# Phases of Stroke Recovery:
# Cellular and Molecular Mechanisms


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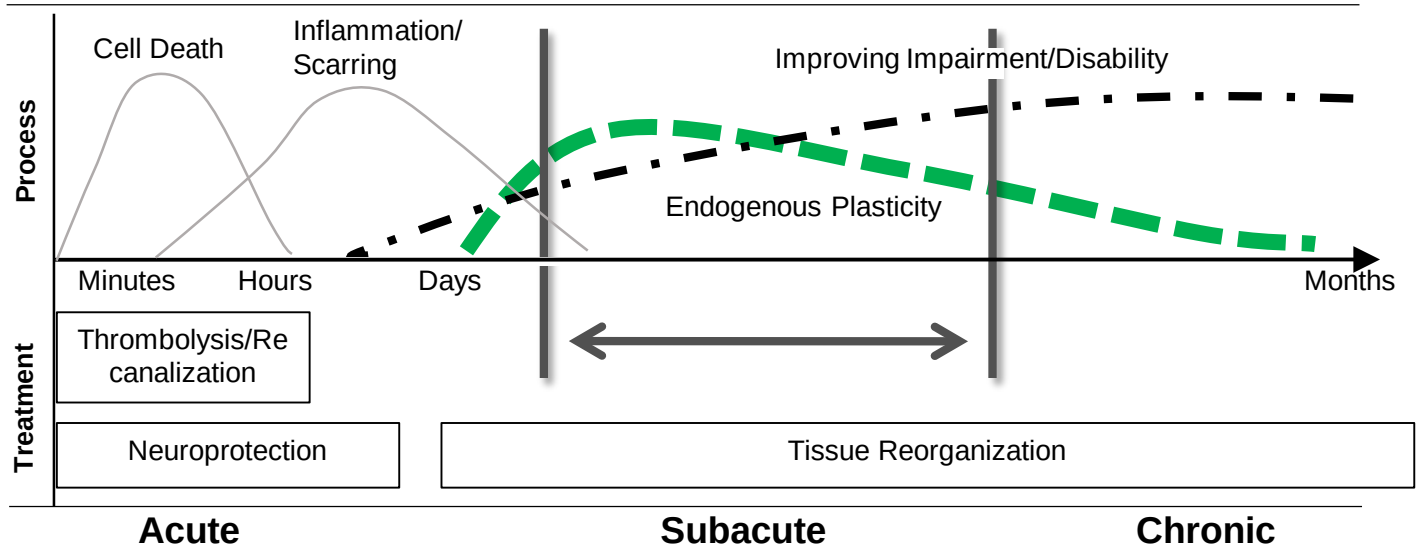
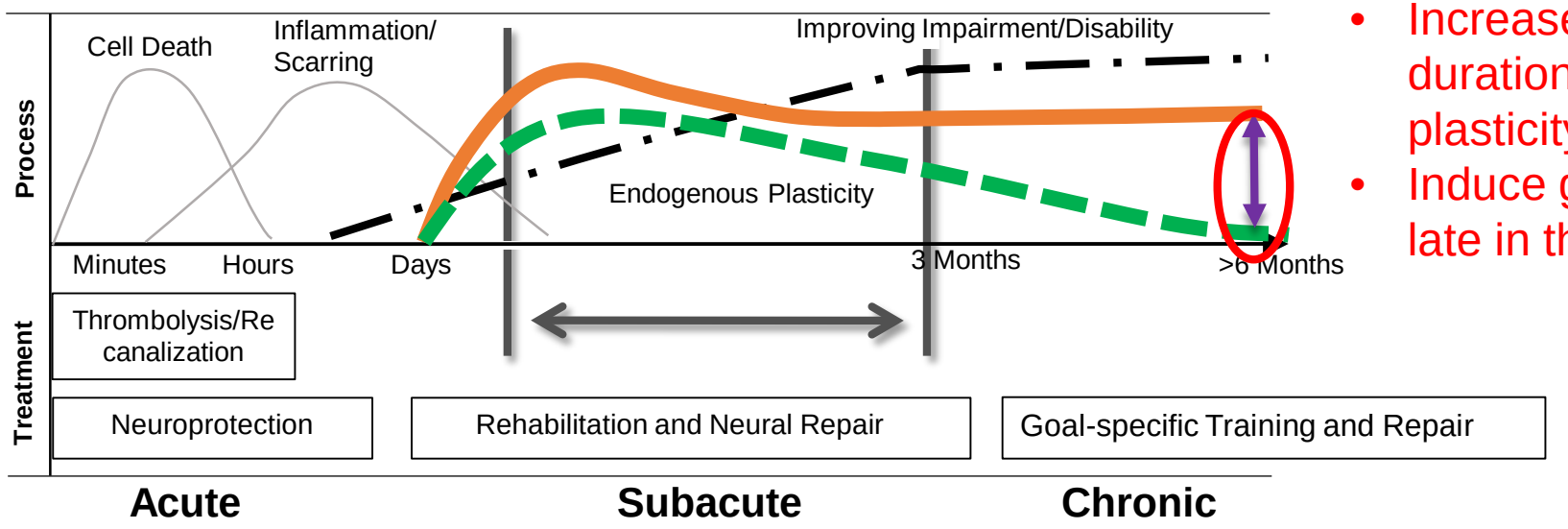
## Normal Progression of Stroke



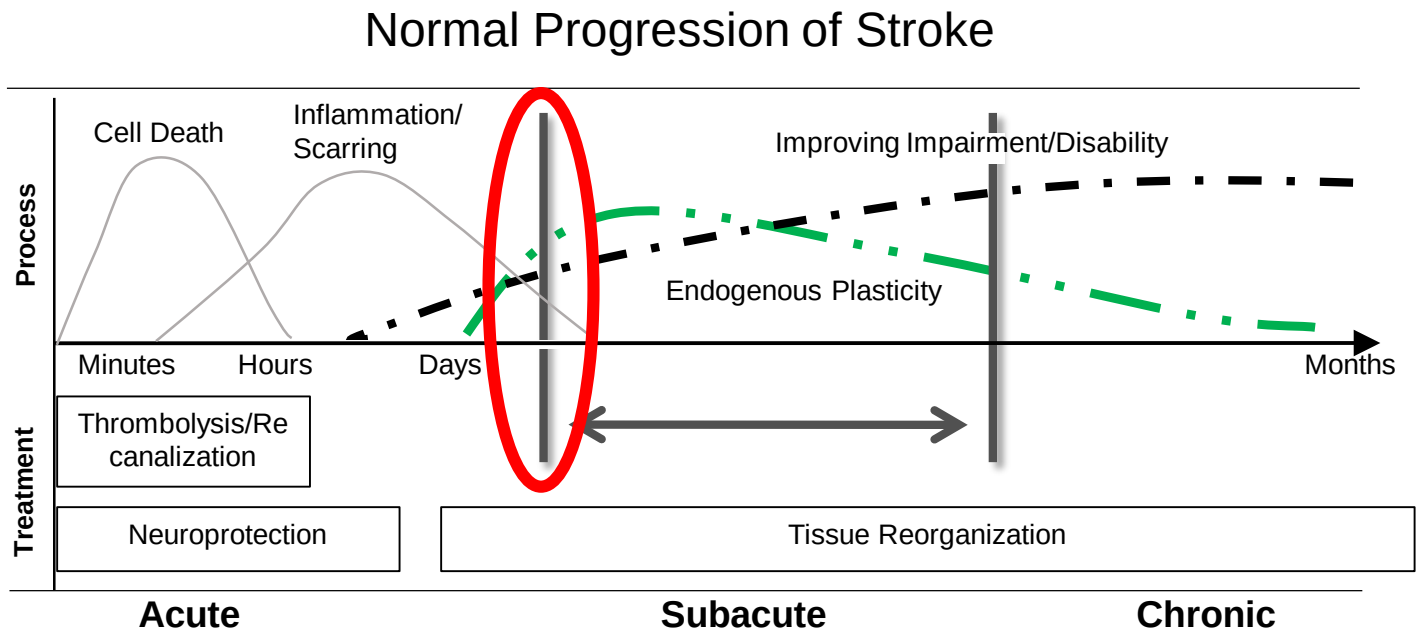

## Goals of Neural Repair Trials




Two goals in neural repair in stroke:

- Increase the amount or duration of early plasticity
- Induce greater plasticity late in the disease

