

The Hebrew University of Jerusalem,
Faculty of Medicine, School of Pharmacy



Prof. Avri Rubinstein

Academic Research and Industrial Development: From Bench to Production Floor



Annual Meeting Dec 10, 2008

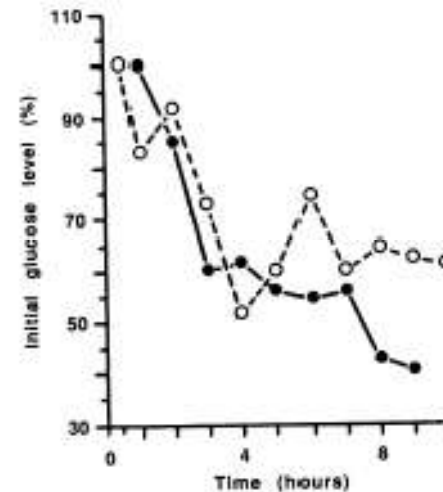
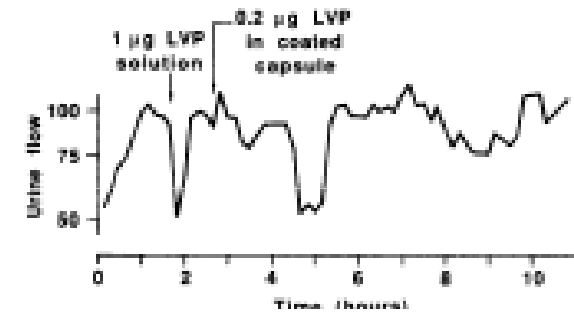
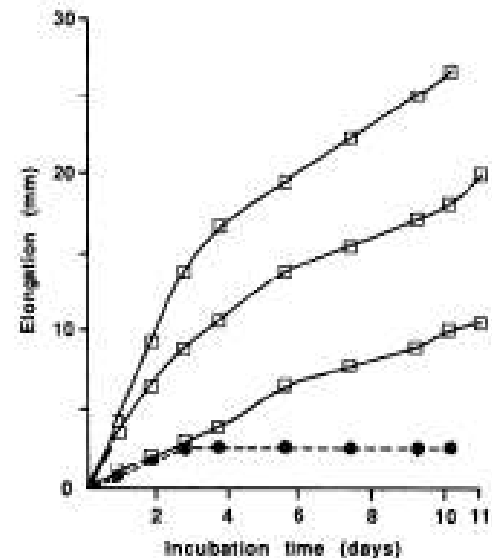
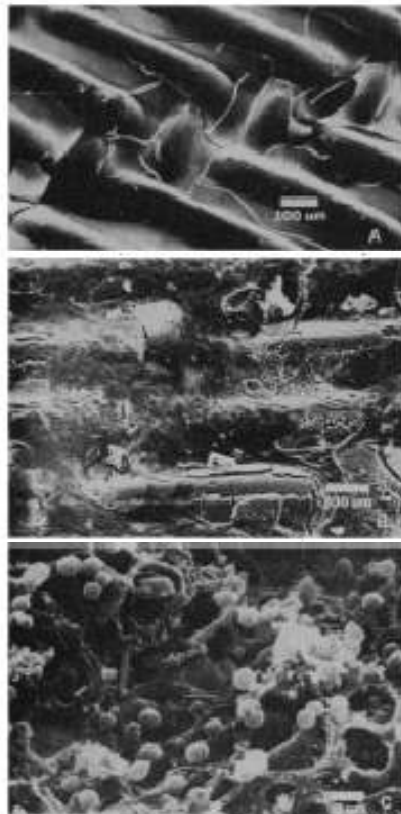
1986



A New Approach to the Oral Administration of Insulin and Other Peptide Drugs

MURRAY SAFFRAN,* G. SUDESH KUMAR,† CELIN SAVARIAR,
JEFFREY C. BURNHAM, FREDERICK WILLIAMS, DOUGLAS C. NECKERS

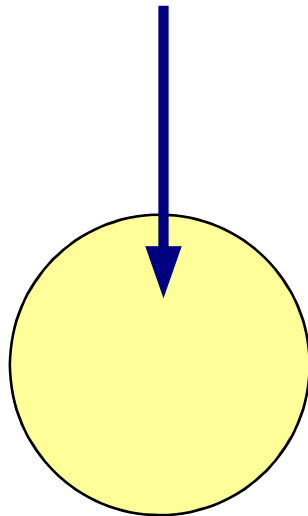
SCIENCE, 233:1081, 1986



Saffran's Approach

Acrylic copolymer coat containing N=N bonds

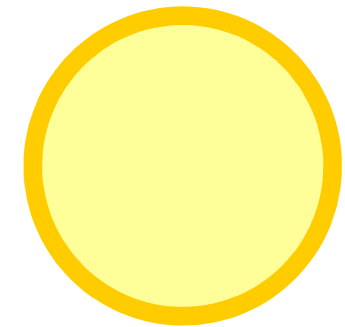
1. Lysine-vasopressine
2. Insulin



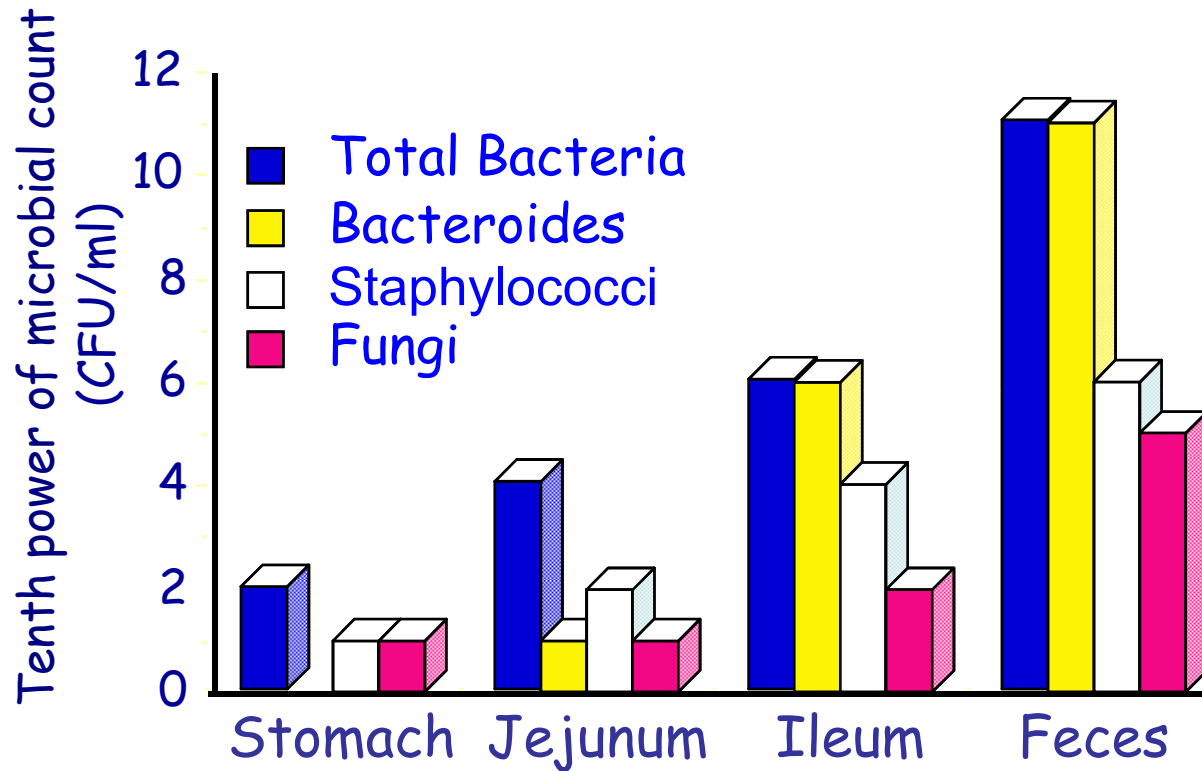
styrene / hydroxyethylmethacrylate



divinylazobenzene



Bacterial-Count Gradient Along the Human GI Tract



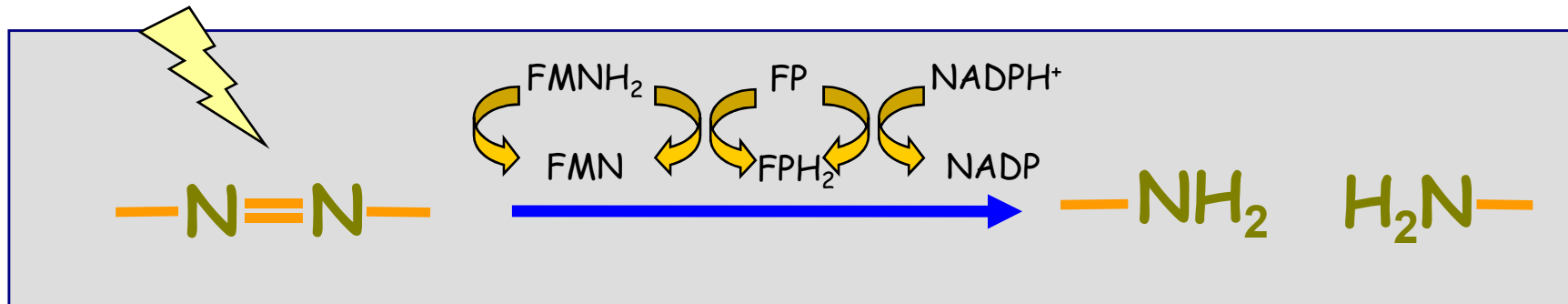
Simon & Gorbach, *Gastroenterology*, 86:174, 1984

