Tumor associated macrophages in endocrine-related cancers

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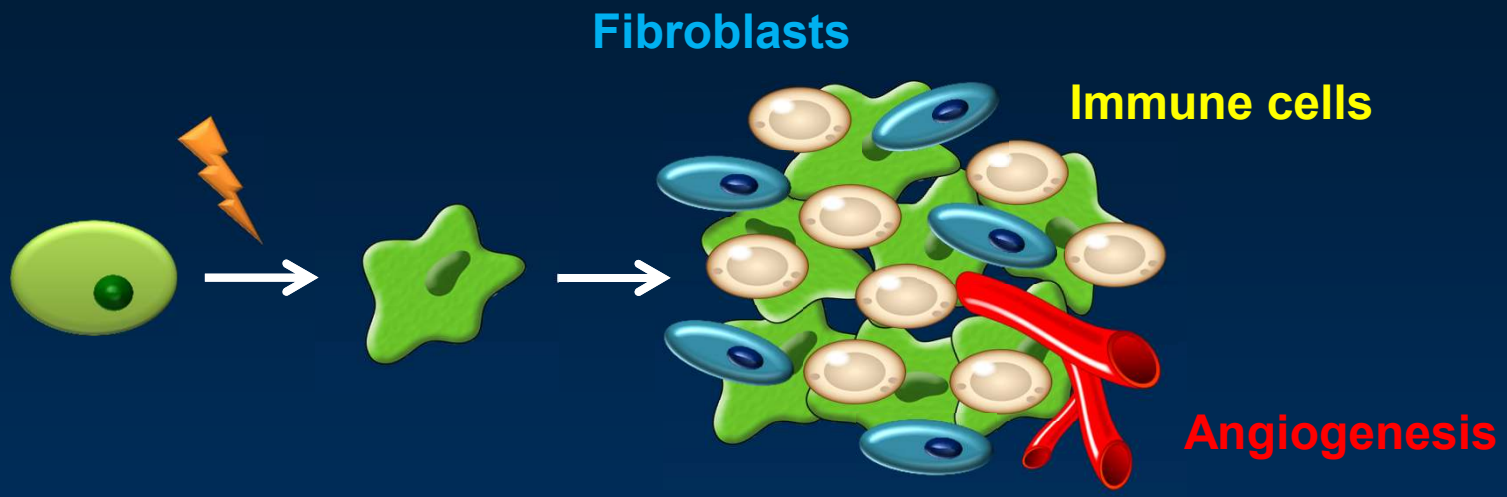
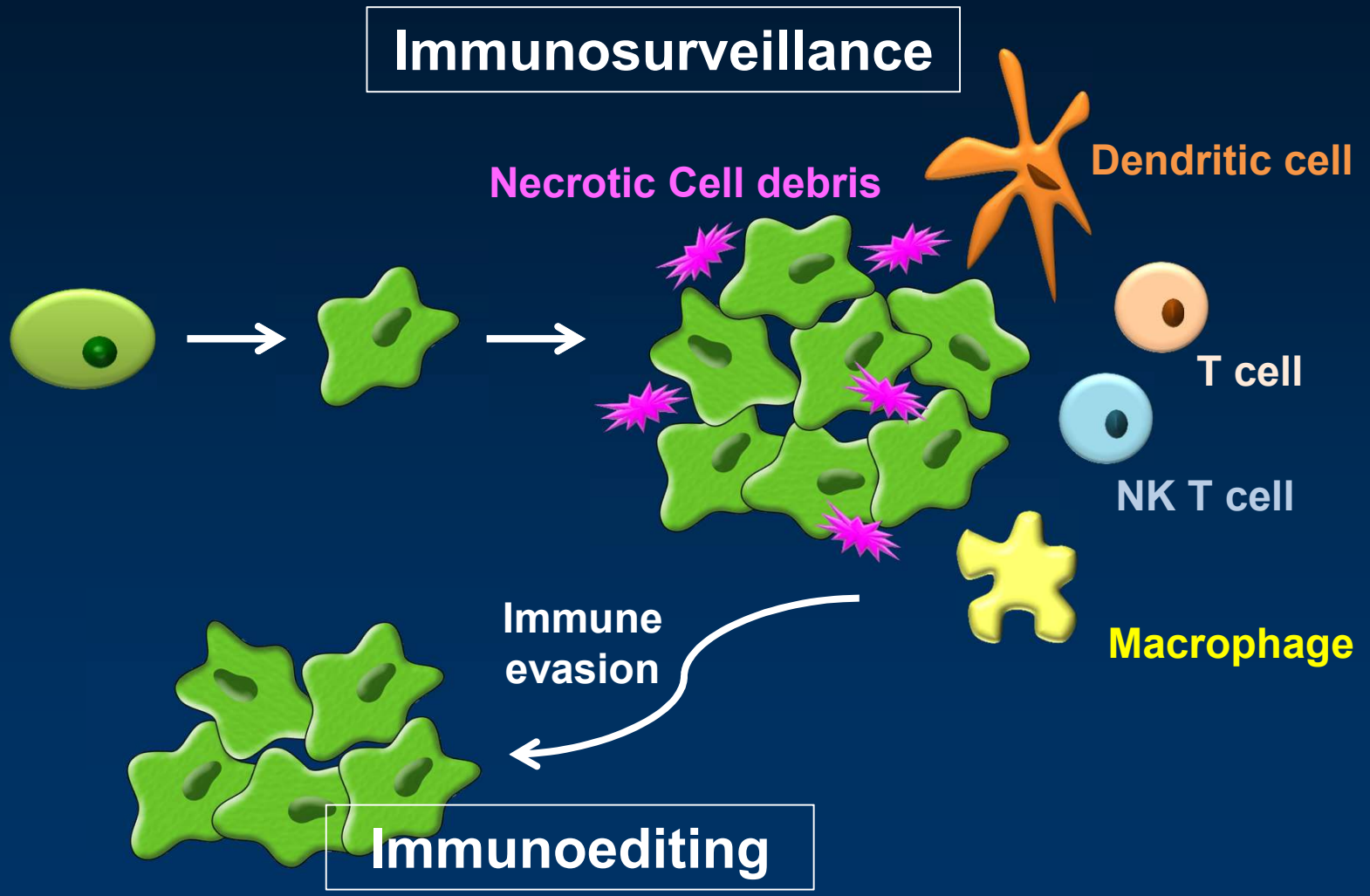
Tumor Microenvironment



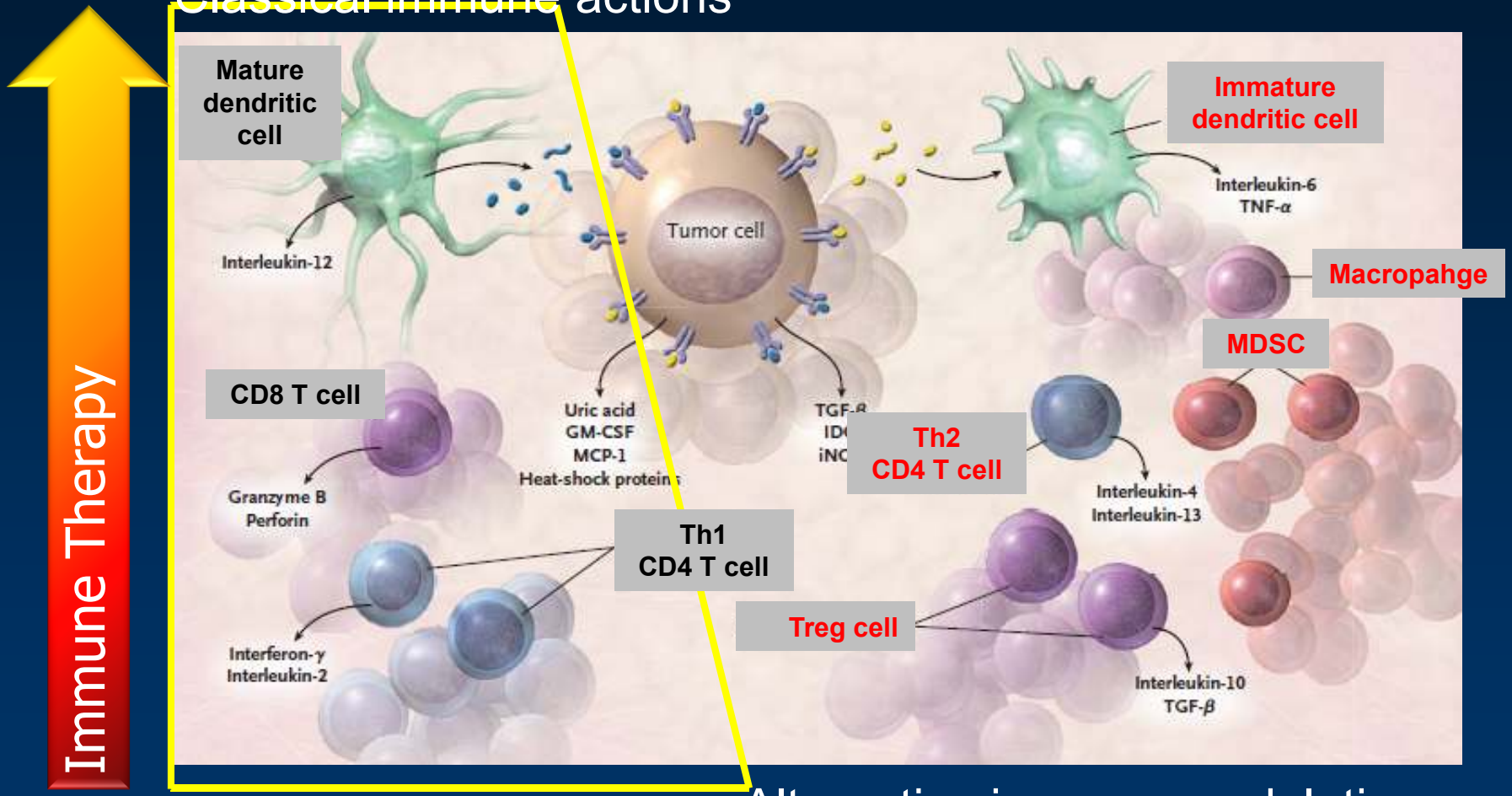
- Tumor microenvironment=cancer cells + stroma
- Heterogeneous and complex