# Defining the First Phase in Neural Repair: the Death to Repair Transition

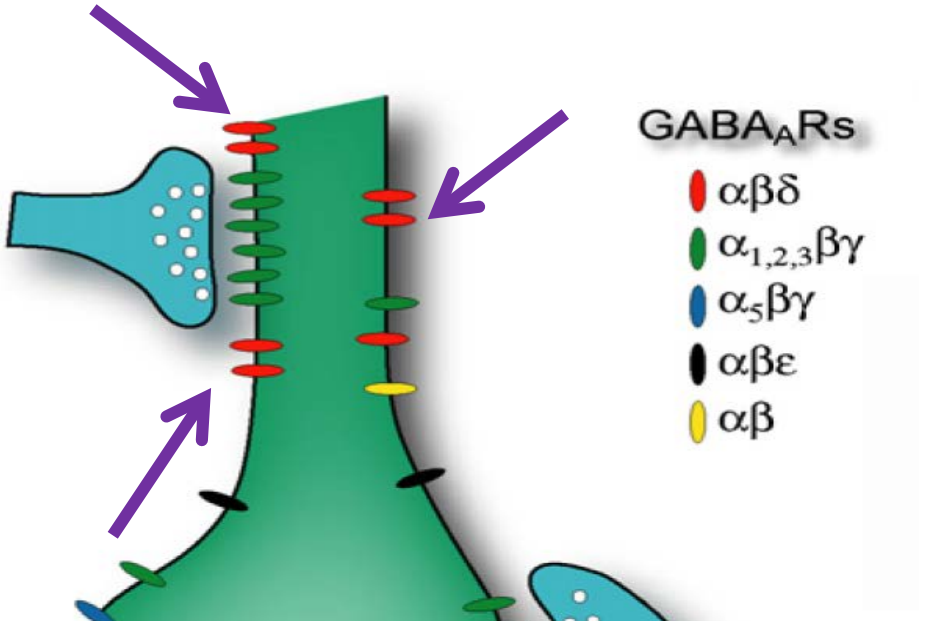



1. Stroke triggers initial hypoxia, excitotoxicity, reperfusion injury and inflammation (in that order)

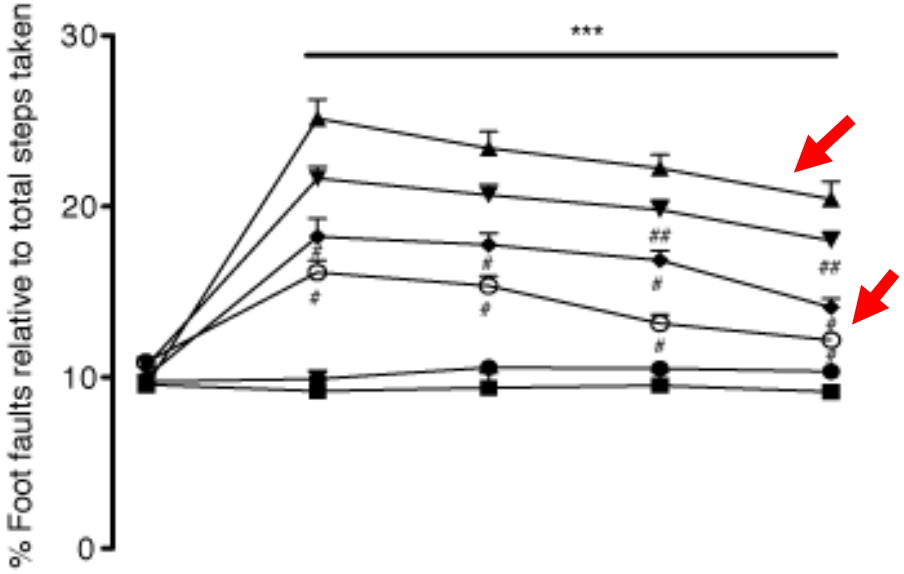
2. Recovery involves stimulating neuronal circuits, enhancing growth programs and demanding cellular energy

