"Inflammation, Gut Microbiome, Bacteriophages, and the Initiation of Colorectal Cancer"

Seminar Lecture

City of Hope

Pasadena, CA

October 20, 2013

Dr. Larry Smarr

Director, California Institute for Telecommunications and Information Technology

Harry E. Gruber Professor,

Dept. of Computer Science and Engineering

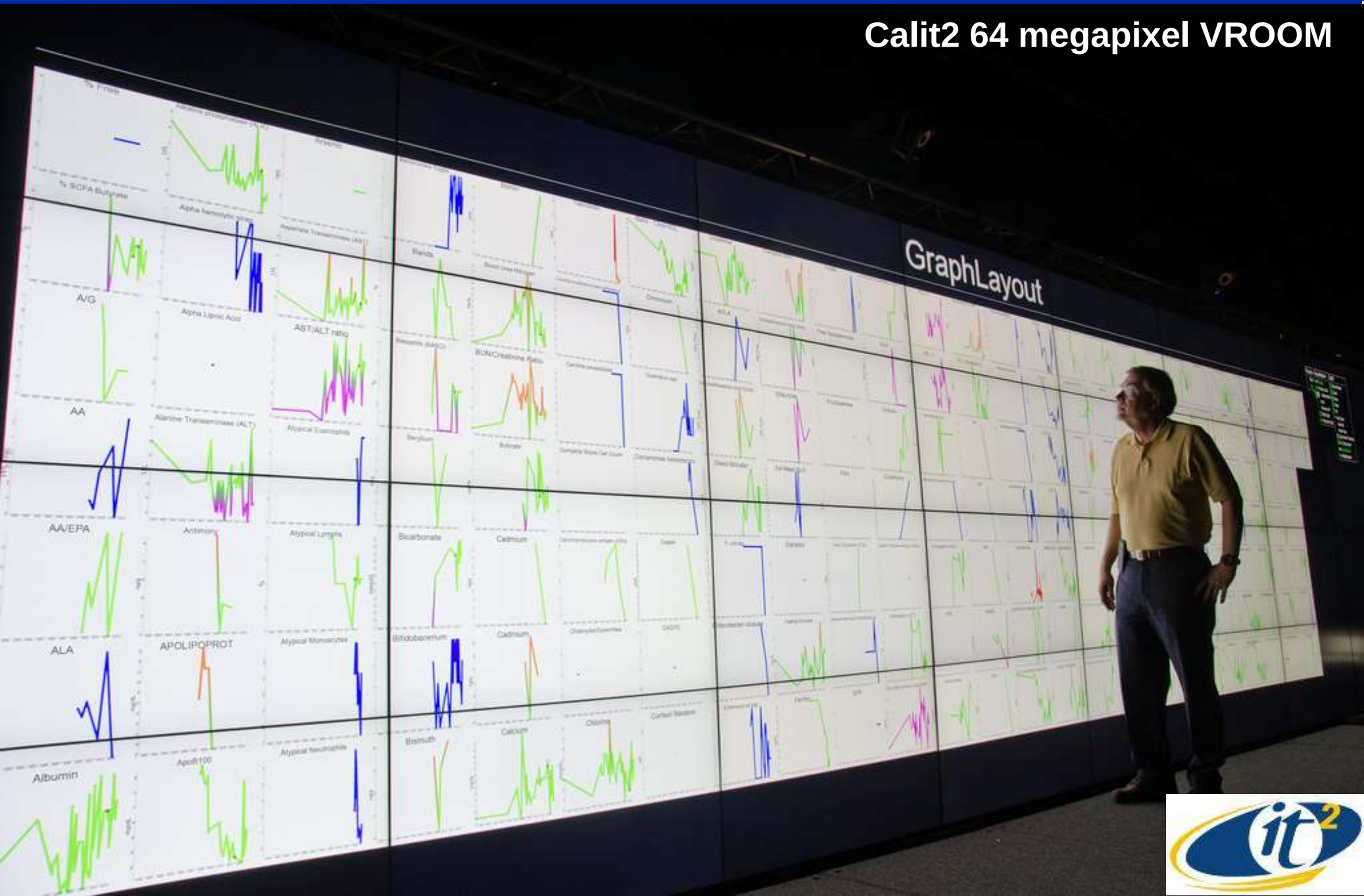
Jacobs School of Engineering, UCSD

http://lsmarr.calit2.net

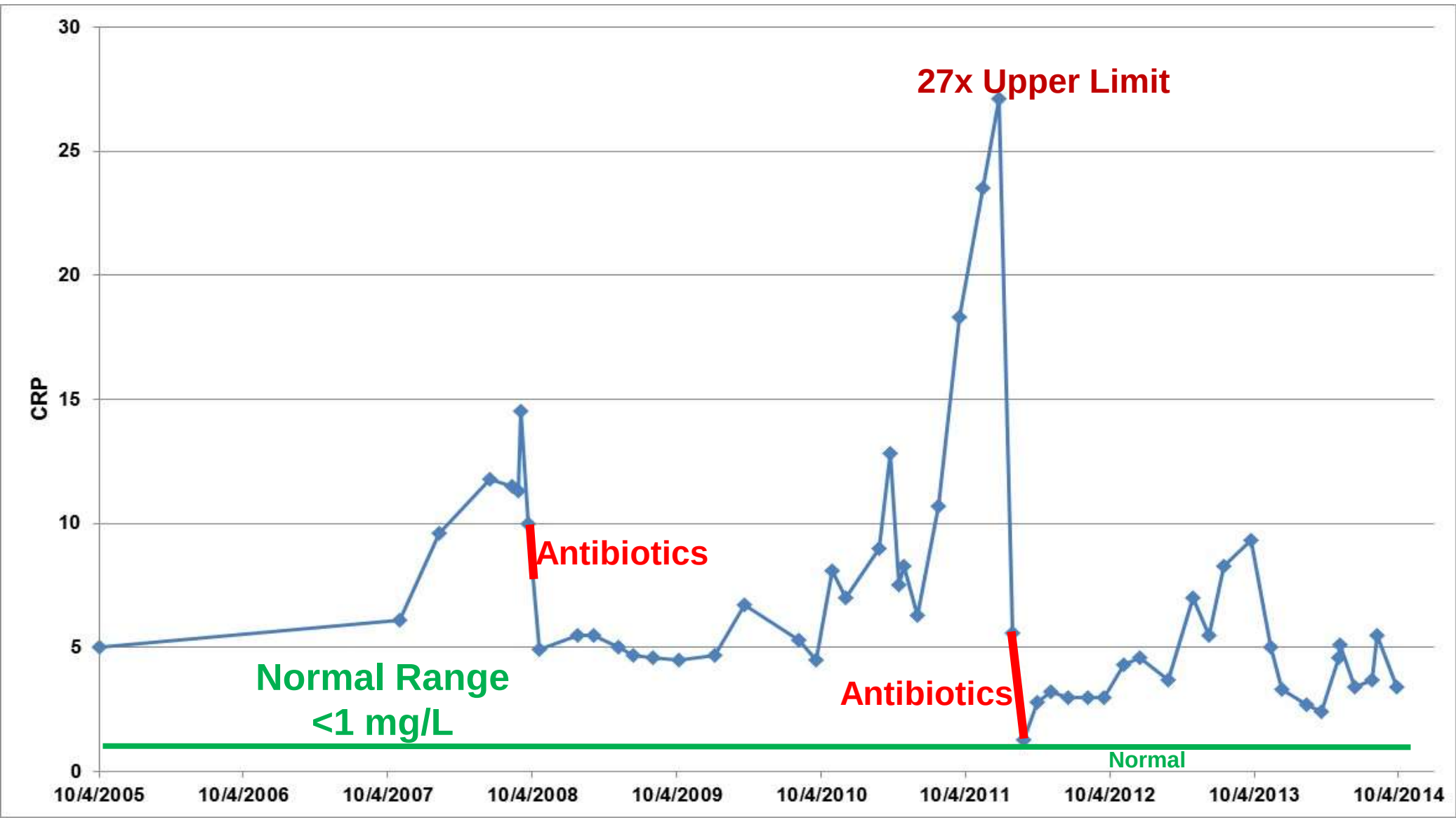
Abstract

The human body contains ten times the number of microbe cells as human cells and these microbes contain 100 times the number of DNA genes that our human DNA does. The microbial component of this "superorganism" is comprised of hundreds of species spread over many taxonomic phyla. The human immune system is tightly coupled with this microbial ecology and in cases of autoimmune disease, both the host immune system and the microbial ecology can have excursions far from normal. I will review some of the known 163 SNPs in the human genome which pre-dispose the host to develop autoimmune IBD. Motivated by a diagnosis that I have Crohn's disease, I have been collecting massive amounts of data on my own body over the last five years. Analysis and graphing of this data demonstrates the episodic evolution of this coupled immune-microbial system. I have also evaluated the relative abundances of Fusobacteria species and E. coli strains that have been hypothesized to be related to colon cancer. To decode the details of the microbial ecology required high resolution metagenomics sequencing at the Venter Institute, several CPU-decades of supercomputer time, coupled to scalable visualization systems. The complexities of my time-varying microbial ecology will be compared to the NIH Human Microbiome Program data on people in states of health and IBD.

Visualizing Time Series of 150 LS Blood and Stool Variables, Each Over 5-10 Years

