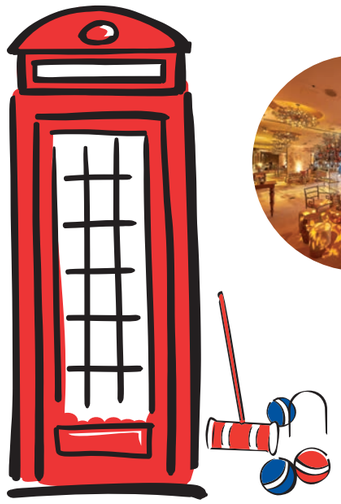
Peter Michael FOUNDATION

2018 YEAR IN REVIEW

PMF | Laser Focused in the Fight Against Prostate Cancer

2019 "…you could say we are mixing it up a bit!"

Stars Atlanta



Stars Knights Valley

Stars Chicago

Stars New York

Stars San Francisco

"…the right mix of exceptional food, wine, philanthropy and jolly good fun."

As I look back on 2018, I am eternally grateful for what the Foundation has become and just how far we have come. We have been hosting 'Stars' fundraising events for 15 years to fund our doctors and researchers and thanks to their dedication and your donor support, last year was a banner year for us.

We hosted a total of seven fundraising dinners in 2018 – five in repeat cities and two new cities. That is more events than any other year and resulted in our best year for fundraising. That's a remarkable accomplishment for our size and we send deep gratitude to each of our friends and supporters who helped us achieve this.

Paul and I are very much looking forward to the year ahead, and we are making some significant and exciting changes to our Foundation events. We hope this will entice previous attendees and attract new ones as well. I guess you could say we are mixing it up a bit!

We kick off 2019 with **Stars Atlanta** on **May 30th** as a part of the Atlanta Food & Wine Festival with five acclaimed chefs preparing the Peter Michael wine-paired dinner. Next up will be our signature Knights Valley event on **June 22nd**. This is the biggest change as this year we are hosting an afternoon event – **Stars By Day** – and it's a month earlier than usual. This will be a festive afternoon garden party with exceptional purveyors, live music, lawn games, a Peter Michael wine tasting & live auction. Be prepared for an English twist to the theme and a glass of Pimm's!

As we move into Autumn, we will be hosting our first **Stars Chicago** dinner on **September 21st** with Michelin-starred Chef Lee Wolen. Our sincere thanks to our wonderful Culinary Advisor Drew Nieporent for making this introduction. The evening's setting will be a rooftop venue looking out towards Lake Michigan and downtown Chicago. **Stars New York** on **October 16th** will take place in the new and much talked about Hudson Yards and we are deeply honored to have Jacques Pépin as our featured chef. THE Jacques Pépin. You can't get more iconic in the French culinary world than Jacques! Our 3rd annual **Stars Sunday Supper** in **San Francisco** will be on **November 3rd**. We are also working on potential Stars events in Boston and Santa Monica before the end of the year. Stay tuned for updates.

We do hope and would love you to join us for one of our events. We are told by many they're always just the right mix of exceptional food, wine, philanthropy and jolly good fun.

Again and, as always, Paul and I send our eternal gratitude for your support and commitment to the great strides we are making in prostate cancer. In the foundation world we may be considered small but with your continued and unwavering support, the progress we continue to make is truly mighty!

Emily Michael

Emily Michael | Founder

2018 was a great year for Peter Michael Foundation

which raised over $1.5 million dollars. This was a record and placed Peter Michael Foundation squarely in the top 10% of all US non-profits.

We accomplished this first and foremost because of YOU, the friends and supporters of Peter Michael Foundation. You are the ones who created this extraordinary achievement.

As most of you know, we raise funds for prostate cancer research through our Stars culinary dinners and the accompanying live auctions and fund-a-need paddle raises. We did 7 Stars dinners in 2018 which was also a record number. By comparison we did 3 dinner events in 2016 and 4 in 2018.

These funds are making a real difference and significant, important advancements in MRI imaging at Memorial Sloan Kettering, photoacoustic theranostics (combination of diagnostics and therapy/treatment) at Stanford University and immunotherapy at the University of California San Francisco.

We were also able to underwrite three different prostate cancer treatment initiatives at the Fred & Pamela Buffett Cancer Center in Omaha. Please see the progress reports for the four above named institutions later in this Year In Review. Stars Omaha was a resounding success because of the dedication and hard work of the local dinner committee that helped raise $500,000.

The Peter Michael Foundation philosophy is to source and vet the “best-of-class” physician/scientists and to make a long term commitment to them and their work. This philosophy has resulted in additional beneficial by-products.

One example is Dr. Hedi Hricak’s ability to attract brilliant young people and motivate them to remain in science and medicine for their careers rather than entering industry and venture capital. Please see her commentary on page 18 for the 13 postdoctoral fellows that she has mentored who are examples of that commitment and success.

Another example is that we are connecting the institutions to work collaboratively on their projects. The Principal Investigator at UCSF has connected with another at Washington University in St Louis to work together on the immunotherapy initiative. We are working towards a collaborative effort between The Buffett Cancer Center and Stanford University on one of their projects.

Stanford expects to have its successful photoacoustic theranostics initiative published in Nature soon. First published in 1869, Nature is the world’s leading multidisciplinary science journal. That journal publication will help propel this novel prostate cancer treatment straight into the clinic.

Equally important, Peter Michael Foundation helps more and more people every week, all year long, who are faced with prostate and other cancer issues.

Please email me if you need information or a referral.

Walter B. Menzel | Executive Director

Friends of the Foundation

Howard and Joia Haber

Montvale, New Jersey

“. . . always a great time and a class event.”

I became aware of the good work of the Peter Michael Foundation through Peter Michael wines. A friend had introduced me to the wines while we were on a family vacation in upstate NY. Les Pavots was on the list and he said “you of all people would love this wine.” Fast forward more than a decade and Peter Michael wines hold a significant amount of real estate in my personal cellar.

Sadly, cancer has touched many lives around me including my grandfather who, according to the doctors at the time, had an undiagnosed cancer in him for years. It was only when it had spread to his bones and was too far progressed to treat was he finally and properly diagnosed. This, along with a few friends’ battles with various cancers, and sadly the loss of one of their teenage daughters to a very rare and misdiagnosed cancer, keeps me interested in the Peter Michael Foundation. Their mission of diagnosis and application versus pure research along with documented evidence of progress is both rare and encouraging.

To the best of my recollection I attended my first “STARS” event in New York City in 2009 at Per Se. It was obvious from the first moment this was not your ordinary group of people and not your run of the mill charity. I was captivated by the focus and frankly the credentials of those in attendance. Clearly this was a cause most if not all in the room believed in rather than just showed up for. Since that time, I have continued to attend whenever possible with family and friends, usually coming as a group or table. Without fail it is always a great time and a class event. The live auctions make the evening and usually wind up with us taking home myriad prized experiences for the year to come.