These two 2 processes will exacerbate each other if they overlap

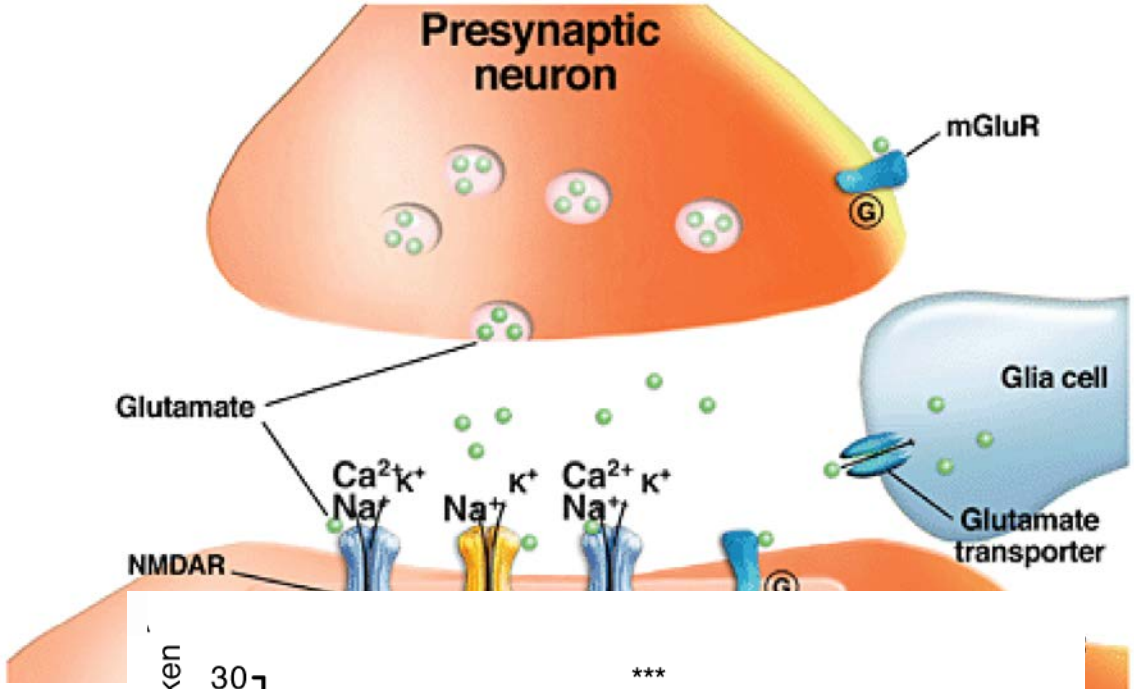
## Blocking Tonic GABA Inhibition

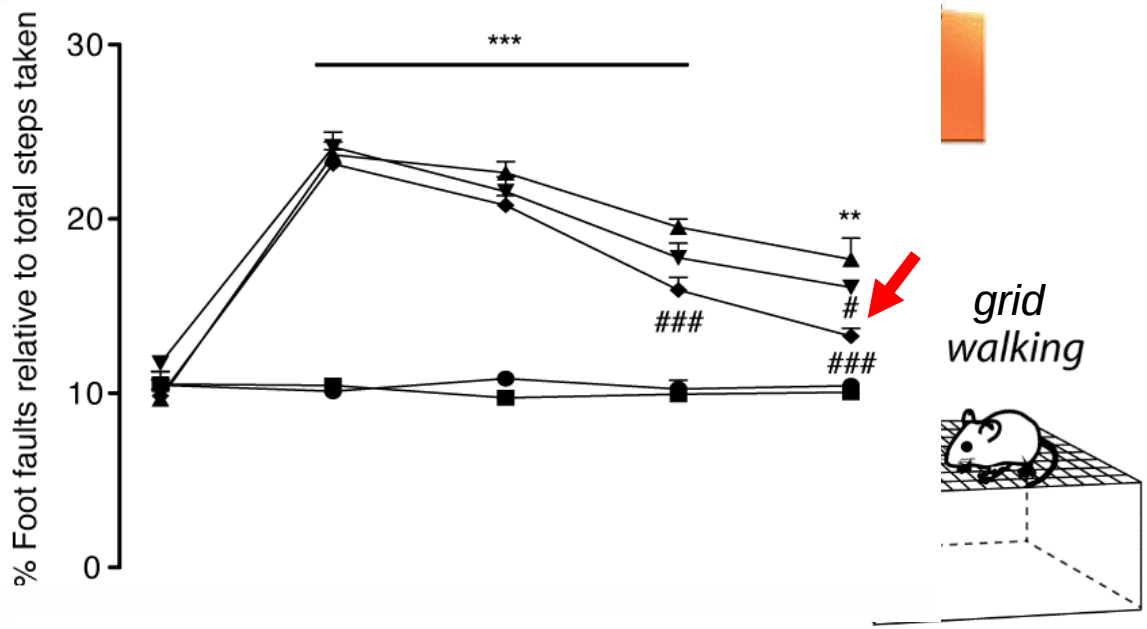



L655,708 treatment

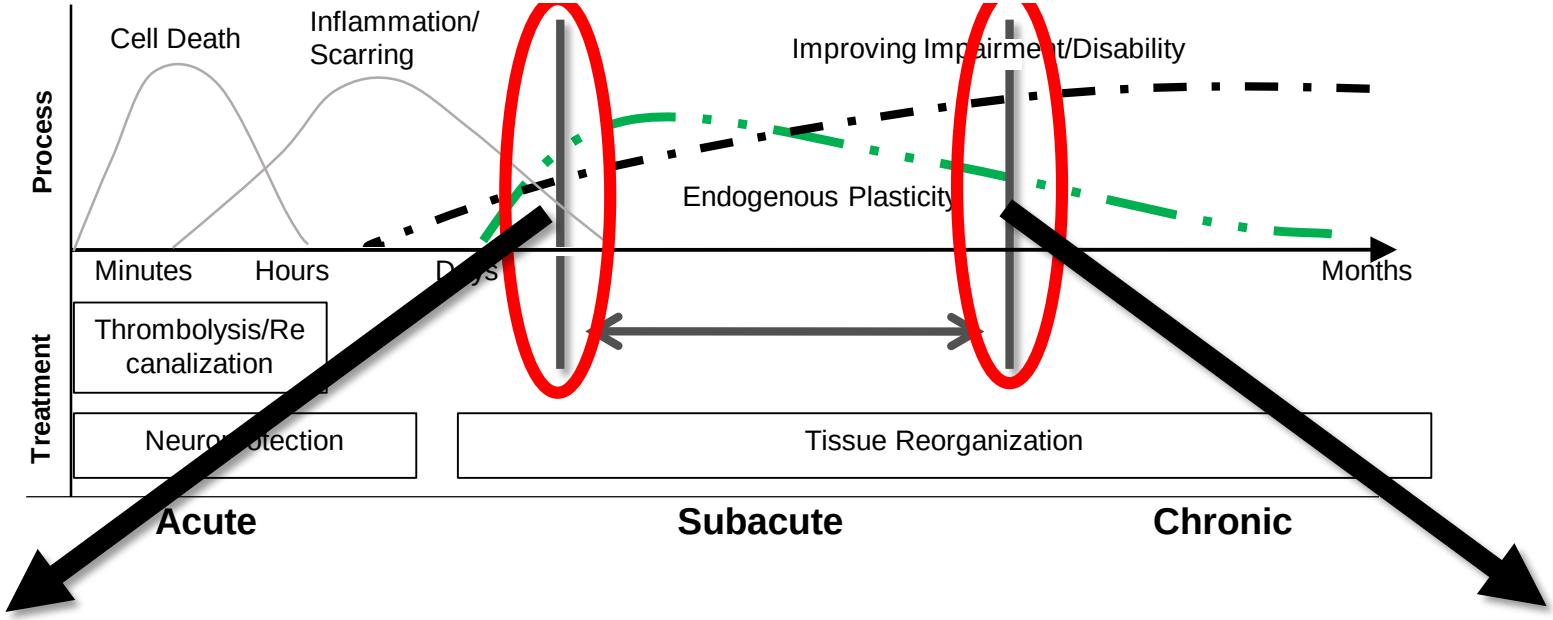


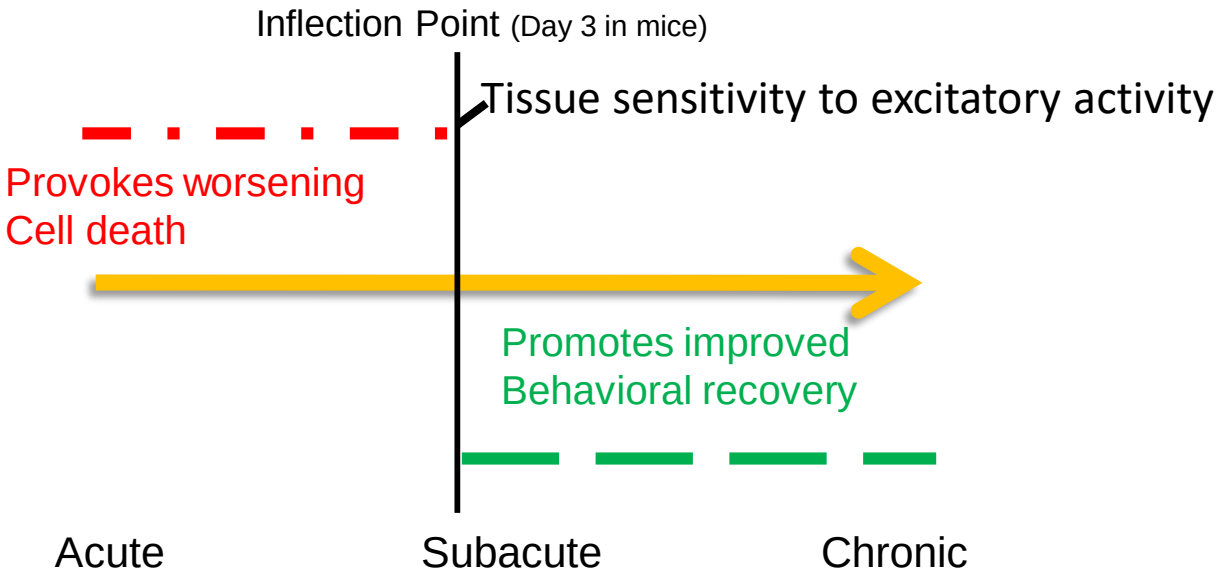

## Enhancing Glutamate Signaling (AMPAR signaling)



# Defining the Second Phase in Neural Repair: Endogenous Plasticity to Chronic Stage




What ends the sensitive period or the Subacute period of substantial recovery?

# Molecular Growth Programs in the Brain after Stroke

**Axonal Sprouting:** formation of new connections

**Neurogenesis:** formation of