

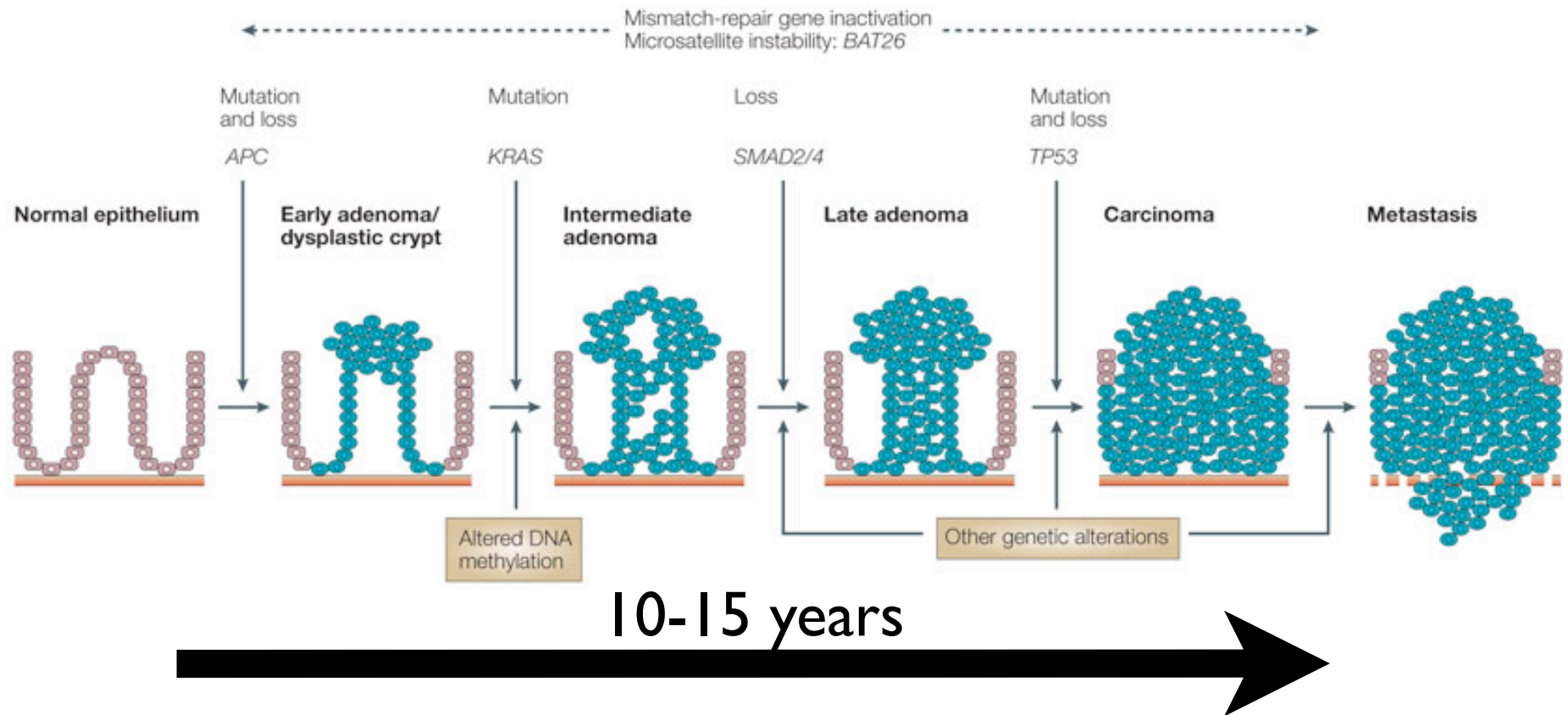
A scanning electron micrograph (SEM) showing numerous rod-shaped bacteria, likely Bacillus or Clostridium species, in shades of blue and purple against a black background. The bacteria are oriented in various directions, some appearing as long, straight rods, while others are shorter or slightly curved. The surface of the bacteria shows fine, regular ridges or striations.

Microbiome and cancer (oncobiome)

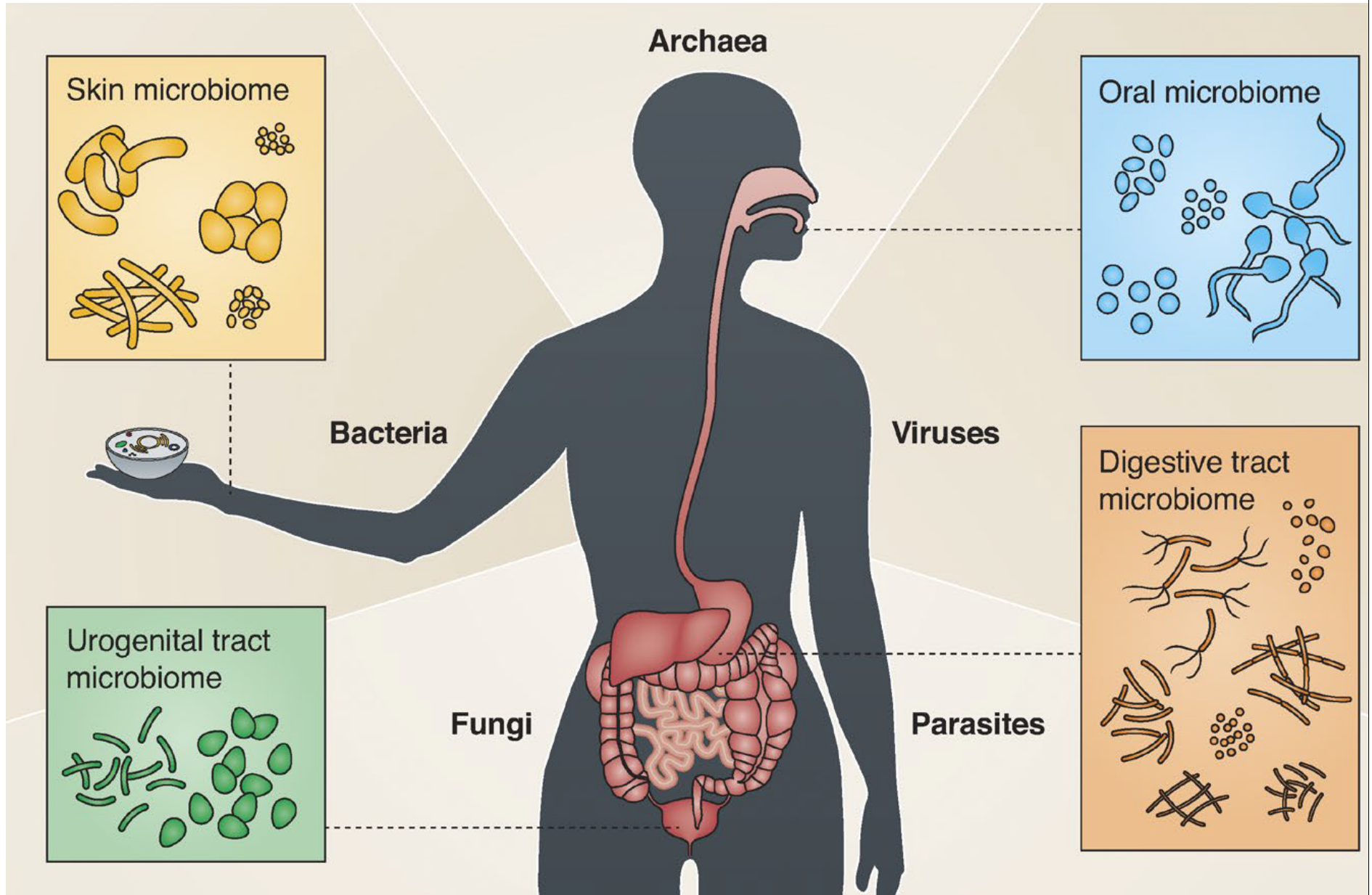
Department of Medicine and Department of Infectious Diseases & Pathology
University of Florida, Gainesville

