Ephrin B2 as a therapeutic strategy against angiogenesis

BiOncoTech Therapeutics

Bilbao, 21 de septiembre de 2012

biospain 2012

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   b) Innovative mechanisms of action
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3. **Partnering Opportunities**

1. The Company

- **Bioncotech Therapeutics** focuses on the development of anticancer agents against aggressive tumors and immunological agents for autoimmune diseases.
- **Bioncotech** emerged as the first cancer-oriented spin-off of the Spanish National Cancer Center (CNIO), one of the leading international cancer centers (5th by high impact factor publications)

The company has its laboratories at the Scientific Park of the University of Valencia and offices in Madrid and Cambridge (MA). Bioncotech actively collaborates with the CNIO, CSIC and other academic and clinical institutions.

Collaborations

BiOncoTech Therapeutics

Universitat de València

cnio

National Cancer Institute

VCU

Paul Fisher
Paola Barral

Hospital Universitario 12 de Octubre

universitätbonn

Thomas Tuting

Yale University

Marcus Bosemberg

Hospital General Universitario Gregorio Marañón

Ciemat Centro de Investigaciones

Miguel A. Morcillo

Hospital Universitario Ramón y Cajal

Institut Pasteur

Lionel Larue

The Wistar Institute

Meenhard Herlyn

Hospital Universitario La Paz

DANA-FARBER CANCER INSTITUTE

Keith Flaherty

Michigan

M. Verhaegen
M Ribblet

La Fe Hospital Universitari

Instituto de Investigación Sanitaria Fundación

UCSF University of California San Francisco

Martin McMahon
Boris Bastian

Principe Felipe Centro de Investigacion

M. Jesús Vicent

ivo Fundación Instituto Valenciano de Oncología

Universidad de Alcalá

Javier de la Mata
Rafael Gomez

CSIC

Balbino Alarcón

Servizo Galego de Saúde

InnoMelanoma

RNAREG

IMMU

SMR

Fundación Mel
Pacientes, Investigadores y Clínicos contra el Melanoma

National Institutes of Health

Gobierno de España
Ministerio de Ciencia e Innovación

Fundación aecc
Investigación contra el Cáncer

AICR

INNPACTO

Bancaja

CDTI

National Cancer Institute

Programa Ingenio 2010

can

Genoma España
InnoCash

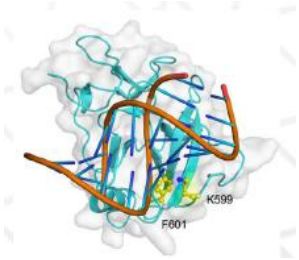
cevi pyme

ivf Institut Valencià de Finances

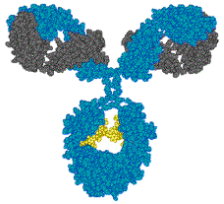
Iniciativa neotec

Pipeline

ONCOLOGY

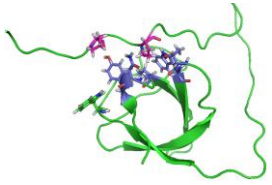


BO-110 Autophagy activator for tumor treatment



BO-011 Antiangiogenic Antibody

INFLAMATORY – AUTOIMMUNE



BA-024 Tcell selective inhibitor

Oncology

Project BO-110

BO-110

- Autophagy
- Apoptosis
- Immune-modulator

High Therapeutic Efficacy

Different types of human tumours

Specific

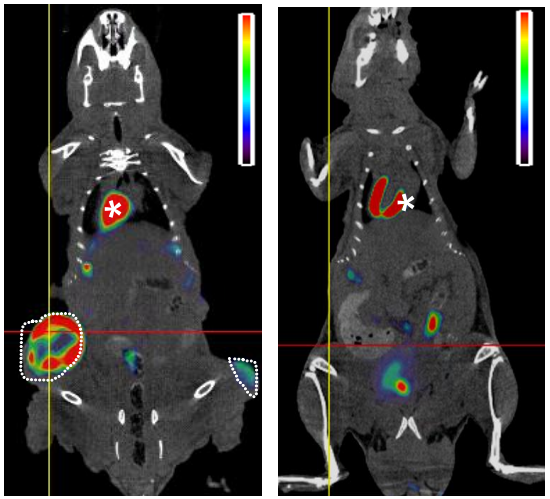
Tumour cells

Without toxicity

Preclinical models

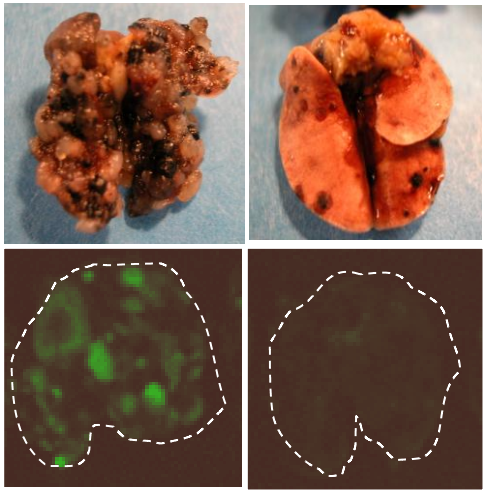
Tyr:NRAS^{Q61K} x INK4a/ARF-/- model

Control BO-110

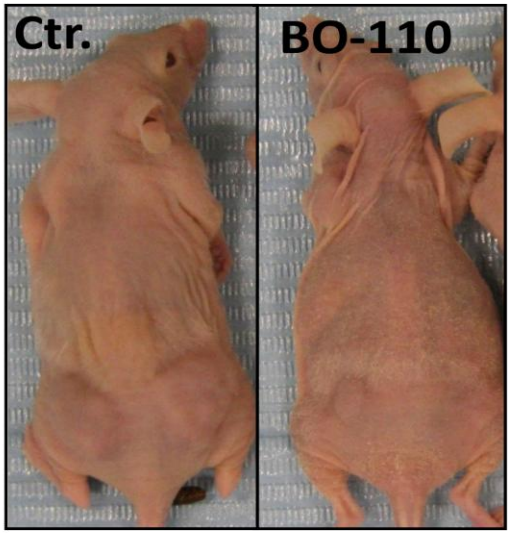


Melanoma model

Control BO-110



Pancreas model



R&D and IP

Tormo *et al.* (Cancer Cell, 2009)

Alonso-Curbelo *et al.* (Autophagy, 2009)

Tormo *et al.* (Clinical & Translational Oncology, 2009)

Poeck *et al.* (Nature Medicine, 2008)

Besch *et al.* (Journal Clinical Investigation, 2009)

IP

PCT/EP2010/059593 Proceeding of identification of therapeutic agents against melanoma and the use of an identified agent

Positive IPER from EPO and FTO – Major claim: Exclusive use of BO-110 as medical product

Entering National Phase: EU, USA, China, Sudafrica, Singapur, Israel, Korea, Mexico, Australia, Brazil, Canada, Chile, India, Rusia, New Zeland, Japan

