THE MICROBIOME, VIRUSES, AND CANCER

February 21-24, 2020  |  Hyatt Regency Orlando  |  Orlando, FL

CONFERENCE COCHAIRS

Cynthia L. Sears
Johns Hopkins University School of Medicine, Baltimore, MD

Giorgio Trinchieri
National Cancer Institute, Bethesda, MD

Jennifer A. Wargo
The University of Texas MD Anderson Cancer Center, Houston, TX

Laurence Zitvogel
Gustave Roussy Cancer Center, Villejuif, France

Program and Proceedings

AACR.org/MicrVir20
AMERICAN ASSOCIATION FOR CANCER RESEARCH

JOIN US IN THE GLOBAL CONQUEST OF CANCER!

THE ESSENTIAL ASSOCIATION FOR YOU AND YOUR COLLEAGUES!

The AACR Special Conference on The Microbiome, Viruses, and Cancer aims to illuminate various areas, including bacterial, viral, and fungal pathogens, and their contributions to the development of cancers.

Nonmember attendees at the conference are invited to join the AACR and connect with other researchers to discuss the most up-to-date findings and to stimulate development of new research discoveries in microbiome and viruses.

No Annual Dues for Associate and Student Members
The AACR fully supports the education, training and professional development of early-career investigators. Graduates, medical students, residents and postdoctoral and clinical fellows who are enrolled in education or training programs that could lead to a career in cancer research **are not required to pay annual membership dues.** Membership is also available for undergraduates and high school students at no charge. Learn more and apply for Associate or Student membership.

Review the many exclusive member benefits, determine which category best fits your qualifications, and **become an AACR member today!**

**WHY YOU SHOULD JOIN:**
- **Substantially reduced registration rates** for AACR Annual Meetings and Special Conferences
- **Privilege of sponsoring abstracts for AACR Annual Meetings**
  - **NEW!** Active, Honorary, and Emeritus members may now sponsor an unlimited number of abstracts for presentation.
- **Early access to housing reservation** for AACR Annual Meetings
- **Exclusive discounts** on subscriptions to AACR’s nine renowned peer-reviewed scientific journals
- **Funding and award opportunities**, including career development resources, research fellowships, scholar-in-training awards, and travel grants
- **Professional development** for early-career investigators and professionals, including education and professional advancement sessions
- **Opportunities to network** and join any of our Association and Scientific Working Groups
- **Free online access to Cancer Today magazine**, a resource for cancer patients, survivors, and their family members and friends
- **Collaboration and resources** through our Survivor and Patient Advocate initiatives

AACR.org/Membership

A Message from
Margaret Foti, PhD, MD (hc)
Chief Executive Officer
American Association for Cancer Research (AACR)

Defeating the global scourge of cancer will require a global effort. The AACR is on the front lines of this fight. Our membership spans 120 countries and we have longstanding partnerships with cancer research organizations around the world to help facilitate the innovative international collaborations we need to achieve the scientific breakthroughs that will lead to future cures.

JOIN US IN OUR MISSION
BECOME A MEMBER TODAY!

Visit the online portal myAACR.aacr.org to access AACR services.

Contact the AACR Membership Department with any questions at membership@aacr.org or 215-440-9300.
An AACR Special Conference on
THE MICROBIOME,
VIRUSES, AND CANCER
February 21-24, 2020 | Hyatt Regency Orlando | Orlando, FL

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February 21, 2020

Dear Colleagues,

On behalf of the American Association for Cancer Research (AACR), it is my pleasure to welcome you to The Microbiome, Viruses, and Cancer, an AACR Special Conference in Cancer Research.

We are very grateful to Drs. Cynthia L. Sears, Giorgio Trinchieri, Jennifer A. Wargo, and Laurence Zitvogel, Conference Co-chairs, for the time and dedication they have put into organizing this exciting program over the past year. This conference has an incredible roster of speakers, and we are thrilled to provide the opportunity for this scientific interaction.

Over the last several years, studies have shown the influence of the microbiota on immune cell function, tumorigenesis, and more. Sequencing studies have shown that the composition of microbial communities differs significantly between those who are healthy and those who are unhealthy, and thus has a profound influence on disease progression and overall health. Within the development of cancer, the microbiota has been implicated in both cause and prevention. The role viruses play in tumor development is also linked to the microbiome. Both genetic and environmental factors can tip the scales from clearance of an infection to the development of cancer. Recent studies have shown that the microbiota is a potential factor that can affect this balance, increasing or decreasing the ability of viral infections to promote carcinogenesis.

The special conference aims to illuminate various areas, including bacterial, viral, and fungal pathogens, and their contributions to the development of cancers. Moreover, the impact of the microbiome on cancers and cancer therapy will also be discussed. The study of the microbiota and its effects on cancer has transformed how we examine therapies and relationships with the immune system. Tumor microenvironments, and the associated tumor microbiota, have also played a role in individualized immunotherapy and the development of novel therapeutics.

Our opening session will feature a keynote lecture by Dr. Matthew Redinbo, from the University of North Carolina at Chapel Hill, titled “Molecular control of the gut microbiome to improve cancer chemotherapy.” Our second keynote will be given by Dr. Marcel R.M. van den Brink of Memorial Sloan Kettering Cancer Center, titled “The role of the intestinal microbiome in allogenic hematopoietic cell transplantation.” Talks throughout the conference will cover a wide range of topics, including the role of the microbiota in metabolism and immunity, oncogenic viruses, and the microbiota in cancer prevention and therapy. Conference sessions will feature short talks highlighting some of the most innovative research from the abstracts submitted.

The AACR extends its thanks to Pfizer for their generous support of this meeting through Professional Educational Grants.

Once again, welcome to this AACR Special Conference. I feel confident that you will find this to be an exciting and engaging meeting, and I am looking forward to your participation. Best wishes for a successful conference!

Sincerely,

Margaret Foti, PhD, MD (hc)

Margaret Foti, PhD, MD (hc)
GENERAL INFORMATION

Certificates of Attendance and Receipts

Certificates of attendance and receipts for conference registration fees are available at the conference registration desk.

Conference Registration

Registration will be held in Plaza D-F Foyer on the following schedule:

- Friday, February 21: 3:00 p.m.-9:15 p.m.
- Saturday, February 22: 7:00 a.m.-5:00 p.m.
- Sunday, February 23: 7:00 a.m.-7:45 p.m.
- Monday, February 24: 7:30 a.m.-12:45 p.m.

Internet

Basic complimentary WiFi is available in the hotel public space and guest rooms, as well as in the meeting space.

Social Media

While we encourage your use of social media in and around AACR conferences, we remind you to adhere to the AACR’s social media guidelines and accepted social media etiquette. Please be aware of the following guidelines:

Do

- Follow us on Twitter @AACR and use the hashtag #AACRMV20 for this conference.
- Follow us on Facebook at facebook.com/aacr.org.
- Blog about the conference and what you are hearing and seeing (but without sharing details of any data presented: follow journal rules about data sharing).
- Converse with other attendees.
- Provide feedback to AACR staff and the program committee—discuss topics of interest and/or speakers for future conferences.
- Communicate with respect, being mindful of diversity and tolerant of differences you may encounter; keep criticism constructive and listen carefully to others to understand their perspectives.

Don’t

- Capture, transmit or redistribute data presented at the conference. This may preclude subsequent publication of the data in a scholarly journal—please do not jeopardize your colleagues’ work!
- Engage in rudeness or personal attacks.

Meeting Policies and Procedures

• Photography and Social Media Policies

  - Photography. Conference attendees may take photographs during oral or poster presentations provided that the photographs are strictly for personal, noncommercial use and are not to be published in any form. Attendees are prohibited from using flash photography or otherwise distracting the presenters or members of the audience.

  - Social Media. Conference attendees may share information from presentations on social media provided that they respect the wishes of presenters. Oral presenters may label any or all slides in their presentations with “DO NOT POST.” Similarly, poster presenters may label their posters with “DO NOT POST.” Attendees must respect the presenters’ requests in these instances and refrain from posting any images from these designated slides or posters on social media.

  - In accordance with the Resolution adopted at the 1968 Annual Meeting of the AACR, registrants must refrain from smoking in all meeting rooms. This regulation applies to all session rooms, including the poster area.

  - Children under 12 years of age are not permitted in any scientific session or poster session at any time. Children cannot be left unattended or unsupervised.

  - Cell phones, pagers, and other electronic devices must be turned off or placed on “silent” mode before entering a session.

  - Lost and Found: Attendees may contact the AACR Registration Desk for any lost items.

  - Poster presenters are solely responsible for placing their poster on the assigned poster board and removing their poster according to the schedule provided. The AACR cannot be responsible for any posters that are not removed at the designated time. Posters left in the Poster Hall after that time may be discarded.
• Poster presenters should not leave any items at their poster board unattended, including poster tubes, meeting bags, programs, personal items, etc. The AACR is not responsible for any items left in the Poster Hall.

AACR Membership

The AACR has more than 42,000 members in 120 countries and territories around the world. Over 30% of members live outside the United States and Canada, and 20% of the AACR’s international members are located in countries with emerging economies. The AACR is a dynamic and vibrant organization that offers its members programs and activities that promote the exchange of timely scientific information, and excellent opportunities to participate more fully in the global conquest of cancer by fostering important relationships and collaborations with cancer scientists internationally. Six categories of membership in the AACR are available to support each aspect of our members’ professional development and enhancement in cancer research. AACR is also eager to support the exchange of knowledge and research with investigators who are located in countries with emerging economies. Significantly reduced membership dues are available for these investigators. Join our mission and apply for AACR membership today!

Elimination of Annual Dues for Associate Members (Predoctoral Students and Postdoctoral and Clinical Fellows)

The AACR fully supports the education, training and professional development of early-career investigators. Graduate students, medical students, residents and postdoctoral and clinical fellows who are enrolled in education or training programs that could lead to a career in cancer research are no longer required to pay annual membership dues. Learn more and apply for Associate Membership today! To join the AACR, candidates may apply online at myaacr.aacr.org. Please contact membership@aacr.org if you have any questions.

Poster Sessions

Poster sessions will be held in the Florida Ballroom on the following schedule:

Session A
Saturday, February 22
12:45 p.m.-2:45 p.m.
Poster Set-up: After 10:30 a.m.

Session B
Sunday, February 23
5:45 p.m.-7:45 p.m.
Poster Set-up: After 12:30 p.m.

Receptions and Meals

Opening Reception: All registrants are invited to attend the Opening Reception on Friday, February 21, from 7:15 p.m.-9:15 p.m. Each registrant will receive one drink ticket that may be redeemed for beer, wine, or a nonalcoholic beverage. Conference badges are required.

Continental Breakfast: Continental breakfast will be served Saturday from 7:30 a.m.-8:30 a.m., Sunday from 7:00 a.m.-8:00 a.m., and Monday from 7:30 a.m.-8:30 a.m. in the Florida Ballroom. All attendees and registered guests are invited to attend. Please wear your conference badge.

Poster Sessions: Lunch will be served in the Florida Ballroom during Poster Session A on Saturday, February 22. Light refreshments will be served in the Florida Ballroom during Poster Session B on Sunday, February 23.

Coffee Breaks: All breaks will be held in Plaza D-F Foyer on the following schedule:

Saturday, February 22 10:30 a.m.-10:45 a.m.
Sunday, February 23 10:00 a.m.-10:15 a.m.
Monday, February 24 10:30 a.m.-10:45 a.m.
SUPPORTERS

The AACR would like to thank the following organizations for their generous support of this conference.

Professional Educational Grants

Pfizer
AWARDS

Scholar-in-Training Awards

Four presenters of meritorious abstracts have been selected to receive awards to attend this conference. All graduate and medical students, postdoctoral fellows, and physicians-in-training who are AACR Associate members and applied were eligible for consideration. The names of the Scholar-in-Training awardees, their affiliations, and the poster or proffered presentation numbers are provided below.

Scholar-in-Training Awards—Supported by the American Association for Cancer Research

**Vidhi Chandra**, The University of Texas MD Anderson Cancer Center, Houston, TX, B27, PR05

**Simone Dallari**, New York University School of Medicine, New York, NY, A13, PR03

**Caroline Um**, American Cancer Society, Atlanta, GA, B12

**Naisi Zhao**, Department of Public Health and Community Medicine, School of Medicine, Tufts University, Boston, MA, B07
CONTINUING MEDICAL EDUCATION (CME)

Accreditation Statement
The American Association for Cancer Research (AACR) is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education activities for physicians.

Credit Designation Statement
AACR has designated this live activity for a maximum of 18.25 AMA PRA Category 1 Credit(s)™. Physicians should only claim credit commensurate with the extent of their participation in the activity.

Credit certification for individual sessions may vary, dependent upon compliance with the ACCME Accreditation Criteria. The final number of credits may vary from the maximum number indicated above.

Claiming CME Credit
Physicians and other health care professionals seeking AMA PRA Category 1 Credit(s)™ for this live continuing medical education activity must complete the online CME Request for Credit Survey by Monday, April 6, 2020. Certificates will only be issued to those who complete the survey. The Request for Credit Survey will be available via a link on the AACR website at aacr.org/mb20cme and via email. Your CME certificate will be sent to you via email after the completion of the activity.

Successful completion of this CME activity, which includes participation in the evaluation component, enables the participant to earn up to 18.25 Medical Knowledge MOC points in the American Board of Internal Medicine’s (ABIM) Maintenance of Certification (MOC) program. Participants will earn MOC points equivalent to the amount of CME credits claimed for the activity. It is the CME activity provider’s responsibility to submit participant completion information to ACCME for the purpose of granting ABIM MOC credit.

To receive ABIM MOC, participants must request MOC in the CME Request for Credit Survey and complete all questions. Once these steps are completed, AACR will submit your completion information via the ACCME’s Program and Activity Reporting System for the purpose of granting MOC points.

Within the human body, the microbiota heavily influences daily health. The microbiota that inhabits the gastrointestinal tract, and other anatomic sites, is an environmental factor that we are continuously exposed to. Over the last several years, the complexity and diversity of gut microbiota within and between individuals has been exposed. The collective genome of the microbiota, referred to as the microbiome, encodes approximately 100-fold more genes than the human genome. Studies have shown the influence of the microbiota on immune cell function, tumorigenesis, and more. Sequencing studies have shown that the composition of microbial communities differs significantly between those who are healthy and those who are unhealthy and thus has a profound influence on disease progression and overall health. Within the development of cancer, the microbiota has been implicated in both cause and prevention.

The proposed special conference aims to illuminate various areas, including bacterial, viral, and fungal pathogens, and their contributions to the development of cancers. Moreover, the impact of the microbiome on cancers and cancer therapy will be discussed. The study of the microbiota and its effects on cancer has transformed how we examine therapies and relationships with the immune system. Tumor microenvironments, and the associated tumor microbiota, have also played a role in individualized immunotherapy, and the development of novel therapeutics. This conference will cover a wide range of topics including the role of the microbiota in metabolism and immunity, oncogenic viruses, and the microbiota in cancer prevention and therapy.

This activity would be most appropriate for physicians and health care workers who work and are interested in how the natural microbiota affects disease progression and treatment, especially those who focus on colon and gastrointestinal cancers.

After participating in this CME activity, physicians should be able to:

1. Analyze the identification of the impact of the microbiome on cancer development and treatment
2. Interpret the role of the microbiota in specific cancers (colon and gastrointestinal cancers)
3. Explain oncogenic viruses and the role the microbiota plays in development of cancers
4. Explain the conversation and evaluation of cancer prevention and therapy in the context of gut microbiota

**Disclosure Statement**

It is the policy of the AACR that the information presented at AACR CME activities will be unbiased and based on scientific evidence. To help participants make judgments about the presence of bias, AACR will provide information that Scientific Program Committee members and speakers have disclosed about financial relationships they have with commercial entities that produce or market products or services related to the content of this CME activity. This disclosure information will be made available in the Program/Proceedings of this conference.

**Acknowledgment of Financial or Other Support**

This activity is supported by a Professional Educational Grant from Pfizer. Any others will be disclosed at the activity.

**Questions about CME?**

Please contact the Office of CME at 215-440-9300 or cme@aacr.org.
UPCOMING SCIENTIFIC CONFERENCES

EACR-AACR Basic and Translational Research Conference: Tumor Microenvironment
In partnership with ASPIC (Portuguese Association for Cancer Research)
Scientific Committee Cochairs: Carlos M. Caldas, Luís Costa, and Lisa M. Coussens
March 2-4, 2020 | Lisbon, Portugal

The Evolving Landscape of Cancer Modeling
Conference Cochairs: Cory Abate-Shen, Andrea Califano, Jos Jonkers, and Calvin J. Kuo
March 2-5, 2020 | San Diego, CA

Evolving Dynamics in Carcinogenesis and Response to Therapy
Conference Cochairs: James DeGregori, Marco Gerlinger, Robert Gillies, and Andriy Marusyk
March 2-5, 2020 | Lisbon, Portugal

Advances in Prostate Cancer Research
Conference Cochairs: Felix Y. Feng, Karen E. Knudsen, and Scott A. Tomlins
March 2-5, 2020 | Lisbon, Portugal

NIH-AACR Cancer, Autoimmunity, and Immunology Conference
Organizing Committee: Julie R. Brahmer, Elad Sharon, Conrie Sommers, Howard Young, Ravi Madan, Katarzyna (Kasia) Bourcier, Marie Mancini, Annette Rothermel, and Lisa Spain
March 23-24, 2020 | Bethesda, MD

 AACR Annual Meeting 2020
Program Committee Chair: Antoni Ribas
April 24-29, 2020 | San Diego, CA

Seventh JCA-AACR Special Joint Conference on the Latest Advances in Pancreatic Cancer Research: From Basic Science to Therapeutics
Organizing Committee: Kohei Miyazono, Masanobu Oshima, Hiroshi Seno, Elizabeth M. Jaffee, Anirban Maitra, and Rosalie C. Sears
June 9-11, 2020 | Kyoto, Japan

Second AACR International Meeting: Advances in Malignant Lymphoma: Maximizing the Basic-Translational Interface for Clinical Application
In cooperation with the International Conference on Malignant Lymphoma (ICML)
Scientific Committee Chair: Ari M. Melnick
June 25-28, 2020 | Boston, MA

Tumor Heterogeneity: From Single Cells to Clinical Impact
Conference Cochairs: Alexander K. Shalek, and Charles Swanton
September 10-13, 2020 | Philadelphia, PA

CRI-CIMT-EATI-AACR Sixth International Cancer Immunotherapy Conference: Translating Science into Survival
Conference Cochairs: Özlem Türeci, E. John Wherry, and Jedd D. Wolchok
September 14-17, 2020 | New York, NY

Pancreatic Cancer
Conference Cochairs: Dafna Bar-Sagi, Elizabeth M. Jaffee, Ben Z. Stanger, and Brian M. Wolpin
September 29-October 2, 2020 | Philadelphia, PA

Myeloma and Plasma Cell Dyscrasias
Conference Cochairs: Kenneth C. Anderson and Irene Ghobrial
October 2-5, 2020 | Boston, MA

13th AACR Conference on the Science of Cancer Health Disparities in Racial/Ethnic Minorities and the Medically Underserved
Conference Chair: John D. Carpten
Conference Cochairs: Gerardo Colon-Otero, Marcia R. Cruz-Correa, Lisa A. Newman, and Steven R. Patierno
October 2-5, 2020 | Miami, FL

Advances in Breast Cancer Research
Conference Cochairs: Jason Carroll, Jenny C. Chang, and Jane E. Visvader
October 9-12, 2020 | San Diego, CA

Epigenetics and Metabolism
Conference Cochairs: Chi Van Dang, Kimberly Stegmaier, Craig B. Thompson, and Matthew G. Vander Heiden
October 15-18, 2020 | Baltimore, MD

Tumor Immunology and Immunotherapy
Conference Cochairs: Timothy A. Chan, Charles G. Drake, Marcela V. Maus, and Arlene H. Sharpe
October 16-19, 2020 | Boston, MA

Please visit AACR.org/meetingcalendar for additional conferences and program updates.
CONFERENCE PROGRAM

Friday, February 21

6:00 p.m.-7:15 p.m. WELCOME / OPENING KEYNOTE ADDRESS
Plaza D-F

Welcome
Cynthia L. Sears, Johns Hopkins University School of Medicine, Baltimore, MD

Molecular control of the gut microbiome to improve cancer chemotherapy
Matthew Redinbo, University of North Carolina School of Medicine, Chapel Hill, NC

7:15 p.m.-9:15 p.m. OPENING RECEPTION
Florida Ballroom

Saturday, February 22

7:30 a.m.-8:30 a.m. CONTINENTAL BREAKFAST
Florida Ballroom

8:30 a.m.-10:30 a.m. PLENARY SESSION 1: MICROBIOTA ROLE IN METABOLISM AND IMMUNITY
Plaza D-F

Session Chair: Giorgio Trinchieri, National Cancer Institute, Bethesda, MD

8:30 a.m.-9:00 a.m. Host microbiome interactions in health and disease
Eran Elinav, Weizmann Institute of Science, Rehovot, Israel

9:00 a.m.-9:30 a.m. Control over colorectal tumor growth via bacteria-specific T-cell activation of the local immune response
Timothy W. Hand, University of Pittsburgh, R.K. Mellon Institute for Pediatric Research, Pittsburgh, PA

9:30 a.m.-10:00 a.m. Title to be announced
Michael A. Fischbach, Stanford University, Stanford, CA

10:00 a.m.-10:30 a.m. Microbiota, metabolites, and antitumor immunity
Kathy McCoy, University of Calgary, Calgary, AB, Canada

10:30 a.m.-10:45 a.m. BREAK
Plaza D-F Foyer
CONFERENCE PROGRAM

10:45 a.m.-12:45 p.m.  PLENARY SESSION 2: MICROBIOTA AND COLON CANCER  
Plaza D-F

Session Chair: Jennifer A. Wargo, The University of Texas MD Anderson Cancer Center, Houston, TX

10:45 a.m.-11:15 a.m.  Colon cancer: Microbes and communities in microbiome translation  
Cynthia L. Sears, Johns Hopkins University School of Medicine, Baltimore, MD

11:15 a.m.-11:45 a.m.  The plasticity of the intestinal microbiota in colorectal cancer  
Christian Jobin, University of Florida, Gainesville, FL

11:45 a.m.-12:15 p.m.  Title to be announced  
Laurence Zitvogel, Gustave Roussy Cancer Center, Villejuif, France

12:15 p.m.-12:45 p.m.  Right-sided colonic biofilms are associated with adenoma formation in patients with Lynch syndrome*  
Carlijn Bruggeling, Radboudumc, Nijmegen, Gelderland, The Netherlands

12:45 p.m.-2:45 p.m.  POSTER SESSION A / LUNCH  
Florida Ballroom

3:00 p.m.-5:00 p.m.  PLENARY SESSION 3: ONCOGENIC VIRUSES—PART 1  
Plaza D-F

Session Chair: Cynthia L. Sears, Johns Hopkins University School of Medicine, Baltimore, MD

3:00 p.m.-3:30 p.m.  The particulars of circulars: Novel RNAs from oncogenic herpesviruses  
Yuan Chang, University of Pittsburgh Medical Center, Pittsburgh, PA

3:30 p.m.-4:00 p.m.  Epigenetic remodeling of host metabolic pathways by Epstein-Barr virus (EBV) immortalization  
Paul M. Liebermann, The Wistar Institute, Philadelphia, PA

4:00 p.m.-4:30 p.m.  Bladder cancers affecting transplant recipients harbor diverse viruses that associate with overall survival  
Christopher B. Buck, National Cancer Institute, Bethesda, MD

4:30 p.m.-4:45 p.m.  Functional characterization of the enteric animal virome as mediator of host health*  
Simone Dallari, New York University School of Medicine, New York, NY

4:45 p.m.-5:00 p.m.  Potential of metformin to modify the gut microbiota and prevent inflammation in nondiabetic people with HIV*  
Jean-Pierre Routy, McGill University Health Centre, Montreal, QC, Canada

*Short talk from proffered abstract

THE MICROBIOME, VIRUSES, AND CANCER
Sunday, February 23

7:00 a.m.-8:00 a.m.  CONTINENTAL BREAKFAST
Florida Ballroom

8:00 a.m.-10:00 a.m.  PLENARY SESSION 4: TUMOR-ASSOCIATED MICROBIOTA
Plaza D-F

Session Chair: Laurence Zitvogel, Gustave Roussy Cancer Center, Villejuif, France

8:00 a.m.-8:30 a.m.  
**Fusobacterium** persistence and antibiotic response in colorectal cancer
Susan Bullman, Dana-Farber Cancer Institute, Boston, MA

8:30 a.m.-9:00 a.m.  Regulation of pancreatic oncogenesis by pathogens
George Miller, New York University Langone’s Perlmutter Cancer Center, New York, NY

9:00 a.m.-9:30 a.m.  Characterizing the tumor microbiome and its effects on response to therapy
Ravid Straussman, Weizmann Institute of Science, Rehovot, Israel

9:30 a.m.-9:45 a.m.  Elucidating role of bacteria during pancreatic ductal adenocarcinoma (PDAC)*
Vidhi Chandra, The University of Texas MD Anderson Cancer Center, Houston, TX

9:45 a.m.-10:00 a.m.  
**Bacteroides fragilis**: A potential pathogen orchestrating EMT and stemness in breast epithelial cells via concomitant activation of Notch and β-catenin axes*
Dipali Sharma, Johns Hopkins University, Baltimore, MD

10:00 a.m.-10:15 a.m.  BREAK
Plaza D-F Foyer

10:15 a.m.-12:15 p.m.  PLENARY SESSION 5: ONCOGENIC VIRUSES—PART 2
Plaza D-F

Session Chair: Cynthia L. Sears, Johns Hopkins University School of Medicine, Baltimore, MD

10:15 a.m.-10:45 a.m.  
Role of human papillomaviruses in carcinogenesis
Massimo Tommasino, International Agency for Research on Cancer, Lyon, France

10:45 a.m.-11:15 a.m.  Prevention of hepatocellular carcinoma through preventative hepatitis C vaccination
Andrea Cox, Johns Hopkins University, Baltimore, MD

*Short talk from proffered abstract
CONFERENCE PROGRAM

11:15 a.m.-11:45 a.m. Interception of premalignant intraepithelial lesions: Lessons learned from HPV
Cornelia Liu Trimble, Johns Hopkins School of Medicine, Baltimore, MD

11:45 a.m.-12:00 p.m. Novel phages targeting the intratumor-associated bacteria Fusobacterium nucleatum*
Lior Zelcbuch, BiomX, Ness Ziona, Israel

12:30 p.m.-2:30 p.m. LUNCH ON OWN

2:30 p.m.-4:30 p.m. PLENARY SESSION 6: MICROBIOTA AND GASTROINTESTINAL CANCERS
Plaza D-F

Session Chair: Giorgio Trinchieri, National Cancer Institute, Bethesda, MD

2:30 p.m.-3:00 p.m. Title to be announced
Florencia McAllister, The University of Texas MD Anderson Cancer Center, Houston, TX

3:00 p.m.-3:30 p.m. Fungal infection and carcinogenesis
Yinling Hu, National Cancer Institute, Bethesda, MD

3:30 p.m.-4:00 p.m. Gut microbiota dysbiosis and dietary fermentable fibers in a pickle: A brew for liver cancer
Matam Vijay-Kumar, University of Toledo, Toledo, OH

4:00 p.m.- 4:30 p.m. Deciphering the human gut microbiome with chemistry
Emily Balskus, Harvard University, Cambridge, MA

4:30 p.m.-5:30 p.m. SECOND KEYNOTE ADDRESS
Plaza D-F

The role of the intestinal microbiome in allogeneic hematopoietic cell transplantation
Marcel R.M. van den Brink, Memorial Sloan Kettering Cancer Center, New York, NY

5:45 p.m.-7:45 p.m. POSTER SESSION B / RECEPTION
Florida Ballroom

*Short talk from proffered abstract
Monday, February 24

7:30 a.m.-8:30 a.m.  CONTINENTAL BREAKFAST
Florida Ballroom

8:30 a.m.-10:30 a.m.  PLENARY SESSION 7: MICROBIOTA IN CANCER PREVENTION AND THERAPY—PART 1
Plaza D-F

Session Chair: Cynthia L. Sears, Johns Hopkins University School of Medicine, Baltimore, MD

8:30 a.m.-9:00 a.m.  Noncanonical cross-presentation uncovers a tissue-resident CD8 T-cell response
Julie Magarian Blander, Weill Cornell Medical College, New York, NY

9:00 a.m.-9:30 a.m.  Engineered Salmonella for drug delivery to solid tumors
Neil Forbes, University of Massachusetts Amherst, Amherst, MA

9:30 a.m.-10:00 a.m.  Tumors alter gut microbiota to suppress immunity and foster progression
Andrea Facciabene, University of Pennsylvania, Perelman School of Medicine, Philadelphia, PA

10:00 a.m.-10:15 a.m.  Novel microbiome-derived peptides modulate immune cell activity and the tumor microenvironment*
Dhwani Haria, Second Genome, South San Francisco, CA

10:15 a.m.-10:30 a.m.  Postmenopause as a key factor in the composition of the Endometrial Cancer Microbiome (ECbiome): Putative role of Porphyromonas somerae in the disease*
Marina Walther-Antonio, Mayo Clinic, Rochester, MN

10:30 a.m.-10:45 a.m.  BREAK
Plaza D-F Foyer

10:45 a.m.-12:45 p.m.  PLENARY SESSION 8: MICROBIOTA IN CANCER PREVENTION AND THERAPY—PART 2
Plaza D-F

Session Chair: Bertrand Routy, Centre Hospitalier de l’Université de Montréal, Montréal, QC, Canada

10:45 a.m.-11:15 a.m.  The role of the tumor and gut microbiome in cancer
Jennifer Wargo, The University of Texas MD Anderson Cancer Center, Houston, TX

11:15 a.m.-11:45 a.m.  Linking the gut microbiome to cancer treatment response
Bertrand Routy

*Short talk from proffered abstract
CONFERENCE PROGRAM

11:45 a.m.-12:15 p.m.  Targeting the microbiome in cancer immunotherapy
Giorgio Trinchieri, National Cancer Institute, Bethesda, MD

12:15 p.m.-12:30 p.m.  Candida albicans infection mediates gastrointestinal track malignancy independently of Il17a in an APECED mouse model*
Feng Zhu, Laboratory of Cancer Immunometabolism, Center for Cancer Research, National Cancer Institute, NIH, Frederick, MD

12:30 p.m.-12:45 p.m.  Entero-mammary microbiota signaling axis regulates dietary influences on breast cancer risk*
Katherine Cook, Wake Forest University School of Medicine, Winston-Salem, NC

12:45 p.m.  CLOSING REMARKS
Plaza D-F

*Short talk from proffered abstract
**INVITED ABSTRACTS**

**IA01 Molecular control of the gut microbiome to improve cancer chemotherapy.** Matthew Redinbo. University of North Carolina at Chapel Hill, Chapel Hill, NC.

