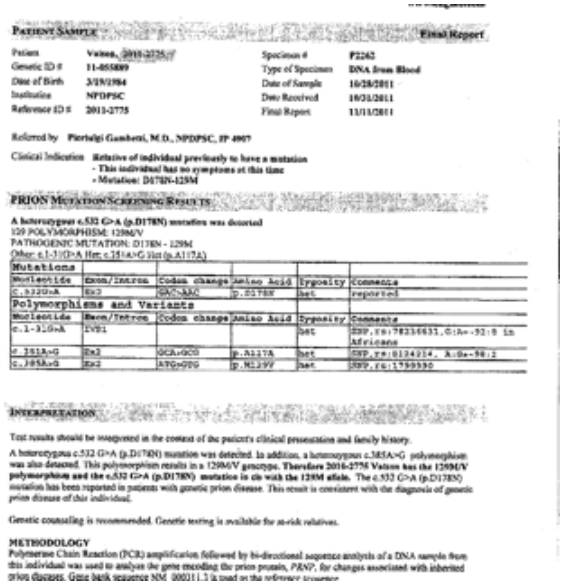
Drug development primer: Part 1, the road to the clinic

Sonia Vallabh
Broad Institute
CJD Foundation Conference
July 20, 2024

The mission of our lab is a treatment in our lifetimes



PATIENT SAMPLE — Final Report

Patient — Genetic ID # 11-055899 — Date of Birth 3/19/1984 — Institution NPDPSC — Reference ID # 2011-2775

Specimen # P2242 — Type of Specimen DNA from Blood — Date of Sample 10/28/2011 — Date Received 10/31/2011 — Final Report 11/11/2011

Referred by Pierluigi Gambetti, M.D., NPDPSC, IP 4907

Clinical Indication Relative of individual previously to have a mutation
- This individual has no symptoms at this time
- Mutation: D178N-129M

PRION MUTATION SCREENING RESULTS

A heterozygous c.532 G>A (p.D178N) mutation was detected
129 POLYMORPHISM: 129M/V
PATHOGENIC MUTATION: D178N - 129M
Other: c.1-31G>A Het; c.351A>G Het (p.A117A)

Mutations					
Mutation/dbSNP	Exon/Intron	Codon change	Amino Acid	Zygosity	Comments
c.532G>A	Ex2	GAC>AAC	p.D178N	Het	reported
Polymorphisms and Variants					
Mutation/dbSNP	Exon/Intron	Codon change	Amino Acid	Zygosity	Comments
c.1-31G>A	IVS1			Het	dbSNP,rs:78234631,G:A=.92:8 in Africans
c.351A>G	Ex2	GCA>GCG	p.A117A	Het	dbSNP,rs:8124214, A:G=.98:.2
c.385A>G	Ex2	ATG>GTG	p.M129V	Het	dbSNP,rs:1799990

INTERPRETATION

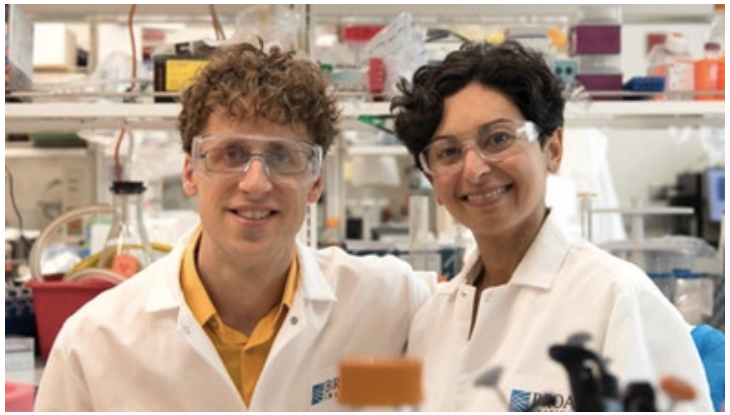
Test results should be interpreted in the context of the patient's clinical presentation and family history.

A heterozygous c.532 G>A (p.D178N) mutation was detected. In addition, a heterozygous c.385A>G polymorphism was also detected. This polymorphism results in a 129M/V genotype. Therefore 2010-2775 Vatsun has the 129M/V polymorphism and the c.532 G>A (p.D178N) mutation in cis with the 129M allele. The c.532 G>A (p.D178N) mutation has been reported in patients with genetic prion disease. This result is consistent with the diagnosis of genetic prion disease of this individual.

Genetic counseling is recommended. Genetic testing is available for at-risk relatives.

METHODOLOGY

Polymerase Chain Reaction (PCR) amplification followed by bi-directional sequence analysis of a DNA sample from this individual was used to analyze the gene encoding the prion protein, *PRNP*, for changes associated with inherited prion diseases. Gene bank sequence NM_000311.3 is used as the reference sequence.



