



“Ver es creer”: aprovechando al máximo la imagen “in vivo” para identificar nuevas vías en la inmunoterapia del cáncer

Álvaro Teijeira, CIMA, Universidad de Navarra

VI SIMPOSIO INTERNACIONAL en INMUNOTERAPIA DEL CÁNCER
Zaragoza, 08.04.2025



JEAN LUC GODARD

“La photographie, c'est la vérité et le cinéma, c'est vingt-quatre fois la vérité par seconde...”

The importance of the 4th dimension

Verité



Verité 24 fois per seconde

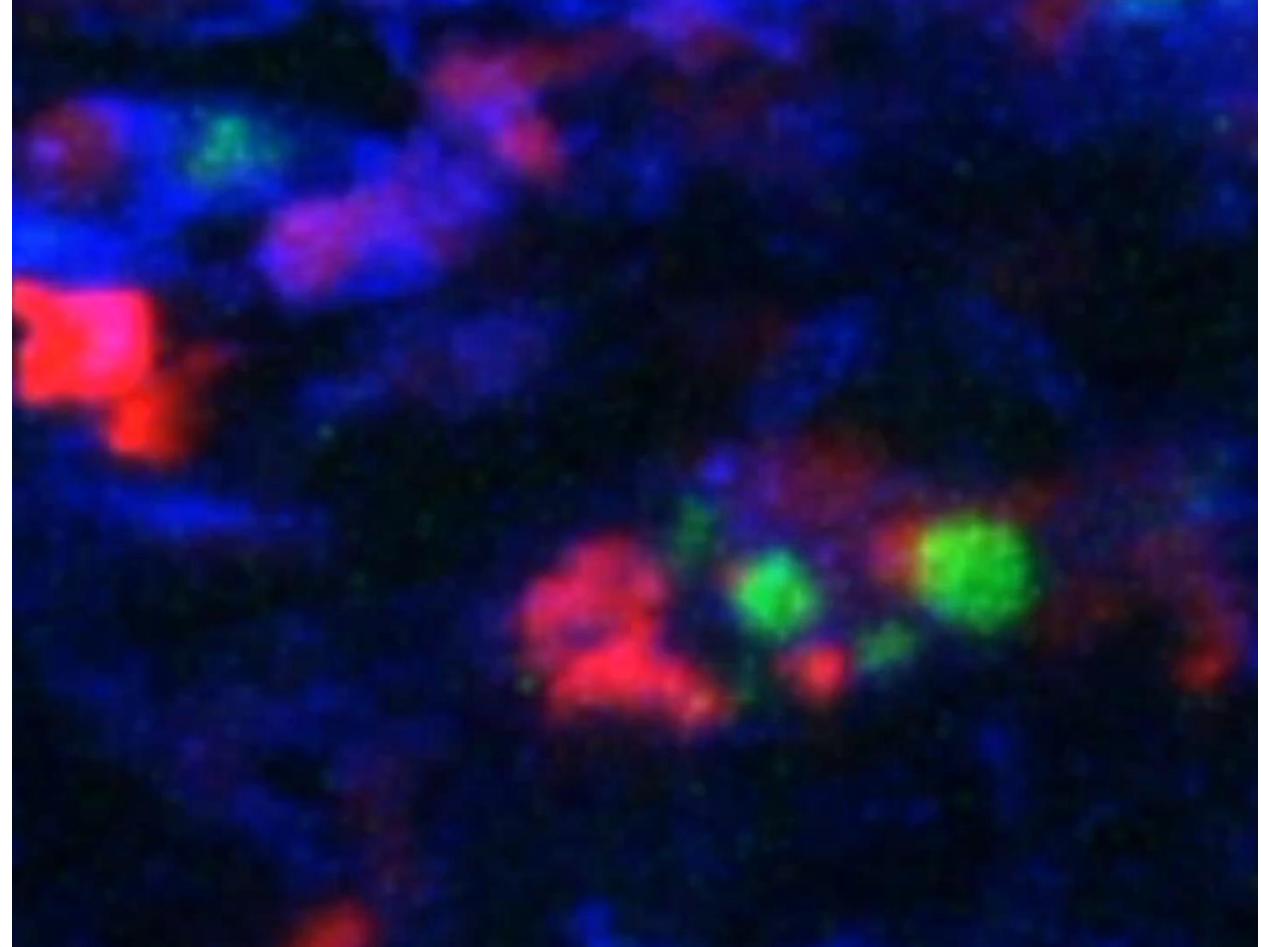
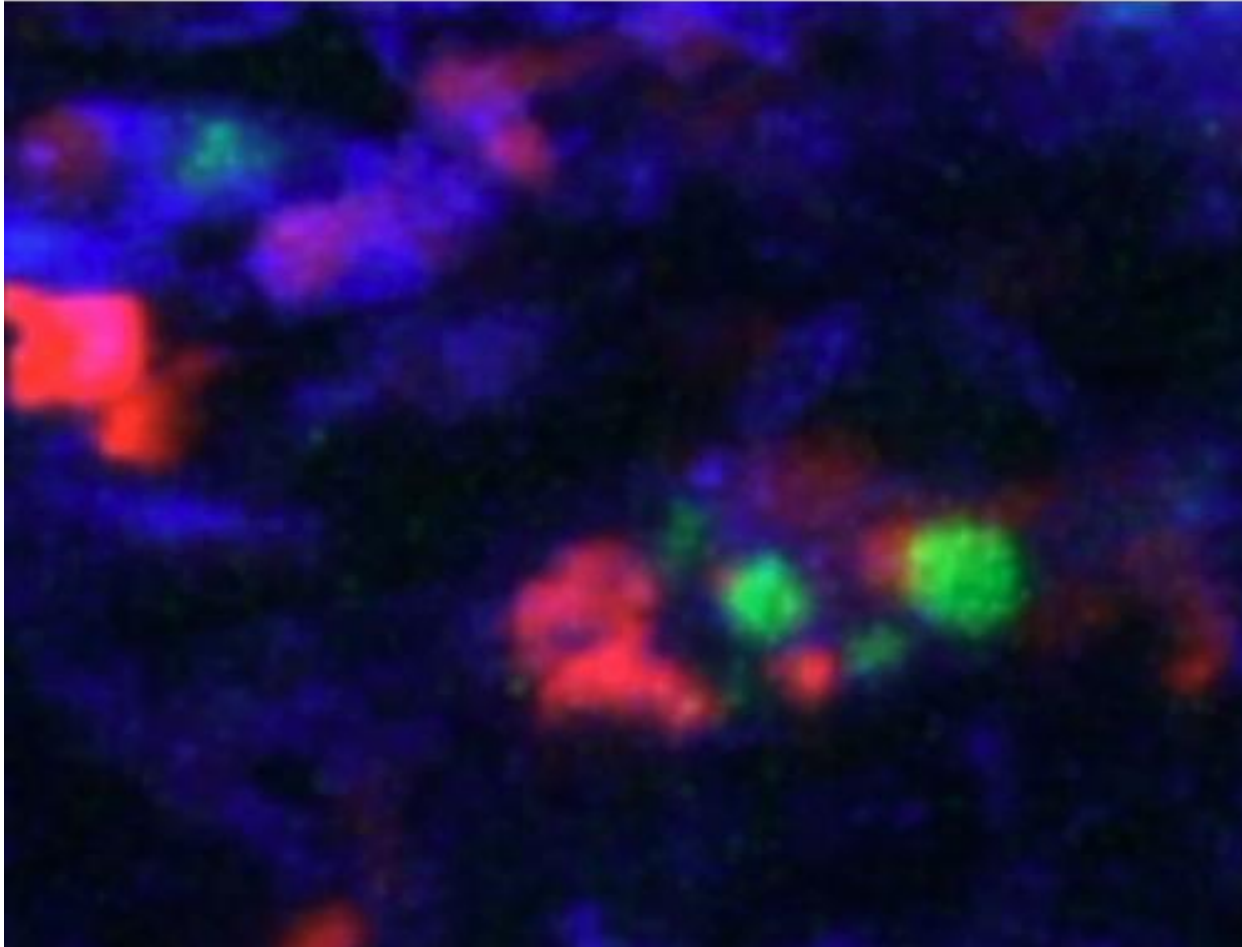


Bande à part, 1964

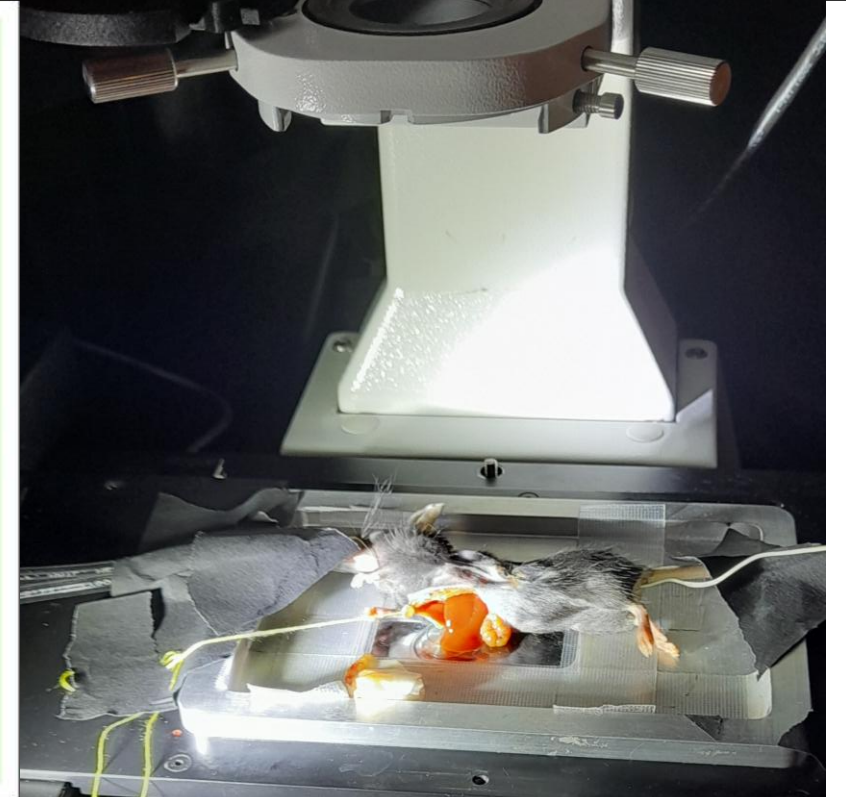
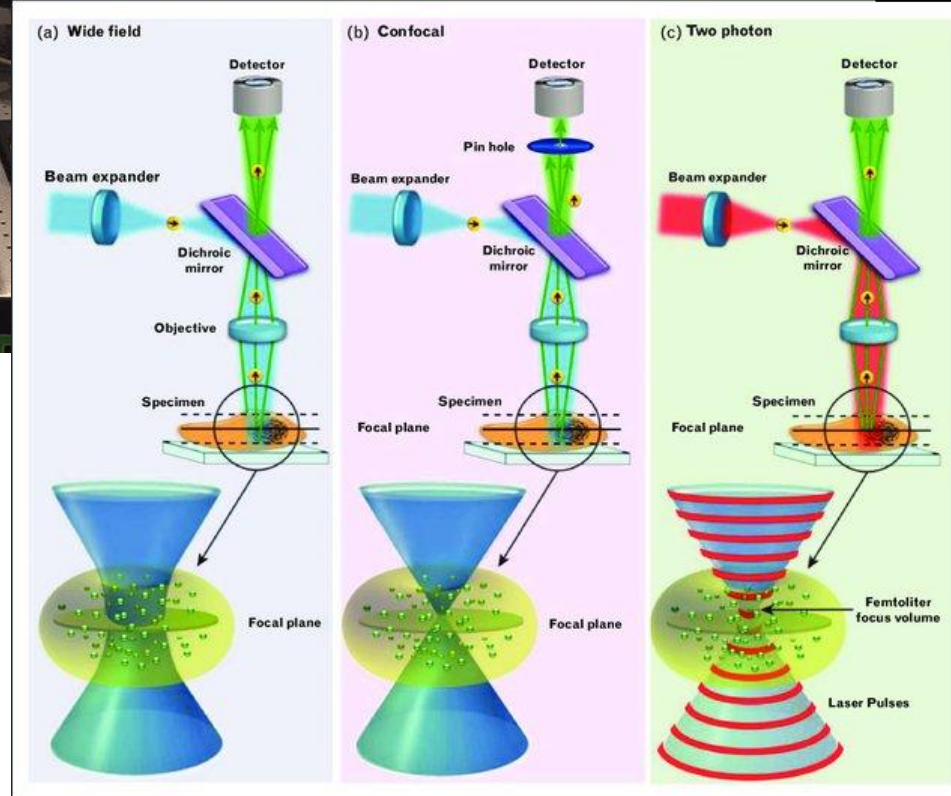
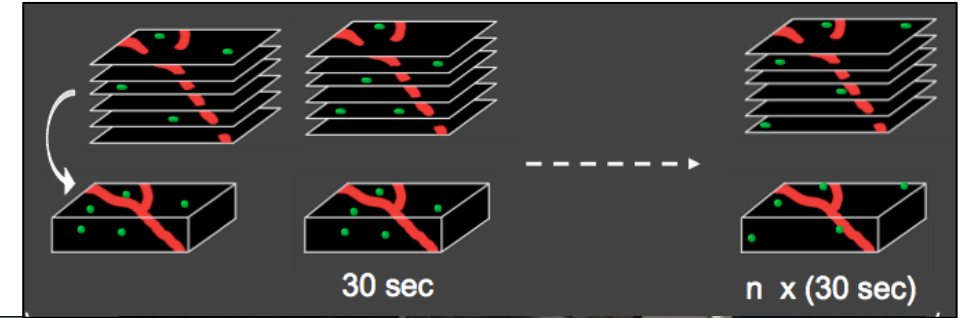
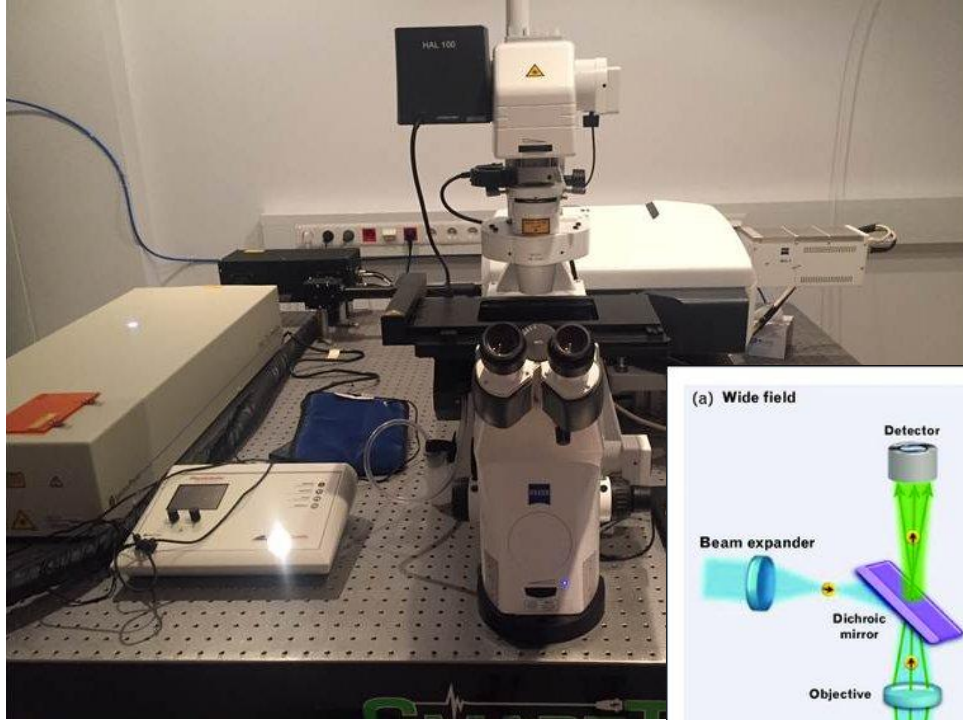
The importance of the 4th dimension

