Disclosures

• Shareholder and employee of Immatics Biotechnologies and its subsidiary Immatics US, Inc. which has a commercial interest in the development of cancer immunotherapy.

• Co-chair of the Regulatory Research Group (RRG) of the Association of Cancer Immunotherapy (CIMT), an international non-profit organization promoting cancer immunotherapy.

• Coordinator of the Glioma Actively Personalized Vaccine Consortium (GAPVAC), a European Union Framework 7-funded consortium of industry and academic partners.

• I will not discuss off-label use.
Agenda

1) Why Personalize?
2) Levels of Personalization
3) GAPVAC Glioma Actively Personalized Vaccine Trial
4) Taking Immunotherapy Personally – Beyond Vaccines
5) Summary and Policy Recommendations
Why Personalize?
Human Leukocyte Antigen (HLA)-presented peptides

© Hans-Georg Rammensee (1991)

The cancer immunopeptidome

Our mission:
**Mapping the human immunopeptidome**
as centrally relevant information for **all** T-cell based immunotherapies.

---

Immunopeptidome

Proteome

Genome / Transcriptome

---

T cell

Peptide

HLA

Protein

mRNA

DNA

Tumor Cell
Quantitative Mass Spectrometry (LC-MS/MS) on tumor and healthy tissues

Example: Collagen, type VI, alpha 3 – HLA*02-restricted peptide COL6A3-002

- Extracellular matrix component found in most connective tissues
- **Cancer-specific splicing of exon 6** (encoding COL6A3-002), and possibly exons 3 and 4
- Overexpression described in several cancer types, including ovarian cancer, pancreatic cancer, colorectal cancer, gastric cancer, and salivary gland carcinoma
- Possible association with cisplatin resistance
- Relevant in a broad range of tumors including lung, pancreas, esophagus, breast, ovary, colon, stomach cancer and others
Mass spec-guided analysis of on-target toxicities
On-target toxicity of a known cancer antigen – CEACAM5

Carcinoembryonic Antigen (CEACAM5) is in clinical testing for various forms of cancer immunotherapy, including TCR transgenic ACT studies.

Expression on normal colon
- Severe colitis
- ACT study aborted
- however, CEA bispecifics are in clinical development.

Using ultra sensitive mass spectrometry and transcriptomics technology
XPRESIDENT® allows for on-target toxicity prediction of TCR/ACT.
Mass spec-guided analysis of off-target toxicities

Off-target toxicity of a TCR to a known cancer antigen – MAGE-A3/Titin

Cardiovascular toxicity and titin cross-reactivity of affinity-enhanced T cells in myeloma and melanoma

Patients who received these T-cells had serious adverse events, including fatal cardiac toxicity

- TCR recognizes similar peptide ESDPIVAQY
- XPRESIDENT® genome screen identifies Titin with expression on heart and muscle

XPRESIDENT® allows for off-target toxicity prediction of TCR ACT
By ultra sensitive mass spec and transcriptomics technology
XPRESIDENT® – Database and Target Discovery Engine
The Human Immunopeptidome Program – HIP

Primary Cancer tissues
AML
Bladder Cancer
Breast Cancer
CLL
Colorectal Cancer
Esophagus Cancer
Gallbladder
Gastric Cancer
Glioma
Liver Cancer
Melanoma
Multiple Myeloma
Non-Hodgkin lymphoma
NSCLC
Ovary
Pancreas Cancer
Prostate Cancer
Renal Cell Carcinoma
SCLC
Uterus

LC-MS/MS
N>600 tumor samples
RNASEq
N>13,000 tumors

LC-MS/MS
N>300 normal samples
RNASEq
N>3,700 normals

Normal Control Tissues
Adipose tissue
Adrenal Gland
Artery
Bladder
Blood cells
Bone Marrow
Brain
Breast
Cartilage
Cervix
Colon
Esophagus
Eye
Gall bladder
Heart
Kidney
Liver
Lung
Lymph node
Muscle

