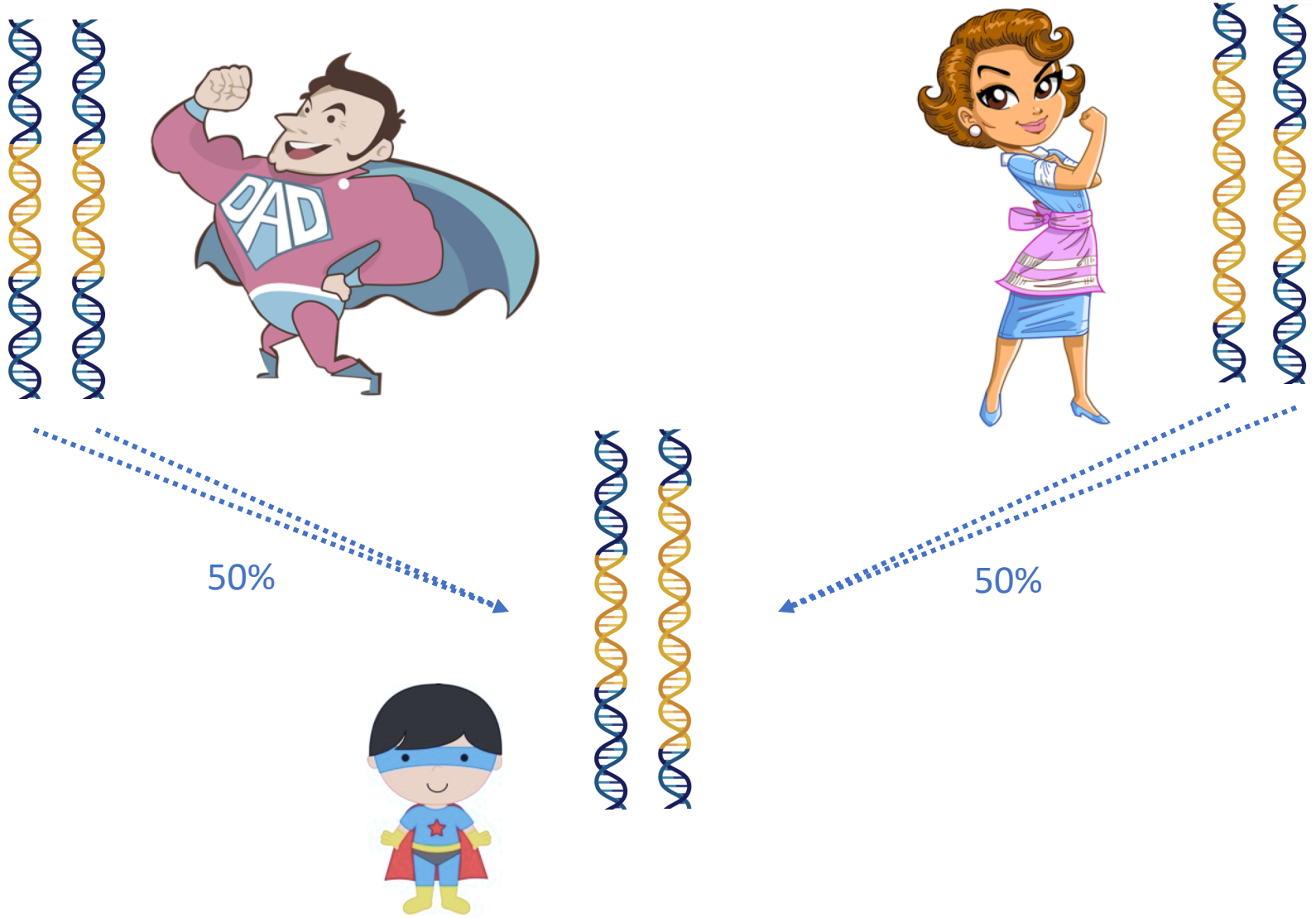
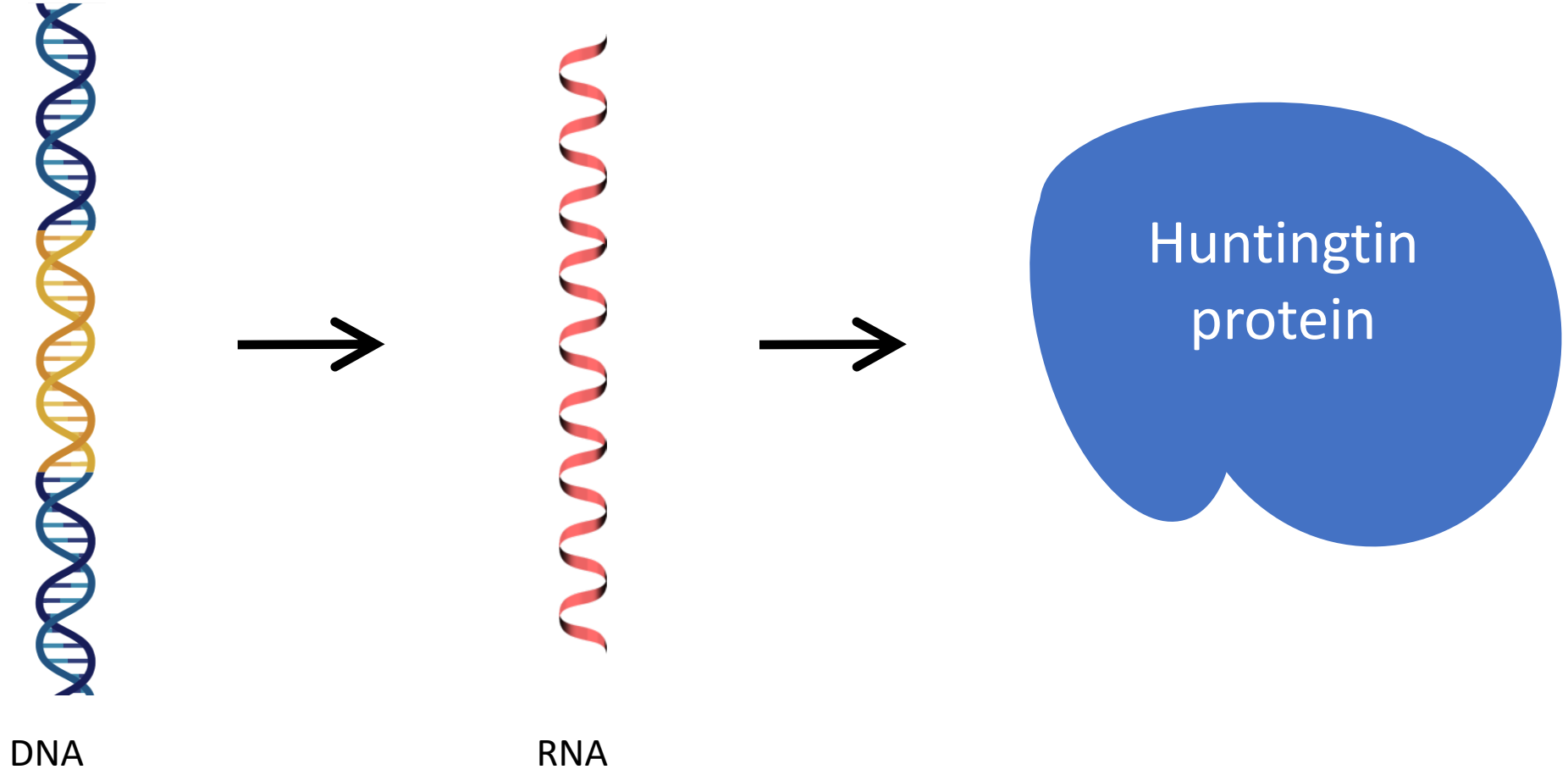
Journey of a thousand miles

