Research Interests:
• Newborn megakaryocytopenesis
• Thrombocytosis in iron deficiency
• Mitochondrial mutations, in Autism, Alzheimer’s, Parkinson’s
• Chemotherapy induced mutations in Neuroblastoma cell lines
• Hodgkin lymphoma/BMT Therapy in Central and South America
• Molecular biology and genetics of ALL in Guatemala
• opsoclonus-myoclonus-ataxia syndrome

Active Projects:
• Education to patients and families about trait and disease
• Transition from pediatric to adult care, including self-efficacy
• Adherence to therapy, mainly hydroxyurea in sickle cell disease
• Education of primary care providers on trait and disease
Dr. Praveen Kumar
Active Project:
Feeding Practices in Extremely Low Birthweight (ELBW) Premature Infants

Dr. James Hocker
Active Project:
Developmental Follow-up of ELBW Infants
Endocrinology

Dr. Anu Vishwanath
Active Project:
TSH Elevation Among Children with Obesity

Dr. Mark Miller
Active Project:
Improved Transparency and Communication with Families via Utilization/Enrollment in OSF MyChart
Pediatric Cardiac MRIs

Dr. Matthew Bramlet
Active Project:
Virtual Reality Technology in Medical Education

Invasive Cardiac Catheterization and Devices

Dr. Priti Patel
Active Project:
Use of Milrinone in Prevention of Post-PDA Ligation Cardiac Syndrome
Nephrology

Dr. Vimal Raj
Active project:
• Urinary Alpha Klotho in Sickle Cell Patients
• Urinary Salt and Blood pressure in children

Hospitalist

Dr. Keith Hanson
Active project:
• PEWS scoring and reduction of PICU transfers
• Propofol dosing in pediatric sedation
• PICC line safety
Critical Care

Quality Improvement and Safety
Dr. Sandeep Tripathi
Active Projects:
• QI in Critical Care Units

Medical Education
Dr. Girish Deshpande
Research Interests:
• Simulation based education and clinical outcomes
• Pediatric CPR
• Device Inventions (prototyping and development)
• Pediatric Pain and Sedation
Pediatric Infectious Diseases

Antibiotic stewardship
- Inpatient stewardship issues
- Outpatient antibiotic stewardship
- Imaging and laboratory utilization

Infection Control and Prevention

Staphylococcal infections at the CHOI

MRSA active surveillance in the NICU

Staphylococcus epidermidis in the NICU

George Johnson, MD
Margaret Heger, PharmD
Ban Al-Sayyed, MD
Barry Gray, MD
General Pediatrics

Dr. Amy Christison
Pediatric Obesity and Clinical Outcomes Research

Active Projects:
• Rural Health ECHO Illinois: building weight management capacity by telehealth learning collaboratives
• POWER: national registry work
• Transition to Health: ALL Survivorship and Wellness
• Composition of gut microbiota in children with various weight status’

Resident Projects:
• Renal insufficiency in children born to mother’s with pre-eclampsia
• Neonatal Screening processes in the NICU
• Down’s Syndrome Guideline Adherence QI
• HFNC usage in patients with bronchiolitis
• PEWS scoring and reduction of PICU transfers
Mission of COR

Exists to conduct multidisciplinary, collaborative research in health systems, health services, and health outcomes.

Will work with clinical departments, affiliated hospitals, and community organizations to conduct and publish the outcomes of interventions intended to improve the quality of healthcare in the community.
Internal Customers at the UICOMP

- Clinical Departments
- Medical Students
- Residencies
- Fellows

Demand for Services

COR
External Partners

- UnityPoint Health Illinois Institute for Addiction Recovery
- OSF-SFMC
- Illinois Neurologic Institute
- JUMP
What the COR Does?

• Provision of outcomes research services.
• Mentorship of faculty, students, residents, and fellows.
• Generation of publications for faculty, students, fellows, and residents.
Skills Base (it takes a village)

• The COR has expertise in
  o Health economics
  o Modeling
  o Various clinical specialties
  o Statistical analysis
  o Programming
  o Database management
Dr. Asche’s research focuses on the use of comparative effectiveness research and cost-effectiveness analysis in health care decision making. In addition to the present book, his academic work has comprised authoring or co-authoring over 75 papers appearing in the medical and economic literature. He is the editor of the book, “Applying Comparative Effectiveness Data to Medical Decision Making: A Practical Guide” (Adis, 2015). He has presented his research at seminars and conferences both nationally and internationally. He has served on numerous national and international health economics-focused boards and committees, including editorial, grant review and advisory bodies.
Dr. Kim is responsible for data management and statistical analysis to support outcome researches, and participates in the development of the research program for the Pulmonary Critical Care Fellowship Program.
Jinma Ren, Ph.D.
Research Assistant Professor

Dr. Ren is responsible for data management and statistical analysis to support outcome researches, and participates in the development of the research program for the Gastroenterology Fellowship Training Program.
Active Funded Research

Patient Centered Outcomes Research Institute (PCORI) Tier 1 Community Involvement Grant

American Cancer Society (ACS) Populations Sciences Grant

Cancer Control and Population Grant, Illinois Cancer Care (ICC) Foundation Grant

Center for Disease Control (CDC) and Prevention

American Physical Therapy Association (APTA)

Technology Evaluation in the Elderly Network (TVN)

U of Illinois Discovery Grant

OSF Foundation / Central Illinois MS Clinic Fund / Caterpillar Foundation Matching Grant
Most Recent Funded Projects

- “Developing a Patient-Led Multiple Sclerosis Research Community”
  o PI: Carl Asche
  o Sponsor: PCORI Tier III award

