CrownBio – Precision Medicine … Translating Oncology Drug Discovery into success in the Clinic, Institut Curie, Paris, June 10th 2016

Addressing challenges in therapeutic cancer vaccine development

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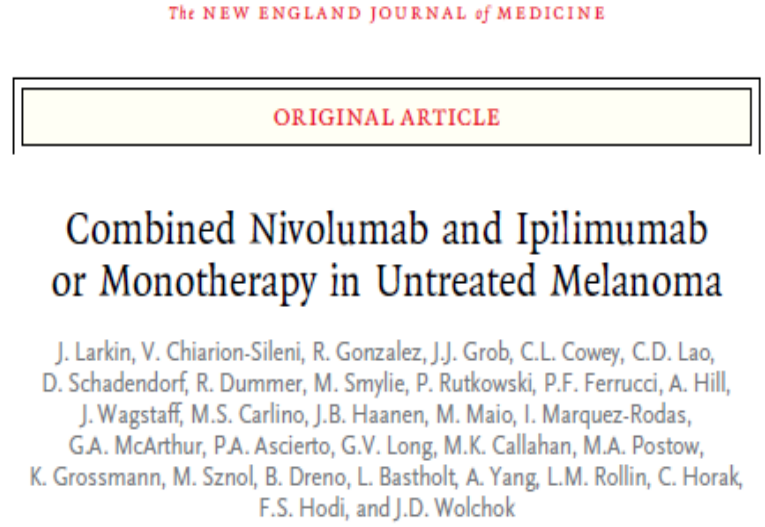
LUDWIG CANCER RESEARCH

UNIL | Université de Lausanne
Faculté de biologie et de médecine

A potential, immune-driven revolution in cancer prevention and control

2013

2014



2015

Anti-CTLA-4, approved in 2011 for metastatic melanoma

Anti-PD-1, approved in 2014 for metastatic melanoma

Anti-PD-1, approved in 2015 for metastatic lung carcinoma

TVEC (HSV-1~GM-CSF), in metastatic melanoma, 2015

Anti-PD-1, approved in 2015 for metastatic renal cell carc.

Anti-PD-1 + anti-CTLA-4, approved in 2015 for met melanom

Anti-PD-1, approved in 2016 for Hodgkin's lymphoma

Anti-PD-L1, in metastatic urothelial carcinoma, 2016

Lessons drawn so far from these successes:

Monotherapies with immunodulatory agents significantly improve survival

Significant immune related toxicities may occur

Measurable responses may be delayed by weeks to months

Absence of pre-existing immune responses may predict a poor response to checkpoint inhibitors

Biomarkers are needed to guide therapy decisions

Vaccines may induce tumor immunity in patients who do not respond to immune modulators (60 -70%)

The goals for cancer vaccines

- Elicit (de novo) tumor antigen specific T cell responses

- High levels of tumor reactive CD8 T cells

- Recruit the highest TCR affinity/avidity clonotypes

- Achieve tumor infiltration and a type I polarity

- Long lived memory T cell immunity

Romero et al. Sci Trans Med 2016

Intense early clinical trial testing, even phase III and one approval in cancer vaccines

Prostate: Provenge (PSMA), GVAX, Prostvac (PSA)

Renal Cell Carcinoma: IMA 109 (eluted peptides), G250

Lung cancer: MAGRIT (MAGE-A3), Tecemotide (MUC-1)

Breast cancer: WT-1 in neoadjuvant in TNBC;
dHER2/AS15 in adjuvant HER2+ BC

Glioblastoma: EGFTvIII (30% gliomas), IMA 950 (eluted peptides)

Melanoma: DERMA (MAGE-A3), peptides, rtvectors, DCs

Lymphomas: Idiotypes

Sequential phase I clinical trials in patients with stage III/IV melanoma in Lausanne 1996 – 2005 vaccinated with Melan-A synthetic peptides

Adjuvant	TLR agonist	Immune response
None	-	0/6
AS02B (GSK Bio)	TLR4	1/12
P40 (P. Fabre)	TLR2	0/9
Montanide (IFA, Seppic)	-	12/17

Liénard D et al. Cancer Immun 2004

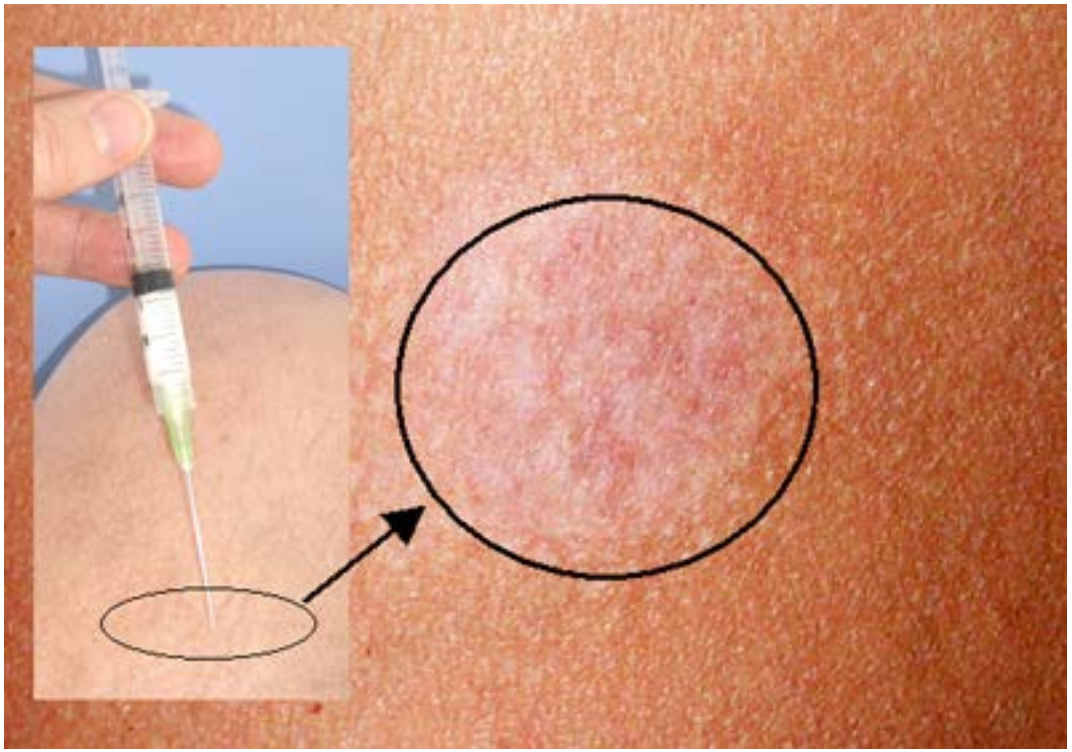
Can Montanide + peptide vaccine be improved?

100 μg peptide (analog or wild type)

500 μg CpG-ODN (type B) [PF 676] – TLR9 agonist

Montanide ISA 51, 1 ml

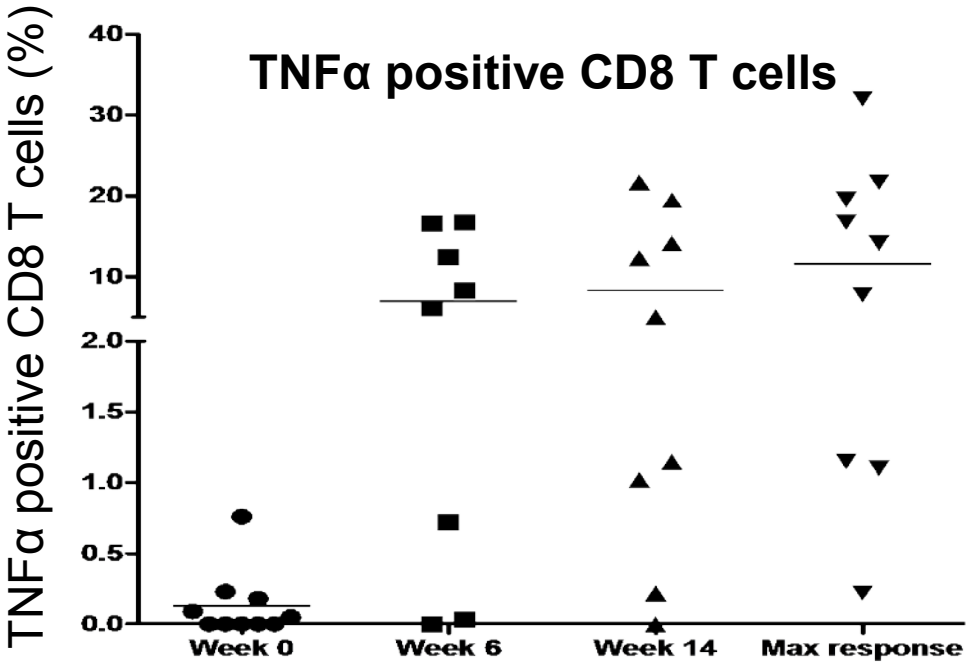
Monthly s.c. injections



Speiser et al. JCI 2005, PNAS 2008

Robust and sustained CD4 and CD8 T cell responses induced by vaccination with long peptide, CpG and IFA

Stage II-IV melanoma patients, 4 low dose vaccinations s.c. in monthly intervals
(long peptide: 0.5 mg NY-ESO-1_{79-108}, 2 mg CpG 7909, 1 ml IFA)



Conclusions

- **CD8 T cell responses irrespective of HLA type**
- **NY-ESO-1_{87-99} = most immunogenic region for CD4 T cell responses**
- **New epitope (and tetramer): NY-ESO-1_{87-99} / HLA-DR7**

Jandus, Baumgaertner et al, in preparation

Pre-clinical study with LSPs

25 – 30 amino acids

Epitope rich regions

NY-ESO-1	**n= 3**
MAGE-A3	**n= 4**
Melan-A	**n= 1**

Three vaccines were shown to provide clinical benefit by 2009 (lymphomas, melanoma and prostate carcinoma).

