Einstein-Montefiore Institute for Clinical and Translational Research

PhD in Clinical Investigation
2011

Under the Auspices of the
Einstein-Montefiore
Institute for Clinical and Translational Research
(ICTR)

Graduate Programs in the Biomedical Sciences
of the Albert Einstein College of Medicine
Dr. Ellie Schoenbaum is the director of the new PhD track in Clinical Investigation and Professor of Epidemiology & Population Health.

The goal of this PhD track is to provide rigorous advanced training for highly motivated PhD and MD/PhD students to become clinical/translational investigators. It is expected that, with receipt of the PhD, these scientists will be prepared for independent research careers and to meaningfully contribute to improving the health and welfare of our society using clinical and translational research methods.

The PhD track in Clinical Investigation (PCI) is designed for Einstein pre-doctoral students enrolled in the Graduate Division (including the MD-PhD Program) who wish to pursue careers in clinical research. This track adheres to the regulations and general requirements that pertain to the Einstein PhD. The Institute for Clinical and Translational Research (ICTR) acts as the sponsoring entity within the Graduate Division, and oversees the curriculum and progress of the PCI students. The ICTR also provides an academic home for students, with seminars, support for local and national meetings and other resources. Students choose a mentor who is an accomplished clinical researcher on our faculty, with whom they work closely to complete their original research and write the dissertation. Students take coursework that provides a foundation in clinical research methods (i.e., epidemiology, biostatistics, bioethics, data analysis, grant writing). The mentor guides further education and career development. The PCI leads to a PhD in Biomedical Sciences.

Selected References:


Key Words: epidemiology, biostatistics, clinical investigation, clinical research, population studies
INDEX OF FACULTY BY RESEARCH INTERESTS:

Adherence, Medication
Arnsten, J
Walker, E

Adolescents
Bauman, L
Silver, E

Aging, Exceptional Longevity
Barzilai, N
Kaplan, R

Anti-DNA Antibodies, Lupus Nephritis
Putterman, C

Auditory Processing
Sussman, E

Behavioral Intervention
Bauman, L
Silver, E
Walker, E
Wylie-Rosett, J

Bioethics (see Research Ethics)

Biomarkers
Kaskel, F
Lipton, R
Prystowski, M
Spivack, S
Wassertheil-Smoller, S (stroke)

Biostatistics
Kim, M

Cancer
Gorlick, R (pediatric osteosarcoma)
Prystowski, M (head & neck)
Rapkin, B (prevention)
Prystowski, M (lung)
Spivack, S (lung)
Strickler, H (epidemiology)

Cardiovascular Disease
Kaplan, R
Schuster, V
Wassertheil-Smoller, S

Chronic Illness, Children and Adolescents
Silver, E

Clinical Trials
Gorlick, R
Keller, M
Kim, M (biostatics)
Lipton, R
Wassertheil-Smoller, S
Wylie-Rosett, J (nutrition, obesity)

Cognition
Sussman, E
Verghese, J

Community Health
Rapkin, B
Wassertheil-Smoller, S (Hispanic health)

Dementia
Lipton, R
Verghese, J
Wassertheil-Smoller, S

Depression
Wassertheil-Smoller, S

Diabetes
Hawkins, M
Walker, E

Disparities (see Health Disparities)

Drug Abuse
Arnsten, J

Eicosanoids
Schuster, V

Epilepsy
Shinnar, S

Epidemiology
Kaplan, R
Kim, M
Lipton, R (neuroepidemiology)
Prystowski, M
Shinnar, S
Spivack, V
Strickler, H
Wassertheil-Smoller, S
Wylie-Rosett, J

Folate
Gorlick, R
INDEX OF FACULTY BY RESEARCH INTERESTS:

Frailty
Verghese, J (falls & gait)

Genetics/Genomics
Barzilai, N
Prystowsky, M
Spivack, S (gene regulation)

Global Health
Daily, J
Hawkins, M
Macklin, R

Hepatitis C Virus
Strickler, H

Health Disparities
Bauman, L
Rapkin, B
Keller, M

Herpes
Keller, M

HIV/AIDS
Arnsten, J
Bauman, L
Kaplan, R
Keller, M

Macklin, R (bioethics)
Rapkin, B
Strickler, H

Hormone Therapy
Wassertheil-Smoller, S

Human Papillomavirus
Strickler, H

Hypertension
Kaskel, F

Wassertheil-Smoller, S

Insulin Resistance
Gorlick, R
Hawkins, M
Heptulla, R
Strickler, H
Keller, M
Kaskel, R
Putterman, C

Lupus Nephritis
Putterman, C

Malaria
Daily, J

Membrane Transplant
Schuster, V

Menopause
Wassertheil-Smoller, S

Mental Health, Children & Adolescents
Bauman, L
Silver, E

Metabolism/Metabolomics
Barzilai, N
Daily, J
Heptulla, R

Microbicides
Keller, M
Migraine
Lipton, R

Molecular Epidemiology
Rohan, T
Strickler, H

Mucosal Immunity
Keller, M

Nephrology
Kaskel, F (Pediatrics)

Nutrition
Rohan, T
Wassertheil-Smoller, S
Wylie-Rosett, J

Obesity
Kaskel, F
Wylie-Rosett, J

Observational Studies
Kaplan, R
Kaskel, F
Strickler, H
Wassertheil-Smoller, S

Parasites
Keller, M

Participatory Research
Rapkin, B
INDEX OF FACULTY BY RESEARCH INTERESTS:

**Pediatrics**
- Gorlick, R (oncology)
- Heptulla, R
- Silver, E
- Shinnar, S

**Prostaglandins**
- Schuster, V

**Proteomics**
- Prystowsky, M

**Quality of Life**
- Rapkin, B

**Reproductive Health Research**
- Macklin, R

**Research Ethics**
- Daily, J
- Macklin, R
- Walker, E

**Seizure Disorders**
- Shinnar, S (febrile seizures)

**Sexual Behavior**
- Silver, E

**Statistical Modeling**
- Kim, M

**Stem Cells**
- Gorlick, R

**Systemic Lupus Erythematosus (SLE)**
- Putterman, C

**Smoking Cessation**
- Arnsten, J

**Virology**
- Keller, M
- Strickler, H
Key Words: drug abuse, HIV, medication adherence, smoking cessation

I am the Chief of the Division of General Internal Medicine and a Professor in the Departments of Medicine, Psychiatry & Behavioral Sciences, and Epidemiology & Population Health. I am also the Director of Substance Abuse Research for the Department of Psychiatry, and the Coordinator of the Clinical Core for the Einstein/Montefiore Center for AIDS Research (CFAR). I have a long-standing interest in behavioral medicine, including adherence with antiretrovirals and other medications, nicotine dependence, and substance abuse. Since joining the Einstein faculty in 1996, I have established a successful research program focused on HIV infection in drug users and other medical complications of substance abuse.

Selected References:
Searching for Longevity Genes in Humans

Why do some people live much longer than others? What allows these individuals to escape age-associated diseases that contribute to mortality in the elderly? Is this a result of favorable genes or merely a healthy life style? If genes do play a role, what are the mechanisms?

To address these questions, we recruited over 1500 Ashkenazi Jews. The Ashkenazi Jewish population is unique as it is derived from a small number (several thousands) of founders. External factors such as ecclesiastical edicts prohibiting all social contact with Jews, the Crusades, the establishment of the Pale of Settlement, numerous Pogroms, and ethnic bigotry resulted in social isolation and inbreeding of the Ashkenazi Jews, and led this population through a genetic bottleneck resulting in founder effects. This population has been utilized for identification of several genes, a prominent example being the breast cancer gene.

The subjects fall into three groups; probands, subjects with exceptional longevity (1:10000 in the general population); their offspring; and a control group consisting of spouses of the offspring and other Ashkenazi Jewish people recruited from the Einstein Aging Study. We studied the genetic and metabolic profile. We found certain physiological characteristics such as high levels of high-density lipoprotein (HDL) as well as significantly larger particle sizes of HDL and low-density lipoprotein (LDL) in the proband and the offspring groups compared to the control group. This phenotype is associated with a lower prevalence of hypertension, CVD, the metabolic syndrome, and homozygosity of the I405V and C(-641)A variant in the CETP and ApoC III genes, respectively. Recently, we discovered a connection between the CETP variant and cognitive function. We showed that the protective genotype of I405V, namely VV, is associated with the highest scores on the MMSE test for cognitive function. Furthermore, we expanded our research to a newly discovered serum protein, adiponectin (ADIPOQ), expressed and secreted exclusively by adipose tissue. We demonstrated for the first time that exceptionally long-lived probands have markedly higher levels of serum ADIPOQ. We also demonstrated that the distribution of ADIPOQ levels in the offspring group is bimodal, suggesting that a subset of the offspring may have inherited the favorable ADIPOQ trait. We demonstrated association of a common ADIPOQ polymorphism with ADIPOQ levels and with exceptional longevity, suggesting that genetic determinants of ADIPOQ may contribute to this rare phenotype of exceptional longevity. Recently, we studied telomere length in our population, demonstrating longer telomeres in our longest living subjects and their offspring compared to control. These finding may indicate longer telomeres at birth or slower attrition rate in their length. Most important, since the trait of longer telomeres is associated with protective lipoprotein profile and less age-related disease, this test may be used as a predictor for longevity.

We also implicated a conserve pathway for longevity, the insulin/IGF-1 signaling pathway, and showed that several centenarians are shorter, have higher IGF-1 levels due to a functional mutations in IGF-1 receptor. We also showed that telomeres are longer in centenarians and this length is inherited in their offspring (several mutations in the telomerase have been identified). Finally, we performed whole genome association analysis to identify mutations in new, uncharacterized genes that may be linked to diseases of aging, such as cardiovascular disease and cancer. We hope this can explain this rare trait and often-desirable state defined as longevity.

This population leads itself to many studies asking the role of important hormones, peptides and pathways in aging and longevity and identifying their genetic origins. It is studied in a program project in collaboration with many basic and clinical investigators at Einstein.

References:


Key Words: adolescent, behavior, health disparities, HIV, mental health

(1) Prevention of mental health problems secondary to physical conditions in children and their parents.

(2) Children affected by parental HIV. Project Care (NIMH) was a succession planning/disclosure intervention for mothers with late-stage HIV/AIDS. It provided legal, social and support counseling to mothers in order to arrange for the future care and custody of children, and was designed to assure that every child had a secure placement after parental death. She also completed a study of child caregivers (children under age 16 who are caring for their ill mothers with HIV/AIDS). Her sample was with families in New York City; Dr. Geoff Foster, her collaborator, studied children in Mutare, Zimbabwe.

