EDAHPVE7 as a therapeutic vaccine against cervix carcinoma

DIGNA BIOTECH

Zaragoza, 6 de junio de 2012

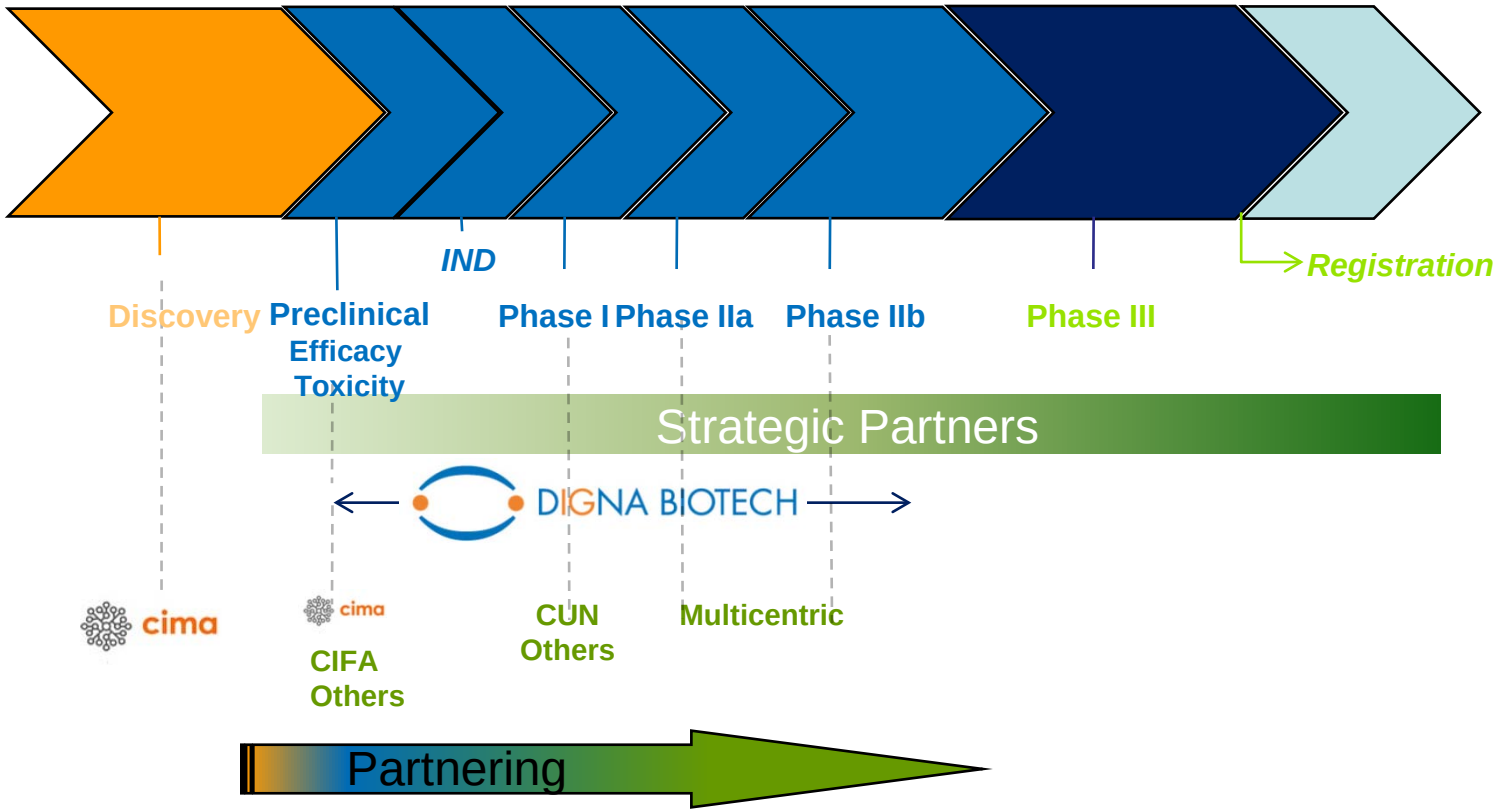
Content

1. **The Company** (DIGNA) **and the research institution** (CIMA)
2. **The Product**
   a) Target indications
   b) Innovative mechanisms of action
   c) Differential features facing the market
   d) Current status of development
   e) IPR protection
   f) Pitfalls & Risks to be considered
3. **Partnering Opportunities**

