FRONTIERS IN MEDICINE AND SCIENCE

A Symposium on Discoveries that Change Lives

Wednesday, October 17, 2018 ● 8 a.m. to 5 p.m.

540 E. Canfield
Scott Hall
Blue Auditorium

School of Medicine

150 YEARS
IN THE HEART OF DETROIT

REGISTRATION IS FREE

Wayne State University School of Medicine

Our story began in 1868 when five physicians who served on the battlefields of the Civil War returned home to found the Detroit Medical College, the forerunner of not only our School of Medicine, but of the great Wayne State University, which has since transformed into a world-class public urban research university.

For 150 years, the Wayne State University School of Medicine has prepared its students to be health care leaders, scientists and advocates who go on to change the world. Our dedication to urban clinical and research excellence and our contribution to Detroit's revitalization is unwavering. Our community service roots run deep, and our focus on a healthier world grows ever stronger. We have a long and proud tradition of producing world-class physicians and medical researchers, pioneering changes in medical treatment, leveling the playing field for those who are underrepresented in medicine and an unbreakable bond in our caring for, and support of, the great city of Detroit and the region.

Our dedication to urban clinical and research excellence and our contribution to Detroit's revitalization is unwavering.

Wayne State University School of Medicine Organizing Committee

Jack D. Sobel, M.D.
Dean
Distinguished Professor

Linda Hazlett, Ph.D.
Vice Dean for Research and Graduate Programs
Distinguished Professor
Committee Chair

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Wayne State University

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Pathology

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Professor of Physiology

Symposium Coordinator

Caryn Volpe
Program Planning and Development
Office of the Dean

School of Medicine

150 YEARS
IN THE HEART OF DETROIT

Wayne State is one of only two urban public universities with Carnegie Foundation's classification for

BEST IN RESEARCH AND COMMUNITY ENGAGEMENT.

AWARD-WINNING
community engagement and service-learning-focused curriculum is unparalleled in the U.S., with 70 clinical and 100 outreach locations.

WAYNE STATE GRADUATES ARE RANKED NO. 4
in the nation for patient care.

More than **23,000** alumni are changing the world through care and innovation in all 50 states and 30 countries.

APPLICATIONS INCREASED
from about 4,000 in 2015 to nearly 9,000 in 2018.

Nearly **3,000** of Michigan's practicing primary care physicians were educated at the Wayne State University School of Medicine and are responsible for some 12 million Michigan health care visits annually.

First- and second-year students volunteer more than **34,000 HOURS** of community service annually.

WARRIOR STRONG

Dear Colleagues:

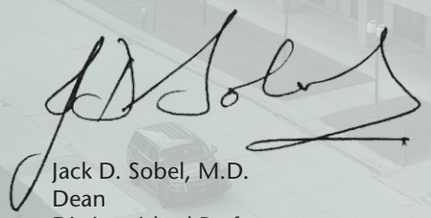
This year marks the 150th anniversary of the Wayne State University School of Medicine. It is my distinct honor to celebrate this milestone by hosting this national symposium on Frontiers in Medicine and Science.

Six distinguished scientists from prestigious U.S. universities and government institutions will present their seminal discoveries and how they have evolved and significantly impacted the field of science and human health. Their areas of expertise include cancer, neurosciences, environmental medicine, ocular and vision sciences, genomics, cardiovascular diseases, inflammation and resolution.

It is fitting that we bring these renowned scientists here, to the heart of Detroit, a city innovating its future and leading the way in the renaissance of the Midwestern metropolis. It is my hope that these lectures will foster deeper learning, ignite new ideas and continue to lead us into the future with scientifically fruitful advances.

I am particularly excited to share with you remarkable Wayne State discoveries and work presented by our students, who are the vision for the future of science. I invite you to visit the Vera P. Shiffman Medical Library for an exhibit on Warrior Medicine Innovators: Discoveries that Change Lives, which features some of our many pioneers and innovators.

While we revere our past, we also have a glorious future ahead of us. Each of us are engaged in laying the foundation for the next 150 years. Like the architects of ancient European cathedrals, we may not survive to see and wonder at the future we are now building, but faith in our vision, belief in our mission and our Warrior spirit will keep us building a brighter future.



Jack D. Sobel, M.D.
Dean
Distinguished Professor
Wayne State University School of Medicine

Message from the Vice President for Research Stephen M. Lanier, Ph.D.

Wayne State University is Michigan's only urban research university, known internationally for its many contributions to science. WSU is committed to advancing ideas and technologies emanating from its research to impact the communities it serves.

Wayne State's Integrative Biosciences Center (IBio) is dedicated to studying and eliminating the many health disparities affecting Detroit's residents. IBio is one of six School of Medicine research facilities and is home to faculty with expertise in environmental sciences, bio and systems engineering, heart disease, diabetes, obesity, asthma and biobehavioral health. The building, strategically positioned near TechTown, will move discoveries and technologies from the laboratory to the community.

Wayne State University is a driving force of technology, innovation and change. Our faculty members are conducting groundbreaking research that is and will continue to impact our economy and lives around the world.

I hope you enjoy this important symposium!

IBio is home to faculty with expertise in environmental sciences, bio and systems engineering, heart disease, diabetes, obesity, asthma and biobehavioral health.

SYMPOSIUM OVERVIEW

7 to 8 a.m. — Continental Breakfast and Meet the Exhibitors

8 a.m.

LINDA HAZLETT, PH.D. – *Welcome*
Vice Dean for Research and Graduate Programs
Distinguished Professor and Vice Chair
Ophthalmology Visual and Anatomical Sciences
Wayne State University School of Medicine

JACK D. SOBEL, M.D. – *Opening Remarks*
Dean, Wayne State University School of Medicine
Distinguished Professor of Internal Medicine and
Obstetrics and Gynecology

STEPHEN LANIER, PH.D. – *Warrior Medicine Innovators*
Vice President for Research, WSU
Professor of Physiology

8:30 a.m. — **PLENARY SESSION I**

Human Ocular Gene Therapy:
Considerations from X-linked Retinoschisis
PAUL SIEVING, M.D., PH.D.
Director of the National Eye Institute of the
National Institutes of Health
Bethesda, Maryland