Rubinstein, *Biopharm. Drug Dispos.*, 11:465, 1992

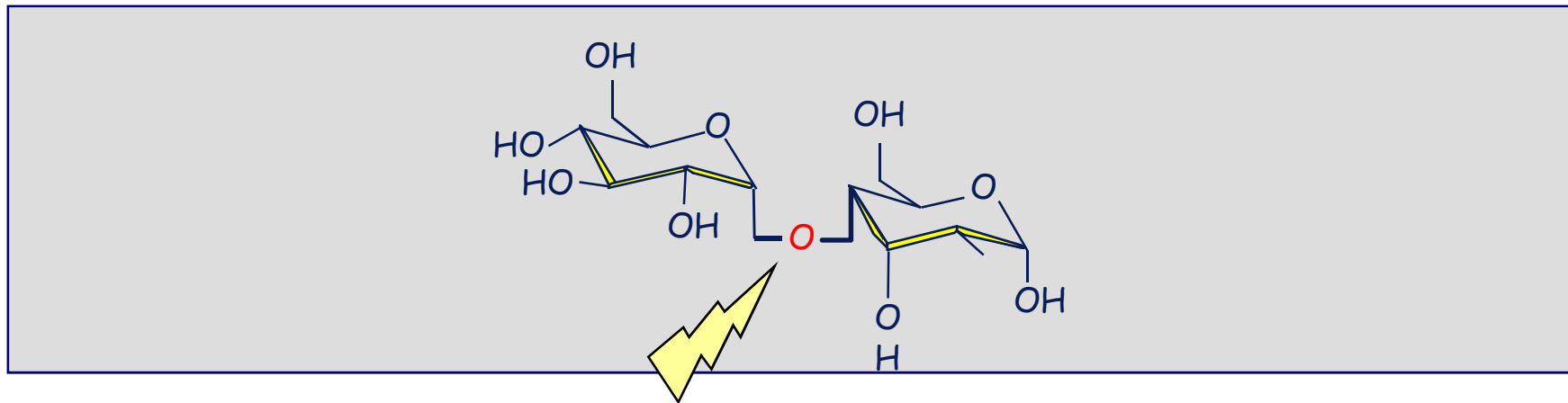


Specific Approaches

Azo bonds reduction:

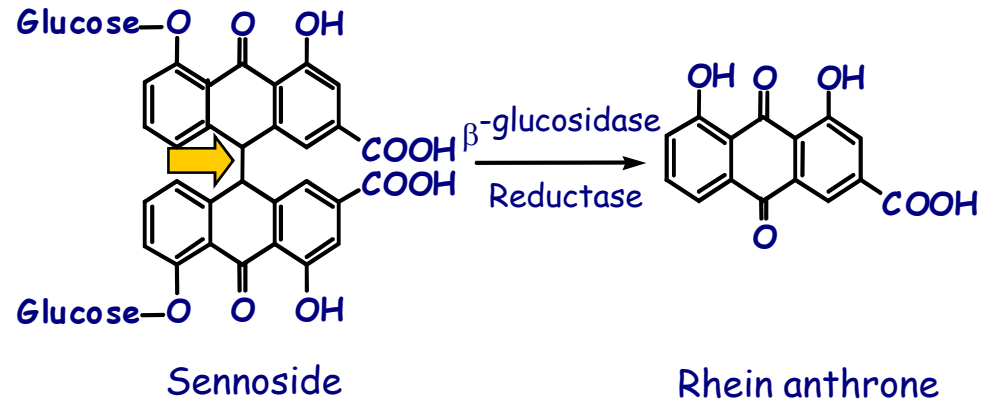


Glycosidic bonds hydrolysis:

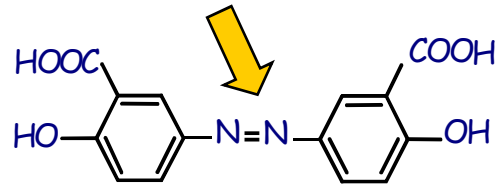


Marketed Prodrugs

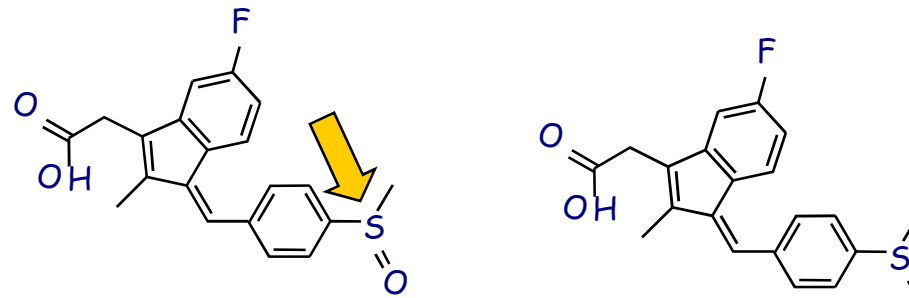
Senna



Olsalazine



Sulindac



Sulindac (sulfoxide)

Sulindac sulfide



Colon-Specific Drug Delivery - Why?

