

Does an Aspirin a Day Keep Cancer Away?

Jennifer R. Grandis, MD

Robert K. Werbe Distinguished Professor

Otolaryngology – Head and Neck Surgery

UCSF

American Cancer Society Clinical Research Professor

Disclosures:

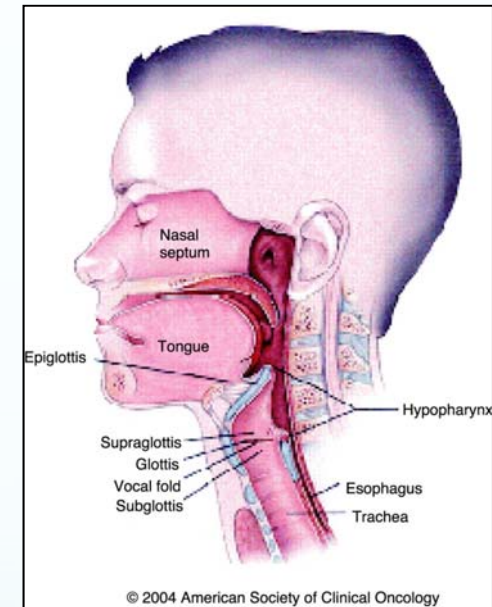
- Co-inventor of cyclic STAT3 decoy
- Consultant: xCures Inc, Ciitizen Inc

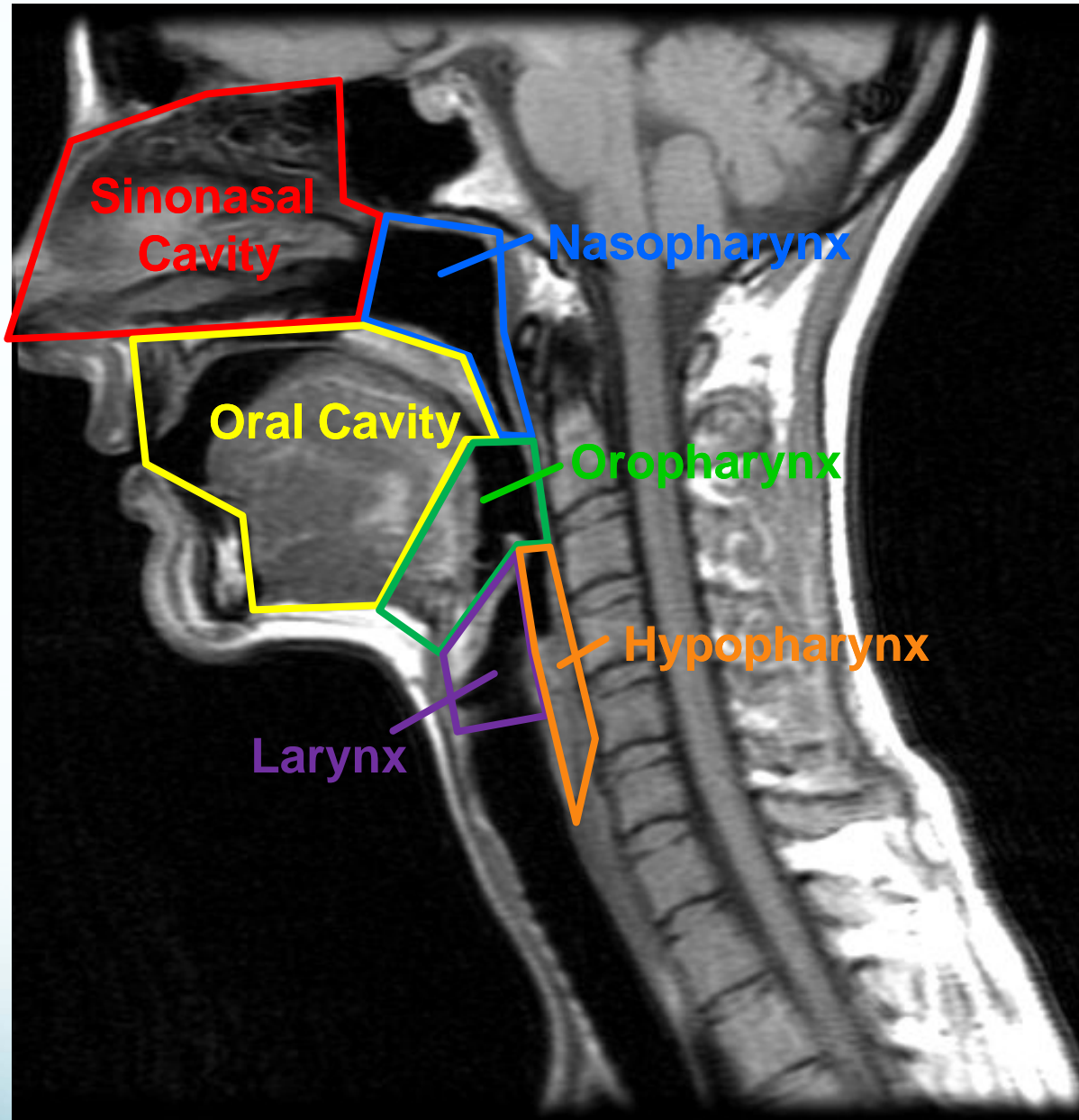


Team Science!

Head and Neck Cancer (HNSCC)

- ~ 60K new cases/year in USA;
~ 550K/year worldwide
- HPV⁻ and HPV⁺
- 5-year survival rates ~50-60%





FILTER CIGARETTES



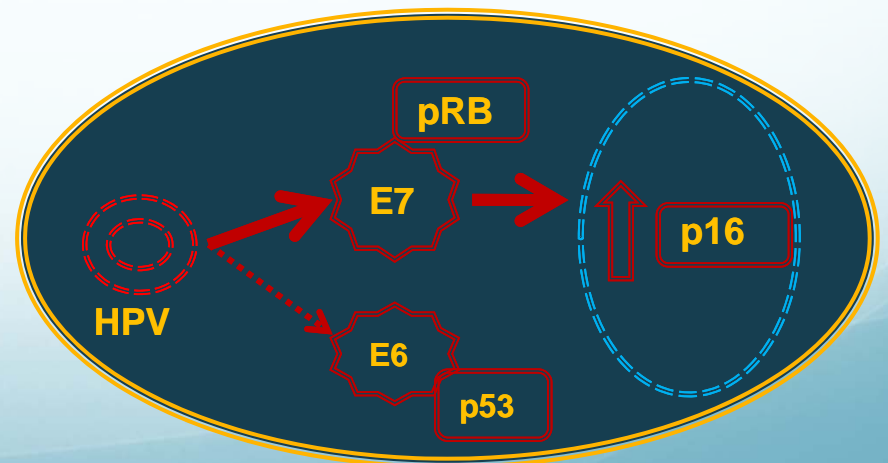
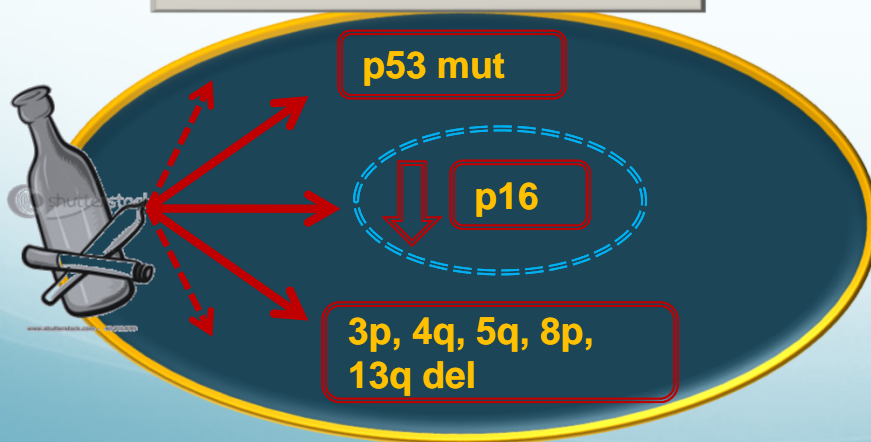
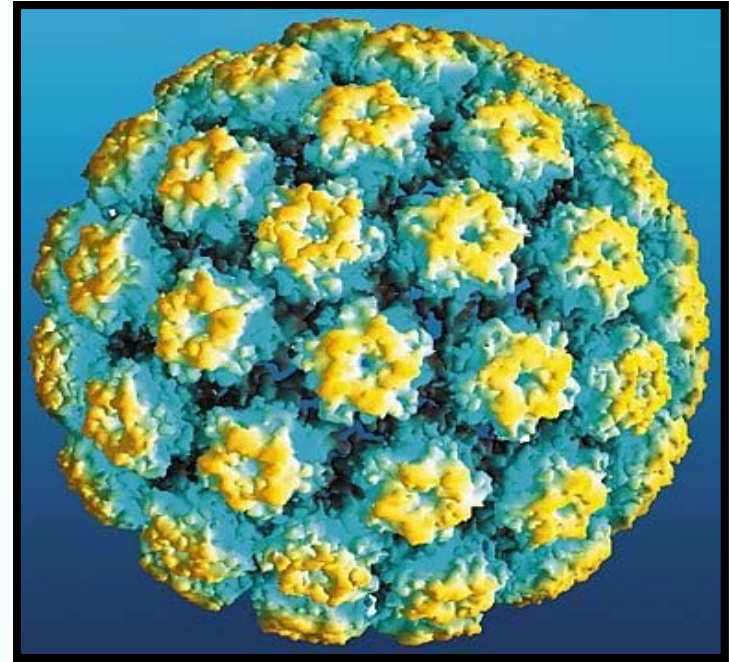
Marlboro



