

University of Minnesota, Stem Cell Institute
Fall 2017 Seminar Series



The Business of Stem Cells

Martin McGlynn

CEO, StemCells Inc., 2001-2016 (Retired)

Chairman, Regenerative Medicine Foundation

Martin McGlynn

- ▶ 1968 UCD, Business & Finance
1970 Irish Institute of Industrial Engineering
- ▶ 30+ year career: B-D(Ire); International Meat Company(Ire); Abbott(Ire/Can); BOC Healthcare/Anaquest(U.S); Pharmadigm(U.S)
- ▶ 1992 Initial exposure to Biotechnology: acquired Delta Biotechnology
Yeast expression systems for recombinant human proteins; first in man (rHA)
- ▶ 2001-2016 CEO, StemCells, Inc. (NASDAQ:STEM)
- ▶ June 2016 joined RMF Board; June 2017 elected Chair

30 Years of R&D

Cellular Medicine

Cellular Medicine: The Pioneers

1980s

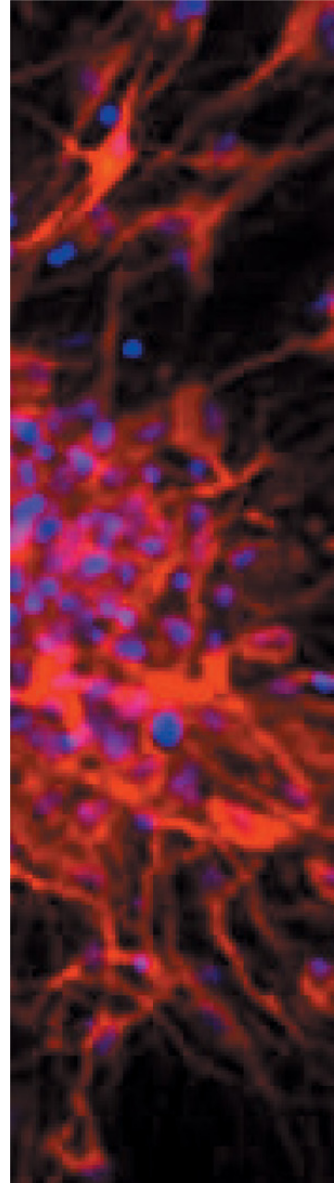
- ▶ hHSCs – Hematopoietic Stem Cells (Weisman/**SyStemix**/Sandoz)

1990s

- ▶ hMSCs – Mesenchymal Stem Cells (Caplan/**Osiris**)
- ▶ hESCs – Embryonic Stem Cells (Thompson/**Geron**)
 - Retinal Pigment Epithelium Cells from hESCs (Lanza/**ACT**/Ocata/Astellas)
 - Pancreatic Progenitors (**Viacyte***)

2000s

- ▶ hNSCs – Neural Stem Cells (Uchida/**StemCells**; Johe/**Neuralstem**; Sinden/**ReNeuron**)
- ▶ hMAPCs – Multipotent Adult Progenitor Cells (Verfaillie/**Athersys**)
- ▶ hMLCs – Mesenchymal Lineage Adult Stem Cells (Itescu/**Mesoblast**)



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Cellular Medicine: Scorecard

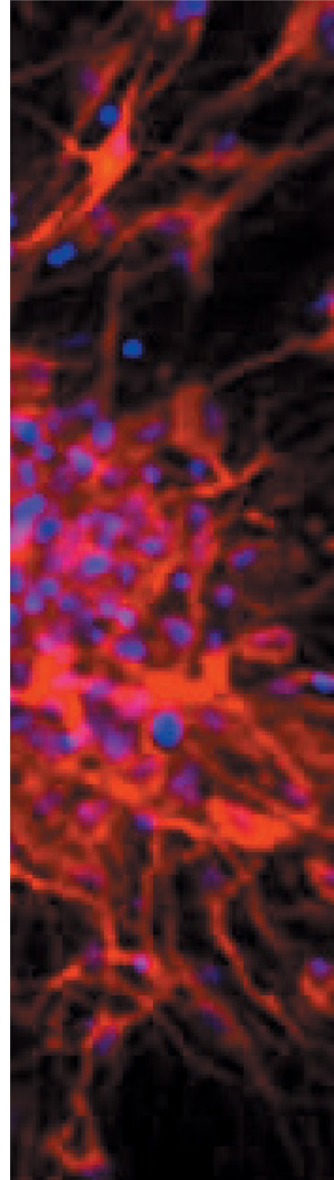
Today

Products brought to market = \emptyset

- ▶ HSC/SyStemix/Novartis
- ▶ Athersys/Pfizer: IBD & Stroke PII setbacks. Chugai, then Healios for Japan
- ▶ Osiris sold assets to Mesoblast: \$50mm* in 2013
- ▶ Mesoblast in PII for HF, RA; Back Pain in PIII. GvHD in Japan; Teva returned HF rights
- ▶ Geron sold drug screening to GE; Biotime, 2013. PI/II SCI trial by Biotime sub (Asterias)
- ▶ Astellas acquired Ocata(ACT) in 2016
- ▶ NSC Technology: StemCells to BOCO; Neuralstem exited. ReNeuron still standing



