

# Acute Endophenotypes Working Group

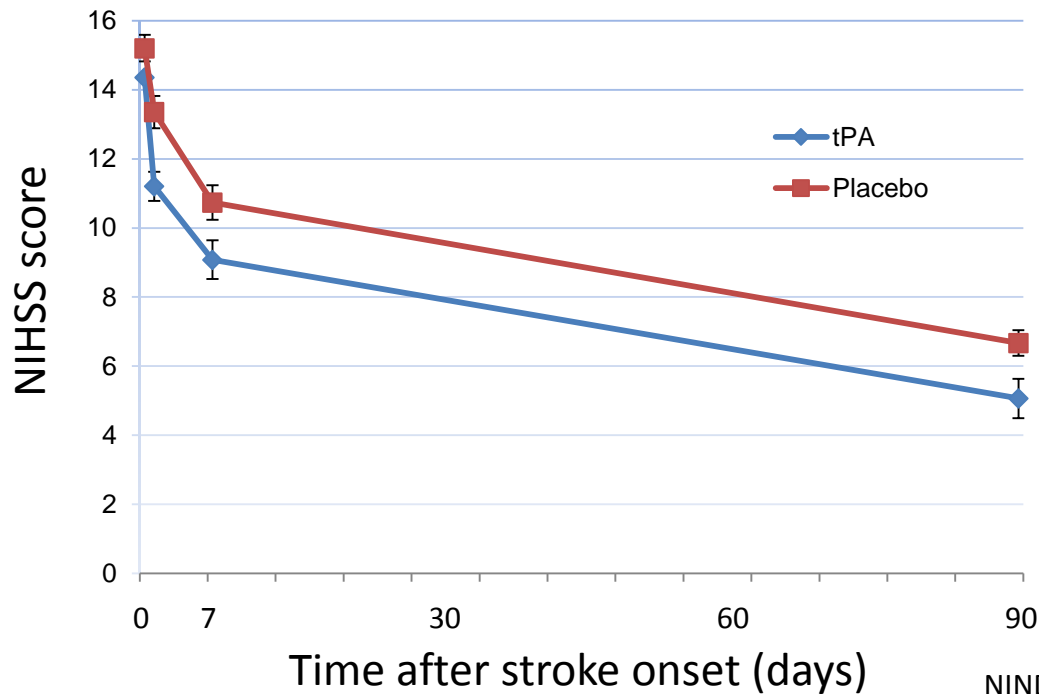
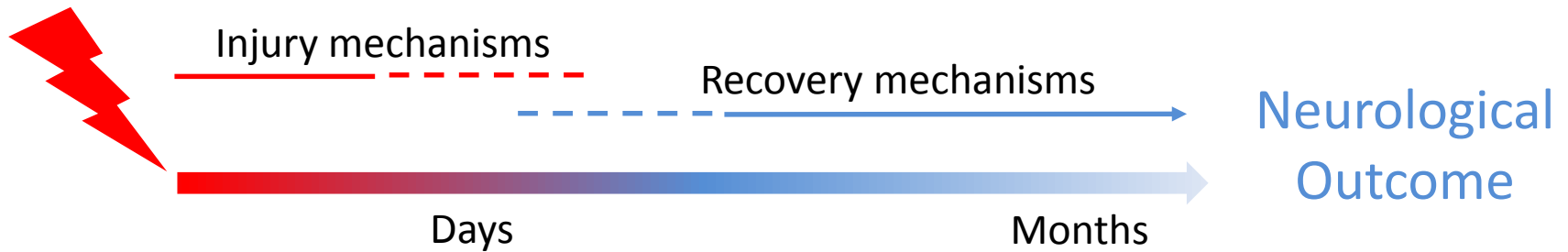
April 4, 2014

International Stroke Genetics Consortium  
University of Utah, Salt Lake City

# Current Participants

- Helsinki University, Finland
  - Turgut Tatlisumak, Daniel Strbian
- Mayo Clinic, Jacksonville, USA
  - James Meschia, Andrea Harriott
- University of Newcastle, Australia
  - Jane Maguire, Chris Levi
- Vall D'Hebron Hospital, Spain
  - Israel Fernandez, Joan Montaner
- Washington University, St. Louis, USA
  - Jin-Moo Lee, Carlos Cruchaga, Laura Heitsch

