Cell adhesion molecules in cancer

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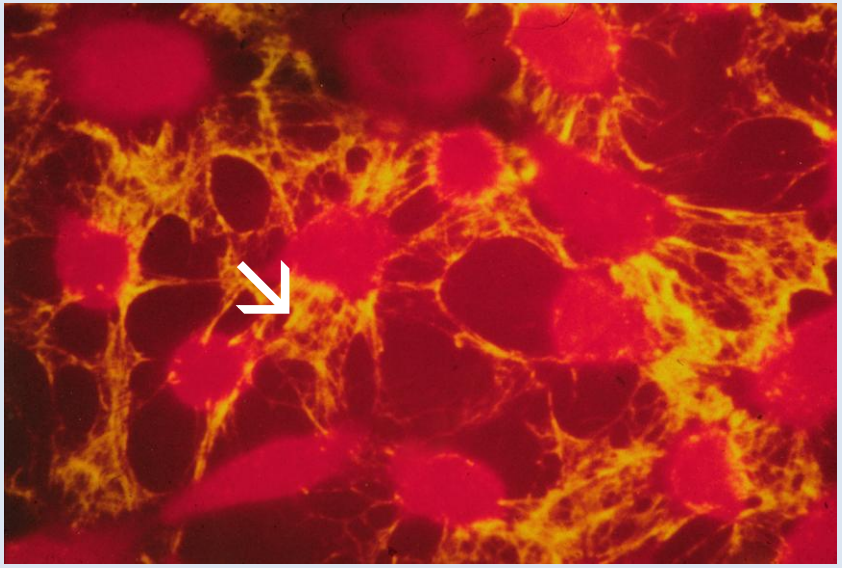
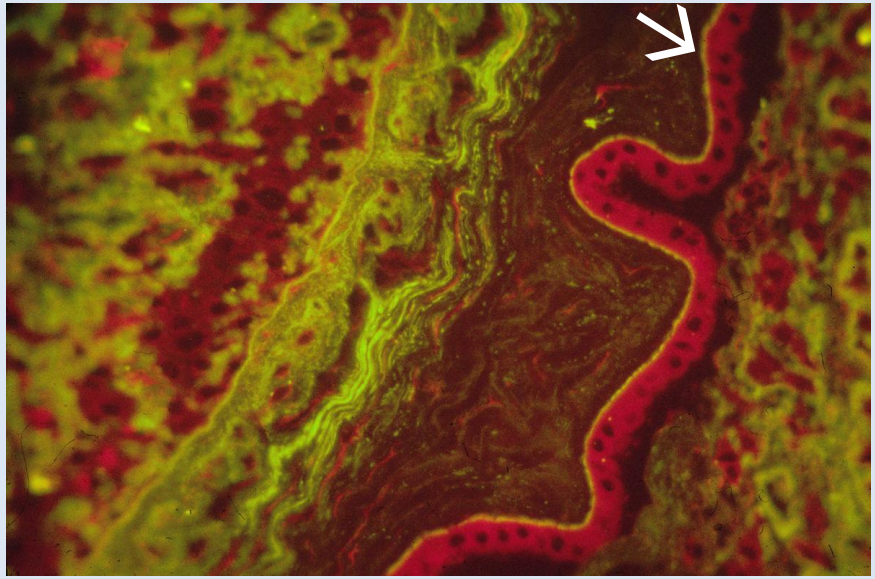


Fibronectin matrix in cell culture

Basement membranes:

Type IV collagen, laminins, nidogen, perlecan (heparan sulfate proteoglycan)

Basement membrane in tissue



Loose connective tissue:

Fibrillar collagens (types I,II, III etc), fibronectin, chondroitin sulfate proteoglycans

EXTRACELLULAR MATRIX COMPONENTS

Collagens

- Nearly 30 types
- Fibrillar collagens (types I-III)
- Non-fibrillar (type IV)

Glycoproteins

- Fibronectin
- Vitronectin
- Laminins
- Nidogens
- Tenascins
- Fibrillin
- Fibulins

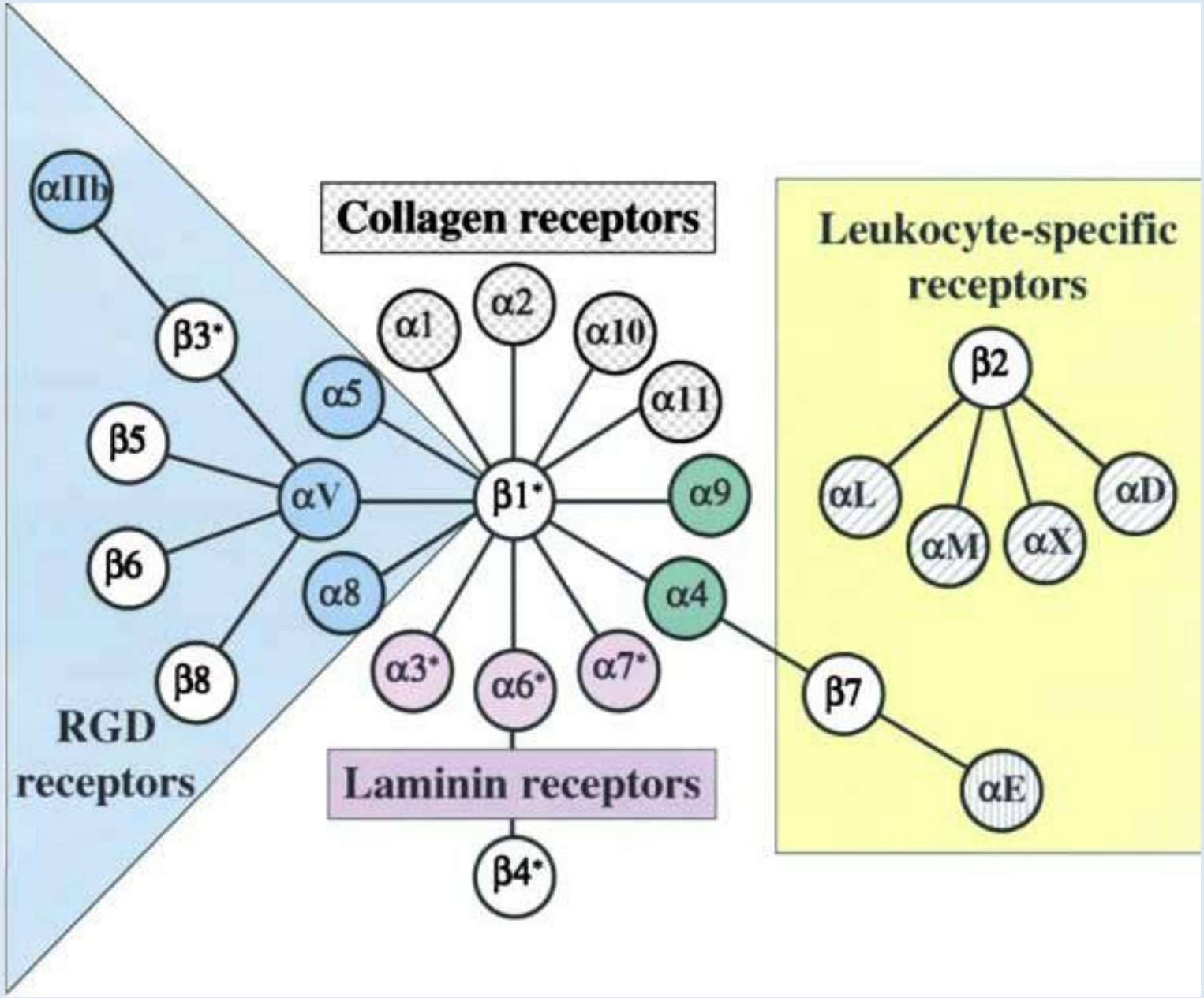
Proteoglycans

- Chondroitin/dermatan sulfate (lecticans, decorin family)
- Heparan sulfate (perlecan)
- Hyaluronic acid (no protein)

Plasma adhesion proteins

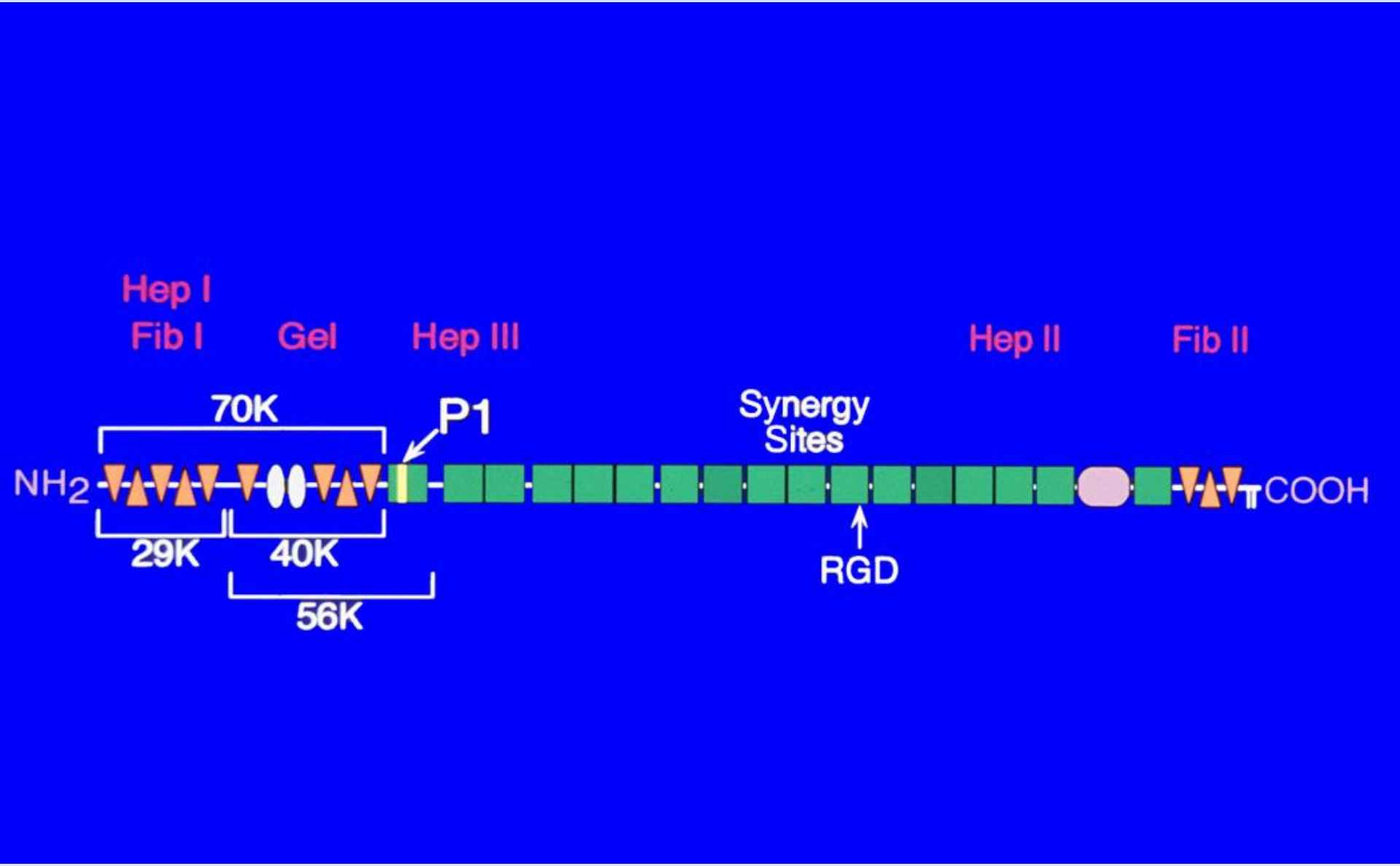
- Fibronectin
- Vitronectin
- Fibrinogen
- von Willebrand factor

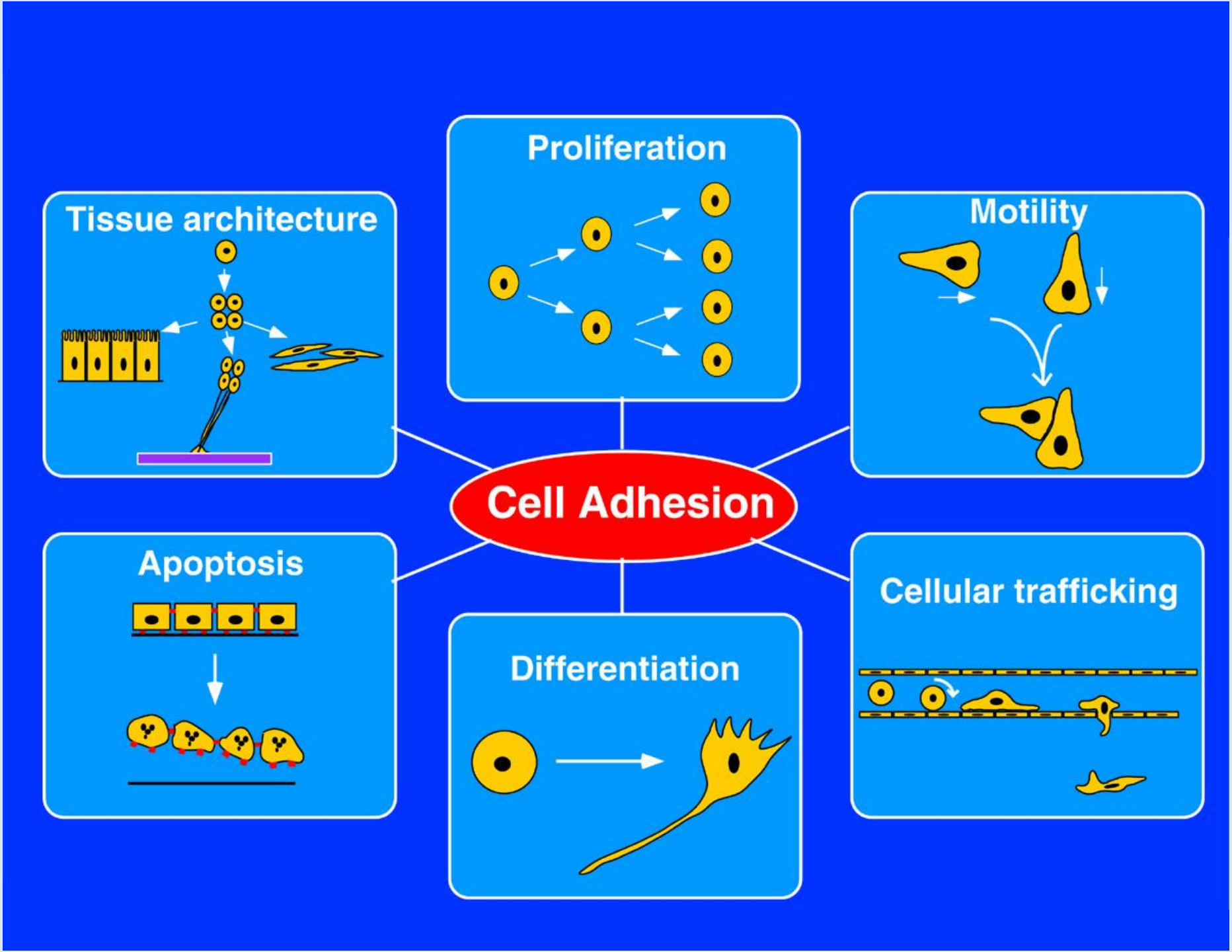
Integrin heterodimers and their binding activities



