ALCHEMAB THERAPEUTICS

Antibodies from resilient individuals: Identifying a potential novel treatment for Huntington's disease modification

Donna Finch Session III Wed April 26th 2023

Vision: To use the power of the human immune system to discover new medicines

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Discovering and developing protective, patient-originated therapeutic antibodies

- Focus on protective antibody responses
- Convergent in resilient individuals
- Target agnostic approach
- Advanced computational approaches

Humans benefit from naturally-occurring protective autoantibodies in many diseases

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SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

A human-derived antibody targets misfolded SOD1 and ameliorates motor symptoms in mouse models of amyotrophic lateral sclerosis

Marcel Maier[1]*, Tobias Welt[2]*, Fabian Wirth[1], Fabio Montrasio[1], Daniel Preisig[2], Jordan McAfoose[2], Fernando G. Vieira[3], Luka Kulic[2], Claudia Späni[2], Thilo Stehle[4], Steve Perrin[3], Markus Weber[5], Christoph Hock[1,2], Roger M. Nitsch[1,2], Jan Grimm[1†]

ALDH4A1 is an atherosclerosis auto-antigen targeted by protective antibodies

https://doi.org/10.1038/s41586-020-2993-2
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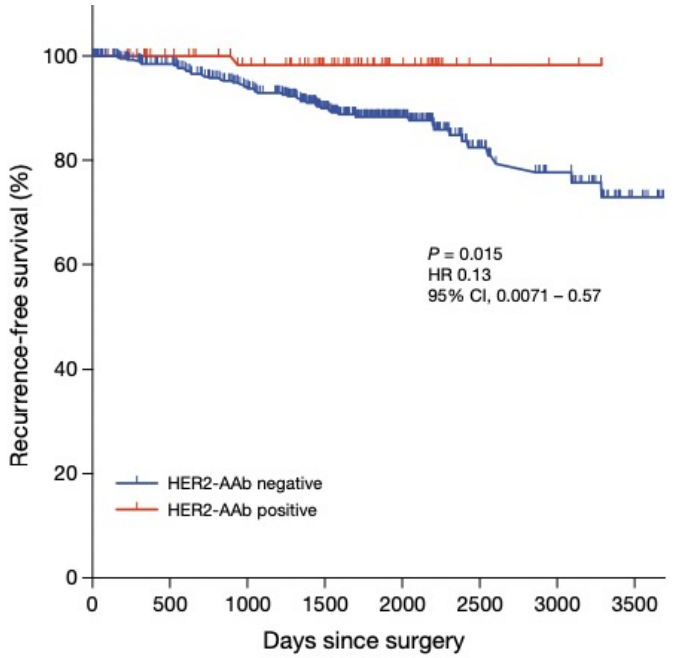
Cristina Lorenzo[1], Pilar Delgado[1,6], Christian E. Busse[2,7], Alejandro Sanz-Bravo[1,7], Inmaculada Martos-Folgado[1,7], Elena Bonzon-Kulichenko[3,4,7], Alessia Ferrarini[3], Ileana B. Gonzalez-Valdes[3], Sonia M. Mur[1], Raquel Roldán-Montero[5], Diego Martinez-Lopez[5], Jose L. Martin-Ventura[4,5], Jesús Vázquez[3,4], Hedda Wardemann[2] & Almudena R. Ramiro[1]✉

Breast Cancer Res Treat (2016) 157:55–63
DOI 10.1007/s10549-016-3801-4

Protective effect of naturally occurring anti-HER2 autoantibodies on breast cancer

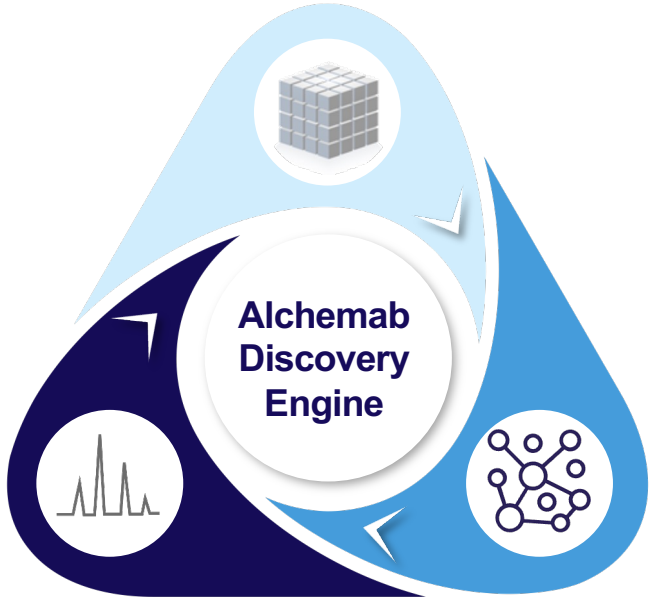
Yukiko Tabuchi[1] · Masafumi Shimoda[1] · Naofumi Kagara[1] · Yasuto Naoi[1] · Tomonori Tanei[1] · Atsushi Shimomura[1] · Kenzo Shimazu[1] · Seung Jin Kim[1] · Shinzaburo Noguchi[1]



Our approach finds naturally occurring protective antibodies, deconvolutes their targets and validates their function

Resilient patient cohort with disease and healthy controls

Repertoire analysis to **select** antibodies



Proteomics to **deconvolute** targets

Phenotypic assay cascade to **screen** for function

Validate function *in vitro* & *in vivo*

Unbiased target and drug discovery

Resilience can take many forms

Patients with years of survival with typically untreatable cancer

Pancreatic cancer survivors, alive 7+ years after diagnosis

Median survival: 10-12 months

Very long-lived, healthy individuals without chronic diseases

Average >100 years, no cognitive impairment nor debilitating illness

~0.004% population

Patients with susceptibility to neurodegenerative disease who do not progress

Confirmed Beta-amyloid in CSF, APOE4 risk allele, no or very slow disease progression

We identify BCR sequences of interest through analysis of deep NGS of patient samples

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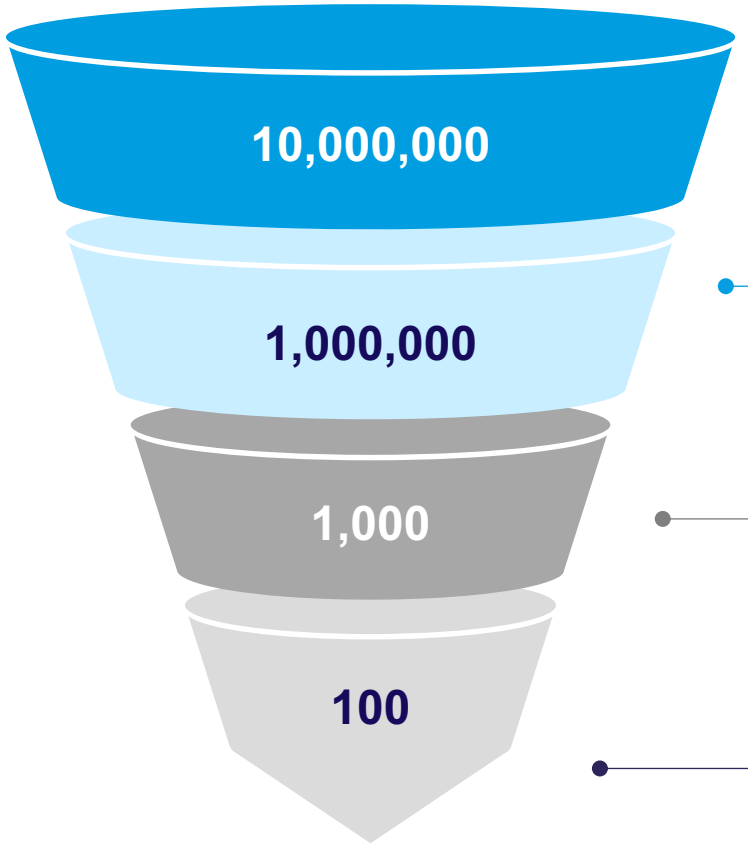
Core Technologies