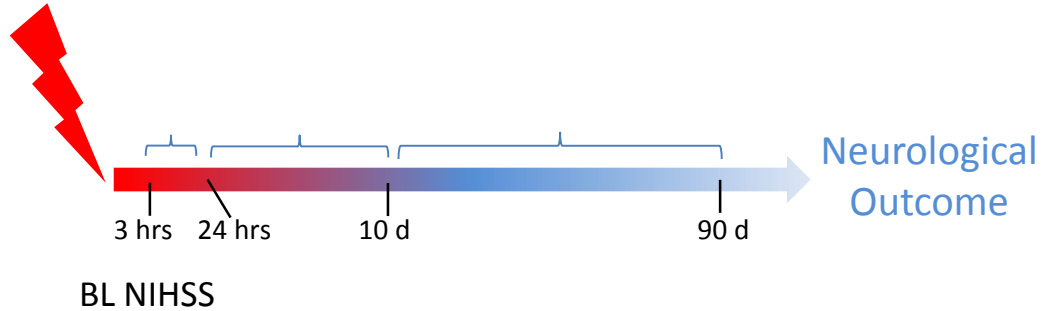
# Acute Ischemic Stroke and Recovery



NINDS tPA study, NEJM, 1995

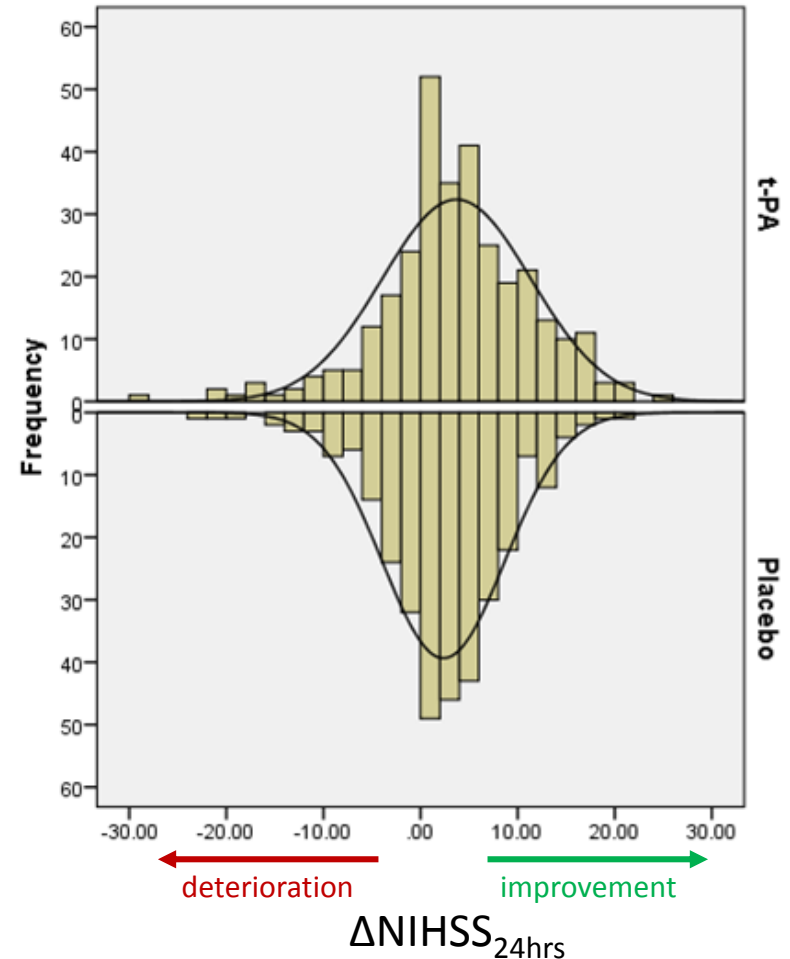
# Acute Endophenotypes

## Rationale



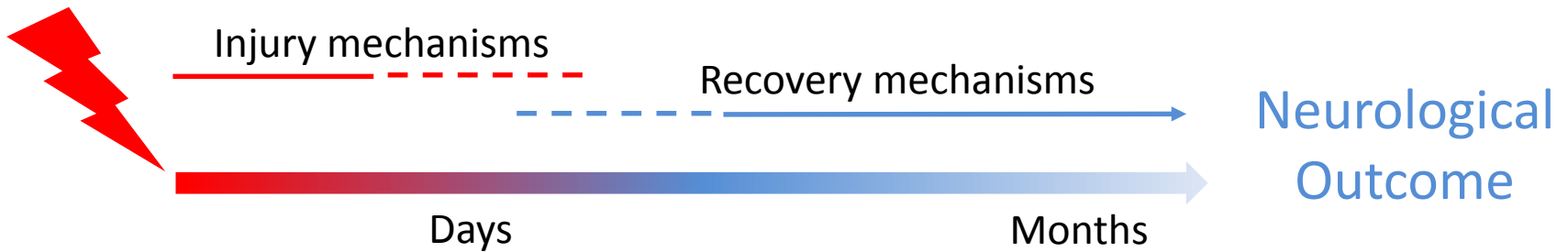
**Table.** Incremental variance in 90d mRS explained by  $\Delta$ NIHSS (adjusted  $R^2$ )

Time interval	Placebo	tPA
Baseline NIHSS	0.25	0.16
$\Delta$ NIHSS <sub>BL-24h</sub>	0.56	0.56
$\Delta$ NIHSS <sub>24h-10d</sub>	0.65	0.65
$\Delta$ NIHSS <sub>10d-90d</sub>	0.71	0.73
	<b>0.31</b>	<b>0.40</b>
	0.09	0.09
	0.06	0.08

