Mr Andrew Clarkson

Senior Research Fellow

University of Otago

Saturday, August 10, 2019

(Plenary)

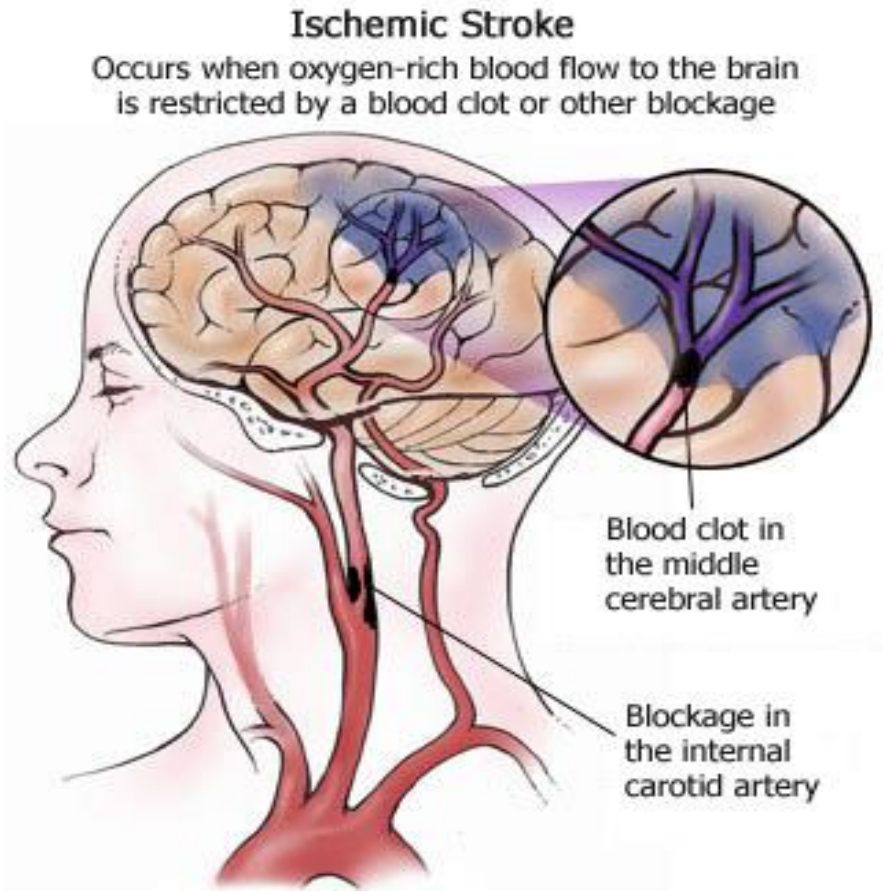
9:50 - 10:05 Novel Pharmacologic Treatments for Stroke Recovery

Novel Pharmacological Treatments for Stroke Recovery

Dr. Andrew Clarkson

Department of Anatomy, University of Otago, Dunedin
Brain Research New Zealand CoRE,
MedTech New Zealand CoRE,
Brain Health Research Center, University of Otago, Dunedin

Stroke



- In NZ about 9,000 people will have a stroke
- Stroke is the 3rd leading cause of adult death in worldwide
- ≈80% of stroke victims survive their stroke
- Most survivors are disabled in some way
- Stroke is thus the leading cause of serious and long term adult disability
- In NZ alone we currently have >60,000 stroke survivors

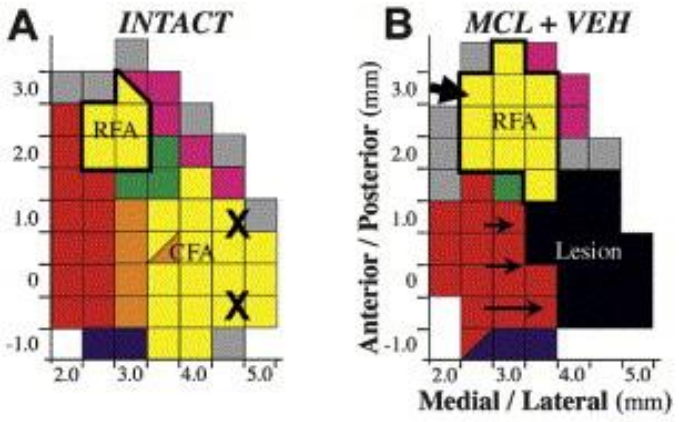
Post stroke disability is largely due to the disruption of axonal and dendritic connections and imbalance between excitation and inhibition throughout the brain.