The diverse and complex communities of GI microbiota play important roles in human health, particularly with respect to cancer chemotherapy. We focused on systems where gut bacteria catalyze reactions that exert a profoundly negative impact on intestinal tissues and prove to be dose limiting for chemotherapy. The anticancer drug irinotecan is used to treat colon and pancreatic cancers and is eliminated as an inactivated drug-glucuronide by the phase II drug metabolism. Irinotecan’s dose-limiting toxicity is severe delayed diarrhea hypothesized to arise from the reactivation of the inactive irinotecan metabolite in the gut. We pinpointed the molecular basis of this reactivation to the beta-glucuronidase sugar-scavenging enzymes present in gut bacteria. We further developed potent, selective, and nonlethal inhibitors to bacterial beta-glucuronidase (GUS) enzymes and demonstrated that they prevented GI injury in mouse models of irinotecan-induced intestinal damage. Bacterial GUS inhibitors also prevent these sites of intestinal damage in mice treated with NSAIDs, which are glucuronidated and used to control cancer-related inflammation. We have since extended this work to the tyrosine kinase inhibitor regorafenib and to a probe-enabled activity-based proteomics pipeline to discover the enzymes driving the production of toxic metabolites. Together, our data demonstrate that enzyme targets in the GI microbiota can be inhibited to improve cancer care in a manner that can advance the promise of personalized medicine. Furthermore, our results shed significant light on the mammalian-microbial axes of chemical communication ongoing between two domains of life in the “higher-order” human superorganism.

**IA02 Host microbiome interactions in health and disease.** Eran Elinav. Weizmann Institute of Science, Rehovot, Israel.

The mammalian intestine contains trillions of microbes, a community that is dominated by members of the domain Bacteria but also includes members of Archaea, Eukarya, and viruses. The vast repertoire of this microbiome functions in ways that benefit the host. The mucosal immune system coevolves with the microbiota beginning at birth, acquiring the capacity to tolerate components of the community while maintaining the capacity to respond to invading pathogens. The gut microbiota is shaped and regulated by multiple factors including our genomic composition, the local intestinal niche, and multiple environmental factors including our nutritional repertoire and biogeographic location. Moreover, it has been recently highlighted that dysregulation of these genetic or environmental factors leads to aberrant host-microbiome interactions, ultimately predisposing to pathologies ranging from chronic inflammation, obesity, the metabolic syndrome, and even cancer. We have identified various possible mechanisms participating in the reciprocal regulation between the host and the intestinal microbial ecosystem and demonstrate that disruption of these factors, in mice and humans, lead to dysbiosis and susceptibility to common multifactorial disease. Understanding the molecular basis of host-microbiome interactions may lead to development of new microbiome-targeting treatments.

**IA03 Control over colorectal tumor growth via bacteria-specific T-cell activation of the local immune response.** Abigail Overacre-Delgoffe, Hannah Bumgarner, Tim Hand. University of Pittsburgh, Pittsburgh, PA.

Colorectal cancer (CRC) is a leading cause of cancer-related death and its incidence is on the rise, particularly in young people. Therapy for late-stage CRC is often ineffective, and colorectal tumors are most often detected at stage 3 or 4. Immunotherapy is revolutionizing the treatment of many types of cancer but is only effective for a very small subset of CRC patients. Thus, there is a tremendous need for improved therapies for CRC. Colorectal tumors grow from the intestinal epithelium and are therefore subject to interaction with the dense and diverse colonic microbiota. Indeed, CRC has been associated with shifts in the composition of the microbiota that affect inflammation and tumor growth. How the microbiota shapes the CRC immune microenvironment is not fully understood. In general, the microbiota can directly shape T-cell responses, directing the differentiation of CD4 T cells to develop into either regulatory (Treg) or effector (Th1, Th17, etc.) T cells. This is particularly true of those T cells local to the intestine that are often specific to antigens derived from intestinal bacteria. We became interested in how colonization with different bacterial taxa might affect the T-cell immune response and control over colorectal cancer. Using a mouse model of CRC, we show that colonization with a single bacterial taxon, after tumors have already developed, leads to a reduction in tumor burden and size. Bacteria-dependent tumor reduction depended upon CD4 T cells but not CD8 T cells as antibody depletion of CD4 T cells completely abrogated the effect. Accordingly, de novo bacterial colonization was associated with a
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colorectal tumor environment that possessed fewer Tregs, increased CD4 IFNγ-producing T cells, and increased CD103+ dendritic cells. We also observed that colonized mice develop increased numbers of organized tertiary lymphoid structures that were adjacent to colonic tumors. Importantly, bacteria-specific CD4 T cells were commonly found in these tertiary lymphoid structures, as were bacteria. Our hypothesis is that microbiota-driven and T cell-dependent development of TLS structures leads to enhanced tumor antigen presentation and augmented antitumor immune responses. This work has the potential to inform CRC therapies via the rational modification of the local microbiota to support TLS formation and antitumor immunity.

IA05 Microbiota, metabolites, and antitumor immunity. Kathy D. McCoy. University of Calgary, Calgary, AB, Canada.

The intestinal microbiome heavily influences development and regulation of the immune system. The microbiome, which includes bacteria, viruses, and fungi, can also influence the initiation, development, and progression of cancer, with modulation of the immune system as one of the key pathways involved. Gut bacteria have also been found to alter the efficacy of cancer therapies, including immune checkpoint blockade therapy. These immunotherapies utilize the therapeutic potential of the immune system and have revolutionized cancer treatment. Yet this promising new strategy is not effective in all individuals (or all cancers) and has shown poor efficacy in colorectal cancer. We therefore investigated whether the intestinal microbiota could play a role in modulating immunotherapy in mouse models of colorectal cancers. We have identified specific intestinal commensal bacteria and a bacterial metabolite that control the efficacy of immune checkpoint blockade in animal models of colorectal cancer. In this session I will discuss the cellular and molecular pathways involved in this novel microbiota-microbe-immune pathway and describe the potential of bacteria-checkpoint blockade cotherapies.

IA06 Colon cancer: Microbes and communities in microbiome translation. Cynthia L. Sears. Johns Hopkins University School of Medicine, Baltimore, MD.

Intensive efforts are under way to understand how the colon microbiome contributes to the pathogenesis of colorectal cancer (CRC) and to determine if and how the microbiome can be utilized in the prevention and/or therapy of CRC. Both single microbes and microbial communities are proposed as contributors to human CRC. Among single microbes, attention to date has focused on enterotoxigenic Bacteroides fragilis (ETBF), (pks+) Escherichia coli, and Fusobacterium spp., although other candidates are emerging. Among communities, one aspect has been the potential contribution of mucus-invasive, dense mucosal microbial communities termed biofilms to CRC disease pathogenesis. This talk will review select concepts within ETBF’s and biofilm contribution to colon carcinogenesis. While ETBF exposure is common, the risk of colon carcinogenesis in an individual is unknown but potentially influenced by colonization state, B. fragilis toxin isotype secreted by ETBF, colon site, and the underlying genomic state of the colonic epithelial cells. With respect to colon biofilms, about 50% of human sporadic colon cancer, particularly in the right colon, display polymicrobial biofilms with marked tumor infiltration with bacteria whereas ~15% of normal colonoscopy biopsies also reveal polymicrobial biofilms. These polymicrobial biofilms are typically composed of Bacteroidetes and Lachnospiraceae with a subset of tumors, but not biopsies, also displaying Fusobacterium. Further, samples from biofilm-positive human colon cancers induce assembly of biofilms in the distal germ-free mouse colon within a week following inoculation and are procarcinogenic (JCI 129:1699, 2019). One of the common hereditary human colon cancers (familial adenomatous polyposis; APC+/-) also displays biofilms but dominated by two bacteria, (pks+) E. coli and ETBF. A mouse model of (pks+) E. coli and ETBF cocolonization exhibited accelerated tumor formation and mortality when cocolonized with the cancer-inducing bacteria, potentially by fostering increased microbial adherence, IL-17, changes in gene expression, and enhanced colonic epithelial cell DNA damage (Science 2018;359:592-97). Current directions of translational research will be presented.


Gene-environment interaction plays a key role in disease susceptibility, including colorectal cancer. Microbiota, particularly the intestinal bacteriome, plays a central role in host physiology, and the composition and activity of this consortium of microorganisms is directly influenced by known cancer risk factors such as lifestyle, diet, and inflammation. Accumulating evidence points to a role of microbiota in carcinogenesis. The mechanism by which microbiota impacts on cancer
development is still unclear, but alteration in genomic stability (genetics and epigenetics) is considered a converging point. Inflammation represents a powerful condition by which microbial composition and biologic activities are altered. Using gnotobiotic technology, microbial genetic manipulation, genetically engineered mice (Apmin−/−; Il10−/−), and microbial genomics, we investigated the role of specific bacterial or consortium of bacteria in the development of colitis-associated colorectal cancer. In this lecture, I will provide evidence that specific microbial genotoxic activities originating from various strains such as *Escherichia coli* and *Campylobacter jejuni* promote development of CRC. For example, the presence of DNA-damaging toxins such as colibactin from adherent invasive *Escherichia coli* or cytolethal distending toxins (cdt) from *Campylobacter jejuni* is critical for development of colorectal cancer. I will address the relationship between inflammation and bacteria-induced carcinogenesis by studying the effect of neutralizing TNFα antibody, a biologic used to manage intestinal bowel disease, on microbial community activity. These studies represent the first step toward understanding mechanisms by which microbiota influences development of colorectal cancer, and shed light on how alteration of environmental factors modulates microbial carcinogenic potential.

**IA09 The particulars of circulars: Novel RNAs from oncogenic herpesviruses.** Yuan Chang. University of Pittsburgh Cancer Institute, Pittsburgh, PA.

Circular RNAs (circRNA) are formed by backsplicing of linear RNA. Due to their covalently joined cyclized nature, circ RNAs are resistant to exonucleases and therefore comparatively more stable than their linear counterparts. Kaposi sarcoma-associated herpesvirus (KSHV/HHV8) and Epstein-Barr virus (EBV/HHV4) have recently been found by RNA sequencing to generate circular RNAs (circRNAs) in infected tissues and cell lines. These molecules represent a novel class of viral RNA that may have a more sustained functional role than linear transcripts. Initial characterization shows that circRNAs are expressed in infection-associated diseases and can be regulated depending on virus life cycle—although the quantity, localization, cell type, and viral life cycle expression of individual circRNAs vary considerably. Some viral circRNAs are incorporated into viral particles for preformed delivery, suggesting a potential function in early infection.

**IA10 Epigenetic remodeling of host metabolic pathways by Epstein-Barr virus (EBV) immortalization.** Jason Lamontagne, Andreas Wiedmer, Paul M. Lieberman. The Wistar Institute, Philadelphia, PA.

Epstein-Barr virus (EBV) reprograms host metabolism and gene expression during B-cell immortalization through a highly orchestrated process. The regulatory mechanisms coordinating this reprogramming are not fully elucidated but reflect important events in viral oncogenesis. One clue to this coordinate regulation is provided by the viral-encoded tegument protein BNRF1 that functions in viral chromatin assembly during primary infection and shares extensive structural similarity to a purine biosynthetic enzyme FGARAT (also called PFAS). FGARAT shows strong evolutionary conservation from bacteria to human. Orthologues of BRNF1 are found in all gamma herpesviruses, including KSHV ORF75, and share the common function of disarming components of the PML-nuclear body (PML-NB) and its antiviral functions. We have previously shown that the BNRF1 interacts with the histone H3.3 chaperone DAXX and displaces its interaction with ATRX. ATRX is thought to target Daxx-H3.3 to GC-rich repetitive DNA to repress viral and host telomeric transcription. We found that the BNRF1-DAXX complex changes these functions to facilitate viral gene expression during primary infection, enabling the establishment of EBV latency. However, it is not yet known how the viral FGARAT homology is linked to cellular metabolism and purine biosynthesis. Using metabolomics mass spectrometry, we provide new data indicating that the metabolic pathways are among the most significantly perturbed by EBV during B-cell immortalization. Integrating gene expression (RNA-Seq), chromatin accessibility (ATAC-Seq), and EBV transcription factor binding (ChIP-Seq) we identified several cellular metabolic genes, including adenine deaminase (ADA) and arginosuccinate synthase (ASS1), as a direct target of EBV transcriptional regulation during EBV immortalization. We find that EBV nuclear antigen EBNA1 binds directly to the ADA transcriptional regulatory regions and induces epigenetic changes at this locus. Failure to activate ADA compromises B-cell immortalization. The relationship between BNRF1, EBNA1, and nucleotide metabolism during EBV immortalization will be discussed. These findings suggest that EBV captured a highly conserved purine biosynthetic enzyme to coordinate epigenetic reprogramming with nucleotide metabolism during EBV induced B-cell immortalization.
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IA11 Bladder cancers affecting transplant recipients harbor diverse viruses that associate with overall survival. Gabriel J. Starrett¹, Kelly Yu¹, David Petersen¹, Petra Lenz², Lars Dyrsjkot², Paul Meltzer¹, Eric Engels³, Christopher B. Bucik¹, ¹NCI, Bethesda, MD, ²Aarhus University, Aarhus, Denmark.

BK polyomavirus (BKPyV) is a ubiquitous virus that establishes a lifelong subclinical infection in the urinary tract. In transplant recipients, BKPyV can reactivate and cause kidney and bladder damage. Recent sequencing studies of tumors from transplant recipients have revealed that BKPyV sequences are present in approximately 25% of bladder tumors. This is dramatically higher than the <1% rate of BKPyV detection observed in muscle-invasive bladder cancers affecting the general population. Like cancer-causing human papillomaviruses (HPVs), BKPyV has been shown to upregulate the human cytosine deaminase APOBEC3B, which has emerged as the second most abundant source of point mutations in human cancers. Furthermore, the APOBEC3-associated mutation signature is the most abundant mutational signature in bladder cancer. To comprehensively assess the role of BKPyV and other viruses in bladder cancer from solid organ transplant recipients, we used a database linking US transplant and cancer registries to identify and collect 44 archived primary bladder tumors, 5 metastases, and 15 adjacent normal tissue specimens. Whole-genome and total RNA sequencing was performed on the samples. From these data, we detected BKPyV in 18% of primary tumors. In five cases, there is clear evidence of BKPyV integration into the host cell genome, and all cases show transcription of the viral tumor antigens. In a separate set of analyses, BKPyV transcription was detected in 3.7% of non-muscle-invasive early-stage bladder cancer cases affecting the general population. Our surveys also detected other viruses, including high- and low-risk HPVs, JC polyomavirus (JCPyV), and anelloviruses, at lower frequencies. Two primary-metastatic pairs maintained clonally integrated HPV or BKPyV and respective viral oncogene expression in the metastatic lesions. Nearly all tumors had dominant APOBEC3B signature mutations, and BKPyV-positive tumors expressed significantly more APOBEC3B compared to virus-negative tumors or normal tissues. Tumors from four kidney transplant patients showed high mutation burden consistent with exposure to aristolochic acid, a nephrotoxic carcinogen found in some herbal supplements. Clinical data indicate that BKPyV-positive tumors are predominantly high grade with invasive behavior. Strikingly, survival was significantly shorter for patients whose tumors harbored BKPyV or JCPyV (9.7 and 8.4 months, respectively) compared to patients with tumors harboring HPV or no detectable viruses (65.8 and 50.2 months, respectively). This study comprehensively characterizes the genomes and transcriptomes of tumors, revealing several distinct tumor etiologies that impact patient outcome.

IA12 Fusobacterium persistence and antibiotic response in colorectal cancer. Susan Bullman, Fred Hutchinson Cancer Research Center, Seattle, WA.

In colorectal cancer (CRC), malignant cells are surrounded by a complex microenvironment encompassing a range of nontransformed cells, but also a diverse collection of microorganisms. A growing body of evidence demonstrates the role of particular microorganisms in modulating inflammatory environments and promoting tumor growth and metastasis. Genomic analyses have consistently revealed an enrichment of the invasive bacterium Fusobacterium nucleatum in human colorectal tumors relative to noncancerous colorectal tissues. Exogenous F. nucleatum infection in animal and cellular models has also supported its cancer-promoting role. We demonstrate via microbiome analysis and microbial culture that Fusobacterium species and their co-occurring microbiota, including Bacteroides, Prevotella, and Selenomonas species, persist in liver metastasis of Fusobacterium-positive CRC. Many of the liver metastasis share the same dominant microbiome as the paired primary CRC tumors. Additionally, we have cultured Fusobacterium species from paired primary and metastatic tumors, and whole-genome sequencing analysis revealed that the same strains of Fusobacterium are present in the primary tumors and distant site metastasis, despite the tissue being resected months or even years apart. In situ hybridization analyses show that Fusobacterium is invasive in the primary tumors and distal metastasis and is associated with malignant cells. We demonstrate via microbiome analysis and microbial culture that Fusobacterium and its co-occurring microbiota also persist and remain viable in patient-derived xenografts of CRC for multiple generations in vivo. Antibiotic treatment of mice harboring these patient colon cancer xenografts led to a significant reduction in tumor Fusobacterium load, cancer cell proliferation, and overall tumor growth, suggesting that microbiome modulation could change the course of this disease. Ultimately, if a bacterial agent can directly or indirectly contribute to cancer initiation or progression, then these organisms are viable targets for cancer prevention and treatment.
IA13 Regulation of pancreatic oncogenesis by pathogens. George Miller. New York University Langone Health Perlmutter Cancer Center, New York, NY.

Pancreatic ductal adenocarcinoma (PDA) is a devastating disease in which the mortality rate approaches the incidence rate. PDA is characterized by immune suppression. Specifically, the PDA tumor microenvironment in the majority of patients and in animal models of disease is associated with a modest T-cell infiltrate, dominated by Th2- and Treg-polarized CD4+ T cells and a paucity of cytotoxic CD8+ T cells. We and others have shown that the tolerogenic T-cell environment in PDA is programmed by suppressive myeloid cell elements. M2-polarized tumor-associated macrophages (TAMs) promote the differentiation of immune-suppressive Th2 cells and Tregs. Further, myeloid-derived suppressor cells (MDSC) veto cytotoxic CD8+ T-cell responses. As a consequence of the resultant immune anergy, immunotherapy has not been efficacious in this disease. Underlying all this, we found that the suppressive myeloid cell programming in PDA is dictated by the distinctive PDA-associated microbiome, which promotes accumulation of MDSC and M2-polarized TAMs via the release of bacterial-derived motifs that ligate diverse pattern recognition receptors in myeloid cells, leading to tumor-promoting myeloid cell differentiation and inflammation, which leads to adaptive immune collapse. In parallel to our interest in the role of the bacterial microbiome in oncogenesis, we developed an interest in the role of the fungal mycobiome. As we became interested in characterizing immune-modulatory sterile ligands for C-type lectin receptors (CLRs), which are cousins to TLRs, we identified Galectin-9 as a binding partner for Dectin-1 and SAP130 as a binding partner for Mincle in the tumor microenvironment. While our identification of sterile ligands for CLRs in cancer is interesting, the “natural” ligands for CLRs are fungal wall carbohydrate polymers. As such, we postulated that fungi may modulate the intratumoral inflammation and influence oncogenesis. We found that human pancreatic tumors and mouse models of this cancer displayed an increase in fungi of about 3,000-fold compared to normal pancreatic tissue. The composition of the mycobiome of PDA tumors was distinct from that of the gut or normal pancreas. Specifically, the fungal community that infiltrated PDA tumors was markedly enriched for Malassezia spp. in both mice and humans. Ablation of the mycobiome was protective against tumor growth, whereas repopulation with a Malassezia species—but not other species—accelerated oncogenesis. We also discovered that ligation of the CLR mannose-binding lectin (MBL), which binds to glycans of the fungal wall to activate the complement cascade, was required for oncogenic progression, whereas deletion of MBL or C3 in the extratumoral compartment—and knockdown of C3aR in tumor cells—were both protective against tumor growth. Collectively, our work revealed that pathogenic fungi promote PDA by driving the complement cascade through the activation of MBL.

IA14 Characterizing the tumor microbiome and its effects on response to therapy. Ravid Straussman. Weizmann Institute of Science, Rehovot, Israel.

The presence of bacteria in human solid tumors has been documented for over 100 years. Still, it is only in recent years that a more thorough characterization of this low-biomass microbiome has been pursued. In my lecture, I will describe our efforts to characterize the type of bacteria present across multiple human solid tumors as well as their intratumor location. I will also describe our efforts to study the effect that intratumor bacteria may have on different tumor phenotypes in general and on response to therapy in particular.


Infectious agents represent a major group of risk factors for cancer development and contribute to about 15% of human cancers worldwide. Six viruses and one bacterium; i.e., human papillomavirus (HPV), hepatitis C virus (HCV), hepatitis B virus, human T-lymphotropic virus type I (HTLV-1), Epstein-Barr virus (EBV), Kaposi sarcoma-associated virus (KSHV), and Helicobacter pylori, have been clearly associated with human carcinogenesis. The mucosal high-risk (HR) HPV types are the etiologic factors of cervical cancers and subset of oropharyngeal cancers. In addition, ongoing studies concerning a subgroup of HPV types that infect the skin suggest their involvement, together with ultraviolet radiation (or solar exposure), in the development of nonmelanoma skin cancer (NMSC). Biologic studies have demonstrated that the products of two early genes from the HR HPV types, E6 and E7, play a key role in cancer development. Both viral oncoproteins are able to target several cellular pathways leading to the evasion of the immune surveillance and cellular transformation. These studies also substantially contributed to our understanding of key mechanisms involved in the normal life of the cell. In the last few years, we have
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performed additional studies on cutaneous and mucosal HPV types and have characterized novel oncogenic viral mechanisms involved in the evasion of the immune response and/or in cellular transformation. A few examples will be presented.

**IA16 Prevention of hepatocellular carcinoma through preventative hepatitis C vaccination.** Andrea L. Cox, Johns Hopkins University, Baltimore, MD.

In the United States, the incidence of hepatocellular carcinoma (HCC) has tripled and mortality rates have doubled since 1980. Between 2006 and 2015, HCC diagnoses increased by approximately 3% annually. Liver cancer is the fifth most common cause of cancer death in men and the seventh among women. Hepatitis C virus (HCV) infection is the primary risk factor for about one-third of cases of HCC in the US population. Hepatitis C virus (HCV) infection is a bloodborne disease with global distribution that affects almost 3% of the world’s population. Less than 20% of acute HCV infections cause acute viral hepatitis symptoms severe enough for the patient to seek medical care, and approximately 75% of all infections become persistent. Individuals with chronic HCV infection usually remain asymptomatic and undiagnosed for decades before chronic hepatitis leads to complications that can include severe fibrosis and cirrhosis, hepatic failure, or HCC. In studies of people with HCV, the risk for HCC increased as much as 3% per year after diagnosis of cirrhosis. Despite effective therapy, HCV remains the leading cause of liver failure requiring transplantation and HCC in many countries. Continuing advances in therapeutic regimens are promising for effecting cures of HCV and may reduce transmission. However, there remain challenges in HCV control. Identifying those with HCV infection is difficult because of its relative silence until end-stage disease develops. It is estimated that fewer than 5% of HCV-infected persons are diagnosed worldwide, and the proportion of patients who access and complete treatment remains low. Even when current HCV therapy is administered successfully, it does not provide immunity against subsequent infection. Intravenous drug users and other high-risk groups, such as health care providers, those living in endemic regions, and HIV-infected men who have sex with men, are at risk for new infections and will continue to be at increased risk of infection despite better regimens for HCV treatment. HCV transmission is likely to persist in areas with limited access to antiviral drugs and poor needle injection and blood product hygiene. These challenges, as well as the cost of therapy, make HCV therapy alone unlikely to block the spread of infection within the total human population and to eradicate HCV. In contrast, in Taiwan immunization of infants against hepatitis B virus (HBV) has substantially reduced HBV transmission and subsequently the risk of developing HCC as children and young adults. Therefore, development of a vaccine to prevent chronic HCV infection, if not to prevent infection altogether, remains a critical aspect of an HCV disease control platform. This talk will discuss the need for a vaccine, the evidence that a vaccine to prevent chronic infection is possible, and the vaccine strategies tested to date.

**IA19 Fungal infection and carcinogenesis.** Yinling Hu, Center for Cancer Research, National Cancer Institute, Frederick, MD.

Increased fungal infection has been reported in oral and esophageal squamous cell carcinomas (SCCs) derived from patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy, immunodeficient patients, and non-autoimmune patients, as well as patients with other cancer types after radiation and chemotherapy. Thus, it is important to understand the role of increased fungal infection in tumor development. Our lab used several animal models to demonstrate that increased oral infection or colonization with *Cladosporium cladosporioide* (one of the most common fungi indoor and outdoor) or *Candida albicans*, which is one of the human commensal yeasts and opportunistic pathogens, promoted SCCs in the oral-esophageal-forestomach organs as well as distal cutaneous carcinogenesis. We revealed the mechanism underlying the relationship of increased fungal colonization with inflammatory pathways, epithelial cell-oncogenic pathways, and bacteria during carcinogenesis. Those fungus-associated pathogenic phenotypes, inflammatory signaling, and epithelial oncogenic pathways observed in mice were also seen in human cancers. Based on these results in mice and human, we speculate that increased oral fungal colonization promotes human carcinogenesis.

**IA20 Gut microbiota dysbiosis and dietary fermentable fibers in a pickle: A brew for liver cancer.** Matam Vijay-Kumar, The University of Toledo, Toledo, OH.

Dietary soluble fibers are fermented by gut bacteria into short-chain fatty acids (SCFA), which are considered broadly health promoting. Accordingly, consumption of such fibers ameliorates metabolic syndrome in a subset (40%) of Toll-like receptor 5-deficient (TLR5KO) mice.
However, incorporating fermentable fiber inulin, but not nonfermentable fiber cellulose, into a compositionally defined purified diet induced hyperbilirubinemia and cholemia as primary clinical symptoms and hallmarks of cholestasis. These cholestatic mice eventually developed robust, multinodular hepatocellular carcinoma (HCC; a type of liver cancer) within 6 months. Inulin-induced HCC progressed via early onset of cholestasis, hepatocyte death, followed by liver inflammation primarily driven by neutrophils. Such neutrophilic inflammation is characterized by elevated levels of neutrophil elastase and myeloperoxidase, and hepatic reactive oxygen species, malondialdehyde and 8-hydroxy-2’-deoxyguanosine, a marker of DNA damage. Pathogenesis of such HCC was microbiota dependent and observed in multiple strains of dysbiotic mice, but not in germ-free or antibiotics-treated TLR5KO mice. Furthermore, inulin-enriched diet induced both dysbiosis and HCC in wild-type (WT) mice co-housed or cross-fostered with TLR5KO mice. Pharmacologic inhibition of fermentation or depletion of fermenting bacteria markedly reduced intestinal SCFA and prevented HCC. Intervening with cholestyramine to prevent enterohepatic recirculation of bile acids also conferred protection against such HCC. Thus, notwithstanding the health benefits of inulin, enrichment of foods with fermentable fiber should be approached with great caution as it may increase risk of HCC and warrants that refined fibers need to be redefined.

IA21 Deciphering the human gut microbiome with chemistry. Emily P. Balskus. Harvard University, Cambridge, MA.

The human body is colonized by trillions of microorganisms that exert a profound influence on human biology, in part by providing functional capabilities that extend beyond those of host cells. In particular, there is growing evidence linking chemical processes carried out by the human gut microbiome to diseases such as colorectal cancer. However, we still do not understand the vast majority of the molecular mechanisms underlying this phenomenon. Major obstacles faced in surmounting this knowledge gap include the difficulty in linking functions associated with the human gut microbiota to specific microbial enzymes and the challenge of controlling these activities in complex microbial communities. This talk will discuss my lab's efforts to characterize gut microbial metabolic activities that are linked to colorectal cancer, including a gut microbial genotoxin called colibactin. Gaining a molecular understanding of cancer-associated gut microbial activities will not only help to elucidate the mechanisms by which these organisms contribute to carcinogenesis but should also enable efforts to treat and prevent disease by manipulating this microbial community.

IA22 The role of the intestinal microbiome in allogeneic hematopoietic cell transplantation. Marcel van den Brink. Memorial Sloan Kettering Cancer Center, New York, NY.

Relationships between microbiota composition and clinical outcomes of patients following allogeneic hematopoietic cell transplantation (allo-HCT) have been described in single-center studies. Geographic variations in the composition of human microbial communities and differences in clinical practices across institutions raise the question of whether these associations are generalizable. Therefore, we studied 8,767 fecal samples from 1,362 allo-HCT patients at four centers on three continents by 16S ribosomal sequencing. In an observational study, we examined associations between microbiota diversity and overall survival during two years of follow-up after allo-HCT with proportional-hazards analysis. We observed reproducible patterns of microbiota disruption characterized by loss of diversity and domination by single taxa. Low diversity in the peri-neutrophil engraftment period was reproducibly associated with increased risk of death (multivariate-adjusted HR 0.48, 95% CI 0.30-0.77, p = 0.002 in the largest cohort). Subset analysis suggested that these reductions in overall survival were in part due to an increased risk of transplant-related mortality and graft-versus-host disease. Baseline pre-HCT samples already bore evidence of microbiome disruption, and low diversity prior to transplantation was associated with poor survival. In addition, we found that Enterococcus faecium dominates the intestinal microbiota of up to 65% allo-HCT patients early after transplant at all four transplant centers. Enterococcus domination was associated with an increased incidence of acute graft-versus-host disease (GVHD), increased GVHD-related mortality, and reduced overall survival. Post-transplant expansion of Enterococci was also observed in mouse models of GVHD in the absence of antibiotic treatment. Spiking a minimal flora with Enterococci in gnotobiotic mice exacerbated lethal GVHD. Metagenomic sequencing of human and murine Enterococci-dominated fecal samples revealed an enrichment of lactose and galactose degradation genes, a pathway necessary for Enterococcus growth in vitro. A lactose-free chow attenuated the intestinal outgrowth of Enterococcus and reduced the severity of lethal GVHD in mice. In patients, a lactose-nonabsorber genotype was associated with an increased Enterococcus abundance.
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after cessation of antibiotic treatment after allo-HCT. In conclusion, the concordance of microbiota disruption patterns and their associations with clinical outcomes suggest that approaches to manipulate the intestinal microbiota with the aim of improving allo-HCT clinical outcomes may be generalizable.

