Transformující růstový faktor – β: rozmanitost přenosu signálu a funkce část 2.

Karel Souček

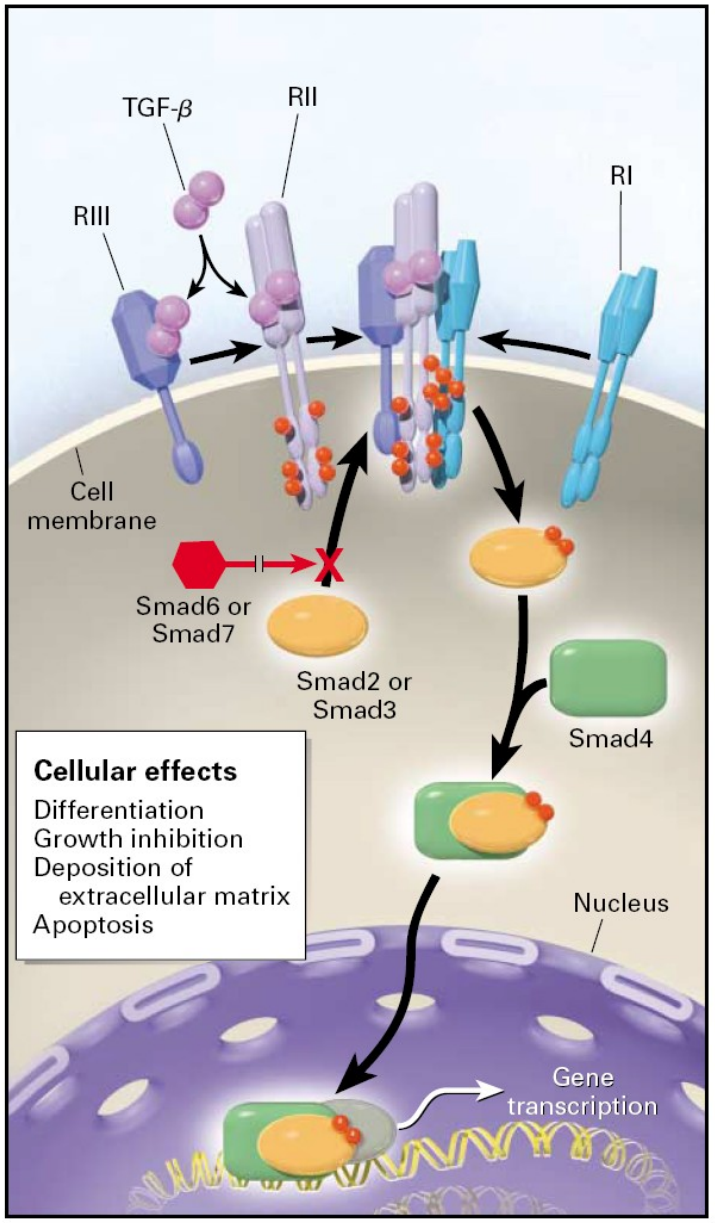
Bi6051 Molekulární fyziologie živočichů

Transforming growth factor -β (TGF-β)

TGF-β rodina ~ TGF-βs, activins, bone morphogenic proteins (BMP)

TGF-β_1

- pleiotropní cytokin
- negativní regulátor



Epstein, F.H., N Engl J Med 2000; 342:1350-1358, 2000

Growth factors in cancer cell signaling

- cancer **is not** single cell disease;
- **tissue microenvironment** plays an important role in tumor initiation and progression;
- **growth factors - cytokines** - play crucial role in cancer development and some of them belong to the **significant autocrine/paracrine factors** produced by various cell types in tumor microenvironment;
- modulation of their signal transduction represent potential target for therapy.

Growth factors in cancer cell signaling

- What is a role of TGF-β family cytokines in cancer progression?
- How we can effectively modify pathological plasticity of the cancer cells?

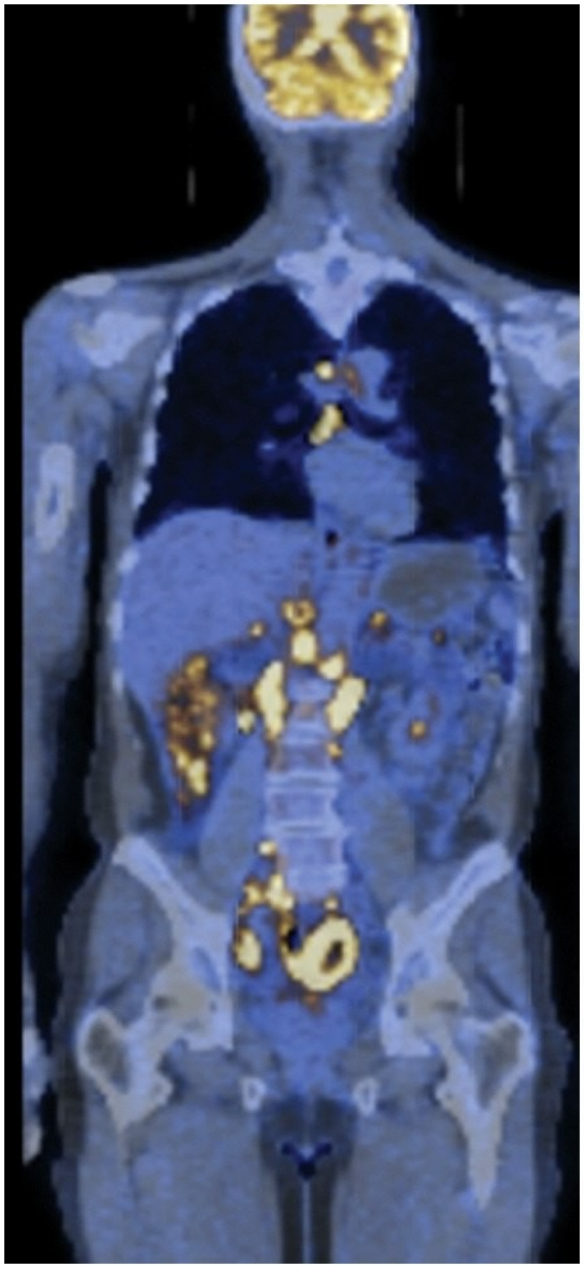


Figure 14.1 *The Biology of Cancer* (© Garland Science 2007)

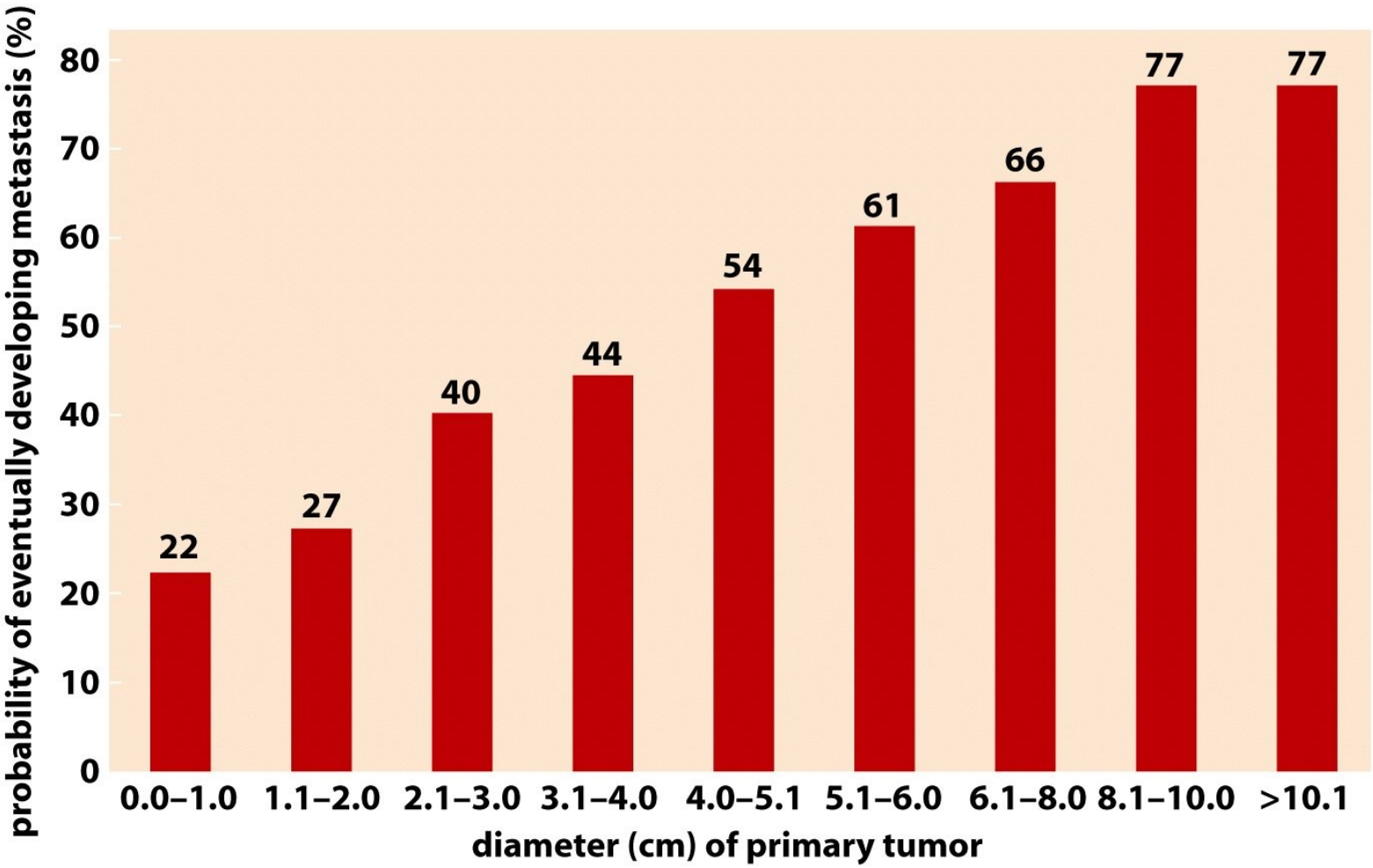


Figure 14.3 *The Biology of Cancer* (© Garland Science 2007)

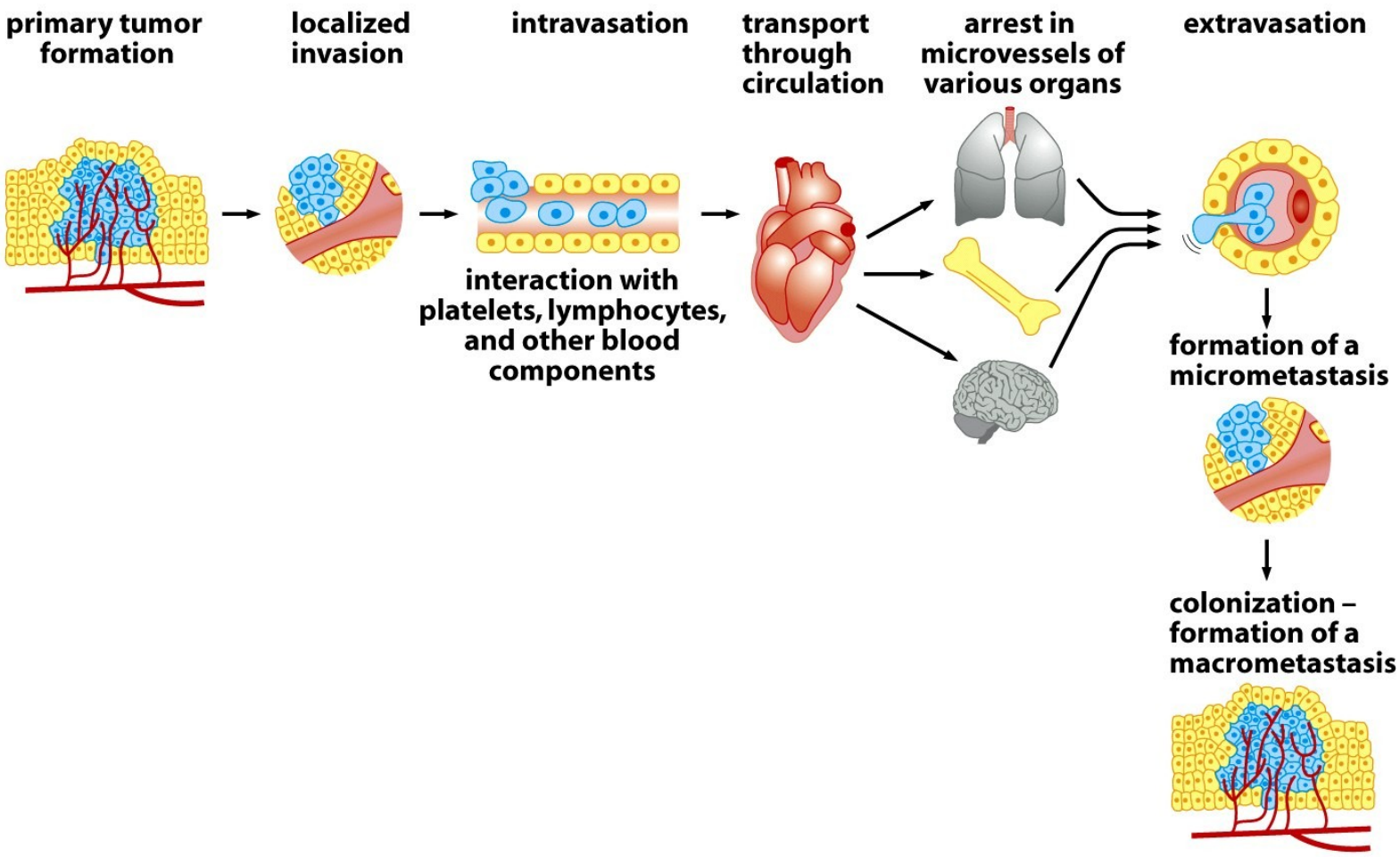
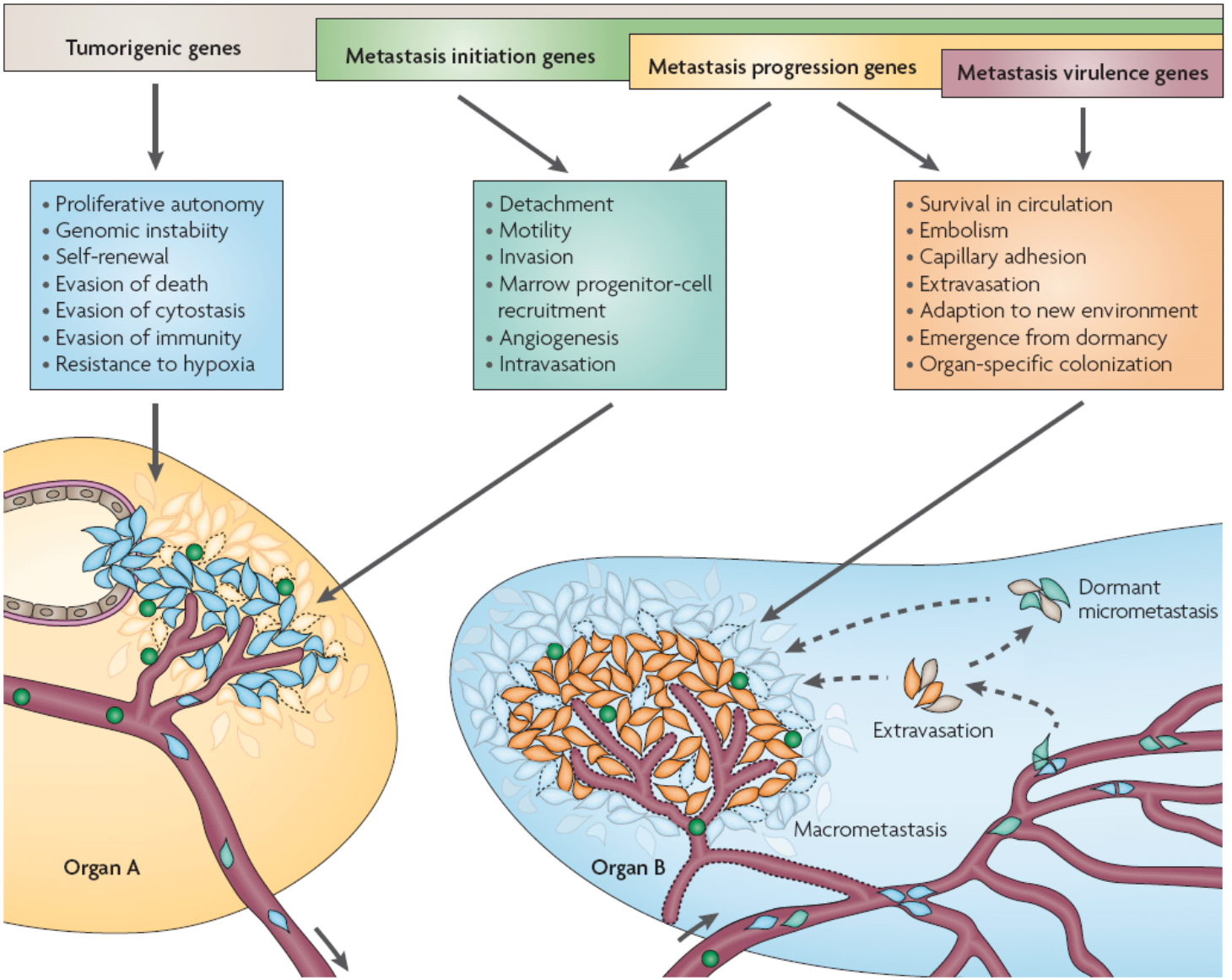


Figure 14.4 *The Biology of Cancer* (© Garland Science 2007)