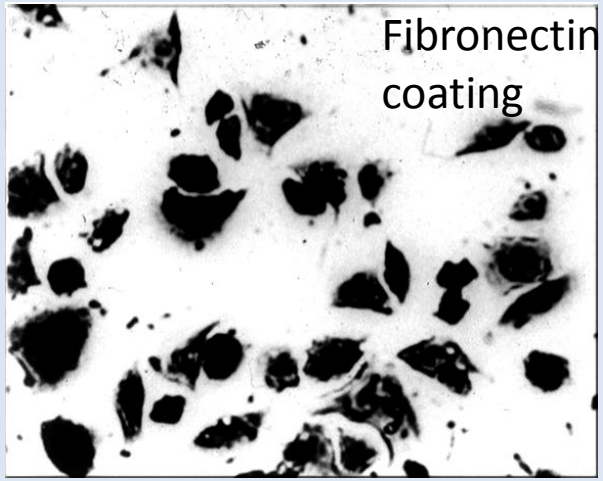
Hynes, Cell, 2002

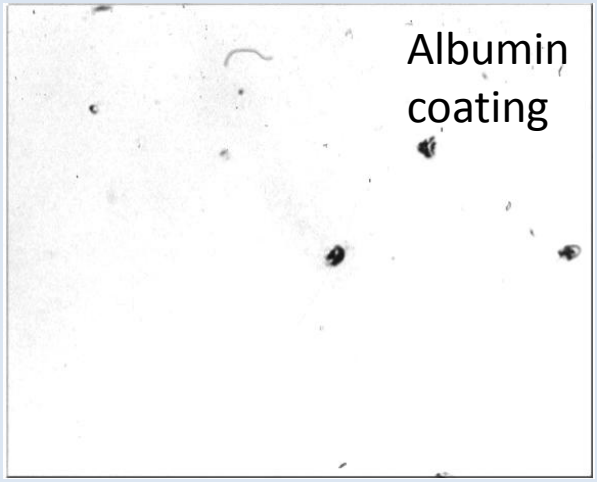
Fibronectin monomer: Domain structure




Proliferation
Tissue architecture
Motility
Cell Adhesion
Apoptosis
Cellular trafficking
Differentiation

Cell attachment assay





Robert Klebe

RGD: the integrin-binding motif

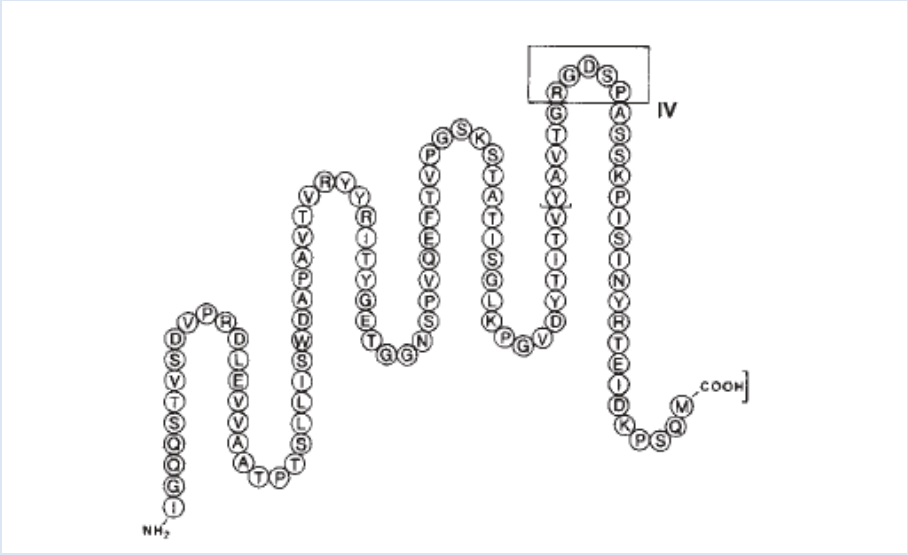
30 ARTICLES NATURE VOL. 309 3 MAY 1984

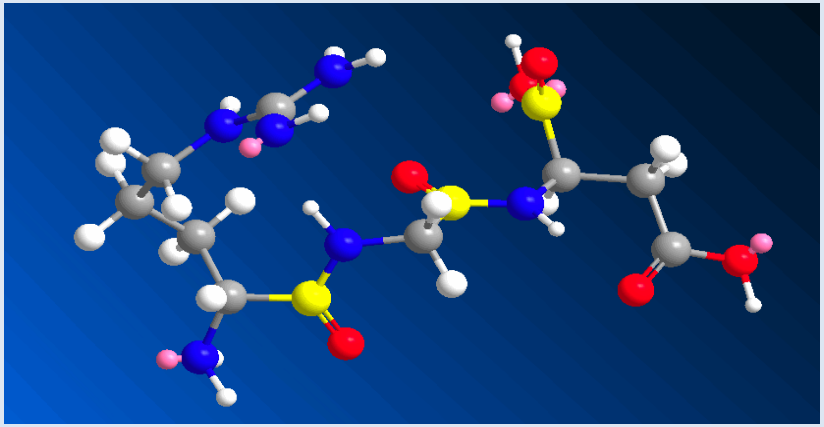
Cell attachment activity of fibronectin can be duplicated by small synthetic fragments of the molecule

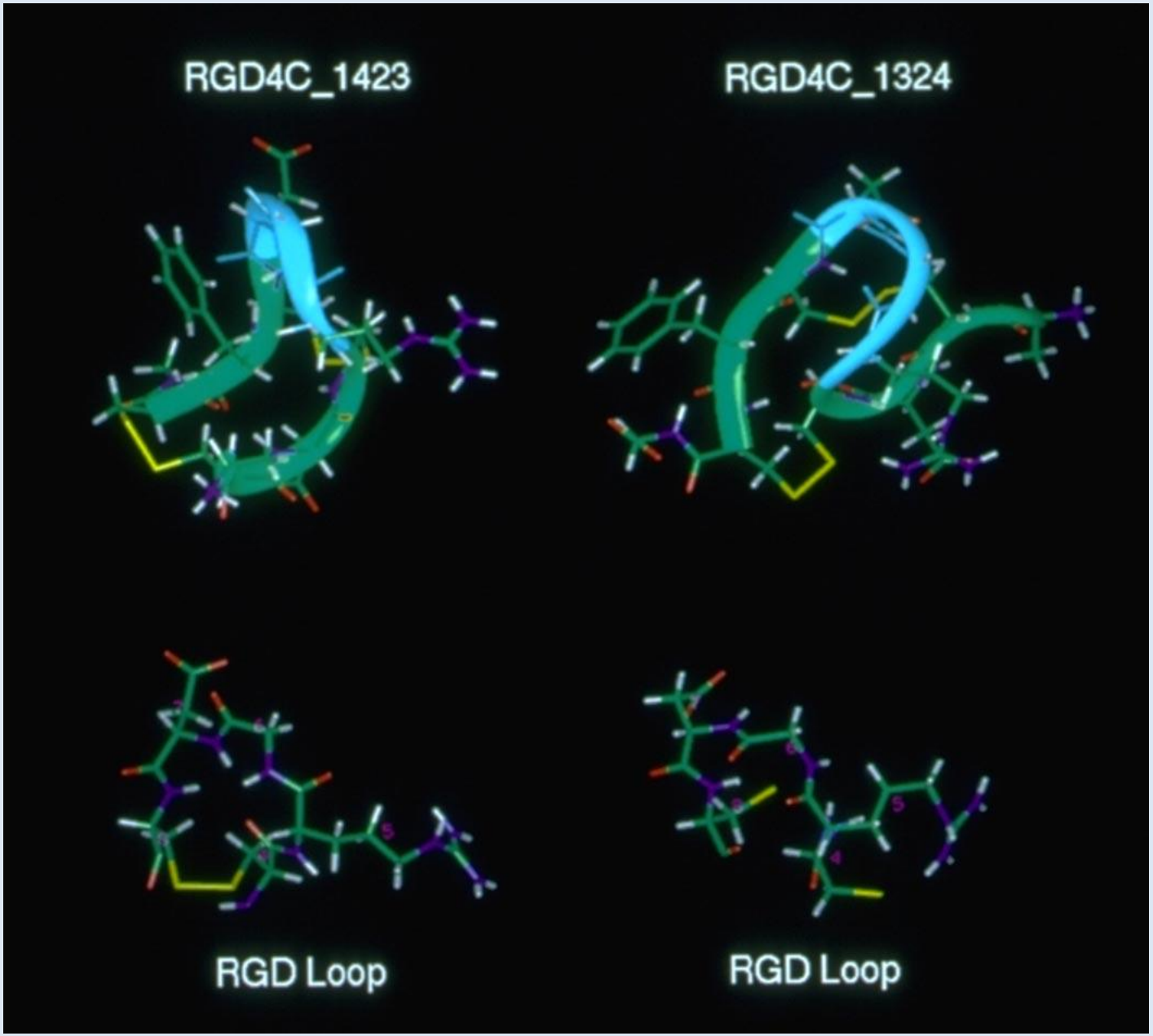
Michael D. Pierschbacher & Erkki Ruoslahti

Cancer Research Center, La Jolla Cancer Research Foundation, 10901 North Torrey Pines Road, La Jolla, California 92037, USA

The ability of fibronectin to bind cells can be accounted for by the tetrapeptide L-arginyl-glycyl-L-aspartyl-L-serine, a sequence which is part of the cell attachment domain of fibronectin and present in at least five other proteins. This tetrapeptide may constitute a cellular recognition determinant common to several proteins.

