Linking Research and Researchers

BU

Boston University Research
Interdisciplinary Biomedical Research Office

www.bu.edu/research/ibro

Evans Center
For Interdisciplinary
Biomedical Research

www.bumc.bu.edu/evanscenteribr

MISSION STATEMENT

Affinity Research Collaboratives (ARCs) consist of faculty and trainees from different disciplines across campuses, and are organized around foci of common research interests. The extraordinary strength in biomedical and physical sciences at Boston University, and the support and development of the ARCs create opportunities for new interdisciplinary approaches to both research and training in biomedical research. Basic science discovery promoted by ARCs are also available to the Clinical and Translational Science Institute and to other centers for collaborative translational applications.

FOUNDED and SUPPORTED BY

The Evans Center for Interdisciplinary Biomedical Research (**Dr. Katya Ravid, Founding Director**), open to faculty across BU campuses, is supported by the Department of Medicine (Dr. David Coleman, Chair), the Clinical & Translational Science Institute (Dr. David Center, Director), BU vice chair for research office (Dr. Gloria Waters) and by the Evans Medical Foundation (2009-present). The Boston University Interdisciplinary Biomedical Research Office (BU IBRO) (2015-present) within the office of BU Associate Provost for Research provide additional collaborations and support.

ARC PATHWAYS TO IMPACT (with achievement of ≥3 deemed as success)

1. **Publish Science** to build a scientific knowledge base to make an impact in research
2. **Obtain grants** to build a scientific knowledge to make an impact in research
3. Engage with corporations to implement **Sponsored Research Agreements** to make an impact in research
4. Engage with corporations to get **licensing agreements** to make an impact in research
5. Engage with corporations and investors to launch **start-up companies** to make an impact in research
6. **Present** science at meetings to catalyze scientific knowledge and collaborators to make an impact in research
7. **Use Science dissemination strategies** to fast-track timely uptake of research by investigators, policy groups, news media and the public to increase visibility and to make an impact in research
8. **Engage in advocacy and community-engagement** to translate research into guidelines, practices & policy to make an impact in research

The Evans Center for Interdisciplinary Biomedical Research (ECIBR) and BU Interdisciplinary Biomedical Research Office (BU IBRO)

Founding Director: Katya Ravid, Professor of Medicine and Biochemistry and Biology, Fulbright Research Scholar

BY THE NUMBERS

ARC Outcomes and Types of Metrics for Monitoring and Evaluating Success (2009-2020). IBRO, established in 2015, serves to promote team science university-wide).

1. 21 multidisciplinary ARCs have received funding to investigate novel research topics since 2009, with about 263 core faculty participants, and **222 predocs** & **149 postdocs**. Minority researchers have similar percent representation as in the faculty body.
2. 4 multidisciplinary **ARCs have engaged with 4 hubs in CTSA network**; an ARC-driven Thrombotic Microangiopathy regional Consortium; Adoption of the ARC Model by 2 hubs in the CTSA network.
3. **915 collaborative publications** catalyzed by ARCs, to date; 75% of co- authors had never published together prior to the ARC.
4. **531 external grants** awarded to ARC affiliated projects out of 674 applied for to date, with at least two ARC faculty in the co-PI or co-I roles.
5. ARCs catalyzed investigators from 13 schools, 25 departments & industry to form multidisciplinary research projects.
6. Average of 12 seminars, 3 workshops, 2 retreats and 4 symposia per year attracted an average of 60 investigators & 25 trainees per event.
7. Dr. Ravid co-developed Masters Programs in Nanomedicine and in Biomedical Research Technologies, currently instructed by some ARC members.
8. We rapidly respond to newly emerging biomedical research challenges, as exemplified by a new ARC focused on COVID-19 pre-clinical studies (developed in 2020).
9. 4 other ARCs developed during 2015-2020: Tobacco Regulatory Sciences; Fibrosis: Connecting Tissues and Investigators; Computational Approaches to the Microbiome; Mobile and Electronic Health
10. 4 publications about the influence of the ARC Model and best practices shared with the CTSA network.

KEYS FOR SUCCESS: THE FIVE Cs (K. Ravid)

1. **Capability**
   Creative research ideas
2. **Cooperation**
   Willingness to learn
3. **Communication**
   Effective scientific exchanges
4. **Coaching**
   Generous mentoring/insights by the Center's Director and ARC leadership
5. **Conditions**
   Supportive resources and academic culture

PUBLICATIONS

"Thrombotic Microangiopathy: A Multidisciplinary Team Approach."
Gordon CE, Chitalia VC, Sloan JM, Salant DJ, Coleman DL, Quillen K, Ravid K, Francis JM.
Am J Kidney Dis. 2017 Nov;70(5):715-721.
>> View at http://bit.ly/2k9qLG8

"Catalyzing Interdisciplinary Research and Training: Initial Outcomes and Evolution of the Affinity Research Collaboratives Model."
Ravid K, Seta F, Center D, Waters G, Coleman D. Acad Med. 2017 Oct;92(10):1399-1405.
>> View at http://bit.ly/2kdXH0g

"Promoting interdisciplinary research in departments of medicine: results from two models at Boston University School of Medicine."
Coleman DL, Spira A, Ravid K.
Trans Am Clin Climatol Assoc. 2013;124:275-82.
>> View at http://bit.ly/2kdYgXW

"Building interdisciplinary biomedical research using novel collaboratives."
Ravid K, Faux R, Corkey B, Coleman D. Acad Med. 2013 Feb;88(2):179-84.
>> View at http://bit.ly/2AKOJhU

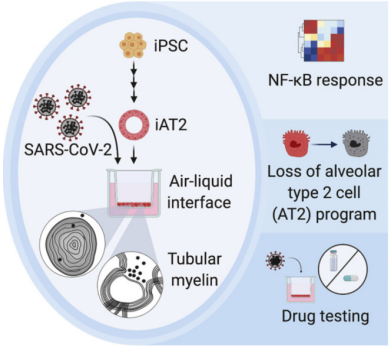
Respiratory Viruses: A Focus on COVID-19

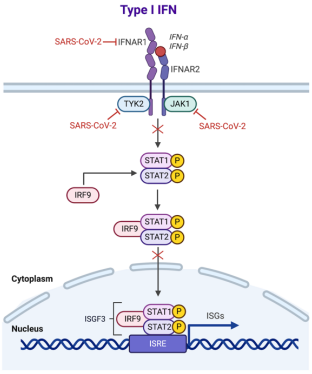
Co-Directors: Drs. Markus Bosmann and Mohsan Saeed
(ARC, 2020-Present)

SYNOPSIS

(This ARC includes 46 faculty from various disciplines)

COVID-19 emerged as a new human disease in November 2019 and it swept through the whole world at a lightning speed, claiming over a million human lives and bringing the global economy to a standstill. The purpose of this ARC was to assemble a team of scientists with expertise in various disciplines of biomedical sciences with the goals to (1) generate tools for the investigation of COVID-19, (2) delineate the molecular mechanisms that underlie the COVID-19 pathophysiology, and (3) to develop therapeutic options for the treatment of COVID-19.





HIGHLIGHTS

A collaborative work by several members of this ARC led to the development of a stem cell-derived model of SARS-CoV-2 infection to interrogate the virus-host interface in a physiologically relevant setting. Using this infection model that comprises the lung type II pneumocytes, the team dissected the mechanisms by which SARS-CoV-2 impairs the normal lung functions.

Also, we established a panel of highly infectable human cell lines representing various SARS-CoV-2 target organs, such as lungs, liver, intestine, brain, heart, and kidneys. We used this panel of cell lines to uncover the molecular details of how SARS-CoV-2 blocks antiviral immune signaling and creates a favorable environment for its replication.

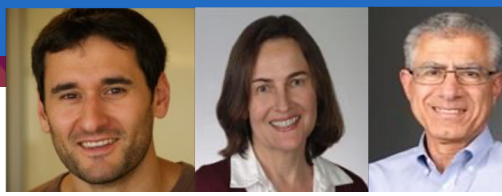
TWO EXAMPLES OF COLLABORATIVE DISCOVERY AMONG SEVERAL

Huang J, Hume AJ, Abo KM, Werder RB, Villacorta-Martin C, Alysandratos KD, Beemann ML, Simone-Roach C, Lindstrom-Vautrin J, Olejnik J, Suder EL, Bullitt E, Hinds A, Sharma A, Bosmann M, Wang R, Hawkins F, Burks EJ, Saeed M, Wilson AA, Mühlberger E, Kotton DN. SARS-CoV-2 infection of pluripotent stem cell-derived human lung alveolar type 2 cells elicits a rapid epithelial-intrinsic inflammatory response. *Cell Stem Cell*. 2020 Sep 18.