IA24 Engineered Salmonella for drug delivery to solid tumors. Neil S. Forbes, University of Massachusetts Amherst, Amherst, MA.

Engineered bacteria have the potential to overcome the limitations that cause cancer therapies to fail. We are engineering bacteria to deliver therapeutic payloads and quantifying the mechanisms that control bacterial therapy. We have shown that bacteria preferentially target tumors and actively penetrate tissue. Bacterial motility has a linear relationship with colonization density. Manipulating chemoreceptors in the membrane can direct bacteria to drug-resistant tumor regions, and inducing inflammation can promote colonization by modifying tumor vasculature. When engineered to express α-hemolysin from Staphylococcus aureus, bacteria kill 99% of culture cells in 5 minutes and reduce tumor volume in mice. Engineering Salmonella with quorum-sensing provides a density-dependent switch that induces protein expression only after bacteria have colonized tumor tissue. This technique prevents system toxicity after delivery of therapeutic molecules. We have also developed bacteria that selectively invade cancer cells and release molecules that modulate epigenetic targets, e.g., EZH2 and PP1. Salmonella were engineered with a genetic cassette that induces lysis specifically after invasion into mammalian cells. Lysis releases the bacterial content into the cytoplasm of cells. In culture, Salmonella lyse inside cancer cells and release GFP, which diffuses throughout the cellular cytoplasm. Releasing a peptide that interferes with the binding of the phosphatase, PP1, with its regulator, NIPP1, induces cell death after bacterial lysis. In three-dimensional tissue culture, administration of these bacteria induces cell death. These techniques establish Salmonella as a tunable platform for cancer therapy. By understanding the mechanisms of bacterial delivery, new strategies will be developed to treat hard-to-treat cancers.


Immune dysfunction is commonly observed in patients with cancer contributing to tumor progression. While previous work established a connection between the gut microbiota and the immune system, the mechanisms by which microbiotas contribute to cancer-associated immune dysfunction are not well understood. Using multiple mouse cancer models, we demonstrated robust alterations of gut microbiota in tumor-bearing mice and a substantial change in antimicrobial peptides produced by the gut epithelium. We identified an overall reduction in IFN-γ T cells in tumor-bearing mice, which was rescued with antibiotics treatment or by co-housing tumor-bearing mice with healthy mice. Similar to mouse, we observed changes in gut microbiota and antimicrobial peptides levels of patients diagnosed with ovarian or lung cancer. We identify Firmicutes Ruminococcus members as key promoters of immune dysfunctions and tumor development. These findings identify a new mechanism of immune modulation utilized by tumors to undermine the immune responses and promote tumor progression.

IA28 Targeting the microbiome in cancer immunotherapy. Giorgio Trinchieri, National Cancer Institute, Bethesda, MD.

Commensal microorganisms colonize barrier surfaces of all multicellular organisms, including those of humans. For more than 500 million years commensal microorganisms and their hosts have coevolved and adapted to each other. As a result, the commensal microbiota affects many immune and nonimmune functions of their hosts, and de facto the two together comprise one metaorganism. The commensal microbiota communicates with the host via biologically active molecules. Recently, it has been reported that microbial imbalance may play a critical role in the development of multiple diseases, such as cancer, autoimmune conditions, and increased susceptibility to infection. The commensal microbiota not only may affect the development, progression, and immune evasion of cancer but has also important effects on the response to cancer immuno- and chemotherapy. In my presentation I will discuss some recent analysis of the role of the microbiome in anti-PD1 therapy in melanoma patients, the preliminary data of a fecal microbiota transfer clinical trial (performed at the University of Pittsburgh Cancer Center) in anti-PD1 refractory melanoma patients, as well as mouse data on the effect of dietary fibers on anti-PD1 cancer therapy.
PROFFERED ABSTRACTS

**PR01 Right-sided colonic biofilms are associated with adenoma formation in patients with Lynch syndrome.** Carlijn Bruggeling1, Vera Witjes1, Daniel Garza1, Milou Fransen1, Joyce Krekels1, Tanya Bisseling1, Mariette van Kouwen1, Nicoline Hoogerbrugge1, Sebastian Lücker2, Bas Dutilh1, Iris Nagtegaal1, Annemarie Boleij1, 1Radboudumc, Nijmegen, The Netherlands, 2Radboud University, Nijmegen, The Netherlands.

Colonic bacterial biofilms are an emerging manifestation in colorectal cancer (CRC); they exhibit carcinogenic properties and are frequently present on right-sided cancerous lesions. Whether bacterial biofilms propose a risk factor for early carcinogenesis in humans is yet unresolved. Therefore, we studied bacterial biofilms in tandem with adenoma formation in patients with Lynch syndrome (LS). LS patients carry a pathogenic germline variant in one of the DNA mismatch repair (MMR) genes, resulting in a variable predisposition to develop colorectal cancerous lesions. A total of 100 LS patients were included in our study, consisting of 23 MLH1, 24 MSH2, 36 MSH6, and 17 PMS2 MMR variants. During regular screening colonoscopies, normal-appearing forceps biopsies were taken from colon ascendens (right colon) and descendens (left colon). Biopsies were screened for bacterial biofilms using fluorescent in situ hybridization by targeting bacterial 16s rRNA. The frequency of colorectal adenomas (tubular adenomas and [tubulo] villous adenomas) before and during colonoscopy was registered. Overall, 60% of patients presented with a biofilm, of which most were right-sided (right-sided: 25%, both sides: 21%, left-sided: 14%). Interestingly, adenomas were more frequently present in patients with a right-sided biofilm (right-sided: 64%, both sides: 58%) than in patients with a left-sided biofilm (29%) or no biofilm (38%). The occurrence of bacterial biofilms was not correlated with age, BMI, or MMR-variant. Statistical analysis revealed that right-sided bacterial biofilms correlated with right-sided adenomas (Pearson: 0.272, p=0.007) and left-sided adenomas (Pearson: 0.227, p=0.026), while left-sided biofilms were not correlated with left- or right-sided adenomas (Pearson: 0.037, p=0.718 and -0.127, p=.213). To model the probability of right-sided adenoma formation, we performed a binary logistic regression analysis and found that age (odds ratio: 1.065 [CI: 1.024; 1.108, p=0.002]) and right-sided biofilms (odds ratio: 3.020 [CI: 1.151; 7.926, p=0.025]) significantly contributed. Our data suggest that right-sided bacterial biofilms are a hallmark for high-risk LS patients and may play a role in early carcinogenesis.

**This abstract is also being presented as Poster A06.**

**PR02 A mutational signature in human colorectal cancer induced by genotoxic pks+ E. coli.** Jens Puschhof1, Cayetano Pleguezuelos-Manzano1, Axel Rosendahl Huber2, Ruben van Bostel2, Hans Clevers1, 1Hubrecht Institute, Utrecht, The Netherlands, 2Princess Maxima Center, Utrecht, The Netherlands.

Various species of intestinal microbiota have been associated with the development of colorectal cancer (CRC), yet a direct role of bacteria in the occurrence of oncogenic mutations has not been established. *Escherichia coli* can carry the pathogenicity island *pks* within their genomes, which encodes a set of enzymes that synthesize colibactin. This compound can alkylate nascent DNA on adenine residues, and it has been shown to induce double-strand breaks in cultured cells. We hypothesized that *pks+ E. coli* are carcinogenic through the mutagenic action of colibactin. To test this, we exposed human intestinal organoids for 5 months to genotoxic *pks+ E. coli* by repeated luminal injection. Whole-genome sequencing (WGS) of clonal organoids before and after exposure revealed a distinct and reproducible mutational signature, which was completely absent in organoids that were injected with isogenic *pks*-deficient bacteria. This signature encompasses a single base substitution trinucleotide signature (SBS-*pks*) with a marked transcriptional strand bias in line with damage on adenine residues, which was accompanied by a specific indel signature (ID-*pks*). Moreover, a distinct preference for the wider sequence context was detected, fitting a structural model of colibactin bound to DNA. This mutational signature was detected in three cohorts containing more than 6,000 human cancer genomes, and contribution of this signature could be detected in a subset of CRC genomes and more rarely in other cancer types. Finally, we identified driver genes harboring the colibactin target motif and could attribute driver mutations from CRC genomes to the signature. Our study describes a highly specific mutational cancer signature that reflects mutagenic activity of *pks+ bacteria* in the intestinal lumen, which can induce oncogenic mutations and could contribute to cancer initiation.

*This abstract is also being presented as Poster A02.*
The enteric virome includes viruses that infect eukaryotic cells in the gut and is one constituent of the mammalian microbiome. Although best known for causing acute diarrheal disease, many of these viruses cause subclinical infections, and indeed are often detected in asymptomatic individuals. The consequences of harboring these viruses are unclear. We recently demonstrated that norovirus mono-colonization promotes the development of the intestinal architecture and the mucosal immune system of germ-free mice in a manner similar to symbiotic bacteria and can protect against models of chemical and microbial injury. It is unclear whether this symbiotic virus-host relationship is a unique feature of murine norovirus strain CR6 colonization. Here, we examined the extent to which members of the eukaryotic enteric virome contribute to the state of the host health. Examination of 10 enteric DNA and RNA viruses representing 6 viral families capable of spreading through the fecal-oral route revealed that many establish a prolonged infection, which often is not limited to the intestinal tissues, in the absence of visible disease after oral inoculation. Further histologic analysis of the small intestinal and colonic tissues confirmed no pathogenic effects on the intestinal tissues. To evaluate the direct impact of asymptomatic viral infections independently from the bacterial microbiome, we performed RNA-seq on intestinal tissues and a comprehensive flow cytometry analysis of intestinal and extraintestinal organs, assessing over 20 immune cell subsets and their cytokine production capacity, following viral mono-colonization of germ-free mice. We found profound effects exerted by the enteric viruses on the immune system in all the tissues tested. In addition to confirming anticipated consequences of viral infection such as expansions of Th1 cells and effector memory T cells, we identified novel virus-specific responses, such as norovirus-induced expansion of type 1 regulatory T cells and parvovirus-mediated induction of regulatory T cells. Interestingly, intestinal T cells and innate lymphoid cells from almost all the virome-colonized mice were more predisposed towards the production of proinflammatory Th1 cytokines, such as IFNγ, and of IL22. An increase in the IL22 signature was also detected in the intestinal transcriptome of virome-colonized mice, suggesting that the virome members support the production of this cytokine already at the steady-state level. Of note, only a few viruses were inducing a type I interferon signature in the tissues, suggesting that pathways other than type I interferon mediate the virome effects on the host. Taken together, these data demonstrate that multiple members of the enteric virome can contribute to the development and function of the mucosal immune system.

This abstract is also being presented as Poster A13.

PR04 Potential of metformin to modify the gut microbiota and prevent inflammation in nondiabetic people with HIV. Stéphane Isnard, John Lin, Brandon Frombuena, Thibaut V. Varin, André Marette, Delphine Planas, Meriem Messaoudene, Bertrand Routy, Claude Van Der Ley, Ido Kema, Petronela Ancuta, Jonathan Angel, Jean-Pierre Routy, 1McGill University Health Centre, Montreal, QC, Canada, 2Laval University, Quebec, QC, Canada, 3Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada, 4University of Groningen, Groningen, The Netherlands, 5The Ottawa Hospital, Ottawa, ON, Canada.

Background: Persisting inflammation is associated with increased risk of comorbidities and cancer development in people living with HIV (PLWH) under antiretroviral therapy (ART). Indeed, our observations show that a low CD4/CD8 ratio is predictive of the number of polyps in the colon in those people. Mechanistically, we and other have shown that coinfection with viruses such as cytomegalovirus and gut damage inducing microbial translocation induce inflammation in ART-treated PLWH. Metformin, an antidiabetic drug with antiaging effect, was shown to decrease inflammation by improving glucose metabolism and changing gut microbiota composition in diabetic people and in nondiabetic women with polycystic ovary syndrome. In healthy men, metformin was also associated with modification of the gut microbiota. In PLWH, the gut microbiota is different than the general population, and its composition was associated with inflammatory profiles. Herein, we report results from the LILAC (CIHR/CTN PT027) pilot clinical trial evaluating the effect of 12 weeks of metformin on blood/gut inflammation and gut microbiota composition in nondiabetic PLWH on ART.

Methods: A total of 22 nondiabetic (HbA1c <6%) PLWH, on ART with undetectable viral load for more than 3 years and CD4/CD8 ratio ≤0.7, received 12 weeks of metformin 850 mg bid. Blood and stools were collected at baseline (V1), after 12 weeks of metformin (V2), and 12 weeks after metformin discontinuation (V3). Soluble CD14 was measured in plasma. DNA was extracted from stools and 16S rRNA sequenced. Bacterial microbiota composition variations were analyzed using LefSe. Serum short chain fatty acids (SCFA) were measured by
LC-MS. The beneficial *Akkermansia muciniphila*, enriched in stools of diabetic people initiating metformin, was quantified by qPCR.

**Results:** CD4 T-cell count, CD4/CD8, and HbA1c levels did not vary between visits; however, plasma sCD14 levels decreased at V2 and V3 compared to V1. Bacterial alpha diversity tended to increase at V2 and V3. However, we observed a significant increase of *Escherichia/Shigella* and *Lachnoclostridium* and a decrease of *Collinsella* abundances at V2 compared to V1. *A. muciniphila* abundance was increased at V2. Abundance of *Lachnospiraceae*, specialized in butyrate production, was increased at V3 compared to V1. Accordingly, we found increased serum butyrate/isobutyrate levels at V2 and V3 compared to V1. No differences were observed for other SCFA propionate, succinate, and methylmalonate.

**Conclusion:** A 12-week metformin therapy in nondiabetic PLWH on ART was safe and decreased plasma levels of the inflammatory marker sCD14 in association with an enrichment of butyrate-producing bacteria in stools and increased serum butyrate levels. As microbiota composition was associated with response to cancer therapy (especially immunotherapy), metformin use should be tested before immunotherapy.

*This abstract is also being presented as Poster A15.*

**PR05 Elucidating role of bacteria during pancreatic ductal adenocarcinoma (PDAC).** Vidhi Chandra1, Olivia Le Roux1, Erick Riquelme1, Yu Zhang2, Anirban Maity1, James R White2, Florencia McAllister1. 1The University of Texas MD Anderson Cancer Center, Houston, TX, 2Resphera Biosciences, Baltimore, MD.

Long-term survival in pancreatic cancer (PC) is rare as only a minority of all resected patients survive for >5 years. Interestingly, somatic mutations do not predict long-term survivorship, highlighting the potential role of extrinsic factors. Recent studies have reported the role of the gut and tumor microbiome in pancreatic tumorigenesis and PC treatment responses. Since intratumoral bacteria have been detected in human PC tumors, possibly arising from relocation of intestinal bacteria, it is possible that intratumoral T cells get primed with microbial antigens within the tumor microenvironment. To reconstruct bacterial phylogenies, we performed prokaryotic 16S ribosomal RNA sequencing and immunoprofiling of PC tumors from “Long-Term Survivors-LTS” (>5y post-resection) and “Short-Term Survivors-STS” (<5y post-resection).

Strikingly, we found that LTS from both discovery and validation cohorts had higher microbial diversity and LTS from both cohorts were enriched for a tumor microbial signature: *Pseudoxanthomonas, Streptomyces, Saccharopolyspora*, and *Bacillus clausii*. Moreover, the most overrepresented species in LTS tumors strongly correlated with enhanced immunoregulation of the tumor microenvironment, suggestive of bacterial-mediated immune cell recruitment and activation. Based on these findings, we hypothesized that gut bacteria affect PC by triggering immune responses either locally by migrating to the tumor or systemically through responses originating in the gut. To test this, we performed in vitro studies and found that single bacterial species identified from LTS tumor microbial signature can induce activation of cytotoxic T lymphocytes (CD8+ CD69+ IFNγ+) only when in direct contact with antigen-presenting cells, suggesting that bacterial antigens need to be processed and presented to intratumoral T cells to induce their activation. Furthermore, through preliminary in vivo studies, we have found that orally administered single bacterial species can be delivered to the pancreas via the gut. Further work needs to determine whether single/specific LTS bacteria play a causative role in regulating tumor immunity in vivo. If the beneficial modulatory role of specific bacteria is established, then bacteriotherapy as single therapy or in combination with fecal microbial transplants could be used as innovative strategies for treatment of pancreatic cancer.

*This abstract is also being presented as Poster B27.*

**PR06 Bacteroides fragilis: A potential pathogen orchestrating EMT and stemness in breast epithelial cells via concomitant activation of Notch and βcatenin axes.** Sheetal Parida, Shaoguang Wu, Nethaji Muniraj, Sumit Siddharth, Arumugam Nagaligam, Christina Hum, Panagiota Mitrrioti, Konstantinos Konstantopoulos, Cynthia Sears, Dipali Sharma. Johns Hopkins University, Baltimore, MD.

**Background:** The last decade established significant contributions of microbiome to many organ-specific cancers. A few recent studies suggested the existence of distinct breast microbiota and a shift in microbial community composition in diseased breast compared to normal breast; however, their functional impact and underlying mechanisms are unknown. The present study was designed to examine the contribution of procarcinogenic bacteria in breast cancer initiation, growth, and progression.
The Microbiome, Viruses, and Cancer

Introduction: Recent studies demonstrate that bacterial species are present within the tumor microenvironment (Geller et al., 2017). The presence of *F. nucleatum* in tumors has been described to increase cancer cell proliferation, promote chemoresistance, and protect tumors against immune cell attack (Zhang et al., 2018). A higher abundance and prevalence of *F. nucleatum* has been associated with advanced tumor stage and poor prognosis in human colorectal carcinoma patients (Mima et al., 2016; Yan et al., 2017). Bacteriophages (“phages”) are viruses that specifically infect bacteria and play a critical role in regulating bacterial populations. Phages can be engineered to deliver therapeutic payloads (Schmidt, 2019). Reduction of intratumor *F. nucleatum* and targeted delivery of anticancer payloads to tumors using phages may offer novel approaches for localized cancer treatment. To date there are only a few reports identifying phages that target *F. nucleatum* (Zheng et al., 2019). Using an initially isolated phage, we have shown that these phages, administered intravenously, can reach tumor-associated *F. nucleatum* in vivo (Kahan-Hanum et al., 2019). The aim of the current study was to discover novel *F. nucleatum*-infesting phages that may serve to decrease intratumor *F. nucleatum* burden and/or deliver a localized payload for anticancer treatment.

Methods: For phage isolation, human saliva samples were screened on lawns of *F. nucleatum* strains, and natural phages were isolated from plaques. Phage sequences were analyzed following sequencing in Illumina using Nextera kits and genome assembly using SPAdes genome assembler. To characterize infectivity, double layer plaque assays on different hosts were carried out. Phage editing was carried out by new molecular tools for *F. nucleatum* that were developed internally.

Results: Twelve novel phages were discovered, including phages against all 4 subspecies of *F. nucleatum*: *animals* (n=2), *vincentii* (n=7), *polymorphum* (n=2), and *nucleatum* (n=1). Sequence analysis revealed that the phages differ greatly from one another and possess many unique features. Both temperate (lysogenic, n=4) and lytic (n=8) phages were isolated as determined by the presence of integrases required for lysogenic integration. Of the eight lytic phages, six share very little similarity with known phages or with each other.

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**PROFFERED ABSTRACTS**

**Abstract:**

*PRO07 Novel phages targeting the intratumor-associated bacteria Fusobacterium nucleatum*.


**Results:** Utilizing extensive data mining and metagenomic analyses, we discovered the presence of toxin-producing *Bacteroides fragilis* (*B. fragilis*) in malignant breast. *B. fragilis* is a procarcinogenic bacteria known for its potential to initiate and/or promote colon cancer, and its pathogenicity has been attributed to its unique toxin “Fragilysin“ or “*B. fragilis* toxin (BFT).” Mice infected with *B. fragilis* exhibited a significant increase in circulating BFT and distinct morphologic alterations in mammary gland. While no changes were observed in cell growth and clonogenicity upon BFT treatment, significant increase in migration and invasion potential and decreased adhesion of MCF10A and MCF7 cells were observed. BFT-treated cells displayed acquisition of fibroblast-like appearance and increased formation of pseudopodia/microtentacles emanating from the cell membrane along with molecular markers of epithelial-to-mesenchymal transition. Decreased expression of epithelial marker E-cadherin along with elevated levels of mesenchymal markers, N-cadherin, and vimentin were observed. BFT also increased the expression and nuclear translocation of EMT-related transcription factors, Snail, Slug, and Twist. BFT-treated cells attained stem cell-like phenotype exhibiting an increased ability to form secondary and tertiary mammospheres and elevated expression of pluripotency-factors (Oct4, Nanog, and Sox2). Mechanic studies showed that BFT induced expression and nuclear translocation of NICD (cleaved NOTCH) and β-catenin, resulting in activation of downstream targets. Inhibition of Notch1 and β-catenin using γ-secretase inhibitor and ICG001 successfully inhibited functional effects of BFT. Further, we found that BFT-pretreated MCF7 cells exhibit increased tumor growth and form multifocal tumors in mice. MCF10A-KRas cells, pretreated with BFT, also showed increased tumor progression and multifocal tumors in mice. In vivo limiting dilution assay using breast tumors from BFT-pretreated MCF7 cells exhibited a striking increase in tumor-initiating cells. Follow-up analyses of these tumors demonstrated increased migratory, invasive, and mammmospheres-forming behavior, confirming that brief BFT exposure elicits long-term molecular changes.

**Conclusion:** Collectively, these findings present the first in vitro and in vivo evidence to show that *Bacteroides fragilis* toxin induces EMT, invasion/migration, and stem cell-like phenotype and leads to concomitant activation of Notch and β-catenin axes.

*This abstract is also being presented as Poster A24.*
Moreover, two of the lytic phages are double-stranded lytic RNA phages, of which only eight have previously been reported. Editing of *F. nucleatum*-targeting phage by synthetic biology tools to introduce new sequences has already been carried out.

**Conclusions:** The newly discovered unique phages against *F. nucleatum* offer the first step in development of a novel therapy targeting intratumor bacteria. Reduction of intratumoral *F. nucleatum* bacterial burden and/or delivery of anticancer or immune-stimulating payloads to colonic tumors associated with *F. nucleatum* may offer novel treatment approaches for patients with colorectal cancer.

*This abstract is also being presented as Poster B20.*

**PR08 Novel microbiome-derived peptides modulate immune cell activity and the tumor microenvironment.** Dhwani D. Haria, Jayamary Divya Ravichandar, Lynn Yamamoto, Bernat Baeza-Raja

The gut microbiota has emerged as an important player in cancer pathology, and increasing evidence supports its role in clinical response to immune checkpoint inhibitor (ICI) therapy. However, the specific microbiome-derived factors responsible for the improved response to ICI therapy remain unknown. Second Genome has developed a unique discovery platform to identify, screen, and validate microbiome-derived peptides that promote response to cancer immunotherapy. Using our multitechnology meta-analysis of published datasets and characterizing the baseline microbiome of melanoma patients treated with anti-PD-1, we have identified gut microbiome strains differentially abundant in responders versus nonresponders that are concordant across multiple cohorts. Next, peptides from strains associated with responder signatures were predicted from their genome sequences. In addition, we predicted peptides from assembled metagenomes that were associated with responders. The predicted peptides were screened using phage display technology to identify binders to immune cells known to play a role in the tumor microenvironment (TME). Peptides that bound to specific immune cells were then evaluated for activity in cell-based assays using isolated primary human T cells, dendritic cells (DCs), and macrophages. We have demonstrated that several microbiome-derived peptides induce secretion of proinflammatory cytokines and chemokines such as CXCL10 and TNF-α by primary human monocyte-derived dendritic cells (moDCs), as well as secretion of effector cytokines such as IFNγ and IL-2 by primary human T cells. We have also identified microbiome-derived peptides with the capacity to inhibit an M2-like phenotype in macrophages (decreased LPS-induced IL-10 secretion). These effects were dose dependent and evident across immune cells derived from multiple human blood donors. In a coculture assay using allogeneic moDCs and T cells from human donors, combination of our DC-activating peptides with CD40 agonistic antibody and/or anti-PD-L1 induced secretion of proinflammatory cytokines such as IFNγ and TNF-α. In vivo, peritumoral administration of a candidate DC-activating peptide into RENCA tumor-bearing mice led to a significant reduction in tumor volume as compared to the control-treated mice. Collectively, these data demonstrate the potential of the microbiome-derived peptides identified by Second Genome’s discovery platform to modulate immune-cell effector functions in vitro and promote antitumor immunity in vivo. These results validate the unique approach of Second Genome’s discovery platform to identify novel microbiome-derived agents with potential for use as therapeutics in cancer immunotherapy.

*This abstract is also being presented as Poster B19.*

**PR09 Postmenopause as a key factor in the composition of the Endometrial Cancer Microbiome (ECbiome): Putative role of *Porphyromonas somerae* in the disease.** Marina Walther-Antonio, Dana Walsh, Alexis Hokenstad, Jun Chen, Jayeun Sung, Gregory Jenkins, Nicholas Chia, Heidi Nelson, Andrea Mariani. Mayo Clinic, Rochester, MN.

Incidence rates for endometrial cancer (EC) are rising, particularly in postmenopausal and obese women. Our previous work has showed that the uterine and vaginal microbiome distinguishes patients with EC from those without. We now examine the impact of patient factors (such as menopause status, body mass index, and vaginal pH) in the microbiome in the absence of EC and how these might contribute to the microbiome signature in EC. We find that each factor independently alters the microbiome and identified postmenopausal status as the main driver of a polymicrobial network associated with EC (ECbiome). Of the 17 taxa we found enriched in EC patients, 8 were also enriched by postmenopause. Because postmenopausal status is a main risk factor
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for endometrial cancer, this system can be thought of as an ecological succession towards a disease state. Organisms within the ECbiome have been previously identified as polymicrobial associations in chronic soft tissue infections, ulcers, morbid obesity, and bacterial vaginosis. This suggests that this microbiome network is likely involved in mechanisms of host disease. Within the ECbiome, *Porphyromonas somerae* stands out because of its very significant and specific association with EC (p = 5.73E-6; Q = 0.009). We had previously identified this species as significantly associated with EC, and hereby validate that finding. Because the association of *P. somerae* with EC was robust and specific enough to potentially be considered as a biomarker for the disease (AUC 76.7%, CI: 67.9-85.5%), we developed a *P. somerae*-specific qPCR assay to detect this species in vaginal swabs. This becomes of particular interest because the lower tract and uterine microbiome are significantly correlated in these patients (p = 0.01), indicating that the vaginal microbiome can be used as a proxy for the uterine environment in EC. In agreement with the 16S rRNA gene sequencing data, *P. somerae* was detected significantly more frequently in vaginal swabs of patients with EC than those without EC (p = 3.02E-7). Overall, the test achieved a sensitivity of 74% and specificity of 63%, with a positive predictive value of 0.86 for obese and postmenopausal patients. In summary, we identify *Porphyromas somerae* presence as the most predictive microbial marker of EC, and we confirm this using targeted qPCR, which could be of use in detecting EC in high-risk, asymptomatic women. Given the established pathogenic behavior of *P.somerae*, we have also explored mechanistic routes through which this microbe and associated consortia may be involved in the mechanisms of disease.

**PR10 Candida albicans infection mediates gastrointestinal track malignancy independently of Il17a in an APECED mouse model.** Feng Zhu1, Jami Willette-Brown1, Trang Phan1, Yongmei Zhao1, Bao Tran1, Scott G. Filler1, Mihalis S. Lionakis1, Yinling Hu1. 1Laboratory of Cancer Immunometabolism, Center for Cancer Research, National Cancer Institute, NIH, Frederick, MD, 2Division of Infectious Diseases, Harbor-UCLA Medical Center, Los Angeles, CA, 3Leido Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD, 4Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD.

The cytokine Il17a plays an important role in protection against fungal infection, yet it also serves as a pathogenic factor in several inflammation-related cancers. Previously we reported that fungal infection promotes the development of esophageal squamous cell carcinoma (ESCC) in the ikKalpha kinase-dead KA knock-in (KA) mice that mimic a human autoimmune disorder, autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy (APECED). Our data showed that KA T cells failed to induce Il17a in response to fungal infection. However, the role of Il17a in fungal infection-mediated esophageal carcinogenesis remains to be further determined. In this study, we crossed KA mice with Il17a-/- mice to generate KA;Il17a-/- double mutant mice. We orally inoculated WT, Il17a-/-, KA, and KA;Il17a-/- mice with *Candida albicans* weekly for 3 months to investigate gastrointestinal (GI) track tumorigenesis, including the SCC development in the oral cavity, esophagus, and forestomach. We found that loss of Il17a leads to much earlier onset of GI track tumors in KA;Il17a-/- mice than that in KA mice. KA;Il17a-/- mice also died much earlier compared to KA mice, which is likely due to increased *C. albicans* burden in the absence of Il17a. The incidence of GI track tumors is comparable between KA and KA;Il17a-/- mice, suggesting that *C. albicans* infection-associated GI track tumorigenesis is independent of Il17a in KA mouse model. To further understand the underlying mechanism, we performed single-cell RNA sequencing analysis for CD45+ immune cells isolated from long-term *C. albicans*-infected mouse esophagi of WT, Il17a-/-, KA, and KA;Il17a-/- mouse cohorts. Interestingly, the neutrophil population was significantly increased in the esophagi of KA and KA;Il17a-/- mice compared to WT and Il17a-/- mice. However, KA neutrophils exhibited reduced capacity in killing *C. albicans* with reduced NETs formation compared to WT neutrophils, suggesting that the defect in NETs formation may play a pivotal role in GI track tumorigenesis in the context of fungal infection. We are currently investigating how the interplay between *C. albicans* infection and host neutrophils regulates *Candida* infection-associated GI track tumorigenesis.