My wife, Joia, and I truly enjoy the events we have attended, again not only for the fun but for the focus as well. We hope the great work that the Peter Michael Foundation sponsors continues its progress and that its work towards early, clear and proper detection of prostate cancer helps prolong the lives of everyone it touches.

Warm regards,

Howard S. Haber

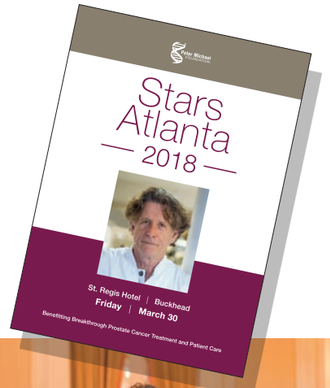
Managing Partner | W&W Glass, LLC

W&W GLASS, LLC

A family owned business with a 70-year history in the metal and glass industry.
The company is one of the largest metal and glass companies in the New York metropolitan area and the largest supplier of structural glass systems in the United States.

Stars *Atlanta*

Michelin-starred Chef Günter Seeger
The St. Regis | Buckhead | March 30



Melissa & Tom Maner, Gloria & Floyd Skinner

l to r: Jenny Koehler, Alicia Casebeer, Chef Günter Seeger, Andrea Kostanecki, Walter Menzel, Karen Fraser

Jenny Ling & Virginia DerMoushegian

Tarryn & Jason Troutman

Jared & Carla York

Carol Anne, Steven & Marian Phillips

Stars *Miami*

Award-winning Chef Michael Schwartz
Amara at Paraiso | Miami | April 14

Alicia Hathaway & Jose Antonio Gonzalez

l to r: Simon & Elina Melik-Levine, Alice Morrison, David Radulski, Alicia Casebeer, Jenny Koehler, Dr. Michael Zinner, Nancy Brinker, Deborah & Leonard Kalman

Dr. Michael Zinner

l to r: Andrea Kostanecki, David Radulski, Alice Morrison

l to r: Yife Tien & Lucy Chua, Barbara Black, Chef Michael Schwartz, Sixta & John Byrnes, Bob Black

r to l: Lisardo Garcia, Maria & Sergio Gonzalez-Arias, Miranda & Jose Martin

Stars *New York*

3 Michelin-star Chef Daniel Humm
NoMad Rooftop | Manhattan | May 3

Paul Michael & Mariko LeBaron

The Magician Dan White

Mary Pasierb, Deb Jaroch

Chrissy & Rupert Banner

I to r: Martina De Santis, Morgan Melkonian, Walter Menzel, Andrea Kostanecki, Jenny Koehler, Chef Daniel Humm, Emily & Paul Michael

I to r: Mark Pasierb, Melissa Boisseau, Mariko LeBaron, Matt LeBaron, Deb Jaroch, Diana & Milan Galik, Mark Danchack, Chris Jaroch, Mary Pasierb, Paul Michael

Howard & Joia Haber

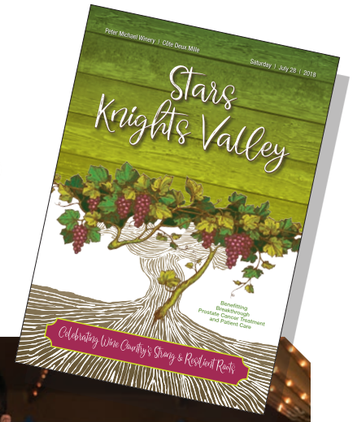
Dr. Hedvig Hricak

Cynthia & Bob Hay

Kimberley & Paul Tanico

Stars Knights Valley

Michelin-starred Chef Christopher Kostow
Côte Deux Mille | Peter Michael Estate | July 28



Paul & Emily Michael, Chef Christopher Kostow, Sir Peter Michael

Chef Christopher Kostow & Ellen Fair

Carey Condy

top: Chris Kostanecki, Jenny Koehler, Jennifer Kostanecki, Larry Sennett;
bottom: Germana Fabbri, Ted van der Linden, Kristin Sennett, Mason Day

Dr. Sam & Aruna Gambhir

Dana McKellar

l to r: Dale & Sharon Fiehler, Mike & Laura Herring, Greg & Lisa Boyce, Elke & Paul Koch, Beth & Gary Goldberg

Arjun Gupta

Arvind & Beverly Sodhani

Brad Jones, Jessica Jones, Scott Perkins, Joan Jones

Kelley Jones & Jim Bailey

Stars *Omaha*

Michelin-starred Chefs Carrie & Rupert Blease
Chef Clayton Chapman
Henry Davis' Private Gallery | Sept 13

Rupert Banner, Emily Michael, Christina Fazzone, Henry Davis

Bill Dyer

Dr. Ken Cowan

Bill & Rae Dyer, Emily Michael, Jackie & Alex Dyer

Rupert Banner, Rupert Blease & Diny Landen

l to r: Jenny Koehler, Martina De Santis, Rupert Blease, Carrie Blease, Clayton Chapman, Morgan Melkonian, Emily Michael, Walter Menzel

Stars *Laguna*

Wolfgang Puck Catered Dinner
Hosts Hanna Struever & Mark Rubin | Oct 13

Patricia Mangold, Dr. Brian Novack, Hannah Struever

Alan VanVliet & Nathalie Vaché

Jon & Margie Masterson

Theresa Golden, Walter Menzel, Alan & Kathryn VanVliet

Chris & Jennifer Derosa

Stars San Francisco

Executive Chef Thomas McNaughton
Central Kitchen | Oct 28

Chris Ehrlich & David White

Matthew Perry, Debbie & Scott Kay

Yat-Pang & Helina Au

l to r: Ron & Allison Abta, Chris & Sara Ehrlich, Scott & Debbie Kay, Mark & Stephanie Breitbard

l to r: Karen Fraser, Spencer Dubuque, Jenny Koehler, Chris Ehrlich, Martina De Santis, Walter Menzel, Lindsay Weiss

Mia & Stephen Tindle

2018 Contributors to
Peter Michael Foundation

STARS VOLUNTEERS
Dawn Beaver
Lynn Borsellino
Christine Corsini
Kathryn Harrison
Emily Sabo
Lindsay Weiss

IN-KIND SUPPORTERS
Chefs Rupert & Carrie Blease
Aida Bogosian
Bonhams
Bryant Family Vineyard
Central Kitchen
Cineteller Productions
Colgin Cellars
Chef Clayton Chapman
Chef Daniel Humm
Kitchen in the Canyon
Chef Christopher Kostow
Lord Stanley
Morlet Family Vineyards
Ne Timeas Restaurant Group
O'Melveny & Myers
Lauren Ridenhour
Chef Michael Schwartz
Chef Günter Seeger
Peter Michael Winery

IN MEMORY OF
In Memory of Dan G. Elmore
In Memory of Margaret Grasso
In Memory of Edith & Leo Multack
In Memory of Erik A. Noteboom

