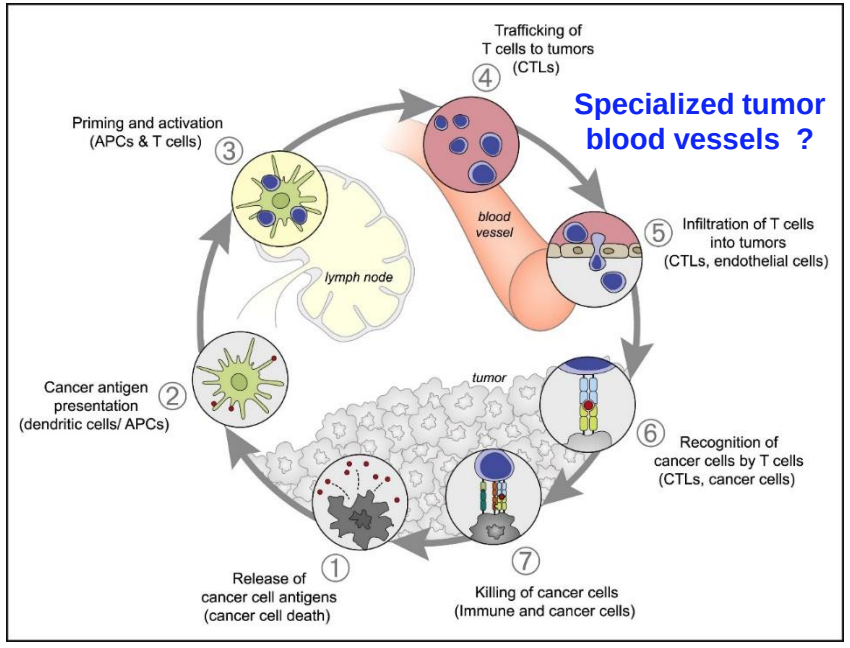
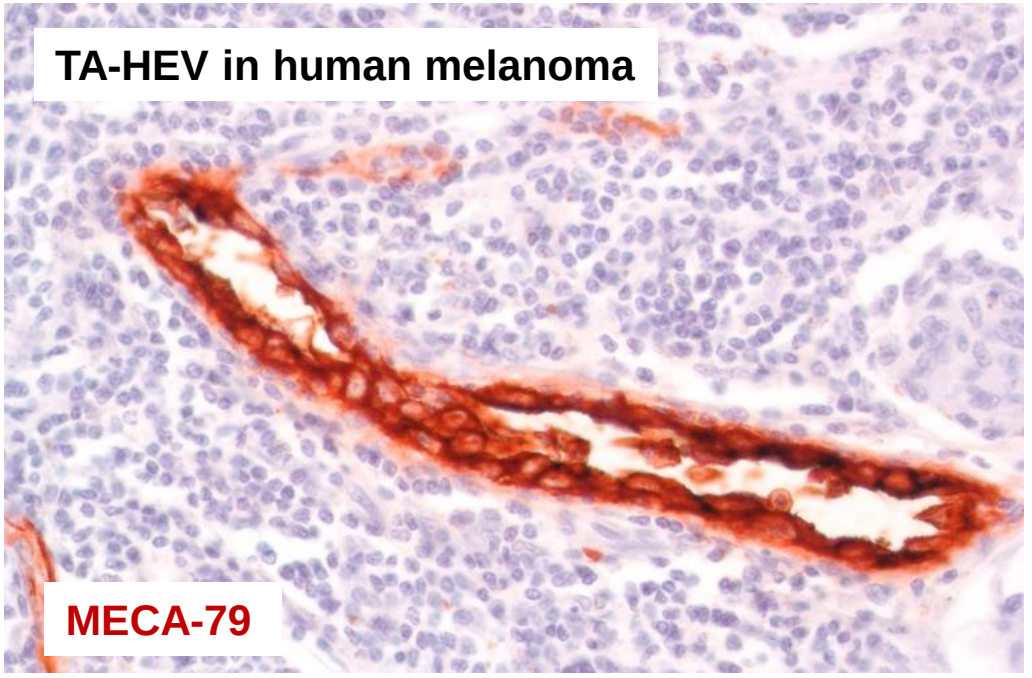
Tumor-associated high endothelial venules (TA-HEVs) : specialized blood vessels for lymphocyte entry into tumors

Mechanisms controlling lymphocyte entry into tumor during cancer immunity and immunotherapy ?



