in HD Research

Stem Cells and DNA Repair

2018 HDSA Annual Convention
June 7-9, 2018
Los Angeles, CA

Huntington's Disease Society of America

HD: A Family Disease

HD: A Family Disease

ca 1920

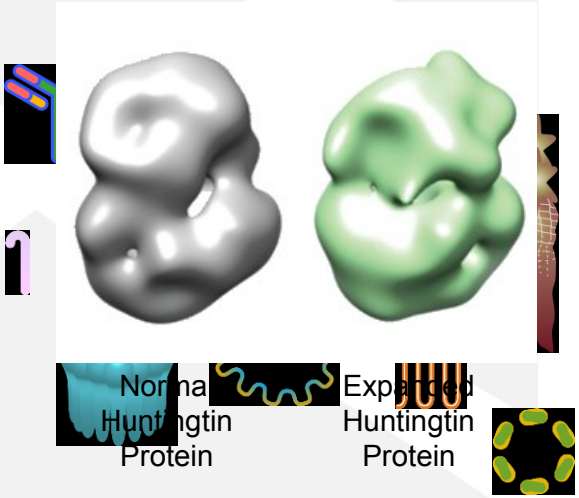
2007

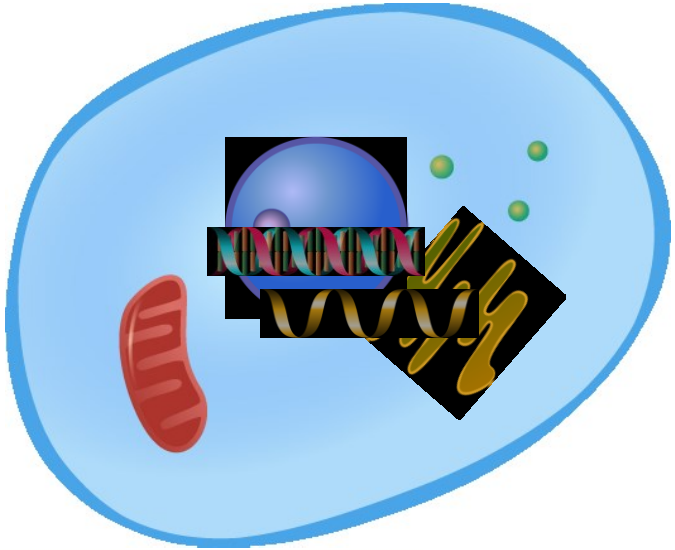
1980

Joining the HD Research Community

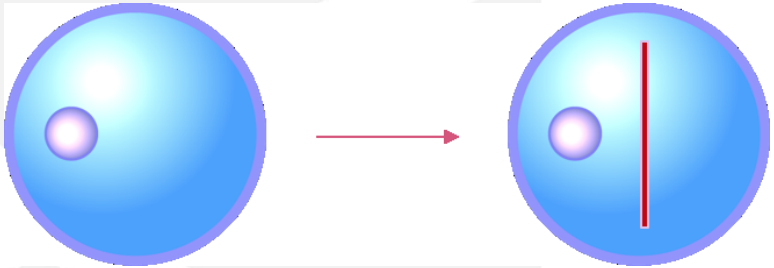
- What is the normal function of the **huntingtin protein**?
- **What is going wrong** when the huntingtin protein is expanded?

From Gene to Protein

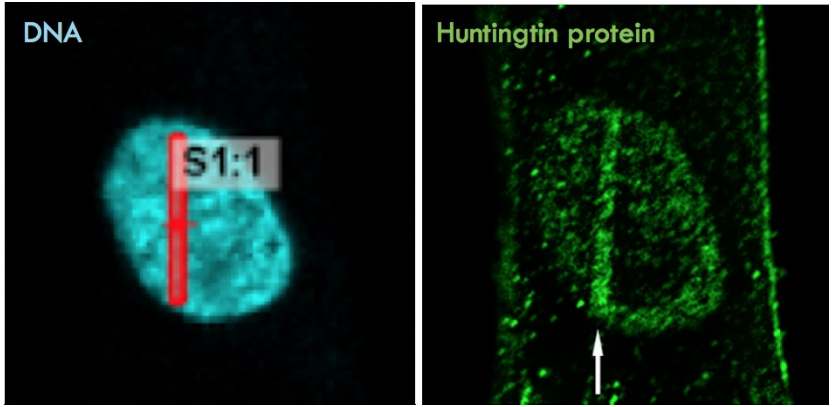




Huntingtin moves to damaged DNA



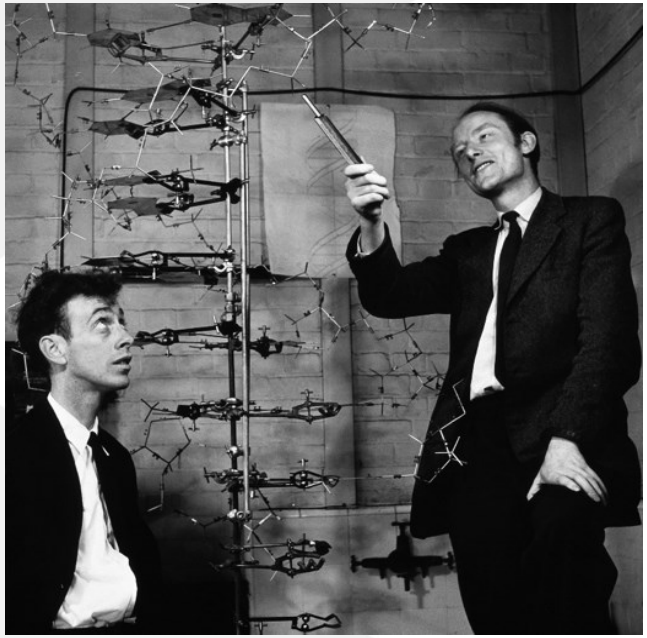
High power laser stripe damages DNA



What is huntingtin's role in DNA repair?

Is this important in HD?

DNA: Kind of a Big Deal



Francis Crick and James Watson solved the structure of DNA in 1953

DNA makes up our genes

Genes are the blueprints for proteins

Proteins do all of the work in the cell

➔ Break down over time

BLUEPRINTS MUST BE PROTECTED!

➔ Cancer

➔ Neurodegenerative diseases

A Major Clue

42 CAG repeats

42 CAG repeats

Cell

Volume 162, Issue 3, 30 July 2015, Pages 516-526

CellPress

Article

Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease

Genetic Modifiers of Huntington's Disease (GeM-HD) Consortium

GENOME WIDE ASSOCIATION STUDY
implicates
"DNA handling and repair mechanisms"

DNA Repair and CAG Repeat Diseases

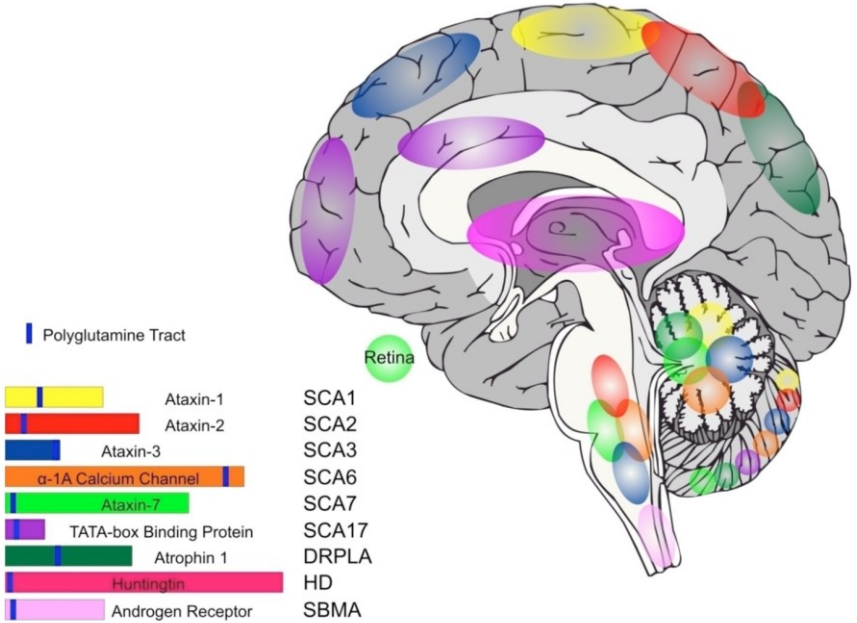
DNA repair genes are **genetic modifiers for other** neurodegenerative diseases caused by CAG expansion

