UPDATE ON NAF RESEARCH

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University of Florida

DISCLAIMER

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- The NAF encourages all attendees to consult with their primary care provider, neurologist, or other health care provider about any advice, exercise, therapies, medication, treatment, nutritional supplement, or regimen that may have been mentioned as part of any presentation.
- Products or services mentioned during these presentations does not imply endorsement by the NAF.

GOALS AND IMPACT OF NAF FUNDING

- Birds-Eye View of Funding Portfolio
  - Making scientific connections between diseases
  - Encouraging young investigators to pursue ataxia research

- Some Examples
  - Genetics 101-2015
  - Four Pioneer Awards
  - Therapeutic strategies to fight ataxia
  - Connections between scientists, diseases, NIH and Industry

NAF'S RESEARCH PROGRAMS

- **Research Seed-Money Grants** – Seed monies in early or pilot phases of studies and ongoing investigations that demonstrate need to attract future funding from other sources.

- **Post-Doc Fellowship Awards** – Intended for researcher to spend a 3rd year in a post-doc position to increase their chance of establishing an independent ataxia research program

NAF'S RESEARCH PROGRAMS

- **Young Investigator and Young Investigator SCA Awards** - Awarded to encourage young investigators to pursue a career in the field of ataxia

- **Pioneer SCA Translational Awards** - This grant is intended for research investigations that will facilitate the development of treatments for the spinocerebellar ataxias (SCAs).

RESEARCH APPLICATIONS RECEIVED

- 33 Seed-money grant applications were received
- 22 Post-Doc Fellowship Applications received
- 15 Young Investigator (non-SCA) applications received
- 14 Pioneer SCA Translational Research Applications received
- 18 Young Investigator SCA Applications received

TOTAL of 102 Applications were submitted

13 COUNTRIES REPRESENTED

- United States
- United Kingdom
- Brazil
- The Netherlands
- Germany
- Portugal
- Australia
- Canada
- Spain
- France
- Italy
- Cyprus
- Mexico

TYPES OF ATAXIA

- SCAs
- Friedreich Ataxia
- Gordon Holmes Syndrome
- Joubert Syndrome
- Mitochondrial
- FXTAS
- A-T
- Episodic Ataxia
- ARSACS
- Spastic ataxia
- AOA
- SCAN
- Sporadic

REVIEW PROCESS

Reviewers are assigned by Dr. Harry Orr and Dr. Laura Ranum

All applications are peer-reviewed by 2 reviewers

Pioneer applications peer-reviewed by 3 reviewers

More than 60 reviewers worldwide

Conference calls are attended by a sub-group of NAF Medical Research Advisory Board members to make funding recommendations

NAF Board of Directors make the final funding decisions

NAF FUNDED RESEARCH

27 Research Projects were Funded totaling more than
$1.1 million of research

9 Seed Money Research Grants
4 Young Investigator Awards
7 Post-doc Fellowship Awards
4 Young Investigator-SCA Awards
3 Pioneer Translational SCA Awards

26% of submitted grants were funded
Success rate is substantially higher than the NIH

RESEARCH SEED GRANTS 2016

Speech Rehabilitation
SCA3
Gene discovery
SCA36
Brain Imaging
Inflammation in Setx
Ataxia Database

Vogel, Adam, PhD
Centre for Neuroscience of Speech Parkville, Victoria, Australia
Intensive home based speech rehabilitation for adults with degenerative ataxia

Simões, Ana, PharmD, PhD
University of Coimbra, Portugal
Calpain-mediated proteolysis in Machado-Joseph disease

Karnebeek, Clara, MD, PhD
University of British Columbia, Vancouver, BC, Canada
Whole Exome Sequencing in the Diagnosis and Management of Atypical Childhood Hereditary Ataxia Conditions

He, Fang, PhD
Texas A&M University, Kingsville, TX
Development of a Drosophila model for Spinocerebellar Ataxia type 36 (SCA36)

Oz, Gulin, PhD
University of Minnesota, Minneapolis, MN
Launching the US-Europe Neuroimaging Partnership in SCA

Burmeister, Margit, PhD
University of Michigan, Ann Arbor, MI
Role of VPS13D in Ataxia

Lavin, Martin, PhD
University of Queensland Centre for Clinical Research (UQCCR) Australia
Assessing the role of senataxin in cellular inflammation, gene regulation, and innate immunity in Setx-/- mice and a human neuronal model

Ribeiro, Sandra, PhD
Instituto de Biologia Molecular e Celular Porto, Portugal
New therapeutic approaches for Machado-Joseph Disease: Chaperoning protein self-assembly

Perlman, Susan, M.D.
University of California Los Angeles, Los Angeles, CA
Web-based National Ataxia Database

NAF GRANT RECIPIENTS YOUNG INVESTIGATORS IN 2016

INVESTING IN THE NEXT GENERATION OF ATAXIA RESEARCHERS

Gene Regulation
Removal of toxic proteins in SCA3
Friedreich's – mitochondrial stress
Cell-Cell communication SCA27
Astrocyte signaling in SCA1
Turning up Frataxin with Crispr/Cas
ASO SCA3
Chemical pathways in Friedreich's
Pathways for polyQ regulation SCA3
Protein networks in ataxia
PUMILIO1 – a new ataxia gene

Yao, Bing, PhD
Emory University, Atlanta, GA
Epigenetic Modulation Mediated by RNA-Binding Proteins in Neurodegeneration
Schmidt, Jana, PhD
University of Tuebingen, Germany
Alleviation of proteasomal inhibition as a therapeutic approach for SCA3
Butler, Jill Sergesketter, PhD
University of Alabama at Birmingham, AL
Reduced expression of mitochondrial aldehyde dehydrogenases contributes to metabolic stress in Friedreich's ataxia
Ben-Johny, Manu, PhD
Johns Hopkins University, Baltimore, MD
Aberrant Regulation of Voltage-gated Na channels in the Pathophysiology of Spinocerebellar Ataxia 27
Cvetanovic, Marija, PhD
University of Minnesota, Minneapolis, MN
Role of astrocyte calcium signaling in the pathogenesis of SCA1
Nageshwaran, Sathiji, MD
Harvard University, Boston, MA
Transcriptional activation using CRISPR/Cas mutant proteins as a novel therapy for Frataxin gene silencing
Khurana, Vikram, MD, PhD
Brigham and Women's Hospital and Harvard Stem Cell Institute, Boston, MA
Systematic edgotyping of ataxin proteins in cellular systems from yeast to patient neurons.
Gennarino, Vincenzo, PhD
Baylor College of Medicine, Houston, TX
PUMILIO1 deficiency: understanding a new ataxia gene and its role in cerebellar dysfunction in mice and humans

NAF GRANT RECIPIENTS POSTDOCTORAL FELLOWSHIPS 2016

INVESTING IN THE NEXT GENERATION OF ATAXIA RESEARCHERS

Brain Structure
Small Molecule Drugs
Motor Neuron Degeneration
RNA Degradation of CAG repeats
Cell-cell communication and protection
Protein dysregulation

•Anderson, Collin J., PhD
University of Utah, Salt Lake City, UT
Development and mechanistic study of deep brain stimulation of dentate nucleus for the treatment of degenerative ataxia.
•Orengo, James, MD, PhD
Baylor College of Medicine, Houston, TX
Unraveling the mechanisms of motor neuron degeneration in Spinocerebellar Ataxia, type1
•Chen, Jonathan, PhD
Scripps Florida, Jupiter, FL
Rapid structure-based lead optimization of a small molecule drug that target r(CAG)exp
•Bott, Laura C., PhD
Northwestern University, Evanston, IL
Transcellular regulation of the proteostasis network in Spinocerebellar ataxia type 3
•Chopra, Ravi, PhD
University of Michigan, Ann Arbor, MI
Identifying Dendro-Protective Ion Channels in Cerebellar Ataxia
•Seminara, Stephanie, MD
Massachusetts General Hospital, Boston, MA
Ataxia with hypogonadotropic hypogonadism due to ubiquitin ligase dysregulation

NAF GRANT RECIPIENTS IN 2016

PIONEER SCA TRANSLATIONAL RESEARCH AWARDS

Moving towards therapies

DNA

RNA

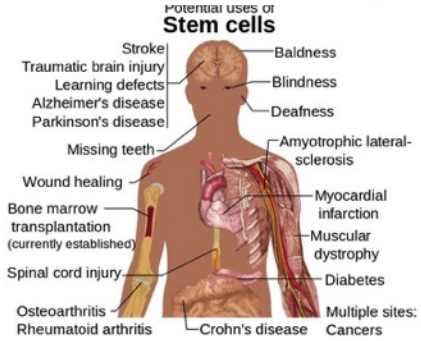
Protein

•Orr, Harry, PhD
University of Minnesota, Minneapolis, MN
Towards an ASO Therapy for Spinocerebellar Ataxia Type 1

•Roon-Mom, Willeke M.C. van, PhD
Leiden University Medical Center, The Netherlands
Advancing the therapeutic potential of exon skipping
•for Spinocerebellar ataxia type 3