- “Long-term Effectiveness of the ‘Don’t Gamble Away our Future’ Program”
  o PI: Jinma Ren
  o Sponsor: UnityPoint Health/ Par-A-Dice
INTERACTIVE TECHNOLOGY SUPPORT FOR PATIENT MEDICATION SELF-MANAGEMENT

Dan Morrow, Mark Hasegawa-Johnson, Thomas Huang, Suma Bhat, Renato Azevedo, Kuangxiao Gu, Yang Zhang (UIUC)
James Graumlich, Victor Sadauskas (UIC Peoria, OSF) & Ann Willemsen-Dunlap, Don Halpin (UIC Peoria, Jump Simulation and Education Center/OSF)
Background

• Chronic illnesses often require medication therapy to avoid symptoms, disability, hospitalization, or death
• Medication non-adherence by patients occurs often and contributes to adverse outcomes
• Low health literacy is a contributing factor to medication non-adherence
• Health literacy is the capacity to obtain, understand, and use information and services needed to make health decisions
Project Goals

• Improve use of Electronic Medical Record (EMR) System for supporting patient/provider collaboration and patient self-care

• Develop tools to translate EMR information into language that supports collaboration, and to present this information in ways that inform and engage patients for self-care.

• Overcome barriers to medication adherence for patients with low health literacy
Specific Aims

Develop Natural Language Processing tool that generates patient-centered language from nonstandard and technical medication information in EMR.

Integrate patient-centered language into Conversational Agent (CA)-based ‘medication adviser’ system supporting collaboration. CA presents medication information, emulating best practices from face-to-face communication.

Enhance CA ability to engage patients by developing interactive capability, such as using “teachback” when communicating with patients.
Specific Aims

Develop Natural Language Processing tool that generates patient-centered language from nonstandard and technical medication information in EMR.

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2 tabs b.i.d.
Take 2 tablets 2 times a day, in the morning and evening
Specific Aims

Develop Natural Language Processing tool that generates patient-centered language from nonstandard and technical medication information in EMR.

Integrate patient-centered language into Conversational Agent (CA)-based 'medication adviser' system supporting collaboration. CA presents medication information, emulating best practices from face-to-face communication.

Enhance CA ability to engage patients by developing interactive capability, such as using “teachback” when communicating with patients.

“Take 2 tablets 2 times a day, in the morning and evening”

2 tabs b.i.d.

Take 2 tablets 2 times a day, in the morning and evening
Please rank: Which computer agent (CA) would you prefer to deliver your health messages? 1 = Highest ranking (most preferred) to 5 = Lowest rank (least preferred)

Cartoon
- 30.8% preference with a mean of 2.49

Realistic
- 23.3% preference with a mean of 2.62
- 8.3% preference with a mean of 4.31
- 25.0% preference with a mean of 2.61

m = mean preference value
Please rank: Which computer agent (CA) would you prefer to deliver your health messages? 1 = Highest ranking (most preferred) to 5 = Lowest rank (least preferred)

- Cartoon
  - 23.3%
  - $m = 2.73$

- Realistic
  - 20.0%
  - $m = 3.18$

- Realistic
  - 22.5%
  - $m = 2.48$

- Cartoon
  - 10.8%
  - $m = 3.78$

- Cartoon
  - 23.3%
  - $m = 2.82$
Cancer Research
Departments of Internal Medicine, Surgery and Pathology

Christopher S Gondi PhD
Overcome Chemo and radiation therapy resistance

Cancer Research

Pediatric

Adult

Intra cranial

Extra cranial

Pancreatic

Intra cranial
Therapeutic targets

SPARC

uPA

TOP-1
The uPA Enigma
TX1111 MIA Paca-2 cells ($p<0.001$, $n=12$) and by 40% in PANC cells ($p=0.002$, $n=12$)
microRNA loaded
Circular RNA

Acknowledgements: Hojin Sun, Manu Gnanamony PhD
What can you achieve?


• TX1111: a peptide homologue of Topoisomerase-1 sensitizes pancreatic cancer cells to gemcitabine. Manu Gnanamony, Victoria Stepanova, Lily Criscione, Jerusha Boyineni, Stephen J. Marshall, AiXuan Holterman, Christopher S. Gondi. Abstract Number: 2154, Monday, Apr 18, 2016, 1:00 PM - 5:00 PM; American Association for Cancer Research 2016.


• Gemcitabine Naive Pancreatic Ductal Adenocarcinoma Primary Cells Acquire Chemoresistance when Exposed to Urokinase Plasminogen Activator, M. L. Rossi, N. Kalva, A. Holterman, C. Gondi; 9th Annual Academic Surgical Congress Abstract Submission ASC20141183, February 4 - 6, 2014, Manchester Grand Hyatt, San Diego, California
**UIC collaborators**
- Neurosurgery (Julian Lin MD)
- Pediatrics (Pedro de Alarcon, M.D.)
- Surgery (J Stephen Marshall, MD)
- Pathology (Pushpa Joseph MD)

**External Collaborators**
- National Cancer Institute, NIH (Perwaz Hussain PhD)
- University of Pennsylvania (Douglas B. Cines MD, Victoria Stepanova PhD)

**Acknowledgements**
- Manu Gnanamony PhD
- Jerusha Boyineini PhD
- Smita Tanpure MS
- Maria Rossi MD
- Wesley Samore MD
- Azeem A Rehman
- Chad M Lampe MD
- Lily Criscione MD
- Monica Rossi MD candidate
- Danny Ge MD candidate
Other projects in the Department of Medicine

- Case reports
- Meta-analysis
- Colonoscopy registry
- Cardiovascular disease
- Cystic fibrosis
Research in Emergency Medicine

UNIVERSITY OF ILLINOIS COLLEGE OF MEDICINE AT PEORIA
Role of Students

Creation of a Student Project
- Requires early approach
- Generating a question
- IRB submission
- Data collection
- Data analysis
- Presentation
- Manuscript generation
- Publication
Role of Students

