

Dipartimento di Diagnostica per Immagini e Medicina di Laboratorio
Department of Morphology, Surgery and Experimental Medicine
Center of Excellence MIUR for the
Study of Inflammation (ICSI)
Ferrara University Hospital
Ferrara, Italy



Les liasons dangereuses: infiammazione e cancro

F. Di Virgilio

Qualità e Innovazione nel Dipartimento
di Diagnostica per Immagini e
Medicina di Laboratorio di Ferrara:
II edizione
25 maggio 2013



Inflammation is all

FEBRUARY 23, 2004

BUSH'S
MILITARY RECORDS
IS DISNEY MOUSETRAPPED?

TIME

THE SECRET KILLER

- The surprising link between **INFLAMMATION** and **HEART ATTACKS, CANCER, ALZHEIMER'S** and other diseases
- What you can do to fight it

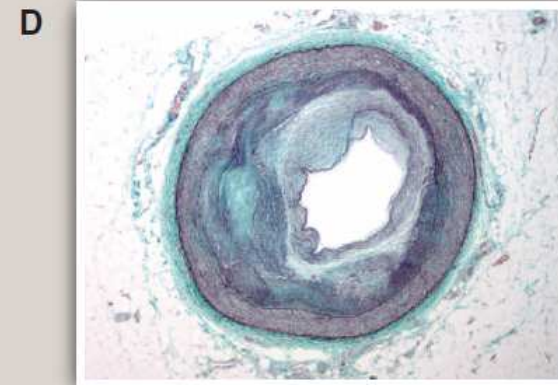
www.time.com AOL Keyword: TIME

The multiple facets of inflammation

Acute tonsillitis



Sprained ankle



Rheumatoid arthritis

Atherosclerotic lesion

How many inflammation subtypes?

Acute inflammation:

purulent inflammation
hemorrhagic inflammation
serous inflammation
catarrhal inflammation
fibrinous inflammation