In preparation: Patent on treatment of Cancer Stem Cell

Autoimmune

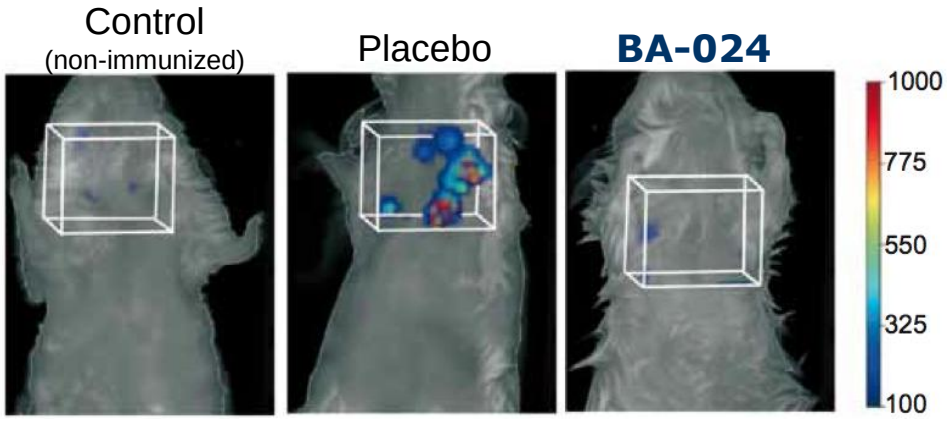
Project BA-024

BA-024

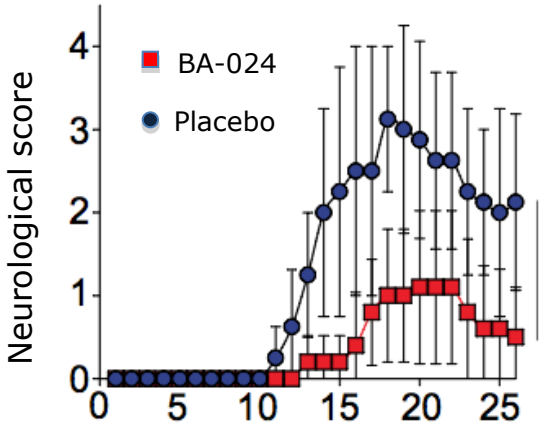
T Cell Inhibition at the TCR level

- Specific Tcell inhibitor
- Therapeutic efficacy for autoimmune diseases (in vitro y in vivo)
- Small Molecule (oral delivery)
- No side effects

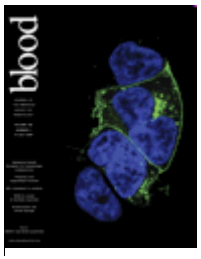
Asthma model



Multiple Sclerosis model



R&D and IP



Alarcón *et al.* (Immunological Reviews, 2003)

Risueño *et al.* (Blood, 2005)

Risueño et al. (PNAS, 2006)

Minguet *et al.* (Immunity, 2007)

Borroto *et al.* (*submitted*)

IP

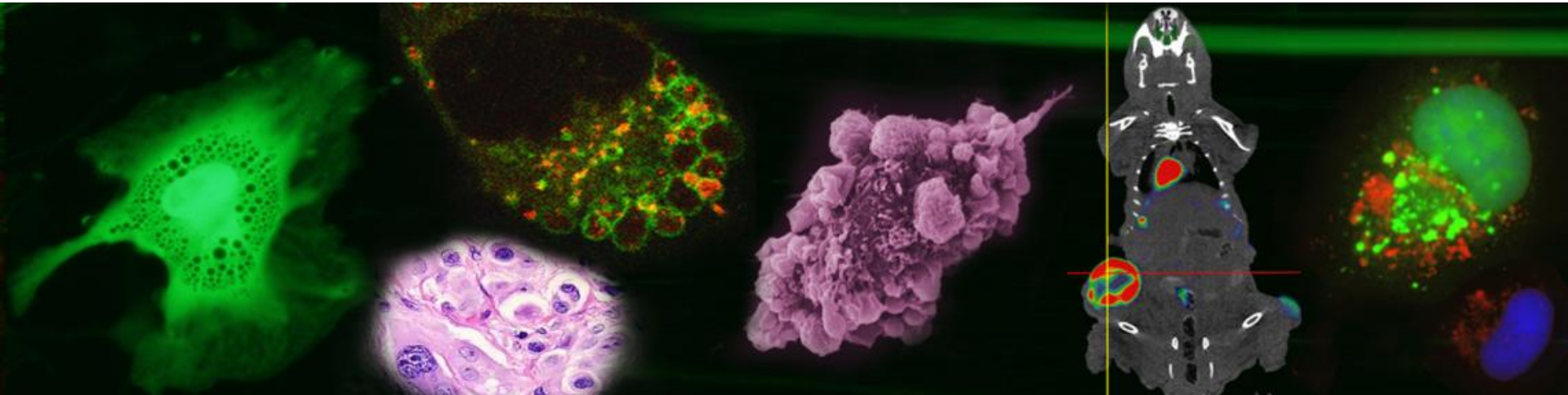
1. WO201000900 Hit compounds under international patent: Immunosupressor based on the interruption of TCR-NCK Interaction. Priority date 30/06/2008

2. PCT/ES2009070239**:** Lead compounds patented

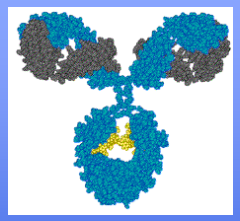
Positive ESR from EPO

ONCOLOGY Project EphrB2 Ab

Antiangiogenic Antibody



2. The Product: Therapeutic focus



EphrinB2 Ab

- Ephrin B2 Ab generated at CNIO (Ab group – Dr. Jorge Martinez
- First in kind human single chain (scFv) antibody fragments against ephrinB2 – inhibition of angiogenesis and lymphoangiogenesis
- Broad Efficacy in vivo. Orphan Disease Category
- No Detectable Secondary Toxicity in Cancer Models

Main Objectives

- Clinical Development B0-011

  Phase I/II Trials

- Pipeline

  Combination therapy,
  NME,

Market Opportunity

Target tumours
Melanoma
Pancreatic cancer
Breast cancer
Colon cancer
Lung cancer

Unmet Medical Need

- High mortality
- High incidence
- Without effective treatment
- ***Lack or failure of conventional anti-angiogenic therapies***
- Side effects
- Social impact

Attractive Market

- Value of global cancer market: 47,7 billons dollars
- Expected value of cancer market in 2014: 76,7 billons dollars
- Multi-billion expenses in medical and palliative case
- Orphan disease

Rationale: Why anti-ephrinB2 antibodies?

Vol 465|27 May 2010|doi:10.1038/nature08995 nature

LETTERS

Ephrin-B2 regulates VEGFR2 function in developmental and tumour angiogenesis

Suphansa Sawamiphak[1], Sascha Seidel[2], Clara L. Essmann[1], George A. Wilkinson[3], Mara E. Pitulescu[4], Till Acker[2]* & Amparo Acker-Palmer[1]*

