ORIGAMI Therapeutics

Transforming the >$50B neurodegenerative disease market with best-in-class treatments

Non-confidential corporate deck

Executive Summary

Imagine a world without neurodegeneration

Who we are

- Lean startup focused on genetic forms of neurodegeneration with lead program in Huntington's disease (HD)
- Team of experienced pharma executives and experts: scientists, drug development, operational leadership

What we do

- Develop novel first-in-class, best-in-class disease modifying treatments with an innovative discovery approach
- Leverage expedited development and regulatory pathways

Why we win

- Targeting underlying cause of disease (precision medicine)
- Unique positioning with key differentiators and limited competition in a growing market of >$9B for HD
- Strong initial traction
- Ability to scale to additional indications

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Impaired proteostasis: A central hallmark of aging & disease

- **Loss of proteostasis** is among the most prominent and early age-related impairments
  - Affects integrity of proteins, organelles such as mitochondria and DNA
  - Accumulation of misfolded proteins appear as protein aggregates, particularly in brain
  - Affects cell's ability to clear damaged proteins, organelles and lipids by autophagy
  - Leads to accelerated aging and disease

Lopez-Otin et al The hallmarks of aging. Cell (2013).

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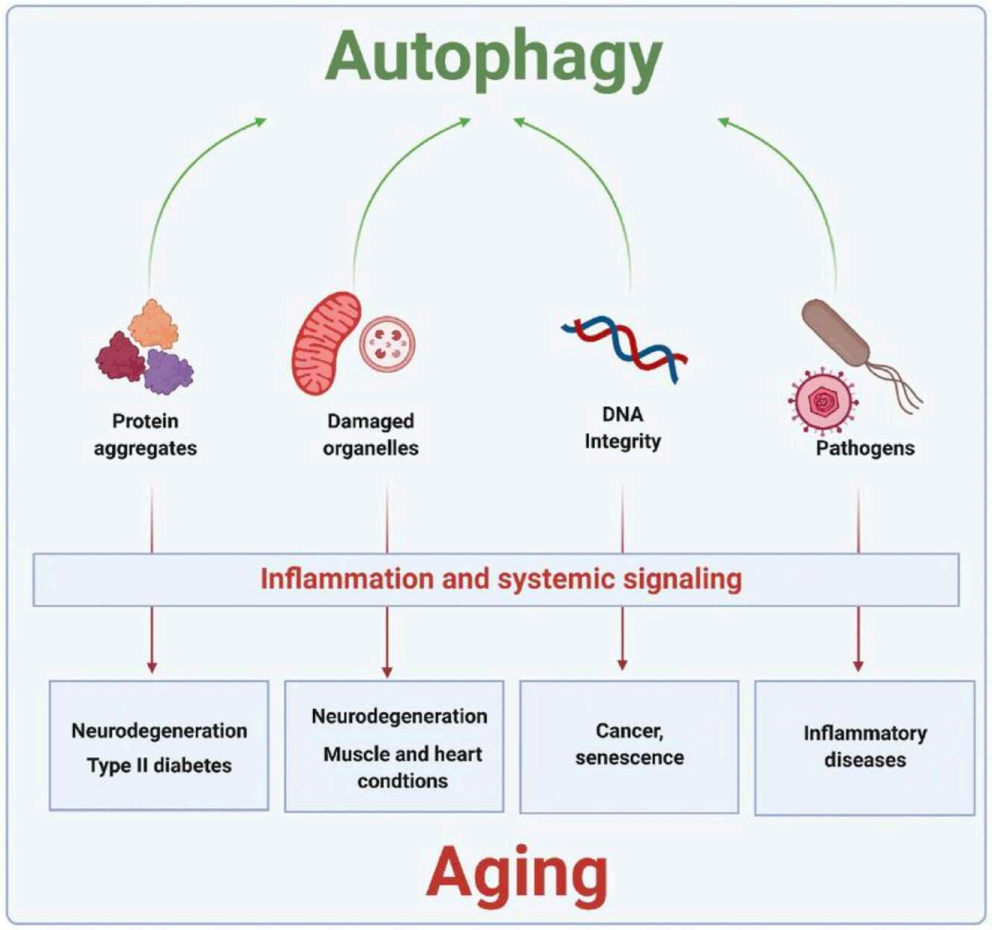
Decline in autophagy correlates with aging & disease



Nieto-Torres & Hansen, Macroautophagy and aging- the impact of cellular recycling on health and longevity. Mol Aspects Med 2021

