# From Off-The-Shelf to Actively Personalized

## Cancer Vaccines in the Era of Biomarkers

**SITC Cancer Immunotherapy Clinical Trials Workshop**
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# Disclosure Information

Harpreet Singh, PhD

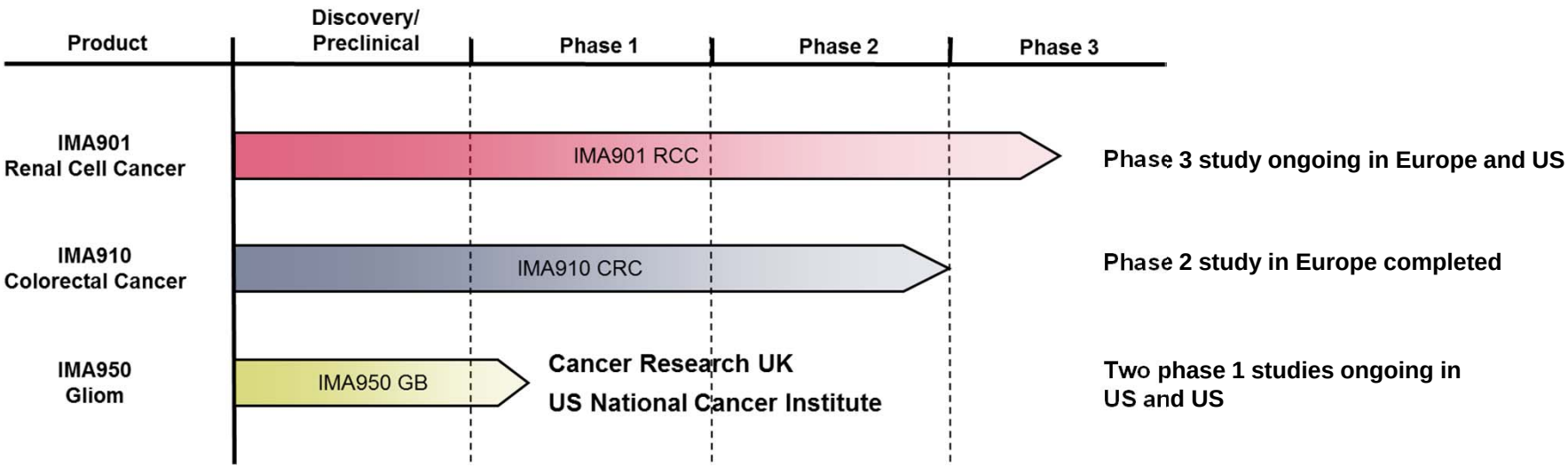
**I have the following financial relationships to disclose:**

- Stockholder in immatics biotechnologies GmbH
- Employee of immatics biotechnologies GmbH

**I will not discuss off-label use and/or investigational use in my presentation.**

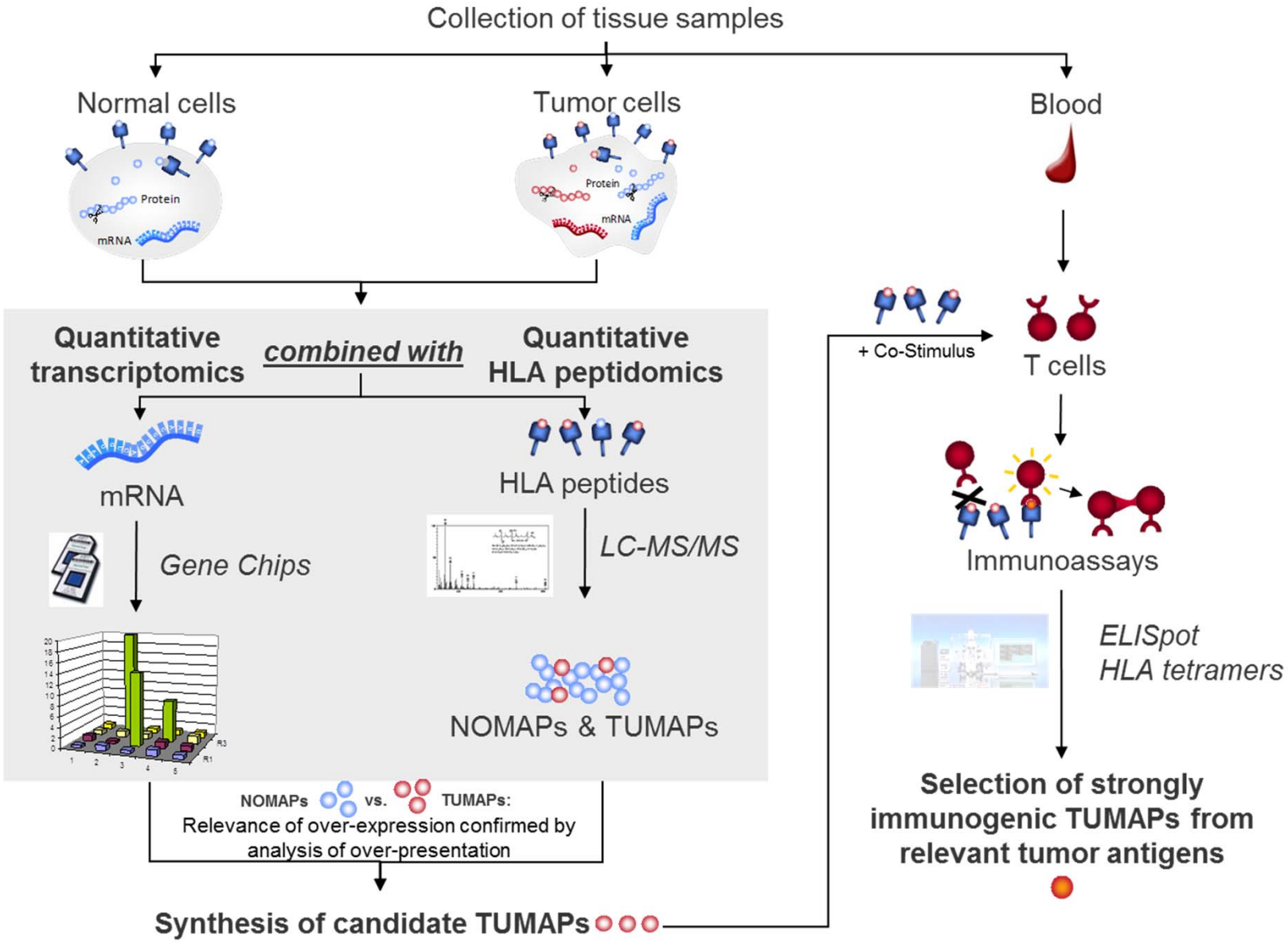
# immatics biotechnologies GmbH

- *immatics* is a biopharmaceutical company dedicated to development of innovative **off-the-shelf therapeutic vaccines** against cancer based on the use of **multiple naturally presented HLA-restricted tumor-associated peptides (TUMAPs)**
- *immatics* was founded in 2000 as a spin-off from the University of Tübingen (Prof. Hans-Georg Rammensee)
- *immatics* is clinically developing three cancer vaccine product candidates

