

MPE Transforms Pathology, Integrating Genomics,
Microbiome, and Immunology

(21 June 2018, 30-35 min)

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One Field MPE

1 + 1 → 100

Big Synergism

CRC = colorectal cancer

MPE = molecular pathological epidemiology

MSI = microsatellite instability

(hypermutator, high neoantigen load)

(Immune checkpoint inhibitor works for MSI-high
solid tumors)

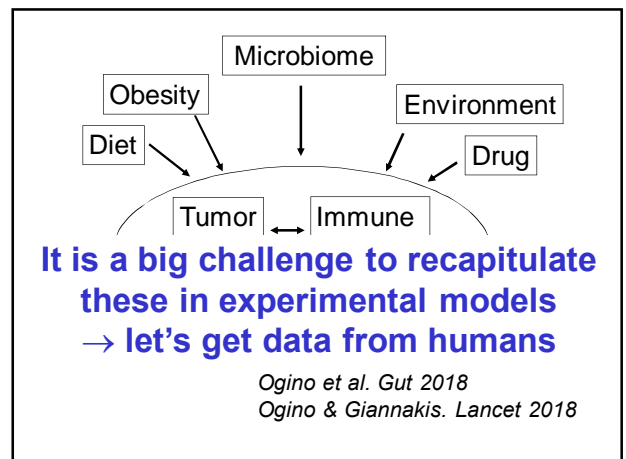
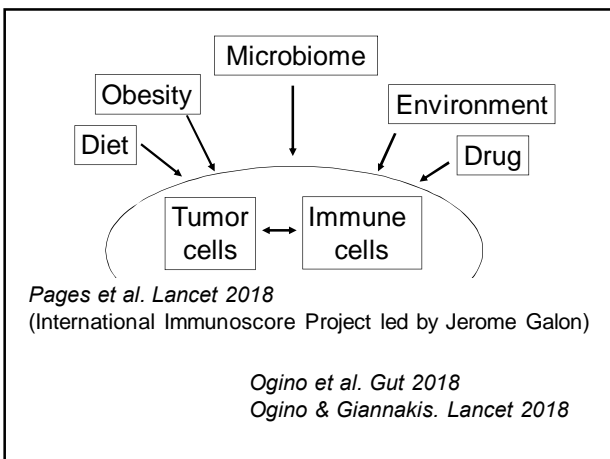
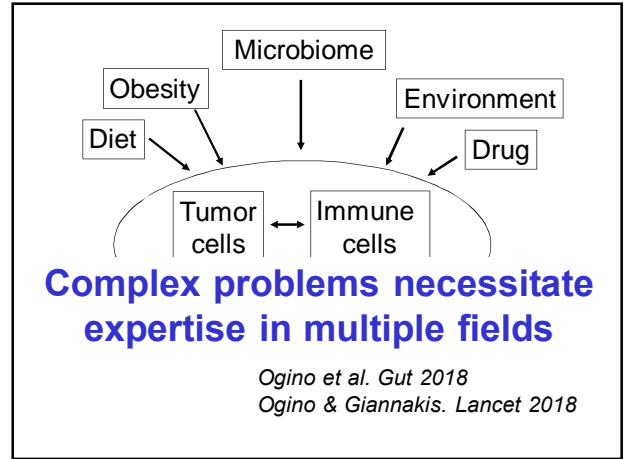
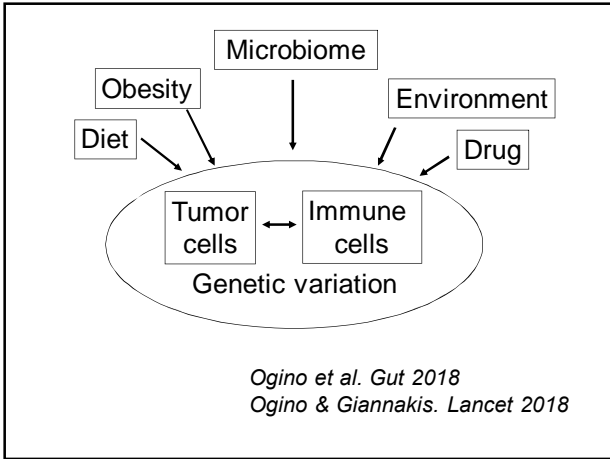
THE 5th INTERNATIONAL
MOLECULAR PATHOLOGICAL
EPIDEMIOLOGY (MPE) MEETING