RESEARCH ARTICLE

DNA Repair Pathways Underlie a Common Genetic Mechanism Modulating Onset in Polyglutamine Diseases

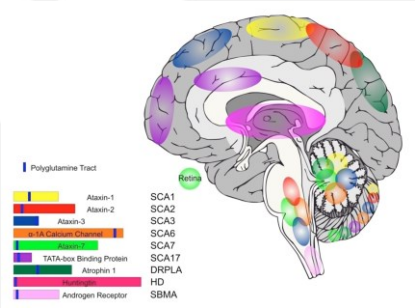
Conceição Bettencourt, PhD,[1,2] Davina Hensman-Moss, MD,[3] Michael Flower, MD,[3] Sarah Wiethoff, MD,[1,4] Alexis Brice, MD,[5,6] Cyril Goizet, MD,[7,8] Giovanni Stevanin, PhD,[5,9] Georgios Koutsis, MD,[10] Georgia Karadima, MD,[10] Marios Panas, MD,[10] Petra Yescas-Gómez, MD,[11] Lizbeth Esmeralda García-Velázquez, MSc,[11] María Elisa Alonso-Vilatela, MD,[11] Manuela Lima, PhD,[12,13,14] Mafalda Raposo, BSc,[12,13,14] Bryan Traynor, MD,[15] Mary Sweeney, BSc,[16] Nicholas Wood, MD,[1] Paola Giunti, MD,[1,17] The SPATAX Network, Alexandra Durr, MD,[5,6] Peter Holmans, PhD,[18] Henry Houlden, MD,[1,16] Sarah J. Tabrizi, MD,[3] and Lesley Jones, PhD[18]

ANN NEUROL 2016;79:983–990



Factor 1: “Somatic” Expansion

Most cells



DNA repair gone wrong

Brain cells

Factor 1: “Somatic Expansion

DNA repair genes

acting as

genetic modifiers

by affecting

somatic expansion

Factor 2: CAG Repeat Genes *are* DNA Repair Genes

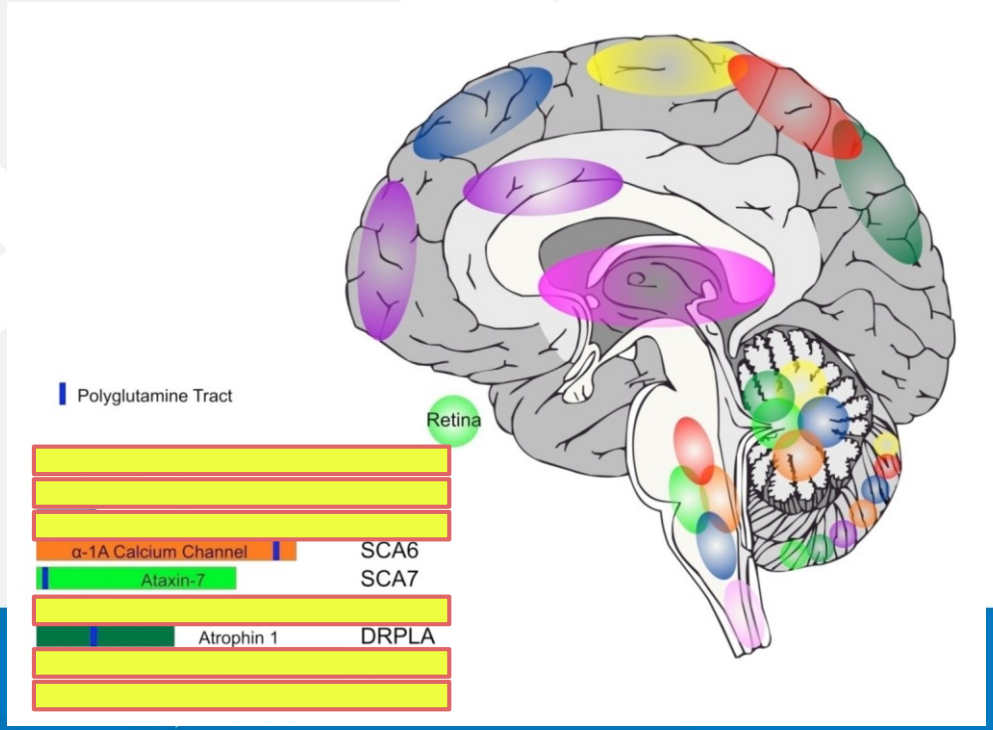
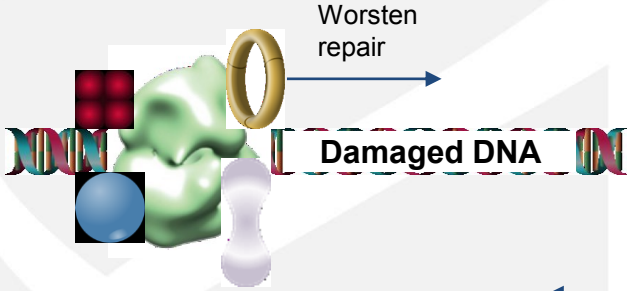


Table 2. Functions of proteins encoded by genes causing CAG repeat diseases, and their links to DNA damage and repair

Disease	Gene	Wild-type protein functions[a]	Expression[b]	Links to DNA damage/repair	References
DRPLA	*ATN1*	Transcriptional co-repressor through	Ubiquitous	None known	
SCA6	*CACNA1A*	Voltage-gated calcium channel abundant in cerebellar Purkinje cells; product of alternative translation functions as a transcription factor involved in neuronal differentiation	Predominantly neuronal	None known	Du et al., 2013
SCA7	*ATXN7*	Component of STAGA chromatin remodelling complex that regulates transcription	Ubiquitous	None known	Wang and Dent, 2014
SCA12	*PPP2R2B*	Regulatory subunit B of PP2A involved in transcriptional regulation, cell growth and division	Predominantly neuronal	None known	Cohen and Margolis, 2016

Factor 2: CAG Repeat Genes *are* DNA Repair Genes



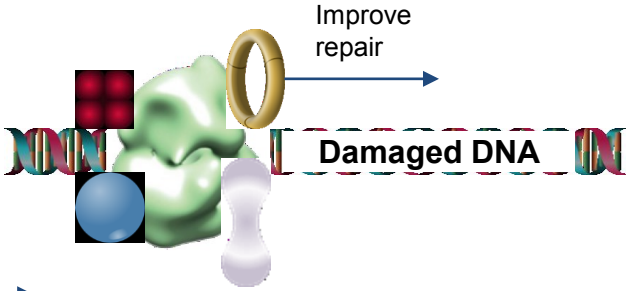
DNA repair genes

acting as

genetic modifiers

by affecting the

function of the expanded protein



HD and DNA Repair: Connections

- Links between DNA repair genes and other neurological disorders
  - *Cockayne Syndrome*
  - *Xeroderma Pigmentosum*
  - *Trichothiodystrophy*
  - *Ataxia with Occulomotor Apraxia-1*
  - *Spinocerebellar Ataxia with Axonal Neuropathy*
  - *Ataxia Telangiectasia*
  - *A-T Like Disease*
  - *ATR-Seckel Syndrome*
  - *Nijmegen Breakage Syndrome*

- Large human genetic studies in HD and SCAs
  - *Identification of Genetic Factors that Modify Clinical Onset of Huntington's Disease, 2015*
  - *DNA repair pathways underlie a common genetic mechanism modulating onset in polyglutamine diseases, 2016*
  - *Identification of genetic variants associated with Huntington's disease progression: a genome-wide association study, 2017*

HD and DNA Repair: Connections

➔ Somatic expansion involves DNA repair

➔ CAG repeat genes have roles in DNA repair

HD and DNA Repair: Connections

➔ Damaged DNA in HD models and samples

Acevedo-Torres, K., et al., *Mitochondrial DNA damage is a hallmark of chemically induced and the R6/2 transgenic model of Huntington's disease.* DNA Repair (Amst), 2009. 8(1): p. 126-36.

