Stroke recovery
So many questions, so few answers
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Outline of talk

- Stroke related disability
- Clinical recovery: what is the recovery that we see?
- Molecular recovery: what is the recovery that we do not see?
- Interventions: what works and what does not.
Acute Stroke interventions

- Thrombolysis: alteplase (tPA) or tenecteplase (TNK)
- Mechanical Thrombectomy
- Hemicraniectomy

**Tenecteplase vs. Alteplase before Stroke Thrombectomy**

- **Reperfusion >50% at prethrombectomy angiogram**
  - Tenecteplase: 22%
  - Alteplase: 10%

- **90-Day Functional Outcome**
  - Tenecteplase: 2
  - Alteplase: 3

No Significant Difference in Adverse Events

*The NEW ENGLAND JOURNAL OF MEDICINE* Campbell et al. 2018

**Modified Rankin Scale Score**

- **Intervention (N=233)**
  - No symptoms: 3
  - 1: 9
  - 2: 21
  - 3: 18
  - 4: 22
  - 5: 6
  - 6: 21

- **Control (N=267)**
  - No symptoms: 6
  - 1: 13
  - 2: 16
  - 3: 30
  - 4: 12
  - 5: 22

MR CLEAN trial

Stroke by the numbers

• **1 in 6 deaths** from cardiovascular disease was due to stroke.

• **795,000 new strokes per year** in the United States.
  • 610,000 of these are first or new strokes.

• **87%** of all strokes are ischemic

• **$53 billion**: stroke-related costs in the United States between 2017 and 2018. (Cost of health care services, medicines to treat stroke, and missed days of work).

• **Number 1**: Stroke is a leading cause of serious long-term disability.

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6-month outcomes in stroke survivors greater than 65 years old

- Hemiparesis (50%)
- Cognitive deficits (46%)
- Depressive symptoms (35%)
- Unable to walk unassisted (31%)
- Social disability (30%)
- Poor subjective health (40%)

<table>
<thead>
<tr>
<th>Neurological deficits (%)</th>
<th>Women (n = 63)</th>
<th>Men (n = 45)</th>
<th>Total (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemiparesis</td>
<td>57.4</td>
<td>40.0</td>
<td>50.0</td>
</tr>
<tr>
<td>Cognitive deficits</td>
<td>49.2</td>
<td>42.2</td>
<td>46.2</td>
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<tr>
<td>Hemianopsia</td>
<td>17.7</td>
<td>22.2</td>
<td>19.6</td>
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<tr>
<td>Aphasia</td>
<td>23.8</td>
<td>11.6</td>
<td>18.9</td>
</tr>
<tr>
<td>Sensory deficits</td>
<td>21.7</td>
<td>6.8</td>
<td>15.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Disability measures (%)</th>
<th>Women (n = 63)</th>
<th>Men (n = 45)</th>
<th>Total (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADL: Barthel &lt;60</td>
<td>33.9</td>
<td>15.6</td>
<td>26.2</td>
</tr>
<tr>
<td>Unable to walk unassisted</td>
<td>40.3</td>
<td>17.8</td>
<td>30.8</td>
</tr>
<tr>
<td>Bladder incontinence</td>
<td>28.6</td>
<td>13.3</td>
<td>22.2</td>
</tr>
<tr>
<td>Depression symptoms</td>
<td>31.9</td>
<td>39.5</td>
<td>35.3</td>
</tr>
<tr>
<td>Social disability</td>
<td>36.8</td>
<td>23.1</td>
<td>29.9</td>
</tr>
<tr>
<td>Institutionalization</td>
<td>34.9</td>
<td>13.3</td>
<td>25.9</td>
</tr>
<tr>
<td>Poor subjective health</td>
<td>40.7</td>
<td>38.1</td>
<td>39.6</td>
</tr>
</tbody>
</table>
Influence of Age on Disability After Stroke

- Severe disability in activities of daily living (ADL) function following stroke
- Defined as Barthel Index < 60
- As age increased, the percent of severely disabled survivors also increased

What factors are associated with post-stroke disability?