Christian Jobin
christian.jobin@medicine.ufl.edu

Are intestinal bacteria bystander to the carcinogenic process?



Microbiota and Humans



Garrett, W.S. (2015). *The Journal of Cell Biology* 210, 7–8.

Humans are a composite of microorganisms

MICROBIAL CELLS
-100 TRILLION
(~70-90%)



MICROBIAL GENES
~2,000,000
(~99%)



Leading Edge

Commentary

Cell



Are We Really Vastly Outnumbered? Revisiting the Ratio of Bacterial to Host Cells in Humans

Ron Sender,¹ Shai Fuchs,^{2,3,*} and Ron Milo^{1,*}



HUMAN CELLS
~30 TRILLION



HUMAN GENES
~23,000



Rapid colonization early in life set microbiota

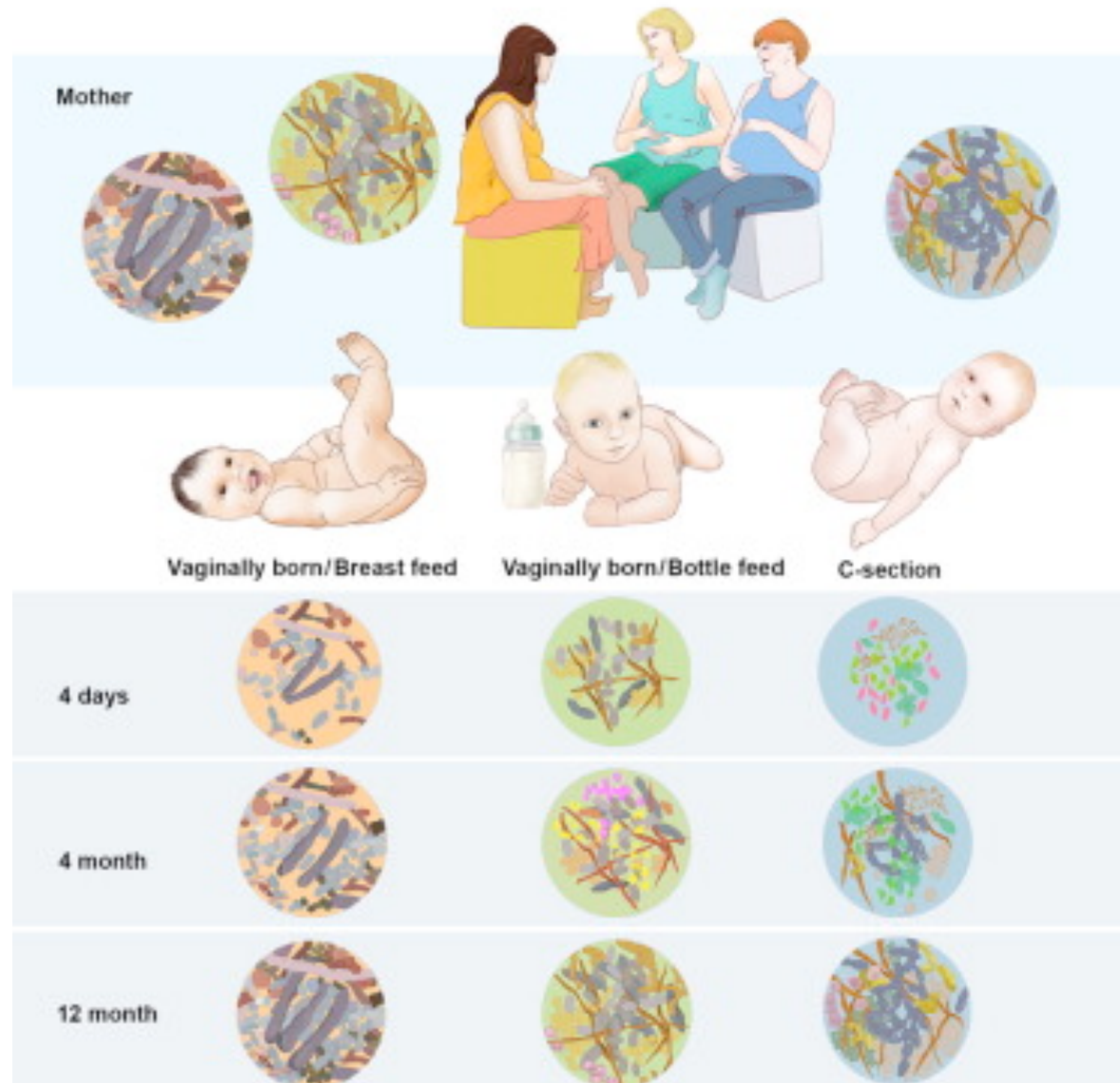
- Bacteroidaceae
- Lachnospiraceae
- Ruminococcaceae
- Prevotellaceae
- Enterobacteriaceae
- Veillonellaceae
- Bifidobacteriaceae
- Clostridiaceae
- Lactobacillaceae