Verité

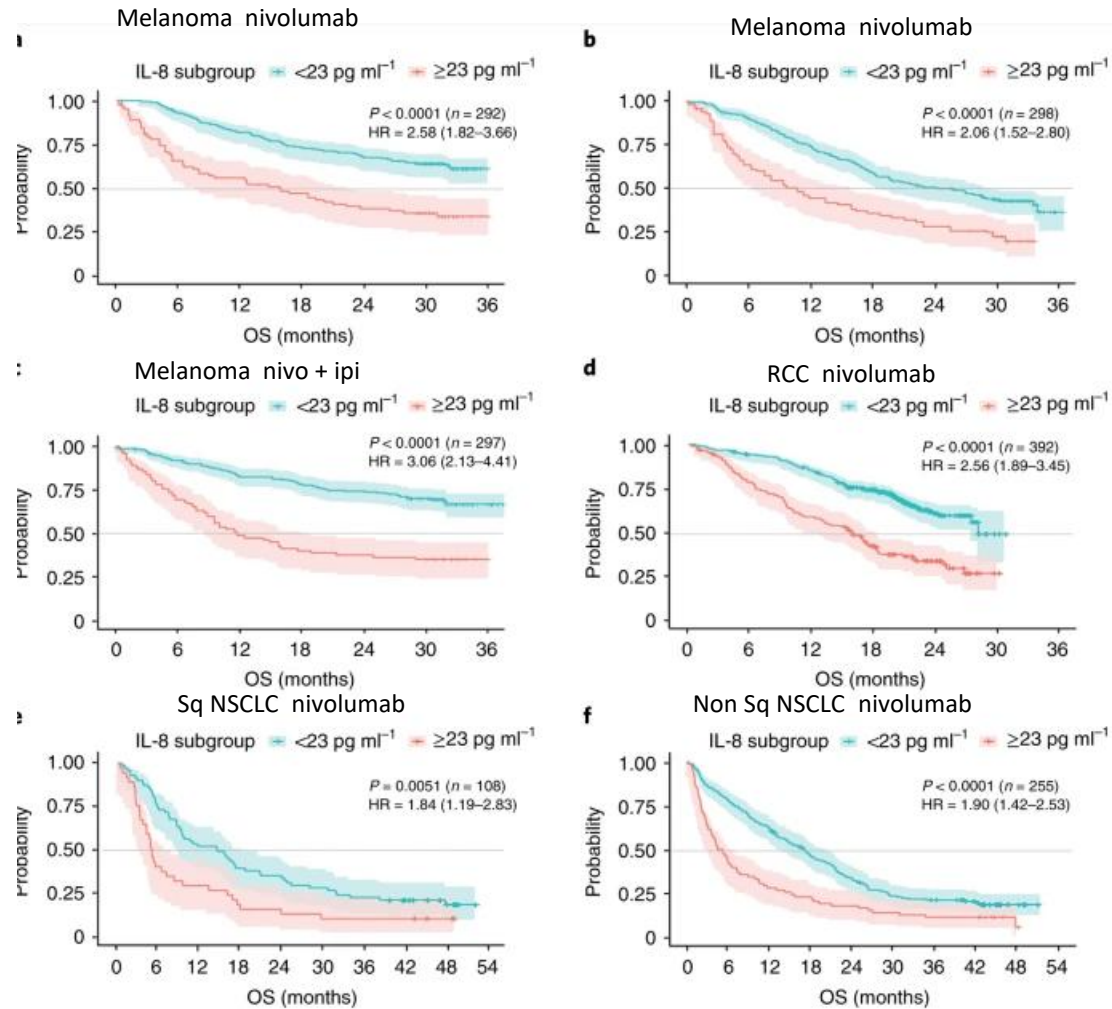
Verité 10 fois per seconde



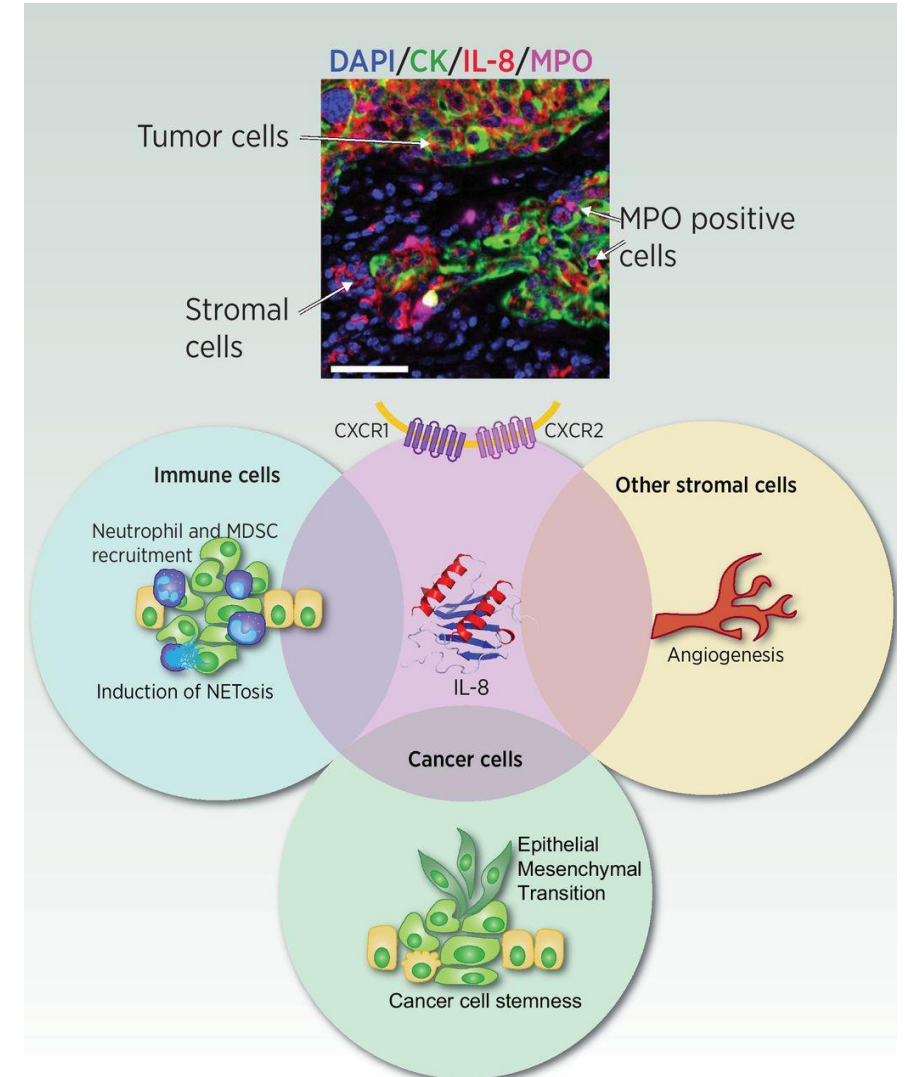
Our setup for live imaging



IL-8 is highly expressed in cancer and identifies patients resistant to ICB

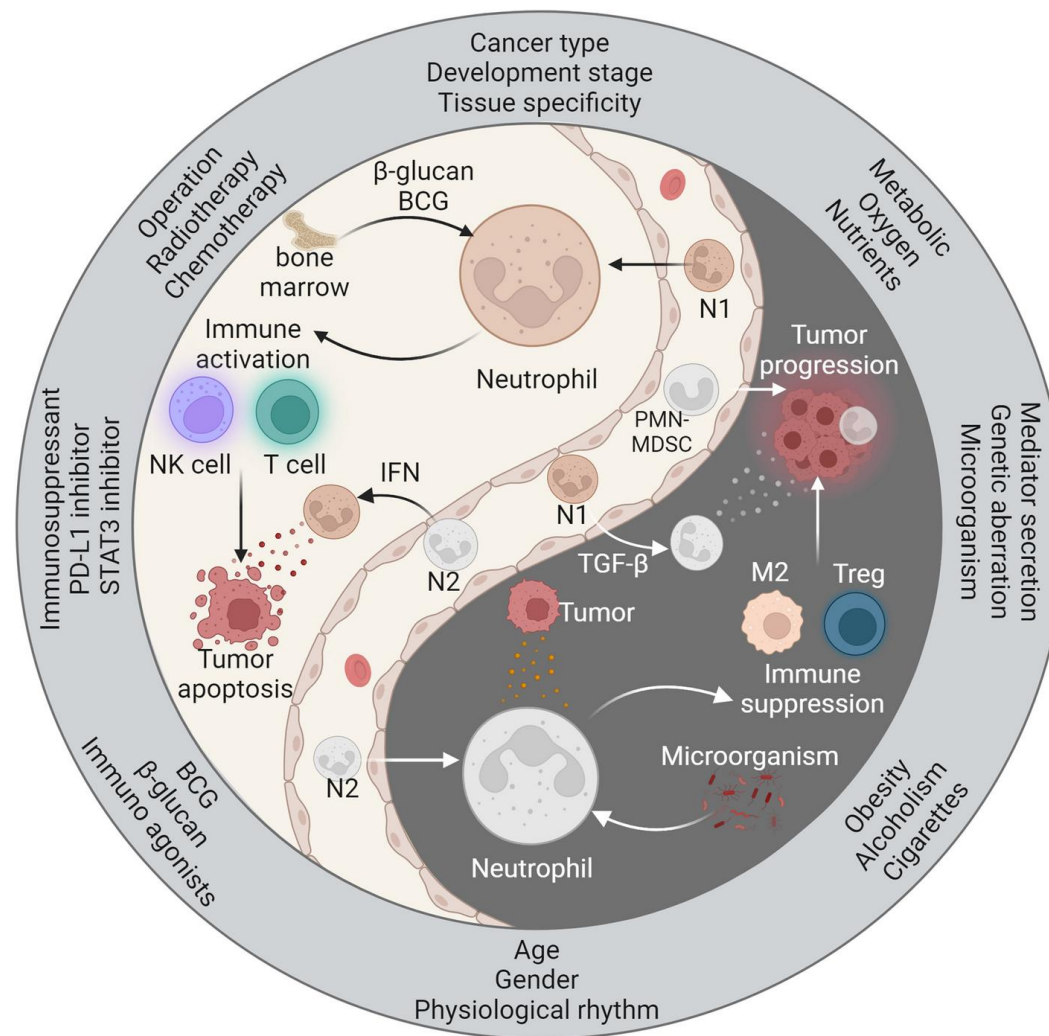


Schalper K et al. Nature Medicine 2020
Mariathasan S et al. Nature Medicine 2020



Alvaro Teixeira et al. Clin Cancer Res 2021

Neutrophils in cancer



Tumors Induce NETosis by Activation of CXCR1 and CXCR2 Chemokine Receptors



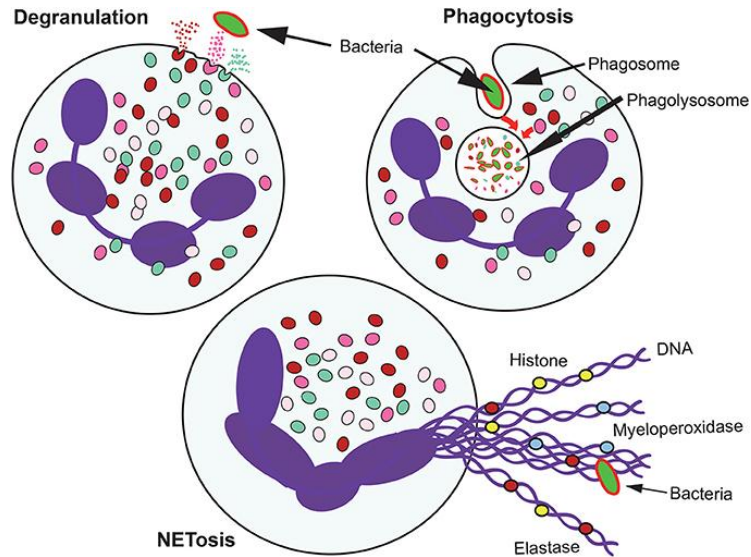
Saray Garasa

HT29 Spheroids in
Co-culture with Human Neutrophils

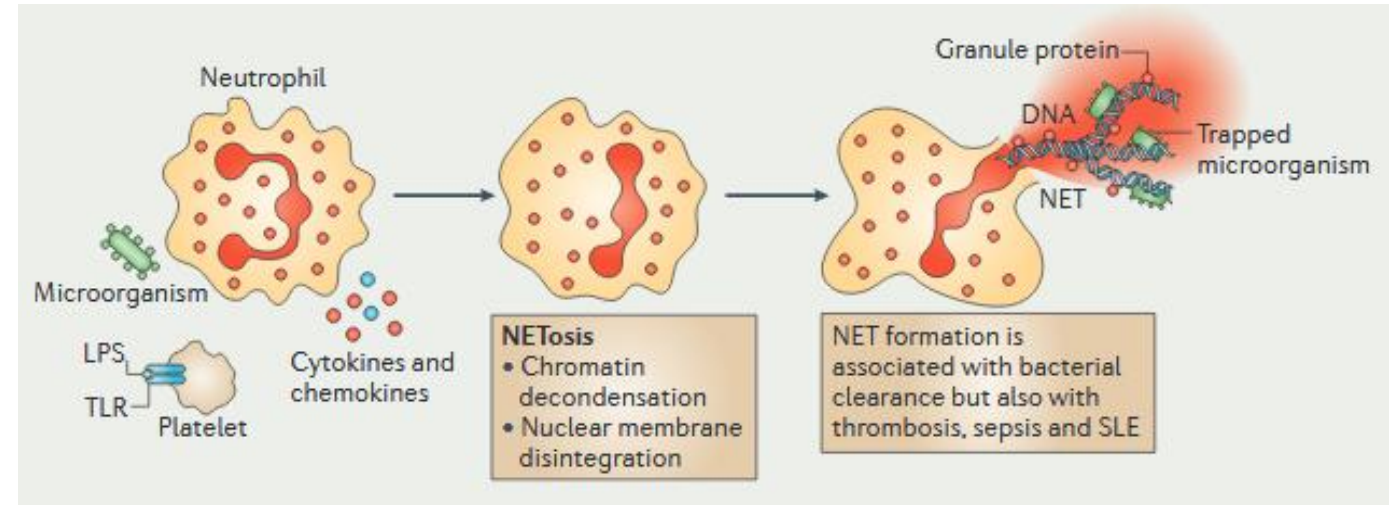
HT29/ CMRA
Neutrophils/ Cell Tracker Deep Red
NETs/ Sytox Green