Genetic determinants of cancer metastasis

Don X. Nguyen and Joan Massagué



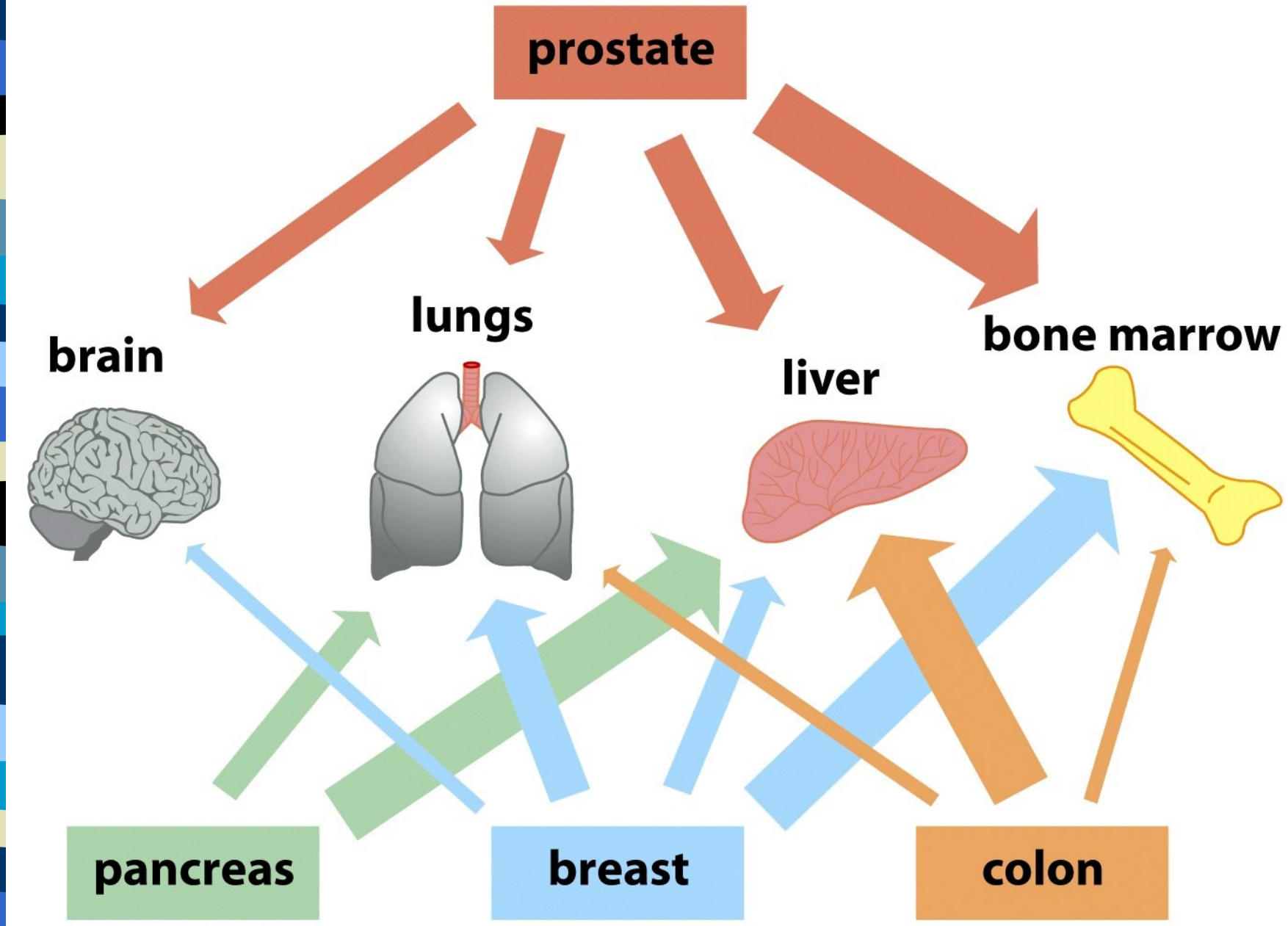
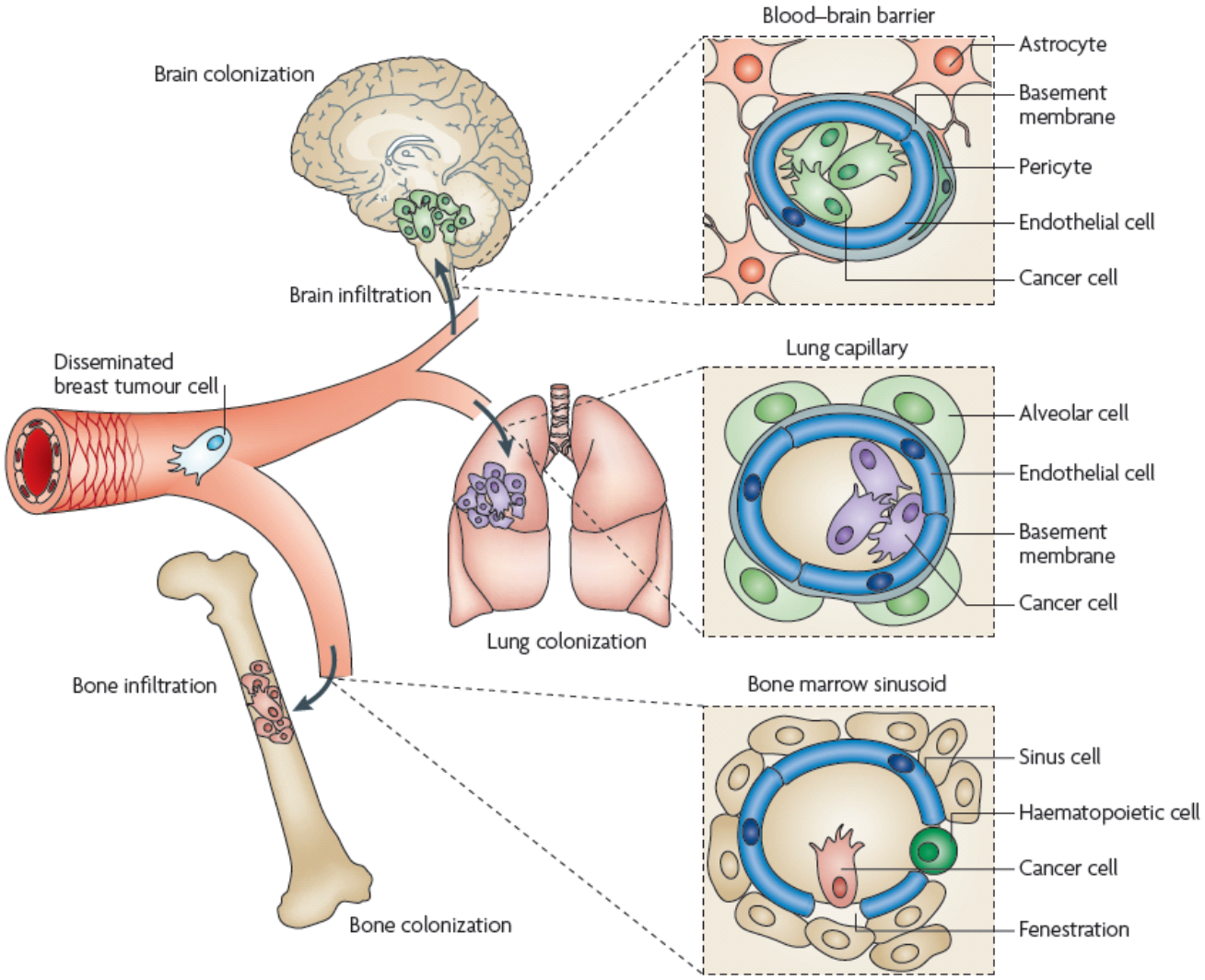


Figure 14.42 *The Biology of Cancer* (© Garland Science 2007)

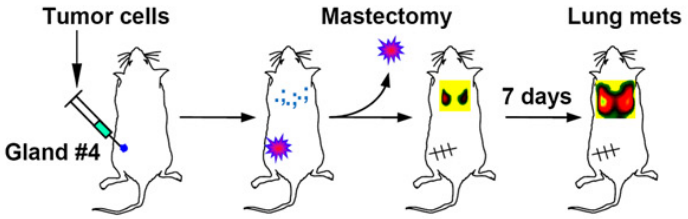
Organ-specific barriers



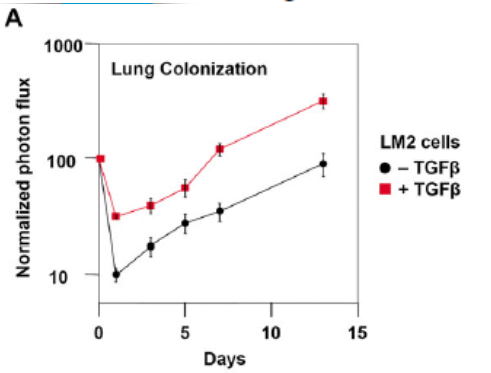
Cell

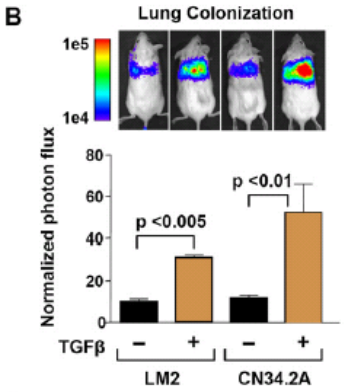
Cell 133, 66–77, April 4, 2008

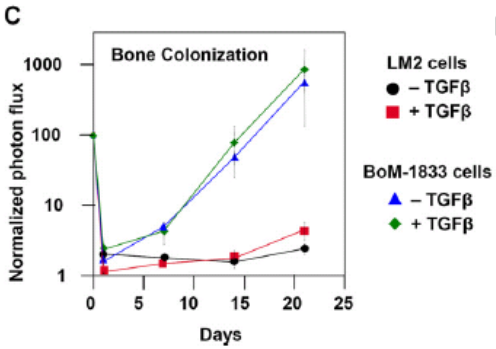
TGFβ Primes Breast Tumors for Lung Metastasis Seeding through Angiopoietin-like 4

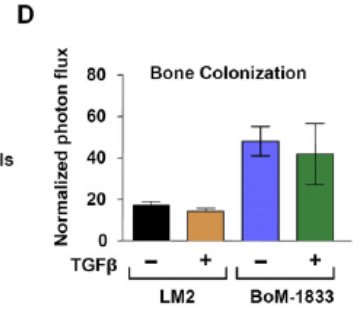


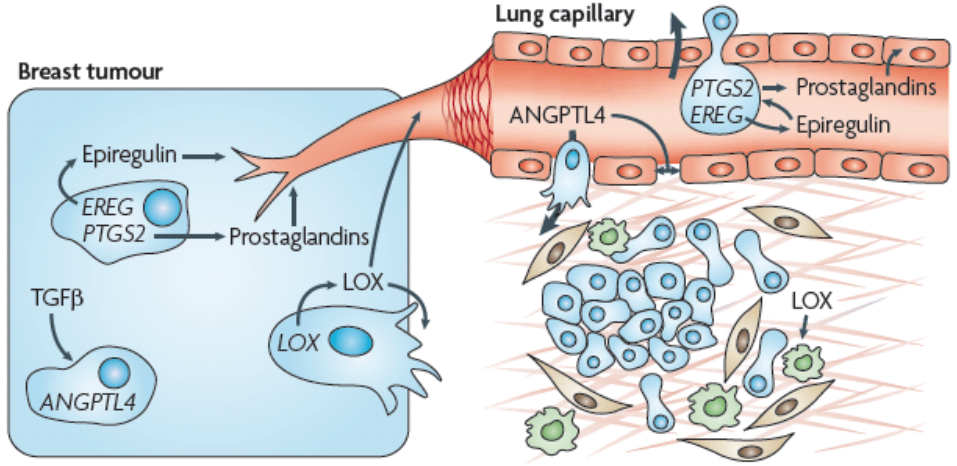
David Padua,[1] Xiang H.-F. Zhang,[1] Qiongqing Wang,[1] Cristina Nadal,[5] William L. Gerald,[2] Roger R. Gomis,[4] and Joan Massagué[1,3,*]







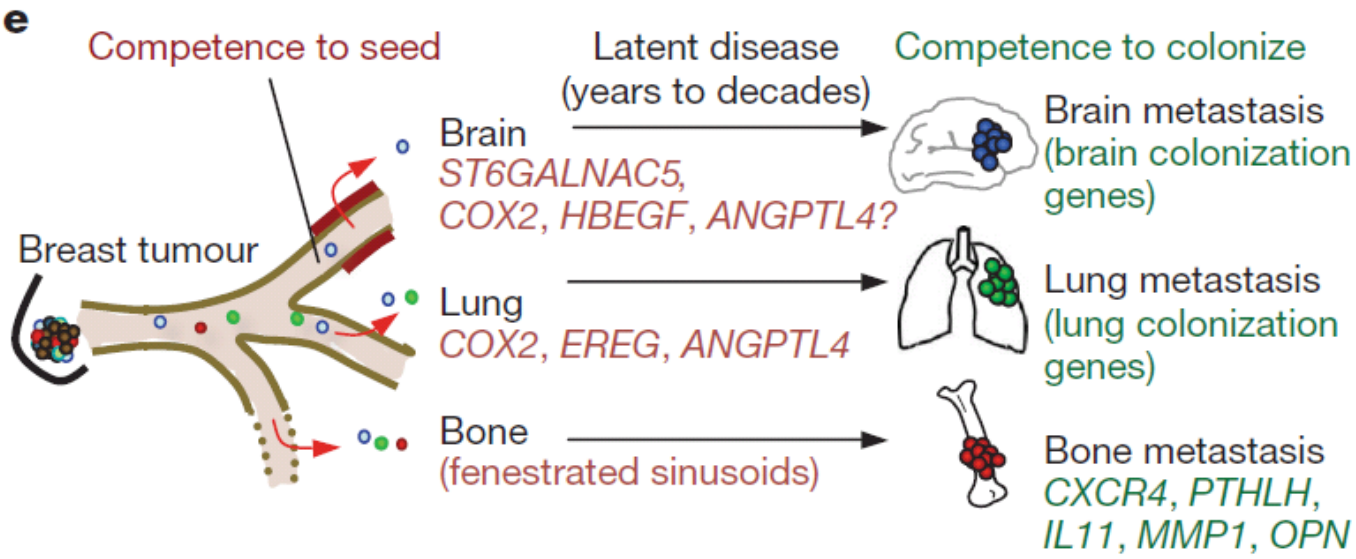


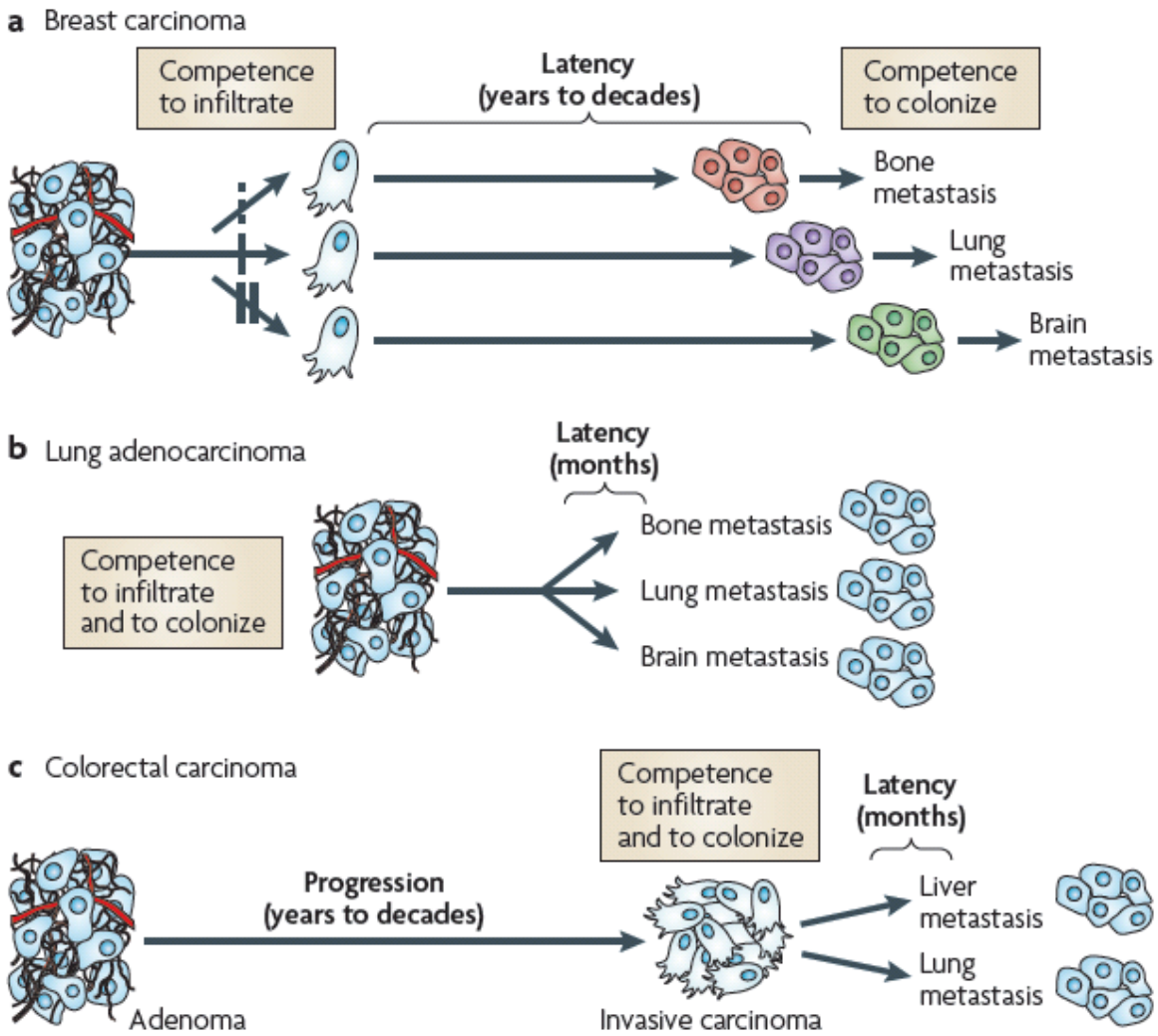


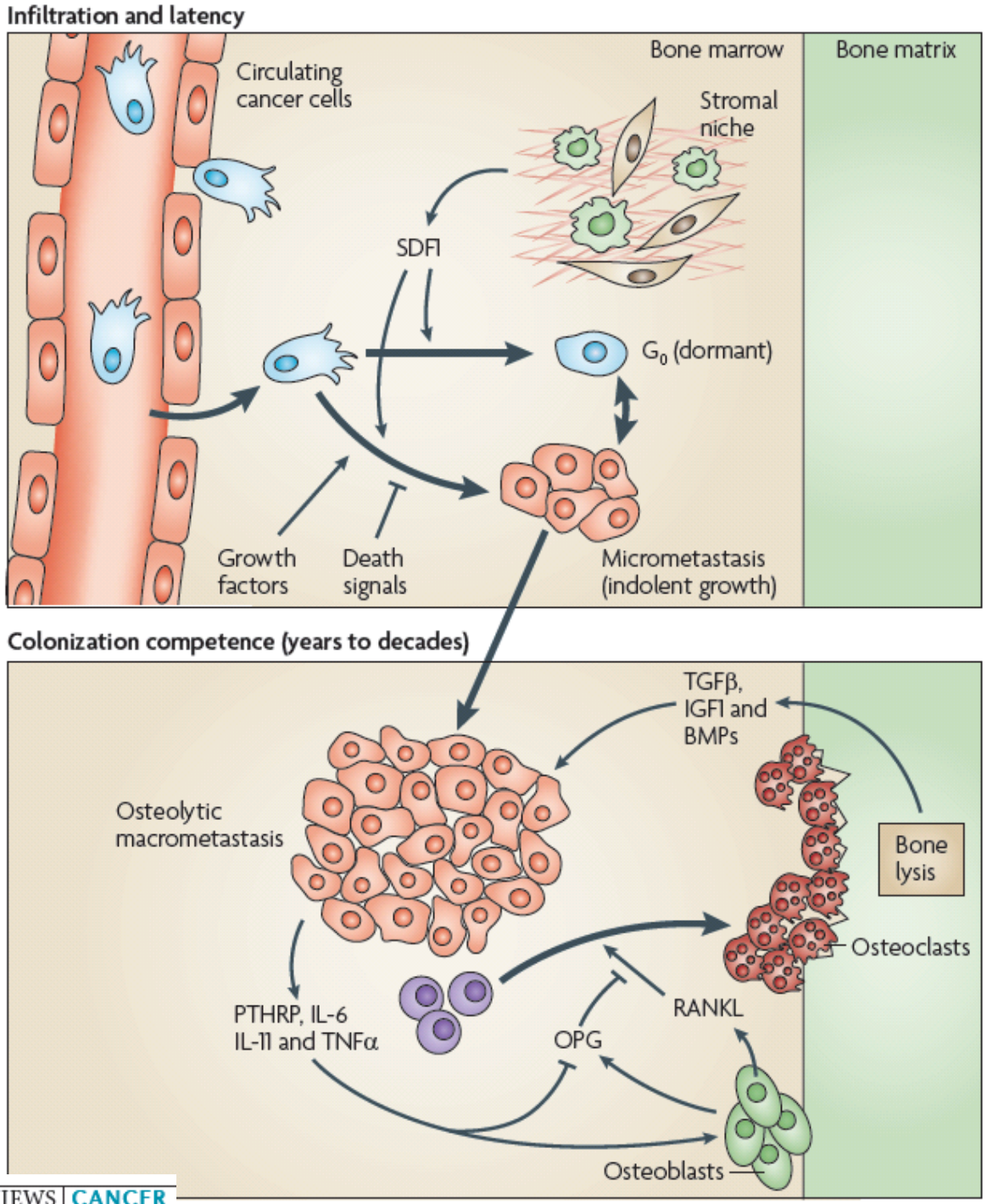
Vol 459|18 June 2009|doi:10.1038/nature08021 nature

Genes that mediate breast cancer metastasis to the brain

Paula D. Bos[1], Xiang H.-F. Zhang[1], Cristina Nadal[1]†, Weiping Shu[1], Roger R. Gomis[1]†, Don X. Nguyen[1], Andy J. Minn[2], Marc J. van de Vijver[3], William L. Gerald[4], John A. Foekens[5] & Joan Massagué[1,6]




a Breast carcinoma
Competence to infiltrate
Latency (years to decades)
Competence to colonize
Bone metastasis
Lung metastasis
Brain metastasis
b Lung adenocarcinoma
Latency (months)
Competence to infiltrate and to colonize
Bone metastasis
Lung metastasis
Brain metastasis
c Colorectal carcinoma
Competence to infiltrate and to colonize
Latency (months)
Progression (years to decades)
Liver metastasis
Lung metastasis
Adenoma
Invasive carcinoma


Infiltration and latency
Bone marrow
Bone matrix
Circulating cancer cells
Stromal niche
SDF1
G_0 (dormant)
Growth factors
Death signals
Micrometastasis (indolent growth)
Colonization competence (years to decades)
TGFβ, IGF1 and BMPs
Osteolytic macrometastasis
Bone lysis
Osteoclasts
PTHRP, IL-6 IL-11 and TNFα
OPG
RANKL
Osteoblasts

Transforming growth factor-β

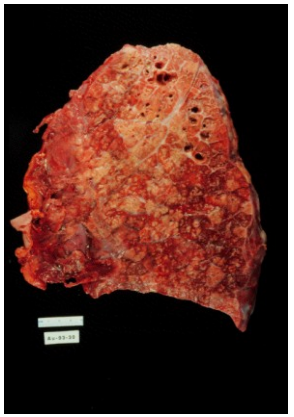
- Role v rozvoji patologických stavů

Biologické funkce TGF-β

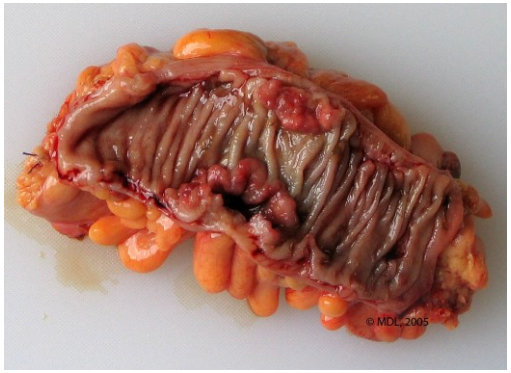
- Hraje klíčovou úlohu během embryogeneze;
- reguluje proliferaci, diferenciaci, buněčnou smrt, motilitu, adhezi (v závislosti na buněčném typu) = ovlivňuje homeostázu;
- reguluje expresi extracelulární matrix;
  - indukuje fibrilární kolagen a fibronectin;
  - inhibuje degradaci ECM (inhibicí MMPs a indukci TIMPs).

