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Targeting the cGMP Pathway to Treat Colorectal Cancer

Giovanni Mario Pitari

Thomas Jefferson University, gmpitari@gmail.com

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Targeting the cGMP Pathway to Treat Colorectal Cancer

GianMario Pitari, M.D., Ph.D.

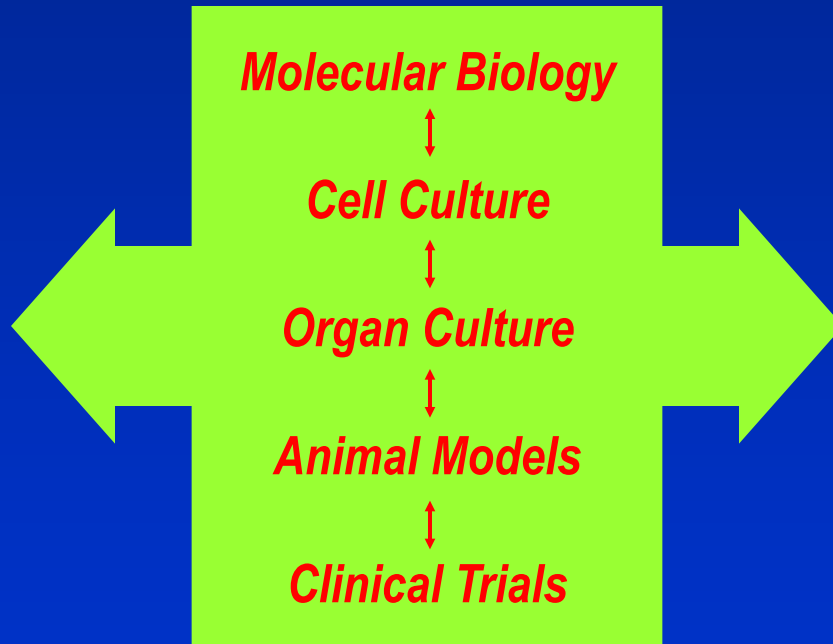
***Department of Pharmacology and
Experimental Therapeutics***

Thomas Jefferson University

Philadelphia, PA 19107

Translational Medicine

Laboratory



Clinic

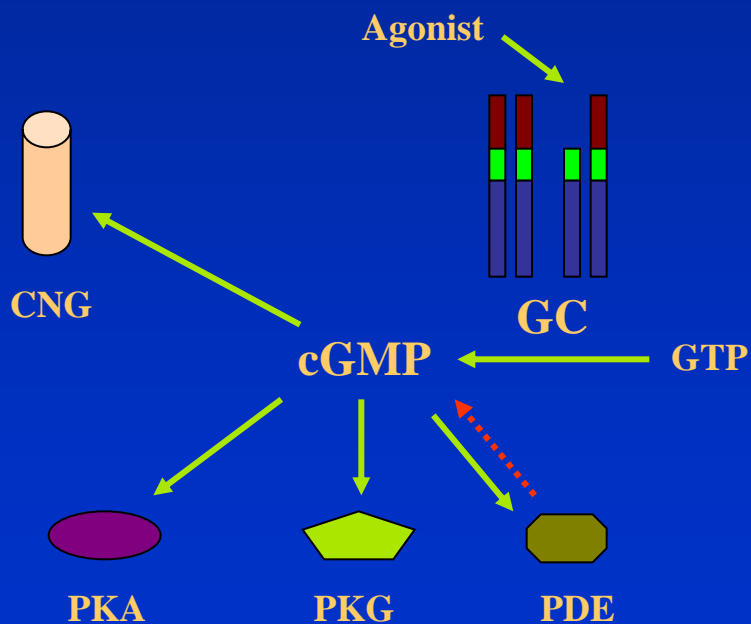
Translational Research Project: from the cGMP Pathway to Colorectal Cancer

Targeting Strategies:

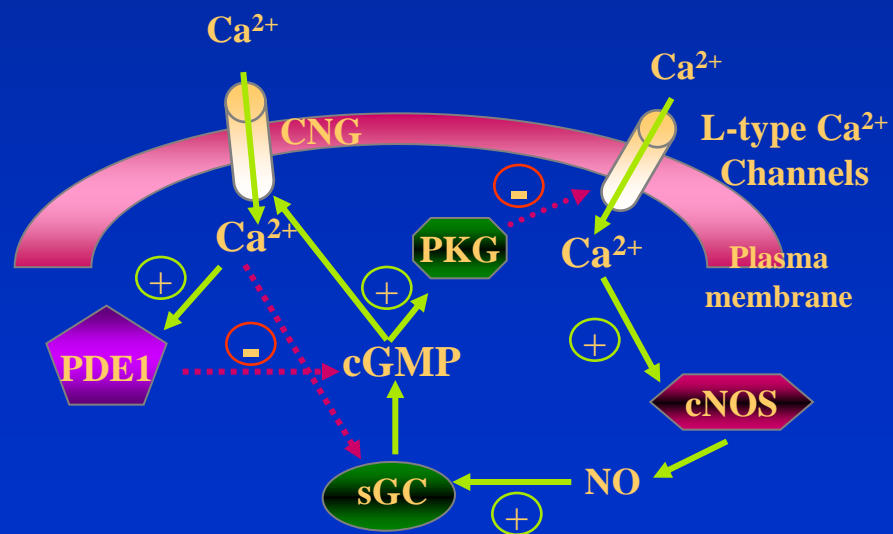
- 1. Cyclic GMP-Dependent Pathway as a Tumor Suppressor System to Prevent Colorectal Tumorigenesis**
- 2. Cyclic GMP-Dependent Pathway as an Antimetastatic Strategy to Disrupt Colorectal Cancer Metastatic Progression**

Cyclic GMP Signaling

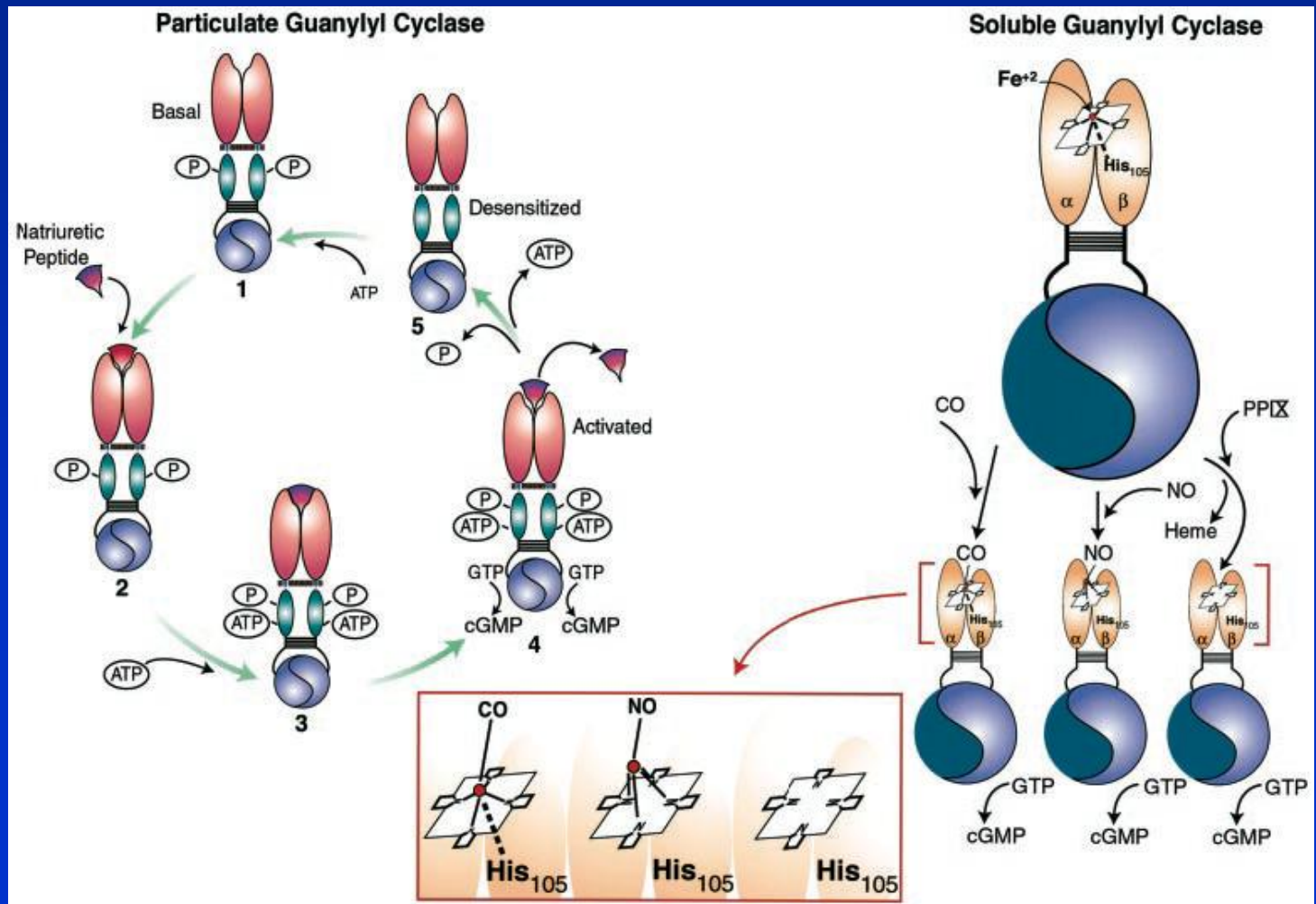
General Model for cGMP Signaling



Pituitary Cells

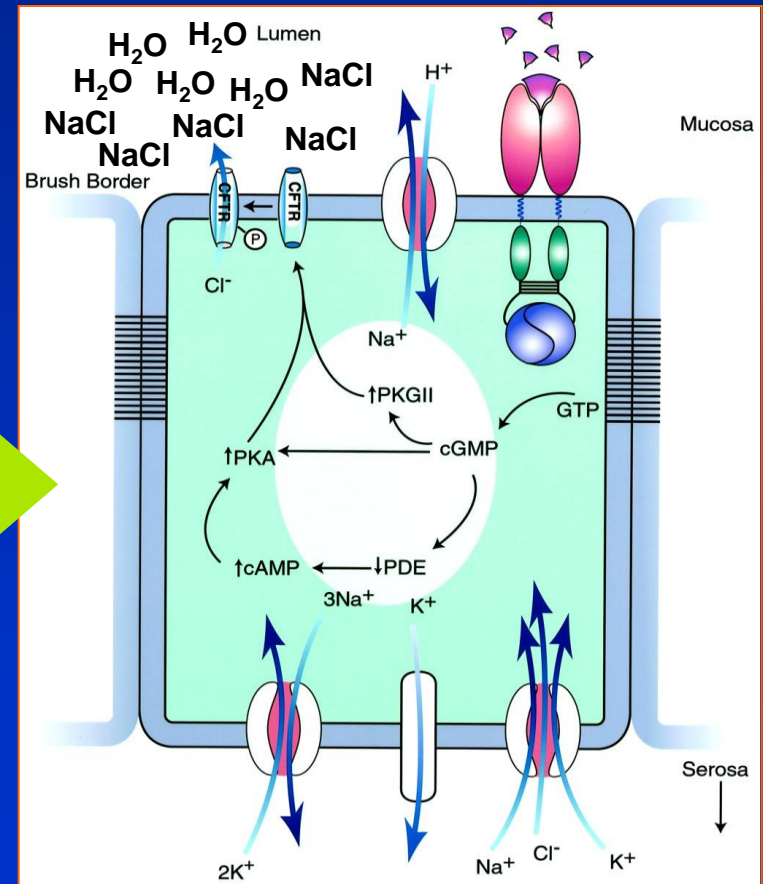
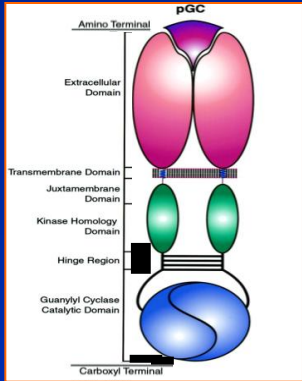