Assistance with a Faculty Lead Project

◦ IRB Requirements
◦ Data capture
◦ Data entry
◦ Limited analysis
◦ Role in presentation and manuscript formation
Overview

Multiple interesting areas of research

- EMS
- Resuscitation
- Pediatrics
- Injury Prevention
- Clinical EM
- Education
- Ultrasound
Types of Studies

Retrospective Chart Reviews
Surveys
Educational interventions
Limited RCTs
Public Health Interventions
Review Articles/Book Chapters
Write-ups of previously done research
Research Opportunities
UICOMP and INI

Neuroscience, Neurology, Neurosurgery
Faculty

Neurology 22 faculty 16 residents
Neurosurgery 9 faculty 10 residents
Neuroradiology 6 faculty 1 fellow
Neuropathology 1 faculty
Neuroscience 5 faculty three laboratories
Specialty Centers

Cerebrovascular-stroke
Brain Tumor
Spine
Epilepsy
Movement Disorders
Neuromuscular Disease
Multiple Sclerosis
Headache
Cognitive Disorders
Pediatric Neurology and Neurosurgery
Functional Neurosurgery
Neurological population health and outcomes
Laboratories

Brain tumor biology - Velpula, Tsung
Brain Ischemia and Injury - Veeravalli, Klopfenstein
Degenerative Brain Processes - Fukuchi, Biernot
Research Opportunities

Laboratory Research
Clinical Research-Specialty Centers
Outcome and Quality Studies
Educational process studies
Simulation, VR and AR in education
Bioengineering projects
Finding an Opportunity

INI Web Site-Medical Student Opportunities

https://www.osfhealthcare.org/services/neurosciences/medical-professionals/medical-student-opportunities/
Infrastructure and Funding

INI Medical Editor  Stanca Iacob MD, PhD
Statisticians H Wang PhD, Y Wang PhD
INI Research Work Group supports study development
INI Neuroscience Medical Student Research Fund
Short term 3 month awards
Year long or greater awards
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Library of the Health Sciences - Peoria

One Illini Drive
PO Box 1849
Peoria, IL 61656

Phone: (309) 671-8490

Reference email: lib-prep@uic.edu

The Library of the Health Sciences - Peoria collaborates with the Colleges of Medicine and Nursing to meet the information needs of students, residents, faculty, staff and researchers affiliated with the University, as well as members of the community.

Popular Resources

- PubMed
- AccessMedicine
- CINAHL
- ClinicalKey
- DynaMed Plus
- UpToDate
- College of Medicine at Peoria
- College of Nursing at Peoria
- UIC Library Catalog

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7:30 a.m. - 11 p.m.

Additional Hours

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• Research Guides – Peoria Medical Students Guide, Mobile Medicine @ UIC, Evidence Based Medicine Guide
• Information Experts – Library Faculty & Staff
Swapna Asuthkar PhD
Assistant Professor
Department of Cancer Biology and Pharmacology
Office – C wing, C-211
Email: asuthkar@uic.edu
Medulloblastoma

Medulloblastoma is most common childhood malignant brain tumor.

**Treatment:** complete surgical removal of tumor, followed by craniospinal (brain and spine) radiation (Delayed in patients < 3 yr) and/or chemotherapy.

**Recurrence:** Despite improved multimodal therapy, medulloblastoma remains incurable in a significant proportion of patients.
Medulloblastoma (MB) Research

I. Targeting the immune compartment of the tumor microenvironment
   a. B7-H3 expression in medulloblastoma and its regulation by c-MYC.
   b. Role of B7-H3 in MB angiogenesis.

II. Targeting histone modifiers in MB tumor growth and progression
   a. Role of Histone-lysine N-methyltransferase (HMTs) in MB.
   b. HMT/transcription factor interactions as crucial players in MB tumor growth.

Ian Purvis  
M3 student

Jose Castellanos  
M3 student

Matthew Law  
M2 student
I. Immune compartment of TME; B7-H3 promising immune checkpoint

Jose R Castellanos et al., 2017
B7-H3 immune checkpoint as the novel target in Medulloblastoma
II. Epigenetic modifiers in medulloblastoma pathogenesis
Collaborations

Dr. Rajeev Vibhakar, MD, PhD, Univ. of Colorado
Dr. Sujatha Venkataraman, PhD, Univ. of Colorado
Dr. Kiran K Velpula, PhD, UICOMP
David J Daniels, MD, PhD, Mayo Clinic
Dr. Julian Lin, MD, INI
Dr. Rama D Sanam, PhD, GVK bio, India
Sarah E. Martin, MD, OSF
Dr. Andrew J Tsung, MD, INI
Dr. Justin Lathia, PhD, Cleveland Clinic

Thank You
The microbiota of bloodstream infections in patients with acute leukemia

Peter Gyarmati
University of Illinois College of Medicine Peoria
Department of Cancer Biology and Pharmacology
Microbiota = microorganisms inhabiting the human body

- Neglected organ
- ~2 kg body mass
- More bacterial cells than human
- >500x more bacterial genes
- Physiological functions
Microbiota in health and disease

- Commensal
- Symbiotic
- Pathogenic

Belkaid & Hand, 2013
Blood microbiota in leukemia

- BSI is a major cause of mortality
- Cancers of the hematopoietic system, which results in non-functional white blood cells (blasts)
- Derived from two hematopoietic stem cell lineages: myeloid (granulocytes, erythrocytes, thrombocytes, macrophages, mast cells) and lymphoid (B, T, NK and plasma cells)
- Due to the circulatory and immune systems, these problems are closely related and often overlap
Blood microbiota - in health