This abstract is also being presented as Poster B01.
**PR11 Entero-mammary microbiota signaling axis regulates dietary influences on breast cancer risk.**

David R. Soto-Pantoja, Kenysha Y.J. Clear, Adam S. Wilson, Greg Kucera, Edward Levine, Akiko Chiba, Katherine L. Cook, Wake Forest University School of Medicine, Winston-Salem, NC.

Several studies indicate a strong link between diet, obesity, and breast cancer risk. We recently showed that dietary patterns shifted mammary gland-specific microbiota populations in a nonhuman primate model. To address the limited evidence linking breast specific microbiota to cancer risk, we designed a combination of dietary murine and clinical human studies exploring this connection. Female 3-week-old BALB/c mice were fed a low-fat (LF) control diet or a high-fat (HF) diet (60% kcal from fat with lard as the fat source). A subset of LF or HF diet-fed mice were given antibiotics in the drinking water to ablate the microbiome or underwent 1x weekly diet-derived fecal transplant. Breast tumors were induced by 7,12- dimethylbenz[a]anthracene to determine the impact of diet-regulated microbiota on breast tumorigenesis. Our study shows that antibiotics reduced breast tumor incidence in both LF and HF diet-fed animals. Furthermore, a HF diet-derived fecal transplant increased tumorigenesis in LF diet-fed mice. Conversely, HF diet-fed mice given a LF diet-derived fecal transplant reduced tumor incidence when compared to HF diet-consuming mice. 16S sequencing of feces and breast tumors indicated that fecal transplant modifies microbiota populations in the gut and in the breast microenvironment. Costaining human breast tumor microarray for gram-positive bacteria, cytokeratin, and CD45 indicates that human breast tumors contain bacteria in non-immune cell populations. Moreover, gram positive-bacteria laden cell content positively correlates with tumor-infiltrating lymphocytes, suggesting tumor bacterial abundance may modulate immune cell infiltration in the tumor microenvironment. Using patient-matched snap-frozen breast tumor and tumor-adjacent mammary gland samples from women administered a placebo or 2 gram fish oil supplements daily during the presurgical window (timeframe between diagnosis and tumor resection), we investigated the effect of oral dietary interventions on the breast tumor and mammary gland microbiota populations. Breast tumors display higher proportional abundance of Lachnospiraceae and Ruminococcus when compared to tumor-adjacent mammary gland tissue regardless of intervention, suggesting tumor microbiota populations differ from surrounding normal mammary gland tissue. Fish oil consumption before surgery significantly decreased Ruminococcus and Bacteriodales abundance in tumor-adjacent mammary glands and

in tumor samples. Placebo-treated patients displayed increased Clostridiales abundance in tumor-adjacent mammary gland tissue, which was not observed with fish oil-supplemented patient tissues. Taken together, we demonstrate how dietary patterns modify the breast microbiota populations and impact mammary tumorigenesis and immune interactions in the tumor microenvironment, thus suggesting that the microbiome is a key mediator of breast cancer risk.

*This abstract is also being presented as Poster B28.*
A01 Fusobacterium nucleatum and clinicopathologic features of colorectal carcinoma: Results from the ColoCare Study. Yannick Eisele1, Patrick M. Mallea1, Biljana Gigic1, W. Zac Stephens1, Christy A. Warby1, Kate Buhre1, Tengda Lin1, Petra Schrotz-King2, Sheetal Hardikar3, Lyen C. Huang3, T. Bartley Pickron3, Courtney Scalfé4, Torsten Koelsch4, Anita R. Peoples5, Maria A. Pietneva5, Mary Bronner5, Martin Schneider5, Alexis B. Ulrich6, Eric A. Swanson6, Adetunji T. Toriola7, Hans Hauner6, June Round6, Cornelia M. Ulrich4, Andrea N. Holowatyj7, Jennifer Ose7, Huntsman Cancer Institute, University of Utah, Salt Lake City, UT, 2Department of General, Visceral and Transplantation Surgery, University Hospital of Heidelberg, Heidelberg, Germany, 3Department of Pathology, University of Utah, Salt Lake City, UT, 4Division of Preventive Oncology, National Center for Tumor Diseases (NCT), German Cancer Research Center (DKFZ), Heidelberg, Germany, 5Division of General Surgery, Department of Surgery, University of Utah School of Medicine, Salt Lake City, UT, 6Department of Population Health Sciences, University of Utah, Salt Lake City, UT, 7Washington University in St. Louis, St. Louis, MO, 8Elise-Kroener-Fresenius-Center for Nutritional Medicine, Technical University of Munich, Munich, Germany.

Background: Fusobacterium nucleatum (Fn), an oral commensal involved in a wide spectrum of infections, has recently been implicated in colorectal cancer (CRC) etiology. However, the role of Fn in treatment-naive CRC patients remains unclear. Therefore, we assessed whether Fn abundance is associated with clinicopathologic characteristics among treatment-naive CRC patients enrolled in the prospective ColoCare Study.

Methods: Quantitative real-time PCR was used to amplify and detect Fn DNA in fecal samples collected prior to surgery from 105 patients. We utilized multivariable regression analysis to investigate associations between Fn abundance and sex, age at surgery, BMI, tumor stage, tumor grade, tumor site, infection with H. pylori, microsatellite instability, alcohol consumption, and smoking history by adjusting for sex, age at surgery, cohort, and BMI.

Results: Compared to patients with undetectable or low abundance of Fn, patients with higher abundance of Fn were more likely to be diagnosed with rectal cancer than colon cancer (Odds Ratio [OR] = 3.01, 95% CI 1.06-8.57 P=0.04). Categorizing the colon into right-sided (proximal) and left-sided (distal) showed that patients with a high abundance of Fn were also more likely to be diagnosed with rectal cancer compared to right-sided colon cancer (OR=5.32, 95% CI 1.23-22.98 P=0.03), thus suggesting an increasing risk of cancer diagnosis along the bowel towards the rectum.

Conclusion: Our study sheds light on the association of high abundance of Fn in fecal biospecimen with colorectal carcinogenesis, which may support future preventive or diagnostic measures.

A02 A mutational signature in human colorectal cancer induced by genotoxic pks’. E. coli. Jens Puschhof1, Cayetano Pleguezuelos-Manzano1, Axel Rosendahl Huber1, Ruben van Bostel1, Hans Clevers1, 2Hubrecht Institute, Utrecht, The Netherlands, 3 Princess Maxima Center, Utrecht, The Netherlands.

This abstract is being presented as a short talk in the scientific program. A full abstract is printed in the Proffered Abstracts section (PR02) of the Conference Proceedings.

A03 Association of Fusobacterium nucleatum (F. nucleatum) with progression-free survival (PFS) and overall survival (OS) with 2nd-line FOLFIRI +/- regorafenib in metastatic colorectal cancer (mCRC). Michael S. Lee1, Temitope O. Koku1, Amber McCoy2, Sara R. Selitsky3, Joel Parker4, Todd Auman5, Kelli Hammond5, Sushant A. Patil1, Ganinju Manyam6, Scott Kopetz5, Hanna K. Sanoff5, Federico Innocenti1, 1University of North Carolina at Chapel Hill, Chapel Hill, NC, 2University of Texas MD Anderson Cancer Center, Houston, TX.

Background: F. nucleatum is an oral anaerobe aberrantly found in up to 43% of CRCs. F. nucleatum presence is associated with additional known prognostic variables, including BRAF mutation and immune infiltration. In nonmetastatic CRC, F. nucleatum is associated with post-chemotherapy recurrence and inferior cancer-specific survival. However, the prognostic value of F. nucleatum in mCRC is not well described. We evaluated the association between F. nucleatum, integrated with other significant prognostic clinicopathologic factors, in a prospective clinical trial cohort of mCRC.

Methods: LCCC1029 was a 2:1 randomized phase II trial of 2nd-line chemotherapy with 5-fluorouracil/irinotecan plus either regorafenib or placebo in mCRC. DNA and RNA were extracted from FFPE archival tumor samples, and quantitative PCR to measure F. nucleatum levels was successfully performed on 73 of those samples. We compared PFS and OS using Kaplan-Meier method and log-rank tests, and univariate and multivariate hazard ratios (HR) were estimated using Cox proportional hazards method.
Results: Among the 73 mCRC patients with *F. nucleatum* quantitated, 20 (27%) had a high level and 53 (73%) had undetectable or low levels of *F. nucleatum*. On univariate analysis, *F. nucleatum* high level was not associated with PFS (HR 0.78, 95% CI 0.46-1.33; log-rank p=0.36) or OS (HR 0.83, 95% CI 0.46-1.51; log-rank p=0.54).

However, the *F. nucleatum* positive subgroup trended toward higher rates of BRAF mutation (12%, vs 2% in *F. nucleatum* low/negative), KRAS/NRAS mutation (47% vs 27%), and MSI-High (12% vs 5%). We thus performed multivariate analyses of PFS and OS including *F. nucleatum* high level, BRAF mutation, KRAS/NRAS mutation, MSI, prior antiangiogenic therapy, and age on the subgroup of 58 patients who had results from all platforms. On multivariate analysis, high *F. nucleatum* expression trended toward association with improved PFS, with HR 0.57 (0.30-1.10, p=0.095). BRAF mutation, prior antiangiogenic therapy, and *F. nucleatum* were significantly associated with improved OS, with high *F. nucleatum* expression having adjusted HR 0.48 (0.23-0.99, p=0.048).

Conclusions: Expression of *F. nucleatum* in the tumor of patients with mCRC was significantly associated with improved OS in mCRC. While results need to be validated, these findings suggest that *F. nucleatum* is associated with prognosis in a context-dependent fashion and may confer differential prognosis in nonmetastatic versus metastatic CRC patients.


**Background:** Several bacterial taxa that are consistently enriched in the gut microbiome of CRC cases are also found in the oral cavity. They exhibit phenotypic traits such as adherence to host epithelial cells, mucus degradation, and biofilm formation, which promote bacterial survival in the colon and may play a role in both oral disease and colorectal carcinogenesis by stimulating an inflammatory response. We evaluated the effect of a 6-week aspirin intervention on the relative abundance of oral bacterial taxa in a randomized placebo-controlled trial.

**Methods:** Fifty healthy subjects, 50-75 years old, were randomized to receive either aspirin (N=30) or placebo (N=20) for 6 weeks. Oral samples were collected at baseline and after treatment (6 weeks) and amplicon sequencing of the V4 region of the 16S rRNA gene was done using Illumina MiSeq technology. The data were analyzed using the standard DADA2 workflow. We used linear regression analysis, PERMANOVA, and negative binomial regressions (DESeq2 package) to assess the association between intervention assignment (aspirin vs. placebo) and α-diversity, β-diversity, and fold change in specific taxa, after adjustment for age, gender, and BMI at baseline and postintervention.

Intervention assignment was hypothesized to influence the following bacterial taxa a priori: *Fusobacterium, Porphyromonas, Prevotella, Gemella, Neisseria, Streptococcus, Haemophilus, Campylobacter, Veillonella, Actinomyces* based on previous studies. We estimated the association between aspirin use and the changes in the relative abundance of the specified taxa from pre- to post-treatment (baseline to week 6) using a mixed-effect regression model (lme4 package) with a binomial distribution in which the log of odds ratio (β estimate) for the interaction term compared aspirin to placebo intervention for post- versus pretreatment.

**Results:** Aspirin treatment was not associated with α- or β-diversity at baseline or postintervention. However, the change in relative abundance of 8 out of the 10 prespecified taxa over time differed between the aspirin and placebo groups. In the aspirin group, there were greater increases in the relative abundances of *Neisseria, Streptococcus, Actinomyces*, and greater decreases in the relative abundance of *Prevotella, Veillonella, Fusobacterium, and Porphyromonas*.

**Conclusions:** These preliminary findings suggest that aspirin may change the relative abundance of oral taxa associated with oral dysbiosis or CRC. Further studies are needed to understand the impact that the duration and dosage of the aspirin intervention may have on the oral microbiome.


**Background:** Several bacteria in the human gut microbiome have been associated with colorectal cancer (CRC) by high-throughput screens. In some cases, molecular
mechanisms have been elucidated that drive
tumorigenesis, including bacterial membrane proteins
or secreted molecules that interact with the human
cancer cells. For most gut bacteria, however, it
remains unknown if they enhance or inhibit cancer cell
growth. Here, we screened bacteria-free supernatants
(secretomes) and inactivated cells of over 150 cultured
bacterial strains for their effect on CRC cell growth.
Five CRC cell lines and one noncancerous kidney
cell line were selected based on their differences
in mutational landscapes. We observed family-
level and strain-level effects that often differed
between bacterial cells and secretomes, suggesting
that different molecular mechanisms are at play.
Secretomes of Bacteroidaceae, Enterobacteriaceae,
and Erysipelotrichaceae enhanced CRC cell growth, while
most Fusobacteriaceae cells and secretomes inhibited
growth, contrasting prior findings. For some bacterial
cells, strong cell line-dependent effects were
observed, such as for Streptococcaceae and HT29 cells.
In some bacteria, the presence of specific functional
genes was associated with CRC cell growth rates,
including the virulence genes TcdA in Clostridiales and
FadA in Fusobacteriaceae, which both inhibited
growth. Bacteroidaceae cells that enhanced growth were
enriched for genes of the cobalamin synthesis pathway,
while Fusobacteriaceae cells that inhibit growth were
enriched for genes in ethanolamine utilization pathway.
Together, our results reveal how different gut bacteria
have wide-ranging effects on cancer cells, contribute
a better understanding of the effects of the gut
microbiome on the human host, and provide a valuable
resource for identifying candidate target genes for
potential microbiome-based diagnostics and treatment
strategies.

A06 Right-sided colonic biofilms are associated
with adenoma formation in patients with Lynch
syndrome. Carlijn Bruggeling1, Vera Witjes1, Daniel
Garza1, Milou Fransen2, Joyce Krekels2, Tanya Bisseling2,
Mariëtte van Kouwen1, Nicoline Hoogerbrugge1,
Sebastian Lücker2, Bas Dutilh1, Iris Nagtegaal1,
Annemarie Boleij2. 1Radboudumc, Nijmegen, The
Netherlands, 2Radboud University, Nijmegen, The
Netherlands.

This abstract is being presented as a short talk in the
scientific program. A full abstract is printed in the
Proffered Abstracts section (PR01) of the Conference
Proceedings.

A07 The involvement of a type VII secretion system in
the interactions between Streptococcus galolyticus
subspecies galolyticus and colorectal cancer. John
Culver Taylor, Jacob Rutherford, Maria Nunez, Yi Xu.
Texas A&M Health Science Center Institute of Biosciences
and Technology, Houston, TX.

Colorectal cancer (CRC) is the 2nd-3rd most common
cancer worldwide and is a leading cause of cancer-
related death. Increasing evidence suggests that the gut
microbiome plays an important role in the development
of CRC. One such organism of the gut microbiome
that plays an important role in CRC is Streptococcus
galolyticus subspecies galolyticus (Sgg). Previously, we
reported that Sgg stimulates CRC cell proliferation in a
β-catenin dependent manner. Using an azoxymethane-
induced mouse model of CRC, we have also shown
that Sgg-treated mice had significantly higher tumor
burden in the colon compared to mice treated with
saline or negative control bacteria, suggesting that
Sgg actively promotes the development of CRC. The
mechanism underlying Sgg’s role in CRC development,
however, has yet to be elucidated. The type VII secretion
system (T7SS), also called the Esx secretion system,
is a specialized secretion system found primarily in
Firmicutes and Actinobacteria and has been shown to
play an important role in virulence in Staphylococcus
aureus and Mycobacterium tuberculosis. Here, we
examined the genome of Sgg and found that it encodes
a putative T7SS (SggT7SS) highly similar to the T7SS in
S. aureus with respect to sequence identity and gene
organization. We further showed that the SggT7SS is
functional. To investigate if the SggT7SS is involved in
the connection between Sgg and CRC, we generated an
Sgg mutant lacking the core components of the T7SS
secretion machinery. Functional characterization of the
mutant indicates that SggT7SS is intimately involved in
the interactions between Sgg and CRC cells. Taken
together, our results suggest that a T7SS system may
be important in inducing specific host responses to Sgg
in the context of CRC. Studies to further elucidate the
activities of T7SS and its role in Sgg’s contribution to
CRC are currently under way.

A08 Tumor microbiome in subtypes of mismatch
repair-deficient colorectal cancer. Jihoon E. Joo1,
Mark Clendenning2, Khalid Mahmood2, Christophe
Rosty1, Ingrid M. Winship2, Mark A. Jenkins1, Daniel
D. Buchanan1. 1University of Melbourne, Parkville,
VIC, Australia, 2Envoi Pathology, Brisbane, QLD,
Australia, 3Royal Melbourne Hospital, Parkville, VIC,
Australia.
**Background:** Colorectal cancer (CRC) comprises different molecular subtypes, including those tumors that develop defective DNA mismatch repair (MMR) evidenced by microsatellite instability (MSI) and/or loss of MMR protein expression (MMR-deficiency). Tumor MMR-deficiency can result from inherited causes, namely germline mutations in the MMR genes (Lynch syndrome) or from somatic inactivation resulting from hypermethylation of the MLH1 gene promoter or from biallelic somatic mutations. Little is known about the etiologies of these cancers or the avenues for risk amelioration. We hypothesized that dysbiosis of the gut microbiome is a risk factor for the development of MMR-deficient subtypes of CRC and that the microbiome composition differs between inherited and somatic MMR-deficient CRC.

**Materials and Methods:** The microbiome composition was determined by 16S rRNA sequencing of the V3-V4 regions in DNA extracted from 94 FFPE-derived tumor specimens comprised of 14 MMR-proficient CRCs and 80 MMR-deficient CRCs from the Australasian Colorectal Cancer Family Registry. The MMR-deficient CRCs comprised three subtypes: 35 people with germline MMR gene mutations (Lynch syndrome), 13 people with sporadic MLH1 hypermethylated CRCs, and 32 people with suspected Lynch syndrome (no germline or MLH1 methylation). LEfSe analyses were used to identify differential abundance in taxa between groups.

**Results:** In all tumor samples, Proteobacteria, Firmicutes, Bacteroidetes, Actinobacteria, and Fusobacteria were most abundant. Of these, the Firmicute population was significantly higher in the MMR-proficient than MMR-deficient CRCs (0.33 v 0.19, P < 0.05). When compared with the Lynch syndrome-related CRCs, we found 22 bacterial species, including *Corynebacteriaceae*, that were significantly more abundant in MLH1 hypermethylated tumors (P < 0.05), whereas we found 4 species significantly more abundant, including *Enterobacter*, in suspected Lynch syndrome group. Although the microbial diversity was notably smaller compared with the sporadic groups, several species of the family *Comamanadaceae* including *Acidovorax* were abundant in Lynch syndrome tumors (P < 0.05). *Fusobacterium nucleatum* was detected in 11/35 (31.4%) Lynch syndrome-related CRCs, 5/13 (38.5%) MLH1 hypermethylated CRCs, 13/32 (40.6%) suspected Lynch syndrome CRCs, and 4/14 (28.6%) sporadic MMR-proficient CRCs.

**Conclusions:** Inherited and somatic subtypes of MMR-deficient CRC show significant differences in their tumor microbiome composition where Lynch syndrome-related MMR-deficient CRC showed a reduced microbiome diversity compared with somatic MMR-deficient CRC. Further validation of these findings will improve our understanding of MMR-deficient CRC tumorigenesis and aid in CRC prevention through the identification of modifiable microbial risk factors.
POSTER SESSION A


Objectives: Head and neck squamous cell carcinoma (HNSCC) is the 6th most common cancer worldwide with a poor prognosis of ~40% at 5 years for HPV-negative disease. Recently, immune checkpoint inhibitors (specifically, anti-PD-1 checkpoint inhibitors that block the PD-L1/PD-1 immunosuppressive axis) have been approved as a treatment for patients with recurrent/metastatic HNSCC. However, most patients (>80%) fail to respond to checkpoint inhibitors. PD-L1 expression on tumors plays an important role in immune evasion and can also influence response to checkpoint inhibitors. Tumor PD-L1 expression has been shown to correlate with checkpoint response. Factors that might affect PD-L1 expression in HNSCC remain unclear. In this study, we explored the effect of periodontal bacteria, which has been associated with oral cancer, on PD-L1 expression in oral cancer cells.

Materials and Methods: 303 HNSCC were compared to 37 adjacent control tissues in the TCGA mRNA expression database (RNASeq V2); the analysis was done based on tumor types. RT-PCR and flow cytometry were used to measure the base line expression of PD-L1 in seven head and neck cancer cell lines and human oral tissues. OQ01, an oral cancer cell line, was infected with four periodontal bacteria (Tannerella forsythia, Treponema denticola, Porphyromonas gingivalis, and Fusobacterium nucleatum). OQ01 and RPMI2650 cells were infected with two different strains of Fusobacteria (F. periodonticum, F. vincentii). The relative changes in expression of PLD1 was measured using RT-PCR in cell lysate after RNA isolation. PD-L1 protein level on the cell surface was measured using flow cytometry.

Results: TCGA data analysis revealed that PD-L1 was significantly (P<0.0005) elevated in total cancer tissues compared to total controls. In the same data analysis, PD-L1 expression was significantly (P<0.05) elevated in oral cavity tumor compared to normal control. Expression of PD-L1 was variable among head and neck cancer patients and cell lines. Both F. nucleatum and P. gingivalis were able to enhance PD-L1 expression in OQ01 cells (10 and 15 fold, respectively). Two strains of Fusobacteria tested (F. periodonticum, F. vincentii) were also able to induce PD-L1 both at the mRNA (P<0.005 and P<0.05 respectively) and protein level in OQ01 and RPMI 2650 cells. Interestingly, the same strains of Fusobacteria enhanced MYC expression in OQ01 and RPMI 2650 cells. As a transcription factor MYC has been reported to regulate PDL1 transcription. These data along with our results suggest that Fusobacterial upregulation of PD-L1 expression might be through MYC enhanced expression.

Conclusions: This study revealed that Fusobacteria enhance PD-L1 expression on HNSCC cancer cell lines, possibly upregulation of MYC. This may have implications on cancer cell immune evasion and checkpoint inhibitor treatment response.

A11 Betel nut chewing, oral Cyanobacteria, and exposure to cyanotoxins. Brenda Y. Hernandez, Xuemei Zhu, Patrick Sotto, Yvette Paulino, University of Hawaii Cancer Center, Honolulu, HI, University of Guam, Mangilao, Guam.

Betel nut from the Areca catechu palm tree, chewed alone or as a quid wrapped in Piper betle leaf, is the 4th most widely used addictive substance globally, primarily in parts of Asia and the Pacific. Betel nut chewing is an independent cause of cancers of the oral cavity and esophagus and has been linked to other malignancies. We evaluated 16S rRNA in oral cavity swabs and saliva obtained from 122 adults (64 current betel nut chewers, 37 former chewers, 21 never chewers) in Guam. Cyanobacteria was detected at 90-fold higher abundance in oral samples from current betel nut compared to both former and never chewers. Cyanobacteria was also the predominant bacterial taxa detected in Areca catechu nuts and Piper betle leaves.16S sequence data were evaluated using PiCRUsT to predict gene families and to generate a composite metagenome. AntiSMASH 5.0 was used for the analysis of gene marker data corresponding to secondary metabolites. Cyanotoxins, including microcystins, nodularins, and cylindrospermopsin, as well as other secondary metabolites were identified as putative secondary metabolites. Subsets of oral and plant samples evaluated via ELISA confirmed the presence of these metabolites. The identification of these cyanotoxins in this population suggests their possible contribution to betel nut-associated carcinogenesis.

**Introduction:** There is evidence to suggest that the human microbiome may play a key role in the development of breast cancer. There is a unique microbial signature in mammary tissue that is associated with breast cancer. Further, there is mounting evidence to support the role of the gut microbiome in promoting or preventing breast cancer. Consequently, specific compositional and/or functional shifts in either of these microbiomes may promote the growth of breast tumors. Short chain fatty acids (SCFAs) are microbial metabolites produced in the large intestine by bacterial fermentation of complex carbohydrates. These metabolites exit the gut and interact with many different cell types throughout the human body, including those in the breast, via g-protein coupled receptors; GPR41, GPR43, and GPR109A. These metabolites have been identified as a potential functional connection between the gut microbiome and breast cancer but have not been studied in breast tissue in the context of breast cancer. To assess the interaction between the microbiome and breast tumor development, we analyzed the expression of these receptors in tissue collected from women who donated healthy, prediagnostic, or cancerous tissue to the Susan G. Komen and Indiana University Simon Cancer Center Tissue Banks.

**Methods:** DNA and RNA (n=60, n = 15 for each tissue subset: healthy, prediagnostic, adjacent normal, and tumor tissue) was copurified from these tissues using the Qiagen AllPrep® PowerFecal® DNA/RNA Kit. The RNA was then reverse transcribed into complementary DNA. Quantitative PCR was performed on the cDNA using four validated primer sets: GPR41, GPR43, GPR109A, and ribosomal 18S (housekeeping gene).

**Results/Conclusions:** We did not identify any significant differences in expression levels of these receptors between the participant groups, suggesting that cancer status is not associated with increased metabolic activity of the microbiome. We are currently conducting sensitivity analyses to determine the role of clinical factors such as age, menopausal status, BMI, etc., on the expression of these receptors in breast tissue. We are also investigating the expression of enzymes and transporters in breast tissue related to host cell metabolism of the most bioactive SCFAs (acetate, propionate, and butyrate). This work will yield valuable information regarding the interaction between the human microbiome and breast tumor development. Ultimately, it may be possible to target SCFA-producing bacteria or SCFA catabolic pathways in breast tissue to prevent or treat breast cancer.

**A13 Functional characterization of the enteric animal virome as mediator of host health.** Simone Dallari, Thomas Heaney, Adriana Rosas-Villegas, Ken Cadwell. New York University School of Medicine, New York, NY.

This abstract is being presented as a short talk in the scientific program. A full abstract is printed in the Proffered Abstracts section (PR03) of the Conference Proceedings.

**A14 Meta-analysis improves identification of microbiome associations with antitumor response in melanoma, lung, and kidney cancer patients treated with checkpoint inhibitors.** Fyza T. Shaikh1, James R. White2, Joell G. Gills1, Jarushka Naidoo1, Evan Lipson1, Drew M. Pardoll1, Cynthia L. Sears1. 1Johns Hopkins School of Medicine, Baltimore, MD, 2Resphera Biosciences, Baltimore, MD.

While immune checkpoint inhibitors (ICIs) have revolutionized the treatment of many cancers by producing durable antitumor responses, only 10-30% of treated patients respond and the ability to predict response to treatment remains elusive. Preliminary studies suggest the gut microbiome may be a novel biomarker for tumor response rates, including high alpha-diversity and a few specific bacterial species that associate with improved tumor responses to ICIs in melanoma, renal cell cancer (RCC), and non-small cell lung cancer (NSCLC). Despite these reports, the specific bacteria or bacterial communities helpful or harmful to ICI responses have been inconsistent across study populations and various malignancies, and further correlation with immune and mutational biomarkers is limited or lacking. We hypothesized that, by use of a larger sample size and a consistent computational approach, we would derive a clearer microbial profile that correlated with immunotherapeutic outcomes in more than one cancer type and in response to ICIs that target different immune checkpoints. To test this hypothesis, we have reanalyzed the available raw 16S rRNA amplicon and metagenomic sequencing data across five recently published studies (n=303) using Resphera Insight v2.2 and MetaPhlAn2, respectively, for taxonomic assignment. We used pathway prediction algorithms (PICRUST) to examine functional characteristics enriched among responders and nonresponders, as well as effect of antibiotic usage and virulence factors using multiple reference databases. Our results confirm signals reported in each study, though some bacteria reported initially were not statistically significant after correction for false discovery rate. Likely, in part, because our analysis allows for comparison.
POSTER SESSION A

of individual species across cohorts, we were able to identify new bacterial signatures associated with clinical response or nonresponse. Further, these new results enabled us to re-evaluate and develop response and nonresponse indicator indexes. When our composite index was compared to an index assembled from the literature, some improvement occurred in a sensitivity and specificity analysis. Moreover, while lower alpha-diversity has been associated with disease states and higher alpha-diversity with healthy states, we found that alpha-diversity was not consistently predictive of response or nonresponse to ICIs. In summary, this bioinformatics platform improves on existing pipelines by standardizing critical preprocessing and downstream analysis tools, enabling comprehensive evaluations of taxonomic and functional signals across sequencing datasets. These analyses allow for identification of novel bacterial signatures associated with clinical responses that could potentially be used as biomarkers in patients undergoing treatment with checkpoint inhibitors. Results from these analyses will be validated in subsequent analyses of ICI therapy and clinical outcomes in our ongoing prospective cohorts.

A15 Potential of metformin to modify the gut microbiota and prevent inflammation in nondiabetic people with HIV. Stéphane Isnard1, John Lin2, Brandon Frombuena1, Thibaut V. Varin1, André Marette2, Delphine Planas1, Meriem Messaoudene3, Bertrand Routy1, Claude Van Der Ley4, Ido Kema5, Petronela Ancuta1, Jonathan Angel1, Jean-Pierre Routy1. 1McGill University Health Centre, Montréal, QC, Canada, 2Laval University, Quebec, QC, Canada, 3Centre de Recherche du Centre Hospitalier de l’Université de Montréal, Montreal, QC, Canada, 4University of Groningen, Groningen, The Netherlands, 5The Ottawa Hospital, Ottawa, ON, Canada.

This abstract is being presented as a short talk in the scientific program. A full abstract is printed in the Proffered Abstracts section (PR04) of the Conference Proceedings.


The present study aimed to screen for and genotype HPV among Saudi women; develop sensitive quantitative polymerase chain reaction (qPCR) assays to detect the viral load for the two most common HPV types, namely 16 and 18; and assess whether HPV viral load could be used as a marker for cervical abnormality and disease progression. This study examined 733 specimens (both formalin-fixed, paraffin-embedded specimens and PAP smear samples) from women who underwent cervical screening. The specimens and samples were processed for DNA extraction and then tested for HPV DNA. Approximately 165 specimens (18%) were positive for HPV. Those specimens were genotyped using a reverse line blotting hybridization assay. The results indicated that the most common HPV types detected were a single infection with HPV 16 (51%) or with HPV 18 (28%) followed by infections with multiple HPV types (~7%). A qPCR TaqMan assay developed in-house was used to determine the viral load for HPV genotypes 16 (n=80) and 18 (n=45). Viral loads for both HPV types were significantly associated with cervical cytology grade (P < 0.05). The odds ratio (OR) for the HPV 16 viral load was high for specimens with cervical cancer (OR, 18.8; 95% CI, 4.3–82.9) or for those with high-grade squamous intraepithelial lesions (OR, 14.7; 95% CI, 2.43–88.49). For the HPV 18 viral load, the OR was significant only for specimens with cervical cancer (OR, 11.1; 95% CI, 2.2–54.9). Logistic regression models for HPV 16 and for HPV 18 viral load levels were significant, with higher viral load associated with cervical abnormalities. These findings indicate that viral load is a predictor significantly associated with cytology abnormality in women who are positive for high-risk HPVs and suggest integrating a viral load test into current clinical screening practices for HPV-positive women.

