



MARIE CURIE ACTIONS



Vitamin D and cancer: promise or reality

Report from International Symposium:
Madrid, March 28-29, 2011





Alberto Muñoz, Donald L. Trump Coordinators of Symposium.

- Roger Buillon: **Vitamin D, a hormone with pleiotropic effects**
- Héctor G. Pálmer: **Effects of vitamin D in mouse skin biology**
- David Feldman: ***Anti-inflammatory effects of vitamin D***
- Ana Aranda: ***The vitamin D receptor heterodimer***
- Carsten Carlber: ***A genomic perspective to vitamin D signalling***
- Luciano Adorini: ***Immunomodulatory effects of vitamin D:
Implications for cancer treatment***





Alberto Muñoz, Donald L. Trump Coordinators of Symposium.

- Michael Holick: **Vitamin D: Antiproliferative activity and the cancer connection**
- Edward Giovannucci: **Epidemiological data**
- Donald L. Trump: **Prevention and Therapy - Clinical data**
- Jörg Reichrath: ***Role of vitamin D in human skin cancers***
- David Feldman: ***Anti-inflammatory effects of vitamin D***
- Varda Rotter: ***Vitamin D and the TP53 tumor suppressor gene***
- Alberto Muñoz: ***Mechanism of action of vitamin D in colon cancer***
- María Jesús Larriba: ***Mechanisms of resistance to vitamin D in colon cancer***
- Moray Campbell: ***Role of vitamin D in prostate cancer***
- JoEllen Welsh: ***Role of vitamin D in breast cancer***
- Román Pérez-Fernandez: ***The Pit-1 transcription factor and vitamin D in breast cancer***
- Candace Johnson: ***Anti-angiogenic and antimetastatic effects of vitamin D***





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Vitamin D and cancer: Molecular Mechanisms

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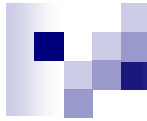