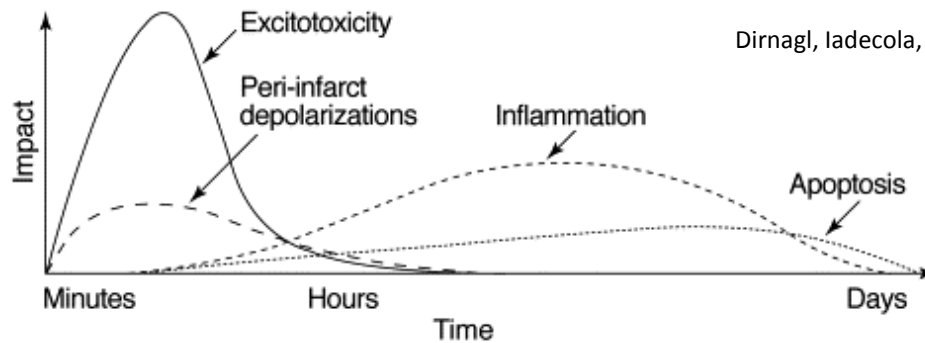


# Stroke Outcomes

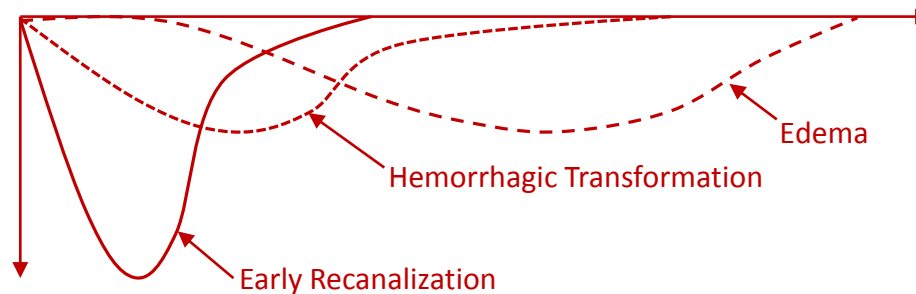
## Mechanisms



Animal Models



Human Stroke



# How to capture these mechanisms?

## Early injury mechanisms

- Carefully chosen endophenotypes can capture specific mechanisms
  - For example, “Neurological improvement”
    - Recanalization / reperfusion
    - Good collateral flow
    - Endogenous neuroprotective mechanisms
- Quantitative endophenotypes provide power for genetic studies
  - For example,  $\Delta\text{NIHSS}_{24\text{hrs}}$ , or hemorrhage volume, etc.