Cancer Immunology



Cancer Immunology

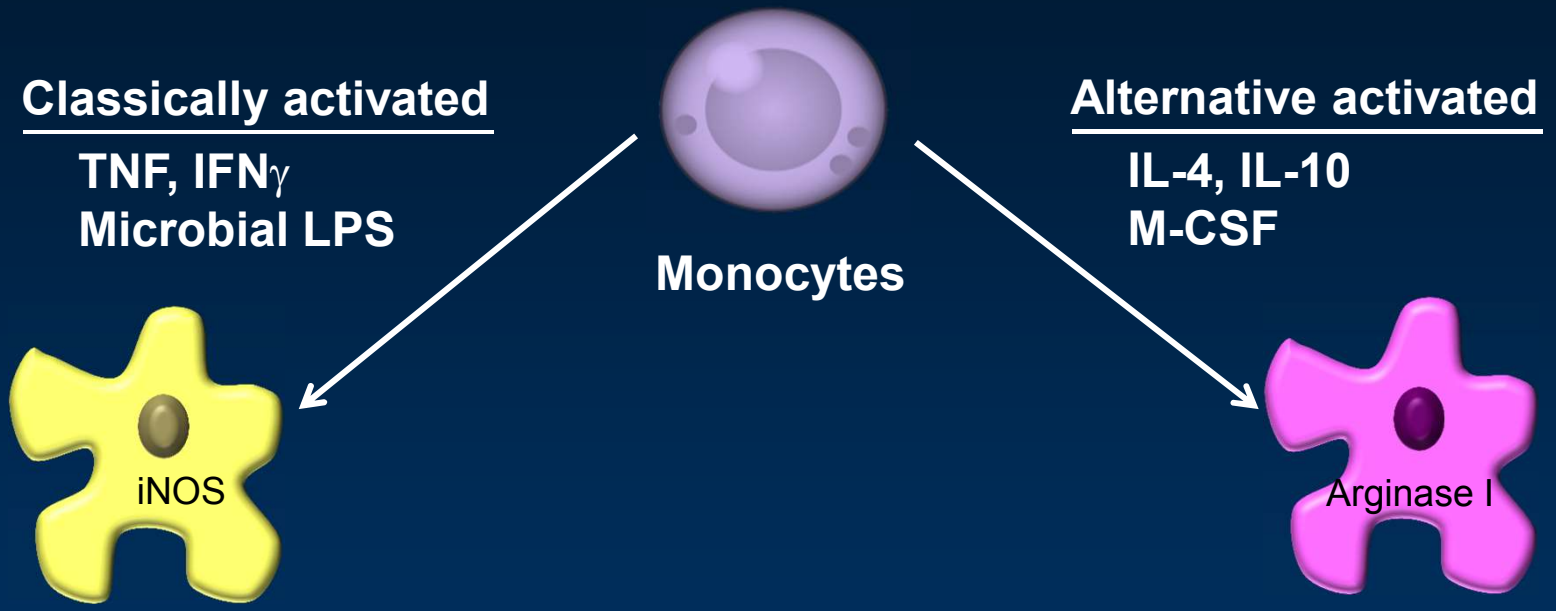
Classical immune actions



Alternative immune modulations
Host defense mechanism

Finn, NEJM. 2008

Tumor-associated macrophage, TAM



M1-macrophage

IL-12, IL-23, TNF,
IL-1, CXCL10

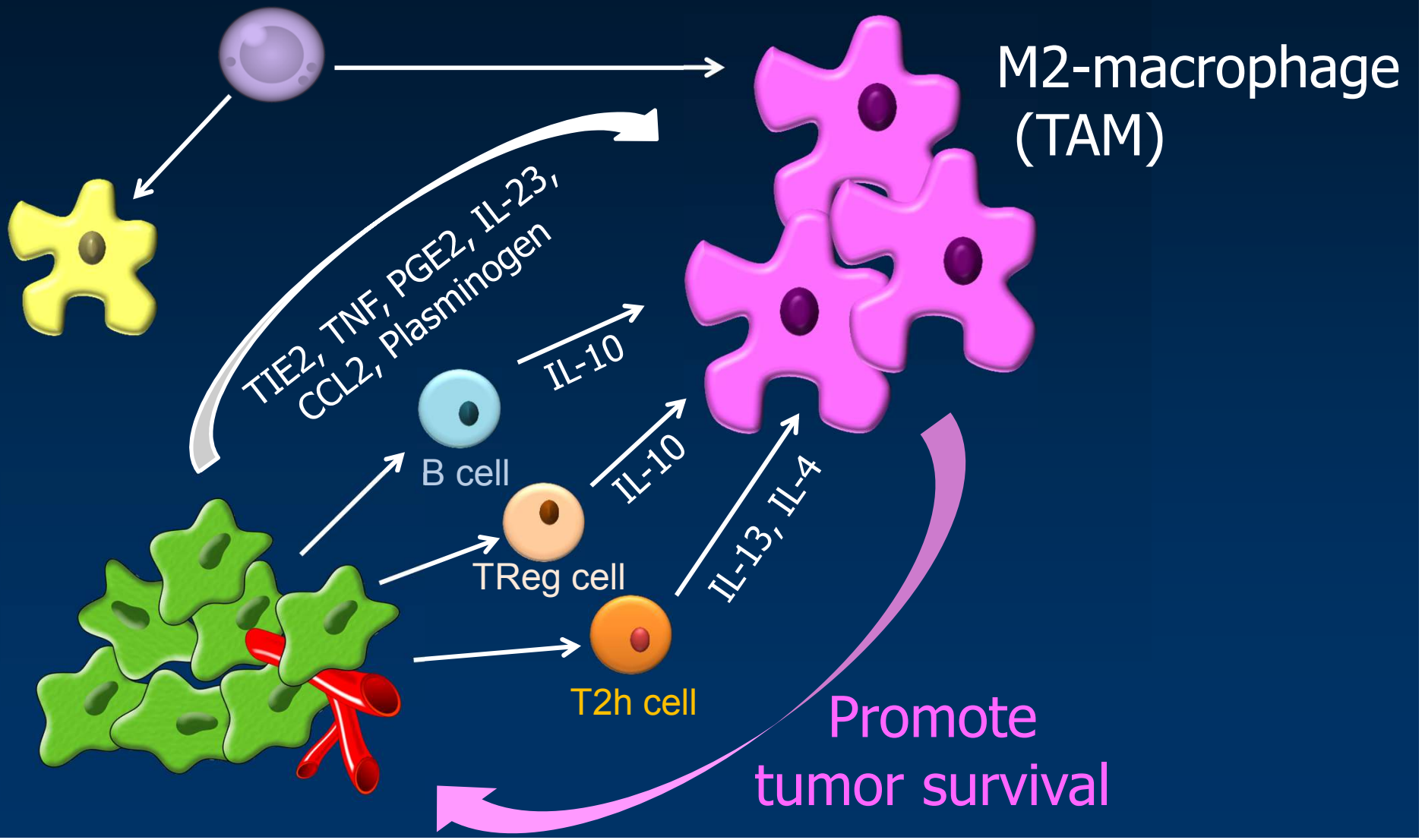
Microbicidal
Tumoricidal

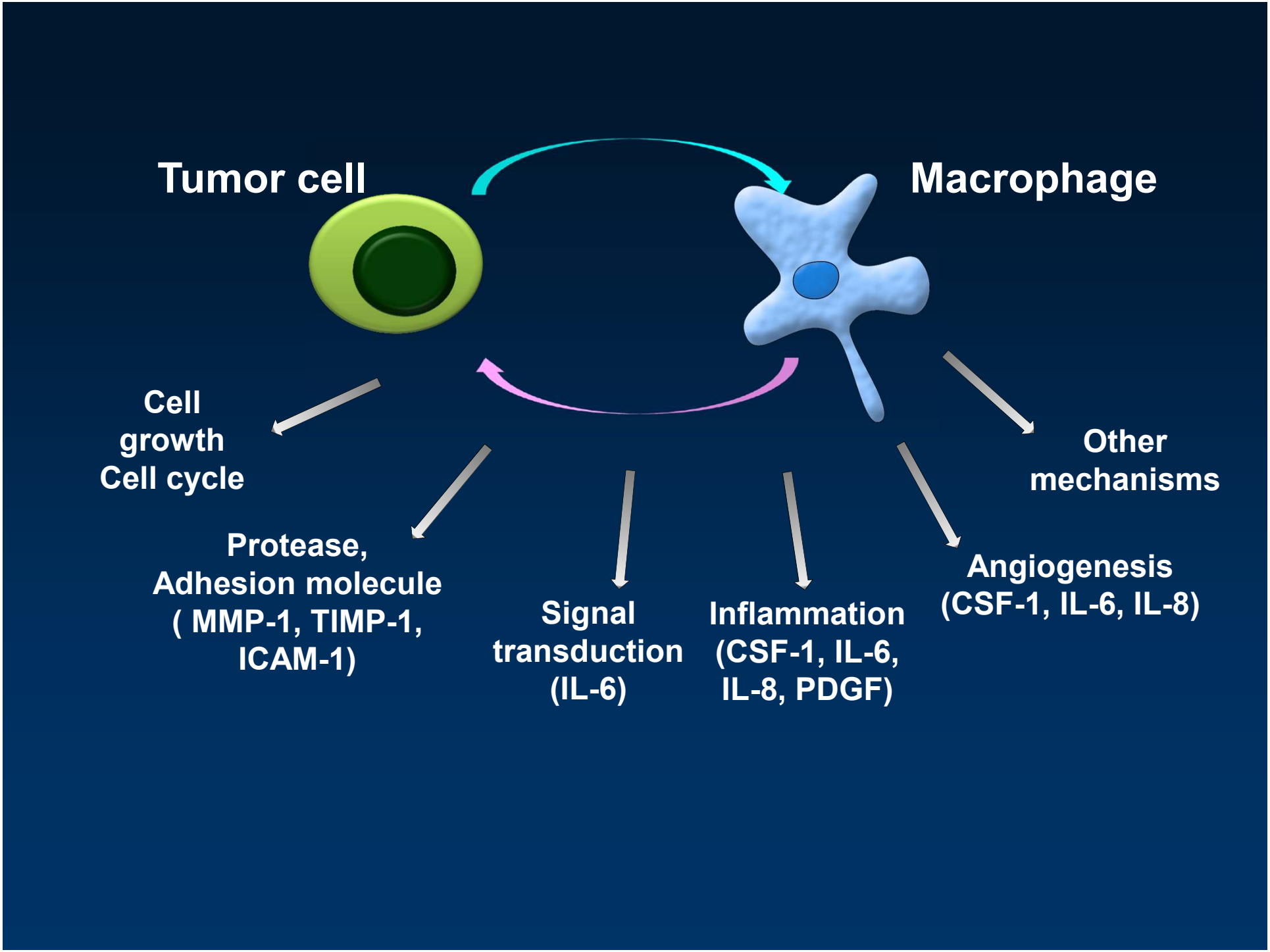
M2-macrophage

IL-10, IL-13, IL-4, CCL22
scavenger, mannose receptor

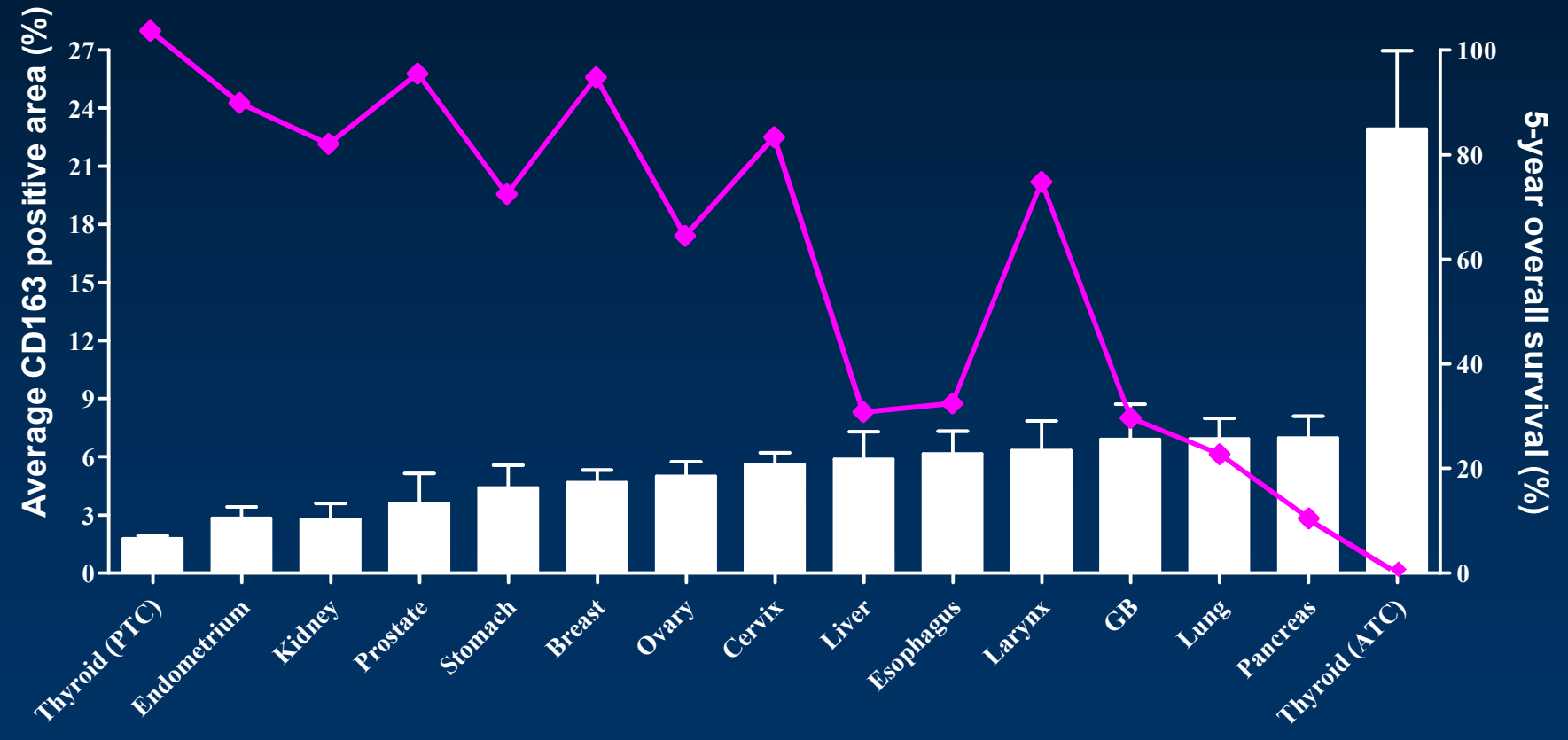
Cell clearance/wound healing
Tumor promotion

