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Guanylyl Cyclase C (GC-C) Inhibits Human Colon Carcinoma Cell Growth

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GUANYLYL CYCLASE C (GC-C) INHIBITS HUMAN COLON CARCINOMA CELL GROWTH

Giovanni Mario Pitari

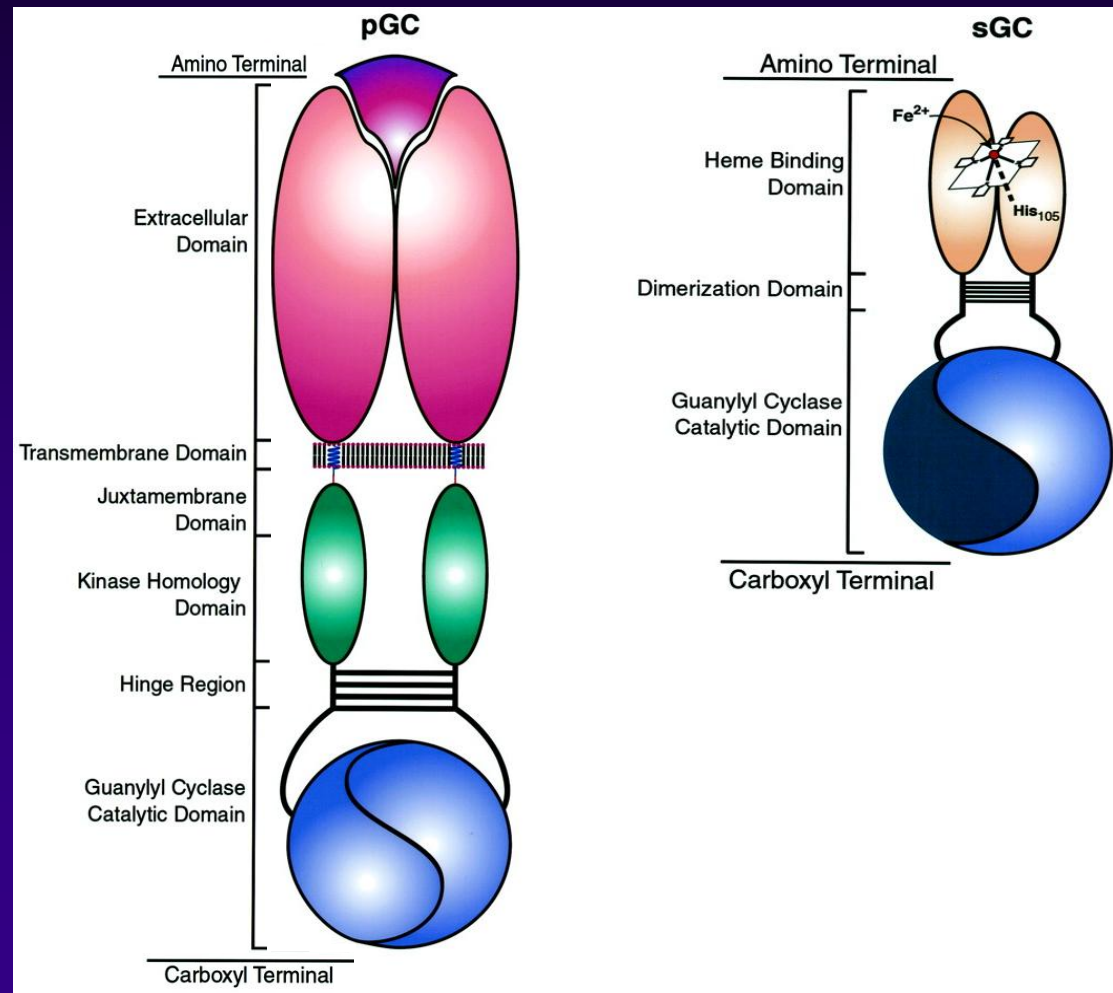
Division of Clinical Pharmacology

Department of Medicine

Thomas Jefferson University

