New Targets for Chemoprevention

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LCBCC

Disclosures

- Patent: Prostacyclin analogs for the prevention of cancer
- Grant, SomaLogic, Inc.

Cancer Chemoprevention Requirements

- Ability to define an appropriately high risk population--Yes
  - 1 of 9 smokers will develop lung cancer
  - Smokers with airflow obstruction are at even higher risk
  - Incidence rate of 1.85% per year in Colorado High Risk Cohort; higher in survivors of lung/head and neck cancer
- Availability of effective agents with acceptable risk profiles—None, other than smoking cessation

Phase III Primary Chemoprevention Trials

Trial	Intervention	No.	RR
ATBC	β carotene/α toco	29,133	1.18
CARET	β carotene/retinol	18,314	1.28
PHS	β carotene/ASA	22,071	1.0
WHS	β carotene/ASA/vitE	39,876	1.43
Linxian	Vitamins, minerals	29,584	Neg
SELECT	Selenium, vit E	35,000	Neg

Phase III Second Primary Chemoprevention Trials

Trial	Intervention	No	Outcome
Euroscan	Retinyl palmitate, NAC, both or placebo	2592	No benefit
US Intergroup	13 cis RA, placebo	1166	No benefit

Strategies for choosing chemoprevention agents for phase III trials

- Epidemiology
- Biology
- Animal models--adenocarcinoma
- Intermediate endpoint biomarker modulation
  - Histology
  - Ki-67 index

Intermediate Endpoint Trials

Trial	Intervention	Endpoint	No.	Outcome
Lee	13 CRA	Metaplasia	40	Neg
Kelly	13 CRA	Dysplasia	100	Neg
Kurie	Fenretinide	Metaplasia	82	Neg
Arnold	Etretinate	Metaplasia	150	Neg
McLarty	B carotene	Sputum atypia	1,067	Neg
Heim	B12/folate	Sputum atypia	73	Neg

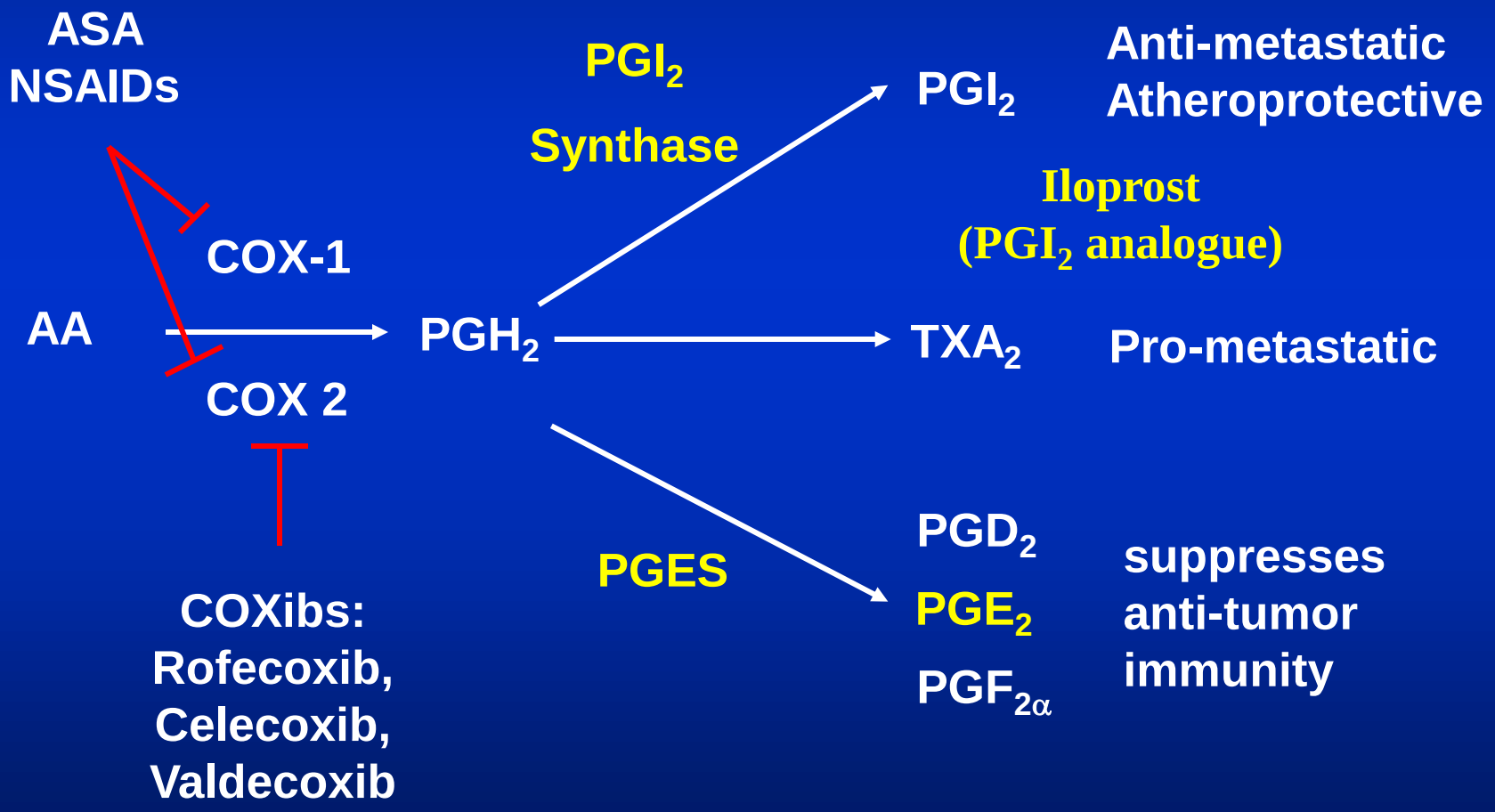
Intermediate Endpoint Trials

Trial	Intervention	Endpoint	No.	Outcome
Lam	Budesonide	Dysplasia	112	Neg
Lam	Anethole Dithiolethione	New lesions	101	Pos*
Kim	Celecoxib	Ki-67	200	Pos
Lam	Myo-inositol	Dysplasia		Promising

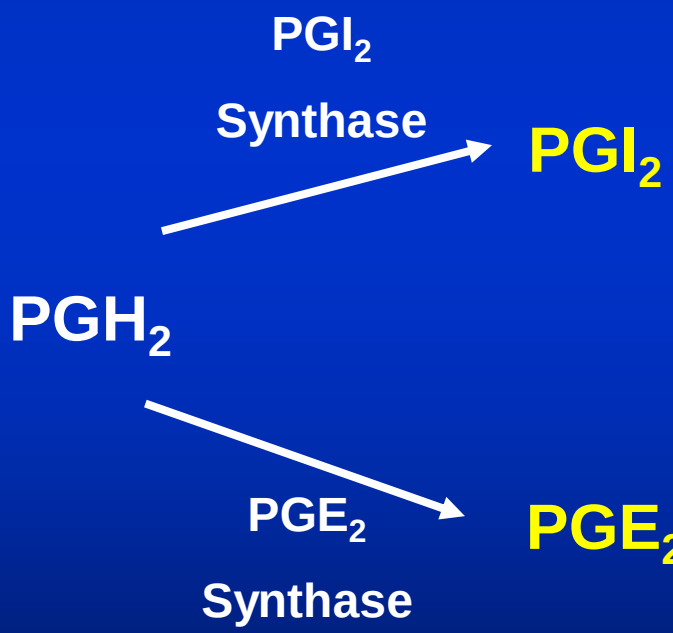
*CR, PR, SD not different

(Phase I)

Regulation of Prostaglandin Production



Prostaglandin Levels in Normal Lung and NSCLC

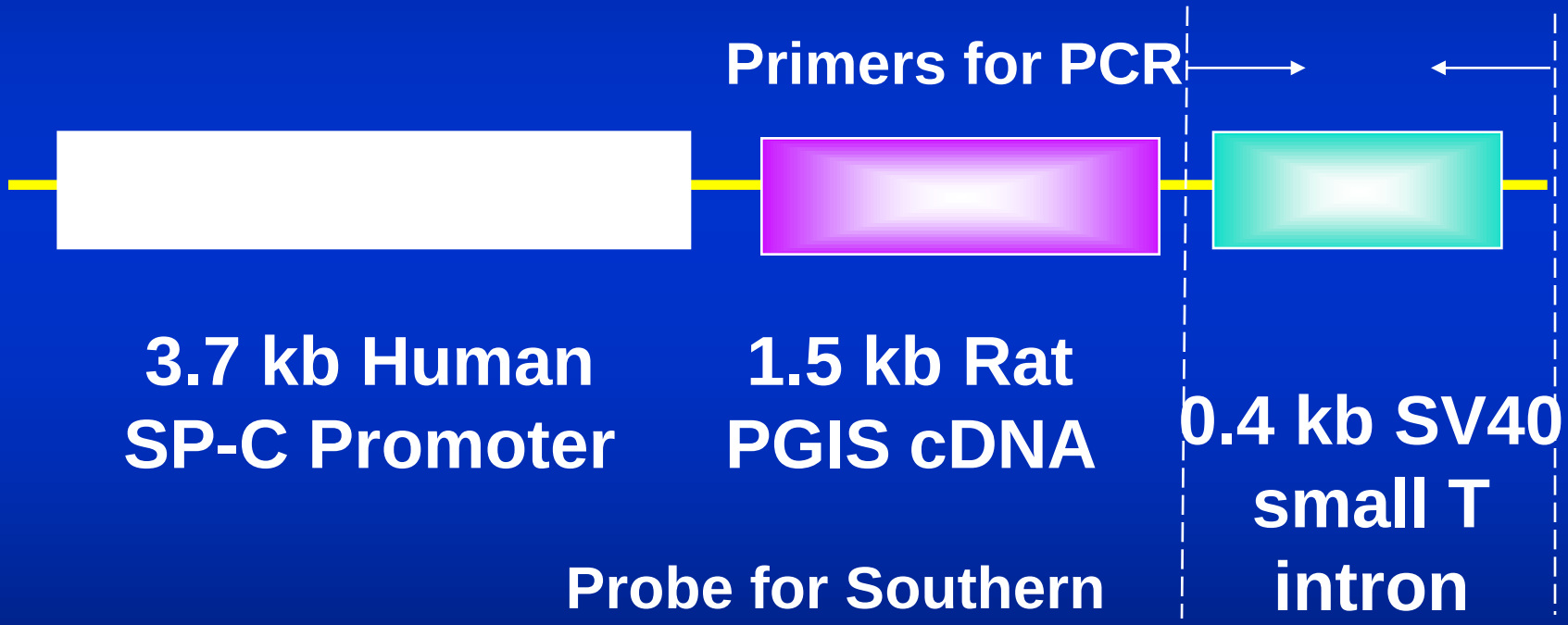


	Normal Lung	NSCLC Cell Lines
PGI_2	3,450 ng/g	333 ng/g
PGE_2	430 ng/g	11,952 ng/g

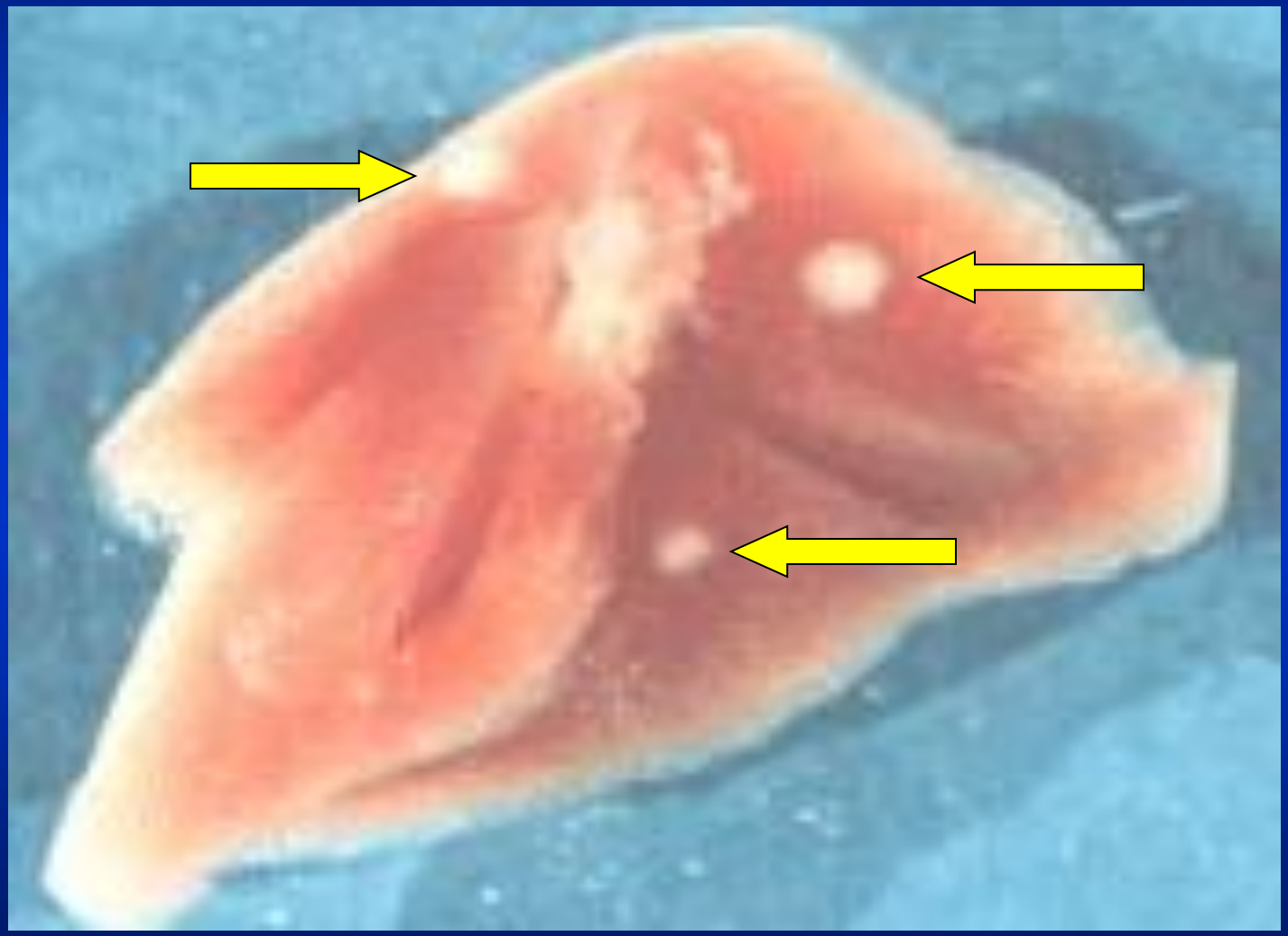
Experimental Strategy

- Prostacyclin has a short half-life, so standard pharmacologic testing not feasible
- Transgenic mouse with prostacyclin synthase expressed under control of the SPC promoter developed

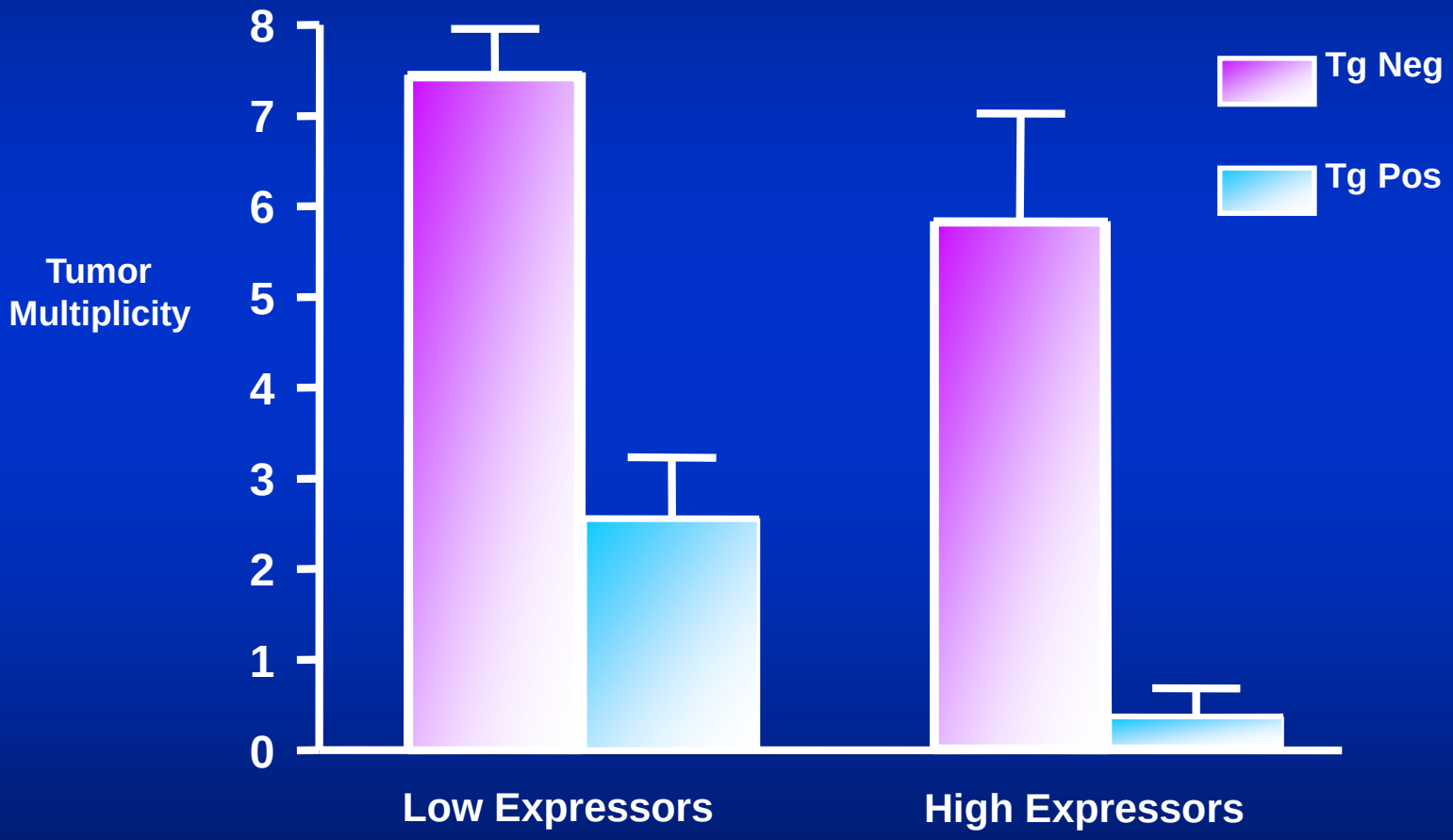
Transgene Construct



Gross Inspection of Lung Adenomas

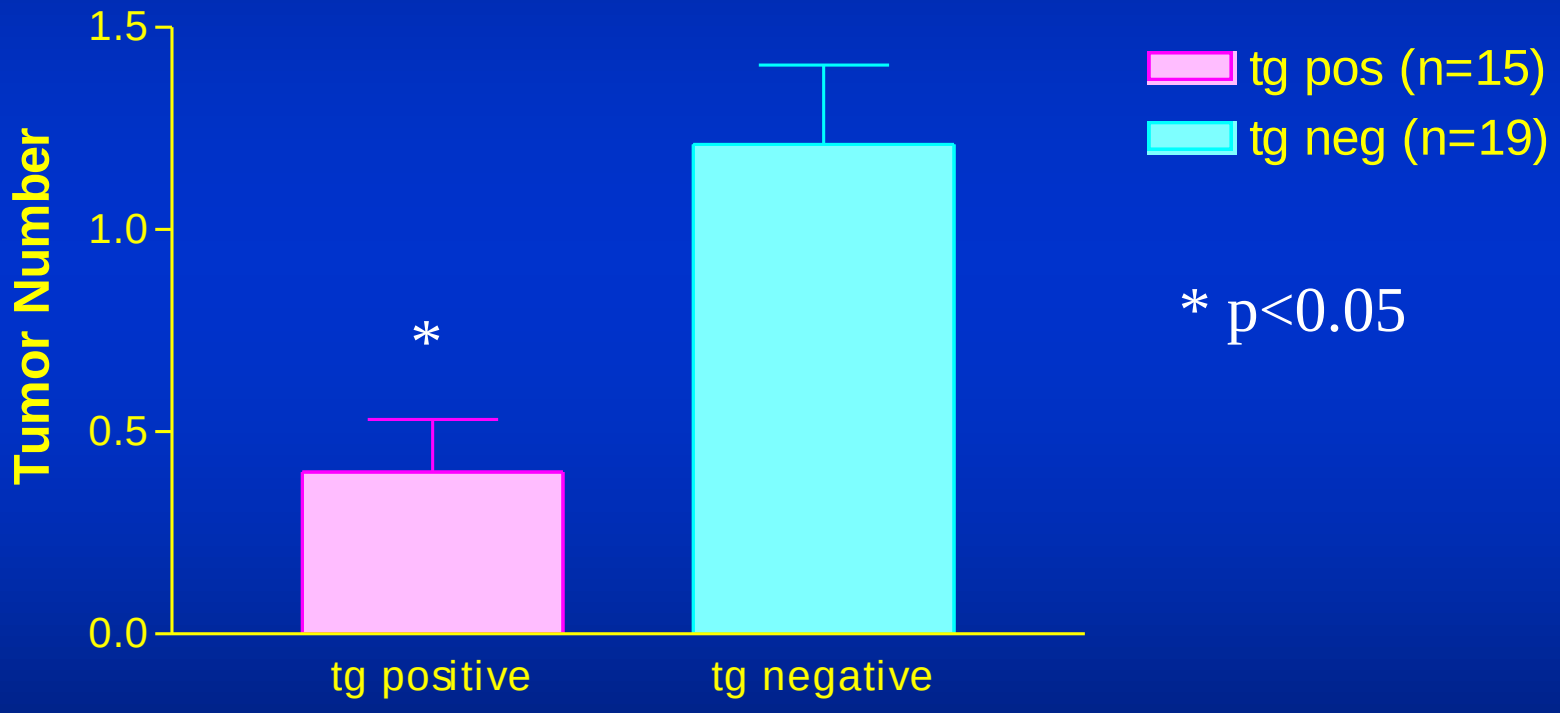


Prostacyclin Synthase Transgene Protects Against MCA/BHT Lung Carcinogenesis



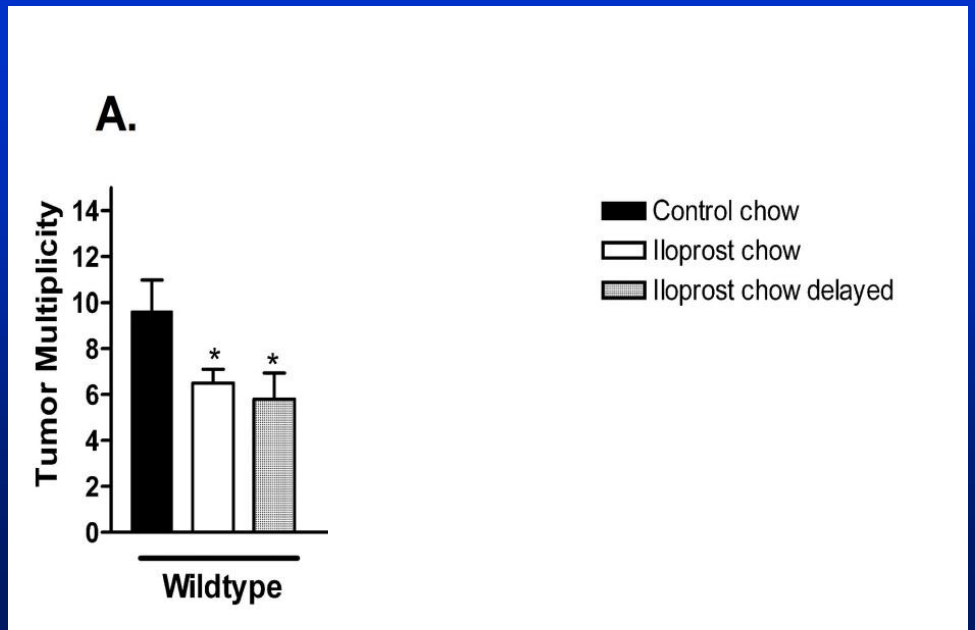
Also confirmed in mouse urethane and smoking models (Cancer Res, 2002, 2004)

Tumor Multiplicity: Smoked PGIS Overexpressors

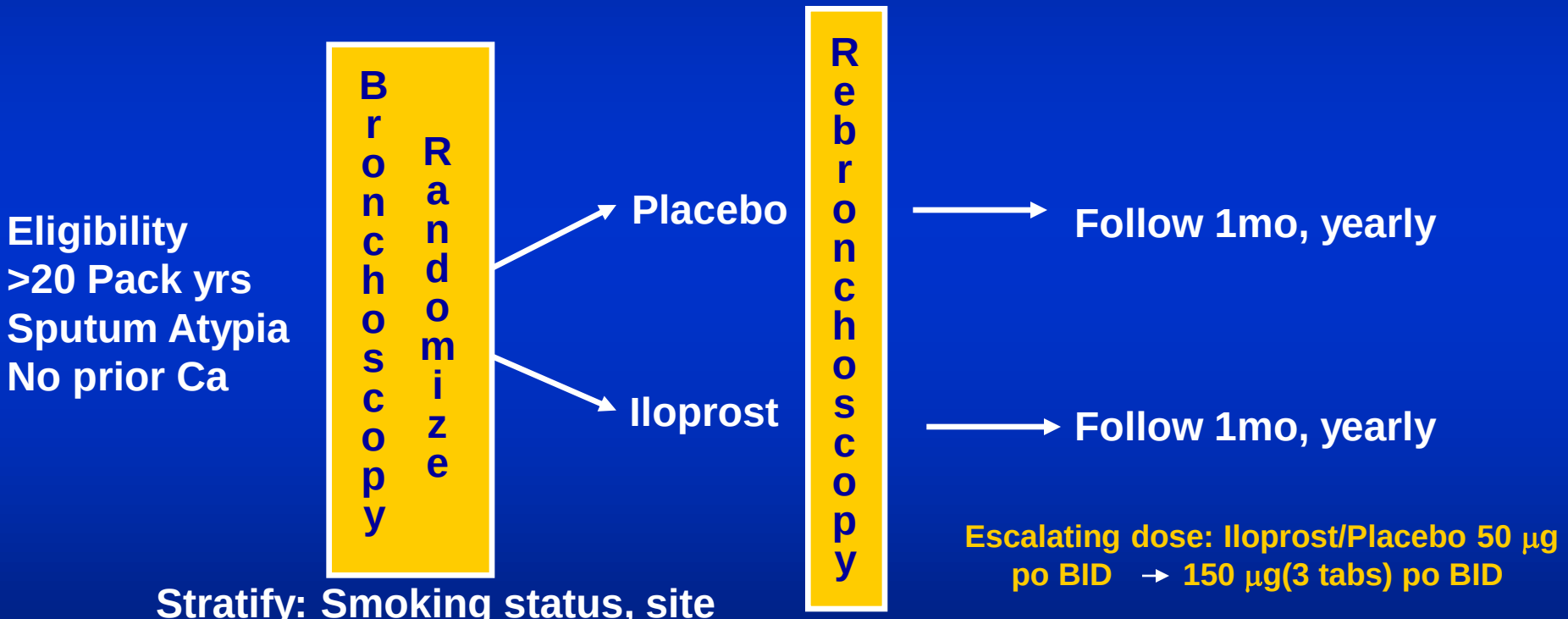


Iloprost chow study

- Oral iloprost also decreases tumor multiplicity in animal models
- Iloprost is FDA approved for pulmonary hypertension, and this intervention may address other common problems in this patient population (secondary pulmonary hypertension, COPD)

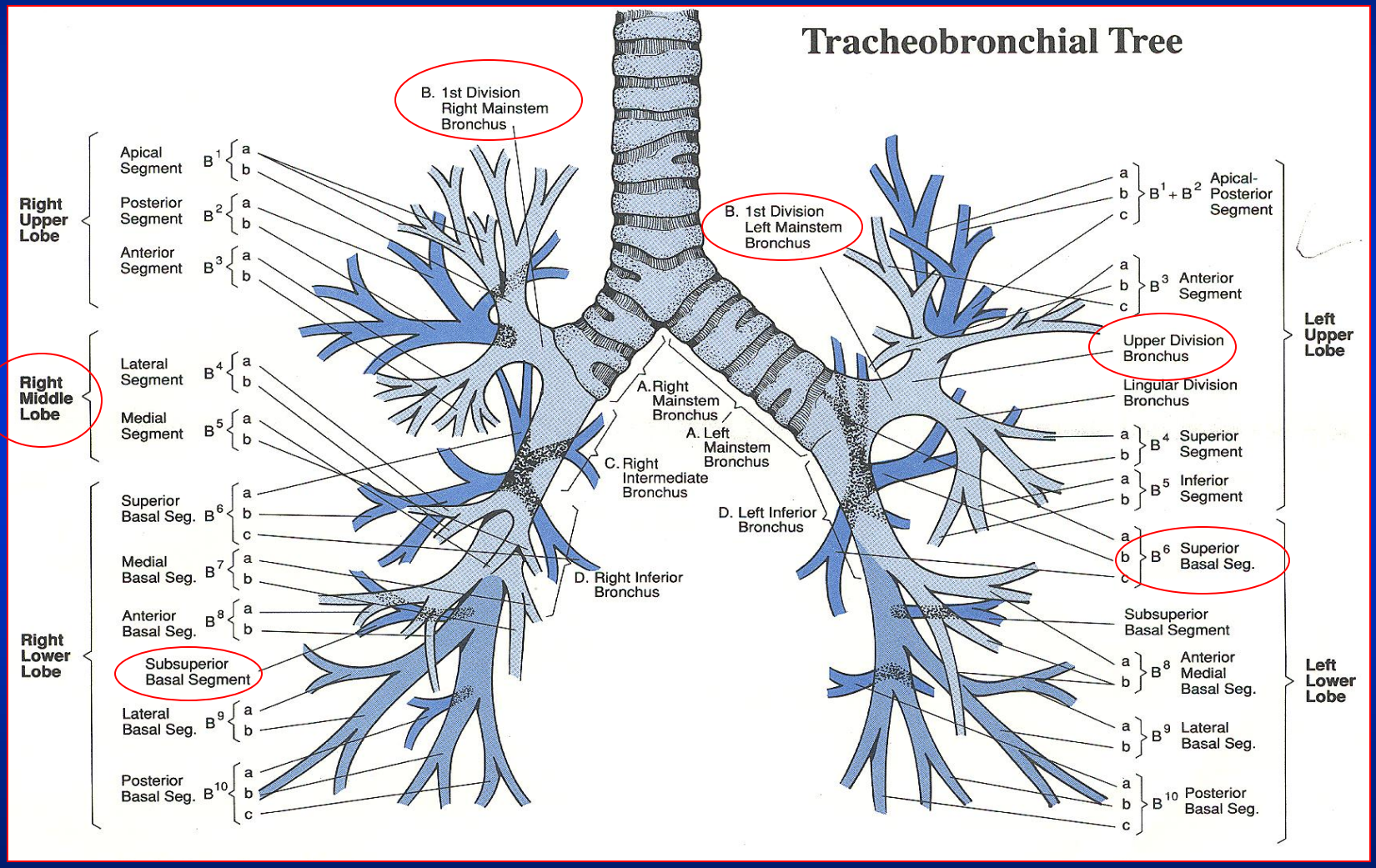


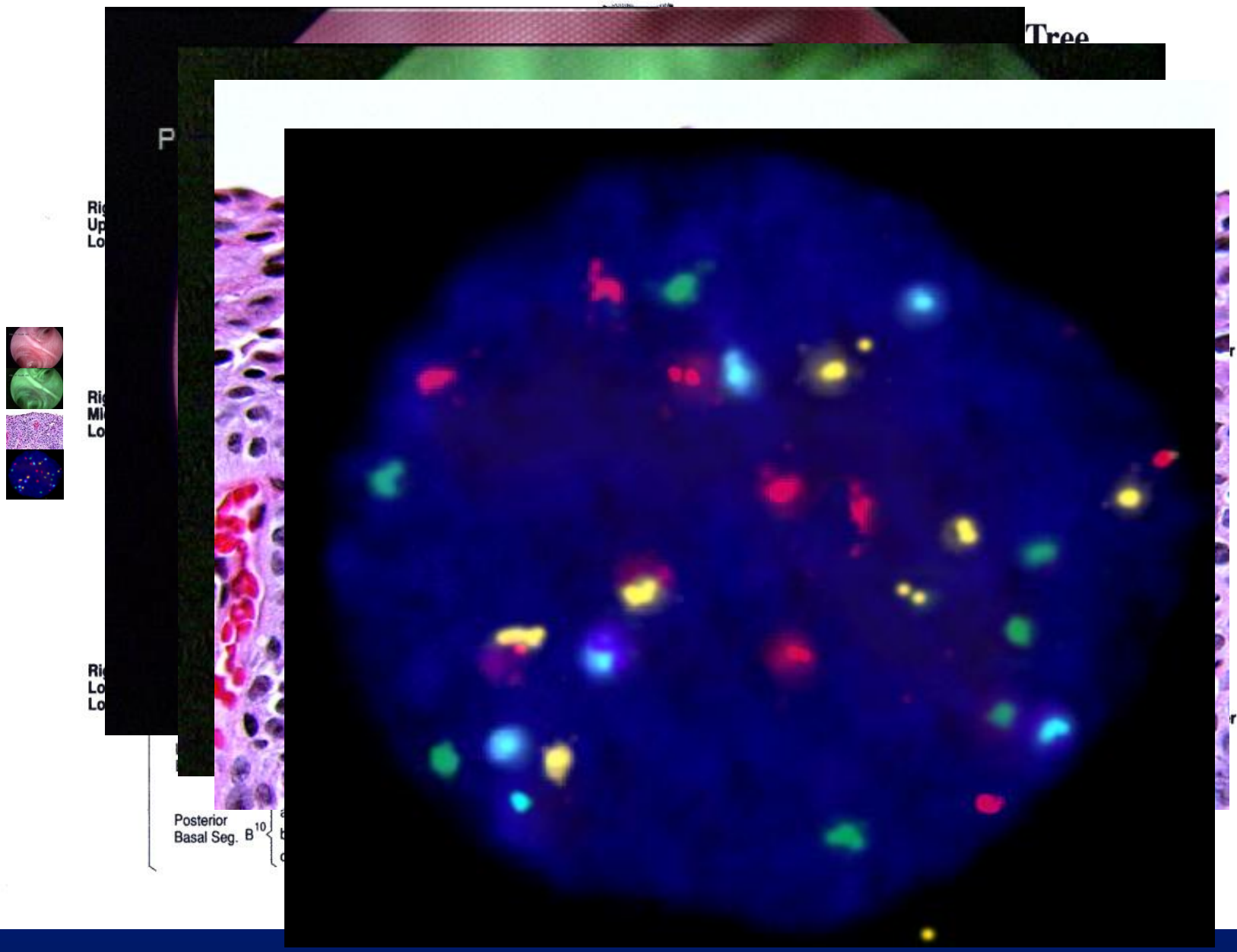
Iloprost Chemoprevention Trial: Design



Endpoints: Bronchial histology; Ki-67; eicosanoid pathway; MCM2; Tyrosine kinase receptor proteins; apoptotic index; microvessel density

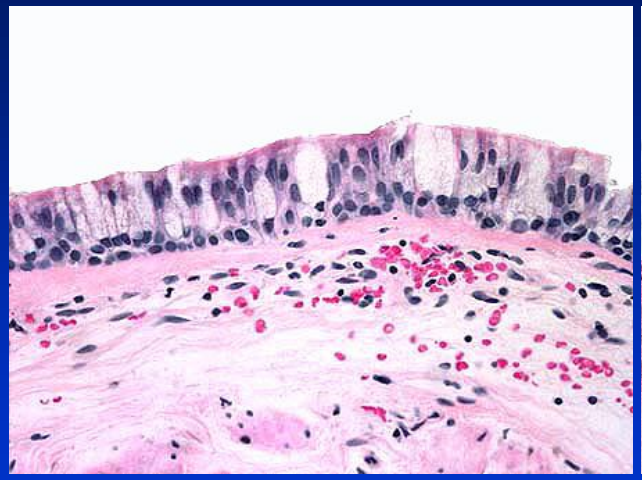
Bronchoscopy Sites



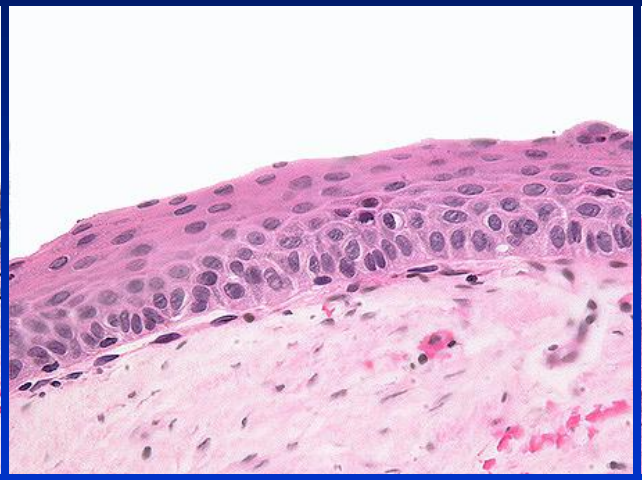


EDRN/NASA/JPL Stacy Scott Abrien Registry

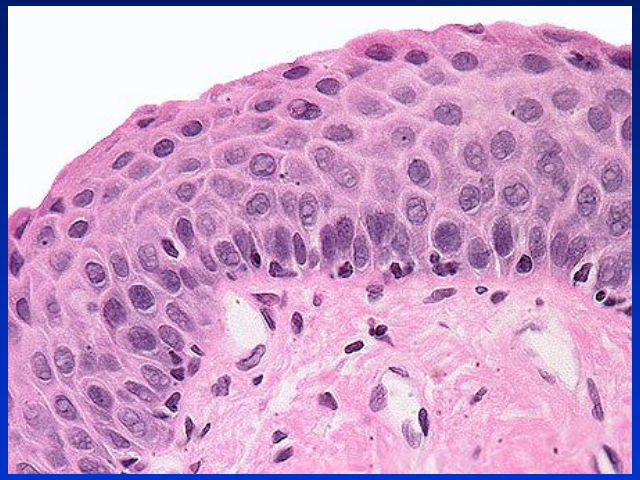
Histology of Bronchial Squamous Epithelium



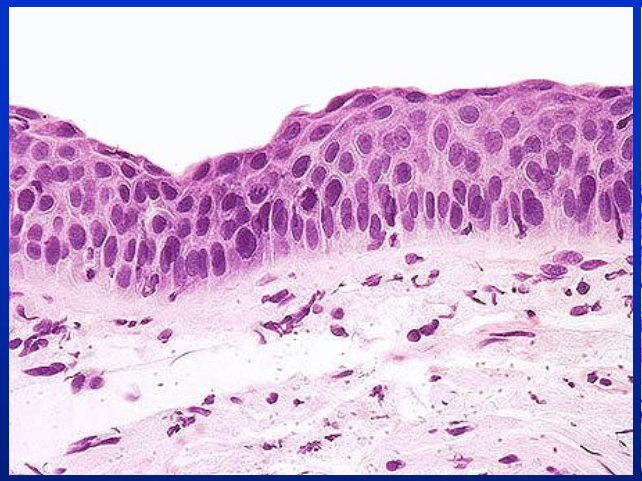
Normal
(Grade 1)



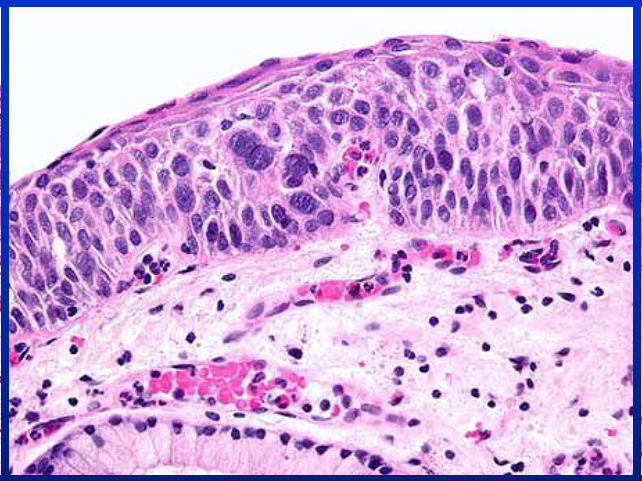
Squamous Metaplasia
(Grade 3)



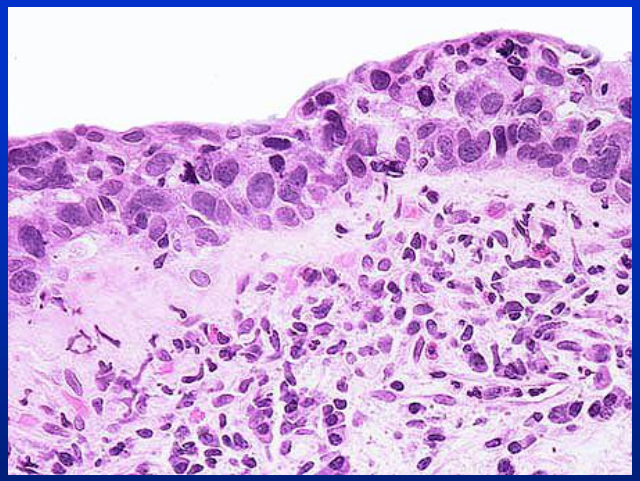
Mild Dysplasia
(Grade 4)
74% in baseline bronch



Moderate Dysplasia
(Grade 5)



Severe Dysplasia
(Grade 6)



Carcinoma *in situ*
(Grade 7)

SPORE Chemoprevention: Methods

Each bronchial biopsy specimen is scored by the WHO classification for preneoplasia:

Histology	Score
Normal	1
Hyperplasia	2
Metaplasia	3
Mild dysplasia	4
Moderate dysplasia	5
Severe dysplasia	6
Carcinoma in situ	7
Invasive cancer	8

Pathology Reproducibility

- Iloprost biopsies scored by a single pathologist (WAF)
- Separate test set of biopsies representing equal numbers of all WHO grades of squamous premalignancy assembled and read by two pathologists (WAF and DM)
- Reliability of WAF: Weighted kappa = 0.71 (0.65-0.77). 86% of biopsies within 1 grade.
- Agreement between WAF and DM: Weighted kappa = 0.66 (0.59-0.73). 84% of biopsies within 1 grade.

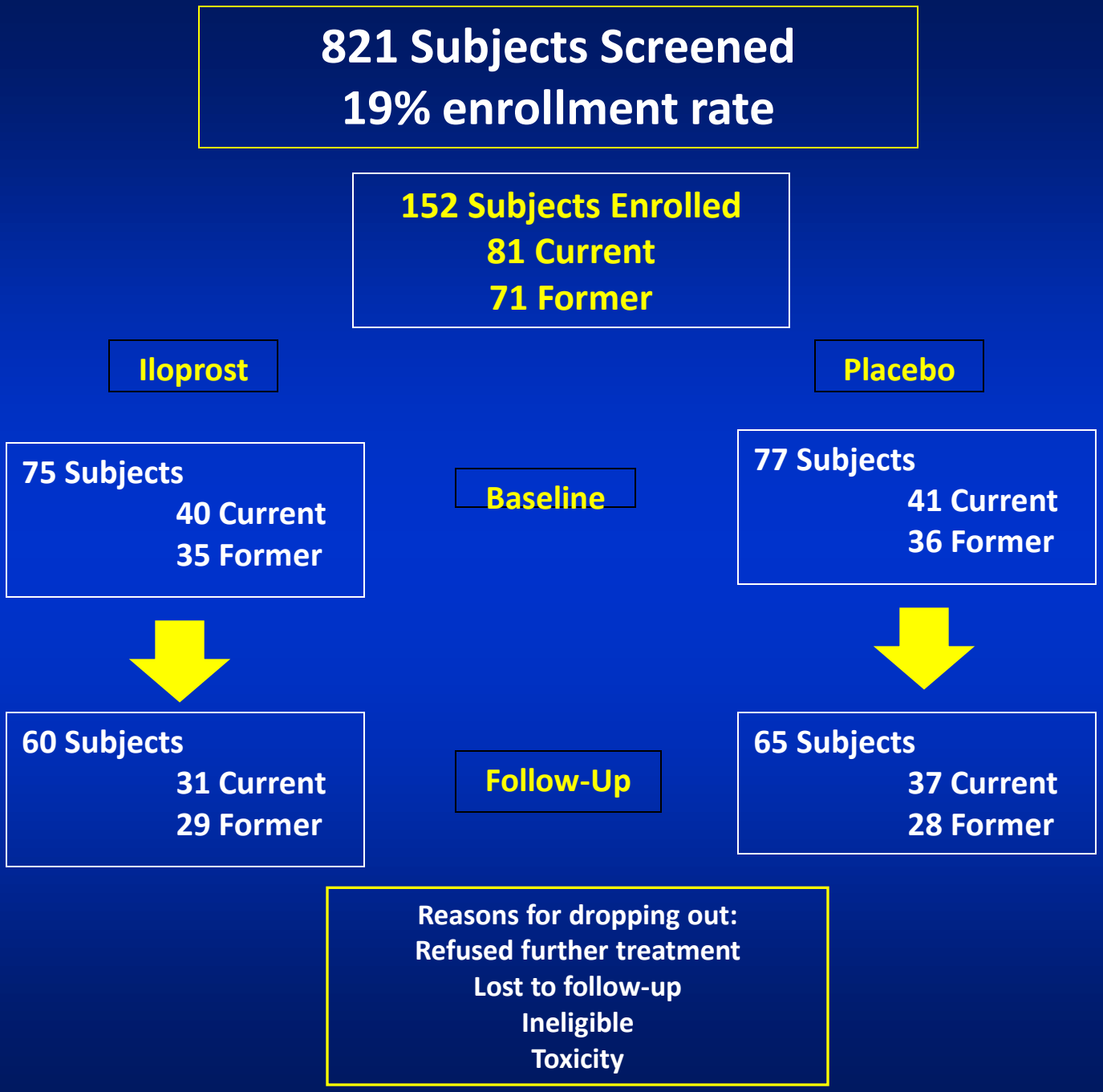

821 Subjects Screened
19% enrollment rate
152 Subjects Enrolled
81 Current
71 Former
Iloprost
Placebo
75 Subjects
40 Current
35 Former
Baseline
77 Subjects
41 Current
36 Former
60 Subjects
31 Current
29 Former
Follow-Up
65 Subjects
37 Current
28 Former
Reasons for dropping out:
Refused further treatment
Lost to follow-up
Ineligible
Toxicity

Table 1: Baseline characteristics[1]

	All Subjects		Former Smokers		Current Smokers	
	Iloprost (N = 75)	Placebo (N = 77)	Iloprost (N = 35)	Placebo (N = 36)	Iloprost (N = 40)	Placebo (N = 41)
Sex of Subject - No. (%)						
Female	23 (30.7)	19 (24.7)	8 (22.9)	9 (25.0)	15 (37.5)	10 (24.4)
Male	52 (69.3)	58 (75.3)	27 (77.1)	27 (75.0)	25 (62.5)	31 (75.6)
Race of Subject - No. (%)						
Black	4 (5.3)	8 (10.4)	0 (0.0)	3 (8.3)	4 (10.0)	5 (12.2)
Other	2 (2.7)	3 (3.9)	1 (2.9)	0 (0.0)	1 (2.5)	3 (7.3)
White	69 (92.0)	66 (85.7)	34 (97.1)	33 (91.7)	35 (87.5)	33 (80.5)
Age (Years)	57.6 ± 10.6	58.3 ± 8.6	61.5 ± 10.7	61.2 ± 9.6	54.2 ± 9.2	55.7 ± 6.8
Smoker Years	34.2 ± 11.2	36.0 ± 10.0	31.4 ± 11.5	32.9 ± 10.4	36.6 ± 10.5	38.7 ± 9.0
Packs per Day	1.5 ± 0.7	1.4 ± 0.5	1.7 ± 0.8	1.4 ± 0.5	1.3 ± 0.4	1.3 ± 0.6
Pack Years	51.4 ± 27.3	49.8 ± 26.4	55.5 ± 30.8	48.6 ± 27.1	47.8 ± 23.7	50.9 ± 26.0
FEV1	2.8 ± 3.6	4.0 ± 10.6	3.3 ± 5.3	3.9 ± 9.7	2.5 ± 0.9	4.2 ± 11.5
FEV/FVC Ratio	62.3 ± 24.0	61.7 ± 25.8	67.0 ± 16.6	65.2 ± 24.6	58.1 ± 28.6	58.6 ± 26.7
Sputum Cytology	4.4 ± 0.7	4.4 ± 0.6	4.4 ± 0.6	4.3 ± 0.5	4.4 ± 0.8	4.5 ± 0.7
Average Histology	2.6 ± 1.1	2.5 ± 1.1	2.1 ± 1.0	2.0 ± 1.1	3.0 ± 1.1	2.9 ± 0.9
Maximum	4.3 ± 1.5	3.8 ± 1.6	3.6 ± 1.8	3.1 ± 1.8	4.8 ± 0.9	4.5 ± 1.1
Dysplasia Index	33.3 ± 28.7	32.8 ± 31.1	20.4 ± 22.2	21.3 ± 28.5	44.6 ± 29.2	42.8 ± 30.1

[1] Mean $\pm$ SD.

Dysplasia

Per subject:

Baseline dysplasia incidence (at least one bx $\geq$ 4) :

Placebo 54/77 – 70%

Iloprost 59/75 – 79%

To date, no lung cancer cases in this cohort

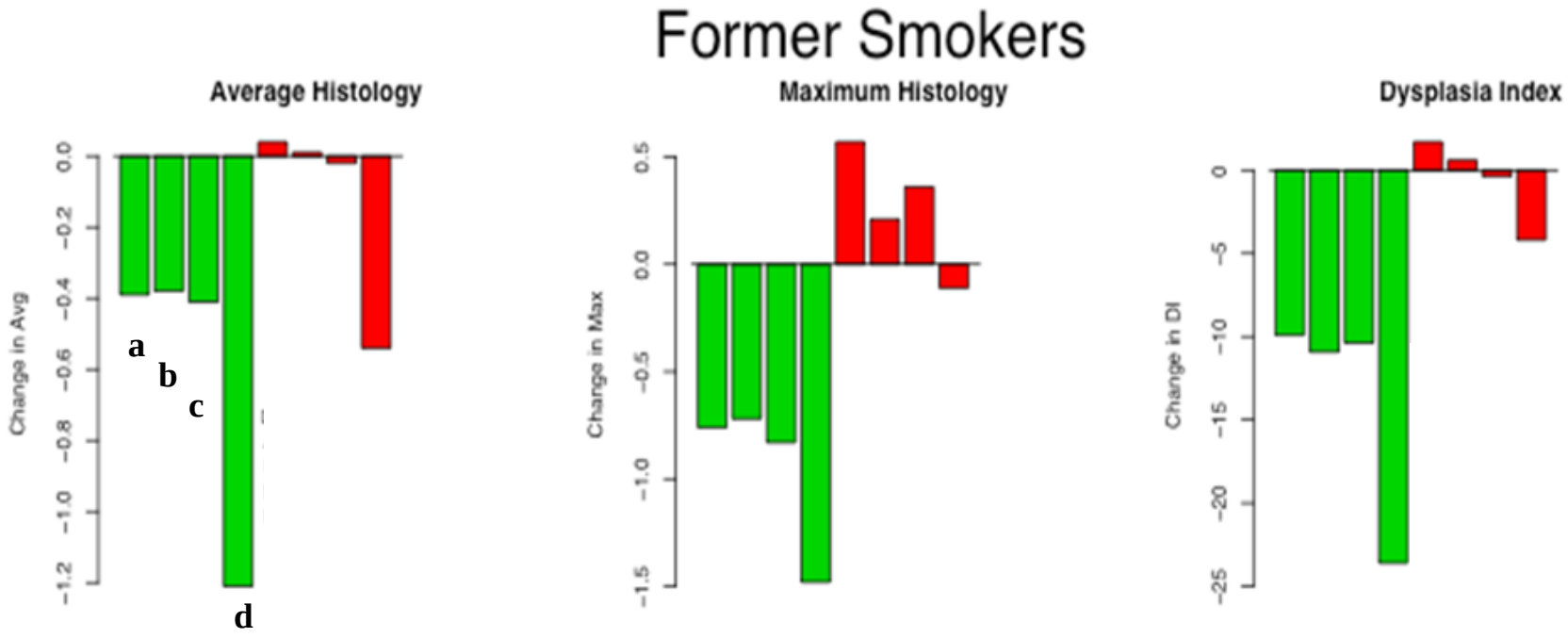
Iloprost Chemoprevention Trial: Primary Results

Table 2: Treatment effect on bronchial histology

	Iloprost			Placebo			Treatment Effect[1]		
	Baseline	6-month	Change	Baseline	6-month	Change	Difference	(95% CI)	P-Value
All Completers									
Average	2.64	2.41	-0.23	2.56	2.54	-0.02	-0.15	(-0.39, 0.09)	0.21
Worst	4.25	3.85	-0.40	3.91	4.14	0.23	-0.43	(-0.84, -0.03)	0.038
Dysplasia Index	35.0	27.3	-7.70	34.2	33.3	-0.92	-5.97	(-13.3, 1.33)	0.11
Response Proportion[2]	24/60 (0.40)			13/65 (0.20)			0.20	(0.04, 0.36)	0.014
Former Smokers									
Average	2.12	1.73	-0.39	2.07	2.11	0.04	-0.41	(-0.71, -0.11)	0.010
Worst	3.59	2.83	-0.76	3.11	3.68	0.57	-1.10	(-1.76, -0.45)	0.002
Dysplasia Index	20.8	10.9	-9.91	22.9	24.6	1.70	-12.4	(-21.0, -3.92)	0.006
Response Proportion[2]	14/29 (0.48)			4/28 (0.14)			0.34	(0.10, 0.58)	0.006
Current Smokers									
Average	3.13	3.05	-0.07	2.93	2.87	-0.06	0.06	(-0.30, 0.42)	0.74
Worst	4.87	4.81	-0.06	4.51	4.49	-0.03	0.12	(-0.36, 0.60)	0.62
Dysplasia Index	48.2	42.6	-5.64	42.8	39.9	-2.90	-0.33	(-11.7, 11.0)	0.96
Response Proportion[2]	10/31 (0.32)			9/37 (0.24)			0.08	(-0.13, 0.29)	0.47

- Response defined as $\geq$1 point reduction in maximum histology (similar magnitude of change as seen comparing current to former)

Iloprost Chemoprevention Trial: Primary Results



a: all sites
b: reference sites
c: matched sites
d: non-normal sites

Iloprost
Placebo

Iloprost Chemoprevention Trial: Adverse Events

Adverse Event	Iloprost (N = 75)	Placebo (N = 77)
Most Common Adverse Events		
Headache	40	17
Flushing	18	6
Nausea	12	6
Pain-Other	12	6
Myalgia	13	1
Fatigue	8	2
Metabolic/Laboratory-Other	3	6
Neuropathic pain	7	1
Severe Adverse Events[1]		
Hypoxia	0	1
Pulmonary fibrosis	0	1
Neuropathy - cranial	0	1
Musculoskeletal-Other	1	2
SGOT (AST)	2	1
Cardiovascular/General-Other	1	3
Hypophosphatemia	2	2
Chest pain	3	2

- Iloprost subjects did have S-E associated with vasodilator use.

Conclusions

- Our enrollment criteria identified subjects with dysplasia and oral iloprost was well tolerated
- No treatment effect was seen in current smokers
- Oral iloprost improves endobronchial dysplasia in former smokers when analyzed by Average score, Worst score, and Dysplasia Index
- Worst score improved in similar magnitude to the difference between current and former smokers
- Iloprost should be strongly considered for a Phase III chemoprevention trial

UCCC Contributors

- **Pulmonary**
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  - York Miller
  - Tim Kennedy
  - Mark Geraci
- **Pathology**
  - Wilbur Franklin
  - Fred Hirsch
  - Dan Merrick
- **Medical Oncology**
  - Paul Bunn
  - Karen Kelly
- **Basic Science**
  - Rafe Nemenoff
  - Al Malkinson
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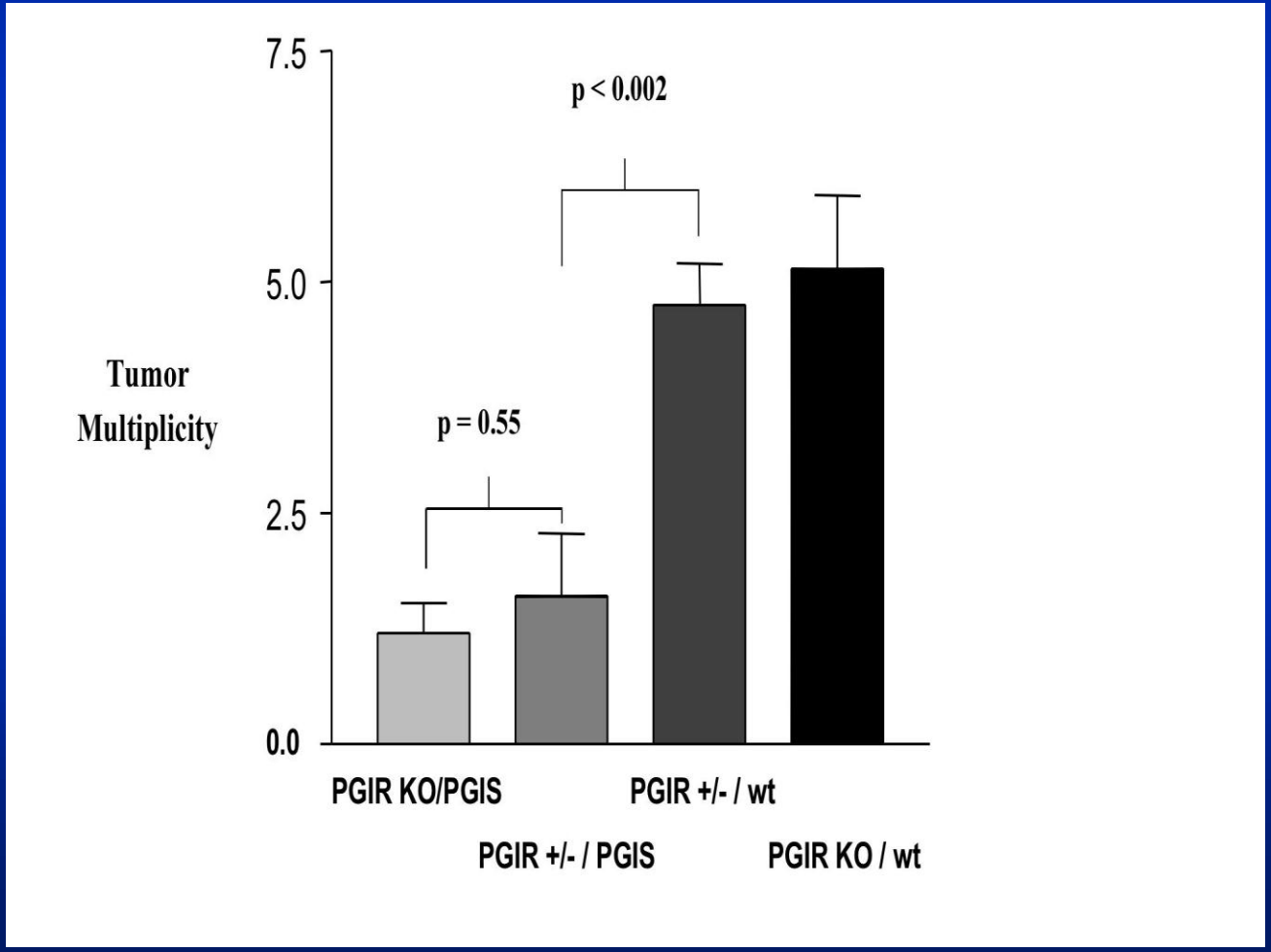
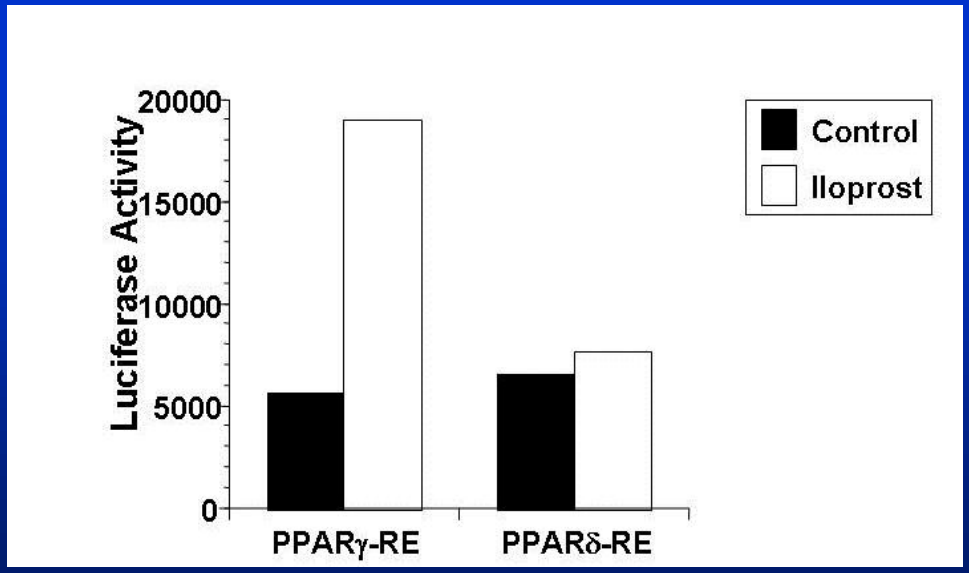
Mechanisms of Prostacyclin Activity

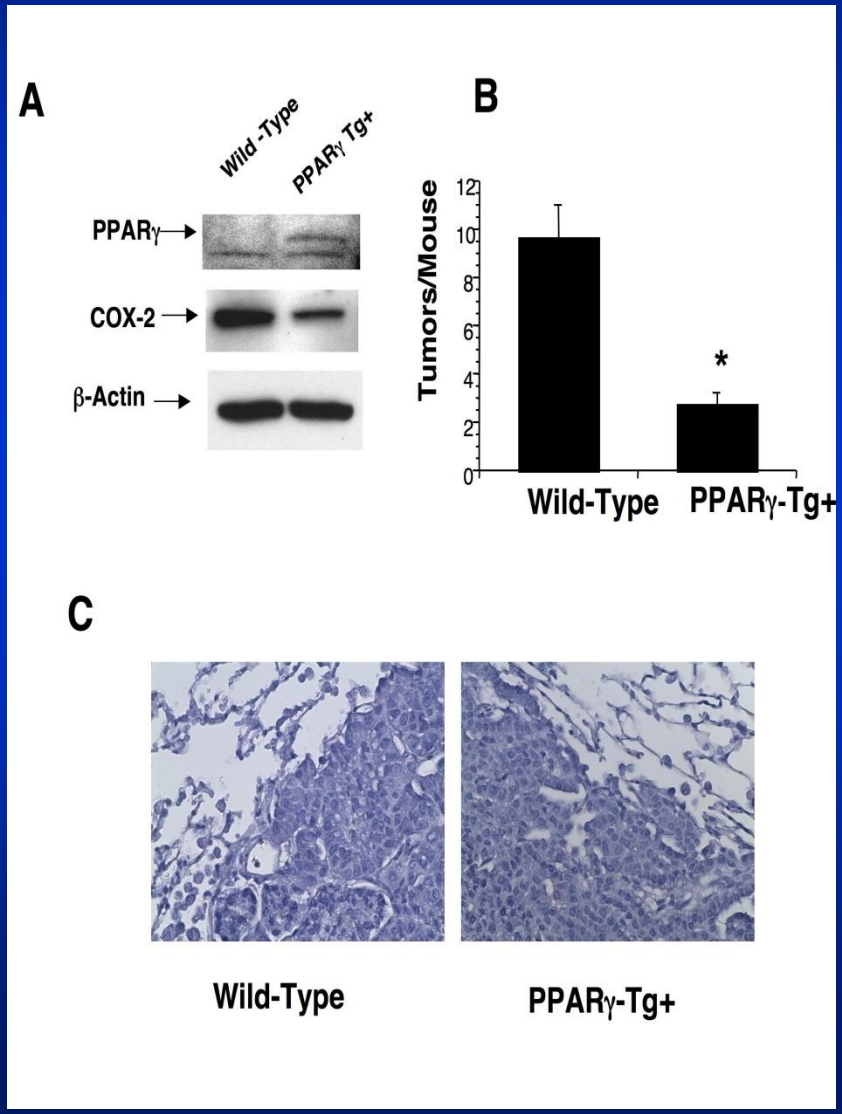
- G-protein coupled membrane receptor (IP)
- Peroxisome proliferator nuclear receptor—PPAR gamma
- PGIS overexpression is equally effective in both IP null and wildtype mice

Protective effects of PGIS are not mediated by cell surface PGIR



Iloprost, PPAR gamma activation and chemoprevention





Relative Risk of Cancer in TZD use

Table 2. Relative Risk of Cancer Development Among Diabetics Treated With TZD

Cancer Diagnosis	Unadjusted				Race/Ethnicity and Age Adjusted*			Covariate Adjusted†			
	Events	HR	*P*	95% CI	HR	*P*	95% CI	Events	HR	*P*	95% CI
Colorectal	1,137	0.90	.33	0.74 to 1.11	0.91	.35	0.74 to 1.11	999	0.88	.16	0.74 to 1.05
Prostate	3,246	0.95	.43	0.84 to 1.07	0.98	.70	0.86 to 1.10	2,849	0.86	.99	0.64 to 1.14
Lung	1,371	0.71	.0009	0.58 to 0.87	0.71	.0012	0.58 to 0.88	1,110	0.67	.0033	0.51 to 0.87

NOTE. The incidence of lung, colorectal, and prostate cancers among diabetic patients using TZD compared with those not using TZD. *P* values are not adjusted for multiple comparisons, so as not to inflate type II error.
Abbreviations: TZD, thiazolidinedione; HR, hazard ratio.
*Adjusted for age and race/ethnicity. The patient denominator for this and the unadjusted analysis was 87,678.
†Adjusted for age, race/ethnicity, body mass index, hemoglobin A_1C, insulin, other oral agents, and drug-drug interactions. The patient denominator for this analysis was 72,323.

Table 3. TZD Use and Cancer Risk Stratified by Race/Ethnicity in Men With Diabetes

Cancer Diagnosis	Unadjusted				Covariate Adjusted*			
	Events	HR	*P*	95% CI	Events	HR	*P*	95% CI
White	50,937†				42,596‡			
Colorectal	748	0.94	.62	0.74 to 1.20	659	0.98	.85	0.80 to 1.21
Prostate	1,881	1.01	.90	0.87 to 1.18	1,659	1.15	.027	1.02 to 1.31
Lung	934	0.72	.0068	0.57 to 0.91	774	0.74	.019	0.58 to 0.95
African American	14,199†				11,666‡			
Colorectal	211	0.75	.36	0.41 to 1.39	195	0.53	.027	0.31 to 0.93
Prostate	718	0.99	.95	0.73 to 1.34	622	1.18	.16	0.94 to 1.50
Lung	260	0.26	.0028	0.11 to 0.63	196	0.38	.034	0.15 to 0.93

NOTE. *P* values are not adjusted for multiple comparisons, so as not to inflate type II error.
Abbreviations: TZD, thiazolidinedione; HR, hazard ratio.
*Adjusted for age, body mass index, hemoglobin A_1C, insulin, and other oral agents.
†Patient denominators for the unadjusted analyses by race/ethnicity.
‡Patient denominators for the covariate-adjusted analyses by race/ethnicity.