9:20 a.m. — **PLENARY SESSION II**

Heart Failure in African Americans; a Puzzle Resolved
CLYDE YANCY, M.D.
Vice Dean of Diversity and Inclusion
Magerstadt Professor of Medicine
Professor of Medical Social Sciences
Chief of Cardiology
Northwestern University Feinberg School of Medicine
Chicago, Illinois

10:10 a.m. — Coffee Break

10:30 a.m. — **PLENARY SESSION III**

Tuning Depression Circuits Using Deep Brain Stimulation
HELEN MAYBERG, M.D.
Director of the Center for Advanced Circuit Therapeutics
Icahn School of Medicine at Mount Sinai
Princeton, New Jersey

11:20 a.m. — **PLENARY SESSION IV**

Lymphocytes as a Drug for the Treatment of Cancer
STEVEN ROSENBERG, M.D., PH.D.
Chief of the Surgery Branch
National Cancer Institute of the
National Institutes of Health
Bethesda, Maryland

12:05 p.m. — Lunch, Poster Session and Exhibitors

1:15 p.m. — **PLENARY SESSION V**

Why Don't We Get More Cancer:
The Importance of Extracellular Matrix and Organ Architecture
MINA BISSELL, PH.D.
Distinguished Scientist, Biological Systems and Engineering
Lawrence Berkeley National Laboratory
University of California – Berkeley
Berkeley, California

2:20 p.m. — **PLENARY SESSION VI**

Big Data and Health
MICHAEL SNYDER, PH.D.
Chair of the Department of Genetics
Stanford W. Ascherman Professor
Stanford University
Stanford, California

3:10 p.m. — **Speaker Panel Discussion (Q&A)**
Moderated by Dr. Hazlett

3:30 p.m. — **LINDA HAZLETT, PH.D.**
CME Evaluation and Closing Remarks

3:40 p.m. — **Reception/Hors d' oeuvres**
Margherio Conference Center

5 p.m. — Symposium ends

Educational Objectives

At the conclusion of this symposium, the participants will be able to:

1. Describe the nature of pathology and the consequences to vision from the conditions of monogenic retinal degeneration.
2. Discuss the development of gene augmentation therapy for genetic retinal degenerative diseases.
3. Review the legacy natural history of heart failure affecting African-Americans.
4. Identify the intersection of clinical science with disparate care.
5. Explore novel hypotheses sufficient to explain differences in clinical outcomes as a function of race.
6. Provide evidence substantiating both the genetics and environmental contributions to heart failure affecting African-Americans.
7. Appreciate strategies to define acute and chronic antidepressant effects of subcallosal cingulate DBS.
8. Assess the emerging data on multimodal biomarkers to guide patient selection, surgical targeting and treatment monitoring for subcallosal cingulate DBS.
9. Recognize the role of immunotherapy in cancer.
10. Explain the principles of cell transfer therapy.
11. Discuss why we don't get more cancer and how to appreciate this fact to make it more of a reality.
12. Describe the importance of studying cancer in 3D and how this impacts therapy.
13. Recognize how big data can inform health.
14. Explain what you can learn from wearables.

Continuing Medical Education

The Wayne State University School of Medicine is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

The Wayne State University School of Medicine designates this live activity for a maximum of ***6.00 AMA PRA Category 1 Credit™***. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Target Audience

The target audience for this conference is researchers, clinician scientists, physicians, nurse practitioners and other health care professionals.

School of Medicine

150 YEARS
IN THE HEART OF DETROIT

Research at medical schools and teaching hospitals added
$25.4 BILLION IN LOCAL COMMUNITY ECONOMIES in 2017.

The School of Medicine received more than
$152 MILLION IN TOTAL RESEARCH AWARDS
in 2017, approximately 70 percent of the university's total Research Awards.

75+ Wayne Medical Political Action and Public Health Leadership student advocates
EDUCATE MICHIGAN LAWMAKERS
on health care issues directly impacting vulnerable communities.

Wayne State is ranked 69TH among the
TOP PUBLIC INSTITUTIONS
for annual research expenditures by the National Science Foundation and 53RD in expenditures specific to health science.

Wayne State University has invested
$200 MILLION
in efforts to eliminate health disparities in Detroit.

More than **25,000** at-risk mothers have been assisted through the School of Medicine and the National Institutes of Health's Perinatology Research Branch. The PRB's economic impact in Michigan is estimated to exceed $347 million by 2023.

WARRIOR STRONG

Paul Sieving, M.D., Ph.D.

Director, National Eye Institute
National Institutes of Health
Bethesda, Md.

Human Ocular Gene Therapy: Considerations from X-linked Retinoschisis

Paul Sieving, M.D., Ph.D., is director of the National Eye Institute, National Institutes of Health. After graduate studies in nuclear physics at Yale University, he attended Yale Law School, and then received his medical degree and doctoral degree in bioengineering from the University of Illinois. He performed his ophthalmology residency under Morton F. Goldberg, M.D., at the University of Illinois Eye and Ear Infirmary, and was a post-doctoral fellow in retinal physiology with Roy Steinberg at University of California, San Francisco.

Dr. Sieving joined the faculty of the University of Michigan and held the Paul R. Lichter Chair in Ophthalmic Genetics. He founded the Center for Hereditary Retinal and Macular Degenerations at U-M and established the first Clinical Laboratory Improvement Amendments-certified laboratory in the United States for Ophthalmic Molecular Diagnostics for hereditary retinal dystrophies. He holds elected membership in the National Academy of Medicine USA and the German National Academy of Sciences.

He originated the "NEI Audacious Goals Initiative," a 15-year effort in human regenerative medicine to replace photoreceptors and retinal ganglion cells lost to disease. He continues clinical and research engagement as a tenured senior investigator in the NIH Intramural Research Program.

He is known internationally for studies of human retinal neurodegenerative diseases, termed retinitis pigmentosa and has published 260 peer-reviewed papers. Dr. Sieving has worked extensively on X-linked retinoschisis (XLRS). He created a transgenic XLRS mouse model (IOVS 2004) and demonstrated that XLRS is a synaptic disease with direct involvement of the rod-to-bipolar synapse. He used gene therapy to deliver a normal RS1 gene into eyes of XLRS mice, reversing the synaptic pathology and closing the retinal schisis cavities. These pre-clinical studies culminated in his successful U.S. Food and Drug Administration submission for an Investigational New Drug Application to initiate a human RS1 gene therapy trial for human XLRS subjects (2015) now underway at the NEI.

Clyde Yancy, M.D., M.Sc.