- **Repertoire analysis**
- **Phenotypic screening**
- **Target deconvolution**



CLUSTERING

Grouping together antibodies based on sequence relatedness

CONVERGENCE

Searching for clusters containing sequences derived from multiple resilient individuals – indicates selection for similar specificities

VALIDATE & TRIAGE

Validating convergent signals, and understanding features of the best antibodies

Alchemab works with leading global collaborators to secure highly curated resilient samples

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AD

EPAD European Prevention of Alzheimer's Dementia Consortium

Delay in progression

Tissue Solutions A BioIVT Company

Delay in progression

PD

Queen Mary University of London

Delay in onset (symptomatic)

Queen Mary University of London

Delay in progression

ALS

TARGET ALS

Delay in progression

UC San Diego

Delay in progression

Casa di Cura del Policlinico

Delay in progression

FTD

GENFI GENETIC FTD INITIATIVE

Delay in onset

HD

CHDI FOUNDATION

Delay in onset

Other

Amsterdam UMC

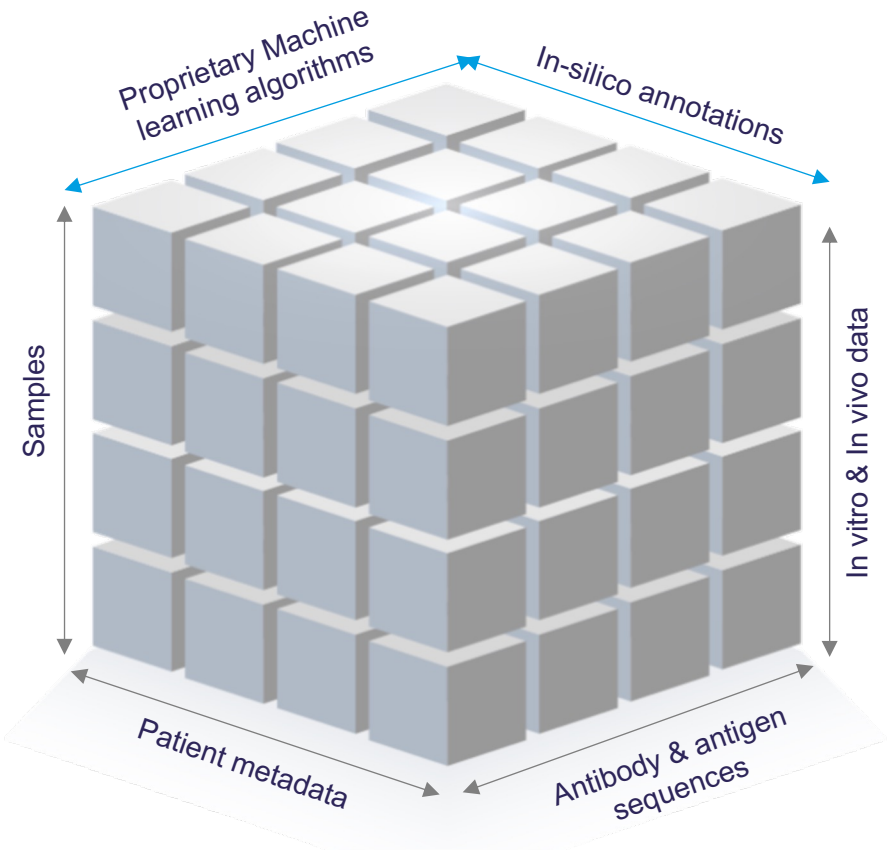
Healthy ageing
100+ cohort

Lumind IDSC Down Syndrome Foundation

AD in Down's

A total of more than 1500 patient samples from across target neurodegenerative indications

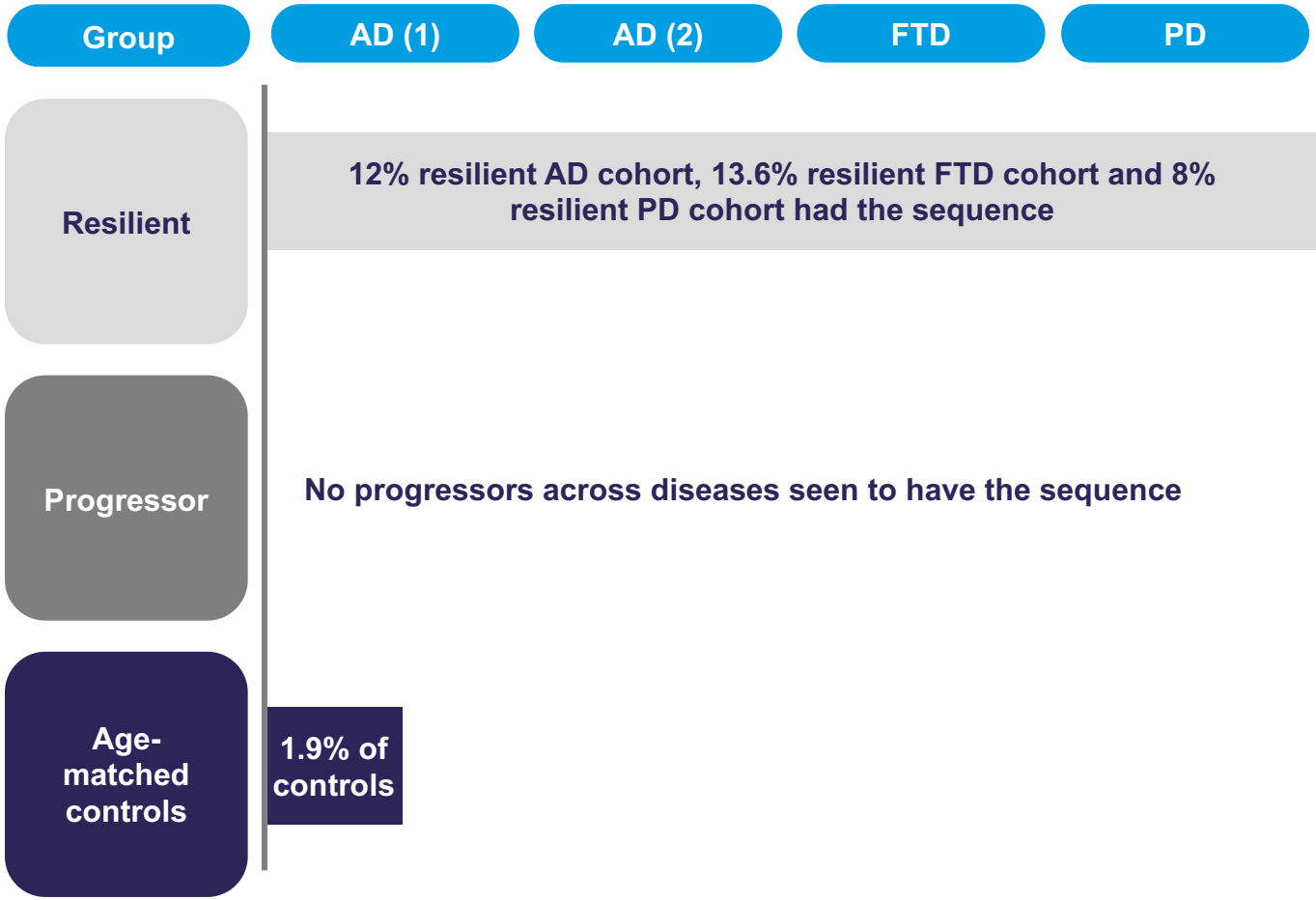
The Data Cube, containing over 350 Million BCR Sequences, generates multiple insights to support the discovery process



