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

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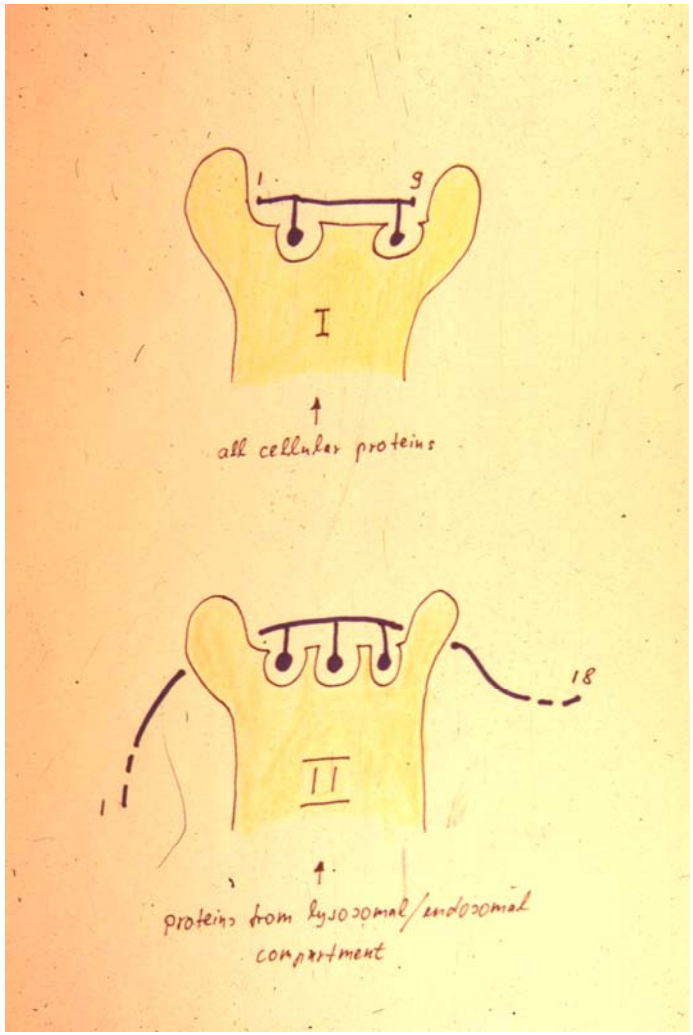
iSBTc 2007, Boston MA

immatics

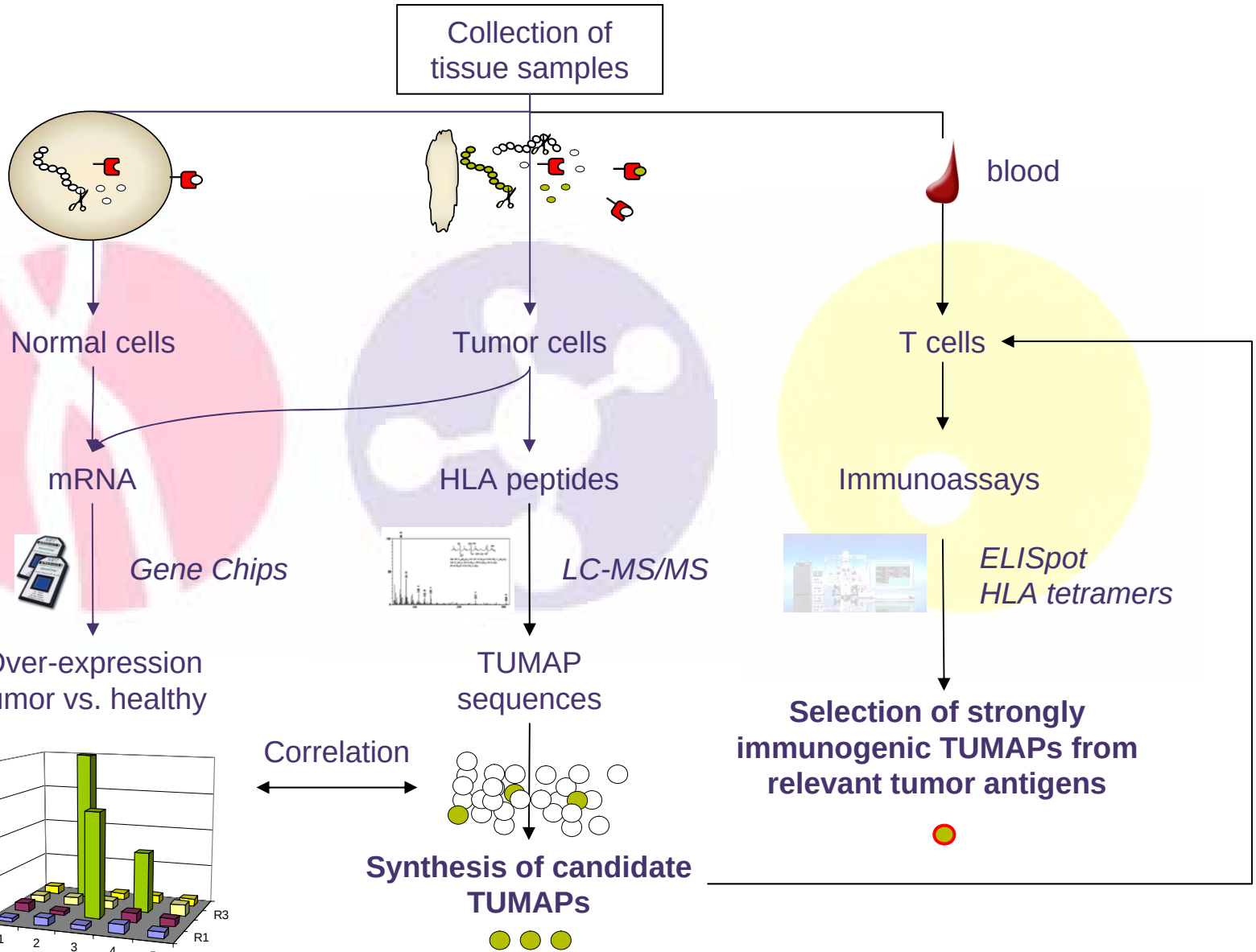
TUMAPs = tumor-associated HLA-binding peptides



