UNIVERSITY OF TORONTO
FACULTY OF MEDICINE

CRND program: from basic research to clinical translation

Ekaterina Rogaeva, PhD

Associate Professor, Faculty of Medicine, University of Toronto

Principal Investigator, Centre for Research in Neurodegenerative Diseases

Toronto Dementia Research Alliance

CRND is an interdisciplinary research institute (directed by Dr. P. St George-Hyslop)

Main mandate:

Research on Alzheimer's disease and related disorders

Structure:

10 laboratories that bring together expertise in

Genetics

Protein Chemistry

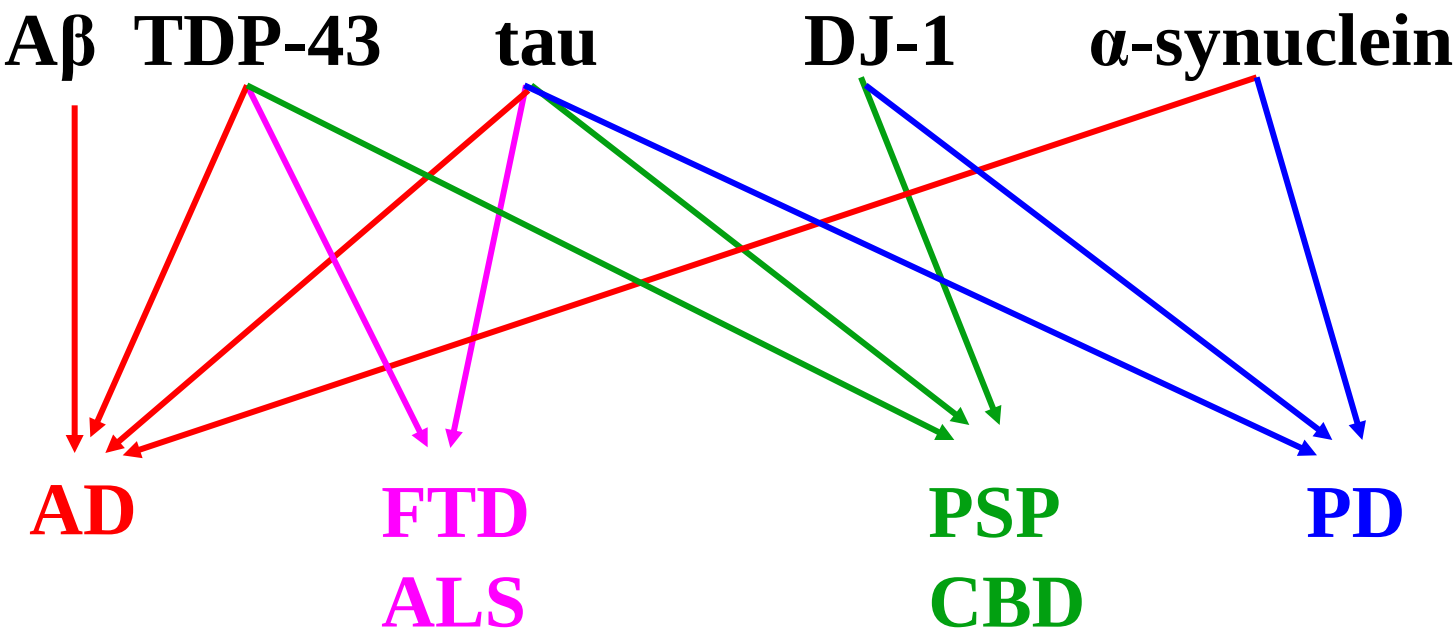
Neuropathology

Neuroimmunology

Molecular and Cell Biology

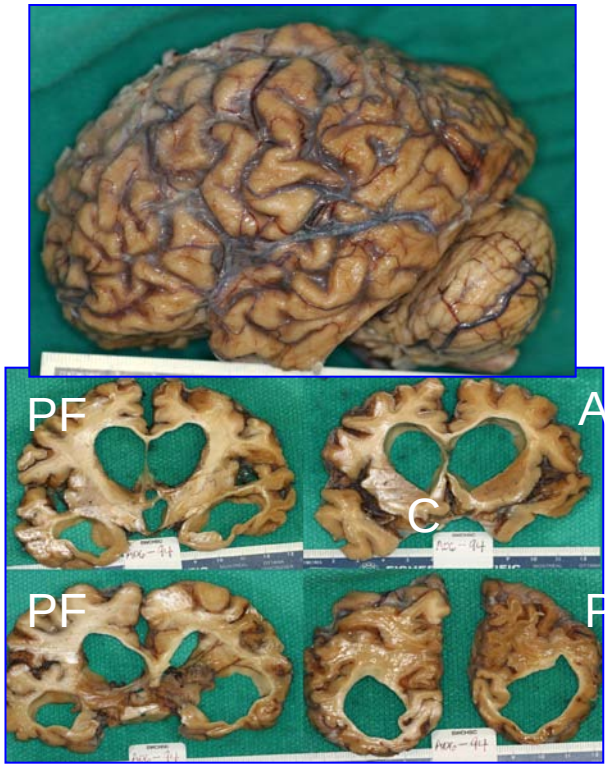
Transgenic Animal Modeling (mouse & worm models)