new neurons

**Gliogenesis:** formation of new astrocytes, OPCs, oligodendrocytes

**Angiogenesis:** formation of new blood vessels

**Synaptic plasticity:** changes in function of synaptic circuits without structural change in these circuits, changes in inhibitory control within these circuits

**Common features:**

--structural growth: growth cone, leading cellular edge, tip cell

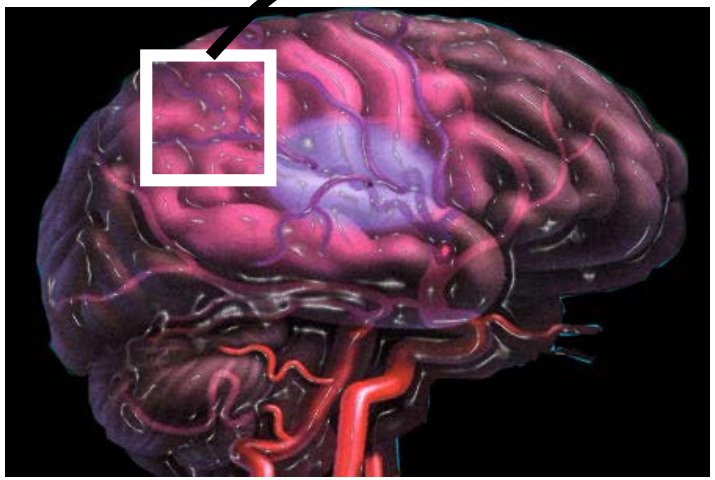
--interactions with other cells that are responding to stroke: neuronal, astrocyte, OPC, vascular interactions

=

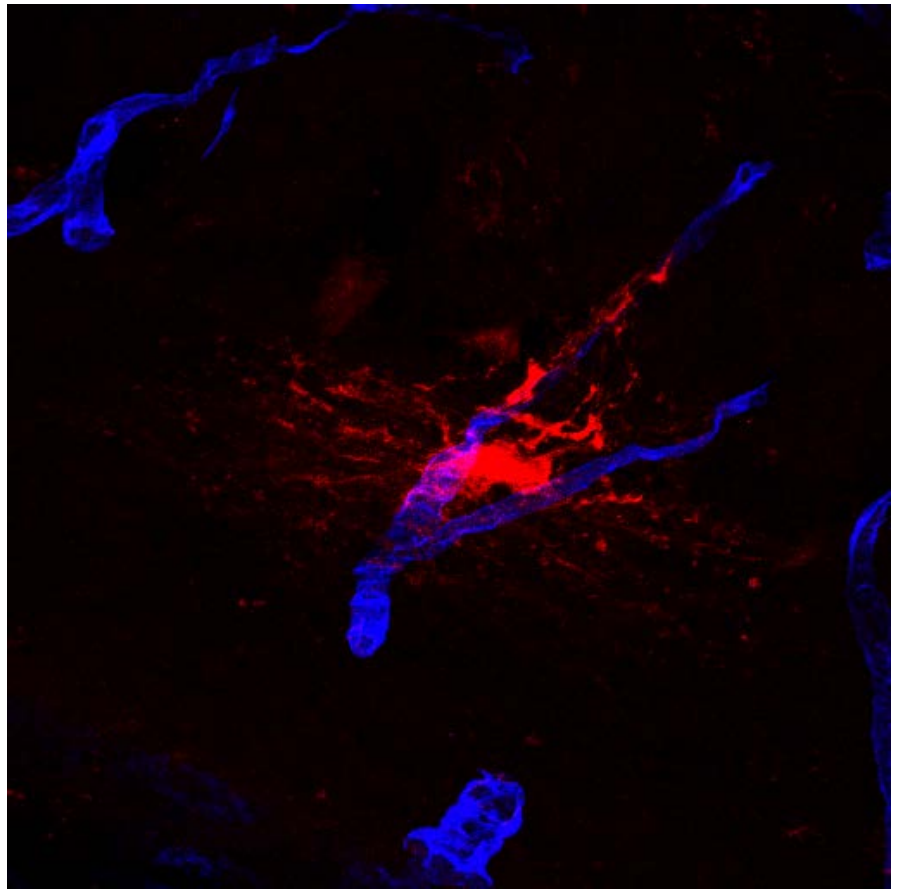
Transient Regenerative Cellular Niches for Neural Repair after Stroke