• “Sterile” in physiological conditions
• Mitochondrial DNA derived from circular bacterial genomes
• Viruses / viral segments / phages are often present in healthy people

HHV7 (Guerrero&Bacon)  
TTV (Itoh et al., 2000)
Blood microbiota in leukemia

- Bacteremia, viremia, fungemia can all occur
- External or internal origin
- Immune barrier failure
- Often induced by chemotherapy / antibiotics
- Lack of colonization resistance
- Bloodstream infection may lead to sepsis
Metagenomics in leukemia

1. Evaluate antibiotics efficacy
2. Recommendations for more specific treatment (avoid antibiotic misuse, shorten hospital stay, decrease healthcare costs)
3. Narrow-spectrum or pathogen-specific antimicrobial treatment instead of broad-spectrum antibiotics
4. Preserve the indigenous microbiota
Thank you!

gyarmati@uic.edu
Cellular Signaling & Therapeutic Opportunities

Sang-Oh Yoon

Department of Cancer Biology & Pharmacology
Cancer treatment

Traditional cancer treatment

Radiotherapy  Surgery  Chemotherapy

Targeted therapy

New generation cancer treatment
Targeted Cancer Therapies
Targeted Cancer Therapies

- Small molecules
- Antibodies
Basis of targeted therapy: Understanding signaling

- Nutrients
- Growth factors/Hormones
- Cytokines
- Extracellular matrix
- Other cells (immune cells, fibroblasts, etc)
- Stress
- Outer environment (hypoxia, acidity, etc)

Simplified cancer cell signaling
Signaling and tumor progression

- Nutrients
- Growth factors/
- Hormones
- Cytokines
- Extracellular matrix
- Other cells (immune cells, fibroblasts, etc)
- Stress
- Outer environment (hypoxia, acidity, etc)
Targeting signaling molecules - Therapeutic potentials

Output

Nutrients
Growth factors/
Hormones
Cytokines
Extracellular matrix
Other cells (immune cells, fibroblasts, etc)
Stress
Outer environment (hypoxia, acidity, etc)
Kinases: Major mediators of signal transduction

Input

- Tumor growth
- Tumor survival
- Tumor invasion/metastasis
- Angiogenesis
- Anti-cancer drug resistance
- Inflammation
Kinases: Major mediators of signal transduction

FDA-approved kinase inhibitors for targeted cancer therapy

- Small molecules (26 inhibitors)
- Antibodies (7 antibodies)
PI3K/Akt/mTOR & Ras/Raf/ERK signaling networks

- Overexpression
- Overexpression
- Mutation
- Overexpression
- Mutation

PI3K → Akt → mTOR → Invasion/metastasis
Ras/Raf → MEK → ERK → Tumor growth/survival/survival/Invasion/metastasis
Research focus 1: Cancer metabolism - Protein synthesis
Research focus 1: Cancer metabolism

Signaling mediators

Metabolic stress
Research focus 2: Anti-cancer drug resistance
Research focus 2: Anti-cancer drug resistance
Research focus 2: Anti-cancer drug resistance

J Clinical Oncology 2011
Research focus 2: Anti-cancer drug resistance
**Goal**
Understanding signaling networks for basis of targeted cancer therapies

**Specific aims**

- **Tumor metabolism**
  - Signaling mediators
  - Metabolic stress

- **Overcoming drug resistance**
Pain-sensing TRP channels regulate hormonal signaling in response to endogenous nociception

Eleonora Zakharian
University of Illinois College of Medicine
Peoria IL 61605

Students Orientation
August 17th, 2017
Stimuli activate TRP channels on skin and signal propagates to CNS.
TRP channels involved in nociception
The role of TRPM8 channels as a cold and menthol receptor is well established in the framework of somatosensory nervous system, and widely used in therapeutics.
Ca$^{2+}$ imagining fluorescent microscopy
Planar lipid bilayers were formed from a solution of synthetic 1-palmitoyl-2-oleoyl-glycero-3-phosphocoline (POPC) and 1-palmitoyl-2-oleoyl-glycero-3-phosphoethanolamine (POPE) in ratio 3:1 in n-decane. The solution was used to paint a bilayer in an aperture of \( \sim 150 \mu \text{m} \) diameter in a Delrin cup between symmetric aqueous bathing solutions.
Steroid sensitivity of TRPM8

100 pM Testosterone

100 pM BSA-Testosterone

2 μM Progesterone

5 μM Estradiol

L. Demirkhanyan et al., submitted
Role of TRPM8 channels in prostate cancer
TRPM8 targeted for degradation in PC
Cell growth/proliferation $\approx$ Apoptosis

Cell Growth

Channel open

\[ \text{Ca}^{2+} \]

\[ \text{PIP}_2 \rightarrow \text{PIP}_3 \rightarrow \text{PI3K/AKT} \rightarrow \text{TRPM8} \rightarrow \text{Testosterone} \rightarrow \text{Ca}^{2+} \]

Channel closed

Mitochondria

\[ \text{MCU} \rightarrow \text{Ca}^{2+} \text{ overload} \rightarrow \text{PTEN} \rightarrow \text{PI3K/AKT} \rightarrow \text{Apoptosis} \]

PM

TRPM8

Normal Prostate Cell

Cell growth/proliferation $\approx$ Apoptosis
Cell growth/proliferation >>> Apoptosis