10 hours video. 450x accelerated

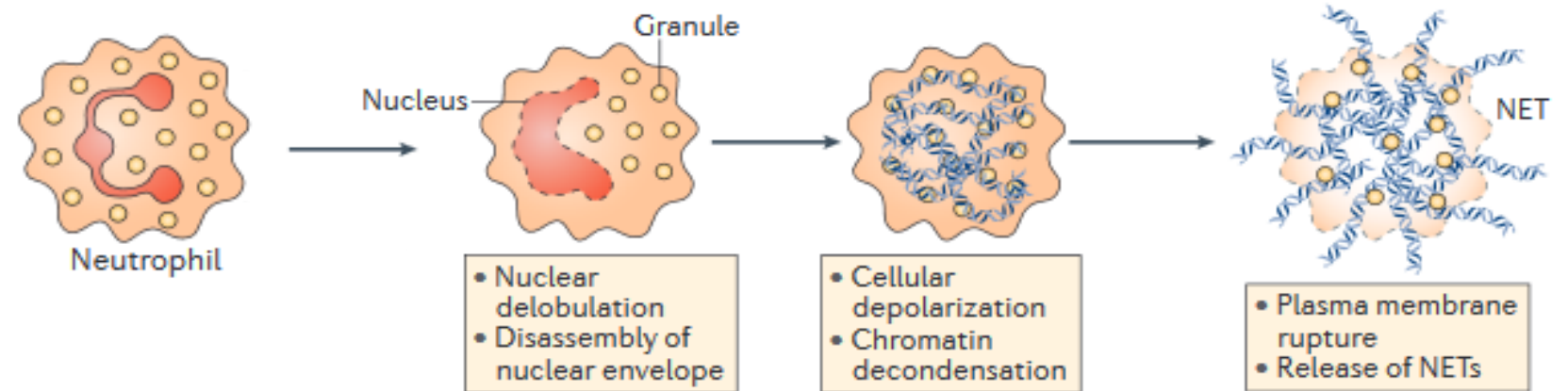
Neutrophil Extracellular Traps



Rosales C. Front Immunol, 2018

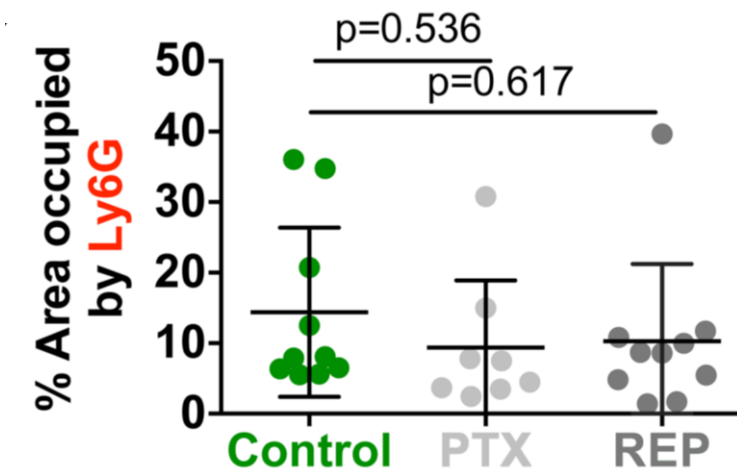
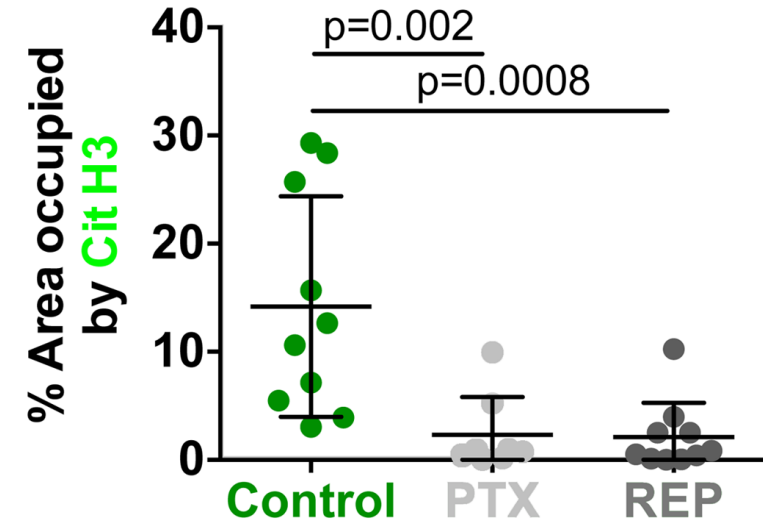
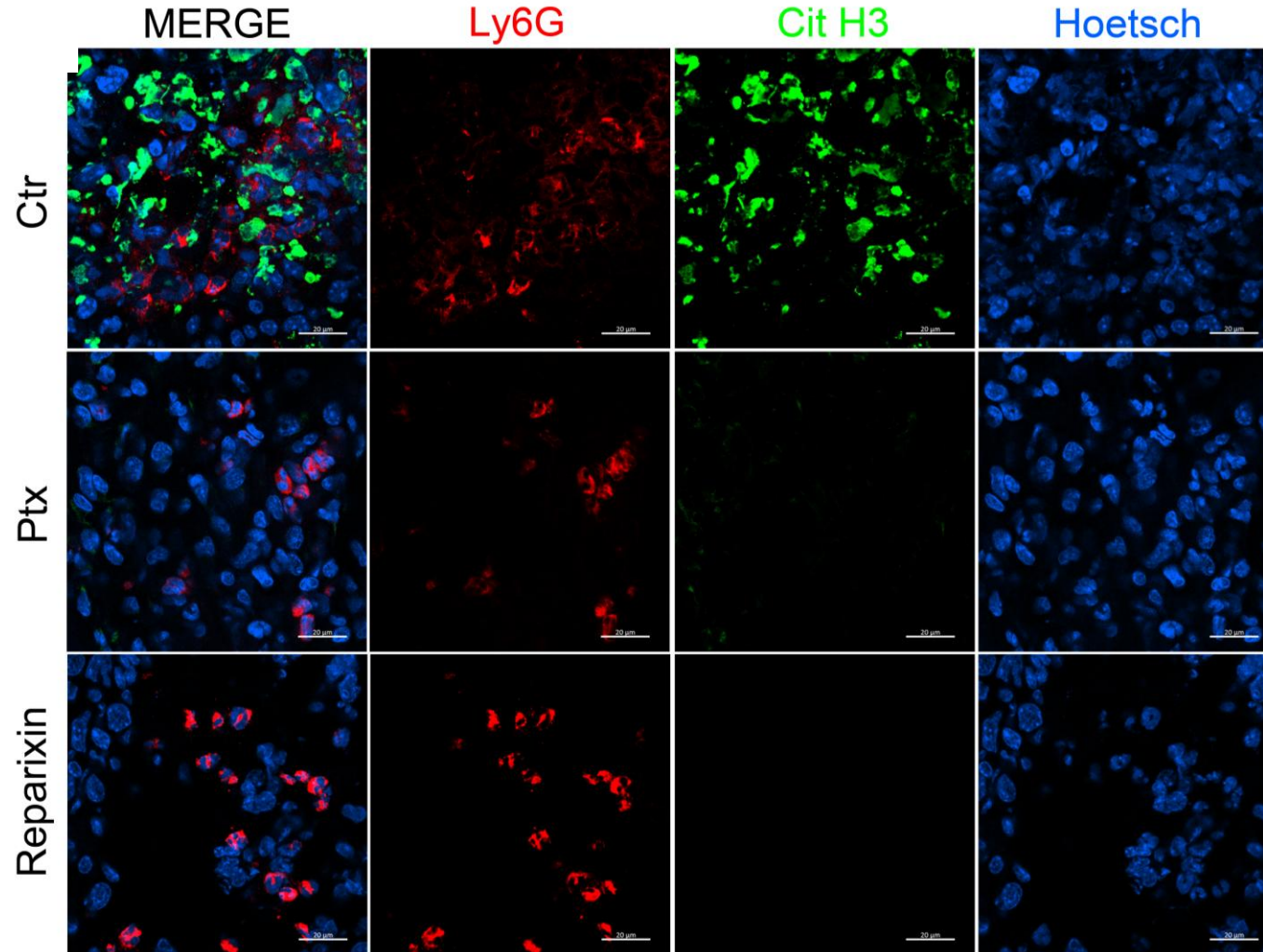


Mantovani et al. 2011

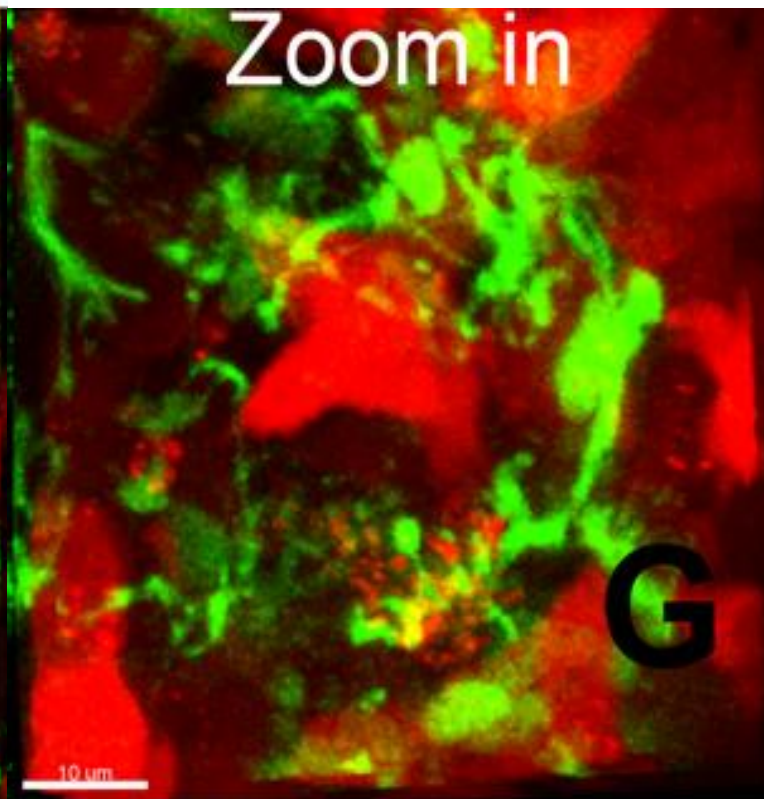
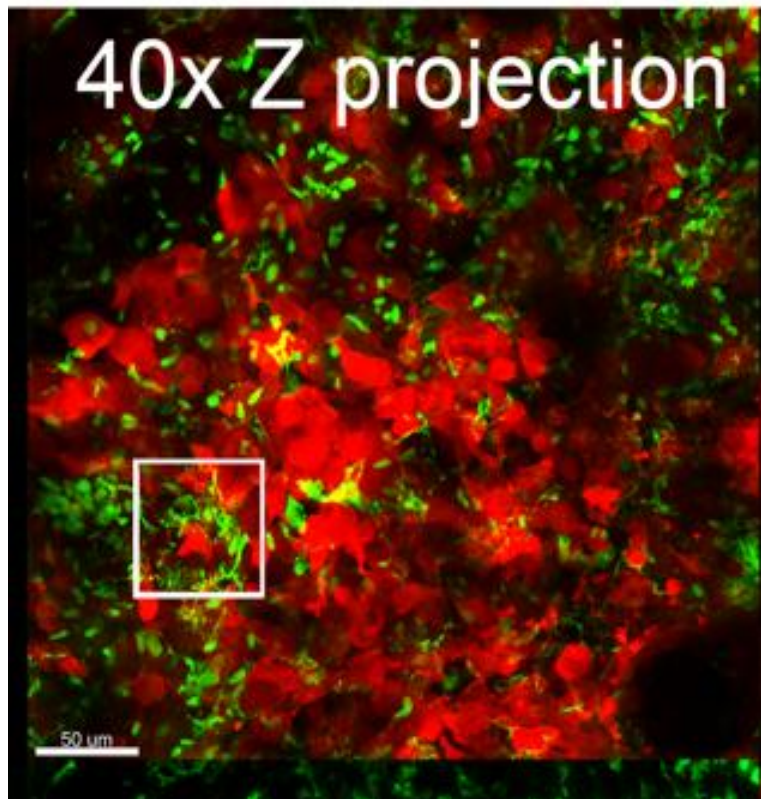


Papayannopoulos 2018

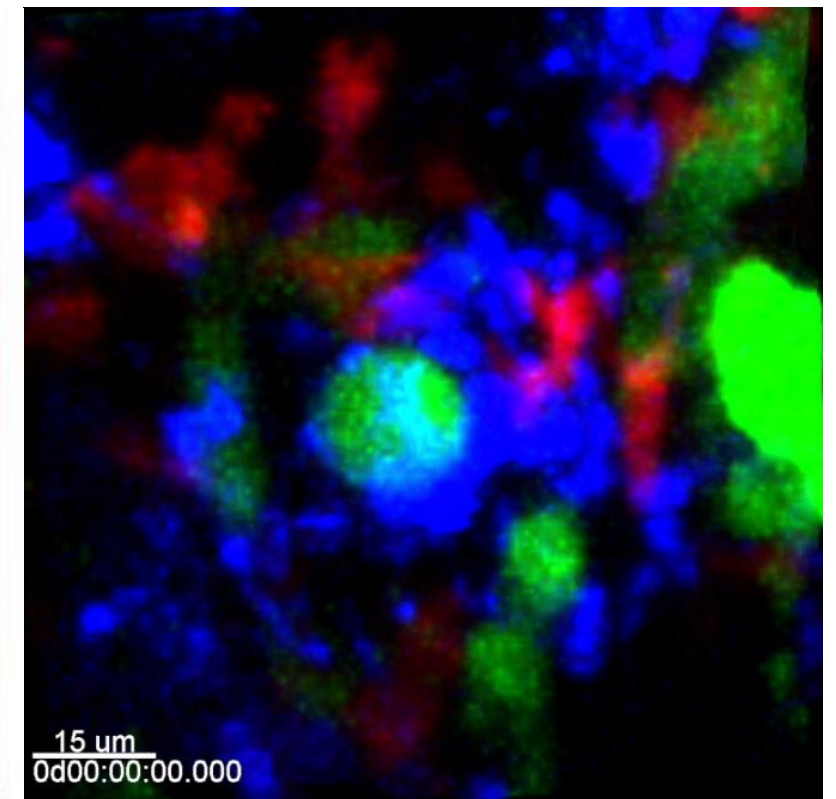
Tumors Induce NETosis by Activation of CXCR1 and CXCR2 Chemokine Receptors