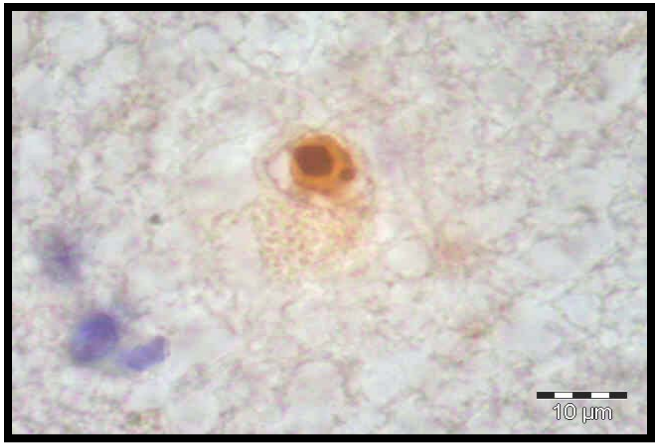
Clinical and neuropathological overlap between Neurodegenerative diseases



CRND is using a comprehensive approach to study these disorders

Brain pathology of FTD patient: neuronal inclusions containing TDP43 protein

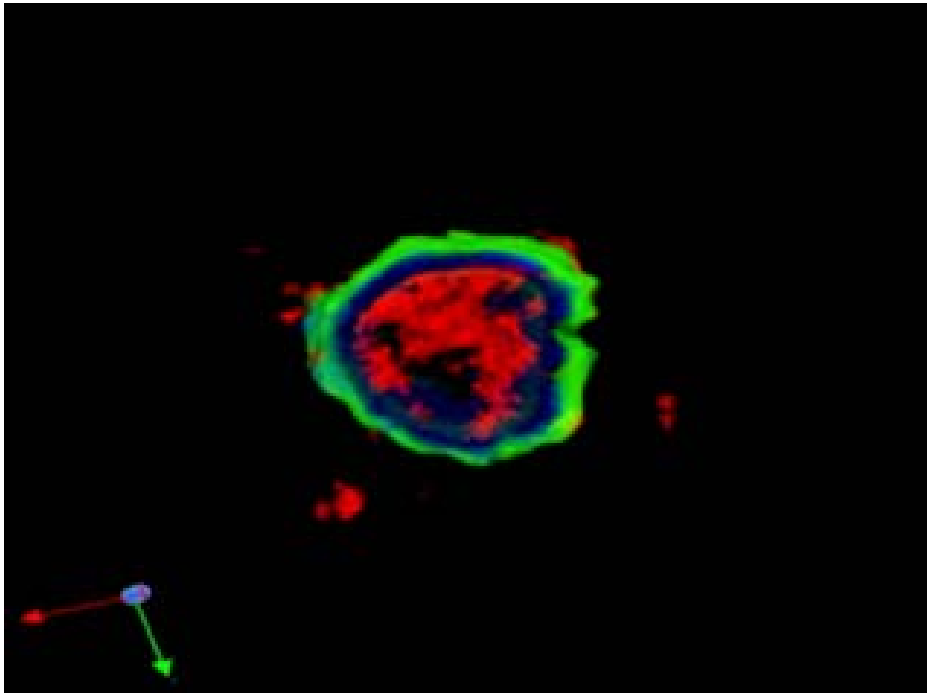




- **TDP43 inclusions are also present in ~20% of AD patients**

- **Knowledge about the mechanism of TDP43 accumulation will help to understand what kills brain cells in AD cases**

3-D imaging of the inclusion: ubiquitinated core is surrounded by TDP-43



TAR DNA/RNA binding protein (TDP-43)