Loss of TRPM8 = No rapid Ca\(^{2+}\) uptake + increased testosterone

Ubiquitin → degradation
TRPM8 knockout mice exhibit altered sexual behaviors

**Copulation**

- **Number of mounts, hr⁻¹**
  - WT
  - TRPV1-KO
  - TRPM8-KO

**Intromission**

- **Intromission, s**
  - WT
  - TRPV1-KO
  - TRPM8-KO

**Mounting frequency**

- **Long vs. Short mounts**

**Ratio of long vs. short mounts**

L. Demirkhanyan et al., submitted
TRPM8-KO mice exhibit altered sexual preference

Male to female mating

Male to male mating
TRPM8 expression along the olfactory-amygdala pathway

- Vomeronasal Organ
- Accessory olfactory bulb
- Olfactory bulb
- Olfactory epithelium
- Anterior olfactory nucleus
- TRPM8 expression along the olfactory-amygdala pathway
- Pheromones
- Hypothalamus
- Sexual behavior
- Endocrine response
- Amygdala
- Piriform cortex
- VNO
- Olfactory tubercle
- OB
- AOB
- OE
- TRPM8
- AON
- OT Pir
- Hypo
 Testosterone is a highly potent and specific agonist of the TRPM8 channel
 TRPM8 regulates testosterone-dependent behavioral repertoire
TRPV1 is a direct ionotrophic oxytocin receptor.

This finding suggests an existence of endogenous regulatory pathways that modulate nociception via direct action of oxytocin on TRPV1, implying its analgesic effect via the channel’s desensitization.
Oxytocin interacts with TRPV1 at the same domain as RTX/DkTx
Study on novel roles of homopolymers, polyhydroxybutyrate (PHB) and inorganic polyphosphate (polyP)
Study on novel roles of homopolymers, polyhydroxybutyrate (PHB) and inorganic polyphosphate (polyP)

Mitochondria from diabetic cardiomyocytes
Contact information:

Eleonora Zakharian

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Office Ph: 309-680-8621
Lab Ph: 309-680-8634
E-mail: zakharel@uic.edu
Research Projects in Fukuchi Lab
(Aβ metabolism & neuroimmunology in Alzheimer’s disease)

Dr. Ken-ichiro Fukuchi
Dr. Junling Yang
University of Illinois College of Medicine Peoria
Reasons for Alzheimer’s research

- 6th leading cause of death in the US: Deaths from AD increased 89% from 2000-2014 while other major diseases have decreased (ex. 1st Heart disease by 14%).
- AD is the only top 10 killer that cannot be prevented, cured or slowed.
- Currently, 5.5 million living with AD, 14 million by 2050. AD will cost the U.S. $259 billion in 2017 and more than $1.1 trillion in 2050 (in 2015 dollars). (The federal budget is $3.8 trillion in 2015)
Research is fun!

- We formulate a hypothesis.
- We design the experiments to test our hypothesis.
- We carry out the experiments to find if our hypothesis is correct.
Amyloid cascade hypothesis

**Familial Alzheimer’s Disease**
- Mutations in the APP or presenilin genes
- Life-long increase in Aβ42 production

**Sporadic Alzheimer’s Disease**
- Genetic risk factors: ApoE4, other risk genes. Aging & environmental risk factors
- Failure of Aβ clearance

- Aβ accumulation and oligomerization
- Gradual deposition of Aβ42 oligomers as diffuse plaques
- Microglial and astrocytic activation, with attendant inflammatory response
- Altered neuronal ionic homeostasis and oxidative stress
- Altered kinase/phosphatase activity. Tangles, synaptic dysfunction, neuron loss.

**DEMENTIA**

1. Microglia (Innate immunity)
2. Aβ efflux transporters at BBB

Risk factors of Alzheimer’s disease (AD)

- **Age**: risk doubles about every 5 years after age 65
- Genetic risk factors including ApoE, TREM2, etc.
  - ~25 genetic variants include many immune loci
- **Cardiovascular risk factors**
  - Hypertension
  - Hyperlipidemia (high cholesterol)
  - Obesity
  - Diabetes
  - Depression
- **Systemic/peripheral inflammation**
- **Lifestyle risk factors**
  - Low education
  - Sedentary, low physical activity
  - Smoking and alcohol
  - Saturated fats
Aβ clearance from the brain across the blood-brain barrier (BBB)

Our hypothesis: Blood exosomal miR-34a in diabetes, obesity and inflammation increases Alzheimer risk by decreasing/targeting Aβ transporters at the BBB
Experimental design: AD animal models

Aim 1. Create a miR-34a-deficient (Mir34a-/-) AD mouse model

Aim 2. Prepare exosomes loaded with miR-34a or its inhibitor, inject the exosomes into AD mice

outcome measures

1. Aβ efflux transporters
2. Evaluate AD-like pathophysiological and behavioral changes
3. Brain expression profiling
Research projects in Fukuchi lab

- Alzheimer’s Disease (AD)
  - Role of miR-34a in the AD pathogenesis
  - Altered exosomal microRNAs and proteins associated with inflammation, obesity and diabetes increase the risk of AD
  - Innate immune dysfunction: altered toll-like receptor signaling in microglia
  - Roles of brain cytokines (IL-17A) in regulating brain glucose metabolism and Aβ transporters at the BBB
Ischemic Stroke: From Mechanisms to Therapeutic Implications

Krishna Veeravalli, PhD

Failure of blood circulation to the brain

- Blockade of Blood Flow

- Bleeding

ISCHEMIC ~85%

Thrombosis
Embolism
Stenosis

HEMORRHAGIC ~15%
Time is Brain

Each minute the treatment is delayed, ~2 million brain cells will be lost.
Current treatment Options

Treatment

Preventive Treatment

Carotid Endarterectomy
Current treatment Options

Treatment
Carotid Endarterectomy

Preventive Treatment
Angioplasty/stents

tPA
Limitations
Reperfusion Injury

- Ischemia
  - Anaerobic: rapid fall-down of intracellular pH
  - Phosphofructokinase inactivation and reduced Ca²⁺ sensitivity of Troponin C
  - Rapid Bulging (asystole)
- Reperfusion
  - Aerobic: prompt recovery of intracellular pH
  - Activation of inflammatory cascades
  - Intracellular Ca²⁺ overload
  - Subcellular signal activation
  - Ca-dependent protease activation
  - Robust ROS generation
- Apoptosis
- Cytokine Release
- Disruption of cell structure = Death