Guanylyl Cyclases

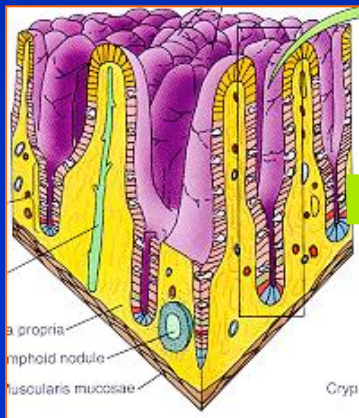


Guanylyl Cyclase C (GCC)

GCC is selectively expressed at brush-border membranes of intestinal epithelial cells and regulates fluid homeostasis



Lucas, et al. (2000) Pharmacol. Rev. 52: 375-413

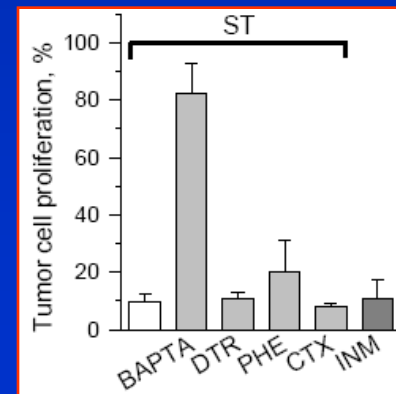
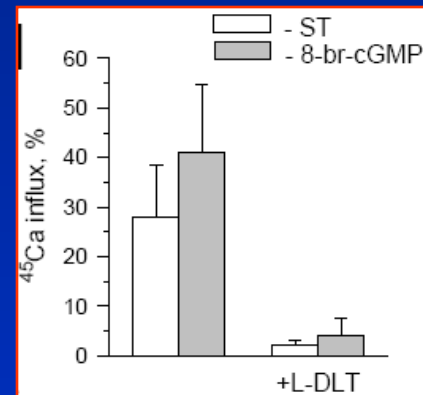
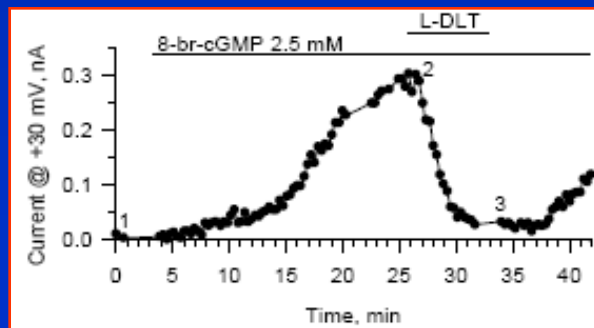
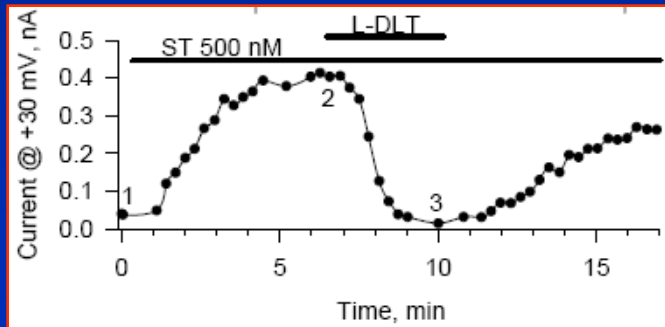
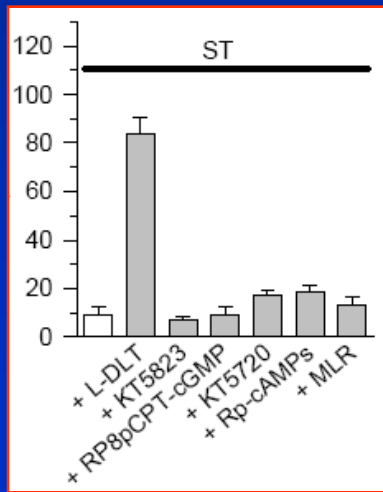


Crypt and Villus Enterocytes

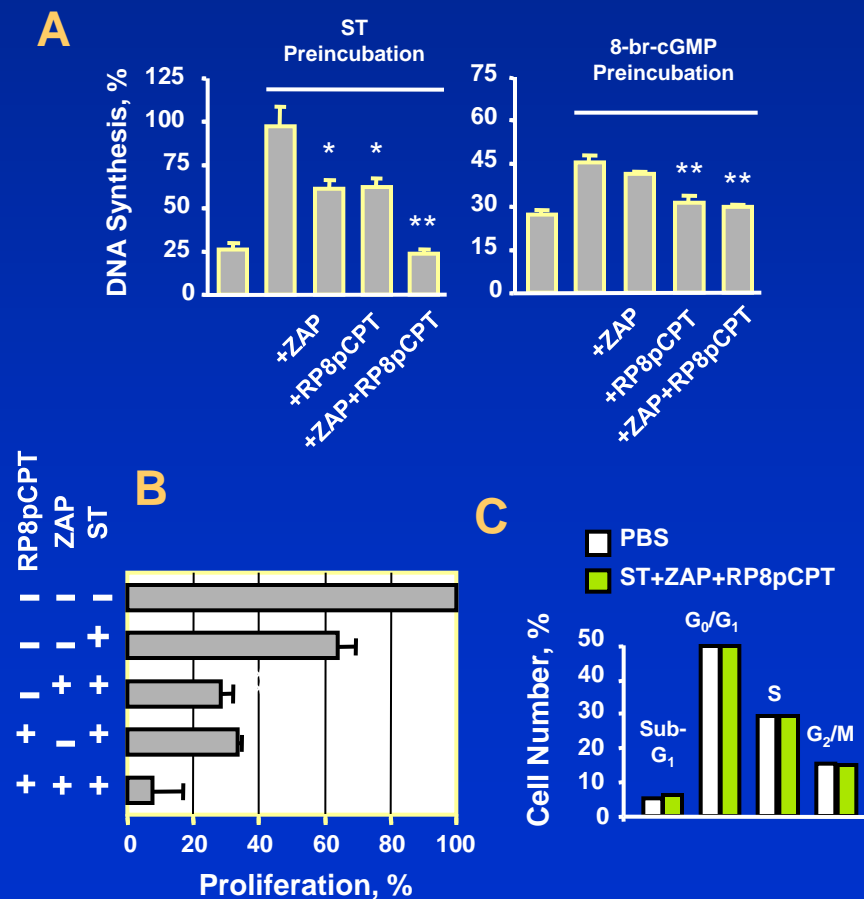


Brush Border Microvilli

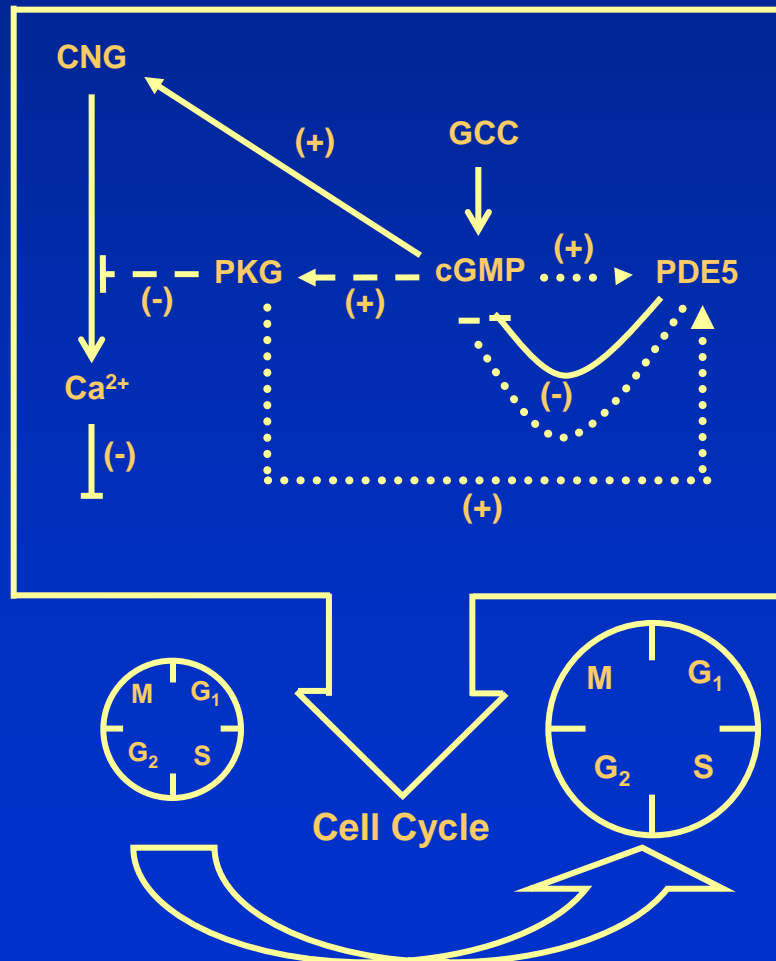
Antiproliferative cGMP Signaling Targets Cyclic Nucleotide-Gated Channel



