Tumor Cell and Non Tumor Cell Cross Talk CSF-1/CSF-1R Axis Targeting

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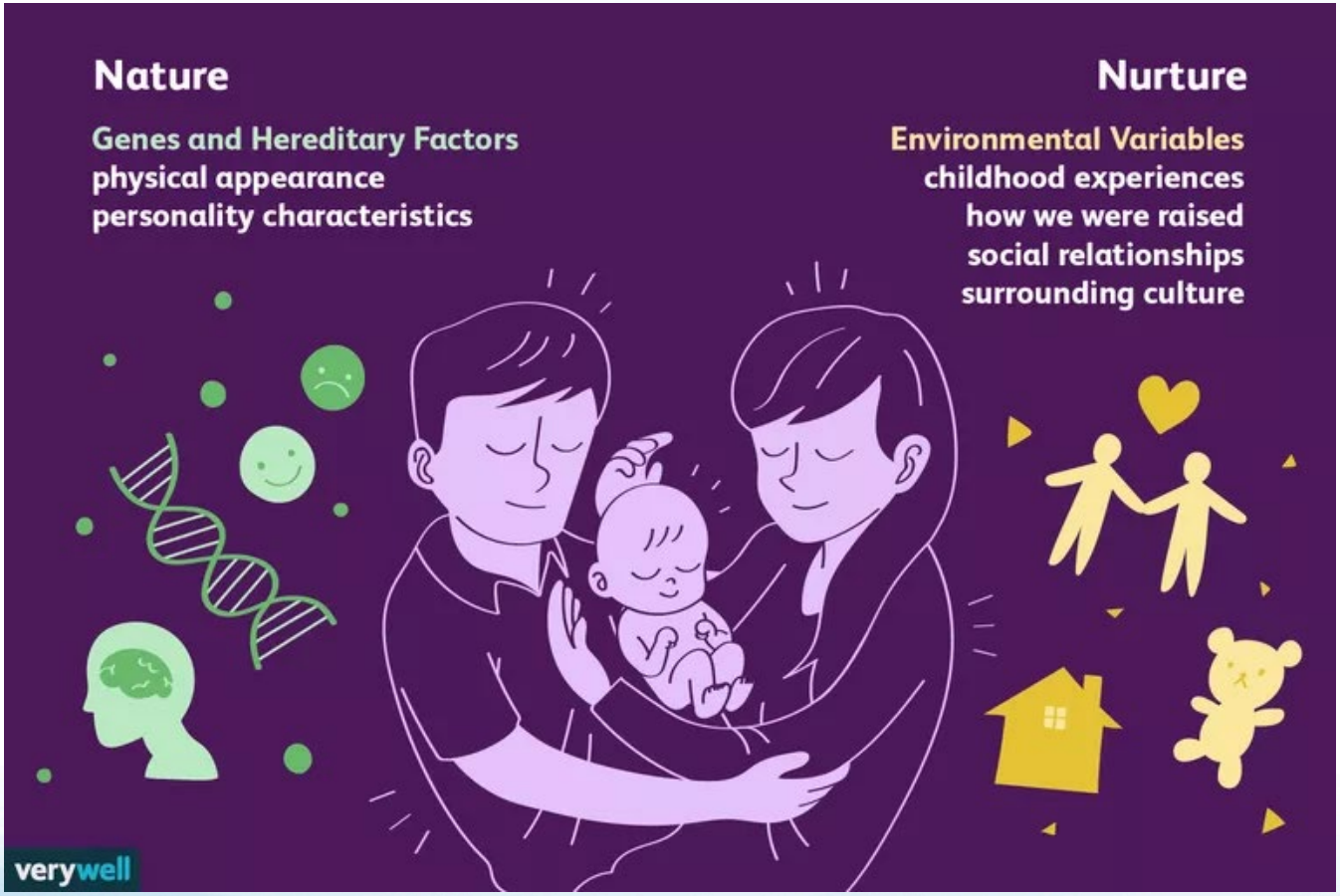
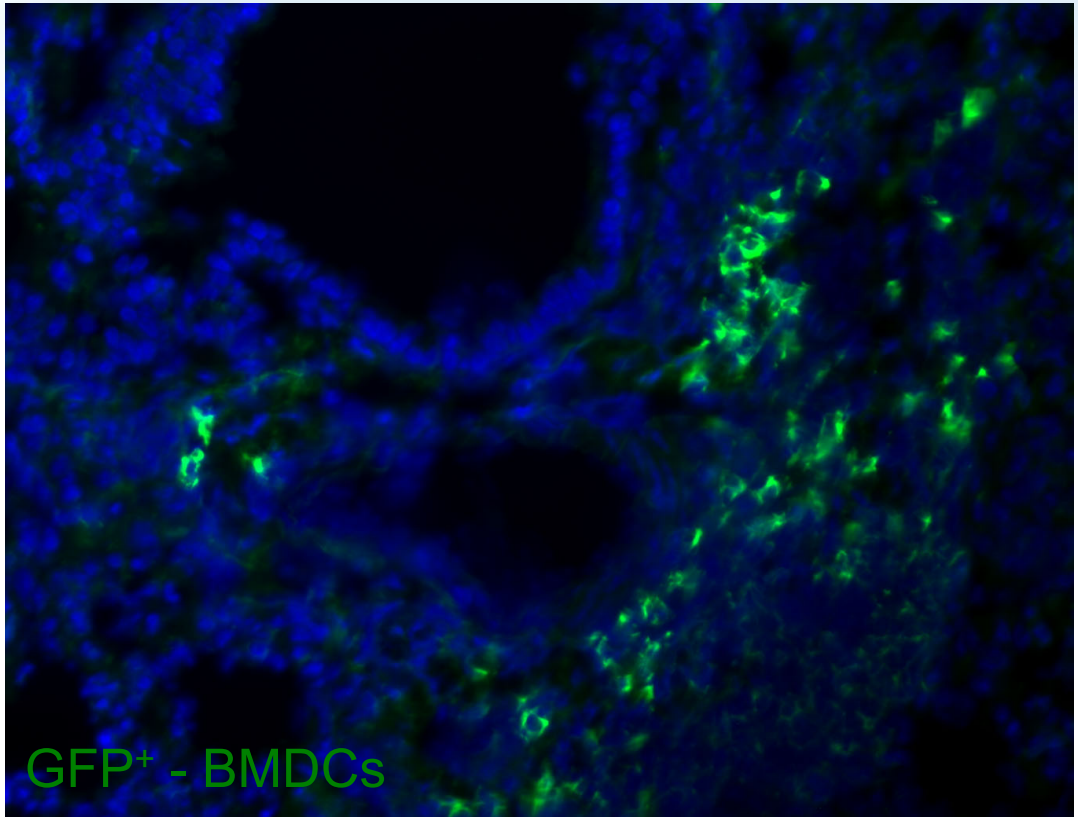
In the real world there is no real nature versus nurture argument, only infinitely complex, moment-to-moment interactions between genetics and environmental effects



The Pre-Metastatic Niche

- Specialized microenvironment that supports disseminated tumor cells



Composed of

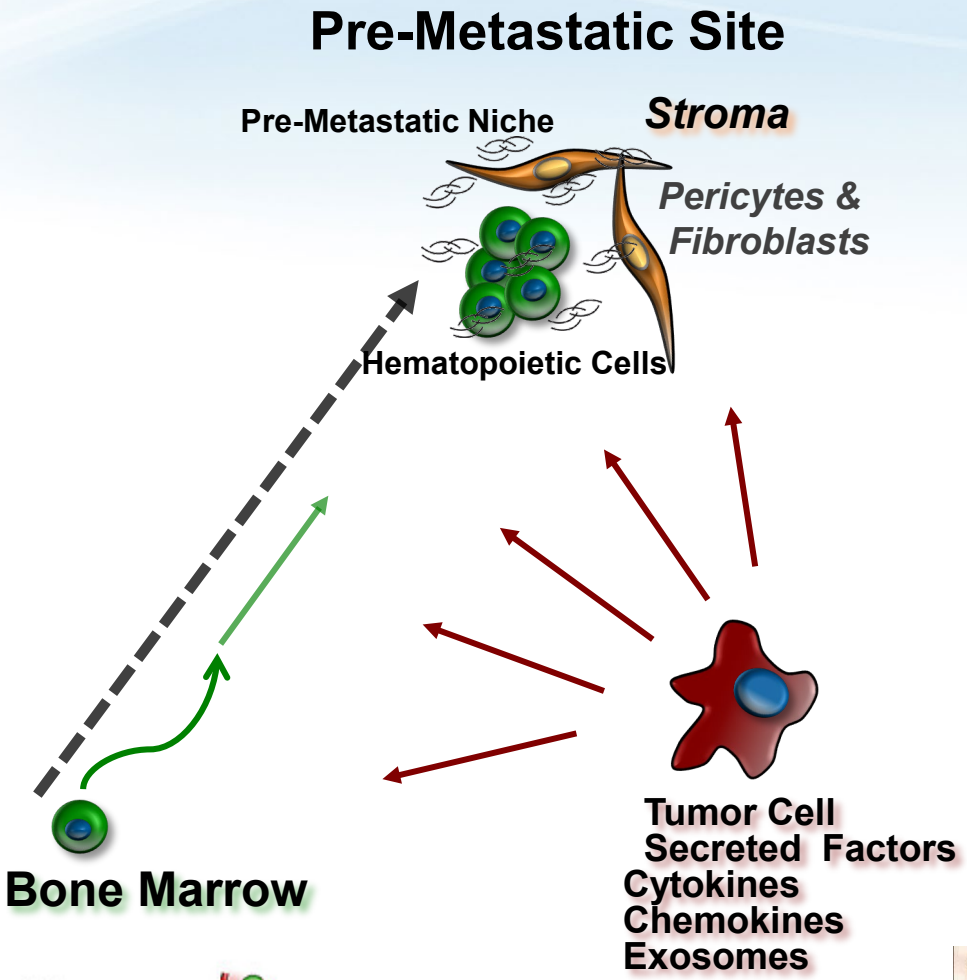
- Activated stromal cells contribute to enhanced extracellular matrix

- Bone Marrow-Derived Hematopoietic Cells:
  - hematopoietic progenitors,
  - myeloid derived suppressor cells
  - neutrophils
  - macrophages

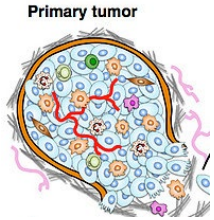
- Signaling cascade within the niche

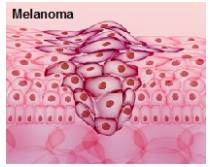
- Dynamic interchange with residents and recruited cell populations

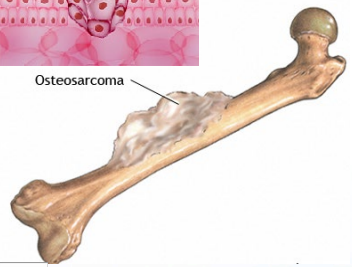
Identifying the Pre-Metastatic Niche

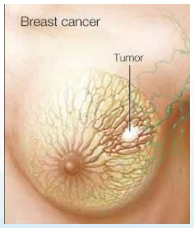


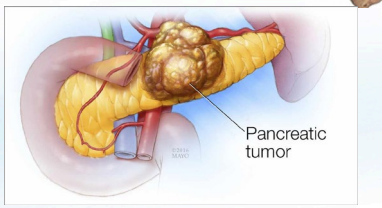
- Dynamic, specialized microenvironment that supports disseminated tumor cells
- Activated mesenchymal cells with associated extracellular matrix remodeling
- Bone Marrow (BM) Derived Myeloid Cells

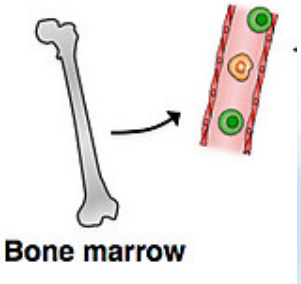




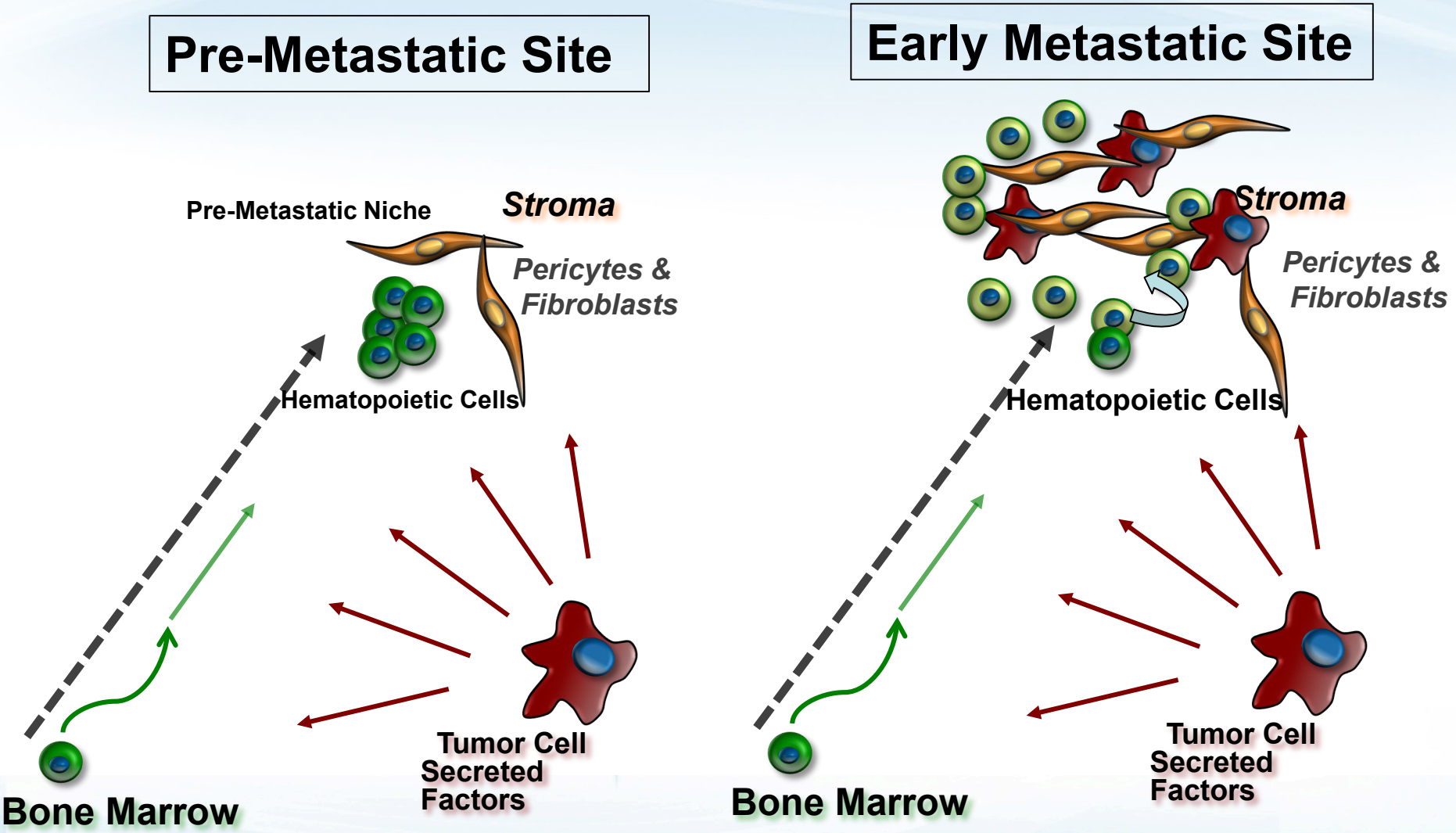




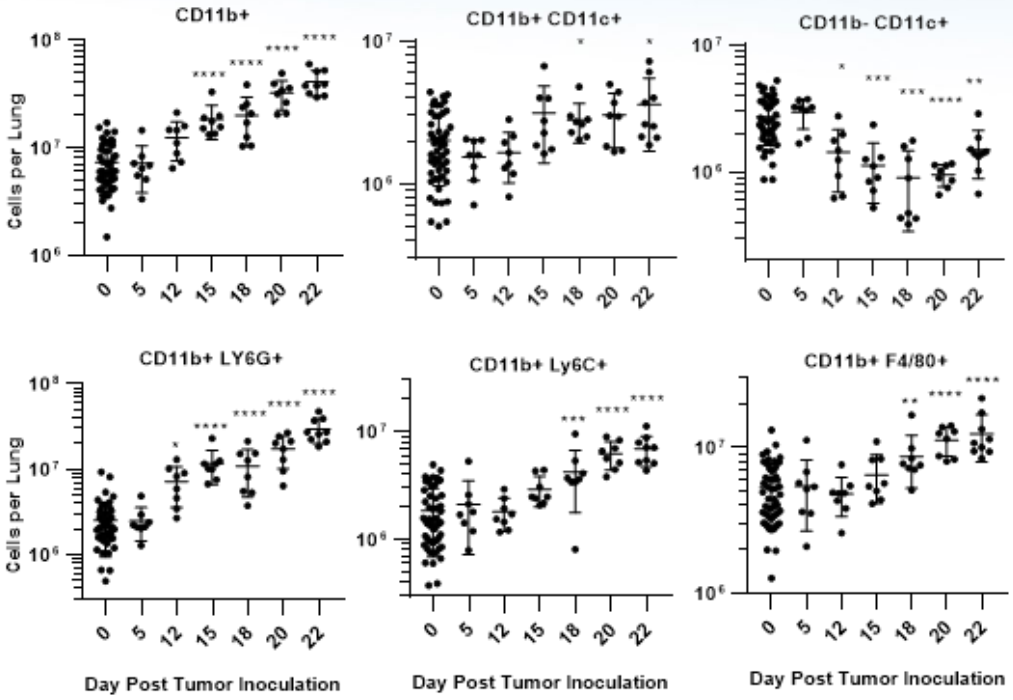


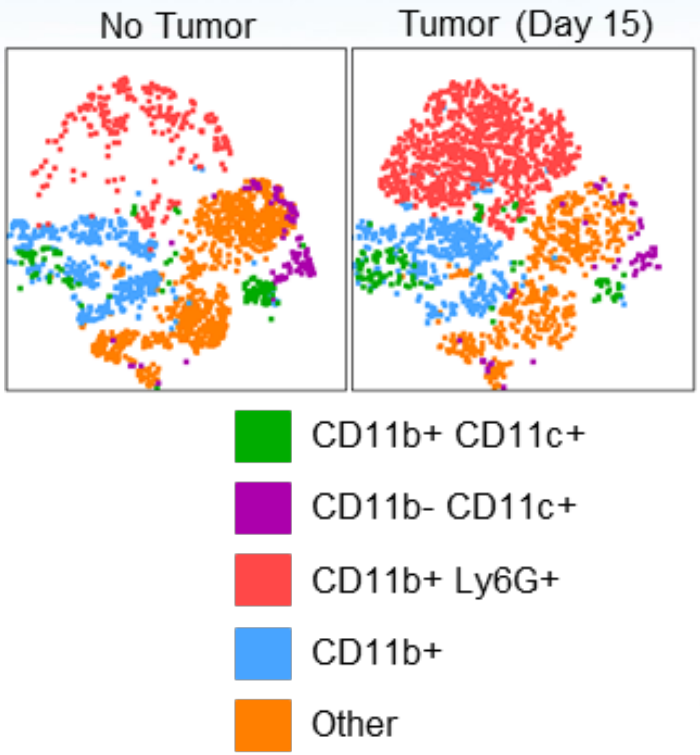


Pre-metastatic Niche: Myeloid Derived Suppressor Cell (MDSC) support immune evasion



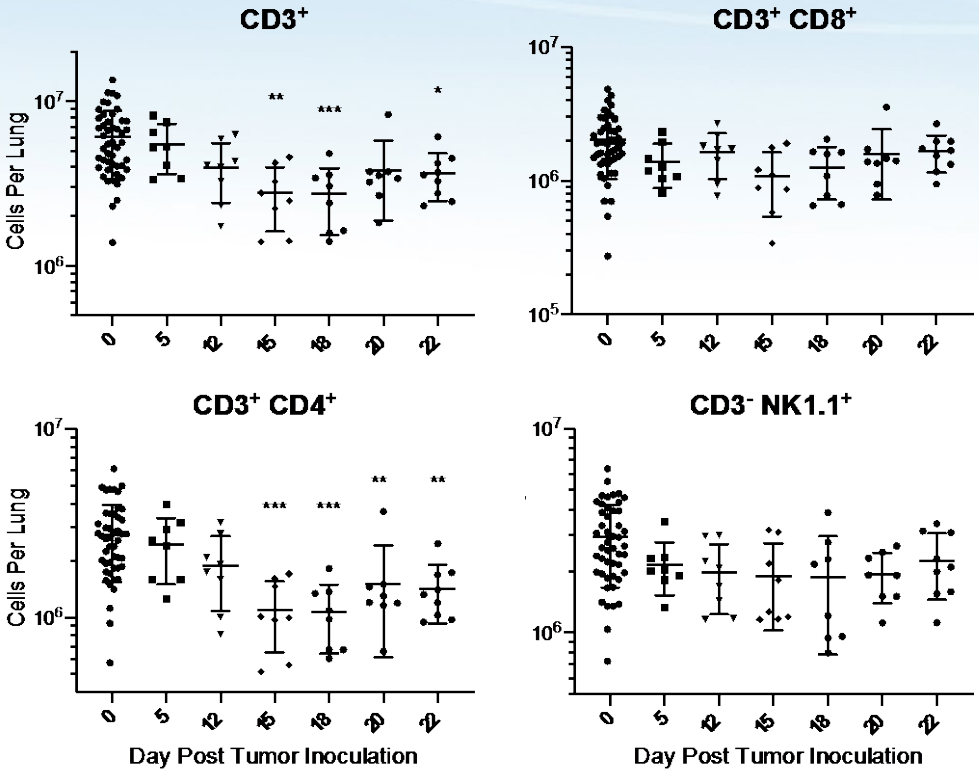
Myeloid Cells Accumulate In the Lungs of M3-9-M-bearing Mice with Increasing Tumor Burden