1.The Company

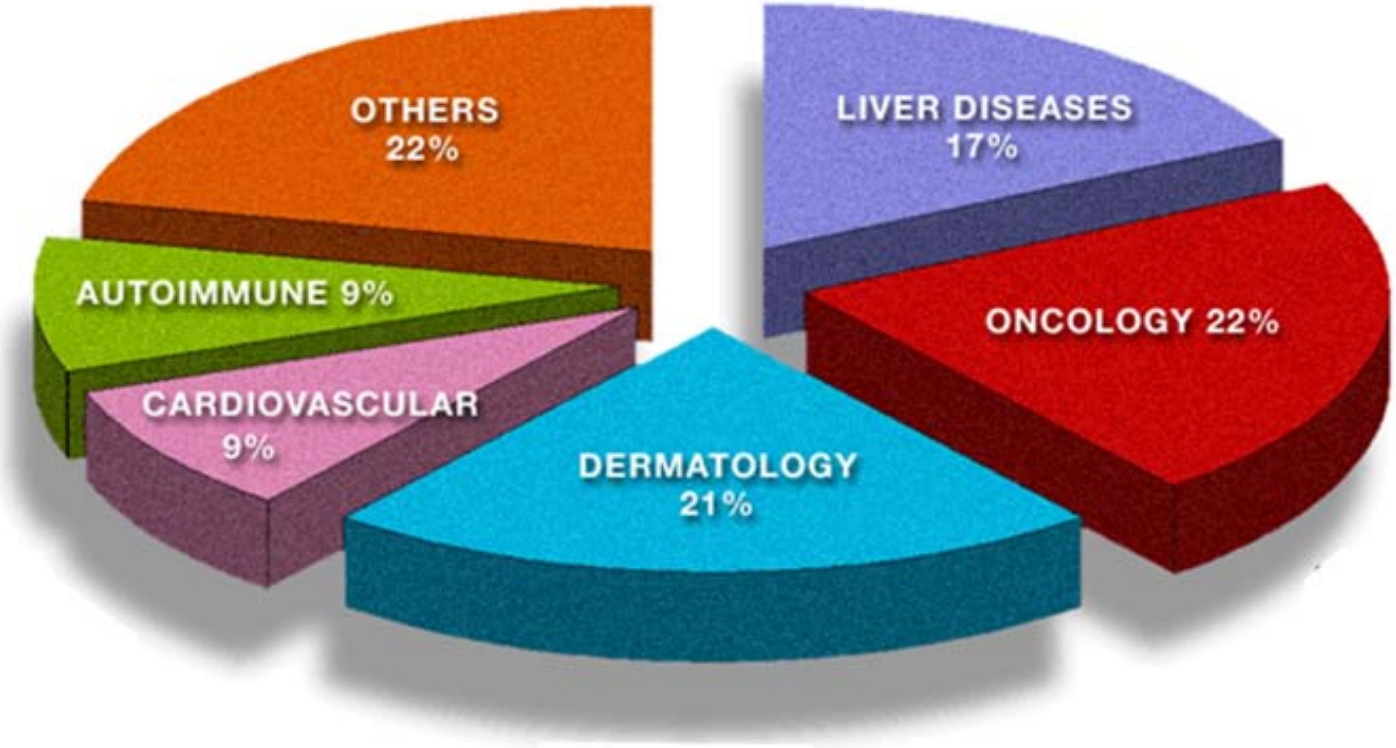
Value proposition

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



Post-PoC Therapeutic pipeline: Markets

- 5 clinical products
- 20+ out-licensing opportunities
- Over 20 different indications



Products

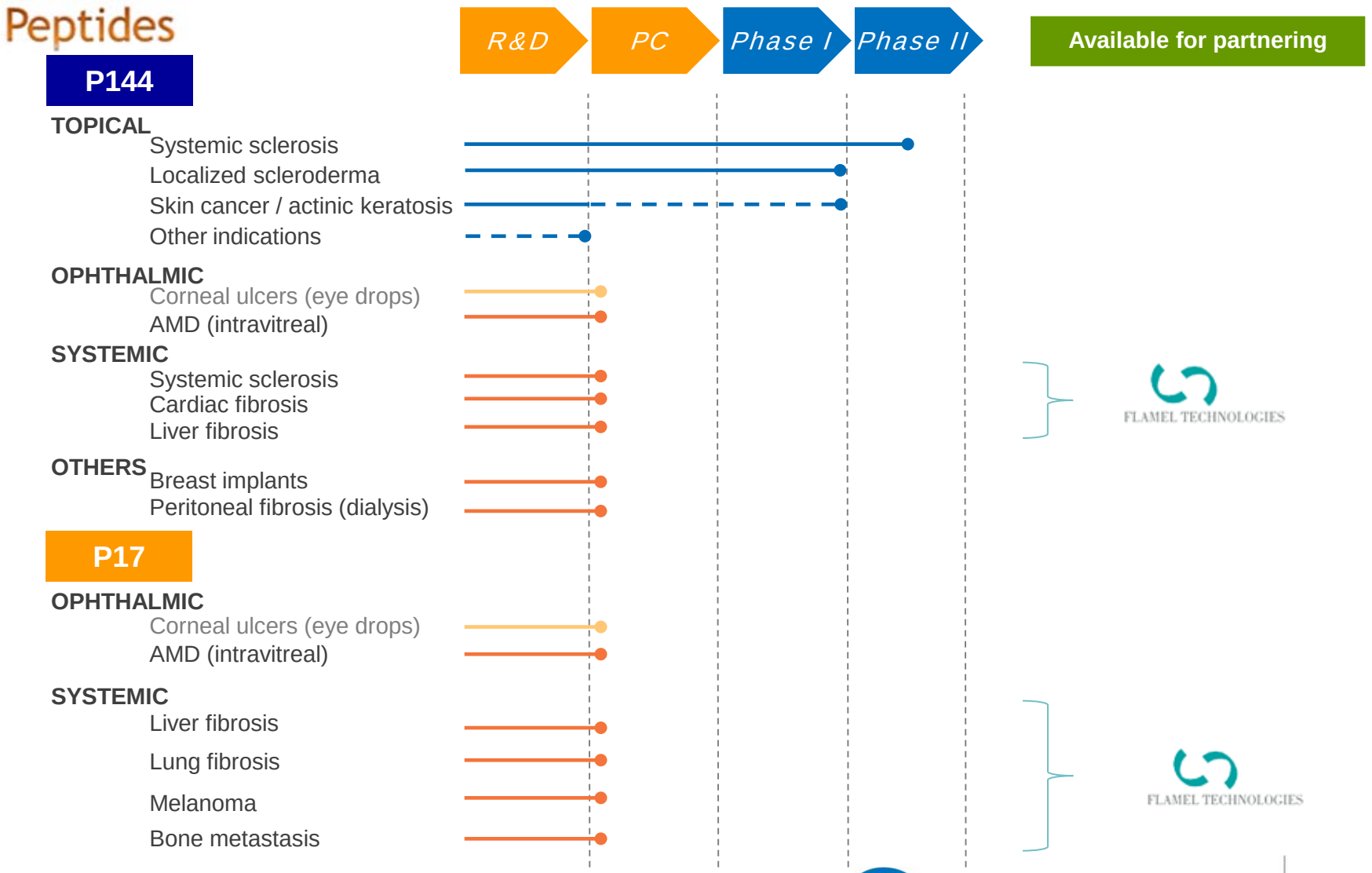
- DIGNA BIOTECH offers therapeutic product candidates from PoC to phases I/II to enhance medium and big pharma pipelines.
- Barrier to entry lowered by Orphan Drug potential
- Our product candidates arise from careful selection, are validated *in vitro* and *in vivo,* and backed by robust preclinical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

