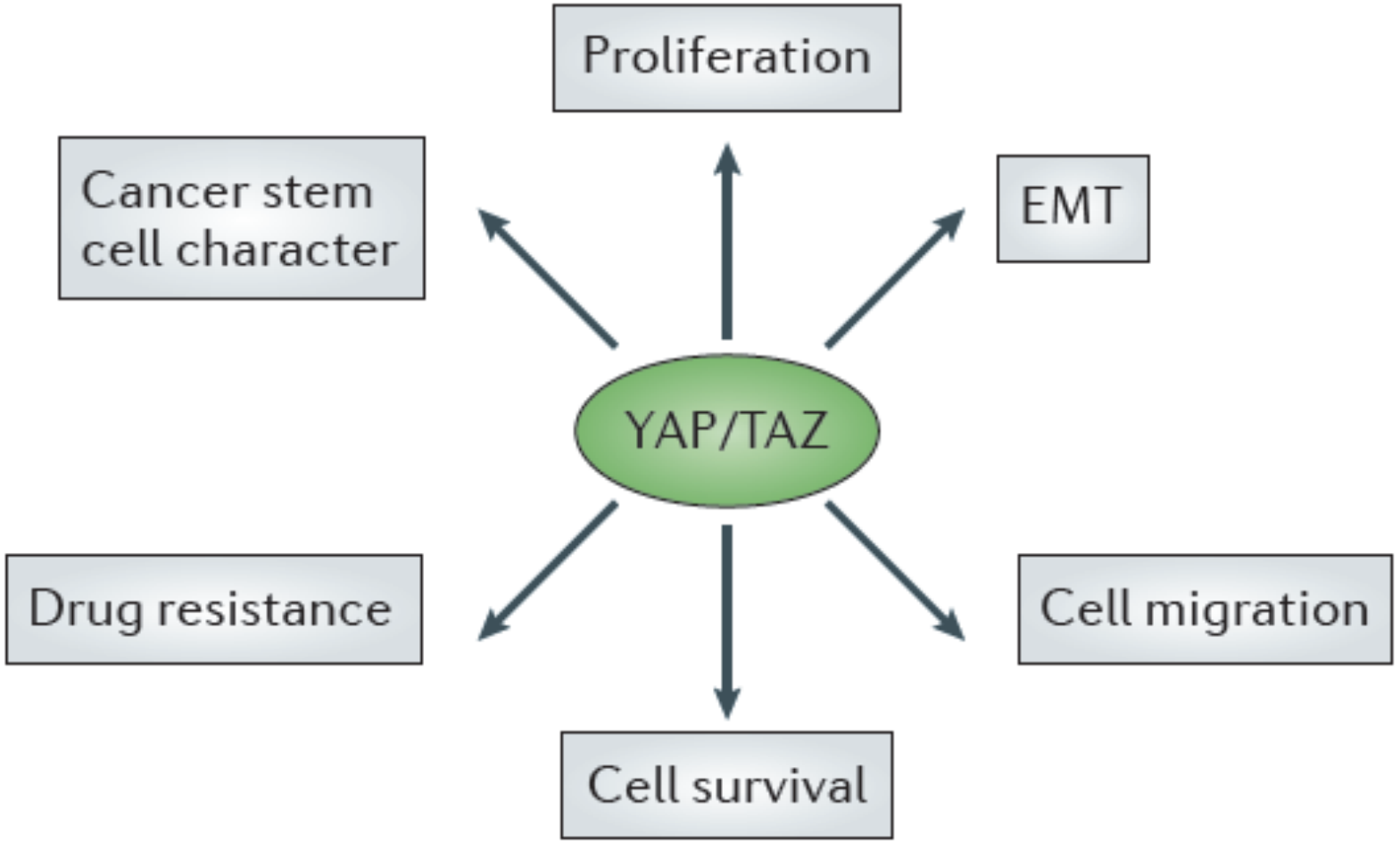
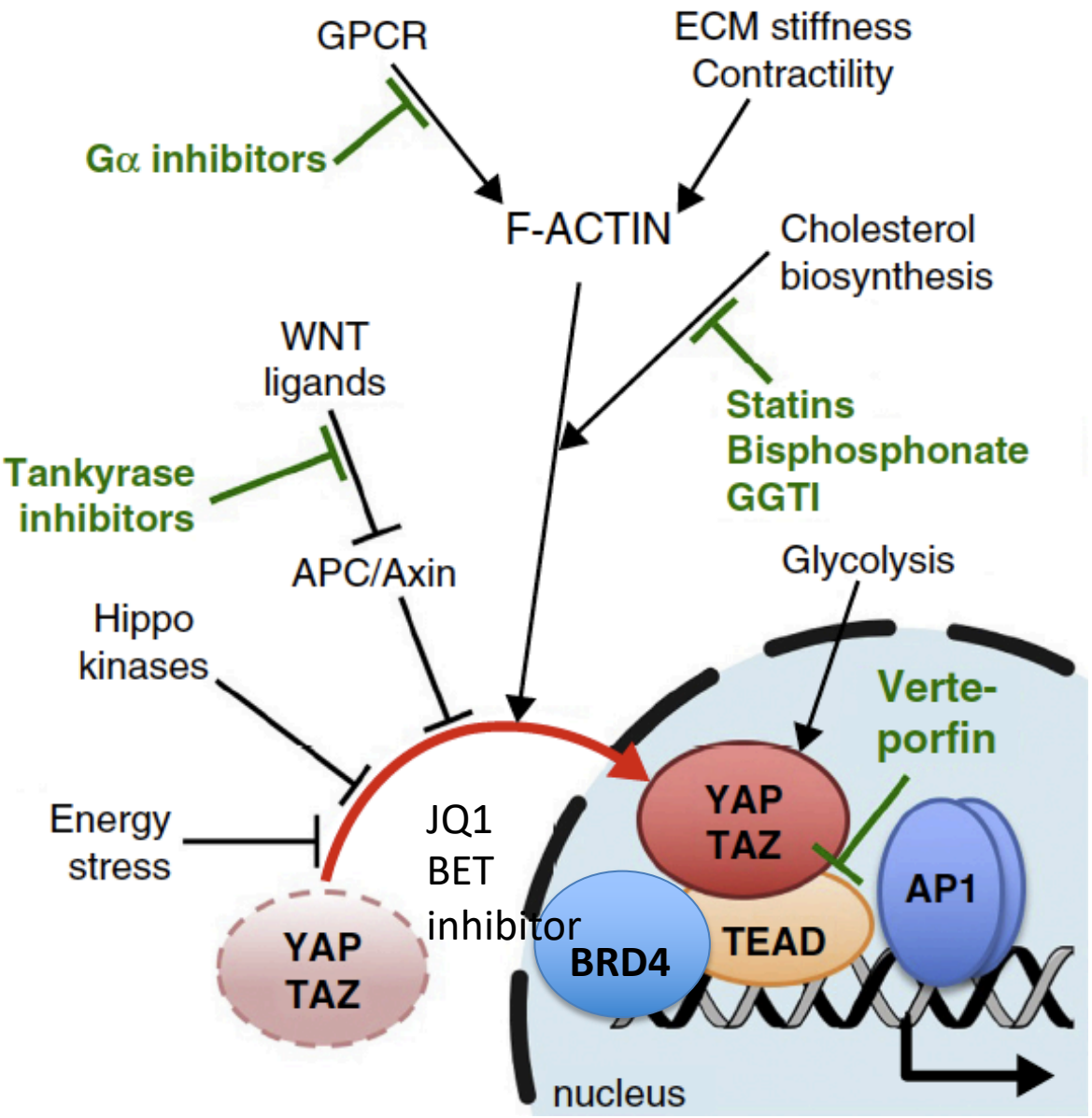
Corso di Biologia Cellulare del Cancro AA 2019-2020

IL MICROAMBIENTE TUMORALE

Roles of YAP/TAZ in cancer



YAP/TAZ come bersagli terapeutici



Inibizione metabolica di YAP/TAZ

ARTICLES

nature cell biology

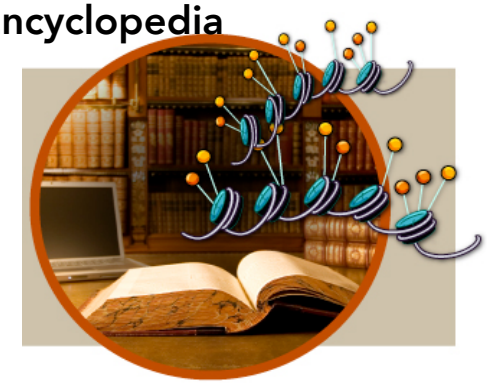
Metabolic control of YAP and TAZ by the mevalonate pathway

Giovanni Sorrentino[1,2], Naomi Ruggeri[1,2], Valeria Specchia[3], Michelangelo Cordenonsi[4], Miguel Mano[5], Sirio Dupont[4], Andrea Manfrin[4], Eleonora Ingallina[1,2], Roberta Sommaggio[6], Silvano Piazza[1], Antonio Rosato[6], Stefano Piccolo[4] and Giannino Del Sal[1,2,7]

Dal bersaglio al farmaco: Mutations and Drugs Portal (MDP) database

Una risorsa open access che combina dati genomici (mutazioni geniche /SNPs) e farmacologici (risposta cellulare a più di 50.000 composti) per rivelare markers genetici di sensibilità a farmaci

Cancer Cell Line Encyclopedia



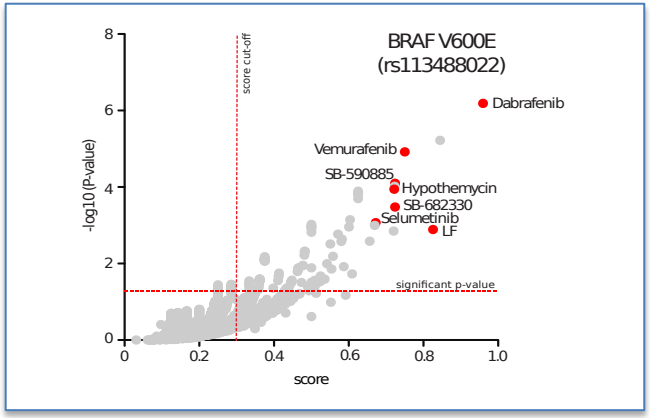
+

NCI60 Screening

Profilo molecolare di linee cellulari tumorali

Attività antitumorale dei farmaci su linee cellulari

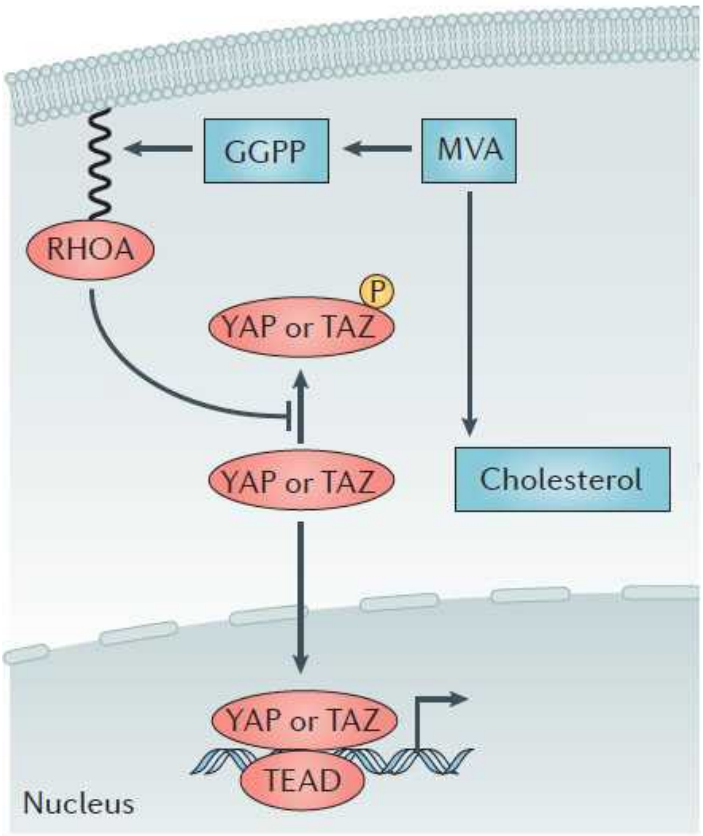
IDENTIFICAZIONE DELLA SENSIBILITÀ AI FARMACI

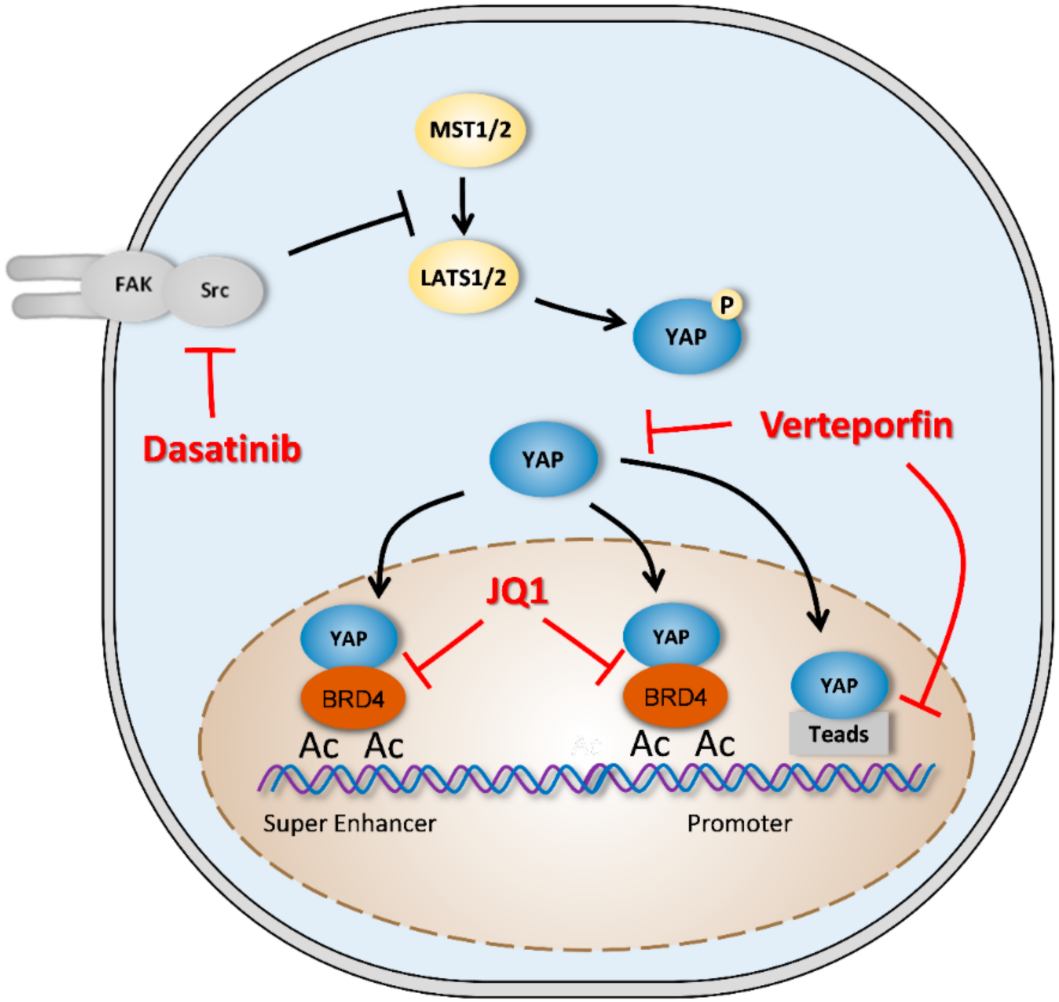


MDP, a database linking drug response data to genomic information, identifies dasatinib and statins as a combinatorial strategy to inhibit YAP/TAZ in cancer cells