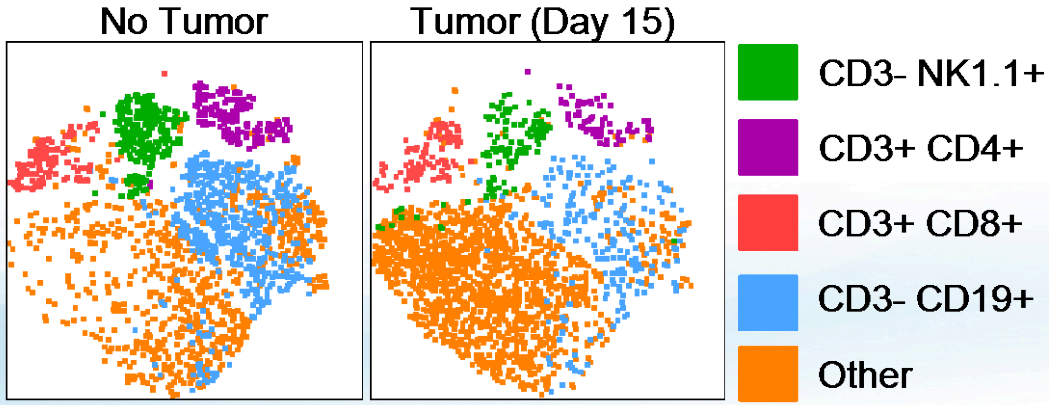




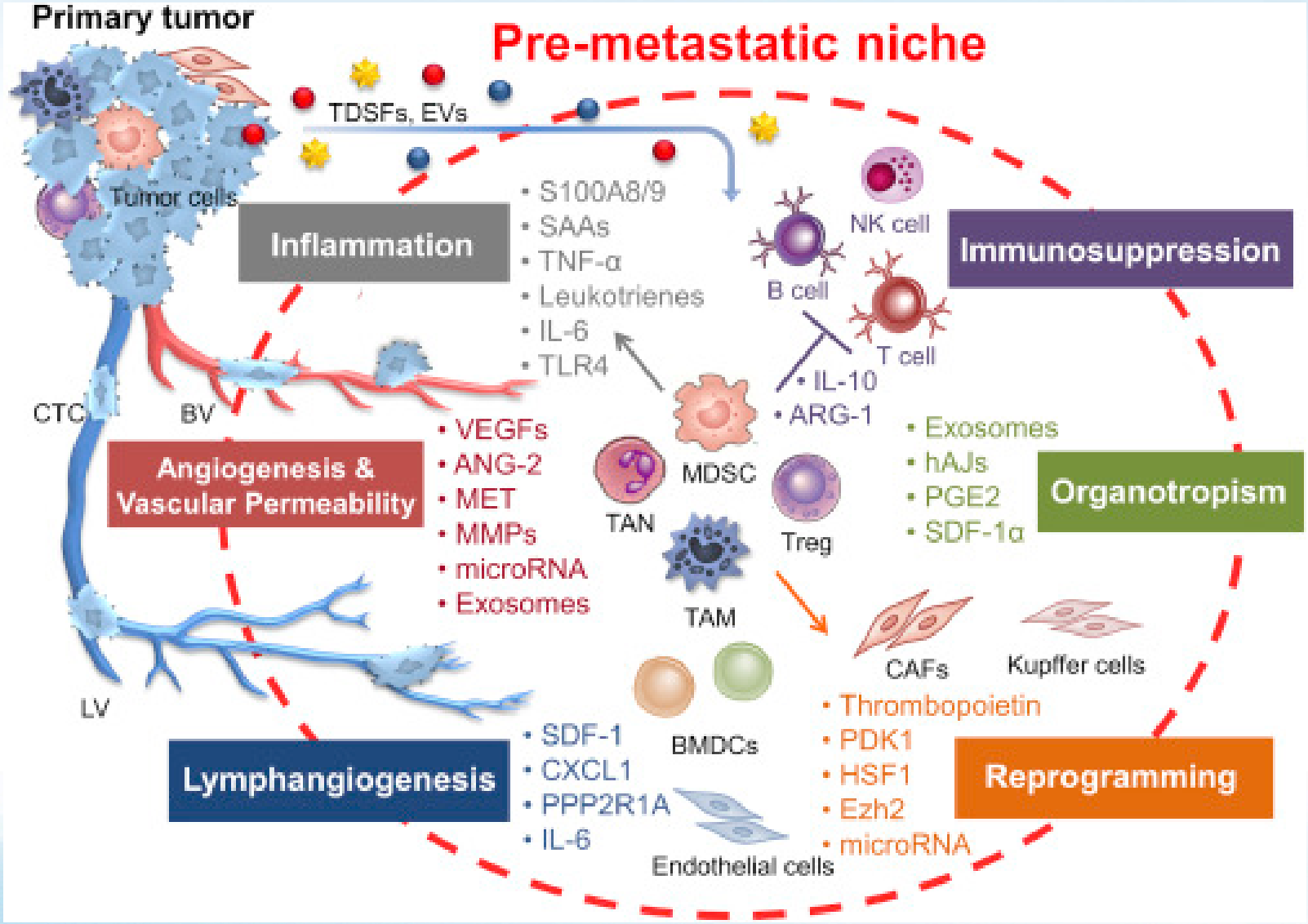
Immune cells are dysregulated in the metastatic niche

Lymphoid Compartment Contracts In the Pre-Metastatic Lung





Pre-Metastatic Niche: The Early Metastatic Microenvironment



Pexidartinib May Decrease Tumor Growth Through Effects On Tumor Microenvironment

- Small molecule inhibitor of CSF1R, kit, oncogenic FLT3 tyrosine kinases
- Can impact tumor growth through
  - Inhibiting paracrine loops between immune cells (myeloid cells, macrophages, mast cells, microglial cells) and tumors
  - Blocking cell migration and angiogenesis
  - Disrupting osteolytic metastases by targeting osteoclasts that express CSF1R

  - Not currently studied in myelodysplastic syndrome

CSF1R Signaling Affects Myeloid Cells

- CSF1R is a type 3 receptor tyrosine kinase
- On myeloid lineage cells: monocytes, macrophages, dendritic cells, osteoclasts
- Binds colony stimulating factor 1 (CSF1)

- Effects on myeloid cells
  - Production, differentiation, and function of macrophages
  - Bone marrow mobilization, migration into target tissues, survival, proliferation

Increased CSF-1R signaling in tumor microenvironment

- CSF-1 is produced by tumor cells
  - Directs integration of macrophages into the tumor parenchyma
  - Modulates myeloid cells and macrophages toward an immunosuppressive phenotype
  - Promotes the production of growth factors and angiogenic factors by TAMs
- Tumor associated macrophages are abundant in pediatric solid tumors
- Inhibition of CSF-1R signaling in mouse models showed tumor regression in solid tumor models (pancreatic, prostate, breast, cervical, thyroid, glial cancers)
- Pigmented Villonodular Synovitis – rare locally aggressive MSK neoplasm with genetic mutation resulting in CSF1 overexpression. Pexidartinib has shown tumor volume reduction and symptom improvement in adults. Phase III trial.

15 Adult Pexidartinib Trials as of 7/2019

Completed: 7

- Relapsed or refractory Hodgkin's lymphoma (II)
- Recurrent GBM (II)
- Advanced metastatic prostate cancer (pilot)
- I SPY 2 TRAIL – neoadjuvant and personalized adaptive novel agents to treat breast cancer
- BRAF-mutated unresectable or metastatic melanoma: combination with vemurafenib (I)
- Two Healthy subject studies

Ongoing: 9 (8 Phase I, 1 Phase III)

- Advanced incurable solid tumors focusing on TGCT (Tenosynovial Giant Cell Tumor): Phase I & Phase III
- Relapsed or refractory AML
- Advanced solid tumors in Asian subjects
- Combination in advanced incurable solid tumors
  - Paclitaxel
  - Pembrolizumab
  - Durvalumab (to open in Met/Advanced Panc and CRC)
- Newly diagnosed GBM: temozolomide and radiation
- Two healthy subject studies- one look at effect of low fat food on PK and one looking at CYP3A4 and CYP2C9 substrates

Key Toxicities from Adult Trials

- Most frequent >=20% among all treated patients
  - Fatigue, nausea, decreased appetite, diarrhea, vomiting, anemia, constipation, hair color changes, headache, increased AST
- Severe skin reactions have been seen: erythema multiformis, DRESS
  - relationship to Pexidartinib has not been established
- Acute febrile neutrophilic dermatosis in AML subjects
- Severe idiosyncratic liver toxicity/liver failure in three patients with TCGT
- Laboratory changes
  - Liver enzymes
  - Mild decreases in ANC, platelet count, and hemoglobin
- The combination of pexidartinib with other chemotherapeutic or targeted therapies may increase the risk and/or severity of adverse findings associated with the individual agents

Pexidartinib Phase I/II Clinical Trial at NCI

- Phase I/II trial of PLX3397 in children and young adults with refractory leukemias and refractory solid tumors including neurofibromatosis type 1 (NF1) associated plexiform neurofibromas (PN)
- Principal Investigator: Rosandra Kaplan, M.D.
- Lead Associate Investigator: John Gold, M.D., Ph.D.
- Pexidartinib manufactured and supplied by Plexxikon, Inc. then Daychii Sanyko Inc.

Pexidartinib Phase I/II Clinical Trial at NCI

- Daily oral medication given in 30 day cycles
- Phase I
  - Rolling-six phase I design with 3 dose levels (DL) for patients with refractory solid tumors, leukemias, NF-1 related plexiform neurofibromas
  - Includes a Phase I expansion of up to 12 patients at the MTD
  - Maximum 24 patients.
  - Goal to determine toxicities and recommended Phase II dose
- Phase II – was placed on hold with liver toxicity but now open
  - Children and young adults with NF1 and plexiform neurofibromas
  - Maximum 17 patients.
  - Goal to determine the activity of Pexidartinib in this population

Patient Enrollment

Phase I

- 12 patients enrolled
  - Peritoneal mesothelioma, osteosarcoma (n=3), Ewings sarcoma, NF1-PN (n=3), CNS PNET, primary brain tumor, MPNST, rhabdomyosarcom
- 11 patients evaluable for MTD (>85% C1)
- NF1 PN patients received 1, 4, & 6 cycles
- Peritoneal mesothelioma patient continues on study in cycle 45 with CR
- All other patients now off study

Phase I expansion

- 3 patients enrolled
  - AML, spindle cell sarcoma, aneurysmal fibrous histiocytoma
- NF1 enrollment was on hold due to concerns about liver injury in adult studies
- Amendment to add pediatric and adult patients with MDS
- Pediatric and young adult patients with relapsed and/or metastatic disease that has been rendered MRD negative.

Patient Demographics and Characteristics

Table 1: Patient Demographics and Baseline Characteristics of Patients Treated with Pexidartinib		
Characteristic		Number of patients (n=16)
Age	Median (range)	16 (4 - 22) years
Sex	Female/Male	7/9
Race	White	10
	African American	3
	Asian	1
	Hispanic	2
Performance Status	Median (Range)	90 (60-90) %
Tumor Type	Sarcomas	7
	NF1 PN	3
	CNS tumors	3
	MPNST	1
	Acute myeloid leukemia	1
	Peritoneal mesothelioma	1
Prior Therapies	Surgery	13
	Chemotherapy	12
	Radiation	9
	Immunotherapy	5
	Targeted therapy	5
	None	1

Toxicity Profile in Pediatric/Adolsecent Trial

Non Dose-Limiting Toxicities Possibly, Probably, and Definitely Related to Pexidartinib in Evaluable Patients During Cycle 1

	Maximum Grade of Toxicity						% of Patients with Toxicity
	DL 1 (n = 3)		DL2 (n = 3)		DL3 (n = 3)		DL 1, 2, and 3 (n = 9)
	1	2	1	2	1	2	
Hematologic							
Anemia	1	1					22%
White blood cell count decreased	2	1	2		1		67%
Lymphocyte count decreased	1		1	1	1		44%
Neutrophil count decreased	1	1				1	33%
Platelet count decreased	2		1				33%
Prolonged APTT	1						11%
Constitutional							
Anorexia	2		1				33%
Fatigue	2		2	1			56%
Gastrointestinal							
Diarrhea			2				22%
Nausea	2						22%
Vomiting					1		11%
Hepatic							
ALT increased			2				22%
AST increased			1		1		22%
Metabolism							
CPK increased	2		2		1	1	67%
Hypoalbuminemia					1		11%
Hypocalcemia					1		11%
Hypercalcemia					1		11%
Hypoglycemia	1		1				22%
Hyperglycemia							
Hypokalemia			1				11%
Hyponatremia			1				11%
Serum amylase increased	1	1	1	1	1		56%
Neurologic/Psychiatric							
Anxiety					1		11%
Dizziness					1		11%
Headache			3			1	44%
Non-cardiac chest pain					1		11%
Pain	1						11%
Restlessness					1		11%
Renal							
Creatinine increased			1				11%
Glycosuria					1		11%
Proteinuria	1	1	1		1		44%
Dermatologic							
Bruise			1				11%
Hair depigmentation			2				22%
Petechiae			1				11%
Rash	1		1				22%
Oral/ENT							
Dysgeusia			2				22%
Epistaxis					1		11%
Mucositis	1						11%
Oral Thrush			1				11%

Reduced Absolute Monocyte Count

Peripheral blood fold change from Day 1

	6-8 Days from C1			14-16 Days from C1			27-29 Days from C1			Repeated Measures ANCOVA	
CBC Parameter (Fold Change from Day 1)	N	P*	Med. Fold Change (95% CI)	N	P*	Med. Fold Change (95% CI)	N	P*	Med. Fold Change (95% CI)	Time Linear	Dose Linear
WBC	13	0.15	0.89 (0.78, 1.07)	13	0.04	0.85 (0.65, 1.06)	10	0.19	0.81 (0.58, 1.28)	0.007	0.10
Hgb	13	0.08	1.03 (0.97, 1.08)	13	0.02	0.97 (0.91, 1.00)	10	0.37	1.03 (0.95, 1.13)	0.91	0.71
Platelet Count	13	0.24	1.10 (0.84, 1.17)	13	0.64	0.97 (0.83, 1.13)	10	0.43	0.94 (0.79, 1.18)	0.59	0.002
Neutrophils % + bands	13	0.13	1.08 (0.96, 1.13)	13	0.07	1.08 (0.96, 1.13)	10	0.85	0.97 (0.78, 1.30)	0.91	0.26
Immature granulocytes	9	0.01	0.50 (0.08, 0.67)	9	0.01	0.46 (0.30, 0.67)	6	0.44	0.24 (0.00, 2.00)		
Lymphocytes %	13	0.79	0.96 (0.81, 1.29)	13	0.95	0.92 (0.87, 1.25)	10	0.28	1.28 (0.47, 1.95)	0.53	0.29
Monocytes %	13	0.002	0.60 (0.40, 0.87)	13	0.002	0.67 (0.52, 0.89)	10	0.05	0.84 (0.26, 1.06)	0.03	0.10
Eosinophils %	10	0.03	0.78 (0.55, 1.04)	11	0.70	0.97 (0.92, 1.53)	8	0.46	0.76 (0.48, 4.19)	0.87	0.79
Basophils %	12	0.16	0.95 (0.50, 1.13)	11	0.04	0.83 (0.50, 1.13)	9	0.01	0.22 (0.00, 0.83)	0.001	0.28
ANC	13	0.74	0.90 (0.77, 1.26)	13	0.41	0.96 (0.64, 1.15)	10	0.49	0.70 (0.46, 1.66)	0.035	0.13
Abs Immature Granulocyte	9	0.09	0.50 (0.10, 1.00)	9	0.02	0.50 (0.19, 1.00)	6	0.69	0.20 (0.00, 2.50)		
ALC	13	0.49	0.97 (0.68, 1.20)	13	0.05	0.88 (0.73, 1.03)	10	0.36	0.86 (0.60, 1.21)	0.075	0.56
AMC	13	0.001	0.58 (0.35, 0.81)	13	0.0002	0.56 (0.40, 0.89)	10	0.002	0.64 (0.26, 0.88)	0.0003	0.95
AEC	10	0.01	0.76 (0.50, 1.07)	11	0.92	1.00 (0.81, 1.27)	8	0.25	0.63 (0.31, 5.37)	0.73	0.97
ABC	12	0.06	0.92 (0.50, 1.00)	11	0.01	0.67 (0.50, 1.00)	9	0.01	0.33 (0.00, 0.67)	0.0006	0.057

*** Two-tailed unadjusted signed rank test p-value for Mu=1**

CSF1 Elevation marker of CSF1R targeting

Serum cytokine analysis fold change from Day 1						
	14-15 Days from C1			27-29 Days from C1		
Cytokine	N	P*	Med. Fold Change (95% CI)	N	P*	Med. Fold Change (95% CI)
IL-10	12	0.021	1.25 (1.11, 1.44)	8	0.64	1.22 (0.81, 1.30)
IL-12p70	12	0.79	0.92 (0.80, 1.25)	8	0.023	0.86 (0.66, 1.05)
IL-6	12	0.85	0.91 (0.78, 1.34)	8	0.95	0.98 (0.64, 2.39)
MCP-1	12	0.003	1.28 (1.01, 1.56)	8	0.023	1.27 (1.11, 1.54)
M-CSF	12	0.0005	3.70 (2.31, 5.24)	8	0.008	4.52 (2.40, 13.3)
*** Two-tailed unadjusted signed rank test p-value for Mu=1**						

Conclusion

- CSF1/CSF1R axis targeting may be a potential approach to investigate in MDS
- Tumor Microenvironment Targeting including manipulation of Myeloid Cell and Stromal Cell Plasticity may be a potential promising approach in myelodysplastic anemia
- Clinical correlates examined in these trials may reveal new microenvironmental approaches in these diseases

Thank You!

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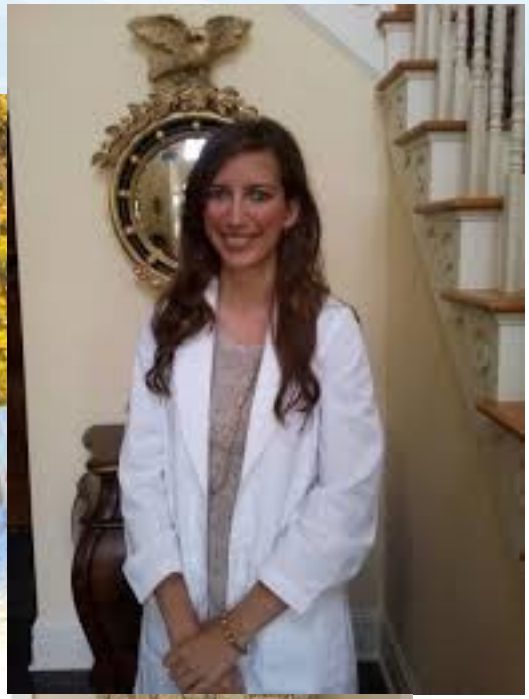
The patients and their families

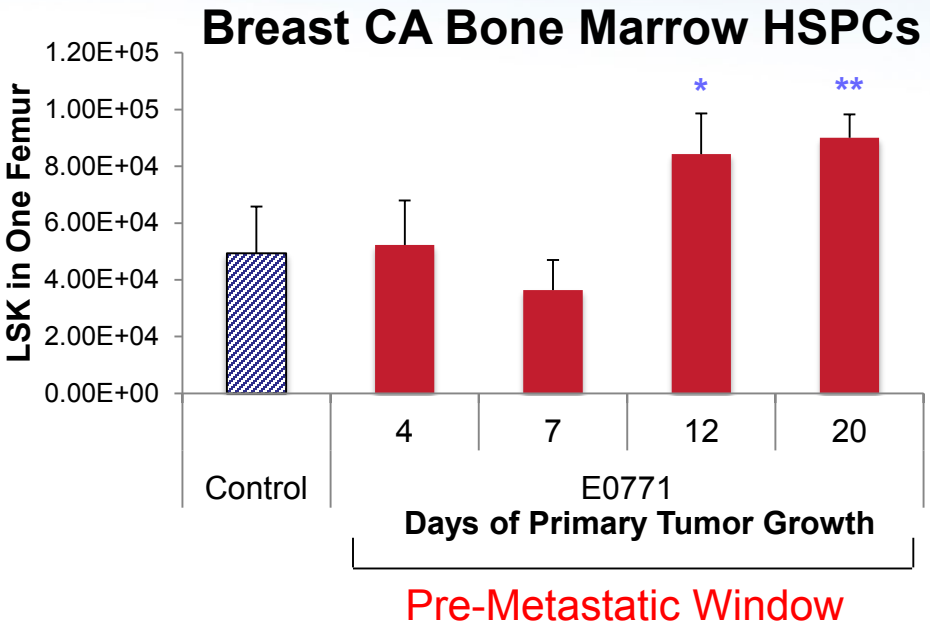
To the patients who inspire me and motivate me every day!