<table>
<thead>
<tr>
<th>Variables</th>
<th>p</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>&lt;0.001</td>
<td>1.06</td>
<td>1.04, 1.08</td>
</tr>
<tr>
<td>Male</td>
<td>0.20</td>
<td>0.7</td>
<td>0.4, 1.1</td>
</tr>
<tr>
<td>High school or above</td>
<td>0.02</td>
<td>0.6</td>
<td>0.4, 0.9</td>
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<tr>
<td>Diabetes</td>
<td>0.75</td>
<td>1.06</td>
<td>0.7, 1.6</td>
</tr>
<tr>
<td>Cardiac Disease</td>
<td>0.69</td>
<td>1.09</td>
<td>0.7, 1.6</td>
</tr>
<tr>
<td>Current smoking</td>
<td>0.09</td>
<td>1.4</td>
<td>0.9, 2.2</td>
</tr>
<tr>
<td>Moderate/Heavy Drinking</td>
<td>0.65</td>
<td>1.1</td>
<td>0.6, 1.9</td>
</tr>
<tr>
<td>Stroke History</td>
<td>&lt;0.001</td>
<td>2.6</td>
<td>1.7, 4.1</td>
</tr>
<tr>
<td>NIHSS score at admission</td>
<td>&lt;0.001</td>
<td>1.1</td>
<td>1.05, 1.1</td>
</tr>
<tr>
<td>Depression at 3 months</td>
<td>0.009</td>
<td>1.8</td>
<td>1.1, 2.9</td>
</tr>
<tr>
<td>Cognitive impairment at 3 months</td>
<td>&lt;0.001</td>
<td>2.7</td>
<td>1.6, 4.7</td>
</tr>
<tr>
<td>Stroke Recurrence within 5 years</td>
<td>&lt;0.001</td>
<td>4.1</td>
<td>2.7, 6.3</td>
</tr>
</tbody>
</table>

Bold values are p<0.05

* adjusting for study site; NIHSS = National Institutes of Health Stroke Scale

Age
Education level
History of stroke
Stroke severity
Depression (3 months)
Cognitive Impairment (3 months)
Stroke recurrence
Strokes don’t just strike the old

- 35% of strokes were in people less than 65

*Number of patients according to age and age-specific occurrence rates per 100,000.*
Cost considerations

- Acute hospitalization: $20,396 ± $23,256
  - Hemorrhagic stroke costs $14,499 more
- At discharge, patients have an average of 11.3 medications (range 3 to 27) with a total monthly cost of ~ $725
- Direct healthcare costs in the first year after stroke were mean 54,012 (SD 54,766)
  - 1-year cost of post-stroke aphasia: $1703
  - 1-year cost for outpatient rehabilitation services and medications: $11,145
- Mean lifetime cost of ischemic stroke: $140,048
- Cost of lost productivity ($15.5 billion) nearly equaled the direct cost of treating stroke ($18.8 billion) in 2008
Outline of talk

- Stroke related disability
- **Clinical recovery: what is the recovery that we see?**
- Molecular recovery: what is the recovery that we do not see?
- Interventions: what works and what does not.
Clinical recovery: what is the recovery that we see?

Motor

Cognitive
Motor recovery

Progression of motor recovery, Twitchell (1951) and Brunnstrom (1956)
When will I get my arm function back?

- 41 patients with first time stroke and some degree of arm motor impairment
- Fugl Meyer Scale to assess motor function
- Inpatient, 3 months, 6 months
- Controlled for age, gender, lesion location, cortical lesion volume
- \( \approx (0.70) \times \text{maximal recovery potential} \)
And who proportionally recovers?

- **Transcranial Magnetic Stimulation**
  - Can assess integrity of corticospinal tract (CST)
  - Intact CST $\rightarrow$ better recovery potential

Predicted potential for motor recovery

Can recovery continue beyond the initial period?

- Kaplan–Meier survival curve: Recovery to modified Rankin Scale score [mRS] < 3 according to their initial mRS.
  - mRS 3 → 63 % recovered
  - mRS 4 → 40 % recovered
  - mRS 5 → 17 % recovered
Clinical recovery: what is the recovery that we see?