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Compared to Technology: Scorecard

Life-changing paradigm shifts for millions of people around the planet



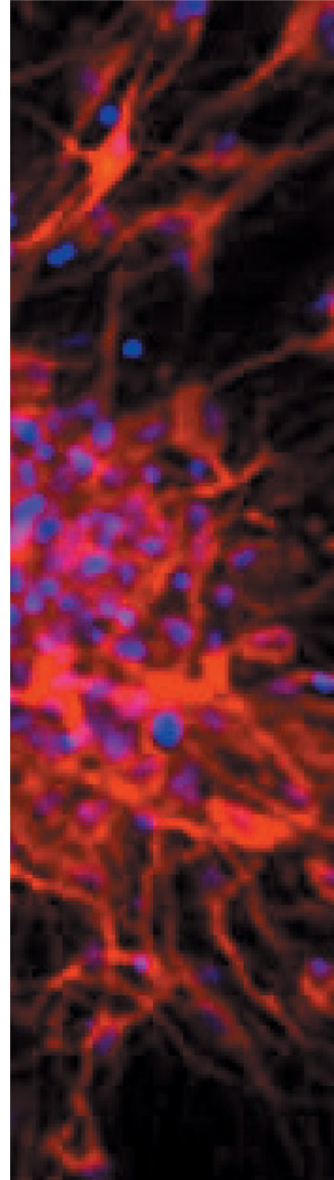
1987



2017



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The Promise of Stem Cells

My Personal Learning Journey

November 2000: Dinner with Irv



“Stem cells, unlike drugs or proteins, self-renew and differentiate in a fashion regulated by the body; they regenerate systems for life from a single therapy.”

— Irving Weissman, MD

StemCells, Inc., Scientific Advisory Board Member

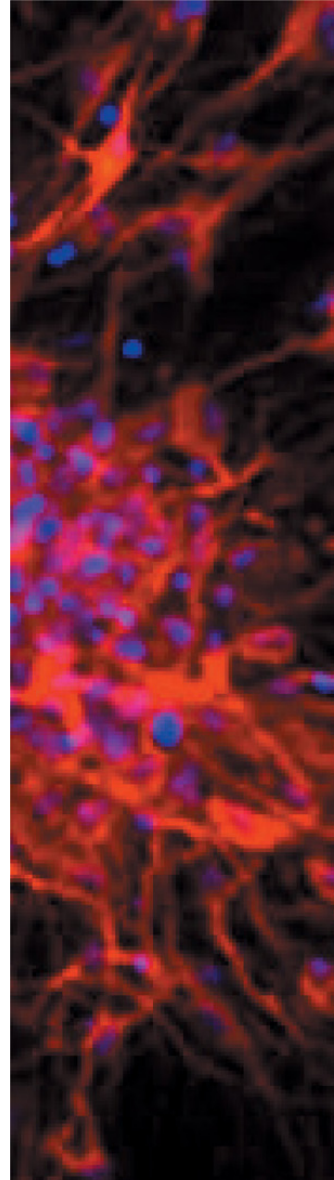
Professor of Pathology & Developmental Biology,
Stanford University

Director of the Stanford Institute for Stem Cell
Biology and Regenerative Medicine

Director of the Stanford Ludwig Center
for Cancer Stem Cell Research



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December 2000: Published in PNAS



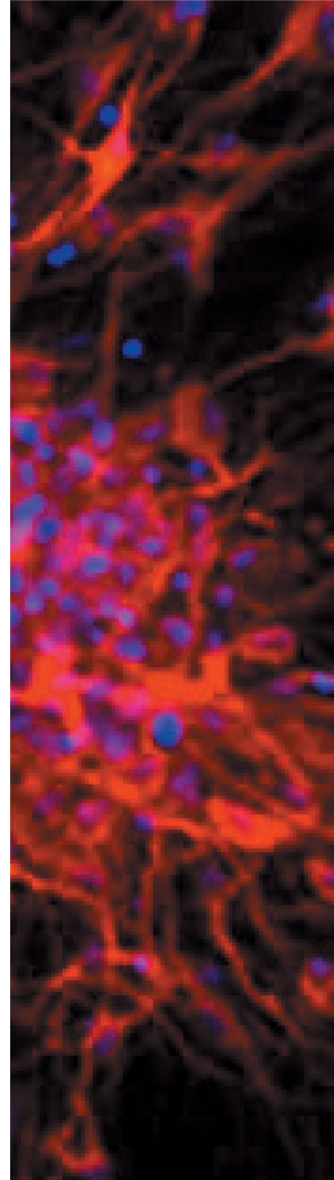
"It's an incredible feeling for researchers like myself to see our dreams brought to reality."