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

Peptides pipeline



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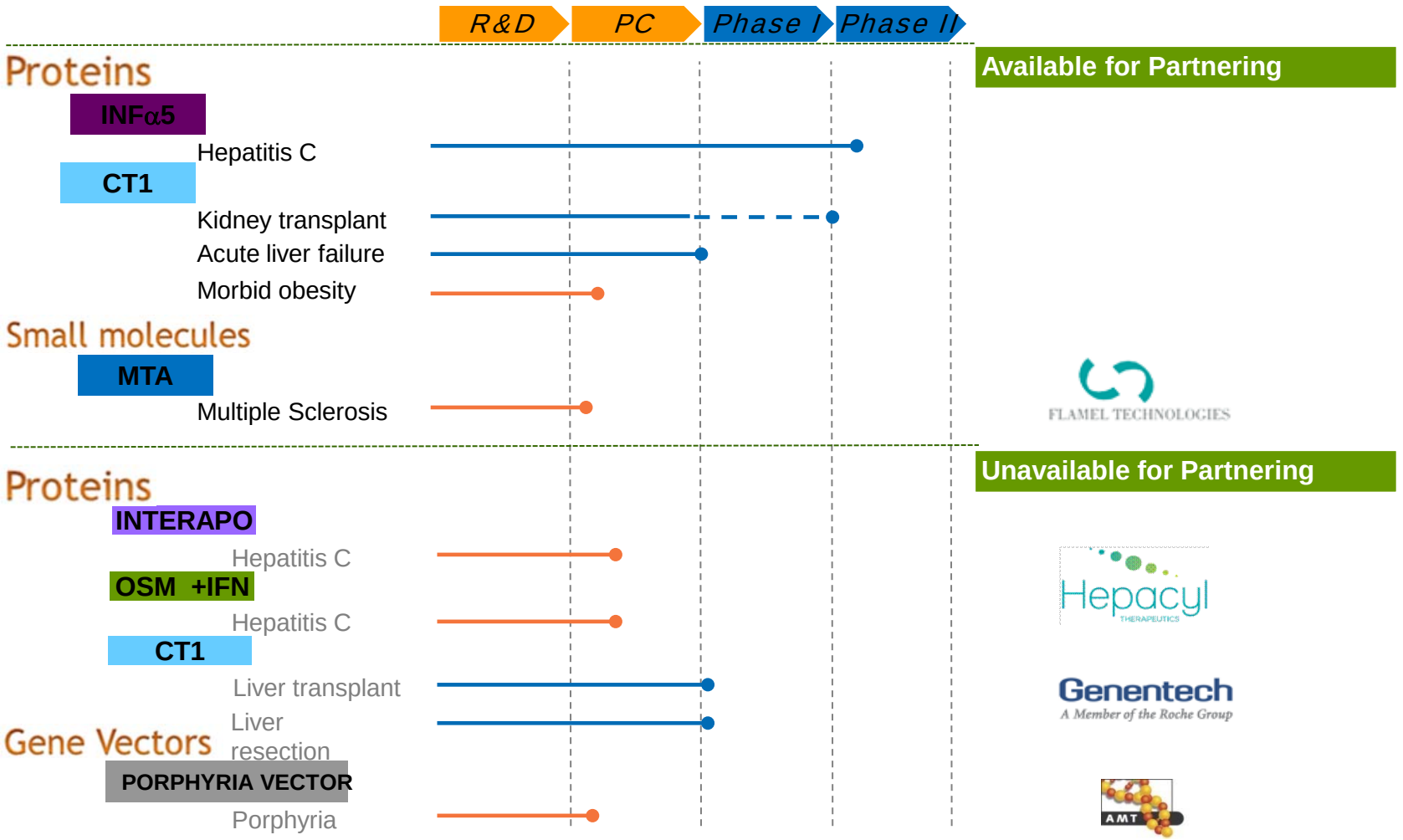
Proteins, Small molecules and gene vectors pipeline