Chen, DY, Khan N, Close BJ, Goel RK, Blum B, Tavares AH, Kenney D, Conway HL, Ewoldt JK, Kapell S, Chitalia VC, Crossland NA, Chen CS, Kotton DN, Baker SC, Connor JH, Douam F, Emili A, Saeed M. SARS-CoV-2 desensitizes host cells to interferon through inhibition of the JAK-STAT Pathway. *bioRxiv*. 2020 Oct 28.

Connecting Tissues and Investigators: Fibrosis ARC

Directors: Drs. Xaralabos Varelas, Maria Trojanowska and Irving Bigio
(ARC, 2017-2020; ARC Program 2020-Present)



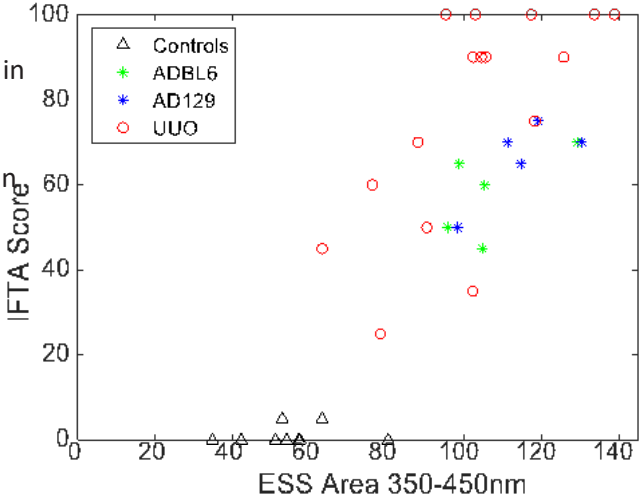
SYNOPSIS

(This ARC includes 26 faculty from various disciplines)

Aberrant fibrogenesis or fibrosis is a common response to chronic tissue injury of almost every organ, contributing to about 45% of all deaths in the U.S. Fibrosis at the phenotypic level shows remarkable similarities across different organ systems, but it is not understood whether cell populations or molecular mechanisms that contribute to the excessive deposition of extracellular matrix are conserved across organs. The central hypothesis is that there are both shared and tissue-specific factors in organ fibrosis that can be utilized to develop improved diagnostics and therapies.

HIGHLIGHTS

- Completed single cell RNA sequencing of fibrosis in a variety of organs, including skin, lungs, adipose tissue, oral cavity and kidneys.
-Developed new portable spatial-frequency domain imaging to measure collagen content in the skin of scleroderma patients.
-Optimized elastic-scattering spectroscopy to quantify interstitial fibrosis/tubular atrophy in kidney
-Identified candidate metabolites to differentiate between diseased and healthy lungs in preclinical model of pulmonary hypertension.



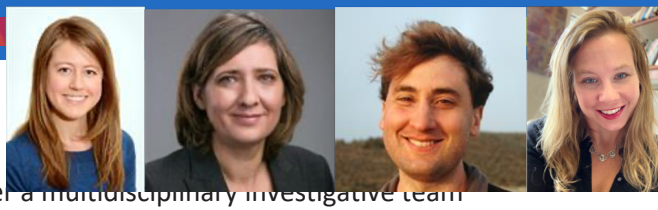
TWO EXAMPLES OF COLLABORATIVE DISCOVERY AMONG SEVERAL

Mostafa E. Belghasem, Ousama A'amar, Daniel Roth, Joshua Walker, Nkiruka Arinze, Sean M. Richards, Jean M. Francis, David J. Salant, Vipul C. Chitalia, Irving J. Bigio. Towards minimally-invasive, quantitative assessment of chronic kidney disease using optical spectroscopy. *Sci Rep.* 2019; 9: 7168.

Applegate MB, Karrobi K, Angelo JP, Austin W, Tabassum S, Aguenounon E, Tilbury K, Saager RB, Gioux S, Roblyer D. OpenSDFI: an open-source guide for constructing a spatial frequency domain imaging system. *J Biomed Opt*. 2020 Jan; 25(1): 016002.

Tobacco Regulatory Sciences

Directors: Drs. Jessica Fetterman, Naomi Hamburg, Andrew Stokes and Stine Grodal
(ARC, 2017-2020; ARC Program 2020-Present)

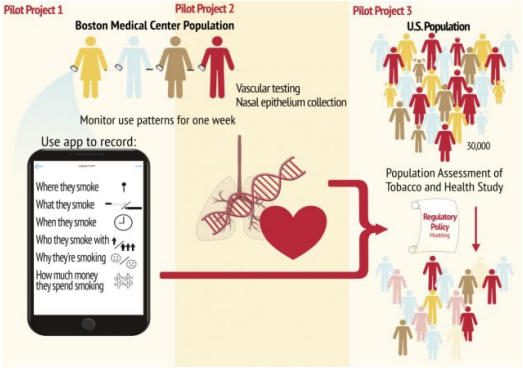


SYNOPSIS

(This ARC includes 32 faculty from various disciplines)

Tobacco Regulatory Science (**TRS**) ARC brings together a multidisciplinary investigative team (Pulmonary/Cardiovascular Medicine; Computational Biology; Global Health; Community Health Sciences; Health Policy & Health Services; Epidemiology; Health Law, Policy, and Management; Biomedical Engineering; Strategy and Innovation; Public Relations, Communication, Computer Sciences) with the mission of understanding complex tobacco use patterns and health impacts in vulnerable populations across the lifecourse.

The safety of e-cigarette use has been called into question with the emergence of EVALI and younger individuals who vape appear to be at greater risk for more severe symptoms and hospitalization with COVID-19 for reasons that are not yet understood. E-cigarettes have been on the market for nearly 10 years but have evolved rapidly, outpacing scientific inquiry into the health effects.



The majority of studies to date evaluating the cardiopulmonary effects of e-cigarettes have focused on e-cigarette products (first- and second- generation devices) no longer in use.

HIGHLIGHTS

A major highlight discovery is that e-cigarette use and some of the product characteristics like flavoring additives are associated with cardiovascular and pulmonary injury. This is the result of a number of publications by the ARC, not one individually but rather the collective.

TWO EXAMPLES OF COLLABORATIVE DISCOVERY AMONG SEVERAL

Osei AD, Mirbolouk M, Orimoloye OA, Dzaye O, Uddin SMI, Benjamin EJ, Hall ME, DeFilippis AP, Stokes A, Bhatnagar A, Nasir K, Blaha MJ. Association between e-cigarette use and cardiovascular disease among never and current combustible-cigarette smokers. *Am J Med*. 2019; 132(8): 949-954.e2.

Fetterman JL†, Keith RJ, Palmisano JN, McGlasson KL, Weisbrod RM, Majid S, Bastin R, Stathos MM, Stokes A, Robertson RM, Bhatnagar A, Hamburg NM. Alterations in vascular function associated with the use of combustible and electronic cigarettes. *JAHA*. 2020. 9(9):e014570.

Precision Medicine for Alzheimer Disease & Related Disorders

Directors: Drs. Rhoda Au, Alice Cronin-Golomb and Lindsay Farrer
(ARC, 2017-2019; ARC Program 2020-Present)

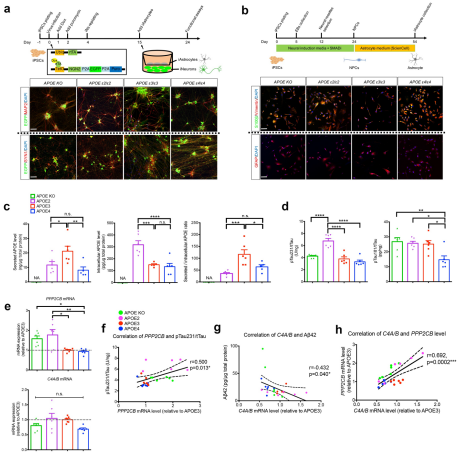
SYNOPSIS

(This ARC includes 33 faculty from various disciplines)

The primary aims of this ARC are to identify subtypes of AD within the Framingham Heart Study (FHS) dataset, validate these subtypes using other available data from the national AD Centers database and other public databases, investigate the biological underpinnings of these subtypes, and identify new therapeutic targets specific for these subtypes. This project introduces a very novel approach for extracting key information from very large and complex datasets that will define subtypes and risk profiles for AD.