First FDA approved in April 2010: Provenge

Autologous DC-like loaded with rtGM-CSF-Prostate Acid Phosphatase. IV infusion

+ 4 months survival

Polypeptide-based cancer vaccines

MAGE-A3: failed the first primary endpoint in both lung cancer and melanoma

HPV-16 long synthetic peptides (LSPs): 50% CRs in premalignant lesions
No impact on OS in cervical carcinoma

IMA 109: short naturally presented peptides in renal cell carcinoma (ESMO 2015)

Reasons for cancer vaccines' modest clinical impact

Tolerant T cell repertoire to self antigen, hence the value of neoantigens and viral antigens

Monovalent antigen vaccines which lead to immune selection and tumor escape

Delivery methods of the vaccine remain suboptimal

Immune suppressive microenvironment

Romero et al. Sci Trans Med 2016

Hurdles in vaccination with polypeptides (SSP, LSP, rtProteins):

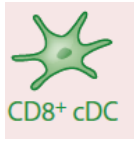
-T cell responses are relatively weak, narrow focus and short lived

-Inadequate induction of CD8 T cells by LSPs and recombinant proteins (cross priming)

- Local immunosuppression

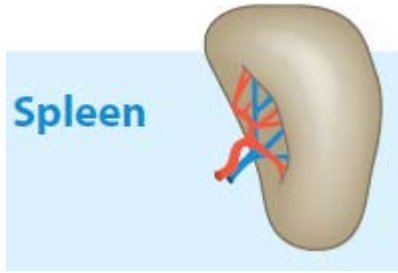
Cross-presenting Dendritic Cells: XCR1$^+$

Resident and migratory cDCs

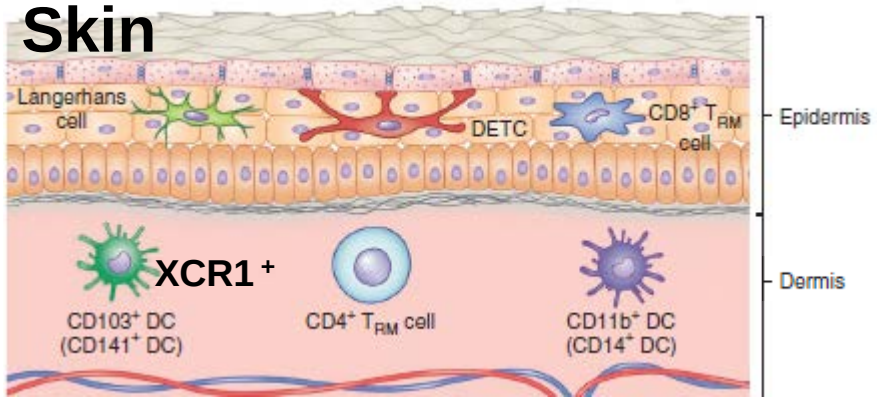


(~70% are XCR1$^+$)

CD8α$^+$ subset (~75% are XCR1$^+$) & CD11b$^+$ subset (XCR1$^-$)



Resident cDCs



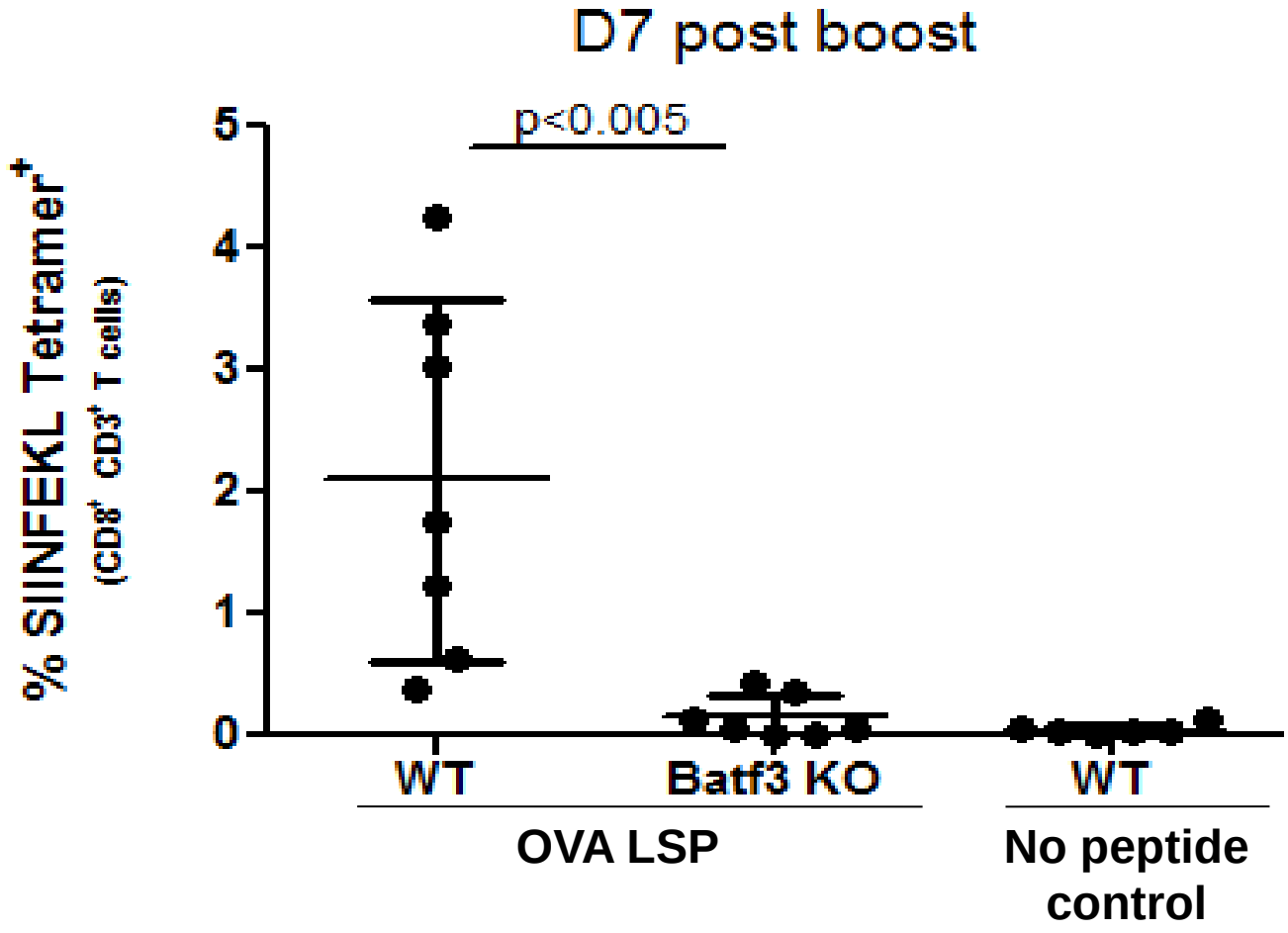
Batf3 – master transcription factor

Abundant TLR3

Human BDCA3+, CLEC9A, CD141+

Adapted from Merad et al, 2013 & Heath et al, 2013

CD8+ T cell response to LSPs is dependent on Batf3



Botelho et al. in preparat 2016

Need to (more) efficiently deliver LSPs & recombinant protein antigens to the cytosolic compartment of maturing/mature dendritic cells

- Tat based antigens

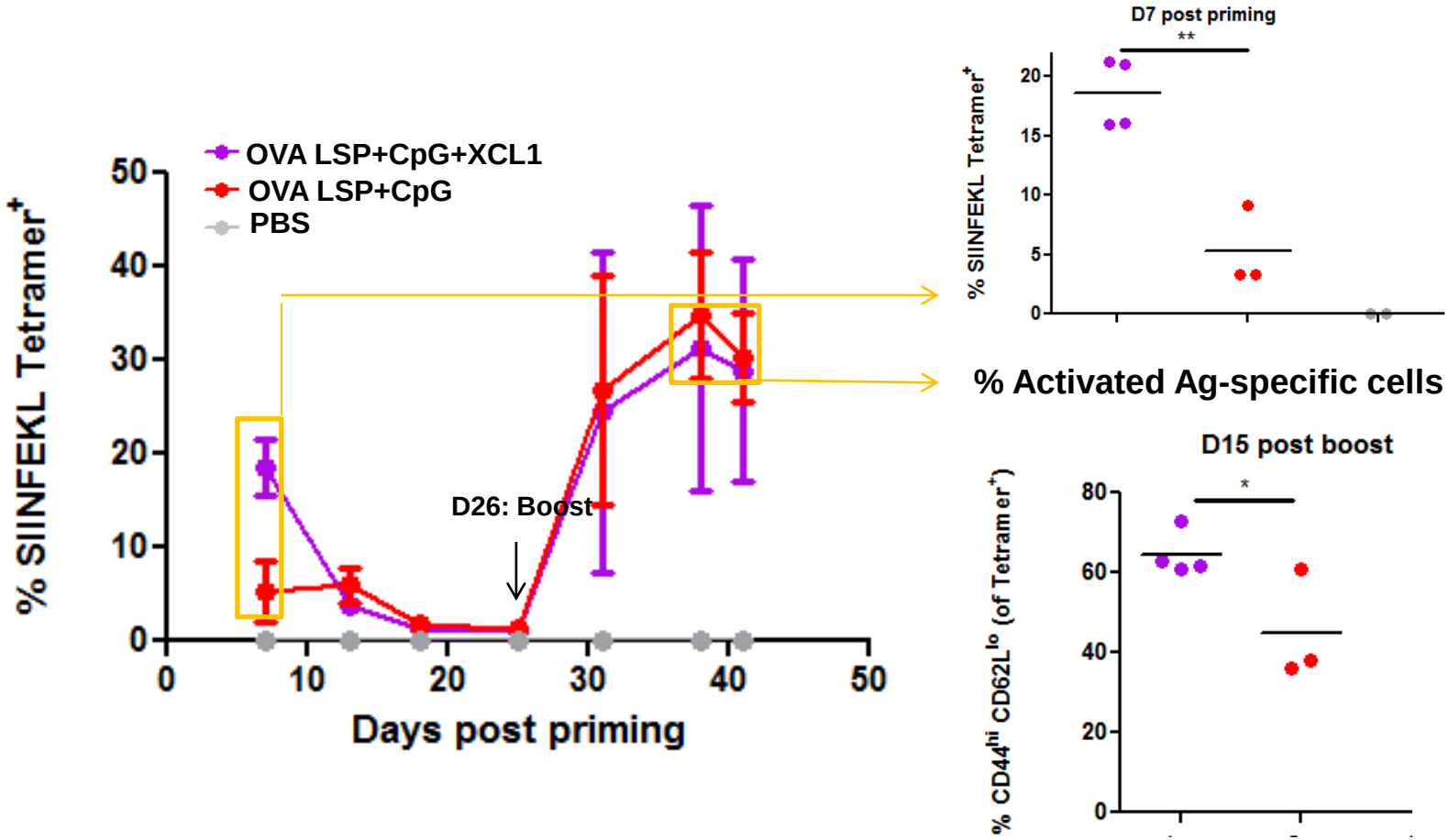
- Other protein translocating « devices »: subunits of bacterial toxins

