Neurons & Synapses: Making a Network
NINDS Summer Internship Program Career Symposium

Alexis Simpkins, MD.PhD.
Assistant Professor
Department of Neurology, Vascular Neurology Division
University of Florida College of Medicine

July 12, 2018

Impacting Patient Care through Clinical Translational Research: Guiding your career
Objectives

- Current clinical and research focus
- My career path
- Setting your own career path
No Financial Disclosures
No Conflict of Interests
Shands/University of Florida

- 3 Hospitals
- Shands Hospital, 683 beds
- Cancer Hospital, 192 beds
- Neuro & Cardiac Hospital, 216 beds
- Clinical team consists of nurse practitioners, residents, medical students, and fellows
Ischemic Stroke

Atherosclerosis, Cardiac disease, Hypercoagulability, Vasculopathy

Vascular remodeling/plaque/Emboli

Drop in Blood Flow To Brain Parenchyma

Brain Damage

A Leading Cause of Death and Disability
Complications from Acute Ischemic Stroke Treatment: Hemorrhagic Transformation

Hemorrhagic Transformation Post IV tPA

National Institute of Neurological Disorders and Stroke
Acute Stroke Imaging Research Roadmap III Imaging Selection and Outcomes in Acute Stroke Reperfusion Clinical Trials

Consensus Recommendations and Further Research Priorities

Steven J. Warach, MD, PhD; Marie Luby, PhD; Gregory W. Albers, MD; Roland Bammer, PhD; Andrew Bivard, MD, PhD; Bruce C. V. Campbell, MD, PhD; Colin Derdeyn, MD; Jeremy J. Heit, MD, PhD; Pooja Khatri, MD; Maarten G. Lansberg, MD, PhD; David S. Liebeskind, MD; Charles B. L. M. Majoie, MD; Michael P. Marks, MD; Bijoy K. Menon, MD, MSc; Keith W. Muir, MD; Mark W. Parsons, MD, PhD; Achala Vagal, MD; Albert J. Yoo, MD; Andrei V. Alexandrov, MD; Jean-Claude Baron, MD, ScD; David J. Fiorella, MD, PhD; Anthony J. Furlan, MD; Josep Puig, MD; Peter D. Schellinger, MD, PhD; Max Wintermark, MD, MAS; for the Stroke Imaging Research (STIR) and VISTA-Imaging Investigators *

Background and Purpose—The Stroke Imaging Research (STIR) group, the Imaging Working Group of StrokeNet, the American Society of Neuroradiology, and the Foundation of the American Society of Neuroradiology sponsored an imaging session and workshop during the Stroke Treatment Academy Industry Roundtable (STAIR) IX on October 5 to 6, 2015 in Washington, DC. The purpose of this roadmap was to focus on the role of imaging in future research and clinical trials.

Methods—This forum brought together stroke neurologists, neuroradiologists, neuroimaging research scientists, members of the National Institute of Neurological Disorders and Stroke (NINDS), industry representatives, and members of the US Food and Drug Administration to discuss STIR priorities in the light of an unprecedented series of positive acute stroke endovascular therapy clinical trials.

Results—The imaging session summarized and compared the imaging components of the recent positive endovascular trials and proposed opportunities for pooled analyses. The imaging workshop developed consensus recommendations for optimal imaging methods for the acquisition and analysis of core, mismatch, and collaterals across multiple modalities, and also a standardized approach for measuring the final infarct volume in prospective clinical trials.

(Stroke. 2016;47:1389-1398. DOI: 10.1161/STROKEAHA.115.012364.)
**Clinical Case**

Witnessed Symptom Onset: 07:23

08:18

**ED: NIHSS 23**

09:00

**IV tPA was given and the patient started to improve drastically.**

2 Hours post-tPA

**NIHSS 9**

Reperfusion Achieved

Embolectomy not needed

24 Hours post-tPA

**NIHSS 1**
IV tPA was given and the patient started to improve drastically.

Can we show that blood brain barrier disruption is reversible in humans and does this effect hemorrhage risk?
Utility of Blood Biomarkers