Motor

Cognitive
How prevalent is cognitive impairment?

- Prevalence estimates vary based on how cognitive information is collected and in what setting.
- Post-stroke dementia or post-stroke cognitive impairment?
How prevalent is post-stroke cognitive impairment?

- How is cognition defined?
- With neuropsychological testing, what is the threshold for diagnosis?
The full extent of cognitive impairment may not be captured during normal screening

- Adults with stroke at age < 50 years old underwent cognitive testing ~ 11 years later
- Performed worse than healthy controls on all cognitive domains except visuospatial construction
South London cohort: longitudinal study

- Cumulative survival after stroke stratified by 3 months cognitive status
- DSM IV or MMSE < 24

(Stroke. 2013;44:138-145.)
Factors associated with post-stroke cognitive impairment

- Stroke volume
- Strategic location
  - Right corticospinal tract, left anteromedial thalamus, left arcuate fasciculis, left middle frontal gyrus, left postero-inferior cerebellum, left angular gyrus
- Total brain volume
- Medial temporal lobe atrophy
- White matter disease
- Presence of microbleeds
Common Behavioral Clusters and Subcortical Anatomy in Stroke

Corbetta et al., 2015, Neuron 85, 927–941
Post-stroke aphasia

- Left posterior superior temporal gyrus
- Left superior longitudinal fasciculus
- Arcuate fasciculus
Cognitive and motor impairments are intertwined
Outline of talk

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Understanding the mechanisms underlying recovery after stroke

• Spike of spontaneous recovery in the first 6 weeks to 3 months, followed by plateau

• “Sensitive period” or period of heightened neuroplasticity corresponding to this time of rapid clinical improvement
Cellular consequences of stroke

- Activation of postsynaptic glutamate receptors (AMPAR, NMDAR, and KAR) leads to Na+ and Ca2+ influxes and cell membrane depolarization.
- Opening of membrane potential-sensitive voltage gated Na+ and Ca2+ channels, which allows further Na+ and Ca2+ influx.
- Cytoplasmic ion overload, protease activation, free radicals production, caspase activation → DNA damage, neuronal cell death.
- Through the compromised BBB, immune cells infiltrate to elicit inflammatory responses, e.g. cytokine release and microglial cell activation.
Reestablishment of Inhibitory Neural Networks After Stroke

**FIGURE 2** | Disruption of balance between excitation (E) and inhibition (I) of the affected and non-lesioned hemispheres throughout the time post stroke.
Molecular pathways that are important in stroke recovery

Brain Derived Neurotrophic Factor (BDNF)
- Promotes neurite outgrowth and neurogenesis post-stroke via TrkB pathway
- Promotes synaptic plasticity
- Genotype can be a predictor of motor and language recovery

NMDA and AMPA receptors
- Play central roles in synaptic plasticity, brain development, learning and memory
- In acute ischemia, mediate excitotoxicity
Figure 2. A time course of immune targets in stroke. Targets are placed according to the predominant role each plays in either neurotoxicity (hours to days post-stroke) or tissue remodeling and repair (weeks post-stroke). Potential therapies are highlighted in parentheses. (Adapted from Servier Medical Art). [The color version of this figure can be viewed at www.wileyonlinelibrary.com/journal/icb]
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Unique Challenges to Stroke Recovery

- Multiple transitions in care
- Rehabilitation is variable and often not driven by clinical need
- Stroke affects the individual in individual ways
- Pragmatic factors of post-stroke subject retention
Stroke Recovery is multidimensional

- Lesion Characteristics
- Cortical Network involvement
- Initial Impairment
- Genetics
- Age
- Premorbid Disability
- Socio-economic Demographics
- Medical Complications & Comorbidities
- Amount and Type of Rehabilitation
- Neuroactive Medications
- Depression
- Social Support Structures
- Fatigue
- Resilience
Interventions to Enhance Plasticity After Stroke

FIGURE 1 | Summary of treatment approaches discussed in this review. The abscissa indicates the readiness of clinical application, and the ordinate indicates the involvement of the healthy hemisphere.
Interventions: what works and what does not.

