CLINICAL TRIAL READINESS

Henry Paulson, MD PhD
Lucile Groff Professor of Neurology
University of Michigan Medicine

WHY?

BECAUSE THE TIME IS RIGHT!

But first, lets go back two decades….

"Ataxiologists" Meet in Minneapolis

Some of this nation's leading ataxia experts, "Ataxiologists", met in Minneapolis on September 8, 1995. The purpose of this meeting was twofold: to develop an agreed upon uniform scoring system for ataxia and to plan for multicenter drug studies.

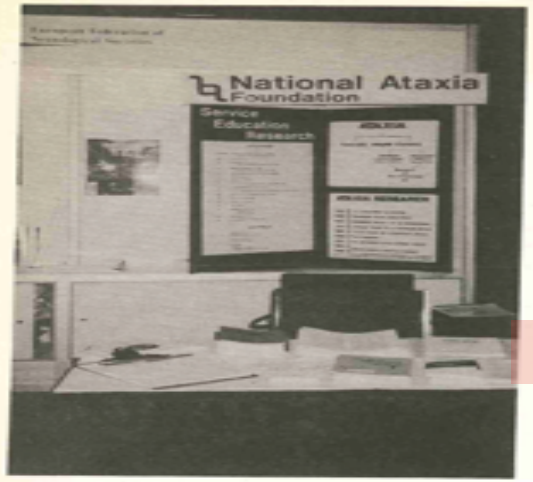
The United Scale for Ataxia (U.S.A.) which is near completion is a necessary first step before embarking on drug trials which will take place at various ataxia centers. Ataxia symptoms must be measurable to determine if a drug is effective.

This group of ataxiologists, which very likely will be expanded to include other centers, needing an identification, a name, decided on Cooperative Ataxia Group or CAG. (As you recall the first ataxia genes were found to have extra repeats of the gene sequence C-A-G.)

Photo: (L) to (R) Doctors Laura Ranum, University of Minnesota; S.H. Subramony, University of Mississippi; Chris Gomez, University of Minnesota; Mark Hallet, NIH; Jau-Shin Lou, University of Rochester, New York; Bala Manyam, Southern Illinois University; Larry Schut, University of Minnesota; Daniel Geschwind, U.C.L.A. Medical Center; and Steve Massaquoi, NIH.

As we write this, the initial phases of this 2 step project are well under way. We will update you on further developments.

IN THE EARLY 1990'S, THE COOPERATIVE ATAXIA GROUP (CAG) WAS ESTABLISHED AS A GROUP OF CLINICAL RESEARCHERS TO PERFORM CLINICAL RESEARCH THAT WOULD LEAD TO IMPROVED TREATMENTS OF THE ATAXIAS.



Meetings in Minneapolis

The **American Academy of Neurology** held its 50th Anniversary Meeting in Minneapolis, Minnesota, the last week of April. Once again, NAF sponsored an information booth in the Exhibit Hall to increase awareness of the ataxias and NAF to the 6400 neurologists, who attended from around the world. NAF has had a booth at this annual meeting since first exhibiting in 1976 with the exception of a few years when it was not financially possible.

The **Cooperative Ataxia Group (CAG)** met in Minneapolis on April 28th. This group of ataxia researchers has been expanded to 17 members. Their goal is to conduct multi- center drug trials when research has advanced to that point.

The following day on April 29th, NAF's **Medical and Research Advisory Board** met to discuss future plans.

Above left, NAF booth at the AAN Meeting in Minneapolis

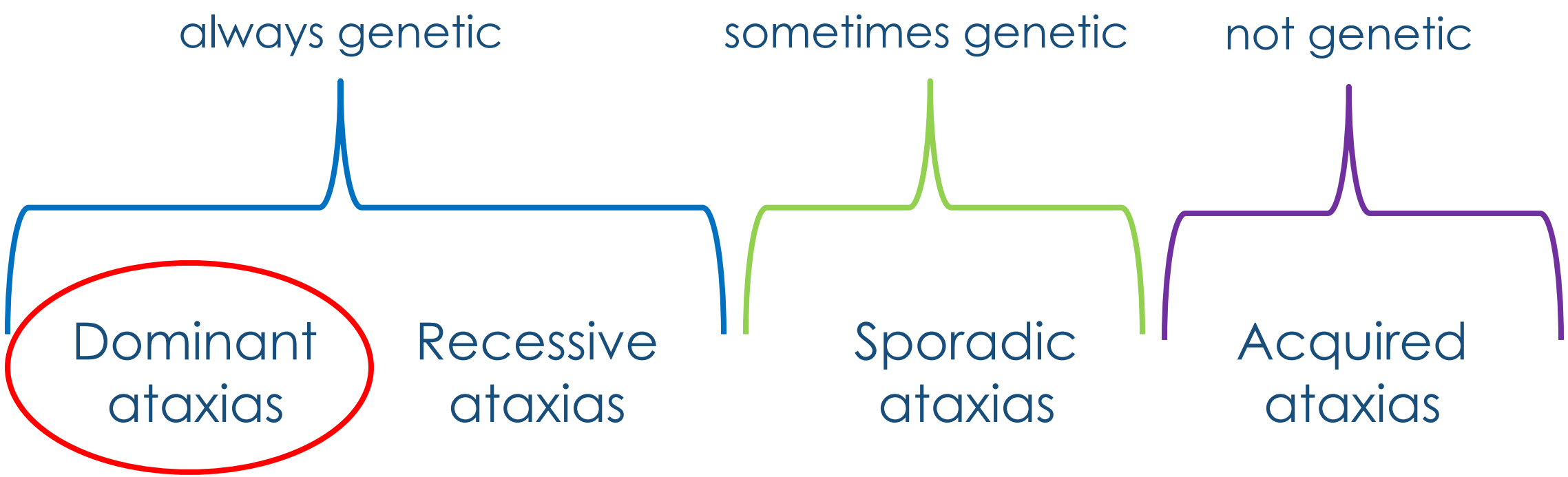
NIH NEWS UPDATE

Harold Varmus, M.D., Director of the National Institutes of Health (NIH), today announced the appointment of Gerald D. Fischbach, M.D., as Director of the National Institute of Neurological Disorders and Stroke (NINDS), the leading federal agency supporting research on the brain and nervous system. Dr. Fischbach is the Nathan March Pusey Professor of Neurology at the Harvard University Medical School. He is Chairman of the Departments of Neurobiology at Harvard Medical School and the Massachusetts General Hospital. He was also the founding Director of the Harvard University Initiative on Mind, Brain, and Behavior. ❖

