2009

Targeting the cGMP Pathway to Treat Colorectal Cancer

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Targeting the cGMP Pathway to Treat Colorectal Cancer

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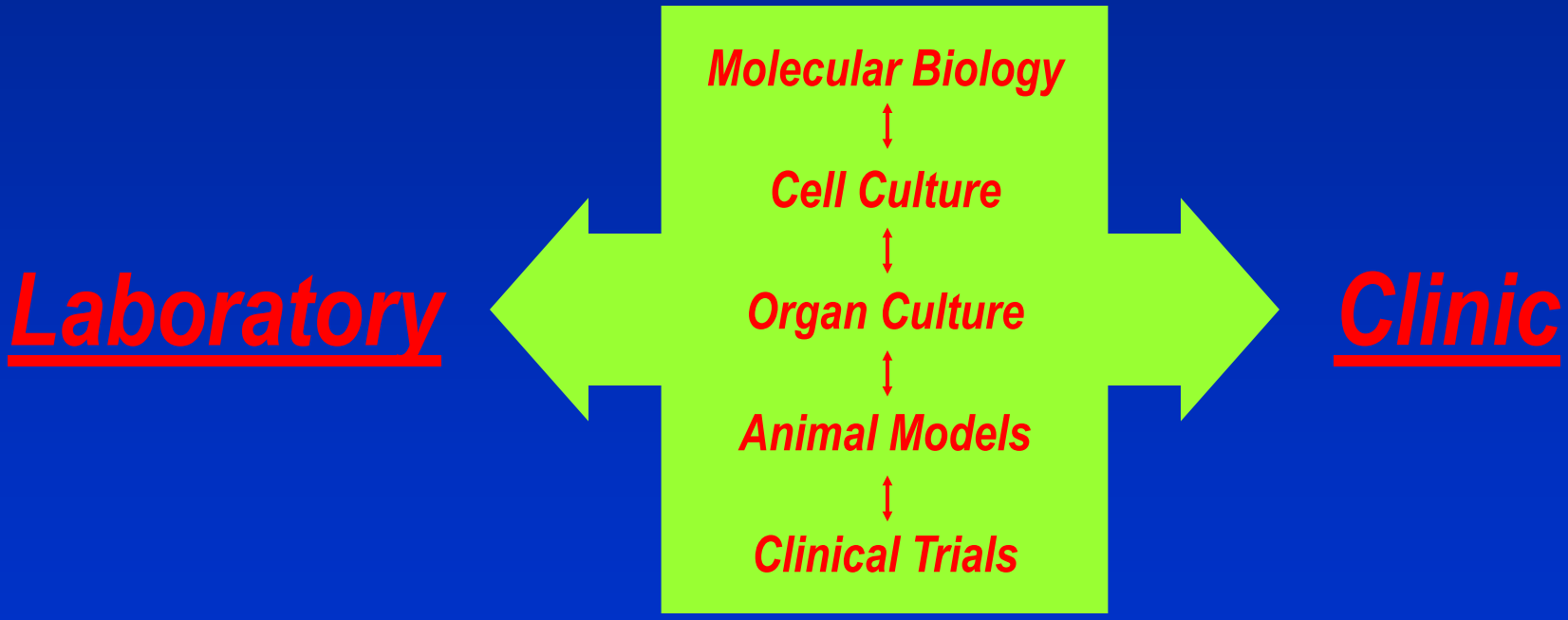
Translational Medicine



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Translational Research Project: from the cGMP Pathway to Colorectal Cancer

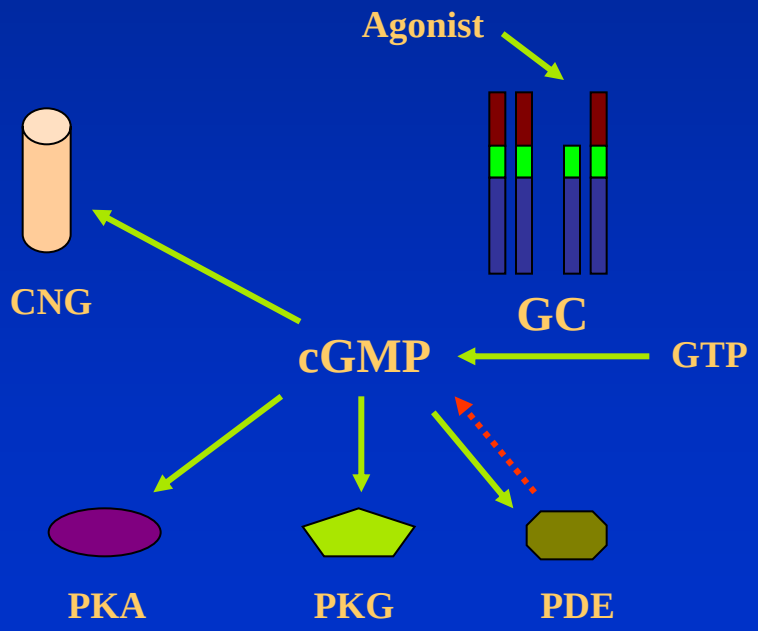
Targeting Strategies:

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***

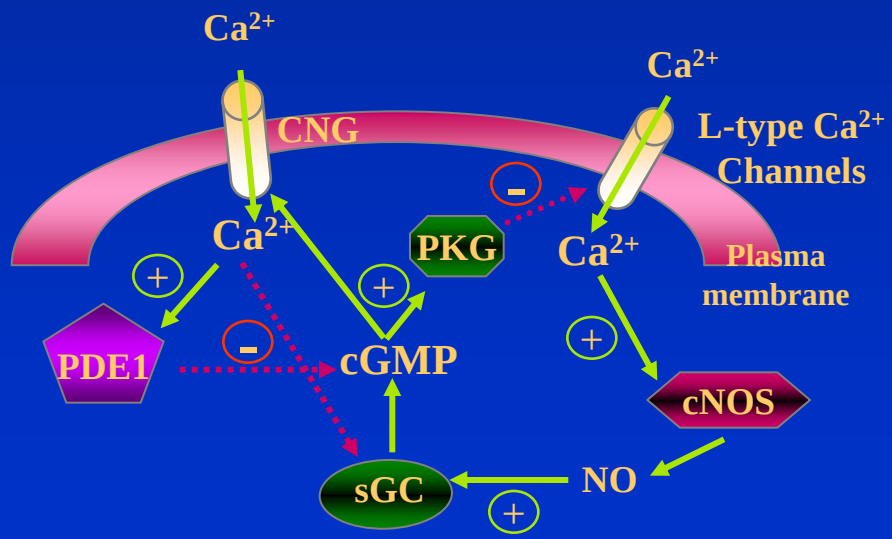
Cyclic GMP Signaling

General Model for cGMP Signaling



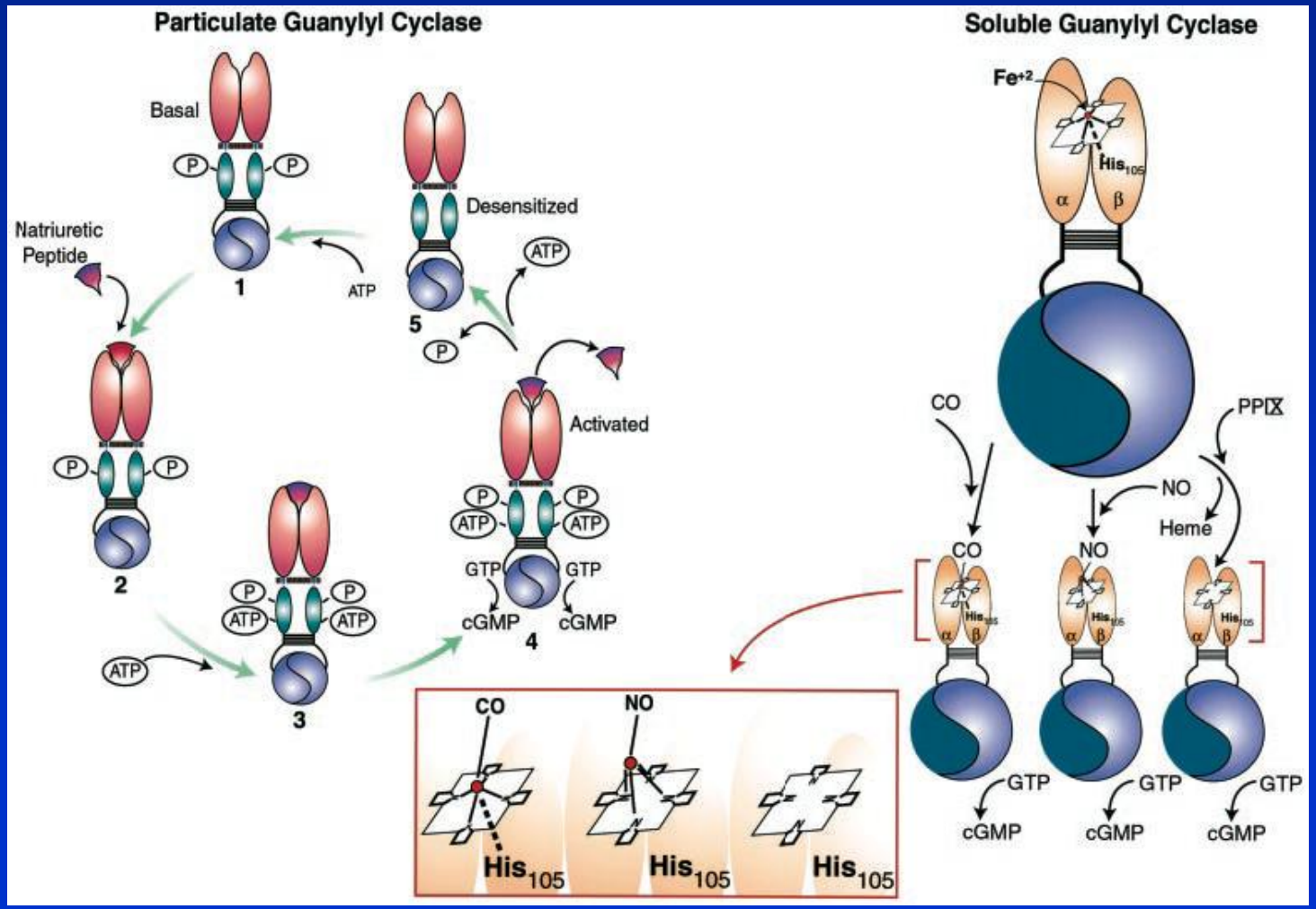
Modified from Li, T. et al. (2003)
Curr. Topics Biochem. Res. 5:181-92

Pituitary Cells



Tiyyagura, S.R. et al. (2004) Vit. Hormones 69:69-94

Guanylyl Cyclases



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

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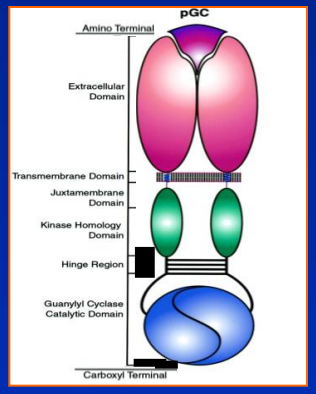
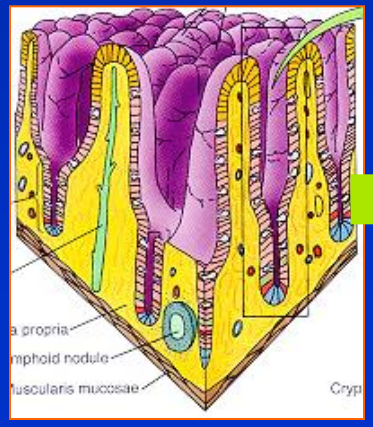
Guanylyl Cyclase C (GCC)

