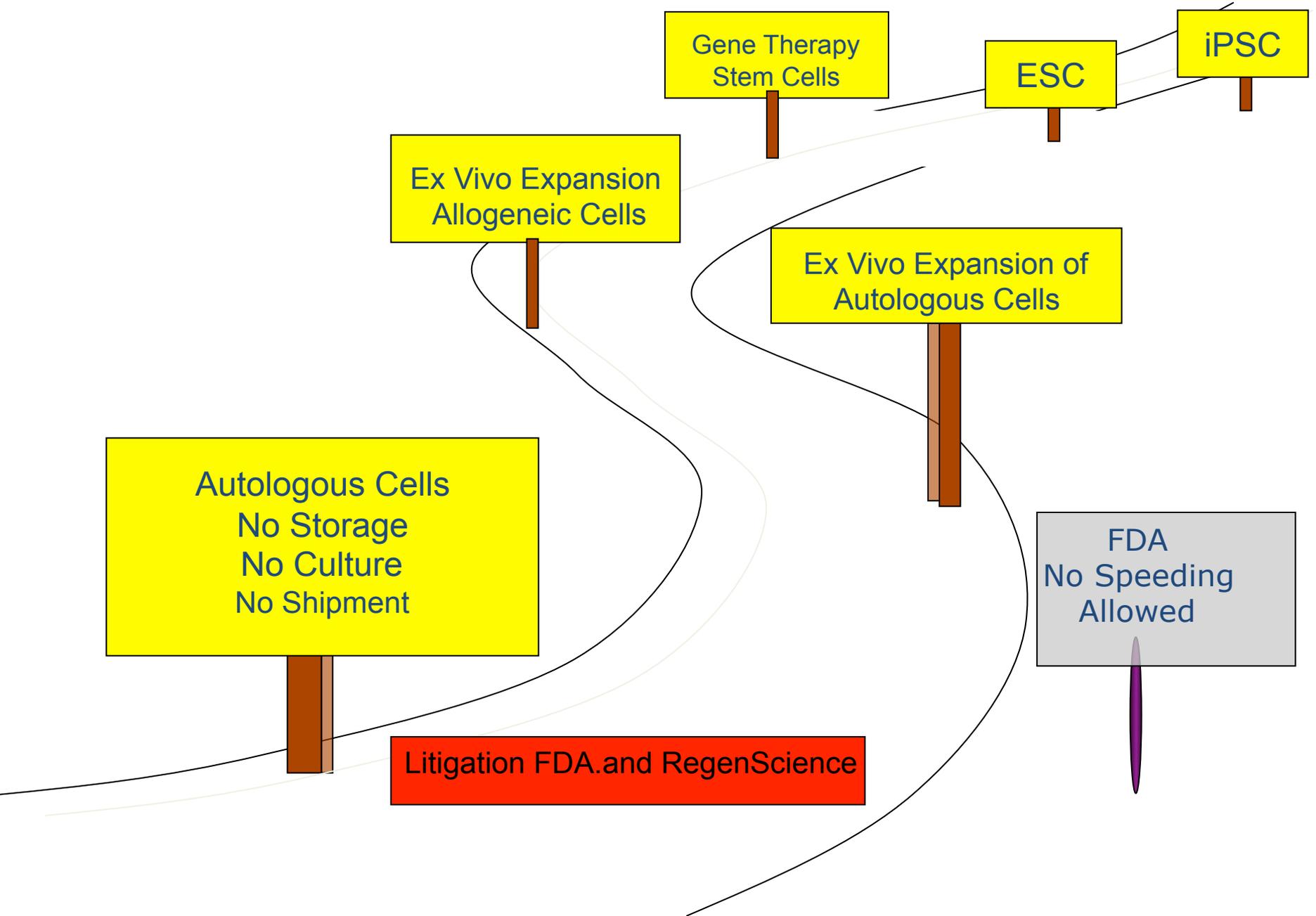
- 1: Biotime**
- 2: ACT**
- 3: Neural Stem cell efforts - tumors, spinal cord injury, etc.**
- 5: RPE efforts**
- 6: TRANSNEURO, Eurostem**
- 7: Limbal cells, MSC and MSC-like (Mesoblast, Osiris, Athersys, Stempeutics, MediStem, etc.)**
- 8: Numerous autologous efforts**
- 9: Adoptive immunity, bone, cartilage, skin, bladder**
- 10: Tissues, scaffolds and bioengineering**
- 11: Initiatives in PSC, macrophages, amniotic fluid cells and other products**

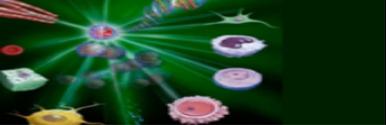
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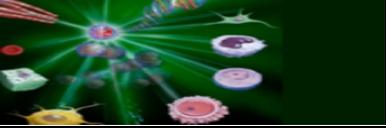
Current Regulatory Environment on the Stem Cell Therapy Highway



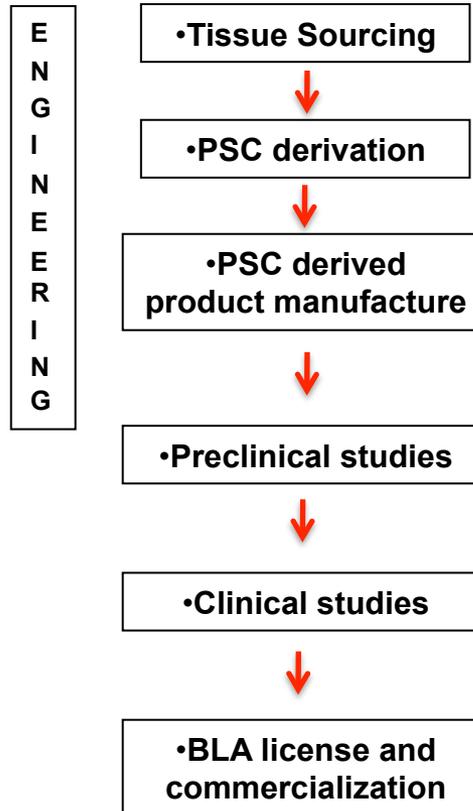


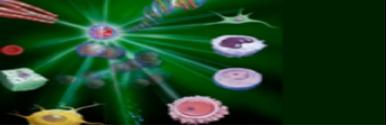
Current Cell Therapy Related Businesses Appear To Fall Into Three Different Models...