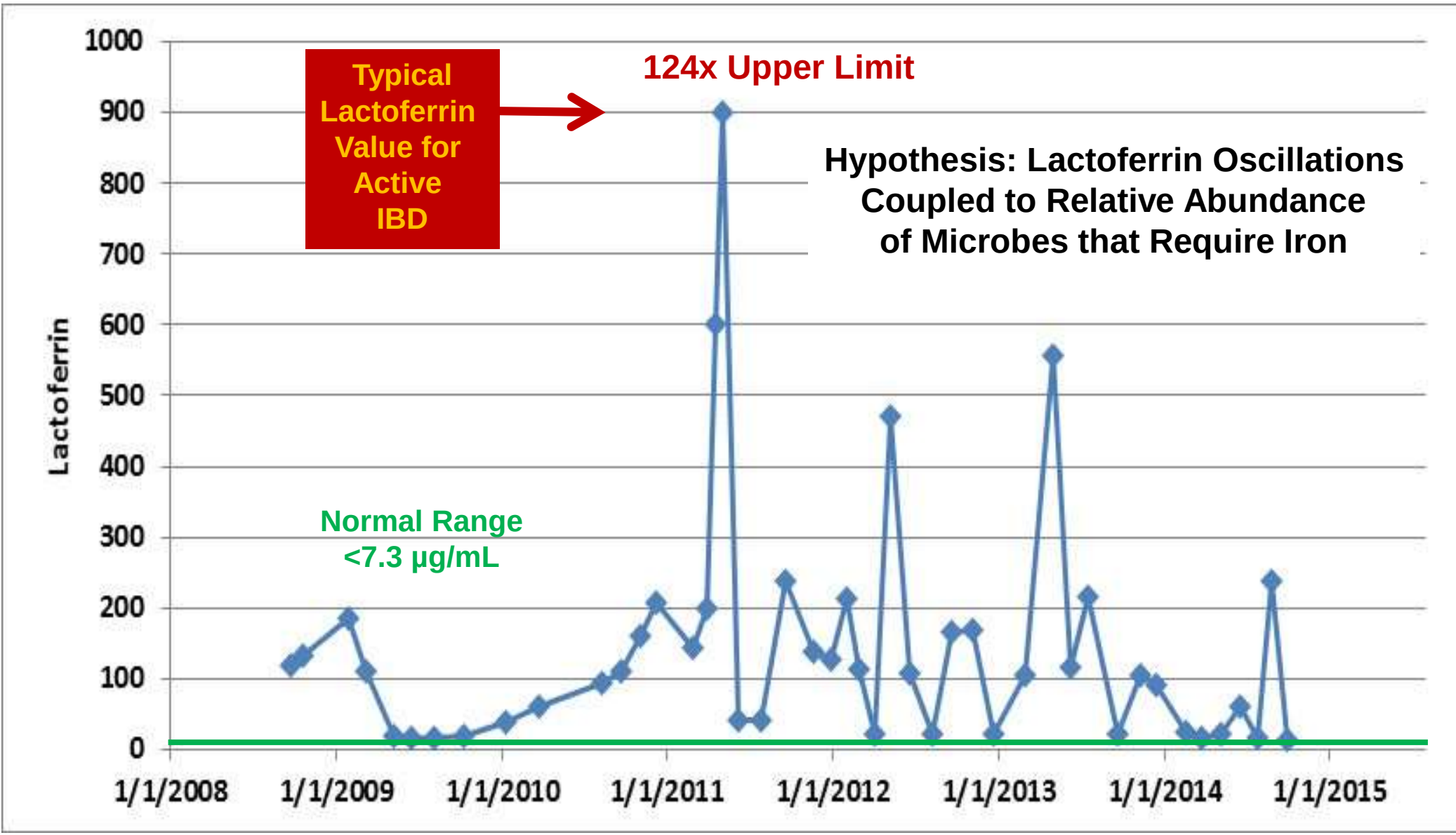


One of My Blood Measurements Was Far Out of Range--Indicating Episodic Chronic Inflammation



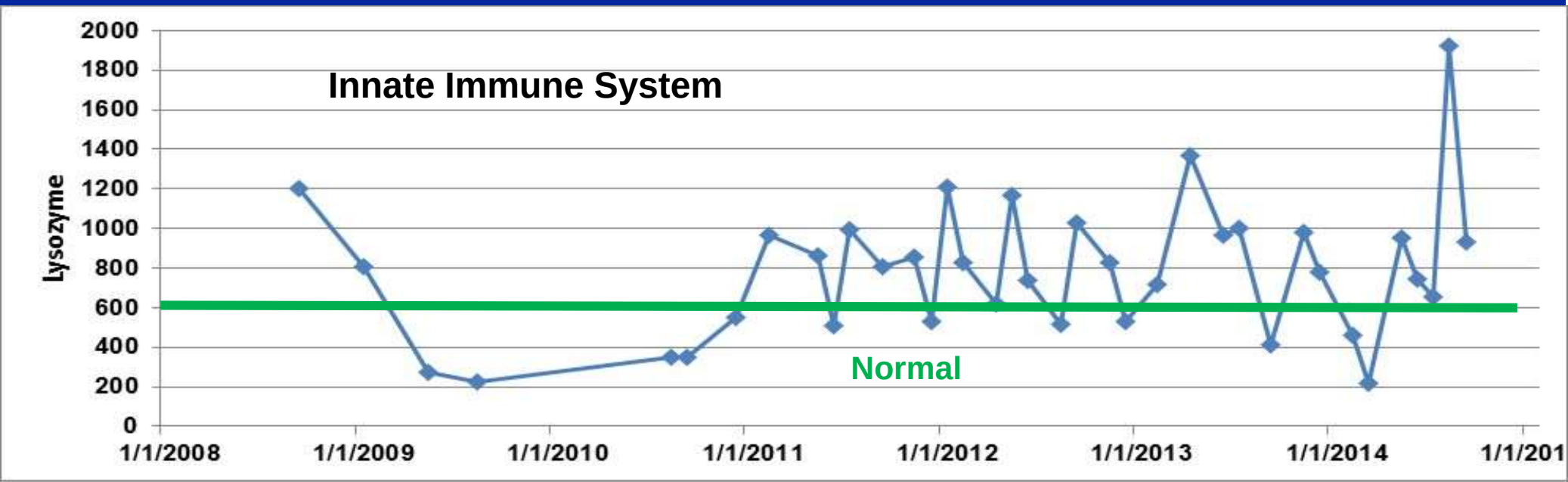
Complex Reactive Protein (CRP) is a Blood Biomarker for Detecting Presence of Inflammation

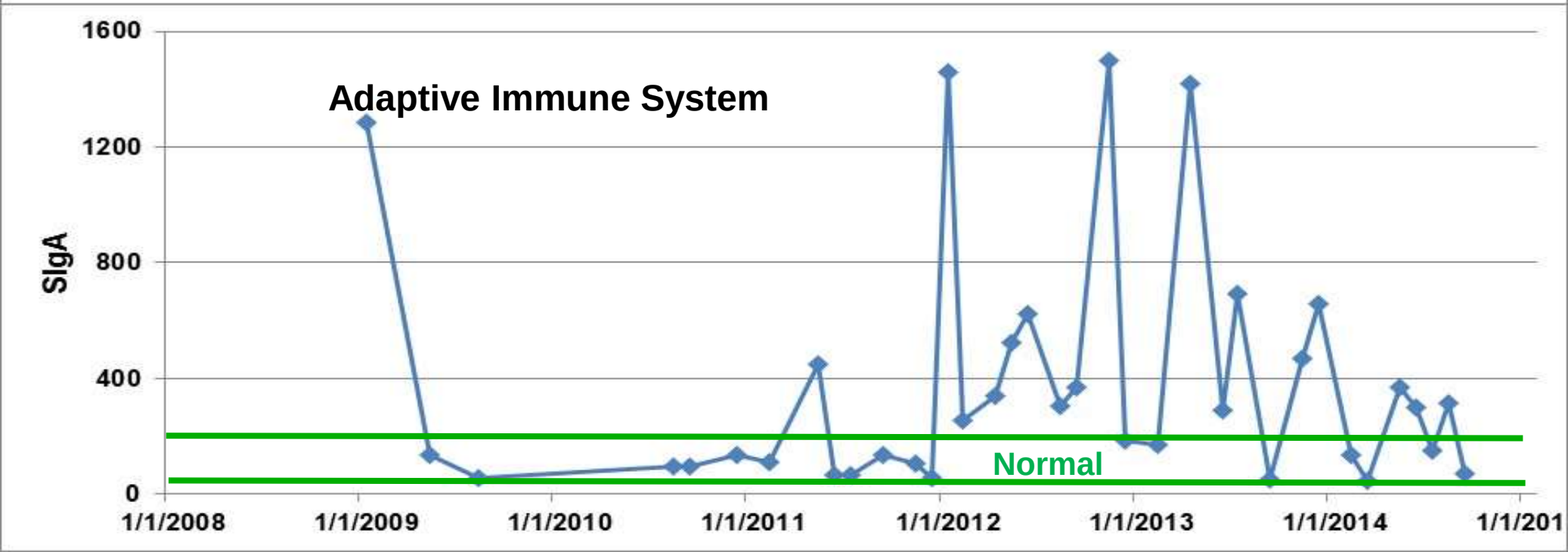
Adding Stool Tests Revealed Oscillatory Behavior in an Immune Variable



Lactoferrin is a Protein Shed from Neutrophils - An Antibacterial that Sequesters Iron

Fine Time-Resolution Sampling Also Reveals Dynamical Innate and Adaptive Immune Dysfunction

