Efficacy of P17, a TGFbeta1 inhibitor peptide, in lung fibrosis and melanoma

DIGNA BIOTECH

Zaragoza, 6 de junio de 2012

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1. The Company (DIGNA) and the research institution (CIMA)

DIGNA BIOTECH

Development and licensing

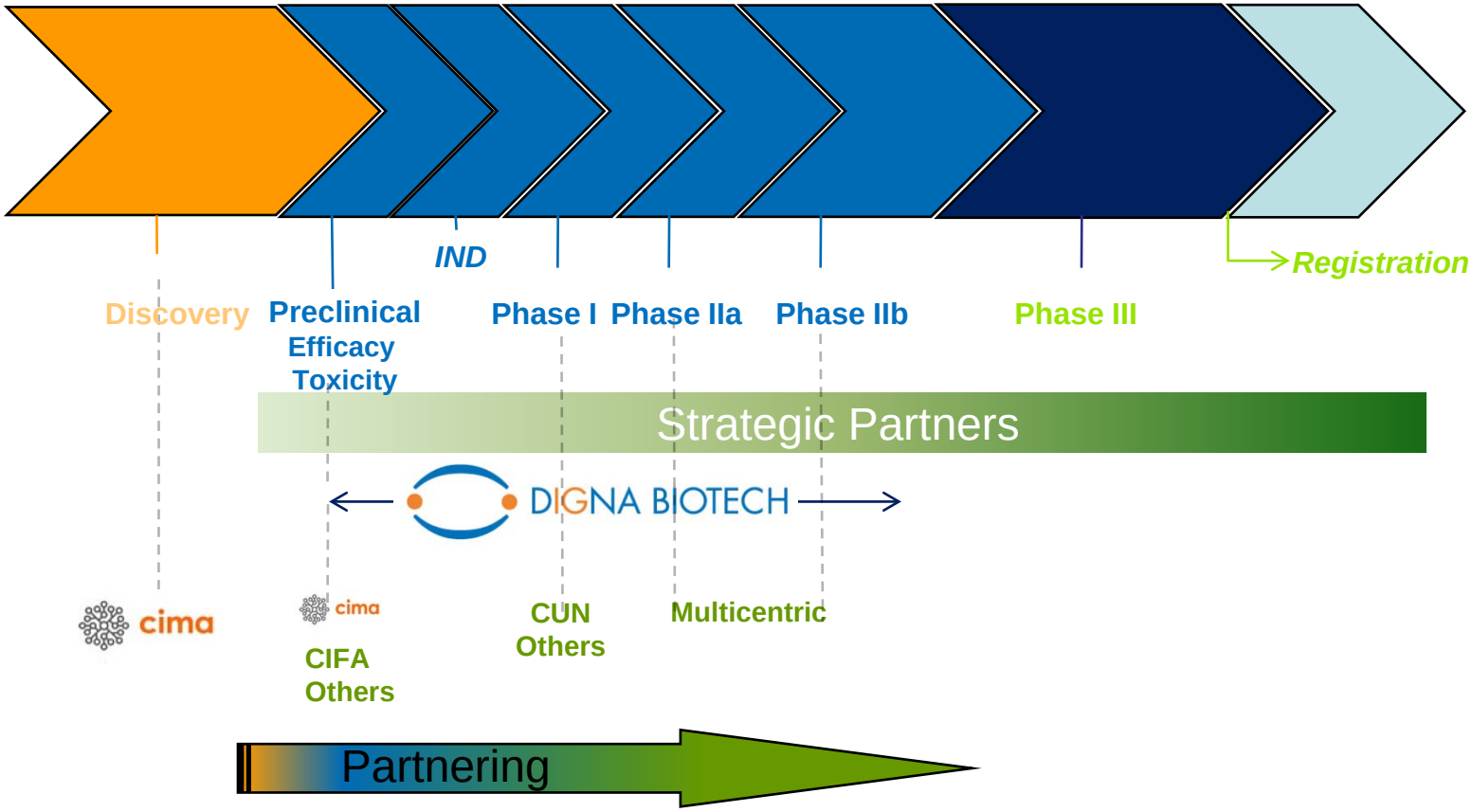
IP

Traslacional research: oncology, cardiology, CNS, hepatology and gene therapy

University of Navarra