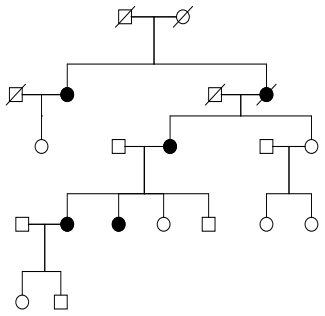
Nuclear factor that regulates transcription and alternative splicing

Sanelli, et al J of Neuropath and Exp Neurology, 2008

(Dr. Robertson's team at CRND)

Clinic

Identification and care of affected or at-risk individuals

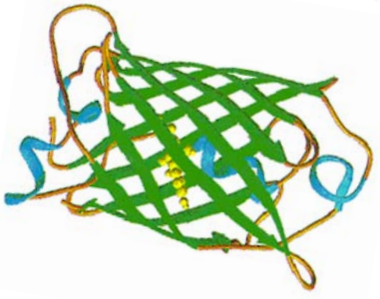


Genetics

Identification of novel genetic causes of AD

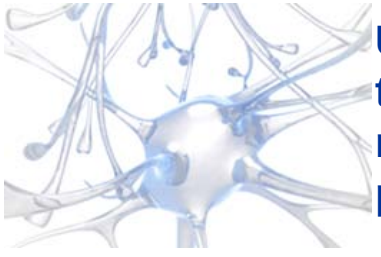
Protien Structure & Biochemistry

Evaluate structure and binding partners that regulate disease progression



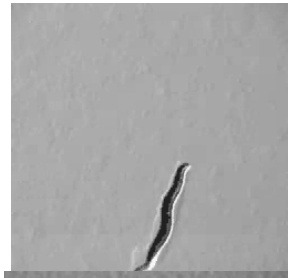
Cell & Molecular Biology

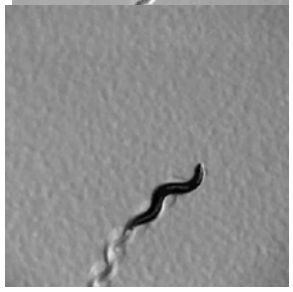
Understand the role of new disease proteins



Animal Models

Mimic AD behavior and pathology, and provide a reproducible platform for testing new drugs





Drug Discovery

Rational drug design based on structure and function

Novel Therapeutics

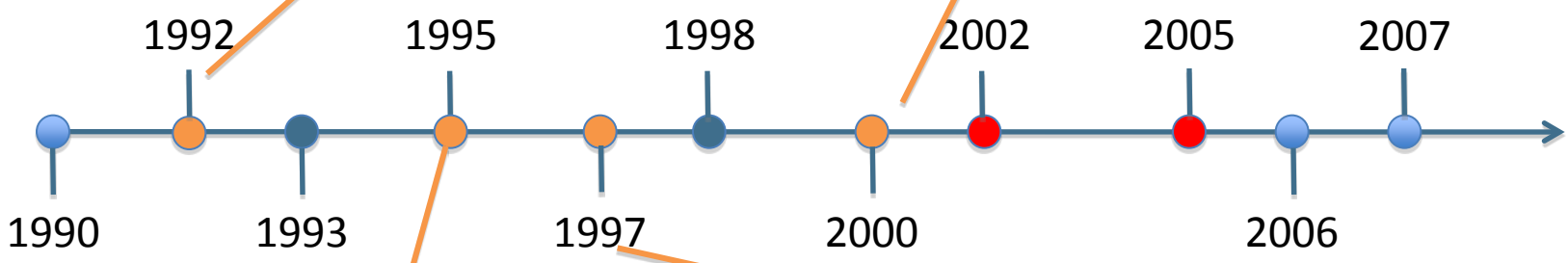
What has been accomplished?

- **Peer reviewed research papers: >100 per annum**
- **International collaborations: >50 scientists in 11 countries**
- **Established collaboration with AD-related Toronto Hospitals**
- **Tractable, but still incomplete concept of mechanisms of AD**

Gene Discovery at the CRND

Identification of chromosome 14 as "hot spot" for early-onset AD
[St George-Hyslop et al, Nat Genet]