# What endophenotypes?

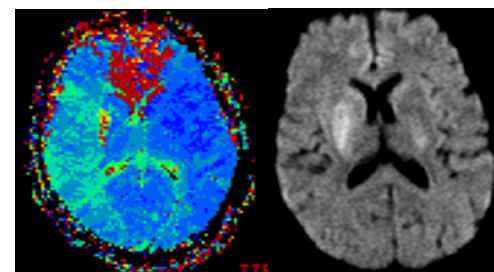
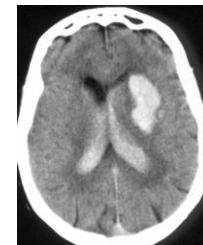
## Clinical endophenotypes

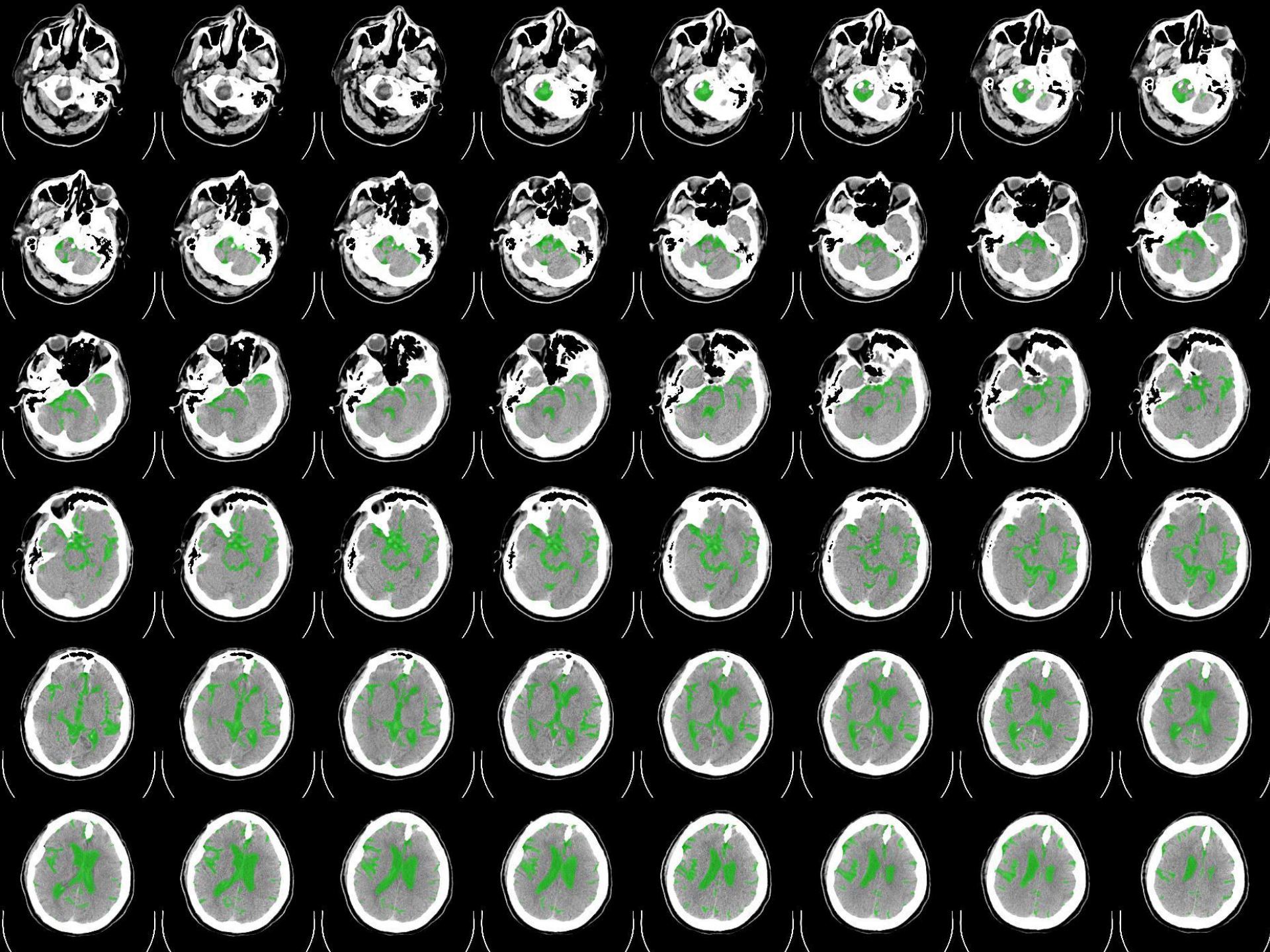
- Early neurological change (rapid improvement / deterioration)
  - $\Delta\text{NIHSS}_{24\text{hrs}} = \text{NIHSS}_{6\text{hrs}} - \text{NIHSS}_{24\text{hrs}}$
- Longer term outcomes
  - Recovery-related mechanisms
  - GISCOME and other prospective studies
- Stroke-related infections
  - Pneumonia, UTI, etc.
  - Genetic susceptibility to infections under stress?