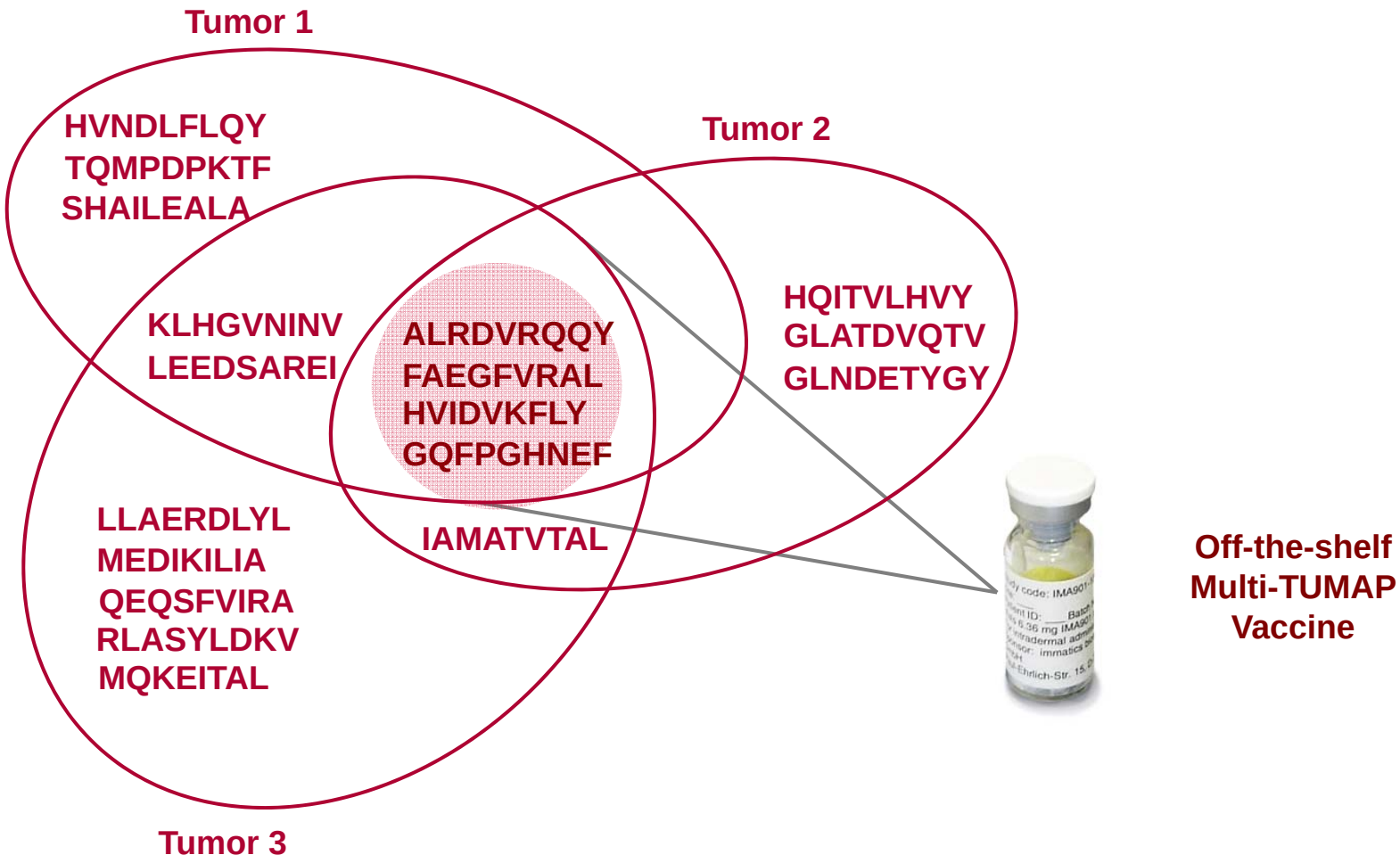


# XPRESIDENT™ Discovery Platform

## Identification, selection and validation of novel tumor-associated HLA-restricted peptides



# Tumor-associated peptides – shared vs. individual



# IMA901 Renal Cell Cancer Vaccine
## 10 tumor-associated peptides

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**Table 1 Composition of the vaccine IMA901 and characteristics of the HBV peptide included in the phase 1 study**

| Peptide | Antigen | HLA | Overexpression | *In vitro* immunogenicity | Remarks on function and tumor relevance | References |
|---|---|---|---|---|---|---|
| ADF-001 (SVASTITGV) | PLIN2 | A*02 | 6.0 | + | Major constituent of the surface of lipid droplets. | 4,49 |
| ADF-002 (VMAGDIYSV) | APOL1 | A*02 | 6.0 | + | Overexpressed in several cancers; established as a marker for RCC. | |
| APO-001 (ALADGVQKV) | | A*02 | 7.0 | + | Secreted major apoprotein of high-density lipoprotein. Overexpression in RCC. | 4 |
| CCN-001 (LLGATCMFV) | CCND1 | A*02 | 3.0 | + | Cell cycle regulation. Overexpression and association with tumorigenesis and metastasis described for various tumors. | 4,50 |
| GUC-001 (SVFAGVVGV) | GUCY1A3 | A*02 | 2.2 | + | cGMP synthesis. Proangiogenic effects in tumors. | 4 |
| K67-001 (ALFDGDPHL) | PRUNE2 | A*02 | 3.4 | + | Largely uncharacterized so far. Overexpression in RCC. | 4,18 |
| MET-001 (YVDPVITSI) | MET | A*02 | 13.6 | + | Hepatocyte growth factor receptor tyrosine kinase, cell signaling. Various implications in malignant transformation and invasiveness of tumor cells. | 4,18,51 |
| MUC-001 (STAPPVHNV) | MUC1 | A*02 | 1.6 | + | Protection against pathogen binding to the cell surface; roles in cell signaling. Altered glycosylation patterns lead to new T cell epitopes in tumors. | 52–55 |
| RGS-001 (LAALPHSCL) | RGS5 | A*02 | 3.5 | + | Regulation of cell signaling. Overexpression during neovascularization in tumors. | 18,56 |
| MMP-001 (SQDDIKGIQKLYGKRS) | MMP7 | DR | 3.3 | + | Breakdown of extracellular matrix during tissue remodeling. Involved in tumor invasion and metastasis, tumor development and progression. Also, roles in apoptosis, cell proliferation and cell differentiation. | 57 |
| HBV-001 (FLPSDFFPSV) | HBV; nucleocapsid protein (HBcAg) | A*02 | NA | + | Marker peptide, not tumor associated. HBcAg is an antigenic determinant of HBV. Serological responses develop in most HBV-infected subjects, used for diagnosis of infection. | 20,58 |

The characteristics of individual peptides contained in IMA901 are shown with peptide code (sequence), source antigen, HLA restriction, overexpression, *in vitro* immunogenicity, remarks on function and references. In the "overexpression" column, the ratios of mean expression in all analyzed RCC samples ($n = 20$) compared with the mean expression in normal tissues are shown. In the column "*in vitro* immunogenicity," "+" indicates that *in vitro* expansion of peptide-specific T cells was observed. NA, not applicable.

