Immuno- and Chemo-prevention for GI Cancers: Are we there yet?

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Digestive Diseases of the Caribbean
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San Juan, Puerto Rico

DISCLOSURES

- *Board member* of AACR, AACI, Cold Spring Harbor NCI Cancer Center, Precision Oncology Alliance Foundation, Alliance for Clinical Oncology Foundation

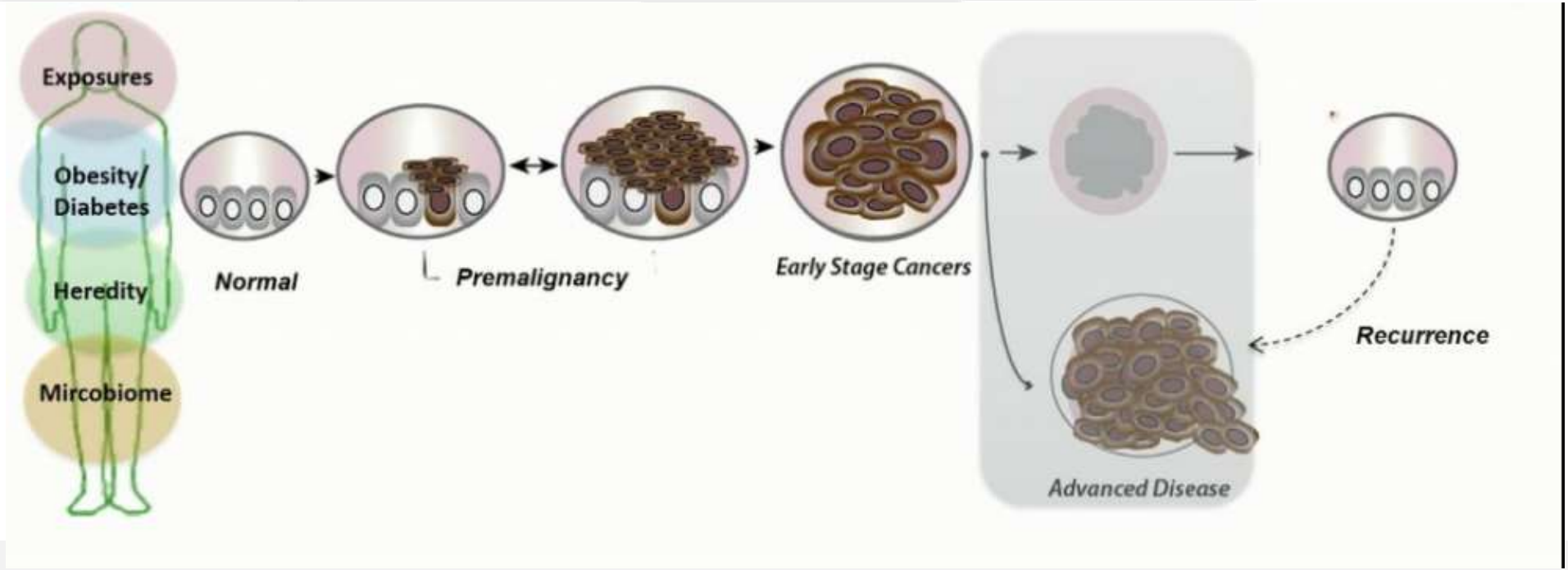
- *Funding* from NCI (CRCHD, DCP) and NIGMS

- *Industry research funding* from Pfizer, Abbvie, BeiGene, BMS, Merck, Janssen, Genentech, QED, SeaGen, Incyte, TAIHO.

- CMO Pan American Center for Oncology Trials

Opportunities for Cancer Prevention: The Cancer Continuum

PREVENTION	INTERCEPTION	DIAGNOSIS	TREATMENT	SURVIVOR



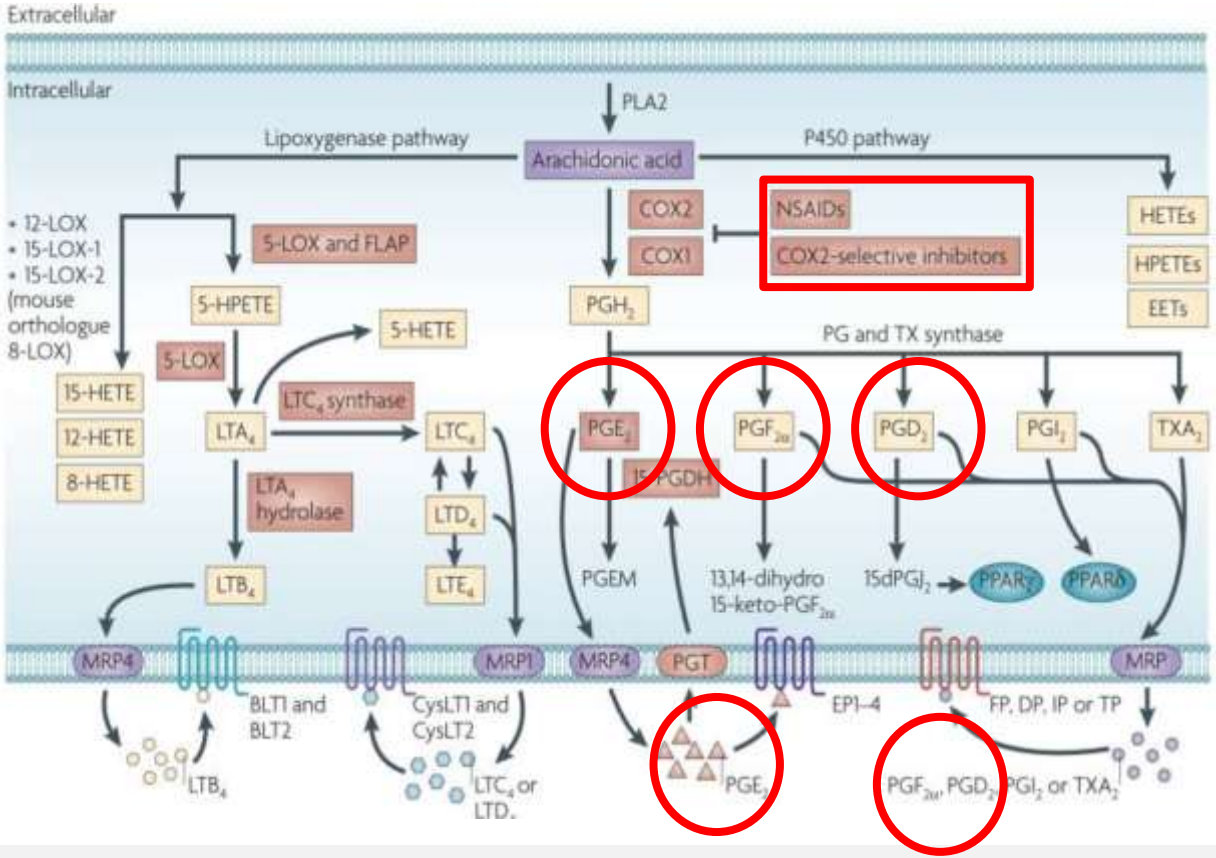
Chemoprevention

"Use of pharmacologic or nutrient agents to prevent, reverse, or inhibit the process of carcinogenesis"

Chemoprevention Strategies

- Ideal agents use for chemoprevention should be **inexpensive** and **nontoxic**
- Chemoprevention interventions are classified as ***primary*, *secondary* and *tertiary*** strategies
- Agents: chemical, nutrient, and dietary
- Ideal target are individuals at high risk for CRC

