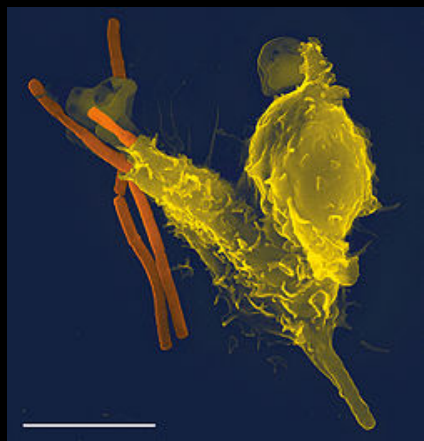


A high-magnification, grayscale electron micrograph showing a dense cluster of cells. The cells exhibit various shapes, including elongated, rod-like structures and more rounded, irregular forms. The overall texture is granular and complex, typical of biological tissue at the cellular level.

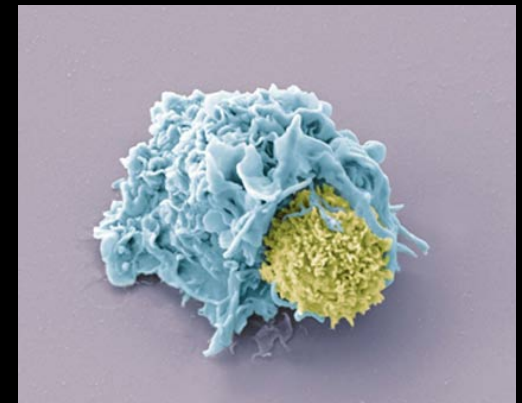
“Differenziamento delle cellule del Sistema Immunitario”

Silvia Campello

Univeristà di Tor Vergata
Roma 24.04.2012



SISTEMA IMMUNITARIO



IMMUNITÀ INNATA

Meccanismi di difesa presenti sempre;
Indipendenti dall'esposizione al patogeno



NON specifici per il patogeno

NON ha tempo di latenza
NON ha memoria

IMMUNITÀ ACQUISITA

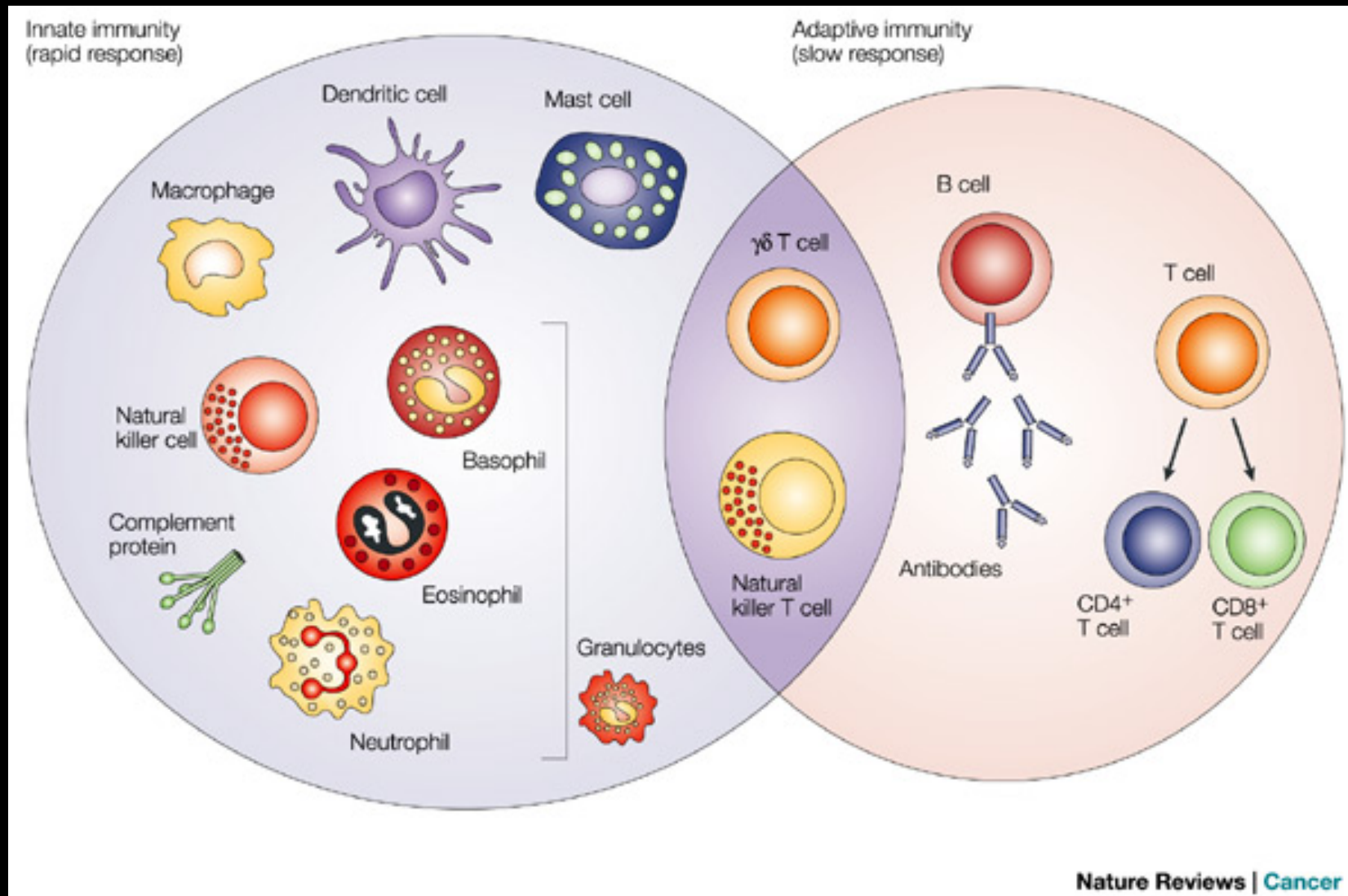
Meccanismi di difesa stimolati
dall'incontro col patogeno



specifici per il patogeno

Ha tempo di latenza
Ha memoria

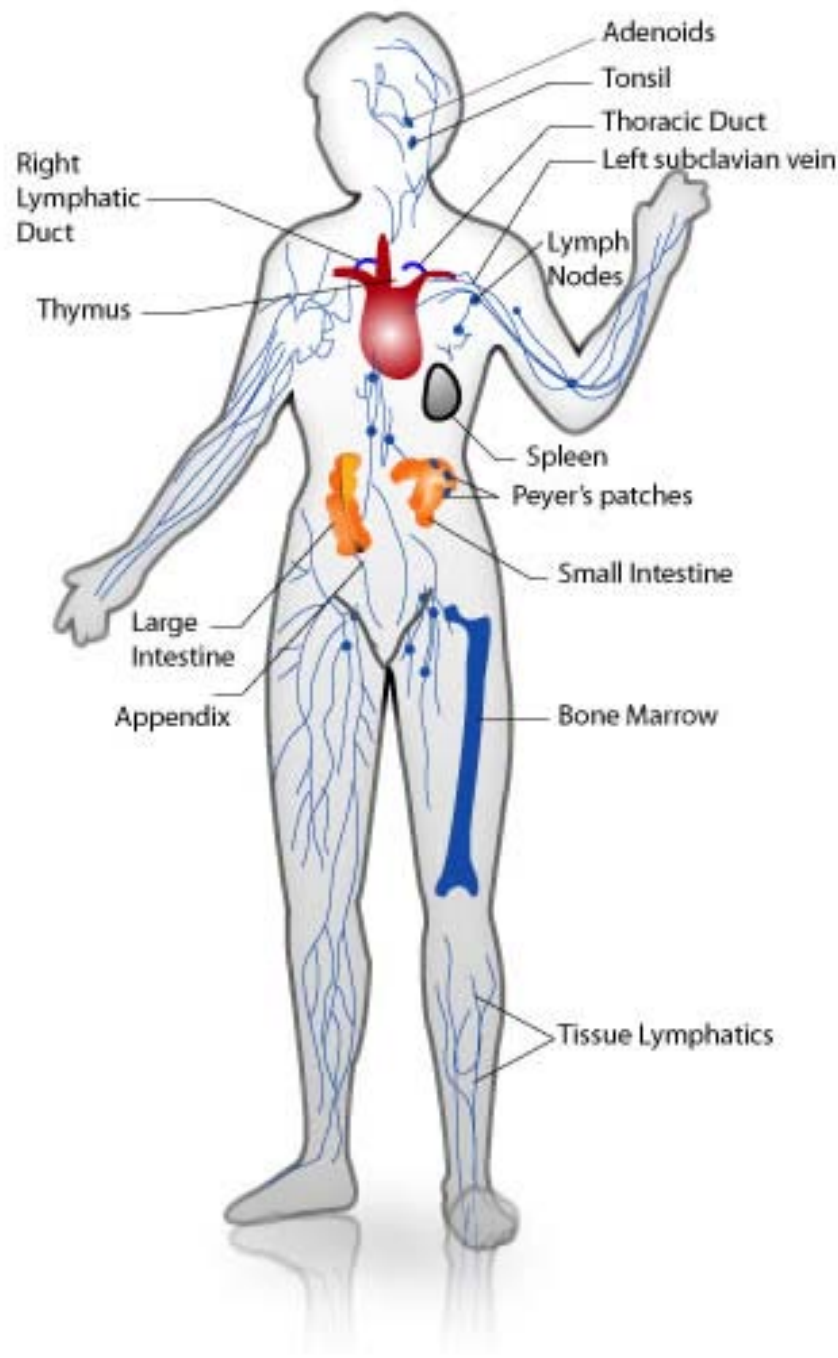
I due sistemi collaborano per l'eliminazione del patogeno



The innate immune response functions as the first line of defence against infection.

The adaptive immune response is slower to develop, but manifests as increased specificity and memory.

LYMPHATIC SYSTEM AND ORGANS

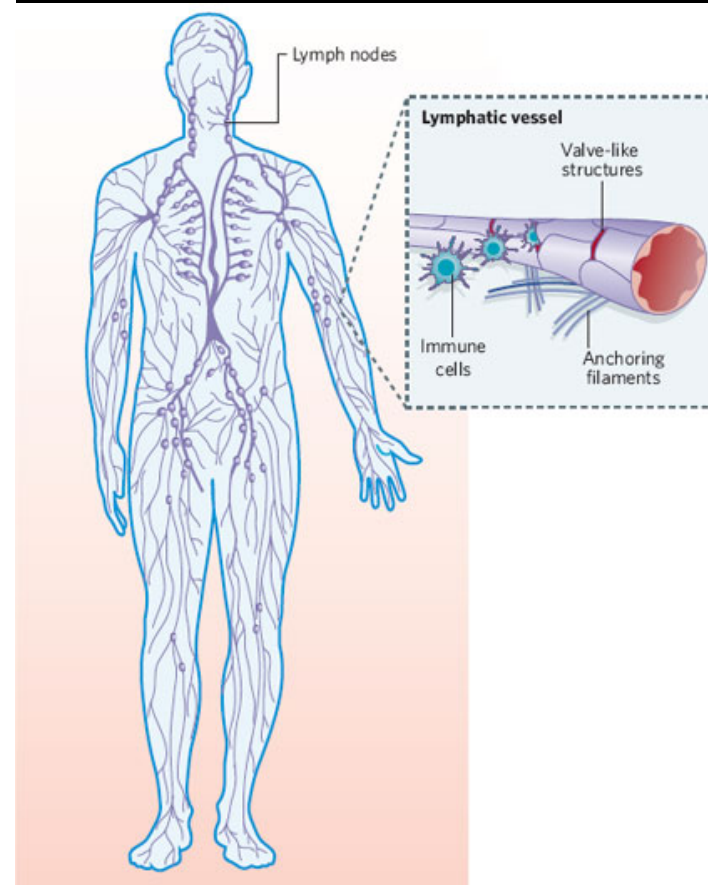


PRIMARY Organs:

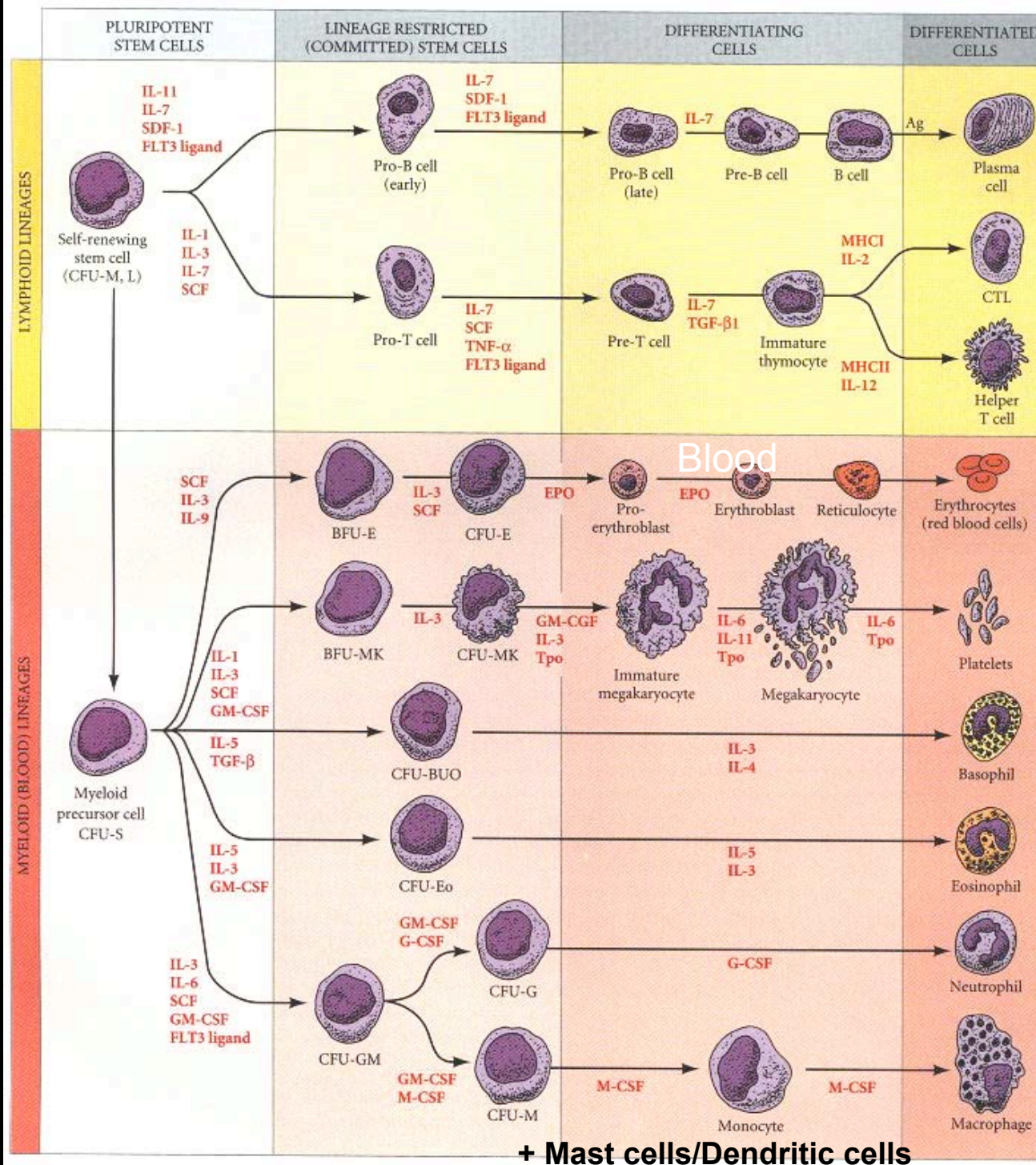
Bone Marrow, Thymus

SECONDARY Organs:

Spleen, Lymph nodes, MALT (GALT - Appendix Placche di Peyer- BALT, NALT).



EMOPOIESIS



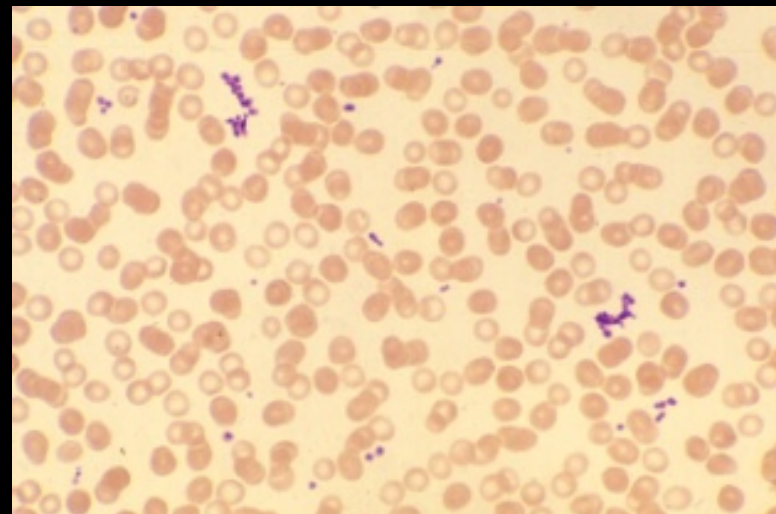
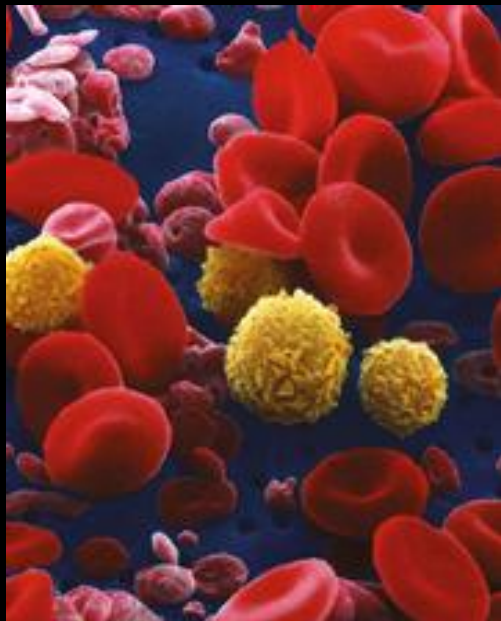
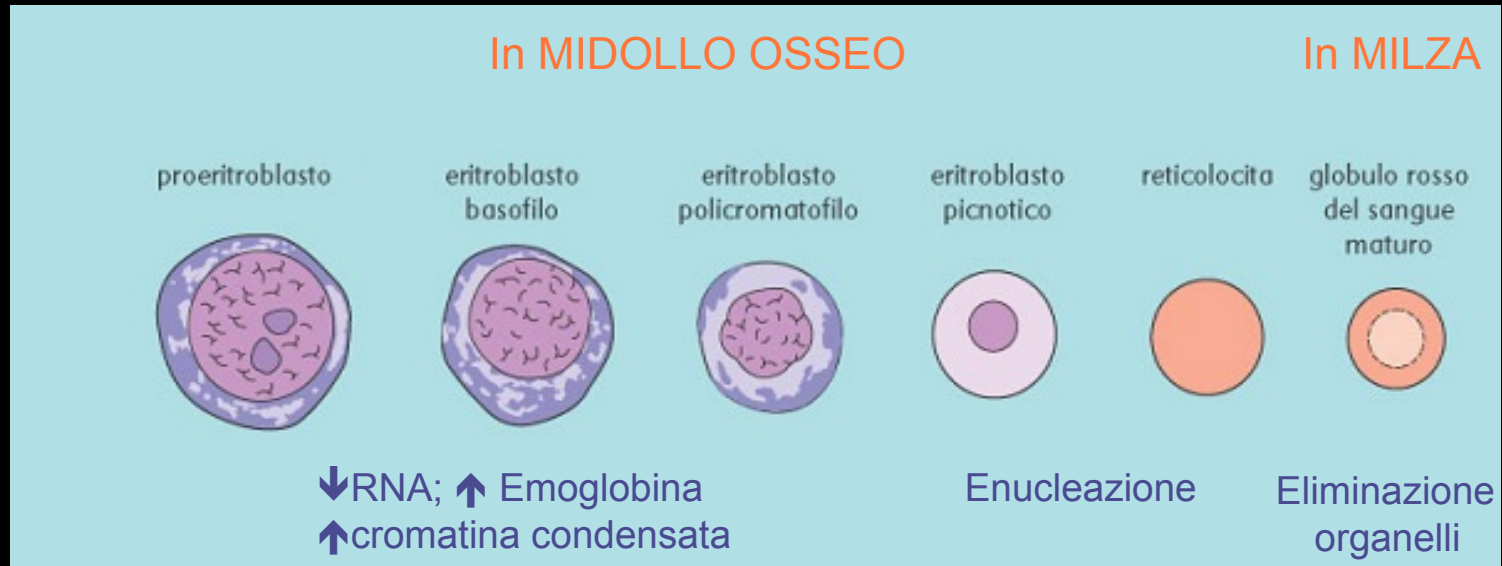
Bone Marrow