Birth



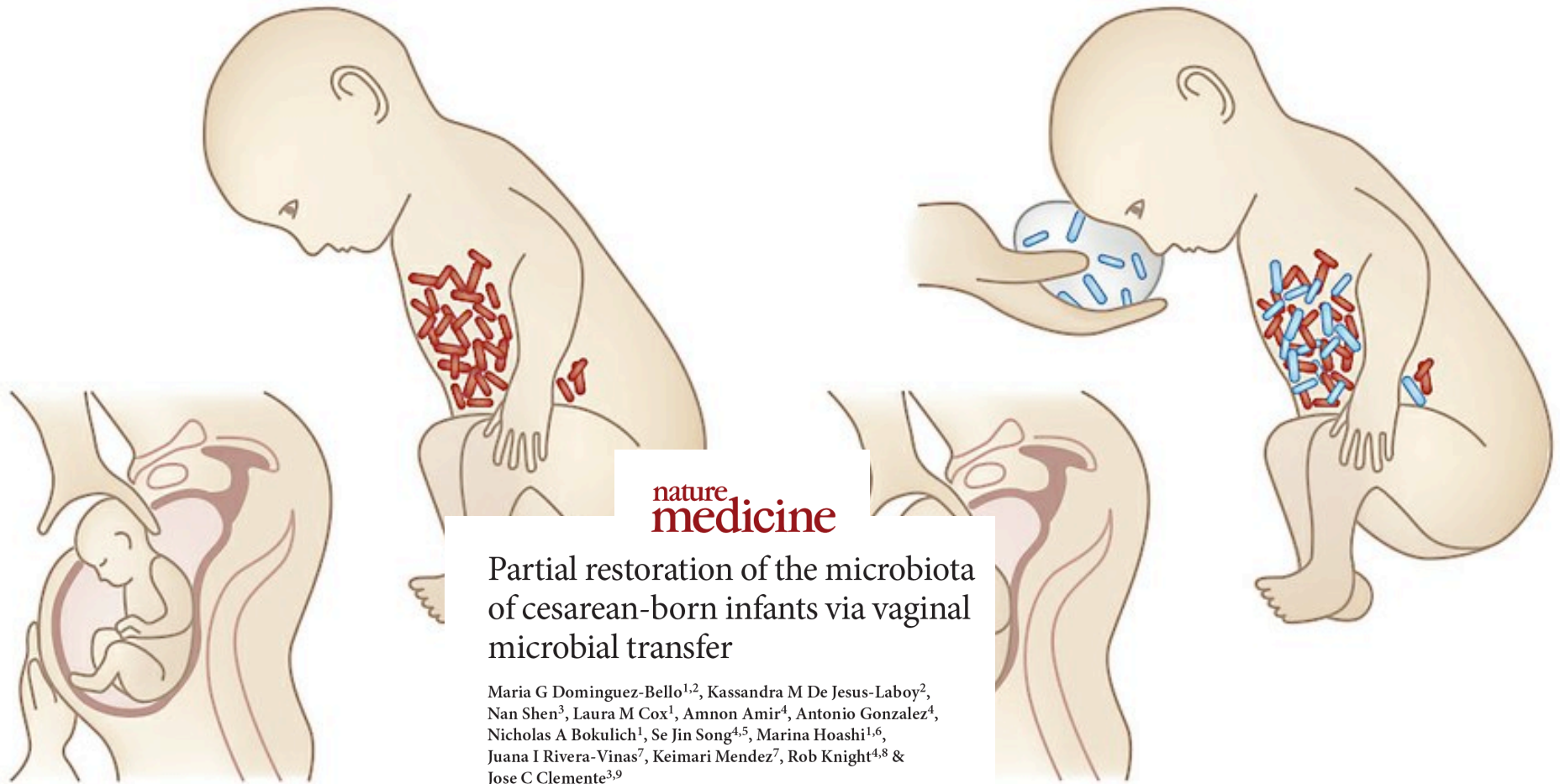
Microbial composition varies according to the original seeding



