Translational Research: Inflammation and post-stroke cognitive decline

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Associate Professor
Stanford Medical School
Disclosures

- Research contract with Biogen
- Funding from NINDS, MJFF, Wu Tsai Neurosciences Institute, AHA, Allen Foundation
- Advisory Board, Omniox
Talk Outline

• Definitions: Post-stroke dementia vs. vascular dementia

• Hypothesis: Is post-stroke dementia an immune-mediated neurodegenerative disease?

• Mechanism: Mouse model of post-stroke dementia

• In progress: Testing the model in humans

• Relationship to other dementias
What is vascular dementia?
Ischemic /stroke (vascular) lesions

White matter disease (periventricular vs. subcortical)

Large Vessel

Microbleeds

Lacunar

Ischemic /stroke (vascular) lesions

White matter disease
(periventricular vs. subcortical)

Large Vessel

Multi-infarct Dementia

Microbleeds (CAA) ICH

Lacunar

Post-stroke dementia lesions

White matter disease (periventricular vs. subcortical)

Large Vessel

Multi-infarct Dementia

Microbleeds CAA ICH

Lacunar

Post-Stroke Dementia

• Stroke doubles the risk of developing dementia in the decades after a stroke

• This is **incident** dementia after accounting for common / known risk factors of dementia (age, HTN, NIDDM, diet, exercise, tobacco)

• Absolute risk and relative risk depends on age

• Unclear mechanism with unknown risk factors

Savva, et al. 2010 *Stroke, 41*(1), e41-e46.
Corraini et al. Stroke. 2017;48:00-00. DOI: 10.1161/STROKEAHA.116.015242
Framingham sub-study

Framingham sub-study

Framingham sub-study

Cognitive trajectory after stroke-REGARDS cohort

Cognitive trajectory after stroke-REGARDS cohort

Incident delayed cognitive decline is high after intracerebral hemorrhage

Figure 2. Incident Delayed Cognitive Decline Among Patients Experiencing Intracerebral Hemorrhage (ICH)

Biffi et al, 2016. JAMA 73(8):969-976
Delayed cognitive decline after ICH is not related to ICH volume or location

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Post-ICH Dementia Risk, HR (95% CI)</th>
<th>Early</th>
<th>P Value</th>
<th>Delayed</th>
<th>P Value</th>
<th>P Value for Heterogeneity</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>619</td>
<td></td>
<td>435</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of patients</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age</td>
<td>1.02 (1.00-1.04)</td>
<td>.03</td>
<td>1.01 (1.00-1.01)</td>
<td>.05</td>
<td>.78</td>
<td></td>
</tr>
<tr>
<td>Educational level (≥10 y)</td>
<td>0.89 (0.61-1.30)</td>
<td>.55</td>
<td>0.60 (0.40-0.89)</td>
<td>.01</td>
<td>&lt;.001</td>
<td></td>
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<tr>
<td>African American race</td>
<td>1.22 (0.96-1.55)</td>
<td>.11</td>
<td>1.48 (1.09-2.02)</td>
<td>.01</td>
<td>.55</td>
<td></td>
</tr>
<tr>
<td>Incident mood symptoms</td>
<td>0.66 (0.04-11.11)</td>
<td>.77</td>
<td>1.29 (1.02-1.63)</td>
<td>.04</td>
<td>.01</td>
<td></td>
</tr>
<tr>
<td>ICH volume (per 10-mL increase)</td>
<td>1.47 (1.09-1.97)</td>
<td>.01</td>
<td>1.10 (0.70-1.73)</td>
<td>.68</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Lobar ICH location</td>
<td>2.04 (1.06-3.91)</td>
<td>.03</td>
<td>1.33 (0.25-7.03)</td>
<td>.74</td>
<td>.02</td>
<td></td>
</tr>
<tr>
<td>CT-WMD severity</td>
<td>1.34 (0.23-7.76)</td>
<td>.74</td>
<td>1.70 (1.07-2.71)</td>
<td>.03</td>
<td>.04</td>
<td></td>
</tr>
</tbody>
</table>

Biffi et al, 2016. JAMA 73(8):969-976
Risk of dementia after stroke in large Danish cohort