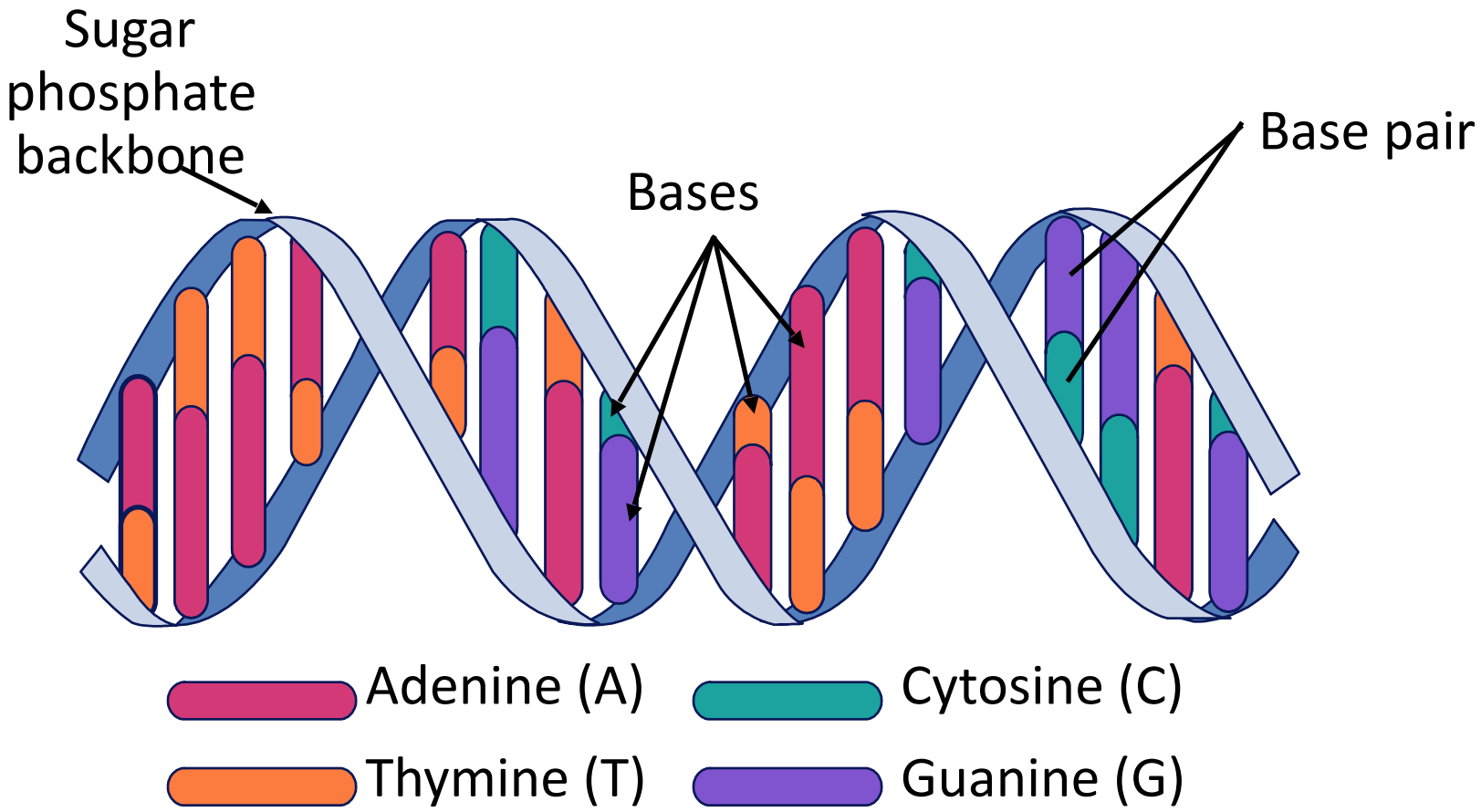
BASIC RESEARCH STEM CELLS

•Maciel, Patrícia, PhD
University of Minho, Braga, Portugal
Testing the therapeutic potential of Mesenchymal Stem Cells and their secretome in an animal model of spinocerebellar ataxia type 3

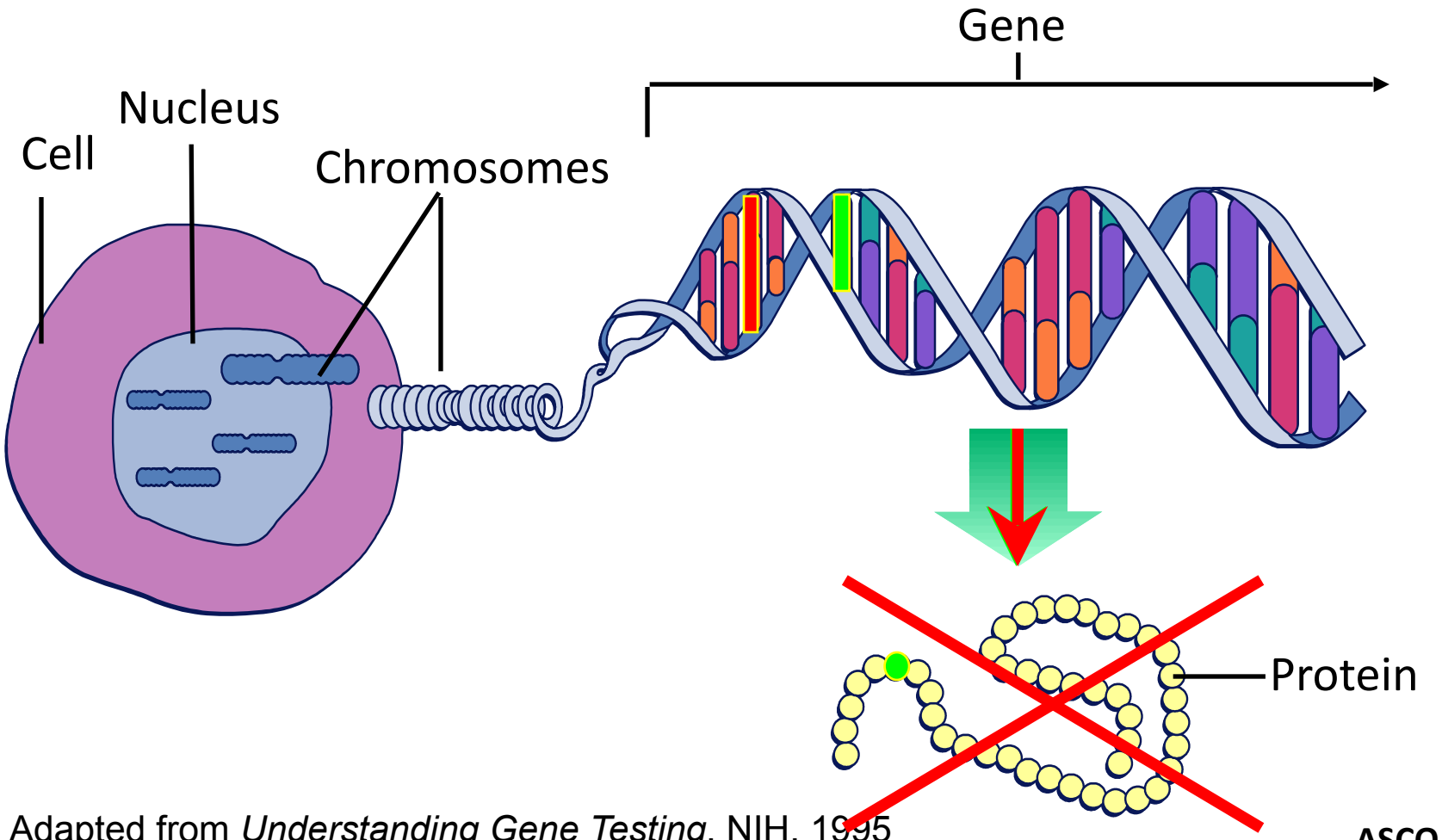


GENE DISCOVERY TO GENE BASED THERAPIES

The DNA Double Helix

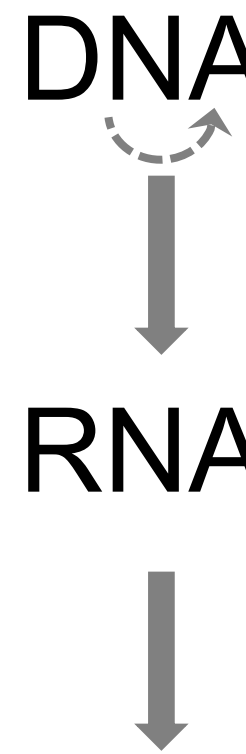


Overview
Chromosomes, DNA, Genes, Proteins



Adapted from *Understanding Gene Testing*, NIH, 1995

Central Dogma



GENOMIC SOFTWARE
“The Code”