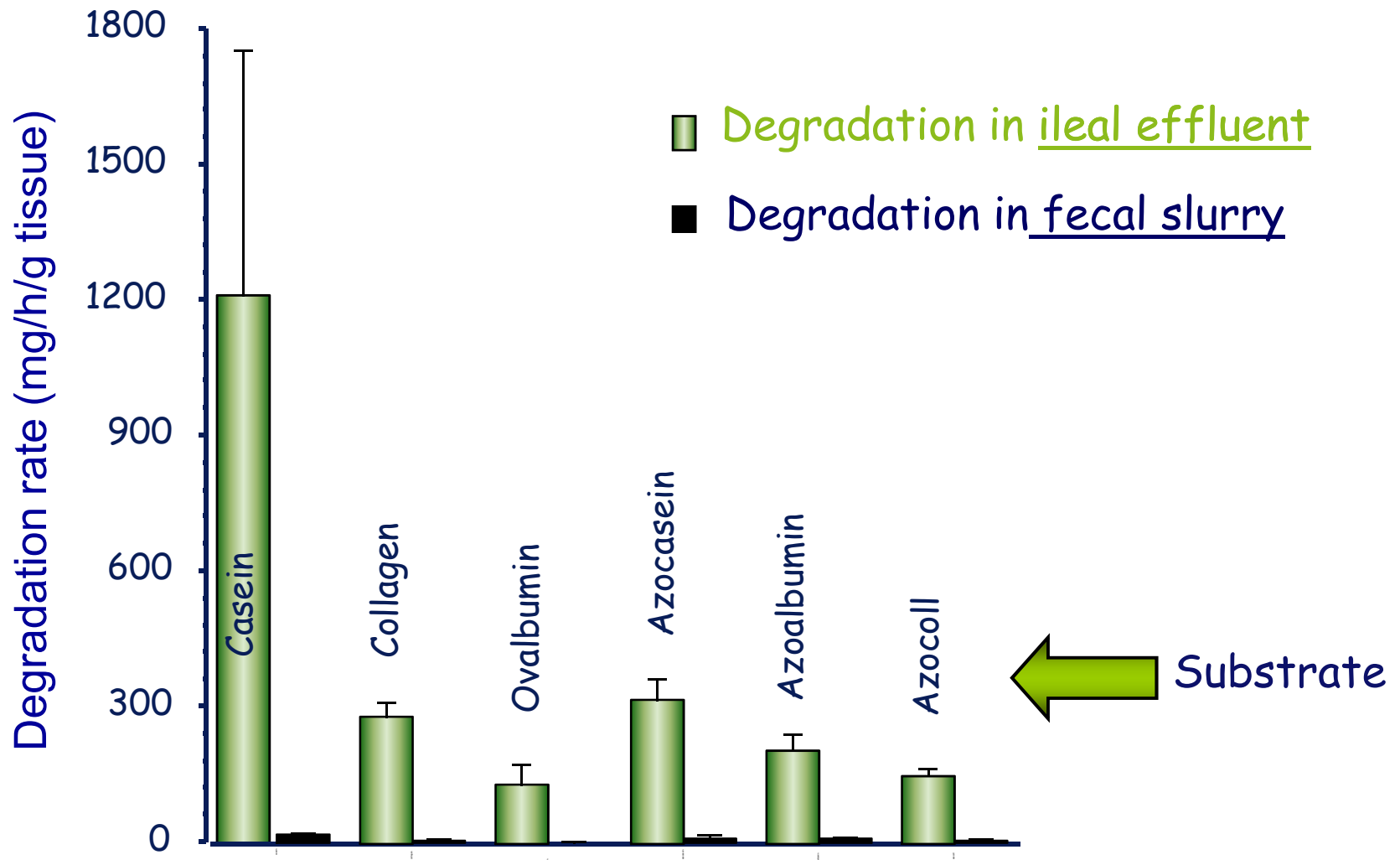
Local treatment of colon diseases

- IBD (Inflammatory bowel diseases)
 - Salicylates: 5-ASA and its prodrugs
 - Corticosteroids: budesonide
- CRC (Colorectal cancer) ?

Absorption of Proteinaceous drugs



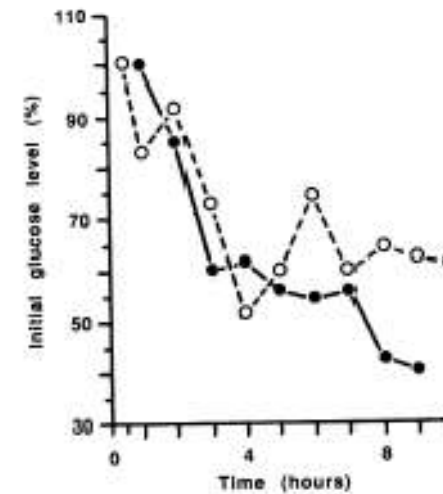
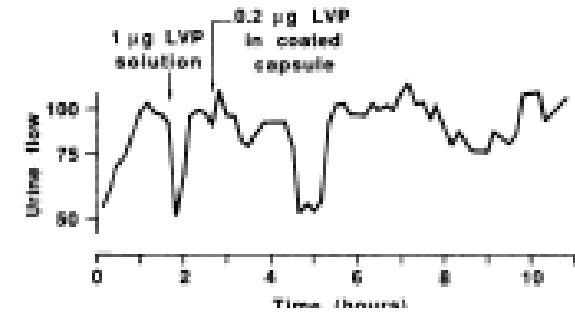
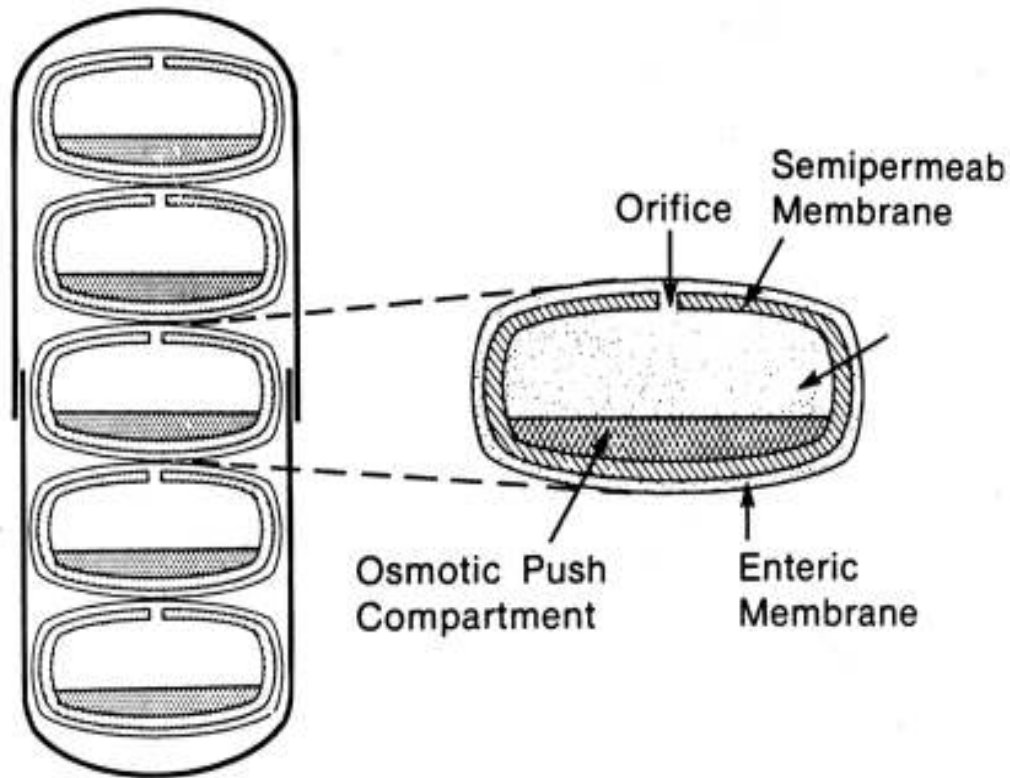
Degradation of Model Proteins in the Human Ileum and Feces



