Transitioning to Independence

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I will discuss investigational PET imaging for Alzheimer's disease



- What does it mean to be "Independent"?
- Consider psychosocial development on the pathway to independence
- What are some of the difficult challenges along this path? from my perspective

What is Independence?

- Financial
- Supporting effort (salary)
- Supporting research projects
- Intellectual
- Developing project ideas
- Writing Grants
- Management
- Coordinators
- Trainees
- Other staff
- Identity
- One that is unique from your mentors

Erikson's Stages of Psychosocial Development

Stage	Age	Virtue	Maldevelopment	Example
1. Trust vs Mistrust	Infancy	Норе	Withdrawal	Secure environment provided by the caregiver with regular access to affection and food
2. Autonomy vs Shame, Doubt	Early Childhood	Will	Compulsion	Caregiver promotes self-sufficiency while maintaining a secure environment
3. Initiative vs Guilt	Play Age Period	Purpose	Inhibition	Caregiver encourages, supports, and guides the child's own initiatives and interests
4. Industry vs Inferiority	School Age Period	Competence	Inertia (passivity)	Reasonable expectations set in school and at home with praise for accomplishments
5. Identity vs Identity confusion	Adolescence	Fidelity	Repudiation	Individual weighs out their previous experiences, social expectations and establishes values and "finding themselves."
6. Intimacy vs Isolation	Young Adulthood	Love	Distantiation	Individual forms close friendships or long-term partnership
7. Generativity vs Stagnation/Self- absorption	Adulthood	Care	Rejectivity	Engagement with the next generation through parenting, coaching or teaching
8. Integrity vs. Despair	Older Age	Wisdom	Disdain	Contemplation and acknowledgement of personal life accomplishments

Adapted from Orenstein GA, Lewis L. Eriksons Stages of Psychosocial Development. [Updated 2022 Nov 7]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan-.

Yale Alzheimer's Disease Research Unit

Erikson's Stages of Psychosocial Development

Stage	C	areer Stag	se	Virtue	Maldevelopment	Example
1. Trust vs Mistrust		Undergrad		Норе	Withdrawal	Secure environment provided by the caregiver with regular access to affection and food
2. Autonomy vs Shame, Doubt				Will	Compulsion	Caregiver promotes self-sufficiency while maintaining a secure environment
3. Initiative vs Guilt		Grad		Purpose	Inhibition	Caregiver encourages, supports, and guides the child's own initiatives and interests
4. Industry vs Inferiority		Postdoc Junior Faculty Senior Faculty		Competence	Inertia (passivity)	Reasonable expectations set in school and at home with praise for accomplishments
5. Identity vs Identity confusion				Fidelity	Repudiation	Individual weighs out their previous experiences, social expectations and establishes values and "finding themselves."
6. Intimacy vs Isolation				Love	Distantiation	Individual forms close friendships or long-term partnership
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- Undergraduate
 - University of Florida
 - Chemistry and Microbiology



Michael Katovich, PhD



Justin Grobe, PhD, Medical College of Wisconsin

Am J Physiol Heart Circ Physiol 292: H736-H742, 2007. First published November 10, 2006; doi:10.1152/ajpheart.00937.2006.

CALL FOR PAPERS | Cardiovascular-Renal Mechanisms in Health and Disease

Prevention of angiotensin II-induced cardiac remodeling by angiotensin-(1–7)

Justin L. Grobe,¹ Adam P. Mecca,¹ Melissa Lingis,¹ Vinayak Shenoy,¹ Tonya A. Bolton,¹ Juline M. Machado,¹ Robert C. Speth,³ Mohan K. Raizada,² and Michael J. Katovich¹

- Undergraduate
 - University of Florida
 - Chemistry and Microbiology
- MD vs MD-PhD



Colin Sumners, PhD

UF College of Medicine UNIVERSITY of FLORIDA



- Undergraduate
 - University of Florida
 - Chemistry and Microbiology
- MD vs MD-PhD
 - F30 Application Cerebroprotection via viralmediated gene delivery of angiotensin AT2 receptors

Cerebroprotection by angiotensin-(1–7) in endothelin-1-induced ischaemic stroke

Adam P. Mecca¹, Robert W. Regenhardt¹, Timothy E. O'Connor¹, Jason P. Joseph¹, Mohan K. Raizada¹, Michael J. Katovich² and Colin Sumners¹



Erikson's Stages of Psychosocial Development

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- Undergraduate
 - University of Florida
 - Chemistry and Microbiology
- UF MD-PhD (2005-2012)
- Residency Psychiatry
 - Yale NRTP



Robert Malison, MD



Christopher Pittenger, MD, PhD

- Undergraduate
 - University of Florida
 - Chemistry and Microbiology
- UF MD-PhD (2005-2012)
- Residency Psychiatry
 - Yale NRTP
 - Yale ADRU



Christopher van Dyck, MD

Director, Yale Alzheimer's Disease Research Unit



Richard Carson, PhD Director, Yale PET Center

RESEARCH



Open Access

PET imaging of mGluR5 in Alzheimer's disease

Adam P. Mecca^{1,2}, Julia W. McDonald^{1,2}, Hannah R. Michalak^{1,2}, Tyler A. Godek^{1,2}, Joanna E. Harris^{1,2}, Erika A. Pugh^{1,2}, Emily C. Kemp^{1,2}, Ming-Kai Chen⁵, Arash Salardini⁴, Nabeel B. Nabulsi⁵, Keunpoong Lim⁵, Yiyun Huang⁵, Richard E. Carson⁵, Stephen M. Strittmatter^{3,4,6*} and Christopher H. van Dyck^{1,2,3,4*}

Developing Expertise Along the Way

• Briefly review the Positron Emission Tomography (PET) methods.

