Annexon's C1q Series: Neurodegeneration Franchise

September 27, 2021

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Welcome

2nd C1q Series: Neurodegeneration

Doug Love, Esq.

President & Chief Executive Officer

Annexon Biosciences

Forward-looking Statements

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This presentation and accompanying oral presentation contain “forward-looking” statements about Annexon, Inc. and our industry that involve substantial risks and uncertainties. All statements other than statements of historical facts, including statements regarding our clinical and preclinical programs, timing and commencement of future nonclinical studies and clinical trials and research and development programs, timing of clinical results, strategic plans for our business and product candidates, including additional indications which we may pursue, our financial position, cash runway, size of addressable markets and anticipated milestones, are forward-looking statements. In some cases, you can identify forward-looking statements by terminology such as “aim,” “anticipate,” “assume,” “believe,” “contemplate,” “continue,” “could,” “design,” “due,” “estimate,” “expect,” “focus,” “goal,” “intend,” “may,” “objective,” “plan,” “positioned,” “potential,” “predict,” “seek,” “should,” “target,” “will,” “would” and other similar expressions that are predictions of or indicate future events and future trends, or the negative of these terms or other comparable terminology.

Forward-looking statements are not guarantees of future performance and are subject to risks and uncertainties that could cause actual results and events to differ materially from those anticipated, including, but not limited to, risks and uncertainties related to: our history of net operating losses; our ability to obtain necessary capital to fund our clinical programs; the early stages of clinical development of our product candidates; the effects of COVID-19 or other public health crises on our clinical programs and business operations; our ability to obtain regulatory approval of and successfully commercialize our product candidates; any undesirable side effects or other properties of our product candidates; our reliance on third-party suppliers and manufacturers; the outcomes of any future collaboration agreements; and our ability to adequately maintain intellectual property rights for our product candidates. These and other risks are described in greater detail under the section titled “Risk Factors” contained in our Annual Report on Form 10-K and Quarterly Reports on Form 10-Q and our other filings with the Securities Exchange Commission (SEC). All forward-looking statements in this presentation speak only as of the date of this presentation. Except as required by law, we undertake no obligation to publicly update any forward-looking statements, whether as a result of new information, future events or otherwise.

This presentation concerns drugs that are under clinical investigation and which have not yet been approved for marketing by the U.S. Food and Drug Administration (FDA). These are currently limited by federal law to investigational use, and no representation is made as to their safety or effectiveness for the purposes for which they are being investigated.

Agenda

TIME (A.M.)	TOPIC	PRESENTER
10:00-10:10	Welcome—2nd C1q Series on Neurodegeneration	**Doug Love**, Esq. President & Chief Executive Officer, Annexon Biosciences
10:10-10:30	C1q and Complement-Mediated Neurodegeneration (CMND)	**Ted Yednock**, PhD Chief Scientific Officer, Annexon Biosciences
10:30-10:40	Neurofilament Light (NfL), an Established Measurement of Neurodegeneration	**Prof Henrik Zetterberg**, MD, PhD Department of Psychiatry and Neurochemistry, University of Gothenburg, Sweden; Institute of Neurology, University College London, UK
10:40-10:55	CMND and Huntington's Disease (HD): Anti-C1q as Neuroprotective Approach in HD	**Prof Beth Stevens**, PhD Assistant Professor of Neurology, Children's Hospital, Harvard Medical School, Boston, MA
10:55-11:05	Huntington's Disease (HD): Clinical Perspective on HD, Including use of NfL	**Prof Ed Wild** FRCP, PhD Consultant Neurologist, NHNN Queen Square Associate Director, UCL Huntington's Disease Centre
11:05-11:15	Amyotrophic Lateral Sclerosis (ALS): Clinical Perspective on ALS, Including use of NfL	**Angela Genge**, MD, FRCP (C) Director, Clinical Research Institute Montreal Neurological Institute and Hospital
11:15-11:30	Overview of Annexon's CMND Clinical Programs	**Sanjay Keswani**, MBBS, FRCP Chief Medical Officer, Annexon Biosciences
11:30-12 noon	Closing Remarks and Q&A	**Doug Love**, Esq. President & Chief Executive Officer, Annexon Biosciences

Unlocking a New Generation of Complement Medicines

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1 mission:

Bring game-changing therapies to patients suffering from serious complement-mediated diseases

2 **Disease processes**

3 **Therapeutic franchises:**
Autoimmune, Neurodegeneration, Ophthalmology

3 **Clinical-stage candidates**

5 **Phase 2+ clinical trials underway**

7 **Clinical data readouts by 2023**

$302M **in cash and cash equivalents (runway through 2023)**

Current cash and equivalents of $302.4M as of 6/30/2021

Diverse Wholly-Owned Classical Complement Pipeline

Neurodegeneration TA poised to answer early questions and drive immense value

FRANCHISE	CANDIDATE	PRECLINICAL / PHASE 1 / PHASE 2 / PHASE 2/3	STATUS
Autoimmune	ANX005 (IV)	Guillain-Barré Syndrome (GBS)	PH 2/3 DATA 2023
	ANX005 (IV)	Warm Autoimmune Hemolytic Anemia (wAIHA)	PH 2 DATA 2022
	ANX005 (IV)	Multifocal-Motor Neuropathy (MMN)*	INITIATE PH 2 1H-2022
	ANX009 (SC)	Lupus Nephritis (LN) *	INITIATE P1b 1H-2022
	ANX1502 (oral)	Autoimmune	SUBMIT IND/CTA YE 2021
Neurodegeneration	ANX005 (IV)	Huntington's Disease (HD)	INITIAL PH 2 DATA Q4 2021
	ANX005 (IV)	Amyotrophic Lateral Sclerosis (ALS)	INITIAL PH 2 DATA 1H 2022
	ANX105 (IV)	Neuro	SUBMIT IND/CTA YE 2021
Ophthalmology	ANX007 (IVT)	Geographic Atrophy (GA)	PH 2 DATA 2023

IV, intravenous; IVT, intravitreal; SC, subcutaneous.

* Newly announced indications

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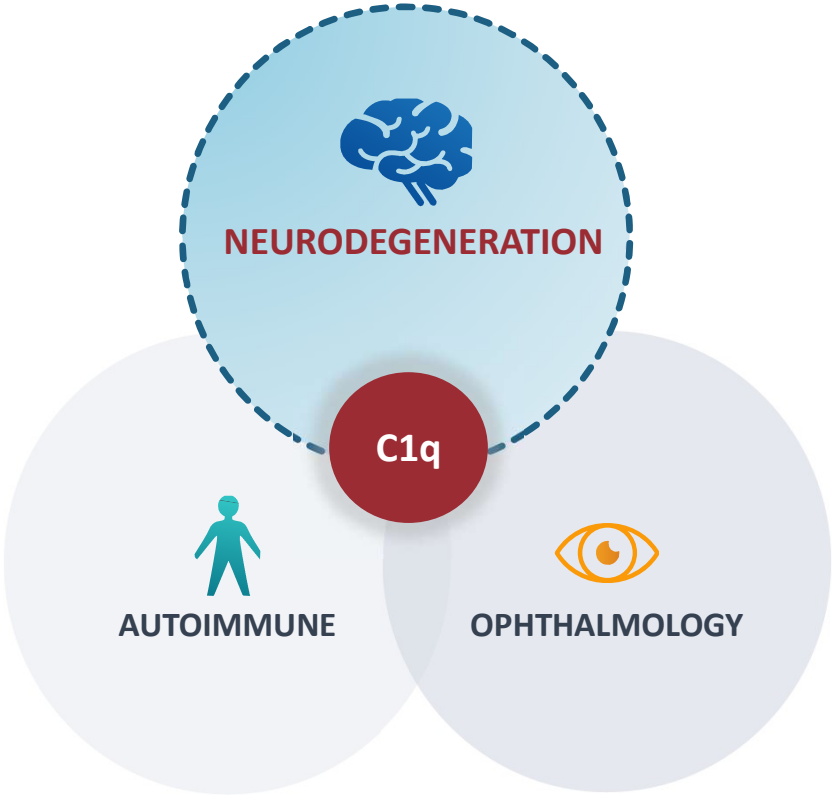
Groundbreaking Approach Targeting Complement-Mediated Neurodegeneration (CMND)



Unique Potential of Anti-C1q Platform

- **Pioneering approach to treat CMND:** Preserve functioning synapses, neuronal health & function
- **Broad therapeutic potential:** CMND major driver of neurodegeneration in a host of brain & eye diseases
- **Established biomarker in early trials (NfL):** Correlates with patient disability; reduction shown to correlate with clinical benefit in multiple diseases
- **Early platform promise:** NfL reduction shown in three therapeutic areas (GBS Ph1 POC, HD & ALS preclinical)

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C1q and Complement-Mediated Neurodegeneration

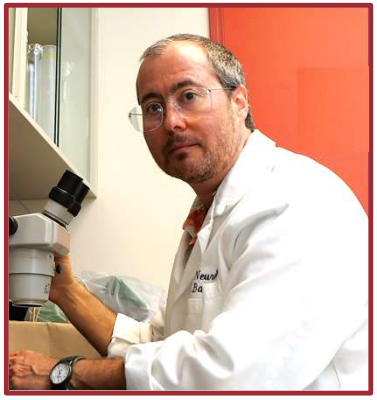
Ted Yednock, PhD

Chief Scientific Officer

Annexon Biosciences

Executive Summary:
Complement Mediated Neurodegeneration (CMND)

- C1q-mediated synapse loss is a **common pathway of neurodegeneration and disability**
- Occurs in multiple diseases **independent of inciting etiology** (e.g., Aβ, tau, intraocular pressure)
- Synapse loss **precedes loss of neurons and correlates with functional decline**
- Protecting synapses with **anti-C1q protects synapses, cognitive behavioral and motor function**
- Important to **inhibit classical pathway at the start** to block all synapse damaging components

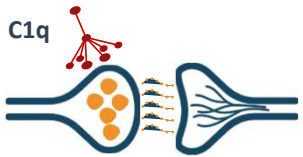


Ben Barres

CMND discovered by Annexon co-founder, the late Dr. Ben Barres and Dr. Beth Stevens

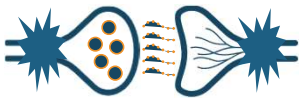
CMND Involves Aberrant Activation of the Classical Pathway to Cause the Loss of Functioning Synapses and Neuronal Decline

Normal
C1q Function



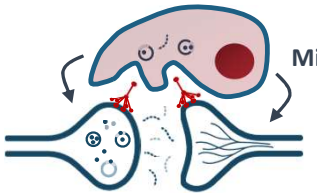
Sculpts the brain and retina in development

Aberrant
Triggers



Neuronal stress may induce aberrant activation of C1q

Disease
C1q Dysfunction



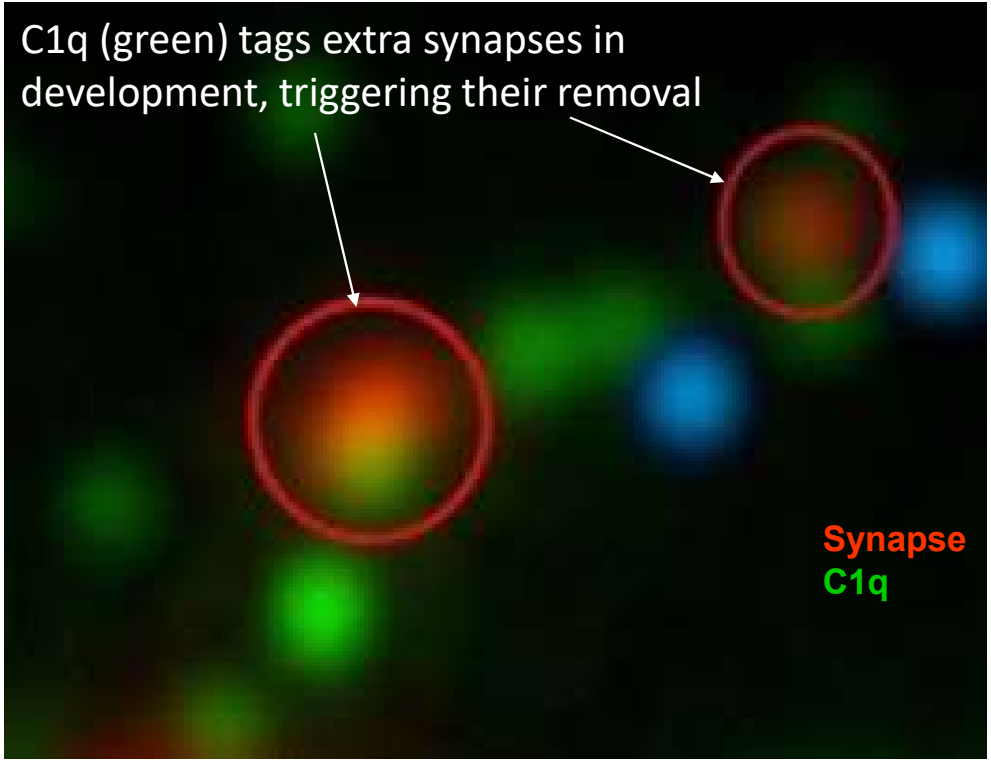
Removes functioning synapses
Anti-C1q potentially protects against synaptic loss

C1q blockade results in functional benefits in multiple disease models, including:*

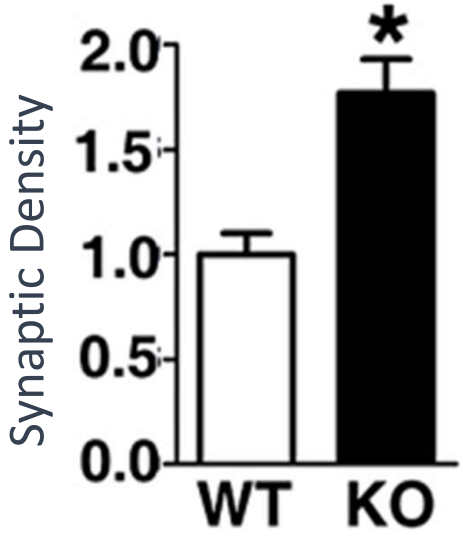
- Huntington's Disease[1]
- Alzheimer's Disease[2]
- Spinal Muscular Atrophy[3]
- Glaucoma[4]
- Geographic Atrophy (AMD)[5]
- Frontotemporal Dementia[6]
- Traumatic Brain Injury[7]
- Amyotrophic Lateral Sclerosis[8]
- Progressive Multiple Sclerosis[9]

*[1]Wilton and Stevens, Harvard, *unpublished*. [2]Fonseca, 2004, *J Neurosci*; Hong, 2016, *Science*; Dejanovic, 2018, *Neuron*; [3]Vukojicic, 2019, *Cell Reports*; [4]Howell, 2011, *J Clin Inves*; Williams, 2016, *Mol Neurodegen*; [5]Jiao, 2018, *Mol Neurodeg*; [6]Lui, 2016, *Cell*; [7]Krukowski, 2018, *Int.J Mol Sci*; Holden, 2021, *Science*; Annexon NfL reduction in SOD1 model, unpublished; [9]Absinta, *Nature*, 2021

C1q Normal Function For Synapse Elimination During Early Development



Mice with genetic deletion of C1q retain more functional synapses throughout development

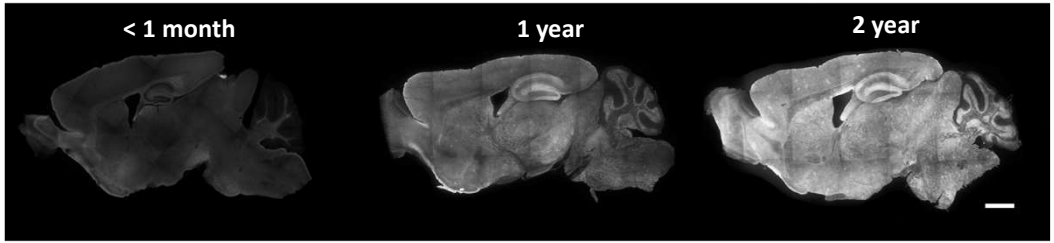


Nearly 2X more synapses survive in the C1q KO mouse

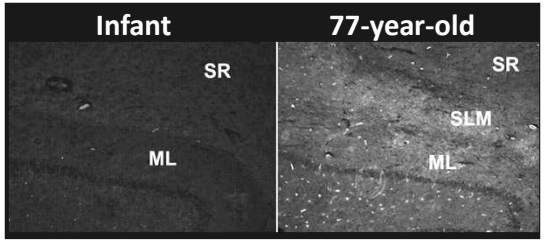
Stevens and Barres Cell 2007

C1q Accumulates on Synapses During Normal Aging, But Remains Silent

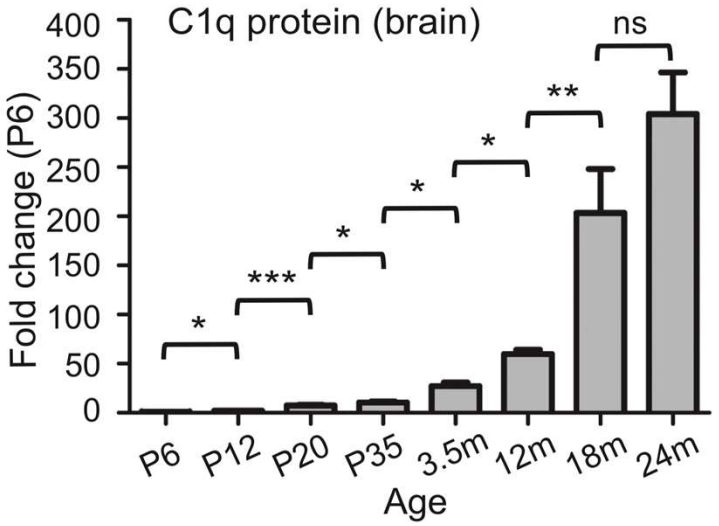
Mouse brain



Human brain



Accumulation of C1q in CNS of mice with age



- ***Aging is the biggest risk factor for neurodegenerative disease***
- ***C1q accumulation / CMND important components of this risk***

Stephan, Barres J. Neurosci. 2013

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The Role of C1q as a Major Driver of Synaptic Loss and Neurodegeneration is Well-Researched

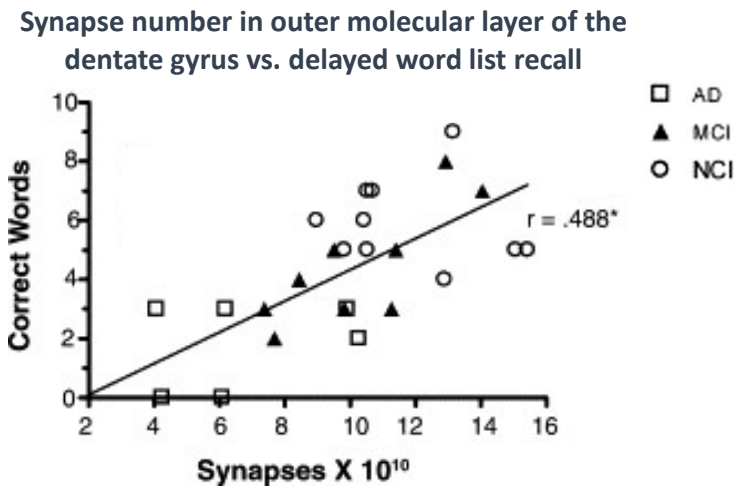
Original discoveries of Annexon co-founder, the late Dr. Ben Barres and Dr. Beth Stevens, on the **role of C1q in neurodegenerative diseases**

- **Spawned entire field that has been validated in laboratories across the world**
- **Synapse loss is a major driver of neurological disability and blindness**
- **Precedes loss of neurons**
- **Correlates with functional loss/cognitive decline**

Why Synapse Loss Matters in Neurodegeneration:

- Precedes loss of neurons
- Correlates with disease progression, decline in cognitive and motor function*

Early Synapse Loss in Alzheimer's Disease

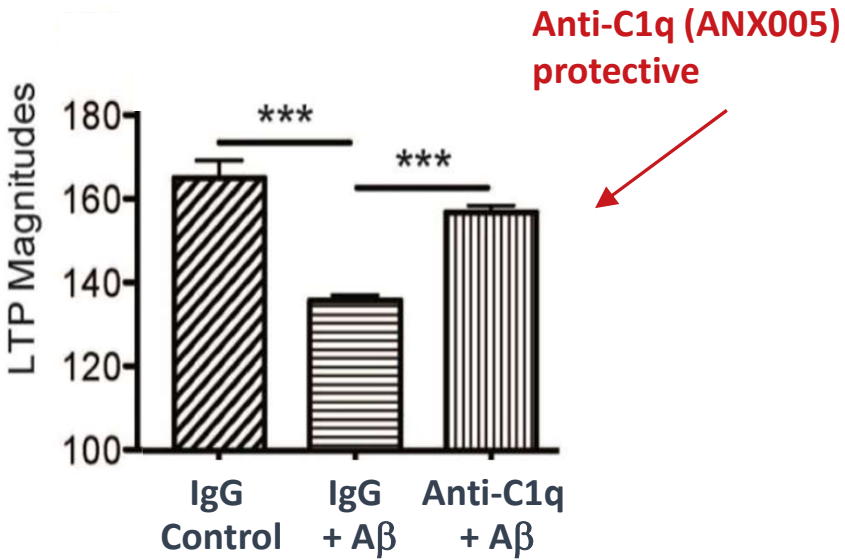


Similar result obtained in patients with Huntington's disease*

Scheff, Neurobiol Aging. 2006. 27:1372
**Wilton and Stevens, Harvard, unpublished*

C1q Inhibition Prevents Synapse Loss and Preserves Function

Anti-C1q prevents Aβ–induced loss of neuronal function in an acute *ex vivo* model of Alzheimer's disease (AD)

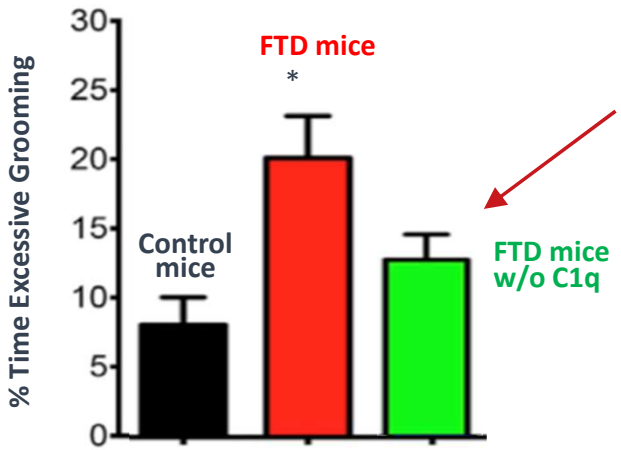


Ex vivo brain slides: % baseline long term potentiation (electrophysiology)

Hong, et al., 2016 *Science*

... C1q Genetic Deletion Protects Behavioral Function

Mouse Model of Frontotemporal Dementia (FTD) (progranulin deletion)