Walter, Weinschenk et al. (2012), Nature Medicine

# Lesson learned from use of off-the-shelf cancer vaccines

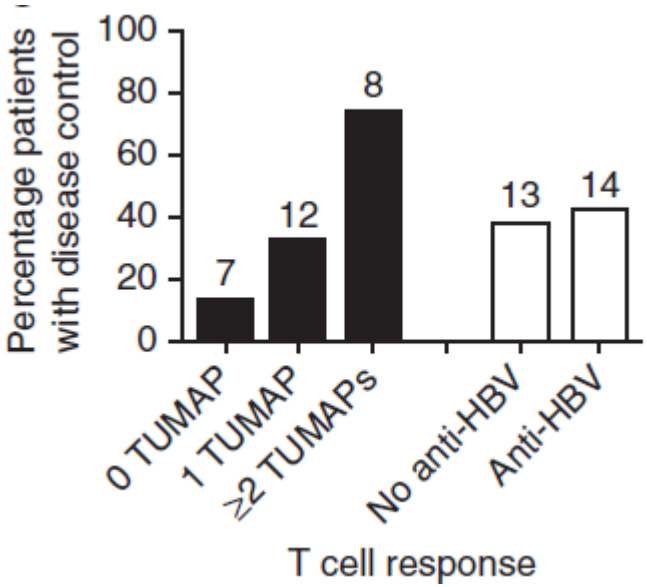
- **Heterogeneity of individual immune response**

- **Heterogeneity of individual tumor antigen signature**

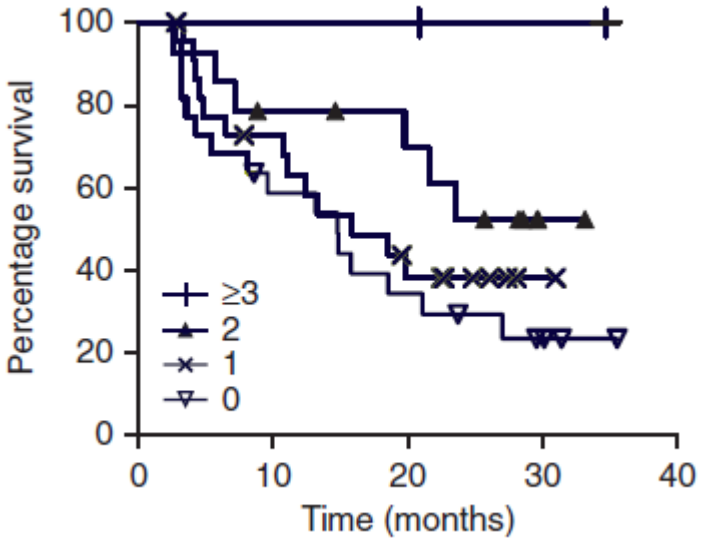
# IMA901 Renal Cell Cancer Vaccine

## Association of multiple immune responses to vaccine with clinical benefit

### IMA901 Phase 1 Study (N=28)




### IMA901 Phase 2 Study (N=68)




Walter, Weinschenk et al. (2012), Nature Medicine

# IMA901 renal cell cancer biomarker program
## Performance of ApoA1/CCL17 serum biomarker signature

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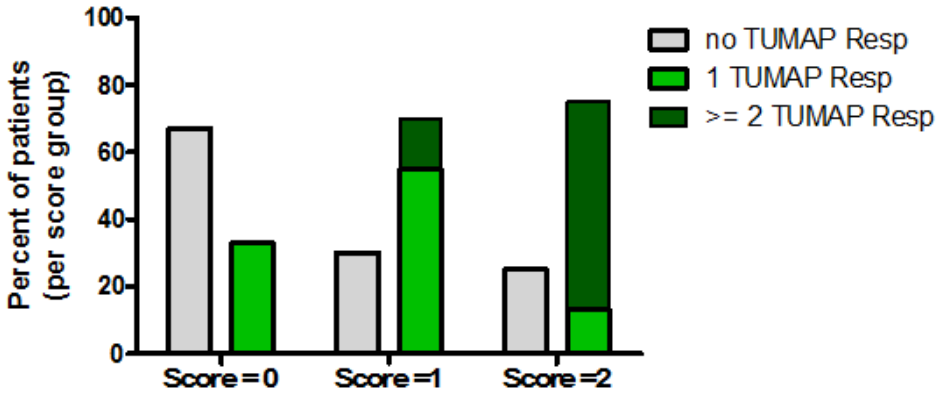
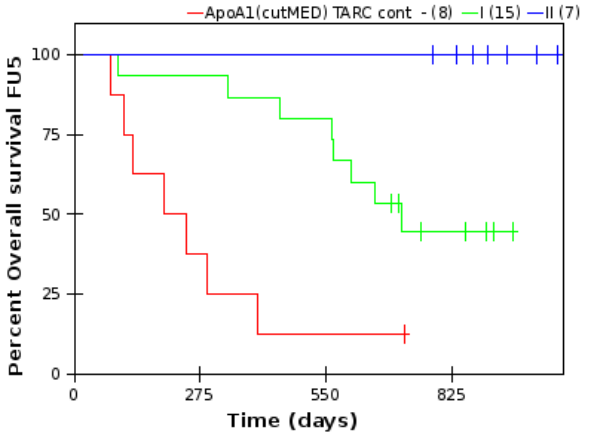
- **Biomarker score:** ***2*** *= both positive /* ***1*** *= one of both positive /* ***0*** *= both negative*
  - Primary hypothesis: **Biomarker-positive subgroup 1 (score >=1)** benefits more from IMA901

### T-cell response prediction




**P < 0.0001**

### Overall survival prediction




(TARC+ **&** ApoA1+, 25% of patients)

(TARC+ **or** ApoA1+, 50% of patients)

(TARC- **&** ApoA1-, 25% of patients)

# TUMAP responses *in vivo* vs *in vitro*

## Project “in vitro veritas“

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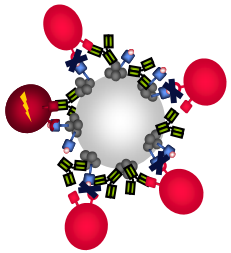
Preclinical