Repair after stroke

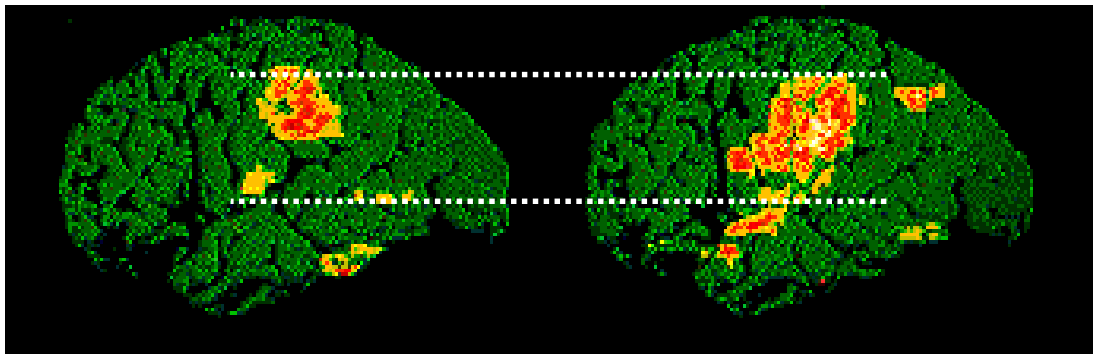
Spontaneous sprouting does occur and is correlated with functional recovery.

Changes in cortical activation patterns are altered following recovery of motor function after stroke in humans and rodents (Chollet et al,'91; Weiller et al., '93; Calautti et al '03; Cramer and Grafton, 2006; Takatsuru 2009; Conner et al, 2005).

Cortical areas distant from cortical ischemic infarct undergo neuroanatomical reorganization (Dancause et al., 2005).



Conner et al, 2005



Weiller et al. 1993

Can we assess changes in plasticity in animal models of stroke?

- Can results from basic science be translated into clinical practice?
- Can clinical observations be translated into relevant basic science experiments?

Pharmacological therapies that increase neuronal excitability show promise

LETTER

doi:10.1038/nature09511

Reducing excessive GABA–mediated tonic inhibition promotes functional recovery after stroke

Andrew N. Clarkson[1]*†, Ben S. Huang[1,2]*, Sarah E. MacIsaac[1], Istvan Mody[1,2,3] & S. Thomas Carmichael[1]

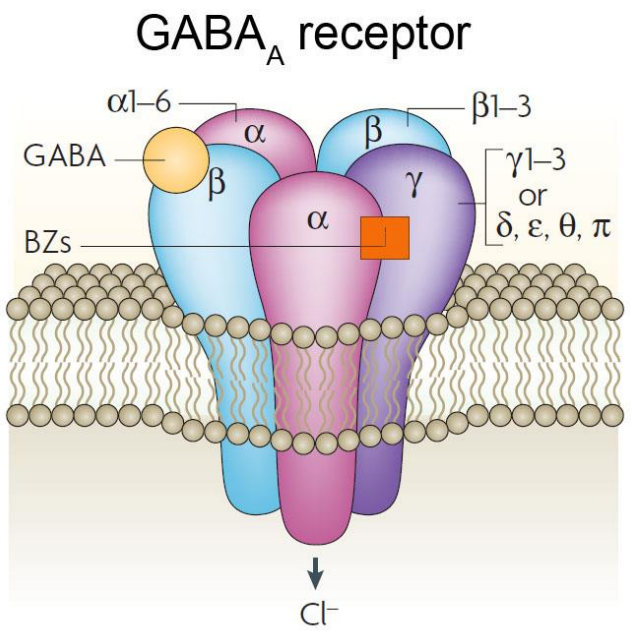
Development/Plasticity/Repair

AMPA Receptor-Induced Local Brain-Derived Neurotrophic Factor Signaling Mediates Motor Recovery after Stroke

