Highlights

Platforms
- Translational medicine, clinical and basic sciences
- Early discovery with deep biology expertise
- Center to bridge academic and industry resources

Portfolio
- Neurosciences
- Fibrosis and inflammation
- Mitochondrial diseases
- Oncology and immunomodulation
- Cardiovascular diseases
- Specialty areas (e.g. SCD)

Pharma Partners
- Confidential (currently under negotiation)

Financials
- >$65M invested in Drug Discovery Building and facilities, opened Oct 2011
- >$200M in extramural research grants
- 19 Smart State Endowed Chairs focused on components of Drug Discovery
Strategy

- Demonstrate outstanding opportunities in the science of drug discovery that add unique value to an industry partner’s pipeline focus or gap

- Pursue a new paradigm for partnerships in drug discovery specifically designed to increase the success rate of translating a key scientific finding into patient benefit

- Build a sustainable model for bridging the expertise and capabilities of multiple industry and academic partners with timely and efficient decision making

- Deliver on scientific milestones, greater understanding of disease processes, and ultimately cutting-edge therapeutic agents
SC Center for Therapeutic Discovery and Development

**CURRENT PARADIGM**

- MUSC FACULTY RESEARCH AND DISEASE GROUPS
- FACULTY GENERATED IP
- LICENSE OR SPINOUT COMPANIES/TECH

**NEW PARADIGM**

1. Drug discovery & development expertise and leadership
2. Project management (strategy, IP, milestones, budget)
3. Data analysis and databases
4. Technicians & support staff
5. Discovery Fund

**Drug Discovery Concept Huddle**

SAB, collaborations, ideas

**CTDD Project Portfolio**

multiple disease areas

**PHARMA & BIOTECH PARTNERSHIP**

**DRUG DISCOVERY WITH IP, DEVELOPMENT AND COMMERCIALIZATION STRATEGY**
Example Project Opportunities

- Neurosciences
  - PTSD
  - Parkinson’s Disease
- Fibrosis & Inflammation
  - Lupus
- Mitochondrial Diseases
- Genetic Diseases: Sickle Cell Disease
- Anti-bacterial agents
Post Traumatic Stress Disorder (PTSD)

Chronic, debilitating disorder – fear-related symptoms develop after exposure to trauma or serious threat:

- Intrusive traumatic memories and nightmares
- Avoidance of trauma-related reminders (cues)
- Negative cognition and mood
- Increased arousal/vigilance-physiological reactivity

Few evidence-based pharmaceutical therapies available

![Diagram showing balance of brain areas in emotional regulation and distorted balance in PTSD](image-url)
Neurobiological Correlates of PTSD

Koch et al 2014
Neurocircuitry of fear and PTSD

Decreased medial prefrontal
Increased amygdalar reactivity

results in

Decreased top-down control of fear
Leading Clinical and Pre-clinical PTSD Research with Targets, Animal Models, and Clinical Trials

Example areas of research interest:

• receptor trafficking and synaptic localization, signal transduction, and dendritic spine dynamics

• glutamatergic, cholinergic and neuropeptide (CRF) signaling systems in the brain

• neuroplasticity at the level of protein biochemistry, neural circuitry, dendritic spine morphology, and behavioral modeling.

• elucidating the fundamental role of extracellular glutamate homeostasis in regulating neurotransmission and neuroplasticity to identify specific proteins as targets for preclinical and clinical studies

• neuroplasticity using electrophysiology, confocal imaging and biochemical analysis to characterize alterations in voltage- and calcium-activated potassium channels that underlie aberrant neuroadaptations in glutamate signaling systems

https://www.youtube.com/watch?v=yQo1My3zQLQ

Kathleen T. Brady, MD, PhD
Distinguished University Professor, Associate Provost, Clinical and Translational Research Director, South Carolina Clinical and Translational Research Institute
Parkinson’s Disease (PD)

Second most common neurodegenerative disorder

~5 Million people affected worldwide
  - 1.5 Million people in US
  - 43,000 people in the Carolinas

Most prevalent in people over 60 years of age, but can affect younger people as well

Degeneration of dopaminergic neurons in substantia nigra, leading to loss of dopamine

Presence of Lewy bodies within cytoplasm

Loss of >50% of normal striatal dopaminergic innervation: onset of motor symptoms
A Timeline for Parkinson's Disease