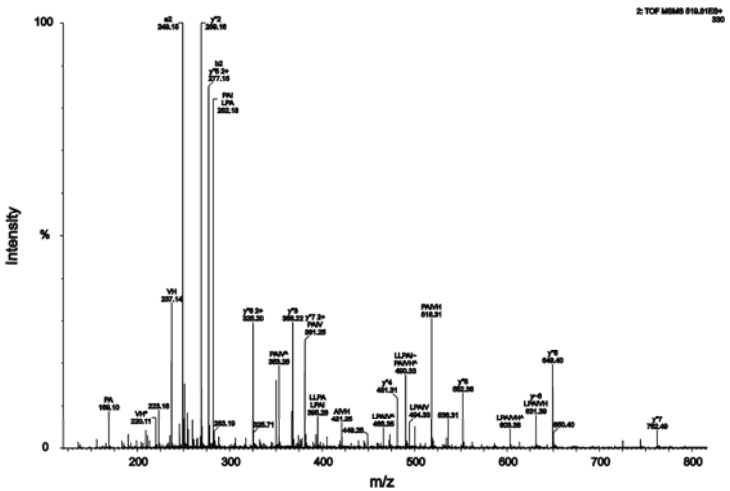
Approach

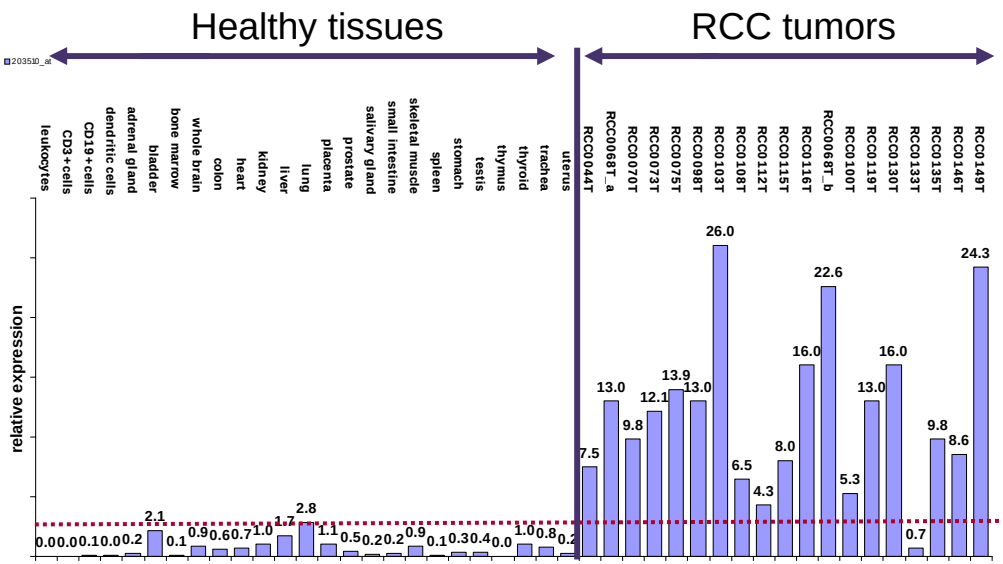
- Develop therapeutic cancer vaccines based on multiple peptides derived from tumor-associated antigens
- Use novel peptides confirmed to be naturally presented on primary tumor tissue
- Multi-peptide vaccines are fully synthetic and provided as stable, lyophilized formulation
- Perform multi-centre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

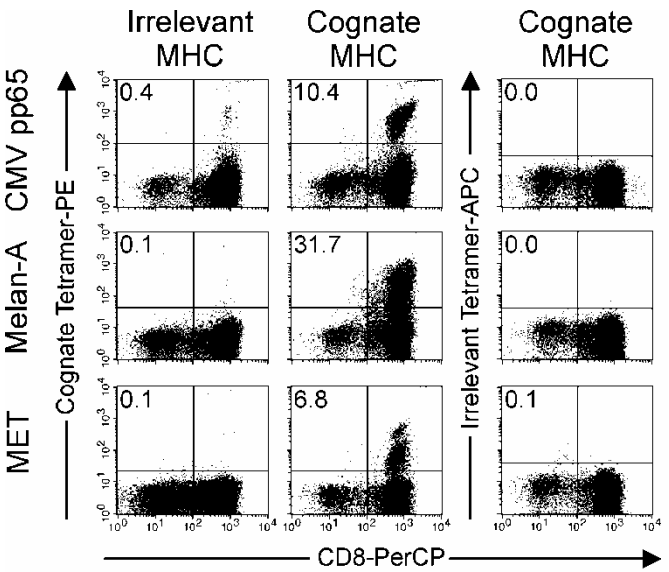
XPRESIDENT™ platform for identification of novel and naturally presented tumor-associated pepties

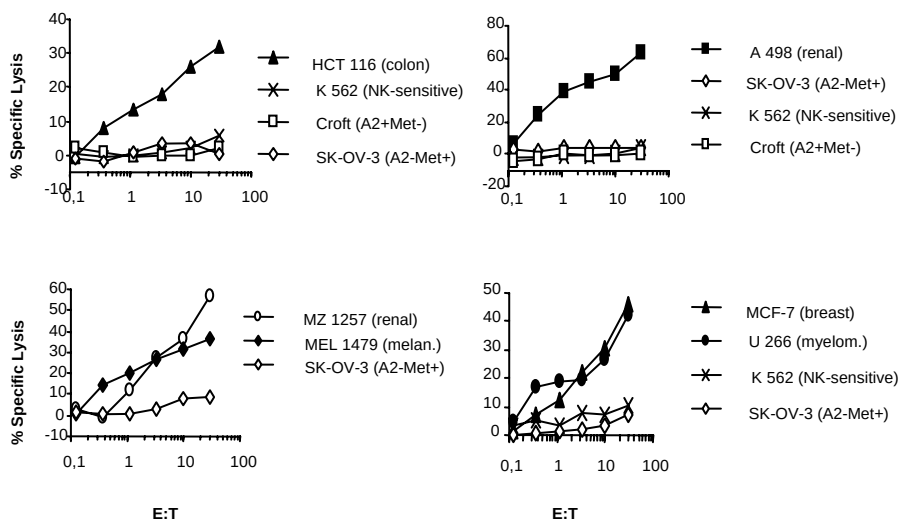


A novel HLA-A*02-biding tumor-associated peptide from c-met proto-oncogene







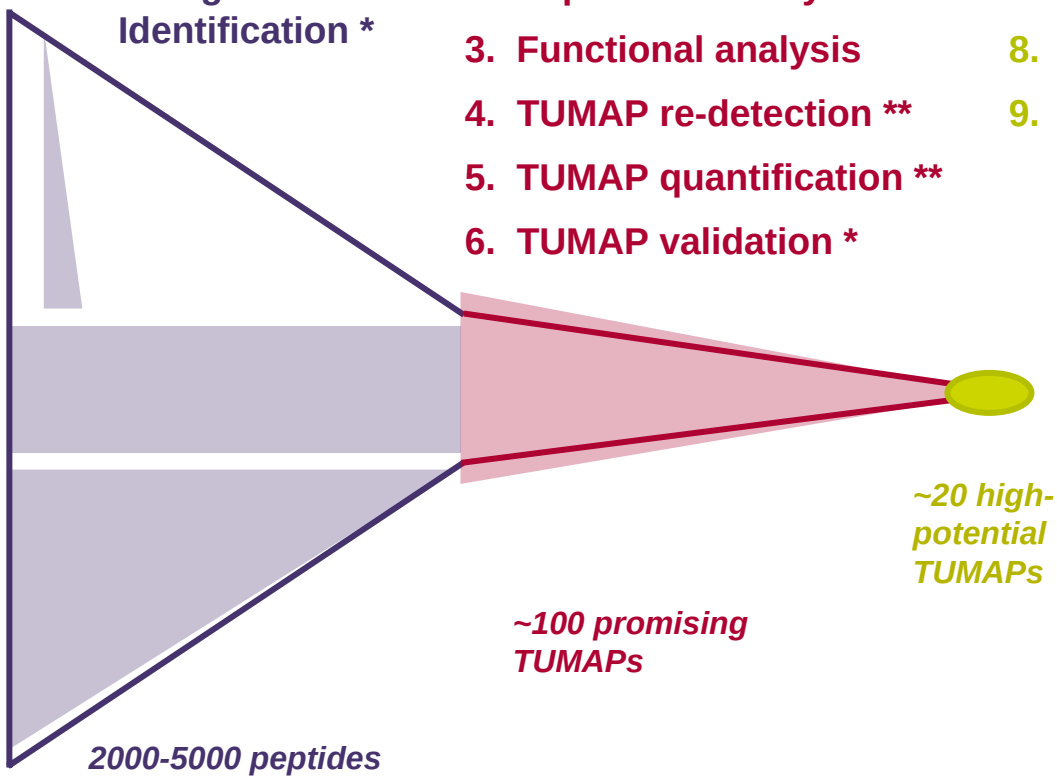


TUMAP Development Platform

Month 0 — Month 12 — Month 24

Screen – Hit – Lead – Drug Candidate → Pre-clinical Development → Phase 1

1. Shotgun Identification *
2. Expression analysis *
3. Functional analysis
4. TUMAP re-detection **
5. TUMAP quantification **
6. TUMAP validation *
7. Pharmaceutical development
8. GMP manufacturing
9. Filing of IMPD/IND



