“PERSPECTIVE ON THE IMPLEMENTATION OF A PHARMACOVIGILANCE SYSTEM”

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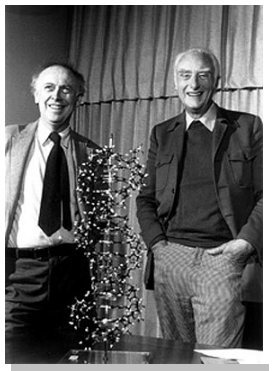
vaxeal
Regional Therapeutic Vaccines

VAXEAL - PROFILE

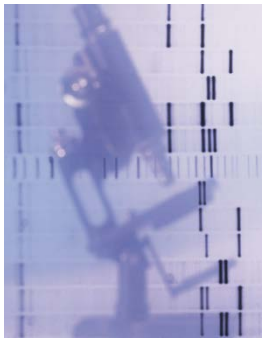
- SME developing a novel generation of Long Synthetic Peptide-based Therapeutic Vaccines
- Primary focus on Cancers and Infectious Diseases where there are major global patient needs
- Experienced management team in Europe to select and develop vaccine candidates
- Extensive experience in Clinical Trials Risk Management
- Science-based pharmacovigilance System: Pre-clinical, clinical … and post-marketing
- The patient is our main concern (Altruist, but also selfish)

BIOPHARMACEUTICALS: A RECENT INDUSTRY WITH HIGH POTENTIAL



DNA Molecule Deciphered

1950s



Genetic Code Cracked

1960s

Basic Biotechnology Enabling Discoveries

1970s

XOMA
A Leader In Therapeutic Antibodies
Genentech
IN BUSINESS FOR LIFE
biogen
Applied Biosystems
AMGEN

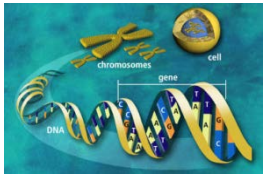
Commercial Biotech Companies Formed

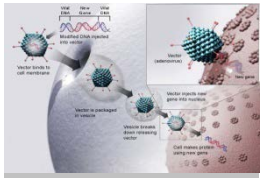
1980s

Enbrel
Remicade
Rituxan
PROCRIT EPREX
Aranesp
EPOGEN
Neulasta
Herceptin
AVONEX
AVASTIN (bevacizumab)
NutropinAq
Dysport

Leading Biotech Products

1990s-Today





Tomorrow

AN INDUSTRY OF THE FUTURE…

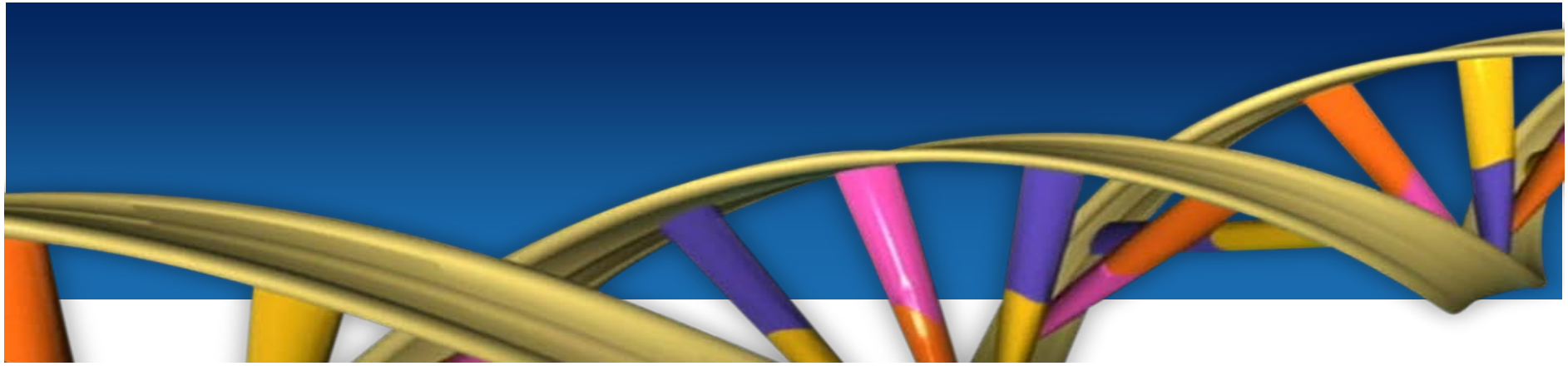
Over the past 30 years, more than 350 million patients have been treated with over 160 biotechnology derived drugs and vaccines