	Autologous Systems Based (Decentralized)	Autologous Service Based (Centralized)	Allogeneic Model (~Centralized)
Process	<ul style="list-style-type: none">• Cells extracted, usually from end user• On-site processing (POC)• End user administration	<ul style="list-style-type: none">• Cells extracted from end user• Off-site processing• End user administration	<ul style="list-style-type: none">• Cells extracted from donor• Processing (off-site or on-site)• End user administration
Clinical Pros/Cons	<p>Pros:</p> <ul style="list-style-type: none">• Single procedure; no time delay• Lower risk of contamination• Low risk of immune response <p>Cons:</p> <ul style="list-style-type: none">• Limited scalability	<p>Pros:</p> <ul style="list-style-type: none">• Low risk of immune response <p>Cons:</p> <ul style="list-style-type: none">• Multiple procedures; up to 1 month time delay• Risk of contamination• Not scalable	<p>Pros:</p> <ul style="list-style-type: none">• Fully scalable <p>Cons:</p> <ul style="list-style-type: none">• Risk of immune response• Risk of contamination
Current Examples	<p>Cytori (Celution System):</p> <ul style="list-style-type: none">• Harvest adipose tissue from patient• On-site processing: Cellution System used to separate / concentrate stem cells• Cells transplanted back patient	<p>Genzyme (Carticel):</p> <ul style="list-style-type: none">• Harvest cartilage from patient• Ship cells to processing facility• Off-site processing: chondrocyte expansion• Ship cells to hospital• Cartilage grafted to patient	<p>Osiris (Osteocell):</p> <ul style="list-style-type: none">• Harvest cells from deceased donor• Mesenchymal stem cell expansion• Grafting onto recipient patient

