IMA901- a novel multi-peptide vaccine for treatment of renal cell carcinoma

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TUMAPs = tumor-associated HLA-binding peptides

© Hans-Georg Rammensee (1991)
### Approach

- Develop therapeutic cancer vaccines based on **multiple** peptides derived from tumor-associated antigens
- Use **novel** peptides confirmed to be **naturally presented** on primary tumor tissue
- Multi-peptide vaccines are fully synthetic and provided as stable, lyophilized formulation
- Perform multi-centre clinical trials with centralized and highly standardized immunomonitoring
XPRESIDENT™ platform for identification of novel and naturally presented tumor-associated peptides

Collection of tissue samples

Normal cells
mRNA
Gene Chips
Over-expression tumor vs. healthy

Tumor cells
HLA peptides
LC-MS/MS
TUMAP sequences

Correlation

Synthesis of candidate TUMAPs

Blood

T cells
Imunoassays

ELISpot HLA tetramers

Selection of strongly immunogenic TUMAPs from relevant tumor antigens
A novel HLA-A*02-biding tumor-associated peptide from c-met proto-oncogene
1. Shotgun Identification *
2. Expression analysis *
3. Functional analysis
4. TUMAP re-detection **
5. TUMAP quantification **
6. TUMAP validation *

~100 promising TUMAPs
2000-5000 peptides associated with selected type of cancer

~20 high-potential TUMAPs

Month 0
Screen – Hit – Lead – Drug Candidate

Month 12
Pre-clinical Development

Month 24
Phase 1

7. Pharmaceutical development
8. GMP manufacturing
9. Filing of IMPD/IND

Product candidate comprising 10-12 TUMAPs

* patented / ** proprietary know how
IMA901: renal cell cancer

- **status**: phase 2 started in September 2007
- >200,000 new incidences worldwide (approx. 3% of all cancers), thereof approx. 60% late-stage
- 5-year survival rate <10% in stage IV disease
- Approved therapies: cytokines, TKIs (sorafenib, sunitinib, temsirolimus)
- RCC known as immunogenic tumor
- HLA class I and class II expression directly by tumor cells

Histology by Karin Klingel, Tübingen
<table>
<thead>
<tr>
<th>#</th>
<th>Peptide ID</th>
<th>Allele</th>
<th>Antigen</th>
<th>Common acronyms and synonyms</th>
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<tbody>
<tr>
<td>1</td>
<td>IMA-ADF-001</td>
<td>HLA-A*02</td>
<td>Adipophilin</td>
<td>adipose differentiation-related protein, ADRP</td>
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<td>2</td>
<td>IMA-APO-001</td>
<td>HLA-A*02</td>
<td>Apolipoprotein L1</td>
<td>APOL1</td>
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<tr>
<td>3</td>
<td>IMA-CCN-001</td>
<td>HLA-A*02</td>
<td>Cyclin D1</td>
<td>CCND1, PRAD1, parathyroid adenomatosis 1, BCL-1</td>
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<td>4</td>
<td>IMA-GUC-001</td>
<td>HLA-A*02</td>
<td>GUCY1A3</td>
<td>guanylate cyclase 1-soluble-alpha 3</td>
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<td>5</td>
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<td>HLA-A*02</td>
<td>KIAA0367</td>
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<td>6</td>
<td>IMA-MET-001</td>
<td>HLA-A*02</td>
<td>c-met proto-oncogene</td>
<td>MET, HGF (hepatocyte growth factor) receptor, HGFR</td>
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<td>7</td>
<td>IMA-MUC-001</td>
<td>HLA-A*02</td>
<td>MUC1</td>
<td>mucin, CD227, episialin, epithelial membrane antigen</td>
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<td>8</td>
<td>IMA-RGS-001</td>
<td>HLA-A*02</td>
<td>RGS-5</td>
<td>regulator of G-protein signalling 5</td>
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<td>9</td>
<td>IMA-ADF-002</td>
<td>HLA-A*02</td>
<td>Adipophilin</td>
<td>adipose differentiation-related protein, ADRP</td>
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<td>HLA-DR</td>
<td>MMP7</td>
<td>matrix metalloproteinase 7</td>
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<td>IMA-HBV-001</td>
<td>HLA-A*02</td>
<td>HBV core Antigen</td>
<td>HBc, HBcAg, cAg</td>
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</tbody>
</table>
An open label study
to evaluate safety and immunogenicity
of the peptide based therapeutic cancer vaccine IMA901
injected intradermally with GM-CSF as adjuvant
in patients with renal cell carcinoma

Phase 1

Study Code   IMA901-101

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P.Y. Dietrich, University Hospital of Geneva
A. Haferkamp / M. Hohenfellner, University of Heidelberg
J. Beck, University of Mainz
T. Eisen, Royal Marsden Hospital, London
IMA901 phase 1 study outline

- **Design** multi-centre, single arm phase 1
- **Patients** 28 patients with advanced renal cell carcinoma (HLA-A*02-positive)
- **Scope** 6 centers, 3 countries (DE, CH, UK)
- **Dose** 4.5 mg (400 µg per peptide) IMA901 i.d. 8x, 75 µg GM-CSF i.d. 8x
- **Primary Endpoint** Systemic safety, local tolerability
- **Secondary Endpoints** - Immunogenicity of IMA901
  - Pharmacokinetics intradermal GM-CSF
  - Any evidence of anti-tumor response
IMA901 phase 1 Vaccination schedule