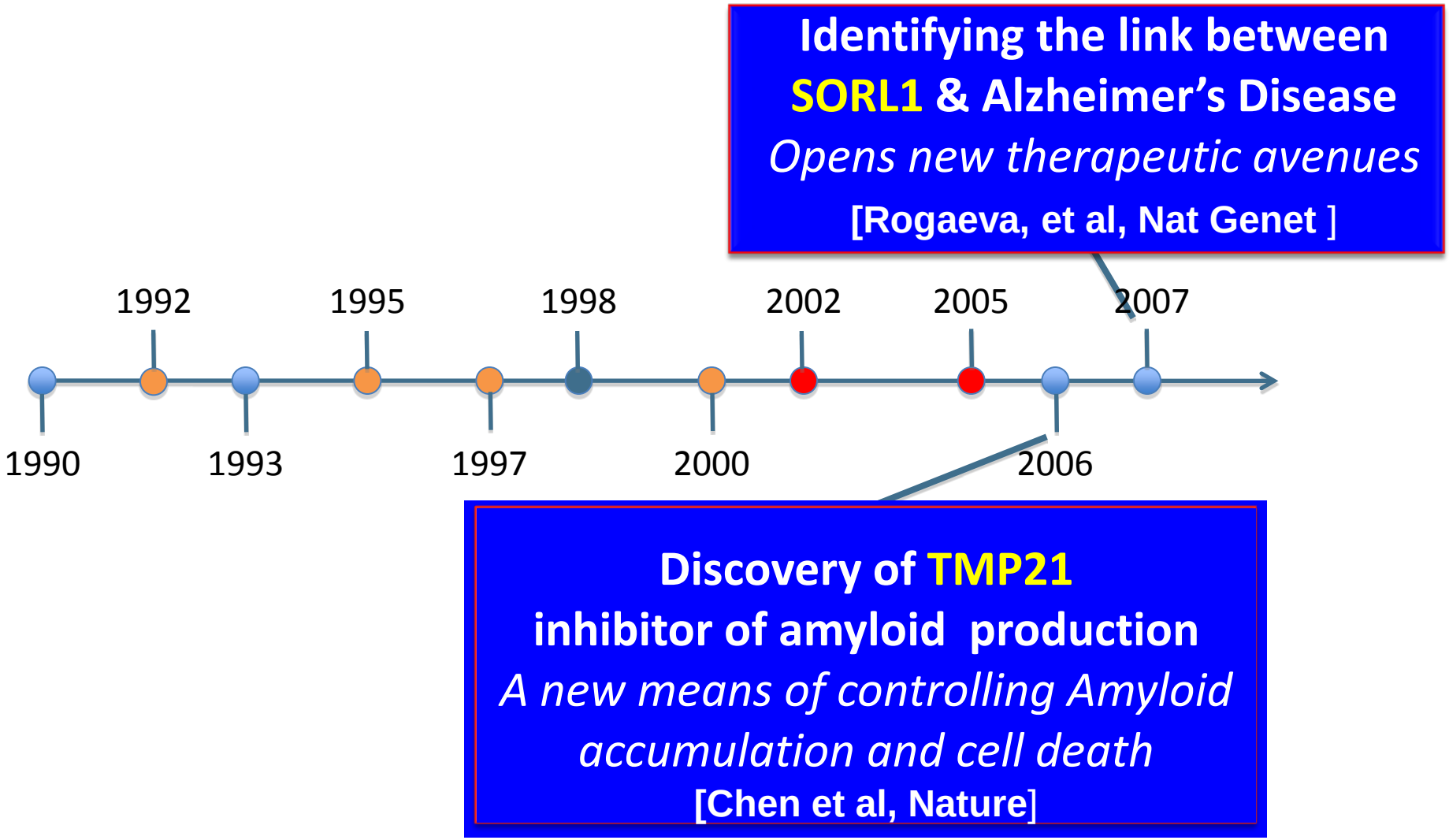
Discovery of the new gene Nicastrin – regulator of Presenilin and amyloid biology
[Yu, et al, Nature]



Discovery of Presenilins 1 & 2 as major causes of familial Alzheimer's disease
[Sherrington et al, Nature]
[Rogaev, et al, Nature]

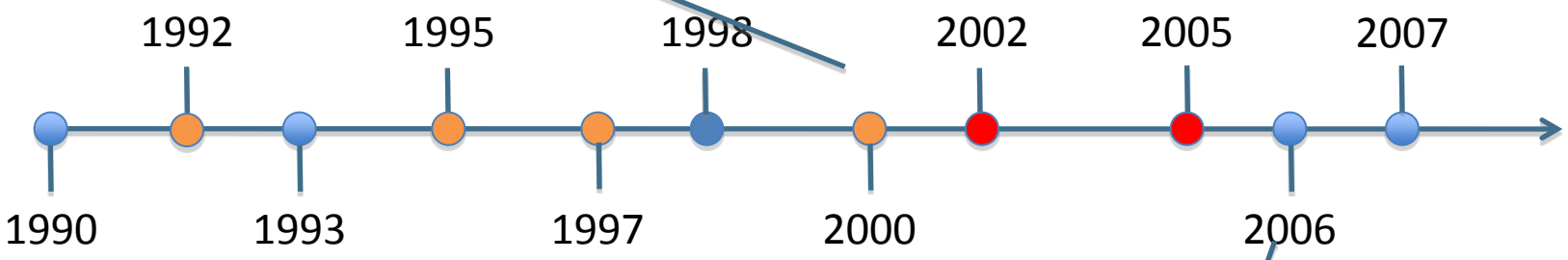
Establishing the link between Presenilins and Amyloid: mutations increase levels of Ab
[Citron, et al, Nat Med]