Chronic inflammation

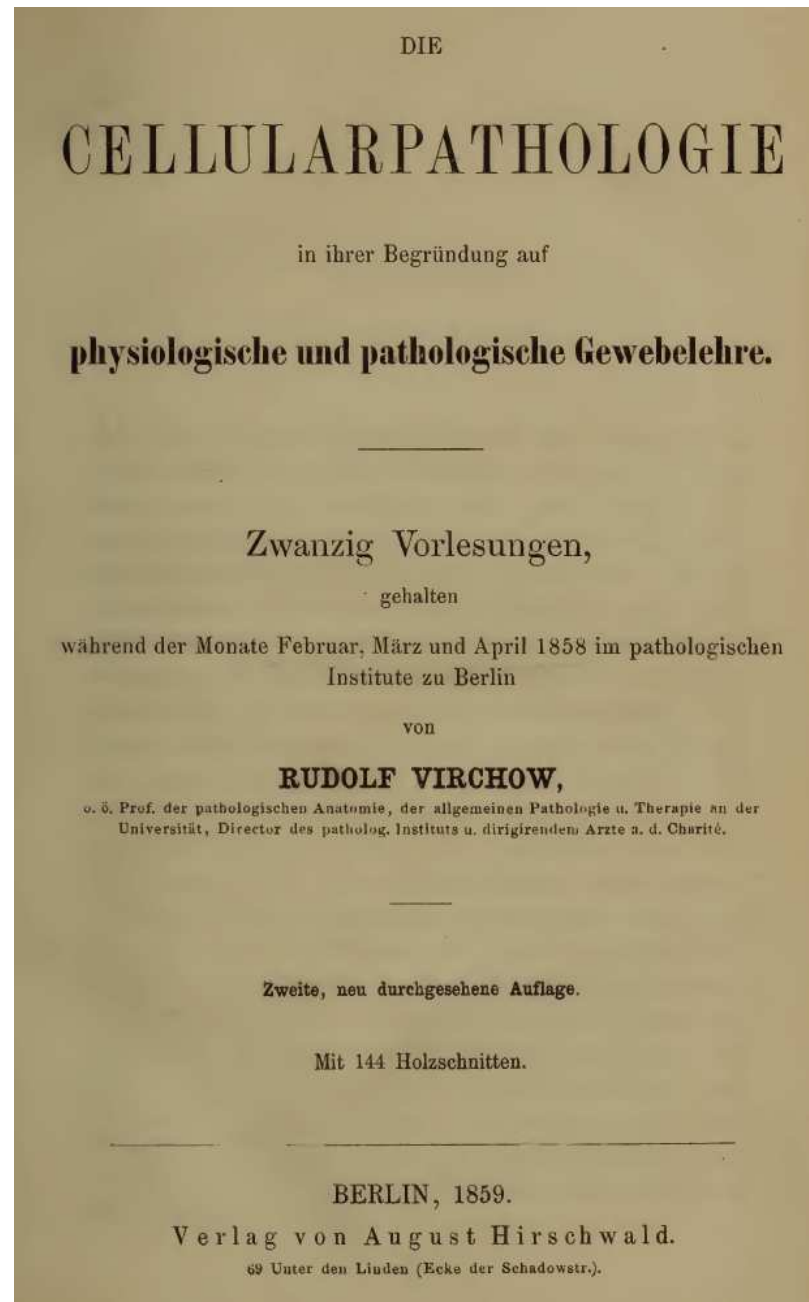
Hypersensitivity

Tolerance

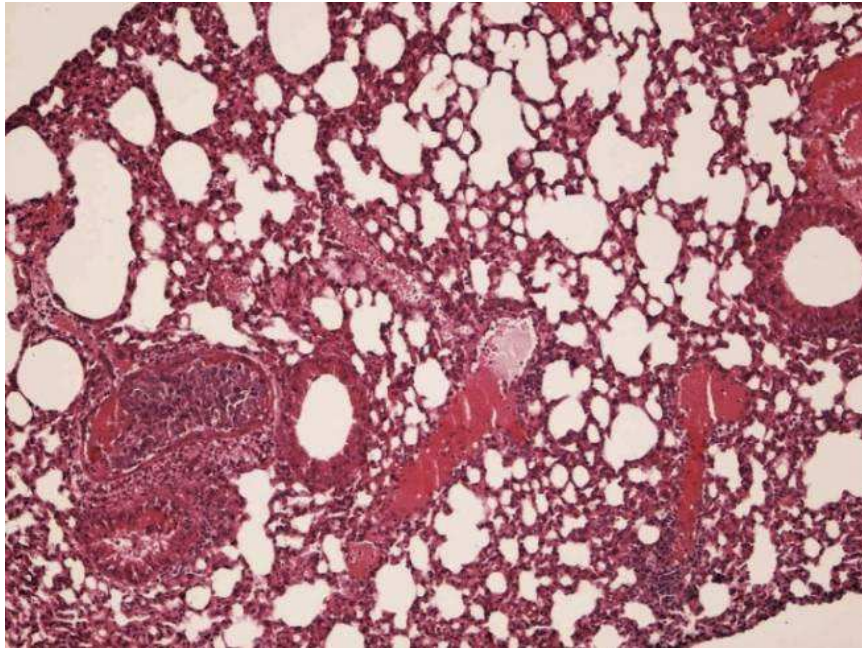
Suppressive immunity

Tumors: “good” inflammation
“bad” inflammation

Virchow described the association of leukocyte infiltrate with cancer, and suggested that this might reflect the origin of cancer at sites of chronic inflammation



Lung metastasis of experimental B16 mouse melanoma



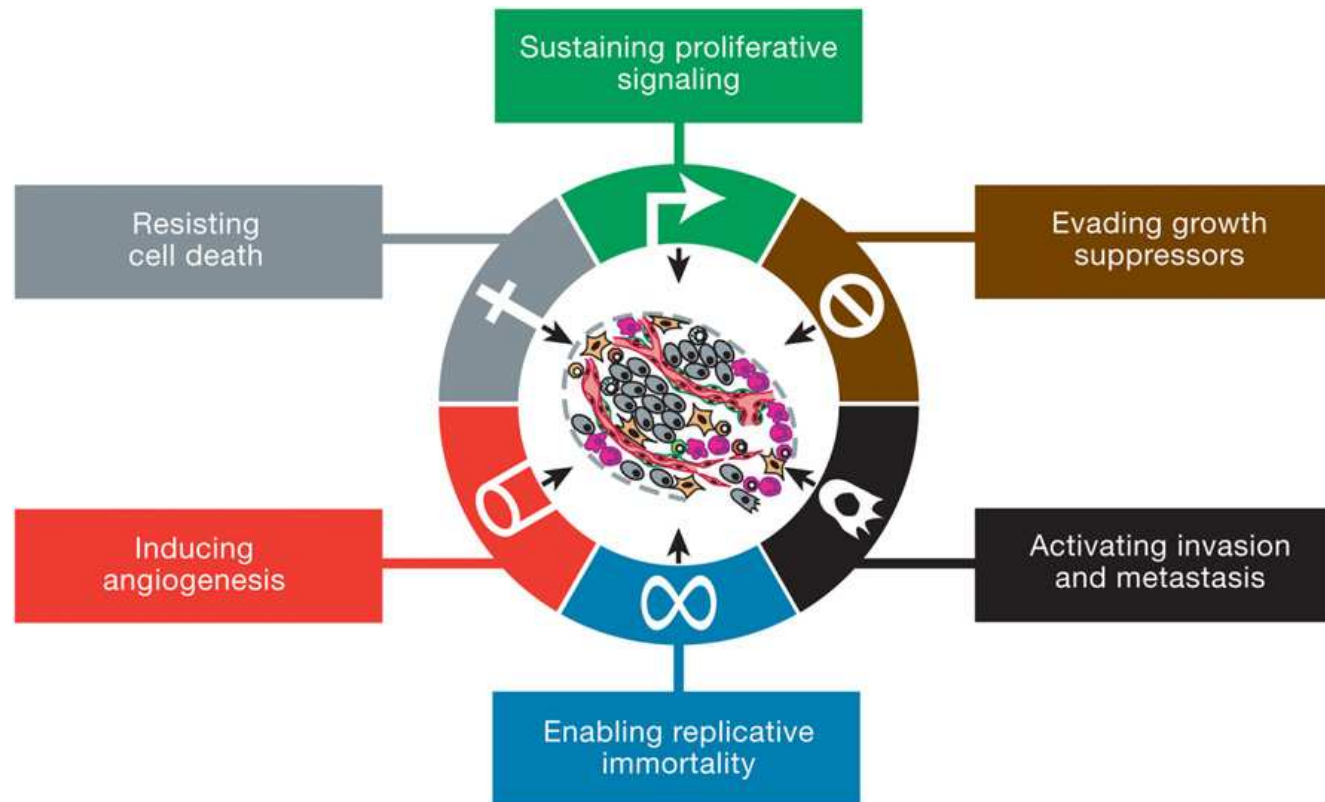
From Adinolfi and Di Virgilio, unpublished