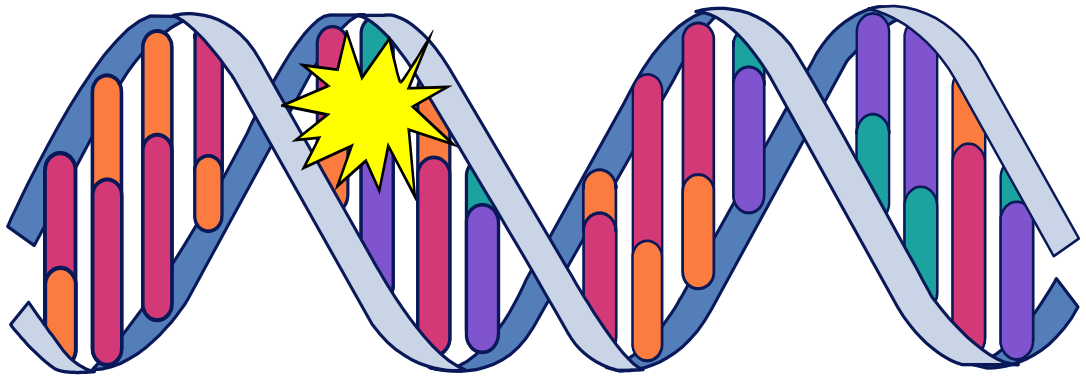
DNA → RNA CODONS→Protein

Genomic DNA	THYBIGRYDDOGRANOUT
Messenger RNA	THEBIGREDDOGRANOUT
Translated Message	THE BIG RED DOG RAN OUT

Genetics of Disease

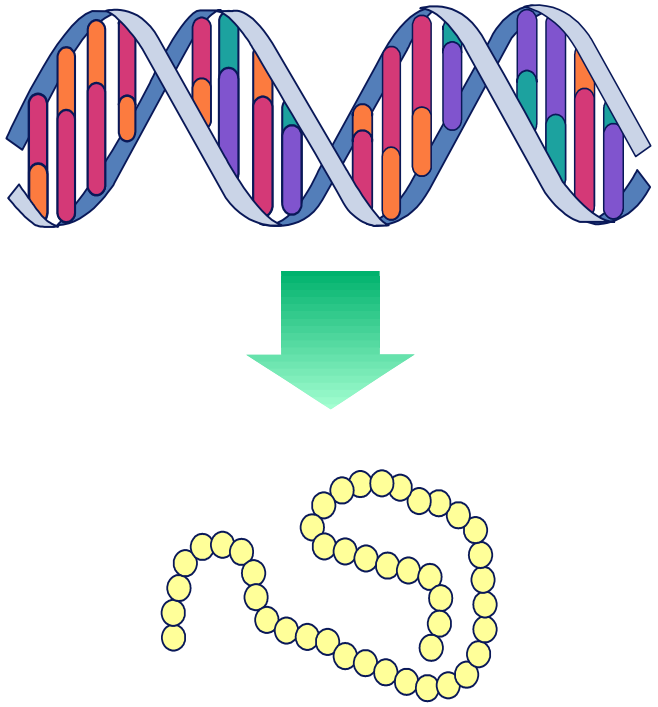
Disease-Associated Mutations

A mutation is a change in the normal base pair sequence

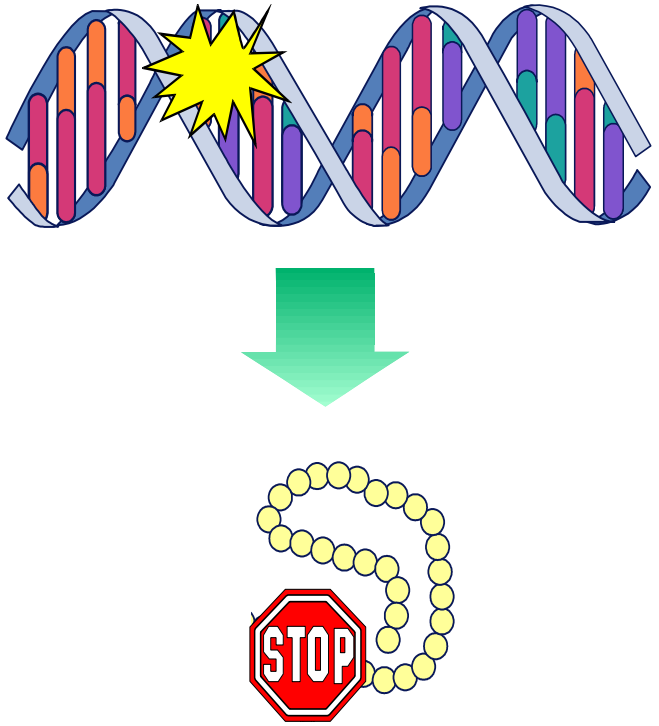


Commonly used to define DNA sequence changes that alter protein function

Disease-Associated Mutations Can Alter Protein Function



Functional protein



Nonfunctional or missing protein

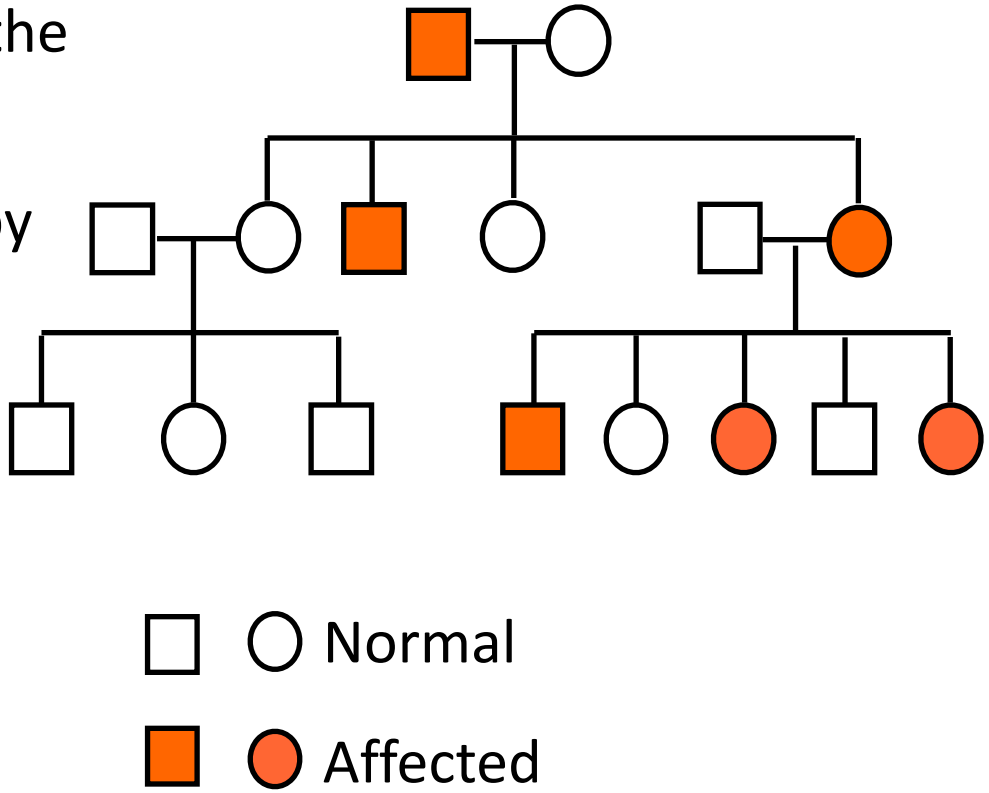
Point Mutations

Normal	THE BIG RED DOG RAN OUT.
Missense	THE BIG RAD DOG RAN OUT.
Nonsense	THE BIG RED.
Frameshift (deletion)	THE BRE DDO GRA.
Frameshift (insertion)	THE BIG RED ZDO GRA.