Identify which antibodies/targets most commonly occur together in resilient patients	Companion therapeutics
Identify which patients are most likely to have disease / respond to therapy based on repertoire	Patient selection
Identify how our chosen antibody could be effective across diseases	Disease selection
Select optimal therapeutic candidate from natural variants based on sequence insights*	Candidate selection

*Includes: Comparison to patented antibody database for variants of known antibodies; Function based on sequence; developability; toxicity

Mining the Data Cube shows HTT antibodies may contribute to resilience in several diseases



HTT sequences convergent across 'at risk' resilient FTD, AD and PD patients, but not in progressors

Related sequences also found in HD patients

Assessing resilience association and increasing HD cohort numbers

Resilience: AD resilience defined using biomarkers or progression rate; PD resilience defined by delay in symptomatic onset; FTD resilience defined using age of onset with genetic driver

Subject distribution for individuals with ATL_005252 homologues (90% CDR3 + V + J and >75% similarity across paratope)

HTT dysfunction may play a role in FTD, AD and other dementias

HTT aggregates are seen across neurodegenerative diseases

- HTT aggregates accumulate in AD brains (Singhrao *et al.,*1998; Axenhus *et al.,* 2020)
- Some FTD and ALS patients have CAG expansions of >40, which is seen x4 more often than in healthy individuals (Dewan *et al.,* 2021)

Aggregated HTT may precede Tau, β amyloid & TDP-43 mediated changes

- Association of HTT with tau fibrils and tangles in both HD and AD (Masnata *et al.,* 2020)
- mHTT increases the seeding properties of aggregated TDP-43 in a cellular model (Coudert *et al.* 2019)

Reasons to believe antibodies targeting extracellular HTT may slow spread of pathology

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Extracellular HTT Exon 1 truncated form is pathogenic

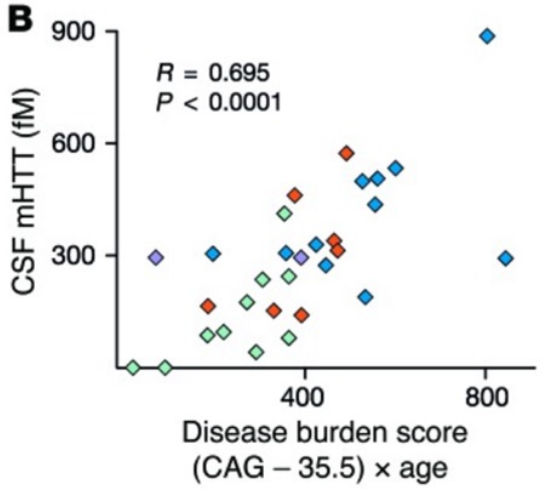
- N-terminal fragments generated by proteolysis and alternative splicing
- Highly and directly neurotoxic in cell systems
- Clear relevant pathology in Exon 1 KI mouse models
- Greater challenge for ASOs to effectively lower truncated forms of HTT

Extracellular mHTT can accelerate pathology by spreading and seeding

- mHTT is present in neuronal grafts in HD patients
- CSF from HD patients contains seed competent mHTT species
- Spreading and seeding activity has been observed in cell-free, cell, and in vivo models

CSF mHTT increases as disease progresses

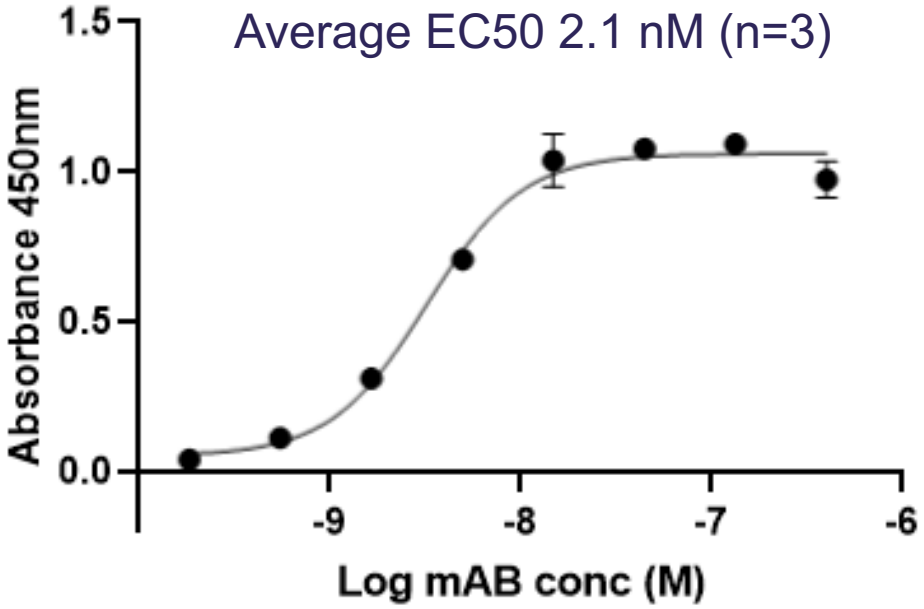
- Correlates with increases in CSF NfL (TRACK-HD)