VITAMIN D

VITAMIN D + CALCIUM





7 - Dehydrocholesterol

Skin

Vitamin D

Liver

25-OHase

Serum
25(OH)D₃

Vitamin D

Diet

Natural Foods, Fortified
Foods, Supplements

KIDNEY

24-OHase

25(OH)D₃ → Metabolites

1α-OHase

Serum
1α,25(OH)₂D₃

24-OHase

**ANTIPROLIFERATIVE
ACTIVITY**

Autocrine / paracrine
1α,25(OH)₂D₃ action

1α-OHase

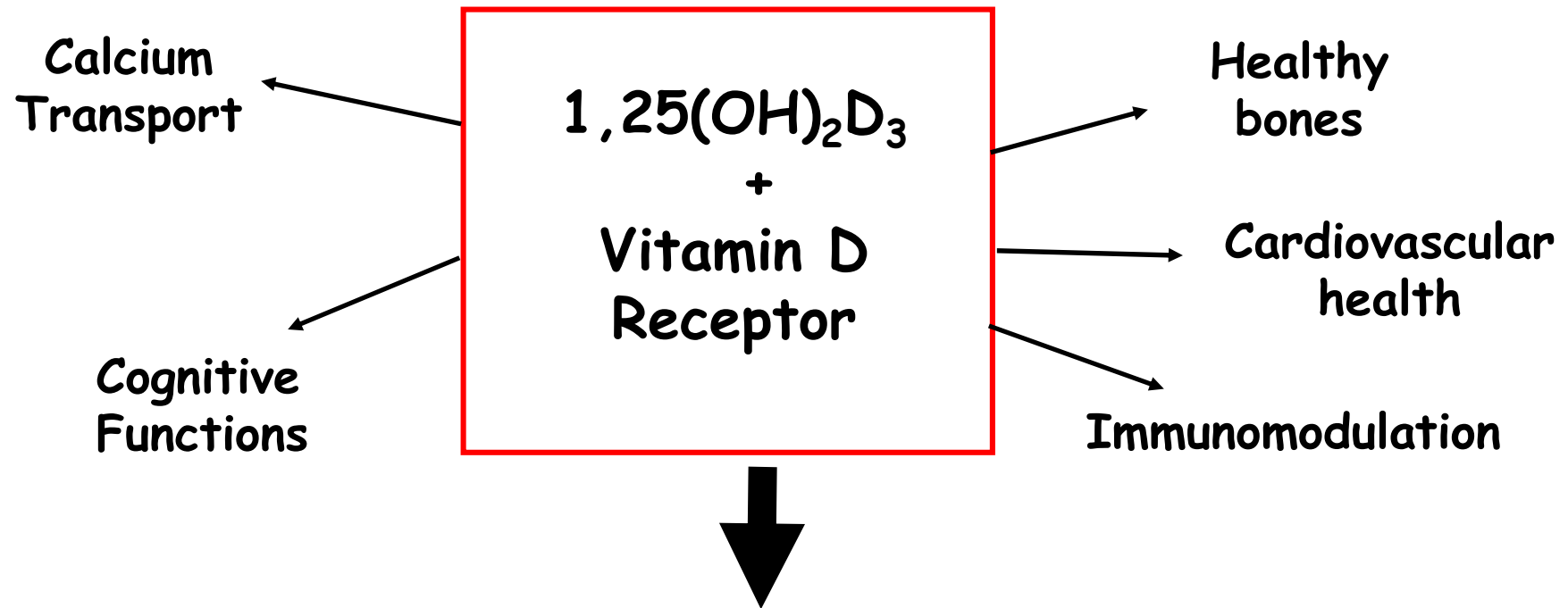
24-OHase

25(OH)D₃ → Metabolites

Extra renal tissues

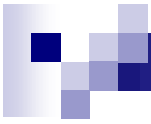


BIOLOGICAL EFFECTS OF VITAMIN D

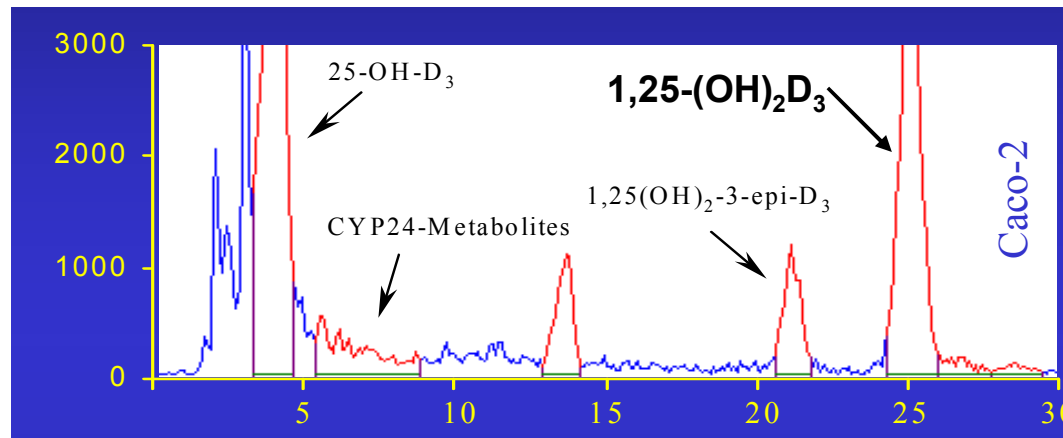
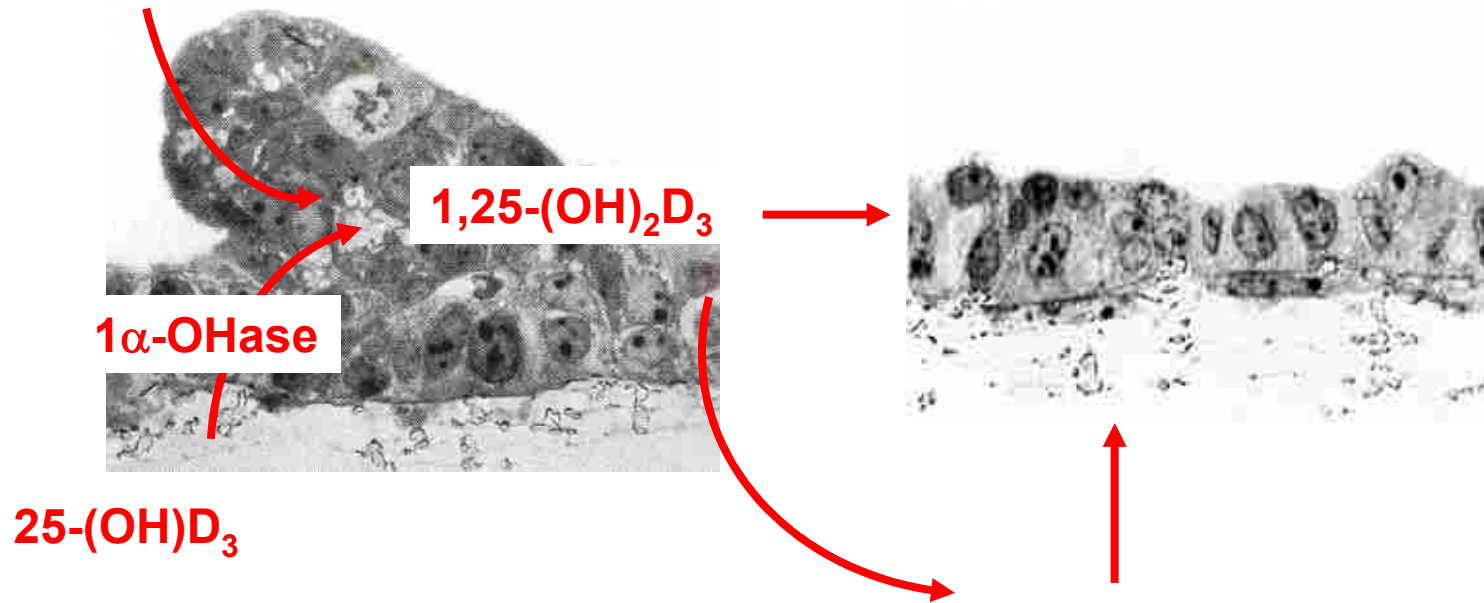