— Nobuko Uchida, PhD
StemCells, Inc., Vice President, Stem Cell Biology

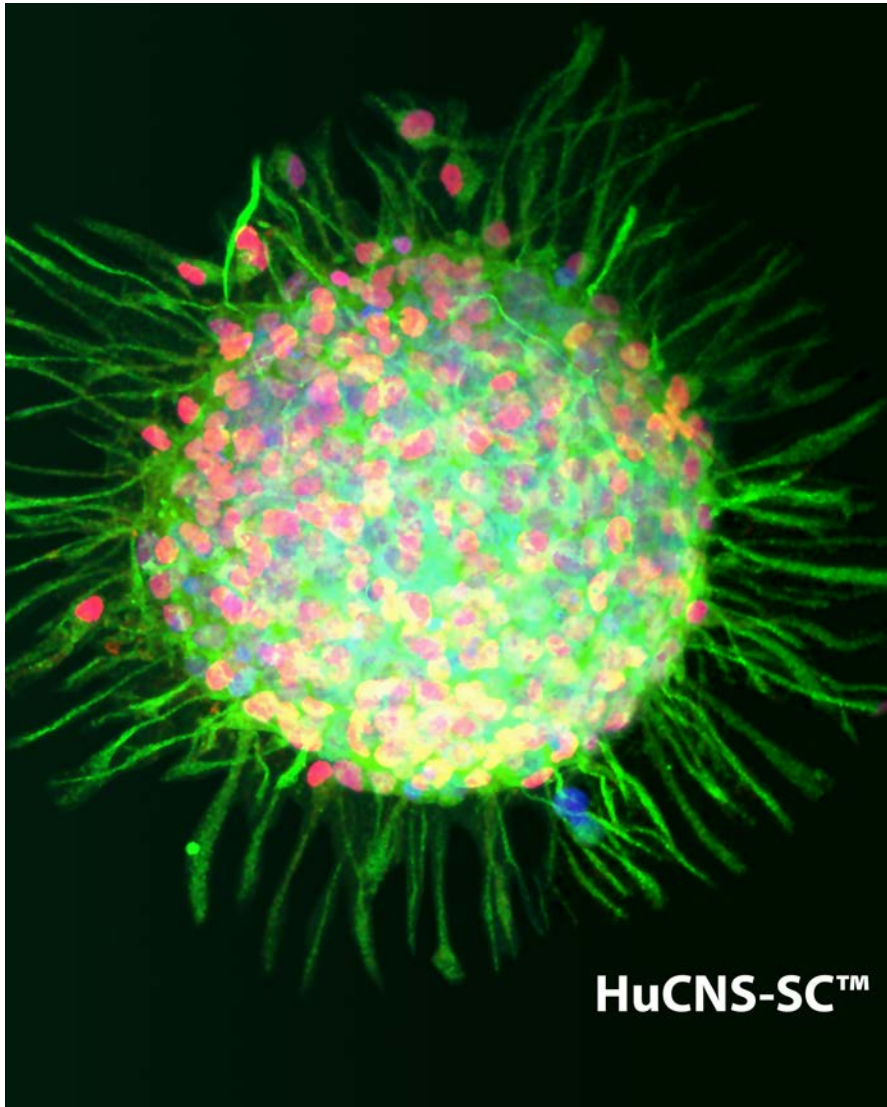
Direct isolation of human central nervous system stem cells

PNAS, December 19, 2000

Nobuko Uchida, David W. Buck, Dongping He,
Michael J. Reitsma, Marilyn Masek, Thinh V.
Phan, Ann S. Tsukamoto, Fred H. Gage,
and Irving L. Weissman



The wonderful world of stem cell biology...

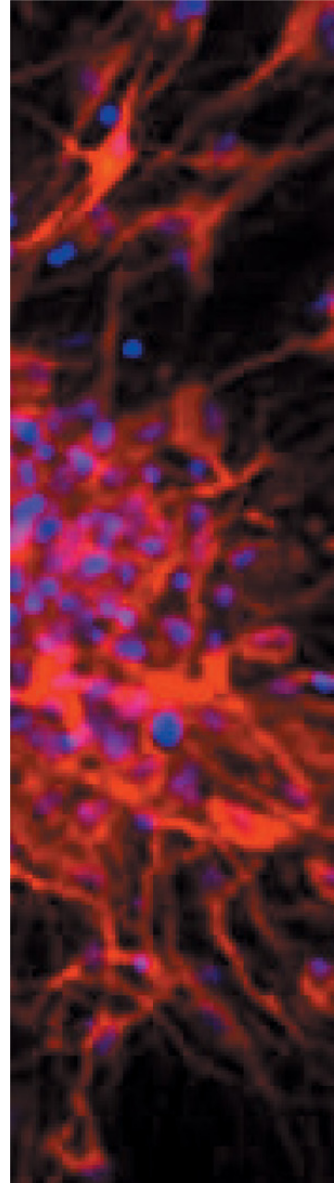


- ▶ Purified: engraft, migrate, differentiate into neurons, astros, oligos
- ▶ Expandable *ex-vivo*!! Remain stable in stem cell compartment in cell banks
- ▶ Harness properties of stem cells to **restore lost function** for life of host
- ▶ SysStemix-Novartis
- ▶ StemCells, Inc., Palo Alto [Nasdaq: STEM]
- ▶ HuCNS-SCs®

...I was hooked!