Gibson *et al*, *Appl. Environ. Microbiol.*, 55: 679, 1989

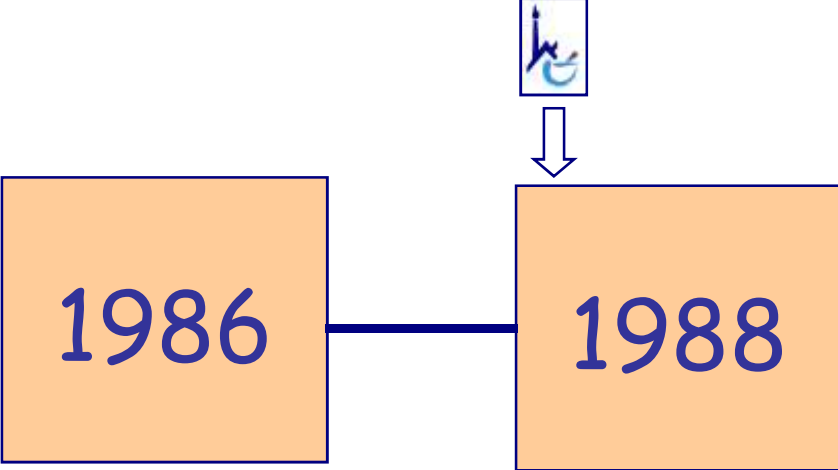


Non-specific Technologies

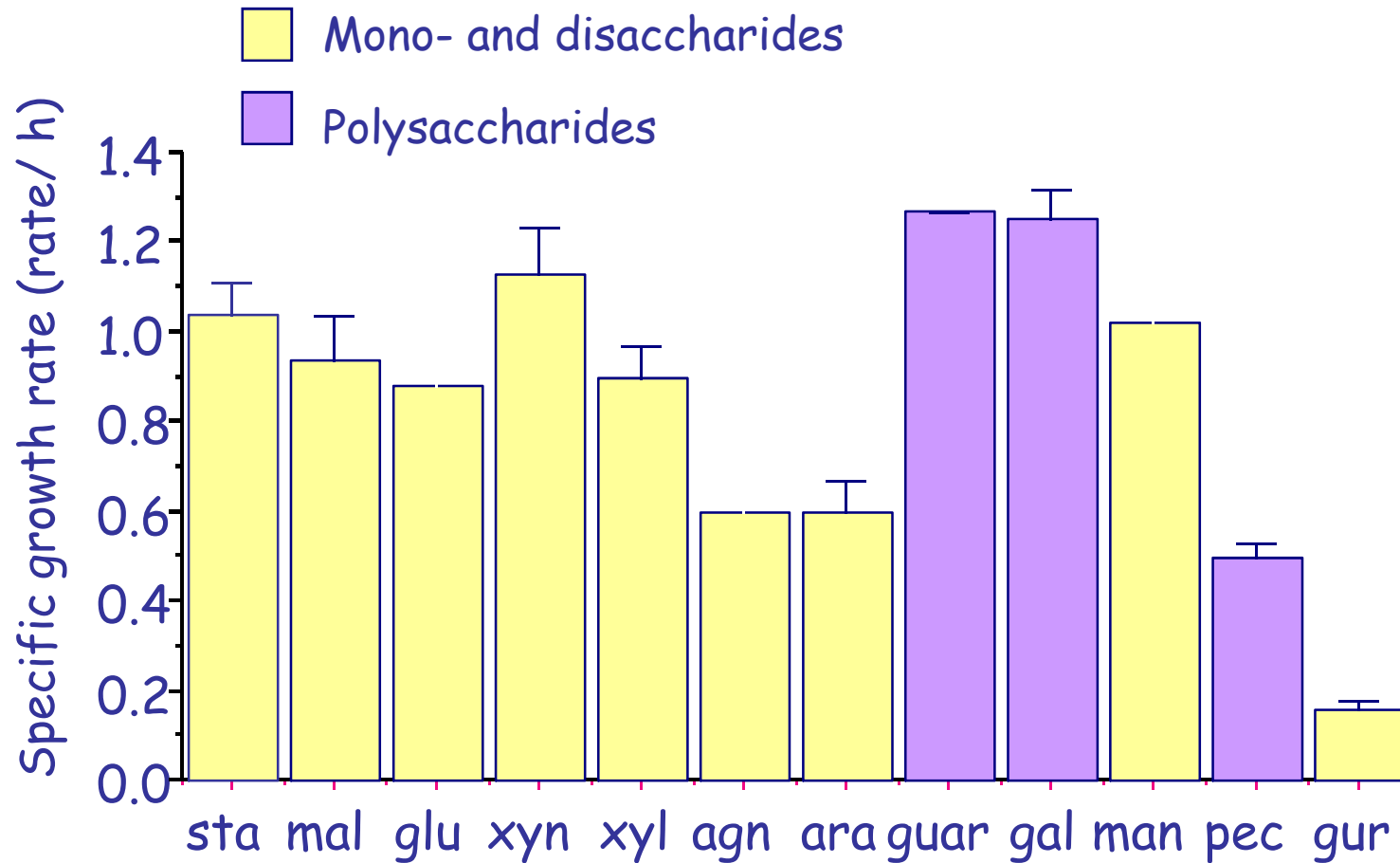


1. Alza's Osmet





Growth Rate of *Bacteroides ovatus* on Different Carbon Sources



Macfarlane, G.T et al., *J. App. Bacteriol.*, 68:179, 1990.

1986



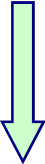
1988



1990



PPL



The Concept of Saccharidic Hydrogels

Crosslinked Chondroitin sulfate

Rubinstein *et al. Pharm. Res.*, 9: 276, 1992.

Rubinstein *et al. Int. J. Pharm.*, 84: 141, 1992.

Calcium Pectinate

Rubinstein *et al. Pharm. Res.*, 10: 258, 1993.

Rubinstein and Radai. *Eur. J. Pharm. Biopharm.*, 41: 29, 1995.

Adkin D.A *et al. Pharm. Res.*, 14: 103, 1997.

Crosslinked Guar

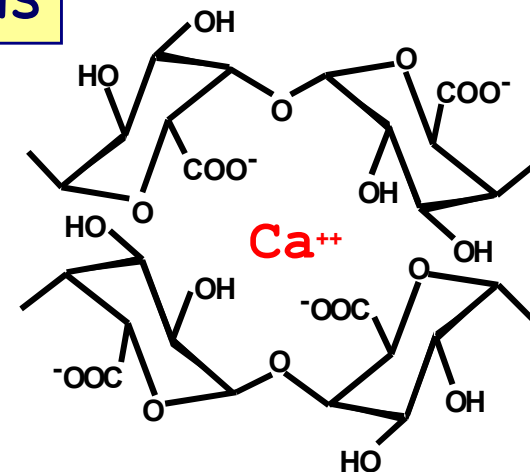
Rubinstein and Gliko-Kabir. *s.t.p. Pharm.Sci.*, 5: 41, 1995.

Gliko-Kabir *et al. Pharm. Res.*, 15: 1019, 1998.

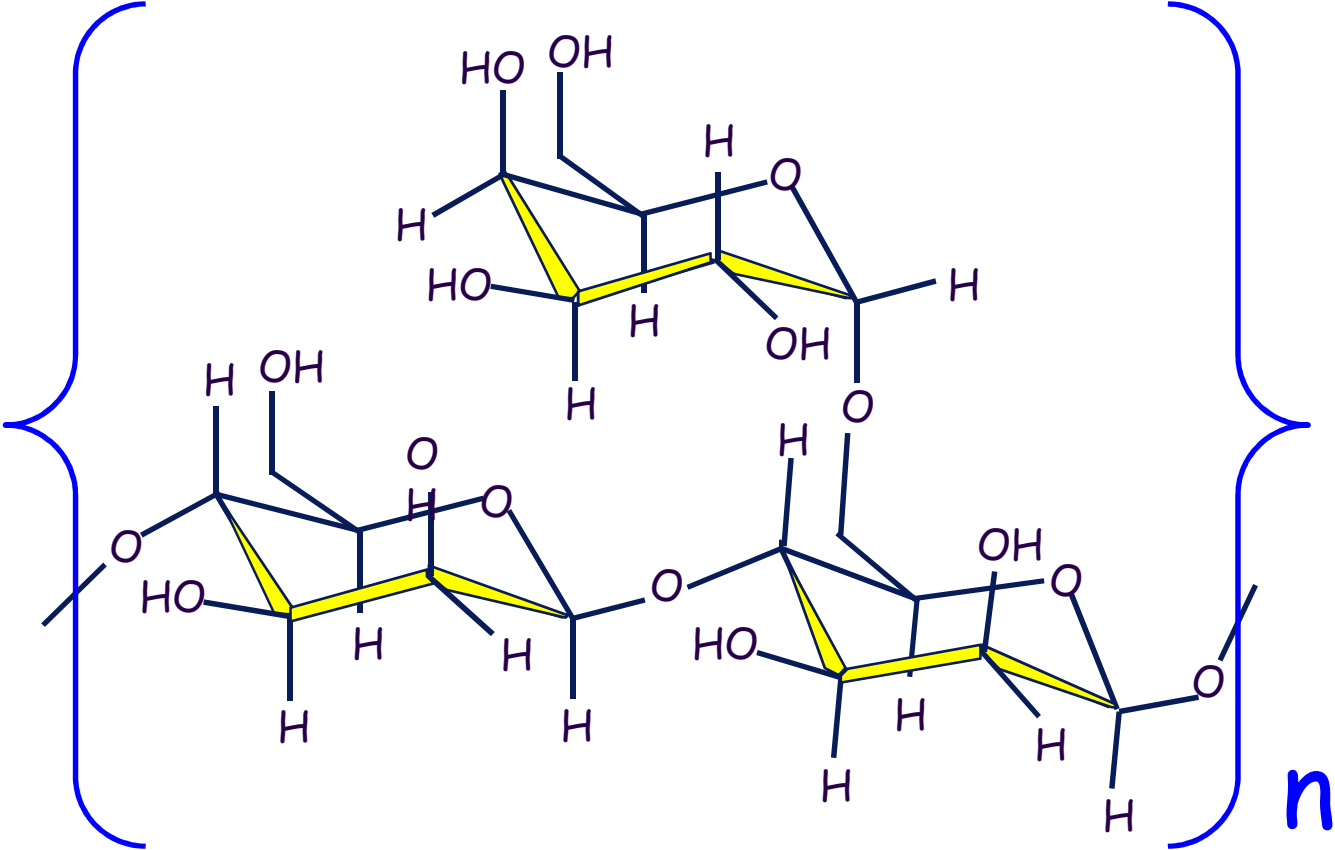
Gliko-kabir *et al. Carbohydrate Res.*, 316: 6, 1999.

Gliko-kabir *et al. J. Contrl. Rel.*, 63: 121, 2000.