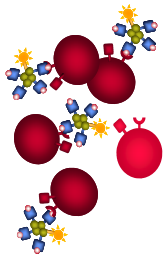
In vitro TUMAP immunogenicity testing

**1) *In vitro* priming with articificialAPC**



proliferation

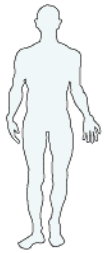
**2) Readout**



Clinical

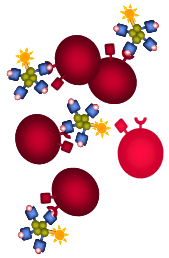
Vaccination

**1) *In vivo* priming**



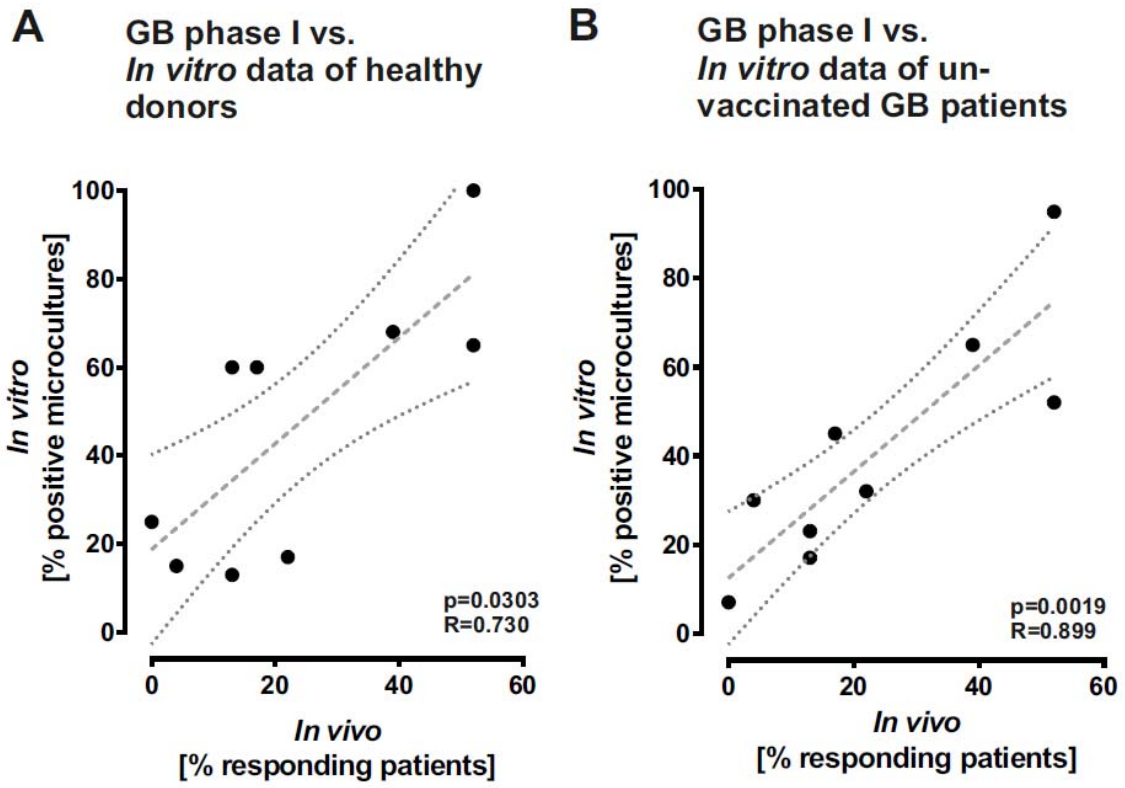
proliferation

**2) Immunomonitoring**



# T-cell response prediction

## preclinical *in vitro* vs. clinical *in vivo* immunogenicity for IMA950 vaccine in glioblastoma



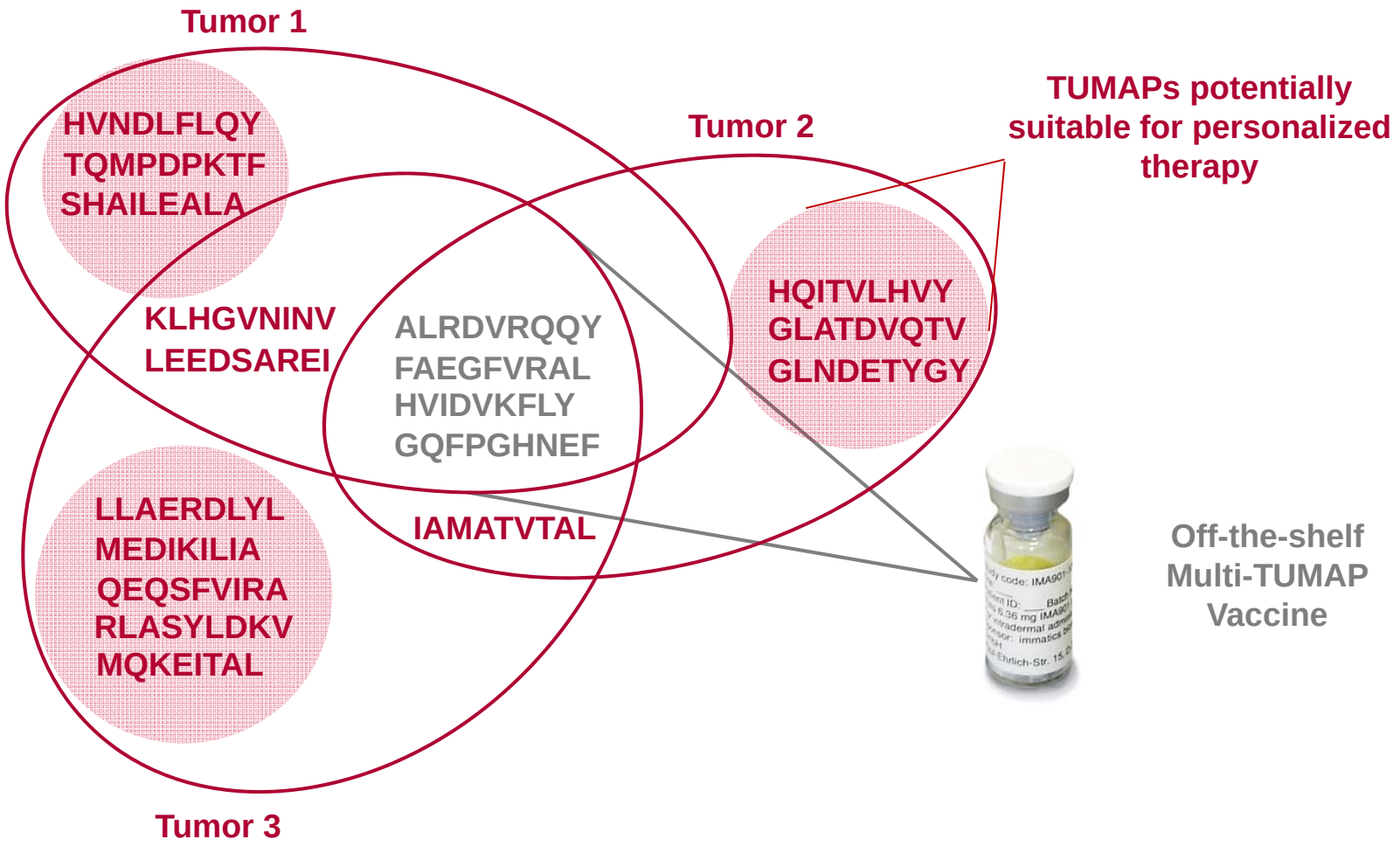

Preliminary *in vivo* immunogenicity is analysed based on **n=23 patients**

R and p values from spearman correlation
Linear regression with 90% confidence intervals