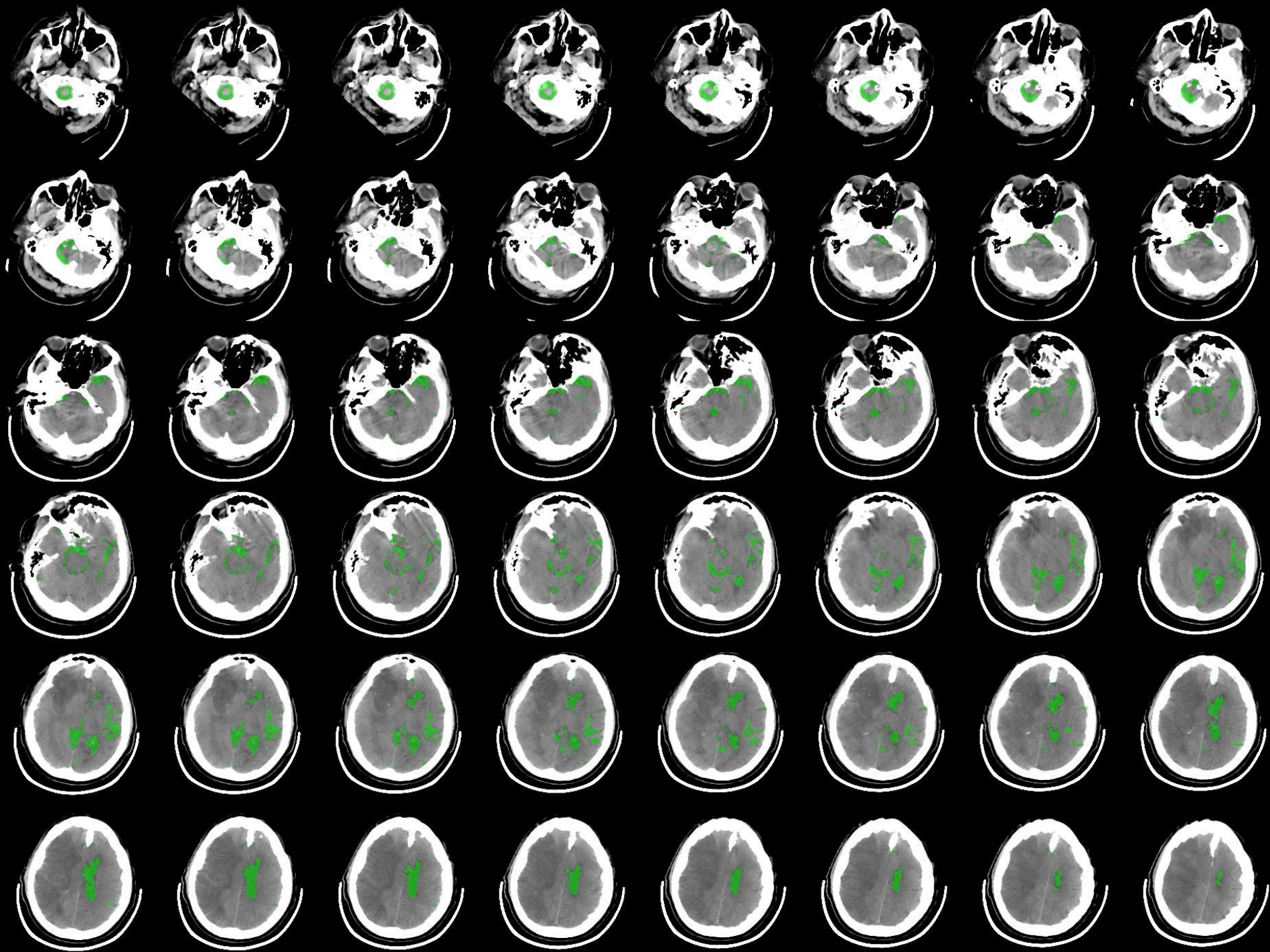
# What endophenotypes?

