Translation of Cellular Therapies for Neural Repair in Stroke: Concepts in Pre-Clinical to Clinical Movement and Clinical Trial Design

CIRM/ Regenerative Medicine Consortium Roundtable
Best Practices in Clinical Design
For First-in-Human Stem Cell-Based Therapy

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Key Clinical Translational Issues in Cell Therapy for Central Nervous System Disease

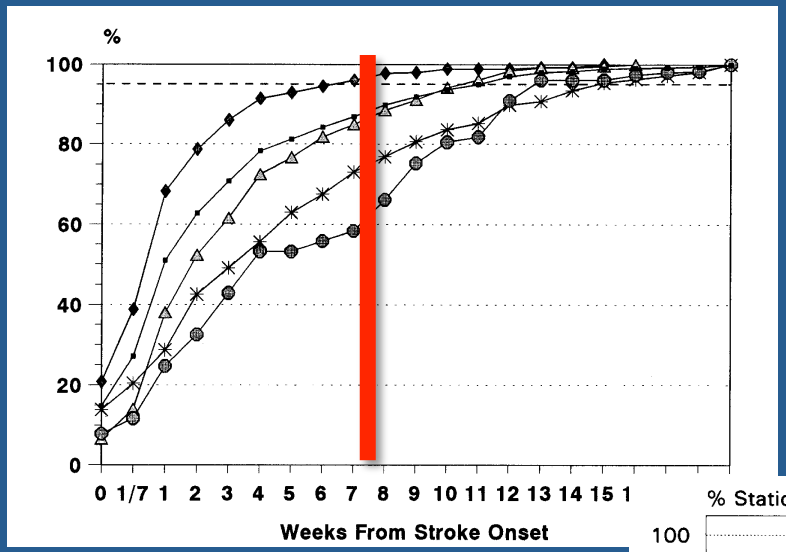
- **Disease heterogeneity:** location, location, location in acute brain injury (especially stroke)
- **Disease evolution:** temporal phases of damage and repair in acute CNS injury
- **Pre-clinical and clinical outcome measures:** matching rodent and human recovery indices
- **Activity of the patient in clinical trials of neural repair**

Disease Heterogeneity

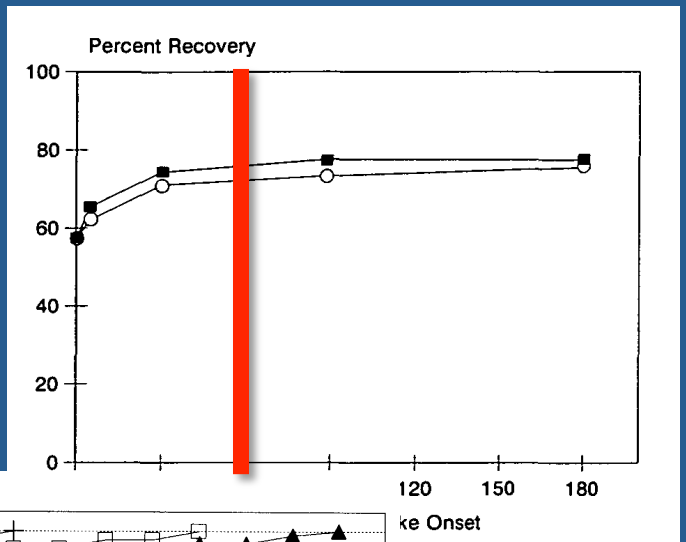
- Stroke occurs in many different brain areas
- Damage disrupts different primary functional regions, and indirectly disconnects distinct circuits
- Certain functions are more difficult to measure in clinical outcome
- Sensorimotor functions are only ones well represented in rodents
- Sum total of these limitations is that clinical trials need to focus on stroke that produces deficits and occurs in locations that are supported by pre-clinical modeling
- For most stroke work this means Middle Cerebral Artery territory infarcts that are centered in the striatum/basal ganglia
- Fortunately this is approx 40% of all human stroke