Genetic deletion of C1q protective against development of obsessive behavior

Mouse model of FTD with genetic deletion of progranulin

Liu et al., 2016 *Cell* 165:921

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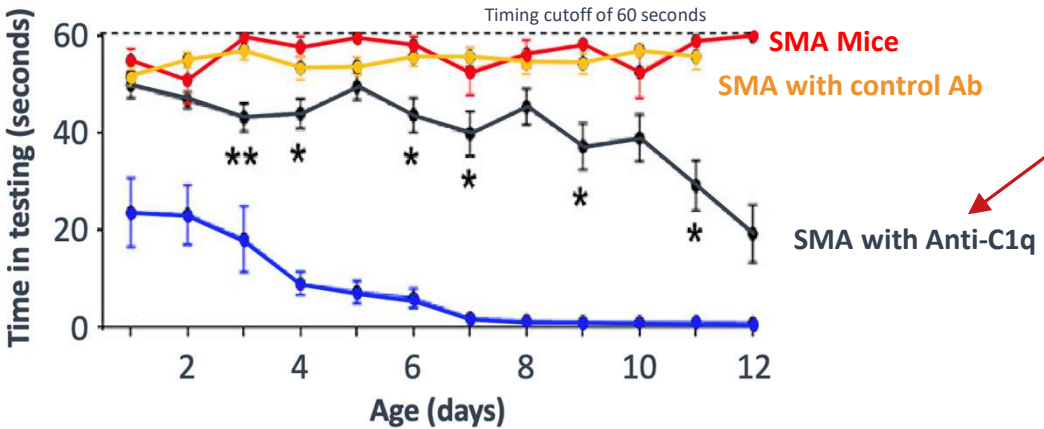
… and C1q Inhibition Protects Motor Function

Allows Gain of Motor Function in Mouse Model of Spinal Muscular Atrophy (SMA)



Anti-C1q (ANX005) allows gain of motor function

Transgenic SMN-Δ7 mouse model of SMA

Vukojicic, 2019 *Cell Reports*29:3087

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Blocking C1q / Classical Complement in CMND

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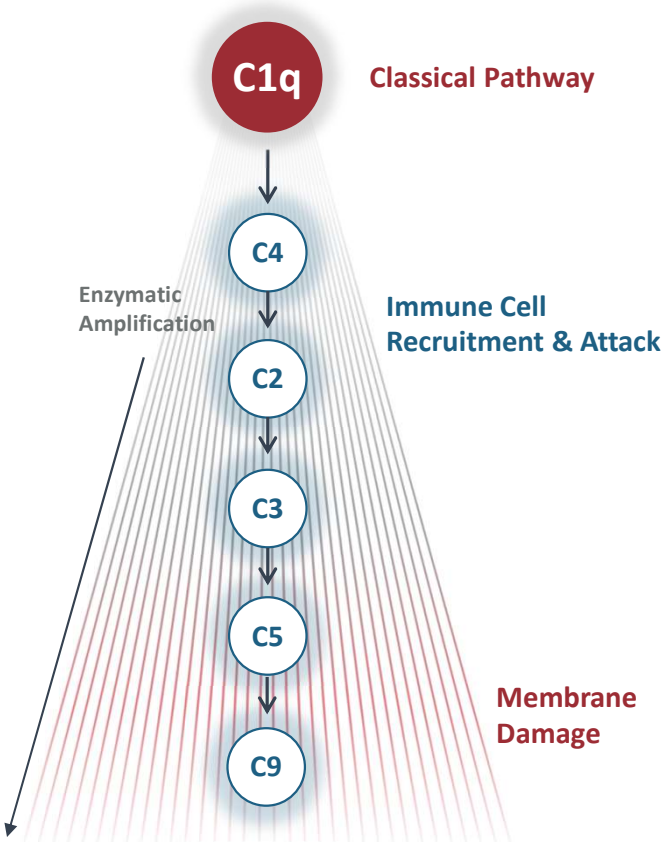
C1q Inhibition Stops Classical Complement Activity at the Start

Prevents downstream activation of all tissue-damaging components



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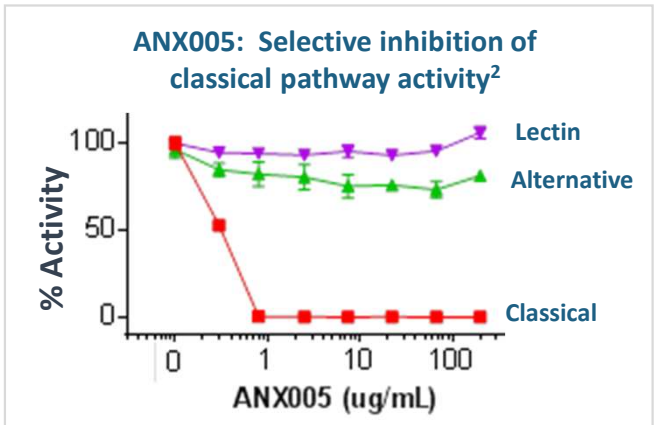
- **Targeting Enhanced Efficacy:** Shuts down all tissue-damaging components of classical pathway (C1q, C4, C3, C5, C9)[1]
- **Targeting Enhanced Safety:** Allows normal immune functions of lectin and alternative complement pathways[1]



[1]Annexon data on file
[2]Wieslab assay; Annexon data on file

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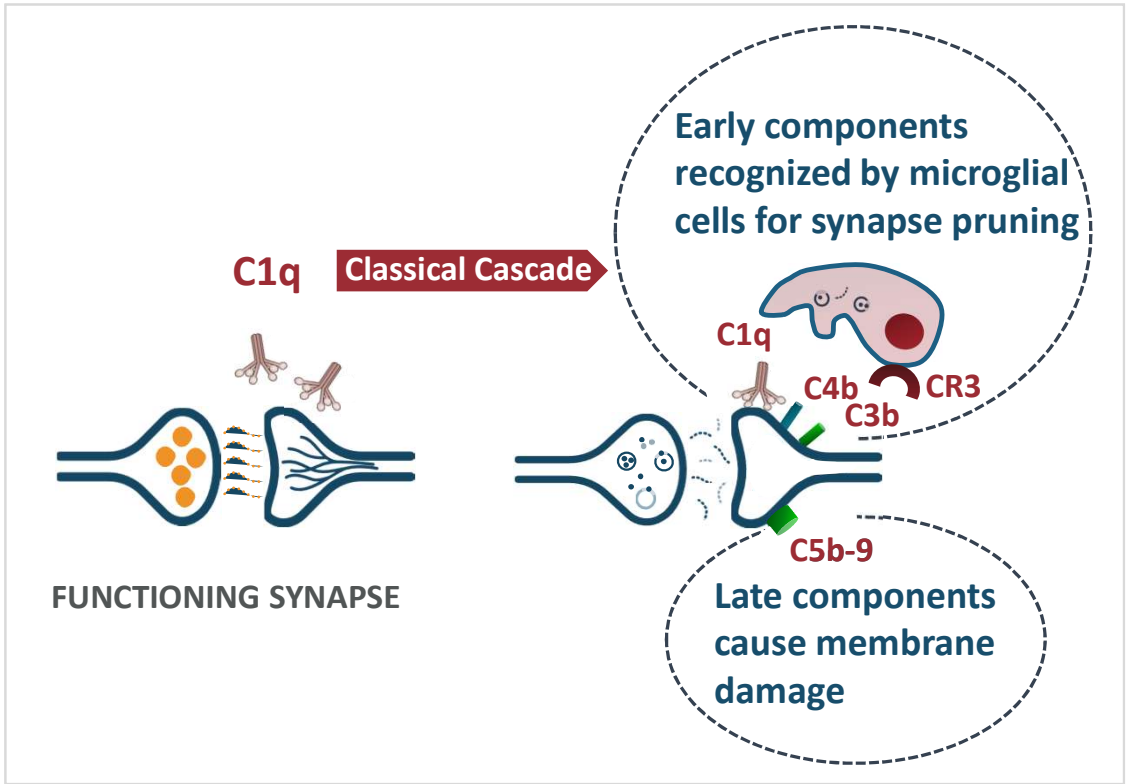
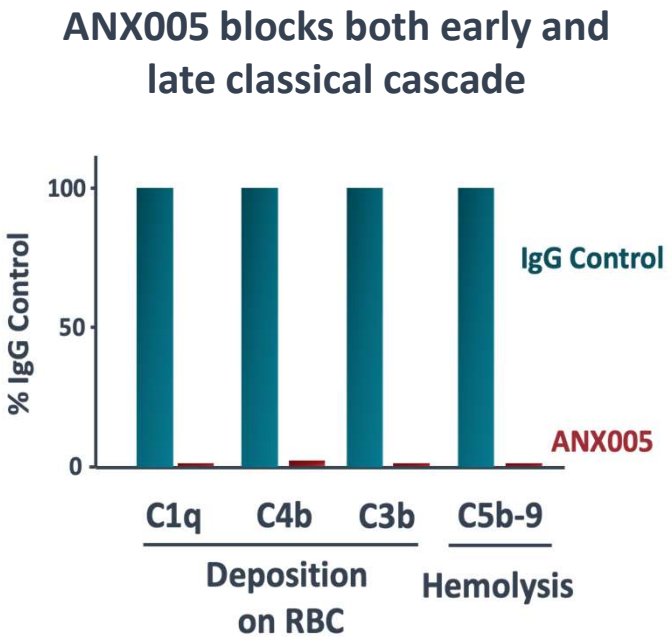
Important to Inhibit Early Components of the Classical Complement Cascade to Block All Aspects of CMND





Mannes, et al., 2021 *Blood* **137** (4):443

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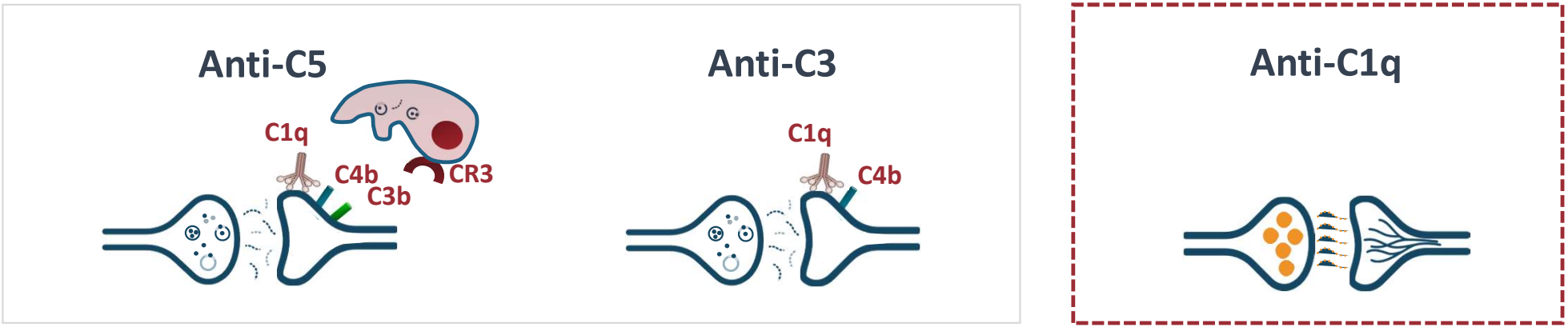
Anti-C1q Differentiated from Other Approaches

Only Way to Block All Early Classical Complement Components involved in CMND



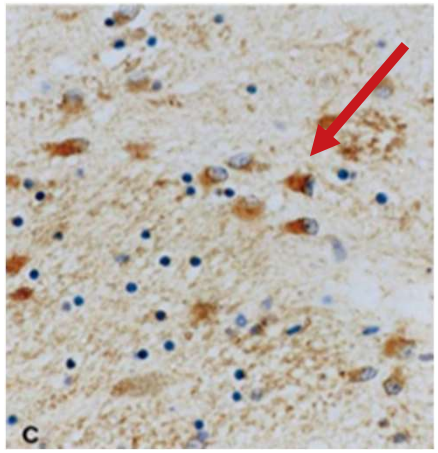
- **C1q, C4b and C3b are the major opsonins of the classical pathway for microglial cell attack**
- **With high or chronic activation, C1q and C4b can drive C3/C5 bypass activity***
- **Important to obtain CNS target engagement to protect against central neurodegeneration**

*Mannes, et al., 2021 *Blood* **137** (4):443

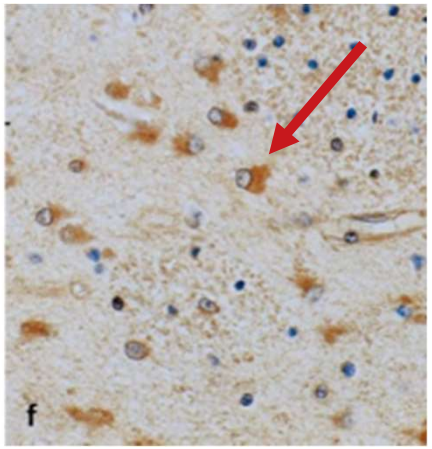
C1q Inhibition in Lead Indications: HD and ALS

Evidence of Classical Complement Activation in Disease-Specific Regions of the CNS in Huntington's Disease

Classical Complement Pathway Activation in the Striatum of HD Brain

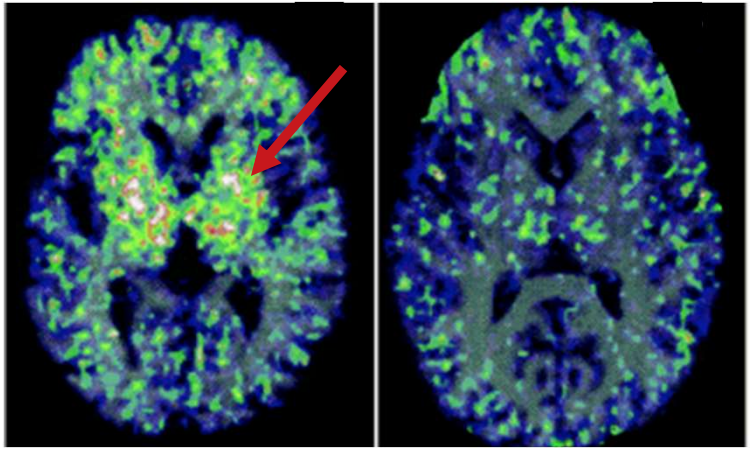


C1q



C3b

Microglial Cell Activation in the Striatum of HD Brain – Cellular source of C1q



HD patient

Healthy adult

Singhrao et al., 1999

MRI/PET scan with PK11195: Pavese, 2006 *Neurology* 66:1638

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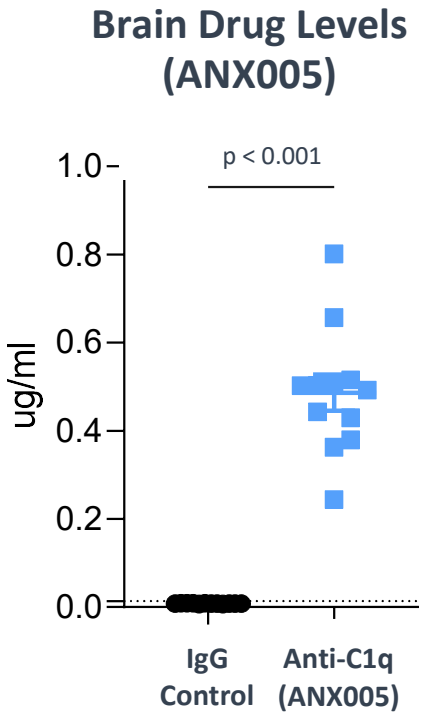
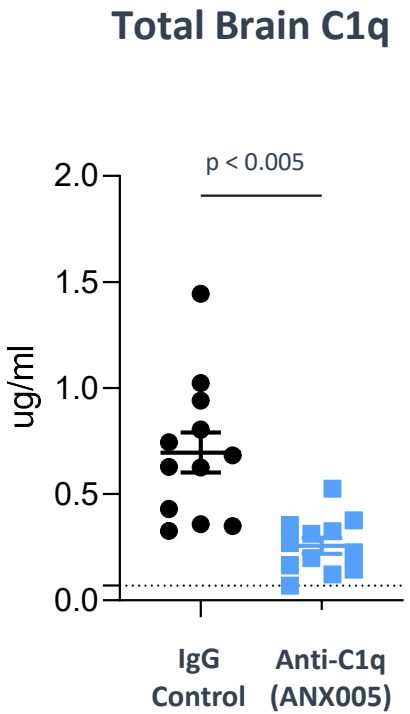
Systemic Treatment with Anti-C1q Blocks C1q in the CNS in HD Mouse Model (R6/2)





Annexon data on file.

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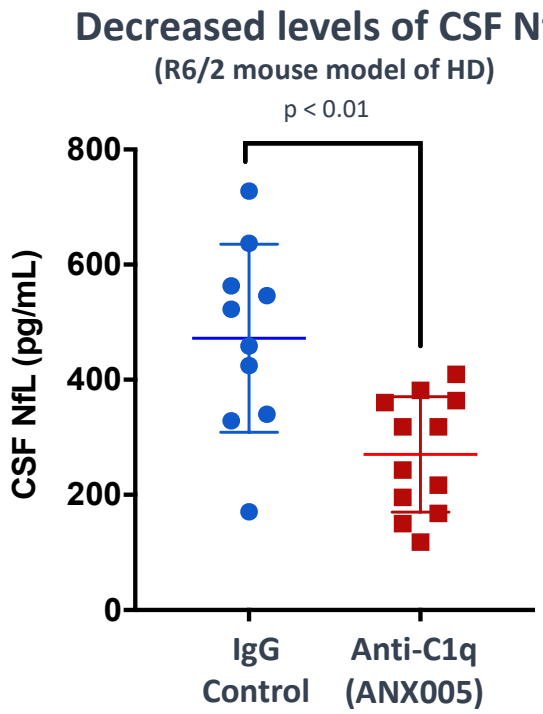
C1q Inhibition Protected Against Neurodegeneration in HD Mouse Model as Measured by NfL



Reduction with anti-C1q (ANX005) over 7 weeks of treatment (4-11 wks of age)

Neurofilament Light Chain (NfL) is released by injured neurons and is used as a marker of neuronal damage

Annexon data on file.

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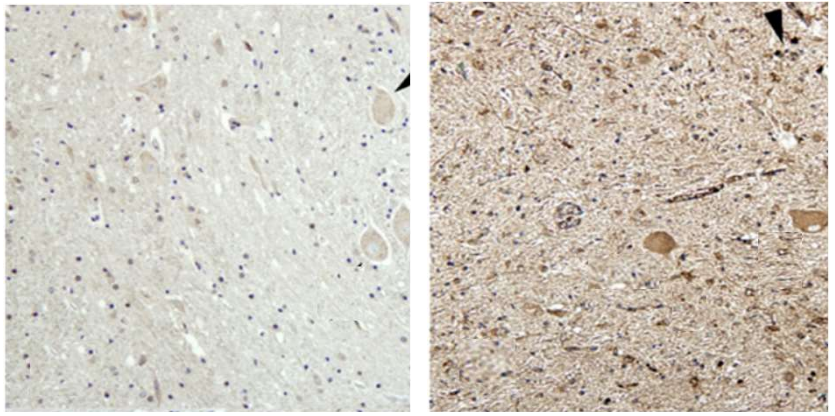
Amyotrophic Lateral Sclerosis (ALS): CNS and PNS Disorder with Evidence of Classical Complement Activation

Enhanced C1q expressed / deposited within the CNS (spinal cord)

Control
No staining with anti-C1q

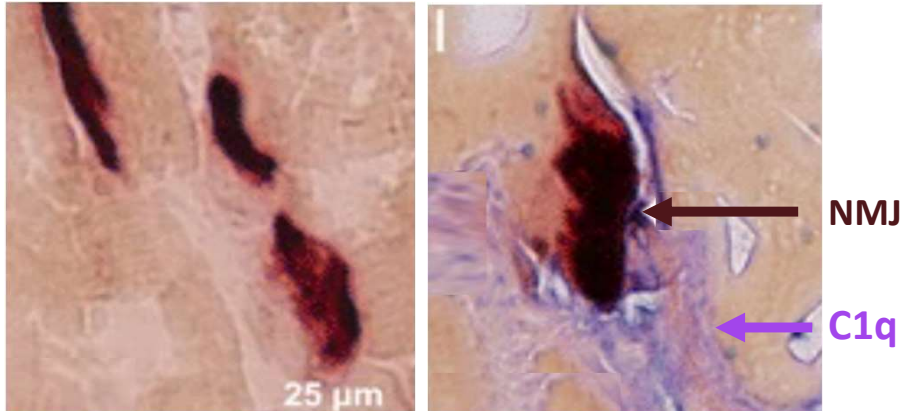
ALS Patient
Broad staining with anti-C1q



C1q deposition on the neuromuscular junction (NMJ) prior to denervation in the PNS

Control

ALS Patient



Sta, et al., 2011 *Neurobiol Disease* **42**:211

Bahia El Idrissi, et al., 2016 *J Neuroinflamm* 13:article 72

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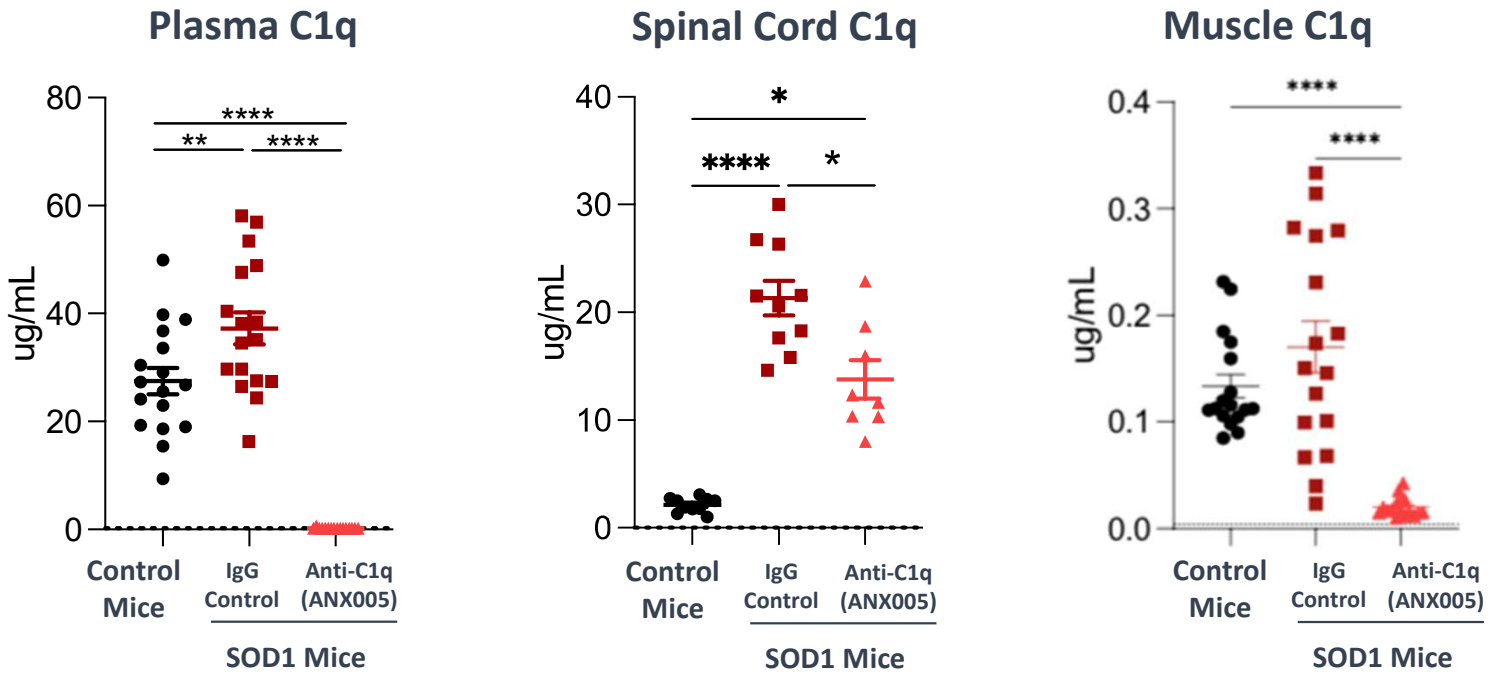
Systemic Administration of Anti-C1q (ANX005) Blocks Peripheral and Central C1q in ALS Mouse Model (SOD1)



