Stroke Cerebroprotection: How to bring translational science to the bedside

Enrique Leira MD, MS
Stoppelmoor-Adams Professor in Vascular Neurology
Professor of Neurology, Neurosurgery & Epidemiology
University of Iowa

The University of Iowa

Disclosure

- Salary Support NIH-NINDS:

  R21NS104579

  U24NS107247

  U01 NS113388
- I have been pursuing a grant on Uric Acid through Strokenet

Two Stroke Neurologists partner in a mission to promote Uric Acid as a Cerebroprotectant agent through StrokeNet.

1. A Call From an Old Friend From Barcelona

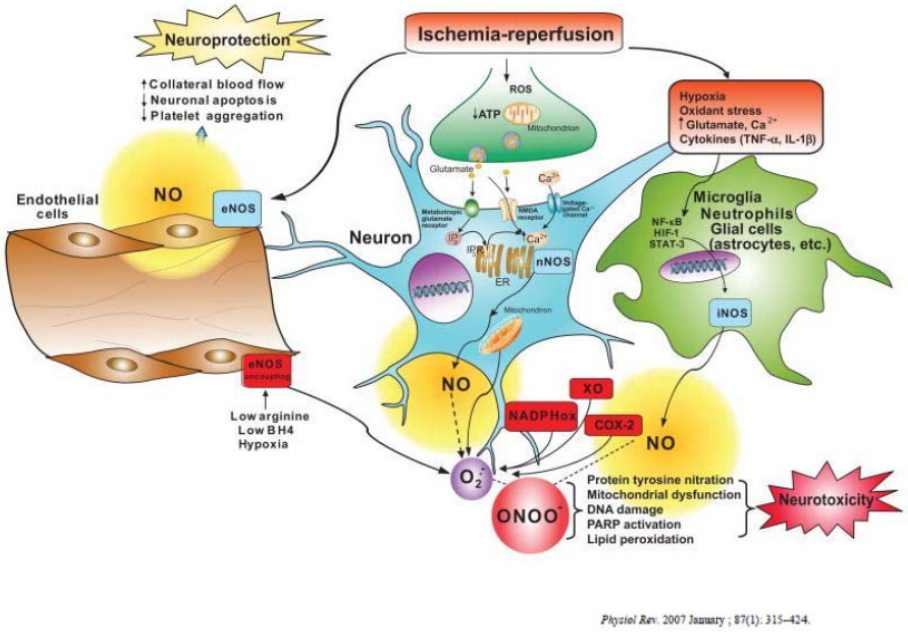
Following the promising results of the URICO-ICTUS trial, in 2015 Angel Chamorro partners with Enrique Leira to propose an acute trial through StrokeNet

Outline

- Importance cerebroprotection
- Mechanism matters
- Translational challenges
- STAIR Redemption
- The SPAN revolution
- Future Pathway Cerebroprotection
- Translational tips

Cerebroprotection: Definition

- Agent administered to preserve brain function independent of reperfusion
- Targets neurons, oligodendroglia, microglia or neurovascular unit
- Specific function
- Clear mechanism

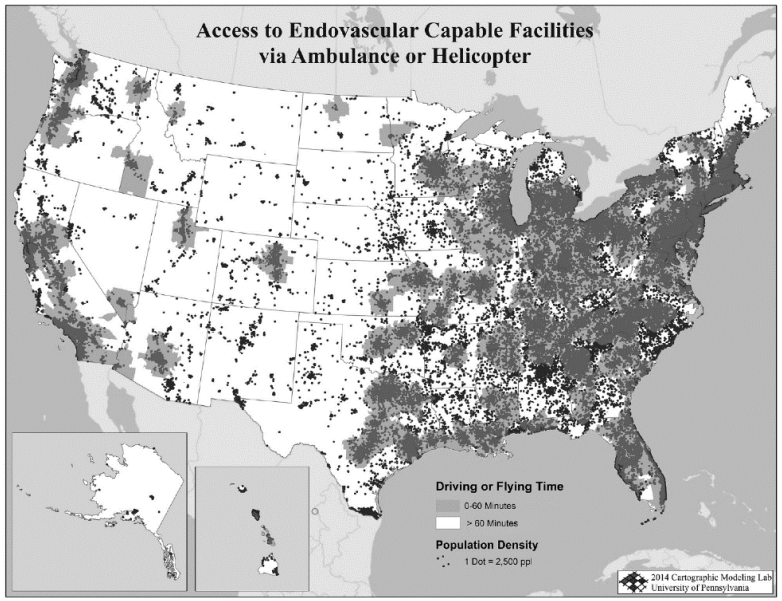


Physiol Rev. 2007 January ; 87(1): 315–424.

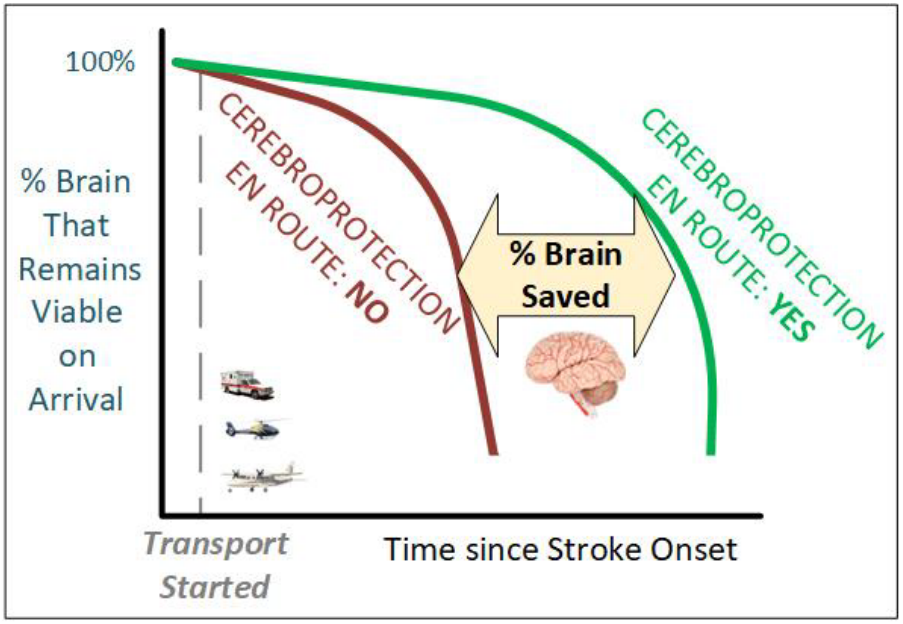
Why Cerebroprotection?

- Most patients untreated
- Elective procedures with risk of stroke
- Limited effectiveness of thrombolysis
- Limited recanalization of MT
- Issue of Microcirculation
- Distance & transportation

Cerebroprotection During Transport



(Adeoye et al 2014)



(Leira et al 2023)

Mechanism Matters?

NO

- Pragmatism
- Not required if unmet needs
- Not required for FDA approval

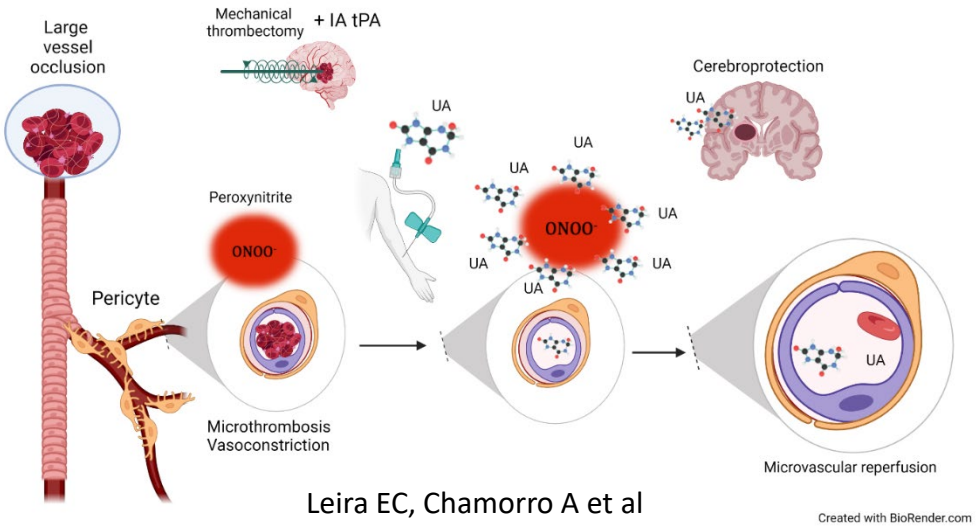
YES

- Critical step for scientific progress in field
- Enables better dosing in therapeutic target
- Stratifies trials to those more likely to respond
- Anticipates side effects better

Davis RL, iScience 2020
Nature Medicine 2010

UA: peroxynitrite scavenger

- Ischemia/reperfusion reactive oxygen species
- NO + superoxide = peroxynitrite
- Powerful oxidant with toxic effects
- Builds mostly in ischemic penumbra
- Pericytes and arterioles → No-reflow phenomenon



Leira EC, Chamorro A et al
Neurology (in press)

Not all antioxidants are equal

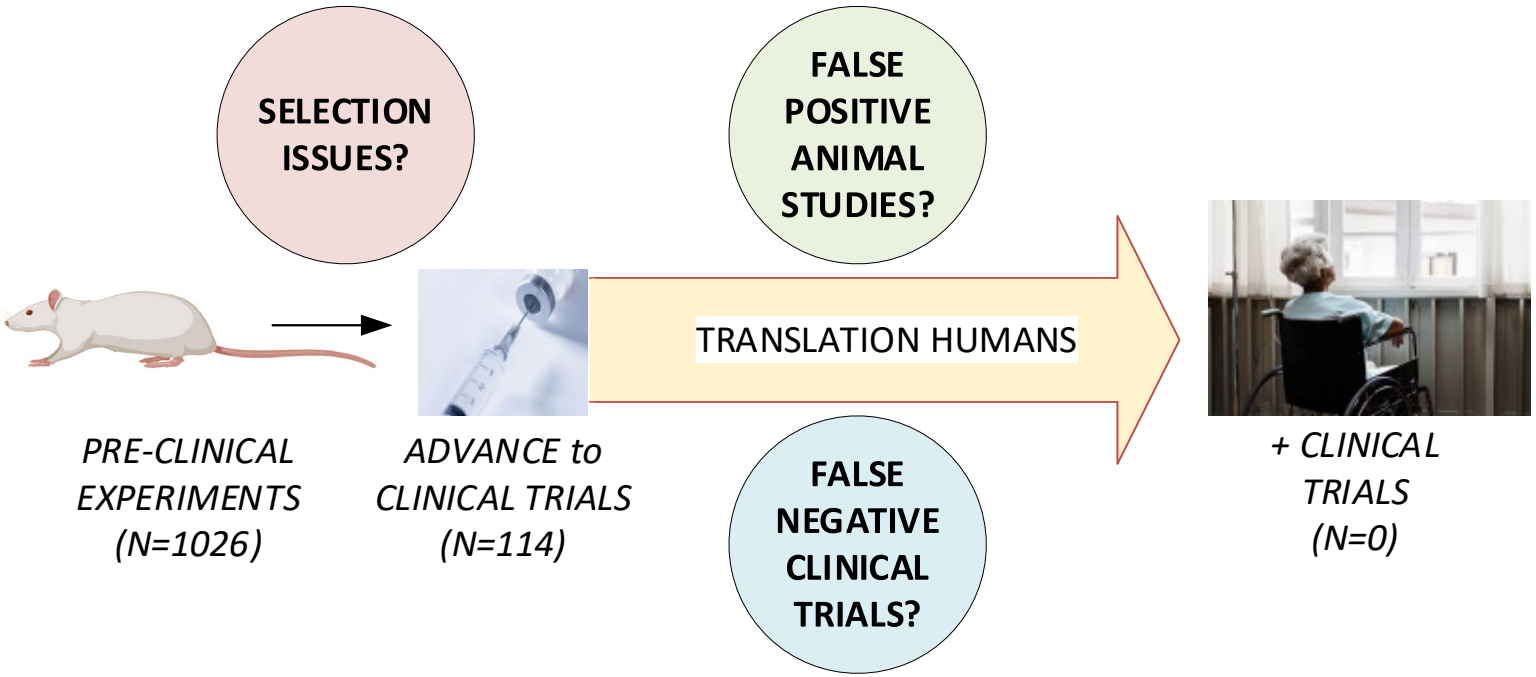
Ability to trap carbon and oxygen centered radicals and prevent the oxidation of salicylate in vitro