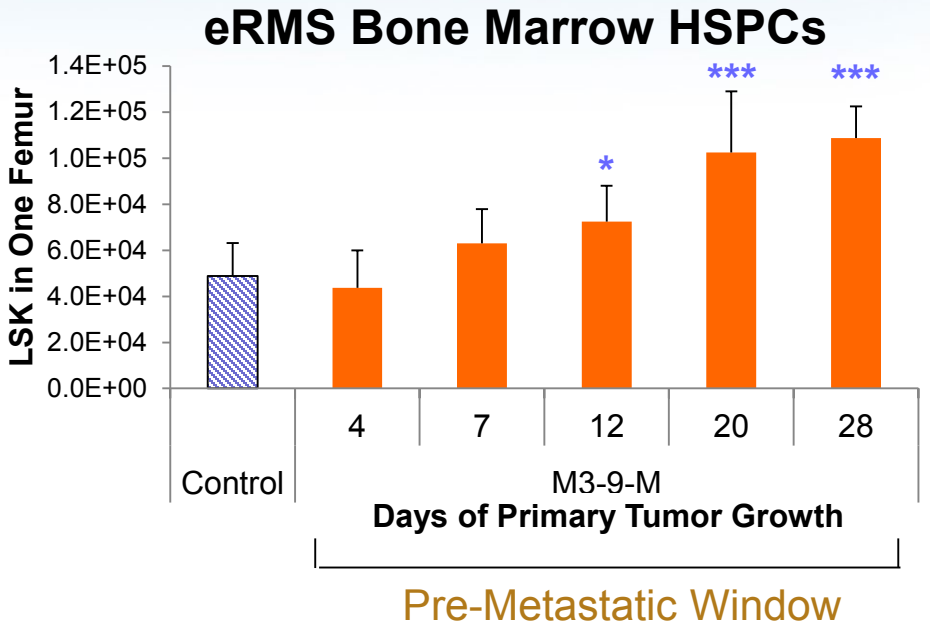


C-kit and CSF1R signaling in plexiform neurofibroma microenvironment

- C-kit in PN Microenvironment
  - Nf1-/- Schwann cells increase production of stem cell factor (scf-1)
  - Increased response to scf-1 by Nf1+/- mast cells vs wild type mast cells
  - Increased c-kit signaling between mast cells and tumor cells contribute to the inflammatory microenvironment
  - Imatinib (small molecule TKI that targets c-kit) with some clinical activity in the PN treatment
- Macrophages in PN Microenvironment
  - ~50% of PN are macrophages - may be inflammatory effectors.
  - Macrophage infiltration correlates with disease progression
- Targeting c-kit signaling and CSF1R signaling within the PN microenvironment may decrease tumor growth

Hematopoietic Stem and Progenitor Cells (HSPCs) Expand During the Pre-Metastatic Window

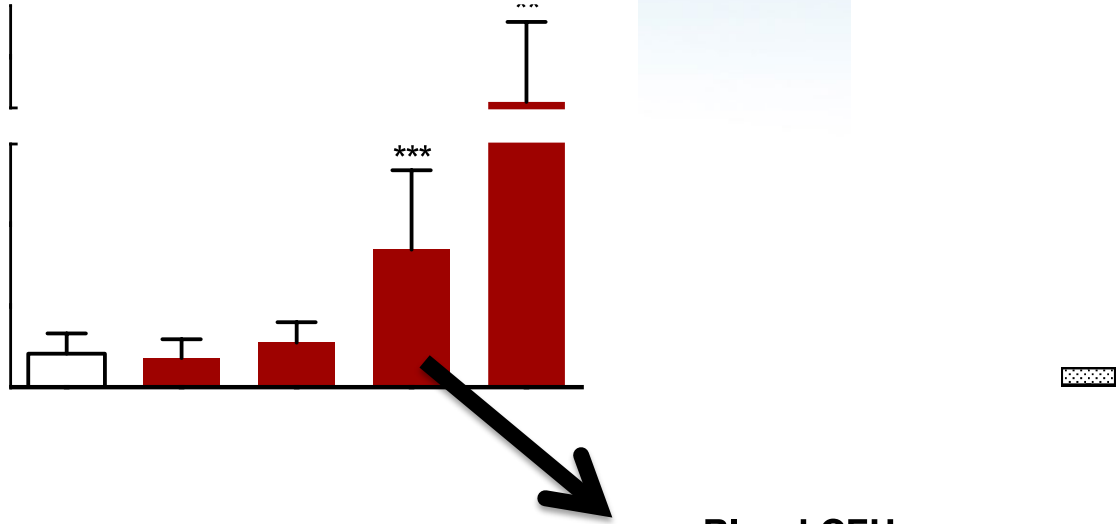


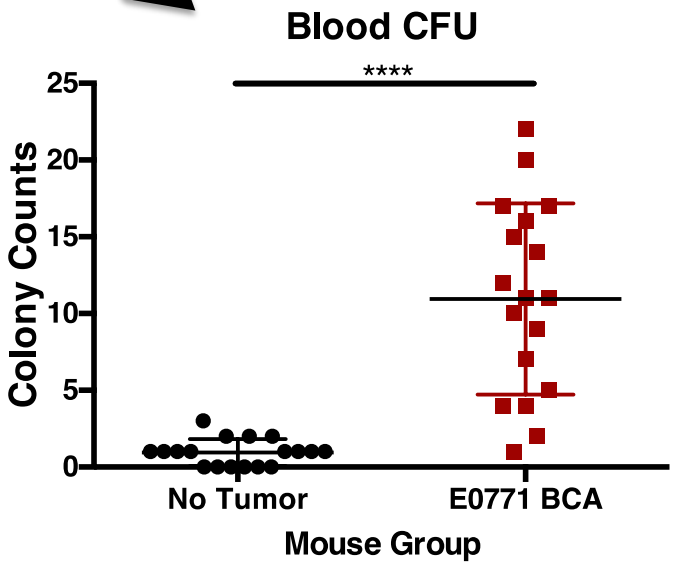


Mouse HSPCs are LSK cells: Negative for **L**ineage markers, expressing **S**ca1 and c**K**it

Giles *et al*. Cancer Res 2016

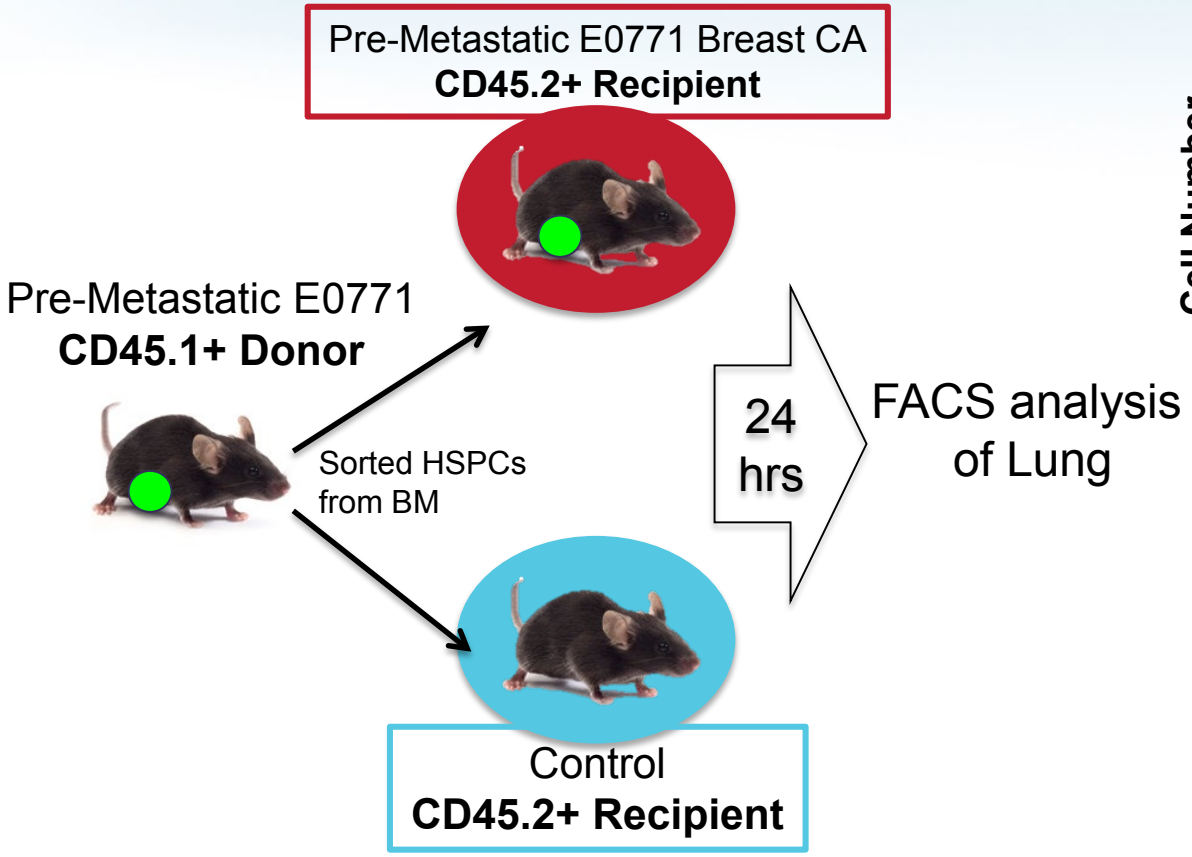
LSK HSPCs are Increased in Circulation of Tumor-Bearing Mice

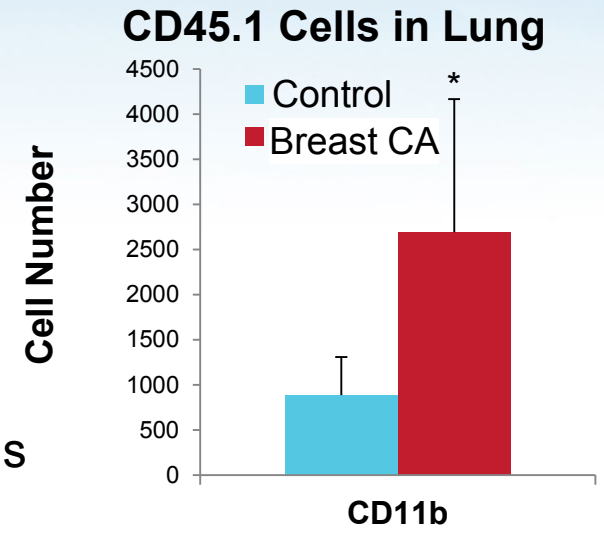


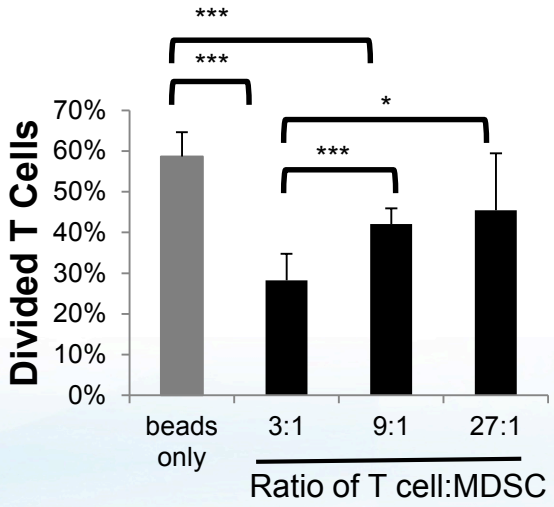


Giles *et al*. Cancer Res 2016

Circulating HSPCs Develop into Myeloid Derived Suppressor Cells (MDSCs) in Metastatic Tissues





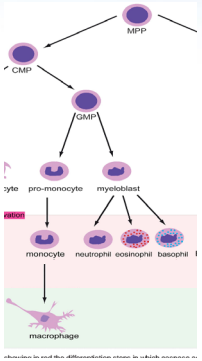


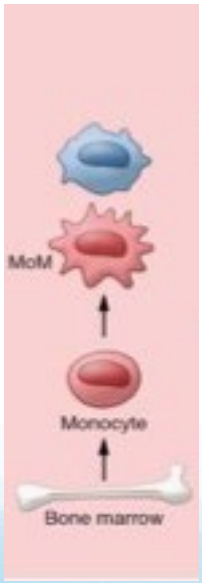
Giles et al Ca Res 2016

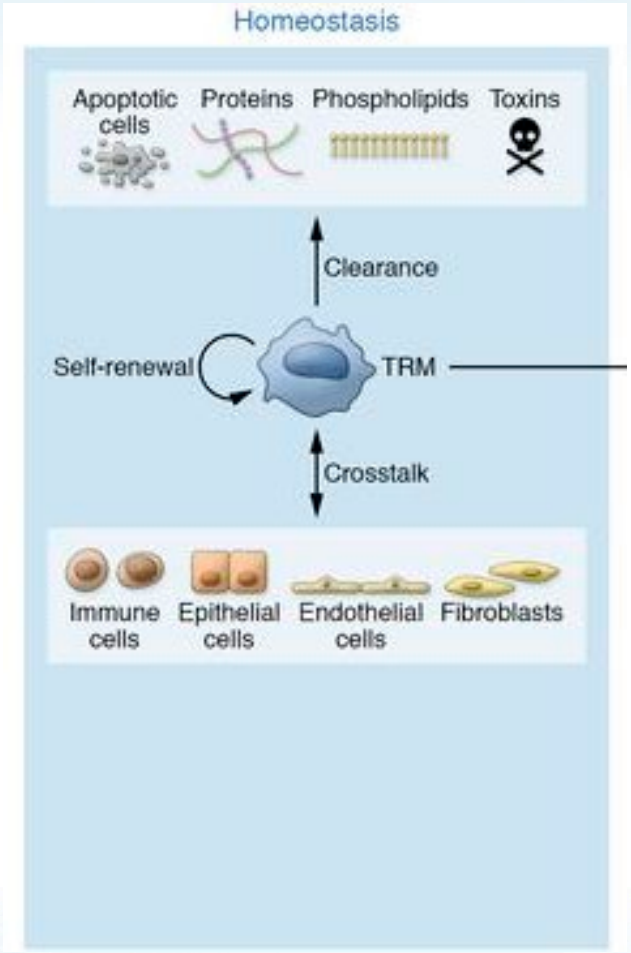
Myeloid Cells and Stromal Cells Maintain Tissue Homeostasis

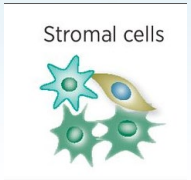
Myeloid Cells

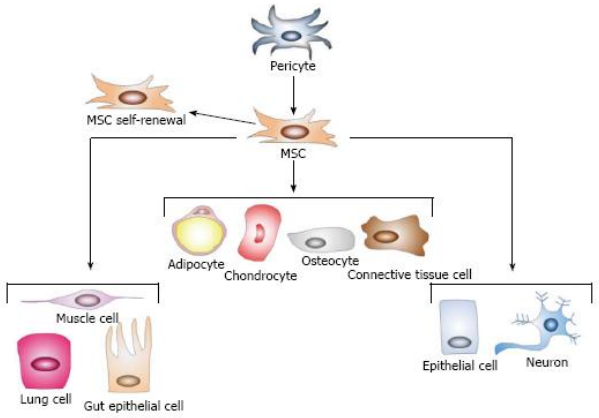
Stromal Cells

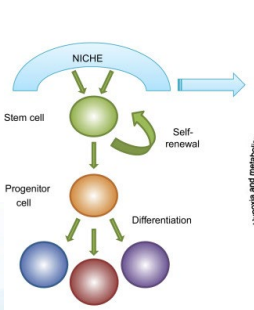


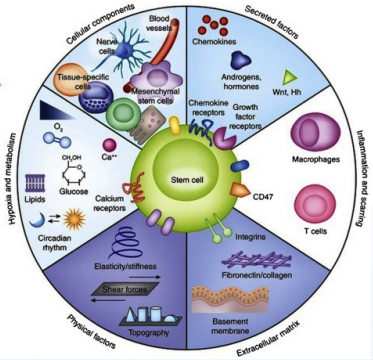




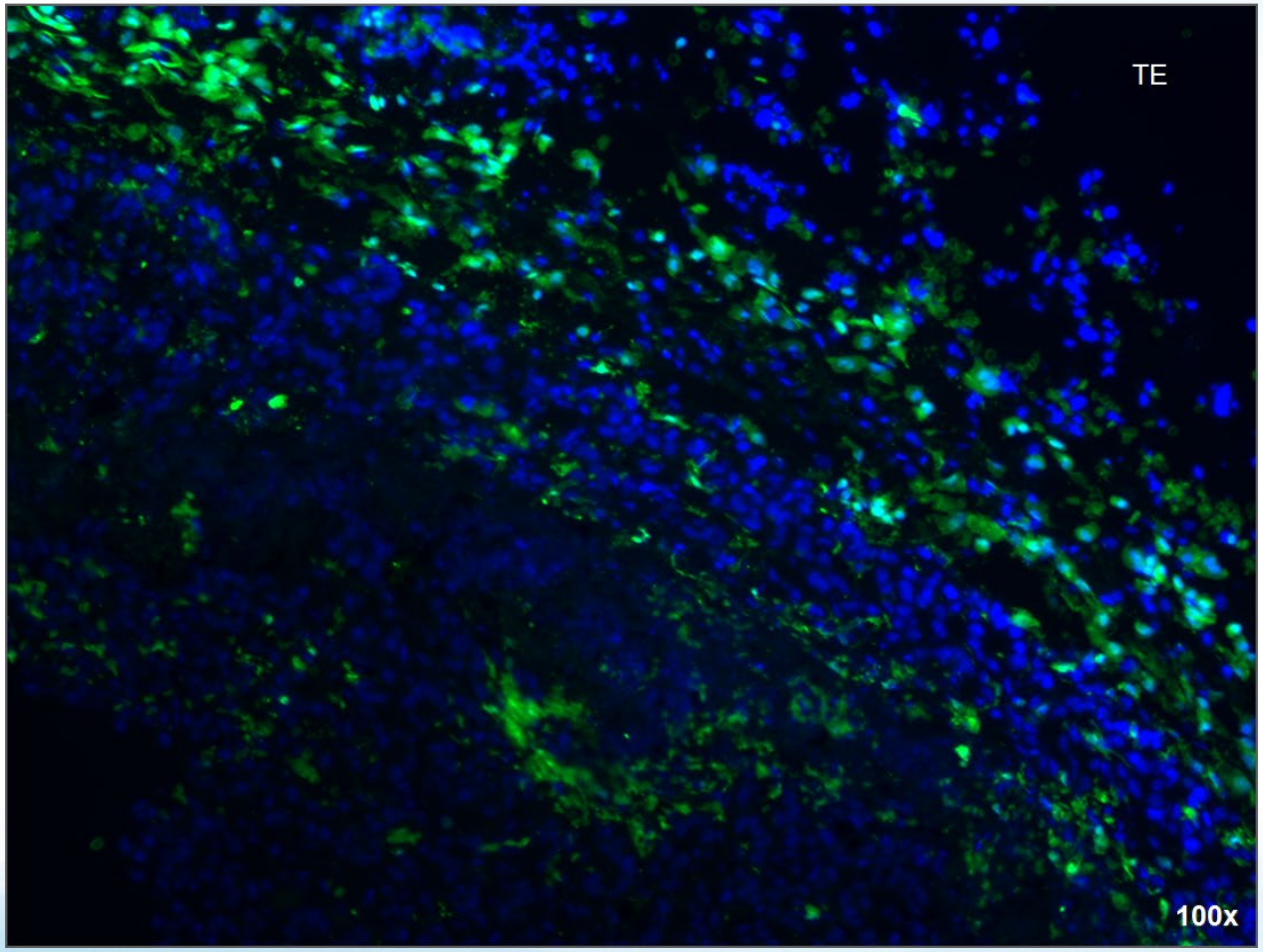








Bone Marrow-derived Cells are Abundant at the Invasive Edge of the Growing Tumor



B16 melanoma Day 15

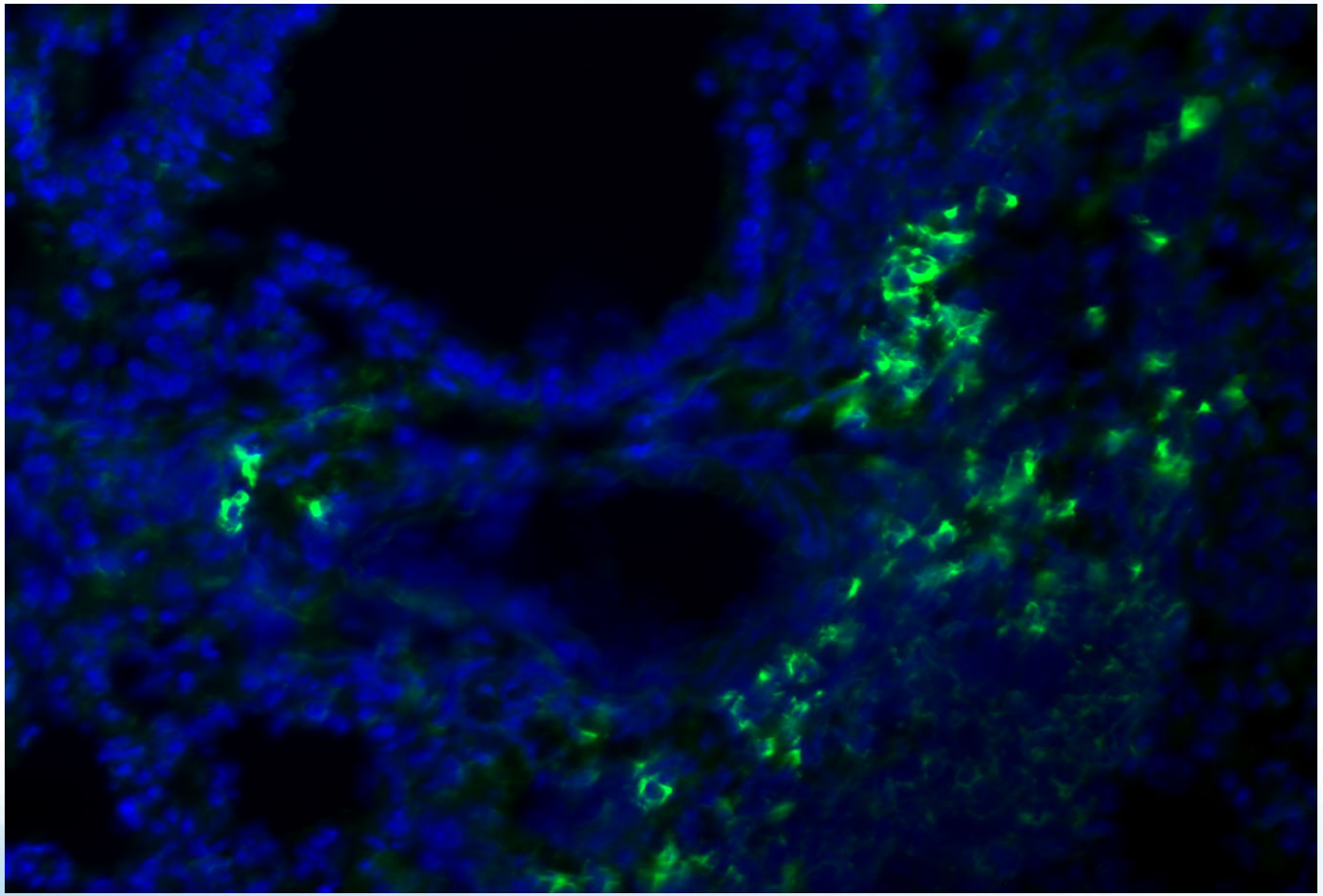
GFP+ Bone marrow-derived cells (BMDCs)