Annexon data on file

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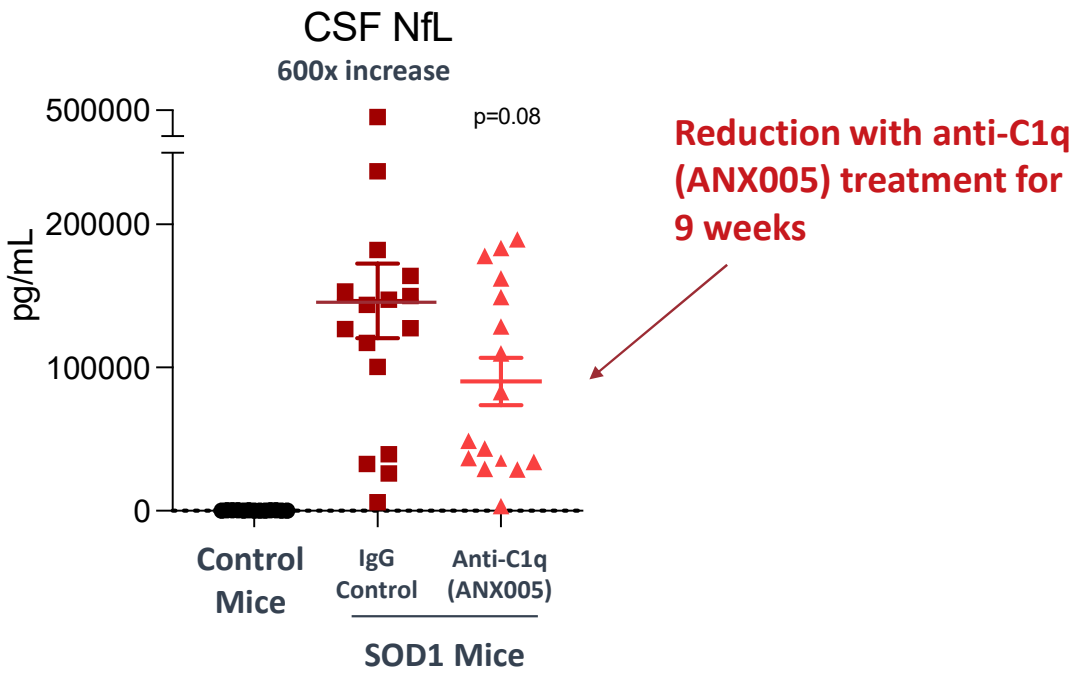
Anti-C1q (mANX005) Protected Against Neurodegeneration as Measured by NfL in ALS Mouse Model (SOD1)

- NfL increases in CSF by 600x with disease
- Anti-C1q reduces NfL in CSF – similar reduction in plasma



Annexon data on file

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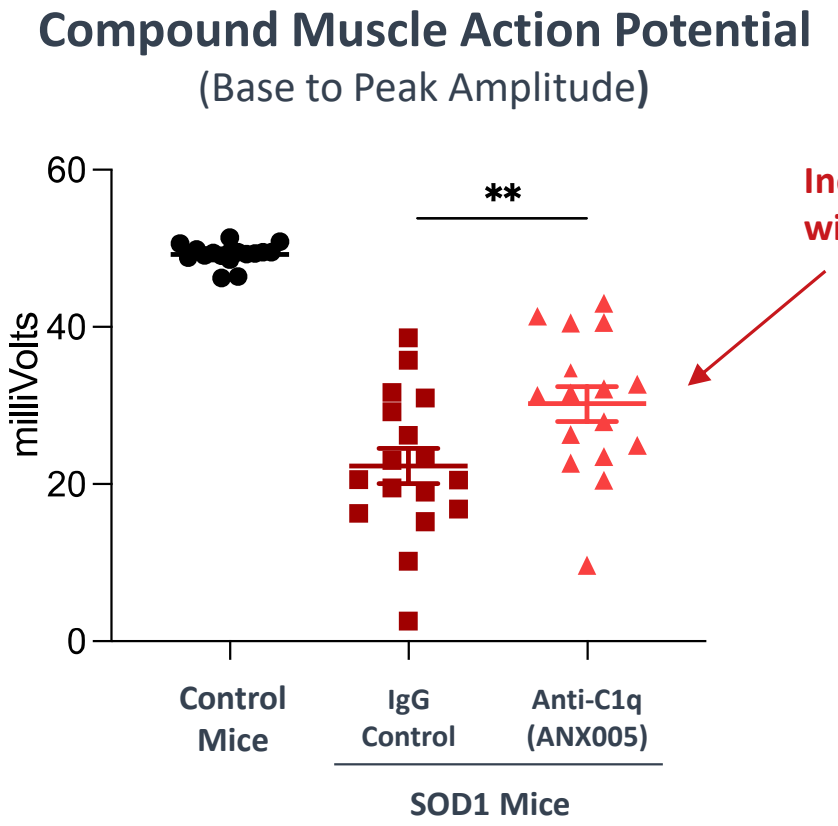
Anti-C1q Protects Neuronal Function / Muscle Force at the Neuromuscular Junction



Increase in muscle force with anti-C1q (ANX005)

Preclinical CMAP and neurofilament heavy chain translated to efficacy with Tofersen in ALS patients

Annexon data on file

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Executive Summary: Complement-Mediated Neurodegeneration (CMND)

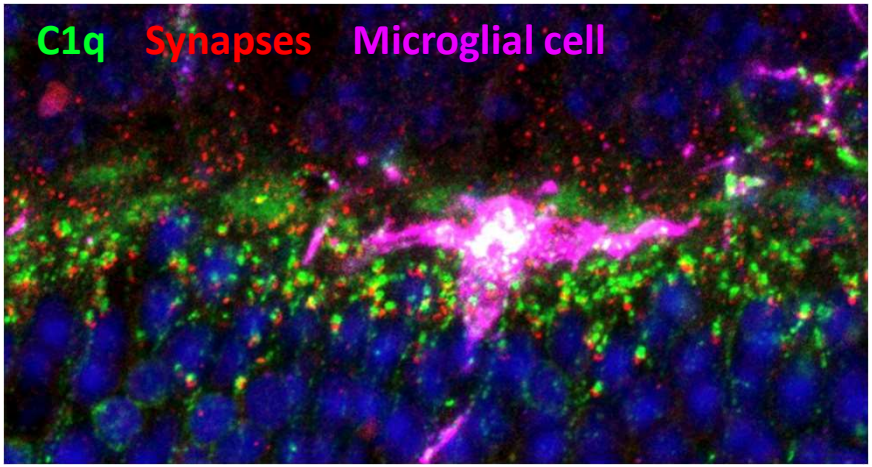
- C1q-mediated synapse loss is a **common pathway of neurodegeneration and disability**
- Occurs in multiple diseases **independent of inciting etiology** (e.g., Aβ, tau, intraocular pressure)
- Synapse loss **precedes loss of neurons and correlates with functional decline**
- Protecting synapses with **anti-C1q protects synapses, cognitive behavioral and motor function**
- Important to **inhibit classical pathway at the start** to block all synapse damaging components

Next Time: CMND in Ophthalmic Diseases / Geographic Atrophy

- C1q rapidly tags synapses on photoreceptor neurons with recruitment of microglial cells post light damage
- C1q tagging correlates with synapse decline and precedes loss of photoreceptor neurons

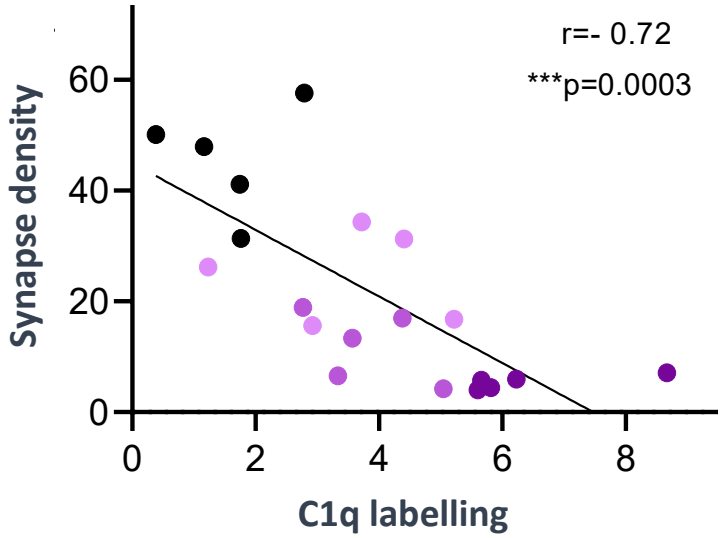
Confocal Image of Mouse Retina

(Three days post damaging light exposure)



Photoreceptor neurons

C1q Labelling vs. Synapse Density



ANNEXON biosciences

ANNEXON biosciences

Neurofilament Light (NfL)

An Established Measurement of Neurodegeneration

Henrik Zetterberg, MD, PhD

Department of Psychiatry and Neurochemistry

University of Gothenberg, Sweden

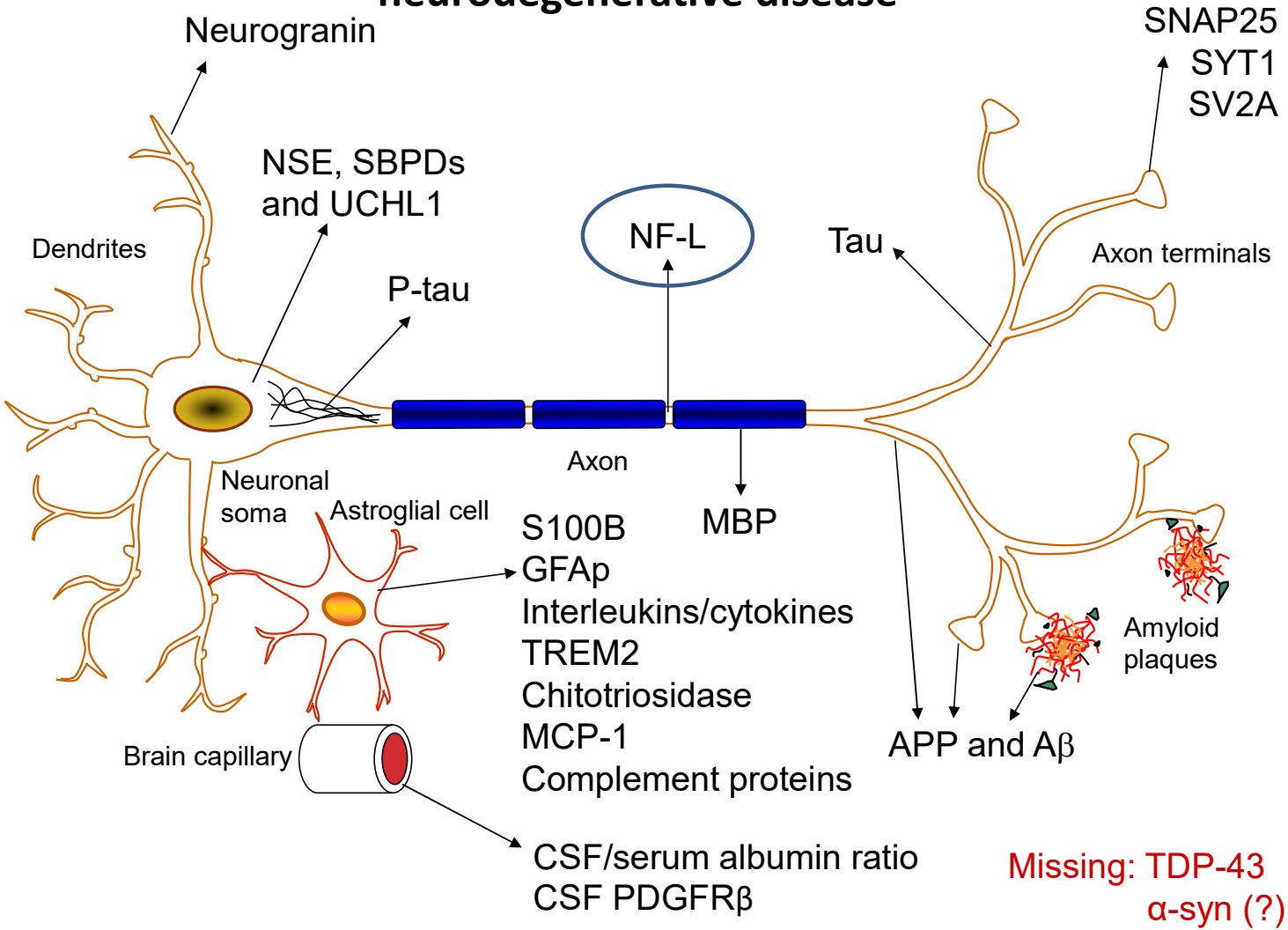
Institute of Neurology, University College London, UK

UK Dementia Research Institute

Perspective on neurofilament light

Henrik Zetterberg, MD, PhD
Department of Psychiatry and Neurochemistry,
University of Gothenburg, Sweden;
Institute of Neurology, UCL, UK

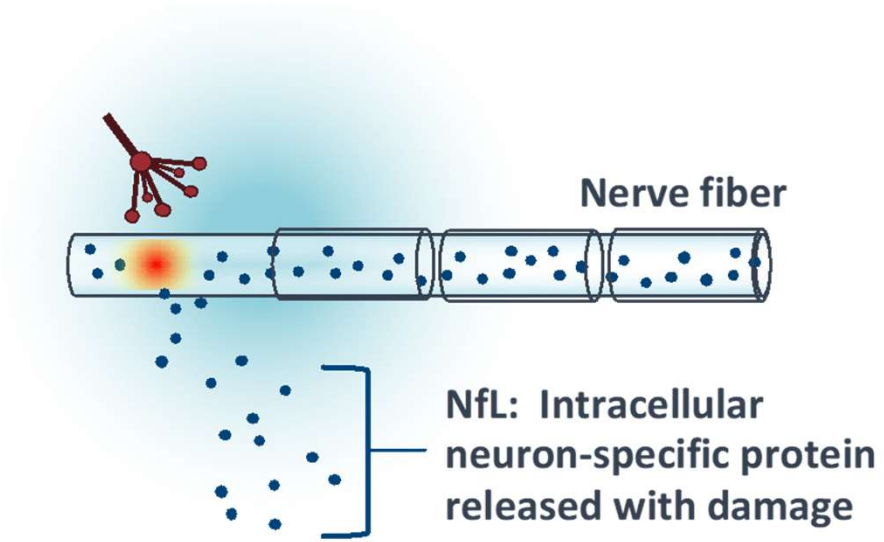
Fluid biomarker candidates of potential relevance to neurodegenerative disease



Missing: TDP-43
α-syn (?)

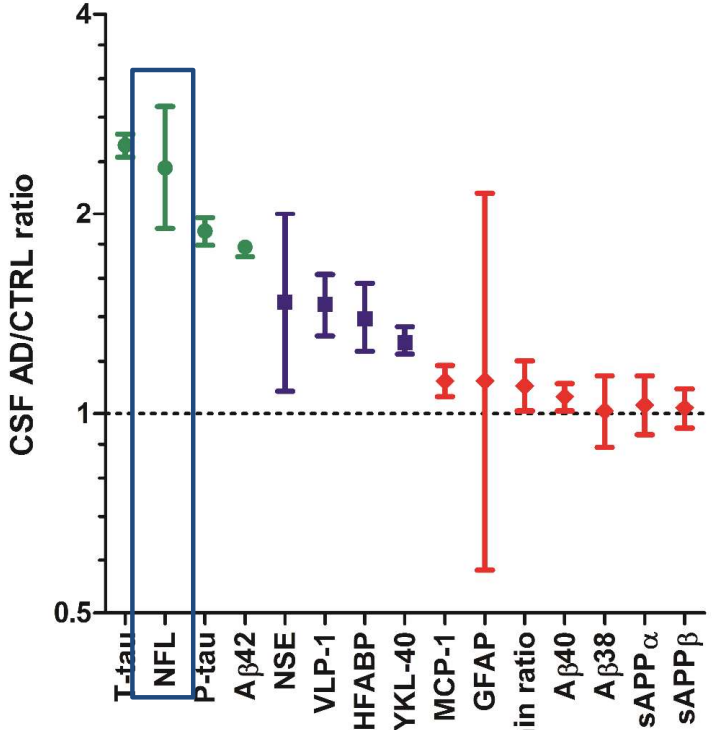
Neurofilament Light Chain (NfL) as a Biomarker for Clinical Development

- Sensitive measure of neuronal damage / degeneration
- Correlates w/ patient disability and predicts outcomes in several diseases (e.g., SMA[1], MS[2], GBS[3], HD[4], ALS[5])
- Reduced by effective therapies for MS and SMA within 3 months of treatment



[1]Olsson, 2019 *J Neurol* 266:2129–2136; [2]Gunnarsson 2011 *Ann Neurol* 69:83; Ferraro 2020 *Acta Neurol Scand* 141:16; [3]Martín-Aguilar, 2020 *medRxiv* 10.1101/2020.03.24.20042200; [4]Byrne, 2017 *Lancet Neurol* 16: 601; ALS; [5]Benatar 2018 *Ann Neurol* 84:130

CSF neurofilament light – an N marker in the A/T/N criteria for Alzheimer's disease?

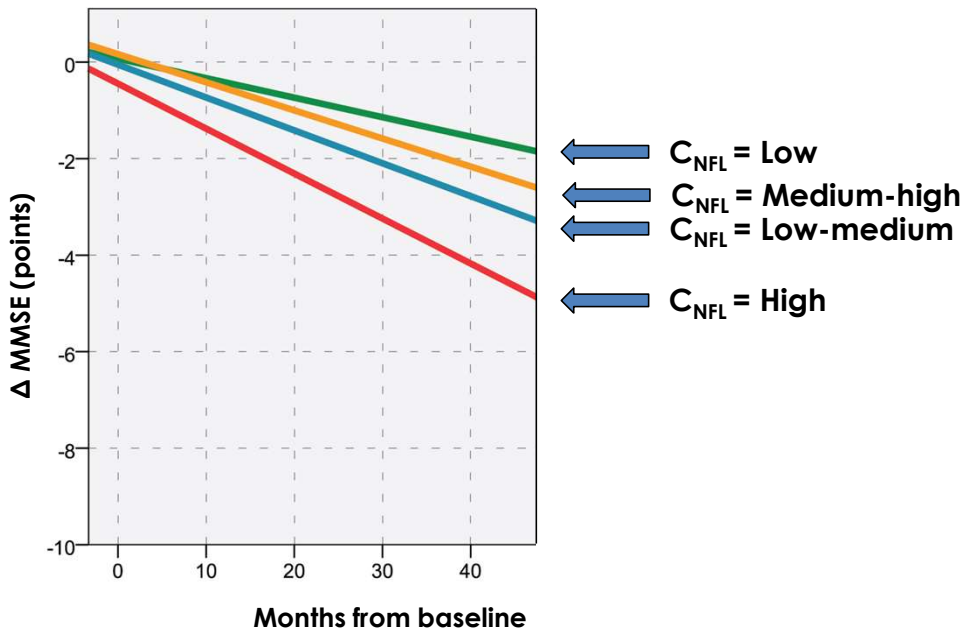


Olsson B *et al*., Lancet Neurol 2016

CSF NFL as a predictor of disease progression in MCI

Association with longitudinal change in MMSE

Based on the baseline CSF NFL levels, all subjects with an MCI diagnosis at baseline were classified into quartiles (low, low-medium, medium-high and high)

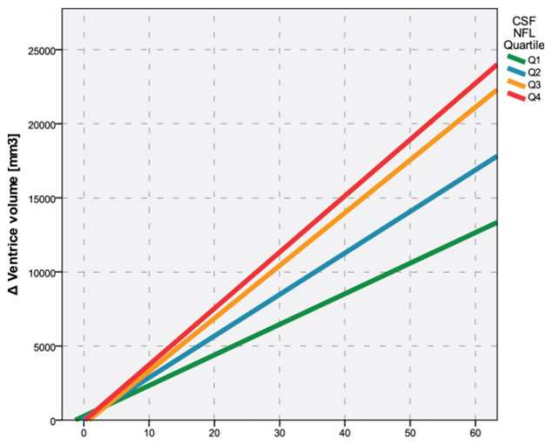


- **Higher CSF NFL levels predict a more pronounced decrease in MMSE scores**

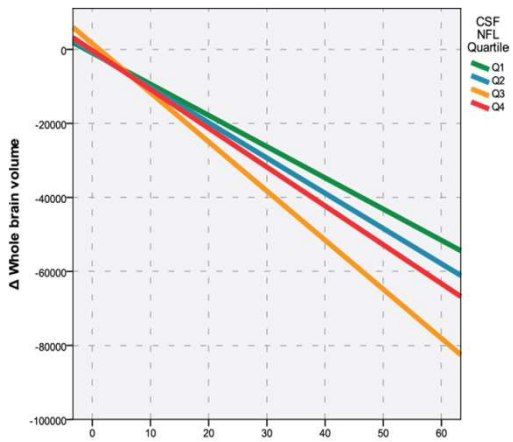
Zetterberg *et al.*, JAMA Neurol 2016

CSF NFL in relation to brain structure

Δ Ventricular volume



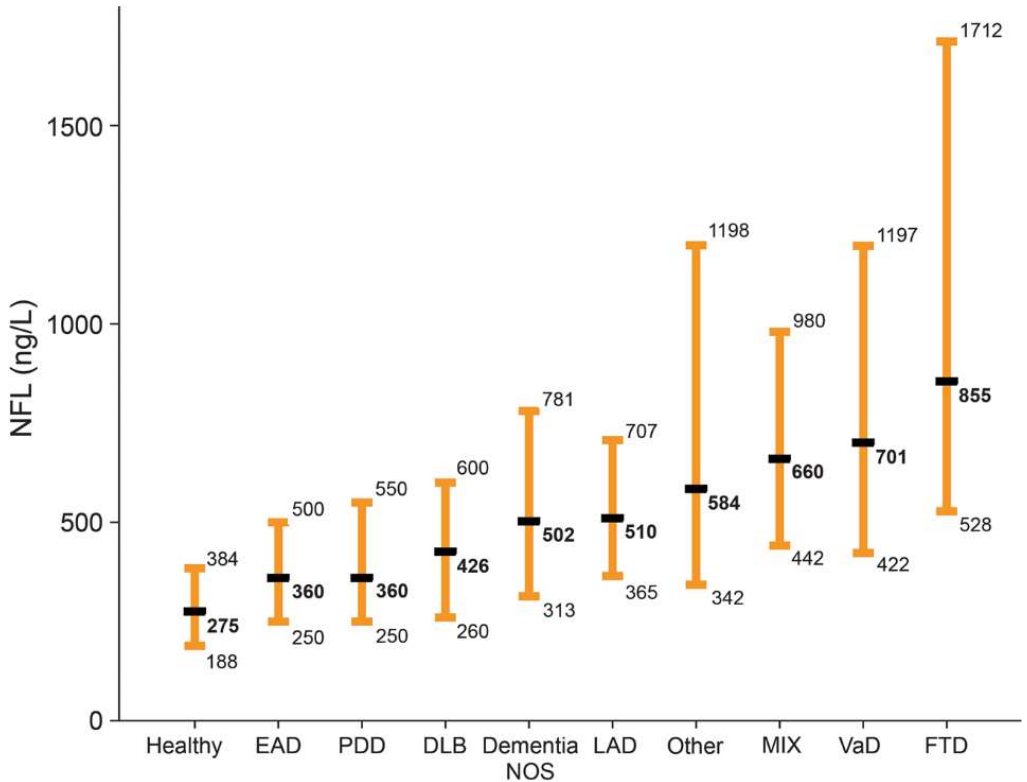
Δ Whole brain volume



- **Higher CSF NFL levels are associated with faster brain atrophy over time as measured by total brain volume and ventricular volume**