Disease Evolution

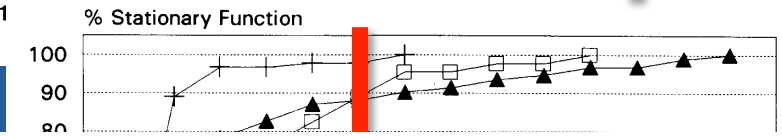
Goal: want to target the CNS disease when prospective therapy is likely to have its maximal effect



Total Neurological Recovery

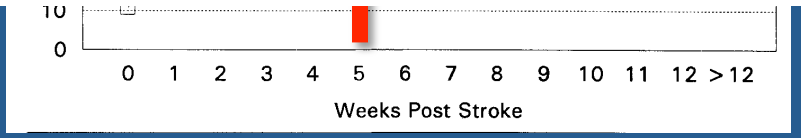


Limb Recovery



80% of stroke recovery occurs by one month
95% of stroke recovery occurs by 3 months
most of the variance (up to 86%) in stroke recovery is accounted for after the first 30 days

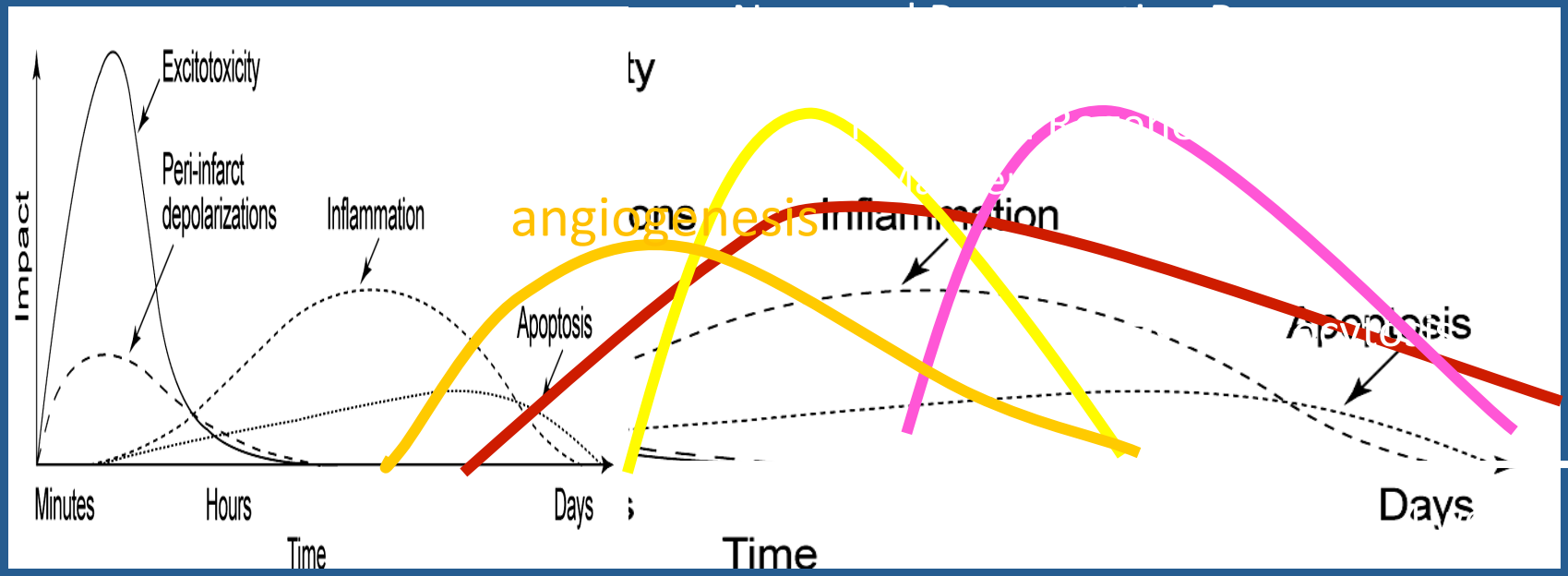
Gains do occur in chronic stroke, but they are smaller (1/10) and require much greater effort