Regulates cellular proliferation, differentiation and apoptosis

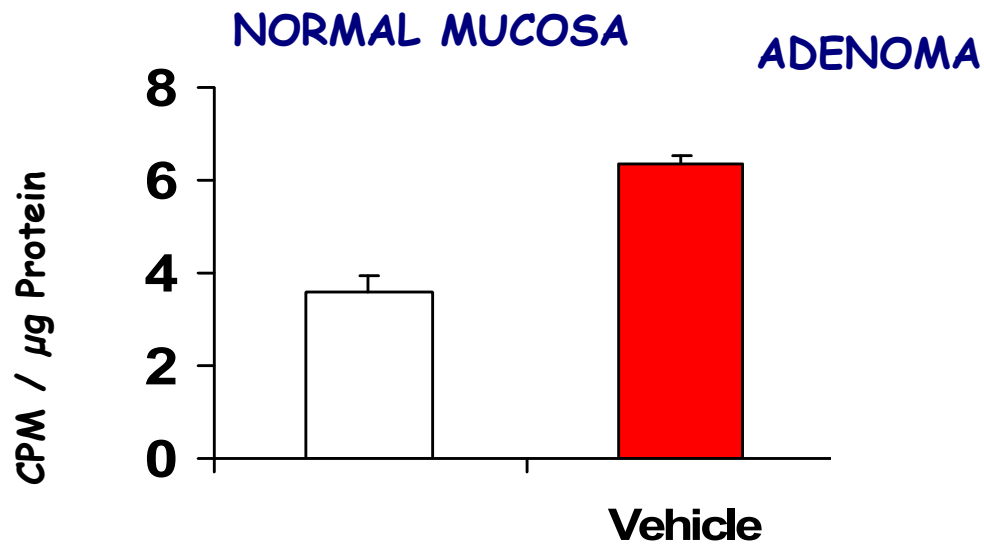




1,25-(OH)₂D₃ (10 nM) Effect of 1,25(OH)₂D₃ on the Proliferation of the Caco-2 Colon Cancer Cell Line



Effect of $1,25(\text{OH})_2\text{D}_3$ on the Proliferation Colon Adenoma Cells





Vitamin D and Cancer

Characteristics of cancer cells

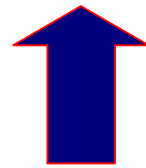
- ❖ Independence of external growth signals
- ❖ Loss of sensitivity for growth inhibiting signals
- ❖ Unlimited growth potential
- ❖ Insensitivity for active cell death (= Apoptosis)
- ❖ Continuous neo-angiogenesis
- ❖ Tissue-invasion and growth in other organs

Effects of Vitamin D

- ❖ Inhibits cell proliferation
- ❖ Enhances cell differentiation
- ❖ Activates apoptosis
- ❖ Inhibits angiogenesis in tumours
- ❖ Decreases metastatic potential
- ❖ Activates the immune system

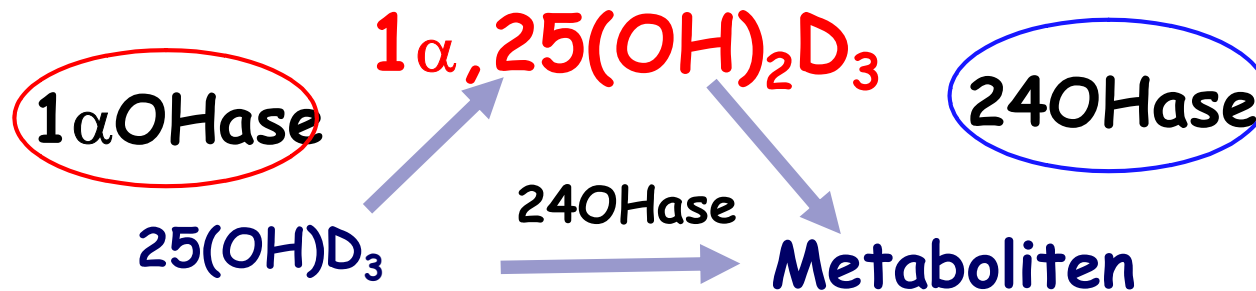


CANCER PREVENTIVE ACTIVITY



Autocrine / paracrine
Action

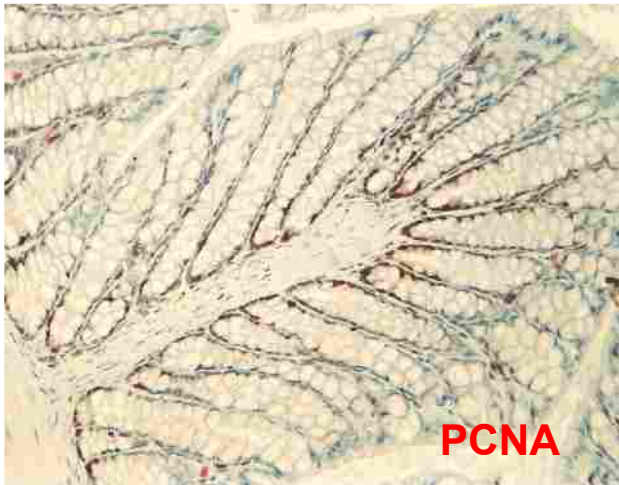
VDR



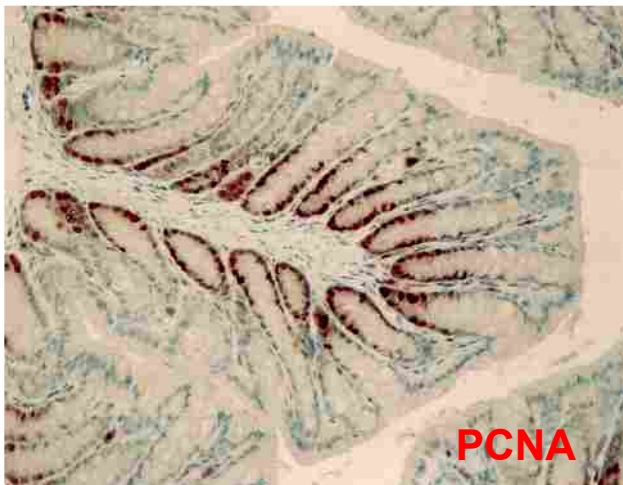
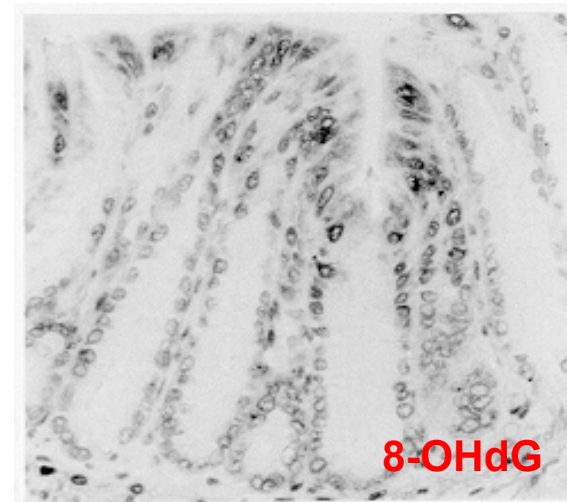
COLON