2000-5000 peptides associated with selected type of cancer

~100 promising TUMAPs

~20 high-potential TUMAPs

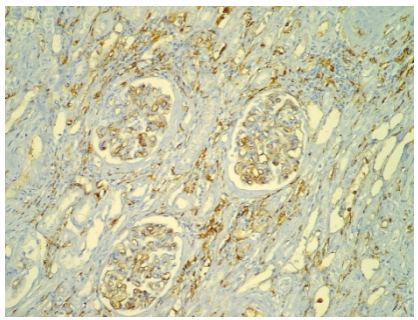
Product candidate comprising 10-12 TUMAPs

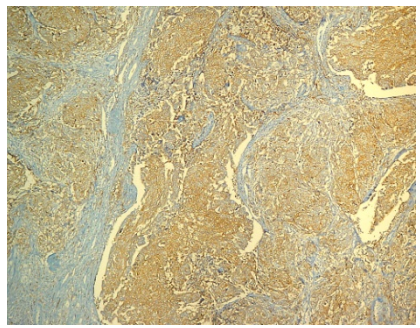
*** patented / ** proprietary know how**

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

HLA class II expression in healthy renal tisusue (endothelial cells and monocytes)





HLA class II expression in RCC

Histology by Karin Klingel, Tübingen

Composition of IMA901 for treatment of renal cell carcinoma

#	Peptide ID	Allele	Antigen	Common acronyms and synonyms
1	IMA-ADF-001	HLA-A*02	Adipophilin	adipose differentiation-related protein, ADRP
2	IMA-APO-001	HLA-A*02	Apolipoprotein L1	APOL1
3	IMA-CCN-001	HLA-A*02	Cyclin D1	CCND1, PRAD1, parathyroid adenomatosis 1, BCL-1
4	IMA-GUC-001	HLA-A*02	GUCY1A3	guanylate cyclase 1-soluble-alpha 3
5	IMA-K67-001	HLA-A*02	KIAA0367	--
6	IMA-MET-001	HLA-A*02	c-met proto-oncogene	MET, HGF (hepatocyte growth factor) receptor, HGFR
7	IMA-MUC-001	HLA-A*02	MUC1	mucin, CD227, episialin, epithelial membrane antigen
8	IMA-RGS-001	HLA-A*02	RGS-5	regulator of G-protein signalling 5
9	IMA-ADF-002	HLA-A*02	Adipophilin	adipose differentiation-related protein, ADRP
10	IMA-MMP-001	HLA-DR	MMP7	matrix metalloproteinase 7
11	IMA-HBV-001	HLA-A*02	HBV core Antigen	HBc, HBcAg, cAg

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

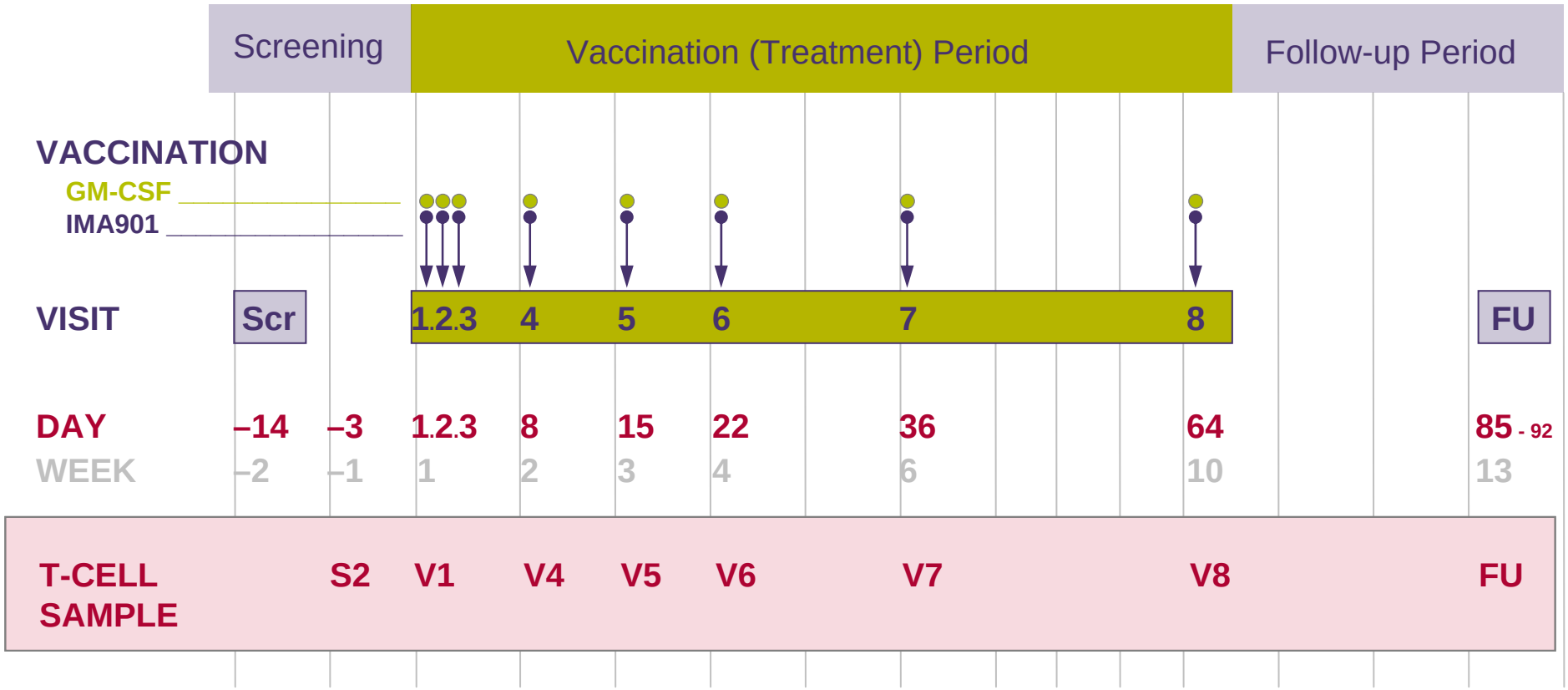
Study Code IMA901-101

A. Stenzl, University Hospital of Tübingen
M. Stähler / Ch. Stief, Klinikum Grosshadern, Munich
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