The Hallmarks of Cancer

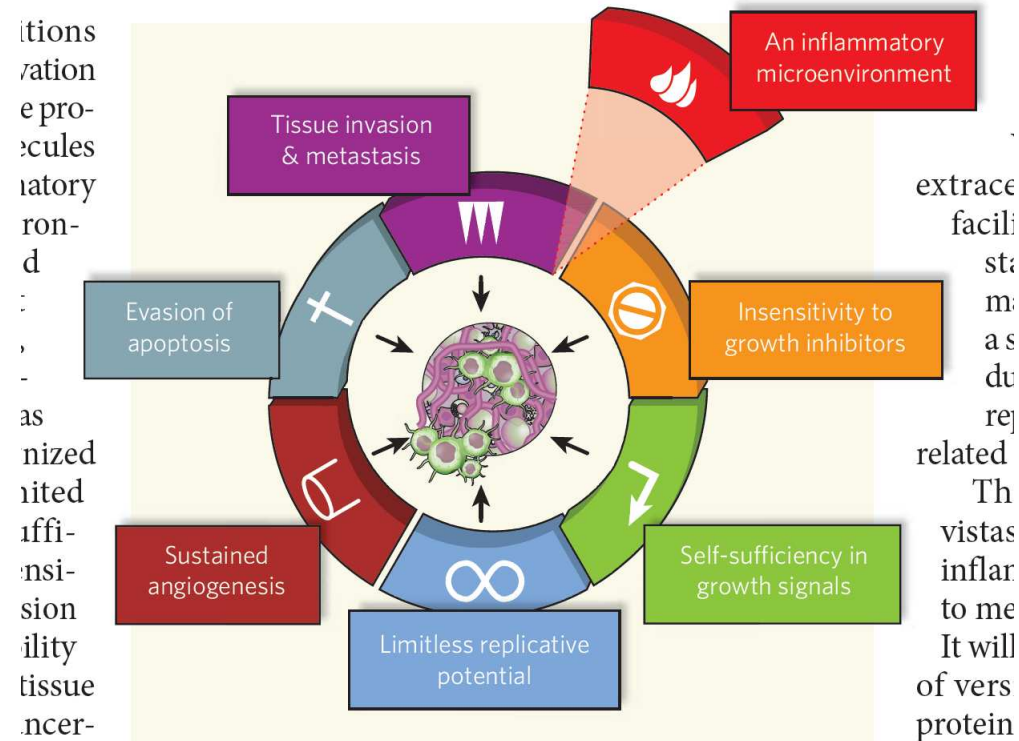
Review

Douglas Hanahan* and Robert A. Weinberg†

evolve progressively from normalcy via a series of pre-



From Hanahan and Weinberg, Cell 2000



From Mantovani, Nature 2009

The inflammation-cancer liaison

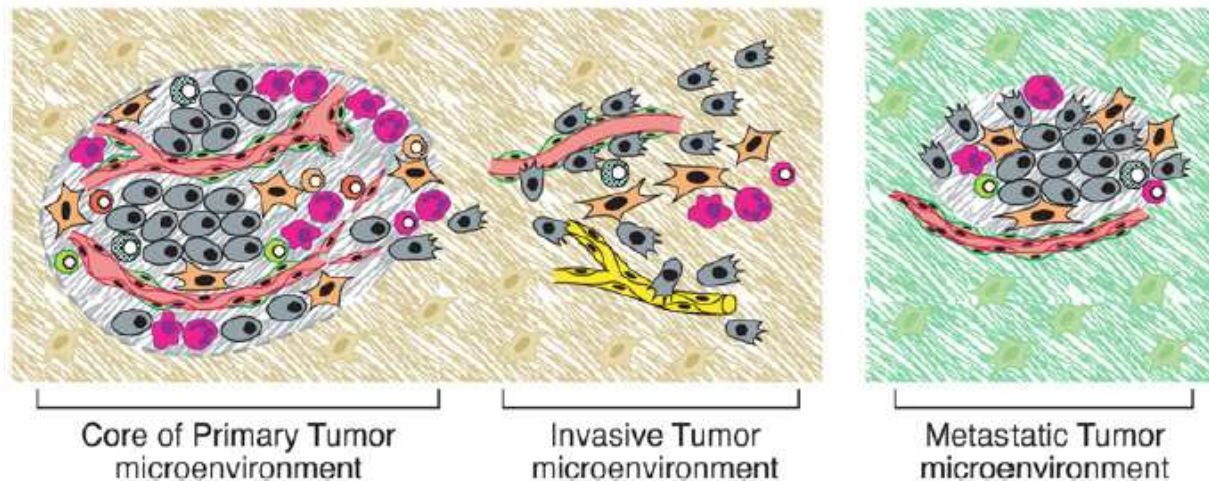
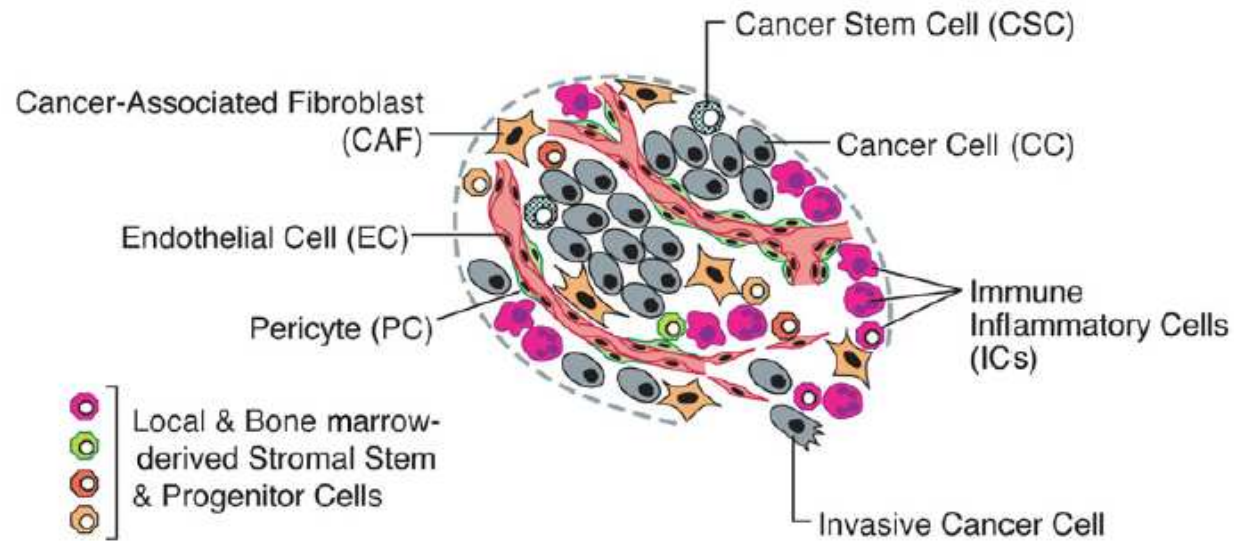
Intrinsic pathway: overexpression of oncogenes and/or inflammation-associated genes.

RAS-RAF, NF- κ B, MYC, IL-1, HIF-1 α , TNF α , COX2, CCL2, CCL20,....