- Aging and development of age-relate diseases correlate with a decline in autophagy
  - Autophagy deficits lead to accumulation of damaged proteins, organelles, DNA integrity
  - Triggers cellular dysfunction followed by tissue damage
  - Tissue damage amplified by inflammation
  - Leads to disease
- Interventions that promote autophagy have beneficial effects on health and lifespan

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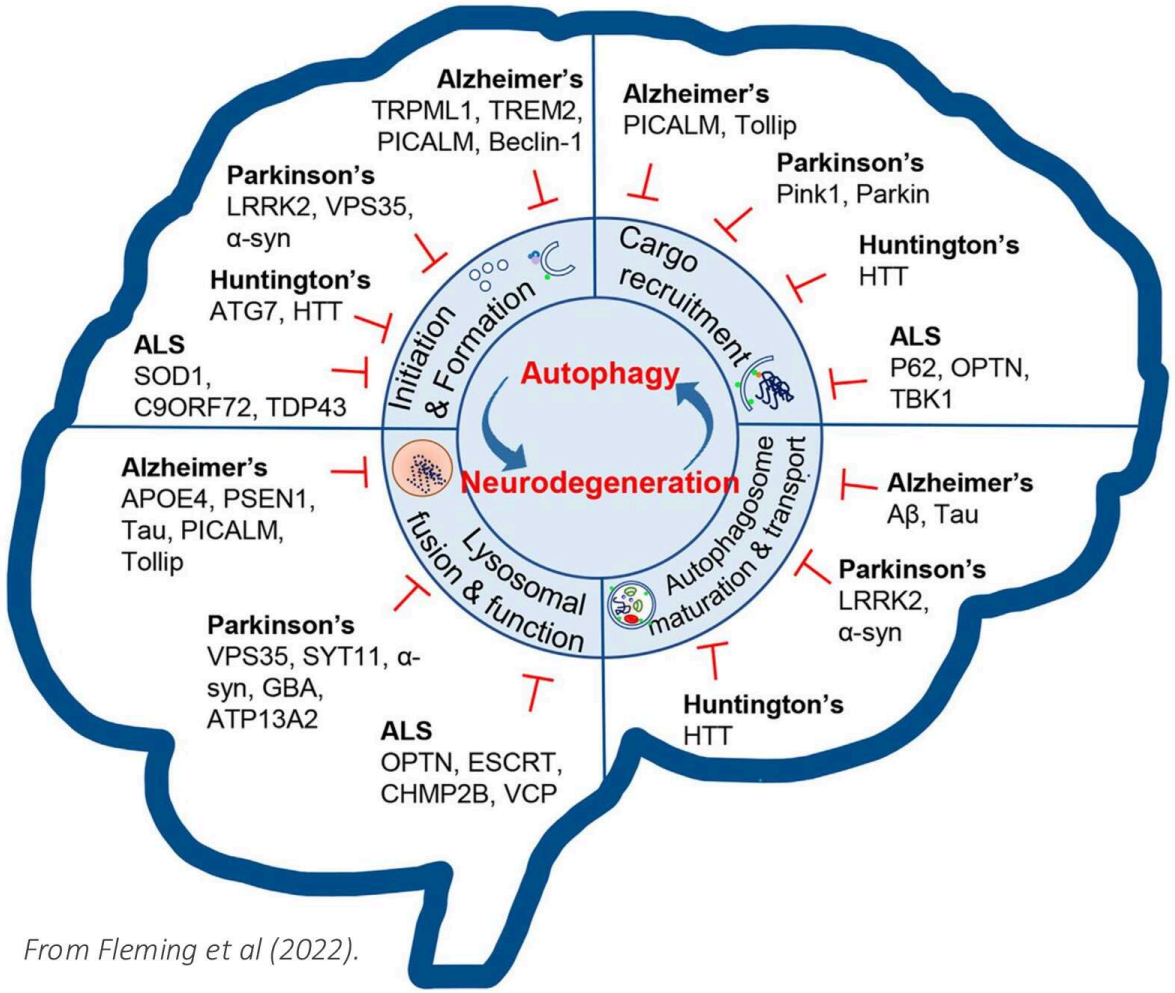
Defective autophagy is implicated in neurodegeneration



From Fleming et al (2022).