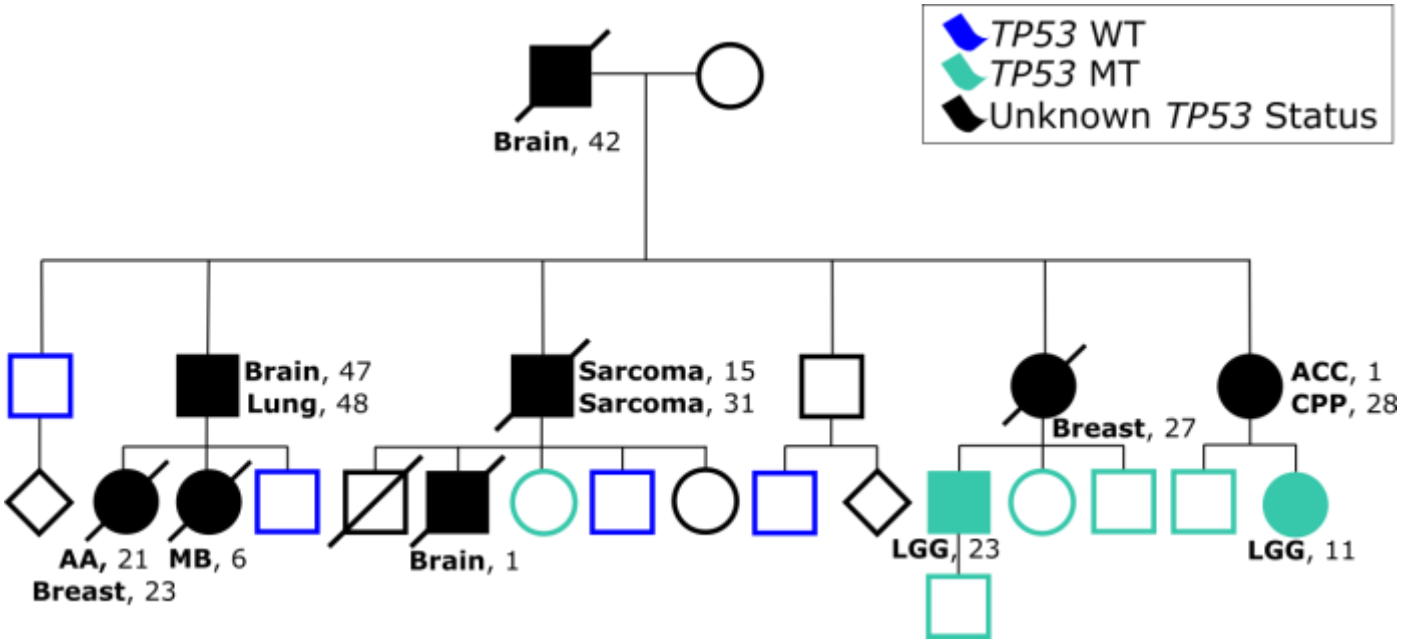
PGD Synthesis pathways for Chemoprevention



https://www.nature.com/articles/nrc2809

Hereditary Cancer: Li-Fraumini Syndrome

Frederick Li and Joseph Fraumeni, 1991.

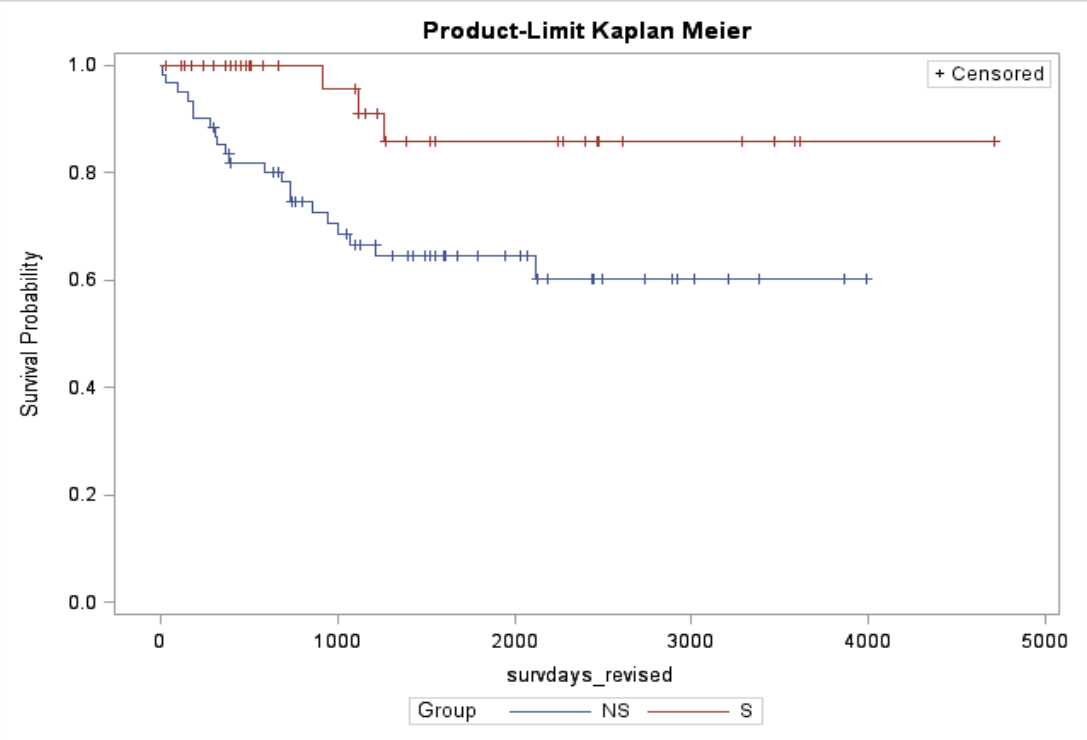


40% < 25 years of age

Cancer lifetime risk: 75% males: 93% females

Bougeard G, et al *J Clin Onc* 33: 2345, 2015
Courtesy of Josh Schiffman

Survival of *TP53* Mutation Carriers in Surveillance and Non-surveillance Groups

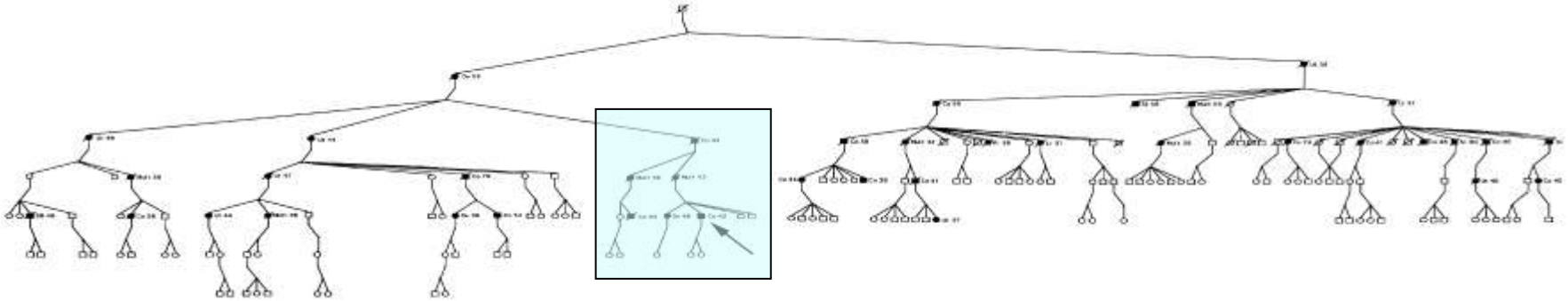


P<0.0001

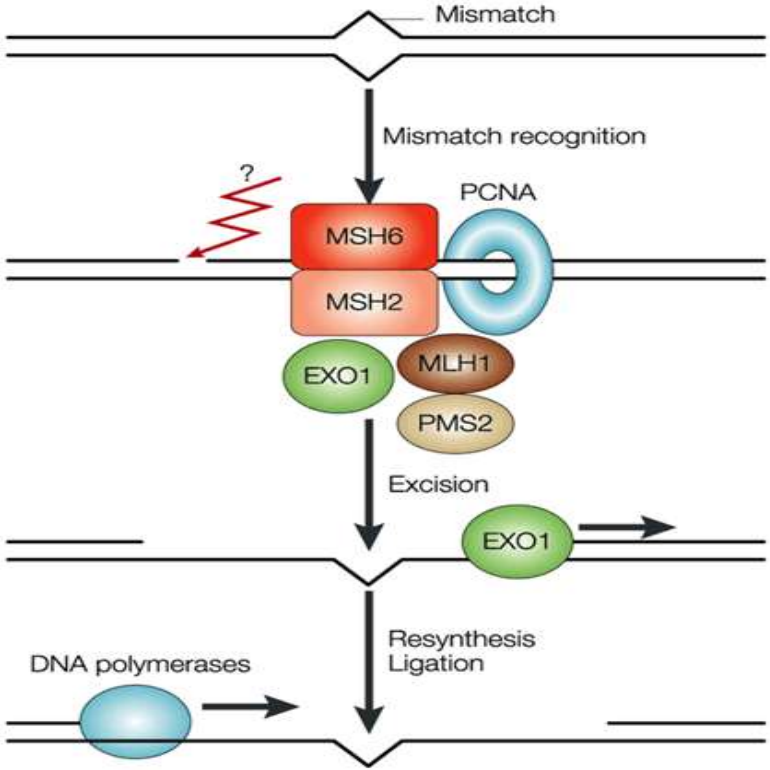
Villani, et al. Lancet Oncology 2016

Lynch Syndrome

1.1 million Americans (1:280 incidence)
Most common colorectal cancer genetic syndrome