Cooperative Ataxia Group met in Minneapolis on April 28, 1998. Many members not shown

AMONG OTHER THINGS, THIS GROUP DEVELOPED RATING SCALES FOR THE ATAXIAS, DESIGNED THE ATAXIA DATABASE AND CREATED AN ATAXIA PATIENT REGISTRY.

The world of ataxias
A very brief primer…

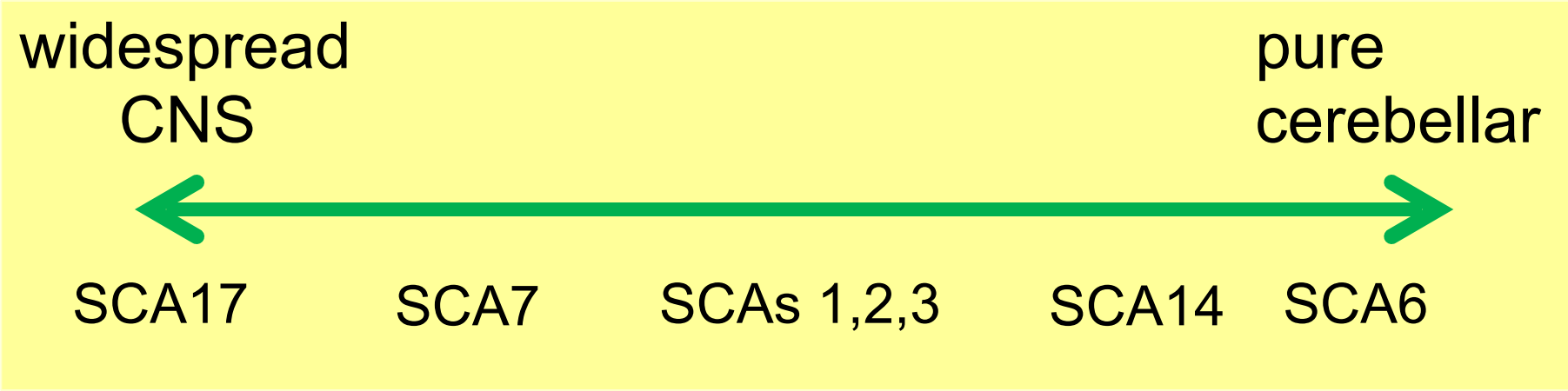


Dominant ataxias = Spinocerebellar Ataxias = SCAs

Many genes, one disease…
or is it many diseases?

Spinocerebellar ataxias (SCAs)

up to SCA43 and still counting!



SCA's: >40 and still accumulating …

Disease	Locus	Gene	Mutation
SCA 1	6p	Ataxin 1	CAG expansion
SCA 2	12q	Ataxin 2	CAG expansion
SCA3 (MJD)	14q1	Ataxin 3	CAG expansion
SCA 4	16q	Unknown	Unknown
SCA 5	11p	B III Spectrin	Non-repeat mutations
SCA 6	19p	CACNA 1	CAG expansion
SCA 7	3p	Ataxin 7	CAG expansion
SCA 8	13q	SCA8	CTG expansion
SCA 10	22q	SCA10	ATTCT expansion
SCA 11	15q	TTBK2/kinase	Non-repeat mutations
SCA 12	5q	PPP2R2B	CAG expansion
SCA 13	19q	KCNC3	Non-repeat mutations
SCA 14	19q	PKRCG	Non-repeat mutations
SCA 15/16	3p	ITPR (IP3)	deletions
SCA 17	6q	TBP	CAG expansion
SCA18	7q	?IFDR1	Non-repeat mutations
SCA19	1p	KCND3	Non-repeat mutations
SCA20	11	(not reported)	?genomic duplication
SCA21	7p	TMEM240	Non-repeat mutations
SCA22	1p	KCND3	Non-repeat mutations