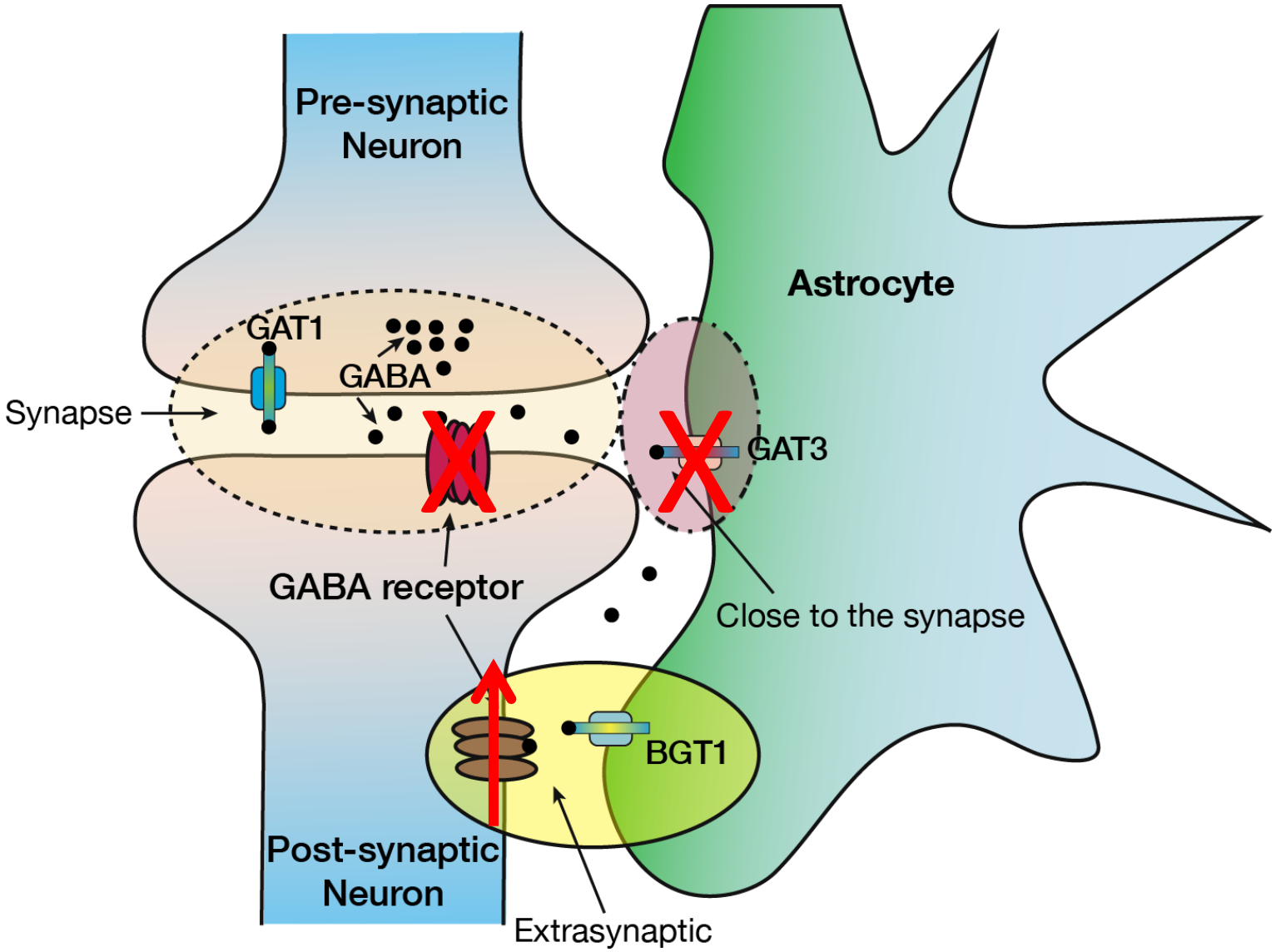
Andrew N. Clarkson,[1] Justine J. Overman,[1] Sheng Zhong,[2] Rudolf Mueller,[2] Gary Lynch,[3,4] and S. Thomas Carmichael[1]

[1]Department of Neurology, David Geffen School of Medicine, University of California, Los Angeles, Los Angeles, California 90095, [2]Cortex Pharmaceuticals, Inc., Irvine, California 92618, and Departments of [3]Psychiatry and Human Behavior and [4]Anatomy and Neurobiology, University of California, Irvine, Irvine, California 92697