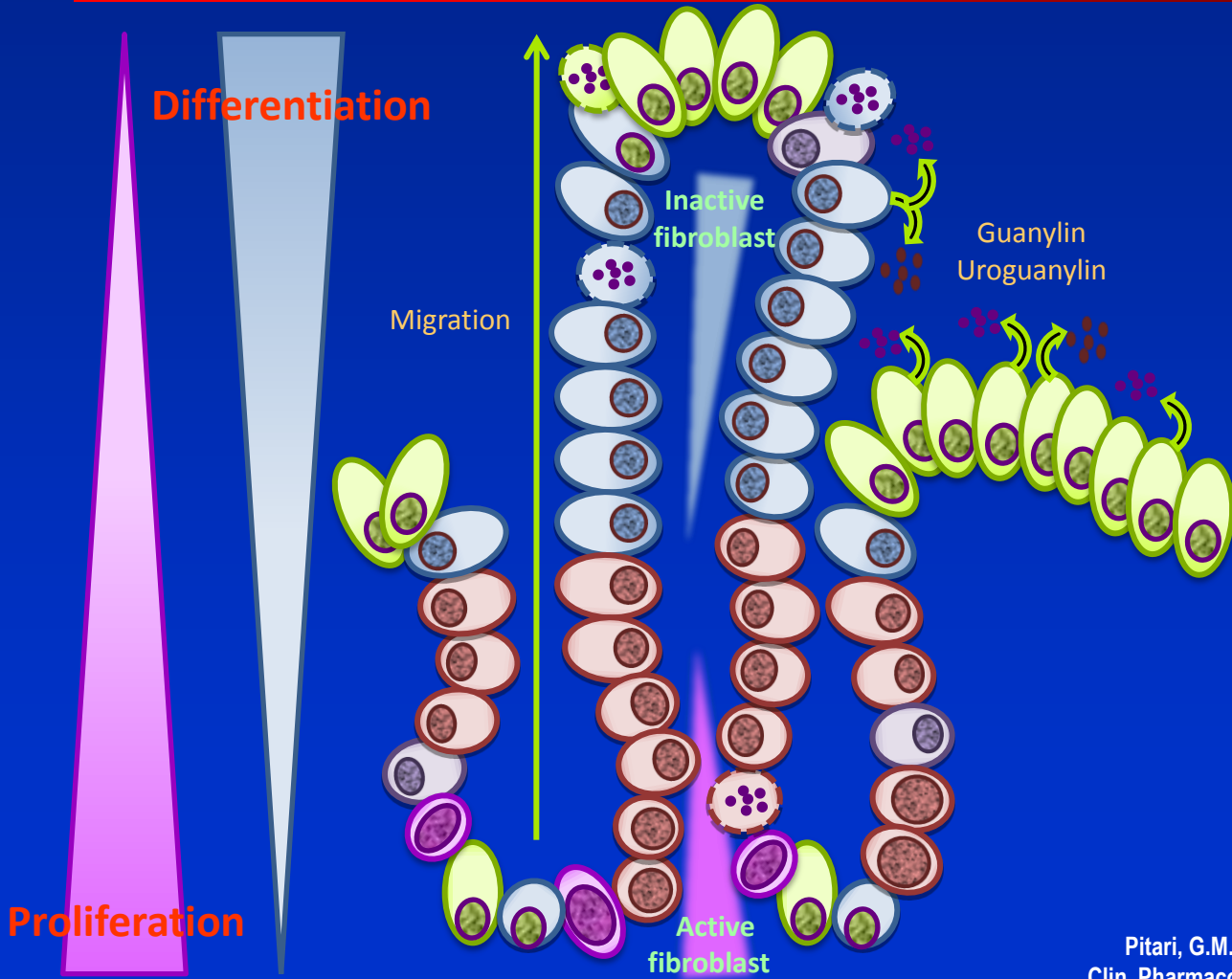
Antiproliferative cGMP Signaling Undergoes Negative Feedback Regulation



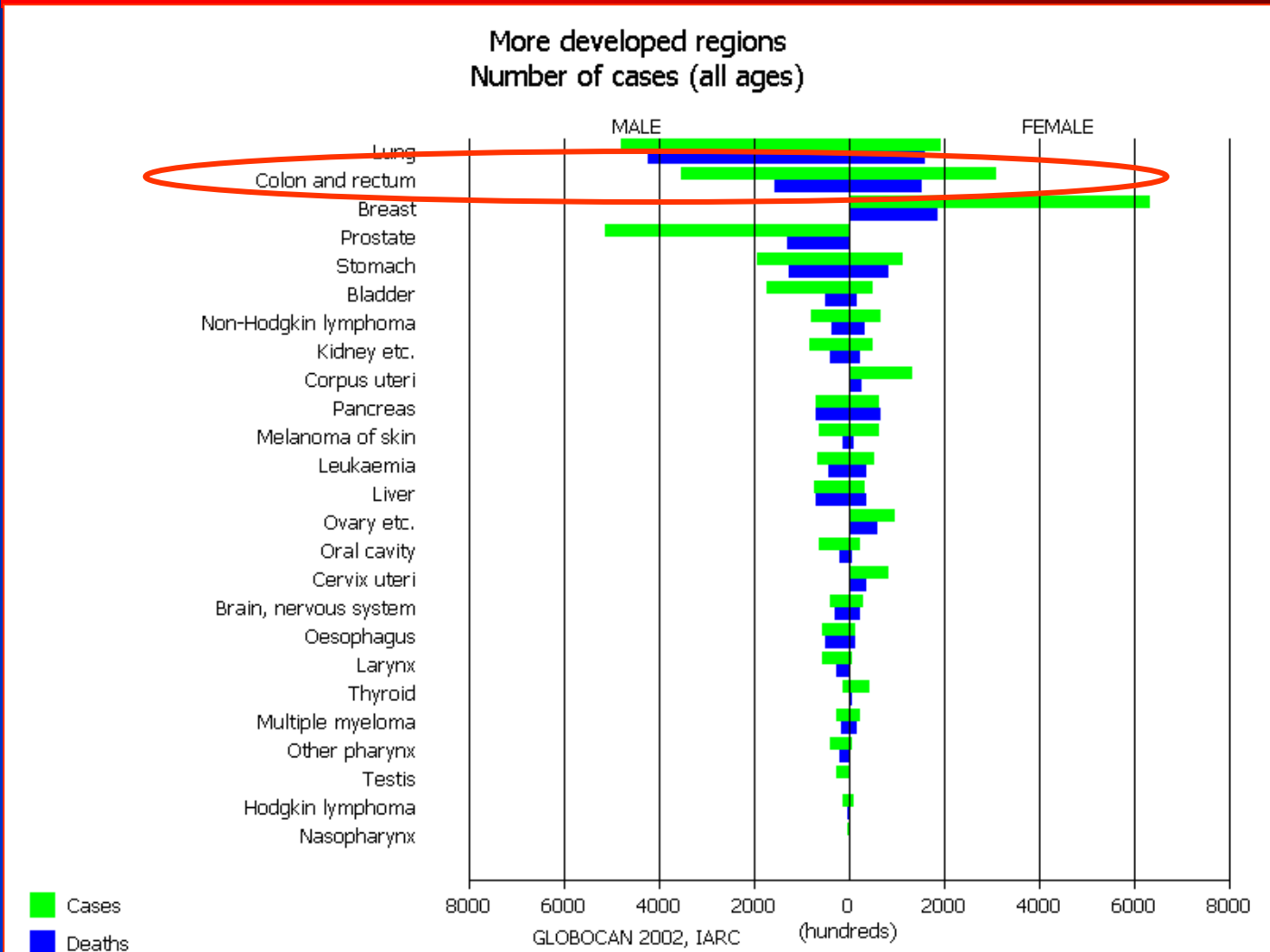
The Antiproliferative cGMP Signaling Pathway in Intestinal Epithelial Cells



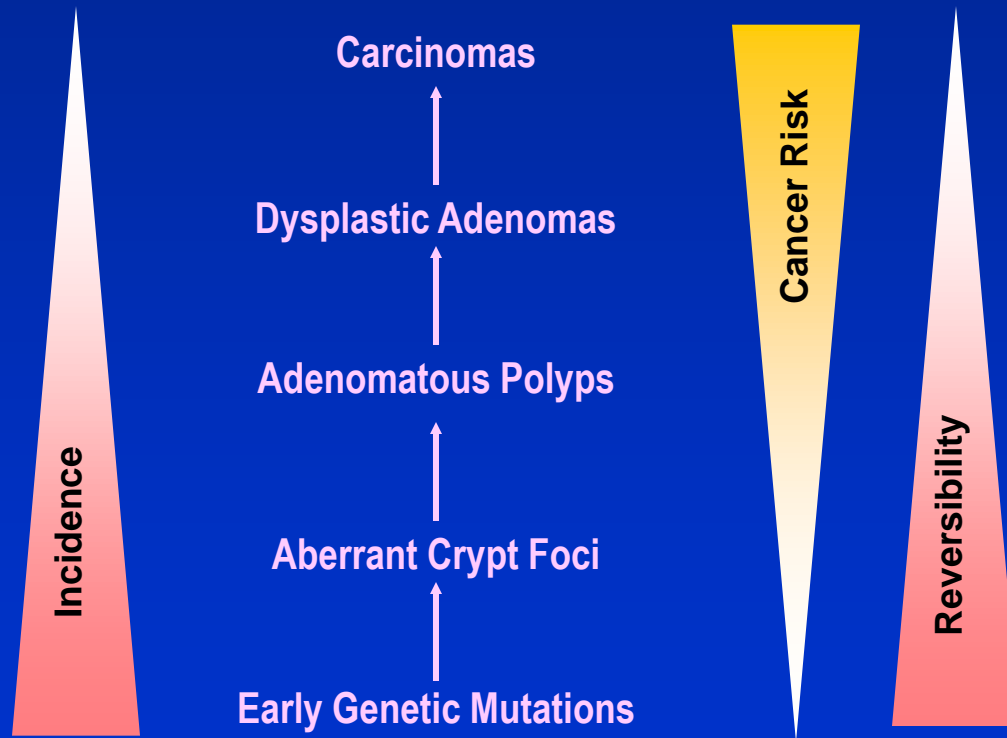
Cyclic GMP Signaling by GCC Controls The Crypt-Villus Homeostasis



Colon Cancer: the 2nd Most Deadly Cancer in Developed Nations



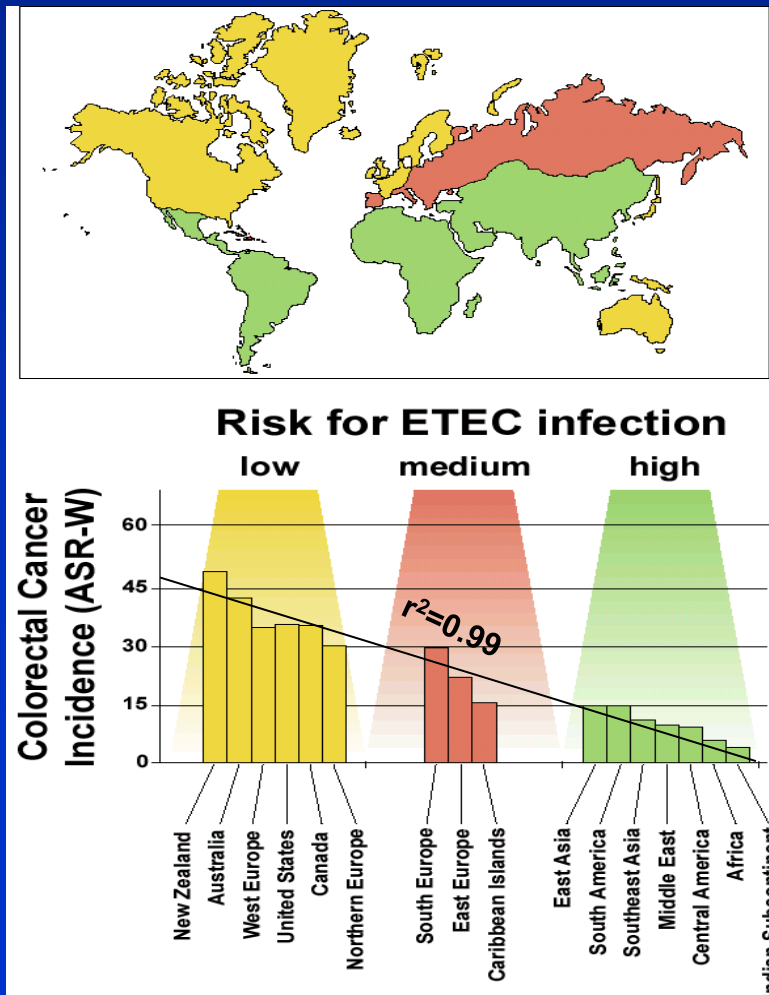
The Pathological Sequence of Colorectal Cancer