Gene Discovery at the CRND



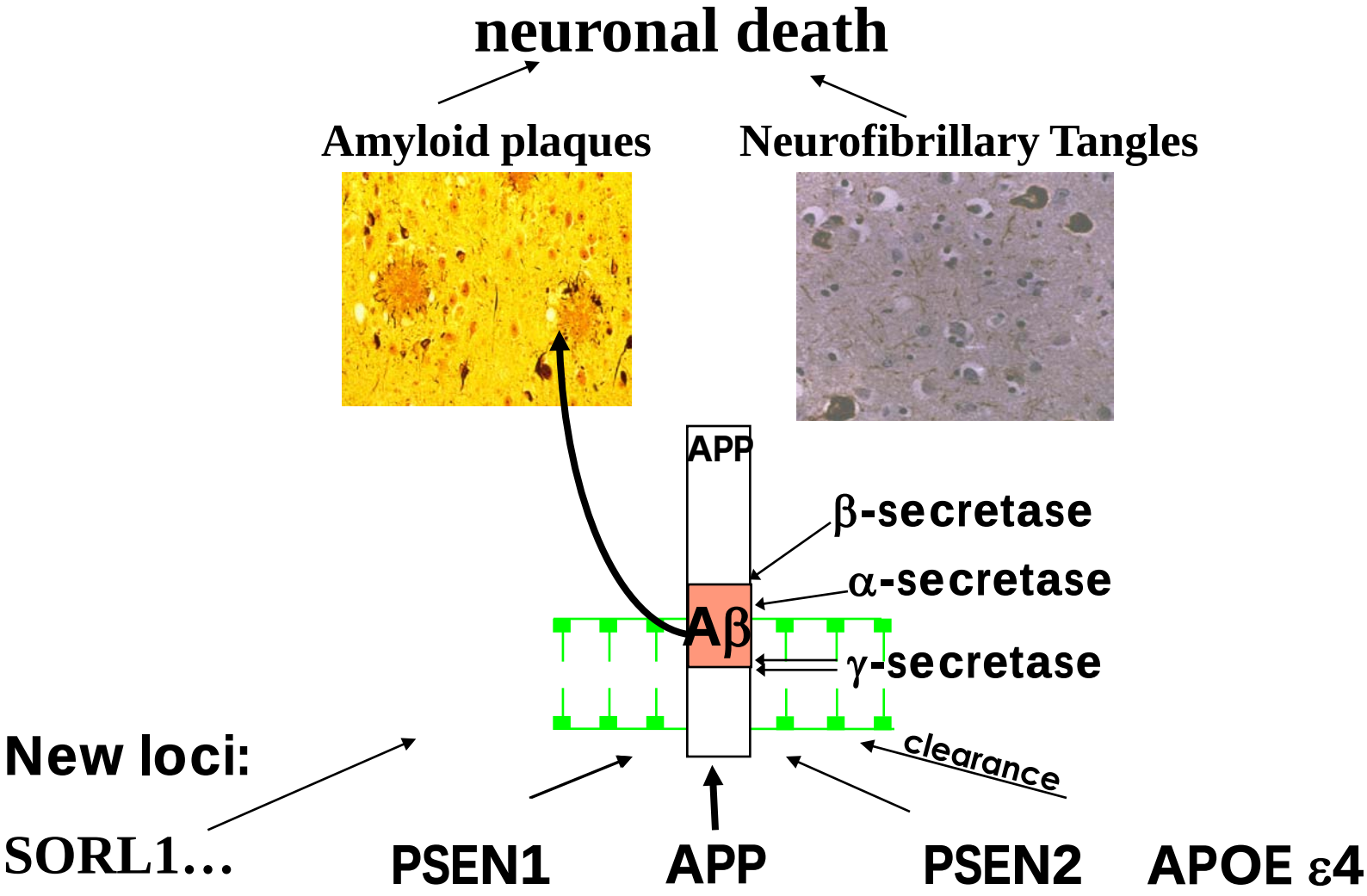
Treatment Strategies at the CRND

Development of amyloid vaccines as a treatment for AD pathology
[Janus, et. al, Nature]