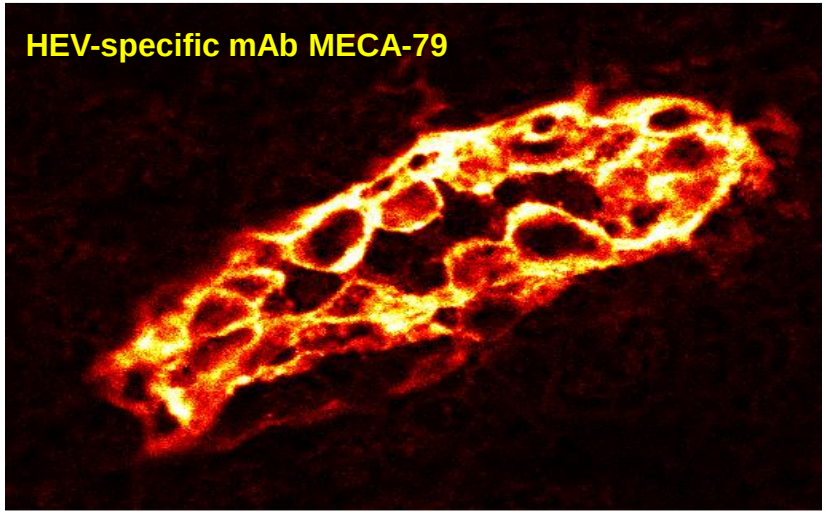
The Cancer Immunity cycle (Chen and Mellman, Immunity 2013)

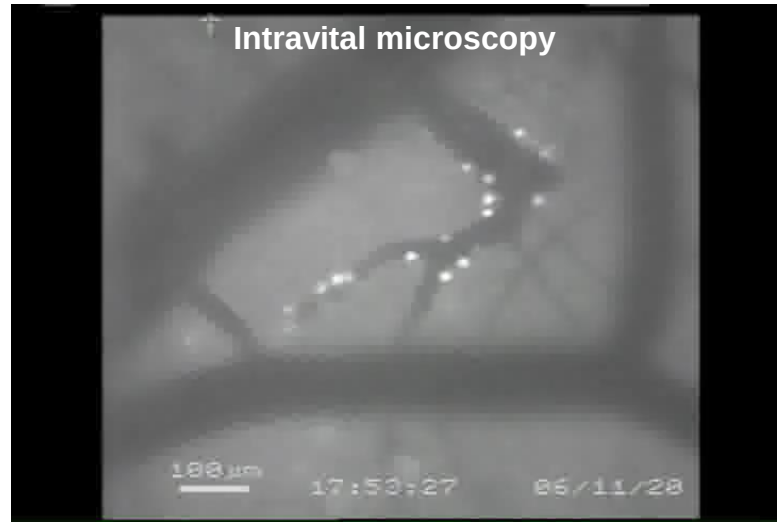


Jean-Philippe GIRARD, Director of Research INSERM
Head, Laboratory of Vascular Biology, IPBS-Toulouse,
CNRS and University of Toulouse

High Endothelial Venules (HEVs): specialized blood vessels for lymphocyte entry into lymphoid organs

(Girard and Springer, Immunity, 1995; Moussion and Girard, Nature 2011; Girard* et al., Nature Rev Immunol 2012)



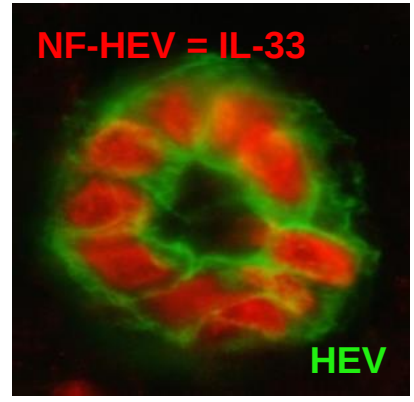


A long standing interest for HEVs (30 years of expertise !)

1st Isolation of HEV endothelial cells
Girard and Springer, Immunity, 1995

Regulation of HEVs by dendritic cells
Moussion and Girard, Nature, 2011

Discovery of interleukin-33 (IL-33/NF-HEV)
Baekkevold…and Girard, Am J Path 2003
Carriere …and Girard, PNAS 2007



Tumor-associated HEVs (TA-HEVs) in human cancer

(Martinet*, Garrido* ...and Girard, Cancer Res 2011)

Microenvironment and Immunology

Cancer Research

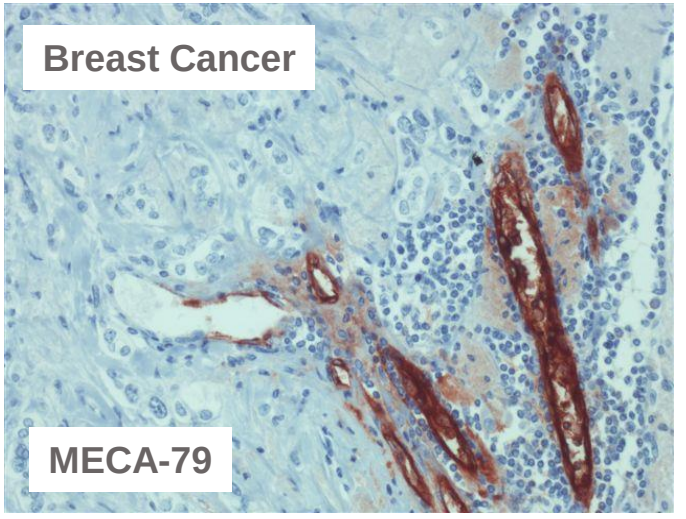
Human Solid Tumors Contain High Endothelial Venules: Association with T- and B-Lymphocyte Infiltration and Favorable Prognosis in Breast Cancer