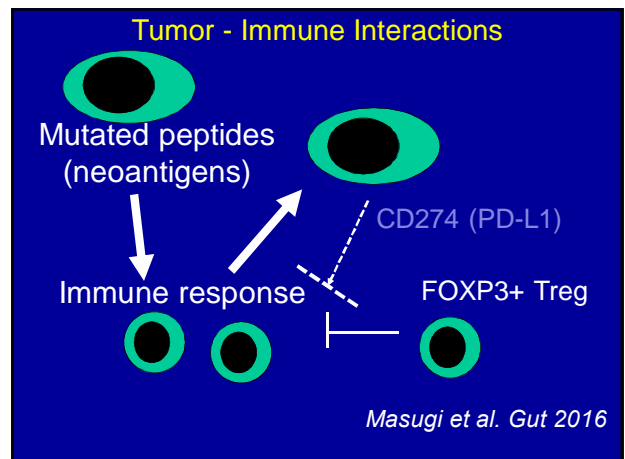
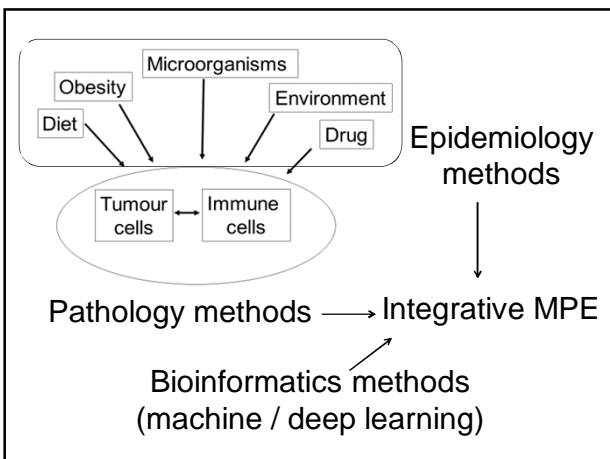
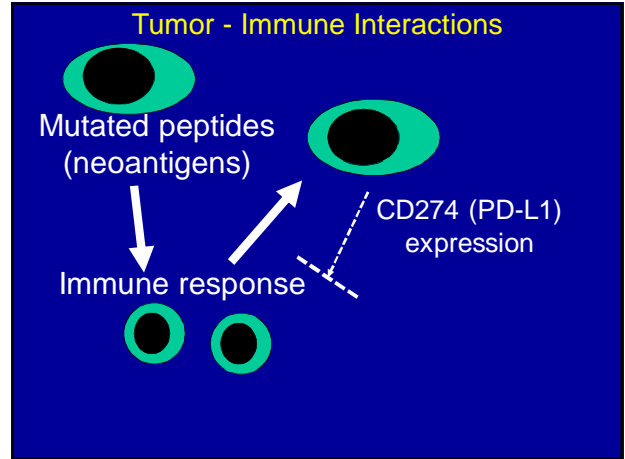
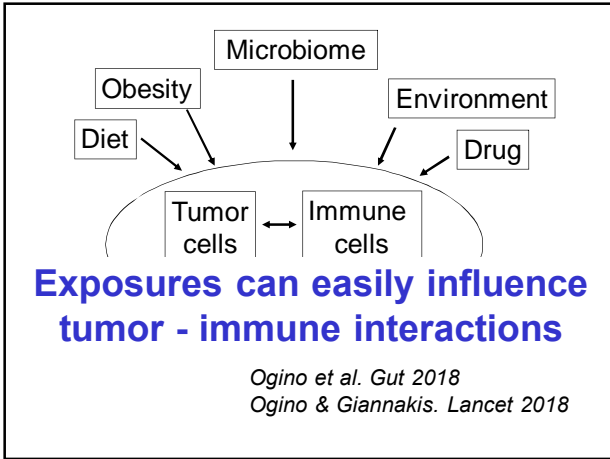
*Discuss Big Data Analysis,
and Think Big!*

June 2020, Boston, USA

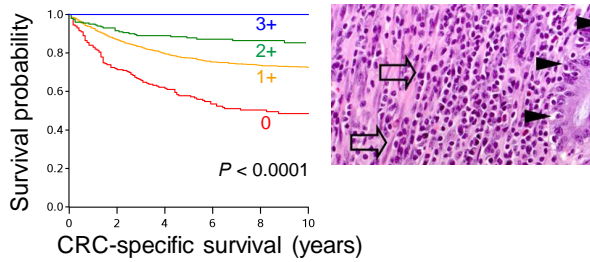
Free registration
Open to public

www.mpemeeting.org



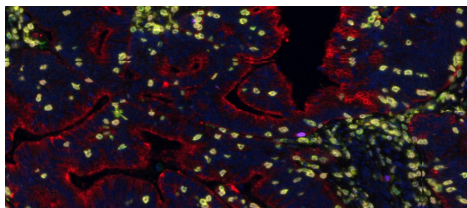


Immune cells in tumor microenvironment
= best prognostic biomarker
(why not clinical decision making?)