XPRESIDENT® Target Database
>47 million quantitative MS/MS spectra
From >9,000 MS experiments
>250,000 unique peptide sequences
>1,500 peptides with tumor association

Numbers as of July 2015, constantly increasing
Overexpressed antigens with low frequency

High specificity often correlates with low abundance

Antigen 1 (PTP-003)
- shared in glioblastoma
- contained in off-the-shelf vaccine IMA950 by immatics (currently developed in phase I trials)
- 5-25x overrepresented vs. median of healthy tissues
- suitable for off-the-shelf and individualized approach

Dutoit et al., Brain 2012

Antigen 2 (undisclosed)
- found in few tumor patients
- exclusively presented in tumors
- suitable for individualized approach for administration in patients with positive expression of this antigen
Mutanome-derived HLA-restricted peptides

Validation of NGS-identified mutations with Mass Spec

C57BL/6 (DNA) → B16F10 DNA & RNA sequencing → Sequence analysis → Mutation identification → IAQTSGKTLAYLLSIAIVHINHQPYLER → Personalized protein database of somatic mutations → YLLSAIVHI → Theoretical spectra → Identification

Yadav et al., Nature 2014
Mass-spectrometry work performed by co-author Toni Weinschenk, VP Discovery Immatics
XPRESIDENT identifies naturally presented peptides
Comparison of MS-identified peptides vs ranking through SYFPEITHI algorithm

In silico prediction of HLA-A*02 peptides

n=50 tumor samples

Peptide copies per cell

Lung Cancer
Ovarian cancer

# of detections on tumor samples

8
20
40

X1
X2
X3

90
10
2200
4100
600
600

• Conclusions: Mass spectrometry
  • reveals the peptides actually presented and is far superior to inaccurate in silico prediction algorithms
  • provides valuable information on varying copy numbers between peptides originating from the same source protein.

3 TUMAPs actually identified By MS/MS

14
Every tumor is different and provides unique antigens

Antigens expressed by each tumor should be ideally assessed in an unbiased fashion
- Neoantigens…but not just neoantigens
  - e.g. Gros et al. Nat Med 2016 (Rosenberg, NCI): NY-ESO, gp100, SSX2
  - Highly overexpressed antigens such as cancer-testis, oncofetal, differentiation targets
  - HLA class I and II

High-sensitive quantitative MS/MS allow robust identification of hundreds to thousands of HLA class I and II-restricted peptides from primary tumor or biopsy material

This is feasible for an individual patient in a therapeutic setting
Levels of Personalization
CIMT - Regulatory Research Group

Regulatory Research Group
(founded 2008)
Chair U. Kalinke & Co-Chairs H. Singh & C. Britten

CRI-CIC Delegate
A. Hoos

- Scientific Sessions
- Comments to Guidelines
- Co-operations
- Research Projects

Goals
- Identification of **regulatory challenges** posed by emerging immunotherapies.
- **Facilitating discussion** between all groups relevant for the translation of scientific knowledge into the hospital.
- Delineation of **new regulatory concepts** to facilitate clinical testing of innovative immunotherapies.
Personalized immunotherapies

(A) Patient

(B) Tumor

(C) Theranostic

Stratification

passive personalization

active personalization („AP“)

Invariant DP

Variant DPs

Variant DPs

Britten, Singh-Jasuja et al., Nature Biotechnology (2013)

© CIMT Regulatory Research Group (RRG)
### Stratification - Examples

<table>
<thead>
<tr>
<th>Drug</th>
<th>Biomarker</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Approved</strong></td>
<td></td>
</tr>
<tr>
<td>Trastuzumab (Herceptin®)</td>
<td>Her2/neu</td>
</tr>
<tr>
<td>Cetuximab (Erbitux®)</td>
<td>Kras wildtype</td>
</tr>
<tr>
<td>Erlotinib (Tarceva®)</td>
<td>Mutated EGFR</td>
</tr>
<tr>
<td><strong>In development</strong></td>
<td></td>
</tr>
<tr>
<td>NY-ESO TCR Adoptive T-cell therapy (UPENN; NCI)</td>
<td>NY-ESO 1</td>
</tr>
<tr>
<td>Rindopepimut (Celldex)</td>
<td>EGFRvIII</td>
</tr>
<tr>
<td>Many peptide-based vaccines</td>
<td>HLA-A*02</td>
</tr>
</tbody>
</table>
### Passive Personalization - Examples