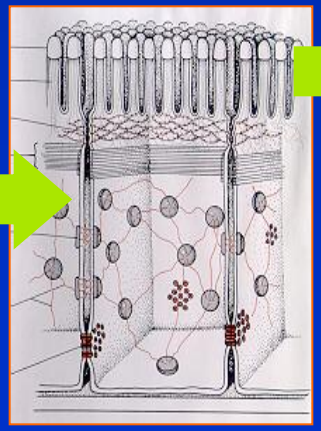


GCC is selectively expressed at brush-border membranes of intestinal epithelial cells and regulates fluid homeostasis



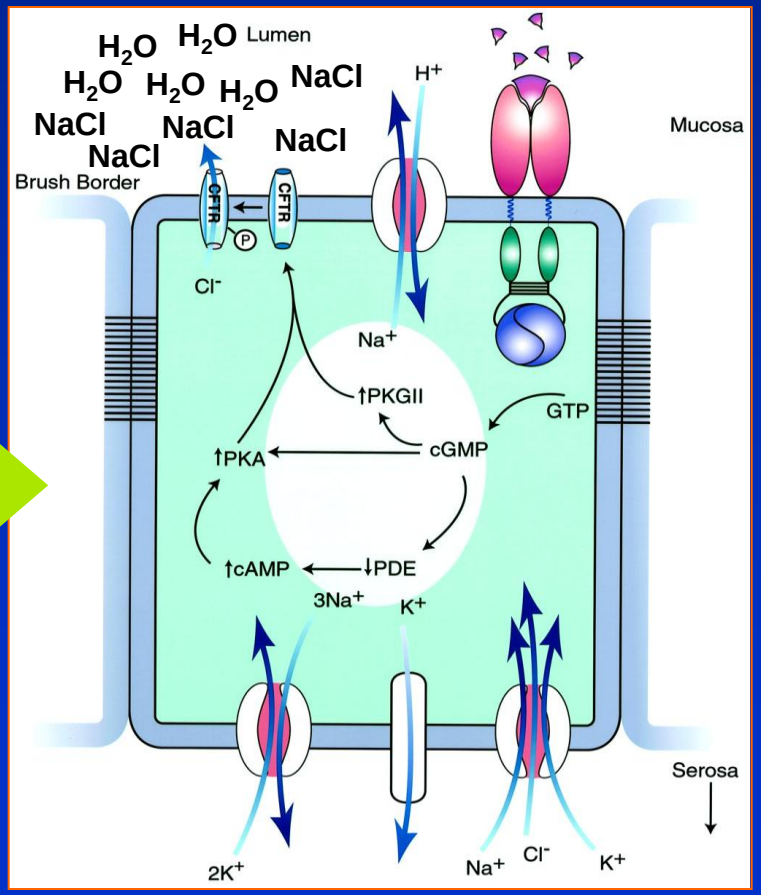
Crypt and Villus Enterocytes

Gartner L.P. (1997) Williams & Wilkins Pub. Co., Baltimore and Hiatt, J.L. Color Textbook of Histology



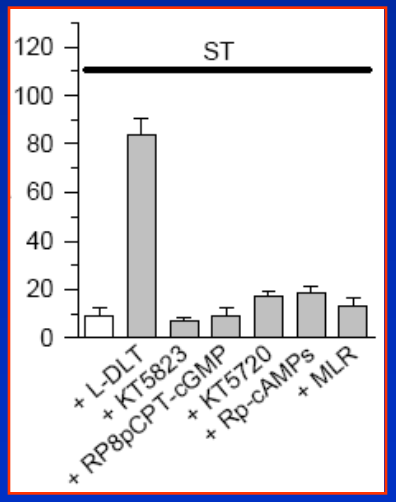
Brush Border Microvilli

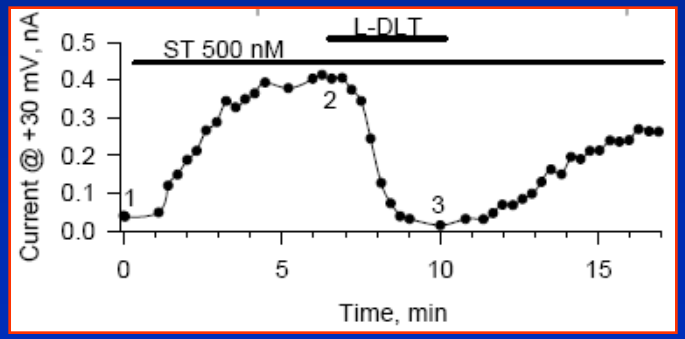
Keeton W.T. and Gould, J.L. Biological Science (1986) W.W. Norton & Co., Inc. New York: p.139

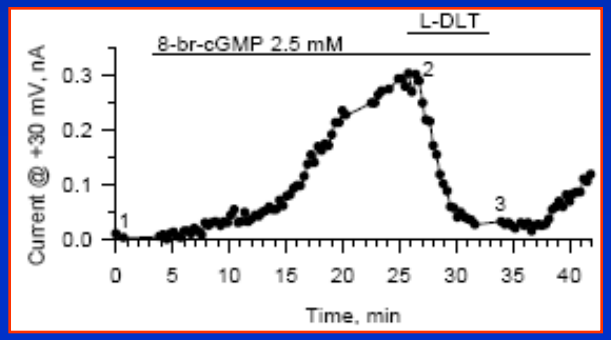


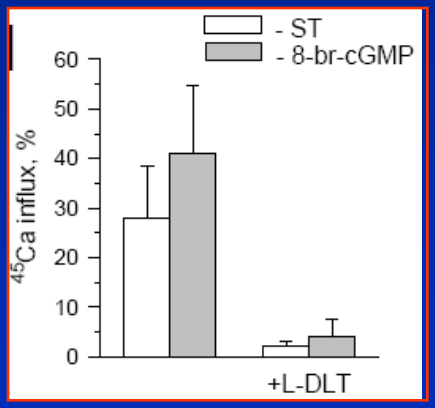
Lucas, et al. (2000) Pharmacol. Rev. 52: 375-413

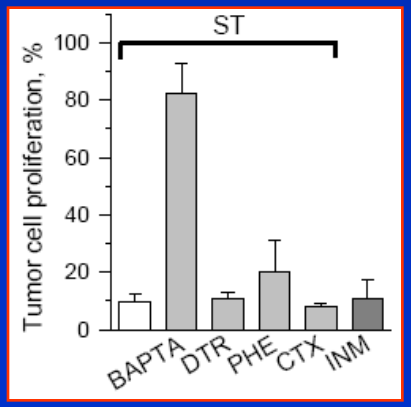
Antiproliferative cGMP Signaling Targets Cyclic Nucleotide-Gated Channel











Pitari, G.M. et al. (2003) Proc. Natl. Acad. Sci. USA 100:2695-99

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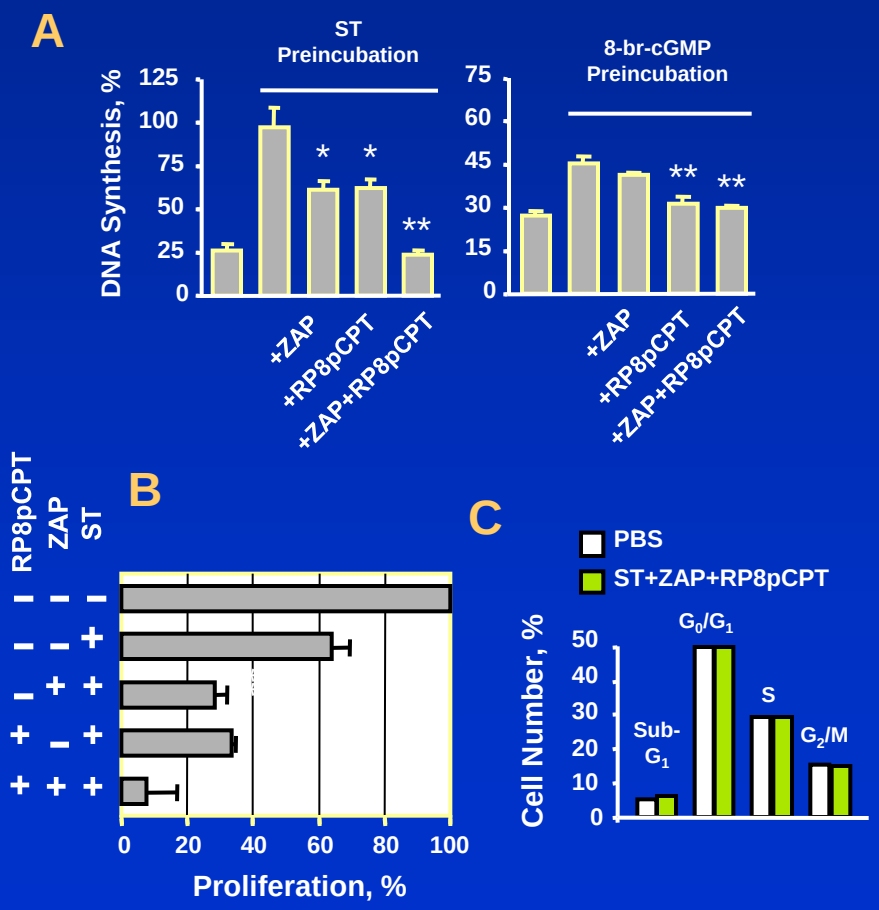
Antiproliferative cGMP Signaling Undergoes Negative Feedback Regulation



Pitari, G.M. et al. (2005) Cancer Res. 65:11129-35

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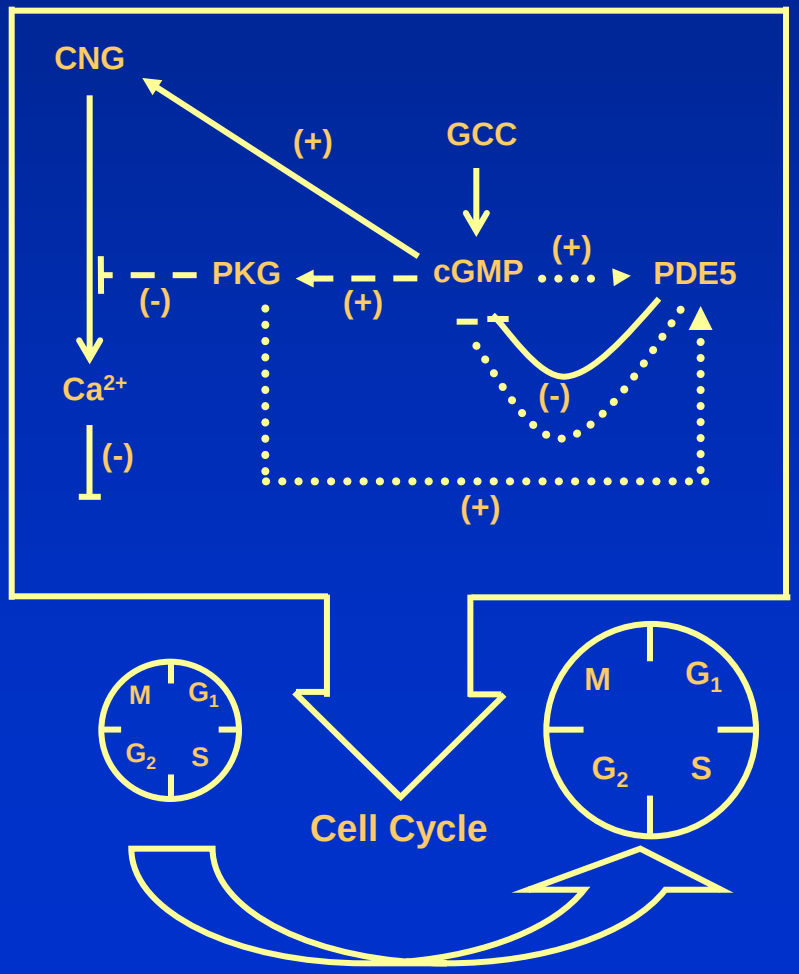
The Antiproliferative cGMP Signaling Pathway in Intestinal Epithelial Cells