Immunology-MPE (immuno-MPE) studies

Multiplex immunofluorescence assays



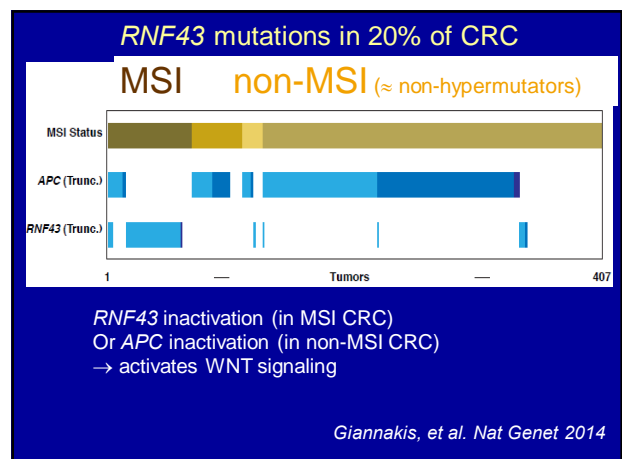
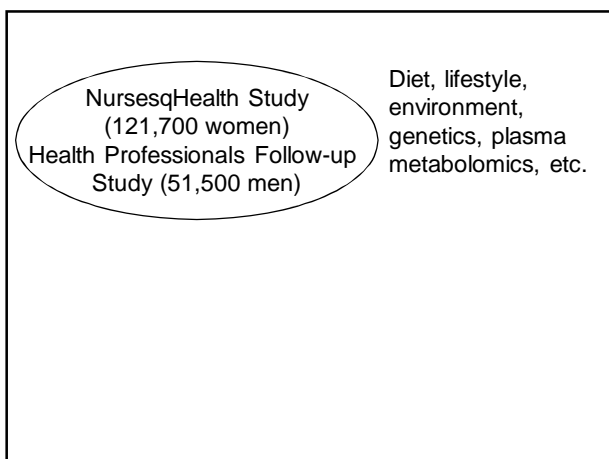
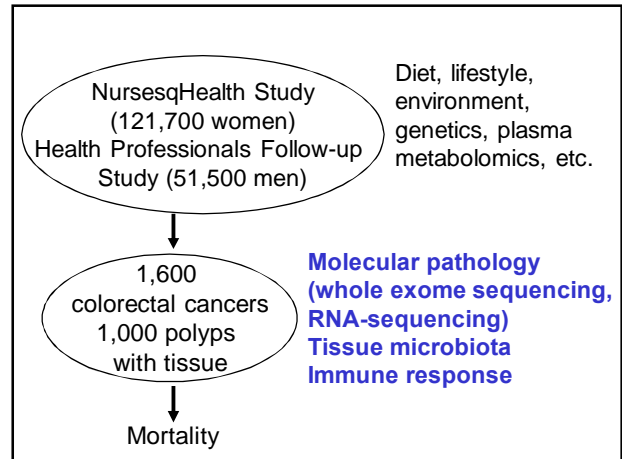
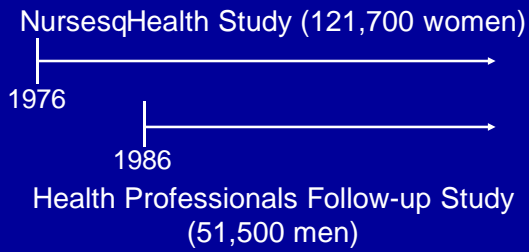
CD3 (brown), CD4 (yellow), CD8 (purple), CD45RO (green), FOXP3 (orange), DAPI (nuclei, blue),
cytokeratin (epithelial cells, red)