2. The Product

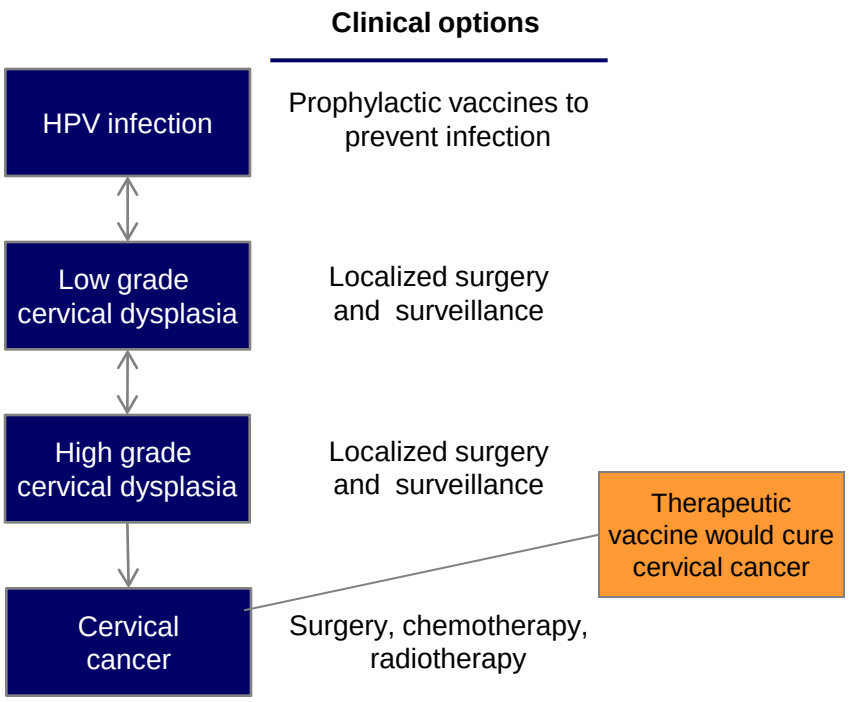
a) Target indications
b) Innovative mechanisms of action
c) Differential features facing the market
d) Current status of development
e) IPR protection
f) Pitfalls & Risks to be considered

Therapeutic focus: Cervical cancer therapeutic vaccine

HPV affects a majority of young women

- **Human Papillomavirus (HPV) is responsible for ~500.000 cervical cancer cases each year**
  - There are 275.000 associated deaths worldwide each year
- **50-80% of sexually active women are infected at least once in their life**
  - Women are usually infected in their 20s and early 30s
  - Cervical cancer occurs most commonly among women in their 40s and 50s
- **Six types of HPV account for about 85% of cervical cancer cases worldwide**
  - Two HPV types, 16 and 18, account for around 70% of cases
- **Currently there are two prophylactic vaccines against HPV, consequently a reduction in the incidence rate of the infection is expected**

HPV infection originates cervical dysplasia, which can result in cancer

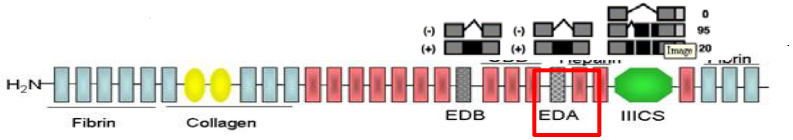


Human papillomavirus (HPV) infection is the major risk factor for the development of cervical cancer

Sources: HPV and Cervical Cancer: Unique challenges and opportunities for disease prevention. July 2005, Path .org;. *Epidemiologic natural history and clinical management of Human Papillomavirus (HPV) Disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model.* BMC Infectious Diseases 2009, 9:119