Clinical Manifestations

20 year prodrome
- Hyposmia
- Constipation
- Bladder dysfunction
- Depression

Onset
- Sleep disorder (RBD)
- Rigidity
- Bradykinesia

Disease Progression
- Tremor
- Poor Balance, Falls
- Dependency
- Bed bound
- Rigidity
- Bradykinesia
- Cognitive decline
- Dementia

Pathological Changes

- Enteric plexus
- Olfactory bulb CNX
- Coeruleus
- Caudal raphe
- Magnocellular cf.
- Substantia nigra
- Amygdala
- Meynert’s nucleus
- PPN
- Temporal lobe
- TEC
- Ca-2 plexus
- Intralaminar thalamic nuclei
- Profronal cortex
- Tertiary sensory associated areas

Progress in understanding PD

Age > 60
Men > women
Rural living
Exposure to well water, pesticides (e.g. paraquat)
Occupational exposure to toxins (welding)
Role of genetic factors
  ◦ Genetic predisposition assumed
  ◦ Young onset PD genes: PINK1, Parkin
  ◦ Late onset PD: LRRK 2
  ◦ Alpha-synuclein gene mutation

Aging, toxins, genes

Leading Clinical and Pre-clinical PD Research with Targets, Animal Models, and Clinical Trials

http://www.muschealth.com/neurosciences/about/movementdisorders/

Vanessa K. Hinson, MD, PhD
Associate professor of neurology
Director of movement disorders
Chief of neurology at the Ralph H. Johnson VA Medical Center.
Dr. Hinson has an active clinical practice, but is also the principal investigator on several clinical trials related to the treatment of Parkinson’s disease and dystonia.

Carroll Campbell Neuropathology Lab (Brain Bank)
Stroke Research and Education Center (SREC)
Murray Center for Research on Parkinson’s Disease and Related Disorders
Institute for Applied Neurosciences (IAN)
Center on Aging
Translational Research Unit (TRU): ALS, Epilepsy, Movement Disorders, NeuroOncology
Systemic Lupus Erythematosus (Lupus)

- Production of autoantibodies (anti-dsDNA)
- Immune complex formation and tissue damage
- Glomerulonephritis affects up to 2/3 of lupus patients
- 20-40% of patients with nephritis progress to end stage renal failure after 5-10 years
- One new FDA-approved drug to treat lupus in the past 50 years
- Mediators of Lupus nephritis (LN) are largely unknown
- Features are common to other kidney diseases mediated by dysfunctional glycosphingolipid metabolism
1.5 million Americans suffer from lupus
Primarily affects young women in their childbearing years
Prevalence of women to men is 10/1 during child bearing years
Prevalence in African Americans compared to Caucasians is 3/1
Morbidity and mortality is highest in people of color
Lupus Nephritis

Occurs in 40-50% of patients, 60% in African Americans

Despite similar treatment, African Americans are 5 times more likely to progress to renal failure than Caucasians

Diagnosis of lupus and lupus nephritis is increasing both due to better awareness/diagnostics, but also due to a true increase in disease prevalence

There are no FDA approved treatments for lupus nephritis

Immune complex mediated disease:
- autoantibodies bind to glomerular deposited antigens with subsequent complement fixation

Subsequent inflammation triggered by:
- alternative complement pathway
- Fc receptor activation and
- activation of TLR pathways

Multiple other interactive pathways also implicated:
- mTOR
- IFN

Disease can be blocked post IC deposition
Lupus Nephritis Needs

Better understanding of key pathways of disease

Better biomarkers for:
- diagnosis
- prognosis
- response to treatment

Better therapies to:
- control disease acutely
- prevent long term deterioration in renal function
  - interstitial disease
  - fibrosis

Pharmacogenomics for selection of best personalized therapy
## Clinical Researchers

### Public Health
- John Vena, PhD – Professor of Public Health Sciences
- Paul Nietert, PhD - Professor of Public Health Sciences
- Edith Williams, PhD - Assistant Professor of Epidemiology

### College of Health Professions
- Hazel Breland, PhD - Assistant Professor of Health Professions

### Adult Lupologists
- Gary Gilkeson, MD - Professor of Microbiology and Immunology
- Diane Kamen, MD - Associate Professor of Rheumatology
- Jim Oates, MD - Associate Professor of Rheumatology
- Melissa Cunningham, MD, PhD – Assistant Professor of Rheumatology
Basic Sciences