Role TGF-β v rozvoji patologických stavů

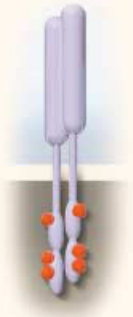
- Fibróza
  - deregulace exprese ECM prostřednictvím indukce proliferace fibroblastů a jejich myofibroblastového fenotypu.



- Nádorová onemocnění
  - ztráta citlivosti epiteliálních buněk k inhibičnímu působeni TGF-β;
  - indukce angiogeneze.

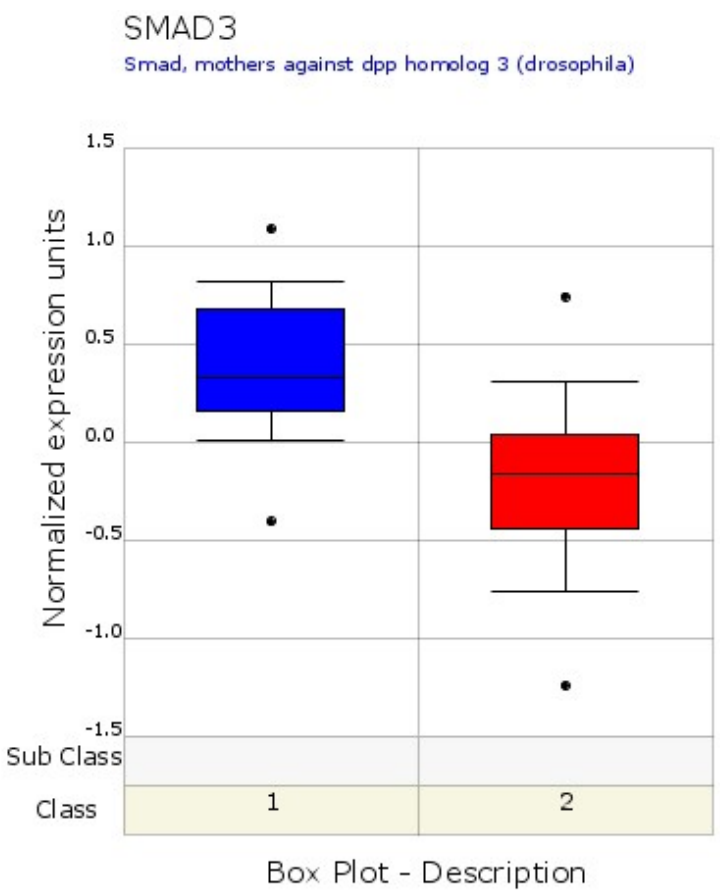


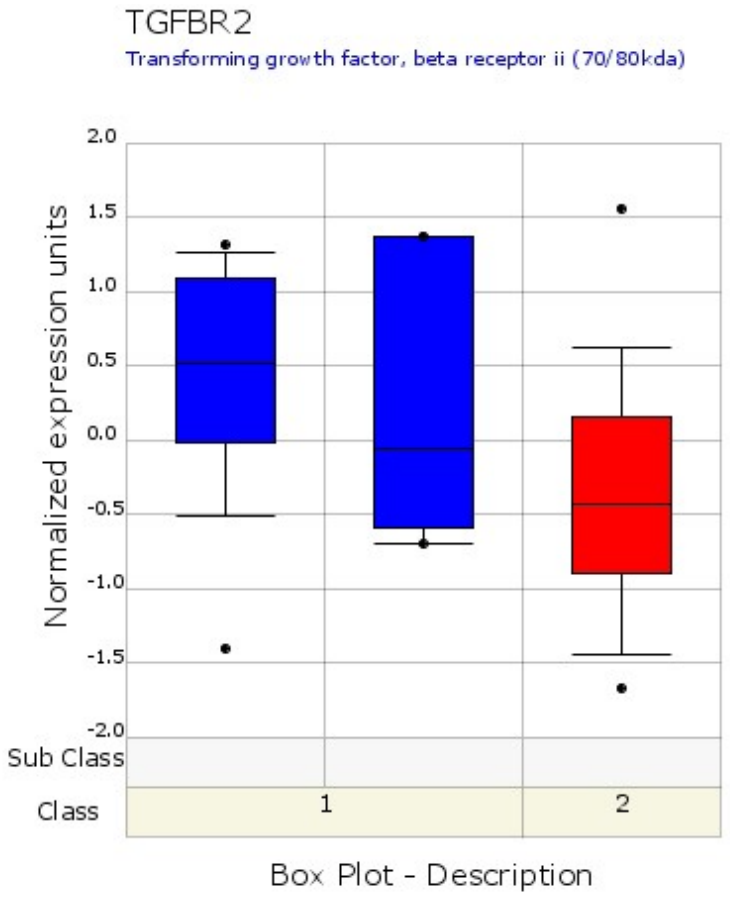
Role TGF-β v carcinogenezi

TGF-β signaling component	TGF-β	Endoglin	Type II receptors	Type I receptors	Smad2	Smad4
						
Cancers (somatic mutations)	Increased expression leads to enhanced invasion and metastasis		Colorectal (30%) Gastric (15%) Endometrial Prostate Breast Lung Hepatic Pancreatic Cervical Glioma Head and neck	Breast (16%) Pancreatic Biliary Cervical Chronic lymphocytic leukemia	Colorectal (11%) Lung (7%) Hepatocellular	Pancreatic (50%) Colorectal (30%) Lung (10%) Breast Prostate Ovarian Head and neck Esophageal Gastric Bladder Hepatocellular Renal cell
Other diseases (germ-line mutations or polymorphisms)	Fibrosis Hypertension Osteoporosis Atherosclerosis	Hereditary hemorrhagic telangiectasia	Atherosclerosis			Familial juvenile polyposis

NEJM 342, **18** (2000) 1350-1358

Role TGF-β v carcinogenezi



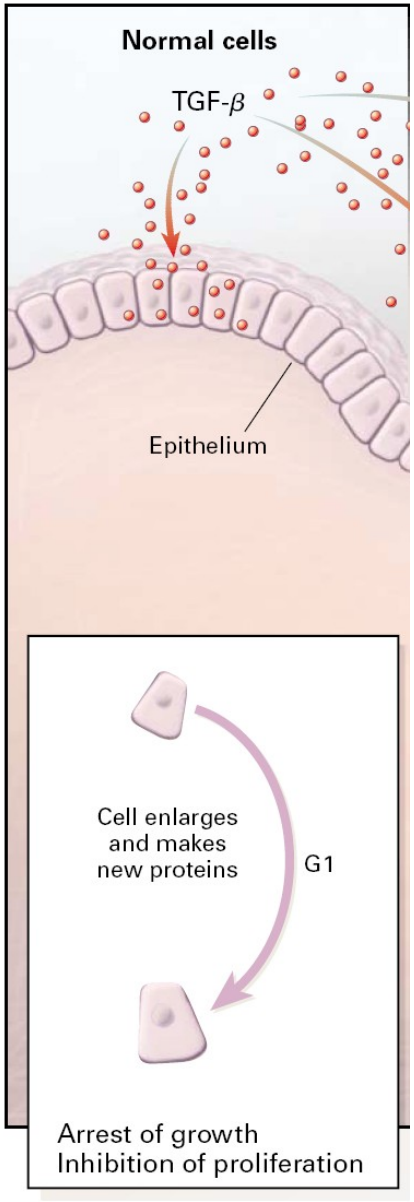


Prostate – normal vs. cancer

normal, hyperplasia vs. cancer

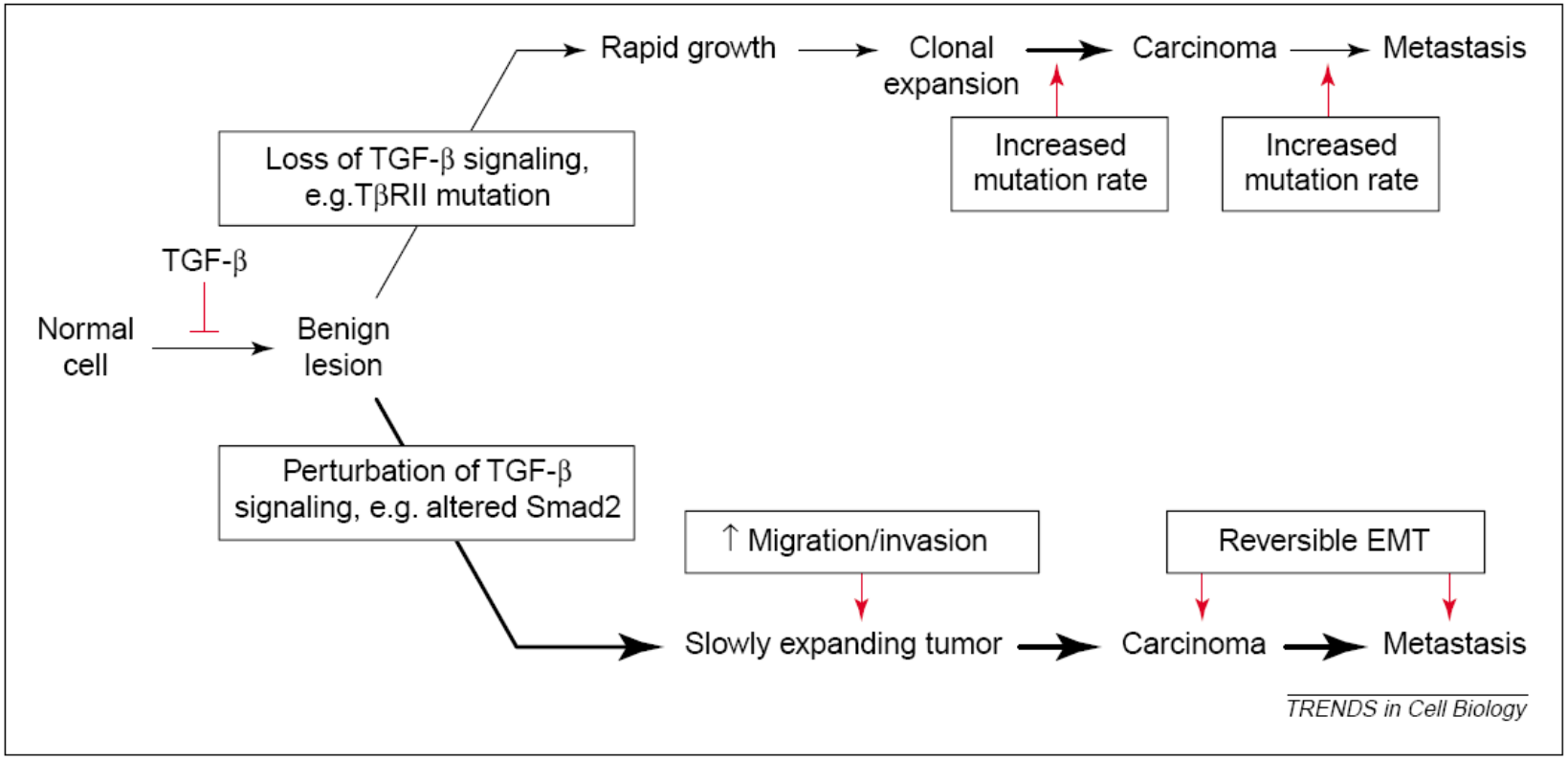
CANCER PROFILING DATABASE ONCOMINE™

Role TGF-β v carcinogenezi



NEJM 342, **18** (2000) 1350-1358

Role TGF-β v carcinogenezi



Epithelial-Mesenchymal Transition (EMT)

- Změna buněčného fenotypu spojená se ztrátou adheze a zvýšením motility

EMT & Cancer

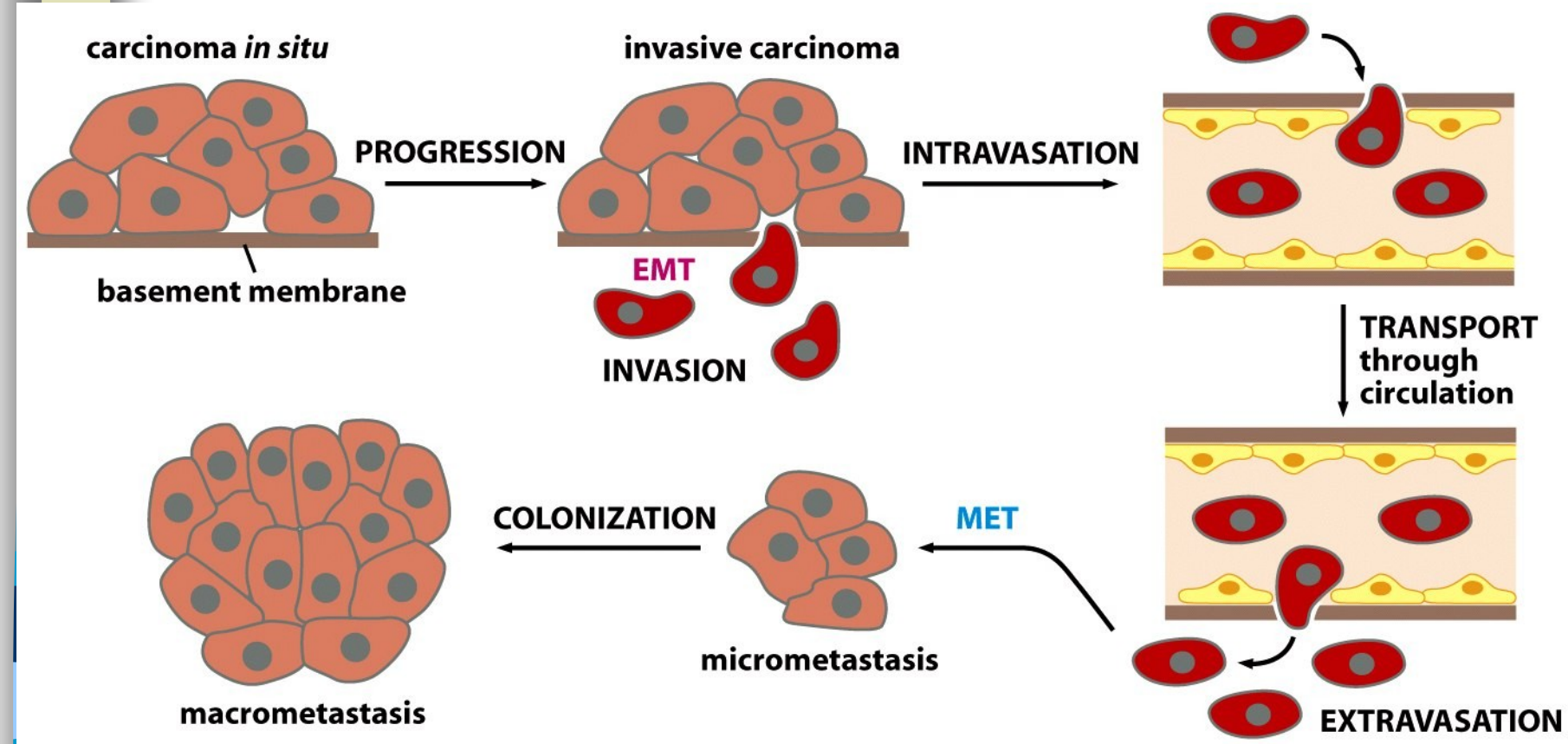
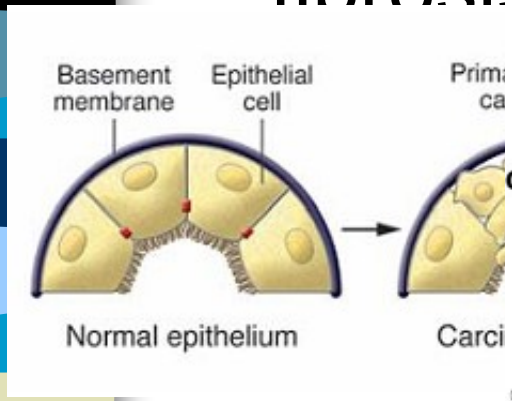
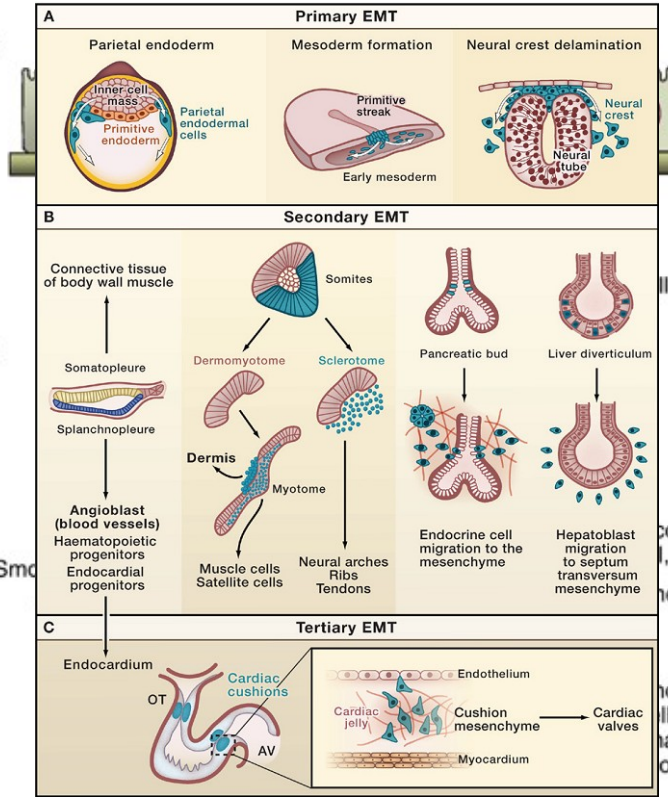


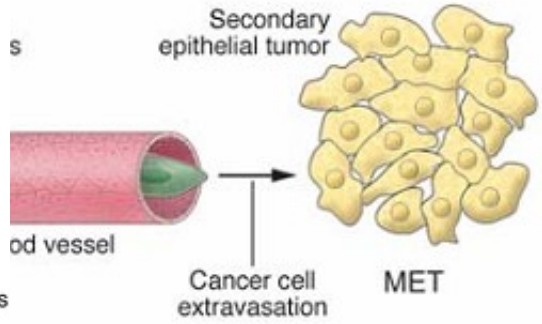
Figure 14.17b *The Biology of Cancer* (© Garland Science 2007)

Epithelial-to-mesenchymal transition (EMT)

- Reversible acquisition of migratory and invasive properties by epithelial cells
- Role ir ment, fibrosi





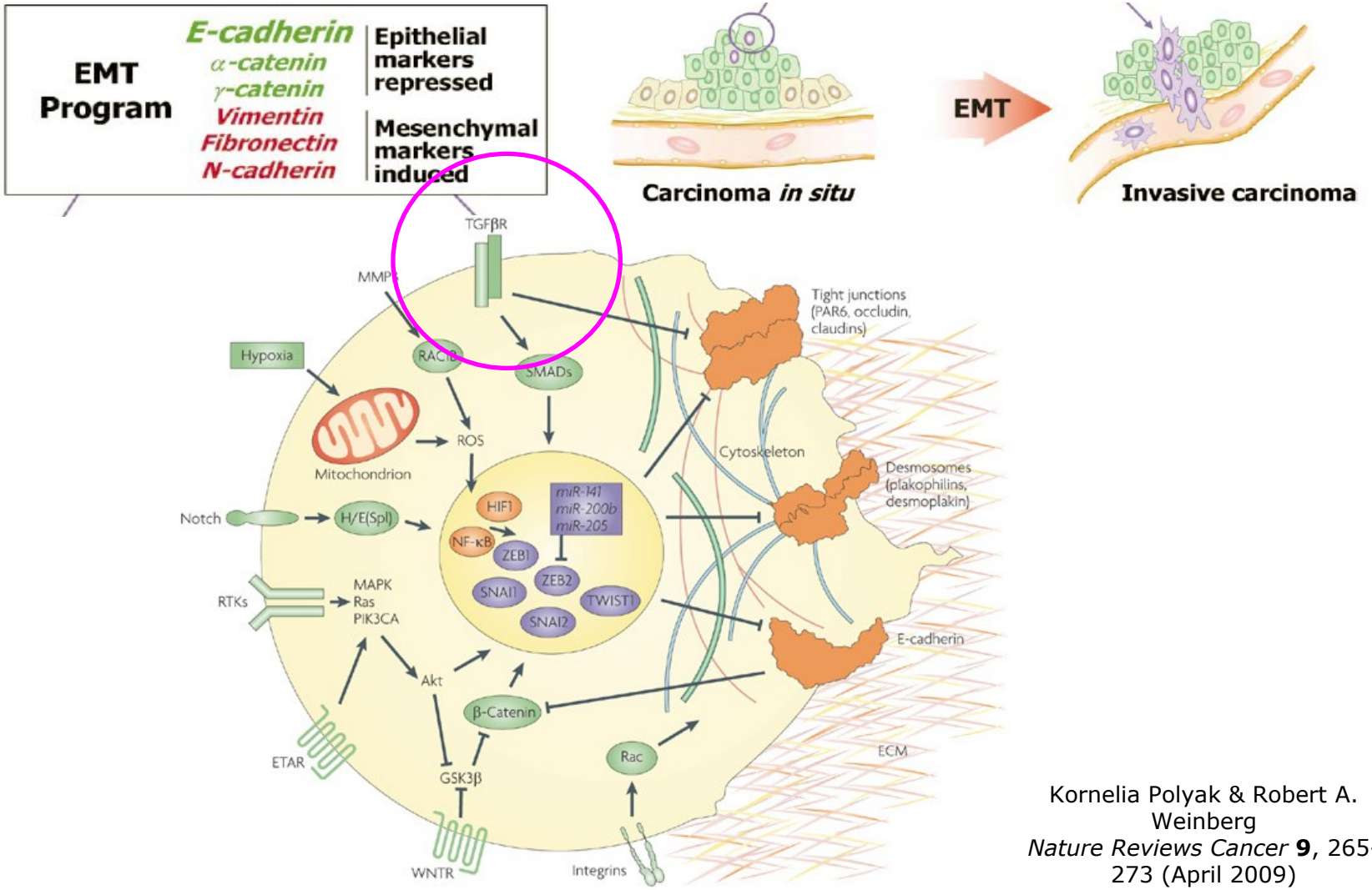


Kalluri, R. and R.A. Weinberg, T

transitions in development and disease. *Cell*, 2009. 139(5): p. 871-90.