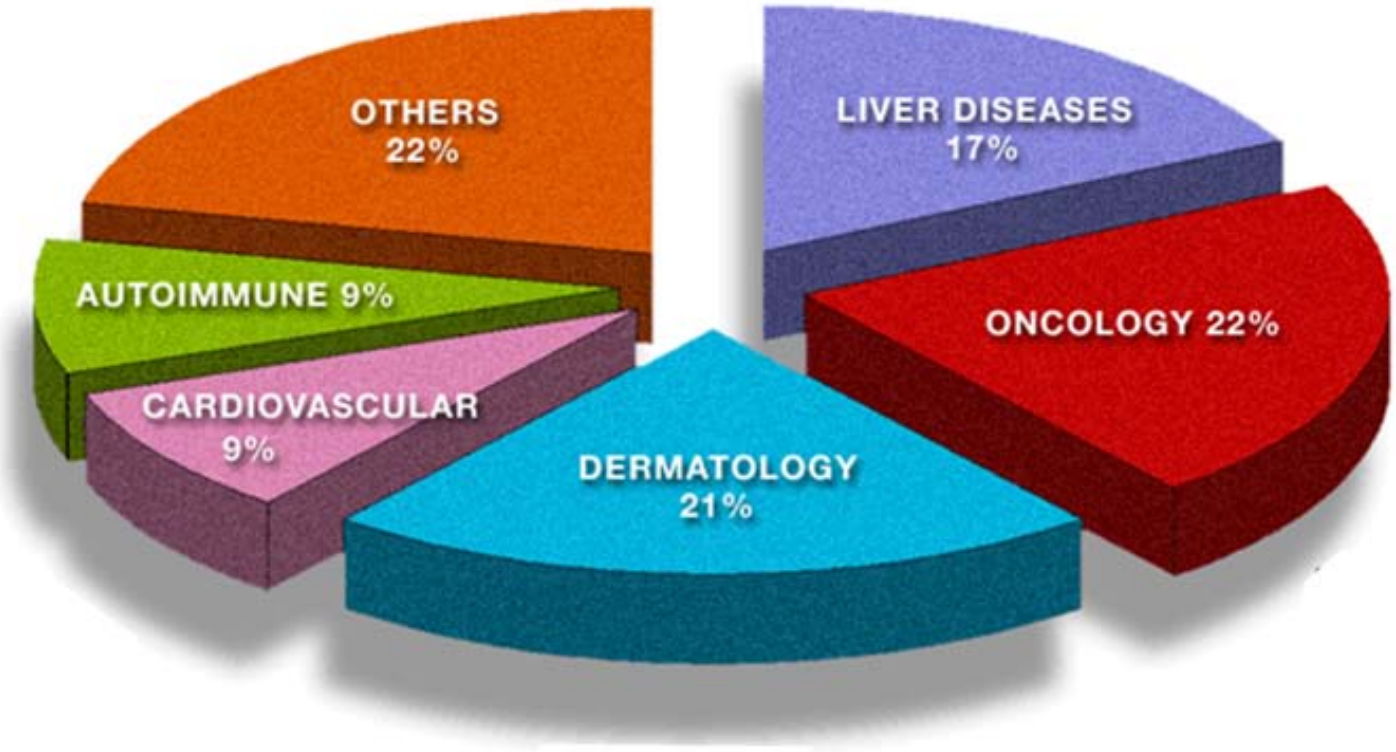
DIGNA: VALUE PROPOSITON

DIGNA leverages world-class scientific and clinical expertise to turn early-stage medical innovations into clinical-stage partnering candidates for further development and subsequent commercialization



DIGNA: POST-PoC THERAPEUTIC PIPELINE: MARKETS

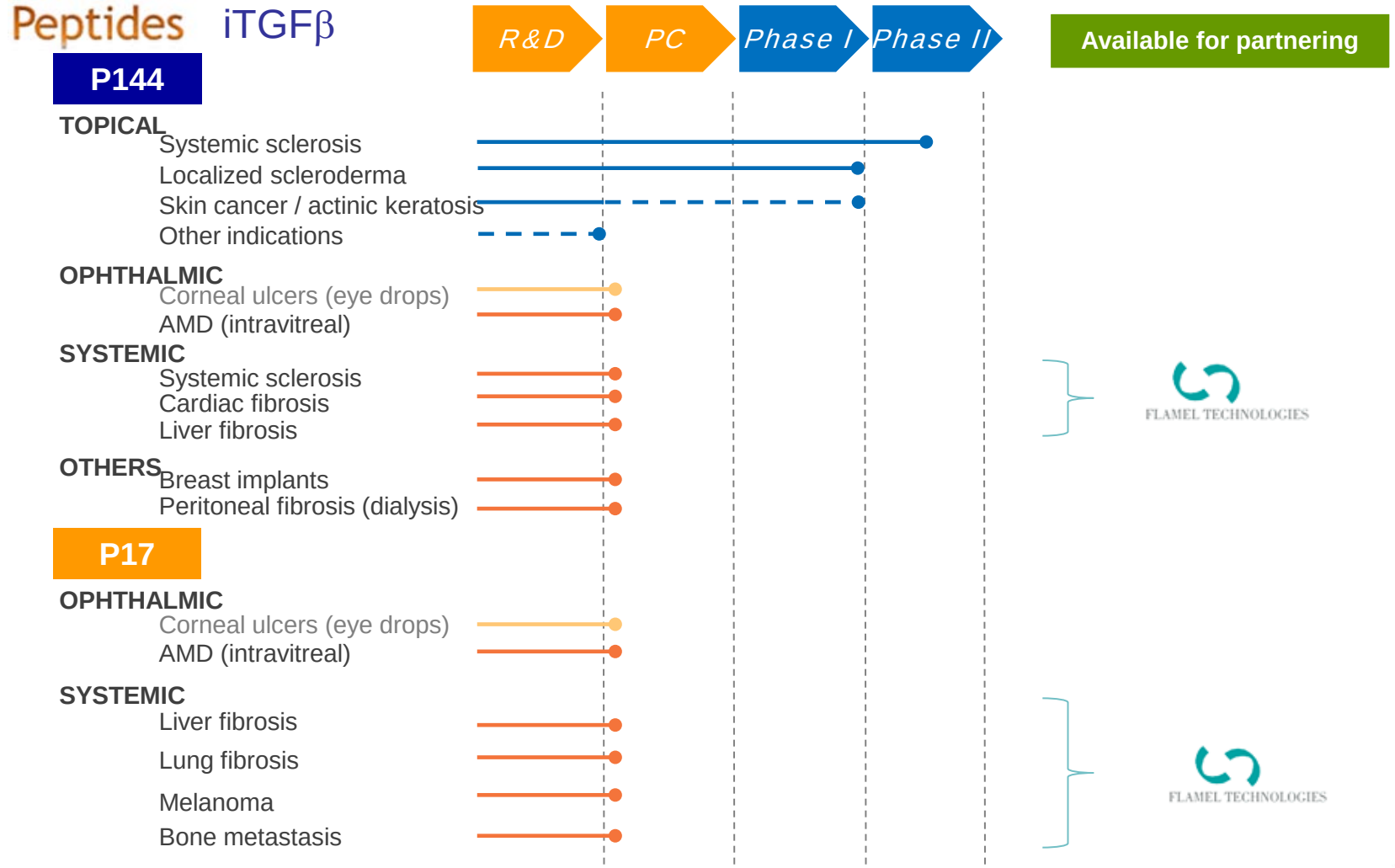
- 5 clinical products
- 20+ out-licensing opportunities