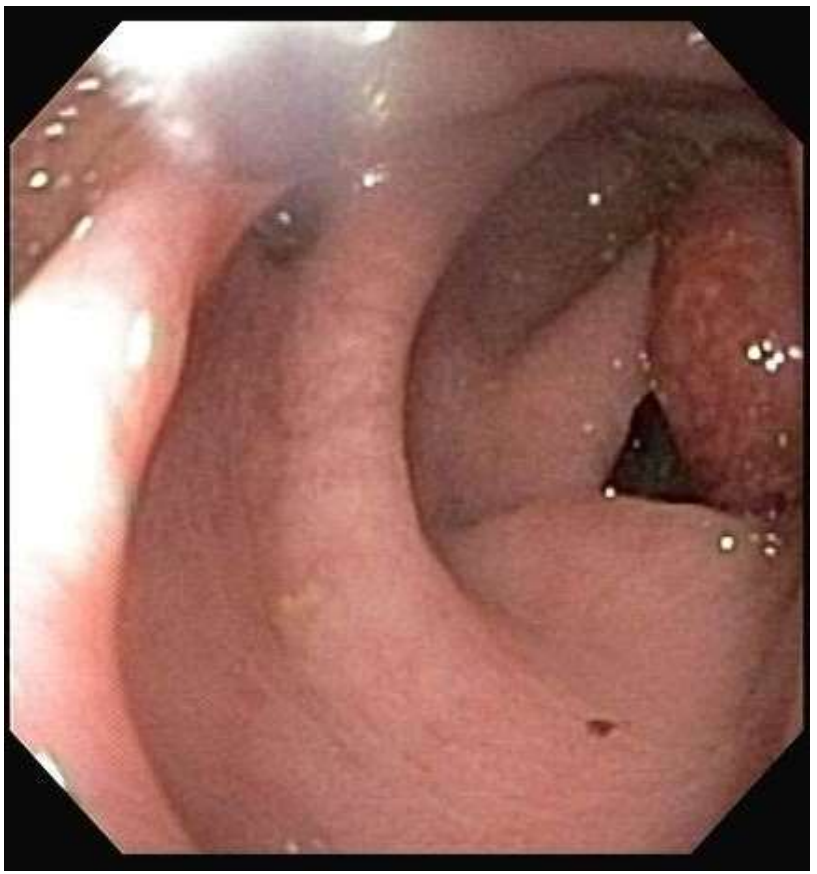




Colonoscopy Images Show Inflamed Pseudopolyps in 6 inches of Sigmoid Colon

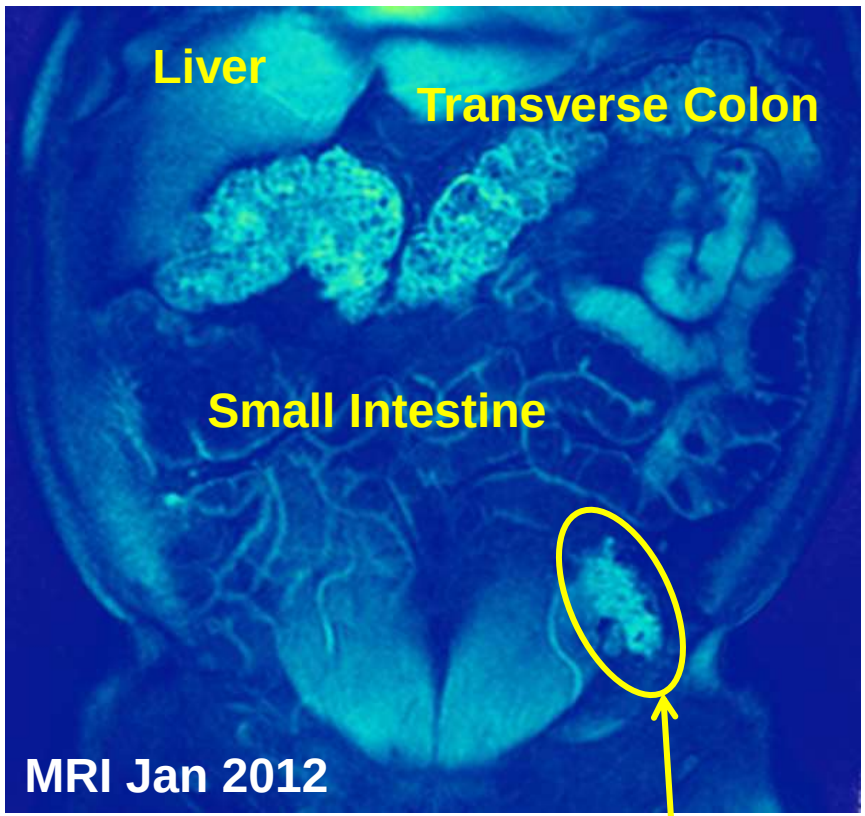


Dec 2010



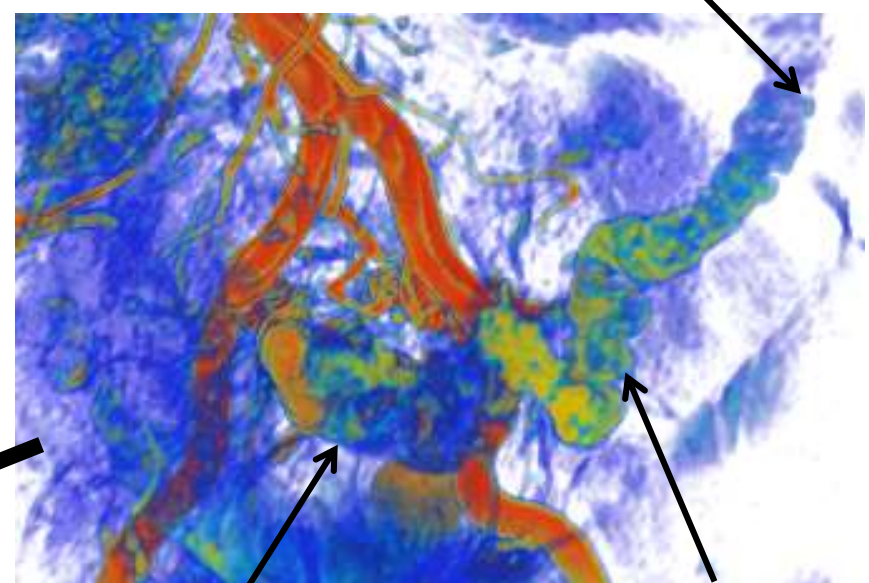
Jan 2012

Confirming the Colonic Crohn's Hypothesis: Finding the "Smoking Gun" with MRI Imaging



I Obtained the MRI Slices From UCSD Medical Services and Converted to Interactive 3D Working With Calit2 Staff & DeskVOX Software

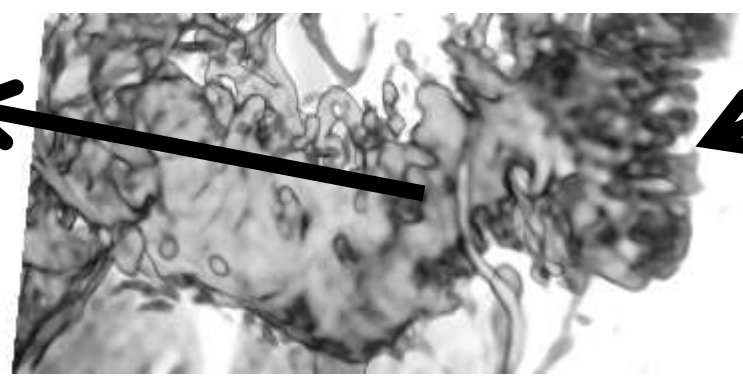
Descending Colon



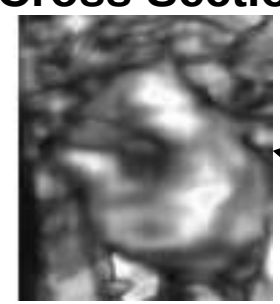
Major Kink

Sigmoid Colon Threading Iliac Arteries

Diseased Sigmoid Colon



Cross Section



Why Did I Have an Autoimmune Disease like IBD?

Despite decades of research,
the etiology of Crohn's disease
remains unknown.
Its pathogenesis may involve
a complex interplay between
host genetics,
immune dysfunction,
and microbial or environmental factors.

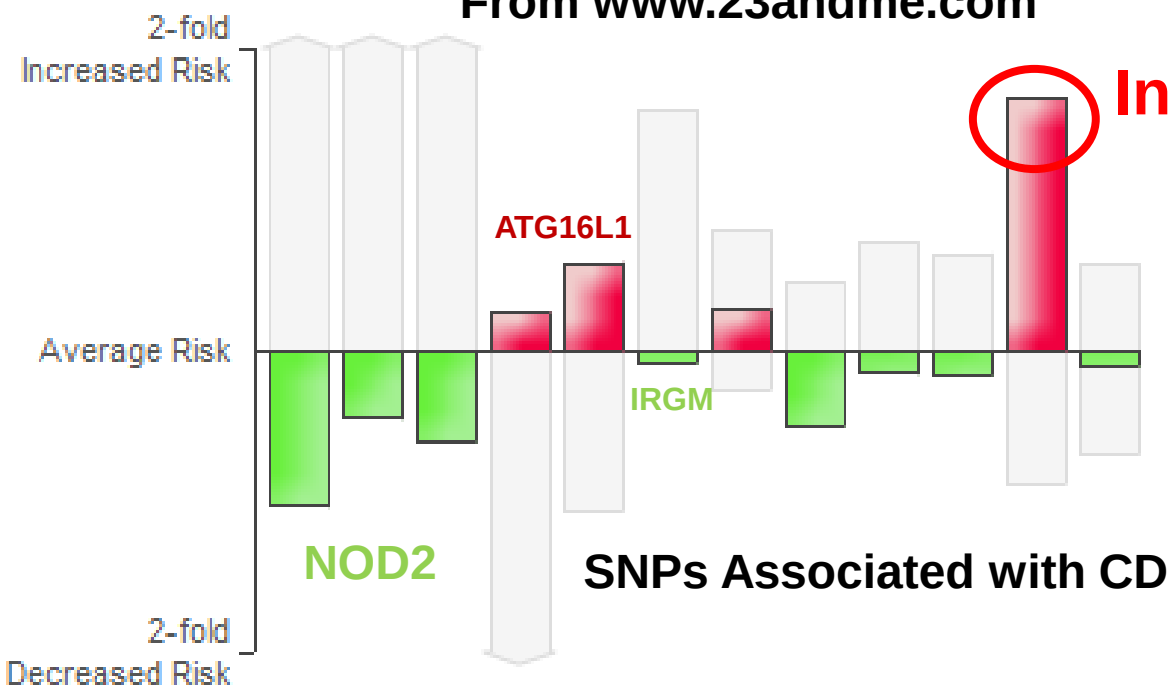
--The Role of Microbes in Crohn's Disease

So I Set Out to Quantify All Three!

Paul B. Eckburg & David A. Relman
Clin Infect Dis. 44:256-262 (2007)

I Found I Had One of the Earliest Known SNPs Associated with Crohn's Disease

From www.23andme.com



Polymorphism in Interleukin-23 Receptor Gene — 80% Higher Risk of Pro-inflammatory Immune Response rs1004819

A Genome-Wide Association Study Identifies *IL23R* as an Inflammatory Bowel Disease Gene

Richard H. Düerr, *et al.*
Science **314**, 1461 (2006)

News and Views

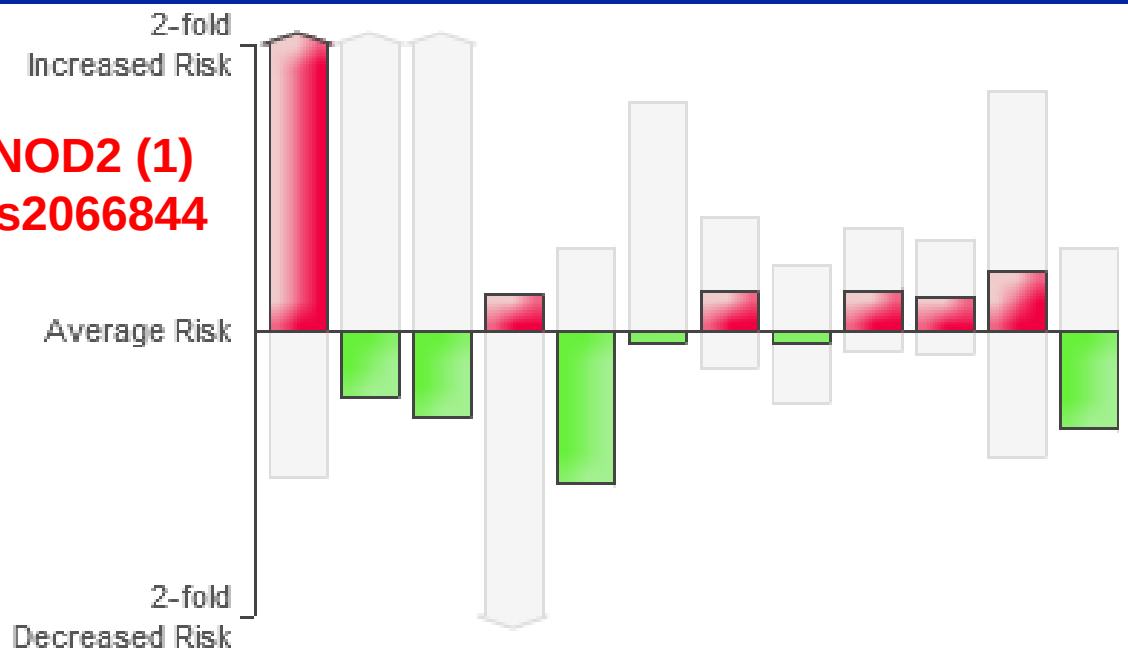
Nature Medicine **13**, 26 - 28 (2007)
doi:10.1038/nm0107-26

IL-23: a master regulator in Crohn disease

Markus F Neurath[1]