- Population-based cohort from national medical databases
- Included all Danish citizens with first time stroke between Jan 1989-Dec 2013
- Observed over 30 years, avg. 5 year f/u
- 279,349 patients with first ever stroke vs. 1,075,558 general population

Corraini et al, Stroke 2017. https://doi.org/10.1161/STROKEAHA.116.015242
Effect of stroke subtype on post-stroke dementia risk

<table>
<thead>
<tr>
<th>Ischemic stroke</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>1.72 (1.66, 1.77)</td>
</tr>
<tr>
<td>First adjusted model</td>
<td>1.66 (1.60, 1.71)</td>
</tr>
<tr>
<td>Second adjusted model</td>
<td>1.66 (1.60, 1.72)</td>
</tr>
<tr>
<td>Third adjusted model</td>
<td>1.62 (1.57, 1.68)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Intracerebral hemorrhage</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>2.70 (2.53, 2.89)</td>
</tr>
<tr>
<td>First adjusted model</td>
<td>2.66 (2.48, 2.86)</td>
</tr>
<tr>
<td>Second adjusted model</td>
<td>2.67 (2.49, 2.87)</td>
</tr>
<tr>
<td>Third adjusted model</td>
<td>2.51 (2.33, 2.70)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Subarachnoid hemorrhage</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unadjusted model</td>
<td>2.74 (2.45, 3.06)</td>
</tr>
<tr>
<td>First adjusted model</td>
<td>2.70 (2.41, 3.02)</td>
</tr>
<tr>
<td>Second adjusted model</td>
<td>2.68 (2.39, 3.00)</td>
</tr>
<tr>
<td>Third adjusted model</td>
<td>2.56 (2.28, 2.88)</td>
</tr>
</tbody>
</table>

https://doi.org/10.1161/STROKEAHA.116.015242
Effect of age on post-stroke dementia risk

https://doi.org/10.1161/STROKEAHA.116.015242
Cardiovascular Health Study – disability trajectories after stroke

Dhamoon et al, 2017 JAMA Neurology (74):12, 1439-1445
What can we learn from prior trials about the causes of post-stroke cognitive decline & dementia?

- **Negative**
  - Blood pressure lowering – PRoFESS w telmisartan
  - Statins – simvastatin (HPS) or pravastatin (PROSPER)
  - IRIS - pioglitazone (JNNP 2018; 89(1), 21-27.)
  - SPS3 – BP reduction+2 anti-plt (Lancet Neuro, 2014; 13(12), 1177-1185.)
  - PODCAST – intensive BP and lipid lowering (PlosOne 2017, 12(1), e0164608)

- **Positive**
  - ARTEMIDA – calf serum derivative, unclear mechanism. 250 treatment, 250 placebo, less ADAS-Cog decline (Stroke 2017;48:1262-1270)
  - PROGRESS trial BP lowering w perindopril

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Antigens and autoimmunity after stroke

• Neuronal and glial proteins go up in the blood after stroke (NSE, GFAP, S100B)

• “Adjuvant” effects reported for non-cognitive outcomes
  – Rats given LPS at reperfusion
    • More proinflammatory Th1 responses to MBP, (66.7% versus 22.2)
    • More profound and persistent neurologic deficits than non-LPS-treated animals.
  – Humans with an infection within 15 days of stroke
    • more likely have a Th1 response to myelin basic protein and glial fibrillary acidic protein 90 days after stroke
    • More robust Th1 responses to myelin basic protein at 90 days were associated with a decreased likelihood of good outcome at 90 days (mRS), even after adjusting for baseline stroke severity and patient age (OR, 0.477; 95% CI, 0.244 to 0.935; P 0.031).

Becker, JCBFM 2005 & Becker, Stroke 2011
### Histopathological changes after human acute ischemic stroke

<table>
<thead>
<tr>
<th>Histopathological changes</th>
<th>n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrogliosis</td>
<td>114 (83)</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>31 (23)</td>
</tr>
<tr>
<td>Mononuclear inflammatory cells</td>
<td>61 (45)</td>
</tr>
<tr>
<td>Macrophages</td>
<td>103 (75)</td>
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</table>

\[ n = 137 \]