Vol 465|27 May 2010|doi:10.1038/nature09002 nature

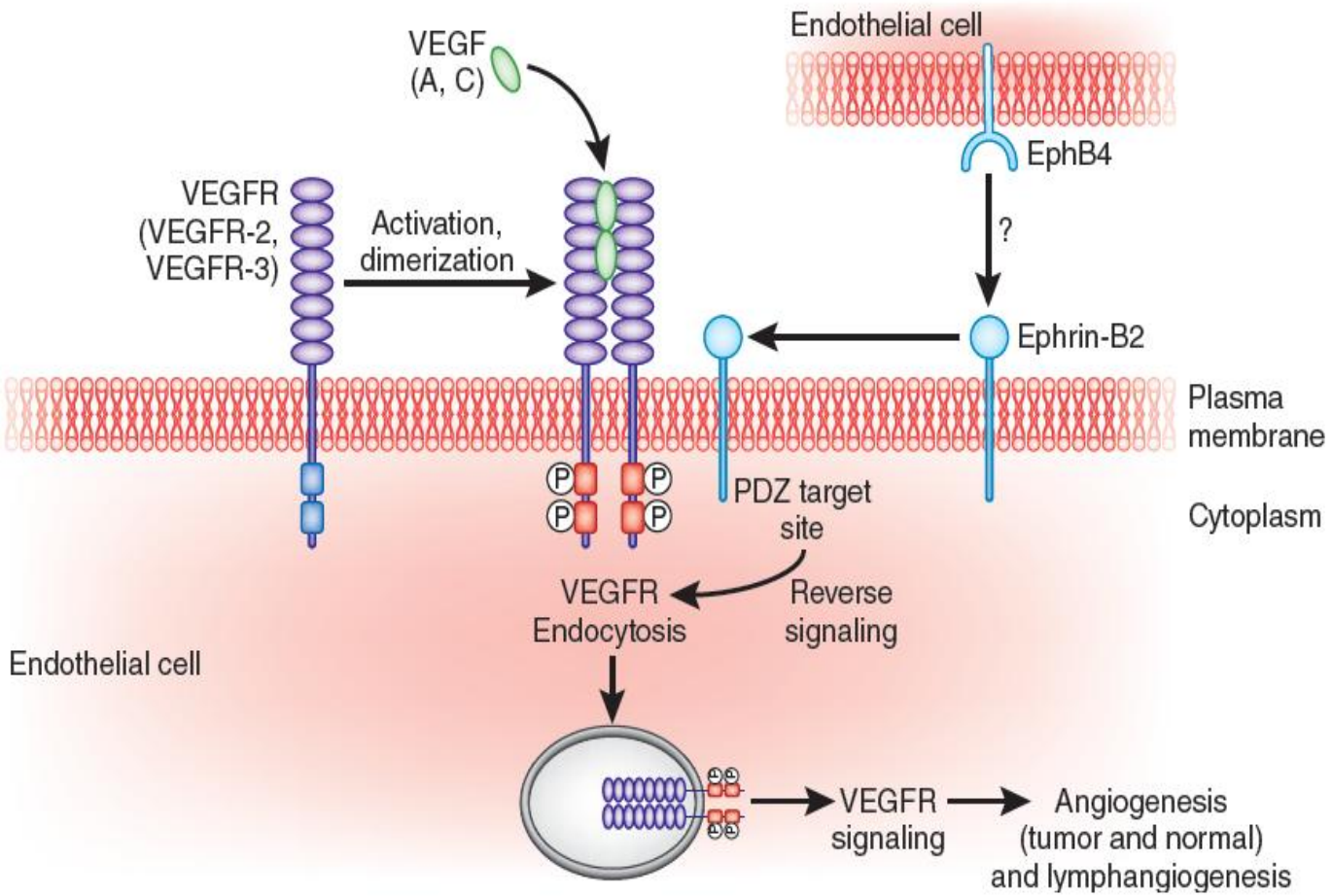
LETTERS

Ephrin-B2 controls VEGF-induced angiogenesis and lymphangiogenesis

Yingdi Wang[1]*, Masanori Nakayama[2]*, Mara E. Pitulescu[2]*, Tim S. Schmidt[1]*, Magdalena L. Bochenek[2,3], Akira Sakakibara[1], Susanne Adams[1,2], Alice Davy[4], Urban Deutsch[5], Urs Lüthi[6], Alcide Barberis[6], Laura E. Benjamin[7], Taija Mäkinen[8], Catherine D. Nobes[3] & Ralf H. Adams[1,2]

nature publishing group npg

Rationale: Why anti-ephrinB2 antibodies?



NATURE MEDICINE VOLUME 16 | NUMBER 7 | JULY 2010
Stéphane Germain & Anne Eichmann

New Generation of anti-angiogenic therapies: Ab Ephrins

Of Ephs and Ephrins: Companies Target Guidance Molecules in Cancer

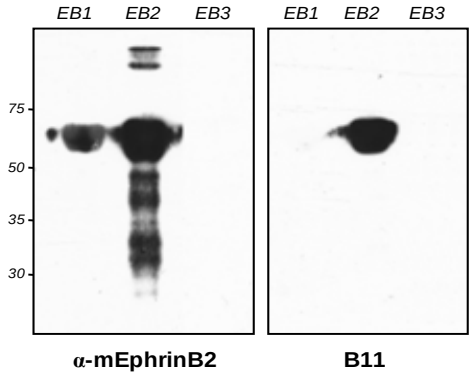
Selected drugs in pipelines targeting Eph and ephrins

Company/sponsor	Agent	Stage
KaloBios	KB004 humanized anti-EphA3 monoclonal antibody	Phase I pending
Vasgene	Soluble EphB4 receptor	Phase I pending
	Anti-EphB4 humanized monoclonal antibody	Preclinical
Pfizer	Anti-EphA2 tyrosine kinase inhibitor	Preclinical
Novartis	NVP-BHG712, anti-EphB4 kinase inhibitor	Preclinical, on hold
Wake Forest University	Ephrin-A1 PE38 QQR, ligand conjugated to *Pseudomonas* toxin	Second-generation monomeric conjugate in early development

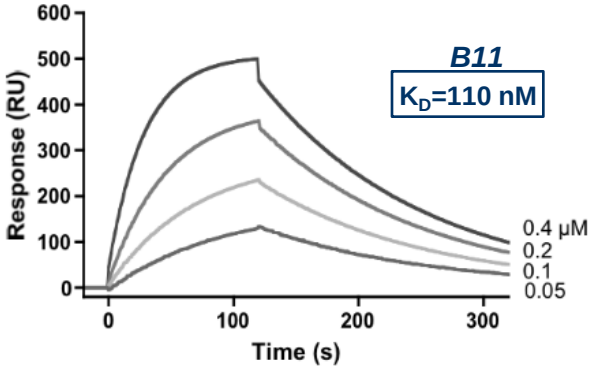
Vol. 102, Issue 22 | November 17, 2010

Genetech – EhprinB2 Ab against ephrin B2 Ab (non therapeutic)
Medimmune – in progress (no data)