- Listeria recombinants

- Viral recombinants: adeno, vaccinia, VSV, MCV, …

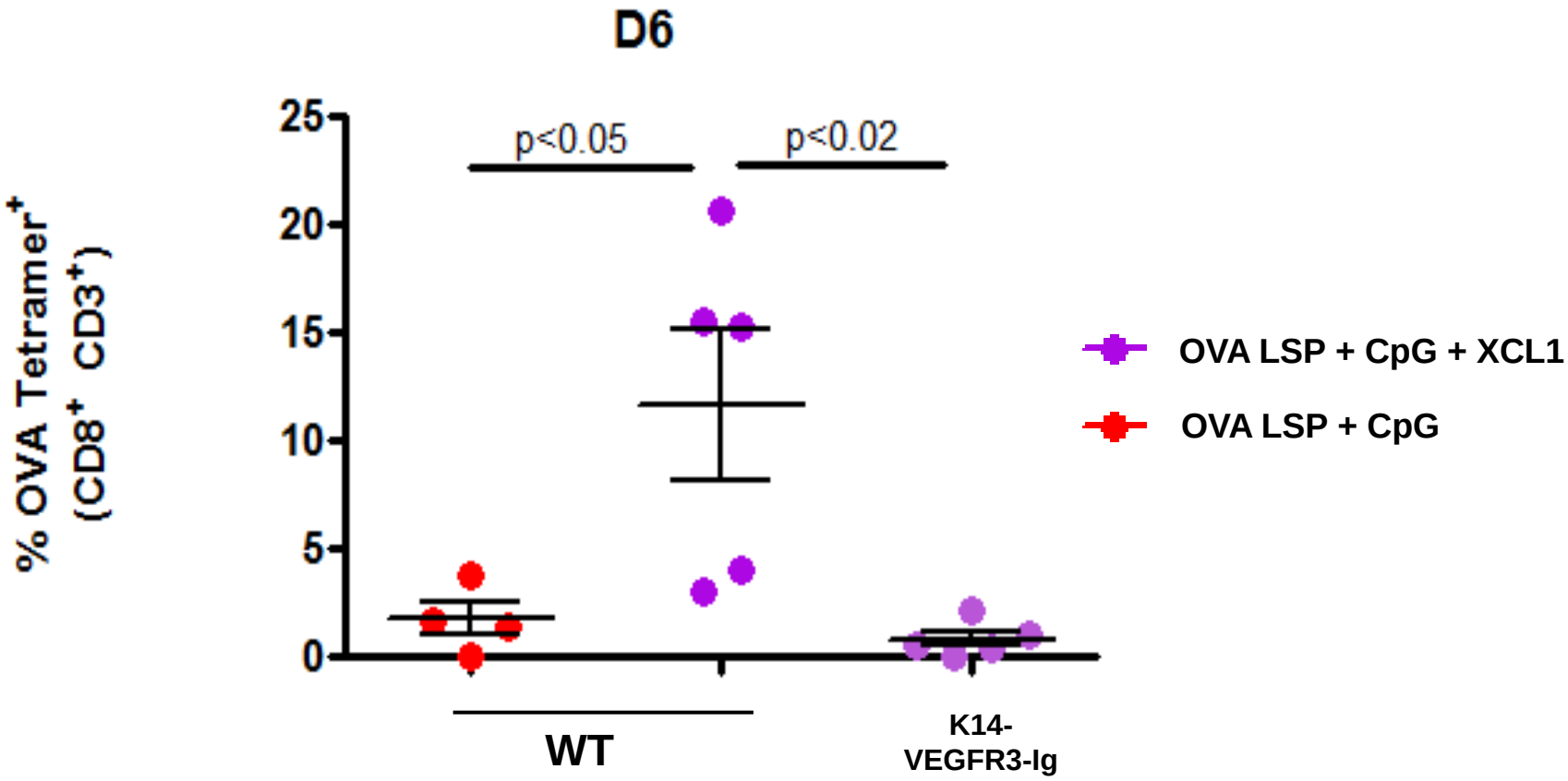
- XCL-1 fusions or mixtures (Dalod, Marseille; Krocezk, Berlin)

Immunisation with OVA LSP + adjuvant and XCL1 gives an initial higher CD8$^+$ T cell IR and increased % of activated OVA-specific CD8$^+$ T cells



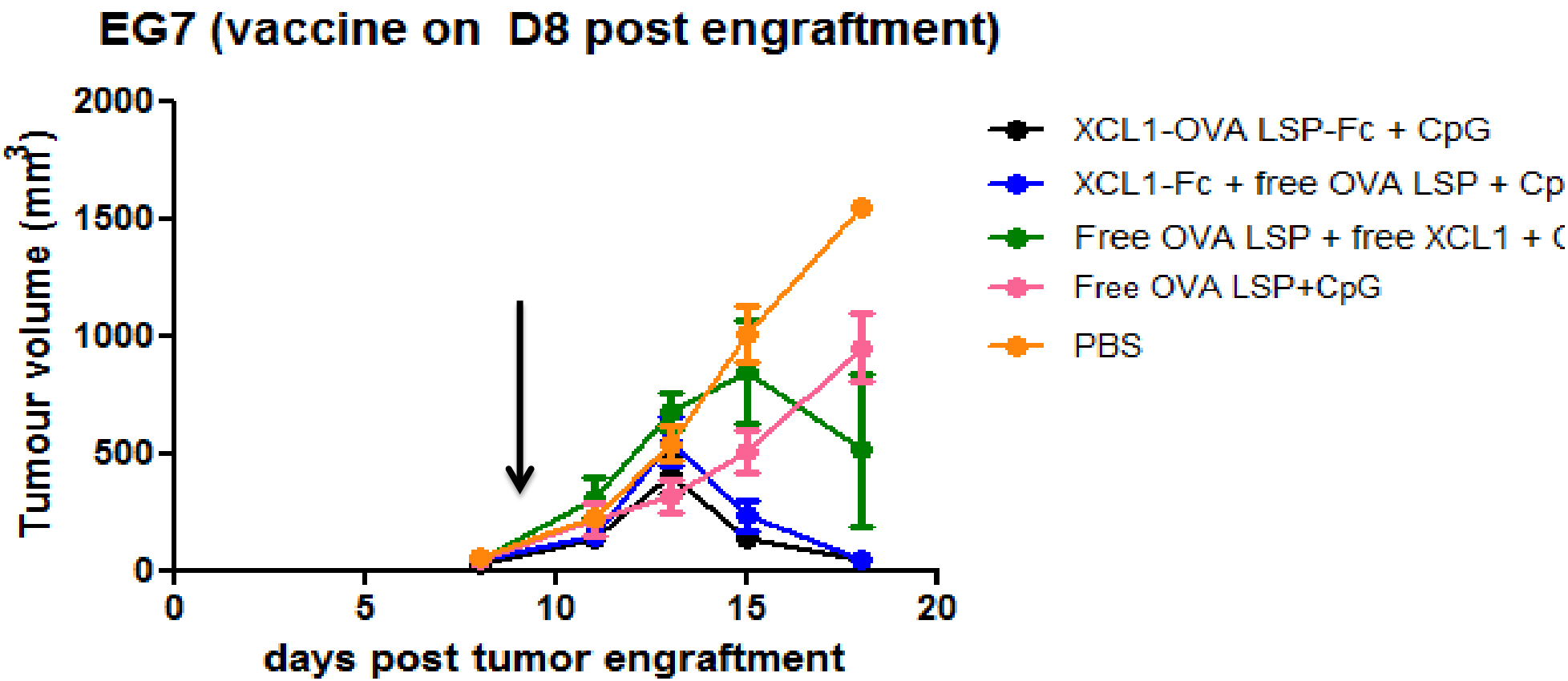
Botelho et al. in preparat 2016

Skin draining LNs are needed for the CD8$^+$ T cell priming with LSP + XCL1 immunisation