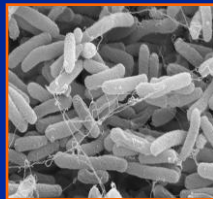
Colon Cancer: Diagnosis and Therapy

	<p><u>Stage I</u> Invasion up to the <i>muscularis propria</i></p> <p>↓</p> <p>Surgery</p>	<p><u>Stage II</u> Invasion of the serosa and adjacent organs</p> <p>↓</p> <p>Surgery</p> <p>↓</p> <p>Chemiotherapy ?</p>	<p><u>Stage III</u> Invasion of regional lymph nodes</p> <p>↓</p> <p>Surgery</p> <p>↓</p> <p>Chemiotherapy</p>	<p><u>Stage IV</u> Distant Metastasis</p> <p>↓</p> <p>Surgery</p> <p>↓</p> <p>Chemiotherapy</p>
5-years survival	~ 95%	~ 80%	~ 65%	~ 7%

ETEC Infections Confer Resistance to Colon Cancer

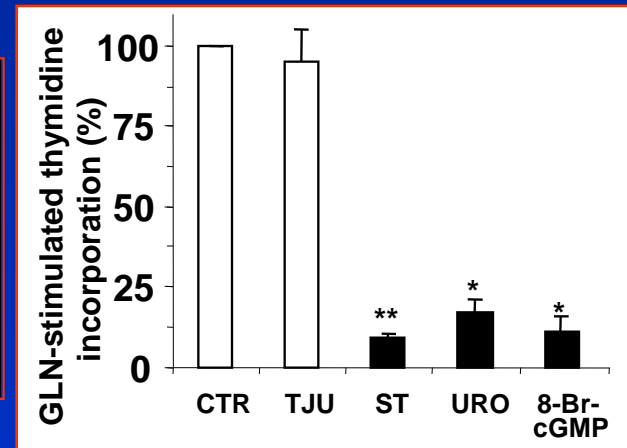
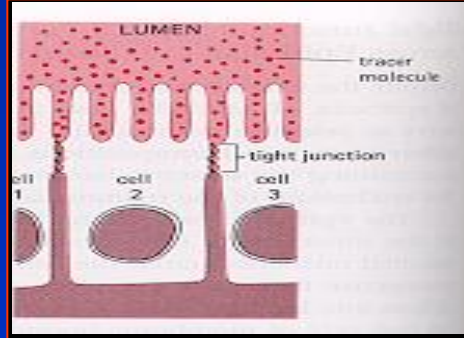
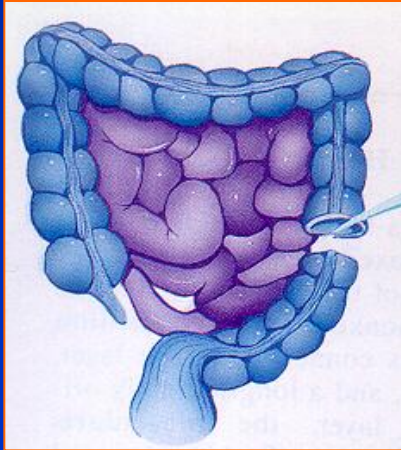
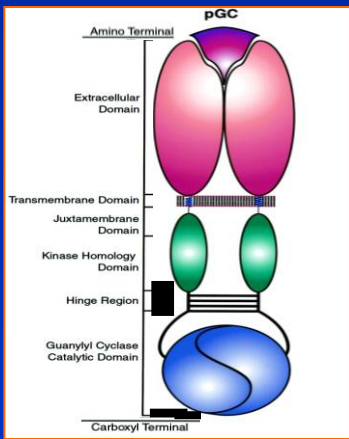


GCC is a Therapeutic Target in Colon Cancer



N T F Y C C E L C C N P A C A G C Y

ST



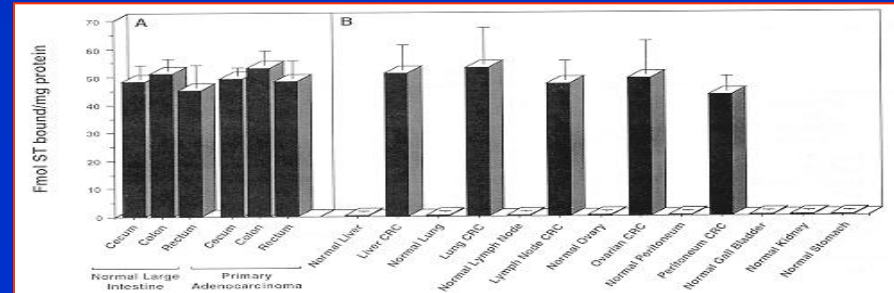
Pitari GM, et al. (2001) Proc. Natl. Acad. Sci. USA 98: 7846-51

N D D C E L C V N V A C T G C L

P G T C E I C A Y A A C T G C

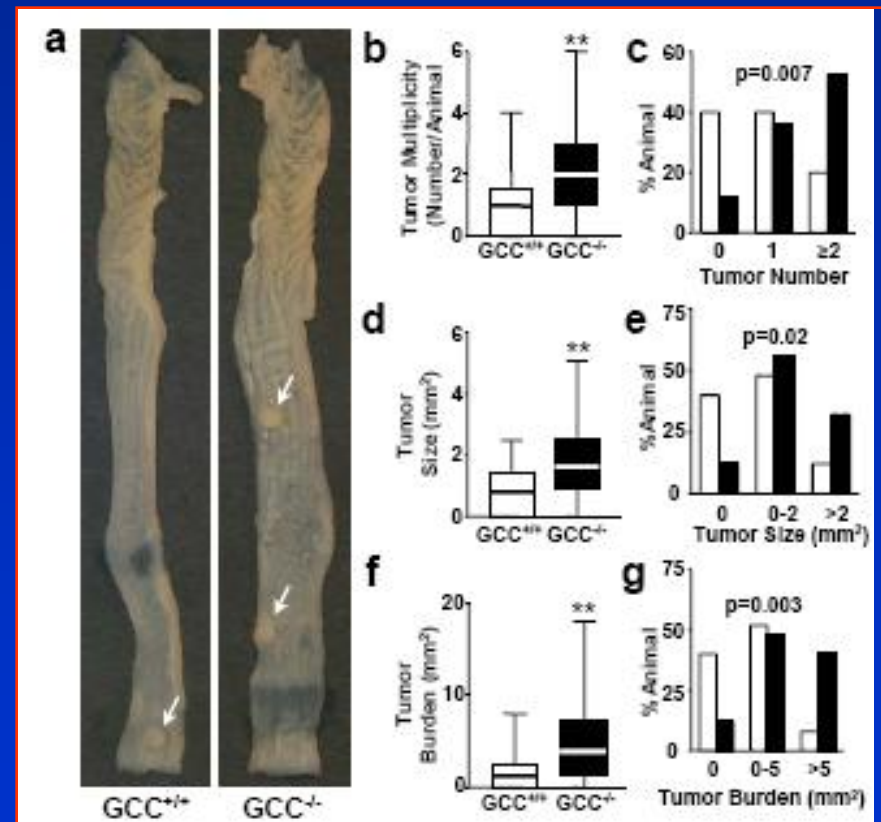
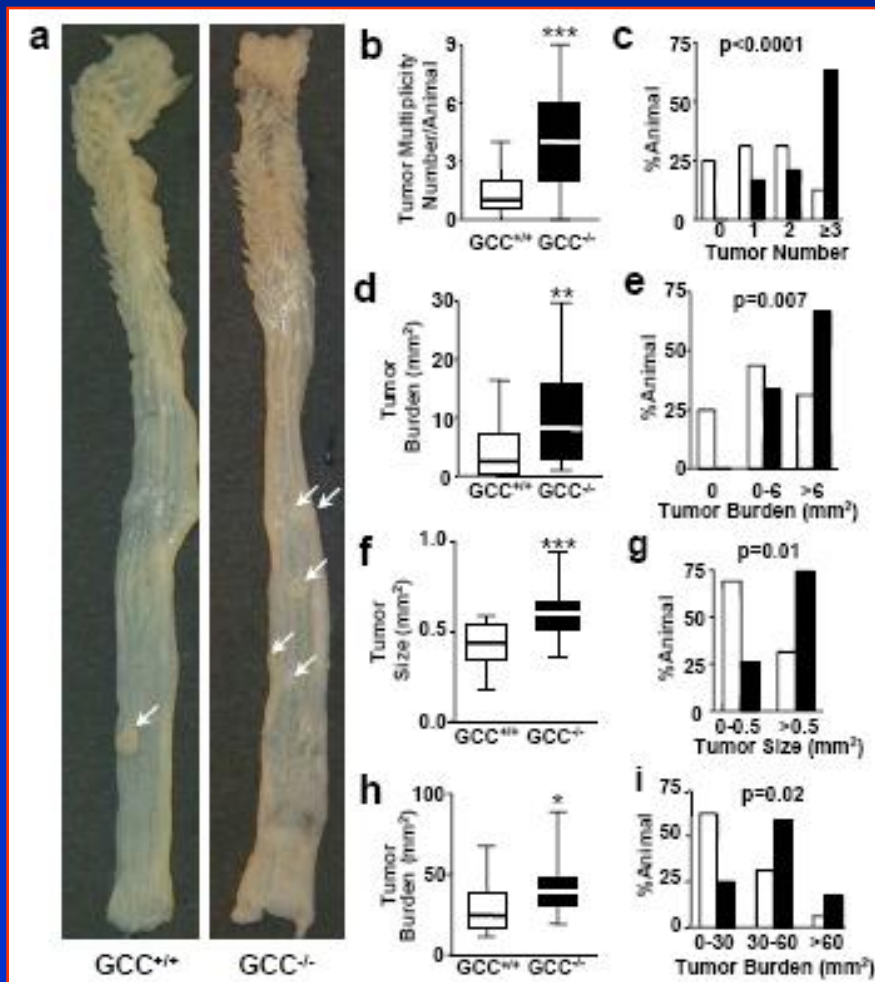
uroguanylin