HIGHLIGHTS

The mechanism(s) underlying the protective effect of the *APOE* ε2 allele against Alzheimer disease (AD) is poorly understood. To evaluate the contribution of other genetic factors to the protective effect of ε2, we conducted a genome-wide association study for AD among ε2 carriers and applied a systems biology approach involving generating and analyzing various 'omic data and performing immunohistochemistry experiments in brain tissue from 761 AD cases and controls, as well as validation experiments in *APOE* allele-specific iPS cells. Collectively, our findings demonstrated for the first time a molecular link between a tau phosphatase and the classical complement pathway, especially C4, and AD-related tau pathology.



TWO EXAMPLES OF COLLABORATIVE DISCOVERY AMONG SEVERAL

Qiu S, Joshi PS, Miller MI, Xue C, Zhou X, Karjadi C, Chang GH, Joshi AS, Dwyer B, Zhu S, Kaku M, Zhou Y, Alderazi YJ, Swaminathan A, Kedar S, Saint-Hilaire MH, Auerbach SH, Yuan J, Sartor EA, Au R, Kolachalama VB. Development and validation of an interpretable deep learning framework for Alzheimer's disease classification. Brain. 2020; 143(6):1920-1933.

Jun GR, You Y, Zhu C, Meng G, Chung J, Panitch R, Hu J, Xia W, The Alzheimer's Disease Genetics Consortium, Bennett DL, Foroud TM, Wang L-S, Haines JL, Mayeux RP, Pericak-Vance MA, Schellenberg GD, Au R, Lunetta KL, Ikezu T, Stein TD, Farrer LA. Protein phosphatase 2A, complement component 4, and *APOE* genotype linked to Alzheimer disease using a systems biology approach. MedRxiv 2020.

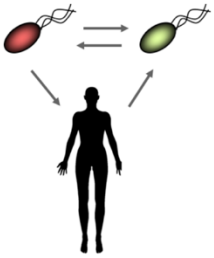
Systems Biology Approaches to Microbiome Research

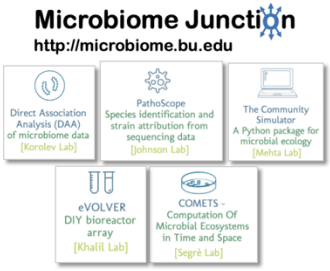
Directors: Drs. Daniel Segrè and W. Evan Johnson
(ARC, 2017-2019; ARC Program 2020-Present)

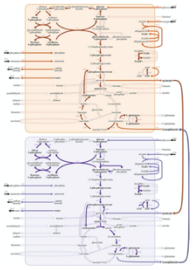
SYNOPSIS

(This ARC includes 47 faculty from various disciplines)

Microbial communities play a crucial role in the health of plants, animals and humans, and of marine and terrestrial ecosystems. Understanding these communities can have great impact in many areas, including agriculture and food production, climate change, immune system function and infectious disease. The goal of our ARC is to develop a new, multi-level mechanistic understanding of how microbe-microbe, microbe-environment, and microbe-host interactions determine microbial community dynamics, diversity and stability, and use this knowledge to understand how to control and engineer microbial communities for defined purposes.







HIGHLIGHTS

We have made significant progress towards the construction of the Microbiome Junction, a hub of computational tools to help conduct quantitative microbiome research. This serves as the point of convergence of multiple data types generated by different investigators, helping them interpret the data in the form of microbial and host interaction networks. We are actively applying these methods and tools in multiple contexts, including cancer (lung, pancreatic, immunotherapies, etc) and infectious diseases (HIV, TB, etc).

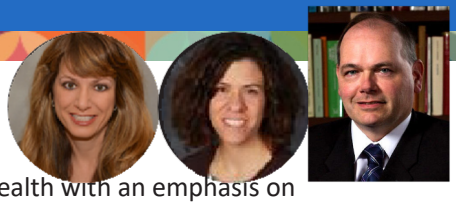
TWO EXAMPLES OF COLLABORATIVE DISCOVERY AMONG SEVERAL

Meghan Thommes*, Taiyao Wang*, Qi Zhao, Ioannis Ch. Paschalidis, Daniel Segrè: Designing metabolic division of labor in microbial communities, mSystems (2019) 4:e00263-18.

Faits T, Walker ME, Rodriguez-Morato J, Meng H, Gervis JE, Galluccio JM, Lichtenstein AH, Johnson WE, Matthan NR. Exploring changes in the human gut microbiota and microbial-derived metabolites in response to diets enriched in simple, refined, or unrefined carbohydrate-containing foods: a post hoc analysis of a randomized clinical trial. Am J Clin Nutr. 2020 Sep 16.

Mobile and Electronic (ME) Health

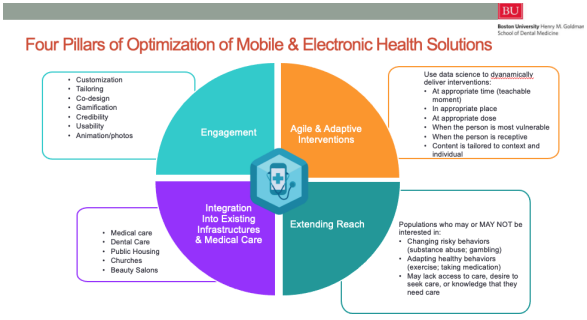
Director: Dr. Belinda Borrelli
Co-Directors: Drs. Lisa Quintiliani and Tibor Palfai



SYNOPSIS

(This ARC includes 175 faculty from various disciplines)

The mission the ME-ARC is to conduct research and training on mobile health with an emphasis on underserved populations and transdisciplinary research. Since, 2017, the ME-ARC has held monthly seminars, annual symposiums, reduced digital silos at BU, and provided mentorship to post-docs, K awardees, and consultation to BU researchers. The ME-ARC has received external funding across a wide variety of areas (e.g., smoking, diet, physical activity, obesity, alcohol, oral health) and digital platforms (Virtual Reality, mobile apps, web, social media, text messaging, connected devices) that have been deployed in real-world clinical and public health settings. The ME-ARC has built strong collaborations with other BU groups (Tobacco-ARC and Framingham Heart Study) resulting in additional publications and external grant award funding. In addition to the leadership team above, the ME-ARC has a steering committee, external advisory board, trainees, and >176 BU members.



HIGHLIGHTS

Dr. Borrelli received a $4.2M five-year award from the NIH that resulted from one of the ME-ARC pilots, entitled, “Delivery of a Smoking Cessation Induction Intervention Via Virtual Reality Headset During a Dental Cleaning.” She also received a $1.8M award from the American Heart Association to study cessation of adolescent vaping using Virtual Reality and texting. This project is part of a multi-project center grant led by Naomi Hamburg of the Tobacco-ARC. In addition, Dr. Lisa Quintiliani was awarded an NIH R01 to develop and test a weight management intervention for public housing residents that uses text messaging and connected devices. ME-ARC members are Co-Is on all of the above projects.

TWO EXAMPLES OF COLLABORATIVE DISCOVERY AMONG SEVERAL

Borrelli, B., Rueras, N., Jurasic, M. (2019). Delivery of a Smoking Cessation Induction Intervention via Virtual Reality Headset during a Dental Cleaning. *Translational Behavioral Medicine*. 2019 Oct 28.

Quintiliani, LM, Foster, M. Oshry, LJ. Preferences of mHealth app features for weight management among breast cancer survivors from underserved populations. Psycho-Oncology. 2019. 28(10):2101-2104.

Thrombosis and Hemostasis in Health and Disease

Directors: Drs. Vipul Chitalia, Katya Ravid and Jean Francis
(ARC, 2015-2019; ARC Program, 2020-present)

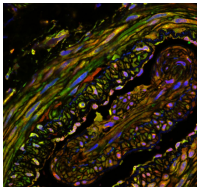


SYNOPSIS

(This ARC includes 34 faculty from various disciplines)

The Thrombosis and Hemostasis in Health and Disease ARC had evaluated several facets of thrombosis spanning from novel mediators to the generation of the animal model up to validating the hypotheses in human cohorts. This ARC has investigated thrombosis using emerging techniques such as machine-learning techniques in the context of organ pathologies (e.g., renal failure), infectious disease (e.g., Shigella-Toxin mediated) and Thrombotic Microangiopathy Collaborative (TMA), a highly complex disease mediated primarily by the aberrant hyperactivation of complement system. The ARC established the first Boston University TMA initiative with BU CTSI.