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most common

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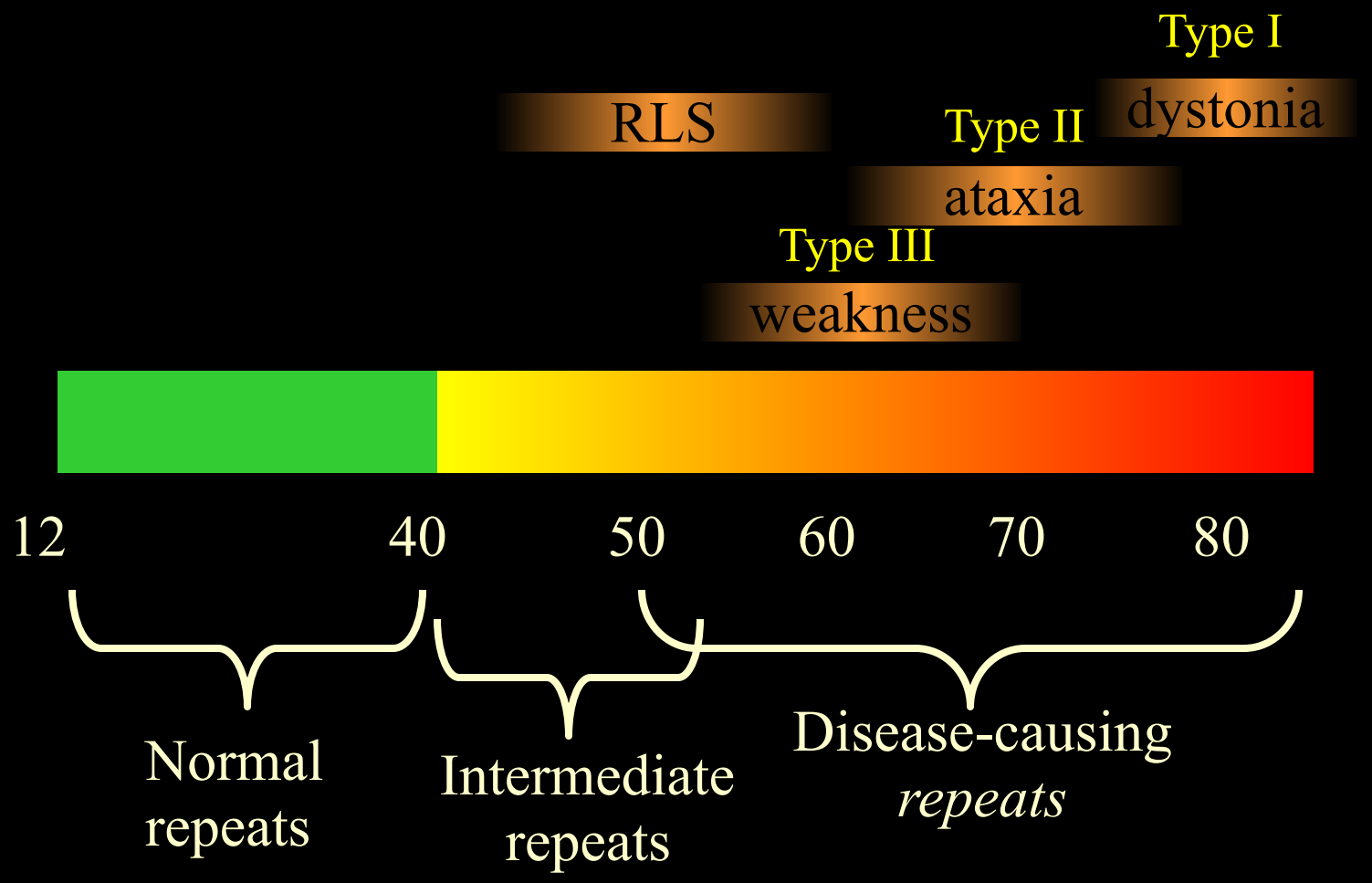
Adding to complexity: differing repeat lengths associated with different phenotype (e.g. of SCA3)



OUR PROBLEM

- Ataxias (including SCAs) are:
  - rare
  - there are LOTS of them
  - they can vary from person to person, even in the same family
- Tend to progress slowly… but we don't know the actual rate of progression and whether it varies for different genetic forms of disease
- Can we perform disease-modifying trials if we don't know the "base rate" we are trying to change?
- How can we design disease-modifying trials if we don't truly know the mechanism of disease?

THE NIH UNDERSTANDS OUR PROBLEM: RARE AND COMPLEX DISEASES

Established in 2003, the **Rare Diseases Clinical Research Network (RDCRN),** an initiative of the Office of Rare Diseases Research, is made up of ~20 research consortia that work together to improve availability of rare disease information, treatment, clinical studies, and general awareness for both patients and the medical community.

TIP OF THE CAP TO OUR FEARLESS LEADER!

IN 2009, DR. ASHIZAWA WAS AWARDED TWO YEARS OF FUNDING FOR THE CLINICAL RESEARCH CONSORTIUM FOR SPINOCEREBELLAR ATAXIAS (CRC-SCA), MAKING US ONE OF 19 CLINICAL RESEARCH CONSORTIA WITHIN THE NIH'S RARE DISEASES CLINICAL RESEARCH NETWORK (RDCRN)

RARE DISEASES CLINICAL RESEARCH NETWORK

Initiative of the National Center for Advancing Translational Sciences (NCATS)

NAF involvement was <u>essential</u> to success in getting the grant and in carrying out the research… thank you NAF!

DR. ASHIZAWA WAS PI FOR THE CRC-SCA. NATIONAL ATAXIA FOUNDATION'S INVOLVEMENT WAS A REQUIREMENT OF THE GRANT.

National Ataxia Foundation

SEPTEMBER 2012, DR. ASHIZAWA SUBMITTED TO AND WAS AWARDED A GRANT FROM THE NATIONAL ATAXIA FOUNDATION FOR A PIONEER SCA TRANSLATIONAL RESEARCH AWARD FOR FISCAL YEAR 2013 TO

CONTINUE THE WORK OF THE CRC-SCA.

…thank you NAF!

ALAS, EFFORTS TO CONTINUE THE WORK OF THE CRC-SCA THROUGH ANOTHER ROUND OF NIH FUNDING (2013) FAILED TO MATERIALIZE… BUT WE PRESSED ON.

TRUTH BE TOLD, WE WEREN'T SMILING QUITE AS MUCH ANYMORE!

WHY WEREN'T WE SMILING?