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Kathi Borkholder
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Miles & Jenny Marks
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Walter B. Menzel
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Suzanne & Walter Scott Foundation
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Bruce & Stacy Simon
Floyd & Gloria Skinner
Richard C. & Linda Slade
David Slosburg
Paul & Annette Smith
R. Bob & Catherine R. Smith
Arvind & Beverly Sodhani
Porter Stansberry
Samantha Steckbeck
Richard & Jodi Steel
Sy & Laurie Sternberg
Hanna Struever & Mark Rubin
Karen Talmadge
Graham & Molly Tanaka
Paul P. & Kimberley Tanico
The Carl and Marilynn Thoma Foundation
Grady G. & Ann Thomas, Jr.
Larry D. & Brenda A. Thompson
Nancy Throne
Yife Tien & Lucy Chua
Stephen A. & Mia Tindle
Charles J. & Linda O. Toeniskoetter
Fred & Mariam Torbaty
Kenneth Trauner
United Way of Metropolitan Chicago
Deryk & Karen Van Brunt
Ted van der Linden
Alan & Kathryn Van Vliet
Blair & Wendy Van Zetten
Julia Vesilind
Nicholas Vujicic
Denny & Diana Walker
Dave & Molly Watkins
Werner Enterprises
Jennifer Wright
Carl E. Wynn Foundation
Michael & Gail Yanney
Kevin York
Jared & Karla York
Connie Young
Jeffrey Zalles
Michael Zinner

Memorial Sloan Kettering Cancer Center

Hedvig Hricak, M.D., Ph.D., Dr. h.c.
Chairman, Department of Radiology
Carroll and Milton Petrie Chair
Professor, Gerstner Sloan Kettering Graduate School of Biomedical Sciences
Professor of Radiology, Cornell University

Peter Michael Foundation Fellows:


Andreas Wibmer, M.D.


Kristin Granlund, Ph.D.


Marius Mayerhoefer, M.D., Ph.D.


Anton Becker, M.D., Ph.D.

The field of prostate MRI started more than 35 years ago. Our team has been leading in development, translation and clinical applications in prostate cancer imaging ever since. With support from the Peter Michael Foundation, the team continues to refine and standardize known MRI techniques while also probing the value of novel imaging and computer analytics tools for evidence-based prostate cancer management.

PMF fellow Dr. Andreas Wibmer has been an essential member of the team for over 5 years. Together with Dr. Amita Dave, in the past year at MSK, they have continued to lead an international study aimed at improving the diagnosis of extraprostatic tumor extension—a feature that influences the initial prostate cancer stage and the choice of treatment. To date, institutions in Europe and the United States have submitted clinical and imaging data on more than 900 patients. The large size and multi-institutional nature of this data set will allow for separate analyses of both a test cohort and a validation cohort within this single study. Dr. Michael Kattan of the Cleveland Clinic, a statistician who is internationally renowned for developing clinically successful predictive statistical models, will complete the analyses, and the results are expected to become available within the next few months.

Dr. Wibmer is also leading a large-scale, longitudinal study of the prognostic value of MRI. The study now includes more than 3,400 patients who underwent surgery or radiation therapy for localized prostate cancer at MSK during the early 2000s. The goal of the study is to establish characteristics of prostate cancer on MRI that are independently associated with the likelihood of post-treatment recurrence and cancer-specific mortality. For the purposes of the study, all MRIs were reinterpreted by 7 sub-specialized oncologic radiologists according to the most recent international reporting guidelines (PIRADS version 2). Given the large size of the population and the exceptionally long follow-up period (up to 18 years), this study will be the first to firmly establish the capacity of prostate cancer features on MRI to independently predict long-term outcome. The study should enable better assessment of the levels of risk posed by newly diagnosed cancers, thus allowing more appropriate, individually tailored patient management decisions.

Furthermore, the interdisciplinary team at MSKCC has been continuing their work on imaging prostate cancer patients with hyperpolarized MRI. This advanced technique allows the researchers to observe real-time metabolic dynamics, in particular the metabolic conversion of pyruvate to lactate, in patients with cancer. In previous work, researchers at MSK showed that with higher Gleason grades, prostate tissues generate higher amounts of hyperpolarized lactate, the metabolic end-product of glycolysis. In order to understand what drives this metabolic phenotype, PMF-funded Fellow Dr. Kristin Granlund has developed image- processing methods to quantify and match hyperpolarized data to immunohistochemical stains of prostatectomy tissue. This work has led to the identification of a putative mechanism for the increased lactate in prostate tissues: the transporter that drives HP pyruvate metabolism (MCT1). Recent data from a substantial patient cohort demonstrate that MCT1 is elevated with higher Gleason grades, and a manuscript describing these findings has recently been submitted for publication. This work will likely change the way primary prostate cancer is imaged.

The team at MSK is now starting to extend the use of hyperpolarized MRI to the imaging of metastatic prostate cancer and has just used the technique for the first time to image a patient with such disease. The preliminary data from this patient demonstrates not only that it is feasible to image bone metastases with hyperpolarized MRI but that bone metastases are highly glycolytic. This work will lay the foundation for critically needed improvements in the imaging of patients with metastatic prostate cancer. In today's world of Machine Learning and Artificial intelligence, the MSK team has been actively engaged in the application of computer analytics that is having a growing impact on radiology is an approach known as "radiomics," in which mathematically defined features not discernible to the human eye (describing, for example, lesion shape or texture) are automatically extracted from digital images and correlated with clinical, genomic or other data to assess their predictive value. PET/MRI, the latest hybrid imaging modality to be introduced into clinical practice, is particularly attractive for radiomic analysis, since the versatility of MRI allows PET/MRI to acquire a wide variety of anatomic and functional MRI sequences along with quantitative PET data. Compared to the more established hybrid modality of PET/CT, PET/MRI

continued next page

also offers the advantage of significantly reduced exposure to ionizing radiation. However, there has been uncertainty as to whether quantitative measurements and radiomic features extracted from the PET component of PET/MRI are comparable to those obtained from the PET component of PET/CT, because PET/MRI and PET/CT use different types of attenuation correction; moreover, it has been unclear whether radiomic features are even comparable between different PET/MRI scanners. Dr. Marius Mayerhoefer, a PMF fellow at MSK, has been involved in a study comparing PET radiomic features obtained with four scanner types (two PET/MRI scanners and two PET/CTs scanners produced by different vendors); the initial results indicated a considerable level of heterogeneity of PET radiomic featuresin various tissues. Therefore, Dr. Mayerhoefer and colleagues are presently testing mathematical approaches for data correction and standardization, which will be necessary to allow widespread use of PET-derived radiomics data for tumor characterization.

Novel computer analytics tools are also being applied by Dr. Anton Becker, who recently joined MSK as a PMF-funded post-doctoral fellow after earning his PhD at ETH-Zurich in Switzerland. Specifically, Dr. Becker is combining the latest technology for interactive data analysis and Web design to create an online portal that will provide users with the latest pooled results from the scientific literature on prostate cancer. The target audience consists of both physicians treating patients with prostate cancer and cancer patients who want to know more about the latest evidence on their disease and its management. The goal of the project is to shorten the time it takes for scientific results to go "from bench to bedside" by making the latest high-quality research immediately accessible and illuminating its impact in the context of previous studies.