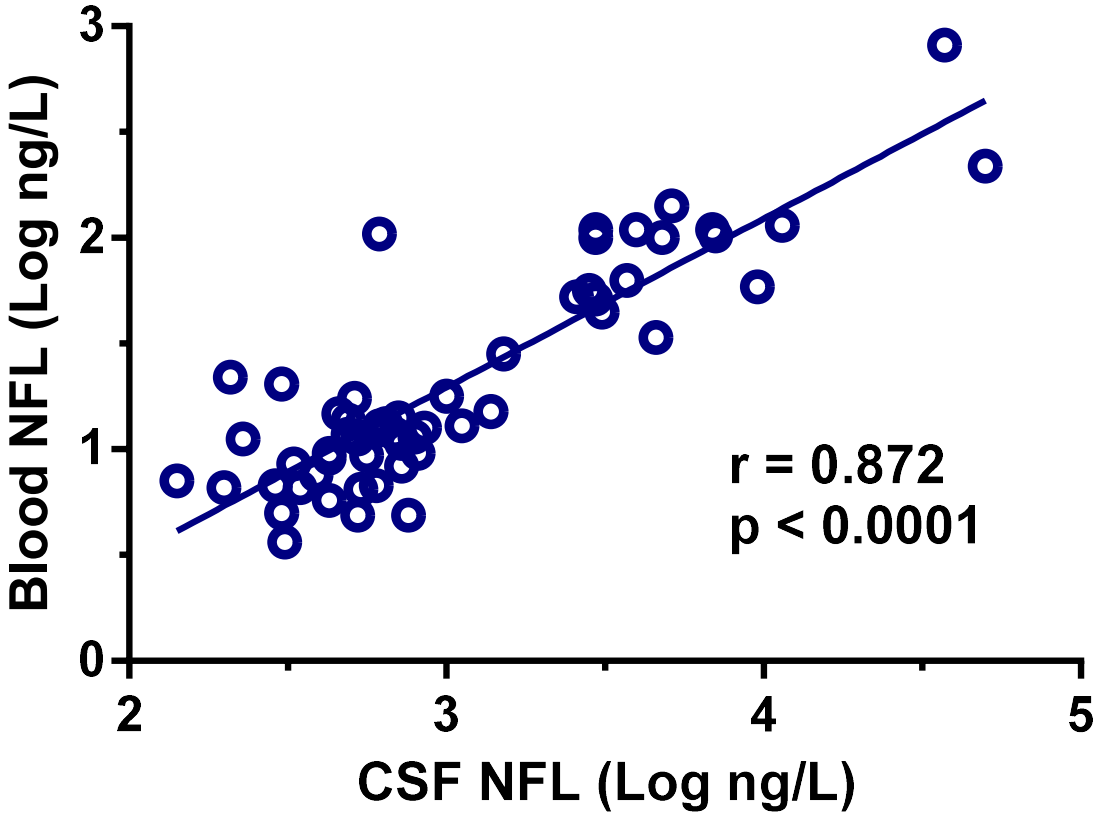
Zetterberg *et al.*, JAMA Neurol 2016

Neurofilament light – positive across neurodegenerative diseases



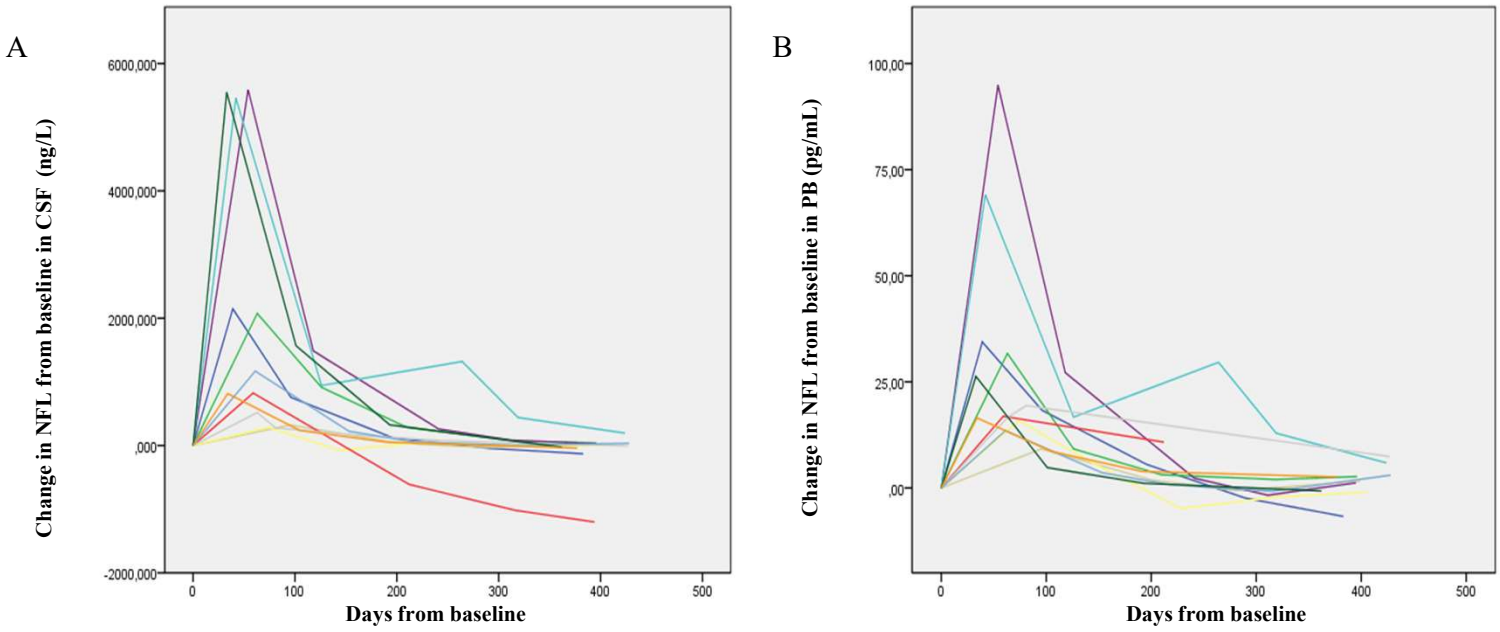
Skillbäck *et al*., Neurology 2014

Plasma NfL correlates with CSF NfL…



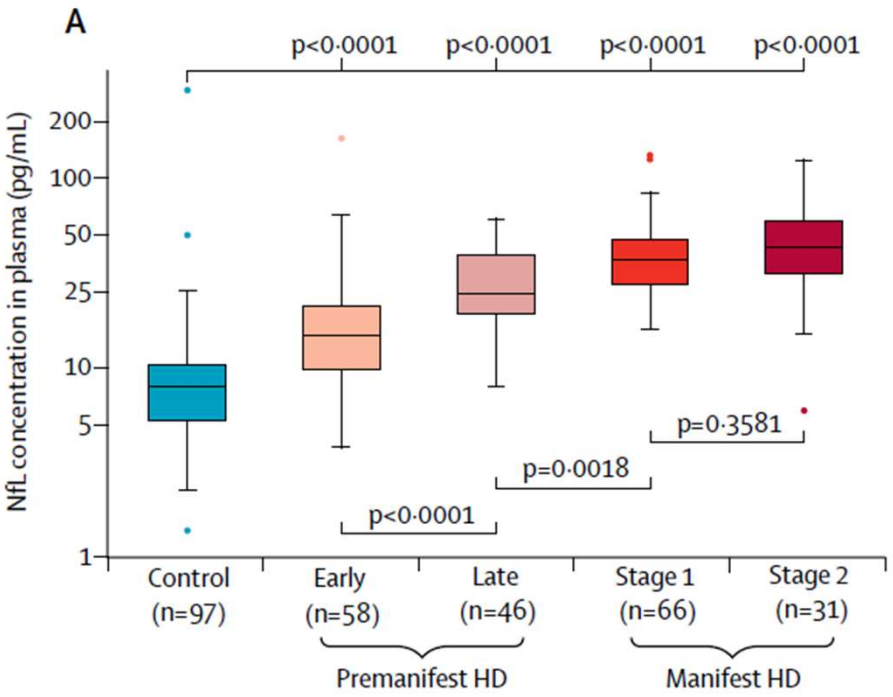
Gisslén et al., 2015

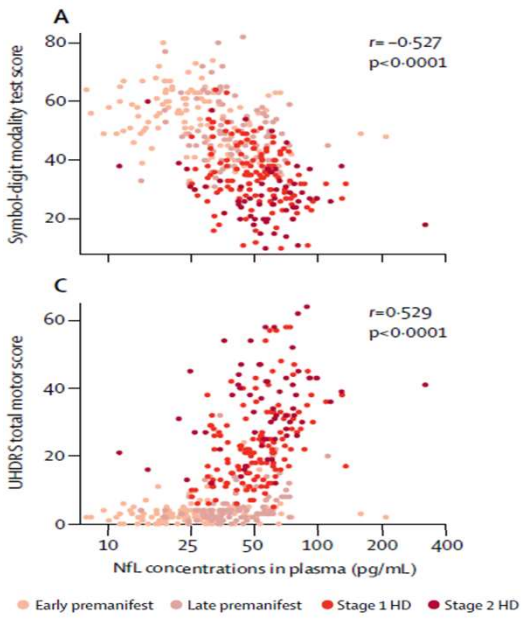
…and shows similar dynamics



Bergman *et al.*, Neurol Neuroimmunol Neuroinflamm. 2016

NfL Concentrations Increase with HD Progression and with Cognitive and Motor Impairment





- **Fig A : Higher plasma NfL levels correlates with lower symbol digit modalities score (worsening)**
- **Fig C : higher plasma NfL levels correlates with higher UHDRS total motor score (worsening)**

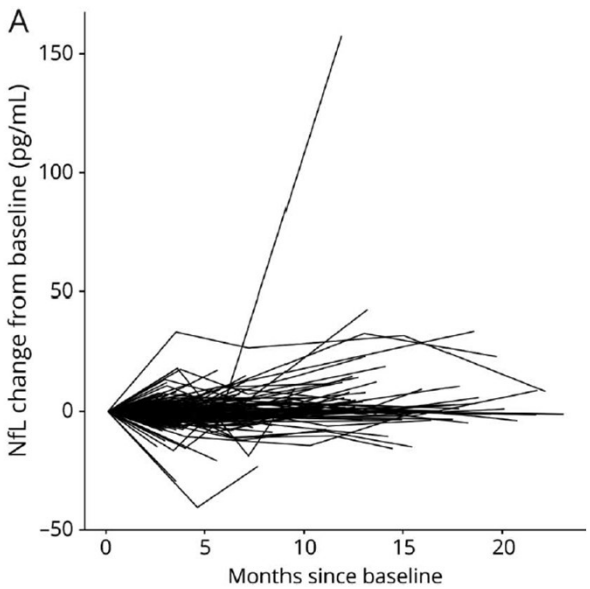
Byrne et al. Lancet Neurology 2017:

NfL is a Prognostic Indicator in ALS

Covariates	Impact on ALSFRS-R slope[a] Estimate (95% CI)	*p* Value	Impact on survival[b] Hazard ratio (95% CI)	*p* Value
Baseline age, y	0.001 (−0.008 to 0.010)	0.89	1.02 (1.00–1.05)	0.049
Male	−0.09 (−0.33 to 0.15)	0.47	1.37 (0.84–2.23)	0.21
***C9ORF72* HREM**	−0.16 (−0.57 to 0.25)	0.45	1.70 (0.91–3.18)	0.10
Site of onset: bulbar	−0.04 (−0.45 to 0.37)	0.84	1.10 (0.53–2.29)	0.80
Site of onset: limb	−0.01 (−0.46 to 0.45)	0.97	1.04 (0.48–2.27)	0.91
Baseline ALSFRS-R	NA	NA	0.96 (0.93–0.99)	0.02
Baseline ΔFRS, points/month	−0.43 (−0.73 to −0.13)	0.006	1.67 (1.09–2.57)	0.02
Baseline log(NfL), log(pg/mL)	−0.42 (−0.62 to −0.21)	<0.001	2.12 (1.39–3.23)	<0.001
Baseline log(pNfH), log(pg/mL)	0.07 (−0.03 to 0.17)	0.17	1.01 (0.84–1.22)	0.88

Abbreviations: *HREM* = hexanucleotide repeat expansion mutation; NA = not applicable; NfL = neurofilament light; pNfH = phosphorylated neurofilament heavy.
[a] Based on multivariate regression analysis, with the ALSFRS-R slope (i.e., ALSFRS-R rate of decline) as outcome.
[b] Based on Cox proportional hazards model, with tracheostomy- and permanent assisted ventilation–free survival as outcome.

Effect of clinical and NfL characteristics on functional decline and survival
N=229 ALS patients



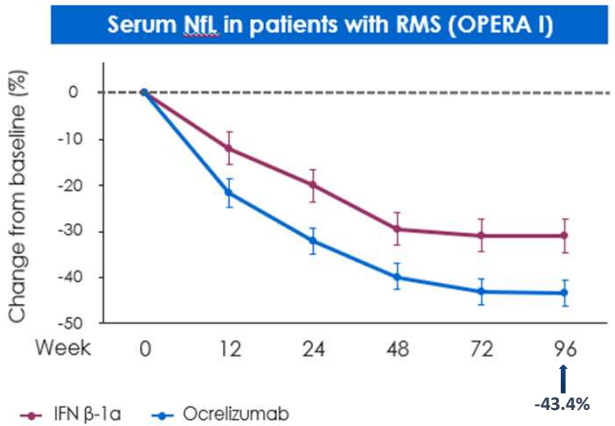
Change in NfL compared to baseline

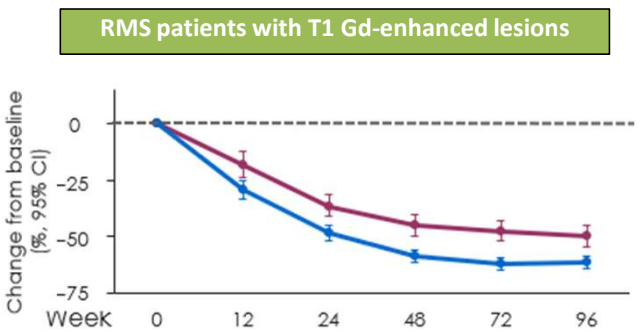
Benatar et al. Neurology 2020

Blood & Cerebrospinal Fluid NfL Reduction with Treatment

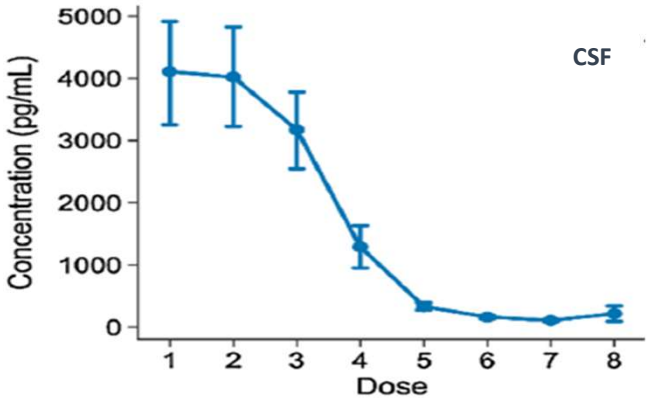
Reductions within 3 months in RMS, SMA and ALS

Ocrelizumab in RMS (ECTRIMS 2019)



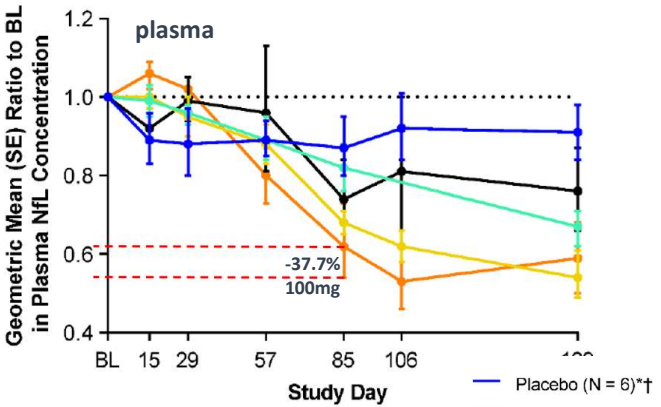


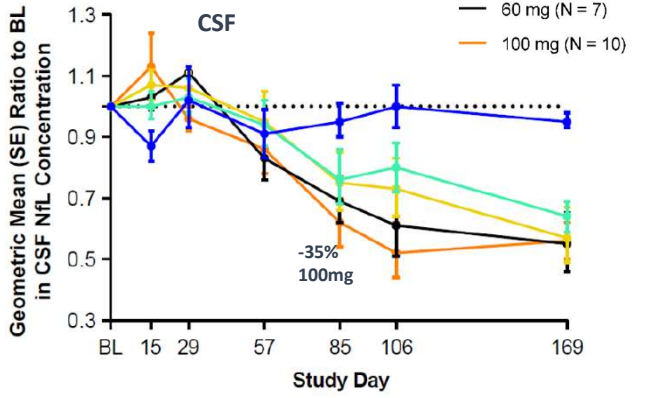
Nusinersen in SMA Type 1 (Olsson 2019)



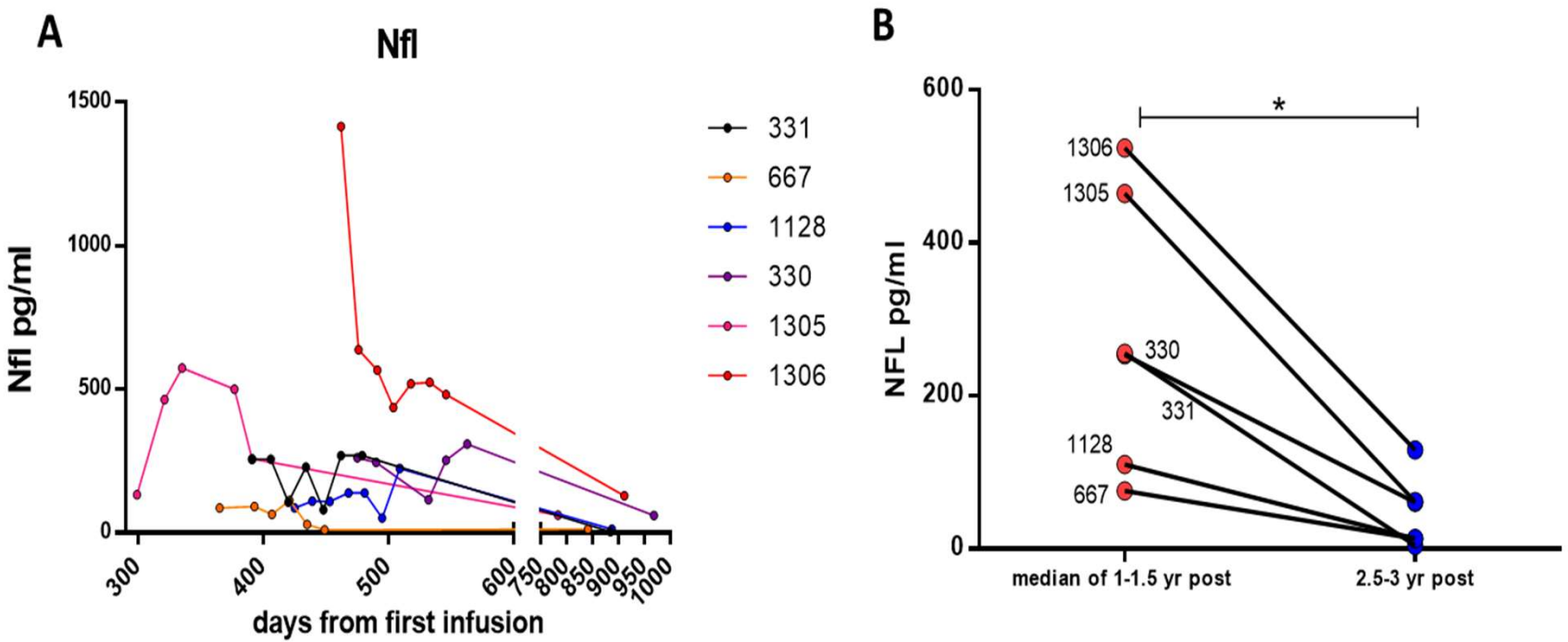
Dose	Weeks post first dose	n	%-Reduction from Dose 1
1	0	12	NA
2	2	10	12.6%
3	4	9	31.0%
4	8	10	72.0%
5	24	10	92.8%
6	40	8	96.5%
7	56	3	97.7%
8	72	2	95.3%

Tofersen in SOD1 ALS (Miller 2020)





CSF NfL dynamics in response to enzyme replacement therapy in neuronal ceroid lipofuscinosis



Heywood *et al*., unpublished

Conclusions fluid biomarkers for neurodegeneration

- CSF and plasma/serum NfL are biomarkers for neurodegeneration/neuroaxonal injury
- They are dynamic
- High levels suggest active neurodegeneration/ongoing injury
- Drugs slowing down neurodegeneration should reduce or stabilize NfL levels
- …but it's a slow marker

Thanks!

henrik.zetterberg@gu.se

ANNEXON biosciences

Huntington's Disease (HD)

Anti-C1q as Neuroprotective Approach in HD

Beth Stevens, PhD

Assistant Professor of Neurology

Children's Hospital Boston

Harvard Medical School

ANNEXON biosciences

Huntington's Disease (HD)