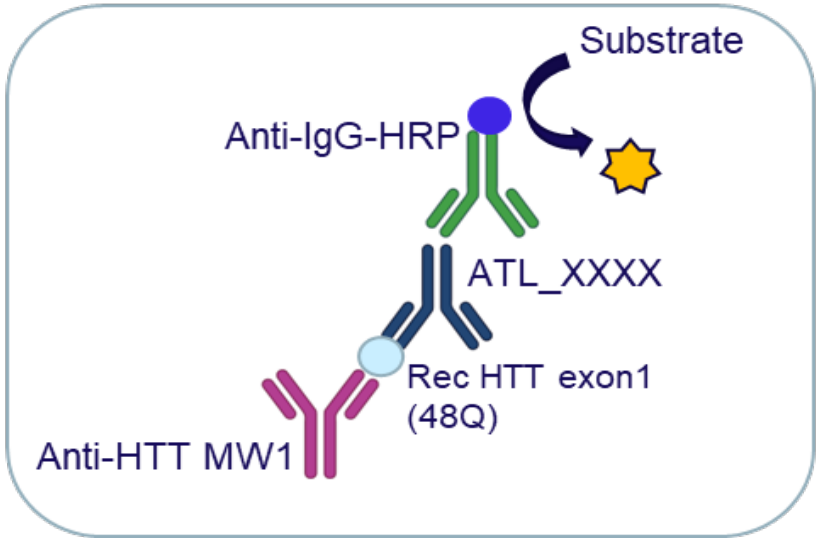


Wild et al 2015

ATLX-1095 binds HTT with high affinity and specificity

Panel of antibody variants of convergent sequence were assessed in ELISA assays

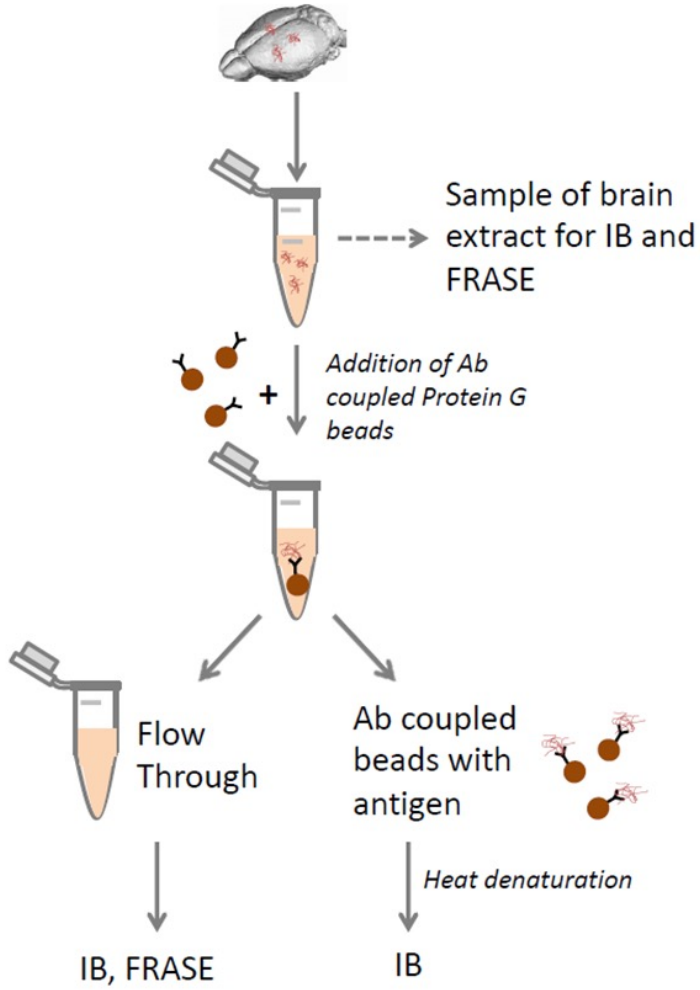




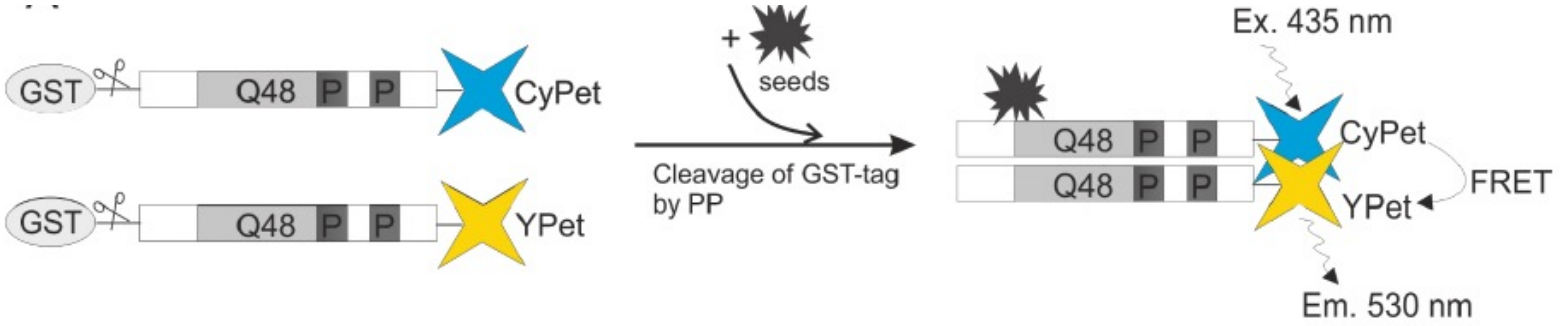
Epitope is within Exon 1 but independent of PolyQ
Retrogenix Cell Microarray proteome platform shows no off-target binding

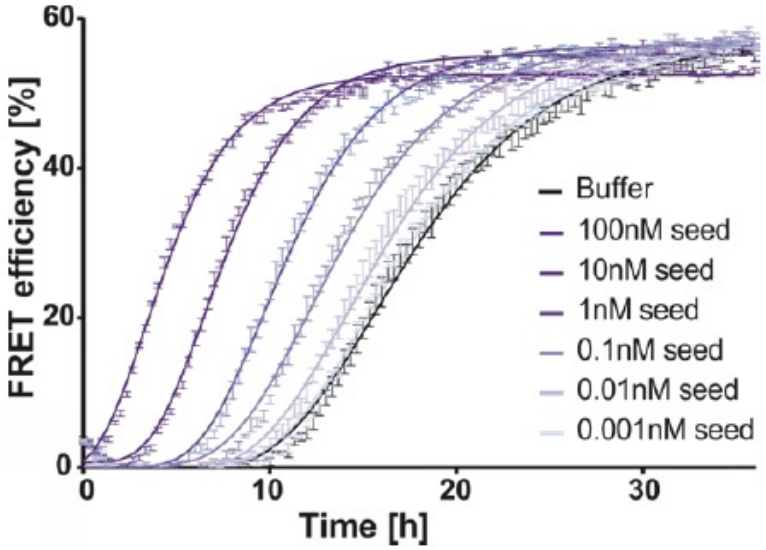
Can ATLX-1095 impact key biological mechanisms of interest?

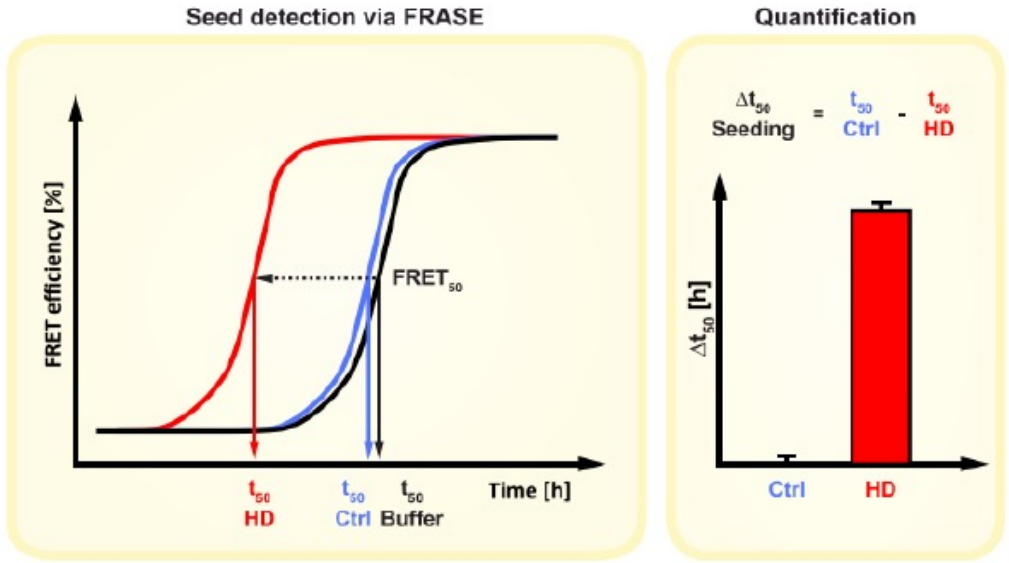
- Can ATLX-1095 bind and immuno-precipitate complex multiple forms of mHTT?
- Can ATLX-1095 impact cell-free seeding of HTT?