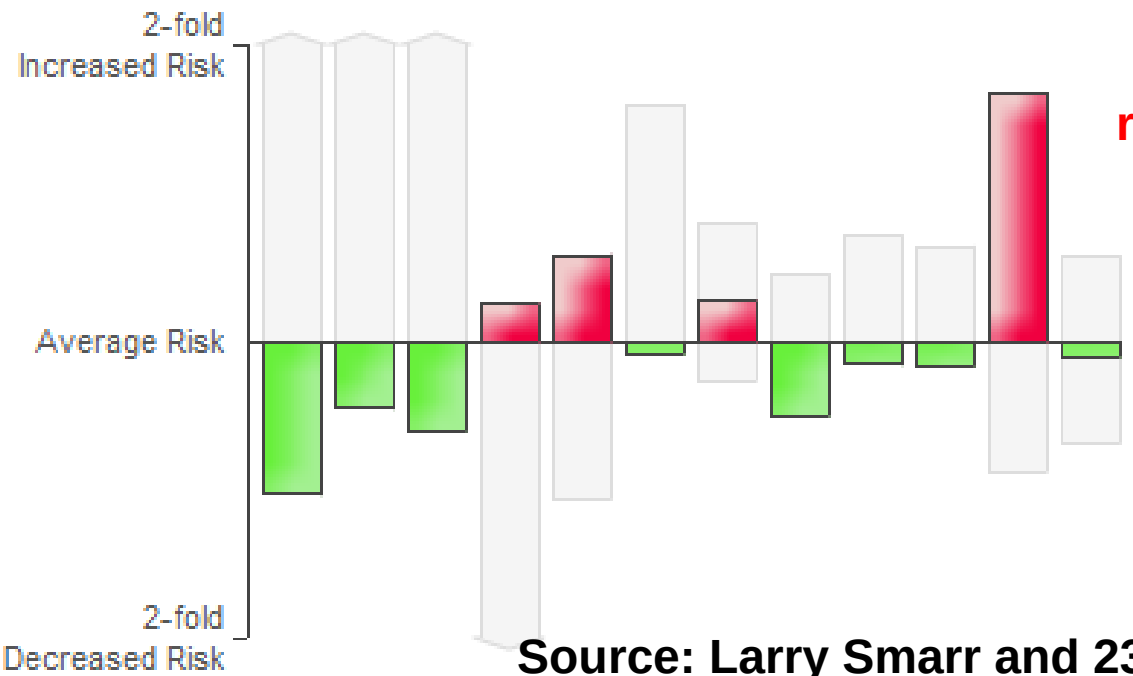
There Is Likely a Correlation Between CD SNPs and Where and When the Disease Manifests

Subject with Ileal Crohn's



Female
CD Onset
At 20-Years Old

Subject with Colon Crohn's



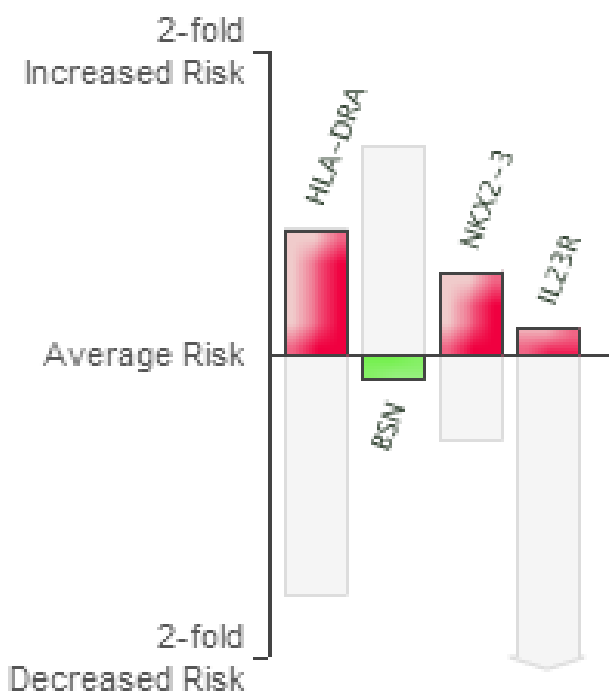
Me-Male
CD Onset
At 60-Years Old

Source: Larry Smarr and 23andme

I Also Had an Increased Risk for Ulcerative Colitis, But a SNP that is Also Associated with Colonic CD



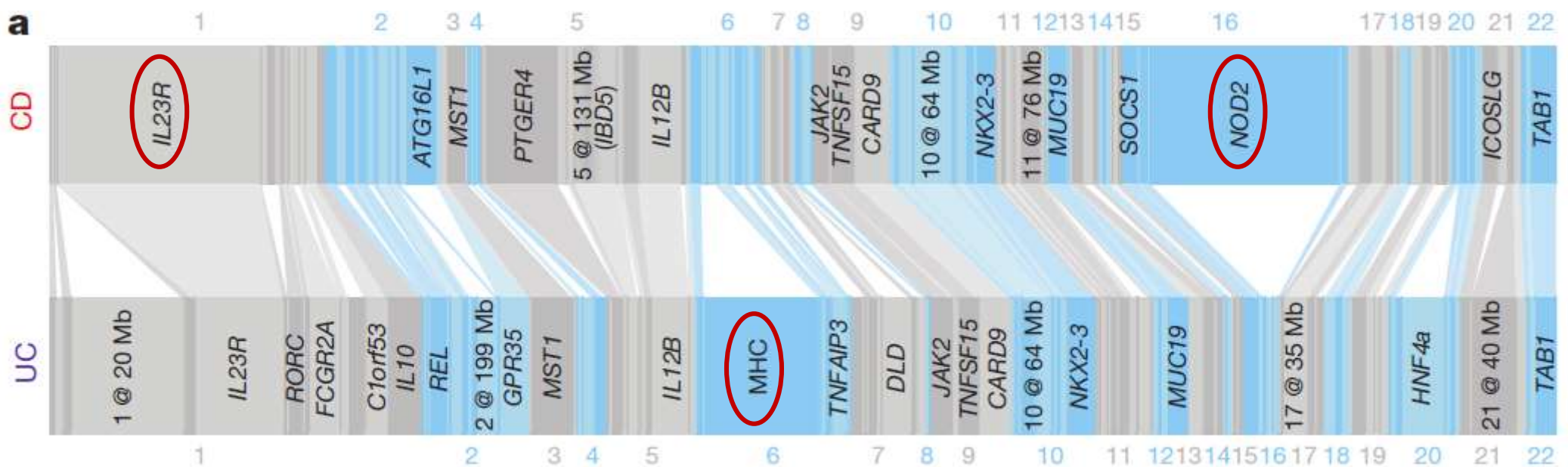
I Have a 33% Increased Risk for Ulcerative Colitis HLA-DRA (rs2395185)



I Have the Same Level of HLA-DRA Increased Risk as Another Male Who Has Had Ulcerative Colitis for 20 Years

"Our results suggest that at least for the SNPs investigated [including HLA-DRA], colonic CD and UC have common genetic basis."
-Waterman, et al., IBD 17, 1936-42 (2011)

23andme is Now Collecting SNPs from 10,000 Patients With IBD to Compare with the 163 Known SNPs Associated with IBD

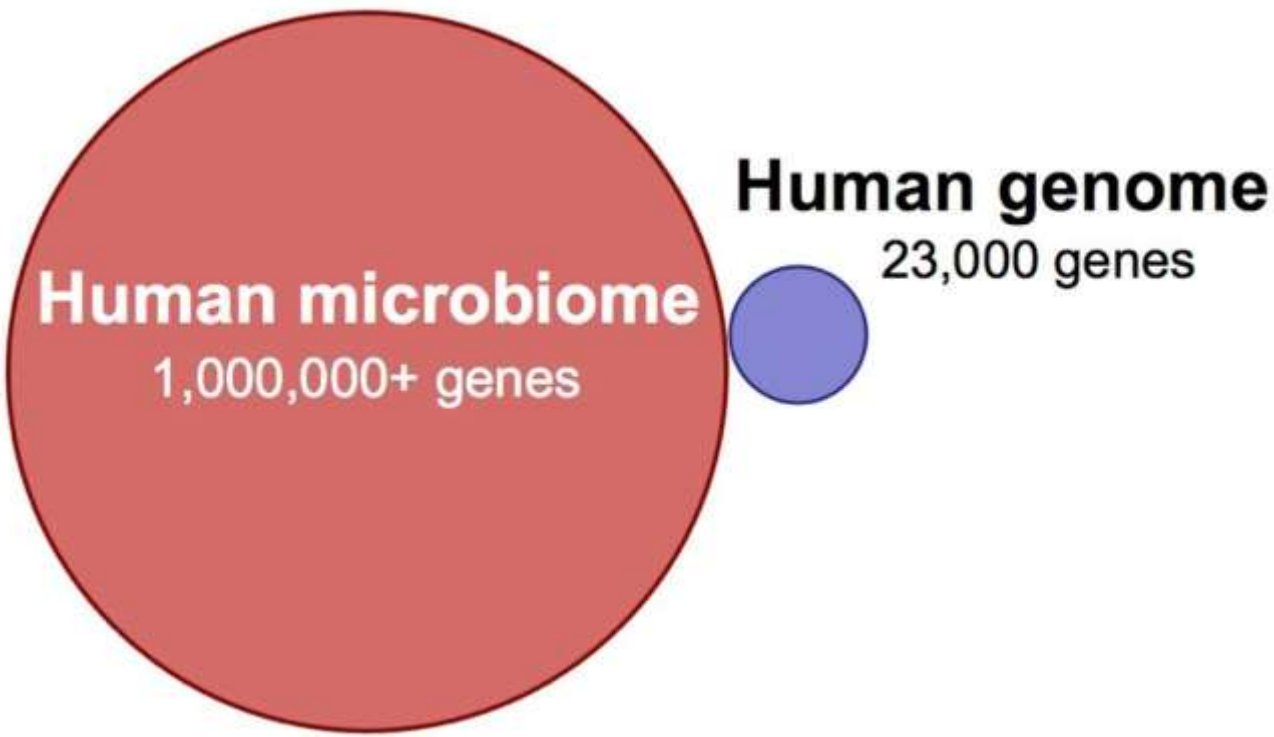


- The width of the bar is proportional to the variance explained by that locus
- Bars are connected together if they are identified as being associated with both phenotypes
- Loci are labelled if they explain more than 1% of the total variance explained by all loci

"Host–microbe interactions have shaped the genetic architecture of inflammatory bowel disease," Jostins, et al. Nature 491, 119-124 (2012)

Inclusion of the Microbiome Will Radically Change Medicine and Wellness

Your Body Has 10 Times As Many Microbe Cells As Human Cells



99% of Your DNA Genes Are in Microbe Cells Not Human Cells

I Will Focus on the Human Gut Microbiome, Which Contains Hundreds of Microbial Species

J. Craig Venter™ INSTITUTE

it²

To Map Out the Dynamics of Autoimmune Microbiome Ecology
Couples Next Generation Genome Sequencers to Big Data Supercomputers

- **Metagenomic Sequencing**
  - JCVI Produced ~150 Billion DNA Bases From Seven of LS Stool Samples Over 1.5 Years
  - We Downloaded ~3 Trillion DNA Bases From NIH Human Microbiome Program Data Base
    - 255 Healthy People, 21 with IBD
- **Supercomputing (Weizhong Li, JCVI/HLI/UCSD):**
  - ~180,000 Core-Hours SDSC's Gordon
  - ~35,000 Core-Hours Dell HPC Cloud
- **Produced Relative Abundance of ~10,000 Bacteria, Archaea, Viruses in ~300 People**
  - ~3Million Filled Spreadsheet Cells