Molecular Targets for Stroke Recovery

- Stem cells
- Growth factors
- Monoclonal antibodies
- Immune factors

Device-based Targets for Stroke Recovery

- Robotics
- Telehealth
- Brain-Computer Interface
- Non-invasive brain stimulation
Embryonic stem cells [ESCs] or induced pluripotent stem cells (iPSCs) can be treated in vitro to generate glia and neurons.

Transplantation of glial and neuronal cells at early stages of their development into stroke-injured brain can lead to promotion of myelogenesis and restoration of astrocyte network or by increasing cellular plasticity and restoring neuronal network.

Thus far, there have been 9 randomized controlled trials and 7 non-randomized studies (NRSs), involving 740 participants.

There was no significant difference in mortality between the stem cell group and the control group.

Most commonly reported adverse effects: Fever, headache, and recurrent stroke.
Cerebrolysin

- mixture of enzymatically treated peptides derived from pig brain whose constituents can include **brain-derived neurotrophic factor (BDNF)**, glial cell line-derived neurotrophic factor (GDNF), nerve growth factor (NGF), and ciliary neurotrophic factor (CNTF).

**CASTA trial:** Administered within 12 hours of symptoms onset to Cerebrolysin daily or placebo for 10 days → no benefit

**CARS trial:** Administered within 24-72 hours of symptom onset to Cerebrolysin placebo daily for 21 days. Paired with a standardized rehabilitation program for 21 days that was initiated within 72 hours after stroke onset → benefit

<table>
<thead>
<tr>
<th>Global Status Day 90</th>
<th>MW Statistic</th>
<th>MW</th>
<th>95% CI</th>
<th>N1/N2</th>
<th>P</th>
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<tbody>
<tr>
<td>ARAT</td>
<td>0.7118</td>
<td>(0.6307 to 0.7928)</td>
<td>104/101</td>
<td>0.0000</td>
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<tr>
<td>GAIT VELOCITY</td>
<td>0.5937</td>
<td>(0.4585 to 0.7289)</td>
<td>34/35</td>
<td>0.1743</td>
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<tr>
<td>9 HOLE PEG</td>
<td>0.5612</td>
<td>(0.4777 to 0.6448)</td>
<td>90/83</td>
<td>0.1509</td>
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<tr>
<td>NIHSS</td>
<td>0.6754</td>
<td>(0.5977 to 0.7530)</td>
<td>104/101</td>
<td>0.0000</td>
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<tr>
<td>BARTHEL</td>
<td>0.6720</td>
<td>(0.5922 to 0.7518)</td>
<td>104/101</td>
<td>0.0000</td>
<td></td>
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<tr>
<td>MRS</td>
<td>0.7339</td>
<td>(0.6612 to 0.8065)</td>
<td>104/101</td>
<td>0.0000</td>
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<tr>
<td>GOODCLASS</td>
<td>0.5614</td>
<td>(0.4938 to 0.6290)</td>
<td>104/101</td>
<td>0.0750</td>
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<tr>
<td>LINE CANC.</td>
<td>0.4696</td>
<td>(0.4041 to 0.5351)</td>
<td>98/100</td>
<td>0.3627</td>
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<tr>
<td>GAP</td>
<td>0.4981</td>
<td>(0.4281 to 0.5681)</td>
<td>97/100</td>
<td>0.9574</td>
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<tr>
<td>SF36 PCS</td>
<td>0.6727</td>
<td>(0.5900 to 0.7553)</td>
<td>102/95</td>
<td>0.0000</td>
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<tr>
<td>SF36 MCS</td>
<td>0.5602</td>
<td>(0.4795 to 0.6409)</td>
<td>102/95</td>
<td>0.1438</td>
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<tr>
<td>DEPRESSION</td>
<td>0.6805</td>
<td>(0.6007 to 0.7603)</td>
<td>102/96</td>
<td>0.0000</td>
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<tr>
<td>Combined (Wei-Lachin)</td>
<td>0.6159</td>
<td>(0.5799 to 0.6518)</td>
<td>104/101</td>
<td>0.0000</td>
<td></td>
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</table>
Erythropoietin

- Binds specifically to neuronal EPO receptors

Beta-hCG+Erythropoietin in Acute Stroke (BETAS) study: multisite, open-label, safety trial that gave 3 doses beginning 1 to 2 days post-stroke followed by 3 erythropoietin doses beginning 7 to 8 days after stroke. This study identified no safety concerns.