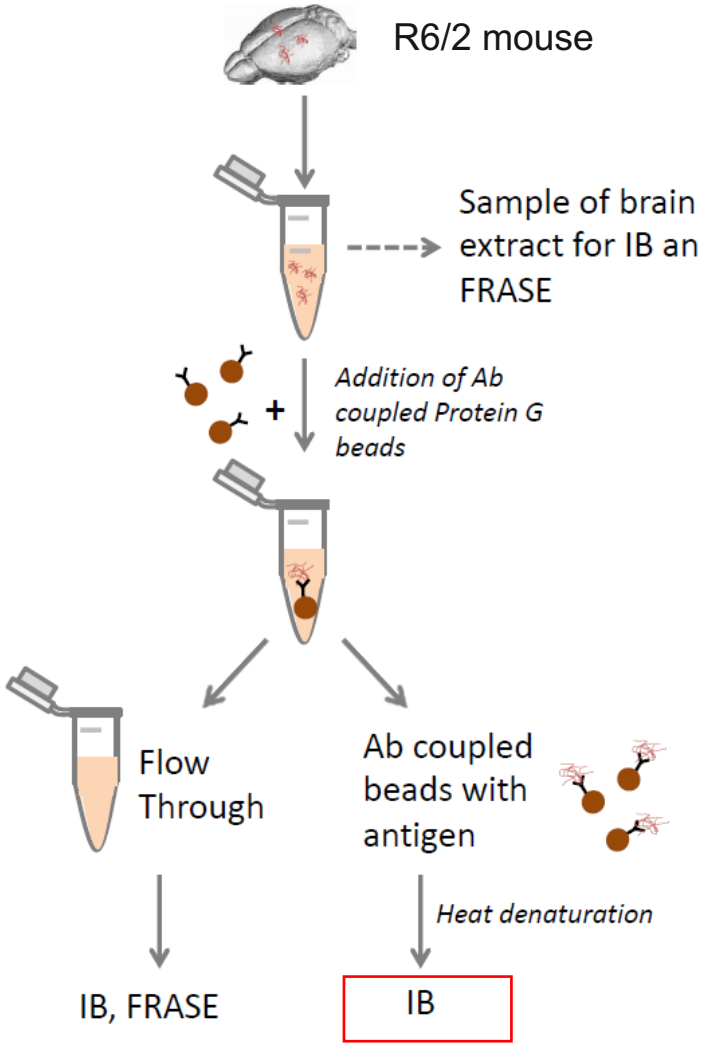
FRASE (FRET based mHTT Aggregate seeding assay) (Ast et al, 2018)

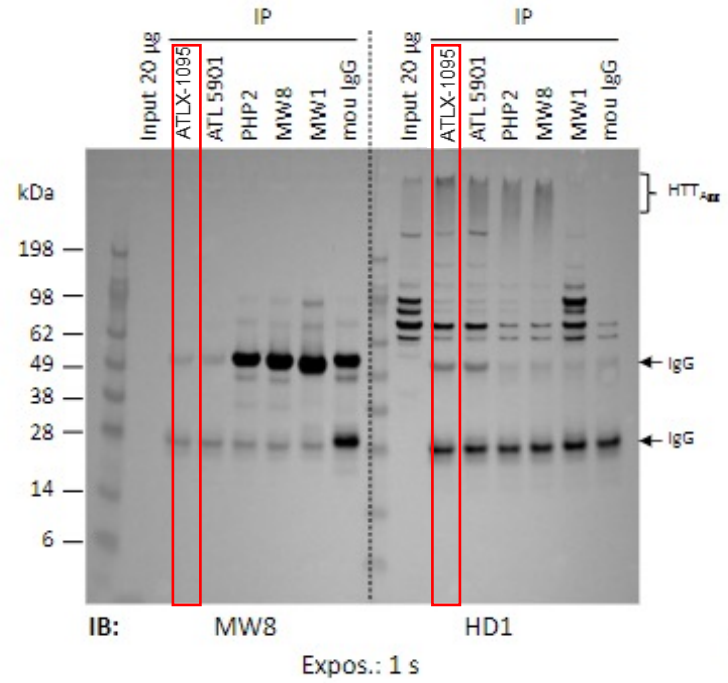




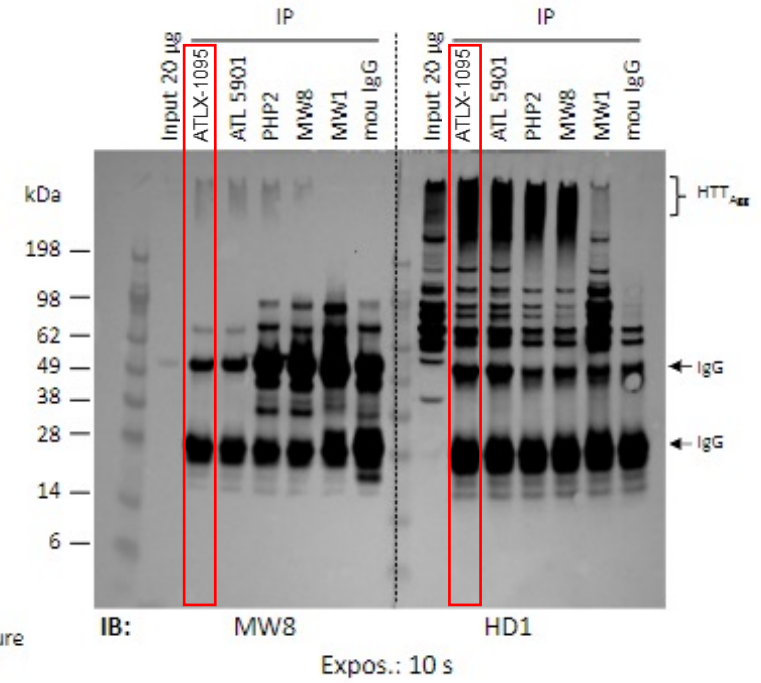


ATLX-1095 immunoprecipitates multiple species of mHTT including high molecular weight aggregates





Longer exposure



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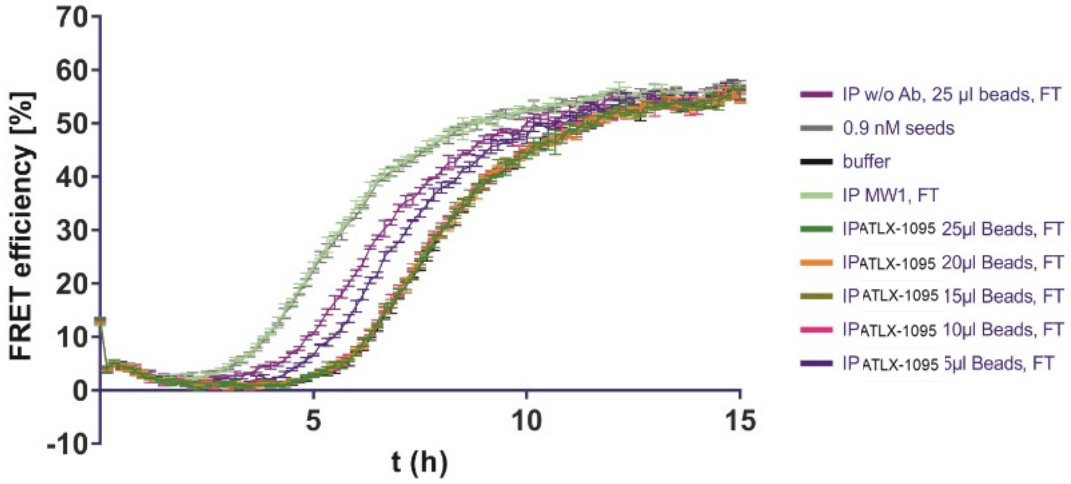
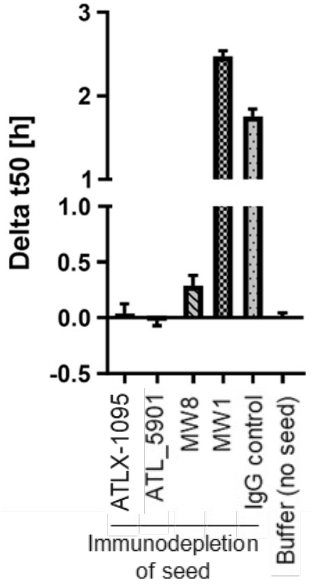
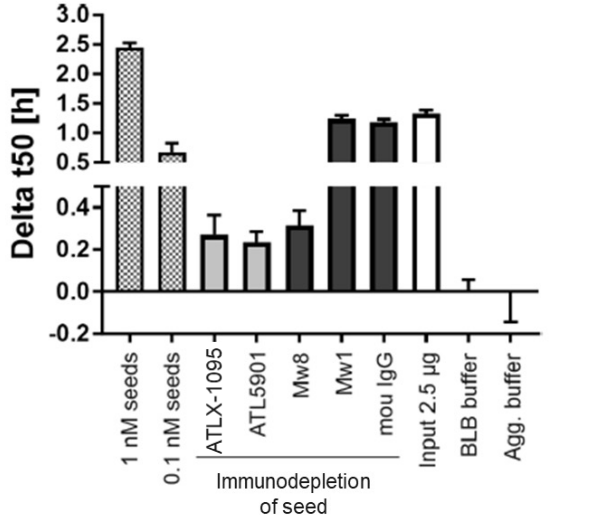
ATLX-1095 reduces rate of aggregation in a FRASE seeding assay