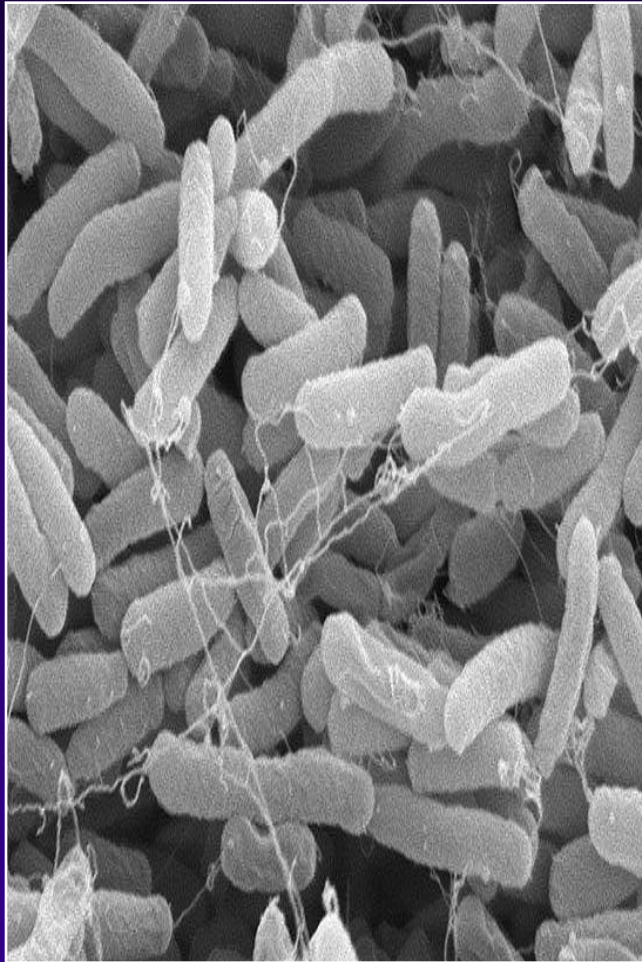
Philadelphia, PA 19107

Guanylyl Cyclase Family





The E. coli Heat-Stable Enterotoxin (ST) Binds GC-C



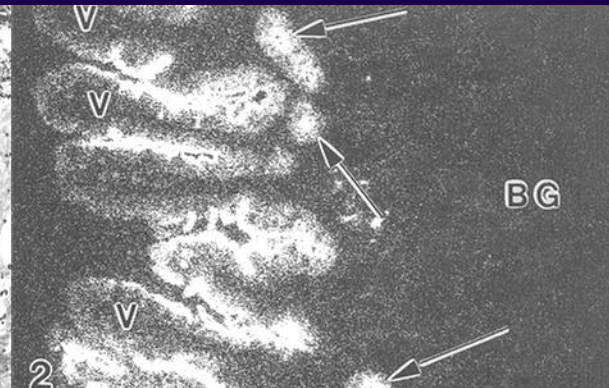
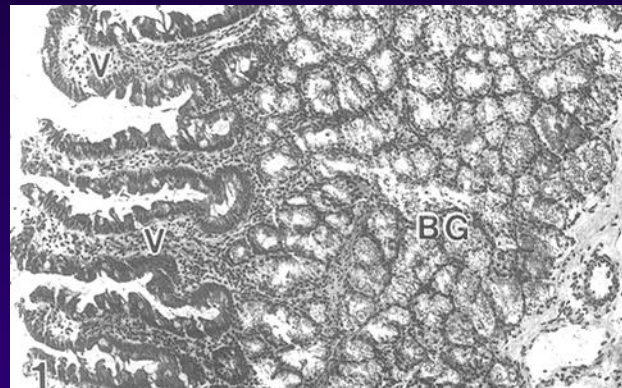
NTFYCCELCCNPACAGCY



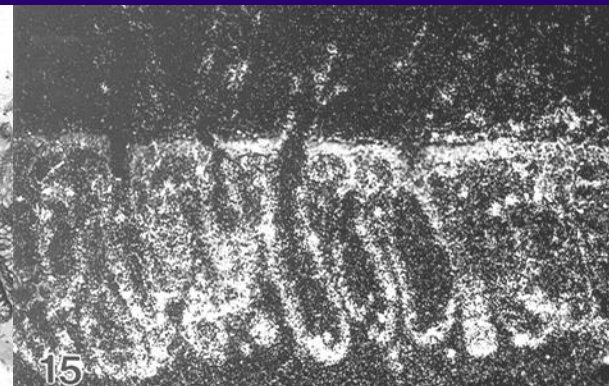
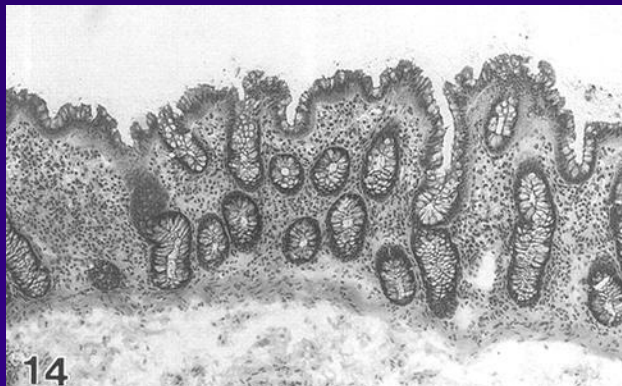
GC-C is Localized to Intestinal Epithelial Cells