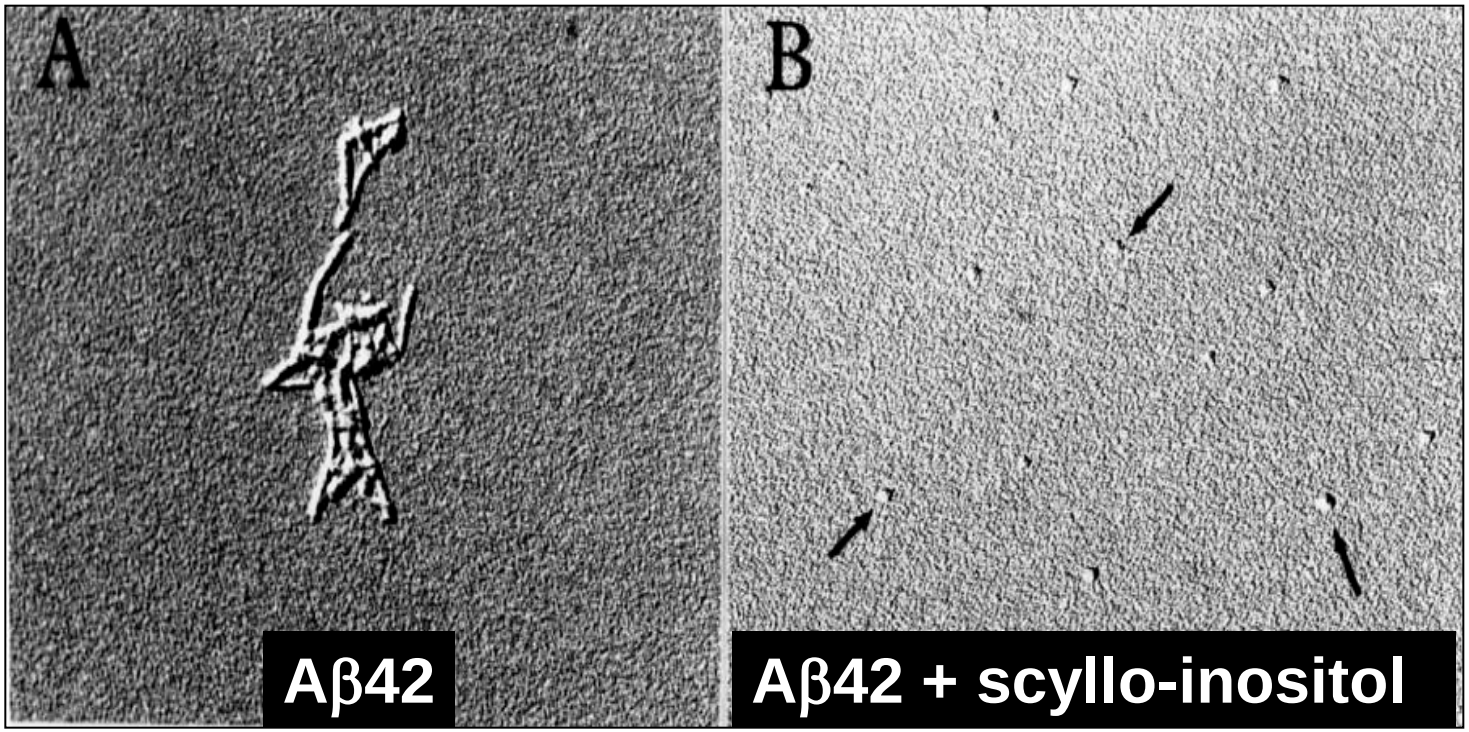
New small molecule anti-amyloid strategies that reduces Aβ toxicity and nerve cell death
[McLaurin, et al Nature Med]