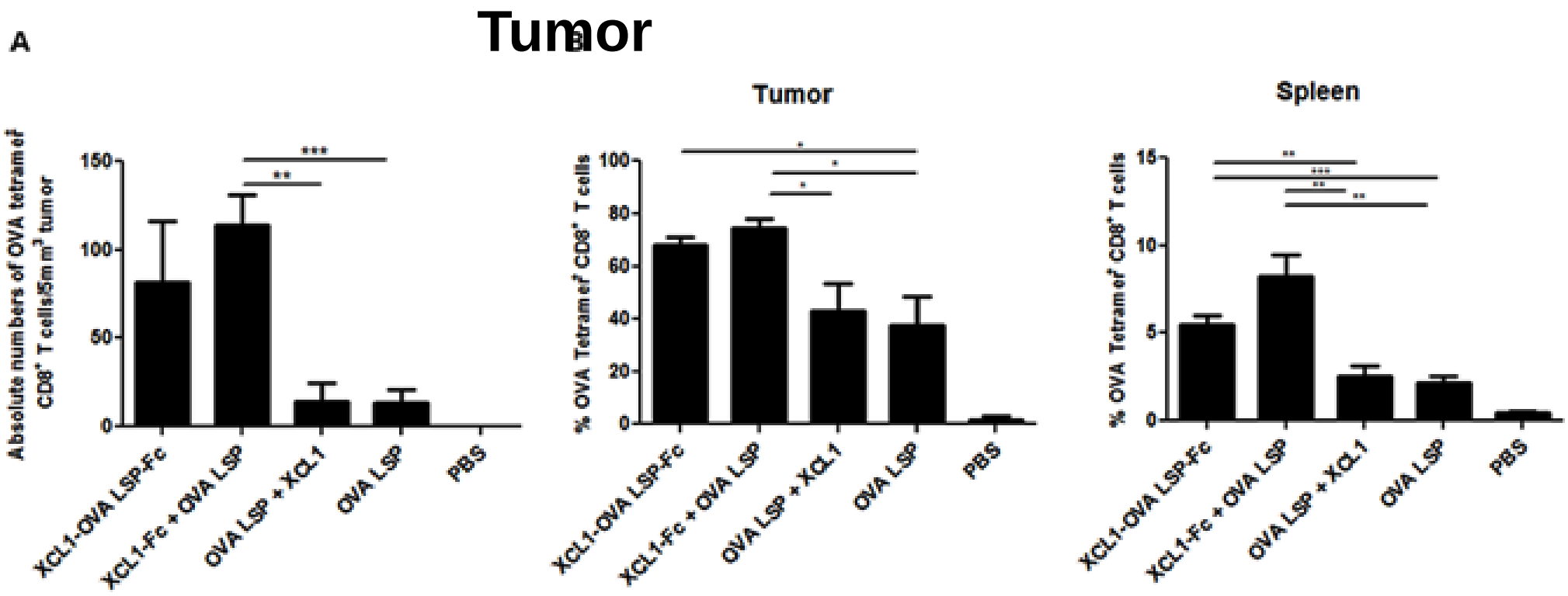
Botelho et al. in preparat 2016

XCL1 fusion proteins protect against tumors in therapeutic vaccination



Botelho et al. in preparat 2016

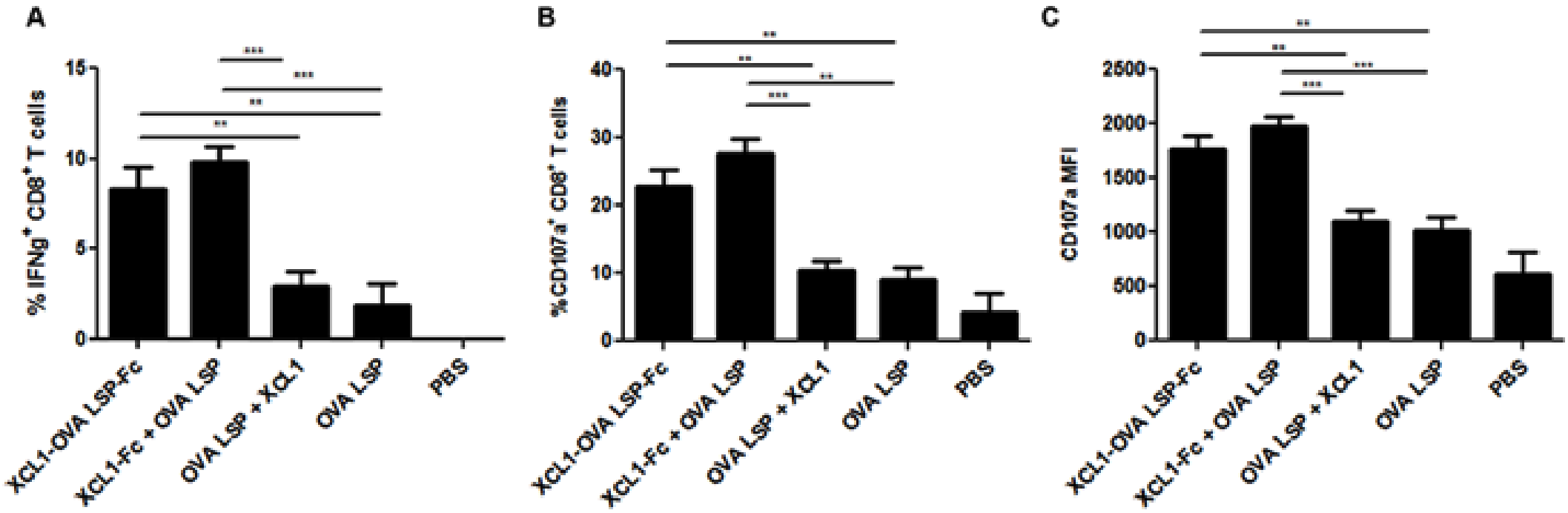
Accumulation of higher numbers of antigen specific CD8 T cells in tumors



Day +10

Botelho et al. in preparat 2016

Accumulation of higher numbers of antigen specific and functional CD8 T cells in tumors



Day +10

Summary

LSP (and proteins) depend on crosspresentation for vaccination

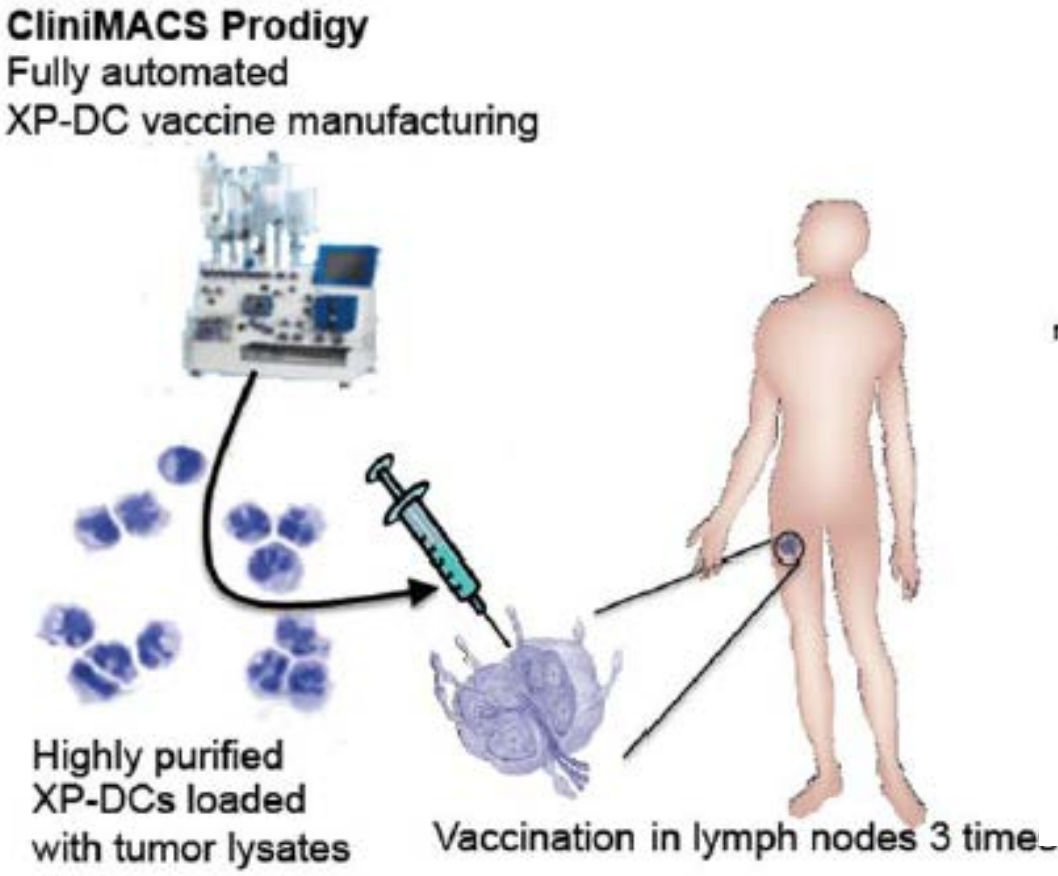
XCL-1 may be used as vaccine component to target antigen to XDCs

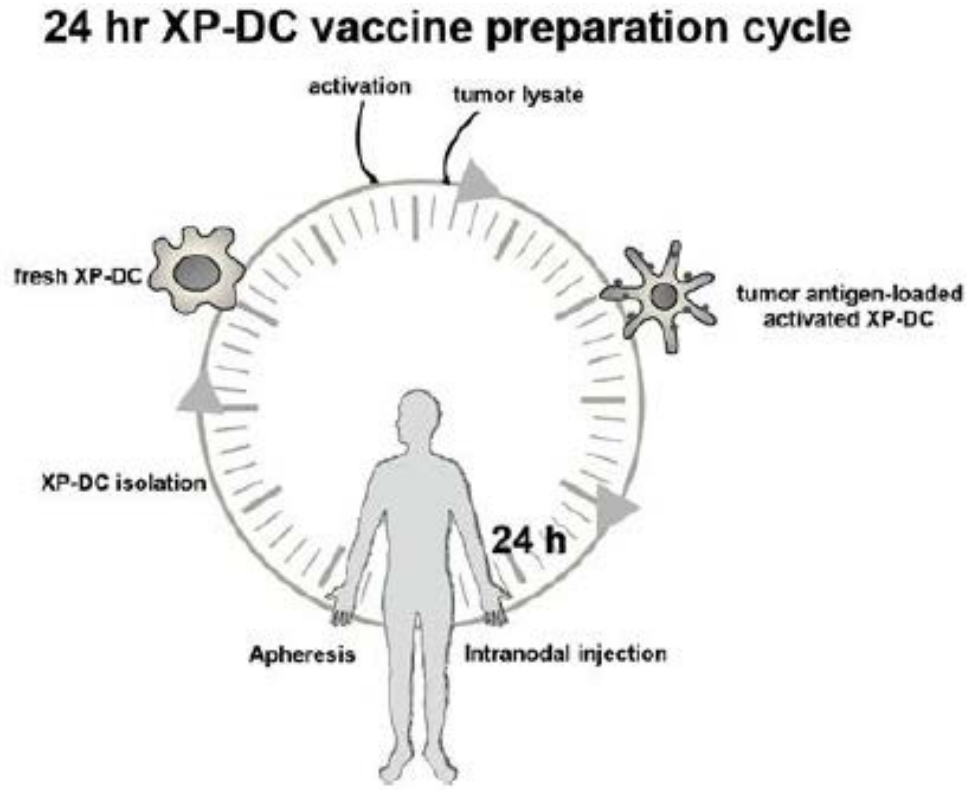
Fusion XCL-1 proteins are interesting candidates to achieve consistently strong CD8 T cell responses and protective immunity