REGENESIS study: randomized, double-blind, placebo-controlled trial of 522 subjects with acute MCA ischemic stroke within 6 hours of symptom onset that gave 2 doses of EPO IV (40 000 IU each) at 24 and 48 hours.

Myelin-associated glycoprotein [MAG]

- Myelin-associated glycoprotein, along with other CNS inhibitors oligo-myelin glycoprotein, and Nogo-A, can block myelin-based inhibitory proteins that inhibit axon outgrowth and therefore neuronal repair.

- Randomized trial of 134 subjects: 2 IV infusions of MAG at 24 to 72 hours after stroke onset

- Primary outcome was gait velocity
CCR5 impact on motor recovery

 aujourd'hui

‣ CCR5:
• White blood cells display CCR5 on their surface to intercept signals from chemokines and coordinate an immune response.
• HIV exploits CCR5 to invade host cells.
• High levels of CCR5 in stroke patients

Reducing CCR5 function in pre-motor cortex neurons induces early motor recovery after stroke.

Joy et al., 2019, Cell 176, 1143–1157
Interventions: what works and what does not.

Molecular Targets for Stroke Recovery
- Stem cells
- Growth factors
- Monoclonal antibodies
- Immune factors

Device-based Targets for Stroke Recovery
- Robotics
- Telehealth
- Brain-Computer Interface
- Non-invasive brain stimulation
Robotics

- Multicenter, randomized, controlled trial involving 127 patients > 6 months after stroke.
  - 49 patients to receive intensive robot-assisted therapy, 50 to receive intensive comparison therapy for 12 weeks of treatment (up to 36 sessions). Twenty-eight were randomized to receive usual care.
  - Robot-assisted therapy did not significantly improve motor function after 12 weeks

Robotics

- **SMARTS2 trial**: multicenter, single-blinded, parallel randomized controlled trial comparing the efficacy of a neuro-animation therapy with time-matched conventional occupational therapy to enhance upper-limb motor recovery after stroke (2 hours a day of therapy for 5 consecutive days over 3 weeks).

Telerehabilitation

- Randomized, assessor-blinded, noninferiority trial of 124 participants across 11 US sites, 124 patients who had experienced stroke 4 to 36 weeks prior and had arm deficits

Table 2. Treatment-Related Change in FM Motor Score

<table>
<thead>
<tr>
<th>Model</th>
<th>Patients, No.</th>
<th>FM Score for IC Group, Mean Change</th>
<th>FM Change (TR-IC), Difference Between Groups (95% CI)</th>
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</thead>
<tbody>
<tr>
<td>Primary analysis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT with multiple imputation of missing outcomes</td>
<td>62</td>
<td>124</td>
<td>8.23</td>
</tr>
<tr>
<td></td>
<td>0.06 (-2.14 to 2.26)</td>
<td></td>
<td></td>
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<tr>
<td>Secondary analyses</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ITT with substitution of “worst-best-case” missing outcomes</td>
<td>62</td>
<td>124</td>
<td>8.58</td>
</tr>
<tr>
<td></td>
<td>-0.19 (-2.29 to 1.92)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete case ITT</td>
<td>59</td>
<td>114</td>
<td>8.36</td>
</tr>
<tr>
<td></td>
<td>0.00 (-2.27 to 2.27)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete case PP</td>
<td>58</td>
<td>113</td>
<td>8.36</td>
</tr>
<tr>
<td></td>
<td>-0.15 (-2.41 to 2.10)</td>
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</tbody>
</table>
Brain-Computer Interface

Figure 1. Illustration of typical brain-computer interface (BCI) systems used in post-stroke motor rehabilitation highlighting sensory feedback modalities. EEG = electroencephalography, NIRS = near-infrared spectroscopy, ECogG = electrocorticography, SMR = sensorimotor rhythm, MRCP = motor-related cortical potential.