#### Approved

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sipuleucel-T (Provenge®, Dendreon)</td>
<td>Autologous antigen-presenting cells loaded with GM-CSF/PAP</td>
</tr>
<tr>
<td>Prophage® (Agenus) [approved in Russia only]</td>
<td>Autologous Gp96 heat shock protein preparation from renal cell cancer tissue</td>
</tr>
</tbody>
</table>

#### In development

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oncovax® (Vaccinogen)</td>
<td>Autologous tumor lysate preparation from colon cancer tissue</td>
</tr>
<tr>
<td>TIL platform (Lion Biotechnologies; NCI; MD Anderson; CCIT Denmark)</td>
<td>Autologous tumor-infiltrating lymphocytes (TILs) isolated from melanoma tissue</td>
</tr>
</tbody>
</table>
### Active Personalization - Examples

<table>
<thead>
<tr>
<th>Drug</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Approved</td>
<td>none</td>
</tr>
<tr>
<td><strong>In development</strong></td>
<td></td>
</tr>
<tr>
<td>GAPVAC EU consortium (Immatics, BioNTech)</td>
<td>Personalized peptide vaccine targeting warehouse and mutated antigens in glioma patients</td>
</tr>
<tr>
<td>MERIT EU consortium (BioNTech)</td>
<td>Personalized mRNA vaccine targeting warehouse and mutated antigens in melanoma patients</td>
</tr>
<tr>
<td>ACTolog (Baylor, MD Anderson, Immatics)</td>
<td>Personalized autologous adoptive cell therapy targeting warehouse antigens in solid cancer patients</td>
</tr>
<tr>
<td>ACT to neoantigens (NCI; Netherlands Cancer Institute)</td>
<td>Personalized adoptive cell therapy (ACT) targeting mutated antigens in cancer patients</td>
</tr>
</tbody>
</table>
GAPVAC – Actively Personalized Vaccination in Glioblastoma Patients
Design strategies and first experiences
Establish an actively personalized vaccination (APVAC) approach for treatment of glioblastoma patients

Consortium with 14 partners funded by EU FP7 with €6 mn

Coordinator: Immatics
Vice-Coordinator: BioNTech

Chief Investigator: Wolfgang Wick (Heidelberg)

Up to 20 glioblastoma patients treated with warehouse and mutanome-derived APVACs

Clinical phase I study started in October 2014, so far 11 patients enrolled, 8 patients treated
Biomarker-driven clinical trial design

Newly diagnosed glioblastoma patients

71 peptides (A*02, A*24, DR) pre-manufactured

Warehouse peptides

Expression Profile
Mutanome
Peptidome
Immunogenicity

Biomarker tests

De novo peptides

Up to 10 peptides

Peptide selection

APVAC 1

APVAC 2

Patient 1

Patient 2

Patient 3

Custom-made

Up to 10 peptides

Peptide selection

APVAC 1

APVAC 2

Patient 1

Patient 2

Patient 3

De novo synthesis

Up to 10 peptides

Peptide selection

APVAC 1

APVAC 2

Patient 1

Patient 2

Patient 3

De novo synthesis
• Warehouse-based vaccine (APVAC1) provided within 3 months
• Neoantigen-based vaccine (APVAC2) provided within 6 months
• Vaccination of APVAC peptide vaccine 6-9x i.d. with GM-CSF i.d. and Hiltonol s.c. (Oncovir) at same site
Taking Immunotherapy Personally – Beyond Vaccines
XPRESIDENT®-derived Warehouse Approach
Envisioned Personalized Development Tracks