Known AD genes involved in Aβ metabolism



Multiple avenues being followed for anti-amyloid therapies

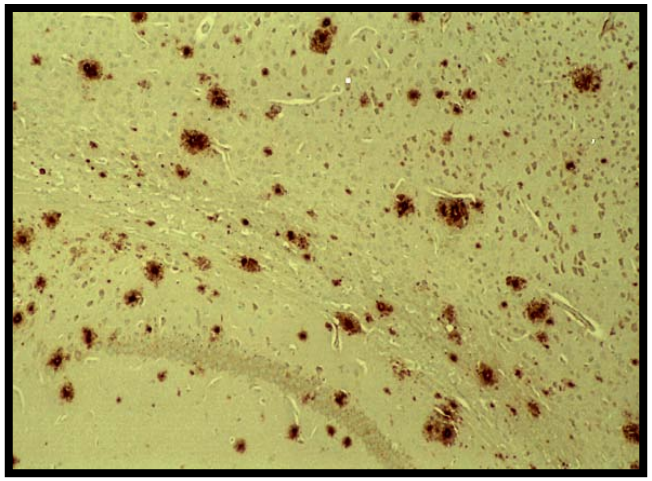
Scyllo-inositol inhibits Aβ fibril assembly & Toxicity (now in clinical trial)



McLaurin, Fraser, Westaway, St George-Hyslop, et al *Nature Med*. **12:**801-808, 2006

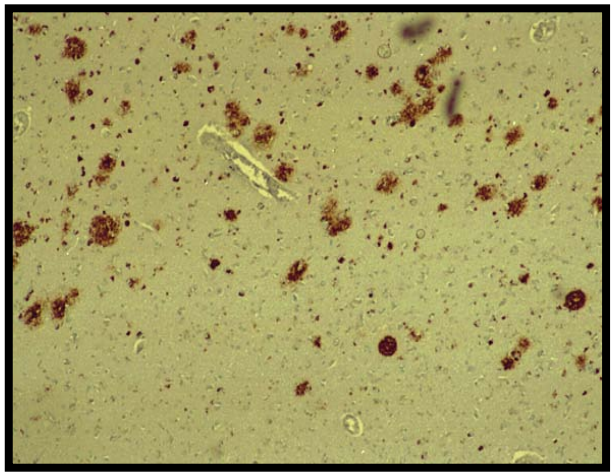
However, correct use of anti-amyloid therapies could be prophylactic (in people at risk)

Why do mice expressing mutant APP show a good response to anti-amyloid therapies?



MOUSE

Amyloid deposition in Tg CRND8 MOUSE brain at 26 weeks



HUMAN

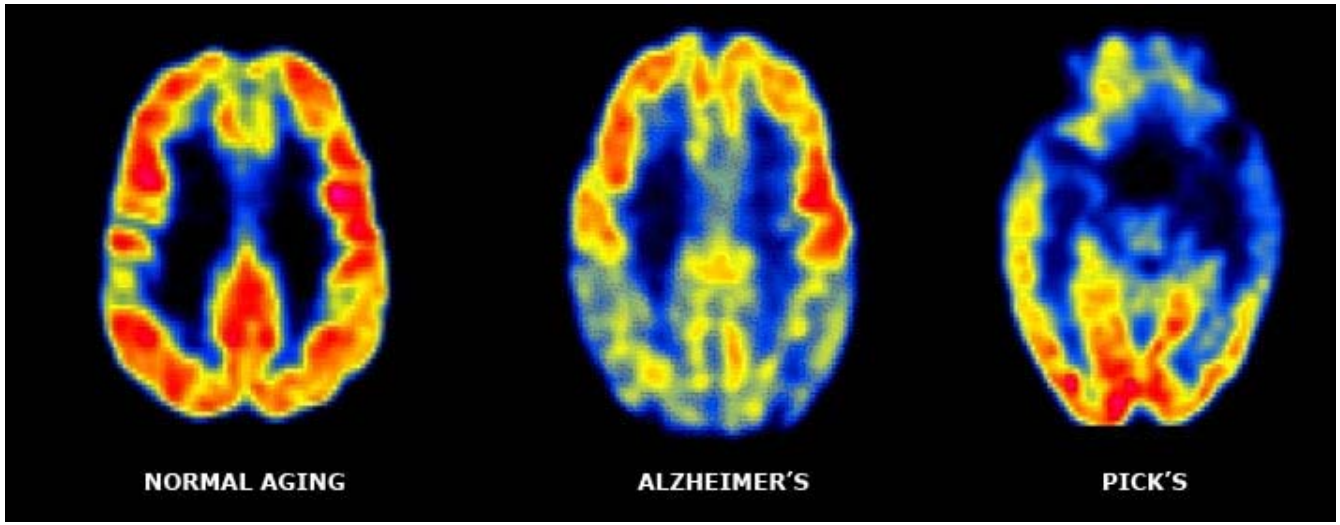
Amyloid deposition in HUMAN AD brain at 70 years

But <u>no</u> tau-pathology & neuronal loss
Preclinical model….