Characterization of Ephrin B2 Ab

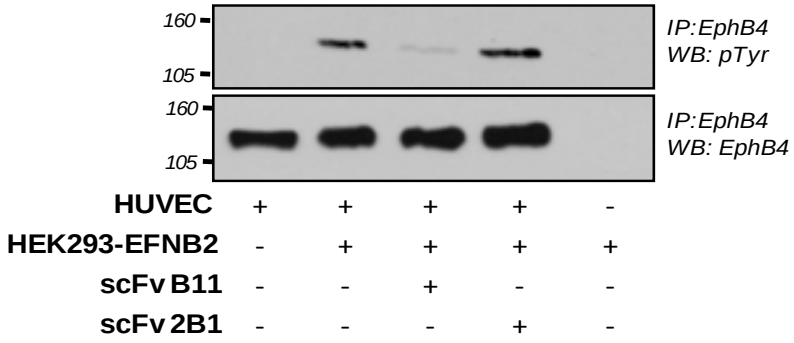


Specificity by WB

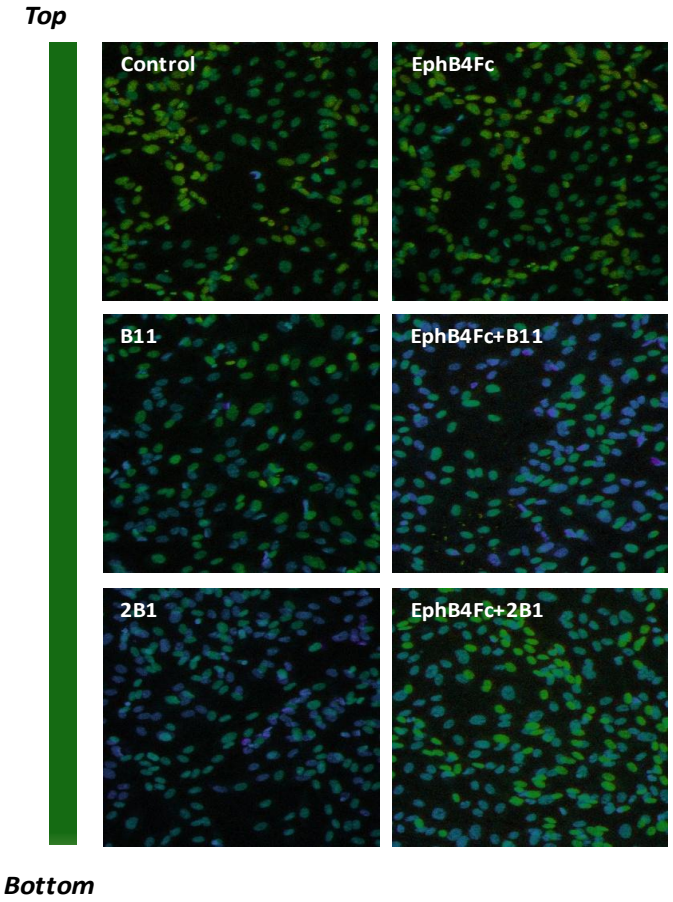


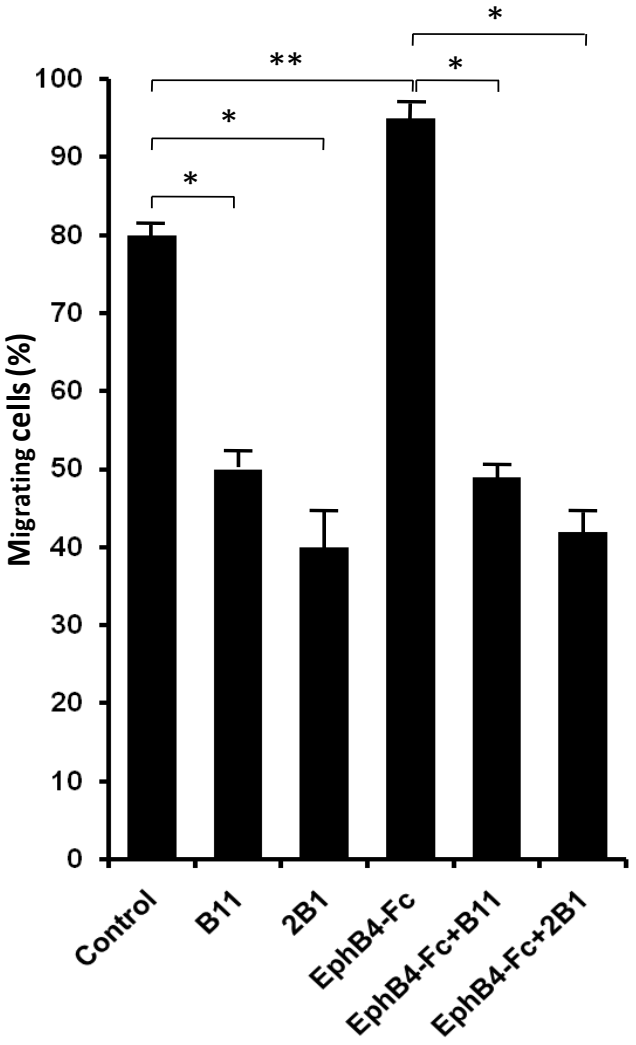
SPR Sensogram

B11 is highly specific for EphrinB2 but not with other related members of the protein family



Antiangiogenic capability of Ephrin B2 Ab

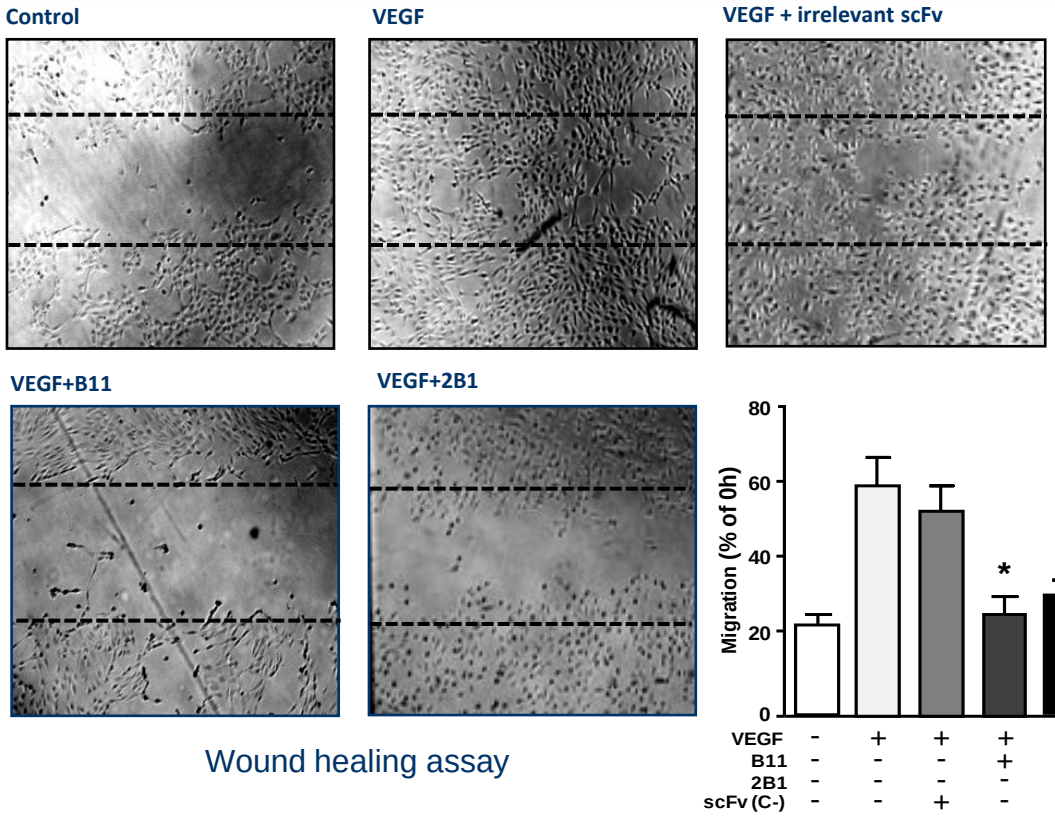




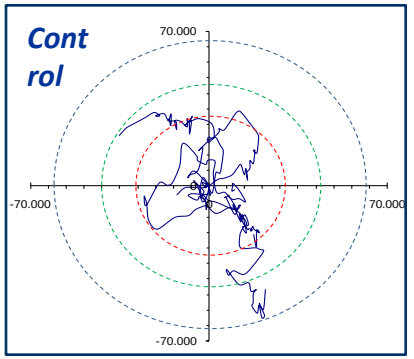
HUVEC migration assay

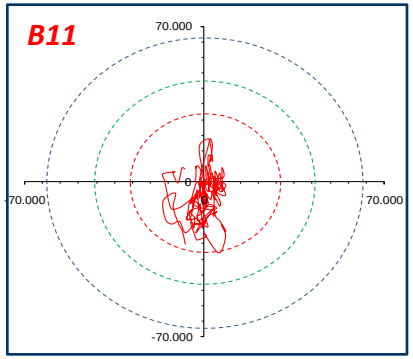
B11 inhibits migration of endothelial cells by 80%