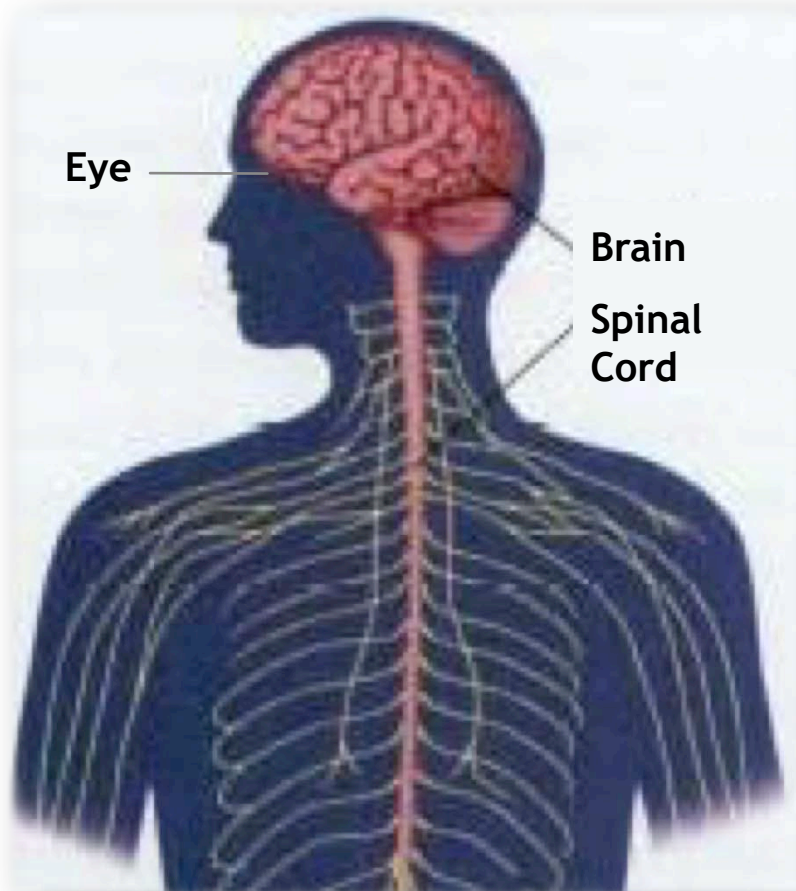


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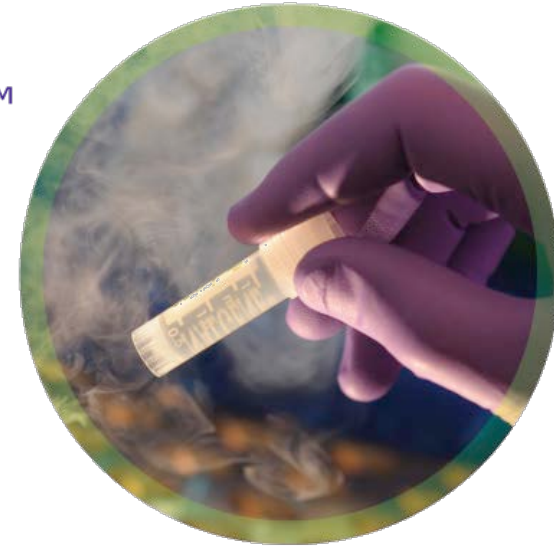


STEM CELLS

Groundbreaking **science**. Breakthrough **medicine**.™



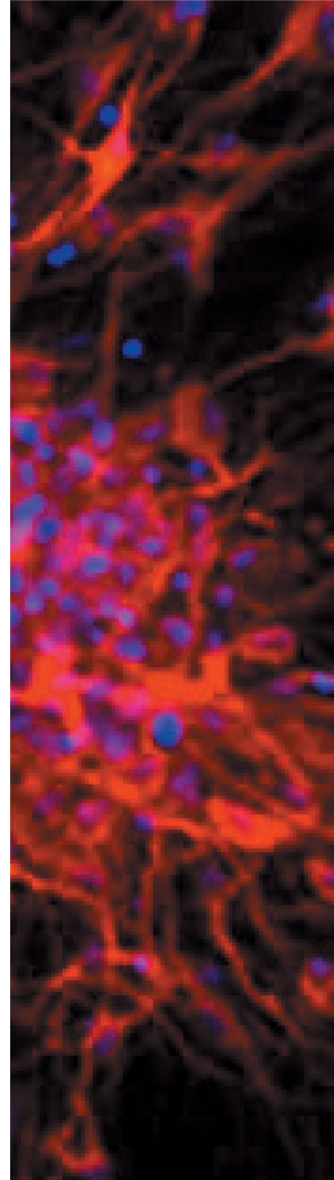
"Stem Cells in a Bottle"



First to transplant
human neural stem cells
into all three regions of the CNS:
brain, spinal cord and eye