GABA Receptors after stroke



Jacob et al., Nature Reviews Neuroscience, 2008



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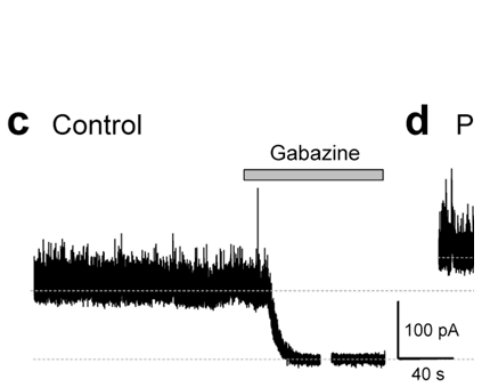
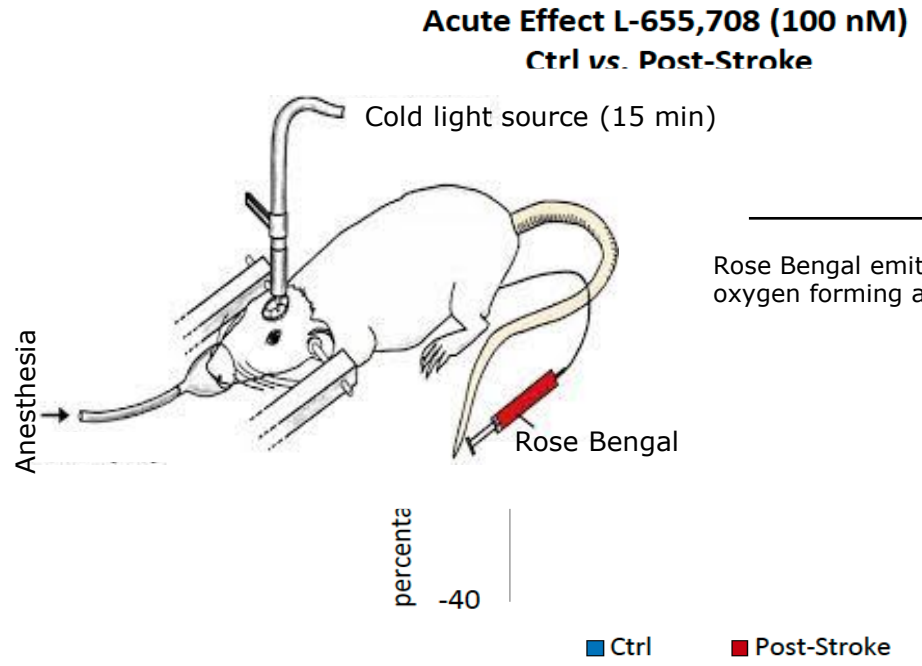
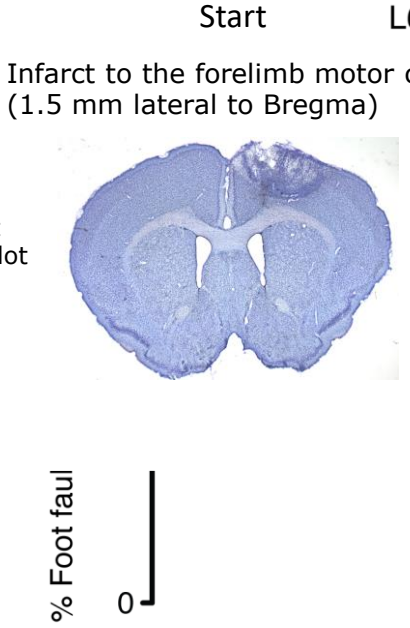
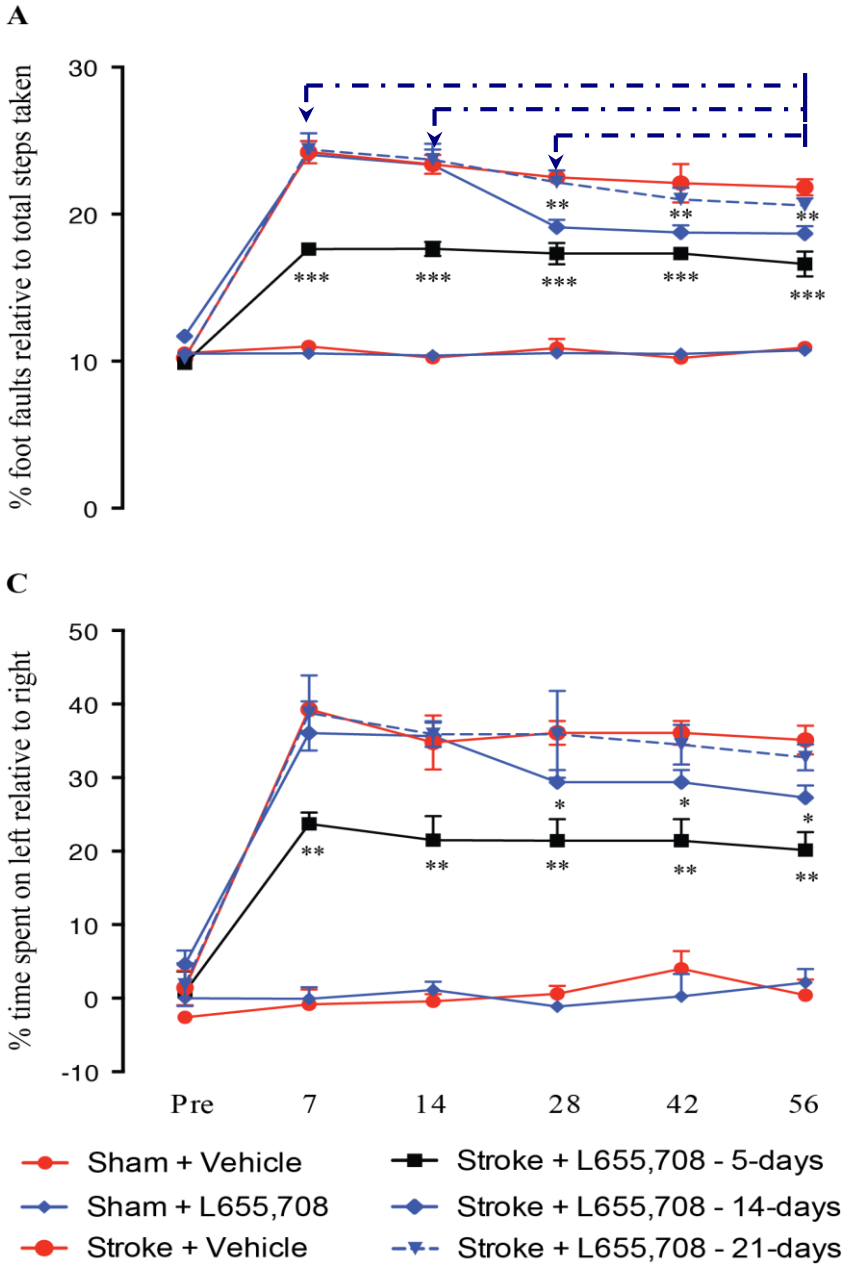