DAPI

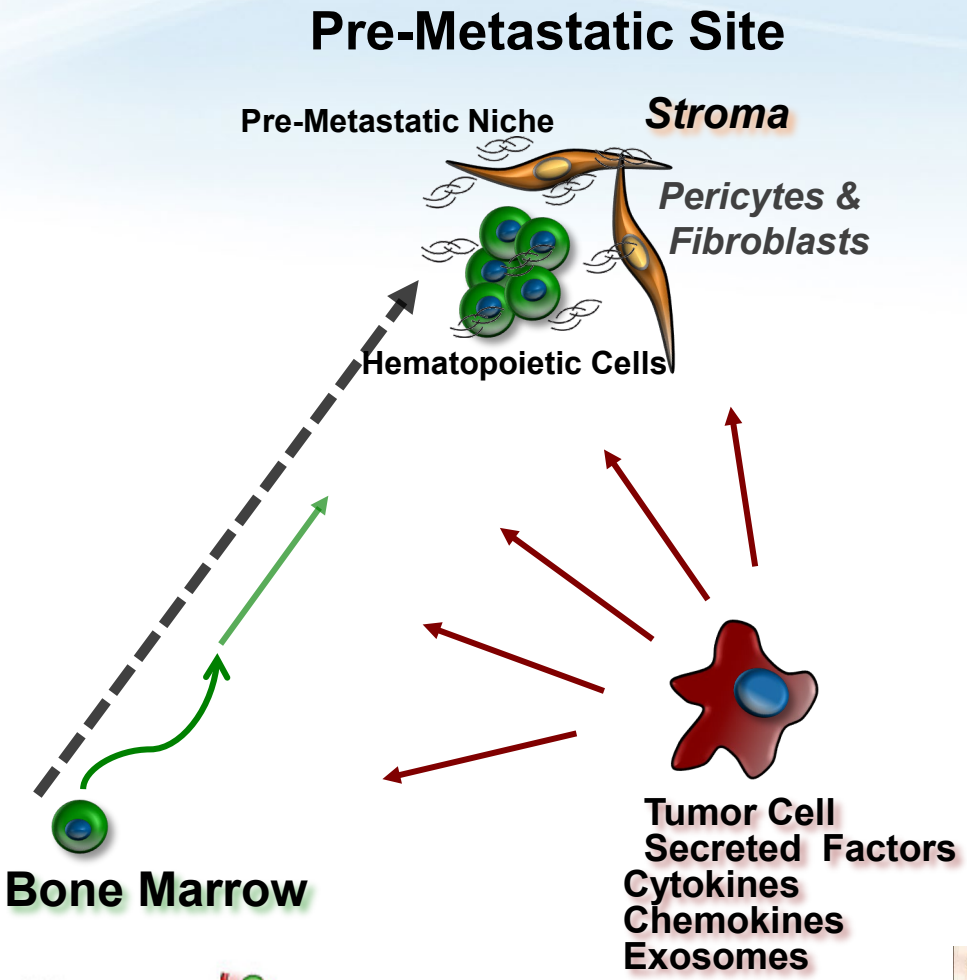
TE = Tumor Edge

Bone Marrow-derived Cells Form Clusters in Distant Metastatic Sites Such as the Lung

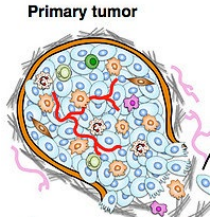
GFP^{+} - BMDCs

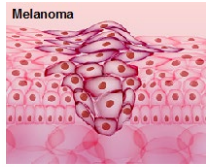


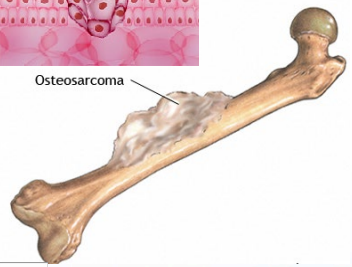
Identifying the Pre-Metastatic Niche

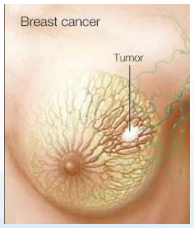


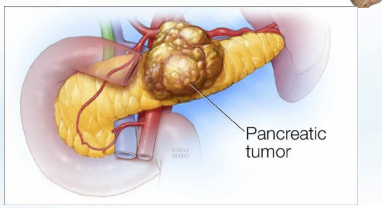
- Dynamic, specialized microenvironment that supports disseminated tumor cells
- Activated mesenchymal cells with associated extracellular matrix remodeling
- Bone Marrow (BM) Derived Myeloid Cells

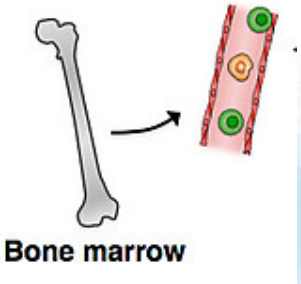








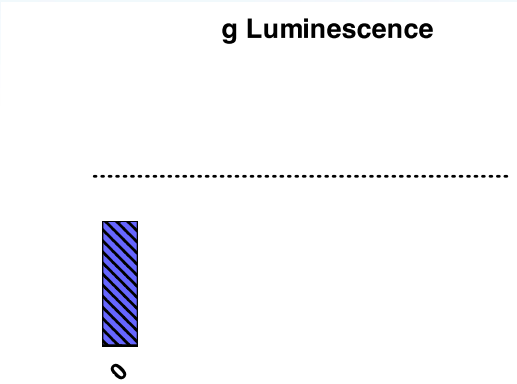


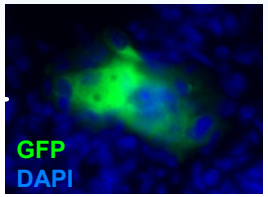


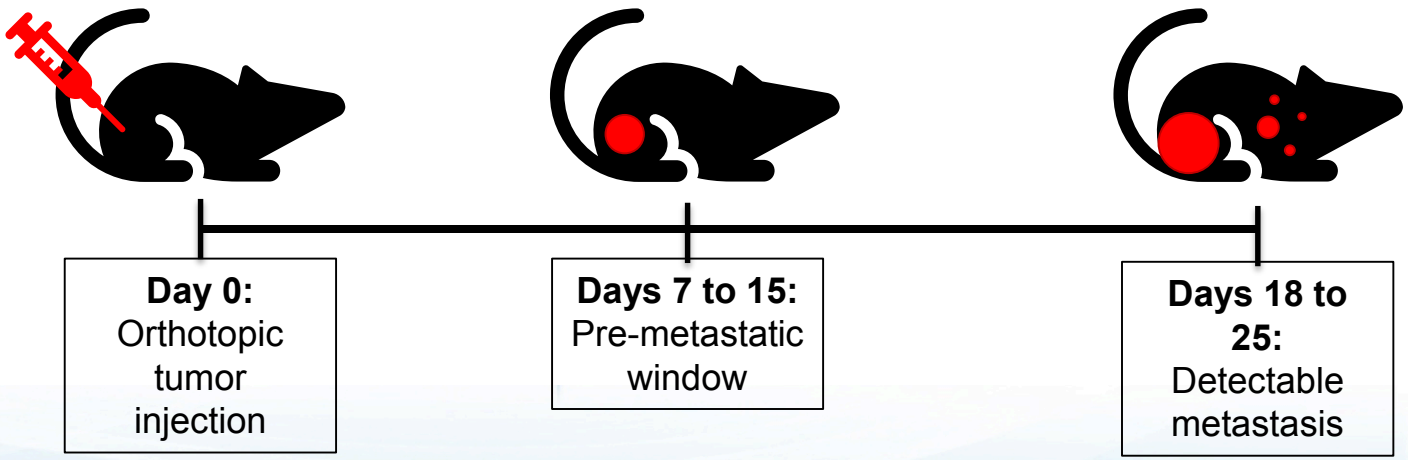
Defining pre-metastatic and metastatic windows

- Whole lung bioluminescence and flow cytometry to quantify total tumor cell burden

- Sequential lung sectioning to identify GFP+ micrometastases





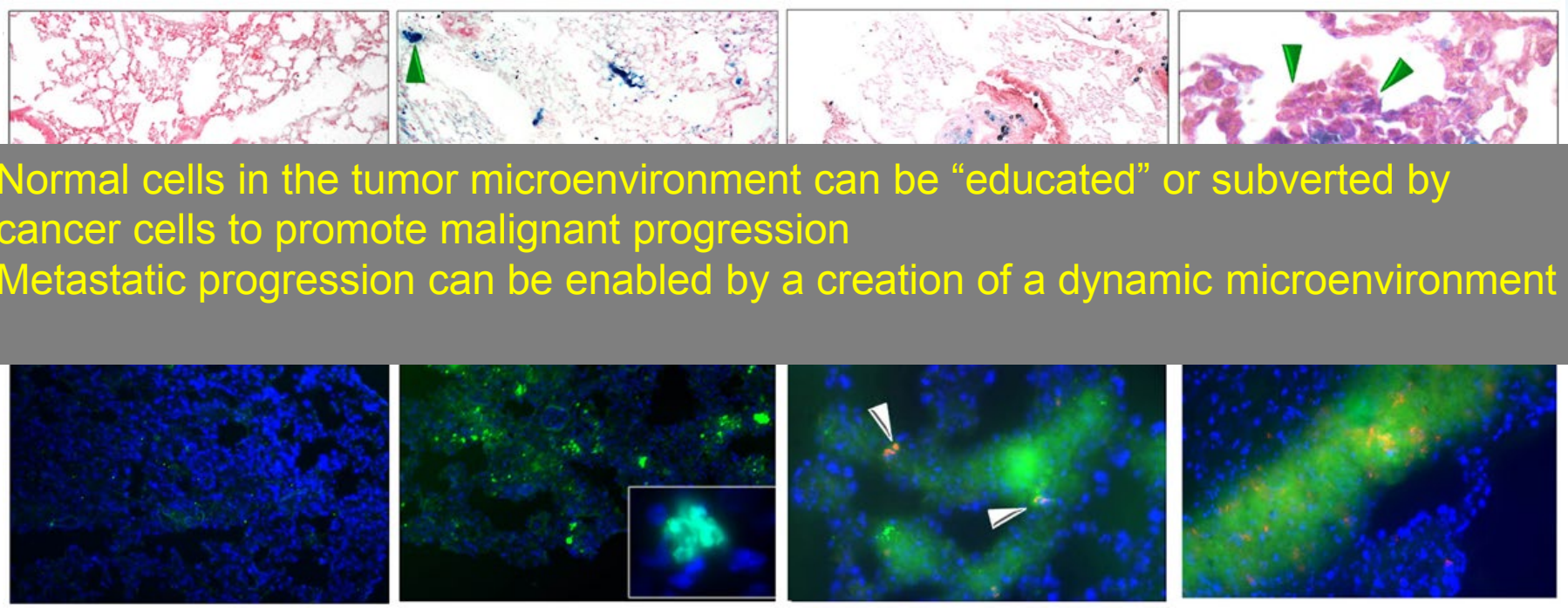


Characterized Murine Models of Spontaneous Metastasis

	Type	Orthotopic Primary	Occurence of Spontaneous Metastasis	Location of Mets
B16-F10	Melanoma	Subdermal Flank	~ Day 18	Lung Lymph nodes
B16-F0	Melanoma	Subdermal Flank	none	none
E0771	Breast Carcinoma (Breast CA)	Mammary Fat Pad	~ Day 20	Lung Lymph nodes
76-9	Embryonal Rhabdomyosarcoma (eRMS)	Gastrocnemius muscle	~ Day 35	Liver Lung Lymph nodes
M3-9-M	Embryonal Rhabdomyosarcoma (eRMS)	Gastrocnemius Muscle	~ Day 35	Lung Lymph nodes
K7M2/K12	High and Low Metastatic Osteosarcoma	Tibia	~ Day 30	Lung
KPC16	Pancreatic Carcinoma	Pancreas	~ Day 28	Liver

Bone Marrow Derived Hematopoietic Cells Form the Pre-Metastatic Niche

Day 0 | Day 14 | Day 16/18 | Day 24

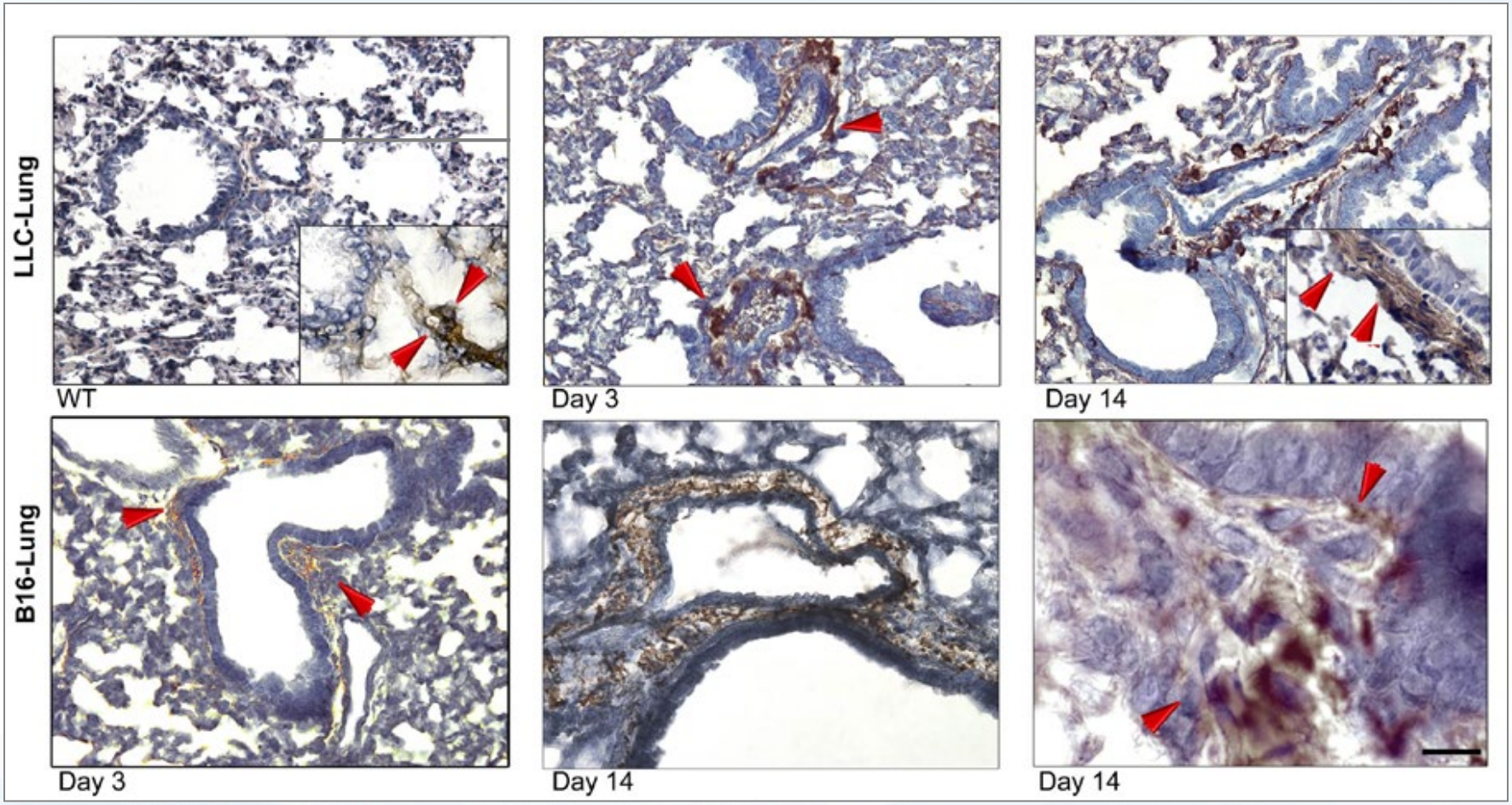


Normal cells in the tumor microenvironment can be “educated” or subverted by cancer cells to promote malignant progression

Metastatic progression can be enabled by a creation of a dynamic microenvironment

Kaplan et al 2005 Nature

Activated Stromal Cells Upregulate Fibronectin to Create the Pre-Metastatic Niche

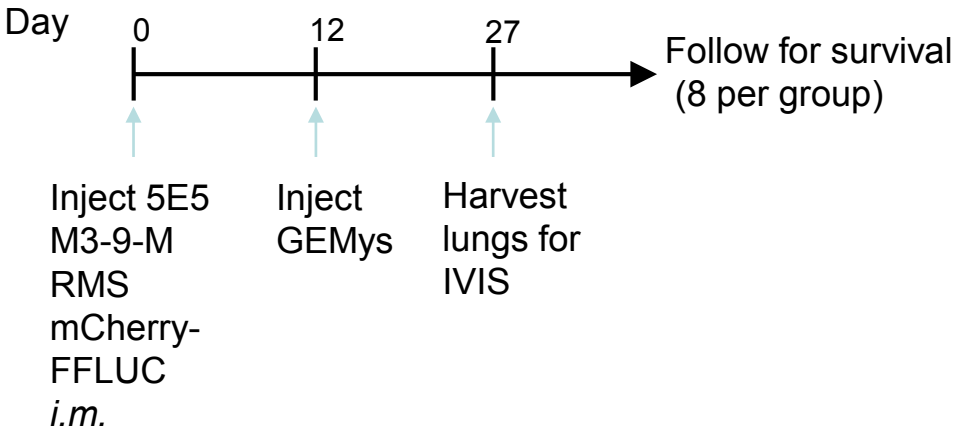


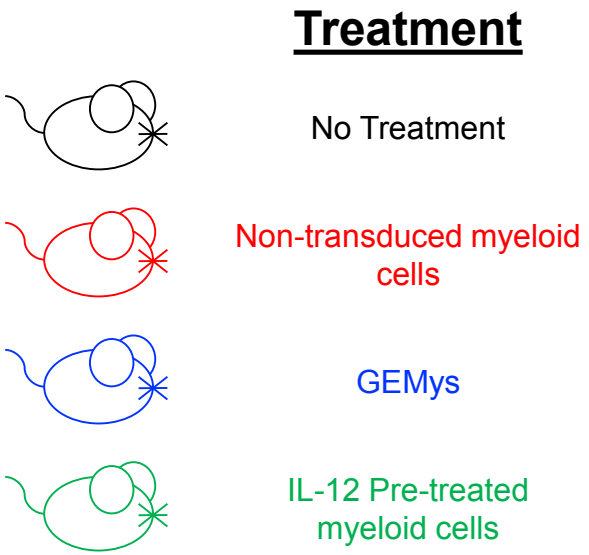
Kaplan et al 2005 Nature

Do GEMys impact metastasis

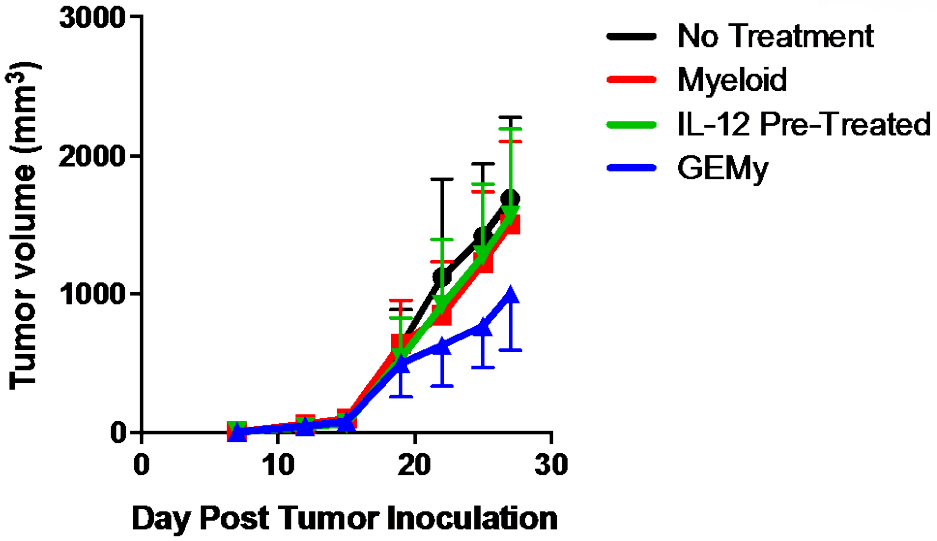
- Can GEMys impact primary tumor growth and survival of rhabdomyosarcoma bearing mice?
- Do GEMys impact lung metastasis?
- Can GEMys treat established metastatic disease?
- Is chemotherapeutic efficacy impacted by GEMys?
- Do GEMys work in other tumor models?