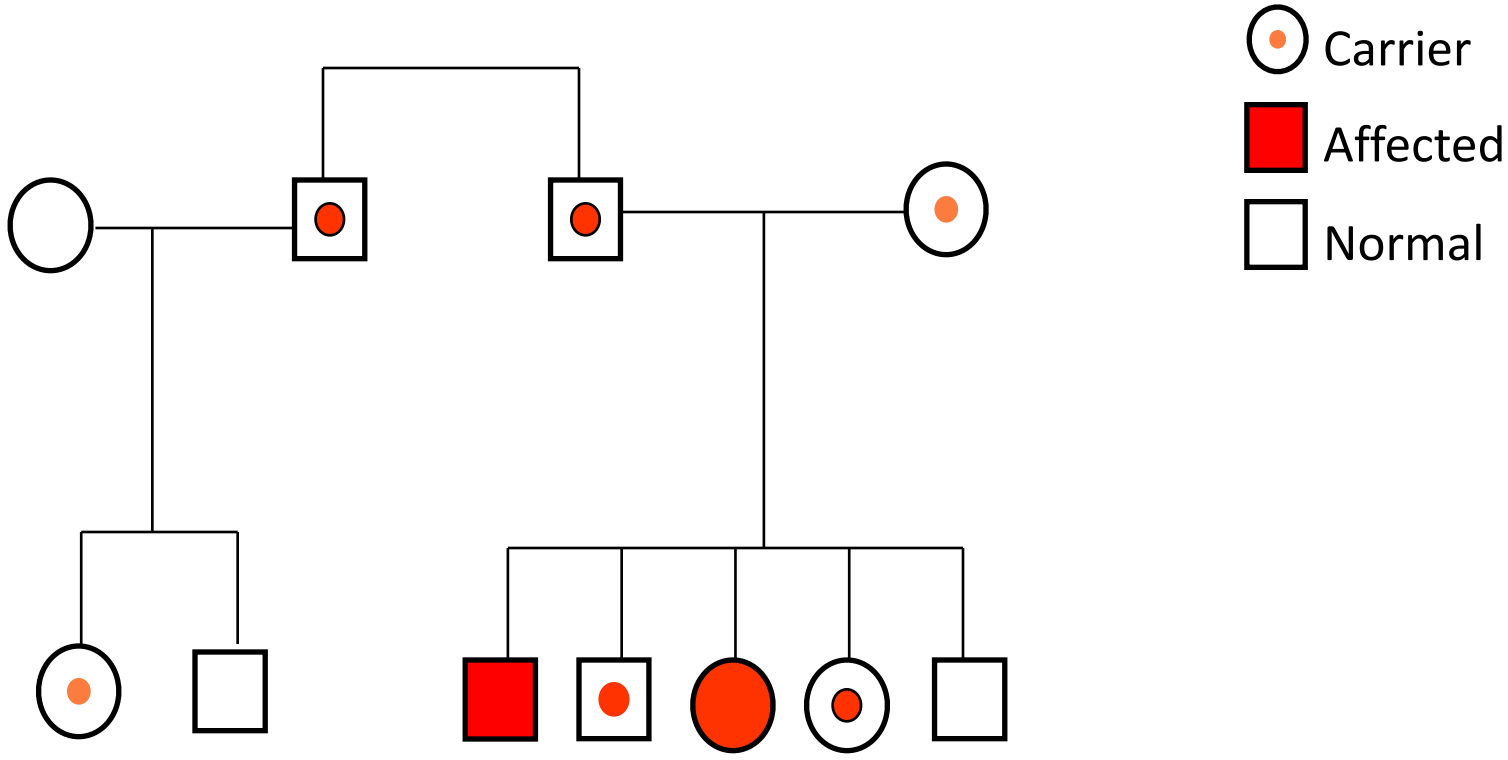
Point mutation: a change in a single base pair

Autosomal Dominant Inheritance

- Each child has 50% chance of inheriting the mutation
- Equally transmitted by men and women



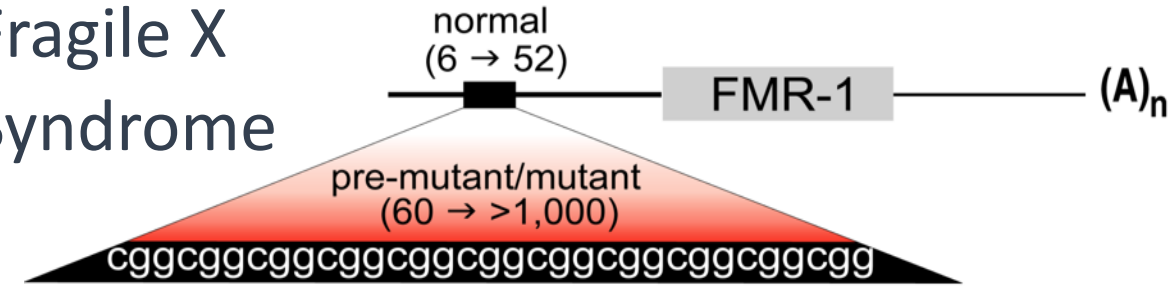
Autosomal Recessive Inheritance



Genetics 101 → 2017

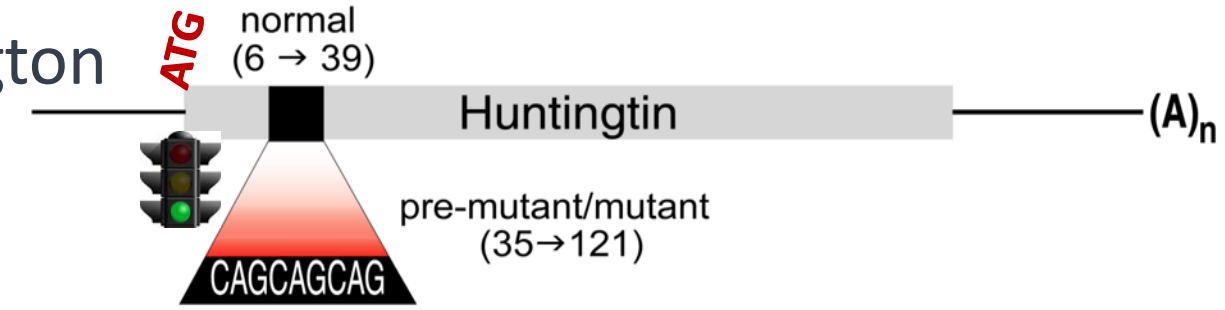
Repeat Expansion Diseases

Fragile X Syndrome



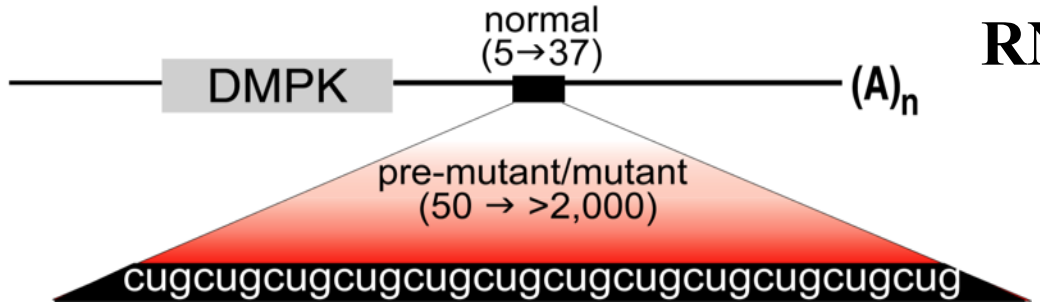
Protein Loss

Huntington Disease



Protein Gain

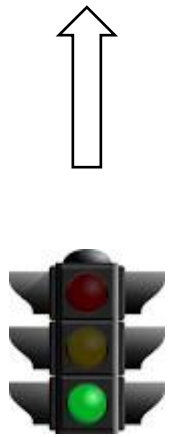
Myotonic Dystrophy



RNA Gain

DNA → RNA CODONS→Protein

Genomic DNA	THYBIGRYDDOGRANOUT
Messenger RNA	THEBIGREDDOGRANOUT
Translated Message	THE BIG RED DOG RAN OUT