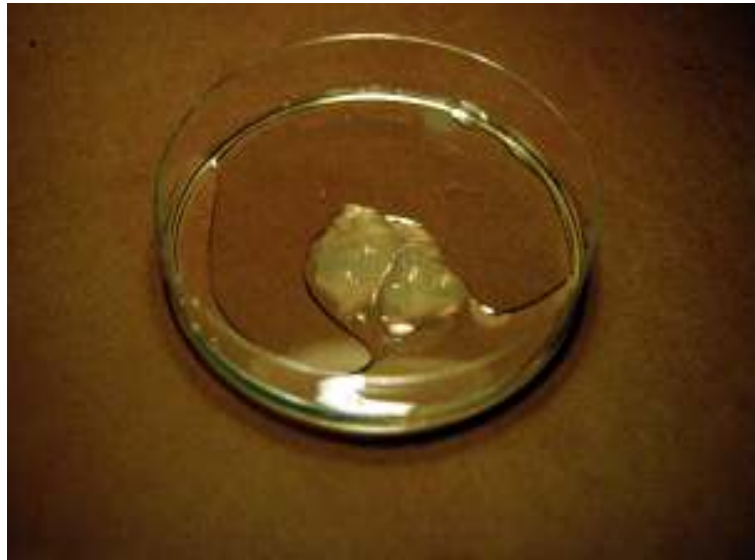
Gliko-kabir *et al. J. Contrl. Rel.*, 63: 129, 2000.



Guar Gum

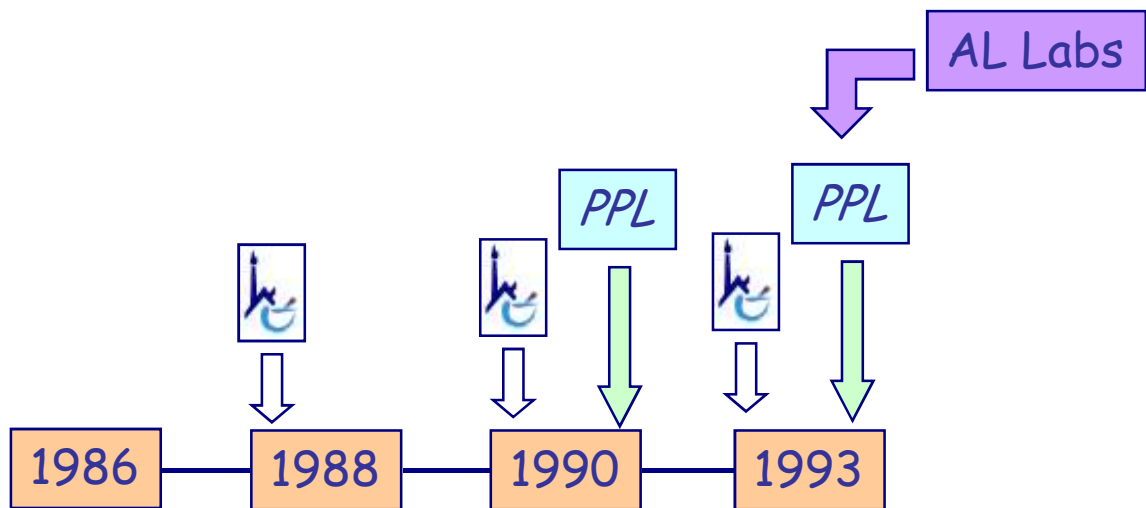


Guar crosslinked with
glutaraldehyde in PBS





After incubation (2 h) with
 β -mannanase + α -galactosidase





Manpower

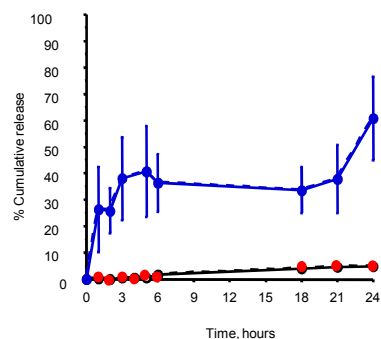
	2	4	5
	1/2	2	10





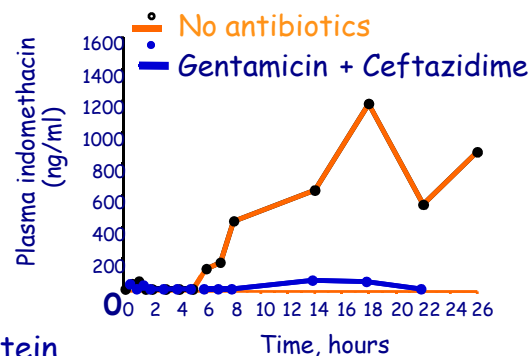
Saccharidic Hydrogels - Specific Degradation Analysis

CaP Tablets +/- Rat Cecal Contents



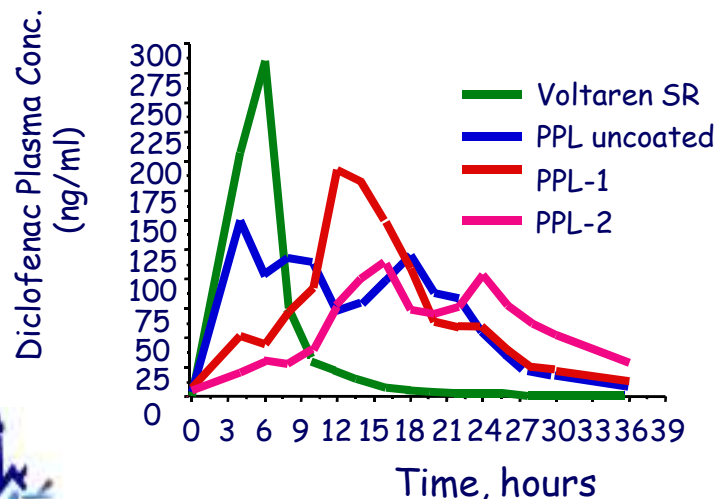
Rubinstein *et al. Pharm. Res.*, 10: 258, 1993

X ChS in Beagles +/- Antibiotics

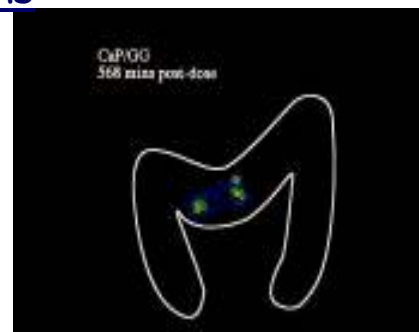


Rubinstein, *Crit. Rev. Ther. Drug Carr. Syst.*, 12:101, 1995

PK of Diclofenac in 12 Volunteers



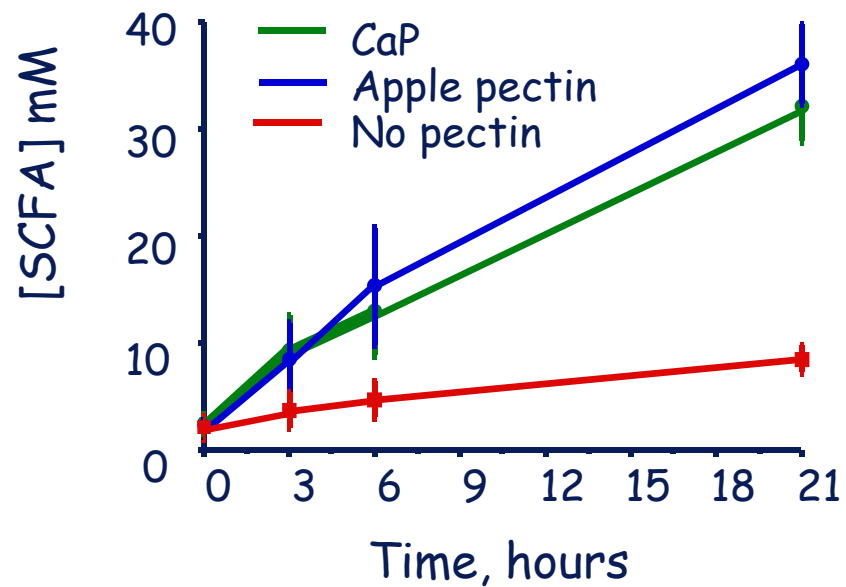
Enteric-Coated CaP-Guar Tablets in Humans