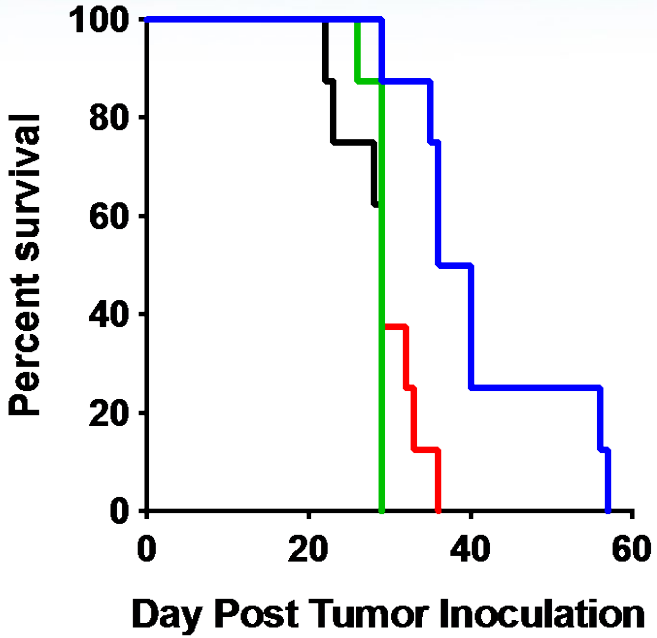
Can GEMys impact primary tumor growth, survival, and metastasis of Rhabdomyosarcoma tumor-bearing mice?



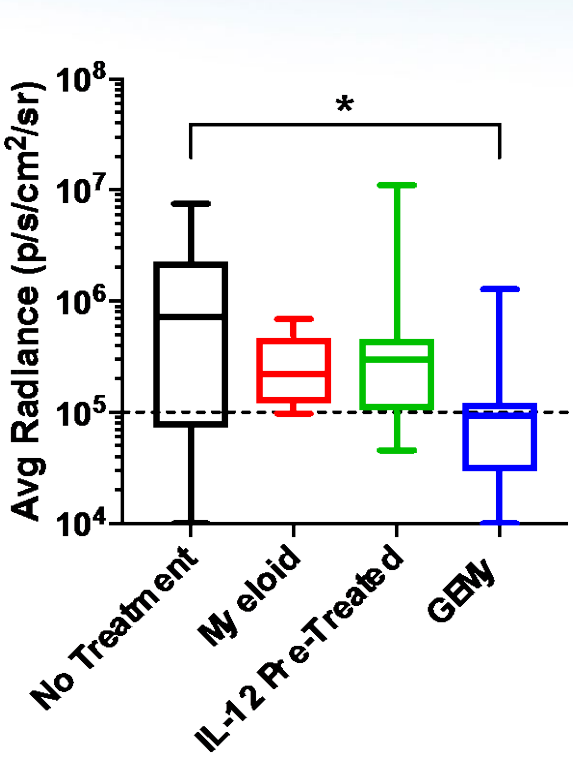


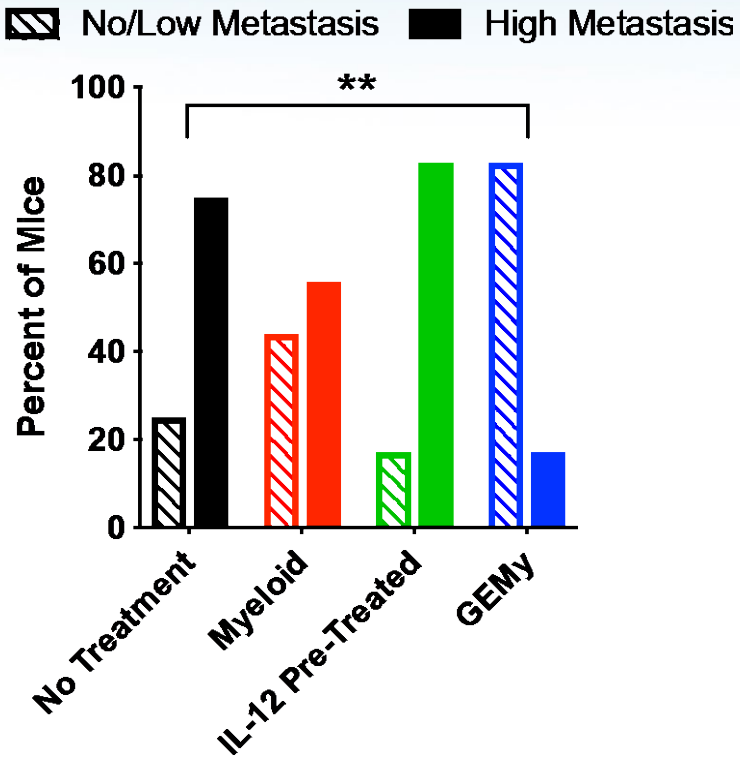
GEMys delay primary tumor growth and extend survival time

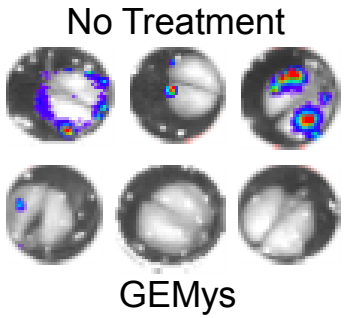




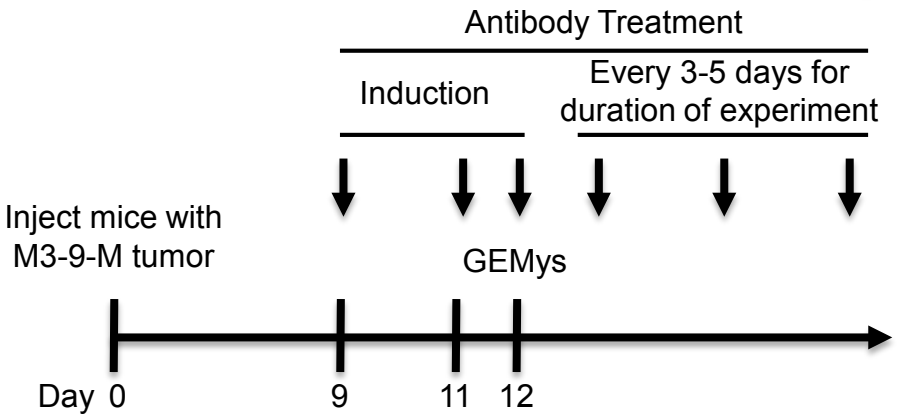
GEMys reduce lung metastasis

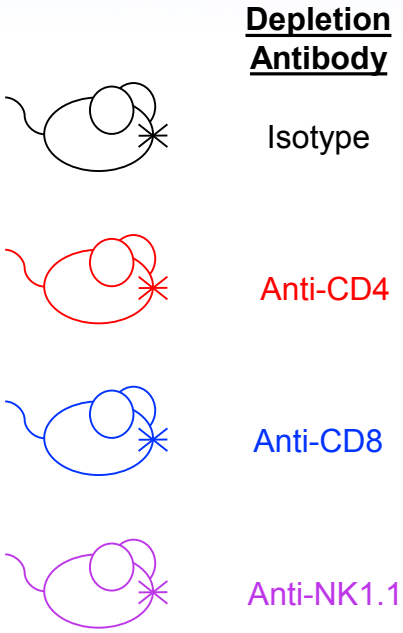




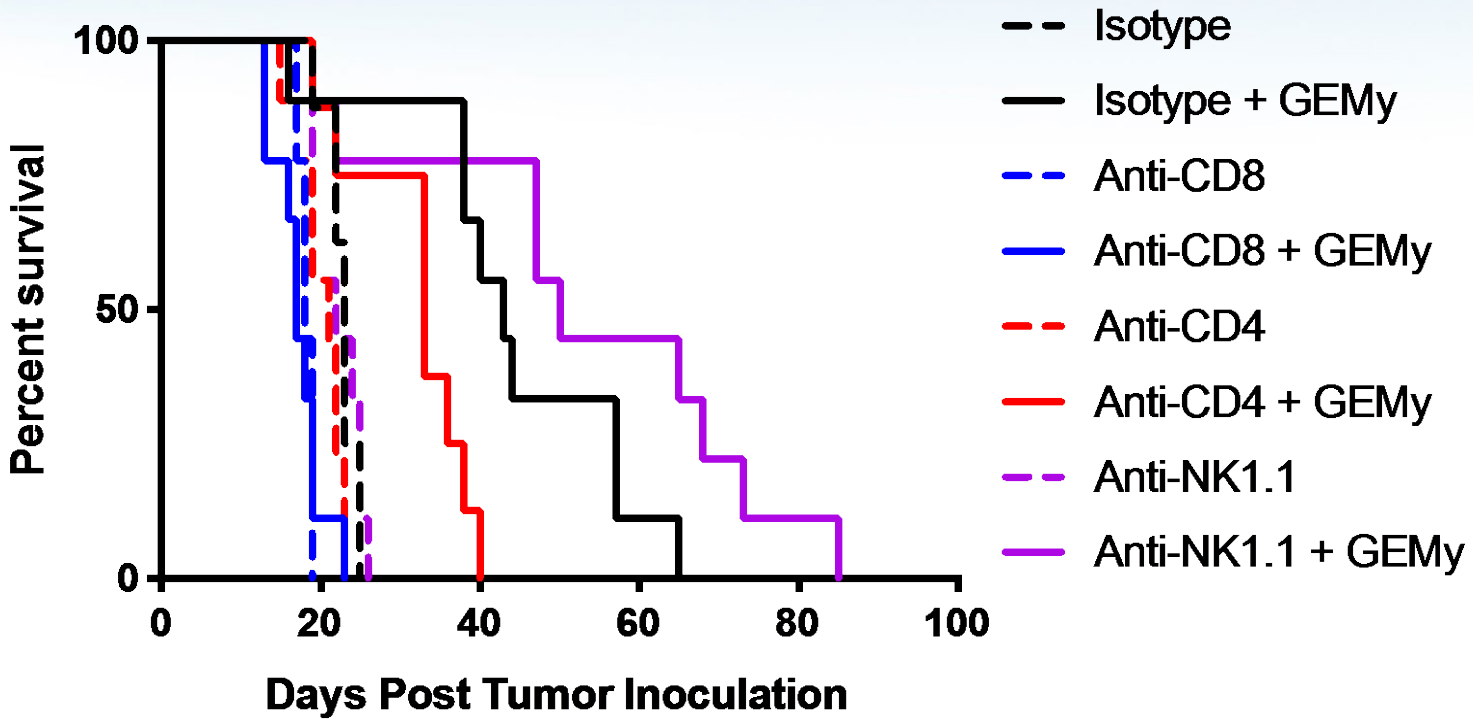


Which immune cell types are required for GEMy function?





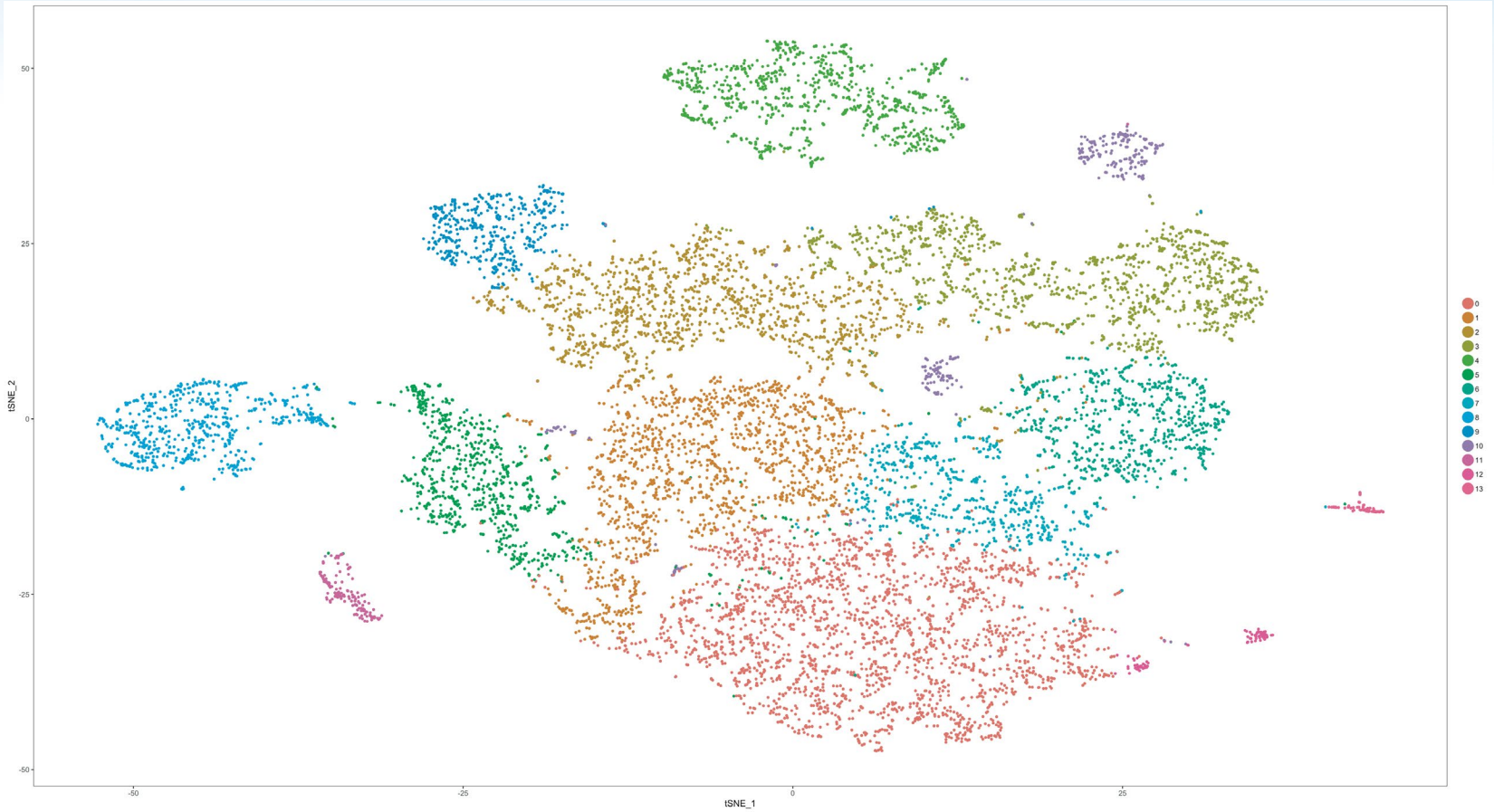
What immune cell types are required for GEMy function?



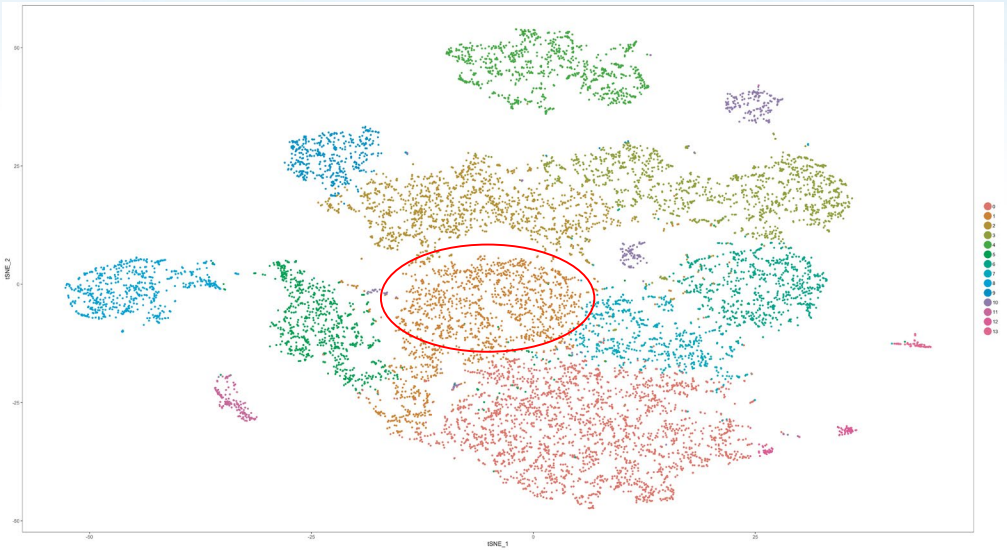
1. $CD8^+$ T cells are necessary for GEMy function.
2. $CD4^+$ T cells contribute to GEMy function.
3. $NK1.1^+$ cells are not required for GEMy function.

Sorting Out the Toys

Recurrent, Metastatic Osteosarcoma Patient Demonstrate Stromal and Immune Plasticity



Activated Stromal Cell Cluster

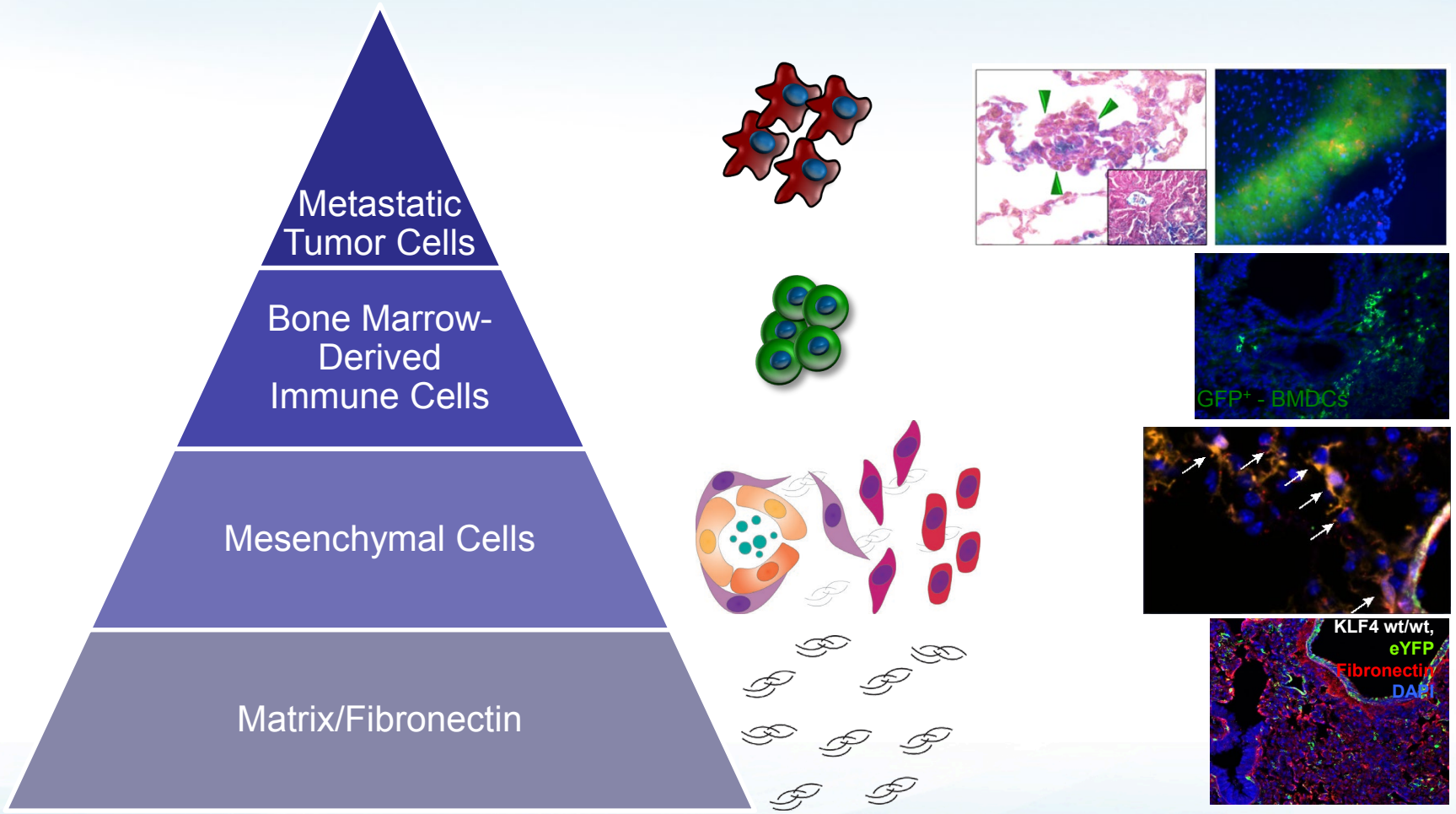


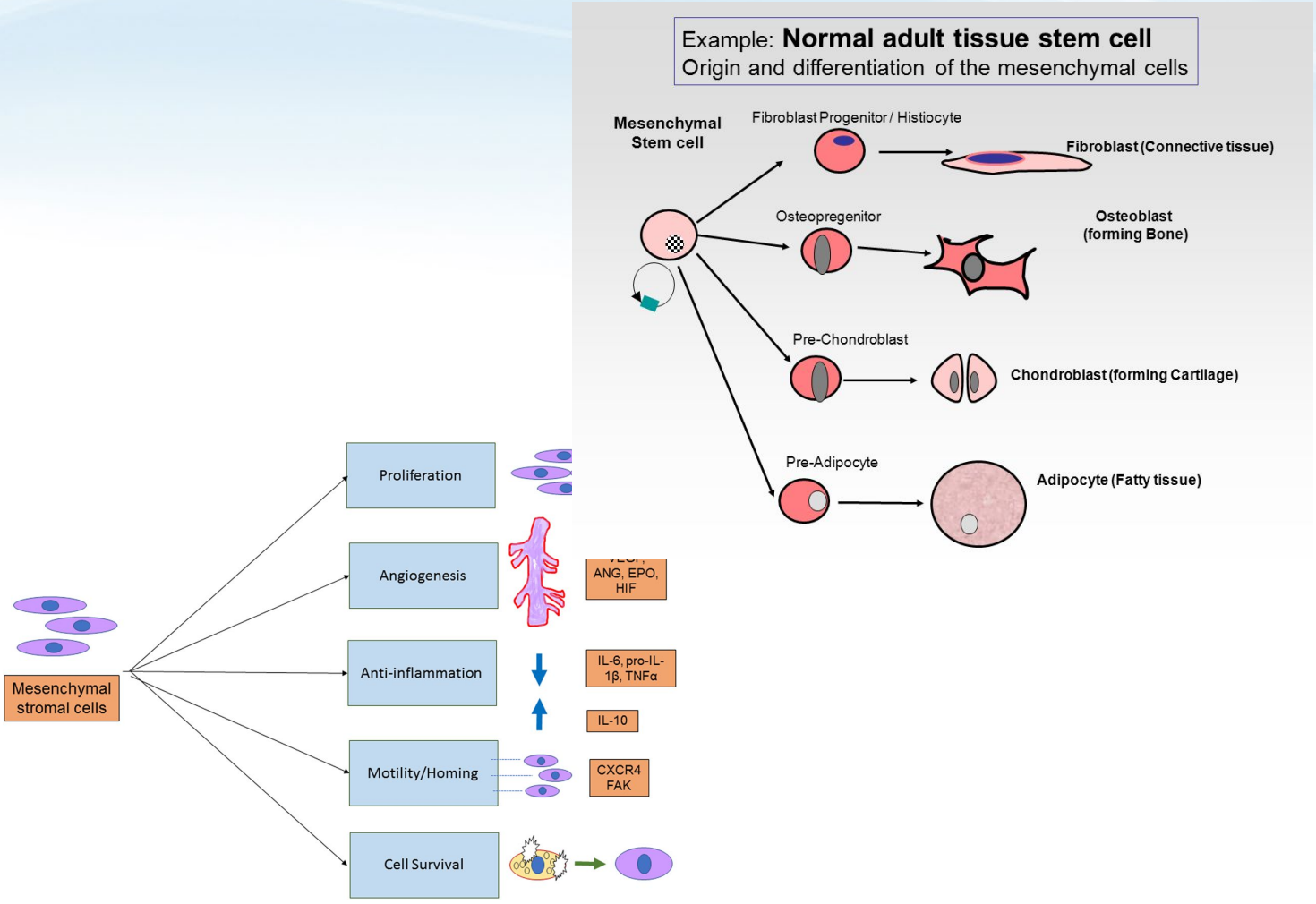
Key Genes in Cluster 4
PDGFRa
TAGLN
ACTA2
PDGFRb
RGS5
POSTN