A19 Male hormones transactivate viral noncoding RNA PAN to promote KSHV lytic replication. Mingzhu Ding1, Yuqi Zhang1, Haixiang Zheng1, Rui Sun1, Lei Bai2, Ke Lan1, Xing Wang1. 1Key Laboratory of Gastrointestinal Cancer (Ministry of Education), School of Basic Medical Sciences, Fujian Medical University, Fuzhou , Fujian, P.R. China, 2State Key Laboratory of Virology, College of Life Sciences, Medical Research Institute, Wuhan University, Wuhan, Hubei, P.R. China.

Male predominance in Kaposi’s sarcoma (KS) is an epidemiologic consensus in the field. However, whether male sex steroids function in KS pathogenesis remains largely unknown. Our results firstly identified the highly increased expression of androgen receptor (AR) in KS lesions and its colocalization with viral oncoprotein LANA in nucleus of spindle cells. Also, the ligand
The relationship with development of uterine cervical expression in patients with cervical cancer and assess the detection of HPV-16 variants and IGF1R E6 AA-a and E-G350 HPV-16 variants. The aim of the was reported that IGF1R is overexpressed by effect of growth factor-1 receptor (IGF-1R). In recent studies, it molecular signaling pathways (such as Insulin-like activation, loss of tumor suppressor genes and aberrant modulation involves tissue oxygenation, oncogene transformation of preneoplastic lesions in invasive and, ultimately, various forms of invasive cancer. The infections persist latently, leading to disease progression cancer cells is provoked at least partly by HPV, especially through gene and protein expression modulation. This modulation involves tissue oxygenation, oncogene activation, loss of tumor suppressor genes and aberrant molecular signaling pathways (such as Insulin-like growth factor-1 receptor (IGF-1R)). In recent studies, it was reported that IGF1R is overexpressed by effect of E6 AA-a and E-G350 HPV-16 variants. The aim of the present study was to prospectively and retrospectively report the detection of HPV-16 variants and IGF1R expression in patients with cervical cancer and assess the relationship with development of uterine cervical cancer. Sixty consecutive patients with invasive cervical cancer were assessed for HPV-16. A total of 35 patients (58.3%) were infected with HPV-16, with a mean age of 51 years (range: 30–76 years). Thirty patients (85.7%) were diagnosed with European HPV-16 variant and five patients (14.3%) were diagnosed with non-European HPV-16 variants. European HPV-16 variants (E-HPV-16) were mainly E-G350 (n = 14; 41.1%) and E-T350 (n = 12; 35.2%) subclasses. Of these 35 patients, 15 received exclusive radiotherapy and four radiochemotherapy, and the remaining 16 did not complete the treatment (NCT). Of the patients who presented an incomplete response, overexpression of IGF1R was detected in all. Of patients NCT, we retrospectively studied one case in IIIB stage FIGO. Samples of preneoplastic lesions and invasive cervical cancer were analyzed to confirm histopathologic diagnosis and detect the presence of HPV variants and overexpression of IGF-1R. Of the results found in this case, in which the patient was diagnosed in 1986 with a high-grade squamous intraepithelial cervical lesion, HPV-16 E-G350 and HPV-33 coinfection as low expression of IGF1R were detected and for the invasive cancer diagnosed in 2002, the presence of HPV-16 AA-c and overexpression of IGF1R was detected. The detection of high-risk HPV in samples of preneoplastic lesions and invasive cancer in a 60-year-old patient at the time of diagnosis showed that HPV33 infection was eliminated. Results such as these suggest that persistent infection with HPV-16 variants, overexpression of IGF1R, such as viral load and age, could be necessary factors for disease progression, and thus contribute to the identification of patients with a high risk of viral persistence and development of cervical neoplasia.

A20 Persistent high-risk HPV infection in the development of uterine cervical cancer. Pablo Moreno Acosta1, Diana Mayorga1, Nicolas Magné2, 1National Cancer Institute, Bogota, Colombia, 2Institut de Cancérologie Lucien Neuwirth, Saint-Priest en Jarez cedex, France.

The early detection and treatment of preneoplastic uterine cervical lesions is certainly a major challenge for developing countries. Preneoplastic lesions result from human papilloma virus (HPV) infection in cells located in the transformation zone of the cervical epithelial tissue, causing low-grade or high-grade lesions. HPV infections are transient and most of the time cleared within a couple of years following exposure. However, 10–20% of infections persist latently, leading to disease progression and, ultimately, various forms of invasive cancer. The transformation of preneoplastic lesions in invasive cancer cells is provoked at least partly by HPV, especially through gene and protein expression modulation. This modulation involves tissue oxygenation, oncogene activation, loss of tumor suppressor genes and aberrant molecular signaling pathways (such as Insulin-like growth factor-1 receptor (IGF-1R)). In recent studies, it was reported that IGF1R is overexpressed by effect of E6 AA-a and E-G350 HPV-16 variants. The aim of the present study was to prospectively and retrospectively report the detection of HPV-16 variants and IGF1R expression in patients with cervical cancer and assess the relationship with development of uterine cervical cancer. Sixty consecutive patients with invasive cervical cancer were assessed for HPV-16. A total of 35 patients (58.3%) were infected with HPV-16, with a mean age of 51 years (range: 30–76 years). Thirty patients (85.7%) were diagnosed with European HPV-16 variant and five patients (14.3%) were diagnosed with non-European HPV-16 variants. European HPV-16 variants (E-HPV-16) were mainly E-G350 (n = 14; 41.1%) and E-T350 (n = 12; 35.2%) subclasses. Of these 35 patients, 15 received exclusive radiotherapy and four radiochemotherapy, and the remaining 16 did not complete the treatment (NCT). Of the patients who presented an incomplete response, overexpression of IGF1R was detected in all. Of patients NCT, we retrospectively studied one case in IIIB stage FIGO. Samples of preneoplastic lesions and invasive cervical cancer were analyzed to confirm histopathologic diagnosis and detect the presence of HPV variants and overexpression of IGF-1R. Of the results found in this case, in which the patient was diagnosed in 1986 with a high-grade squamous intraepithelial cervical lesion, HPV-16 E-G350 and HPV-33 coinfection as low expression of IGF1R were detected and for the invasive cancer diagnosed in 2002, the presence of HPV-16 AA-c and overexpression of IGF1R was detected. The detection of high-risk HPV in samples of preneoplastic lesions and invasive cancer in a 60-year-old patient at the time of diagnosis showed that HPV33 infection was eliminated. Results such as these suggest that persistent infection with HPV-16 variants, overexpression of IGF1R, such as viral load and age, could be necessary factors for disease progression, and thus contribute to the identification of patients with a high risk of viral persistence and development of cervical neoplasia.

A21 Promotion of colorectal cancer by Streptococcus galolyticus—a novel mechanism. John Taylor1, Ritesh Kumar1, Amir Sarshkeeh2, Jennifer Davies2, Scott Kopetz2, Juan Xu1, Yi Xu1, 1Texas A&M HSC, Houston, TX, 2The University of Texas MD Anderson Cancer Center, Houston, TX.

Streptococcus galolyticus subsp. galolyticus (Sgg) is an opportunistic gut pathobiont. It has a longstanding clinical association with colorectal cancer (CRC). We previously demonstrated that Sgg stimulates CRC cell proliferation and promotes tumor growth in mouse models of CRC (Kumar et al., 2017). Recent studies also indicated that Sgg induced an immune-tolerant environment in the mouse colon conductive for tumor development (Zhang et al., 2018). These results provide strong experimental support for Sgg being an active promoter of tumor development. The molecular mechanism underlying Sgg’s tumor promoting activity was unknown. We investigated the effect of Sgg on
CRC cells by analyzing mass spectrometry proteomics data. We found that several types of collagen were upregulated in Sgg-treated cells compared to cells cultured in media only. The upregulation was further confirmed by RT-qPCR and Western blot. Transforming growth factor beta (TGFbeta) is a master regulator of the extracellular matrix. Therefore, we examined the effect of Sgg on the TGFbeta signaling pathway. The results showed that Sgg-treated cells had significantly higher level of phosphorylated Smad2. Sgg treatment also induced the expression of TGFbeta target genes. The effects of Sgg on CRC cells were significantly decreased in the presence of inhibitors for TGFbeta signaling. In addition, we observed that Sgg induced similar effects in mouse colon. Together, these results demonstrate that Sgg activates the TGFbeta signaling pathway in vitro and in vivo. Furthermore, we found that activation of TGFbeta by Sgg is mediated by specific Sgg genes. Deletion of these genes abolished the effect of Sgg on CRC cells in vitro and its ability to promote tumor growth in a mouse model of CRC. These results suggest that TGFbeta activation is a mechanism underlying Sgg’s contribution to tumor growth. Next, we tried to determine if these findings are relevant to CRC patients. Examination of tumor tissues from CRC patients revealed that Sgg-positive tumors exhibit significantly enhanced TGFbeta activity compared to Sgg-negative tumors, suggesting that Sgg-positivity correlates with stronger TGFbeta signaling activities in CRC patients. Taken together, our results highlight a previously unrecognized mechanism in which a colonic microbe activates the TGFbeta signaling pathway to promote the development of CRC. Studies to further delineate this novel mechanism are currently under way.


Glioblastoma multiforme (GBM) is one of the less survivable and most malignant brain tumors. The average survival period is less than 2 years despite multiple therapies including chemotherapy and radiation. Furthermore, GBM showed severe resistance against immunotherapies such as immune checkpoint blockade mainly targeting CD8 T cells (1). Recently, several studies showed that γδ T cells can be an alternative target of immunotherapy. Unlike conventional T cells, γδ T cells recognize stress-induced surface antigens such as NKG2D-ligands and phosphor-antigens (2). Because GBM cells highly express NKG2D-ligands, γδ T cells could be proper targets for immunotherapy. However, a basic understanding of γδ T cell-mediated antitumor immunity remains unclear. Using single-cell transcriptomic analysis, we analyzed the characteristics of GBM-infiltrating γδ T cells. γδ T cells are highly suppressed by oxygen tension of tumor microenvironment in the brain tumor. We inhibited respiration of tumor cells by metformin, which is the drug for type 2 diabetes. Inhibition of tumor cell respiration sufficiently reinvigorated γδ T cells. Reinvigorated γδ T cells highly expressed NKG2D and multiple cytokines. In conclusion, this study highlights the importance of γδ T cells and the druggable pathways through reinvigoration of γδ T cells.

**A23 Association of gut microbiome diversity with obesity and breast density in postmenopausal women.** Lusine Yaghjian1, Xuefeng Wang2, Maria Ukhanova1, Yessica Martinez1, Shannan Rich1, Volker Mai2, Kathleen Egan2. 1University of Florida, Gainesville, FL, 2Moffitt Cancer Center, Tampa, FL.

**Purpose:** The plausible roles of the gut microbiome (GM) in obesity as well as breast cancer have been discussed in recent reviews. The associations of GM with mammographic breast density (BD), a well-established strong breast cancer risk factor, also associated with body mass index (BMI), are poorly studied. We examined GM profiles in relation to BD and BMI in a sample of healthy postmenopausal women.

**Methods:** Women were recruited in mammography clinics at Moffitt Cancer Center and via recruitment announcements at the University of Florida. Eligible women were postmenopausal, had a BMI ≤35 kg/m2, and had not taken oral/IV antibiotics within 30 days and/or more than two separate antibiotic regimens within the previous three months. All women provided a fecal sample and comprehensive information on breast cancer risk factors including body weight and height. Mammographic BD was available for 69 women recruited at Moffitt and was classified according to the American College of Radiology’s BI-RADS BD classification system. For this analysis, BD was dichotomized as low (BI-RADS I or II) or high (BI-RADS III and IV). DNA was isolated from fecal samples and the V1-V2 hypervariable regions of 16S rRNA amplified using barcoded primers for sequencing on the Illumina MiSeq platform. Chao1, Inverse Simpson, and Shannon indices were used to classify within sample diversity. The two-sample Wilcoxon test was used to examine associations of GM with BD and BMI. Associations were also examined according to the ratio of the two main phyla in the human GM (Firmicutes and Bacteroidetes;
F/B ratio) that has been linked to obesity in previous studies.

**Results:** Among 69 women with BD data, 39 had low BD and 30 had high BD. BMI was inversely associated with BD (mean BMI=23.8 in women with high BD and BMI=28.0 in women with low BD, p=1.07×10^-5). The F/B ratio was not associated with BMI (median F/B ratio=0.90, 0.84, and 0.96 for normal weight, overweight, and obesity, respectively, p=0.57). Similar levels of diversity were found across weight groups according to the Shannon (4.05, 3.97, and 3.96, respectively, p=0.83); inverse Simpson (20.6, 20.1, and 19.3, respectively, p=0.97); and choa1 (433, 441, and 419, respectively, p=0.31) indices. F/B ratio and microbiota diversity were both suggestively greater in women with high vs. low BD (median F/B ratio=1.15 for high and 0.94 for low BD, p=0.35; Shannon index: 4.24 for high and 4.15 for low BD, p=0.14; inverse Simpson= 25.3 for high and 21.0 for low BD, p=0.15; choa1= 519 for high and 429 for low BD, p=0.17). Highest levels of alpha diversity were observed in women who had both high BD and low BMI. Taxonomic families that distinguished women with high vs. low BD included Ruminococcaceae, Mogibacteriaceae, Bacteroidaceae, Lachnospiraceae, Christensenellaceae, and Coriobacteriaceae.

**Conclusion:** Results suggest that women with high and low BD may differ with respect to GM alpha diversity and GM composition.

**A24 Bacteroides fragilis: A potential pathogen orchestrating EMT and stemness in breast epithelial cells via concomitant activation of Notch and β-catenin axes.** Sheetal Parida, Shaoguang Wu, Nethaji Muniraj, Sumit Siddharth, Arumugam Nagaligam, Christina Hum, Panagiotis Mistriotis, Konstantinos Konstantopoulos, Cynthia Sears, Dipali Sharma. Johns Hopkins University, Baltimore, MD.

This abstract is being presented as a short talk in the scientific program. A full abstract is printed in the Proffered Abstracts section (PR06) of the Conference Proceedings.

**A25 Combinatorial therapy using oncolytic viruses and immunoregulatory probiotics for the treatment of colorectal cancer.** Yoanna Poutou Paumier1, Christiano Tanese de Souza1, Galaxia Rodríguez1, Elvira Maria Herbert1, Lucila Saavedra2, Carolina Ilkow1. “Centre for Innovative Cancer Research, Ottawa Hospital Research Institute, Ottawa, ON, Canada, 2Reference Centre for Lactobacillli-CERELA, Tucuman, Tucuman, Argentina.

Colorectal cancer (CRC) is the third most commonly diagnosed cancer and has the second-highest mortality. Surgery and chemotherapy are still the main treatment for CRC, but surgery is effective only if tumor cells have not metastasized to distant organs. Tumors’ genetic heterogeneity, the immunosuppressive tumor microenvironment as well as additional factors affecting the overall host health such as the intestinal microbiota, which is known to shape the host immune system, contribute to establish a constantly evolving protumor microenvironment in which malignant cells can proliferate and escape conventional therapeutic approaches. CRC is a complex disease, which makes its treatment with a single therapy ineffective, highlighting the need for development of innovative multimodal approaches to increase the conventional treatments’ efficacy. Oncolytic viruses (OVs) represent an exciting new multimechanistic therapeutic platform for the treatment of cancer. These viruses specifically infect and replicate in cancer cells and induce antitumor immunity while leaving normal tissues unaffected. On the other hand, probiotics such as lactic acid bacteria (LAB) are microorganisms that confer a health benefit on the host. Recent reports have shown that certain LAB strains can potentiate the activity of various anticancer agents due to their immunomodulatory, anti-inflammatory, and anticarcinogenic properties. In recent years, it has become evident that effective cancer therapeutics will be those that have both direct antitumor activity and the ability to concomitantly engage or activate the patient’s immune system. Our studies suggest that this will be best accomplished by optimizing a combination therapeutic approach. We describe here the in vitro antiproliferative effect of different strains of LAB. In addition, our data show that certain LAB stimulate the antitumor immune response and can boost/synerize with the OVs for the treatment of peritoneal colon cancer metastases model in C57BL/6 mice.
A26 Comparison of DNA extraction kits for metagenomic studies in feces. Isabella Kuniko T. Takenaka1, Bruno S. Moda1, Thais F. Bartelli1, Maria G. Amorim1, Gabriela E. Albuquerque1, Andrew M. Thomas2, Emmanuel Dias-Neto3, Diana N. Nunes1, 1.A.C.Camargo Cancer Center, São Paulo, SP, Brazil, 2.Università Degli Studi di Trento, Trento, TN, Italy.

DNA extraction is a critical step in metagenomic studies since it requires the proper lysis of cell walls, allowing the recovery of nucleic acids that would represent the total diversity of communities. Recent studies indicated that the use of different DNA extraction methods in the same sample yielded distinct microbial profiles, highlighting the importance of standardization in DNA extraction methodologies to accurately measure the human microbiome. These issues are even more critical when limiting amounts of samples are available, or when studies target communities with reduced abundance, such as fungi, which represents only 0.1% of total gut microbiota, as has been poorly explored. Here we investigated the performance of three commercial kits for DNA extraction from human fecal samples: QIAamp DNA Stool Mini Kit (Qiagen), E.Z.N.A. Stool DNA Kit (Omega), and ZymoBIOMICS DNA Kit (Zymo), all with or without adding an enzymatic extraction with MetaPolyzme (MAC4L - Sigma), in an attempt to improve the microbiome community profiling. After extraction, DNA-quality and yield were evaluated using Qubit and real-time PCR, V4-V5 16S rRNA and ITS2 followed by DNA sequencing, as well as further analysis using shotgun DNA sequencing. No significant differences were observed in DNA yield as evaluated by Qubit; an average of 40.3 ng/ul of DNA was obtained for all samples and kits. For both fungi and bacteria analysis, the addition of MAC4L in the extraction protocol apparently did not change the alpha diversity (observed and Shannon) for both individuals. Our analysis for samples extracted with different kits, with or without MAC4L, indicated the percentage of reads from bacteria to vary between 85-90%, whereas fungi were between 0.29-0.49%. Human DNA was also found, as expected, and relative amounts varied from 0.1 to 0.3%. qPCR showed that for all kits up to 50ng of DNA/15uL reaction can be safely used, with no significant DNA polymerase inhibition. These results showed similar efficacy for the three kits in representing bacteria and fungi from feces, and maybe because all these kits had a bead-beading step we had no clear benefits from adding extra enzymatic digestion steps with MAC4L. Finally, we decided to use the Omega kit in our lab, since it combines a simple extraction protocol and is reliable and cost-effective.


Background: The use of antibiotics is known to alter the gut microbiome and it is hypothesized that use of antibiotics may also alter the response to checkpoint inhibitors (CPI). As data are limited from real-world settings, we performed a retrospective audit of patients who received CPI along with concomitant antibiotics.

Patients and Methods: This study is a retrospective audit of prospectively collected database of patients who received CPI for advanced solid tumors in any line between August 2015 and November 2018 at Tata Memorial Hospital, Mumbai, India. Antibiotic use was recorded from two weeks before the start of CPI and concomitantly with CPI. All statistical calculations were performed using SPSS statistical software for Windows version 20.0.

Results: A total of 155 patients were identified to have received CPI during the study period, of which 70 (44%) patients received antibiotics. Median PFS in patients who received antibiotics was 1.7 months (95% CI: 1.1-2.3) against 3.6 months (95% CI: 2.3-4.8) for patients who did not receive antibiotics (p=0.912). Median OS in the patients who received antibiotics was 3.9 months (95% CI: 1.8-11.4) as compared to 9.2 months (95% CI: 4.2-12.3) for patients who did not receive antibiotics with a trend to significance with p=0.053 (HR-1.023; 95%CI: 1.00-1.04). Among the patients who received antibiotics, median OS for patients who received ≤10 days of antibiotics was 8.8 months (95% CI: 4.2-11.2) while for patients receiving >10 days of antibiotics, it was 2.8 months (95% CI: 1.2-4.4), p=0.025 (HR 2.0, 95% CI: 1.1-3.7).

Conclusions: This study shows that judicious use of antibiotics is required in patients on CPI or scheduled to be started on CPI.


MicroRNAs (miRNAs) play important roles in various biologic processes, and aberrant miRNA expression...
is one of the mechanisms of tumorigenesis. Previous studies indicate that oncogenic HPV infection interrupts the expression of tumor-suppressive miR-34a and contributes to the development of cervical cancer. In addition, the traditional Chinese medicine *Gynostemma pentaphyllum* (Thunb.) Makino may exert its pharmacologic effects through modifying the gut microbiota by regulating hepatic miR-34a expression. MiR-449 miRs are members of the tumor suppressor miR-34 family and are evolutionarily conserved. In this study, we demonstrated that, in lung cancer cells, ectopic expression of miR-449, including miR-449a, miR-449b, and miR-449c, decreased the levels of several G1 phase proteins including cyclin D1, cyclin D3, CDK4, and CDK6 via directly targeting their mRNA’s 3’-UTR. We also observed a differential induction of apoptosis vs. senescence by the miR-449 cluster. While miR-449a and miR-449c induced senescence, miR-449b induced apoptosis and sensitized cancer cells to apoptotic stimuli, such as serum deprivation. Interestingly, among this cluster miRNAs, only miR-449a could induce significant senescence-associated secretory phenotype (SASP), e.g., expression of IL-8, IL-6, IL-1b, and TNF-alpha. Moreover, we also found that miR-449a increased NF-κB phosphorylation at S276, but not phosphorylation site of S536, and promoted the expression of IL-8 mRNA. In this regard, the gut microbiota has been indicated to induce proinflammatory cytokines such as IL-8 to influence the outcomes of cancer patients. In addition to MRX34 (a miR-34a mimic) used in clinical trials, miR-449 family may also potentially become a new therapeutic candidate for NSCLC and other solid tumors’ treatment.

**A31 Genome-wide association study (GWAS) of host DNA sequence variation and the gut microbiome in the Multiethnic Cohort.** Meredith A. Hullar1, Johanna W. Lampe1, Timothy Randolph1, Keith R. Curtis1, Unhee Lim2, Lynne R. Wilkens3, Loic Le Marchand2, Bruce S. Kristal1, Kris R. Monroe4, Kechen Zhao2, Daniel Stram5, Iona Cheng6, 1Fred Hutchinson Cancer Research Center, Seattle, WA. 2University of Hawaii Cancer Center, Honolulu, HI, 3Brigham and Women’s Hospital, Boston, MA, 4University of Southern California, Los Angeles, CA, 5University of California San Francisco, San Francisco, CA.

Patterns of microbiome diversity vary across human populations, and although variation is largely driven by diet and lifestyle, genetically encoded differences between hosts may be important in shaping the microbiome and health outcomes, including cancer. We report preliminary results from a GWAS of the gut microbiome in 6,217 individuals from the Multiethnic Cohort Study, including African Americans, Japanese Americans, Native Hawaiians, Latinos, and Whites. Genome-wide SNP data was based on existing data from a variety of Illumina Infinium arrays (500,000 to 2.5 million single nucleotide polymorphisms (SNPs); n=4,363) as well as genotyping 1,853 individuals using the Illumina MEGA EX array. SNP imputation was conducted using a cosmopolitan reference panel of all 1000 Genomes samples. The stool microbiome was assessed by paired-end sequencing (Illumina MiSeq) of the16S rRNA gene *(V_{3-6})*. SNP-genera association tests were conducted using linear regression of covariate-adjusted bacterial genera abundance quintiles on SNP genotype. The chi-square statistics were adjusted by the genomic inflation factor. A threshold of p=5x10^{-8} was used to determine genome-wide statistical significance. The covariate-adjusted genera values were computed as the residuals of a logistic ordinal regression of genera abundance quintiles on variables expected to affect the microbiome (i.e., age, sex, genetic ancestry proportions, sample month, and sequencing batch). Initial results yielded 22 genome-wide significant associations across SNPs in 15 different human chromosomes and 11 bacterial genera. Notably, Fusobacteria was significantly associated with star-related lipid transfer domain (STAR03, chromosome 13q13; p=2.8x10^{-8}), voltage-dependent calcium channel gamma 3 subunit (CACNG3, chromosome 16p12; p=3.1x10^{-8}), organic anion transporter polypeptide (OATP, SCLO2B1, chromosome 11q13; p=2.8x10^{-8}), and E-cadherin (CDHR3, chromosome 7q22, p=1.6x10^{-8}). Some Fusobacterial species have been associated with increased risk of colon tumors. *Coprobacillus* was significantly associated with ubiquitin modifier activating enzyme 2 (UBA2, chromosome 19q13, p=4.1x10^{-8}). The pathogen *Slackia* was significantly associated with variants in the zinc finger 850 gene (ZNF850, chromosome 19p13; p=4.3x10^{-8}). These results suggest that host gene variants may be important in shaping the microbiome and influence bacterial pathogen-associated cancer outcomes.

**A32 Identifying actionable pathway malfunction scores with ML algorithm for omics data.** Dmitrii Chebanov1, Nadezhda Tatevosova1, Irina Mikhaylova1, 1Biolg Corp., Walnut, CA, 2New York Medical College, Valhalla, NY, 3National Medical Research Center n.a. N.N. Blokhin, Moscow, Moscow, Russian Federation.

**Background:** Driver mutations are traditionally considered as actionable biomarkers for targeted drugs, but the resistance and relapse effects often occur even when these events are precisely discovered. At the same
time, primary DNA mutations can be only the triggers for cell malignancy and further development of the tumor occurs due to following pathways imbalance, which may be reflected in gene expression. The goal is to detect preaffected pathways that are most close to the oncogenic affected state, so during the treatment strategy planning we could consider these pathways as the next potential targets after nonresponse or relapse.

**Methods:** We took the data from TCGA Pan-Cancer Atlas on whole-exome sequencing and RNA expression for 33 cancers. Mutations were filtered based on their pathogenicity (1,2). The training set included data on mutations and corresponded RNA levels of 1821 cancer pathways-related genes (3). ML method-logistic regression, with 5-fold cross-validation with a test set, was realized on Python 3.7.

**Results:** Using gene expression data, 9 most common actionable events were predicted: oncogenic mutations affecting Ras, Raf, Ras/Raf/MEK, PI3K, CDK protein families, amplifications of EGFR, ERBB2, CDK4 genes, with an accuracy of 80% - 93%. Results were the probabilities of events: range 10-30% occurrence is shown.

**Discussion:** We considered the obtained molecular events probabilities as the scores of corresponding pathways' malfunctions. For some molecular events, more than one-third of patients has >10% affected (unbalanced) pathway state. This approach after validation can be used in clinical research practice for patient cohorts risk stratification, or as additional reinforcement for drug companion tests.

References: 1. COSMIC; 2. Chakravarty et al., 2017a; 3. KEGG.

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**A33 Intratissutal and urinary microbiome in therapy-naive bladder cancer patients: Definition of a gender-specific common microbiome.** Filippo Pederzoli, Roberto Ferrarese, Virginia Amato, Irene Locatelli, Elisa Alchera, Roberta Lucianò, Manuela Nebuloni, Alberto Briganti, Andrea Gallina, Valentina Murdica, Renzo Colombo, Andrea Necchi, Massimo Clementi, Francesco Montorsi, Nicasio Mancini, Andrea Salonia, Massimo Alfano.

Comparing neoplastic vs. non-neoplastic paired tissues, beta-diversity did not show distinct clustering of the samples. At the taxonomic level, the genus *Burkholderia* was enriched in the neoplastic specimens in both genders. When we compared urines of patients vs. controls, the male and female urinary microbiome was dominated by members of the three major bacterial phyla Proteobacteria, Firmicutes, and Bacteroidetes. At lower taxonomic levels, the bacterial taxa differently represented in BCa and controls in men and women, respectively. Comparing paired urinary and tissue-associated microbiome, we defined the “common BCa microbiome,”

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**Background:** Despite being actively investigated for several other malignancies, the impact of the microbiome on tumorigenesis, response to therapy, and patient outcomes has not been thoroughly assessed in urothelial bladder cancer (BCa). Of note, the relationship between urinary and bladder tissue microbiomes has not yet been investigated. Herein, we aimed to assess: i) the gender-specific microbiome differences in the urine and bladder tissue; ii) the extent to which paired urine samples mirror the bladder tissue-associated microbiome.

**Methods:** A total of 166 biologic samples were analyzed: morning, mid-stream voided urines from 49 therapy-naive patients (36 males, 13 females) undergoing radical cystectomy for MIBC and from 59 age-matched healthy controls (34 males, 25 females), plus bladder tissue specimens (paired BCa/non-BCa tissues) of 29 patients (21 males, 8 females). Exclusion criteria included history of recurrent urinary tract infections, positive urine dipstick test at the time of sample collection, recent antibiotic therapy, history of intravesical or neoadjuvant treatment for BCa. Microbiome was analyzed by amplicon-based approach. Sequences with a high-quality score >Q30 and length >250bp were used for the taxonomic analysis and were processed using the QIIME (Quantitative Insights Into Microbial Ecology) software package (v1.9.1). Intra- and interdiversity between samples and identification of taxonomic biomarkers by using the linear discriminant analysis (LDA) effect size (LEfSe) were considered significant at p-value ≤0.05.

**Results:** Comparing neoplastic vs. non-neoplastic paired tissues, beta-diversity did not show distinct clustering of the samples. At the taxonomic level, the genus *Burkholderia* was enriched in the neoplastic specimens in both genders. When we compared urines of patients vs. controls, the male and female urinary microbiome was dominated by members of the three major bacterial phyla Proteobacteria, Firmicutes, and Bacteroidetes. At lower taxonomic levels, the bacterial taxa differently represented in BCa and controls were gender-specific, with 18 and 36 bacterial taxa differentially represented in BCa and controls in men and women, respectively. Comparing paired urinary and tissue-associated microbiome, we defined the “common BCa microbiome,”
representing 34 and 16 bacterial families (>80% of total relative abundance) shared in the urines and tissues of male and female patients, respectively.