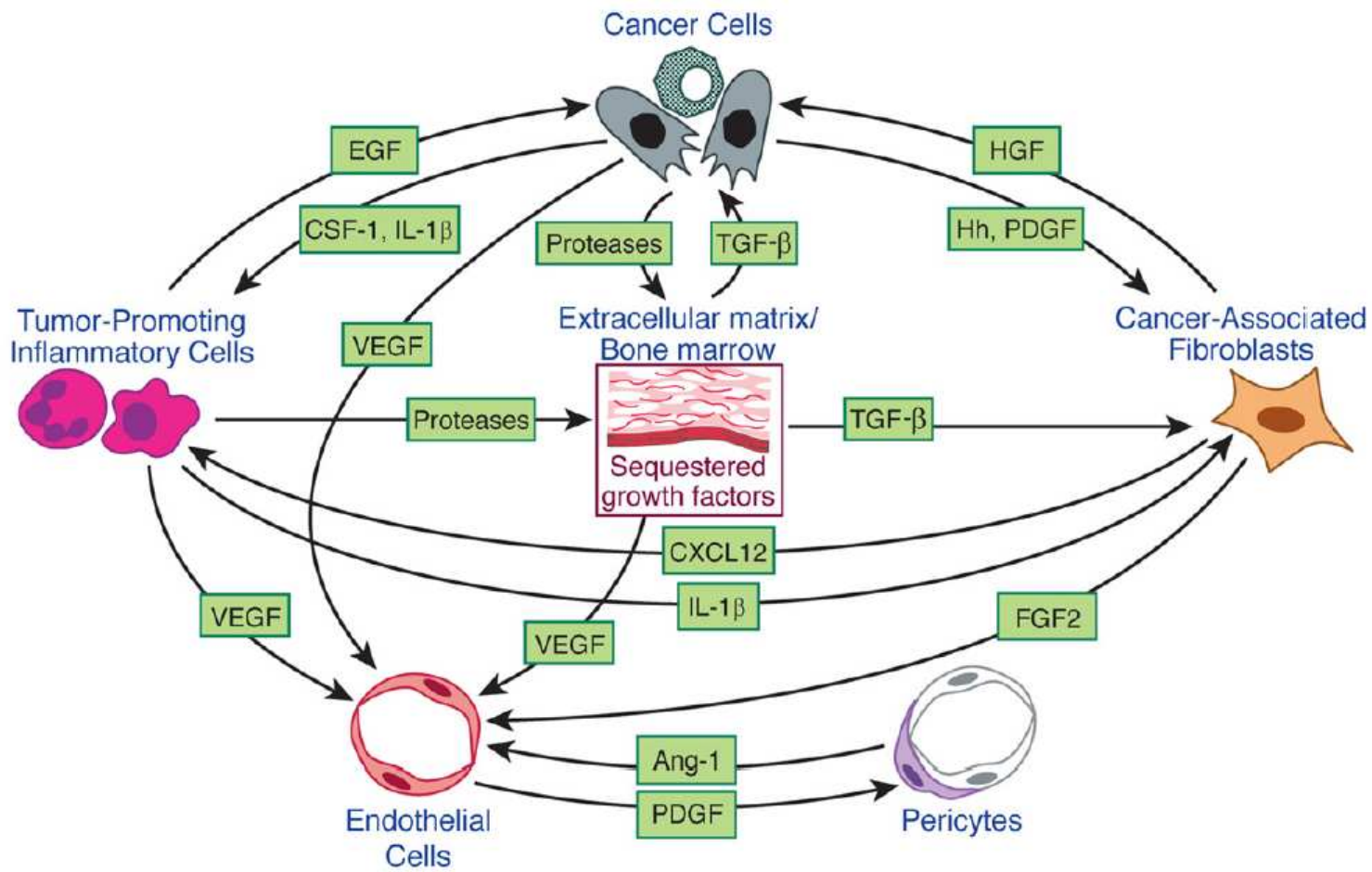
Extrinsic pathway: inflammatory infiltrate.

Macrophages (TAM), Dendritic cells, Mast cells, Th1, Th2, Treg, NK, Cytotoxic T Lymphocytes, Granulocytes, MDSCs, tumour-associated fibroblasts,....