Thymus

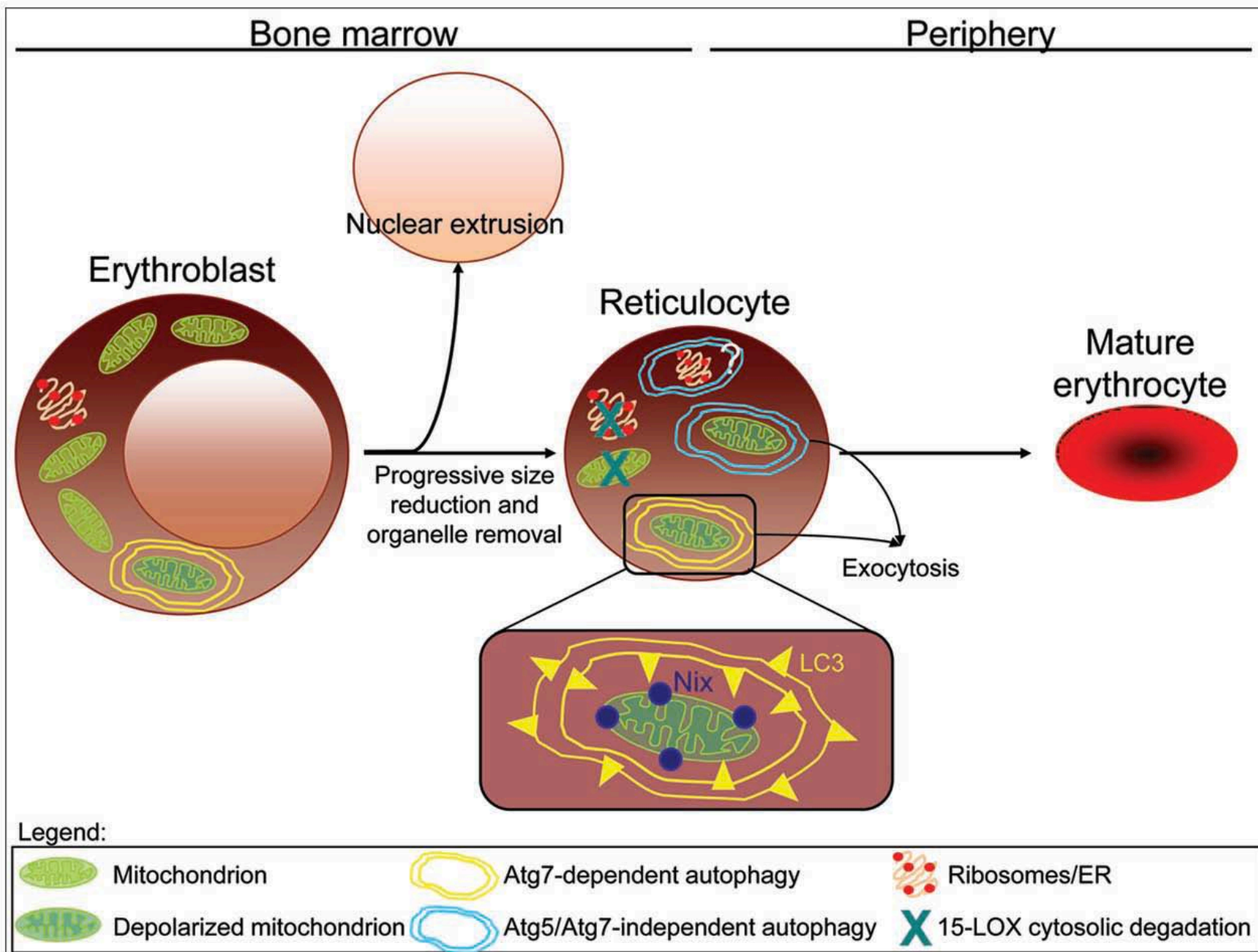
Spleen

Tissues

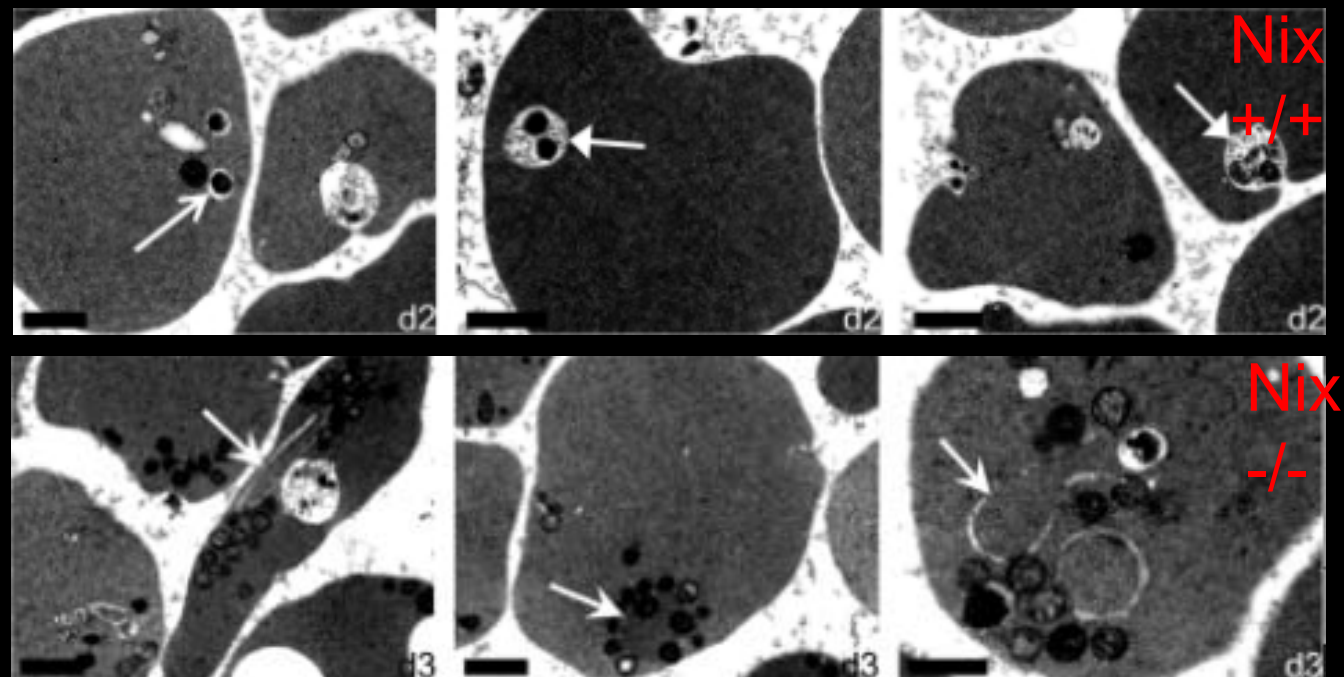
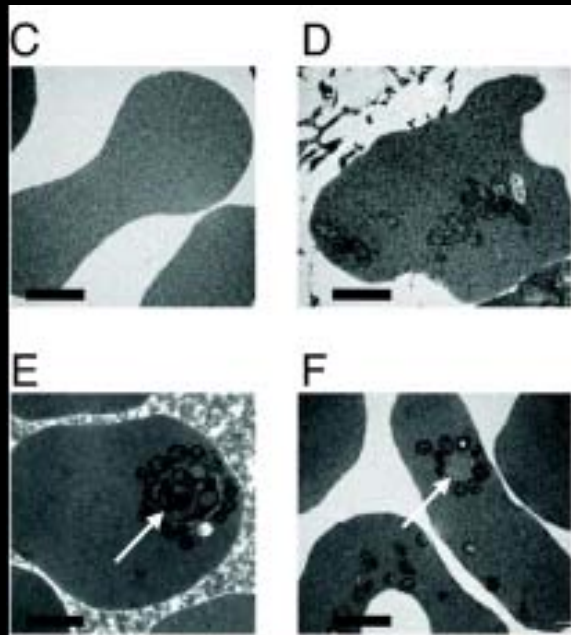
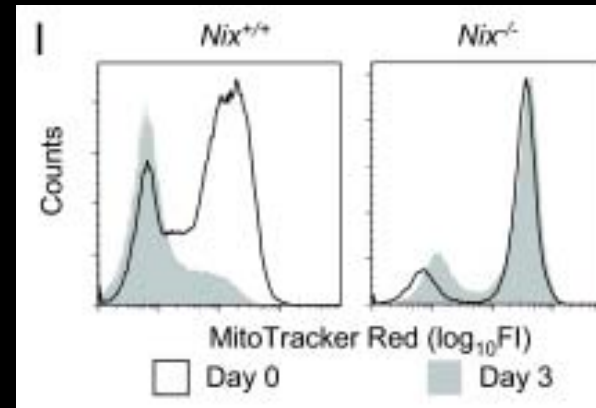
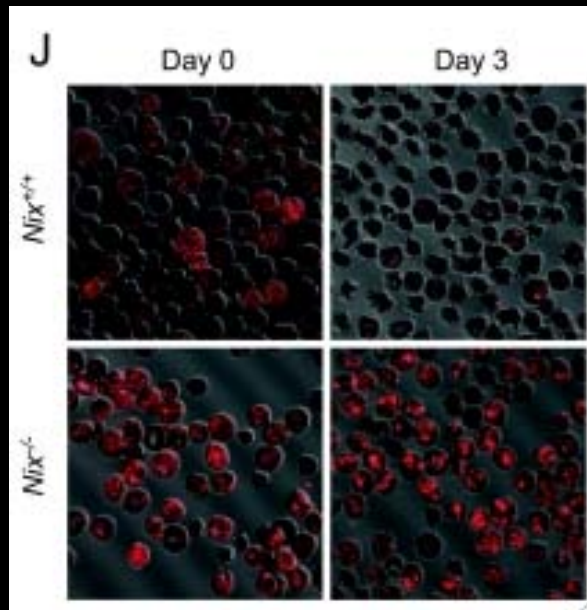
SVILUPPO E DIFFERENZIAMENTO DEGLI ERITROCITI



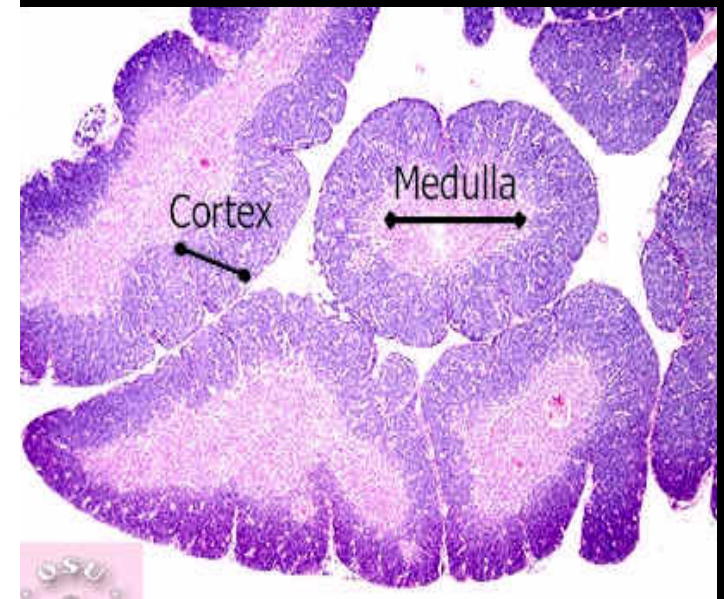
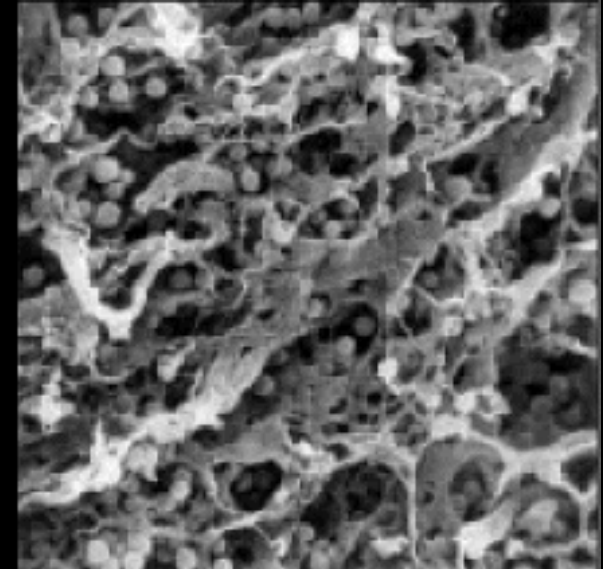
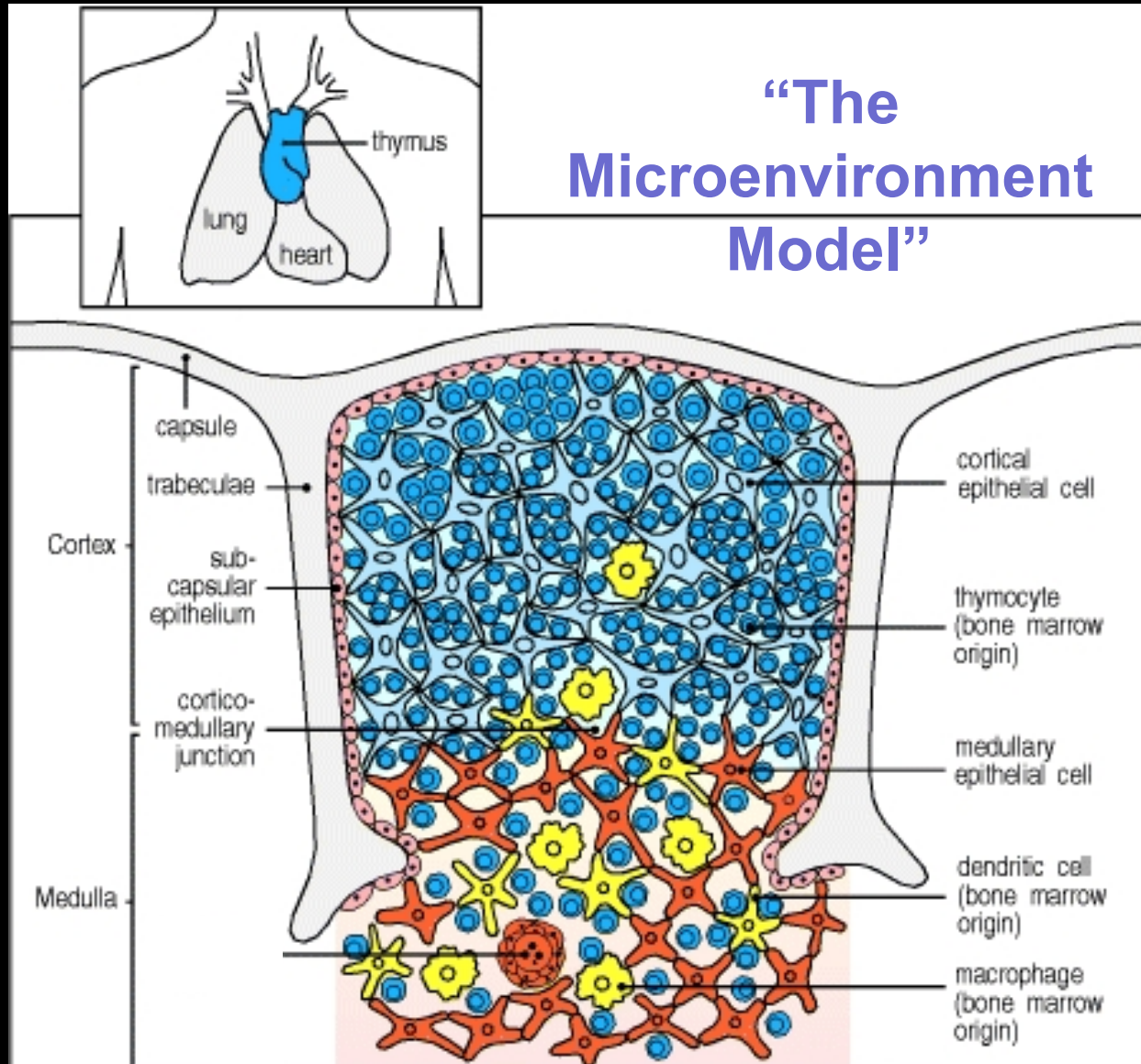
Eliminazione dei mitocondri via MITOFAGIA: **NIX**



Eliminazione dei mitocondri via MITOFAGIA: **NIX**



SVILUPPO E DIFFERENZIAMENTO DEI LINFOCITI T



Cellule T immature



RIARRANGIAMENTO
geni del recettore



REPERTORIO RECETTORIALE:
Recettori unici
(milioni di differenti varianti geniche)

(Notch)



$\alpha\beta$ T cells



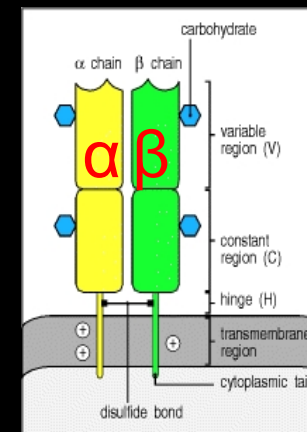
$\gamma\delta$ T cells



Ampio processo di
SELEZIONE



Il **98%** muore per apoptosi
prima di lasciare Timo



Exp: trapianti di tessuti da
TOPI mutanti (*scid; nude*)