H&E

^{125}I -ST Binding

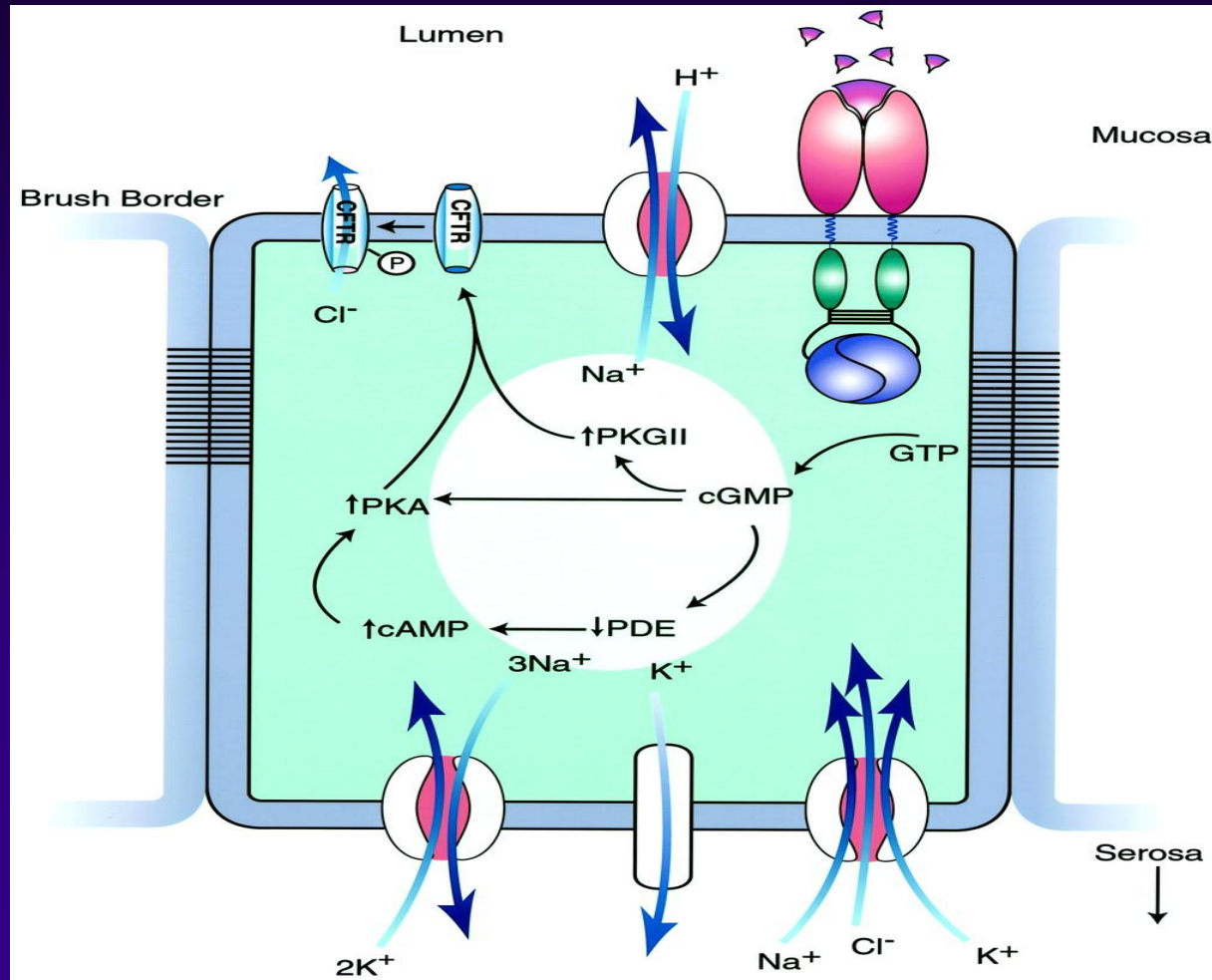


Small
Intestine



Large
Intestine

GC-C Signaling Cascade





Does GC-C Mediate More Than Fluid Transport in Intestine?

- *Does GC-C regulate intestinal epithelial cell proliferation?*
- *What are the molecular mechanisms by which GC-C regulates intestinal cell proliferation?*