**Fumer peut
entraîner
une mort lente
et douloureuse**

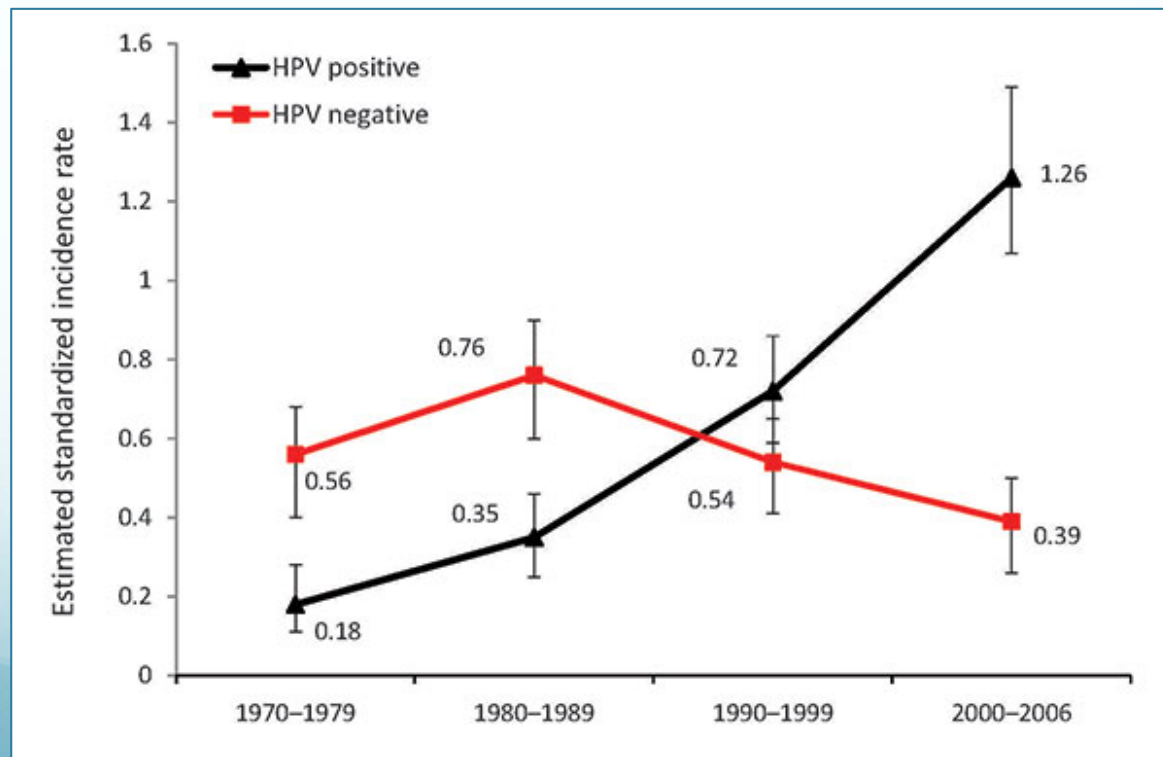
Pour arrêter de fumer :
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Two Distinct Forms of Head and Neck Cancer



HPV-Associated HNSCC: an Emerging Epidemic

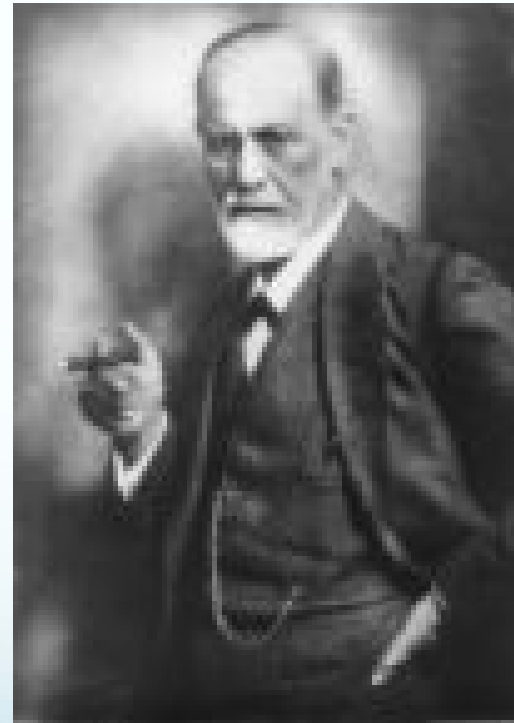
- The incidence of HPV(+) oropharyngeal HNSCC increased ~225% from 1988 to 2004
- HPV is now the primary cause of tonsil cancer in North America and Europe





Ulysses S. Grant

Sigmund Freud



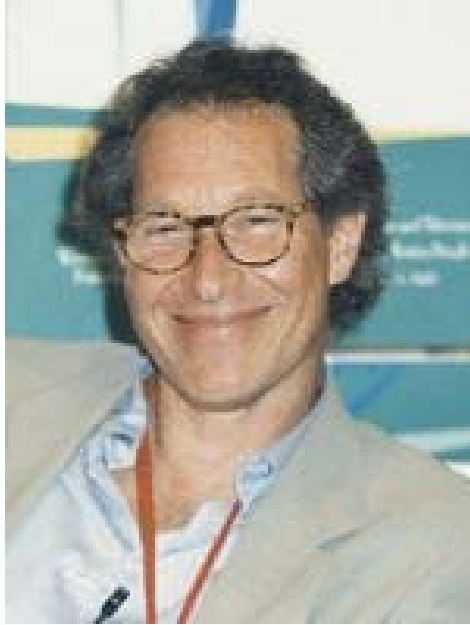


J. Robert Oppenheimer

Babe Ruth



Bruce Paltrow



Ann Richards



Michael Douglas

Can HNSCC be prevented?

➤ Smoking



Can HNSCC be prevented?

- Smoking
- Chewing betel quid



Can HNSCC be prevented?

- **Smoking**
- **Chewing betel quid**
- **Inhalation of airborne pollutants**



Can HNSCC be prevented?

- Smoking
- Chewing betel quid
- Inhalation of airborne pollutants
- Vaccination



Primary Prevention

An Opportunity for Chemoprevention

Second primary tumors

- 3-6%/year
- Leading cause of mortality
- Tobacco cessation moderates risk after 5 yrs; insufficient to return risk to baseline

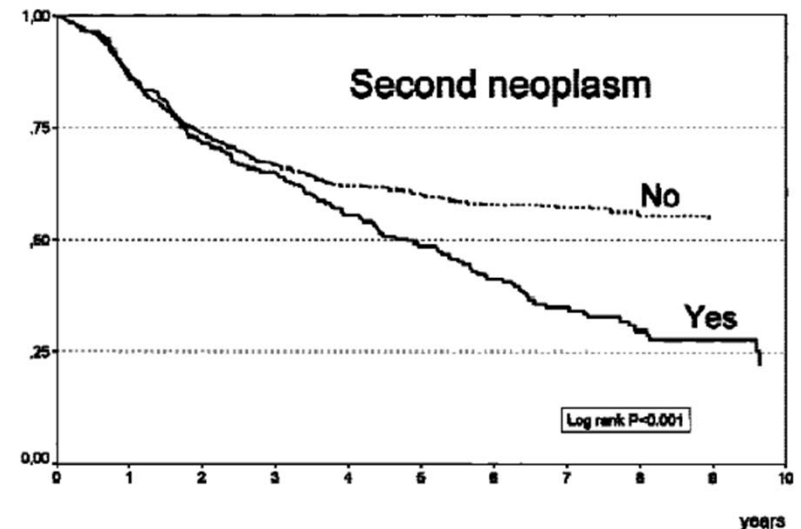


FIGURE 2. Actuarial observed survival for patients with index tumors in the oral cavity, oropharynx, and larynx in relation to the appearance of second neoplasm.

Slaughter, DP et al., *Cancer* 6(5):963-8, 1953.
Leon, X, et al., *Head Neck* 21(3):204-10, 1999.

High Dose Isotretinoin (retinoic acid) Prevented SPTs (but too toxic)

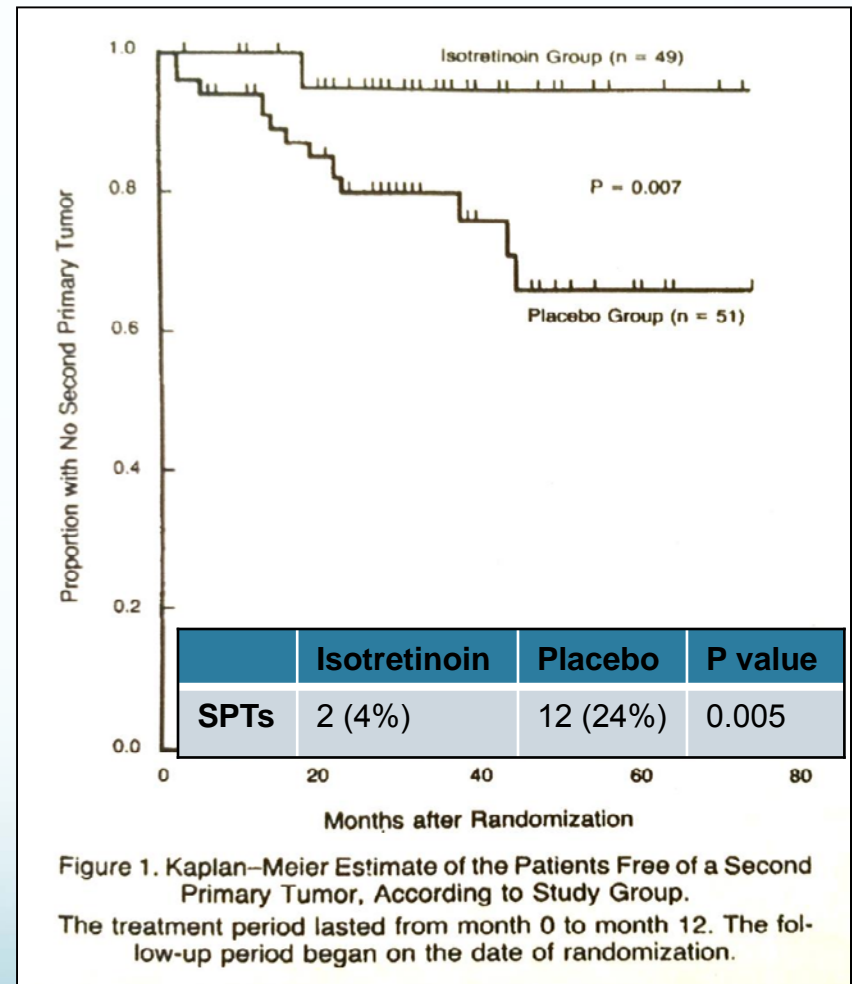
Treatment: 50-100 mg/m²/day (n=49)
vs. placebo (n=51) x 1 year