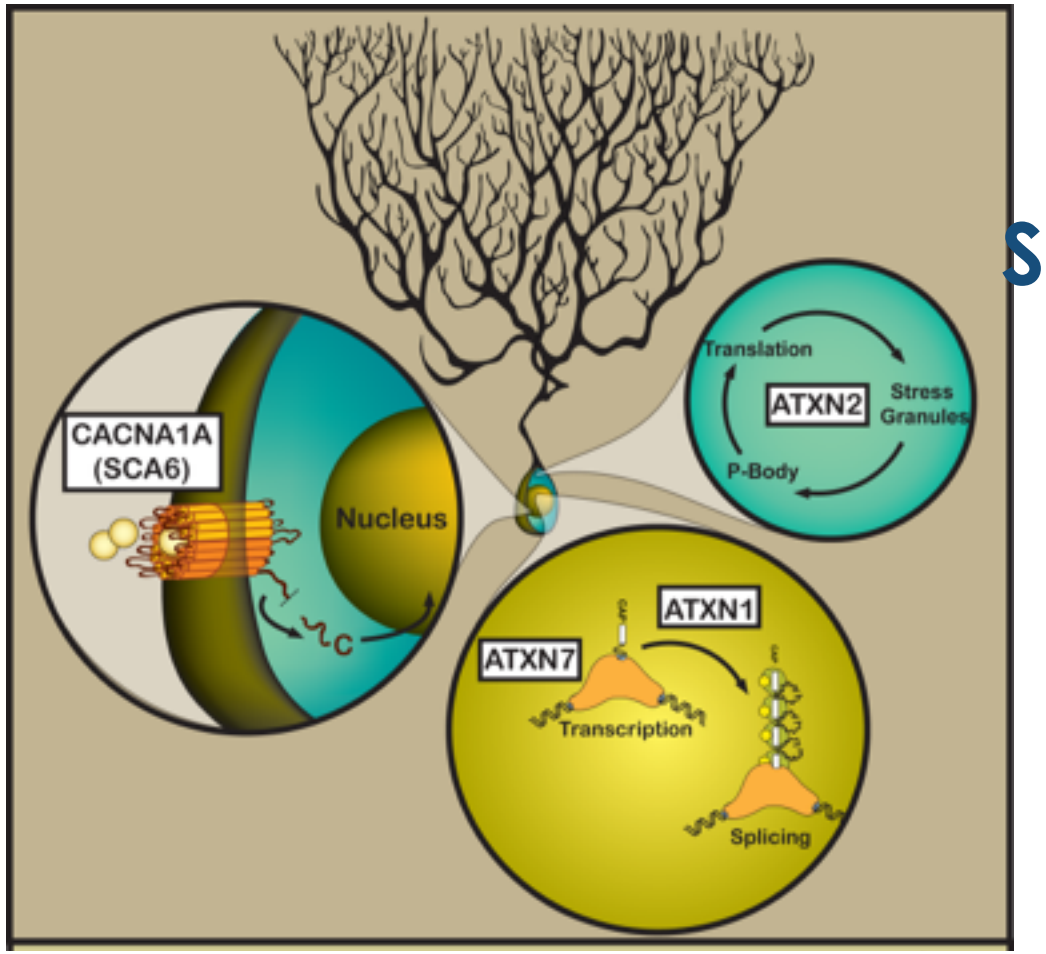
It's hard to carry out research when there is no money to pay for it!

We tried to continue the clinical research, but with increasing pressures bearing down on academic "ataxiologists", it was virtually impossible

Meanwhile NAF (and other groups like NIH) continued to fund research to understand how disease occurs

Different genes, different proteins, different mechanisms?