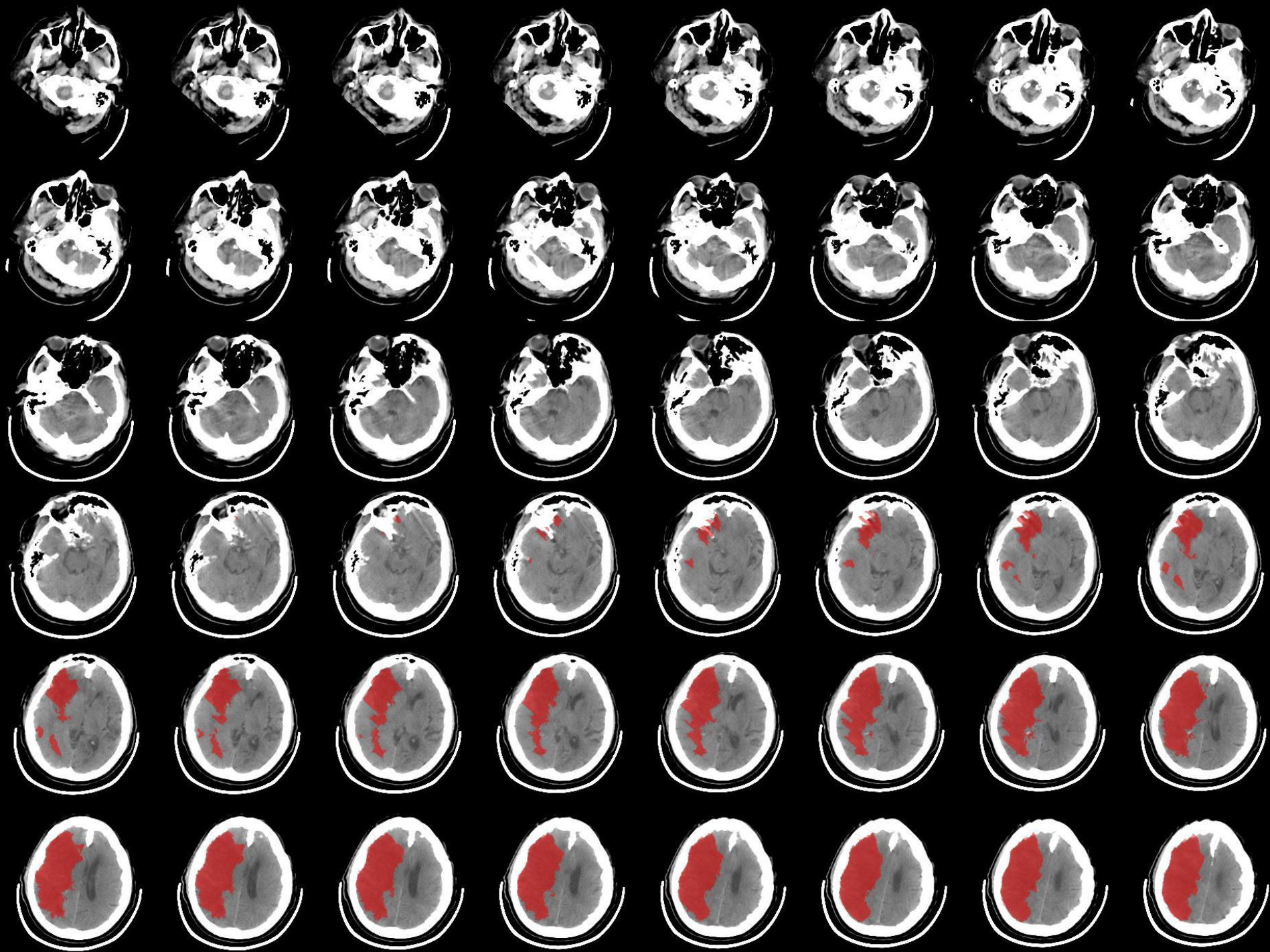
## Imaging endophenotypes

- Hyperdense MCA sign
  - Genetic influence on MCA clot formation?
- Hemorrhagic Transformation
  - Genetic susceptibility to HT or tPA-related HT?
- Recanalization (TCD/CTA/MRA)
  - Genetic predisposition for recanalization?
- Penumbra Imaging (MRI)
  - Diffusion-Perfusion mismatch
  - Genetic influences on penumbral signature on MRI?
- Post-stroke cerebral edema
  - Automated CSF volume quantification
  - Genetic influences on edema?











# What endophenotypes?

## Laboratory endophenotypes

- White blood count
  - Related to post-stroke infection/inflammation
  - Genetic susceptibility to stroke-related inflammation?
- Blood biomarkers of stroke risk or outcomes
  - E.g., C-reactive Protein,  $\alpha$ -2 macroglobulin, Plasminogen activator inhibitor-1, IL-6, etc.
- Troponin
  - Genetic predisposition to MI or stroke-induced troponin leak?
  - May shed light on mechanisms?

# tPA Pharmacogenomics

- tPA-related endophenotypes
  - Hemorrhagic transformation
  - tPA-induced recanalization (MCA)
  - tPA-induced rapid neurological improvement
- GxE interaction
  - Stratify cohort by tPA treatment
  - Compare effect sizes of each sub-strata
  - GxE interactions between  $\Delta\text{NIHSS}_{24\text{h}}$  and tPA treatment
    - $\Delta\text{NIHSS}_{ijk} = u + \beta_{\text{covariates}} X_{\text{covariates}} + \beta_{\alpha} \text{SNP}_{aj} + \beta_{\text{tPA}} \text{tPA}_k + \beta_{\alpha * \text{tPA}} (\text{SNP}_{aj} * \text{tPA}_k) + e_{ijk}$