guanylin

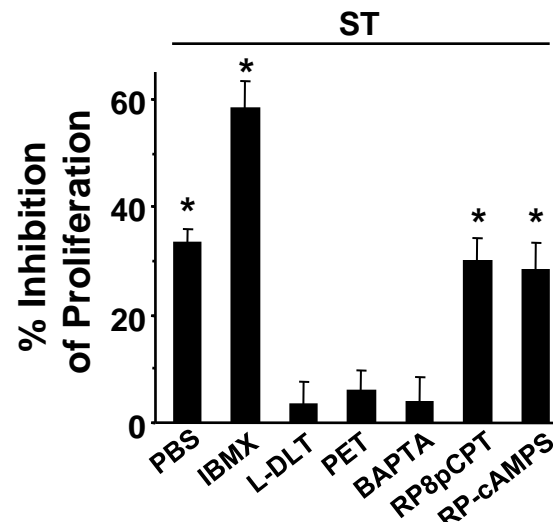
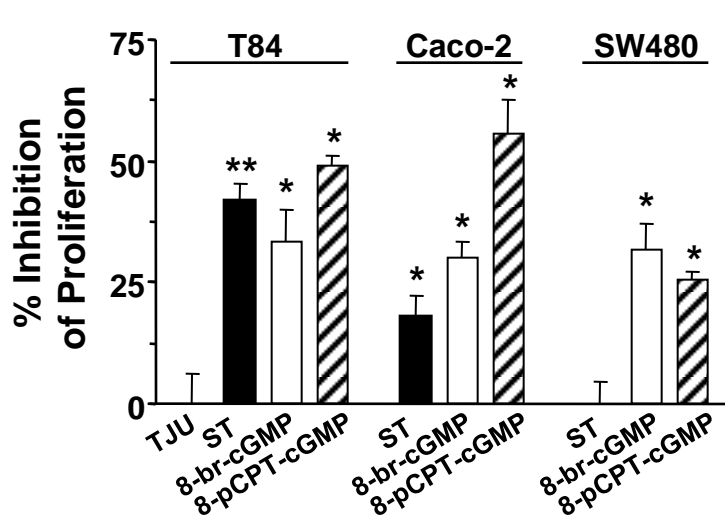
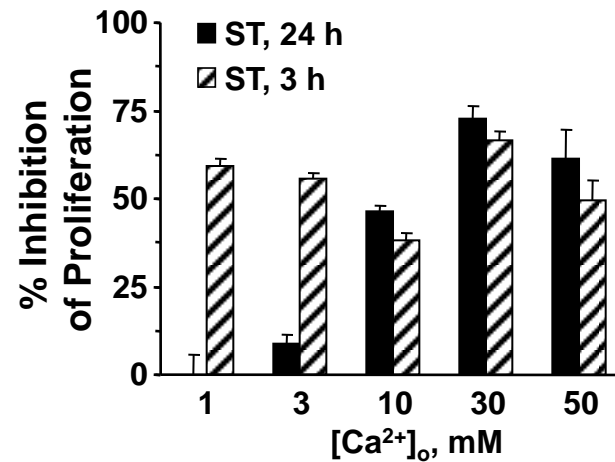
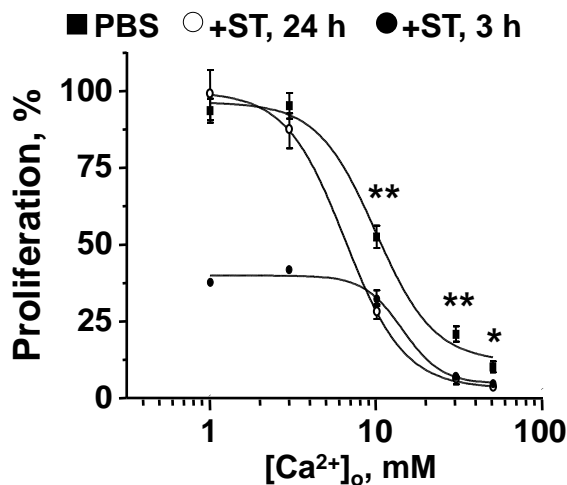


Carrithers S, et al. (1996) Proc. Natl. Acad. Sci. USA 93: 14827-32

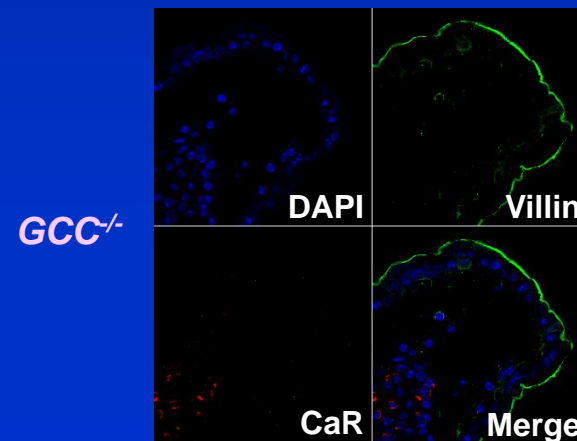
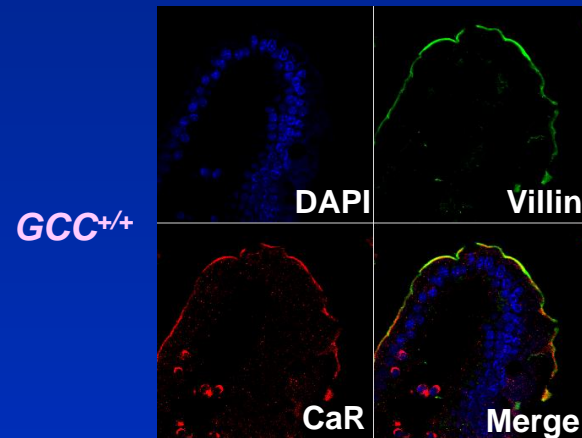
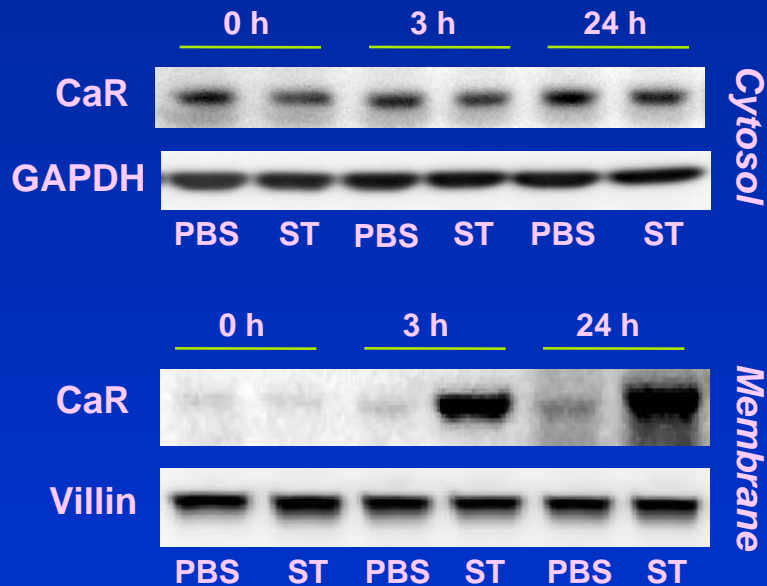
GCC is a Novel Intestinal Tumor Suppressor



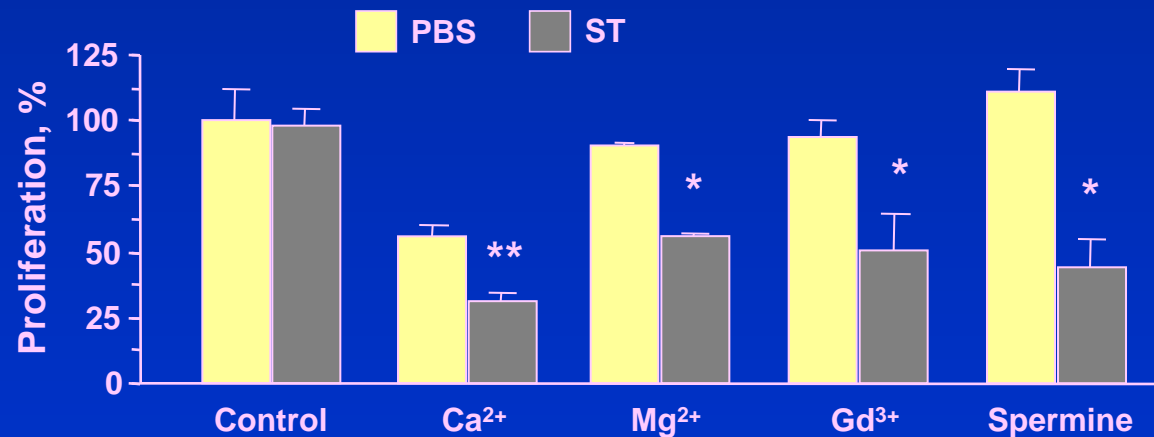
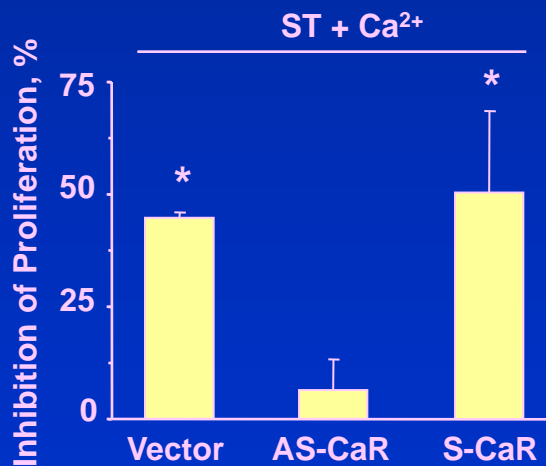
GCC Signaling through cGMP Potentiates Cytostatic Calcium Effects



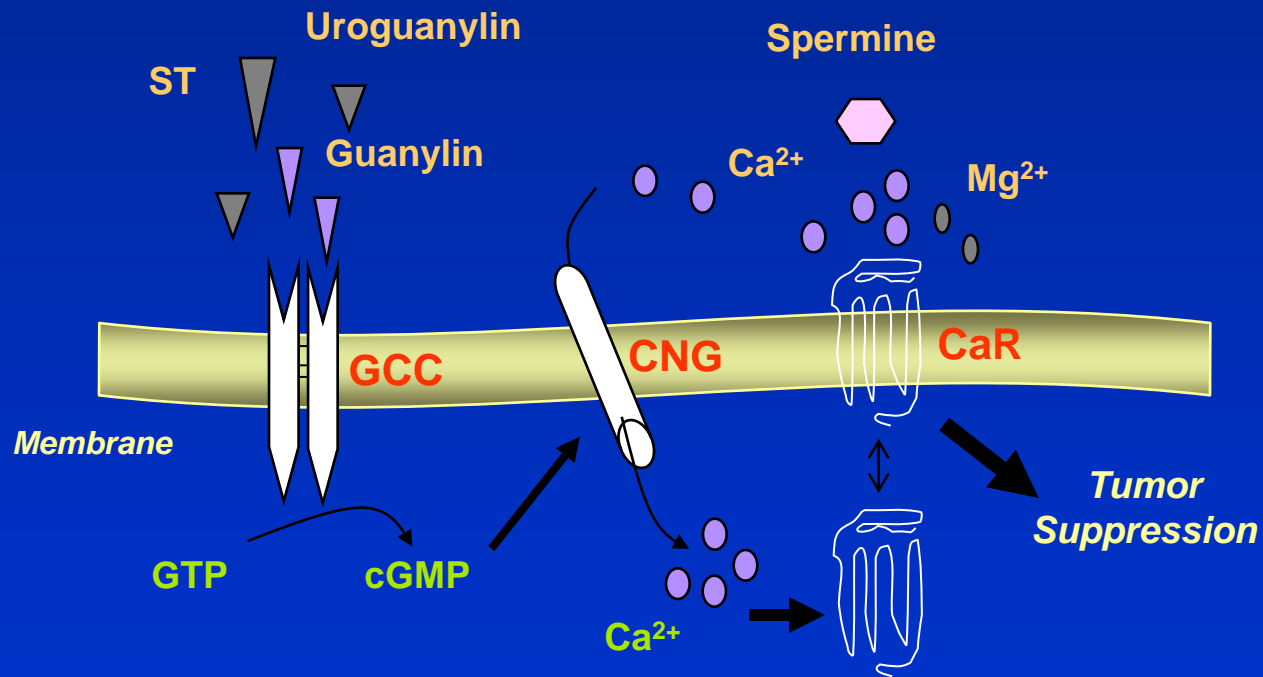
GCC Regulates the Function of Calcium-Sensing Receptor (CaR) in the Intestine