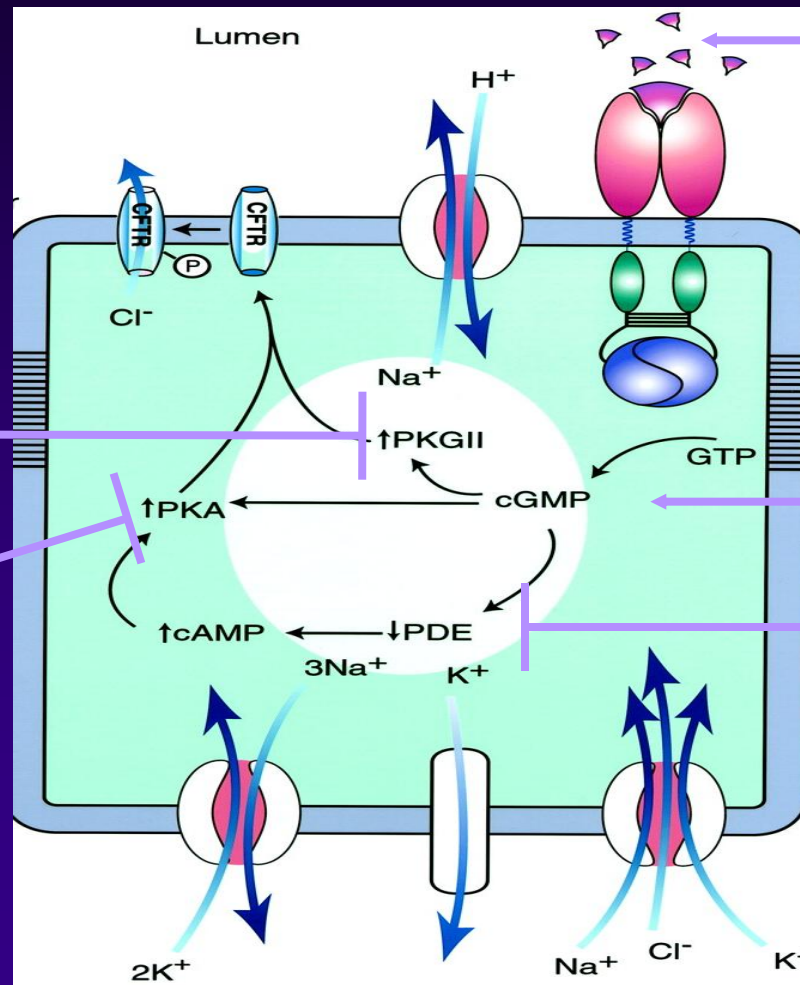
Protocol Design & Materials

Cell Lines:
T84, Caco-2, SW480

Pro-Proliferative Agents:
FBS, L-Glutamine

KT5823
RP8pCPT-cGMP

KT5720
Rp-cAMPs



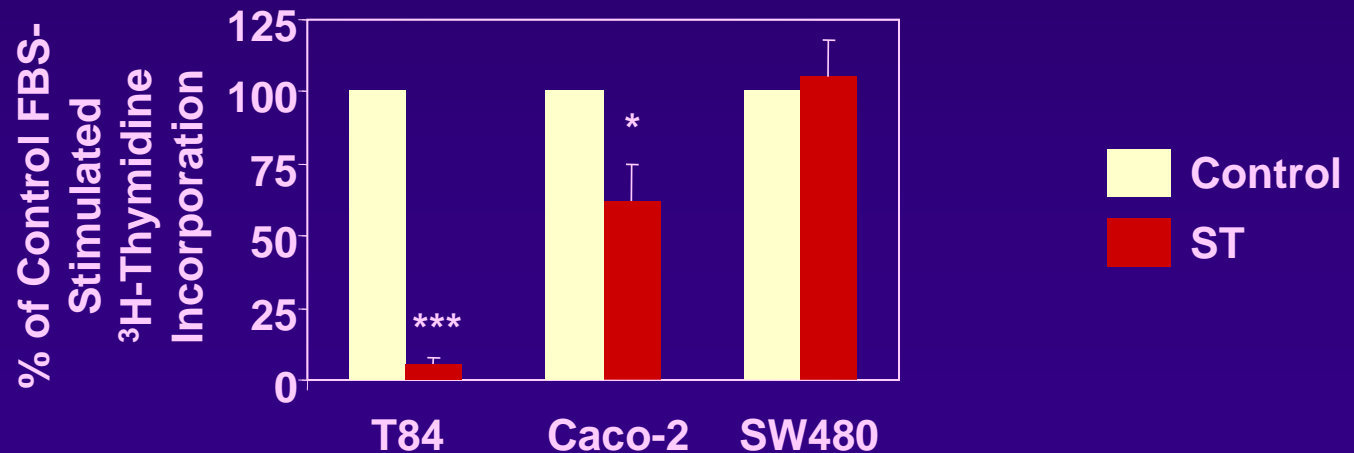
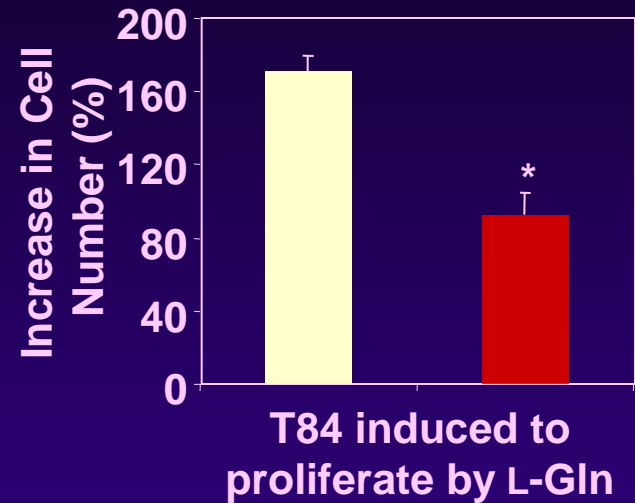
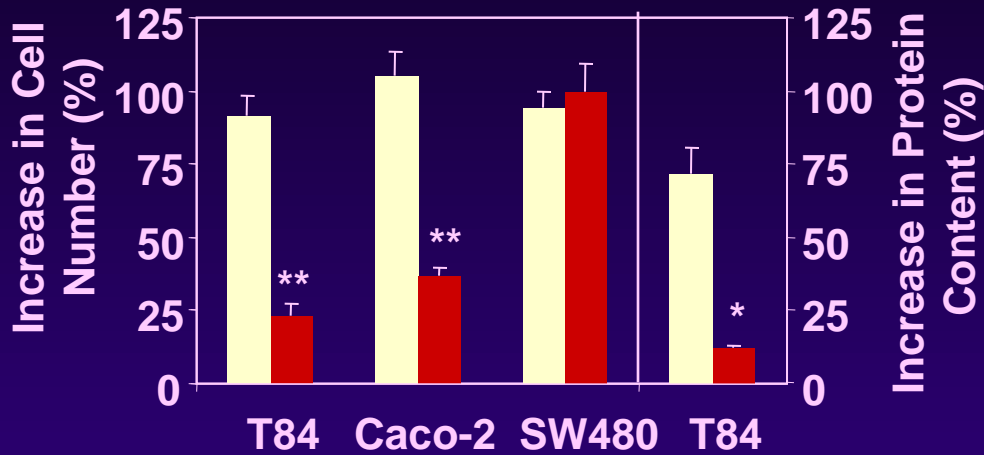
ST
Uroguanylin