Figure 2. Intervention effect measured as changes in upper extremity Fugl-Meyer Assessment (FMA-UE) scores between pre- and postintervention (standardized mean difference SMD, Random-Effects). The mean effect is represented as a diamond in the forest plot, whose width corresponds to the 95% CI, whereas the P is shown as a bar superposed to the diamond. Box sizes reflect the contribution of the study toward the total intervention effect.
(Non) invasive brain stimulation: Vagal Nerve Stimulator

- To enhance the reorganization potential of the brain following stroke is via cholinergic and monoaminergic modulation of motor cortex neurons

- VNS-REHAB: randomized, triple-blind, sham-controlled trial, we assigned participants with moderate to severe arm weakness, at least nine months after ischemic stroke
  - FDA approval following this study

Non-invasive stimulation: Remote ischemic conditioning

Non-invasive brain stimulation: Transcranial Magnetic Stimulation

Aphasia:
- Common impairment after stroke
- Standard of care is currently therapy with a speech and language pathologist

**Figure 7.** Forest plot for aphasia quotient: (a) rTMS versus Sham rTMS, and (b) rTMS versus Conventional rehabilitation.

Source: Conventional rehabilitation (speech and language training, physical exercises, or acupuncture, etc.); SD: standard deviation; 95% CI: 95% confidence interval; Std. mean difference: standard mean difference; IV: inverse variance.
Non-invasive brain stimulation: Transcranial Direct Current Stimulation

- **Motor**
  TRANSPORT2: tDCS + Constraint-Induced Movement Therapy to improve arm function within 30 days to 6 months of acute stroke

- **Cognitive**
  TRAINS: tDCS + cognitive therapy to improve attention and other cognitive functions within 3 months of acute stroke
TRAINS: Transcranial Direct Current Stimulation and Rehabilitation to Ameliorate Impairments in Neurocognition after Stroke

- tDCS potentiates depolarization of neurons, leading to hyperexcitability and learning
- Different effects depending on site stimulated and task performed while stimulated
- In our study, we are stimulating the left dorsolateral prefrontal cortex with a learning task involving memory and attention.

**Figure 1.** Trajectory of cognitive recovery post-stroke and hypothesized accelerated recovery by optimizing neuroplastic processes.

- Pre-stroke cognition
- Acute stroke onset
- Heightened neuroplasticity
- Ideal recovery
- Actual recovery
- Neuromodulation intervention

3 months - 6 months

<table>
<thead>
<tr>
<th>Time after stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient admitted to PIRM from UPHS after stroke admission</td>
</tr>
<tr>
<td>Visit 1: Screening and informed consent</td>
</tr>
<tr>
<td>Visit 2: Baseline assessments*</td>
</tr>
<tr>
<td>Visit 3-7: tDCS v sham during 5 daily SLP sessions</td>
</tr>
<tr>
<td>Visit 8: Post-intervention assessments* (Immediate)</td>
</tr>
<tr>
<td>Visit 9: Post-intervention assessments (3 months)</td>
</tr>
</tbody>
</table>

Penn Institute for Rehabilitation Medicine
*Indicates assessments are part of clinical assessments performed at PIRM

Home or SNF
**Molecular Targets for Stroke Recovery**

- Stem cells
- Growth factors
- Monoclonal antibodies
- Immune factors

**Device-based Targets for Stroke Recovery**

- Robotics
- Telehealth
- Brain-Computer Interface
- Non-invasive brain stimulation

**What works?**

Many interventions have potential
Few have consistent results
Only one (VNS) has FDA approval
Stroke recovery: Summary

- Stroke is the leading cause of adult disability in the United States.
- Predictive models are being developed to estimate motor recovery potential: currently, the proportional recovery rule indicates that 70% of lost function has the potential to be recovered.
- Many promising interventions are in various stages of conception, development, clinical testing.
- Stroke recovery is complex, multifaceted and predictably unpredictable.
- Studies are needed to comprehensively evaluate “recovery”
Thank you!

Roy Hamilton, MD
Branch Coslett, MD
Scott Kasner, MD
Pranav Ramkumar
Daniela Sacchetti

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