INSTITUT CLAUDIUS REGAUD

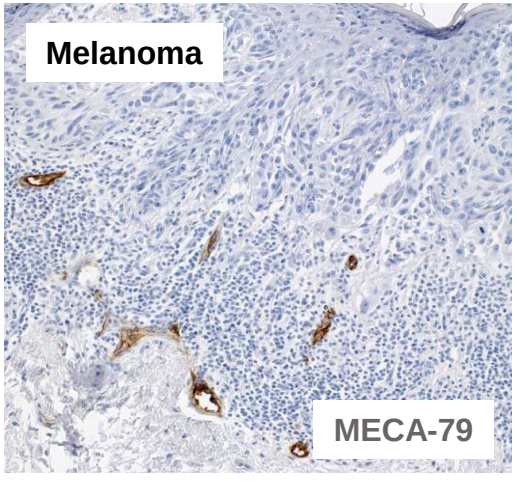
Ludovic Martinet[1,2], Ignacio Garrido[1,2,4], Thomas Filleron[4], Sophie Le Guellec[4], Elisabeth Bellard[1,2], Jean-Jacques Fournie[3,5], Philippe Rochaix[4], and Jean-Philippe Girard[1,2]

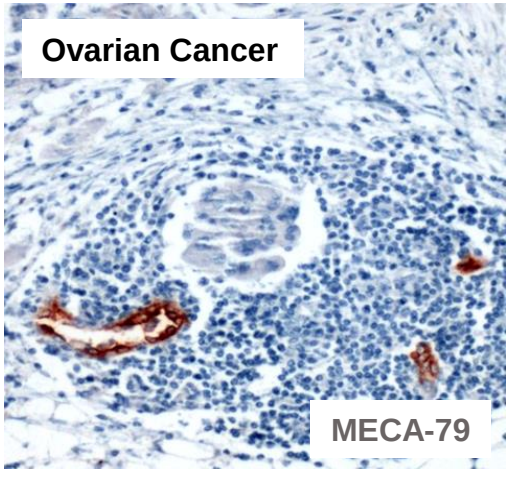
Cancer Res; 71(17) September 1, 2011

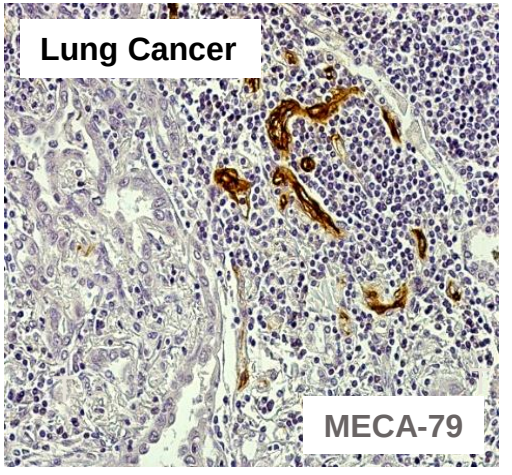
American Association for Cancer Research

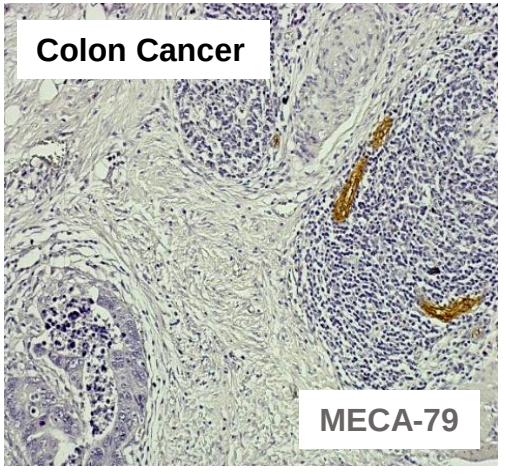


Human primary melanomas n = 225 (TA-HEVs in 60-70 % of tumor samples) Human primary breast tumors n = 273