Pitari, G.M. et al. (2005) Cancer Res. 65:11129-35

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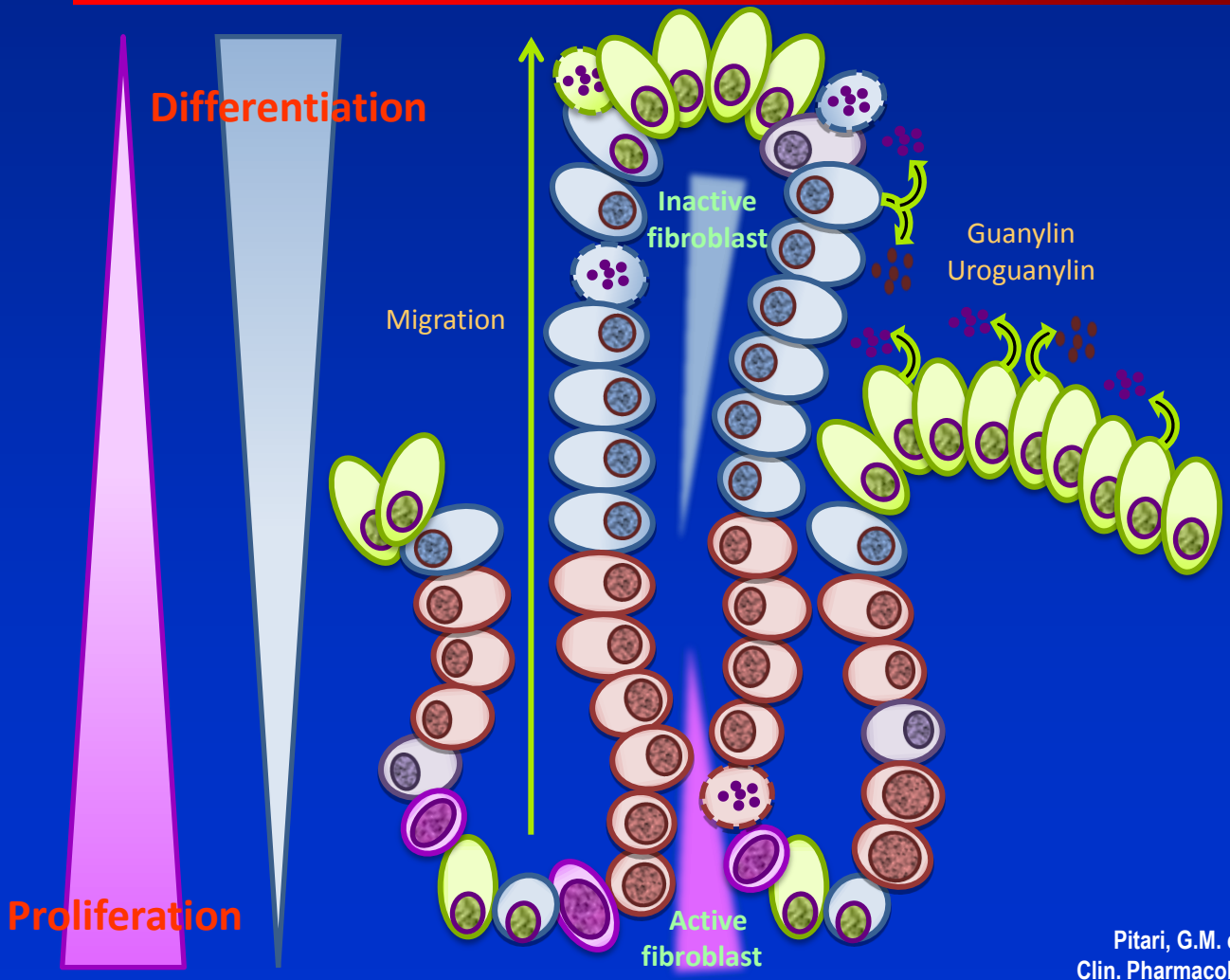
Cyclic GMP Signaling by GCC Controls The Crypt-Villus Homeostasis



Pitari, G.M. et al. (2007)
Clin. Pharmacol. Ther. 82:441-7

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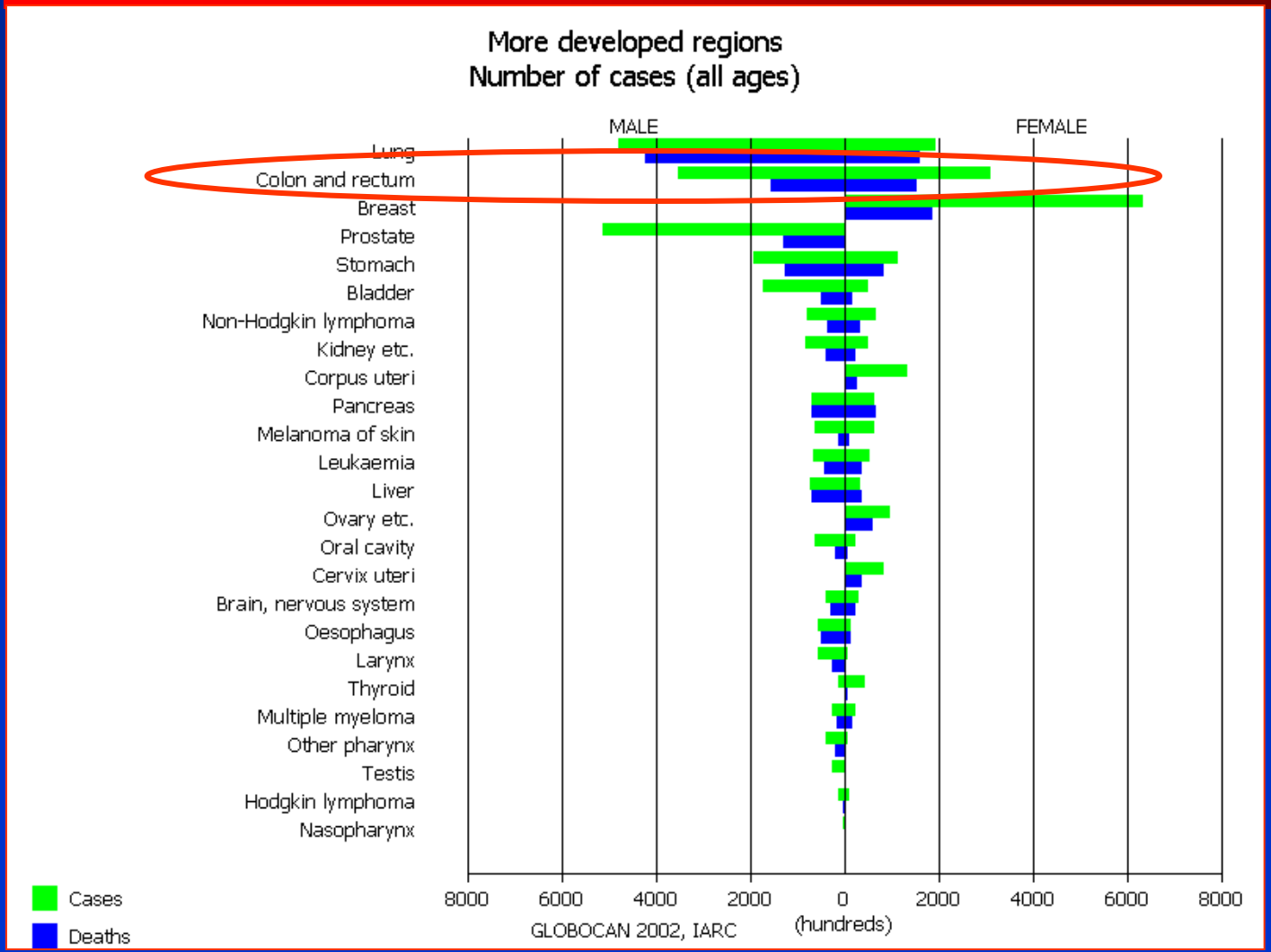
Colon Cancer: the 2nd Most Deadly Cancer in Developed Nations



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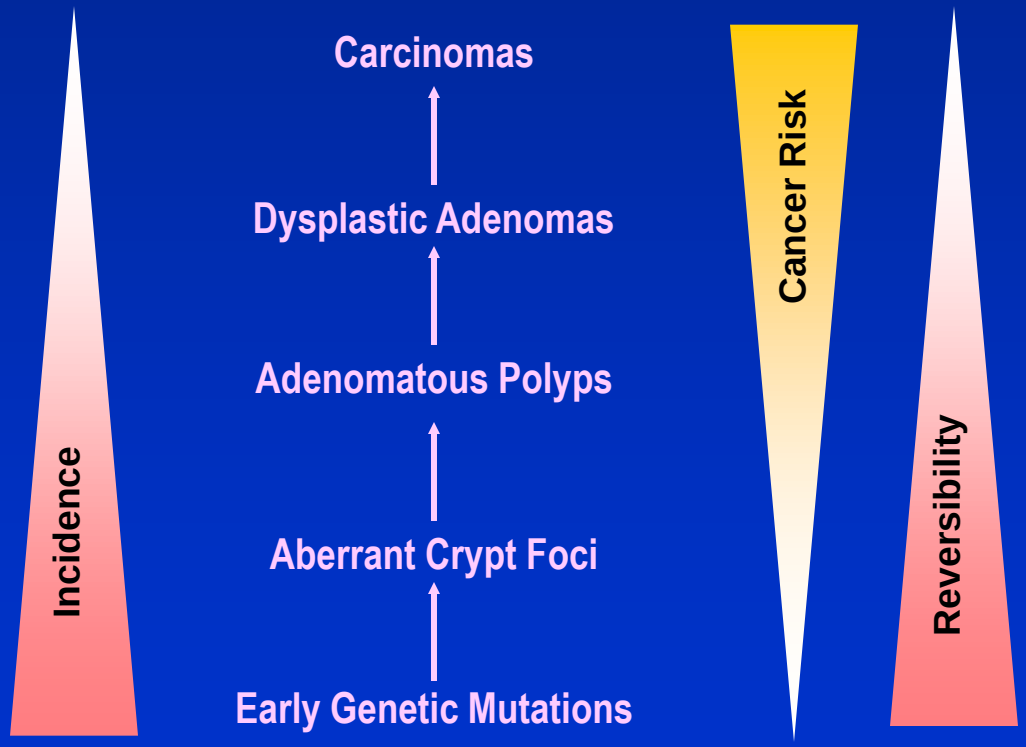
The Pathological Sequence of Colorectal Cancer