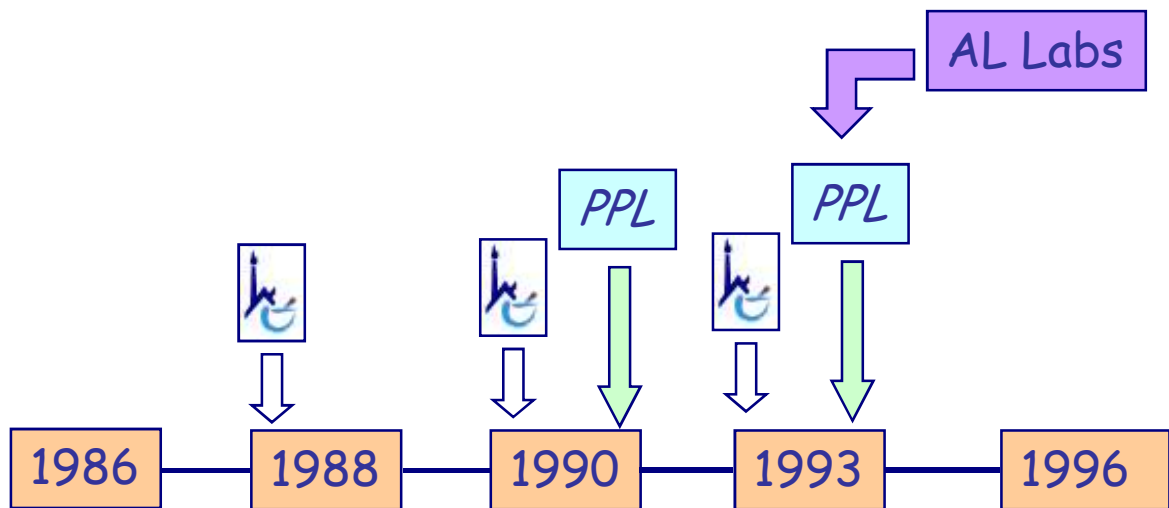


γ -Scintigraphy

Adkin *et al. Pharm. Res.*, 14: 103, 1997

Total SCFA Measured in Batch Culture of Human Feces with Apple Pectin and LM-CaP

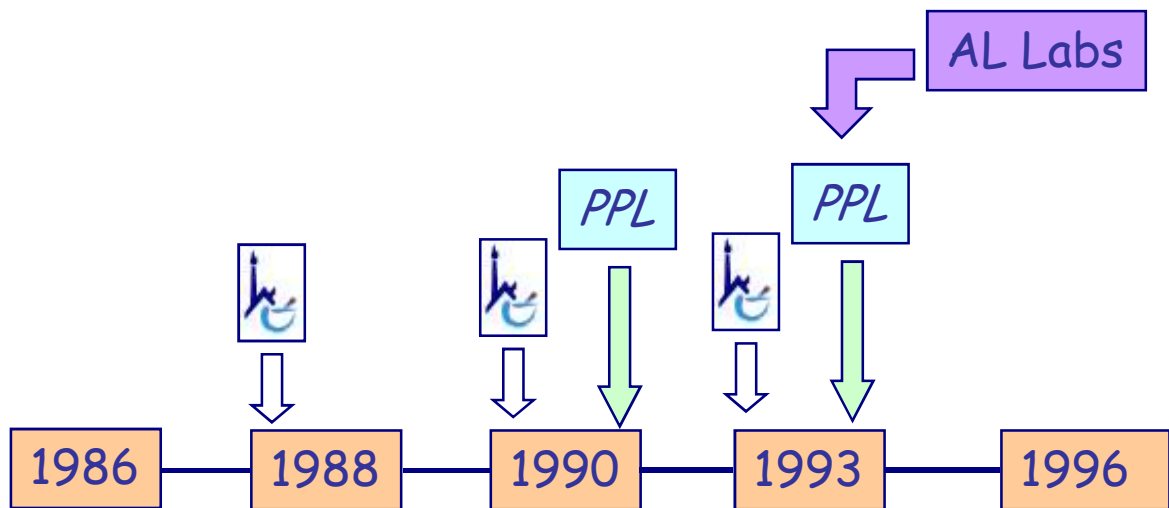




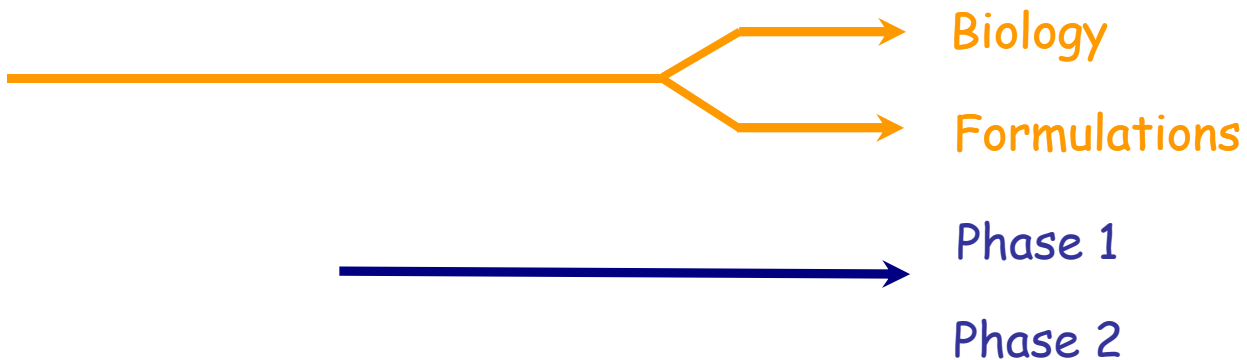
Manpower

	2	4	5	4
	1/2	2	10	50

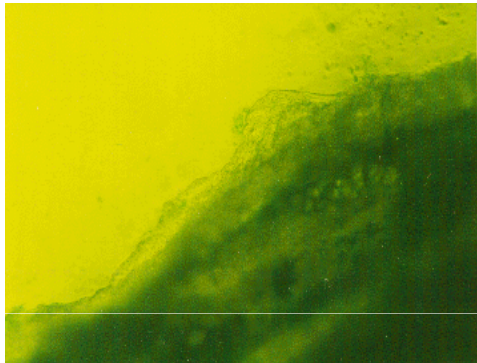
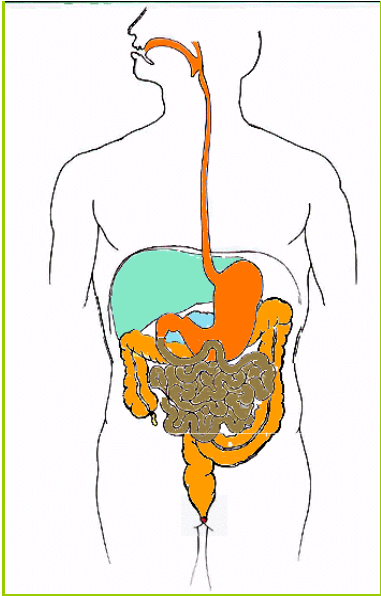




Activity



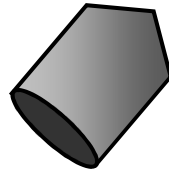
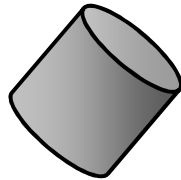
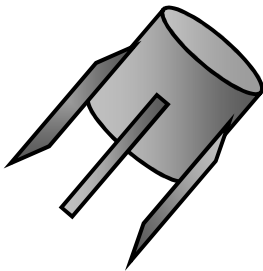
The Targets



Rubinstein & Tirosh,
Pharm. Res., 11:794, 1994

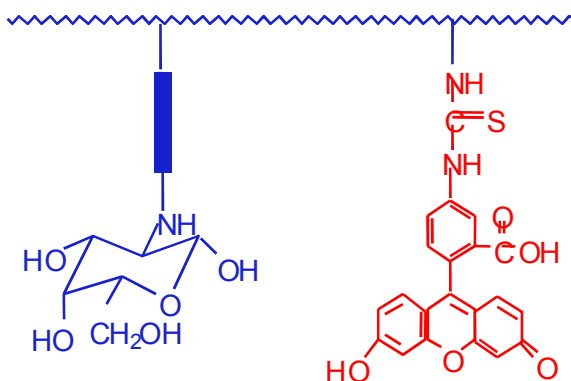


Haupt et al.,
Pharm. Res., 19:832, 2002

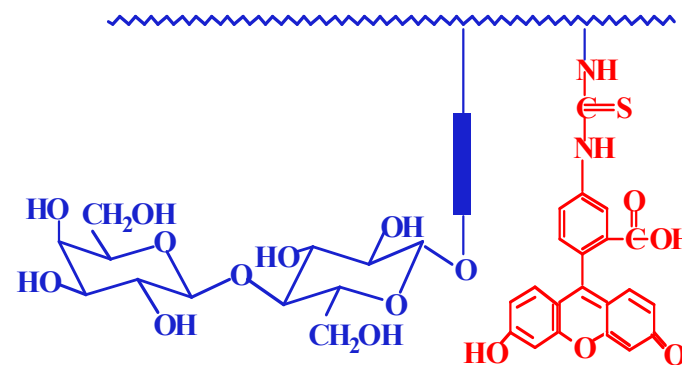


Targeting Colon Cancer Cells: Cluster Effect and Cooperative Effect: Galactosidated HPMA