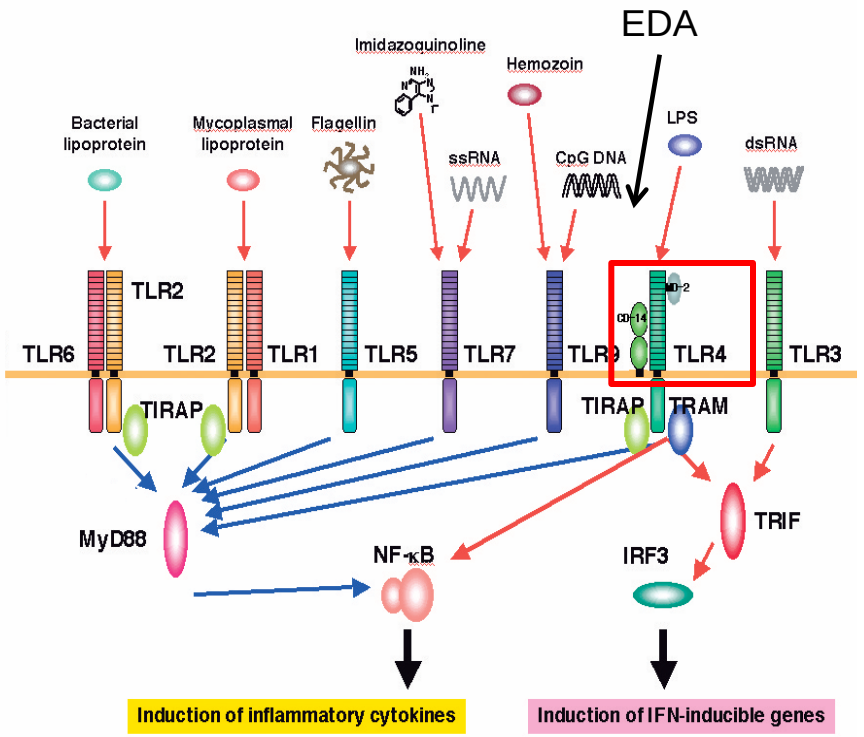
Innovative mechanism of action: EDA signalling pathway

Fibronectin Extra Domain A (EDA)

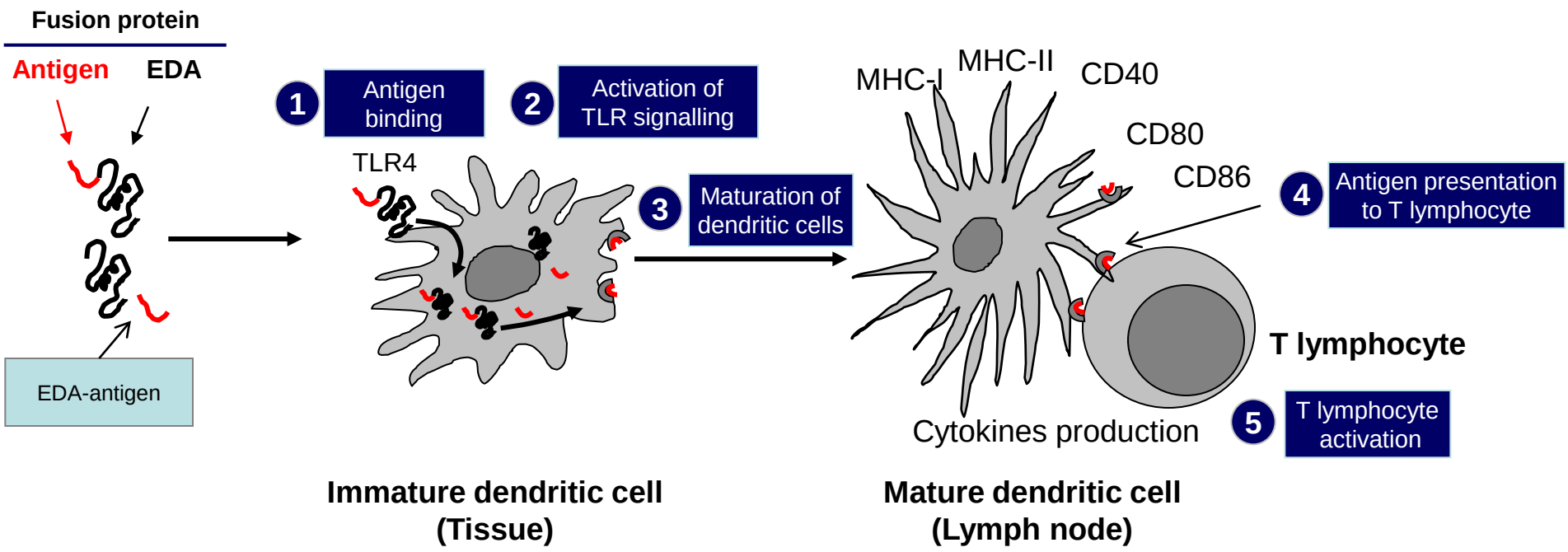


- Fibronectin is a multidomain glycoprotein involved in several cellular processes, including tissue repair, embryogenesis, blood clotting and cell migration/adhesion
- Extra Domain A from fibronectin (EDA) is produced by alternative splicing of fibronectin in response to tissue injury (Rheumatoid arthritis, wound healing, epithelial fibrosis, vascular intimal proliferation, inflammation).
- EDA is related to the immune system:
  - Induces expression of proinflammatory citokines
  - Activates TLR4 signaling.