The approach needs to be optimized and may be combined with nanoparticle delivery

Botelho et al. in preparat 2016

Translating to the clinics: Horizon 2020 grant (ProCrop)





Three clinical sites: Pamplona, Nigmejen, Lausanne

Three research sites: Pamplona, Madrid, Lausanne

A company: Miltenyi, Cologne

TLR agonists as polypeptide vaccine adjuvants

CpG-ODNs and Poly(I:C) dramatically increase the antigen-specific Teff:Treg ratio in the lymphoid organs, skewing the immune response in favour of a functional anti-tumor effect.

CpG-ODNs and Poly(I:C) rapidly induce a Th1 polarised cytokine milieu, which fits with a reported mechanism for the adjuvant activity of TLR ligands.

Perret et al. Can Res 2013

Harnessing NKT for vaccination

HER-2-CD1d or CEA-CD1d fusion proteins efficiently function both as vaccine adjuvants and driving Th1 shifts in the tumor microenvironment, partly through transactivation of NK cells

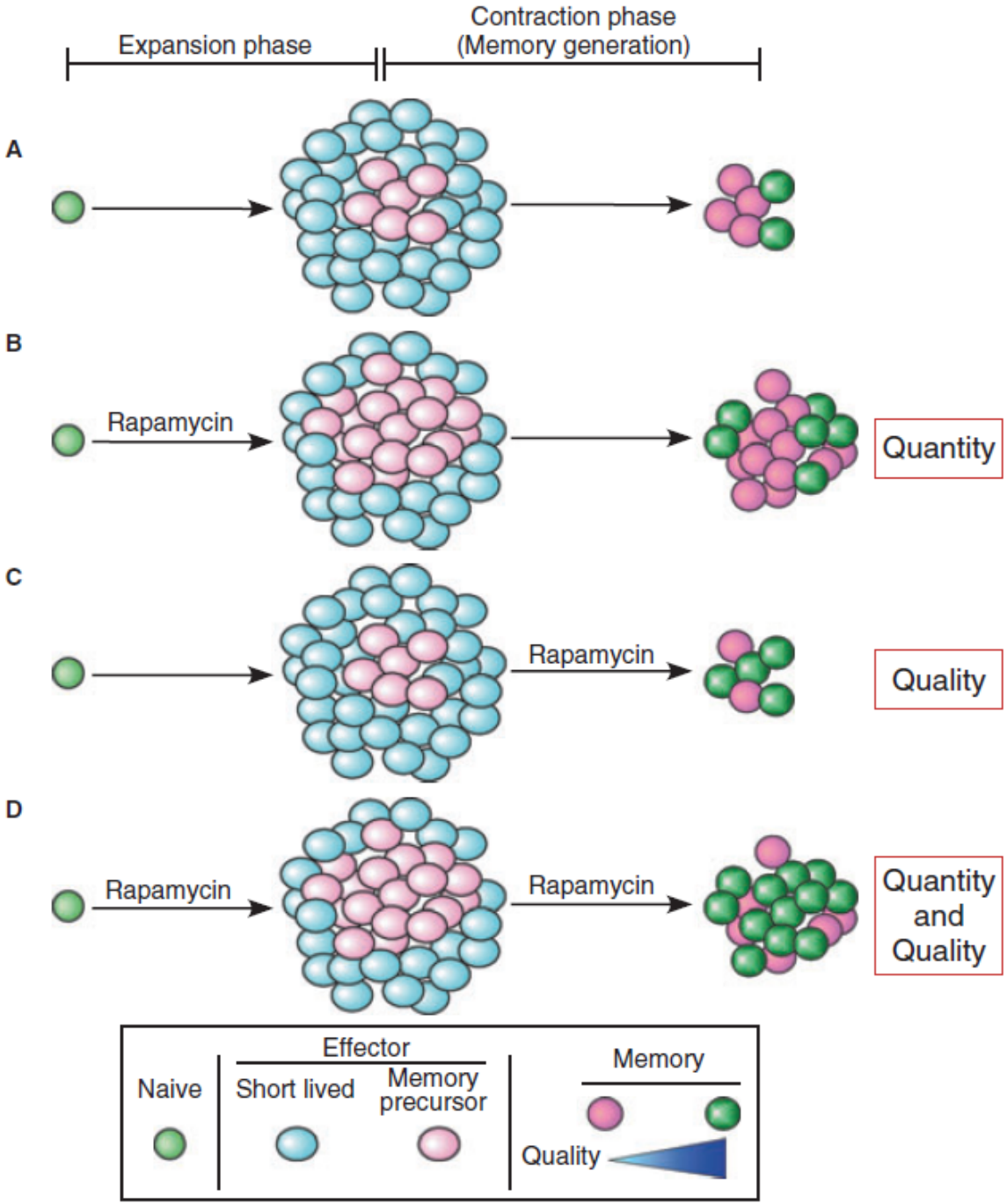
Corgnac et al. JITC Nov 2014

Inducing robust and long lived memory CD8 T cell responses

Concomitant induction of ag-specific CD4 T cell immunity

New targets emerging from the understanding of the molecular basis of memory T cell committment

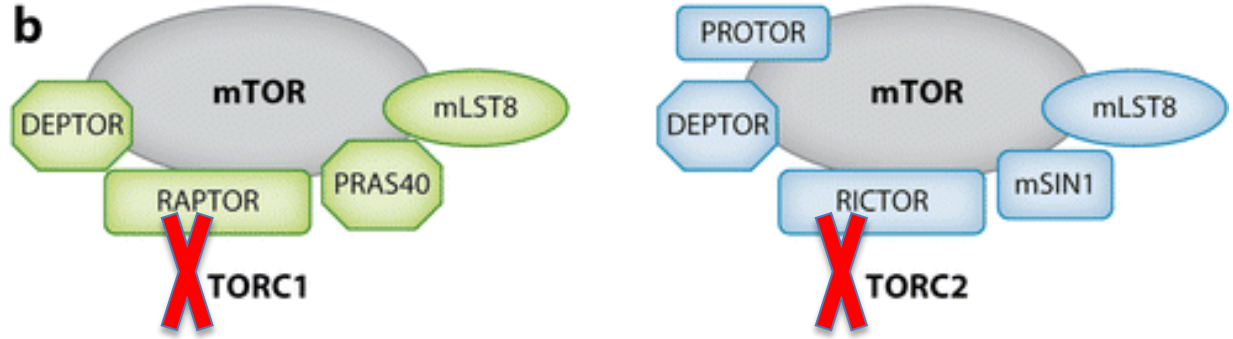
- **mTOR pathway**
- **Wnt signaling**
- **miRNAs**
- **Stemness**
- **PD-1 ??**



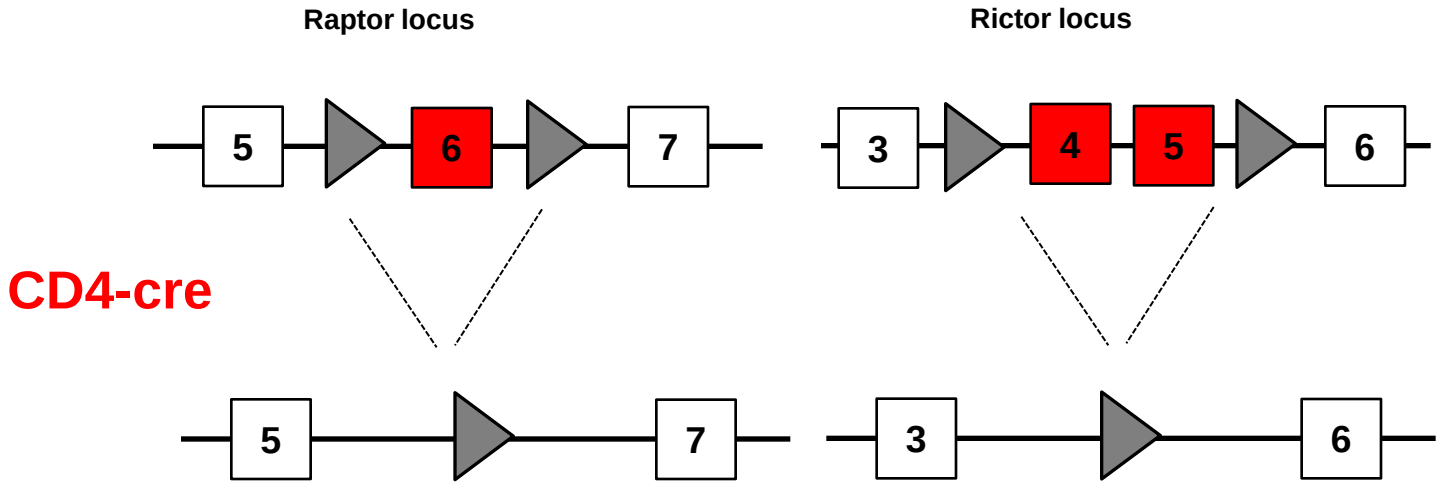
Rapamycin improves the quantity and quality of memory CD8+ T cells.