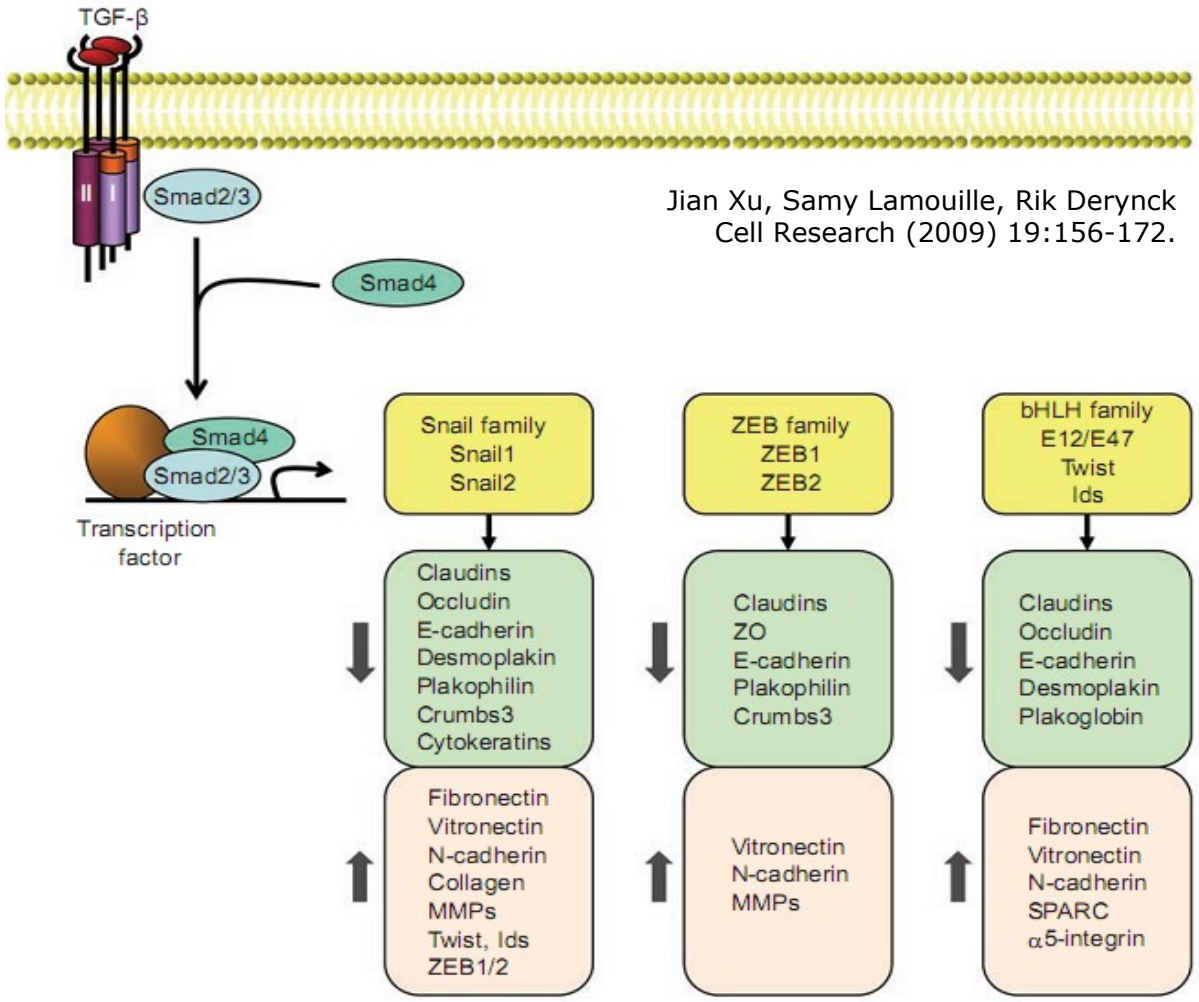
M S Simonson
Kidney International **71**, 846-854 (May (1) 2007)

Markers and regulators of EMT



Kornelia Polyak & Robert A. Weinberg
Nature Reviews Cancer **9**, 265-273 (April 2009)

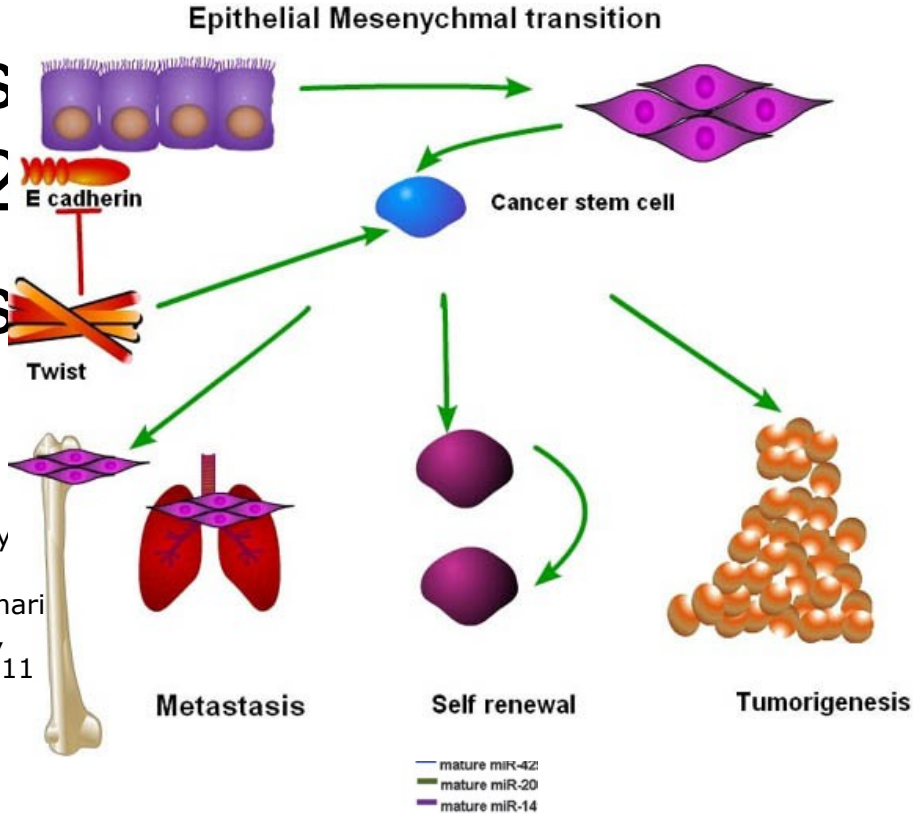
Transforming growth factor-β (TGF-β)

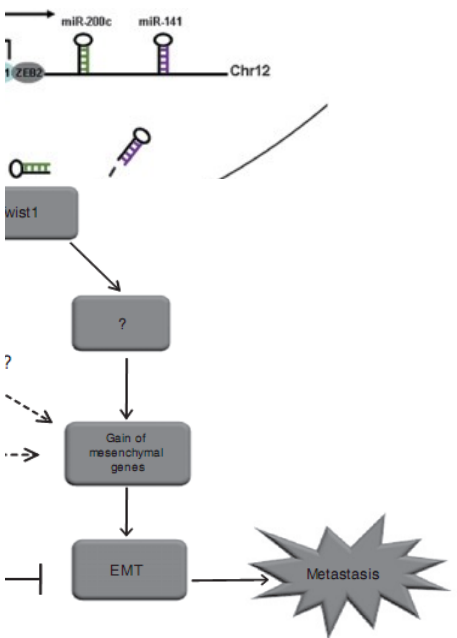


Jian Xu, Samy Lamouille, Rik Derynck
Cell Research (2009) 19:156-172.

Recent discoveries in the EMT field

- EMT creates cells with cancer stem cell characteristics **Mani** SA, et al., Cell. 2008 May 16;133(4):704-15.
- Cross 31/2 and miR-2
- Cross Slug





Esmeralda Casas, Jihoon Kim, Andrés Bendesky, et Cancer Res; 71(1) January 2011

Prachi Jain, Suresh K. Alahari Frontiers in Bioscience 16, 1824-1832, January 1, 2011

H Zhang, Y Li and M Lai *Oncogene* **29**, 937-948 (18 February 2010)

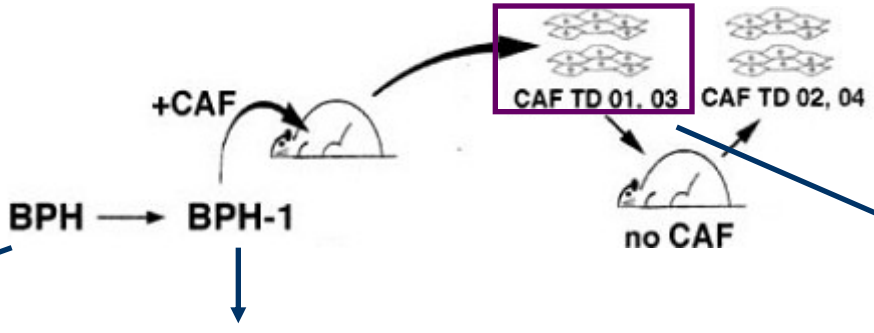
Experimental approach

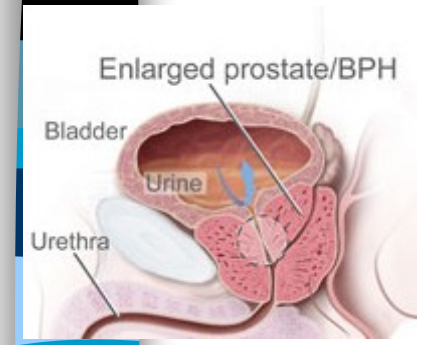
ESTABLISHMENT AND CHARACTERIZATION OF AN IMMORTALIZED BUT NON-TRANSFORMED HUMAN PROSTATE EPITHELIAL CELL LINE: BPH-1

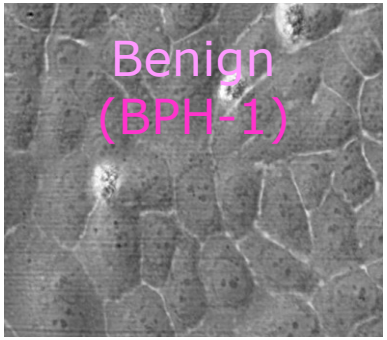
S. W. HAYWARD, R. DAHIYA, G. R. CUNHA, J. BARTEK, N. DESHPANDE, AND P. NARAYAN

Malignant Transformation in a Nontumorigenic Human Prostatic Epithelial Cell Line[1]

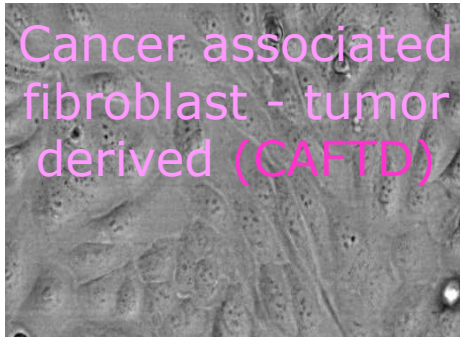
Simon W. Hayward,[2] Yuzhuo Wang, Mei Cao, Yun Kit Hom, Baohui Zhang, Gary D. Grossfeld, Daniel Sudilovsky, and Gerald R. Cunha







EMT



TGF-β

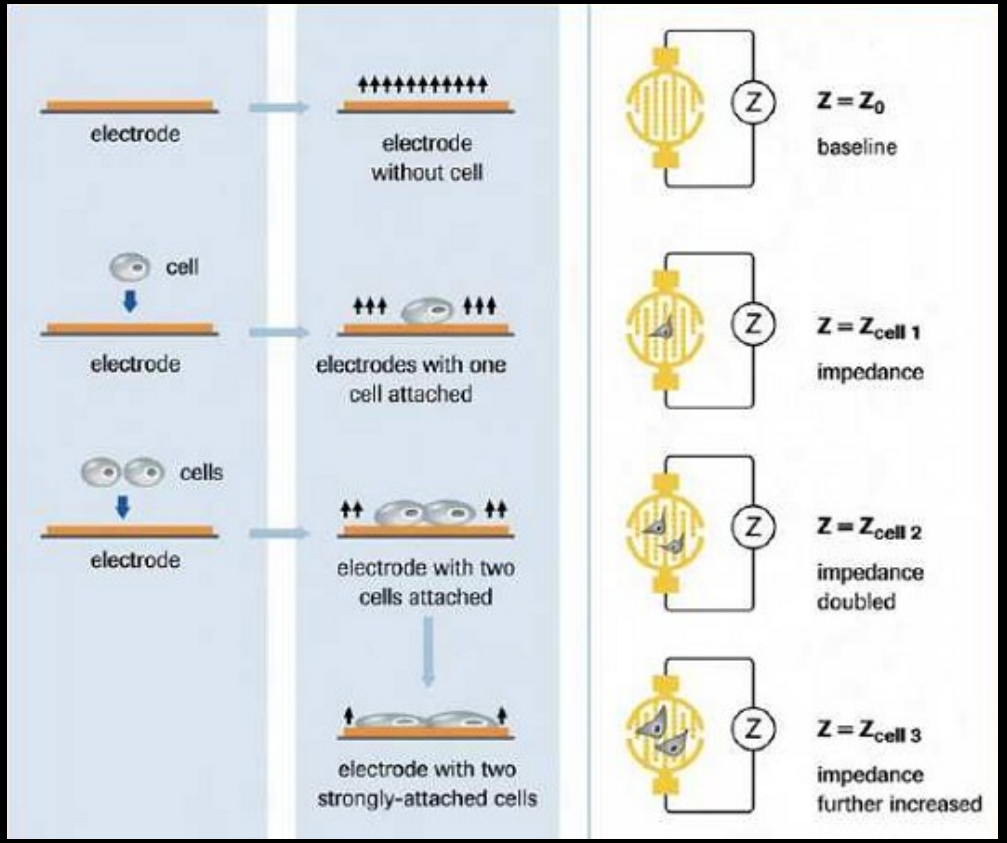
EMT

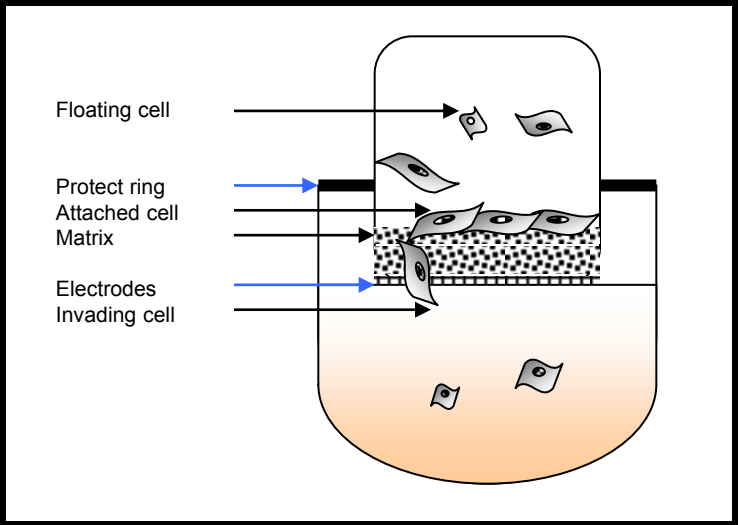
- EMT markers
- EMT regulators
- Cell shape and behavior

TGF-β

EMT

xCELLigence – analýza migračního potenciálu





Dvojí úloha TGF-β v carcinogenezi

- Deregulace inhibice proliferace epiteliálních buněk;
- Epithelia-mesenchymal transition
- podpora migrace, metastázování a angiogeneze.

Role TGF-β v diagnóze, prognóze a léčbě

- Vysoká sérová hladina TGF-β1 je spojena s nádory tlustého střeva, prostaty a rozvojem fibrózy;
- polymorfismus genu pro TGF-β1 vedoucí k jeho zvýšené produkci určuje predispozici k fibróze, hypertenzi a osteoporéze;
- blokování produkce a aktivity TGF-β má velký potenciál pro léčbu fibrózy;
- protektivní účinek retinoidů a vitamínu D3 může být způsoben prostřednictvím TGF-β.

GDF-15: tumor promoter or supresor?