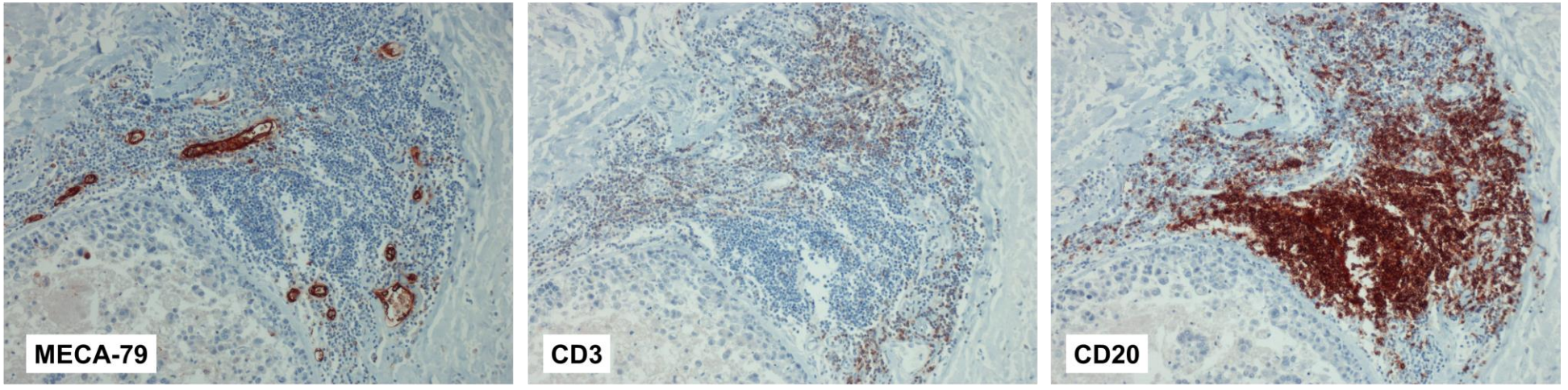




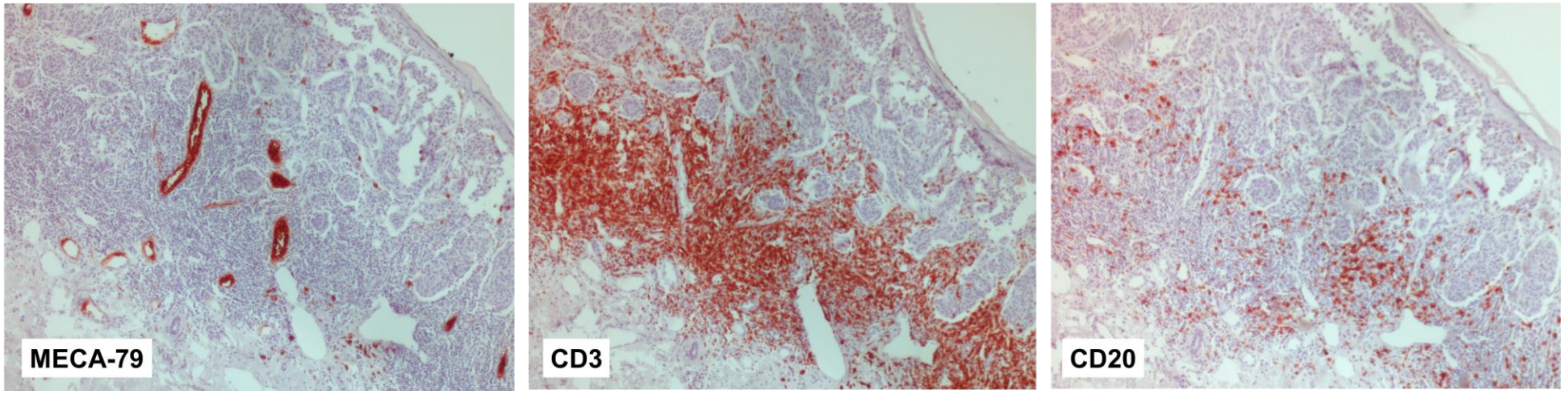
Tumor-associated HEVs (TA-HEVs) in human cancer

(Blanchard and Girard, Angiogenesis, 2021)

a TA-HEVs in a CD20⁺ B cell-rich TLS (breast cancer)



b TA-HEVs in a CD3⁺ T cell-rich area (melanoma)



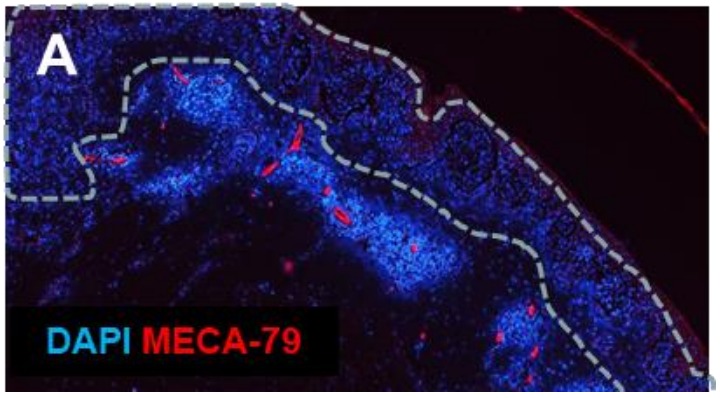
TA-HEVs are located in the stroma and invasive margin

RESEARCH PAPER
OncoImmunology 1:6, 829–839; September 2012; © 2012 Landes Bioscience