One such transient regenerative cellular niche is the ***regenerative neurovascular niche:***

- Angiogenic blood vessels signal to neural progenitor cells to causally mediate neurogenesis
- This niche may also have a role in axonal sprouting
- This niche times out



*Concept: when these niches expire, it is part of the transition to the chronic, less plastic stroke state.*

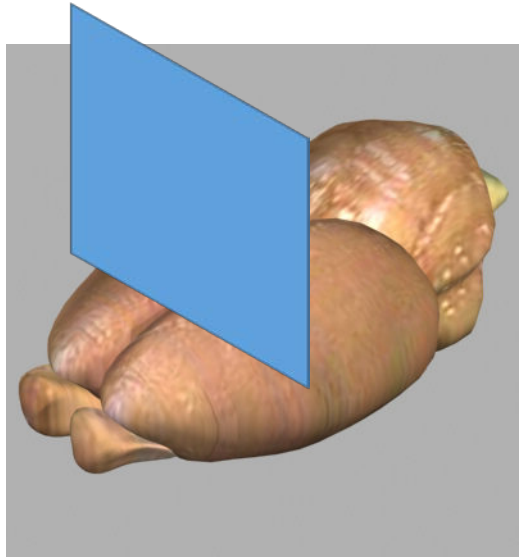


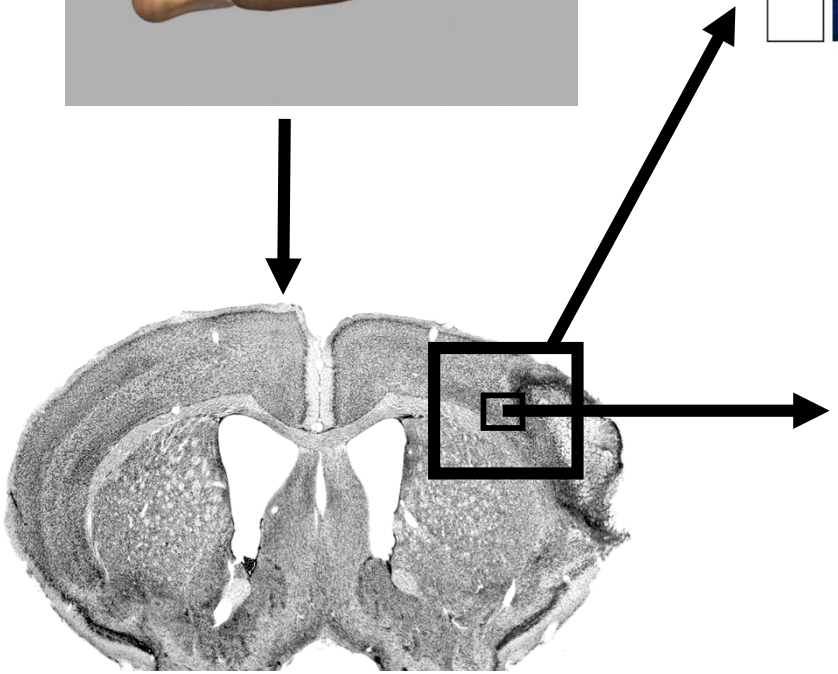
PDGFRα/Glut-1

Regenerative Gliovascular Niche also exists early after stroke

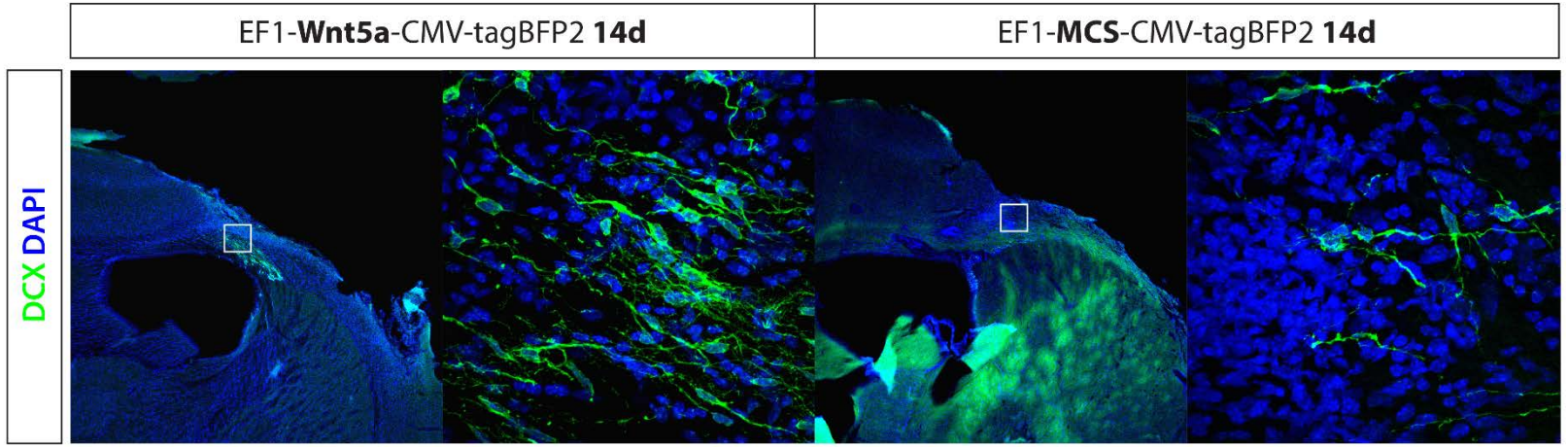


Brumm and Carmichael, Nat Med 18:1609

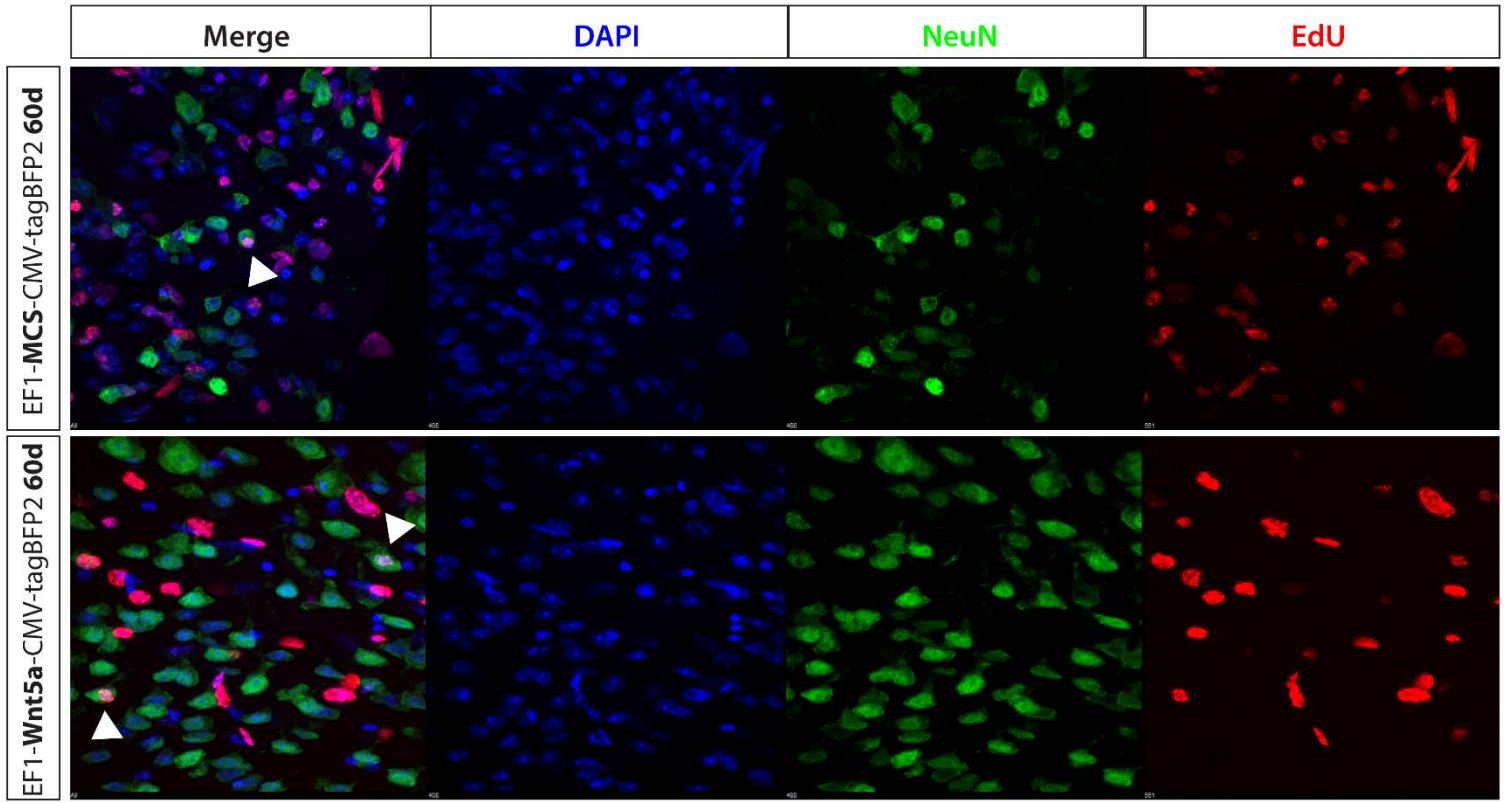




14d neuroblast recruitment: Wnt5a overexpression 19% ↑ than control




60d neuronal differentiation: Wnt5a overexpression 31% ↑ than control




Wnt5a/Frz2,7 signaling can prolong the regenerative neurovascular niche

# Molecular Closure of Sensitive Period in Subacute Phase after Stroke: Axonal Growth Program

**#1. Just the molecular action is reduced in later phases of stroke**

**Axonal Sprouting Transcriptome**

Gene regulation day 7 after stroke

804 up
542 down

Gene regulation day 21 after stroke

572 up
164 down

Li et al.Nat Neurosci 13:1496

**#2. However, the specific classes of genes that are induced during the sensitive period in stroke, and then decrease indicate loss of a coordinated growth state**

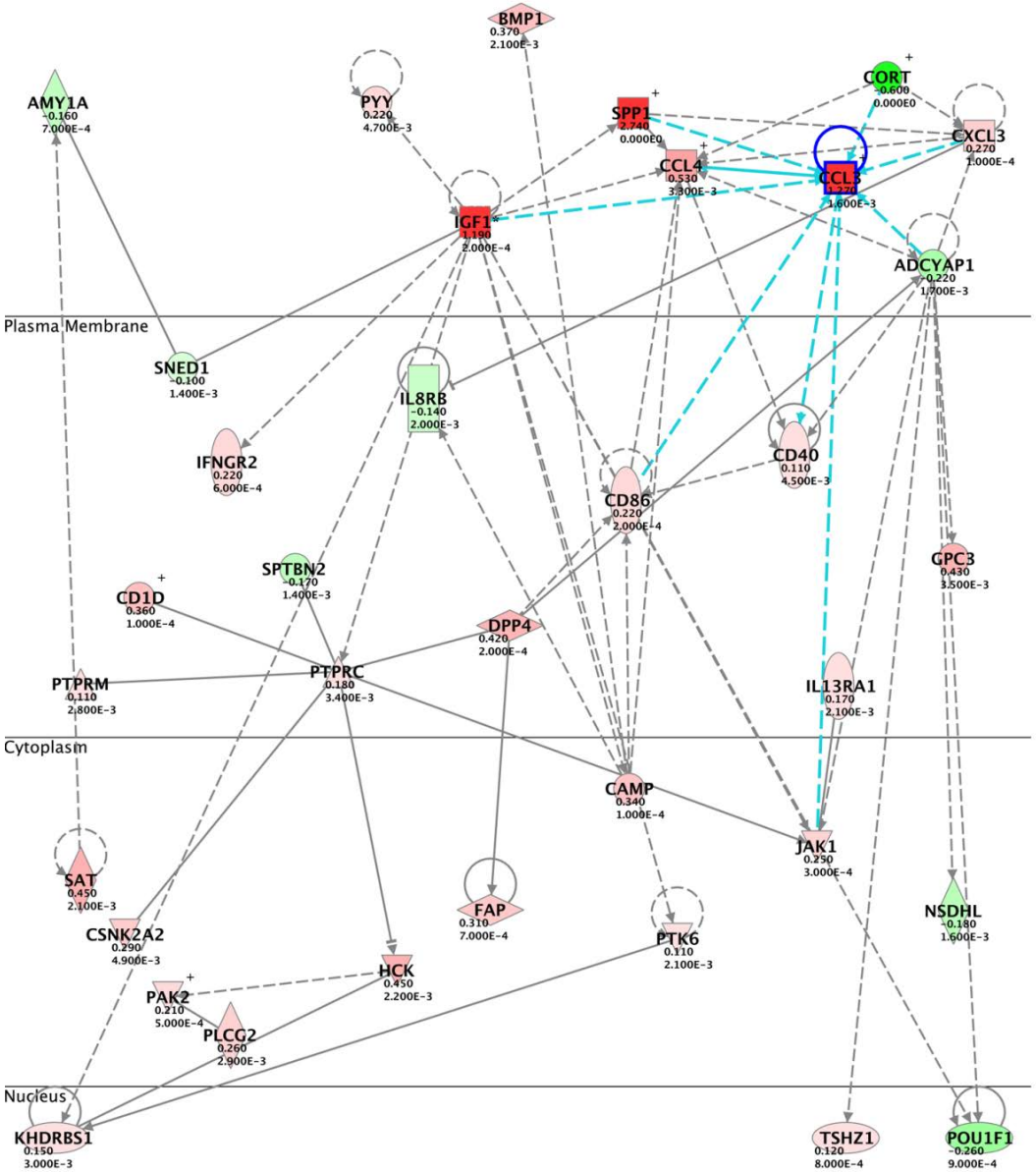
Adhesion molecule
Axonal outgrowth and guidance
Calcium signaling, calcium homeostasis
Intracellular phosphorylation cascade
Cell surface receptor
Extracellular matrix
Growth factor
GTPase and G protein–coupled receptor
MCH1, immune system, complement
Ubiquitin and proteasome
Cytoskeleton, trafficking, migration
Transcription factor
Neuron-specific or related
Cytokine, chemokine
Epigenetic or DNA-modifying

# Molecular Closure of Sensitive Period in Subacute Phase after Stroke: Axonal Growth Program

#3. Molecular Networks are activated in the sensitive period and then shut down after the sensitive period:

IGF-1 Signaling Network in Sprouting Neurons after Stroke

- Induced at day 7
- Linked to an entire molecular pathway from cell surface to intracellular transc factors
- Controls signaling network early in post-stroke recovery