Illumina HiSeq 2000 at JCVI



SDSC Gordon Data Supercomputer

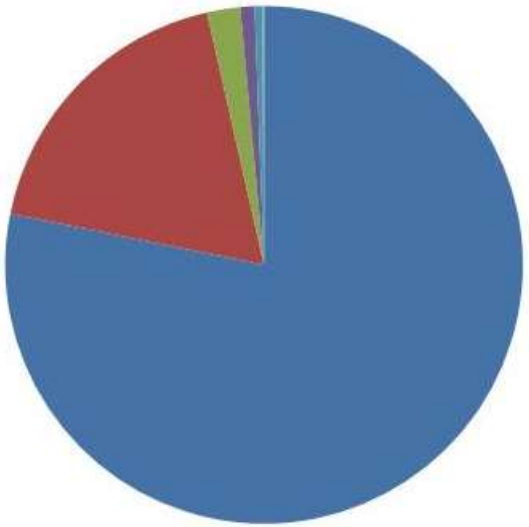


Dell Solutions Center
Industry Solutions Lab
SANGER DSU

J. Craig Venter INSTITUTE SDSC DELL NIH HMP CRBS it²

We Found Major State Shifts in Microbial Ecology Phyla Between Healthy and Two Forms of IBD

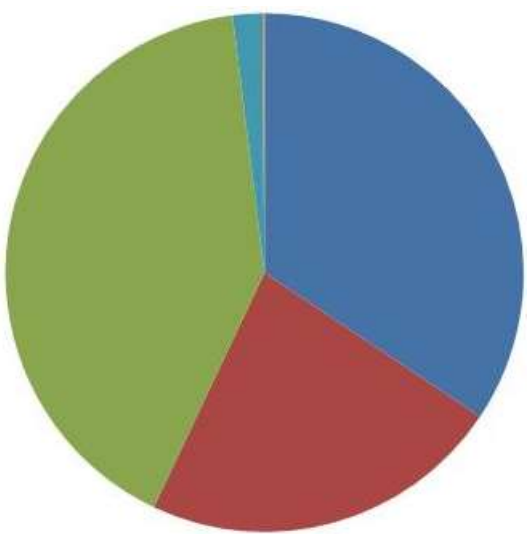
Average HE



- Bacteroidetes
- Firmicutes
- Proteobacteria
- Verrucomicrobia
- Actinobacteria
- Fusobacteria
- Euryarchaeota

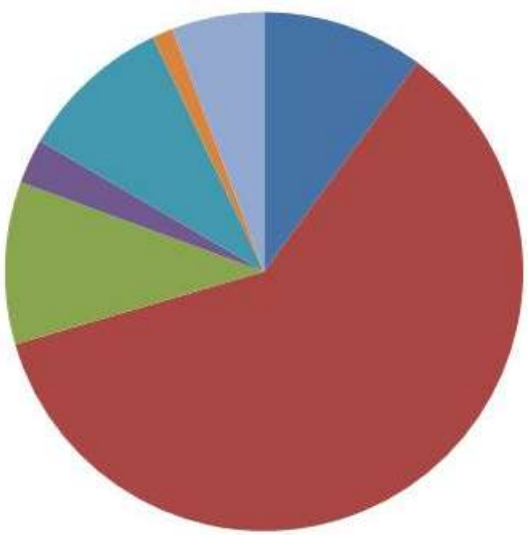
Most Common Microbial Phyla

Average Ulcerative Colitis



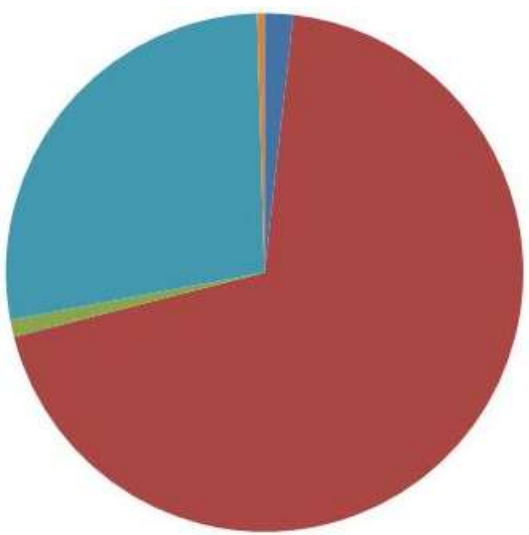
Explosion of Proteobacteria

Average LS



Hybrid of UC and CD
High Level of Archaea

Average Crohn's Disease



Collapse of Bacteroidetes
Explosion of Actinobacteria

Can the Gut Microbiome Intermediate Between Inflammation & The Development of Some Colorectal Cancers?

- **Colorectal Cancer (CRC) is the Most Common Cancer Among Inflammatory Bowel Disease (IBD) Patients**

- **However, IBD-Related CRC is Only 2% of All CRC**

"The root cause of CRC is unclear, but inflammation is a well-recognized risk factor." (Wu et al. 2009; McLean et al. 2011)

A Link Between IL-23, Gut Microbes, Inflammation, and CRC

"IL-23 is another cytokine that is up-regulated in various types of cancer, including colon cancer; specific polymorphisms in the gene encoding its receptor were associated with Crohn's disease and ulcerative colitis."

Inflammation and Colon Cancer, Terzic, et al.,
GASTROENTEROLOGY 2010;138:2101–2114

Recall my IL-23R SNP

"The commensal microflora regulates basal colonic IL-23 expression in naïve mice."

"IL-23 controls CRC inflammation and tumorigenesis."

Adenoma–linked barrier defects and microbial products drive IL–23/IL–17–mediated tumour growth

Grivennikov, et al. 254 | NATURE | VOL 491 | 8 NOVEMBER 2012

The Emerging Role of the Human Gut Microbiome in the Transition to CRC

"Inflammation is thought to induce or promote intestinal cancer through the effects of immune cells on epithelial cells, leading to oxidative stress, DNA damage, and cell turn- over. However, the notion that chronic inflammation can lead to the accumulation of cancer-promoting bacteria begins to shift greater attention toward the microbiota."



Bacteria Deliver a Genotoxic Hit
Robert F. Schwabe and Timothy C. Wang
Science **338**, 52 (2012);
DOI: 10.1126/science.1229905

Fusobacteria Are Found To Be More Abundant In Colonrectal Carcinoma (CRC) Tissue

Two Cancer Studies Find Bacterial Clue in Colon

The New York Times

By GINA KOLATA
Published: October 17, 2011

Genomic analysis identifies association of *Fusobacterium* with colorectal carcinoma Aleksandar D. Kostic, **et al.**

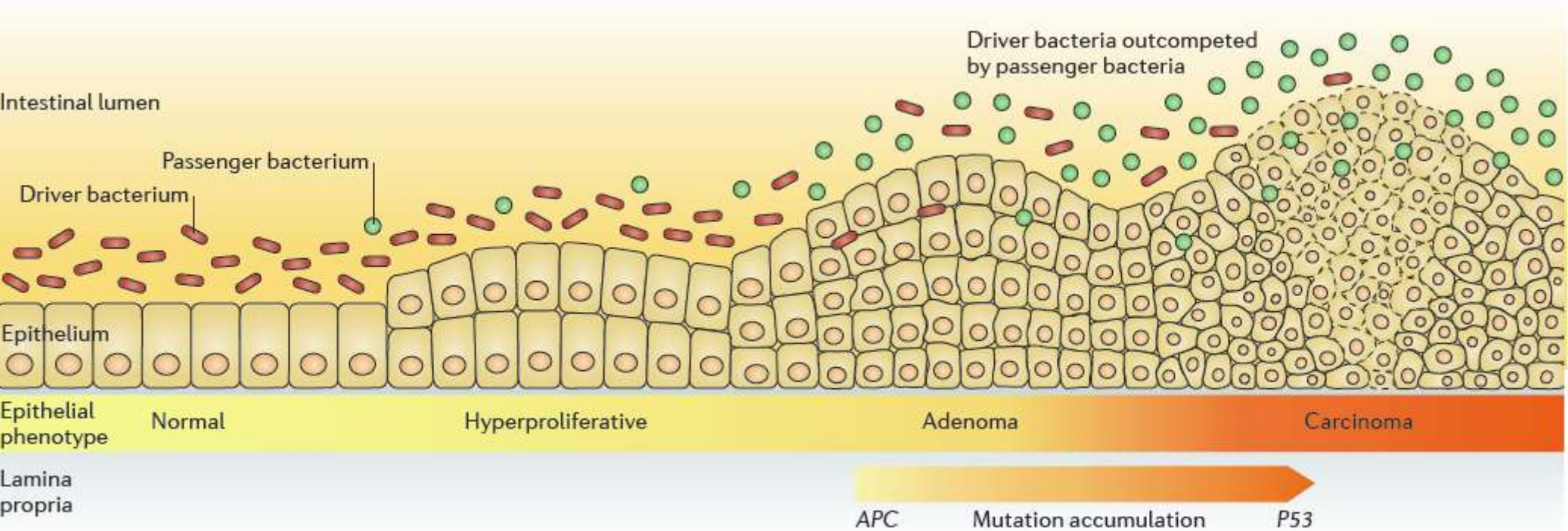
Fusobacterium nucleatum infection is prevalent in human colorectal carcinoma Mauro Castellarin, **et al.**