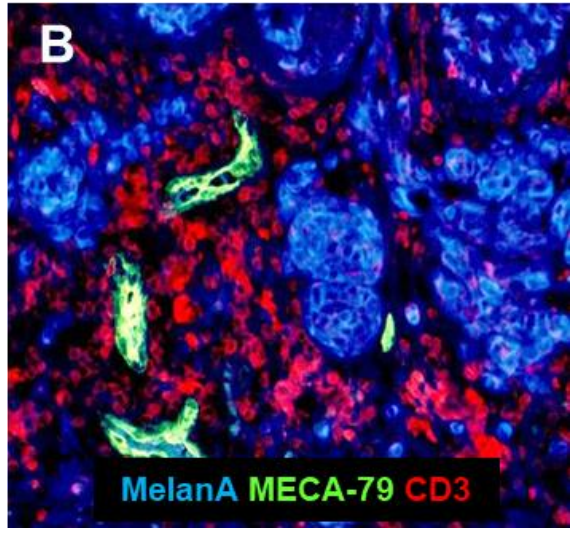
High endothelial venules (HEVs) in human melanoma lesions

Major gateways for tumor-infiltrating lymphocytes

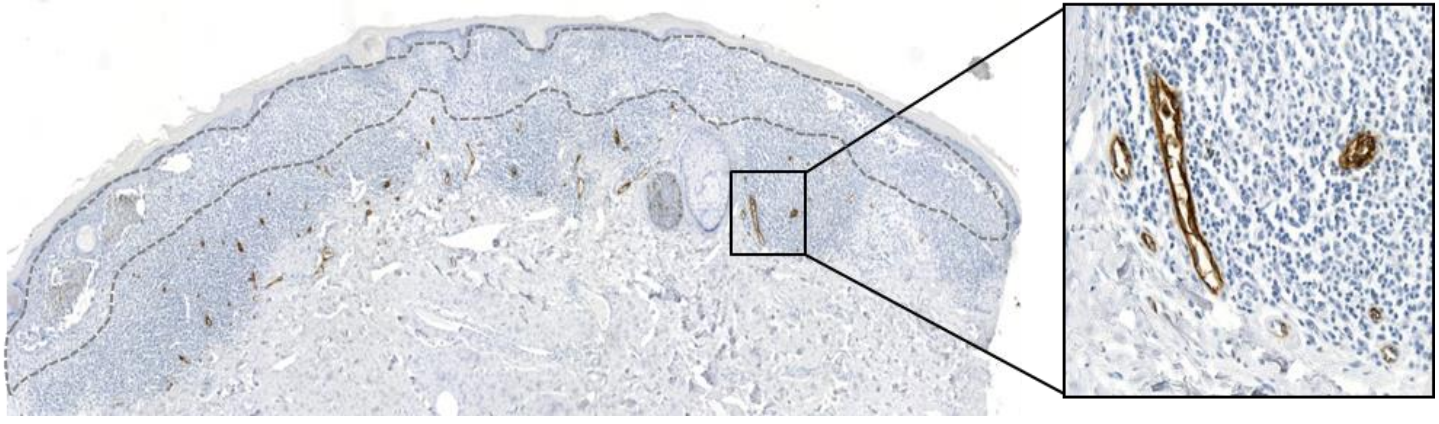
Ludovic Martinet,[1,2,3] Sophie Le Guellec,[3] Thomas Filleron,[3] Laurence Lamant,[2,4,5] Nicolas Meyer,[5] Philippe Rochaix,[3] Ignacio Garrido[1,2,3,5] and Jean-Philippe Girard[1,2,*]



TA-HEVs are located in the tumor stroma



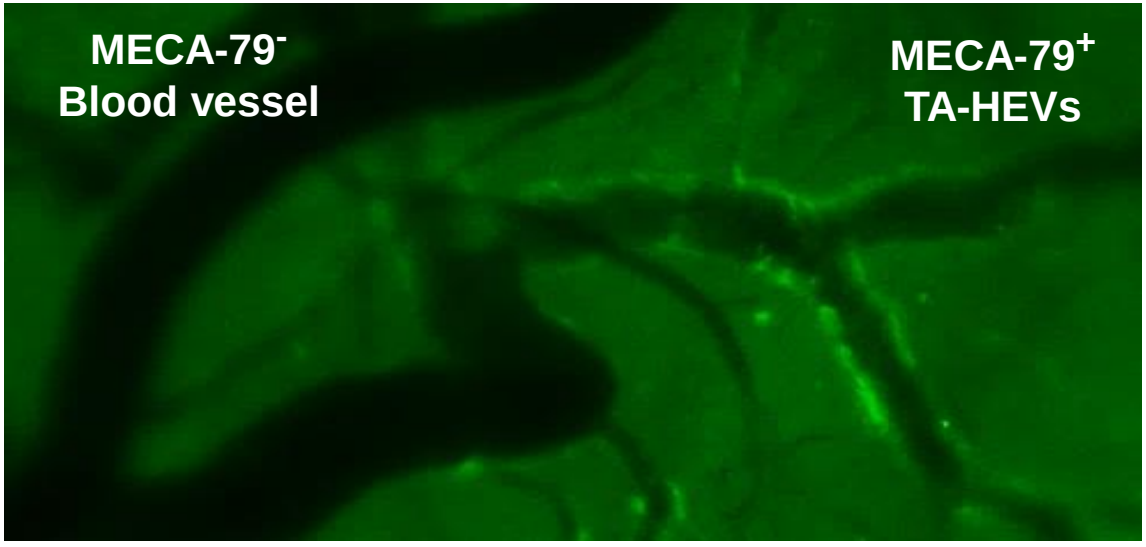
TA-HEVs are enriched at the invasive margin of melanoma lesions (not in the tumor core)