NETs Inhibit Immune Cell Cytotoxicity by Impeding Contact with Tumor Cells

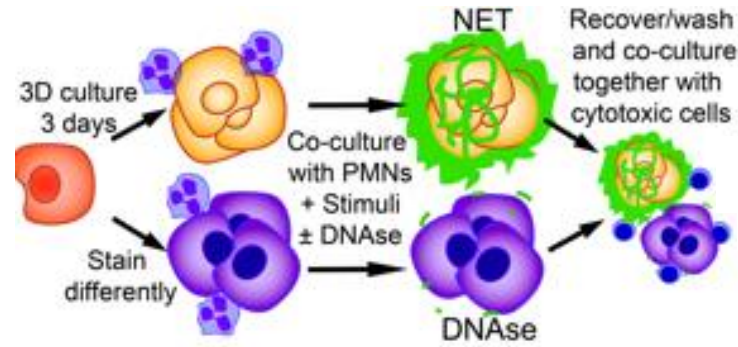


Sytox Green (extracellular DNA)/ Tumor cells



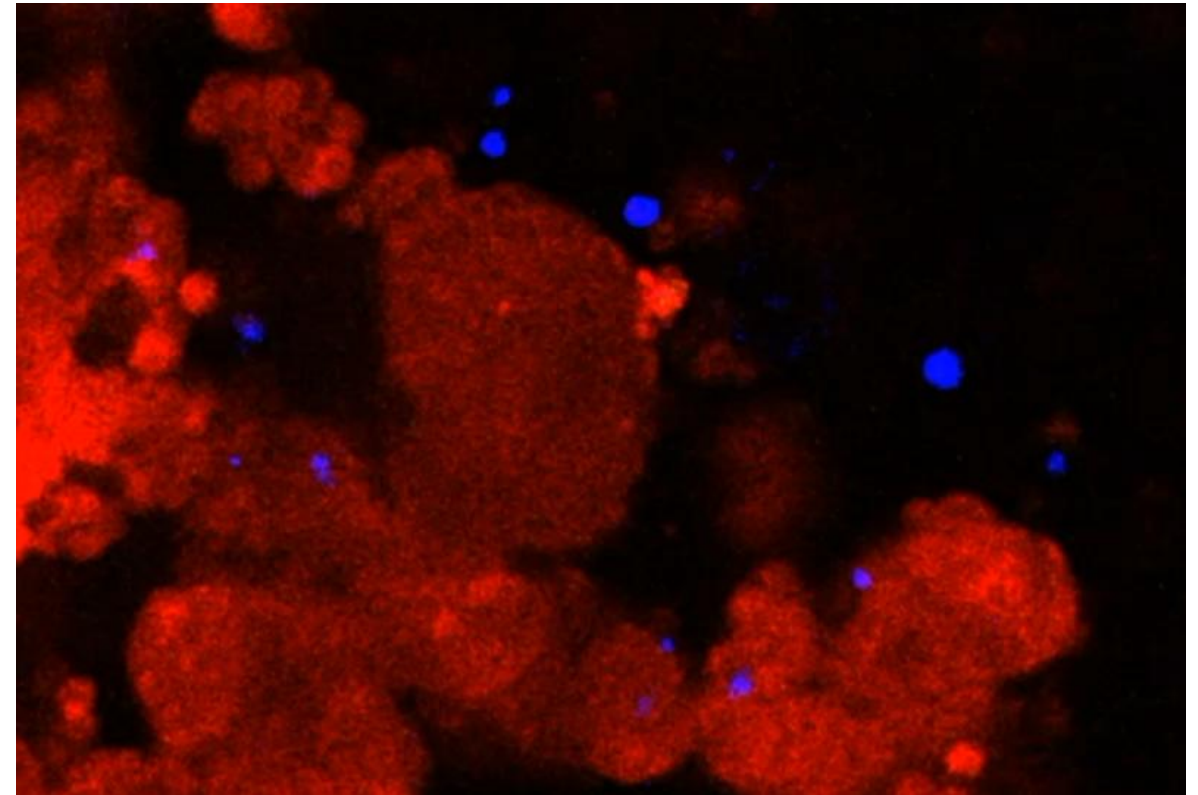
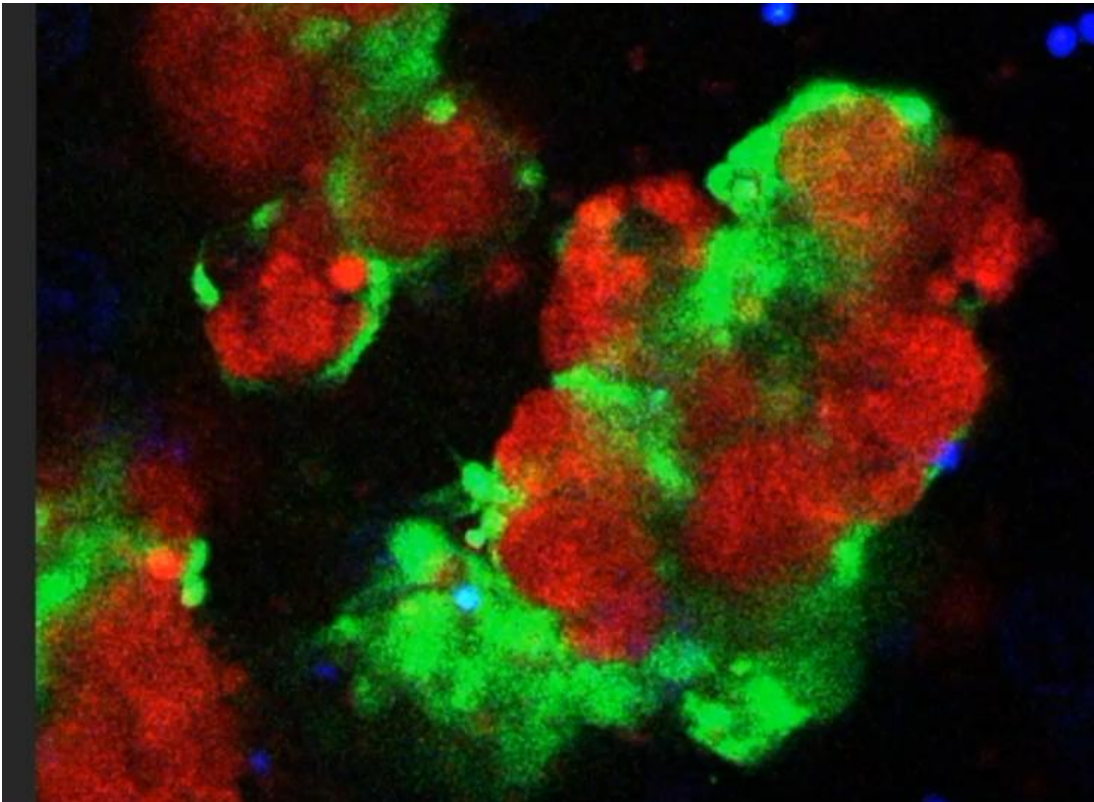
Neutrophil Elastase/ Tumor cells

NETs Inhibit Immune Cell Cytotoxicity by Impeding Contact with Tumor Cells



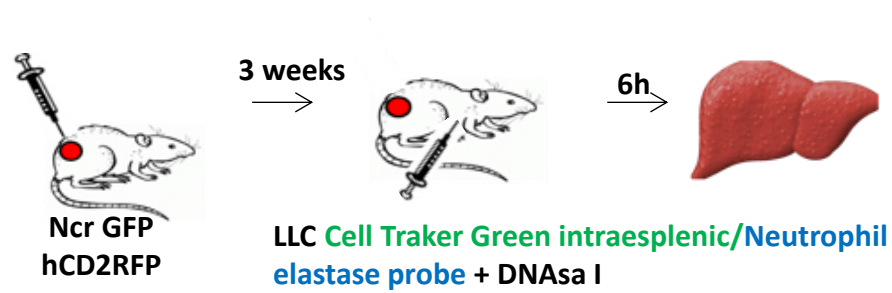
NET coculture

+DNase I



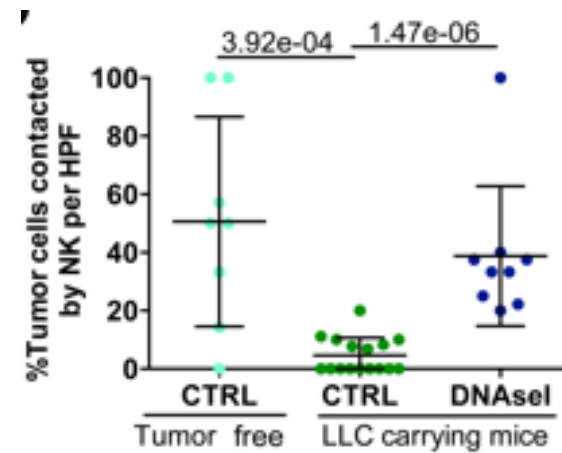
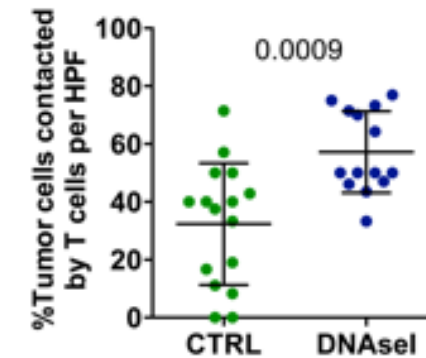
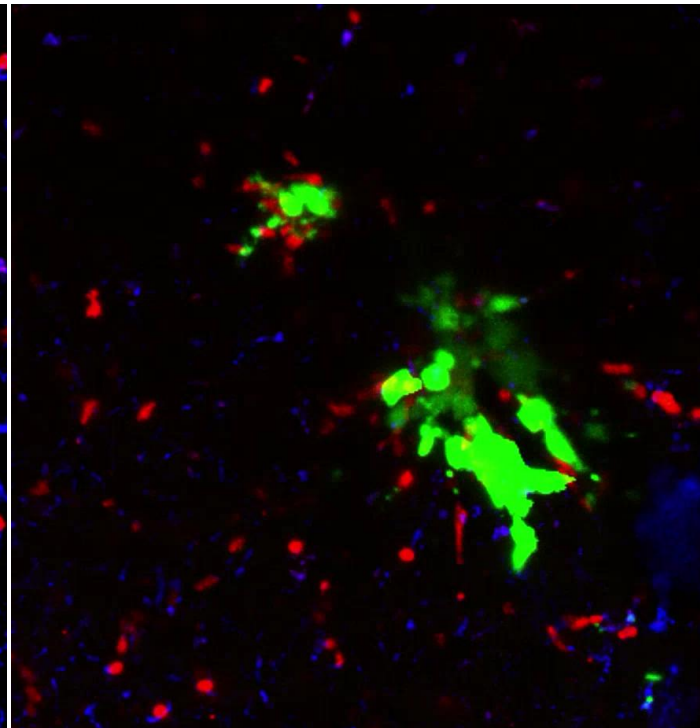
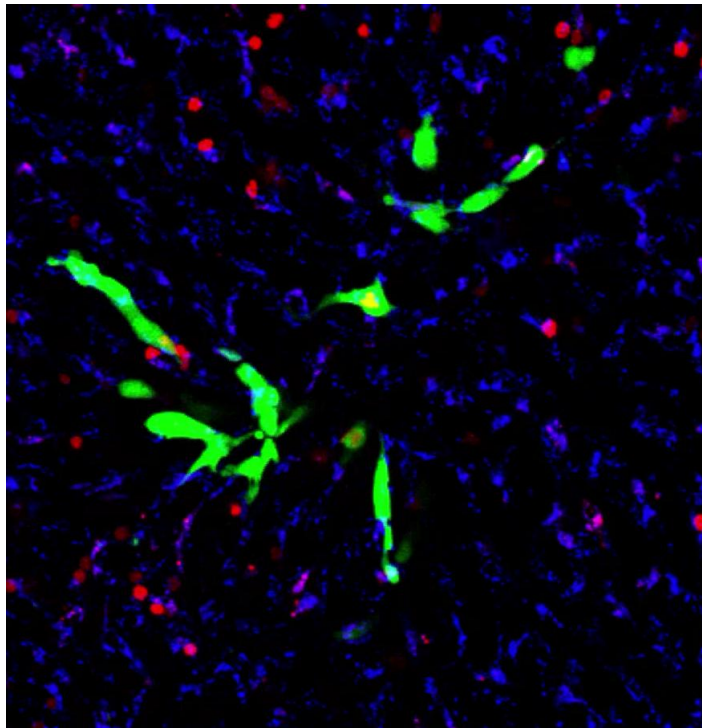
Sytox Green (extracellular DNA) / Tumor cells / T cells

NETs Inhibit Immune Cell Cytotoxicity by Impeding Contact with Tumor Cells



CTRL

DNase I

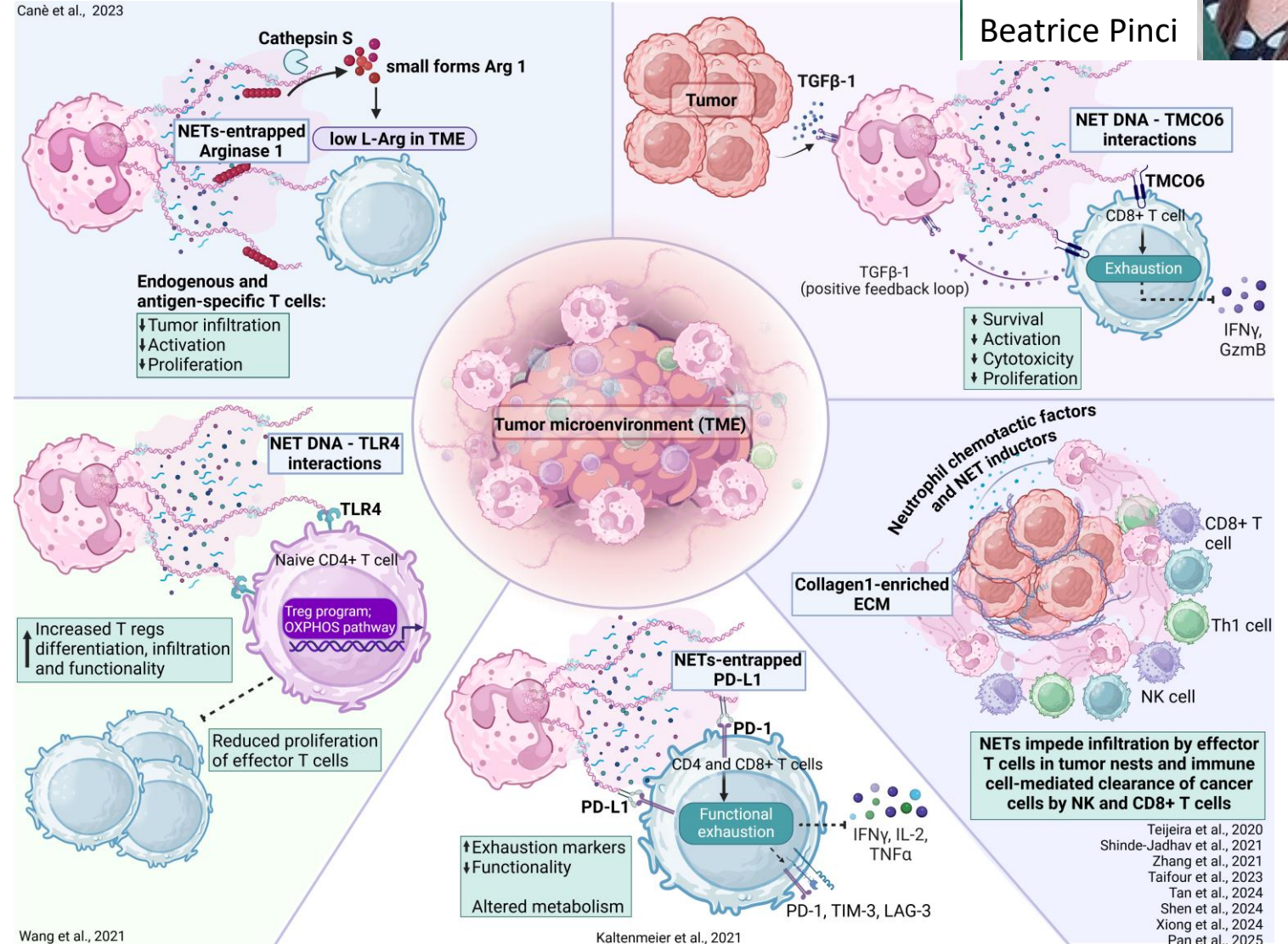
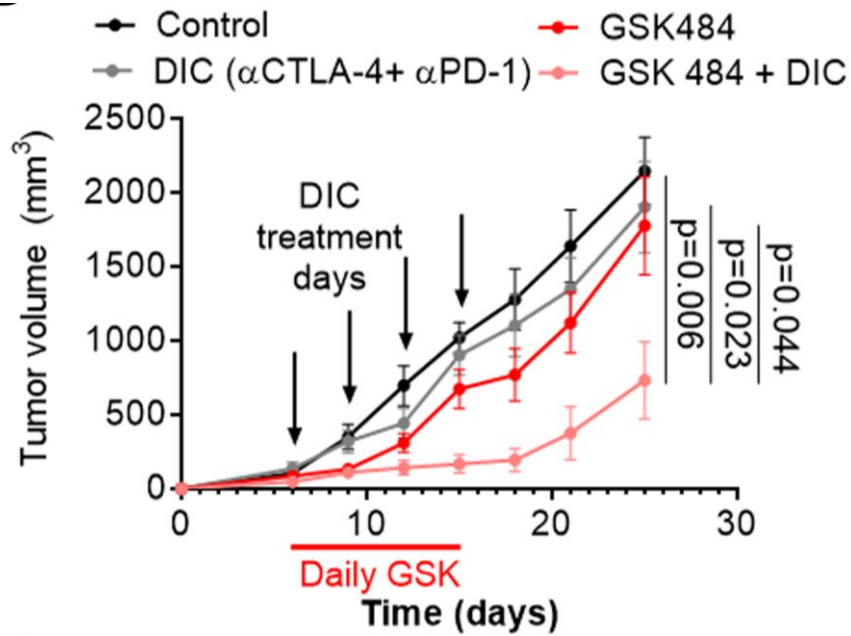