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Colon Cancer: Diagnosis and Therapy

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

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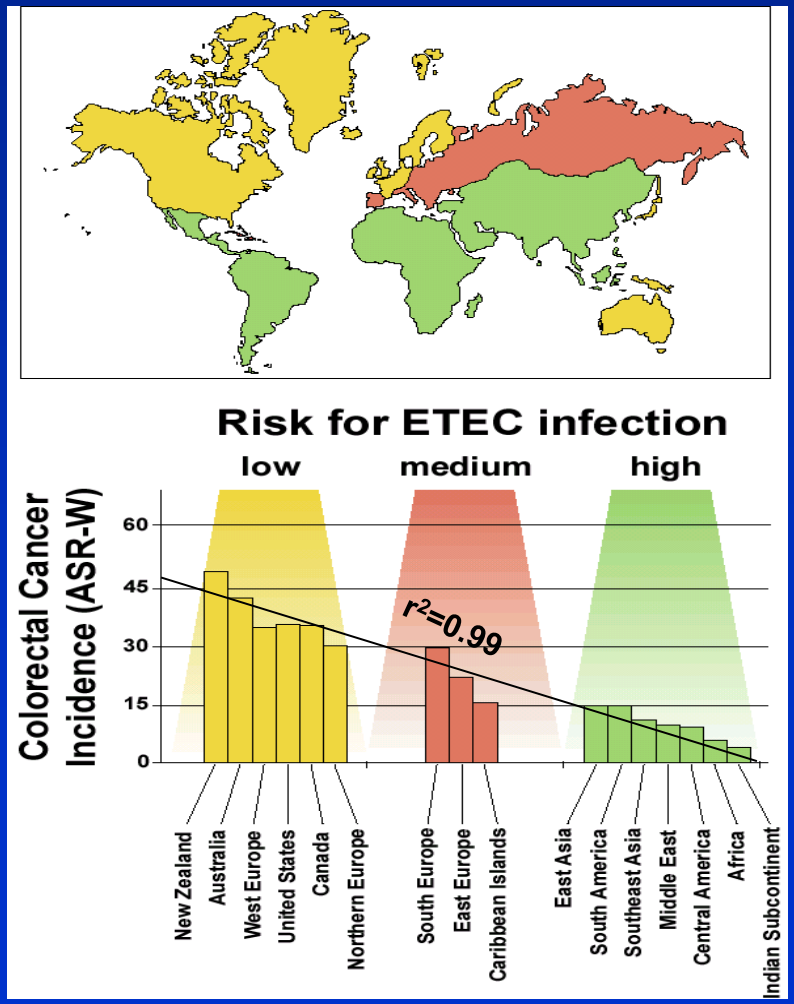
ETEC Infections Confer Resistance to Colon Cancer



Pitari, G.M. et al. (2003)
Proc. Natl. Acad. Sci. USA 100:2695-99

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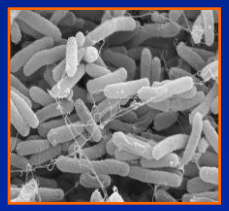
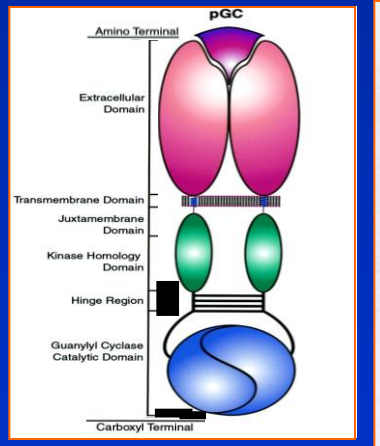
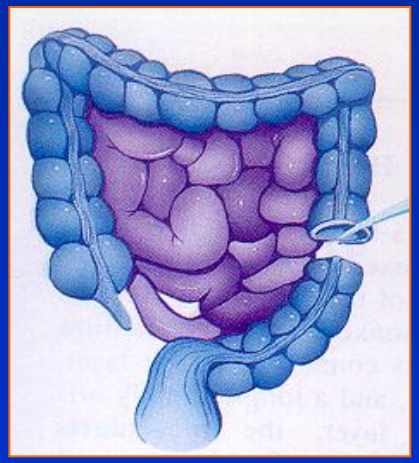
GCC is a Therapeutic Target in Colon Cancer

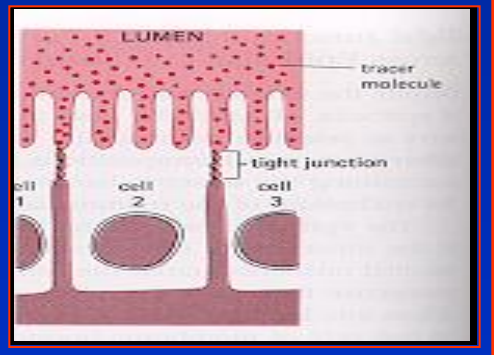


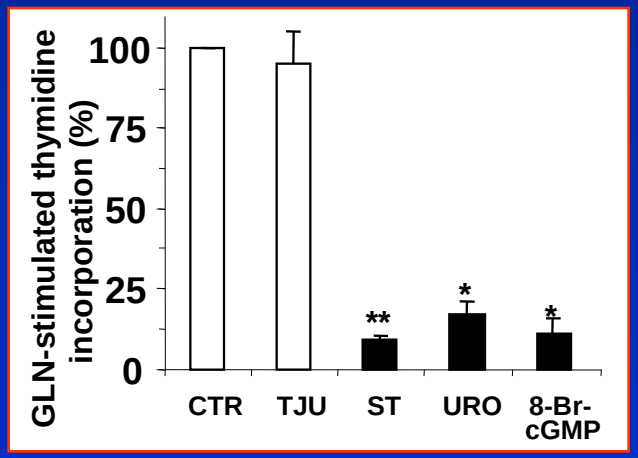
N T F Y C C E L C C N P A C A G C Y

ST









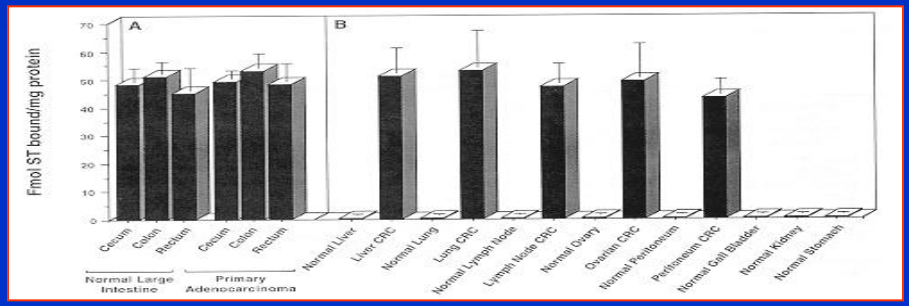
Pitari GM, et al. (2001) Proc. Natl. Acad. Sci. USA 98: 7846-51

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

uroguanylin

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

guanylin



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

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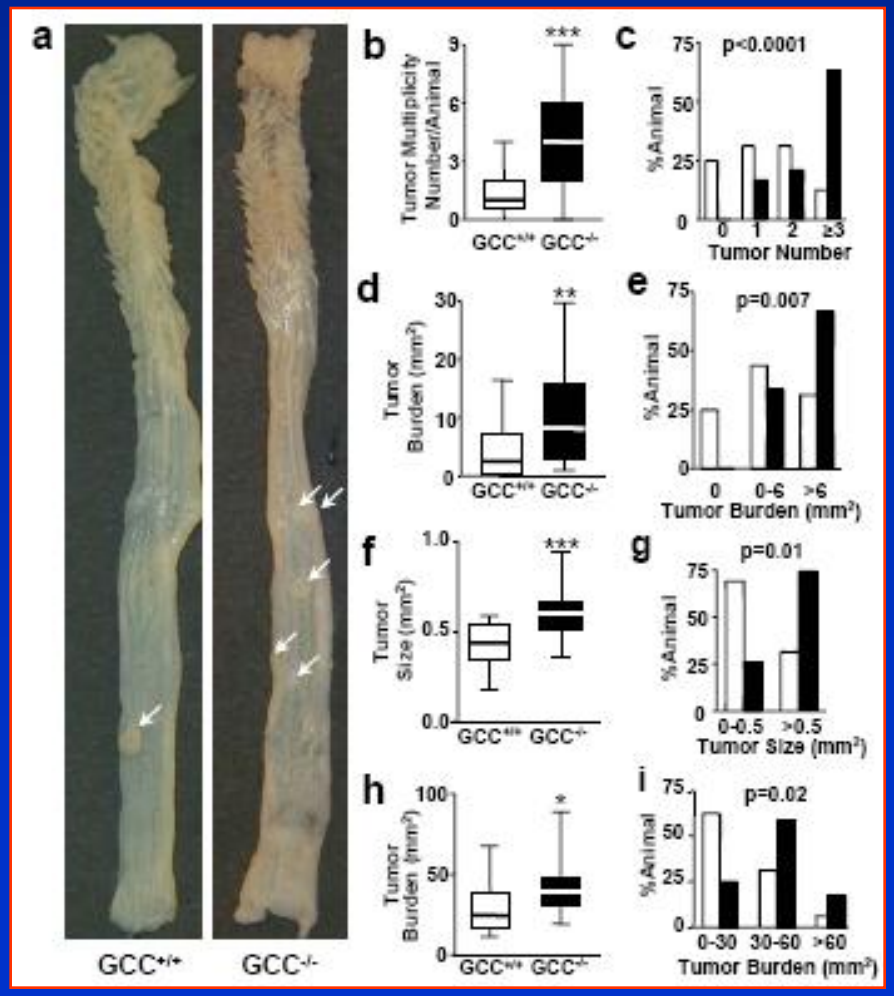
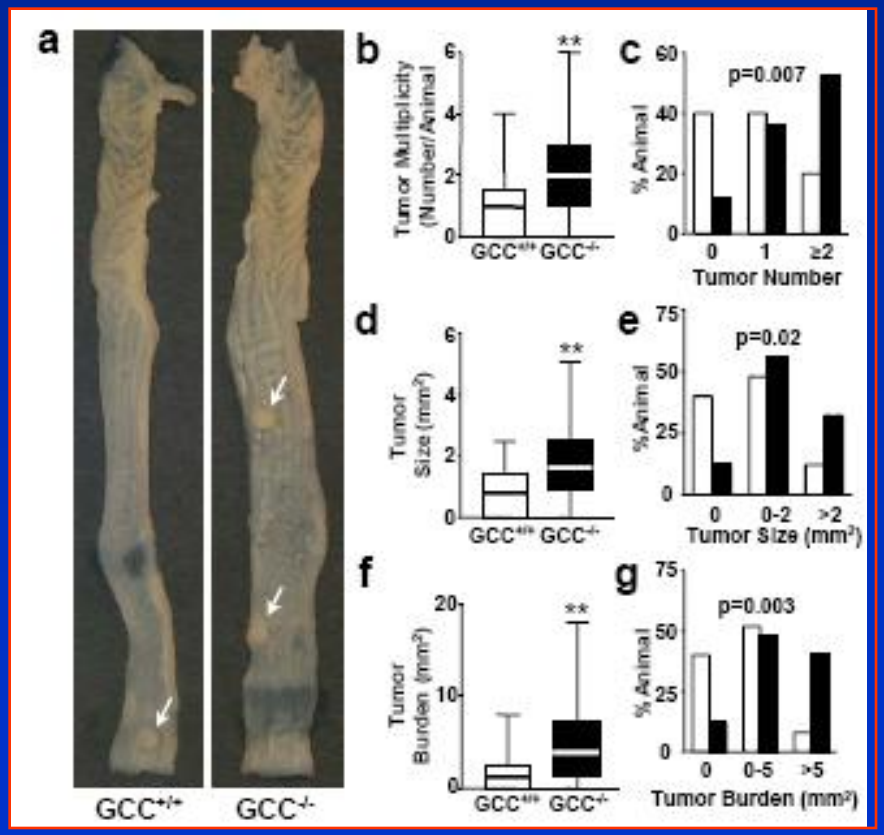
GCC is a Novel Intestinal Tumor Suppressor