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

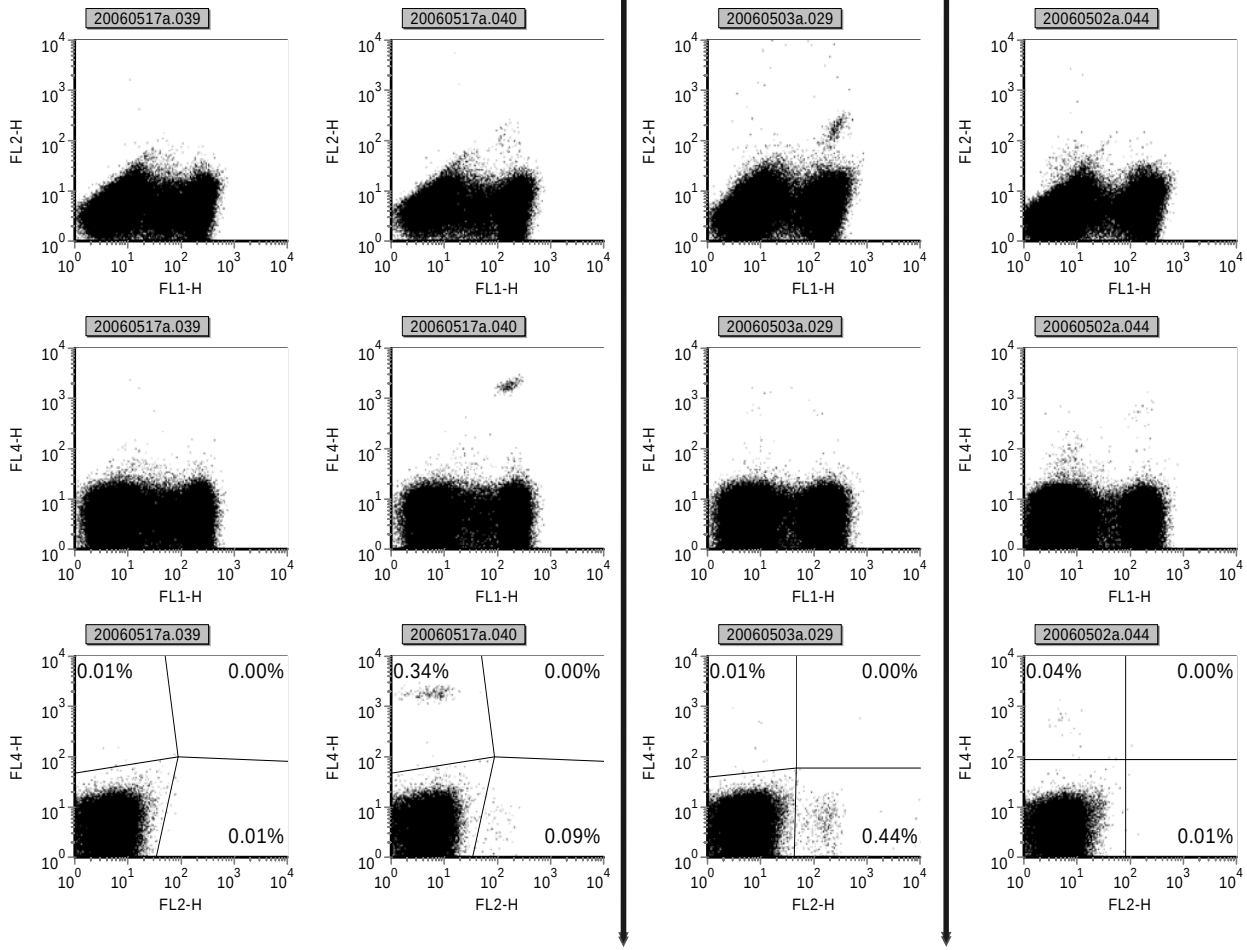
IMA901 Phase 1 Immunomonitoring
Example for raw data in tetramer assay

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

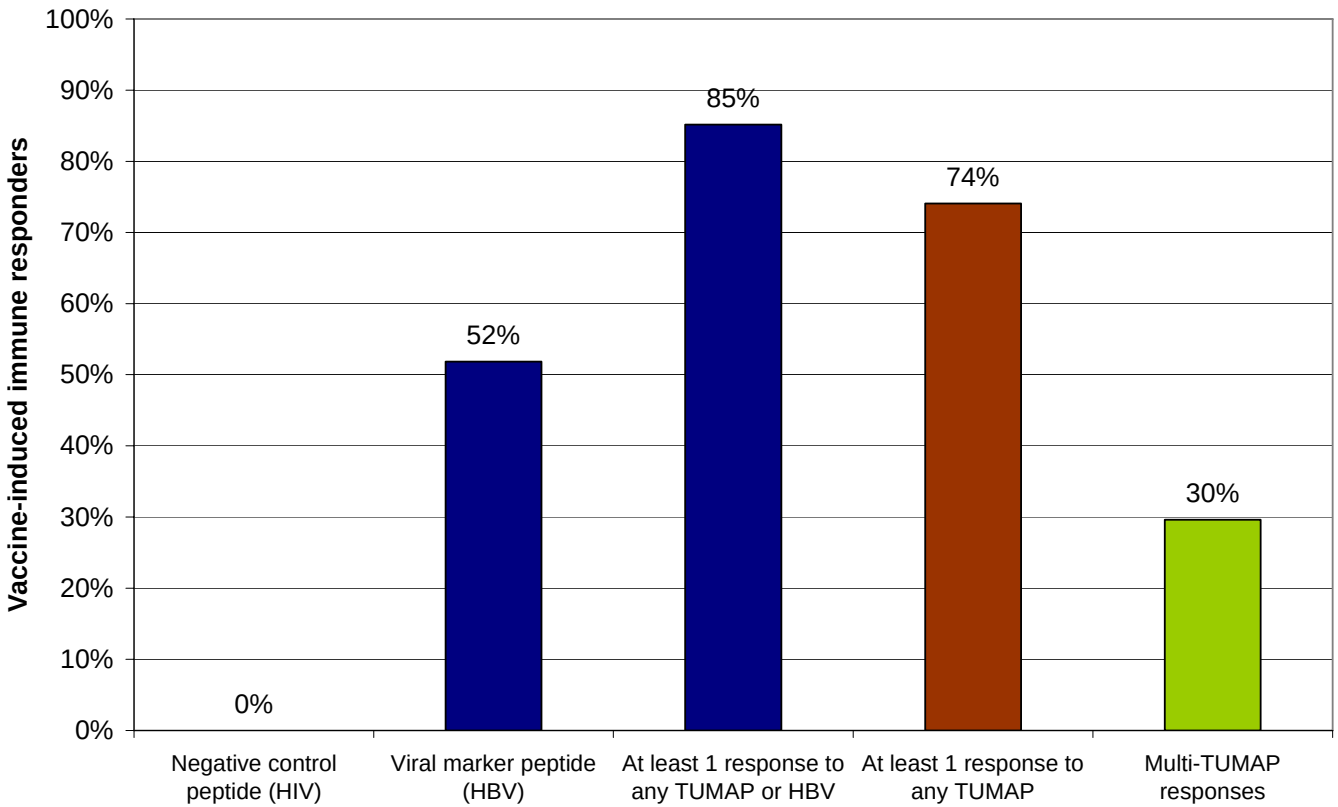
03-003 V4+V5
FL1: CD8
FL2: rK67-001
FL4: MET-001