Rose Bengal emits singlet oxygen forming a blood clot



L655,708 therapeutic window



L655,708 facilitates early functional recovery

A. Clarkson; *et al,* manuscript submitted

Watch this space: phase IIb clinical trials

- Servier & Egis – trial in the UK & Australia
  - Developed on the back of our work
  - Started Oct 2016
  - Outcome expected in the next couple of months
- Hoffman La-Roche – trial in Europe (Basmisanil)
  - We did full preclinical testing
  - Young vs age; male vs female; three models of stroke
  - Start of 2017 – Discontinued end of 2017 (slow recruitment)
- Boehringer Ingelheim
  - Preclinical testing and Phase I trial have started and are running concurrently

RESTORE Brain Study

Randomised **E**fficacy and **S**afety **T**rial with **O**ral S44819 after **R**ecent ischaemic cerebral **E**vent

A there month international, multi centre, randomised, double-blind, placebo control, Phase II trial.

Treatment (placebo, or S44819 (150mg or 300mg bid) started 48hrs post-stroke

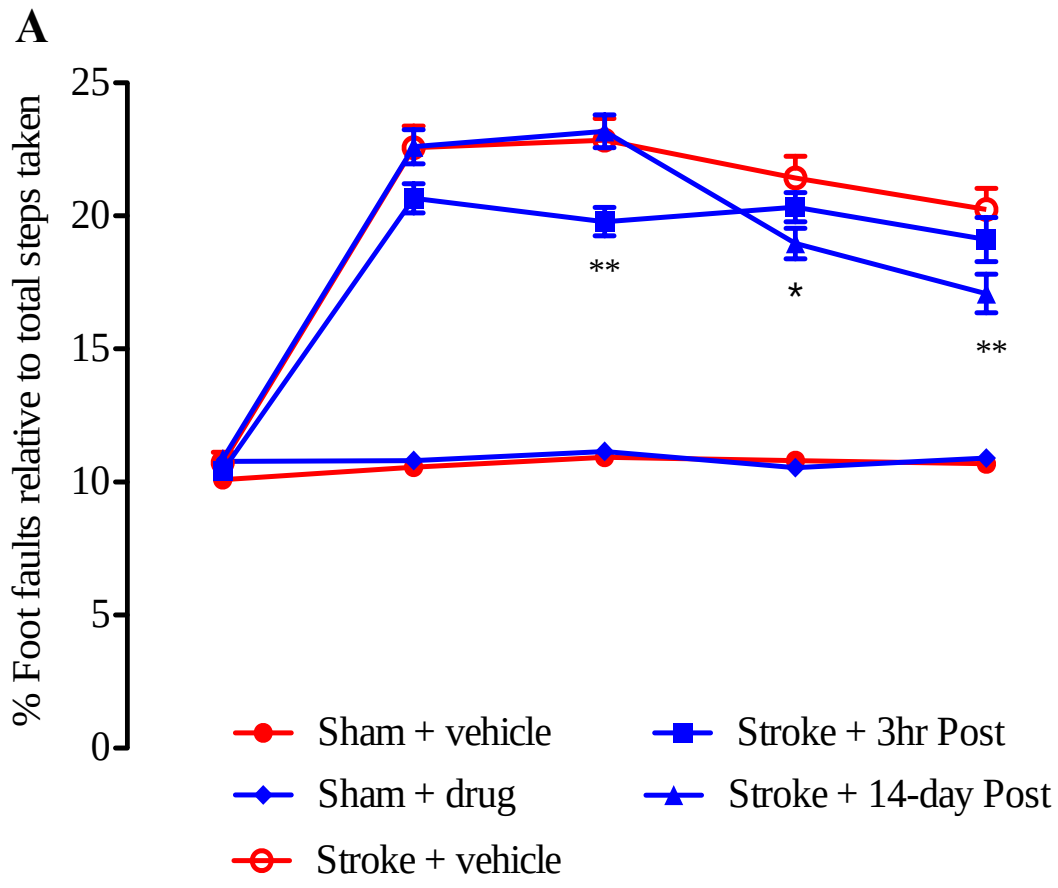
Evidence that modulating inhibition improves function following stroke?