Li, P. et al. (2007) Gastroenterology 133:599-607

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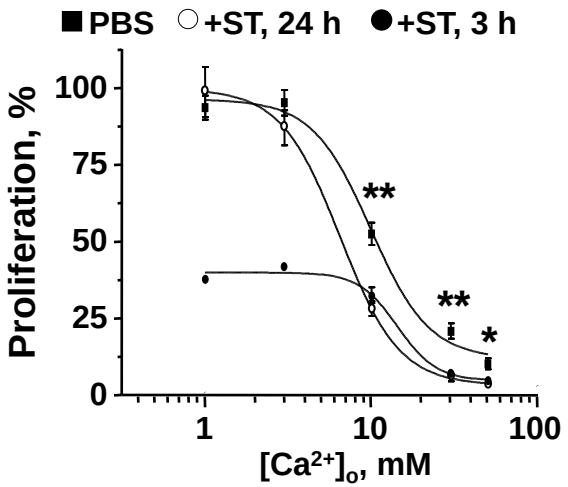
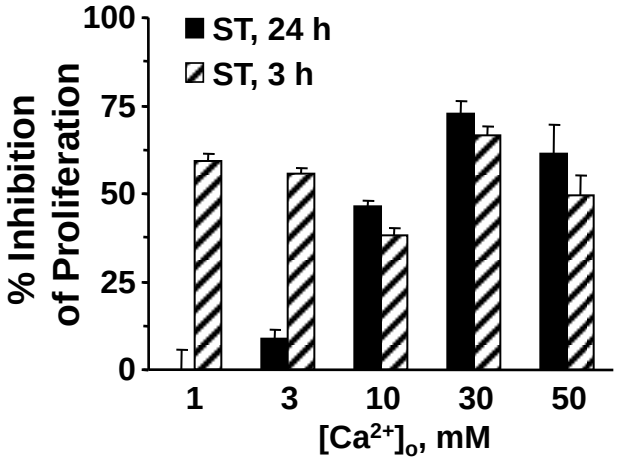
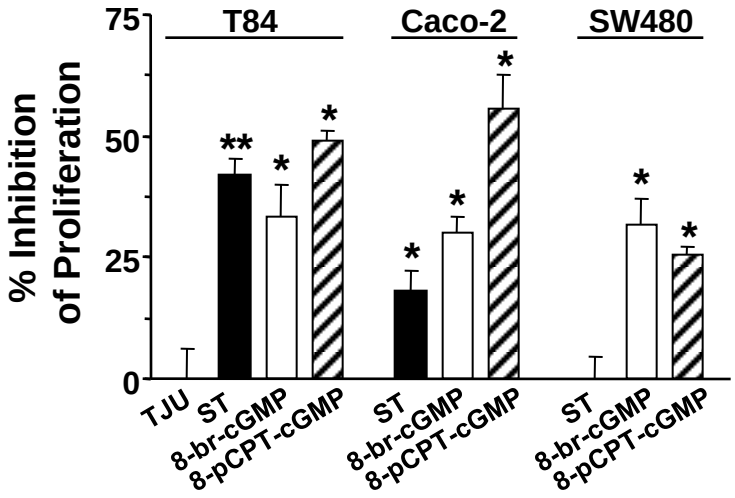
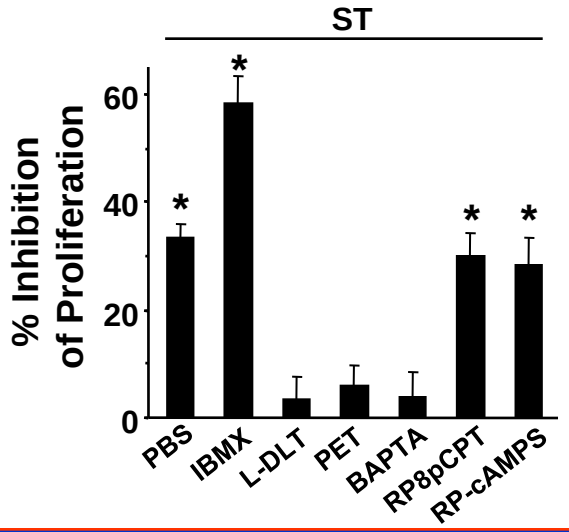
GCC Signaling through cGMP Potentiates Cytostatic Calcium Effects









Pitari, G.M. et al. (2008)
Carcinogenesis 29:1601-7

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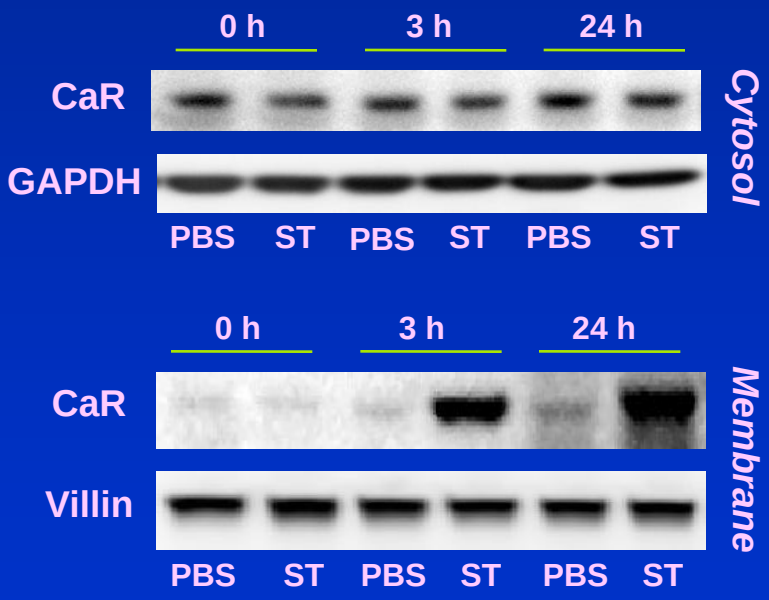
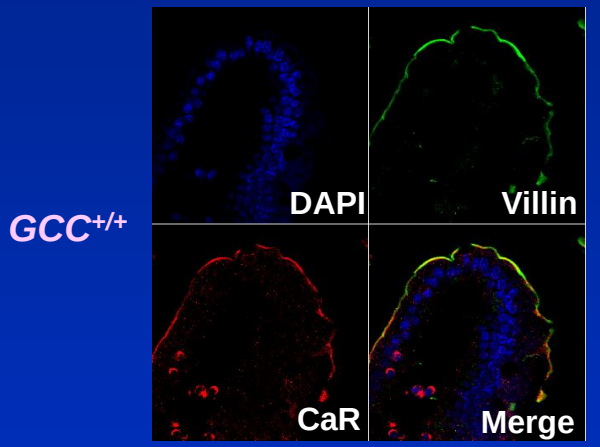
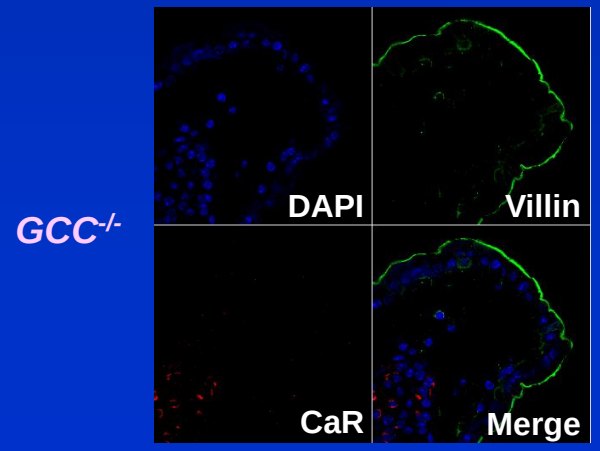
GCC Regulates the Function of Calcium-Sensing Receptor (CaR) in the Intestine