SPT Development: 4% vs. 24%
(p=0.005)

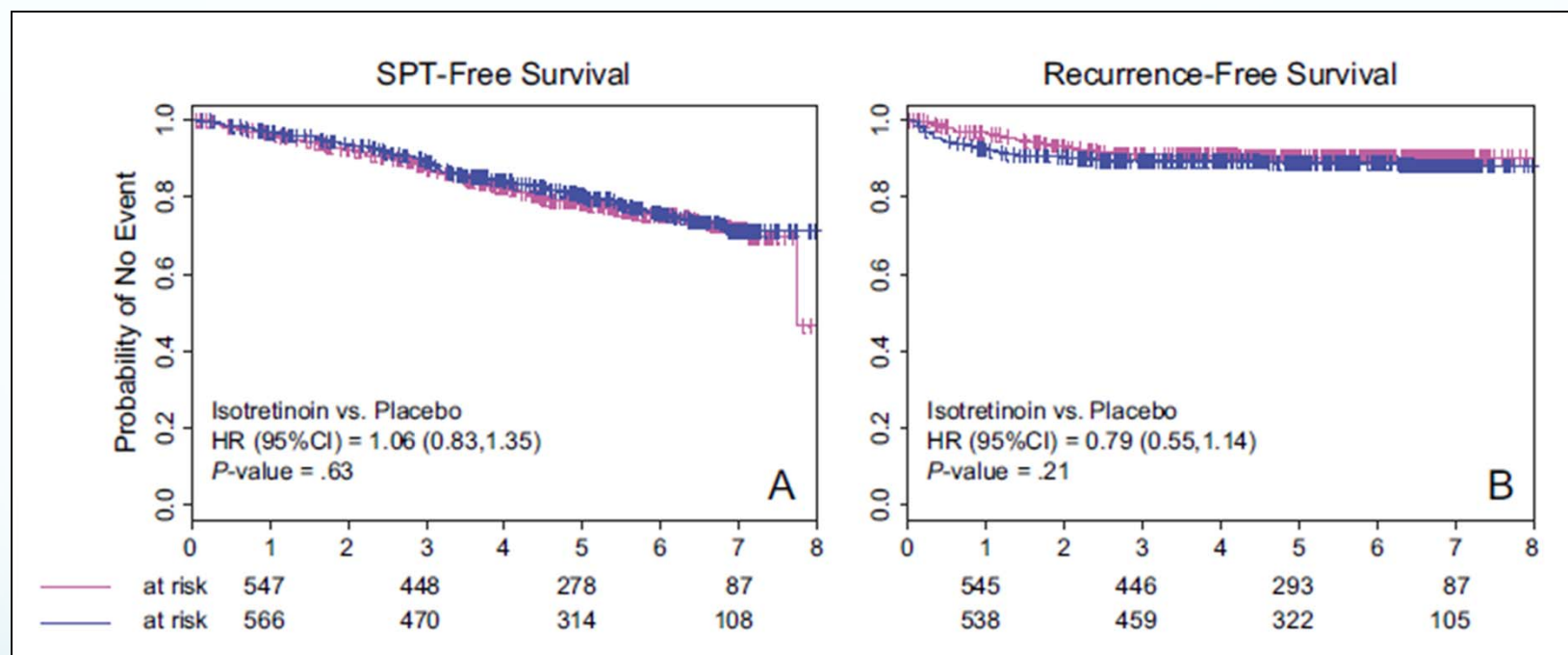
Limitations:

- Tolerability: dose reduction in 33%
- Risk returned to baseline after d/c of treatment

Conclusion: HD isotretinoin is not feasible for chronic administration to healthy patients



Low Dose Isotretinoin (Phase III) was Tolerable but Ineffective

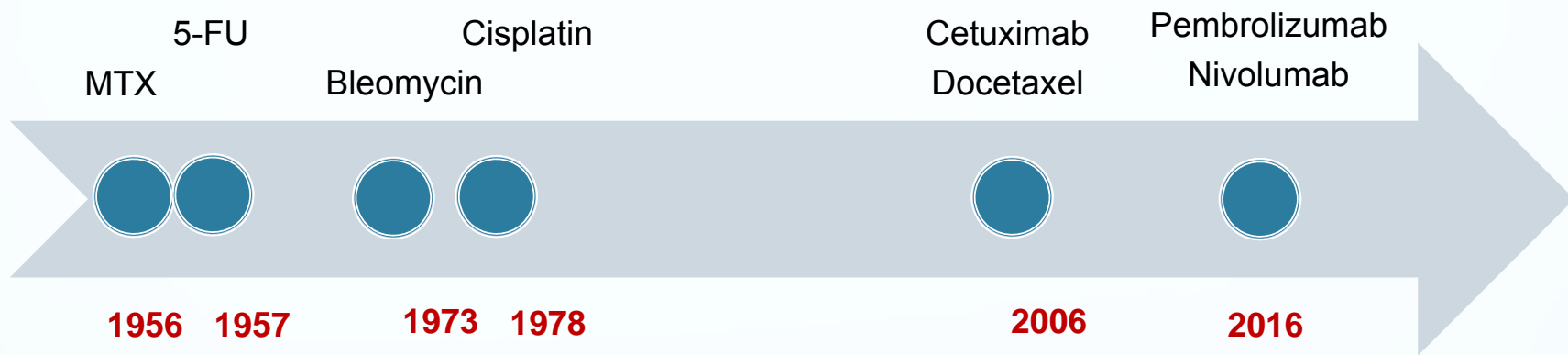


Treatment: 30 mg/day (n=590) vs. placebo (n=600) x 3 years

	Isotretinoin	Placebo	HR
SPTs	130 (22%)	131 (22%)	1.06

**There are no FDA-approved chemopreventive agents
for individuals at high risk of developing
HNSCC SPTs!**

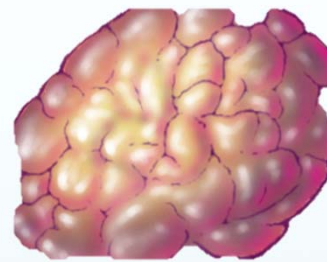
8 FDA-Approved Drugs in HNSCC



Yesterday's Medicine: One size (dose) fits all



Tomorrow's Medicine: Targeting the genetic changes specific to each patient's cancer



Tumor

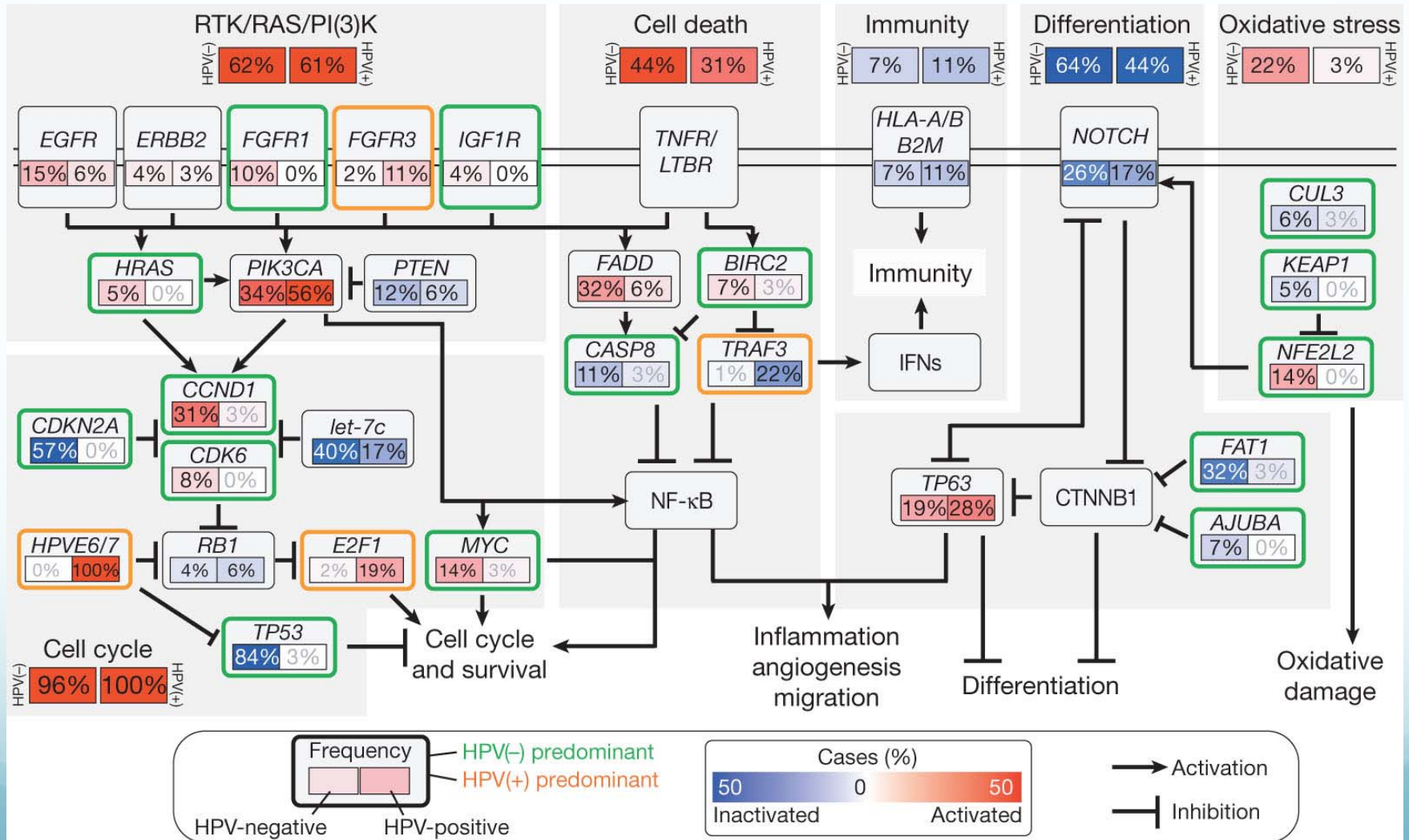


1892:

“If it were not for the great variability among individuals, medicine might as well be a science, not an art.”