(3) Prevention of HIV transmission among youth. Project Safe (NIMH) was a three-group randomized trial of 600 youth aged 14-17 that successfully reduced unsafe sexual behavior among high-risk teenagers. She is currently PI of three related studies. StaySafe is a three-group randomized trial (n=600) funded by NICHD; it targets teenagers aged 13-16 who are not yet sexually active through programs addressing how gender norms increase risk for HIV and STDs. It Takes 2 is funded by NIDA. This two group randomized trial (n=400) is testing a new version of Project Safe which includes gender norms and addresses how relationship characteristics (e.g., love, trust, expectations of monogamy, future commitment) affect risk behavior. Adolescent Relationships and HIV/STD Risk (NIMH) is a basic research study of 360 adolescent couples to identify how love, trust, expectations of monogamy, future commitment power and communication are related to HIV risk reduction.

(4) Community Based Participatory Research. Dr. Bauman is currently PI of Bronx Youth as Partners in Community Based Participatory Research to Reduce Health Disparities (NCMHHHD) is a three-year project which is using a community-based participatory action research model to reduce health disparities among African American and Latino youth in the Bronx, NY. This project defines its community as Bronx adolescents, and it proposes to design, implement and conduct a process evaluation of an intervention developed to reduce one health disparity selected by the community. Adolescents are the lead decision-makers. There are two levels of partnership, Albert’s Leaders of Tomorrow (A.L.O.T.) and The Bronx Coalition for Adolescent Health (Coalition). A.L.O.T. has the decision-making responsibility for all aspects of the project, and it is composed of 14 Bronx teenagers age 14-19 and 6 adults (researchers, program specialists and physicians). The Coalition is composed of 40 Bronx organizations that have a demonstrated commitment to serving Bronx youth and have agreed to be part of the participatory action research process. A.L.O.T. chose to focus on mental health, and we are in the process of developing a mental health intervention.

Selected References:


10. Calderon, Y.; Cowan, E; Nickerson, J; Mathew, S; Fettig, J; Rosenberg, M; Brusalis, C; Chou, K; Leider,J; **Bauman, L.** Educational effectiveness of an HIV pre-test video designed for adolescents: a randomized controlled trial. *Pediatrics*, in press.
Key Words: drug resistance, global health, malaria, metabolomics, parasite and host transcriptional profiling, research ethics, stress response, virulence mechanisms

MALARIA PARASITE PHYSIOLOGY AND HOST RESPONSE TO INFECTION

Our primary research interest is in pathogenesis and parasite biology in the natural setting in the malaria parasite *Plasmodium falciparum*. Patients infected with this parasite can be completely asymptomatic or develop severe disease resulting in death. The goal of our research has been to define the molecular mechanisms that underlie this variation in disease outcomes in *P. falciparum*. Toward this goal, we have developed a new pathogenesis model through the analysis of *in vivo* parasite biology and associated host factors using a whole genome approach. We have identified novel parasite biology when it resides in the human host; this biology has not been reported under *in vitro* cultivation and may play a role in enhanced virulence and/or transmission capacity. To further understand the implications of these novel *in vivo* states we will study the parasite under *in vitro* conditions that mimic host blood stream conditions. We are also studying host response to infection using whole genome approaches to identify host factors that associate with severe disease outcomes. We are now defining the small molecule repertoire of the parasite and the changes in human plasma metabolome associated with malaria infection. The long term goal is to identify parasite and host processes involved in disease to serve as targets for vaccine or chemotherapeutic development. We carry out field based translational studies in cohorts infected with malaria in Africa and these inform our experimental work using basic molecular biology approaches in the laboratory.

Selected References:


**Key Words:** antifolate resistance, insulin like growth factor receptor, mesenchymal stem cells, osteosarcoma, pediatric oncology, preclinical and clinical trials cancer

Brief description of your research interests: My clinical interests are focused upon the care of children, adolescents and young adults afflicted with sarcomas. My clinical research activities include Phase 1, 2 and 3 clinical trials as well as supportive care, biology and quality of life studies as institutional, Children’s Oncology Group (COG) and the Sarcoma Alliance for Research through Collaboration Group studies. Clinical interests include maintaining a tissue bank, clinical correlative studies identifying prognostic and predictive markers and the aforementioned clinical trials. The longstanding focus of our laboratory has been the mechanisms of antifolate resistance that are observed in osteosarcoma. We are interested in defining the signal transduction pathways that are relevant to osteosarcoma in part to identify key genes involved in osteosarcoma pathogenesis. It is felt that these signal transduction pathways may be amenable to inhibition by targeted therapies enhancing the standard treatment with cytotoxic chemotherapy. We are interested in understanding the cell of origin of osteosarcoma, which may be a mesenchymal stem cell or a more differentiated osteoblast. The laboratory performs preclinical drug studies utilizing osteosarcoma xenografts as a site for the NCI funded Pediatric Preclinical Testing Program. Our laboratory serves as a national osteosarcoma tissue repository for the COG.

References: (Selected from 2011 only)


Key Words: global diabetes, global health, glucose effectiveness, insulin resistance

Research Description:
Meredith Hawkins is Professor of Medicine and Director of the Global Diabetes Initiative at the Albert Einstein College of Medicine. Her current research interests include the regulation of hepatic glucose production by hyperglycemia per se in type 2 diabetes mellitus, and the effects of nutrient excess on metabolic features of the insulin resistance syndrome. Challenging a generally 'insulin-centric' view of hepatic glucose metabolism, Dr. Hawkins has highlighted the importance of defective 'glucose effectiveness' to suppress glucose production in diabetes mellitus. Significantly, she proved the efficacy of several therapeutic modalities to restore this regulation in humans with diabetes: activating hepatic glucokinase, normalizing circulating fatty acid levels, and inhibiting gluconeogenesis. More recently, Dr. Hawkins has made novel and important observations about the role of fatty acids in systemic inflammation, through effects on adipose tissue macrophages. Her work suggests that adipocyte-derived factors "prime" adipose macrophages to respond to nutritional regulation. Additionally, Dr. Hawkins has a tremendous interest in the burgeoning epidemic of obesity and diabetes in the developing world.