Bogdanov, M.B., et al., *Increased oxidative damage to DNA in a transgenic mouse model of Huntington's disease.* J Neurochem, 2001. 79(6): p. 1246-9.

Browne, S.E., et al., *Oxidative damage and metabolic dysfunction in Huntington's disease: selective vulnerability of the basal ganglia.* Ann Neurol, 1997. 41(5): p. 646-53.

Chen, C.M., et al., *Increased oxidative damage and mitochondrial abnormalities in the peripheral blood of Huntington's disease patients.* Biochem Biophys Res Commun, 2007. 359(2): p. 335-40.

Hersch, S.M., et al., *Creatine in Huntington disease is safe, tolerable, bioavailable in brain and reduces serum 8OH2'dG.* Neurology, 2006. 66(2): p. 250-2.

Kovtun, I.V., et al., *OGG1 initiates age-dependent CAG trinucleotide expansion in somatic cells.* Nature, 2007. 447(7143): p. 447-52.

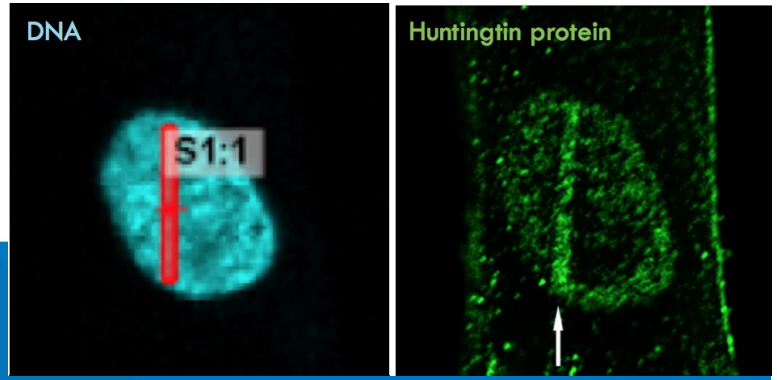
Long, J.D., et al., *8OHdG as a marker for Huntington disease progression.* Neurobiol Dis, 2012. 46(3): p. 625-34.

Siddiqui, A., et al., *Mitochondrial DNA damage is associated with reduced mitochondrial bioenergetics in Huntington's disease.* Free Radic Biol Med, 2012. 53(7): p. 1478-88.

Stack, C., et al., *Triterpenoids CDDO-ethyl amide and CDDO-trifluoroethyl amide improve the behavioral phenotype and brain pathology in a transgenic mouse model of Huntington's disease.* Free Radic Biol Med, 2010. 49(2): p. 147-58.

Enokido, Y., et al., *Mutant huntingtin impairs Ku70-mediated DNA repair.* J Cell Biol, 2010. 189(3): p. 425-43.

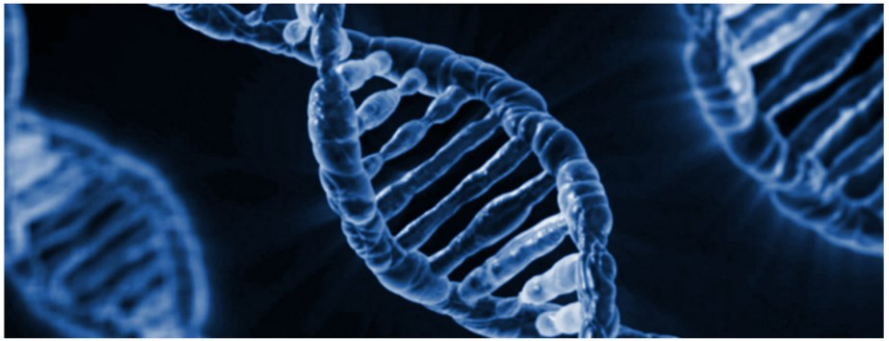
➔ Huntingtin moves to sites of damage and scaffolds DNA repair proteins



How can we use this knowledge?

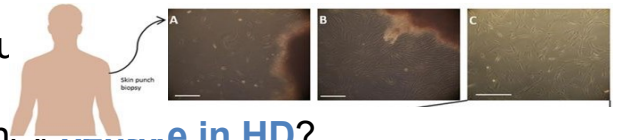
How can we use this knowledge?

Berman/Topper HD Career Development Fellowship



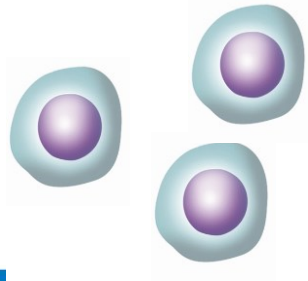
Enroll-HD

Finding hu



How do they behave in HD?

Can we fix them?



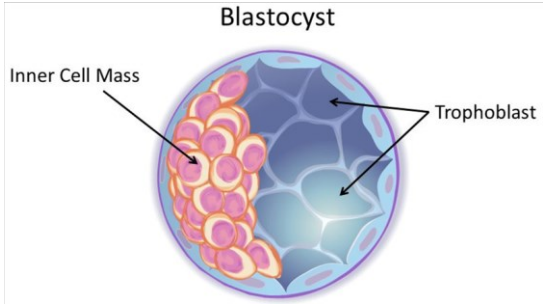
Various types of stem cell exist

What is a stem cell?

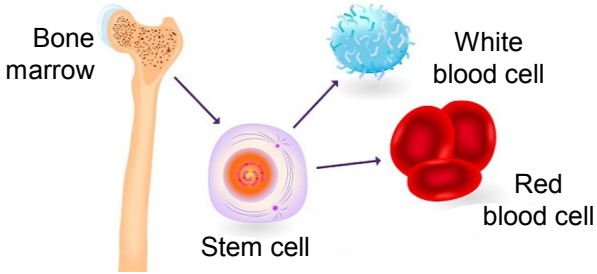
A single cell that can

Image prepared by Catherine Twomey for the National Academies,
Understanding Stem Cells: An Overview of the Science and Issues
from the National Academies, http://www.nationalacademies.org/stemcells.
Academic noncommercial use is permitted.