XPRESIDENT® Target Database
- >47 million quantitative MS/MS spectra
- >250,000 unique peptide sequences
- >1,500 peptides with tumor association

Peptide Warehouse
- APVAC
  Actively Personalized Vaccines

HLA/peptide multimer warehouse
- ACTolog®
  Adoptive Cellular Therapy with endogenous T cells

TCR Warehouse
- ACTengine®
  Adoptive Cellular Therapy with engineered T cells
Actively Personalized Immunotherapy
Modalities for Vaccines and Cellular Therapies

**APVAC**
Actively Personalized Vaccines

**ACTolog®**
Adoptive Cellular Therapy with endogenous T cells

**ACTengine®**
Adoptive Cellular Therapy with engineered T cells

*In vivo*
T-cell navigation & expansion

*Ex vivo*
T-cell navigation & expansion

*Ex vivo*
T-cell gene therapy & expansion

Peptide Vaccine

HLA/peptide-multimer (fishing rod for T cell)

Retrovirus encoding synthetic T-cell receptor
ACTolog®

Autologous T cells – endogenous TCRs

2 Biomarker profiling
- Identify suitable antigens based on patient’s tumor (and T-cell pre-cursors)
  - HLA/peptide-multimer
  - IFNγ capture/activation marker

1 Tumor target
- Tumor sample
- Leukapheresis

3 T-cell generation process
- priming
- selection
- expansion with IL-21

Cancer patient

Clinical Proof of Concept

Prof. Cassian Yee, MD Anderson Cancer Center

- PET scan reveals hypermetabolic lesions in the right lung and the left inguinal–iliac node that are consistent with metastases (arrowheads)
- The lesions colocalized to tumor nodules on CT scans.
- After infusion with NY-ESO-1–specific CD4+ T cells, PET scans show that the tumor nodules have regressed, and no evidence of disease can be detected. Uptake in liver, spleen, and bladder represents normal background signal and did not co-localize to any lesions on CT scans.

Biomarker profiling

Tumor target

T-cell generation process

Process established at MD Anderson Cancer Center
Immatics-sponsored trial in solid tumor patients planned to start mid 2016
Co-funded by State of Texas CPRIT grant
Summary and Policy Recommendations
• Personalization of immunotherapy is driven by
  • Differences in cancer target expression
  • Suitable cancer targets occurring only in very few or single patients
    • Not just neoantigens
  • Differences in the host immune system

• Biomarker-guided personalized immunotherapy may involve
  • Selection of suitable patients (stratification)
  • Selection of immunotherapy targets, immunomodulators and other agents for an individual patient (active personalization)

• Active personalization is applicable for various immunotherapies
  • Vaccines
  • Adoptive T-cell therapy (endogenous TCR and engineered TCR)
  • Combination therapies
Regulatory Pathway for APVACs

Briefing meeting report

Actively Personalized Vaccines (APVACs)
Association of Cancer Immunotherapy (CIMT)
Regulatory Research Group (RRG)

Briefing meeting held at the European Medicines Agency (EMA)
on 06 January 2012

Published by Britten, Singh-Jasuja et al., Nature Biotechnology (2013) - Supplement
• There are no relevant toxicity-predicting animal models for HLA-restricted peptides
  - Non-transgenic animals do not harbor HLA recognized by human T cells
  - HLA-transgenic animals do not express the relevant components of human antigen processing machinery and thus present different peptides on their HLA receptors compared to humans

• Any information derived from such animals may be misleading
Animal toxicology

CIMT proposed due to the known limited predictive value of animal models for testing of human antigens and moreover and due to the fact that extended animal toxicology studies, will not be feasible for the de novo synthesis approach—that animal studies should be substituted by well designed in vitro experiments for selected epitopes. Such in vitro data could address issues such as of cross-reactivity of mutated antigens.