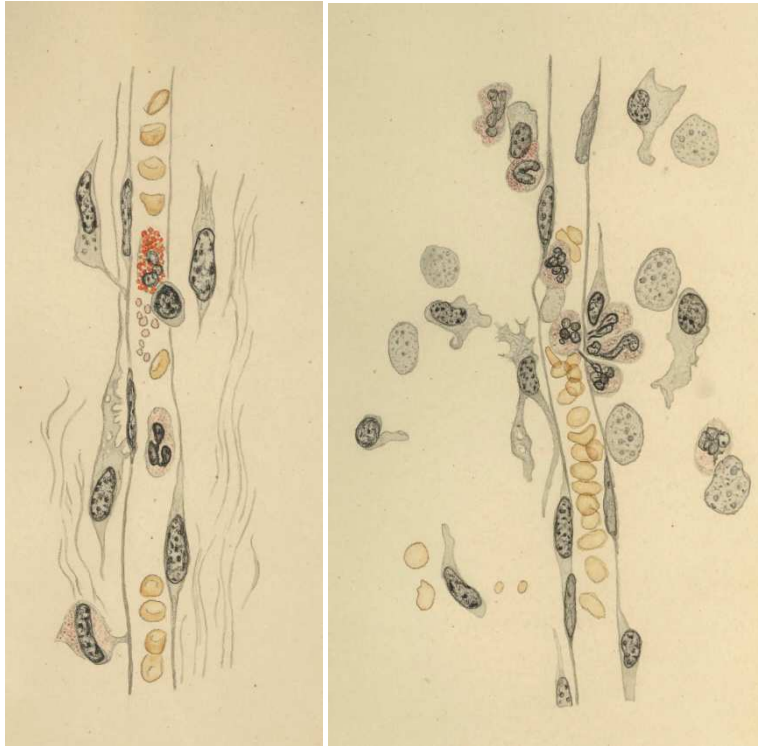
Tumor microenvironment



How cancer cells mould their microenvironment



Hanahan and Weinberg, Cell 2011



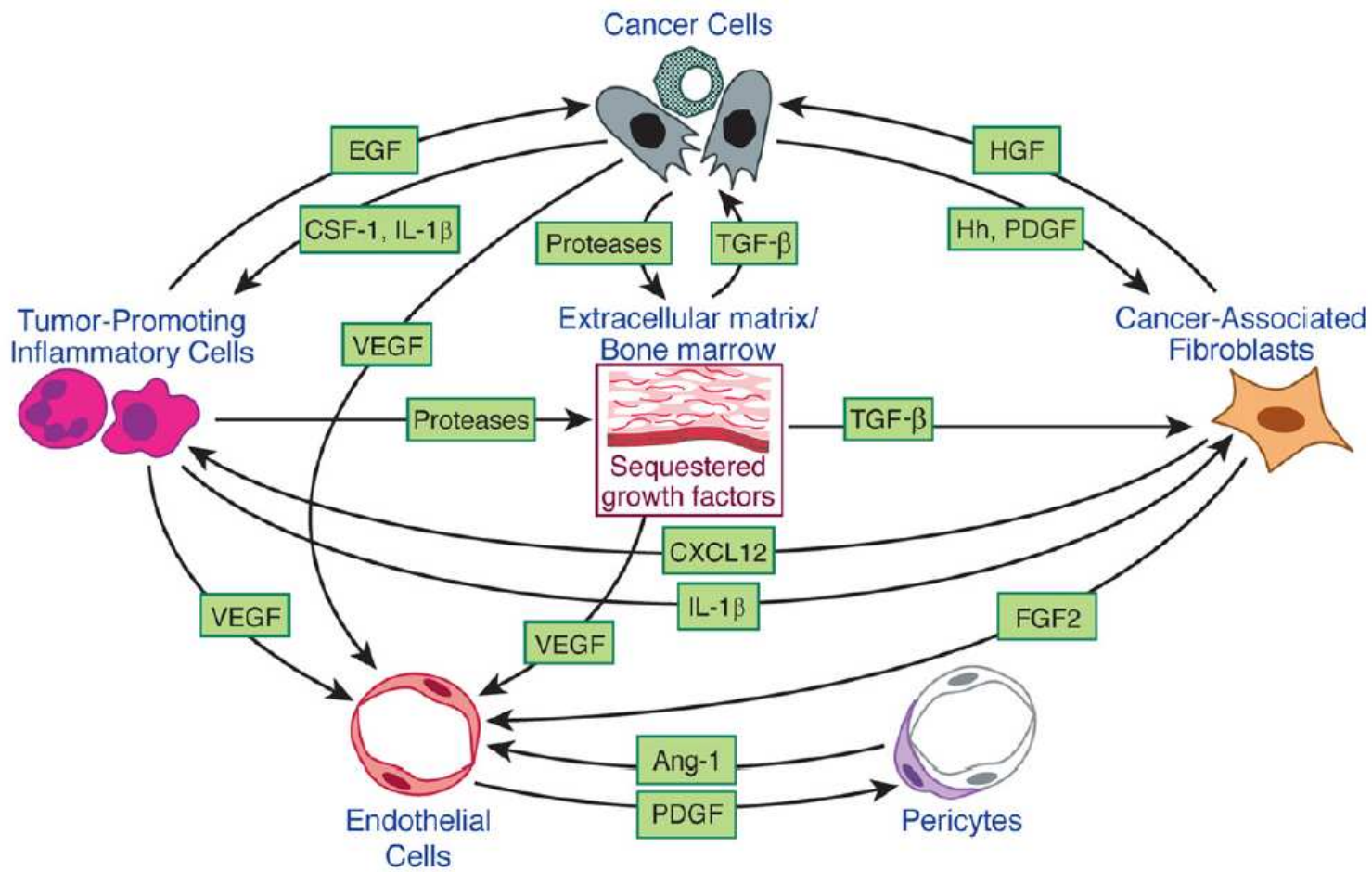
L. Krehl und F. Marchand
Leipzig 1921 "Handbuch
der Allgemeine Pathologie"

The inflammatory microenvironment

Cells: Mast cells, PMNs, Lymphocytes, Macrophages, Lymphocytes, Fibroblasts, Endothelial cells.....

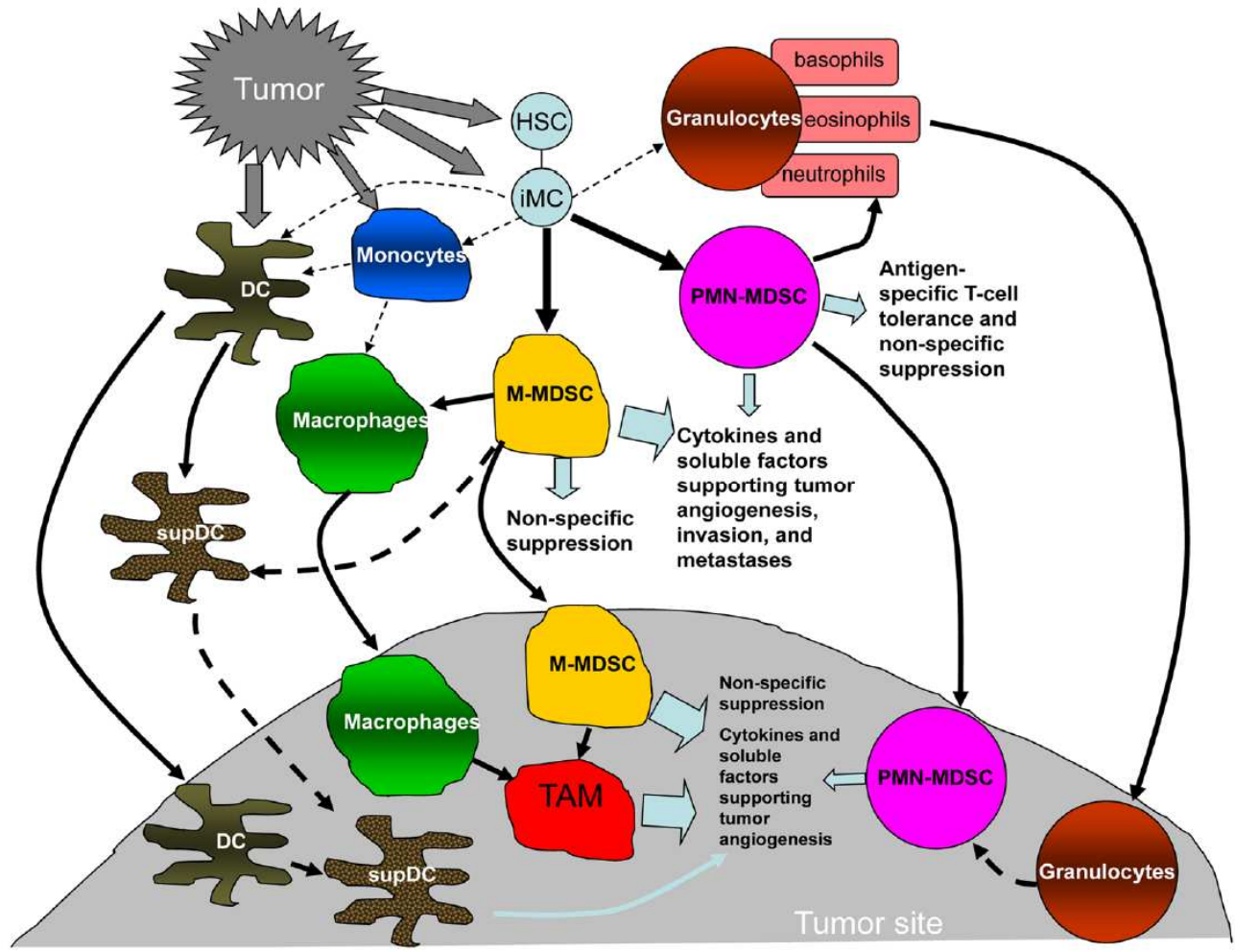
Soluble factors: Histamine, Serotonin, Lysosomal enzymes, Zn-proteases, Prostaglandins, Leucotrienes, PAF, Cytokines, Chemokines Kinins, Coagulation factors, Activated complement fragments, NO, nucleosides, nucleotides, growth factors.....