Embryonic



Adult

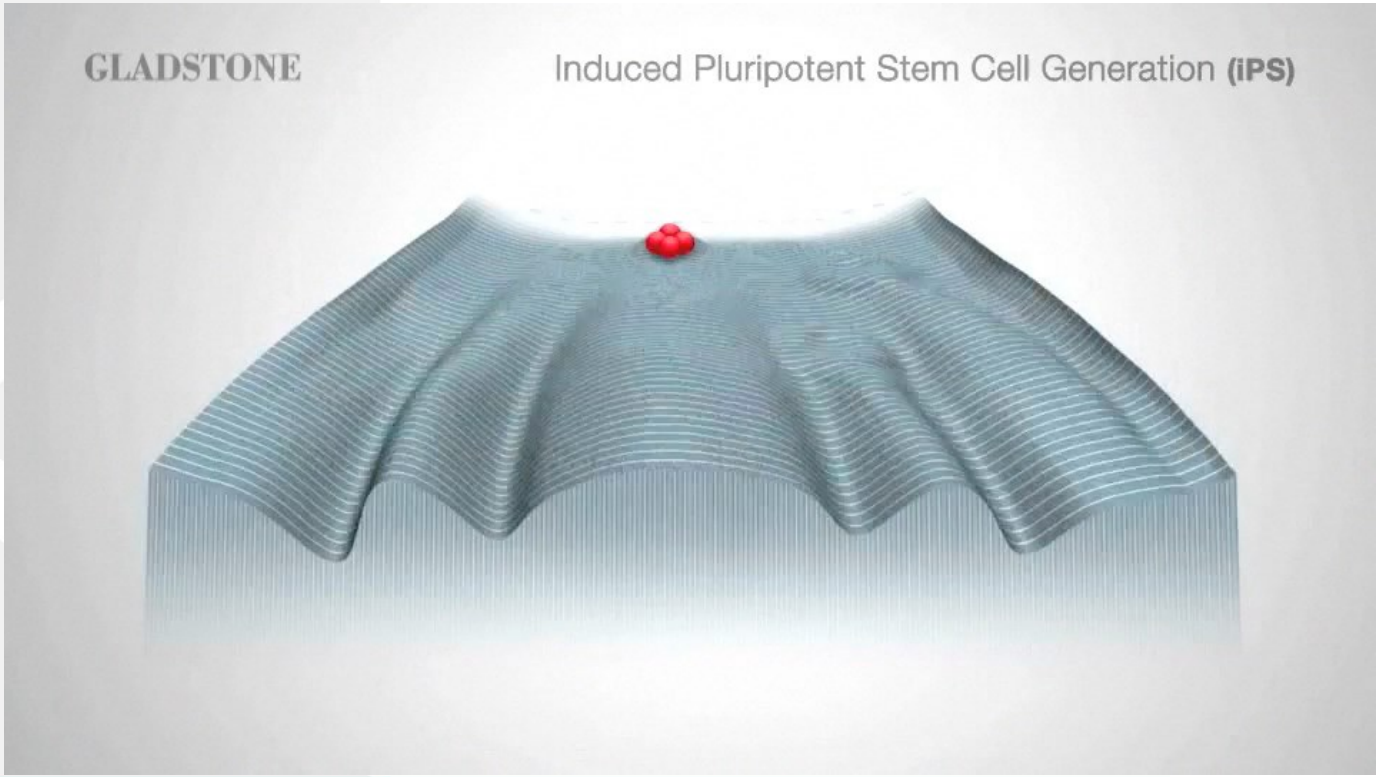


Induced pluripotent

Huntington's Disease Society of America

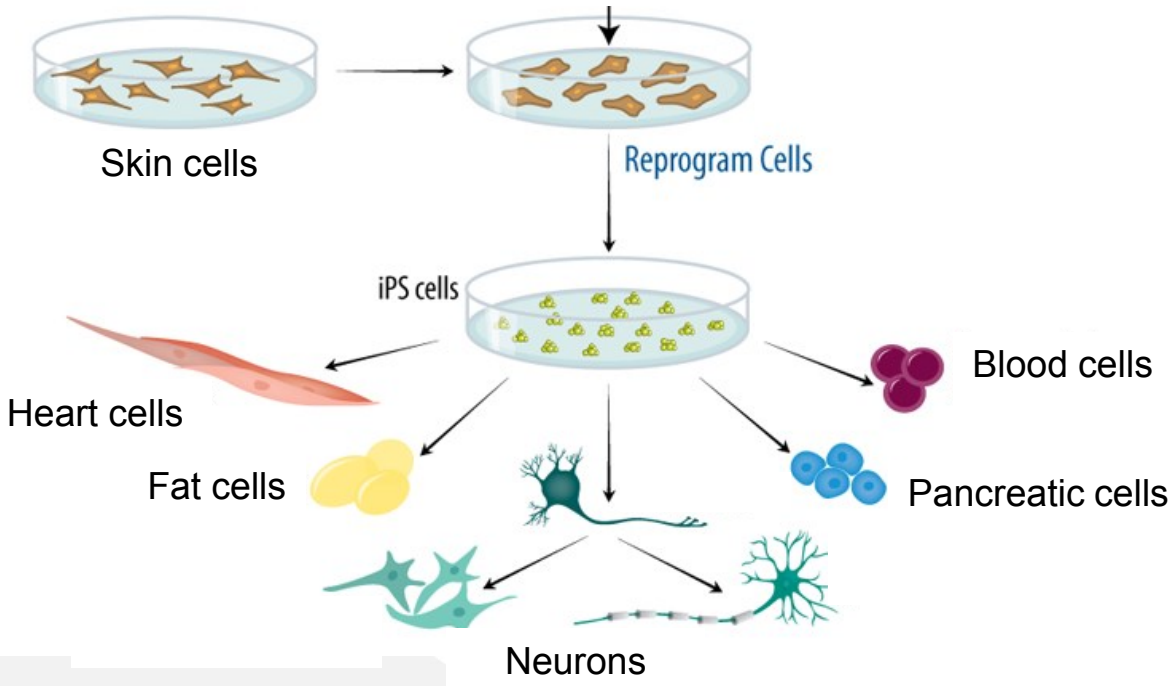
http://slideplayer.com/slide/5665981/
https://www.singularityweblog.com/stem-cells-ips-cells/
http://www.justscience.in/articles/potential-benefits-risks-involved-stem-cell-research/2017/12/09

Cell type can be controlled through cellular *de*differentiation

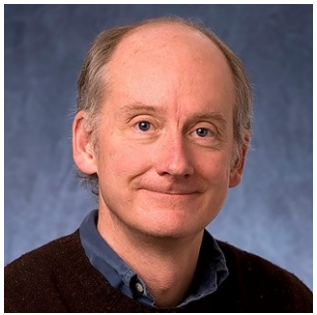


Courtesy of S. Finkbeiner

Reverse engineering skin cells



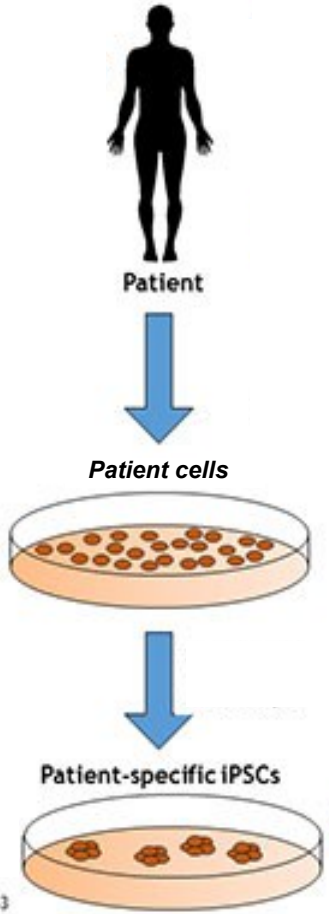
Shinya Yamanaka,
Kyoto University; UCSF



Jamie Thompson,
University of Wisconsin

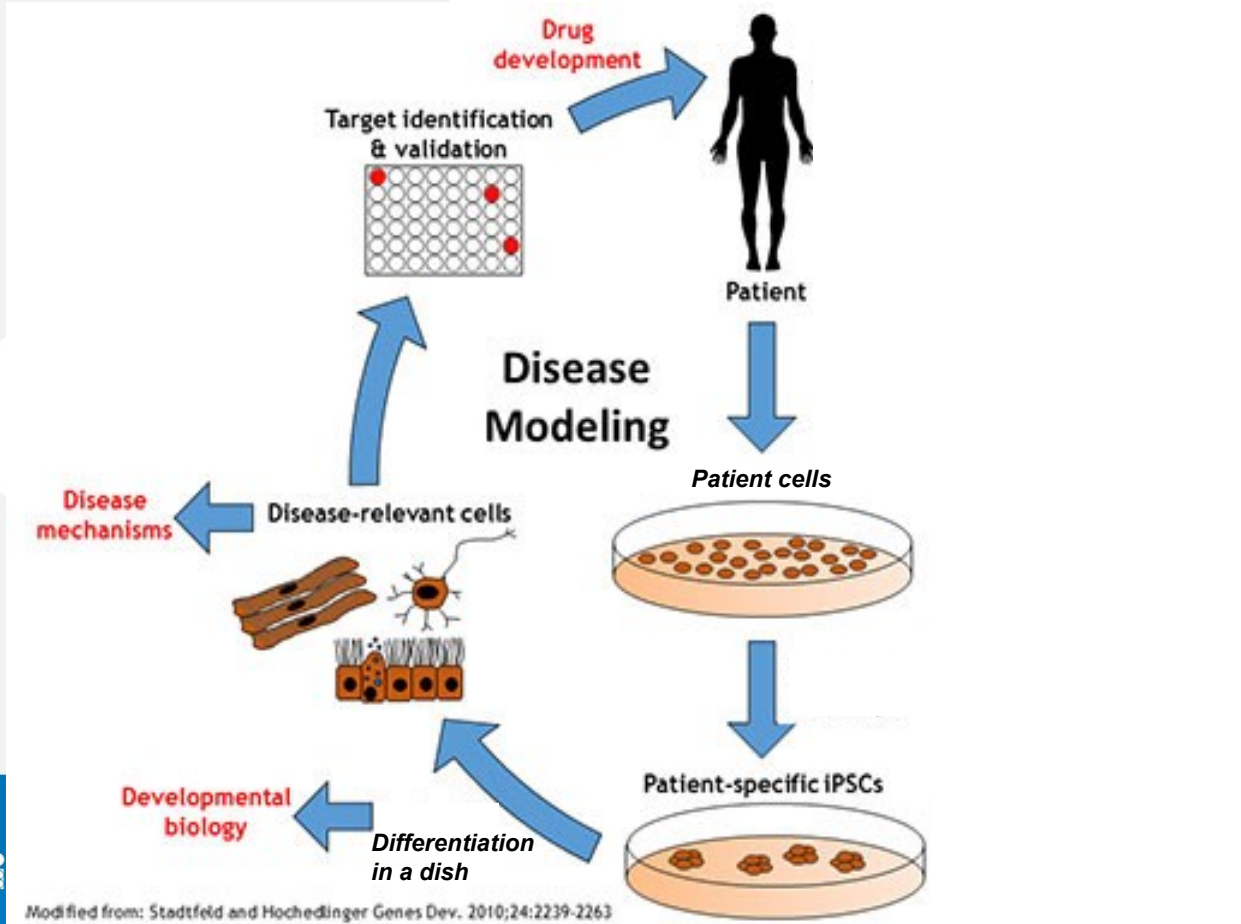
https://www.rndsystems.com/resources/articles/differentiation-potential-induced-pluripotent-stem-cells