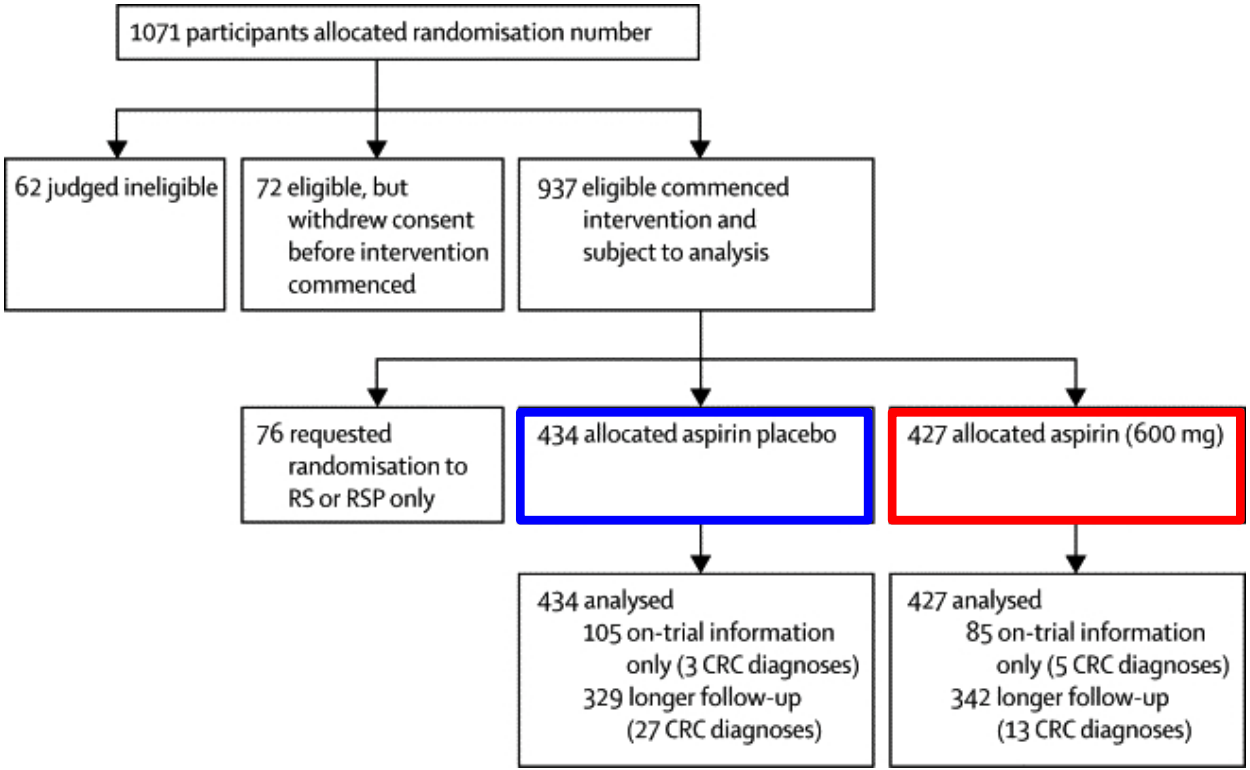
Lynch Syndrome



- Autosomal Dominant
- Tumors Microsatellite Unstable
- Highly infiltrated with lymphocytes
- **Highly Immunogenic**
- Tumors respond to anti PDL-1/PD1 immunotherapy

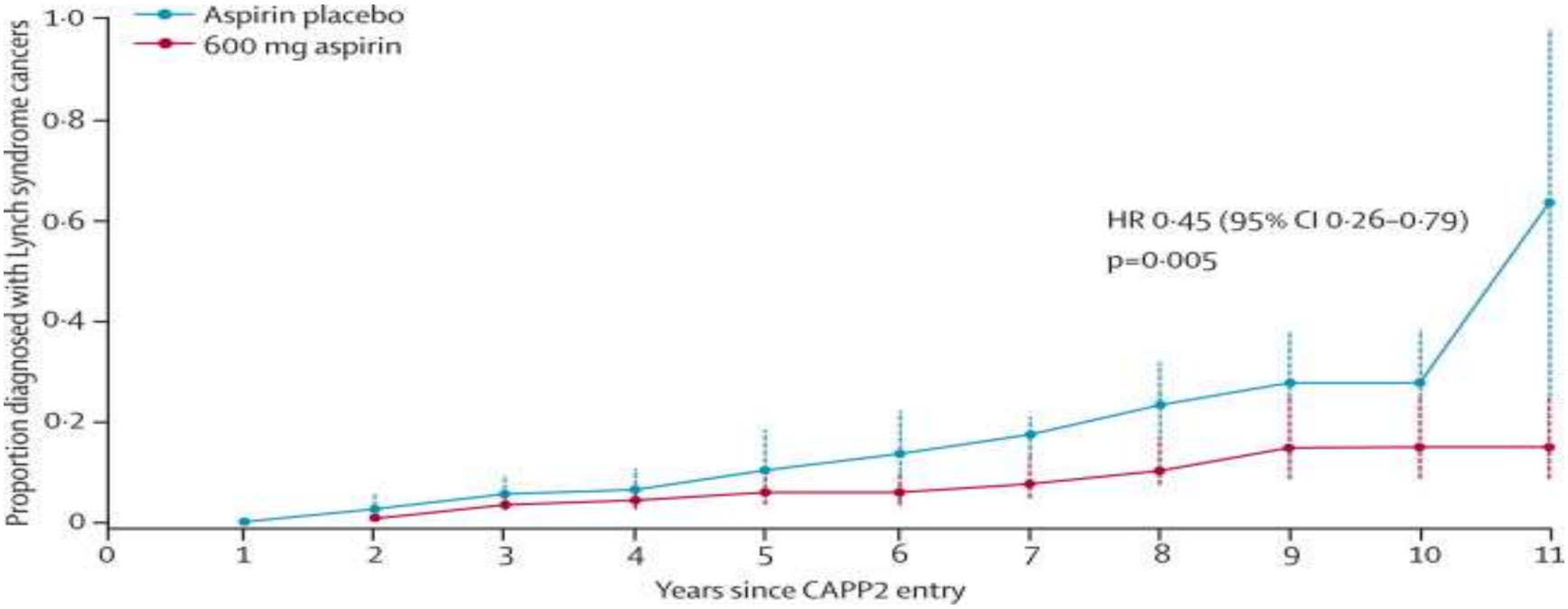
Martin A., Scharff, Nature Reviews, Immunology 2012

The Colorectal Adenoma/carcinoma Prevention Program (CAPP)