The tumor microenvironment is an inflammatory microenvironment



Hanahan and Weinberg, Cell 2011

Phenotypic changes occurring in myeloid cells in cancer



From Gajjar et al Nat Rev Immunol 2012

Seeing is believing

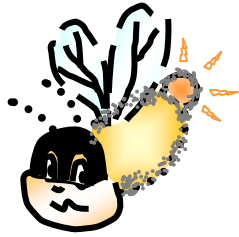


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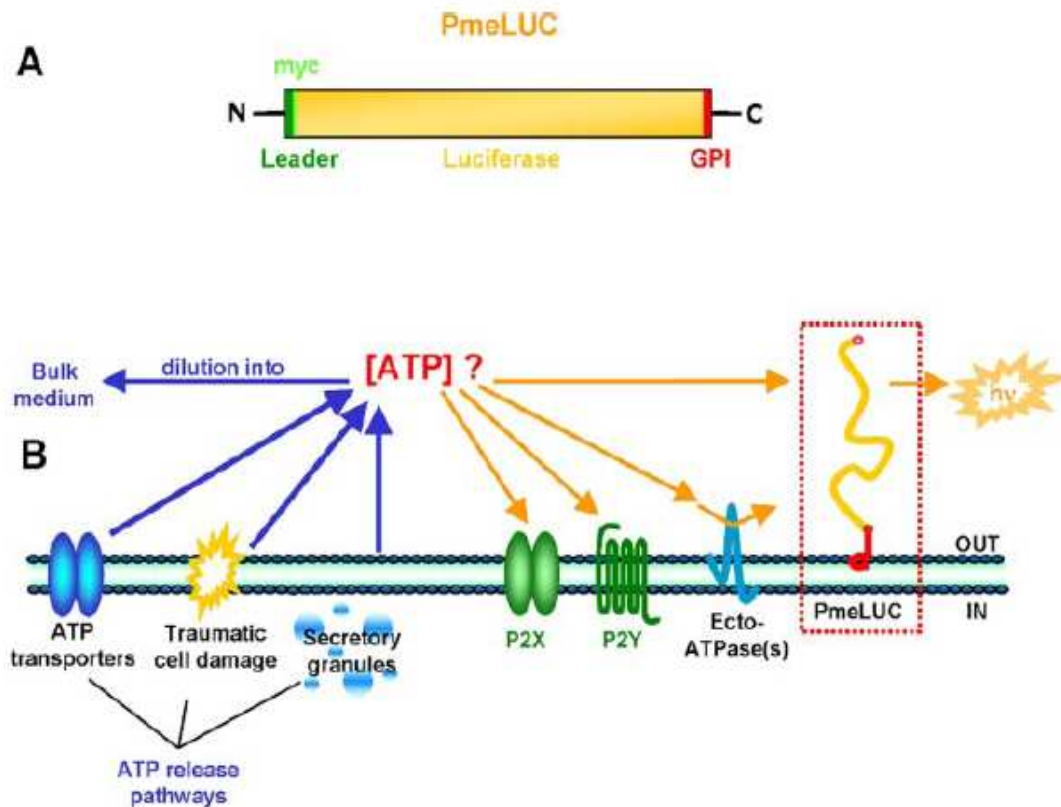
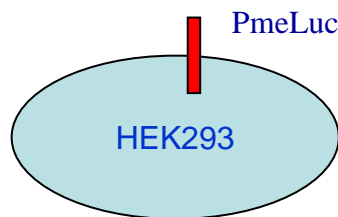
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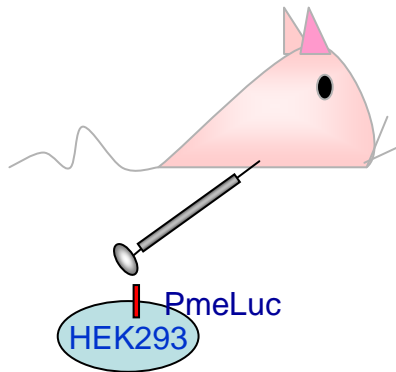
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Luciferase from the firefly *Photinus pyralis* is an extraordinarily sensitive bioluminescent ATP sensor. This protein is found in the light-emitting organ known as the lantern within the abdomen of the insect and its used *in vivo* by the firefly to emit flashes of light to attract its mate.



HEK293 cells stably transfected with pmeLuc.
A probe for in vivo extracellular ATP measurement?