Vasa vasorum: tissue factor (red) and its cognate ubiquitin ligase, STUB1 (green); On the Cover of *Science Translational Medicine*



HIGHLIGHTS

This ARC has successfully brought together basic and translational research through a cross-disciplinary approach to gain deeper understanding of thrombosis pathogenesis and to develop novel personalized predictive tools and therapeutic targets. As reported earlier, ARC members have initiated and developed the first Thrombotic Microangiopathy (TMA) program in BUSM. An additional unique, innovative contribution of the TtoH ARC has been a focus on *organ pathology-induced changes in thrombosis and vascular hemostasis*, which in the past year has been expanded to initiate studies related to mechanisms of cancer-induced thrombosis. Thrombotic mechanisms related to chronic kidney disease and bone marrow myelofibrosis have been probed, both used as model systems to examine *this newly studied paradigm*, resulting in notable publications and new grant support. Our collaborative pursuits led to identifying certain human plasma metabolites retained in chronic kidney disease, such as Kynurenine, as thrombogenic. Further, the secreted enzyme in myelofibrosis, lysyl oxidase, was found to enhance platelet activation and thrombosis in vivo in mice, and more recently new collaborative proteomic approaches led to identifying in in bone marrow malignant cells modified integrins known to participate in promoting thrombosis.

TWO EXAMPLES OF COLLABORATIVE DISCOVERY AMONG SEVERAL

Shashar M, Belghasem ME, Matsuura S, Walker J, Richards S, Alousi F, Rijal K, Kolachalama VB, Balcells M, Odagi M, Nagasawa K, Henderson JM, Gautam A, Rushmore R, Francis J, Kirchhofer D, Kolandaivelu K, Sherr DH, Edelman ER, Ravid K, Chitalia VC. Targeting STUB1-tissue factor axis normalizes hyperthrombotic uremic phenotype without increasing bleeding risk. Sci Transl Med. 2017 Nov 22;9(417).

Matsuura S, Thompson CR, Belghasem ME, Bekendam RH, Piasecki A, Leiva O, Ray A, Italiano J, Yang M, Merill-Skoloff G, Chitalia VC, Flaumenhaft R, Ravid K, Platelet Dysfunction and Thrombosis in JAK2V617F-Mutated Primary Myelofibrotic Mice. Arterioscler Thromb Vasc Biol. 2020 Oct;40(10):e262-e272.

Protein Trafficking and Neurodegenerative Disease

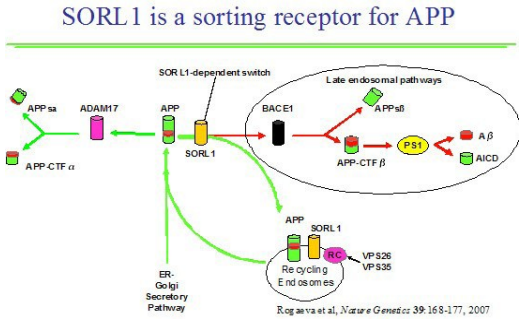
Director: Dr. Lindsay Farrer

ARC, 2009-2012; ARC Program 2013-Present

SYNOPSIS

(This ARC includes 20 faculty from various disciplines)

Recycling of the amyloid precursor protein (APP) from the cell surface via the endocytic pathways plays a key role in the generation of amyloid ß-peptide (Aß), the accumulation of which is thought central to the pathogenesis of Alzheimer disease (AD).



This ARC explores the role of vesicular sorting proteins and other genes involved in protein trafficking in the etiology and pathophysiology of AD and other neurodegenerative disorders. The power of this ARC lies in its diverse, interdisciplinary expertise, and ability to validate any finding using independent approaches of genetic epidemiology, cell biology, model systems and pathology.

HIGHLIGHTS

Notably, cognitive decline has been observed disproportionately in persons affected with MS and to a lesser extent with celiac disease, suggesting that these three diseases share a common immune or inflammatory pathway. Future studies of the protective mechanism of these *HLA* alleles may provide insight into the neurobiology of cognitive decline and dementia and novel therapeutic approaches for these disorders.

TWO EXAMPLES OF COLLABORATIVE DISCOVERY AMONG SEVERAL

Ma Y, Jun GR, Chung J, Zhang X, Kunkle BW, Naj AC, White CC, De Jager PL, Bennett DA, Alzheimer's Disease Genetics Consortium, Mayeux R, Haines JL, Pericak-Vance MA, Schellenberg GD, Farrer LA, Lunetta KL. CpG-related SNPs in the MS4A Region have a dose-dependent effect on risk of late-onset Alzheimer disease. Aging Cell 2019; 18(4):e12964.

Li M, Reisman J, Morris-Eppolito B, Qian SX, Kazis LE, Wolozin B, Goldstein LE, Xia W. Beneficial association of angiotensin-converting enzyme inhibitors and statins on the occurrence of possible Alzheimer's disease after traumatic brain injury. Alzheimers Res Ther. 2020; 12(1):33.

Mitochondrial Dynamics in Health and Disease (mtARC)

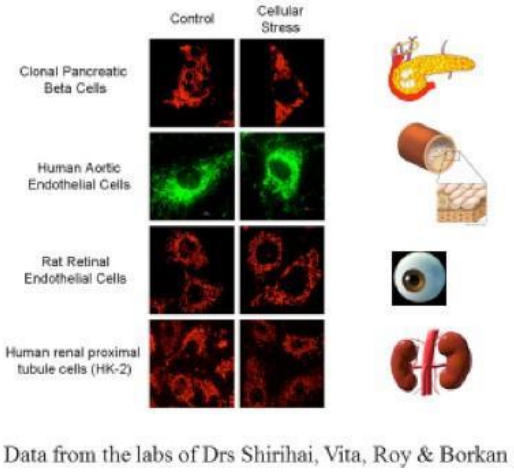
Directors: Drs. Orian Shirihai and Andrea Havasi

(ARC, 2009-2012; ARC Program, 2013-2016; The ARC gave rise to a Bioenergetics Core)

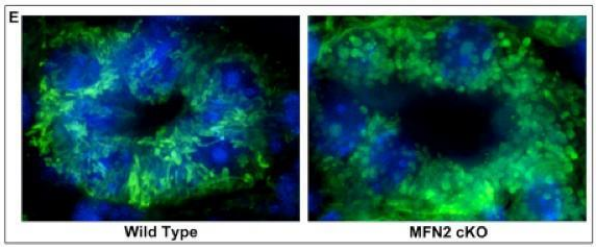
SYNOPSIS

(This ARC included 28 faculty from various disciplines)

The mtARC focused on the role of mitochondria in physiology and pathophysiology. Diverse membership encompassed 12 sections/departments with representation from both the Medical and Charles River Campuses. In addition, membership included labs from other universities and from industry. This ARC also provided training and tools for investigating mitochondrial bioenergetics, dynamics and reactive oxygen species (ROS) in various systems.



Data from the labs of Drs Shirihai, Vita, Roy & Borkan



HIGHLIGHTS

The mitochondrial ARC collaboratively discovered a role for mitofusin 2 (Mfn2) and mitochondrial dynamics in neurodegeneration and metabolic diseases in different organ systems, and was shown to have an important role in organ survival after ischemia. This ARC gave rise to an institutional Research Core focused on Bioenergetics.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Liesa M, Luptak I, Qin F, Hyde BB, Sahin E, Siwik DA, Zhu Z, Pimentel DR, Xu XJ, Ruderman NB, Huffman KD, Doctrow SR, Richey L, Colucci WS, Shirihai OS. Mitochondrial transporter ATP binding cassette mitochondrial erythroid is a novel gene required for cardiac recovery after ischemia/reperfusion. Circulation. 2011 Aug 16; 124(7):806-13.

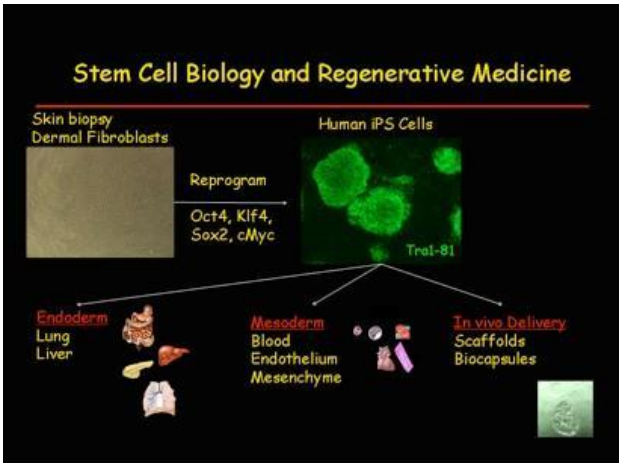
BU iPS Cell Bank

Directors: Drs. Darrell Kotton, Gustavo Mostoslavsky and George Murphy
(ARC, 2009-2012; ARC Program, 2013-2014; CReM (2014-Present)

SYNOPSIS

(This ARC included 15 faculty from various disciplines)

The discovery that mature somatic cells can be reprogrammed into induced pluripotent stem (iPS) cells provides unprecedented opportunities to better understand and treat a variety of human diseases.