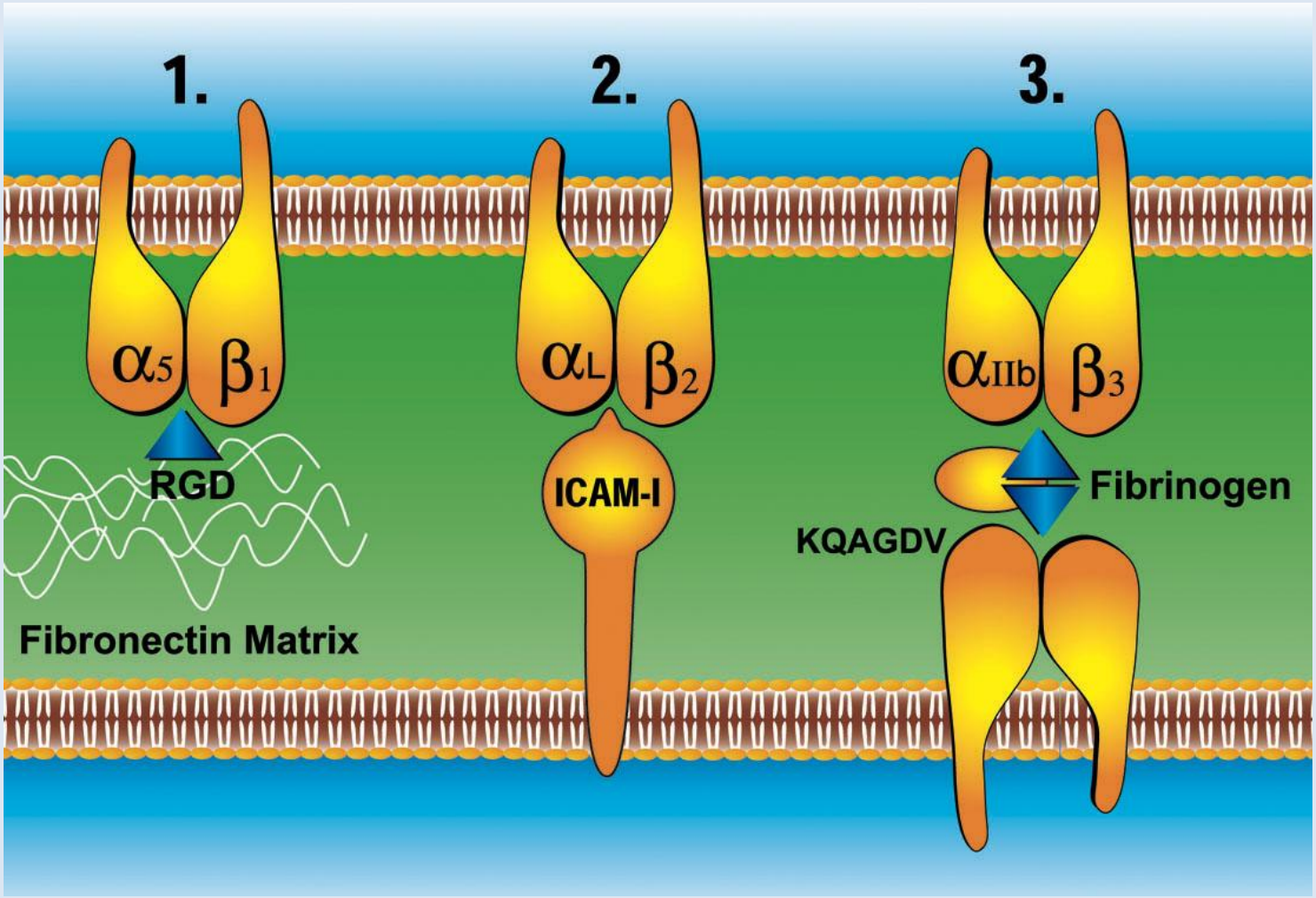


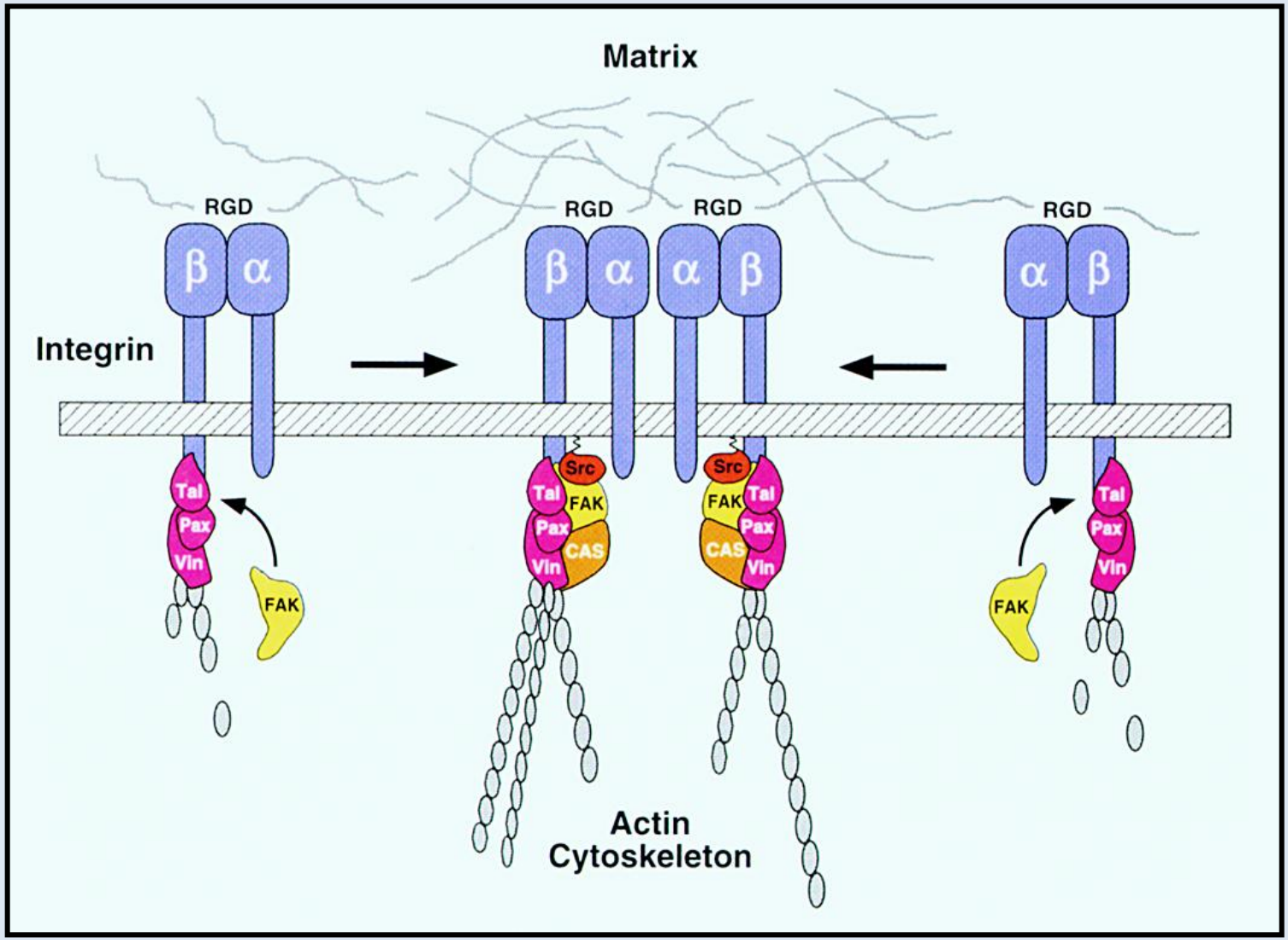




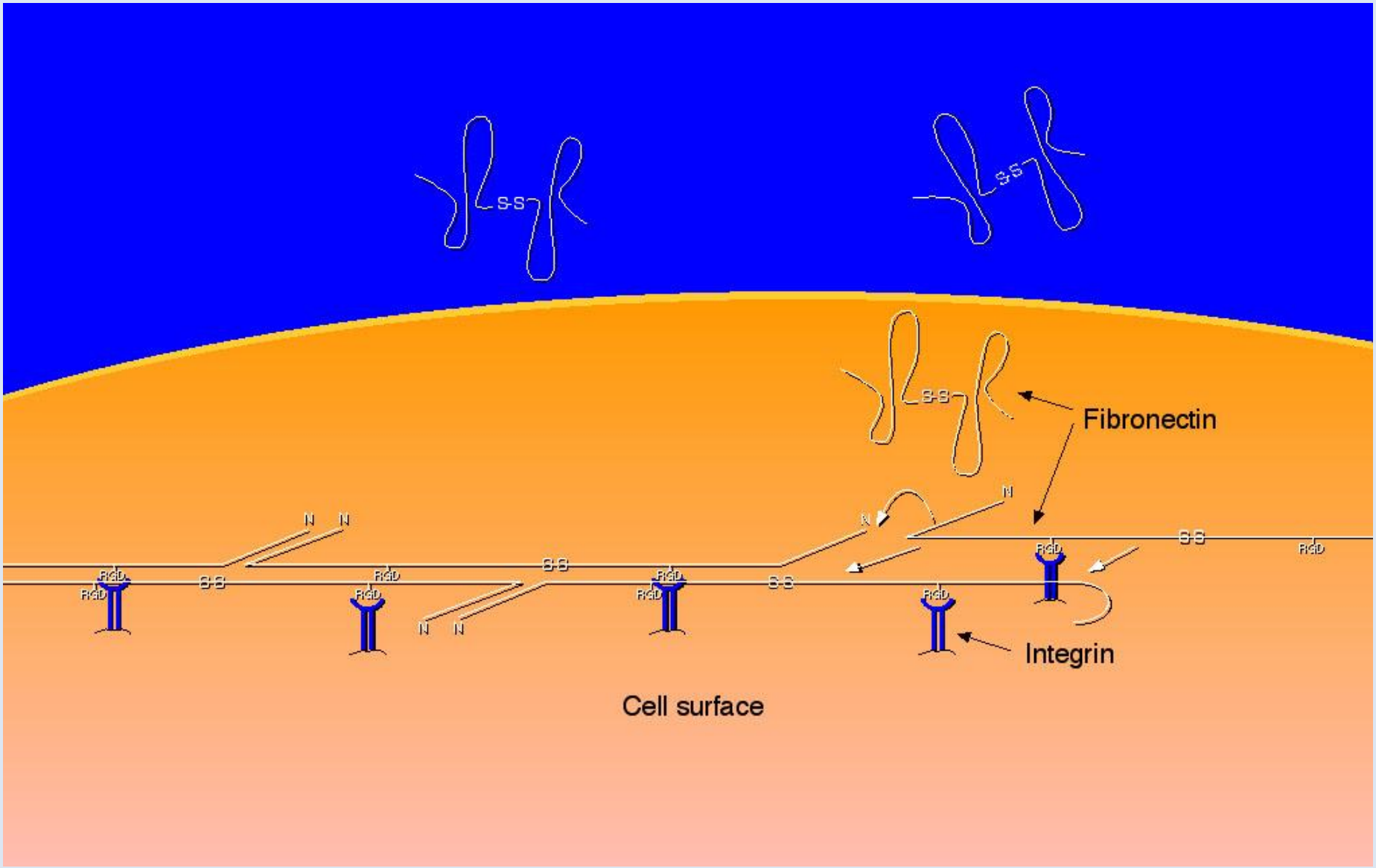
Assa-Munt at a., *Biochemistry, 2001*

Integrins mediate cell adhesion through multiple mechanisms

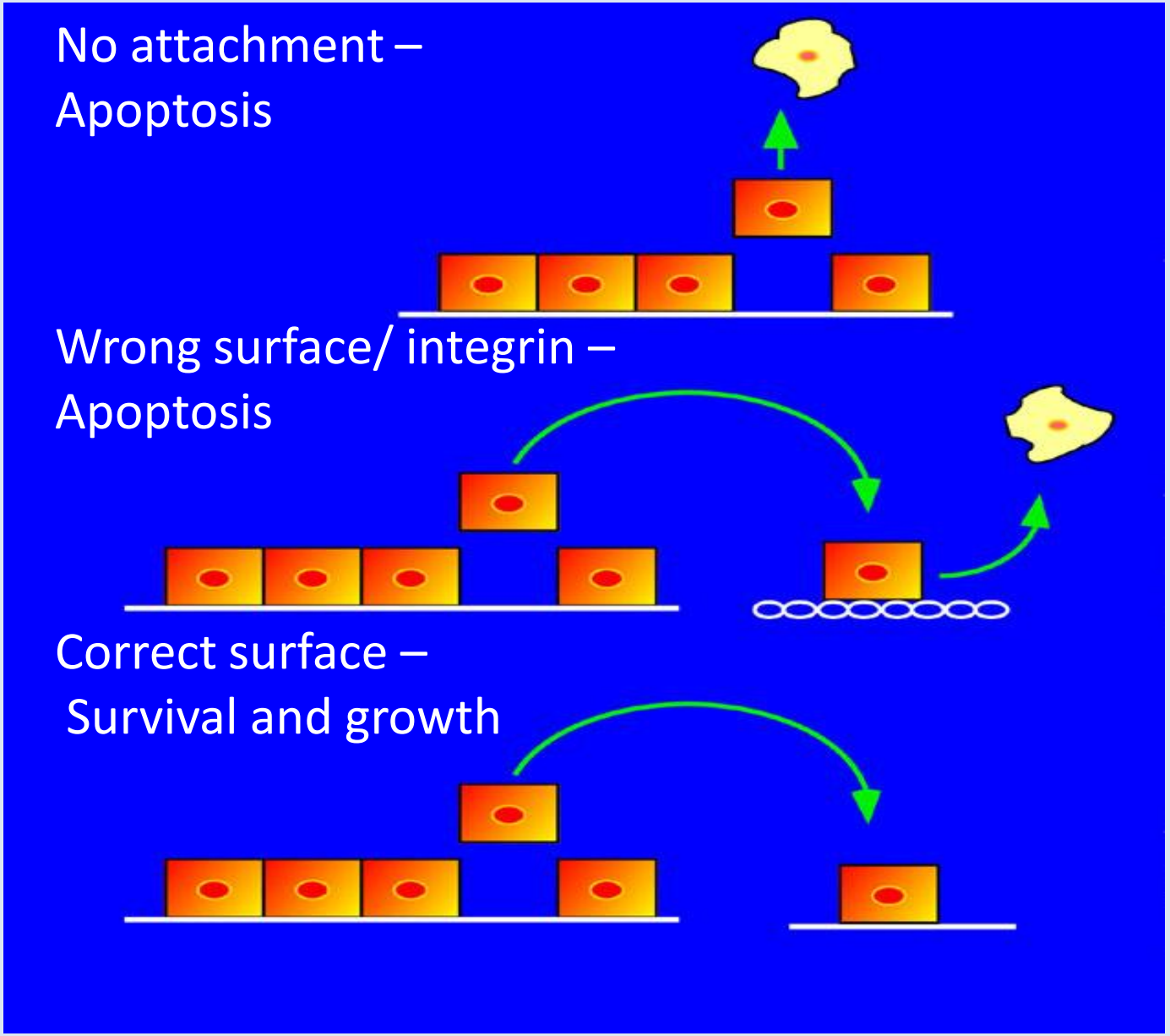



Matrix
RGD
RGD
RGD
RGD
Integrin
β
α
α
β
Tal
Pax
Vin
FAK
Src
FAK
CAS
Actin
Cytoskeleton