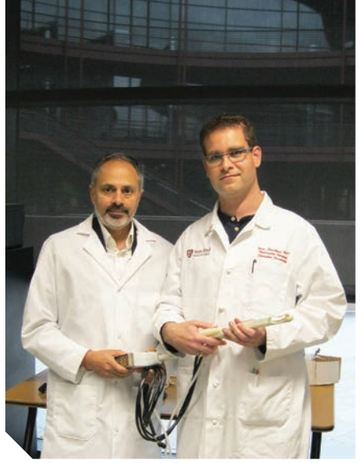
During his PhD training, Dr. Becker acquired expertise in deep learning techniques while collaborating with the computer vision group of Prof. Ender Konukoglu on work that was prominently featured at the 2018 RSNA annual meeting (see http://bit.ly/ai-rad). At MSK, Dr. Becker will also pursue projects that employ the latest deep learning techniques, with the goals of improving the diagnostic accuracy of multiparametric prostate MRI and shortening examination times to decrease patient discomfort.

MSK's Prostate Imaging team is very grateful to PMF for their trust and continuous support.

Peter Michael Foundation Fellows

Dr. Hedvig Hricak, Chair of Radiology, has consistently attracted the best and the brightest postdoctoral fellows and successfully motivated them to remain in science and medicine.

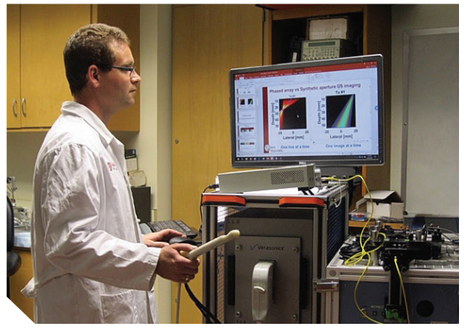
Jan Grimm, MD, PhD *1/31/2007-1/31/2009*	Lab Head, Molecular Pharmacology, MSK, Currently is PI on ***four (4) NIH-funded R01 grants***. Associate Attending Radiologist, Molecular Imaging & Therapy Service, Department of Radiology, MSK. One of these is focused on a ***bio-engineering approach to further evaluate prostate-specific membrane protein (PSMA) as a new biomarker for tumor neovasculature.***
Alberto Vargas, MD *1/2/2010-10/23/2010*	Chief, Body Imaging Service, Department of Radiology, MSK - Much of Dr Vargas' research is focused on prostate cancer, most recently with the biomarker 18F- FDHT, PSMA and multiparametric MR imaging.
Olivio Donati, MD *10/20/2012-4/20/2013*	Attending Radiologist, University Hospital Zurich, Assistant Professor - Currently serves as Head or prostate cancer imaging research at University Hospital Zurich. His recent and current projects include the use of biomarkers to detect local recurrence in prostate cancer patients.
Omer Aras, MD *10/2012-4/2013*	Assistant Attending Radiologist, Body Imaging Service, Department of Radiology, MSK - Dr Aras has focused on pre-clinical studies to develop probes for non-invasive imaging and for surgery.
Andreas Wibmer, MD *5/4/2013-08/23/2014;* *10/15/2016-06/23/2018*	Assistant Attending Radiologist, Molecular Imaging & Therapy Service, Department of radiology, MSK. His research continuous to in prostate cancer including Radiomics - texture analysis studies for prostate cancer detection and Gleason Score assess ment. He is currently finishing two large-scale international studies.
Francois Cornelis, MD, PhD *08/24/2013-08/23/2014*	Professor of Radiology, Tenon Hospital of the Sorbonne University, Paris. Head, IR department, responsible for all prostate cancer related procedures such as cryoablation or IRE, as well as all palliative treatments on bone mets.
Andreas Hoetker, MD *07/12/2014-11/15/2014*	Radiologist, University Hospital Zurich; excels in a number of prostate cancer related MR imaging studies.
Nicola Robertson, MBChB *10/31/2015-04/16/2016*	Royal Free London NHS Foundation Trust; Royal Free · Department of Radiology - continuous to actively pursue clinical MR multi-parametric imaging in Prostate cancer.
Ivana Blazic *11/14/2015-11/26/2016*	Radiologist, Clinical Hospital Centre, Zenum, Belgrade - very active in her work with WHO and global cancer outreach Including imaging prostate cancer.
Natally de Sousa Horvat, MD, PhD *9/3/2016-1/7/2017*	Attending Radiologist, Hospital Sirio Libanes
Marius Mayerhoefer, MD, PhD *2018-present*	Associate Professor of Radiology, Department of Biomedical Imaging and Image-guided Therapy, Medical University of Vienna, Austria. Dr. Mayerhoefer and colleagues at MSK are presently developing hybrid imaging and testing math ematical approaches for data correction and standardization, which will be necessary to allow widespread use of PET-derived radiomics data.
Kristin Granlund, PhD *6/13/2015-1/6/2018; 6/9/2018-present*	Research Associate, MSK - Dr Granlund is developing new techniques for imaging in vivo cancer metabolism using MRI. In particular, she is interested in translating hyperpolarized MRI to clinical use and is currently studying hyperpolarized pyruvate metabolism in prostate cancer patients.
Anton Becker, MD, PhD *3/5/2019-present*	Research Fellow, MSK - Dr Becker plans to pursue projects that employ the latest deep learning techniques, with the goals of improving the diagnostic accuracy of multiparametric prostate MRI and shortening examination times to decrease patient discomfort.



STANFORD CANCER INSTITUTE
Stanford University Medical Center

Mentor: Sanjiv Sam Gambhir, M.D., Ph.D. (above left)
Virginia and D. K. Ludwig Professor of Cancer Research
Chair, Department of Radiology
Professor by courtesy, Departments of Bioengineering and Materials Science & Engineering
Director, Molecular Imaging Program at Stanford (MIPS)
Director, Canary Center at Stanford for Cancer Early Detect

Peter Michael Foundation Fellow: Idan Steinberg, Ph.D. (pictured right)



A. Progress on Dual Modality Transrectal Ultrasound and Photoacoustic Imaging of Prostate:

In recent years, we have developed and translated bench-to-bedside an integrated transrectal ultrasound and a photoacoustic device that synergizes the strengths of transrectal ultrasound and photoacoustic imaging. As no cancer-specific photoacoustic molecular imaging agent is FDA approved yet, this device was used to image patients with suspected prostate cancer with non-specific Indocyanine green (ICG) contrast agent for assessing the device capabilities. Conventional beamforming algorithms were used to provide real-time imaging for both photoacoustic and ultrasonography although they provide relatively low contrast to background ratio.