How HD basic research feeds the clinical trial pipeline

HD gene inheritance



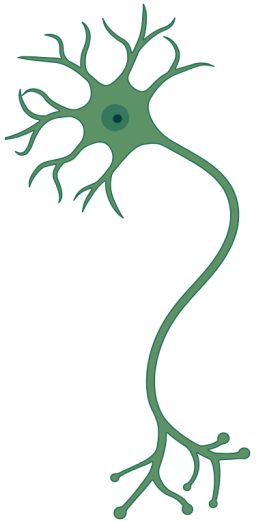
From gene to protein



Unexpanded huntingtin gene

Normal huntingtin protein

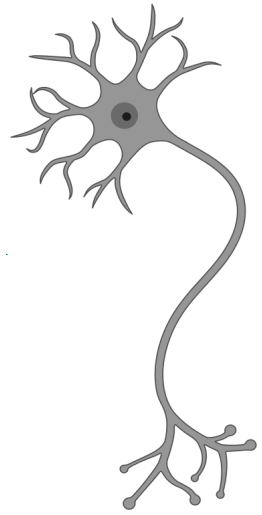
Healthy nerve cells



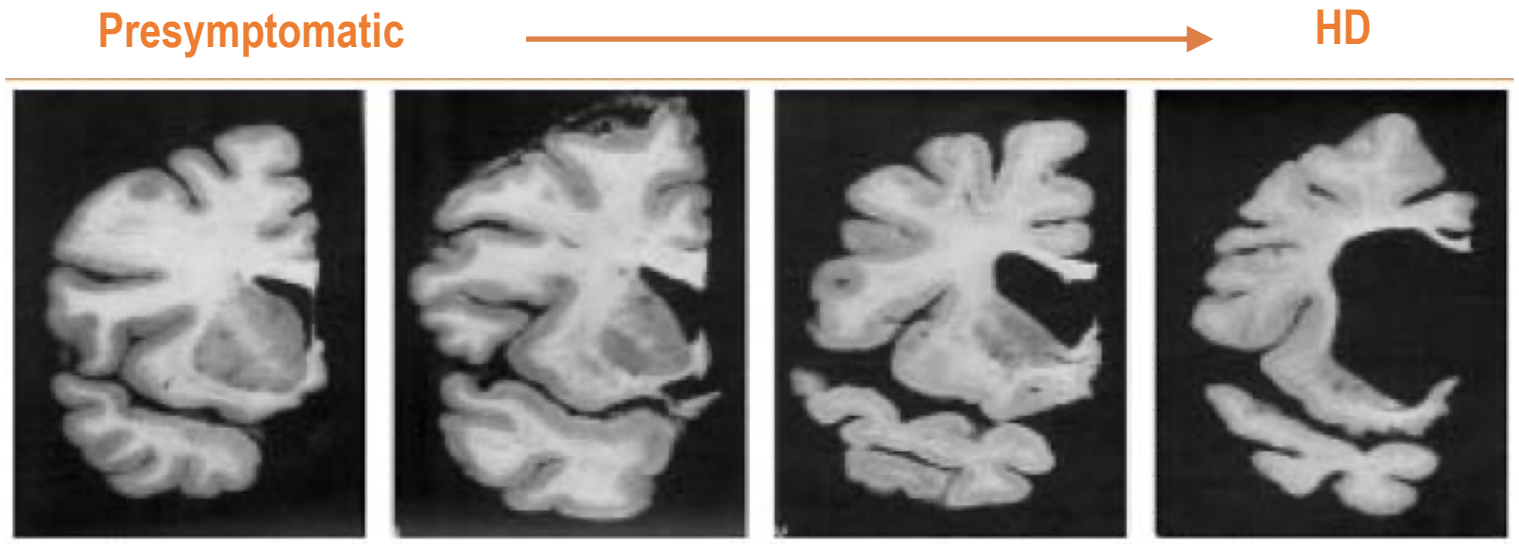
Expanded huntingtin gene

Expanded huntingtin protein

Huntington’s disease



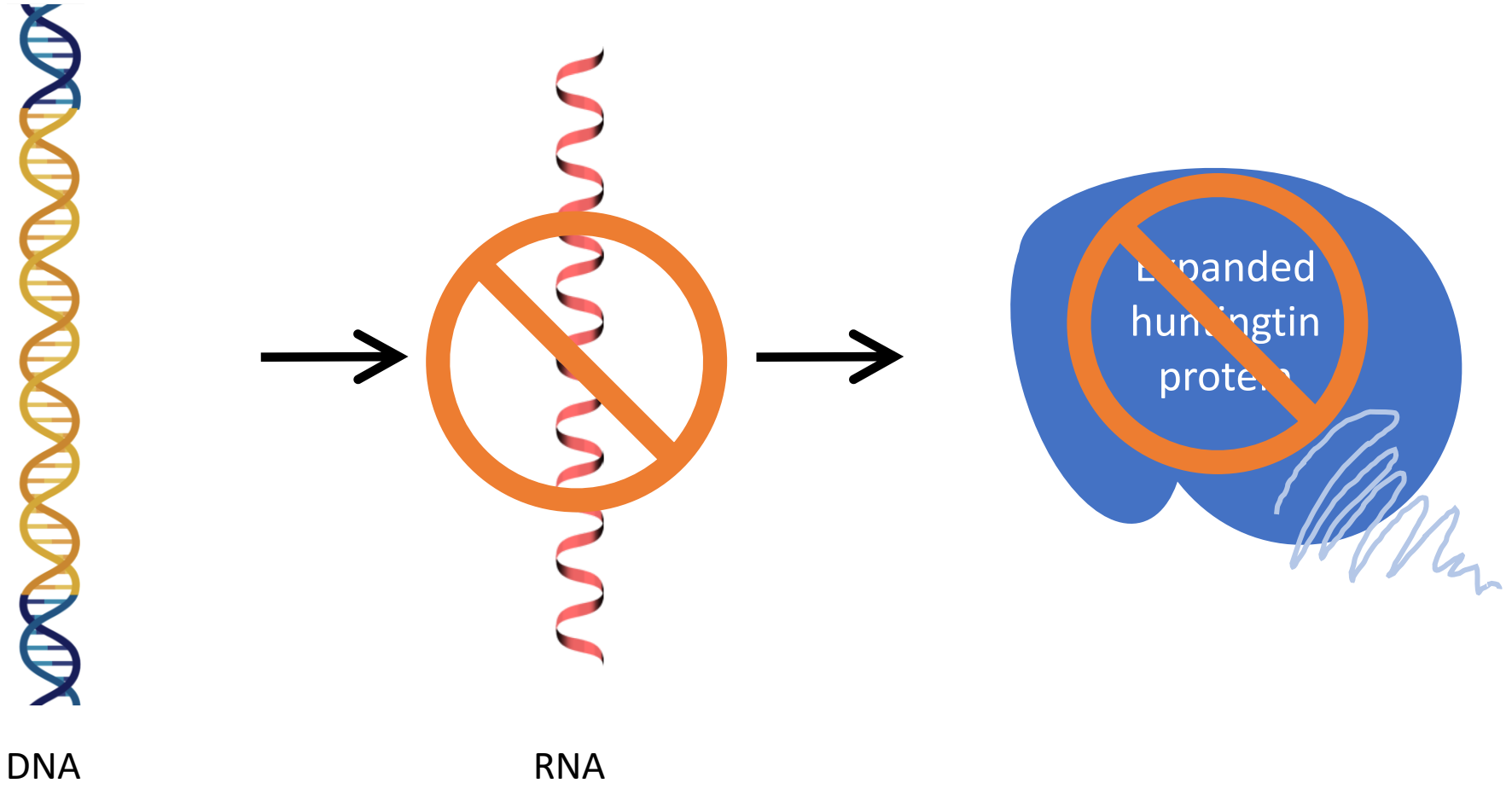
What really causes neurodegeneration?



http://www.buckinstitute.org/site/index.php?option=com_content&task=view&id=41&Itemid=147

- Loss of function?
- Gain of toxic function?
- Why do we care? Just find a treatment!
  - Two approaches

Turning off the toxic protein



Multiple approaches to lowering huntingtin

- Antisense oligonucleotides (ASOs)
  - Lumbar puncture delivery
  - More precise dosing
  - Transient (weeks/months)
  - Can stop in case of adverse events

- RNAi (gene therapy)
  - Intracranial delivery
  - Permanent

- Small molecules
  - Oral delivery

Clinical trials: recent, current, upcoming

Huntingtin-lowering

IONIS-HTTRx

IONIS-HTTRx OLE

GENERATION-HD1

PRECISION-HD1/2

UniQure gene therapy

PTC small molecule

Observational

Enroll-HD

HD Clarity

HD Natural History

Neuroinflammation

LEGATO

SIGNAL

Symptom alleviation

FIRST-HD and ARC-HD

ExAblate

HART and PRIDE-HD

Working out what the huntingtin protein does is difficult

It's huge

The huntingtin protein is 7 times larger than the average human protein

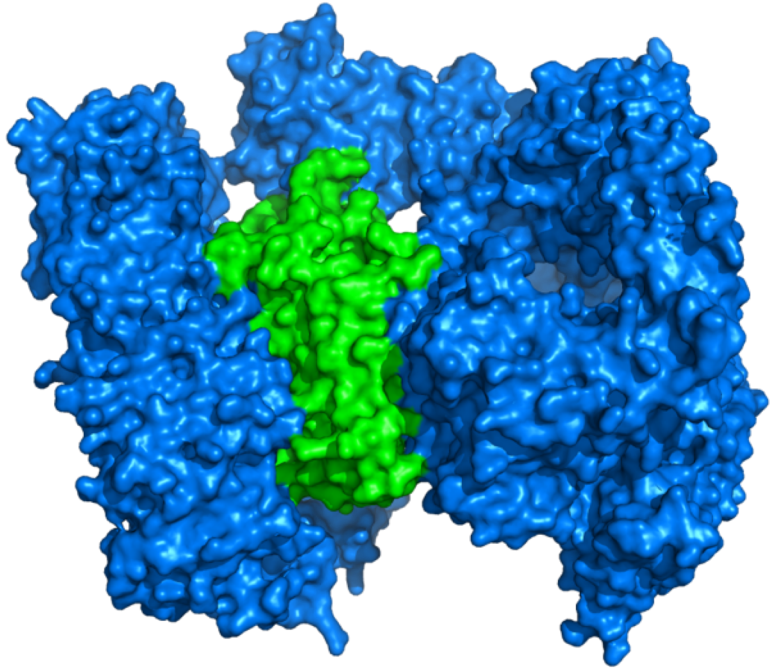
It's very sticky

The huntingtin protein is reported to bind to 100s of different molecules

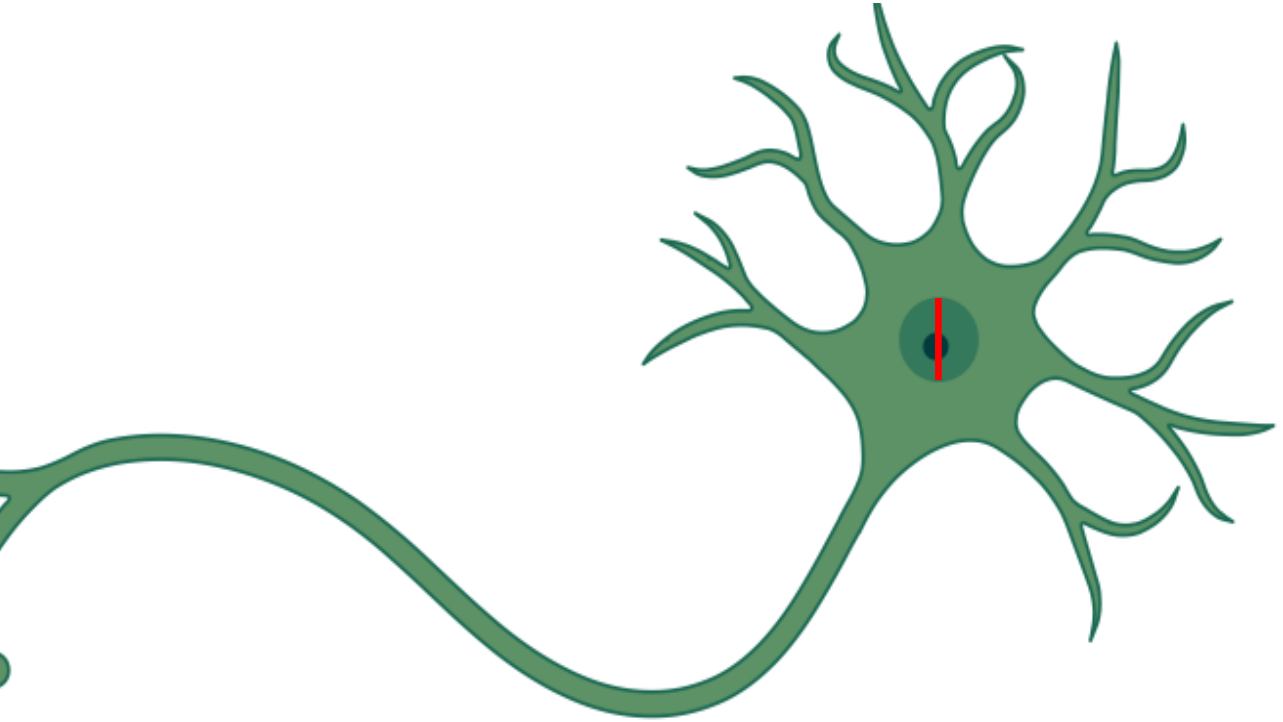
It's very pesky

Lot's of our normal tricks in the lab just don't work for the huntingtin gene and protein

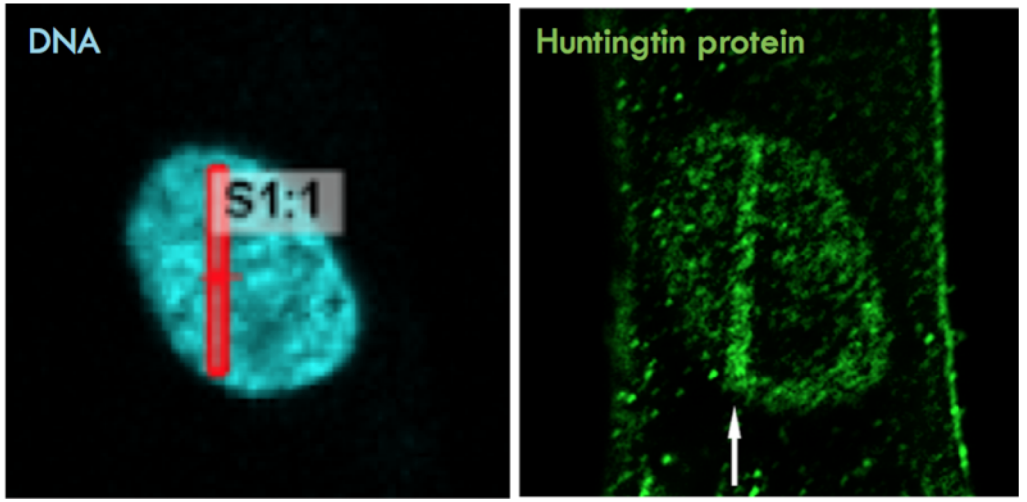
What does the huntingtin protein do?

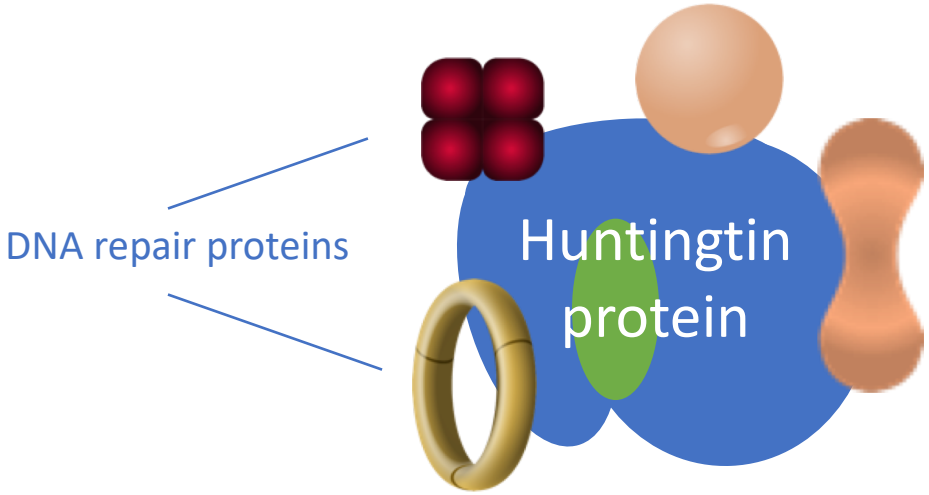


Huntingtin moves to damaged DNA



High power laser stripe damages DNA





A Major Clue

42 CAG repeats
Symptoms **early** in life

42 CAG repeats
Symptoms **late** in life

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"

https://en.hdbuzz.net/200

https://en.hdbuzz.net/217

DNA repair and CAG repeat diseases

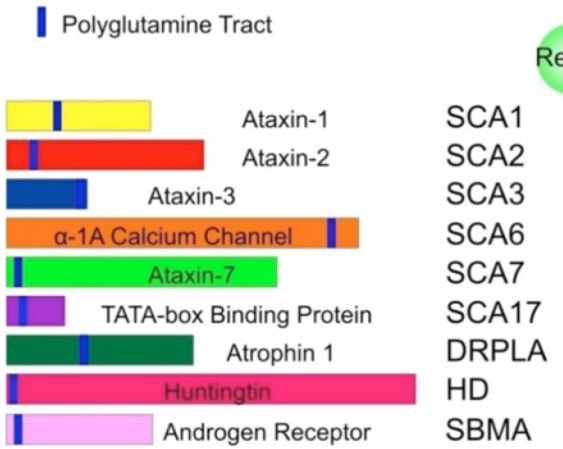
DNA repair genes are
genetic modifiers for other
neurodegenerative diseases caused by
CAG expansion