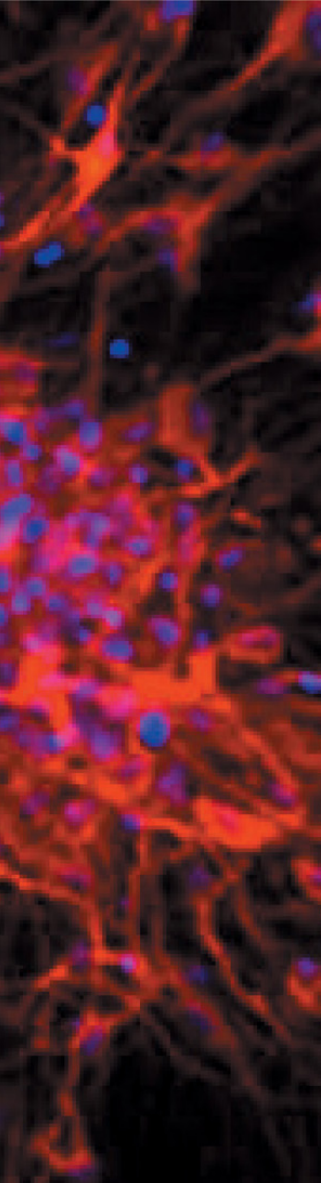


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STEM CELLS

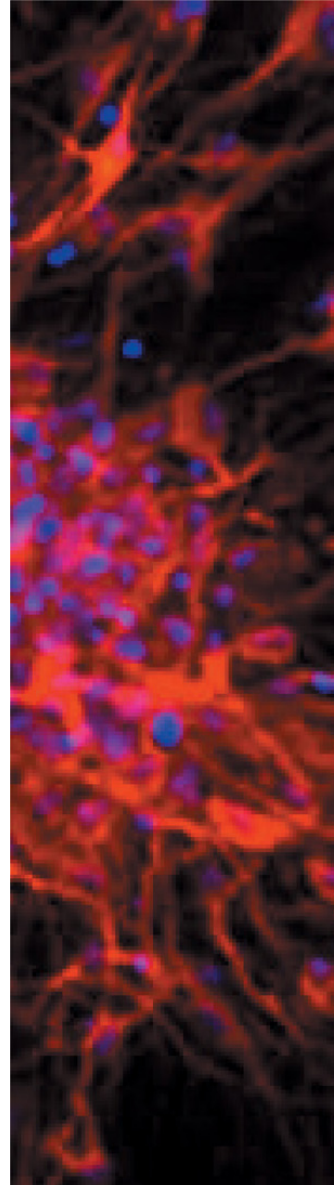
- 2006: **First ever** FDA-authorized clinical trial of human neural stem cells — First Batten's patient (PI & PI/II OHSU), 6 subjects
- 2009: **First** MRI evidence of *de novo* myelin in a human patient suffering from a myelination disorder — PMD (PI/II UCSF), 4 subjects
- 2011: **First** to demonstrate clinical evidence of efficacy for stem cells in chronic thoracic SCI — PI/II Thoracic Spinal Cord Injury: Switzerland and Canada, 12 subjects
- 2012: **First** FDA-authorized clinical trial of human neural stem cells in the eye — PI/II Dry-AMD (U.S.), 16 subjects
- 2015: Initiated PII POC in Cervical SCI, Goal: 42 subjects
- 2015: Initiated PII POC in Dry AMD, Goal: 60 subjects



STEM CELLS

A lot went right...

- ▶ Demonstrated engraftment, migration and enduring cell presence for years (brain tissue autopsy)
- ▶ Demonstrated cells and surgical procedures well tolerated
- ▶ Evidence of improved sensory and motor function in SCI
- ▶ Evidence of reduced rate of macular degeneration in dry AMD
- ▶ Improved hippocampal synapse formation and density in animal models relevant to Alzheimer's (CIRM)



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Research Initiatives



Batten Disease in the News BDSRA

Rare Disease Awareness / Advocacy
NORD - Awards Tony with Portrait of
Courage
Rare Disease Day
Global Genes

Spotlight On Batten's Disease (CIRM) at
Stanford (08/13/08)

Stem Cells, Inc. - Long Term Follow up
Study Results (10/21/13)

BioMarin releases promising clinical trial
results (1/12/15)

In the News

**FDA Approves first treatment for
Batten Disease - 4/27/17**

[http://investors.bmrn.com/
releasedetail.cfm?ReleaseID=890846](http://investors.bmrn.com/releasedetail.cfm?ReleaseID=890846)

For two years we searched for a diagnosis. We went to see every specialist imaginable. Drew gradually lost his speech, use of his hands and the ability to walk and eat. It is devastating to watch your child lose skills and not be able to get answers. His will and determination have not wavered. Every day is a struggle, but he continues to smile. He has gone from a child who once ran, jumped and played to a child needing constant care.