Vice Dean of Diversity and Inclusion
Magerstadt Professor of Medicine
Professor of Medical Social Sciences
Chief of Cardiology
Northwestern University Feinberg School of Medicine
Chicago, Ill.

Heart Failure in African Americans; a Puzzle Resolved

Clyde Yancy, M.D., M.Sc. is chief of Cardiology at Northwestern University, Feinberg School of Medicine, and associate director of the Bluhm Cardiovascular Institute at Northwestern Memorial Hospital. He holds the Magerstadt Endowed Professor of Medicine Chair and also holds an appointment as Professor of Medical Social Sciences. He concurrently serves as vice dean of Diversity and Inclusion, Northwestern University, Feinberg School of Medicine.

The Louisiana native earned a bachelor's degree (honors) from Southern University, a medical degree (Alpha Omega Alpha) from Tulane University School of Medicine and an master's of science degree from the University of Texas - Dallas School of Business and Management (Beta Gamma Sigma). He completed an internship and residency in Internal Medicine at Parkland Memorial Hospital in Dallas. He completed his fellowship in cardiology at the University of Texas Southwestern Medical Center at Dallas. He has held professional appointments at the University of Texas Southwestern Medical Center (professor of Medicine, medical director- Heart Failure and Heart Transplantation and Carl Westcott Chair in Cardiovascular Research) and Baylor University Medical Center (chief of Cardiothoracic Transplantation and director of the Baylor Heart and Vascular Institute).

He is a former president of the American Heart Association and has held several volunteer leadership positions with the American College of Cardiology. He has also served in various positions with the National Institutes of Health, the National Heart, Lung, and Blood Institute, the Patient-Centered Outcomes Research Institute and the U.S. Food and Drug Administration. He has more than 450 peer-reviewed publications, has been named one of the most highly cited investigators and is a deputy editor for JAMA Cardiology. In 2016, he was elected to the National Academy of Medicine.

Helen Mayberg, M.D.

Director of the Center for Advanced Circuit Therapeutics
Icahn School of Medicine at Mount Sinai
New York, N.Y.

Tuning Depression Circuits Using Deep Brain Stimulation

Helen Mayberg, M.D. is professor of Neurology, Neurosurgery, Psychiatry and Neuroscience, and the Mount Sinai Professor in Neurotherapeutics at the Icahn School of Medicine. She was recruited to New York after 14 years at Emory University in Atlanta, where she was professor of Psychiatry, Neurology and Radiology, and the Dorothy Fuqua Chair in Psychiatry Neuroimaging and Therapeutics.

Her research has characterized neural systems mediating major depression and its recovery, defined imaging-based illness subtypes to optimize treatment selection and introduced the first use of deep-brain stimulation for treatment-resistant patients.

Dr. Mayberg received a bachelor's degree in Psychobiology from the University of California, Los Angeles, and a medical degree from the University of Southern California. She completed her Neurology residency at the Neurological Institute of New York, and fellowship training in nuclear medicine at Johns Hopkins. She is a member of the National Academy of Medicine, the National Academy of Arts and Sciences, and the National Academy of Inventors, and has written more than 200 publications. She participates in a wide variety of advisory and scientific activities across multiple fields in neuroscience.

Dr. Mayberg is renowned for her study of brain circuits in depression and for her pioneering deep-brain stimulation research, which has been heralded as one of the first hypothesis-driven treatment strategies for a major mental illness. She is the founding director of Mount Sinai Health System's Center for Advanced Circuit Therapeutics, which advances precision surgical treatments for neuropsychiatric disorders through the rapid conversion of neuroscience and neuroengineering innovations that correct brain circuit abnormalities to restore mood as well as motor and cognitive functioning.

Steven Rosenberg, M.D., Ph.D.

Chief of the Surgery Branch
National Cancer Institute of the National Institutes of Health
Bethesda, Md.

Lymphocytes as a Drug for the Treatment of Cancer

Steven Rosenberg, M.D., Ph.D., is chief of the Surgery Branch at the National Cancer Institute and professor of Surgery at the Uniformed Services University of Health Sciences and at the George Washington University School of Medicine and Health Sciences. He received a bachelor's degree and medical degree at The Johns Hopkins University, a doctoral degree in Biophysics at Harvard University. After completing his residency in surgery in 1974 at the Peter Bent Brigham Hospital in Boston, Dr. Rosenberg became chief of Surgery at the National Cancer Institute.

Dr. Rosenberg pioneered the development of immunotherapy that resulted in the first effective immunotherapies for selected patients with advanced cancer. His studies of cell transfer immunotherapy resulted in durable complete remissions in patients with metastatic melanoma. He pioneered the development of gene therapy and was the first to successfully insert foreign genes into humans. His studies of the adoptive transfer of genetically-modified lymphocytes resulted in the regression of metastatic cancer in patients with melanoma, sarcomas and lymphomas.

He received the Meritorious Service Medal from the U.S. Public Health Service in 1981 and 1986, the Friedrich Sasse Prize from the University of West Berlin in 1986, the Nils Alwell Prize from Stockholm in 1987, the Distinguished Alumnus Award from The Johns Hopkins University in 1987, the Griffuel Prize for Research from the French Association for Research on Cancer in 1988 and the Milken Family Foundation Cancer Award in 1988. He received the Armand Hammer Cancer Prize "for pioneering work in cancer research" in 1985 and 1988. In 1991, he received the Karnofsky Prize, the highest honor given by the American Society of Clinical Oncology. He received the Flance-Karl Award, the highest honor given by the American Surgical Association in 2002 and in 2003 received the annual prize for scientific excellence in medicine from the American-Italian Cancer Foundation. He also has received the Richard V. Smalley, M.D., Memorial Award, the highest honor given by the International Society for Biological Therapy of Cancer; the Karl Landsteiner Prize from the American Association of Blood Banks, the Keio Medical Science Prize, the Massry Prize and the Medal of Honor from the American Cancer Society. A member of the American Society of Clinical Oncology, he is also a member of the National Academy of Medicine, the Society of University Surgeons, the American Surgical Association, the American Association for Cancer Research and the American Association of Immunologists. Dr. Rosenberg has written more than 1,100 articles on cancer research and eight books.

Mina Bissell, Ph.D.

Distinguished Scientist, Biological Systems and Engineering
Lawrence Berkeley National Laboratory
University of California – Berkeley
Berkeley, Calif.