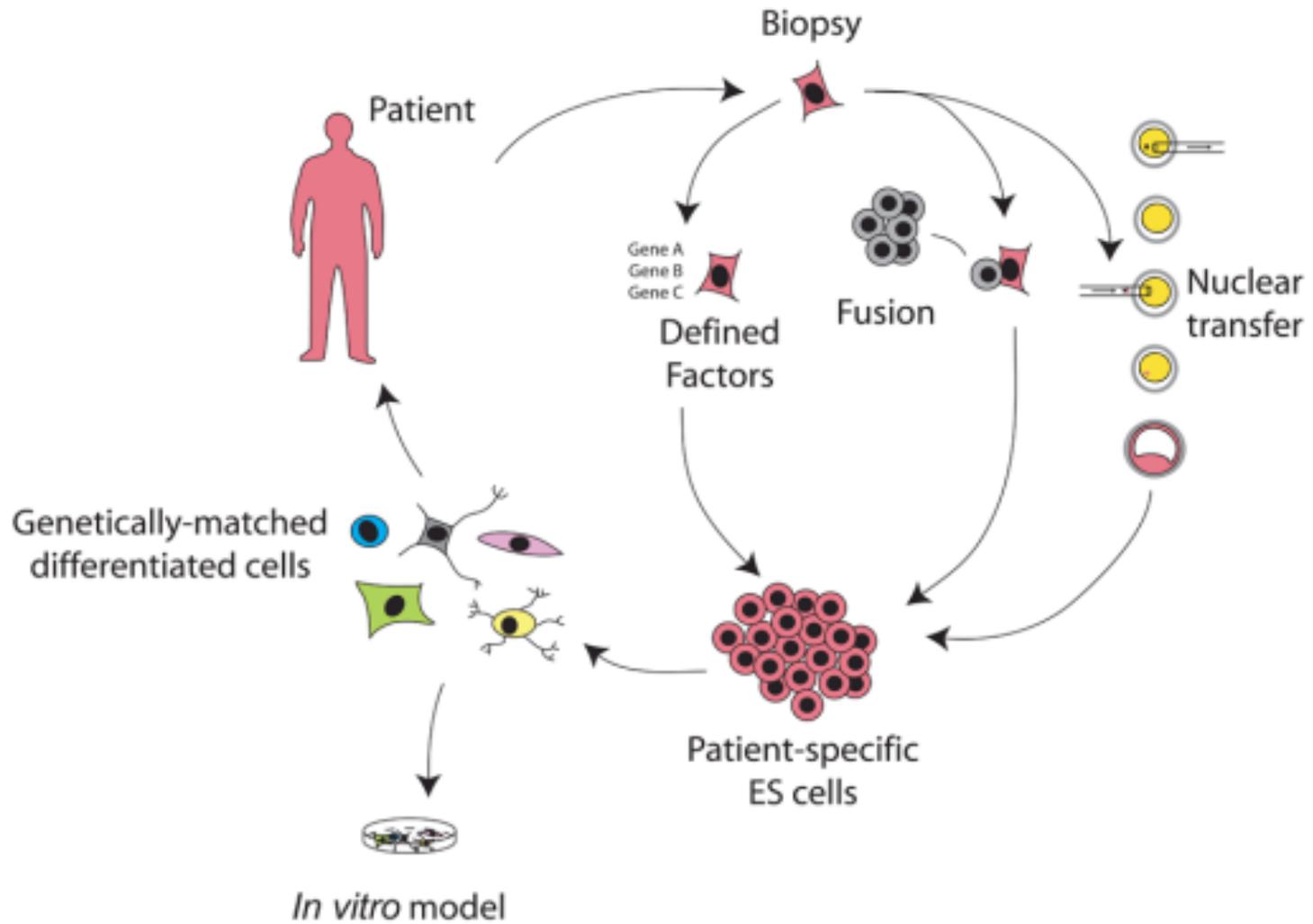


Cell Based therapy

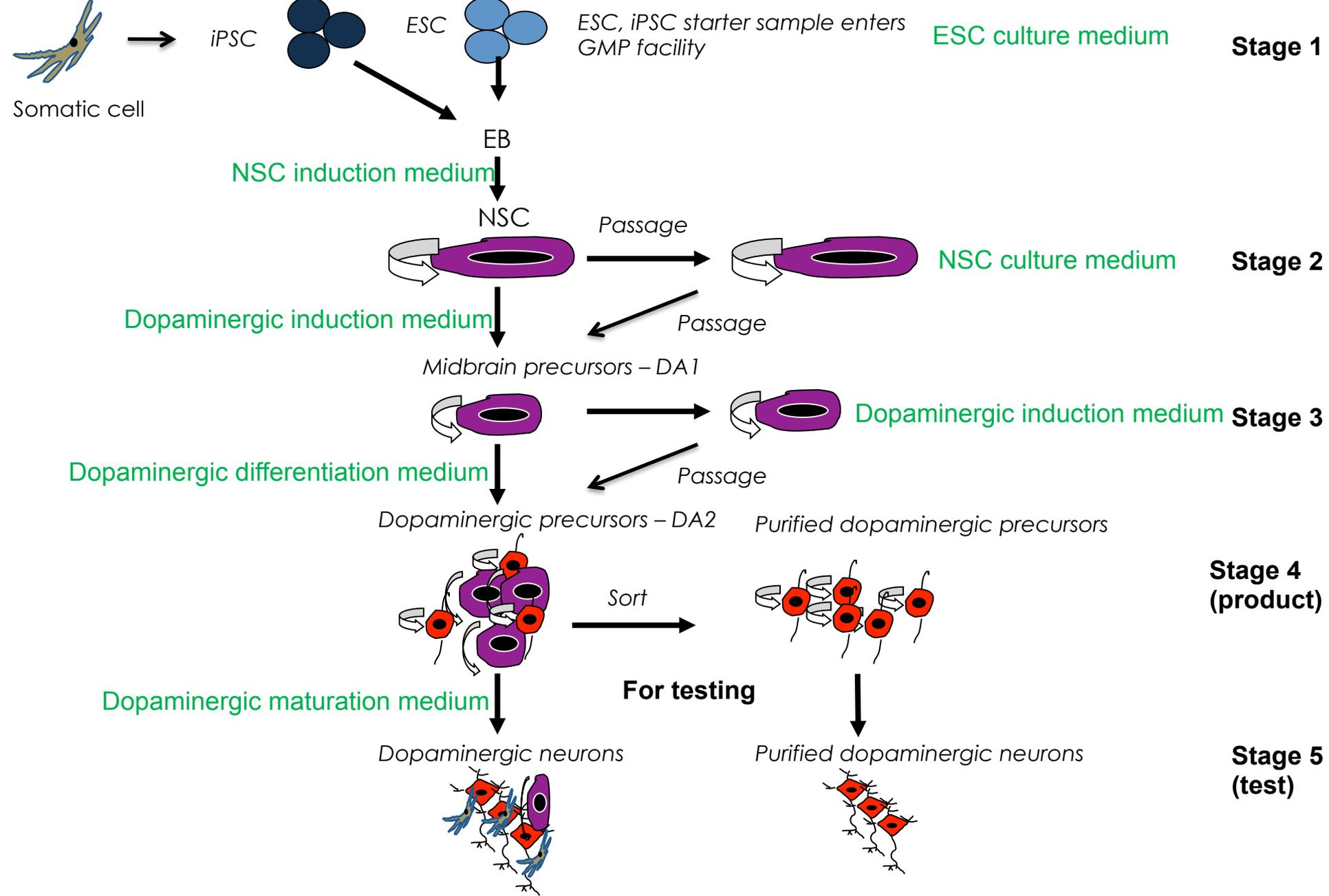
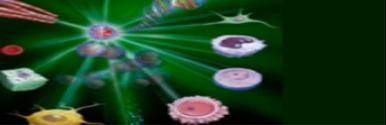