Microbial composition varies according to the original seeding

C-section

C-section + vaginal sponge

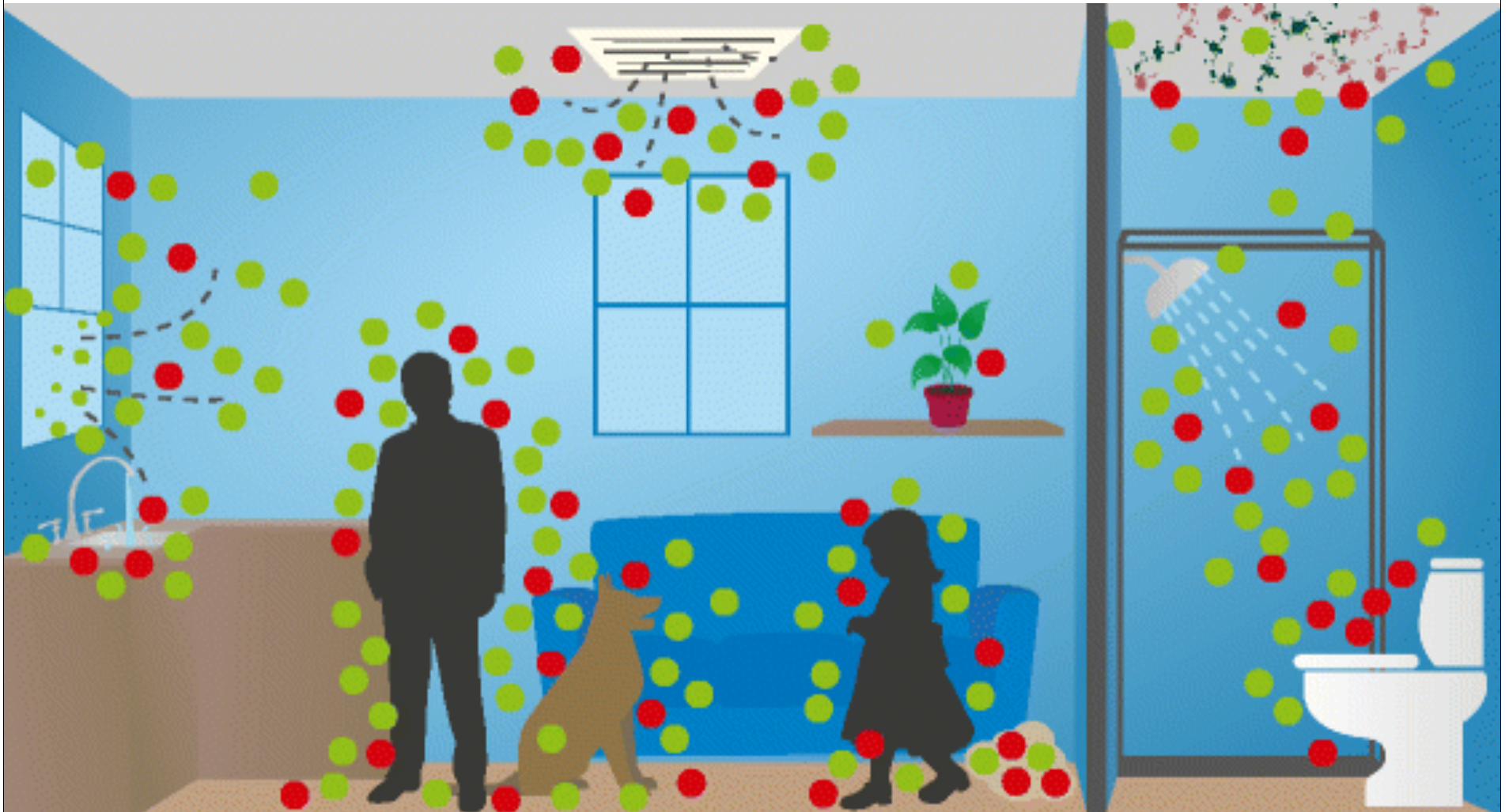


nature
medicine

Partial restoration of the microbiota of cesarean-born infants via vaginal microbial transfer

Maria G Dominguez-Bello^{1,2}, Kassandra M De Jesus-Laboy², Nan Shen³, Laura M Cox¹, Amnon Amir⁴, Antonio Gonzalez⁴, Nicholas A Bokulich¹, Se Jin Song^{4,5}, Marina Hoashi^{1,6}, Juana I Rivera-Vinas⁷, Keimari Mendez⁷, Rob Knight^{4,8} & Jose C Clemente^{3,9}

The environment represents another important source of microbial exposure (seeding and transient)



Double threat phenomenon

Inside



Outside



Microbes and cancer: The infectious route

$\sim 4 \times 10^{30}$ microbes on earth

Outside



10 organisms are
designated as
carcinogenic
(International Agency
for Cancer Research)

Epstein-Barr virus (EBV): Lymphomas

Human papillomavirus virus: Cervical cancer and other cancers

Human herpes virus: Kaposi's sarcoma

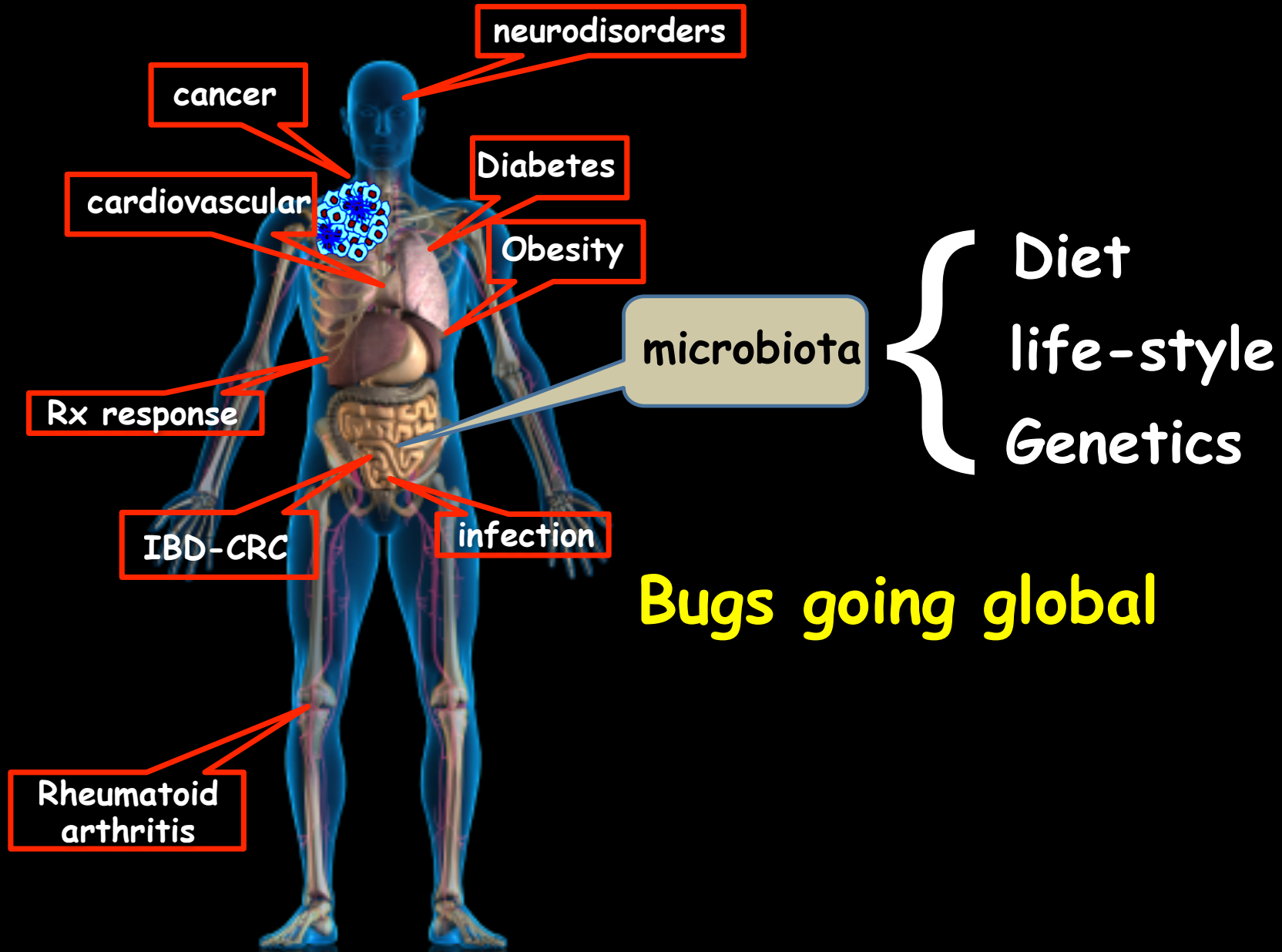
Hepatitis B virus (HBV) and hepatitis C virus (HCV): non-Hodgkin lymphoma, liver cancer

Helicobacter species: stomach, biliary tract, and gallbladder cancer.