Why Don't We Get More Cancer?: The Importance of Extracellular Matrix and Organ Architecture

Mina Bissell, Ph.D. is a Distinguished Scientist, the highest rank bestowed at Lawrence Berkeley National Laboratory, and serves as senior advisor to the Laboratory Director on Biology. She is a faculty member of four graduate groups at University of California, Berkeley: Comparative Biochemistry, Endocrinology, Molecular Toxicology and Bioengineering. The breast cancer research pioneer's body of work has provided much impetus for the current recognition of the significant role that extracellular matrix signaling and microenvironment play in gene expression regulation in both normal and malignant cells. Her laboratory developed novel 3D assays and techniques that demonstrate her signature phrase: after conception, "phenotype is dominant over genotype."

Dr. Bissell earned her doctoral degree in microbiology and molecular genetics from Harvard Medical School, won an American Cancer Society fellowship for her postdoctoral studies, and soon after joined LBNL. She was founding director of the Cell and Molecular Biology Division and associate laboratory director for all Life Sciences at Berkeley Lab, where she recruited outstanding scientists and developed a strong program in cell and molecular biology and breast cancer. She has more than 400 publications. Her honors include the U.S. Department of Energy's E.O. Lawrence Award, the American Association for Cancer Research's G.H.A. Clowes Memorial Award, the Pezcoller Foundation-AACR International Award, the Susan G. Komen Foundation's Brinker Award, the Breast Cancer Research Foundation Jill Rose Award, Berkeley Lab's inaugural Lifetime Achievement Prize, the American Cancer Society's Medal of Honor, the MD Anderson Cancer Center's highest honor – the Ernst W. Bertner Award, the Honorary Medal from the Signaling Societies in Germany, the American Society for Cell Biology's highest honor – the E.B. Wilson Medal, and the 2017 AACR Award for Lifetime Achievement in Cancer Research.

The University of Porto, Portugal, established the Mina J. Bissell Award, given every three years to a person who has dramatically changed a field. She is the recipient of honorary doctorates from both Pierre & Marie Curie University in Paris, France, and University of Copenhagen in Denmark. Dr. Bissell is an elected fellow of most U.S. honorary scientific academies, including the National Academy of Sciences, the National Academy of Medicine and the American Philosophical Society.

Michael Snyder, Ph.D.

Chair of the Department of Genetics
Stanford W. Ascherman Professor
Director, Center for Genomics and Personalized Medicine
Stanford University
Stanford, Calif.

Big Data and Health

Michael Snyder, Ph.D. is the Stanford Ascherman Professor and Chair of Genetics and the director of the Center of Genomics and Personalized Medicine at Stanford University. He received his doctoral training at the California Institute of Technology and carried out postdoctoral training at Stanford University. He is a leader in the field of functional genomics and proteomics, and is one of the major participants of the Encyclopedia Of DNA Elements, or ENCODE project.

His study was the first to perform a large-scale functional genomics project in any organism, and he has developed many technologies in genomics and proteomics. These including the development of proteome chips, high-resolution tiling arrays for the human genome, methods for global mapping of transcription factor binding sites (ChIP-chip now replaced by ChIP-seq), paired end sequencing for mapping of structural variation in eukaryotes, de novo genome sequencing of genomes using high-throughput technologies and RNA-Seq. These technologies have been used for characterizing genomes, proteomes and regulatory networks.

Seminal findings from the Snyder laboratory include the discovery that much more of the human genome is transcribed and contains regulatory information than was previously appreciated, and a high diversity of transcription factor binding occurs both between and within species.

He has combined state-of–the-art "omics" technologies to perform the first longitudinal detailed integrative personal omics profile (iPOP) of person and used this to assess disease risk and monitor disease states for personalized medicine. He is a cofounder of several biotechnology companies, including Protometrix (now part of Life Technologies), Affomix (now part of Illumina), Excelix, Personalis and Q Bio. He serves on the board of a number of companies.

Abstracts

1 Assessing the importance of apoptosis related genes in ovarian cancer

Sophia R. Chaudhry[1], Leah Hardy[1], Nancy Levin[2], Michael A. Tainsky[1,2]

[1]Molecular Genetics and Genomics at Wayne State University School of Medicine
[2]Department of Oncology, Wayne State University of Medicine

Ovarian cancer (OVCA) is a lethal malignancy and has a five-year mortality rate above 50%. The majority of known genetic risk often results from mutations in BRCA1 and BRCA2, which are part of the OVCA panel consisting of 24 genes associated with increased risk. However, the aberrations in these genes account for less than half of all OVCA familial cases. The genes associated with OVCA are involved in DNA repair and cell cycle regulation, indicating that mutations in genes of other pathways need to be explored.

We examined a cohort of 48 ovarian cancer patients that are BRCA1/2 wildtype, making them an optimal group to discover rare novel mutations in pathways other than DNA repair and cell cycle regulation that may result in increased risk of disease. Whole exome sequencing and variant assessment of the patients' blood DNA identified 18 high impact mutations in apoptosis associated genes. Of interest is the TP53I3 S252* (rs145078765, MAF = 0.002) truncation found in two unrelated patients. This gene is transcriptionally activated by p53 during p53-mediated apoptosis and maintains DNA damage response. We have found that knocking down TP53I3 results in defects in DNA repair, cell viability and cell proliferation. Another patient carries the Bcl-2-associated transcription factor (BCLAF1) E403* truncation (rs61731960, MAF = 0.007). BCLAF1 is involved in multiple biological processes including apoptosis and its splice variant increases the risk of colon cancer.

The current paradigm is that if DNA repair fails, cells undergo programmed death, such as apoptosis. Defects in the execution of apoptosis increase cancer incidences, so apoptosis following DNA damage is a protective mechanism that prevents carcinogenesis. The crosstalk in DNA damage response and apoptosis suggests that novel mutations in association to OVCA can be found in genes involved in both pathways. Therefore, the purpose of our study is to extend the scope of the pathways associated with ovarian cancer to apoptosis. We plan to test the variants of interest in ovarian cellular models to assess their impact on known OVCA associated pathways and highlight the relevance of apoptosis. We propose that by functionally assessing these mutations using DNA repair, cell cycle regulation and apoptosis assays, new clinically relevant genes and pathways could be identified for increased risk of OVCA.

