CRND program: from basic research to clinical translation

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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

(Dr. Robertson’s team at CRND)
Drug Discovery
Rational drug design based on structure and function

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

Clinic
Identification and care of affected or at-risk individuals

Genetics
Identification of novel genetic causes of AD

Protein Structure & Biochemistry
Evaluate structure and binding partners that regulate disease progression

Cell & Molecular Biology
Understand the role of new disease proteins

Novel Therapeutics

CRND

Rational drug design based on structure and function

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

Understand the role of new disease proteins

Evaluate structure and binding partners that regulate disease progression

Identification of novel genetic causes of AD

Identification and care of affected or at-risk individuals
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
Establishing the link between Presenilins and Amyloid: mutations increase levels of Ab
[Citron, et al, Nat Med]

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

Discovery of Presenilins 1 & 2 as major causes of familial Alzheimer’s disease
[Sherrington et al, Nature]
[Rogaev, et al, Nature]
Discovery of TMP21 inhibitor of amyloid production
A new means of controlling Amyloid accumulation and cell death
[Chen et al, Nature]

Gene Discovery at the CRND

Identifying the link between SORL1 & Alzheimer’s Disease
Opens new therapeutic avenues
[Rogaeva, et al, Nat Genet]
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
Known AD genes involved in Aβ metabolism

Neuronal death

Amyloid plaques

Neurofibrillary Tangles

New loci:

SORL1...

β-secretase

α-secretase

γ-secretase

Clearance

APOE ε4

PSEN2

PSEN1

APP
Multiple avenues being followed for anti-amyloid therapies

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


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 no 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?
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…