T cells/NETs/ Tumor cells

NETs are a new immunosuppressive mechanism in cancer



Beatrice Pinci

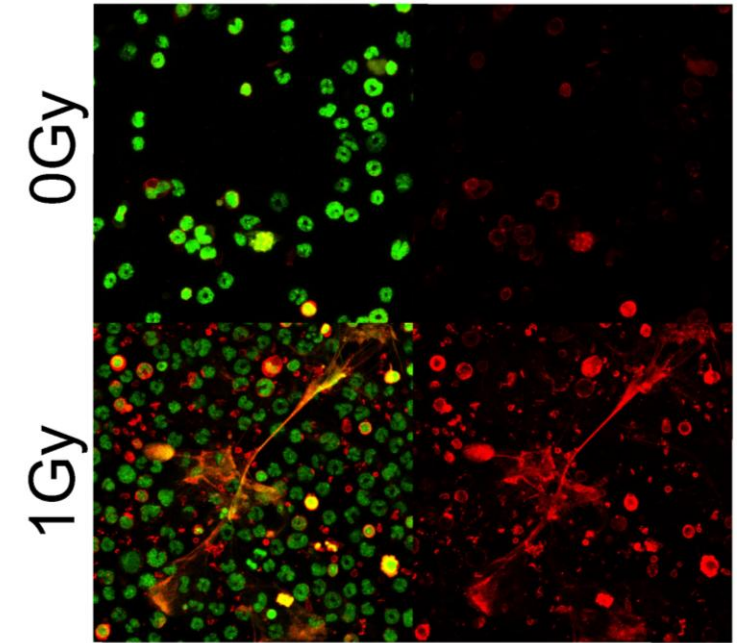
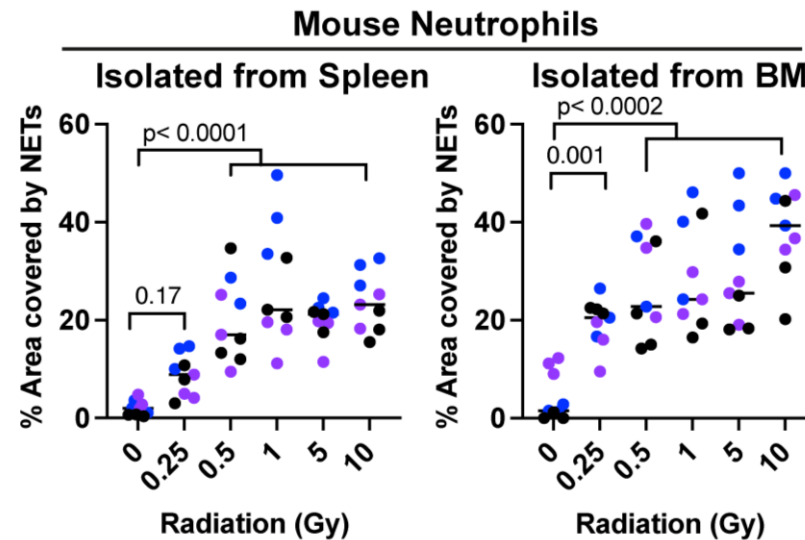
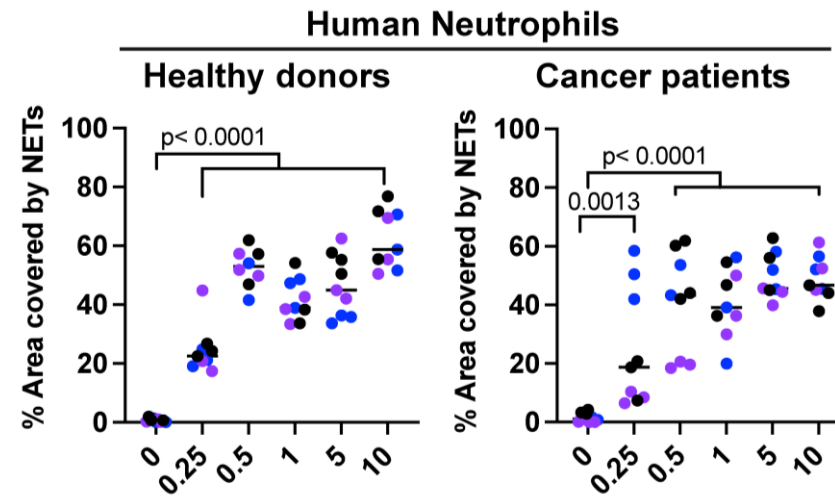
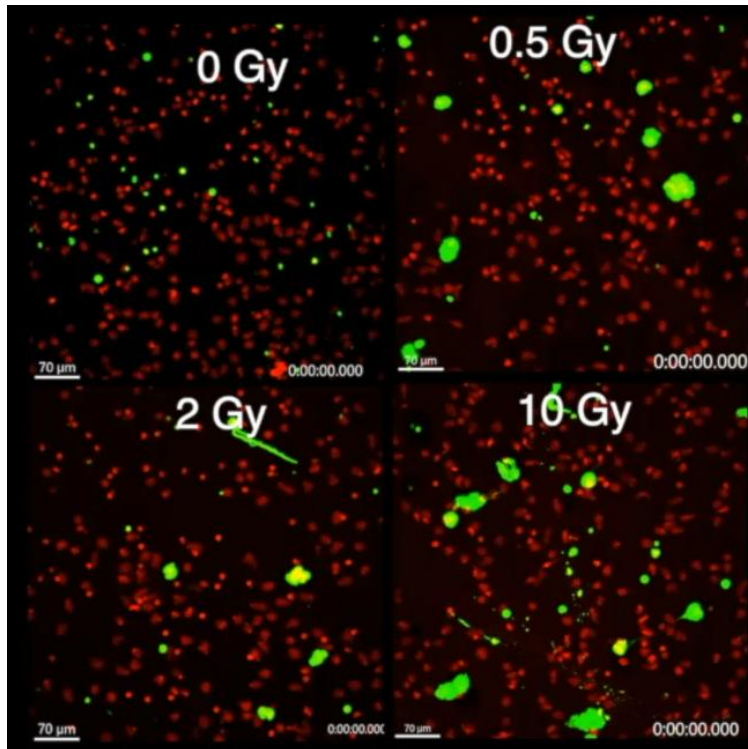


NETs are induced by Radiation

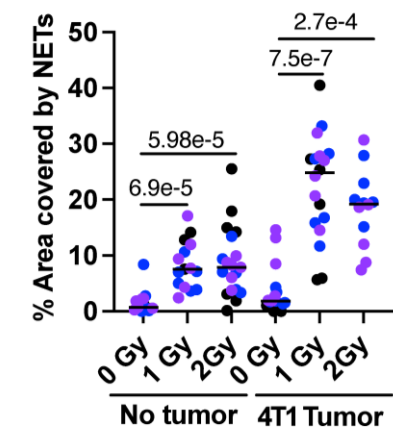


Ex vivo Radiation

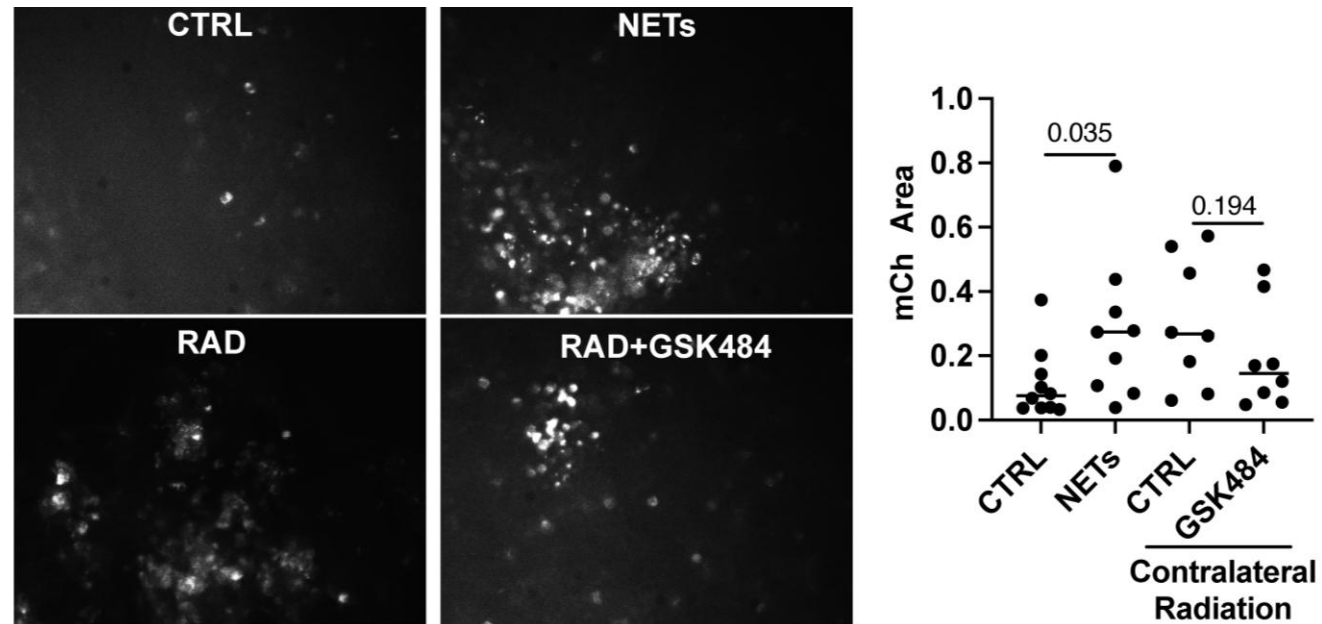
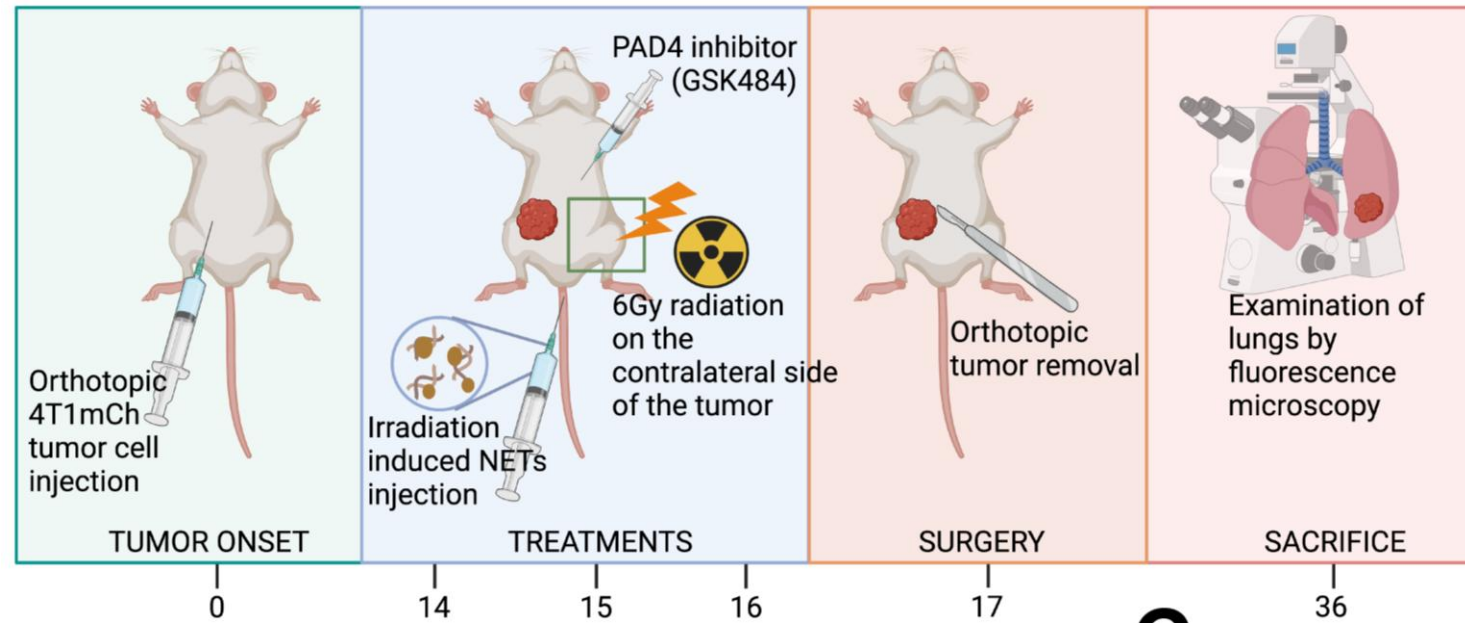
In vivo Radiation



DNA/CitH3



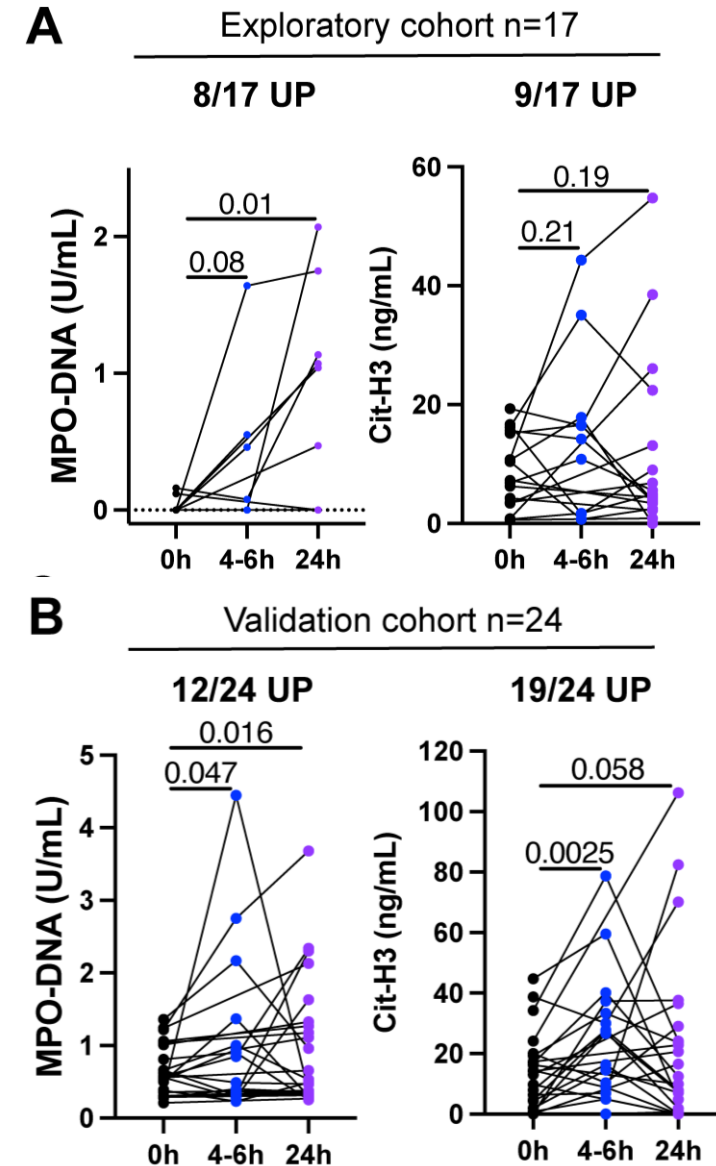
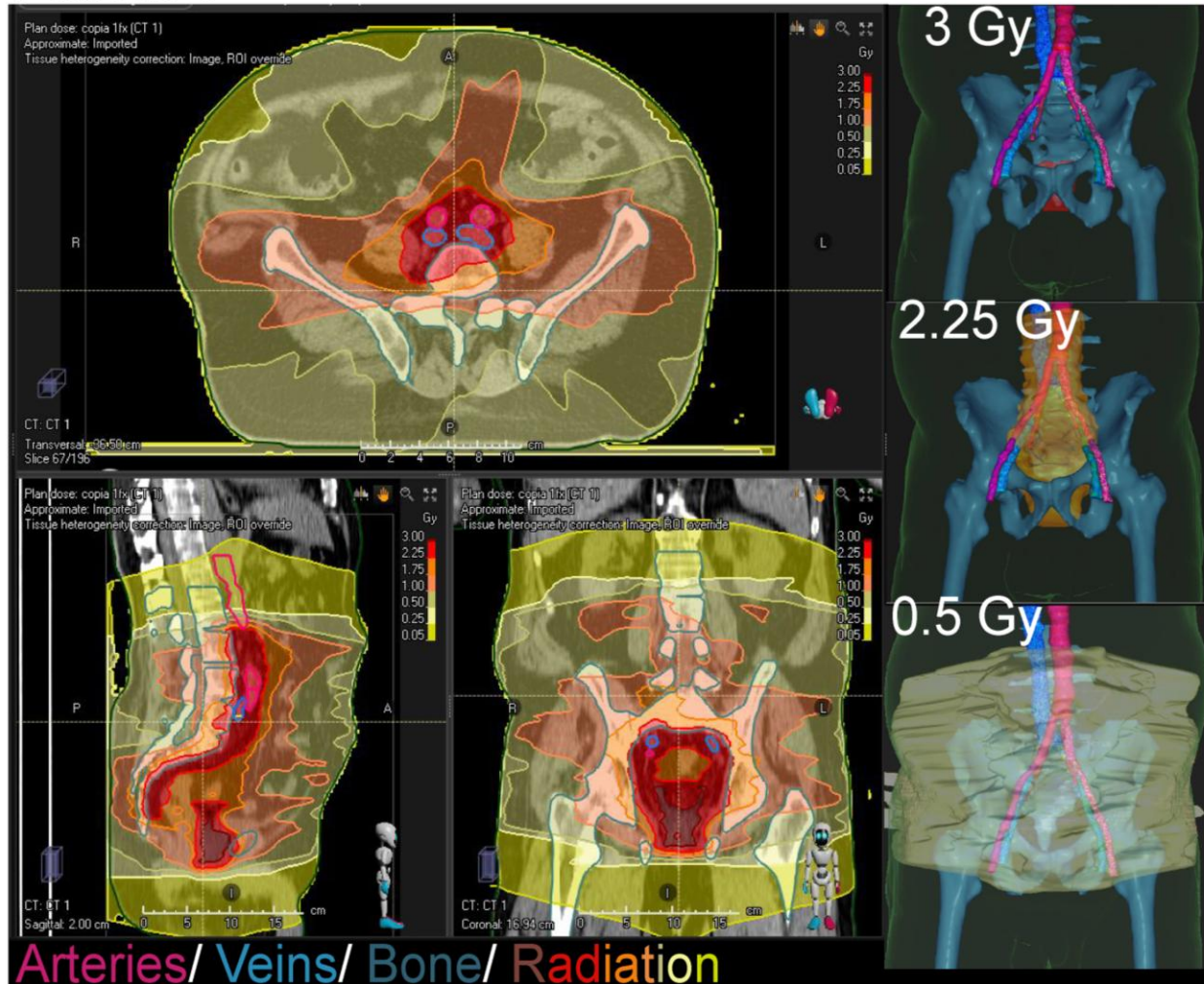
Radiotherapy-induced NETs and mouse irradiation promotes metastases