Sample references:
Rubina Heptulla, MD
Department of Pediatrics (Endocrinology)
Rosenthal Pavilion, Room 1
718-920-4664; rubina.heptulla@einstein.yu.edu

Key Words: children, insulin resistance, metabolism

Research Description:
Type 1 diabetes: Dr. Heptulla is interested in the role of post-meal glucose mechanisms and the role of glucagon suppressors such as the role of amylin and GLP-1. We are using novel technology such as the artificial pancreas and the closed loop system to deliver multi-hormonal therapy to adults and children with diabetes and many other areas of research such as depression. Quality of life, cost of diabetes care, adherence to regimens and disaster preparedness are all the areas we cover in our laboratory.

Dr. Heptulla is an internationally recognized pediatric endocrinologist and was awarded the McNair Scholar for Juvenile Diabetes by the Janice and Robert McNair Foundation. She is also the recipient of many grants from the Juvenile Diabetes Research Foundation and the National Institute of Health. Her areas of research expertise encompass all aspect of diabetes from the artificial pancreas project to using innovative therapies to treat both type 1 and 2 diabetes. She has many peer reviewed publications in leading journals. Dr. Heptulla serves as a grant reviewer committee for the NIH and serves as a journal reviewer for many leading diabetes journals. Dr. Heptulla is the Division Chief of Pediatric Endocrinology at The Children’s Hospital at Montefiore and under her leadership she is transforming the division in many areas and is recruiting leading researchers in many areas of endocrinological research.

Sample references:
1) Cardiovascular disease in HIV-infected individuals: Patients with long-standing HIV infection appear to have accelerated atherosclerosis and increased risk of clinical cardiovascular events. Our ongoing research is examining whether vascular risks in HIV-infected individuals may be due to side effects of antiretroviral medications, sustained elevations of inflammation markers, coinfections, or other sequelae of HIV infection.

   References:

2) Health of Latino populations: Albert Einstein was selected as one of four Field Centers for the 16,000-person SOL project ("Study of Latinos"). This will be a landmark study of heart disease, stroke, diabetes, obesity, and other disorders in Hispanic/Latino adults.

   Reference:

3) Insulin-like growth factors and risk of vascular disease and other age-related conditions: Insulin-like growth factor-1 (IGF-I), a major anabolic hormone, is the main mediator of effects of growth hormone and an important regulator of cell cycle/differentiation and cell survival. We are investigating whether the age-related decline in IGF-I levels may contribute to elevated risks of cardiovascular disease, mortality, declining physical function, and other outcomes among older adults.

   Reference:
Key Words: biomarkers, hypertension, kidney failure, obesity, observational studies

I have been involved in both basic and clinical investigations into the mechanisms of the major kidney disorders in pediatrics. The opportunity to examine the physiology and pathophysiology of normal and abnormal development and function of the kidneys throughout the critical periods of growth and maturation extending into adolescence and young adulthood is unique, especially since the antecedents of adult disease manifest themselves during the pediatric age range. Of the major causes of progressive glomerular diseases, focal segmental glomerulosclerosis is the most common and often devastating entity in pediatric and adult nephrology. We are actively involved in an NIH-funded clinical trial of this condition aimed at defining the most efficacious therapy while investigating the molecular etiologies for its expression. This translational research is further extended into another NIH-supported longitudinal study involving chronic kidney disease in children and its attendant morbidities of abnormalities in: growth and neurocognitive development, and the risk factors for cardiovascular disease and renal progression. Our Division of Pediatric Nephrology has expertise in clinical hypertension and translational research into biomarkers of renal progression, development nephrology, and our collaborations with investigators in Pediatric Neurology and Internal Medicine Nephrology offer an extensive research environment.

Selected References:
**Key Words:** clinical trials, genital tract mucosal immunity, herpes, HIV, microbicides

Marla Keller, MD is Associate Professor of Medicine (Division of Infectious Diseases), Obstetrics and Gynecology & Women’s Health. She directs a clinical research program focused on the clinical testing of microbicides, drugs in development for vaginal application to prevent the transmission of human immunodeficiency virus (HIV) and other sexually transmitted infections. Her work also focuses on defining the factors that contribute to innate mucosal immunity in the adult female genital tract. The ultimate goal of her work is to identify optimal combinations of candidate microbicides to prevent HIV and other STI without deleteriously altering the mucosal environment. Dr. Keller has conducted clinical trials in HIV infected and uninfected women. She is currently conducting clinical trials to evaluate the safety and antiviral activity of candidate microbicide gels and rings, including tenofovir, dapivirine and acyclovir. She recently completed 3 investigator-initiated Phase I clinical trials to examine the antiviral activity and effects on mucosal immunity of 0.5% PRO 2000 gel. Her group played a major role in identifying the importance of examining the impact of semen on the efficacy of candidate microbicides by conducting in vitro and postcoital human studies. She is currently conducting studies in women with genital herpes to examine the factors in cervicovaginal secretions that mediate innate protection against HSV infection and to determine how changes in the mucosal environment increase the risk for HIV transmission or acquisition.