Uses of iPSCs

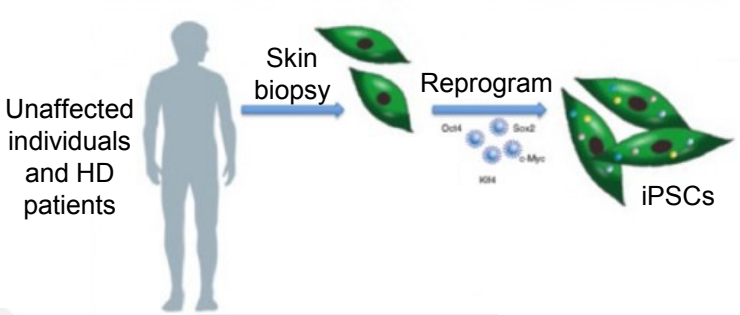


Modified from: Stadtfeld and Hochedlinger Genes Dev. 2010;24:2239-2263

Uses of iPSCs: Disease modeling



Stem cell advancements in HD research: HD iPSC Consortium

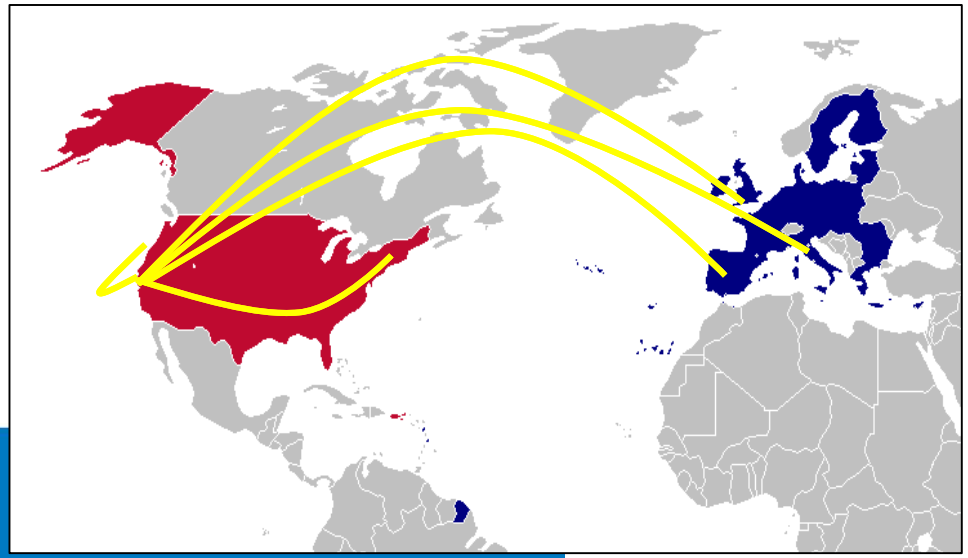


CAG length of available iPSC lines		
Control	*Adult onset*	*Juvenile onset*
18	43	60
20	46	66
21	50	71
28	53	77
33	57	109
		180

Mission of the HD iPSC Consortium:

1. Create a unique, patient-derived stem cell resource available for the HD research and industrial community

1. Combine international expertise to better understand HD and collaboratively tackle problems that would be difficult for a single lab to pursue



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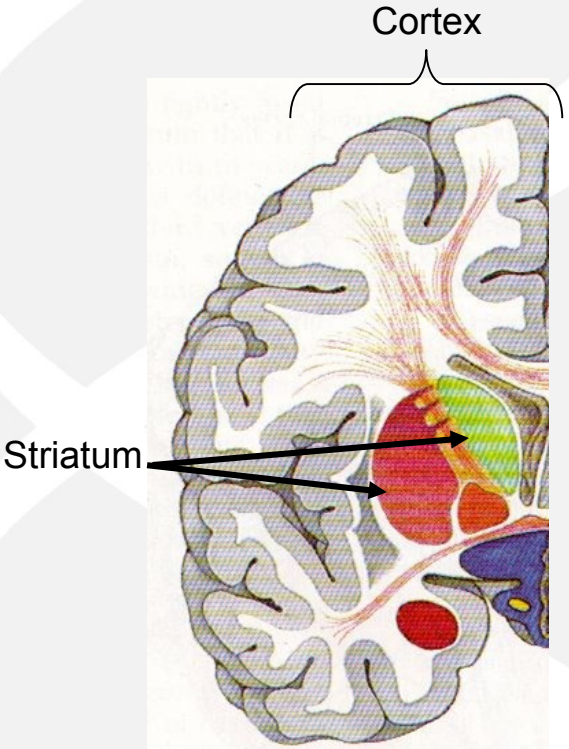
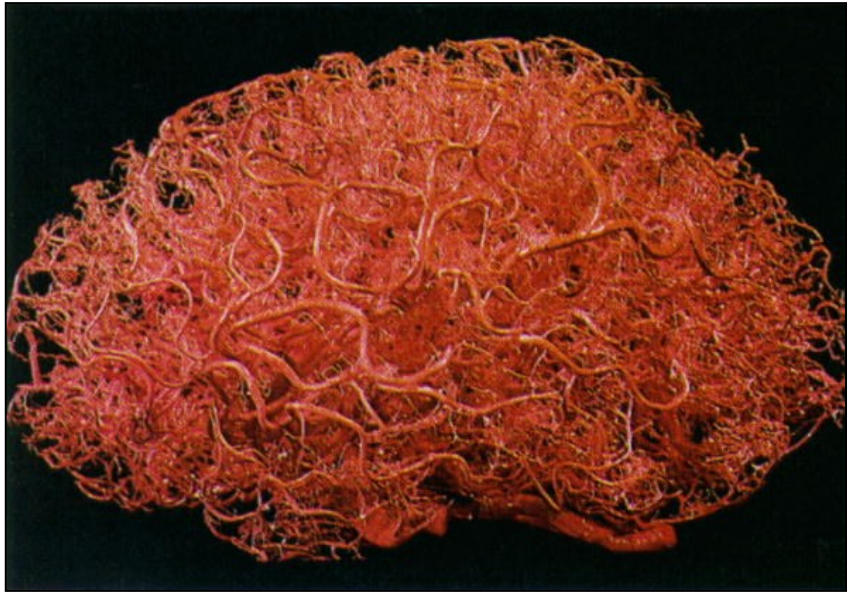
Disease modeling: Modeling HD-affected cell types

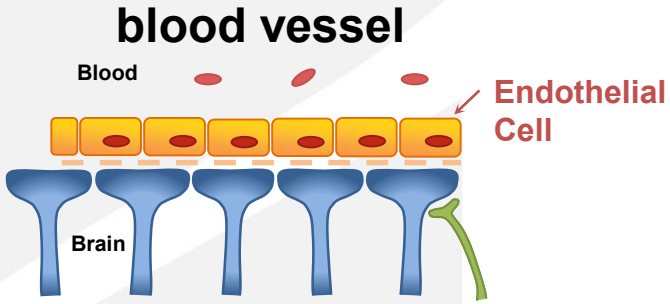


Sweeney, M. D., et al. (2015). *Journal of Cerebral Blood Flow & Metabolism*, *35*(7), 1055-1068.