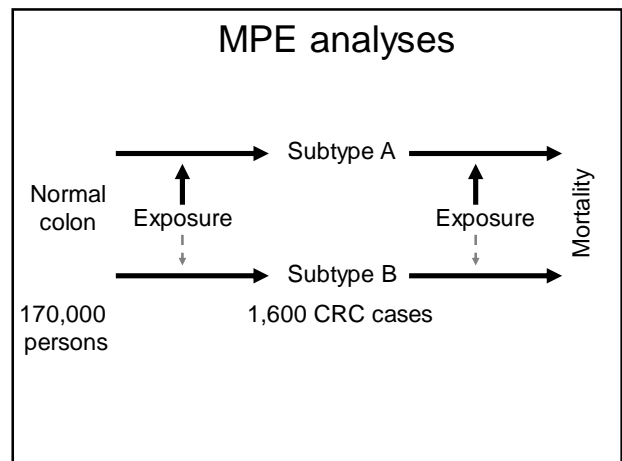
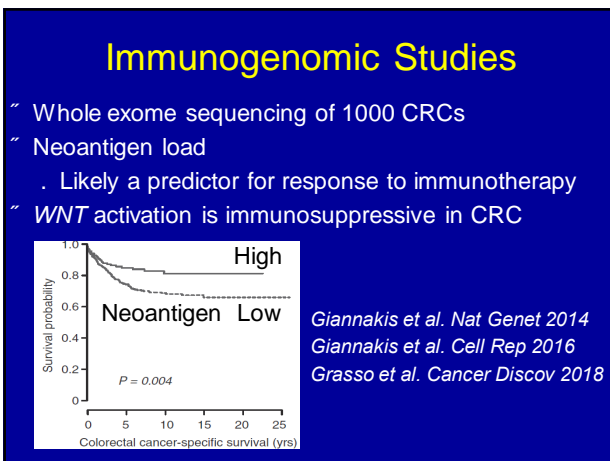
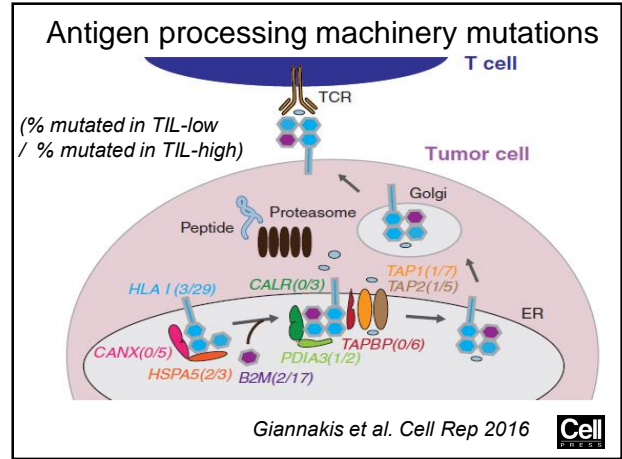
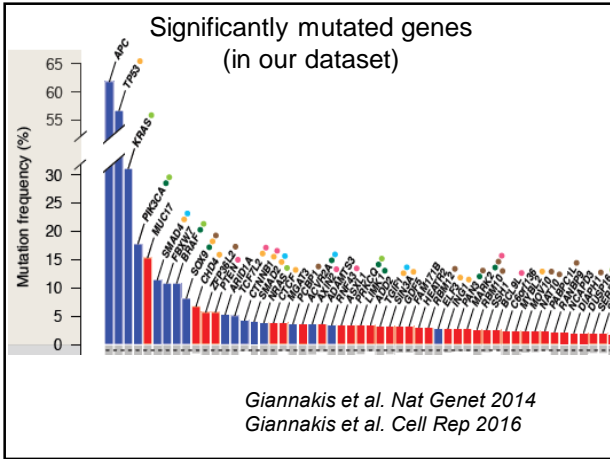
Borowsky, et al.

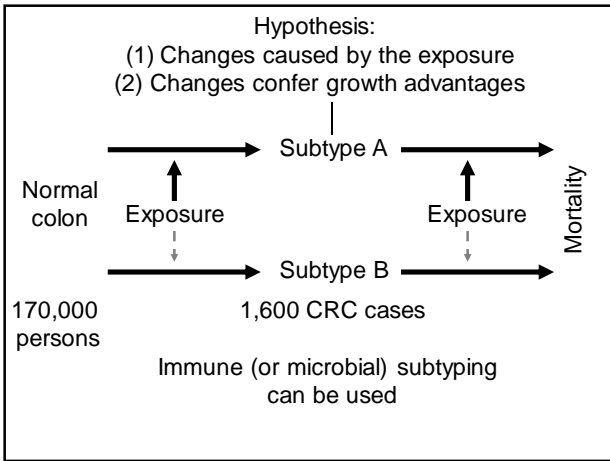
Colon has rich microbiota & immune tissue
Known risk (or protective) factors
Best model for immunology-MPE



Prospective Cohort Studies

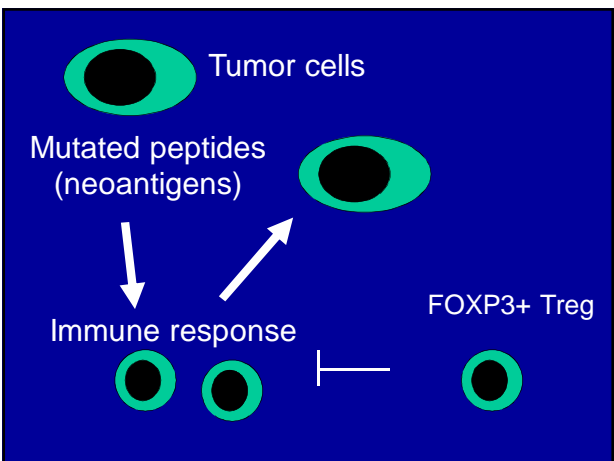
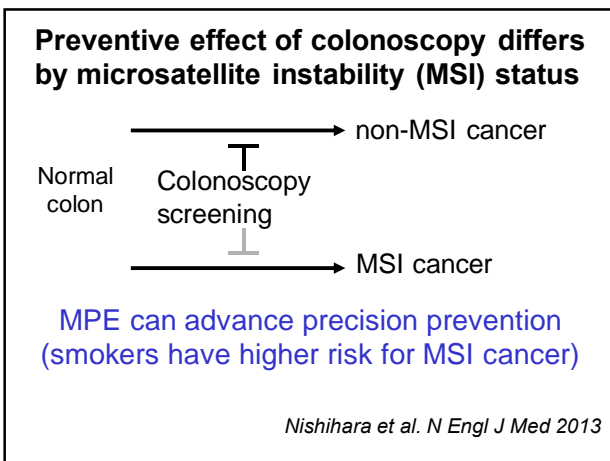