**Selected References:**

Key Words: biostatistics, clinical trials, epidemiologic methods, statistical modeling

Dr. Kim’s research focuses on statistical methods for designing and analyzing clinical trials and epidemiologic studies. Most randomized clinical trials aim to demonstrate superiority of an experimental treatment relative to a standard treatment or placebo. An increasing number of trials, however, are focused on showing that the effects of two treatments on a particular outcome are equivalent, or that one treatment is not inferior to another. These goals are of interest when the new therapy offers benefits such as reduced cost, toxicity, and invasiveness relative to a standard therapy. Dr. Kim is investigating the effects of non-compliance, outcome misclassification and measurement error on the estimates of treatment effects, type I error rate, and power of equivalence trials and non-inferiority studies and developing new approaches for defining the non-inferiority margin.

Her research also includes the development of methods for analyzing interval-censored survival data. Interval-censored data can arise when outcomes are not directly observable but are detected from periodic clinical examinations or laboratory tests. The exact times of the events are not known since the event could have occurred at any time during the interval between the last visit when the subject was determined to be negative for the outcome and the first positive visit. Dr. Kim is developing approaches for the analysis of interval-censored data when multiple outcomes are of interest in the same study, and on evaluating the effect of covariates on the gap times between interval-censored recurrent events.

References:

1. Kim MY and Goldberg JD. The effect of outcome misclassification and measurement error on the design and analysis of therapeutic equivalence trials; Statistics in Medicine (2001); 2065-2078.
3. Kim MY and Xue X. Likelihood ratio and a Bayesian approach were superior to standard noninferiority analysis when the noninferiority margin varied with the control event rate; Journal of Clinical Epidemiology (2004); 57: 1253-1261.
RICHARD B. LIPTON, MD
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Key Words: biomarkers and genetics, brain aging and Alzheimer’s disease, clinical trials, migraine and pain, neuroepidemiology

As a neurologist and neuro-epidemiologist my work has focused in two broad areas: cognitive aging and dementia as well as migraine headaches and other pain disorders. For the past 18 years, I have directed an NIH funded Program Project, the Einstein Aging Study (EAS), which aims to identify the earliest cognitive, metabolic, anatomic, and neuropathological markers that distinguish 'normal aging' from early dementia. We also have a project focused on the influence of longevity genes on brain aging and several collaborative R01’s assessing a variety of biochemical and imaging approaches to early detection of brain changes in during the preclinical onset of AD. Our long-term goal is to “make Alzheimer’s disease a memory” by preventing illness through risk factor modification, disease modifying pharmacologic treatments as well as behavioral interventions. Our strategies for early detection include the assessment of midlife risk factors, novel cognitive measurement strategies, assessment of genetic and biochemical markers as well as neuroimaging. In addition to our work on dementia, our research team also studies predictors of successful brain aging, the preclinical onset of Parkinson’s disease as well as gait and motor function in the elderly. Our group is committed both to research and research education. Our trainees have included many CRTP students and K-supported junior faculty members.

As the Director of the Montefiore Headache Center, my interests include classification, natural history, diagnosis and treatment of migraine and other headache disorders. Our group includes neurologists, psychologists, an emergency medicine physician and neuroradiologists among others. Our research has focused on headache epidemiology and genetics, migraine comorbidity, neuroimaging, and biological markers as well as risk factors for and the prevention of chronic daily headache. Our largest current study, the American Migraine Prevalence and Prevention Study, is a longitudinal study following 11,000 migraine sufferers from the general population to examine natural history and risk factors for headache progression. We also have a number of clinical trials, diary studies, family aggregation, neuroimaging and biomarker studies. We have a strong interest in migraine genetics, in the role of obesity, inflammation and allodynia in migraine progression.

Selected Publications (selected from over 530 original articles):

Key Words: bioethics, HIV/AIDS research, international collaborative research/global health, reproductive health research, research ethics

My research covers all aspects of bioethics, but focuses on human subjects research, especially on HIV/AIDS and reproductive health research conducted in developing countries. Topics include informed consent, risk-benefit assessments, justice in research, avoiding exploitation of research subjects.

References:

We have developed a multidisciplinary group including surgery, oncology, pathology, molecular biology, protein chemistry, systems biology, epidemiology and biostatistics to study Head and Neck Squamous Cell Carcinoma (HNSCC) (http://www.einstein.yu.edu/headandneck/). Our studies employ cutting edge genomic and proteomic technologies to elucidate molecular mechanism regulating tumor behavior. Studies on primary human cancer and in model systems have identified candidate signatures that will be tested for use in optimizing initial treatment selection for patients with HNSCC.

Our goals are:
• To develop new diagnostics that will identify optimal treatments at initial diagnosis.
• To assess early genetic changes in smokers to identify individuals at greatest risk for developing cancer and to develop effective interventions.
• To identify potential new targets for drug development.

References:
Systemic lupus erythematosus (SLE) is a systemic autoimmune disease that typically affects young women in their reproductive years. In lupus, a dysregulated immune system recognizes the body’s own tissues as foreign, leading to immune-mediated inflammation and tissue damage in multiple organs. Although the prognosis of patients with SLE has greatly improved over the last few decades, there remains a substantial degree of morbidity and mortality associated with this disease. Current treatments, while effective, only control disease activity but are not curative. Furthermore, therapeutic modalities that are employed for the treatment of patients with lupus are non-specific – and commonly affect normal cells that are essential for the defense against foreign pathogens, in addition to suppressing the disease-relevant autoreactive B cells.

The presence of serum antibodies against double stranded (ds) DNA is a characteristic hallmark of patients with SLE. It has become increasingly clear that not only are anti-DNA antibodies an important diagnostic marker for SLE, but that these antibodies also play an important role in disease pathogenesis, particularly in the kidney. It is believed that anti-DNA antibodies are instrumental in lupus nephritis by virtue of binding to a non-DNA kidney protein, the nature of which is unknown. The laboratory is involved in multiple projects that address two central questions in SLE:

1. What is the nature of the antigenic trigger for anti-DNA antibodies in SLE?
2. What is the mechanism by which anti-DNA antibodies induce kidney inflammation (lupus nephritis) in lupus patients, and what is the target antigen bound by these antibodies in kidney tissue?