2 APOBEC3 enzymes mediate efficacy of DNA interstrand crosslinking agents by activating base excision repair and mismatch repair

Kayla Conner[1], Asra Shaik[1], Jordan White[1], Wen Lei[2], Seongho Kim[2], Michele Cote[2], Steve Patrick[2]

[1]Cancer Biology Graduate Program 2Department of Oncology, Wayne State University School of Medicine

Cisplatin, carboplatin and cyclophosphamide are DNA damaging agents that form intrastrand adducts and interstrand crosslinks (ICLs) that induce replication fork collapse and lead to apoptosis. Multiple DNA repair pathways can remove these DNA-adducts, including homologous recombination (HR) and nucleotide excision repair (NER). These chemotherapeutics form ICLs by binding between two guanines on opposing strands of DNA, distorting the helix and forcing the cytosines flanking the adduct site to become extrahelical. This structure is unique to cisplatin/carboplatin/cyclophosphamide, as other ICL-inducing agents don't form extrahelical cytosines. We have previously shown that base excision repair (BER) and mismatch repair (MMR) nonproductively process the DNA adjacent to cisplatin/carboplatin ICLs as a consequence of cytosine deamination. In this mechanism, BER/MMR sensitize cells to cisplatin/carboplatin/cyclophosphamide by physically preventing the productive removal of the ICL by other repair pathways. The APOBEC3 (A3) protein family of cytidine deaminases have been implicated in cancer development, and here we show they mediate cisplatin/carboplatin and cyclophosphamide response through deamination of the extrahelical cytosines. Knockdown of A3 family members using shRNA results in a resistant phenotype to cisplatin/carboplatin compared to control. Knockdown of A3D through siRNA results in resistance to cisplatin/carboplatin. Induction of A3s with PHA or IFN-α2b sensitizes cells to cisplatin/carboplatin and cyclophosphamide. These data suggest that specific A3 members deaminate ICL induced extrahelical cytosines, and results in activation of BER. The subsequent nucleotide misincorporation by Pol-beta followed by MMR protein binding would physically block HR and NER proteins from repairing the ICL, therefore conferring sensitivity to cisplatin, carboplatin and cyclophosphamide.

3 Dual Targeting Mitochondrial and Cytosolic One-Carbon Metabolism with Novel Small-Molecule Inhibitors Results in Potent In-vivo Antitumor Efficacy

Aamod Dekhne[1*], Khushbu Shah[2], Junayed Nayeen[2], Gregory S. Ducker[3], Jade M. Katinas[4], Jennifer Wong[4], Xun Bao[1], Carrie O'Connor[1], Zhanjun Hou[1], Jing Li[1], Lisa Polin[1], Joshua D. Rabinowitz[3], Charles Dann III[4], Aleem Gangjee2, Larry H. Matherly[1]

[1]Department of Oncology, Wayne State University School of Medicine, and the Karmanos Cancer Institute, Detroit, MI, [2]Division of Medicinal Chemistry, Graduate School of Pharmaceutical Sciences, Duquesne University, Pittsburgh, PA, [3]Department of Chemistry / Lewis-Sigler Institute for Integrative Genomics, Princeton University, Princeton, NJ, [4]Indiana University Department of Chemistry, Biochemistry Graduate Program, Bloomington, Indiana

One-carbon metabolism (1CM) is compartmentalized in the mitochondria and cytosol and generates a host of metabolites critical to tumor propagation. Although drug-targeting of cytosolic 1CM remains a clinically-relevant mainstay, development of clinically-useful agents targeting mitochondrial 1CM remains elusive. Of particular pharmacological interest is the mitochondrial 1CM enzyme, serine hydroxymethyltransferase2 (SHMT2). SHMT2 expression correlates with the oncogenic phenotype in lung, colon, breast, glioma, and liver cancer and is the fifth-most upregulated metabolic enzyme in cancer overall. Despite the unequivocal oncogenic importance of SHMT2, there are no clinically relevant inhibitors of this enzyme. In this study, we sought to engineer small-molecules that would synergistically dual-target mitochondrial SHMT2 and cytosolic 1CM, specifically purine nucleotide biosynthesis enzymes glycinamide ribonucleotide formyltransferase (GARFTase) and/or 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase (AICARFTase). By depleting SHMT2-derived formate, these compounds would potentiate their own inhibition of the formate-dependent GARFTase and AICARFTase. We generated these compounds (AGF291, AGF320, and AGF347) by melding structures of SHMT2 cofactor 5,10-methylene tetrahydrofolate with our previously reported purine inhibitors. In-vitro targeted metabolomics in H460 (large cell lung carcinoma), HCT-116 (colorectal carcinoma), and MIA PaCa-2 (pancreatic ductal adenocarcinoma) human tumor cell lines and in-vitro cell-free assays confirmed direct targeting of SHMT2 and GARFTase/AICARFTase. In-vivo, AGF347 demonstrated potent antitumor efficacy against MIA PaCa-2 xenografts in SCID mice with tumor growth delay (T-C) of 38.8 days and one out of five treated mice tumor-free 120+ days after treatment. In-vivo metabolomics on these xenografts confirmed purine inhibition. Collectively, our studies establish the exceptional therapeutic potential of dual-targeting mitochondrial and cytosolic 1CM.

4 Detecting endocrine disruptor exposure from human sperm RNA-seq

Molly S. Estill[1], Russ Hauser[3], Alan C. Moss[4], Stephen A. Krawetz[1,2]

[1]Center for Molecular Medicine and Genetics, Wayne State University School of Medicine, Detroit, MI [2]Department of Obstetrics and Gynecology, Wayne State University School of Medicine, Detroit, MI [3]Vincent Memorial Obstetrics and Gynecology Service, Massachusetts General Hospital, Harvard Medical School, and Departments of Environmental Health and Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, [4]Department of Gastroenterology, Beth Israel Deaconess Medical Center, Boston, MA.