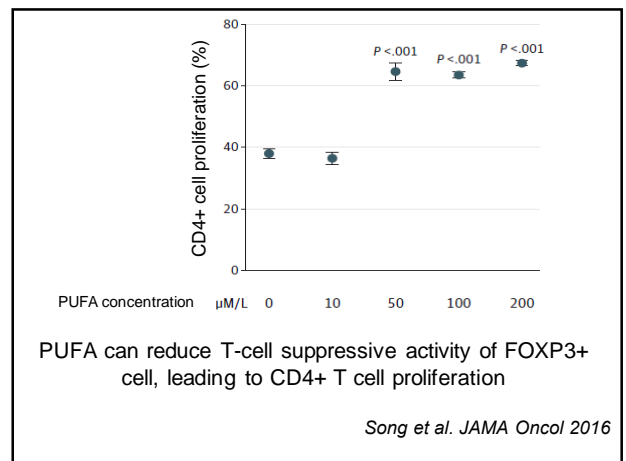
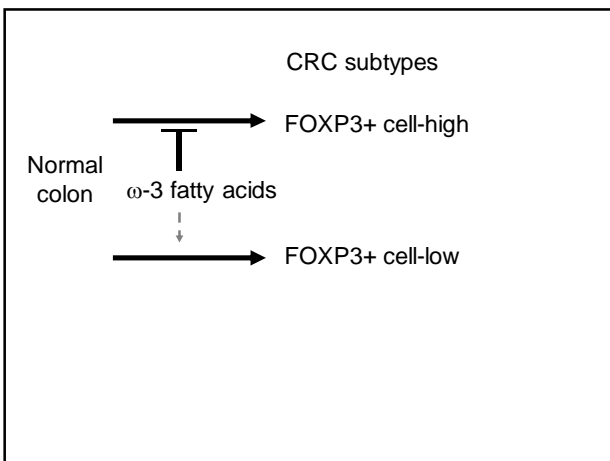
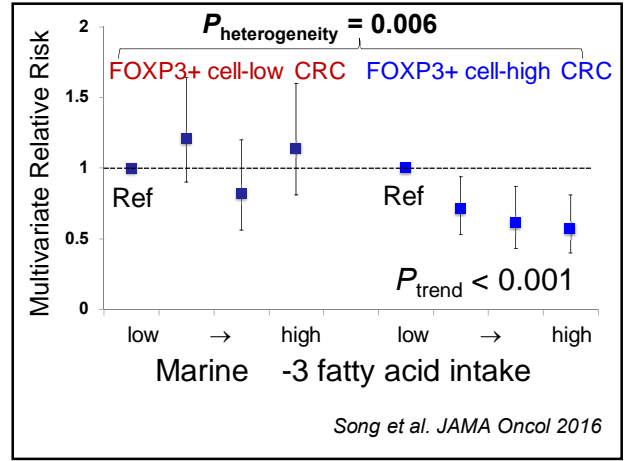
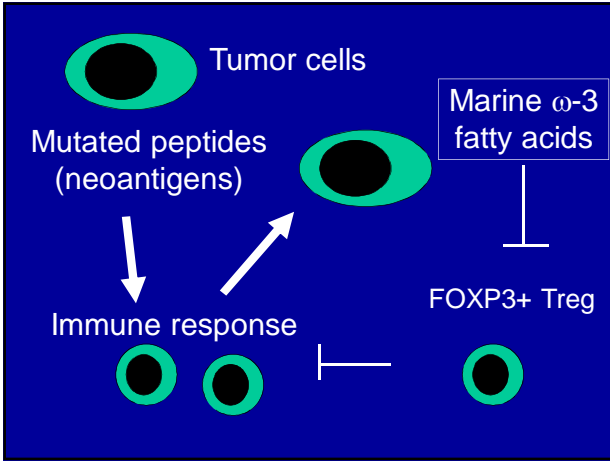