Language Recovery

Timeline of Stroke from Damage to Repair

The pre-clinical evidence from most studies of cellular therapies in stroke is that they modify processes of neural repair: angiogenesis, neurogenesis, formation of new connections, inflammation



Spectrum of Injury to Benefit in Excitation

Clarkson et al Nature 2010, J Neurosci 2011

Pre-Clinical and Clinical Outcome Measures

Principles:

- Linearity
- Matching functions
- Measuring impairments

Linearity

Problem with pre-clinical stud

Motor tests

Raising rat by tail (normal=0; maximum=3)	*(3)*
Flexion of forelimb	1
Flexion of hindlimb	1
Head moved >10° to vertical axis within 30 s	1

Table 1. Behavioral Outcome Measures across Stroke Studies with Cell-Based Therapies

Behavioral Test	Assessment of	Frequency Used	Positive Treatment Effects
mNSS	motor and sensory functions, balance and reflexes	29/70 (41%)	28/29 (97%)
Adhesive tape removal	forelimb sensory asymmetry	25/70 (36%)	[illegible]
Rotarod	coordination, balance, and gross motor functions	18/70 (26%)	17/18 (94%)
Limb-placing	responses to tactile and proprioceptive stimulation	11/70 (16%)	9/11 (82%)
Cylinder	spontaneous use of forelimbs	8/70 (11%)	4/8 (50%)
Treadmill	motor functions, gait	5/70 (7%)	5/5 (100%)
Tapered beam-walking	hindlimb functions	3/70 (4%)	0/3 (0%)
Montoya's staircase	skilled forelimb use	1/70 (1%)	0/1 (0%)
Water maze, passive avoidance	cognitive functions	14/70 (20%)	11/14 (79%)
Others (e.g., spontaneous activity, apomorphine/amphetamine-induced rotation)		20/70 (29%)	

Hicks et al Cell Stem Cell 2009

Pinna reflex (head shaken when auditory meatus is touched)	1
Corneal reflex (eye blink when cornea is lightly touched with cotton)	1
Startle reflex (motor response to a brief noise from clapping hands)	1
Seizures, myoclonus, myodystony	1
Maximum points	*(18)*

One point is given for an absent reflex tested or for the animal's inability to perform a task: 1-6 mild injury, 7-12 moderate injury, 13-18 severe injury

Matching Functions

Linear measures of rodent sensorimotor function to linear measures of human sensorimotor function

Grid walking, 'Cat Walk test' to comfortable gait test
Cylinder, grid walking, vibrissal-paw,reach or distal limb control to Fugl Meyer, ARAT, Wolf Motor Function Tests

Measuring Impairments, and not disabilities

Cell therapies in pre-clinical trials prod
specific aspects of sensory function, m
sensorimotor integration