Overview of the role of macroautophagy in the nervous system in health and neurodegeneration

- Defective autophagy is a common symptom in neurodegeneration
- Genetic mutations in multiple autophagy proteins are causative in neurodegenerative diseases
- Experimental increase in autophagy slows or reverses neurodegeneration in cell and animal models of neurodegeneration

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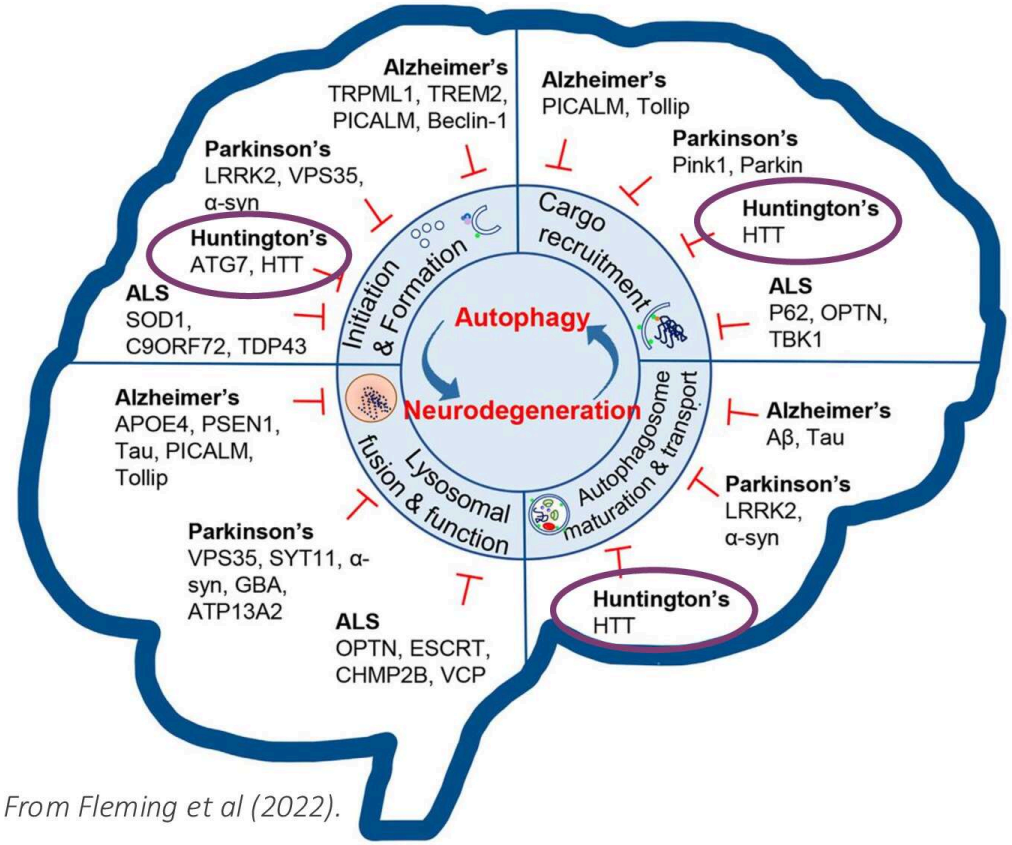
Fleming et al, The different autophagy degradation pathways & neurodegeneration. Neuron (2022).
Zhang et al, Autophagy in Alzheimer's disease pathogenesis: Therapeutic potential & future perspectives. Ageing Res Rev (2021).
Fujikake, Shin & Shimizu, Association between autophagy and neurodegenerative diseases. Front Neuroci (2018).

Huntington's disease (HD): Origami's beachhead indication



From Fleming et al (2022).

Why Huntington's disease first?

- HD is a disease of accelerated aging
- Genetic disease caused by a mutation in a single gene called huntingtin (HTT)
- Mutant huntingtin (mHTT) protein misfolds and becomes toxic
  - Blocks autophagy at multiple points in pathway
- We know what an effective drug should do
- We know who to treat & what to measure in clinical trials

Huntington's disease by the numbers

- Autosomal Dominant: 50% progeny affected
- Average onset: 35 yrs (range: 30-50 yrs)
- Duration: 10 - 25 yrs
- Affected: 185,000 WW/ 45,000 US
  250,000 US at risk (~50% HD)
- TAM: >$9B projected global sales in 2030*

**Coherent Market Insights, assuming 60% current symptomatics*

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The Problem

Huntington's disease (HD) treatment options are grim

3 drugs with a single mechanism only partially treat movement symptoms with considerable side effects

No disease modifying treatment options exist

Prodromal
10-15 yrs

- Movement abnormalities
- Cognitive changes
- Personality changes
  - Depression
  - Suicide

Early
~ 5-7 yrs

- Involuntary movements
- Loss of coordination
- Cognitive deficits
- Depression/ Suicide