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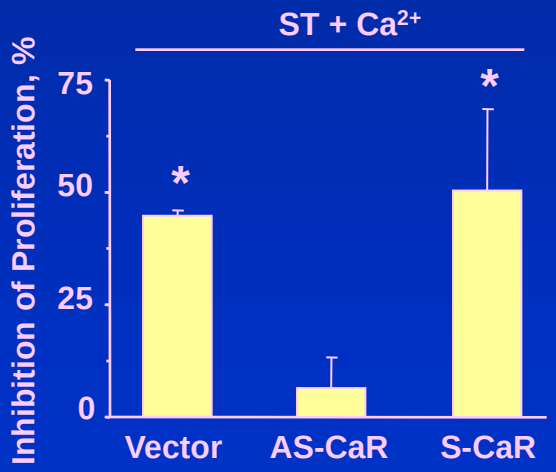
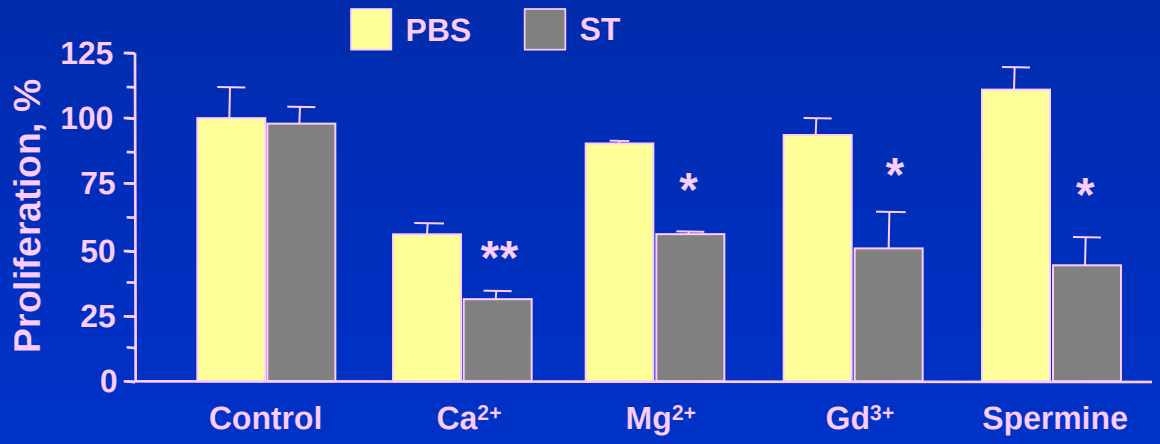
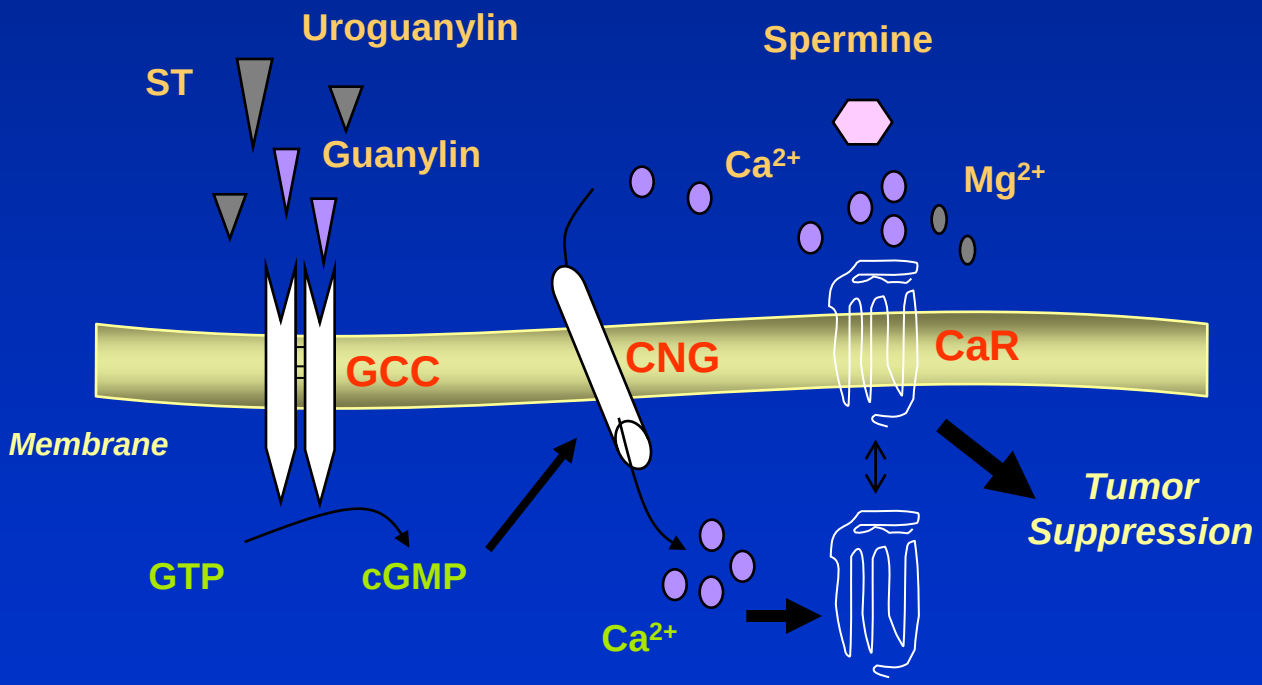
GCC-Targeted Therapy in Combination with Dietary Calcium





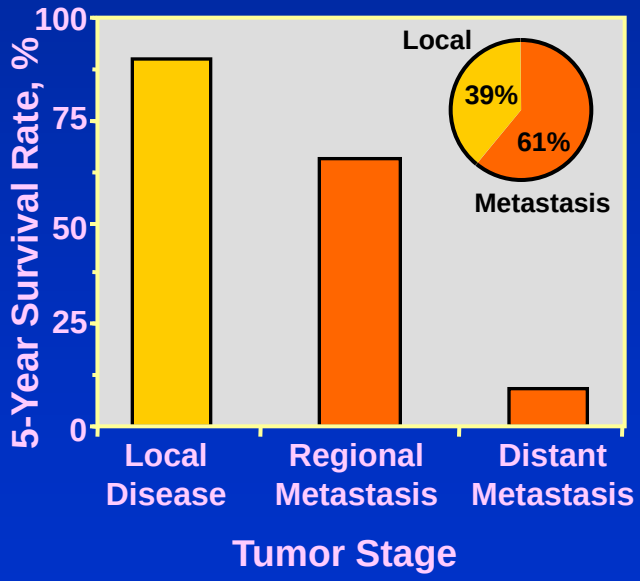
Pitari, G.M. et al. (2008) Carcinogenesis 29:1601-7

A Tumor Suppressor cGMP Signaling Pathway in Colon Cancer

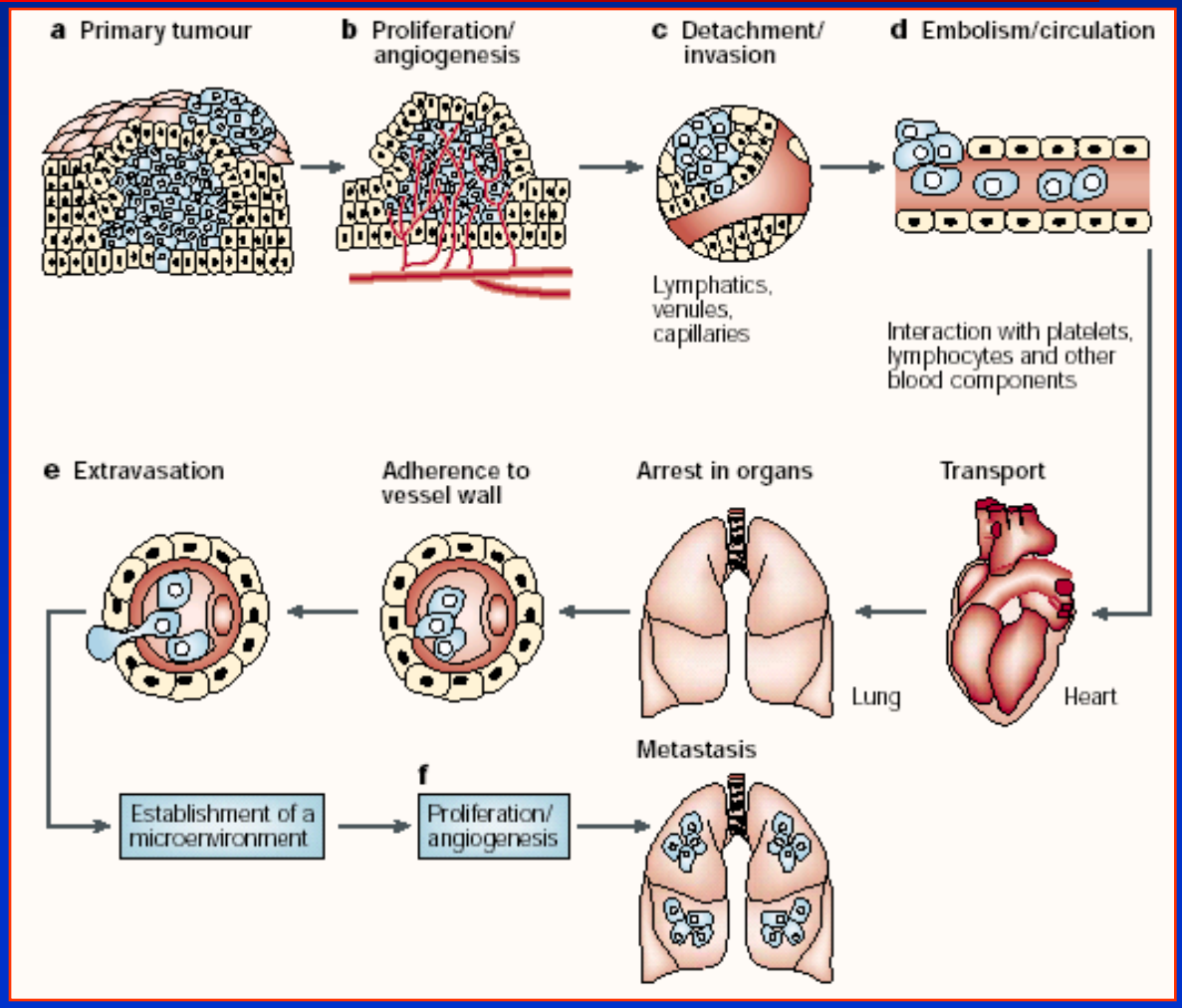


Pitari, G.M. et al. (2008)
Carcinogenesis 29:1601-7

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

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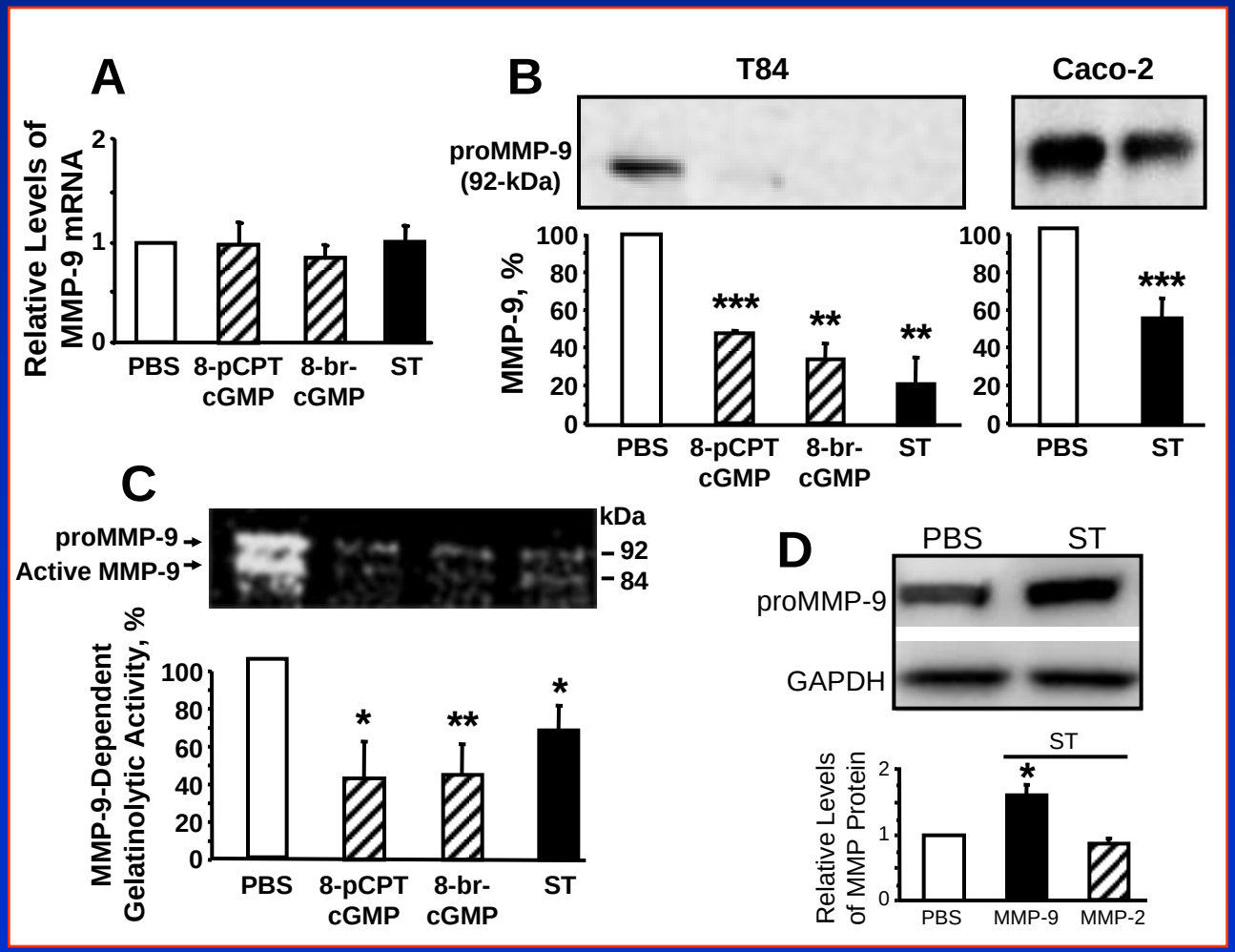
Cyclic GMP Induces Functional Remodeling of Cancer Cell MMP-9