A disability (vs. impairment) scale catc

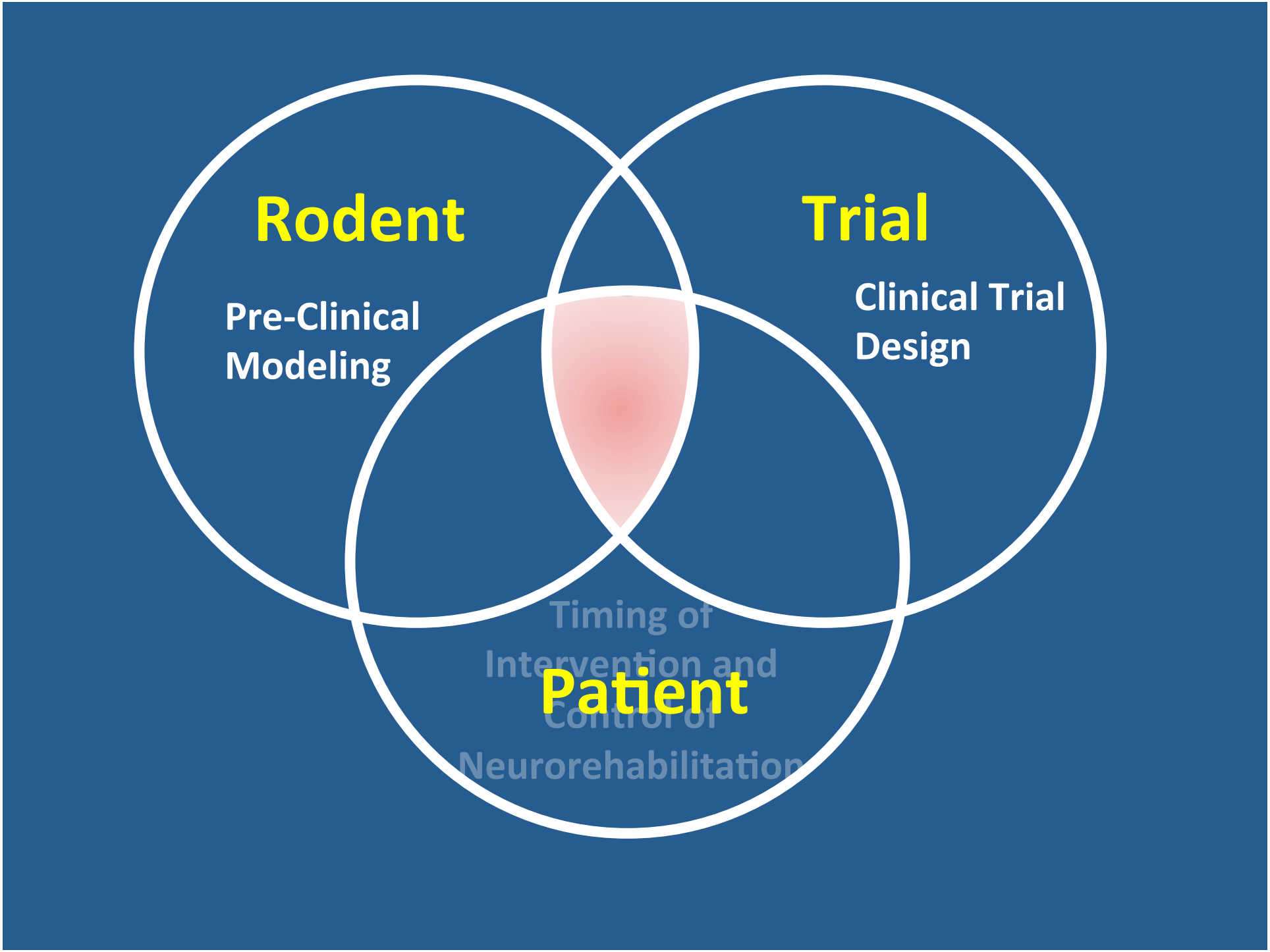
- Good inter-rater reliability, strong test-re-test reliability, good construct validity (for acute stroke)
- Terrible ability to detect elements of recovery, relate to pre-clinical data, resolve compensation vs. recovery

TABLE 1. Modified RSs

Grade	mRS
0	No symptoms at all
1	No significant disability: despite symptoms, able to carry out all usual duties and activities
2	Slight disability: unable to perform all previous activities but able to look after own affairs without assistance
3	Moderate disability: requiring some help but able to walk without assistance
4	Moderately severe disability: unable to walk without assistance and unable to attend to own bodily needs without assistance
5	Severe disability: bedridden, incontinent and requiring constant nursing care and attention
6	Death*

Activity of the Patient

- Unlike any other organ system, CNS plasticity and recovery are directly related to behavioral activity of the patient
- Physical activity (in neurorehabilitation) has a dose effect
- Several clinical trials in stroke and spinal cord injury showed no improvement compared with very good rehab (LEAPS, MIT robot, SCILT [body weight treadmill training in spinal cord injury])
- Chronic stroke patients can exhibit a limited recovery to neurorehab alone (note that this is not detectable in mRS)
- Pre-clinical evidence for “training the transplant”


Rodent
Pre-Clinical Modeling
Trial
Clinical Trial Design
Timing of Intervention and Control of Neurorehabilitation
Patient