Radiotherapy increases circulating NETs in cancer patients



Patient 1



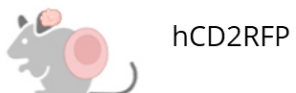
Intravital microscopy of subcutaneous tumours



Almudena Manzanal

Immune reporter/double reporter mice

T cells



hCD2RFP

Neutrophils



Ly6G
dTomato

LysMGFP

Dendritic cells



CD11cGFP

NK cells



NCREGFP

**T cells +
Neutrophils**



CD2RFP x LysMGFP

**T cells +
Dendritic cells**



CD2RFP x CD11cGFP

Fluorescently labelled tumor cell lines

LLC: Lewis lung carcinoma

- LLC GFP
- LLC mCherry

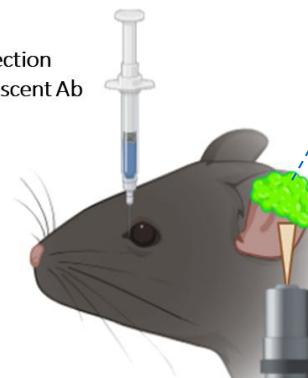
E0771: triple-negative breast cancer

B16F10: melanoma (orthotopic):

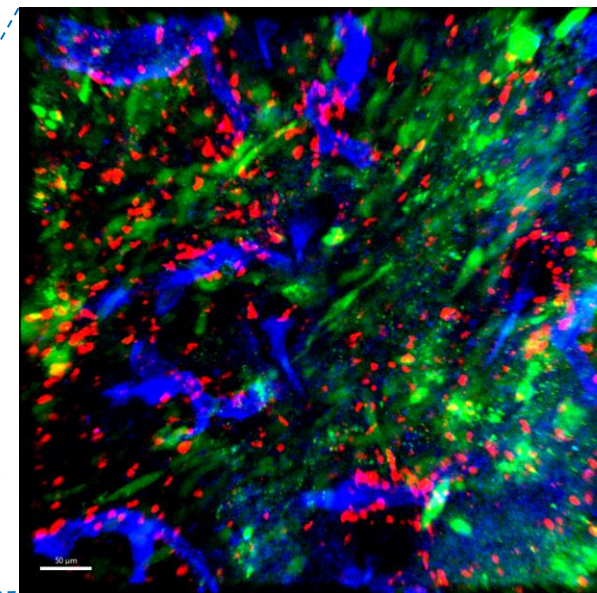
- B16 GFP



IV injection
fluorescent Ab



Exposed
(fluorescent)
tumor in the
ear dermis

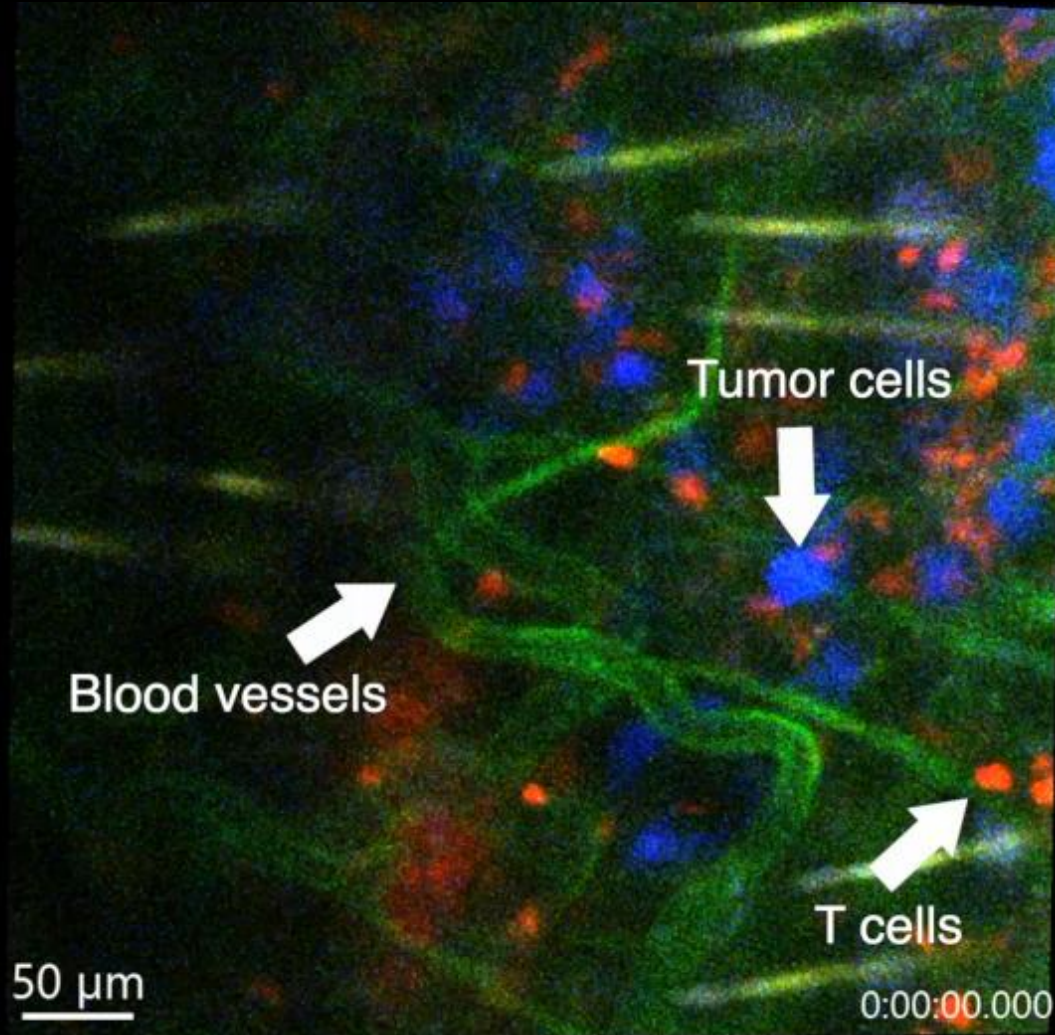


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T cells only interact with extravascular blood vessels

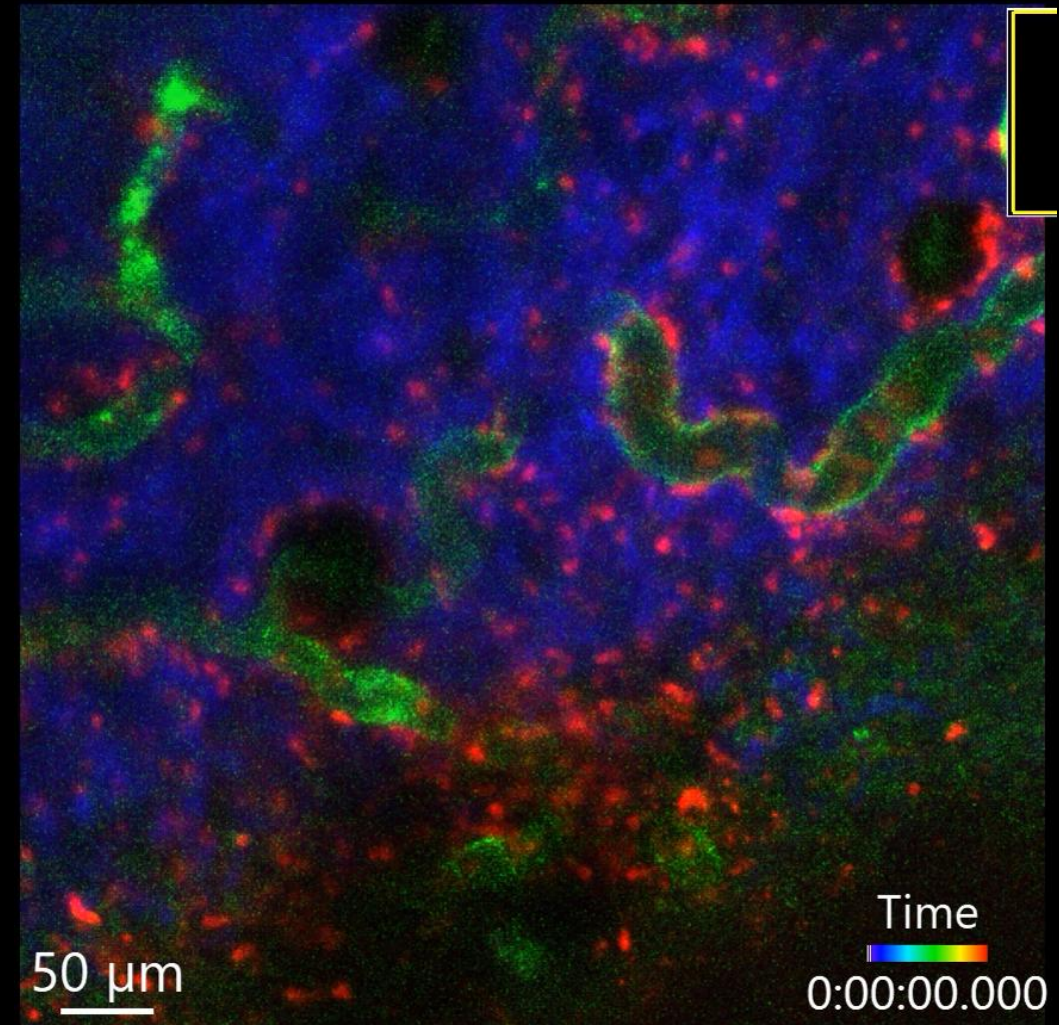


Peritumoral



Vessels/Tumor cells/T cells

Intratumoral

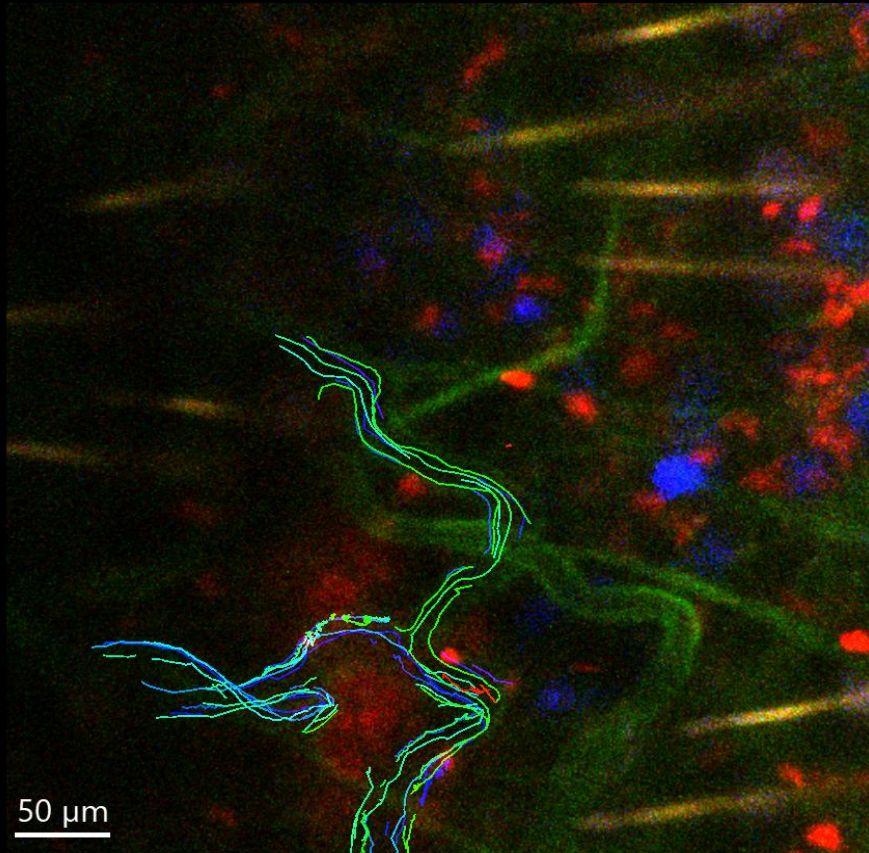


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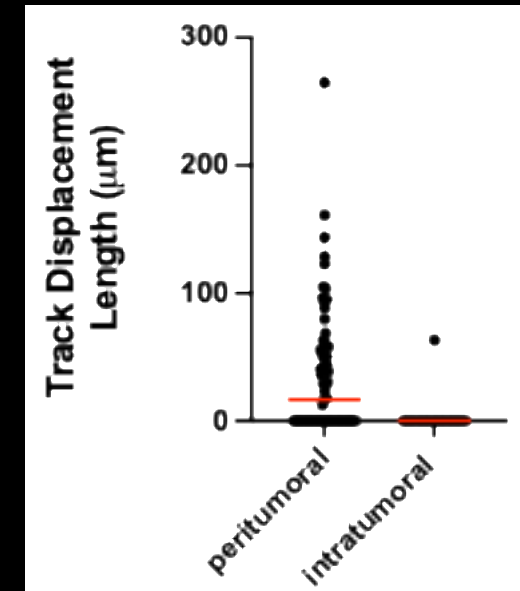
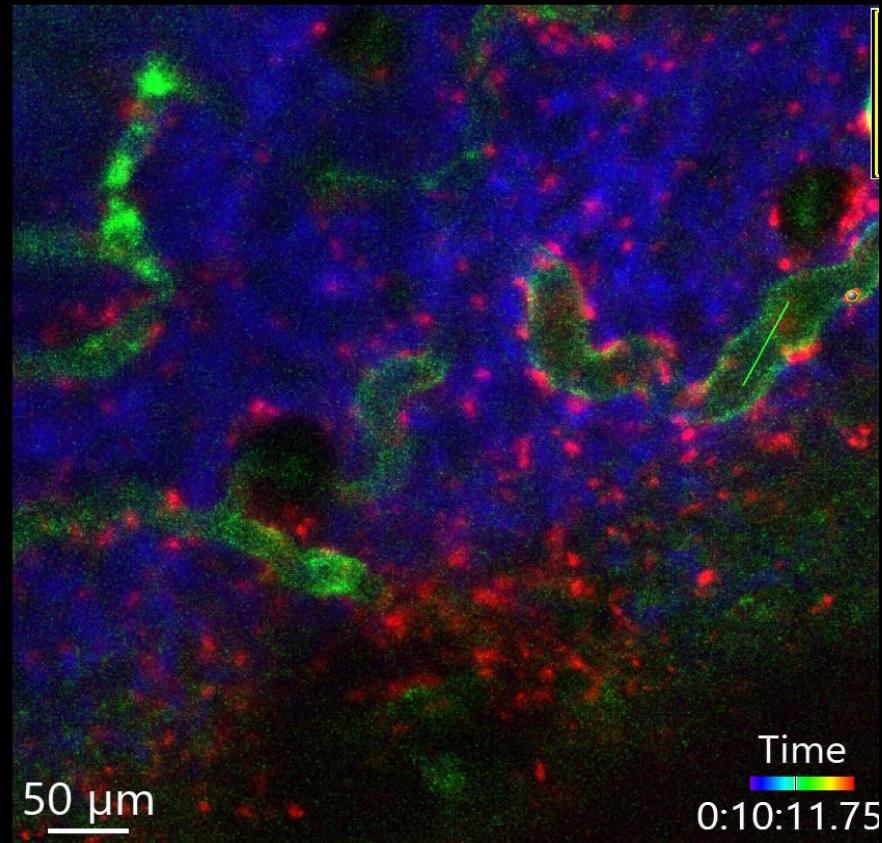
T cells only interact with extravascular blood vessels