ARC members developed in the past a novel reagent, the lentiviral 'stem cell cassette' vector (STEMCCA) that allows the most efficient generation of iPS cells.

This ARC utilized this vector to develop an extensive bank of human iPS cells from individuals with diseases commonly found in the Boston Medical Center patient population: Sickle Cell Anemia, Amyloidosis, Emphysema, Inflammatory Bowel Disease, Scleroderma, and Diabetes.

HIGHLIGHTS

The iPS Cell Bank, Regenerative Medicine ARC initiative, among the first ARCs to be awarded at Boston University, facilitated the launch of an Open-Source stem cell bank that has grown over the years into one of the most widely shared NIH-sponsored stem cell repositories in the US. Today, this repository continues to serve as the heart of an new ARC- facilitated born Center for Regenerative Medicine, and has become the largest bank of disease- specific induced pluripotent stem (iPS) cells for studying sickle cell disease, amyloidosis, and genetic lung diseases including alpha-1 antitrypsin deficiency, cystic fibrosis, and a wide variety of genetic neonatal lung disorders.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Somers A1, Jean JC, Sommer CA, Omari A, Ford CC, Mills JA, Ying L, Sommer AG ,Jean JM, Smith BW, Lafyatis R, Demierre MF, Weiss DJ, French DL, Gadue P,Murphy GJ, Mostoslavsky G, Kotton DN. Generation of transgene-free lung disease-specific human induced pluripotent stem cells using a single excisable lentiviral stem cell cassette. Stem Cells. 2010 Oct. 28 (10):1728-40.

Sex Differences in Adipose Tissue Biology and Related Metabolic Disease

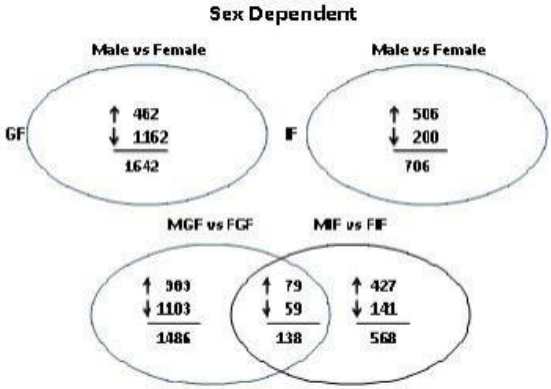
Directors: Drs. Susan K. Fried and Paul Pilch

(ARC, 2009-2012; ARC Program, 2013-2015; continued BNORC collaboration)

SYNOPSIS

(This ARC included 21 faculty from various disciplines)

This ARC focused on the role of adipose tissue biology in the metabolic complications of obesity in men and women. Members have complementary expertise in biochemistry, cell biology, immunology and translational research in obesity, diabetes and cardiovascular disease. This ARC had a close relationship to an existing NIH-funded center, the Boston Nutrition and Obesity Research Center, and has initiated novel collaborations resulting in interdisciplinary grant proposals, including 'brite' adipocytes, adiporedoxin, a novel adipocyte dysfunction in insulin resistance. The ARC also engaged in fruitful ARC-ARC collaborations with four other ARCs: Mitochondria, Arterial Stiffness, Cancer and Inflammation, and Metabolic Disease and Insulin Resistance: Studies in Patients Undergoing Bariatric Surgery.



HIGHLIGHTS

The ARC team found that glucocorticoids (GC) have profound effects on adipose tissue, adipogenesis and adipose tissue metabolic and endocrine function. With chronic excess GC, produced systemically or through local adipose tissue conversion, fat accumulates in central adipose depots and contributes to metabolic derangements.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Jedrychowski MP, Liu L, Laflamme CJ, Karastergiou K, Meshulam T,Ding SY,Wu Y,Lee MJ, Gygi SP, Fried SK, Pilch PF. Adiporedoxin, an upstream regulator of ER oxidative folding and protein secretion in adipocytes. Mol Metab. 2015 Sep 18;4(11):758-70.

Cardiovascular Consequences of Metabolic Disease

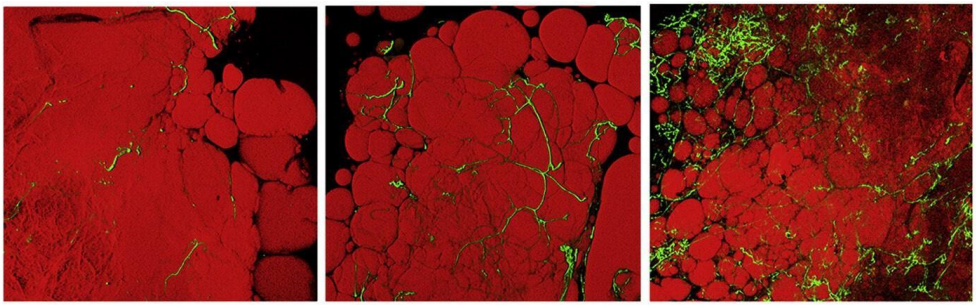
Director: Dr. Kenneth Walsh

(ARC, 2009-2010; Successful completion with achievement of an NHLBI-funded PPG)

SYNOPSIS

(This ARC included 14 faculty from various disciplines)

Obesity promotes a chronic inflammatory state, which contributes to the development of insulin resistance and cardiovascular disease. This ARC intended to promote translational research by bringing basic and clinical research laboratories together to study the cardiovascular consequences of obesity and diabetes. Activities of basic science labs and clinical research labs were coordinated to assess the interrelationship between metabolic dysfunction and vascular disease.



Angiogenesis in adipose tissue (Walsh and Aprahamian et al.)

HIGHLIGHTS

The ARC identified and studied the role of angioenesis in adipose tissue biology, with focus on fat cell expansion.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Bretón-Romero R1, Feng B1, Holbrook M1, Farb MG1, Fetterman JL1, Linder EA1, Berk BD1, Masaki N1, Weisbrod RM1, Inagaki E1, Gokce N1, Fuster JJ1, Walsh K1, Hamburg NM2. Endothelial Dysfunction in Human Diabetes Is Mediated by Wnt5a-JNK Signaling. Arterioscler Thromb Vasc Biol. 2016 Mar;36(3):561-9.

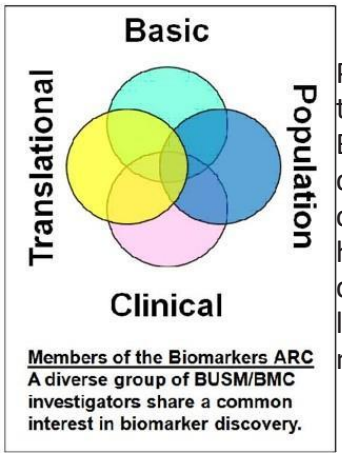
Biomarkers of Disease

Directors: Drs. Mark McComb, Richard A. Cohen and Catherine Costello

(ARC, 2009-2012; ARC Directors re-directed efforts into a newly funded NIH grant to support a National Proteomic Center at BU)

SYNOPSIS

(This ARC included 17 faculty from various disciplines)

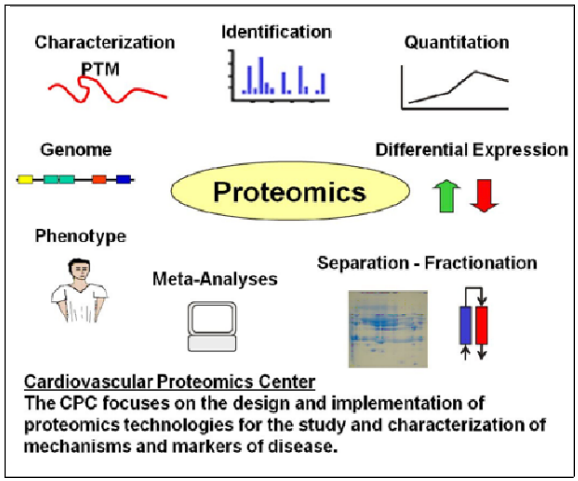


Members of the Biomarkers ARC
A diverse group of BUSM/BMC investigators share a common interest in biomarker discovery.