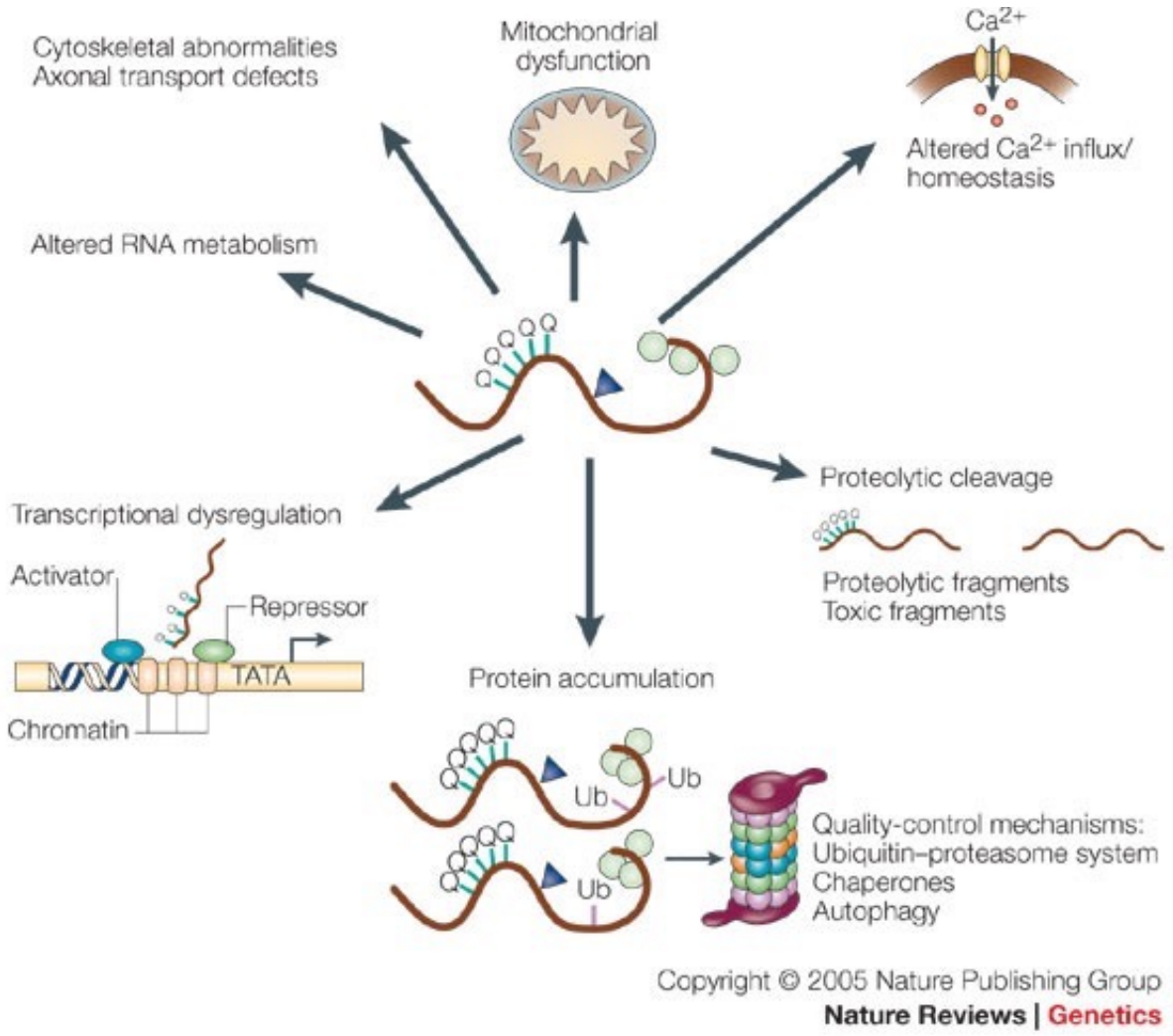


The code is read three letters at a time and the ATG sets the reading frame

DNA → RNA → Protein

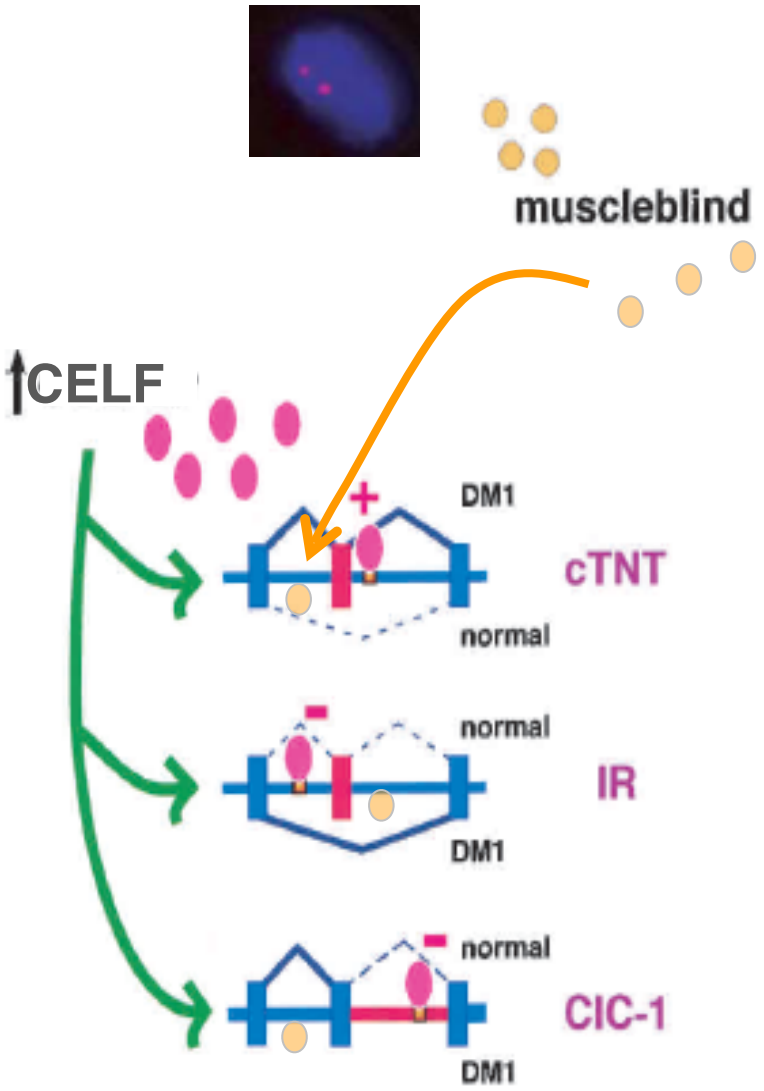
Genomic DNA	THYBIGRYDRYDRYDRYDDOGRANOUT
Messenger RNA	THEBIGREDREDREDREDDOGRANOUT
Translated Message	 THE BIG RED RED RED RED DOG RAN OUT

PolyQ Protein Problems



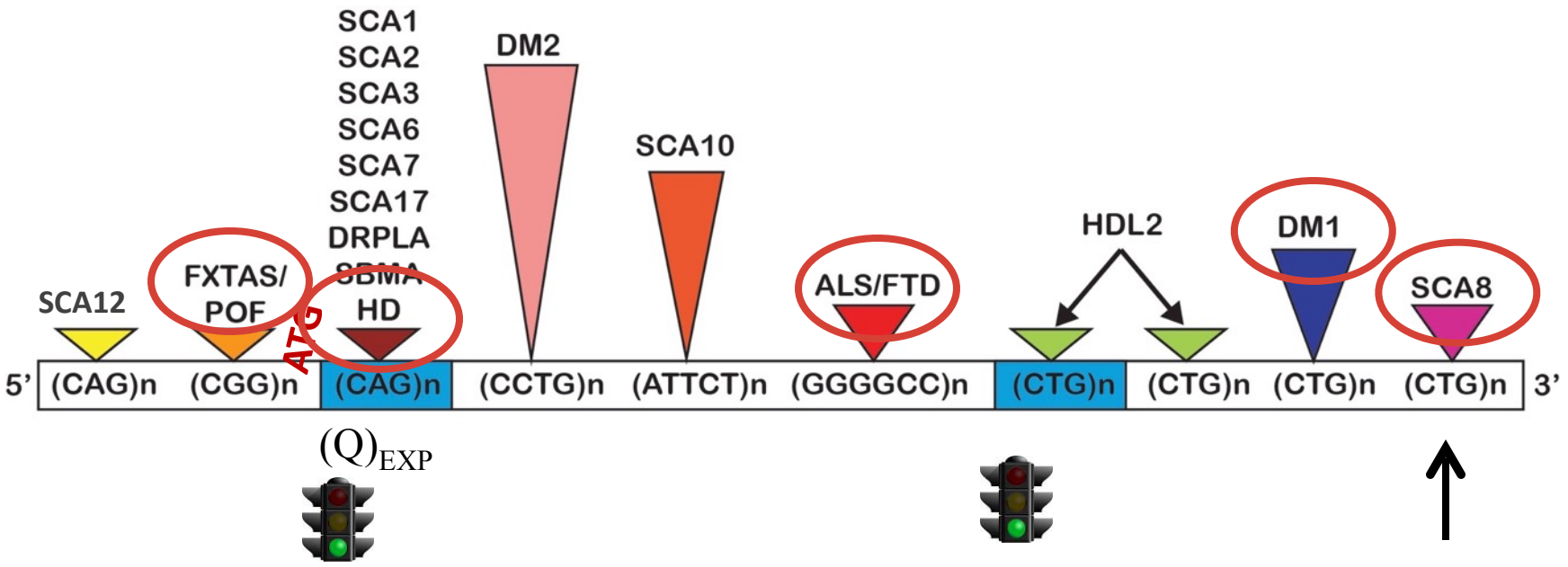
Gatchel &Zoghbi, *Nature Reviews Genetics*, 2005