- Karel Souček, Eva Slabáková, Zuzana Pernicová, Eva Slavíčková, Radek Fedr

Department of Cytokinetics
Institute of Biophysics AS CR

Center of Biomolecular and Cellular Engineering
International Clinical Research Center FNUSA-ICRC

Brno, Czech Republic

Proc. Natl. Acad. Sci. USA
Vol. 94, pp. 11514–11519, October 1997
Immunology, Cell Biology

MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-β superfamily

MICHELLE R. BOOTCOV*†, ASNE R. BAUSKIN*†, STELLA M. VALENZUELA*, ANTHONY G. MOORE*, MOHINDER BANSAL*, XIAO YAN HE*, HONG PING ZHANG*, MELISSA DONNELLAN*, STEPHEN MAHLER‡, KIMBERLEY PRYOR*, BRADLEY J. WALSH*, RICHARD C. NICHOLSON*, W. DOUGLAS FAIRLIE*, SUZANNE B. POR*, JOAN M. ROBBINS*, AND SAMUEL N. BREIT*§

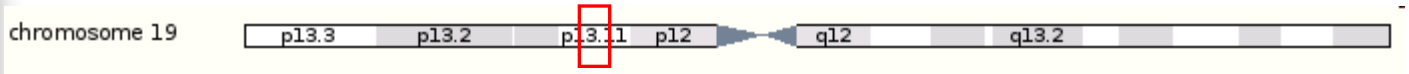
*Centre for Immunology, St. Vincent's Hospital, and University of New South Wales, Sydney, 2010, Australia; and ‡Department of Biotechnology, University of New South Wales, Sydney, 2010, Australia

22/3/2011 ~ 894 records

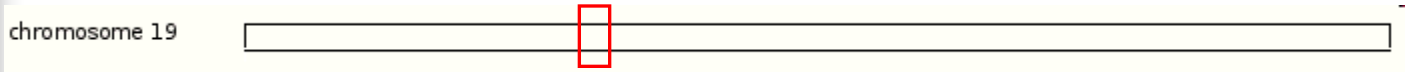
- Membrane receptor(s) – not identified
- Signal transduction – not identified
- Target genes – not identified
- Function – not clear

GDF15 gene

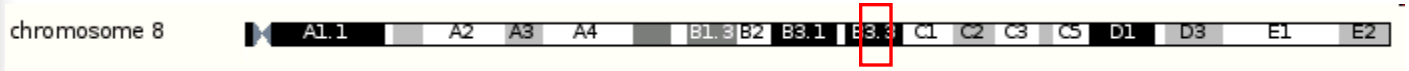
Homo sapiens

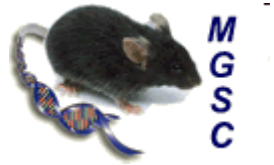


Pan troglodytes

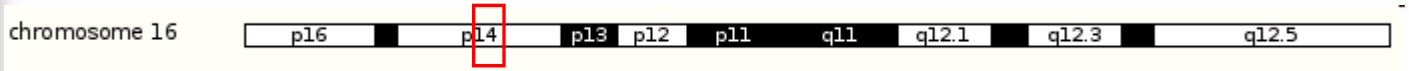


Mus musculus

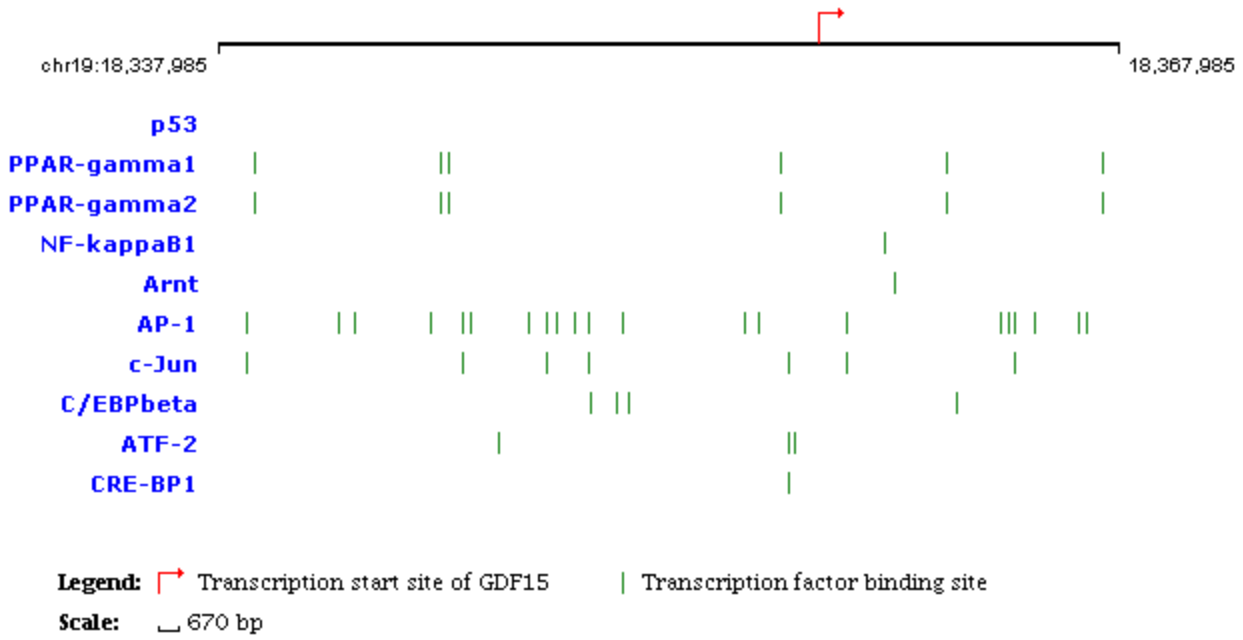




Rattus norvegicus

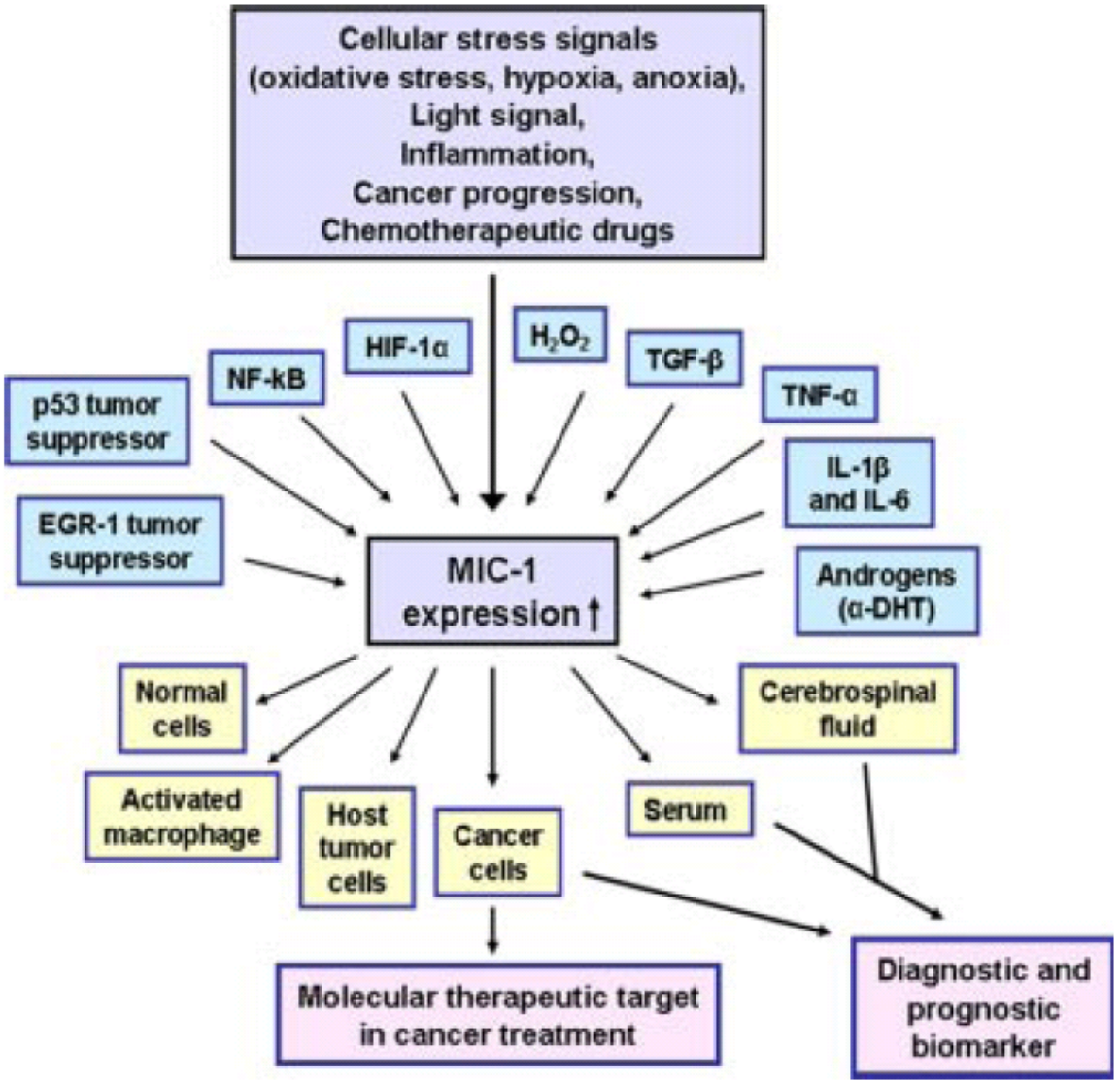


Control of *GDF15* expression



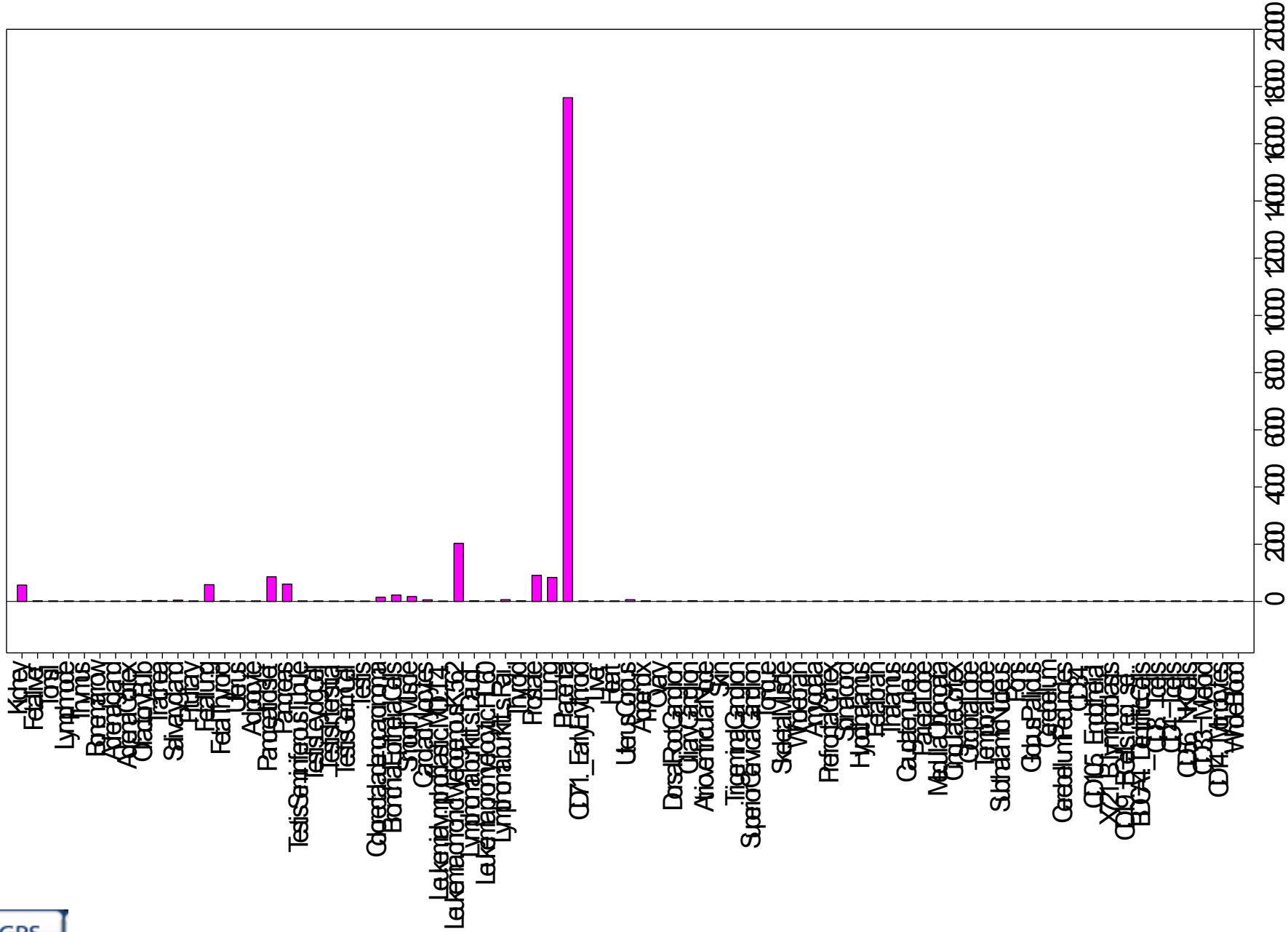
SABiosciences™

GDF-15 regulation



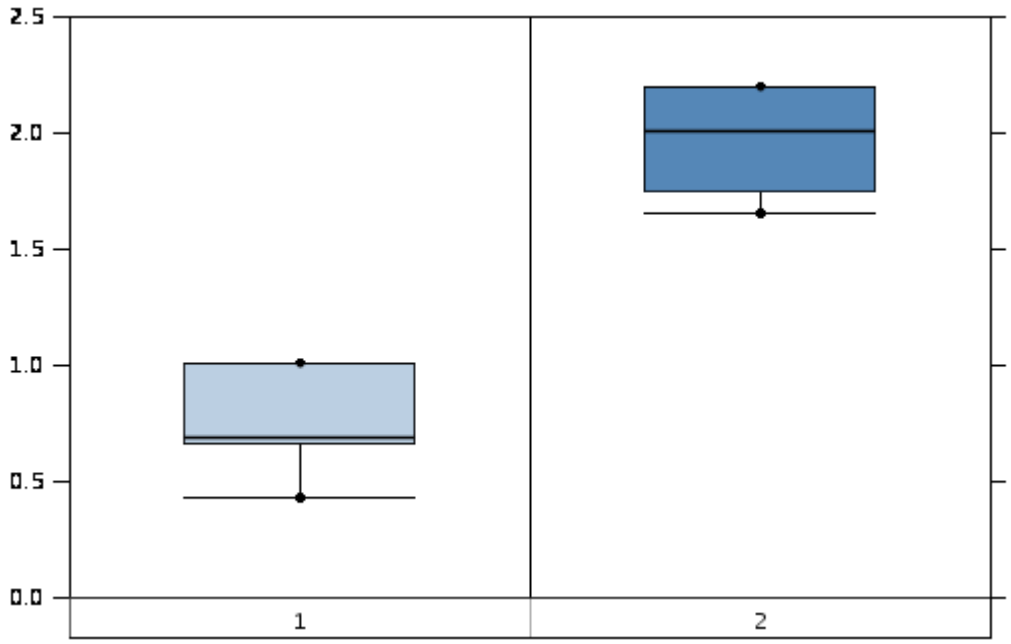
M, Mimeualt, JCP 2010

human GDF15 mRNA expression



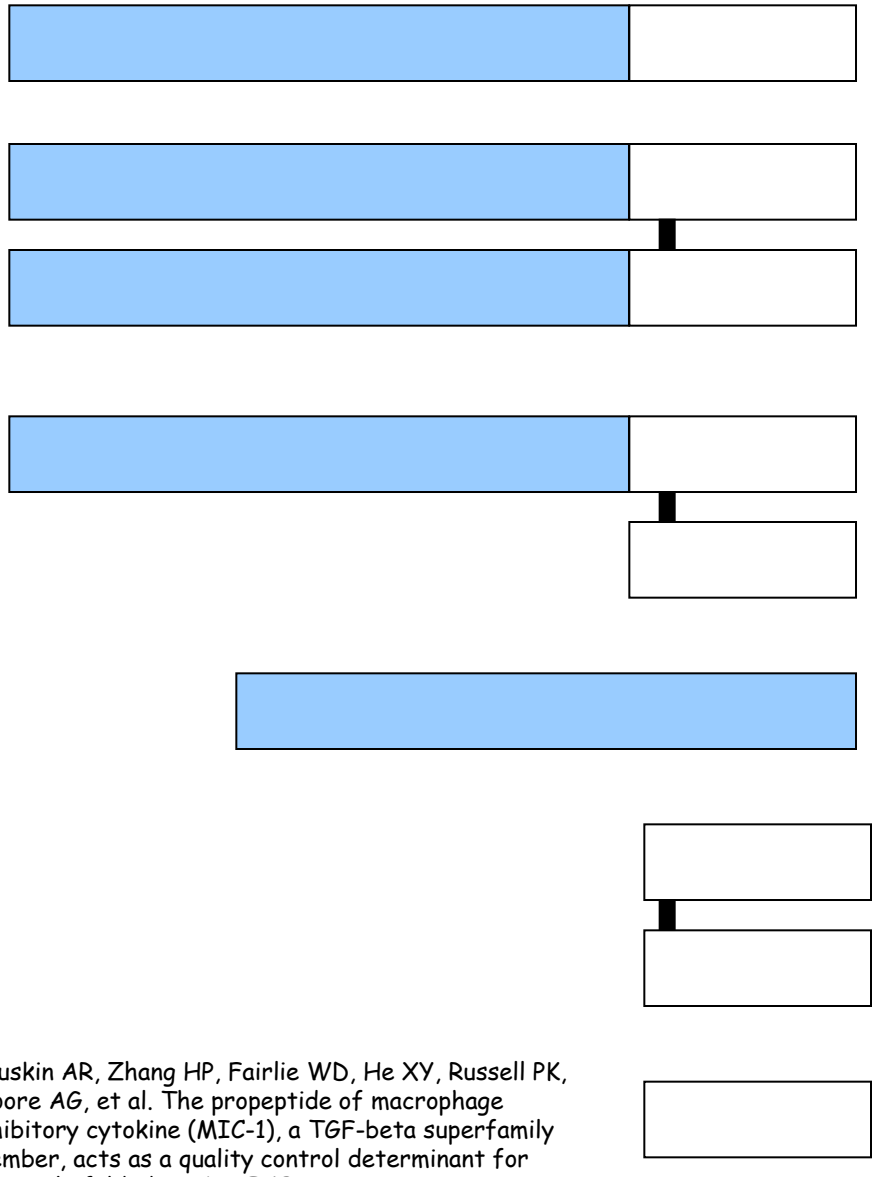
BioGPS

GDF15 mRNA
normal vs. prostate adenocarcinoma



Varambally, S. et al., *Cancer Cell* **8** (5), 393 (2005).

Various forms of GDF-15



pro-GDF-15 monomer ~40kDa

pro-GDF-15 dimer ~80kDa

pro-GDF-15 hemidimer ~55kDa

propeptide ~28kDa

mature GDF-15 dimer ~30kDa

mature GDF-15 monomer ~15kDa

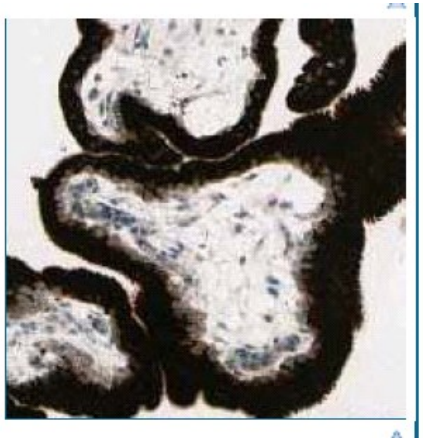
Bauskin AR, Zhang HP, Fairlie WD, He XY, Russell PK, Moore AG, et al. The propeptide of macrophage inhibitory cytokine (MIC-1), a TGF-beta superfamily member, acts as a quality control determinant for correctly folded MIC-1. **EMBO J** 2000;19:2212-20.

HUMAN PROTEIN ATLAS

alph. sort order

Normal Tissues - IHC

Adrenal gland	cortical cells
Appendix	glandular cells
	lymphoid tissue
Bone marrow	bone marrow poietic cells
Breast	glandular cells
Bronchus	respiratory epithelial cells
Cerebellum	cells in granular layer
	cells in molecular layer
	purkinje cells
Cerebral cortex	glial cells
	neuronal cells
Cervix, uterine	glandular cells
	squamous epithelial cells
Colon	glandular cells
Corpus, uterine 1	cells in endometrial stroma
	glandular cells
Corpus, uterine 2	cells in endometrial stroma
	glandular cells
Duodenum	glandular cells
Epididymis	glandular cells
Esophagus	squamous epithelial cells
Fallopian tube	glandular cells
Gall bladder	glandular cells
Heart muscle	myocytes
Hippocampus	glial cells
	neuronal cells
Kidney	cells in glomeruli
	cells in tubules
Lateral ventricle	glial cells
	neuronal cells
Liver	bile duct cells
	hepatocytes
Lung	alveolar cells
	macrophages
Lymph node	lymphoid cells outside reaction centra
	reaction center cells
Nasopharynx	respiratory epithelial cells
Oral mucosa	squamous epithelial cells
Ovary	follicle cells
	ovarian stromal cells
Pancreas	exocrine glandular cells
	islet cells
Parathyroid gland	glandular cells
Placenta	decidual cells
	trophoblastic cells
Prostate	glandular cells
Rectum	glandular cells
Salivary gland	glandular cells
Seminal vesicle	glandular cells
Skeletal muscle	myocytes
Skin	adnexal cells
	epidermal cells
Small intestine	glandular cells
Smooth muscle	smooth muscle cells
Soft tissue 1	mesenchymal cells
Soft tissue 2	mesenchymal cells
Spleen	cells in red pulp
	cells in white pulp
Stomach 1	glandular cells
Stomach 2	glandular cells
Testis	cells in seminiferus ducts
	leydig cells
Thyroid gland	glandular cells
Tonsil	lymphoid cells outside reaction centra
	reaction center cells
	squamous epithelial cells
Urinary bladder	urothelial cells
Vagina	squamous epithelial cells
Vulva/anal skin	squamous epithelial cells

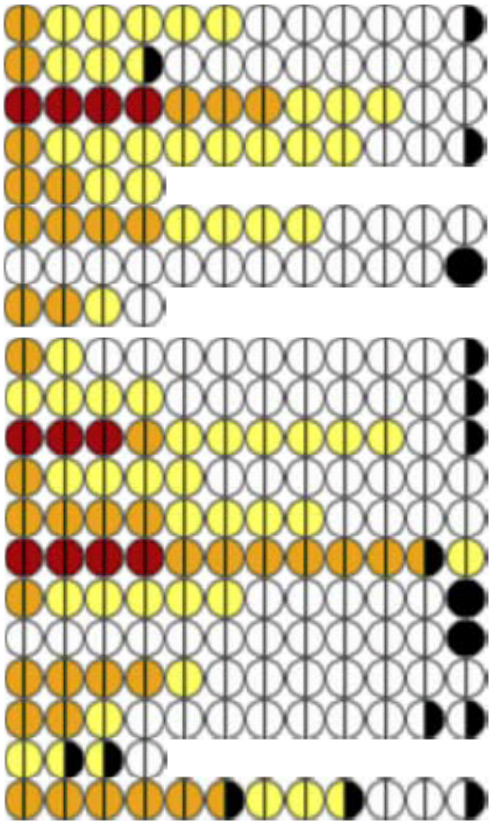


Protein expression

- Strong
- Moderate
- Weak
- Negative
- Not representative

HUMAN PROTEIN ATLAS

Breast cancer
Cervical cancer
Colorectal cancer
Endometrial cancer
Head & neck cancer
Liver cancer
Lung cancer
Malignant carcinoid
Malignant glioma
Malignant lymphoma
Malignant melanoma
Ovarian cancer
Pancreatic cancer
Prostate cancer
Renal cancer
Skin cancer
Stomach cancer
Testis cancer
Thyroid cancer
Urothelial cancer