Microbes and cancer: Intestinal biota



Intestinal microbiota in health/diseases



Microbiota composition in colorectal cancer?



State of microbial dysbiosis in CRC patients

Enterococcus, Escherichia/Shigella, Klebsiella, Streptococcus, and Peptostreptococcus

Sobhani I, et al. Microbial dysbiosis in colorectal cancer (CRC) patients. PLoS One. 2011;6(1):e16393.

Lachnospiraceae

Wang T, et al. Structural segregation of gut microbiota between colorectal cancer patients and healthy volunteers. ISME J. 2011 Aug 18;6(2):320-9.

Sanapareddy N, et al. Increased rectal microbial richness is associated with the presence of colorectal adenomas in humans. ISME J. 2012 Oct;6(10):1858-68.

Marchesi JR, et al. Towards the Human Colorectal Cancer Microbiome. Ahmed N, editor. PLoS One. 2011 May 24;6(5):e20447.

Chen W, et al. Human Intestinal Lumen and Mucosa-Associated Microbiota in Patients with Colorectal Cancer. Moschetta A, editor. PLoS One. 2012 Jun 28;7(6):e39743.

Castellarin M, et al. Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma. Genome research. 2012 Feb;22(2):299-306.

Kostic AD, et al. Genomic analysis identifies association of Fusobacterium with colorectal carcinoma. Genome research. 2012 Feb;22(2):292-8.

McCoy, A. N., et al. Fusobacterium Is Associated with Colorectal Adenomas. 2013 PloS one, 8(1), e53653.

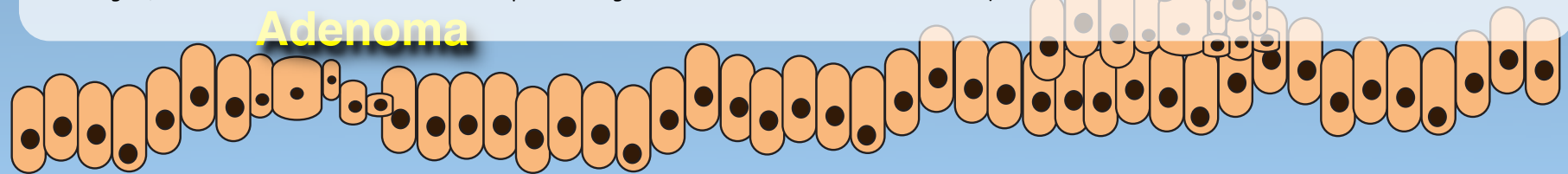
Burns, M.B., et al Virulence genes are a signature of the microbiome in the colorectal tumor microenvironment. 2015 Genome Medicine 1-12.

Firmicutes, Bacteroidetes, Fusobacterium and Proteobacteria

Feng, Q., et al. (2015). Gut microbiome development along the colorectal adenoma-carcinoma sequence. Nat Commun 6, 1-13.

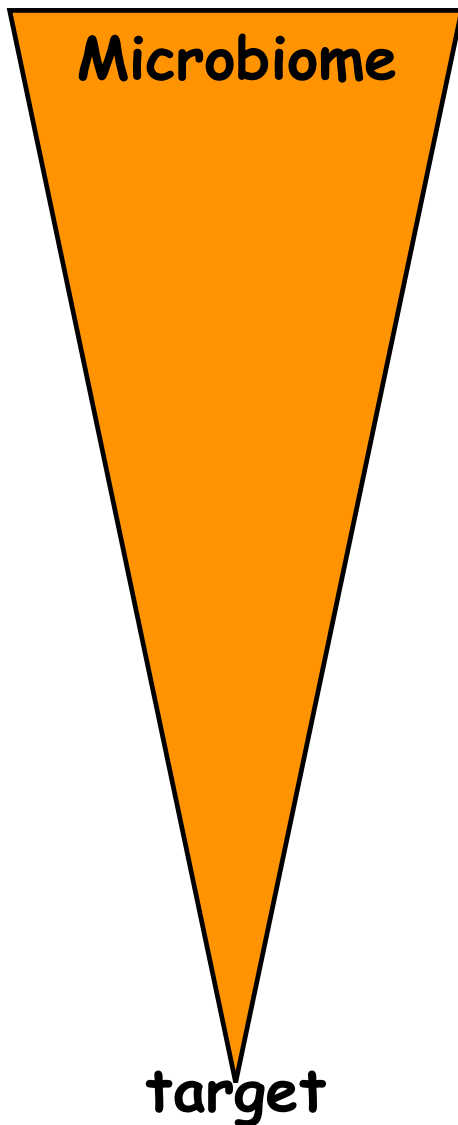
Adenoma

Adenocarcinoma



Functional impact of CRC-dysbiosis?

Drilling down the microbiome world



o'mics approaches
(metagenome, metatranscriptome,
proteome, metabolome)