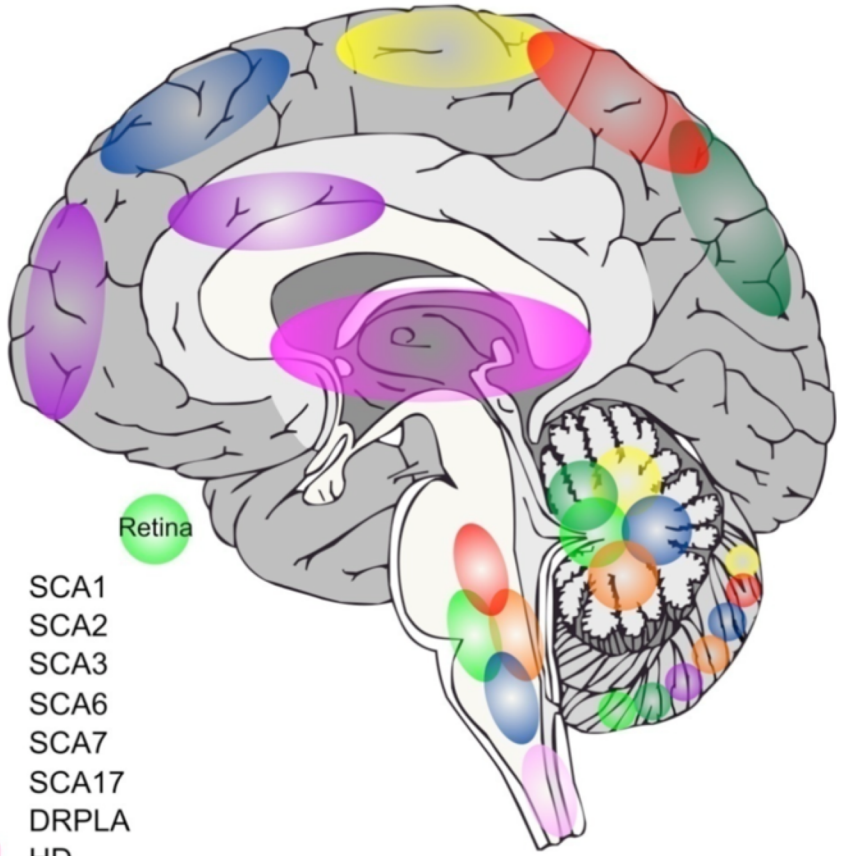
RESEARCH ARTICLE

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





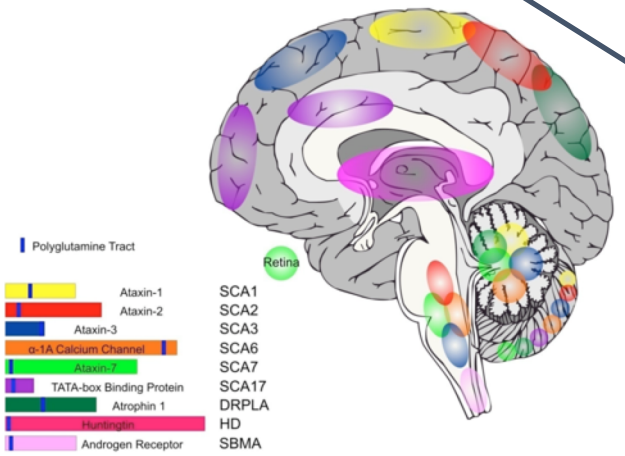
https://en.hdbuzz.net/200 https://en.hdbuzz.net/217

Factor 1: somatic expansion

CAG gene

Most cells

Brain cells



DNA repair gone wrong

Factor 1: somatic expansion

Symptoms **early** in life

DNA repair genes

acting as

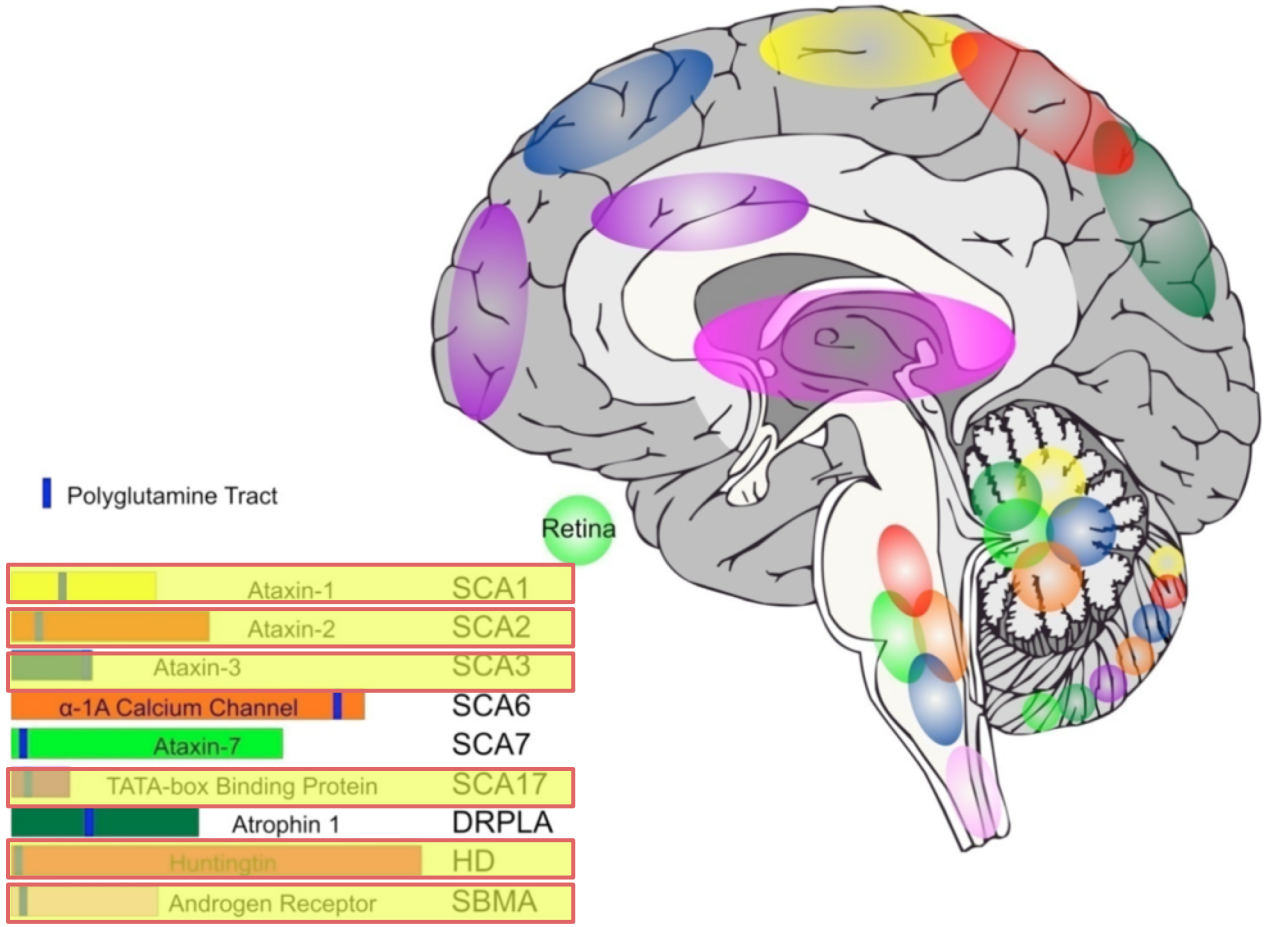
genetic modifiers

by affecting

somatic expansion

Symptoms **late** in life

Factor 2: CAG repeat genes *are* DNA repair genes



Disease Models & Mechanisms (2018) 11, dmm031930. doi:10.1242/dmm.031930

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
HD	*HTT*	Transcriptional regulation; molecular scaffolding and vesicle trafficking; neurodevelopment; cell survival	Ubiquitous	N-terminus (M8) functions as a ROS sensor leading to nuclear translocation	DiGiovanni et al., 2016
				DNA damage leads to phosphorylation (serines 1181 and 1201) by Cdk5 as part of DDR	Anne et al., 2007
				Recruited by ATM to sites of DNA damage	Maiuri et al., 2016
				Quiescent human HD fibroblasts are defective in DSB repair. Mutant HTT may sequester ATM in cytoplasm	Ferlazzo et al., 2014
				Exaggerated DDR following oxidative stress in HD fibroblasts	Giuliano et al., 2003
DRPLA	*ATN1*	Transcriptional co-repressor through recruiting NR2F1	Ubiquitous	None known	
SBMA	*AR*	Transcription factor when bound to androgen	Testis, breast, liver, platelets. Low levels elsewhere	AR with expanded polyglutamine can sequester PTIP (containing glutamine-rich region) away from DNA repair pathways, leading to accumulation of DNA damage in cell models	Xiao et al., 2012
SCA1	*ATXN1*	Brain development via transcriptional co-repressor complex with capicua protein; alternative splicing; cell signalling through Notch; modulation of PP2A	Ubiquitous	Polyglutamine-containing ATXN1 (or HTT, AR, ATXN7) can sequester multifunctional VCP, leading to functional deficiency in DNA repair and accumulation of DNA damage in cells	Fujita et al., 2013
				Overexpression of DNA repair factor RpA1 in mouse or *Drosophila* models of SCA1 can ameliorate phenotype	Barclay et al., 2014; Taniguchi et al., 2016
SCA2	*ATXN2*	RNA metabolism; regulation of translation	Ubiquitous	shRNA knockdown of ATXN2 in HeLa cells leads to increased DNA damage (DSBs and R-loops), partially rescued by Mg^{2+} supplementation	Abraham et al., 2016
				Exaggerated DDR following oxidative stress in SCA2 fibroblasts	Giuliano et al., 2003
SCA3	*ATXN3*	Transcriptional regulation (stress response); protein homeostasis through ubiquitin-proteasome system (ataxin-3 is a deubiquitinase)	Ubiquitous	RAD23A/B have roles in NER and proteasome function. They bind ATXN3 and protect it from proteasomal degradation	Blount et al., 2014
				ATXN3 with expanded polyglutamine sequesters PNKP outside nucleus and inhibits its 3′-phosphatase activity, leading to increased DNA strand breaks in cell and mouse models, and postmortem human brains	Chatterjee et al., 2015; Gao et al., 2015
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
SCA17	*TBP*	Binds TATA box in gene promoters as part of TFIID, which is required for initiation of transcription by RNA polymerase II	Ubiquitous	TBP can bind damaged DNA at or near TATA boxes	Aboussekhra and Thoma, 1999; Jung et al., 2001

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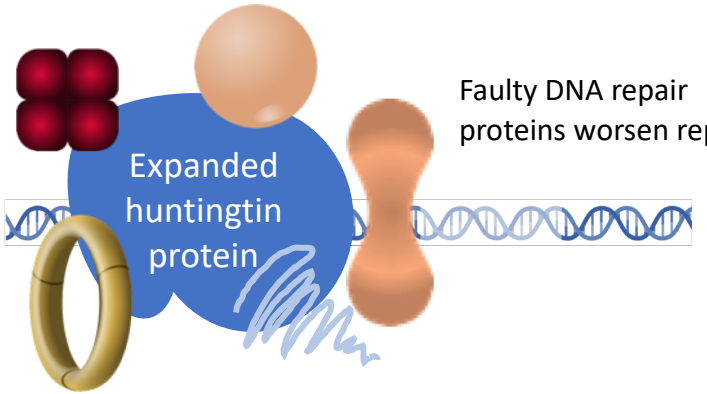
Factor 2: CAG repeat genes *are* DNA repair genes