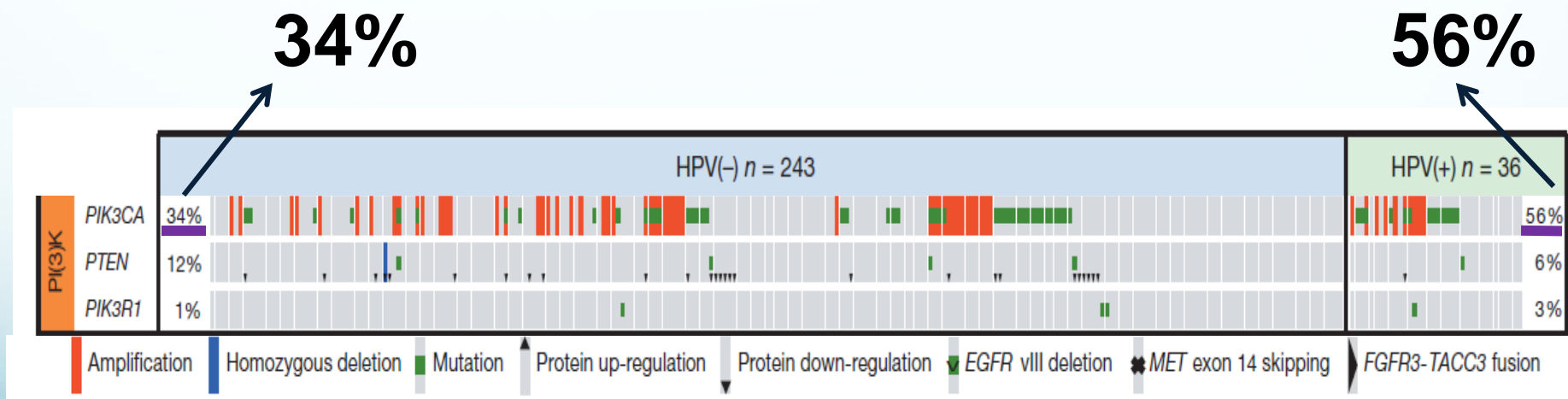
Sir William Osler, Physician

Genes implicated in HNSCC

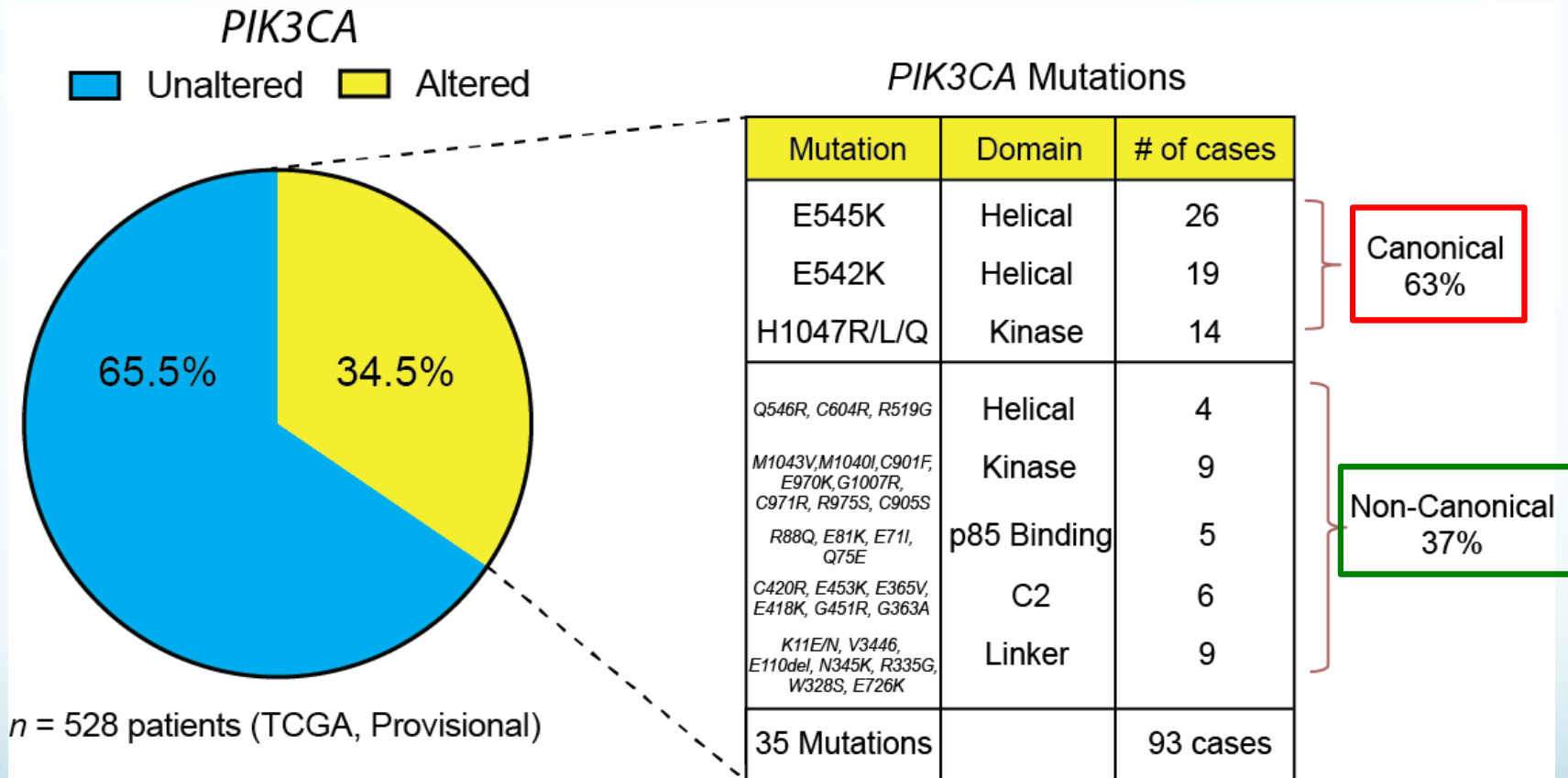


Comprehensive genomic characterization of head and neck squamous cell carcinomas

The Cancer Genome Atlas Network*



PIK3CA Mutational Landscape in HNSCC



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aspirin Use, Tumor *PIK3CA* Mutation, and Colorectal-Cancer Survival

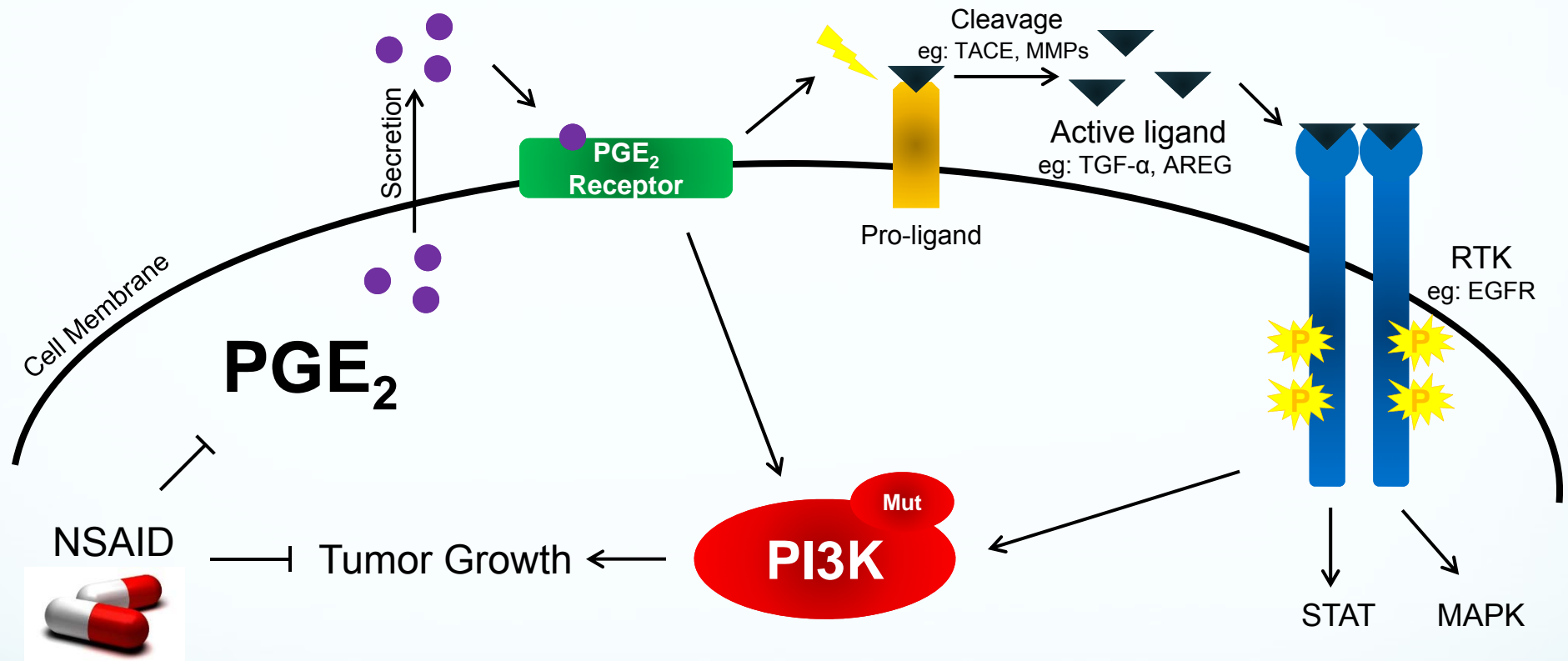
Xiaoyun Liao, M.D., Ph.D., Paul Lochhead, M.B., Ch.B., Reiko Nishihara, Ph.D.,
Teppei Morikawa, M.D., Ph.D., Aya Kuchiba, Ph.D., Mai Yamauchi, Ph.D.,
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Kaori Shima, D.D.S., Ph.D., Ruifang Sun, M.B., Katsuhiko Nosho, M.D., Ph.D.,
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and Shuji Ogino, M.D., Ph.D.