Foxn1, Hoxa3,
Pax-1, Pax-9



Epithelial +
Mesenchymal
cells

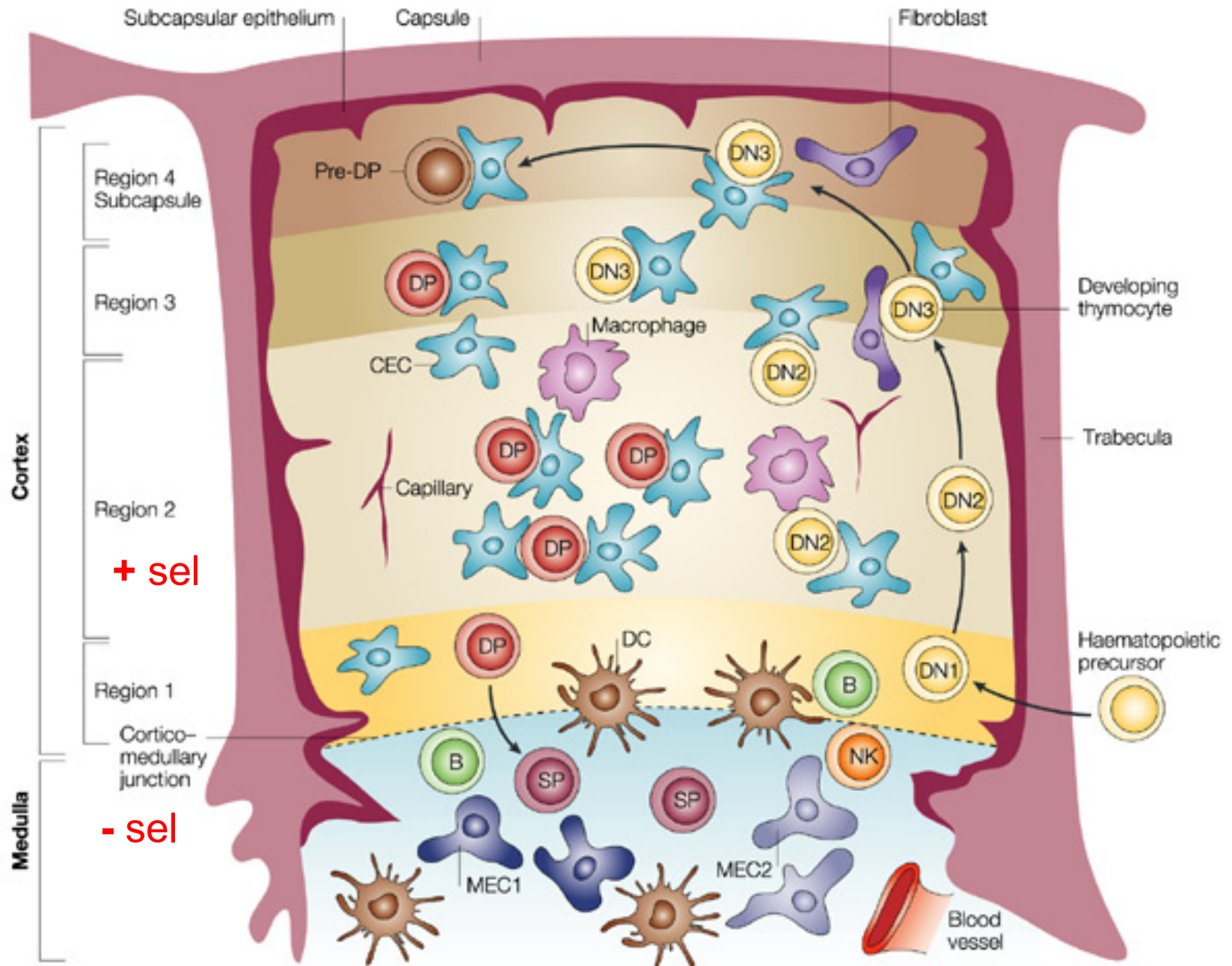
“Thymic
cross-talk”

+ sel

“Thymic
cross-talk”

- sel

RelB
(NFkB)



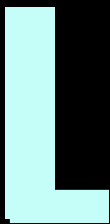
Autonomous step

(SUMMARIZING)

DN
(≈ 60%)
Riarrangiamento
locus catena β



DP
CD4+ CD8+
Riarrangiamento
locus catena α
+ ↓ livelli TCR



*Positive
Selection*



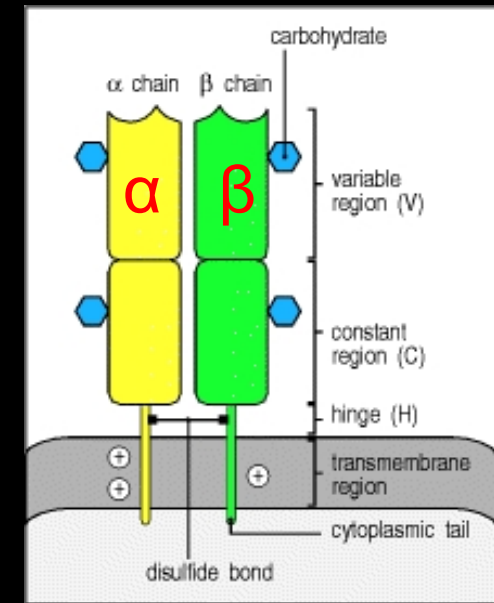
SP
CD4+/CD8+
+ ↑ livelli TCR



*Negative
Selection*
(≈ 2%)

→ 20% → **Yδ**

△ 20% → **NK**
(variabilità
recettoriale ↓↓)



Fine maturazione
(CD24, CD62L, CD69)
+ ESPANSIONE

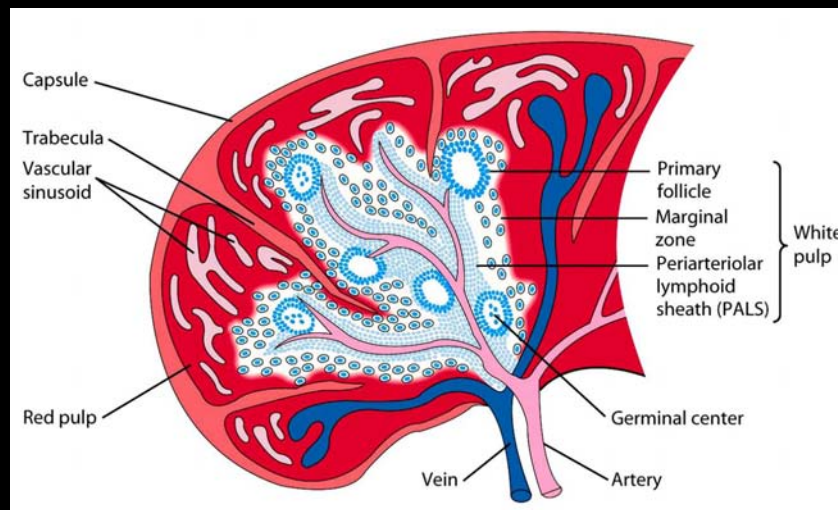
In circolo sanguigno (dopo ≈ 3 settimane)



ATTIVAZIONE E DIFFERENZIAMENTO (PRIMING) DEI LINFOCITI T

ORGANI LINFOIDI PERIFERICI (o secondari):

- Stessa architettura di base. Linfociti, cellule stromali, macrofagi e DCs.
- Dove avviene il PRIMING (+ proliferazione e differenziamento) / 4-6 giorni.
- Molto importanti le CHEMOCHINE per localizzazione esatta di tutte le cellule.



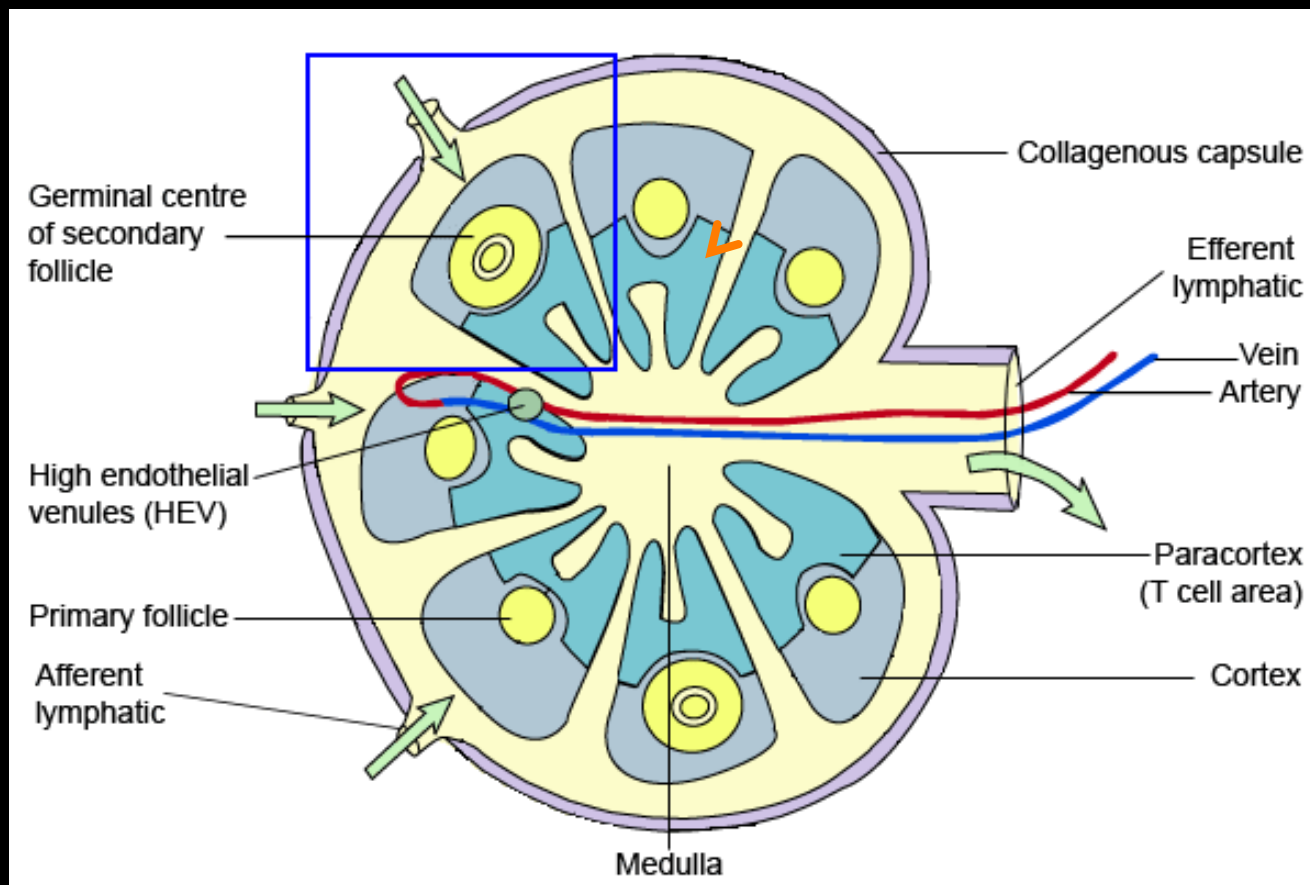
SPLEEN

-Polpa bianca (attivazione T cells)

-Polpa rossa (eliminazione vecchi eritrociti)

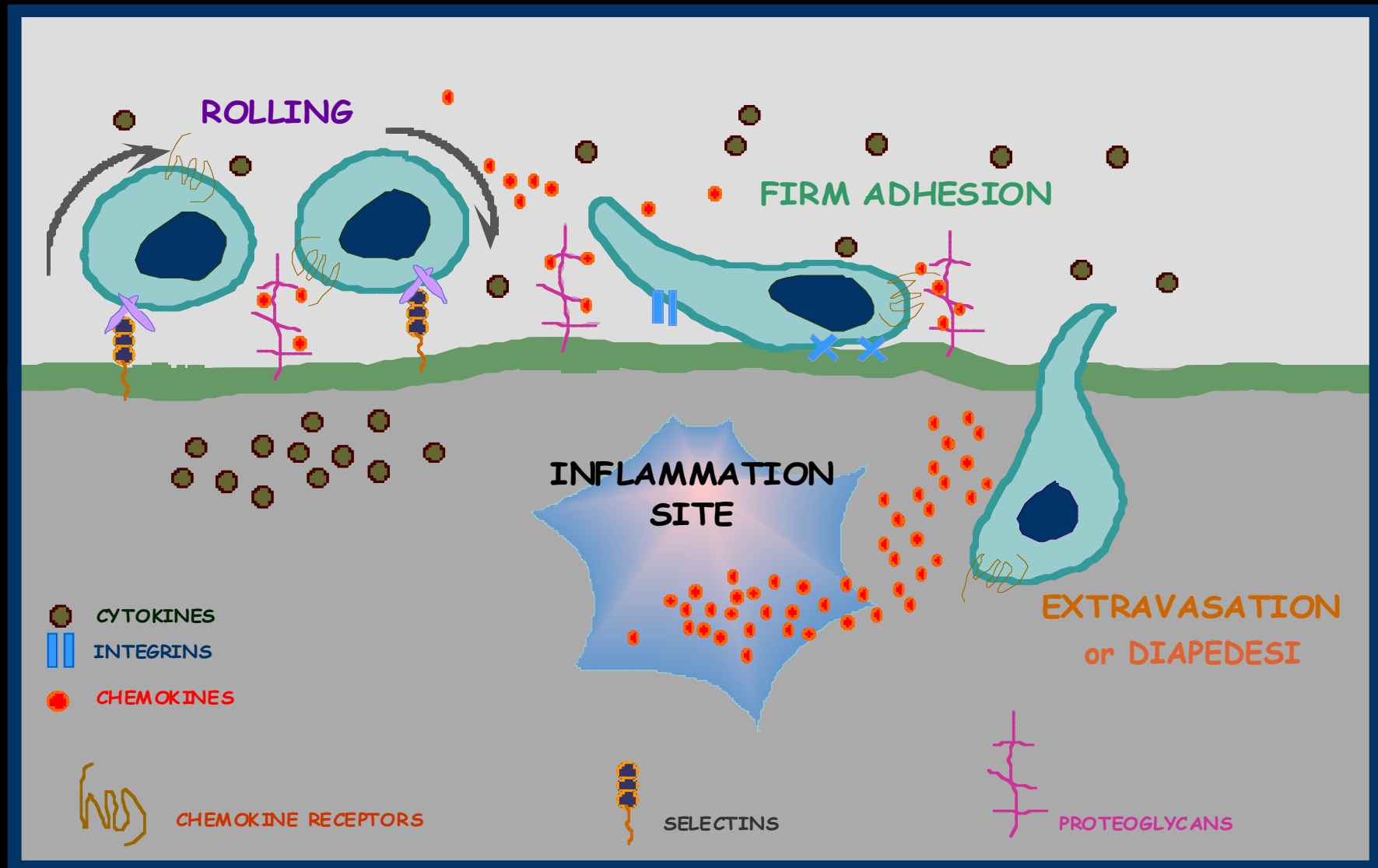
LYMPH NODE

T cell activation in peri-cortical region



The basic features of leukocyte migration:

HOMING



Linfociti inattivi = “NAIVE”

ATTIVAZIONE/PRIMING =
attivazione, espansione clonale
e differenziamento di una cellula naive
al suo incontro iniziale con l'Ag