Endocrine disruptors perturb a spectrum of pathways suspected of affecting reproductive function. Low-dose exposures to endocrine disruptors such as phthalates, widely used as plasticizers, are commonplace. Individuals with Inflammatory Bowel Disease (IBD) are often prescribed mesalamine, a medication formulated as "Asacol" (with a di-butyl phthalate (DBP)-containing coating) or as "Pentasa/Lialda" (without a DBP-containing coating). This afforded the opportunity to evaluate whether DBP exposure impacts the sperm transcriptome. A longitudinal study was designed in which patients entering the study provided baseline samples, reflective of their current medication e.g., Asacol/Pentensa, then switched to Pentasa/Asacol for 4 months before providing the corresponding crossover samples. Subjects then returned to Asacol/Pentensa for 4 months before providing the final Crossback samples. RNA-seq was performed on the sperm samples, and assessed as a function of pre-annotated sperm RNAs, as well as novel RNAs. When comparing each arm of the study to fertile individuals, transcriptomic changes associated with IBD were consistently observed in the Pentasa-start group, with marked increases in hetereogeneity among the Asacol-start group. Longitudinal modeling of each arm suggests that DBP-naïve individuals, compared to chronically exposed individuals, undergo larger shifts in transcriptome in response to DBP exposure. This suggests that males chronically exposed to DBP attain a homeostatic state. Notably, small RNAs, such as piRNAs, miRNAs, and endogenous retroviruses modulated in response to DBP exposure may serve a regulatory function of the sperm transcriptome. In-vivo DBP exposure provides insight into the chronic and low-level effects of DBP on human sperm RNAs that can impact reproductive health.

Funding/Acknowledgments
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5 Isoflavones increase radiation-induced apoptosis and modify proinflammatory signaling in EAhy926 endothelial cells

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Background: Therapeutic x-ray ionizing radiation (XRT) is limited by off-target injury and toxicity of normal tissues due to XRT cell death, including necrosis and mitotic catastrophe. Our lab has shown that soy isoflavones (SIF) reduce chronic XRT-induced inflammation and fibrosis. We now investigated the effect of SIF and XRT on endothelial cell death in vitro, which could play a role in SIF mitigation of the inflammatory response. Methods: EA.hy926 endothelial cells were treated with or without 30μM SIF for 24 hours prior to 3.0 or 8.0 Gy XRT and assessed at various time points. Cell death and inflammatory pathways were assessed by viability assays, immunofluorescence, western blot, and flow cytometry.

Results: Endothelial cell viability was decreased for SIF+XRT compared to XRT alone or SIF alone ($p < 0.05$). SIF+XRT treatment increased endothelial Annexin-V+ staining, reduced NFκBp65 activation, prolonged γ-H2AX foci ($p < 0.05$) and increased pro-apoptotic caspases compared to XRT alone.

Conclusions: Our finding that SIF enhances XRT-induced apoptosis of endothelial cells suggests a mechanism of SIF-mediated radioprotection to redirect uncontrolled cell death-induced inflammatory signaling responsible for XRT organ fibrosis.

6 Optogenetic Vision Restoration with Improved ChR Variants in A Blind Mouse Model under Ambient Light Conditions

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Severe photoreceptor cell death in inherited or acquired retinal degenerative diseases, such as retinitis pigmentosa (RP) and age-related macular degeneration (AMD), could lead to partial or complete blindness. Optogenetics is one of the promising approaches to restore vision to the blind. Our early study demonstrated the feasibility of this strategy by AAV-mediated expression of channelrhodopsin-2 (ChR2) in retinal ganglion cells in animal models (Bi et al., 2006). However, a major drawback of using ChR2 in particular and channelrhodopsins (ChRs) in general for vision restoration is their lower light-sensitivity. Thus, the development of more light-sensitive ChRs is desired. We previously reported a strategy of improving light-sensitivity of ChR2 by slowing down its kinetics, or off rate, through site-direct mutagenesis (Pan et al., 2014). Recently, a new natural ChR, CoChR, was reported to show large photocurrent but relatively fast kinetics (Klapoetke et. al., 2014). Using this same strategy, we created several more light-sensitive CoChR mutants. The light-sensitivity of the CoChR mutants was assessed by electrophysiological recordings and visually guided animal behavior in a blind triple knock-out (TKO; Gnat1-/-Cnga3-/-Opn4-/-) mouse model. For the most light-sensitive CoChR mutant, CoChR-H94E/L112C/K264T (CoChR-3M), optomotor responses were observed in CoChR-3M virus vector-injected TKO mice with a computer display-based virtual optomotor system. Visual acuity up to 0.20 cycles/degree (c/d) and contrast sensitivity up to 5 at the spatial frequency of 0.042 c/d were observed. In conclusion, we have developed highly light-sensitive CoChR mutants which enable functional vision restoration in a blind mouse model under ambient light conditions

7 Angiotensin Converting Enzyme inhibitors (ACEi) increase antifibrotic biomarkers in African American patients with hypertension and left ventricular hypertrophy

Shobi Mathew, Cesar A. Romero, Brian Reed, Aaron Brody, Rachelle Dawood, Oscar A. Carretero, Phillip D. Levy

ACEi are the first line treatment in hypertension; however, there is controversy regarding the benefit over other antihypertensive drugs. ACEi have pressure independent effects that may make them preferable for certain patients. We aimed to evaluate the impact of ACEi on antifibrotic biomarkers in hypertensive patients with left ventricular hypertrophy (LVH). We conducted a post hoc analysis of a randomized controlled trial where hypertensive African American patients with LVH and vitamin D (VTD) deficiency were randomized to receive standard antihypertensive therapy plus VTD supplementation or placebo. We selected patients who had detectable lisinopril in plasma at one year follow-up and compared them to subjects who did not. The profibrotic marker propeptide of procollagen type I (CPIP) and the antifibrotic markers: matrix metalloproteinase-1 (MMP-1), tissue inhibitor of MMP1 (TIMP-1), the MMP-1/TIMP-1 ratio, telopeptide of collagen type I (CITP) and Ac-SDKP peptide were measured. Sixty six patients were included. Table 1 shows patients characteristics. Patients with lisinopril had lower blood pressure at one-year but no differences were observed in left ventricular mass index (LVMI). The antifibrotic markers Ac-SDKP (3.9±2.6 vs 6.3±2.8; $p<0.001$), MMP1 and MMP1/TIMP-1 ratio were higher in patients with detectable ACEi (all $p<0.05$). In a model adjusted for systolic blood pressure, low LVMI ($p=0.01$), MMP1/TIMP-1 ($p=0.02$) and Ac-SDKP ($p<0.001$) levels were associated with lisinopril. We conclude that ACEi increase antifibrotic biomarkers in African Americans with hypertension and LVH, suggesting that they may be offer added benefit over other agents in such patients.