CSH PRESS

GENOME RESEARCH

The Bacterial Driver-Passenger Model for Colorectal Cancer Initiation

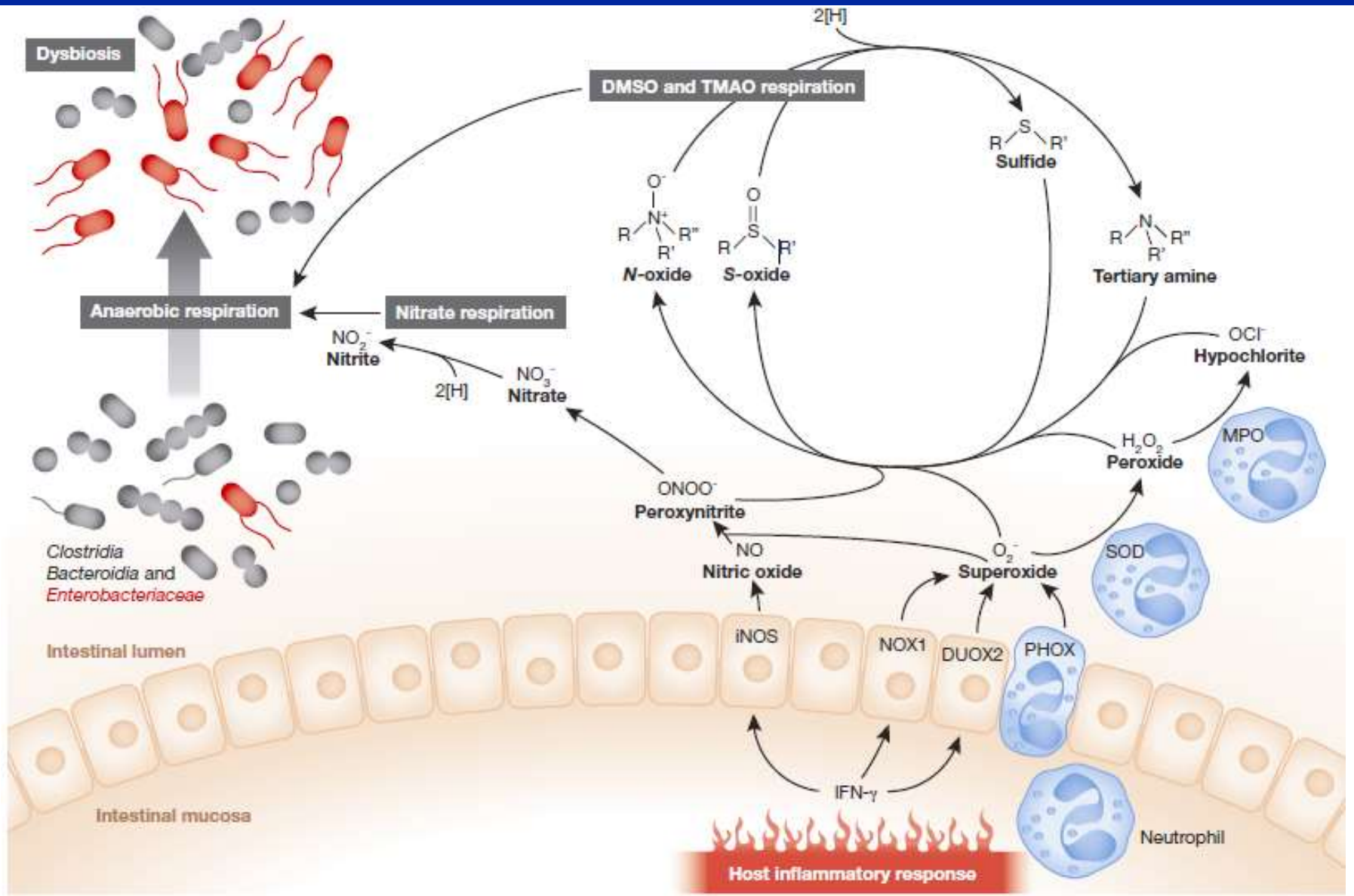
Is Fusobacterium nucleatum a "Driver" or a "Passenger"



"Early detection of Colorectal Cancer (CRC) is one of the greatest challenges in the battle against this disease & the establishment of a CRC-associated microbiome risk profile could aid in the early identification of individuals who are at high risk and require strict surveillance."

Tjalsma, et al. Nature Reviews Microbiology v. 10, 575-582 (2012)

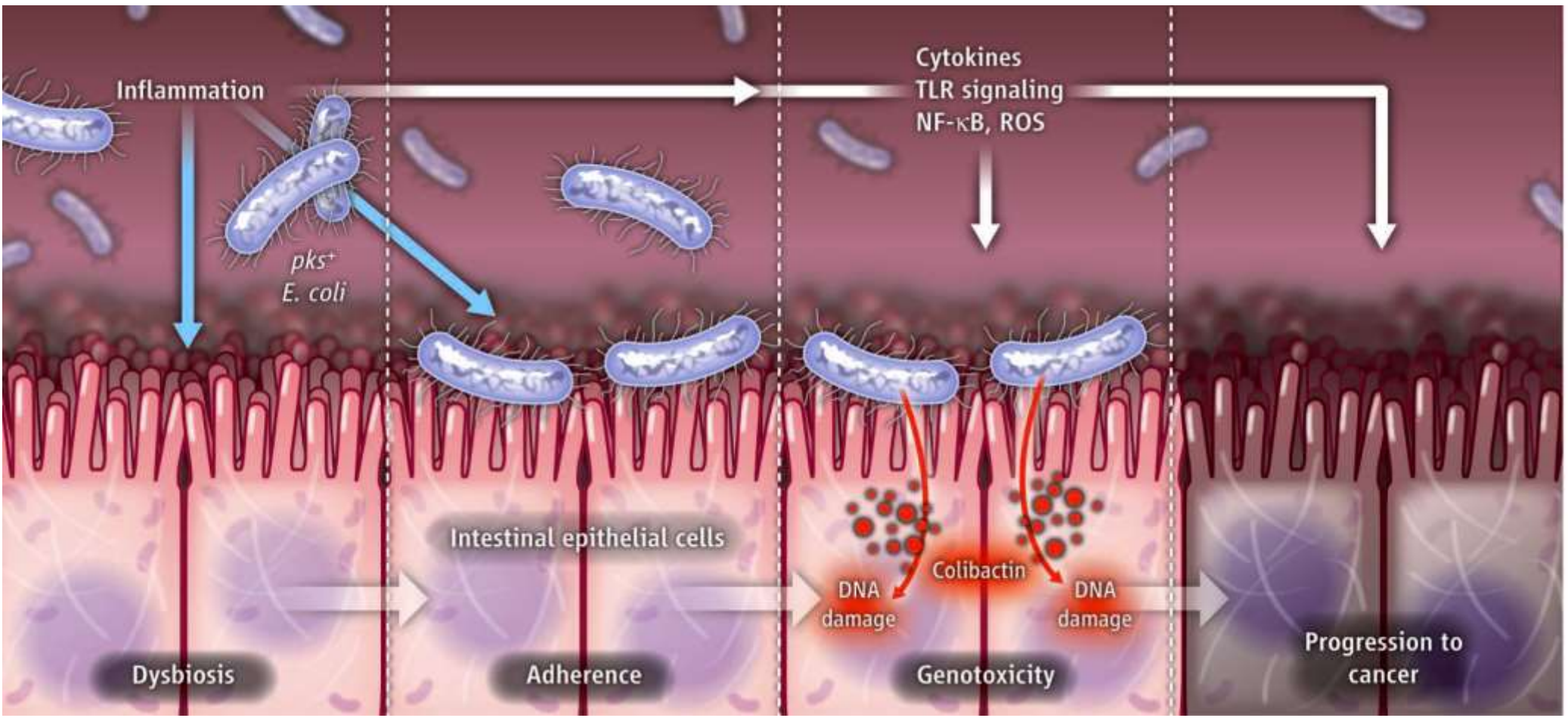
Inflammation Enables Anaerobic Respiration Which Leads to Phylum-Level Shifts in the Gut Microbiome



Sebastian E. Winter, Christopher A. Lopez & Andreas J. Bäumler,
EMBO reports VOL 14, p. 319-327 (2013)

Chronic Inflammation Can Accumulate Cancer-Causing Bacteria in the Human Gut

Escherichia coli Strain NC101



Science
AAAS

Bacteria Deliver a Genotoxic Hit
Robert F. Schwabe and Timothy C. Wang
Science **338**, 52 (2012);
DOI: 10.1126/science.1229905

E. coli claims the driving seat for cancer

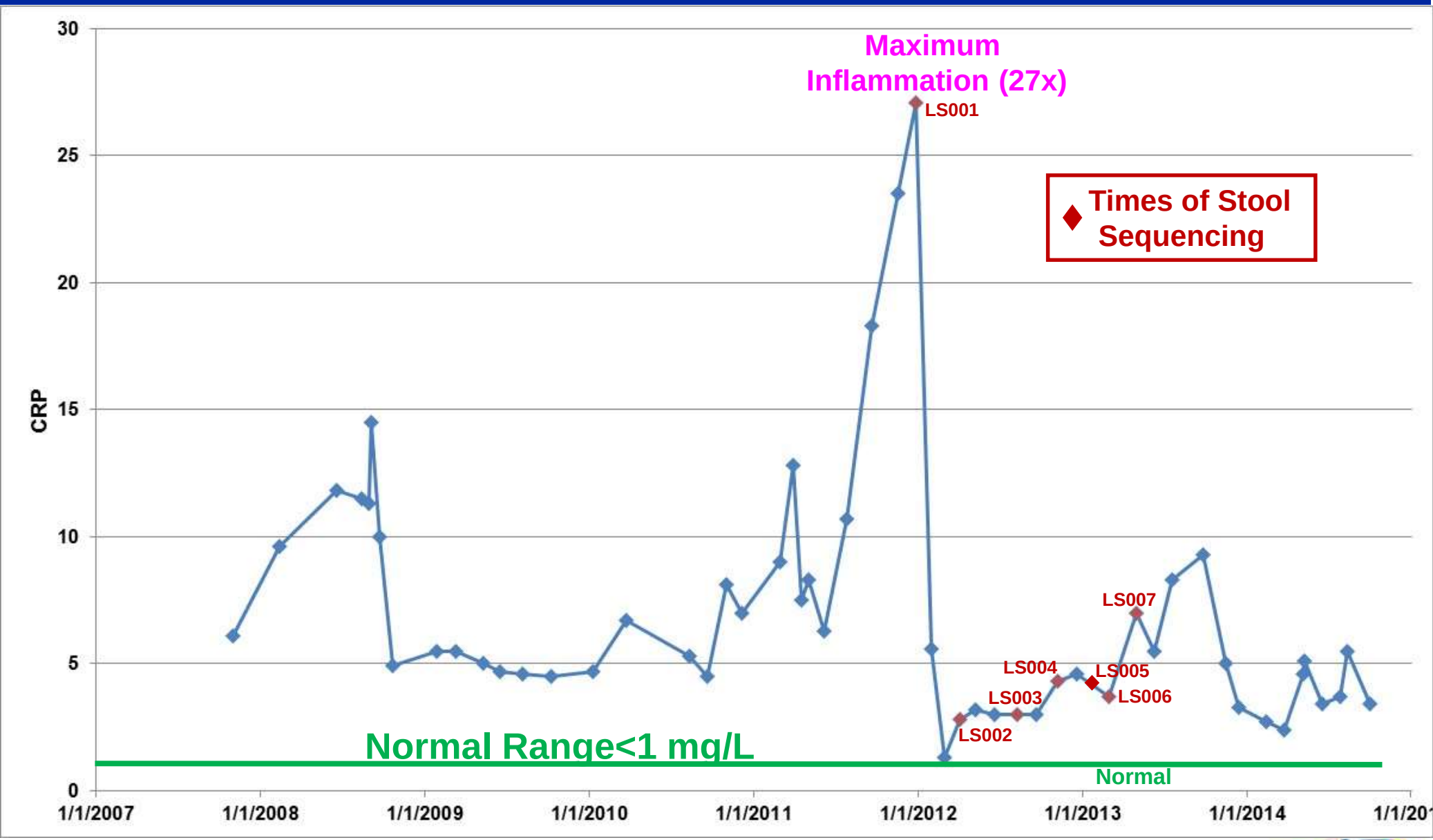
"Arthur *et al.* provide evidence that inflammation alters the intestinal microbiota by favouring the proliferation of genotoxic commensals, and that the *Escherichia coli* genotoxin colibactin promotes colorectal cancer (CRC)."