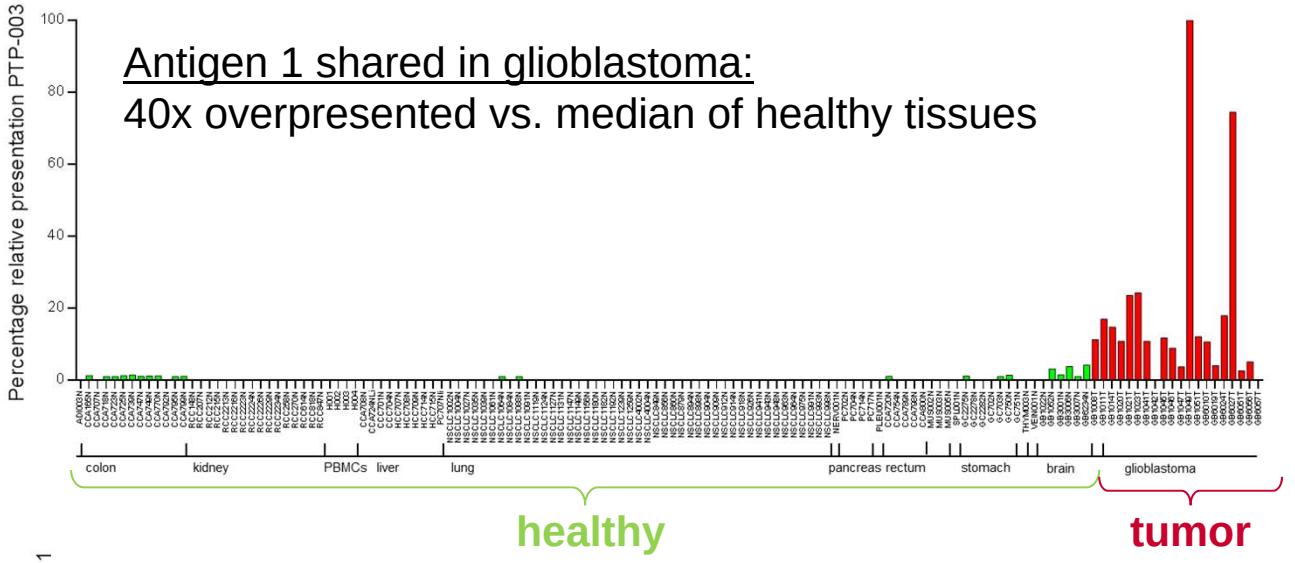
# Lesson learned from use of off-the-shelf cancer vaccines

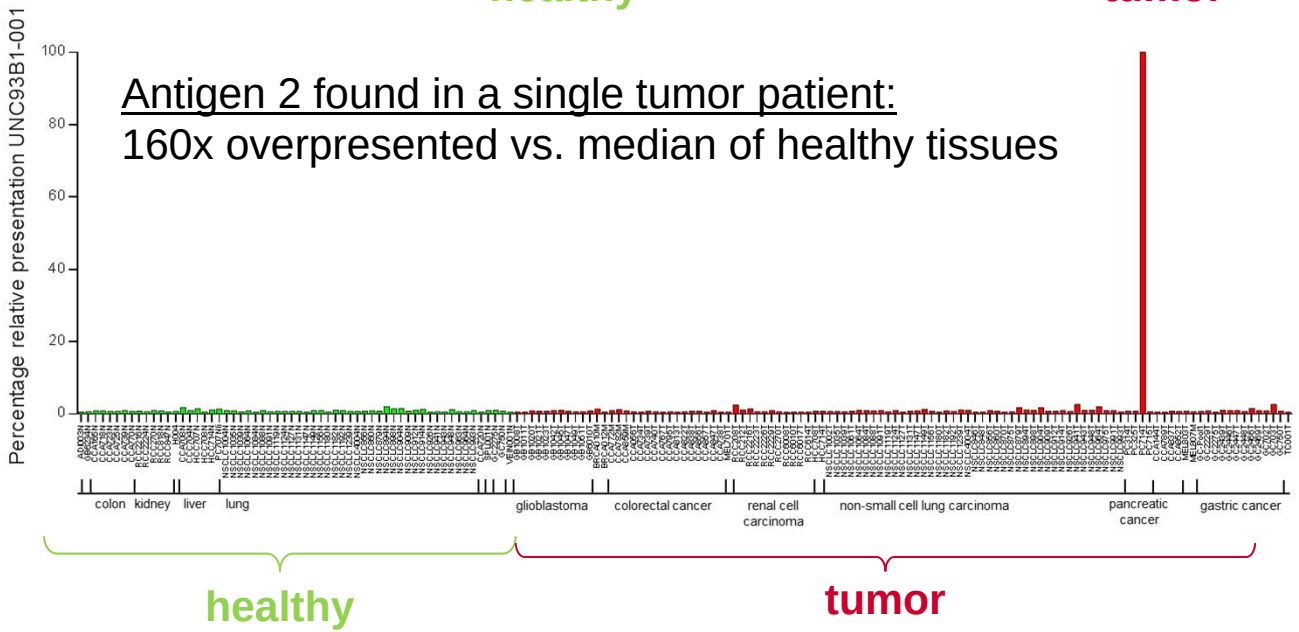
- Heterogeneity of individual immune response
- Heterogeneity of individual tumor antigen signature

# Tumor-associated peptides – shared vs. individual



# Quantitative HLA peptidomics with LC-MS/MS



# Lesson learned from use of off-the-shelf cancer vaccines

## Heterogeneity of individual immune response

→ Could be overcome by personalization:

- Selecting patients with higher likelihood for immune response
  (e.g. ApoA1/CCL17 serum biomarker candidate or in vitro testing)
- Selecting antigens with highest immunogenicity in individual patient

## Heterogeneity of individual tumor antigen signature

→ Could be overcome by personalization:

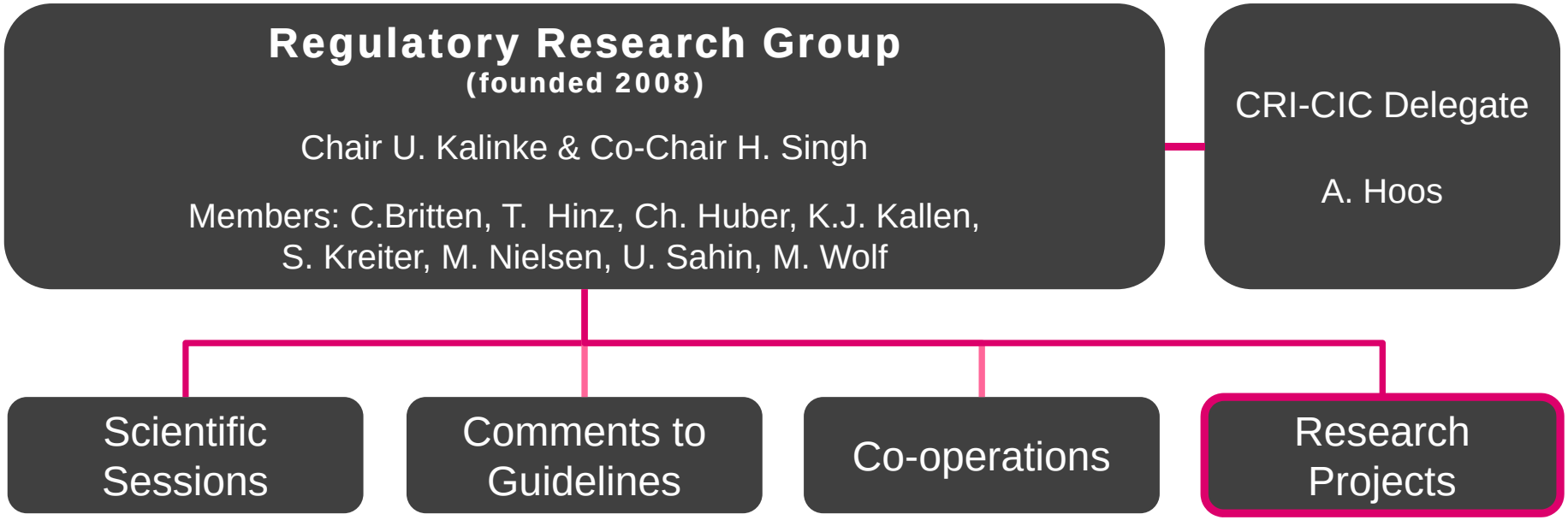
- Selecting patients with sufficient antigen expression
  (e.g. MAGE-A3 for GSK vaccine)
- Selecting antigens fitting to the antigen profile of individual tumor