Peritumoral



Intratumoral

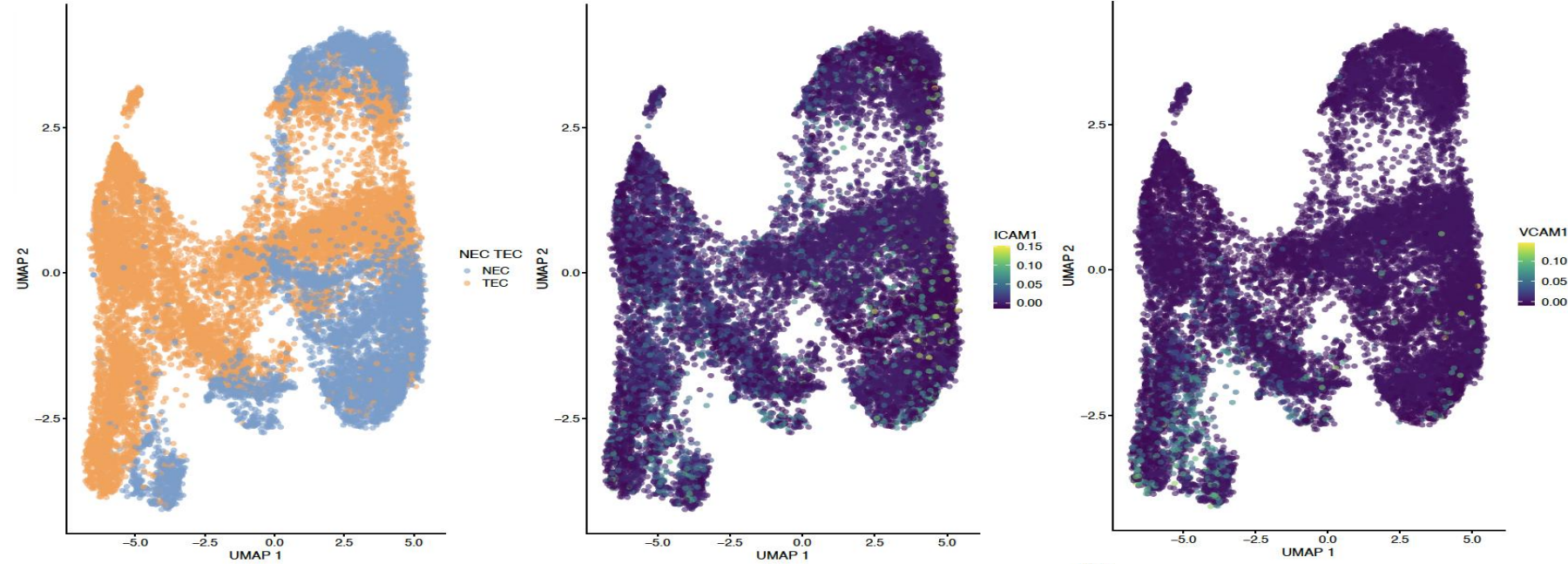


Tumor blood vessels tend to express less recruitment molecules

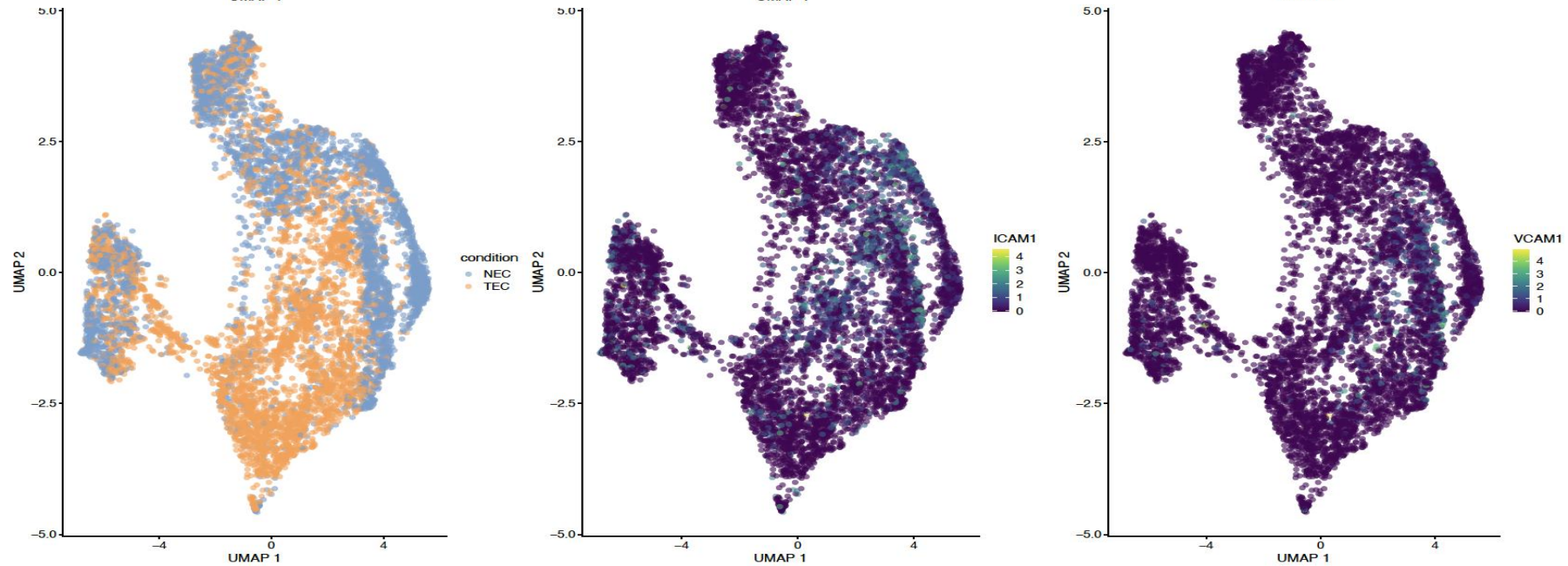


David Ruiz

NSCLC



Breast Cancer

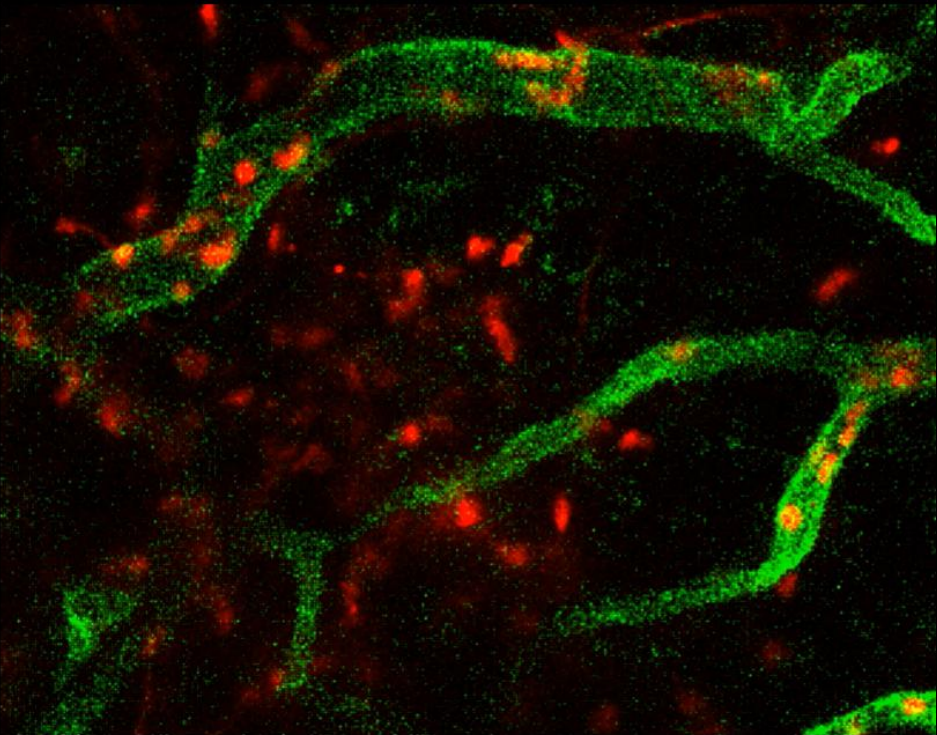


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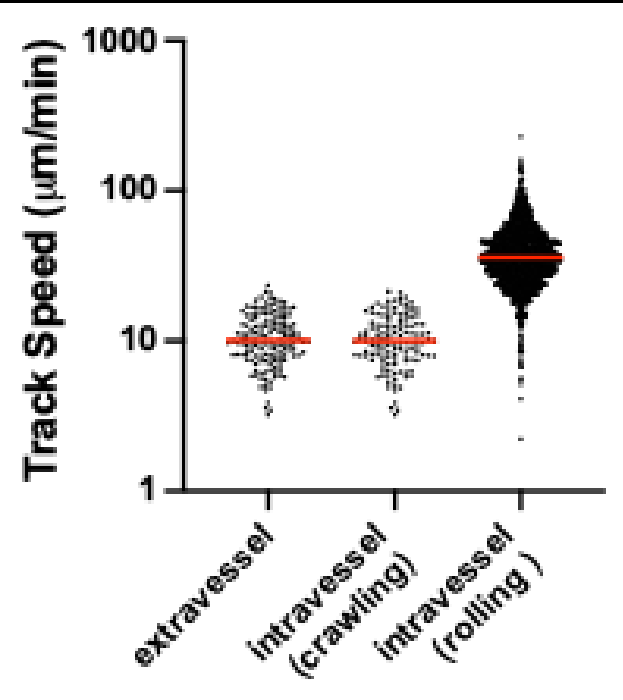
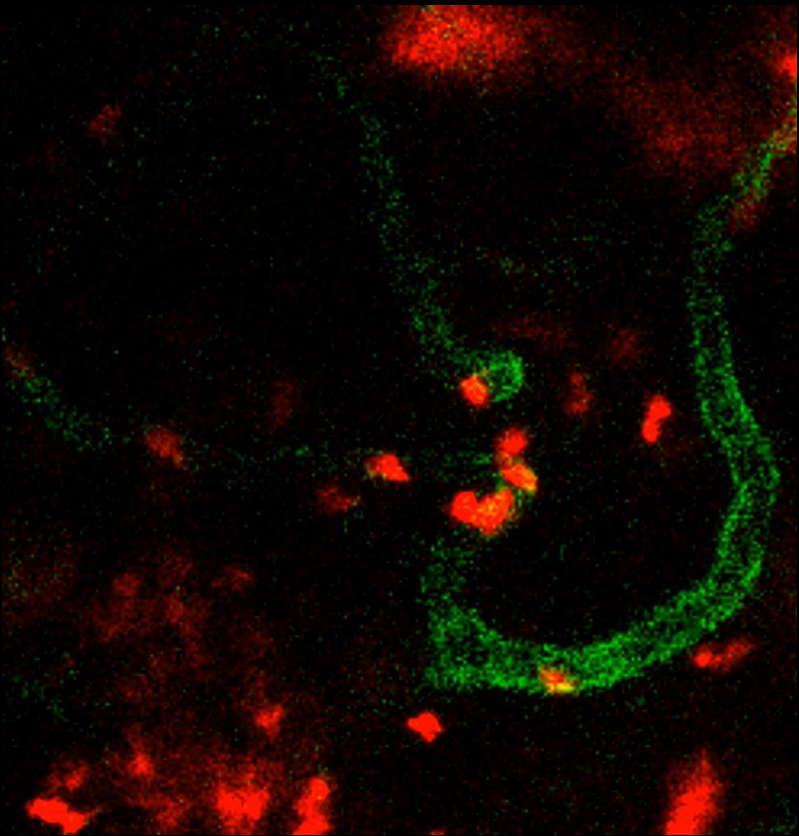
Neutrophils interact also with intratumor blood vessels



Peritumoral



Intratumoral

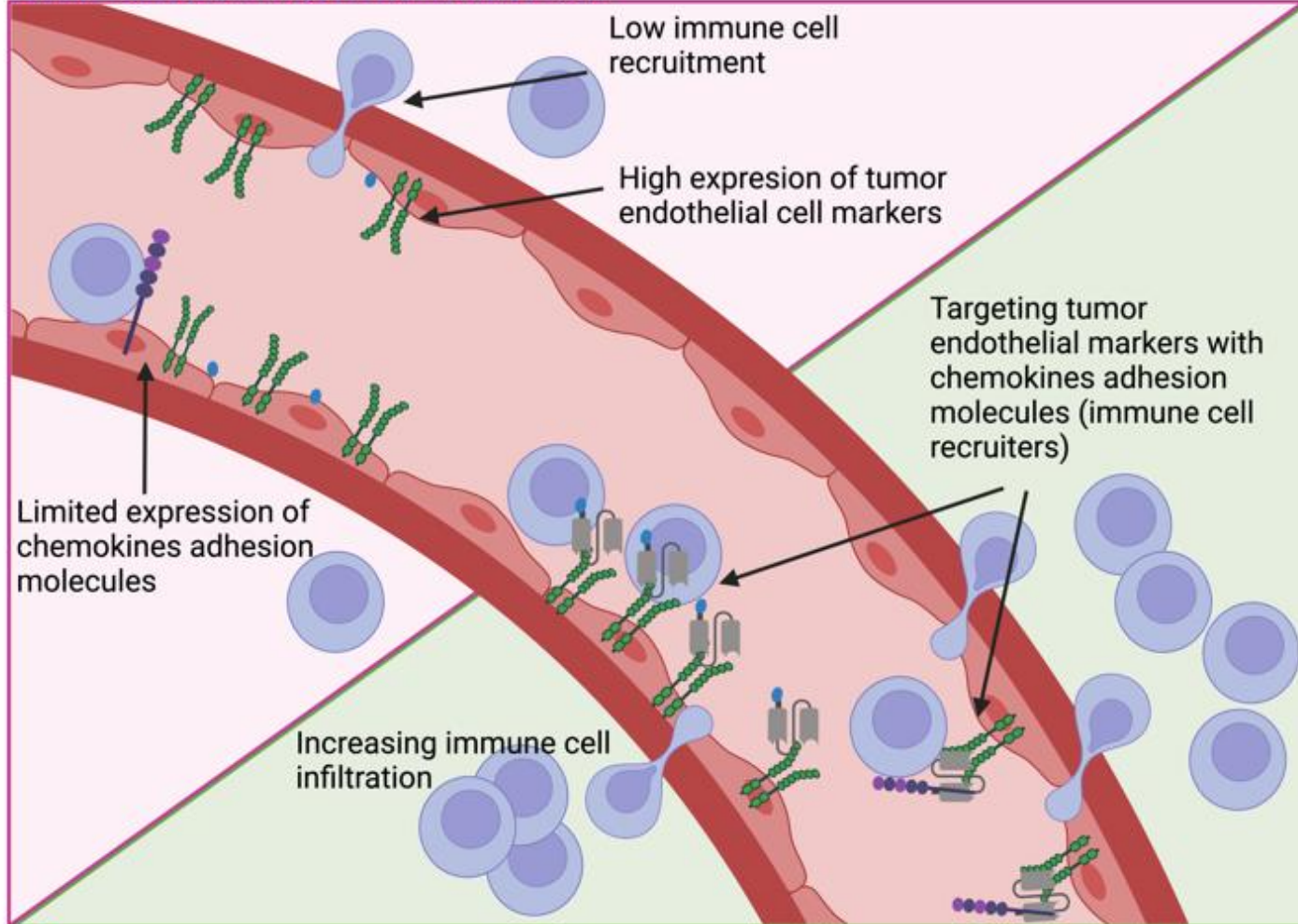


Vessels/Neutrophils

Therapeutic Solution: Immune Cell Recruiters



ANTI-TUMOR IMMUNITY LIMITATION



Hypothesis: Immune-cell recruiters (ICR) could allow better immune infiltration of tumors and sensitize such tumors to immune checkpoint blockade.