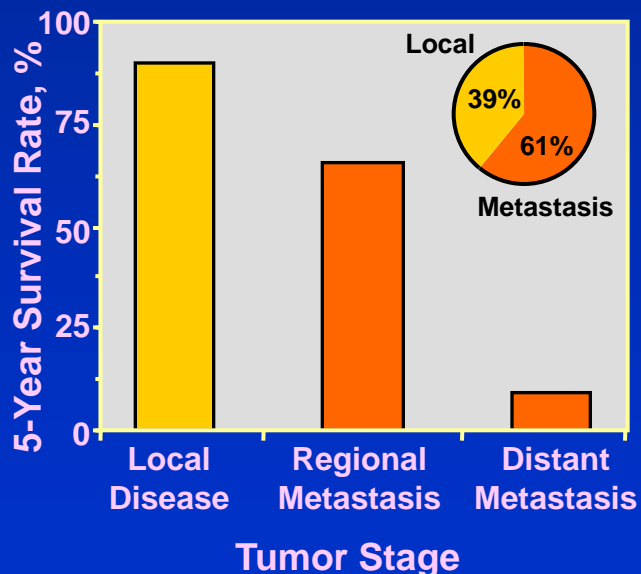
GCC-Targeted Therapy in Combination with Dietary Calcium



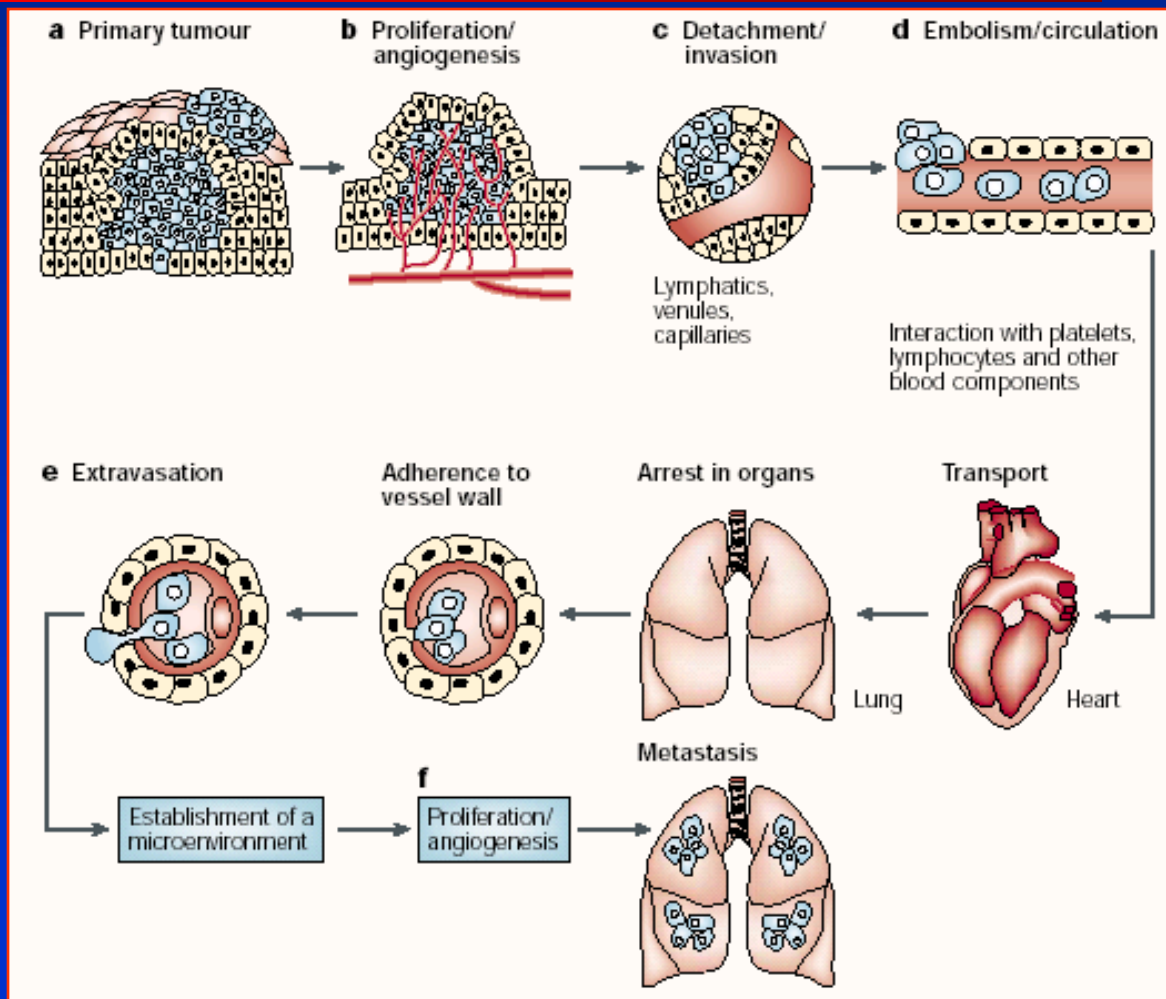
A Tumor Suppressor cGMP Signaling Pathway in Colon Cancer



Colon Cancer Mortality Reflects Metastatic Disease Progression

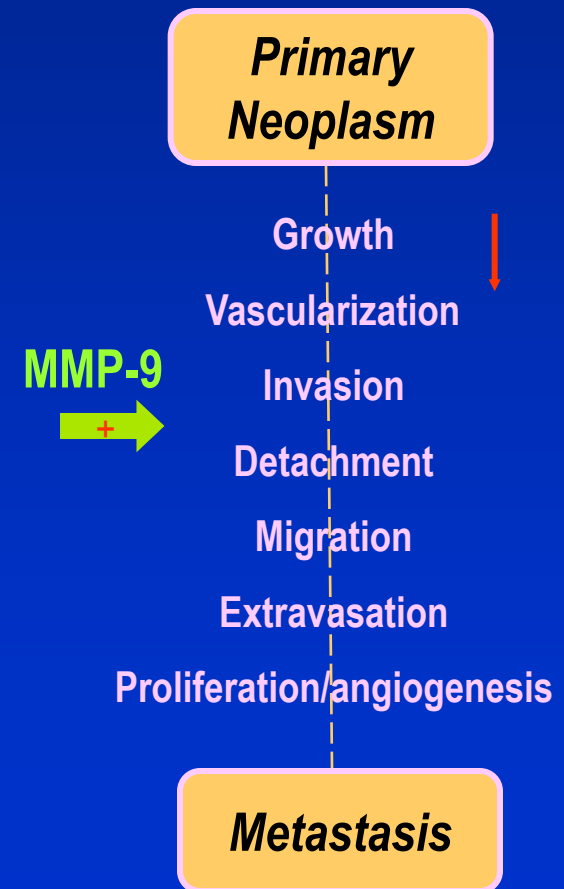
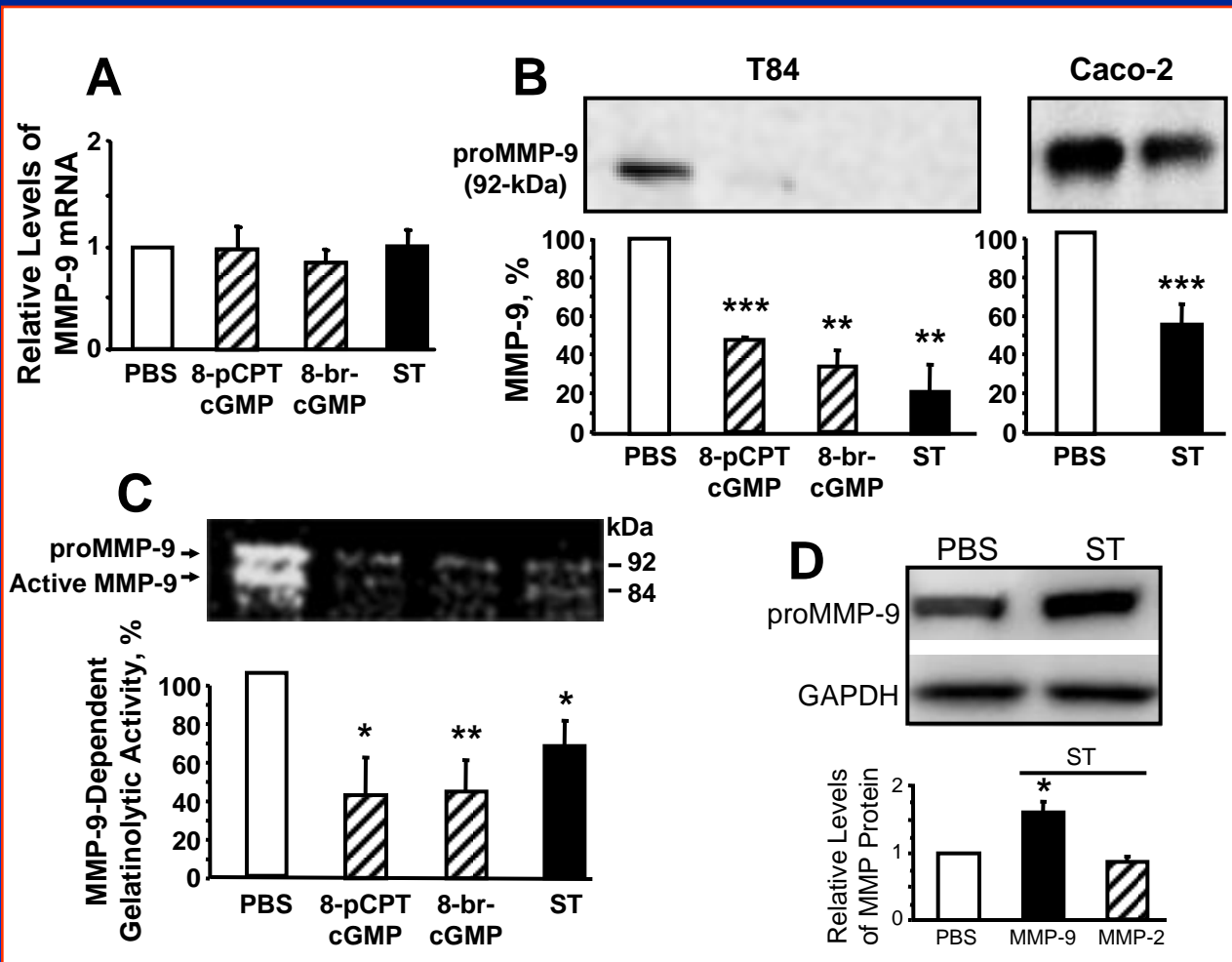