Conclusions: We provide novel characterization of the gender-specific microbiome in the urines and paired bladder tissues of BCa patients. A gender-specific "common BCa microbiome" was detailed, highlighting potentially actionable bacterial taxa.

A34 Lung and salivary microbiome in electronic cigarette users, never-smokers, and smokers: A pilot cross-sectional study. Kevin L. Ying¹, Min-Ae Song¹, Daniel Y. Weng¹, Quentin A. Nickerson¹, Joseph P. McElroy¹, Theodore M. Brasky¹, Noah B. Whiteman¹, Mark D. Wewers², Jo L. Freudenheim², Ewy A. Mathe¹, Peter G. Shields¹. ¹Ohio State University, Columbus, OH, ²University of Buffalo, Buffalo, NY.

Background: Little is known about the microbiomes of the lung and oral cavity with electronic cigarette (e-cig) use and how they compare to those of smokers and never-smokers. E-cigs have been promoted as a safe alternative to smoking cigarettes. Given the recent outbreak of E-cigarette or Vaping product use Associated Lung Injury (EVALI), there is an urgent need for understanding the biologic effects of e-cig use on the lung and oral cavity, including effects on the microbiome. Previous studies have been limited to 16S-rRNA sequencing, which was used to detect bacteria genera. In this study, we used metatranscriptome profiling to study differentially abundant bacteria species in the oral and lung microbiome of never-smokers, smokers, and e-cig users.

Methods: A cross-sectional study of 10 never-smokers, 8 cigarette smokers, and 10 e-cig users was conducted, with saliva and bronchoalveolar lavage (BAL) collected for each study participant. RNA was extracted from saliva and BAL samples for total transcriptome RNA-seq analysis. Sequences were aligned with bowtie2 v.2.2.8 to the human genome (hg19) and nonaligned reads were aligned and annotated using NCBI metagenomes database and Kraken v.1. Differences in the microbiome by smoking status were determined by pairwise comparisons using limma-voom with FDR q-value cutoffs <0.2.

Results: The distribution of richness and evenness of bacterial communities measured by Shannon diversity in our metatranscriptome data did not significantly differ between the three smoking status groups. When comparing levels of bacteria species between groups in the saliva, 234 were differentially abundant between smokers and never-smokers, and 39 were differentially abundant between smokers and e-cig users. In the lung, 87 bacterial species were differentially abundant between smokers and never-smokers and 36 were differentially abundant between smokers and e-cig users. Notably, no bacteria species were differentially abundant when comparing e-cig users and never-smokers in both the saliva and lung samples. There are 50 bacterial species found to be differentially abundant in both the lung and saliva samples, 47 of which are decreased in smokers. These 47 bacteria species included common commensal oral microbiome species such as Haemophilus parainfluenzae, Capnocytophaga gingivalis, and Neisseria species. The 3 species that were increased in smokers were Lactobacillus species.

Conclusion: Our findings suggests that smoking cigarettes may alter populations of common commensal species in both the oral and lung microbiome. The lack of differentially abundant bacterial species between electronic cigarette users and never-smokers indicates that e-cigs may alter bacterial species to a lesser extent than smoking.

A35 Methanobrevibacter is associated with cervical dysplasia in Hispanics with HPV infections. Filipa Godoy-Vitorino¹, Josefina Romaguera¹, ¹University of Puerto Rico, Department of Microbiology and Medical Zoology, San Juan, PR, ²University of Puerto Rico, Department of OB/GYN, San Juan, PR.

Bacteria have been extensively associated with several disease phenotypes. Archaea, a major neglected component of the microbiome, accounts for a relatively small percentage of the microbiota and has mostly been studied in the gastrointestinal tract. We hypothesized that dysbiosis in the genital tract included changes in both bacterial and archaeal organisms according to human papillomavirus infections and levels of dysplasia. We analyzed 62 patient samples from recruited patients coming for colposcopy clinics at the UPR and San Juan City clinics (Puerto Rico). From these, 52 were HPV positive and 10 were HPV negative and were stratified according to cytology results. From genomic DNA extracted from cervical swabs, we sequenced 16S rRNA genes and selected 10 patient samples for additional shotgun metagenomics. The patients were grouped in those without epithelial lesions, CIN 1 and CIN3. DNA data analyses were done with shotgun and QIME. Analyses of the 16S rRNA reads revealed 16 archaeal OTUs, revealing an abundance of Methanobrevibacter associated with CIN3 lesions. Shotgun data revealed
**POSTER SESSION A**

*Methanosarcina* to be dominant across all samples with higher dominance in patients without lesions and an increased dominance in *Methanobrevibacter* and *Methanococcus* in CIN3 lesions. No archaean significant differences were found according to HPV risk (HPV infection); however, a significant decrease in *Lactobacilli* was associated with dysplasia. We found that archaea are commensals of the cervical mucosa and may contribute to dysbioses. Acetoclastic *Methanosarcina* are dominant across samples, and CIN3 lesions revealed a higher dominance of hydrogenotrophic methanogens such as *Methanobrevibacter*. The significance of these preliminary results may indicate that archaea cannot be taken out of the ecological context for future cervical cancer prevention strategies.

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**A36 Oral microbiota associated to periodontal disease as a risk factor for oropharyngeal cancer, in patients from sexually transmitted infection clinics in Puerto Rico.** Filipa Godoy-Vitorino¹, Cynthia Perez², Kimil Acosta¹, Brayan Vilanova³, Jeslie Ramos-Cartagena², Jose Vivaldi⁴, Ana P. Ortiz¹.

**Introduction:** Oropharyngeal cancer is on the rise in the US, and despite advances in cancer treatments, oral cancer has a poor prognosis. Tobacco, marijuana, and alcohol use are considered risk factors for oral cancer, as well as periodontal disease (PD) and chronic inflammation, which are considered a significant increase in risk for oral cancer. An altered microbiota is linked with several oral diseases, as several pathogenic species lead to chronic inflammation, and its metabolites may induce permanent genetic alterations and epithelial carcinogenesis. We aimed to relate human papilloma virus (HPV) infection and severity of periodontal disease with the oral microbiota. This ongoing cross-sectional study is recruiting patients aged 21 to 49 from sexually transmitted infection clinics in Puerto Rico. A total of 73 patients were assessed using face-to-face interviews collect sociodemographic, behavioral, oral, and medical characteristics, along with a full-mouth periodontal examination following the NHANES protocol.

Periodontitis was defined according to the Centers for Disease Control/American Academy of Periodontology (CDC/AAP) case classification. The saliva collected was used for genomic DNA extractions and 16S rRNA genes were sequenced with Illumina MiSeq. Samples were analyzed according to HPV status (4 HPV+, 69 HPV-) and periodontal disease severity (44 without PD, 14 mild PD, and 15 moderate to severe PD). Sequence data were deposited in QIITA and data analyses were done in QIIME. While 5% of study participants had oral HPV infection, 60% had no periodontitis, 19% had mild, 18% had moderate, and 3% had severe periodontitis. A total of 2.56 million reads were binned into 4,119 bacterial OTUs and 27 were archaea. We found a total of 32 phyla, no significant differences in structure nor in alpha diversity according to HPV infections nor when stratified by gender (likely due to low sample number), BMI, tobacco, or marijuana use. Significant higher alpha diversity was found in periodontitis patients. Those with severe periodontitis had increased amounts of Verrucomicrobia and Firmicutes. *Akkermansia* had higher abundance in patients with mild periodontitis while *Veillonella* was more abundant in those with severe periodontitis. Although more patients are needed, our preliminary data seem to indicate that oral microbiota dysbiosis is associated with periodontal disease, suggesting a possible role in oral cancer development.

**A37 Restoration of oral microbiota dysbiosis in head and neck squamous cell carcinoma after surgery.** Jason Y.K. Chan, Bowie Wong, Eddy W.Y. Wong, Paul Chan, Zigui Chen. CUHK, Shatin, Hong Kong SAR.

**Introduction:** Increasing reports have indicated the association between oral microbiota dysbiosis and HNSCC, while it is unclear how the oral microbiota responds to surgery. In this study, we longitudinally collected oral rinse samples from patients with HNSCC right before and after surgery at 1, 3, and 6 months, in order to elucidate the dynamic changes of oral microbiota upon treatment.

**Materials and Methods:** A total of 91 HNSCC patients were recruited, with 20 having been collected for a longitudinal set of samples for 6 months. Meanwhile, 93 healthy subjects were selected as controls. The microbiota from oral rinses was classified by 16S rRNA gene V3-V4 amplicon sequencing and QIIME2 algorithm.
Results: Although there was no obvious difference in the alpha- and beta-diversities of oral microbiota between HNSCC patients and healthy subjects, we observed a number of bacterial genera significantly discriminating cases from controls. Further analysis of oral microbiota in HNSCC between pre- and post-surgery found that the community diversity was dramatically depressed at 1 month after surgery (p=0.001), but this was able to restore to the normal level from 3 months with no significant difference between 3 months and preop (p>0.05). The relative abundance of the commensal bacteria, including Streptococcus, Rothia, Corynebacterium, and Granulicatella, consistently increased along 1-, 3-, and 6-month recovery, while the periodontal pathogens Fusobacterium and Peptostreptococcus decreased.

Conclusions: The findings indicate that a taxonomically defined microbial consortium is associated with HNSCC and the oral microbiota is able to restore to the community, trending to healthy status after surgery.

A38 RNA-seq analysis identified candidate pathogens for prostate cancer. Shingo Ashida1, Chiaki Kawada1, Masanori Daibata2, Keiji Imoue1, Hideaki Nakagawa1. 1Department of Urology, Kochi Medical School, Nankoku, Kochi, Japan, 2Department of Microbiology and Infection, Kochi Medical School, Nankoku, Kochi, Japan. Laboratory for Cancer Genomics, RIKEN Center for Integrative Medical Sciences, Yokohama, Kanagawa, Japan.

There is an abundance of evidence that chronic inflammation is linked to prostate cancer (PC), and pathogen infection is considered to be one of the possible causes for PC. Prostate infections by bacteria or viruses have been widely investigated. However, most of these studies have showed conflicting and controversial results. Most studies have focused on the PCR-based targeted detection of bacteria or viruses, and pathogen for PC remains to be found. To identify pathogen for PC, we investigated the transcriptomes of human prostate samples using whole-genome next-generation sequencing. The prostate specimens obtained by radical prostatectomy from 20 PC patients were sliced and divided into four sections. High-quality RNAs were extracted from the sections including PC. RNA-seq libraries were constructed according to the Illumina protocol and next-generation sequenced on a HiSeq 2000 instrument. To explore the potential of other pathogens being associated with PC, we performed de novo assembly of unmapped reads from the RNA-seq data from 20 PC samples. RNA-seq analysis identified four bacteria as candidate pathogens, which included Cutibacterium acnes, uncultured Chroococcidiopsis, Micrococcus luteus, and Moraxella osloensis. Among these candidate pathogens, Cutibacterium acnes was detected in 19 of 20 PC tissue samples by immunohistochemistry. We also performed PCR to detect other candidate pathogens (uncultured Chroococcidiopsis, Micrococcus luteus, and Moraxella osloensis) in PC samples for validation. Our findings provide further evidence of Cutibacterium acnes infections in human PCs as a promising pathogen for PC, and suggest that uncultured Chroococcidiopsis, Micrococcus luteus, and Moraxella osloensis could be novel candidate pathogens for PC. Further research is required and ongoing to clarify the molecular mechanisms underlying bacterial pathogenesis of PC.

A39 The human oral microbiota and risk of lung cancer: An analysis of three prospective cohort studies. Emily Vogtmann1, Xing Hua1, Gaoqin Yu1, Autumn Hullings2, Yunhu Wan2, Casey L Dagani2, Kristine Jones1, Belynda D. Hicks1, Amy Hutchinson1, Shalabh Suman1, Bin Zhu1, Barry Graubard1, Mitchell H. Gail1, J. Gregory Caporaso1, William Wheeler4, Dale Sandler1, Laura E. Beane Freeman1, Linda Liao1, Neal D. Freedman1, Neil Caporaso1, Rashmi Sinha1, Jianxin Shi1, Christian C Abnet1, 1NCI, Bethesda, MD, 2University of Kansas Medical Center, Kansas City, KS, 3Northern Arizona University, Flagstaff, AZ, 4IMS, Rockville, MD, 5NIEHS, Research Triangle Park, NC.

Background: The oral microbiota may be associated with lung cancer risk through direct mechanisms, including infection, immune responses, and periodontal disease, and through indirect mechanisms such as the modification of the oral microbiota by tobacco. We conducted a case-cohort study nested within three US prospective cohort studies to evaluate the association between oral microbiota ascertained years before a cancer diagnosis and risk of lung cancer.

Methods: Incident lung cancer cases within the Agricultural Health Study (AHS; N=244), NIH-AARP Diet and Health Study (N=376), and the Prostate, Lung, Colorectum, and Ovarian Cancer Screening Trial (PLCO; N=700) who provided an oral wash sample were identified. The median time between oral sample collection and diagnosis was approximately 6.6 years, 3.4 years, and 4.5 years for AHS, NIH-AARP, and PLCO, respectively. A referent subcohort was randomly selected by strata of age, sex, and cigarette smoking history. We extracted DNA using the DSP DNA Virus Pathogen kit, and the V4 region of the 16S rRNA gene
was PCR amplified and sequenced using the MiSeq. The sequencing data were processed using QIIME2 with the DADA2 plugin and we generated alpha and beta diversity metrics. Cox proportional hazards models were used to evaluate the hazard ratios (HR) and 95% confidence intervals (CI) for the association between the oral microbial measures and the risk of lung cancer with adjustment for known lung cancer risk factors, and estimates from the three cohorts were meta-analyzed.

**Results:** Increased alpha diversity was associated with decreased lung cancer risk, although only the association with the Shannon Index reached statistical significance (HR for 5th quintile versus 1st quintile 0.74; 95% CI 0.60, 0.92) with no evidence of between-study heterogeneity (p = 0.5968). Specific principal coordinate vectors from the beta diversity matrices were also significantly associated with lung cancer risk, suggesting differing bacterial communities between future lung cancer cases. When stratified by histologic subtypes, the inverse association with alpha diversity was restricted to squamous cell carcinoma, with all alpha diversity metrics reaching statistical significance (e.g., Faith’s phylogenetic diversity HR for 5th quintile versus 1st quintile 0.57; 95% CI 0.37, 0.87). Similarly, when stratified by smoking history, the inverse association with alpha diversity was restricted to former smokers (e.g., observed species HR for 5th quintile versus 1st quintile 0.63; 95% CI: 0.44, 0.89).

**Conclusions:** In oral wash samples collected years before diagnosis, we found significant associations between both alpha and beta diversity metrics of the oral microbial communities and risk of lung cancer. Additional work is required to understand the associations by histologic subtype and smoking history.

**A40 The SIAMCAT R package enables statistical and machine learning analyses for case-control microbiome datasets.** Jakob Wirbel¹, Konrad Zych¹, Morgan Essex¹, Nicolai Karcher¹, Ece Kartal¹, Guillem Salazar², Peer Bork¹, Shinichi Sunagawa², Georg Zeller³. ¹EMBL, Heidelberg, Germany, ²ETH Zürich, Zürich, Switzerland.

Alterations in microbiome composition have been linked to many human diseases, including colorectal cancer or precancerous liver diseases. Findings from microbiome-association studies are increasingly explored as promising avenues for clinical applications due to their diagnostic or therapeutic potential. However, microbiome data complexity and the lack of integrated computational tools make it difficult to arrive at robust associations and predictive disease models. Here, we present the SIAMCAT R package as a modular and user-friendly toolbox for machine learning workflows, statistical analysis, and confounder detection for case-control microbiome datasets. Previously, we conducted a machine learning meta-analysis of colorectal cancer metagenomics studies (Wirbel, Pyl et al., Nat Med 2019) using the functionalities of SIAMCAT, which is now available to the wider community via Bioconductor. We showcase how SIAMCAT is a versatile tool by applying it to a large set of metagenomic datasets that have been processed with a wide variety of taxonomic and functional profiling tools. We furthermore demonstrate how SIAMCAT can help to detect confounding factors in microbiome association studies. By making stringent machine learning workflows and analysis pipelines available through a user-friendly and flexible interface, SIAMCAT will facilitate microbiome data analyses, biomarker discovery, and thus the translation of microbiome research to clinical applications, while simultaneously improving statistical rigor and safeguarding against common machine learning pitfalls.
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B01 Candida albicans infection mediates gastrointestinal track malignancy independently of IL17a in an APECED mouse model. Feng Zhu1, Jami Willette-Brown1, Trang Phan1, Yongmei Zhao1, Bao Tran1, Scott G Filler2, Mihalis S Lionakis3, Yinling Hu4. 1Laboratory of Cancer Immunometabolism, Center for Cancer Research, National Cancer Institute, NIH, Frederick, MD; 2Division of Infectious Diseases, Harbor-UCLA Medical Center, Los Angeles, CA; 3Leido Biomedical Research, Inc., Frederick National Laboratory for Cancer Research, Frederick, MD; 4Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, NIH, Bethesda, MD.

This abstract is being presented as a short talk in the scientific program. A full abstract is printed in the Proffered Abstracts section (PR10) of the Conference Proceedings.


E-cigarette (E-cig) vaping has gained popularity among middle and high-school students within the last decade, being advertised as a safer alternative to cigarette smoke. While acute lung illness has been reported, it is too early to have epidemiologic data suggesting a role of E-cig on oral squamous cell carcinoma. However, recent studies point to its potentially adverse effects on the human epithelium and the oral human microbial flora. Staphylococcus aureus is a resident of the oral microbiota and its carriage has been shown to be significantly higher in the periodontal pocket of patients with actively progressing periodontitis, which is a chronic inflammatory disease and known precursor for oral squamous cell carcinoma (OSCC). Additionally, S. aureus has also been isolated from OSCC tissues. In this study, we aim to identify the response of S. aureus and the oral epithelium to E-cig vape exposure and, further, to determine the effect of E-cig vape on the interaction of S. aureus with the oral epithelium. To measure differences in the ability to form biofilm upon E-cig vape exposure with (3mg/mL) and without nicotine, we analyzed two clinical S. aureus strains isolated from healthy individuals following a 30s puff delivery and a 5-minute incubation. We observed that E-cig vape induced significantly higher biofilm formation than control air exposure in a specifically designed vape chamber regardless of nicotine content (p<0.01). Furthermore, S. aureus strain obtained from cigarette smokers had a significantly higher attachment capacity to oral epithelial cells than sequence-type matched strains from healthy controls (p<0.05), suggesting an augmented potential for oral colonization upon E-cig vape and cigarette smoke exposure. Oral epithelial cells, when exposed to E-cig vape alone, showed a proinflammatory response, through an increase in COX2, TNFα, and IL8 gene expression by qRT-PCR. Additionally, we observed that E-cig vape induced an increase in the DNA damage marker, p-H2A.X, seen by immunofluorescence staining. E-cig vape and S. aureus exposure induced inflammatory signaling as demonstrated by qRT-PCR for COX2 and TNFα, and nuclear translocation of NF-κB seen by immunofluorescence staining. Furthermore, we observed an epithelial stress response through p-ERK1/2 signaling activation by Western blot. Our research suggests that E-cig exposure could be supporting increased oral carriage of S. aureus, therefore perpetuating an inflammatory response and causing extended DNA damage, which could eventually initiate OSCC.


E-cigarette (e-cig) use is rising, but much is unknown about the effects of its vapor. This vapor contains chemicals such as propylene glycol, a known antimicrobial, and nicotine, whose derivatives are carcinogenic. Here, we study the effects of vapor on resident bacteria of the oral cavity and on oral cell inflammation, which is linked to tumorigenesis. Streptococcus mutans, Streptococcus sanguinis, and Streptococcus gordonii species are significant residents in the oral cavity, with S. mutans the primary cause of dental caries. Growth and biofilm formation is enhanced upon exposure to traditional cigarette smoke in vitro. We aim to analyze the interplay between e-cigarette vapor and oral streptococci colonizing of the oral epithelium. S. mutans, S. sanguinis, and S. gordonii were treated using nicotine-free and 3mg nicotine vapor, as well as double-shot menthol freeze flavored 3mg nicotine vapor in a vape chamber designed to phenocopy physiologically relevant exposure. Next, we analyzed the effects on growth and biofilm formation. Nicotine-independent inhibition of growth occurred upon exposure in all three species. Interestingly, biofilm formation was enhanced in S. mutans while decreased...
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in S. sanguinis and S. gordonii. Upon exposure to the same conditions in the vape chamber, oral epithelial cells showed activation of survival pathways, such as ERK 1/2, by Western blot. Upon coculturing of bacterial and oral epithelial cells at a multiplicity of infection of one for five hours exposed to the same conditions, we observed activation of survival and inflammatory pathways, by Western blot. The pioneer colonizers S. gordonii and S. sanguinis generally antagonize caries-causing S. mutans, which can become a predominant member of the community under appropriate conditions, leading to dental caries formation. The observed decrease in the biofilm formation of the commensals S. sanguinis and S. gordonii upon e-cig vapor exposure indicates the opportunistic colonization of S. mutans, whose biofilm-forming abilities increased. Following e-cig usage, dental caries, periodontitis, and eventually cancer in the oral epithelium may result from this dysbiosis of the microbiome in the oral cavity.

B04 Gender-based impact of chemo-radiotherapy in the gut microbial diversity and short-chain fatty acid levels of adults with rectal cancers. Carlos Sola-Morla, Velda Gonzalez-Mercado, Josue Perez-Santiago. University of Puerto Rico Comprehensive Cancer Center, San Juan, PR. College of Nursing - University of South Florida, Tampa, FL.

Background: The gut microbiome is essential in maintaining the host immune system and may influence the host response to cancer therapies. Particularly, by the production of short-chain fatty acids (SCFA) through fermentation of dietary fibers, the gut microbiota helps regulate the immune system. SCFA levels can be affected by changes in gut microbiome composition either by chemo-radiotherapy treatment (CRT) or by gender disparities. We had previously observed that CRT significantly reduced Shannon diversity index and the observed operational taxonomic units (OTUs) during CRT in rectal cancers. Here, we examined the impact of CRT on the levels of SCFAs in adults with RC and investigated gender disparities in the gut microbiome associated with CRT.

Methods: We evaluated the gut microbiome of 35 newly diagnosed RC patients scheduled to receive CRT. Demographics, health forms, and stool samples were collected before and after CRT (12-16 treatments). We sequenced the V3-V4 hypervariable region of the 16S rDNA and measured levels of SCFA (from Acetate [C2] to Octonoate [C8]) by LC-MS/MS and results were expressed in log2 (nmol/mg). Alpha diversity (Shannon index [community diversity]) and Observed OTUs [community richness]) was calculated using the QIIME2 software and all statistical analyses were performed in R statistical software.

Results: Study participants were 35 subjects (20 males vs. 15 females) with an average age of 61.1±9.8 years, even though females tended to be younger than males (57.9±9.8 vs. 63.8±9.3, p=0.08). While females had a trend for a higher Shannon index when compared to males before CRT (6.46±0.31 vs. 6.11±0.43, p=0.09), they had significantly lower Shannon index (5.26±0.31 vs. 5.94±0.60, p=0.02) and observed OTUs (117±7.6 vs. 170±61.0, p=0.03) after CRT, and females had a higher reduction than males (p=0.04). In regard to SCFA, there was an overall increase on the levels of propionate after CRT compared to before CRT (4.10±0.78 vs. 3.64±1.00, p=0.02). However, while there was no difference in the levels of SCFA based on biologic gender after CRT, females had significantly higher levels of propionate (4.32 ±0.68 vs. 3.60±0.90) and butyrate (2.73 ± 0.82 vs. 1.70±1.29) at the end of CRT, while men did not show any significant difference in SCFA during CRT.

Conclusion: Chemo-radiotherapy resulted in dysbiosis of the gut microbiome and also changed the levels of SCFA. However, these changes in the microbiome associated with CRT were different in females versus males. Our findings suggest that biologic sex may play a key role in the development of personalized cancer treatment strategies.


Introduction: Pancreatic ductal adenocarcinoma (PDAC) is the 3rd leading cause of cancer-related death in the United States. Our group and others have demonstrated that the intestinal microbiota accelerates pancreatic carcinogenesis. The relationship of intestinal bacteria, immune response, and PDAC development is unclear. To that end, we investigated the role of intestinal bacterially soluble factors in modulating the immune environment of PDAC and its progression.

Methods: Mice intestinal microbiota was depleted with wide-spectrum antibiotics. The human PDAC cell line, L3.6pl, was heterotypically implanted into Rag1-/- mice, while the syngeneic murine PDAC cell line, Pan02, was orthotypically implanted into the pancreas of C57Bl/6 mice. Tumor and pancreas infiltrated natural killer (NK)
cells were quantitated by flow cytometry. In vivo NK cell depletion was attained by intraperitoneal injection of anti-Asialo-GM1 antibody twice weekly. Germ-free (GF) and conventionally housed Rag1-/- mice stool was cultured and bacteria-free supernatant extracted. The ability of these bacteria-free supernatants to regulate NK-92mi cell cytotoxicity and migration was tested in vitro by flow cytometry and a Transwell assay, respectively.

**Results:** Compared to microbiota-intact Rag1-/- mice, microbiota depletion yielded 74% smaller tumors (p<0.05) with a 1.5-fold increase in PDAC infiltrating NK cells (p<0.001). Confirmation by immunohistochemistry demonstrated a 6.5-fold increase in NK cell tumor infiltration in microbiota-depleted mice (p<0.0001). Notably, a 3-fold increase of intrapancreatic NK cells in GF Rag1-/- mice versus conventionally housed mice was noted, suggesting that bacteria regulate immune cell trafficking. Antibody-mediated NK cell depletion with concomitant microbiota depletion increased PDAC tumor growth, negating the antitumor phenotype of microbiota depletion alone in both immunodeficient Rag1-/- (2.8-fold increase; p<0.05) and immunocompetent C57Bi/6 mice (2.4-fold increase; p<0.05). Quantitative PCR revealed 9-fold higher IFN-gamma gene expression in PDAC xenografts of microbiota-depleted mice versus microbiota-intact (p<0.05). Cell-free stool bacteria culture supernatant from conventionally housed Rag1-/- mice, but not from GF mice, inhibited NK-92mi cell migration by 26% (p<0.05) and cytotoxicity against L3.6pl cells by 51% (p<0.01). Compared to NK-92mi cells exposed to cultured stool supernatant from GF Rag1-/- mice, SPF cultured stool supernatant resulted in decreased gene expression associated with activation/recruitment of NK cells including FASLG, CCL18, IL-13, CXCR2, CCL4, and increased expression associated with inhibition of NK cell activity including CCR1 and IL-6.

**Conclusion:** These findings suggest that intestinal bacteria modulate PDAC development through suppression of NK cell recruitment and activation, a phenomenon potentially mediated by yet to be identified small molecules.

**B06 Investigating the microbial etiology of Tanzanian esophageal squamous cell carcinoma. Jason Nomburg¹, Susan Bullman², Eric Collisson², Beatrice Mushii³, Msiba Seleka³, Charlie Vaske², Yulia Newton², Amie Radenbaugh², Larry Akoko³, James A. DeCaprio³, Matthew Meyerson³, Elia J. Mmbaga⁴, Katherine Van Loon⁴,¹Dana-Farber Cancer Institute, Boston, MA, ²Fred Hutchinson Cancer Research Center, Seattle, WA, ³University of San Francisco, San Francisco, CA, ⁴Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania, ⁵ImmunityBio, Santa Cruz, CA.

**Background:** Esophageal cancer is a leading cause of cancer-associated deaths worldwide. Notably, there is a disproportionately high incidence of esophageal squamous cell carcinoma (ESCC) throughout the eastern corridor of Africa. One possible explanation for the unique geographic distribution of ESCC may be the human microbiome, which has been shown to influence other gastrointestinal (GI) cancers, including gastric and colorectal cancer (CRC).

**Methods:** To address this question, we conducted RNA sequencing (RNAseq) and whole-genome sequencing (WGS) of samples from 61 Tanzanian ESCC patients. We used the computational microbial identification and classification software PathSeq to conduct a microbial abundance analysis of these samples. Next, we implemented linear discriminant analysis with LEfSe to determine which, if any, microbial taxa are enriched in the ESCC tumors of Tanzanian patients relative to ESCC samples from North America patients available through The Cancer Genome Atlas (TCGA).

**Results:** Analysis of these RNAseq and WGS data reveals an extremely high abundance of *Fusobacterium, Prevotella*, and *Streptococcus* in the tumors of a subset of these patients. Based on the WGS data in particular, 14, 45, and 27 of the 61 ESCC samples maintain at least 10% relative abundance of *Fusobacterium, Prevotella*, and *Streptococcus*, respectively. The RNAseq data are consistent and reveal that as much as 75% of all bacterially derived reads in these samples are from these genera. Furthermore, LEfSe analysis suggest that these bacteria are significantly enriched in Tanzanian ESCC samples compared to North American ESCC samples.

**Discussion:** These data suggest that the microbiome may be involved in ESCC incidence in Tanzania. *Fusobacterium, Prevotella*, and *Streptococcus* are notable for their association with CRC and are correlated with distinct clinical and molecular CRC characteristics. Members of these bacterial genera have been observed to modulate...
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the carcinogenesis of GI cancers in a variety of ways, including through the selective stimulation or inhibition of various classes of immune cells. Furthermore, species within these genera have been observed invasively within cancerous GI tissues. Current studies are under way to visualize these microorganisms in tumor tissue, to characterize their association with molecular subtypes of ESCC, and to understand the relationship between tumor-associated bacteria and bacteria in the oral microbiome of ESCC patients in Tanzania.