Linfociti attivati = EFFETTORI

3
funzioni



UCCISIONE
ATTIVAZIONE
REGOLAZIONE



Alcuni diventano
CELLULE DELLA MEMORIA

OMEOSTASI in periferia:

Serve **IL-7** per sopravvivenza di T cells in periferia non attivate

PRIMO INCONTRO APC / T CELL:

T cell smette di migrare, s'ingrossa, cromatina meno densa, sintesi di nuovo mRNA e proteine → **LINFOBLASTI**



PROLIFERAZIONE
(4-5 giorni)



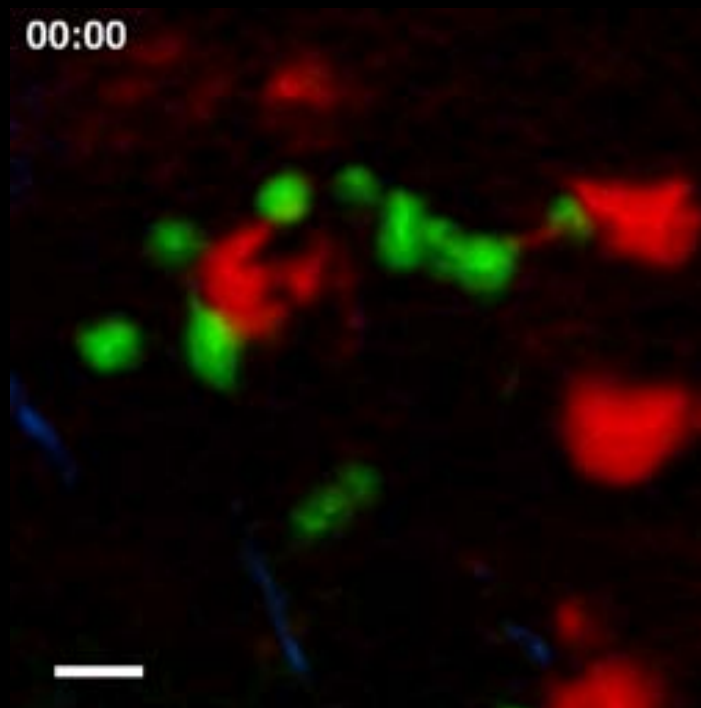
DIFFERENZIAMENTO



Lasciano organi
linfatici per raggiungere
sedi di infezione

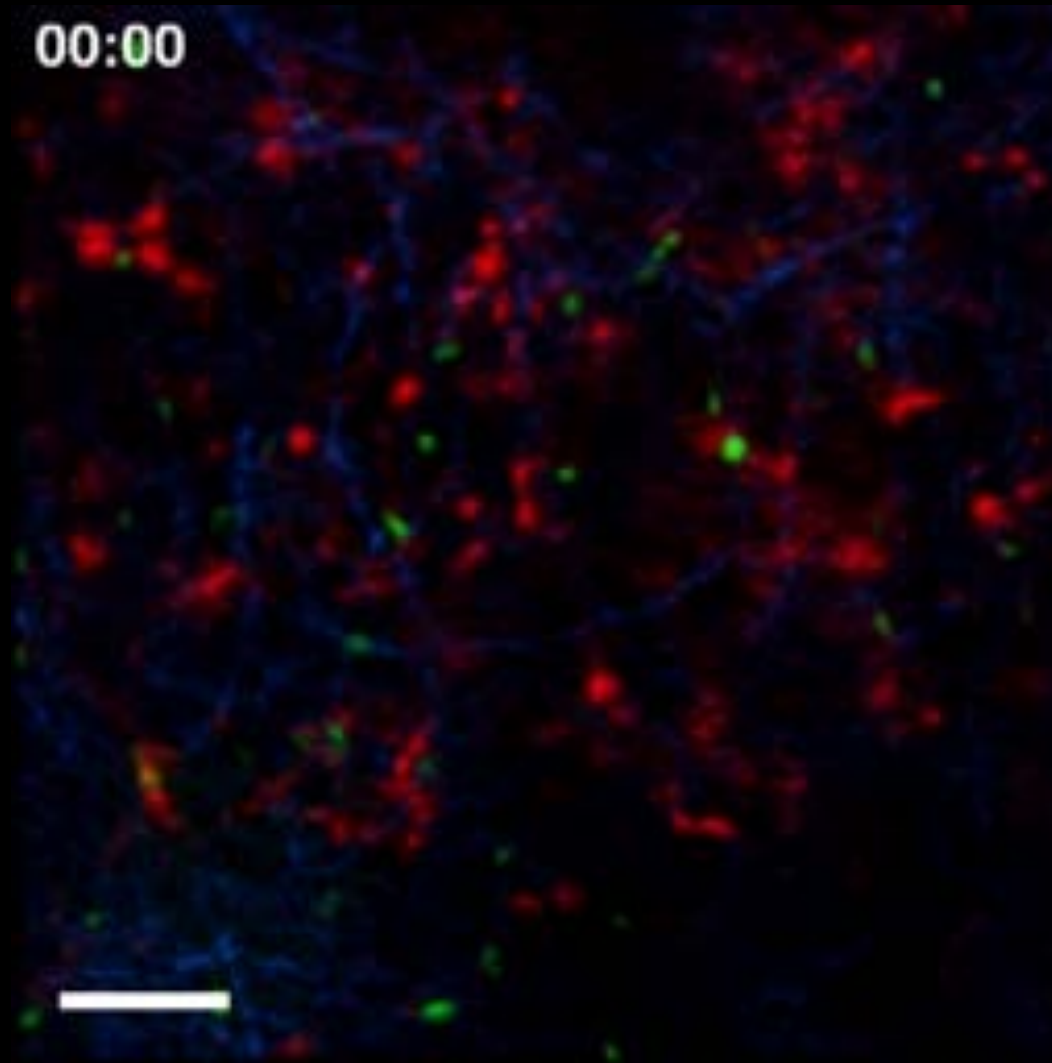


Rimangono negli
organi linfatici per
attivare cellule B



LINFOCITA T
CELLULE DENDRITICHE

LHYMPH NODE TRAFFICKING



LINOCITA T
CELLULE DENDRITICHE
CELLULE STROMALI

3 diversi segnali tra APC/T cell:

Segnale 1:

Attivazione antigene-specifica del TCR.

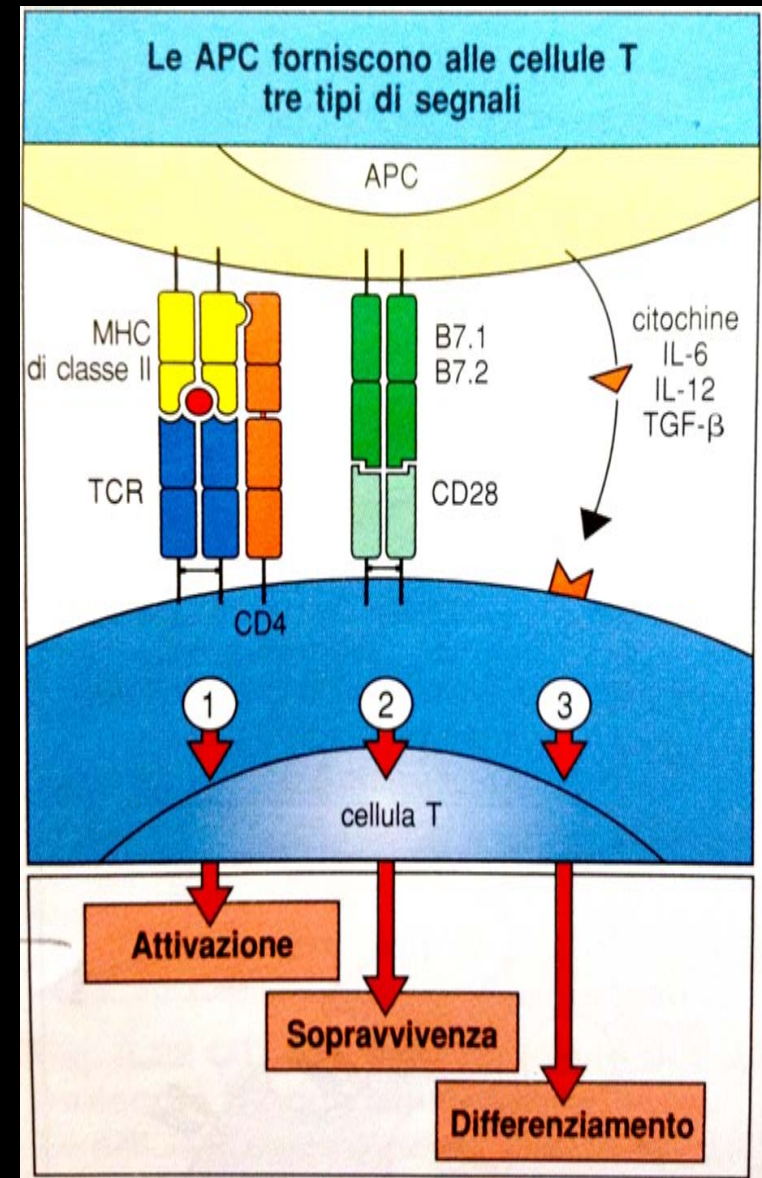
Segnale 2:

Molecole costimolatrici (B7/CD28).
Sopravvivenza ed espansione.

Segnale 3:

Produzione di citochine che controllano il differenziamento in diversi tipi di cellule effettrici.