Cristian Taccioli[1,*], Giovanni Sorrentino[2,3,*], Alessandro Zannini[2,3], Jimmy Caroli[1], Domenico Beneventano[4], Laura Anderlucci[5], Marco Lolli[6], Silvio Bicciato[1], Giannino Del Sal[2,3]

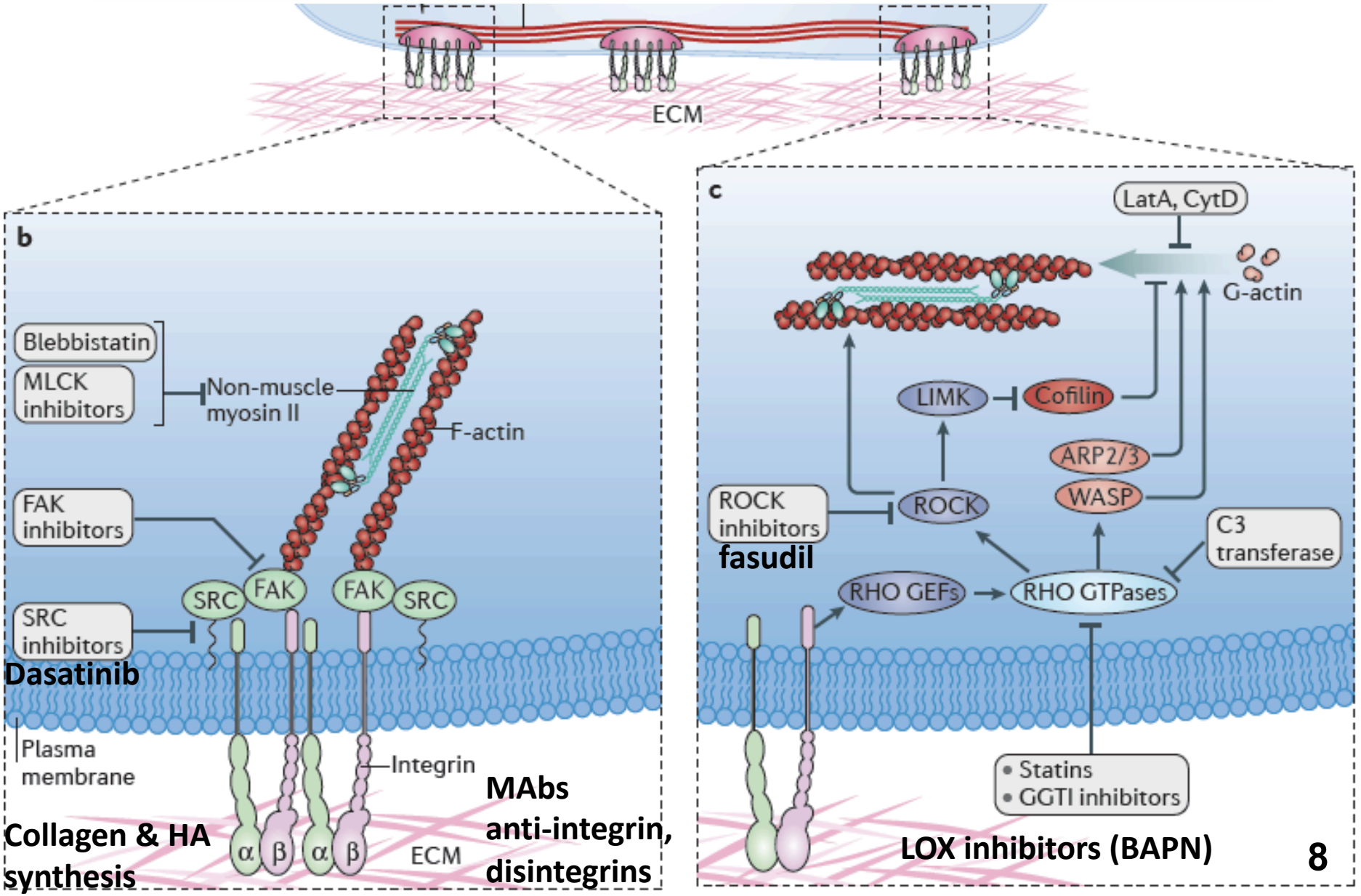
As proof of performance, we interrogated MDP to identify both known and novel pharmacogenomics associations and unveiled an unpredicted combination of two FDA-approved compounds, namely statins and Dasatinib, as an effective strategy to potently inhibit YAP/TAZ in cancer cells.





Mullen et al., 2016 *Nat. Rev. Cancer*

Terapie anti-meccanosegnalazione



ROCK inhibitors

SCIENCE TRANSLATIONAL MEDICINE | RESEARCH ARTICLE

CANCER

Transient tissue priming via ROCK inhibition uncouples pancreatic cancer progression, sensitivity to chemotherapy, and metastasis

Claire Vennin,[1,2]* Venessa T. Chin,[1,2]* Sean C. Warren,[1,2†] Morghan C. Lucas,[1,2†]

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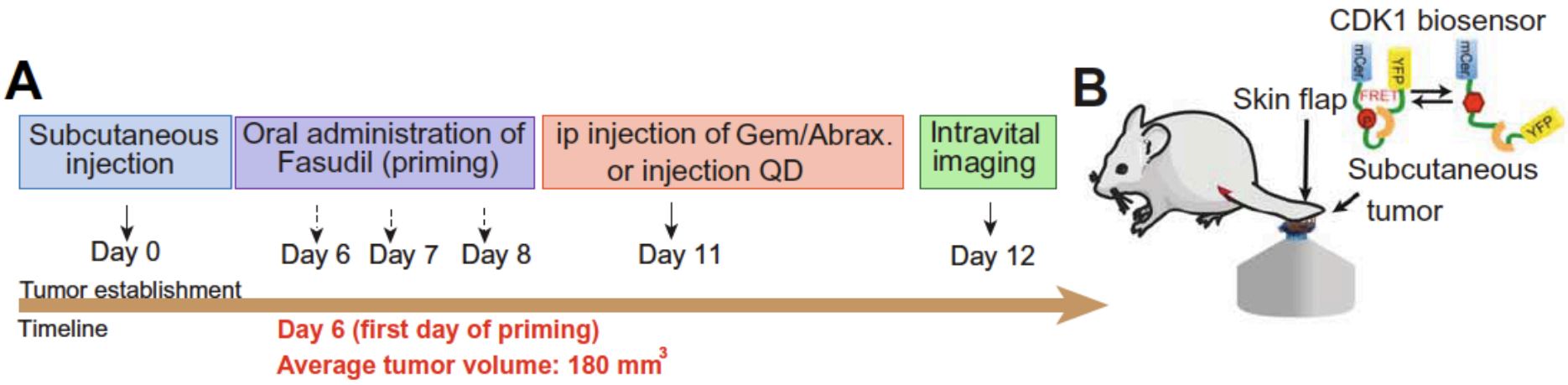
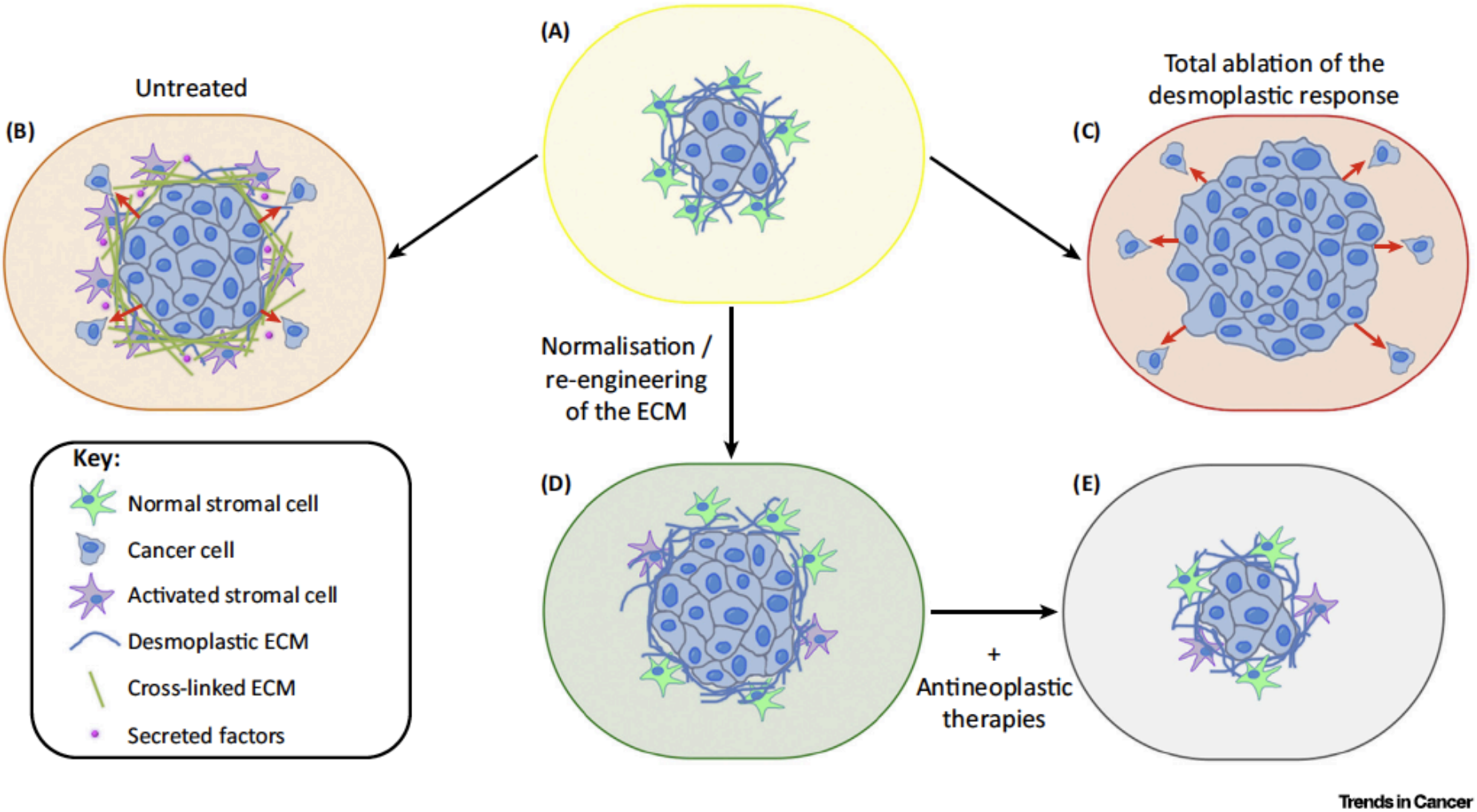


Terapie anti-meccanosegnalazione



Terapie anti-meccanosegnalazione

Potential pharmacological interventions to **overcome extracellular matrix stiffening** are emerging clinically.
The **ECM and its adhesion receptors** constitute tractable **therapeutic targets** that might prove useful for preventing or treating cancer or at the very least might prove useful as a combinatorial treatment with classic chemotherapies or with targeted therapies.