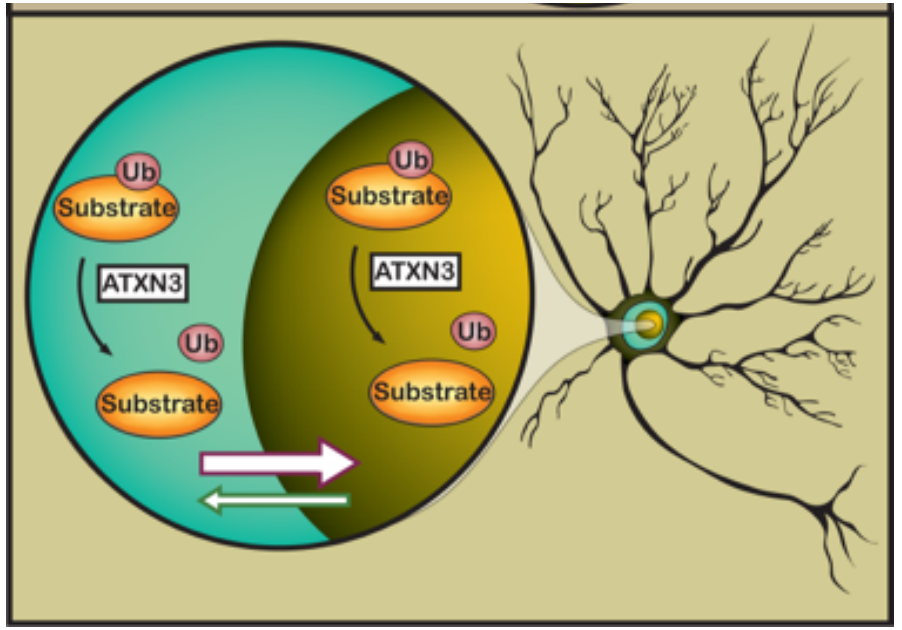
SCA6



SCA1,7

SCA2

SCA3



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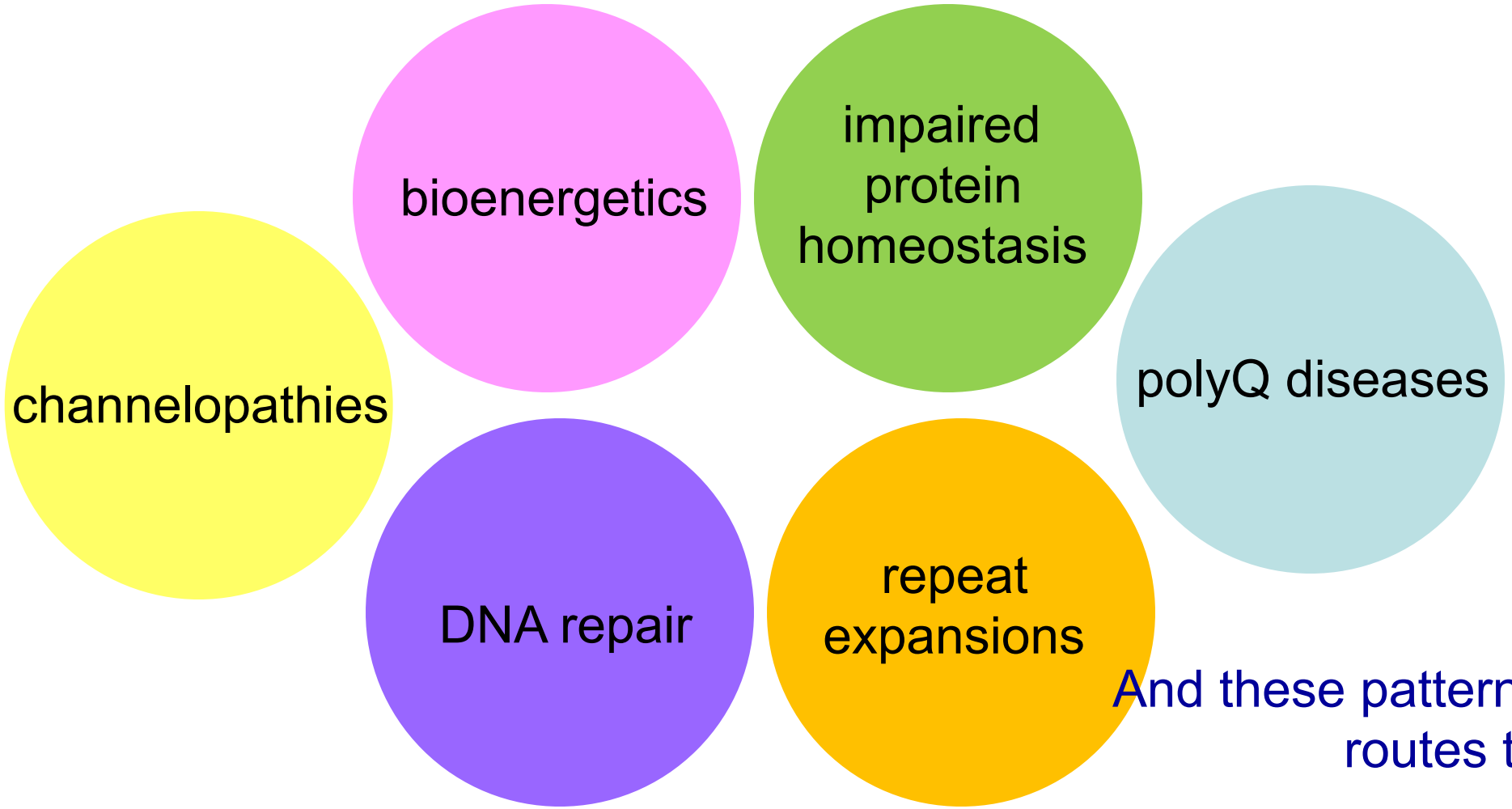
1996: a few genes, but that's about it

2016: many genes, many insights into disease mechanisms…
AND emerging strategies for treatment

Yes, there are many ataxia disease genes…

…but we are beginning to see patterns of pathogenic mechanisms:

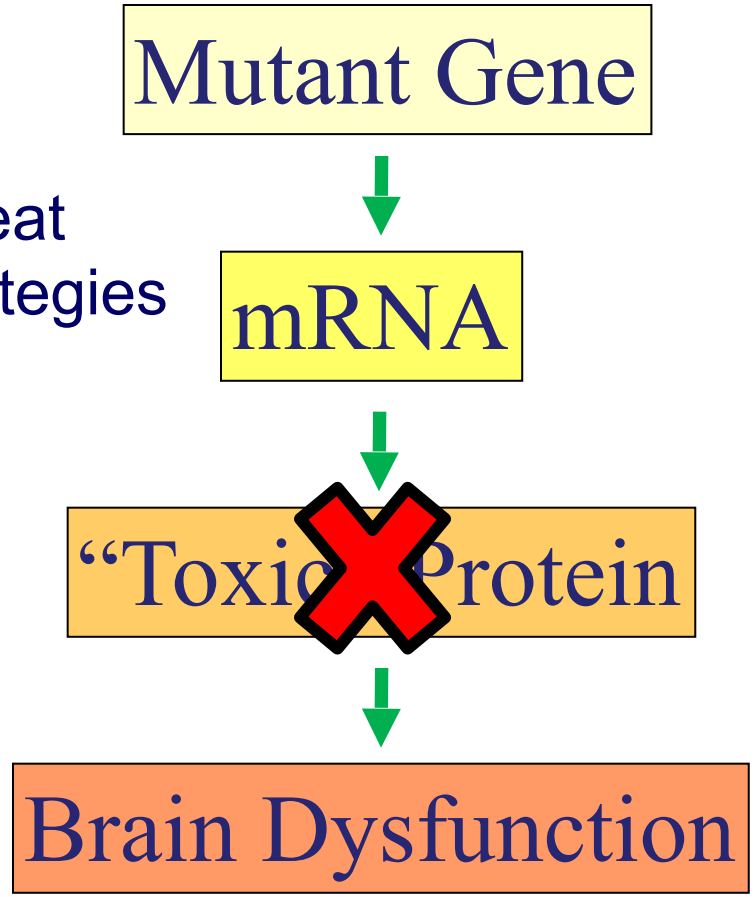


And these patterns suggest routes to therapy.