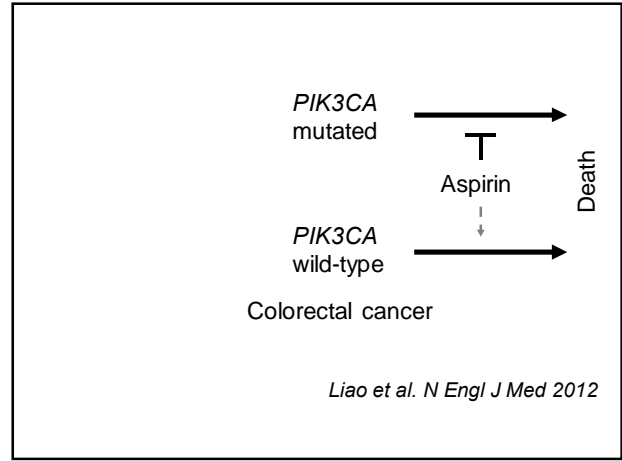
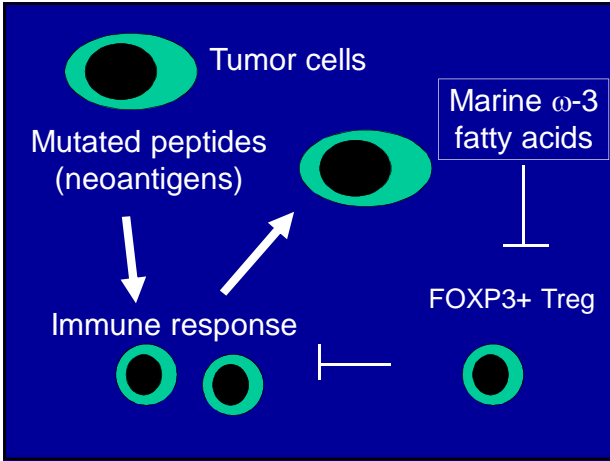


Marine ω -3 polyunsaturated fatty acids (rich in fish oil)

- ~ (?) reduce CRC risk
- ~ Marine ω -3 fatty acids can inhibit regulatory T cells \rightarrow stimulate effector T cells



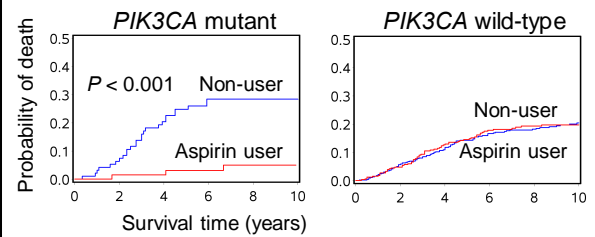




Exposures (or risk factors) influence risk of CRC immune subtype

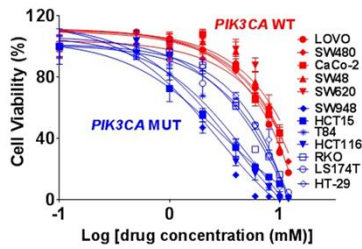
- ~ Marine ω -3 PUFAs (Song. JAMA Oncol 2016)
- ~ IBD risk SNP (Khalili. Carcinogenesis 2015)
- ~ Vitamin D (Song. Gut 2016)
- ~ Aspirin (Cao. Gastroenterology 2016)
- ~ Inflammatory diet (Liu. Gastroenterology 2018)
- ~ Smoking (Hamada. JNCI in press)
- ~ Calcium intake

MPE can advance precision medicine (Aspirin may be used for PIK3CA-mutated CRC)



Liao et al. N Engl J Med 2012

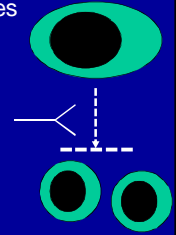
PIK3CA-mutated colon cancer cells are more sensitive to aspirin



Gu, et al. *Oncotarget* 2017
(Similar data by Zumwalt et al. *Cancer Prev Res* 2017)

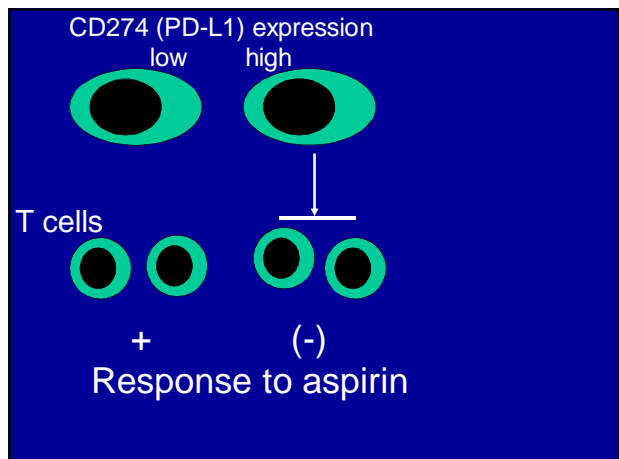
Aspirin

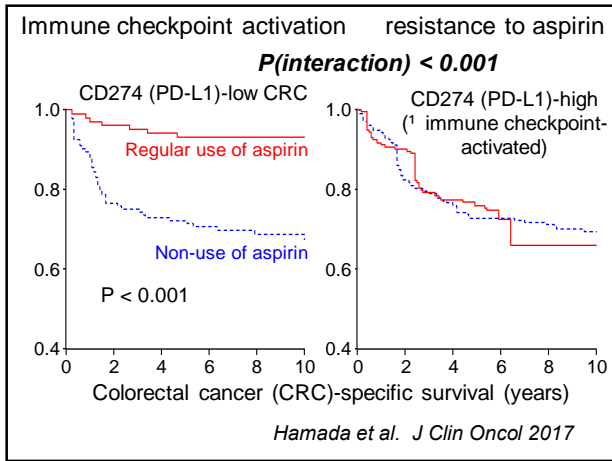
- “ Inhibits PTGS2 (cyclooxygenase-2)
→ reduces prostaglandins enhances adaptive anti-tumor immunity
- “ Synergism of aspirin and immune checkpoint blockade
- “ Hypothesis: Immune checkpoint activation → resistance to aspirin