About 250 biotechnology derived therapeutic solutions and many more expecting a regulatory registration

> 1000 new products in clinical development phase

> 300 in advanced phase

Half of the therapeutic solutions currently being developed are biotechnology derived drugs



… LINKED TO MANY ENTREPRENEURIAL RISKS

Long development cycles (over 10 years)

Very complex products : High risk of failure

Science and technology continue to evolve

… NEED OF A PROACTIVE PHARMACOVIGILANCE SYSTEM

PHARMACOVIGILANCE AS AN EVOLVING DISCIPLINE

- Pharmacovigilance is defined as the pharmacological science relating to the detection, assessment, understanding and prevention of adverse effects, particularly long-term and short-term adverse effects of medicines
- Pharmacovigilance is an important and integral part of clinical research
- Both clinical trials safety and post-marketing pharmacovigilance are critical throughout the product life cycle
- With a number of recent biomedical drugs on the market, the biotech, pharmaceutical industries and regulatory agencies have raised the bar
- Early detection of signals from both clinical trials and postmarketing surveillance studies have now been adapted by major companies
- Signal detection and risk management have added a new dimension to the field of pharmacovigilance
- **Pharmacovigilance requires ongoing refinement in order to increase its applicability and value to public health**

VAXEAL IMPLEMENTATION - OPENNESS AND TRANSPARENCY

- Prevention of adverse drug reactions or any other drug related problems
  - ❖ **Better knowledge (product, patient, environment)**
- The human safety data extrapolated from animal studies are not conclusively predictive
  - ❖ **Development of Relevant Human Assays**
- clinical trials reveal a fair percentage of ADRs, but they may not always give the fuller picture due to relatively fewer number of patients
  - ❖ **Predictive Human T Cell Assays, HLA binding assays**
- In addition to these, clinical trials may not always pick up rare adverse reactions
  - ❖ **HLA Restriction, Observational Studies (random follow-up)**
- Bringing a reporting culture
  - ❖ **Transparency, responsibility**

STRATEGIES AND PROPOSALS (1)

- Building and maintaining a Robust pharmacovigilance system, including science-based
- Ensuring that all data is captured and analyzed for rapid detection of signals and of putting effective measures in place to overcome the risks
- Making pharmacovigilance reporting mandatory and introducing pharmacovigilance inspections
- System document operating within the company, which would serve as the base for future pharmacovigilance inspections
- Strengthen the company with independent trained scientific and medical assessors for pharmacovigilance, and Intensive training of the team
- **Pharmacovigilance Intelligence**: Access to all relevant data from various competitors and stakeholders

STRATEGIES AND PROPOSALS (2)

- Permanent discussion with pharmacovigilance experts and pharmacopeidemiologists (EMA, FDA, Swissmedic, physicians…)
- Permanent monitoring the safety and benefit-risk balance of our products (IT Data base)
- Communication with other healthcare stakeholders (Patient associations, EVM, EBE, EFPIA…)
- Risk management plan - effectiveness of risk management measures during product development and lifetime
- Periodic safety update reports
- **Guidelines for SMEs, Task Forces, Multidisciplinary Scientific Committees**

VAXEAL IMPLEMENTATION OF SCIENCE-BASED PHARMACOVIGILANCE SYSTEM

PRE-CLINICAL AND CLINICAL TRIALS

PREDICTIVE SAFETY AND EFFICACY

Risk Management - Standardization Programs

- Immunogenicity for biological products
    - development of novel Immuno-assays to detect Abs anti-drug and identification of B epitopes
- HLA Class I & II binding Assays
- Predictive T cell assays
- Monitor the immune response in both systemic and mucosal sites in animal models
- Characterization of T cell response during and after vaccine and immuno-therapies

IMMUNOPREVALENT TREATMENTS

- Due to the polymorphism of HLA class II molecules, immunogenic antigens vary from one individual to another
- Vaxeal has created a bank of HLA class II molecules to account for this diversity and it is composed by the most preponderant HLA class II molecules

HLA II Alleles	Frequency in population (%)
DRB1*0101	9.3
DRB1*0401	5.6
DRB1*1101	9.2
DRB1*0701	14.0
DRB1*0301	10.9
DRB1*1301	6.0
DRB1*1501	8.0
DRB5*0101	7.9
DRB3*0101	9.2
DRB4*0101	28
DPB1*0401	40
DPB1*0402	11