Faulty DNA repair proteins worsen repair

Symptoms **early** in life

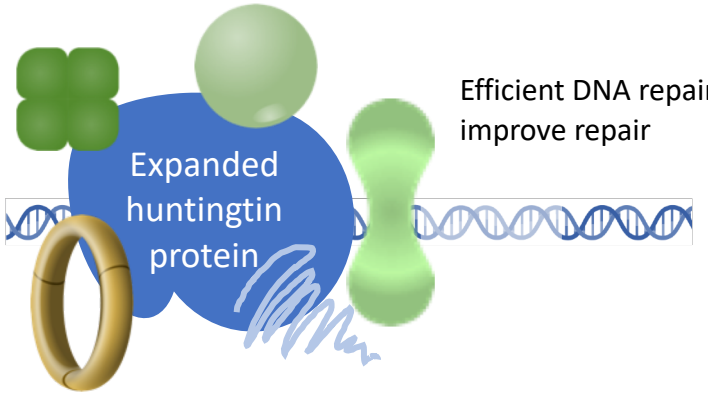
DNA repair genes

acting as

genetic modifiers

by affecting the

function of expanded huntingtin



Efficient DNA repair proteins improve repair

Symptoms **late** in life

https://en.hdbuzz.net/200

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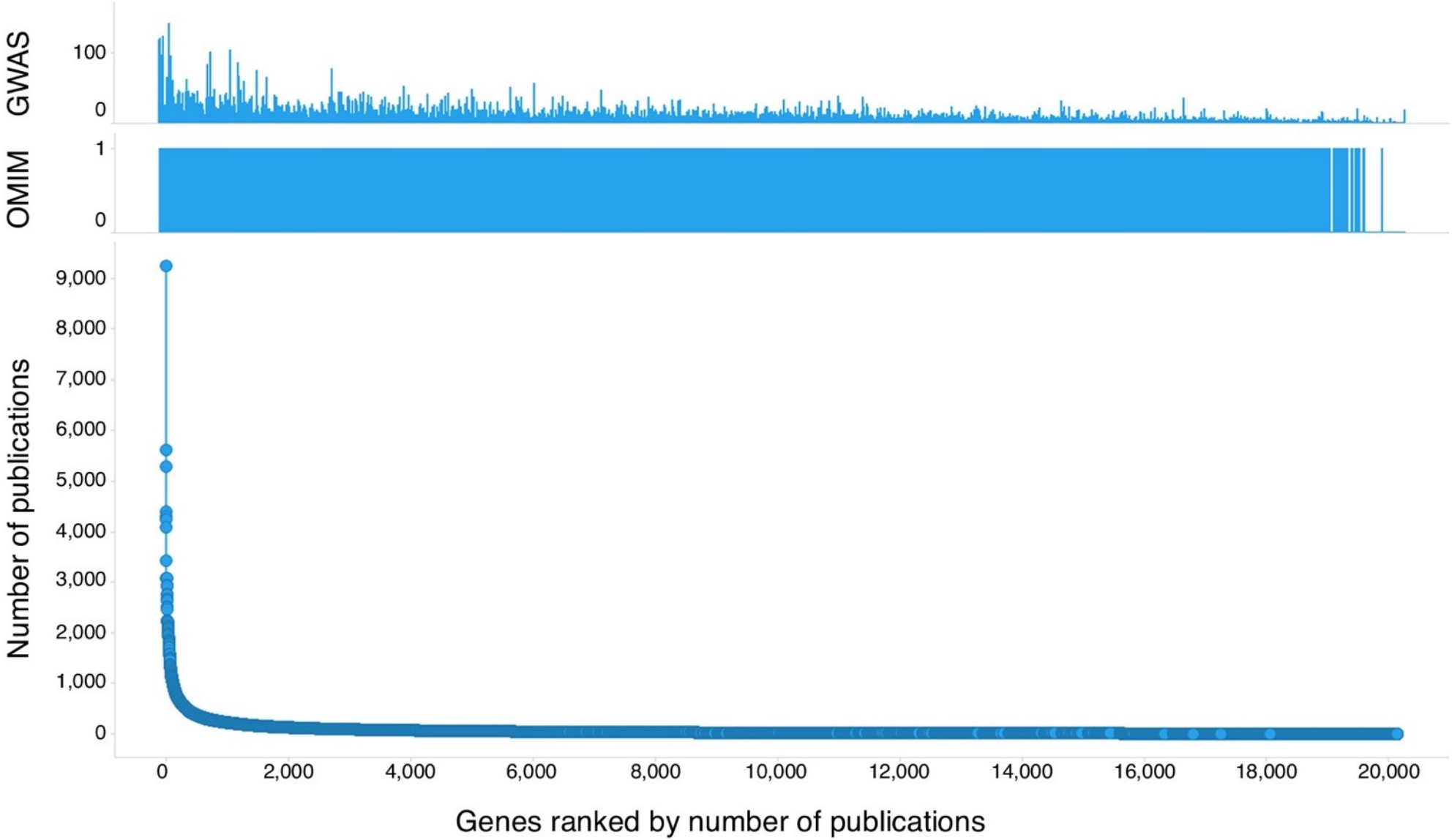
Scientists often look for answers in the same places rather than taking a systematic approach

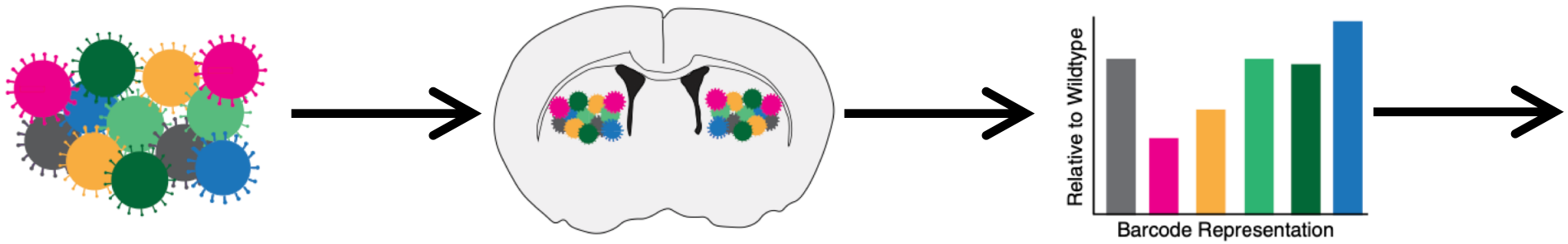


Genome-wide *In Vivo* CNS Screening Identifies Genes that Modify CNS Neuronal Survival and mHTT Toxicity

Neuron

Mary H. Wertz,[2,3] Mollie R. Mitchem,[2,3] S. Sebastian Pineda,[3,7,8] Lea J. Hachigian,[1,2,3] Hyeseung Lee,[2,3] Vanessa Lau,[2,3] Alex Powers,[2,3] Ruth Kulicke,[2,3] Gurrein K. Madan,[1] Medina Colic,[4] Martine Therrien,[2,3] Amanda Vernon,[1,2,3] Victoria F. Beja-Glasser,[1,3,5] Mudra Hegde,[3] Fan Gao,[2,6] Manolis Kellis,[3,7] Traver Hart,[4] John G. Doench,[3] and Myriam Heiman[1,2,3,9,*]

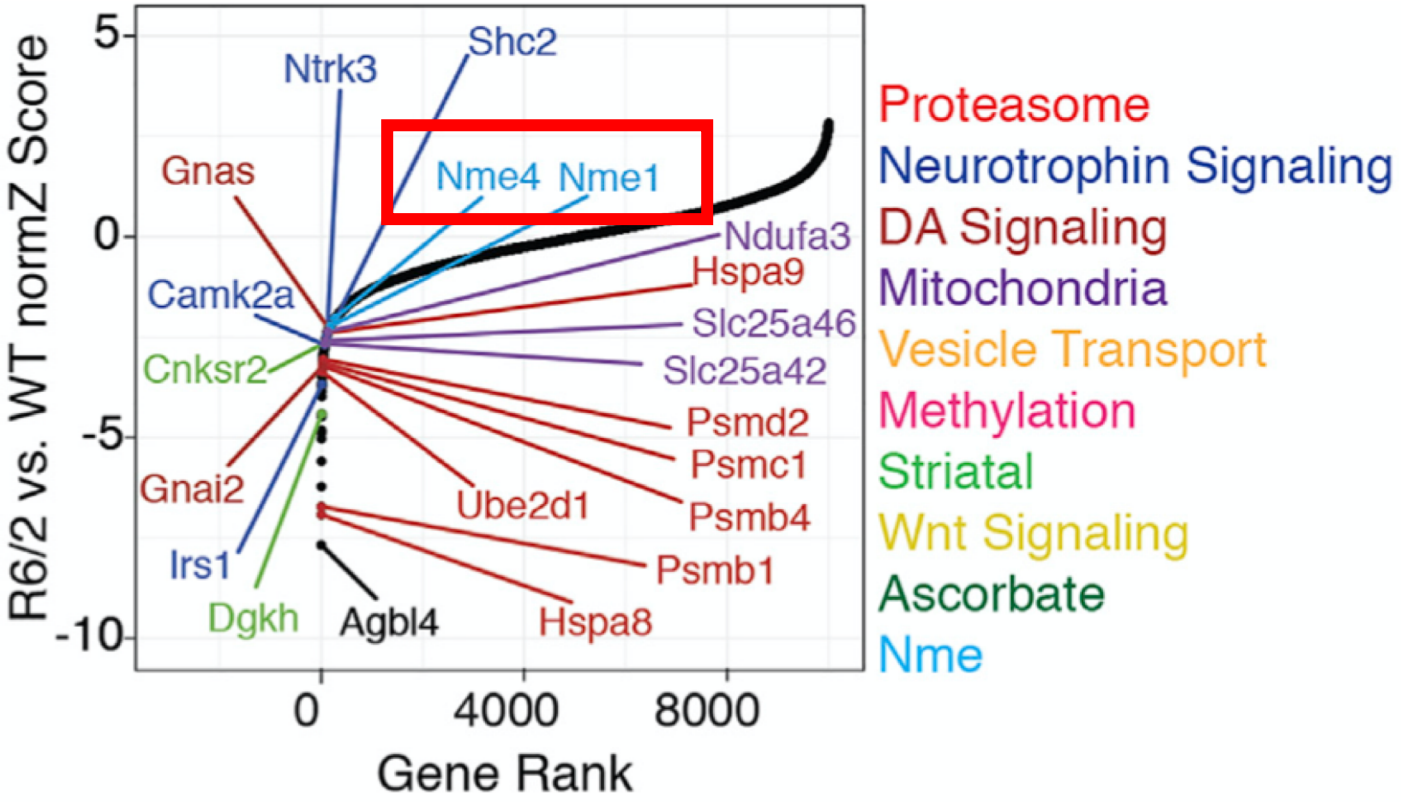
20,000+ genes were systematically investigated in mouse models of HD to see which modified disease progression

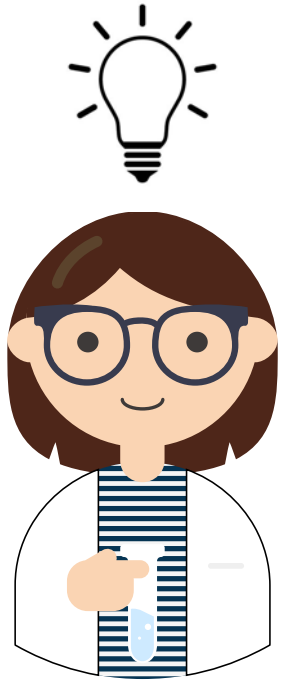


Which genes modify HD in mouse models?

https://en.hdbuzz.net/279

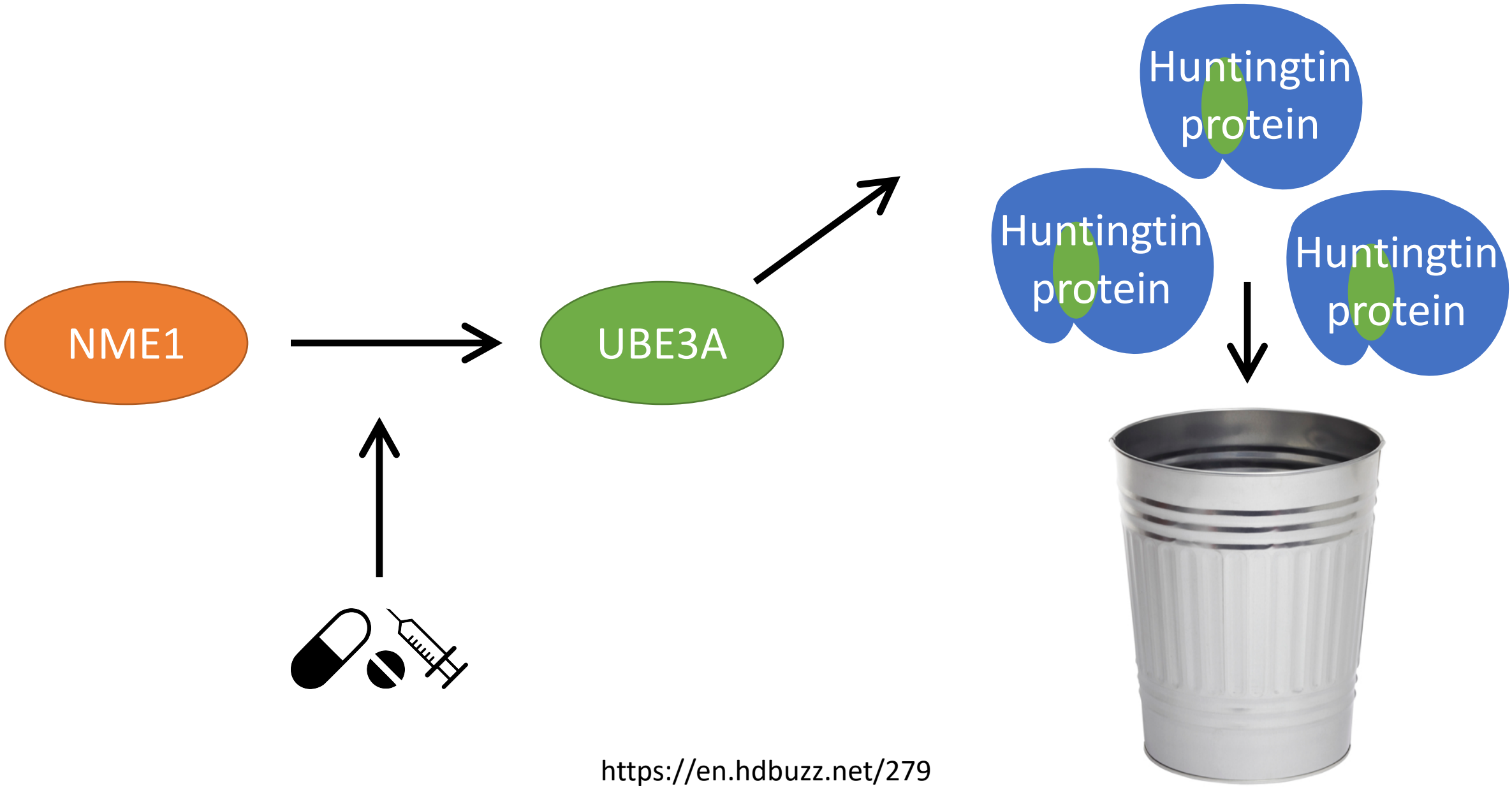
Unbiased approaches turn up new findings





https://en.hdbuzz.net/279

Could targeting the Nme pathway be a new way to lower HTT?