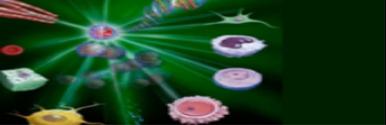


Pluripotent cells solve the source issue

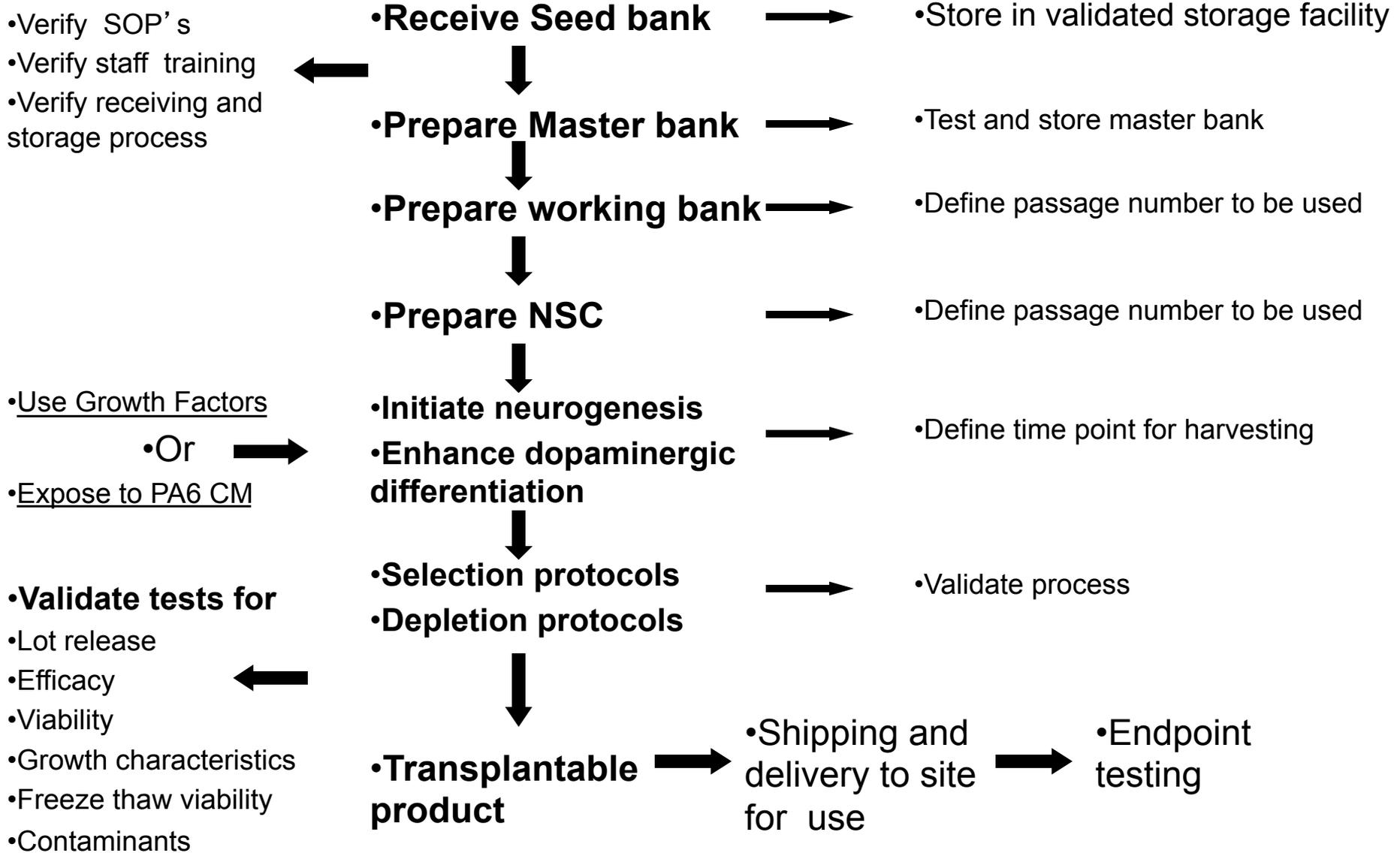


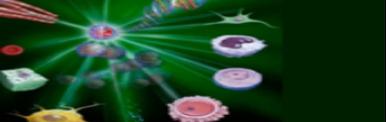
Dopaminergic neuron culture in GMP facility



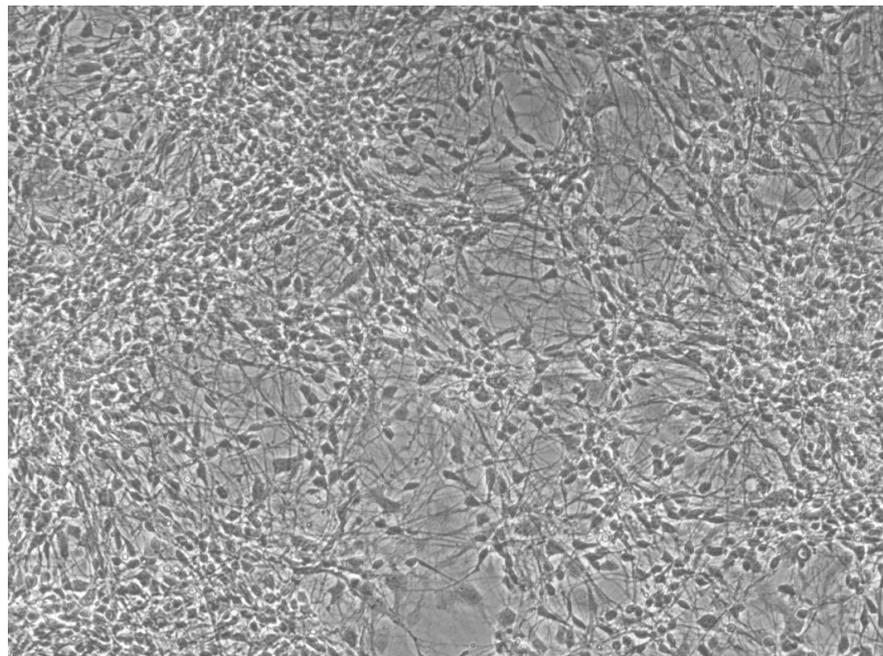
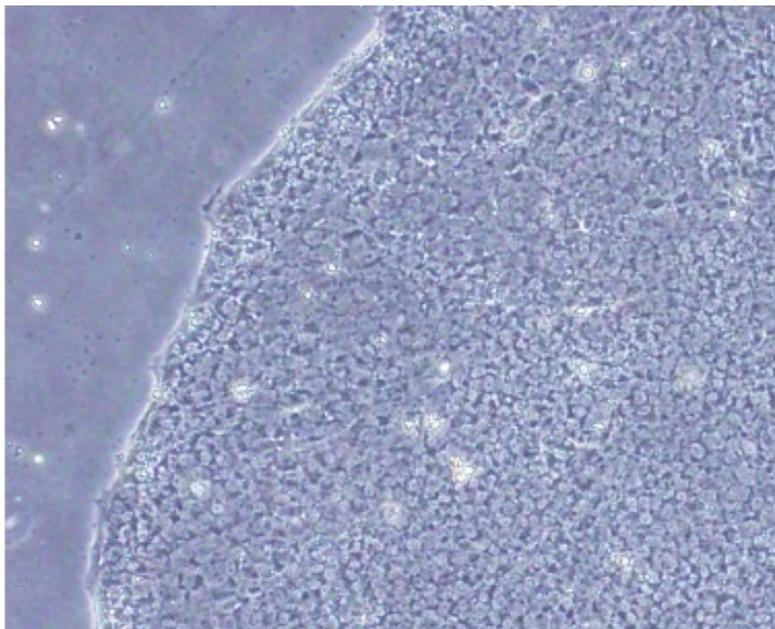