Simonetta

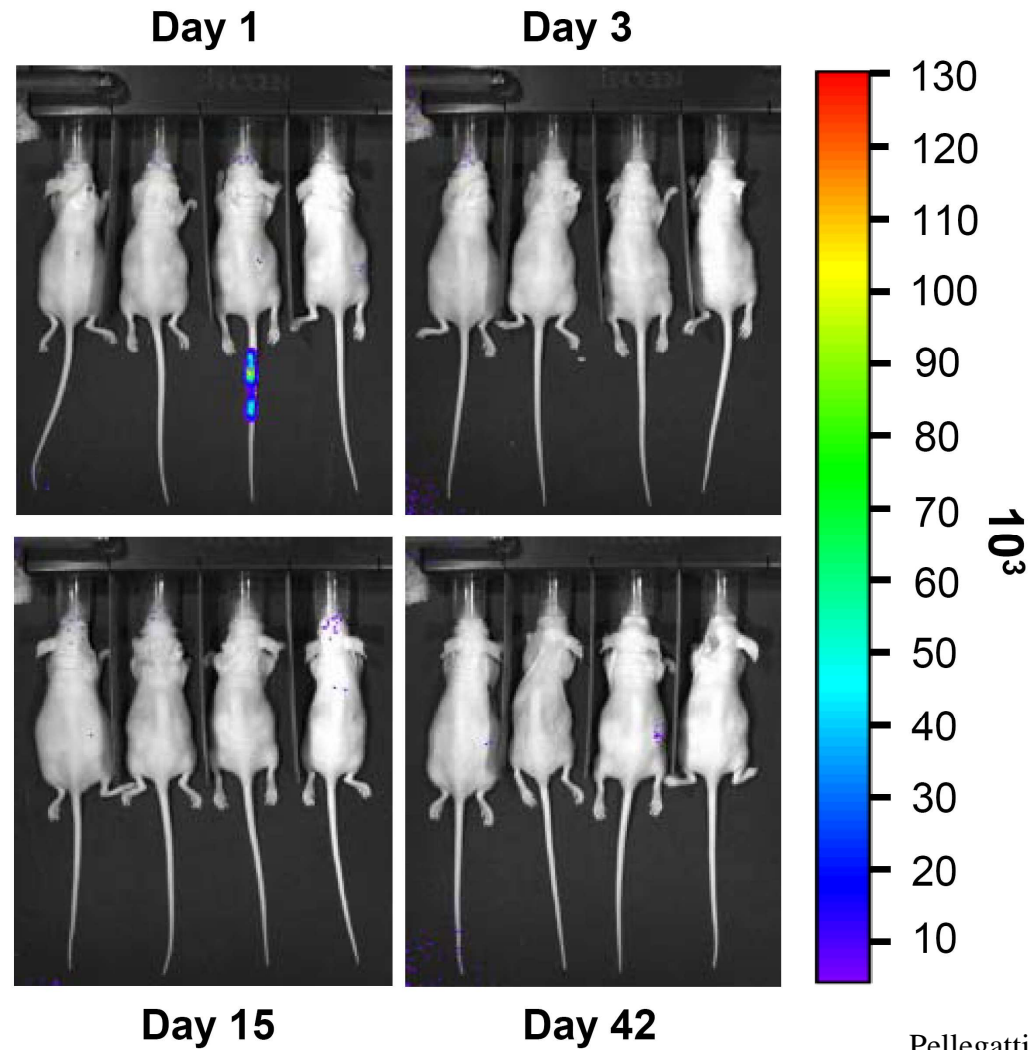
Mickey (mouse)



Patrizia

Total body luminometer

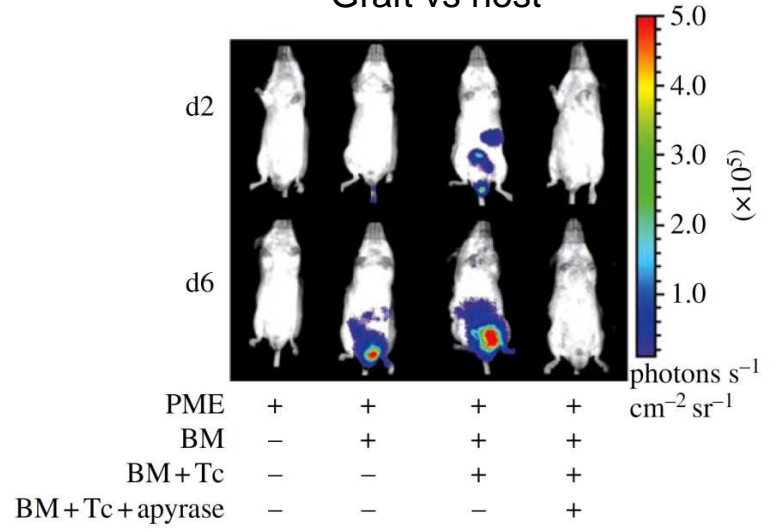
Inoculation of HEK293-pmeLUC i.v.
into healthy mice



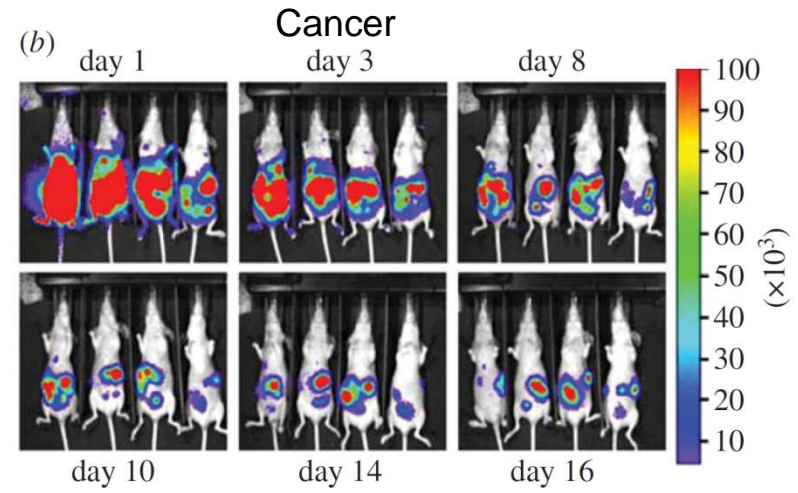
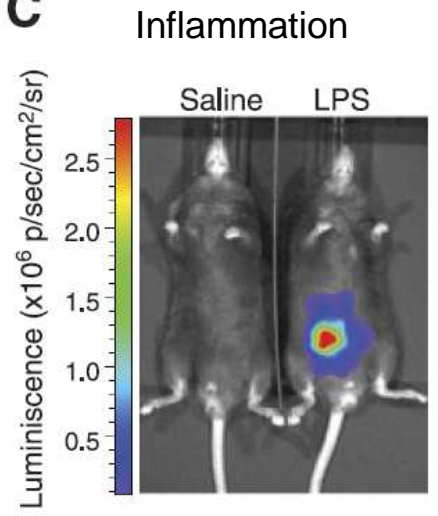
ATP is increased in the inflammatory microenvironment