8 Pax2 Controls Multiple Aspects of Ocular Morphogenesis in Drosophila

K Mendiratta, M Charlton-Perkins, J Mast, A Goldberg, T Cook

Renal coloboma syndrome (RCS), or papillorenal syndrome, is an autosomal dominant disease associated with renal hypoplasia and optic nerve dysplasia. Some RCS patients may also present with microphthalmia, hearing loss, and joint laxity. While 50% of RCS cases show mutations in the Pax2 transcription factor, the molecular basis of Pax2's function in the eye is still largely undefined. Previous studies by our lab and others have demonstrated an important role for Pax2 in the development and morphogenesis of the Drosophila eye, suggesting its roles in ocular development are deeply conserved. Here, using cell-specific RNAi, we further defined the temporal and cell-specific roles for Pax2 during Drosophila eye formation. These results reveal that, like in RCS patients, loss of Pax2 results in microphthalmia. Further analyses reveal non-autonomous defects in overall retinal integrity, pigment cell patterning, and photoreceptor elongation. Complementary transcriptomic analysis of Pax2 mutants uncovered changes in genes present in the coloboma gene network, as well as genes associated with key signaling pathways, cell junction complexes, and cytoskeletal elements. Together, these studies suggest that Pax2 controls conserved survival and morphology-inducing properties in highly specialized sensory organs like the eye. Given the ease at which these phenotypes can be scored in Drosophila, this provides a simplified model to delineate Pax2-dependent pathways involved in normal organogenesis and phenotypes associated with renal coloboma syndrome

9 FOXQ1 interacts with the KMT2/MLL core complex to promote transcriptional activation of the epithelial to mesenchymal transition (EMT) program

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The epithelial to mesenchymal transition (EMT) is a proposed cellular mechanism for mediating both chemotherapeutic resistance and distant metastasis in many solid tumor types. The human forkhead box transcription factor, FOXQ1, is a potent inducer of EMT in aggressive triple negative breast cancer (TNBC). However, the epigenetic mechanisms regulating FOXQ1 activity remain elusive. To address this problem, we identified FOXQ1-binding proteins using tandem affinity proteomics. Three proteins (RbBP5, WDR5, ASH2L) that define the core complex of mixed lineage leukemia (MLL/KMT2) family of histone methyltransferases, were identified as highly abundant FOXQ1-interacting proteins. These three proteins (RbBP5, WDR5, ASH2L) complex with an MLL enzyme to facilitate the histone-3 lysine-4 trimethylation (H3K4me3) within promoters of actively transcribed genes. We hypothesize that FOXQ1 binding to the MLL core complex is required for activation of critical downstream genes that facilitate EMT and promote tumor progression. Analysis of chromatin localization (ChIP-seq) of FOXQ1 and RbBP5, within a model of breast EMT, revealed 92% of the FOXQ1 activated promoters were also occupied by RbBP5. These downstream gene targets are specifically enriched functions in EMT signaling pathways and well-characterized EMT transcription factors, including TWIST1, ZEB1, SIX2 and FOXC2. In addition, shRNA downregulation of RbBP5 in HMLE/FOXQ1 cells reduced transcript abundance of the targets with FOXQ1 and RbBP5 co-bound promoters and diminished the acquired stem-like phenotype, assessed by mammosphere formation and stem cell surface markers. These data support cooperation of FOXQ1 and the MLL core complex is critical for regulating the EMT transcriptional program.

10 Deletion of calponin 2 attenuates the development of calcific aortic valve disease

Olesya Plazyo, Rong Liu, M. Moazzem Hossain, J.-P. Jin

Calcific aortic valve disease (CAVD), the second-leading cause of cardiovascular mortality, currently lacks treatment options other than valve replacement. Although the pathology of CAVD involves perturbation of valvular cells by the mechanical stimuli including shear stress, pressure and leaflet stretch, the intracellular mechanism requires further elucidation. We recently demonstrated that knockout (KO) of the gene Cnn2 that encodes calponin isoform 2, a mechanoregulated cytoskeleton protein (Liu et al. Gene 585:143-153, 2016), attenuates atherosclerosis in ApoE KO mice (Liu et al. J Mol Cell Cardiol 99:87-99, 2016). Considering that CAVD and atherosclerosis share many pathogenic processes with common risk factors, we hypothesized that calponin 2 may also contribute to the development of CAVD. We found that Cnn2 KO indeed decreased calcification of the aortic valve in ApoE KO mice, an established model of CAVD. Although myeloid cell-specific Cnn2 KO highly effectively attenuated vascular atherosclerosis in ApoE KO mice, it did not reduce aortic valve calcification. This finding indicates a significant difference between the pathogeneses of atherosclerosis and CAVD. Calponin participates in myofibroblast differentiation, a cellular process in the development of CAVD. The aortic valves of ApoE KO mice exhibited increased expression of calponin 2 and smooth muscle actin (SMA), a hallmark of myofibroblasts. Using primary cultures of sheep aortic valve interstitial cells (AVICs) as a model system, we induced differentiation into myofibroblast-like cells and studied the calcification phenotypes. We found that myofibroblast differentiation of AVICs increased the expression of calponin 2 that co-localized with SMA. By further assessing the effect of Cnn2 KO on myofibroblast differentiation and the effect of knocking-down Cnn2 on decreasing calcification phenotypes in AVICs, our study proposes a novel hypothesis that calponin 2 may contribute to the development of CAVD by promoting myofibroblast differentiation.

11 Sex-specific versus general risk factors for adolescent anxious and depressive symptoms

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Pubertal timing and early adversity, such as trauma exposure (TE), have been linked to adolescent risk for anxiety and depression. Pubertal timing (PT) characterizes an individual's pubertal development relative to their age and sex, therefore, it can be accelerated or delayed relative to peers. We examined the effects of PT and TE on anxious and depressive symptoms in female and male adolescents. Based on prior studies, we hypothesized that TE would predict symptoms for both sexes, but that accelerated PT might predict symptoms only in females. Participants were 35 female and 37 male African-American 8- to 15-year-olds and their caregivers from a low-income, urban population. Participants reported their pubertal status. Caregivers reported their child's experience of traumatic events, as well as anxious and depressive symptoms. Pubertal timing was calculated by taking the residual of a linear regression of pubertal status on age. Anxious and depressive symptoms were associated with TE for both females and males, all $rs > .29$ and $ps < .01$. Accelerated PT was associated with elevated anxious, $r(31) = .40$, and depressive, $r(31) = .38$, symptoms for girls, both $ps < .04$, but not boys, both $ps > .42$. For girls, this association remained marginally significant even when controlling for TE, both $rs > .30$ and $ps < .11$. These preliminary results suggest that accelerated PT could be a risk factor for anxiety and depression for girls but not boys, whereas TE impacts both sexes similarly. Forthcoming analyses will examine these associations longitudinally.