Demonstrating scalable production

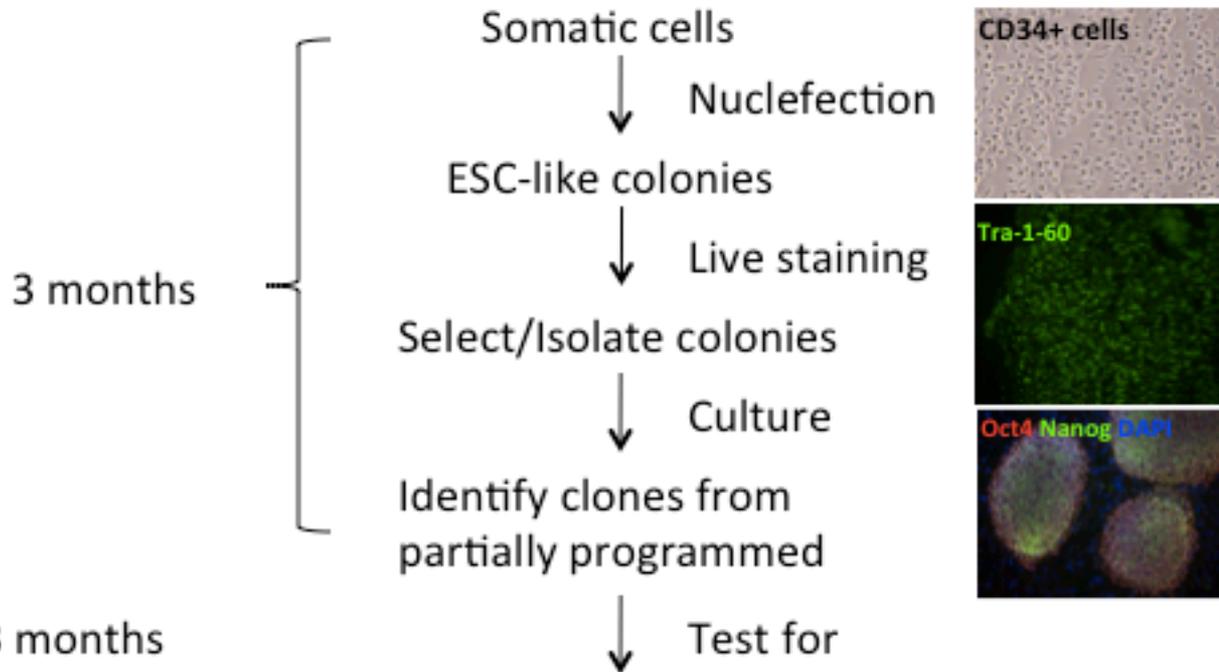
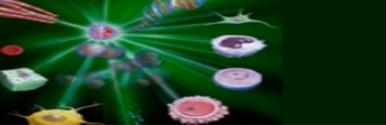




iPSC Solve the immune issue



The same process can be used for iPSC lines as for ESC



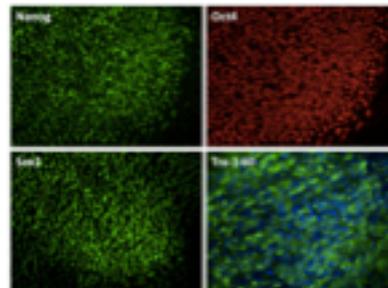
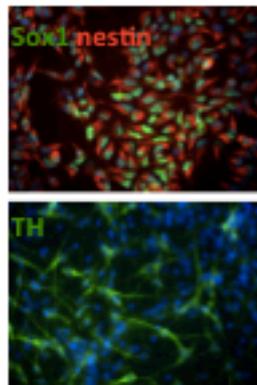
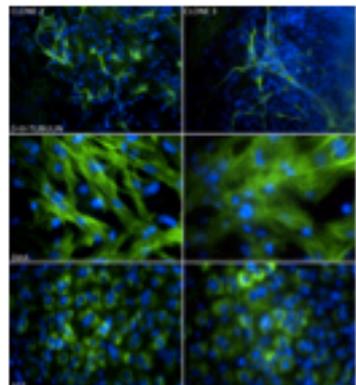
Differentiation via EB