Stroke Progression: Early Neurologic Decline

- **Patient Similar to Case with Similar Outcome**
  - Date: 11/2/14
  - Time: 7:30am
  - Last time seen normal
  - Symptom Discovery: Found with AMS and facial droop
  - ED: NIHSS \( \text{Baseline} = 23 \)
  - IV tPA was given, baseline functional status precluded embolectomy
  - NIHSS \( 2 \) Hours post-tPA = \( \text{NIHSS} = 16 \)
  - NIHSS \( 24 \) Hours post-tPA = \( \text{NIHSS} = 29 \)

Early Reduction: Early Neurologic Improvement

- **Similar Patient Different Outcome**
  - Date: 11/24/14
  - Time: 7:23am
  - Witnessed Onset
  - ED: NIHSS \( \text{Baseline} = 19 \)
  - IV tPA was given
  - NIHSS \( 2 \) Hours post-tPA = \( \text{NIHSS} = 9 \)
  - NIHSS \( 24 \) Hours post-tPA = \( \text{NIHSS} = 0 \)
From Bedside back to the Bench

1. Define more clinically relevant imaging biomarkers of clinical outcome
2. Look new therapeutic targets
3 MRI Biomarkers
- Infarct volume at 24 hours (FIV)
- Percent early reperfusion (PER)
- Early changes in stroke volume (ECS)

ECS that occur after thrombolysis are associated with early neurologic improvement, and may be a useful imaging biomarker for response to thrombolysis.
Early Change in Stroke Size Performs Best in Predicting Response to Therapy

- 3 MRI Biomarkers
  - Infarct volume at 24 hours (FIV)
  - Percent early reperfusion (PER)
  - Early changes in stroke volume (ECS)

- ECS that occur after thrombolysis are associated with early neurologic improvement, and may be a useful imaging biomarker for response to thrombolysis.
Red – orange pixels represent the most severely affected regions

BBB Disruption Reversed with Reperfusion in the Patient Presented in this Case Presentation
Diffuse Mild BBB Disruption is Reversible with Reperfusion

Focal Severe BBB Disruption is Associated with Intracranial Hemorrhage After Thrombolysis


- Logistic regression of severe focal BBB disruption (continuous variable) with the subsequent development of parenchymal hematoma (binary variable):
  - Focal severe BBB permeability on the pre-treatment scan was associated with an increased risk of development of a intra-parenchymal hematoma after thrombolysis (p=0.016)
  - Odds ratio of 1.63 for every 10% increase in the focal BBB permeability.
From Bedside back to the Bench

1. Define more clinically relevant imaging biomarkers of clinical outcome
2. Look for new therapeutic targets
At risk for bleeding
Wake Up stroke safe for IV tPA
Stroke Progression
Systems Biology of Ischemic Stroke
Clinical Outcomes
Use Drug X BBB stabilization

Next Generation RNA sequencing: mRNA and miRNA

Gene expression in blood changes rapidly in neutrophils and monocytes after ischemic stroke in humans: a microarray study.

This study was supported by National Institute of Neurological Disorders and Stroke of the NIH under Grant Number NS-25519.
Patients having an acute stroke and present within 12 hours from last seen normal are enrolled in the Natural History of Stroke study being conducted within the NINDS stroke division.

- Serial high resolution 3T MRI at baseline (prior to intervention), 2 hours, and 24 hours
- Serial blood draws collected within 30 minutes of the MRI
- NIHSS are performed at each research time point
- Follow up out to 90 days for modified Rankin Scores

Next generation RNA sequencing of mRNA and miRNA conducted on the whole blood samples:
- Samples collected in Paxgene tubes

EXCLUSION CRITERIA:
- Recent Infection
- Recent surgical procedure
- Chronic Infection
- Contraindication to MRI
- Baseline Blood not drawn
- Concurrent immunomodulating therapy
- Autoimmune disorder

INCLUSION CRITERIA:
- > 18 years old
- Within 12 hours from last seen normal
- MRI confirmed acute ischemic index lesion
- Present either of the 2 sites

Created by John T. Pendy
IV tPA was given, baseline functional status precluded embolectomy.