Histopathological changes after human acute ischemic stroke

<table>
<thead>
<tr>
<th>Histopathological changes</th>
<th>n (%)</th>
<th>Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Astrogliosis</td>
<td>114 (83)</td>
<td>2 days-53 years</td>
</tr>
<tr>
<td>Neutrophils</td>
<td>31 (23)</td>
<td>1–37 days</td>
</tr>
<tr>
<td>Mononuclear inflammatory cells</td>
<td>61 (45)</td>
<td>3 days–53 years</td>
</tr>
<tr>
<td>Macrophages</td>
<td>103 (75)</td>
<td>3 days–53 years</td>
</tr>
</tbody>
</table>

n = 137

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Modeling post-stroke dementia in a mouse

• Hypothesis: stroke -> chronic inflammation -> neurodegeneration / dementia

• Needed a mouse model that has no immediate cognitive impairment

Hypothesis: stroke $\rightarrow$ chronic inflammation $\rightarrow$ neurodegeneration / dementia
Cresyl violet shows no gross hippocampal cell loss
The stroke core contains immune cells 7 weeks after stroke

Doyle et al, J Neuroscience 2015
Hypothesis: stroke →
chronic inflammation →
neurodegeneration / dementia
Hippocampal LTP is normal 1 week after stroke and then progressively worsens

Doyle et al, J Neuroscience 2015
Object Location Task
Deficits appear between weeks 1 and 7 in the Object Location Task

Doyle et al, J Neuroscience 2015
Are B lymphocytes necessary for the cognitive deficit?
Anti-CD20-treated mice do not develop cognitive deficits

Doyle et al, J Neuroscience 2015
Post-Stroke Dementia Mouse Model

• Normal mice can develop delayed cognitive impairment after stroke
• This is associated with prolonged inflammation in the stroke core that includes B lymphocytes
• In the absence of B cells mice do not develop delayed cognitive impairment after stroke
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• Relationship to other dementias
There are more B lymphocytes in the stroke core in people with stroke and dementia than in the controls.

Doyle et al, J Neuroscience 2015
(collaboration with Julie Schneider at Rush)
There are also more T lymphocytes in the stroke core in people with stroke and dementia than in the controls.

Doyle et al, J Neuroscience 2015
(collaboration with Julie Schneider at Rush)
What about the relationship between post-stroke cognitive trajectory and autoantibodies? (CASIS Cohort)

• 58 prospectively enrolled adults with ischemic stroke admitted to Harborview Medical Center from 2005-2009
• 40 subjects with no history of stroke as controls
• Serum autoantibody titers to MBP were determined by ELISA
• Antibody titers >95th percentile of the control group at any timepoint were considered significant.
• MMSE tested at 30, 90, 180 and 365 days after stroke

Shibata et al, 2012; Becker & Buckwalter2016
Serum autoantibodies: High anti-MBP antibody titer was associated with increased risk of MMSE decline

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>IV tPA use (controlled for NIHSS)</td>
<td>3.88 (0.62, 24.14)</td>
<td>0.14</td>
</tr>
<tr>
<td>Age (per decade)</td>
<td>1.63 (0.59, 4.48)</td>
<td>NS</td>
</tr>
<tr>
<td>History of hypertension</td>
<td>4.34 (0.57, 32.95)</td>
<td>0.16</td>
</tr>
<tr>
<td>History of hyperlipidemia</td>
<td>1.03 (0.06, 24.14)</td>
<td>NS</td>
</tr>
<tr>
<td>Myelin basic protein (MBP) antibody titer &gt;95% controls</td>
<td>9.02 (1.18, 68.90)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

MMSE=mini-mental state exam, OR=odds ratio, CI=confidence interval, IV tPA=intravenous tissue plasminogen activator, NS=P≥0.20

Becker et al, J Neuroimmunol, 2016
StrokeCog

• A 5 year prospective clinical cohort study through the Stanford Stroke Recovery Program, first funded by the Wu Tsai Neurosciences Institute, now by an AHA/Allen Brain Health Initiative
• Goal 200 patients 6-12 months after ischemic stroke
• Yearly: level one cognitive battery, depression and fatigue scales, diet questionnaire, blood for CyTOF, plasma and serum
• Sister studies for additional immune biomarkers: StrokeCog LP (N=50) and StrokeCog PET (N=10)
CyTOF: Can we detect peripheral immune signatures after stroke?