B07 Oral, intestinal, and pancreatic microbiomes are correlated and exhibit co-abundance in patients with pancreatic cancer and other gastrointestinal diseases. Mei Chung1, Naisi Zhao1, Richard Meier2, Devein C. Koestler3, Erika Del Castillo4, Guojun Wu5, Bruce J. Paster3, Kevin Charpentier3, Jacques Izard6, Karl T. Kelsey7, Dominique S. Michaud7, 1Department of Public Health and Community Medicine, School of Medicine, Tufts University, Boston, MA, 2Department of Biostatistics, University of Kansas Medical Center, Kansas City, KS, 3The Forsyth Institute, Cambridge, MA, 4Department of Biochemistry and Microbiology, Center for Nutrition, Microbiome and Health, New Jersey Institute for Food, Nutrition and Health, Rutgers University, New Brunswick, NJ, 5Department of Surgery, Rhode Island Hospital, Providence, RI, 6Department of Food Science and Technology, University of Nebraska, Lincoln, NE, 7Center for Environmental Health and Technology, Brown University, Providence, RI.

Growing research has examined the association of oral microbiome with pancreatic cancer risk, but results have been inconsistent. Our previous study showed that bacterial taxa known to inhabit the oral cavity were common in the pancreas microbiome, and that bacterial DNA profiles in the pancreas were similar to those in the duodenum tissue of the same subjects regardless of disease state. These data suggest that bacteria may be migrating from oral into the gut and pancreas. We collected oral swabs and at least one pancreatic tissue or intestinal samples from subjects who underwent surgery for pancreatic diseases or diseases and characterized 16S ribosomal RNA genes using high-throughput DNA sequencing. We then quantified bacterial communities (Amplicon Sequence Variant level) at different body sites, investigated their co-abundance patterns, and analyzed the correlations between microbiome at oral sites and that in pancreatic tissue and intestinal samples using concordance statistics and Pairwise Stratified Association (PASTA) testing. The present analysis included 52 subjects (46% with pancreatic cancer; aged from 31 to 86 years old) contributing a total 324 samples. We identified a total of 73 unique Amplicon Sequence Variants (ASVs) that were shared between oral and pancreatic or intestinal samples. Accounting for pairing and within-subject correlation, 7 ASVs showed significant concordance (Kappa statistics) and 5 ASVs exhibited significant or marginally significant PASTA between oral samples and pancreatic tissue or intestinal samples. Of these, our PASTA analyses identified two specific bacterial species (Gemella morbillorum and Fusobacterium nucleatum subsp. vincentii) that showed consistent presence or absence patterns between oral and intestinal or pancreatic samples. Lastly, our microbial co-abundance analyses showed several distinct ASVs clusters and complex correlation-networks between ASV clusters in buccal, saliva, duodenum, jejunum, and pancreatic tumor samples. Oral, intestinal, and pancreatic microbiomes are correlated. Bacteria of oral origin exhibit co-abundance relationships and demonstrate complex correlation patterns in the intestinal and pancreatic tumor samples. Growing evidence has shown that bacterial species may survive, decline, and adapt as interdependent functional groups. Future studies should aim to uncover the co-abundance of specific microbial communities for studying etiology of microbiota-driven carcinogenesis in prospective and longitudinal studies.


Although numerous studies have shown the relevance of the gut microbiome in several diseases, underlying questions remain concerning the stomach microbiome and the establishment of a causal link between the microbiota and the development of gastric diseases, much beyond Helicobacter pylori and Epstein Barr virus. In this study, we aimed to characterize the bacterial composition of the stomach of subjects undergoing upper endoscopy, including gastric cancer (GC) individuals, aiming to identify fluctuations in bacterial populations that might be associated with stomach health. During endoscopic examination at A.C. Camargo Cancer Center (Sao Paulo, Brazil), gastric fluids (GF) were recovered from either GC patients (113) or individuals with gastric-related complaints, such as superficial gastritis (SG; 79), atrophic gastritis (AG; 12), and intestinal metaplasia (IM; 33). For eubacteria
identification, the V3-V4 region of the 16S rRNA gene was amplified and paired-end sequenced (Illumina MiSeq). Analyses were carried out using Qime2 and phyloseq packages. On average, we identified between 14 and 104 OTUs per subject, evidencing the potential of GFs for determining the stomach microbial composition and the interindividual variation. Testing of sample richness between GC and controls showed significant differences between the number of OTUs observed in each group (an average of 44 and 52 OTUs, respectively—Mann-Whitney test, p<0.05) and SG patients had a significantly increased alpha diversity (Shannon, p<0.05) as compared to AG, IM, and GC patients (both intestinal and diffuse subtypes), indicating dysbiosis already in early carcinogenesis steps. Additionally, the prolonged use of proton pump inhibitors or the presence of H. pylori (except for SG) did not seem to interfere with bacterial diversity. Specific genera are enriched in the sample subsets, including a lower presence of Corynebacterium and increased Streptococcus (Linear discriminant analysis Effect Size, LDA score >2) in AG samples as compared to SG patients, which are also increased in the IM, and GC. These results indicate these bacteria to be potentially associated with the stomach dysbiosis that may lead to the carcinogenesis cascade. Besides the regular turnover of the gastric epithelial tissue and pouring of cells onto the gastric cavity, GF certainly contains a high proportion of transient oral-derived bacteria, while stomach-resident microbiota is expected to be in close contact with the gastric epithelia. Preliminary data analyzing the bacterial content of the saliva x GF in a subset of patients showed no significant beta-diversity differences, but both fluids differ significantly from their biopsies’ composition. We are currently performing culturomics and transcriptomics to identify bacteria that are alive in the stomach. As GC is a complex malignancy with limited treatment options, these results may contribute to developing new interventions to treat and to better understand this disease.

B10 Antibacterial defense and metastatic progression—lessons from head and neck cancer. **Maria Kondratyev**, Aleksandra Pesic, Carl Virtanen, Marianne Koritzinsky, Brad Wouters. UHN, Toronto, ON, Canada.

HNSCC is the 6th most common malignancy in the world. The prognosis is favorable during early stages; however, the disease is rarely diagnosed early due to the lack of symptoms. Most HNSCC patients present with metastatic disease for which the survival rates remain low. Hypoxia serves as a bad prognostic factor with metastatic process in HNSCC. The prognosis is favorable during early stages; however, the disease is rarely diagnosed early due to the lack of symptoms. Most HNSCC patients present with metastatic disease for which the survival rates remain low. Hypoxia serves as a bad prognostic factor with metastatic disease for which the survival rates remain low. Hypoxia serves as a bad prognostic factor with metastatic process in HNSCC. We hypothesized the beta defensin 2 can serve as a serum biomarker of hypoxia and metastasis in HNSCC patients. Utilizing a commercial ELISA kit developed to detect and quantify levels of beta-defensin in human sera, we demonstrated that media collected from cell lines derived from metastases contained higher levels of beta-defensin compared to the cell lines derived from the primary tumors. Moreover, sera from HNSCC patients showed higher levels of beta defensin compared to the normal controls. As a next step, we tested sera samples from 40 HNSCC patients, of whom 20 had lymph node metastasis and 20 did not. While these data are still under analysis, preliminary results suggest that higher concentrations of beta-defensin correlate with the presence of lymph node metastasis in HNSCC patients. Utilizing two large chemical libraries that together contain about 4,000 FDA-approved drugs, we performed high-throughput screening of the HNSCC lines described above in order to discover new drugs targeting head and neck cancer, including drugs that target selectively metastatic cells compared to their primary tumor counterparts. Interestingly, many of the metastasis-specific drugs were antibiotics. Together with the findings described above, these data clearly suggest a connection between patient microbiome and the metastatic process in HNSCC.
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B11 Comparisons of microbial composition identified via 16S rRNA sequencing and whole-genome sequence-based analysis using gut samples for patients with cervical cancer. Greyson Biegert1, Xiaogang Wu2, Tatiana V. Karpinet3, Melissa Mezzari1, Jianhua Zhang1, Lauren Colbert1, Ann Klopp1. 1The University of Texas MD Anderson Cancer Center, Houston, TX, 2Baylor College of Medicine, Houston, TX.

Introduction: 16S RNA sequencing and whole-genome sequencing (WGS) techniques have been previously shown to have a significant degree of correlation, particularly for higher-order-level taxa. However, the large majority of those studies utilize data derived from samples collected in similar but not identical contexts. This project provides a unique opportunity in that both 16S RNA and WGS sequencing datasets were derived from a single fecal sample originating from each patient while undergoing chemoradiation therapy. Using this high-quality information, we investigated the correlation of these two datasets in terms of microbial composition and taxa abundances.

Methods: Forty-one rectal swab samples were collected at the time of pelvic examination before the initiation of chemoradiation treatment and sequenced via Illumina platforms. Alpha and beta diversity was compared by using PCoA analysis of Bray-Curtis, Jaccard, Weighted and Unweighted UniFrac, and Euclidean. Diversity measures from different data analysis tools were also compared to highlight differences in data processing. Taxa with the highest relative abundances within each set of sequencing data were used to evaluate consensus between the datasets.

Results: Alpha diversity assessed by different measures from WGS analysis correlated (Spearman rho value) with the same measures derived from 16S rRNA sequencing. These measures include OTU abundances (rho = 0.763, p = 6.61e-09), Shannon diversity (rho = 0.809, p = 4.40e-03), and InvSimpson (rho = 0.797, p = 2.11e-03). Beta diversity analysis highlighted a greater level of similarity within WGS samples than 16sRNA samples and a high degree of dissimilarity between the two datasets. Among the top fourteen most abundant taxa identified in 16S rRNA sequencing, the four best correlated with WGS results were Faecalibacterium, rho = 0.475, p = 1.68e-02; Mollicutes, rho = 0.302, p = 5.48e-02; Clostridiales, rho = 0.021, p = 8.98e-01; and Bacteria, rho = 0.016, p = 9.23e-01. The remaining ten taxa were negatively correlated.

Conclusions: The use of whole-genome sequencing approaches in microbiome analysis is expanding in order to provide greater depth of information about microbial function. However, comparisons of results from 16S rRNA sequencing and WGS will need to be evaluated with caution due to differences in the interpretation of relative abundances of specific taxa. Future efforts may help to better harmonize these analyses to facilitate comparisons across platforms.

B12 Cross-sectional analysis of grain, gluten, and fiber intakes and gut microbiota in the Food and Microbiome Longitudinal Investigation (FAMILI) Study. Caroline Y. Um1, Brandilyn A. Peters2, Emilia N. Cobbs3, Hee Sun Choi3, Dia B. Beggs3, Richard B. Hayes3, Marjorie L. McCullough1, Susan M. Gapstur1, Jiyoung Ahn3, 1American Cancer Society, Atlanta, GA, 2Albert Einstein College of Medicine, Bronx, NY, 3New York University School of Medicine, New York, NY.

Whole grains are recommended as part of a healthy dietary pattern for the prevention of chronic diseases, including colorectal cancer. Greater whole grain consumption may beneficially alter gut microbiota, and it is unclear if gluten, a protein component of grains, is also associated with altered microbiota. To examine the association between grain, gluten, and fiber intake with gut microbiota, we analyzed data from the ongoing prospective Food and Microbiome Longitudinal Investigation Study. This cross-sectional analysis included 300 men and 501 women of White, Black, Hispanic, and Asian race/ethnicity who completed a 137-item semiquantitative food frequency questionnaire. Gluten intake was estimated using the protein content of grain products. Bacterial 16S rRNA genes from stool samples collected via RNAlater tubes were amplified, sequenced, and assigned to bacterial taxa. We examined associations of whole and refined grain, gluten, and dietary fiber intakes with gut microbiota diversity and composition using multivariable-adjusted linear regression models and permutational multivariate analysis of variance, respectively, and with microbial taxa abundance using analysis of composition of microbiomes (ANCOM). In this diverse study population, the highest quartiles of energy-adjusted refined grain and gluten intake, when compared to the lowest quartiles, were associated with lower Shannon diversity (P-trend=0.03 and P-trend=0.01, respectively), but no other associations with alpha- or beta-diversity measures were observed. The highest quartile of dietary fiber was not associated with alpha-diversity measures but was associated with shifts in overall gut microbial composition (P-trend=0.02). Whole grain
intake was not statistically significantly associated with these microbiome parameters. However, the highest quartile of whole grain intake, compared to the lowest quartile, was associated with greater abundance of several gut taxa, including classes Erysipelotrichi (family Erysipelotrichaceae), Clostridia (genus Faecalibacterium and Lachnospira), and Bacteroidia (Bacteroides plebeius). Higher whole grain intake was also associated with lower abundance of classes Bacteroidia (family Rikenellaceae and Bacteroides uniformis) and Clostridia (genus Oscillariospira and Ruminococcus). Similarly, the highest quartile of dietary fiber intake was associated with greater abundance of classes Erysipelotrichi (family Erysipelotrichaceae) and Clostridia (genus Lachnospira) and lower abundance of class Bacteroidia (family Rikenellaceae). Higher intakes of refined grain and gluten were not statistically significantly associated with altered abundance of gut taxa. Though this study is cross-sectional, identification of gut microbes associated with higher intakes of whole grain and fiber may expand our understanding of how these nutritional factors lower risk for colorectal cancer.

**B13 Development of a low-cost method for collecting fecal samples in clinical trials.** Kimberly E. Peloza1, Joell J. Gills1, Fyza Y. Shaikh1, James R. White2, Sara Glass1, Carisse Lansiquot1, Courtney Stevens1, William Assan1, William H. Sharman3, Dung T. Le3, Jarushka Naidoo1, Evan J. Lipson1, Drew M. Pardoll1, Cynthia L. Sears1. 1Johns Hopkins University School of Medicine, Baltimore, MD, 2Resphera Biosciences, Baltimore, MD.

Although immune checkpoint inhibitors (ICIs) have shown promise in treating various cancers, fewer than half of patients with most tumor types experience a durable response. Thus, there is a need for biomarkers to better predict outcomes. Recent studies suggest that the presence of a handful of microbial species and greater alpha-diversity in the gut may serve as a biomarker for and might facilitate ICI responses. However, the specific bacteria, or bacterial communities, that associate with improved ICI responses vary across study populations, and the factors that contribute to these discrepant findings remain elusive. Thus, a standardized method by which biospecimens may be collected, transported, and stored for gut microbiome studies in the context of ICI therapy is needed. In this study, we evaluated a method for shipping fecal samples using a low-cost (< $3.00) ThinPrep Pap Test® methanol-based preservative kit. Under an IRB-approved protocol, we recruited patients with melanoma, Merkel cell carcinoma, endometrial cancer, and non-small cell lung cancer who had experienced >1 year of durable tumor response after ICI therapy. Patients were provided with stool collection kits and either asked to collect fecal samples at home within 48 hours of their clinic visit and store at 4°C (fresh) or asked to place stool in preservative and ship at ambient temperature to our laboratory (fixed). For fresh samples, a portion of each sample was frozen and another portion placed into preservative as a paired control. DNA was extracted using Zymo Quick-DNA™ Fecal/Soil Microbe kit. For fixed samples, methanol was removed by evaporation prior to DNA extraction. Microbial composition was analyzed with 16S rRNA amplicon sequencing with V3-V2 primers with 150bp paired-end sequencing using an Illumina platform. Among n=10 samples collected in clinic, fixed portions demonstrated decreased alpha-diversity and a uniform shift in beta-diversity compared to the paired frozen portions. In all fixed samples, Faecalibacterium and Roseburia relative abundance decreased with a corresponding increase in Bacteroides. Among a second set of n=11 samples that were placed in preservative by patients and then shipped to our laboratory, we analyzed the effects of shipping by comparing fresh stool samples and shipped fixed samples collected by the same patient within one month. The data revealed similar trends, suggesting that fixation, rather than shipping, drives the overall effect. We are currently verifying the relative abundance of specific bacterial species in both sets of samples using quantitative RT-PCR. Our data show that methanol-based preservation must be optimized prior to clinical utilization for accurate assessment. If optimized, we have identified a low-cost method to collect fecal samples that could be adopted in community practices and low-income areas. Ongoing work from our group includes optimization of processing procedures, ratio of fecal matter to preservative, and storage conditions.

**B14 Flow cytometry for targeted culturomics of gut commensal species and rapid overview of microbiota composition.** Samuel Bellais1, Mélanie Nehlich1, Aurore Duquenoy1, Maryne Ania2, Jan Baijer3, Iliia Belotserkovsky1, Vincent Thomas3, 1BIOASTER, Paris, France, 2MaaT Pharma, Lyon, France, 3CEA, Fontenay-aux-Roses, France.

An ever-increasing number of studies report the importance of the composition of the intestinal microbiota in the treatment of cancers. The mechanisms involved are varied. The reciprocal interaction of drugs with bacteria can have an effect on the efficacy as well as the toxicity of treatments. In addition, some species or strains are able to stimulate CD8+ T cell production and the effectiveness of immune checkpoint blockers (ICBs). As part of these treatments, there is
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therefore a potential interest in being able to isolate and cultivate bacterial species associated with the response to ICBs in different cancers. The objective is to better understand the mechanisms involved and possibly develop complementary therapeutic and/or diagnostic solutions. However, this approach is still limited by the fact that a large number of commensal bacterial species in the intestine are difficult to cultivate, due to specific nutritive requirements, extreme oxygen sensitivity (EOS), or under-representation in the whole bacterial population. In an attempt to circumvent these limitations, we developed flow cytometry (FCM) and cell sorting in anaerobic conditions. A series of polyclonal antibodies specific to commensal species known to be beneficial to the host such as Faecalibacterium prausnitzii, Akkermansia muciniphila, Christensenella minuta, and Eubacterium hallii have been produced and used in combination with viability and Gram staining to rapidly detect, sort, and culture species of interest. This strategy has enabled a rapid collection of strains to be built up from the stools of healthy volunteers, demonstrating the usefulness of the approach.

Developments are under way to apply reverse genomics strategies to identify sequences encoding immunogenic proteins in order to produce antibodies even in the absence of already cultivated strains, which is still the case for approximately 70% of the human gut microbiota species. In conclusion, our work confirms that FCM is well adapted for complex bacterial microbiota studies. When used in conjunction with appropriate staining, it gives a general overview of microbiota composition and variations in longitudinal studies, including bacterial load, which is an important piece of information. In addition to sorting and cultivating target species of interest, it can be used for a quick and easy assessment of microbiota composition, either before starting a drug treatment or for monitoring the effects of the treatment on commensal microbiota.

B15 Gut microbiome populations modulate neoadjuvant chemotherapy responsiveness in preclinical triple-negative breast cancer murine model.

Kenysha Clear¹, Adam Wilson¹, Akiko Chiba², Katherine L. Cook³, Alaa Bawaneh⁴, ¹Department of Surgery, Wake Forest University School of Medicine, Winston-Salem, NC, ²Department of Surgery, Wake Forest Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC, ³Department of Surgery, Department of Cancer Biology, Wake Forest Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, NC, ⁴Integrative Physiology and Pharmacology-Department of Surgery, Wake Forest University School of Medicine, Winston-Salem, NC.

Triple-negative breast cancer (TNBC) is a highly aggressive subtype with a 5-year survival rate significantly worse when compared to other breast cancer types. There are no targeted therapy options, limiting these patients to cytotoxic chemotherapy regimens. Our group demonstrated increased tumoral Pseudomonas abundance in breast cancer patients receiving neoadjuvant chemotherapy, suggesting that systemic anticancer therapy administration may modulate microbiota populations. The purpose of our study was to determine whether gut microbiota populations correlate with chemotherapeutic responsiveness and may be a predictive biomarker outcome. We wanted to determine the impact of shifting the microbiome on chemotherapeutic outcome. To do so, 8-week old female BALB/c mice were injected with 4T1-luciferase cells in the mammary fat pad. Once tumors reached 100 mm³, mice were either untreated (control group), treated with 1x weekly 2.5 mg/kg doxorubicin (DOX) for 4 weeks, or treated with doxorubicin +antibiotics (mixture of streptomycin, ampicillin, and colistin in the drinking water to ablate the microbiome). Tumor size was monitored. Tumors and lungs were collected after the study. Fecal samples were collected at T₀ (before treatment) and T₇ (after treatment). Mice receiving DOX were stratified into DOX-responders or DOX-nonresponders based upon tumor size. Mice from DOX-responders and DOX +antibiotics groups displayed reduced tumor weight and decreased lung metastatic burden. 16S-bacterial sequencing indicates elevated fecal Ruminococcus correlates with DOX-nonresponsiveness and increased abundance of Oscillibacter and Bacteroidales is associated with better therapeutic outcome. Protein analysis of tumor tissue indicates a significant increase in apoptosis in DOX-responders and DOX +antibiotic groups. To determine whether modulating the gut microbiome influences drug responsiveness, BALB/c mice were stratified into a control group or group receiving lard diet-derived fecal transplant (LDFT) by oral gavage. Mice were injected with 4T1-luciferase cells in the mammary fat pad. Once tumors reached 100 mm³, mice were treated with 1x weekly 2.5 mg/kg DOX for 4 weeks. Tumors and lungs were collected at the end of the study. Fecal samples were collected at T₀ (before gavage), T₇ (after 3 weeks of LDFT and before DOX-treatment), and T₆ (at end of study). All tumors from LDFT-group were larger and displayed reduced chemotherapy responsiveness when compared with control animals, suggesting gut microbiome populations can modulate chemotherapy resistance. Taken together, our data demonstrate that...
chemotherapy efficacy is modulated by gut microbiome and suggest that modulation of the gut microbiome through dietary or probiotic interventions may affect therapeutic outcomes. Moreover, fecal microbiota populations could be used as a predictive biomarker of chemotherapeutic responsiveness.

**B16** High-resolution metagenomic profiling revealed gut microbiome features for the response to cancer immunotherapy reproducible among multiple cohorts of patients. Chan Yeong Kim, Beung-Chul Ahn, Min Hee Hong, Yoo Jin Chun, Hye Ryun Kim, Insuk Lee. Yonsei University, Seoul, Republic of Korea, Yonsei University College of Medicine, Seoul, Republic of Korea.

Cancer immunotherapy is currently standard of treatment showing significant clinical benefits to cancer patients, but the beneficial effects are limited to a relatively small subset of patients. Of various factors that may affect the efficacy of cancer immunotherapy, the gut microbiome is receiving more attention because of its strong correlation with immune regulation. Recently, independent studies based on Western populations have identified several taxa that are differentially abundant between responders and nonresponders. However, the reported taxa associated with anti-PD-1 response differ entirely among these studies. In this study, we performed 1) deep (>100M reads in average) metagenome shotgun sequencing on the fecal sample of 49 Korean non-small cell lung cancer (NSCLC) patients, 2) taxonomic profiling using a highly comprehensive gut microbiome-specific genome database, and 3) gene-level profiling with the gut microbiome specific gene catalog to improve the resolution of metagenomic analysis. With the high-resolution metagenomic profiling, we found several taxonomic and functional signatures associated with the response of anti-PD-1 therapy. Interestingly, we found that some of the signatures were reproduced in five independent datasets regardless of the cancer types (melanoma, NSCLC, and renal cell carcinoma) and the type of immunotherapy (anti-PD-1, anti-CTLA4, and the combination of them).

For instance, a responder-enriched taxon in the Korean cohort was more frequently detected in the responders in all cohorts (abundance fold-change > 2) and significantly enriched (p<0.05) in two cohorts. Moreover, when we performed an association analysis with the combined profile, the taxon was identified with the highest significance among the differentially abundant taxa (fold-change=2.41, p=2.5e-06). Consistent with the result of the taxon-level analysis, we found that the genes encoded by the taxon were also enriched in responders in multiple studies. In summary, using high-resolution metagenomic profiling, we identified gut microbiome features for the response to cancer immunotherapy shared across multiple cohorts for the first time, to the best of our knowledge.

**B17** IKKα/STAT3 antagonistic signaling regulates fungi-bacteria endosymbiosis-associated carcinogenesis. Na-Young Song, Xin Li, Jonathan H. Badger, Jami Willette Brown, Xhonghe Sun, Gongping Shi, Feng Zhu, Chengfei Jiang, Colum O’hUigin, Xiaolin Wu, Giorgio Trinchieri, Yinling Hu. Yonsei University, Seoul, Korea, National Institutes of Health, Frederick, MD, Leidos Biomedical Research, Inc., Frederick, MD.

Clinically, oral fungating lesions frequently occur in cancer patients following radiation and chemotherapy. However, their role in carcinogenesis has not been fully understood. Our previous finding showed that defective IKKα-mediated autoreactive T cells promote fungal infection and esophageal malignancy, but whether IKKα-mediated altered epithelial properties regulate fungal colonization and carcinogenesis remains to be tested. To investigate whether IKKα-mediated altered epithelial properties regulate fungal colonization and carcinogenesis, we orally infected mice lacking Ikκα (IkκαΔSOE) or both Ikκα and Stat3 (IkκαΔSOESOE Stat3ΔSOE) in the stem cells of the skin and mouth with fungi. We found that oral fungal infection enhanced Ikκα ablation-mediated skin and oral carcinogenesis in association with increased oral and skin bacteria counts and altered oral bacteria phylum from gram-positive to gram-negative. Enhanced oral fungal/bacterial infection increased inflammasome activities and systemic IL-17A/IL-1β signals. Surprisingly, Stat3 ablation rescued these phenotypes in IkκαΔSOESOE Stat3ΔSOE mice. In addition, amoxicillin treatment inhibited skin carcinogenesis and oral/skin bacteria counts and reversed oral bacteria phyla in fungal-inoculated IkκαΔSOE mice. These findings highlight that cancer cell IKKα/STAT3 antagonizing pathways determine susceptibility to fungal and bacterial colonization, which impacts carcinogenesis. Human head and neck squamous cell carcinomas also share oncogenic pathways and bacteria sequences/counts with mice, suggesting that oral fungating/ulcerating lesions enhance local and distal tumorigenesis in humans.
B18 Microbiome regulates the capacity for immune surveillance of soft tissue sarcoma and response to oncolytic virus immunotherapy. Saif U. Sikdar1, Daesun Kim2, Tie Wang1, Franz Zemp2, Douglas Mahoney1. 1Department of Microbiology, Immunology and Infectious Disease, University of Calgary, Calgary, AB, Canada; 2Charbonneau Cancer Research Institute, Calgary, AB, Canada; 3Alberta Children’s Hospital Research Institute, Calgary, AB, Canada.

Oncolytic virus immunotherapy (OVIT) is based on a special class of wild-type or engineered viruses that can re-engage host immune surveillance to attack and kill tumor cells. However, like other cancer drugs, response to OVIT differs among patients, for reasons not fully understood. We are investigating whether the microbiome is a broadly acting modulator of cancer immune surveillance, how it influences anticancer immunity, and whether it has an impact on OVIT. To test the impact of the microbiome in immune surveillance of soft tissue sarcoma, we orthotopically implanted immunogenic and syngeneic rhabdomyosarcoma (RMS) models into C57BL/6 mice sourced from different repositories such as Charles River (CR), Taconic Farms (TAC), and Jackson Laboratories (JAX). We found that the composition of the microbiome is different, and the capacity for immune surveillance of RMS is higher in JAX vs. CR or TAC mice. To overcome the potential effects of genetic polymorphisms that accrue in mice bred at different facilities, we generated inbred mice that acquire divergent microbiomes since the first day of birth (IMDM-JAX or IMDM-CR). Experiments in these mice confirmed that the JAX microbiome leads to enhanced capacity for cancer immune surveillance. Pilot 16S metagenomic sequencing identified an uncharacterized genus of the family Ruminococcaceae as being positively associated with cancer immune surveillance. Exposure to broad-spectrum antibiotics dampened antitumor immunity in JAX mice while enhancing it in CR or TAC mice, indicating plasticity in the microbiome’s impact on immune surveillance. To identify the immune cell types involved in this phenomenon, we conducted flow cytometry and antibody-mediated cell depletion experiments. We observed fewer myeloid-derived suppressor cell and more tumor-specific CD8+ T cell in tumors established in mice harboring JAX vs. CR microbiome. Additionally, CD8+ T-cell depletion abrogated anticancer immunity in both groups. We also found that mice harboring JAX vs. CR microbiome have different metabolomic profiles and hematopoietic precursor cells, suggesting a potential mechanistic route of microbiome-mediated modulation of anticancer immunity. To test if the anticancer immunity enhanced by the microbiome provides therapeutic benefit to T-cell dependent OVITs, we tested two different rhabdoviral OVITs—Farmington Virus (FARV) monotherapy and Vesicular Stomatitis Virus delta M51 (VSVdeltaM51) in combination with a SMAC mimetic called LCL161. Our experiments showed that both OVITs cure more mice that acquired anticancer immunity-promoting microbiome. Collectively, our studies suggest that a specific composition of the microbiome enhances the capacity for baseline cancer immune surveillance, which augments treatment outcome of OVITs. Ongoing studies seek to validate this conclusion using metagenomic sequencing of fecal samples and single-cell sequencing of the immune cells.


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B21 The gastrointestinal microbiota controls cancer cell intrinsic mechanisms to promote the progression of acute lymphoblastic leukemia. Wadie Mahauad-Fernandez, Soumaya Zlitni, Ami Bhatt, Dean Felsher. Stanford University, Stanford, CA.
Acute lymphoblastic leukemia (ALL) is the most common pediatric cancer and the second most common acute leukemia in adults. Despite best existing therapy, older children and elderly ALL patients have poor prognoses. Thus, there is a need to identify alternative therapeutics for these patients. There has been controversy about the function of the gut microbiota in cancer, with some reports showing that it supports tumor growth and others showing tumor growth inhibition. Recently, Dr. Melvyn Greaves proposed that ALL development may have a microbial trigger; however, gut microbiota studies in ALL are scarce. Little is known about the role of the gut microbiota in ALL progression and in reshaping cancer cell-intrinsic pathways that are as important as immune responses in the outcome of ALL. Recently, we found that gut microbiota depletion in immunocompromised mice reduces ALL growth by inducing apoptosis and inhibiting proliferation. We show that in immunocompromised microbiome-depleted mice, the rate of ALL tumor growth is reduced compared to microbiome-competent mice. Molecularly, we found that microbiome ablation results in changes in cancer cell-intrinsic pathways of apoptosis and proliferation in these tumors. To further understand how the gut microbiota affects these cancer cell-intrinsic pathways, we have performed RNA sequencing on tumors from microbiome-competent and microbiome-depleted mice accompanied by 16s rRNA sequencing from stool samples and mass spectrometry of blood serum to identify metabolites secreted by the gut microbiota that reach the tumor site, affecting cancer cell growth. Our goal is to define bacterial species and metabolites involved in ALL progression and to mechanistically determine how these bacterial species and metabolites regulate ALL growth via regulation of cancer cell-intrinsic pathways. These data suggest that the gut microbiota may regulate ALL progression in an immune-independent manner via transcriptional changes of cancer cell-autonomous pathways. We envision that the gut microbiota can be reshaped in ALL patients who are elderly, chemo-refractive, and/or immunocompromised to alter cancer cell-intrinsic pathways to treat ALL. The clinical impact of these findings is significant given that ALL patients who are immunocompromised could still benefit from therapeutics aiming at modulating the gut microbiota.