Basic Researchers
Jim Oates, MD - Associate Professor of Rheumatology
Tamara Nowling, PhD - Assistant Professor of Rheumatology
Melissa Cunningham, MD, PhD - Assistant Professor of Rheumatology
Paula Ramos, PhD - Assistant Professor of Rheumatology
Gary Gilkeson, MD - Professor of Microbiology and Immunology

Micro Immunology
Zihai Li, MD, PhD - Professor of Microbiology and Immunology
Wei Jiang, MD, PhD - Assistant Professor of Microbiology and Immunology
Chenta Vasu, PhD - Associate Professor of Microbiology and Immunology
Steve Tomlinson, PhD - Professor of Microbiology & Immunology
Mitochondrial dysfunction is recognized as a mediator of acute and chronic diseases:

- **Acute**: acute organ failure (stroke, heart, liver, kidney)
- **Chronic**: neurodegenerative diseases, cancer, epilepsy
- **Mitochondrial Diseases**: muscular dystrophies
MITOCHONDRIAL HOMEOSTASIS AND FUNCTION

The highly regulated process of fission/fusion, biogenesis, and autophagy are critical to maintain mitochondrial and thereby cellular health. We and others have hypothesized that loss of mitochondrial homeostasis underlies many degenerative pathologies.
DEPARTMENT OF DRUG DISCOVERY AND BIOMEDICAL SCIENCES

EXPERTISE

Rick Schnellmann, PhD
Craig Beeson, PhD
Zhi Zhong, PhD
John Lemasters, MD, PhD
James Chou, PhD
Sherine Chan, PhD

TECHNOLOGIES

Mito-metabolomics Core

in vivo and in vitro imaging Core

Zebrafish Core

Development of Drugs to Protect and Restore Mitochondrial Function
Sickle Cell Disease: a health disparity in need of drug discovery

The most common inherited blood disorder in the United States

SCD is caused by an autosomal recessive single gene defect in the β-globin chain of adult hemoglobin (HbA) that produces a mutant form of hemoglobin known as sickle hemoglobin (HbS)

The result of a single point mutation is a significant change in hemoglobin structure which leads to an entire disease

Sickle cell anemia occurs if HbS is inherited from both parents (HbSS genotype)

Other compound heterozygotes can have SCD when HbS is co-inherited with another abnormal hemoglobin, such as hemoglobin C (HbC), or β-thalassemia

Note: The Sickle hemoglobin image is drawn at 50% of the size of the Normal hemoglobin
Sickle Cell Disease: An Overview

UNITED STATES

SCD produces hemoglobin S which causes red blood cells to distort into a sickle, or crescent, shape, causing vasoconstriction, reduced RBC life, inflammation, and vasculopathy.

Affects up to 100,000 persons in the US

2,000 patients with SCD in the Low country of South Carolina

The disease is estimated to occur in 1:300-1:500 African Americans and 1 in 1,000 to 1,400 Hispanic Americans.

Median age at death is approximately 42 years for men and 48 years for women

WORLD-WIDE

300,000 SCD children born annually in Africa (6-9 million total). 32% of these cases occur in Nigeria

Over 50% of children with SCD in low-resource areas die before five years of age

CURRENTLY: Only ONE FDA approved medication (Hydroxyurea) for adults with SCD
# Disparate health care in SCD

## Orphan Disease
- Highly misunderstood
- Poorly publicized
- Not adopted by the medical research and funding communities because it disproportionately affects African-Americans in the lower socio-economic communities
- Fewer than 200,000 people nationwide

## Clinical
- Lack of specialized providers (gets worse as children get older)
- Disparity in health care coverage
- One FDA approved medication
- Disease-based Stigmatization

## Research
- From the identification of SCD in 1910 until the National Sickle Cell Control Act in 1972 only $1 million had been spent on SCD research (16K/year)
- SCD research is still not on par with other diseases that affect far fewer people (cystic fibrosis, muscular dystrophy, etc) due to lack of a combined national focus
- Orphan disease status creates the possibility of fast-track FDA approval