8-Br-cGMP

Milrinone



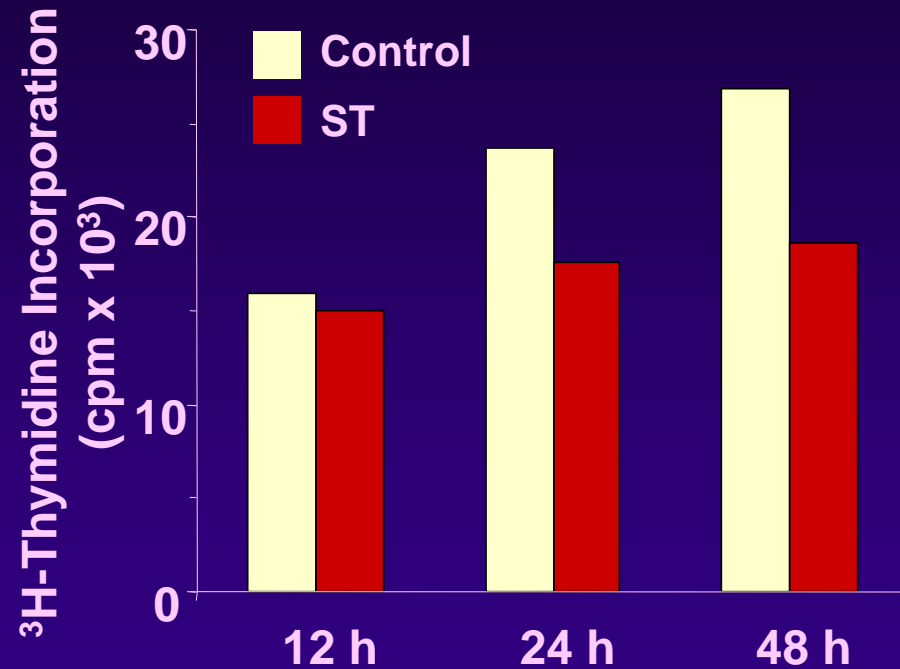
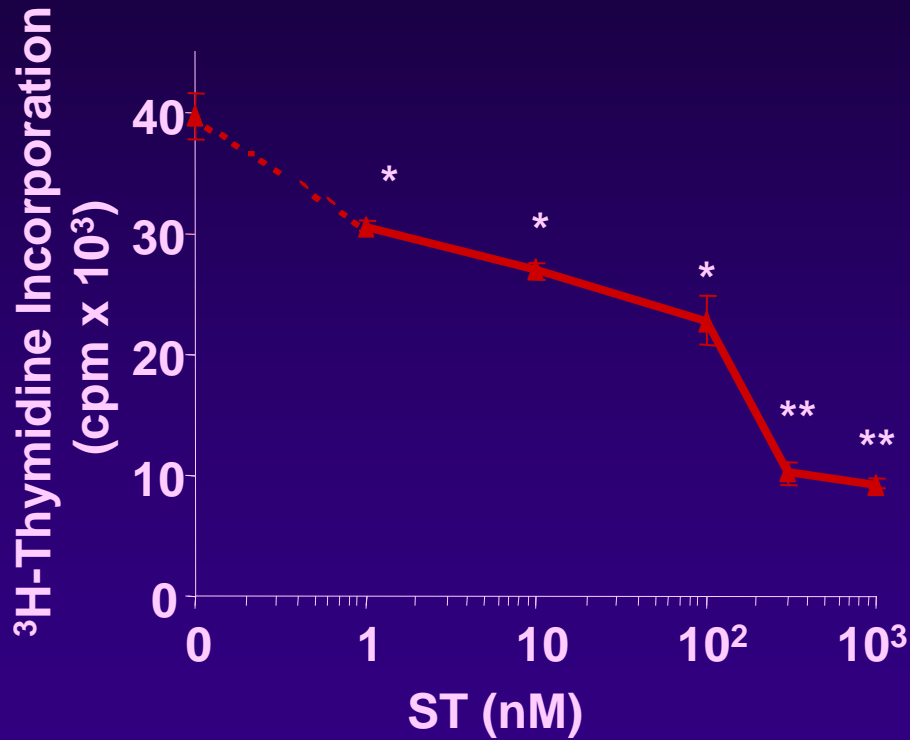
ST Inhibits Intestinal Cell Proliferation