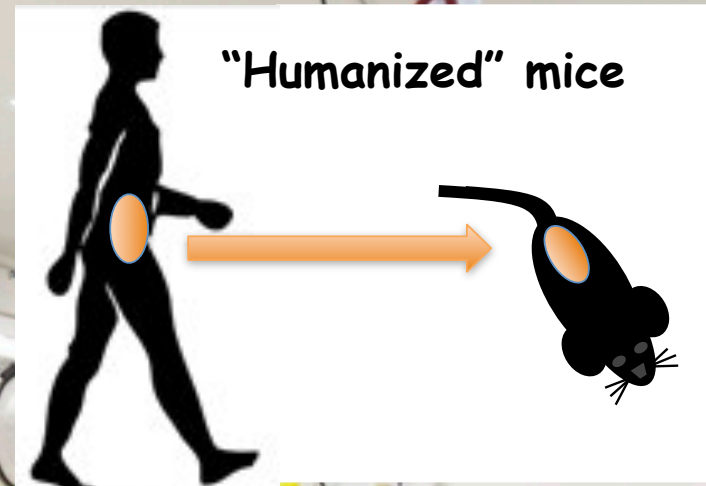


Informative but associative results



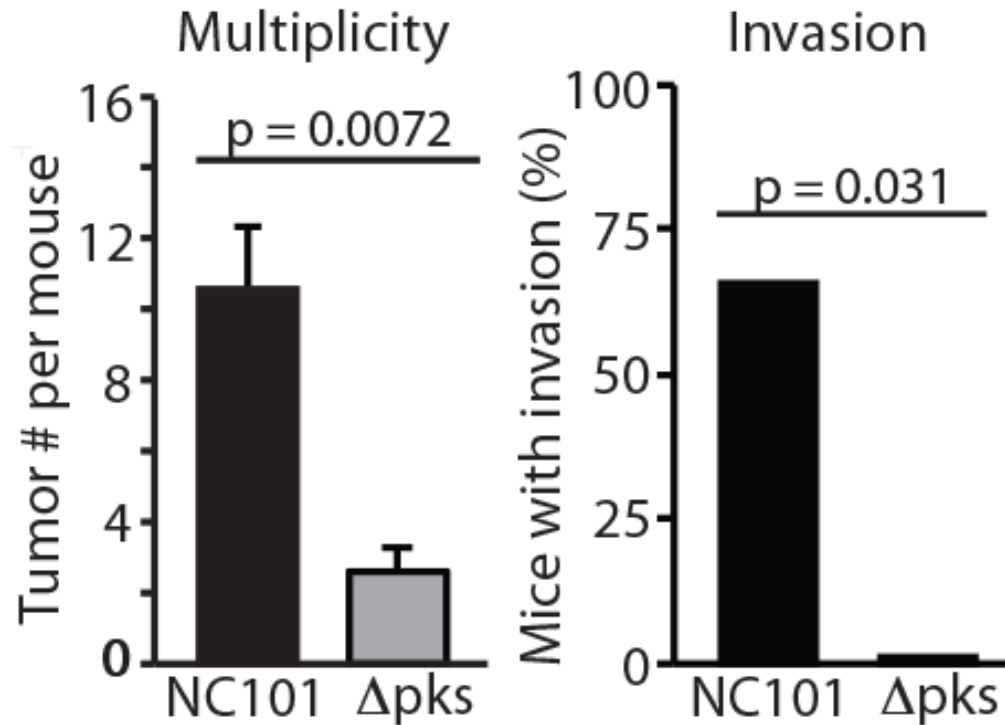
functional?

gnotobiotics, humanized mice, microbial
gene manipulation, bioreactors,
structural chemistry, small molecules



The enemy within

Comet Assa



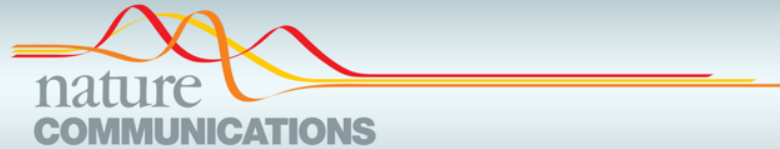
T (non-CRC)

-10^{-/-} (CRC)

E.coli Δpks



Drilling down the microbiome world



ARTICLE

Received 27 Dec 2013 | Accepted 17 Jul 2014 | Published 3 Sep 2014

DOI: 10.1038/ncomms5724

Microbial genomic analysis reveals the essential role of inflammation in bacteria-induced colorectal cancer

Janelle C. Arthur^{1,*}, Raad Z. Gharaibeh^{2,3,*}, Marcus Mühlbauer¹, Ernesto Perez-Chanona^{4,5}, Joshua M. Uronis^{1,†}, Jonathan McCafferty², Anthony A. Fodor² & Christian Jobin^{5,6}

nature
microbiology

LETTERS

PUBLISHED: 11 JANUARY 2016 | ARTICLE NUMBER: 15009 | DOI: 10.1038/NMICROBIOL.2015.9

MATE transport of the *E. coli*-derived genotoxin colibactin

Jarrold J. Mousa^{1†}, Ye Yang^{2†}, Sarah Tomkovich², Ayaka Shima^{3,4,5,6,7}, Rachel C. Newsome¹, Prabhanshu Tripathi¹, Eric Oswald^{3,4,5,6,7}, Steven D. Bruner^{1*} and Christian Jobin^{2,8*}

Microbial dysbiosis in CRC patients



Enterococcus, Escherichia/Shigella, Klebsiella, Streptococcus, and Peptostreptococcus

Lachnospiraceae



click for updates

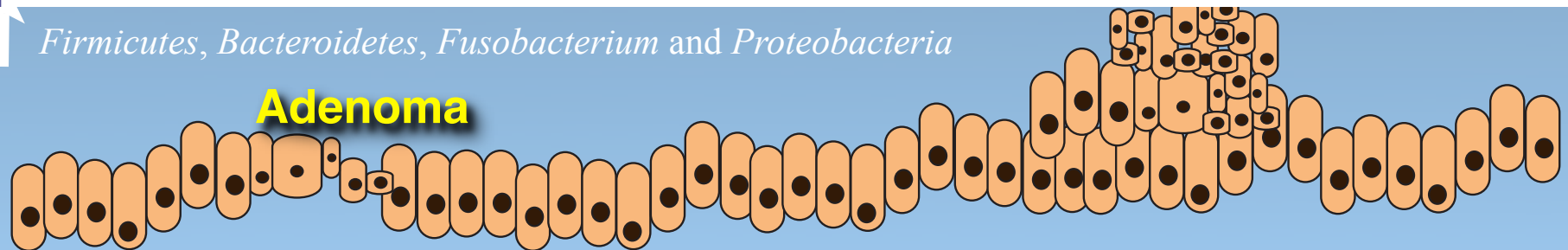
Biofilm correlates with 5X increase CRC rates