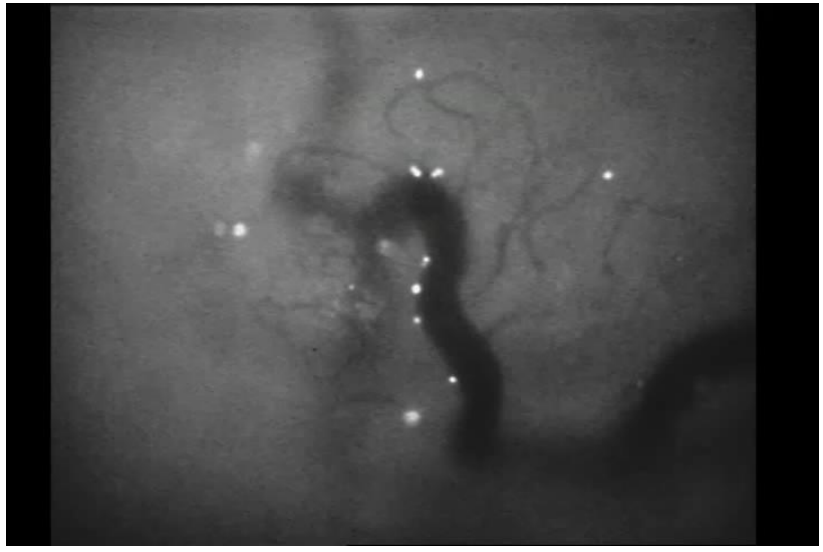
TA-HEVs are the main sites of lymphocyte entry into tumors treated with anti-PD-1/anti-CTLA-4 immunotherapy

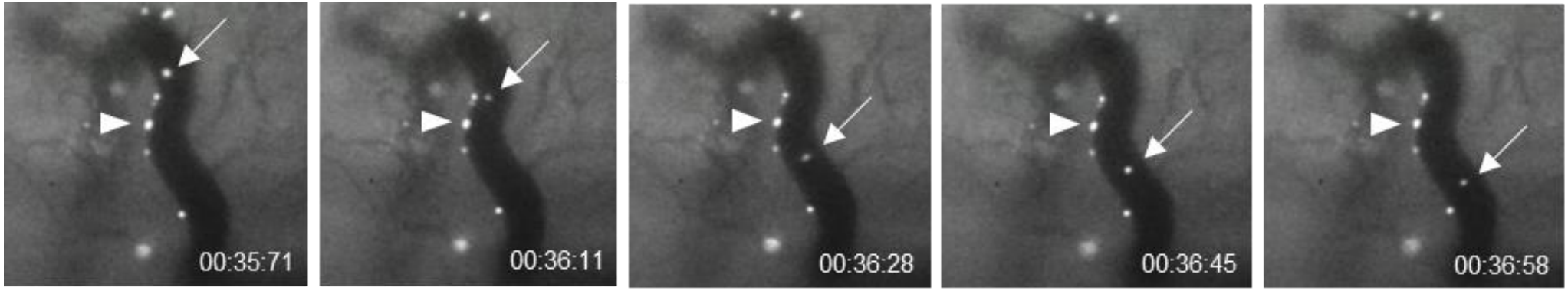
(Asrir*, Tardiveau*, Coudert*, Laffont*, Blanchard*, ...and Girard, Cancer Cell 2022)

In vivo imaging of TA-HEVs with fluorescent mAb MECA-79



Wide field intravital microscopy (real time)