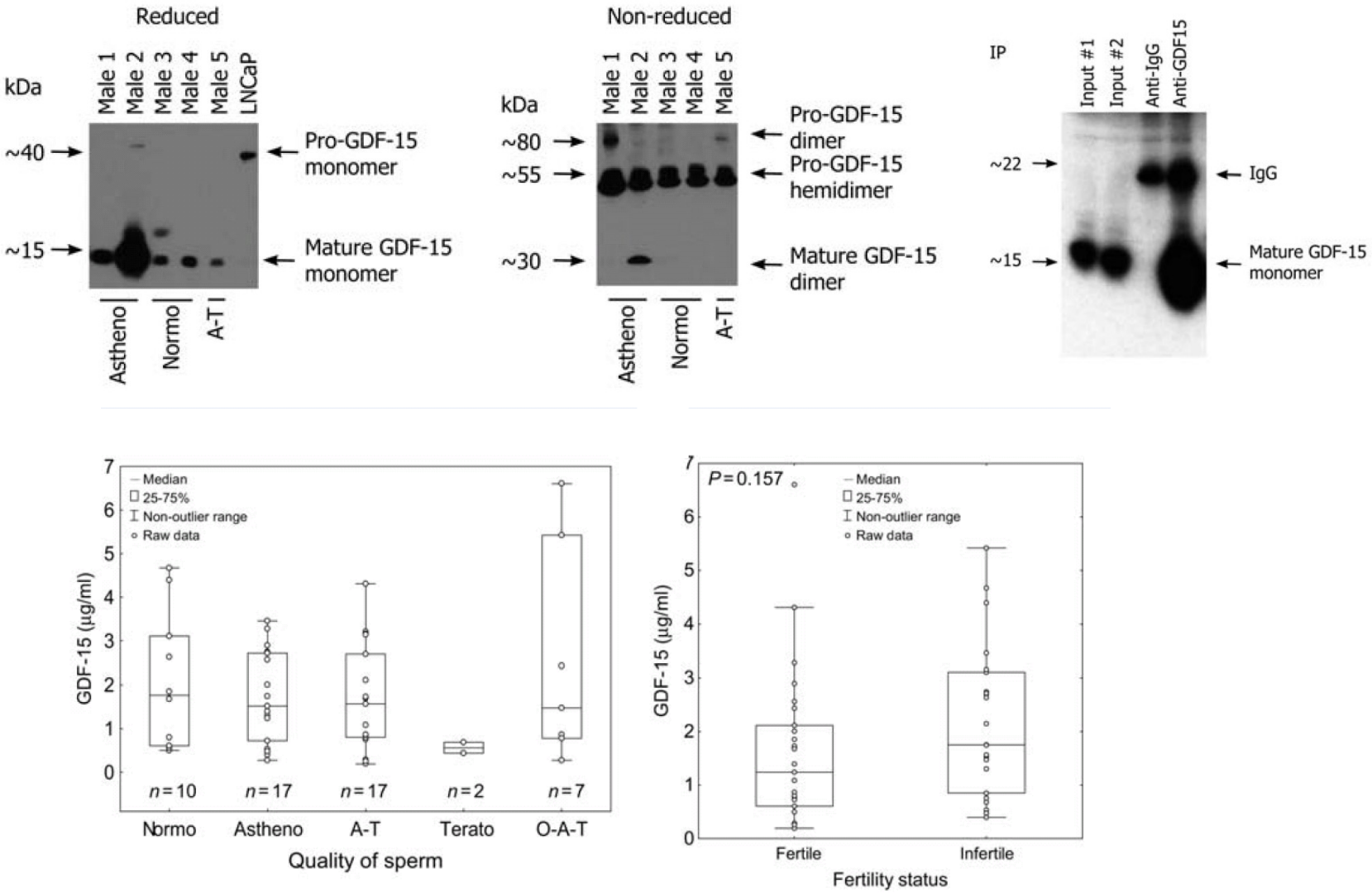


Protein expression

- Strong
- Moderate
- Weak
- Negative
- Not representative

GDF-15	Concentration	Reference
Normal	450 50 pg/ml	Tanno, T. et al., Nat Med 13 (9), 1096 (2007)
beta-thalassemia syndrome	66,000 9,600 pg/ml	
CSF - non-neoplastic	156 pg/m	Sophie Shnaper et al., *International Journal of Cancer* **in press** (2009).
CSF - gliosblastoma	229 pg/ml	
normal	495 pg/ml	Brown, D. A. et al., *Clin Cancer Res* **9** (7), 2642 (2003).
Adenomatous polyps	681 pg/ml	
High-grade dysplasia	1114 pg/ml	
colorectal carcinoma	783 pg/ml	
Congenital dyserythropoietic anemia	10 239 3049 pg/ml	Tamary, H. et al., *Blood* **112** (13), 5241 (2008).
Normal	16.1 23.4 pg/ml	Baek, K. E. et al., *Clinica Chimica Acta* **401** (1-2), 128 (2009).
Gastric cancer	164.5 183.7 pg/ml	
Prostate cancer Grade 3	2,326.1 pg/ml	Selander, K. S. et al., *Cancer Epidemiology Biomarkers & Prevention* **16** (3), 532 (2007).
Prostate cancer Grade 2	2,054.1 pg/ml	
Prostate cancer Grade 1	761.5 pg/ml	
normal	859 619 pg/ml	Brown, D. A. et al., *Clin Cancer Res* **12** (1), 89 (2006).
BPH	983 850 pg/ml	
Prostate cancer	731 500 pg/mL	
Women with cardiovascular events	618 pg/mL	Brown, D. A. et al., *The Lancet* **359** (9324), 2159 (2002).
Women w/o cardiovascular events	538 pg/mL	

Growth/differentiation factor-15 is an abundant cytokine in human seminal plasma



K. Souček et al., Human Reproduction 2010

0021-972X/00/$03.00/0
The Journal of Clinical Endocrinology & Metabolism
Copyright © 2000 by The Endocrine Society
Vol. 85, No. 12
Printed in U.S.A.

The Transforming Growth Factor-β Superfamily Cytokine Macrophage Inhibitory Cytokine-1 Is Present in High Concentrations in the Serum of Pregnant Women*

A. G. MOORE†, D. A. BROWN†, W. D. FAIRLIE, A. R. BAUSKIN, P. K. BROWN, M. L. C. MUNIER, P. K. RUSSELL, L. A. SALAMONSEN, E. M. WALLACE, AND S. N. BREIT

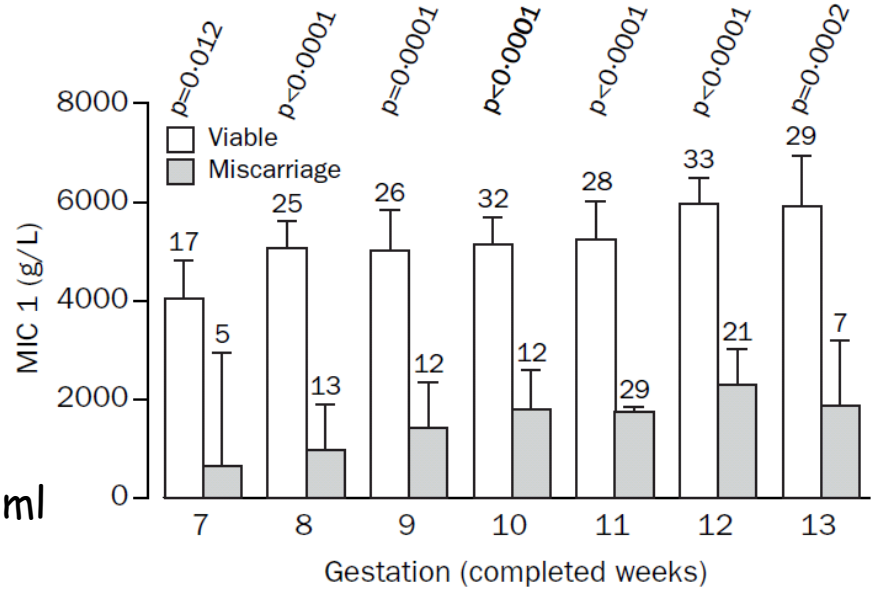
Centre for Immunology (A.G.M., D.A.B., W.D.F., A.R.B., P.K.B., M.L.C.M., P.K.R., S.N.B.), St. Vincent's Hospital and University of New South Wales, Sydney, New South Wales, Australia; Department of Obstetrics and Gynecology (E.M.W.), Monash University, Clayton, Victoria, Australia; and Prince Henry's Institute of Medical Research (L.A.S.), Clayton, Victoria, Australia

normal 0.36 0.04 ng/mL
first trimester 6.3 ± 0.02 ng/mL
second trimester 12.2 ± 0.5 ng/mL
third trimester 15.3 ± 1.3 ng/mL

Serum concentrations of macrophage inhibitory cytokine 1 (MIC 1) as a predictor of miscarriage

Stephen Tong, Budi Marjono, David A Brown, Sheila Mulvey, Samuel N Breit, Ursula Manuelpillai, Euan M Wallace

Lancet 2004; **363:** 129–30



? x E-02 mg/ml

J Cancer Res Clin Oncol
DOI 10.1007/s00432-009-0691-4

ORIGINAL PAPER

Received: 15 July 2009 / Accepted: 16 September 2009
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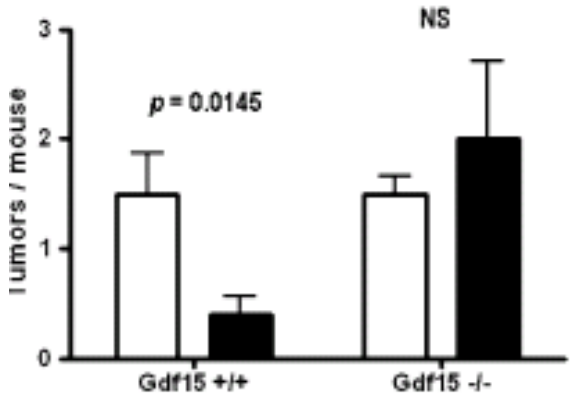
Loss of GDF-15 abolishes Sulindac chemoprevention in the $Apc^{Min/+}$ mouse model of intestinal cancer

Teresa A. Zimmers · Juan C. Gutierrez · Leonidas G. Koniaris

?



Oncogene (2009), 1–10
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www.nature.com/onc

ORIGINAL ARTICLE

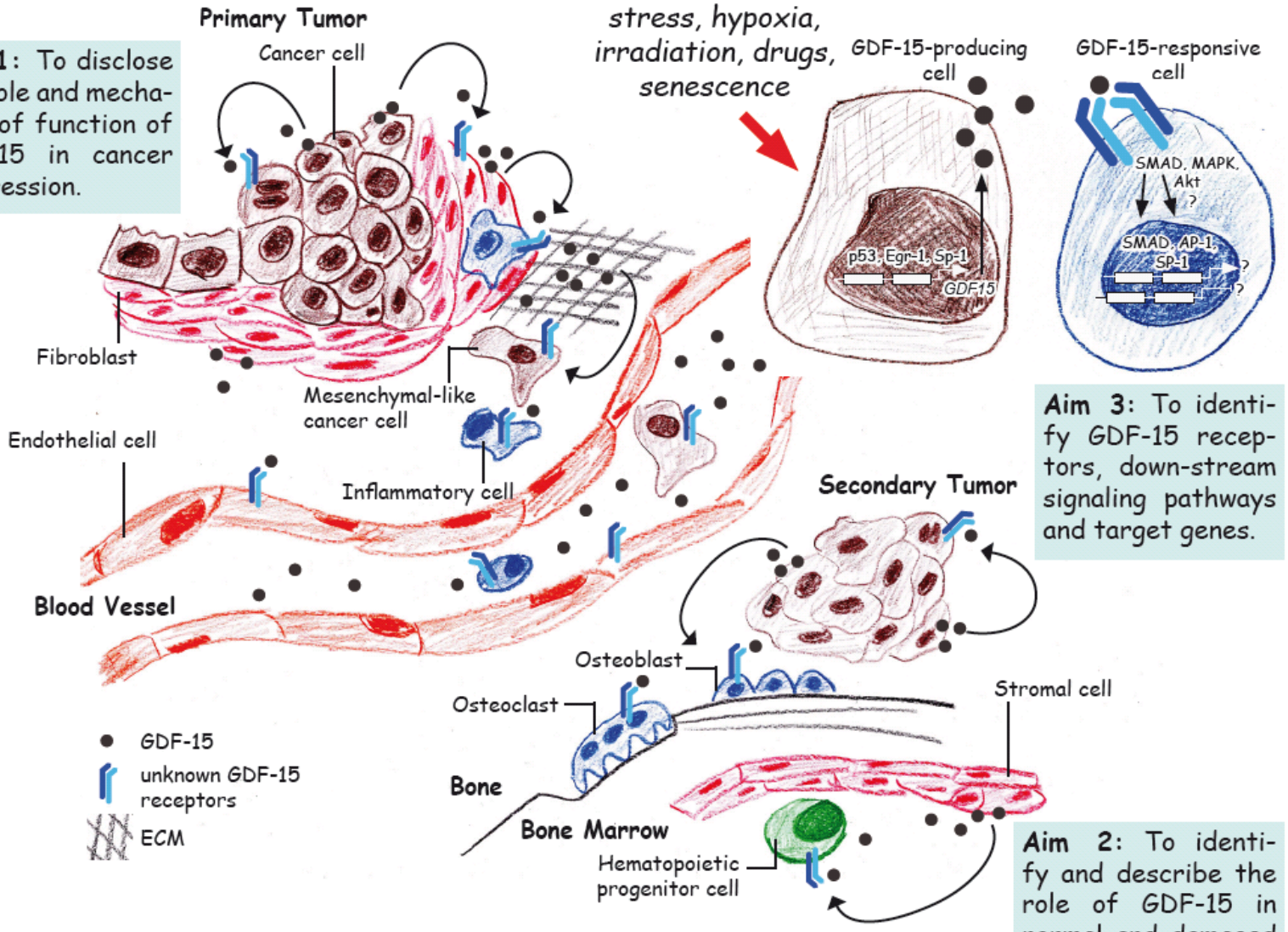
Overexpression of macrophage inhibitory cytokine-1 induces metastasis of human prostate cancer cells through the FAK–RhoA signaling pathway

S Senapati[1], S Rachagani[1], K Chaudhary[1], SL Johansson[2,3], RK Singh[2,3] and SK Batra[1,3]

[1]Department of Biochemistry and Molecular Biology, University of Nebraska Medical Center, Omaha, NE, USA; [2]Pathology and Microbiology, University of Nebraska Medical Center, Omaha, NE, USA and [3]Eppley Institute for Research in Cancer and Allied Diseases, University of Nebraska Medical Center, Omaha, NE, USA

GDF-15/MIC-1 in cancer

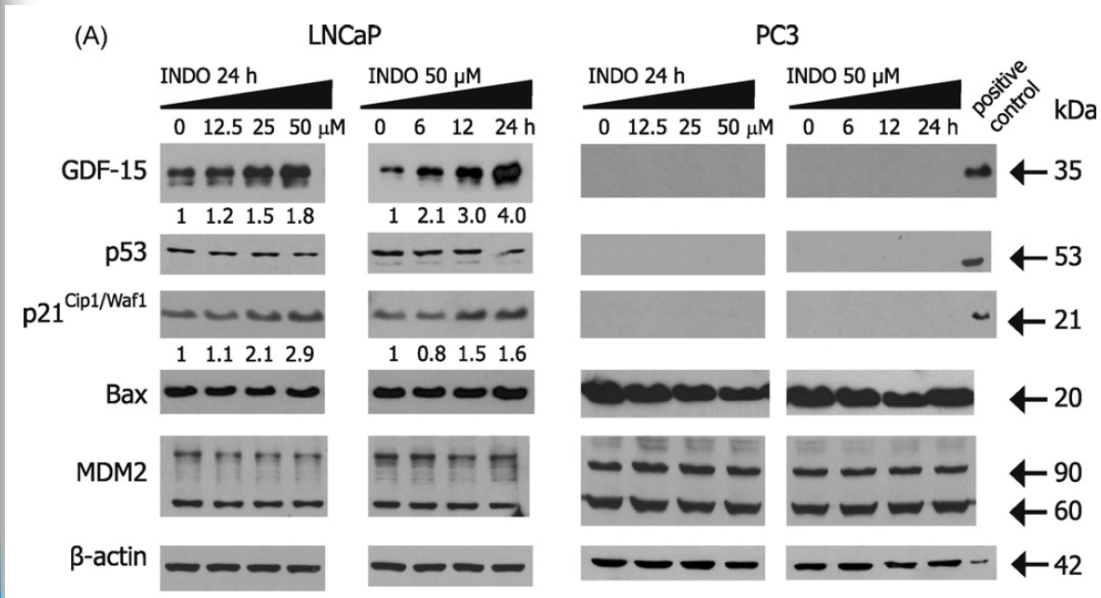
Aim 1: To disclose the role and mechanism of function of GDF-15 in cancer progression.

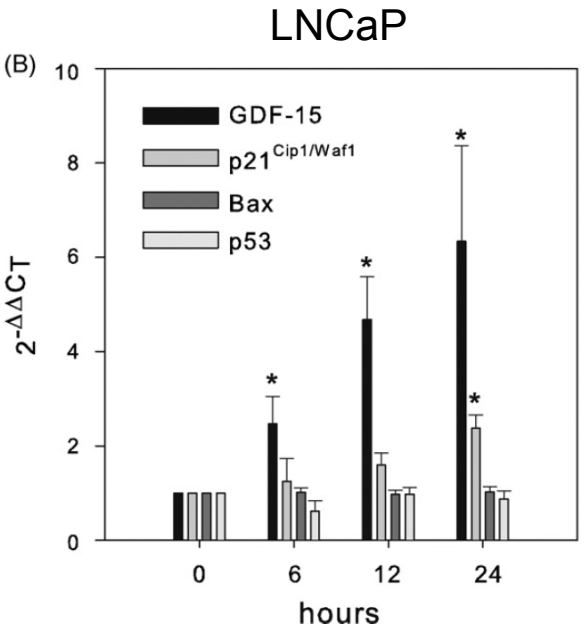


Aim 3: To identify GDF-15 receptors, down-stream signaling pathways and target genes.

Aim 2: To identify and describe the role of GDF-15 in normal and damaged hematopoiesis.

