Stroke & Alzheimer’s Disease: An Inflammatory Duo
Stroke and Dementia

- One in 3 will experience a stroke, dementia or both
- 64% of persons with a stroke have some degree of cognitive impairment and up to a third have dementia
- Postmortem: 34% of dementia cases show cerebrovascular pathology
- Risk factors for cerebrovascular disease are the same for cognitive impairment
- Prevalence of vascular cognitive impairment (with or without dementia, 2 million in the US)
Why Study Stroke & Alzheimer’s Together?

- The combination of “silent strokes” and low level Alzheimer’s results in dementia – Nun Study
- Both share the same risk factors
- Strokes damaged areas exhibit pathological precursors of Alzheimer’s
- Inflammation is a dominant force in neurodegenerative properties of stroke and Alzheimer’s
- Clinical stroke and dementia are not treatable
- **Vascular cognitive impairment** preceding stroke and Alzheimer’s is treatable, i.e. during the “brain at risk stage”
- The interactions between small strokes and Alzheimer’s Disease during the “brain at risk stage” (preceding clinical stroke and dementia) may suggest targets for therapy
Animal Models

- β amyloid toxicity (AD): transgenic mice or Amyloid β25-35 icv in the rat
- Small ‘silent’ strokes: endothelin injections in the striatum
- Outcomes
  - AD-like pathology
  - Neuroinflammation
  - cognitive deficits
  - infarct size
Why the combination of AD and CI?

Pathways

Alzheimer’s

APP

\(\text{A}\beta\)

\(\text{NF}\kappa\text{B}\)

Cytokines

\(\text{TNF}\alpha, \text{IL-1}\beta\)

Stroke

Cell Death
Rat Model of Cerebral Ischemia in Striatum

• Endothelin injections: vasoconstriction
Rat Model of Small Striatal Infarcts

AD-like pathology

- APP
- Tau-2

Neuroinflammation

- OX-6
- GFAP
- NFκB
Rat Model of $\beta$ Amyloid Toxicity

(AD-like pathology)

- Amyloid $\beta$ injections: intracerebroventricular
β Amyloid Toxicity and APP Immunostaining

Immunostaining 21 days after bilateral Aβ (25-35) injections

- Anterior Cortex
- Cortex
- Corpus Callosum
- Hippocampus
β Amyloid Toxicity and new β Amyloid (Aβ immunostaining) in the hippocampus

21 days after Aβ (25-35) injections
Interactions: Inflammation in the hippocampus

Levels in the hippocampus 21 days after Aβ (25–35) injections and/or endothelin injections

- Control
- Endothelin (stroke)
- Aβ (25-35) (Alzheimer’s)
- Aβ and Endo
  Stroke & Alzheimer’s
<table>
<thead>
<tr>
<th>Brain Area</th>
<th>Protein</th>
<th>Sham</th>
<th>Endothelin</th>
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Cognitive Testing
Barnes Circular Platform Test
Circular Platform Test

Training Phase
- 14 trials
- Surgery
  - Recovery Period (7, 14 or 28 days)
  - Test
Circular Platform Test

Training Phase

14 trials

Surgery

Recovery Period
(7, 14 or 28 days)

Test (1 single trial)

Re-acquisition (14 trials)
Circular Platform Test

Sham - Control

Training Phase
- 14 trials

Surgery

Recovery Period
- (7, 14 or 28 days)

Test
- 1 single trial

Re-acquisition
- 14 trials
Circular Platform Test

Interaction: Aβ and Endothelin
Progressive increase in infarct size in presence β amyloid toxicity.
Pathways

(Alzheimer’s Pathway)

APP

Aβ

NFκB

Cytokines

TNFα, IL-1β

Stroke

Cell Death
NF-κB Activation Pathway

Inflammatory proteins

Inflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines, adhesion molecules, COX-2, etc.

Cytoplasm

Activation signals

Cytokines (IL-1β, TNF-α), oxidative stress, Aβ, LPS, phorbol esters, etc.

Nucleus

Target genes

mRNA

Inflammatory proteins

Inflammatory cytokines (IL-1β, IL-6, TNF-α), chemokines, adhesion molecules, COX-2, etc
## Immunostaining of Alzheimer’s-related Pathological Markers

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<tr>
<th></th>
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<th>Aβ (25-35)/Vehicle</th>
<th>Aβ (25-35)/PDTC</th>
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Inflammation: COX-2

**Reactivity Grade**

- COX-2 Dentate Gyrus

- DG

- Sham/Vehicle
- Aβ (25-35)/Vehicle
- Aβ (25-35)/PDTC

**Legend**

- a,b (*)&
- c (*)

**Notes**

- 100 μm
Behavioral Testing Results

Aβ25-35/Vehicle (n = 8)

Aβ25-35/PDTC (n = 9)

The change in latency from trial 15 of test to trial 14 of training

Legend:
- Sham/Vehicle
- Sham/PDTC
- Aβ25-35/Vehicle
- Aβ25-35/PDTC

Statistical significance:
- a, b (**)
- c (*)
Fluorescent Stain – Cerebral Blood Vessels (1)

Aβ (FITC)  VCAM-1 (TR)  Merge Image

CBV  CBV  CBV

Aβ 25-35
Summary: Animal Models

- Efficient, reproducible model of Alzheimer-like pathology with progressive neurdegeneration & cognitive impairment
- Combination beta amyloid toxicity and cerebral ischemia: enhanced pathology, neuroinflammation, cognitive impairment and infarct size
- NFkappaB inhibition prevents pathological and cognitive deficits
- Combinations of models required (Alzheimer’s with diabetes, hypertension, and atherosclerosis)
• Vladimir Hachinski
• Shawn Whitehead
• John Kiernan
• Guangliang Cheng
Preclinical Assessment of New Therapies

• Anti-inflammatory?
• Anti-oxidant?
• Upregulation of gap junctions?
• Enhanced neurogenesis?
• Cholinergic (cholinesterase inhibitors)?
• Amyloid lowering agents?
Future

• Multiple animal models

• Diverse group of collaborators to assess most of the key mechanisms of neurodegeneration: David Hill, Rob Bartha, Ting Lee, Peter Cain, Edith Arany, David Munoz, Stephen Pasternak, Vladimir Hachinski

• Clinical affiliation for translational research (Vladimir Hachinski)