Projects designed by this ARC were to build on existing expertise and to take advantage of preliminary research studies performed at BUMC in transgenic mice and animal models of metabolic disease. A discovery-based proteomics approach was designed to identify candidate biomarkers related to metabolic disease. The studied hypothesis was that metabolic changes in diseased tissues may be detected by changes in plasma protein abundances that betray leakage of tissue-specific proteins, and bypost-translational modifications (PTMs) that reflect abnormal tissue metabolism.

HIGHLIGHTS

This ARC team discovered changes in metabolic function that may be maladaptive, leading to a situation in which substrate supplied to the heart for energy generation is adequate in amount but cannot be fully utilized. They provided a model to offer specific molecular insights regarding the cellular and physiological mechanisms that lead to metabolic heart disease.



Cardiovascular Proteomics Center
The CPC focuses on the design and implementation of proteomics technologies for the study and characterization of mechanisms and markers of disease.

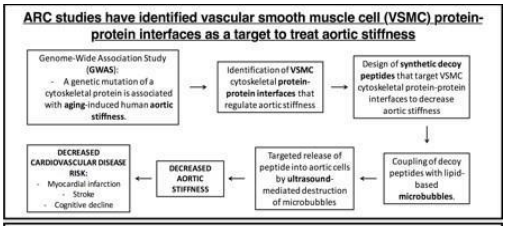
EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

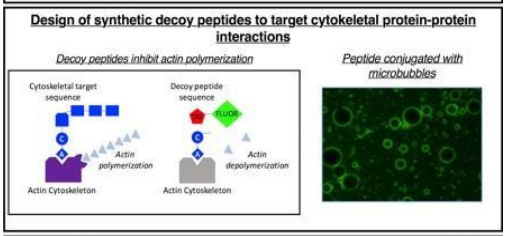
Behring JB, Kumar V, Whelan SA, Chauhan P, Siwik DA, Costello CE, Colucci WS, Cohen RA, McComb ME, Bachschmid MM. Does reversible cysteine oxidation link the Western diet to findings that demonstrate that noncanonical Wnt5a signaling and JNK activity contribute to vascular insulin resistance and endothelial dysfunction and may represent a novel therapeutic opportunity to protect the vasculature in patients with diabetes mellitus. FASEB J. 2014 May; 28(5):1975-87.

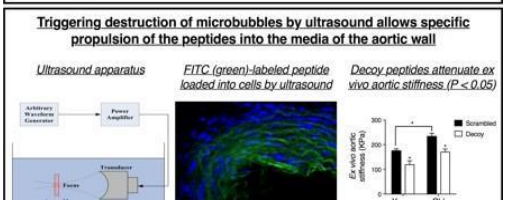
Molecular, Biomechanical and Genetic Mechanisms of Arterial Stiffness

Directors: Drs. Richard Cohen, Kathleen Morgan and Francesca Seta

(ARC, 2010-2013; ARC Program, 2014-2018; Arterial Function Core)







SYNOPSIS

(This ARC included 16 faculty from various disciplines)

Arterial stiffness, a vascular condition characterized by loss of elastic compliance of large arteries, is an independent predictor of, and probable cause of, subsequent adverse cardiovascular events. Targeting arterial stiffness could represent a novel approach to decrease the risk of developing cardiovascular diseases, which remain the major cause of mortality and morbidity in US. The Arterial Stiffness ARC was conceived as an interdisciplinary collaborative group of basic scientists, epidemiologists and bioengineers, from BUSM/BMC, The Framingham Heart Study and CRC, to tackle the complex question of what causes arterial stiffness with the common goal of identifying therapeutic targets.

HIGHLIGHTS

This ARC team initiated efforts to identify therapeutic target molecules to prevent or reverse aortic stiffness, discovered that activation of the lysine deacetylate sirtuin-1 has potent anti-inflammatory and anti-oxidant effects on the vascular wall decreasing arterial stiffness in a model of diet-induced obesity, and successfully applied GWAS data to identify candidate molecules to develop cell permeant, microbubble targeted decoy peptides that are effective in decreasing aortic stiffness in an aged rodent model.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

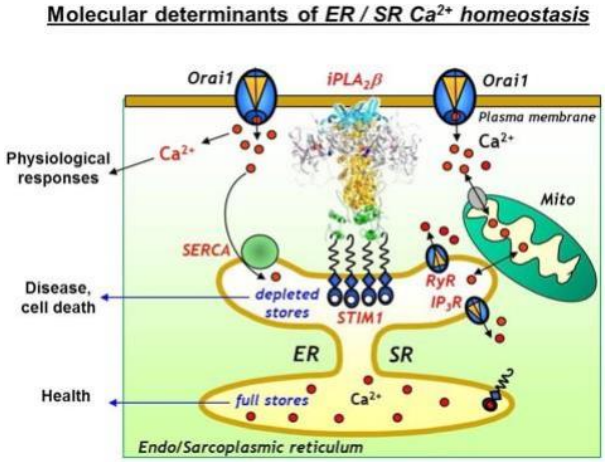
Fry JL, Al Sayah L, Weisbrod RM, Van Roy I, Weng X, Cohen RA, Bachschmid MM, Seta F. Vascular Smooth Muscle Sirtuin-1 Protects Against Diet-Induced Aortic Stiffness. Hypertension. 2016 Sep;68(3):775-84.

Calcium Homeostasis in Health and Disease

Directors: Drs. Victoria Bolotina and Michael Kirber
(ARC, 2010-2013; ARC Program, 2014-2015)

SYNOPSIS

(This ARC included 26 faculty from various disciplines)



Comprised of experts in complementary fields from 18 laboratories in 15 Sections/ Departments from BUSM and Charles River BU campuses, this ARC looked at the mechanisms of cellular function from many different perspectives, which enabled the group to identify common molecular determinants and mechanisms of Ca2+ signaling in diverse cell types, and allowed their translation to human disease to address the mechanisms of impairment in Ca2+ homeostasis in cardiovascular, neurological, pancreatic and other systems.

HIGHLIGHTS

Calcium ARC supported a ground-breaking discovery of a novel Ca2+ signaling mechanism of Parkinson's disease, and has provided school-wide expertise in the study of calcium homeostasis.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

ZhouQ, Yen A, Rymarczyk G, Asai H, Trengrove C, Aziz N, Kirber MT, Mostoslavsky G, Ikezu T, Wolozin B, Bolotina VM. Impairment of PARK14-dependent Ca(2+) signaling is a novel determinant of Parkinson's disease. Nat Commun.2016 Jan 12;7:10332.

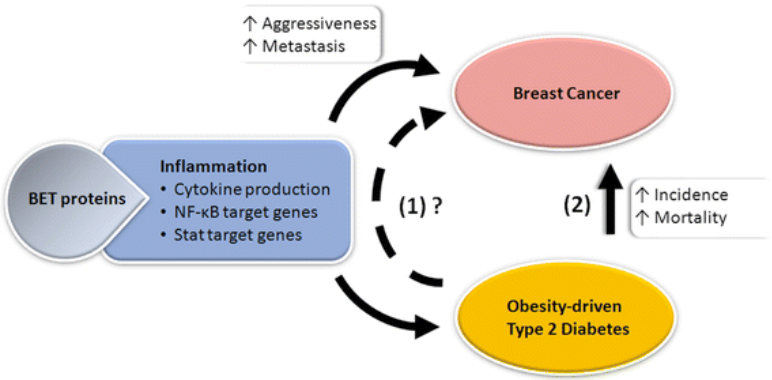
Obesity, Inflammation and Cancer

Directors: Drs. Gerald V. Denis and Barbara Nikolajczyk
(ARC, 2010-2013)

SYNOPSIS

(This ARC included 9 faculty from various disciplines)

Population studies identify cohorts of high body mass index (BMI) subjects with unexpectedly reduced risk for breast and colon cancer, and normal BMI subjects with unexpectedly elevated risk for breast cancer, provoking hard thinking about cellular and molecular mechanisms that most strongly couple obesity to cancer occurrence or progression. Emerging work suggests that abnormal metabolism and its associated chronic inflammation make the difference.



Nichols et al, *Cell Molecular Life Science* **74(2)**: 231-233, 2017

HIGHLIGHTS

Discoveries made by this ARC support a new hypothesis: metabolic disease in obesity promotes breast cancer incidence and metastasis.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Nicholas DA1,2, Andrieu G1, Strissel KJ1, Nikolajczyk BS2, Denis GV3,4. BET bromodomain proteins and epigenetic regulation of inflammation: implications for type 2 diabetes and breast cancer. Cell Mol Life Sci. 2017 Jan;74(2):231-243.