Mutant RNA problems – myotonic dystrophy



Ranum and Cooper Ann Rev Neurosci, 29:259; 2006

Repeat Expansion Mutations in Neurologic Disease



Protein Loss / Protein Gain / RNA Gain of Function

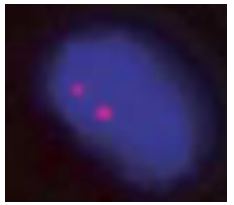
Bidirectional Expression

Repeat Associated Non-ATG (RAN) translation

Expansion mutations produce unexpected proteins in multiple frames

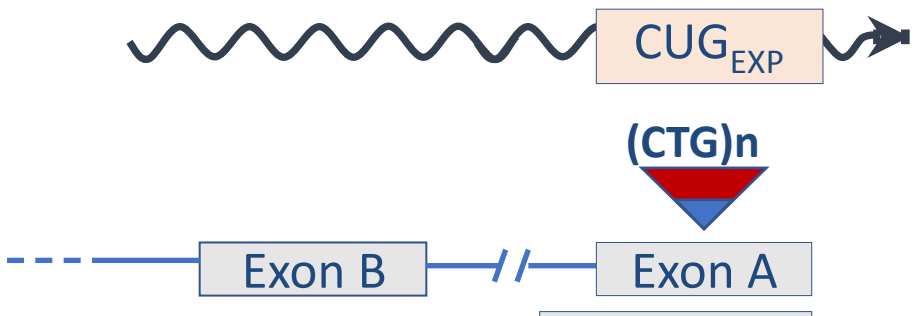
Spinocerebellar Ataxia Type 8
SCA8

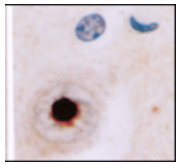
SCA8: one mutation two genes



Toxic RNA Mechanism

Daughters et al. 2009
PLoS Genetics



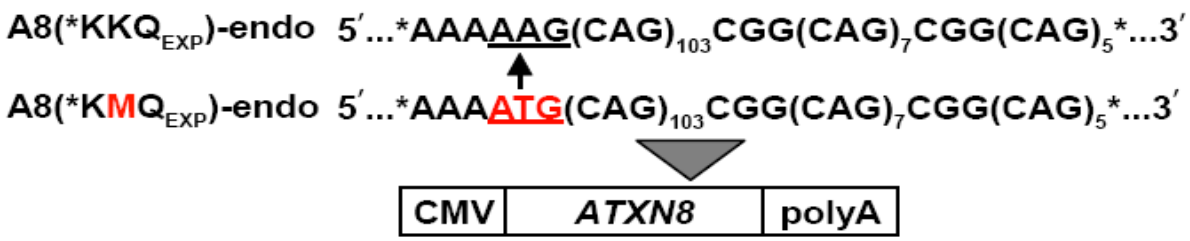


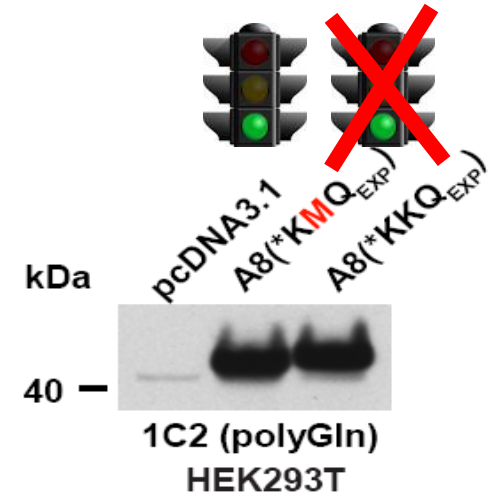
Toxic PolyQ Mechanism?

Moseley et al., 2006
Nature Genetics

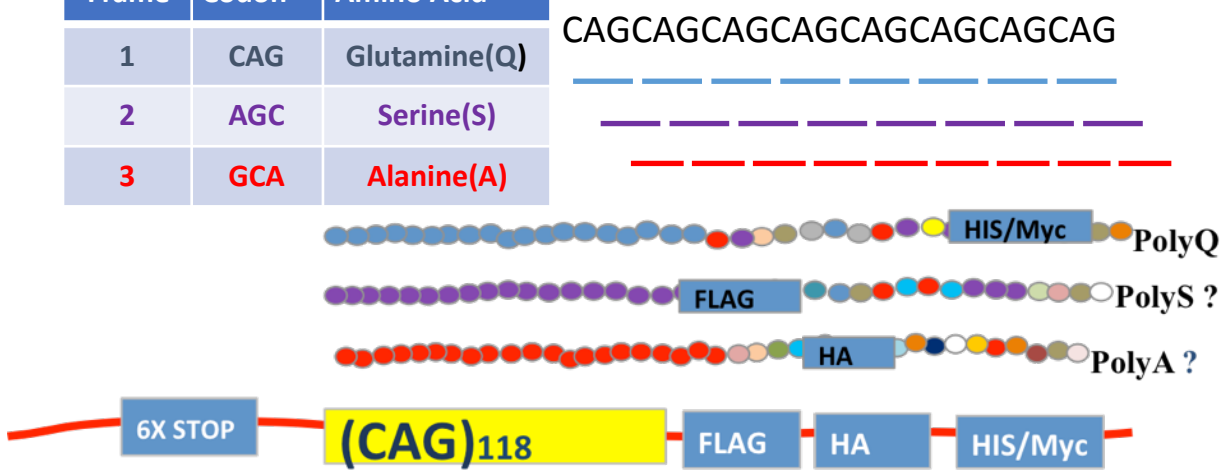
*AAA**ATG**(CAG)$_{EXP}$***

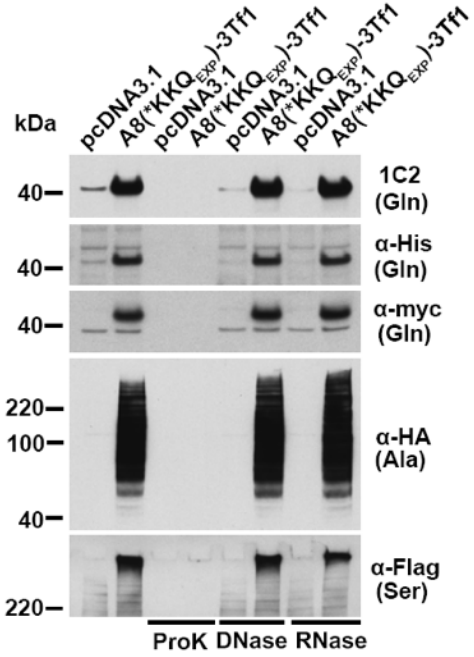
Discovery of Repeat-Associated Non-ATG Translation (RAN translation)





Frame	Codon	Amino Acid
1	CAG	Glutamine(Q)
2	AGC	Serine(S)
3	GCA	Alanine(A)





Zu et al., PNAS 2011

DNA → RNA → Protein

Genomic DNA THYBIGRYDRYDRYDRYDDOGRANOUT

Messenger RNA THEBIGREDREDREDREDDOGRANOUT

Translated Message


THE BIG RED RED RED RED DOG RAN OUT


RED RED RED RED DOG RAN OUT

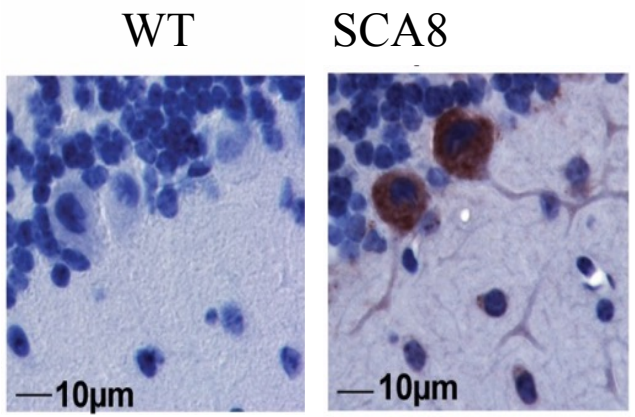

EDR EDR EDR EDD OGR ANO UT


DRE DRE DRE DDO GRA NOU T

Repeat Associated Non-ATG (RAN) translation

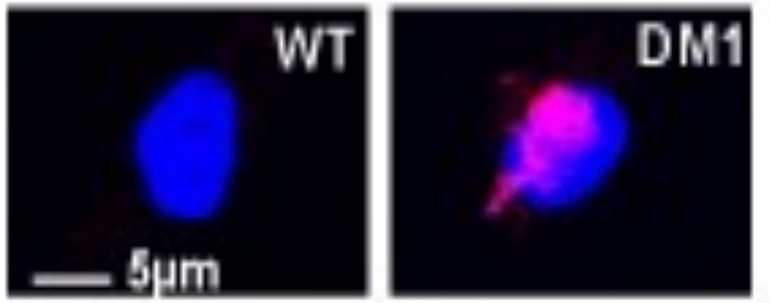
RAN Translation in vivo: SCA8 and myotonic dystrophy