Middle
~ 5-7 yrs

- Requires constant care
- Dementia

Late
~ 5 yrs

- Institutionalization
- Bedridden
- Non-verbal

Key Considerations for Therapeutic Design

- **Systemic disease affects brain and body**
- **Normal HTT protein is critical for normal cell function**
- **Reducing mutant HTT (mHTT) halts & reverses disease in HD models**
- **Reduction of HTT validated by genetics and clinical trials (PTC518, AMT-130)**

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Our Solution

We are pioneering a groundbreaking approach aimed at

- Slowing, halting or reversing disease progression of Huntington's disease for all patients
- Targeting underlying cause of disease, toxic misfolded protein, via protein degradation through selective autophagy
- Using small molecule modality to treat entire disease (brain & body) and democratize access to our medicines

Our precision medicine approach represents a paradigm shift by selectively targeting toxic misfolded protein to restore normal function and extend health span

ORI-003

Potential first-in-class, best-in-class disease modifying treatment for HD

What is ORI-003?

- Small molecule discovered by Origami via proprietary screening approach and medicinal chemistry
- Analogue of ORI-113, an early lead

ORI-003 is efficacious in patient-derived HD fibroblasts and HD neurons by reversing

- Impaired proteostasis by eliminating mHTT via selective autophagy
- Aberrant gene expression
- Aberrant protein expression

ORI-003 and analogs demonstrated efficacy and safety in mouse models of HD

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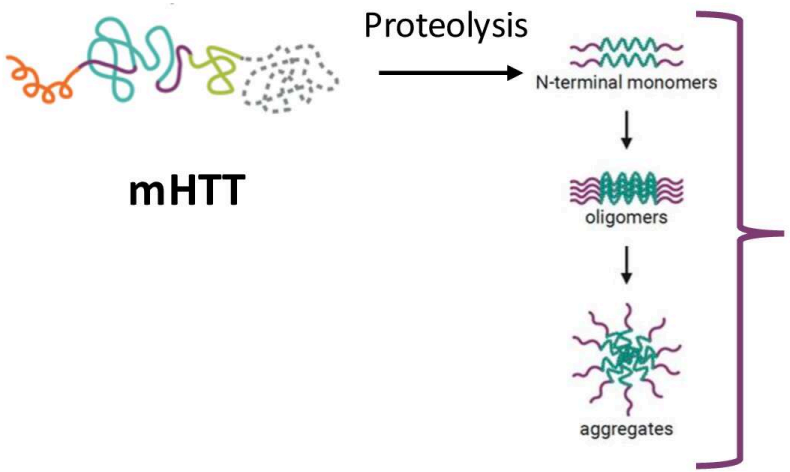
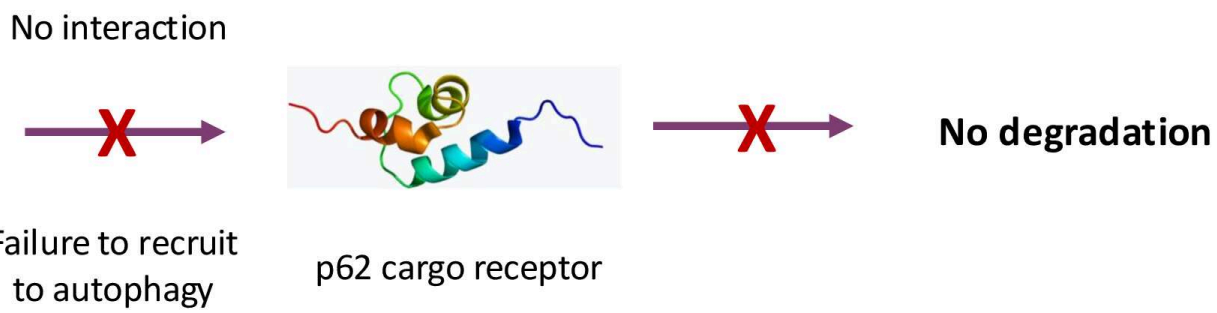
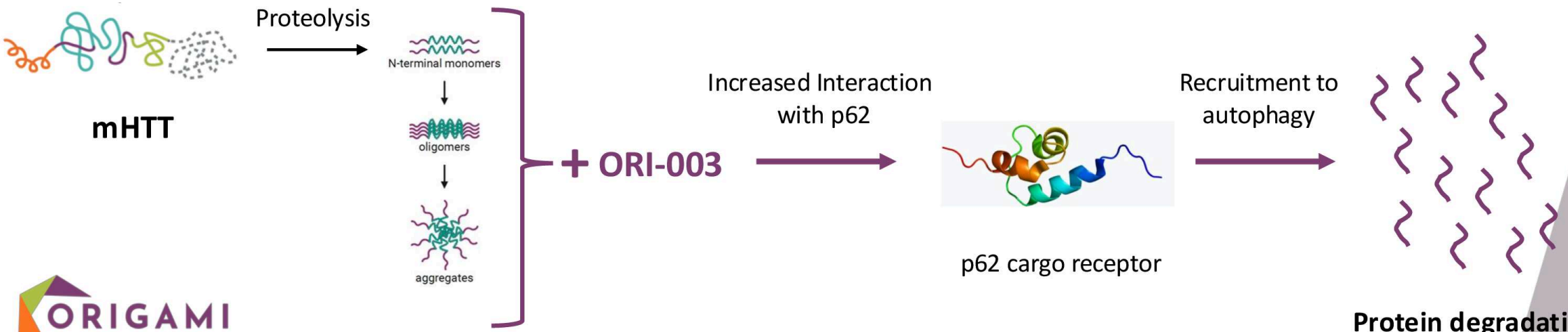
ORI-003 corrects aberrant metabolism
via pathway central to neurodegeneration and aging