MMP-9 (+)

- Growth
- Vascularization
- Invasion
- Detachment
- Migration
- Extravasation
- Proliferation/angiogenesis

Primary Neoplasm → ***Metastasis***

Lubbe, W.J. et al. (2009) Cancer Res. *On Line First*

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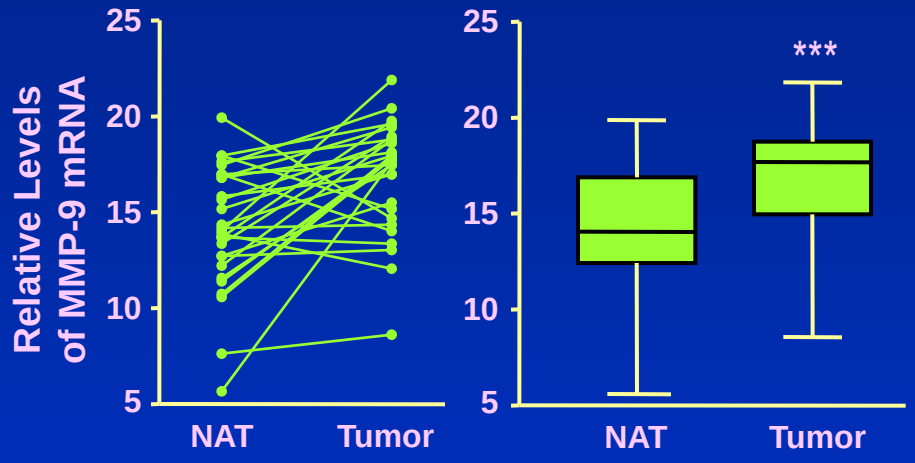
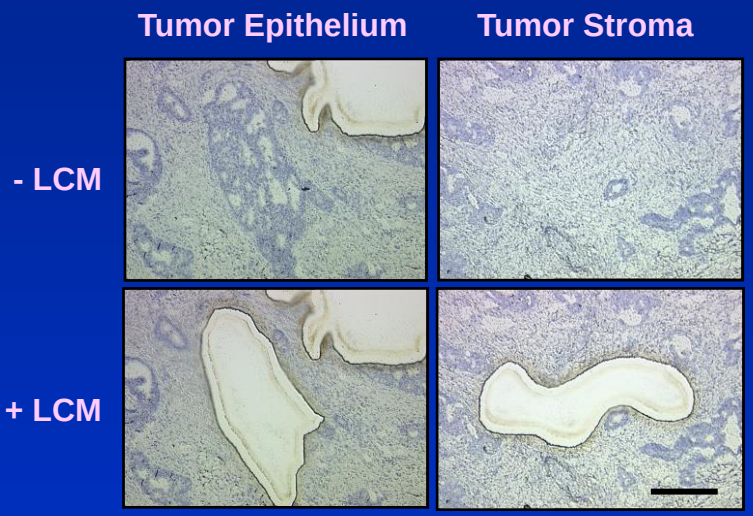
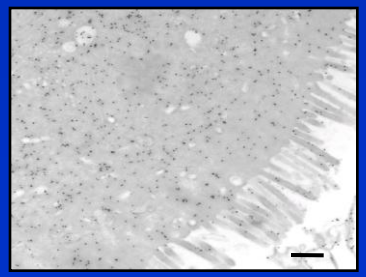
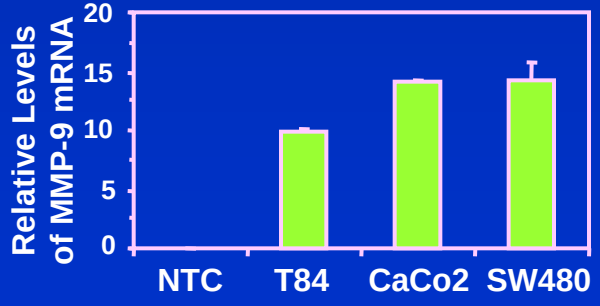
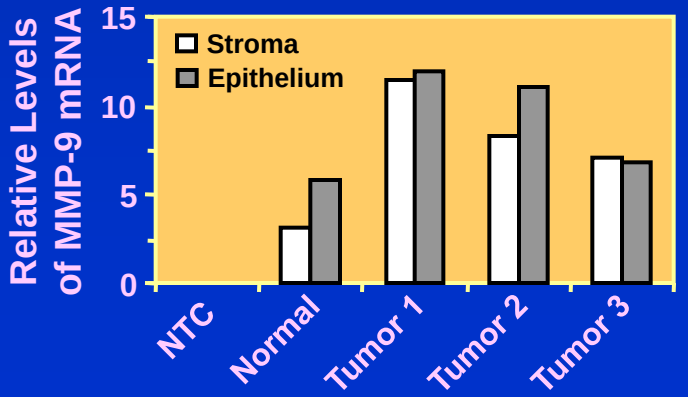
MMP-9 Promotes Metastasis in Colon Cancer