We made significant progress in defining the renal antigen bound by cross-reactive anti-DNA antibodies, in both murine and human SLE. We discovered that α-actinin is a major cross-reactive target for the anti-dsDNA antibody response in murine lupus, and that both human monoclonal and polyclonal anti-dsDNA antibodies bind to α-actinin as well. In current studies, we are investigating if α-actinin can serve not only as a target but also as an antigenic trigger for anti-DNA antibodies, whether anti-α-actinin antibodies are associated with specific disease features (analysis of patient cohorts), and what might be the mechanism by which these antibodies induce damage in kidney cells (proteomic and microarray approaches).

Members of the TNF-superfamily of ligands are centrally involved in normal immune responses, and in the pathogenesis of autoimmune disorders. In a second group of related projects, we are investigating the role of a relatively new member of the TNF superfamily (TWEAK) and its receptor Fn14 in the pathogenesis of lupus, specifically lupus nephritis. We have shown that TWEAK induces a pro-inflammatory profile of cytokines and chemokines in kidney epithelial and mesangial cells, and thus contributes to the influx of inflammatory cells observed in the early stages of lupus nephritis. Modulation of the TWEAK/Fn14 pathway in SLE may be an important target for novel therapies for this disease. Furthermore, we are exploring the role of TWEAK, and other inflammatory mediators, as potential biomarkers for disease activity in lupus and lupus nephritis.

References (selected from 140):


Key Words: cancer detection, community capacity building, community psychology, participatory research, health disparities & inequities, HIV prevention, quality of life

Bruce Rapkin, Ph.D. is Professor in the Division of Community Collaboration and Implementation Science in the Department of Epidemiology and Population Health at Einstein and Director of Cancer Prevention and Control Research at the Albert Einstein Cancer Center. He received his doctorate in community and clinical psychology from the University of Illinois at Urbana-Champaign. His research focuses on access to care and quality of life for diverse, medically-underserved patients, families and communities. His primary emphasis is on the development of community-academic partnerships to reduce barriers and improve standard of care. He has led several projects to develop strategies to promote evidence-based practice through collaborative research. The first such project was the Family Access to Care Study (R01-MH063045) examined the feasibility of partnerships between frontline providers and health researchers to disseminate mental health interventions for families. The second study, the Queens Library HealthLink Project, is designed to promote community organization, outreach and cancer education to diverse underserved communities, in conjunction with the Queens Borough Public Library System (R01-CA119991). Dr. Rapkin is also principal investigator of two projects involving quality of life appraisal and response shift: The recently completed HIV Choices in Care Study, sponsored by the New York State Department of Health AIDS Institute, employs appraisal methods to ensure a more accurate assessment of patient reported outcomes in a comparison of different Medicaid health service delivery models. More recently, Dr. Rapkin and colleagues initiated a Prospective Study of Quality of Life in Patients with Invasive Bladder Cancer, to examine how differences in appraisal affect quality of life and adaptation to three different options for surgical reconstruction. Dr. Rapkin’s collaborative research with community organizations, public health systems and health providers has led to the development of new research designs and assessment methodology to promote evidence-based interventions in public health. In particular, he has been working on participatory approaches that use both process and outcomes data to support community-based interventions. Dr. Rapkin is on the editorial board of the Journal of Community Psychology, and is a member of the NIMH Consortium on HIV/AIDS and the Family, and serves on the American Cancer Society’s National Council for Extramural Research.

References


Key Words: cancer etiology, molecular epidemiology, nutritional epidemiology

Dr. Rohan’s research focuses largely on the roles of molecular, nutritional, and lifestyle factors in the etiology and pathogenesis of cancer, in studies that involve national and international collaborations. Ongoing projects include:

1) A cohort study of the molecular pathogenesis of breast cancer. The cohort consists of approximately 16,000 women who had a biopsy for benign breast disease, for whom the formalin-fixed breast tissue is accessible, and who have been followed up to determine the subsequent occurrence of breast cancer. Recently, funding was obtained to examine the association between miRNA expression in benign breast disease tissue and risk of subsequent breast cancer. The cohort is also being used to examine the feasibility of proteomic profiling of formalin-fixed benign breast disease tissue.

2) A cohort study that Dr. Rohan established in Canada to investigate the roles of diet, lifestyle factors, and molecular makers in relation to cancer risk. The cohort involves about 74,000 subjects who were recruited predominantly between 1995 and 1998. Ongoing studies in the cohort focus on the etiology of breast and prostate cancer; ultimately other endpoints (e.g., colorectal and lung cancer) will also be studied.

3) A study to investigate the association between a new, potential prognostic marker for breast cancer (Tumor Microenvironment of Metastasis) and risk of distant metastasis.

4) Collaboration on studies involving pooling of data from many centers to study the association between various exposures and cancer risk.

Selected References:


Key Words: cardiovascular disease, eicosanoids, membrane transport, prostaglandins, signaling

Molecular Biology of Prostaglandin Transport

Prostaglandins (PGs) are context-dependent signaling molecules that signal diverse and important biological functions such as fever, inflammation, ulcer protection, etc. Our laboratory discovered the first known membrane carrier (PGT) for PGs. PGT is broadly expressed in cell types that synthesize and release PGs, including endothelial cells, kidney glomeruli and collecting tubules, the prostate gland, and platelets. PGT catalyzes uphill, active PG transport. Our data indicate that PGs are released from cells by simple diffusion and then PGT mediates signal termination by PG re-uptake and oxidation in the same cell. Mice lacking PGT die on post-natal day 01 from patent ductus arteriosus, a result of an inability to lower plasma PGE2 levels after birth. We are currently using a high-affinity PGT blocker to study the role of PGT in cardiovascular disease (hypertension, arterial thrombosis, and atherosclerosis).