Based on mechanistic insights, investigators began pushing forward with therapeutic strategies in disease models…

ke

Simple view of disease process* applicable to many SCAs



CAG repeat targeting strategies

gene editing

reduce transcription

exon skipping

target splice isoforms

transcript clearance

block translation

enhance protein clearance

*also applies to other diseases with "toxic" accumulation of protein

Nov. 3-4, 2015

- At the NAF Board Retreat, one of five goals in NAF's strategic plan was to have the SCA community become clinical trial ready.

April 1, 2016

- At NAF's annual MRAB meeting, a working group, headed by Dr. Henry Paulson (that's me), was selected to write a proposal to present to the NAF Board of Directors on how

May 2016

- A working group was selected to prepare a questionnaire that would be distributed to potential sites for clinical trial readiness research to determine the selection of the sites.

WHAT WE WROTE TO NAF

"…the NAF consistently supports mechanistic research that has led to new insights into the ataxias. Partly because of this support, the ataxia field has reached an exciting new phase: therapeutic targets have been identified, disease mechanisms are better understood, and pharmaceutical companies and academic investigators are planning symptomatic and disease-modifying clinical trials for various dominantly inherited ataxias, or SCAs.

Presentations and discussions … made it clear that now is precisely the time for the NAF and other groups to facilitate this push for therapies. Many investigators and industry partners, however, have raised concern that the network of ataxia clinical research sites across the United States is not truly "trial ready.""

WHAT WE WROTE TO NAF

- "NAF could have a tremendous impact on the field by directing funds earmarked for SCA research to clinical research that will enhance trial readiness.
- This commitment would: i) move investigators more quickly to the point where they are testing therapies for the SCAs, and ii) fulfill the primary wish of the ataxia families served by NAF, namely to find cures for these diseases.
- The return on investment (ROI) is expected to be tremendous, since a modest infusion of funds would "reboot" the SCA-CRC formally funded by the NIH and staffed by the country's leading experts ready to get to work.
- Trial readiness efforts would focus on SCAs, especially the more common SCAs. But all persons with ataxia would be encouraged to enroll in the CoRDS patient registry. Thus, this new NAF-funded initiative would benefit all ataxia patients, expanding the national registry of patients available for clinical research while also setting the stage for symptomatic and disease-modifyin clinical trials in the SCAs."

ON MAY 13, 2016, I SUBMITTED OUR PROPOSAL TO MIKE PARENT AND DR. HARRY ORR, REQUESTING $248,000 TO FUND 14 SITES FOR CLINICAL TRIAL READINESS. WE ASKED THEM TO SEND IT ON TO THE NAF BOARD FOR CONSIDERATION OF FUNDING.

And NAF said, “Darn right, now’s the time!”

(Not really. What they actually said was, “We love the idea! …Now, can you do it for a little less?”)

Thanks to NAF, we are rebooted and pushing ahead!

Clinical Research Consortium for the Study of Cerebellar Ataxia (CRC-SCA)

Primary Objective: Obtain progression rate of SCAs 1,2,3,6,7,8 and 10 using a validated neurological rating scale, timed performance measures, and patient reported outcome measures

Primary Outcome Measures: SARA scores, timed 25 foot walk, and 9 hole pegboard test

Secondary Study Objectives: Establish the validity of a novel neurological rating scale (BARS), cognitive measure (CCAS-scale) and neurobehavioral measure (CNRS)
Discover genetic modifiers of age at onset, phenotype and progression rate