A. Fe (II) System 2,5-DHBA Results.

Compound	IC_{50} (μM)	R^2
PBN	141	1.00
S-PBN	178	0.98
NXY-059	441	0.99
Cysteine	278	0.98
Glutathione	185	1.00
Ascorbate	323	0.97
Uric Acid	104	0.99
Tempo	115	0.99
Trolox	208	0.99
Tirilizad	Increased	–

Free Radic Res 2001; 34:417– 426

Translational Challenges



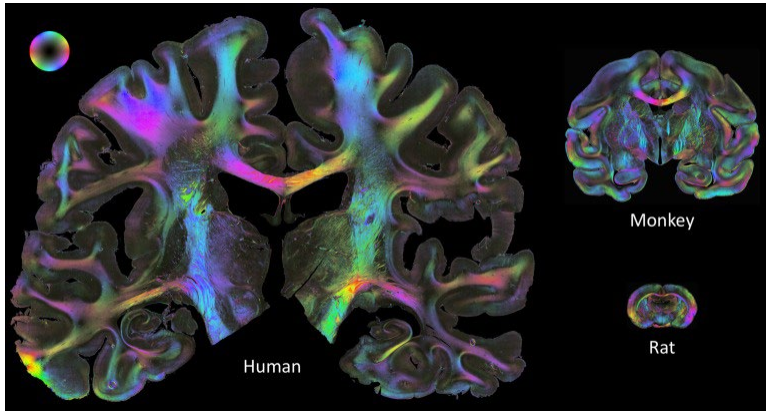
Ann Neurol 2006;59:467–477

Pre-clinical Challenges

- Biological differences
- Baseline differences
- Mechanism Stroke
- Dose & mode administration
- Time window
- Methodological Rigor

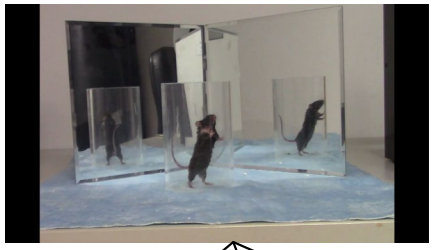
Rodent Biological Differences

- Genetic & epigenetic
- Brain anatomy
- Functional organization
- Vascular anatomy
- Immunological

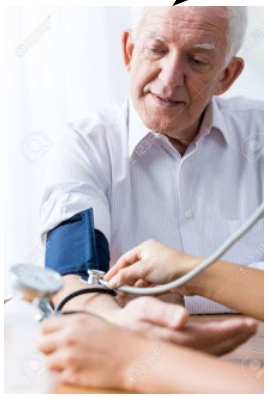


Sommer CJ, Acta Neuropathol 2017

Baseline Differences



?



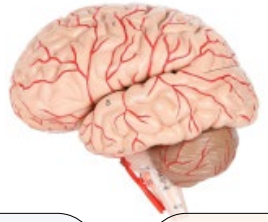
Sommer CJ, Acta Neuropathol 2017S

Mechanism Stroke

CARDIOEMBOLISM
(20%)

LARGE ARTERY ATHERO
(25%)

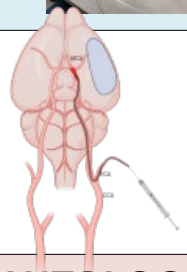
OTHER CAUSES
(5%)



SMALL ARTERY (LACUNAR)
(25%)

CRYPTOGENIC
(25%)

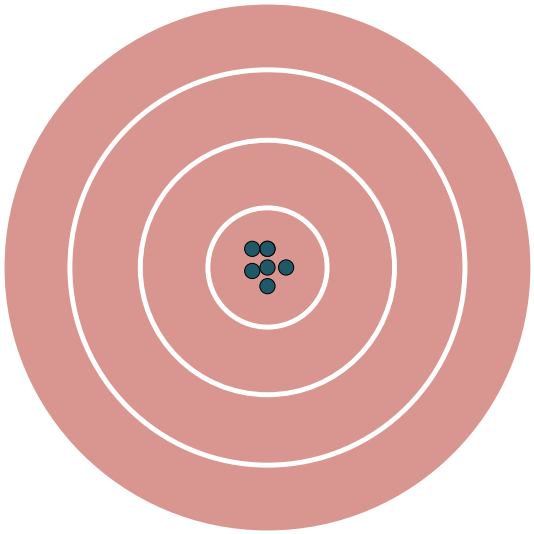
FILAMENT MODEL (85%)



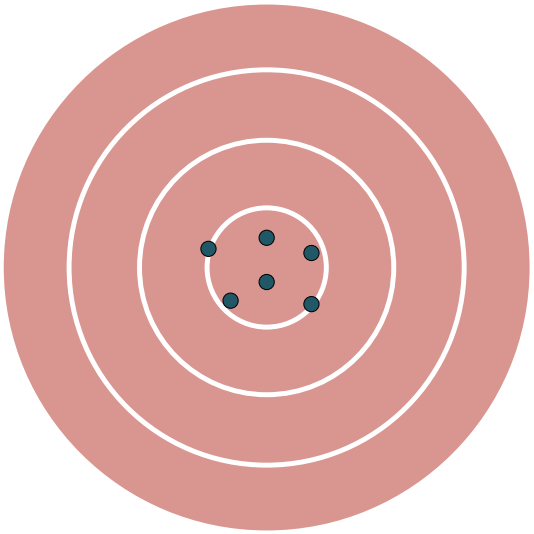
OTHER MODELS
(5%)

AUTOLOGOUS CLOT MODEL (15%)

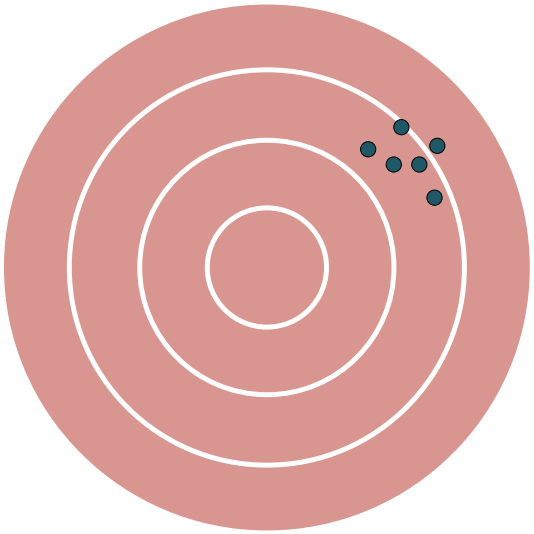
Preclinical Methodological Biases



No Error



Random Error

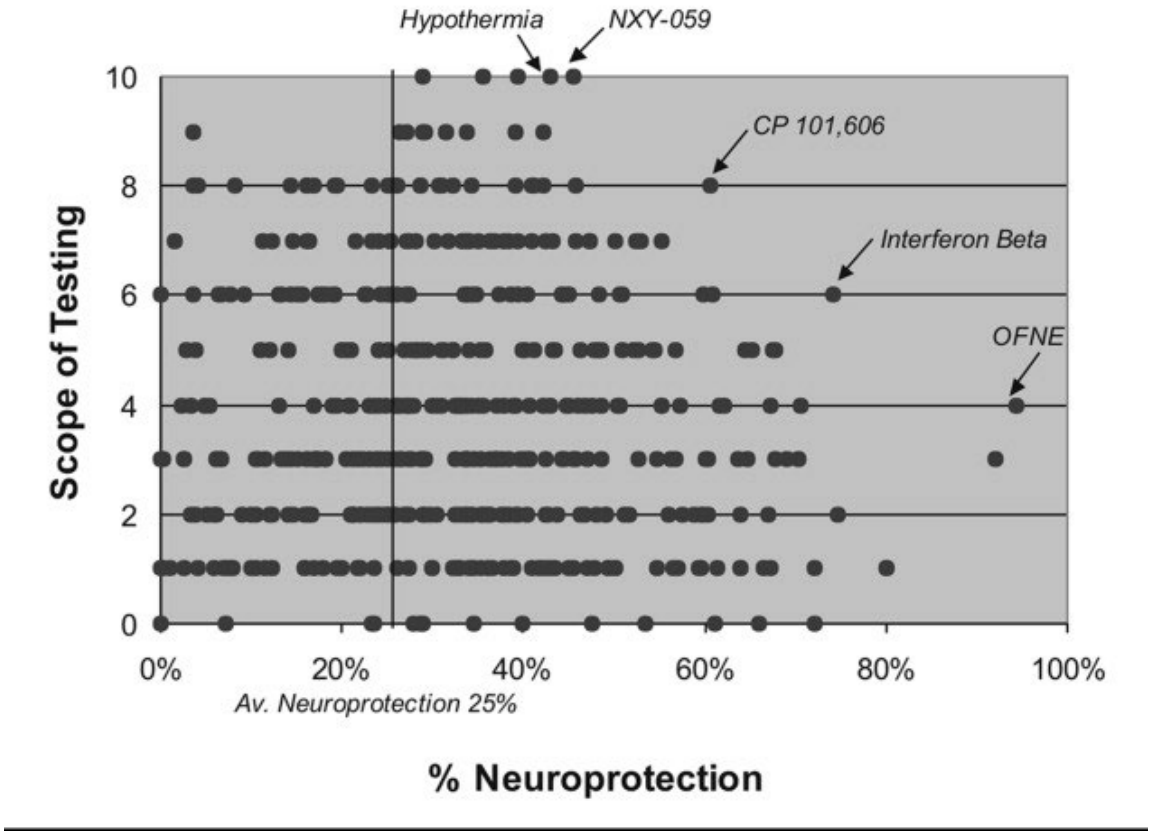


Systematic Error

Preclinical Rigor Issues

Lacking Issue	Resulting Bias
Sample /power	Significant results
Randomization	Selection
Intention to Treat (ITT)	Attrition
Masking Intervention	Ascertainment
Blinded Assessment	Detection

Methodological Rigor vs. Magnitude Effect

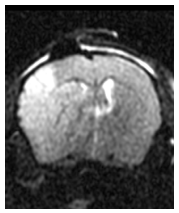


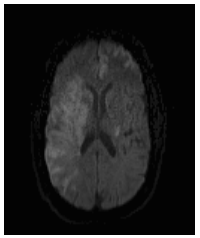
Ann Neurol 2006;59:467–477

Clinical Trial Issues

- Expectations of effect
- Heterogenous patients
- Interaction with IVT
- Variable reperfusion
- Variable rehabilitation
- Outcome measures used

Outcome Measures Challenges





Bederson Score

mNSS

NIHSS

Scandinavian Stroke S.

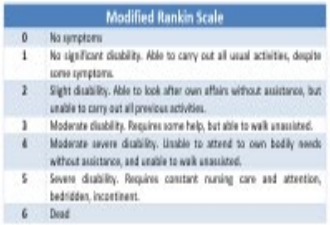
Corner Test

Grid Walk

Time up and go (TUG)

Functional Gait Assessment

?