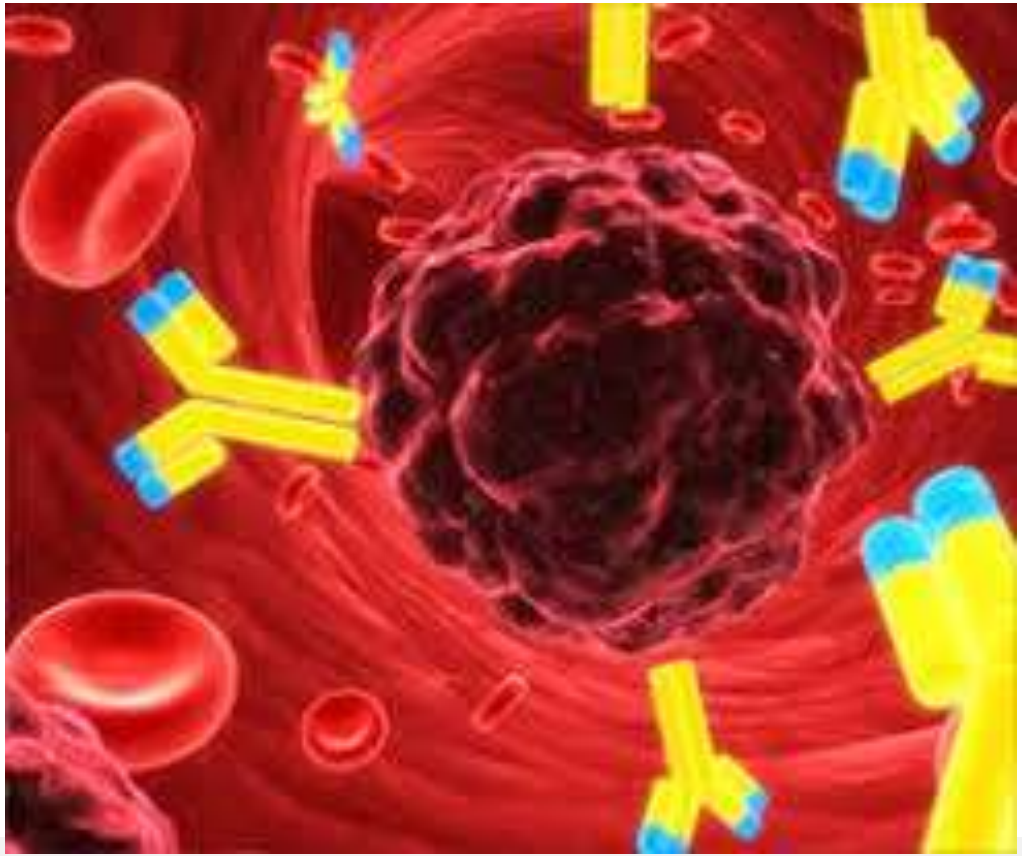
Burn J, et al. Lancet 2011

Decreased Risk of Lynch-Cancers Among ASA Users

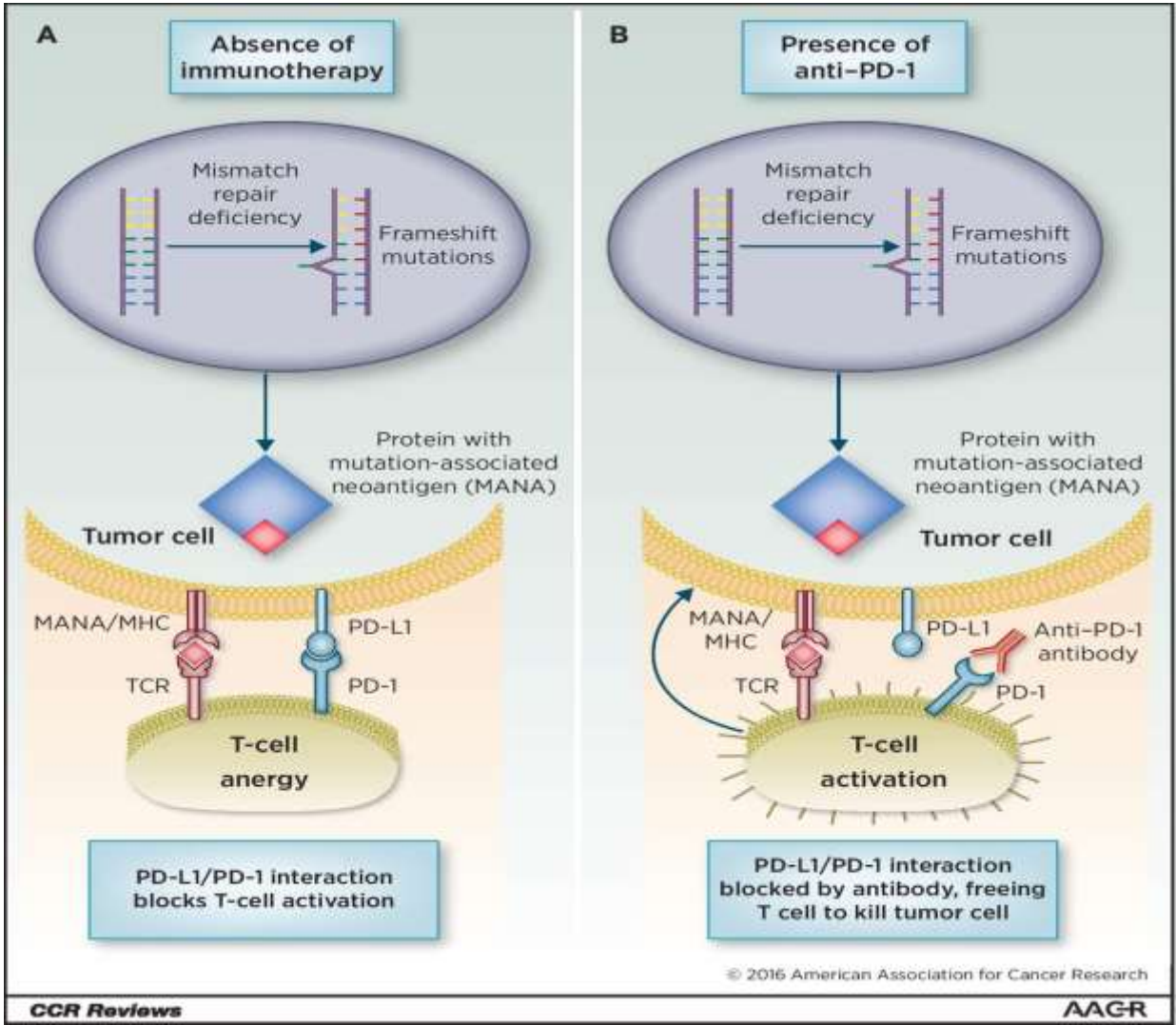


Burn J, et al. Lancet 2011

Interception
Immuno Prevention



Lynch Syndrome MSI & PD-1 Pathway



Yu Y, Front. Med 2017

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

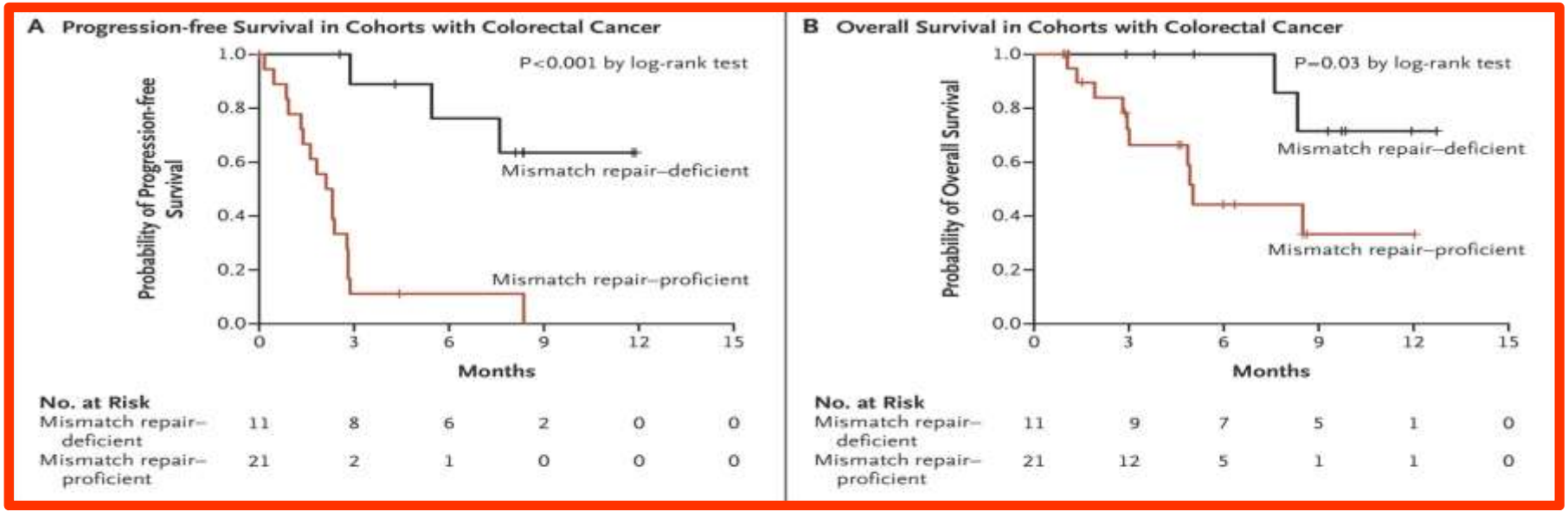
PD-1 Blockade in Tumors with Mismatch-Repair Deficiency

D.T. Le, J.N. Uram, H. Wang, B.R. Bartlett, H. Kemberling, A.D. Eyring, A.D. Skora, B.S. Luber, N.S. Azad, D. Laheru, B. Biedrzycki, R.C. Donehower, A. Zaheer, G.A. Fisher, T.S. Crocenzi, J.J. Lee, S.M. Duffy, R.M. Goldberg, A. de la Chapelle, M. Koshiji, F. Bhaijee, T. Huebner, R.H. Hruban, L.D. Wood, N. Cuka, D.M. Pardoll, N. Papadopoulos, K.W. Kinzler, S. Zhou, T.C. Cornish, J.M. Taube, R.A. Anders, J.R. Eshleman, B. Vogelstein, and L.A. Diaz, Jr.