Diverse Myeloid Cell Populations

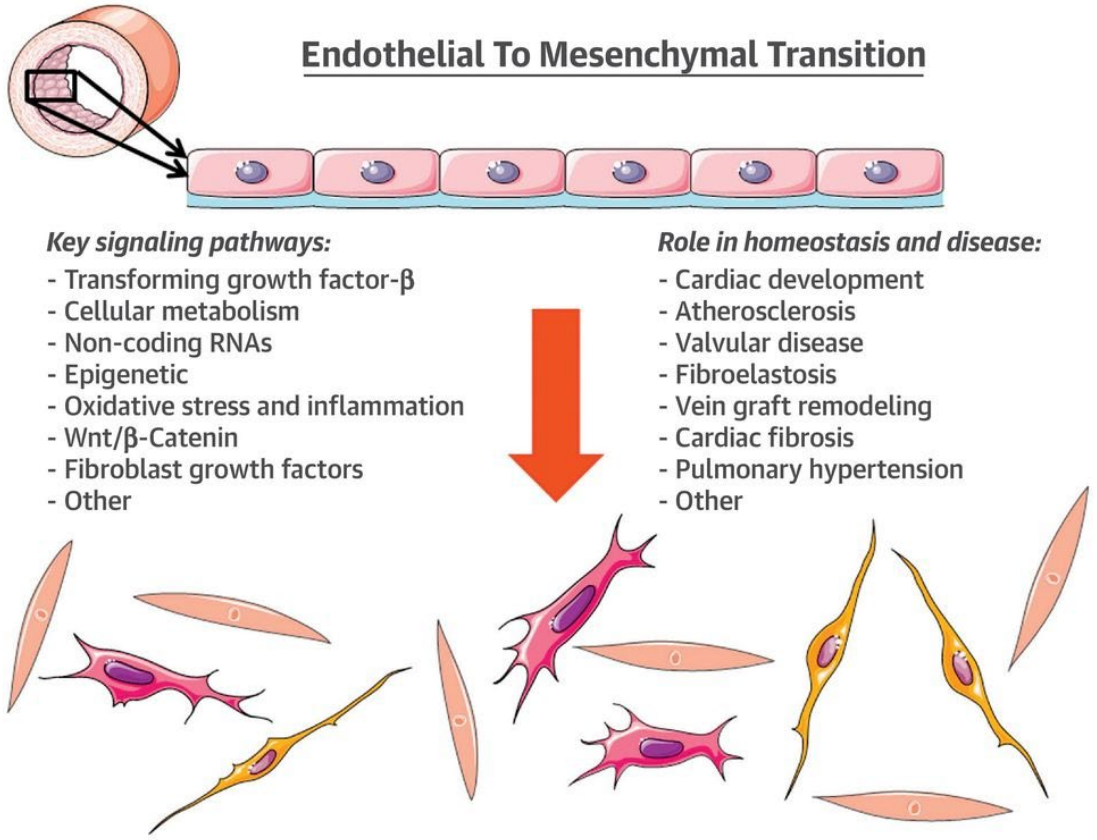
Key Genes:
CSF1R
CD163
CEBPB
MMP9
HIF1a

The Pre-Metastatic Niche: The Process of Building A Metastatic Microenvironment

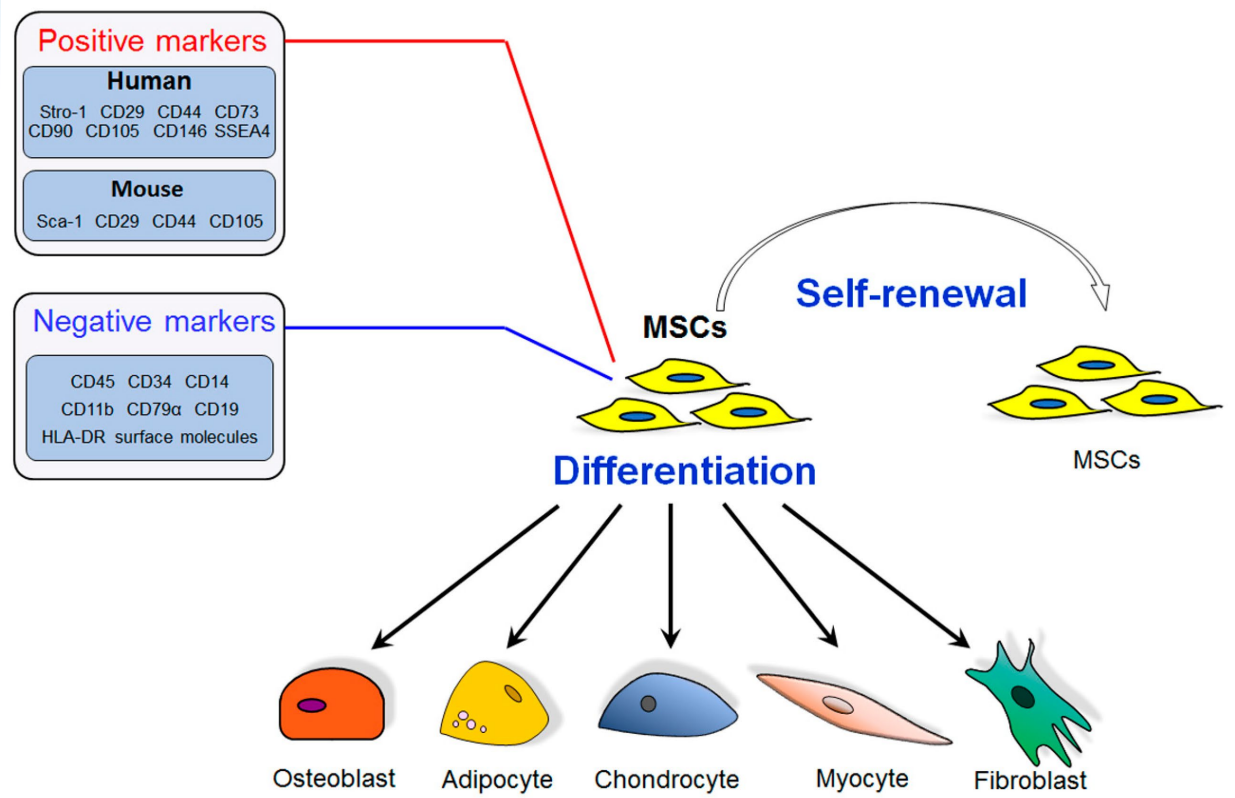


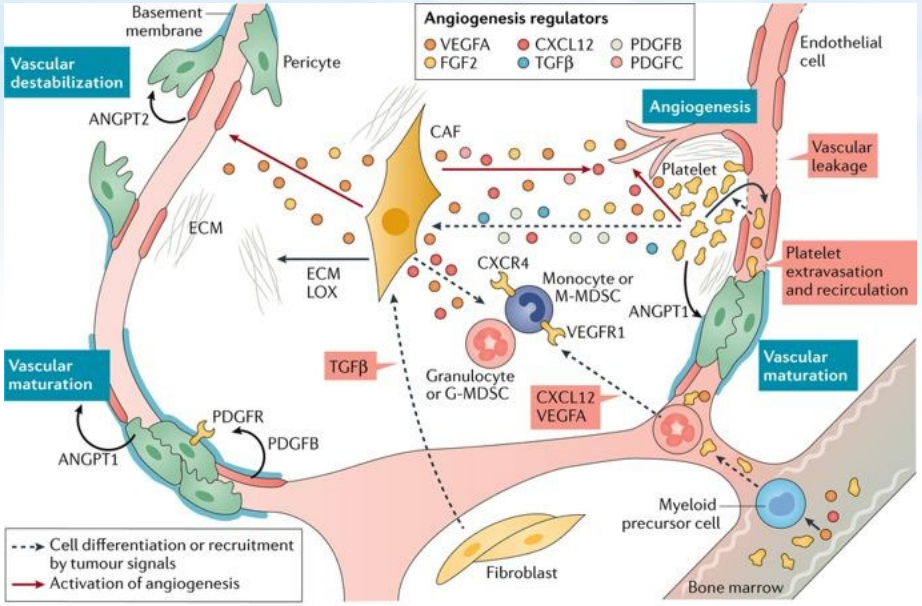

Example: Normal adult tissue stem cell
Origin and differentiation of the mesenchymal cells
Mesenchymal Stem cell
Fibroblast Progenitor / Histiocyte
Fibroblast (Connective tissue)
Osteopregenitor
Osteoblast (forming Bone)
Pre-Chondroblast
Chondroblast (forming Cartilage)
Pre-Adipocyte
Adipocyte (Fatty tissue)
Mesenchymal stromal cells
Proliferation
Angiogenesis
ANG, EPO, HIF
Anti-inflammation
IL-6, pro-IL-1β, TNFα
IL-10
Motility/Homing
CXCR4
FAK
Cell Survival

CENTRAL ILLUSTRATION: Endothelial to Mesenchymal Transition in Cardiovascular Disease: Key Mechanisms and Clinical Translation Opportunities

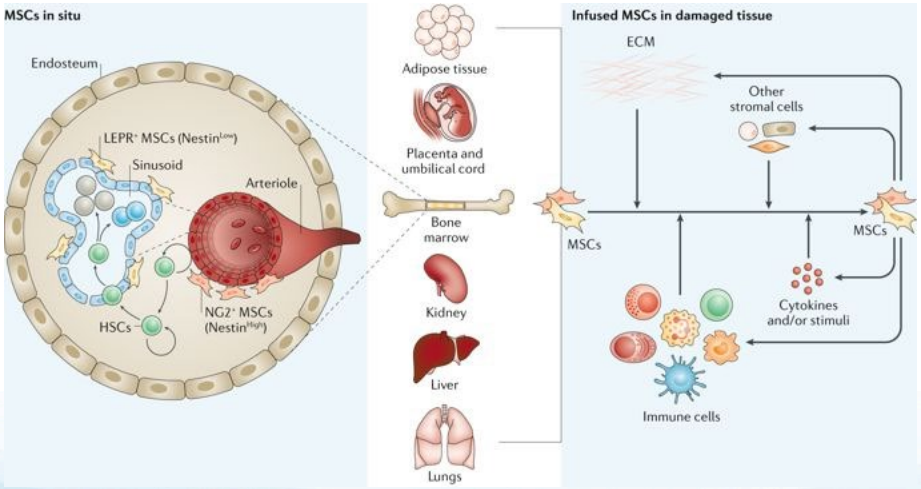


Kovacic, J.C. et al. J Am Coll Cardiol. 2019;73(2):190-209.

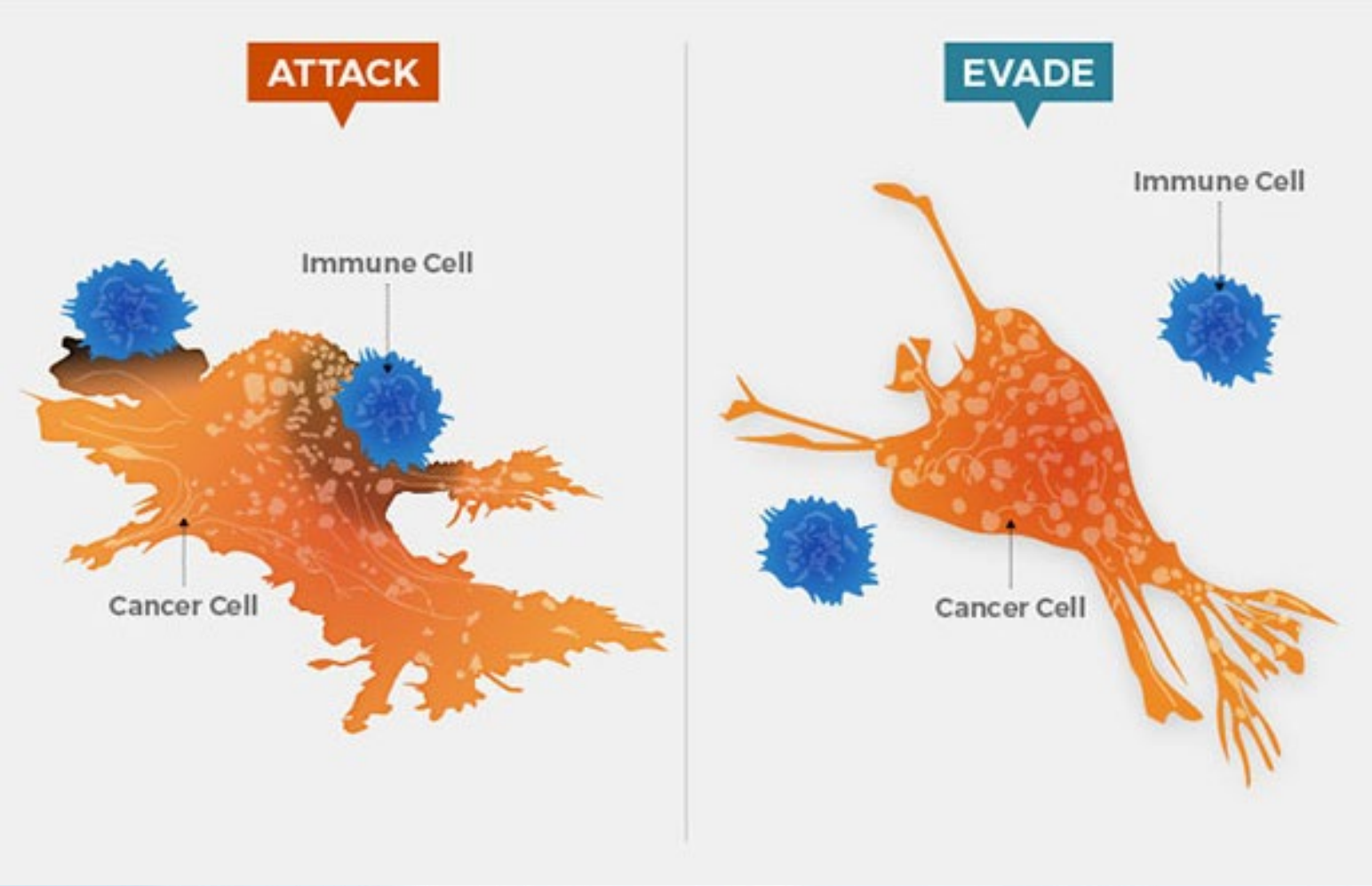

Positive markers
Human
Stro-1 CD29 CD44 CD73
CD90 CD105 CD146 SSEA4
Mouse
Sca-1 CD29 CD44 CD105
Negative markers
CD45 CD34 CD14
CD11b CD79α CD19
HLA-DR surface molecules
MSCs
Self-renewal
MSCs
Differentiation
Osteoblast
Adipocyte
Chondrocyte
Myocyte
Fibroblast