https://en.hdbuzz.net/279

Understanding biology at the molecular level

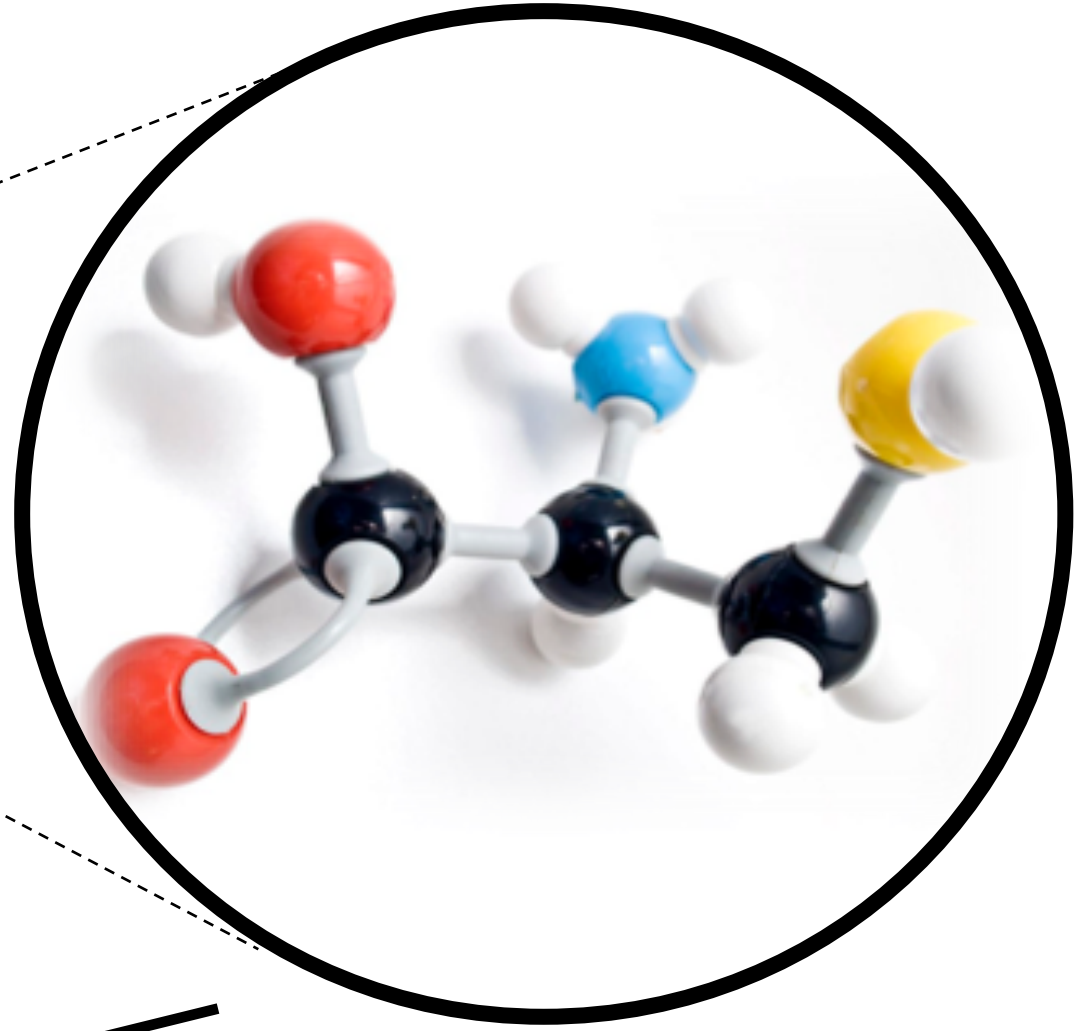
2 metres
2 m

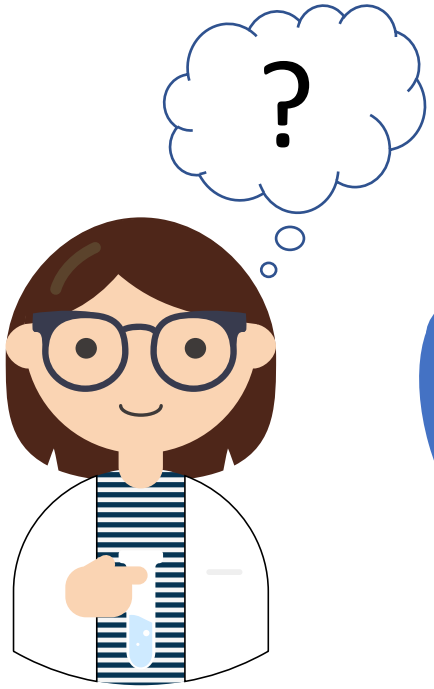
15 centimetres
0.15 m

20 micrometres
0.00002 m

5 nanometres
0.000000005 m

Huntingtin protein





Expanded

Huntingtin protein

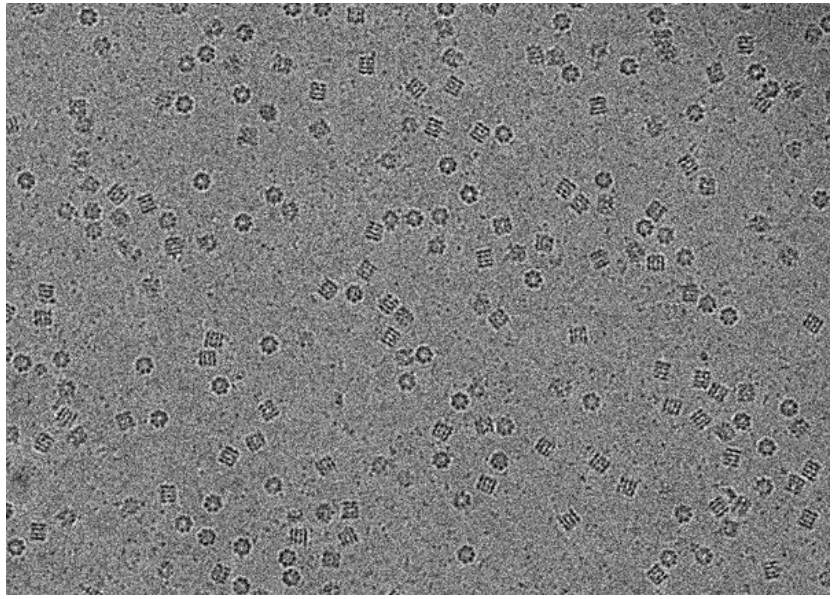
Unexpanded

Huntingtin protein

Spot the difference…

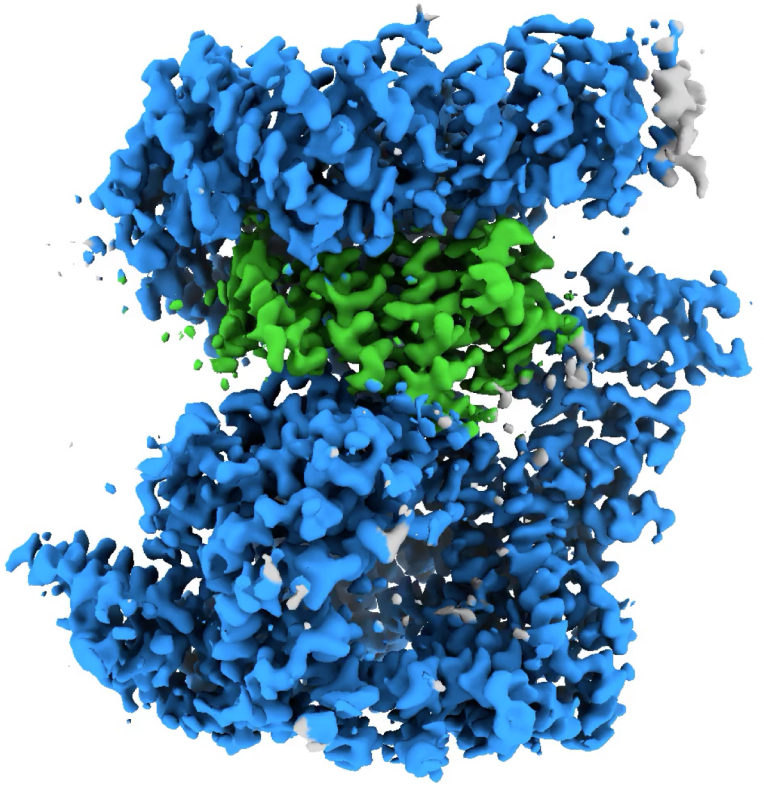
Seeing what molecules look like can give us hints about what they do

Cutting-edge microscopes can look at protein molecules

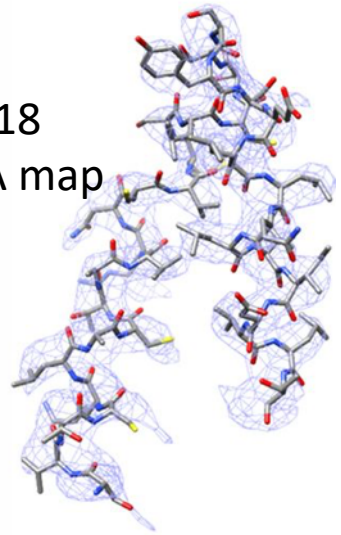


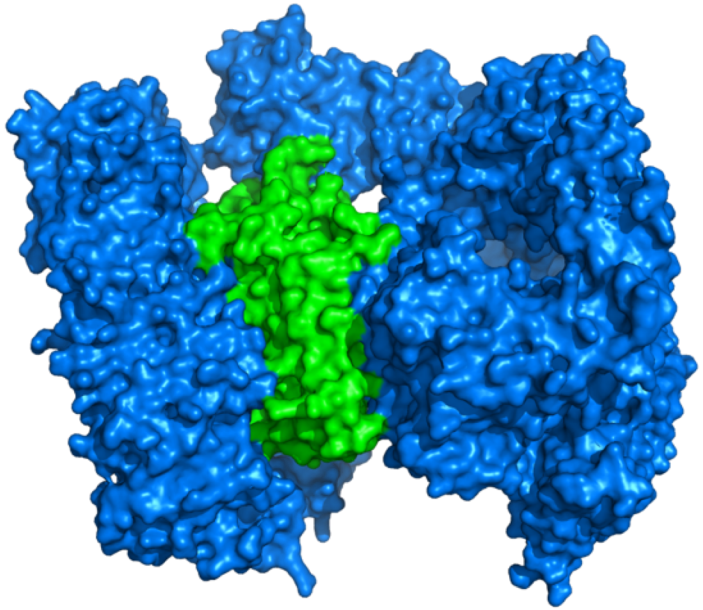
These microscopes can see the tiny single molecules of protein which can be used to build models