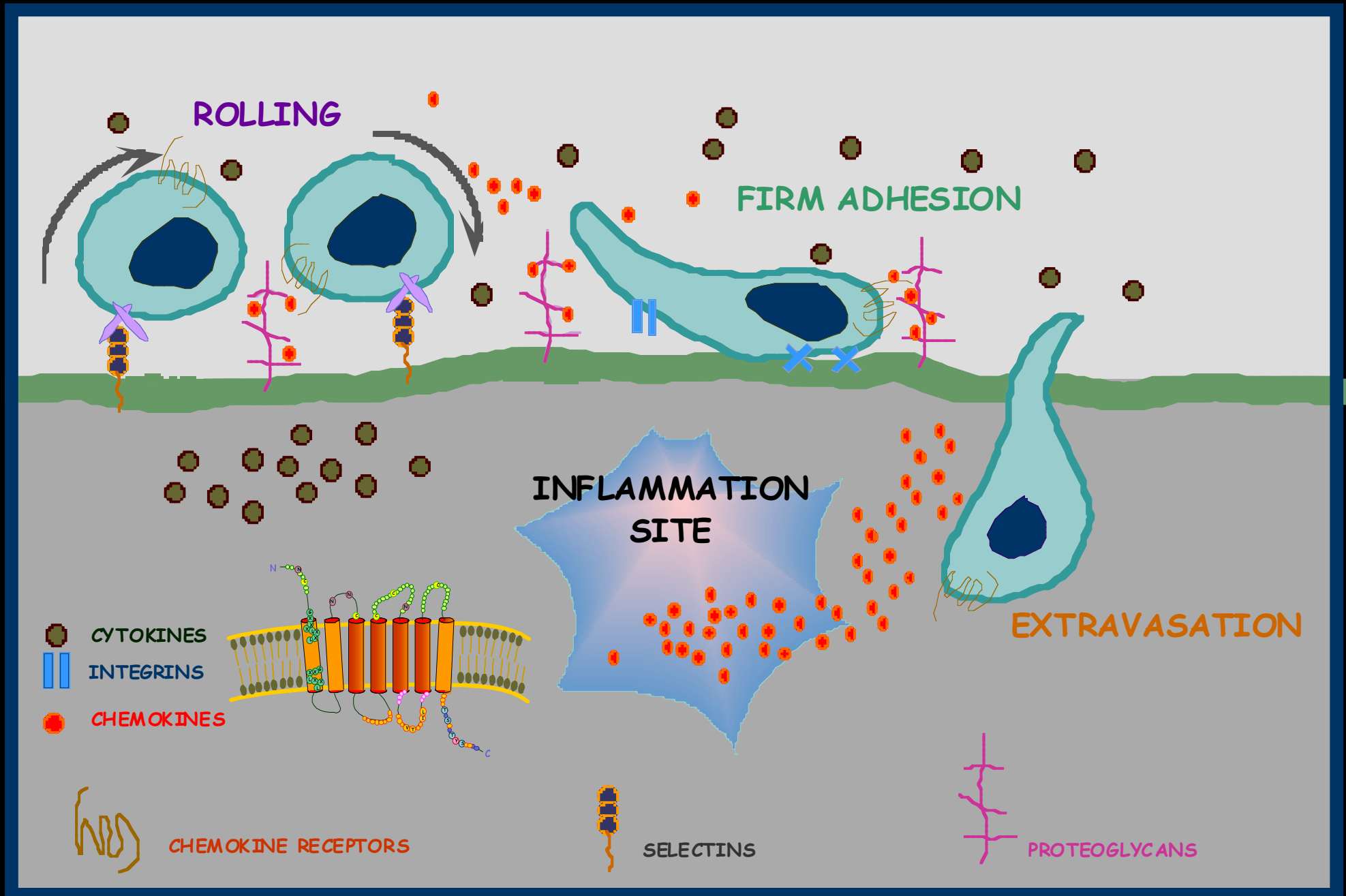
Espressione II-2



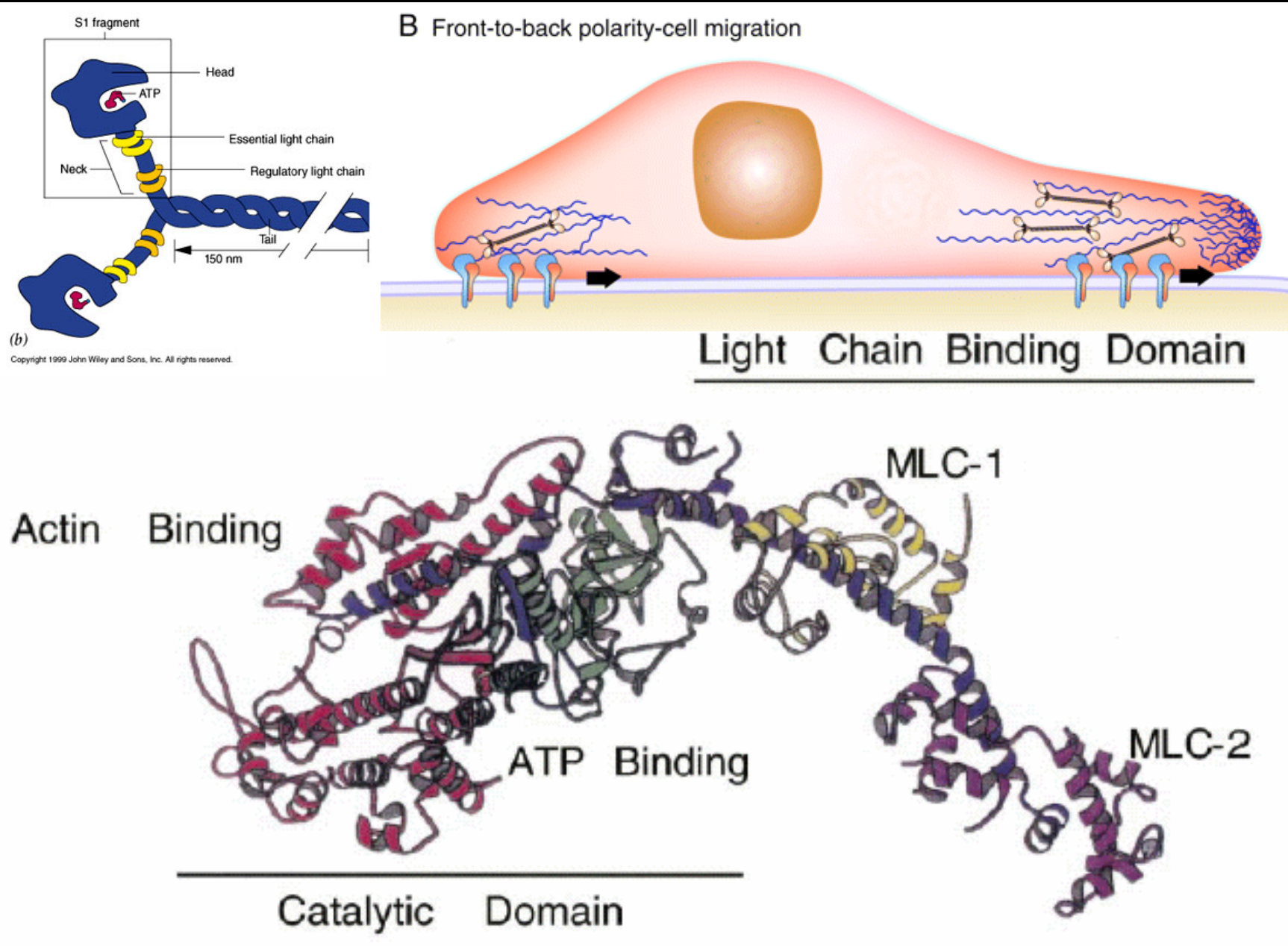
TIPI DI CELLULE EFFETTRICI

		FUNZIONE	SEGNALE 3	CITOCHINE PRODOTTE DA T CELLS
	CD8 citotossici	Uccidono cellule bersaglio		
CD4 T _{HELPER}	T _H 1	Stimolano macrofagi e produzione Ab da B	IFN γ + Il-12	IFN γ + Il-2
	T _H 2	Stimolano produzione Ab da B	Il-4	Il-4 + Il-5
	T _H 17	Stimolano neutrofili	Il-6 + TGF- β	Il-17
	T _{reg}	Sopprimono attività T effettrici	diversi	Il-10 + TGF- β

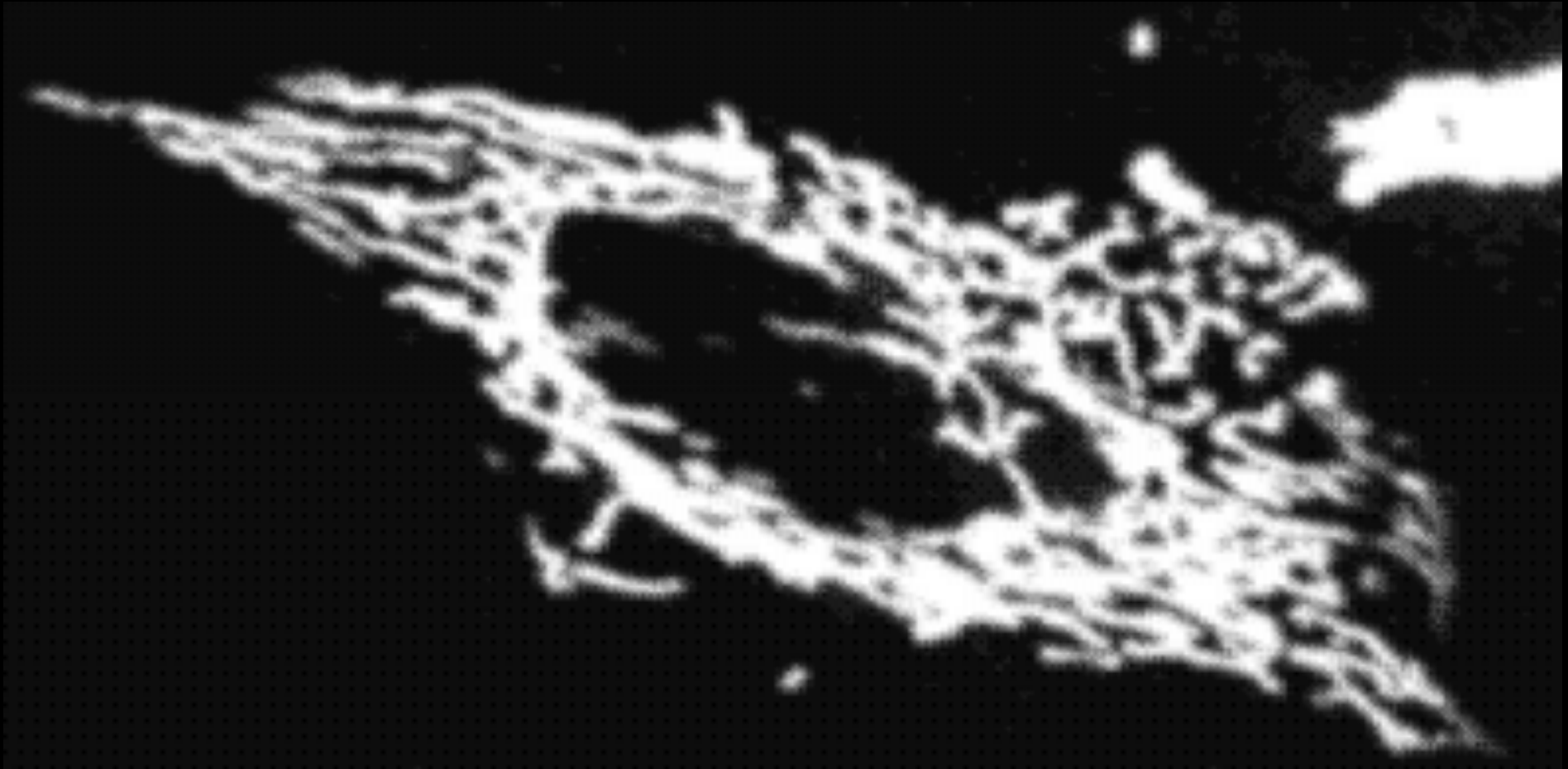
PROBLEM SOLVING



The motor of the cell: MYOSIN



Mitochondrial morphology is varied and responds to changes in mitochondrial function



Cereghetti et al., *PNAS* 2008

Mammalian mitochondria-shaping proteins

DRP1

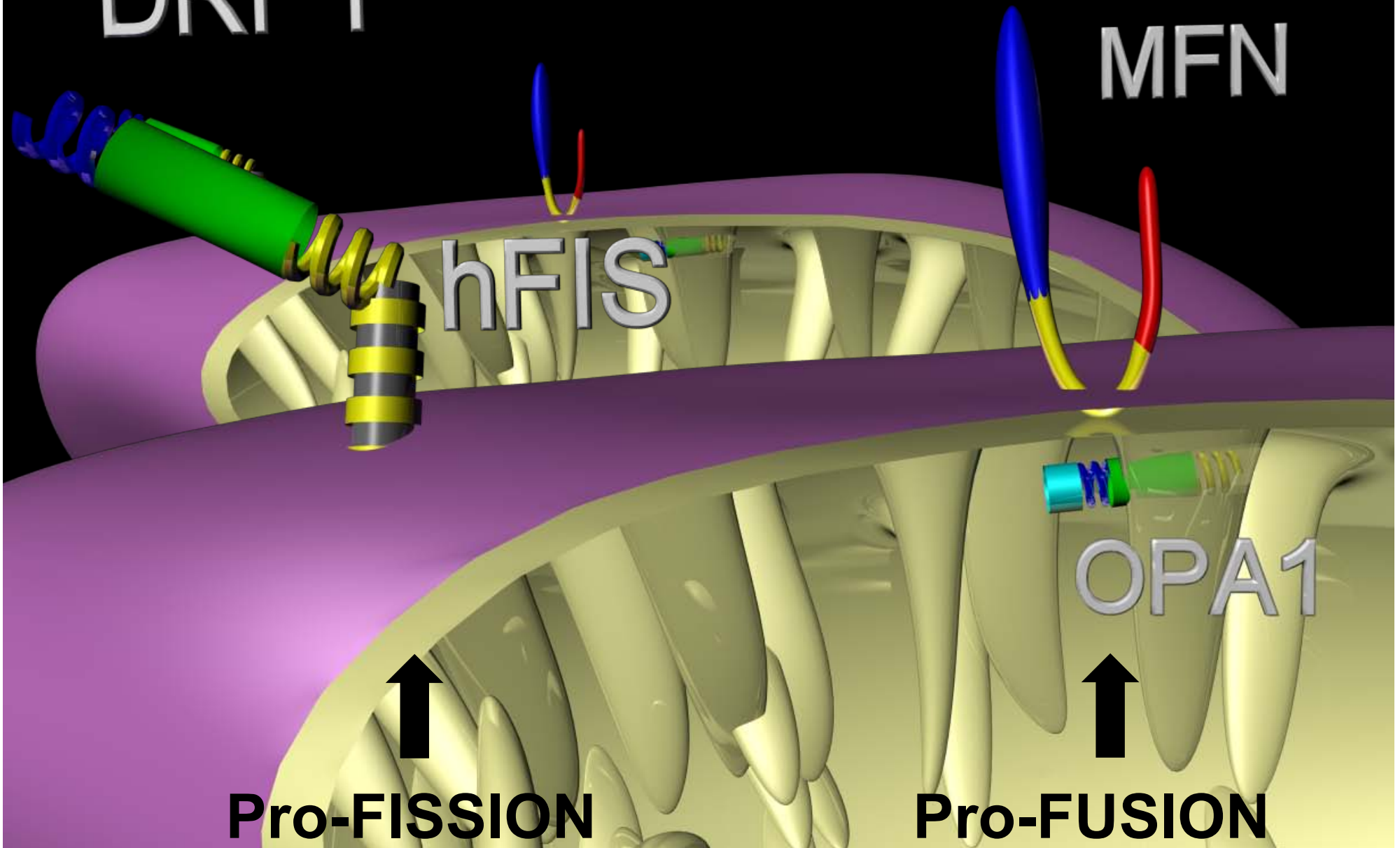
MFN

hFIS

OPA1

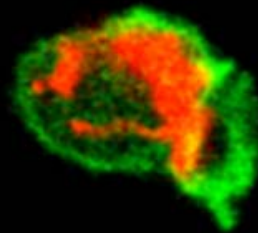
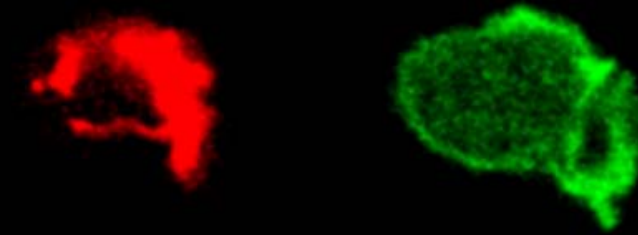
Pro-FISSION