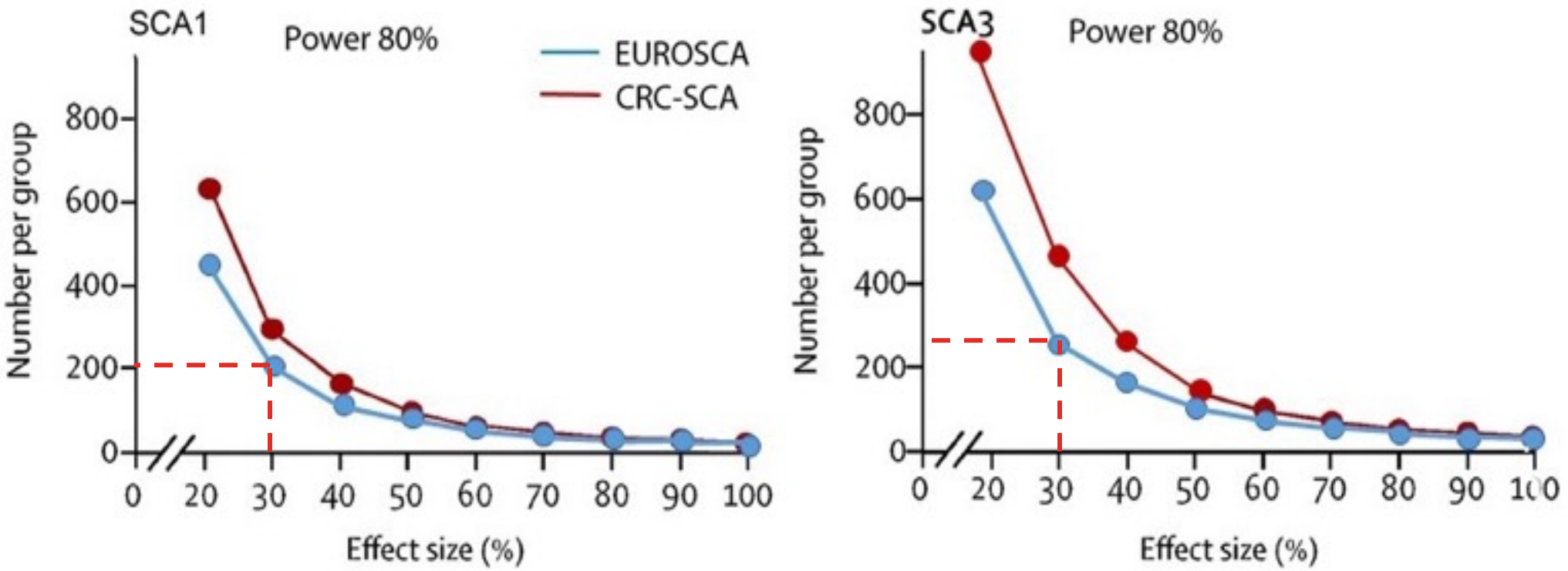
CRC-SCA investigators and sites

Columbia University – Sheng Han Kuo, MD
Baylor College of Medicine – Paolo Moretti, MD
Emory University – George Wilmot, MD, PhD
Houston Methodist Research Institute– Tetsuo Ashizawa, MD
Johns Hopkins University – Liana Rosenthal, MD and Chiadikaobi Onyike, MD
Harvard University/Massachusetts General Hospital – Jeremy Schmahmann, MD
Northwestern University – Puneet Opal, MD, PhD
Stanford University – Dr. Sharon Sha
University of Alabama Birmingham – Talene Yacoubian, MD, PhD
University of California Los Angeles– Susan Perlman, MD
University of California San Francisco – Michael Geschwind, MD, PhD
University of Colorado – Lauren Seeberger, MD
University of Chicago – Christopher Gomez, MD, PhD
University of Florida – SH Subramony, MD
University of Michigan – Henry Paulson, MD, PhD and Vikram Shakkottai, MD, PhD
University of Minnesota – Khalaf Bushara, MD
University of Rochester Medical Center – Erika Augustine, MD
University of South Florida – Theresa Zesiewicz, MD
University of Utah – Stefan Pulst, MD
University of Texas Southwestern – Pravin Khemani, MD

Short term outcomes of this investment are expected to include:

- i) the launching of one or more industry –sponsored clinical trials
- ii) several investigator-initiated clinical research grants that test specific therapeutic agents, biomarkers or new outcome measures Ashizawa to the rescue again: UO1 SCA1/SCA3 trial readiness application
- iii) formalized relationships with industry partners resulting in additional funds or in-kind support to enhance research.

How many participants do we need to perform a trial of a potential disease-modifying drug?



Sample size estimates. Required sample size/group in two-group interventional trials of 1-year duration for various effect sizes at $p<0.05$ in SCA1 (left) and SCA3 (right). The figure was constructed from CRC-SCA data (red) and EUROSCA data (blue).

Aims of UO1 grant application
(submitted last month)

- **Aim 1.** To establish the world's largest cohorts of premanifest and early stage SCA1 and SCA3 patients by combining and expanding existing cohorts, COA data and biofluid samples (blood, cerebrospinal fluid) from US and Europe.
- **Aim 2.** To validate magnetic resonance (MR) morphological, biochemical (MRS) and functional (fMRI) biomarkers in pre-manifest and early SCA1 and SCA3.
- **Aim 3.** To adapt recent developments on statistical design and analysis of small population trials to SCAs.

Multiple PI's: Ashizawa, Oz, Paulson, Klockgether, Durr

Candidate therapeutics for UO1 application

Selected based on: a) strong preclinical experimental studies; and b) emerged from unbiased screens or target proximal steps in disease cascade.