Models of the huntingtin protein help us better understand Huntington's disease

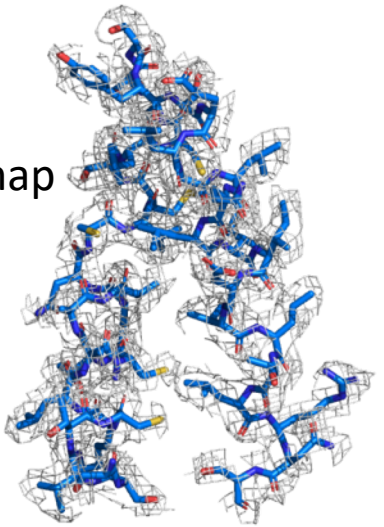


2018
4 Å map

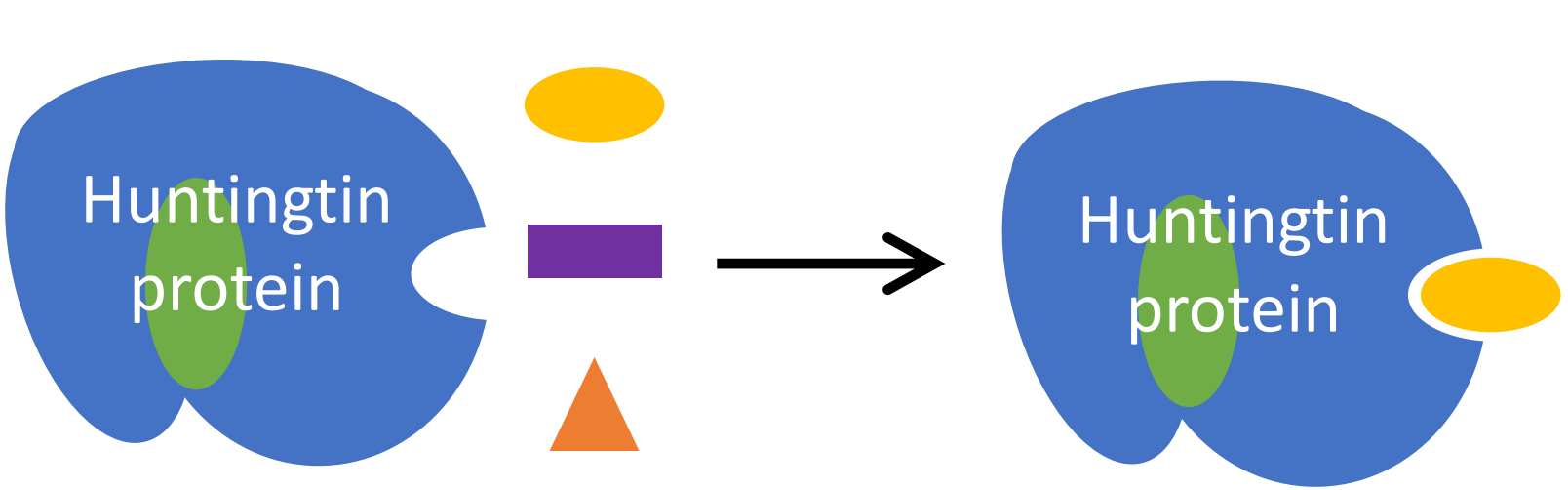


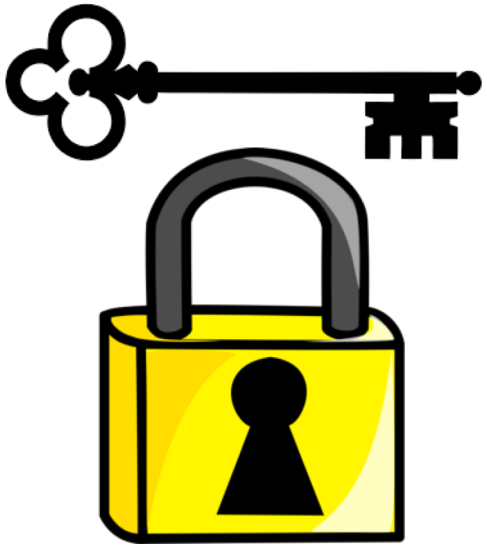


2020
2.6 Å map



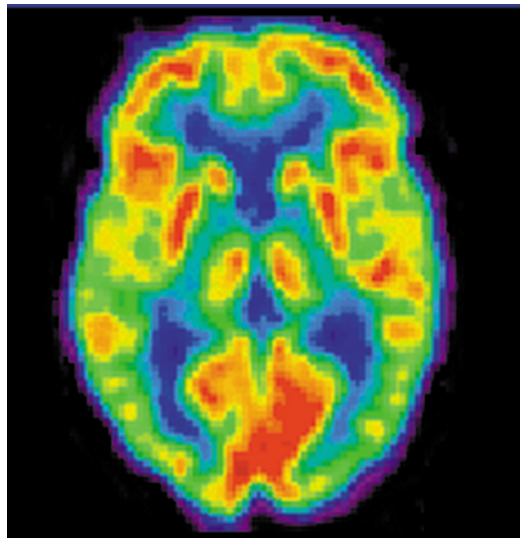
But we still don’t fully understand how the expanded and unexpanded huntingtin protein molecules look different…..yet!

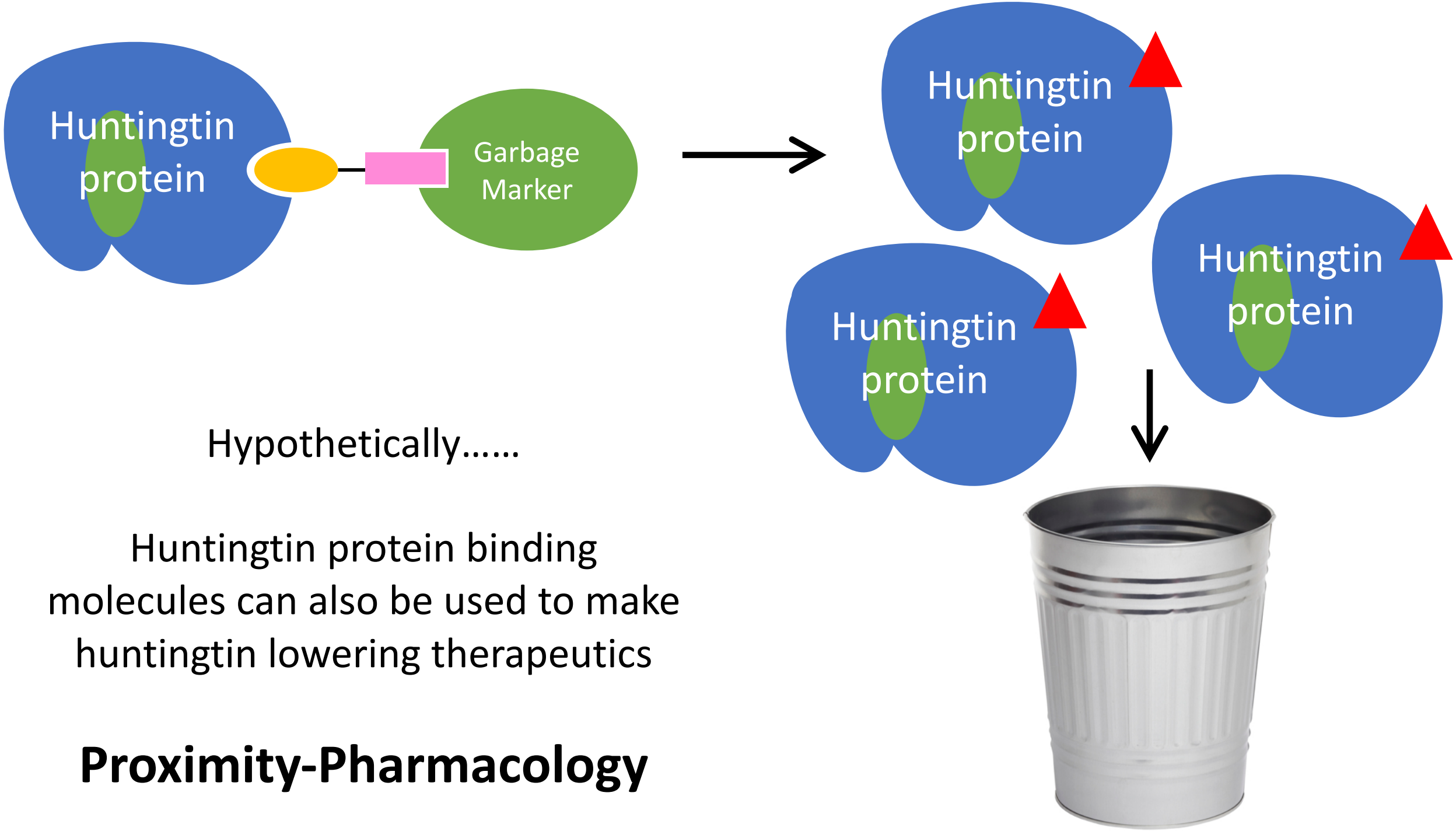




Huntingtin protein binding molecules could be developed into a number of different tools

PET ligand





Hypothetically……

Huntingtin protein binding molecules can also be used to make huntingtin lowering therapeutics

Proximity-Pharmacology

Could molecular handcuffs lower the protein that causes Huntington's disease?

Article

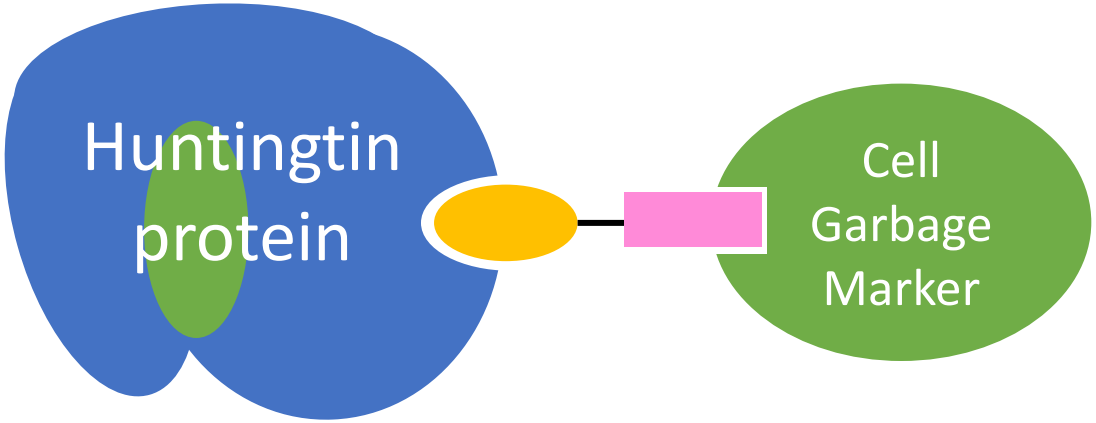
Allele-selective lowering of mutant HTT protein by HTT–LC3 linker compounds