11/2/14
7:30am
Last time seen normal

11/2/14
8:05am
Symptom Discovery: Found with AMS and facial droop

11/2/14
10:10am
ED: NIHSS 23
Temporary Waiver of Consent

11/2/140
11:03am
NIHSS 16
NIHSS 29

2 Hours post-tPA

24 Hours post-tPA
Early Neurologic Decline (END): Increase in the NIHSS of 4 or greater within 24 hours of presentation.

Associated with change in expression of 214 mRNA transcripts (1.5 to -1.5 fold change with corrected p value of < 0.05) at 24 hours.
My Career Path: Grade School
My Career Path: High School
My Career Path: High School
My Career Path: High School

High School Day

College at Night
My Career Path: College

- Chemistry Major/Biology Minor
- Organic chemistry teacher Dr. Strobel encouraged me to participate in research
- Mentors: Dr. Susan Fagan, Dr. David Hess, and Dr. Elizabeth Fanning
- Student Scholar in Cerebrovascular Disease, American Stroke Association 2001
M.D./Ph.D. student brings lifetime of learning

She has yet to earn her first graduate degree, but Anna Simpson already is making science...

As an M.D./Ph.D. student, she is able to combine her passion for science with her commitment to helping others.

She is a member of the Medical College of Georgia's Undergraduate Research Program, which provides students with opportunities to conduct research in various fields.

Anna Simpson's work has been recognized with several awards, including the Medical College of Georgia's Student Research Award.

Her research has been published in several scientific journals, and she has presented her findings at national conferences.

Anna's advice to other students is to never give up on their goals, even when faced with challenges.

She is determined to make a difference in the world of medicine and science, and she is dedicated to using her education to help others.
My Career Path: Medical School Combined MD PhD

- Medical and graduate school funded by MD/PhD program, Stoney Brook Scholarship
- **Mentors:** Dr. Inscho, Dr. Pollock, Dr. Rudic, Dr. Dorrance, Wilma Sykes Brown, Dr. Rosie Allen Noble, Dr. McKie, Dr. Catravas, Dr. Perveze, Dr. Stahler

**PhD in Vascular Biology and Ischemic Stroke in Dr. John D. Imig’s Lab:**
- NIH funding: T32, Individual F31
- Thesis work: 3 Publications and 5 abstracts
- Platform talk at ISC and an invited symposium talk at Experimental Biology
- Runner-up Graduate Student Best Abstract Award, ASPET, 2008; Caroline Tum Suden/Frances Hellebrandt Award, APS 2007 and 2008; Minority Graduate Student Travel Award, ASPET 2008; Epoxide Hydrolase in Toxicology and Pharmacology Symposium Travel Award, ASPET 2008; Acres of Diamonds Award, Minority Trainee Research Forum 2007; Donald J. Reis Memorial Trainee Award, APS 2007

**VA Chief of Neurology Award 2009, several cases report abstracts**


My Career Path: Off to Residency...Match Day
My Career Path: Neurology Residency

- Internship at the Medical College of Georgia
- Neurology Residency at Johns Hopkins University, 3 years in Baltimore, Maryland.
- Vigorous training program
- R25 Research funding support through NINDS

4 ½ years: College
8 years: medical school and graduate school
1 year: Internal medicine internship
3 years: Neurology residency

16 years of training....
My Career Path: Vascular Neurology Fellowship

- Combined clinical research fellowship
- **Mentors:** All of stroke faculty, research team, nurses, other physicians/fellows
- **Publications:** 2 first author publications, 5 publications in total.
  - Simpkins AN, Dias C, Leigh R, on behalf of the NIH Natural History of Stroke Investigators. Early Changes in ADC Volume is an Imaging Biomarker of Early Neurologic Improvement in Ischemic Stroke Treatment.
- **Fellow Committees:** ClinFelCOM Representative, GMEC committee, Distinguished Clinical Teaching Award Committee
My Career Path: Vascular Neurology Fellowship

9th Annual Power To End Stroke JAZZ BRUNCH & Awareness Fair

Live jazz music by: Café Red | Hosted by: Konan from 92Q

FREE EVENT
Saturday, May 7 • 11 am - 2 pm
Albert H. Coons Auditorium, Koch Cancer Research Building
1350 Orleans Street, Baltimore, MD 21287

To RSVP or for more information, contact: Gayle Pollack at 443.287.4902 or petsbrunch@jhmi.edu

Community Outreach
My Career Path:
Assistant Professor of Neurology
Question 1: What do you want to do?