On January 30, 2007 we received the devastating news that Drew has Late Infantile Neuronal Ceroid Lipofuscinoses (LINCL), more commonly known as Batten Disease. Batten Disease is a fatal degenerative neurologic disease that leaves children blind and bedridden with a life expectancy of 8-12 years. Those with Batten's disease are unable to produce an enzyme needed to clear toxins from the brain. Without it, permanent brain damage occurs that affects the child's ability to talk, walk, see and even eat. Its onset usually occurs between the ages of 2 and 4 years.

Immediately after diagnosis, we focused our energy on finding a cure. Doernbecher Children's Hospital in Portland, Oregon hosted a clinical trial for children with Batten's Disease. On July 31st, 2007 Drew had surgery to implant neural stem cells into his brain in the hopes they will produce the enzyme his brain is lacking. He recovered quickly and the doctors are pleased with his progress. He is very alert and aware. This trial provides hope for Drew. It is unknown how the stem cells will work, yet we are extremely hopeful.



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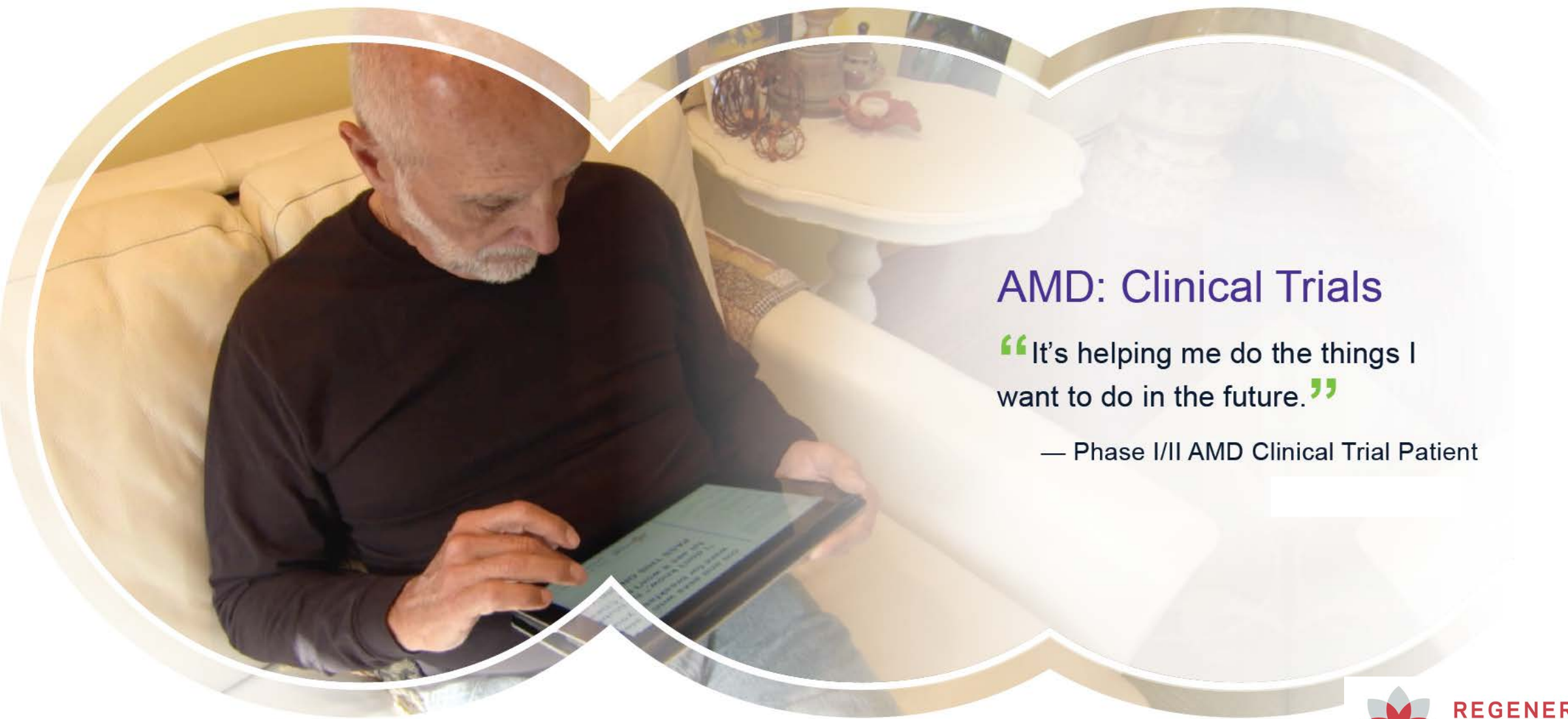
SCI: Clinical Trials

“Almost immediately after the transplant, I had gained some sensation back in my right foot.”

— Phase I/II SCI Clinical Trial Patient



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AMD: Clinical Trials

“It’s helping me do the things I want to do in the future.”