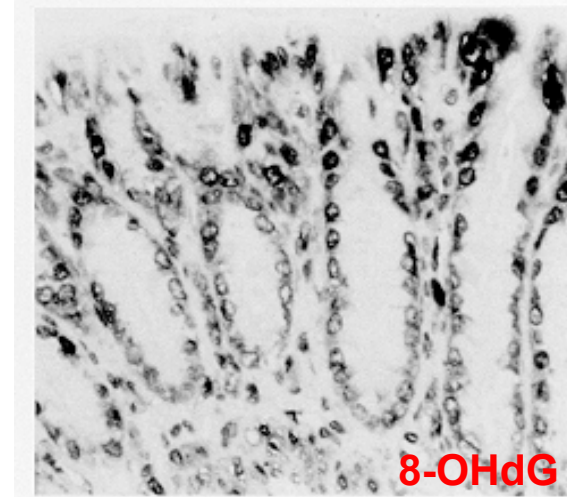
The Impact of VDR Loss in the Colon



VDR^{+/+}



VDR^{-/-}

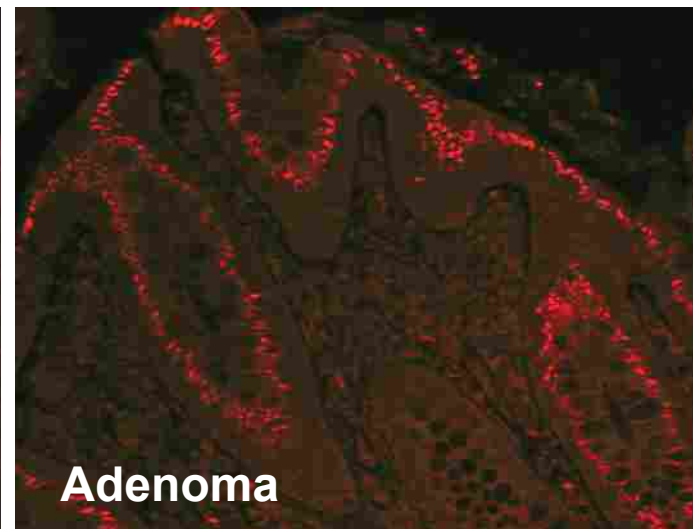
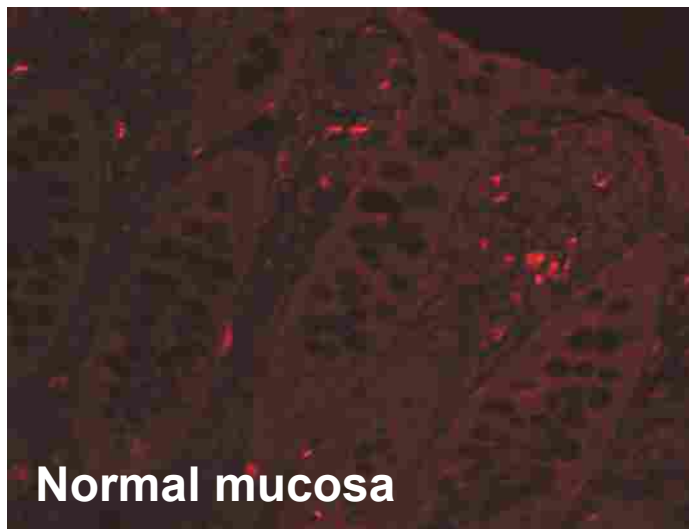


Expression of VDR, 1α OHase and 24OHase mRNA in Colorectal Tumours

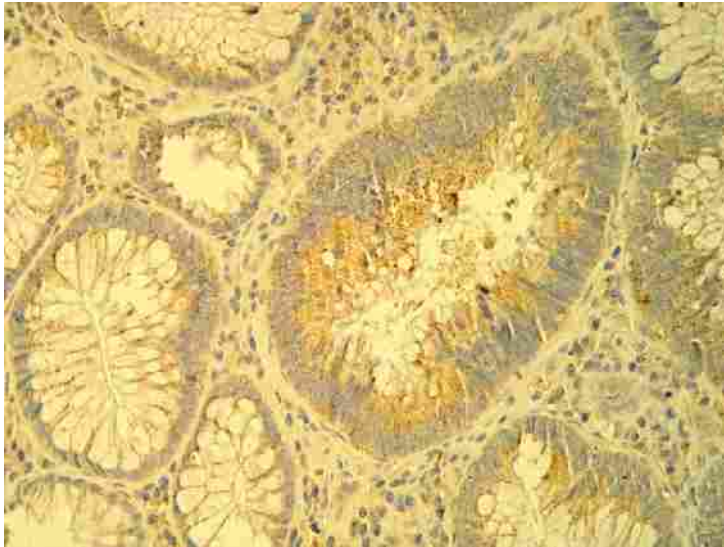
	VDR	1α OHase	24OHase
Normal Mucosa	0,749 \pm 0,05	2,261 \pm 0,92	1,353 \pm 0,38
Benign Lesions	0,455 \pm 0,06***	2,365 \pm 0,90	11,93 \pm 5,77*
Adenocarcinomas	0,412 \pm 0,07***	1,183 \pm 0,50	3.876 \pm 1,41*