LESION

IMPAIRMENT

FUNCTION

DISABILITY

Schaar et al *Exp Transl Stroke Med* 2010

The STAIR Redemption

- Stroke Therapy Academy Industry Roundtable
- Community response to failures
- Neurologists, physicians, industry, regulators
- Enhance acute and restorative therapies
- Initial recommendations 1999
- Preclinical methodology
- Clinical trial methodology

Fisher et al Stroke 1999

Update of the Stroke Therapy Academic Industry Roundtable Preclinical Recommendations

Marc Fisher, MD; Giora Feuerstein, MD; David W. Howells, PhD; Patricia D. Hurn, PhD; Thomas A. Kent, MD; Sean I. Savitz, MD; Eng H. Lo, PhD; for the STAIR Group

Table 1. Initial STAIR Preclinical Recommendations

1. Adequate dose-response curve
2. Define the time window in a well-characterized model
3. Blinded, physiologically controlled reproducible studies
4. Histological and functional outcomes assessed acutely and long-term
5. Initial rodent studies, then consider gyrencephalic species
6. Permanent occlusion then transient in most cases

Fisher et al Stroke 1999

STAIR Updates

- Sample Size Calculation
- Inclusion and exclusion criteria
- Randomization
- Allocation concealment
- Reporting excluded animals
- Blinded assessment of outcome
- Transparency COI/funding
- Linking animal models to clinical stroke

Fisher et al, Stroke 2009

Two Stroke Neurologists partner in a mission to promote Uric Acid as a Cerebroprotectant agent through StrokeNet.

1. A Call From an Old Friend From Barcelona

Following the promising results of the URICO-ICTUS trial, in 2015 Angel Chamorro partners with Enrique Leira to propose an acute trial through StrokeNet

2. Uric Acid Meets Mr. STAIR

The URIC trial proposal advances through the Strokenet commitees, but the STAIR recommendations are a serious challenge

Uric Acid STAIR Initial Checklist

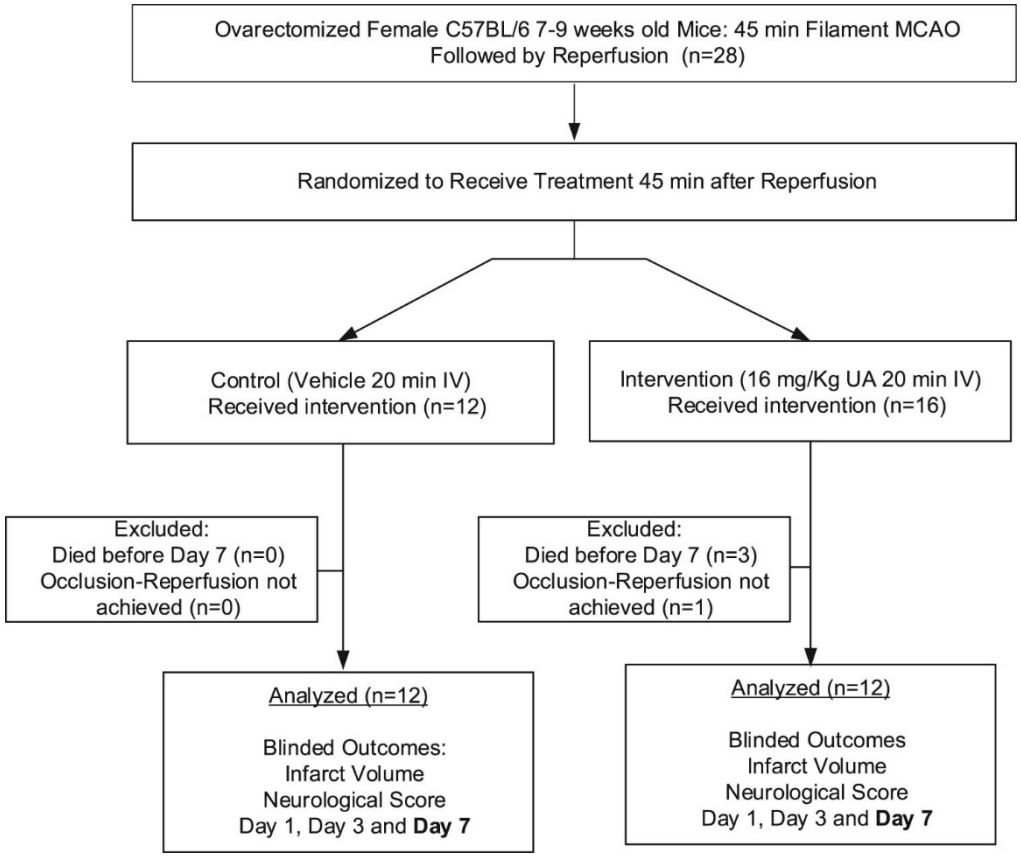
Mechanism established √
Different Species √
Animal Co-morbidities √
IV route of administration √
Dose established √
Interaction with rtPA √
Different Laboratories ?
Sex differences ?
Rigor to minimize biases ?
Long-term outcomes ?

Beefing up STAIR Pedigree?

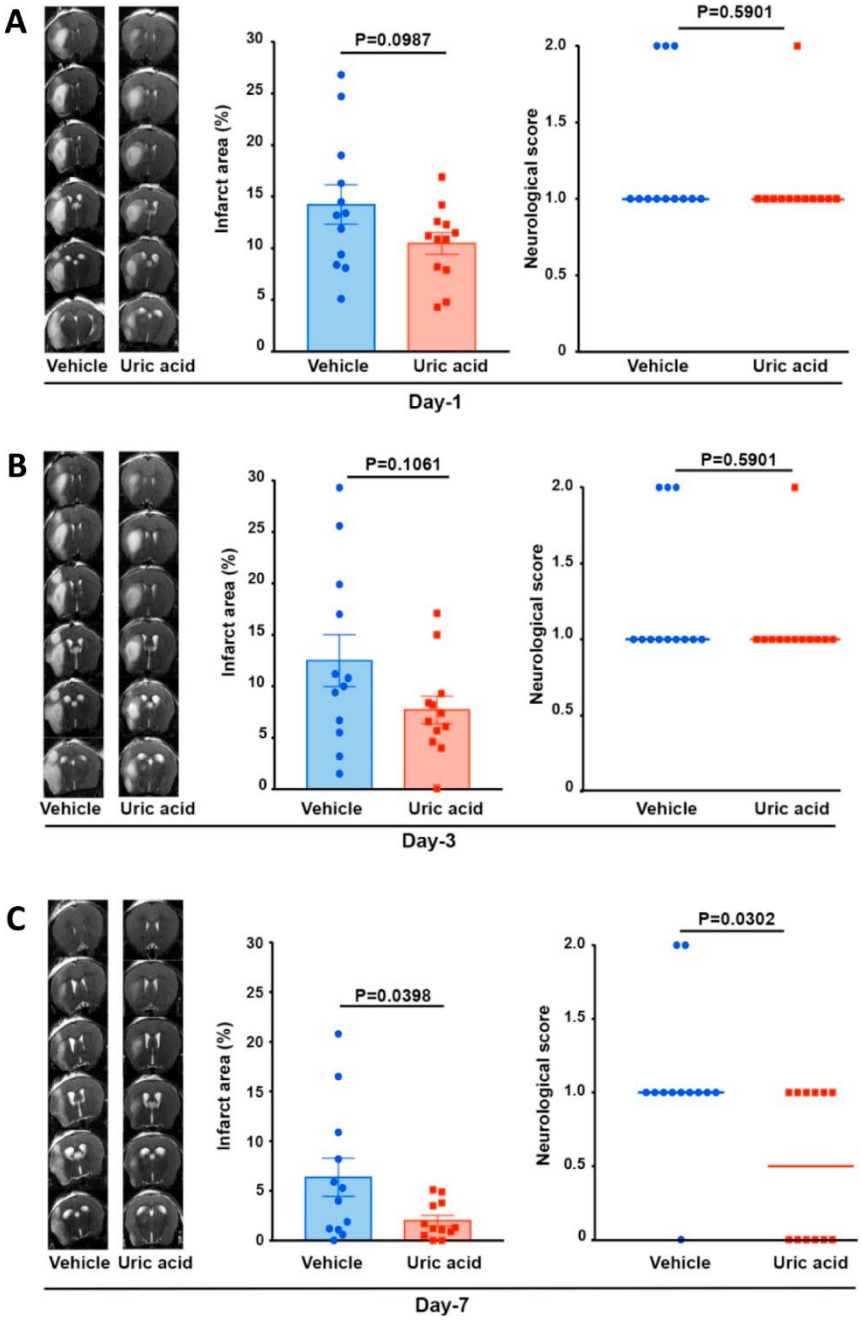
- How much is enough?
- Which laboratory will do it?
- Confirmatory science less appealing
- Co-morbid models expensive
- Increase mortality
- Cost of long-term outcomes
- Funding?

Treatment with Uric Acid Reduces Infarct and Improves Neurologic Function in Female Mice After Transient Cerebral Ischemia

Nirav Dhanesha, PhD,* Edwin Vázquez-Rosa, PhD,†,‡
Coral J. Cintrón-Pérez, MBA,† Daniel Thedens, PhD,‡ Alexa J. Kort, HS,†
Vicky Chuong, BA,† Adriana M. Rivera-Dompenciel, BA,†
Anil K. Chauhan, PhD,*,1 Enrique C. Leira, MD, MS,§,‖,1 and
Andrew A. Pieper, MD, PhD†,§,1



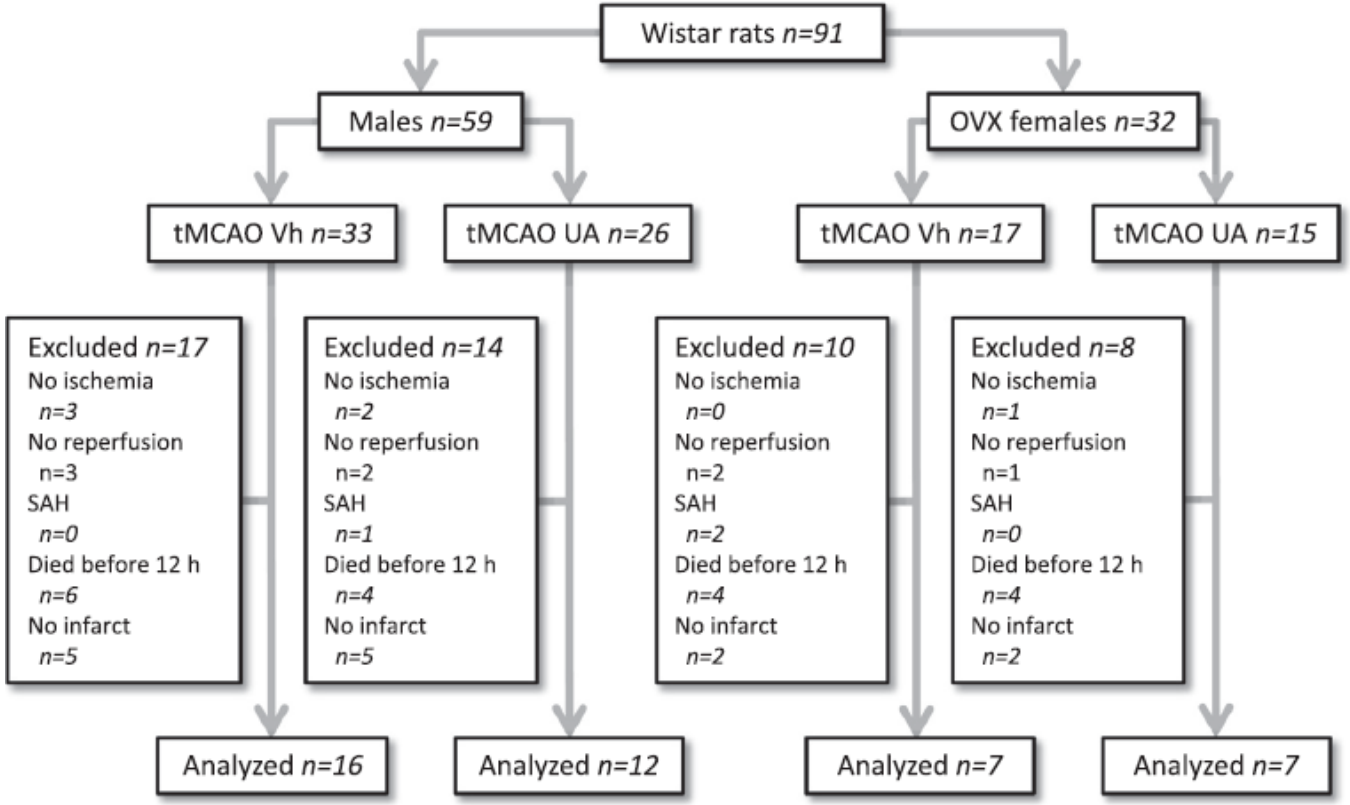
Dhanesha et al J Stroke Cerebrovasc Diseases 2018