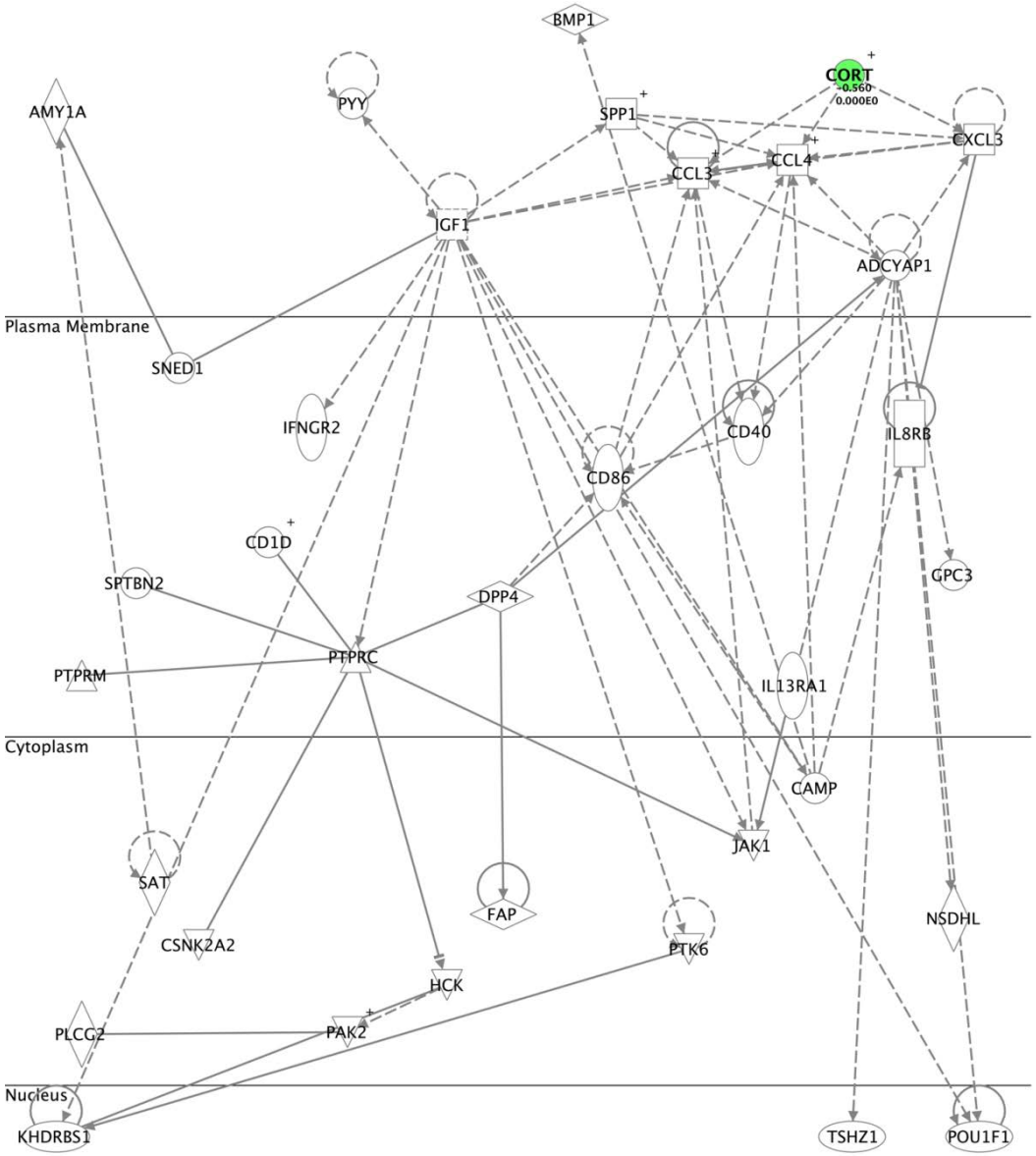

Li et al.Nat Neurosci 13:1496

# Molecular Closure of Sensitive Period in Subacute Phase after Stroke: Axonal Growth Program

#3. Molecular Networks are activated and then shut down after the sensitive period:

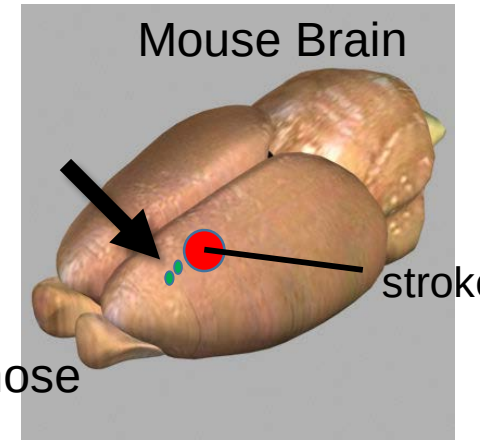
IGF-1 Signaling Network in Sprouting Neurons after Stroke

- Shut off by day 21



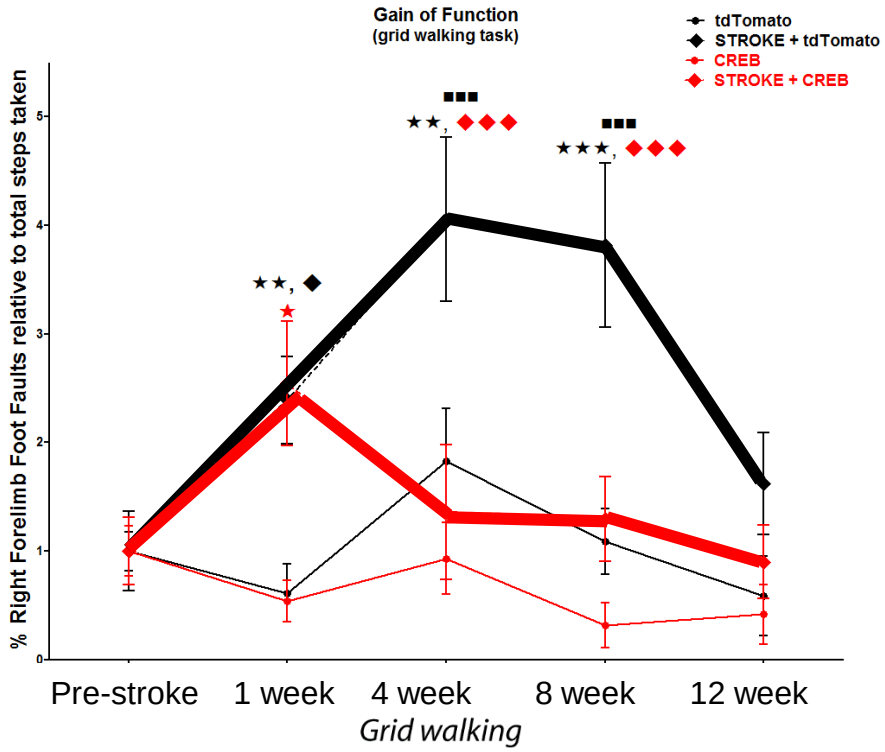

Li et al.Nat Neurosci 13:1496

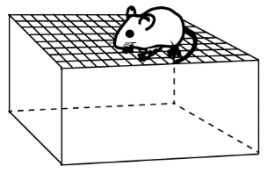
# Molecular Control of the Sensitive Period/Subacute Period in Stroke Recovery

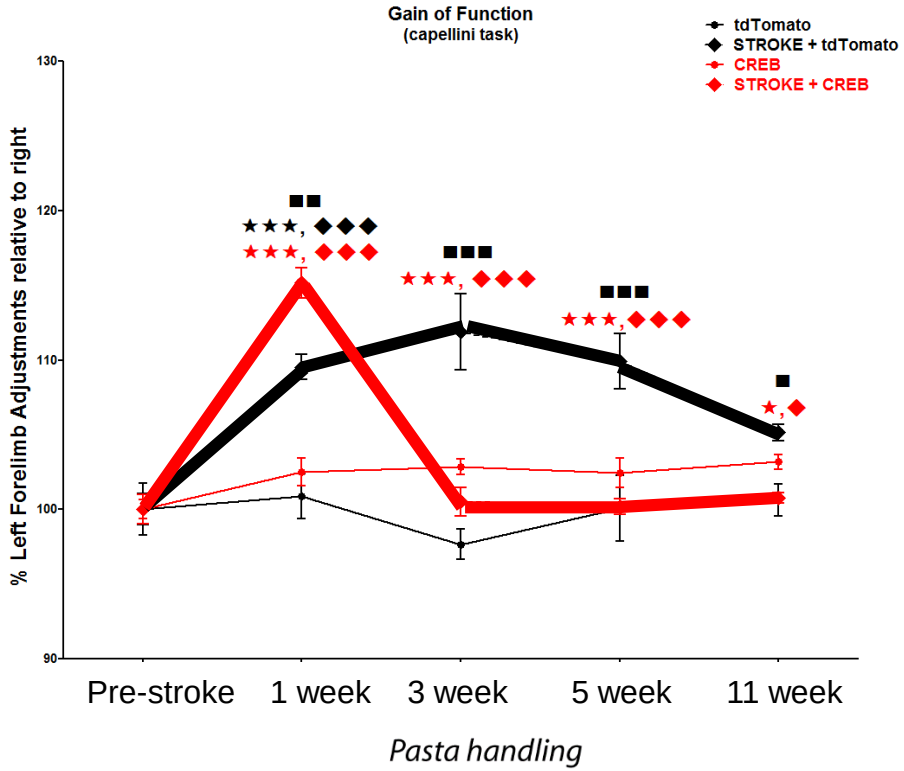


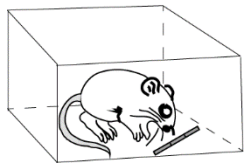

CREB transcription factor controls motor recovery after stroke-switching recovery on and off

- Lenti-CREB
- Lenti-tdTomato
- Microinjections into motor cortex adjacent to stroke
- Test of circuitry in motor recovery