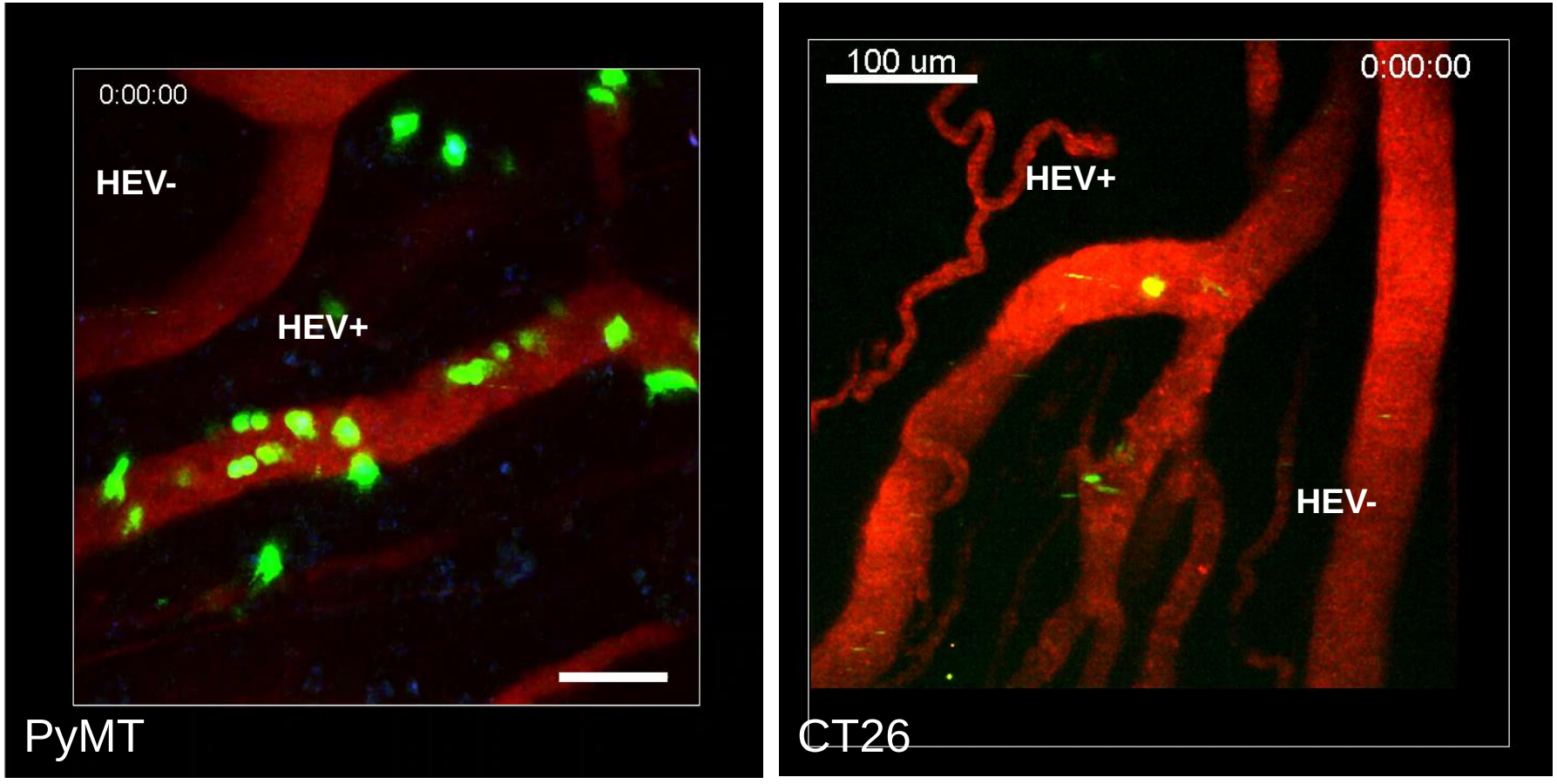


Intravital microscopy (real time) - lymphocyte rolling and sticking in a MECA-79+ TA-HEV
(Combined immunotherapy with anti-CTLA-4 and anti-PD-1 mAbs)

TA-HEVs are the main sites of lymphocyte entry into tumors treated with anti-PD-1/anti-CTLA-4 immunotherapy

(Asrir*, Tardiveau*, Coudert*, Laffont*, Blanchard*, ...and Girard, Cancer Cell 2022)