Antiangiogenic capability of Ephrin B2 Ab



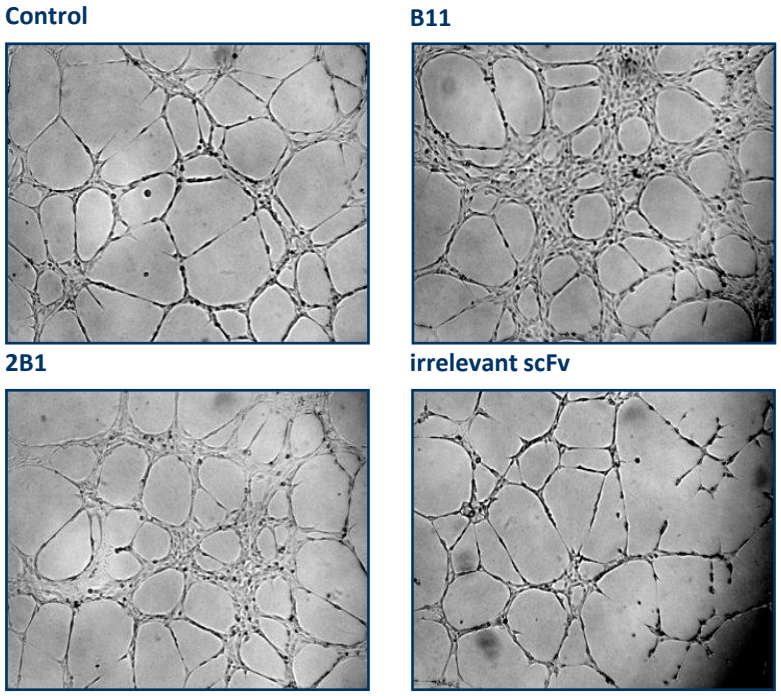
Wound healing assay

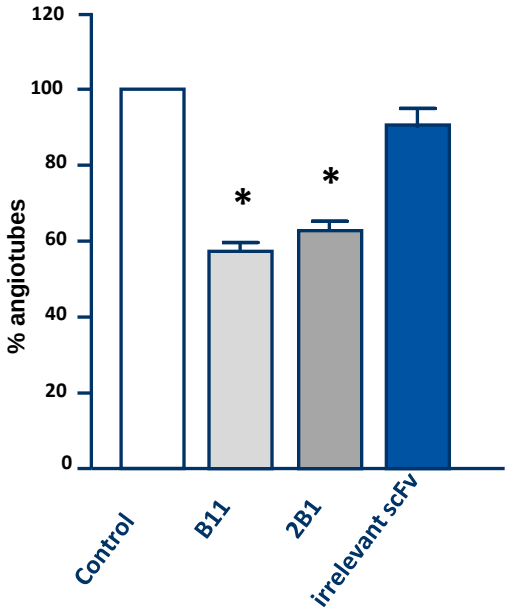




B11 inhibits VEGF-induced migration of endothelial cells

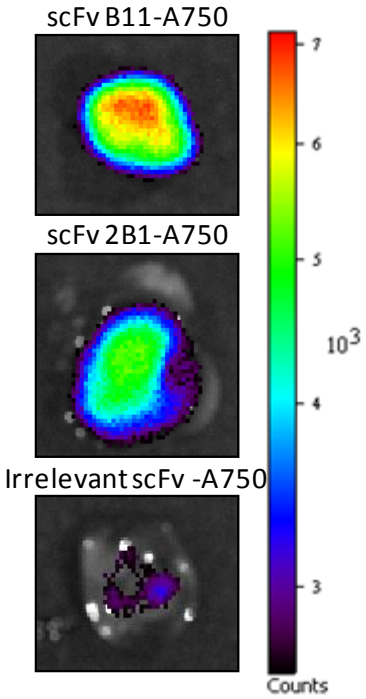
Antiangiogenic capability of Ephrin B2 Ab

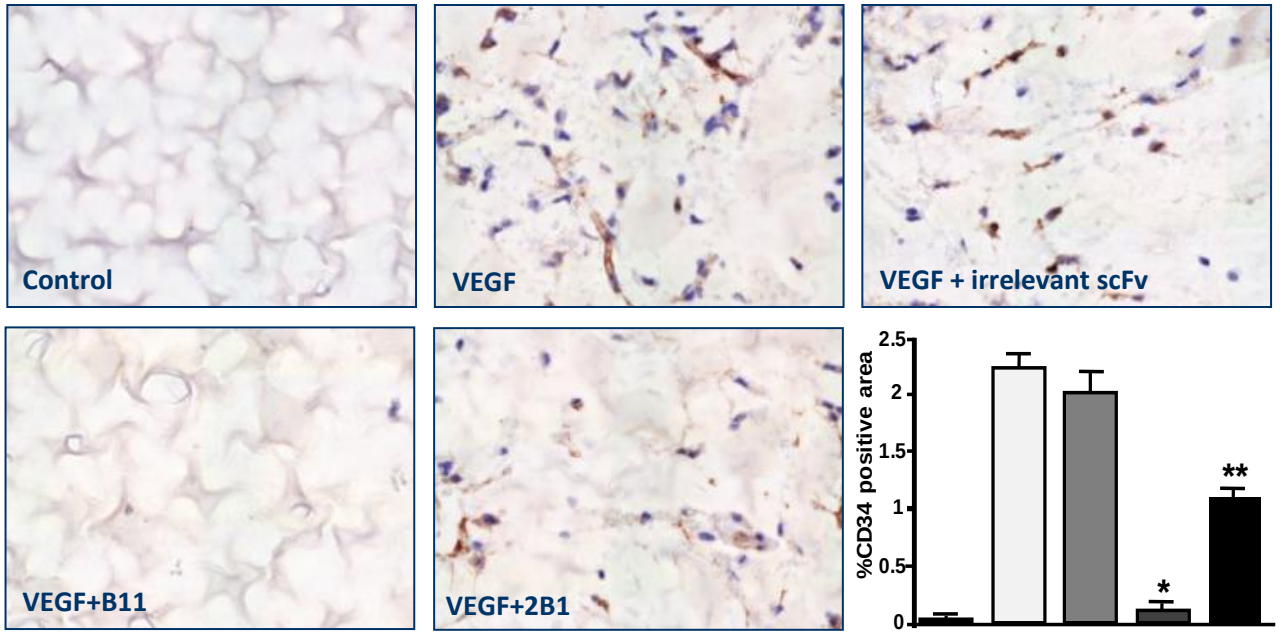




B11 inhibits the formation of tube-like structures (> 40%)