Mutant HTT (mHTT) causes a deficit in autophagy (inhibits protein, lipid and mitochondria regulation)





ORI drug overcomes this deficit by directly targeting the mutant misfolded proteins, the underlying cause of disease



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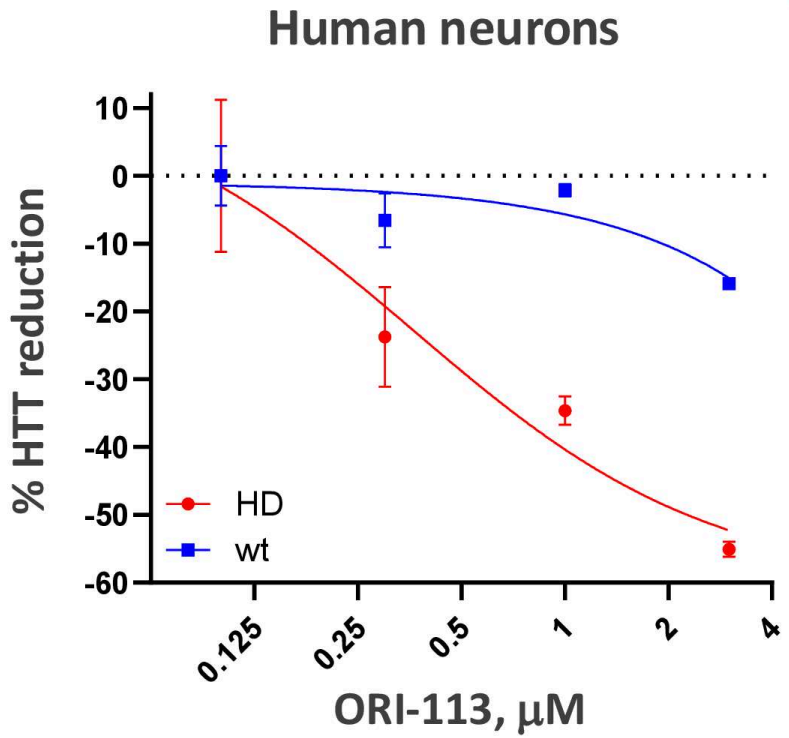
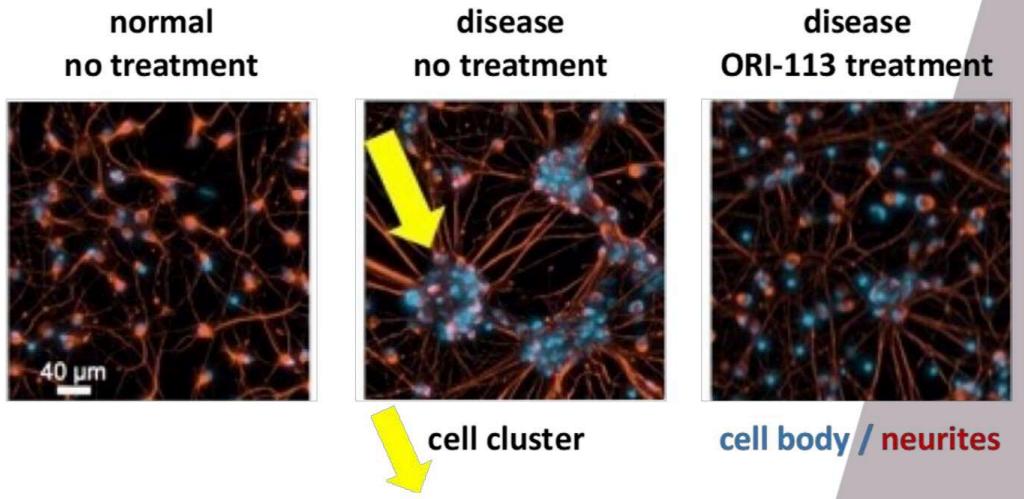
Lead chemical series with excellent drug attributes