During the past year, we have finished developing a second-generation instrument and reconstruction algorithm aimed to improve the contrast and sensitivity of images. This new device is based on a commercial piezo-composite 192-element concave ultrasound array, integrated with a multi-port light-guide that allows the generation of various illumination patterns. Those multiple patterns are important in order to generate faithful photoacoustic reconstruction. The outer casing was 3D printed from a biocompatible material shown in Fig 1a. The fully assembled device is shown in Fig. 1b. Acoustic characterization of the device showed a very wide bandwidth (103% in photoacoustic mode - shown in Figure 1c) and high sensitivity. Fig 1d shows that even a weak, subwavelength target is still visible 70 dB above the background.

For photoacoustic imaging, a non-negative model-based reconstruction technique was developed and described in previous reports. For ultrasound imaging, a synthetic transmit aperture was used. Unlike traditional ultrasound where the image is acquired sequentially one image line at a time, synthetic aperture techniques acquire one full image per transmission thus achieving higher resolution for the final compounded image. Those algorithms were implemented on the graphics processing unit for fast computation, which allowed for ten frames per second imaging rate (a 1400-fold improvement in speed compared to naïve serial implementation).
To assess the improvement gained by the algorithm alone, the algorithm was applied to the data acquired with the previous device. Fig 2a & b shows the results of imaging a wire phantom with the previous algorithm vs. the new one. It demonstrates the marked improvement in axial resolution as well as a contrast-to-background ratio. Fig 2c shows an ultrasound image of a patient with suspected prostate cancer. Fig 2d - g shows the photoacoustic signal from the same patient, before and after ICG injection with the previous algorithm vs. the new one. It is clear that the new algorithm does much better in highlighting the contrast agent, which is otherwise invisible with the previous one.

To conclude, we are almost done developing the second generation of transducer and reconstruction algorithms. Preliminary testing's show superior performance compared to the previous generation. We will soon be re-initiating clinical trials to test this new instrument in patients.

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B. Future directions:

A) We are in the process of building the back-end optical system that will allow the use of the multi-port waveguide.

B) We are finalizing the parallel implementation of both new ultrasound and photoacoustic imaging algorithms. A new graphical user interface is being developed as well.

C) To support the continuation of this research, we will image another 24 prostate cancer patients with ICG administration. We are in the process of obtaining all the necessary approvals.

C. Figures:

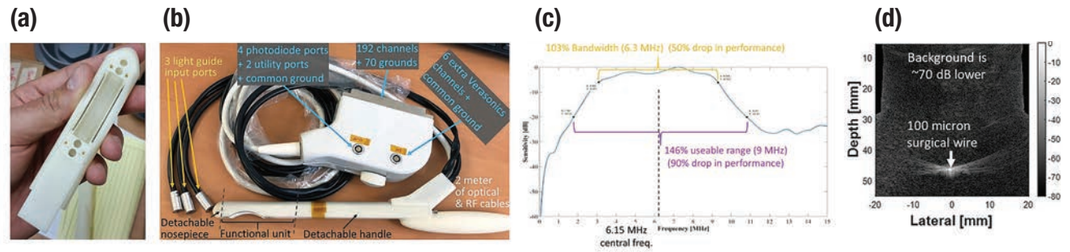

Figure 1: ***2nd generation combined photoacoustic and ultrasound imaging transducer***
(a) The device body, which was 3D printed from a biocompatible resin. Such a material has the advantage of being strong, chemically resistant and optically reflective to avoid photoacoustic signal generation within the device. **(b)** The final assembled device which includes a 2-meter optical and RF cables and connectors as well as a modular device body. **(c)** Acoustic testing on the bandwidth in receive only (photoacoustic) mode. Central frequency is 6 MHz with a broad 103% bandwidth. **(d)** Ultrasound imaging of a 100-micron (sub-wavelength) surgical wire. The wire is shown to be >70dB (3200-fold) stronger than the background.

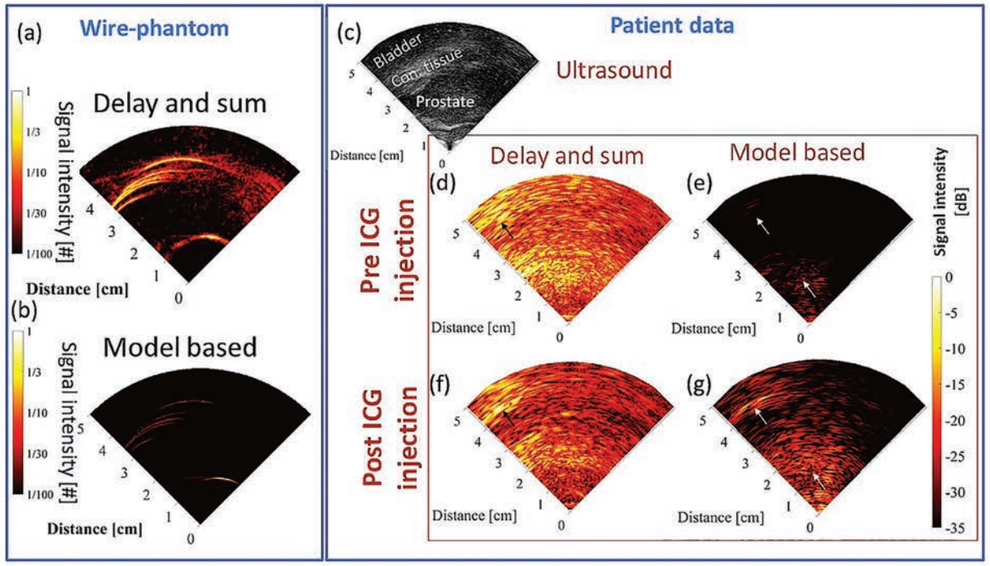

Figure 2: ***New reconstruction algorithm applied to patient data acquired with the previous instrumen***t
(a) Photoacoustic image of 100-micron black wires in water using delay and sum reconstruction. The contrast between the wires and their surroundings is about 20 dB (~10 fold). A lot of clutter is shown around the wires **(b)** The same but with model-based reconstruction. The contrast between the wires and their surroundings is about 40 dB (~100 fold). Both 'a' and 'b' are displayed in log-scale with a 40-dB range. **(c)** Sagittal B-mode ultrasound image of a patient with suspected prostate cancer. The prostate, connective tissue, and bladder are highlighted. **(d)** Photoacoustic image of the same patient using delay and sum reconstruction. There is a signal from all parts of the tissue, and it is not correlated with the actual photoacoustic intensity which makes it very hard to interpret. **(e)** The same as 'd' but with model-based reconstruction. Very little is signal is present deep in the tissue due to light's poor penetration. This correlates well with physical reality. **(f)** The same as 'd' but after the injection of contrast. It is not clear if the contrast has increased compared to 'd'. **(g)** The same as 'f' but with model-based reconstruction. It is very clear that the injection of ICG has increased the contrast in the vascularized prostate and bladder regions but not in the poorly vascularized connective tissue. Images 'd' to 'g' are all displayed in log-scale with a 35-dB range.