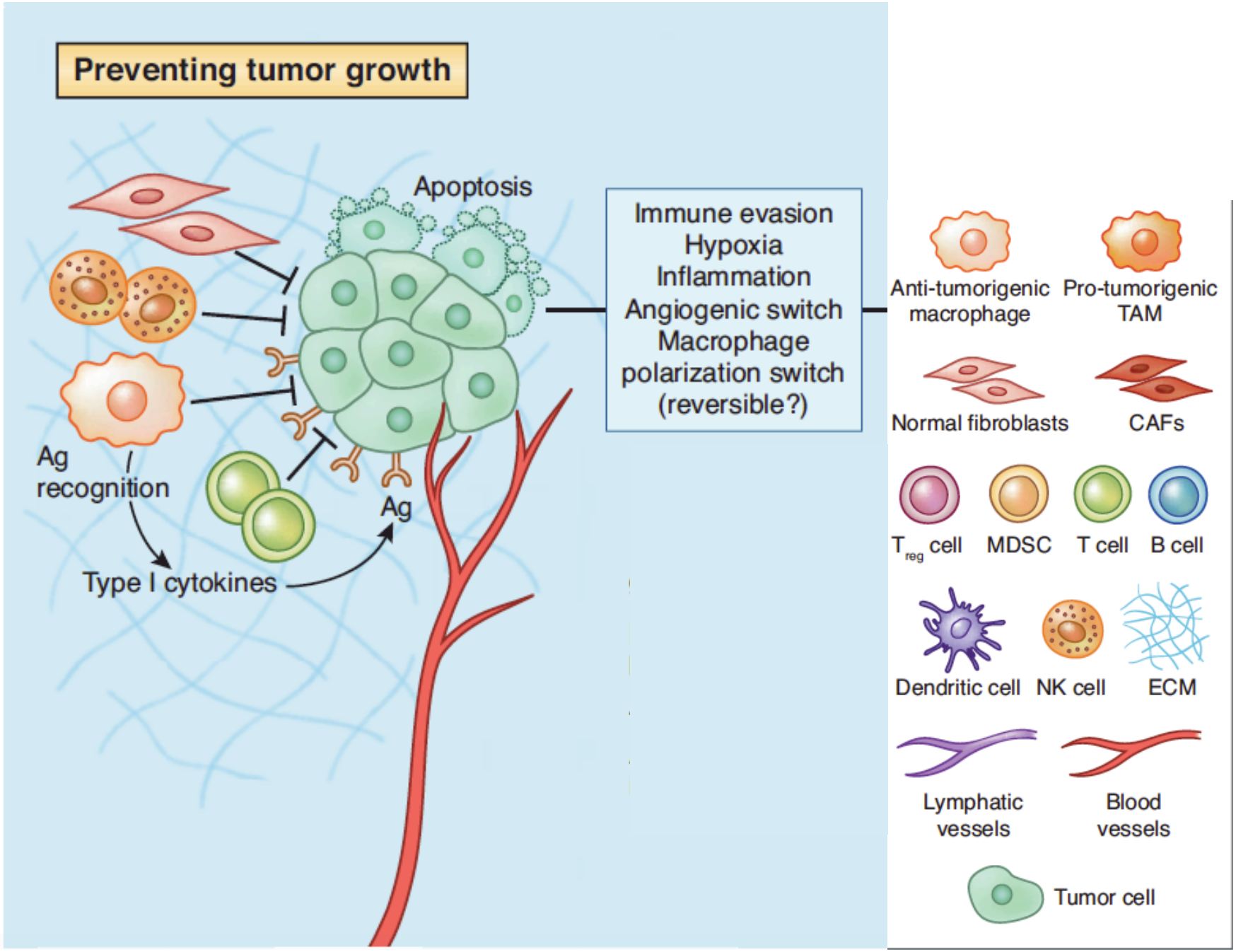
Aside from **targeting stiffening directly**, alternative approaches to mitigate the effects of increased matrix stiffness aim to identify and **inhibit the downstream cellular response** to matrix stiffness.

Numerous **FAK inhibitors** have been developed and tested in clinical trials. Preliminary studies in these patients show that these drugs slow **tumor growth** as well as the **metastatic** nature of late stage cancers (clinicaltrials.gov, GSK2256098).

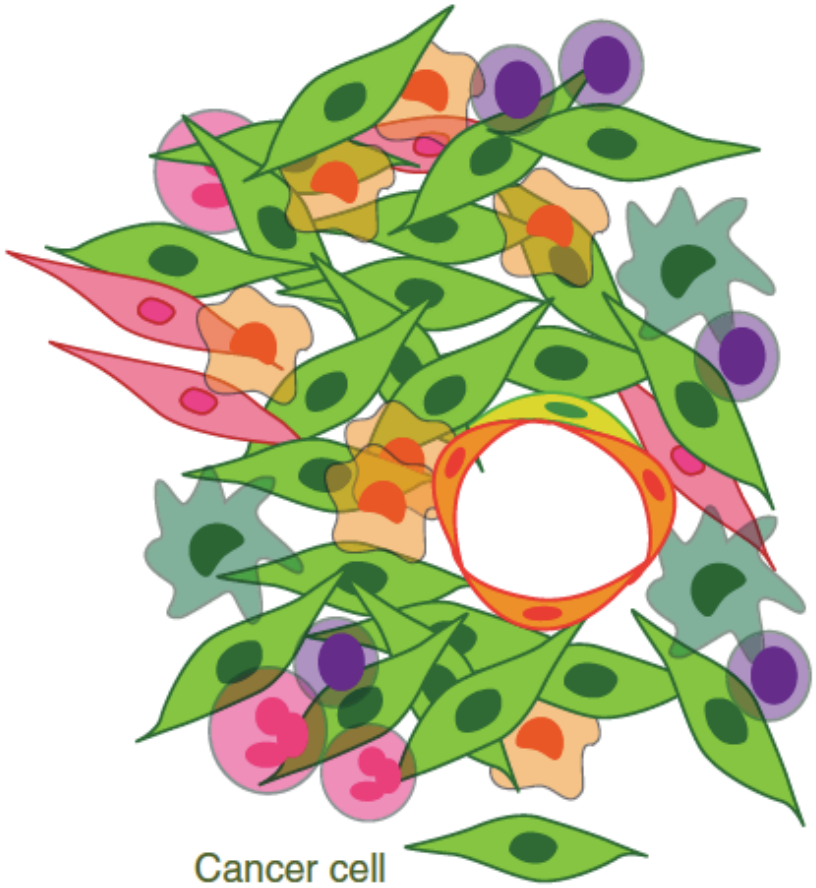
ROCK inhibitors

IL MICROAMBIENTE TUMORALE:

LA COMPONENTE CELLULARE


Preventing tumor growth
Apoptosis
Ag recognition
Ag
Type I cytokines
Immune evasion
Hypoxia
Inflammation
Angiogenic switch
Macrophage polarization switch (reversible?)
Anti-tumorigenic macrophage
Pro-tumorigenic TAM
Normal fibroblasts
CAFs
T reg cell
MDSC
T cell
B cell
Dendritic cell
NK cell
ECM
Lymphatic vessels
Blood vessels
Tumor cell

Funzioni dei diversi tipi cellulari del microambiente tumorale

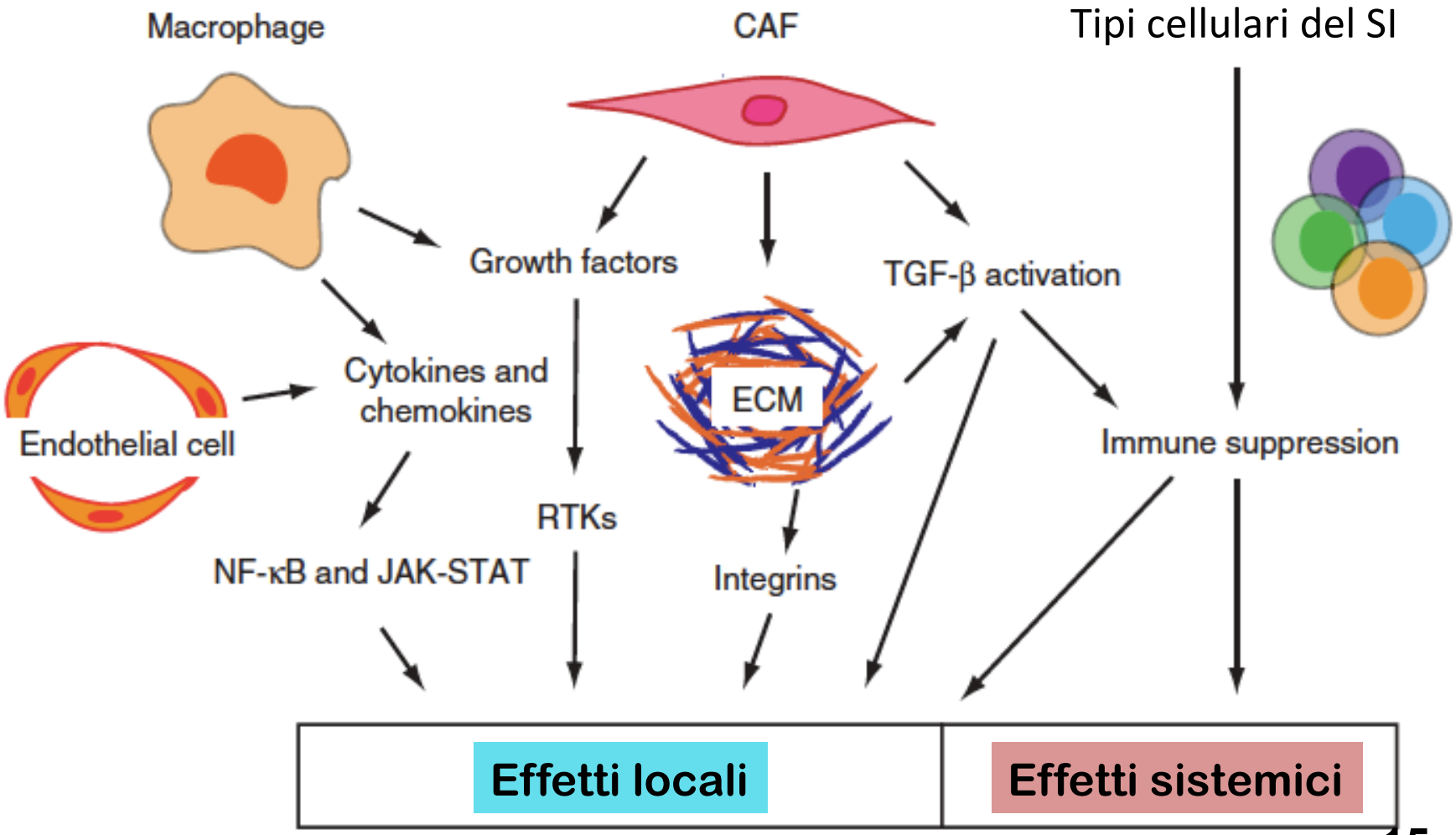


Cell type		Roles within tumor
Endothelial cells		Generate blood vessels that provide nutrients and oxygen. Provide escape route for metastatic cells. Local "angiocrine" signals can protect cancer cells.
Fibroblasts		Produce HGF, CXCL12, TGF-β, and many other soluble factors. Produce and physically remodel the tumor extracellular matrix
Macrophages		Depending on subtype, can either favor or antagonize T-cell function. Promote cancer cell migration via EGF and vessel leakiness via VEGF.
Neutrophils		Can be both pro- and antitumorigenic. Can boost stem cells.
Dendritic cells		Gather antigens to present to T cells
Cytotoxic T cells		Kill tumor cells expressing tumor neo-antigens. Activity can be limited by PD-1, CTLA-4, and other microenvironmental factors.

Figure 1. Major components of the tumor microenvironment. Illustration of the main cellular types found within tumors alongside a table listing their main roles within the tumor.

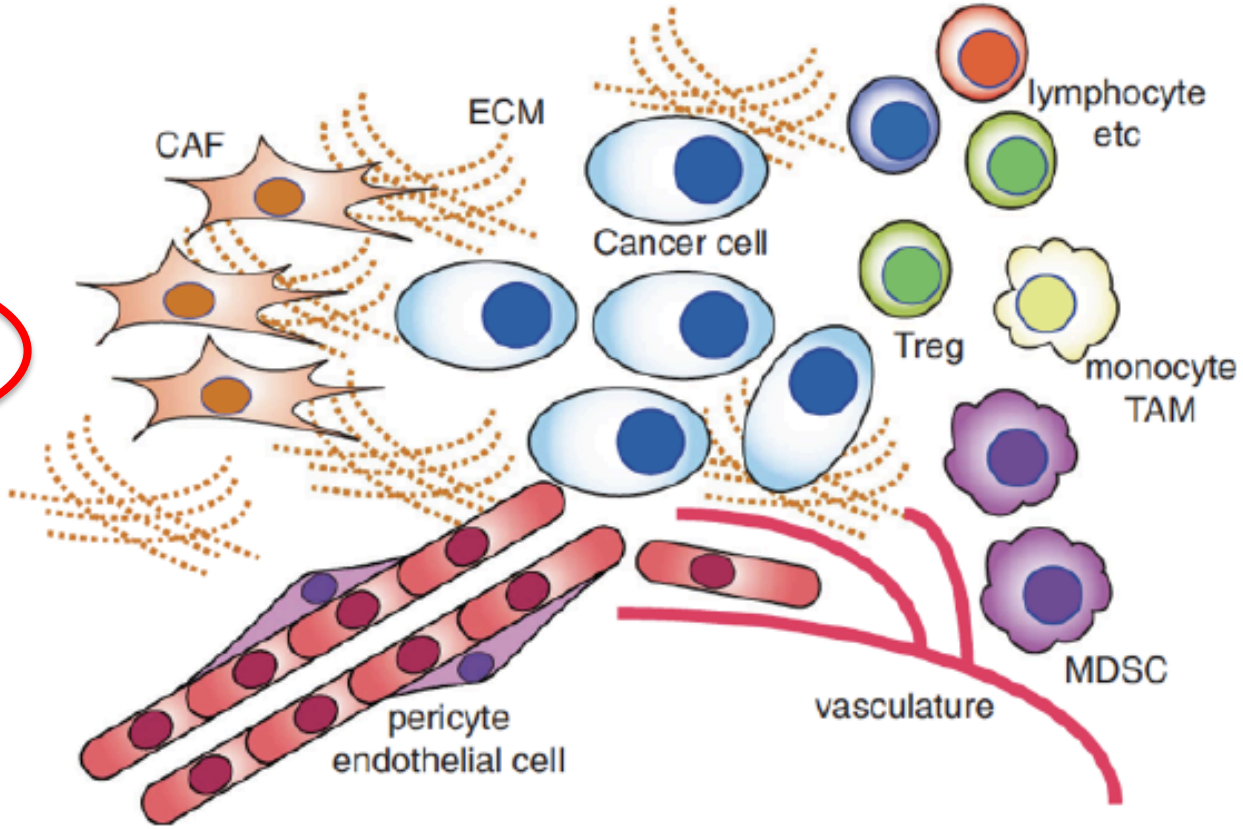
Funzioni dei diversi tipi cellulari del microambiente tumorale

E. Hirata and E. Sahai



Il crosstalk tra le cellule tumorali e lo stroma

- Extracellular Matrix deposition and stiffening;
- Fibroblast activation (CAF);
- Neo-angiogenesis;
- Recruitment of cells from bone marrow.