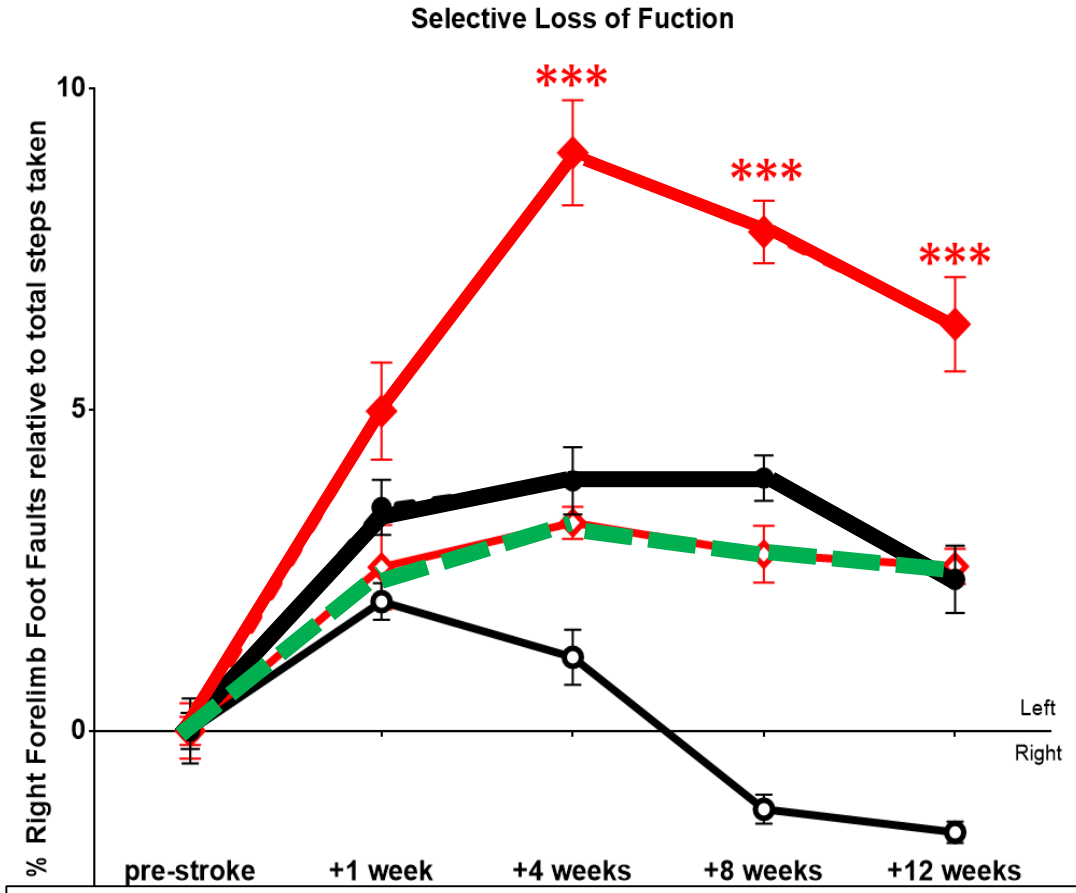


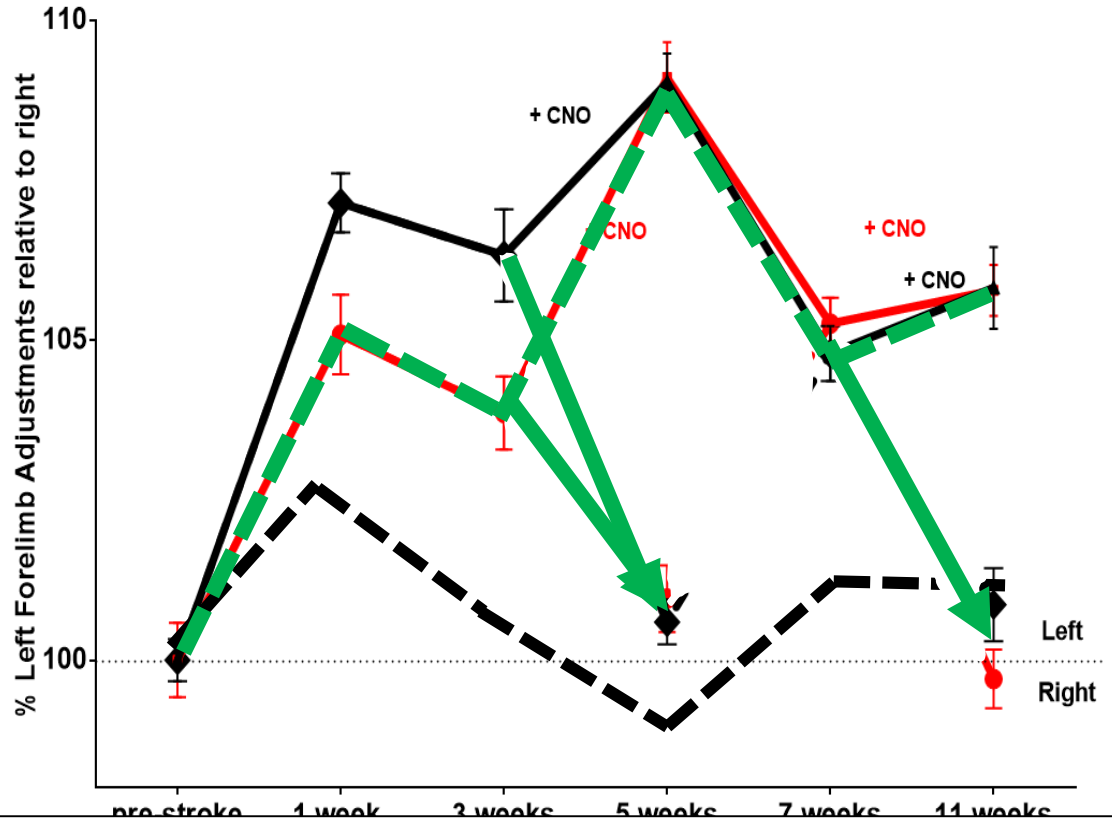





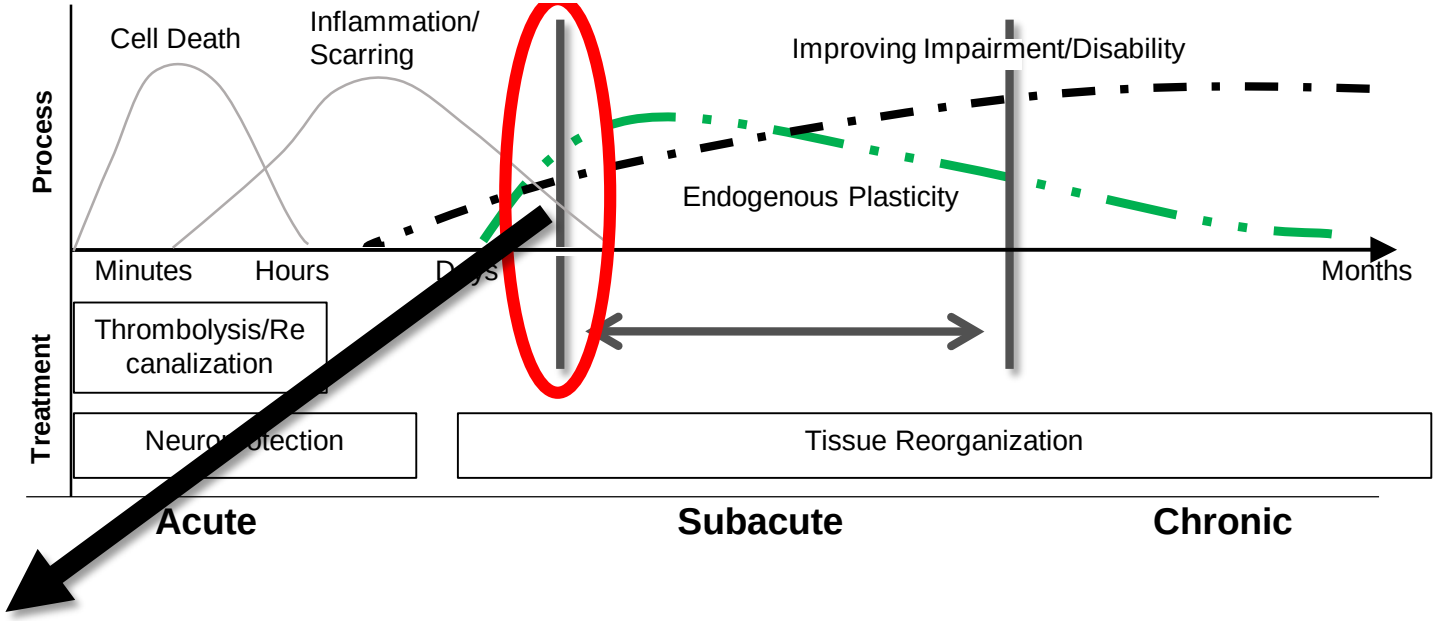
# Turning off CREB-Induced Motor Neurons during Recovery Process

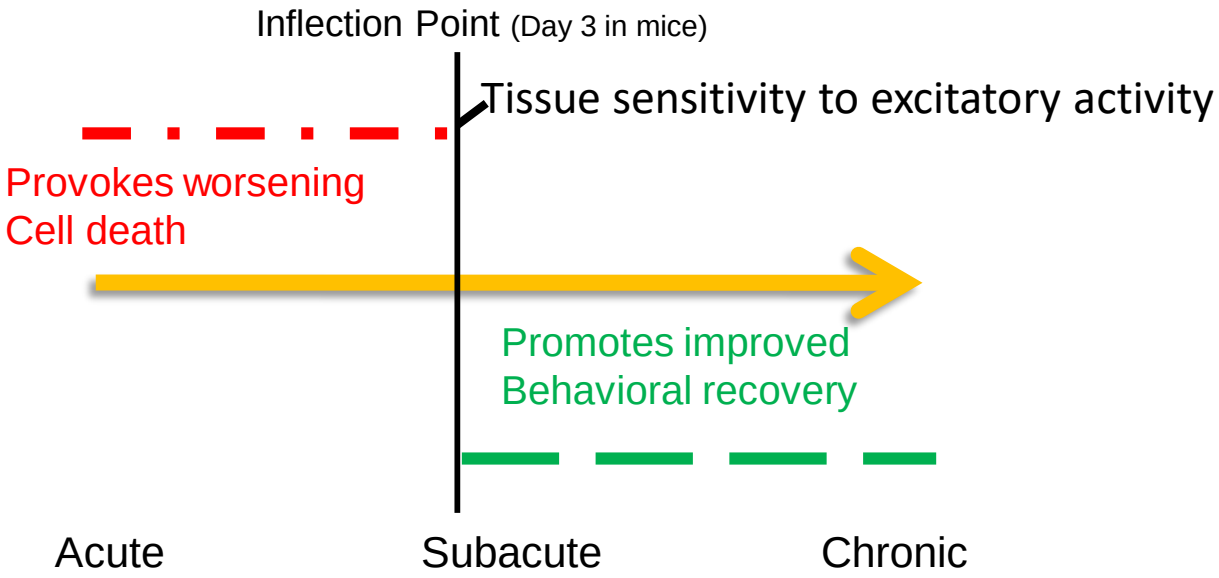



CREB transduces activity signals after stroke to stimulate motor network plasticity and recovery
CREB enables neurons to capture more network “territory”
This also occurs in normal motor performance
Stroke induces a state of “metaplasticity”.