Graphs showing time courses of ischemic injury, reperfusion injury, and reperfusion salvage.
**ARterial Occlusion**
- Reduction in Blood flow
- Water Accumulation
- Expression of Cell Adhesion Molecules
- BBB disruption and edema
- Leukocyte Recruitment

**Inflammation**
- INFLAMMATION
- Activation of COX2
- Inflammatory Mediators
  - Cytokines (IL-1,6, TNFa)
  - Activation Cyt c
  - BAD, BAX
- Activation of
  - NMDA, AMPA
  - Metabotropic receptors
- Ca²⁺ release from Intracellular stores
- Ca²⁺ overload mitochondria
- Depletion of GSH
- Catalase, SOD, Ascorbate, Tocopherol
- Burst of free radicals from mitochondrial transition pore
- Release of Pro-apoptotic Molecules like Cytochrome c, Caspases
  - SMAC/DIABLO
  - AIF

**Release of Glutamate**
- Ca²⁺ release from Intracellular stores
- Intracellular Ca²⁺, Na⁺, and Cl⁻
- Membrane Degradation
- Increased Intracellular Ca²⁺, Na⁺, and Cl⁻
- Mitochondrial Failure
- NO Synthase activation
- NO Production
- Failure of Free radical scavenging
- Release of Pro-apoptotic Molecules like Cytochrome c, Caspases
  - SMAC/DIABLO
  - AIF

**NeCrosis**
- Anaerobic Glycolysis
- Ca²⁺/K⁺-ATPase pump failure
- Cell membrane Depolarization
- Extracellular K⁺
- Causes depression
- Acidosis
- Failure of Energy metabolism
- Water Accumulation
- Ca²⁺ over load mitochondria
- Membrane Degradation
- Membrane Disruption
- Cell Lysis
- Cell membrane Depolarization
- Activation of
  - - Endonucleases
  - - Calpains
  - - Calmodulin
- Activation of
  - - Kinases
  - - Proteases
  - - Lipases
- Phospholipase A2 activation
- Bursting
- Release of Arachidonic Acid
- Production of Cytokines
- Formation of Free radicles
- Production of Cytokines
- Production of Cytokines
- Inflammatory Mediators
  - Cytokines (IL-1,6, TNFa)
  - Inflammatory Mediators
  - Cytokines (IL-1,6, TNFa)

**Lipid Peroxidation**
- Cell Membrane Disruption
- Increased NO Synthase activation
- Increased NO Production

**Apoptosis**
- Necrosis
- Oxidative Stress

**Aggarwal et al., Int J of Pharma and Bio Sciences 2010; 1: 1-24**
<table>
<thead>
<tr>
<th>SYSTEMIC/CELLULAR EVENTS</th>
<th>DYNAMICS</th>
<th>minutes to hours</th>
<th>minutes, hours to days</th>
<th>hours to days</th>
<th>days, weeks to months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Necrosis</td>
<td>Apoptosis</td>
<td>Inflammation</td>
<td>Repair Remodeling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Plasticity</td>
<td></td>
</tr>
<tr>
<td>ATP↓, Ca^{2+}↑, glut↑</td>
<td></td>
<td>caspase↑, AIF-accumulation↑</td>
<td>cytokines↑, (IL-1β, TNFα)↑</td>
<td>angiogenesis↑, MMP-13↑, aggregan↑, ECM-reorganisation↑, cell-cycle proteins↑, cyclines↑</td>
<td>axonal sprouting↑, glial scar formation↑</td>
</tr>
<tr>
<td>NO↑, ROS↑, TF↑, IEGs↑, μ-calpain↑</td>
<td></td>
<td>mitochondria-collapsen, cytoskeleton-breakdown</td>
<td>adhesion molecules↑, (ICAM, selectin)↑</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Secondary damage: Inflammation, Programmed cell death

Energy failure, excitotoxicity, depolarizations, necrosis

Endogenous brain protection

Plasticity, regeneration, repair

Complications
Research Focus

Mitigate the brain injury caused by Ischemia & Reperfusion

Facilitate the recovery process after ischemic stroke

COMBO Therapy

Gene Silencing

Stem Cell transplantation
Metabolic alterations in glioblastoma: The Warburg Effect

Kiran Velpula, PhD
Principal Investigator

Assistant Professor,
Department of Cancer Biology and Pharmacology,
Department of Neurosurgery,
UICOMP

Associate Professor,
Department of Microbiology,
Yogi Vemana University,
Kadapa, India
Laboratory Mission

- Research
- Drug Discovery
- Professional Academic services
- Medical Student Education
- Service to University
- Community Service
The idea

HYPOTHESIS

Our Approach at UICOMP

1. Big data analysis (data mining approach)
2. Metabolic analysis
3. Validation via Cancer Stem Cell, crisp cas-9, and miRNA approach
4. Homology modelling
5. Nanoparticle mediated drug delivery system development
6. Pharmacokinetic testing in animal models
7. Development of a mice model to highlight our findings using RCAS model
Map of metabolic pathways
Hallmarks of Cancer

Emerging Hallmarks

1. Deregulating cellular energetics
2. Avoiding immune destruction
3. Genome instability and mutation
4. Tumor-promoting Inflammation

Enabling Characteristics

Hanahan et al., Cell 2011
The Warburg effect

“most cancer cells predominantly produce energy through a high rate of glycolysis followed by lactic acid fermentation, rather than through oxidative phosphorylation in the mitochondria”

Otto Warburg, Science 24 Feb 1956

Dr. Otto H. Warburg
Glioblastoma
Target EGFR

Cord Blood Stem Cells Inhibit Epidermal Growth Factor Receptor Translocation to Mitochondria in Glioblastoma

Target PDK1

PDK1: a new therapeutic target for glioblastoma?