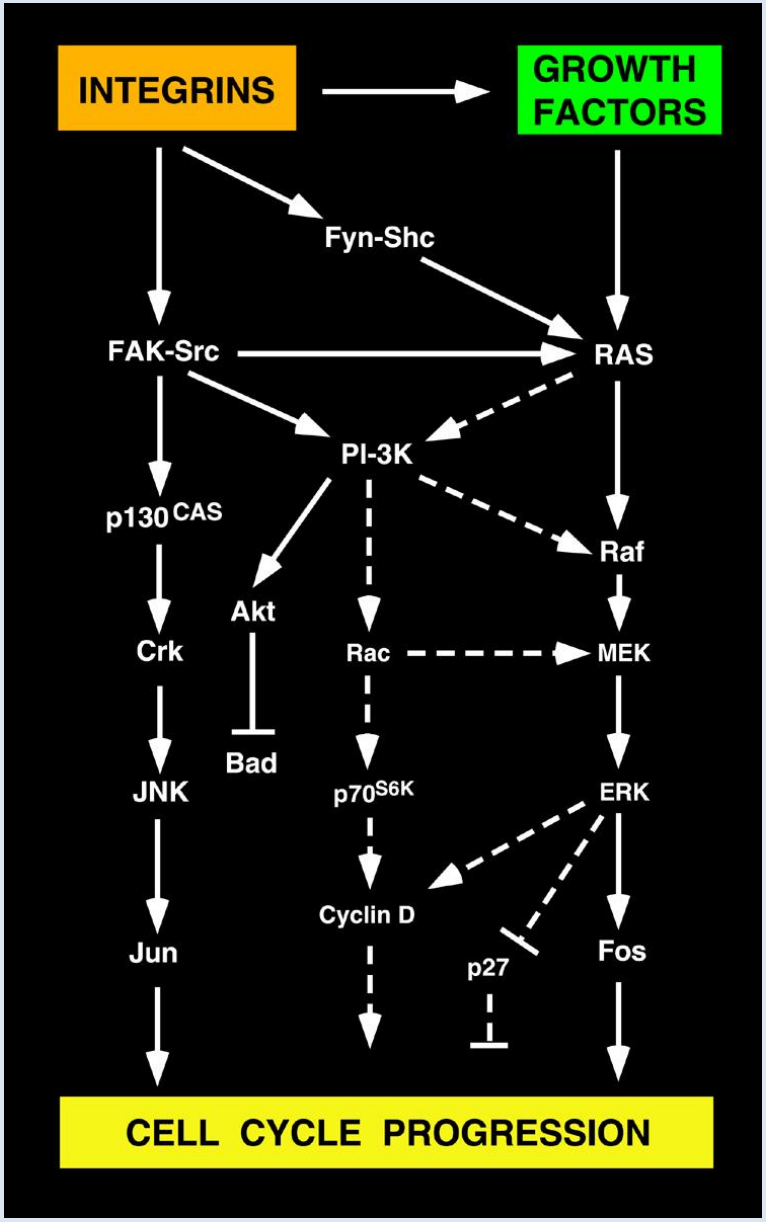
Integrins assemble fibronectin matrix



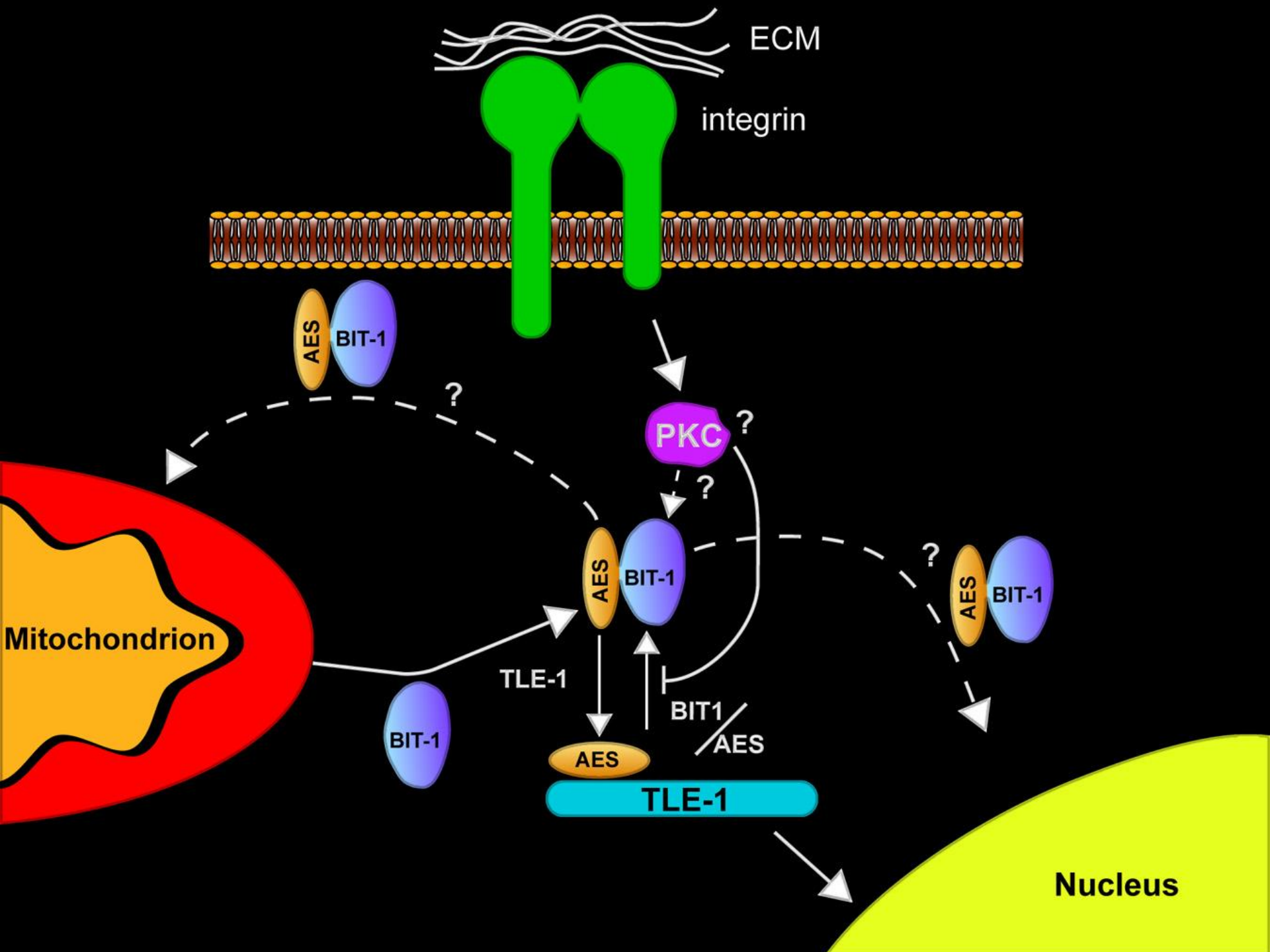
Anoikis: Cell death by apoptosis upon detachment



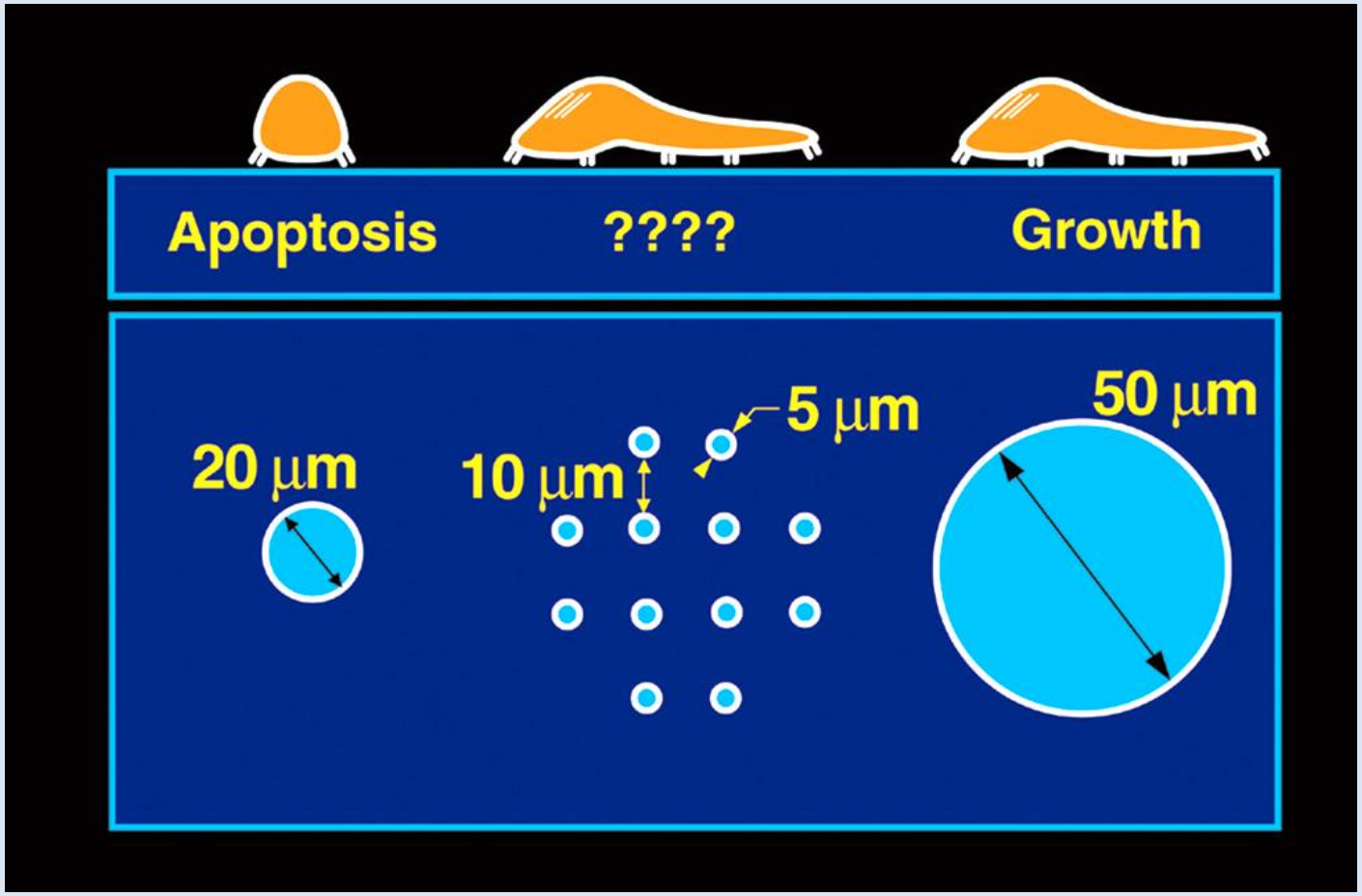
Cell adhesion-growth factor interplay



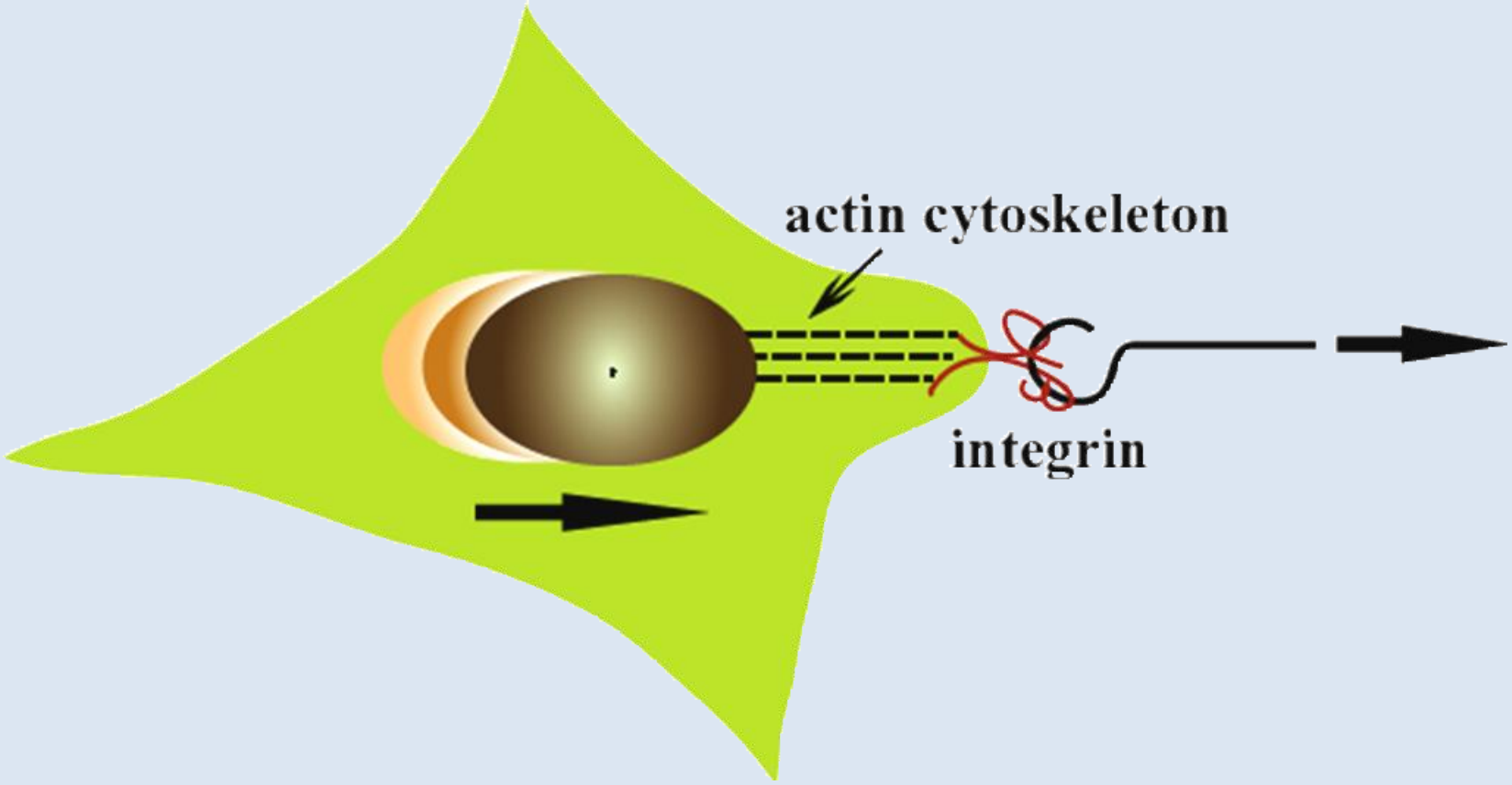
Giancotti and Ruoslahti, *Science*, 1999


ECM
integrin
AES
BIT-1
?
PKC
?
?
AES
BIT-1
?
AES
BIT-1
Mitochondrion
TLE-1
BIT-1
BIT1
AES
AES
TLE-1
Nucleus