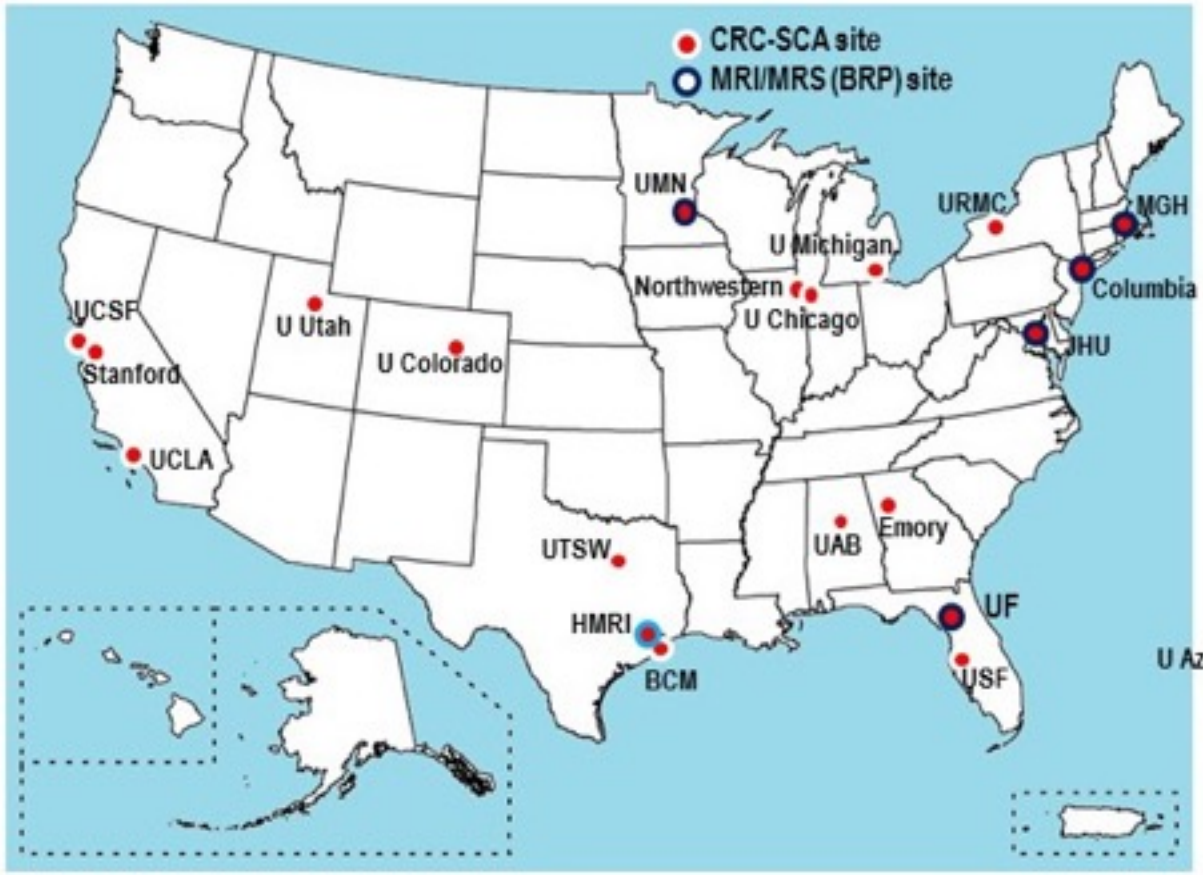
SCA1

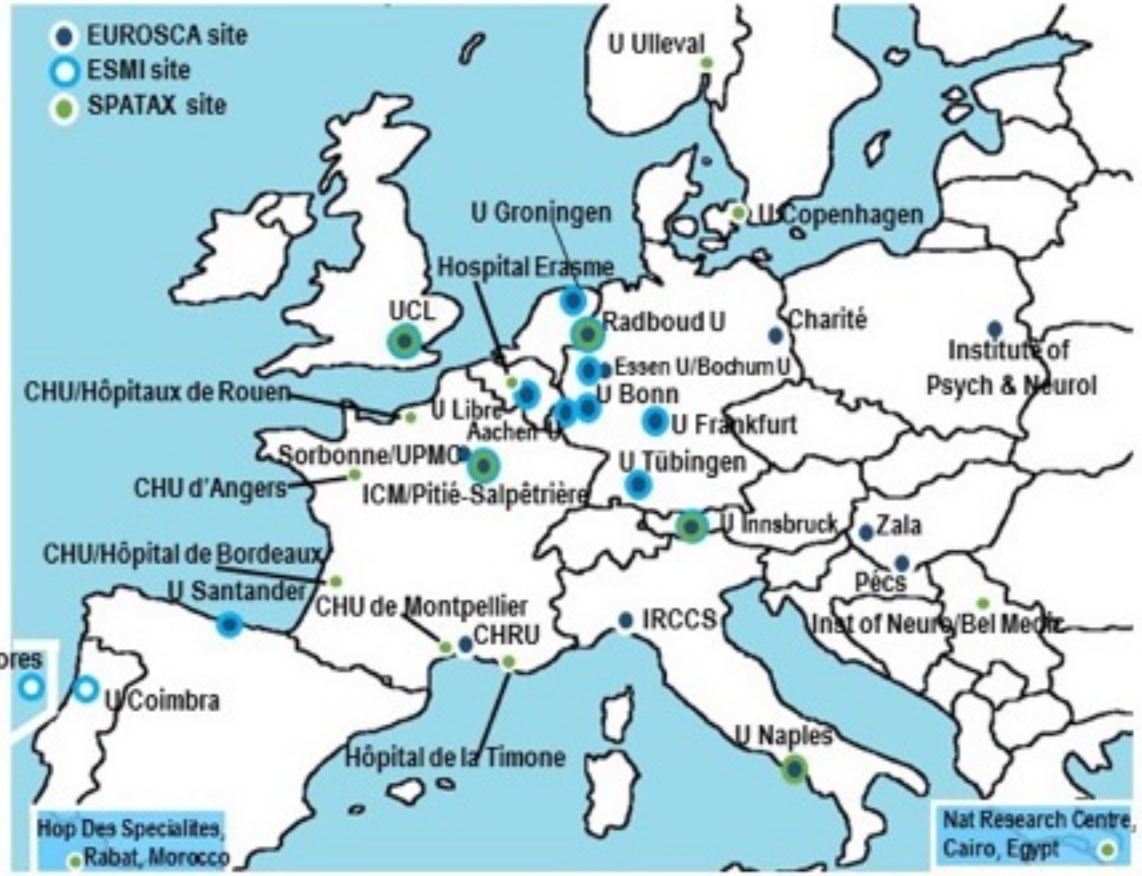
Inhibitors of mitogen- and stress-activated protein kinase 1 (Dr. Huda Zoghbi)
Stereotactic viral delivery of microRNA-like RNAi (Dr. Beverly Davidson)
Antisense oligonucleotides targeting *ATXN1* gene (Dr. Harry Orr, Ionis Pharmaceuticals)

SCA3

Citalopram (Celexa) (Dr. Patricia Maciel)
Antisense oligonucleotides targeting *ATXN3* gene (Dr. Henry Paulson, Ionis Pharmaceuticals)

A TRULY INTERNATIONAL EFFORT





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1996? Maybe not quite the time yet.

2017? It MUST be the right time!

ACKNOWLEDGMENTS

- Thanks to Sue Hagen. The best!!
- To NAF and its visionary leadership
- To my fantastic UM ataxia colleagues Vikram Shakkottai, Peter Todd, Elizabeth Sullivan (and many others)
- To my lab mates, who are pushing hard for therapies in SCA3 every day
- To all of the ataxiologists in the CRC-SCA – keep it up!
- And most of all to YOU, who inspire all of us who are working toward a cure!