Epidemiologic Evidence in HNSCC

Large Randomized Screening Trial (NCI PLCO) Demonstrated a Protective Effect of NSAIDs Against HNSCC Development

- **No biomarkers of response**
- **Data from unselected populations**
- **No molecular mechanisms**

What We Know From Studying HNSCC Signaling

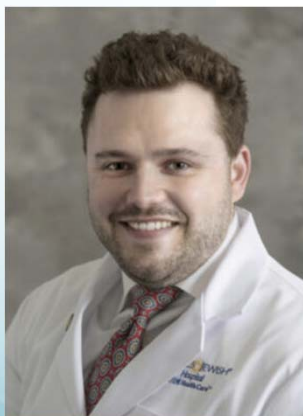
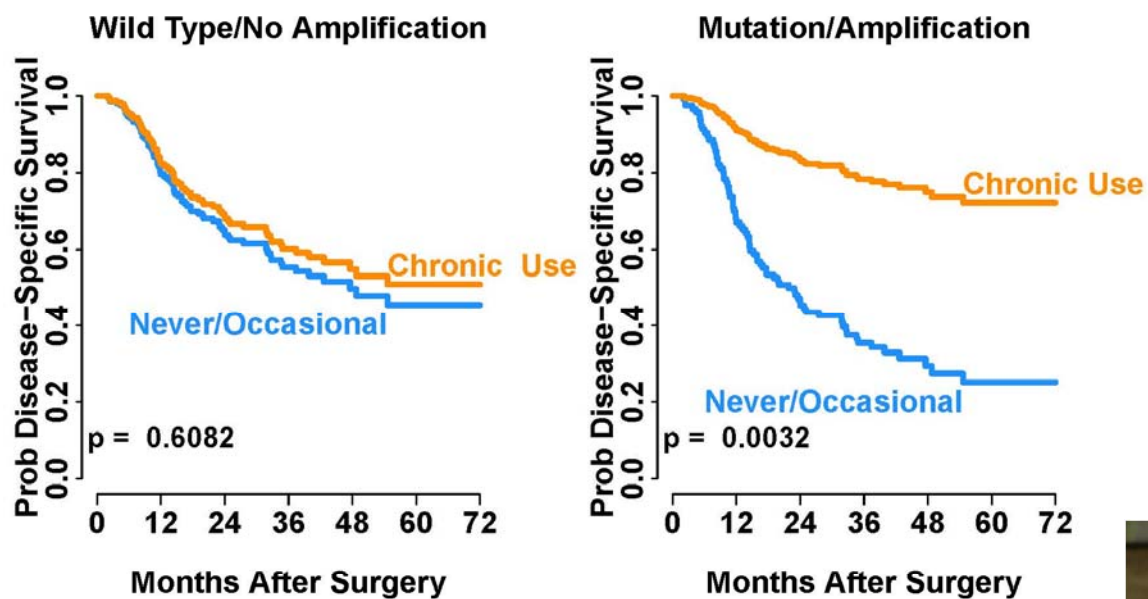


1. Lui, Thomas et al. 2003 (CCR)
2. Zhang, Thomas et al. 2004 (Oncogene)
3. Thomas, Bhola et al. 2006 (Cancer Res)
4. Zhang, Bhola et al. 2007 (MCT)
5. Zhang, Bhola et al. 2008 (Cancer Res)
6. Bhola, Thomas et al. 2011 (MCR)

So, we did a study...

- HNSCC cohort with tissue and phenotypic data (why it is important to prospectively collect tissue and phenotypic data!)
- Chronic NSAID use defined as ≥ 6 months (generally baby ASA)
- *PIK3CA* FISH on TMAs
- *PIK3CA* sequencing (all exons)
- HPV by ISH and p16 IHC
- 266 cases for final analysis
- Disease-specific and overall survival recorded

NSAIDs Use Associated with Improved Survival in HNSCC



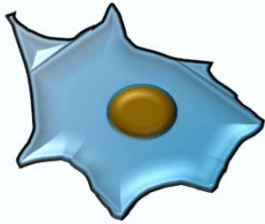
Matt Hedberg



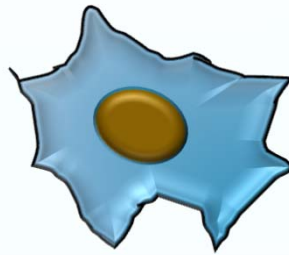
Noah Peyser

Hedberg *et al.* *J Exp Med* 216: 419-427, 2019

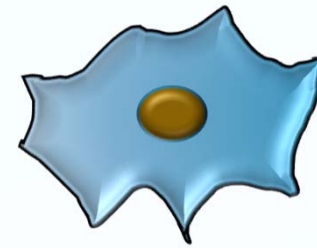
Cell line models



HNSCC cells
endogenous
WT or MT
PIK3CA



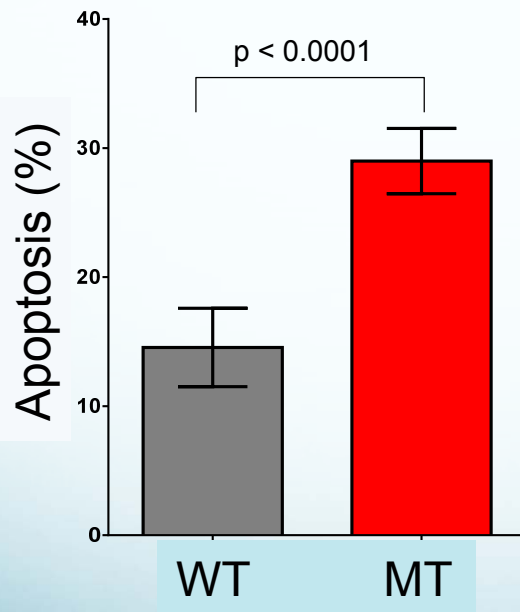
NSCLC cells
endogenous
WT or MT
PIK3CA



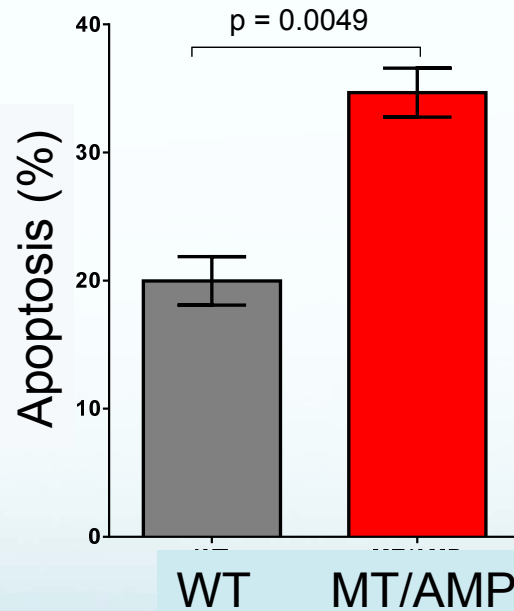
Isogenic HNSCC cells
engineered for
WT or MT
PIK3CA

HNSCC and NSCLC Cells with *PIK3CA* Alterations Exhibit Enhanced Response to NSAIDs

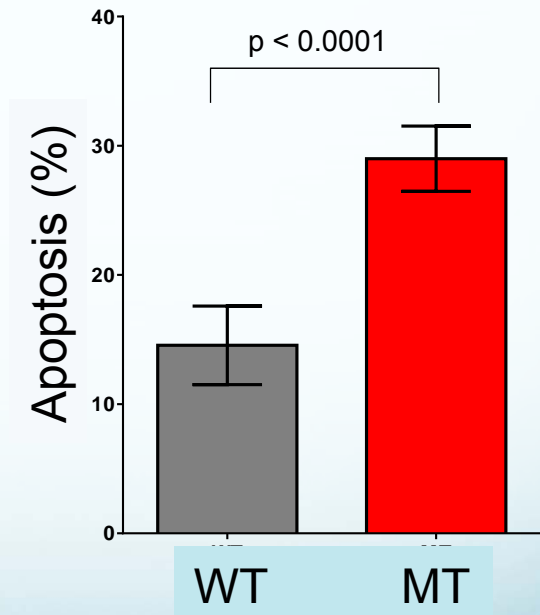
HNSCC lines with endogenous WT or MT *PIK3CA*