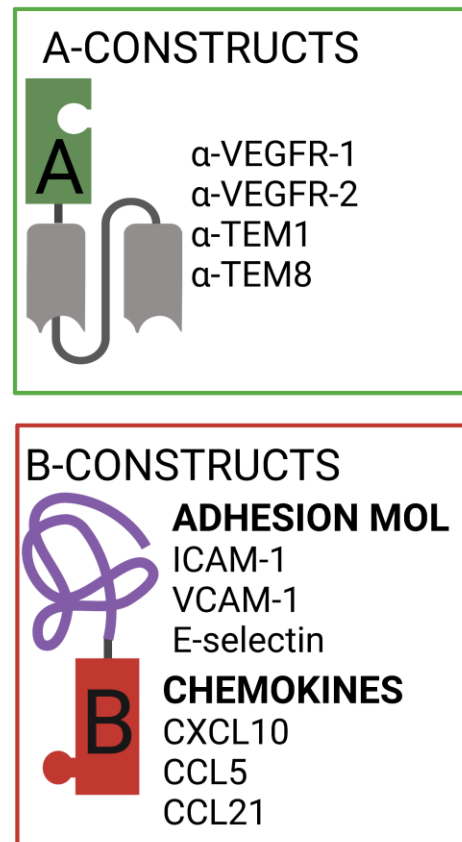
THERAPEUTIC INTERVENTION WITH IMMUNE CELL RECRUITERS

Therapeutic Solution: Immune Cell Recruiters



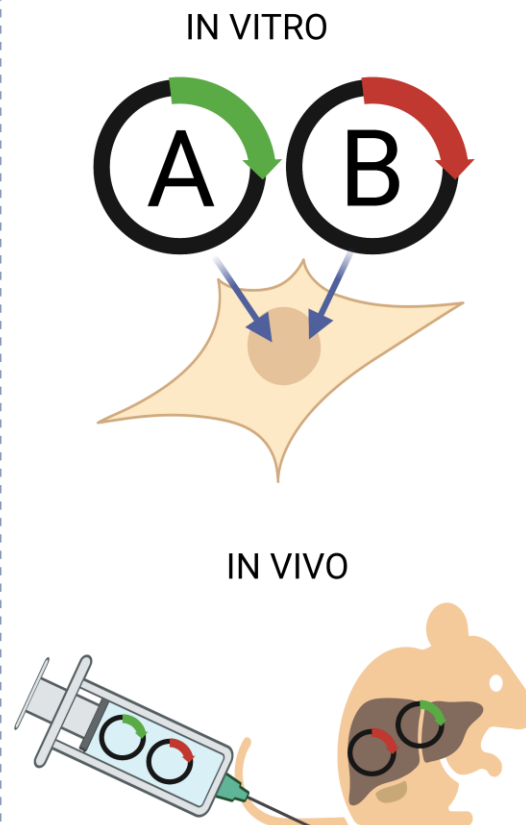
1

Construct Design



2

Transfection



3

Production of A, B constructs



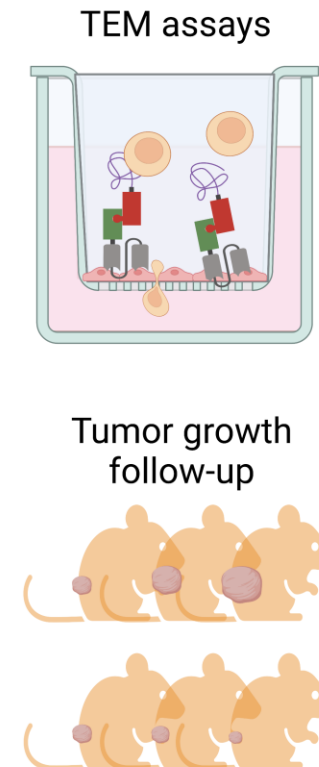
4

Pairing



5

Screening

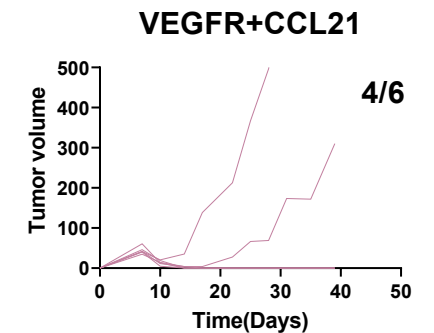
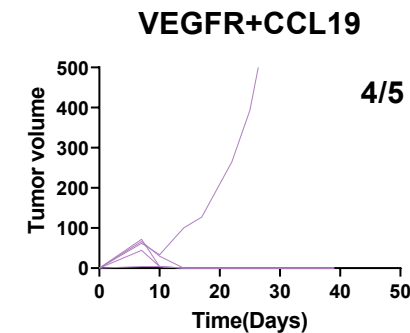
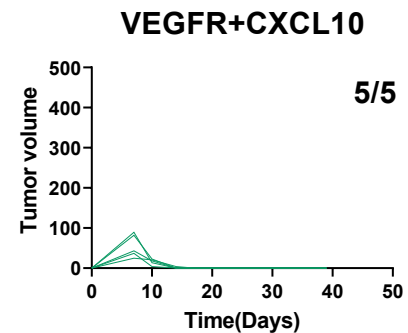
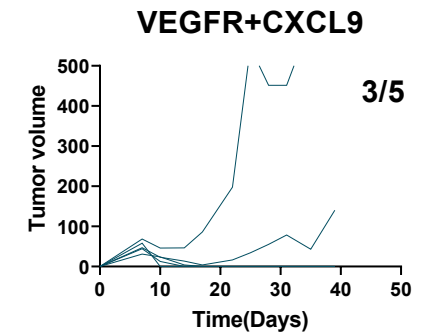
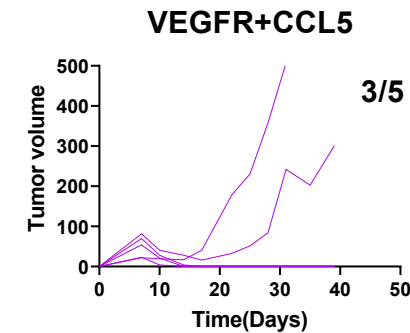
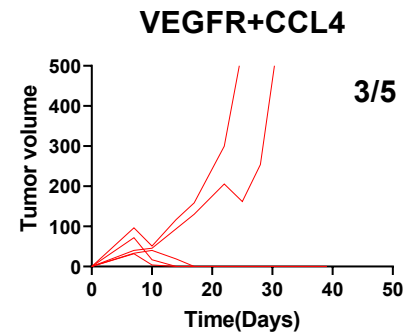
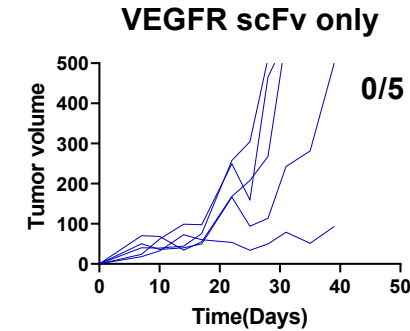
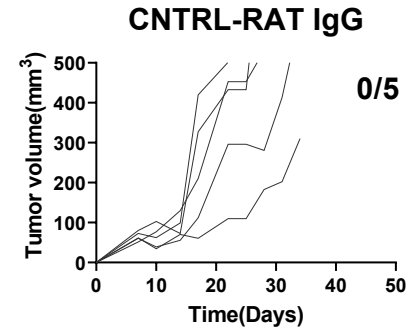
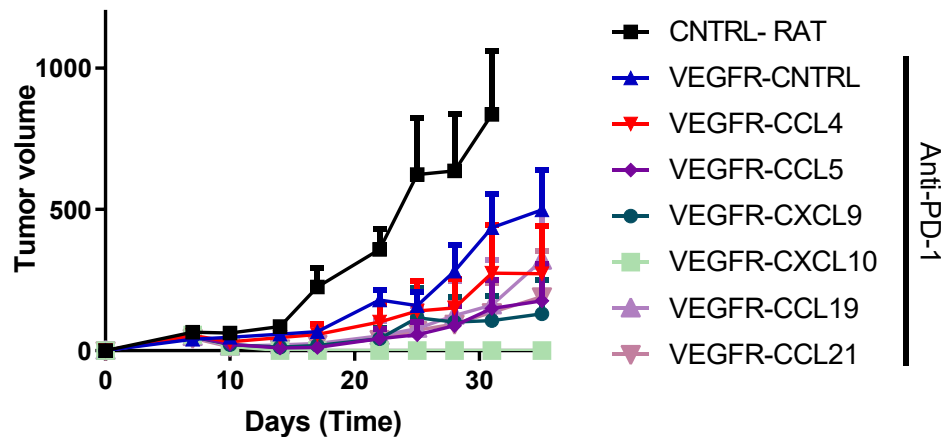
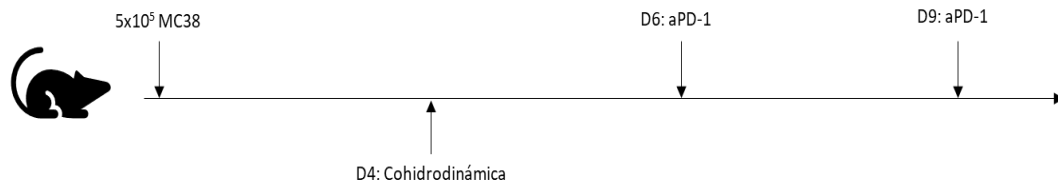


In collaboration with Pedro Berraondo

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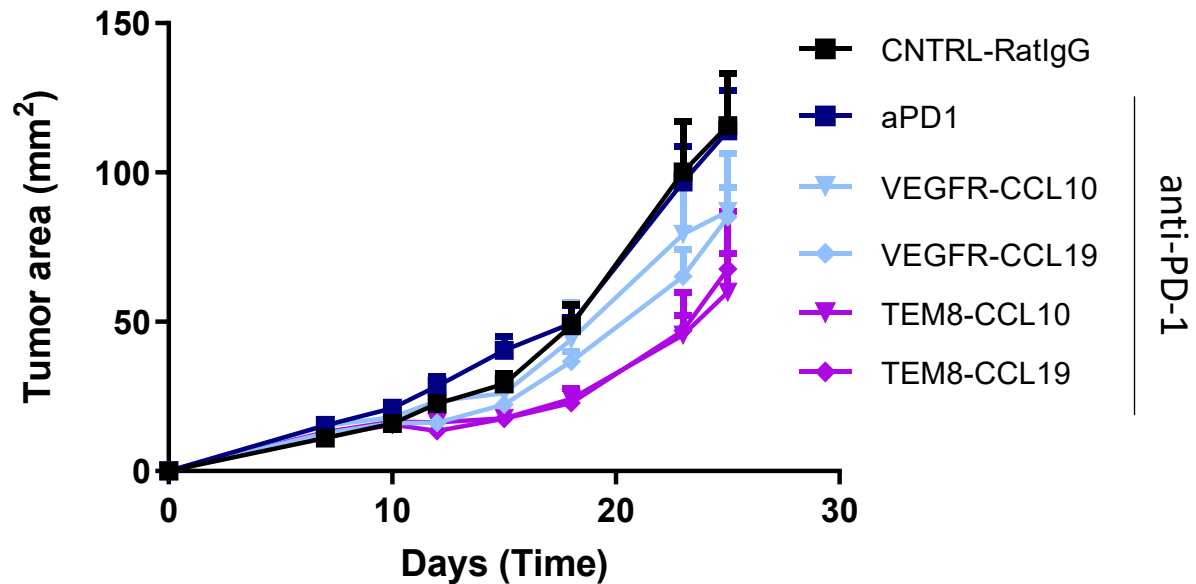
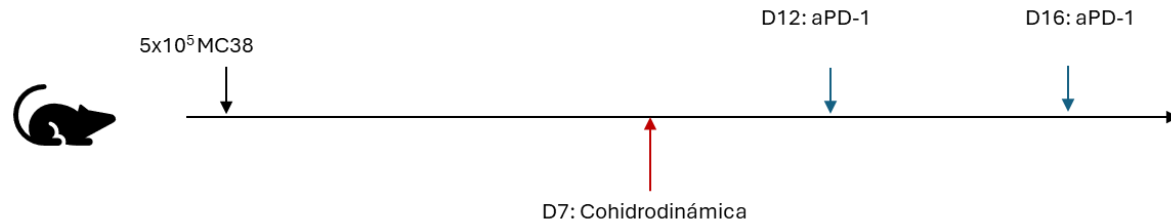
Chemokine Screening



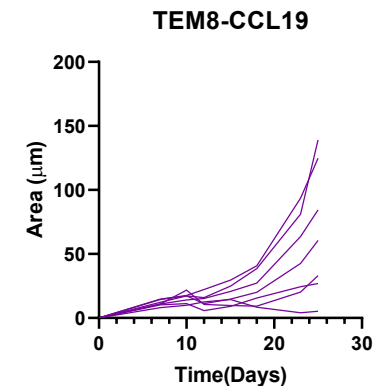
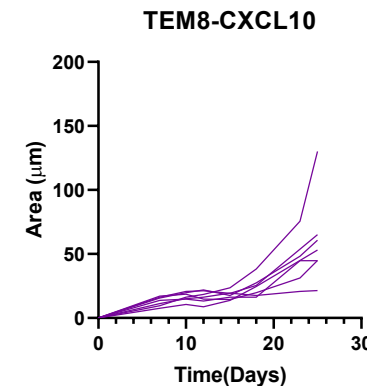
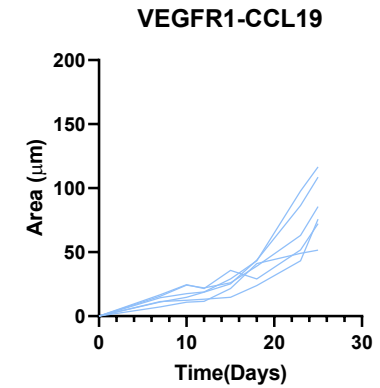
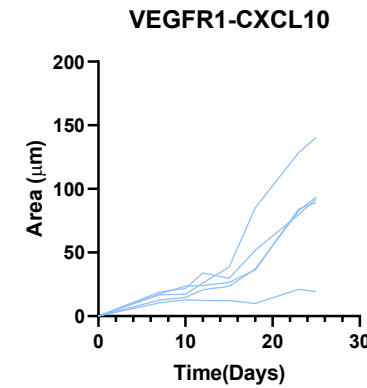
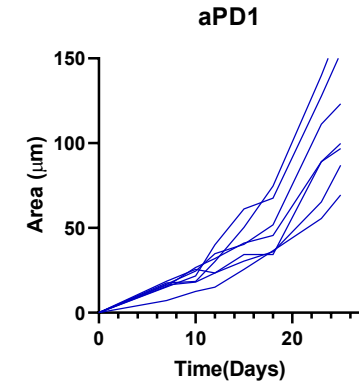
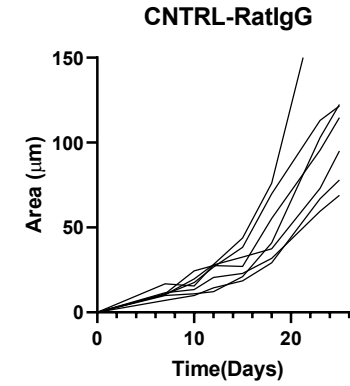
Developing candidates for Immune Cell Recruiters



VEGFR1/TEM8 + CXCL10/CCL19 + PD1
Single Molecule



In collaboration with Pedro Berraondo



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Lab members

Saray Garasa (former)

Beatrice Pinci

Almudena Manzanal

Carlos Luri-Rey

Maria Lucia Chiclana

David Causapé

Leticia Odriozola

Diana Alcobia

Mercedes Leal

Ainhoa Urbiola y Cristina

Ederra (Imaging service)

CIMA, Universidad de Navarra

Pedro Berraondo

Ignacio Melero

Maria Rodriguez

CNIC, Yale

Andrés Hidalgo, David Sancho



worldwide
cancer
research



fundación científica
asociación española
contra el cáncer



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