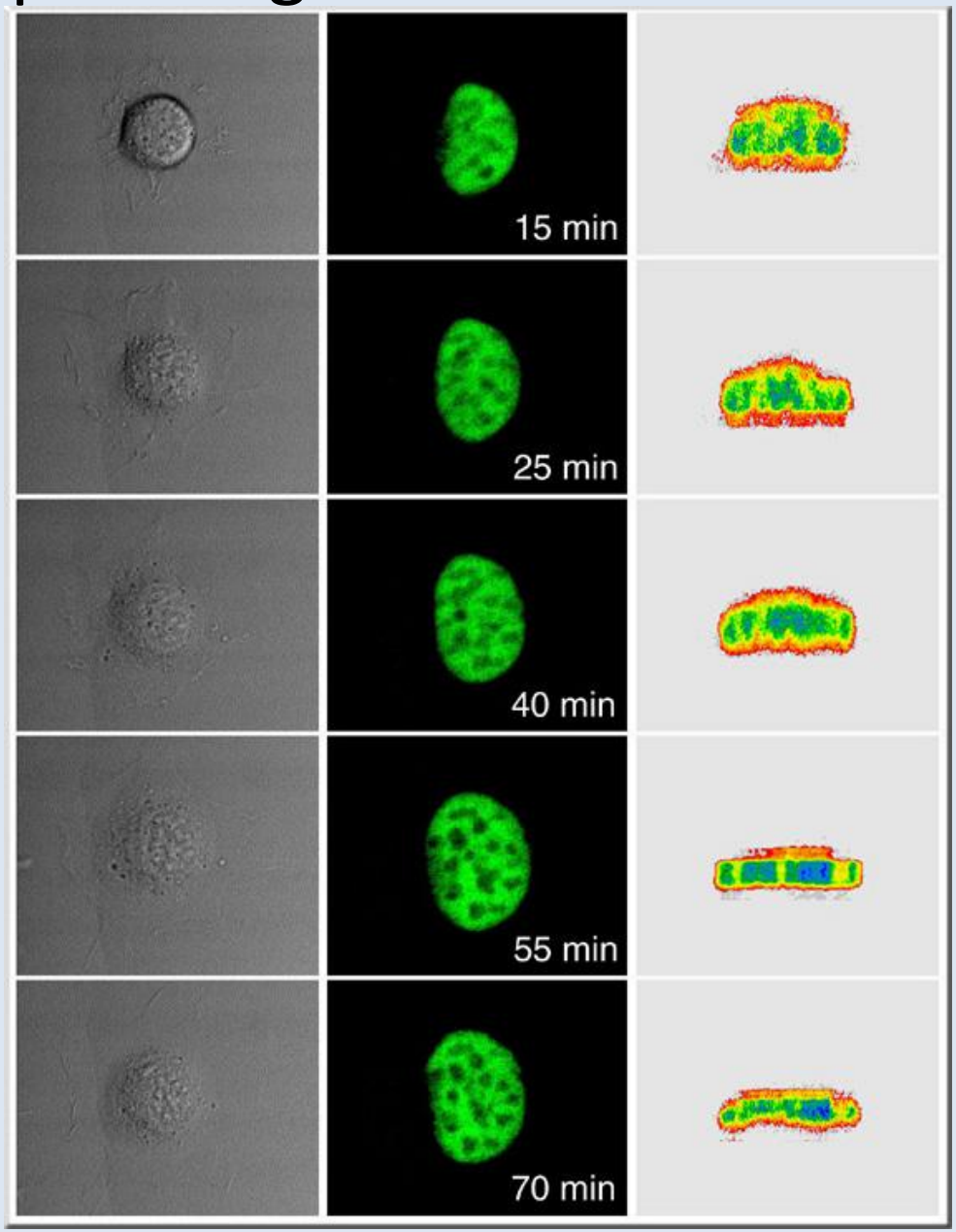
Cell spreading promotes survival and growth