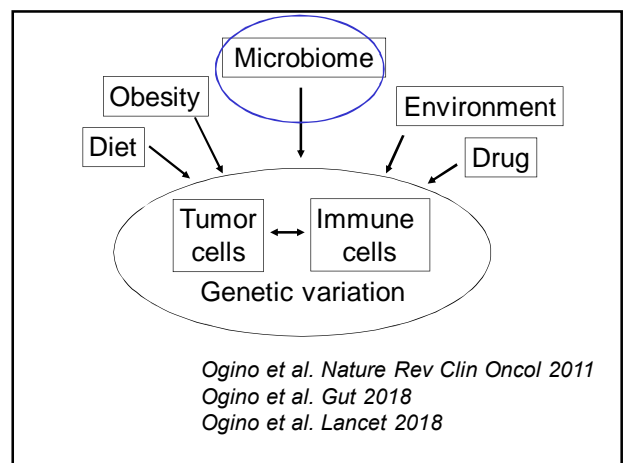
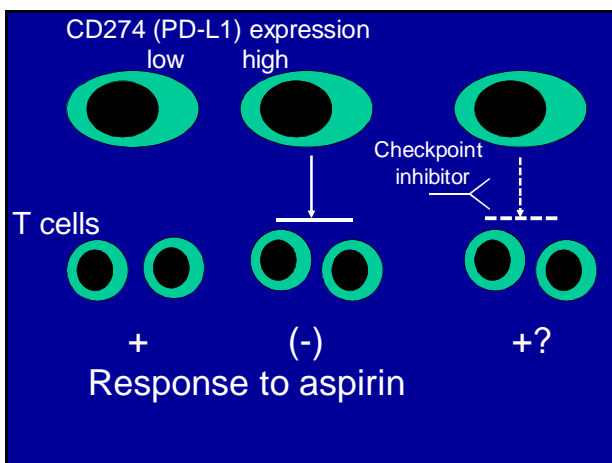
Aspirin for *PIK3CA*-mutated CRC

- “ Possible mechanisms
 - . Aspirin down-regulates PI3K signaling
 - . Immunity and inflammation
 - . Tumor thrombosis and metastasis





Microbiology-MPE



Fusobacterium nucleatum in CRC tissue

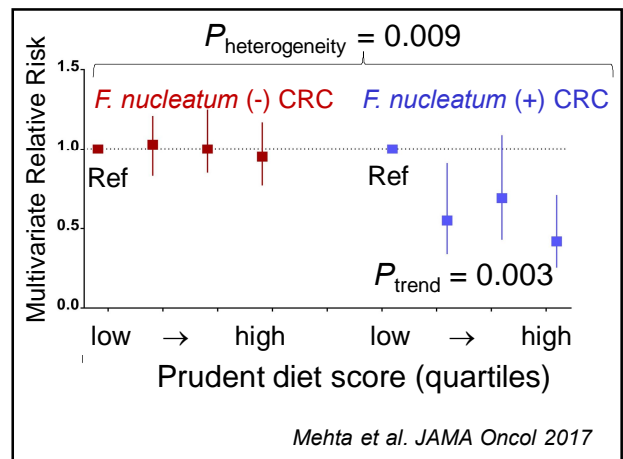
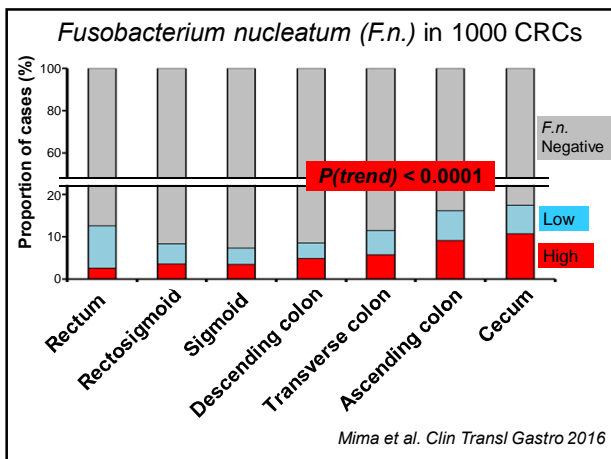
Immunosuppressive → lower T cells
 Higher stage → shorter survival
 MSI-high
 Highest in cecal cancer
 Go with metastasis