EDA signaling pathway



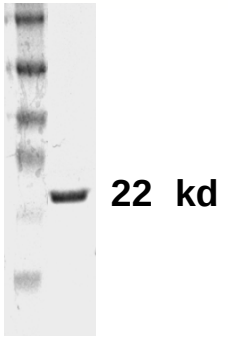
Innovative mechanism of action: Rational



Activation of dendritic cells is a key step in the immune response, because they are key regulators of T and B lymphocytes

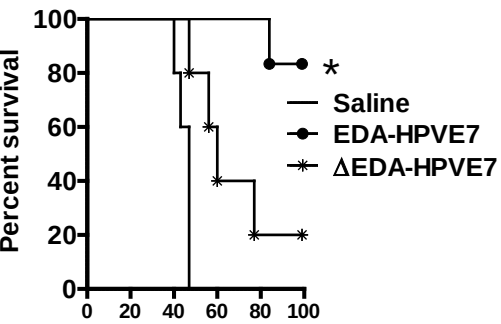
Source: The extra domain A from Fibronectin targets antigens to TLR4-expressing cells and induces cytotoxic T cell responses in vivo, J Immunol, 2007; 178: 748-756

Innovative mechanism of action: In vivo PoC in TC-1 murine tumor model



5-8 mm tumor
5X daily It
EDAHPVE7

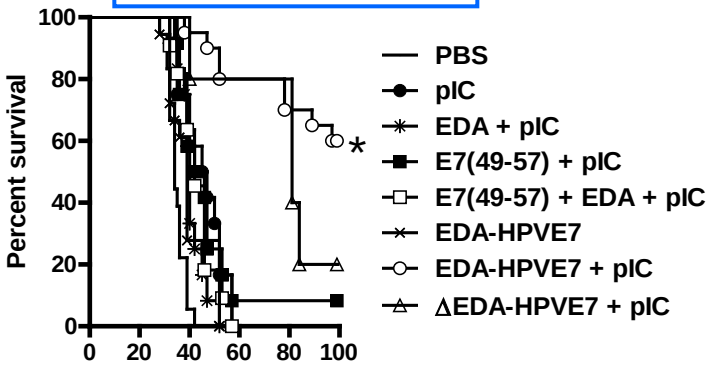
83% protection



Days after tumor inoculation

5-8 mm tumor
1x Iv
EDAHPVE7+PIC

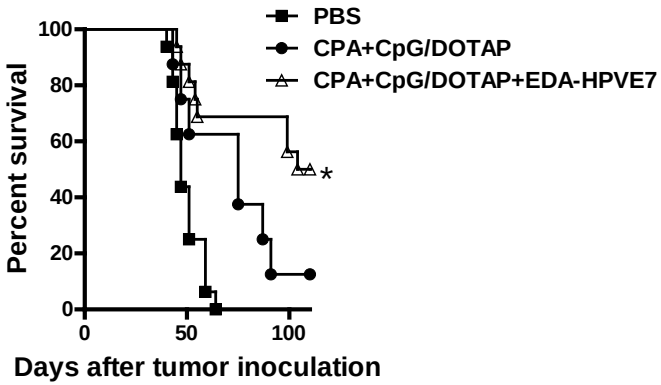
60% protection



Days after tumor inoculation

12 mm tumor
2x Iv
EDAHPVE7+CpG+CPA

50% protection



Days after tumor inoculation

Mansilla et al, Int J Cancer,2010

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Differential features facing the market:

Advantages of EDA-Fusion Protein Vaccines

- Efficient Antigen Delivery To And Simultaneous Maturation Of Dendritic Cells
- Robust Th1 Cell And Cytotoxic T Cell Responses
  - Necessary for Tumor Destruction and Elimination of Persistent Viral Infections
- Low Humoral Immune Response To EDA Moiety After Vaccination
  - No Obstacle To Repeat Immunizations
- Synergy With Other Vaccine Platforms and/or TLR 7 agonist
- Human origen of the protein
- EDA fusion proteins as a Platform for generates different candidates already proven with EDA-NS3; EDA-MLM

Differential features facing the market:

EDA offers several advantages over alternative TLR-adjuvants

TLR dependent adjuvants family	Description	Origin	Fusion protein	Single adjuvant	Main application	Receptor location	Myeloid / Plasmacytoid response
TLR-9 ligand (DNA-based)	• Unmethylated CpG dinucleotides from bacteria or virus	Bacterial Viral	✓	✓	Therapeutic / Prophylactic	Endosome	Plasmacytoid
TLR-5 ligand (Flagellin)	• Protein from the bacterial flagellae	Bacterial	✓	✓	Prophylactic	Cellular membrane	Myeloid
TLR-4 ligand (MPL-derived)	• Derived from detoxified lipopolysaccharide from *Sal. minnesota*	Bacterial Synthetic	—	—	Prophylactic	Cellular membrane	Myeloid
TLR-4 ligand (EDA)	• Derived from the human protein fibronectin	Human	✓	✓	Therapeutic (Prophylactic)	Cellular membrane	Myeloid

EDA advantages

- Human origin induces less reactogenicity against adjuvant
- Fusion protein promotes antigen binding and ensures coupling of antigen delivery and adjuvant action
- Single adjuvants are typically simpler from a development and regulatory viewpoint
- Therapeutic vaccines are usually focused on more attractive markets
- Cellular membrane location more accessible to target than internal endosome
- Myeloid dendritic cells generate more effective immune responses

Source: Medtrack database. Stakeholder opinions: Vaccine adjuvants. Datamonitor, September 2008; Stakeholder opinions: Therapeutic vaccines. Datamonitor, December 2009; Biolty analysis

Differential features facing the market:
Companies developing therapeutic cervical cancer vaccines