Nanotheranostics

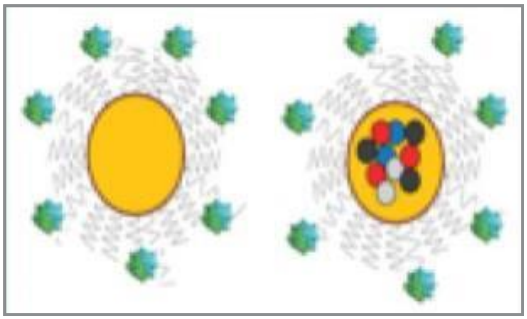
Directors: Drs. Victoria Herrera, Mark Grinstaff, Joyce Wong and Karl Karlson

(ARC, 2012-2015; ARC Program, 2015-2017 giving rise to Master of Science and research programs in Nanomedicine)

SYNOPSIS

(This ARC included 26 faculty from various disciplines)

Nanotheranostics is defined as the integrated combination of target-specific diagnostics and delivery of therapeutics based on nanotechnology platforms. The ARC-program has provided the opportunity to utilize prototype nanotechnology platforms and proof of concept imaging formats. Operationalization of the experiments to test the diagnostics, therapeutic and intraoperativesurvival visualization and resection required the inter-disciplinary expertise and capabilities of several departments: Chemistry, Biomedical Engineering, Molecular Medicine, Pathology, and Surgery.



HIGHLIGHTS

The ARC discovered and proved that low pH-responsive expansile nanoparticles (eNPs) home to and selectively localize intracellularly in pancreatic cancer cells in xenograft model of pancreatic peritoneal carcinomatosis, while sparing peri-tumoral normal cells – endothelium, mesothelium, adipocytes, pancreatic tissue, and all normal intra-abdominal organs including the liver and spleen where all other nanoparticles typically end-up by default.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Herrera VL, Colby AH, Tan GA, Moran AM, O'Brien MJ, Colson YL, Ruiz-Opazo N, Grinstaff MW. Evaluation of expansile nanoparticle tumor localization and efficacy in a cancer stem cell- derived model of pancreatic peritoneal carcinomatosis. Nanomedicine (Lond). 2016 May;11(9):1001-15.

Metabolic Diseases and Insulin Resistance: Studies in Patients Undergoing Bariatric Surgery

Directors: Drs. Neil Ruderman, Konstantin Kandror and Caroline Apovian

(ARC, 2012-2014; 2015-on, members joined other metabolic-related ARCs)

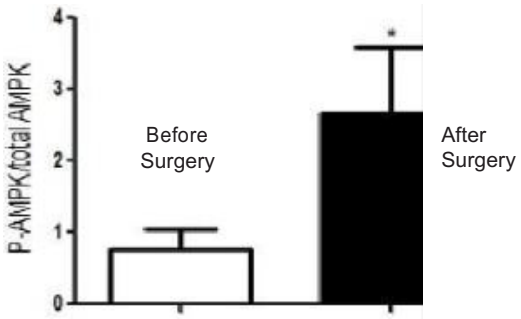
SYNOPSIS

(This ARC included 4 faculty from various disciplines)

Morbidly obese individuals are predisposed to a wide range of diseases including type 2 diabetes, atherosclerotic cardiovascular disease (ASCVD), fatty liver disease, and certain cancers, all of which can be improved or prevented by bariatric surgery. This ARC team along with a few other groups, have observed that approximately 25% of morbidly obese individuals are insulin sensitive (IS) and the remainder are insulin resistant (IR). Intriguingly, compared to the IR group, the IS patients are less likely to develop ASCVD, and presumably other obesity- associated comorbidities.

HIGHLIGHTS

The ARC found that the activity of fuel sensing enzyme AMP-activated protein kinase (P-AMPK)in adipose tissue is markedly diminished (70%) in the insulin resistant patients at the time of surgery. Likewise, 3-months post-operatively decreased AMPK activity was eliminated.



Comparison of AMPK phosphorylation in the subcutaneous fat of 11 matched pre- and post-bariatric surgery patients (*p<0.05).

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Xu XJ, Apovian C, Hess D, Carmine B, Saha A, Ruderman N. Improved Insulin Sensitivity 3 Months After RYGB Surgery Is Associated With Increased Subcutaneous Adipose Tissue AMPK Activity and Decreased Oxidative Stress. Diabetes. 2015 Sep;64(9):3155-9.

Computational Genomics Models of Environmental Chemical Carcinogenicity

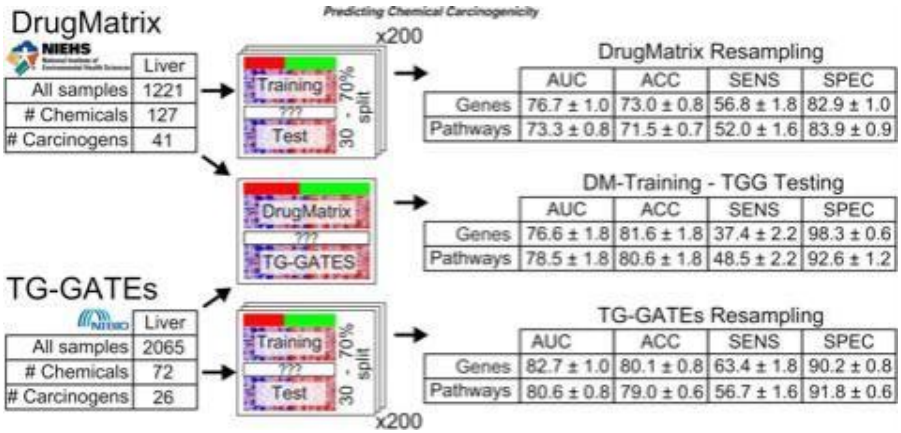
Directors: Drs. Stefano Monti and David Sherr

(ARC, 2013-2016; ongoing discussions related to a new Environmental Toxicants Program)

SYNOPSIS

(This ARC included 12 faculty from various disciplines)

This project was centered around the over-arching goal of developing genomic models of carcinogenicity for cancer prevention and tailored treatment, the goal being to develop accurate and cost-effective methods for the identification of threats to our health from exposure to chemical and environmental carcinogens. An essential component of this ARC is the research into development and application of novel computational approaches to the analysis and integration of multi- dimensional, multi-omics data.



HIGHLIGHTS

The ARC team confirmed the hypothesis that the genomic profile of human cells generated in response to short term exposure with environmental chemicals in vitro can predict, with up to 83% accuracy, a long term biologic consequence, in vivo cancer development. This discovery paves the way for predicting which of the 85,000 chemicals in consumer and industrial use are human carcinogens. To date, only ~2.5% of those chemicals have been tested for carcinogenicity.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

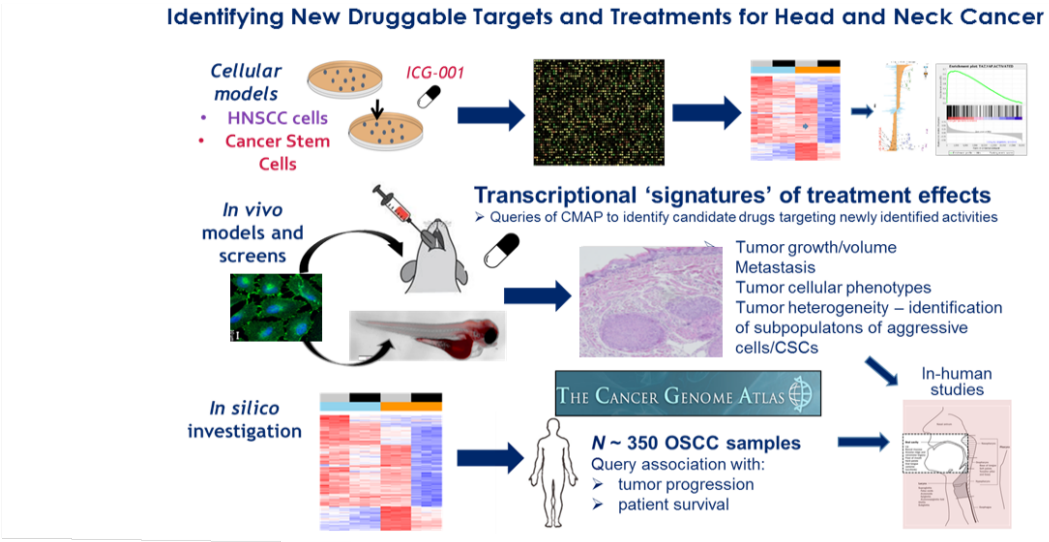
Gusenleitner D, Auerbach SS, Melia T, Gomez HF, Sherr DH, Monti S. Genomic models of short-term exposure accurately predict long-term chemical carcinogenicity and identify putative mechanisms of action. PLoS One. 2014;9(7):e102579.