PREDICTIVE IMMUNOLOGICAL ASSAYS

HLA class II binding assays

APC Recognition

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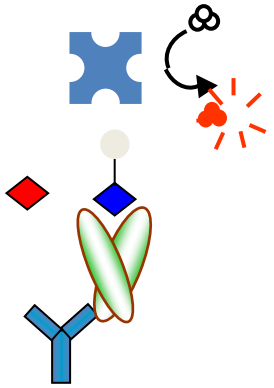
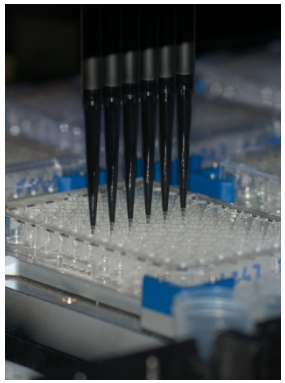
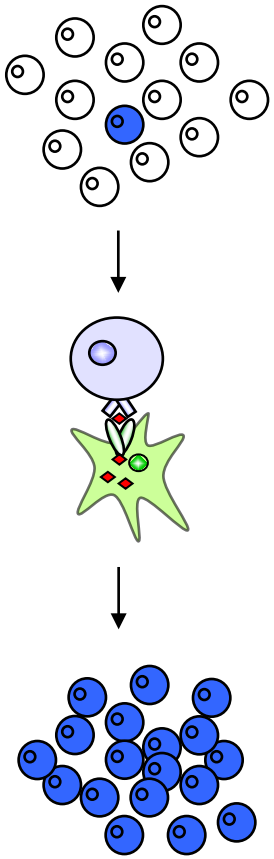




Quantitative predictive T cell assays

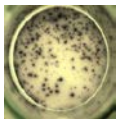
T Cell Priming



Quantification of pre-existing antigen-specific T cells in naïve donors

Antigen specificity

Control



+ peptide

HLA CLASS II BINDING ASSAYS

- To evaluate the binding affinity of each antigen for HLA class II molecules (APC/DC)
- To identify antigens with a broad specificity for HLA class II molecules
- To evaluate the influence of natural sequence variations on the binding properties
- To optimize the sequence for the binding to HLA class II molecules

QUANTITATIVE PREDICTIVE T CELL ASSAYS

- Our assays do not evaluate recognition by T cells collected in already primed donors (antigenicity) but capacity to elicit a T cell response (immunogenicity).

- This assays allows:
  - To evaluate the intensity of the T cell response raised against tested peptides or proteins in each donor;
  - To evaluate the frequency of responders of the tested peptides or proteins (immunoprevalence);
  - To rank tested peptides or proteins based on their immunogenicity;
  - To identify CD4+ and CD8+ T cell stimulating peptides with a wide frequency of responders;
  - To evaluate cross reactivity of natural variants;
  - To evaluate the lytic ability of peptide specific T cells

EXAMPLE - CD4+ AND CD8+ T CELL RESPONSES FOR VXS-1

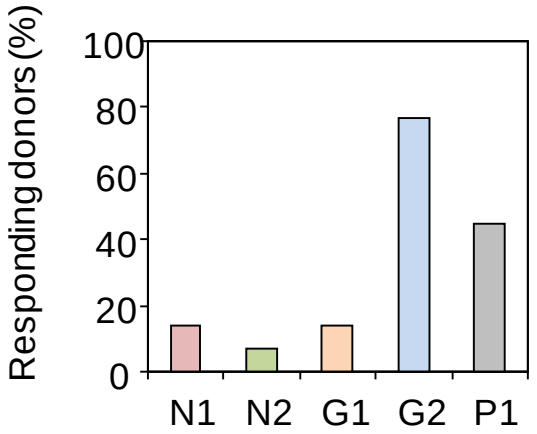
Epitope		No. cell lines	No. donors	HLA I or II Restriction	Native Protein	Tumor cell lysates	Tumor cells	Spontaneous response
5-34	17-31	28	5/8	HLA-DR4, DR7, DR15, DRB4, DRB5, DP4	+	+		
	20-34	9	3/8	HLA-DR4, DR7, DR11, DP4	+		+	
84-110	84-98	11	4/8	ND	+			+
	90-104	19	7/8	HLA-DR7, DR11, DR15, DRB4, DRB5	+			-
	93-107	9	4/8	HLA-DR7, DP4	+			-
	96-110	23	7/8	HLA-DR4, DR7, DP4	+			-
122-142	128-142	17	6/8	DR15, DRB5	+			-
CD8	5-14	6	3/3	HLA-A*0201	+		+	
	13-21	2	2/3	HLA-A*0201	+		-	