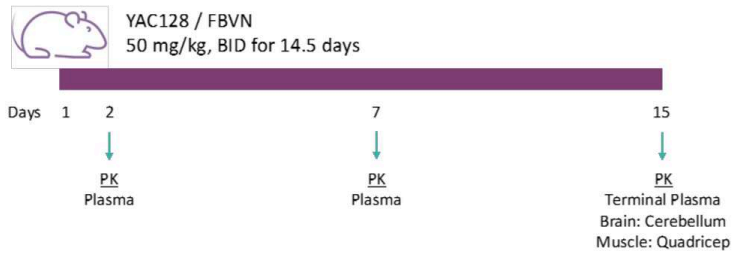
- Selectively reduces mHTT and restores cell morphology, protein expression in HD neurons
- Reverses autophagy deficits in HD fibroblasts (novel mechanism of action)
- Excellent brain penetration after oral administration
- Efficacy in 2 mouse models of Huntington's disease (HD)

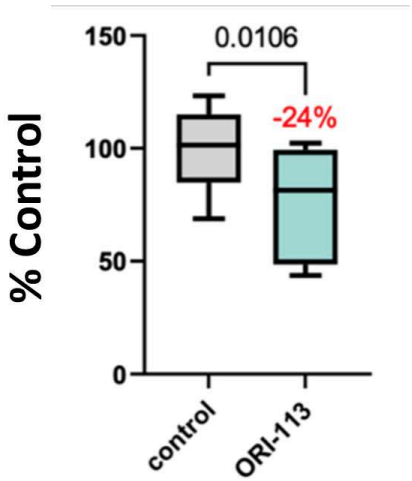




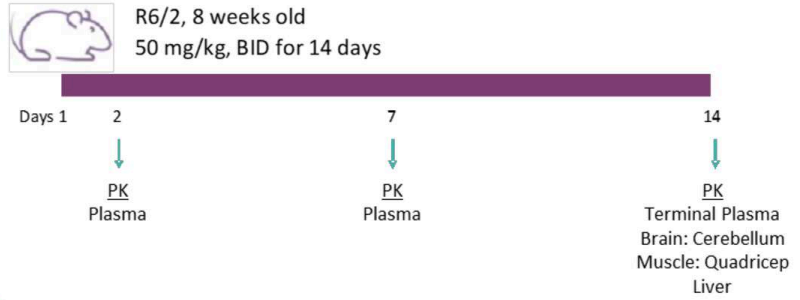
Lead compound demonstrates in vivo efficacy in 2 HD models

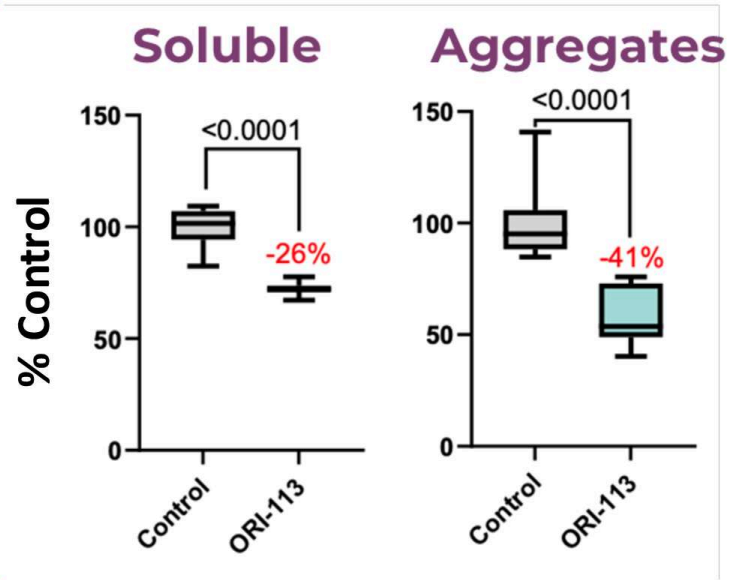
Pre-symptomatic
Full length mHTT (Q128)





Symptomatic
Exon1 mHTT (Q120)