Araki K et al. Immunol Rev 2010

Lianjun ZHANG: Cre-Loxp based conditional KO strategy

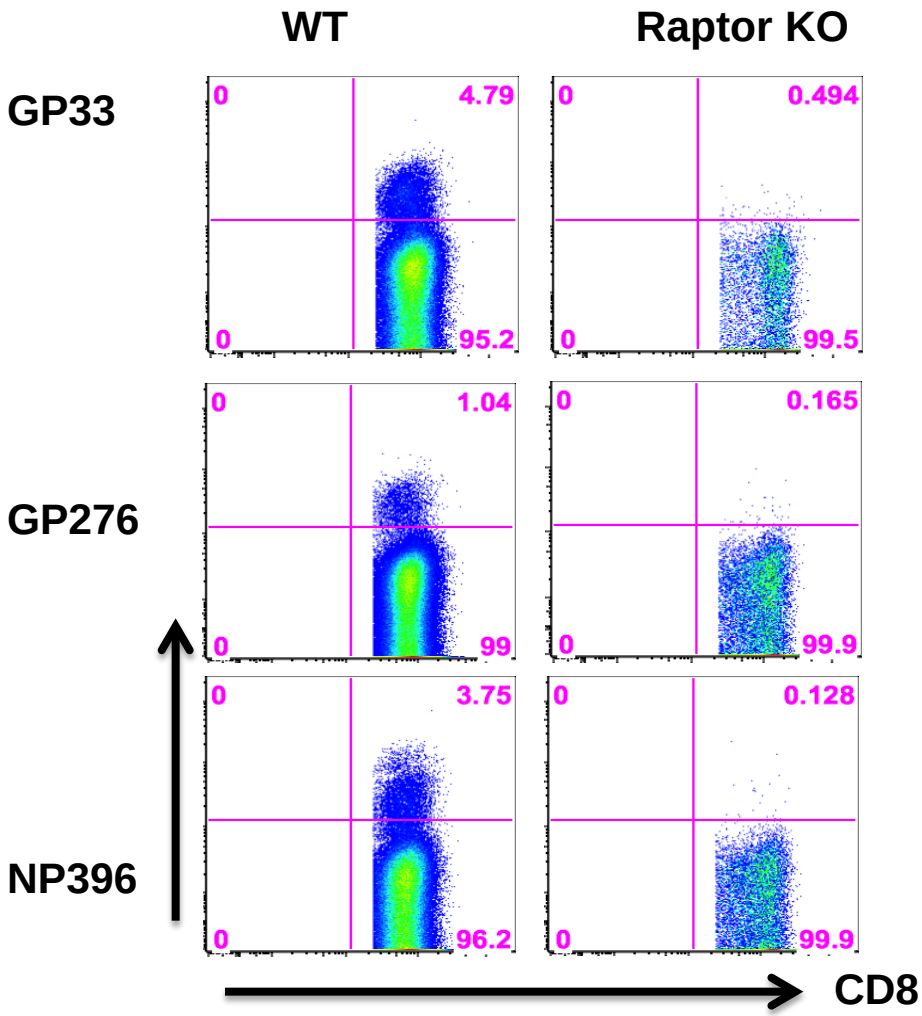


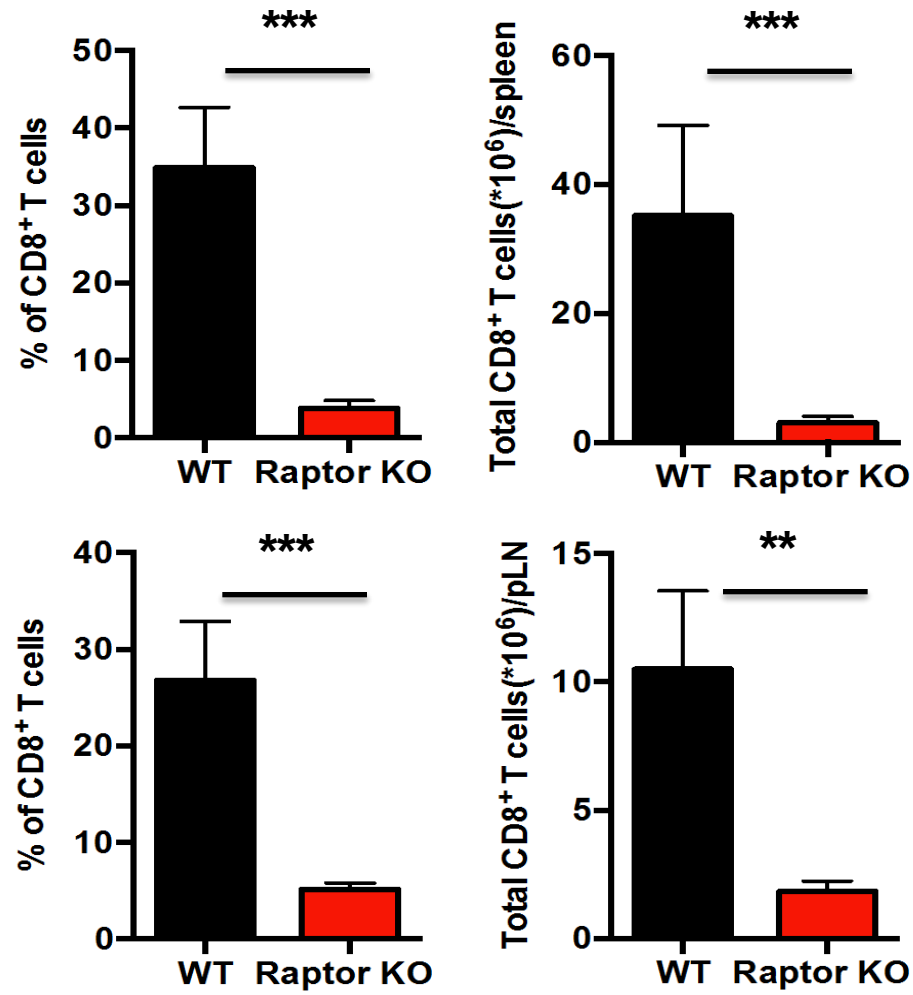
Powell JD, et al. 2012.
Annu. Rev. Immunol. 30:39–68



T cell specific loss of mTORC1 and mTORC2 activity;
In collaboration with Michael Hall and Markus Ruegg from University of Basel

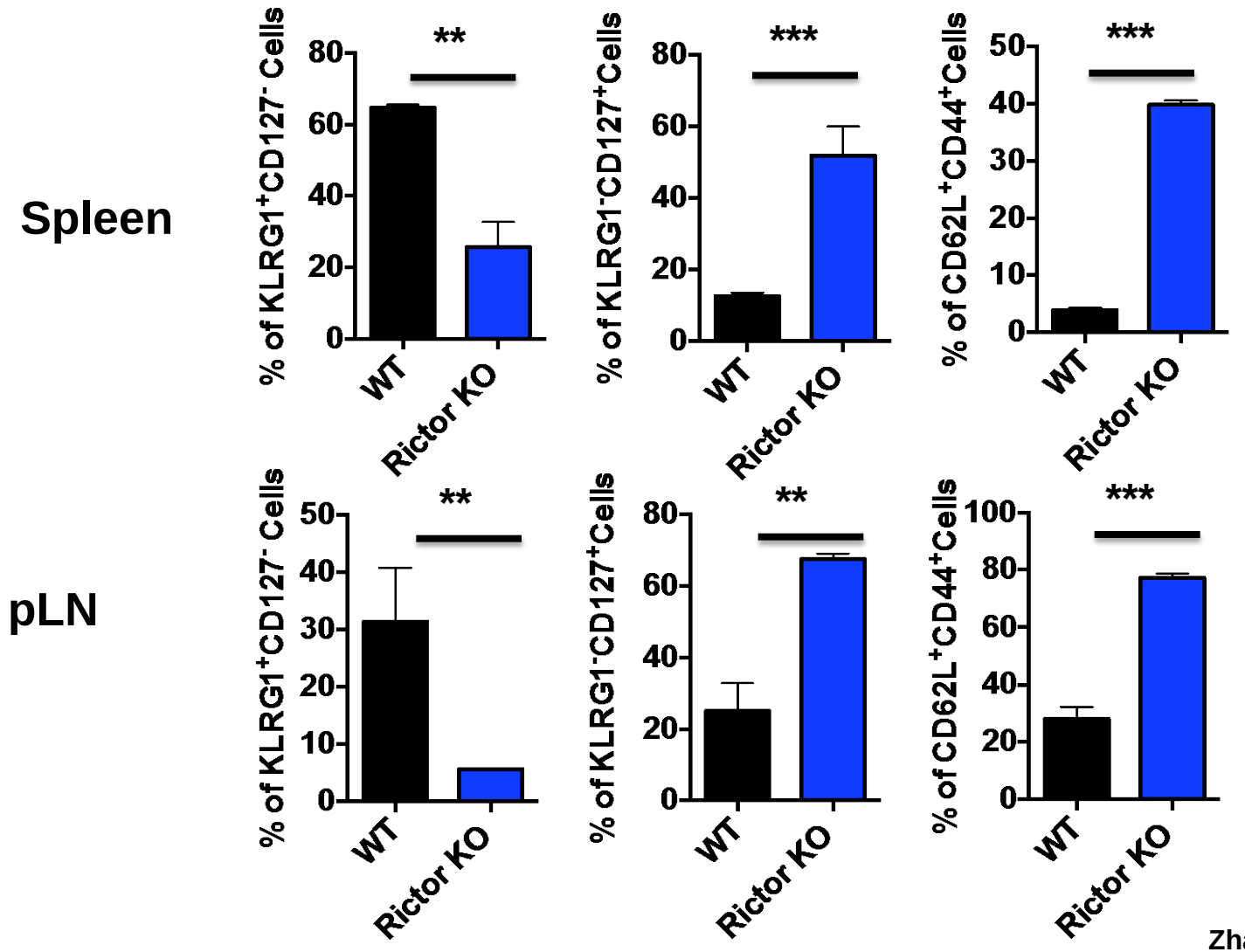
Impaired expansion of CD8 T cells in the absence of Raptor