Clinical Perspective on HD, including use of NfL

Ed Wild, FRCP, PhD

Consultant Neurologist, National Hospital for Neurology and Neurosurgery

Associate Director, University College London, Huntington's Disease Centre

Huntington's disease and neurofilament light

Prof Ed Wild FRCP PhD
Consultant Neurologist, NHNN Queen Square
Associate Director, UCL Huntington's Disease Centre

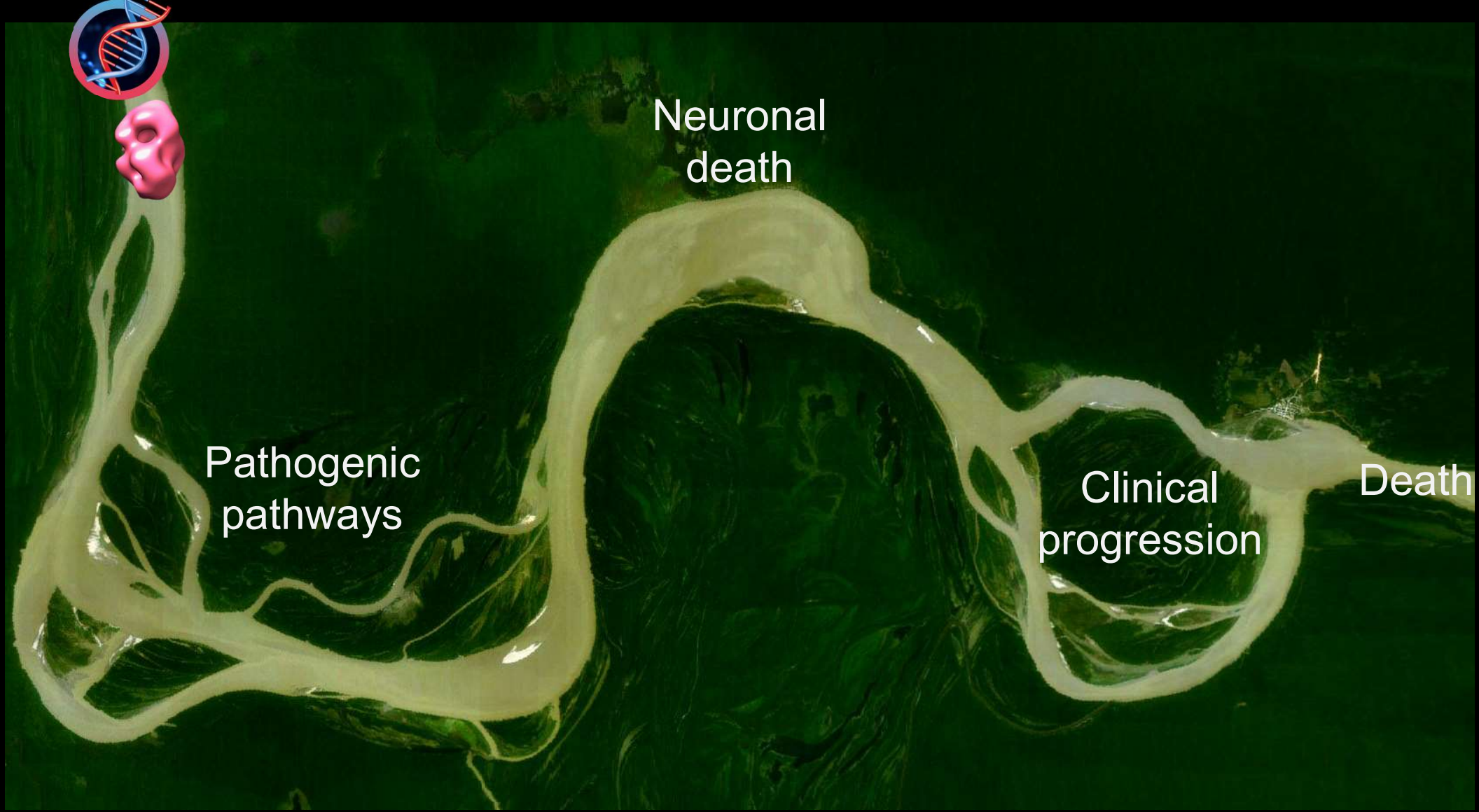
UCL

HUNTINGTON'S DISEASE CENTRE

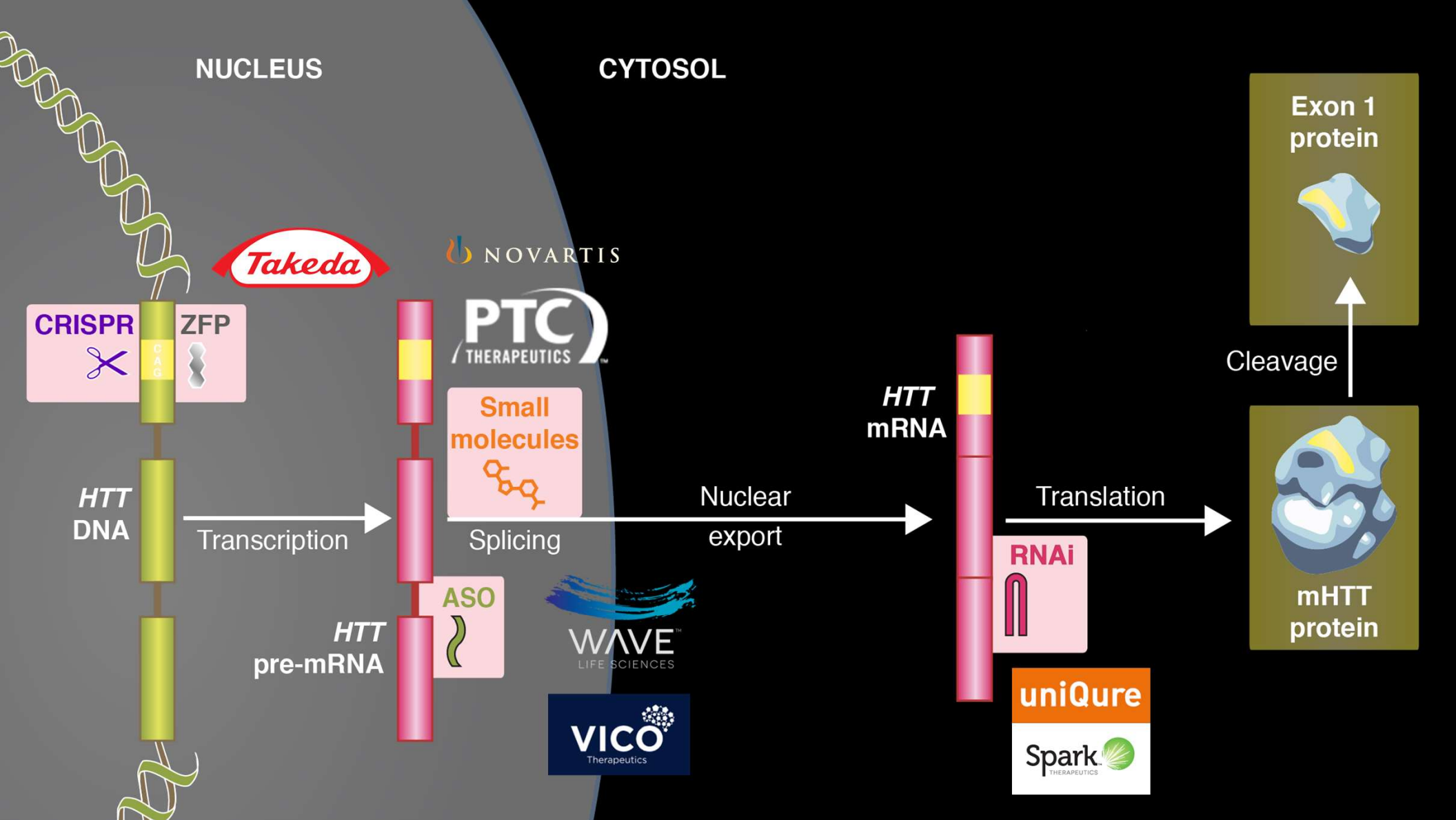
@ProfEdWild

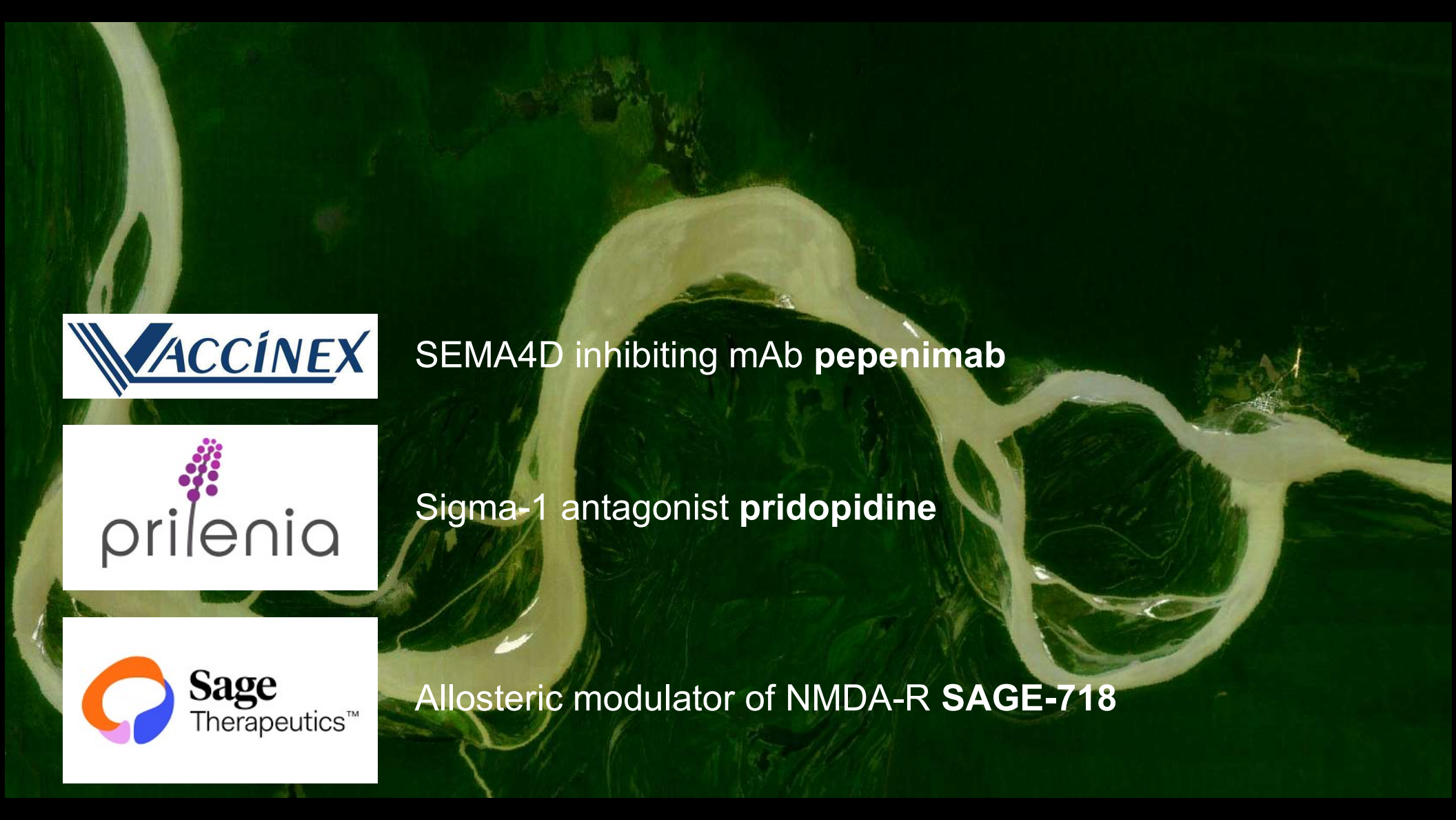
Tetrabenazine
Cognitive, behavioural, voluntary motor

Nothing


Neuronal death
Pathogenic pathways
Clinical progression
Death


Roche

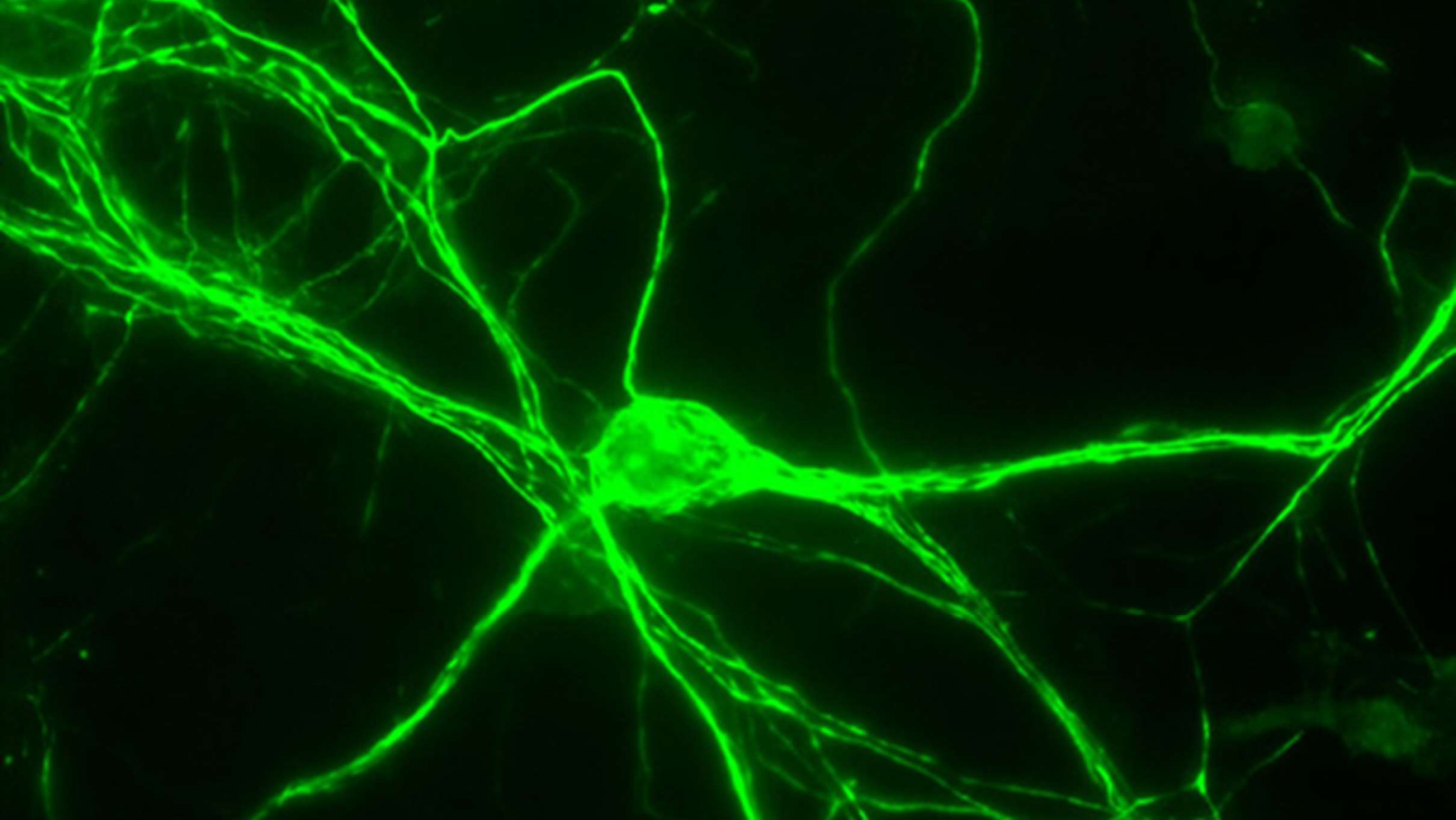

NUCLEUS
CYTOSOL
Takeda
NOVARTIS
PTC THERAPEUTICS
CRISPR
ZFP
CAG
HTT DNA
Transcription
HTT pre-mRNA
Small molecules
Splicing
ASO
WAVE LIFE SCIENCES
VICO Therapeutics
Nuclear export
HTT mRNA
RNAi
uniQure
Spark THERAPEUTICS
Translation
Cleavage
Exon 1 protein
mHTT protein


VACCINEX
SEMA4D inhibiting mAb **pepenimab**
prilenia
Sigma-1 antagonist **pridopidine**
Sage Therapeutics™
Allosteric modulator of NMDA-R **SAGE-718**

What’s missing in ‘downstream’ pathway interventions for HD:

agents targeting **solid**, **well-described** derangements

with **biomarker support** to suggest translation will work safely in patients

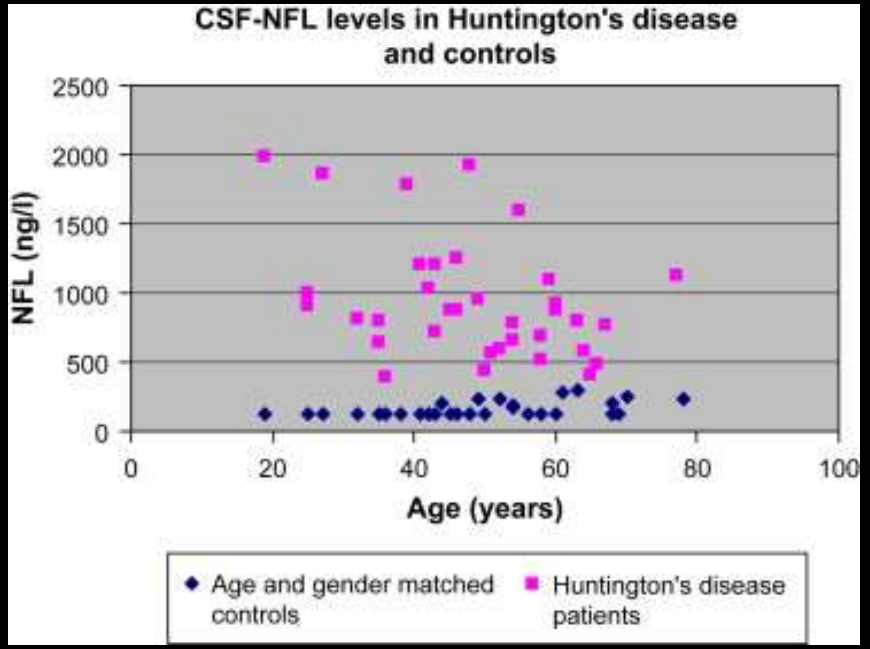


Parkinsonism & Related Disorders
Volume 15, Issue 3, March 2009, Pages 245-248

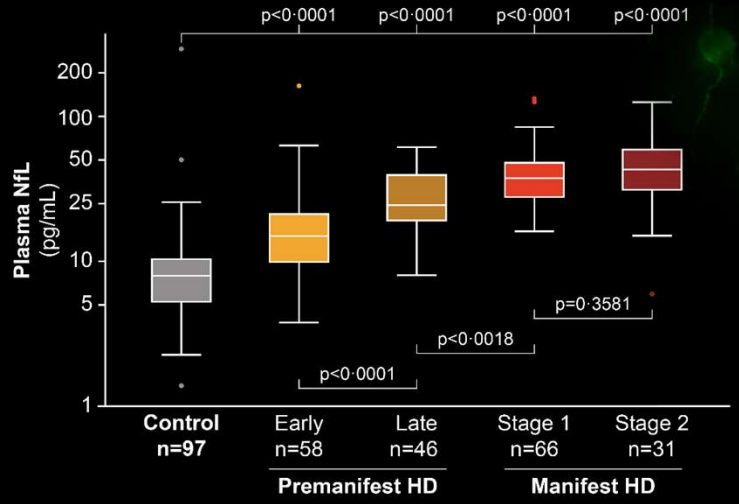
Short communication

Levels of the light subunit of neurofilament triplet protein in cerebrospinal fluid in Huntington's disease

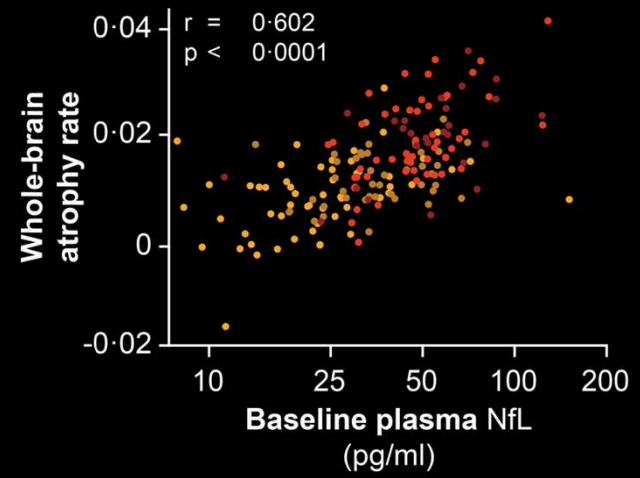
Radu Constantinescu [a], Megan Romer [b], David Oakes [c], Lars Rosengren [a], Karl Kieburtz [b]



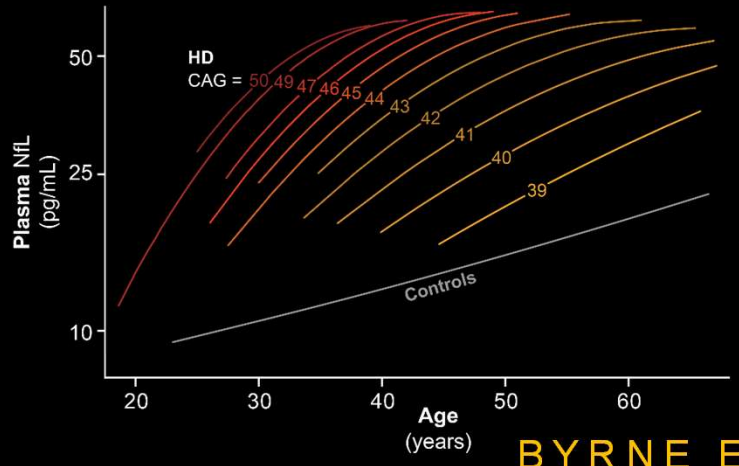
NfL is elevated with increasing disease stage