Expression of 1α hydroxylase in human colon



Expression of the 25 Hydroxyvitamin D₃ 24 Hydroxylase in Colorectal Tumours



Adenoma



Adenocarcinom

	24OHase Expression	
	Neg/+	++/+++
Norm. mucosa	73.4%	26.6%
Benign lesions	77.1%	22.9%
Adenocarc.	31.3%	68.7%



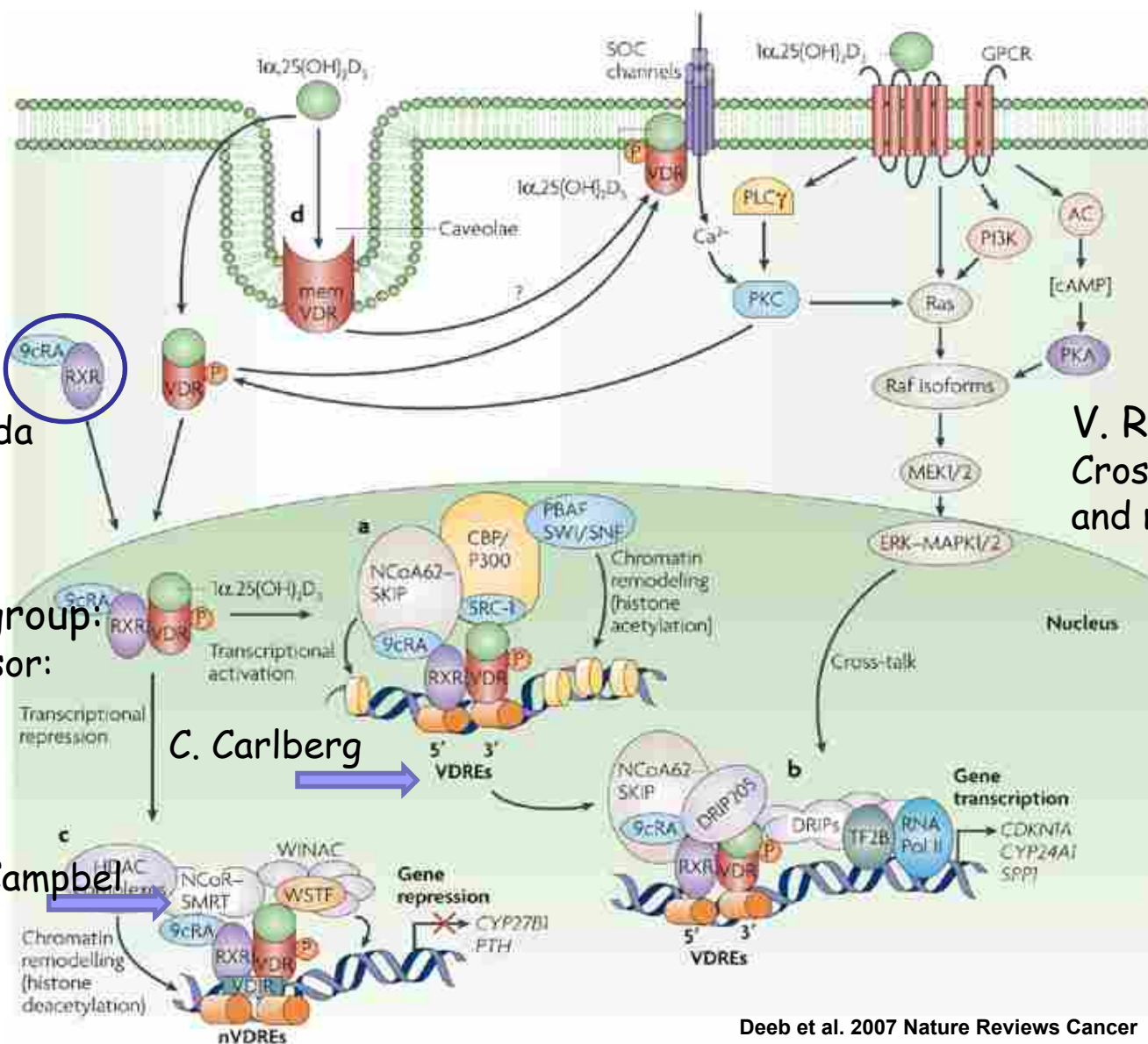


Relevance for Cancer Treatment

- Calcitriol vs. cholecalciferol
- Calcitriol vs. analogs
- Alone or in combination with other drugs?