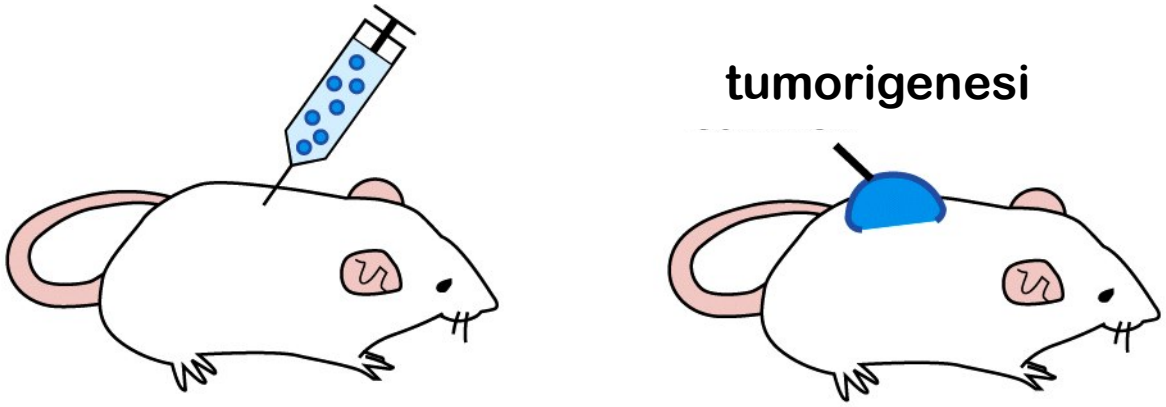
Suzuki *et al*, *Oncogene* 2015

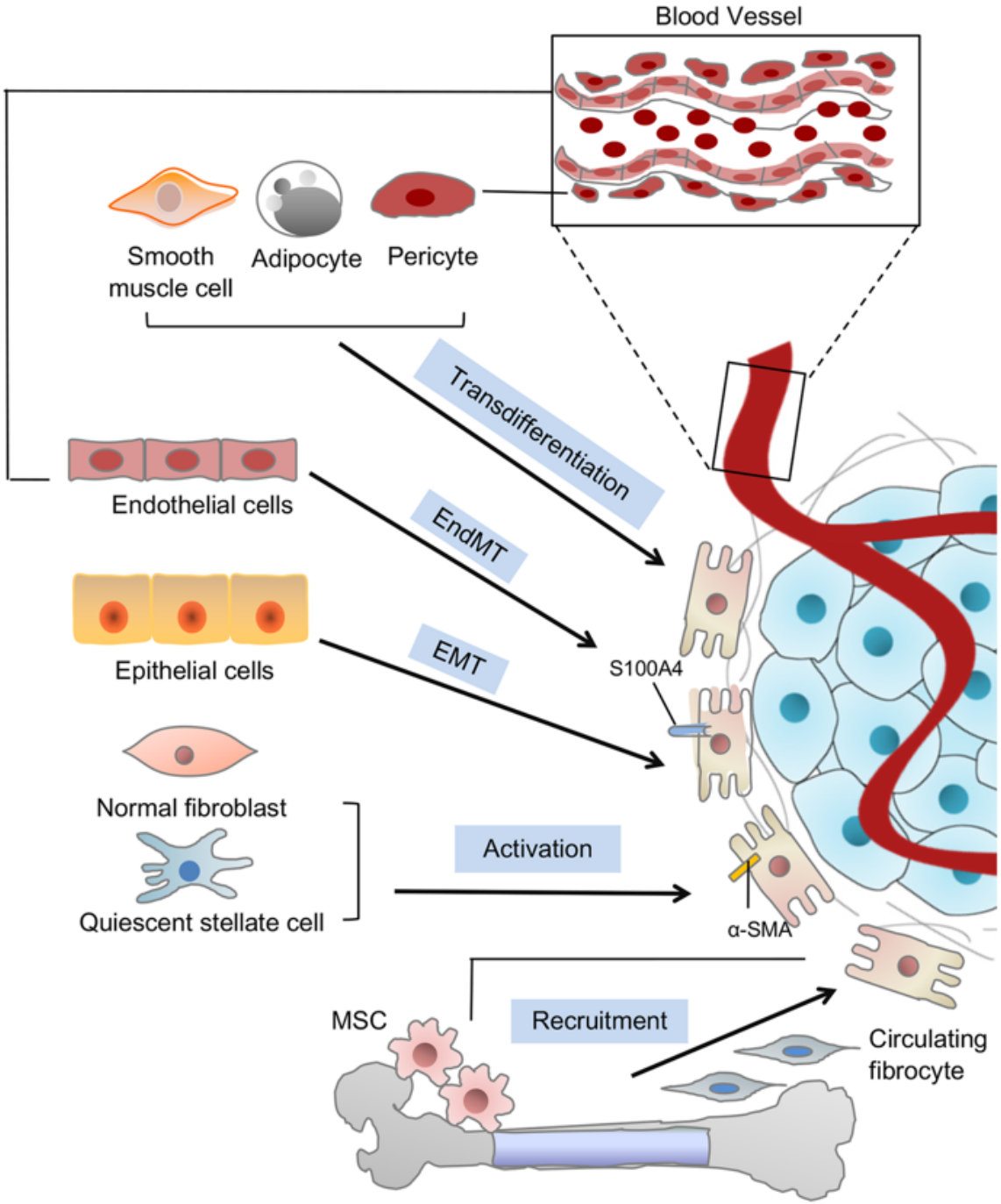
Cancer-Associated Fibroblasts

Popolazione cellulare prevalente nel microambiente tumorale
Popolazione eterogenea dalle molteplici origini (vedi prossima slide)

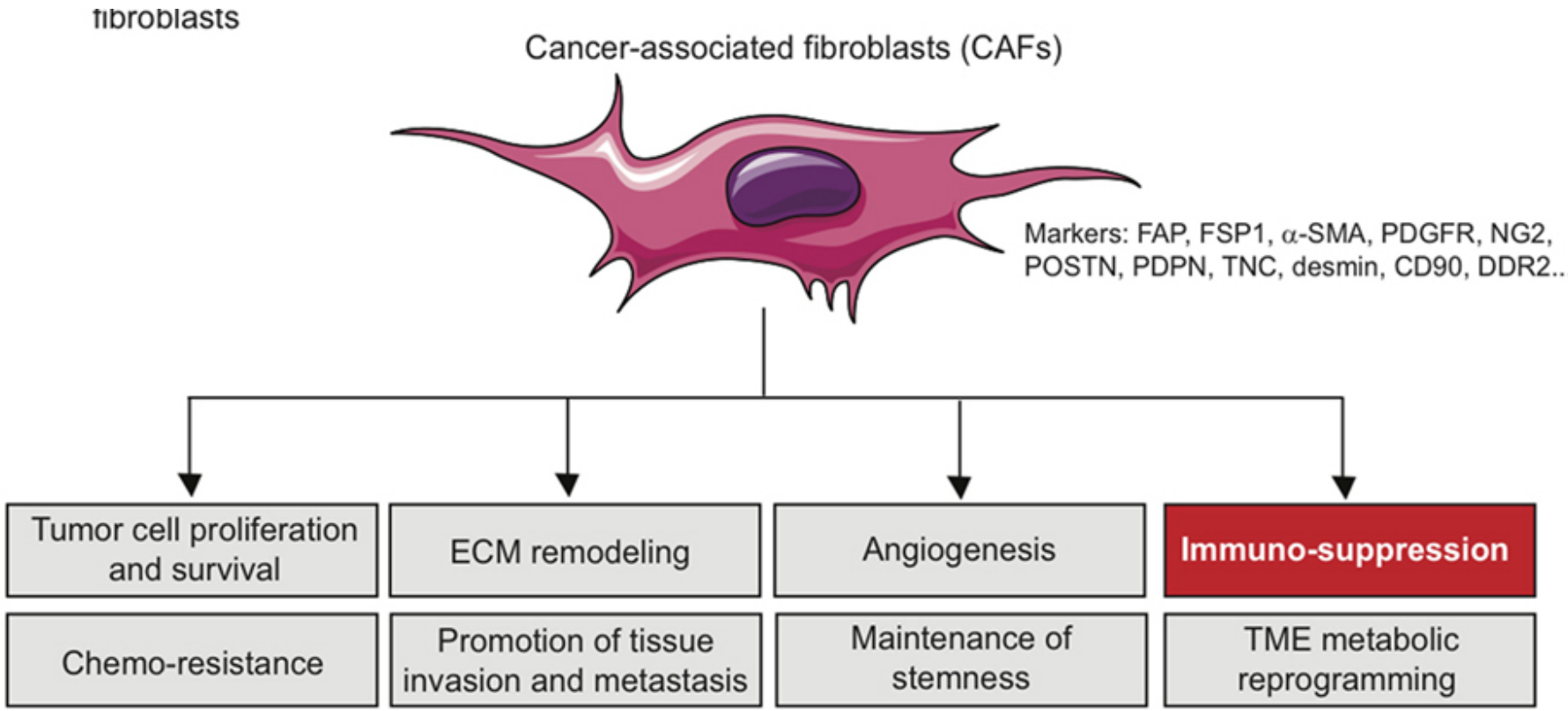
Hanno caratteristiche dei miofibroblasti
che sono normalmente attivati nel processo di wound healing
esprimono SMA (smooth muscle actin)

Le attività pro-tumorigeniche dei CAF sono state dimostrate mediante co-trapianto con cellule pre-neoplastiche



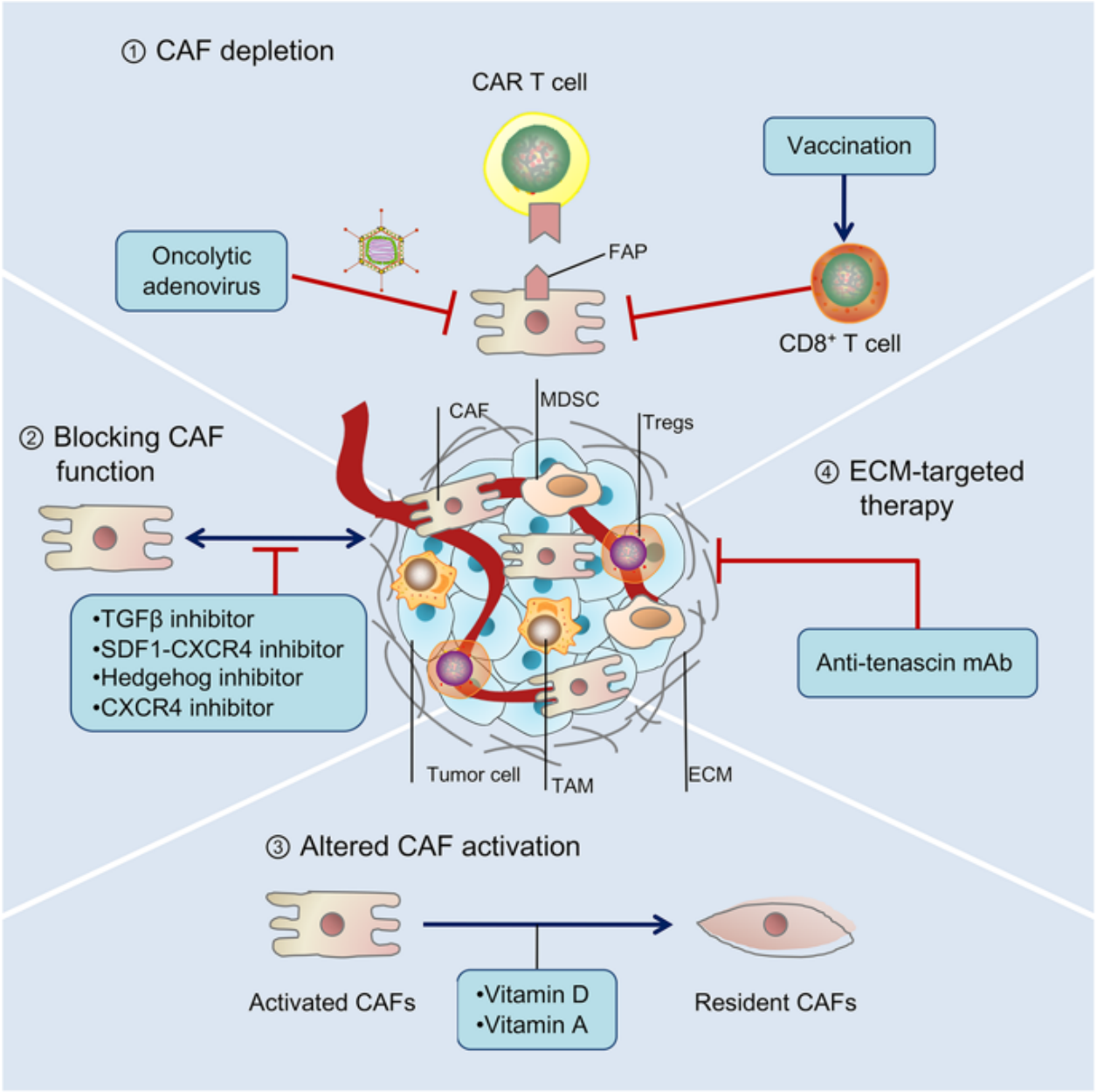

Blood Vessel
Smooth muscle cell
Adipocyte
Pericyte
Transdifferentiation
Endothelial cells
EndMT
Epithelial cells
EMT
S100A4
Normal fibroblast
Quiescent stellate cell
Activation
α-SMA
MSC
Recruitment
Circulating fibrocyte

Cancer-Associated Fibroblasts



Producono e secernono ECM
supportano survival, proliferazione, angiogenesi, EMT, metastasi via secrezione di TGFβ, HGF, EGF, FGF, PDGF…