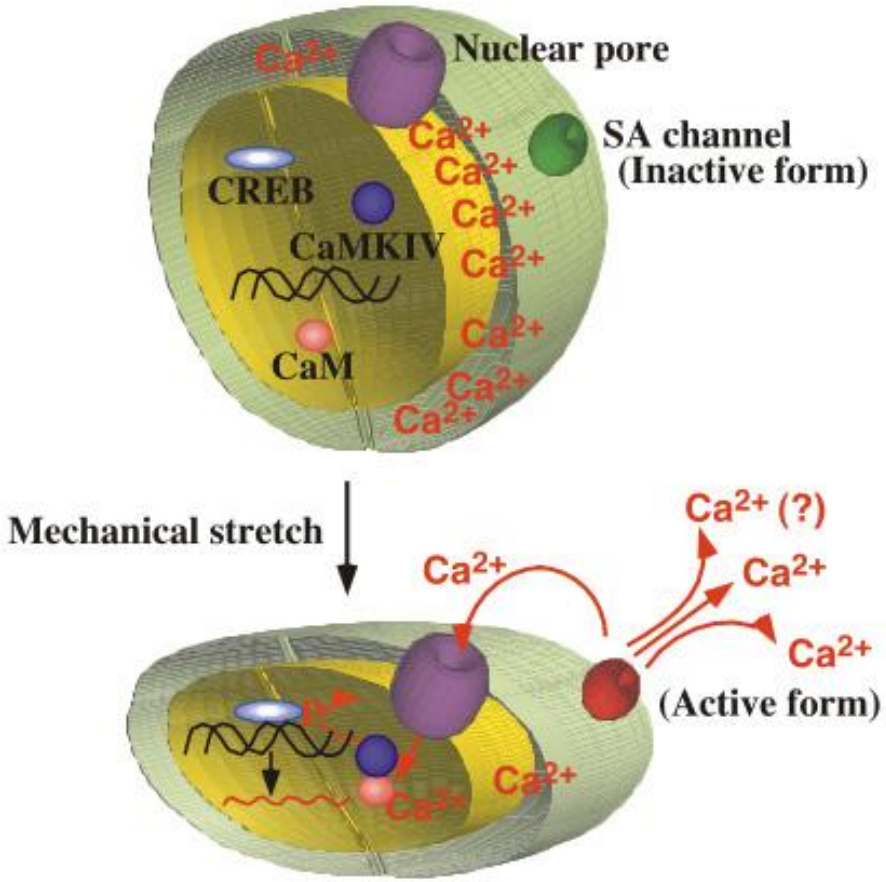
Inberg et al., *Science,* 1998

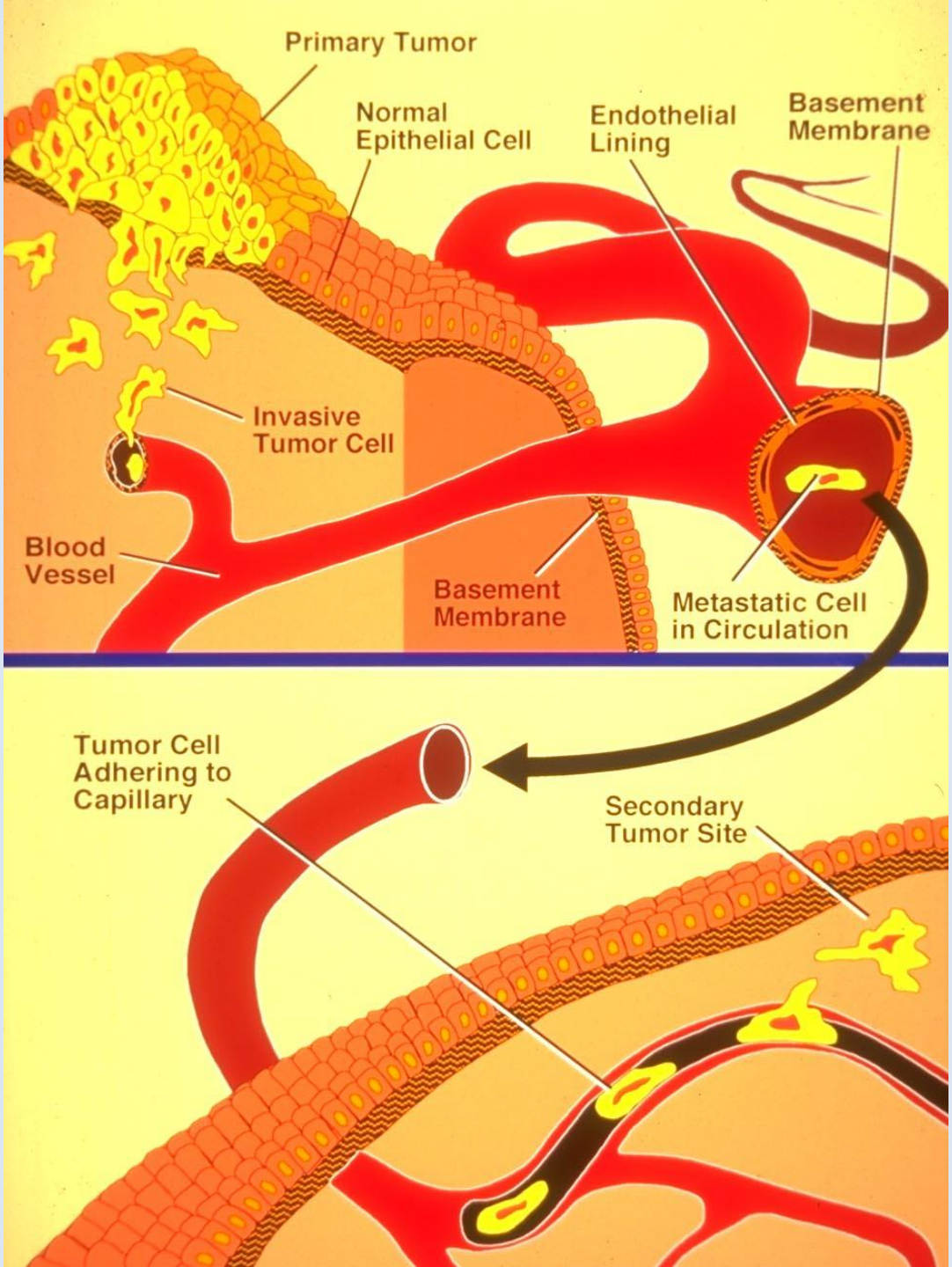

actin cytoskeleton
integrin

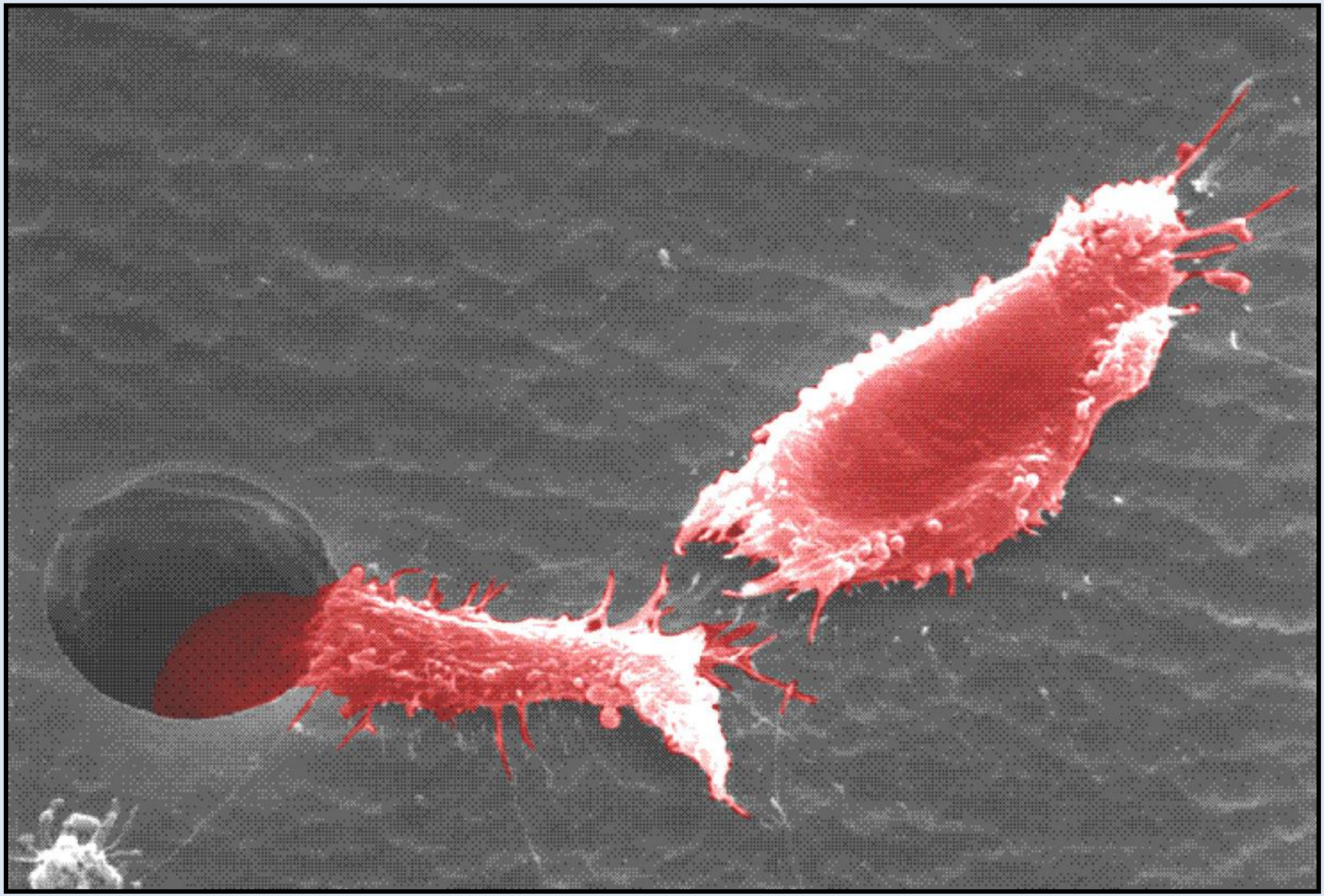
Cell spreading stretches the nucleus



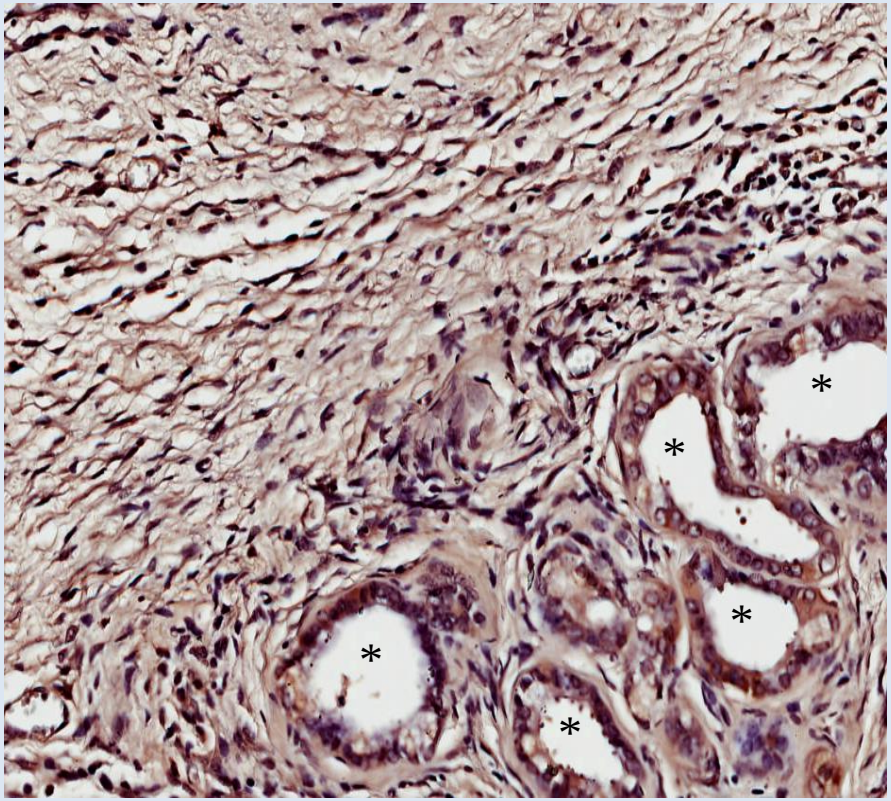
Itano et a., *PNAS,* 2003

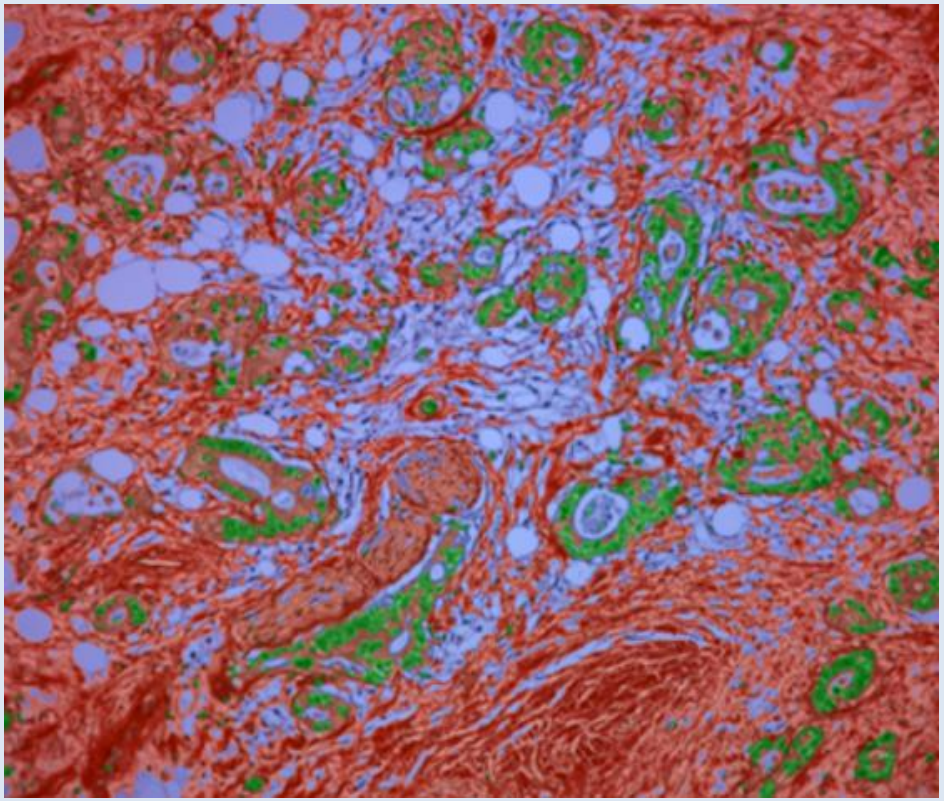

Nuclear pore
SA channel
(Inactive form)
CREB
CaMKIV
CaM
Ca2+
Mechanical stretch
Ca2+ (?)
(Active form)


Primary Tumor
Normal Epithelial Cell
Endothelial Lining
Basement Membrane
Invasive Tumor Cell
Blood Vessel
Basement Membrane
Metastatic Cell in Circulation
Tumor Cell Adhering to Capillary
Secondary Tumor Site



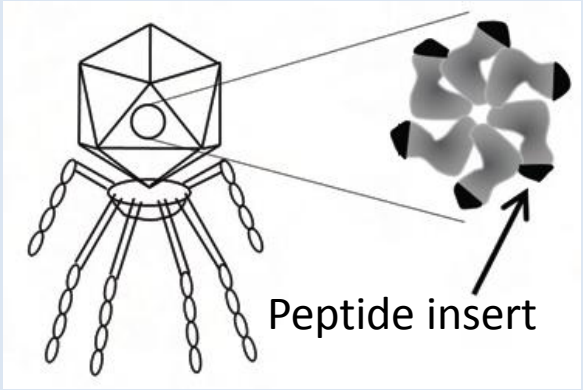
Fibrosis in tumors





In vivo vascular targeting with phage libraries: Vascular zip codes

T7 phage

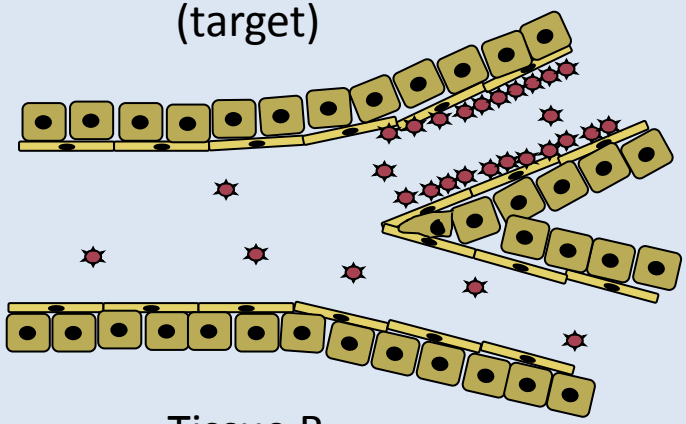


Pasqualini and Ruoslahti, *Nature*, 1996

Vascular zip codes

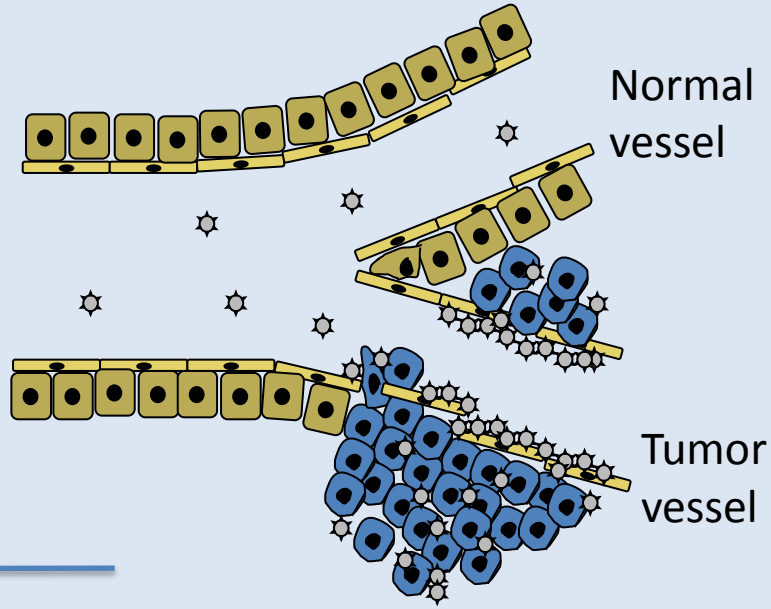
Target a normal organ

Tissue A
(target)



Tissue B
(non-target)

Target tumor vasculature



Homing peptide → Synaphic drug targeting

Vascular Zip codes

- The vasculature of each normal tissue expresses markers unique to that tissue (brain, kidney, heart, lung, pancreas, muscle, fat, adrenal, retina, uterus, placenta, prostate)
- Tumor blood vessels differ from vessels in normal tissues (tumor-penetrating peptides)
- Tumor lymphatics differ from lymphatics in normal tissues
- Wound vasculature differs from normal vasculature
- Atherosclerotic plaque endothelium differs from normal endothelium (overlap with cancer)
- Inflammation has a zip code that partially overlaps with cancer
- Other diseases will also likely put a specific signature to the vessels in the lesions
- The markers of vessels enable: specific imaging probes, guided drugs, and discovery of druggable targets

Tumor-homing Peptides

Peptide	Receptor	Reference
Blood Vessels		
CRGDC and NGR motif	$\alpha_v\beta_3$ and $\alpha_v\beta_5$ integrins	Arap et al.,*Science*, 1998
F3, 34-aa peptide	Cell surface nucleolin	Porkka et al., *PNAS*, 2002;; Christian et al., *JCB*, 2003
CGKRK	p32/gC1qR	Hoffman et al., *Cancer Cell*, 2003; Agemy et al. unpubl.
CAR (CARSKDKC)	Variant heparan sulfate?	
CRK (CRKDKC)	Not known	Jarvinen and Ruoslahti, 2007
iRGD (CRGDK/RGPDC)	Integrins and neuropilin-1	Sugahara, Teesalu et al., Cancer Cell, 2009; Science, 2010
Lymphatic Vessels and Tumor Macrophages		
LyP-1 (CGNKRTRGC)	p32/gC1qR	Laakkonen et al., *Nat. Med.* 2002; *PNAS*, 2004
LSD, REA 9-aa cyclic peptides	Not known	Zhang et al., *Cancer Res. 2006*
Vessel/Tumor ECM		
CSG (9-aa cyclic peptide)	Epitope in matrigel	Hamzah, Biliran et al., unpublished
Plasma Clots		
CLT1/2 (10-aa cyclic peptides)	Epitope in fibrin/fibronectin deposits	Pilch et al., *PNAS*, 2006
CREKA	Epitope in fibrin deposits	Simberg et al., *PNAS*, 2007; Agemy et al., *Blood*, 2010