Combined targeting EGFR+PDK1

Combined Targeting of PDK1 and EGFR Triggers Regression of Glioblastoma by Reversing the Warburg Effect

Combined targeting EGFRvIII+PDK1

Metabolic targeting of EGFRvIII/PDK1 axis in temozolomide resistant glioblastoma
Glioblastoma:
1. Targeting EGFR/EGFRvIII in understanding altered metabolism
2. Methylation regulate HEY1 expression in GBM
3. GLUT1, tubulins and glucose availability: Reversing the Warburg effect in glioblastoma
4. Identification of novel drugs that regulate mitochondrial metabolism in EGFR over expressing cells
5. Characterizing extra-metabolic roles of PDK1 in mesenchymal subtype in GBM
6. Co-stimulatory targets in PDK1 mediated immunotherapy in glioblastoma

Medulloblastoma:
Otx-2 interacts with c-Myc to determine the pathogenicity of medulloblastoma subtypes

Breast Cancer:
Nano conjugated miR-211 reduce the proliferation of triple negative breast cancers
VELPULA-TSUNG’S RESEARCH GROUP

Meet the lab

Kiran K. Velpula, PhD
Andrew J. Tsung, MD

Maheedhara R. Guda, PhD
Visiting Research Scholar

Collin Labak
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MD Candidate, 2019 James Scholar

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MD Candidate, 2019

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MD Candidate, 2020

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MD Candidate, 2020

Pooja Agarwal
MD Candidate, 2020

Jacob Stewart
MD Candidate, 2021


Our Collaborators

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2. Jeremy N. Rch, Cleveland Clinic
3. Jann Sarkaria, Mayo Clinic
4. Craig Horbinski, Northwestern
5. Michael Olin, Univ. of Minnesota
6. Ichiro Nakano, Univ. of Alabama
7. Jack Tuszyński, Univ. of Alabama
8. Neil Greg, NIH
9. John Kuo, Univ. of W.Madison
10. Krishna Bhatt, MD Anderson, TX

Medulloblastoma
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2. David Daniels, Mayo Clinic
3. Sarah E. Bach, UICOMP
4. Durbaka Prasad, YU, India

Breast Cancer
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2. Satish Mungamuri, Mount Sinai
3. Neil Price, USDA, Peoria
4. Goverdhan Das, JNU, India

Thank you!

William E. Mc Elroy
Foundation
Neurotoxicity of Environmental Chemical Exposures

Stephen M. Lasley, Ph.D.

Cancer Biology and Pharmacology
UICOM-P
Model of Neuroinflammation

- “Sickness behavior”
  - Impaired cognition
  - Fatigue
  - Depression
  - Muscle/joint pain
  - GI disturbances

- ↑ expression of inflammatory mediators – IL-1β, TNF-α

- Relation to Gulf War Illness? Pesticide applicators?
Mouse Model

- OP AChase inhibitors (sarin, DFP, chlorpyrifos) → small ↑ brain inflammatory mediator expression
- Period of stress hormone → ‘priming’ of inflammatory mechanisms; cellular immune pathways?
- Stress hormone + single dose OP → huge ↑ in inflammatory response
- Repeated intermittent stress hormone + OP enhances neuroinflammation – LPS as immune stimulus
Mouse Model

- Peak in cytokine/chemokine gene expression occurs 6-12 hr post-OP
- Peak in protein expression within 24 hr(?)
- Neuroinflammation → impaired cognition
  - What is time course of inflammation effects on synaptic plasticity genes?
  - What is duration of the cognitive impairment?
Model Components

CORT + AChE inhibitor

↑↑ Neuroinflammation

‘sickness behavior’

↓ neurogenesis, CNS plasticity
Gulf War Illness Project

- Establish stress + OP (+ LPS) regimen that → enduring behavioral effect (spatial learning paradigms)
- Assess neurogenesis
- Determine electrophysiological capacity for plasticity and related expression of plasticity genes
Future Steps

- Test experimental therapies for GWI
  - Drugs to enhance neurogenesis
  - Unconventional anti-inflammatory agents

- Extend findings to general exposures to pesticides and exposed individuals
Uncovering the Molecular Mechanisms Underlying Development of Pediatric Brain Tumors

Sergey Malchenko MD, PhD
and
Marcelo Bento Soares, Ph.D.
Radial Glia

Radial glial (RG) cells are a pivotal cell type in the developing central nervous system (CNS) involved in key developmental processes, from patterning and neuronal migration to their recently discovered role as precursors during neurogenesis. They arise early in development from neuroepithelial cells.

State of the art stereotactic mice brain surgery instruments
Ventricular system

The ventricular system is a set of four interconnected cavities (ventricles) in the brain, where the cerebrospinal fluid (CSF) is produced. Within each ventricle is a region of choroid plexus, a network of ependymal cells involved in the production of CSF. The ventricular system is continuous with the central canal of the spinal cord (from the fourth ventricle) allowing for the flow of CSF to circulate.

GFP labeling of choroid plexus in different brain sections of mice ventricular system

(Méndez-Gomez et al., Molecular Therapy-Methods & Clinical Dev. 2015)
Orthotopic transplantation sites
(red arrows)

(The images were taken from Harvard Medical School High Resolution Mouse brain Atlas)
The differentiation of GFP positive RG cells after being injected into motor cortex of NOD-SCID mice (15 weeks post-injection)
Orthotopic transplantation of the wild type RG cells to SVZ of 3rd ventricle

Dr. H. Hashimoto - Osaka University, Japan
PNET

• PNET (primitive neuroectodermal tumor) is a name used for tumors which appear identical under the microscope to medulloblastoma, but occur primarily in the cerebral hemisphere.