Control
ST

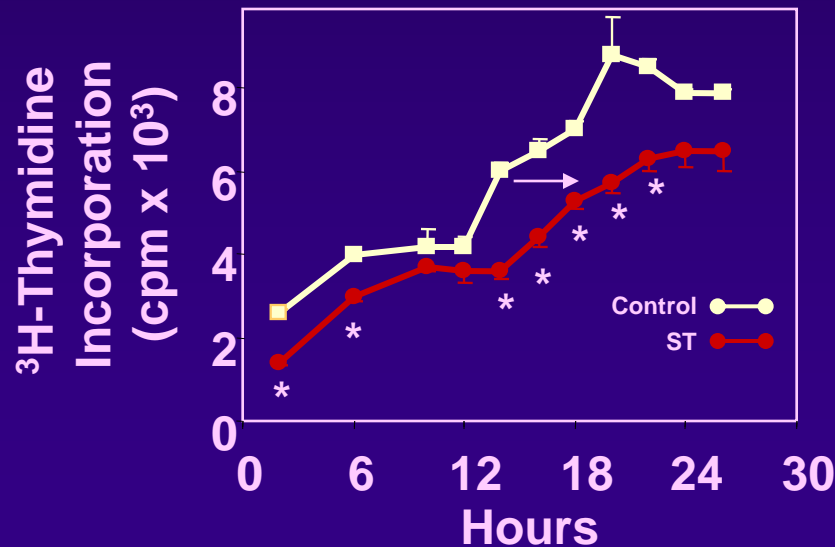
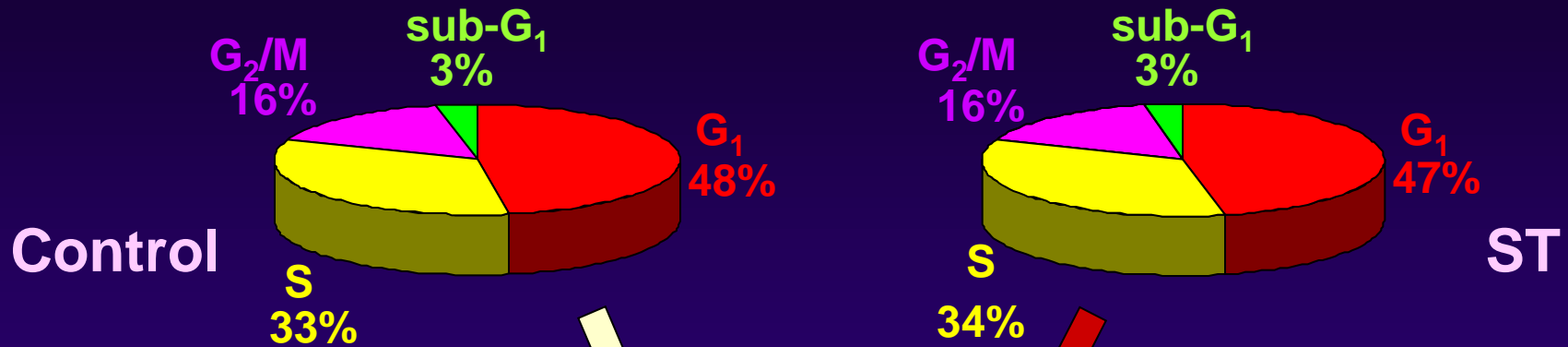