Terapie anti-CAFs



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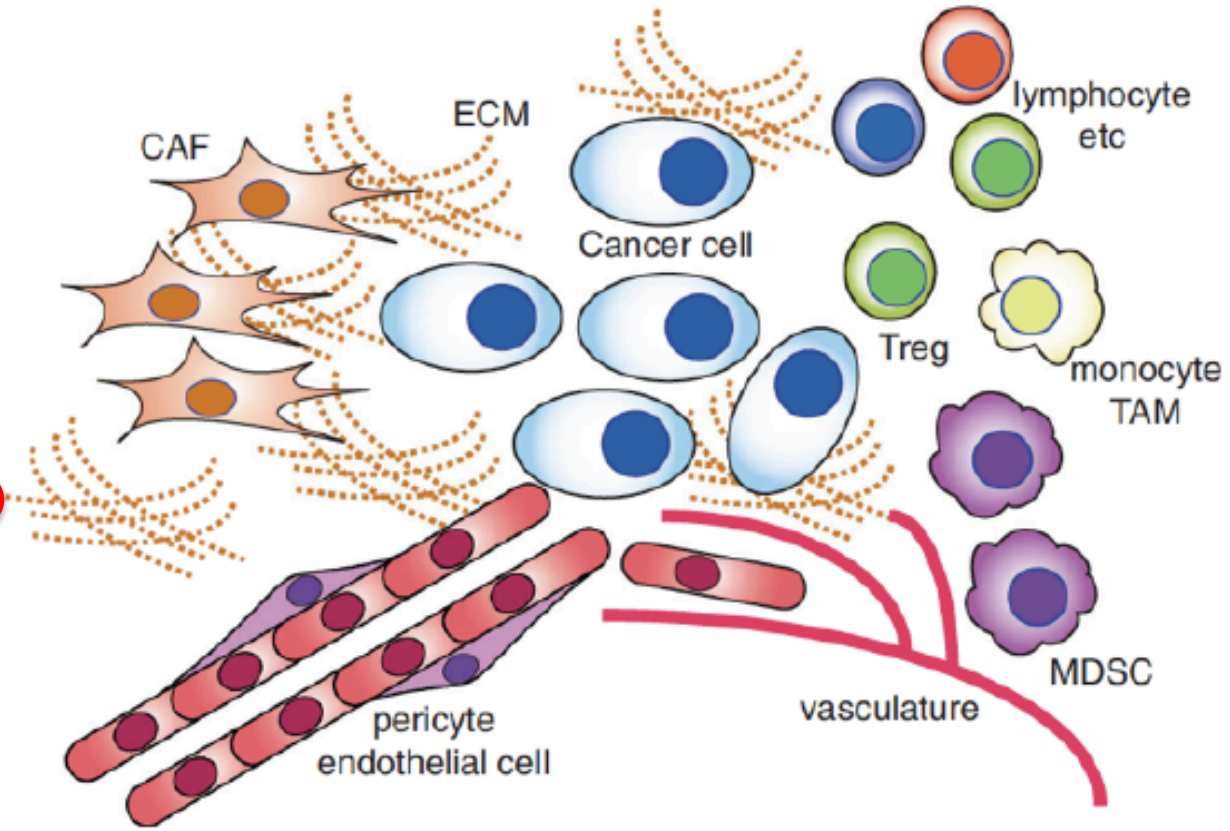
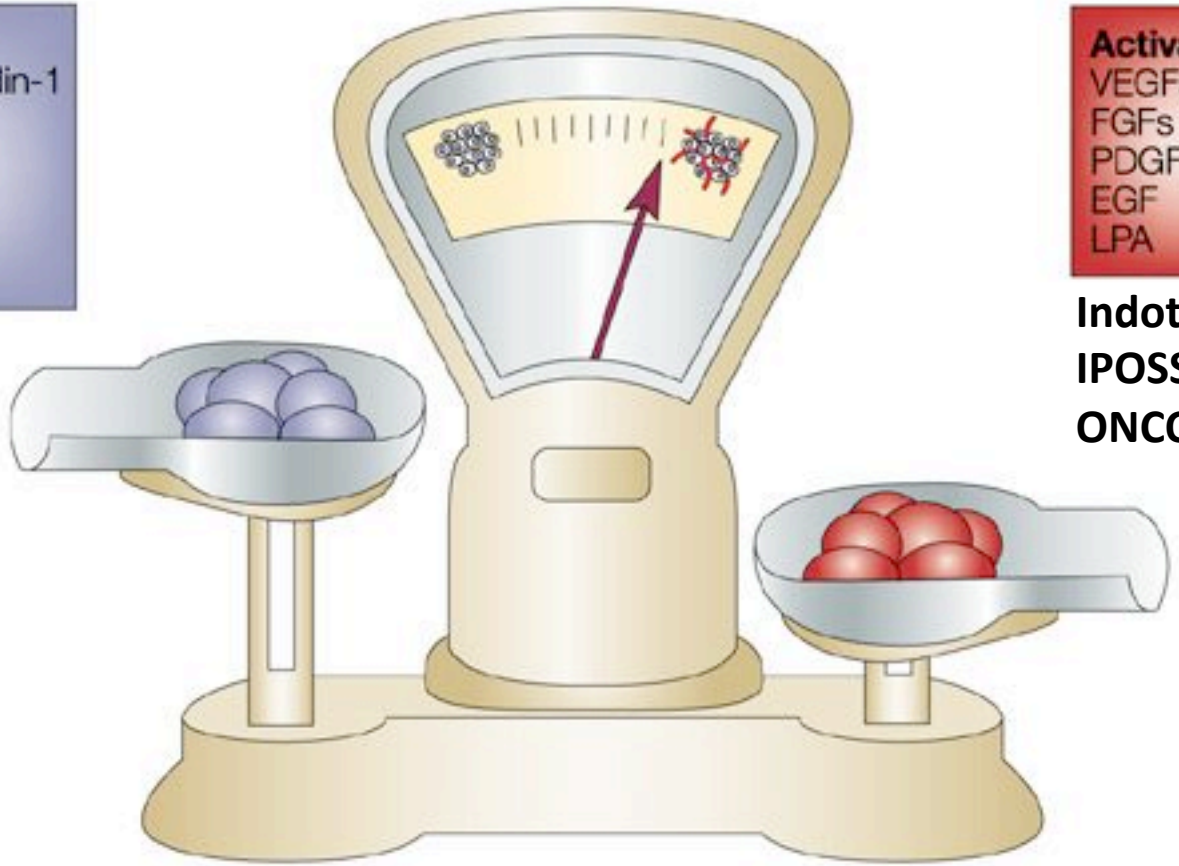


Suzuki *et al*, *Oncogene* 2015

Lo switch angiogenico

p53
pRB →

Inhibitors:
Thrombospondin-1
The statins:
Angiostatin
Endostatin
Canstatin
Tumstatin