— Phase I/II AMD Clinical Trial Patient



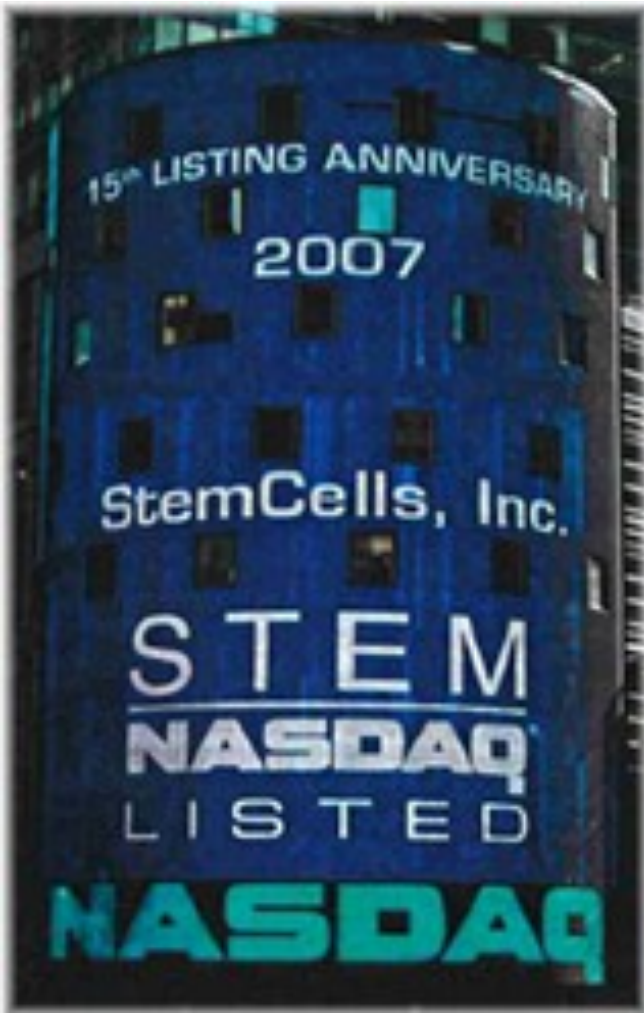
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STEM CELLS

But there were challenges...

- ▶ PI trials: most severely impacted
- ▶ Efficacy handicapped
- ▶ One center, one surgeon
- ▶ Sequential enrollment and rolling safety checks
- ▶ Adaptive PI Study Design in Thoracic SCI in Switzerland/Canada
- ▶ Phase II CERVICAL SCI in U.S.
- ▶ Four PI/II studies/37 subjects/eight years

STEMCELLS



After \$300M raised...

- ▶ 2015: “Investor Fatigue” set in by the start of Phase II
- ▶ May 2016: “wind-up” and sale of assets announced

The Fall from Grace

StemCells, Inc. was not alone

The Pioneers: Regulatory Challenges

Old model didn't fit

- ▶ FDA's drug development paradigm applied to cell therapy
- ▶ FDA staffers lacked expertise in cell biology
- ▶ Discovery to IND filing —
Stem cell treatments: 8 years (*vs. Pharma/BioTech drugs: 3.2 years*)

"Regulatory framework for the development of human cells and tissues....has been in place for 15 years, without a single stem cell product being approved."

— CIRM Strategic Plan, 2016 and beyond

Social, Political, Religious Challenges

Dark cloud over entire field

- ▶ August 2001 Bush Administration's ban on use of Federal Funds
- ▶ NIH funding dried up
- ▶ "Chinese walls" in labs
- ▶ R&D involving embryonic or fetal tissue severely impacted
- ▶ Patchwork of state laws banning research; criminal offense in some
- ▶ Investigators & institutions backed away
- ▶ IRBs very skittish and slow
- ▶ Young scientists, technicians and engineers shied away

“Valley-of-Death”: Trials & Tribulations

No cell therapy product has made it!!

- ▶ Development runways too long/costly
- ▶ Labor-intensive pilot-scale manufacturing for PI and PII
- ▶ Costly to scale-up facilities and systems suitable for pivotal trials
- ▶ Numerous clinical setbacks/re-starts
- ▶ Serial dilutive and costly financings and declining market “caps”
- ▶ Serial reverse stock splits further alienated the market
- ▶ Attracted traders, not “investors” > investor “fatigue”

The Field Today

Shifting Paradigms

New Ideas & Innovations

Transformative scientific & technological advances

- ▶ Confluence: cell, gene & immunotherapy
- ▶ Moving away from unmodified allogeneic stem cell platforms
- ▶ Autologous, patient-specific, gene-modified cells in cancer
- ▶ Immunotherapy offers great potential for much broader applications
- ▶ iPSC platform offers non-controversial source for cells

Renewed Support & Fresh Investment

- ▶ 21st Century Cures Act
- ▶ Philanthropy and growth of academic stem cell institutes and RM centers
- ▶ “Smart Money” investing



Concerns Still Remain...

- ▶ Immunogenicity & tumorigenicity
- ▶ Neurotoxicity
- ▶ Manufacturing costs & complex logistics
- ▶ Cost of treatment and reimbursement

...But “Some Day” is Finally Here

- ▶ 750 RM companies worldwide
 - ▶ 271 cell and gene therapies in PI/II
 - ▶ 66 products in PIII
-

First CAR-T therapy approved 8.30.2017



The Future

Think Globally. Act Locally.