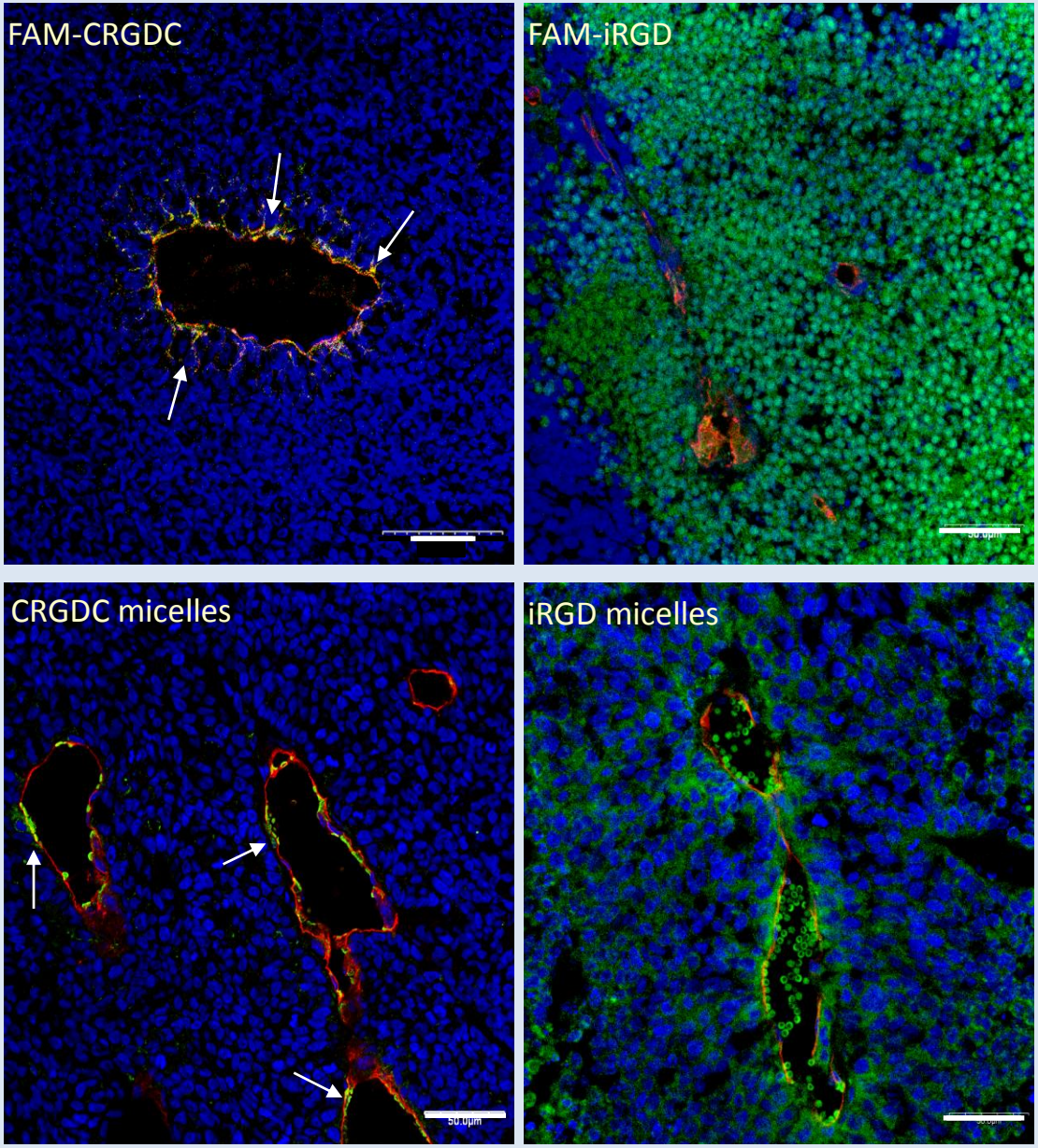
iRGD penetrates into tumor tissue

Old RGD technology

New iRGD technology

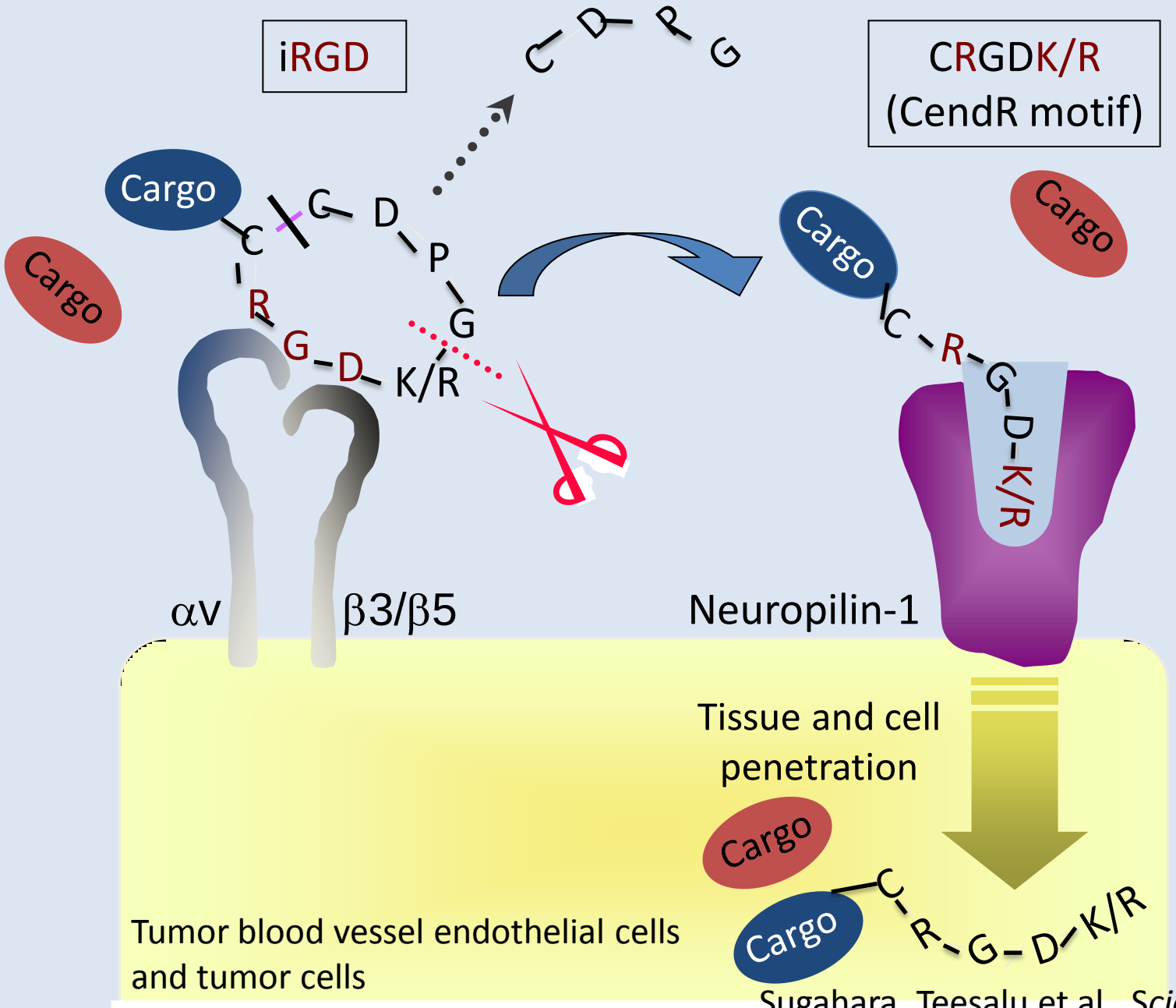
Synthetic peptides

Nanoparticles



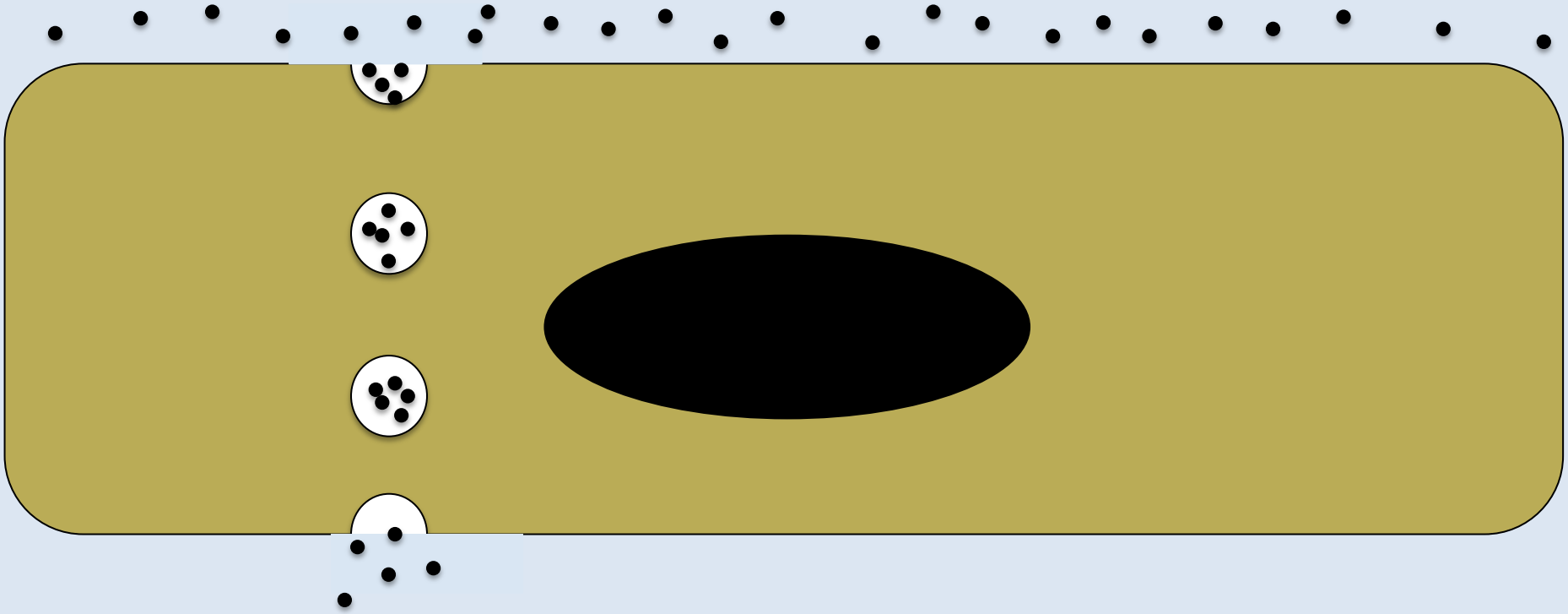
Sugahara, Teesalu et al., *Cancer Cell*, 2009

iRGD enhances tumor penetration of coupled and non-coupled cargo

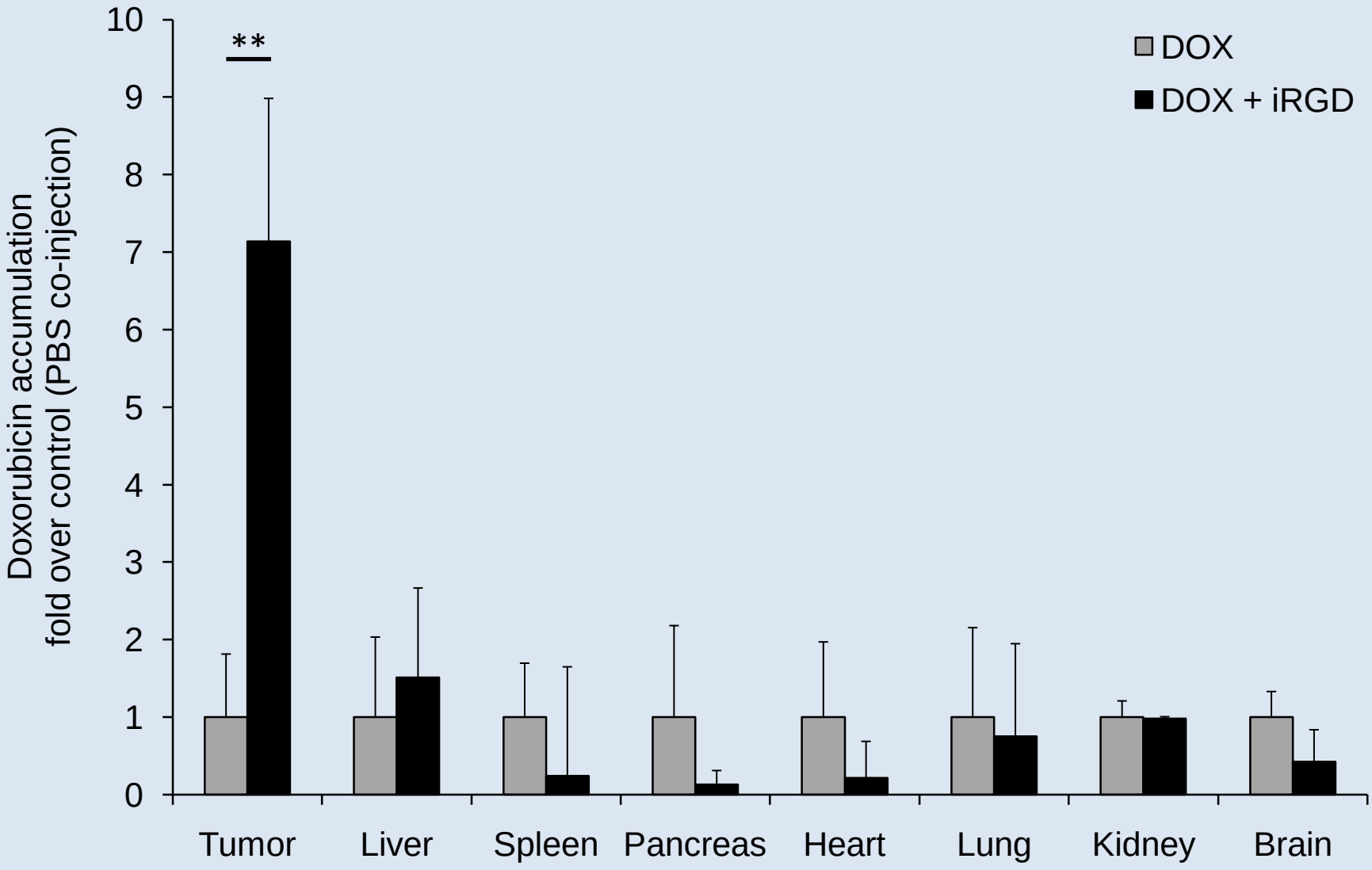


Sugahara, Teesalu et al., *Science*, 2010

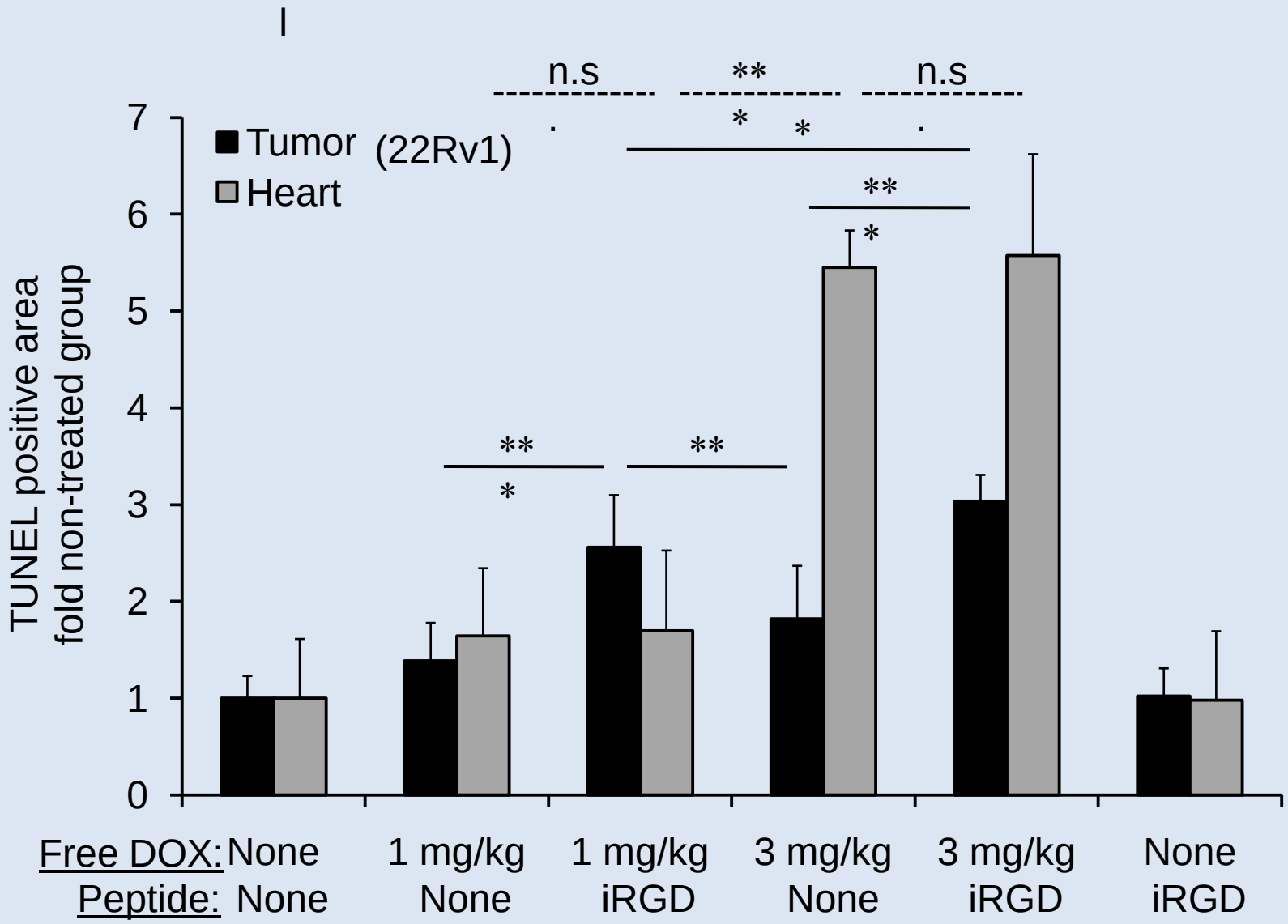
Hypothetical mechanism of CendR transport