https://doi.org/10.1038/s41586-019-1722-1

Received: 5 February 2019

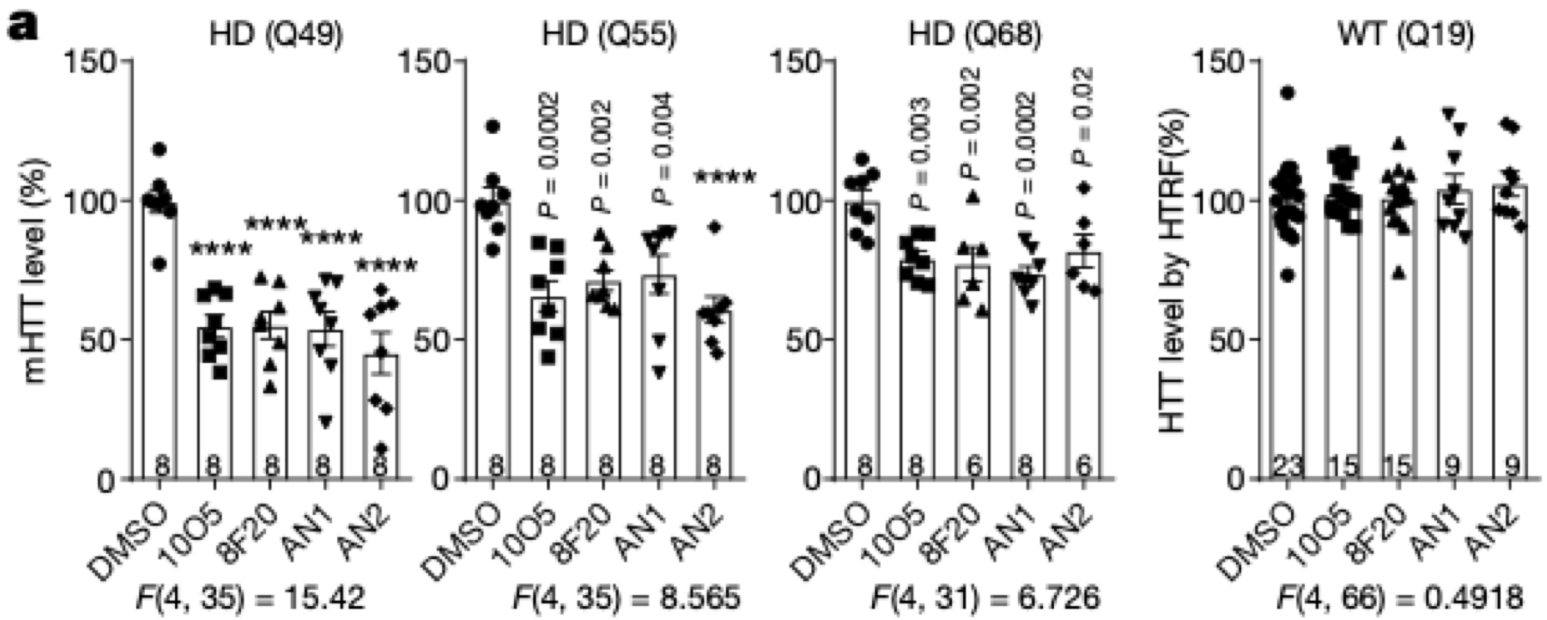
Accepted: 24 September 2019

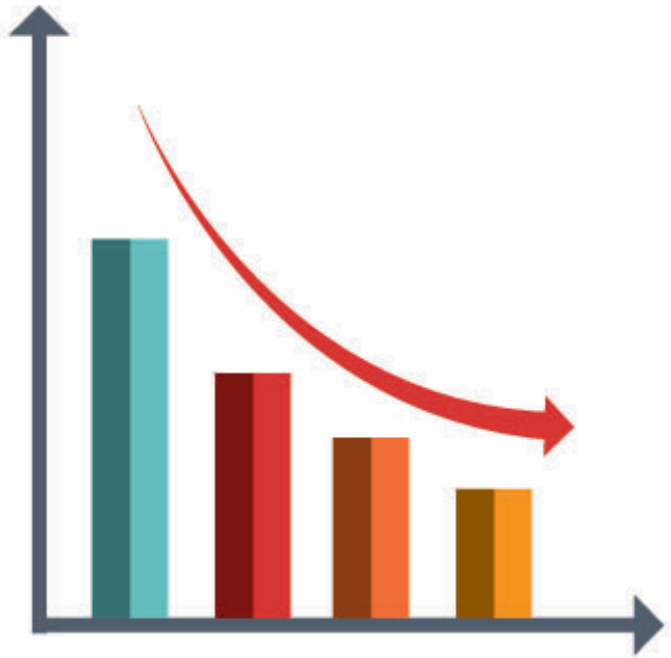
Zhaoyang Li[1,9], Cen Wang[1,9], Ziying Wang[1,9], Chenggang Zhu[2,9], Jie Li[3], Tian Sha[1], Lixiang Ma[4], Chao Gao[5], Yi Yang[6], Yimin Sun[1], Jian Wang[1], Xiaoli Sun[1], Chenqi Lu[1], Marian Difiglia[7], Yanai Mei[1], Chen Ding[1,10], Shouqing Luo[6,10], Yongjun Dang[8], Yu Ding[1]*, Yiyan Fei[2]* & Boxun Lu[1]*



https://en.hdbuzz.net/276

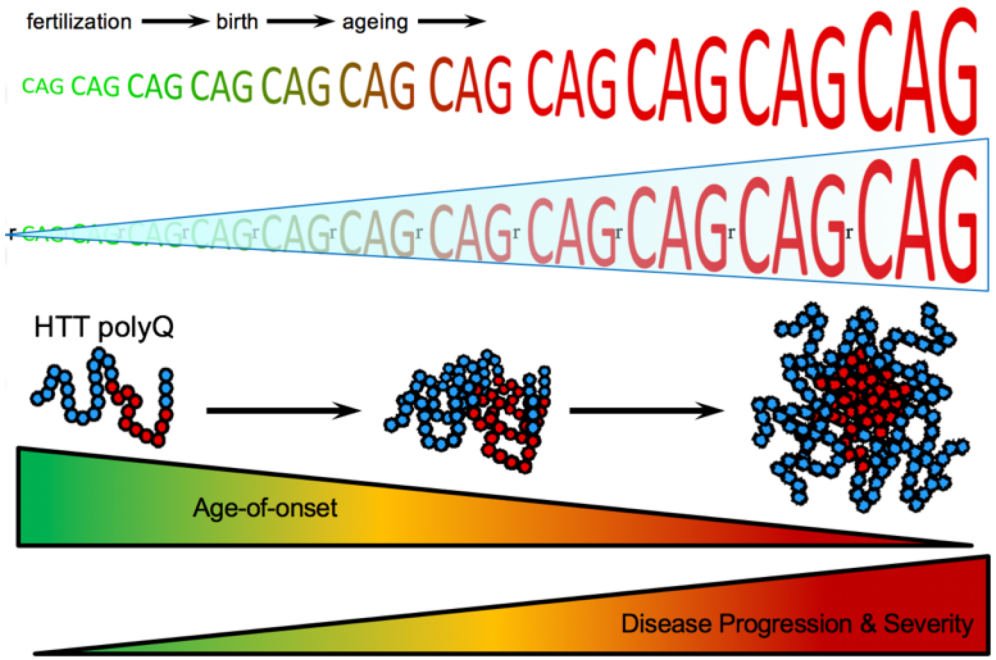
Could molecular handcuffs lower the protein that causes Huntington's disease?





https://en.hdbuzz.net/276

New molecule can reverse the Huntington's disease mutation in lab models



ARTICLES
https://doi.org/10.1038/s41588-019-0575-8
nature genetics

A slipped-CAG DNA-binding small molecule induces trinucleotide-repeat contractions in vivo

Masayuki Nakamori[1,12], Gagan B. Panigrahi[2,12], Stella Lanni[2,12], Terence Gall-Duncan[2,3], Hideki Hayakawa[1], Hana Tanaka[1], Jennifer Luo[2,3], Takahiro Otabe[4], Jinxing Li[4], Akihiro Sakata[4], Marie-Christine Caron[5,6], Niraj Joshi[5,6], Tanya Prasolava[2], Karen Chiang[2,3], Jean-Yves Masson[5,6], Marc S. Wold[7], Xiaoxiao Wang[8], Marietta Y. W. T. Lee[8], John Huddleston[9,10], Katherine M. Munson[9], Scott Davidson[2], Mehdi Layeghifard[2], Lisa-Monique Edward[2], Richard Gallon[11], Mauro Santibanez-Koref[11], Asako Murata[4], Masanori P. Takahashi[1], Evan E. Eichler[9,10], Adam Shlien[2], Kazuhiko Nakatani[4], Hideki Mochizuki[1] and Christopher E. Pearson[2,3]*

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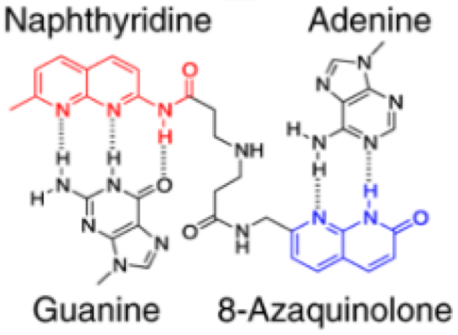
SickKids®

New molecule can reverse the Huntington's disease mutation in lab models

Naphthyridine Azaquinolone (NA)



NA is a small molecule which can change the CAG-repeat length in different lab models of Huntington’s disease

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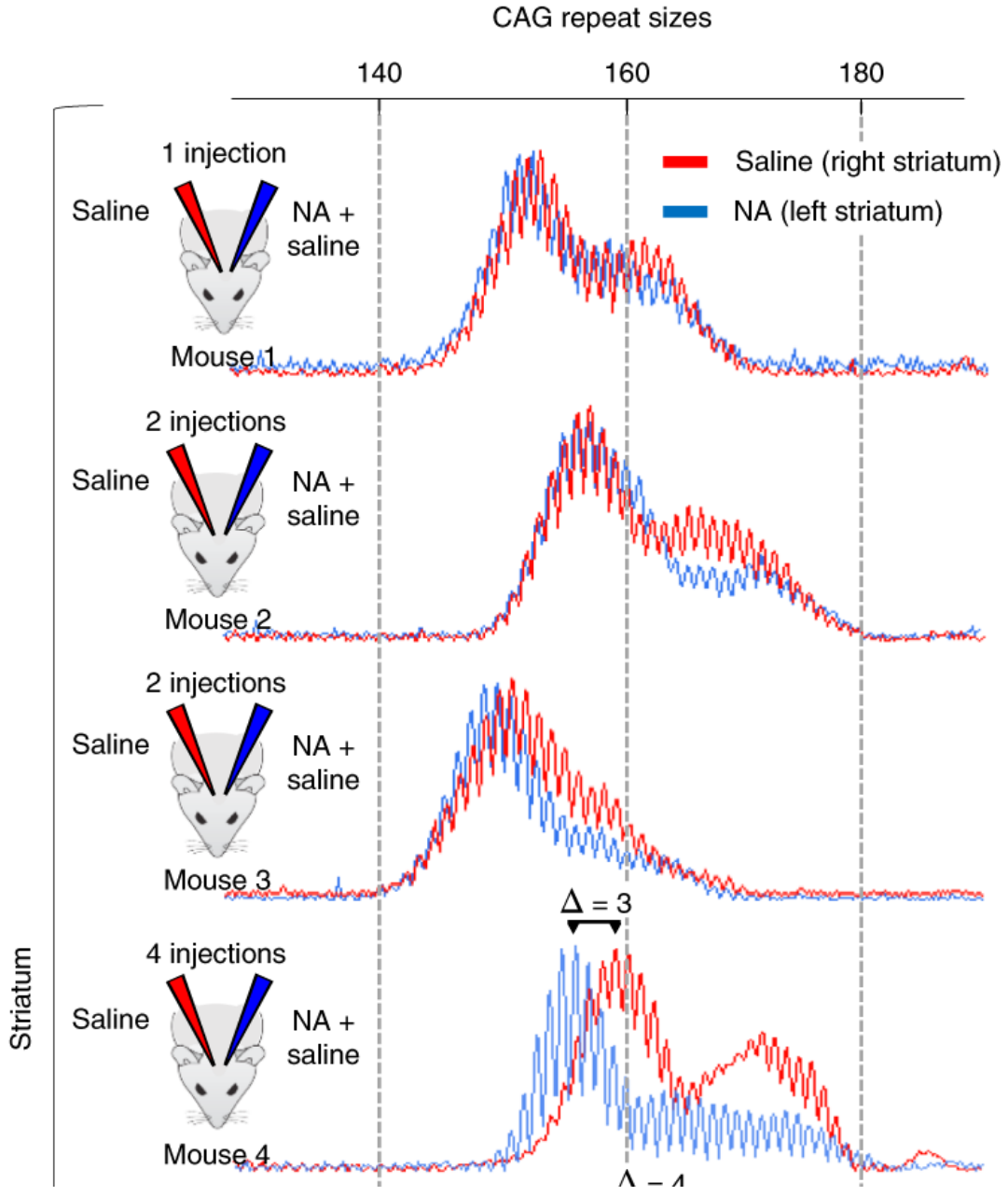


A few HD super scientists

Mahmoud Pouladi
Singapore

Developing cutting edge models to understand disease processes underlying HD

Lesley Jones
UK

Helped identify genetic modifiers by GWAS. Studying DNA repair pathways and how they affect disease onset

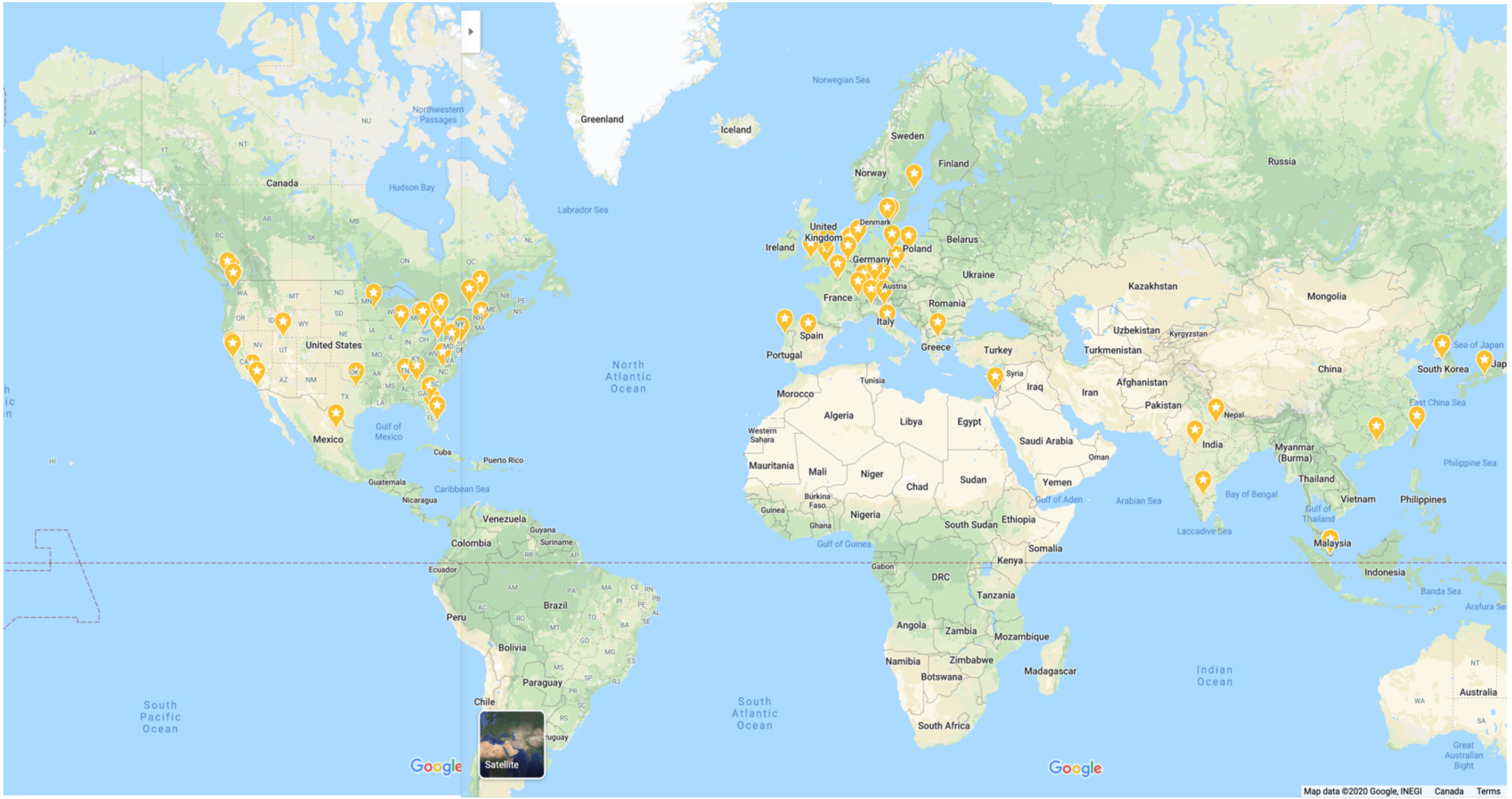
Vanessa Wheeler
US

Was on to somatic expansion WAY before everyone else. Studying mechanisms of somatic expansion

Hilal Lashuel
Switzerland

Uses high-tech approaches to study protein misfolding and and it contributes to neurodegenerative diseases

Many HD super scientists!