Recombinant seed



R6/2 brain derived seed



MW1 (polyQ) has no impact on seed-induced acceleration of aggregation
ATLX-1095 significantly reduces rate of seeding induced by recombinant or brain-derived seed

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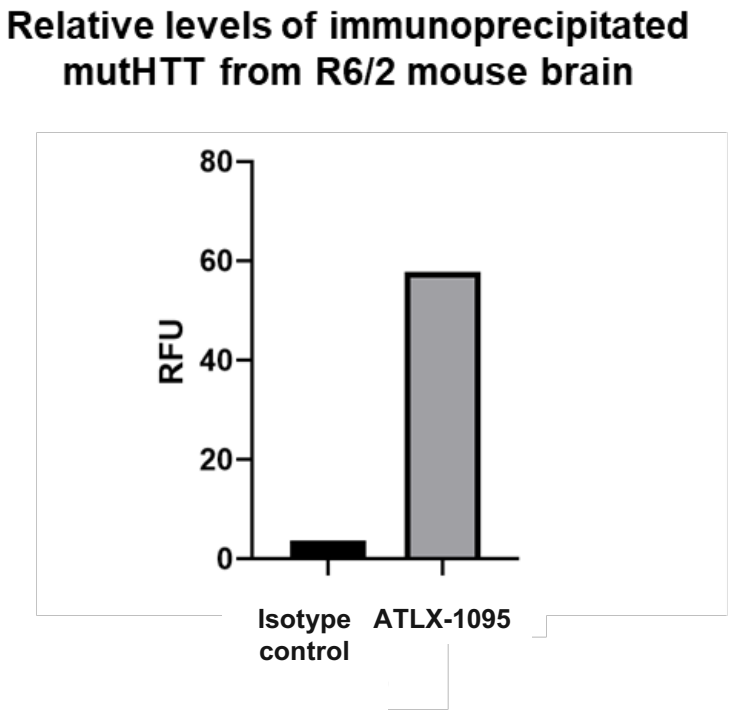
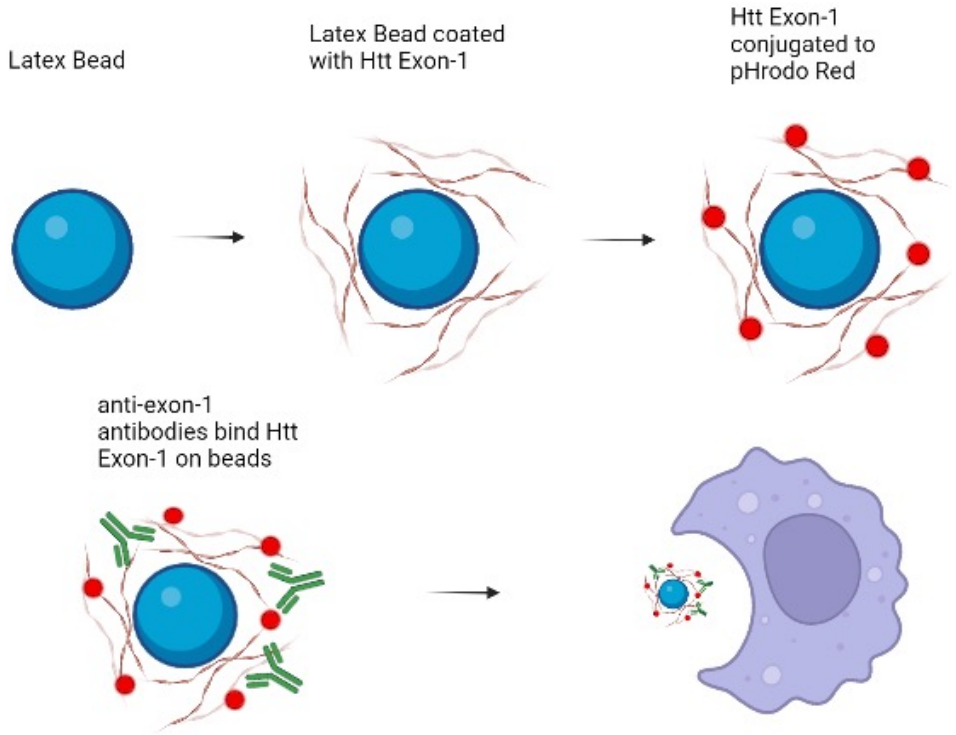
ATLX-1095 binds to multiple forms of muHTT

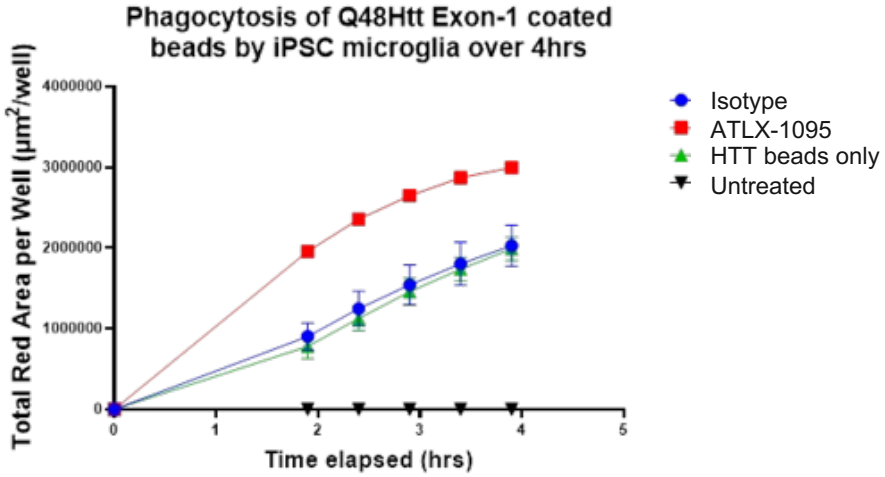
- 25Q and 48Q recombinant Ex1 HTT ELISA binding
- Immunoprecipitation with a variety of detection abs shows multiple forms of HTT are pulled down
  - mHTT over-expressing cell line lysate (LoQus23 proprietary cell line))
  - HTT R6/2 mouse brain lysate- soluble and aggregated forms