Interactions between macrophage and tumor cells



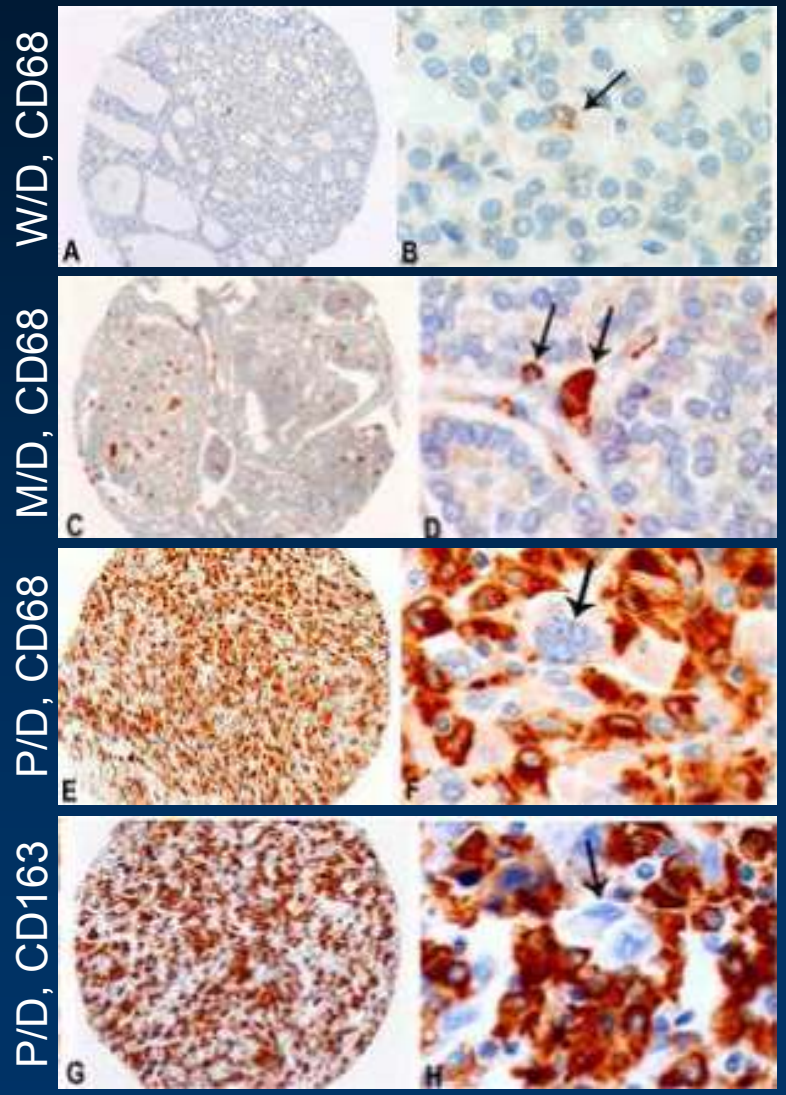

Tumor cell
Macrophage
Cell growth Cell cycle
Protease, Adhesion molecule (MMP-1, TIMP-1, ICAM-1)
Signal transduction (IL-6)
Inflammation (CSF-1, IL-6, IL-8, PDGF)
Angiogenesis (CSF-1, IL-6, IL-8)
Other mechanisms

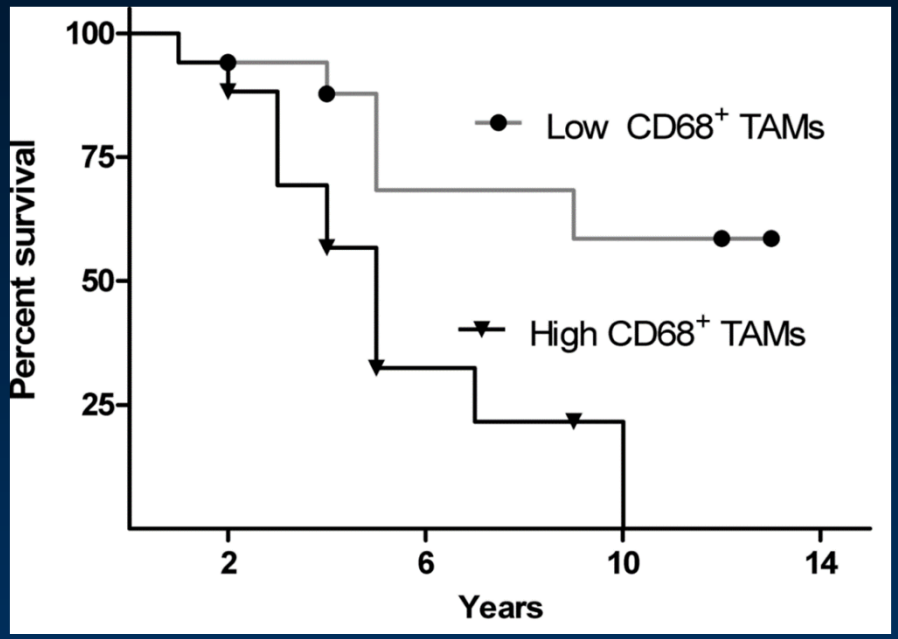
The relationship between macrophage densities and 5-yr survival rates of human cancers



CD163	1.8	2.8	2.8	3.6	4.4	4.7	5.0	5.6	5.9	6.1	6.3	6.9	6.9	7.0	22.9
5yr OS	100	86.5	78.8	92	69.4	91.3	61.6	80.1	28.6	30.2	71.7	27.5	20.7	8.7	NA

TAM densities in thyroid cancers

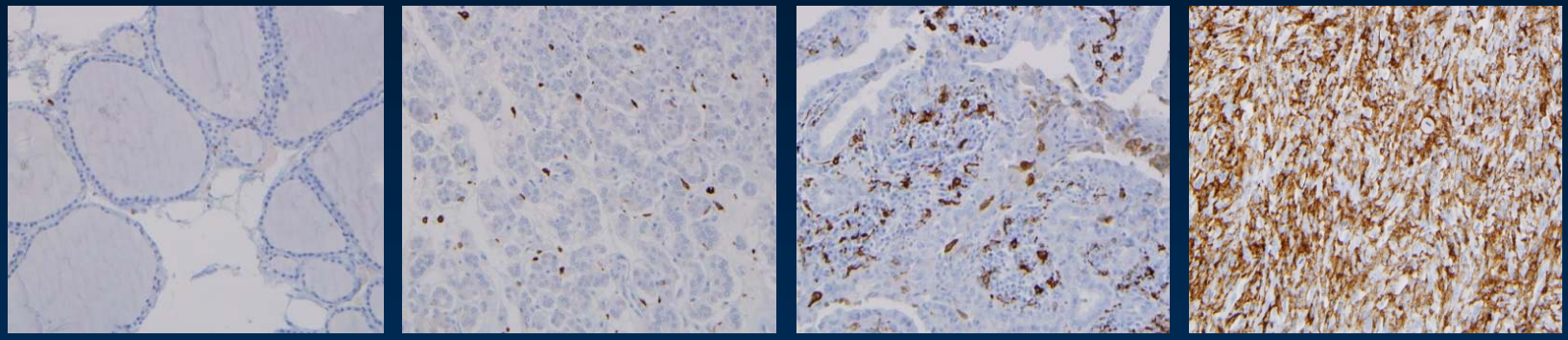




High density of TAMs in PDTC correlates with invasion and decreased cancer-related survival.

Ryder et al. Endocr Relat Cancer. 2008

TAM densities in thyroid tissues

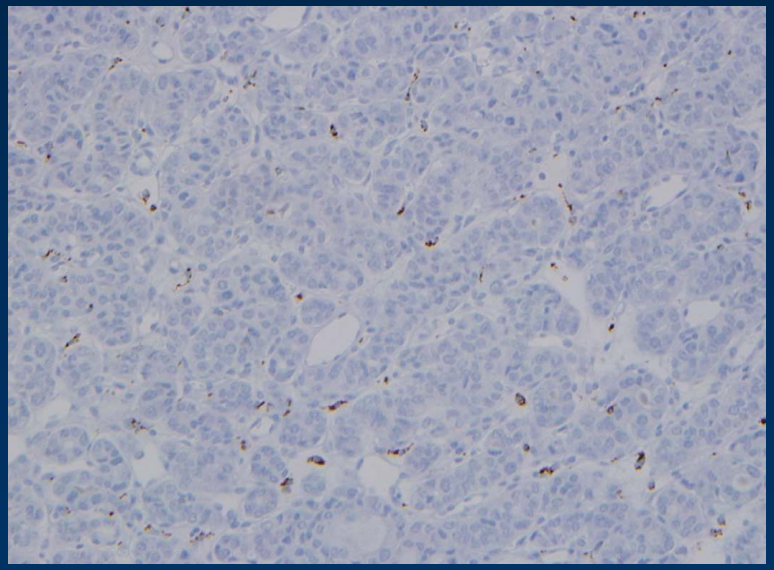


Macrophage	Normal (N=7)	Adenoma (n=57)	PTC (n=148)	ATC (n=17)	P-value
Negative	6 (86 %)	0	0	0	<0.001
Low density	1 (14 %)	41 (72 %)	78 (57 %)	3 (18 %)	
High density	0	16 (28 %)	58 (43 %)	14 (82 %)	

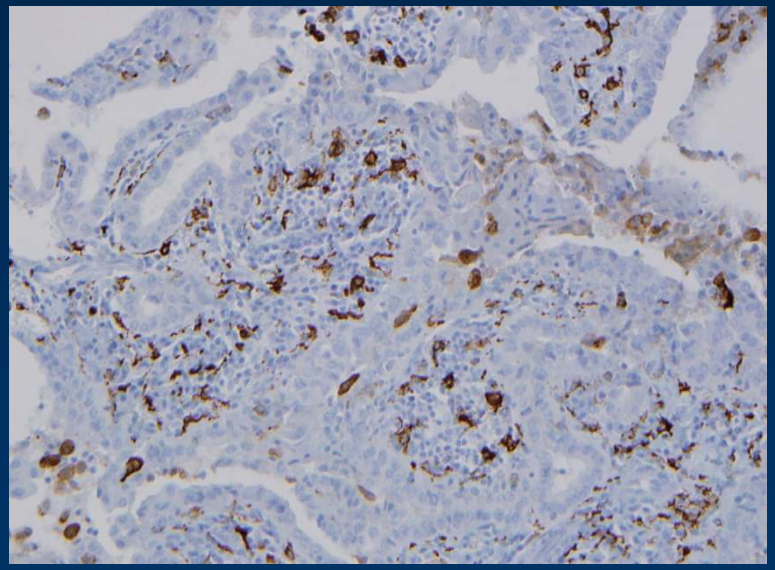
TAM densities in Papillary thyroid cancers

- TAMs were scored by the number of CD68+ cells/total tumor cells

Low (<25%)



High (25% to 70%)

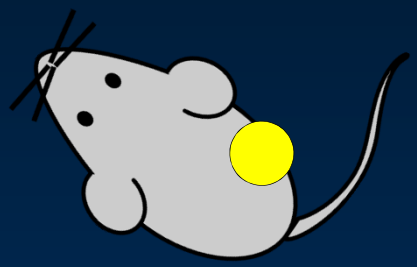


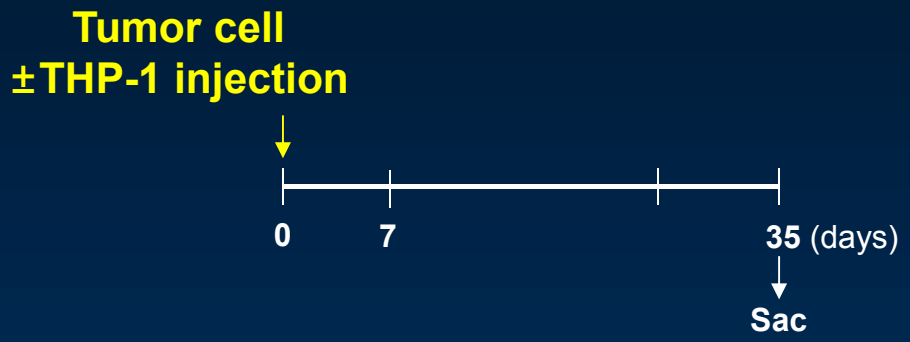
Kim, Cho et al. EnM 2013

Clinical characteristics according to the TAM densities

TAM density	CD163		P-value
	Low (n=79)	High (n=64)	
Sex (M/F)	13/66	12/52	0.720
Age of diagnosis	45.3 ± 15.8	43.5 ± 16.6	0.500
Tumor size (cm)	2.3 ± 1.1	2.8 ± 1.7	0.042
Extrathyroidal invasion	15 (22%)	13 (22%)	0.997
LN metastasis	38 (62%)	48 (80%)	0.031
Recurrence or metastasis	5 (16%)	9 (23%)	0.429
$CD31^+$ cell (%)	3 (5%)	11 (19%)	0.016
$CD68^+$ cell (%)	3 (5%)	25 (40%)	<0.01