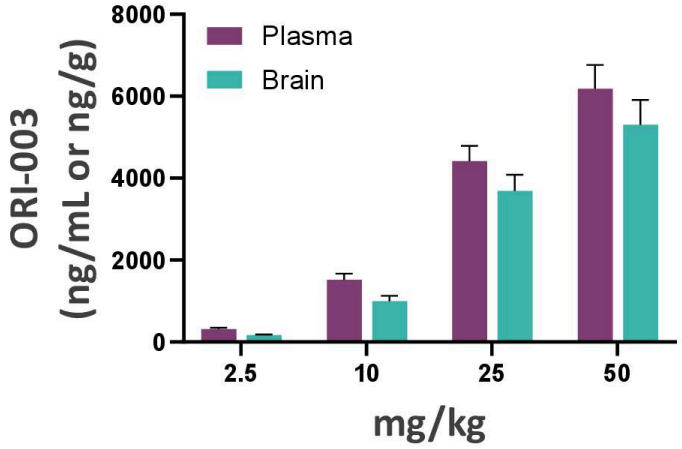
ORI-113 reduces mHTT full-length protein and protein fragments including Exon1 in pre-symptomatic & symptomatic stages of disease

ORI-003 possesses optimal drug characteristics

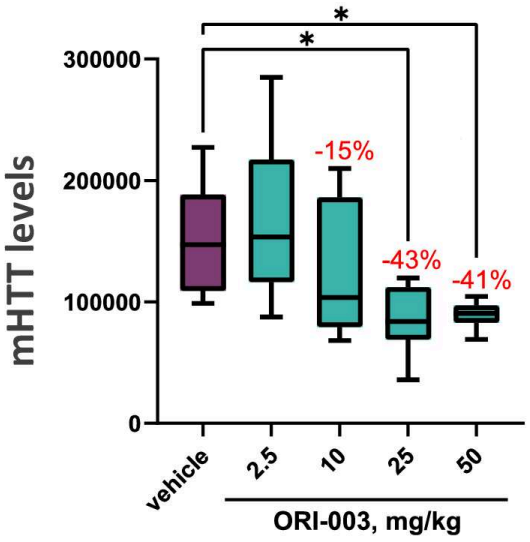
- >85% orally bioavailable, PK consistent with once daily dosing
- Highly brain penetrant
- Well-tolerated, no adverse effects after 2 weeks of daily dosing
- Next steps:
  - Disease-modifying treatment
  - Non-GLP toxicology studies
  - Apply for Orphan Designation

Generate a development candidate package to advance to IND-enabling studies

Well-distributed in brain and body



Dose-responsive lowering of mHTT protein

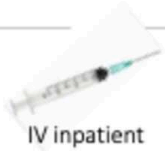


* p<0.05

Origami differentiators
Compared to the competitors in HTT-lowering

Origami's differentiators

- Targets mHTT proteins, not mRNA
- Oral administration for systemic treatment to treat entire disease (brain + body)
- >100-fold selective for mHTT protein, sparing normal HTT to restore normal function
- Elimination of existing toxic mHTT protein fragments including Exon1

	ORIGAMI Therapeutics	Alnylam	VICO Therapeutics	SKYHAWK THERAPEUTICS	Roche	WAVE LIFE SCIENCES	uniQure	PTC THERAPEUTICS
Delivery		 Spinal	 IV inpatient		 Spinal	 Spinal	 Brain Surgery	
Approach	Small molecule ***Mutant HTT***	siRNA Total HTT	ASO ***Mutant HTT***	Small molecule Total HTT	ASO Total HTT	ASO ***Mutant HTT***	siRNA / AAV Vector Total HTT	Small Molecule Total HTT
Target	***Protein***	mRNA	mRNA	mRNA	mRNA	mRNA	mRNA	mRNA
Target Organ(s)	***Brain + Body***	Brain	***Brain + Body***	***Brain + Body***	Brain	Brain	Brain	***Brain + Body***
Phase	Preclinical	Phase 1	Phase 1	Phase 1	Phase 2	Phase 2	Phase 2	Phase 2

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Fast-track opportunity to key value inflection point & beyond

- **Expedited regulatory and clinical path**
  - Potential for Orphan, Breakthrough & Fast-Track designations after FDA review
  - Registrational endpoints are well developed and accepted by FDA
    - Dedicated pre-competitive consortium for regulatory – HD-RSC* Critical Path Institute
  - Clinical trials: Phase I plan includes proof-of-mechanism & biomarkers in HD patients
    - Strong dedicated support for clinical studies: endpoints, staging, patient recruitment
    - Precedent for clinical trials from PTC518 Phase 1 and Phase 2 trials
    - Peripheral blood biomarkers validated in PTC518 clinical trials
- **Commercial opportunity**
  - 2030 projected global HD sales: $9.2BWW**
  - Reimbursement: Anticipated for demonstration of disease modification
- **Intellectual property rights**
  - All assets discovered and wholly-owned by Origami
  - Patents for 5 chemical scaffolds filed (LOE 2041 and beyond), ≥2 additional filings in 2025