Lubbe, W.J. (2006) Clin. Cancer Res. 12:1876 -82

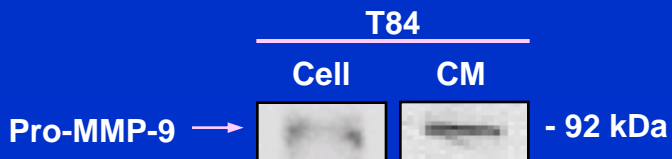
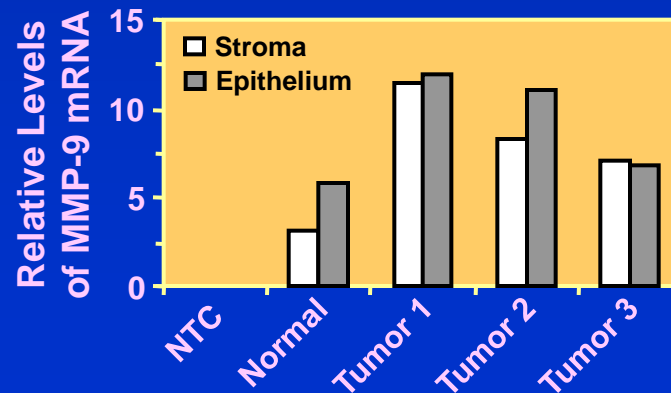
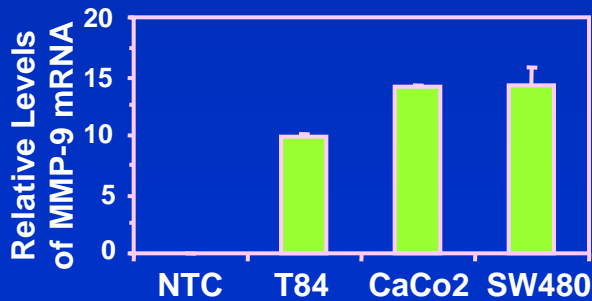
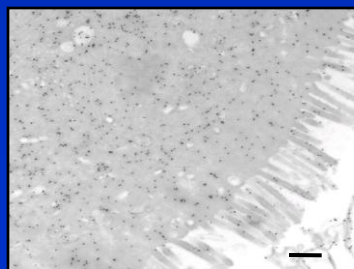
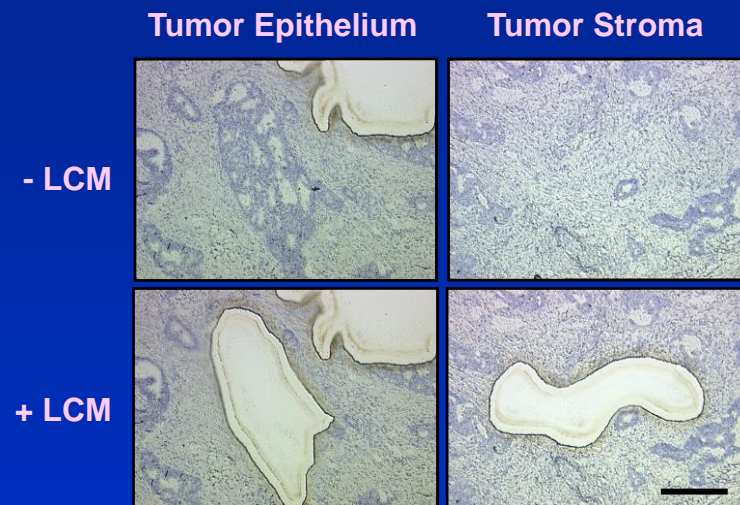
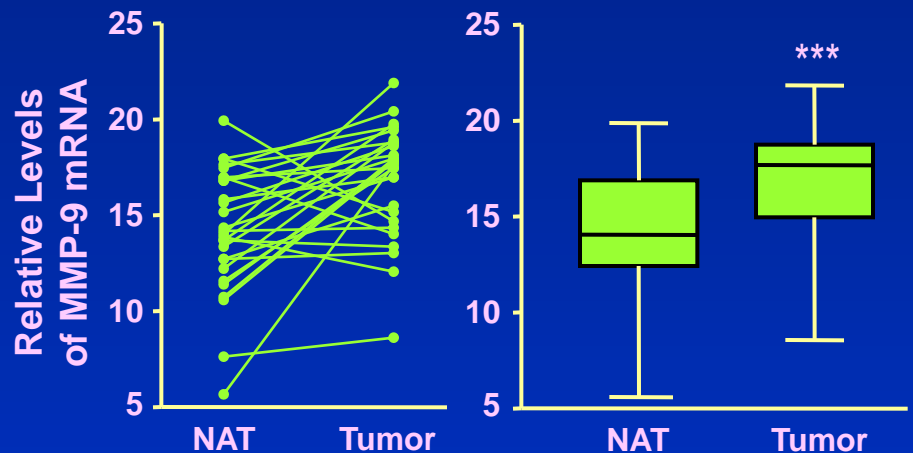


Fidler IJ. (2003) Nat. Rev. Cancer 3: 453 -458

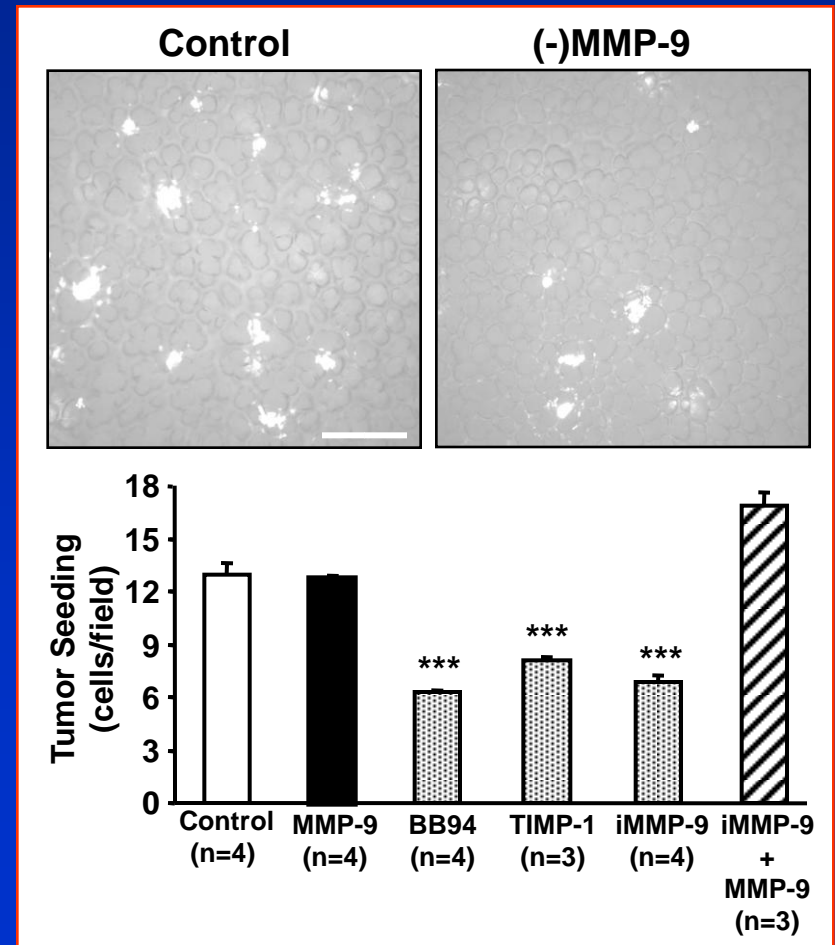
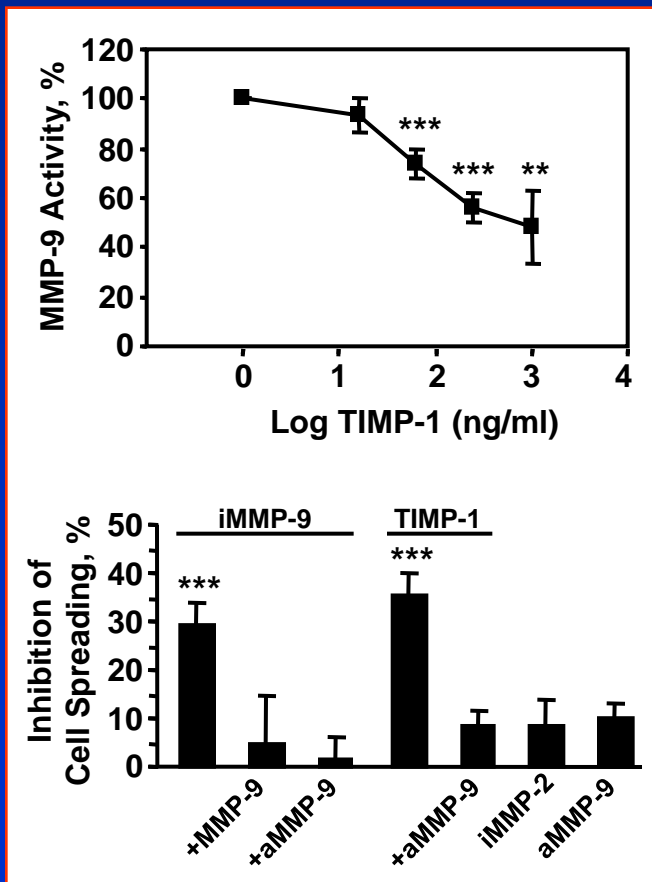
Cyclic GMP Induces Functional Remodeling of Cancer Cell MMP-9