(38 antibodies, 27 cell surface and 11 intracellular markers)

Tsai et al., Brain 2019
Immunization & role of adjuvants

https://www.invivogen.com/review-vaccine-adjuvants
Immunization & role of adjuvants

Does the peripheral immune response act as an adjuvant after stroke?

And can we even detect an effect of stroke on the peripheral immune response?

https://www.invivogen.com/review-vaccine-adjuvants
CyTOF: Can we detect peripheral immune signatures after stroke?

(38 antibodies, 27 cell surface and 11 intracellular markers)

Tsai et al., Brain 2019
Mass Cytometry

Brice Gaudilliere

Nima Aghaeepour

Grant, 2011, The Scientist
<table>
<thead>
<tr>
<th>Subject</th>
<th>Days</th>
<th>Stroke Size (cc)</th>
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<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>6.5</td>
</tr>
<tr>
<td>2</td>
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<td>37.6</td>
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<td>3</td>
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<td>1</td>
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<td>4</td>
<td>3</td>
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<td>5</td>
<td>5</td>
<td>1</td>
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<td>6</td>
<td>7</td>
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<td>7</td>
<td>14</td>
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<td>8</td>
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<td>1</td>
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<td>9</td>
<td>90</td>
<td>1</td>
</tr>
<tr>
<td>10</td>
<td>365</td>
<td>1.2</td>
</tr>
<tr>
<td>11</td>
<td></td>
<td>14.5</td>
</tr>
<tr>
<td>12</td>
<td></td>
<td>1</td>
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<tr>
<td>13</td>
<td></td>
<td>9</td>
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<tr>
<td>14</td>
<td></td>
<td>18.5</td>
</tr>
<tr>
<td>15</td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>16</td>
<td></td>
<td>47.3</td>
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<tr>
<td>17</td>
<td></td>
<td>59.6</td>
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<td>12.3</td>
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<td>22</td>
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<td>16.7</td>
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<tr>
<td>23</td>
<td></td>
<td>101.1</td>
</tr>
<tr>
<td>24</td>
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<td>1</td>
</tr>
<tr>
<td>25</td>
<td></td>
<td>1</td>
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</tbody>
</table>

Tsai et al., Brain 2019
Elastic Net Models

Tsai et al., Brain 2019
EN1 model top values are highly inter-correlated
Subject-to-subject variability

Tsai et al., Brain 2019
How does the d2 inflammatory response compare to the post-surgical immune response?

Tsai et al., Brain 2019
Acute phase EN model

Tsai et al., Brain 2019
Acute phase EN model predicts stroke size

Tsai et al., Brain 2019
Acute phase EN model predicts change in cognition

Tsai et al., Brain 2019
Acute phase EN model predicts change in cognition

Tsai et al., Brain 2019
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Lovestone, 1998

Infarcts and vascular pathology in old brains

Religious Orders Study
Rush Memory and Aging Project
(>65 age longitudinal study)

1143 brains
age 84-93

Pathological analysis

No dementia
43% with infarcts
67% with vascular pathology

Alzheimer’s disease
56% with infarcts
78% with vascular pathology

Schneider, Bennett 2016
Buckwalter lab:
Kristian Doyle
Kristy Zera
Judy Zhu
Lisa Quach
Kendra Lechtenberg
Tawaun Lucas
Evan Brahms

Stanford Stroke Recovery Program:
Maarten Lansberg
Elizabeth Osborn
Michael Sharp
Emily Huang
Alay Parikh
Kara Flavin

Stanford Collaborators:
Brice Gaudilliere
Nima Aghaeepour
Amy Tsai
Rob Malenka
Gilberto Soler-Llavinia
Sandra Jurardo
Michelle James
Aisling Chaney
Marc Stevens

Beth Mormino
Greg Zaharchuk
Audrey Fan
Tony Wyss-Coray
Hanadie Yousef
Frank Longo
Vivian Nguyen
Rush University ADRC
Julie Schneider
University of Washington
Kyra Becker

Funding
American Heart Association
NIH-NINDS, NINR,
NIA/Stanford ADRC
Wu Tsai Neurosciences Institute
Plasma cells are also present in the stroke core

Doyle et al, J Neuroscience 2015
At 7 weeks after stroke, IgG is present in the tissue surrounding the stroke lesion

Doyle et al, J Neuroscience 2015
Is it valid to use d365 as baseline?