12 Influences of clinical and genetic factors on PD-L1 expression in patient derived NSCLC specimens

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Lung cancer is the leading cause of cancer related mortality and non-small cell lung cancer (NSCLC) accounts for 85% of all lung cancers. Immunotherapy, in the form of checkpoint blockade, has altered the standard of care in NSCLC. This therapy is indicated as first line in patients whose tumors express high PD-L1 or as first line in combination with chemotherapy in patients whose tumors express low or no PD-L1 for advanced stage disease. Although PD-L1 testing is considered essential for determining treatment course, little is known about the regulation and induction of PD-L1 in lung tumors. Additionally, PD-L1 expression is valuable in predicting treatment response and disease progression in combination with checkpoint inhibitors; however, the prognostic value of PD-L1 expression in NSCLC tumors outside checkpoint inhibitor use remains controversial. We explored the influence of clinical, demographic, tumor compositional, and transcriptomic factors on the expression of PD-L1 in patient derived NSCLC and their role in prognosis. To conduct this study we utilized NSCLC specimens, clinical characteristics, and follow-up from two independent patent cohorts (KCI N=280, MOFFIT N=235). PD-L1 expression (IHC 22c3) was apparent on 36% and 23% of specimens upon pathologist review. Expression of PD-L1 was not significantly associated with any clinical or demographic factors across both cohorts and was not prognostic in either cohort ($p=0.82$, $p=0.43$). Infiltrating immune cell profiling revealed that PD-L1 positive tumors contained greater numbers of M2 macrophages and resting Dendritic cells ($p<0.05$). Additionally, an immune-centric transcriptome signature containing 24 genes, including the PD-L1 gene (CD274), was strongly predictive of the expression of PD-L1 on tumor cells ($p\leq0.001$, $q<0.1$, AUC=0.875). This gene expression signature was significantly enriched for Positive Immune Response Regulation, Leukocyte Signaling, and CD28 Co-stimulation pathway members ($p<0.05$). These data suggest that NSCLC PD-L1 states are influenced by the immune signatures of the tumor-immune microenvironment and are independent of the clinical presentation at diagnosis.

13 Imaging TRA-1-60 and TRA-1-81 antigens to detect pluripotent cancer stem cells

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Background: The TRA-1-60/81 (TRA) antigens are present in pluripotent cancer stem cells (PCSC), markers of poor outcome in metastatic castration resistant prostate and pancreatic ductal adenocarcinoma. In this study, we examine an IgG antibody Bstrongomab (Bsg, anti-TRA, Curemeta, LLC.) as an immunoPET imaging probe labeled with 89Zr ($t1/2 = 3.27$ d) to detect PCSCs present in DU-145 prostate and BxPC-3 pancreatic xenografts.

Methods: Bsg was conjugated to a DyLight 488 fluorophore (DL488, in vitro) or Alexafluor 680 (AF680) and SCN-Bn-desferrioxamine (DFO) followed by labeling with 89Zr ($t1/2 \sim 3.27$ d) for in vivo imaging. Flow cytometry validated the presence of TRA on BxPC-3 pancreatic DU-145 prostate cells. BxPC-3, DU-145 and PC-3 xenograft models were established subcutaneously. Palpable tumors (100-150 mm3) were utilized for PET imaging (4-120 h post injection) with 89Zr-Bsg-AF680 or 89Zr-IgG-AF680. Biodistribution studies using 89Zr-Bsg (25-50 µCi, 5-10 µg) for BxPC-3, and DU-145 were conducted 24-120 h p.i. (n=4-5 mice per time point).

Results: 89Zr-Bsg-AF680 tumor uptake in BxPC-3 was shown as early as 4 h p.i. with 4.12±0.42%ID/g, increasing three-fold 24 h p.i. to 12.22±1.98%ID/g and was retained between 48 and 120 h p.i. The tracer uptake in DU-145 xenografts was also detectable 4 h p.i. at 5.70±1.22%ID/g, which increased to 9.64±1.55%ID/g 24 h p.i. and plateaued at 12.33±1.87%ID/g 120 h p.i.; 89Zr-IgG-AF680 uptake remained two-fold lower in both tumor models. PC-3 tumor uptake of 89Zr-Bsg-AF680 remained between 4.26-5.26%ID/g from 24-120 h p.i. Biodistribution studies exhibited comparable uptake.

Conclusion: We have successfully developed 89Zr-Bsg-AF680 and demonstrated specific uptake in tumors expressing TRA.

14 The Effect of Depression on Fear Extinction

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Background: Positive affect has been associated with enhanced ability to suppress conditioned fear responses in safe environments and prevent reemergence of extinguished fears. In contrast, depression, a condition of low positive affect, may interfere with fear extinction. Impairments in fear extinction and dysfunction of the underlying neural circuitry hallmark fear-based disorders, conditions that often comorbid with depression. However, no investigation of effects of depression on fear extinction exists.

Methods: 62 adults (ages 18-45) completed a novel adaptation of an established Pavlovian fear conditioning and extinction paradigm. During acquisition, two conditioned stimuli (CSs) were presented: CS+ was paired with an aversive unconditioned stimulus (US), whereas CS- was never paired with the US. The CS+ was subsequently extinguished. 24 hours later extinction learning was tested by presenting CS+; the recovery of fear was tested by presenting the CS+ in the fear acquisition context. Depressive symptoms were measured using the Beck Depression Inventory (BDI-II). Neuroimaging data were collected during recall and renewal.

Results: During extinction recall, individuals with more depressive symptoms exhibited lower activation of the right hippocampus and precuneus to the previously extinguished CS+. Similar findings observed during fear renewal indicate that individuals with more depressive symptoms show lower activation in the precuneus to the previously extinguished CS+.

Conclusions: Increasing depressive symptoms modulate activity in core regions of the default mode network (DMN) during fear recall and renewal. Alterations in morphology and activation of DMN regions have been reported in individuals with depression and may contribute to impaired safety learning and recall.

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