What are your strengths?

It is okay to adapt and change as you grow

Expose yourself to different career options

Do what you are passionate about
Question 2: How are you going to reach your goal?

- Plan and Prepare
- Focus = Decisions in alignment with your goals
- Develop a plan for your self and re-evaluate your plan as you advance to make sure it is still in alignment with your goals
Question 3: Are you building your resources?
- Who are your mentors
- Are you seeking out information on your own
- Does your training plan fit the career that you would like?
- Surround your self with a support network, and continue to learn new skills.
Question 4: What about the “set backs” and work life balance?

Resilience comes with work life/balance and changing your perception of “success”

Focus on solving relevant problems, do what you enjoy, and don’t forget to enjoy the journey.


Question 4: What about the “set backs” and work like balance?

- Resilience comes with work life/balance and changing your perception of “success”
- Focus on solving relevant problems, do what you enjoy, and don’t forget to enjoy the journey.
Acknowledgements

CLINICAL TEAM
- Dr. Saeed Alqahtani
- Dr. Richard Benson
- Shannon Burton, NP
- Dr. Tina Burton
- Dr. Nidhi Gupta
- Dr. Amie Hsia
- Dr. Rich Leigh
- Dr. John Lynch
- Dr. Chandi Kalaria
- Dr. Zurab Nadareishvili
- Dr. Imama Naqvi
- Dr. Dennys Reyes
- Dr. Amjad Shehadah
- Stroke nurse responders and MRI technicians at Washington Hospital Center and Suburban Hospital

RESEARCH TEAM
- Christian Dias
- Emi Hitomi
- Devon Kelley
- Dr. Eunhee Kim
- Dr. Puneet Gohtra
- Dr. John Hallenbeck
- Dr. Kory Johnson
- Dr. Omar Khan
- Dr. Lawrence Latour
- Kathryn Lee
- Dr. Avi Nath
- Gina Norato
- Lanre Oshin
- John T. Pendy
- Mary Jo Rucker, RN
- Byron Udegbe
- Dr. Mario Udegbe
- Dr. Nidhi Gupta
- Dr. Amie Hsia
- Dr. Rich Leigh
- Dr. John Lynch
- Dr. Chandi Kalaria
- Dr. Zurab Nadareishvili
- Dr. Imama Naqvi
- Dr. Dennys Reyes
- Dr. Amjad Shehadah
- Stroke nurse responders and MRI technicians at Washington Hospital Center and Suburban Hospital
- Christian Dias
- Emi Hitomi
- Devon Kelley
- Dr. Eunhee Kim
- Dr. Puneet Gohtra
- Dr. John Hallenbeck
- Dr. Kory Johnson
- Dr. Omar Khan
- Dr. Lawrence Latour
- Kathryn Lee
- Dr. Avi Nath
- Gina Norato
- Lanre Oshin
- John T. Pendy
- Mary Jo Rucker, RN
- Byron Udegbe
- Dr. Mario Udegbe
- Dr. Nidhi Gupta
- Dr. Amie Hsia
- Dr. Rich Leigh
- Dr. John Lynch
- Dr. Chandi Kalaria
- Dr. Zurab Nadareishvili
- Dr. Imama Naqvi
- Dr. Dennys Reyes
- Dr. Amjad Shehadah
- Stroke nurse responders and MRI technicians at Washington Hospital Center and Suburban Hospital

National Institute of Neurological Disorders and Stroke

NISC
NHLBI
Dr. Pouya Fahadan
Dr. Mud Alvi
UF Health’s Stroke Program

Vascular Neurology

Endovascular Neurosurgery

Nursing