Etiology & Pathogenesis of Oral Cancer

Directors: Drs. Maria Kukuruzinska, Maria Trojanowska and Avrum Spira
(ARC, 2014-2017; ARC Program, 2017-2019)

SYNOPSIS (This ARC included 14 faculty from various disciplines)

Studies conducted by the Etiology & Pathogenesis of Oral Cancer (EPOC) ARC have been conducted by an array of faculty from different schools, aiming at developing new pathways and understanding of this pathology.



HIGHLIGHTS

EPOC activities have led to significant new findings related to: 1) the mechanisms of oral squamous cell carcinoma (OSCC) development and progression with a focus on the early pathways involving the N-glycosylation/ß-catenin/TAZ-YAP signaling axis, as well as the role of aryl hydrocarbon receptor in tumor initiation in collaboration with the oral microbiome; 2) the remodeling and activation of OSCC tumor stroma and its role in cancer progression; and 3) personalized early detection and treatment of oral cancer, with emphasis on early detection and amelioration of radiation treatment-induced fibrosis.

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Stanford EA, Ramirez-Cardenas A, Wang Z, Novikov O, Alamoud K, Koutrakis P,Mizgerd JP, Genco CA, Kukuruzinska M, Monti S, Bais MV, Sherr DH. Role forthe Aryl Hydrocarbon Receptor and Diverse Ligands in Oral Squamous Cell Carcinoma Migration and Tumorigenesis. Mol Cancer Res. 2016 Aug;14(8):696-706.

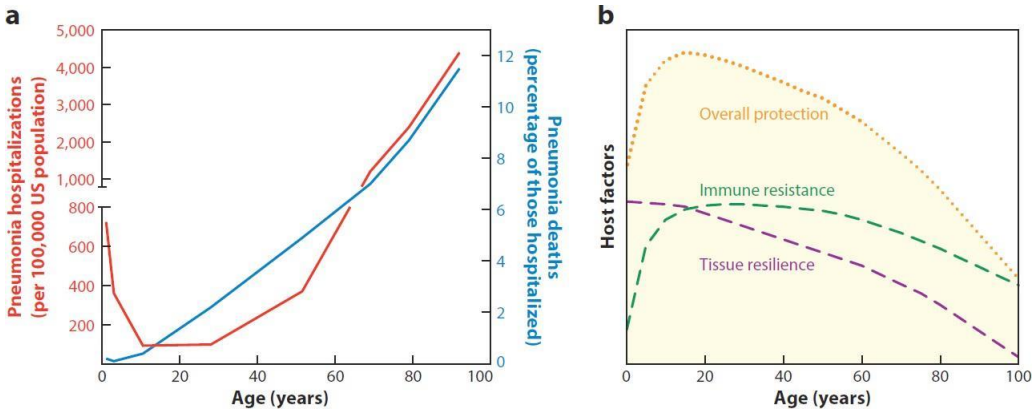
PneumoniARC

Director: Dr. Joseph 'Jay' Mizgerd
(ARC, 2015-2017)

SYNOPSIS

(This ARC included 9 faculty from various disciplines)

A multidisciplinary team was gathered, integrating critical distinct perspectives into this complex disease process, including the basic biology disciplines of Lung Biology, Immunology, and Microbiology, combined with clinical research realms from those caring for children (Pediatrics) or older adults (Pulmonary & Critical Care Medicine), to form the PneumoniARC. In order to attack the problem of high-susceptibility to pneumonia, this ARC is coordinating the knowledge bases, research tools, and investigational activities of 9 principal investigators from 4 academic units across 6 different buildings, all of whom have studies that are complementary with others in the group and relevant to pneumonia.



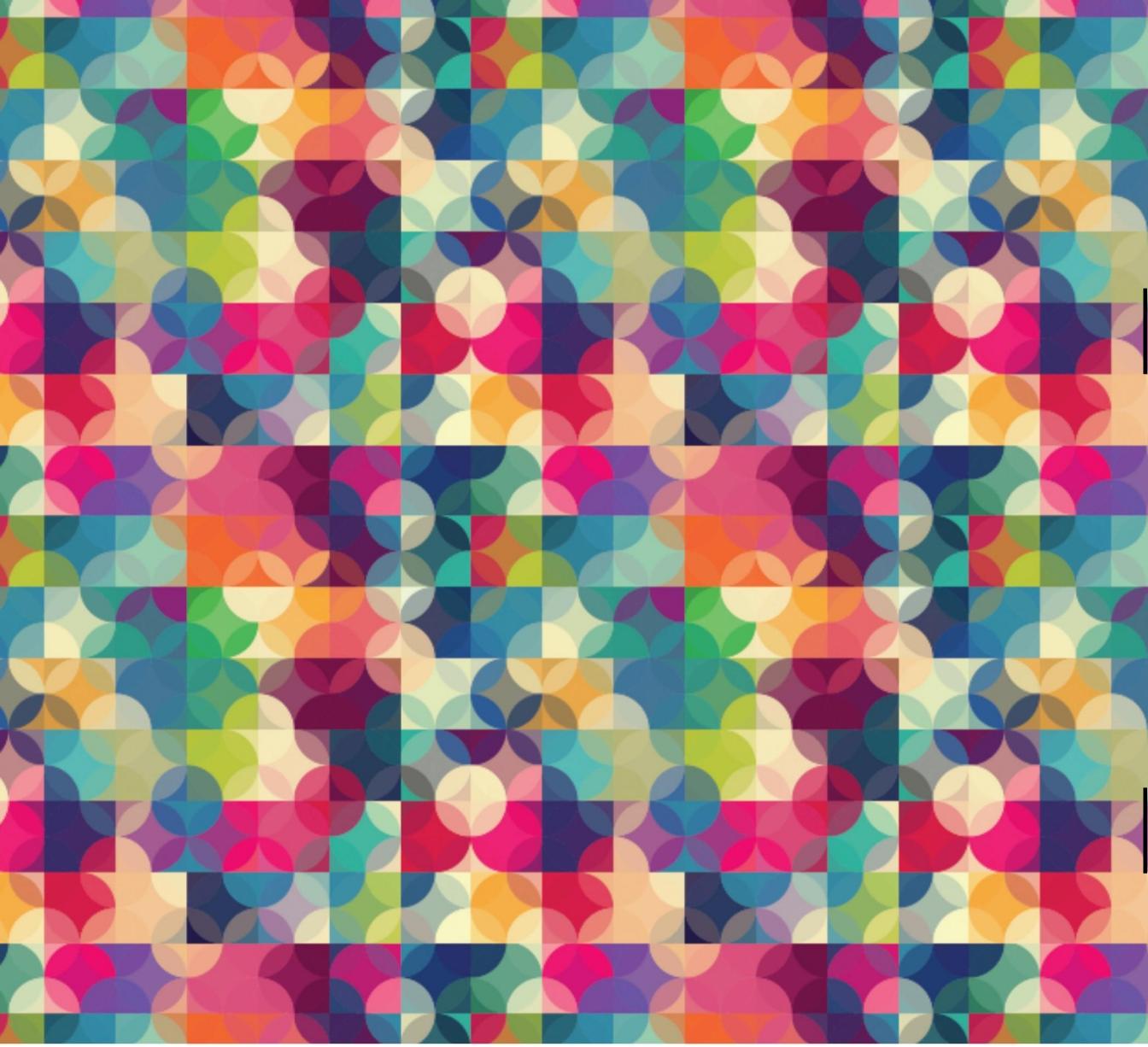
From Annual Rev Physiol, 2015

HIGHLIGHTS

The ARC identified the B cell repertoire as a window into the nature and impact of the lung "Virome."

EXAMPLE OF A COLLABORATIVE DISCOVERY AMONG SEVERAL

Kristie L. Hilliard, Eri Allen, Katrina E. Traber, Kazuko Yamamoto, Nicole M. Stauffer, Gregory A. Wasserman, Matthew R. Jones, Joseph P. Mizgerd, Lee J. Quinton. The Lung-Liver Axis: A Requirement for Maximal Innate Immunity and Hepatoprotection during Pneumonia Am J Respir Cell Mol Biol. 2015 Sep; 53(3): 378–390.



BU

Email to Robin MacDonald, Exec Admin [remac@bu.edu]

Boston University Research
Interdisciplinary Biomedical Research Office

Spring 2021