# What is personalization?

**Selecting the patient for the vaccine?**

**Or fitting the vaccine to the patient?**

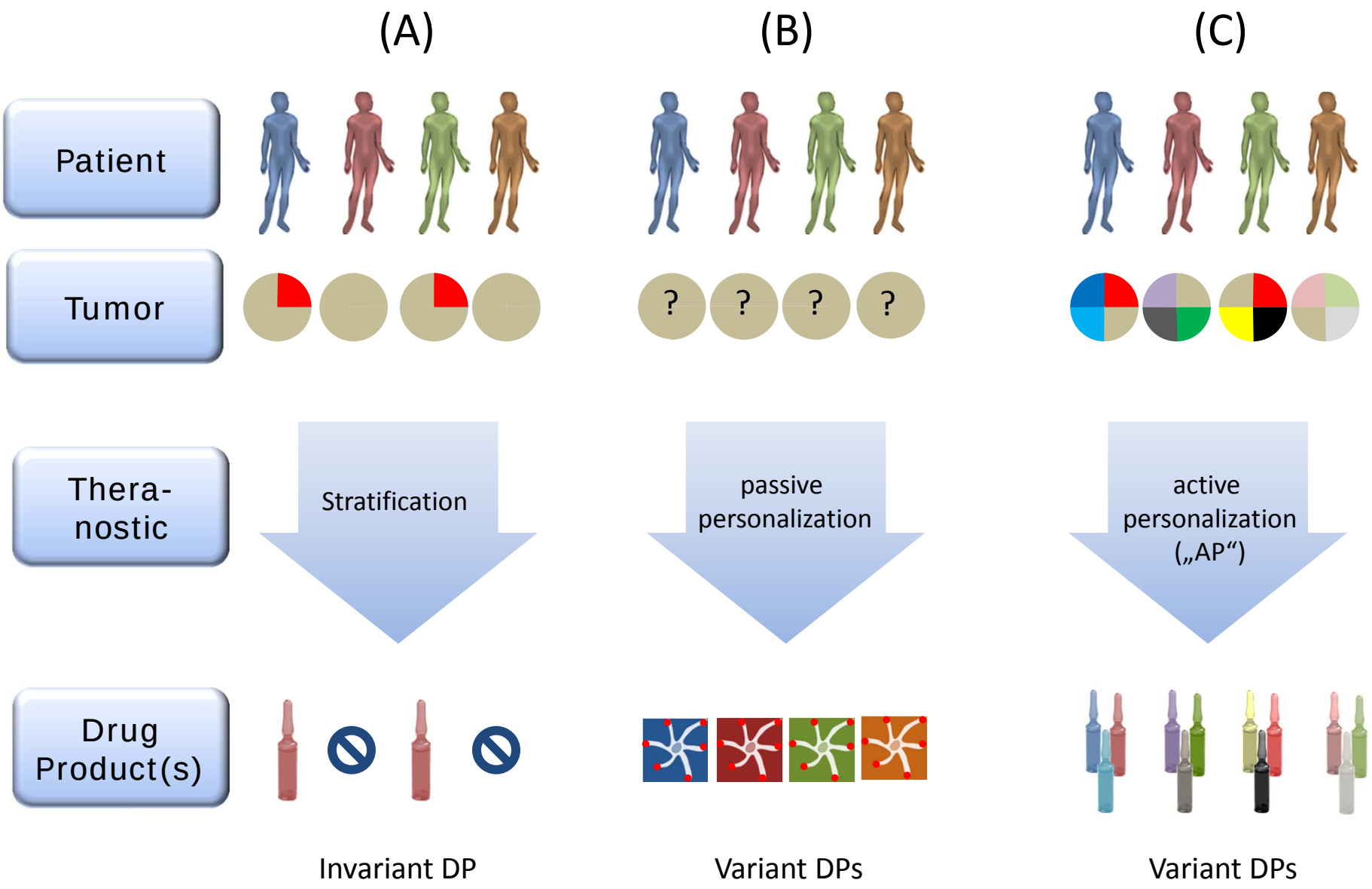
# CIMT – Regulatory Research Group RRG



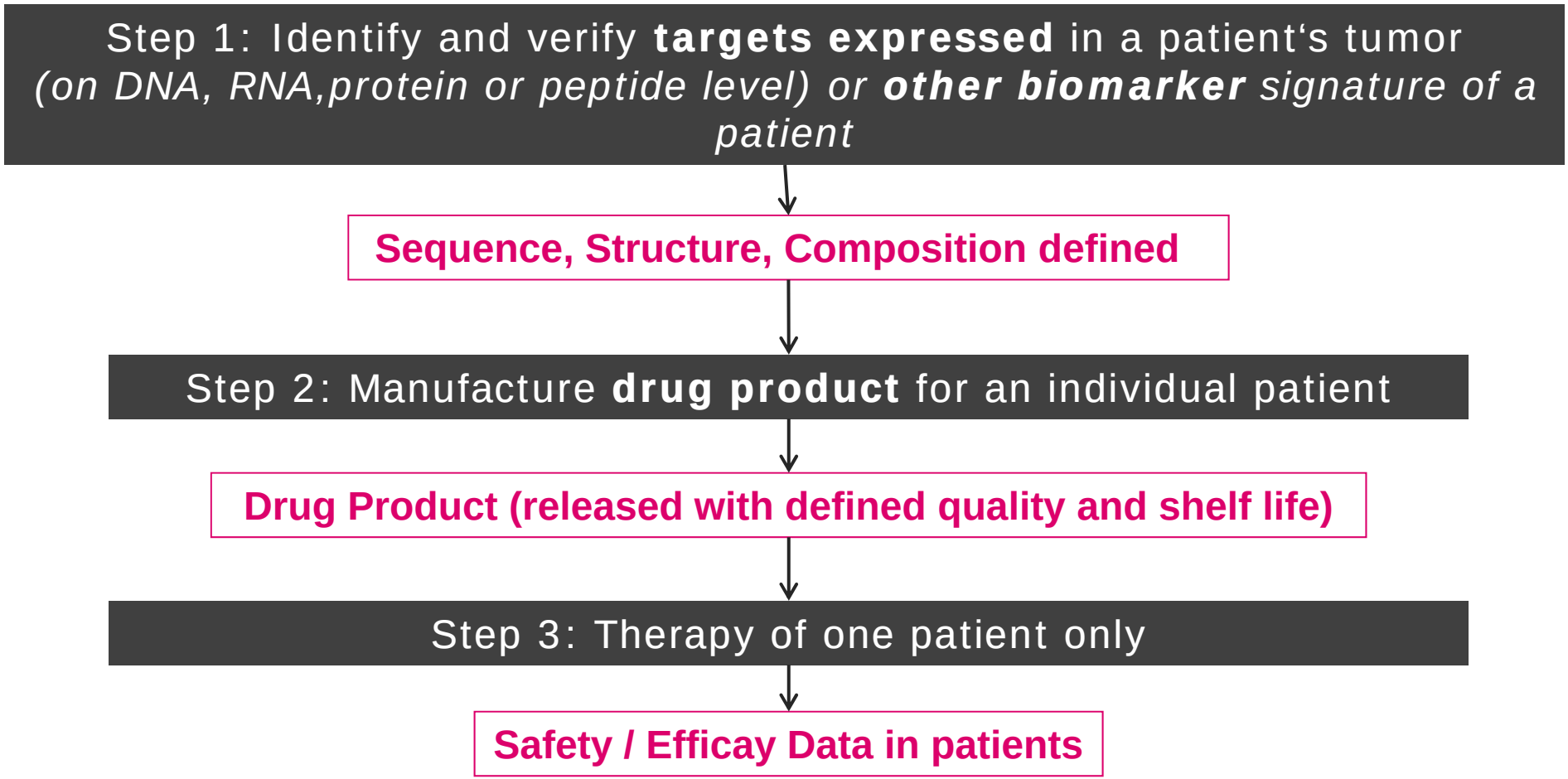

**RRG's main goal is to facilitate the translation of scientific knowledge from bench to bedside by**

- 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.

# Three Levels of Personalization



# Actively Personalized Vaccines - APVACs




There are two ways on how to obtain the individually tailored DPs - the **"warehousing"** approach and the **"*de novo* synthesis"** of DP components. **Typically** such approaches will address **multiple targets**.

# APVACs in the clinic – WAREHOUSING APPROACH

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Example: Phase I trial of a personalized peptide vaccine for patients positive for human leukocyte antigen A24 with glioblastoma multiforme.
Level: C
Developer: K. Itoh et al., Japan

Concept: (1) **Pool** of 14 known A24-restricted **peptide** candidates that (i) caused no serious adverse reactions, (ii) were capable of inducing peptide-specific cellular and specific humoral immunity and (iii) that had been administered to clinically responsive patients in previous trials
(2) **Personalized selection based** on existence of **pre-existing** humoral **immunity**. The **4** peptides showing the highest humoral titers were selected. Patients received 6 injections a 1,3 or 5 mg per peptide emulsified in Montanide ISA51.

Results: **Patients:** n=12 (glioblastoma)
**Safety:** No serious adverse drug reactions were encountered, and treatment was well tolerated.
**Immune responses:** CTL and humoral responses against fractions of peptides in fractions of patients
**Clinical efficacy:** 2 PR, 5 SD, 5 PD

*Terasaki et al., JCO 2011*

# APVACs in the clinic – DE NOVO SYNTHESIS

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Example: Individualized mutant p53-/K-ras-derived peptide vaccine
Level: C
Developer: J.A. Berzofsky et al., NCI, USA

Concept: (1) Genetic analysis of individual tumors for mutations in p53 and K-ras
(2) Custom GMP synthesis of 17-mer peptides corresponding to individual mutations
(3) Ex vivo pulsing of irradiated autologous PBMCs with patient-tailored peptides and re-administration i.v.

Results: **Patients:** n=39 (lung, colon, pancreas, ovarian; adjuvant and met)
**Safety:** No toxicities observed.
**Immune responses:** CTL lysis in 10/38 pts; CTL IFN-g responses in 16/38 pts.
**Clinical efficacy:** 5 SD in 29 pts with measurable disease.

*Carbone et al., JCO 2005*

# APVACs – Whole genome sequencing

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Example: Personalized whole genome-derived mutation-based vaccine
Level: C
Developers: HG Rammensee, University Tübingen, Germany (peptide-based)
U Sahin, University Mainz, Germany (RNA-based)

Concept: (1) Genetic analysis of individual tumors for somatic mutations based on whole genome analysis
(2) Selection and verification of mutiple mutations
(3) Custom GMP synthesis of vaccine encoding the selected individual mutations
(4) Vaccination of patients

Expansion: Due to the **whole genome** approach **mutations** will be identified that were **previously unknown.**
There is a scientific rationale for targeting **multiple mutations** in each individual patient.