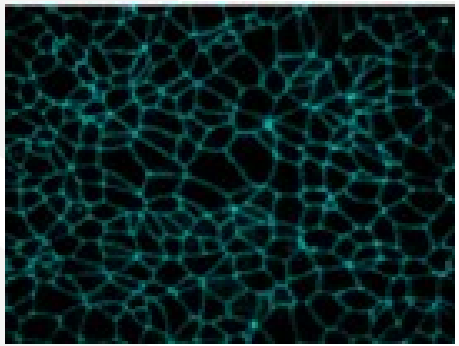


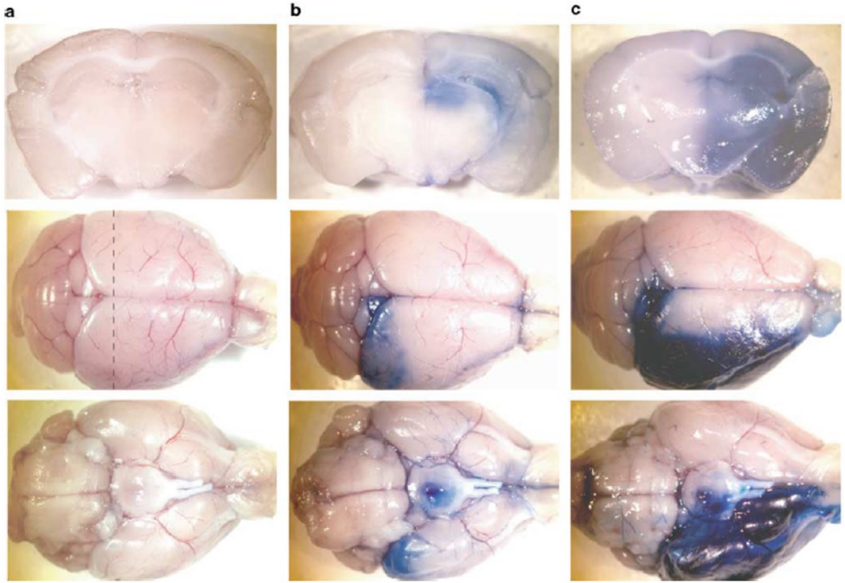
Zlokovic, Berislav; Apuzzo, Michael Neurosurgery. 43(4):877-878, October 1998.

Disease modeling: the HD BBB *in vitro*



Genes expressed & functional experiments





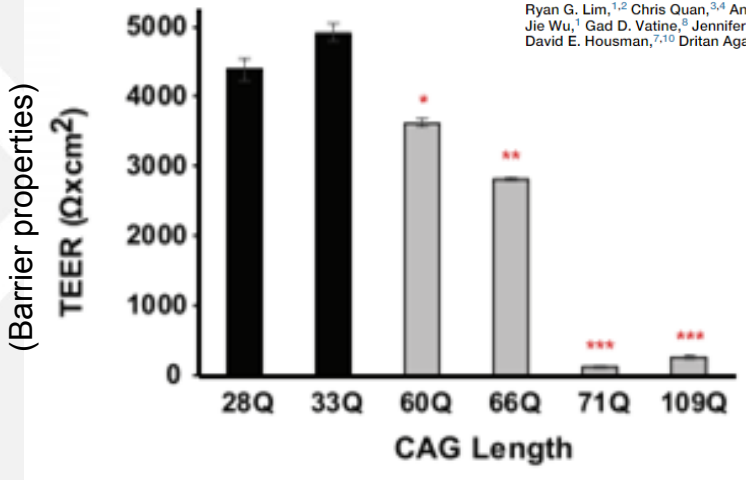
Liu R, Gene Ther. 2005;12(8):647–54.

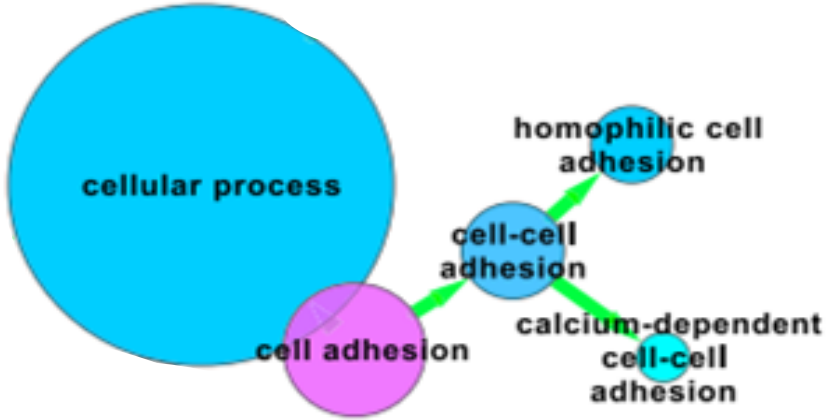
Disease modeling: BBB is altered in HD

Cell Reports
Article

Huntington's Disease iPSC-Derived Brain Microvascular Endothelial Cells Reveal WNT-Mediated Angiogenic and Blood-Brain Barrier Deficits

Ryan G. Lim,[1,2] Chris Quan,[3,4] Andrea M. Reyes-Ortiz,[1] Sarah E. Lutz,[5] Amanda J. Kedaigle,[6] Theresa A. Gipson,[7,10] Jie Wu,[1] Gad D. Vatine,[8] Jennifer Stocksdale,[2] Malcolm S. Casale,[9] Clive N. Svendsen,[8] Ernest Fraenkel,[11] David E. Housman,[7,10] Dritan Agalliu,[5,12,*] and Leslie M. Thompson[1,2,9,13,14,15,*]