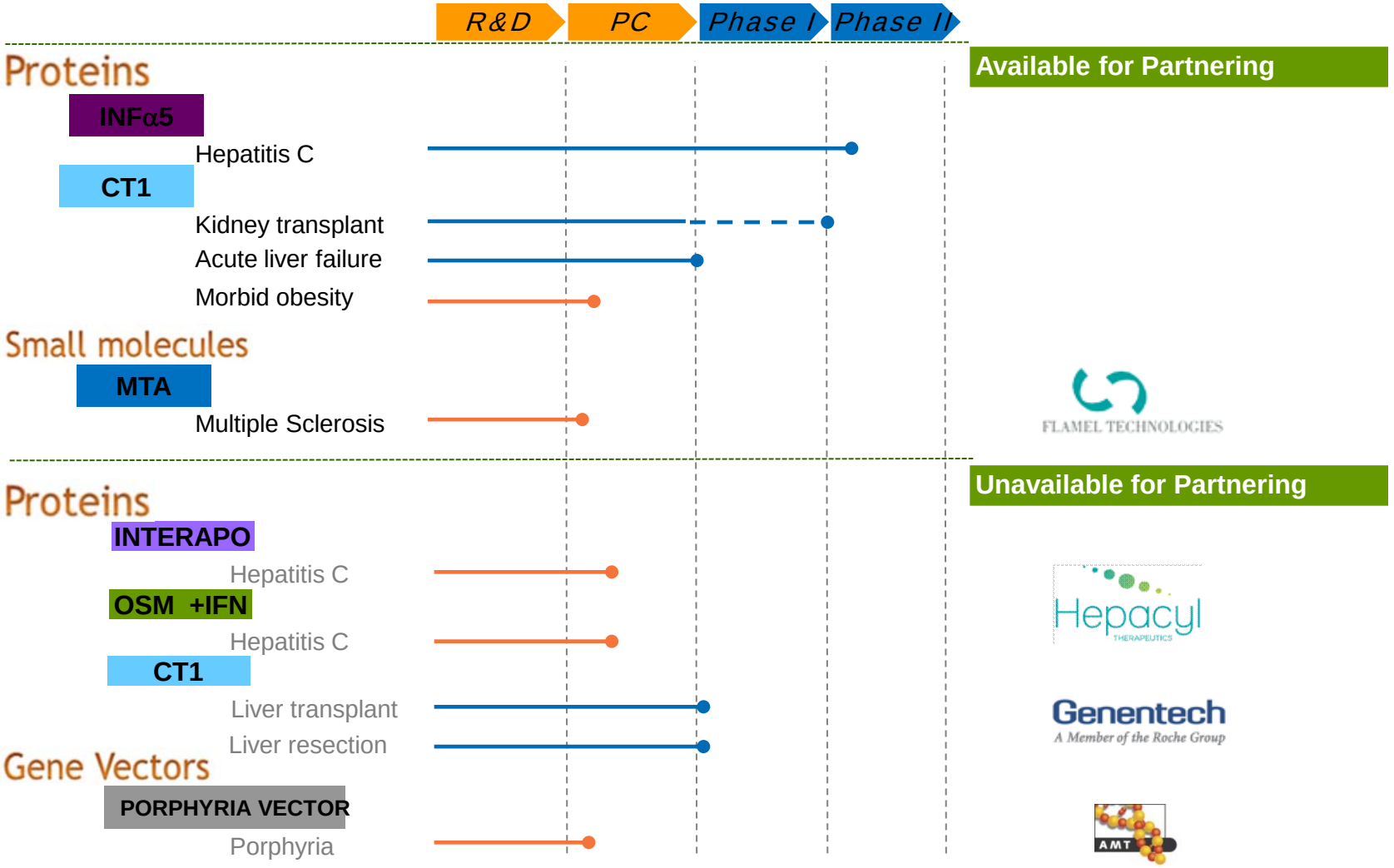
DIGNA: *PRODUCTS*

- DIGNA BIOTECH offers therapeutic product candidates from PC to phases I/II to enhance medium and big pharma pipelines.
- Barrier to entry lowered by Orphan Drug potential
- Our product candidates arise from careful selection, are validated *in vitro* and *in vivo,* and backed by robust preclinical and clinical data.

DIGNA: PRODUCTS



DIGNA: *PRODUCTS*



DIGNA: *MILESTONES*

- **Creation of DIGNA-US 2Q 2012.**
- **Negotiate and execute licensing agreements for key products 4Q 2012**
- **Reach the clinical milestones of our currently pursued co-development projects**

Licensees & Co-development Partners	Exclusivity	Subject Matter
UNIQURE — AAV Production + Commercialization	YES	AAV
Genentech — 1st option + Commercialization	YES	CT-1 liver surgery & transplant
FLAMEL TECHNOLOGIES — Drug Delivery + Co-development	NO	P144 & p17
FLAMEL TECHNOLOGIES — Drug Delivery + Co-development	NO	MTA
Hepacyl THERAPEUTICS — Drug Delivery + Co-development	NO	Inter-APO, Oncostatin, p60