α-SCA8 poly-GCA-Ala



Mouse Cerebellum

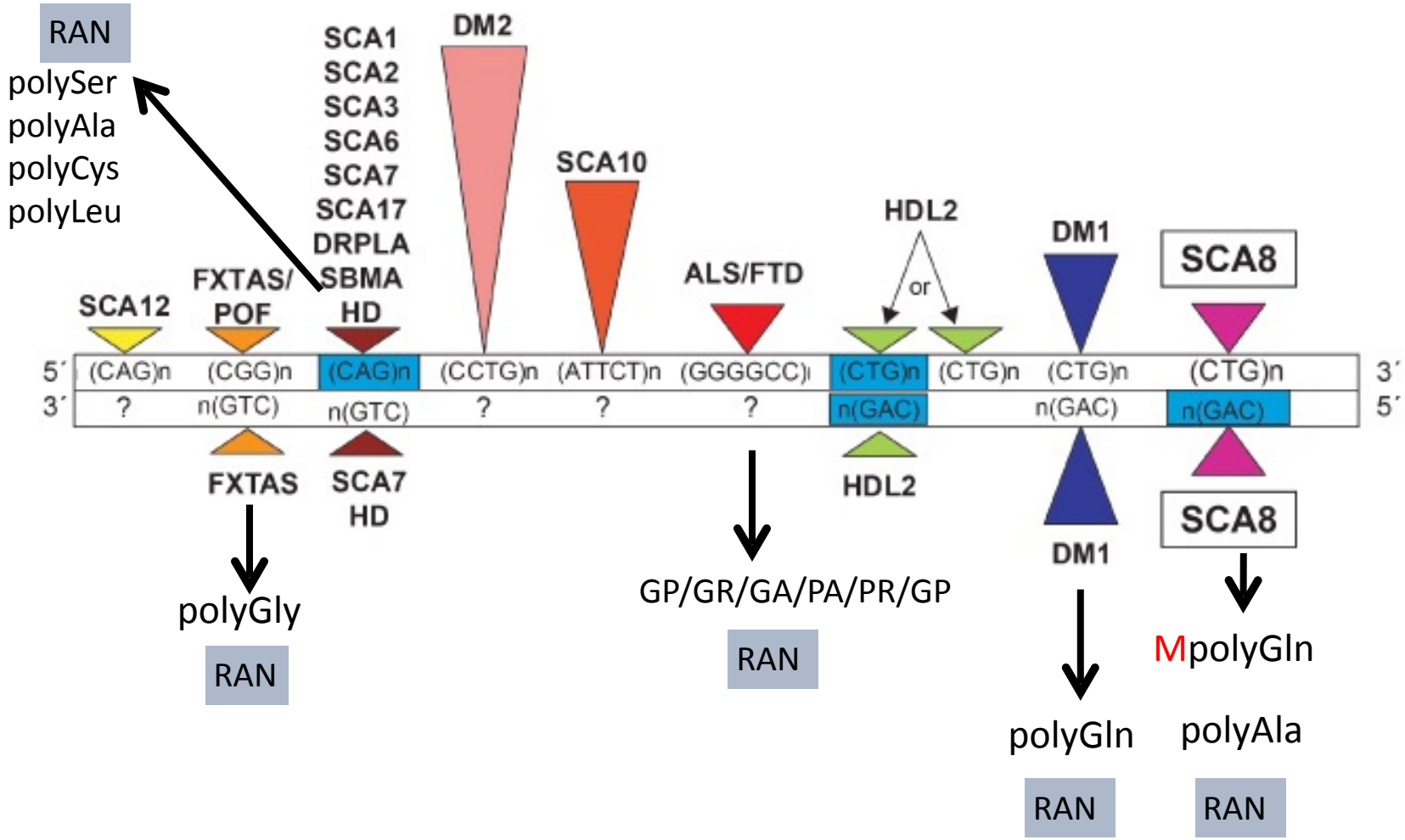
α-DM1 poly-CAG-Gln



Human Myoblasts

Zu et al., PNAS 2011

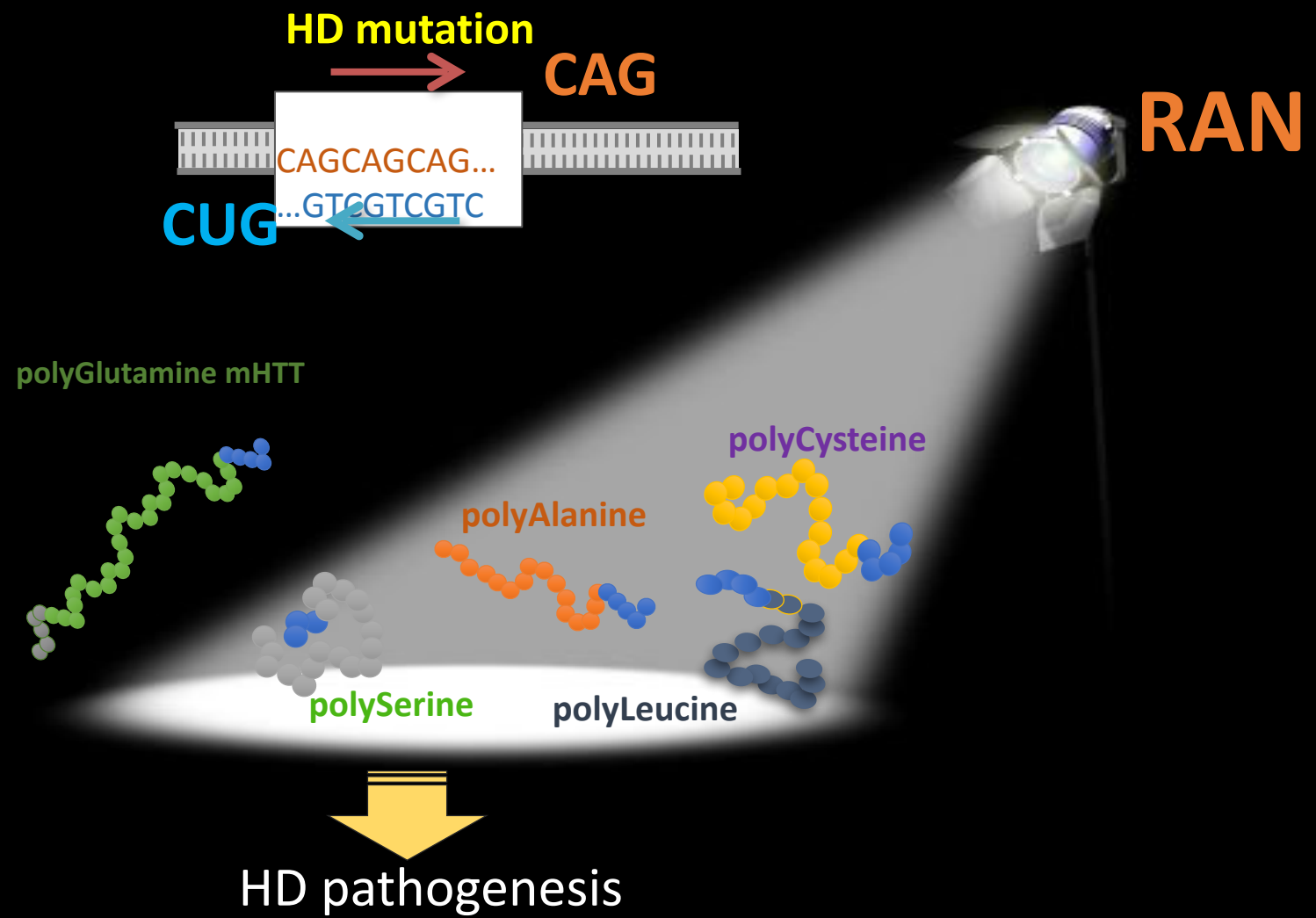
Growing trends in many expansion diseases



Framework for understanding disease mutations needs revision.

- Bidirectional expression is common
- Repeats express unexpected proteins
- RAN proteins now found in RNA and “polyQ” diseases

RAN Proteins in Huntington's Disease



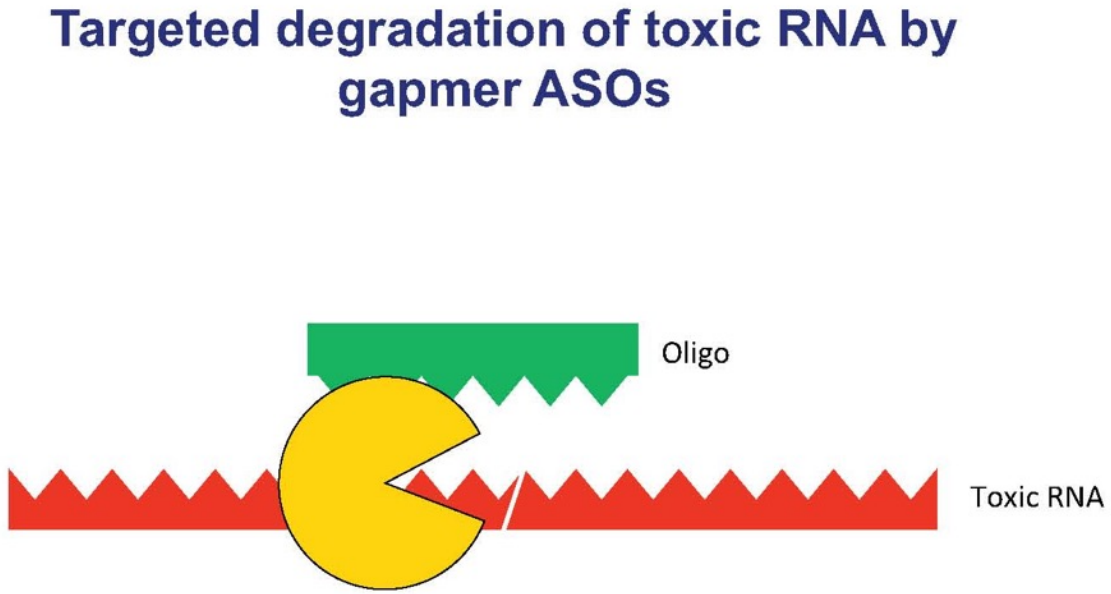
WHAT ABOUT THE POLY-Q ATAXIAS?