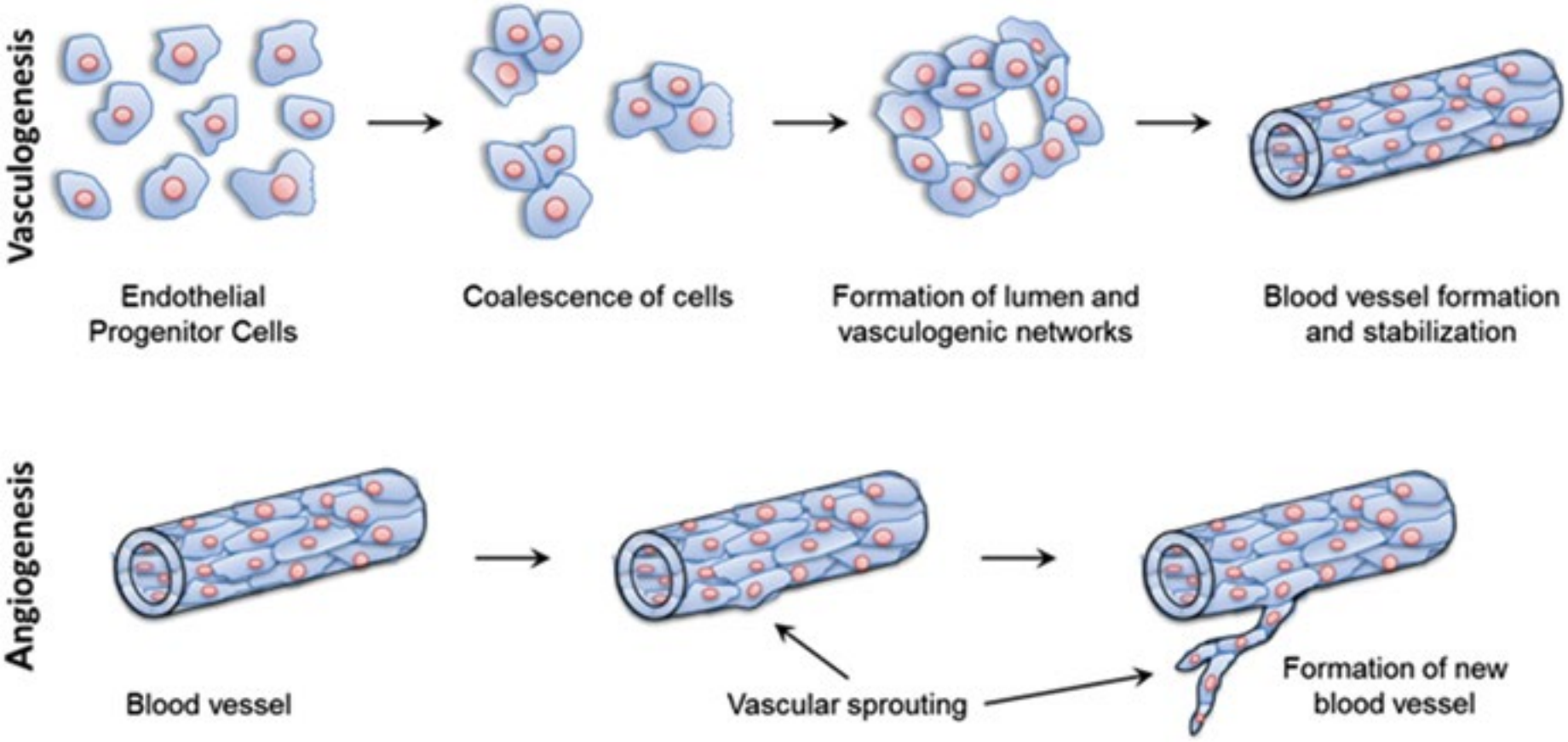
Activators
VEGFs
FGFs
PDGFB
EGF
LPA

Indotti da:
IPOSSIA
ONCOGENI

Nature Reviews | Cancer

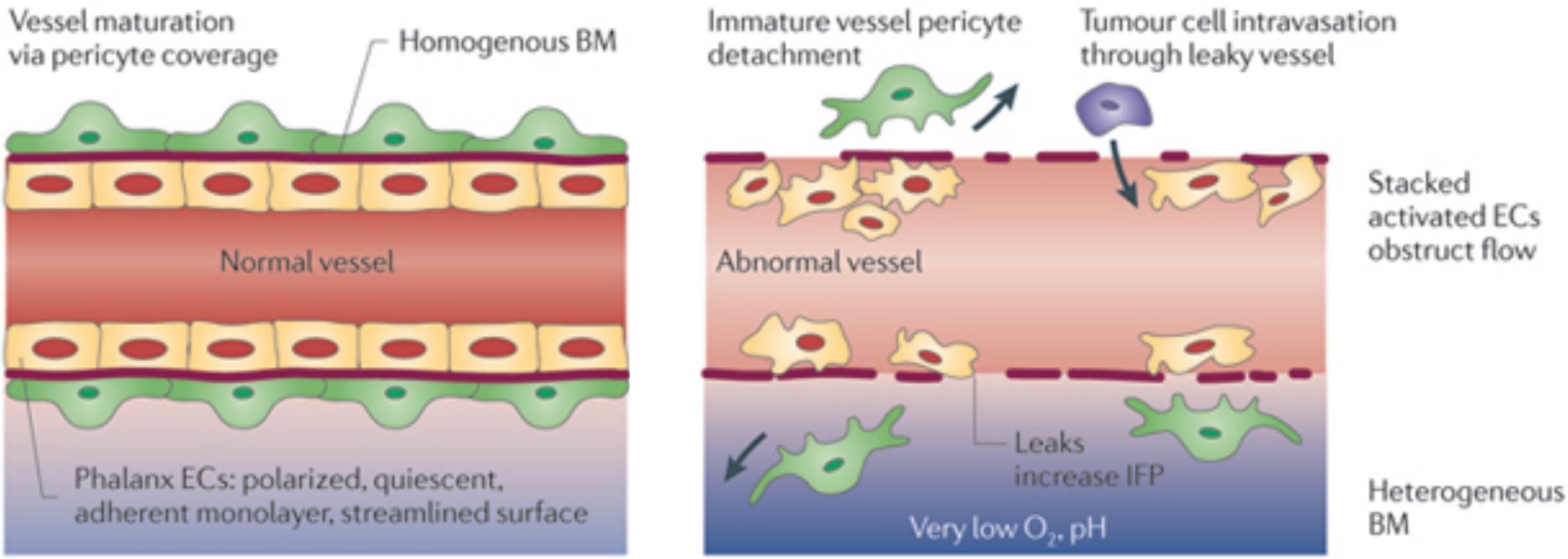
Angiogenesi e vasculogenesi

Reclutamento di precursori endoteliali derivati dal midollo osseo

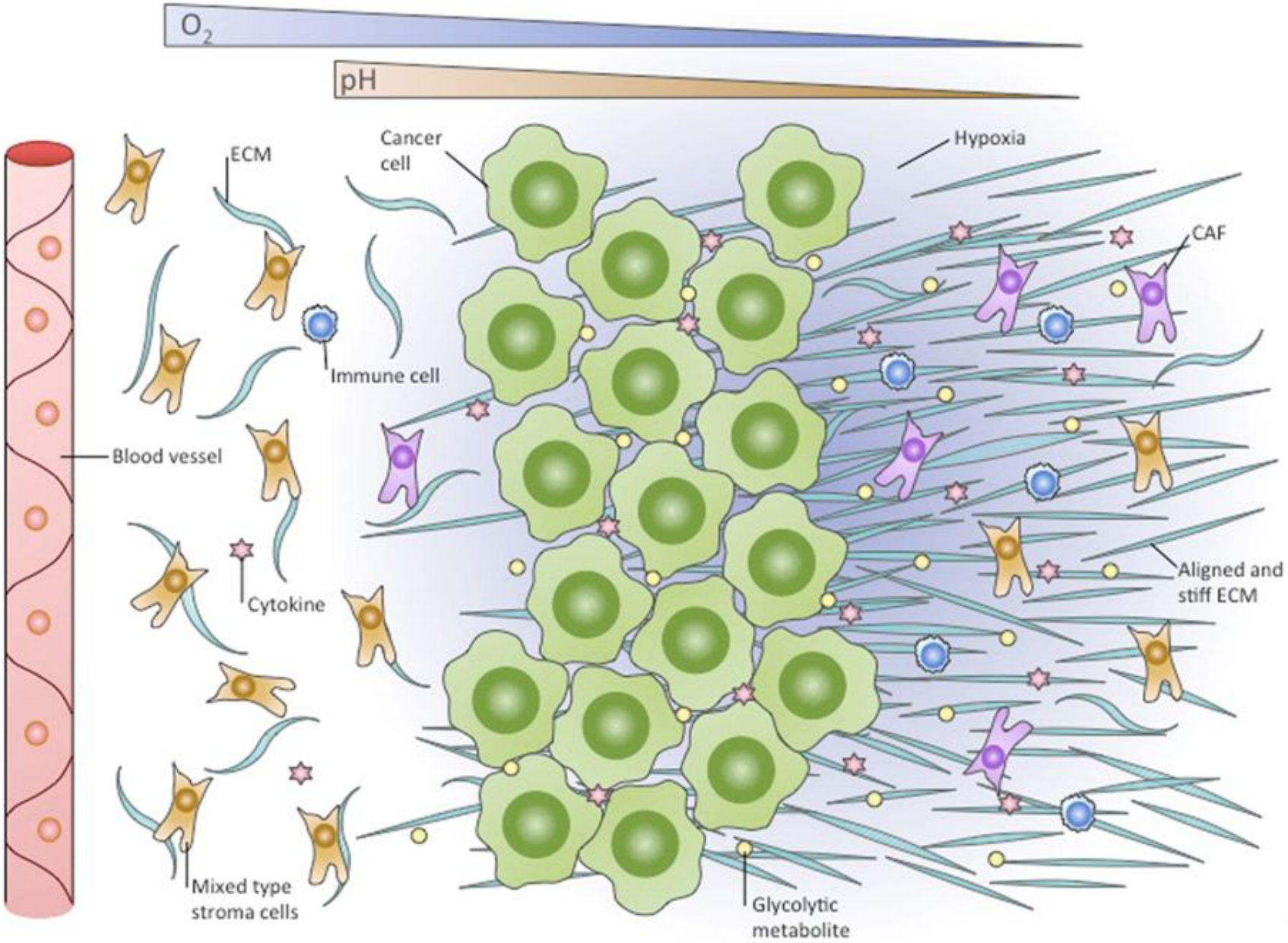


Reclutamento di periciti

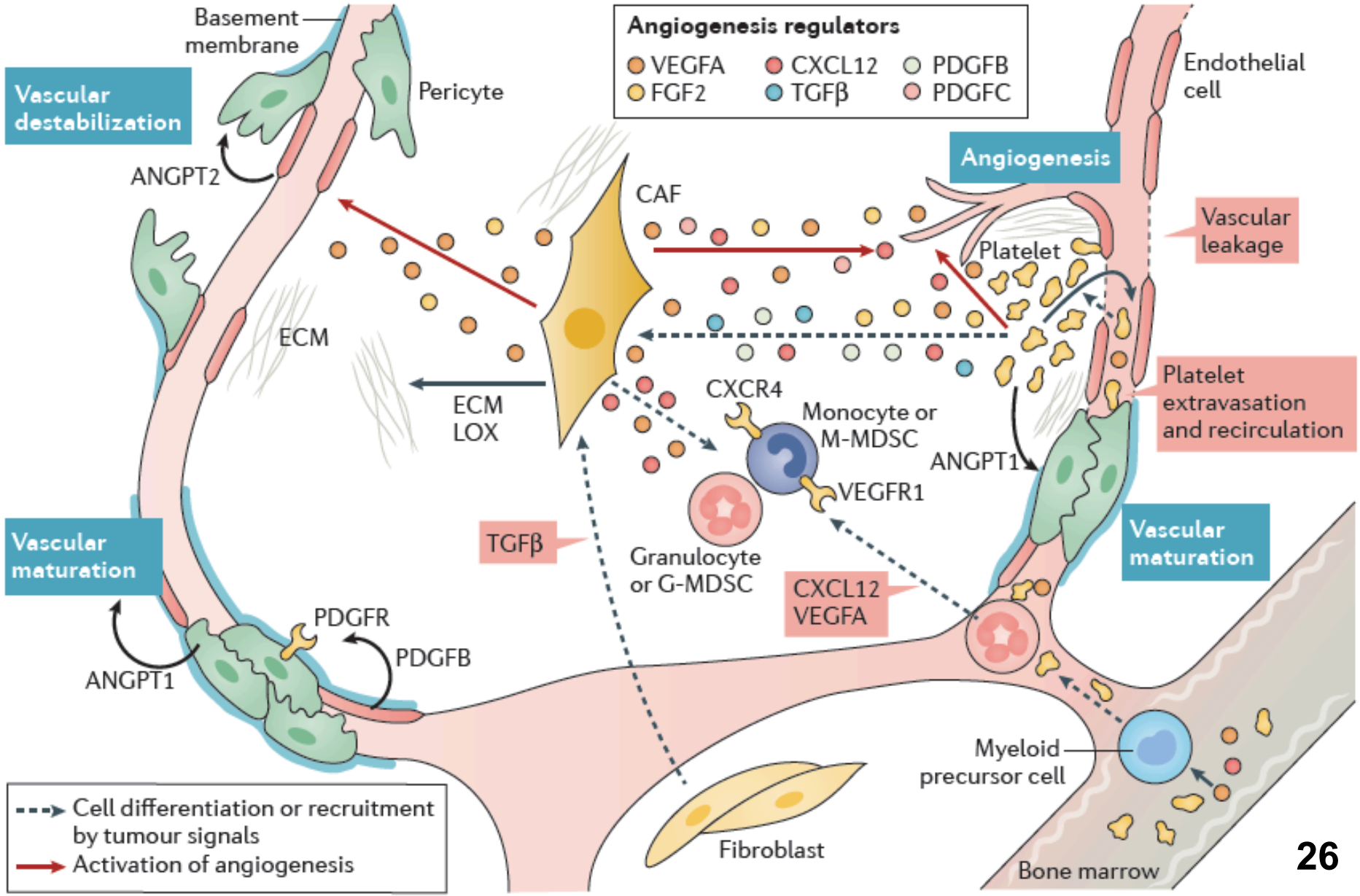
La vascolatura tumorale è aberrante e favorisce l'extravasazione e la chemioresistenza



Il microambiente ipossico



Il ruolo dei CAF



Risposta cellulare all'ipossia: HIFs = hypoxia-induced factors

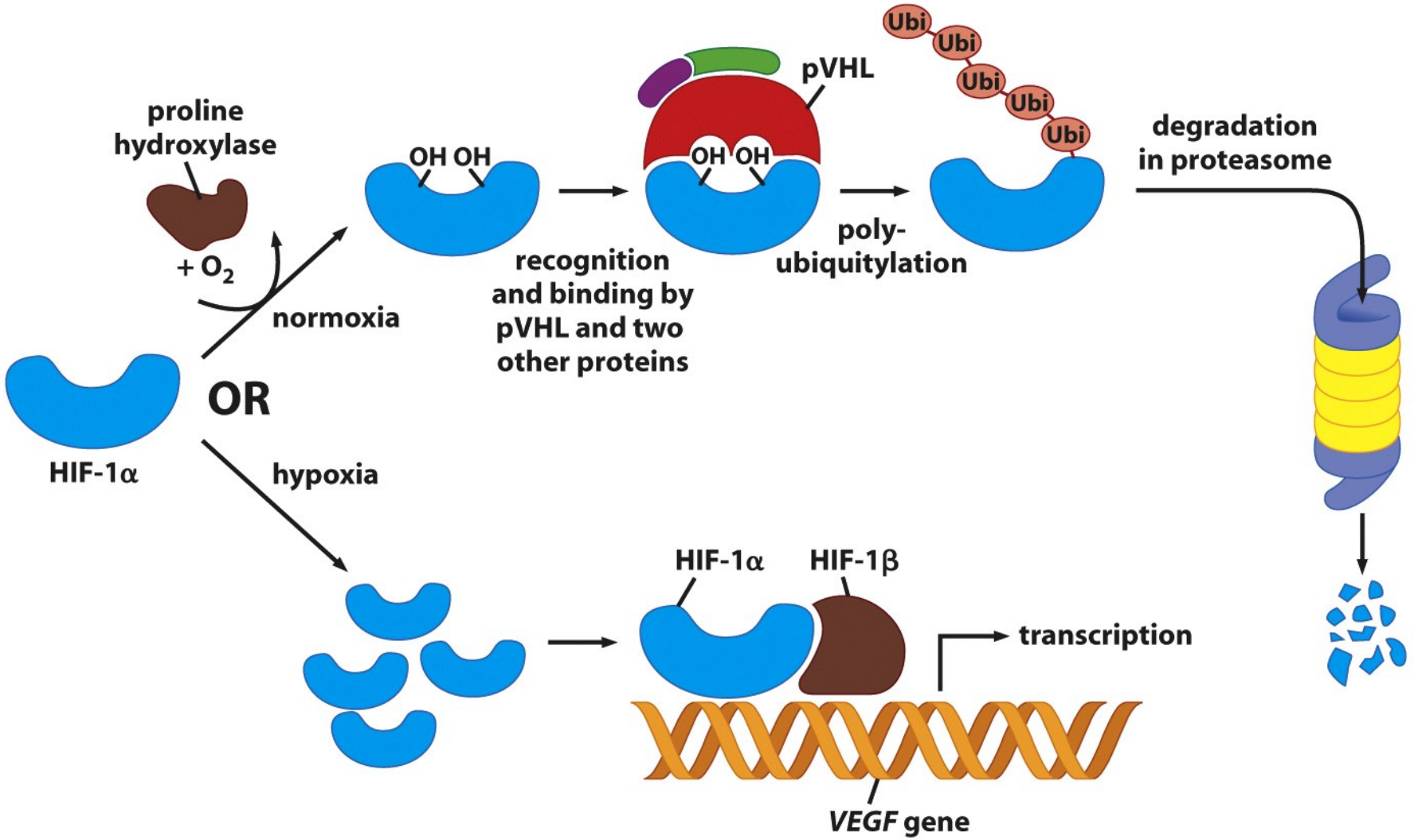
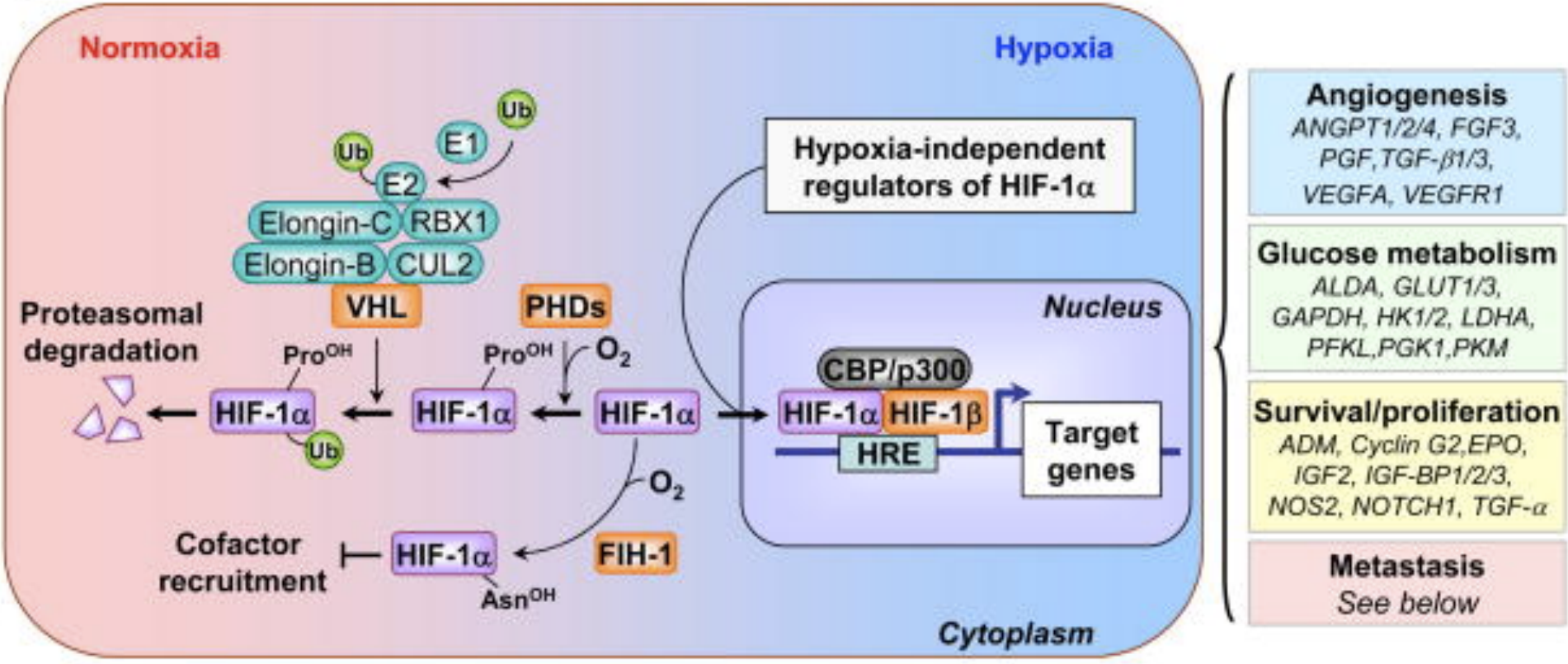


Figure 7.28a *The Biology of Cancer* (© Garland Science 2007)