B22 The human skin bacteria *Staphylococcus epidermidis* ameliorates UVB-induced free radicals through reduction of labile iron. **Arun Balasubramaniam**, Sunita Keshari, Prakaso Adi, Chun-Ming Huang. National Central University, Zhongli, Taoyuan, Taiwan.

UVB-induced skin damage results in various inflammatory disorders through the induced generation of reactive oxygen species (ROS) that quickly inactivate tissue antioxidants and chronic disorders; in severe cases it can lead to skin cancer. We investigated efficacies of human skin commensal bacteria *S. epidermidis* (ATCC12228) with glycerol, which on fermentation produces electrons. In vivo affirmation on ICR mice has confirmed the antioxidative role of topically applied *S. epidermidis* with glycerol against UVB irradiation and maintained sufficient expression of 4-hydroxynonenal (4-HNE) and cyclobutane pyrimidine dimer (CPD), a major biomarker for lipid peroxidation and DNA damage. Upon UVB irradiation in keratinocyte cell lines treated with glycerol mediated *S. epidermidis* fermentation product show the reduced intracellular oxidative stress. *S. epidermidis* or glycerol alone in in vivo topical application in mice skin and in vitro fermentation product treatment in keratinocytes does not influence the level of oxidative stress. Further electrochemical behavior of glycerol mediated *S. epidermidis* fermented medium found to produce electron transfer; this result suggests the electrogenic and antioxidant property of *S. epidermidis*. The electrons produced by *S. epidermidis* fermentation product initiate reduction of free radicals by converting toxic Fe3+ (ferric ion) back to nontoxic Fe2+ (ferrous ion); thereby it terminates Fenton’s reaction and maintains iron hemostasis. The novel pathway linking electrons produced by probiotic skin bacteria and iron metabolism has been further analyzed.

B23 The mammary tissue microbiome in breast cancer development. **Jaelyn Gabel**, Courtney Hoskinson1, Annie Kump2, Karin B. Michels3,4, Natascia Marino1,5, Leah T. Sliemsma1. 1Natural Science Division, Seaver College, Pepperdine University, Malibu, CA, 2Department of Epidemiology, Fielding School of Public Health, University of California, Los Angeles, Los Angeles, CA, 3Institute for Prevention and Cancer Epidemiology, Faculty of Medicine and Medical Center, University of Freiburg, Germany, Breisgau, Germany, 4Division of Hematology/Oncology, Department of Medicine, Indiana University, Bloomington, IN, 5Susan G. Komen Tissue Bank at Indiana University Simon Cancer Center, Bloomington, IN.
**Introduction:** Breast cancer is the most prevalent type of cancer among women (other than some nonmelanoma skin cancers), with approximately one in eight women diagnosed with breast cancer during their lifetime. The mammary tissue microbiome has recently been characterized, and shifts in the abundance of mammary tissue bacterial taxa have been associated with benign and malignant breast tumors. This suggests particular bacterial taxa as oncogenic and key in driving breast cancer development. However, these studies utilized mammary tissue obtained from breast reduction or enhancement surgery as healthy control tissue, which has significant histologic abnormalities compared to tissue from normal healthy donors. The Susan G. Komen Tissue Bank (KTB) at the Indiana University Simon Cancer Center (IUSCC) is a unique and precious repository of normal breast tissue, ideal for compositional and functional analyses of the mammary tissue microbiome. We have also identified a subset of women who donated healthy tissue to the KTB and later developed breast cancer. This provides us with a rare opportunity to study shifts in the mammary microbiome composition that may preclude breast cancer development. Our research objective is to compare the composition of the mammary microbiome in healthy and prediagnostic tissue to that of cancerous tissue.

**Methods:** Our cohort comprises four tissue subsets: healthy (n = 50), prediagnostic (n = 15), adjacent normal (n = 50), and tumor (n = 50) selected from the KTB and IUSCC Tissue Banks. DNA was isolated from all 165 tissue samples. DNA from three of these samples, two positive controls, and two negative controls was submitted for Illumina Miseq paired-end sequencing of the V4 region of the 16S gene at the University of California, Davis Host Microbe Systems Core Lab. Samples underwent DNA extraction followed by 16S rRNA metagenomic analysis and taxonomic profiling using Divisive Amplicon Denoising Algorithm (DADA)-2 pipeline. Microbiomes from all body sites were compared and correlated to disease protocol; responses were recorded per RECIST 1.1 and AEs per CTCAE 5.0. Samples underwent DNA extraction followed by 16S rRNA metagenomic analysis.

**Results/Conclusions:** The breast tissue samples display microbiome compositions dominated by three phyla: Proteobacteria, Firmicutes, and Bacteroidetes. Negative controls displayed fewer than 10 reads and positive controls yielded accurate percentages of several difficult-to-lyse bacteria. In January 2020, all 165 DNA samples will be submitted for 16S rRNA metagenomic sequencing for analysis of the microbiome composition among the four tissue subsets. We will use multivariate linear modeling to adjust for clinical factors such as age, BMI, and menopausal status and to determine if microbiome composition is modified by cancer status. This work will be fundamental in characterizing the composition of the healthy mammary tissue microbiome and identifying microbial determinants of breast cancer.

**B24 The microbiome in lung cancer under immunotherapy: Significant compositional differences associated with treatment response and AEs.**

Justin J. Chau1, Meeta Yadav2, Muhammad Furqan1, Keri Mercer1, Evan Eastman1, Shailesh Shahi1, Qun Dai1, Carlos Chan1, George Weiner2, Taher Abu Hejleh1, Ashutosh Mangalam1, Jun Zhang1, 1University of Iowa Holden Comprehensive Cancer Center, Iowa City, IA, 2University of Iowa, Division of Pathology, Iowa City, IA, 3University of Iowa, Division of Internal Medicine, Iowa City, IA, 4University of Kansas Medical Center, Division of Medical Oncology, Kansas City, KS.

**Background:** In recent years, attention has shifted to modification of tumor response to immunotherapy via the host microbiome. The mechanisms of these interactions, causative or consequential, remain incompletely understood. We seek to explore this further with a longitudinal study of lung cancer patient microbiomes and immunotherapy-related adverse effects (AEs) preceding and during immunotherapy.

**Methods:** Patients with lung cancer (LC) treated with immunotherapy (anti-PD-1/L1 agents including pembrolizumab, nivolumab, atezolizumab, and durvalumab) with or without chemotherapy at the University of Iowa from November 2018–April 2019 were consented for this ongoing study. Fecal samples and nasal and buccal swabs were obtained prior to therapy. Patients were treated and monitored per respective disease protocol; responses were recorded per RECIST 1.1 and AEs per CTCAE 5.0. Samples underwent DNA extraction followed by 16S rRNA metagenomic analysis and taxonomic profiling using Divisive Amplicon Denoising Algorithm (DADA)-2 pipeline. Microbiomes from all body sites were compared and correlated to treatment response and AEs. In addition, baseline LC gut microbiomes were compared to fecal samples provided by healthy controls (HC) in the same geographic location. This project is registered on clinicaltrials.gov (NCT03688347).

**Results:** Gut microbiota significantly differed compared to oral and buccal microbiota in all patients. Gut microbiota from LC patients was compared to HC samples from the same geographic area. LC patients exhibited drastically different baseline composition, including dramatic increases in Firmicutes, Actinobacteria, and Verrucomicrobia, and significant decreases in Bacteroidetes, Proteobacteria, and Cyanobacteria. We noticed a clear inversion of Firmicutes/Bacteroidetes ratio between HC and LC patients, differences also reflected at the genus level. NSCLC patients experiencing immunotherapy-related adverse events were found to have at baseline markedly
fewer Bifidobacterium and Desulfovibrio (p < 0.05 and FDR <0.05) when compared to those who did not experience AEs, regardless of grouping parameters (e.g., grade 0 vs. 1-4; 0-1 vs. 2-4; and 0 vs. 1-2 vs. 3-4). In addition, patients who responded to combined immunotherapy and chemotherapy (best response >= PR) exhibited enriched baseline Clostridiales (phylum Firmicutes, p=0.018) but reduced Rikenellaceae (phylum Bacteroidetes, p=0.016).

**Conclusion:** Our study found promising trends in microbiome constitution. Compared to HC, we found significant differences in baseline LC gut microbiome at phylum and genus levels. More importantly, there are notable differences comparing LC patients who suffered AEs to those with none and between immunotherapy responders vs. nonresponders. Our project marks an important first step in a long-term study that could shed new light on the microbiome’s influence on immunotherapy treatment outcomes.


Recent reports show that colorectal tumors contain microbiotas that are distinct from those that reside in a “normal” colon environment and that these microbiotas can contribute to cancer progression. *Fusobacterium nucleatum* is the most commonly observed species in the colorectal tumor microenvironment and reportedly influences disease progression through numerous mechanisms. However, a detailed understanding of the role of this organism in cancer progression is limited, in part due to challenges in maintaining *F. nucleatum* viability under standard aerobic cell culture conditions. Herein we describe the development of a 3-dimensional (3D) tumor spheroid model that can harbor and promote the growth of anaerobic bacteria. Bacteria-tumor cell interactions and metabolic crosstalk were extensively studied by measuring the kinetics of bacterial growth, cell morphology and lysis, cancer-related gene expression, and metabolomics. We observed that viable *F. nucleatum* assembles biofilm-like structures in the tumor spheroid microenvironment, whereas heat-killed *F. nucleatum* is internalized and sequestered in the cancer cells. Lastly, we use the model to coculture 28 *Fusobacterium* clinical isolates and demonstrate that the model successfully supports coculture with diverse fusobacterial species. This bacteria-spheroid coculture model enables mechanistic investigation of the role of anaerobic bacteria in the tumor microenvironment.

**B26 Comparative analysis of breast tumor microbiome in Black non-Hispanic (BNH) and White non-Hispanic (WNH) women.** Srikantha Thyagarajan1, Yan Zhang1, Santosh Thapa1, Michael S. Allen1, Nicole Phillips1, Jamboor K. Vishwanatha1.1University of North Texas Health Science Center, Fort Worth, TX, 2Baylor College of Medicine, Houston, TX.

African American women are approximately twice as likely to be diagnosed with highly aggressive estrogen receptor-negative (ER-) and TNBC subtypes of breast cancer than Caucasian women. Among biologic factors, microbiota has been implicated in the etiology of several kinds of cancer including breast cancer. Few recent studies have shown that the breast niche-specific microbiota may have a major influence on breast tumorigenesis as shown by a decreased abundance of bacterial species with known immunomodulatory and probiotic effect in paired tumor tissue as compared to normal tissue derived from healthy patients, including different microbiota profiles in different subtypes of breast cancer. To understand whether the breast tissue harbors microbiota profiles that are uniquely race-specific we have analyzed tumor and matched normal and tumor tissue using 16S rRNA targeted sequencing strategy. Two distinct breast tumor types derived from women were included in this study: triple-negative breast cancer (TNBC) and triple-positive breast cancer (TPBC) derived from BNH and WNH women. The data were analyzed for microbiota composition, abundance, and diversity parameters, alpha diversity and beta diversity. The preliminary microbiome analysis revealed specific differences in abundance both at the phylum and genus levels between WNH and BNH women breast tissues; the alpha diversity matrix, Shannon index measuring both richness and evenness of microbiota diversity showed differences in microbial diversity between normal breast tumor tissue and the matched normal adjacent to tumor tissue. The microbiota richness was relatively lower in BNH TNBC tumor tissue as compared to its matched normal adjacent to tumor zone as defined by pathologic analysis. In contrast, the microbiota richness was higher in WNH TNBC tumor tissue as compared to its matched normal breast tissue. The multivariate analysis of beta diversity revealed a distinct clustering in BNH and WNH TNBC microbiota between both tumors as compared to normal tissue and BNH as compared to WNH racial groups. Research reported in this publication was supported...
B27 Elucidating role of bacteria during pancreatic ductal adenocarcinoma (PDAC). Vidhi Chandra1, Olivereen Le Roux1, Erick Riquelme1, Yu Zhang1, Anirban Maitra1, James R. White2, Florencia McAllister1. 1The University of Texas MD Anderson Cancer Center, Houston, TX; 2Respha Biosciences, Baltimore, MD.

This abstract is being presented as a short talk in the Proffered Abstracts section (PR05) of the Conference Proceedings.

B28 Entero-mammary microbiota signaling axis regulates dietary influences on breast cancer risk. David R. Soto-Pantoja, Kenysha Y.J. Clear, Adam S. Wilson, Greg Kucera, Edward Levine, Akiko Chiba, Katherine L. Cook. Wake Forest University School of Medicine, Winston-Salem, NC.

This abstract is being presented as a short talk in the Proffered Abstracts section (PR11) of the Conference Proceedings.


Introduction: Endometrial cancer (EC) is the 4th most common cancer in US women. The relentless rise of EC frequency and mortality is due in part to the obesity epidemic (Annual Report to the Nation on the Status of Cancer, 2019). Obesity is associated with higher risk of both developing and dying from EC. The microbiome is known to play a complex role in the regulation of obesity and cancer, yet the inter-relationship of obesity, the uterine tumor microbiota, and EC pathogenesis is unknown, including the potential influence of menopausal status. Thus, we characterized the microbiota of the malignant uterus using pre- and postmenopausal, obese and lean genetically engineered mouse models of endometrioid EC.

Methods: The Lkb1flo/flp53flo/fl mouse is a genetically engineered, preclinical model of endometrioid EC. At 3 wks of age, Lkb1flo/flp53flo/fl mice were fed a low-fat diet (LFD, 10% calories from fat) versus a high-fat diet (HFD, 60% calories from fat) to mimic diet-induced obesity. At 6 wks of age, the right uterine horn was injected with AdenoCre virus to delete Lkb1 and p53 and induce EC. Concurrently, mice either underwent bilateral oophorectomy to induce the postmenopausal state or retained their ovaries to maintain a premenopausal status. EC tumors were collected from all mice 12 wks after tumor induction. The microbiota profiles were characterized by bacterial 16S rRNA high-throughput sequencing, and the data were analyzed using Qiime2 and MicrobiomeAnalyst.

Results: When analyzed by obesity and menopausal status, we observed significant differences in the EC microbiota composition of Lkb1flo/flp53flo/fl mice at the phylum and genus level. OD1 and TM7 phyla abundance was higher among obese post- versus premenopausal mice (p<0.05). At the genus level, there was a significant increase in the abundance of Deltia (p<0.01) in obese premenopausal mice whereas the abundance of Helicobacter (p=0.01), Oscillospira (p<0.01), and Ruminococcus (p<0.01) was increased in obese postmenopausal mice. In lean mice, the phylum-level abundance of Proteobacteria (p<0.01) was increased in obese versus premenopausal mice. There was also a higher abundance of Deltia (p<0.01) in lean pre- versus postmenopausal mice at the genus level. In postmenopausal mice, the relative abundance of Helicobacter (p=0.02) was increased in obese versus lean mice.

Conclusion: There were distinct differences in the bacterial composition of the ECs in Lkb1flo/flp53flo/fl mice according to obesity and menopausal status, suggesting that the microbiome may play a role in the pathogenesis of obesity-driven EC.

B30 Intratumoral microbes correlate with tumor-infiltrating lymphocytes in lung cancer RNAseq. Daniel Spakowicz1, Rebecca Hoyd1, YunZhou Liu2, Janhavi Sahasarabudhe2, Malvenderjit J. Singh1, Isaac Arefi2, Andrew Denney2, David Carbome1, Xiaokui Mo1. 1The Ohio State University Comprehensive Cancer Center, Columbus, OH; 2The Ohio State University, Columbus, OH.

Nonhuman sequences have been found in many tumors, but their effect on outcomes remains poorly understood. We hypothesize that intratumoral microbes...
affect the recruitment of immune cells through local immunostimulatory effects including activation nucleic acid sensing pathways. We obtained RNA-seq data from 480 tumor biopsies including melanoma (16), bladder (104), colorectal (20), renal cell carcinoma (20), sarcoma (118), and lung (202) from patients treated at The Ohio State University Comprehensive Cancer Center as part of the Oncology Research Information Exchange Network (ORIEN). Reads were aligned to human and exogenous genomes using TopHat2 and Kraken2/Bracken, respectively. Human gene expression was deconvoluted to absolute abundances of immune cells using CIBERSORT. An average of 99.87% of reads aligned to the human reference genome across all samples. Inferred counts of tumor-infiltrating lymphocytes (TILs), and particularly the immune cell types CD8+ T-cells and M1 macrophages, were significantly enriched in lung cancer relative to the other tested cancers (p-values <0.0001). TILs significantly correlated with both RIG-I and cGAS expression (p-values <0.0001). Exogenous reads aligned to 1328 genomes of bacteria, archaea, viruses, and fungi after filtering. The most abundant phyla within exogenous counts were the Proteobacteria (39.5%), Firmicutes (20.1%), and Actinobacteria (5.16%). Lung cancer samples showed positive correlations between *Acinetobacter junii* and CD8+ T-cells (p-value=0.035) and between *Acidipropionibacterium virtanenii* and activated NK cells (p-value=0.035). This suggests a mechanism by which intratumoral microbes may affect immune cell infiltration and cancer outcomes.

### B31 Microbiota composition in bilateral healthy breast tissue and breast tumors

**Emily M. Klann**, Jessica M. Williamson, Massimiliano S. Tagliamonte, Maria Ukhanova, Jaya Ruth Asirvatham, Harvey Chim, Lusine Yaghiyan, Volker Mai, University of Florida, Gainesville, FL, 2UF Health Shands Hospital, Gainesville, FL.

**Purpose:** The purpose of this pilot study was to assess the differences in breast tissue microbiota composition by breast side (left versus right) within an individual woman and compare the microbiota of healthy and breast tumor tissue between women. We further aimed to determine whether certain bacterial taxa may be associated with breast tumors.

**Methods:** Bilateral healthy breast tissue samples (n=36) were collected from ten women who received routine mammoplasty procedures at the University of Florida Department of Surgery. Archived breast tumor samples (n=10) were obtained from an established biorepository. Bacterial DNA was extracted from tissues, amplified via polymerase chain reaction (PCR), and sequenced on the Illumina MiSeq platform. Microbiota data were analyzed using QIIME and RStudio.

**Results:** The most abundant phyla in both tumor and healthy tissues were Bacteroidetes, Firmicutes, Proteobacteria, and Actinobacteria. A total of 38 operational taxonomic units (OTUs) were found to be significantly different in terms of differential abundance between tumor and healthy tissues (absolute effect size range: 0.761-3.98). The OTUs with the largest absolute effect size associated with higher relative abundance in breast tumors were of *Flavobacterium* species (R2=3.98), *Acinetobacter* species (R2=3.64), [Mogibacteriaceae] family (R2=3.34), and Clostridiales order (R2=3.21). Alpha diversity (Shannon Diversity Index) was similar in healthy and tumor tissue (4.98 vs. 4.84; p=0.350). Based on unweighted UniFrac measures, breast tumor samples clustered distinctly from healthy samples (R2=0.10; p=0.001). Microbiota composition in healthy samples clustered within women (R2=0.20; p=0.012) and by breast side (left or right) within a woman (R2=0.36; p=0.001).

**Conclusion:** We identified significant differences in microbiota composition between women and between breasts of the same woman. These results warrant further investigation to elucidate the potential relationship between breast tissue microbiota and breast cancer.

### B33 Racial differences in tumor-associated microbes in early colorectal carcinogenesis

**Kristin Wallace**, David N. Lewin, Christine Bookhout, Shaoli Sun, Brianna Bronsky, Chentha Vasu, Brenda J. Hoffman, John A. Baron, Alexander V. Alekseyenko, Medical University of South Carolina, Charleston, SC, 2University of North Carolina, Chapel Hill, NC.

African Americans (AA) have a higher incidence of colorectal cancer (CRC) than Caucasian Americans (CA). Emerging evidence indicates that pathogenic tumor-associated microbes (TAMs) within preinvasive lesions may promote carcinogenesis. Since AAs are more prone than CAs to robust inflammatory responses to bacteria and fungi, especially at younger ages, infiltrates in early neoplasms may differ by race and age. To study this issue, we selected a convenience sample of 35 preinvasive cases diagnosed between October 2013 and October 2016 at the Medical University of South Carolina for microbial analysis. The study pathologist diagnosed the degree of dysplasia and predominant histology for each lesion. We extracted DNA from 10-micron-thick FFPE sections and sequenced 16S rRNA gene amplicons...
to determine the microbial communities. We normalized the data using central log ratio transformation with pseudo-counts and selected 20 microbes previously associated with CRC for analysis. Linear regression was used to assess associations between TAMs and race while adjusting for age and sex. We also examined these associations by colorectal location (distal, proximal), degree of dysplasia (high, not high), and age (< 55, 55+). Using product interaction terms in our statistical models, 49% of cases were AAs, 57% were female, and 51% were less than 55 years of age. We analyzed 4 serrated polyps, 6 tubular adenoma, 16 tubulovillous adenomas, and 9 villous adenomas. 40% of the cases had high-grade dysplasia (including focal) and 51% of all lesions were from the distal colon (and rectum). We observed that AAs compared to CAs had a significantly higher microbial abundance of genus *Escherichia* (coef. 1.42, p=0.005), species *Escherichia coli* (coef. 1.38, p=0.007), and genus *Shigella* (coef. 1.15, p=0.02). Moreover, AAs had relatively higher TAM infiltration with these microbes in distal colorectal lesions than CAs, but there were no differences by race in the proximal colon. Finally, we observed that in comparison to older CAs, older AAs had relatively higher abundance of *Escherichia* (coef. 2.50; p = 0.001; p for interaction=0.056). *E. coli* (coef. 2.45, p=0.001; p for interaction=0.04), and *Shigella* (coef. 2.24, p=0.001; p for interaction=0.04), but there were no significant differences in younger patients by race. Two additional microbes, *Porphyromonas* (p=0.01) and *Ruminococcus gnavus* (p=0.02), were found in lower relative abundance in AAs vs. CAs. We identified racial differences in TAMs associated with the Enterobacteriaceae family. The stronger racial differences in TAMs observed in the older but not younger patients may reflect age-related differences in bacterial clearance. In future studies, it will be important to compare the TAMs, immune reactions with markers of tumor progression.

**B34 The ALPK1/TIFA/NF-kB axis links a bacterial carcinogen to replication stress and DNA damage.** Michael Bauer1, Zuzana Nascakova1, Anca Mihai2, Anne Muller1. 1Institute of Molecular Cancer Research, University of Zurich, Zurich, Switzerland, 2Institute of Molecular Genetics, Academy of Sciences of the Czech Republic, Prague, Czech Republic.

Exposure of gastric epithelial cells to the bacterial carcinogen *Helicobacter pylori* causes DNA double-strand breaks. Here, we show that *H. pylori*-induced DNA damage occurs co-transcriptionally in S-phase cells that activate NF-kB signaling upon innate immune recognition of LPS biosynthetic intermediates, such as ADP-heptose, by the ALPK1/TIFA pathway. DNA damage is accompanied by replication fork stalling as determined by DNA fiber assay and can be observed also in gastric organoids derived from bariatric surgery patients. We link *H. pylori*-induced DNA damage to the formation of RNA/DNA hybrids (R-loops), as overexpression of the R-loop-processing enzyme RNase H1 prevents DNA damage and replication stress. R-loops form in infected cells as a consequence of ADP-heptose/ALPK1/TIFA/NF-kB signaling. Factors associated with R-loop processing and prevention are recurrently mutated in gastric cancer. In summary, our results link bacterial infection and NF-kB-driven innate immune responses to DNA damage, replication stress, and carcinogenesis.

**B35 The effect of patient demographics and polyp histologic characteristics on immune gene expression in microenvironment is mediated by infiltrating microbiome.** Alexander V. Alekseyenko1, Chentha Vasu1, Brianna Bronsky1, David N. Lewin1, Shaoli Sun1, Christine Bookout2, John N. Baron1, Kristin Wallace1. 1Medical University of South Carolina, Charleston, SC, 2University of North Carolina, Chapel Hill, NC.

We apply new panomic distance mediation analysis with feature selection to understand the effect of polyp-infiltrating microbes on host microenvironment immune response. Multivariate omnibus distance mediation analysis (MODIMA) allows for testing for mediation in the context of multivariate exposure-mediator-responsne triples, such as polyp characteristics, microbiome composition, and expression, respectively. Here we extend MODIMA to allow for selection of individual components of the response and mediator responsible for mediation effects. Next we apply the method to new data from 30 colorectal polyps with simultaneous measurements of expression of 594 immune-related genes ascertainment via the NanoString Immunology panel and microbiome composition via a 16S rRNA gene amplicon sequencing assay. The polyp specimens are derived from a cohort consisting of 11 female and 19 male subjects, of whom 17 are black and 25 are older than 55. The polyp biopsies come from proximal (17), distal (6), and rectal (7) locations of the colon. According to pathology evaluation, half of the polyps have evidence of high-grade dysplasia. The distribution across tubular, tubular villous, and villous histology is likewise approximately even (10, 9, and 11 specimens, respectively). Microbial DNA has been extracted from formalin-fixed, paraffin-embedded polyp tissues and analyzed using Illumina.
database; the differential expressed repetitive elements normal brain tissues studies were obtained from public 111 GBM tissue studies, 30 GBM cell lines studies, and 45 normal brain. The 1,077.4 GB of sequencing data contain expression profile of LTRs in the GBM compared with of our study was to comprehensively characterize the various biologic processes. However, our understanding believed to be relics from ancient viral infections. Recent a group of long terminal repeat (LTR) elements that are challenging. Human endogenous retrovirus (HERVs) are for GBM makes the development of its immunotherapy the most aggressive therapies; the lack of biomarkers makes the etiology of GBM and future application of these elements as biomarkers for GBM treatments.

**B38 Virome assembly and annotation in brain tissue based on next-generation sequencing.** Zihao Yuan, Xiaohua Ye, Ningyan Zhang, Zhiqiang An, Wenjin Zheng. University of Texas Health Science Center at Houston, Houston, TX.

Glioblastoma multiforme (GBM) is one of the most lethal brain tumors, and the virosphere in brain and its correlation with GBM triggering is controversy. The previous research in brain virosphere was mainly limited to the presence of human cytomegalovirus (HCMV); a comprehensive assessment of the brain virome based on the recently sequenced data and the understanding of the novel sequences that cannot be mapped to the known reference sequences are lacking. Here, we characterized the virome from 111 GBM samples and 57 normal brain samples from 8 projects in SRA database by known and novel viruses in a tested and comprehensive assembly approach. The annotation of those contigs showed most of the viral sequences belongs to the Retroviridae. A novel picornavirus, which was recently discovered from the invertebrate, can be detected in some GBM samples in full genome length. Furthermore, our analysis showed that the herpes virus fragments that are annotated as Epstein-Barr virus (EBV) only exist in the GBM with less than 1% of the EBV whole genome, supporting the absence of herpes virus in GBM. The further analysis showed that the contigs that have no annotations from the known databases may have the antibody properties and antibody epitopes to be the future drug targets. In this study, we characterized the virosphere in GBM and normal brain at a global level, to provide a basis for future GBM research and therapies.

**B37 Analysis of the differential expression of human endogenous retrovirus in glioblastoma multiforme.** Zihao Yuan, Ningyan Zhang, Zhiqiang An, Wenjin Zheng. University of Texas Health Science Center at Houston, Houston, TX.

Glioblastoma multiforme (GBM) is the most aggressive and deadly brain tumor. It is primarily diagnosed at older ages and has 5-year survival rate less than 6% even with the most aggressive therapies; the lack of biomarkers for GBM makes the development of its immunotherapy challenging. Human endogenous retrovirus (HERVs) are a group of long terminal repeat (LTR) elements that are believed to be relics from ancient viral infections. Recent studies have found their important roles in regulating various biologic processes. However, our understanding of the LTR elements is greatly lacking. The purpose of our study was to comprehensively characterize the expression profile of LTRs in the GBM compared with normal brain. The 1,077.4 GB of sequencing data contain 111 GBM tissue studies, 30 GBM cell lines studies, and 45 normal brain tissues studies were obtained from public database; the differential expressed repetitive elements were analyzed between GBM and normal brain samples. 48 LTR elements were found differentially expressed (p-value < 0.05) between GBM and normal brain, of which 46 are HERV elements. 34 out of 46 significantly changed HERVs belong to the ERV1 superfamily. Most (43/46) of the differential expressed HERV elements are upregulated in GBM compared with normal brain. Our results suggest a potentially important role of HERVs in the etiology of GBM and future application of these elements as biomarkers for GBM treatments.

MiSeq 16S rRNA gene amplicon sequencing assay. After preprocessing, the species and genus level data have been normalized using central log ratio transformation with pseudo-counts. Species and genera with literature evidence for association with colorectal polyps and cancers have been selected for further analysis. Using these data, we evaluate the hypothesis that infiltrating microbiome mediates the immune gene expression in response to histodemographic characteristics. We expand the histodemographic data into a complete 6-way interaction design matrix. Euclidean distances have been used for all data types in all analyses. After feature selection, the joint expression of 140 immune genes is associated with polyp characteristics (dCor t-test, T = 2.9, bias corrected dCor = 0.14, p = 0.002). Likewise, 4 microbial features are jointly associated (dCor t-test, T = 2.1, bias corrected dCor = 0.10, p = 0.02). Within these data 9 genes (BCL2, CD19, CLEC6A, IRAK3, IRF3, NLRP3, PSMD2, TBX21, POLE2A) and 2 taxa (Bifidobacterium and Alistipes sp.) are jointly associated to each other (dCor t-test, T = 4.7, bias corrected dCor = 0.23, p < 10⁻5). MODIMA analysis after feature selection suggests a significant mediation effect of these microbes on the association between polyp characteristics and the expression of the 9 genes (MODIMA stat = 0.03, p-value = 0.01). Further univariate analysis corroborates these associations and suggests a role for the infiltrating microbiome in Th1 signaling, apoptosis, and interferon and expression regulation.
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## DISCLOSURES OF FINANCIAL RELATIONSHIPS

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