N ENGL J MED 372;26 NEJM.ORG JUNE 25, 2015

Clinical Benefit of Pembrolizumab Treatment According to Mismatch-Repair Status

Le DT et al. N Engl J Med 2015;372:2509-2520.

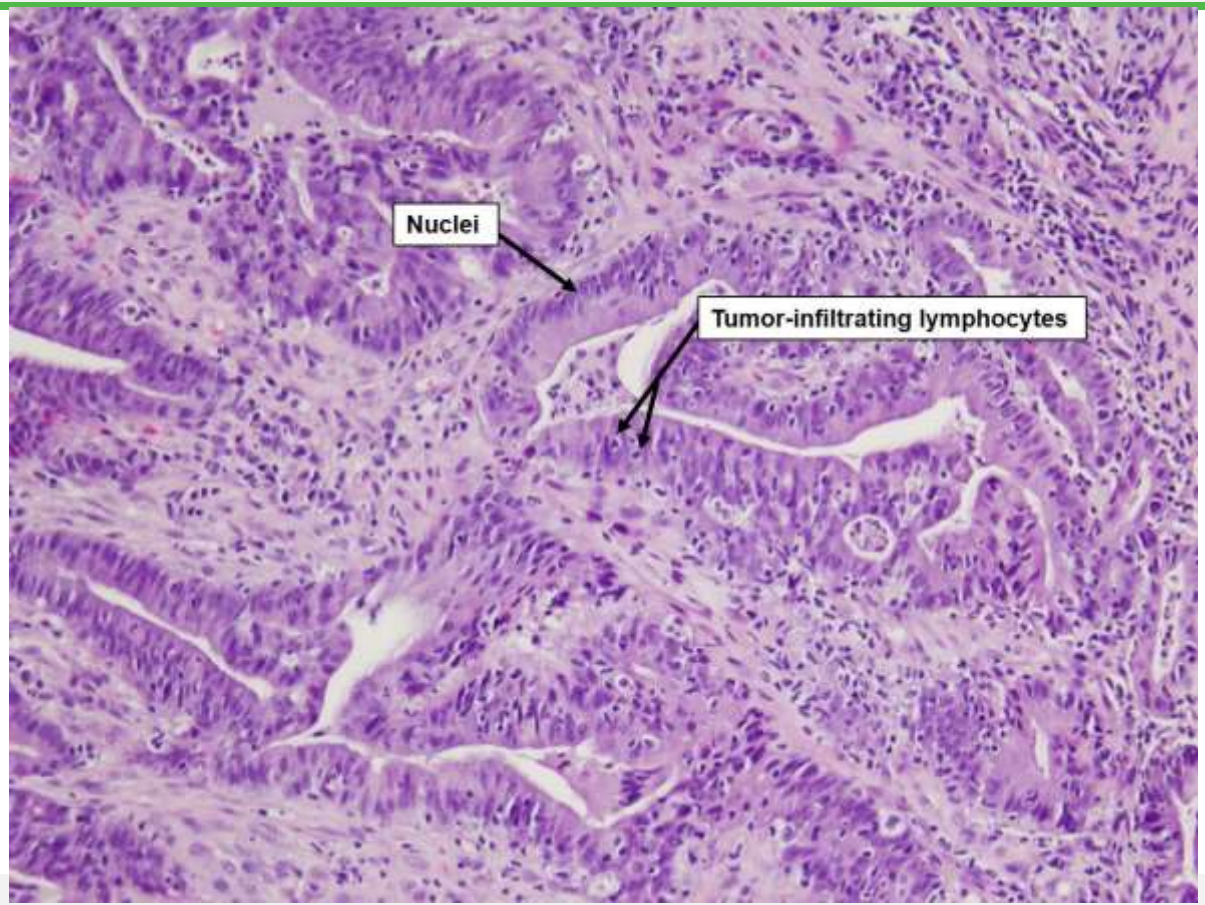


Next Generation Sequence of LS Colorectal Cancer: Highly Mutagenic

Results with Therapy Associations

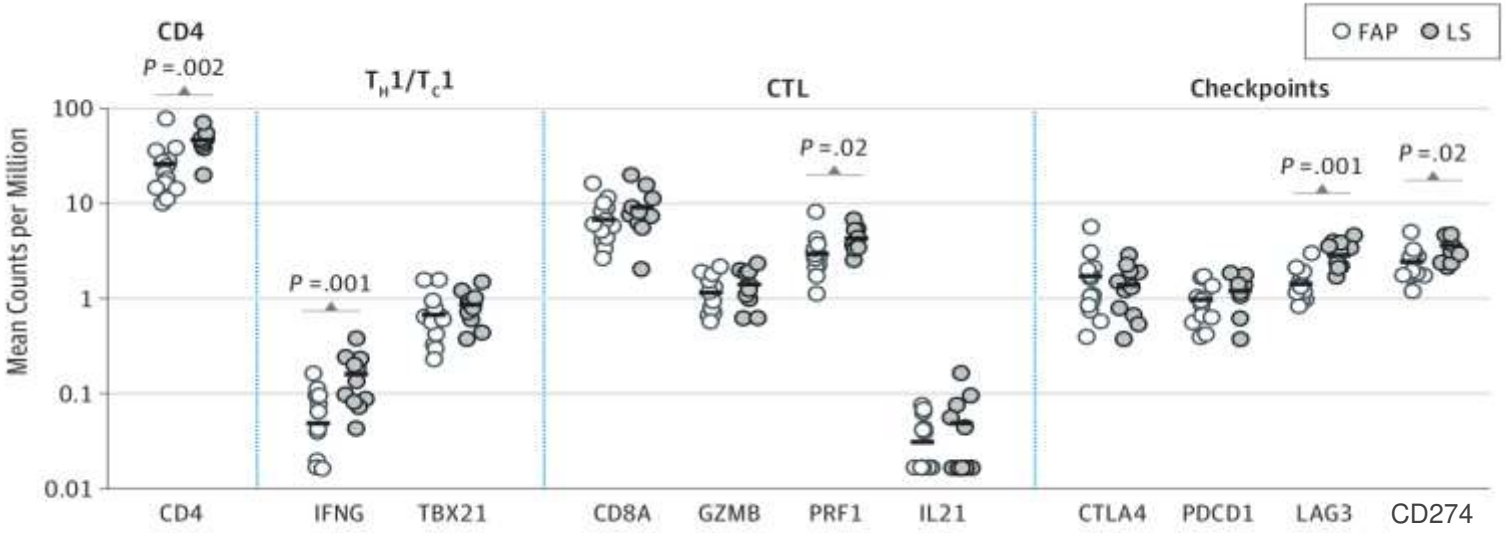
BIOMARKER	METHOD	ANALYTE	RESULT	THERAPY ASSOCIATION		BIOMARKER LEVEL*
KRAS	**Seq**	**DNA-Tumor**	**Mutation Not Detected**	**BENEFIT**	**cetuximab, panitumumab**	**Level 2**
Mismatch Repair Status	**IHC**	**Protein**	**Deficient**	**BENEFIT**	**dostarlimab, nivolumab, nivolumab/ipilimumab combination, pembrolizumab**	**Level 2**
MSI	**Seq**	**DNA-Tumor**	**High**	**BENEFIT**	**nivolumab, nivolumab/ipilimumab combination, pembrolizumab**	**Level 2**
NRAS	**Seq**	**DNA-Tumor**	**Mutation Not Detected**	**BENEFIT**	**cetuximab, panitumumab**	**Level 2**
TMB	**Seq**	**DNA-Tumor**	**High, 47 mut/Mb**	**BENEFIT**	**pembrolizumab**	**Level 2**
BRAF	Seq	DNA-Tumor	Mutation Not Detected	BENEFIT	cetuximab, panitumumab	Level 2
ERBB2 (Her2/Neu)	IHC	Protein	Negative | 0	LACK OF BENEFIT	lapatinib, pertuzumab, trastuzumab	Level 2