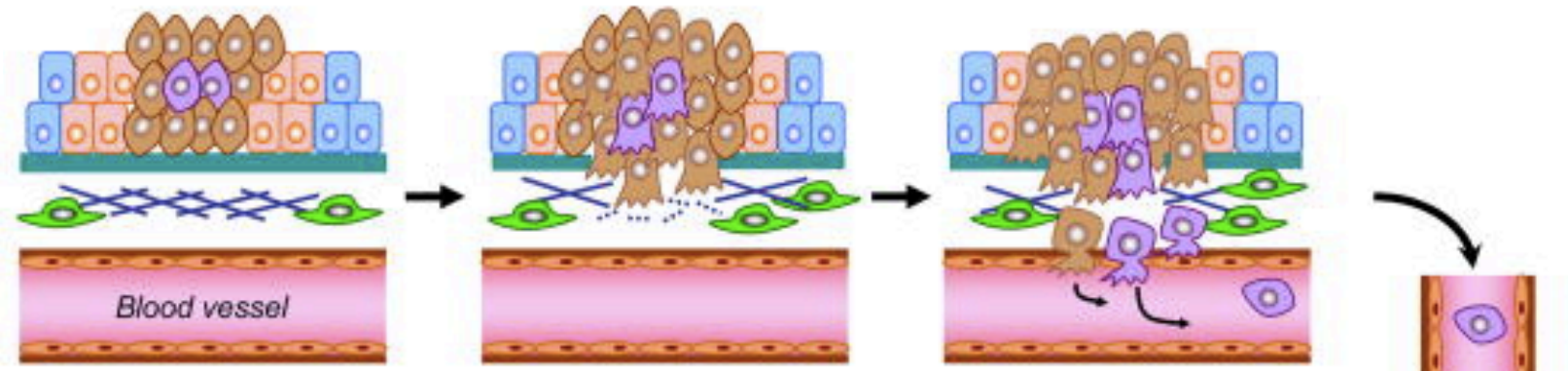
La risposta all'ipossia nelle cellule tumorali

oxygen pressure < 5–10 mm Hg



L'ipossia è associata a prognosi negativa
Sovraespressione di HIF-1α and HIF-2α è associata a metastasi
HIF1α è regolato da oncogeni ERBB2, SRC, RAS/MAPK, PI3K-Akt-mTOR, mut-p53
Mutazioni di oncosoppressori (*PTEN, VHL…*), **e ROS**

HIF attiva un programma trascrizionale pro-metastatico

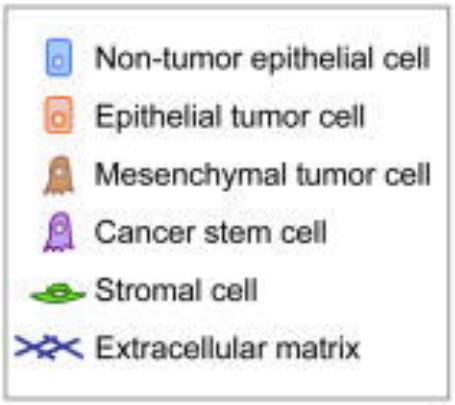


Primary tumor
Angiogenesis: VEGFA
EMT: **Snail, TWIST, ZEB**
CSC self-renewal: **Notch**

Motility and invasion
LOX
MMPs, fibronectin

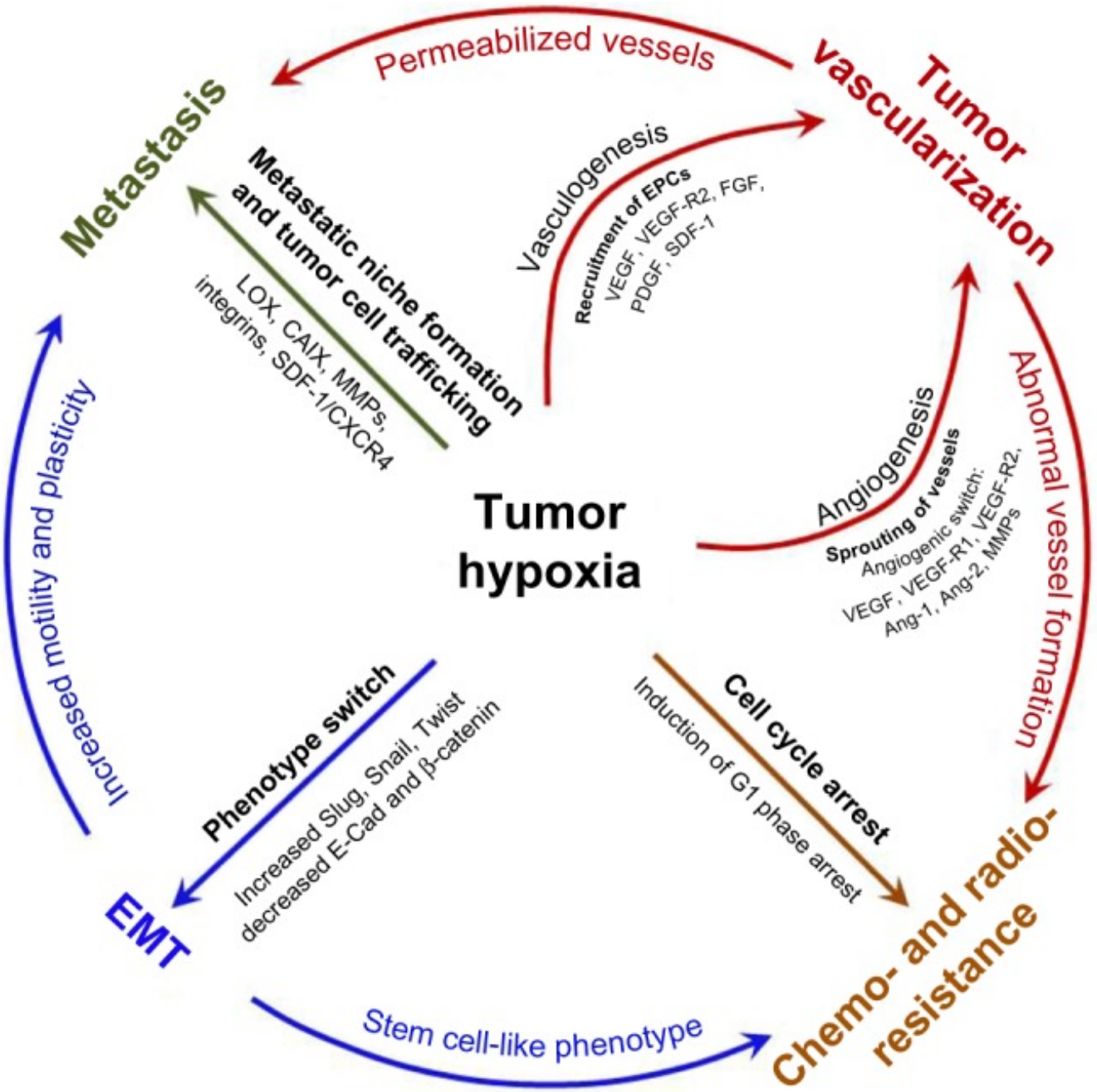
Intravasation
MMPs

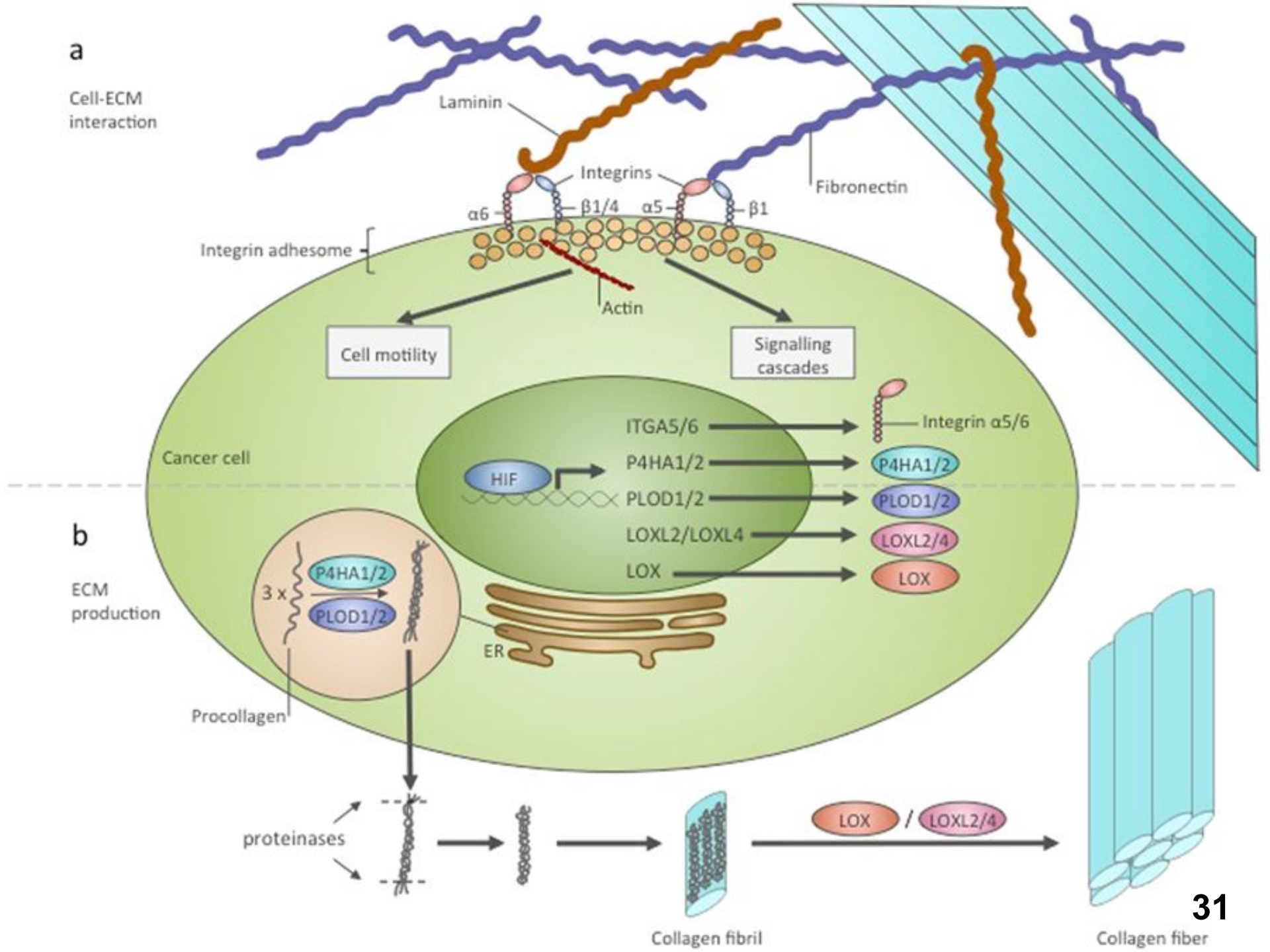
Circulation
Resistance to anoikis



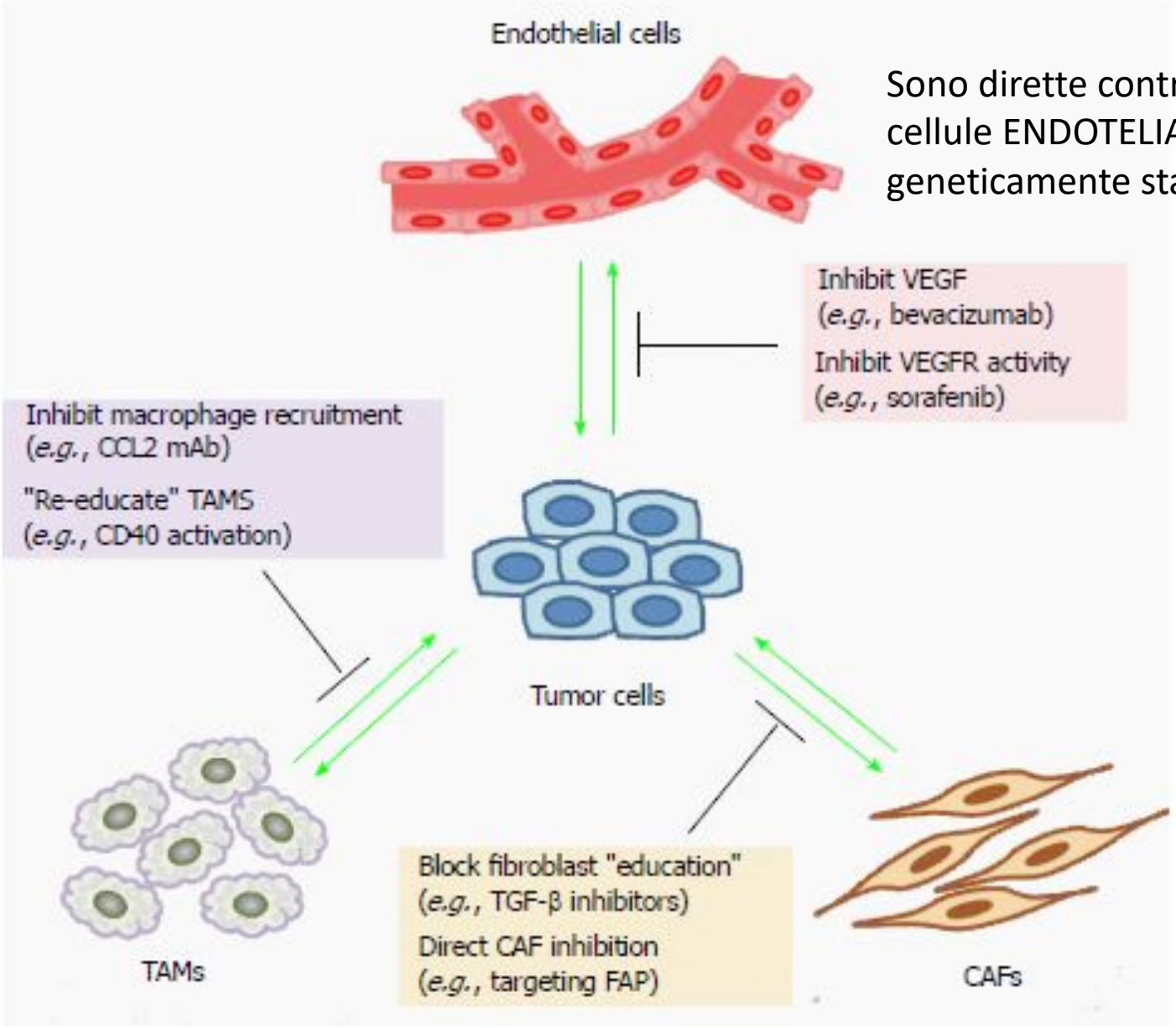
Metastatic outgrowth:
Angiogenesis
Tumor-stromal interactions: Il-6, IL-8…