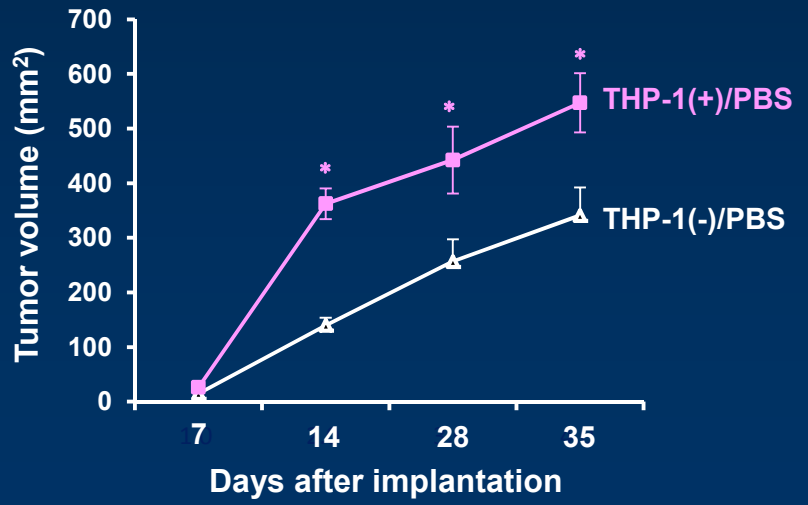
Macrophages support tumor growth



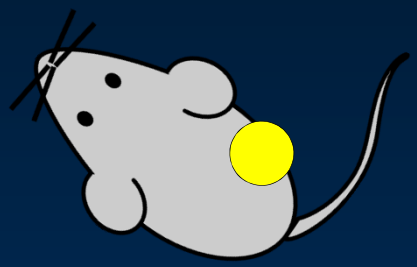


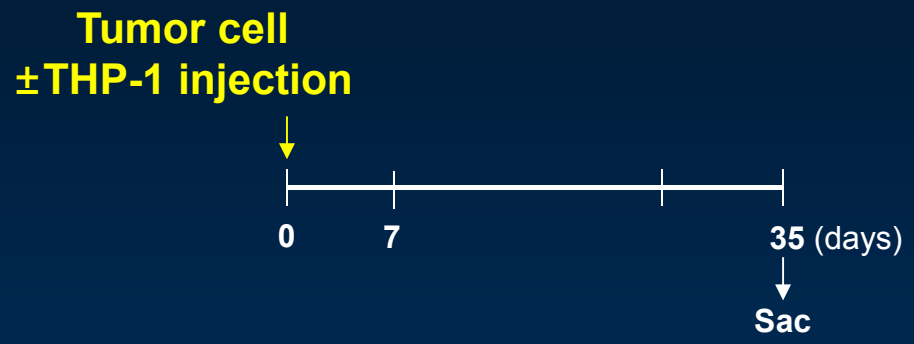
BHP10-3 only

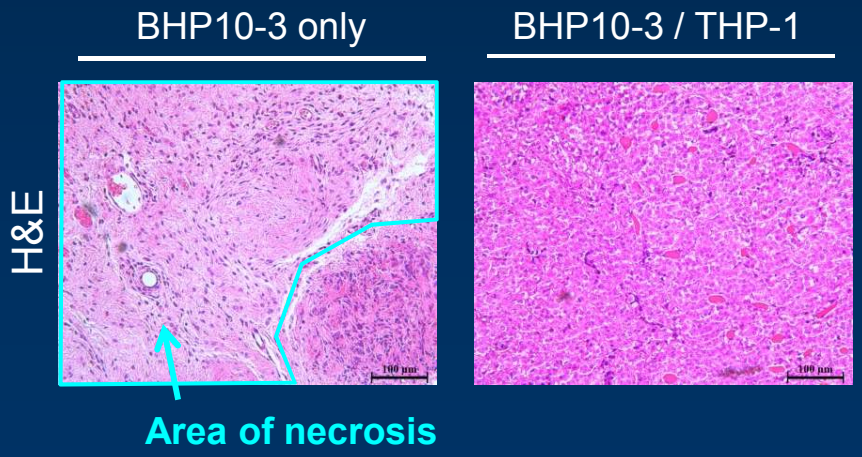
BHP10-3/THP-1

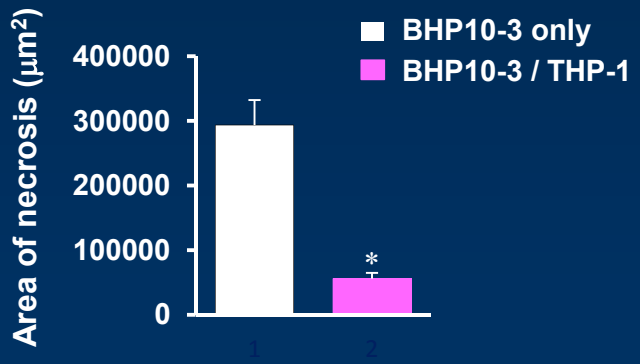


Macrophages support tumor growth

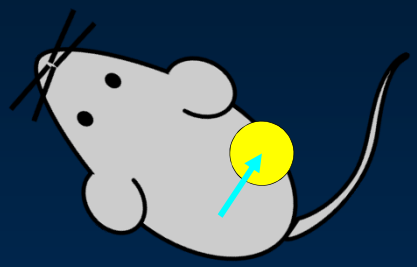








Clodronate liposome inhibited macrophage-related tumor growth



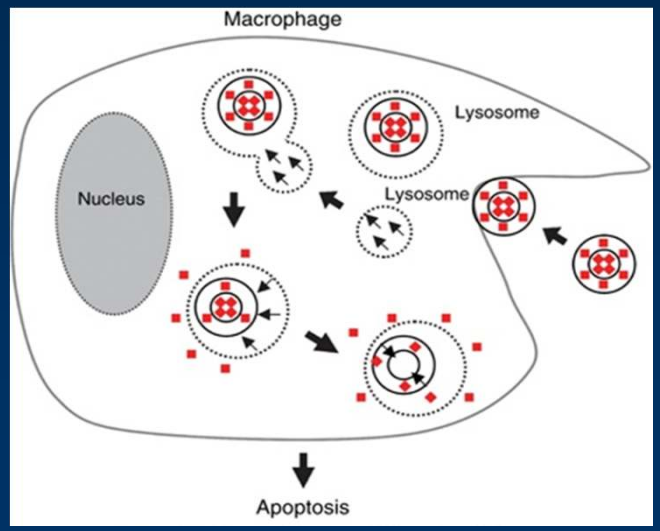
Tumor cell
±THP-1 injection

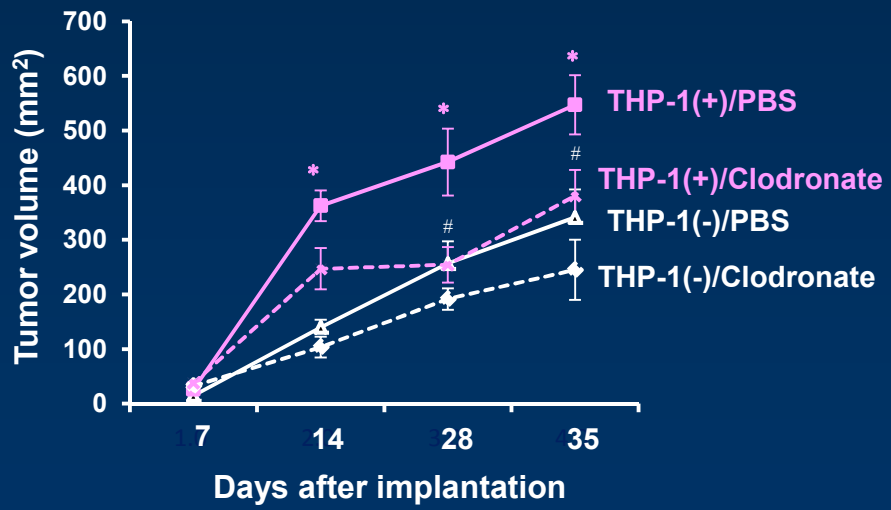
Clodronate liposome
Peritumoral injection
(3 times/ week)

0 7 35 (days)

Sac

Clodronate liposome





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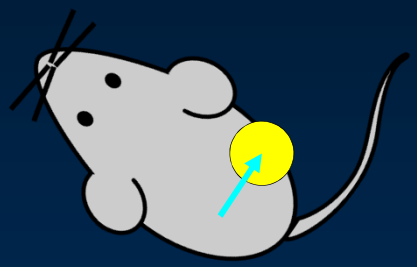
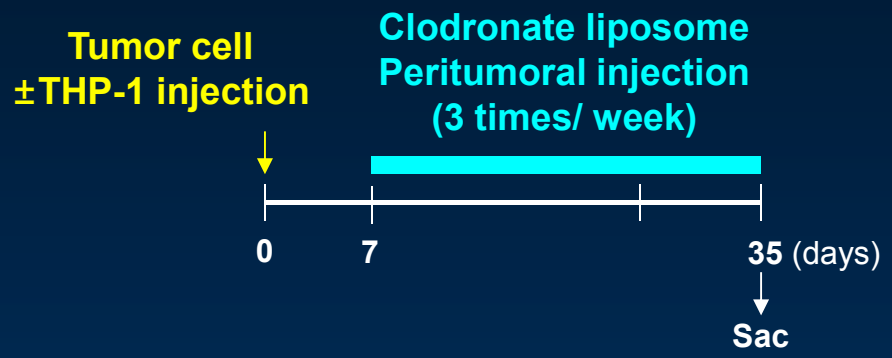
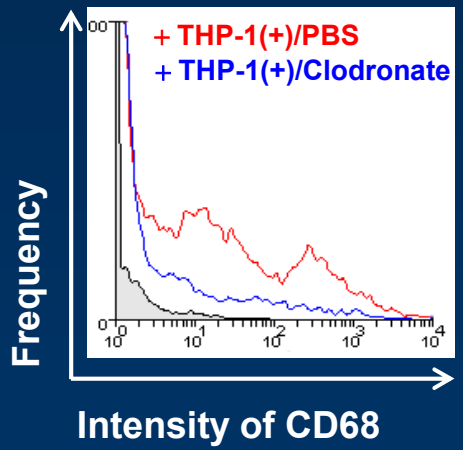
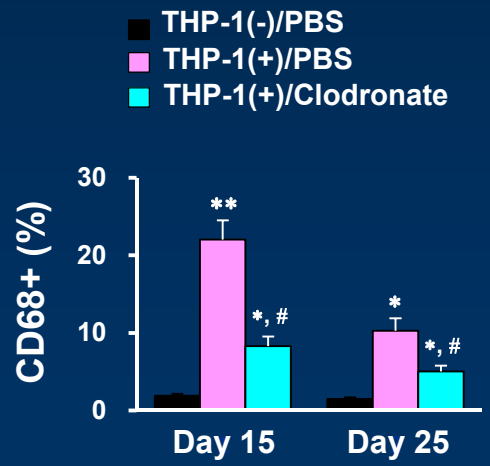


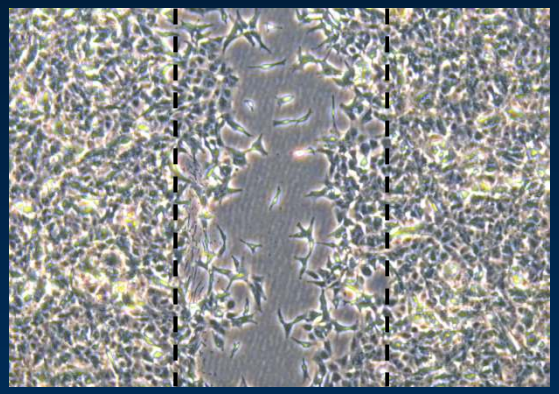
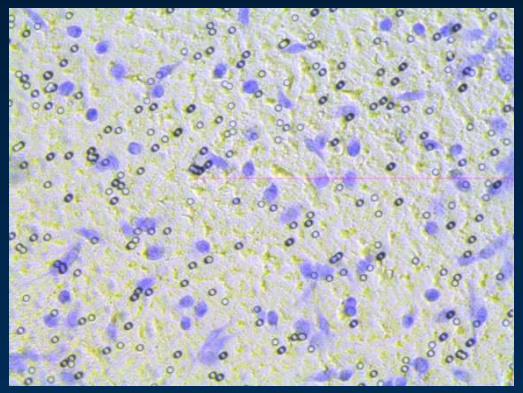
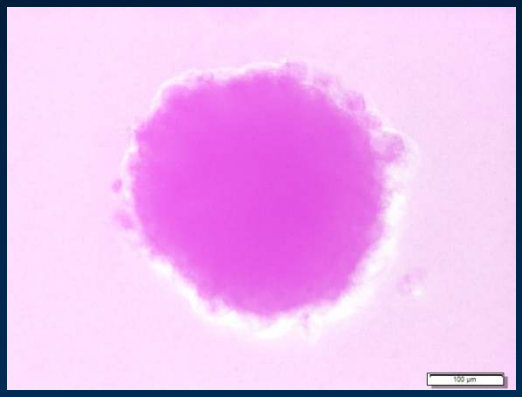