Therapy development

New Genetic Tools

Gene Editing
RNA Targeting

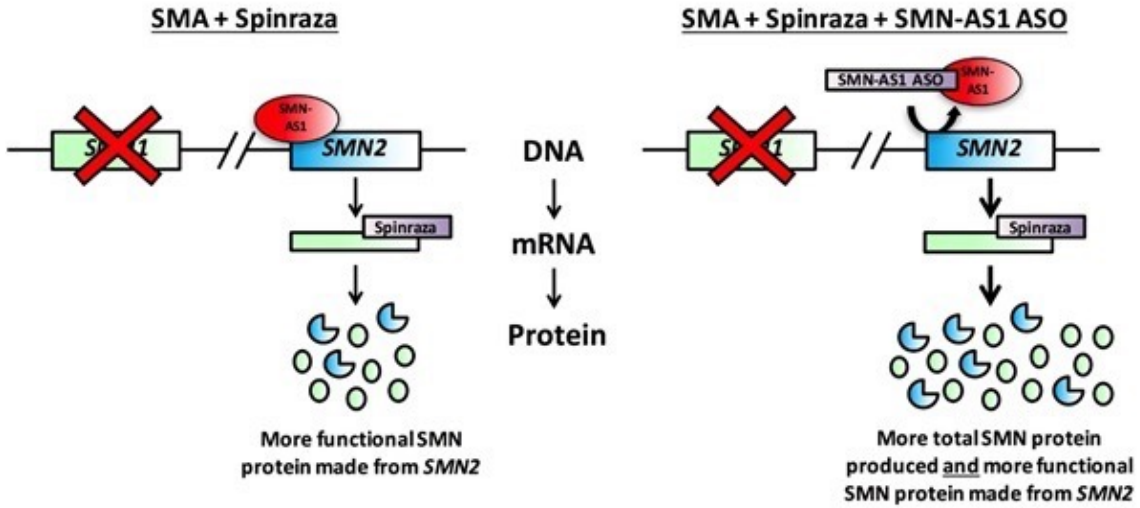
Targeting the RNA



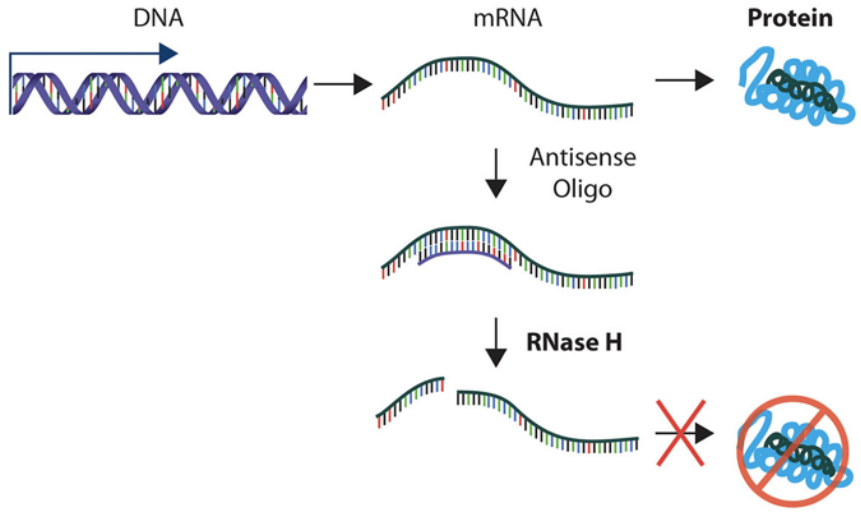
ANTISENSE OLIGONUCLEOTIDE THERAPY

FDA approval for Biogen and Ionis Pharmaceuticals – Spinaraza

Spinal Muscular Atrophy

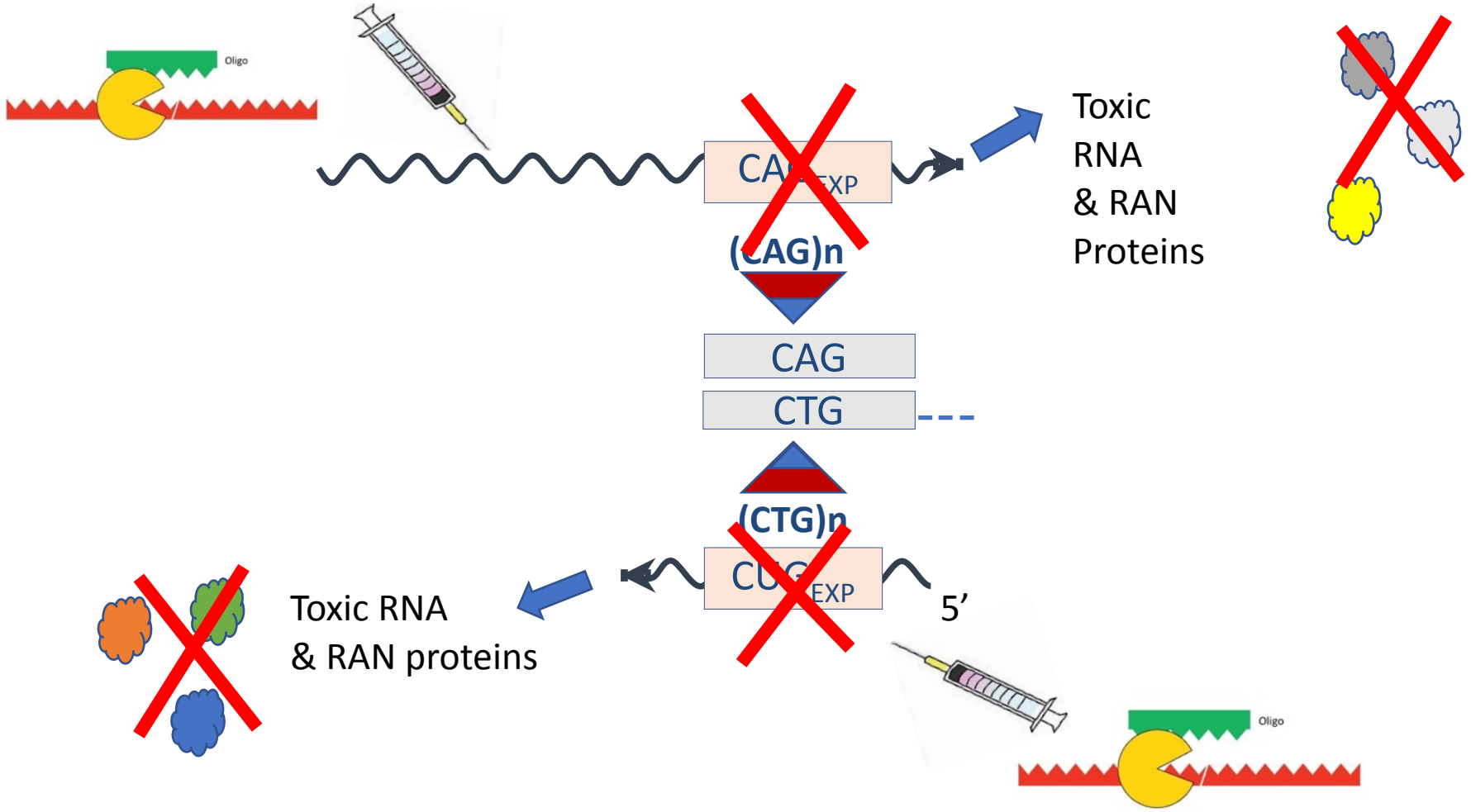


DRUG WAKES UP A SLEEPING GENE



SIMILAR DRUGS CAN REMOVE RNA

SCA8 targeting the problems: one or both RNAs?



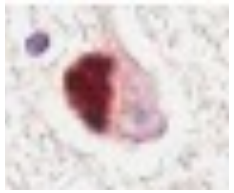
Similar strategies being applied for many of the SCAs including SCA1 and SCA3

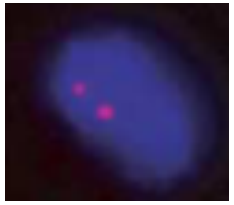
PARTNERING WITH YOU

GENE DISCOVERY

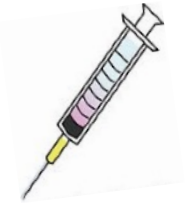
HOW GENETIC MUTATIONS CAUSE DISEASE

THERAPY DEVELOPMENT





Conclusions



THANK YOU!!!!!!

- NAF funding critically important for understanding the causes of ataxia and developing treatments
- Therapeutic efforts to target RNA and protein pathways and to repair genes are underway.
- Lessons from one disease connect to other diseases
  - How mutations cause disease
  - Therapy development