ST Inhibition is Dose- and Time-Dependent



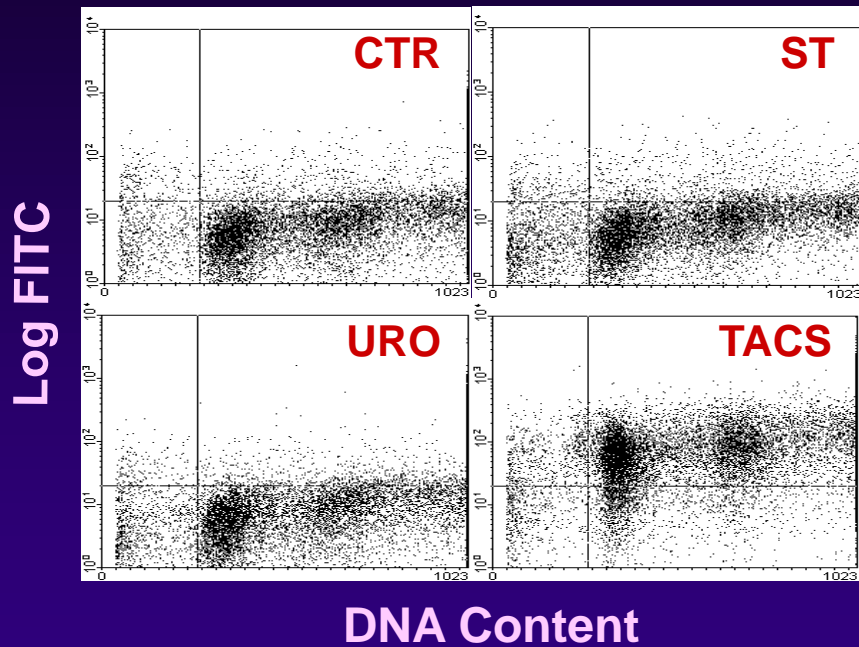


ST Delays, But Does Not Arrest, the Cell Cycle





GC-C Agonists Do Not Induce Apoptosis or Necrosis



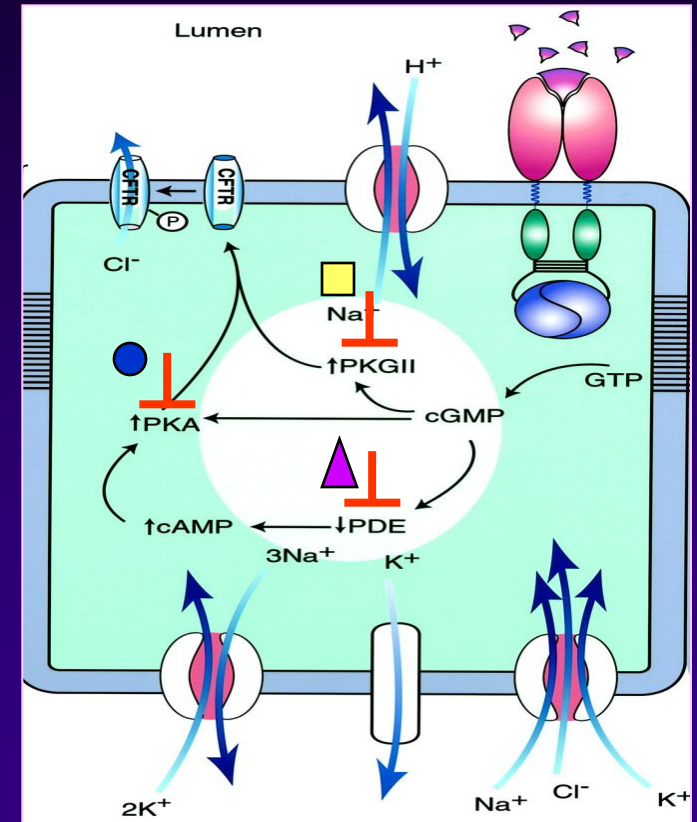
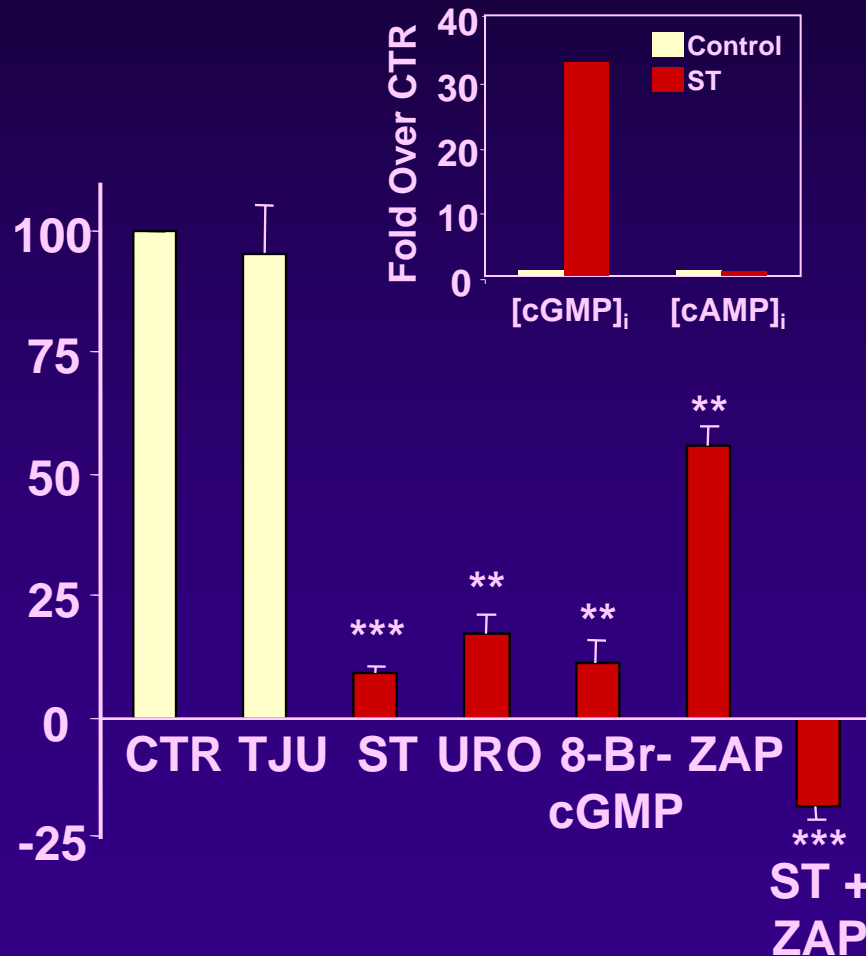
	Control	ST (1 μ M)	Uro (1 μ M)	TACS
% Apoptosis	7.4 \pm 0.5	9.1 \pm 1.2	6.9 \pm 0.9	75.3 \pm 2.1**