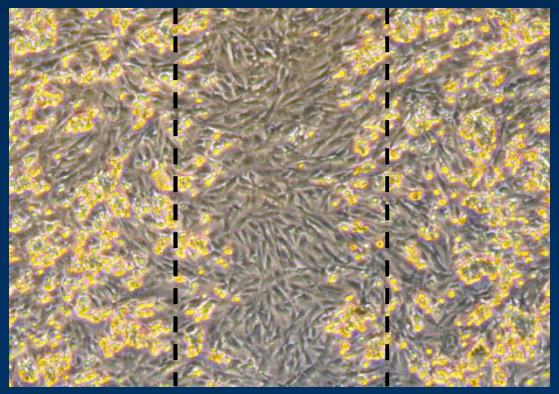
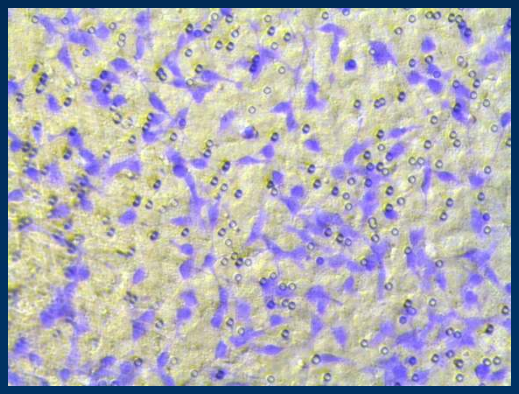


TAMs support tumor cell migrations

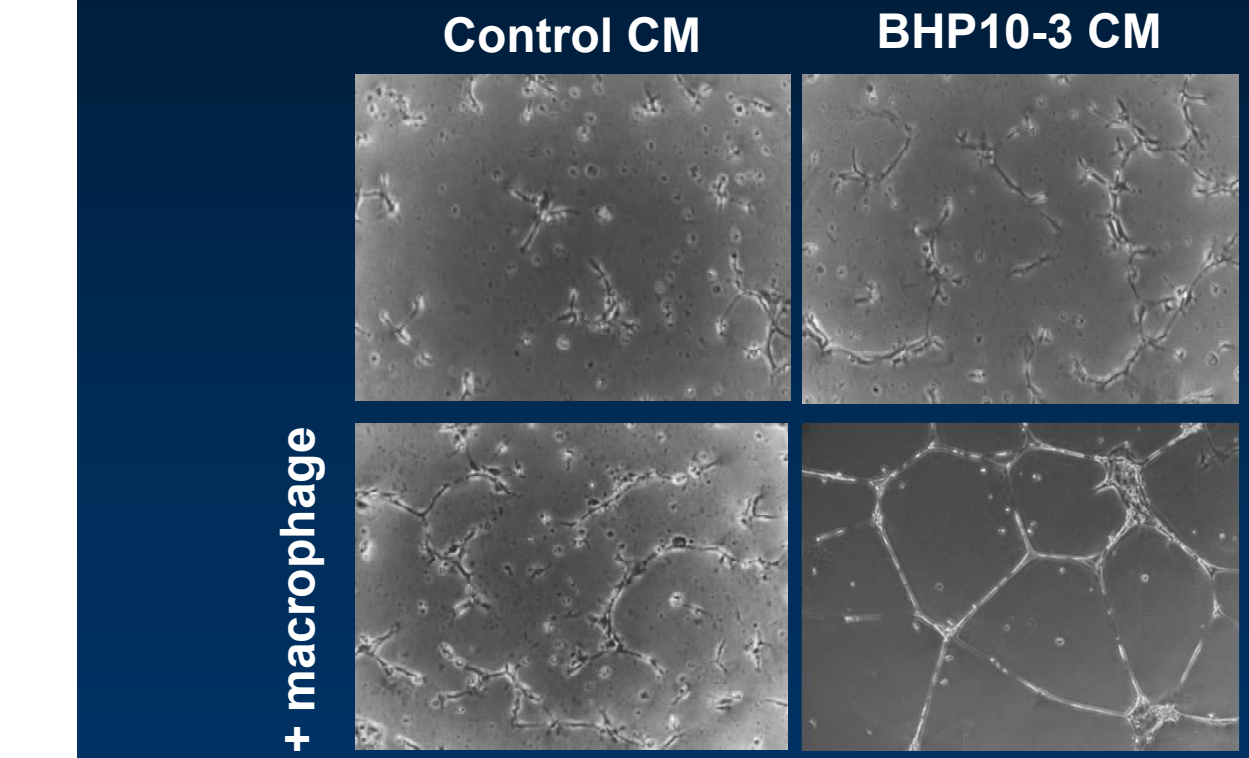
Wound healing assay | **Transwell assay** | **3D invasion assay**

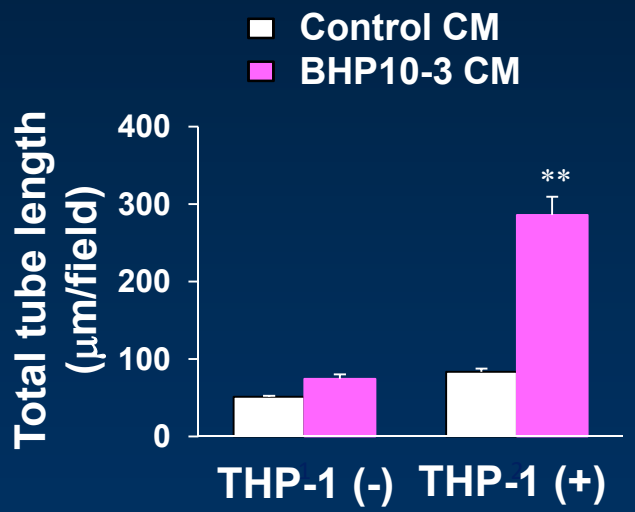




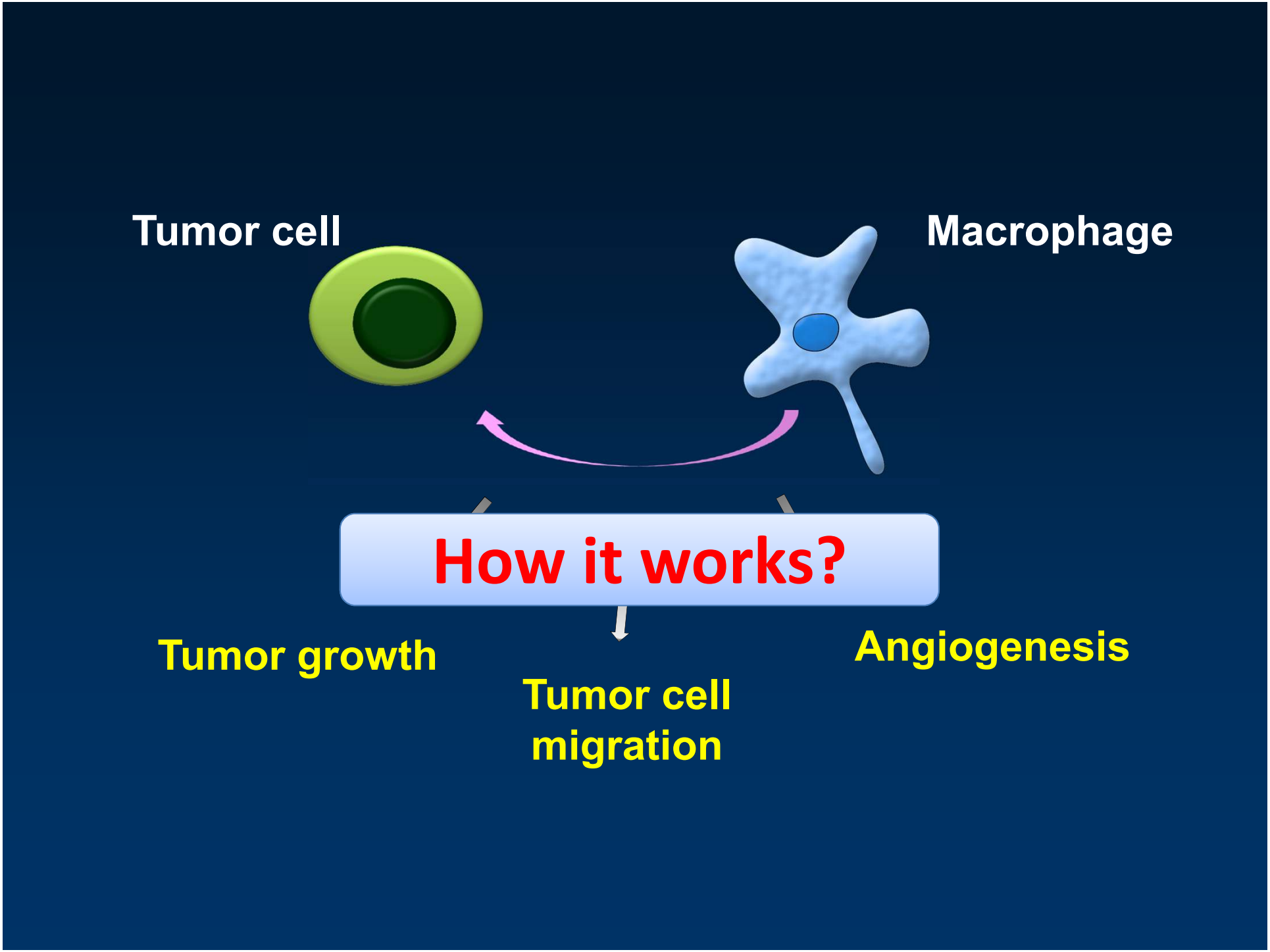
+ macrophage


TAM increased angiogenesis in tumor microenvironment





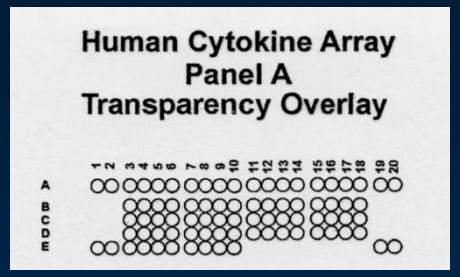

Tumor cell
Macrophage
How it works?
Tumor growth
Tumor cell migration
Angiogenesis

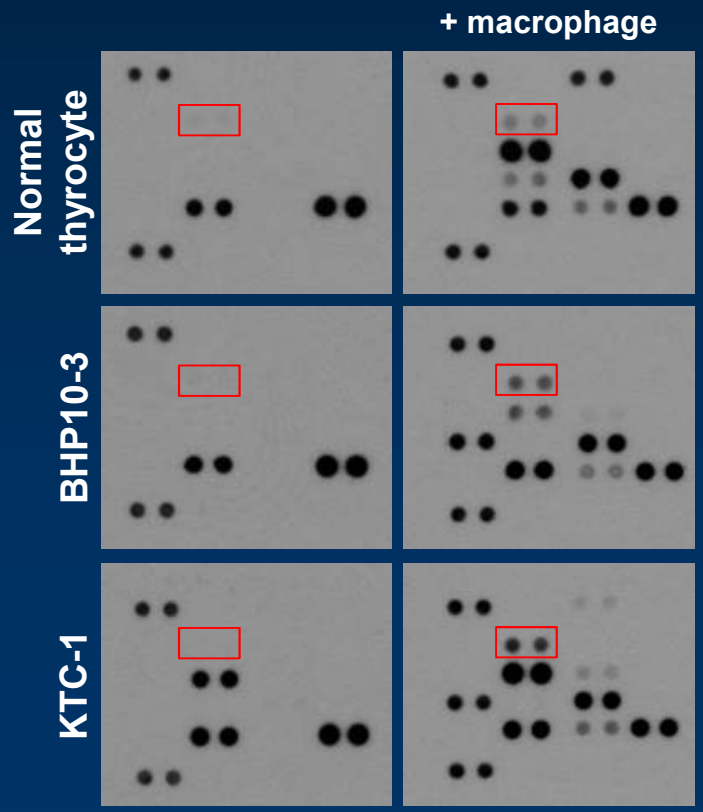
CXCL16 expressions in tumor/macrophage co-cultures

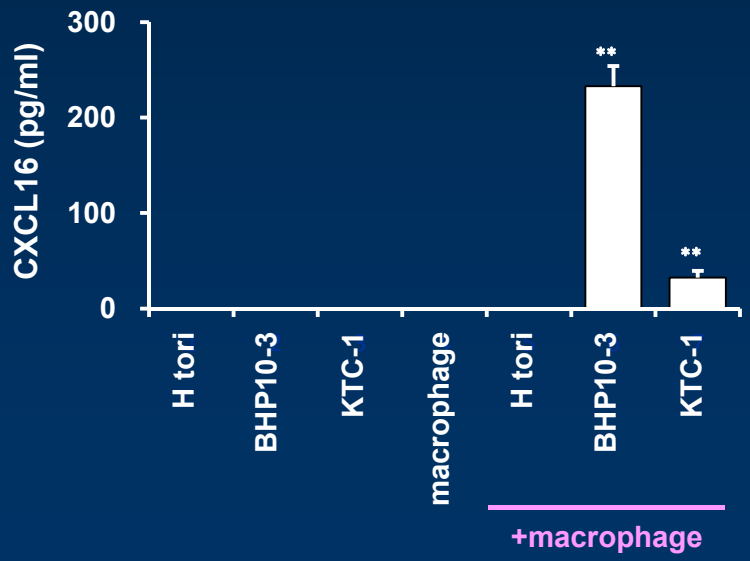
- H.Tori (normal thyroid cells)
- BHP10-3, KTC-1 (PTC cells)