Christina Tobin Kåhrström
Associate Editor,
Nature Reviews Microbiology

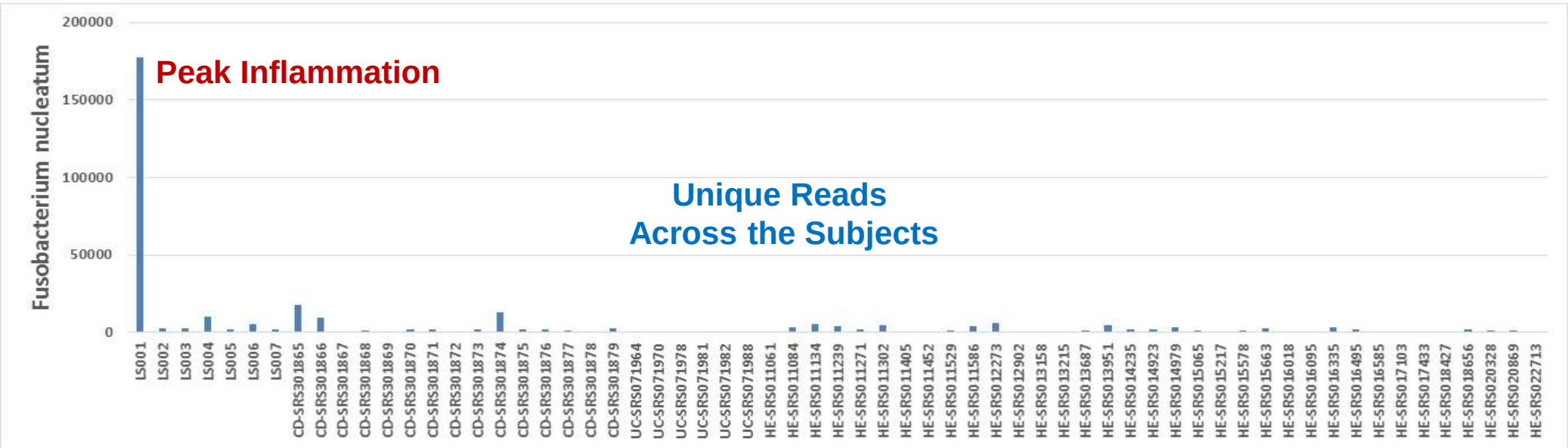
VOLUME 12 | OCTOBER 2012
NATURE REVIEWS | CANCER

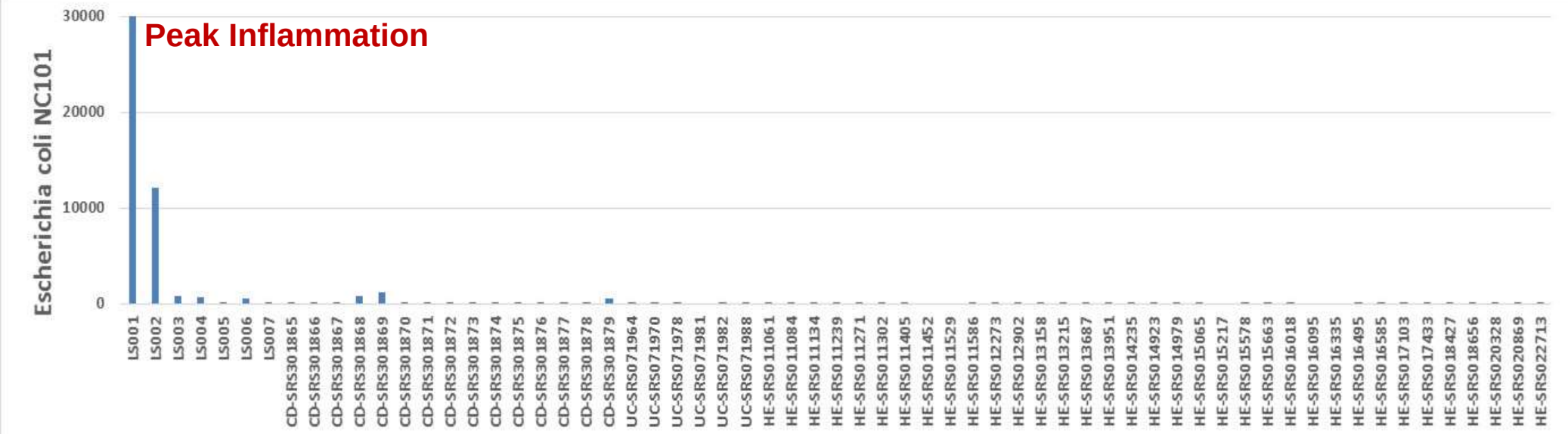
Tracking My Serum Inflammation and Comparing with My Microbiome Population



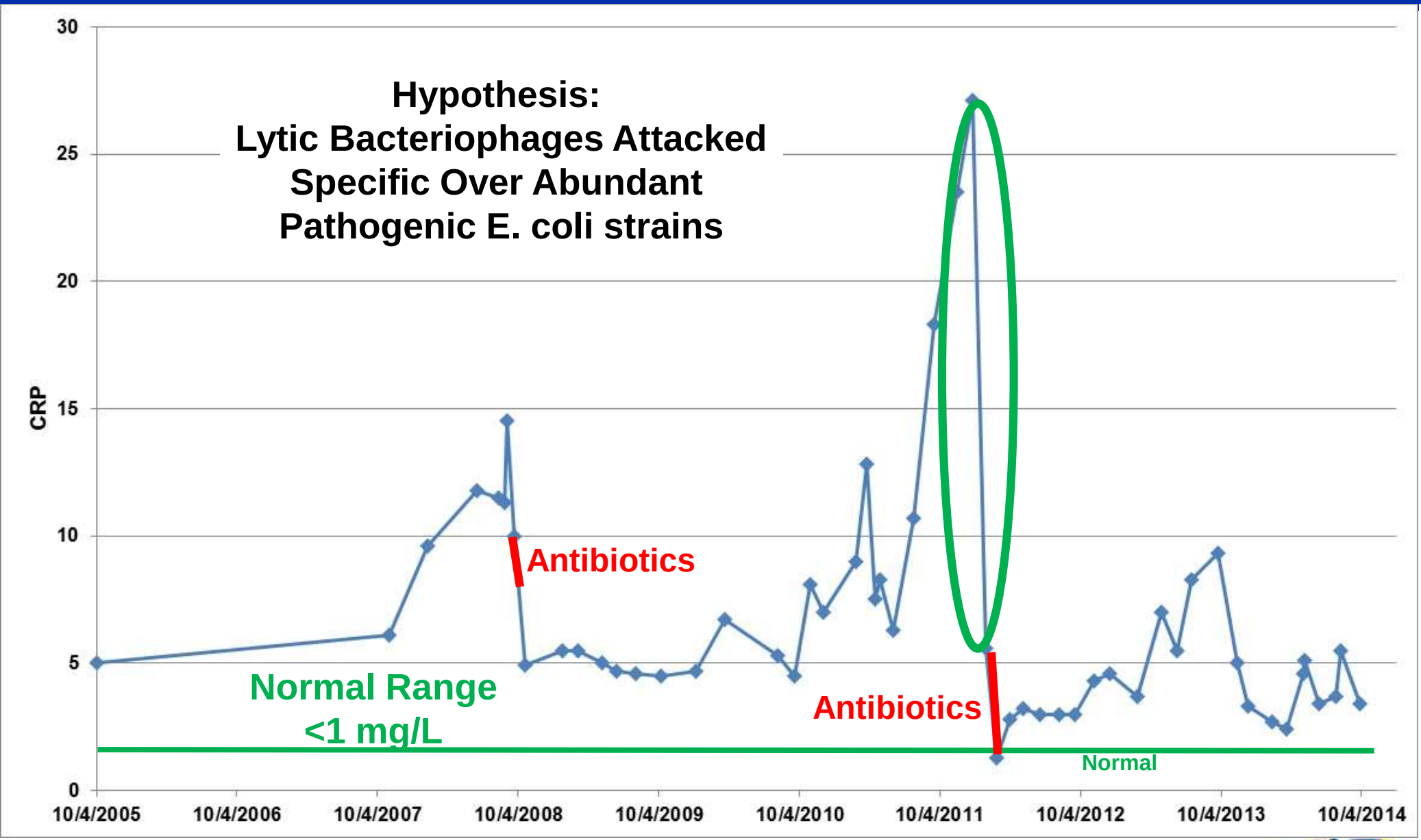
Complex Reactive Protein (CRP) is a Blood Biomarker for Detecting Presence of Inflammation

I Had the Highest Values of E. coli NC101 and Fusobacterium nucleatum at My Highest Inflammation