Experts at EMA principally agreed that the application of human antigens in animal models may have limited predictive value. Although in vitro studies seem to be appropriate such studies should be accompanied by safety studies in animal models challenged with animal antigens. More detailed discussion is required in the context of scientific advice so that the approach chosen for either the warehouse or the de novo synthesis manufacturing strategy is duly designed and justified.

It was preliminarily concluded that in light of feasibility considerations (restricted time frame in APVAC setting) and generally good tolerability of antigen-specific cancer immunotherapeutics, proceeding into the clinical setting could be considered for the de-novo synthesis APVAC products if adequate scientific background data were available and appropriate risk mitigation measures are in place in the respective clinical study (see below).
Policy Recommendations - Toxicity

• There are no relevant tox-predicting animal models for HLA-restricted peptides
  • Non-transgenic animals do not harbor HLA recognized by human T cells
  • HLA-transgenic animals do not express the relevant components of human antigen processing machinery and thus present different peptides on their HLA receptors compared to humans
  • → any information derived from such animals may be misleading

• Minimize risk of on-target toxicity
  • Comprehensive study of target expression (RNASEq) and peptide presentation (mass spec) on tumor and healthy tissue

• Minimize risk of off-target toxicity
  • Not/less relevant for approaches using endogenous T cells (vaccines, ACTolog = endogenous T cells with natural TCRs)
  • For TCR-based approaches determine motif of TCR by Ala scanning and check against genome and peptidome databases to determine cross-reactivities
    • In case of putative cross-reactivities further in vitro T-cell studies testing recognition of cell lines and primary cells (if available)
Policy Recommendations - Specific Issues with Personalized Immunotherapies

• Every actively personalized immunotherapy product is different, manufactured “on demand” and needs to be administered as fast as possible
  • Preclinical proof-of-principle studies performed, animal tox studies (if relevant model available), stability and shelf life
    • only applicable/feasible for “warehouse”-based drug substances (e.g. single vaccine antigens),
    • not for drug substances manufactured on demand (e.g. mutated antigens) and
    • not for drug product manufactured on demand

• Development of actively personalized immunotherapy is not vastly different from current immunotherapy protocols
  • Safety and efficacy to be established similarly to non-personalized products
  • Personalized clinical development requires even stronger focus on comprehensive biomarker measurement
    • Late-stage trials and market \(\rightarrow\) standardization of target selection (validated biomarker assays, selection algorithms) and manufacturing (in-process controls, validated potency assays)
    • Early-stage, hypothesis-generating trials \(\rightarrow\) allow higher degree of flexibility
  • Measures for assuring sample quality need to be place in all clinical trials regardless of development stage
Acknowledgments

IMA901 Renal Cell Cancer Studies
Arnulf Stenzl (Tübingen)
Brian Rini (Cleveland)
Tim Eisen (London)
…on behalf of the IMA901 investigators

IMA910 Colorectal Cancer Study
Frank Mayer (Tübingen)
…on behalf of the IMA910 investigators

IMA950 Glioblastoma Studies
James Ritchie (CR-UK)
Sarah Haldorf (CR-UK)
Roy Rampling (Glasgow)
Joohee Sul (NCI)
Pierre-Yves Dietrich (Geneva)
Christel Herold-Mende (Heidelberg)
Philipp Beckhove (Heidelberg)

GAPVAC Glioblastoma Study
Wolfgang Wick (Heidelberg)
Pierre-Yves Dietrich (Geneva)
…on behalf of the GAPVAC investigators

University of Tübingen
Hans-Georg Rammensee
Stefan Stevanovic
Cecile Gouttefangeas

The patients and their families
Thank you

Immatics
Paul-Ehrlich-Str. 15, 72076 Tuebingen, Germany
Phone +49-7071-5397-0 Fax +49-7071-5397-900

7000 Fannin Suite 2115/2120, Houston, Texas 77030, USA
Phone +1-346-204-5400 Fax +1-346-204-5931

www.immatics.com info@immatics.com