Alzhimer's disease Pathology



Deyn, P. P. D. (2015) Cerebrospinal fluid biomarkers in dementias Nat. Rev. Neurol. doi:10.1038/nrneurol.2015.175

PET Methods - Radiochemistry



Nabulsi et al. JNM 2016.

PET Methods - Biochemistry







$$L + R \xrightarrow[koff]{koff} LR$$

PET – Signal Detection



http://www.triumf.ca/radiochemistry-for-pet-imaging

PET – Kinetic Modeling



Finnema et al. Neurology 2016.

1100

PET – Image Processing



- Undergraduate
 - University of Florida
 - Chemistry and Microbiology
- UF MD-PhD (2005-2012)
- Residency Psychiatry (NRTP)
 - Cognitive disorders clinical research
 - PET
 - MRI



We need to be independent



Program Purpose

The purpose of this program is to increase and maintain a strong cohort of new and talented, NIHsupported, independent investigators. This program is designed to facilitate a timely transition of outstanding postdoctoral researchers or clinician-scientists from mentored research positions to independent, tenure-track or equivalent faculty positions, and to provide independent NIH research support during the transition that will help these individuals launch competitive, independent research careers.

Independence is a confusing concept



It's human to feel this as a struggle at times



- Undergrad UF (2005-2012)
- UF MD-PhD (2005-2012)
- Psych Residency/NRTP (2012-2016)
- Geriatric Psychiatry Fellowship (2016-2017)
 - K23 application: Investigation of molecular changes in mGluR5 and SV2A to study synaptic alterations in Alzheimer's disease using PET.



Paul Kirwin, MD Tulane School of Medicine



Michelle Conroy, MD

Surrogate Markers of Synaptic Density: Synaptic Vesicle Glycoprotein 2 (SV2)

- Essential component of synaptic vesicles, located in presynaptic terminals
- Modulates synaptic exocytosis and endocytosis
- Isoforms SV2A, B, C: **SV2A** ubiquitously expressed in virtually all synapses
- Radioligand binding to SV2A may be useful for measurement of synaptic density



Richmond, 2007; Sudhof, 1999

Synaptic density and cognitive performance in AD



Mecca AP et al., Alzheimer's Dement. 2022; Online ahead of print.

Future Directions



- Undergrad UF (2005-2012)
- UF MD-PhD (2005-2012)
- Psych Residency/NRTP (2012-2016)
- Geriatric Psychiatry Fellowship (2016-2017)
- Instructor of Psychiatry Yale (2017)
 - Associate Director ADRU
- Awarded K23 (2017)
- Assistant Professor (2017 2023)
- Associate Professor (2023)

- U01 (PI Strittmatter) 2020
 - Drug development program
 - Phase 1a Clinical Trial

BMS-984923 is a Silent Allosteric Modulator



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Phase 1a Study Design

Open-label, Single Ascending Dose



- Undergrad UF (2005-2012)
- UF MD-PhD (2005-2012)
- Psych Residency/NRTP (2012-2016)
- Geriatric Psychiatry Fellowship (2016-2017)
- Instructor of Psychiatry Yale (2017)
 - Associate Director ADRU
- Awarded K23 (2017)
- Assistant Professor (2017 2023)
- Associate Professor (2023)

- U01 (PI Strittmatter) 2020
 - Drug development program
 - Phase 1a Clinical Trial
- R01 (2021)–
 - A Phase 1b Multiple Ascending Dose Study of the Safety and Tolerability of BMS-984923 in Alzheimer's Disease

Thank You

Research Participants

Yale PET Center

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- Michael Schöll Kaj Blennow
- Henrik Zetterberg

Faculty Mentors

Christopher van Dyck, Director ADRU Richard Carson, Director Yale PET Center



Yale ADRU: Ryan O'Dell Susan Good Martha MacAvoy Jeanine May Carol Gunnoud Monica Caning-Ball Elaheh Salardini Juan Young Kaitlyn Melino Emma Waldner Jamie Georgelos Julia Wazak Mackenzie Morehouse Anna Chupak Kara Bates Hannah Weibley Jesica Lam Tyler Godek Meghan Donahue Emma Cooper Alyssa Miller Wenzhen Zhao

Current and Past Yale Collaborators:

Ming-Kai Chen Joanna Harris Hugh Bartlett Takuya Toyonaga Mika Naganawa Arash Salardini **Emmie Banks** Victoria Kominek Srinath Ramanan Amy Arnsten Nabeel Nabulsi Keunpoog Lim Soheila Najfzadeh Jim Ropchan **Yiyun Huang** Brent Vander Wyk **Stephen Strittmatter**