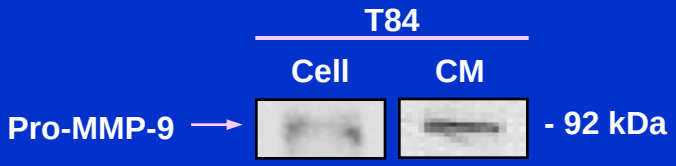






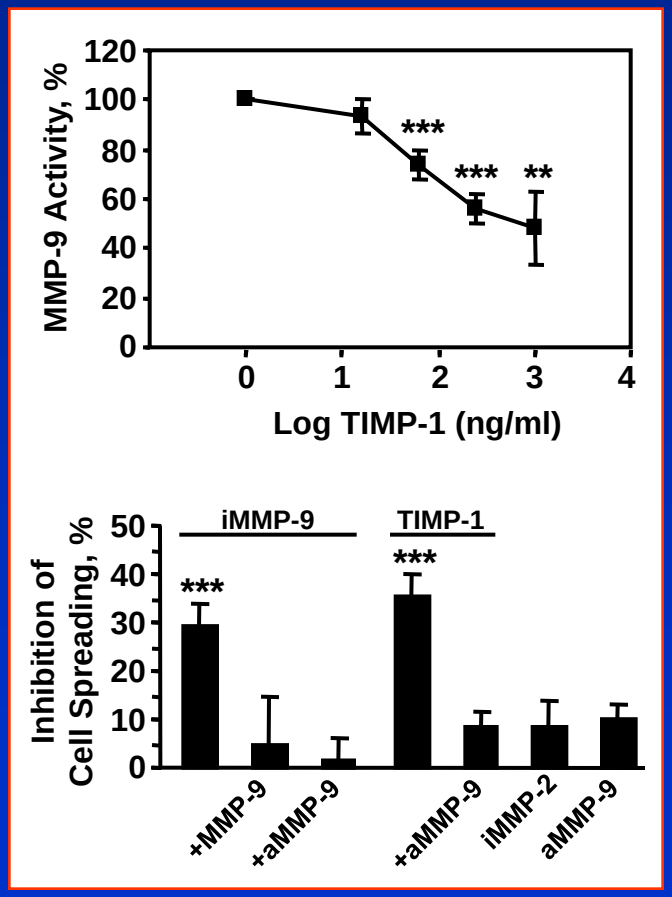


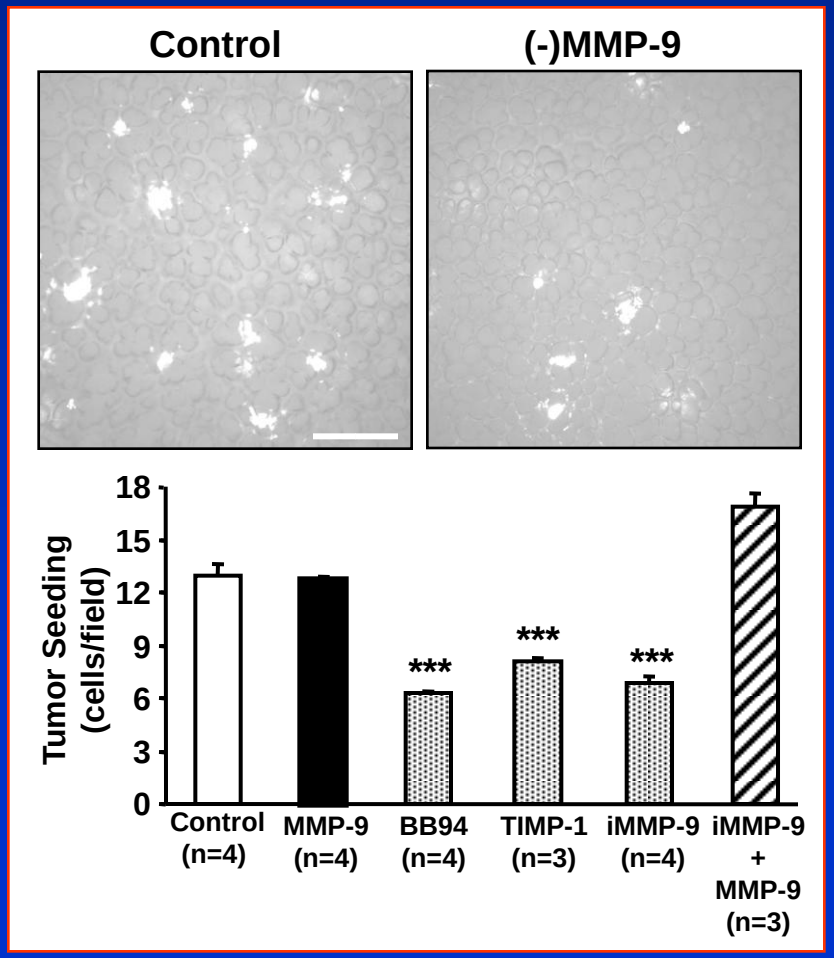




Lubbe, W.J. et al. (2006) Clin. Cancer Res. 12:1876-82

Colon Cancer Cell MMP-9 Induces Metastatic Seeding





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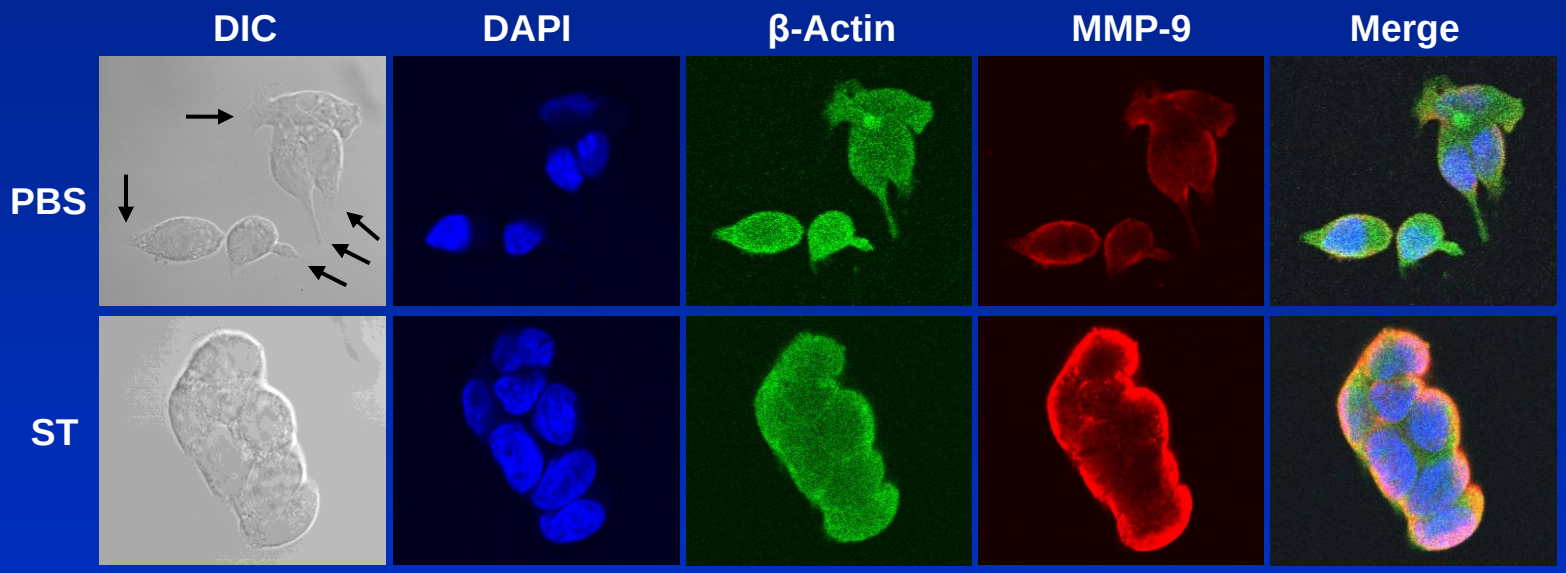
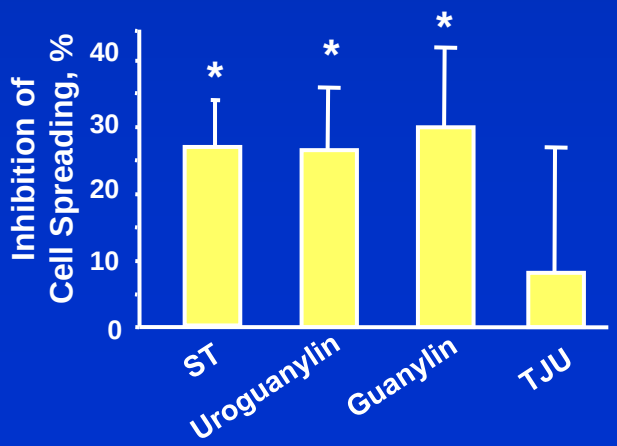
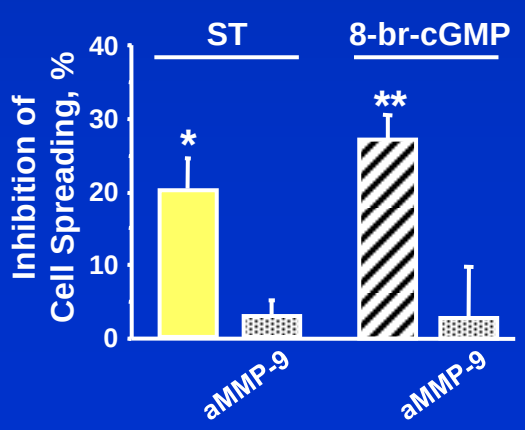
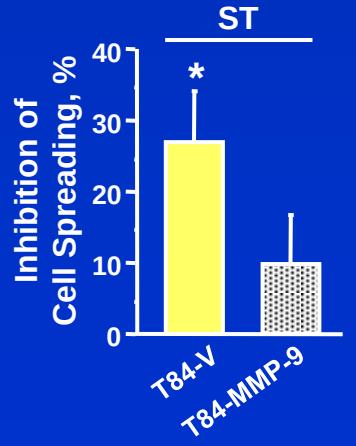
GCC and cGMP Signaling through MMP-9 Regulates Colon Cancer Cell Shape and Spreading









Lubbe, W.J. et al. (2009)
Cancer Res. *On Line First*

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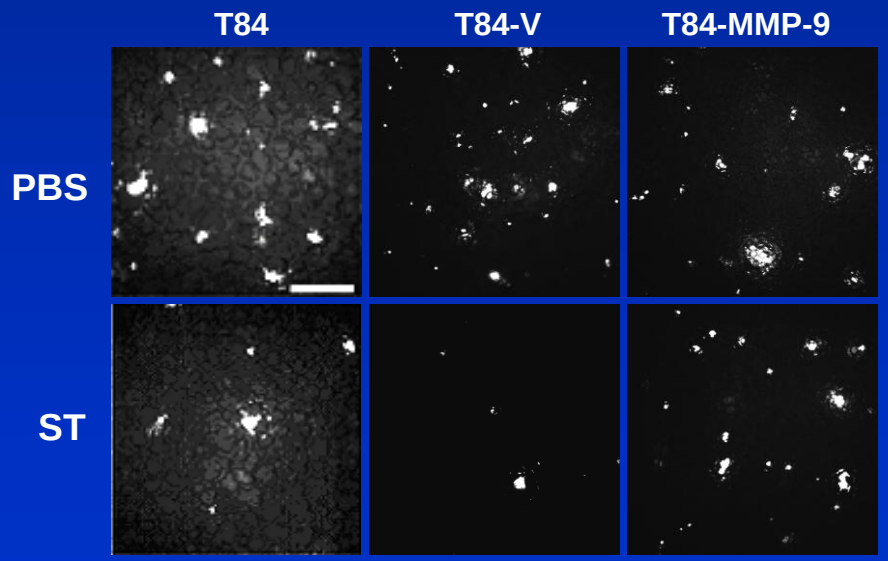
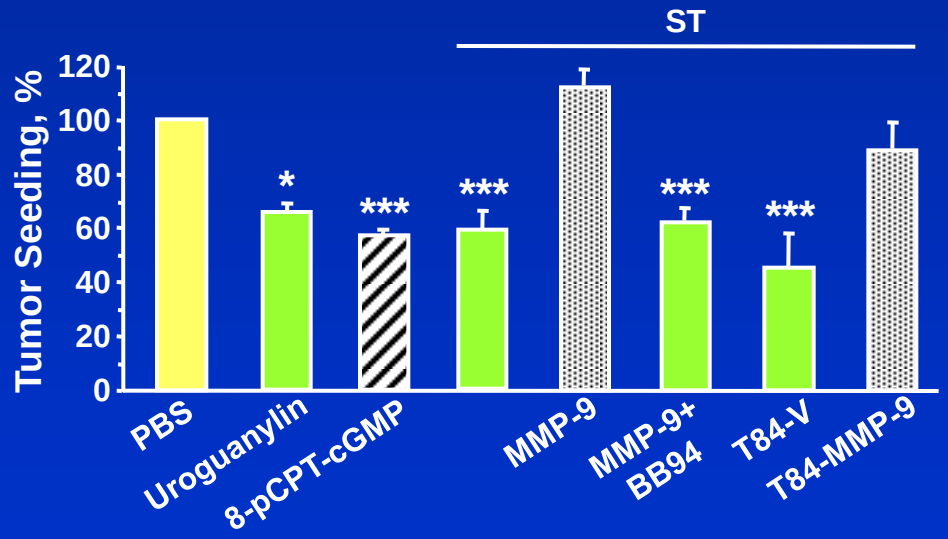
GCC and cGMP Signaling through MMP-9 Suppresses Metastatic Seeding by Colon Cancer Cells



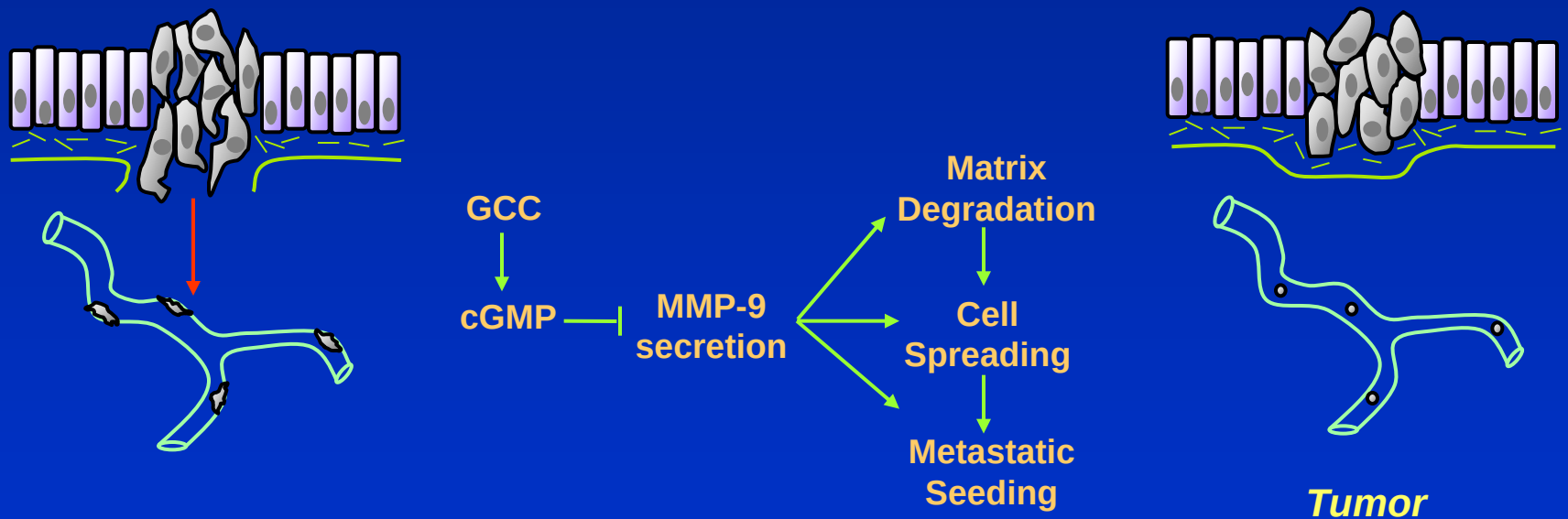


Lubbe, W.J. et al. (2009) Cancer Res. *On Line First*

The Antimetastatic cGMP Signaling Pathway in Colon Cancer Cells

(-) cGMP Pathway

(+) cGMP Pathway



Metastasis

Tumor Containment / Vascular Clearance

Lubbe, W.J. et al. (2009) Cancer Res. *On Line First*

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