+ macrophage

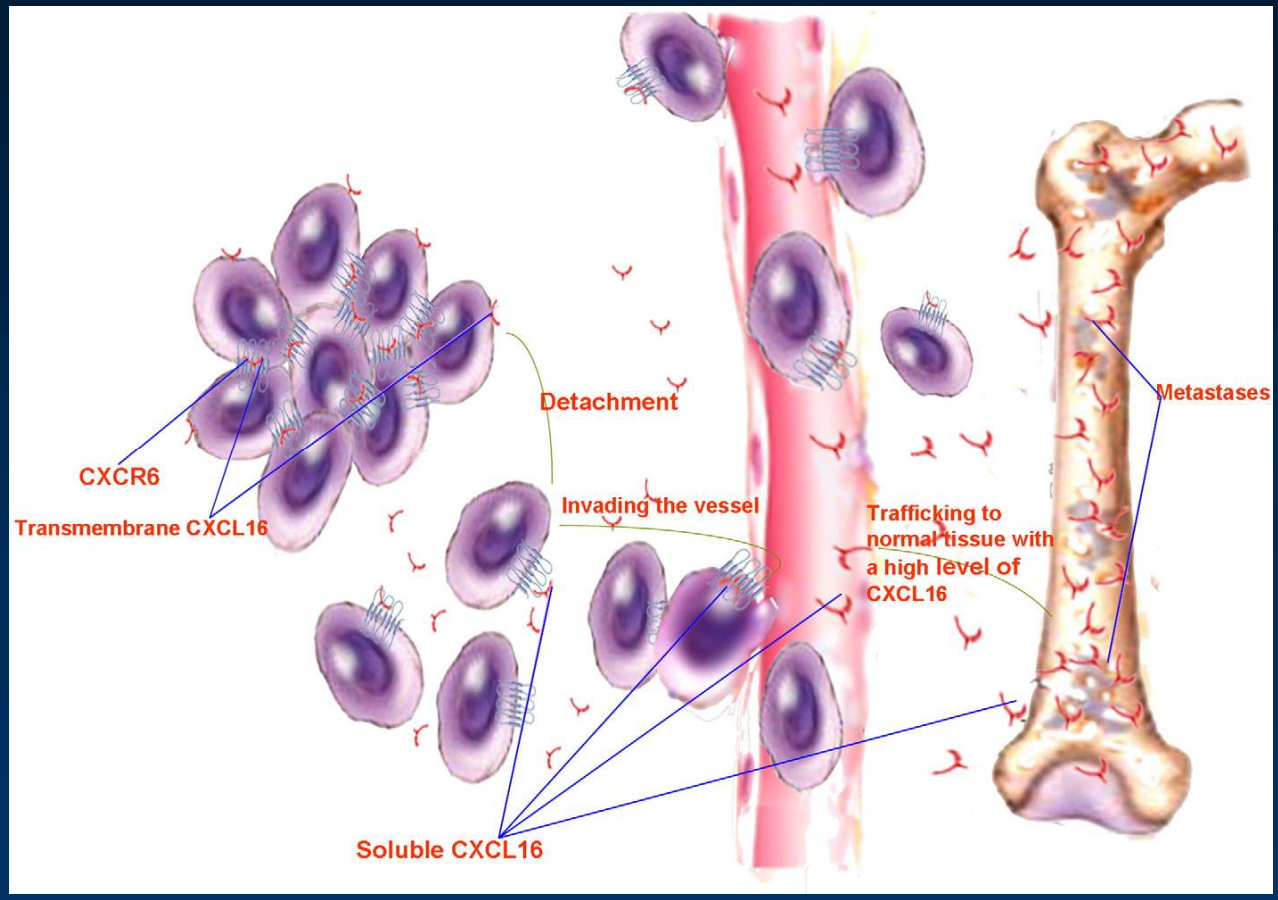
Conditioned medium (CM)







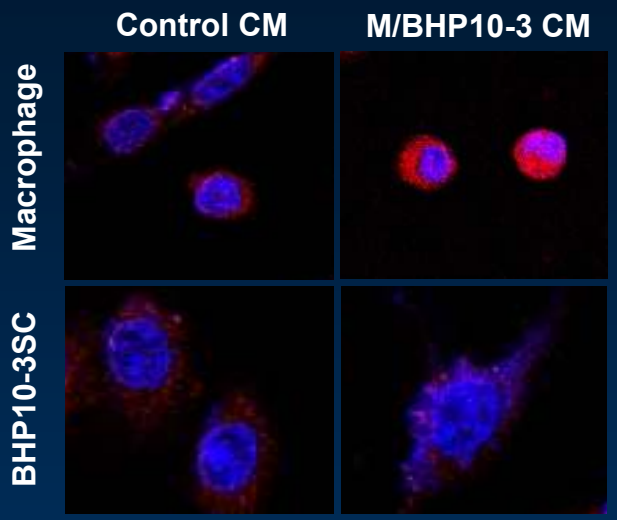
CXCL16/CXCR6: a regulator of cancer metastasis

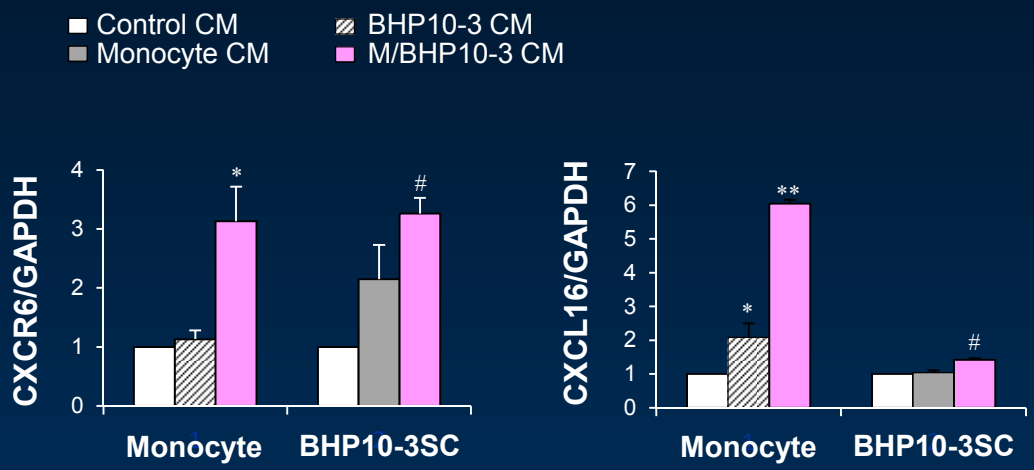


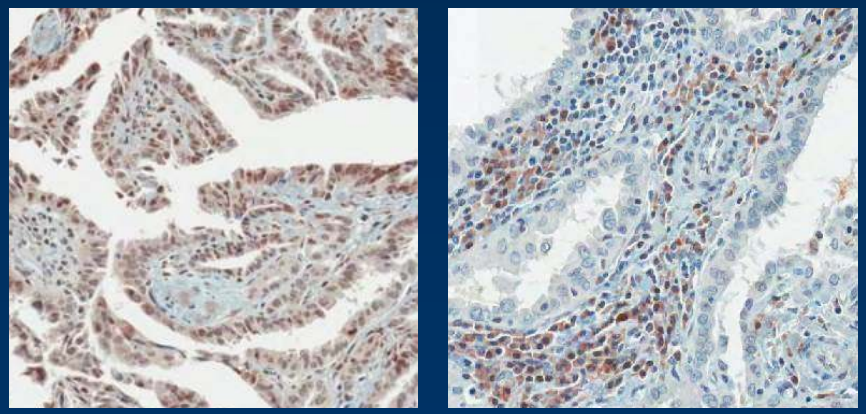
Transmembrane CXCL16: growth

Soluble CXCL16: metastasis

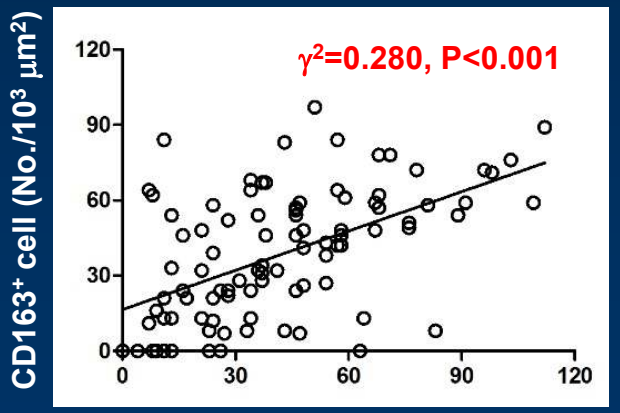
CXCL16 expressions in PTCs



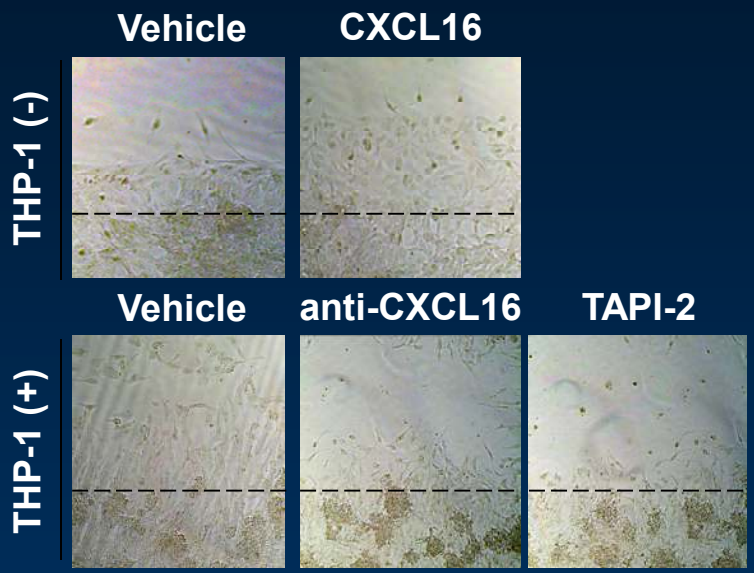


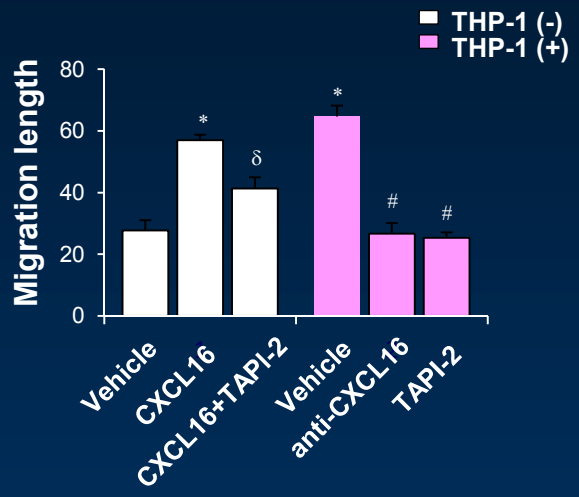


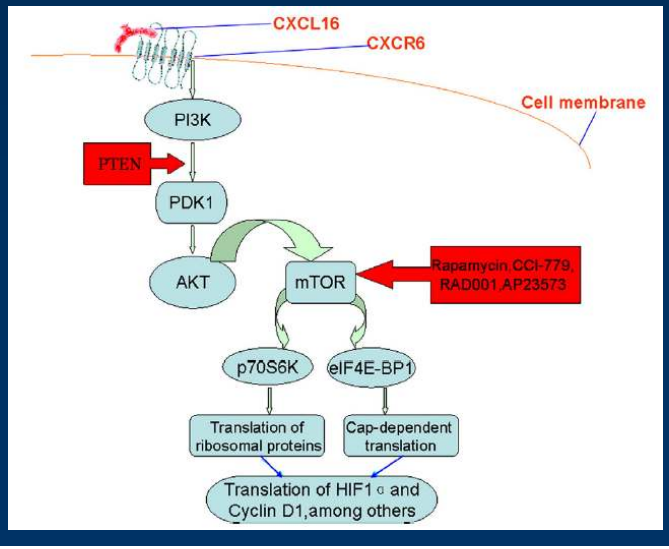
CXCR6 expressions in both tumor cell and stroma