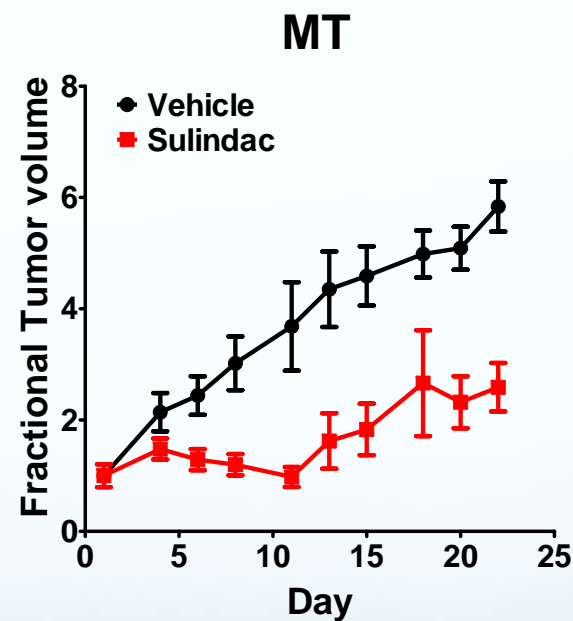
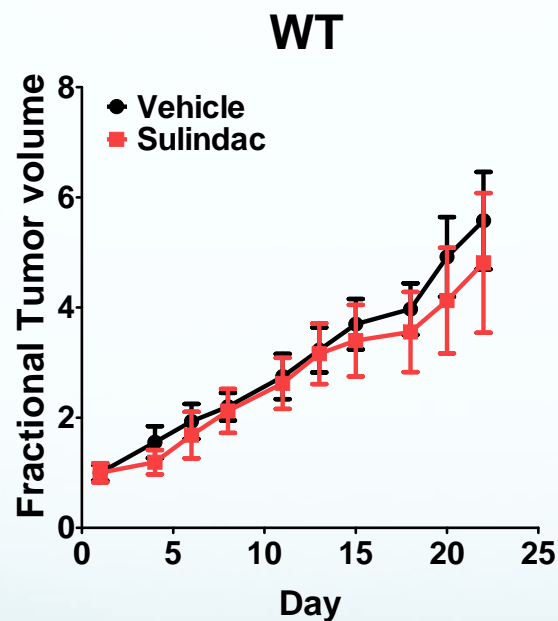
NSCLC lines with endogenous WT or MT *PIK3CA*



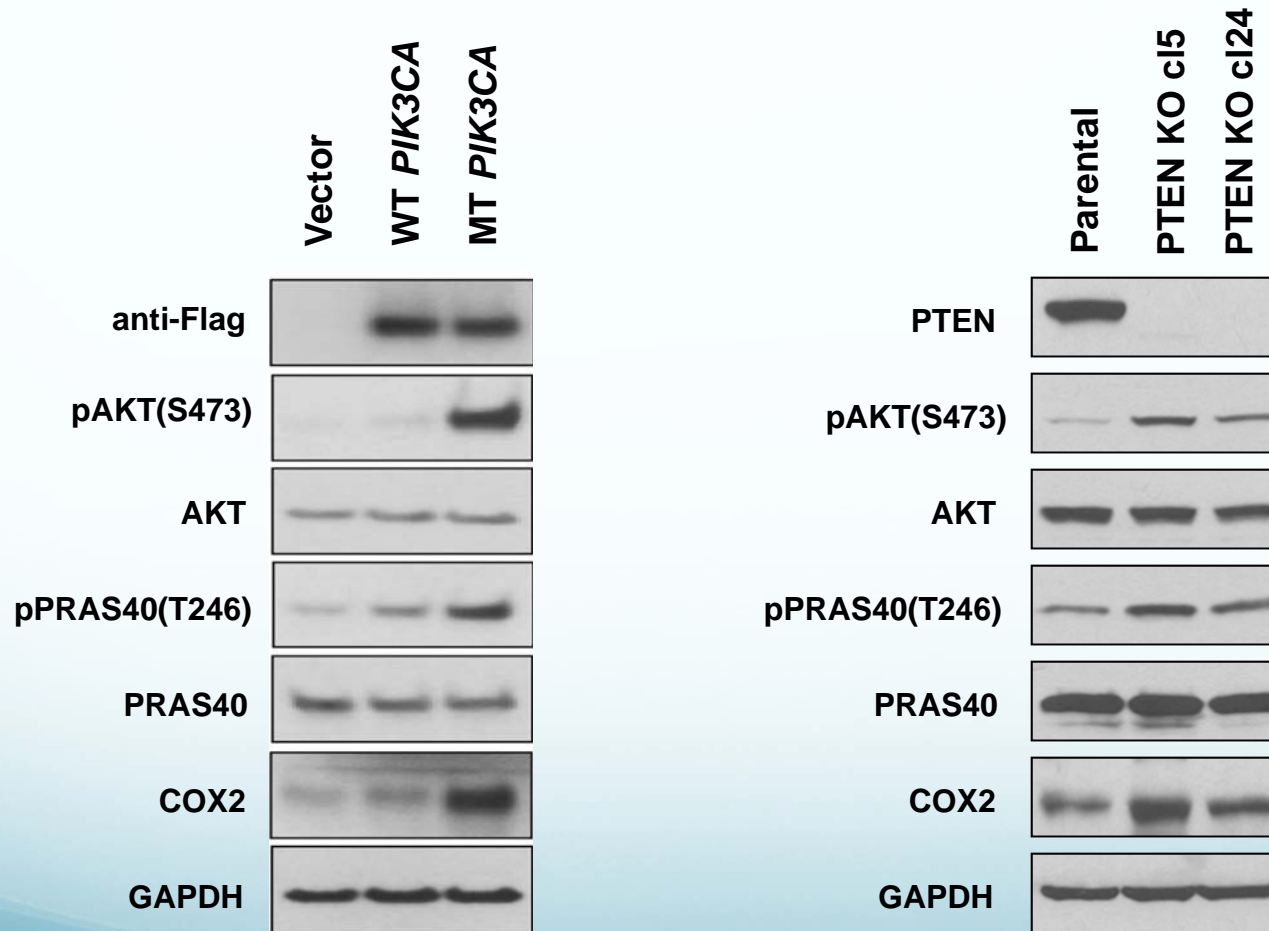
Isogenic HNSCC lines Engineered for WT or MT *PIK3CA*



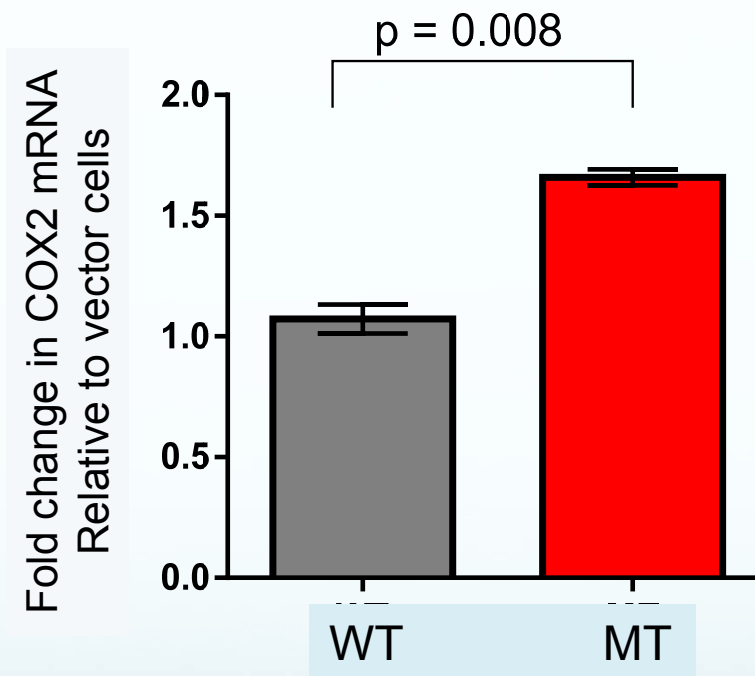
HNSCC PDXs with *PIK3CA* Alterations Exhibit Enhanced Response to NSAIDs



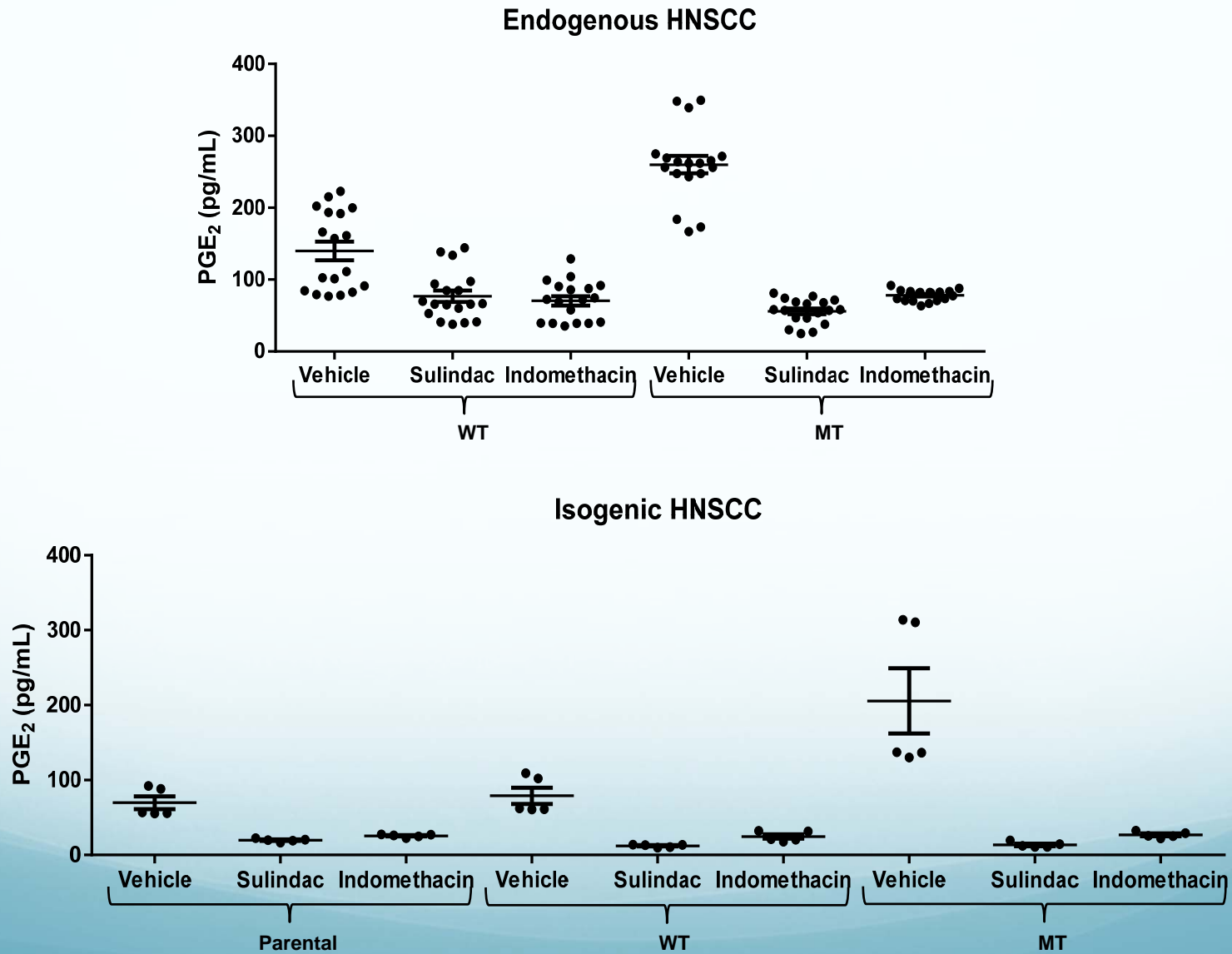
Isogenic HNSCC Cells Engineered for Mutant *PIK3CA* or *PTEN* Loss Have Elevated COX2