Figure S2. EN components in patients one year after stroke compared to a control cohort.

Tsai et al., Brain 2019
Becker et al, J Neuroimmunol, 2016

<table>
<thead>
<tr>
<th>Patient Characteristics</th>
<th>Entire Cohort N=58</th>
<th>MMSE decrease by ≥2</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No N=48</td>
<td>Yes N=10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>52 (42, 63)</td>
<td>49 (41, 62)</td>
</tr>
<tr>
<td>Sex (female)</td>
<td>21/58 (36%)</td>
<td>18/48 (38%)</td>
</tr>
<tr>
<td>Past medical history</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>25/58 (43%)</td>
<td>18/48 (38%)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>39/58 (67%)</td>
<td>30/48 (62%)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>12/48 (25%)</td>
<td>9/48 (19%)</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8/56 (14%)</td>
<td>7/48 (15%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13/58 (22%)</td>
<td>10/48 (21%)</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>17/58 (29%)</td>
<td>16/48 (33%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Stroke Characteristics</th>
<th>Entire Cohort N=58</th>
<th>MMSE decrease by ≥2</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>No N=48</td>
<td>Yes N=10</td>
</tr>
<tr>
<td>NIHSS score</td>
<td>8 (3, 14)</td>
<td>7 (3, 14)</td>
</tr>
<tr>
<td>Infarct volume (cc)</td>
<td>4.6 (0.5, 46.9)</td>
<td>4.1 (0.4, 43.5)</td>
</tr>
<tr>
<td>Treatment with IV tPA</td>
<td>14/48 (29%)</td>
<td>9/48 (19%)</td>
</tr>
<tr>
<td>Serum Antibodies</td>
<td>Entire Cohort N=58</td>
<td>MMSE decrease by ≥2</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------</td>
<td>---------------------</td>
</tr>
<tr>
<td></td>
<td>No N=48</td>
<td>Yes N=10</td>
</tr>
<tr>
<td><strong>Brain</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myelin basic protein &gt;95% control</td>
<td>13/58 (22%)</td>
<td>7/48 (15%)</td>
</tr>
<tr>
<td>Proteolipid protein &gt;95% control</td>
<td>10/58 (17%)</td>
<td>8/48 (17%)</td>
</tr>
<tr>
<td><strong>Anti-phospholipid</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anticardiolipin IgM positive</td>
<td>26/58 (44%)</td>
<td>21/48 (44%)</td>
</tr>
<tr>
<td>Anticardiolipin IgG positive</td>
<td>10/58 (17%)</td>
<td>7/48 (15%)</td>
</tr>
<tr>
<td>β-2-glycoprotein IgG positive</td>
<td>6/58 (10%)</td>
<td>6/48 (12%)</td>
</tr>
<tr>
<td>Tetanus toxin (TT) &gt;95% control</td>
<td>9/58 (16%)</td>
<td>9/48 (19%)</td>
</tr>
</tbody>
</table>

Becker et al, J Neuroimmunol, 2016
Is the delayed cognitive dysfunction due to hypoxia?

DH stroke in C57BL/6J  DMCAO in BALB/c

Doyle et al, J Neuroscience 2015
Delayed cognitive dysfunction is not due to hypoxia.

Doyle et al, J Neuroscience 2015
MCAO (Suture Model)

Doyle et al, J Neuroscience 2015
Are B lymphocytes responsible for the cognitive deficit?
Validation of muMT mice
MuMT mice do not get delayed OLT impairment

Doyle et al, J Neuroscience 2015
Anti-CD20 Antibody treatment 5 days after stroke ablates B cells

Doyle et al, J Neuroscience 2015
Stroke-induced Immunodepression

Dirnagl et al, Stroke. 2007;38(part 2):770-773
Stroke-induced Immunodepression

Infection
Microbiota differences

Becker Stroke 2011
Sadler Brain Behav Imm 2017
Dirnagl et al, Stroke. 2007
Y-maze performance deteriorates between weeks 1 and 7 after stroke.
DH stroke

Inflammation 7 weeks after stroke

Sham cortex
- Contralateral
- Ipsilateral

Stroke cortex
- Contralateral
- Ipsilateral

Gene expression heatmap showing cytokines and chemokines expression in contralateral and ipsilateral cortices.