HD-RSC HUNTINGTON'S CONSORTIUM CRITICAL PATH INSTITUTE

HUNTINGTON STUDY GROUP

EHDN EUROPEAN HUNTINGTON'S DISEASE NETWORK

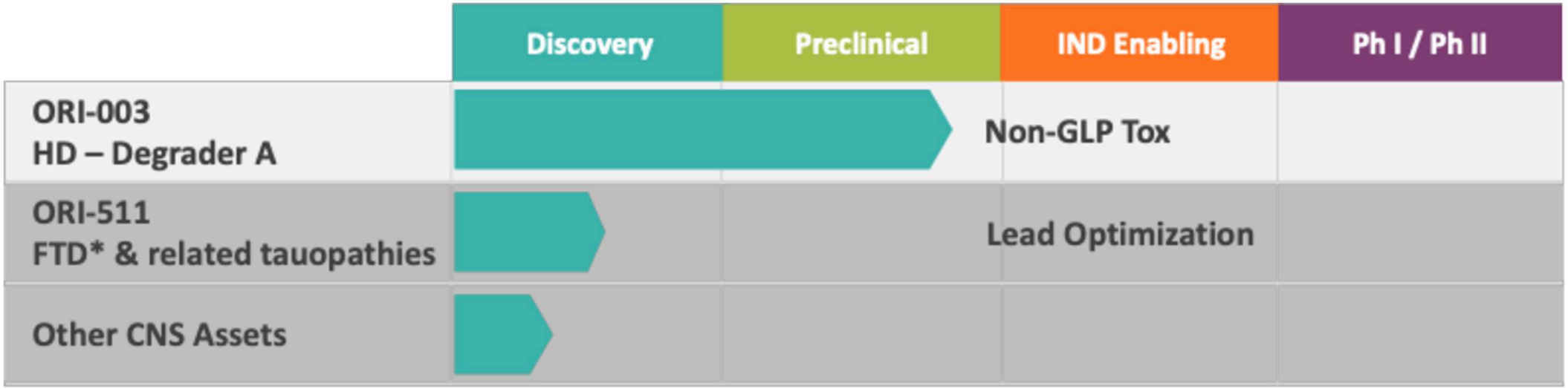
Huntington's Disease Society of America

ORIGAMI Therapeutics

*HD-RSC = Huntington's Disease Regulatory Science Consortium

** *Coherent Market Insights, assuming 60% current symptomatics, 8/2021*

Origami's current pipeline



*Frontotemporal dementia, tau degrader

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Foundational leadership team and advisors

Accomplished scientific & drug development leaders with > 100 years experience

Leadership

Beth Hoffman, Ph.D.
Founder, President and CEO

25 years of CNS drug discovery experience, > 30 assets in clinic; 5 marketed drugs for Cystic Fibrosis & pain

Leslie Schulze, CPA, CGMA
Co-Founder and CFO

Over 20 years of finance experience in life sciences

Martin Eglitis, Ph.D.
Advisor, Strategy

25 years of pharma business development & strategy

Katherine Widdowson, Ph.D.
Advisor, Chemistry

Over 25 years of industry experience in infectious disease, other therapeutic areas

Advisors

Jody Corey-Bloom, M.D.,Ph.D.
Professor, UCSD Director & Director of HD Clinical Center
Translational research & clinical trials

Steven Finkbeiner, M.D., Ph.D.
Professor, Neurology & Physiology, UCSF Director, Taube/Koret Center of Neurodegenarative Disease Research & Center for Systems and Therapeutics, Gladstone Institutes

Kalpana Merchant, Ph.D.
President & CEO, TransThera Consulting Adjunct Professor, Feinberg School of Medicine, Northwestern University
CEO & CSO roles at several start-ups

Robin Mansukhani
CEO, Deciduous Therapeutics
Previously Co-founder, CEO, Alzeca Biosciences
Previous experience in VC/I-Banking

Board of Directors:

Beth Hoffman, Ph.D./ Mohamedi (Mo) Kagalwala, Ph.D., Co-founder & COO, Alleo Labs/ *open position*

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Contact: [redacted]