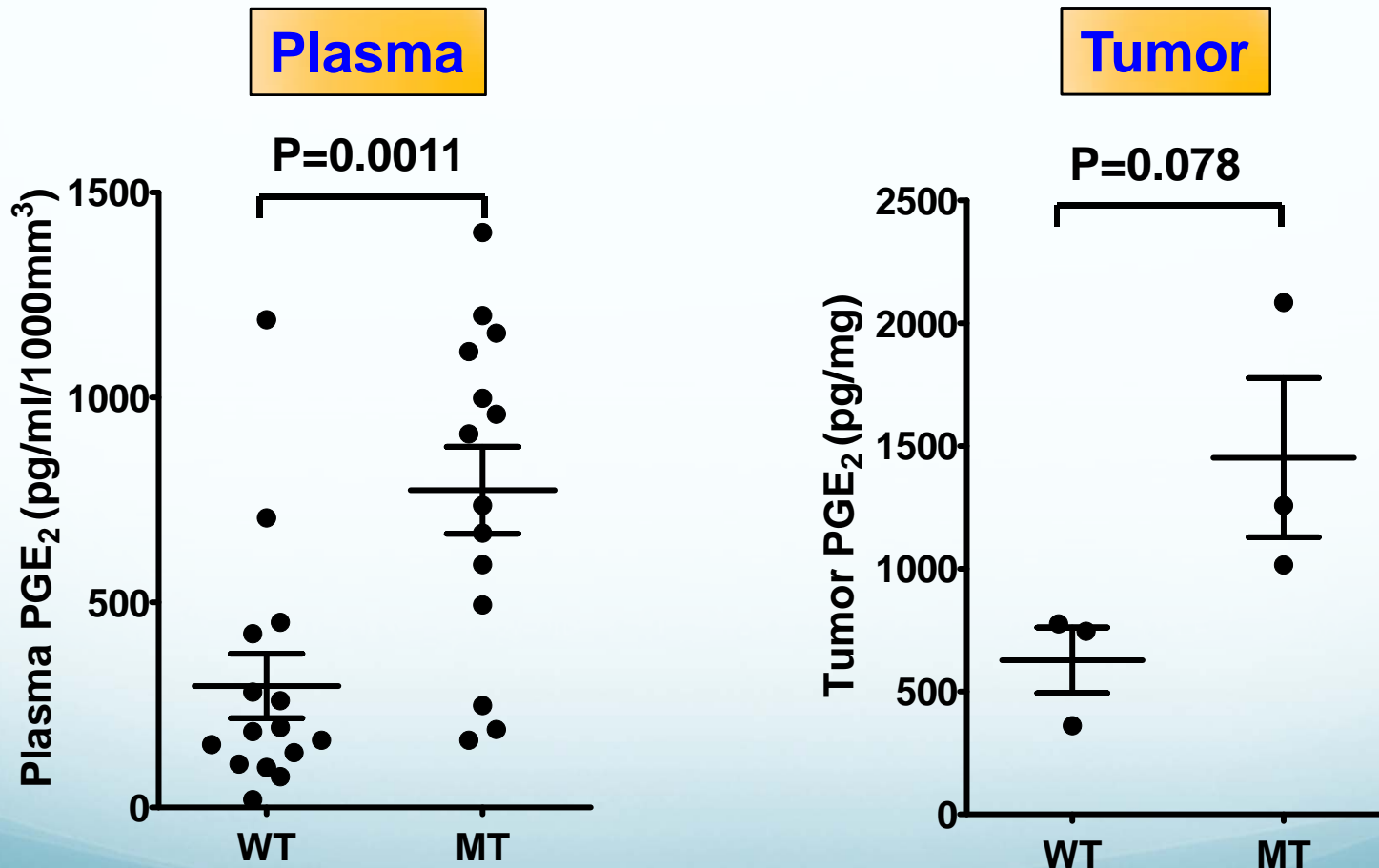
Mutant *PIK3CA* Induces COX2 mRNA



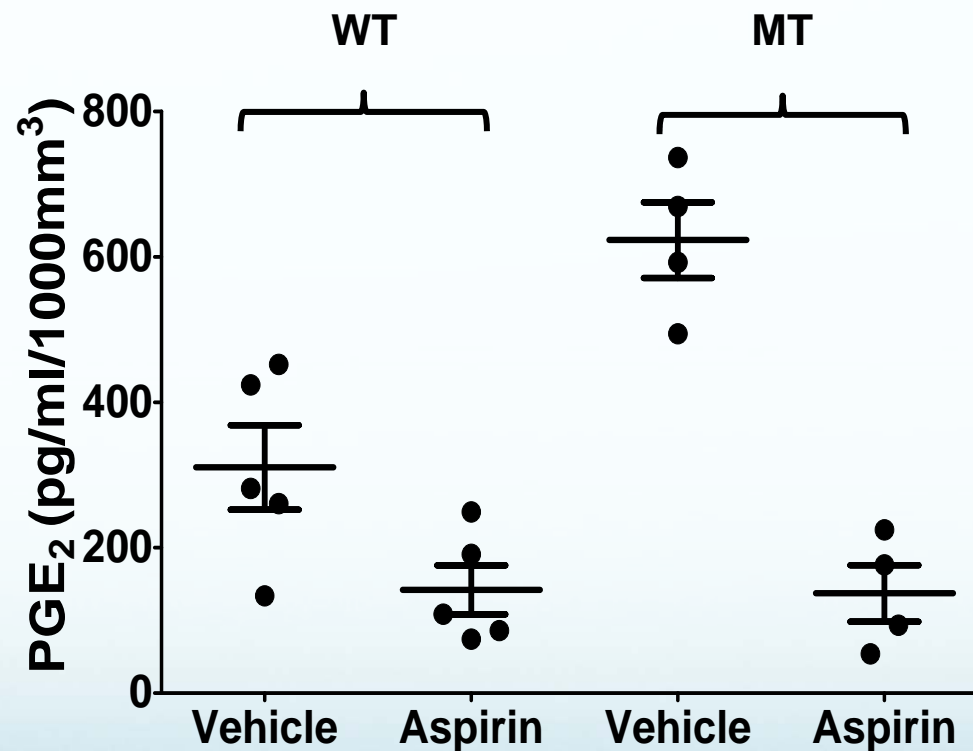
HNSCC Cells with Mutant *PIK3CA* Have Elevated PGE₂