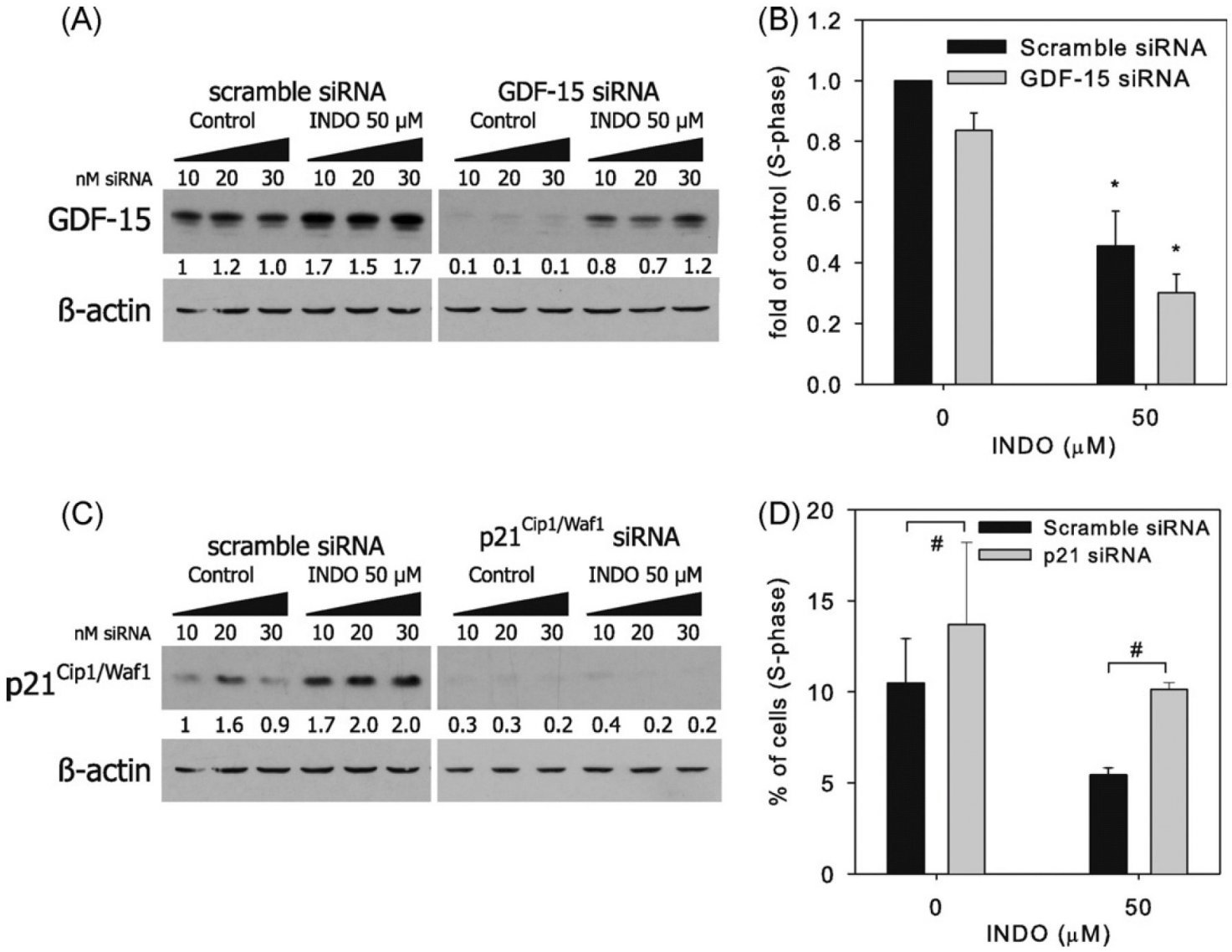
GDF-15 & NSAIDs





E. Lincová (Slabáková) et al., Biochem. Pharmacol. 2009

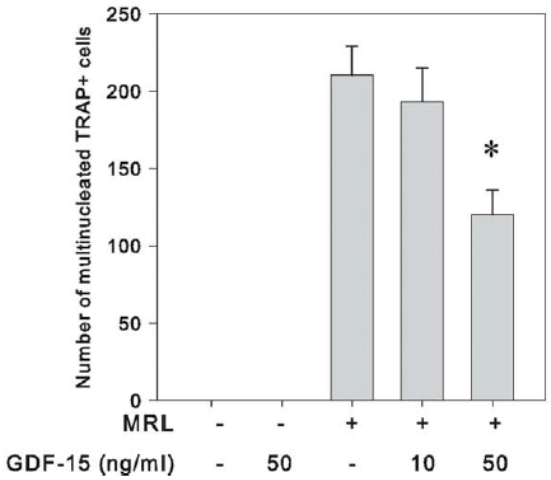
GDF-15 & NSAIDs



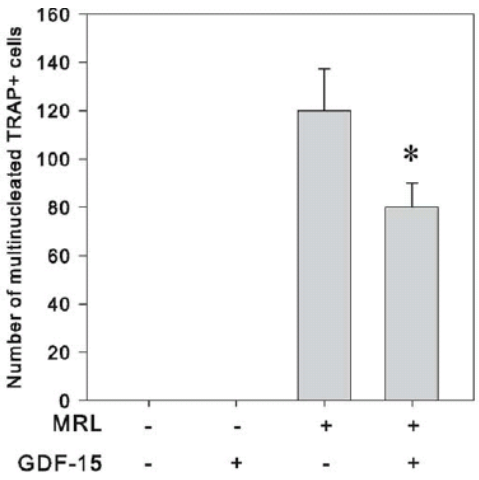
E. Lincová (Slabáková) Biochem. Pharmacol. 2009

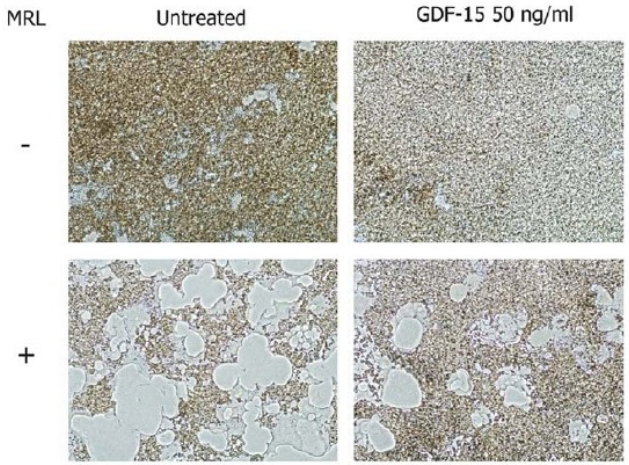
Growth-differentiation factor-15 **inhibits** differentiation into osteoclasts - A novel factor involved in control of osteoclast differentiation

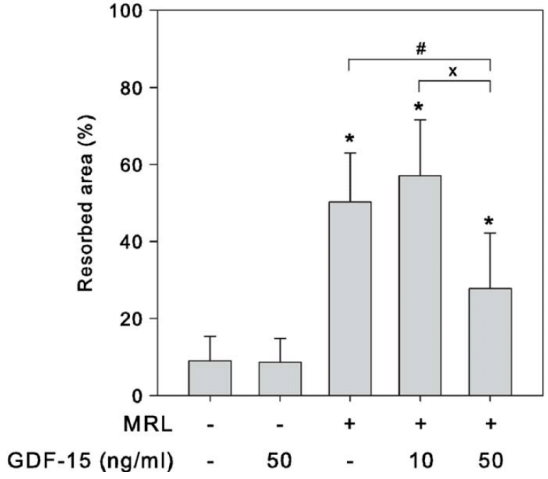
RAW264.7 -



primary bone marrow - derived osteoclasts







P. Vaňhara & E. Lincová (Slabáková) Differentiation 2009

BIOLOGY OF REPRODUCTION 80, 1036–1045 (2009)
Published online before print 21 January 2009.
DOI 10.1095/biolreprod.108.074658

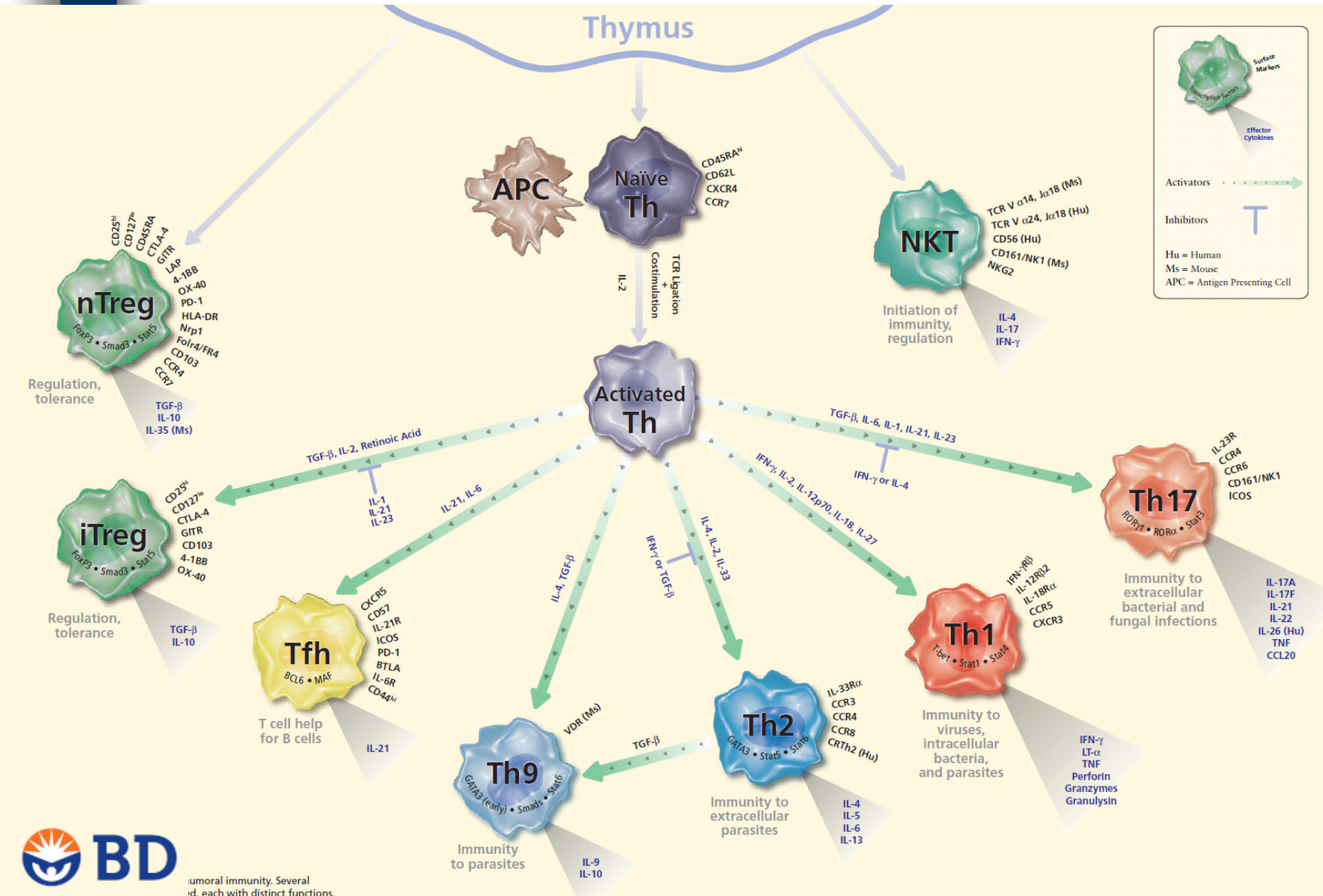
Seminal Fluid Drives Expansion of the $CD4^+CD25^+$ T Regulatory Cell Pool and Induces Tolerance to Paternal Alloantigens in Mice[1]

Sarah A. Robertson,[2] Leigh R. Guerin, John J. Bromfield, Kim M. Branson, Aisling C. Ahlström, and Alison S. Care

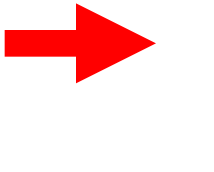
Research Centre for Reproductive Health, School of Paediatrics and Reproductive Health, University of Adelaide, Adelaide, South Australia, Australia

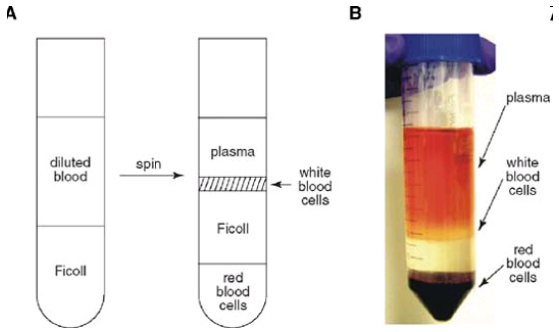
……Both seminal plasma and sperm components of the seminal fluid are necessary to confer full tolerance and elicit the Treg cell response, potentially through provision of immunedeviating cytokines and antigens, respectively

CD4+ T Cell Differentiation



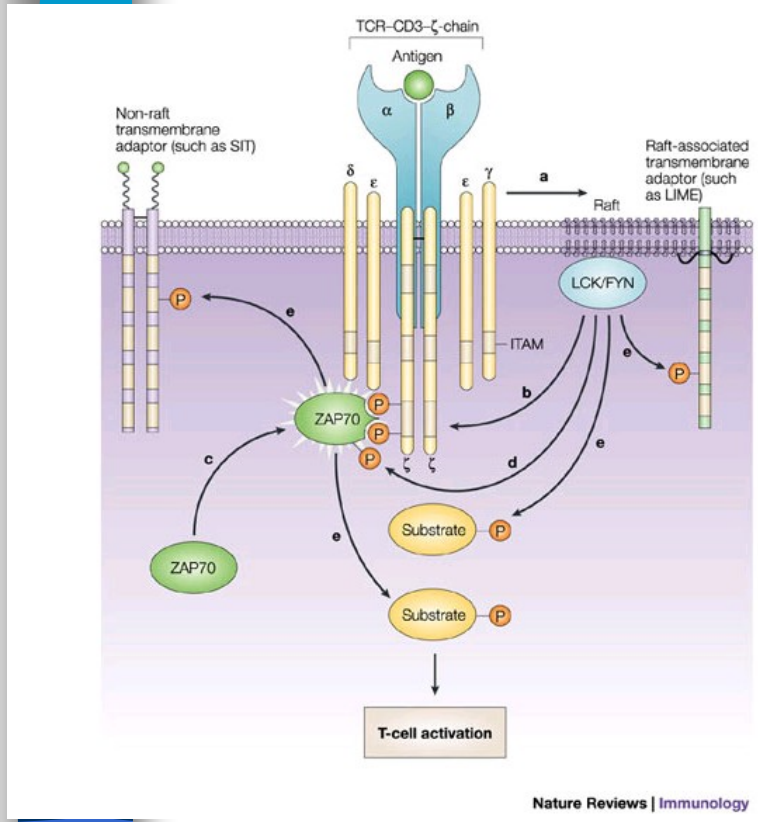
umoral immunity. Several
d, each with distinct functions.



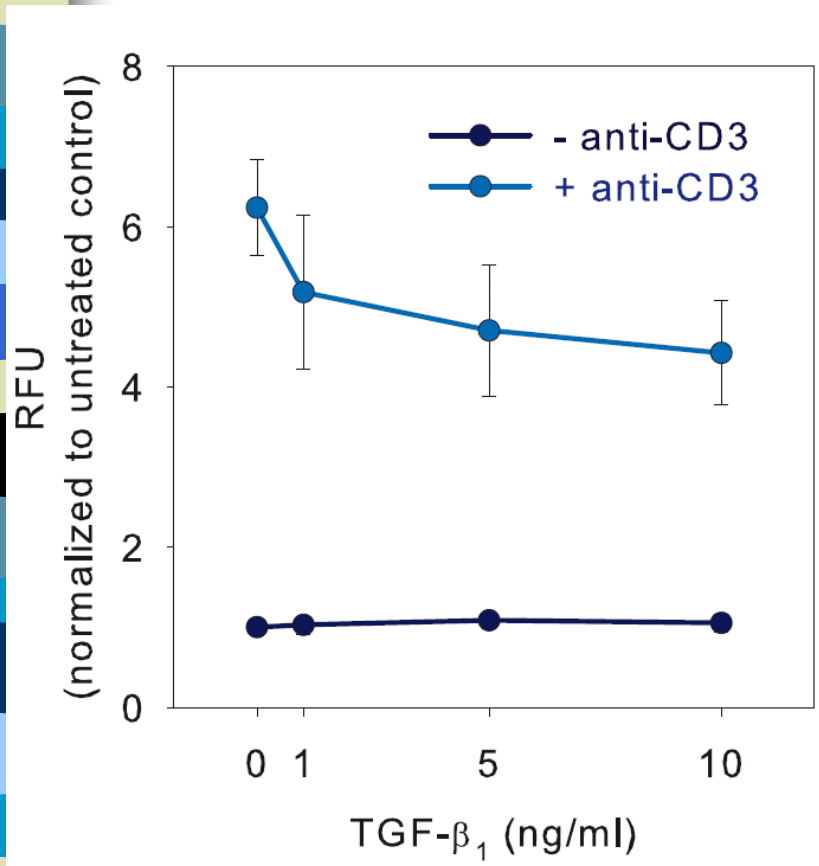


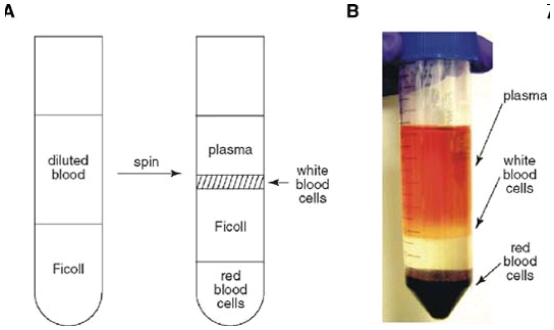
CD3-coated plates +
in vitro treatment

cells quantification - CyQuant

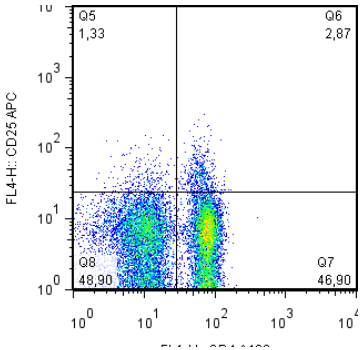


Naïve T-cells activation

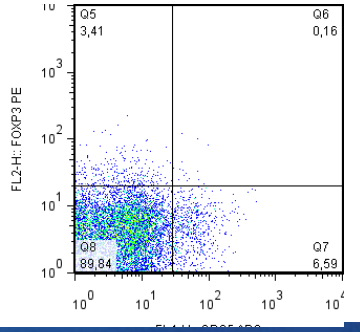




FACS

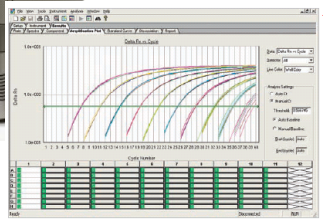


flow cytometry
FOXP3 +/-

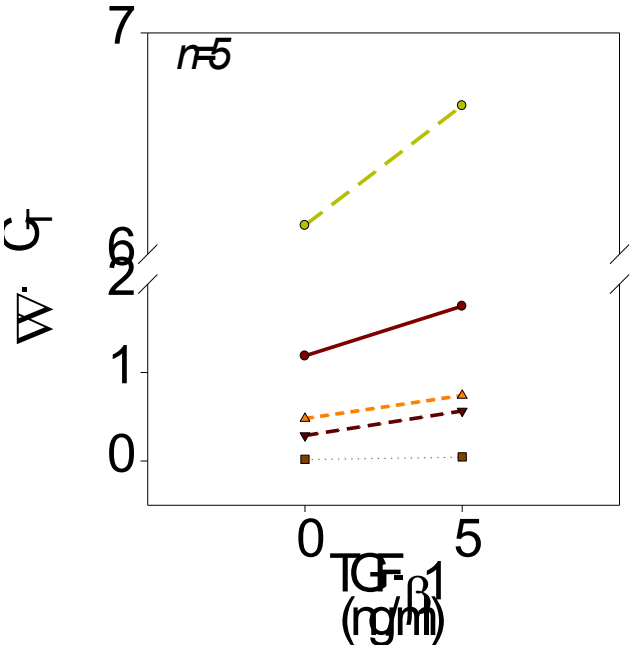


CD4+CD25+

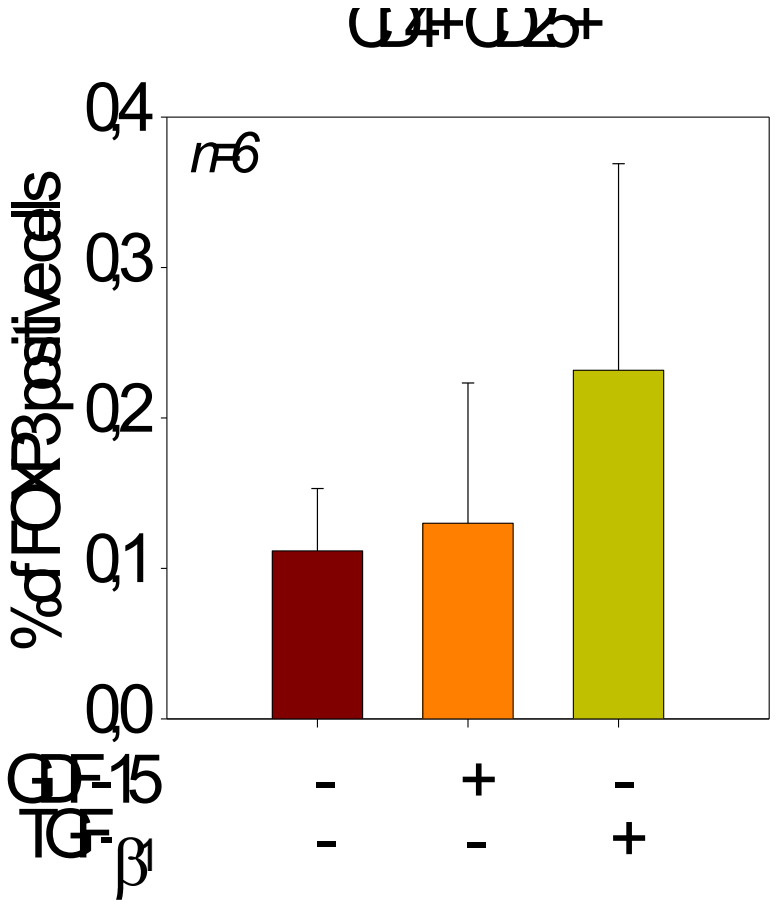
qRT-PCR
FOXP3



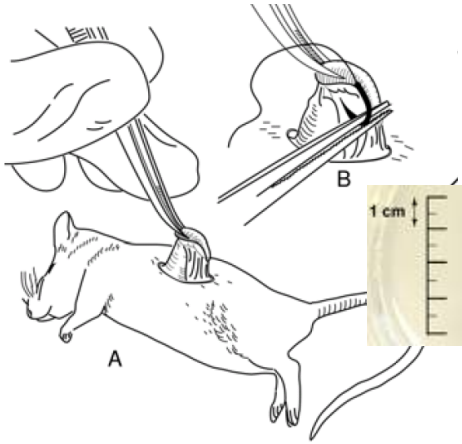
FOXP3 – qRT-PCR
CD4+CD25+ human cells treated for 24h