Janus et al *Nature*, 2000

Novel Diagnostics for Alzheimer's Disease

- **Development of radiolabelled compounds with specific binding to aggregated Aβ peptide.**
- **Testing in CRND transgenic model of amyloid pathology.**
- **Collaboration with University Health Network imaging specialists (Dr. David Jaffray).**

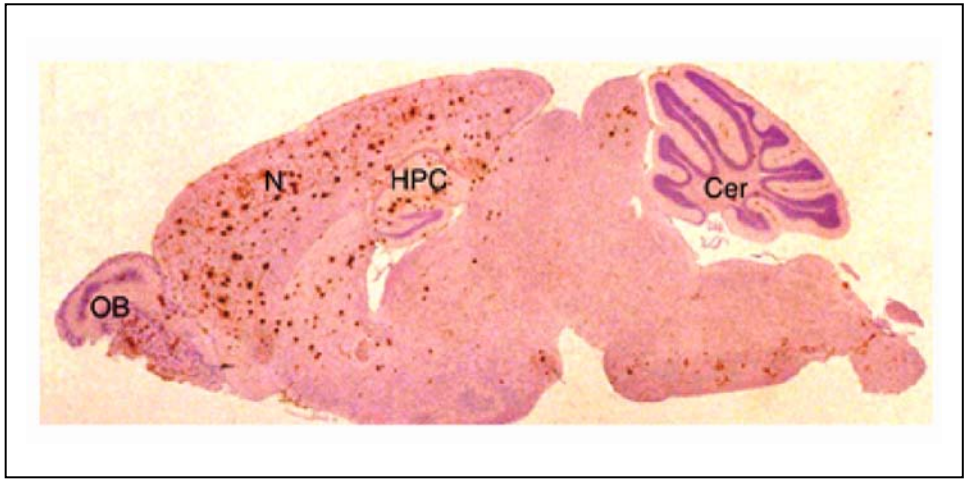


Positron Emission Tomography (PET) – Functional Metabolism

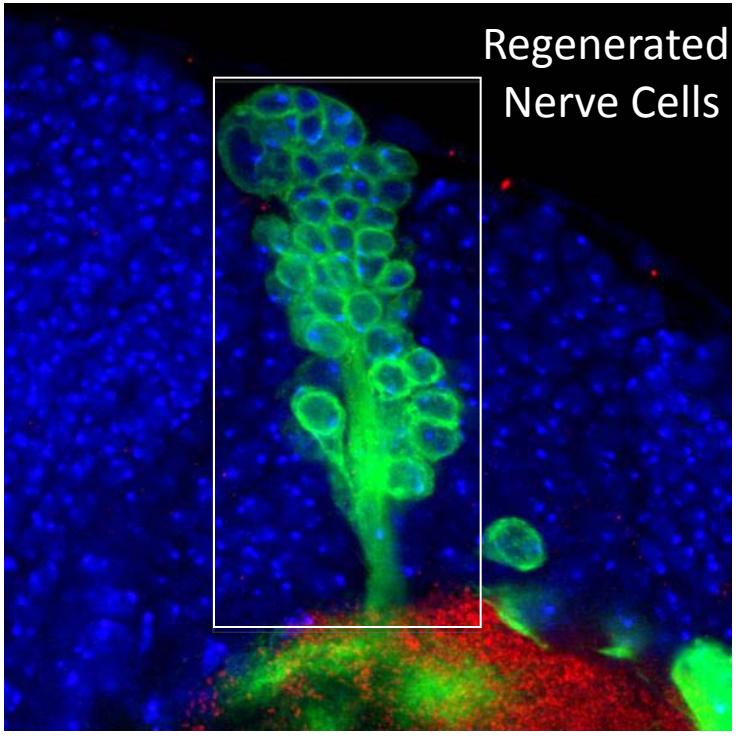
Neuronal Neogenesis in Alzheimer's Disease

"Birth of new nerve cells"

- Is it possible to generate new nerve cells to repair damaged brain tissue?
- What role does the plaque and tangle pathology play in preventing this process?
- Can this process be enhanced or accelerated to treat AD patients?



Testing in TgCRND8 Model
of AD Amyloid Pathology



Where to go next?

- **Need more details on molecular mechanisms of AD to detect new therapeutic targets.**

- **Developing approaches for prophylactic AD therapies;**

- **Need new diagnostics to detect disease before symptoms (e.g. novel imaging techniques, genetics);**

Conclusion: we do need an expansion of interdisciplinary collaboration…