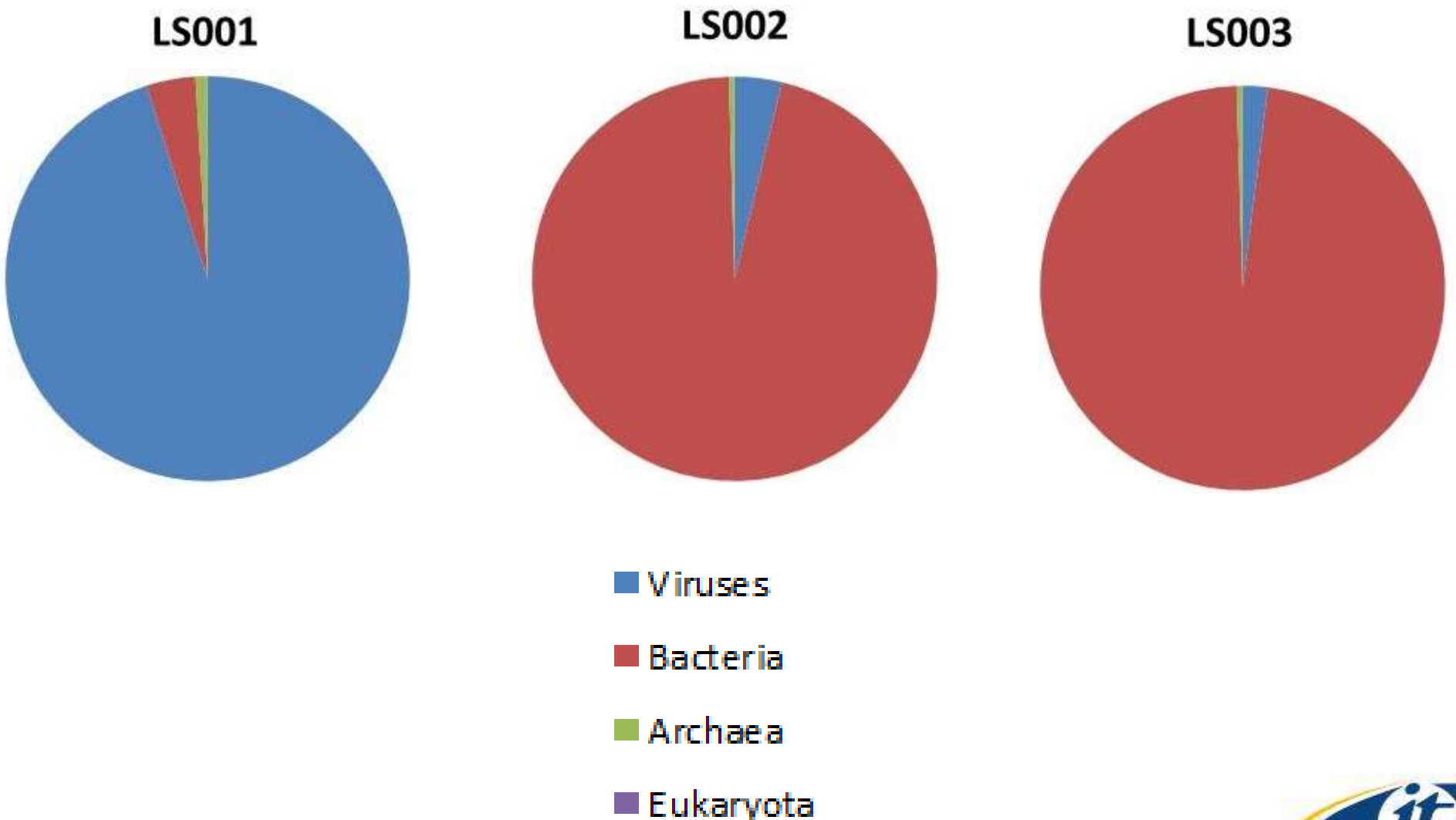




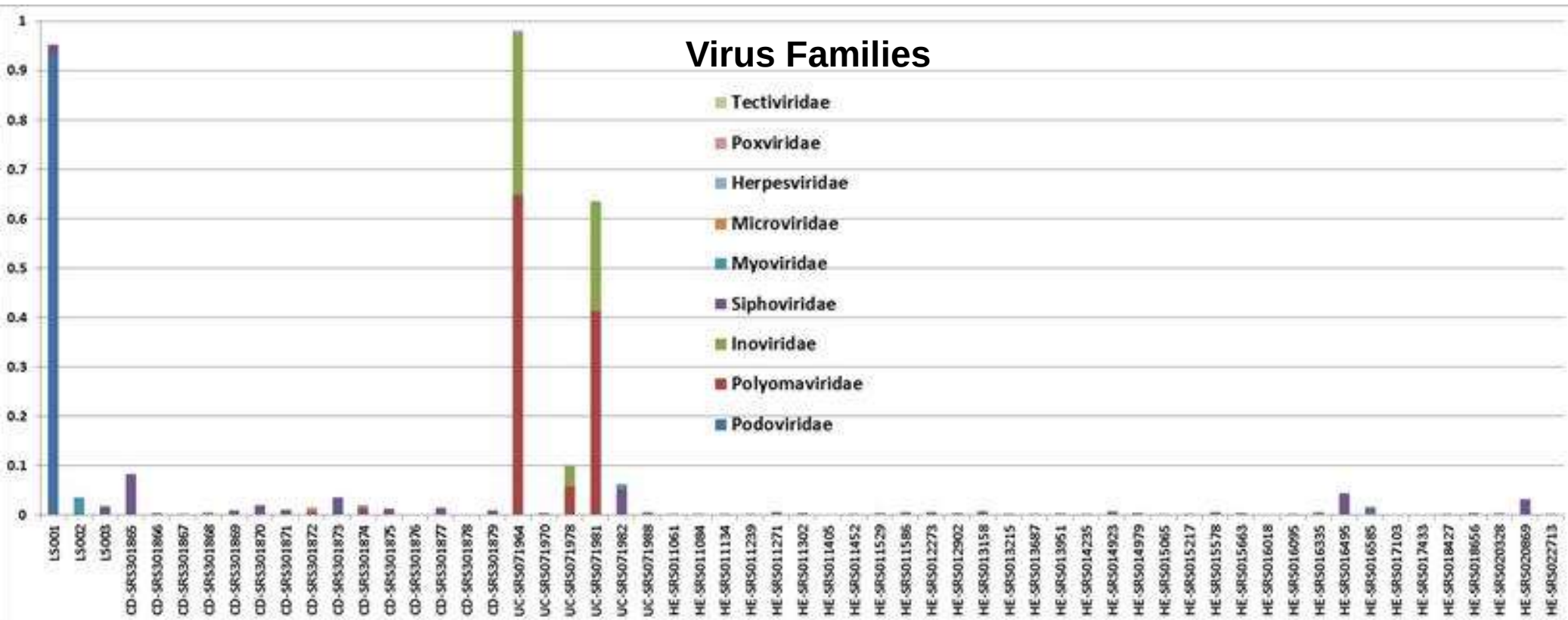
What Caused the Dramatic Drop in My Inflammation Before Taking Antibiotics?



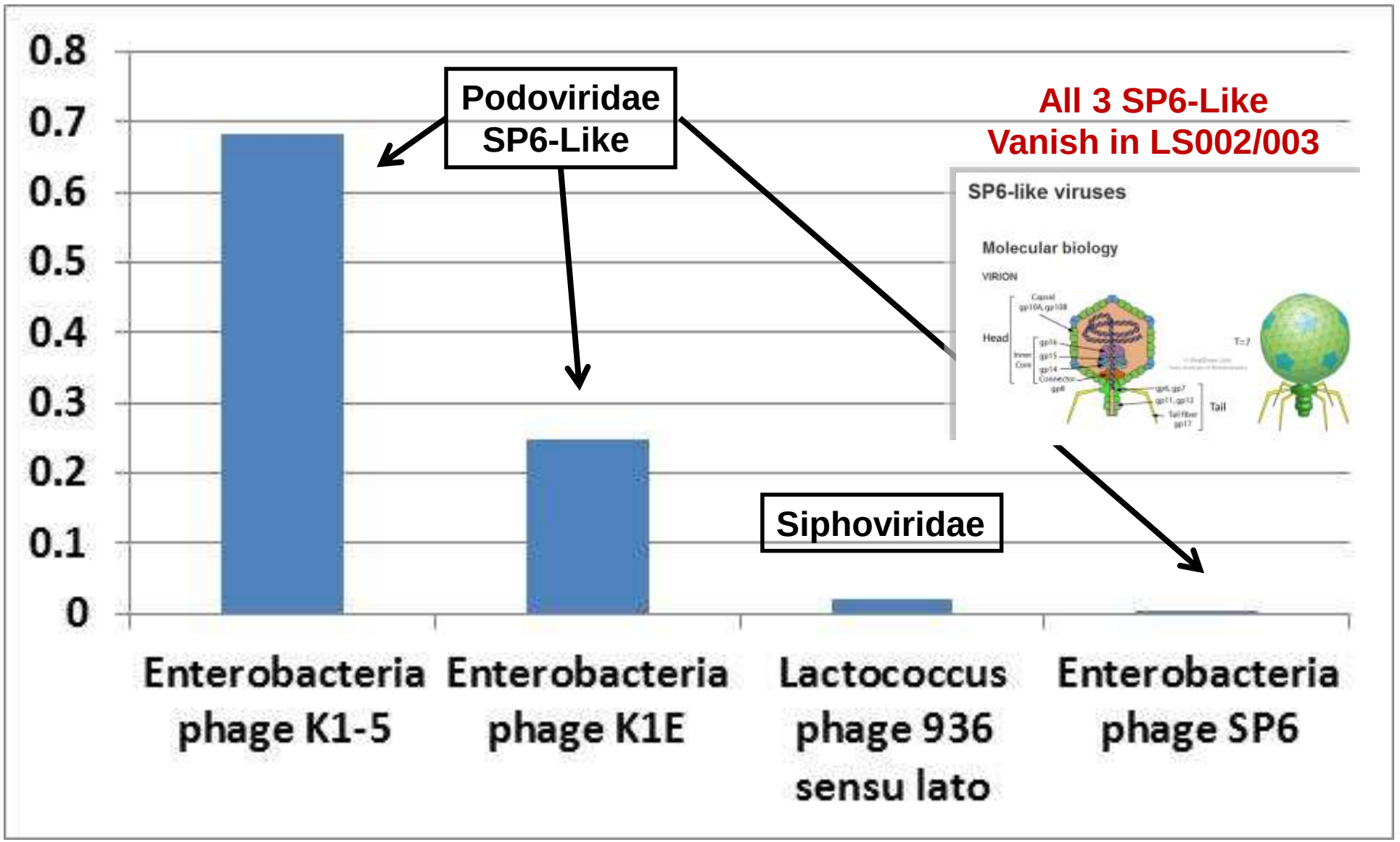
Radical Shift in Relative Abundance After Therapy



LS001 Viral Abundance is Similar to Some UC Patients, But Different Families

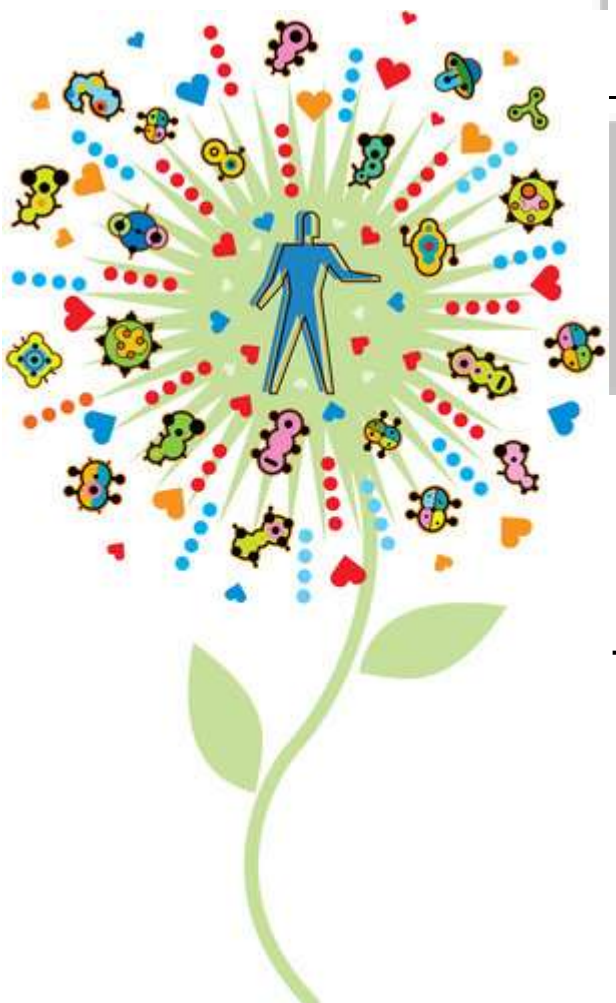


LS001 Relative Abundance of Viruses Among All Virus, Bacteria, Archaea, Eukaryota



Abundance >0.1%
Out of 493 Viral Reference Species

Next Decade Will See New Microbiome "Gardening Tools"



The New York Times — Science

Tending the Body's Microbial Garden

By CARL ZIMMER
Published: June 18, 2012

"I would like to lose the language of warfare,"
said Julie Segre, a senior investigator at
the National Human Genome Research Institute.
"It does a disservice to all the bacteria
that have co-evolved with us
and are maintaining the health of our bodies."

Will Medical Foods Provide New Tools for Altering Gut Microbiome?

Could Bacteria-Fighting Viruses Replace Overused Antibiotics? [Preview]

Long ignored by mainstream researchers, the viruses that infect bacteria have a role to play in modern medicine, Vincent Fischetti says

By Brendan Borrell

SCIENTIFIC AMERICAN™

August 7, 2012

Review Article

Immunocompatibility of Bacteriophages as Nanomedicines

Journal of Nanotechnology (2012)

Thanks to Our Great Team!

UCSD Metagenomics Team

Weizhong Li
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JCVI Team

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