LS Tumors: High numbers of Tumor Infiltrating Lymphocytes



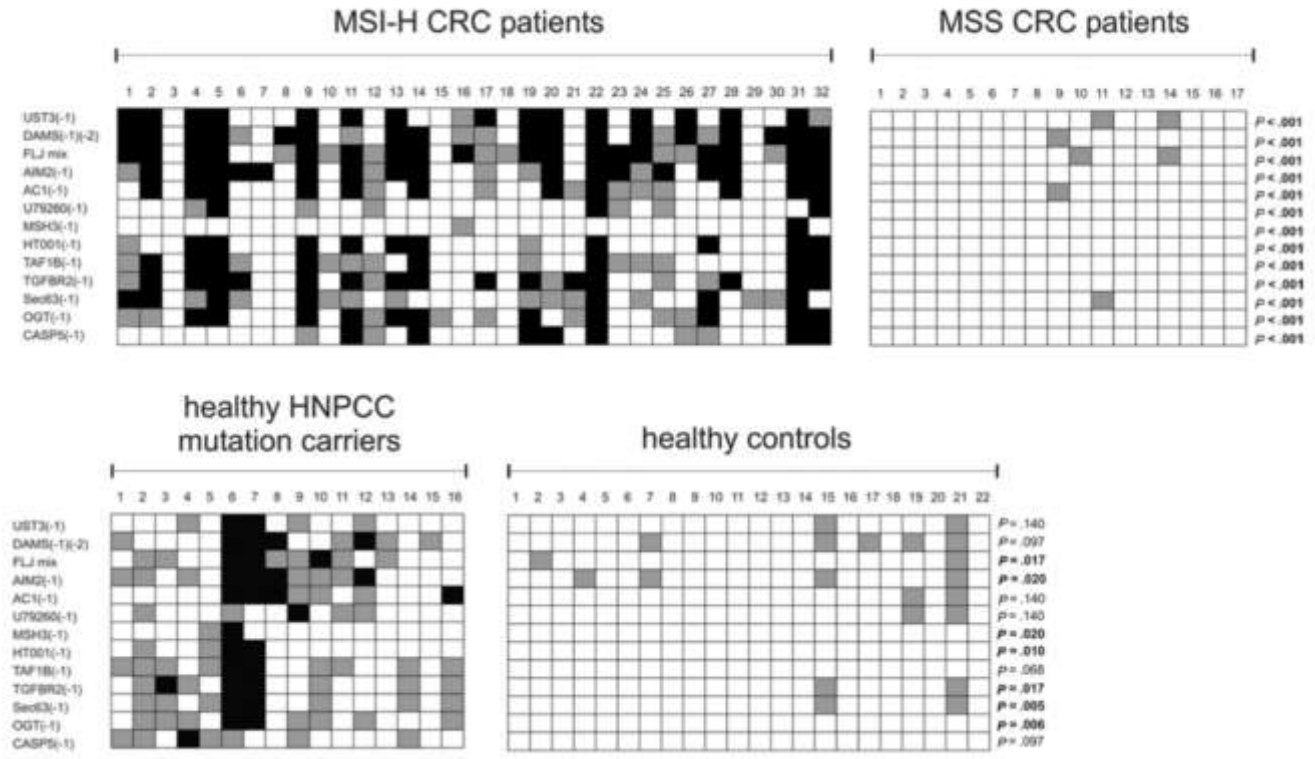
LS Colon Adenomas have Elevated Immune Surveillance

Lynch syndrome vs. MMR-proficient **colon adenomas** have higher rates of CD4 T cells, CD8 T cells (CTL) and PD1 (CD274) and LAG3 immune checkpoints.



E.Vilar-Sanchez, JAMA Oncology 2018

Lynch Patients have Endogenous T-Cell Reactive Against Recurrent FSP Neoantigens



Kloor, Gastroenterology 2008

Pre-neoplastic Lynch normal colon crypts are MMR-D

Crypt Foci
***MSH2* LS patient**

Crypt Foci
***MLH1* LS patient**

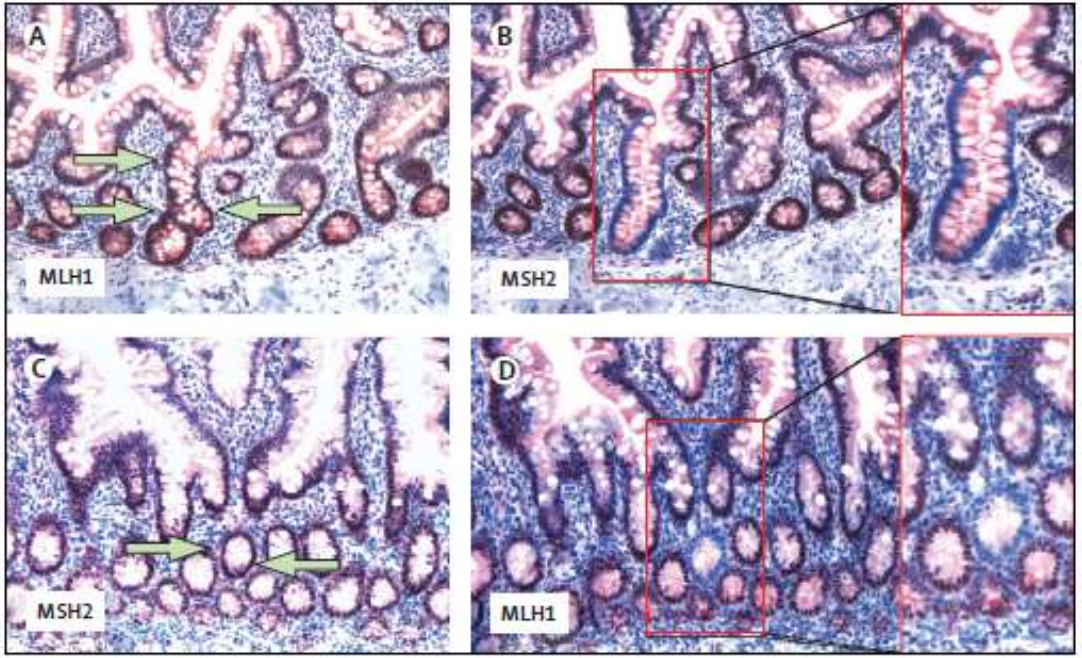
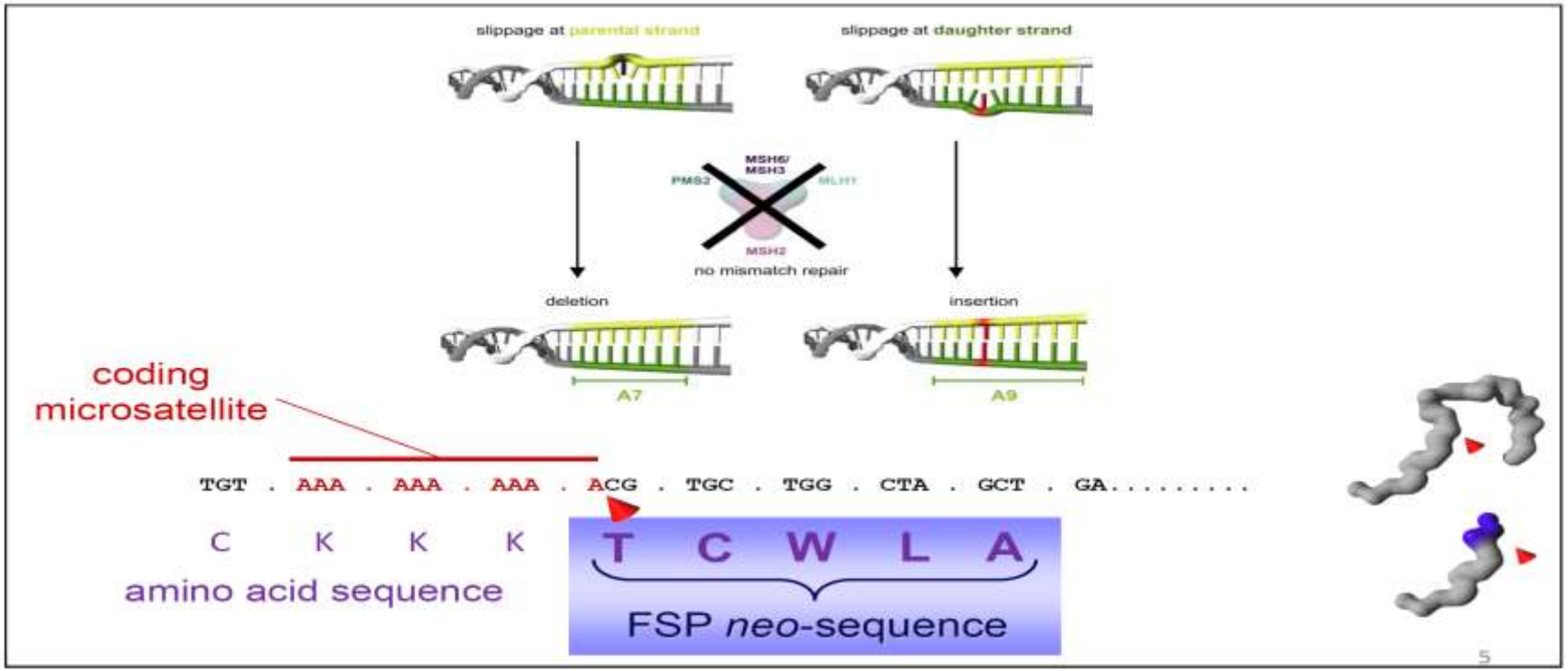