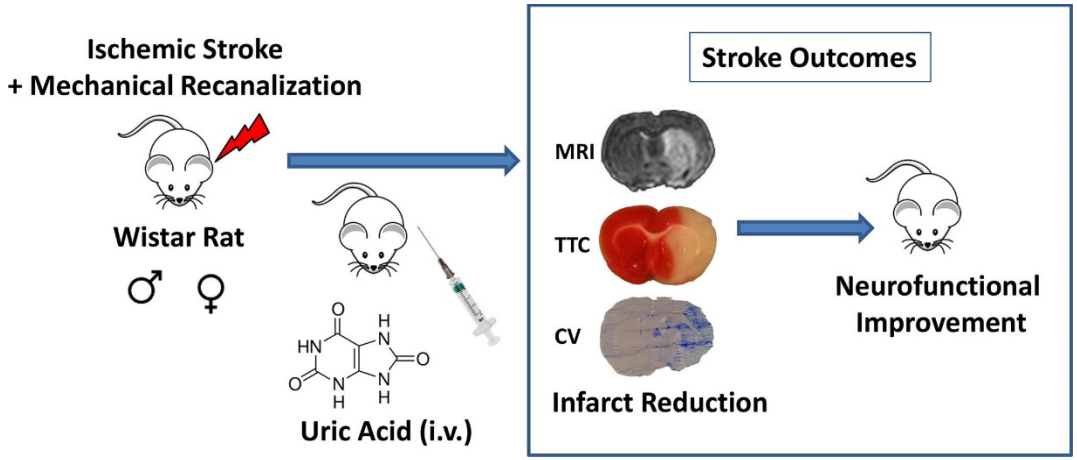


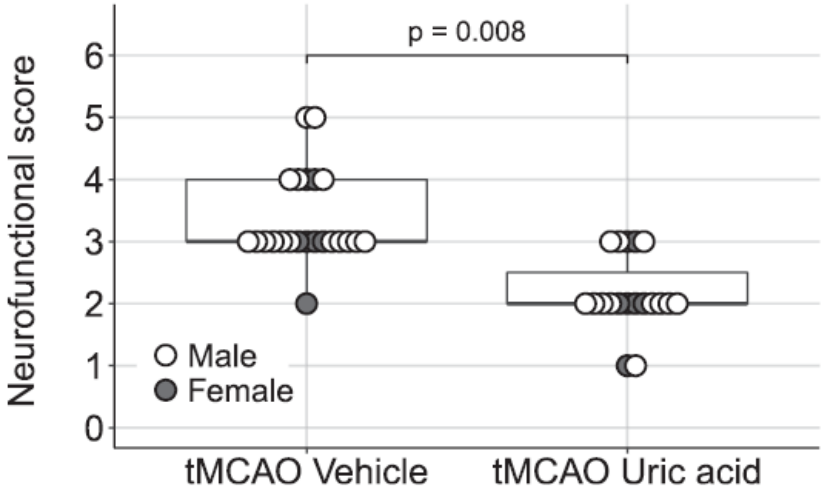
Dhanesha et al J Stroke Cerebrovasc Diseases 2018

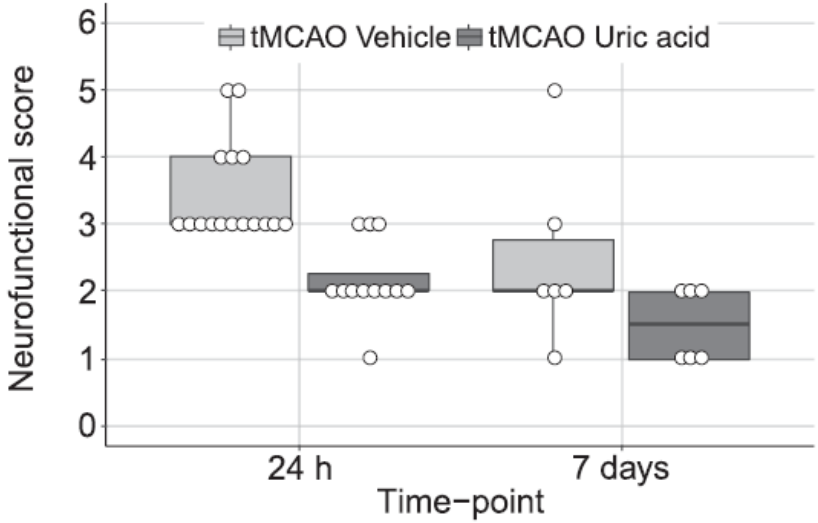
Emergent Uric Acid Treatment is Synergistic with Mechanical Recanalization in Improving Stroke Outcomes in Male and Female Rats

Alicia Aliena-Valero, [a,b†] Mikahela A. López-Morales, [a†] María C. Burguete, [a,b†] María Castelló-Ruiz, [a,c*] Teresa Jover-Mengual, [a,b] David Hervás, [d] Germán Torregrosa, [a] Enrique C. Leira, [e] Ángel Chamorro [f,g] and Juan B. Salom [a,b]




Ischemic Stroke
+ Mechanical Recanalization
Wistar Rat
♂ ♀
Uric Acid (i.v.)
Stroke Outcomes
MRI
TTC
CV
Infarct Reduction
Neurofunctional
Improvement


p = 0.008
Neurofunctional score
Male
Female
tMCAO Vehicle
tMCAO Uric acid


tMCAO Vehicle
tMCAO Uric acid
Neurofunctional score
24 h
7 days
Time−point

Two Stroke Neurologists partner in a mission to promote Uric Acid as a Cerebroprotectant agent through StrokeNet.

1. A Call From an Old Friend From Barcelona

Following the promising results of the URICO-ICTUS trial, in 2015 Angel Chamorro partners with Enrique Leira to propose an acute trial through StrokeNet

2. Uric Acid Meets Mr. STAIR

The URIC trial proposal advances through the Strokenet commitees, but the STAIR recommendations are a serious challenge

3. The SPAN Revolution

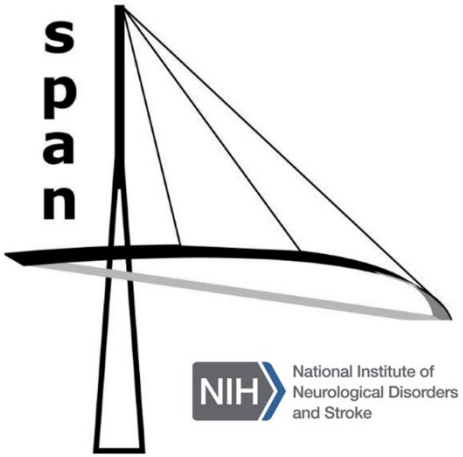
Uric Acid investigators join a promising new rigorous network established by the NIH to advance cerebroprotection

The SPAN Revolution 2019

- 1 Coordinating Center
- 6 Performing Centers

Stroke Preclinical Assessment Network (SPAN) to Support Translational Studies for Acute Neuroprotection - Coordinating Center (U24 Clinical Trial Not Allowed)

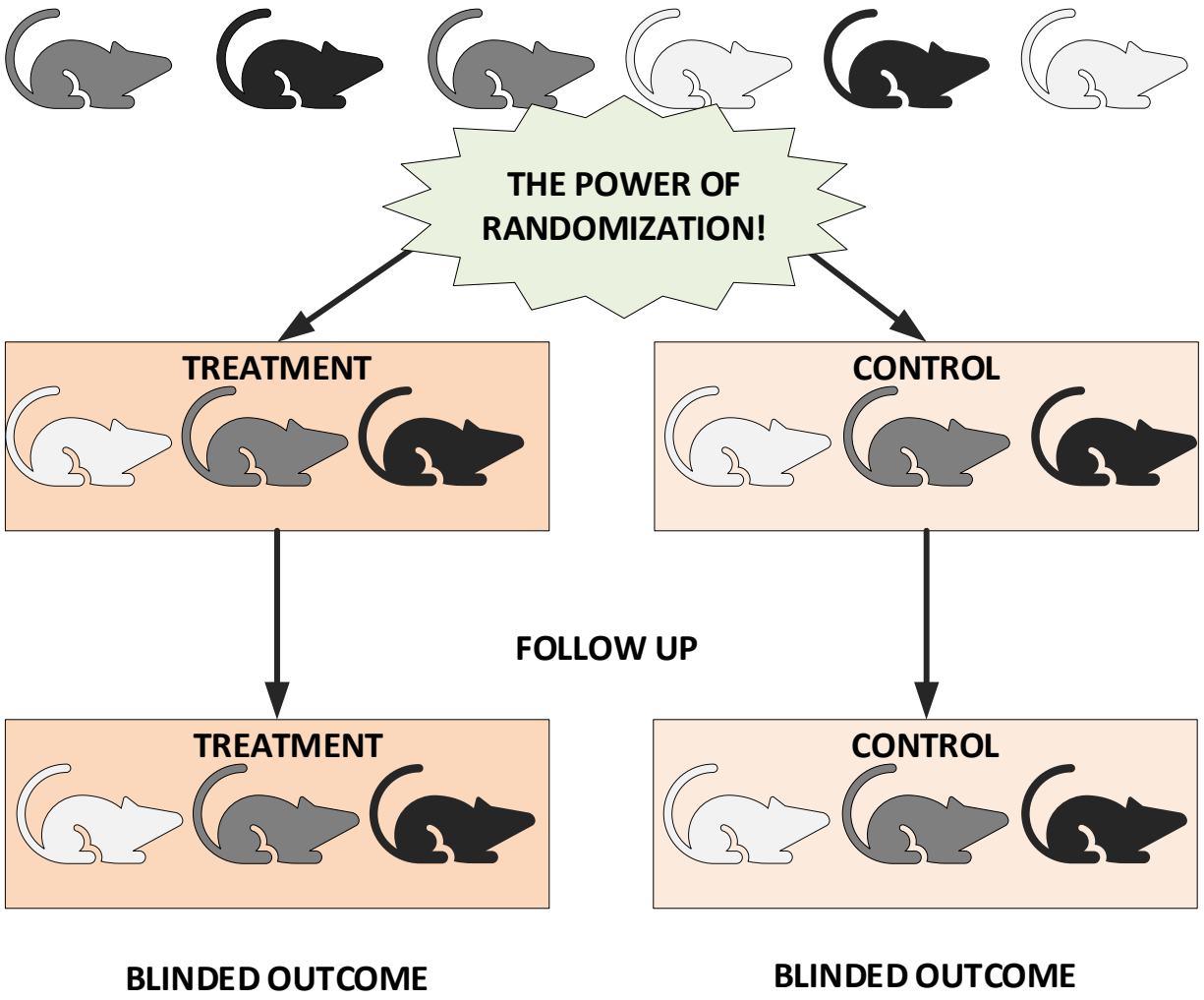
U24 Resource-Related Research Projects – Cooperative Agreements