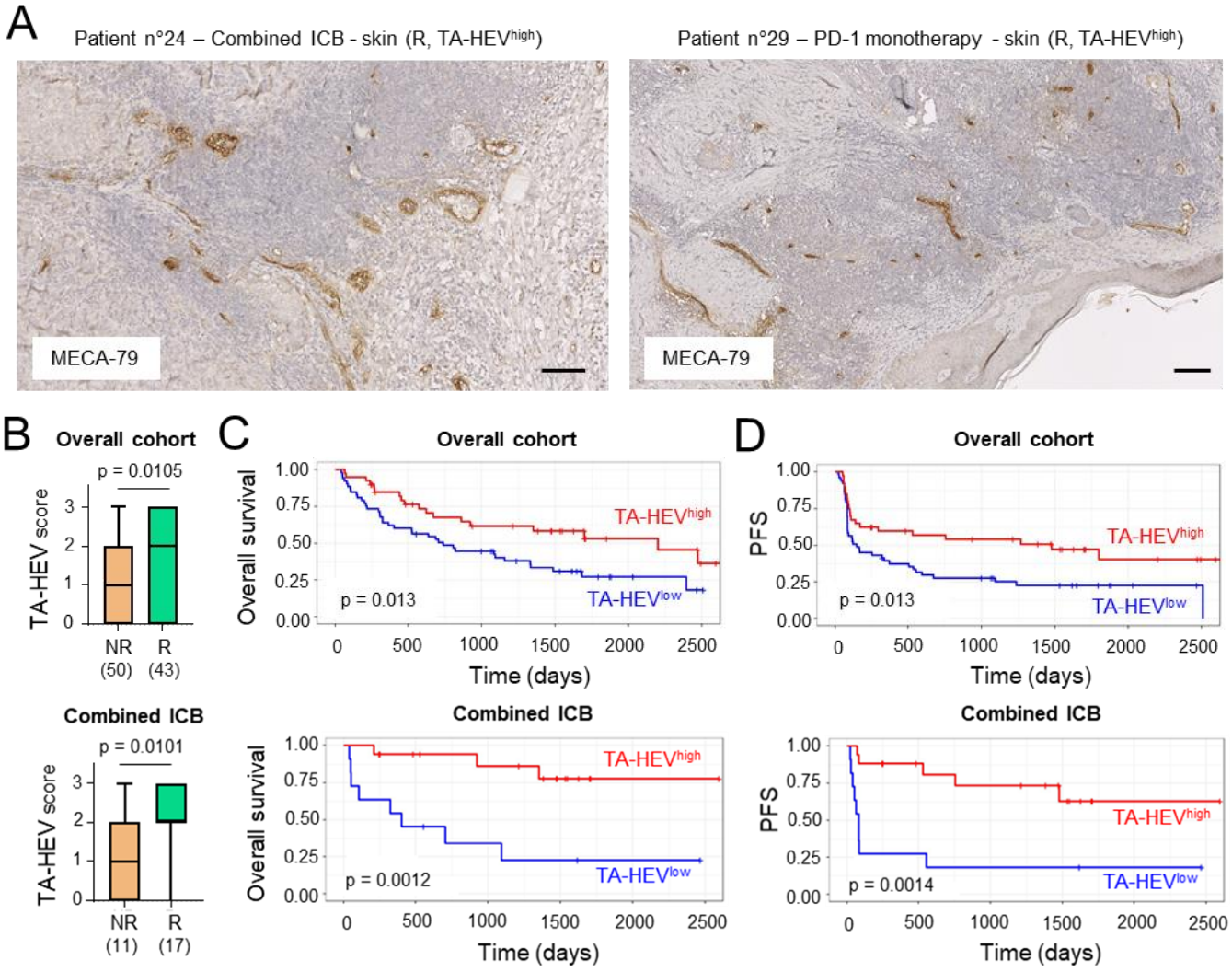
Multiphoton *in vivo* imaging (time lapse) - lymphocyte extravasation in MECA-79$^+$ TA-HEVs



PyMT mammary carcinoma and CT26 colon carcinoma tumor-bearing mice treated with combined ICB
Fluorescent lymphocytes from tumor-bearing mice treated with combined ICB (anti-CTLA-4 + anti-PD-1 mAbs)

TA-HEVs predict response and survival of metastatic melanoma patients treated with combined immunotherapy

(Asrir*, Tardiveau*, Coudert*, Laffont*, Blanchard*, ...and Girard, Cancer Cell 2022)



GUSTAVE ROUSSY
CANCER CAMPUS
GRAND PARIS

Collaborative study with Pr **Caroline Robert** (GR Villejuif)

Large cohort of patients with unresectable stage III or IV metastatic melanoma (n=93) treated with anti-PD-1 (n=65) or anti-CTLA-4/anti-PD-1 (n=28)

Increasing TA-HEVs with an agonist of the lymphotoxin beta receptor (LTβR) ameliorates the efficacy of combined immunotherapy

(Asrir*, Tardiveau*, Coudert*, Laffont*, Blanchard*, ... and Girard, Cancer Cell 2022)

DCs regulate HEV phenotype and function through the LTβR signaling pathway

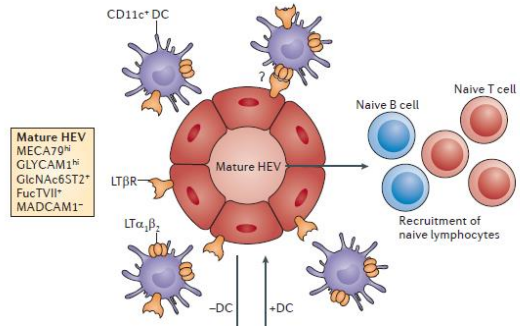
LETTER

doi:10.1038/nature10540

Dendritic cells control lymphocyte entry to lymph nodes through high endothelial venules

Christine Moussion[1,2] & Jean-Philippe Girard[1,2]

Nature 2011



Anti-CTLA-4/anti-PD-1 induce regression of non-regressing tumors when the function of TA-HEVs is increased by treatment with an agonist of LTβR (T, Triple therapy)