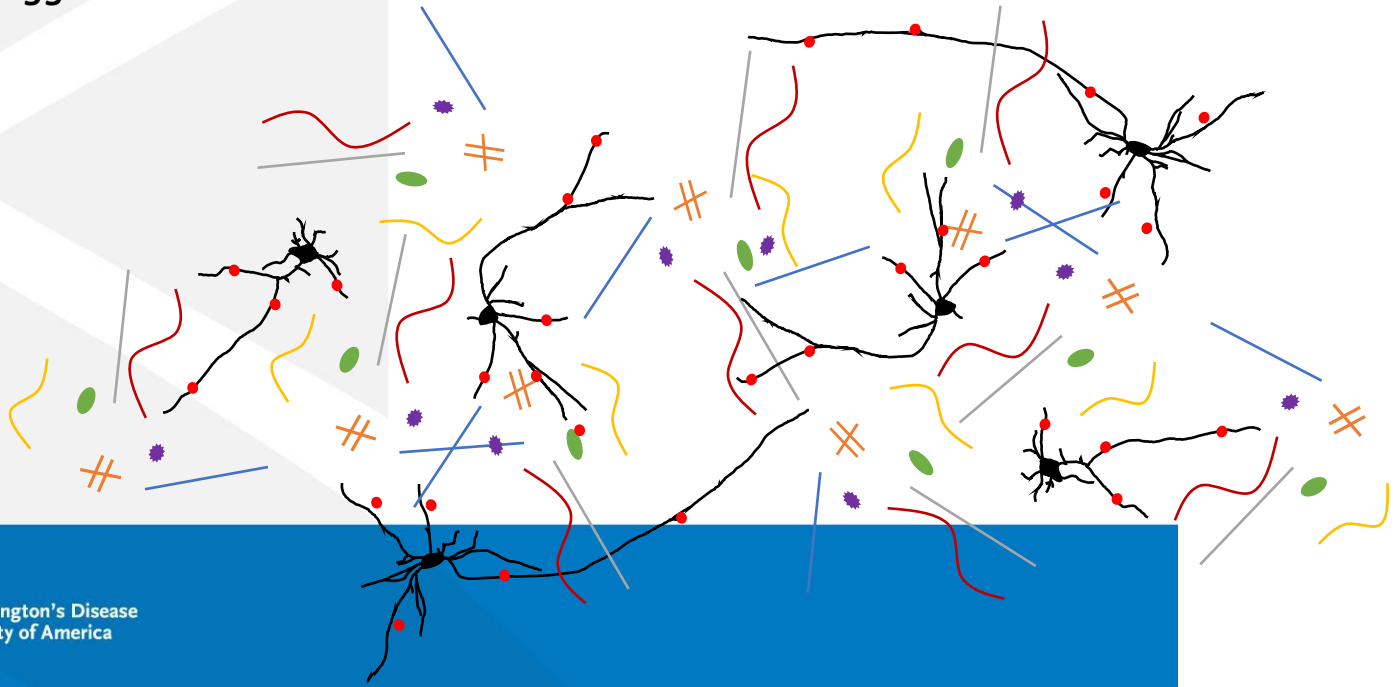




- Barrier properties decrease with Q length

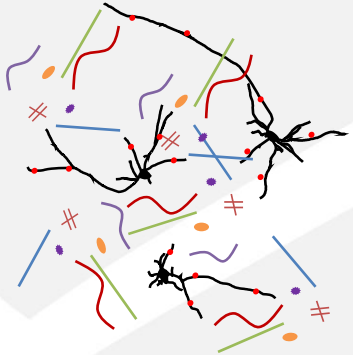
Disease modeling: the Extracellular Matrix (ECM)

- ECM = cellular infrastructure
- Cells contribute to, and are influenced by, the ECM
- The ECM is constantly being remodeled to guide cell attachment, cellular movement, and cell survival
- In the brain, the ECM coordinates synaptic activity and provides neuroprotection
- ***Highly druggable***

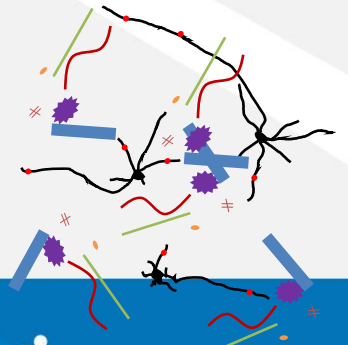


Overall goal: is the ECM therapeutic for HD?

Unaffected ECM environment



HD ECM environment



Investigate expression and function *of the ECM in HD cell models*

- What exactly are these changes?
- How are these changes affecting the cells?

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Drugs against ECM currently used to treat cancer

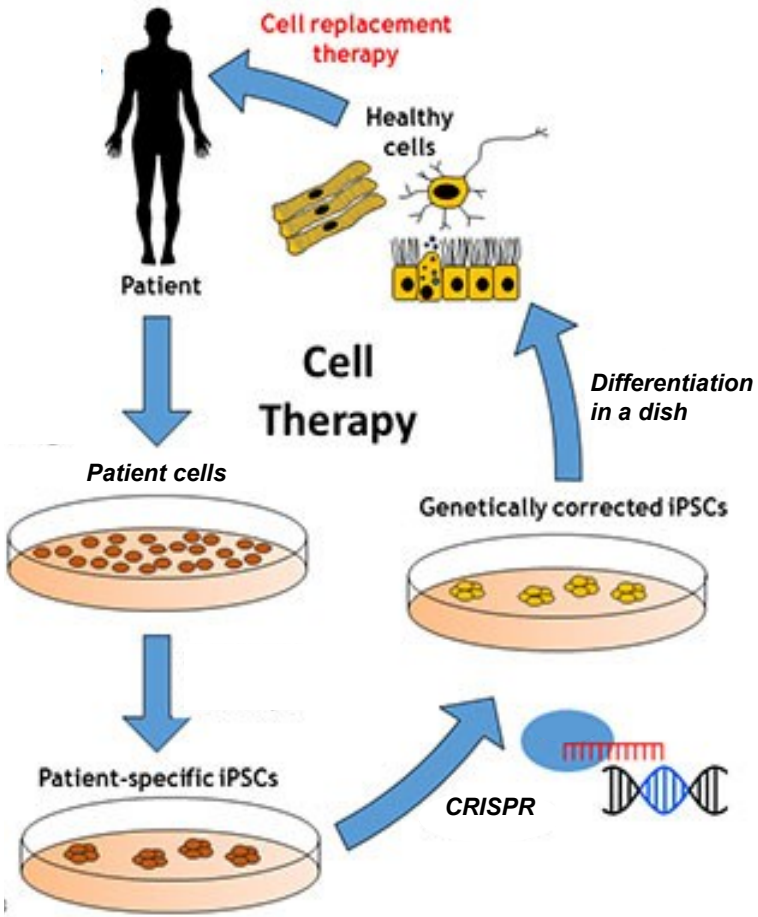
- Vectibix (panitumumab)

- FDA approved Sept. 27, 2006
- Approved by European agencies in 2007
- Approved by Canadian agencies in 2008

- Used to treat certain advanced, metastatic colorectal cancers
- Phase III trials for use in esophageal cancer, urothelial carcinoma, metastatic head and neck cancer, and liver metastasis in colorectal cancer

- Immune therapy
- Blocks ability of cell to communicate with the ECM

Uses of iPSCs: Cell therapies



Cell therapies: Fetal cell transplants into HD patients show variable results

Table 1 Description of the Published Studies

	Los Angeles	Créteil	Tampa	NEST-UK	London	Florence	MIG-HD German Extension
Articles	Kopyov et al. (1998), Keene et al. (2007, 2009), Philpott et al. (1997), and Ross et al. (1999)	Bachoud-Lévi et al. (2000b), Bachoud-Lévi et al. (2000a), Gaura et al. (2004), Bachoud-Lévi et al. (2006), Douaud et al. (2006), and Douaud et al. (2009)	Cisbani et al. (2013), Furtado et al. (2005), Hauser et al. (2002), and Cicchetti et al. (2014)	Rosser et al. (2002) and Barker et al. (2013b)	Reuter et al. (2008)	Gallina et al. (2008), Gallina et al. (2010, 2014), Mascalchi et al. (2014), Paganini et al. (2014), and Porfirio et al. (2015)	Capetian et al. (2009) and Lopez et al. (2014)
Grafted patients (*N*)	14	5	7	5	2	16	22
Available clinical data (*N*)	6	5	7	5	2	10	10
Autopsied cases (*N*)	3	–	4	–	–	1	1
Mean funct. capacity	FAS 17 ± 2.9	TFC 11.1	TFC 6.6	TFC 8	TFC 4 and 8	FAS 9.7 ± 7.3[a]	TFC > 9
Pre-/postop. follow-up	1–10 years	2–6 years	1–10 years	1–8 years	6 year ± 2.8	Median 4.3 years (2.8–5.1)	6–36 months
Nongrafted cohort (*N*)	–	22 External	–	12 randomized	6 external	16 external	–
Related adverse events	1 SDH 1 Bone infection 1 Overgrowth 2 Cysts	Thin SDH Graft necrosis Noncompliance immunosup.	3 SDH Brain infection Wound infection ↑Urea/creat.	Anemia 4 ↑ Urea/creat.	1 ↑ Urea/creat. 1 Meningoencephalitis?	1 SDH Overgrowths aberrant transplants 1 Tight abscess	1 Cyst
HLA antibodies	–	–	–	–	–	9/16	5/10
Durable benefit (*N*)	0	3(1)	0	0	1(1)	–	(1)

Abbreviations: creat, creatine; immunosup., *immunosuppressant;* N, *number of patients;* SDH, *subdural hematoma;* X, *transient improvement.*
[a]*Functional scores in this chapter ranged between 1 and 18 (using a reverse range 25 (normal) to 0 for the usual FAS).*

Stem cell research advancing rapidly, with the goal to use for transplantation

Huntington's Disease Society of America

Bachoud-Lévi, Anne-Catherine. *Progress in brain research*. Vol. 230. Elsevier, 2017. 227-261.