GOBIERNO DE ESPAÑA MINISTERIO DE ECONOMÍA Y COMPETITIVIDAD

MEDICAMENTOS INNOVADORES
Plataforma Tecnológica Española

DIGNA BIOTECH

farmaindustria

1. The Product

a) Target indications
b) Innovative mechanisms of action
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e) IPR protection
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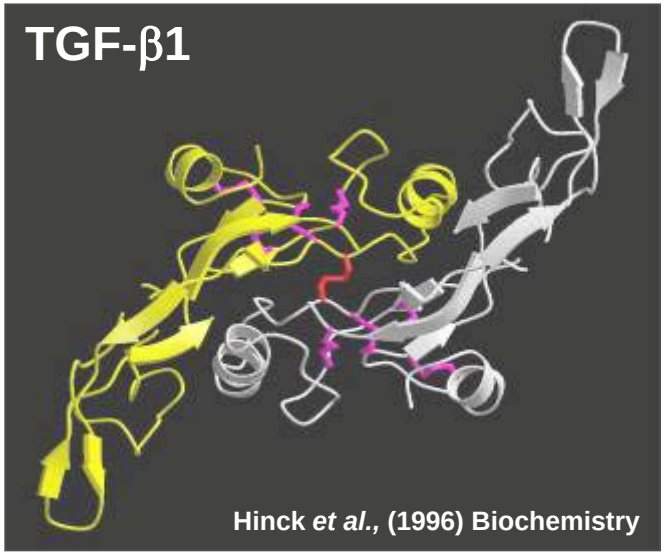
Target indications: Lung Fibrosis and Melanoma

P17 ⟶ TGFβ

Homodimer of 25 KDa made up of 2 subunits (112 aa) linked by a disulphide bridge



Pleiotropic cytokine implicated in different biological processes and pathologies:

Cell proliferation
Embryonic development
Fibrosis → **LUNG FIBROSIS**
Immuno-modulation
Angiogenesis
Tumor progression → **MELANOMA**
Metastasis

Innovative mechanisms of action: Lung Fibrosis

Lung Fibrosis

- **Idiopathic pulmonary fibrosis (IPF) is defined as a specific form of chronic, progressive fibrosing interstitial pneumonia of unknown cause, primarily occurring in older adults, limited to the lungs, and associated with the histopathologic and/or radiologic pattern of usual interstitial pneumonia (UIP).**
  - **Worldwide, the incidence of idiopathic pulmonary fibrosis is estimated to be 10.7 cases per 100,000 person-years for males and 7.4 cases per 100,000 person years for females. The prevalence of idiopathic pulmonary fibrosis is estimated to be 20 cases per 100,000 persons for males and 13 cases per 100,000 persons for females**
  - **Idiopathic pulmonary fibrosis portends a poor prognosis, with an estimated mean survival of 2-5 years from the time of diagnosis. Estimated mortality rates are 64.3 deaths per million in men and 58.4 deaths per million in women.**

- **The previous theory regarding the pathogenesis of idiopathic pulmonary fibrosis was that generalized inflammation progressed to widespread parenchymal fibrosis. Based on this pathogenetic concept, anti-inflammatory agents and immune modulators were used to treat idiopathic pulmonary fibrosis (IPF). However, it is currently believed that idiopathic pulmonary fibrosis is an epithelial-fibroblastic disease, in which unknown endogenous or environmental stimuli disrupt the homeostasis of alveolar epithelial cells, resulting in diffuse epithelial cell activation and aberrant epithelial cell repair.**

  Antioxidants (NAC) + azathioprine

  rTNFR (Etanercept), IFNγ

  Endothelin-1R antagonist (Bosentan)

  Tyrosine Kinase inhibitor (Imatinib)

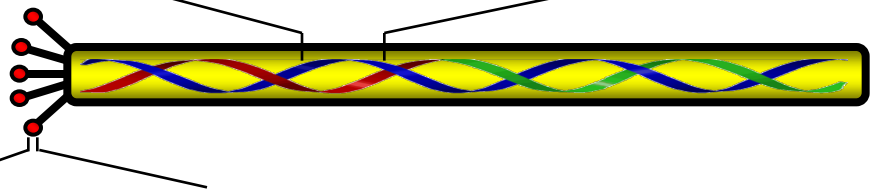
  Pirfenidone (antifibrotic) FDA aproval 2012

TGFβ is the major risk factor associated with lung fibrosis

P17 efficacy in lung fibrosis

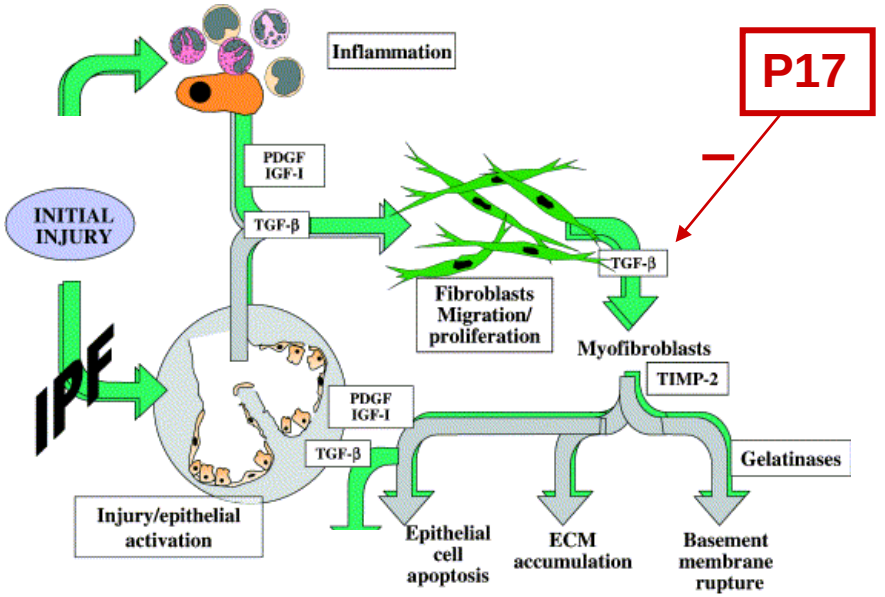
(Foreign sequence inserted into pIII gen)