NSC/DA

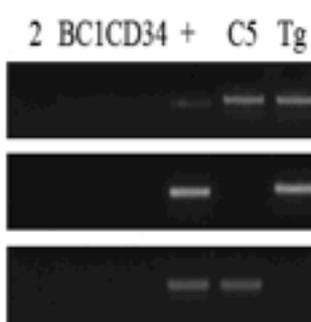
Pluripotency

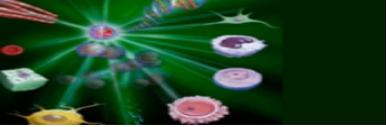
Genomic stability

integration-free



EBNA1
TG
SK





ESC/iPSC-derived dopaminergic neurons for therapy for PD- where we are

- Documentation of clinical-grade lines: consent, donor and acquisition tests, xeno exposure tests, karyotype, identity, tracking documentation, etc (CIRM funded)
- Established a GMP-compatible scalable process of producing transplant ready dopaminergic neurons from hESC and iPSC
- Transferred the process to City of Hope's GMP facility and banked/ manufactured cells at NSC and DA stages for one clinical ESC line under CIRM funded grant
- Ongoing animal studies using cells manufactured at COH: Safety studies with Jackson's Laboratory; efficacy studies at the Buck under CIRM funded grant
- In discussion with the NIH Clinic Center (Dr. Lonser) on using autologous and/or allogeneic iPSC-derived cells for a Phase I trial
- Other clinical partners- Europe- Parkinsons Initiative (with Dr. Rao)
- Other industrial partners – eg Lonza

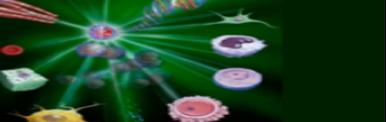
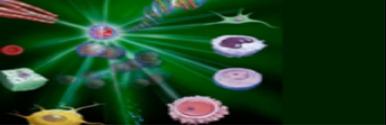


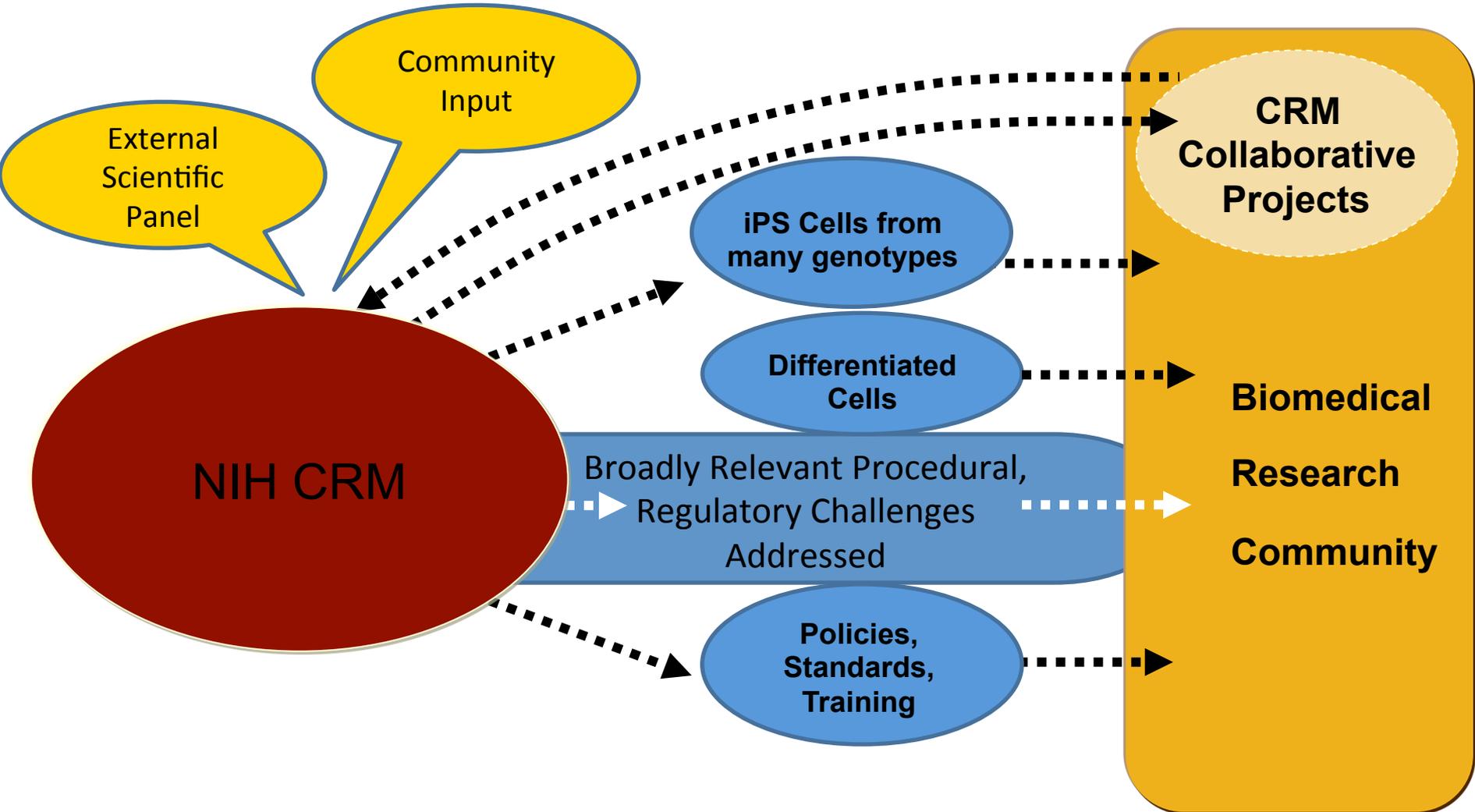
Table 1. Current Roadblocks to Stem Cell Therapy

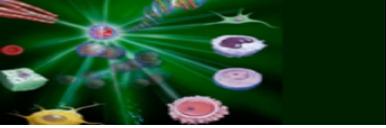
- | | |
|-----|--|
| 1. | Periods of limited government involvement due to legal, political and ethical issue |
| 2. | Lack of mature regulatory policy |
| 3. | Absence of uniform regulations and activity across countries |
| 4. | Absence of uniform global patent interpretations on pluripotent stem cells |
| 5. | Absence of standards and controls |
| 6. | Lack of successful business models thus far for autologous therapy |
| 7. | Limited availability of investment in new business models |
| 8. | Issues of consent and sourcing related to cell-based manufacture |
| 9. | Limited expertise in scaled-up cell manufacturing |
| 10. | Issues of risk management, reimbursement, and long-term follow-up in cell-based therapy trials |