Baseline NfL predicts subsequent brain atrophy

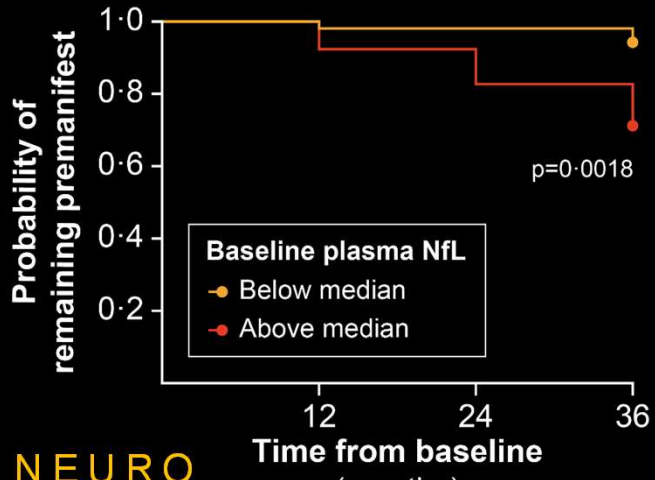


NfL is elevated in a CAG dependent manner



TRACKHD

Baseline NfL predicts disease onset

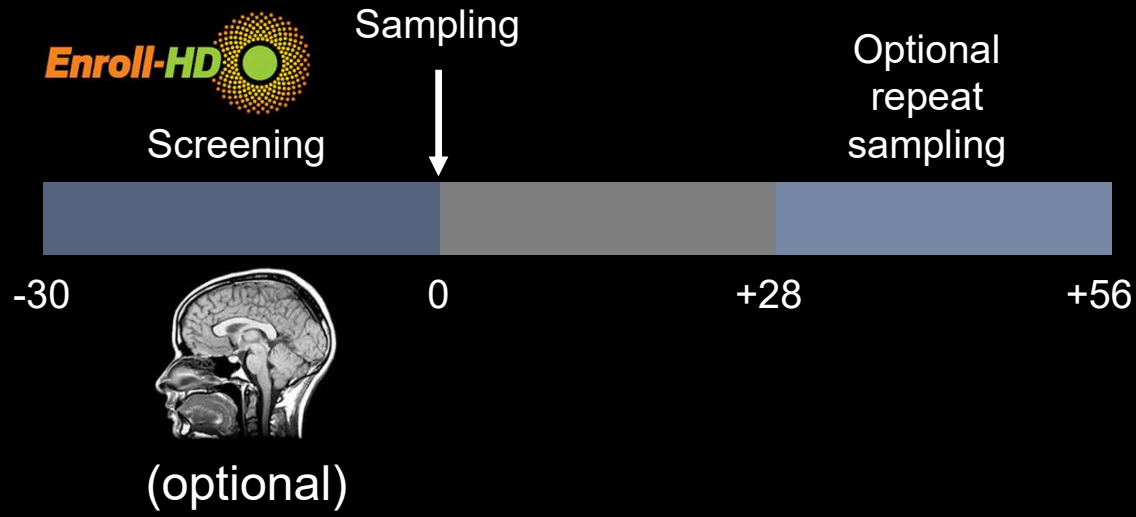


BYRNE ET AL (2017) LANCET NEURO

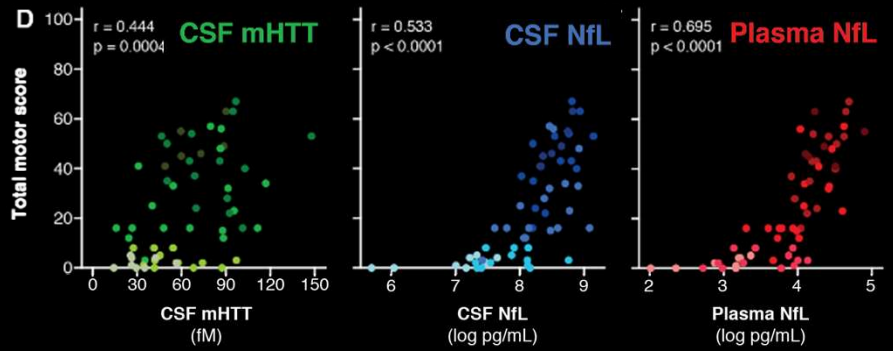
HD-CSF

Studying cerebrospinal fluid to understand
key CNS pathobiological targets in Huntington's disease

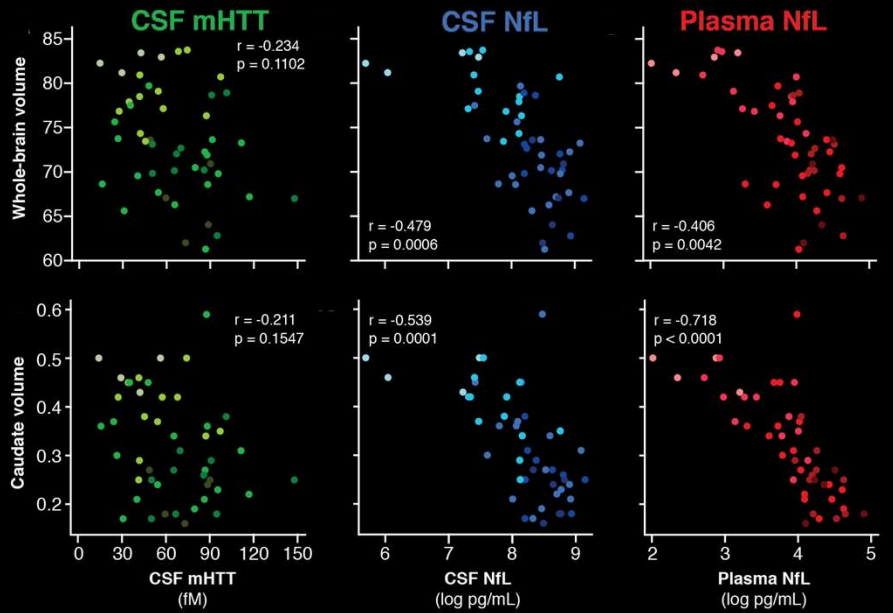
- 80 participants:
  - 20 control
  - 20 preHD
  - 40 early HD > mod HD
- 24-month Follow-up
  - Repeat of all assessments



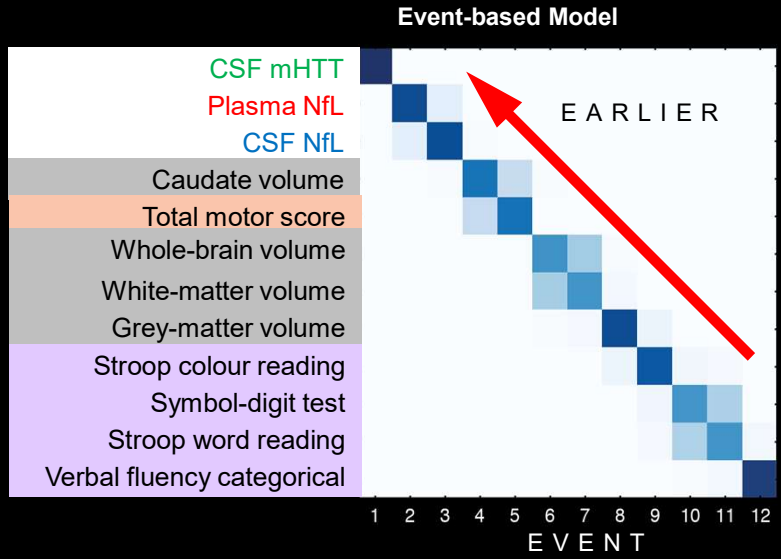
NfL has strong associations with clinical scores



NfL has strong associations with brain volume

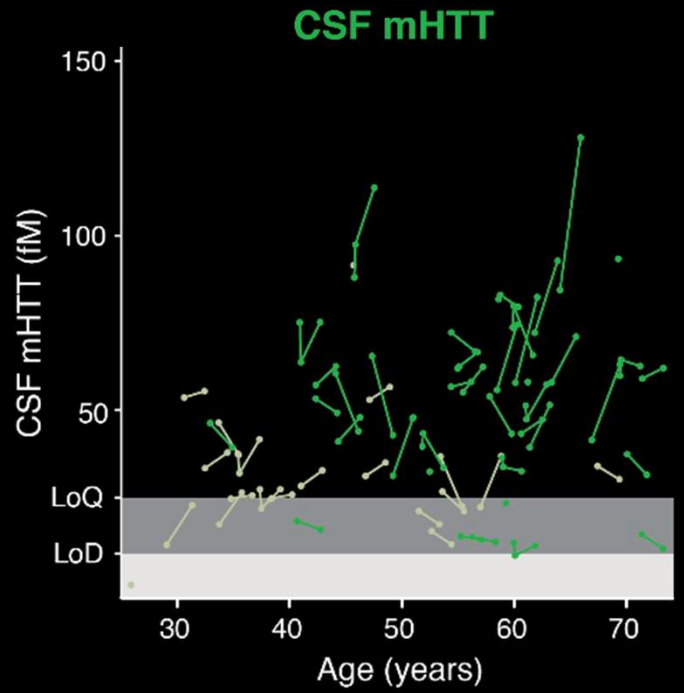


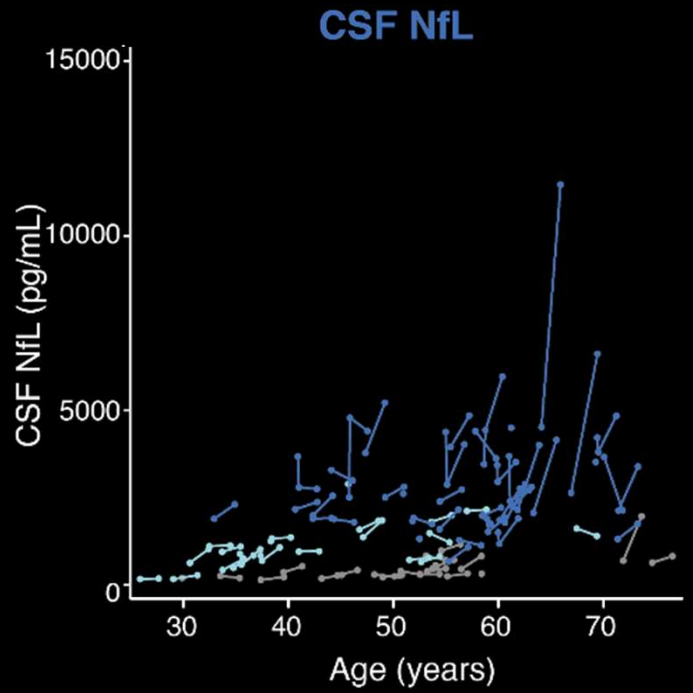
Among earliest detectable changes in HD

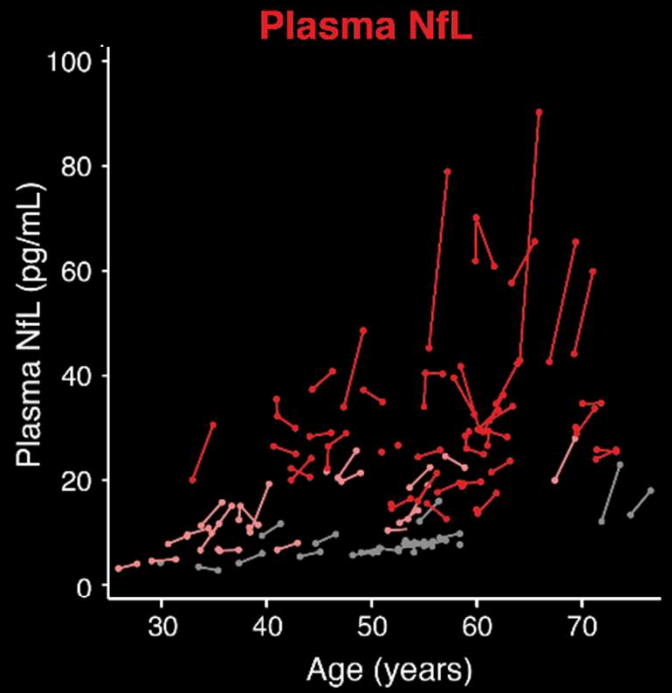


BYRNE/RODRIGUES ET AL (2018) SCI TRANS MED

2-year longitudinal analysis



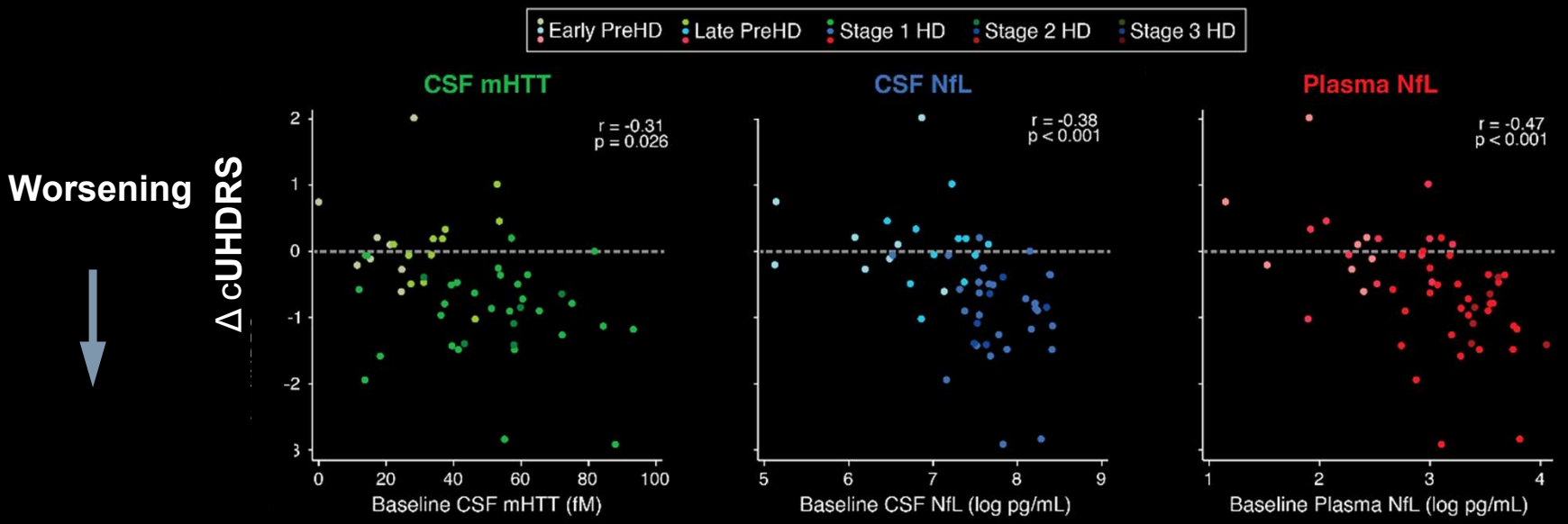




	fM/year [95% CI]	pg/mL/year [95% CI]	pg/mL/year [95% CI]
Healthy Controls	N/A	20.05 [18.57 to 21.53]	0.28 [0.27 to 0.29]
PreHD	1.03 [0.95 to 1.11]	79.16 [74.92 to 83.40]	0.84 [0.80 to 0.87]
Manifest HD	1.00 [0.95 to 1.05]	98.85 [93.01 to 104.70]	1.04 [1.00 to 1.08]

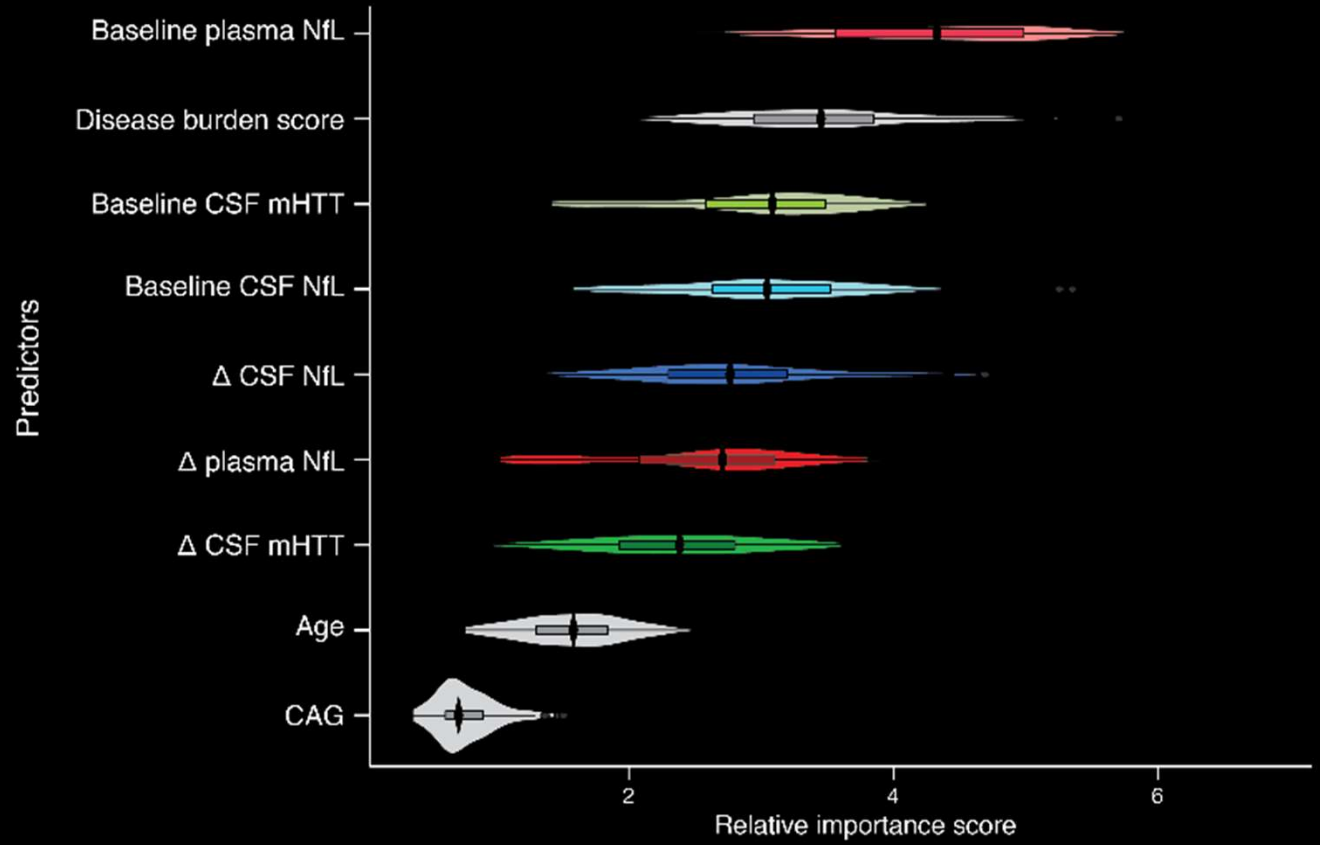
RODRIGUES/BYRNE ET AL (2020) SCI TRANS MED

Association with overall clinical progression as measured by Δ cUHDRS



RODRIGUES/BYRNE ET AL (2020) SCI TRANS MED

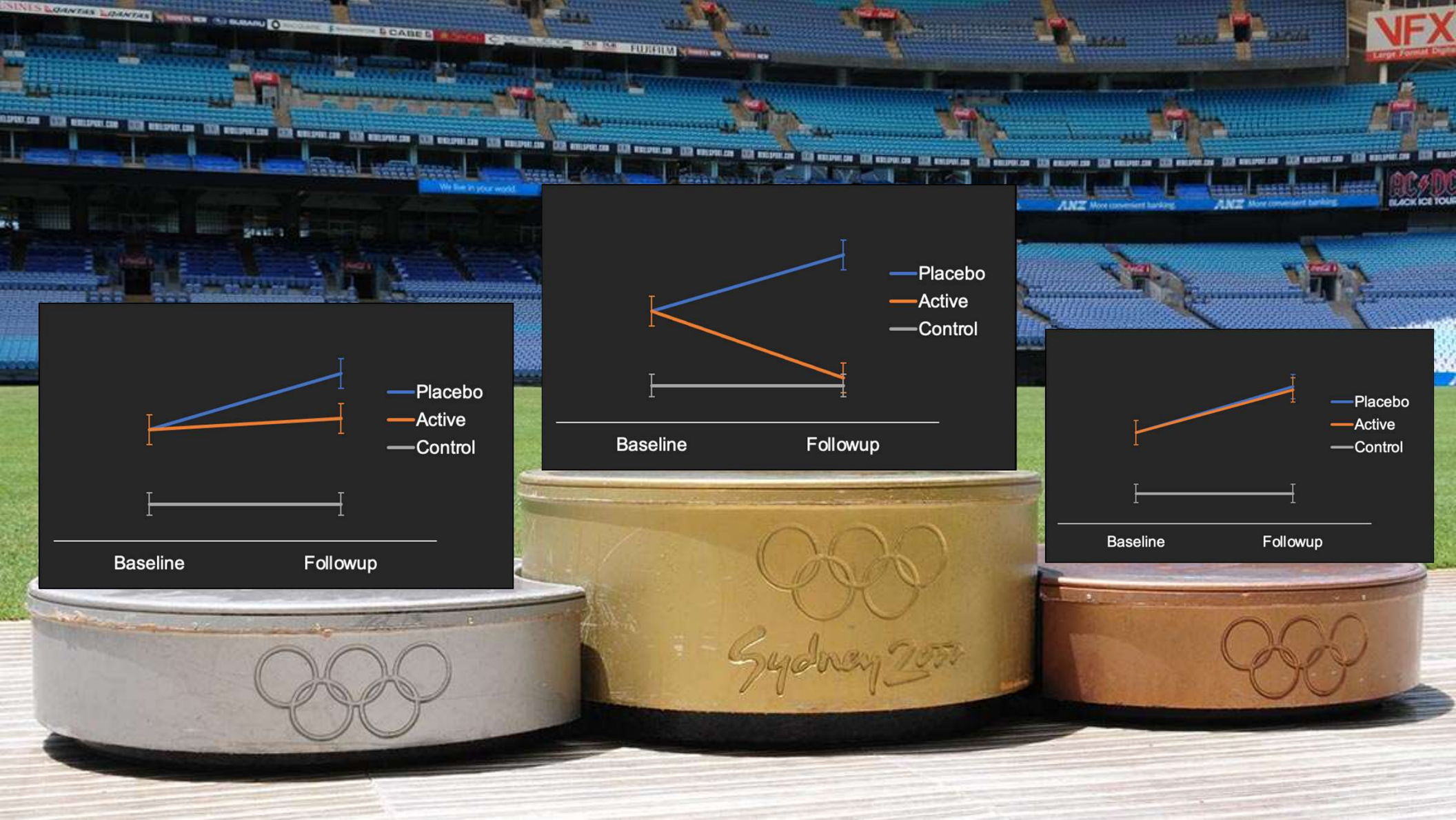
Random forest analysis:
Baseline plasma NfL is the strongest predictor of clinical progression



RODRIGUES/BYRNE ET AL (2020) SCI TRANS MED

Cross-sectional data	CSF mHTT	CSF NfL	Plasma NfL
Higher in HD v C	Yes[6]	Yes[25]	Yes[15]
Rises with disease stage	Yes[6]	Yes[26]	Yes[15]
Baseline level associated with clinical severity	Yes[6]	Yes[14]	Yes[15]
Baseline level associated with brain volume	Yes	Yes[14]	Yes[15]
Longitudinal data			
Baseline level predicts onset	?	?	Yes[15]
Baseline level predicts clinical progression	Yes	Yes	Yes[15]
Baseline level predicts brain atrophy	Yes	Yes	Yes[15]
Change predicts clinical progression	Yes(TMS only)	Yes	Yes
Change predicts clinical atrophy	Yes	Yes	Yes