UCSF Helen Diller Family Comprehensive Cancer Center

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Chien-Chun Steven Pai, Ph.D.
Lawrence Fong, M. D.

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Mentor: Lawrence Fong, M.D.
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Peter Michael Foundation Fellows: Serena S. Kwek, Ph.D. | Chien-Chun Steven Pai, Ph.D.

Introduction

Prostate cancer is the second most commonly diagnosed cancer and metastatic castration resistant prostate cancer (mCRPC) remains an incurable disease. Immunotherapy with checkpoint-blockade in cancer treatment has shown efficacy in various types of advanced cancer such as melanoma, kidney cancer and non-small cell lung cancer. However, for mCRPC, Phase III trials with anti-CTLA-4 antibodies (ipilimumab) did not show improvement in overall survival (OS) with mCRPC before (1) or after treatment with chemotherapy (2). The only immunotherapy approved by the FDA for asymptomatic or minimally symptomatic men with mCRPC is Sipuleucel-T (Provenge), where the patient's own dendritic cell precursors were purified, activated with PA2024 fusion protein (prostatic acid phosphatase, a prostate antigen, conjugated with GM-CSF, a cytokine) and reinfused into the patient. Sipuleucel-T improved overall survival by 4.1 months in the treatment group when compared with placebo in a Phase III trial (3).

Objectives

Our laboratory has been carrying out Phase I/II clinical trials for mCRPC with combination immunotherapy agents with the following objectives:

1. Improve efficacy of immunotherapy by combination therapy versus monotherapy in mCRPC patients.
2. Screen for immune biomarkers especially before treatment, that can potentially enable the selection for cancer patients that will benefit from the treatment.
3. Determine immune pathways that are inhibitory to immunotherapy treatment that can be potential therapeutic targets.

Results

I. Phase 1b (with expansion cohort) clinical trial with Ipilimumab plus GM-CSF

42 mCRPC with no prior treatment with steroids, chemotherapy, or immunotherapy were treated with increasing doses of ipilimumab per cohort of 6 patients (from 0.5mg/kg to 10mg/kg) every 4 weeks for 4 doses and with GM-CSF at a constant dose of 250 mg/m2 on days 1 to 14 of each 28-day cycle.

23 of 42 patients (54%) had some decline in PSA. Five of 42 patients (11.9%) experienced a 50% or greater decline of PSA from baseline. Objective tumor response and $\geq$ 50% PSA decline were not observed in cohorts treated at less than 3 mg/kg/dose. As this was a Phase Ib trial, there was no placebo arm. Analysis of median OS post hoc was 23.6 months (range: 2 months to 106 months with two patients still alive as of censor date of the trial). Four of the 5 patients who had clinical responses had OS greater than the median of the group.

Using flow cytometry to detect expression of immune markers on peripheral blood mononuclear cells (PBMC) and median OS as the cutoff for short-term survivors versus long-term survivors for patients treated with 3 mg/kg or more per dose, we found that lower levels of PD-1 expressing CD4 T effector cells at pre-treatment and not at the later post-treatment time points associated with longer survival (Fig.1). This data and the results of the clinical trial have been published (4,5). In order to determine the immune pathways of PD-1 that are related to its inhibitory effects resulting in the lack of response in immunotherapy, we sequenced the transcriptome

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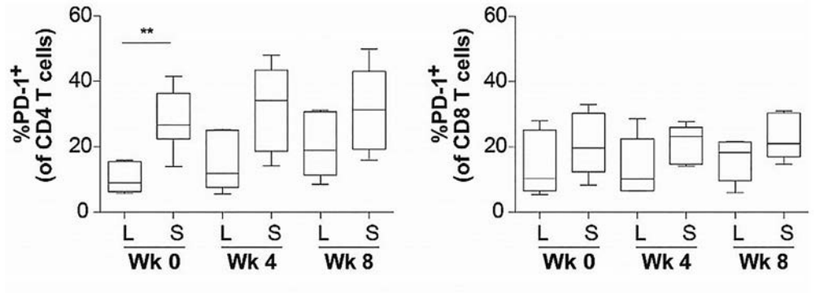

Figure 1: %PD-1+ cells of CD4 Teff and CD8 T cells in long-term (L) vs short-term survivors (S) at week 0 (pre-treatment), and at week 4 and week 8 after treatment with ipilimumab and GM-CSF.

(RNAseq) of both bulk and single cell of sorted PD-1 high expressing CD4 T effector cells and PD-1 low expressing cells from PBMC of the patients in this trial. The same populations from PBMC of cancer-free prostatitis patients were sorted and sequenced for comparison. Differential analysis of RNASeq for the different populations revealed genes that are significantly different between short-term (S) and long-term (L) survivors (Fig. 2 & 3). Canidate genes will be validated by quantitative PCR.

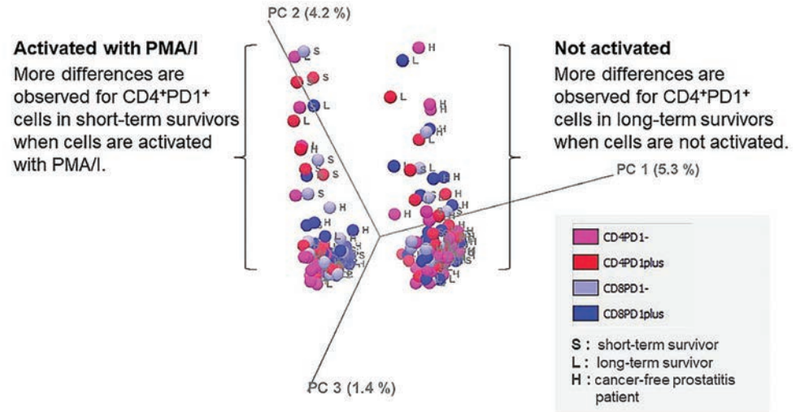

Figure 2: PCA plot of RNASeq data of CD4 Teff PD1+ vs CD4 Teff PD1- cells in metastic prostate cancer and cancer-free prostatis patients.

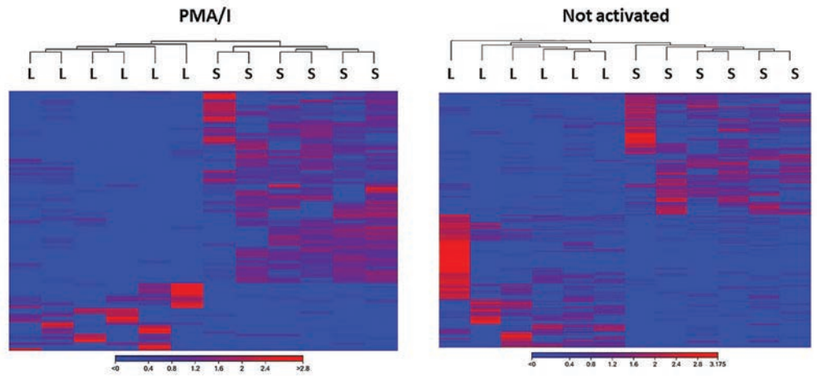

Figure 3: Unsupervised heat-map of differentially significant RNA expression ($p<0.001$) in CD4 Teff PD1$^+$ cells in long-term (L0 vs short-term survivors.