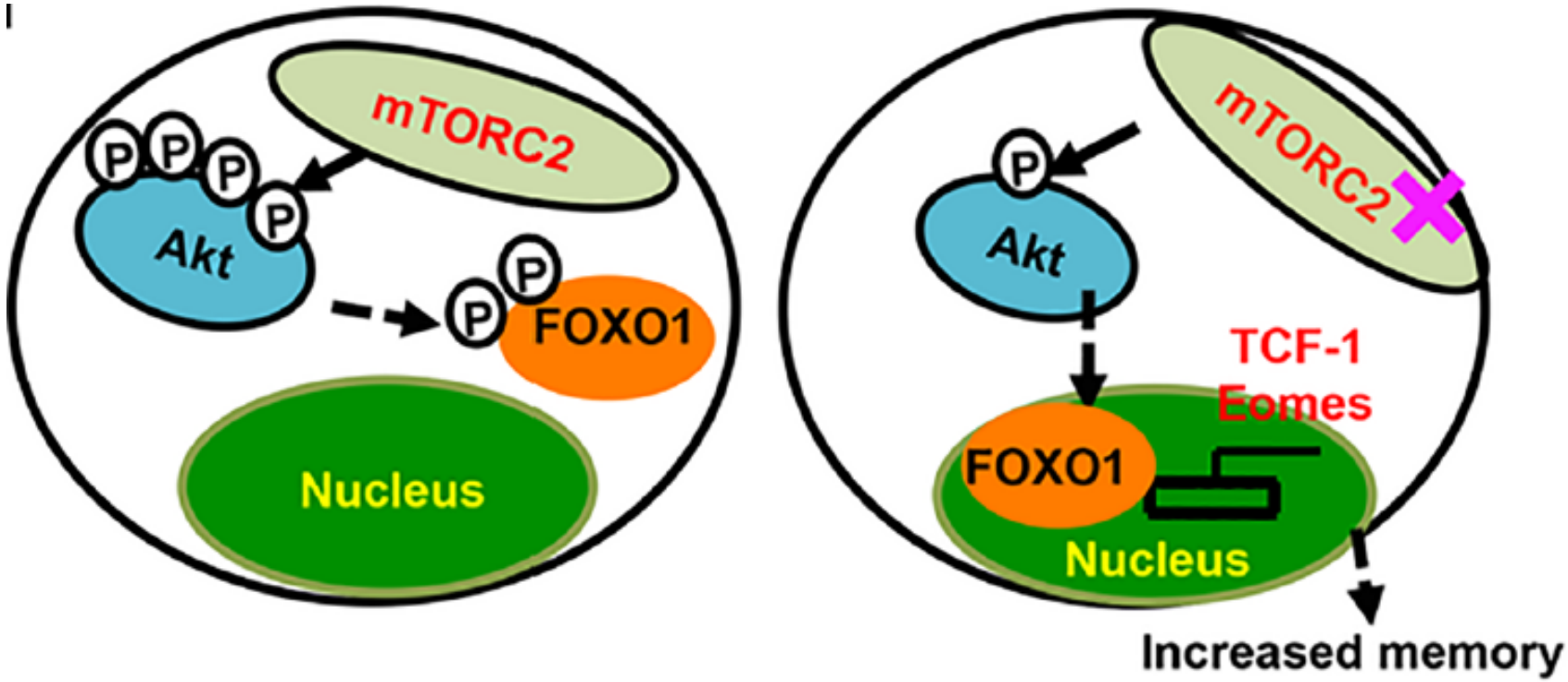
Spleen, day 8 after LCMV WE

mTORC2 deficiency promotes MPEC differentiation while reducing SLEC generation



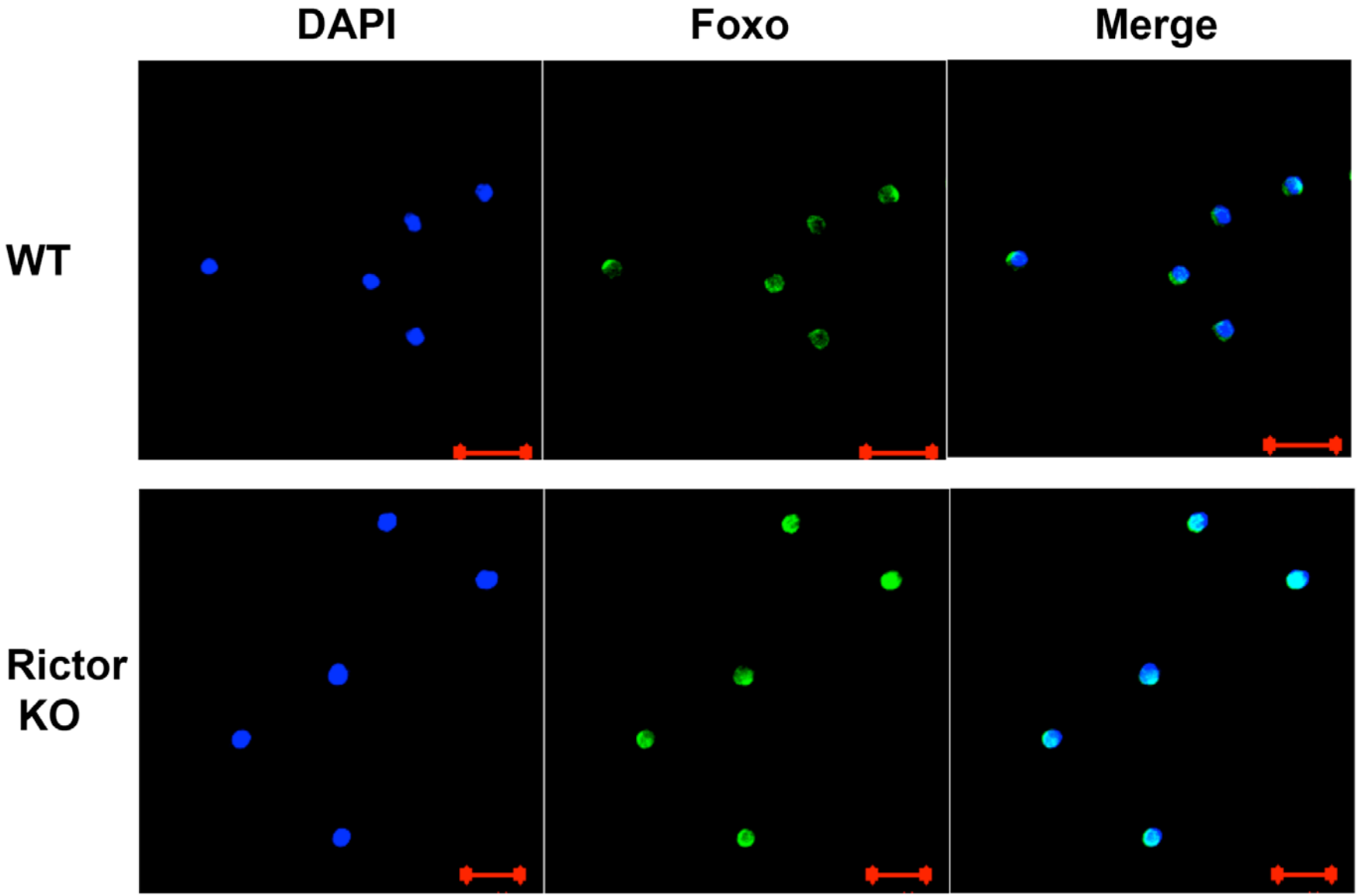
Zhang et al. Cell Reports 2016

Hypothesis for the increased memory in Rictor KO mice

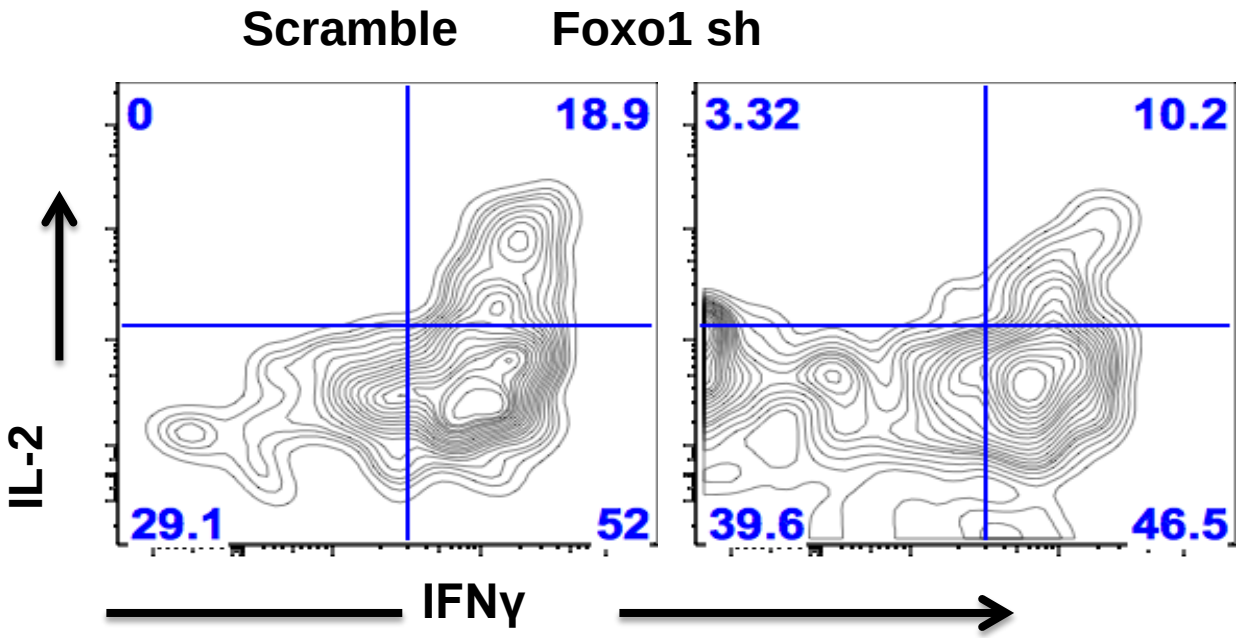


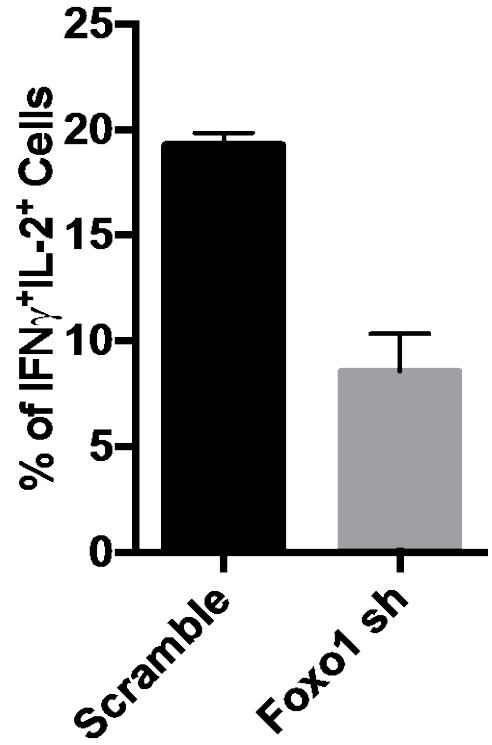
Zhang et al. Cell Reports 2016

Increased nuclear Foxo1 accumulation in Rictor KO cells



Foxo1 silencing reverses the increased IL-2 production in Rictor KO CD8 T cells





Zhang et al. Cell Reports 2016

Summary

mTORC2 is not required for homeostatic proliferation but is needed for TCR driven effector accumulation triggered by either high or low affinity ligands.

mTORC2 deficiency does not affect effector function during a primary response.

mTORC2 deficient memory CD8 T cells mount much potent recall response.

mTORC2 deficiency enhances memory formation by up-regulating Tcf-1, Eomes and IL-2 production but decreasing T-bet expression, via stablizing Foxo1 in the nucleus.

Identifying the molecular events downstream of FOXO1 regulating memory differentiation may provide clues to immunointervention, i.e. compounds that may confer vaccine formulations the ability to induce strong and long lived antigen specific memory responses