References:

Dr. Shinnar is well known for his research on a variety of topics relating to childhood seizures and language regression, including when to initiate and discontinue antiepileptic drug therapy, prognosis following a first seizure, prognosis following discontinuation of medications in children with seizures, status epilepticus, febrile seizures, mortality and language regression and its relationship to autism and seizures. He has been the principal investigator and co-investigator on a variety of NIH-funded research studies. He is the Principal Investigator of a large multicenter study “Consequences of Prolonged Febrile Seizures in Childhood”. He is also a member of the executive committee and co-investigator of a large multicenter NIH funded study “Childhood Absence Epilepsy: Rx, PK-PD-Pharmacogenetics”. He has also been involved in industry-sponsored trials of new medications. Dr Shinnar is a recipient of the Research Recognition Award of the American Epilepsy Society. He has authored over 150 papers and is the senior editor of the book Childhood Seizures and coeditor of the recently published Febrile Seizures. Dr Shinnar has served as a reviewer and editorial board member for a variety of journals. He has mentored students, fellows and junior faculty members interested in clinical research.

Selected References:

Much of my work focuses on sexual risk behavior in urban adolescents. This includes evaluating several current and previous STI/HIV preventive interventions with my colleague, Dr. Laurie Bauman, and a recently funded project of my own to examine the feasibility and acceptability of combining a risk reduction program for 14-17 year old urban teens with educational workshops for their parents. I also have a pilot grant from the Einstein Global Health Center to extend work we did in the Bronx on romantic relationships and sexual risk in teens to college students in 2 major cities in India. I also am a member of the Social and Behavioral Research Faculty at the Einstein-Montefiore Center for AIDS Research. In addition, I am a co-investigator on a study using community participatory research methods to learn about health disparities for Bronx minority youth, through which we are evaluating a mental health intervention for teens that is being delivered in several community-based organizations. My other previous and current work primarily involves children’s physical health and psychological adjustment, including studies of the impact of childhood chronic illness on family members, on factors affecting access to health care for children with conditions, and on the impact of intensive care unit hospitalization on children and their families. I am currently involved in other studies focused on parenting and early child development and on reducing childhood obesity.

Selected References:

Key Words: airway biomarkers, gene regulation, lung carcinogenesis, lung disease

Genetic and Epigenetic Risk for Lung Disease, for ICTR website:

The translational goal of the Spivack laboratory is to identify individuals at particularly high risk for lung cancer and selected non-malignant lung diseases such as asthma and COPD, to enhance prevention and early detection efforts. The group determines Gene x Environment interaction signatures in members of different populations, currently explored in a case-control context; we have plans to engage a specific prospective cohort.

The molecular biomarkers of risk being developed include quantitative gene (mRNA) expression phenotypes, and DNA sequence, methylation, microRNA, and other epigenetic features potentially underlying these expression phenotypes, in human lung and it’s noninvasively-collected surrogates (exhaled nucleic acids, expectorated nucleic acids, and brush-exfoliated buccal cells).

The clinical background, environmental exposures, and biomarker studies are of equal interest to the current explorations of genetic machinery, and include tobacco, air pollutant, and dietary exposures. The overall aim is to develop informative non-invasive risk profiling, preventive, and early disease detection strategies for the lung in human populations.

While there are both mechanistic and translational components to the studies, the translational aspects are listed here. Specifically, biomarkers of risk are being established by pairing laser capture microdissected human lung and several unique, non-invasively collected surrogate specimens developed in the laboratory, such as mRNA expression signatures from brush-exfoliated buccal mucosa cells, DNA methylation analyses from exhaled breath condensate, a first report for a new airway biomarker class, and exhaled microRNA assays, an imminent first report. These airway-derived specimens continue to accrue from a sampling (currently n>750 with complete blood sets, and subsets of 150-400 with various airway/lung samples) of an at-risk population assembled in our lung cancer case-control context. Clinical, exposure, family, and dietary data are also available.

The biospecimens are being studied for quantitative gene expression in several cancer and inflammation-relevant pathways, by our different molecular genetic approaches. The expression, genetic, and epigenetic data are being linked to precise plasma measurements of tobacco exposure, and to downstream biological events, as an approach to putting a real metric to individual Gene x Environment interaction.

Work is supported predominantly by NIH funding, including an NCI Mid-Career K24 Award aimed at mentoring young investigators.

Selected clinical/translational publications:


Primary research interests involve viral and cancer epidemiology, especially as it relates to: The viral causes of cancer such as human papillomavirus (HPV) and simian virus 40 (SV40)

1. Immunogenetic factors that influence viral infection with HPV, human immunodeficiency virus (HIV), and hepatitis C virus (HCV)
2. The effects of growth factors (e.g., IGF) on viral infection and on tumorigenesis (including cervical, breast, endometrial, and colorectal cancer)

Our studies involve collaborations in large multi-institutional prospective cohort investigations as well as the development of new (targeted) cohort and cross-sectional studies.