1 α ,25(OH) $_2$ D $_3$ -Mediated Transcription



A. Aranda

V. Rotter:
Cross talk VDR
and mutant p53

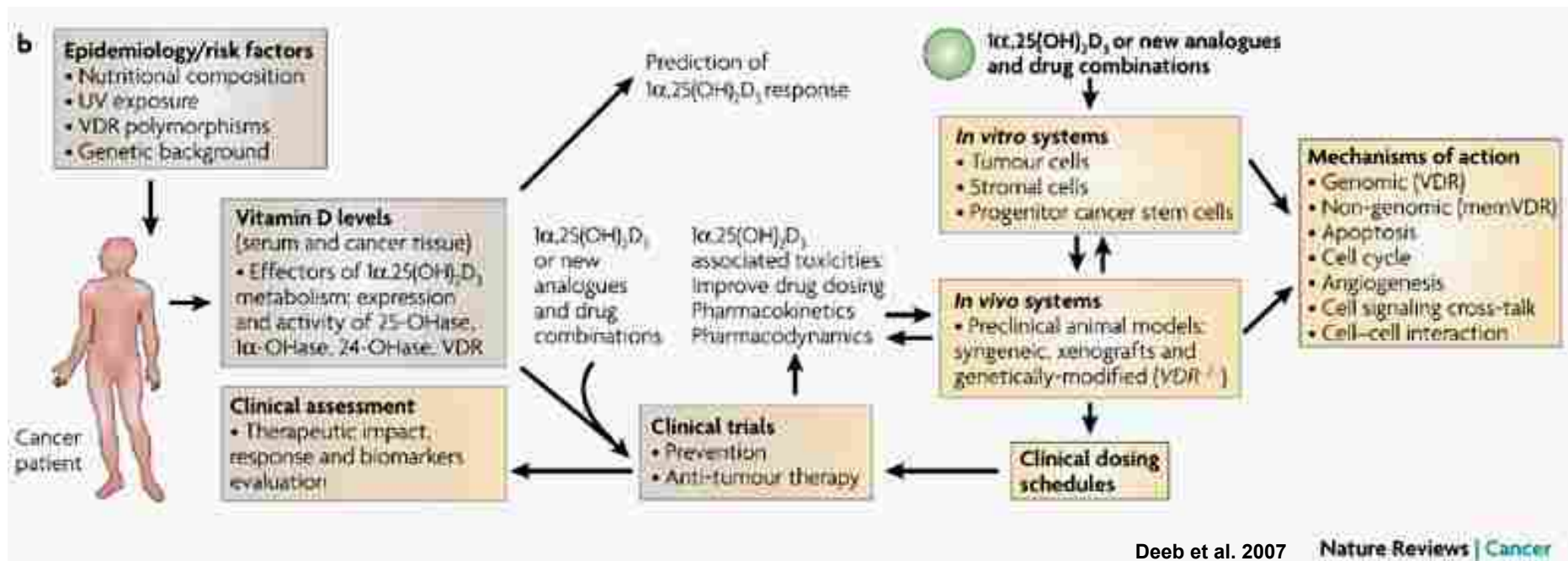
A. Munoz group:
VDR Repressor:
Snail

C. Carlberg

M. Campbell

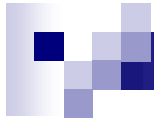


Paradigm for development and clinical translation of $1\alpha,25(\text{OH})_2\text{D}_3$ as an anticancer agent.



Establishment of in vitro and in vivo experimental systems is crucial to developing $1,25(\text{OH})_2\text{D}_3$ or vitamin D analogues that target vitamin D metabolism and signalling. These systems allow the mechanisms of action of $1,25(\text{OH})_2\text{D}_3$ to be studied along with novel analogues (also in combination with cytotoxic drugs) in multiple transformed cell types and their biological effects (tumour and normal tissues) in animals.





VITAMIN D

VITAMIN D + CALCIUM





Cancer Research 2008 October 1; 68: (19), 7803-7810.

„Dietary Induction of Colonic Tumors in a Mouse Model of Sporadic Colon Cancer“ by Kan Yang and her colleagues at the Strang Cancer Research Laboratory.

„Colonic tumors were prevented by elevating dietary calcium and vitamin D₃ to levels comparable with upper levels consumed by humans, but tumorigenesis was not altered by similarly increasing folate, choline, methionine, or fiber...“





Vitamin D and Cancer

Characteristics of cancer cells

- ❖ Independence of external growth signals
- ❖ Loss of sensitivity for growth inhibiting signals
- ❖ Unlimited growth potential
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- ❖ Tissue-invasion and growth in other organs

Vitamin D Effects

- ❖ Inhibits cell proliferation
- ❖ Enhances cell differentiation
- ❖ Activates apoptosis
- ❖ Inhibits angiogenesis in tumours
- ❖ Decreases metastatic potential
- ❖ Activates the immunsystem