Metastatic seeding:
Homing
Extravasation
Pre-metastatic niche


Tumor vascularization
Permeabilized vessels
Metastasis
Vasculogenesis
Recruitment of EPCs
VEGF, VEGF-R2, FGF, PDGF, SDF-1
Metastatic niche formation and tumor cell trafficking
LOX, CAIX, MMPs, integrins, SDF-1/CXCR4
Angiogenesis
Sprouting of vessels
Angiogenic switch:
VEGF, VEGF-R1, VEGF-R2, Ang-1, Ang-2, MMPs
Abnormal vessel formation
Tumor hypoxia
Increased motility and plasticity
Phenotype switch
Increased Slug, Snail, Twist
decreased E-Cad and β-catenin
Cell cycle arrest
Induction of G1 phase arrest
EMT
Stem cell-like phenotype
Chemo- and radio-resistance


a
Cell-ECM interaction
Laminin
Integrins
Fibronectin
α6
β1/4
α5
β1
Integrin adhesome
Actin
Cell motility
Signalling cascades
Cancer cell
ITGA5/6
Integrin α5/6
P4HA1/2
HIF
PLOD1/2
LOXL2/LOXL4
LOX
b
ECM production
3 x
P4HA1/2
PLOD1/2
ER
Procollagen
proteinases
LOX / LOXL2/4
Collagen fibril
Collagen fiber

Terapie anti-angiogeniche

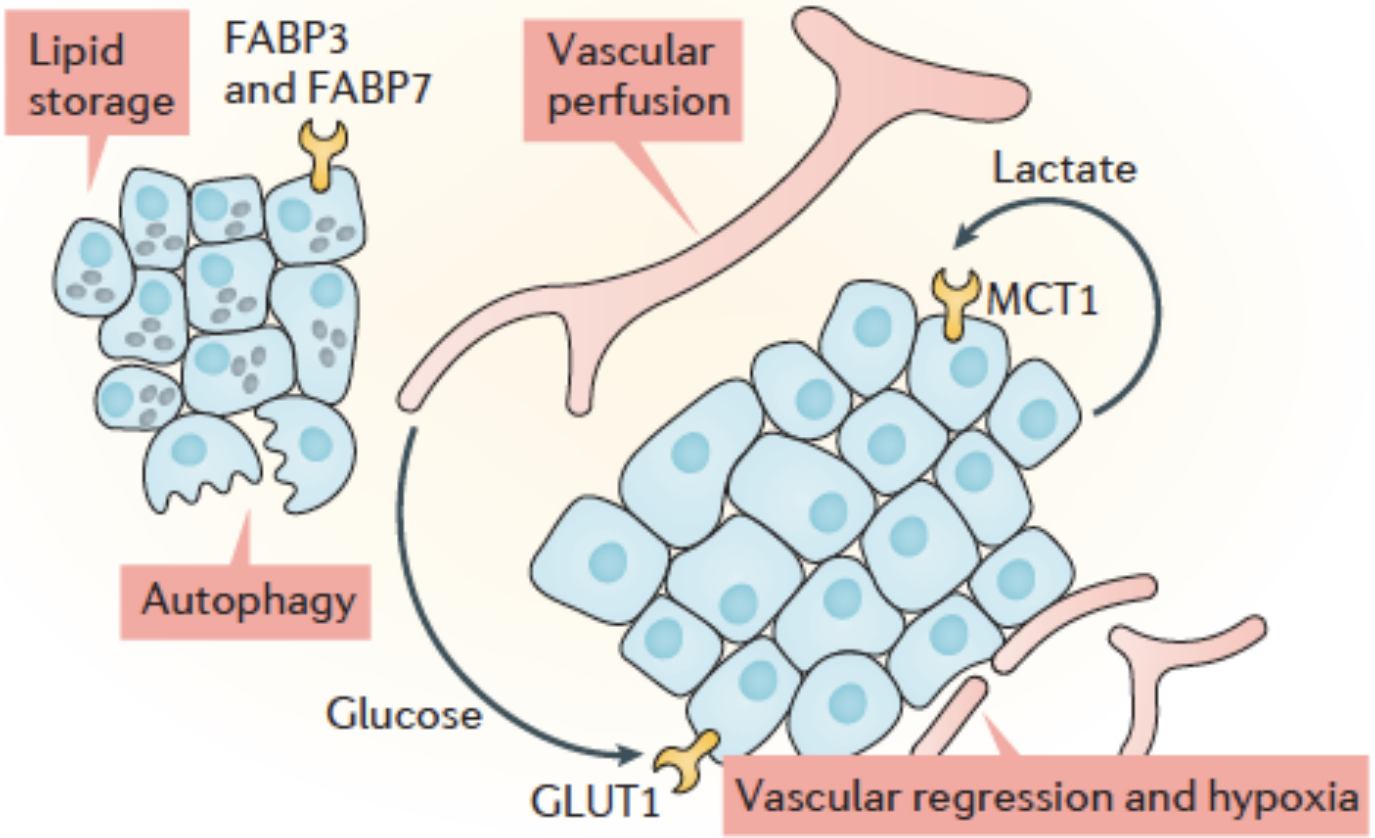


Sono dirette contro le cellule ENDOTELIALI, geneticamente stabili

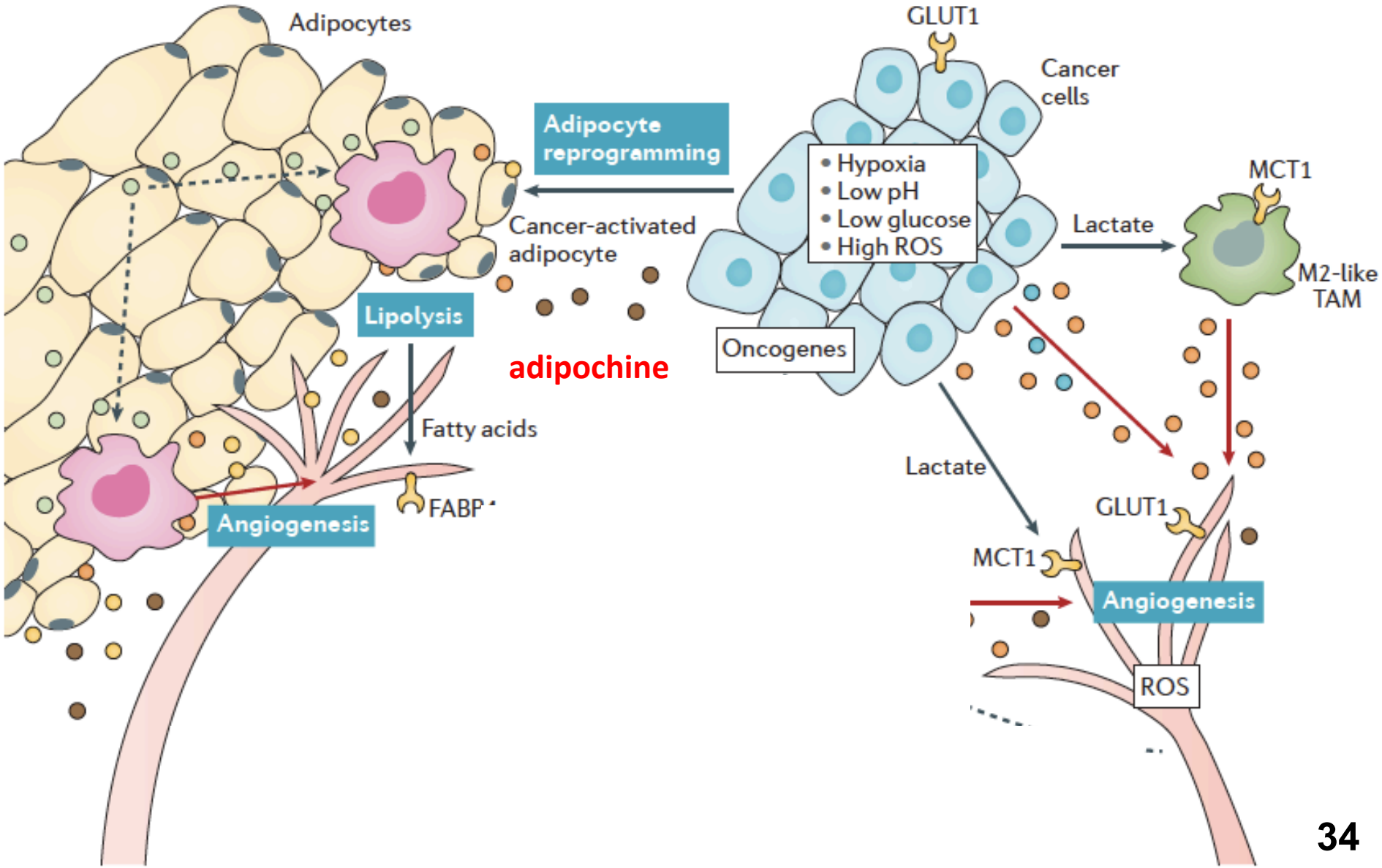
Bloccano VEGF/VEGFR:

SORAFENIB
SUNITINIB
AVASTIN

Adattamento metabolico e simbiosi metabolica nella resistenza alle terapie anti-angiogeniche

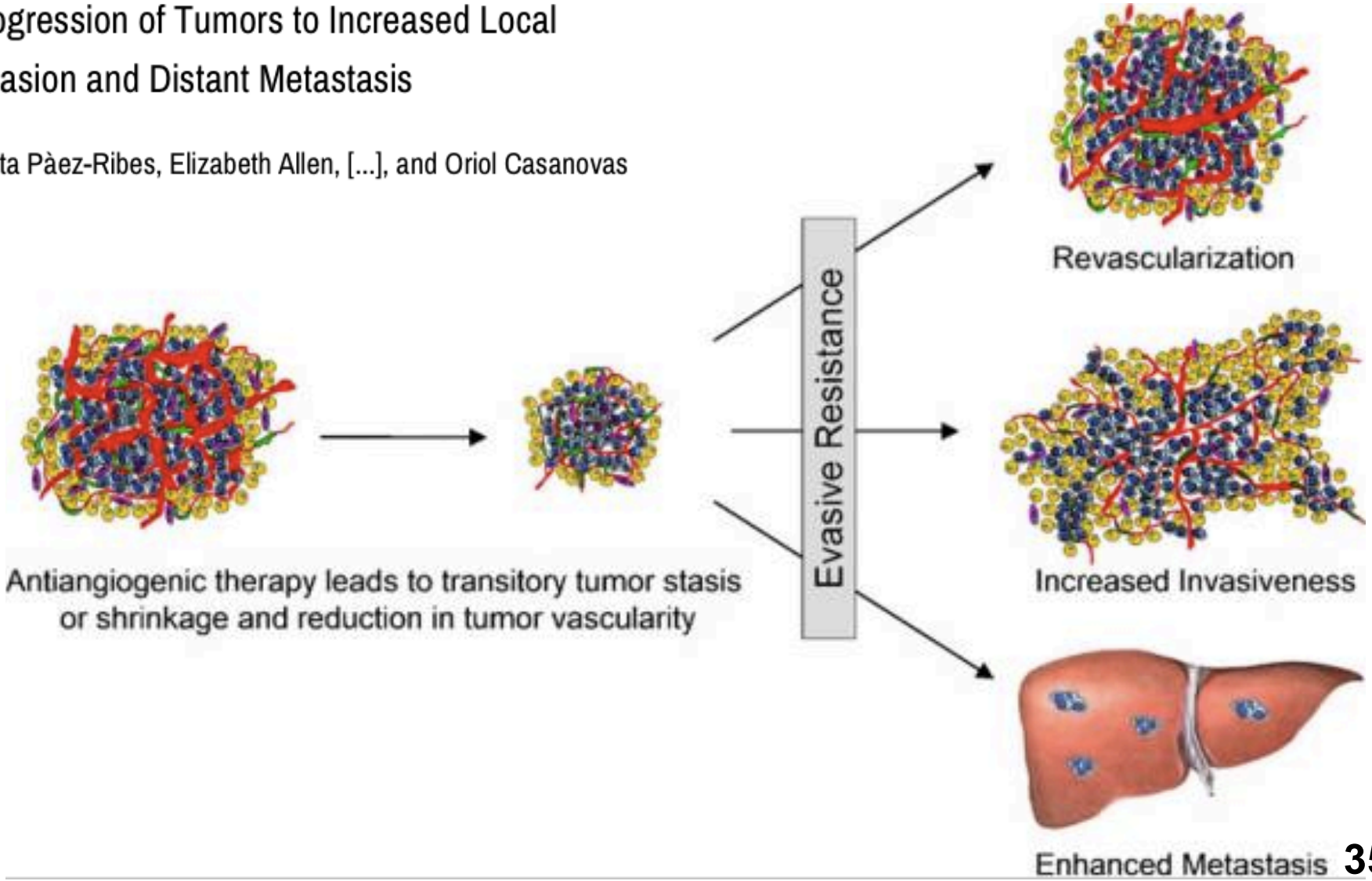


Il tessuto adiposo e i metaboliti secreti



Cancer cell
Author Manuscript
NIH Public Access

Cancer Cell 2009

Antiangiogenic Therapy Elicits Malignant Progression of Tumors to Increased Local Invasion and Distant Metastasis

Marta Pàez-Ribes, Elizabeth Allen, [...], and Oriol Casanovas