# Glioma Actively Personalized VAccine Consortium

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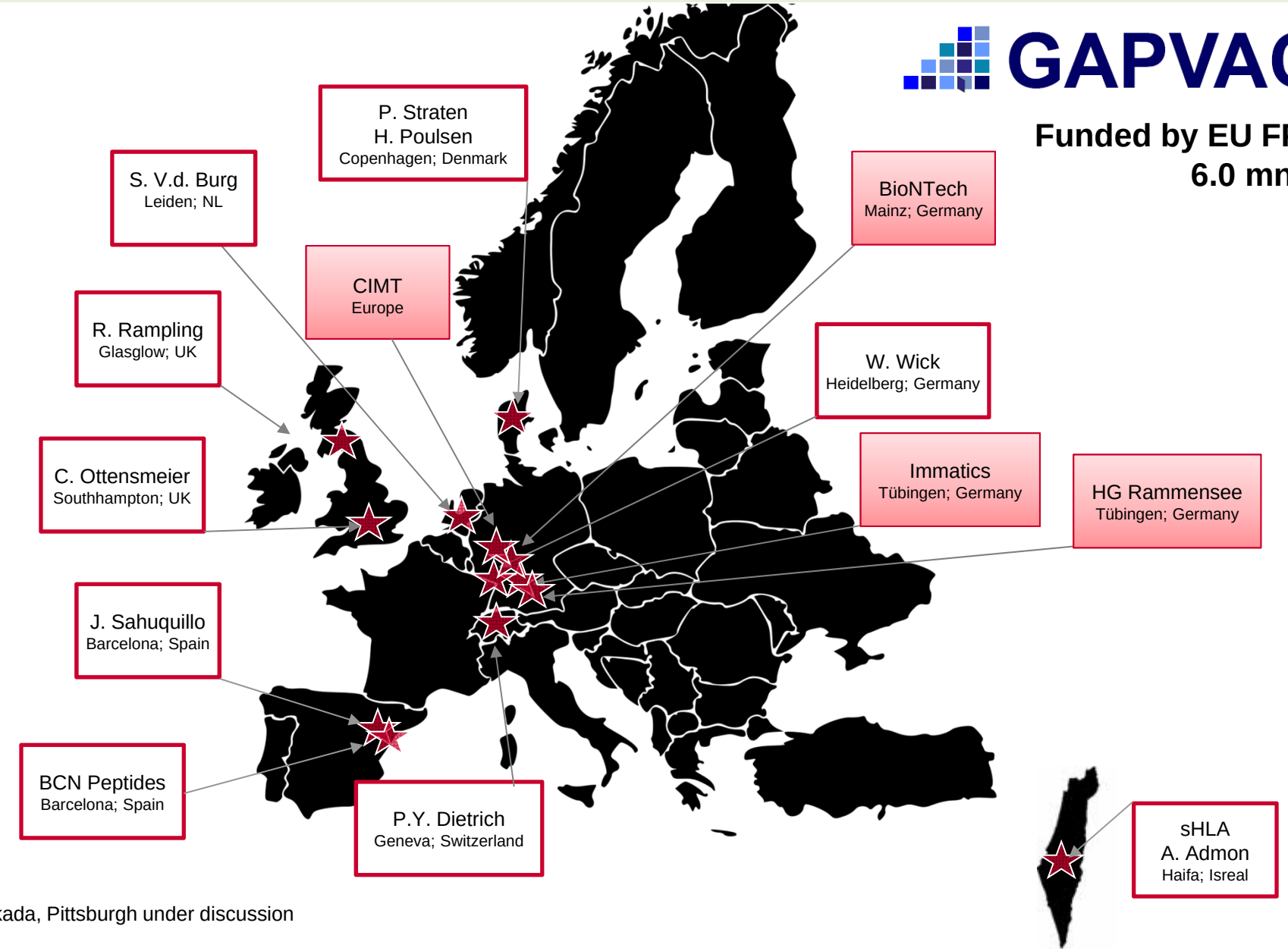
GAPVAC

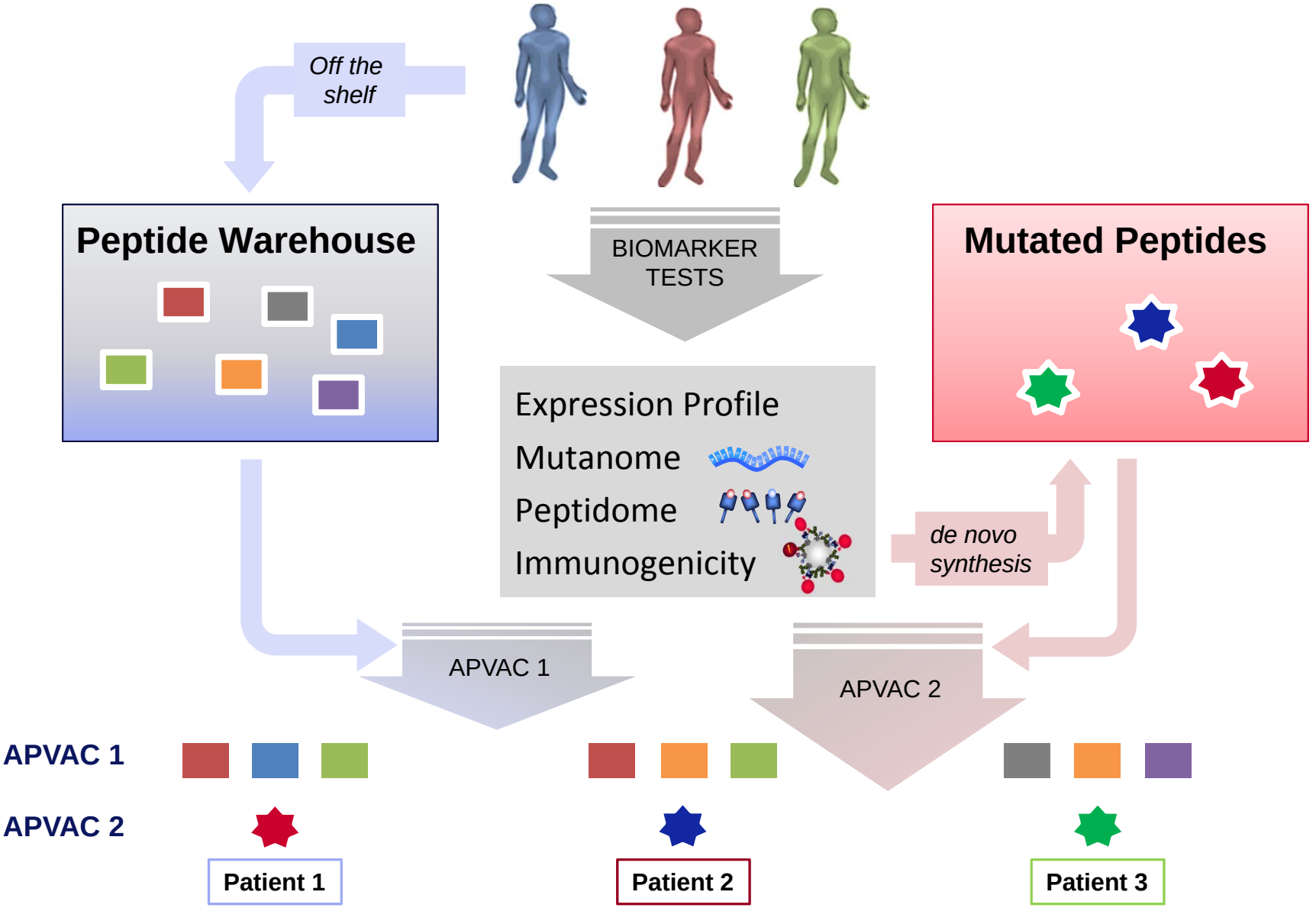
**Funded by EU FP7**
**6.0 mn €**




H. Okada, Pittsburgh under discussion

# GAPVAC Vaccine Approach

## Combining warehouse and de novo synthesis approach



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