# Defining the Second Phase in Neural Repair: Endogenous Plasticity to Chronic Stage



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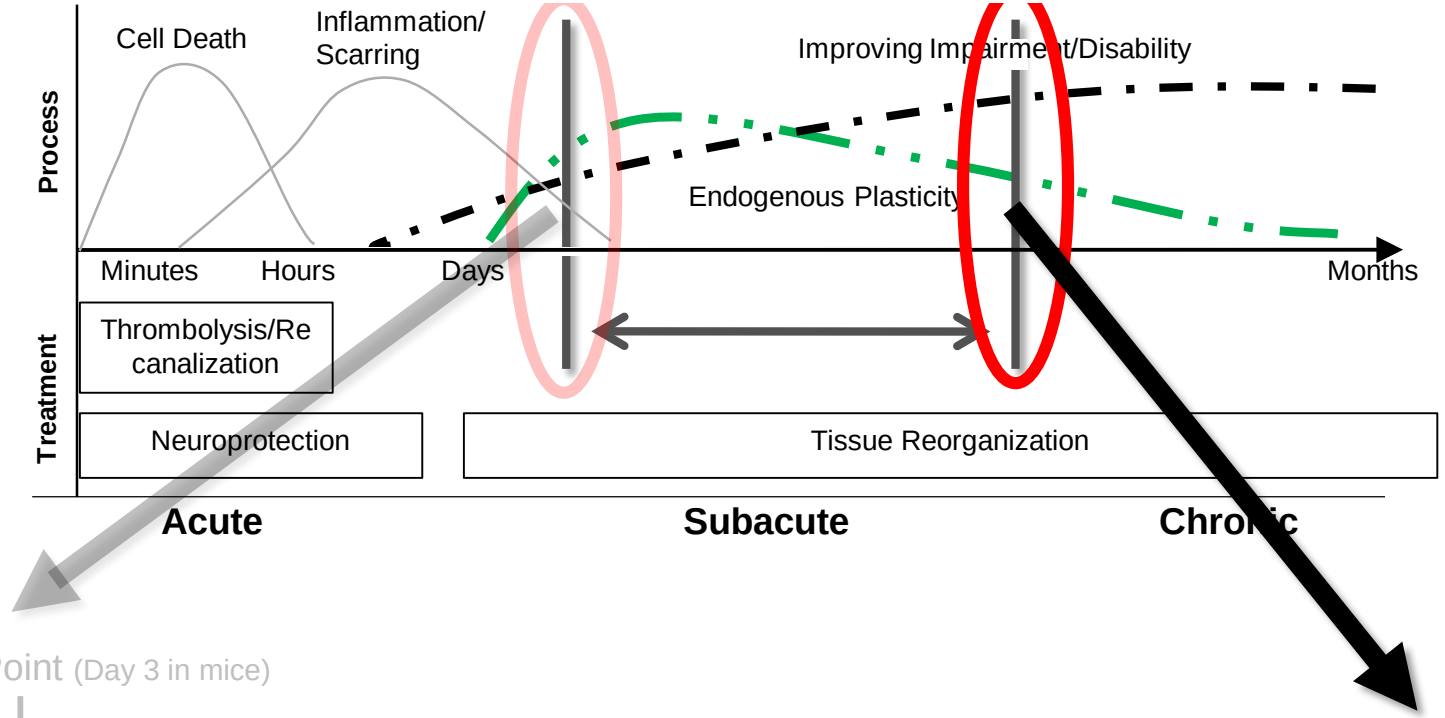
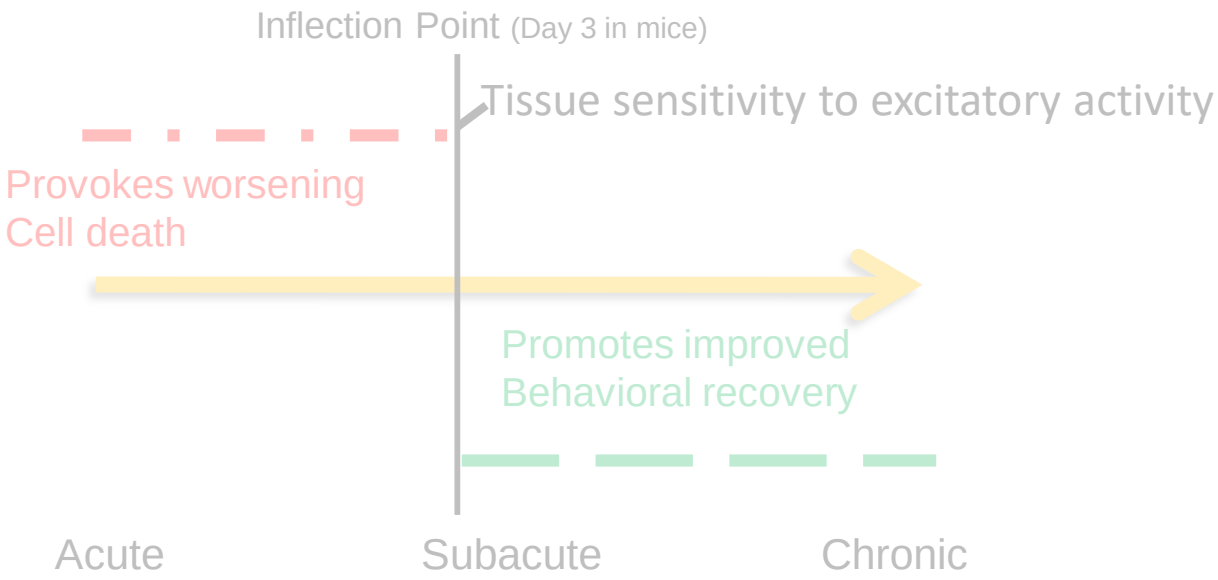



Stroke triggers a specific and highly detailed molecular growth program and induces regenerative cellular niches. These time out. Certain molecular signals can prolong them.

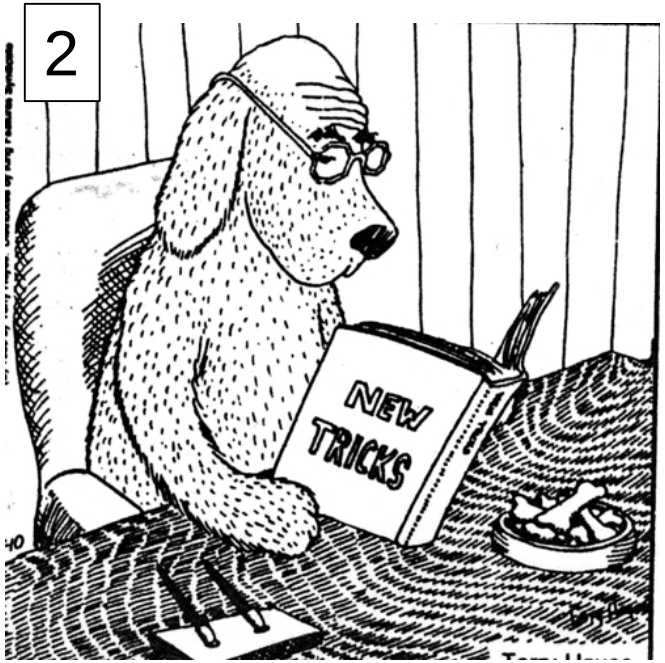
Can they be induced once again in the chronic state?

# Paradigms for Extending the Sensitive Period in Stroke, or for Enhancing Endogenous Plasticity for Recovery into a Period in which We Learn Few New Tricks: *Approaches for an Old Dog*

1


**Enrich Training in Subacute period:**
Recognizes limits for chronic stroke
*But bumpy road for this approach.*

2




**Enhance practice in chronic period:**
Activity drops off in chronic period.
*Maybe boosting rehabilitative training will promote recovery.*
*But: LEAPS, iCARE*

3


**Adopt a New Paradigm:**
Tissue repair times out only weeks after stroke
*Molecular and cellular neurorehab to boost regeneration.*
*But therapeutics still in the pipeline, pharma and biotech frankly hysterical about any new stroke trials (even though not neuroprotection)*