CLINICAL EXAMPLE OF RELEVANCE – PREDICTIVE ASSAYS VS CT RESULTS

Cocktail of 5 Lipidated HIV-LSPs

ANRS: *Salmon et al, AIDS, 2010*

Multicenter, randomized, double-blind,**132** volunteers

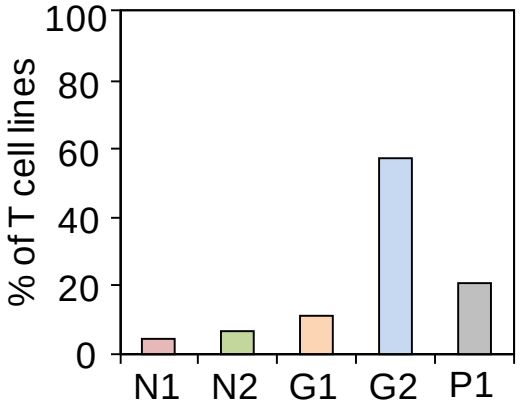


CD4 T cell response

Same epitope hierarchy

Quantitative predictive T cell assays

Seronegative donors



- The intensity of the T cell response against each peptide is similar to the clinical results
- The epitope hierarchy is respected, demonstrating the relevance of Vaxeal *in vitro* quantitative CD4 T cell assays

PRE-CLINICAL PLATFORM

- This platform has **standardized various assays** to monitor immune response in both systemic and mucosal sites in mice

  - Assays developed: Tetramer, Elispot, luminex, CFSE labelled cells, cytotoxicity assay…

  - In addition, various animal models have been standardized
    - HLA class I and II transgenic mice (HEGP, Paul Brousse)
    - Spontaneous tumor models mimicking Her2/neu human adenocarcinoma or HPV associated cancers
    - Human cell lines derived from various **human cancers** to be grafted in immunodeficient mice

IMMUNOMONITORING PLATFORM (1)

- This platform is dedicated to the detection and characterization of T cell response after vaccine and immunotherapy protocols.
- We have participated to **quality control and standardization programs in France**

- This platform includes innovative assays for :
  - the characterization of T cells such as the Elispot assay
    - able to detect single cells producing various immunoreactive substances, such as cytokines
    - Moreover, accumulative data now demonstrated that the multifunctionality of T cell induced after vaccine correlated with vaccine efficacy.
  - Fluorospot assay:
    - Detection of T cells simultaneously producing multiple cytokines (IFNα, IL-2, IL-17…)
    - Regulatory T cells with an immunosuppressive activity (co-expression of IL-10 and IFNγ)

IMMUNOMONITORING PLATFORM (2)

- As it is important during immunotherapy to be able to characterize both effector cells and cells with immunosuppressive activity, the ratio of which may be related to vaccine efficacy, **Vaxeal is engaged in a program to standardize test to detect these suppressive cells**

  - We have assessed the prognostic value of regulatory T cells ($CD4^+CD25^+Foxp3^+$ cells) in cancer patients by cytometry and by *in situ* immunofluorescence assays

  - These assays are completed by the characterization of $PD1^+$T cells and myeloid derived suppressive cells (MDSC)($CD34^+CD33^+CD11b^+CD13^+CD14^-HLADR^-$)

SOME RECENT APPLICATIONS OF VAXEAL PLATFORM

Platforms	Representative Results
Pre-Clinical	Screening of the activity of various Adjuvants Assessment of synergy between anti-angiogenic molecules and cancer vaccines
Immunomonitoring	A randomized phase II clinical protocol assessing the efficacy of recombinant vaccinia virus encoding the Muc1 tumor antigen and IL-2 in patients with Lung cancer A randomized double blind safety and efficacy phase I/II study in malignant melanoma stage IV patients with mature or immature dendritic cells Randomized phase II study evaluating MVA-Muc1-IL-2 in patients with metastatic renal cell carcinoma

CONCLUSION – VAXEAL PHARMACOVIGILANCE IMPLEMENTATION

- Pharmacovigilance system because the patient is our main concern
  - **We have to be imaginative – Product/Target Patients/Environment**

- Building and maintaining a Robust pharmacovigilance system
  - **Including Science-Based Pharmacovigilance System**

- Pharmacovigilance is an important and integral part of clinical research
  - **Permanent discussion with pharmacovigilance experts**
  - **Access to all relevant data from various past and present experiences**
  - **Predictive Safety and Efficacy**

- Signal detection and Risk management plan
  - **Surveillance/Observational studies**
  - **Transparency, responsibility**

vaxeal

THANK YOU !

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