Transient Improvement of Aphasia with Zolpidem

TO THE EDITOR: There is currently no effective pharmacologic treatment for chronic aphasia, a frequent and incapacitating consequence of hemispheric stroke. We report the case of a 52-year-old right-handed woman, who had a stroke that affected her left insula, putamen, and superior temporal gyrus. Three years later, her speech was still restricted to stereotyped syllables, with not a single identifiable word. Language comprehension was better preserved. Because of occasional insomnia, zolpidem (10 mg) was prescribed. To the amazement of the patient and her family, ingestion of the first dose was followed by a dramatic improvement in her speech, which persisted until the patient went to bed later in the night. On the following morning, aphasia had returned at its usual level of

Cohen et al, N Engl J Med 2004

Zolpidem improves functional recovery in aged



Clarkson, unpublished data

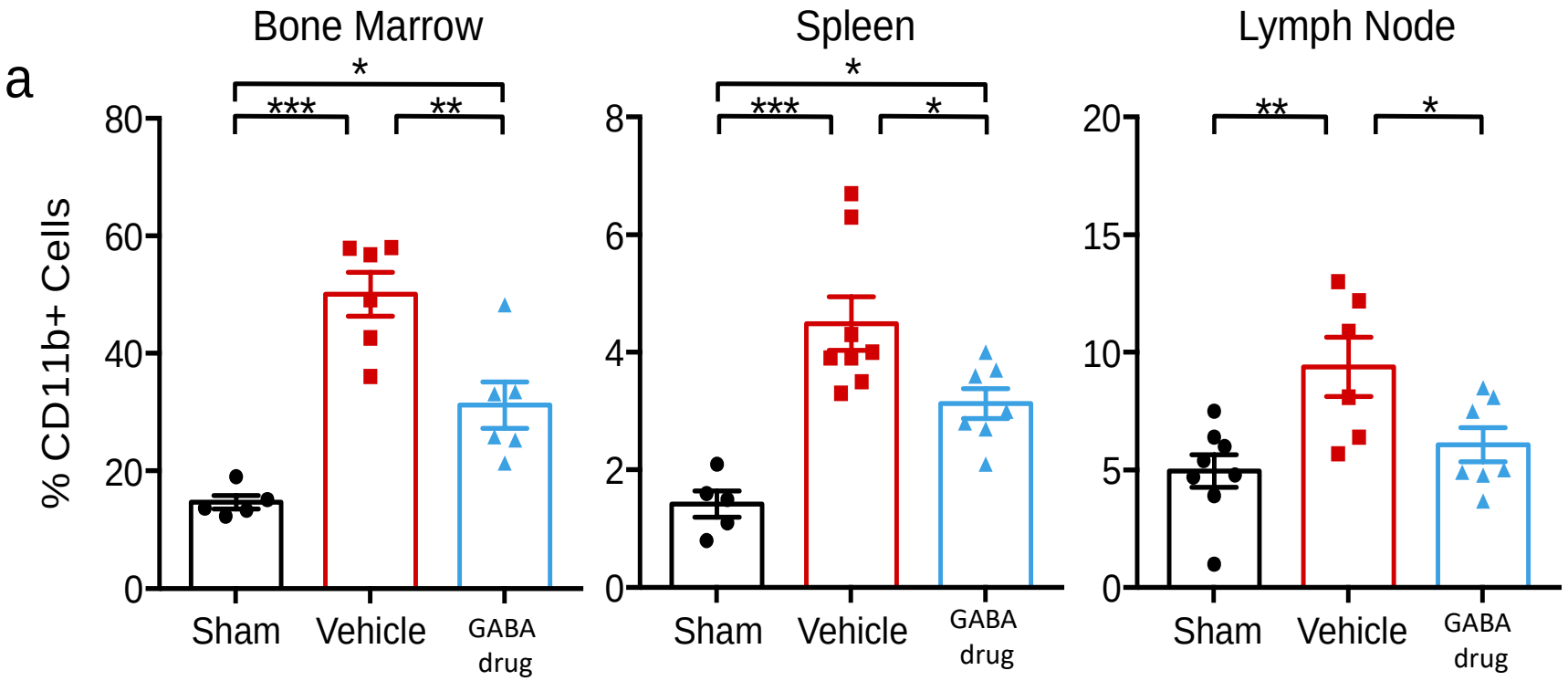
Dosing needs to be 10-100 fold lower the what is used clinically for insomnia.