**Recent Observations:**
- Highly active antiretroviral therapy (HAART) is associated with reduced burden of HPV and cervical neoplasia in HIV-positive women.
- Specific HLA class I and II alleles are associated with increased risk of HCV viremia.
- Women with low IGFBP-3 levels have ≥50% reduction in risk of incident clinical AIDS.
- IGF-I is associated with increased risk of HPV persistence and HCV disease progression.
- High insulin levels explain the relation of obesity with postmenopausal breast cancer.
- Endogenous estrogen levels are associated with risk of colorectal cancer.

**Selected References:**
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Key Words: attention, auditory, cognitive neuroscience, electrophysiology, memory

THE NEUROBIOLOGICAL BASES OF AUDITORY SCENE ANALYSIS
My research is in the field of Cognitive Neuroscience and is focused on understanding the neural basis of auditory information processing in healthy adults and children, and how the process breaks down in impaired populations. Our laboratory’s research uses a combination of non-invasive recordings of human brain activity (event-related potentials [ERPs]) and functional magnetic resonance imaging (fMRI), in conjunction with measures of behavioral performance, to specify the processes and brain structures that contribute to the organization, storage and perception of a coherent sound environment.

Selected References:

Dr. Joe Verghese graduated from St. John's Medical College, Bangalore, India in 1989. He then completed postgraduate training in Internal Medicine and Neurology in the United Kingdom. He completed his Neurology residency at the Albert Einstein College of Medicine, Bronx, NY in 1998. He did fellowship training in Neurophysiology as well as Aging & Dementia in 1999 at the same institution. He received a Master of Science degree in Clinical Research Methods with Distinction in 2001. Dr. Verghese is board-Certified in Neurology. Dr. Verghese is Professor of Neurology at the Albert Einstein College of Medicine; Murray D. Gross Memorial Faculty Scholar in Gerontology and Director, Division of Cognitive and Motor Aging. He is also Clinical Director of the Einstein Aging Study, a NIH-funded longitudinal aging study. Dr. Verghese is a recipient of the Beeson award from the National Institute on Aging and the Outstanding Scientific Achievement for Clinical Investigation Award from the American Geriatrics Society. His research interest is the effects of disease and aging on mobility and cognition in older adults, and he has had several publications in this area. His current projects include studying the influence of cognitively stimulating activities on reducing risk of dementia and the role of divided attention tasks such as walking while talking in predicting outcomes such as disability and cognitive decline, and global dementia issues.

Selected References:


**Key Words:** behavioral intervention research, measuring risk perception, medication adherence, research ethics, telephonic interventions, type 2 diabetes

Elizabeth A. Walker, PhD, RN, is the director of the Prevention and Control Division for the Diabetes Research and Training Center (DRTC) at the Albert Einstein College of Medicine. Dr. Walker is currently the principal investigator of a large NIH-funded behavioral intervention study with the New York City Department of Health in minority diabetes populations, using telephonic interventions in Spanish and English to promote medication adherence, lifestyle change, screening for complications, and other self-management behaviors. She is a behavioral scientist and co-investigator for the multi-center Diabetes Prevention Program Outcomes Study, and she co-chairs the DPP medication adherence workgroup. She is co-PI, along with a community health center executive director, of an NIH study to promote community health research through building research capacity at community health centers. Dr. Walker was PI of a community-based study, *Los Caminos*, in which a culturally-sensitive diabetes self-management program was developed and evaluated using peer educators in the Bronx. Through the Prevention and Control Core of the DRTC she provides or facilitates various intervention and evaluation services to multiple health disparities grants in the community. Dr. Walker is a behavioral scientist and diabetes nurse specialist; she has been a certified diabetes educator since 1986. She was co-chair of a CDC Expert Panel on Risk Perception and Decision Making in Chronic Disease. In 2000, she served as the national President, Health Care & Education, of the American Diabetes Association.

**Selected References:**

Key Words: blood biomarkers of stroke, cardiovascular disease, clinical trials, dementia, depression, Hispanic health, hormone therapy, hypertension, lifestyle risk factors, long-term observational studies, nutrition, postmenopausal women's health

My research has spanned both cancer and cardiovascular disease, and both these areas of investigation have been brought together in my role as the Principal Investigator in the Women's Health Initiative (WHI). The WHI is a multi-center, multi-part national study of the major causes of morbidity and mortality in older women. It consists of several interrelated clinical trials, and a long-term observational study whose overall objectives are to prevent cancer, heart disease and osteoporosis in post-menopausal women and to identify biomarker, genetic, and lifestyle risk factors for these and other diseases in postmenopausal women. My current research also includes studies on the effects of hormone therapy on dementia and cognition, of blood biomarkers and risk of stroke, and of diet, depression and other psychosocial variables and cardiovascular risk. My research also includes another landmark prospective study, the Hispanic Community Health Study (HCHS), which is looking at cardiovascular health and disease in different Latino subgroups, and also includes research on cognition, genetics, hearing and dental conditions, pulmonary health and mental health.

Selected References:

Key Words: behavioral intervention, clinical trials, epidemiology, lifestyle, nutrition, obesity

My research has focused on the role of nutrition in chronic disease prevention and control and factors related to disparate rates of obesity and health risks. As a result, I have been collaborated in multicenter clinical trials and other studies that address translation of care recommendations into health care for people with diabetes, heart disease, cancer, and obesity.

My current investigator-initiated research includes: 1) a randomized controlled clinical trial to evaluate how a comprehensive approach to family weight management affects cardiometabolic biomarkers, 2) a cross-sectional examination of acculturation in relation to biomarkers of cardiovascular risk among Chinese immigrants, 3) translation evaluation of simplified tools to promote addressing obesity in primary care and community settings, and 4) examination of nutrition-related questions in existing databases.

References: