



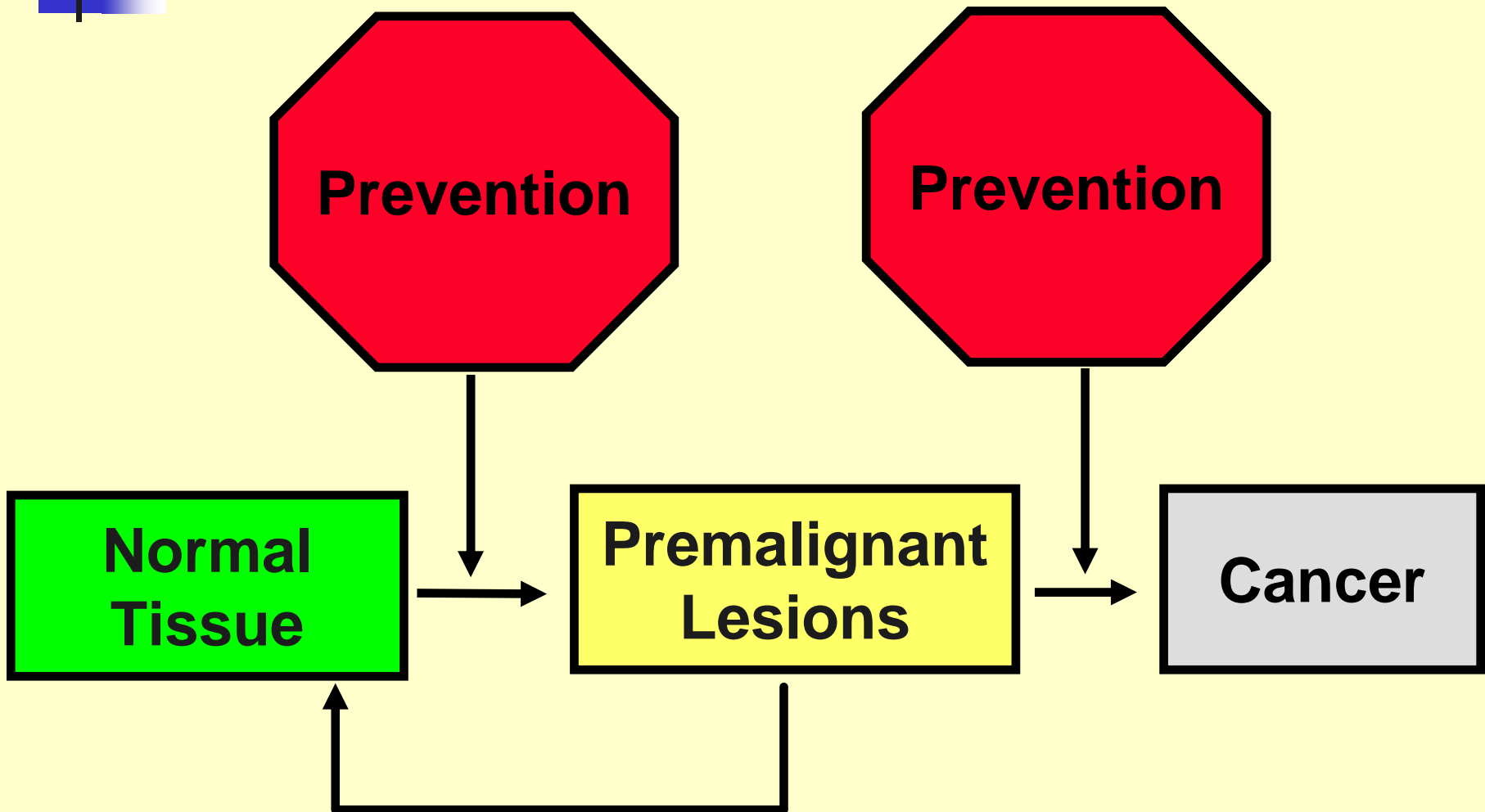
*Strategies for the Early Detection
and Prevention of Cancer
in Mouse Models*

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Director of Chemoprevention Research*

FOX CHASE
CANCER CENTER

Chemoprevention

Use of substances to delay the onset of cancer or inhibit tumor formation.



Cancer Chemoprevention



Molecular Basis of
Cancer Risk

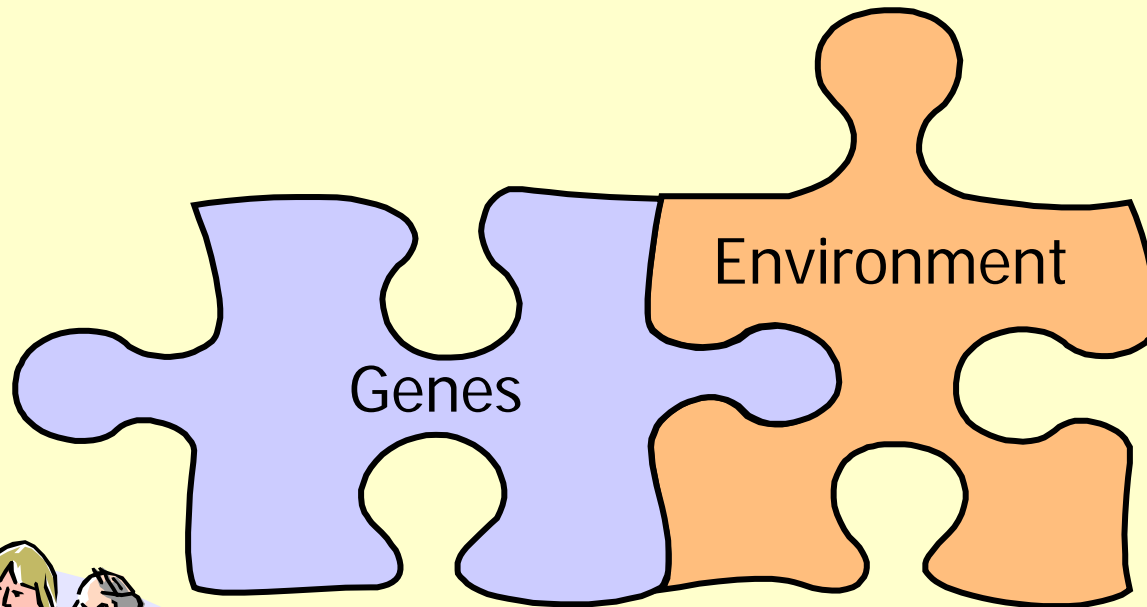
Early Detection
of Cancer

Promising Agents and
their Mechanisms

Therapies for Individuals at Increased Risk for Cancer



Molecular Basis of Cancer Risk



Lung Cancer in Women

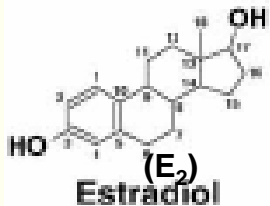
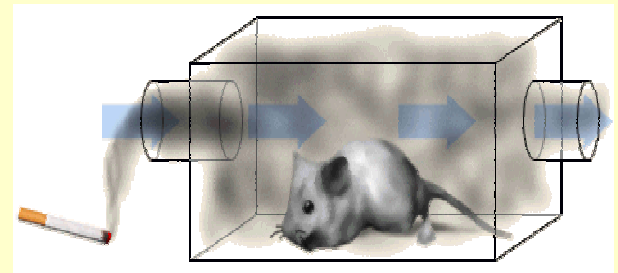
Lung Cancer

- Leading cause of cancer-related death in women
- Majority of nonsmokers who develop lung cancer are women

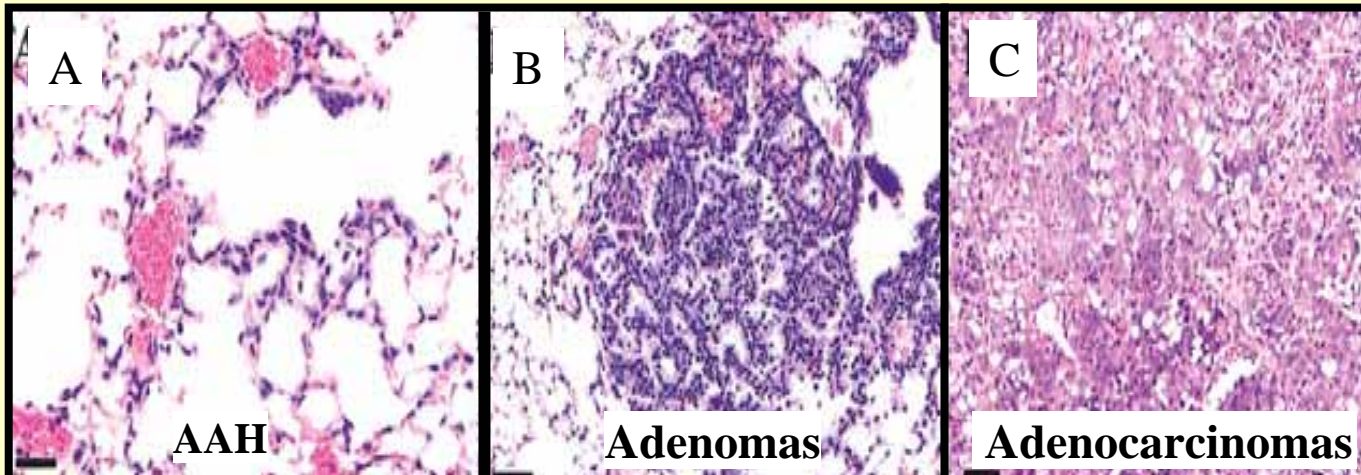
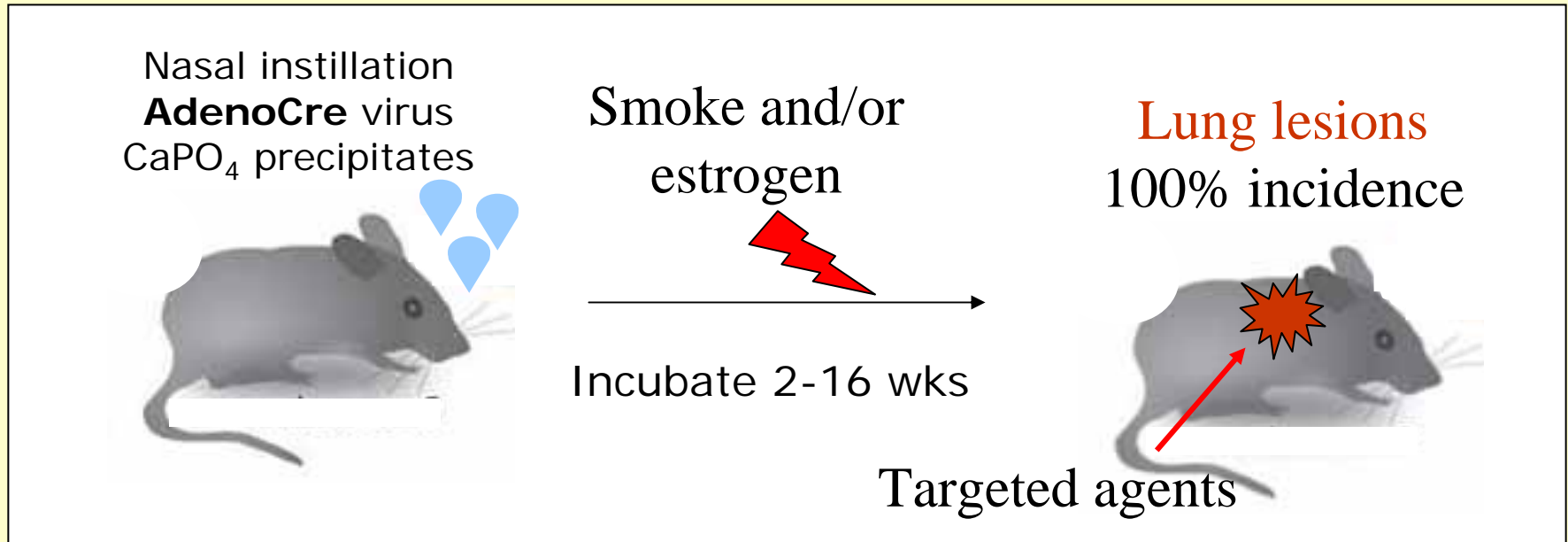
Risk Assessment Program

- Tobacco Smoke Exposure
- Hormonal Treatment
- Gene-gene and gene-environment interactions
- Incidence of primary breast and lung cancer

DNA adducts
and oxidative
damage



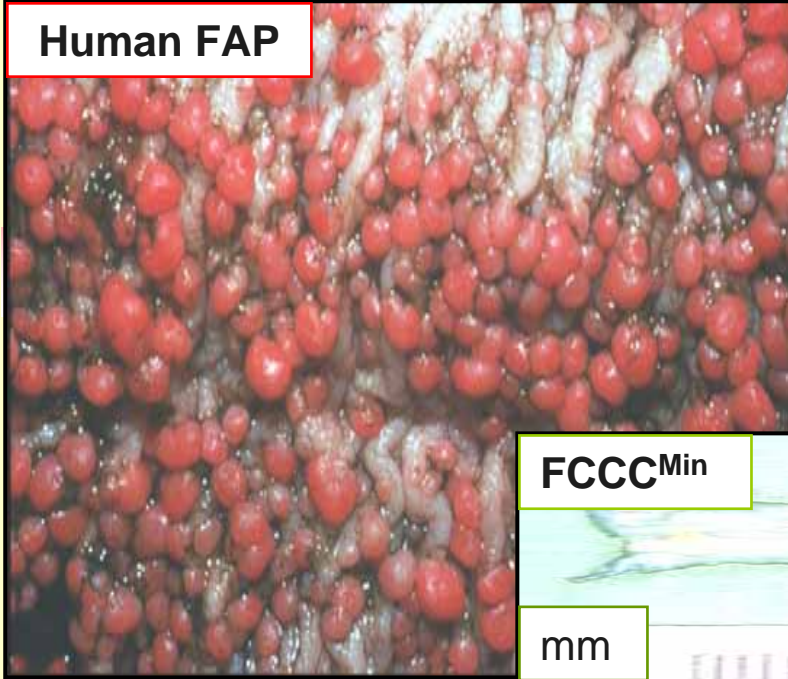
LSL-G12D K-ras Model of Lung Cancer





*Imaging Strategies for
the Early Detection of Cancer*

Human FAP

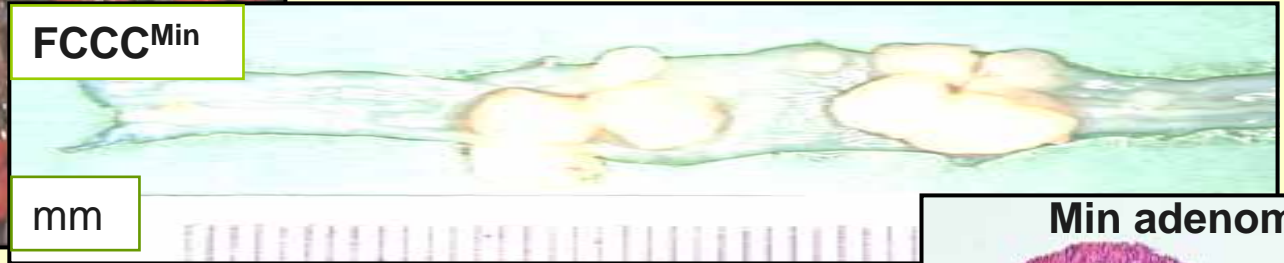


FCCC APC^{Min/+} Mice Develop Colonic Adenomas Spontaneously

(C57BL/6J *Apc^{Min/+}* x C57BL/6J *Apc^{+/+}*)

FCCC^{Min}

mm



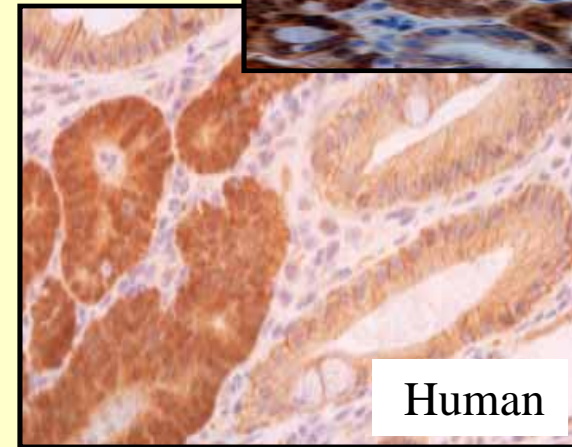
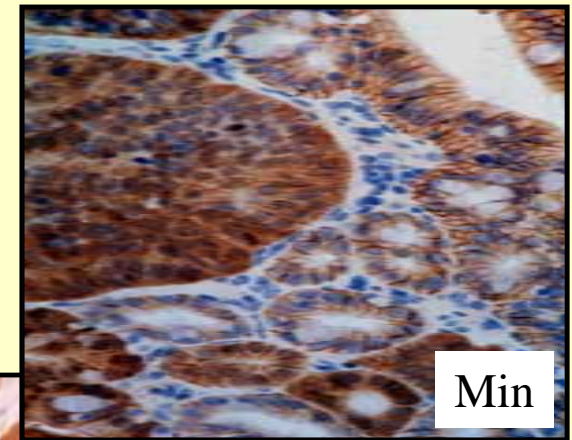
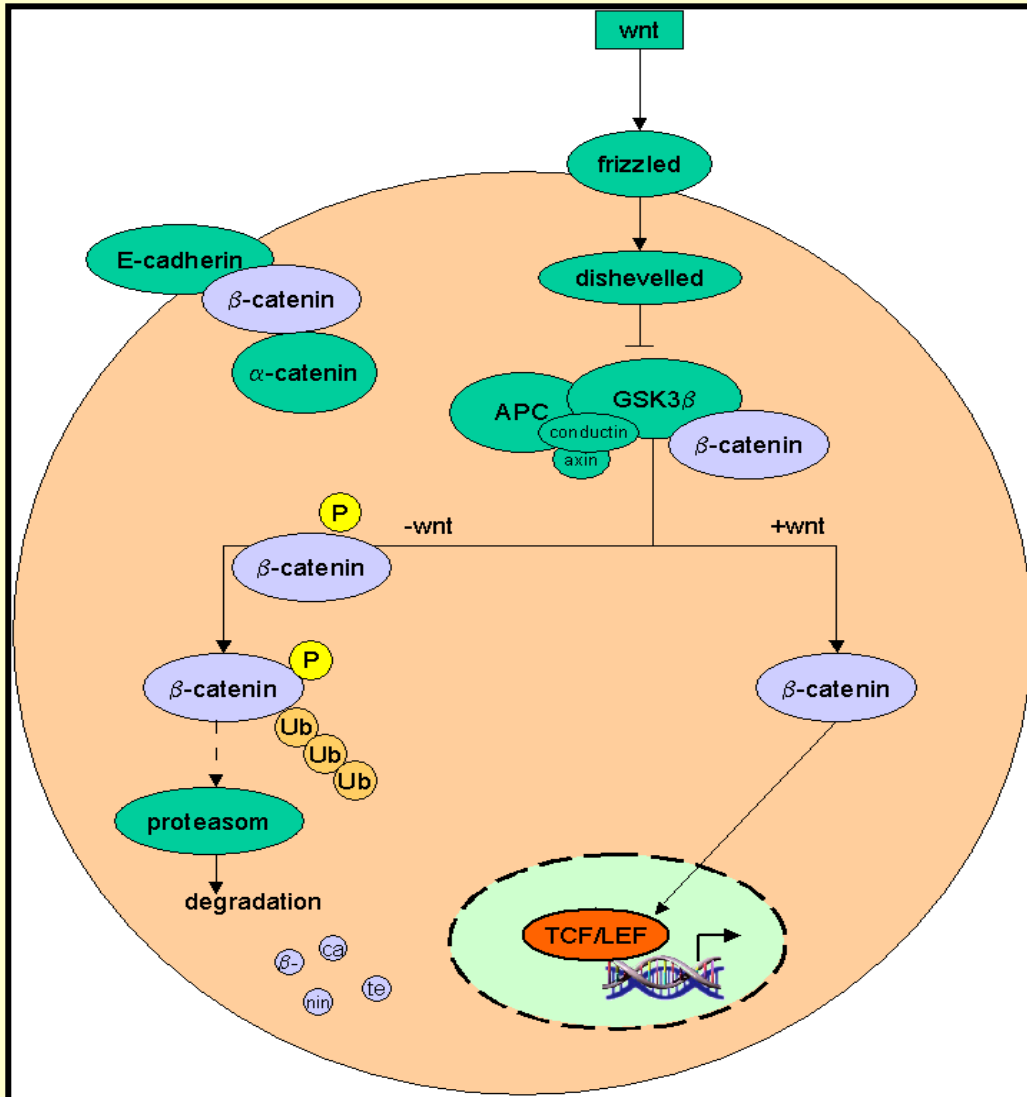
Min adenoma



- Multiple colon adenomas per mouse
- Small intestinal phenotype is maintained
- Gender difference in the multiplicity of colon adenomas
- Extended life span – 180 days

Opportunity for early intervention in adenoma formation

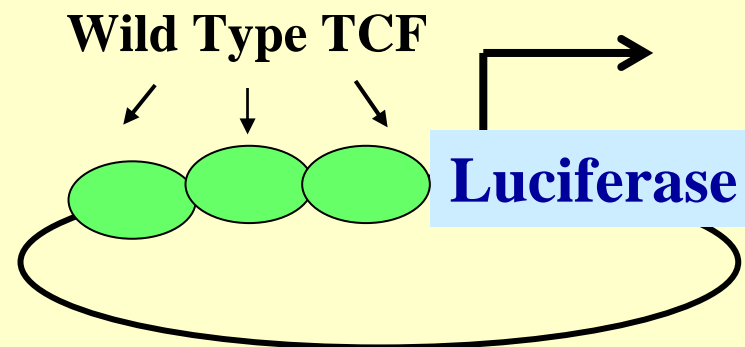
Tcf-Mediated β -catenin Signaling



Target Genes Elevated
(>10-fold) in Min Adenomas

MMP7
PTGS-2
CDKN2A (p16)

*FCCC Apc^{Min/+} Mice
Bearing a
TCF Luciferase Reporter*



BAT-Luc2 (B6(Cg)-Tyr^{c-2J}/J) X FCCC Apc^{Min/+} /B6(Cg)-Tyr^{c-2J}/J



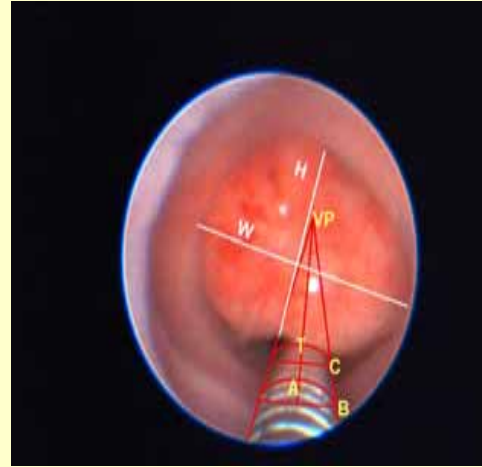
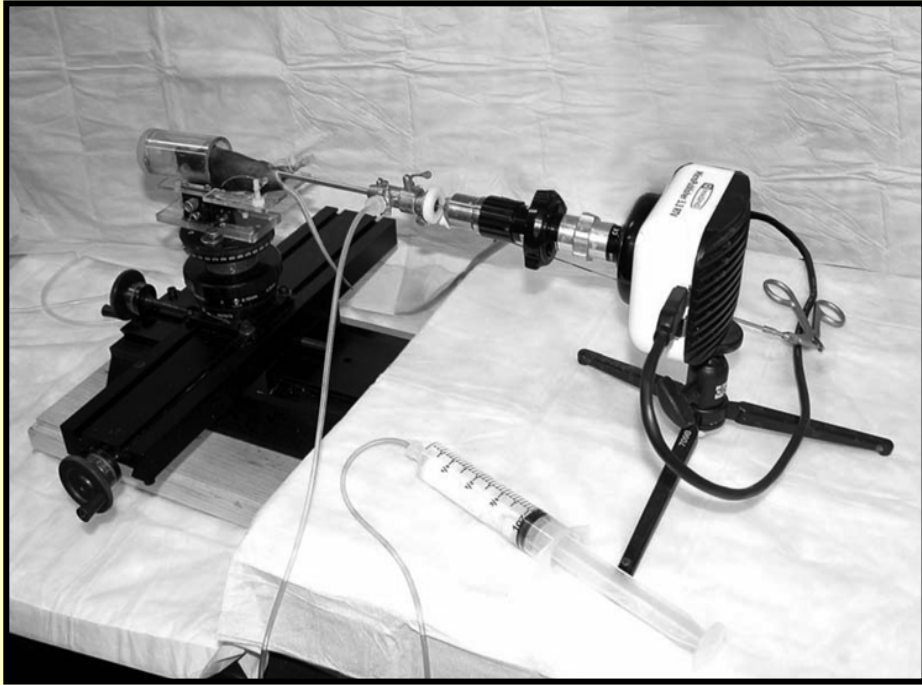
BAT-Luc2/ Apc^{Min/+}

Produced by Caliper Life Sciences

Goals

- Develop a sensitive method for monitoring β -catenin signaling in individual lesions.
- Establish the time course of TCF-mediated β -catenin signaling *in vivo* during tumor formation.
- Identify agents that disrupt TCF-mediated β -catenin signaling and assess their chemopreventive activity *in vivo*.

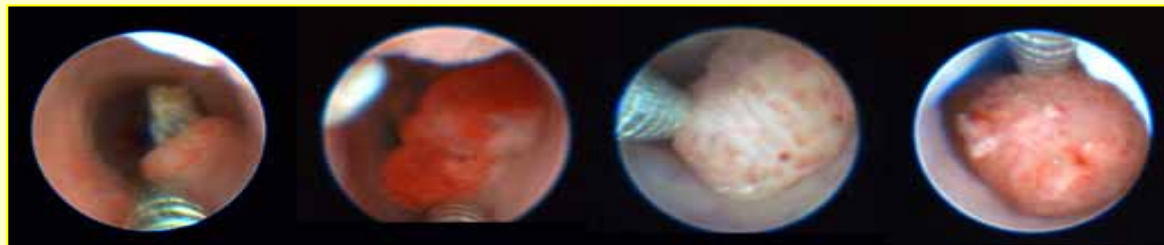
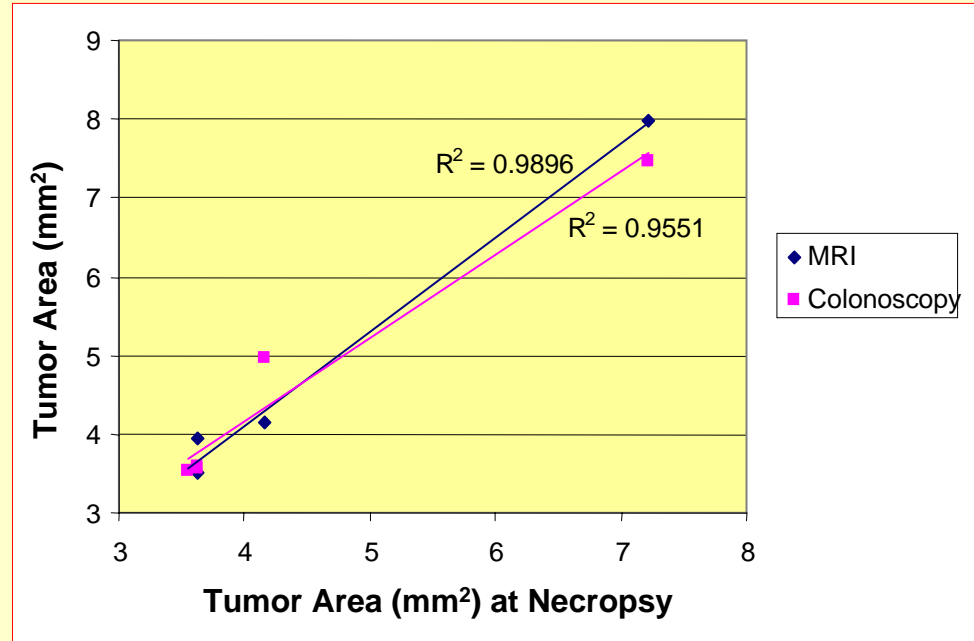
Endoscopic Quantitation of Lesion Size



$$\text{Area} = (W \times L)\pi/4$$

- Circumvents the need to sacrifice an animal to obtain biological information.
- Allows one to monitor the same tumor over time *in vivo*.
- Provides an opportunity to correlate the genetic changes in a tumor with its growth pattern.

Image Analysis of Colon Tumors Over Time



Week	0	2	4	6
Tumor Area (mm ²)	1.2	4.5	6.5	6.1 mm ²

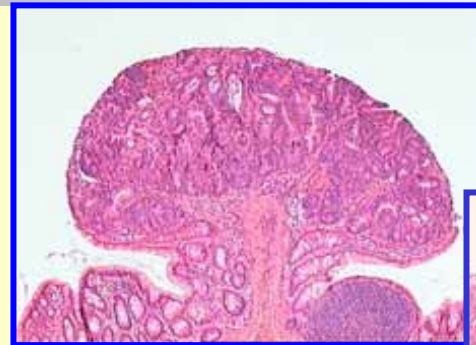


*Development of Therapies for the
Prevention of Cancer*

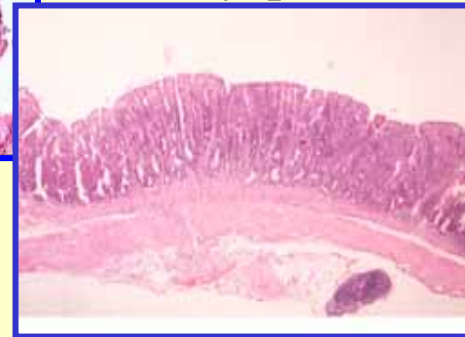
Mouse Model of Dextran Sulfate Sodium - Induced Colitis

- Histology resembles that of human dysplasias and cancers.

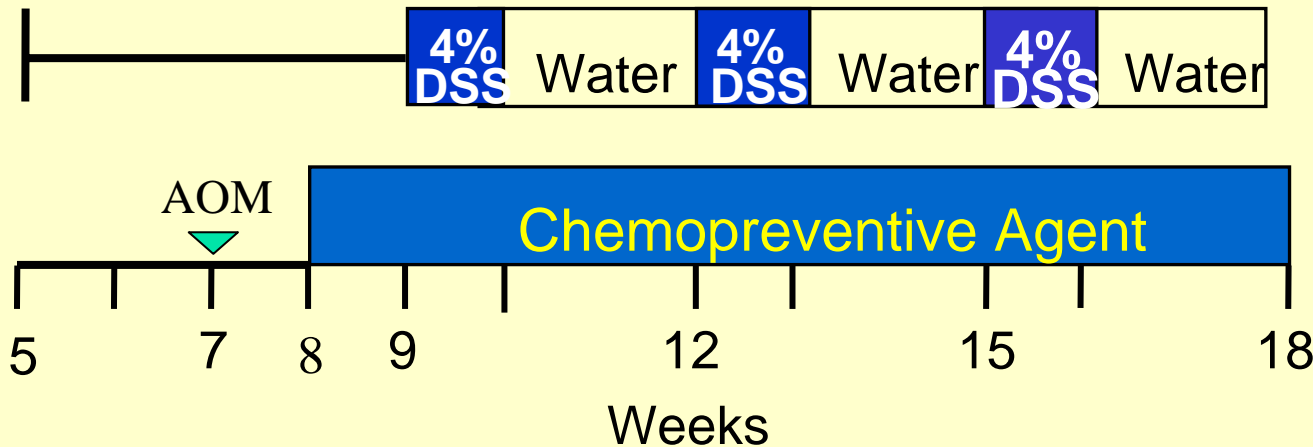
- Inflammation plays a significant role in the progression of lesions.



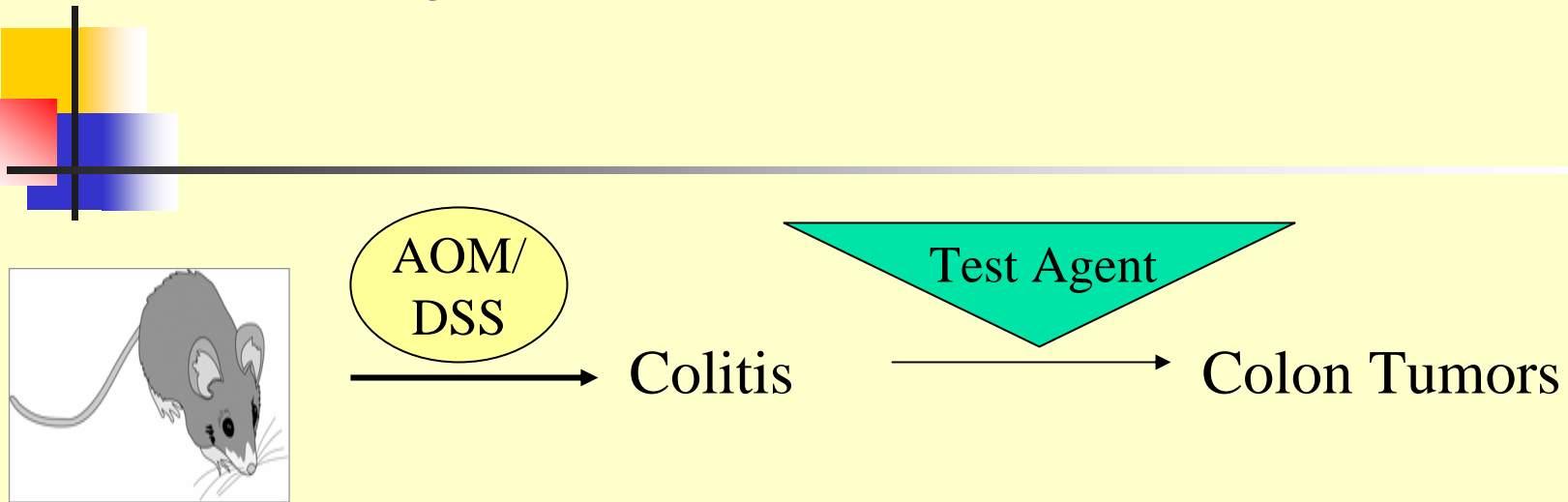
Polypoid dysplasia



Flat dysplasia



Inhibition of Colitis-associated Colon Tumors



- 5-Aminosalicylic Acid

Gold standard treatment for the symptoms of colitis

Decreases the formation of tumors by 50% (*Clapper et al. IBD, in press*)

- Celecoxib (Celebrex)

Anti-inflammatory agent used for arthritis

Decreases the formation of tumors by 50%

- Oltipraz

Synthetic antioxidant similar to those found in broccoli

Prevents the formation of all cancers.

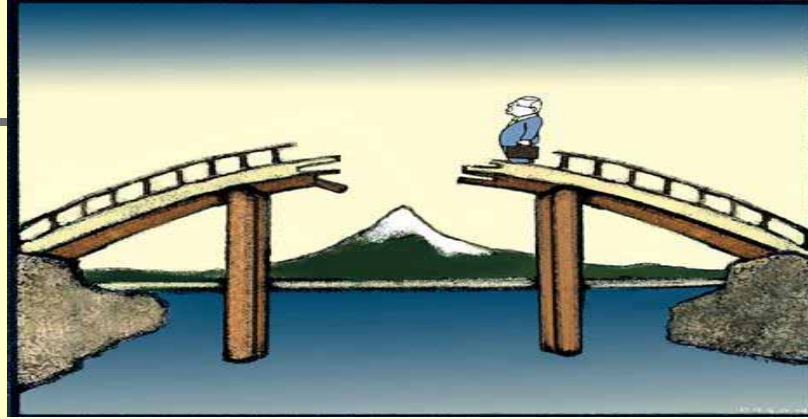


Collaborators

- Prime contractor – Preclinical Efficacy and Intermediate Endpoint Assays, Division of Cancer Prevention, NCI
- Member – NCI consortium at the Mayo Clinic for Phase I/II Clinical Trials of Cancer Chemoprevention Agents
- Preclinical/clinical testing site – Molecular Libraries Screening Center, University of Alabama
- Preclinical testing site – Hormel Institute/Mayo Clinic Translational Research Center

Personalized Cancer Risk and Prevention

Keystone Program



Cancer Risk
Assessment Program
(110,000 individuals)

Preclinical
Chemoprevention
Research

Breast/Ovary
Melanoma
Gastrointestinal
Prostate
Lung/Head and Neck*

Mouse Models
Imaging
Biomarker Identification
Human Tissue Analyses
Drug Development

* Being Established

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