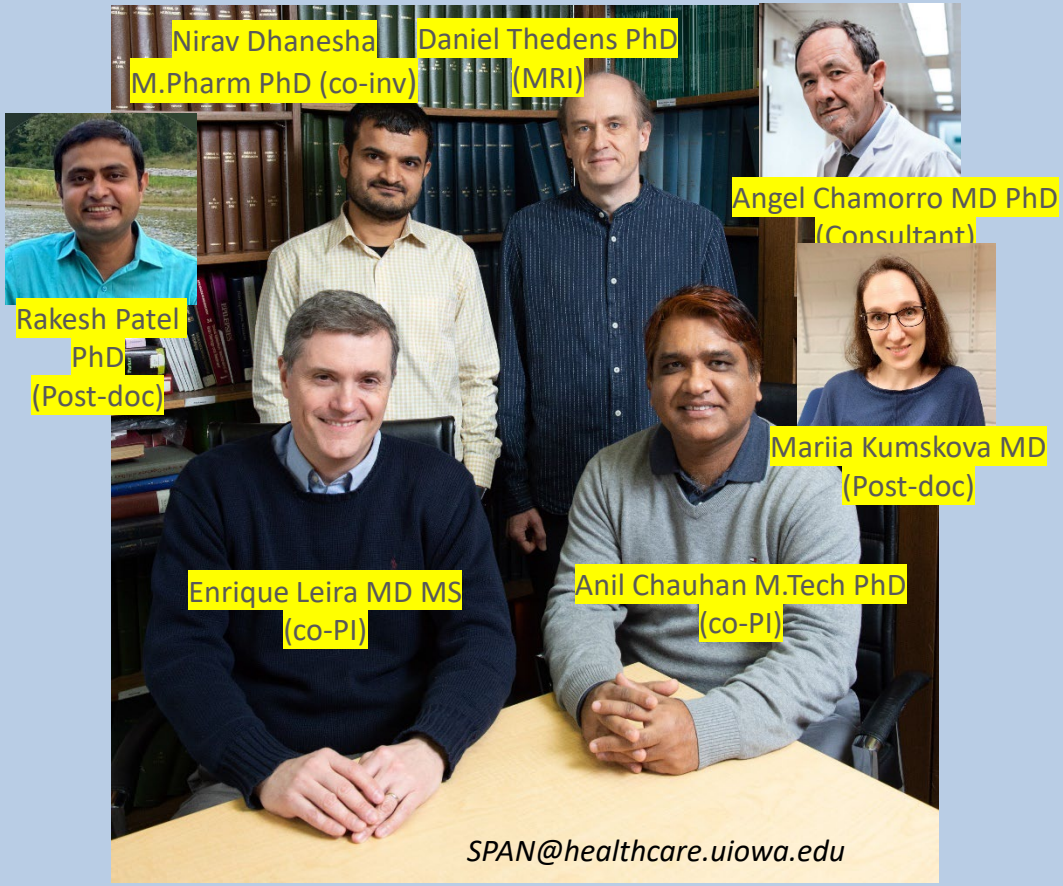
SPAN Revolution

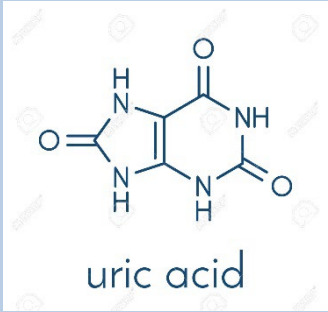
- STAIR way to heaven
- Rigor of pre-clinical cerebroprotection
- Centers applied with a proposed intervention
- Central masking and shipping
- Randomized animals with ITT
- Blinded surgeons & raters

SPAN: Methodological Rigor



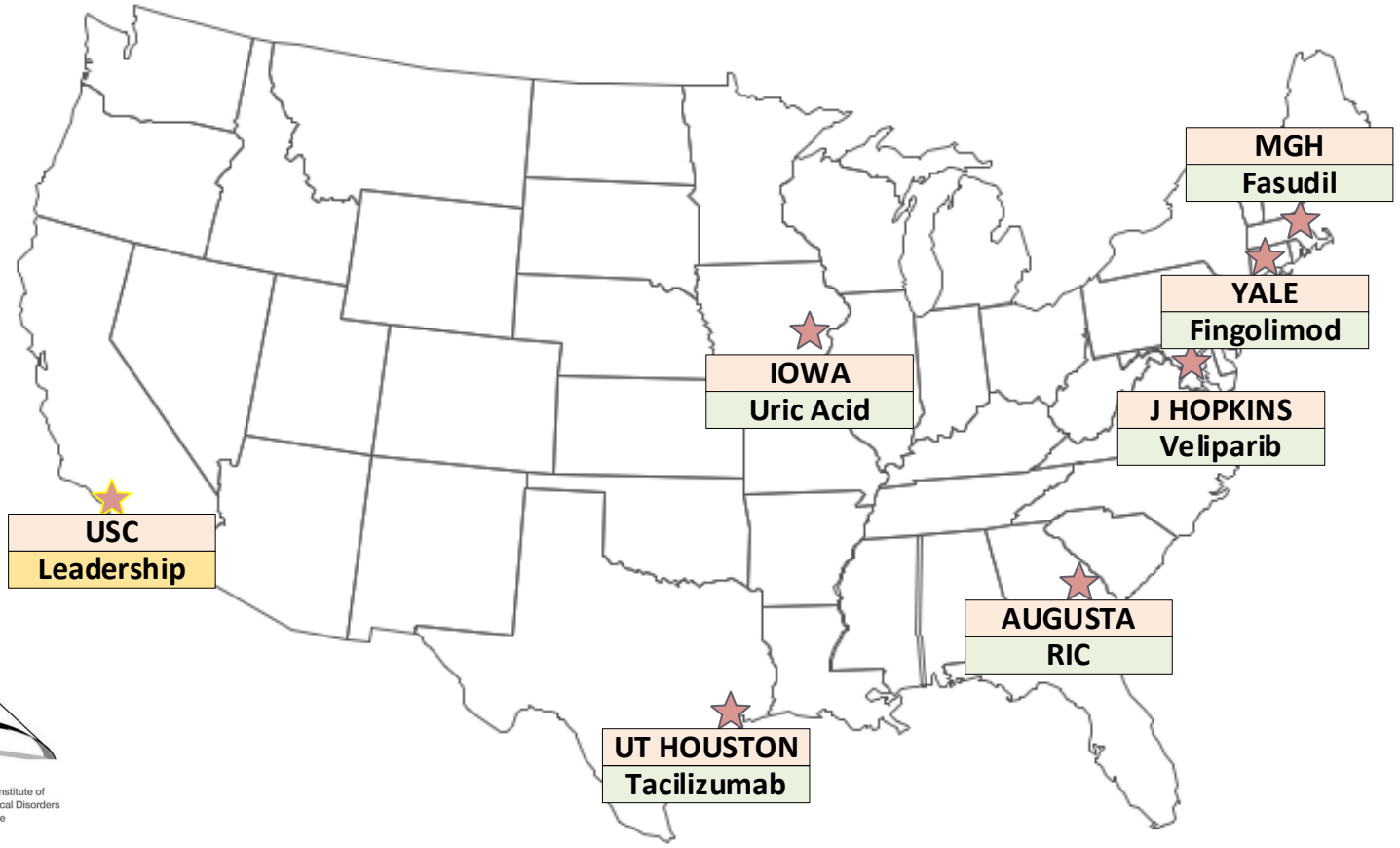
University of Iowa SPAN





THE UNIVERSITY OF IOWA

SPAN 1.0 NIH Network



span

NIH National Institute of Neurological Disorders and Stroke

SPAN Revolution (2)

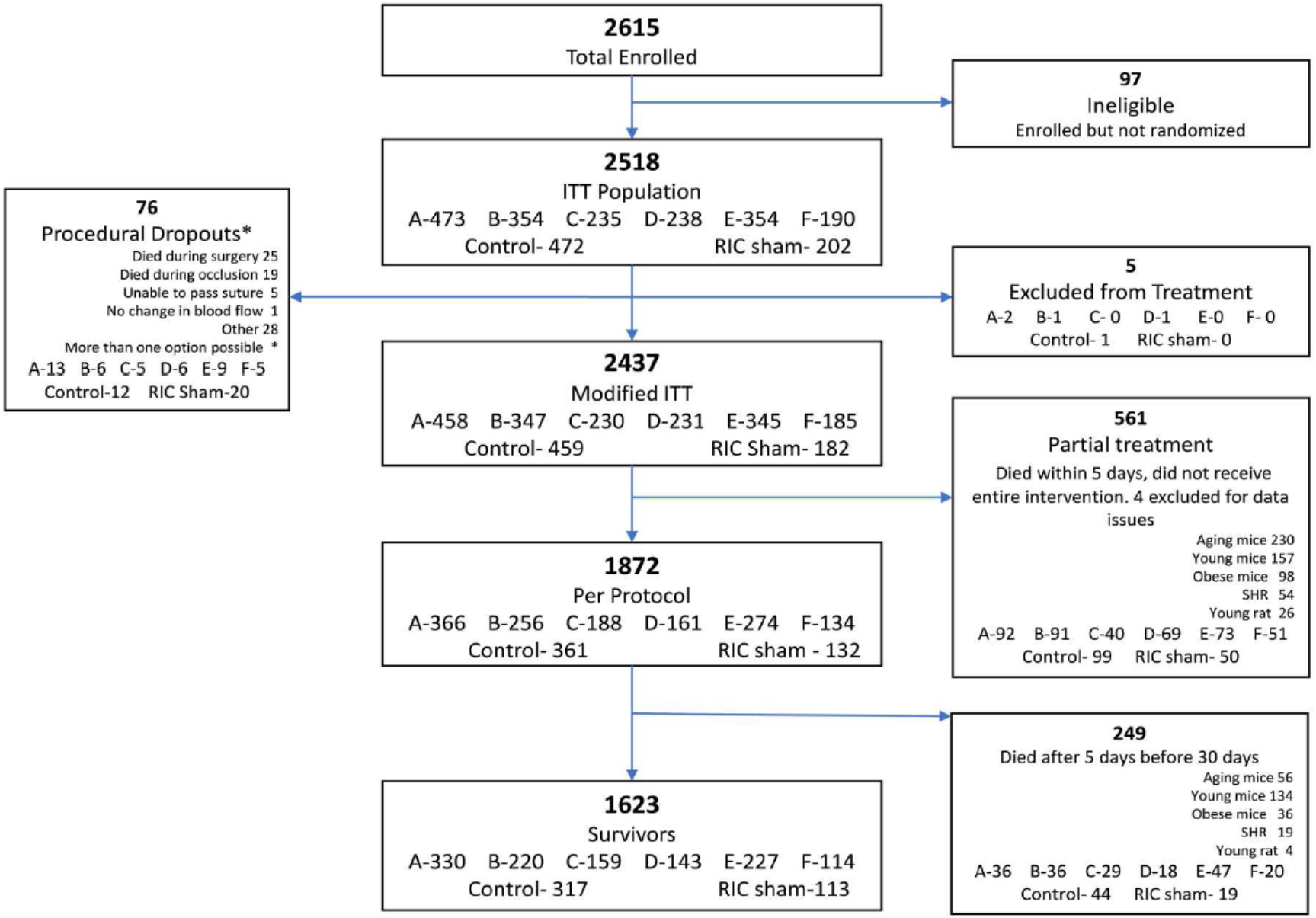
- Challenges building a new network
- Changing the laboratory culture
- Standardize practices
- Establishing consensus
- Design experiments
- Agree on primary outcome
- Imaging secondary