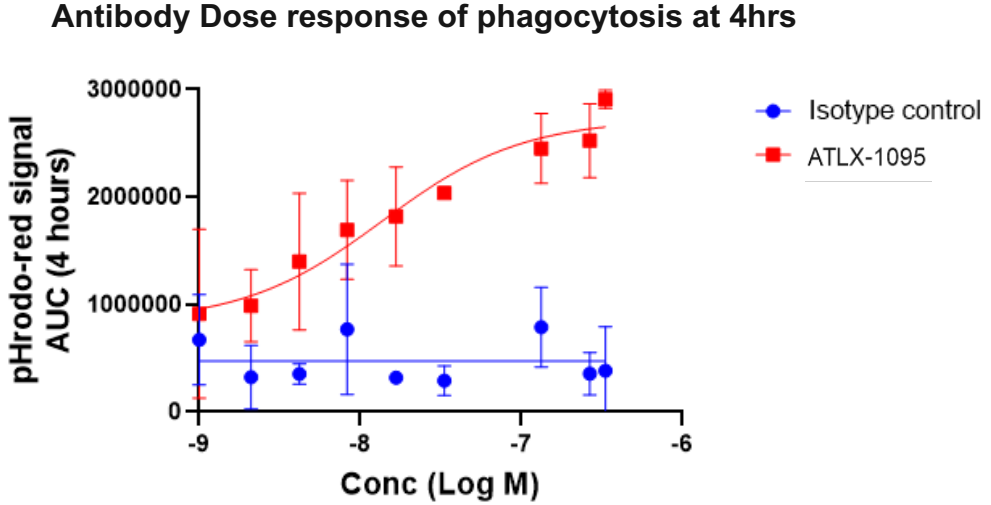


Recognizes high molecular weight aggregated and soluble forms of HTT

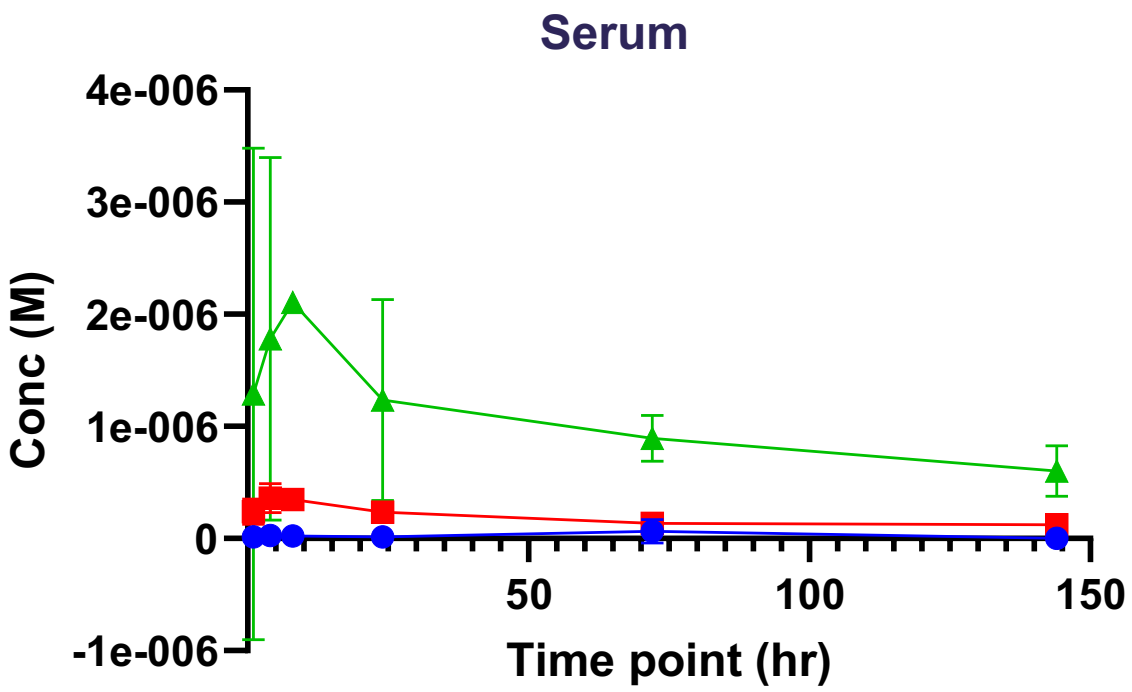
ATLX-1095 increases phagocytosis of mHTT by human iMicroglia

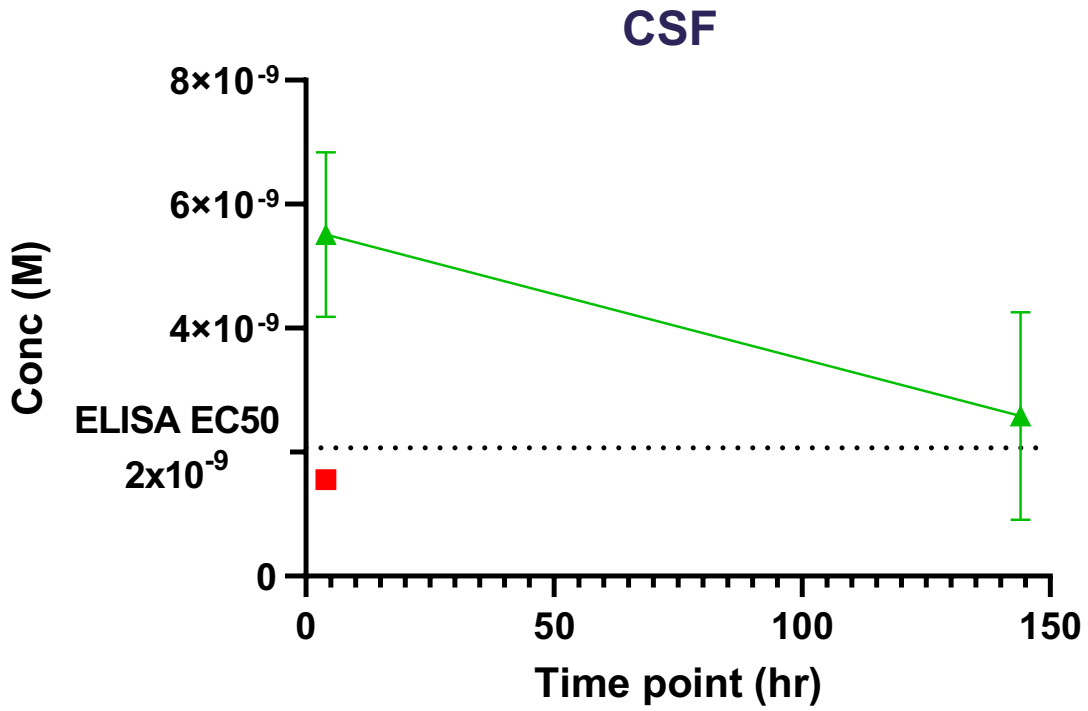






CNS exposure of ATLX-1095 above EC50 at achievable dose

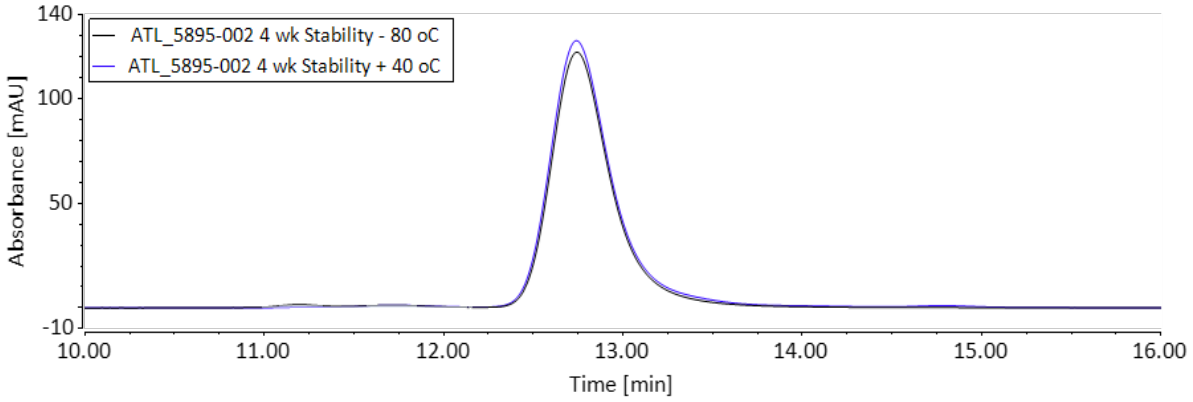




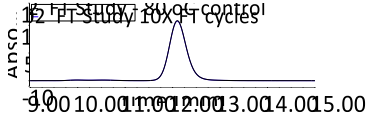
Typical half-life of IgG1 in WT mice of 3-5 days
Typical IgG1 0.1-0.3% CNS penetrance