Pro-FUSION



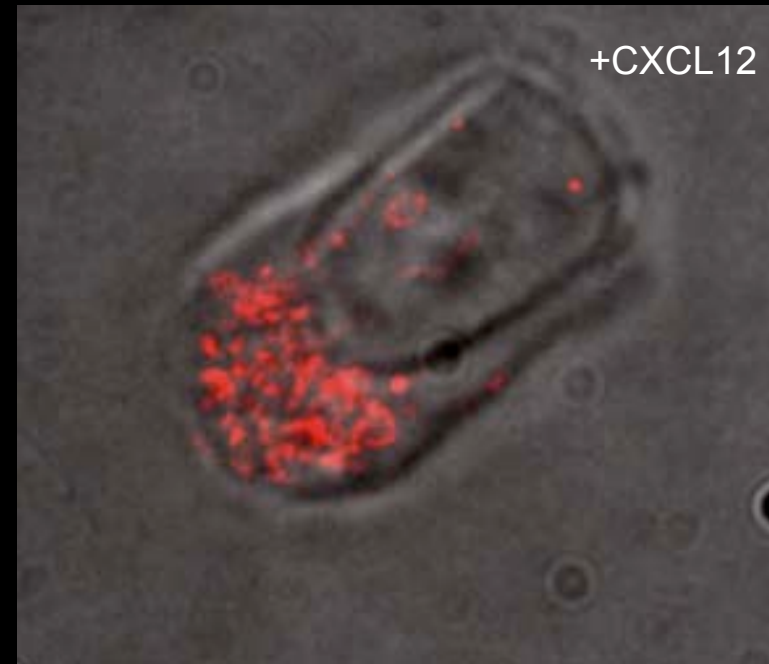
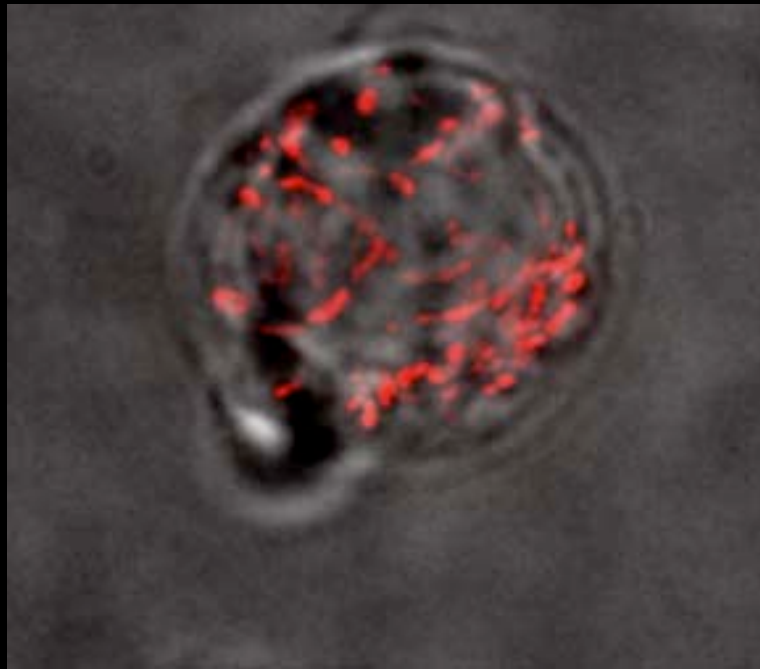
Mitochondrial redistribution at the back of the cell

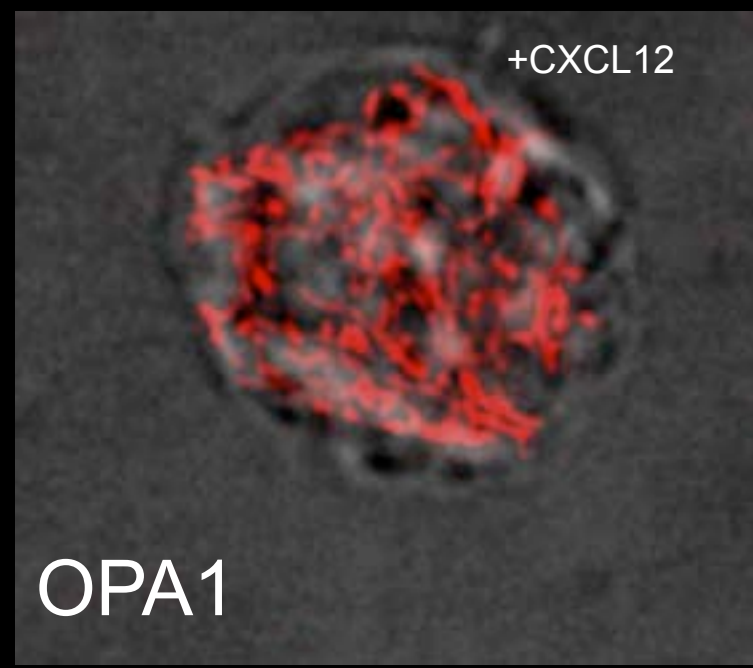
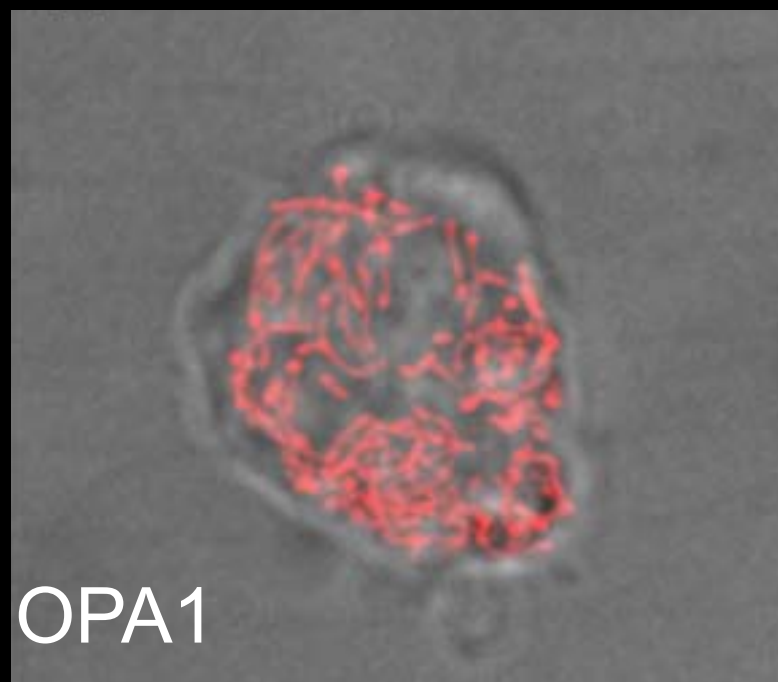
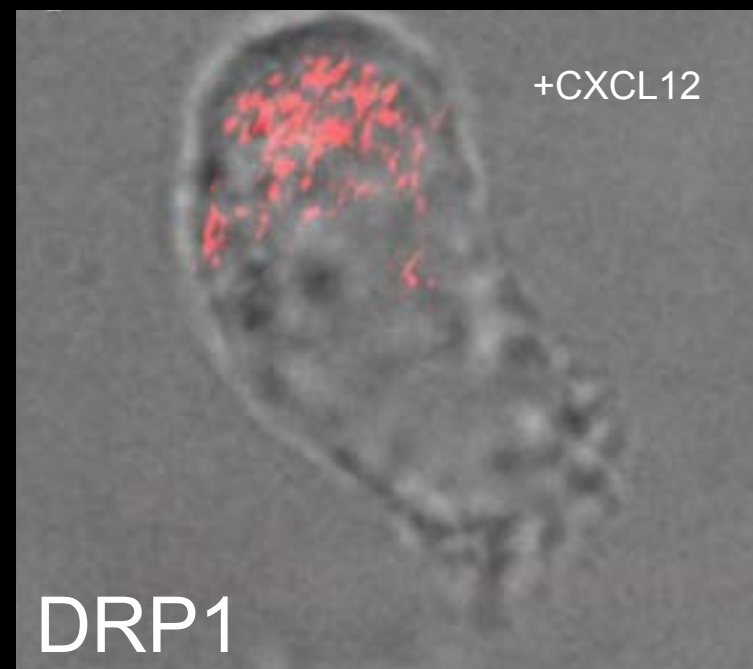
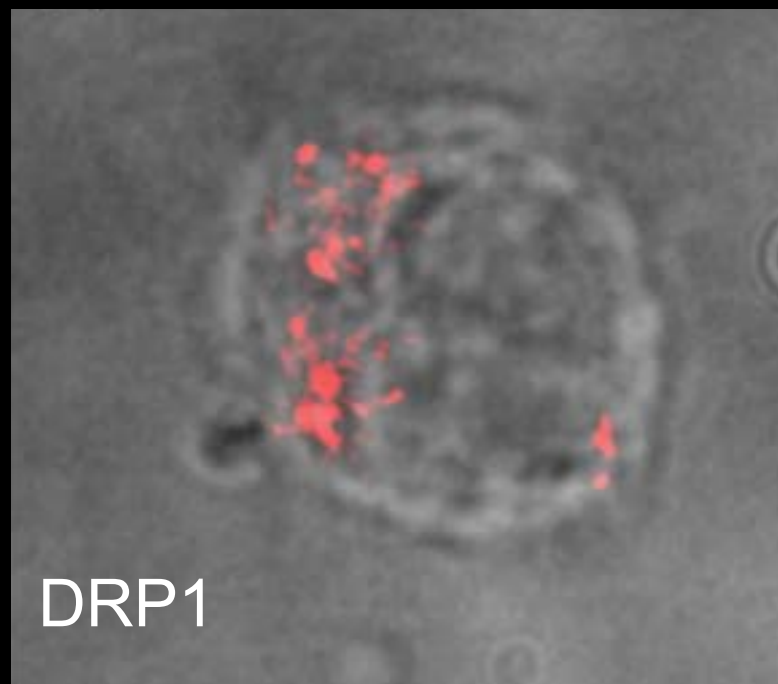
+ Chemoattraente
(fMLP)