Impairment of VEGF-induced Matrigel angiogenesis in vivo by Ephrin B2 Ab

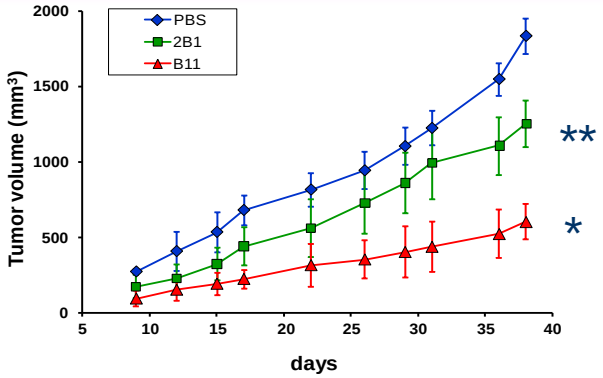




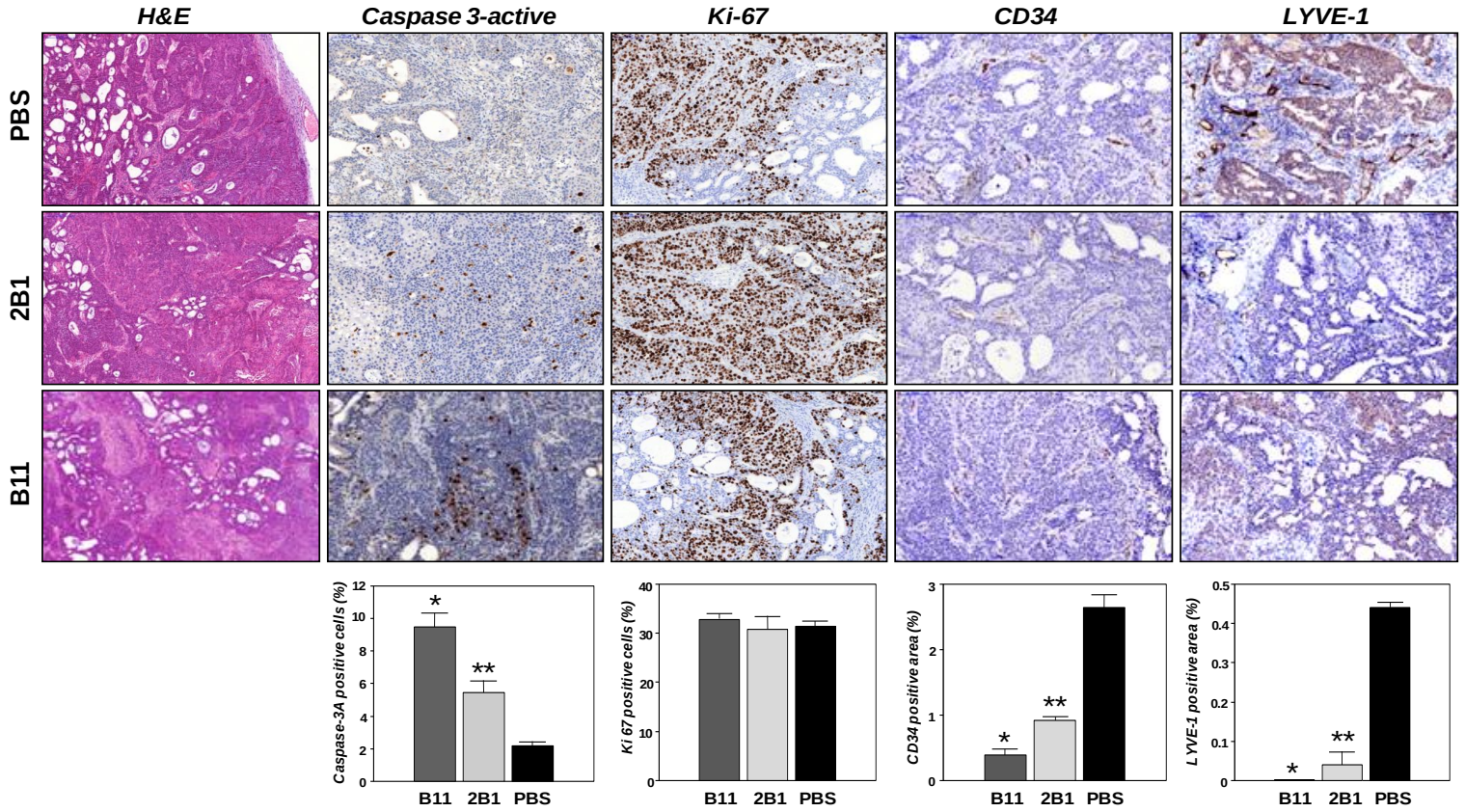
VEGF-Matrigel plug assay in vivo

EphrinB2 -B11 is able to inhibit efficiently angiogenesis and functional blood vessel formation in vivo

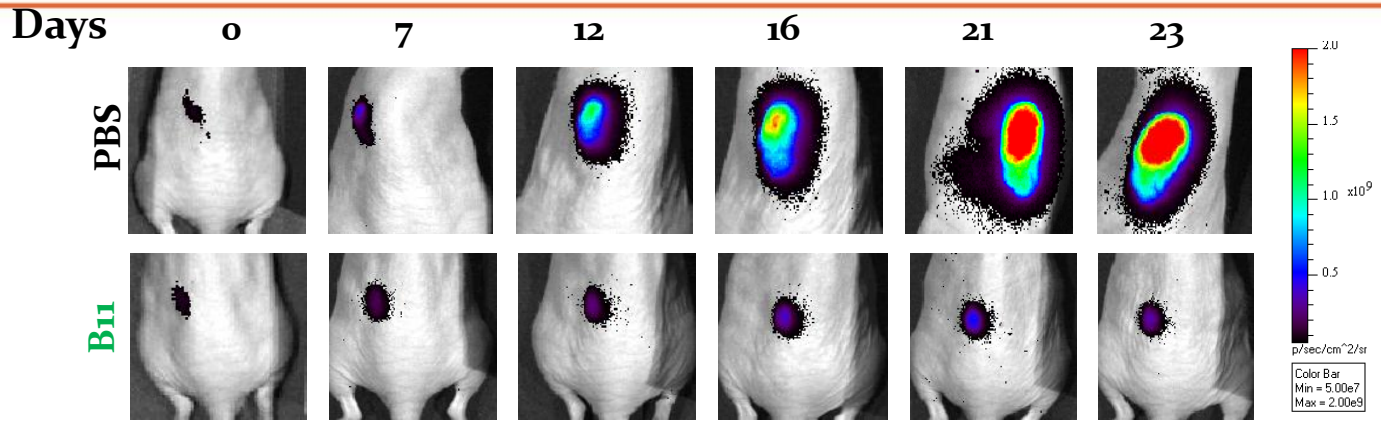
ANTITUMOR ACTIVITY OF THE EPHRINB2 ON PANCREAS CANCER (BxPC3)