## MUSC
- Created a new, lifespan clinic to improve access to care for persons with SCD
- Using telehealth to enhance treatment options for patients in rural areas
- Dedicated a new academic position to sickle cell disease research
- Working to obtain joint commission accreditation for sickle cell disease treatment
Leading Clinical and Pre-clinical SCD Research with Targets, Animal Models, and Clinical Trials


Julie Kanter-Washko, MD
Board Certified in Pediatrics: Pediatric Hematology-Oncology.
Director of Sickle Cell Research at MUSC.
Anti-Bacterial Agent for Neisseria Gonorrhoeae

- Gram-negative diplococcus
- Causative agent of STD gonorrhea
- Infects urogenital tract and pharynx

- 88 million cases worldwide per year
- 334,826 cases reported in the US in 2012, but actual number is estimated at 600,000
- Rates are rising in the US (including in the elderly)

- 5-fold increase in HIV transmission
- Pelvic inflammatory disease leads to infertility
- Disseminated gonococcal infection (DGI) causes arthritis-like condition
- Epididymitis
- Ectopic pregnancies
- Neonatal eye infections

*Nat Immunol. 2002 3:229-236*
PorB1B

MtrCDE Efflux Pump

Overexpression activates PorB1B mutations

Decreased influx

Antibiotic Efflux

Decreased inhibition

β-lactam

Outer Membrane

PorB1B

Cytoplasmic Membrane

PBP 1

PBP 2

β-lactam

Overexpression activates PorB1B mutations

Decreased influx

Antibiotic Efflux

Decreased inhibition

β-lactam
SBDD & Screening technologies

The *penA* gene from H041 confers large increases in resistance to ceftriaxone and cefixime.

Crystal structure of PBP2 from N. gonorrhoeae Powell et al, (2009) JBC 284, 1202-1212 (MUSC – Davies lab - has Xray of mutant form)

Molecular mechanism of Beta-lactam resistance

FP for PBP2 – can be applied to other pathogens
Leading the Understanding of Antibiotic Resistance at the Structural Level

- Gonorrhea is becoming increasingly untreatable globally
- PBPs are validated drug targets
- We have developed an FP-based high-throughput assay for PBPs
- Inhibitors of wild-type *N. gonorrhoeae* PBP2 that exhibit anti-gonococcal activity identified
- HTS against PBP2-H01 protein
- Virtual screening against PBP2-H041 structure
- Molecular design based on ligand-bound complex
- Applying assay technology to other pathogens

Christopher Davies, PhD
Professor
Director of Graduate Studies
Department of Biochemistry & Molecular Biology
The SC Center for Therapeutic Discovery & Development

Target to Treatment

MUSC offers significant research and development capabilities.

**Early discovery with deep biology expertise**
- Genomics and Bioinformatics Resource
- Computational Biology Resource Center
- SC COBRES: Oral Health, Biomaterials and Tissue Regeneration, Cardiovascular Disease, Oxidants and Stress Signaling, Lipidomics and Pathobiology

**Lead discovery and optimization**
- Compound design and synthesis, peptide synthesis, peptidomimetics
- Cheminformatics: QSAR, pharmacophore, docking, virtual screening, molecular dynamics, homology modeling, scaffold hopping, predicative ADME-TOX
- Live cell assays (Flux, viability, localizations, translocation, high-content)
- Center for Structural Biology: protein purification, NMR and Xray crystallography

**Phenotypic assays & mechanism of action studies**
- Animal Models Core and Small Animal Imaging: *in vivo* models of efficacy and toxicity
- Drug Metabolism Core, Mass Spectrometry Core, biomarker studies
- Gene Targeting & Knockout Shared Resource

**Translational medicine and clinical sciences**
- Drug Metabolism and Clinical Pharmacology Core
- Biostatistics
- Biorepository and Tissue Analysis Shared Resource
- SC Translational Research Institute
- Hollings Cancer Center (NCI Designation)
- Institute for Applied Neuroscience
Summary

• We are creating a world class academic drug discovery and development center focused on providing deep biology expertise and insights into disease pathology, translation medicine and clinical sciences.

• The Center will provide the organizational structure and capabilities to link the resources of the pharmaceutical and biotechnology industry with the disease experts in the medical university.

• The intellectual property and licensing will be a component of the master agreement, allowing all scientific staff to rapidly progress the project from target/phenotype to clinical proof of concept.

• The overall objective is to significantly improve the success rate and speed of translating a scientific finding into patient benefit.