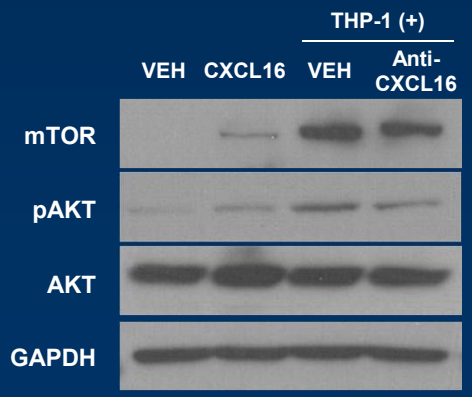


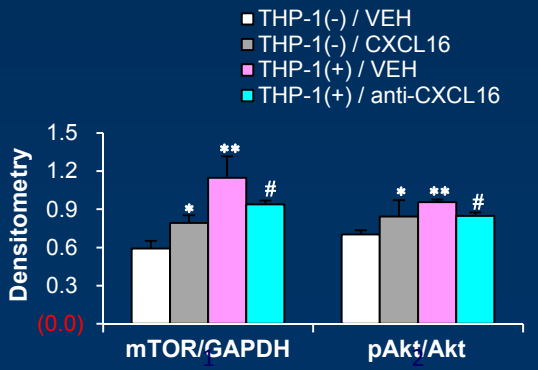
CXCL16 mediated macrophage effects on tumor cell migration



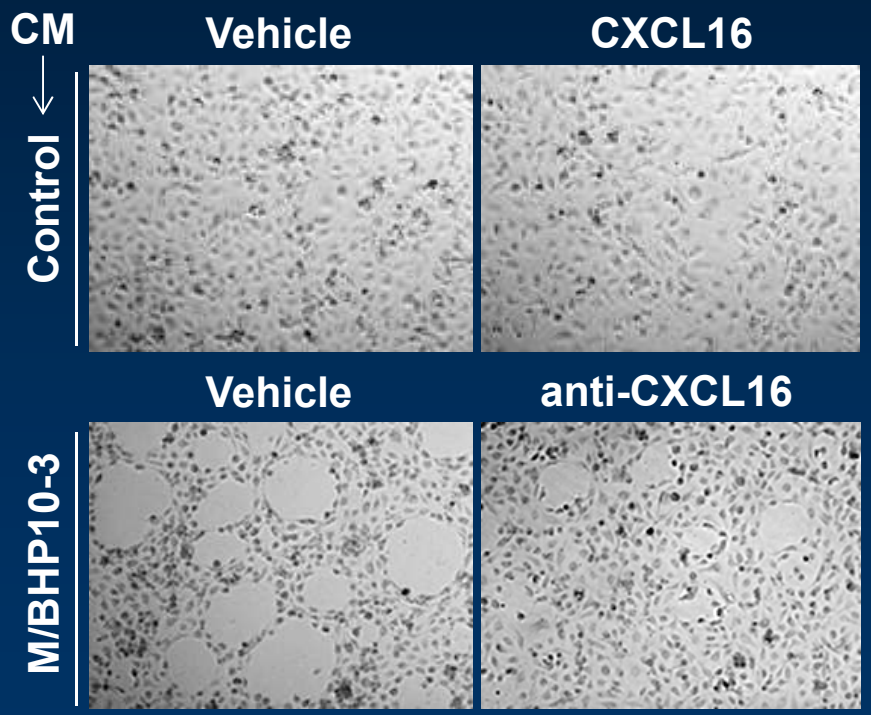


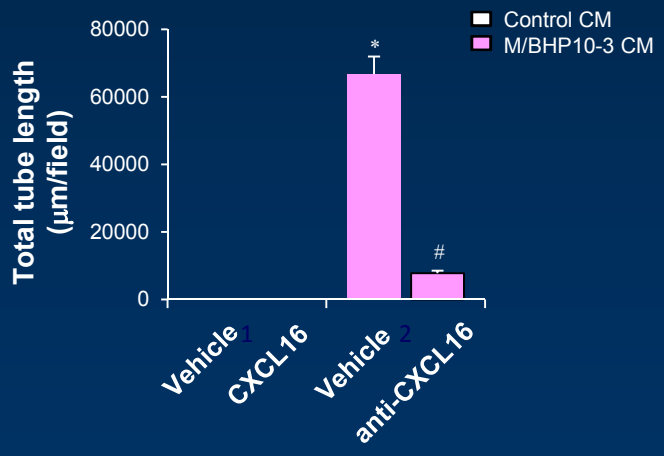


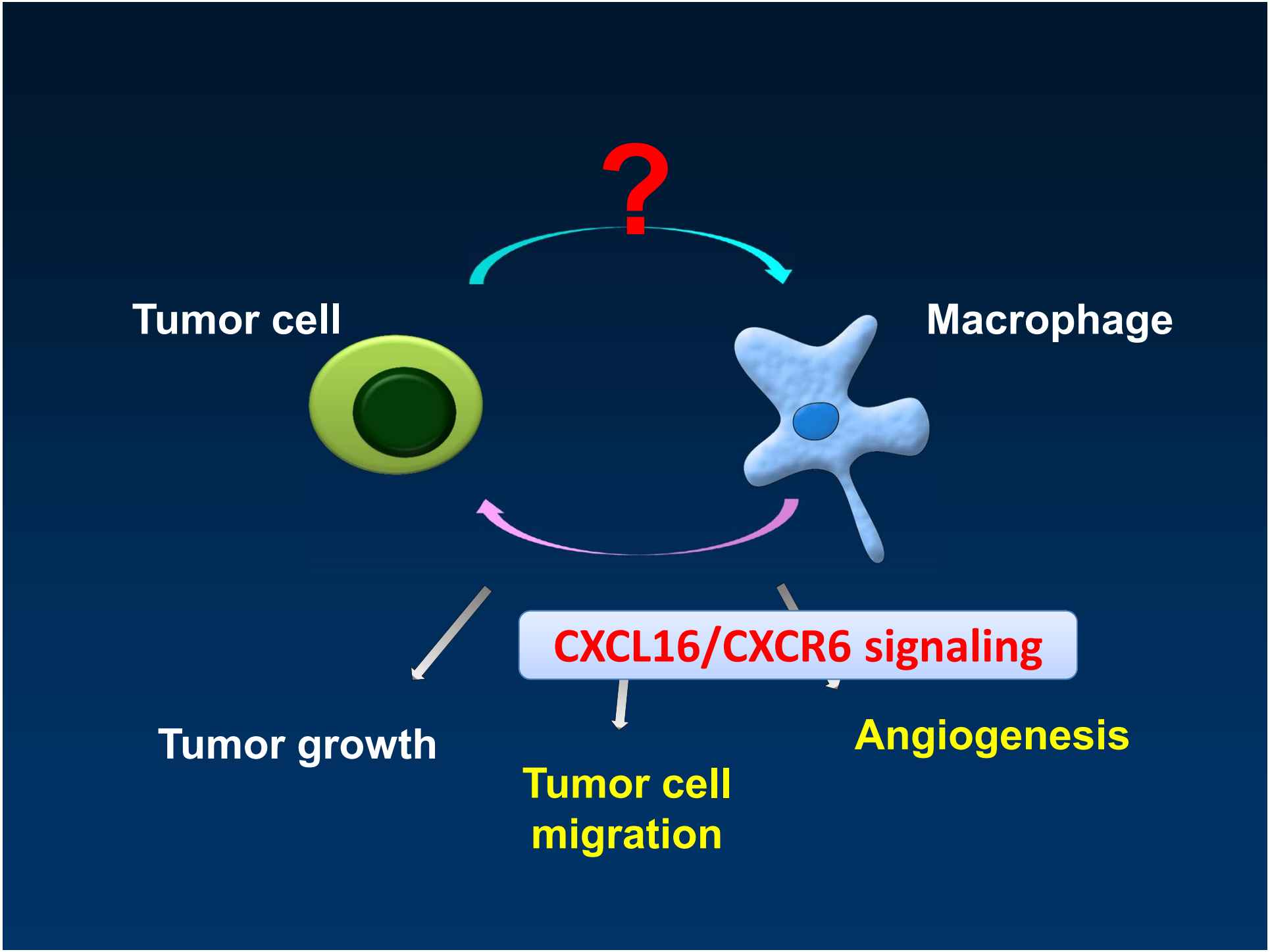




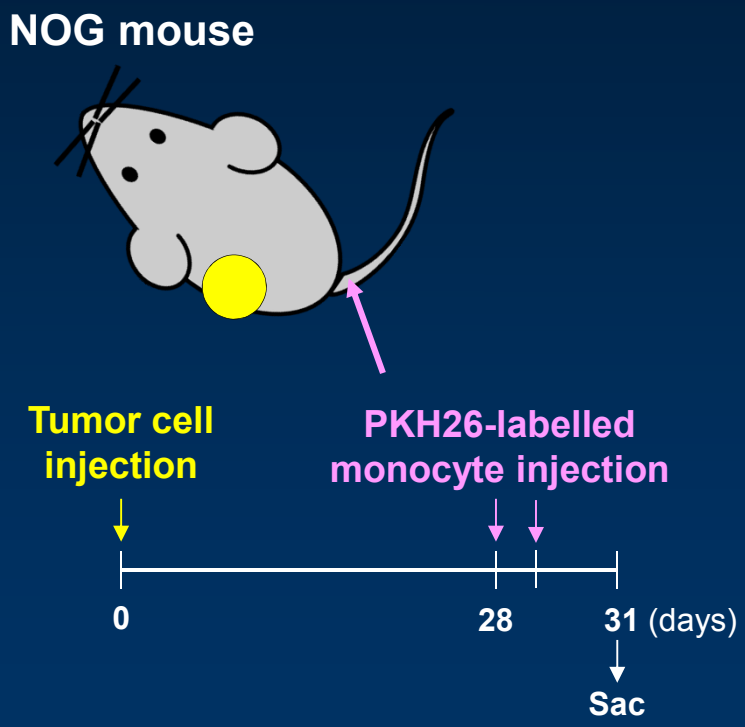
CXCL16 mediated macrophage effects on angiogenesis

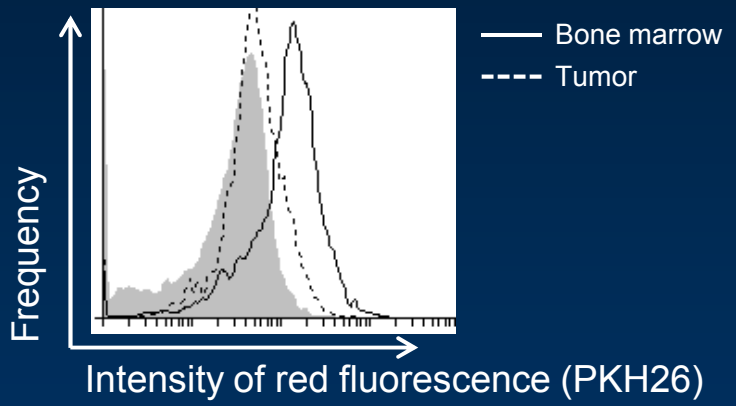





?
Tumor cell
Macrophage
CXCL16/CXCR6 signaling
Tumor growth
Tumor cell migration
Angiogenesis

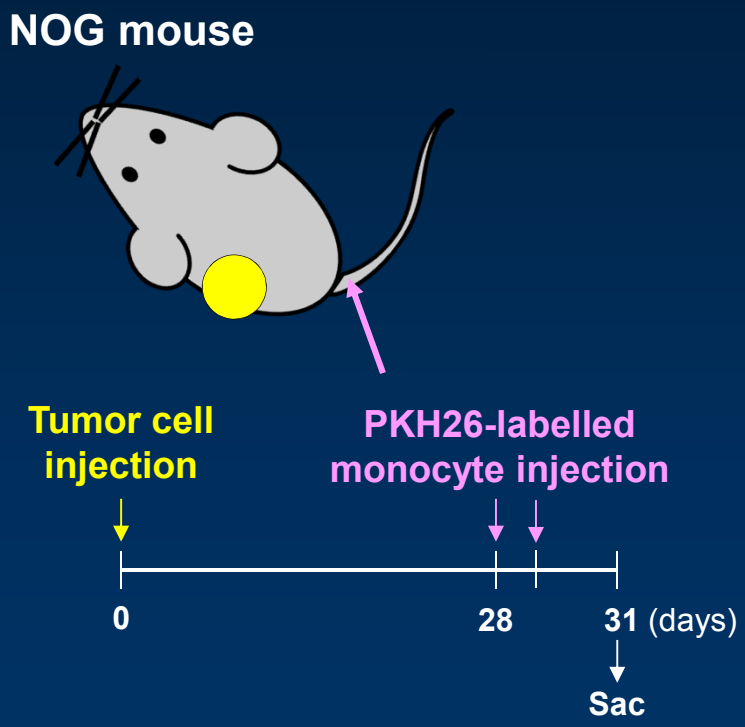
Tumor recruit circulating monocytes and switch into M2-macrophages