Follow the Money

- ▶ Athersys (MAPCs): PII/PIII — \$185M USD
- ▶ Mesoblast (MLCs): PIII — \$689M USD
- ▶ Cynata (MCAs) — \$53M AUS
- ▶ Asterias (hESCs) — \$163M USD
- ▶ ReNeuron — \$58M US
- ▶ Sanbio PII — ¥530M JPY
- ▶ Vericel — \$113M USD

Immuno-Oncology

- ▶ Juno — \$3.8B USD
 - ▶ Kite/Gilead — \$10.0B USD
 - ▶ Bluebird — \$4.8B USD
 - ▶ Novartis — \$193.8B USD
- Wonderful irony:
patient-specific business model!

Japan On the Move

November 2014, established expedited pathway to approval and commercialization for cell therapy products

- ▶ Catalyst: Yamanaka's 2012 Nobel Prize for iPSC work
- ▶ Bold and disruptive move:
 - Already accelerating cell therapy treatments and cures
 - Creates competitive advantage for Japanese companies
 - Creates incentive for foreign companies to partner with them
 - Japanese Pharma lured into the field
 - Eye on the prize: US Market

Japan On the Move

2014

- ▶ Dainippon-Sumitomo — JV with Riken and Healios
- ▶ SanBio, Inc. — JV with Dainippon Sumitomo for chronic stroke in U.S & Canada

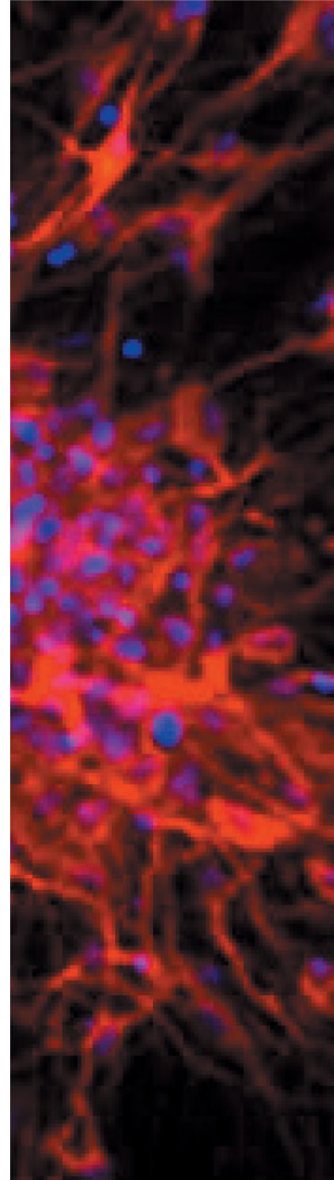
2015

- ▶ CCI acquired by Fujifilm for \$307M
- ▶ Ocata (ACT) acquired by Astellas for \$379M

2016

- ▶ Mesoblast/JCR Pharma gained full approval for GvHD for MScs; now seeking conditional approval for heart disease
- ▶ Hitachi acquired 19.1% stake in PCT (Caladrius*)
- ▶ Universal Cells & Healios formed partnership
- ▶ Athersys/Healios PII stroke trial approved by PMDA
- ▶ Fujifilm created new RM subsidiary (CDI and Japan Tissue Engineering)

* Acquired PCT outright in March 2017 for \$75M cash.



China Not Far Behind

Moratorium on cell therapy trials still in place, yet:

- ▶ Guidance documents slowly emerging
- ▶ Intends to be competitive with Japan
- ▶ Investing in the science: “twinning” of companies and academia
- ▶ Acquiring assets and “know how”:
 - Boyalife >>> Cesca (Kool)
 - BOCO >>> StemCells (STEM)
 - Sanpower >>> Dendreon/Valeant

Will The Next Generation Fare Better?

- ▶ **iPSC Technology:** Japan could be a game changer!
 - **Key players:** Fujifilm, Sumitomo, Hitachi, JCR Pharma, Astellas, Healios
- ▶ **HSCs(+/-HLA matching):** Reboot immune system in leukemia, lymphoma, autoimmune disorders; CSFs: non-toxic conditioning regimens, improved BM harvesting and cell expansion
 - **Key Players:** Magenta and Nohla
- ▶ **Immunotherapy solves I/S issue:** Adds gene insertion step and chemotherapy conditioning regimens
 - **Key players:** Novartis, Kite/Gilead, Juno, Bluebird.
- ▶ **CSFs:** Manufacturing costs, logistics, pricing
 - **Key players:** Quintiles-IMS, GE Healthcare/Vitruvian Networks

Opportunities for Academia

Success creates critical mass & attracts a greater talent pool to the institution and local community

- ▶ Ramp up investment in translation; establish translation centers
- ▶ Lobby for more State investment (CIRM, Maryland SCRF, FIRM, RMM, etc.)
- ▶ Engage local philanthropists
- ▶ Educate local community
- ▶ Partner with:
 - Local VCs (WFIRM)
 - Local and regional Pharma, BioTech, MedTech
 - Major healthcare providers

Thank You