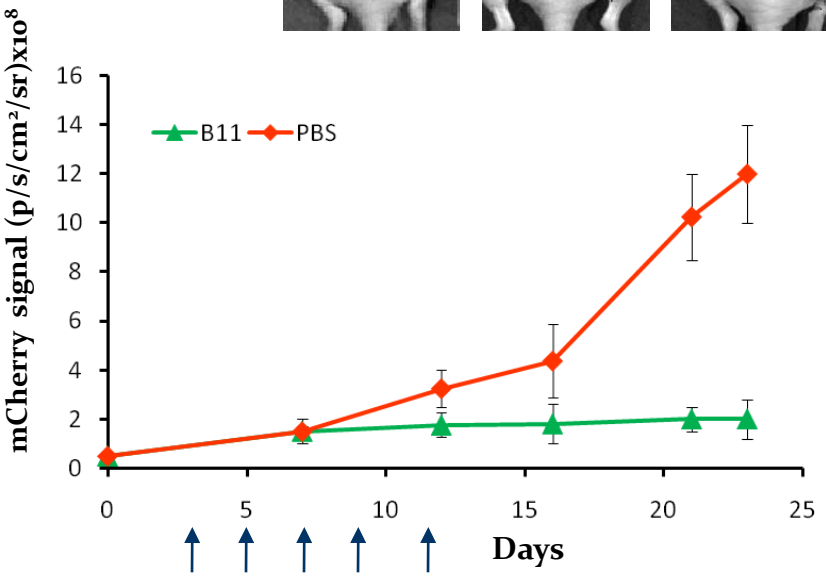


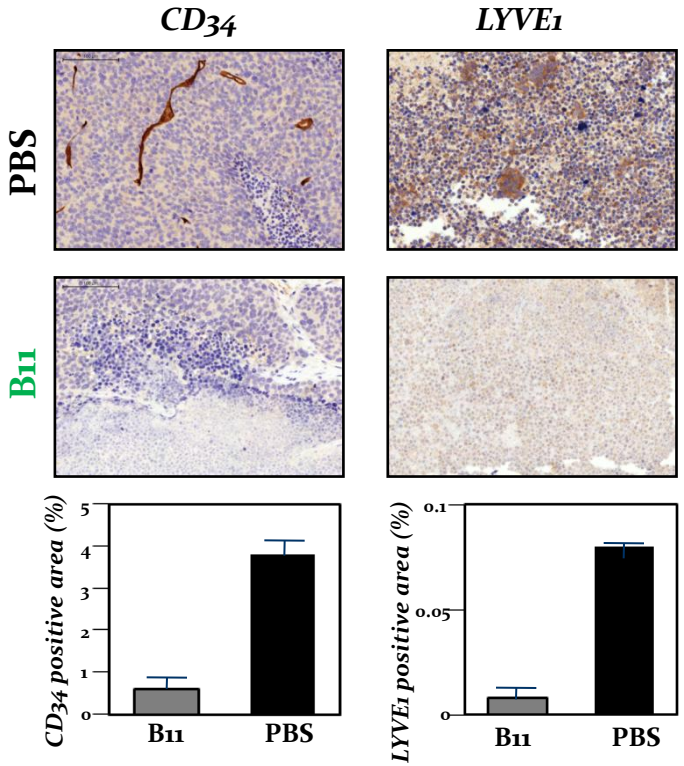
B11 inhibited tumor progression and tumor angiogenesis and lymphangiogenesis in mice bearing BxPC3 Pancreas cancer xenografts



ANTITUMOR ACTIVITY OF THE EPHRINB2 ON COLON CANCER (SW620)

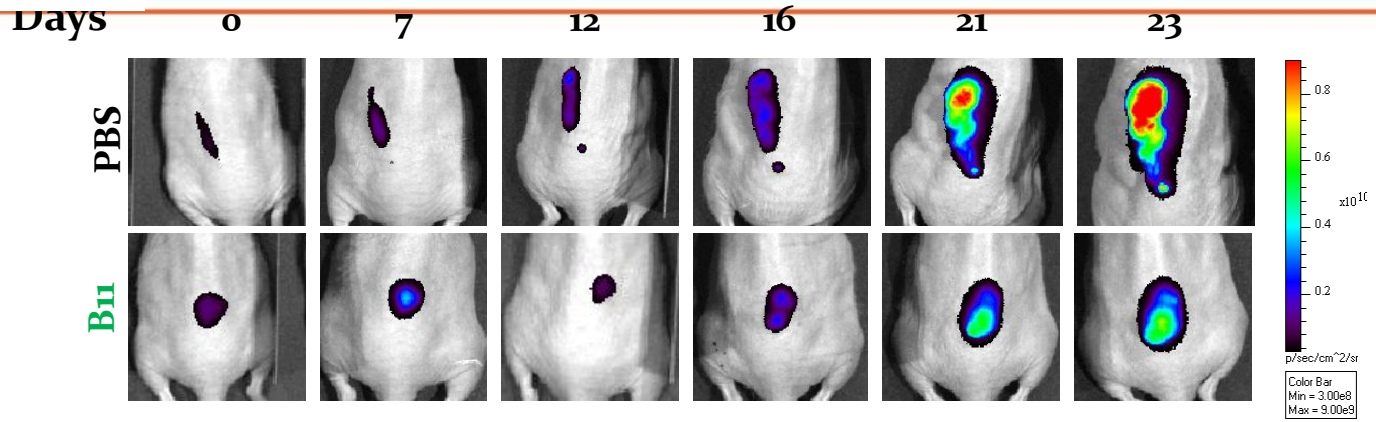


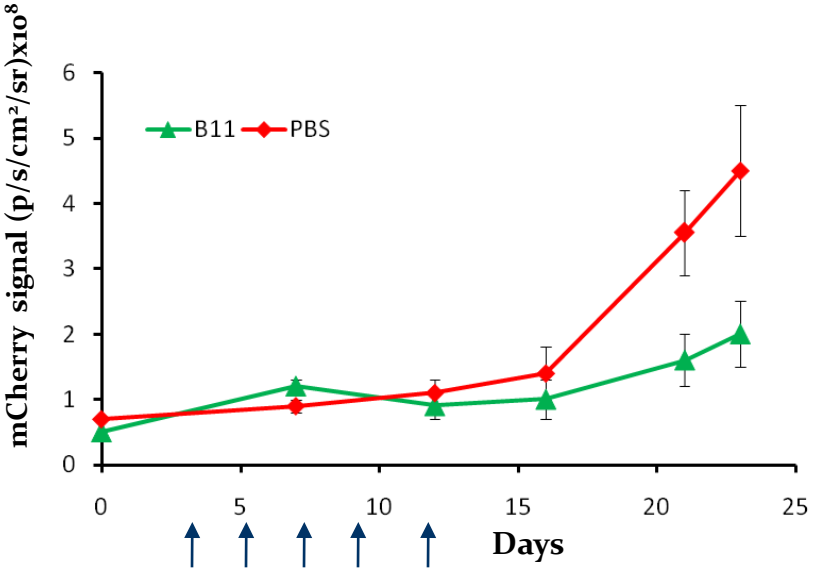


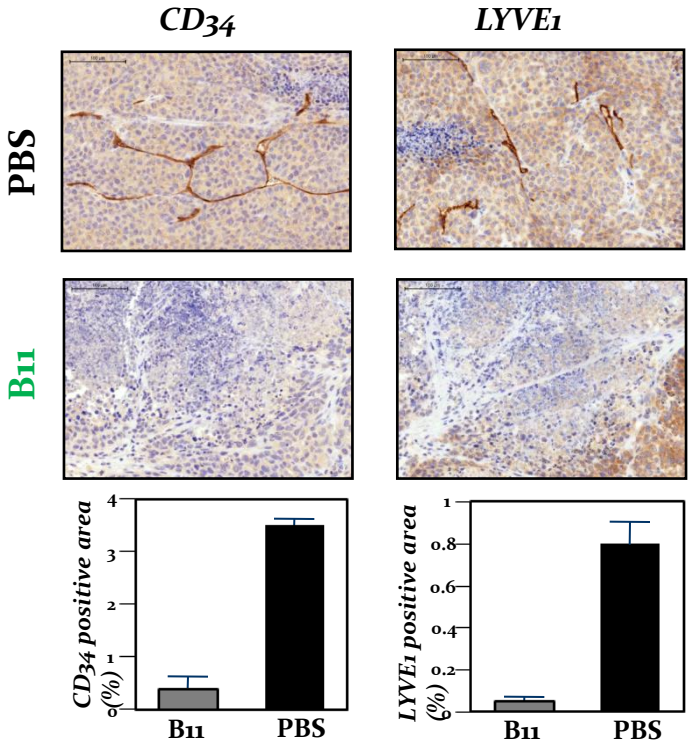


B11 inhibited tumor progression and tumor angiogenesis and lymphangiogenesis in mice bearing SW620 colon cancer xenografts

ANTITUMOR ACTIVITY OF THE EPHRINB2 ON LUNG CANCER (H460)



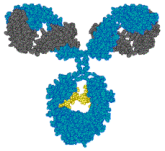




B11 inhibited tumor growth and tumor angiogenesis and lymphangiogenesis in H460 lung cancer xenografts

Innovative Product

Anti-Ephrin B2



Inhibition of angiogenesis

High affinity and specificity

Both *in vitro* and *in vivo* (scFV conformation).