- Not all z-drugs have the same effect.
- Zopiclone (Imovane) doesn't work
- Eszopiclone (Lunesta) more similar to zolpidem

Stroke is a whole body event

Peripheral immune cells infiltrate CNS from 2-3 post-stroke
- Macrophages and T and B-lymphocytes

Dampen circulating immune cells

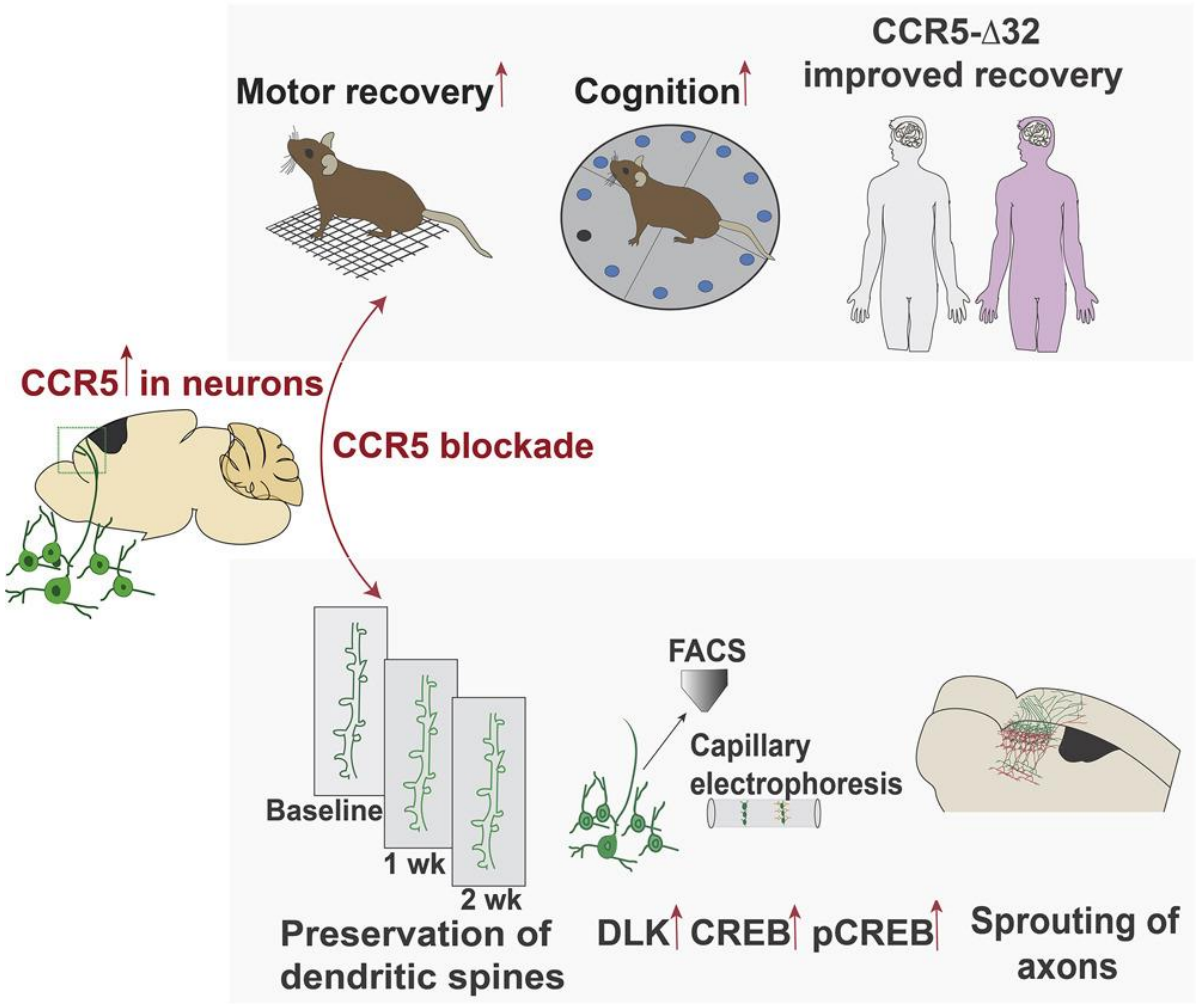


Specific GABA drugs can dampen circulating immune cells

Similar data when assessed 7 & 14 days post-stroke

Neumann, Barwick, Sobey, Clarkson, manuscript in preparation.