The NEW ENGLAND JOURNAL of MEDICINE

The Patient-Scientist's Mandate

Sonia M. Vallabh, Ph.D.

Eight years ago, at the age of 27, I learned that I had inherited a fatal genetic mutation in the prion protein gene (*PRNP*). Pathogenic mutations in this gene

questions we fielded from day one: whether it was wise to pursue genetic testing for a currently incurable disease; how we would weather the setbacks inherent in

drome, testing drugs in healthy carriers will require a primary prevention strategy based on genetic risk. This realization has defined our priorities for the past

Our lab's focus:

- Develop a therapy
- Race to the first drug – AND the best drug
- Make meaningful clinical trials possible
- Enable both treatment and prevention

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The Vallabh/Minikel lab

vallabhminikel.org

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NEUROLOGY

2014: Our first conversation with Ionis

What about **antisense oligos** (ASOs)?

Yes – our technology could be a fit for your disease biology

IONIS

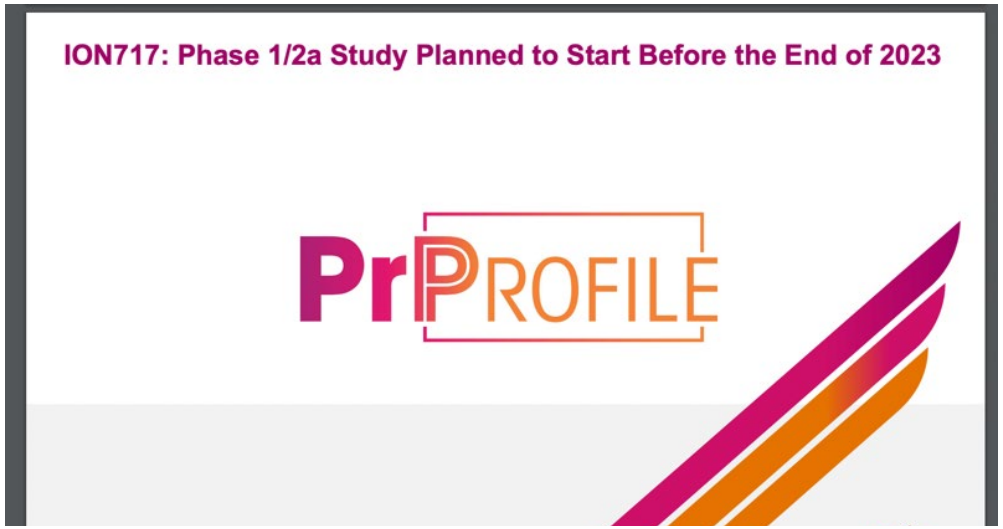
HD BUZZ

Huntington's disease research news.
In plain language. Written by scientists.
For the global HD community.

NEWS | GLOSSARY | ABOUT | FOLLOW | SEARCH HDBUZZ

10 years later

ION717 enters trials



RECRUITING

A Study to Assess the Safety, Tolerability, Pharmacokinetics and Pharmacodynamics of ION717.

ClinicalTrials.gov ID NCT06153966

Sponsor Ionis Pharmaceuticals, Inc.

Information provided by Ionis Pharmaceuticals, Inc. (Responsible Party)

Last Update Posted 2023-12-21

https://clinicaltrials.gov/study/NCT06153966

What all has to happen between the first conversation and the first dose?

Stages of “preclinical” drug development

- **Target selection**: what do we want the drug to do?
- **Proof of concept**: does it do it?
- **Candidate selection**: what will be exact drug molecule be?
- **IND-enabling**: manufacture and test the drug to clear FDA