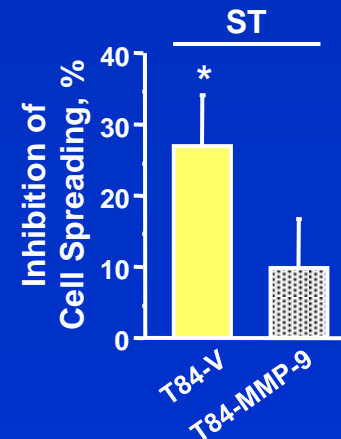
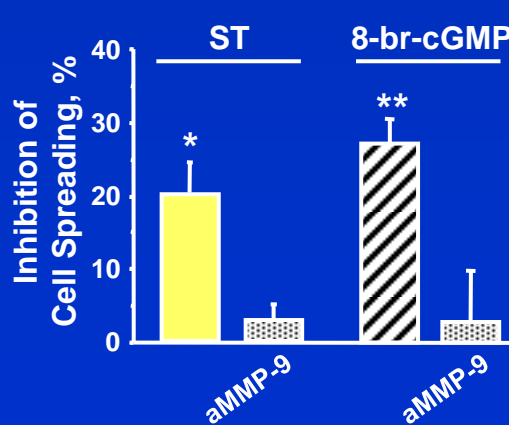
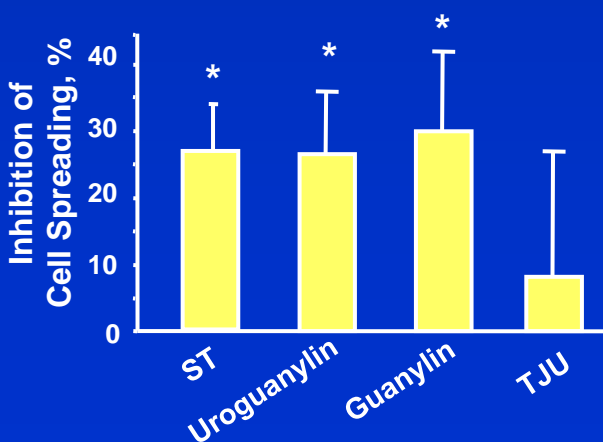
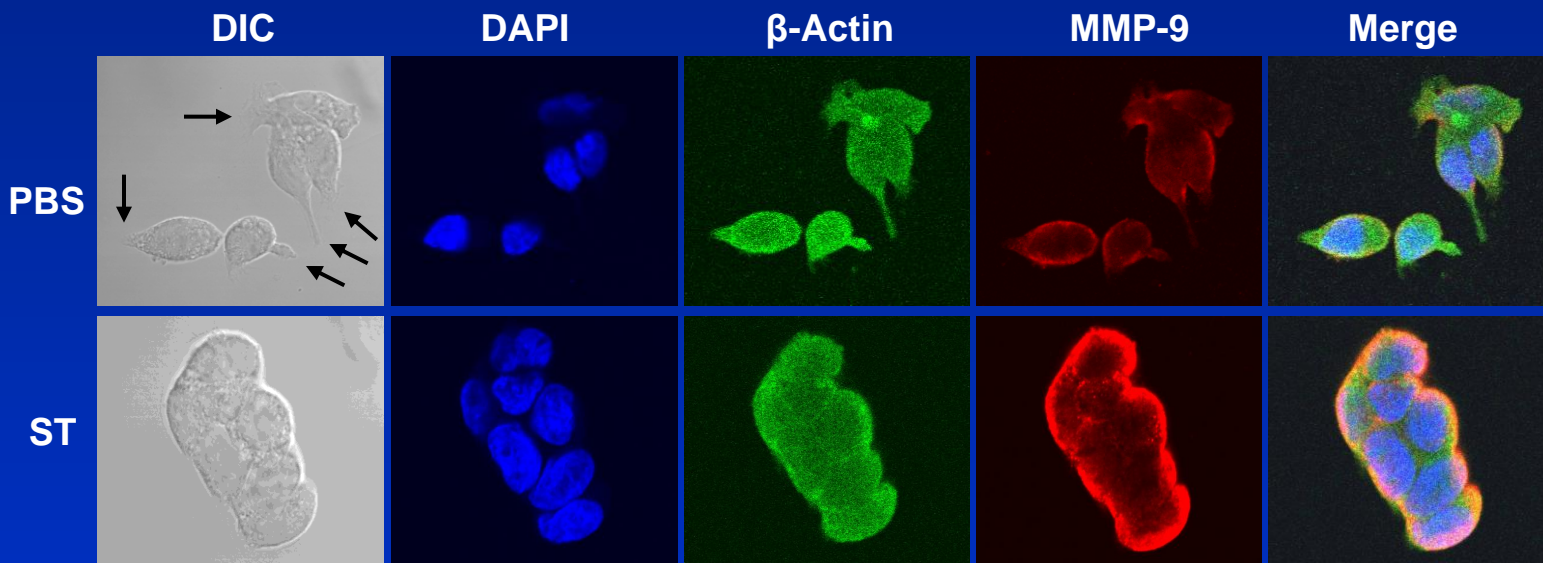
MMP-9 Promotes Metastasis in Colon Cancer



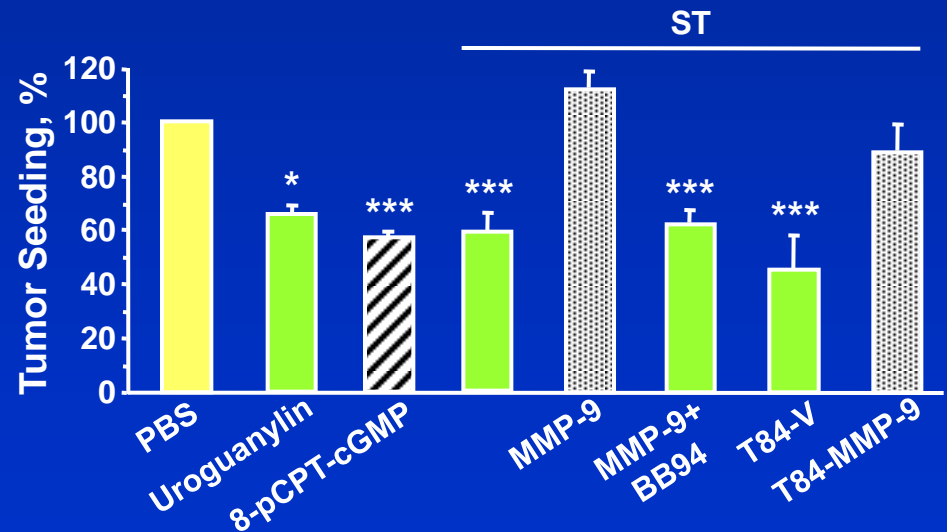
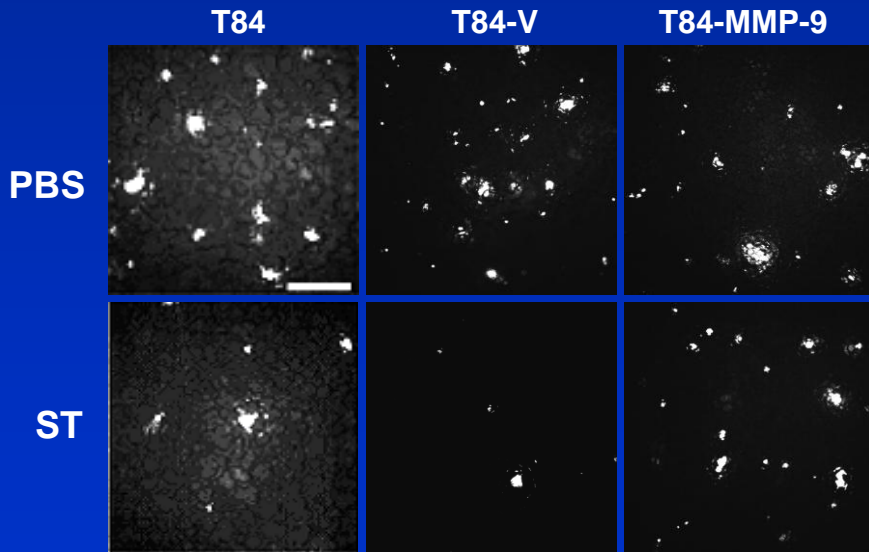
Colon Cancer Cell MMP-9 Induces Metastatic Seeding



GCC and cGMP Signaling through MMP-9 Regulates Colon Cancer Cell Shape and Spreading

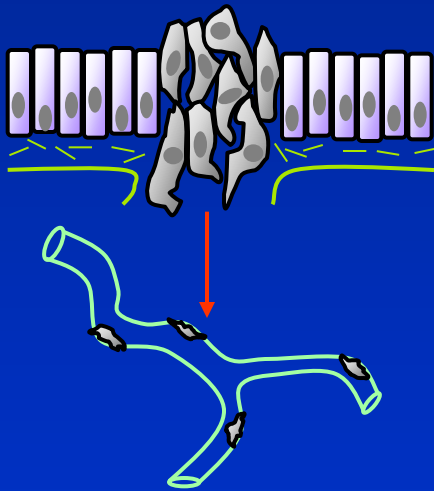


GCC and cGMP Signaling through MMP-9 Suppresses Metastatic Seeding by Colon Cancer Cells



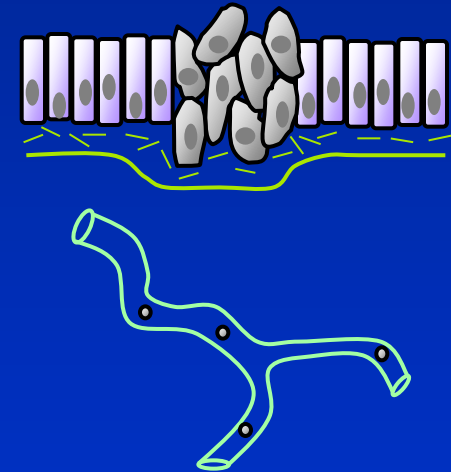
The Antimetastatic cGMP Signaling Pathway in Colon Cancer Cells

(-) cGMP Pathway

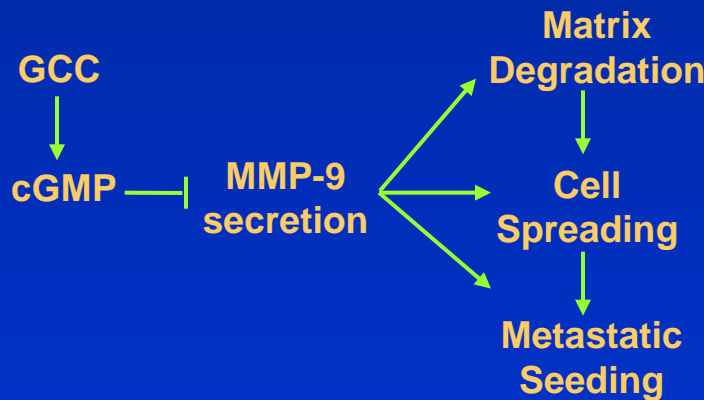


Metastasis

(+) cGMP Pathway



Tumor Containment / Vascular Clearance



Summary

- *The cGMP pathway in intestinal epithelial cells regulates the crypt-villus axis and opposes colorectal tumorigenesis*
- *GCC, a guanylyl cyclase receptor selectively expressed by normal and malignant intestinal epithelial cells, coordinates a paracrine tumor suppressor system in the intestine*
- *The cGMP pathway potentiates the cytostatic effects of extracellular calcium by regulating the activity of CaR*
- *The cGMP pathway reduces the metastatic potential of colorectal cancer cells, in vitro and in vivo, in part by regulating the function of MMP-9*
- *Cancer cell MMP-9 regulates metastatic functions, including actin polymerization and cell spreading, and in vivo seeding of target organs*

Translational Significance

- *GCC ligands represents novel agents for the prevention of primary and metastatic colon cancer*
- *GCC ligands represents novel agents for the treatment of primary and metastatic colon cancer*
- *Combinatorial strategies with GCC ligands and dietary calcium may provide a novel paradigm for the treatment of colon cancer*
- *Cancer cell MMP-9 is a highly selective and effective molecular target for preventing metastatic progression of colorectal cancer*