Cervical carcinoma vaccines pipeline

	Company	Product	Molecule	Phase	Characteristics versus EDA
No adjuvant	ISA Pharmaceuticals	ISAHPV01	Synthetic Long Peptide containing nine overlapping E6 and E7 peptides	I	- Not adding an adjuvant limits intensity or persistence of immune response, potentially limiting efficacy
Ag-encapsulated	PDS Biotechnology	PDS0101	Lipidic nanoparticles with HPV16 E7 antigen	PC	- Non human origin could induce immunotoxicity against adjuvant - Delivery vehicle, no immune system enhancer - Delivery not very specific, limiting efficacy
Immuno stimulant	APOIMMUNE	ApoVax104	Streptavidin + 4-1BB ligand and HPV16 E7 antigen	PC	- EDA elicits a more comprehensive immune response, activating several related immune system pathways and acting at different levels in the immune response - Usage mainly as mixture has the risk of decoupling antigen delivery from adjuvant action, reducing efficacy
EDA (TLR-4)	DIGNA BIOTECH	EDA cervical cancer vaccine	EDA+ HPV16 E7	PC	- Human origin reduces immunotoxicity against adjuvant -Fusion protein ensures antigen delivery and binding -Receptor located in myeloid dendritic cells, generating a more effective immune response
Vector	ADVAXIS	ADX11001	*Listeria monocytogenes* secreting HPV16 E7	I	- Non human origin could induce immunotoxicity against vehicle - Risk of development of replication-competent virus - Potentially additional side effects due to genetic mechanism - Risk of contamination
DC Targeting	GENTICEL	Procervix	Bivalent vaccine HPVE7 16 and 18 in the recombinant Adenylate Cyclase protein vector (CyaA)	I	- Non human origin could induce immunotoxicity against vehicle - Targeting vehicle, no immune system enhancer

Sources: Companies websites, Clinicaltrials,com, May 2010; Biolty analysis

Current status of development:

-**Positive PoC in the most accepted model of the disease.**

-**Positive PoC in established tumors in combined treatment with other TLR agonist (TLR-3, TLR-7, TLR-9)**

Mansilla et al, Int J Cancer,2010

-**Preliminary toxicological studies EDA alone in rat:**

- Acute toxicology (iv)
- Local tolerance (im, sc)
- Repeated dose
- Immunotoxicity

-Full development plan till Phase I in place

IPR protection: EDA current IP includes one approved patent covering the EDA platform and two filed patents focused on particular indications

Agents and methods based on the use of EDA domain of fibronectin

ES 200501412

Phase: Accepted, Spain, Europe, Russia, Australia, Japan, Mexico

Status: PCT

Filing Date: 13th June 2005

Summary: Protect the use of the EDA domain of fibronectin in combination with an antigen, or forming a fusion protein, which can bind to TLR4; the production methods and applications of said agents

Therapeutic compositions for the treatment of diseases caused by HPV

ES 200901847

Phase: Filed

Status: PCT

Filing Date: 11th September 2009

Summary: Protects a therapeutic compositions for the treatment of diseases caused by HPV and more specifically to compositions comprising at least one antigenic peptide derived from HPV E7 and EDA

New compositions based in the EDA for the treatment of melanoma

EP 10382036.1

Phase: Filed

Status: PCT

Filing Date: 16th February 2010

Summary: Protect methods for the treatment of melanoma by specifically directing an antigen to antigen presenting cells by the use of a conjugate comprising the antigen and a ligand which binds specifically to said antigen-presenting cells

Pitfalls & Risks to be considered:

- GMP protein production for any candidate
- No knowledge on humoral response
- First in class
- Potential of autoinmunity exarcebations
- Small market of the first candidate

3. Partnering Opportunities

Digna has recently created an spin-off: To mature technology

- IP will be licensed to the new Co
- Digna will start development of the candidate under a service contract till the new team is selected and contracted
- New Co will develop 2 candidates

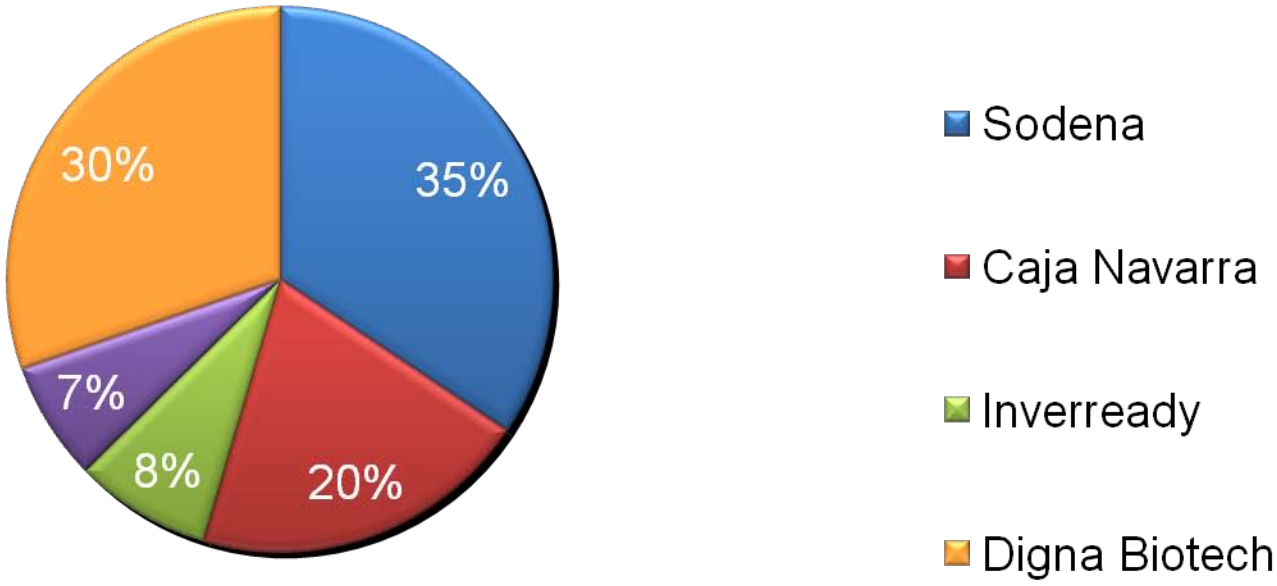
EDA- HPVE7 Therapeutic vaccine for cevical carcinoma