T-cell Responses in Phase 1
IMA901-101 Immunomonitoring

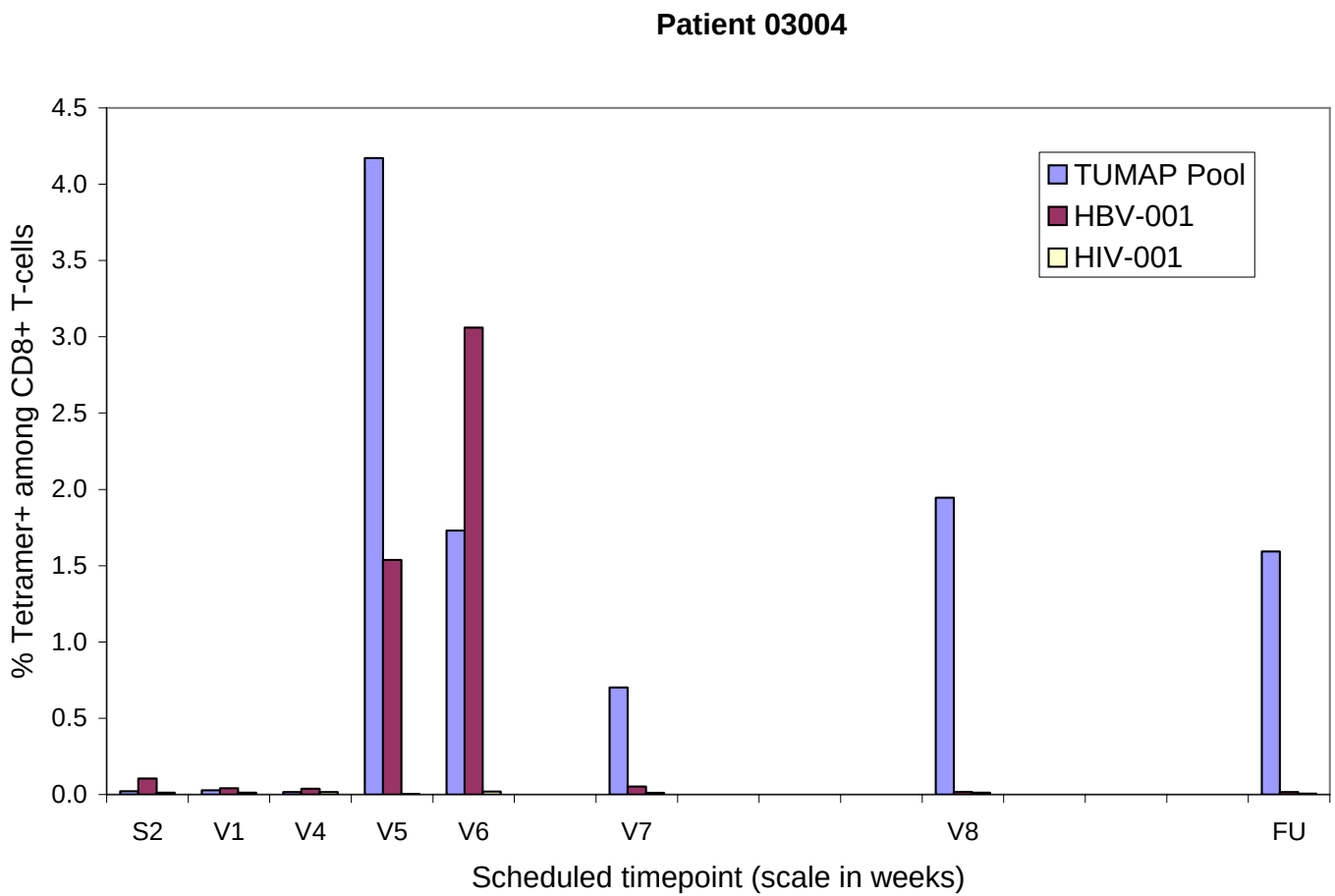
Vaccine-induced T-cell responses

- N=27 patients evaluable for immune response
- T-cell response measured with ELISpot and tetramer assays



IMA901 Phase 1 Immunomonitoring Kinetics

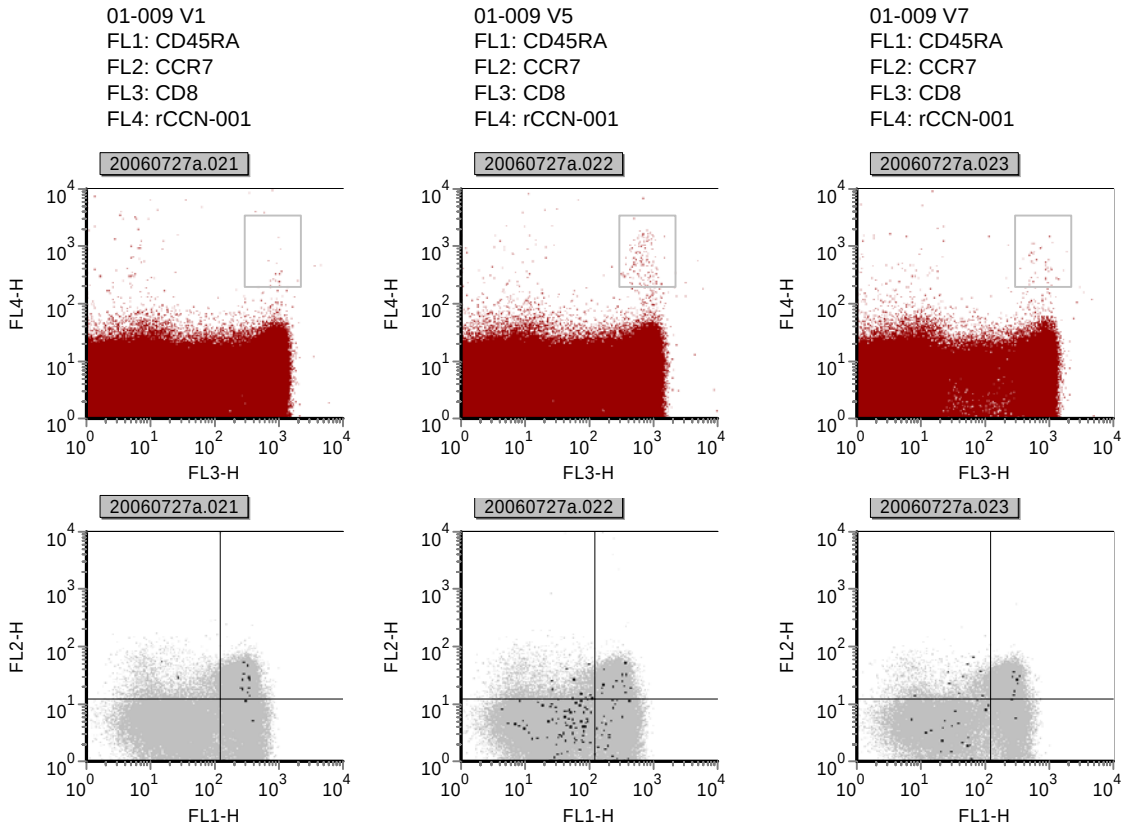
T-cell response kinetics (representative patient)



IMA901 Phase 1 Immunomonitoring
Ex vivo phenotyping

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

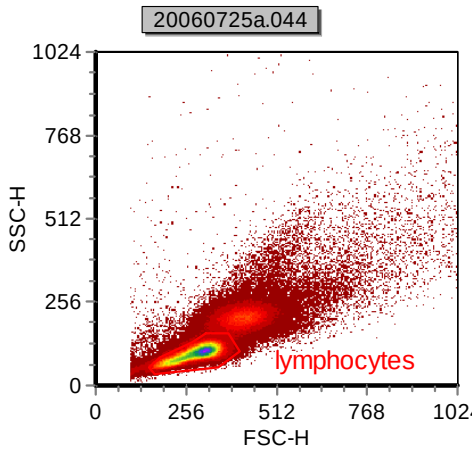
FL1: CD4
FL2: Foxp3
FL3: CD45

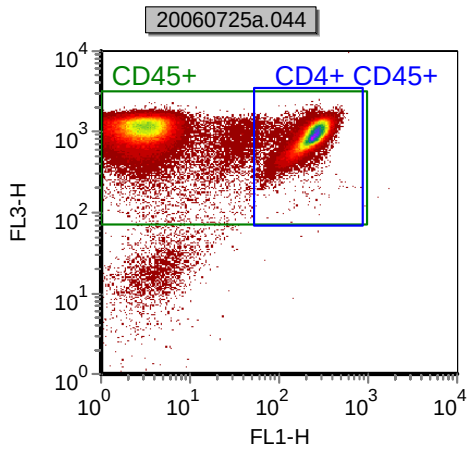
Gated on all cells.

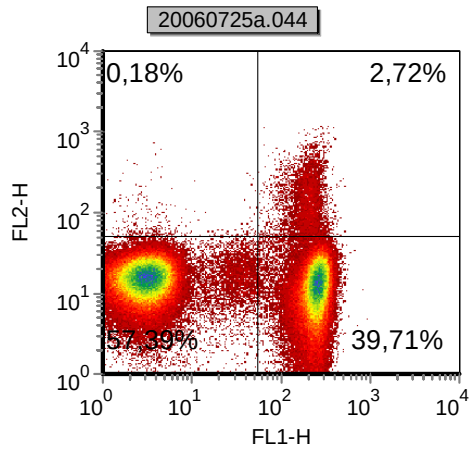
Gated on lymphocytes.