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II. Phase II clinical trial with Ipilimumab plus Sipuleucel-T (SipT)

This trial is currently on-going. The primary objective of this trial is to determine if timing of ipilimumab administration (early versus delayed of ipilimumab at day 1 or 3 weeks following the final dose of SipT) impacts PAP and PA2024 specific immune response induced by SipT. Secondary objectives are safety between the early vs. delayed arms, clinical activity, and modulation of effector and regulatory T cells. As of now, 4 out of 24 patients (16.7%) have $\geq$ 50% PSA decline from baseline. It is too early in the trial to determine the overall survival rates.

Detection of immune markers by previous fluorescence flow cytometry is limited by the number of fluorophores that can be used together in one experiment (up to 20). Current immune monitoring in our laboratory is now being carried out with mass cytometry (Cytof) that can detect the expression of up to 50 immune markers (6). Using Scaffold analysis, we observed that at the pre-treatment time point, the responders $\geq$ 50% PSA decline) demonstrated globally lower percentage of cells that were CTLA-4+, most notably in the NK cells, CD8 T cells, CD4 T cells, Tregs, conventional DCs, all monocytes subtypes (Fig.4).

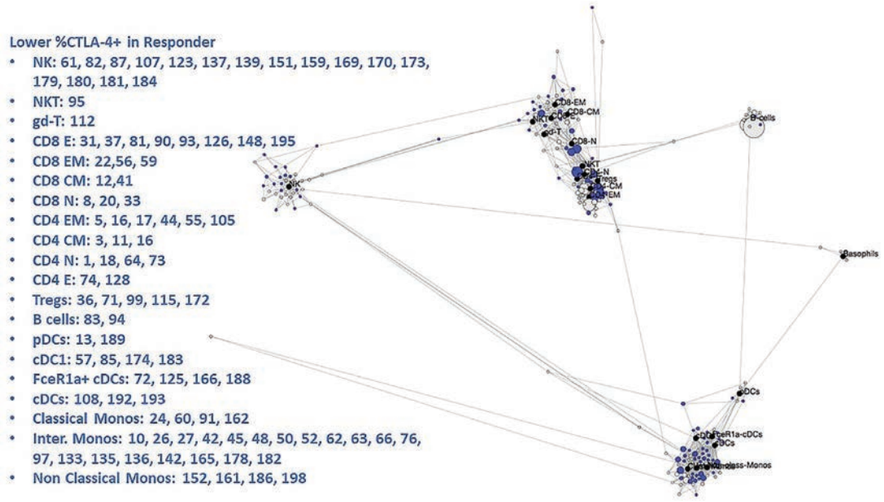

Figure 4: %CTLA4+ is lower in various populations in Responders vs non-responders (% PSA decline) by Scaffold.

The current result of this trial differs from the Ipilimumab plus GM-CSF trial, possibly because of the different combination of treatments. Survival data is also currently not available for this trial. Nevertheless, both PD-1 and CTLA-4 are both immune inhibitory proteins that impede immune responses, and their lower expression associated with responders. At the completion of this trial, the data will be reanalyzed with both PSA and OS and RNAseq will be similarly carried out for differential populations to further identify new biomarkers and immune targets for immunotherapy.

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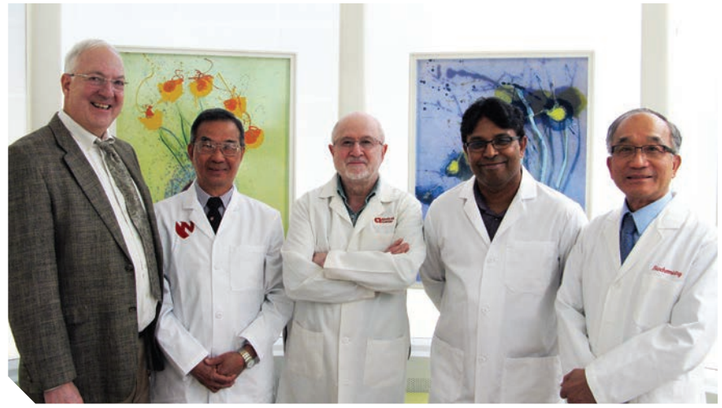

l to r: Kenneth Cowan, M.D., Ph.D., director of the Fred & Pamela Buffett Cancer Center, Pi-Wan Cheng, Ph.D., Angie Rizzino, Ph.D., Kaustubh Datta, Ph.D. and Ming-Fong Lin, Ph.D.

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Project Title: Identification of Aggressive Prostate Cancer based on Prostate Specific Antigen Decorated with High Mannose N-Glycans

Principal Investigator and co-investigators: Pi-Wan Cheng, PhD, Professor of Biochemistry and Molecular Biology, is the principal investigator. He will coordinate the efforts to carry out the proposed study and manage other project-related obligations. The three co-investigators include **Chad LaGrange, MD**, Professor of Urology; **Subodh Lele, MD**, Professor of Pathology; **Jiangtao Luo, PhD**, Associate Professor of Biostatics at UNMC. Dr. LaGrange will assist the effort to collect urine and serum samples from patients with Gleason 6, 3+4, 4+3, 8, and 9+10 groups and help guide the clinically relevant research effort. Dr. LeLe will assist the Gleason classification of the surgically removed prostate tumors to help patient selection. Dr. Luo has helped the biostatistics planning of the proposed research and will continue to help analyze the experimental data. Dr. Cheng, Dr. LaGrange, and Dr. LeLe are members of the Fred & Pamela Buffett Cancer Center at UNMC.

Abstract: Prostate cancer ranks #1 in incidence and #3 in death for men with cancer. Serum level of prostate-specific antigen (PSA) has been routinely used for screening prostate cancer. But, its poor specificity for clinically significant prostate carcinoma has led to under-diagnosis of high-grade prostate carcinoma in patients with PSA level in the normal range and over-diagnosis of un-important prostate cancer in patients with PSA level in the higher range. The inability of this test to distinguish aggressive from indolent prostate carcinoma has resulted in over-treatment of many indolent prostate cancer, thus causing unnecessary suffering for these patients. Therefore, there is a pressing need to develop a test that can distinguish aggressive from indolent prostate carcinoma to facilitate treatment decision, i.e. active surveillance for indolent cancer and immediate treatment for aggressive cancer. The goal of the proposed study is to develop an assay based on % PSA that contains high mannose N-glycans (HMNG) to identify aggressive prostate cancer at different degree of aggressiveness. The proposed study is based on our recent discovery that defective giantin in aggressive prostate cancer cells causes a shift of Golgi targeting of glycosylation enzymes, resulting in production of HMNG. This phenomenon has been extended to PSA, which is a glycoprotein. In Aim 1, we propose to validate the proposed idea by analyzing N-glycans associated with PSA isolated from urine and serum samples collected from patients with Gleason 6, 3+4, 4+3, 8, and 9+10. They represent prostate cancer ranging from non-aggressive one (Gleason 6) to aggressive ones with increasing degree of aggressiveness. We propose to show that the increase in % PSA that contains HMNG in these samples correlates with the increase in Gleason scores. In Aim 2, we propose to establish an immuno and lectin assay of % PSA that contains HMNG using the samples described in Aim 1. The results will provide the rationale for launching a large scale study to further prove the specificity of this test for aggressive prostate cancer. This assay should improve the utility of PSA screening for aggressive prostate cancer.