Figure 2: **Monocryptic MMR-deficient crypt foci**
Objective magnification is 10× for all panels. Except for absence of MMR expression, monocryptic MMR-deficient crypt foci are commonly indistinguishable from the surrounding MMR-proficient crypts (A–D). In an MMR-deficient crypt focus from a patient with MSH2-associated Lynch syndrome (LS2), MLH1 expression is retained (A, arrows) whereas the expression of MSH2 is lost (B). Vice versa, an MMR-deficient crypt focus from a patient with *MLH1*-associated Lynch syndrome (LS4) expresses MSH2 (C, arrows), but not MLH1 (D) proteins.

Kloor, Lancet Oncology 2012

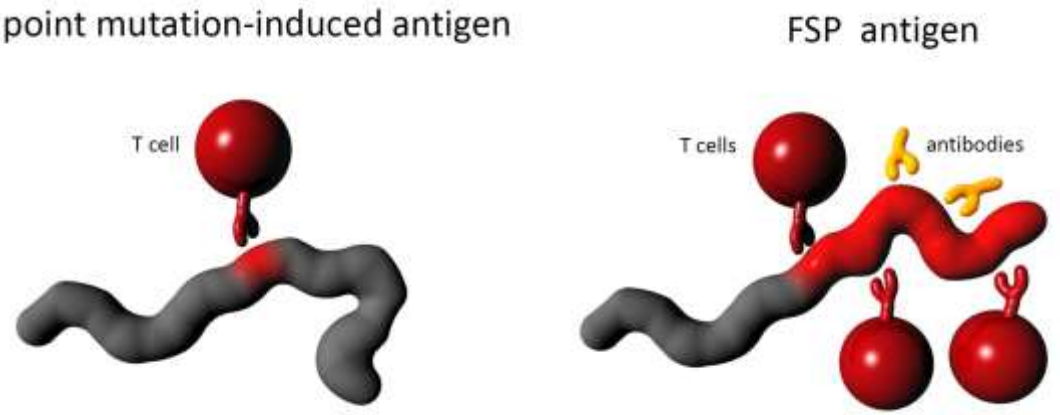
Neoantigen Vaccine Against Frameshift Peptides

FSP (frameshift peptide) antigens are shared immunogenic tumor antigens in MSI-H CRC



Lynch syndrome CRC Immunoprevention Vaccine

1. *FSPs are the most immunogenic cancer neoantigens*

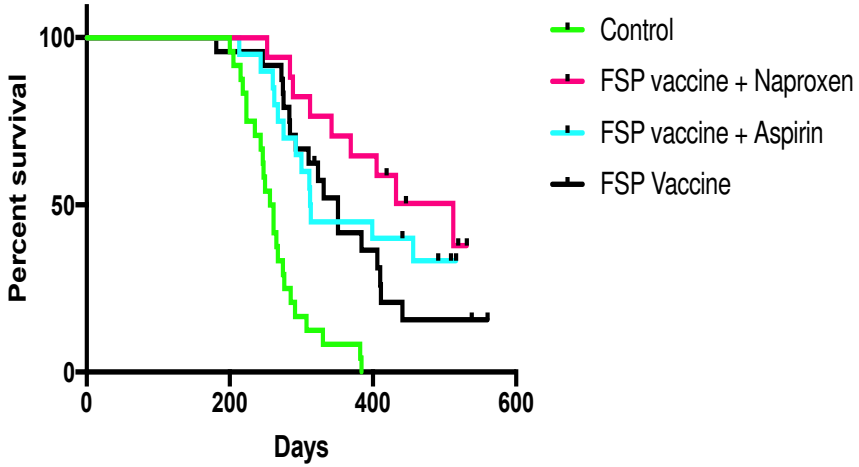


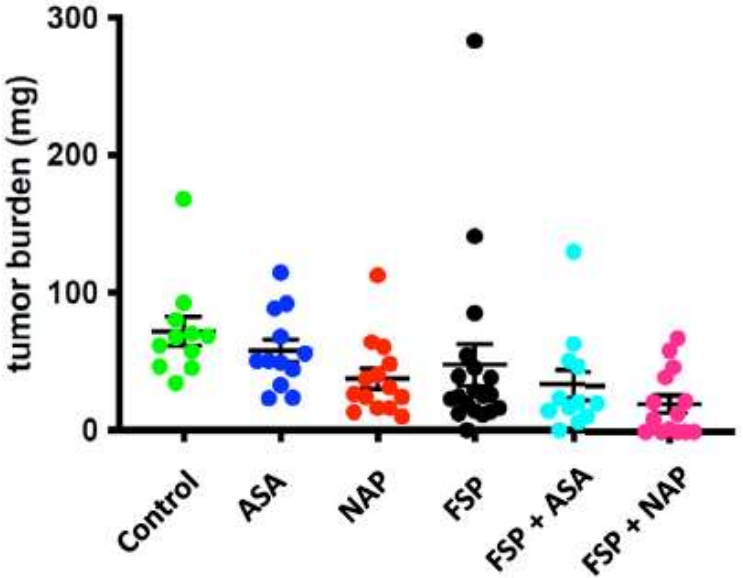
2. *FSP mutations drive PD1/PD-L1 inhibitor immunotherapy response.*

Recurrent Frameshift Neoantigen Vaccine Elicits Protective Immunity With Reduced Tumor Burden and Improved Overall Survival in a Lynch Syndrome Mouse Model

Johannes Gebert,[1,2] Ozkan Gelincik,[3] Mine Oezcan-Wahlbrink,[1,2] Jason D. Marshall,[4] Alejandro Hernandez-Sanchez,[1,2] Katharina Urban,[1,2] Mark Long,[5] Eduardo Cortes,[5] Elena Tosti,[6] Eva-Maria Katzenmaier,[1,2] Yurong Song,[4] Ali Elsaadi,[3] Nan Deng,[7] Eduardo Vilar,[7] Vera Fuchs,[1,2] Nina Nelius,[1,2] Yan P. Yuan,[8] Aysel Ahadova,[1,2] Shizuko Sei,[9] Robert H. Shoemaker,[9] Asad Umar,[9] Lei Wei,[5] Song Liu,[5] Peer Bork,[8,10,11] Winfried Edelmann,[6] Magnus von Knebel Doeberitz,[1,2] Steven M. Lipkin,[3] and Matthias Kloor[1,2]

Chemo-Immunoprevention in Lynch Mice





UPDATE 12-11-2018 (Ozkan Gelincik - Lipkin Lab)

Cancer Preventive Vaccine Nous-209 for Lynch Syndrome Patients (NCT05078866)