ATLX-1095 has an excellent early manufacturability profile

- ATLX-1095 has been engineered to remove sequence liabilities and to revert framework mutations to germline
- Good thermostability
  - No aggregation observed following incubation at 40 °C for 4 weeks (SEC-HPLC)
  - No aggregation observed following 10 freeze-thaw cycles (SEC-HPLC)
- Main species is within appropriate range for downstream processing (pH 7.5 – 9.0)

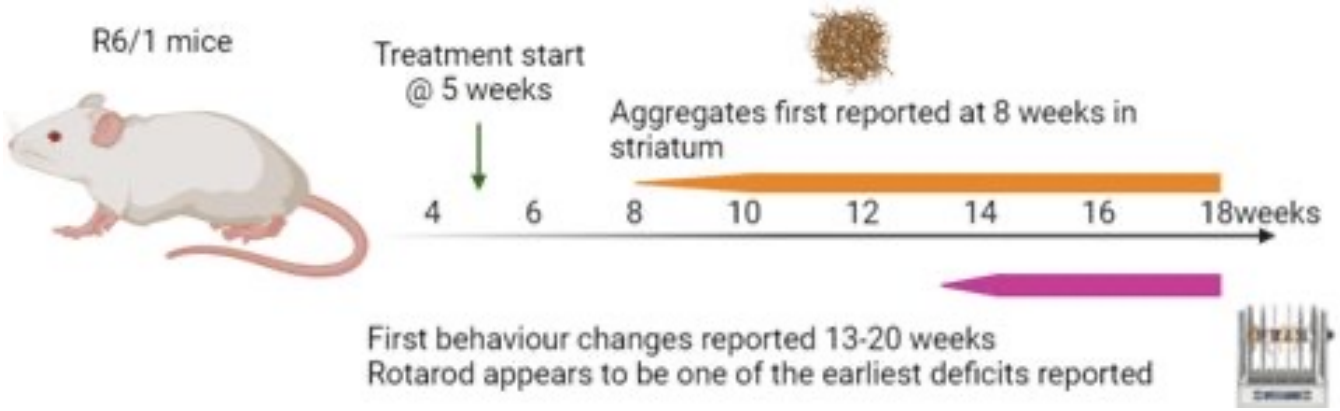


40°C 4 weeks vs -80°C 4 weeks

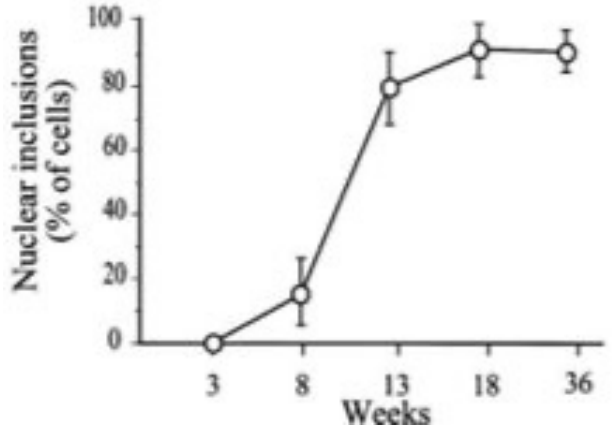


Control vs 10x FT cycles

Pharmacology plans in R6/1 mice- Proof of concept study



Development of inclusion bodies in R6/1 brains over time



Hansson et al, 2001

Initial proof of concept study R6/1 mouse model

Weekly doing at 60mg/kg
Start dosing at 5wks of age
Endpoints at 9 wks, 13 wks and 17 weeks of age
Free and total HTT Immunoassays
Aggregated HTT in brain by IHC
Behavioural endpoints (multiple)
Neurofilament light chain

Pharmacology plans in R6/1 mice- Considering Translation to Clinic

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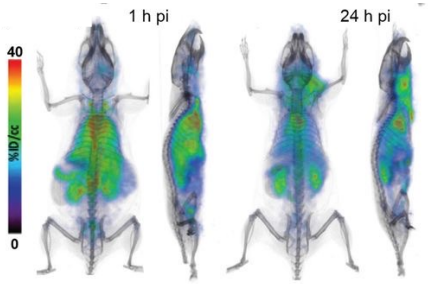
In vivo Pharmacokinetics, Biodistribution (PET Imaging)

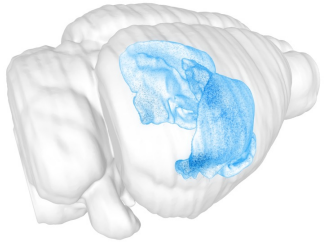
Antibody radiolabelling

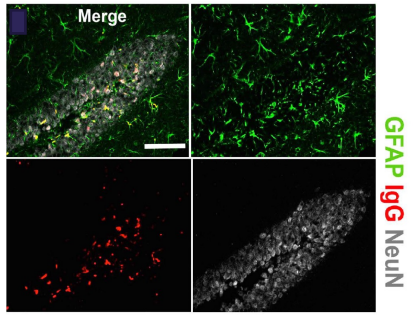
High performance PET/CT



Whole-body biodistribution

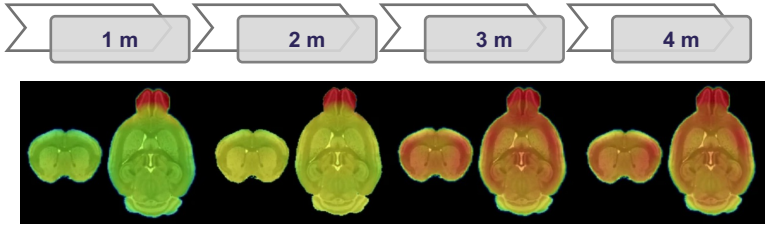
Ex vivo brain penetrance – Target Engagement (Fluorescence Imaging)





Antibody localisation in mouse brain slices

Non-invasive monitoring of disease state using [^{18}F-CHDI-] PET radiotracers for mutant huntingtin



CATAPULT Medicines Discovery

CHDI FOUNDATION

ATLX-1095

- Discovered in Resilient Individuals ‘at risk’ of Neurodegeneration
- Naturally optimised and differentiated binding profile
- Targets multiple forms of mHTT
- Potential for add-on to other HD lowering modalities

Acknowledgements

- **Patient cohorts and volunteers**
- Alchemab team
- Max Delbrūch Center for Molecular Medicine, Berlin
  - Erich Wanker
  - Annett Böddrich
- CHDI Foundation
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- Caroline Benn and LoQus23 Therapeutics
- All our scientific advisers
- **Innovate UK Biomedical Catalyst Fund**