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

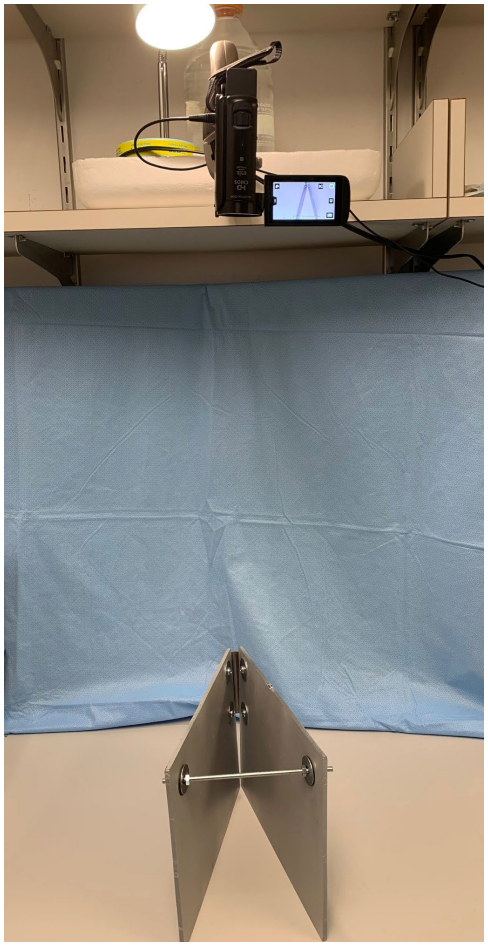
STROKE

A multi-laboratory preclinical trial in rodents to assess treatment candidates for acute ischemic stroke

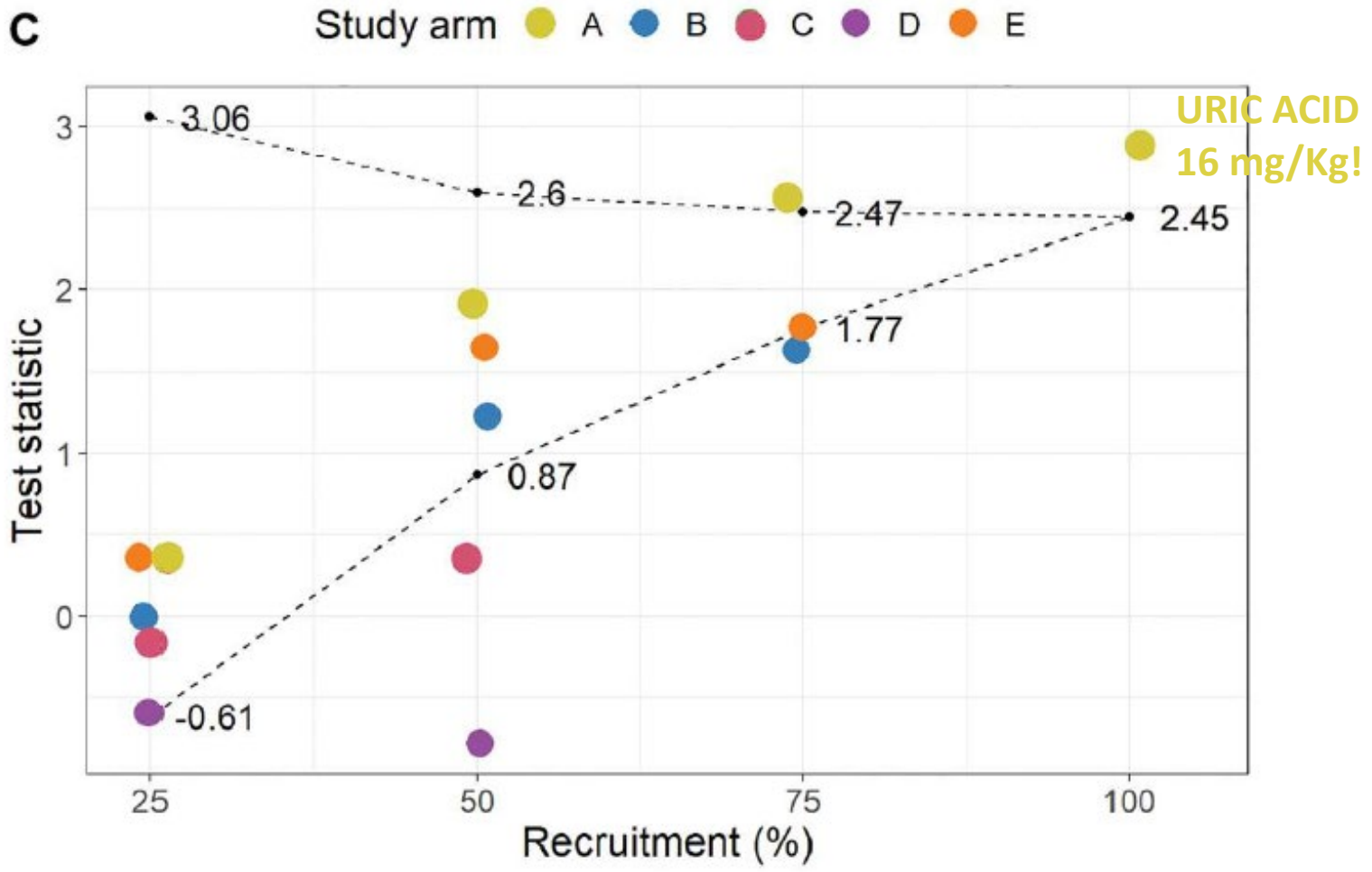
Patrick D. Lyden[1,2*], Márcio A. Diniz[3], Francesca Bosetti[4], Jessica Lamb[1], Karisma A. Nagarkatti[1], André Rogatko[3], Sungjin Kim[3], Ryan P. Cabeen[5], James I. Koenig[4], Kazi Akhter[6], Ali S. Arbab[7], Brooklyn D. Avery[8], Hannah E. Beatty[9], Adnan Bibic[6], Suyi Cao[8], Ligia Simoes Braga Boisserand[9], Angel Chamorro[10,11], Anjali Chauhan[12], Sebastian Diaz-Perez[13], Krishnan Dhandapani[14], Nirav Dhanesha[15], Andrew Goh[12], Alison L. Herman[9], Fahmeed Hyder[16,17], Takahiko Imai[18], Conor W. Johnson[9], Mohammad B. Khan[19], Pradip Kamat[19], Senthilkumar S. Karuppagounder[20], Mariia Kumskova[15], Jelena M. Mihailovic[16], Joseph B. Mandeville[18], Andreia Morais[18], Rakesh B. Patel[15], Basavaraju G. Sanganahalli[16], Cameron Smith[19], Yanrong Shi[8], Brijesh Sutariya[15], Daniel Thedens[21], Tao Qin[18], Sofia E. Velazquez[9,13], Jaroslaw Aronowski[12], Cenk Ayata[22], Anil K. Chauhan[15], Enrique C. Leira[10,23,24], David C. Hess[19], Raymond C. Koehler[8], Louise D. McCullough[12], Lauren H. Sansing[9,13]


2615
Total Enrolled
97
Ineligible
Enrolled but not randomized
2518
ITT Population
A-473 B-354 C-235 D-238 E-354 F-190
Control- 472 RIC sham- 202
76
Procedural Dropouts*
Died during surgery 25
Died during occlusion 19
Unable to pass suture 5
No change in blood flow 1
Other 28
More than one option possible *
A-13 B-6 C-5 D-6 E-9 F-5
Control-12 RIC Sham-20
5
Excluded from Treatment
A-2 B-1 C- 0 D-1 E-0 F- 0
Control- 1 RIC sham- 0
2437
Modified ITT
A-458 B-347 C-230 D-231 E-345 F-185
Control- 459 RIC Sham- 182
561
Partial treatment
Died within 5 days, did not receive entire intervention. 4 excluded for data issues
Aging mice 230
Young mice 157
Obese mice 98
SHR 54
Young rat 26
A-92 B-91 C-40 D-69 E-73 F-51
Control- 99 RIC sham- 50
1872
Per Protocol
A-366 B-256 C-188 D-161 E-274 F-134
Control- 361 RIC sham - 132
249
Died after 5 days before 30 days
Aging mice 56
Young mice 134
Obese mice 36
SHR 19
Young rat 4
A-36 B-36 C-29 D-18 E-47 F-20
Control- 44 RIC sham- 19
1623
Survivors
A-330 B-220 C-159 D-143 E-227 F-114
Control- 317 RIC sham-113

Primary Outcome: Corner Test



Multi-Arm Multi-Stage Model



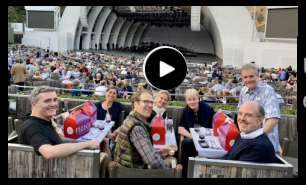
Two Stroke Neurologists partner in a mission to promote Uric Acid as a Cerebroprotectant agent through StrokeNet.

1. A Call From an Old Friend From Barcelona

Following the promising results of the URICO-ICTUS trial, in 2015 Angel Chamorro partners with Enrique Leira to propose an acute trial through StrokeNet

2. Uric Acid Meets Mr. STAIR

The URIC trial proposal advances through the Strokenet commitees, but the STAIR recommendations are a serious challenge

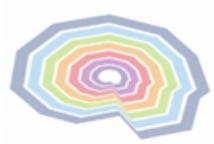


3. The SPAN Revolution

Uric Acid investigators join a promising new rigorous network established by the NIH to advance cerebroprotection

4. STEPS of Hope

The new StrokeNet thrombectomy platform is an opportunity to simultaneously validate uric acid and SPAN