Vitamin D, Calcium and Cancer

Characteristics of cancer cells

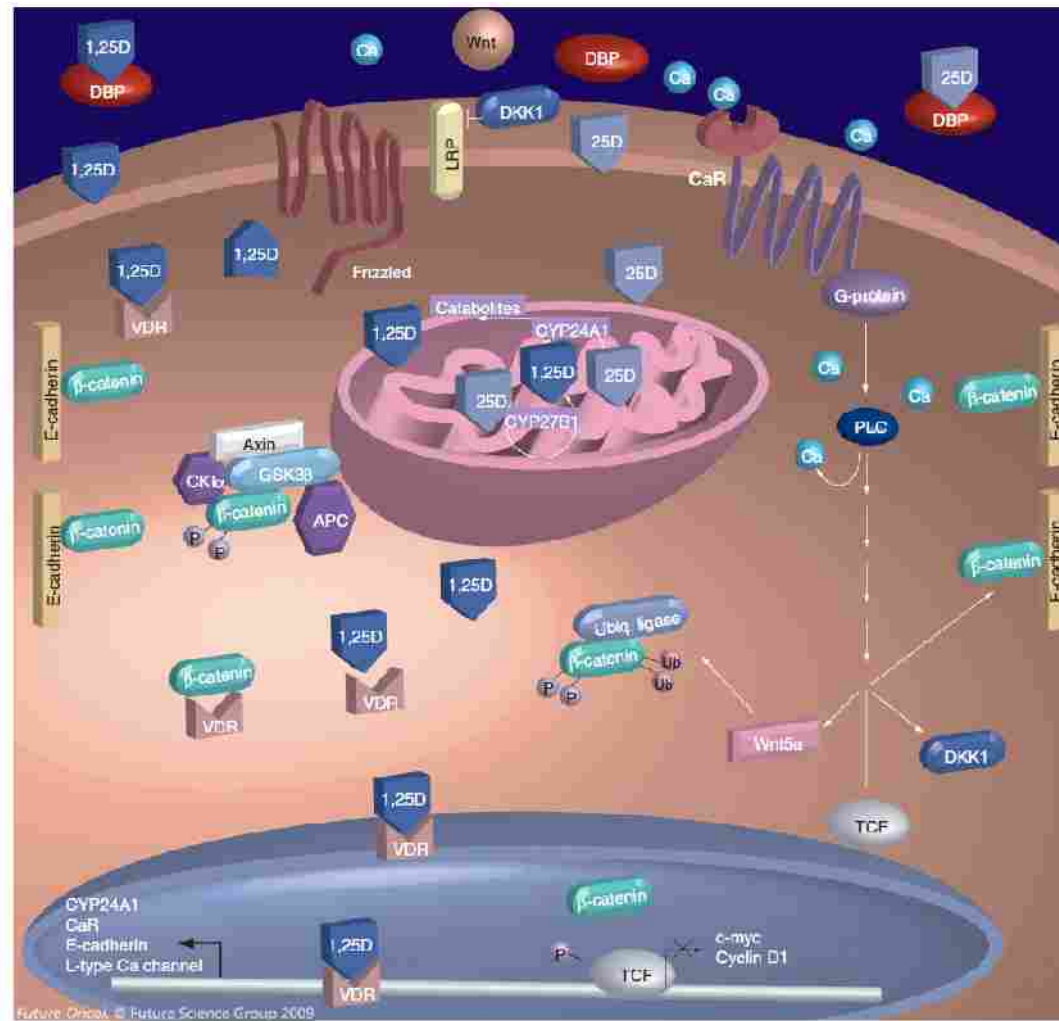
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Calcium Effects

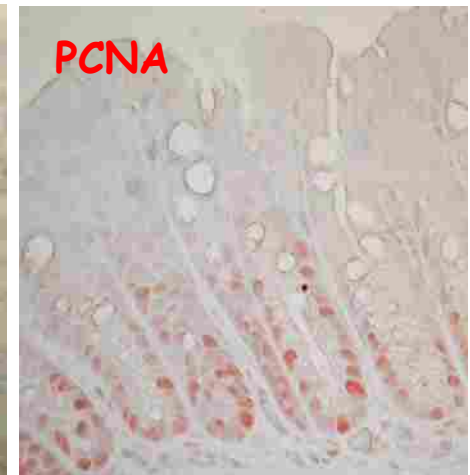
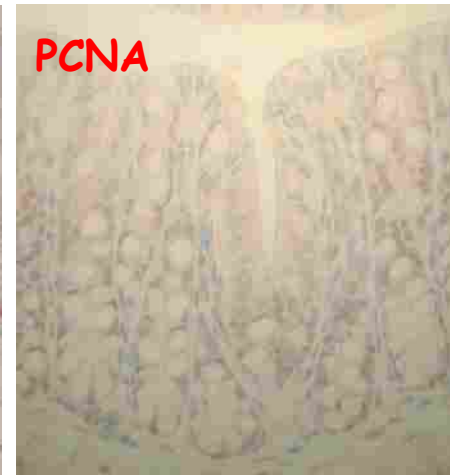
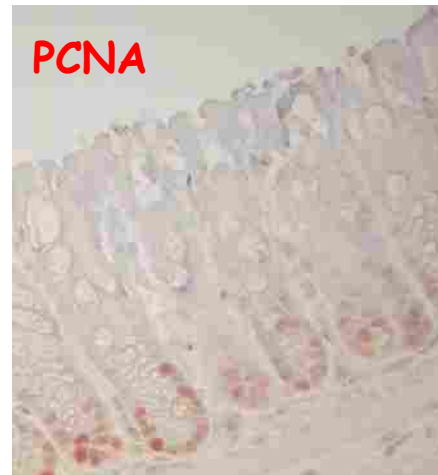
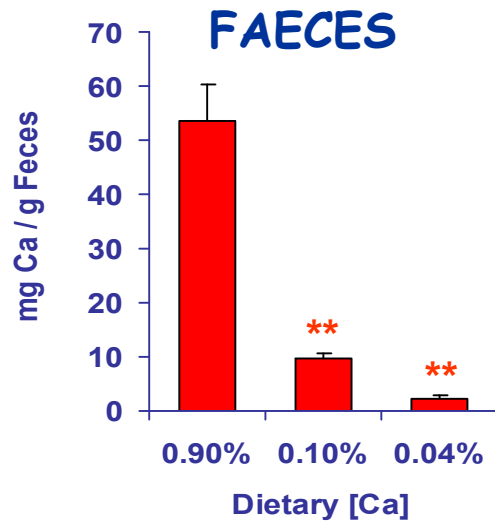
- ❖ Inhibits cell proliferation
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Influence of $1,25(\text{OH})_2\text{D}_3$ and calcium on the Wnt pathway