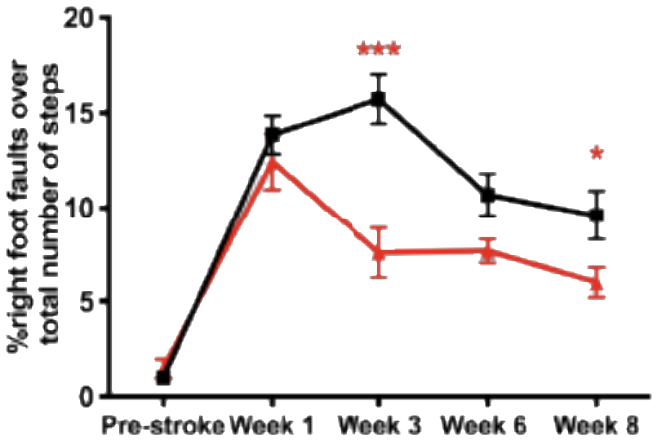
HIV drug, Maraviroc, improves recovery following stroke and TBI



- CCR5 is differentially upregulated in neurons after stroke
- Knockdown of CCR5 induces motor recovery after stroke and improves cognition after TBI
- Treatment with an FDA-approved drug, maraviroc induces recovery after stroke and TBI
- Human carriers for CCR5delta32 have better outcomes after stroke

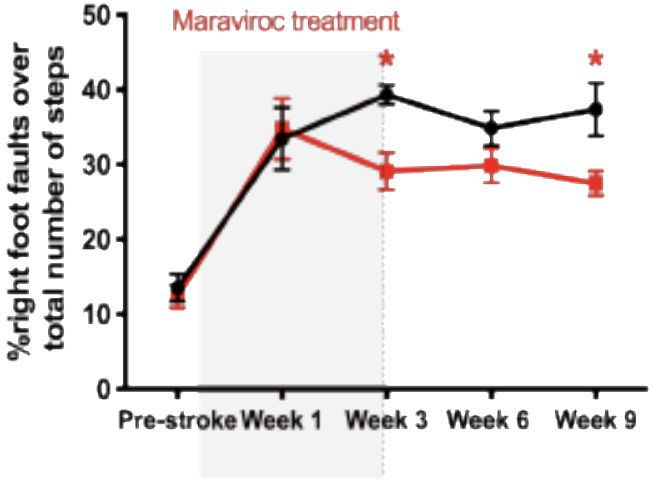
Joy…. Carmichael, 2019 Cell

HIV drug, Maraviroc, improves recovery following stroke and TBI



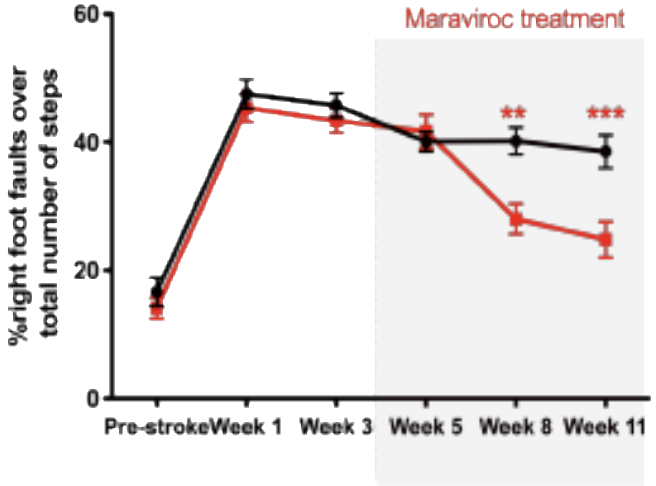
Treatment 24hrs after stroke

Maraviroc treatment induces improved motor recovery after stroke



Treatment 24hrs to 3weeks after stroke

Motor recovery is maintain following a 3week dose



Treatment from 4-11weeks after stroke

Initiation of treatment in chronic phase improves motor recovery

Maraviroc to Augment Rehabilitation Outcomes After Stroke (MAROS) ClinicalTrials.gov Identifier: NCT03172026

Joy…. Carmichael, 2019 Cell

Summary

- Three separate windows of treatment
- Increased GABA activity early looks to afford significant protection against cell death
- Acute window with L655,708 dosing is out to around 14-days post-stroke and corresponds to when we see secondary cell death in thalamic nuclei
- Zolpidem is effective in chronic stroke patients. Not all Z-drugs have the same effect. Zopiclone (Imovane) doesn't act like Zolpidem, but eszopiclone (Lunesta) maybe similar to zolpidem.
- Stroke is a whole body event
- GABA modulators can dampen circulating immune cells
- HIV drug, Maraviroc, improve motor and cognitive function following stroke and TBI
- Cyclosporine being fast-track for the treatment of traumatic head injury
  https://www.empr.com/home/news/drugs-in-the-pipeline/treatment-for-traumatic-brain-injury-gets-fdas-fast-track-status/

Acknowledgements

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