Gated on CD45+ lymphocytes -> **automatic quadrant setting!**

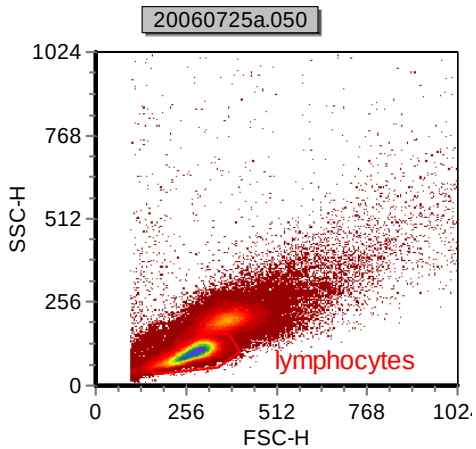
Patient 03-003 pre-vacc.

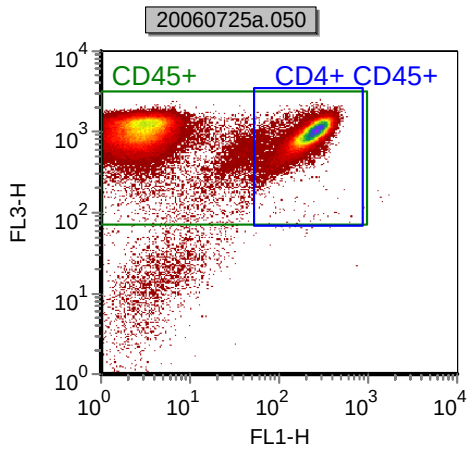


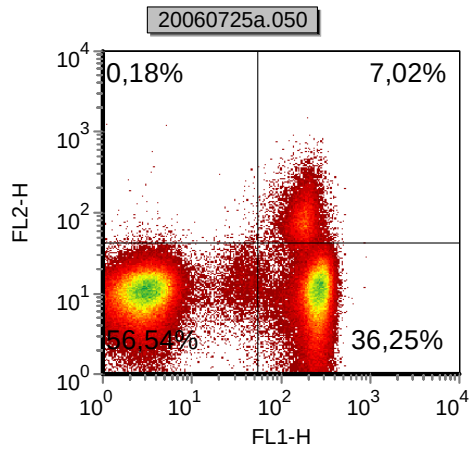




Patient 03-006 pre-vacc.







IMA901 phase 1 immunomonitoring
Regulatory T cells and **T-cell response**

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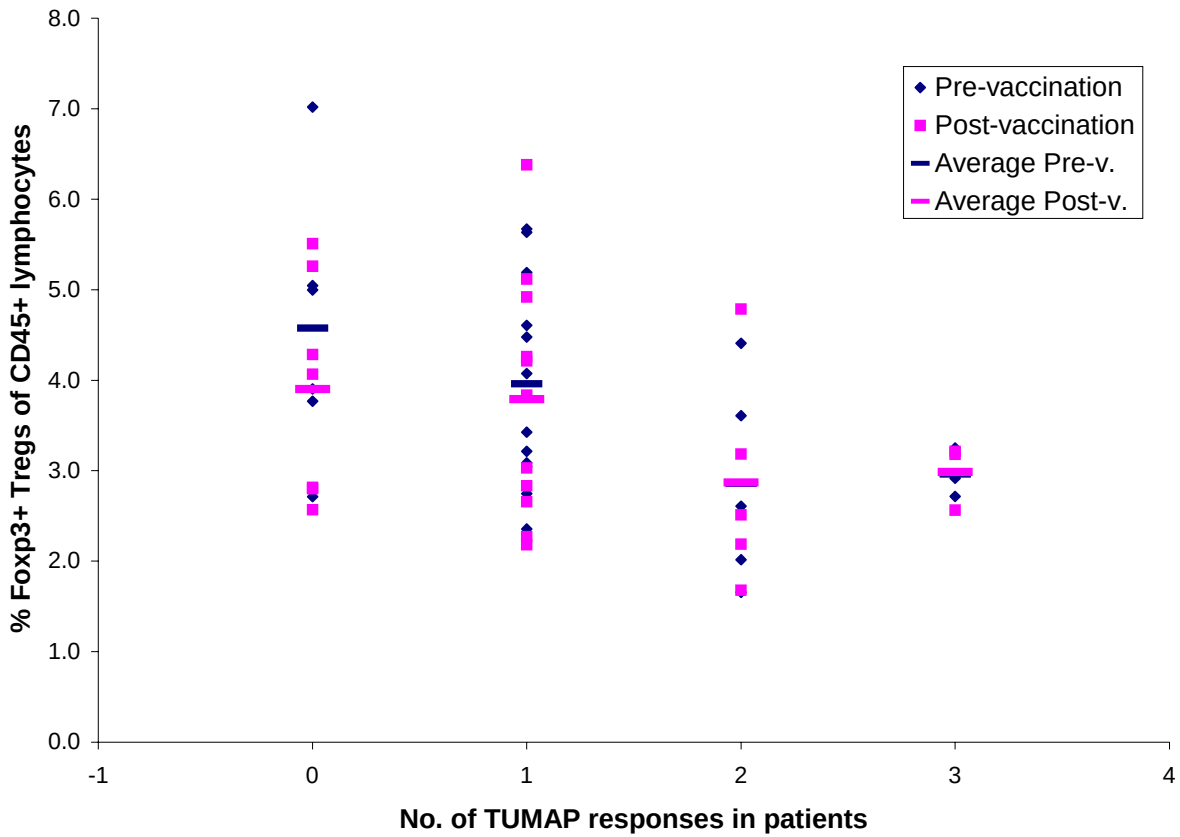
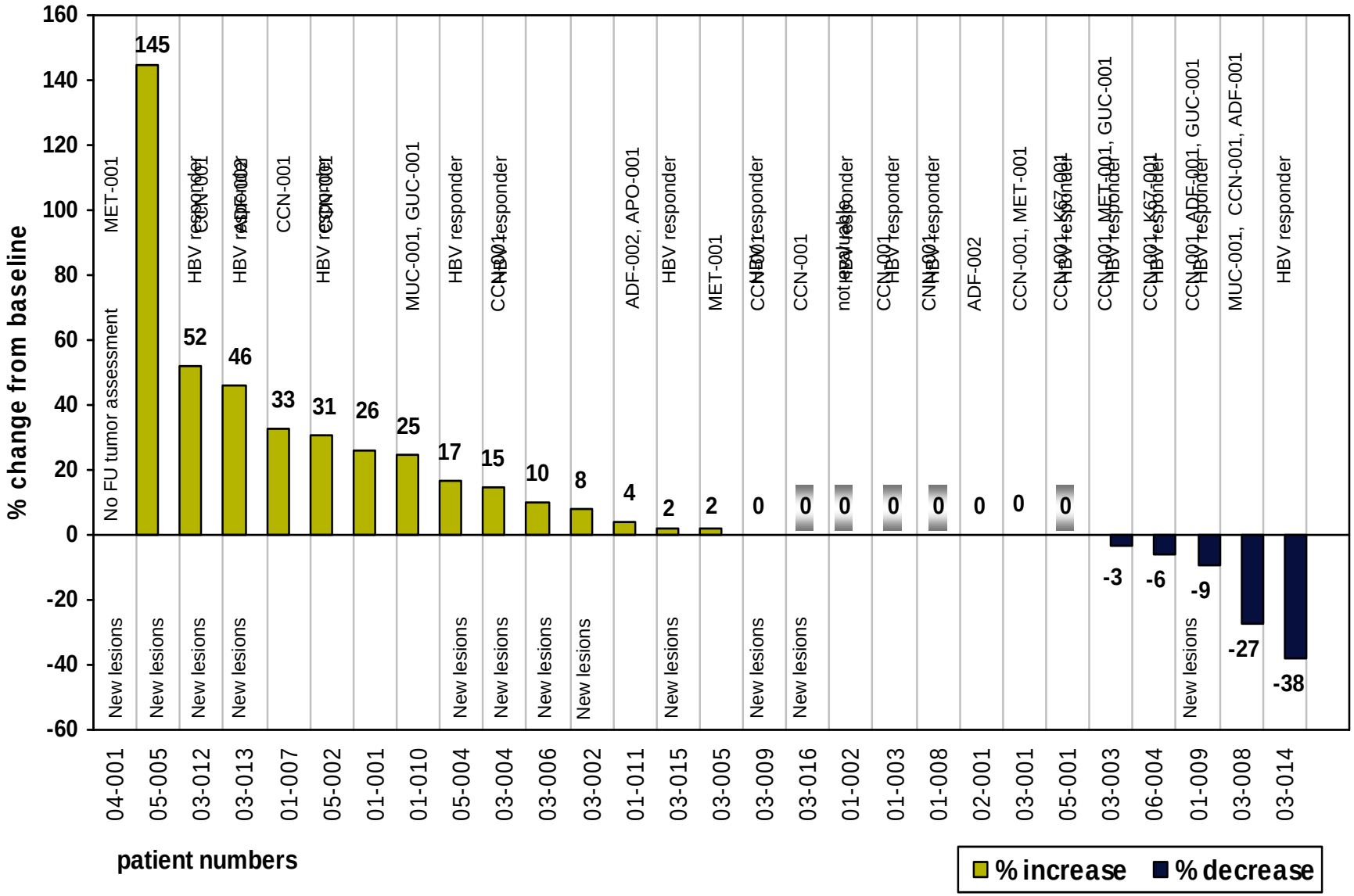
Patients with <u>multiple</u> TUMAP responses have significantly lower T_{REG} levels in the periphery than patients with 0-1 TUMAP responses (p=0.016 Wilcoxon Test, N=26 pts)