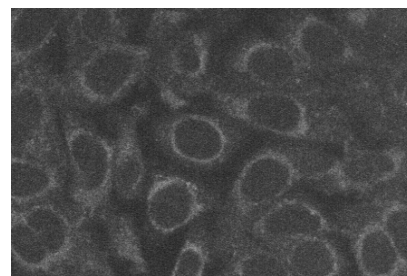
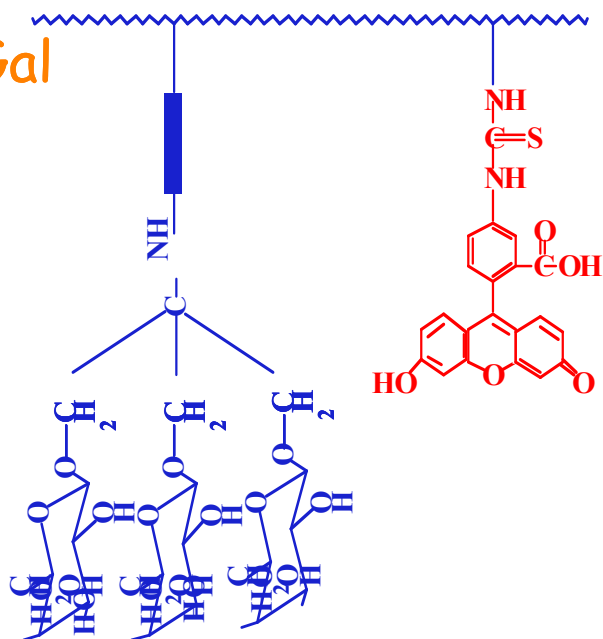
P-Gal



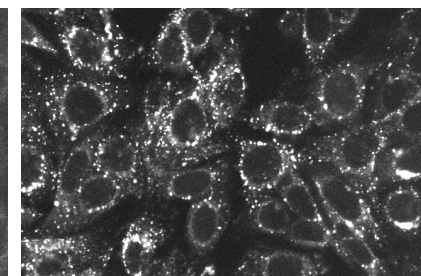
P-Lac



P-TriGal



Control

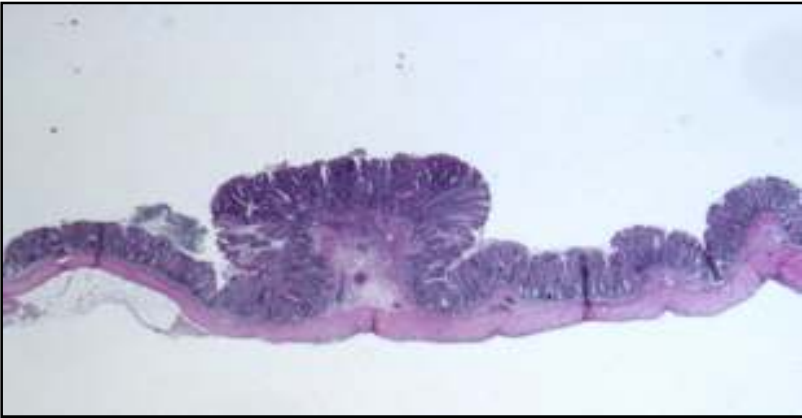
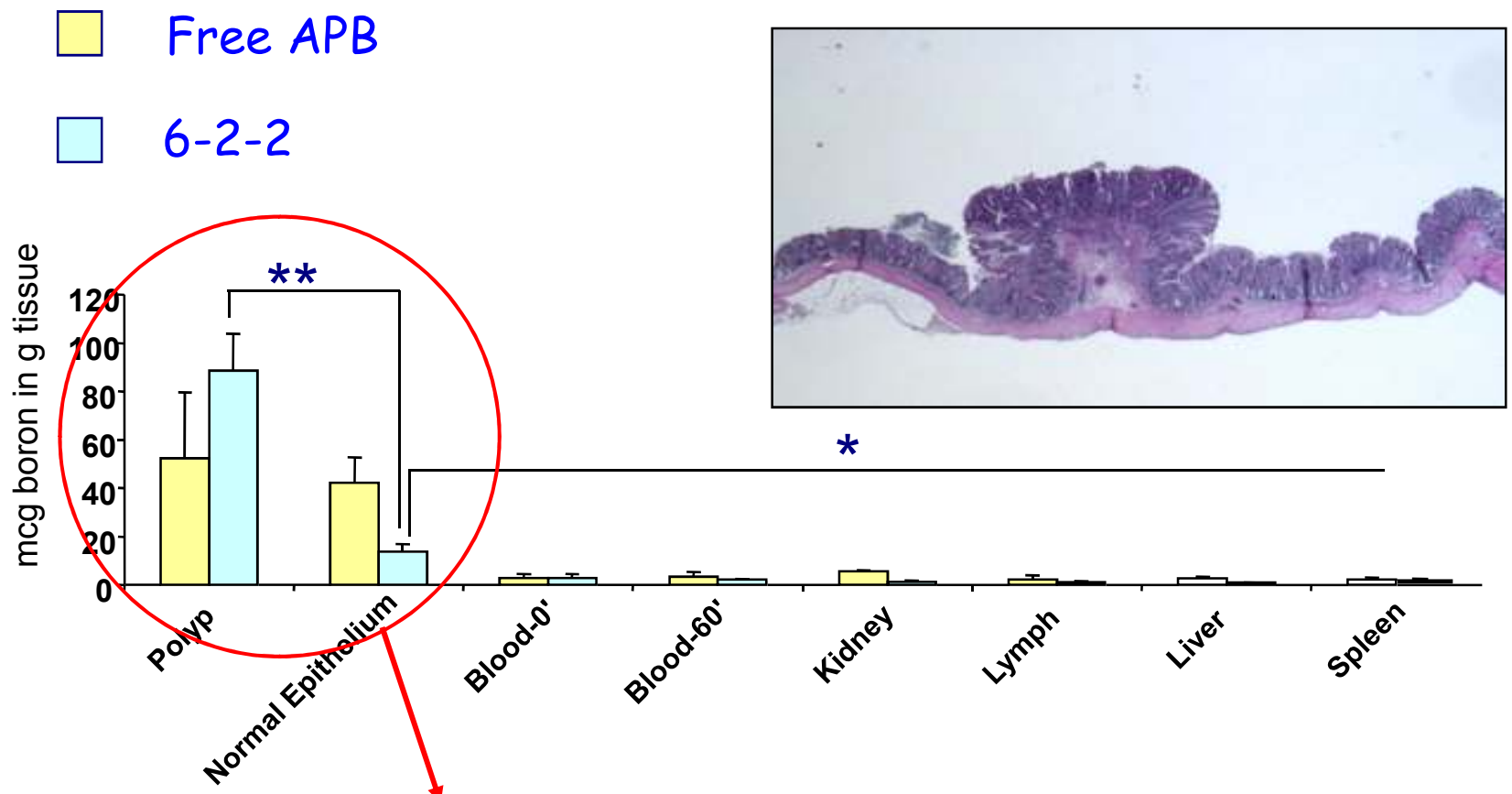


20% P-TriGal

David A. *et al.*, *Bioconjugate Chem.*, 12:890, 2001
David A. *et al.*, *Pharm. Res.*, 19: 1114, 2002



Body Distribution of Free APB and the ABC 6-2-2 Copolymer in the DMH Rat Preparation After Luminal Administration in the Colon