5´-GCC GAC GGG GCT $(NNK)_{15}$GGG GCC GCT CCC GCC-3´

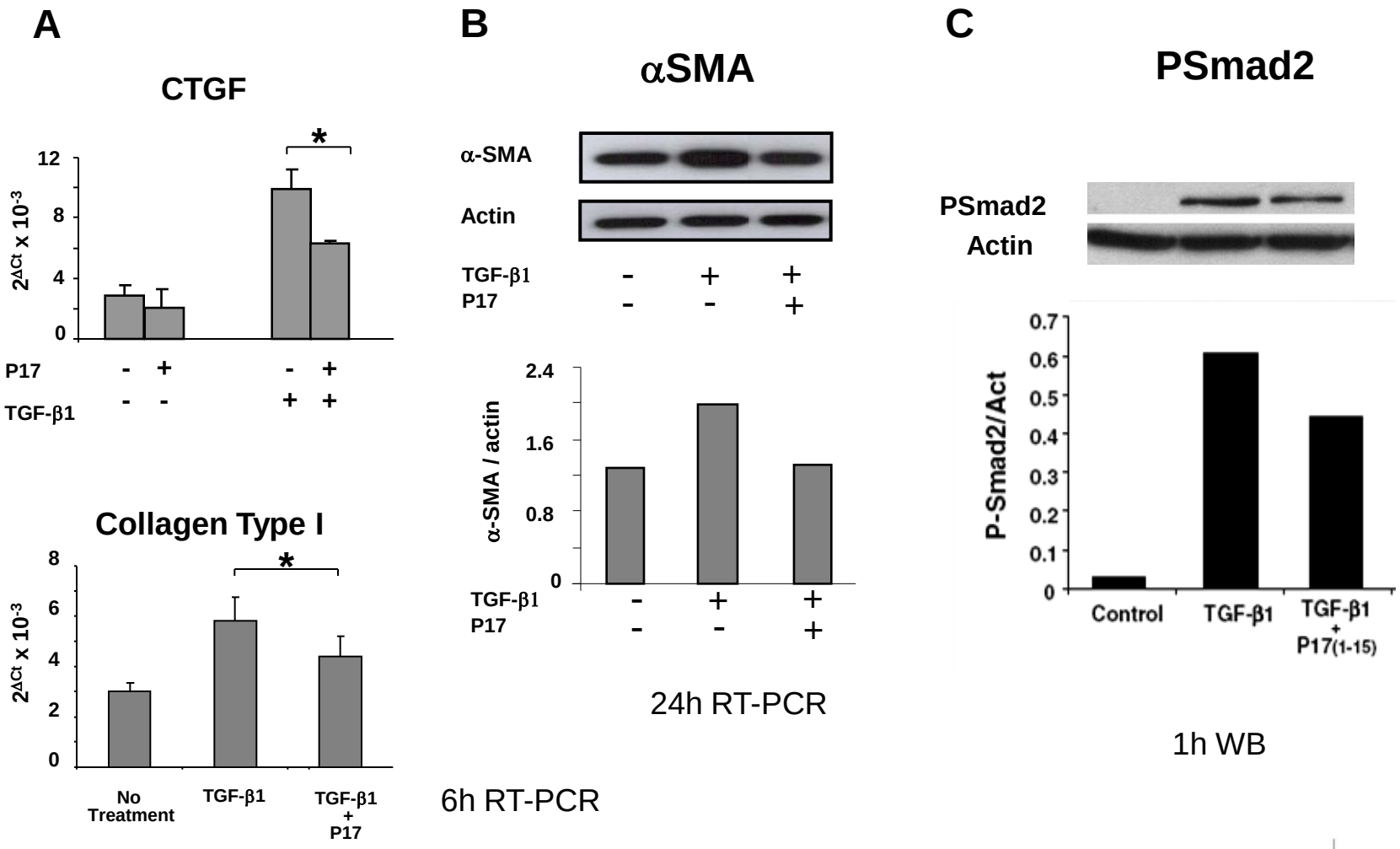


NH_2-ADG-X_{15}-GAAGA-pIII coat protein

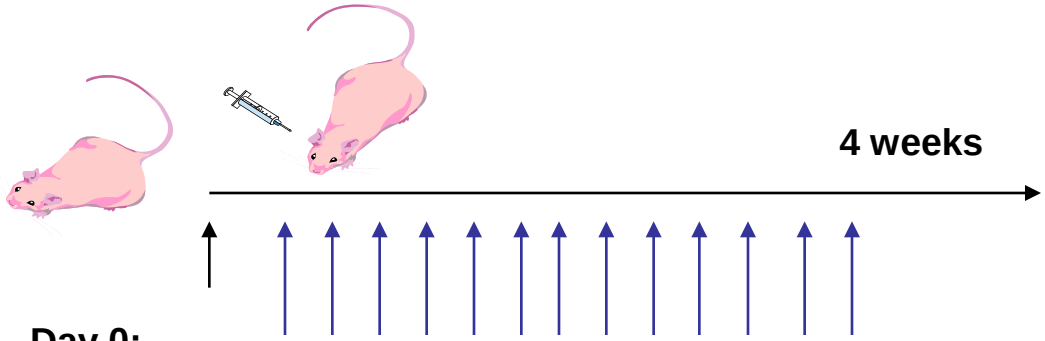
Antifibrotic effect in liver fibrosis



P17 efficacy in lung fibrosis: P17 inhibits CTGF, Collagen Type I, aSMA and PSmad2 expression induced by TGBb in IMR90 human lung fibroblasts



P17 efficacy in lung fibrosis (Model of lung fibrosis in mice induced by Bleomycin)