EDA- HbsAg or EDA-HbcAg Therapeutic vaccine for Hepatitis B

Partnering Opportunities

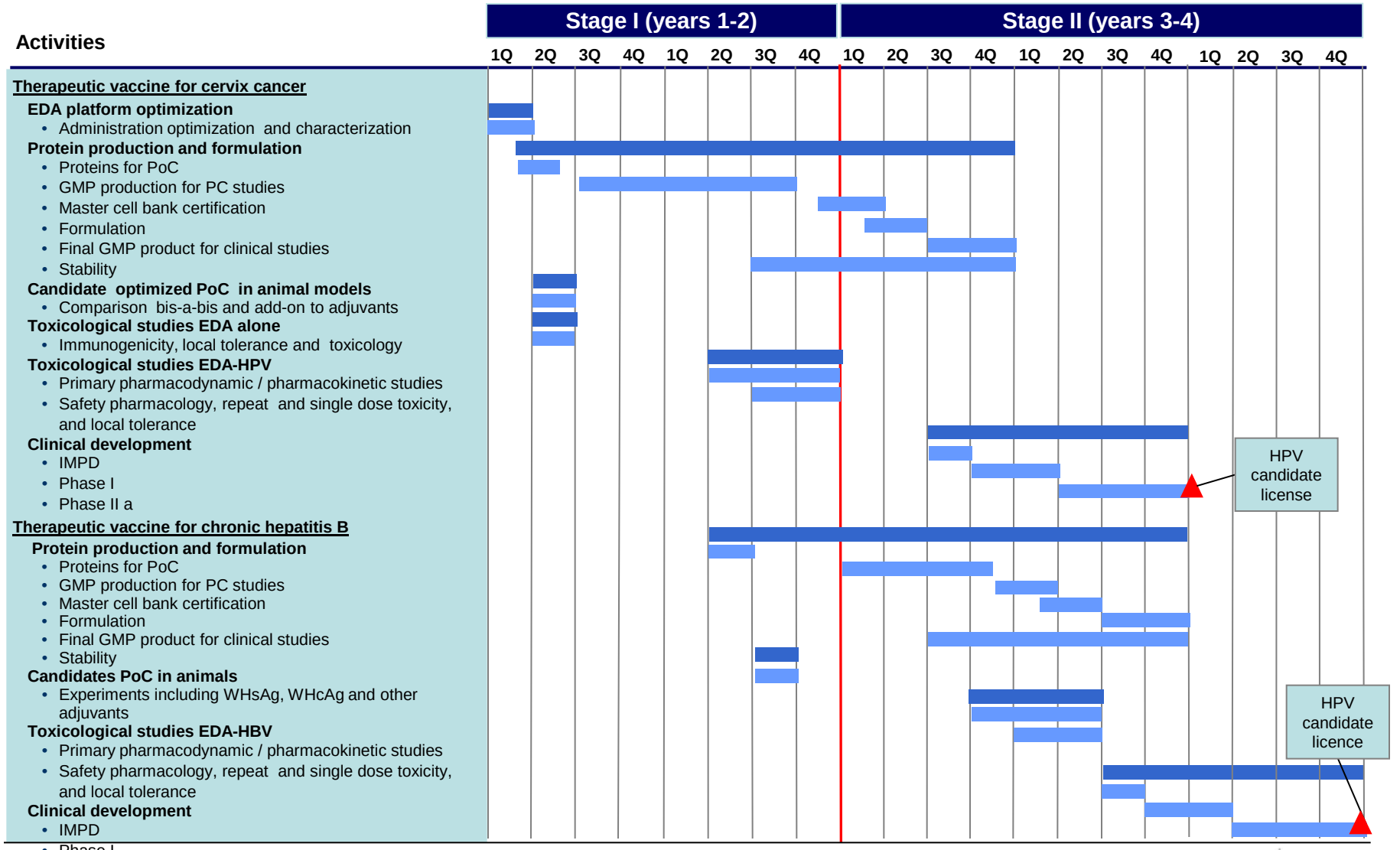
Investors committment : 3,2 Millions

Value of th Platform for Digna in shares: 30 %



We are looking a investor for the 7% (260.000 €) that would be able to continue after Phase I

Operative plan will take first candidate close to clinical stage and start development of second candidate during the first two years



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