RODRIGUES/BYRNE ET AL (2020) SCI TRANS MED


Placebo
Active
Control
Baseline
Followup
Placebo
Active
Control
Baseline
Followup
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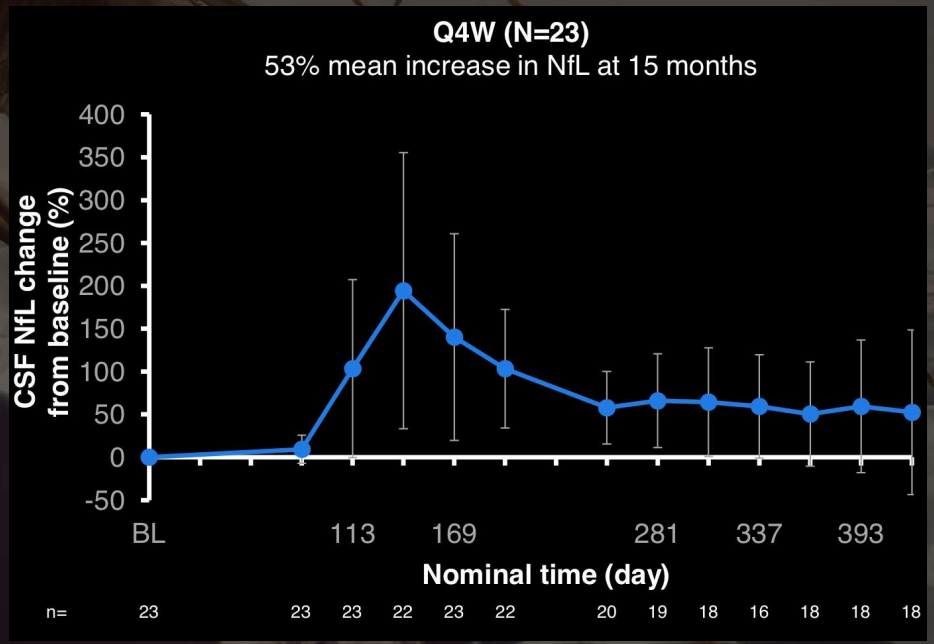
Followup
Sydney 2000


Q4W (N=23)
53% mean increase in NfL at 15 months
CSF NfL change from baseline (%)
400
350
300
250
200
150
100
50
0
-50
BL
113
169
281
337
393
Nominal time (day)
n=
23
23
23
22
23
22
20
19
18
16
18
18
18


@ProfEdWild

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CMND and Amyotrophic Lateral Sclerosis (ALS)

- Clinical Perspective on ALS, including use of NfL

Angela Genge, MD

Director, Clinical Research Institute

Montreal Neurological Institute and Hospital

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Montreal Neurological Institute-Hospital

Clinical Research Unit

Overview of ALS

Dr. Angela Genge

Director – Clinical Research Unit

Montreal Neurological Institute and Hospital

AD/PD 2021

McGill

Centre universitaire de santé McGill

McGill University Health Centre

Dr. Angela Genge

- **Executive Director**, Clinical Research Unit at the Montreal Neurological Institute and Hospital
- **Director** of the ALS Center of Excellence
- **Consultant** for Health Canada, AL-S Pharma, Quralis, Biogen, Alexion, Amylyx, WAVE Life Sciences, Cytokinetics, MT Pharma, Orphazyme,
- **DMSB board** for CLENE, TRICALS, and AZT Therapeutics

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Significant Unmet Need for People Living with ALS

- ALS is a fatal neurodegenerative disorder, characterized by progressive loss of upper and lower motor neurons
- 75% initially present with muscle weakness of the limbs[2]
- 25% initially present with difficulty with speech and swallowing[2]
- ALS affects 225,000 people globally. ~90% of cases are sporadic and death typically occurs 3-5 years from disease onset

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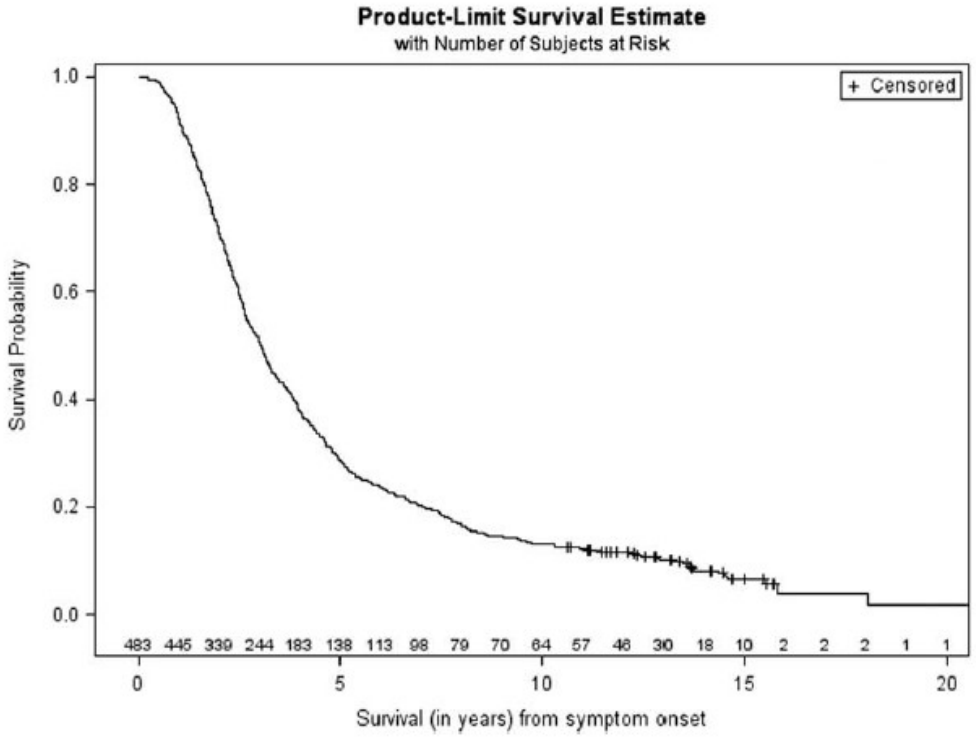
Sources: 1. Bahia El Idrissi N, et al. *J Neuroinflammation.* 2016;13(1):72.
2. Kjældgaard, AL, et al. *Mol Immunol.* 2018;102:14-25.

Disease progression of ALS

- Progressive decline in motor function and activities of daily living
  - ALSFRS-R, a validated scale measuring the domains of gross motor, fine motor, bulbar and respiratory function declines on average 1 point per month in clinical trials
- Median survival from onset: 36 months (3 years)
- Survival probabilities from onset
  - 12 months: 92.1%
  - 5 years: 28.6%
  - 10 years: 13.3%
- Death due to respiratory failure typically occurs between 3-5 years



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ALS affects both the CNS and PNS

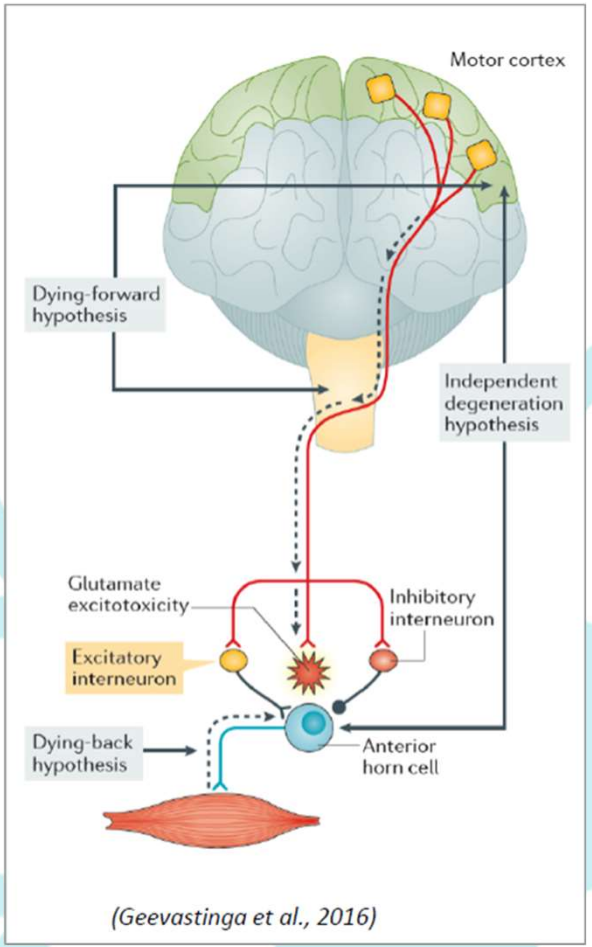
ALS is a mixed upper and lower motor neuron disease

Central Nervous System

- Upper motor neurons
  - Derived from corticospinal and corticobulbar fibers that originate in the brain's primary motor cortex
  - Responsible for carrying impulses for voluntary motor activity from the cerebral cortex to the spinal cord

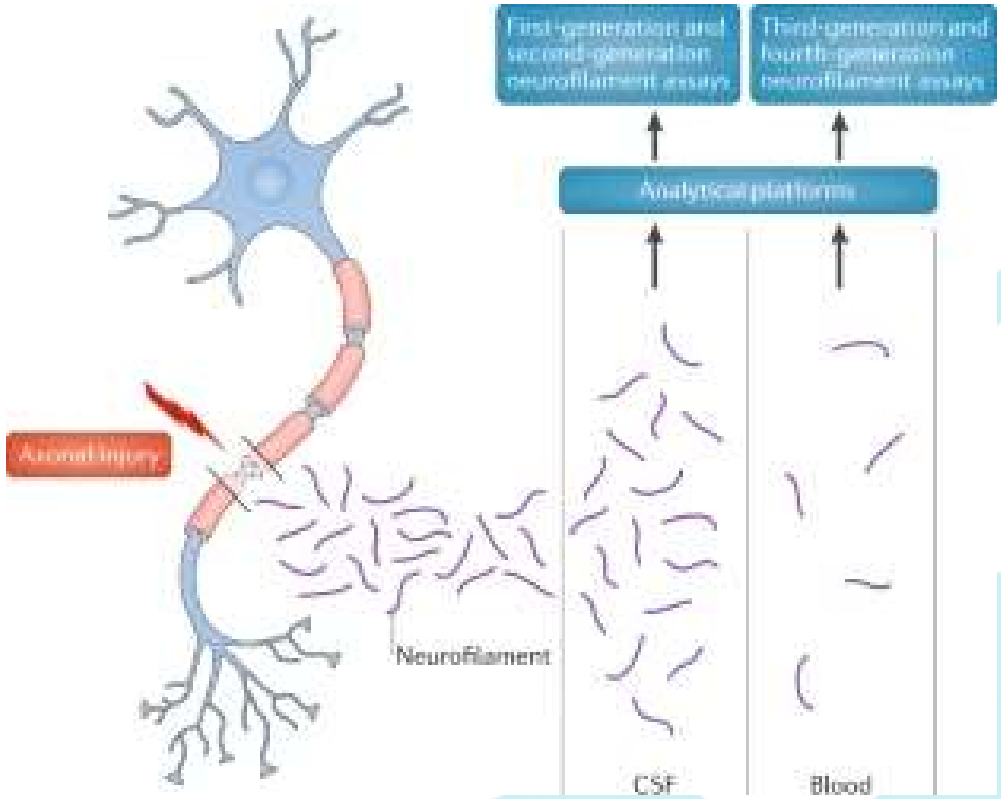
Peripheral Nervous System

- Lower motor neurons
  - Carry impulses from the spinal cord to peripheral structures



Natural History Studies of Neurofilaments in ALS

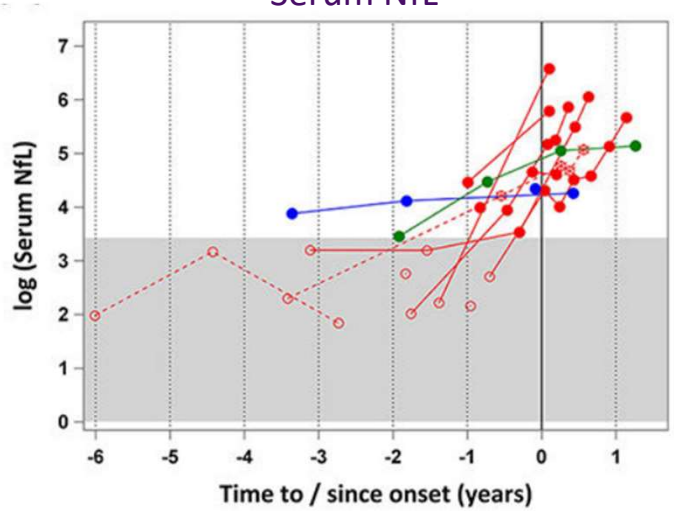
- Natural History studies suggest that:
  - NF elevation correlates with symptom onset in ALS patients
  - NF levels correlate with rate of clinical progression
- Fourth-generation single-molecule array (Simoa) assays have enabled reliable and sensitive measurements of neurofilaments, including NfL



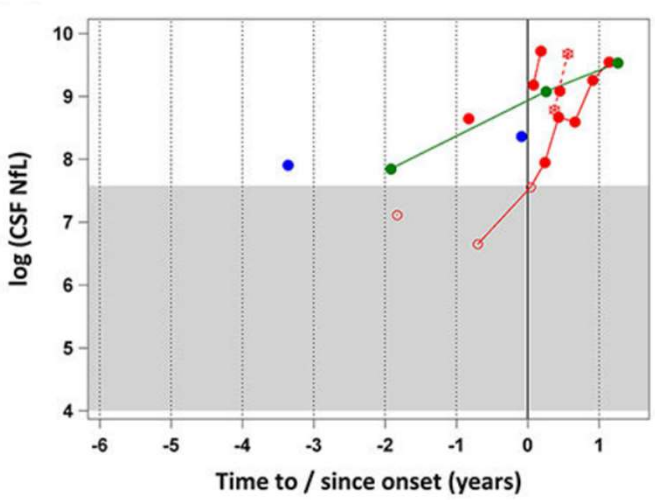
Khalil et al. 2018. Nature Reviews Neurology 14 (10)

NfL levels (serum & CSF) rise 1 year prior to symptom onset in Familial ALS

Serum NfL



CSF NfL



Benatar et al. Amyotrophic Lateral Sclerosis Frontotemporal Degeneration. 2019

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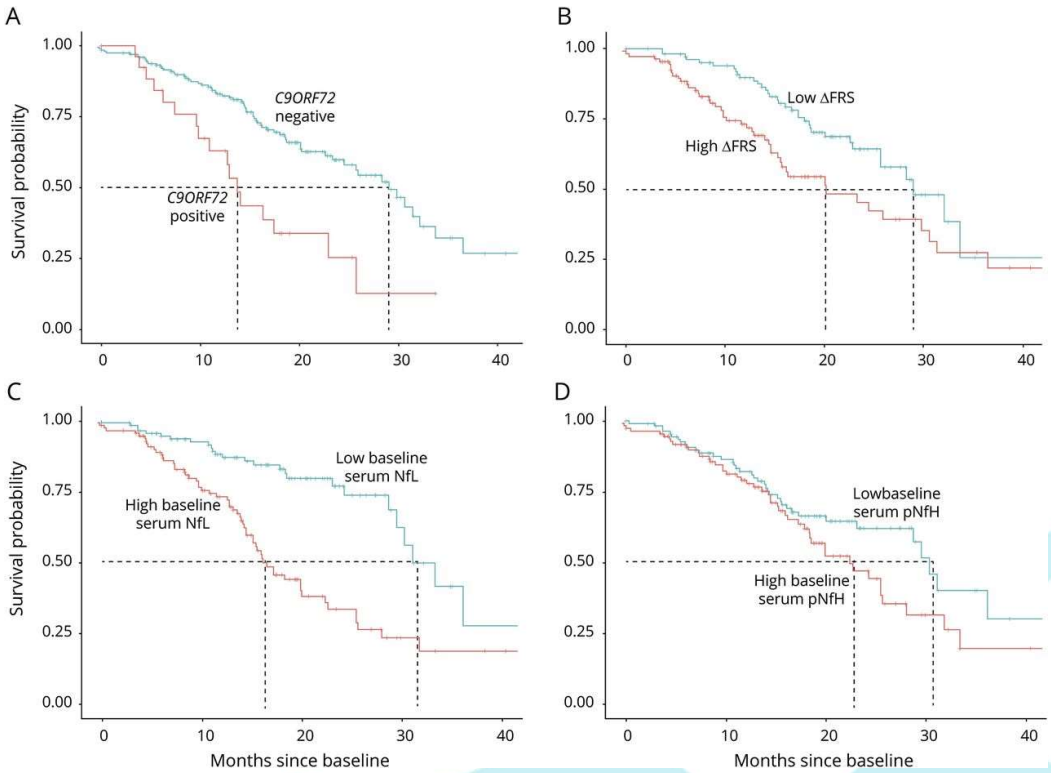
Serum NfL is a clinically validated prognostic biomarker for ALS[1]

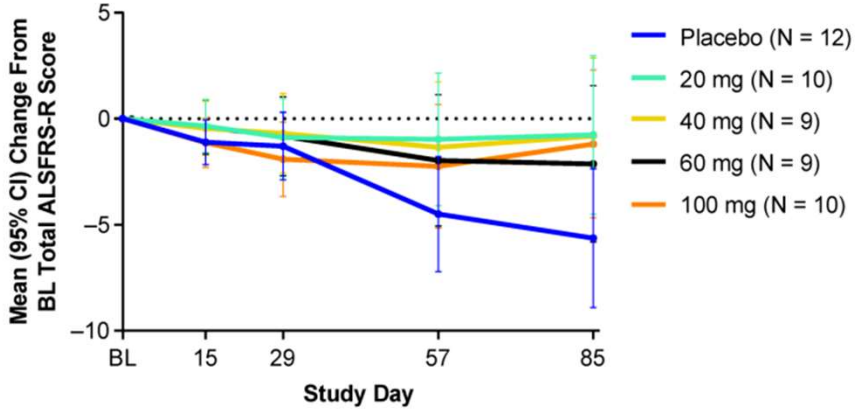
- Prospective, multicenter, longitudinal observational study of patients with sporadic & familial ALS (n = 229)
- Serum NfL stable over time in natural history study
- Stronger correlation between serum and CSF for NfL than for pNfH
- Serum NfL is prognostic of future ALSFRS-R decline (slope of decline) and survival

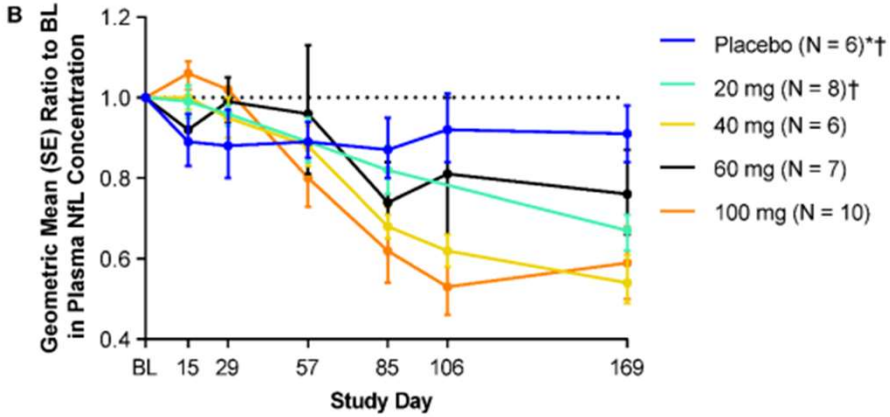


1. Benatar et al, Neurology, July 7, 2020

NfL reductions in SOD1 ALS patients associated with functional benefit – ALSFRS-R

- Tofersen is an ASO to mutant SOD1
- NFs were higher in the fast-progressing subgroup
- Over the course of the blinded phase of the trial
  - SOD1 levels decreased from baseline
  - NfL and pNFH decreased from baseline
  - Evidence of slowing in decrease for ALSFRS-R





Miller et al. 2020. NEJM 383 (2)

Summary

- ALS is a fatal neurodegenerative disorder, with significant and urgent need for therapies
- ALSFRS and survival remain as key endpoints in registrational studies
- Potential for NfL as viable surrogate biomarker in ALS
  - A large increase in NfL occurs at symptom onset and then stabilizes at elevated levels
  - Reduction in NfL by a therapeutic agent is likely to be associated with clinical benefit

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Thank you!