Lay abstract: Prostate cancer ranks #1 in incidence and #3 in death for men with cancer. Poor specificity of serum PSA test for aggressive prostate cancer has led to over-diagnosis and over-treatment of indolent cancer, and caused unnecessary

continued next page

suffering of these patients. Therefore, there is a pressing need to develop an assay that can distinguish aggressive from non-aggressive prostate cancer. Based on our recent discovery that altered carbohydrates are found in aggressive but not non-aggressive prostate cancer cells, we propose to develop an assay based on % PSA that contains altered carbohydrates to identify aggressive prostate cancer showing different degree of aggressiveness. We will validate the proposed idea by analyzing the carbohydrates associated with PSA isolated from urines and sera collected from prostate cancer patients with cancer ranging from non-aggressive to very aggressive. We propose to show that the increase in % PSA that contains altered carbohydrates correlates with the increase in aggressiveness of the cancer. Then, we will use standardized urines and sera to establish an assay for measuring % PSA that contains these altered carbohydrates. The specificity for aggressive prostate cancer provided by this assay should improve the utility of PSA-based screening of prostate cancer.

Project Title: p66Shc Oxidase as a Biomarker for Prostate Cancer Disparity

Principal Investigator: Ming-Fong Lin, Ph.D.

Lay Abstract

Background:

Africa American (AA) men have the highest prostate cancer (PCa) incidence and death rate among all ethnicity groups in US. Since castration-resistant (CR) PCa is lethal, we propose AA PCa cells exhibit higher degree of progression toward CR PCa, leading to higher death rate and disparity. In US, AA patients have higher androgen levels and 5-alpha reductase activity than other ethnic groups, contributing to PCa disparity. In parallel, aberrant reactive oxygen species (ROS) signal can promote CR PCa progression. p66Shc is an androgen-sensitive oxidase and elevated in clinical PCa and rapid-growing PCa cells, including androgen-independent and androgen-treated cells. Increased p66Shc/ROS in PCa cells enhances PCa tumorigenecity and obtains the CR phenotype.

Goals:

We hypothesize that p66Shc promotes CR PCa progression by increasing tumorigenicity under androgen-reduced conditions and thus plays a role in disparity. Our goals are 1) to determine p66Shc's role in PCa disparity. We will perform immunohistochemistry (IHC) staining of p66Shc protein in clinical PCa archival specimens from the AA vs. Caucasian patient origin. We will correlate its level with clinico-pathological progression. 2) To determine p66Shc's effect on PCa tumorigenicity. We will investigate ex vivo tumorigenicity by examining tumor local invasion in orthotopic model in male animals with castration.

Expected Outcomes:

We expect that p66Shc protein is higher in AA PCa specimens and contributes to PCa disparity and tumorigenicity in orthotopic model. p66Shc can serve as a biomarker for assessing CR PCa progression at the early stage and also as a target for developing precision therapy.

Project Title: SOX2-Induced Prostate Cancer Tumor Quiescence

Principal Investigators: Angie Rizzino, Ph.D., and Kaustubh Datta, Ph.D.

Abstract

The 5-year survival for men with disseminated prostate cancer (PCa) is <30%. Thus, there is a pressing need to identify new strategies to treat advanced PCa. To meet this challenge, we are studying the transcription factor SOX2, which increases during PCa progression. Recent studies provide compelling evidence that targeting SOX2 or its mode of action could substantially improve the treatment of advanced PCa. Previous studies determined that knockdown of SOX2 in castration-resistant PCa (CRPC) cells, such DU145 cells, reduces tumor growth. Recently, we determined that elevating SOX2 with an inducible promoter in PCa cells causes growth inhibition in vitro. Additionally, we determined that elevating SOX2 in the CRPC cell line DU145 in vivo halts tumor growth until SOX2 returns to endogenous levels. We also determined that elevating SOX2 in androgen- dependent LNCaP cells increases the expression of several neuroendocrine markers and paracrine factors, while retaining luminal PCa adenocarcinoma markers. These are exciting findings because, if generally true, it could provide a powerful platform for studying a critical tumor cell population - quiescent PCa cells. Additionally, it provides an opportunity for identifying SOX2 regulated genes that inhibit the growth of CRPC cells. The studies proposed here will test the hypothesis that elevating SOX2 in vivo induces a reversible state of PCa quiescence in a broad spectrum of PCa cell types. To test this hypothesis and to determine how elevating SOX2 inhibits the growth of PCa cells, we propose three Specific Aims. 1) Determine whether elevating SOX2 with the aid of an inducible promoter inhibits tumor growth of both androgen-dependent and androgen-independent PCa cells and induces a reversible state of tumor quiescence until SOX2 returns to endogenous levels. 2) Determine whether disseminated CRPC cells, which metastasize to the bone but fail to proliferate, express elevated levels of SOX2. 3) Determine how elevating SOX2 in PCa cells alters the expression of luminal and neuroendocrine markers. Overall, the studies proposed here are innovative because they seek to create a novel tumor model consisting primarily of quiescent PCa cells that express both luminal and neuroendocrine markers.

Lay Abstract

The 5-year survival for men with disseminated prostate cancer (PCa) is less than 30%. Thus, there is a pressing need to identify new strategies to treat PCa. Many studies indicate that a better understanding of the transcription factor SOX2 could improve the treatment of PCa. Recently, we determined that elevating SOX2 in castration-resistant prostatic cancer cells halts tumor growth until SOX2 returns to endogenous levels. We also determined that elevating SOX2 in androgen-dependent PCa cells increases the expression of several neuroendocrine markers and paracrine factors, while retaining luminal markers. These are exciting findings, because they could provide a powerful platform for identifying drugs able to target an important, but understudied, tumor cell population - quiescent PCa cells. Additionally, it provides an opportunity for identifying SOX2 regulated genes that inhibit the growth of PCa cells. The studies proposed here will test the hypothesis that elevating SOX2 in vivo induces a reversible state of PCa quiescence in a broad spectrum of PCa cell types. Overall, the proposed studies are innovative because they seek to create a novel tumor model consisting primarily of quiescent PCa cells that express both luminal and neuroendocrine markers.

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