Efficacy - Change of tumor size and T-cell response (ITT, n=28)



IMA901 Clinical Study Phase 1
Conclusions

- **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 vaccinaton (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)

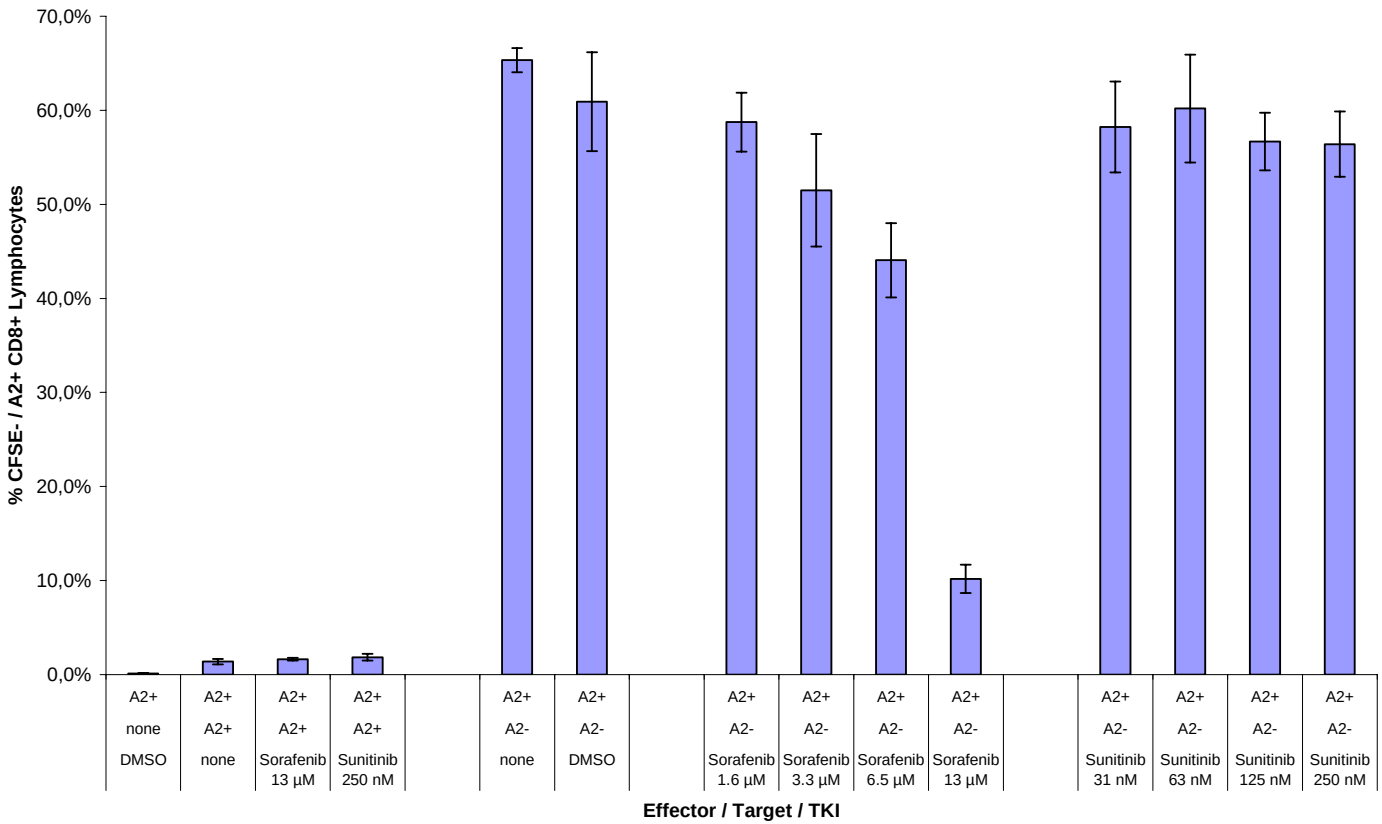
Impact of sunitinib and sorafenib on immune cells

- **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**

Impact of sunitinib and sorafenib on immune cells

Sorafenib but not sunitinib inhibits human T-cell activation in (allogeneic) mixed lymphocyte culture