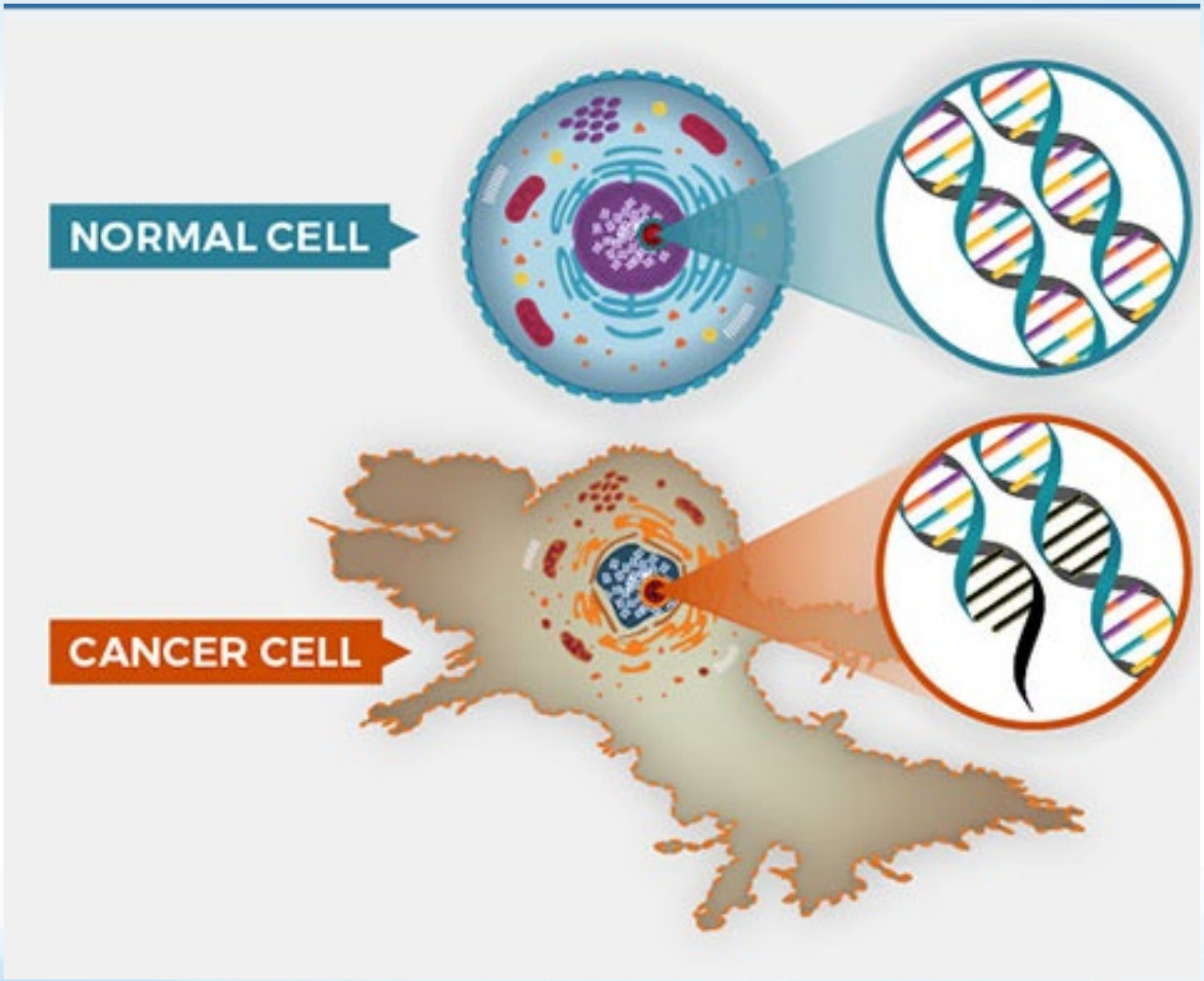
Nature Reviews | Cancer



Myeloid Derived Suppressor Cells

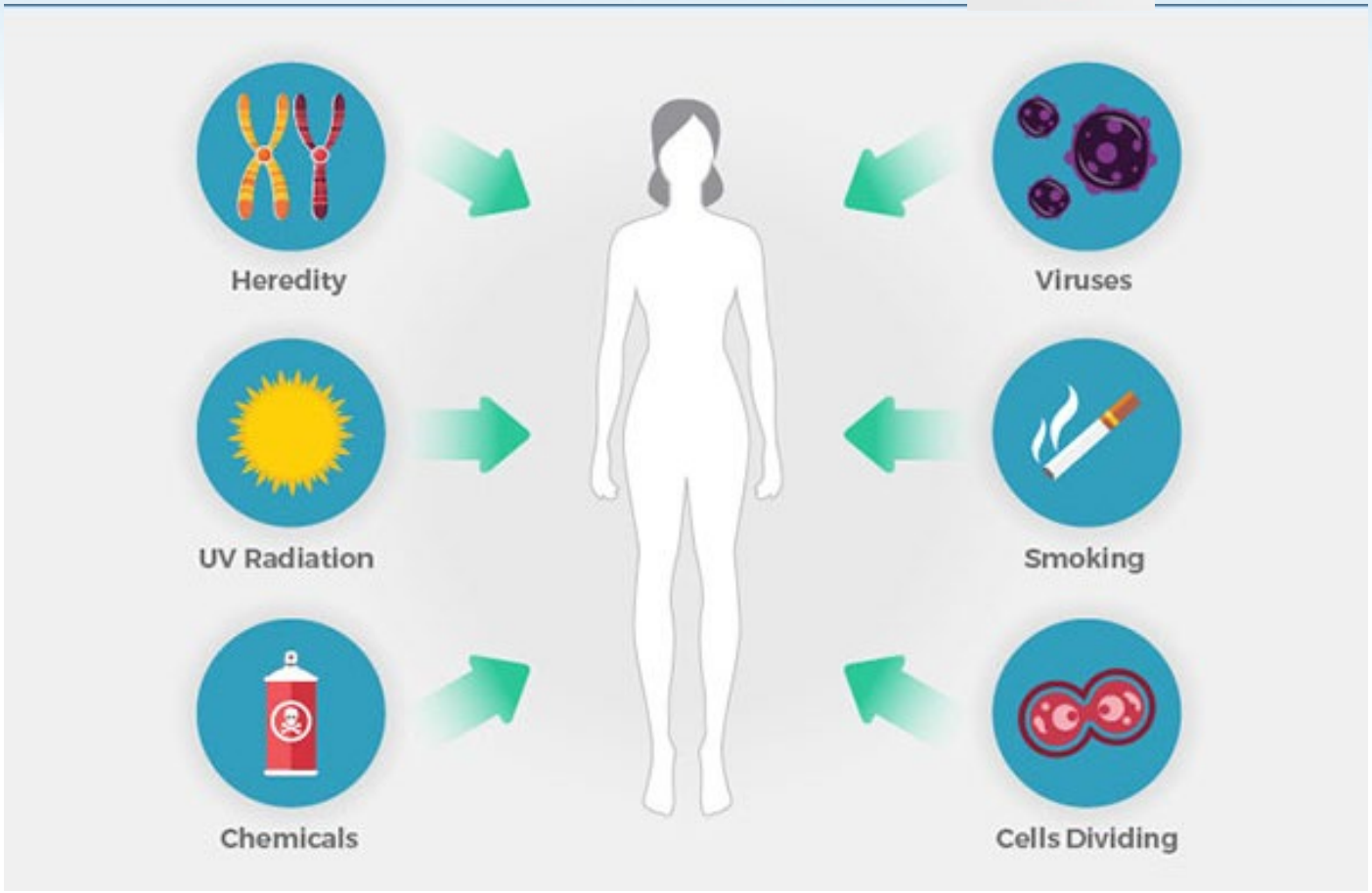


Genetic Changes in Cells Can Cause Cancer

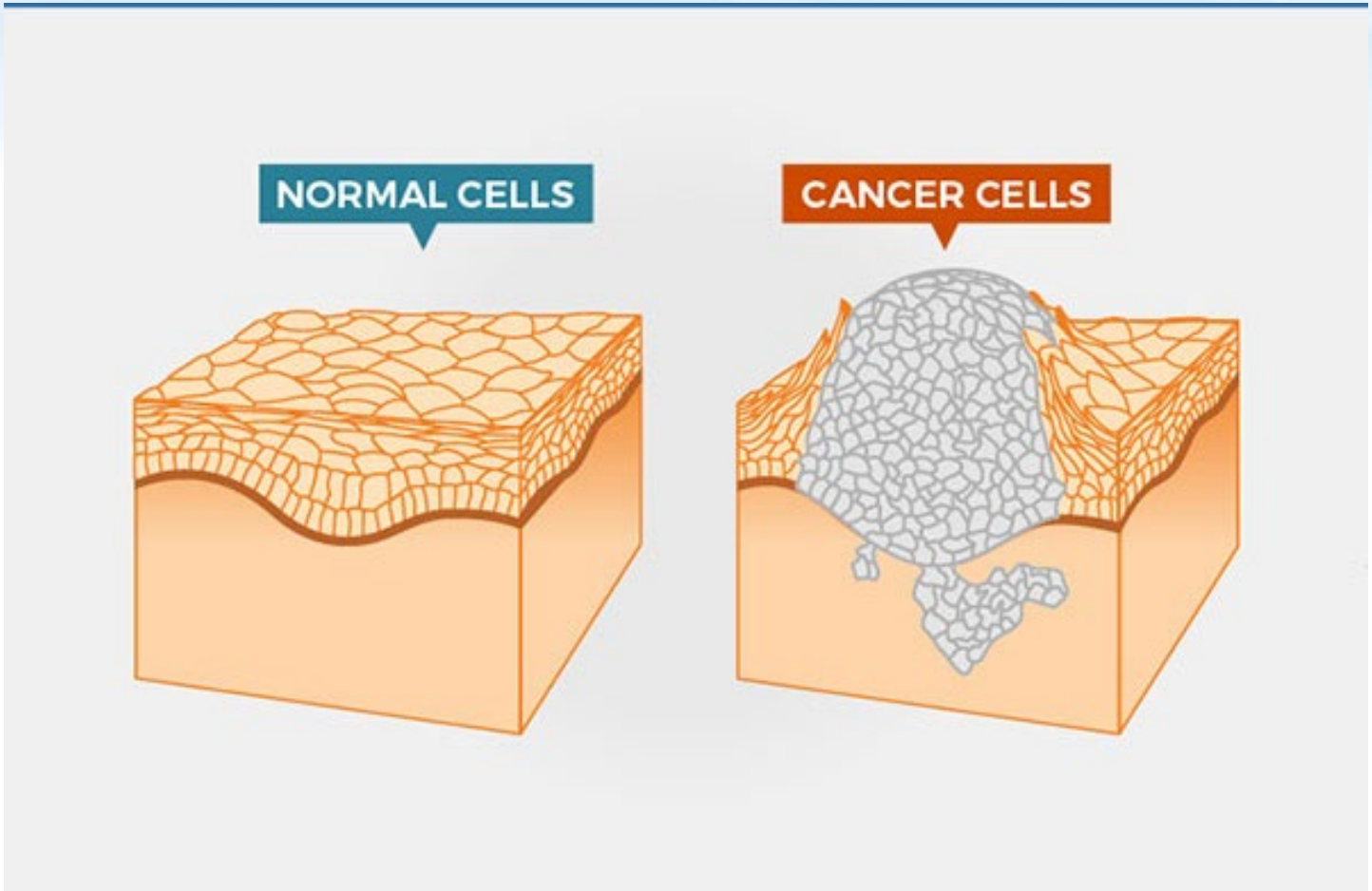


What Causes Genetic Changes

Developmental Abnormality



Cancer : Altered Balance in Homeostasis

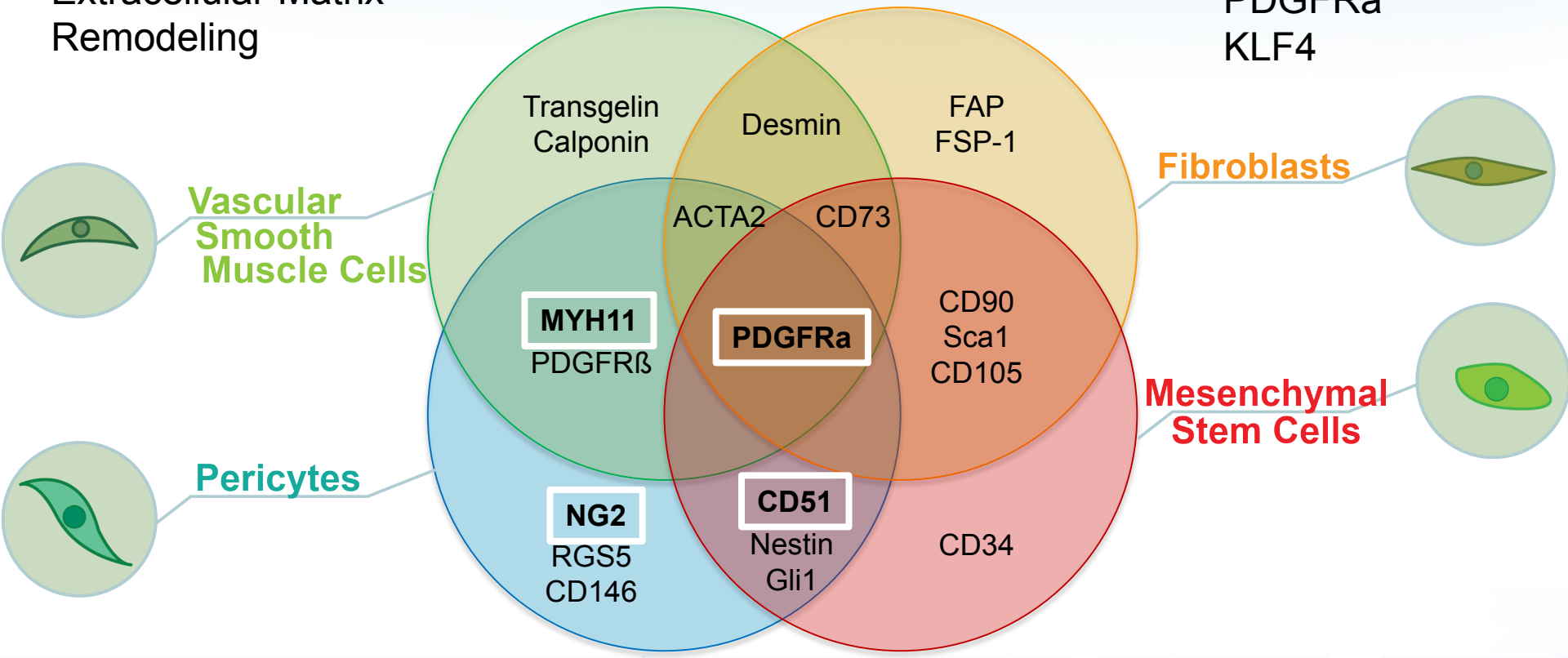


Cancer is when a cell develops changes in its DNA and grow faster or have a longer life cycle than the other similar neighbor cells

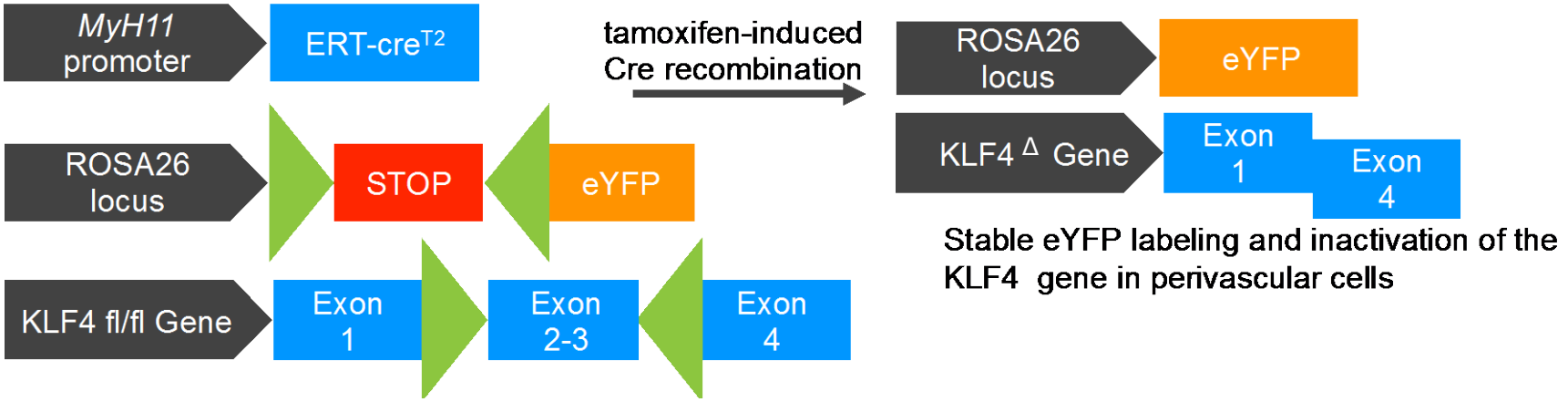
Investigations into Stromal Cell Populations

Key Pathways:
TGFB
Extracellular Matrix
Remodeling

Key Genes:
SMAa
NG2
PDGFRa
KLF4

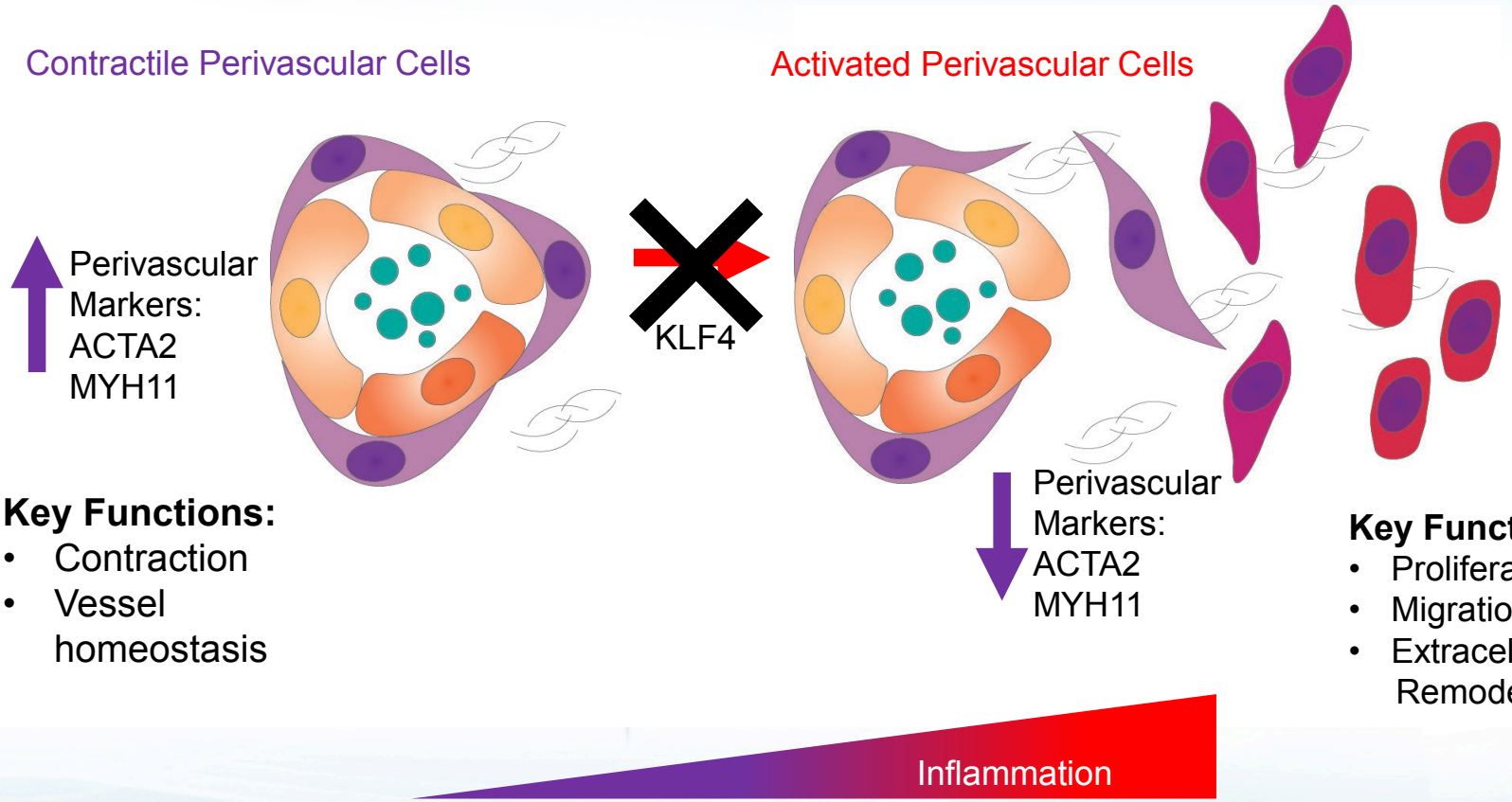


Perivascular Cell Specific KLF4 Deletion Mouse Model to Inhibit Perivascular Cell Plasticity

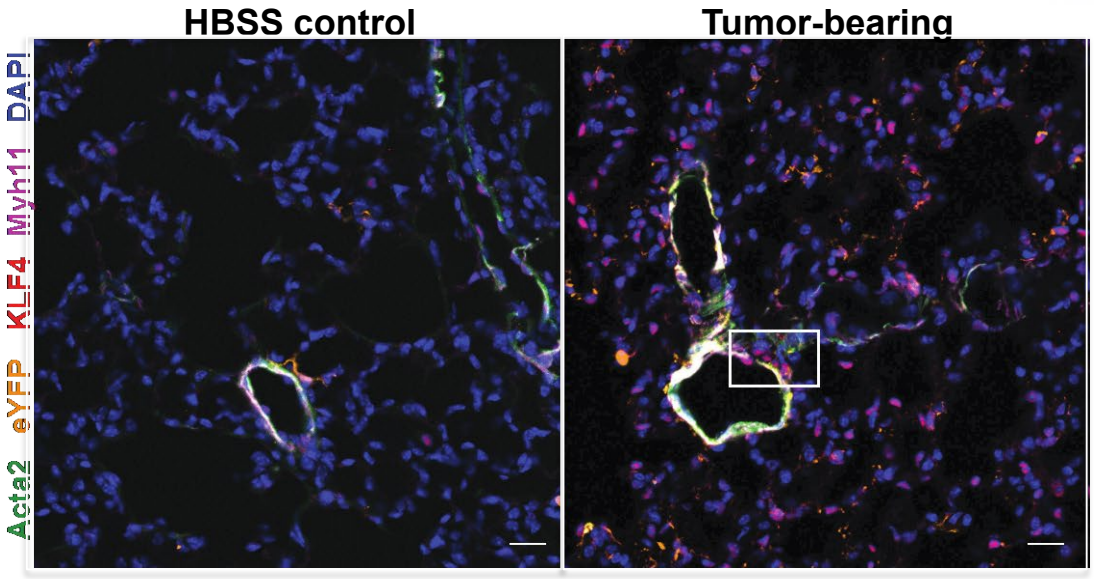


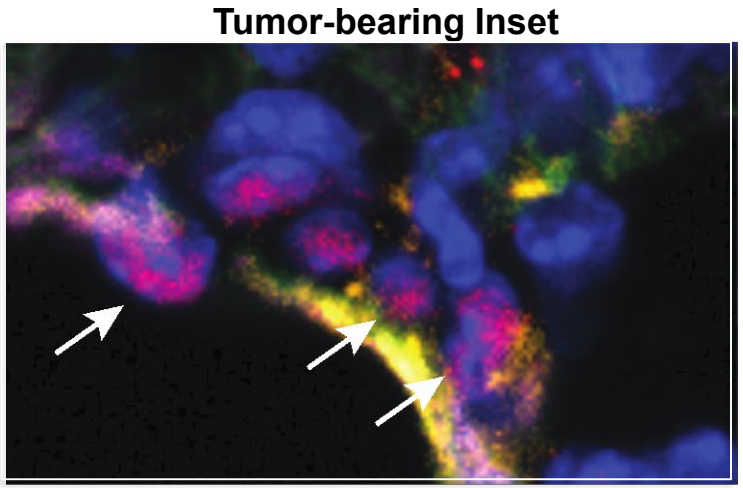
Murgai et al Nature Med 2017

Perivascular Cells Become Activated with Inflammation/Disease and Lose Marker Expression



KLF4 is expressed in perivascular cells in pre-metastatic lung



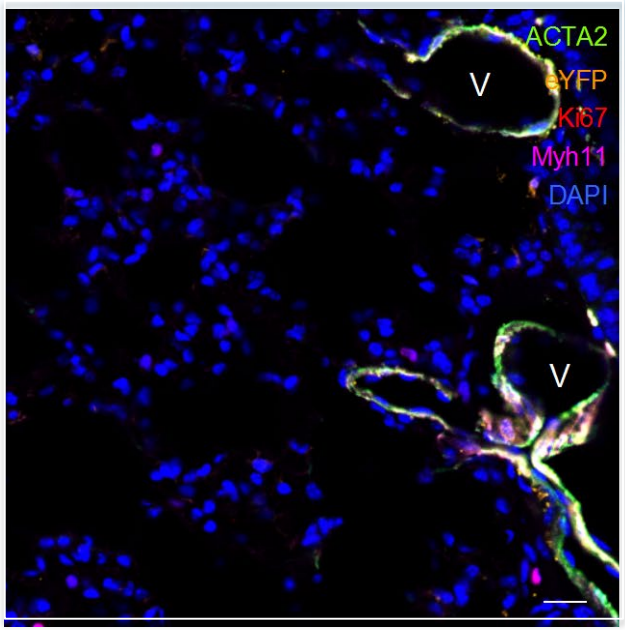


How does the distant primary tumor induce perivascular KLF4 expression?