NIH Center for Regenerative Medicine

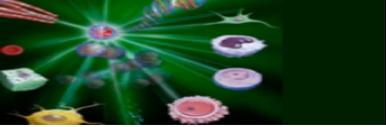
A resource for the entire community





What Next

Genetic Correction
Personalized Medicine



Clinical grade iPSC from fibroblasts

STEM CELLS

EMBRYONIC STEM CELLS/INDUCED PLURIPOTENT STEM CELLS

Reprogramming of Human Fibroblasts to Induced Pluripotent Stem Cells under Xeno-free Conditions

IGNASI RODRÍGUEZ-PIZÀ,^a YVONNE RICHAUD-PATIN,^{a,d} RITA VASSENA,^a FEDERICO GONZÁLEZ,^a MARÍA JOSÉ BARRERO,^a ANNA VEIGA,^{a,b,c} ANGEL RAYA,^{a,d,e} JUAN CARLOS IZPISÚA BELMONTE^{a,f}

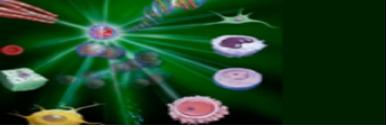
^aCenter for Regenerative Medicine in Barcelona, Dr. Aiguader 88, 08003 Barcelona, Spain; ^bServei de Medicina de la Reproducció, Institut Universitari Dexeus; ^cDepartament de Ciències Experimentals i de la Salut, Universitat Pompeu Fabra; ^dNetworking Center of Biomedical Research in Bioengineering, Biomaterials and Nanomedicine (CIBER-BBN); ^eInstitució Catalana de Recerca i Estudis Avançats (ICREA); ^fGene Expression Laboratory, Salk Institute for Biological Studies, 10010 North Torrey Pines Road, La Jolla, California 92037

Key Words. Cell culture • Clinical translation • Embryonic stem cells • iPS cells • Good Manufacturing Practice

PROTOCOL

A protocol describing the genetic correction of somatic human cells and subsequent generation of iPS cells

Ángel Raya^{1,2,3,8}, Ignasi Rodríguez-Pizà¹, Susana Navarro^{4,5}, Yvonne Richaud-Patin^{1,3,8}, Guillermo Guenechea^{4,5}, Adriana Sánchez-Danés^{1,9}, Antonella Consiglio^{1,6,9}, Juan Bueren^{4,5} & Juan Carlos Izpisúa Belmonte^{1,7}



IPSC from a clinically accessible source

Generation of Induced Pluripotent Stem Cells from CD34+ Cells across Blood Drawn from Multiple Donors with Non-Integrating Episomal Vectors

Amanda A. Mack*, Stacie Kroboth, Deepika Rajesh, Wen Bo Wang

Cellular Dynamics International, Inc., Madison, Wisconsin, United States of America

RESEARCH

Open Access

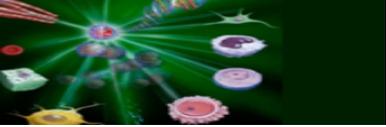
Induced pluripotent stem cells from GMP-grade hematopoietic progenitor cells and mononuclear myeloid cells

Seiga Ohmine¹, Allan B Dietz², Michael C Deeds², Katherine A Hartjes¹, David R Miller², Tayaramma Thatava¹, Toshie Sakuma¹, Yogish C Kudva^{2,3} and Yasuhiro Ikeda^{1*}

PROTOCOL

Generation of induced pluripotent stem cells from human cord blood cells with only two factors: Oct4 and Sox2

Alessandra Giorgetti^{1,5}, Nuria Montserrat^{1,5}, Ignacio Rodriguez-Piza¹, Carmen Azqueta², Anna Veiga¹ & Juan Carlos Izpisua Belmonte^{1,3,4}



ESC/iPSC to HSC

Brief Report: Efficient Generation of Hematopoietic Precursors and Progenitors from Human Pluripotent Stem Cell Lines

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Key Words. Differentiation • Hematopoiesis • Hematopoietic progenitors • Pluripotent stem cells