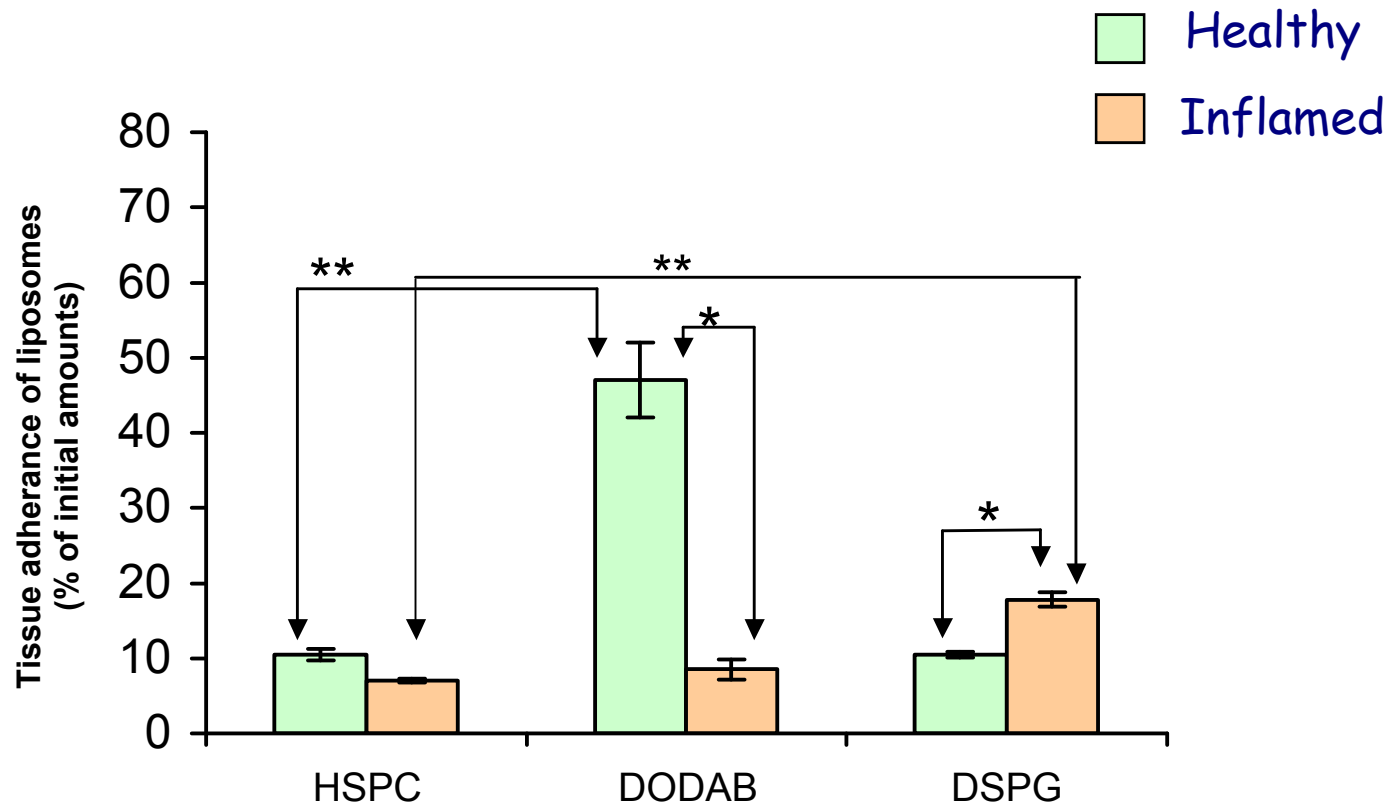
Boron Ratio (Polyp/adjacent normal epithelium)

Free APB 1.23 ± 0.82
 Polymeric APB 6.57 ± 2.05

Azab et al.,
J. Contr. Rel., 106: 14,
 2005



Adherence of Neutral, Cationic (DODAB, 22 mol%) and Anionic (DSPG, 22 mol%) Liposomes onto Healthy and Inflamed Epithelium of the Rat Colon Sac Preparations (75 min)

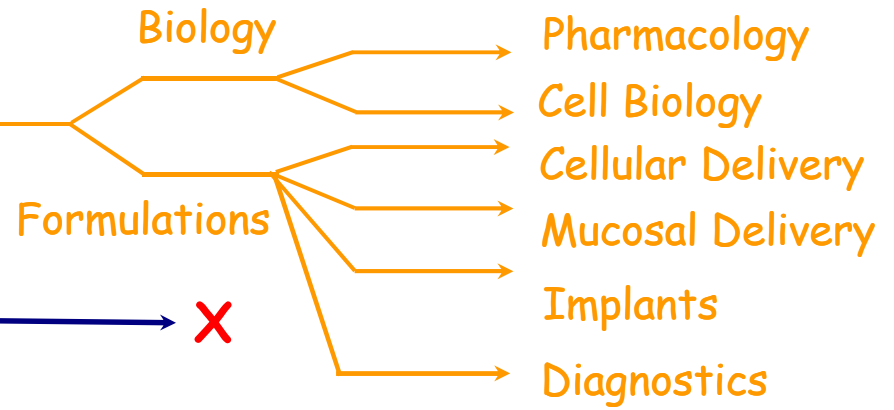


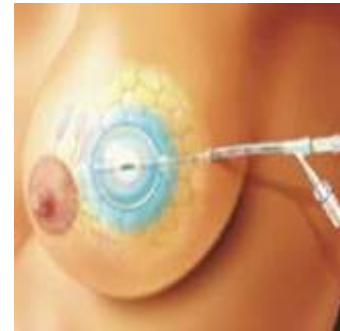


Activity



PPL





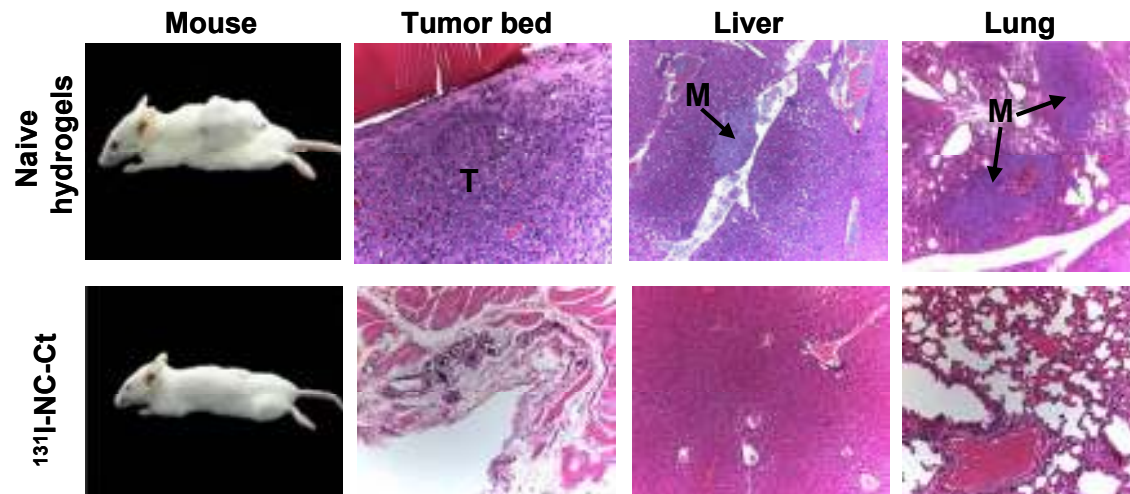
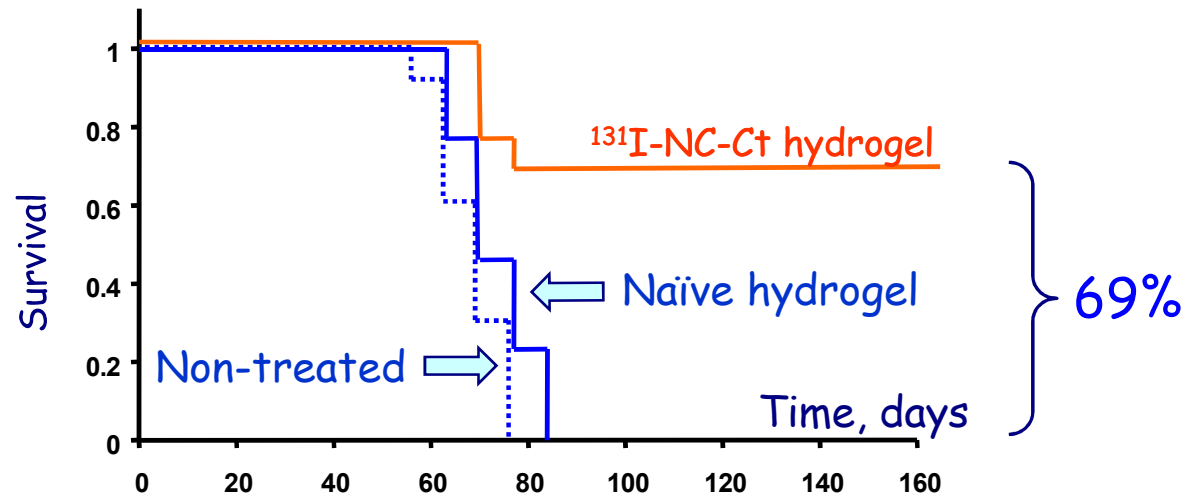
MammoSite®



Crosslinked chitosan

The Effect of ^{131}I -NC loaded SDG on Tumor Recurrence in the Adjuvant Therapy Mouse Model

Kaplan-Meier Analysis





Acknowledgments

Dr. Amnon Sintov, BGU

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