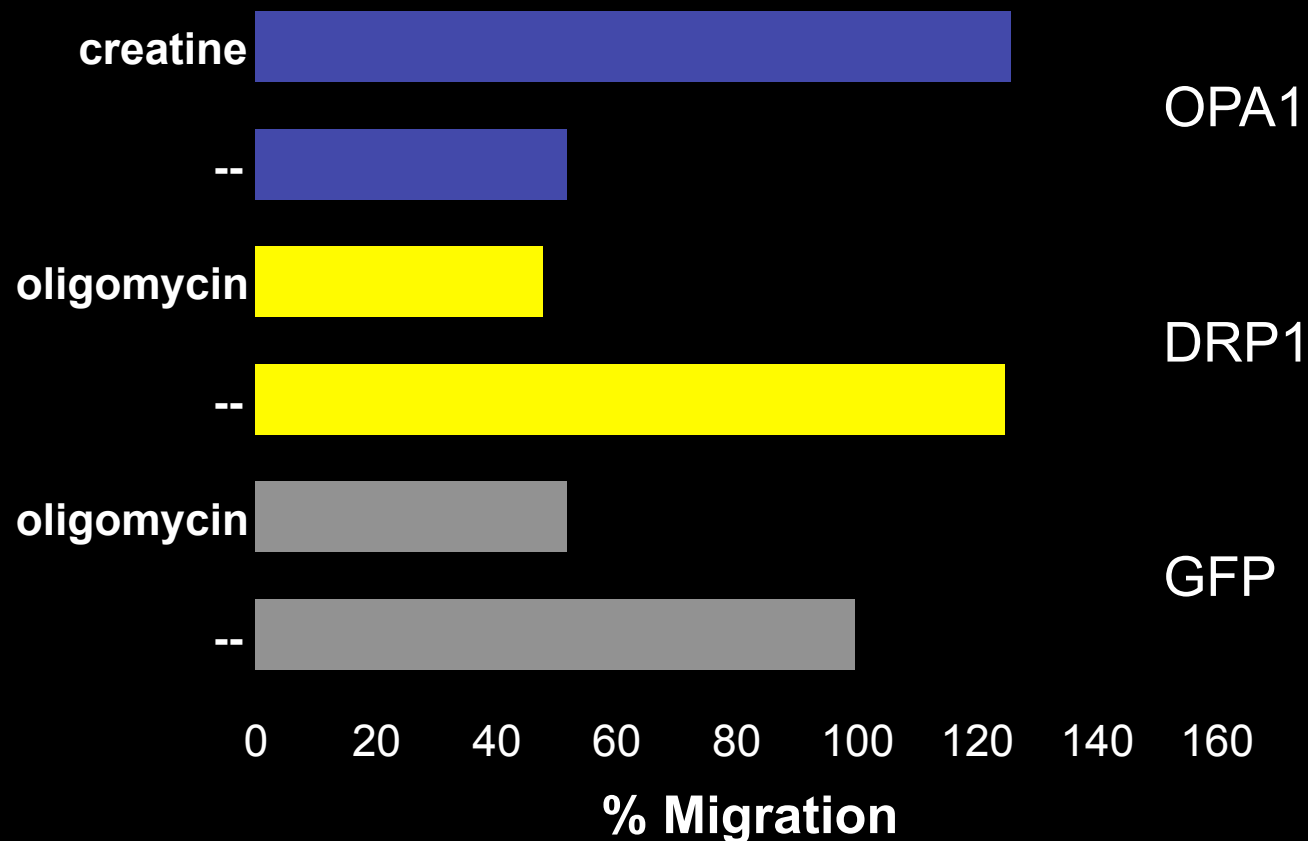
Mitochondria Akt-pleckstrin

Leukocyte polarization is regulated by mitochondrial shape



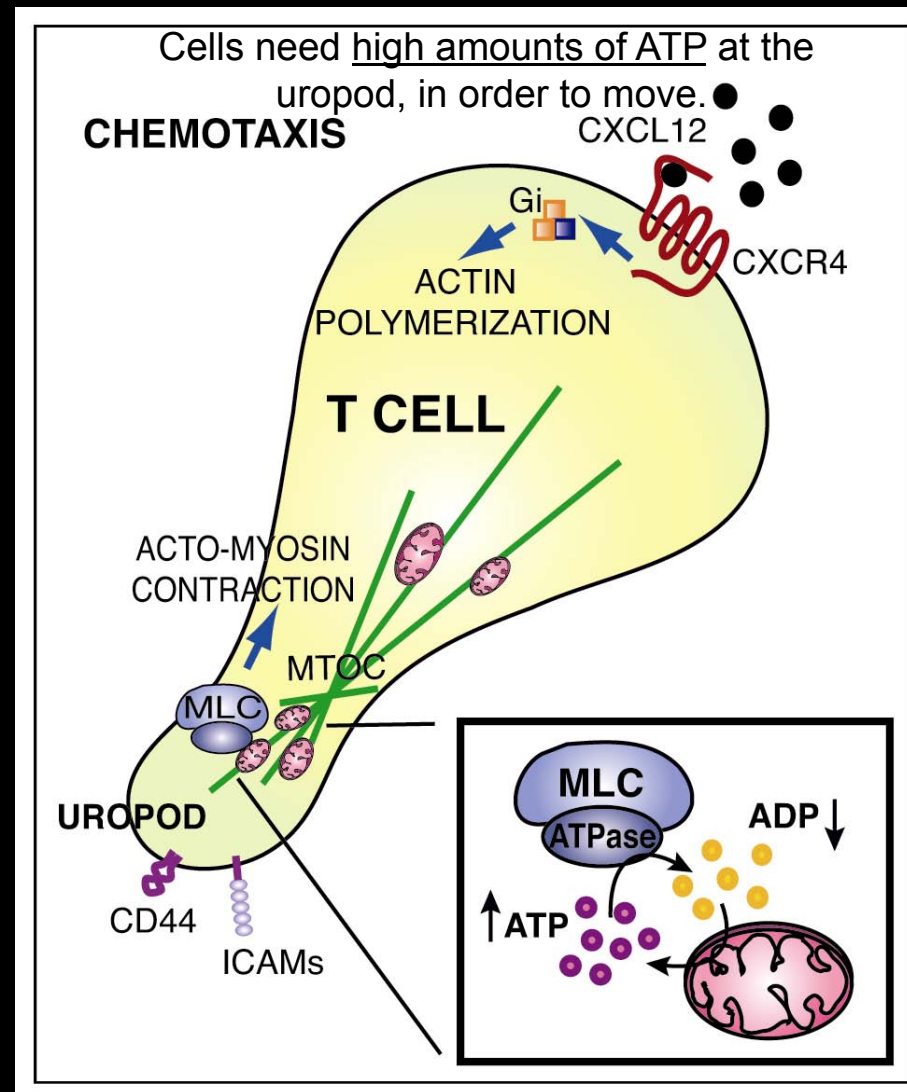


Mitochondrial ATP is required for T cell migration

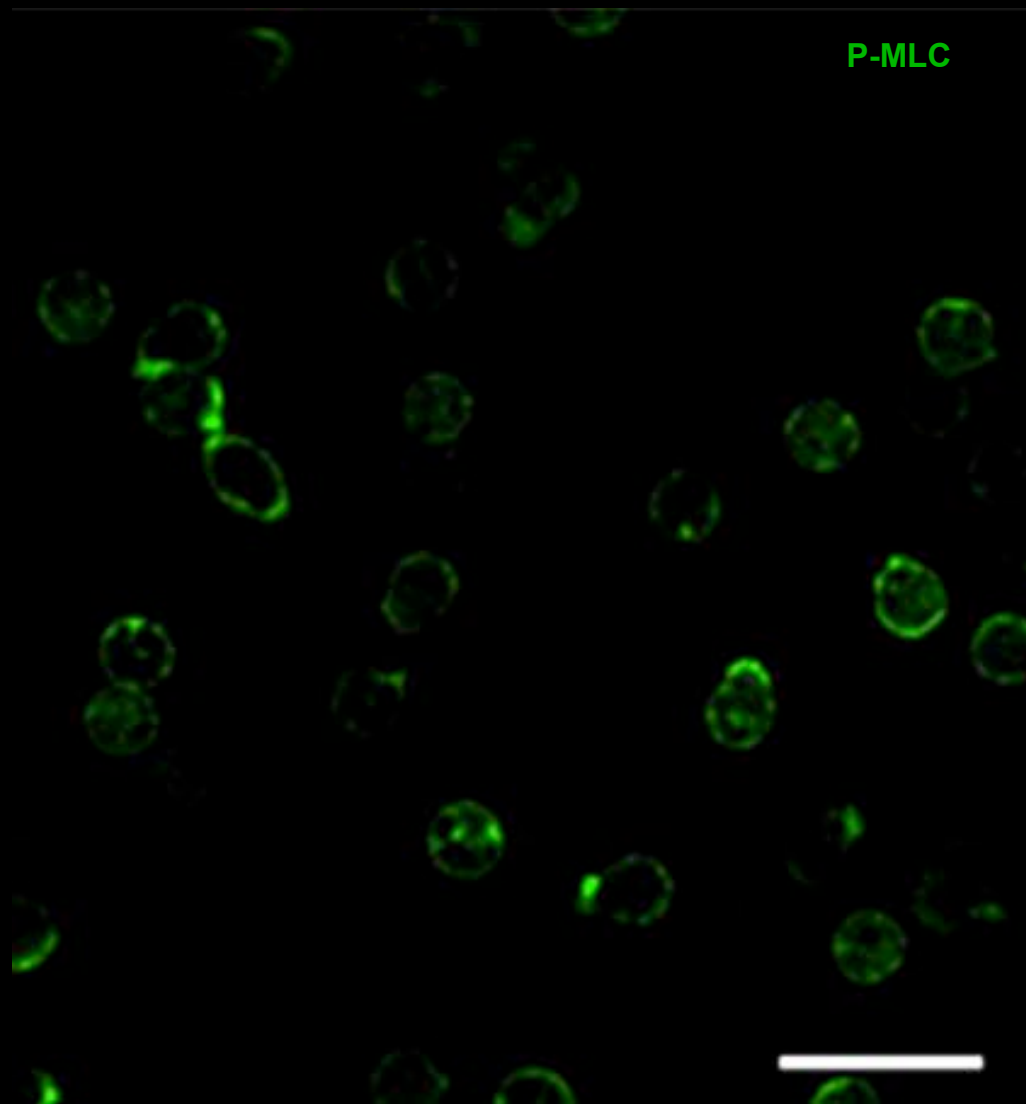


(Oligomycin: pharmacological inhibition of mitochondrial ATP production
Creatine: artificial production of ATP)

to fuel the motor of the migrating cell



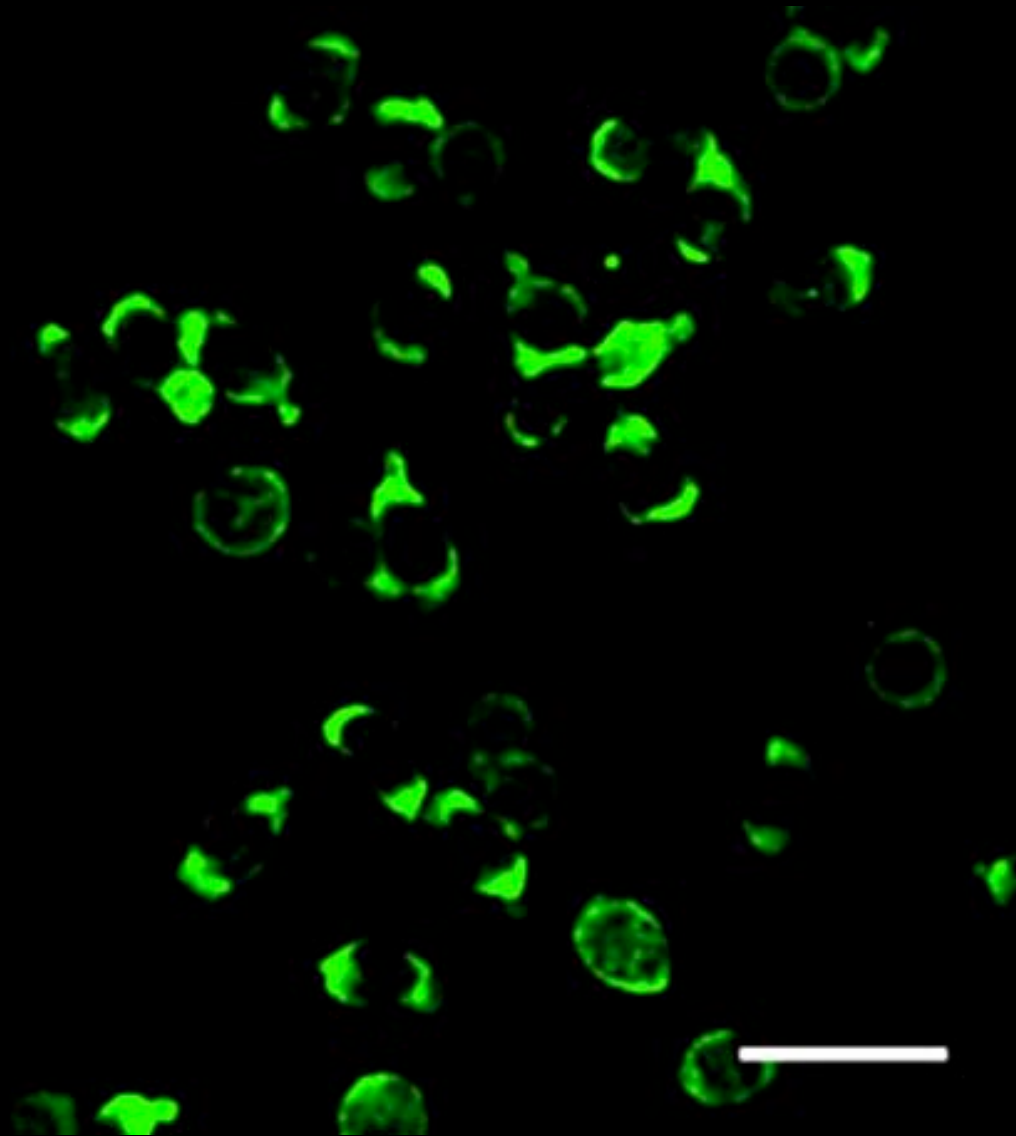
pMLC of myosin II



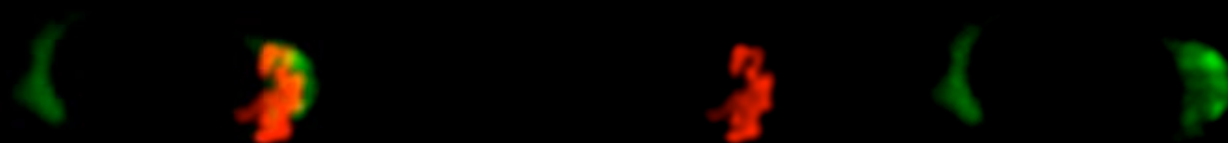
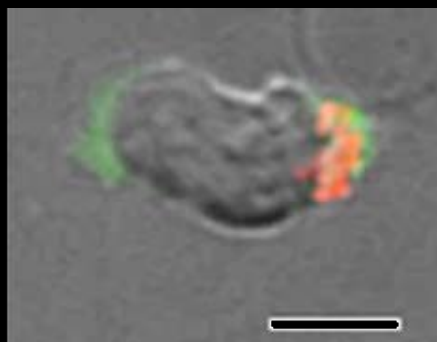
P-MLC

pMLC of myosin II

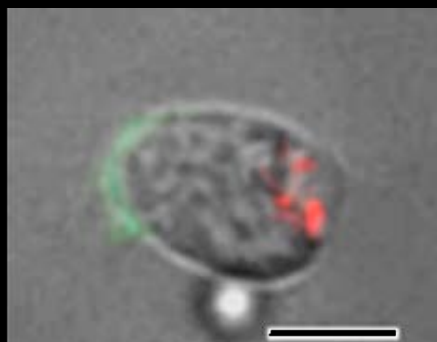
+ CCL21 (chemoattractant)



pMLC of myosin II



+oligomycin





2011 118: 6258-6268
Prepublished online October 12, 2011;
doi:10.1182/blood-2011-07-356006

From stem cell to red cell: regulation of erythropoiesis at multiple levels by multiple proteins, RNAs, and chromatin modifications

Shilpa M. Hattangadi, Piu Wong, Lingbo Zhang, Johan Flygare and Harvey F. Lodish

**LYMPHOSTROMAL INTERACTIONS
IN THYMIC DEVELOPMENT AND
FUNCTION**

Graham Anderson and Eric J. Jenkinson

NATURE REVIEWS | IMMUNOLOGY | VOLUME 1 | OCTOBER 2001 | 31

**Orchestration of lymphocyte chemotaxis
by mitochondrial dynamics**

Silvia Campello,¹ Rosa Ana Lacalle,² Monica Bettella,¹ Santos Mañes,²
Luca Scorrano,³ and Antonella Viola^{1,4}

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Vol. 203, No. 13, December 25, 2006 2879–2886 www.jem.org/cgi/doi/10.1084/jem.20061877

Janeway's, Immunobiologia (Cap. 1, 7, 8)