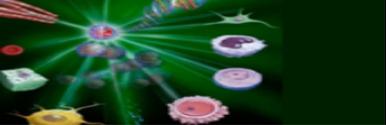
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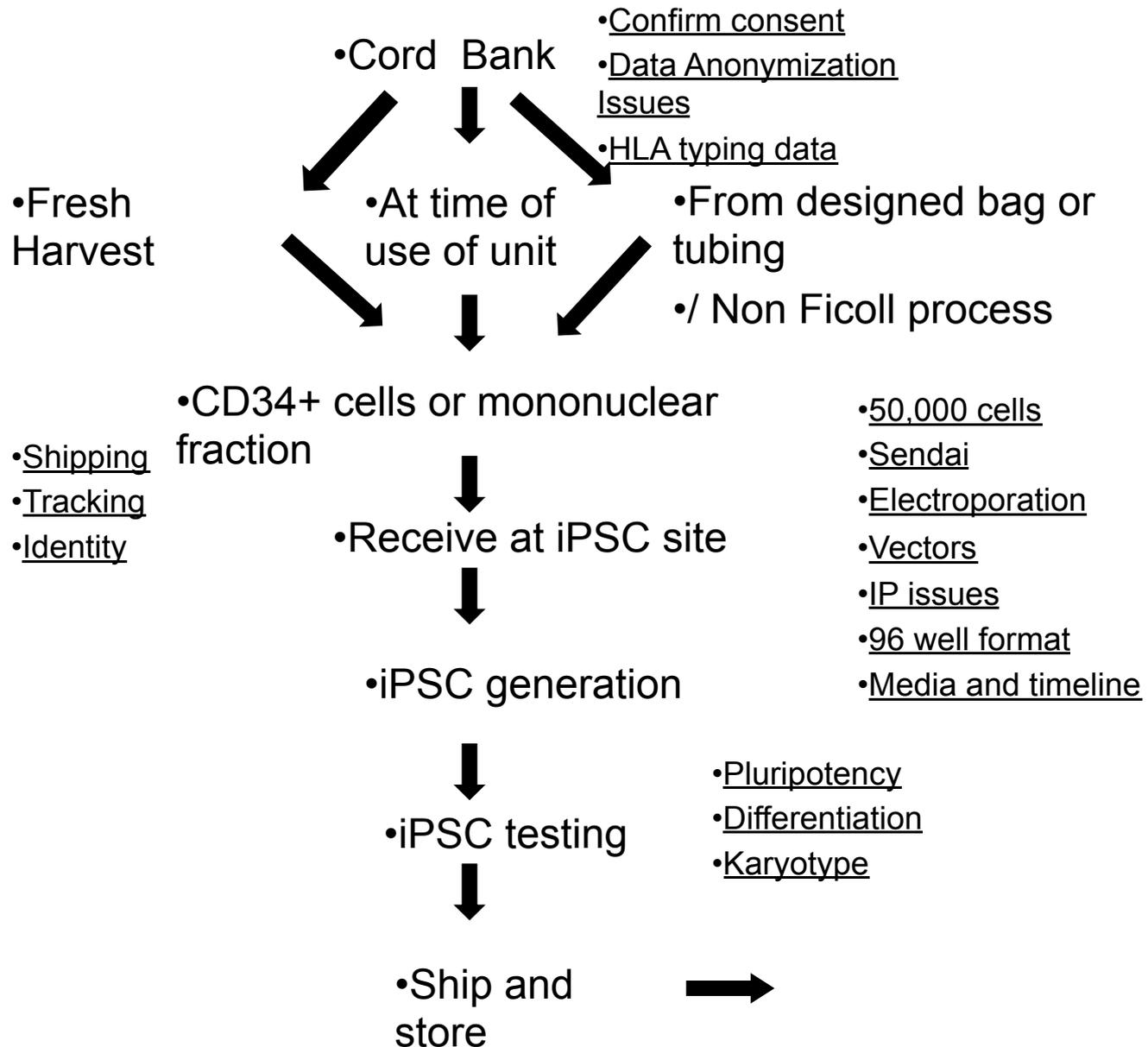
A Novel Serum-Free Monolayer Culture for Orderly Hematopoietic Differentiation of Human Pluripotent Cells via Mesodermal Progenitors

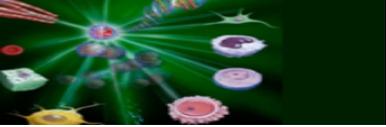
Akira Niwa^{1,2}, Toshio Heike², Katsutsugu Umeda^{2,4}, Koichi Oshima¹, Itaru Kato^{1,2}, Hiromi Sakai⁵, Hirofumi Suemori³, Tatsutoshi Nakahata^{1,2}, Megumu K. Saito^{1,2*}

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iPSC from blood or cord blood





ESC/iPSC to MSC

Derivation and Characterization of Human ESC-Derived Mesenchymal Stem Cells

Ruenn Chai Lai, Andre Choo, and Sai Kiang Lim

Derivation and Immunological Characterization of Mesenchymal Stromal Cells from Human Embryonic Stem Cells

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Enrichment of Human ESC-Derived Multipotent Mesenchymal Stem Cells with Immunosuppressive and Anti-Inflammatory Properties Capable to Protect Against Experimental Inflammatory Bowel Disease

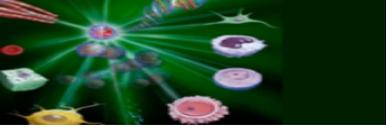
LAURA SÁNCHEZ,^a IVÁN GUTIERREZ-ARANDA,^a GERTRUDIS LIGERO,^a RUTH RUBIO,^a MARTÍN MUÑOZ-LÓPEZ,^a JOSÉ L. GARCÍA-PÉREZ,^a VERÓNICA RAMOS,^a PEDRO. J. REAL,^a CLARA BUENO,^a RENÉ RODRÍGUEZ,^a MARIO DELGADO,^b PABLO MENENDEZ^a

EMBRYONIC STEM CELLS/INDUCED PLURIPOTENT STEM CELLS

Induced Pluripotent Stem Cell - Derived Mesenchymal Stem Cells: Progress toward Safe Clinical Products

Yunjoon Jung^{a,c}, Gerhard Bauer^{a,b,c}, and Jan A. Nolte^{a,b,c}

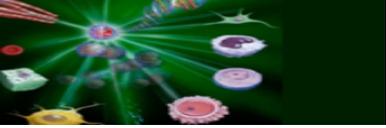
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Why source from cord blood banks

- 1: Tissue sourcing is well organized and validated
- 2: HLA typing data is already being collected by banks
- 3: Existing samples can be used without compromising their ultimate use
- 4: A remuneration model already exists
- 5: Zerofootprint methods work well with cord blood cells
- 6: A Xenofree media and protocol has been developed so clinical grade iPSC lines can be made
- 7: Cord blood is the youngest source of stem cells one may obtain reliably and easily
- 8: Stem cells in general have specific mechanisms to maintain genomic integrity , delay senescence and protect against transformation.
- 9: The process can be easily extended to blood banks and marrow derived CD34 cells using the same infrastructure
- 10: Somatic memory and differentiation bias may work in our favor for early therapeutic efforts
- 11: May revive the cord blood banking business

Table 1: The relative advantages of making iPSC from either a private or a public cord blood bank are listed.



Thank You

Questions- email
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