# Funding/Grants

- Current funded grants
  - NIH R01 “Genetic Architecture of Acute Human Brain ischemia”
    - Lee/Cruchaga (Wash U), Montaner/Fernandez (Barcelona)
    - GWAS of  $\Delta\text{NIHSS}_{24\text{hr}}$  (early neurological improvement/ deterioration)
    - Impact of eQTL’s of stroke-related plasma analytes on early outcome
    - Pharmacogenomics of tPA-related early outcome ( $\Delta\text{NIHSS}_{24\text{hr}}$ )
- Pending grants in application
  - EU Horizons 2020 “GENE-rtPA”
    - Fernandez/Montaner
    - GWAS/rare variant/EWAS of hemorrhagic transformation & recanalization
    - Develop microfluidics device for rapid genotyping
  - Australian grant application: “Targeting optimal Thrombolysis Outcomes” (TOTO Study)
    - Holliday/Levi/Maguire
    - Develop and validate clinical/genetic decision rules to guide thrombolysis
- Sharing of grants across countries for independent funding through country-specific granting agencies?

# Join Us!

## Acute Endophenotypes Working Group

- Sharing data (phenotypes/genotypes)
  - Currently have > 2,000 patients with phenotypes & genotypes
  - Collectively, accumulating samples at a rate of ~1,000 per year
- Sharing ideas
- Supporting common goals
- Collective Grant Opportunities
- Contact:
  - Israel Fernandez ([israelcadenas@yahoo.es](mailto:israelcadenas@yahoo.es))
  - Jin-Moo Lee ([leejm@wustl.edu](mailto:leejm@wustl.edu))
  - Jane Maguire ([jane.maguire@newcastle.edu.au](mailto:jane.maguire@newcastle.edu.au))