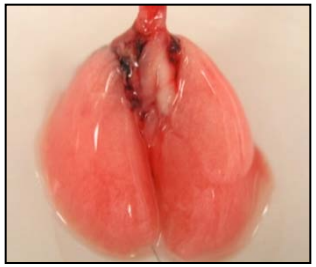
4 weeks

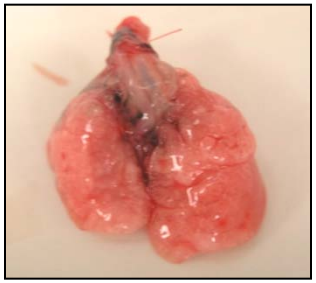
Animals were sacrificed to determine the fibrotic damage in the lungs by histological analysis

Day 0:
Bleomycin 0.08U
200 μl

Day 2:
Peptide treatment (3 i.p. administrations per week) for 4 weeks with :

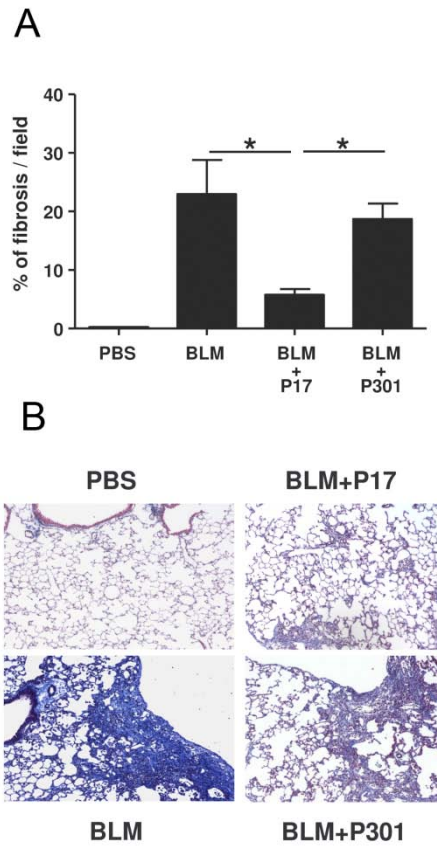
P17 (75 μg)
P301 (control peptide, 75 μg)



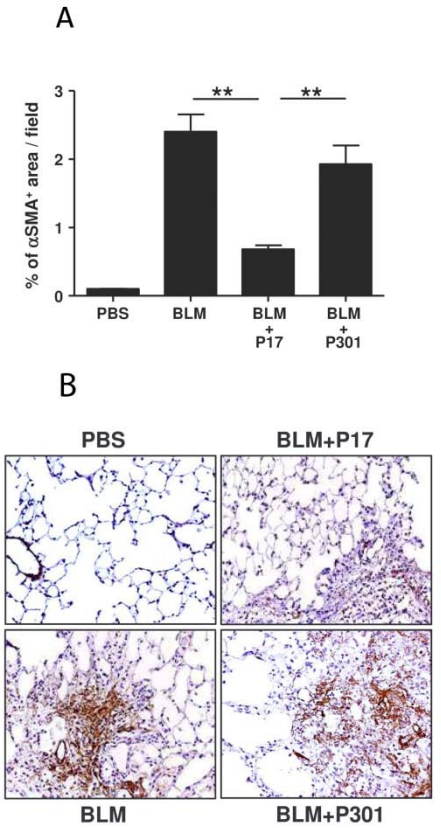


Lung fibrosis was induced by bleomycin (an antibiotic with an antineoplastic effect which has been used in the treatment of some carcinomas and lymphomas and its administration has a toxic effect in the lung in a 3-5% of the patients.
P17 and a control peptide P301 were administrated ip every 2 days and after 4 weeks animals were sacrificed to determine the lung damage

P17 efficacy in lung fibrosis

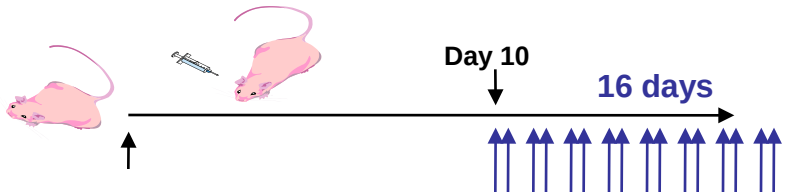


Collagen reduction



αSMA reduction

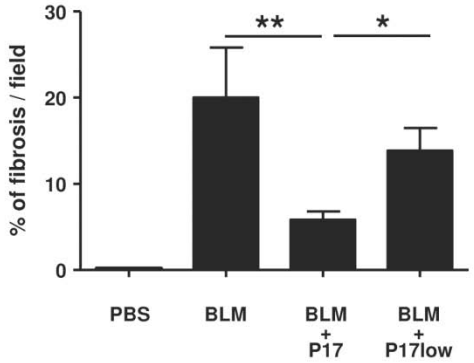
Therapeutic effect of P17 in lung fibrosis



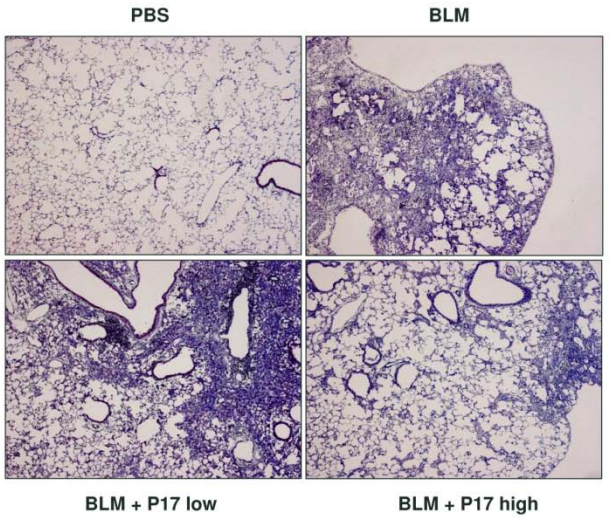
Day 0:
Bleomycin 0.08U
200 µl

Day 10:
Peptide treatment: 16 daily doses
P17 (75 µg and 25 µg)
P301 (control peptide, 75 µg)