Pellegatti et al., PLoS ONE 2008
 Wilhelm et al. Nat Med 2010
 Weber et al. J Exp Med 2010
 Michaud et al., Science 2011
 Barberà-Cremades et al FASEB J 2012

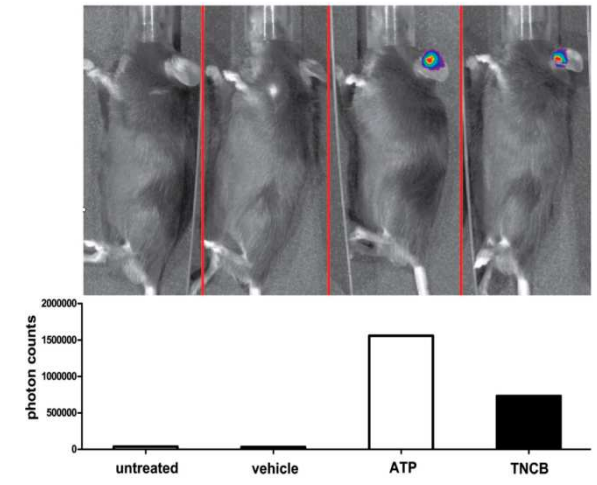
Graft vs host



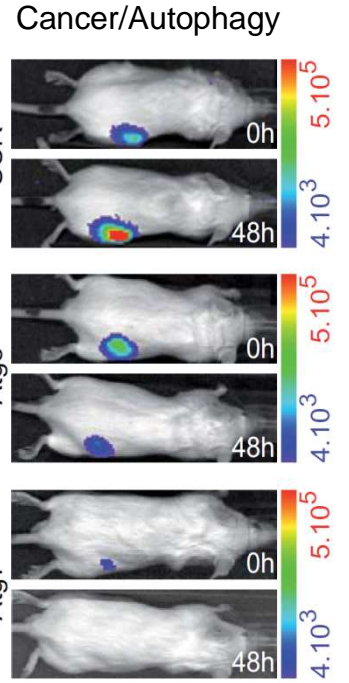
C



Contact dermatitis

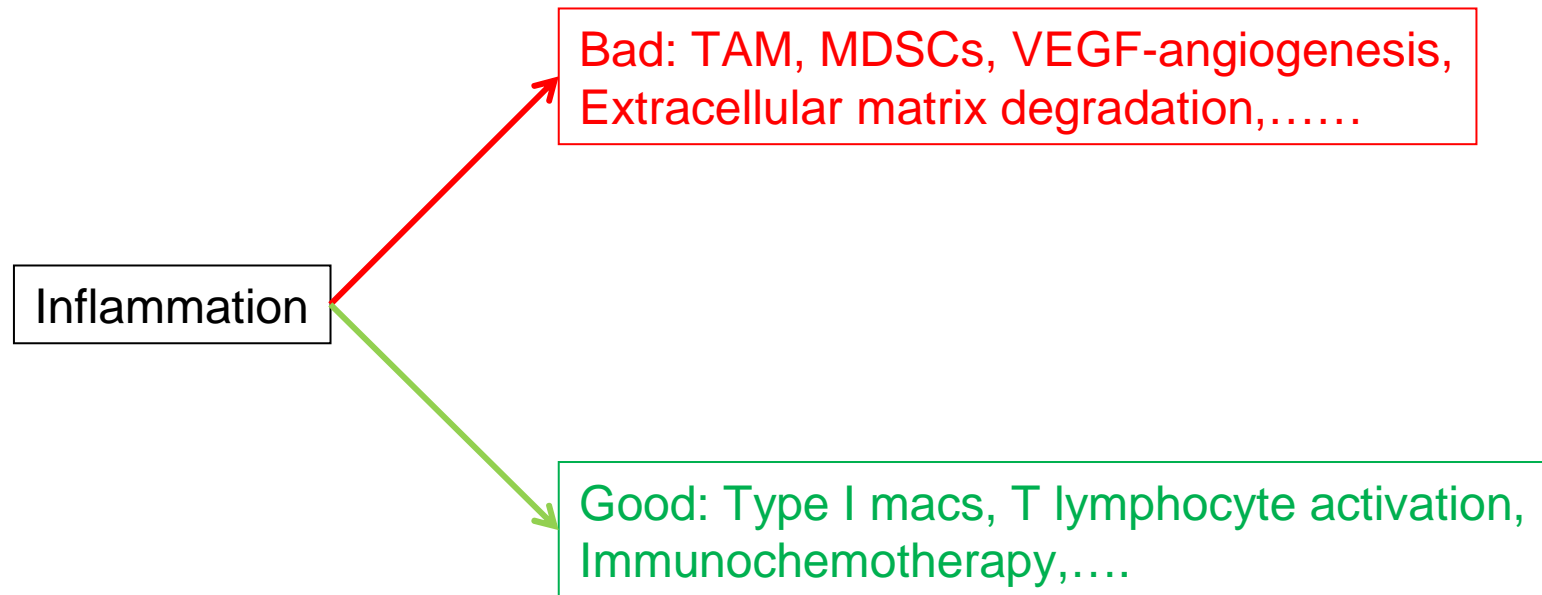


E



Inflammation and cancer

Is Virchow always right?



Conclusions and take-lab message

1. Inflammation and cancer are intimately intertwined.
2. Sometimes inflammation is protective, other times (more often) is cancer-promoting.
3. If we learn how to re-program cancer-associated inflammation, this might provide novel therapies for cancer.



Associazione Italiana per la Ricerca sul Cancro

Con la ricerca, contro il cancro.

The Lab: geld, geschick und geduld (gluck)



Affectis AG

ARPA
Emilia-Romagna
Programma Monitor



European Community
FP7-HEALTH-2007-A



European Community
ERA-NET
Nanostroke 2012