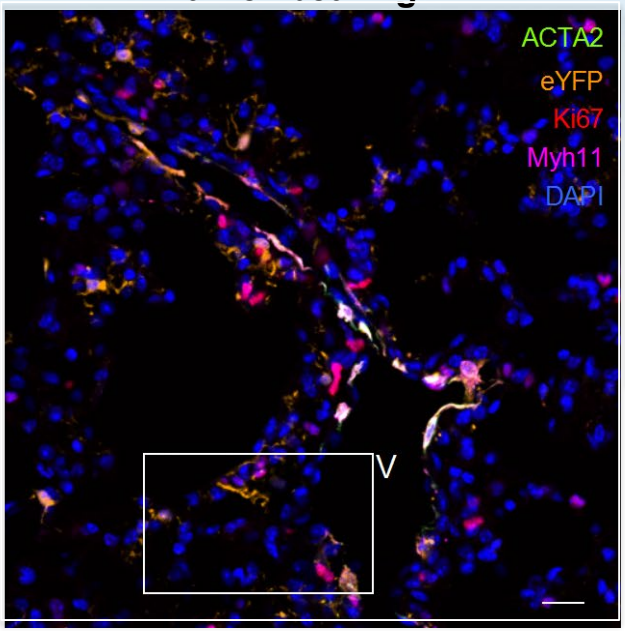
Murgai et. al., Nature Med 2017

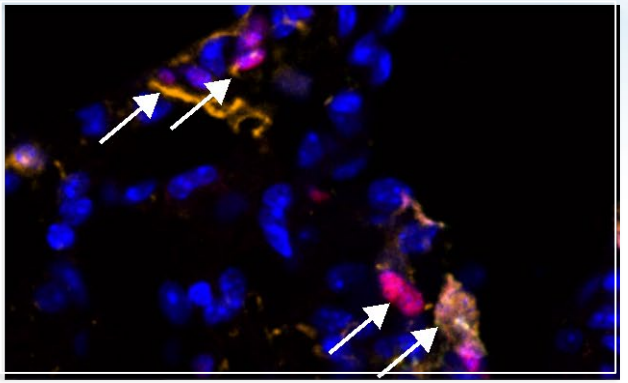
Perivascular cells proliferate in pre-metastatic lungs

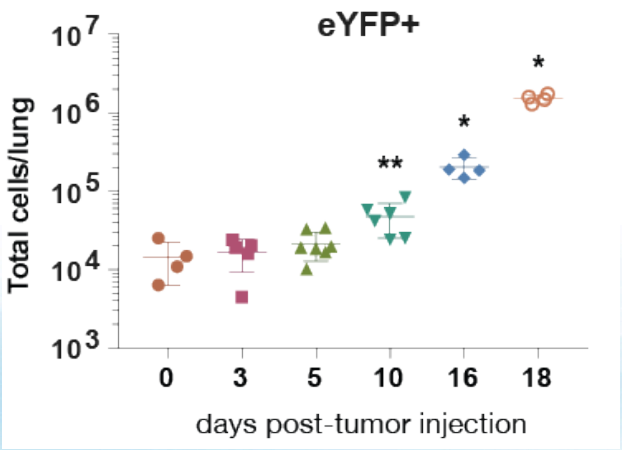
HBSS control

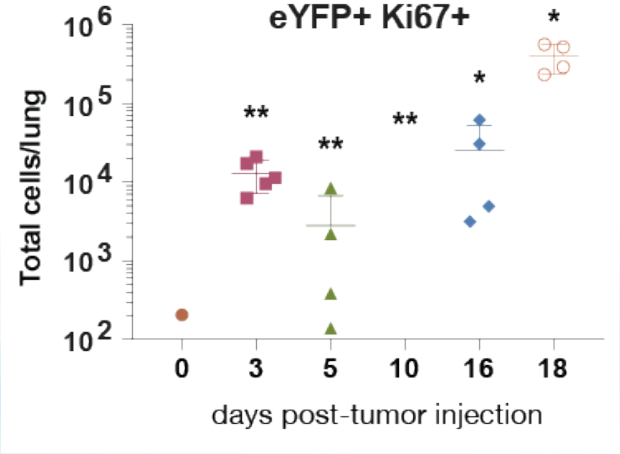


Tumor-bearing









Murgai et. al., Nature Med 2017

Metastasis is a Long Standing Problem

"When a plant goes to seed, its seeds are carried in all directions, but they can only live and grow if they fall on congenial soil."

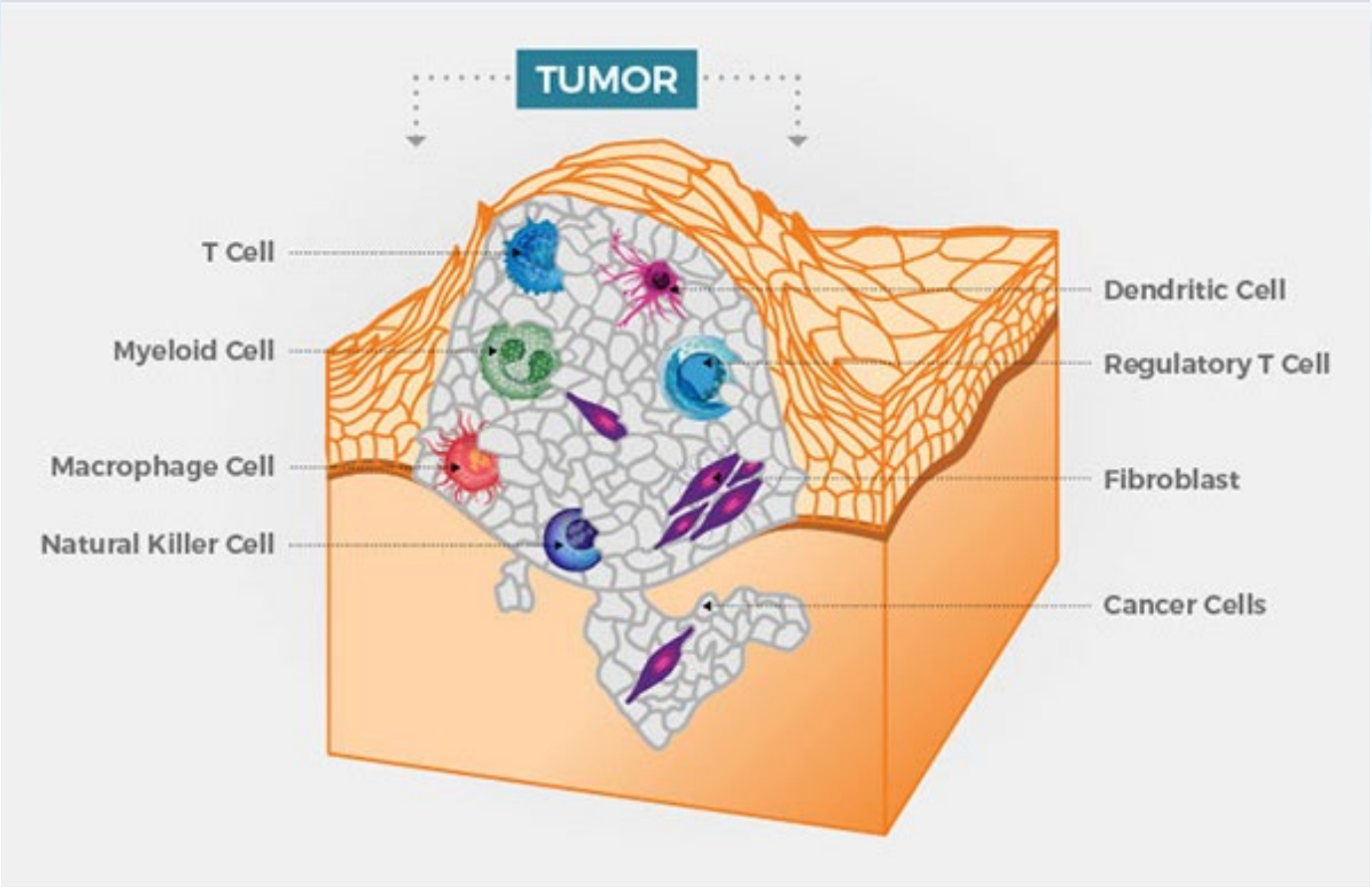
–Stephen Paget, The Lancet 1889

Tumor Cell Heterogeneity

Different Microenvironments

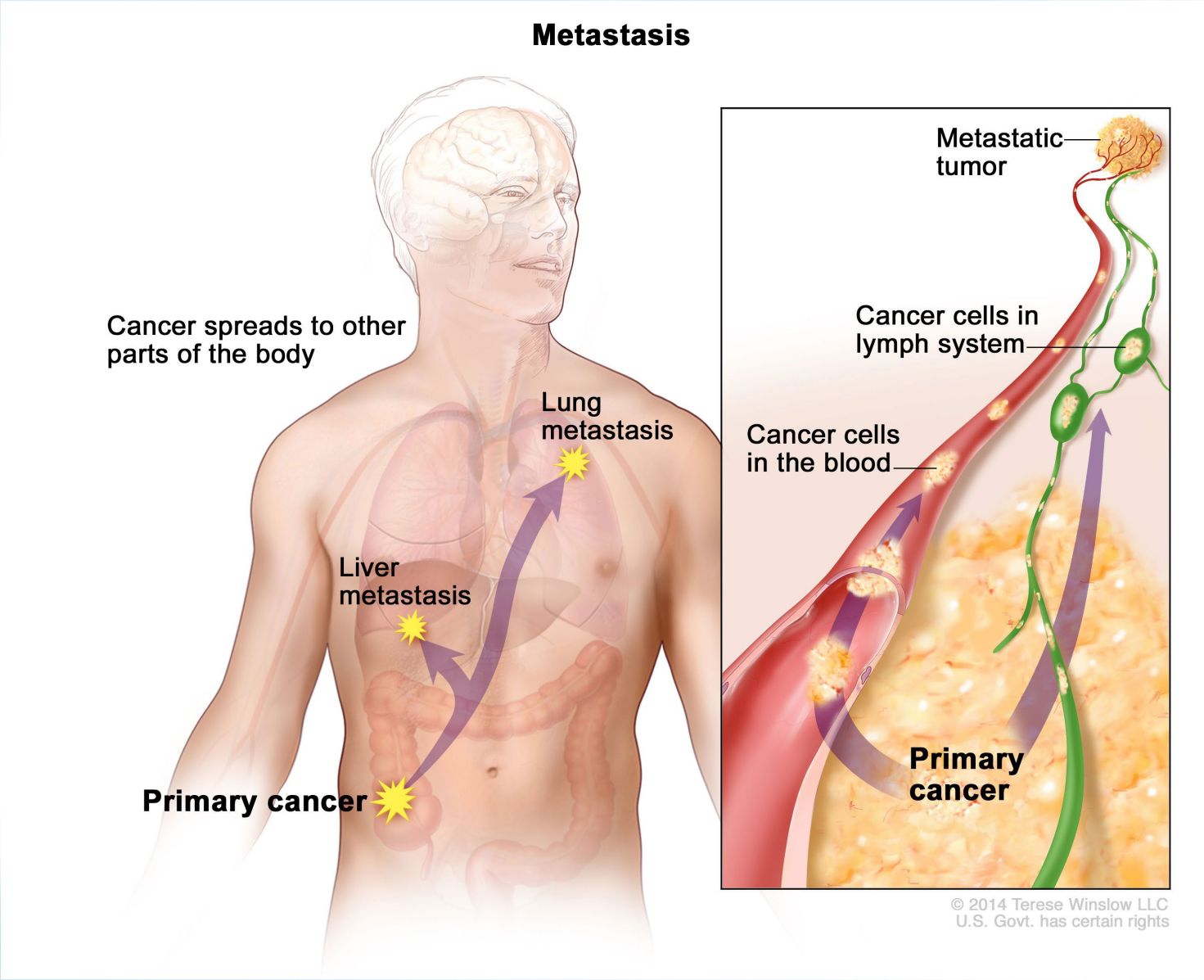
Reciprocal Nature of the Process

The Tumor Microenvironment

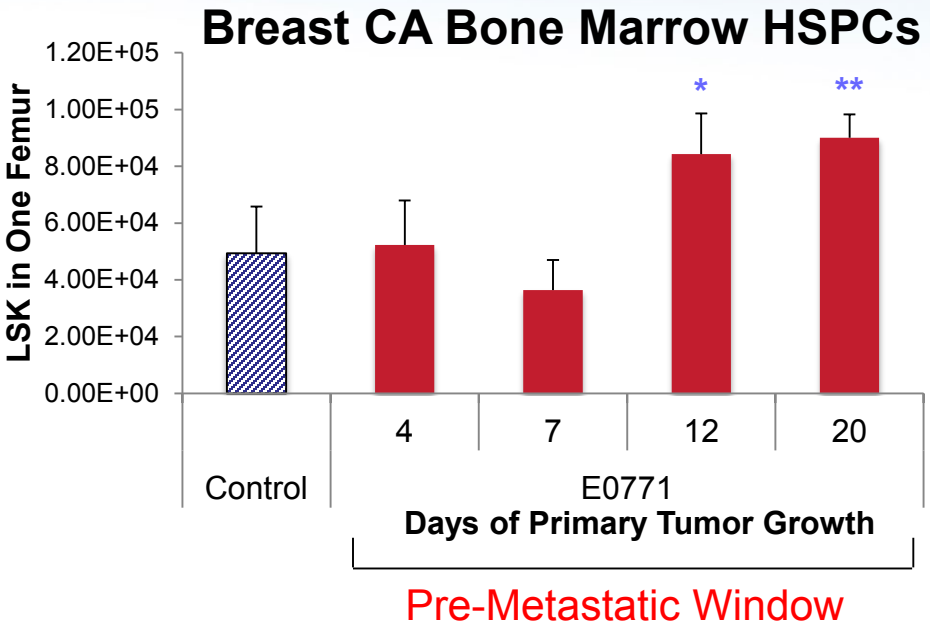


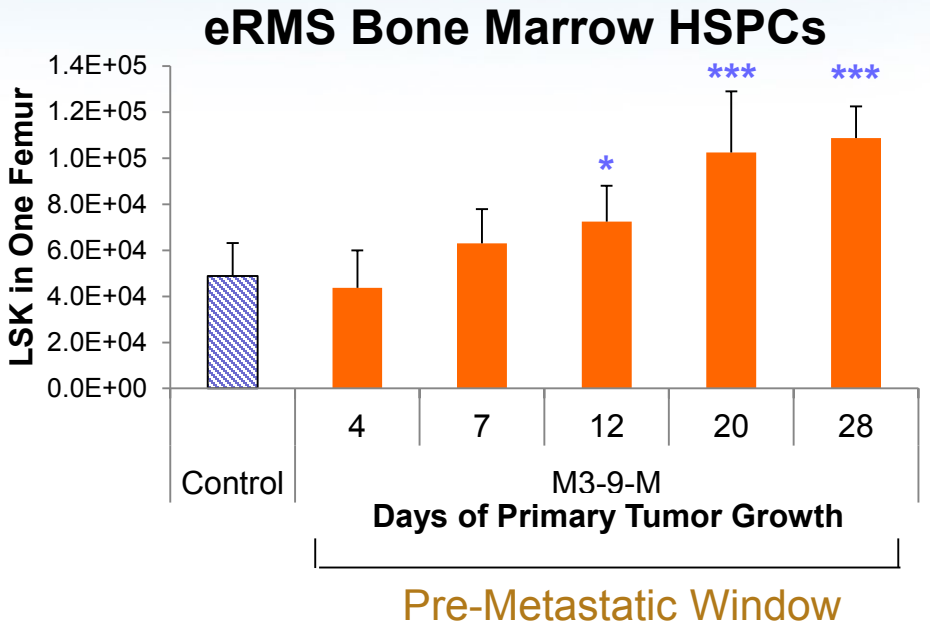
All tissue is in a state of balance with cell growth and death maintaining the organ structure. Every organ has specialized cells and other important cells such as stromal cells such as fibroblasts, endothelial cells and immune cells including T cell and macrophages

Metastasis is the spread of tumor cells from one site to another site



Hematopoietic Stem and Progenitor Cells (HSPCs) Expand During the Pre-Metastatic Window

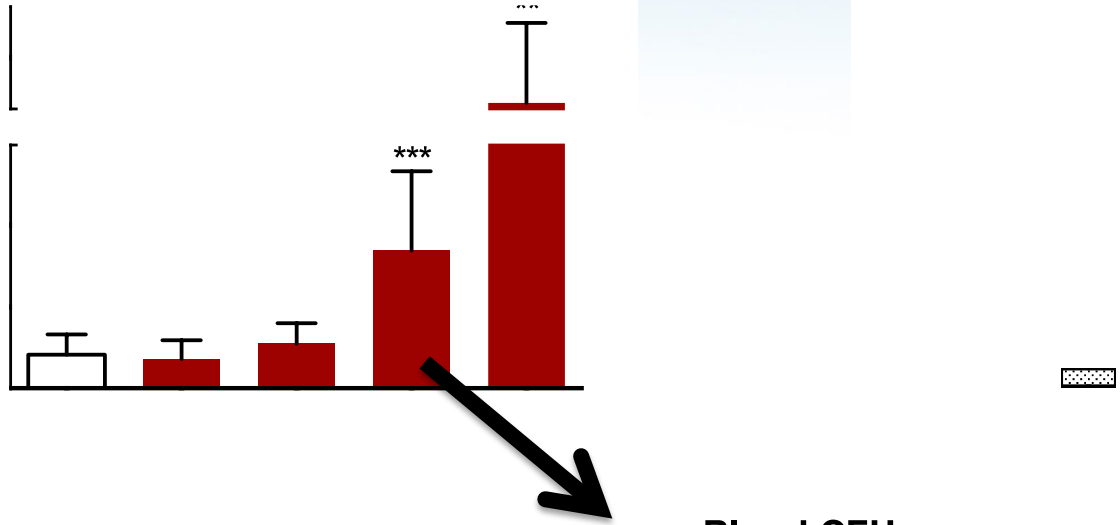


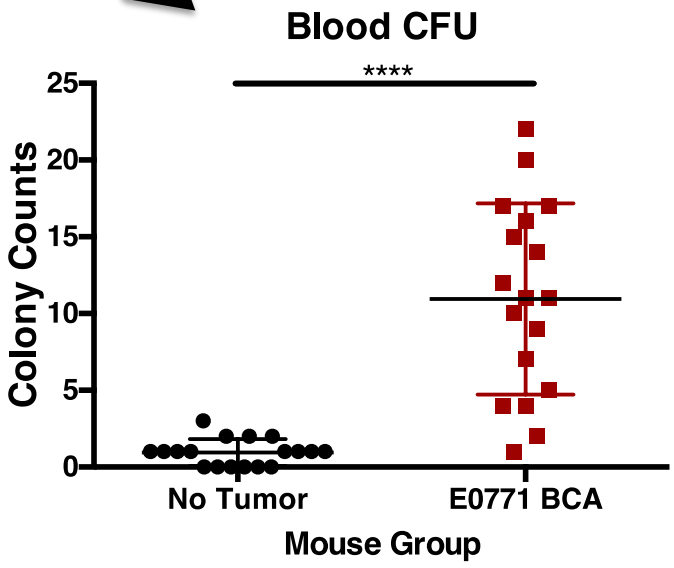


Mouse HSPCs are LSK cells: Negative for **L**ineage markers, expressing **S**ca1 and c**K**it

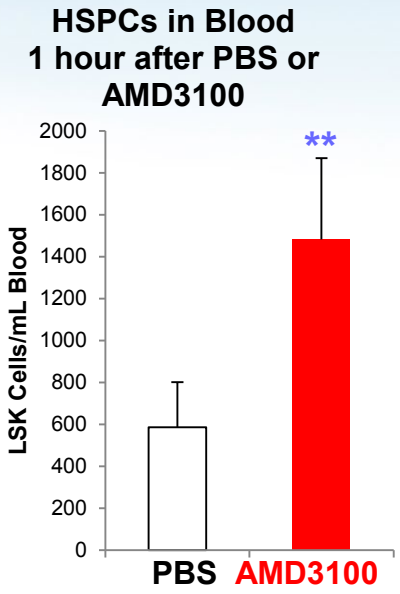
Giles et al Ca Res 2016

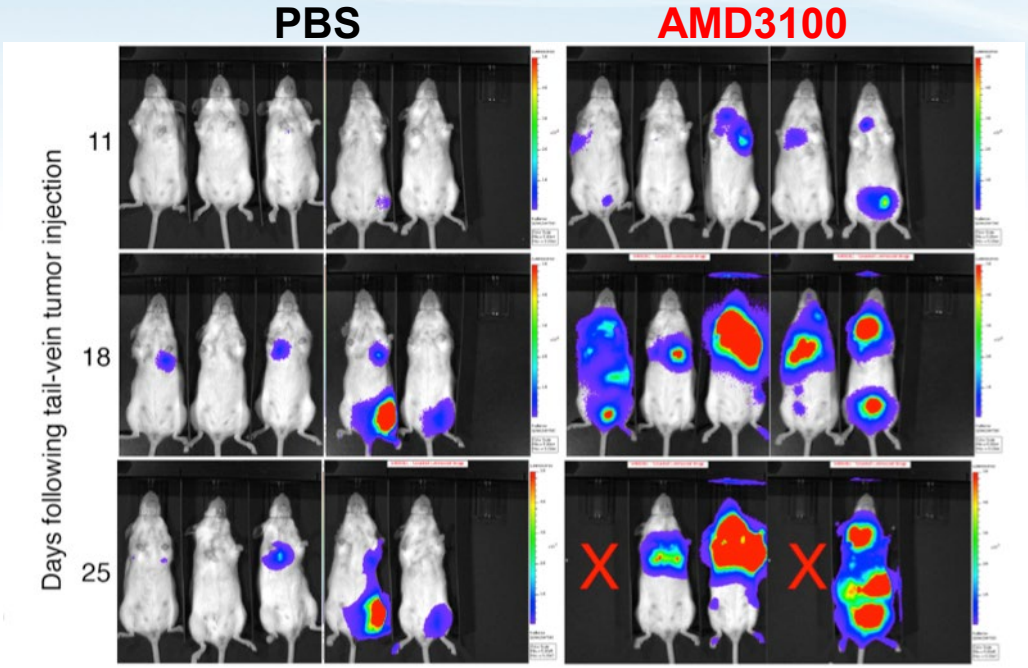
LSK HSPCs are Increased in Circulation of Tumor-Bearing Mice





Mobilization of HSPCs Enhances Experimental Metastasis





Inject mice:
PBS or
AMD3100

Inject mice:
BCA (ffluc-eGFP)
tail-vein

1 hour

Readout:
IVIS imaging (weekly)
Survival Curve