A

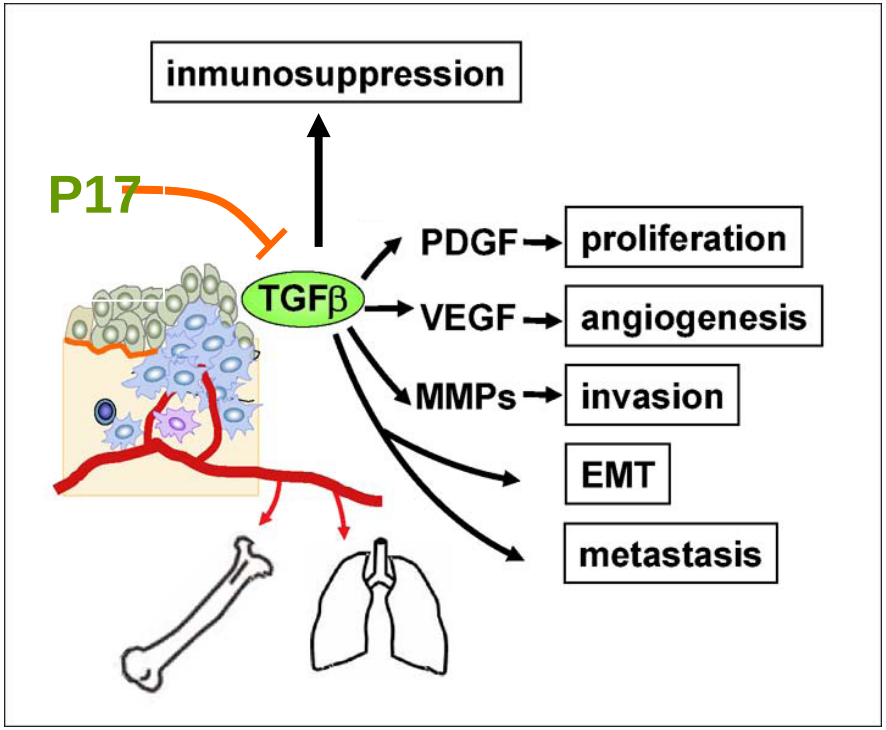


B



Collagen reduction

Innovative mechanisms of action: Melanoma

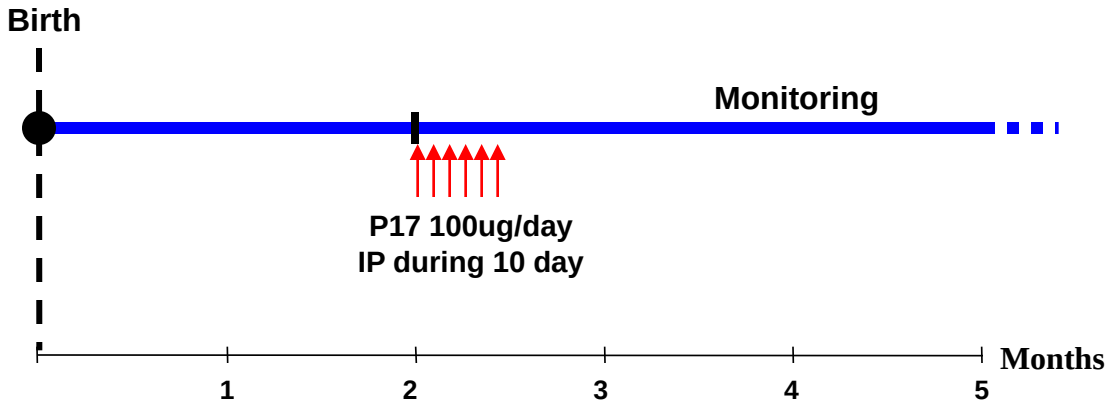


Melanoma

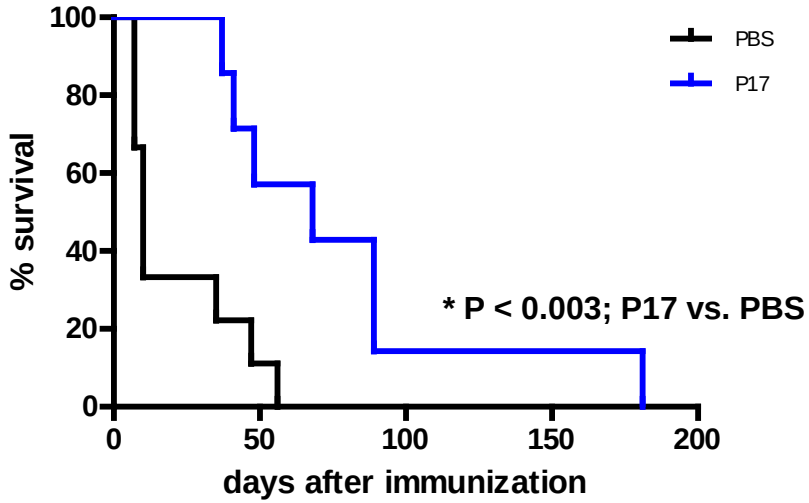
- Melanoma is a common cancer of the skin. Melanoma, also known as malignant melanoma, is the most deadly type of skin cancer because it can spread quickly (metastasize) to other organs of the body. The incidence of melanoma is growing faster than any other type of cancer, primarily because of the popularity of sunbathing and the use of tanning beds.
- At current rates, 1 in 63 Americans will develop an invasive melanoma over a lifetime.
- Determining melanoma stage is important for planning appropriate treatment and assessing prognosis. (Stages I and II, surgery) (Stages IV chemotherapy/radiotherapy).