Co-administration of iRGD increases the accumulation of doxorubicin (DOX) in orthotopic 22Rv1 prostate tumors



iRGD co-injection increases DOX anti-tumor activity but not its cardiotoxicity In the 22Rv1 model

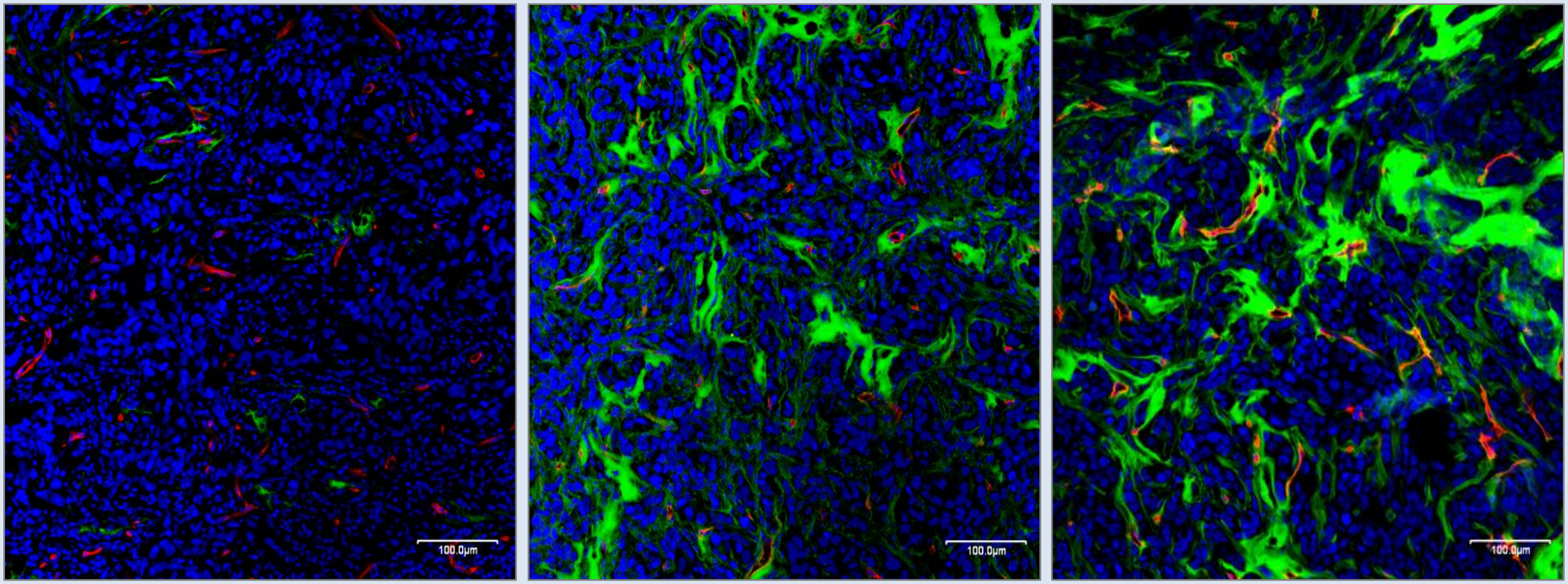


Spreading of Abraxane (ABX) in BT474 breast tumors after delivery with the iRGD co-administration method

FAM-ABX

iRGD-ABX (conjugate)

iRGD+ABX (combination)



FAM-ABX, CD31, DAPI

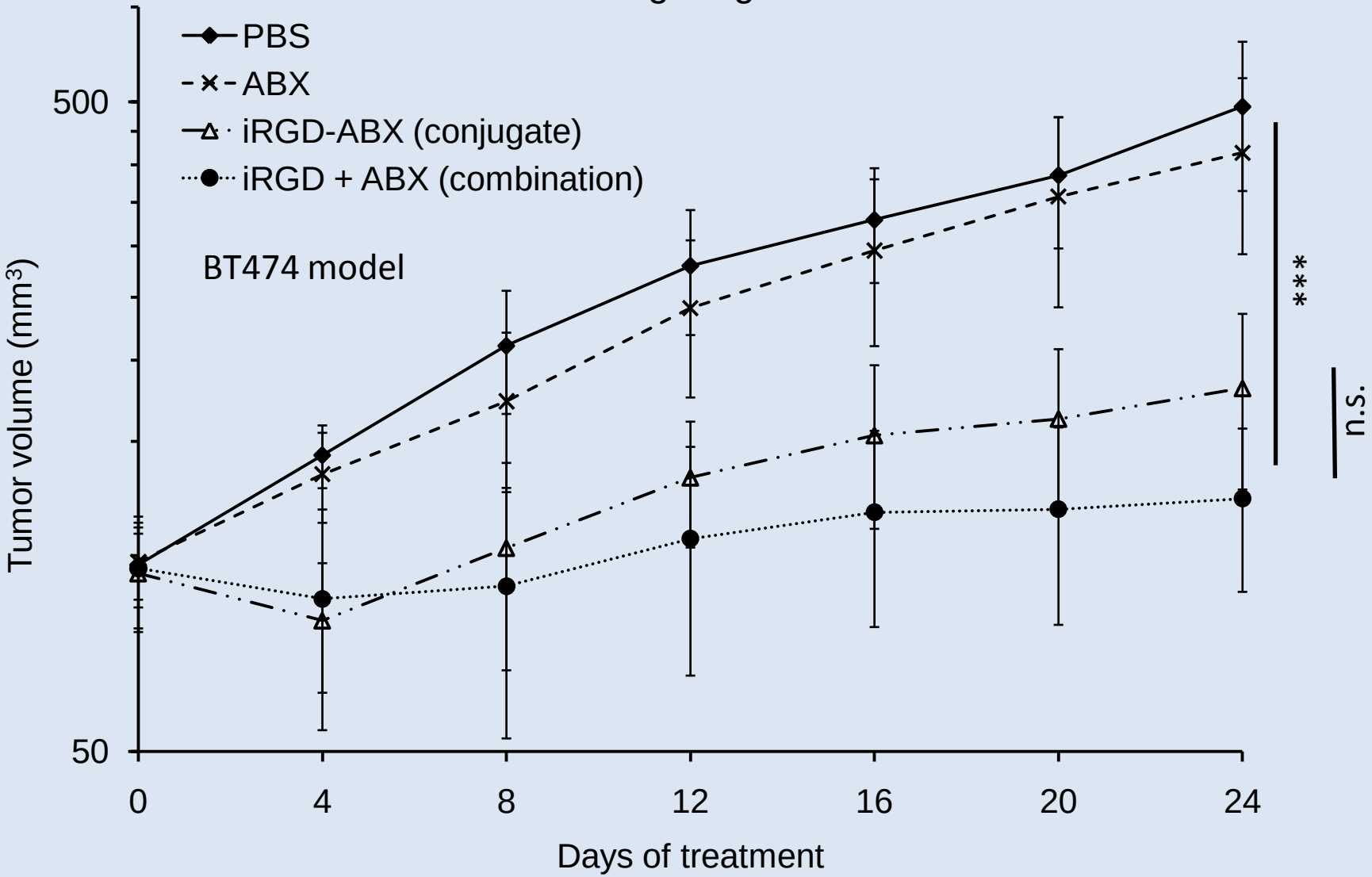
ABX compounds (3 mg/kg) were intravenously injected and allowed to circulate for 3 hours

Sugahara, Teesalu et al., *Science*, 2010

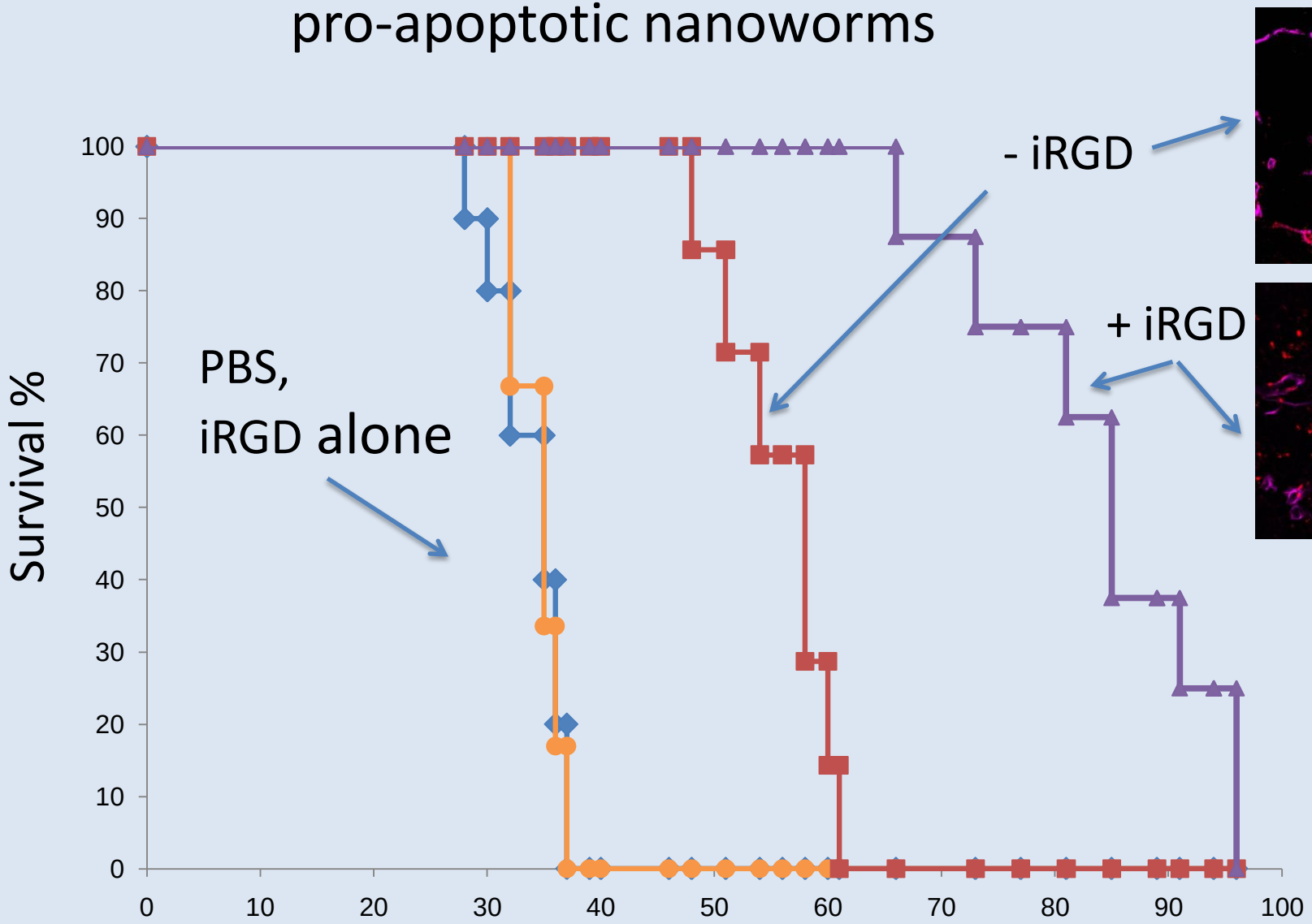
iRGD enhances the activity of Abraxane

Co-administering iRGD and Abraxane is at least as efficient as the conjugate

Overcoming drug resistance?



iRGD enhances the activity of targeted, pro-apoptotic nanoworms



Agemy, Friedmann-Morvinski et al., *PNAS,* 2011

Summary on homing peptides

- Homing peptides can deriver drugs diagnostics, and other compounds to a specific target tissue, cell, and subcellular sites
- Tumor-penetrating and tissue-penetrating peptides make it possible to deliver targeted payloads beyond the vasculature

”Cell adhesion molecules in cancer”

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Conflict of interest disclosure:

- CendR Therapeutics Inc
- Vascular BioSciences Inc.
- EnduRx Therapeutics Inc.