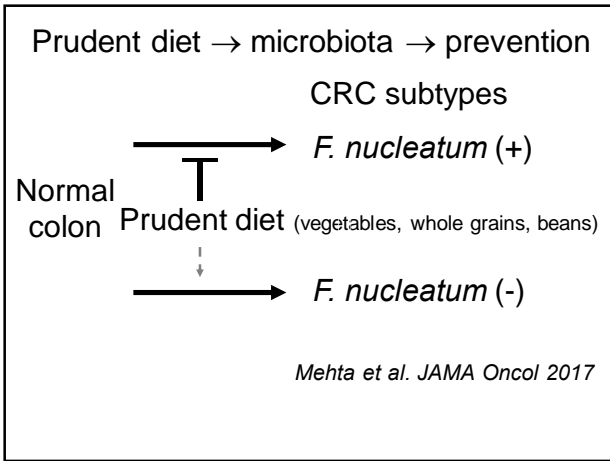


Mima et al. JAMA Oncol 2015
 Mima et al. Gut 2016
 Mima et al. Clin Transl Gastro 2016
 Bullman et al. Science 2017

Diet → Gut microbiota → Cancer

Prudent diet → Good microbiota (↓ bad bacteria) → *Fusobacterium nucleatum*(+) CRC



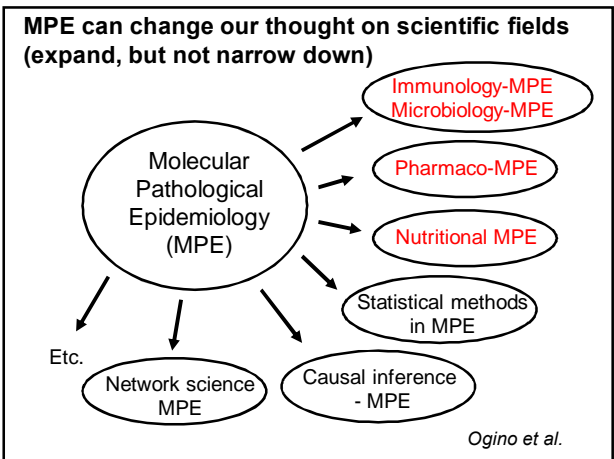
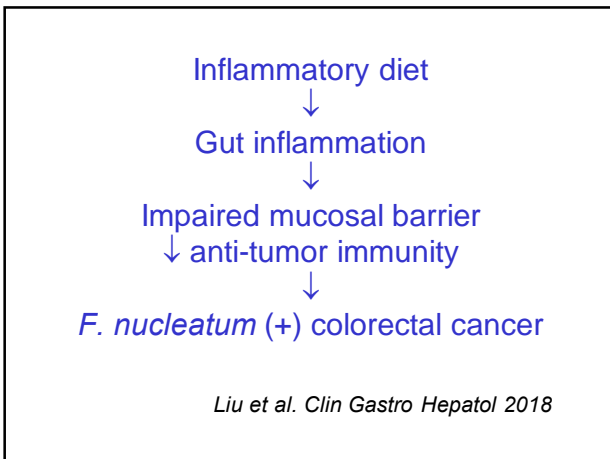


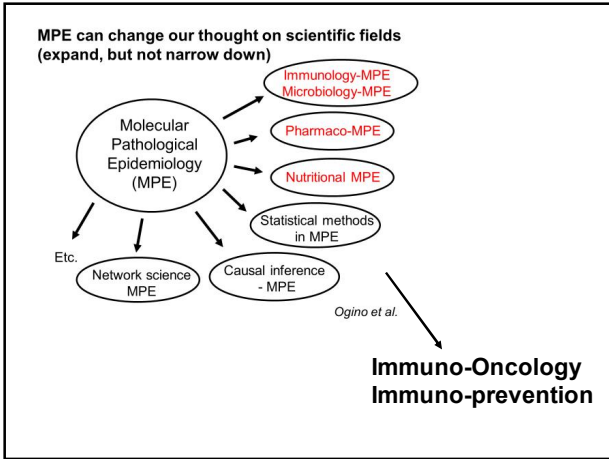
Inflammatory diets

- Red and processed meat
- Refined grains
- Sugar

(anti-inflammatory)

- Tea
- Coffee
- Vegetables (dark yellow; green leafy)





Summary 2

~ Let's do %Immuno-MPE+and %microbiology-MPE+studies!

Ogino et al. Nature Rev Clin Oncol 2011
Ogino et al. Gut 2018
Ogino et al. Lancet 2018

Summary

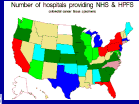
- ~ Immunology-MPE (Molecular Pathological Epidemiology) can provide new insights
 - . Exposures can easily influence microbiota. tumor. immune interactions
 - . Immunoprevention & therapy (using nutrients & lifestyle)
- ~ MPE is making new frontiers
- ~ There are widely open opportunities!

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