Microbiota organization is a distinct feature of proximal colorectal cancers

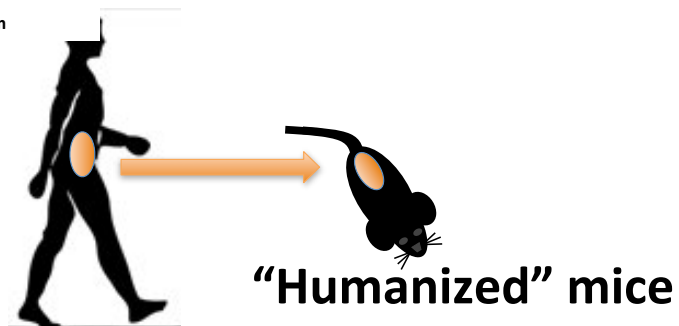
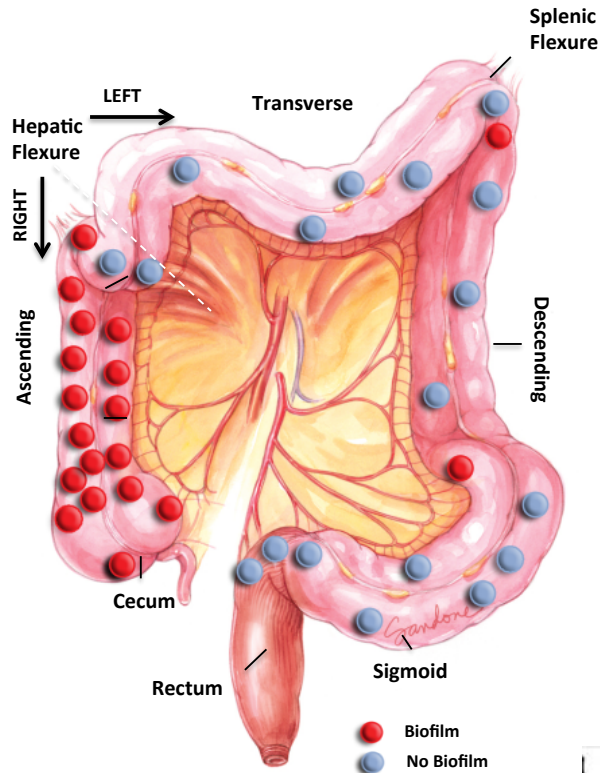
Christine M. Dejea^a, Elizabeth C. Wick^b, Elizabeth M. Hechenbleikner^b, James R. White^{c,1}, Jessica L. Mark Welch^d, Blair J. Rossetti^d, Scott N. Peterson^{e,2}, Erik C. Snestrud^{e,3}, Gary G. Borisy^d, Mark Lazarev^f, Ellen Stein^f, Jamuna Vadivelu^g, April C. Roslani^h, Ausuma A. Malik^h, Jane W. Wanyiri^f, Khean L. Gohⁱ, Iyadorai Thevambiga^g, Kai Fu^j, Fengyi Wan^{j,k}, Nicolas Llosa^l, Franck Housseau^k, Katharine Romans^{m,n}, XinQun Wu^f, Florencia M. McAllister^k, Shaoguang Wu^f, Bert Vogelstein^{m,n}, Kenneth W. Kinzler^{m,n}, Drew M. Pardoll^{f,k}, and Cynthia L. Sears^{a,f,k,4}

Firmicutes, Bacteroidetes, Fusobacterium and Proteobacteria

Adenoma



How to dissect contribution of microbe in carcinogenesis?



Microbes and cancer: Bacteria as therapeutic adjuvant?

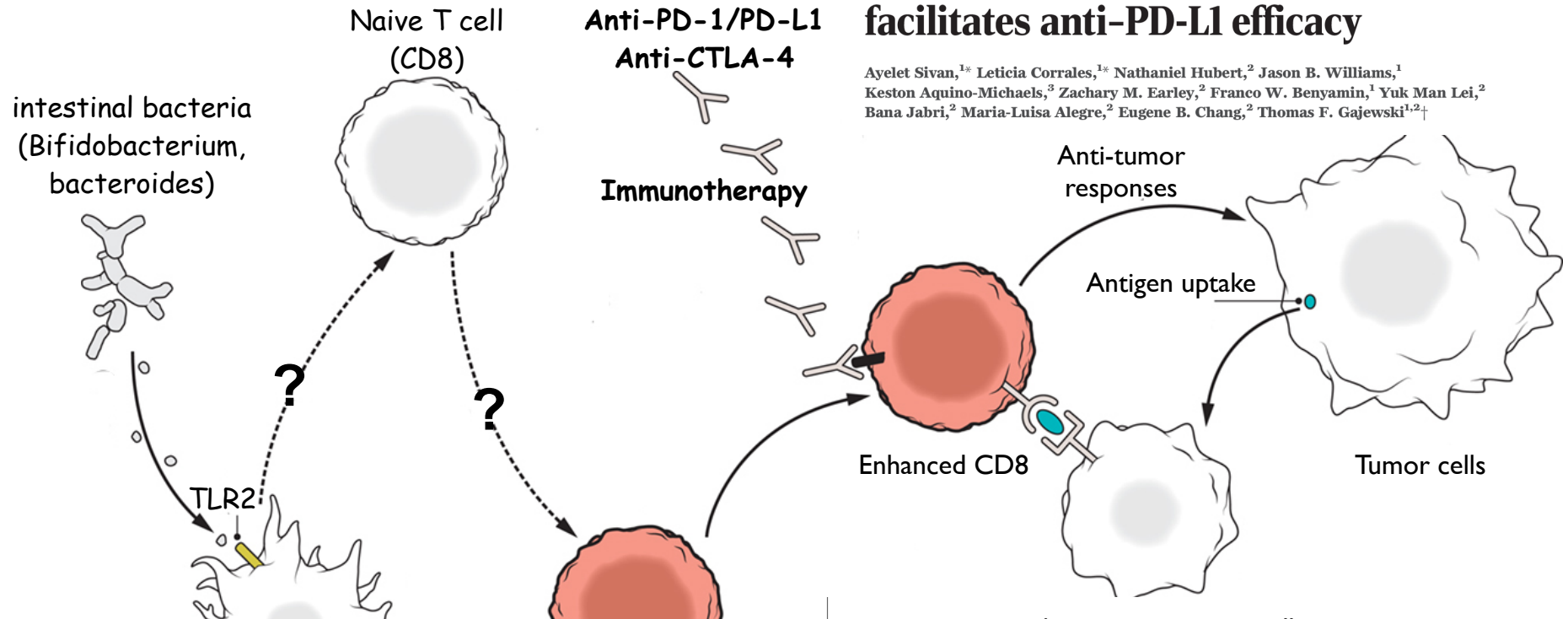


Microbes and cancer therapy

CANCER IMMUNOTHERAPY

Commensal *Bifidobacterium* promotes antitumor immunity and facilitates anti-PD-L1 efficacy