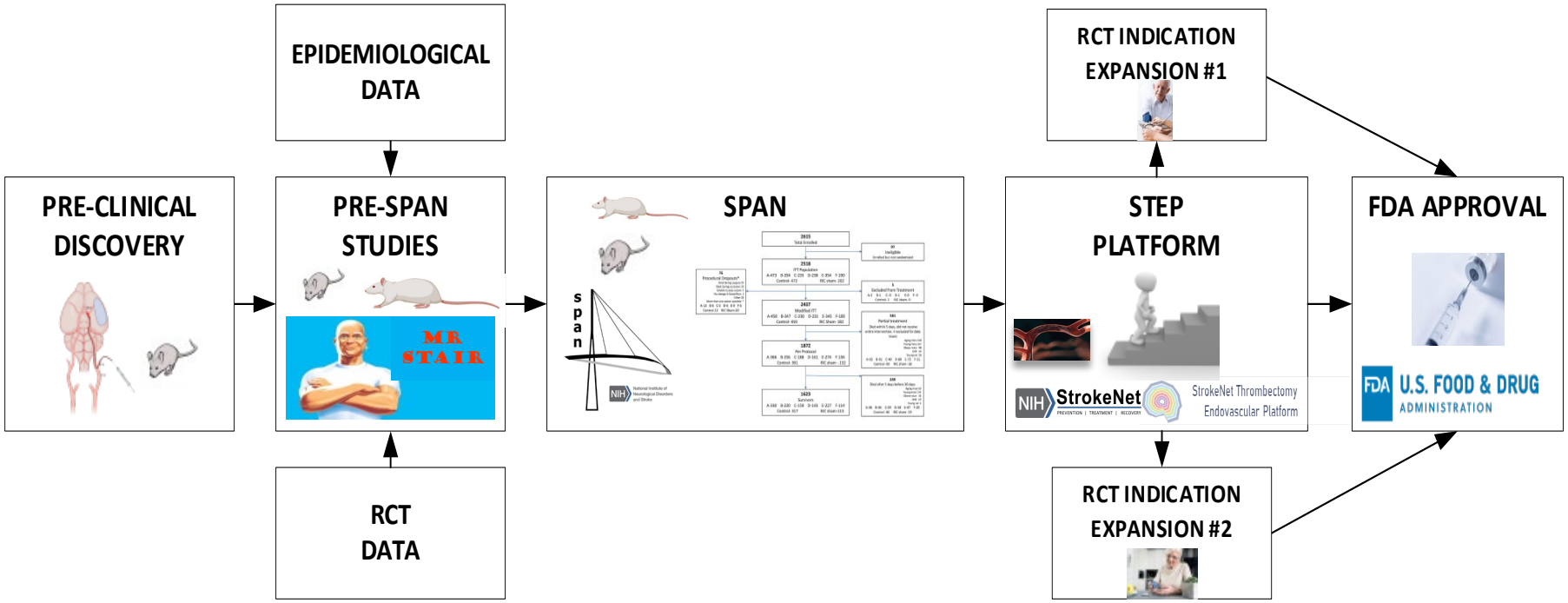


StrokeNet Thrombectomy Endovascular Platform

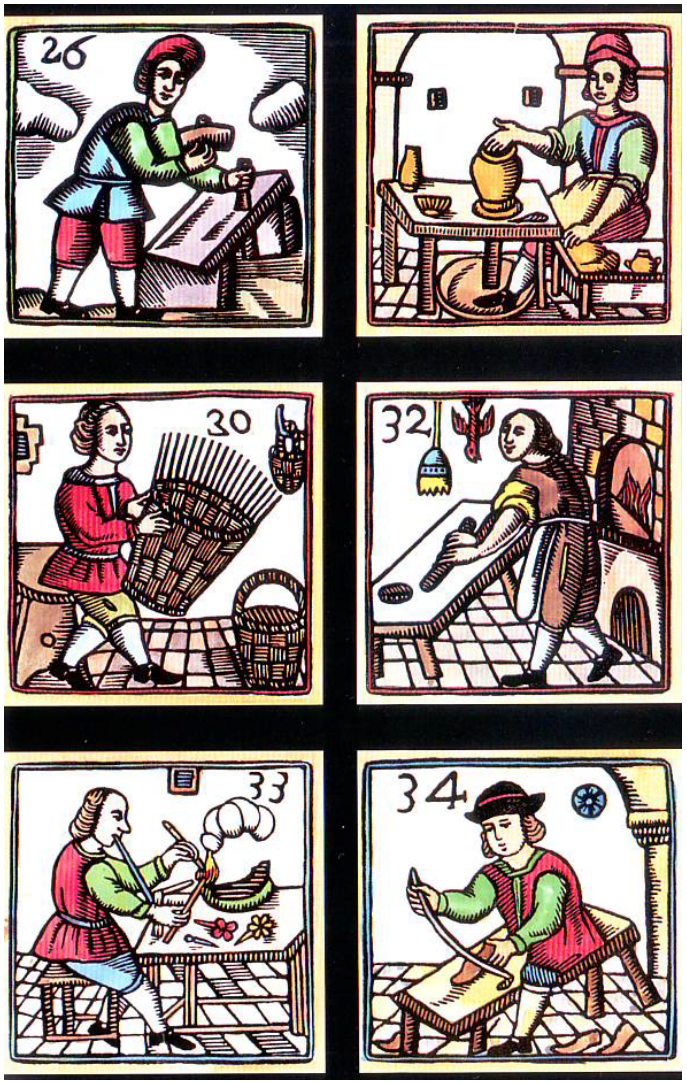
STEP

- Dedicated Strokenet EVT platform
- Randomized Multifactorial Adaptive Platform design
- Leverages existing registries for data collection
- Test multiple hypotheses of EVT indication expansion with cerebroprotection

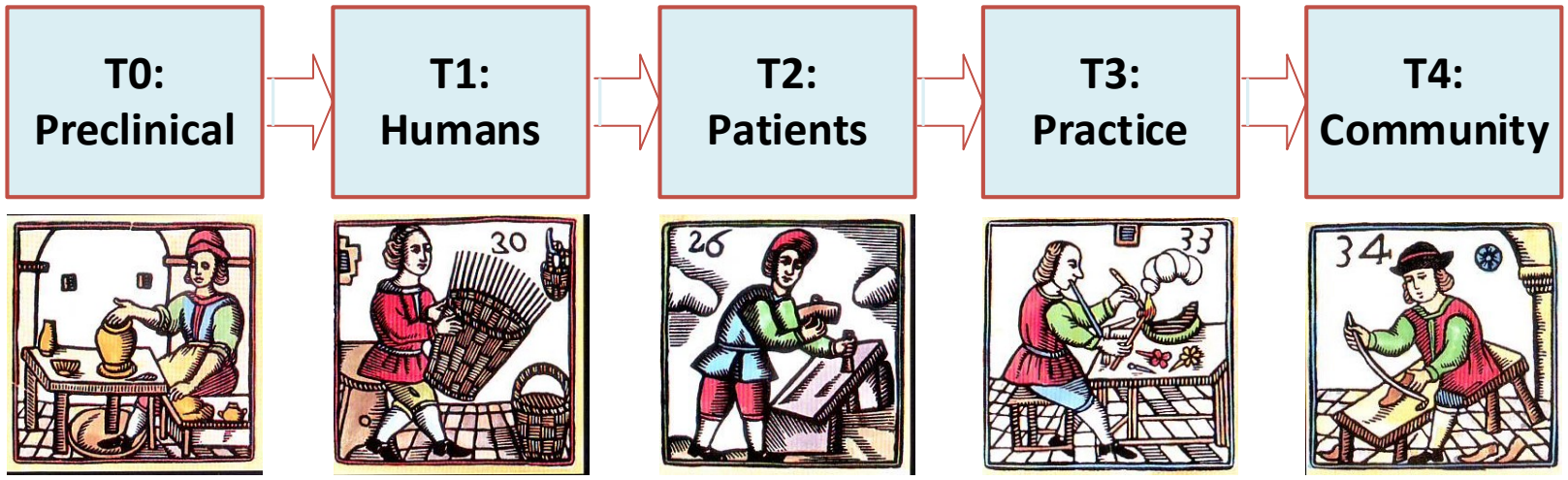
Future Pathway to Cerebrotection



Medieval Guilds

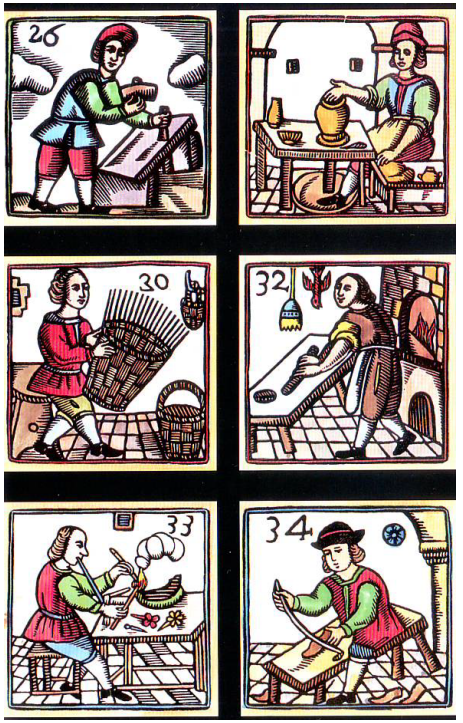


Scientific Guilds in Translation?



Guilds Translation: Causes

- Training & mentoring
- Experience
- Inertia
- Pack mentality
- Methodological
- Funding



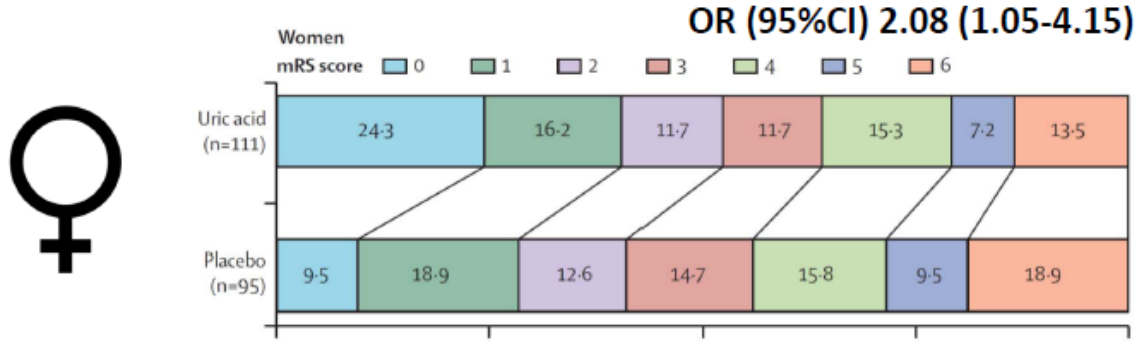
Pre-Clinical Tips

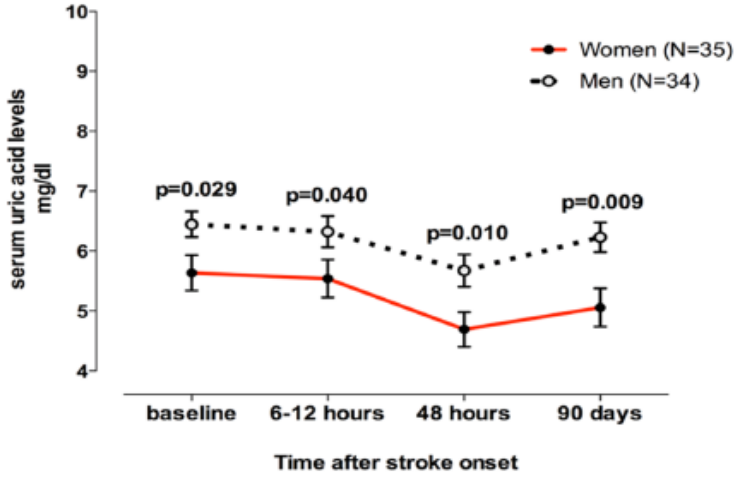
- Partnership with a laboratory
- Choose well intervention & lab
- Find scientific & personal synergies
- Respect lab hierarchy
- Make it a long-term win-win for team
- Bring Funding
- Be prepared to ask (beg)
- Leverage pre-clinical & human data

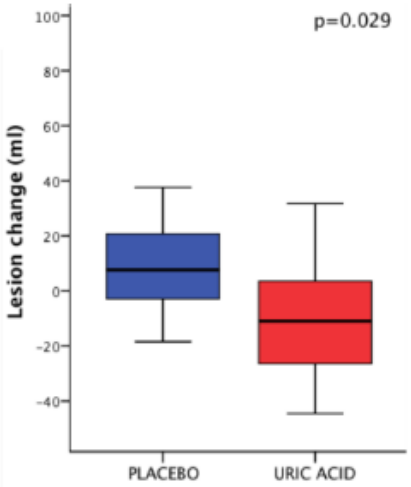
Uric Acid Supplementation Benefit Those with Lower Baseline Levels

11% Absolute benefit ¡¡¡

OR (95%CI) 2.08 (1.05-4.15)