** p<0.01



ST Cell Signaling Pathway for the Inhibition of Proliferation

GLN-stimulated Thymidine Incorporation (%)



- ▲ Milrinone
- KT5823, RP8pCPT-cGMP
- KT5720, Rp-cAMPs

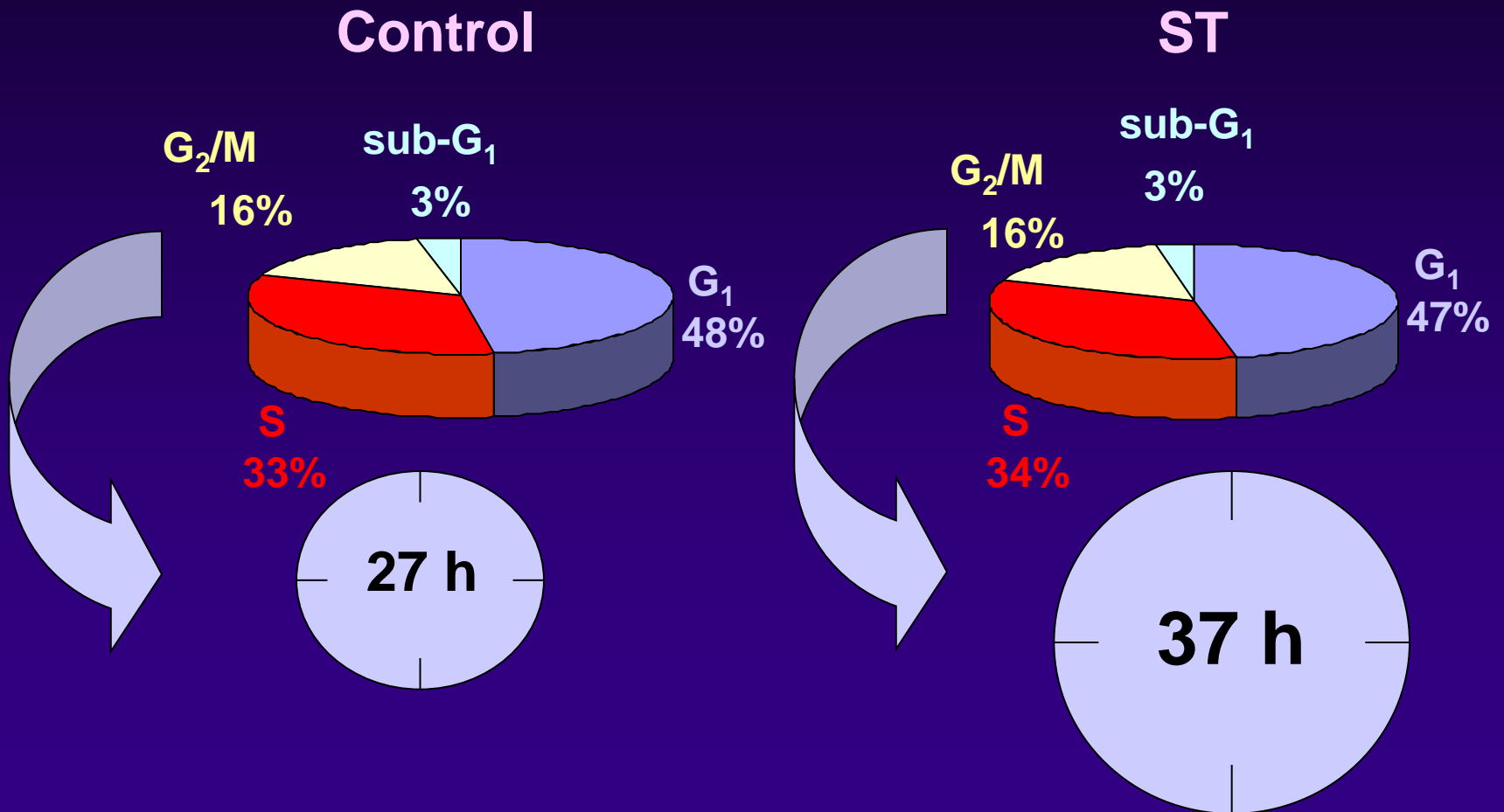


Summary

- *GC-C activation inhibits colon carcinoma cell proliferation in vitro*
- *Inhibition of proliferation results from a prolongation of the cell cycle, not cell death*
- *The cytostatic effect of ST is mediated by an increase in $[cGMP]_i$*



ST-Dependent Cytostasis Does Not Reflect Arrest, but Retardation, of the Cell Cycle





Implications of GC-C Regulation of Proliferation

- *Endogenous GC-C ligands (guanylin and uroguanylin) may represent cell cycle regulators*
- *Along the crypt-to-villus axis, GC-C may regulate the transition of intestinal epithelial cells from proliferative to differentiated states*
- *GC-C agonists may be utilized as novel cytostatic agents for the prevention and treatment of colorectal cancer*



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