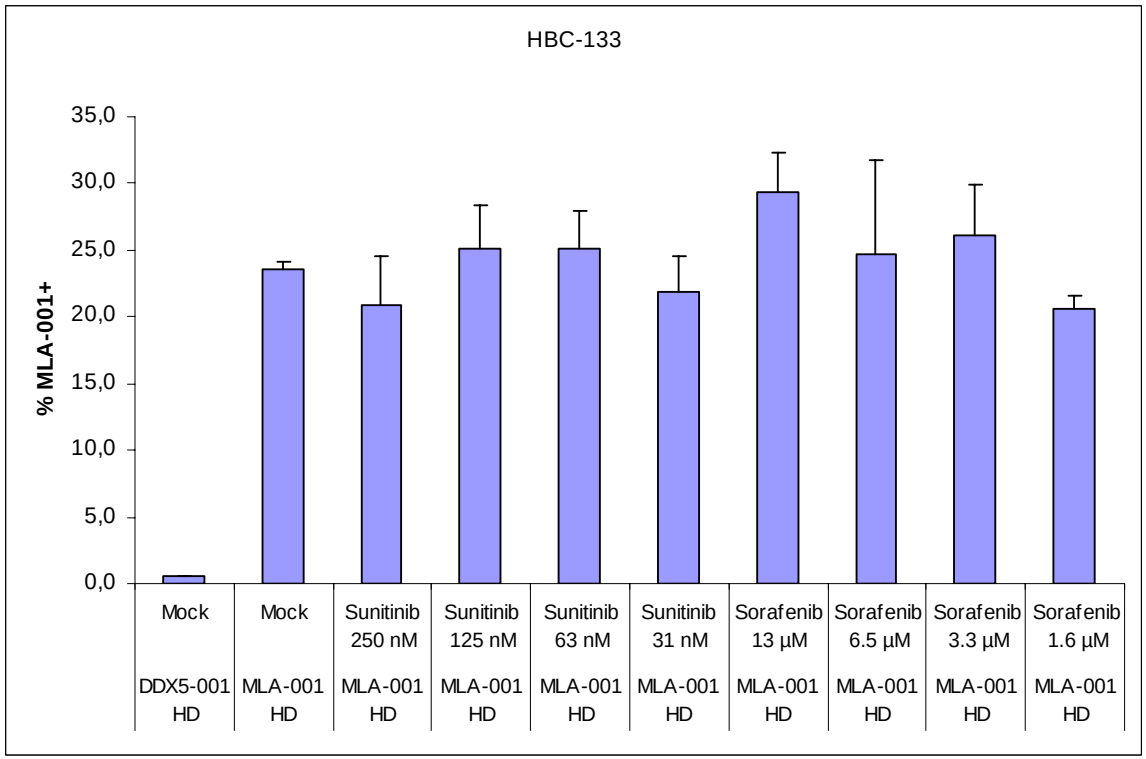
CD8+



- Data not shown: very similar observation for CD4+ T cells

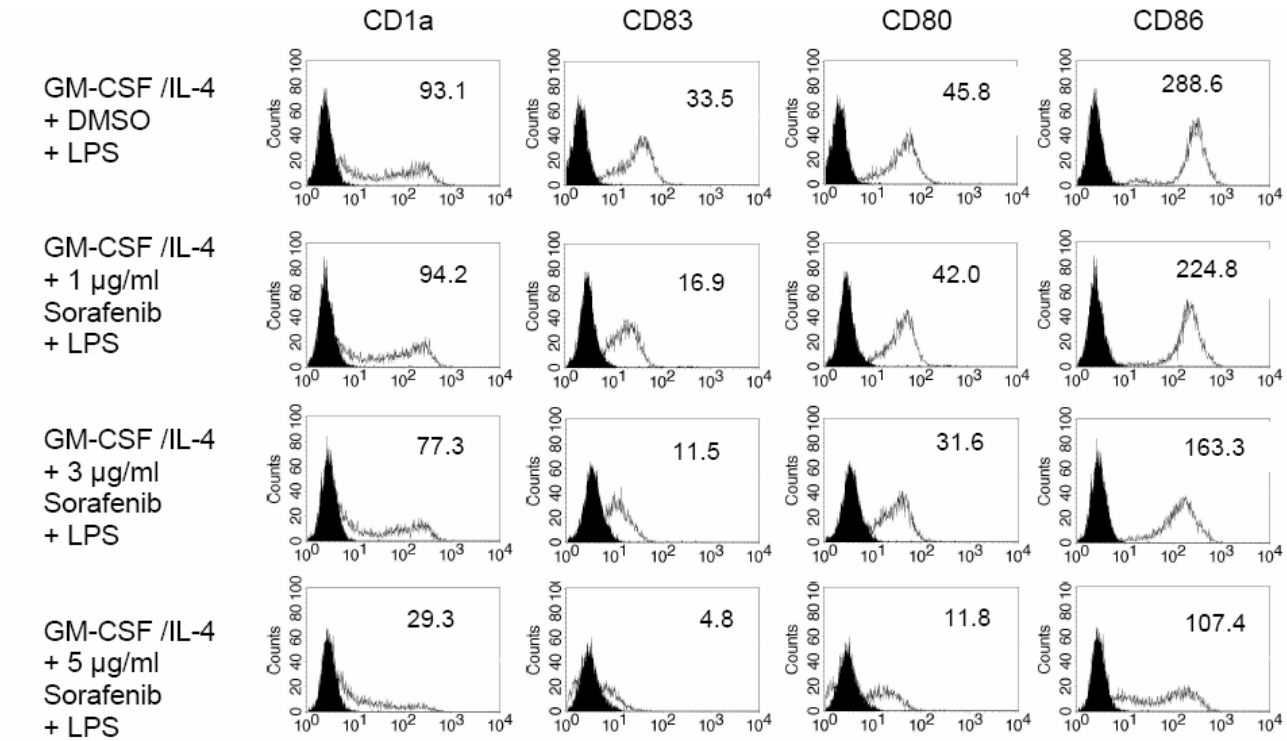
Impact of sunitinib and sorafenib on immune cells

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

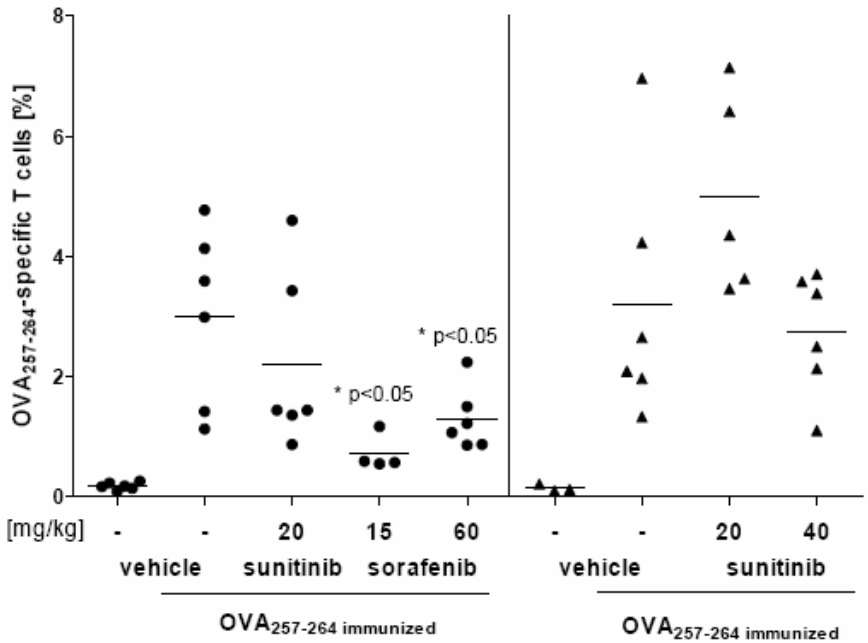


- Data not shown: no effect of sunitinib on maturation of mDCs
- Data not shown: sorafenib but not sunitinib affects the migrations capacities of mDCs and downmodulates CCR7

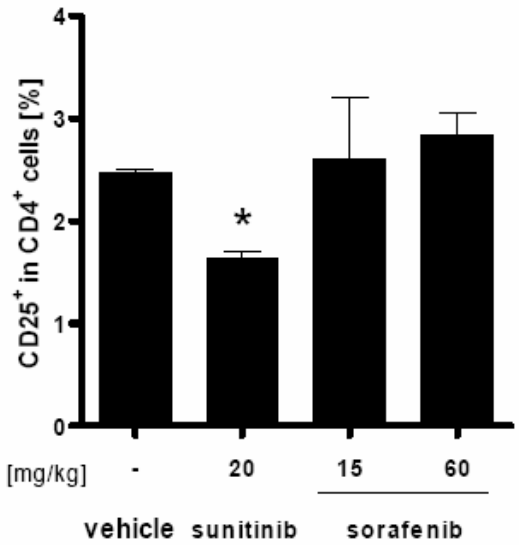
Hipp et al., submitted

Impact of sunitinib and sorafenib on immune cells

Combination of peptide vaccination in mice and TKI <u>simultaneously</u>: sorafenib but not sunitinib inhibits OVA peptide-induced T-cell responses in C57BL/6 mice



OVA-specific T cells (tetramer)



CD4+CD25hi Tregs

Hipp et al., submitted

Impact of sunitinib and sorafenib on immune cells
Conclusions

- **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

immatics

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