Ayelet Sivan,^{1*} Leticia Corrales,^{1*} Nathaniel Hubert,² Jason B. Williams,¹ Keston Aquino-Michaels,³ Zachary M. Earley,² Franco W. Benyamin,¹ Yuk Man Lei,² Bana Jabri,² Maria-Luisa Alegre,² Eugene B. Chang,² Thomas F. Gajewski^{1,2†}



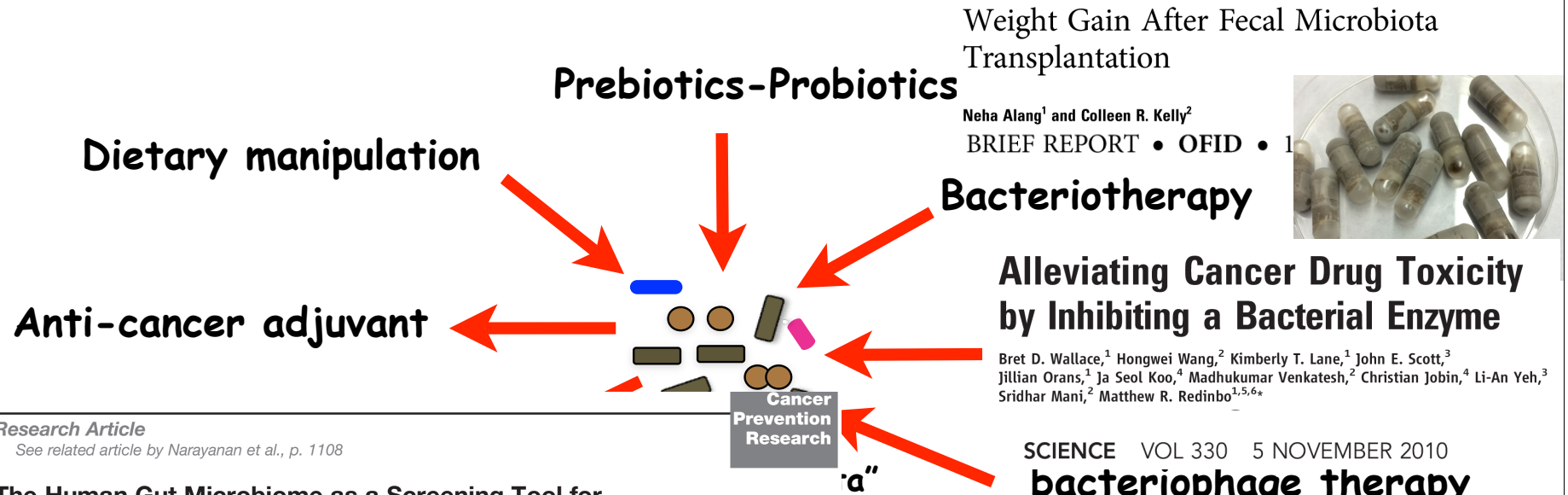
Forbes / Pharma & Healthcare

10 Stocks to Sell for 2016

NOV 4, 2015 @ 04:00 AM 4,043 VIEWS

Fighting Cancer With Microbes, Flagship Bets on a \$35M Startup

Microbes and cancer: Now what?



Weight Gain After Fecal Microbiota Transplantation

Neha Atang¹ and Colleen R. Kelly²

BRIEF REPORT • OFID • 1



Bacteriotherapy

Alleviating Cancer Drug Toxicity by Inhibiting a Bacterial Enzyme

Bret D. Wallace,¹ Hongwei Wang,² Kimberly T. Lane,¹ John E. Scott,³ Jillian Orans,¹ Ja Seol Koo,⁴ Madhukumar Venkatesh,² Christian Jobin,⁴ Li-An Yeh,³ Sridhar Mani,² Matthew R. Redinbo^{1,5,6*}

SCIENCE VOL 330 5 NOVEMBER 2010

bacteriophage therapy

Research Article

See related article by Narayanan et al., p. 1108

The Human Gut Microbiome as a Screening Tool for Colorectal Cancer

Joseph P. Zackular¹, Mary A.M. Rogers², Mack T. Ruffin IV³, and Patrick D. Schloss¹

Potential of fecal microbiota for early-stage detection of colorectal cancer

Georg Zeller^{1,†}, Julien Tap^{1,2,†}, Anita Y Voigt^{1,3,4,5,†}, Shinichi Sunagawa¹, Jens Roat Kultima¹, Paul I Costea¹, Aurélien Amiot², Jürgen Böhm^{6,7}, Francesco Brunetti⁸, Nina Habermann^{6,7}, Rajna Hercog⁹, Moritz Koch^{10,‡}, Alain Luciani¹¹, Daniel R Mende¹, Martin A Schneider¹⁰, Petra Schrotz-King^{6,7}, Christophe Tournigand¹², Jeanne Tran Van Nhieu¹³, Takuji Yamada¹⁴, Jürgen Zimmermann⁹, Vladimir Benes⁹, Matthias Kloor^{3,4,5}, Cornelia M Ulrich^{6,7,15}, Magnus von Knebel Doeberitz^{3,4,5}, Iradj Sobhani^{2,*} & Peer Bork^{1,5,16,**}

Cancer



Jobin Lab

Ye Yang

Jillian Pope

Ernesto Perez-Chanona

Sarah Tomkovich

Christina Ohland

Xiaolun Sun

Josee Gauthier

Danielle Ferrugeti

Rachel Newsome

Sasha Oleksandr

University of Florida

Jarrood Moussa

Steven Bruner

Fundings:

R01 DK73338

R01 DK47700

R01 AT08623

R21 CA195226

RO1 minority supplement

UF Research Opportunity Seed Fund

UF SoM Gatorade

Genome Canada

John Hopkins

Cynthia Sears

Christine Craig

UNC-Charlotte

Anthony Fodor

Raad Gharaibeh

INSERM Toulouse

Eric Oswald

Ayaka Shima

Temple University

Jean Pierre Issa

Ang Sun