Conclusions

Therapeutic vaccines are promising IO approaches requiring well designed optimization

Signaling pathways controling T cell expansion, memory formation and survival remain relevant targets for vaccine development

Optimal molecularly defined adjuvants are now available for clinical testing

Immunosuppressive tumor environment, a major hurdle going forward

Incubated by the International AIDS Vaccine Initiative

Led by W Koff and T Schenkelberg

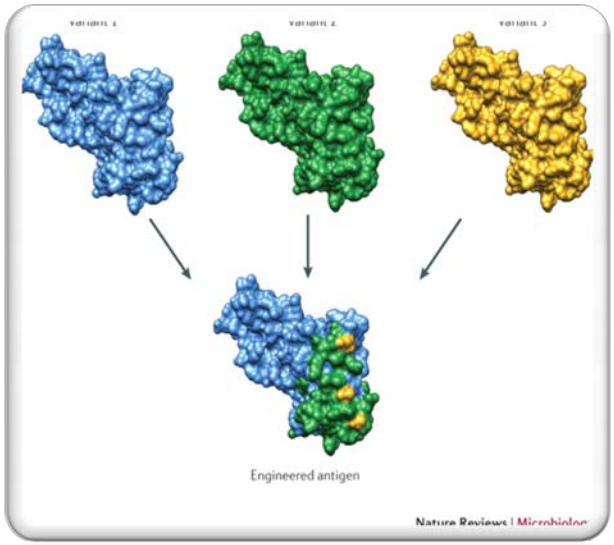
First proposed in 2013

Seed fund: Robert Wood Johnson Foundation

New Tools

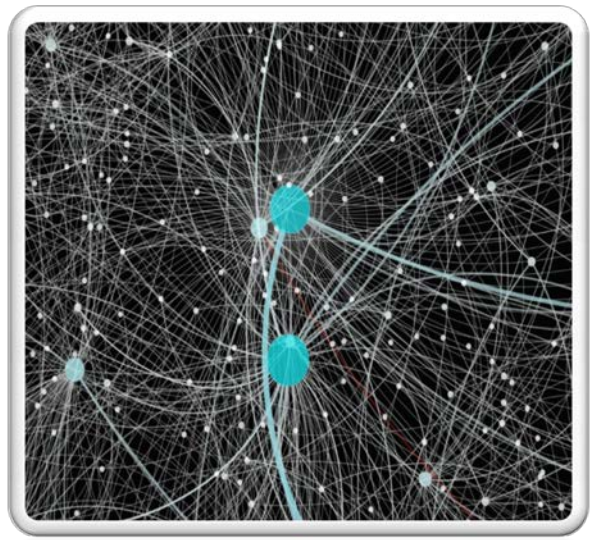
The Human Genome has now been deciphered, and tools are now available to decode the human immune system

Structural and Computational Biology



Genomics and Immune Monitoring

Bioinformatics and Systems Biology

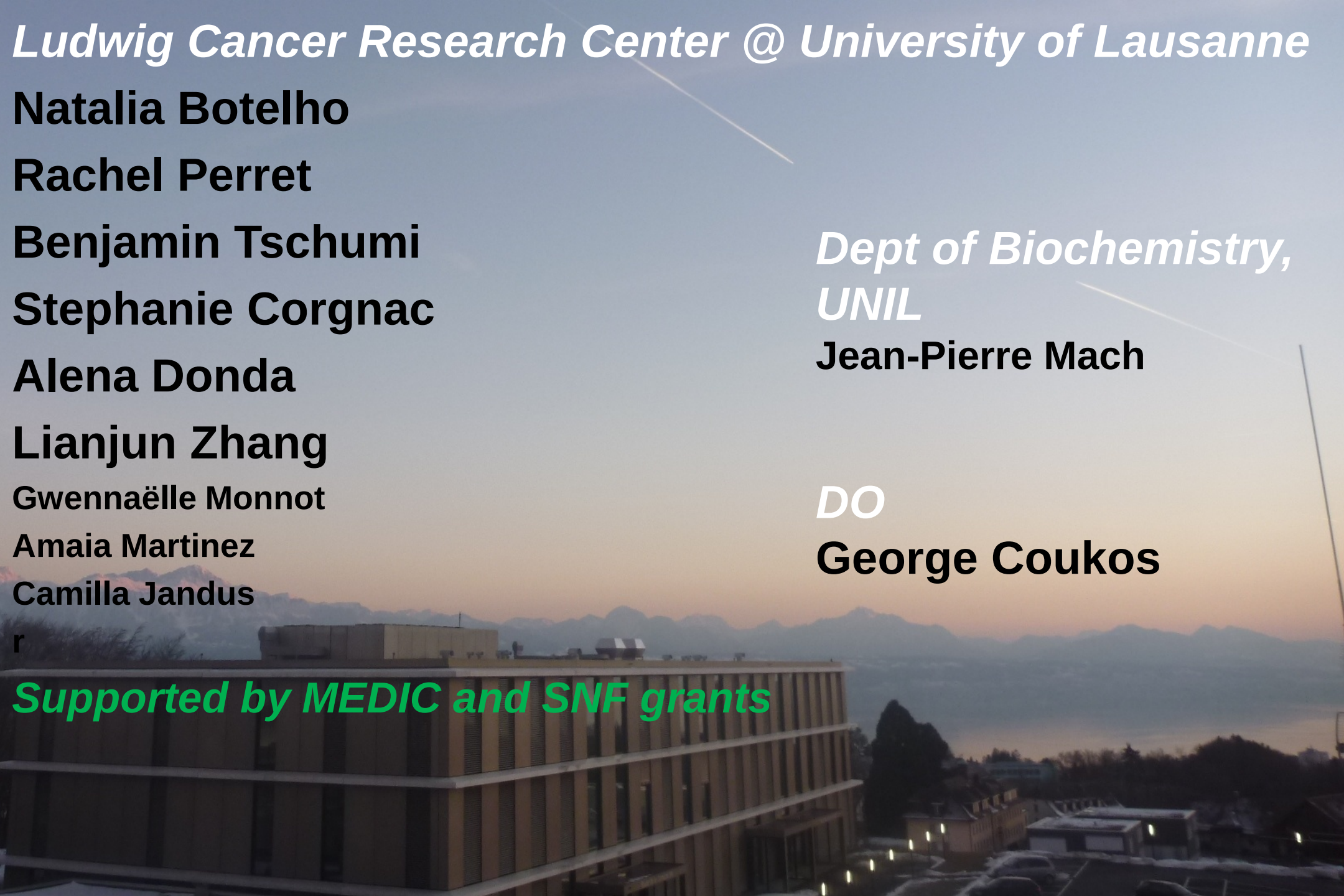


Mission

A new, global, nonprofit with the mission to:

Accelerate the Development of Vaccines and Immunotherapies against major global infectious diseases and cancers by Decoding the Human Immune System

Romero et al. Sci Trans Med 2016



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Supported by MEDIC and SNF grants