• PNETs contain underdeveloped brain cells, are highly malignant, and tend to spread throughout the central nervous system.

• Surgery is the standard initial treatment for these tumors. Because of their large size, tendency to spread, and extensive blood supply, total removal is rarely possible. Very young children are usually not treated with chemotherapy until they are older.

• Comprehensive set of diagnostic/prognostic markers as well as development of new drugs and delivery systems are needed to tailor the individualized therapeutic strategies.
There is growing evidence that brain tumorigenesis is driven by alterations that occur in neural stem cells (NSCs), which ultimately give rise to brain tumor initiating cells (BTICs).

However, despite the **key role in tumor maintenance, tumor relapse, metastatic dissemination and drug resistance**, there is no comprehensive characterization of CNS-PNETs BTICs up to date.
Brain tumors harvested 4-12 weeks post-inoculation. Histopathological analyses revealed hallmarks of tumor of neuroectodermal origin: CNS primitive neuroectodermal tumors (PNETs).

RG cells injected into the subventricular zone of the 3rd ventricle of the brain in immunocompromised mice. Upon differentiation, both tumor and RG cells neurospheres generate neurons, astrocytes, and oligodendrocytes.

Tumor cells were dissociated into single-cell suspension and then incubated in the same neural stem cell culture conditions as RG cells. Human radial glial (RG) cells incubated in neural stem cell culture conditions.
BTIC self-renewal and differentiation
PCA of RNA-seq data
Genes significantly up-regulated in the TCL self-renewing cells

- BTIC markers
- Cell growth, Proliferation
- Invasion, Migration
- Metabolism
- Hypoxia
- Tumor suppressors
- Anti-apoptosis
Brain tumors harvested 4-12 weeks post-inoculation

Histopathological analyses revealed hallmarks of tumor of neuroectodermal origin: CNS primitive neuroectodermal tumors (PNETs)

RG cells injected into the subventricular zone of the 3rd ventricle of the brain in immunocompromised mice

First gen.

Tumor cells were dissociated into single-cell suspension and then incubated in the same neural stem cell culture conditions as RG cells

Human radial glial (RG) cells incubated in neural stem cell culture conditions

Second gen.

Tumor cells injected into the subventricular zone of the 3rd ventricle of the brain in immunocompromised mice

Tumor cells were dissociated into single-cell suspension and then incubated in the same neural stem cell culture conditions as RG cells

Histopathological analyses revealed hallmarks of tumor of neuroectodermal origin: CNS primitive neuroectodermal tumors (PNETs)

Brain tumors harvested 4-12 weeks post-inoculation

Experimental design
Cell Proliferation

[Images showing DAPI, FITC, and merged images for different samples]

[Bar chart showing cell proliferation percentages for different samples]
Epi-drug screening of RG and BTIC
PNET-Nanotech.
PNET-Nanotech.

EGF directed killing of cancer cells using single walled carbon nanotube (SWCNT)-cisplatin delivery vector. Nanotubes coated with EGF ligand bind to the cognate EGF receptor on the cancer cell surface and internalize via receptor-mediated endocytosis. Quantum dot nanoparticles (Qdots) allow detection of the nanotubes

(C Patel et al., Pharmaceutics 2011)
PNET-Nanotech.
EXOSOME BASICS
Exosomes are small membrane vesicles secreted by most cell types. Internal vesicles form by the inward budding of cellular compartments known as multivesicular endosomes (MVE). When MVE fuse with the plasma membrane, these internal vesicles are released as exosomes, which can travel to distant tissues to influence various aspects of cell behavior and physiology.

FROM FORMATION TO TARGET
In the first step of exosome formation, MVE bud inward to form small internal vesicles containing proteins, mRNAs, and miRNAs from the cytoplasm. These internal vesicles are released as exosomes when MVE fuse with the cell membrane. Alternatively, MVE can fuse with lysosomes, which degrade MVE contents. Upon reaching their destinations, usually determined by the binding of specific ligands on their surfaces, exosomes can enter target cells in one of two ways: by being taken up by the target cell's endocytic pathway or by fusing to the target cell's membrane and releasing its contents directly into the cytoplasm. Cells also secrete other membrane-derived vesicles, such as ectosomes, shed vesicles, or microvesicles, which bud directly from the cell's plasma membrane. These vesicles are also known to carry active proteins and RNAs, as well as some compounds never before described in exosomes, but little is known about their effects on distant tissues.
## PNET - Liquid Biopsy Markers

### Liquid Biopsy

- Biofluids are readily accessed and carry a lower risk of complications
- Allows for real-time, serial and longitudinal monitoring during cancer therapy
- Provides a more comprehensive view of the tumor’s molecular make-up by collecting biological material from cells throughout the tumor
- Given the non-invasive nature of liquid biopsies, multiple samples can be collected as needed

### Tissue Biopsy

- Invasive surgical tissue procedures may not be practical
- Provide a snapshot of disease at a single time point
- May not provide a complete understanding of the tumor’s molecular makeup, as tumors can be quite heterogeneous
- Yield a limited sample size that can quickly become depleted if tissue needs to be divided and utilized for various diagnostic purposes
Lab techniques involved in studying PNET animal modeling

- Human neural stem cell derivation
- Different Stem Cell culturing and immunohistochemistry techniques
- Exosome, DNA, RNA isolation, cDNA construction, RT-PCR, Western Blot, etc.
- Apoptosis, invasion, cell proliferations, drug screening assays
- Mice breeding, stereotactictic brain surgery, etc.