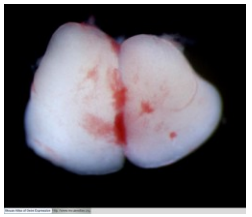


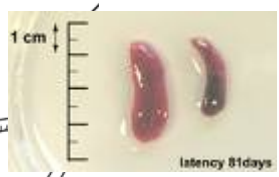
FACS analysis – CD4+CD25+FOXP3+ in human cells treated for 24h



Male (CBAxC57Bl/10)F1

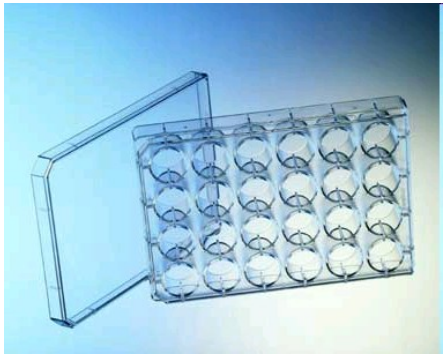




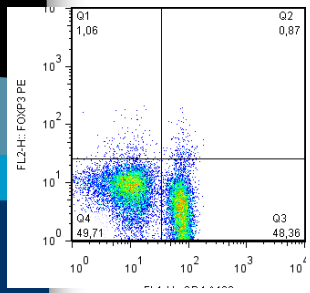


pan-T MACS

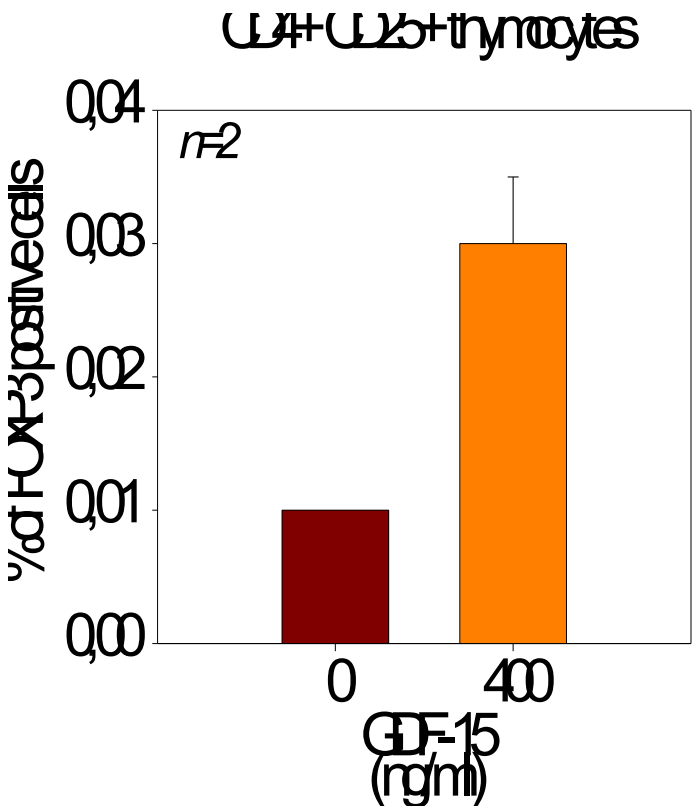
in vitro treatment

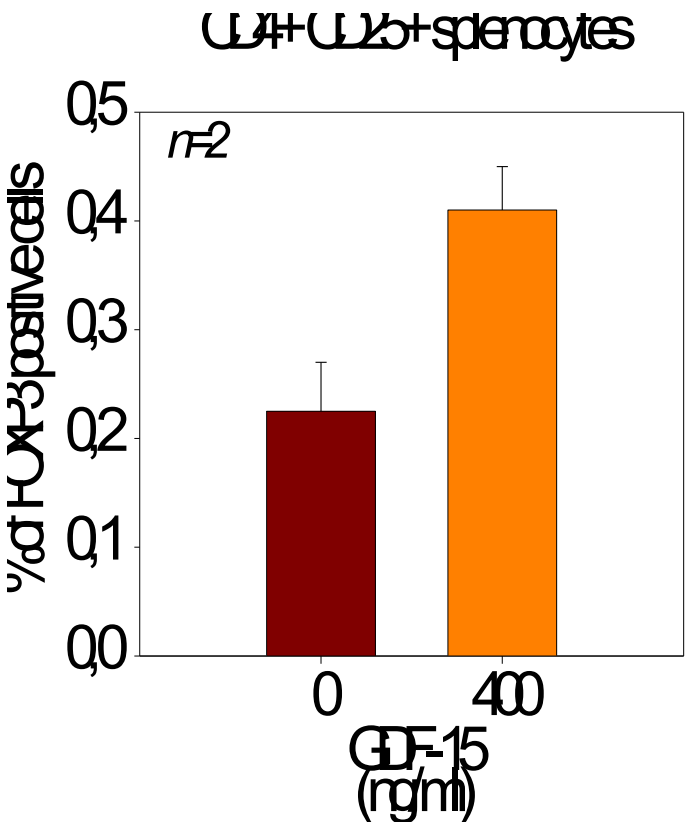


flow cytometry
CD4+CD25+FOXP3 +/-



FACS analysis – CD4+CD25+FOXP3+ in mouse cells treated for 48h





GDF-15 & mice prostate cancer

•The TRAMP-C1 (ATCC - CRL-2730) cell line was derived in 1996 by Norman Greenberg from a heterogeneous 32 week primary tumor in the prostate of a PB-Tag C57BL/6 (TRAMP) mouse.

• TRAMP is a transgenic line of C57BL/6 mice harboring a construct comprised of the minimal -426/+28 rat probasin promoter (426 base pairs of the rat probasin (PB) gene promoter and 28 base pairs of 5'-untranslated region) to target expression of the SV40 large T antigen to prostatic epithelium.

•TRAMP-C1 cells are tumorigenic when grafted into syngeneic C57BL/6 hosts.

ATCC
The Global Bioresource Center™

- control GFP
- mGDF-15 GFP
transfected TRAMP-C1 cells

control GFP+ cells

mGDF-15 GFP+ cells

♂ C57Bl/6 wild type

tumor mass determination

TRAMP-C1 cells

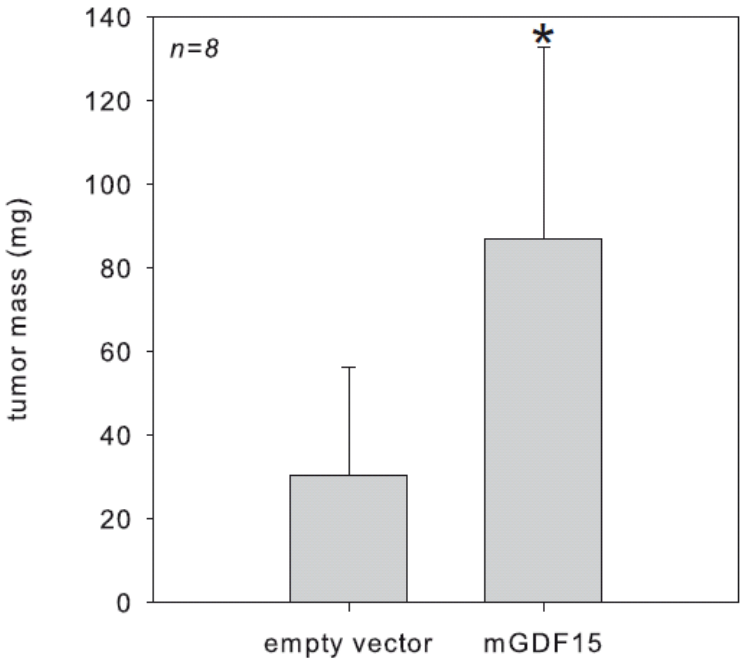
♂ C57Bl/6

GDF-15$^{+/+}$

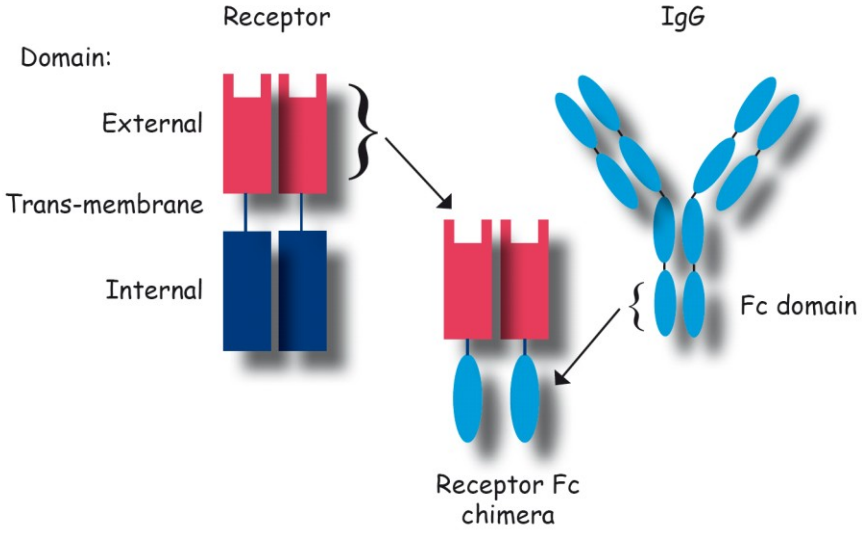
GDF-15$^{-/-}$

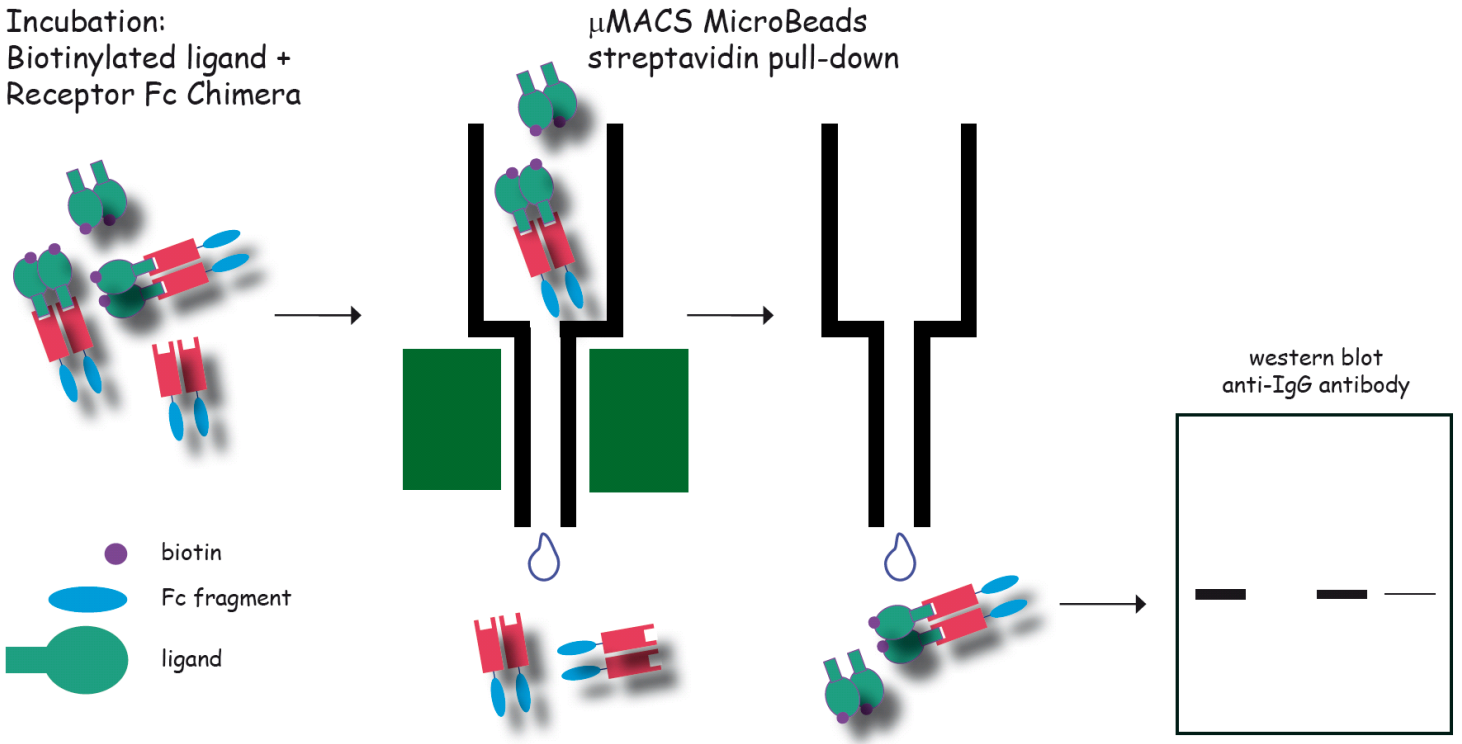
tumor mass determination

GDF-15 stimulates growth of syngeneic grafts of TRAMP-C1 cells

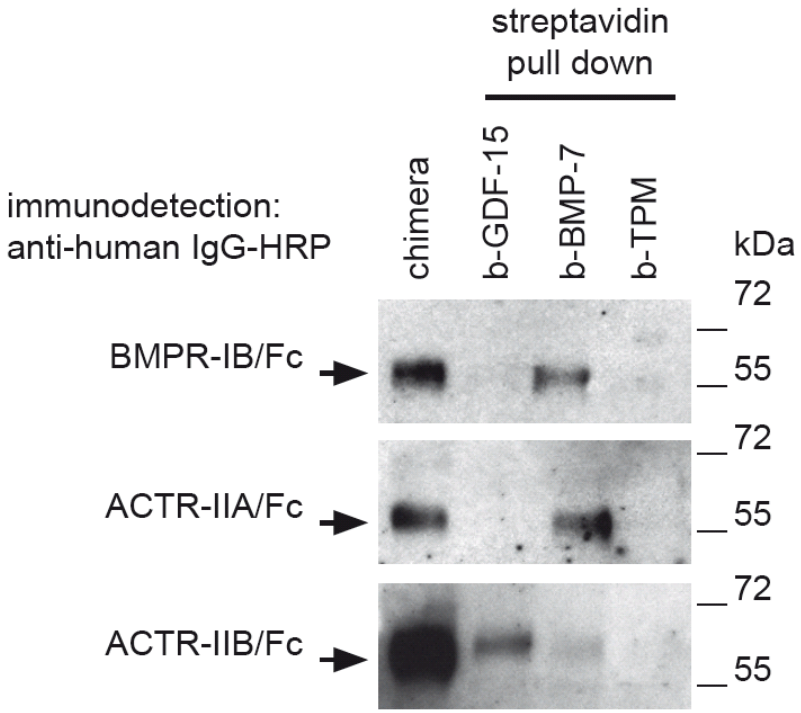


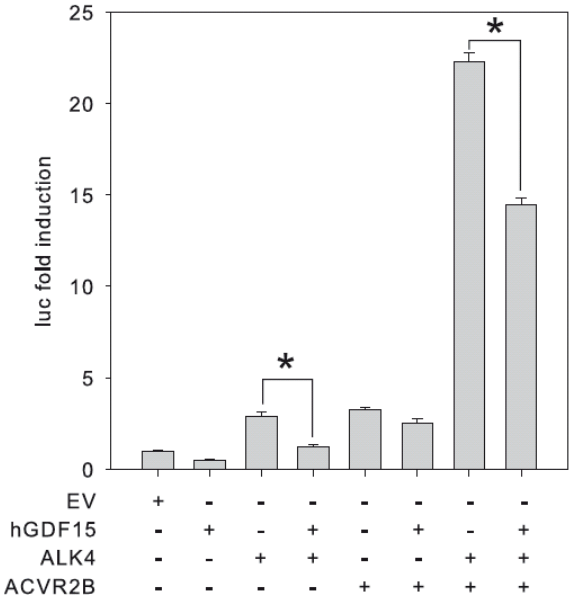
GDF-15 signaling





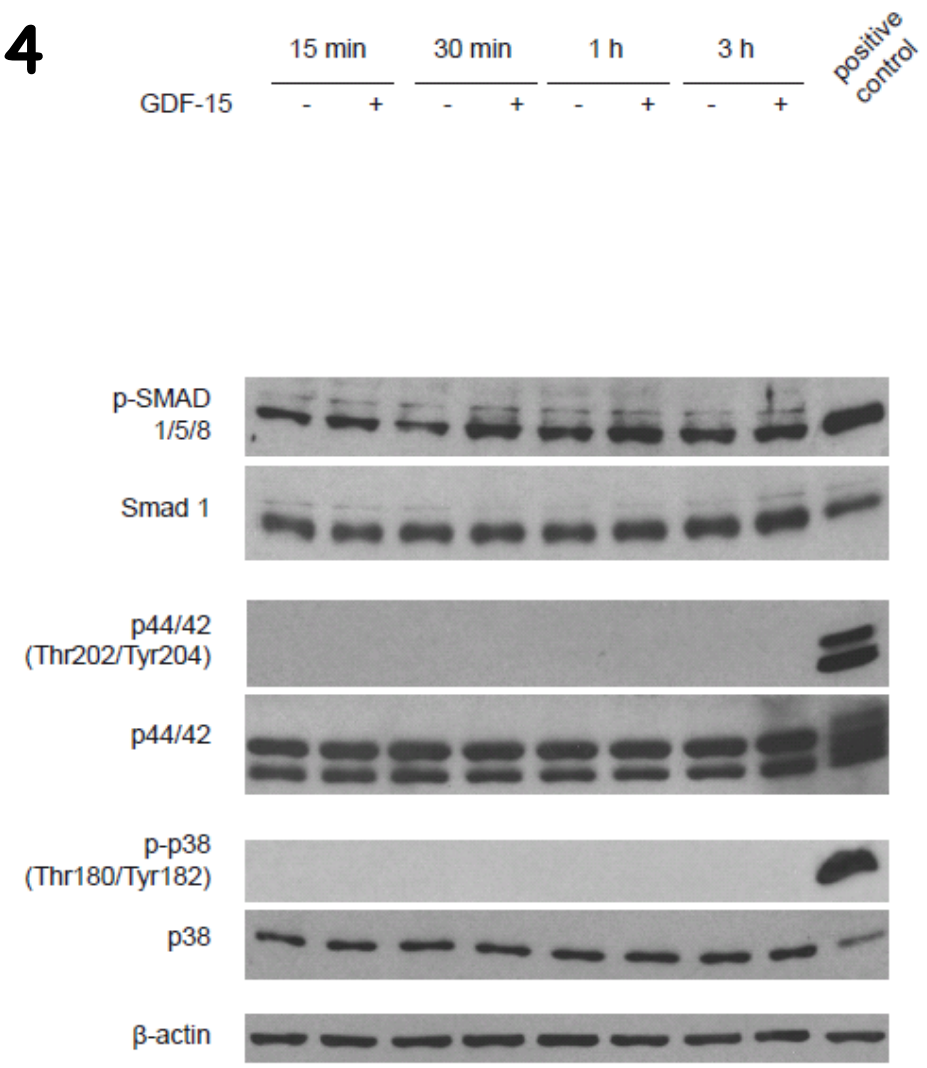
GDF-15 signaling





GDF-15 signaling

LAPC-4



Summary

GDF-15:

- inhibits naïve T-cells activation (proliferation) and induce Treg *in vitro;*
- its overexpression potentiate tumor graft progression in syngeneic hosts;
- tumor graft progression is significantly potentiate by ectopic overexpression of mGDF-15 and inhibited in GDF-15 knockout mice;
- GDF-15 binds ACVR2B receptors and activates SMAD2 in LAPC-4 cells

Shrnutí přednášky

- TGF-β hraje významnou roli v rozvoji karcinogeneze a dalších patologických stavů.
- EMT je významný proces ovlivňující schopnost nádorových buněk diseminovat
- GDF-15 hraje důležitou úlohu v nádorové progresi

Na konci dnešní přednášky by jste měli:

1. být schopni vysvětlit úlohu TGF-β v karcinogenezi;
2. charakterizovat proces EMT včetně hlavních znaků a regulátorů;
3. popsat známé vlastnosti GDF-15.