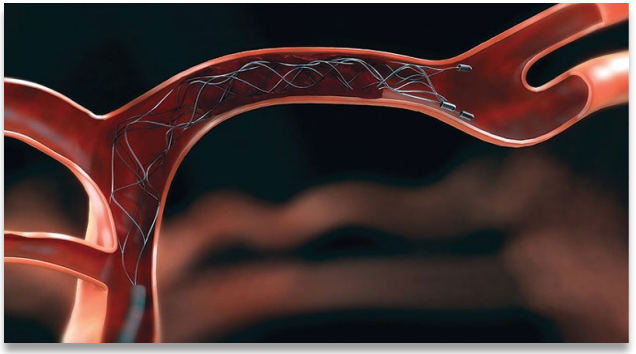




Manuscript number: STROKE/2015/009960DR1

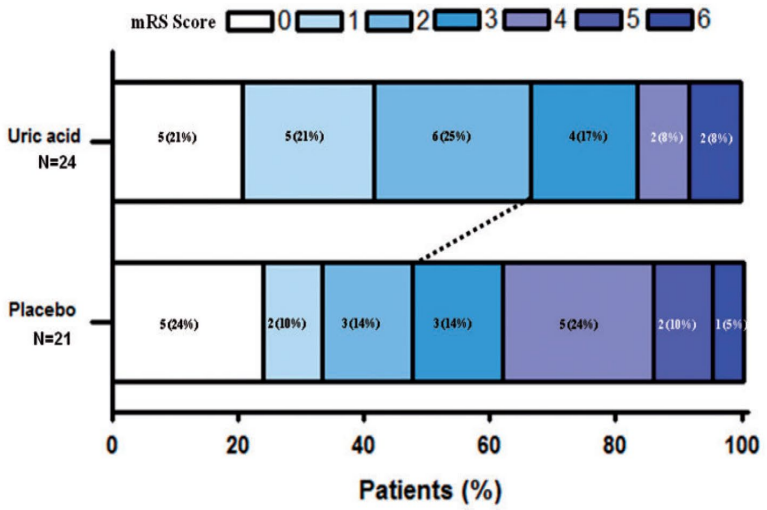
Uric Acid & “Filament Model” Humans

	UA N=24	PLACEBO N=21
Age, yr	78 (70-80)	68 (64-76)
NIHSS	17 (13-30)	15 (10-20)
Groin time	205 (163-271)	186 (155-230)



aOR 6.12 (95%CI 1.08-34.56)

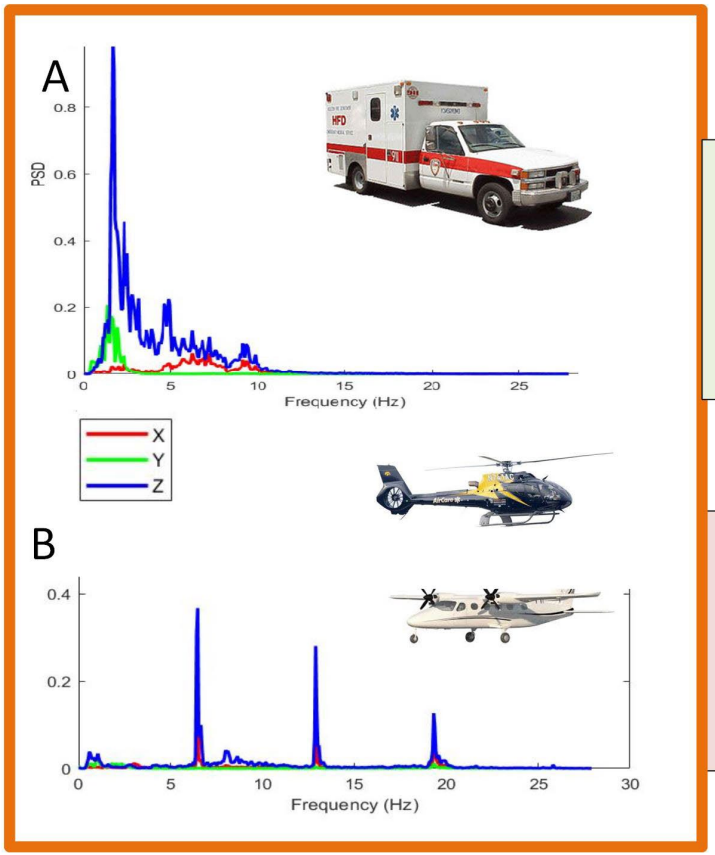
	UA N=24	PLACEBO N=21
RESULTS		
MRS 0-2 d 90	67%	48%
*Age, NIHSS, time to rtPA, afib, pre.MRS		



Chamorro *et al.* Int J Stroke. 2017;12:377-382

Expansion Indication Post-STEP

- Impact broader stroke population stroke
- Accept modest gains
- Thrombolysis adjuvant
- Periprocedural prevention
- Protection penumbra in transport
- Factor the physical environment



BENEFICIAL PHYSICAL FACTORS (LFV) +

DETRIMENTAL FACTORS (Noise, Toxic Fumes, Hypobaric Hypoxia) −

IMPACT PATIENT OUTCOMES?

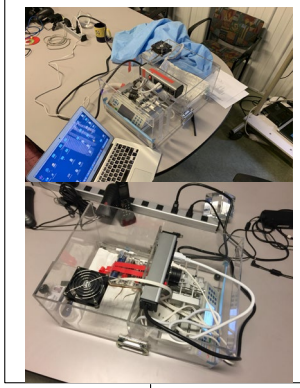
Leira et al, Unpublished data

3 Pairs of adult C57BL/6J male mice underwent eMCAO procedures < 15 minutes apart (n=101)

Ground transportation From Animal Lab to airport and LFV Simulation Lab using constant route

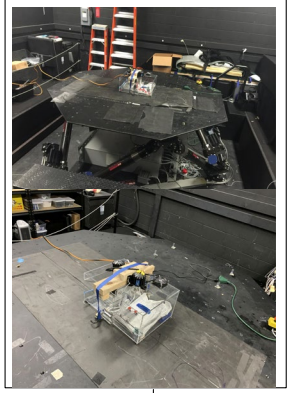
90 min Post-MCAO Pairs are Assigned Sequentially to Three Groups (2h appart) in a Blinded Random Order

Hangar Ground Control
+
10 mg/Kg rtPA (1h)
(n=37)



Mi2 Local Helicopter Flight
+
10 mg/Kg rtPA (1h)
(n=32)

LFV Vibration Simulator
+
10 mg/Kg rtPA (1h)
(n=32)



Ground transportation back to Animal Lab using same constant route

Survived Mission: 87%
Hyperacute 7T MRI:
BBB Permeability
Infarct Volume

Survived 24h: 81%
24h 7T MRI:
Final Infarct Volume
% Bederson Score (0-2)

Survived Mission: 85%
Hyperacute 7T MRI:
BBB Permeability
Infarct Volume

Survived 24h: 78%
24h 7T MRI:
Final Infarct Volume
% Bederson Score (0-2)

Survived Mission: 85%
Hyperacute 7T MRI:
BBB Permeability
Infarct Volume

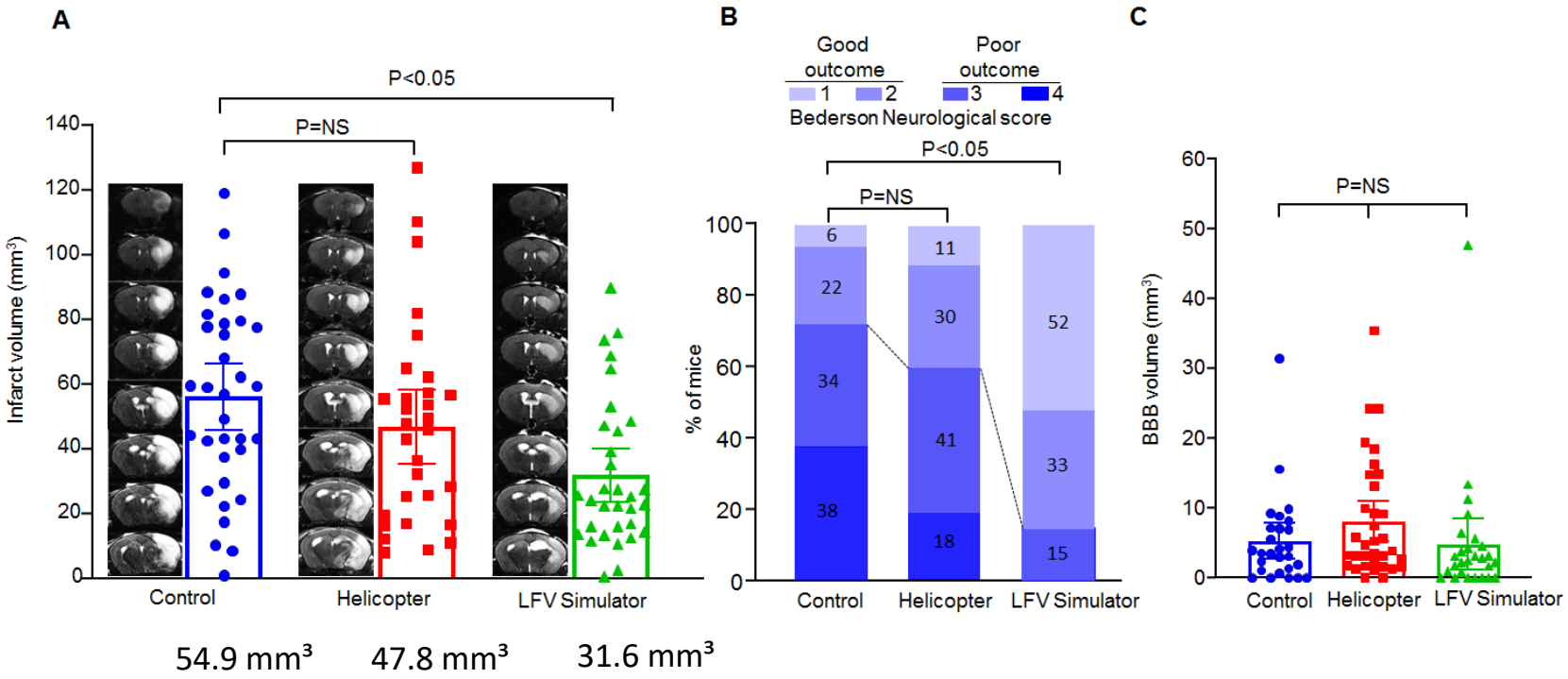
Survived 24h: 81%
24h 7T MRI:
Final Infarct Volume
% Bederson Score (0-2)

Low-Frequency Vibrations Enhance Thrombolytic Therapy and Improve Stroke Outcomes

Nirav Dhanesha, PhD; Thomas Schnell, PhD; Salam Rahmatalla, PhD; Jonathan DeShaw, PhD; Daniel Thedens, PhD; Bradley M. Parker; M. Bridget Zimmerman, PhD; Andrew A. Pieper, MD, PhD; Anil K. Chauhan, PhD; Enrique C. Leira, MD, MS

Stroke, June 2020

Physical Factors Transport Impact Outcome



Adjusted for: time to rtPA infusion start, outside temperature, barometric pressure, dew point, total vibration during exposure, and vibration during ground transportation

Conclusions

- Exciting time cerebroprotection
- SPAN is likely the future paradigm
- Need to get rid of guilds
- True team science
- Ensure right interventions move to SPAN
- Plans to expand it beyond MT

NIH StrokeNet
PREVENTION | TREATMENT | RECOVERY
REGIONAL COORDINATING CENTER

THE UNIVERSITY OF IOWA