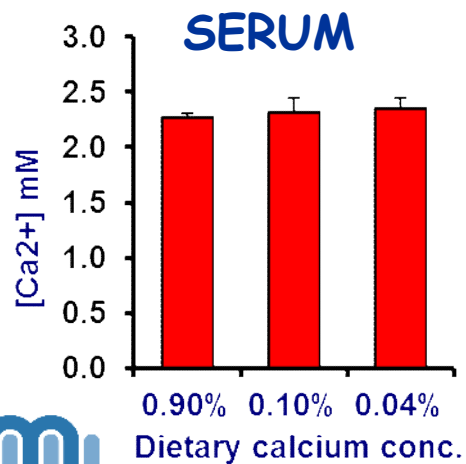
Influence of dietary calcium on colonic proliferation (PCNA expression)



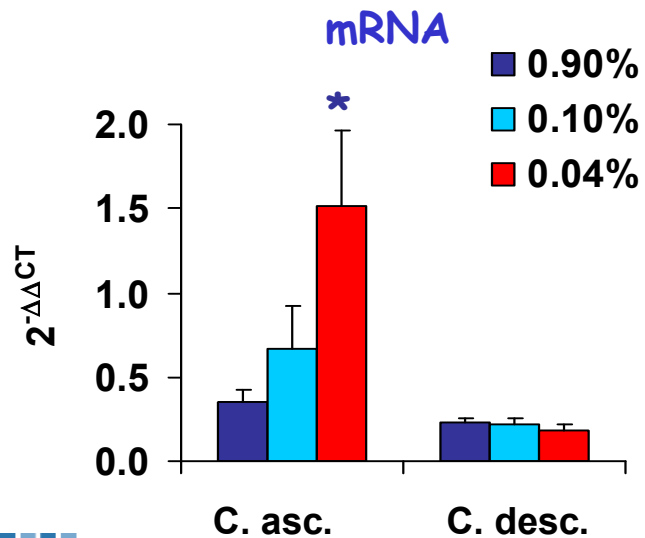
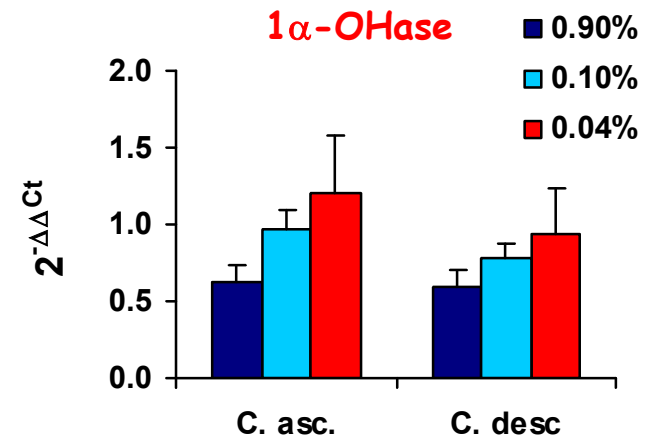
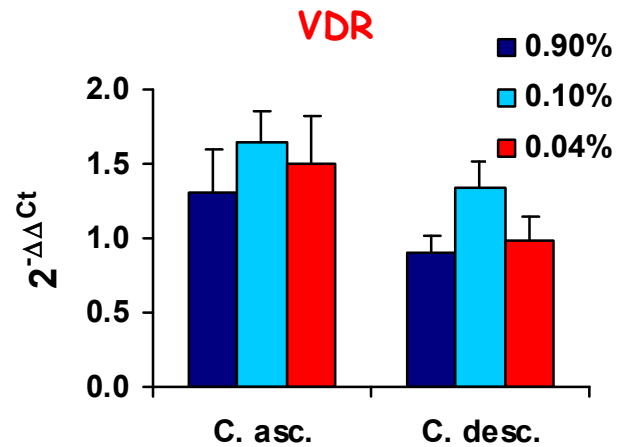
0.9% Calcium

0.1% Calcium

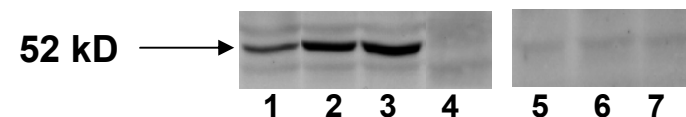
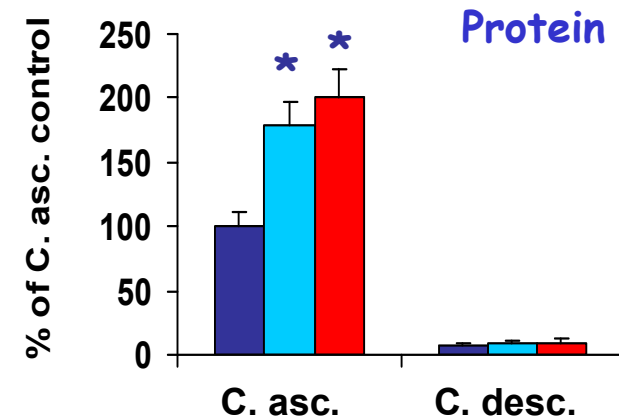
0.04% Calcium



Effect of Dietary Calcium on Expression of the Vitamin D System



24-OHase





Vitamin D and Calcium
one Team in

PREVENTING
Colorectal Cancer



Collaborators:

Raj Thakker, Oxford University,

Rose Bland, Warwick University.

Pamela Hershberger, Univ. Pittsburgh

M. Lipkin, P. Holt, Strang Cancer Center, New York,

M. Hewison, UCLA;

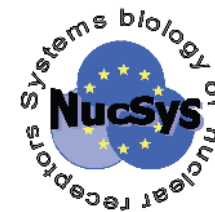
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H. Horvath, Semmelweis Univ. Budapest;

H. Cross, M. Peterlik, Med. Univ. Vienna.



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