Cell therapies: CA Institute for Regenerative Medicine

Mission: to accelerate stem cell treatments to patients with unmet medical needs

43

Total clinical trials

703

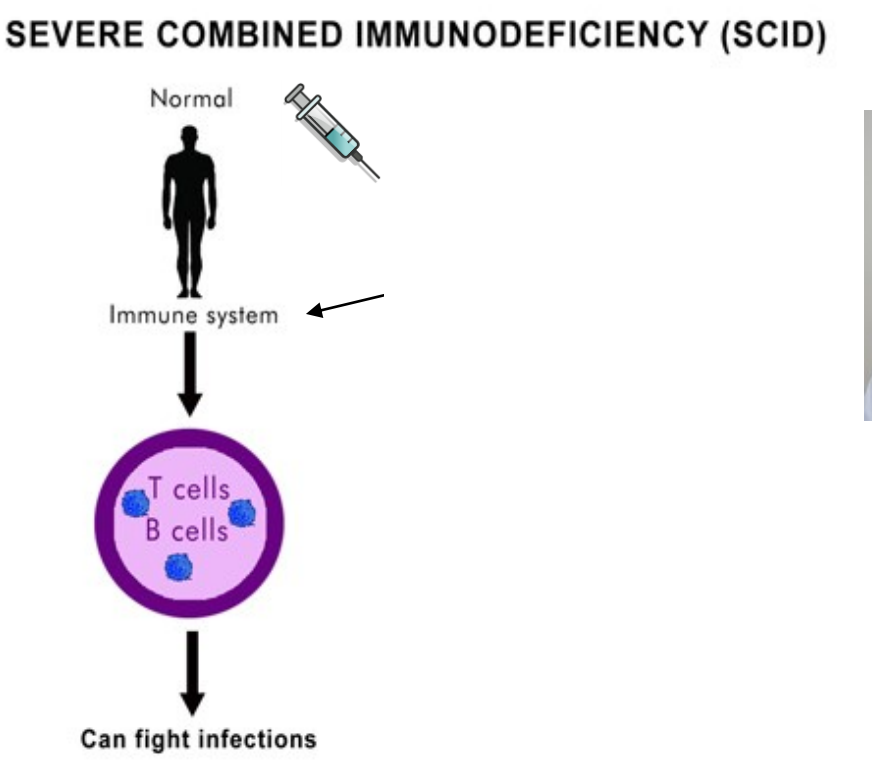
Total patients enrolled in CIRM-funded clinical trials

16

New clinical trials in 2017 addressing devastating diseases for which there currently are no known cures

These trials have the potential to change the landscape of medicine and the future of those who suffer from these debilitating conditions

Cell therapies: Curing immune diseases



Donald Kohn,
UCLA

David Vetter

Vacarro family

Huntington's Disease Society of America

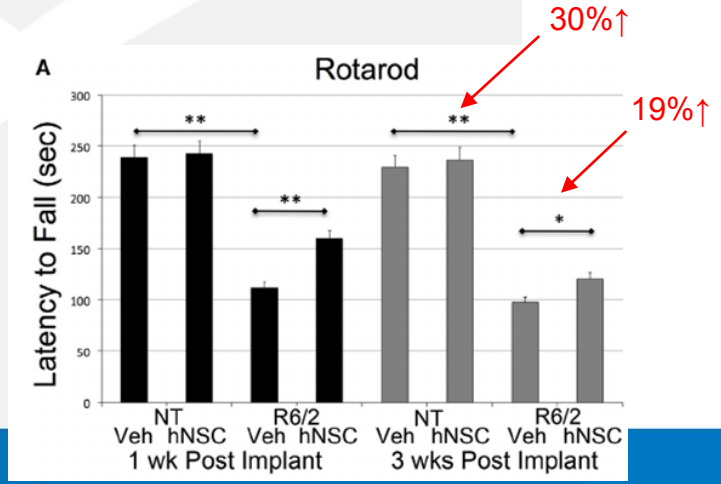
https://www.newbornscreening.info/Parents/otherdisorders/SCID.html

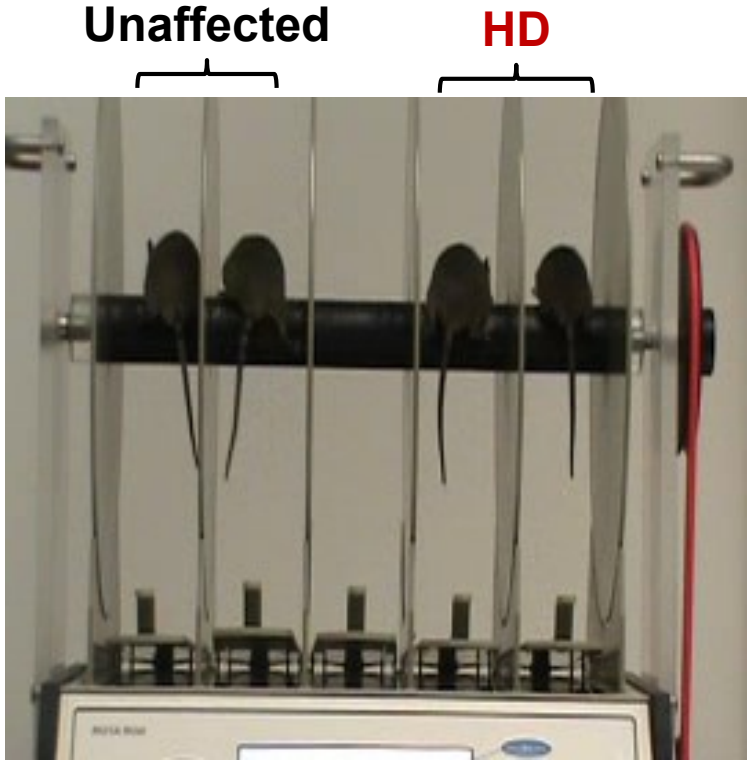
Cell therapies: HD NSC transplants successful in mouse models

Stem Cell Reports
Article
ISSCR
OPEN ACCESS

Human Neural Stem Cell Transplantation Rescues Functional Deficits in R6/2 and Q140 Huntington's Disease Mice

Jack C. Reidling,[1,11] Aroa Relaño-Ginés,[2,11] Sandra M. Holley,[3,11] Joseph Ochaba,[4] Cindy Moore,[5] Brian Fury,[6] Alice Lau,[7] Andrew H. Tran,[1] Sylvia Yeung,[1] Delaram Salamati,[1] Chunni Zhu,[2] Asa Hatami,[2] Carlos Cepeda,[3] Joshua A. Barry,[3] Talia Kamdjou,[3] Alvin King,[4] Dane Coleal-Bergum,[6] Nicholas R. Franich,[2] Frank M. LaFerla,[1,4] Joan S. Steffan,[1,7] Mathew Blurton-Jones,[1,4,8] Charles K. Meshul,[5,9] Gerhard Bauer,[6] Michael S. Levine,[3,10] Marie-Francoise Chesselet,[2] and Leslie M. Thompson[1,4,7,8,*]





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Joseph Ochaba

HD community building on successful efforts

Huntington's Disease Society of America

Exciting time in HD research

HOT TOPICS

Enroll-HD

Hereditary Disease Foundation

CHDI FOUNDATION

Roche

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HUNTINGTON
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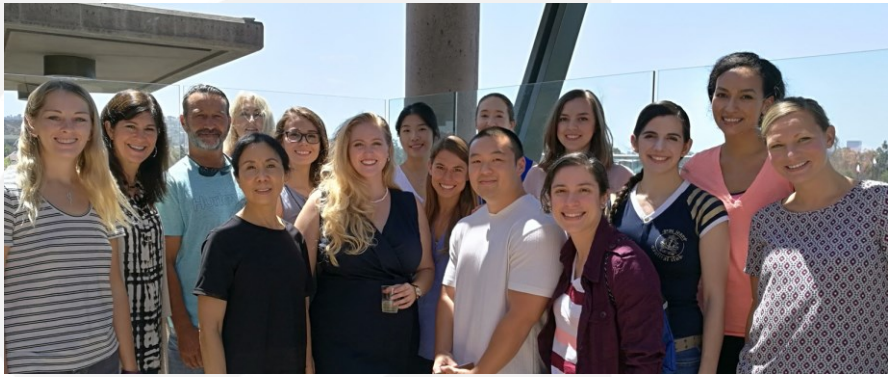

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