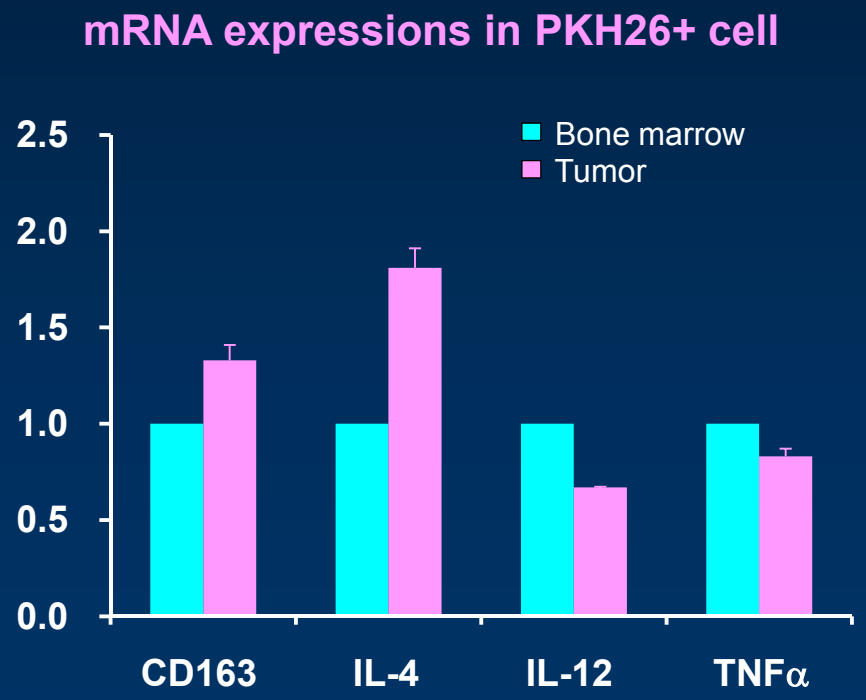


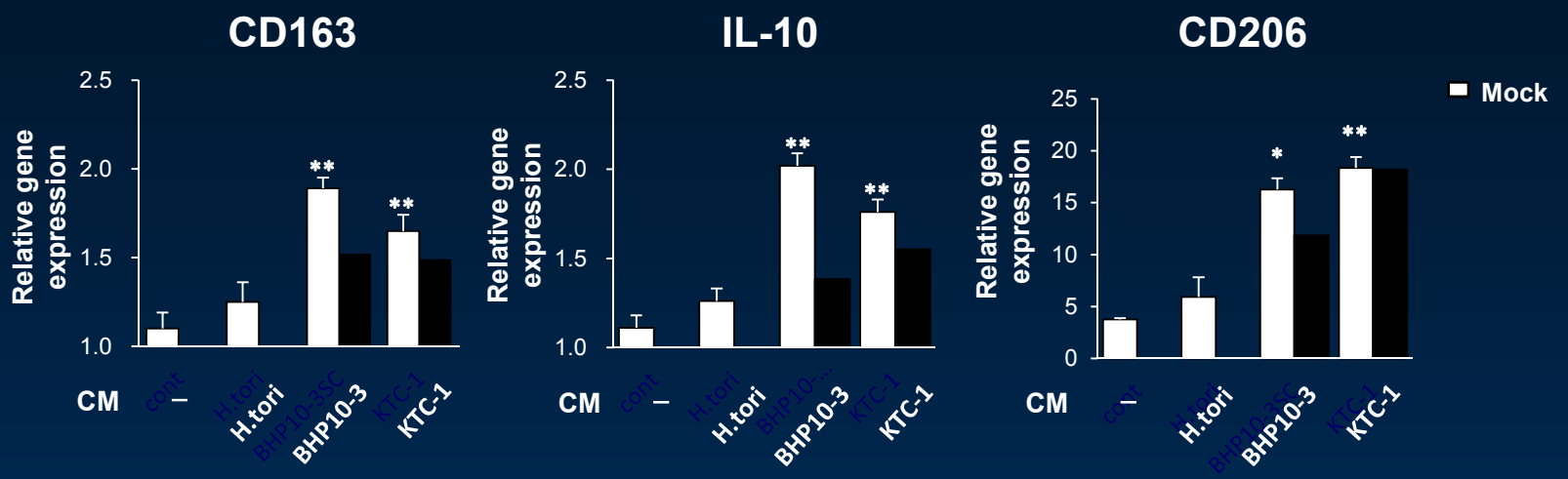


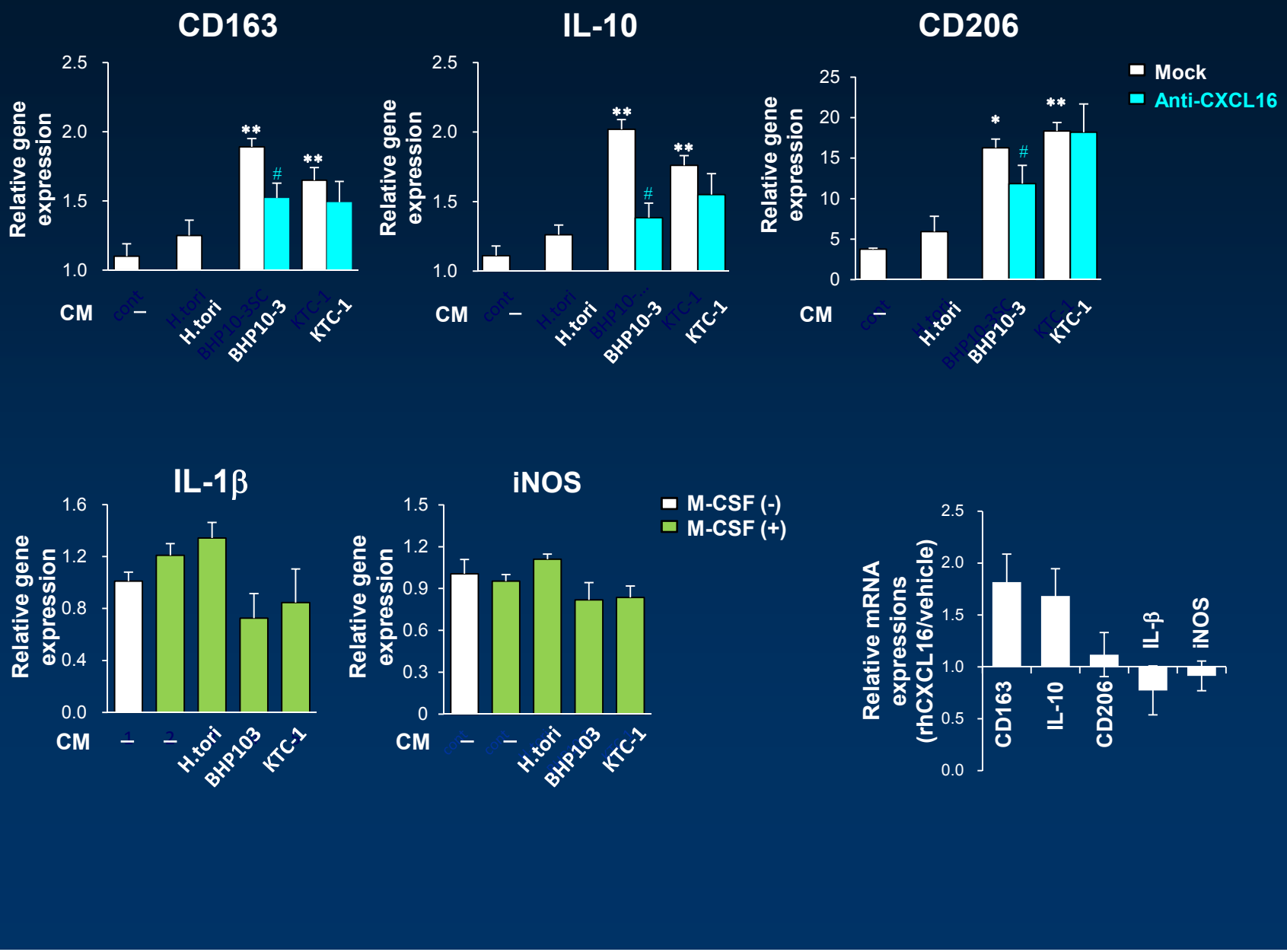
PKH+ cell (%) in 10^6 cells	
Peripheral blood	0
Bone marrow	6.3 ± 0.7
Tumor	13.3 ± 3.7

Tumor recruit circulating monocytes and switch into M2-macrophages

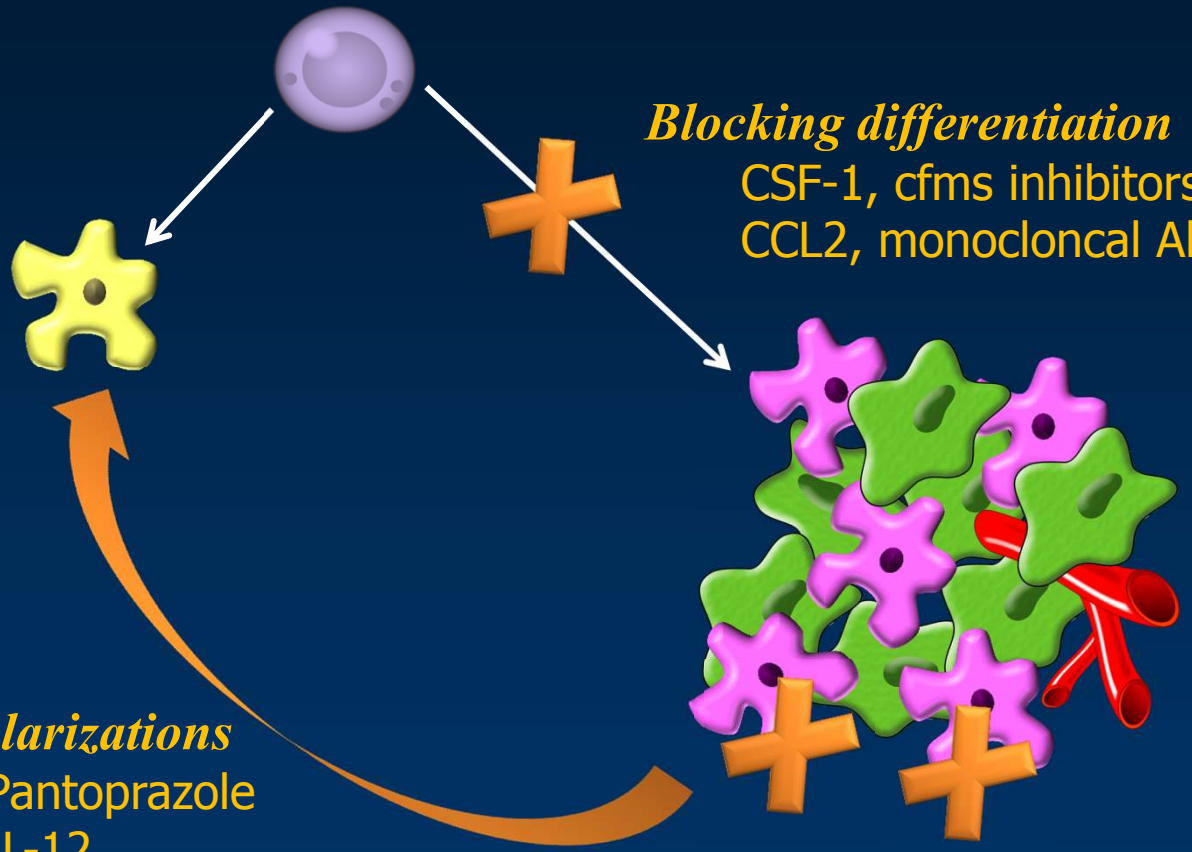





CD163
IL-10
CD206
Relative gene expression
2.5
2.0
1.5
1.0
25
20
15
10
5
0
**
*
Mock
CM
–
cont
H.tori
BHP10-3SC
BHP10-3
KTC-1


CD163
IL-10
CD206
Relative gene expression
CM
cont
–
H.tori
BHP10-3SC
BHP10-3
KTC-1
Mock
Anti-CXCL16
IL-1β
iNOS
M-CSF (-)
M-CSF (+)
BHP103
Relative mRNA expressions (rhCXCL16/vehicle)
IL-β

TAM, as a therapeutic target in cancer therapy



Blocking differentiation

CSF-1, cfms inhibitors

CCL2, monocloncal Ab (MLN1202)

Repolarizations

Pantoprazole

IL-12

Killing TAM in the tumor microenvironments

Clodronate-loaded liposomes (CLIP)

Zoledronic acid

Conclusions

- TAMs support tumor growth, invasion, and metastasis.
- CXCL16 signaling mediated TAM actions in human papillary thyroid cancers.

- TAM might be a potential therapeutic targets of human cancers.

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