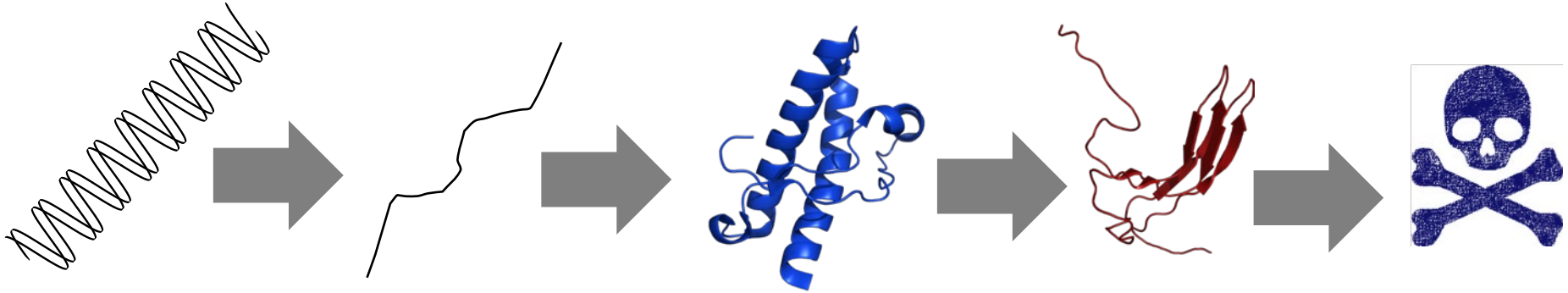
IND = investigational new drug

Target selection

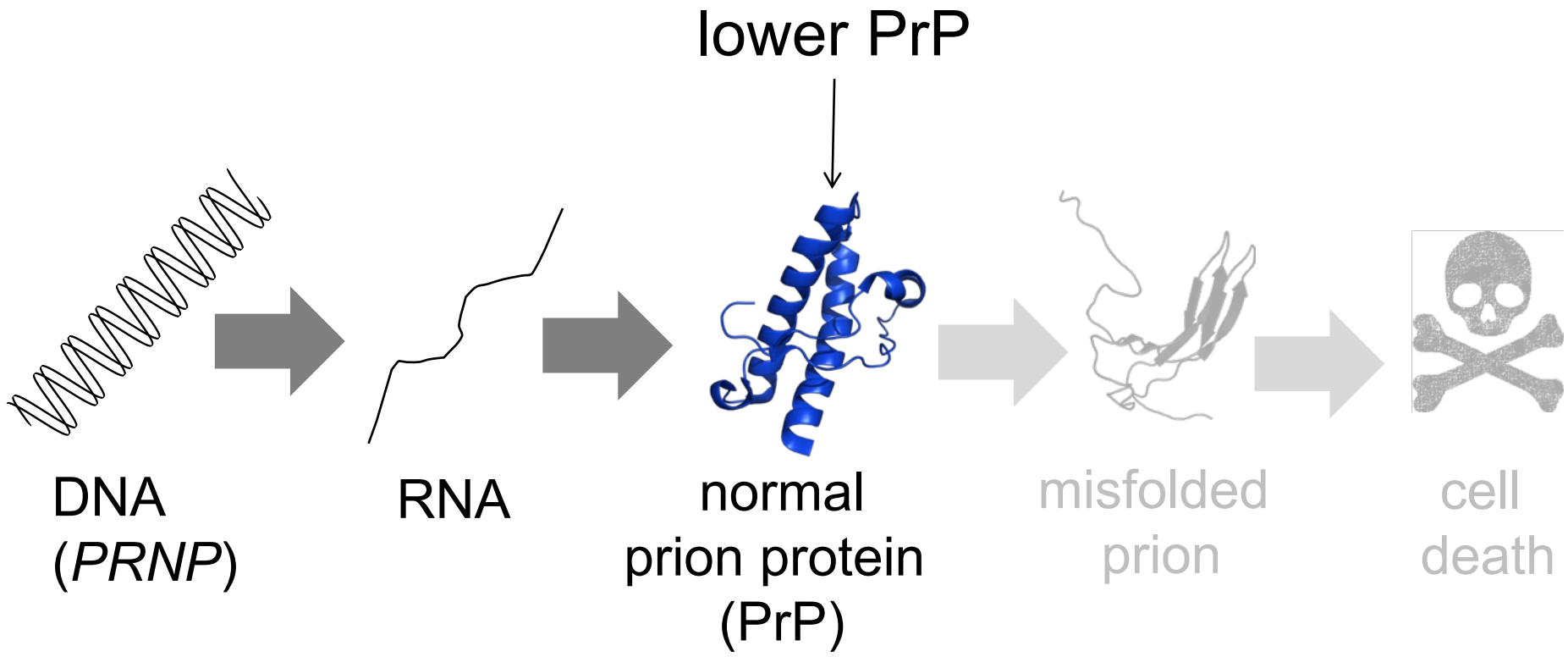
Our lab's philosophy

- Drug development is really hard – <10% of drugs that reach Phase I clinical trials in people are ultimately approved.
  - Not to mention the many thousands of potential drugs that never make it to humans.
- While drugs fail for many reasons, a big one is not having the right target – i.e., the drug wasn't trying to do the right thing in the first place.
- Therefore if we lucky enough to have a clear target in our disease, we should leverage this and not "fly blind."
- The more lines of evidence we have that we're going after the right target, the more we can bias our odds toward success.

The molecular blueprint of prion disease



Our therapeutic strategy



Why do we believe PrP is a worthwhile target?

- **Biochemical evidence**
  - A prion disease brain contains abnormal deposits of PrP
  - Prions can be made in a test tube using purified PrP

- **Human genetic evidence**
  - All genetic prion disease is caused by changes in the prion protein gene that cause changes in PrP
  - Other changes in PrP can be protective against disease

- **Animal genetic evidence**
  - Without PrP, an animal can’t get prion disease
  - The more PrP an animal has, the faster it gets sick, and vice versa
  - PrP matters at all stages of disease

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When you see other drug targets being explored for our disease – look for these categories of evidence

Case study

Thank you and wish us luck!