HNSCC PDXs with Mutant *PIK3CA* Have Elevated Circulating and Tumor PGE₂

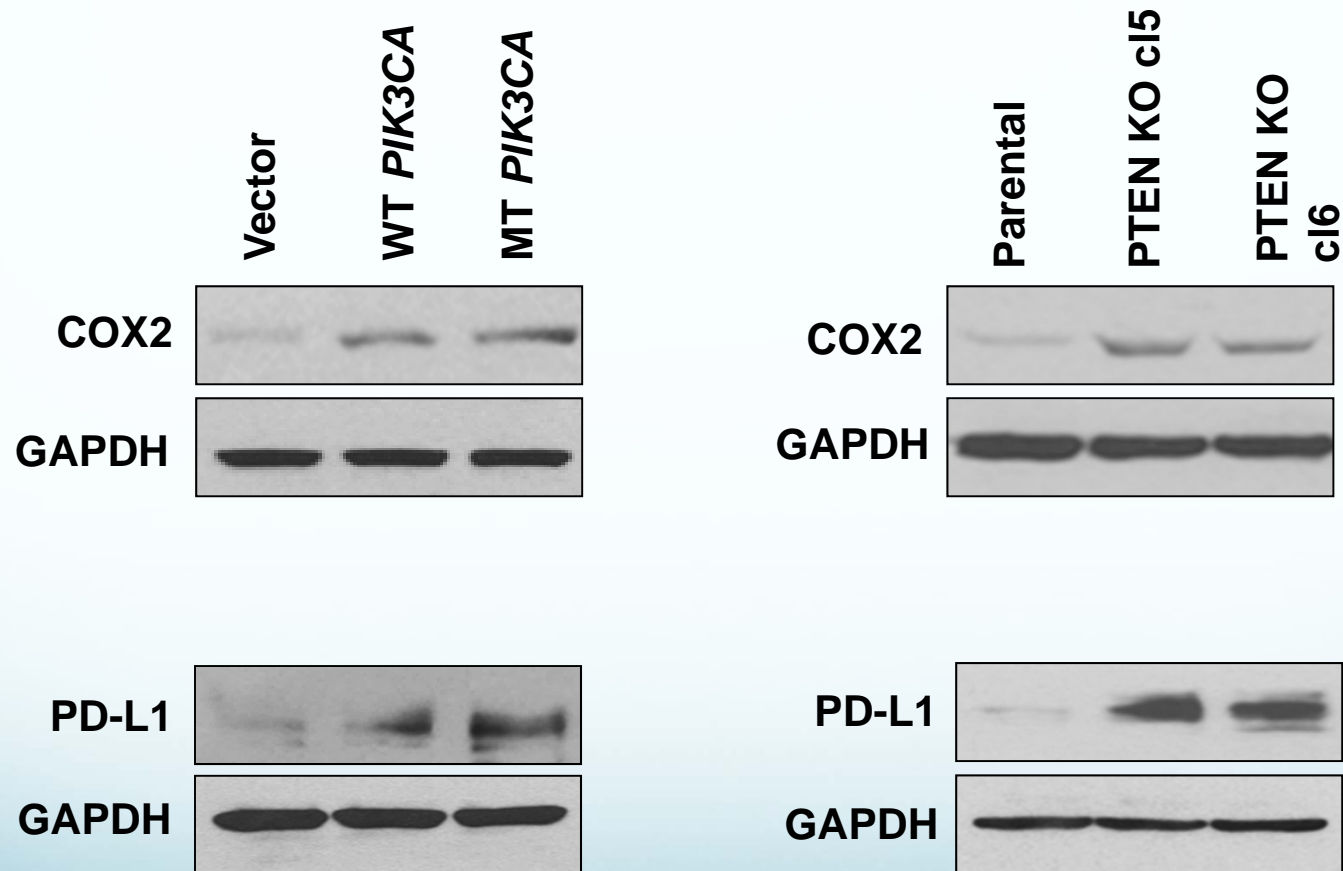


HNSCC PDXs with Mutant *PIK3CA* Respond to NSAIDs with Large Loss of PGE₂

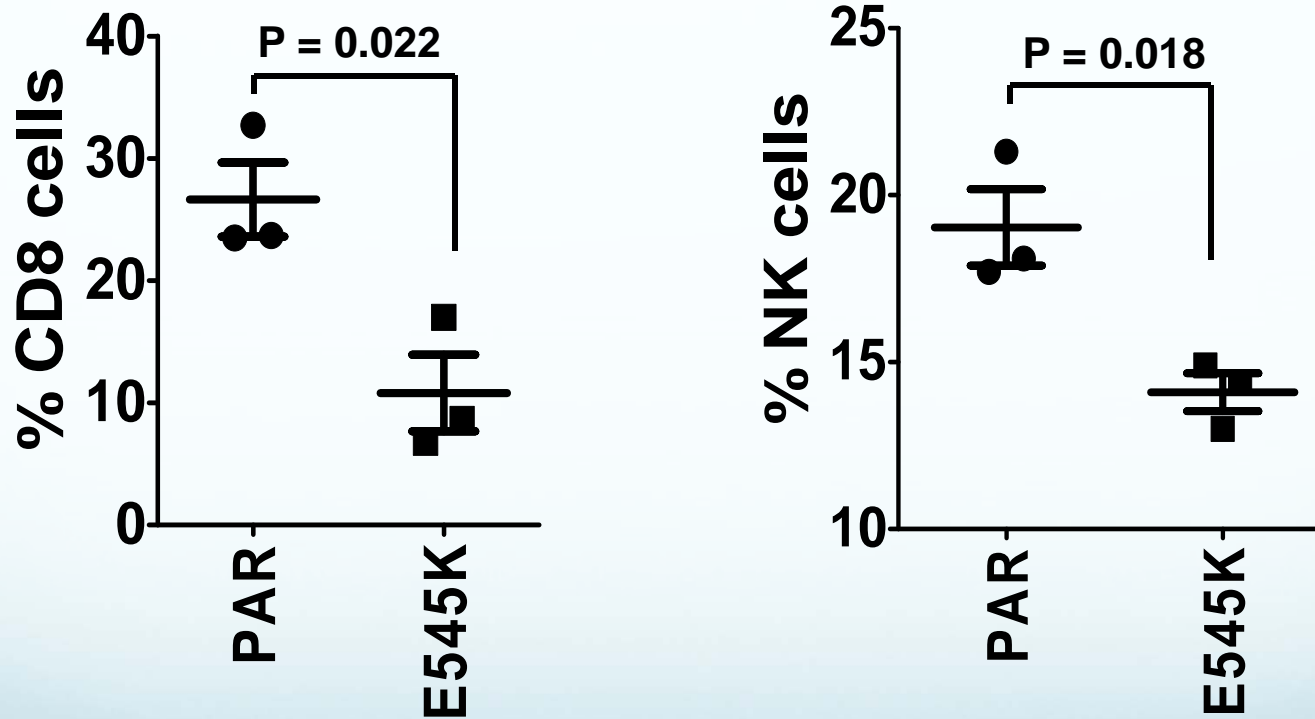


Hypothesis: *PIK3CA* mutation will be associated with a more immunosuppressive tumor microenvironment

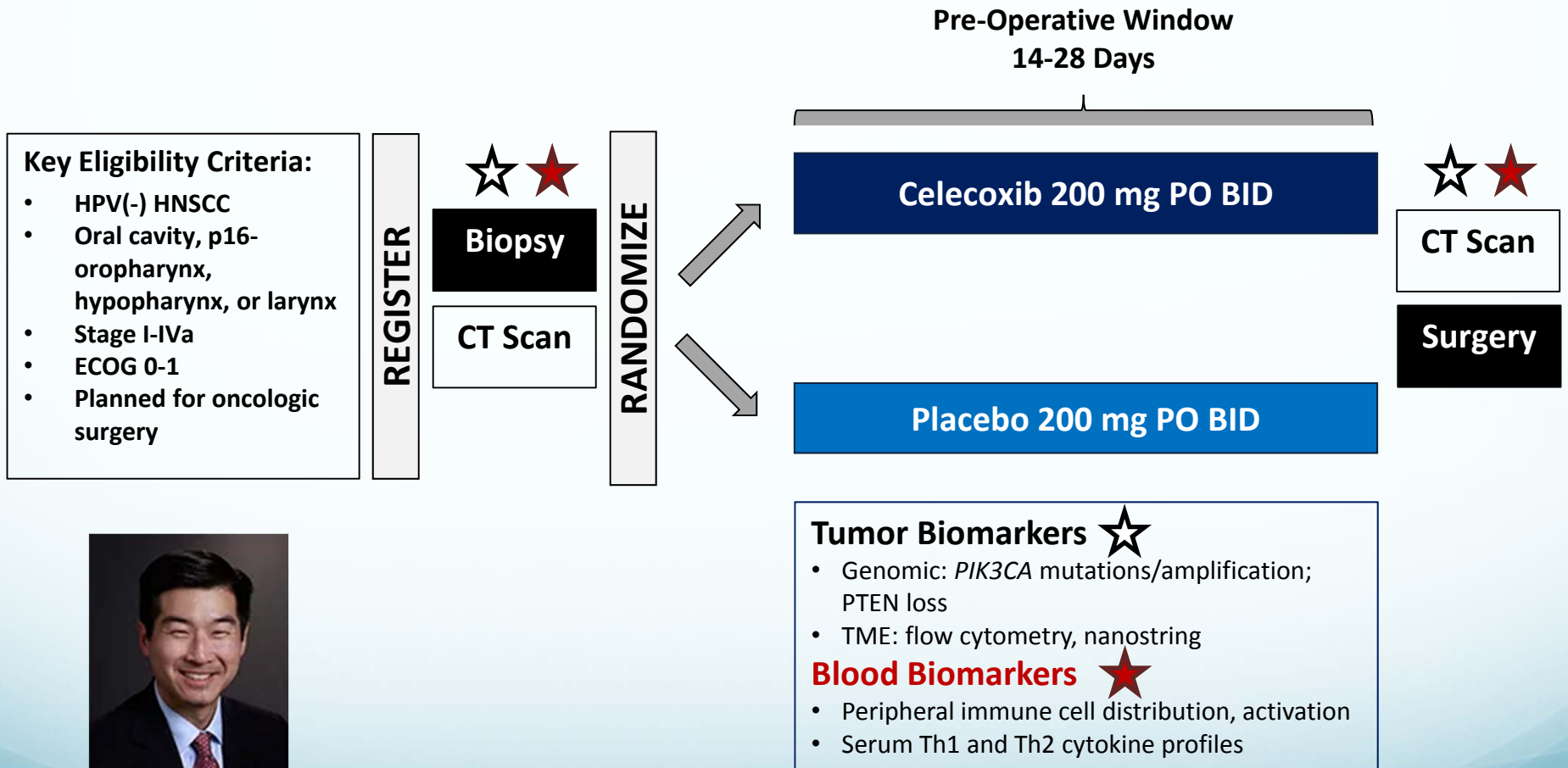
MOC1 (Mouse Oral Cancer) Cells Engineered for Mutant *PIK3CA* or Loss of *PTEN* Exhibit Elevated COX2 and PD-L1



MOC1 Tumors with Mutant *PIK3CA* Exhibit Reduced CD8⁺ T Cells and NK Cells



Proposed Window Trial of NSAIDs in *PIK3CA* Mutant HNSCC



Patrick Ha

Proposed Clinical Trial Schema

Eligibility (n=300):

- HNSCC s/p curative treatment
- No evidence of disease
- High risk for recurrence
 - Oral Cavity: Stage III-IVb
 - HPV⁻ Oropharynx, Hypopharynx: Stage II-IVb
 - Larynx: Stage III-IVb
 - HPV⁺ Oropharynx: Stage III
- ECOG 0-1
- Tissue available for *PIK3CA* sequencing/FISH

RANDOMIZE 1:1*

ASA 81 mg daily
2 years

Placebo daily
2 years

Median DFS

- 1) *PIK3CA*-altered
- 2) *PIK3CA*-WT



Julie Bauman

*Stratify:

- *PIK3CA* Alteration (yes vs. no)
- Composite Stage/HPV Status (AJCC v.8)
 - Stage II-III HPV⁻ vs. Stage IV HPV⁻ vs. Stage III HPV⁺

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