<table>
<thead>
<tr>
<th>Screening</th>
<th>Vaccination (Treatment) Period</th>
<th>Follow-up Period</th>
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<tbody>
<tr>
<td>VISIT</td>
<td>VACCINATION</td>
<td></td>
</tr>
<tr>
<td>DAY</td>
<td>GM-CSF</td>
<td></td>
</tr>
<tr>
<td>WEEK</td>
<td>IMA901</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.2.3 4 5 6 7 8</td>
<td></td>
</tr>
<tr>
<td>T-CELL SAMPLE</td>
<td>S2  V1  V4  V5  V6  V7  V8</td>
<td>FU</td>
</tr>
</tbody>
</table>

Immunomonitoring: - peptide-specific T-cell responses (ELISpot/tetramer)
- Foxp3+ Tregs pre and post vaccination
Tumor assessment: - according to RECIST criteria at screening and follow-up
Example for raw data in tetramer assay

05-001 S2+V1
FL1: CD8
FL2: rK67-001
FL4: rCCN-001

05-001 V4+V5
FL1: CD8
FL2: rK67-001
FL4: rCCN-001

03-008 V6+V7
FL1: CD8
FL2: MUC-001
FL4: ADF-002

03-003 V4+V5
FL1: CD8
FL2: rK67-001
FL4: MET-001
Vaccine-induced T-cell responses

- N=27 patients evaluable for immune response
- T-cell response measured with ELISpot and tetramer assays
T-cell response kinetics (representative patient)

Patient 03004

Scheduled timepoint (scale in weeks)

% Tetramer+ among CD8+ T-cells

- TUMAP Pool
- HBV-001
- HIV-001
**Phenotyping of T-cell response (ex vivo, N=1)**

- Pre-vaccine T cells are of naïve phenotype
- Post-vaccine T cells are of effector memory phenotype
IMA901 Phase 1 Immunomonitoring
Example for Treg quantification

FL1: CD4
FL2: Foxp3
FL3: CD45

Gated on all cells.

Gated on lymphocytes.

Gated on CD45+
lymphocytes ->
automatic quadrant setting!

Patient 03-003
pre-vacc.

Patient 03-006
pre-vacc.
Patients with multiple TUMAP responses have significantly lower $T_{\text{REG}}$ levels in the periphery than patients with 0-1 TUMAP responses ($p=0.016$ Wilcoxon Test, N=26 pts)
Efficacy - Change of tumor size and T-cell response (ITT, n=28)
IMA901 is safe and well tolerated (data not shown)

IMA901 is immunogenic

- Vaccine-induced immune responses in 74% of pts.
- Multiple vaccine-induced responses in 30% of pts.

Multiple vaccine-induced immune responses to IMA901

- seem to inversely correlate with the level of regulatory T cells prior to vaccination (p=0.016)
- seem to correlate with the clinical outcome (partial response and stable disease according to RECIST) (p=0.015)

Next: multi-centre phase 2 trial in Europe (started Sept 2007)

- ~70 met RCC pts., 2nd line after TKI or cytokine therapy failure
- continous vaccination for 9 months, evaluation of the disease control rate at 6 months
- Evaluation of the impact of low-dose cyclophosphamide on Tregs, MDSC and immune responses in a randomized fashion (+/- CY)
Broad-spectrum tyrosine kinase inhibitors (TKIs) were recently approved for treatment of metastatic RCC pts

Question: can TKIs be combined with vaccination simultaneously or sequentially?

Assessment of impact of sorafenib and sunitinib on immune cells in vitro and in vivo
Sorafenib but not sunitinib inhibits human T-cell activation in (allogeneic) mixed lymphocyte culture

- Data not shown: very similar observation for CD4+ T cells
Sorafenib and sunitinib have no impact on human T-cell activation by artificial peptide-presenting APCs in vitro

Melan-A-specific CD8+ T-cell in vitro priming
Sorafenib but not sunitinib inhibits the LPS-mediated maturation of human mDCs in vitro

- Data not shown: no effect of sunitinib on maturation of mDCs
- Data not shown: sorafenib but not sunitinib affects the migrations capacities of mDCs and downmodulates CCR7

Hipp et al., submitted
Combination of peptide vaccination in mice and TKI simultaneously: sorafenib but not sunitinib inhibits OVA peptide-induced T-cell responses in C57BL/6 mice.

Hipp et al., submitted
Sunitinib is compatible with

- *in vitro* antigen-induced T-cell expansion (human and mouse)
- *in vitro* TLR-mediated DC maturation (human)
- *in vivo* peptide-induced T-cell proliferation (mouse)

On the other hand, sorafenib significantly inhibits all of these immunological endpoints

- **but:** the inhibition by sorafenib is reversible within days in mice (not shown)

Sunitinib but not sorafenib slightly decreases regulatory T cell levels in mice

Sorafenib but not sunitinib affects MyD88-dependent and MyD88-independent signaling pathways in APCs (not shown)
Co-workers and Collaborators
IMA901 Pre-clinical and Phase 1 / TKI project

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