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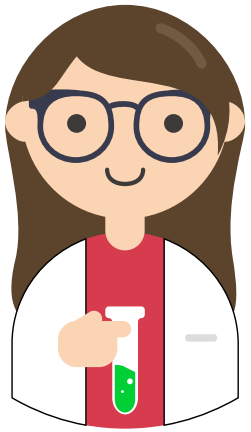

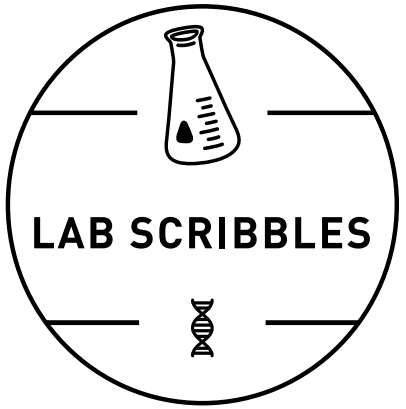

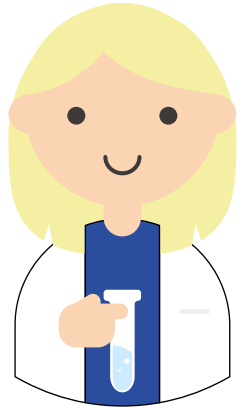

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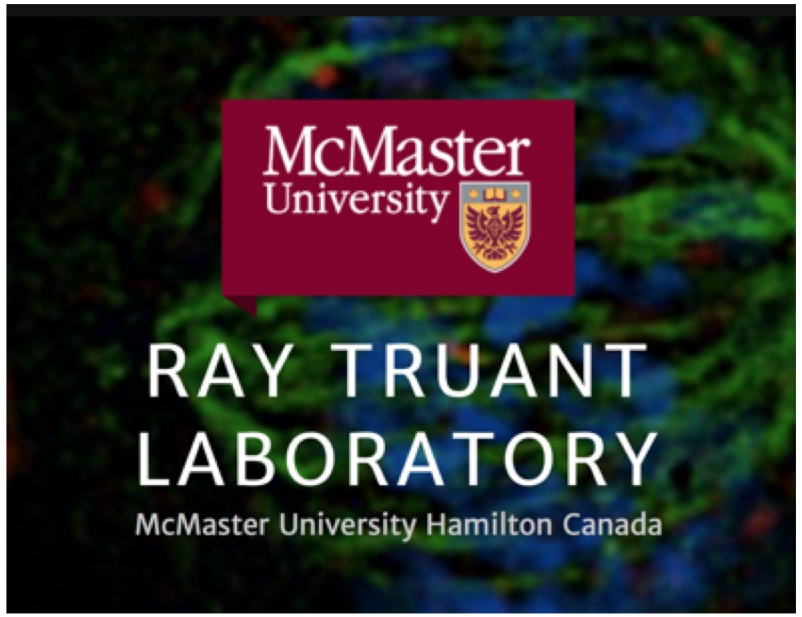
HD Research in plain language

Open Notebooks



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HD patient and family communities

SGC

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Thank you!!

Questions?

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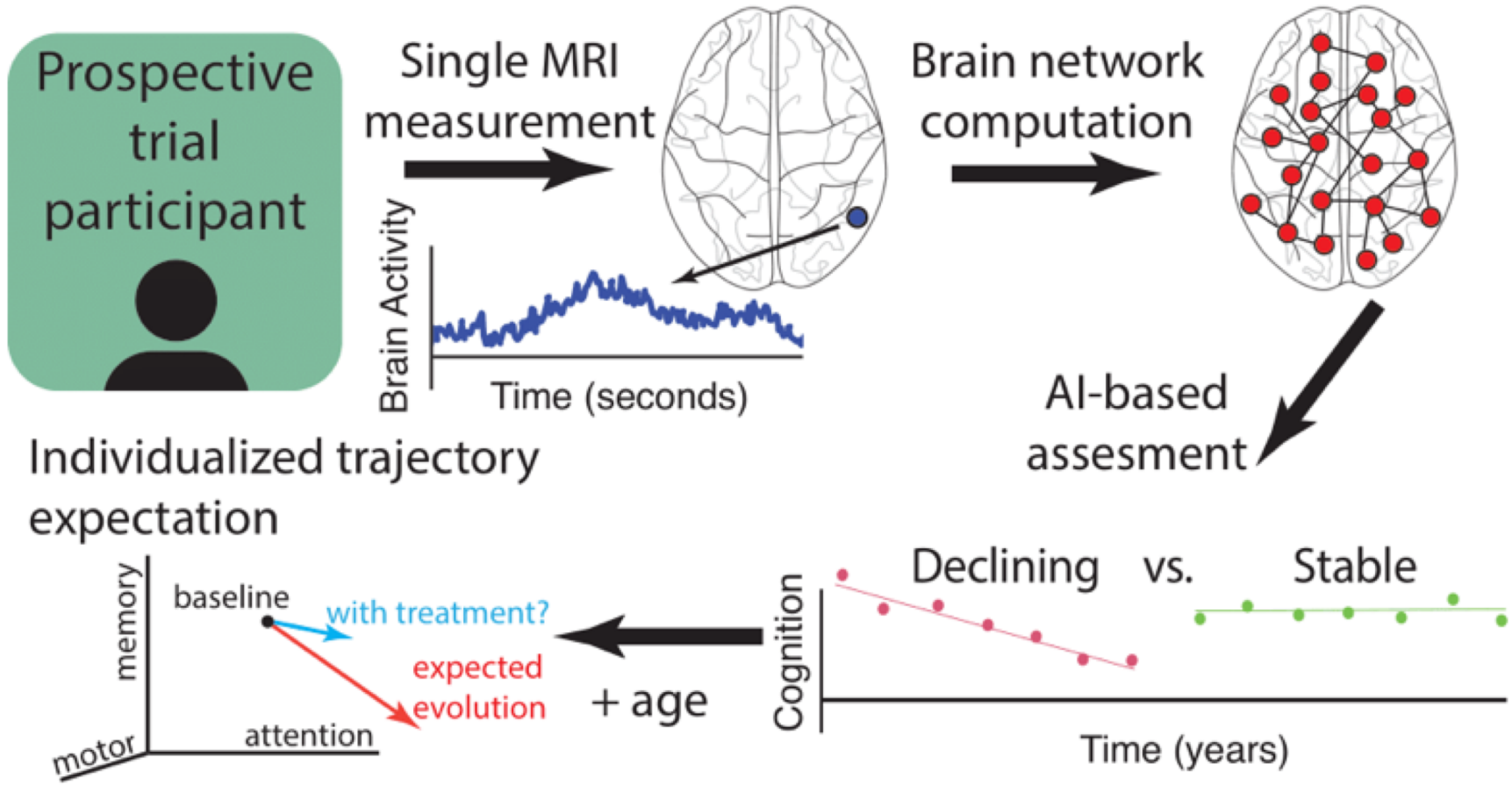
Resting-state connectivity stratifies premanifest Huntington's disease by longitudinal cognitive decline rate

Pablo Polosecki ✉, Eduardo Castro, Irina Rish, Dorian Pustina, John H. Warner, Andrew Wood, Cristina Sampaio & Guillermo A. Cecchi

Scientific Reports **10**, Article number: 1252 (2020) | Cite this article



BRAIN
A JOURNAL OF NEUROLOGY

Blood and brain gene expression trajectories mirror neuropathology and clinical deterioration in neurodegeneration

Yasser Iturria-Medina ✉, Ahmed F Khan, Quadri Adewale, Amir H Shirazi, the Alzheimer's Disease Neuroimaging Initiative Author Notes

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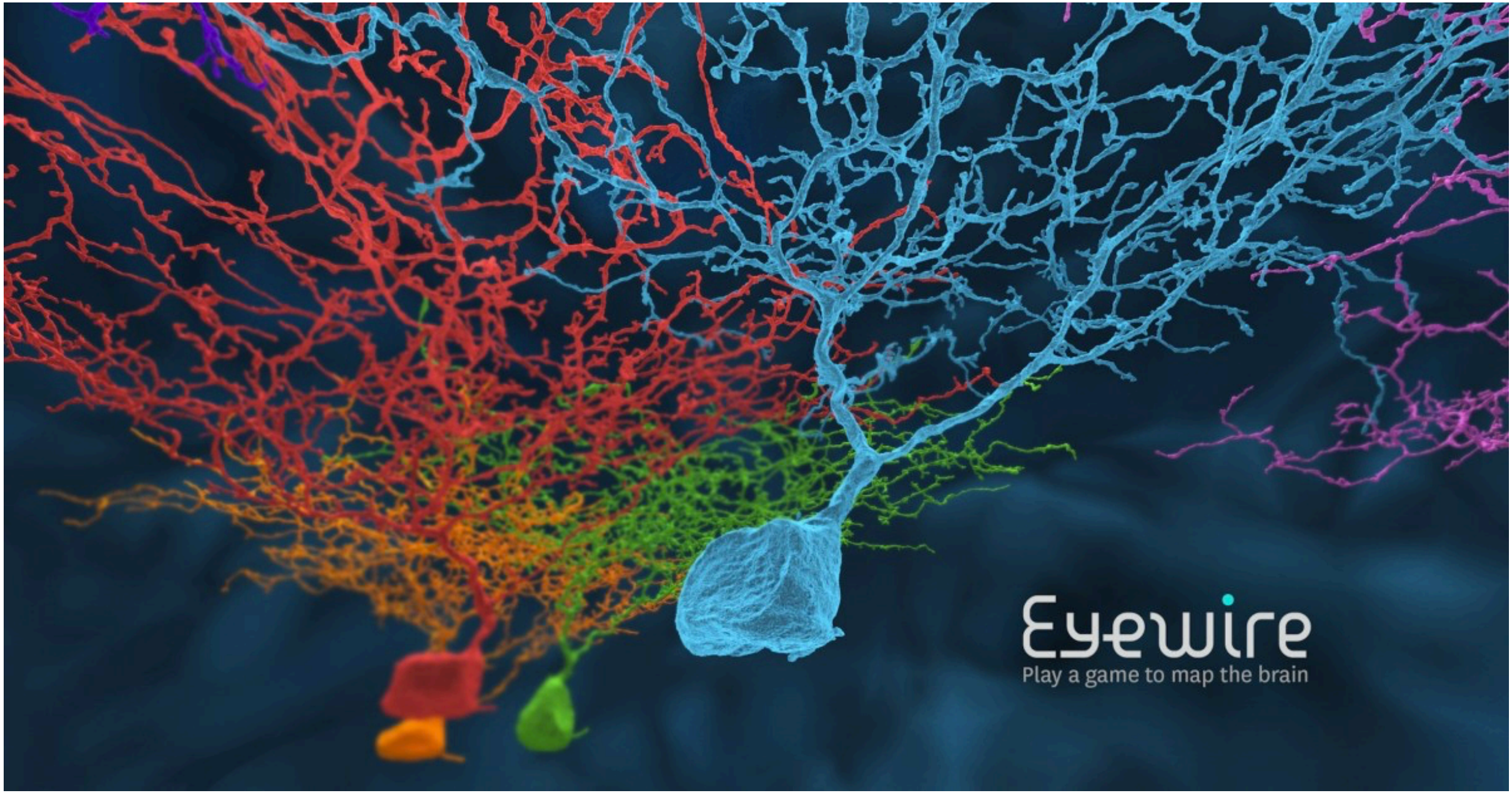
Published: 28 January 2020 **Article history** ▾

Artificial Intelligence Can 'See' Progression of Illnesses Like Huntington's in Blood Sample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