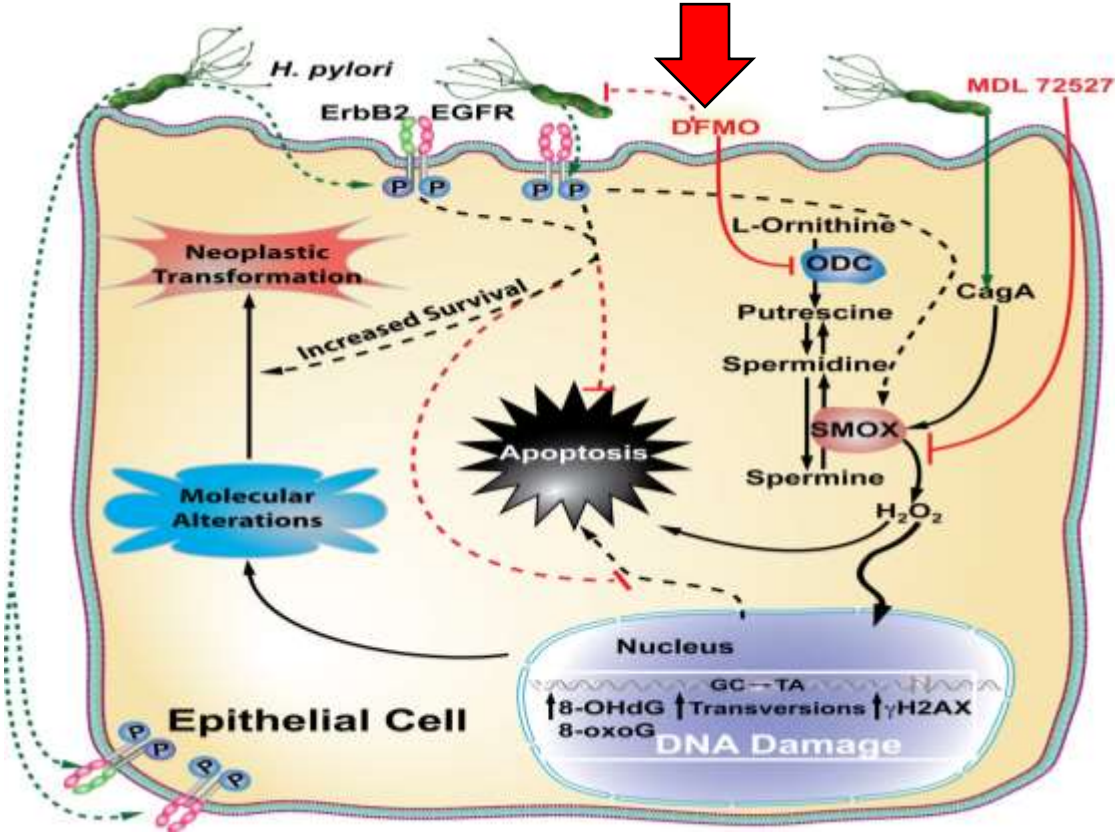
- Design – Phase IB/II trial to evaluate safety and efficacy of the Nous-209 vaccine in Lynch Syndrome patients
- Intervention - Nous-209 is a vaccine made with man-made neoantigens. Patients will receive GAd20-209-FSPs IM on day 1 and at week 8
- Outcomes –
  - Safety of Nous-209 vaccine is safe to give to patients with Lynch syndrome
  - Immunogenicity defined as reactivity to 1 of 16 synthetic FSP antibodies using an enzyme-linked immune absorbent spot (ELISpot) assay
  - T cells, ctDNA, colonic adenomas, CRC, others.
- Sites: City of Hope, MD Anderson, Fox Chase and **University of PR**

PD-1 antibody for the Prevention of Adenomatous Polyps and Second Primary Tumors in Patients with Lynch Syndrome: An Open-Label, Multicenter, RCT

- NCT 04711434
- RCT – Anti-PD1 (Tripleitriumab 240 mg IV) vs. Placebo every 3 months x 1 year
- Main Outcome – Percentage of patients who develop colonic polyps or second primary tumors from time of randomization (up to 5 years)
- Secondary Outcomes
  - Overall survival, Adverse events, stratification by genotypes, etc.
- Sites – Republic of China

Eflornithine (DFMO) in chemoprevention

R Chaturvedi and KT Wilson, Oncogene 2015



H. pylori infection:

- ✓ **Increases activity of** ornithine decarboxylase (**ODC**) and spermine oxidase (**SMOX**)
- ✓ Producing hydrogen peroxide (H2O2), leading to DNA damage

DFMO inhibits ODC

Randomized, Double-blind, Placebo-controlled Phase IIB CT for Chemoprevention of Gastric Carcinogenesis in GIM

- Eflornithine (DFMO)
- Inclusion criteria:
  - Age 30-60 years
  - GIM
- Main outcome: Difference in **cell DNA damage** at 18 months.
- Intervention drug: DFMO x 18 months
  - Inhibits Ornithine Decarboxylase enzyme

Randomized, Double-blind, Placebo-controlled Trial of Meriva (curcominoids) as a Candidate Chemoprevention Agent for Gastric Carcinogenesis

Mayo Clinic, Honduras and University of PR

Curcuminoids modulates:

- Inflammatory cytokines (TNF, IL-1)
- Enzymes (COX-2, LOX, MAPK, mTOR, Akt
- Adhesion molecules (ELAM-1, ICAM-1, VCAM-1)
- Apoptosis-related proteins (Bcl-2, caspases, DR)
- Transcription factors (NFkB) and its pathways

Endpoints:

Primary

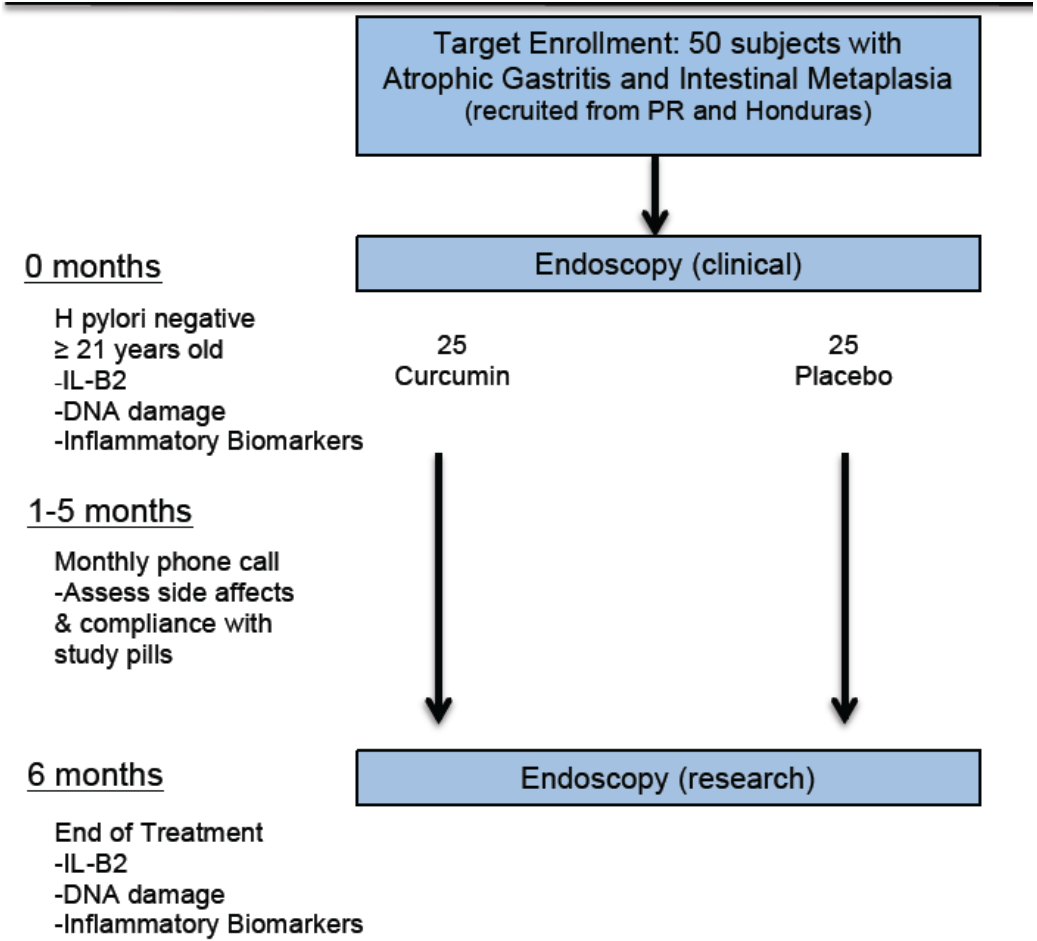
- Absolute change in ***IL-1B cytokine*** levels in gastric mucosa from baseline to 6 months

Secondary

- Histology Gastric Score
- Mucosal cytokines IL-8, TNF, IP-10
- Gastric mucosal DNA damage

Phase II B Randomized Clinical Trial

(NCI-Division of Cancer Prevention)



Summary and Future Directions

- **Immuno prevention** is rapidly evolving within pre-clinical and clinical models and promises to intercept the natural history of cancer
- **Chemoprevention** agents – integration of targeted oncologic therapies such as anti-EGFR and anti-PD1
- **Germline driven hereditary syndromes** serve as models for interception trials (Lynch Syndrome, Li-Fraumini, FAP, BRCA, etc)
- Risk **behavior modification** with increase in *omega-3,* exercise, decrease in animal protein requires implementation and policy efforts
- Where is the magic pill? **Maybe is the magic vaccine!**