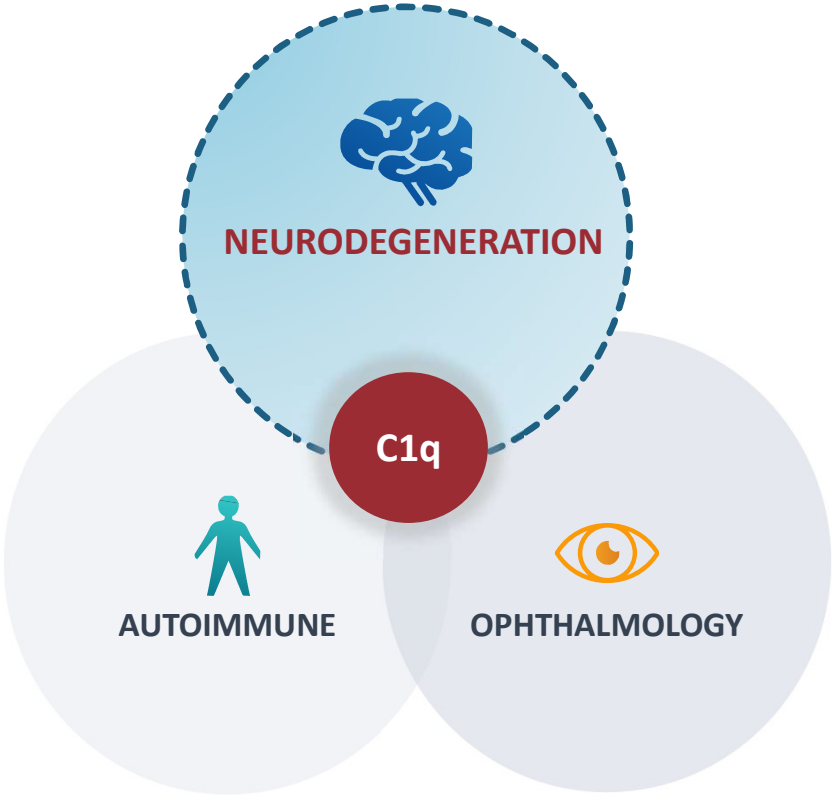
Overview of Annexon's CMND Clinical Program

Sanjay Keswani, MBBS, FRCP

Chief Medical Officer

Annexon Biosciences

Groundbreaking Approach Targeting Complement-Mediated Neurodegeneration (CMND)



Unique Potential of Anti-C1q Platform

- **Pioneering Approach to Treat CMND:** Preserve functioning synapses, neuronal health & function
- **Broad Therapeutic Potential:** CMND major driver of neurodegeneration in a host of brain & eye diseases
- **Established Biomarker in Early Trials (NfL):** Correlates with patient disability; reduction shown to correlate with clinical benefit in multiple diseases
- **Early Platform Promise:** NfL reduction demonstrated in three diseases: GBS Ph1 POC, HD & ALS preclinical

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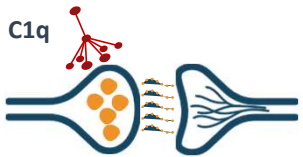
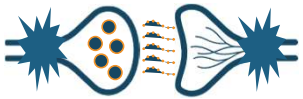
C1q Inhibition Protects against Synapse Loss and Neurodegeneration in a Host of Diseases

Normal
C1q Function



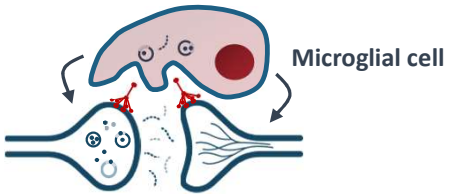
Sculpts the brain and retina in development

Aberrant
Triggers



Neuronal stress may induce aberrant activation of C1q

Disease
C1q Dysfunction



Removes functioning synapses
Anti-C1q potentially protects against synaptic loss

C1q blockade results in functional benefits in multiple disease models, including:*

- Huntington's Disease[1]
- Alzheimer's Disease[2]
- Spinal Muscular Atrophy[3]
- Glaucoma[4]
- Geographic Atrophy (AMD)[5]
- Frontotemporal Dementia[6]
- Traumatic Brain Injury[7]
- Amyotrophic Lateral Sclerosis[8]
- Progressive Multiple Sclerosis[9]

*[1]Wilton and Stevens, Harvard, *unpublished*. [2]Fonseca, 2004, *J Neurosci*; Hong, 2016, *Science*; Dejanovic, 2018, *Neuron*; [3]Vukojicic, 2019, *Cell Reports*; [4]Howell, 2011, *J Clin Inves*; Williams, 2016, *Mol Neurodegen*; [5]Jiao, 2018, *Mol Neurodeg*; [6]Lui, 2016, *Cell*; [7]Krukowski, 2018, *Int.J Mol Sci*; Holden, 2021, *Science*; Annexon NfL reduction in SOD1 model, unpublished; [9]Absinta, *Nature*, 2021

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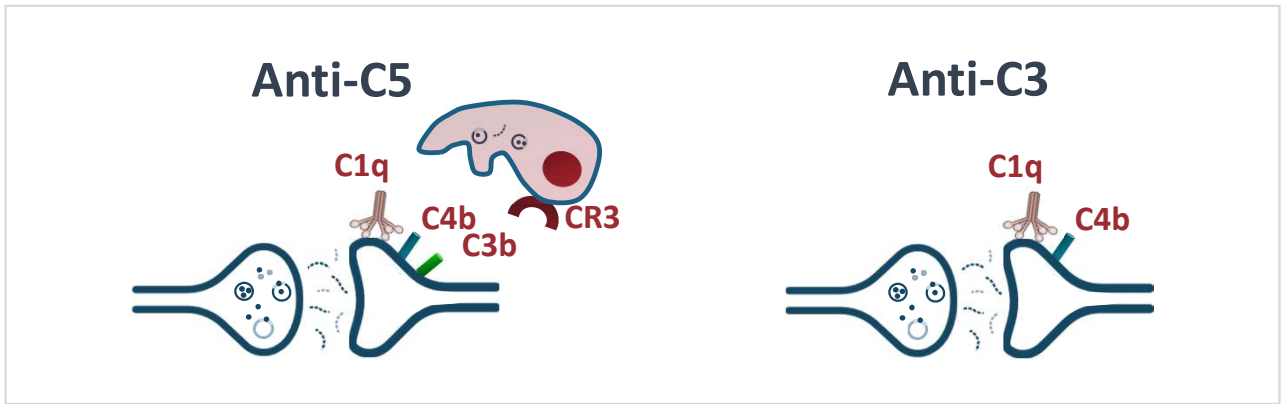
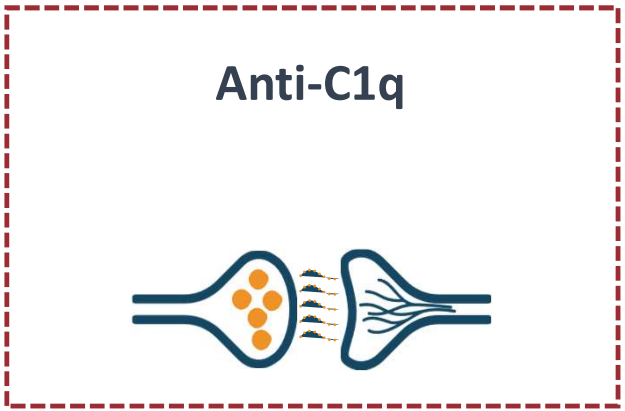
Anti-C1q is Differentiated from Other Complement Approaches





Only way to block all early classical complement components involved in CMND

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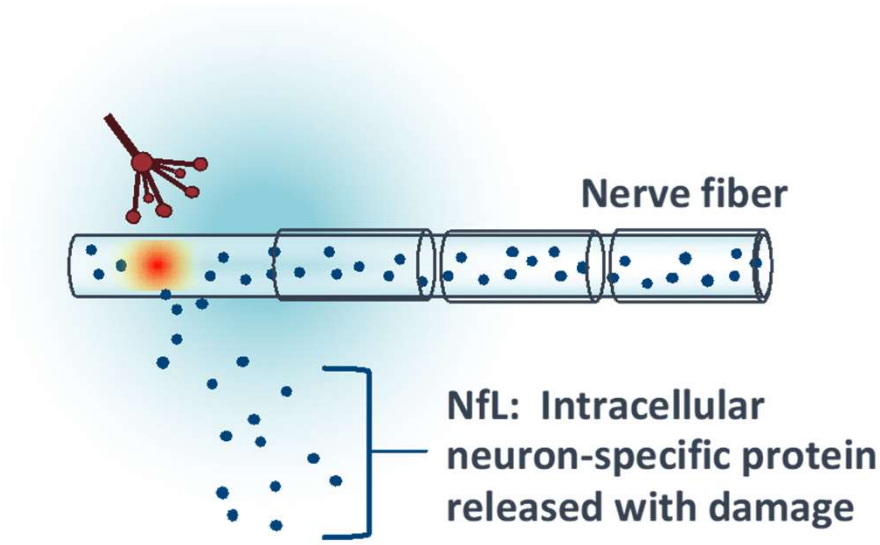
Neurofilament Light Chain (NfL) Biomarker Underpins Our Neurological Approach

Significantly Informs Clinical Development

- ✓ Sensitive measure of neuronal damage / degeneration
- ✓ Correlates w/ patient disability and predicts outcomes in several diseases (e.g., SMA[1], MS[2], GBS[3], HD[4], ALS[5])
- ✓ Reduced by effective therapies for MS, SMA and ALS within 3 months of treatment
- ✓ ANX005 NfL reduction in clinical (GBS) and preclinical (HD & ALS) studies
- ✓ Key measure in on-going HD and ALS Phase 2 trials



[1]Olsson, 2019 *J Neurol* 266:2129–2136; [2]Gunnarsson 2011 *Ann Neurol* 69:83; Ferraro 2020 *Acta Neurol Scand* 141:16; [3]Martín-Aguilar, 2020 *medRxiv* 10.1101/2020.03.24.20042200; [4]Byrne, 2017 *Lancet Neurol* 16: 601; ALS; [5]Benatar 2018 *Ann Neurol* 84:130

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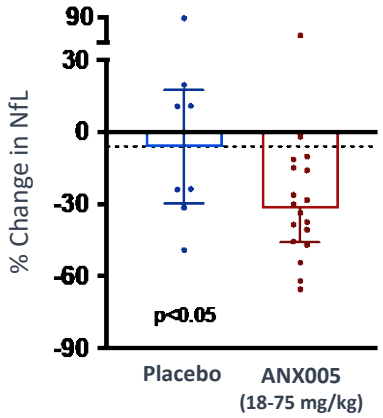
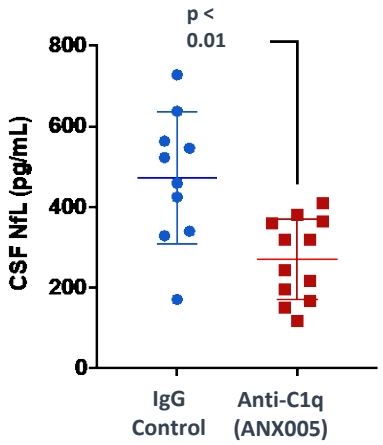
C1q Inhibition Has Reduced NfL in Patients and in Animal Models

Significant NfL Reduction
GBS Patients (Ph 1b)



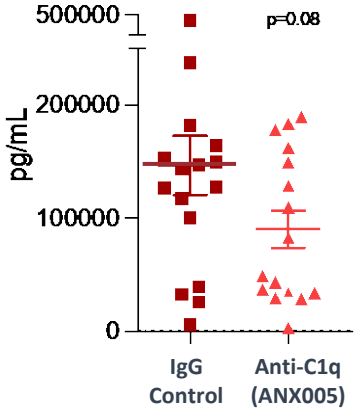
n=8 n=18

Significant NfL Reduction
HD Preclinical Model



Study run in R6/2 model

Significant NfL Reduction
ALS Preclinical Model



Study run in SOD1 model

Annexon data on file

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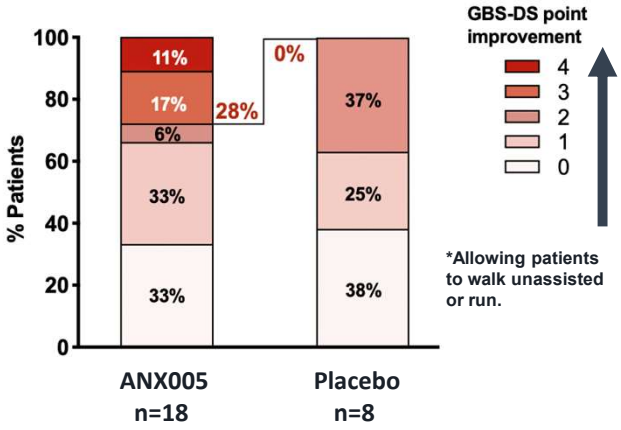
C1q Inhibition Has Also Provided Functional Benefit in Patients and in Animal Models

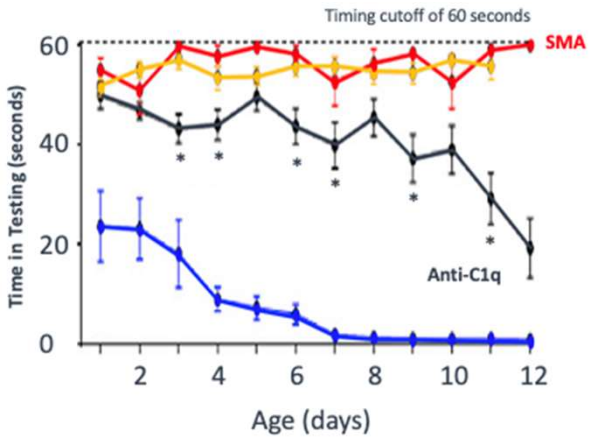
Significant NfL Reduction GBS Patients (Ph 1b)



High-Dose ANX005 (18-75 mg/kg) vs Placebo

Annexon data on file

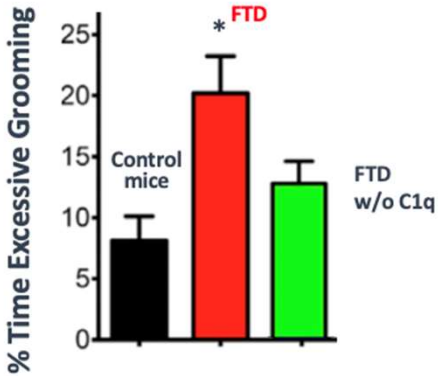
Allows Gain of Motor Function in Spinal Muscular Atrophy



Transgenic SMN-Δ7 mouse model of SMA

Vukojicic et al., 2019 *Cell Rep* 29, 3087-3100

Prevents Obsessive Behavior in Frontotemporal Dementia



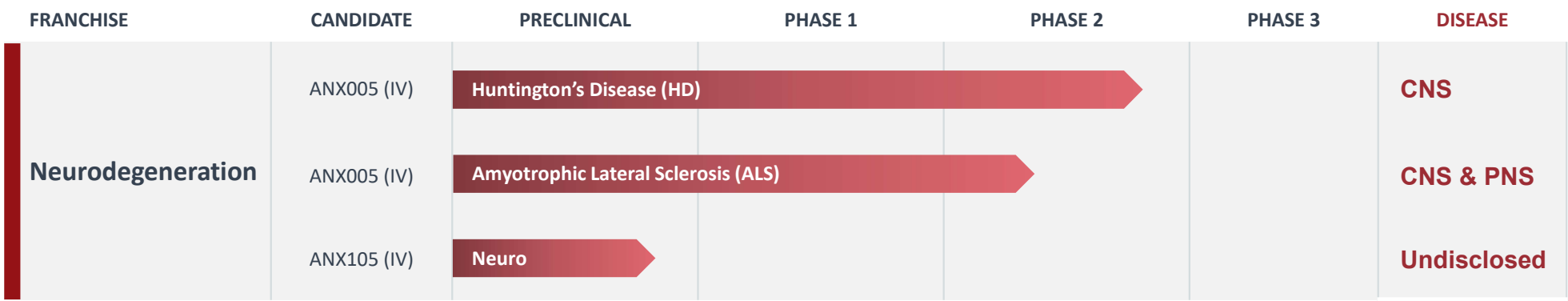
Mouse model of FTD with progranulin genetic deletion

Liu et al., 2016 *Cell* 165:921

ANNEXON biosciences

Annexon Pipeline in Neurodegenerative Diseases of the Brain

Diversified approach in CNS and CNS/PNS diseases



ANNEXON biosciences

Strong Rationale for Targeting CMND in HD

Robust biological rationale for targeting C1q in HD

- Aberrant C1q activation noted in synapses from HD patients
- Anti-C1q is efficacious in preclinical models of HD

NfL is an objective measure of neurodegeneration in Phase 2

- Elevated NfL levels in HD correlate with disability
- Published NfL longitudinal data in HD showing increasing levels over time
- ANX005 rapidly reduced NfL in acute GBS patients

Anticipate full CNS target engagement with ANX005

- Full CSF target engagement demonstrated for ANX005 in clinical (GBS) and preclinical studies

HD Phase 2 Trial Overview

Targeting ‘early manifest’ patients and leveraging natural history cohorts

Study Population

- Adults with, or at risk for, manifest HD
- **Total CAP score >400**
- **UHDRS independence score ≥ 80%**

Primary Endpoints

- **Safety and tolerability of ANX005**
- **PK and PD of ANX005 in serum & cerebrospinal fluid (CSF)**
- **NfL reduction in plasma and CSF**

Exploratory Endpoints

- Quantitative EEG (qEEG)
- Composite UHDRS and its components

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HD Phase 2 Status

Initial data readout anticipated Q4 2021

Key Trial Metrics

- Last Patients enrolled: May 2021
- 6-month treatment completion: Q4 2021
- Trial completion including 3-month follow-up: Q2 2022

Initial Data

- Data on subset of patients (N ~16) that **completed 6-month treatment period**
- **Safety and tolerability of ANX005 chronic dosing**
- **ANX005 CSF & serum C1q target engagement**
- **NfL reduction (CSF & plasma)**

Final Data

- Q2 2022
- On & Off treatment
- Primary & exploratory endpoints

ANNEXON biosciences

Strong Rationale for Targeting CMND in ALS

Biological rationale for targeting C1q in ALS

- Aberrant C1q activation noted in CNS and PNS from ALS patients
- Anti-C1q is efficacious in preclinical model of ALS

NfL is an objective measure of neurodegeneration in Phase 2

- Elevated NfL levels in ALS correlate with disability
- Published NfL longitudinal data in ALS showing stability over time
- ANX005 rapidly reduced NfL in acute GBS patients

Anticipate full CNS & PNS target engagement with ANX005

- Full CSF and blood target engagement demonstrated for ANX005 in clinical (GBS) and preclinical studies

Ongoing Phase 2 ALS Trial

Leveraging biomarkers to inform the next stage of development

Study Population

- **Targeting all forms of ALS**
- Diagnosis of ALS according to the World Federation of Neurology revised E1 Escorial criteria
- Onset of weakness within 3 years prior to enrollment
- Slow Vital Capacity ≥ 60% of predicted normal
- ALSFRS-R ≥ 30

Primary Endpoints

- **Safety and tolerability of ANX005**
- **PK/PD of ANX005 in serum**
- **NfL reduction in plasma**

Exploratory Endpoints

- Electrical Impedance Myography (EIM)
- ALSFRS-R score
- ALSAQ-40
- Hand-Held Dynamometry
- Slow Vital Capacity

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ALS Phase 2 Status

Initial data readout anticipated 1H 2022

Key Trial Metrics

- Enrollment ongoing in North America
- Enrollment completion: 1H 2022
- Initial data readout anticipated: 1H 2022

Data Anticipated

- Safety and tolerability of ANX005 chronic dosing
- **ANX005 PK and C1q target engagement**
- **NfL reduction in plasma**
- Exploratory clinical data

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Summary

- **C1q-mediated synapse loss is a common pathway of neurodegeneration** and disability in multiple diseases, regardless of inciting etiology
- **Anti-C1q is protective in several disease models** of neurodegeneration including HD and ALS
- Elevation of **neurofilament light chain (NfL) is a common biomarker of neuronal damage across a host of neurodegenerative diseases** and correlates with patient disability
- Our **objective in Phase 2 studies of HD and ALS is to show reduction in NfL** as a demonstration of impact of anti-C1q on the neurodegenerative disease process

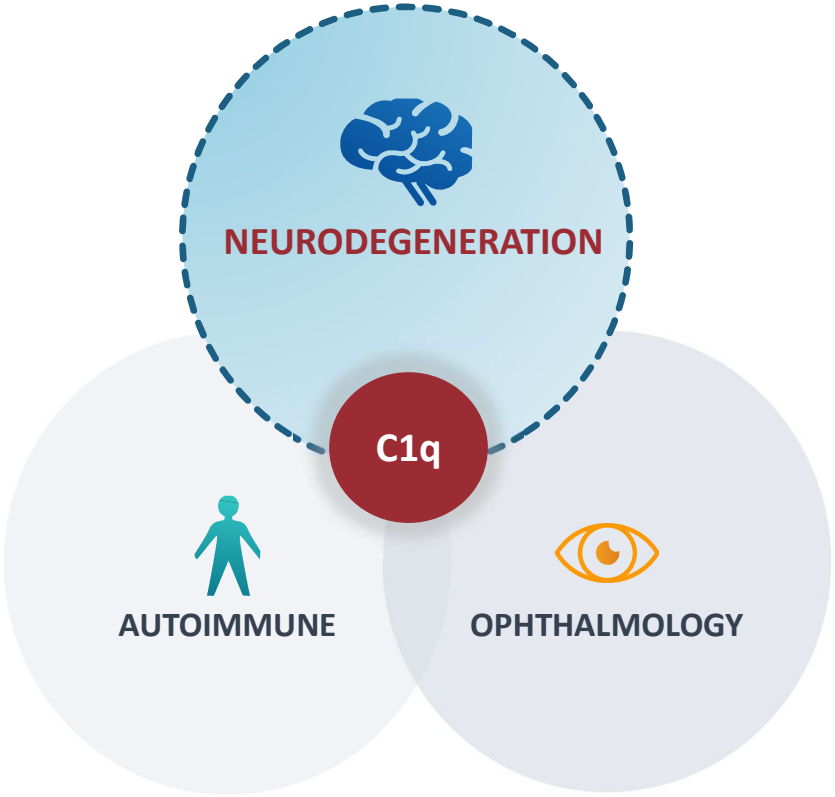
Closing Remarks & Q&A

Doug Love, Esq.

President & Chief Executive Officer

Annexon Biosciences

Groundbreaking Approach Targeting Complement-Mediated Neurodegeneration (CMND)



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- **Early Platform Promise:** NfL reduction demonstrated in three diseases: GBS Ph1 POC, HD & ALS preclinical

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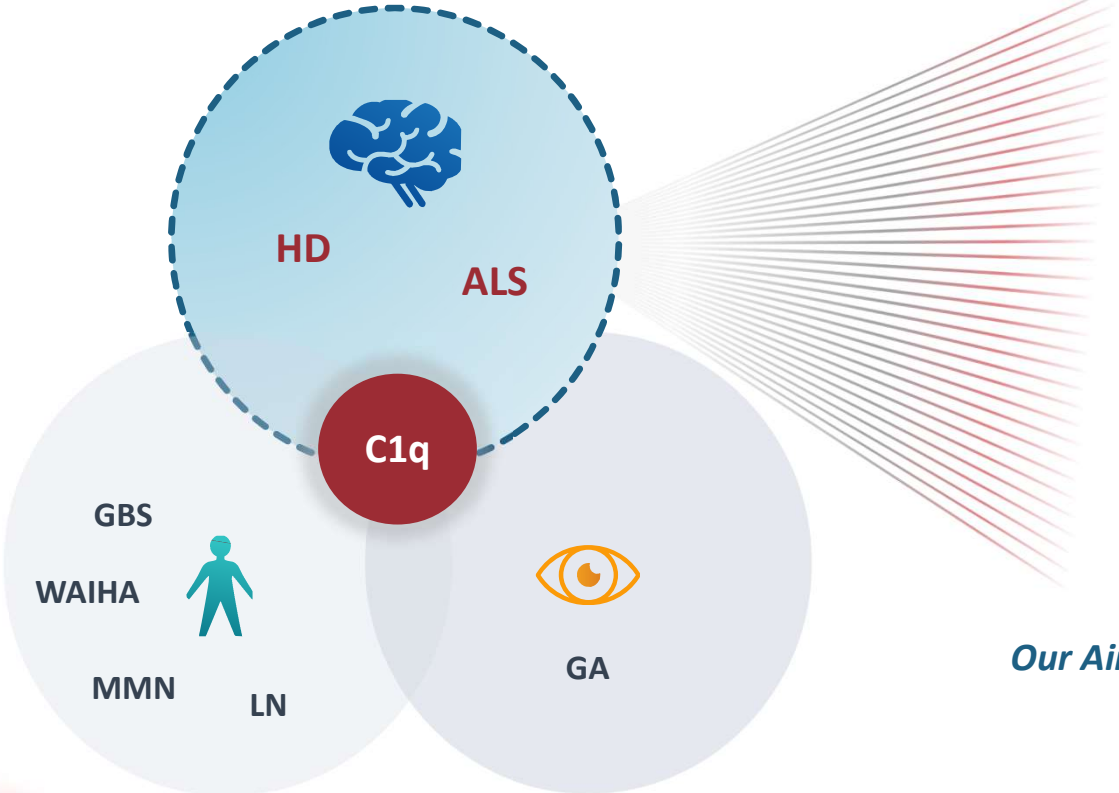
Significant Patient Need Across Our Classical Pathway Platform

Neurodegeneration therapeutic area itself has immense need and value opportunity



NEURODEGENERATION

HD	ALS
~80,000 (WW prevalence)	~75,000 (WW prevalence)
2030 Market $2B	$1B

Our Aim is to Bring Game-changing Therapies to These Patients

Patient numbers and market forecasts: GlobalData and Delvinsight market research

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Annexon is Well-Positioned to Drive Significant Value Over the Next 2 Years

- **Anti-C1q platform with broad and deep applicability** across autoimmune, neurodegenerative & ophthalmic diseases
- **Platform foundation established** with robust target engagement, POC data and 5 diverse drug candidates
- **Poised for significant value creation** with 7 mid to late-stage data sets anticipated over next 2 years
- **Winning team and well capitalized** to achieve milestones over next 2 years

Thank You!