TGFβ is one of the main risk factors associated with melanoma progression

Antitumor effect of p17 in ret transgenic tumor bearing mice in vivo



Viktor Umanski
German Cancer Research Institute (Heidelberg)



Effects of P17 on the melanoma growth using a ret transgenic melanoma mouse model. This transgenic mouse model resembles human melanoma with respect to tumor genetics, histopathology and clinical development.

P17 injections into melanoma bearing mice resulted in the prolongation of mouse survival.

Differential features facing the market: Advantages of P17 treatment

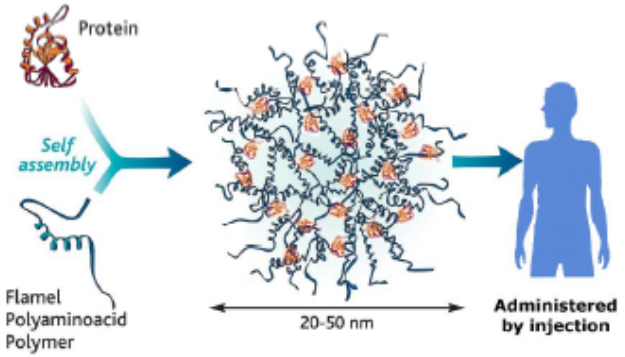
- Antifibrotic effect (Fibrosis attenuation)
- Inhibits tumor progression (Increase of survival in mice which develop spontaneously melanoma)
- No detection of an immune response (Abs) in mice treated with P17. Nor or poor immune response expected in patients.

Current status of development: P17 systemic development with Flamel

API	• **GMP manufacturing by EU supplier with European and US facilities** • **GMP/GLP Stability data:** - Stable for 24 months at -135 ºC - Stable under Argon at 5 ºC ± 3 up to 42 months
Formulations	• **Preliminary Ophthalmic formulation** • **Systemic formulation development**
Pharmacokinetic Studies	• **Pharmacokinetic study after IV and SC administration in rats: 7.5 mg/kg.** - CMax 80.6 mg/ml - Half life: 25 seconds - Clearance: 0.618 ml/sec - Distribution volume: 22.5 ml
Toxicity Studies	• **Systemic single dose** - i.v. acute tox in wistar rats: LD50 at 27.5 mg/kg. Histology - sc acute tox in wistar rats: LD50 >2000 mg/kg. Histology - i.v acute tox in rabbits: LD50 at 55 mg/kg. Histology - sc acute tox in rabbits: LD50 >2000 mg/kg. Histology • **Repeat dose toxicity** - Preliminary, non-GLP, 14 days IM in rats: 250-500 mg/kg. Only muscle histology. No macroscopic alterations in any tissue • **Genotoxicity** - Ames test - In vitro chromosome aberration test • **Local tolerance** - sc in rats: 7.5 mg/kg - sc in rabbits: 7.5 mg/kg

Current status of development: P17 systemic development with Flamel

- MEDUSA polymer is made of glutamic acid and Vitamin E
- The polymer is amphiphilic and spontaneously forms stable nanoparticles in water
- Complexes are robust over a wide range of pH values and can be stored as either stable liquid or stable dry forms that can be easily reconstituted in water

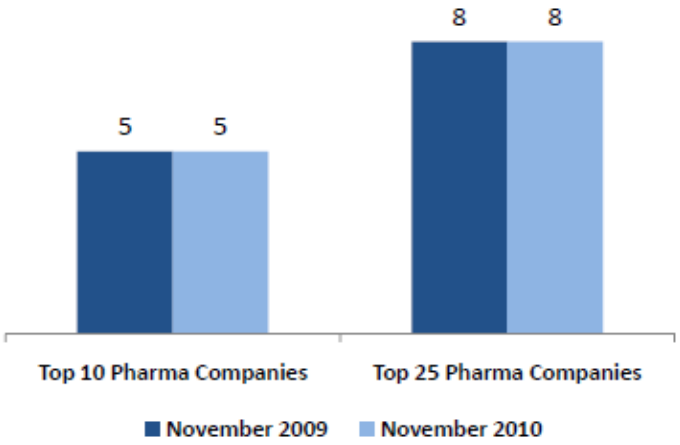


Current status of development: P17 systemic development with Flamel

FLAMEL TECHNOLOGIES

- Flamel works with leading companies to provide the best drug delivery solutions to improve existing products and bringing new products to market
- We currently work with 8 of the top 25 pharmaceutical companies in the world
- Leverage partner's expertise to develop our platforms
- Total up-front, milestones, and technology access fees received in 2009: $15.7 million

Baxter · GlaxoSmithKline · MERCK SERONO · Pfizer



IPR protection

REFERENCE: 2002007 iTGFb1 II
PRIORITY: ES 200302020; 22/08/2003
TITLE: Peptides which can bind to transforming growth factor Beta 1 (TGF-Beta1)

REFERENCE: 2005030 iTGFb1 INMUN
PRIORITY: PCT/ES2005/000569; 24/10/2005
TITLE: Use of TGF-beta 1 inhibitor peptides in the preparation of an immune response modulating agent

A new patent with the Flamel Technology will be filled after PK data is available

Pitfalls & Risks to be considered

- The TGF signaling pathway has been shown to regulate such diverse processes as cell proliferation, differentiation, motility, adhesion, organization, and programmed cell death.
- No clinical validation of TGF beta inhibition in the systemic treatment of pulmonary fibrosis.
- Peptide with a PK/PD dissociation
- Strong competition in cancer

3.- Partnering Opportunities

Licensing / co-development till Phase II (PoC)

and looking for a world partner if PoC is positive