Efficient, a priori, in any tumour

The angiogenic process is universal

Low immunogenicity

Complete IgG

High lifetime

Complete IgG

R&D and IPR

Blocking ephrinB2 with highly specific antibodies inhibits angiogenesis, lymphangiogenesis, and tumor growth

María Angeles Abéngozar,[1] Sergio de Frutos,[2] Sergio Ferreiro,[3] Joaquín Soriano,[4] Manuel Perez-Martinez,[4] David Olmeda,[5] Marco Marenchino,[6] Marta Cañamero,[7] Sagrario Ortega,[5] Diego Megías,[4] Antonio Rodríguez,[2] and Jorge L. Martínez-Torrecuadrada[1]

Patent ANTIBODY AGAINST EPHRIN B2 AND USE

Priority: 21 Sept 2010 (ES1599.10, PCT1599.10)
Applicant: Centro Nacional Investigaciones Oncologicas
International Searching Office: European Patent Office
License: Exclusive for Bioncotech (July 2012)
Major Claims Protects the use of antibodies targeting EphrinB2
Positive IPER from EPO

Pitfalls & Risks

Attribute	Base case	Risks
Compound	**First in kind human single chain (scFv) antibody fragments against ephrinB2 + Backup**	
Indication (*in vitro*)	Impaired migration, tubule formation and invasion of endothelial (HUVEC) cells *in vitro*	Different in vivo (humans)
Indication (*in vivo* probe)	Inhibition tumour growth of pancreatic, colon,melanoma and lung cancer and other potential tumours	No effect in vivo (humans
Safety	No toxicity evidence *in vitro*	
	No toxicity evidence *in vivo*	Toxicity in humans
Drugability	IgG	No posible to get full IgG for therapeutic use
Patent Expiry	2030	

EphrinB2 Platform

COMPLETE IgG GENERATION

Biochemical and functional characterization

Validation (*in vivo*)

CLINICAL DEVELOPMENT IgG ANTIEPHRIN B2

Melanoma

Pancreatic cancer

Lung cancer

Colon cancer

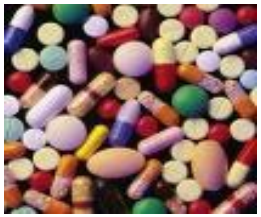
PIPELINE

Reformulation

NME

Collaboration: CNIO

COMBINATIONS



Combination with existing antiangiogenic treatments: anti-VEGF (Avastin)

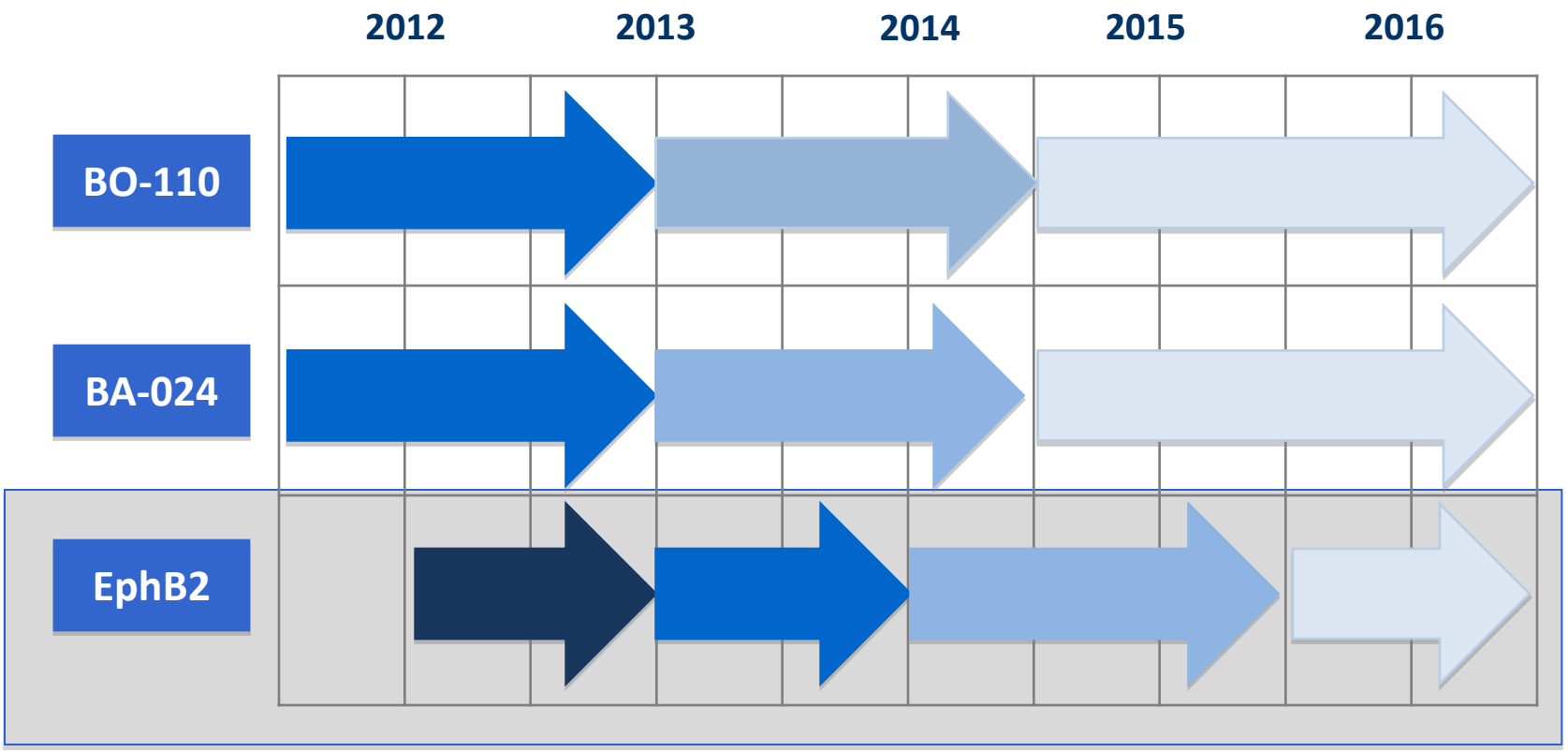
Milestones:

2012 – Complete IgG antiephrin B2 Production

2013 – Regulatory Preclinical Studies

2014 – Phase I Clinical Studies

Milestones


2012
2013
2014
2015
2016
BO-110
BA-024
EphB2
Development lead & Manuf
Preclinical
Phase I
Phase II

3. Partnering opportunities

Co-development

Out-License

BiOncoTech Therapeutics

INNOVATION FOR HEALTH SOLUTIONS

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