PCI Biotech

Unlocking the potential of innovative medicines

Photochemical enhancement of CD8 T-cell response to vaccines – new application of PCI, an innovative technology platform in clinical development.

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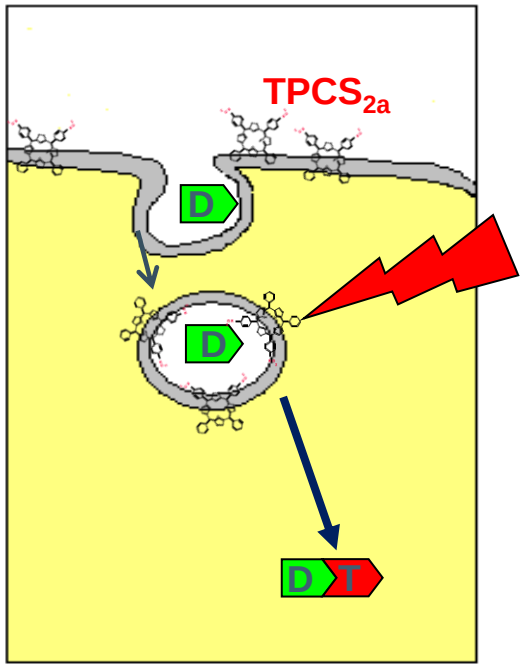
PCI Biotech AS

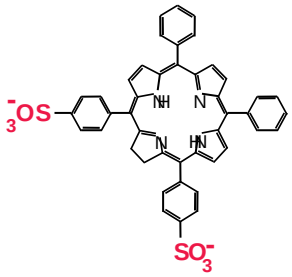
- Norwegian publicly listed company spun out from The Norwegian Radium Hospital
- 14 employees based in Oslo - extensive network of consultants and advisors
- Developing Photochemical Internalisation (PCI) technology, a photochemical technology with multiple uses.
- PCI uses light + a photosensitizer ($TPCS_{2a}$) to induce release of molecules from endosomes in target cells
- Phase I clinical study finished - two new clinical studies on-going with small molecule cytotoxic drugs (head and neck cancer, bile duct cancer)
- When used on antigen presenting cells, PCI can stimulate cytotoxic T-cell responses due to release of antigen to the cytosol and improved presentation on MHC class I

Principle of photochemical internalisation – endosomal escape through illumination

- Many drugs D (large molecules, hydrophilic molecules, nanomedicines) have problems in reaching targets T inside the cell
- Can be taken up by endocytosis, but are trapped in endosomes



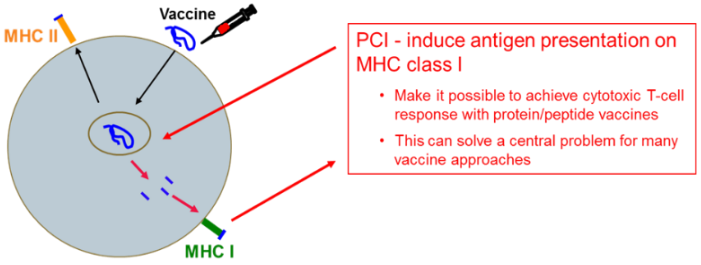
- PCI uses a photosensitising compound ($TPCS_{2a}$) that localises selectively in endosomal membranes.



- Upon illumination photochemical reactions are induced leading to permeabilisation of these membranes and release of the drug.
- The drug can then find its target in the cytosol or e.g. in the cell nucleus

PCI / $TPCS_{2a}$ - in drug development and therapeutic vaccination

Therapeutic Vaccination



PCI - induce antigen presentation on MHC class I

- Make it possible to achieve cytotoxic T-cell response with protein/peptide vaccines
- This can solve a central problem for many vaccine approaches

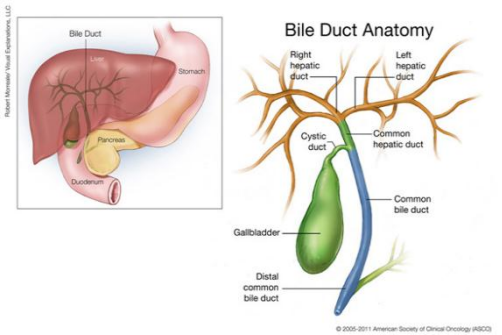
$TPCS_{2a}$ PCI

Head and neck cancer (phase II)

($TPCS_{2a}$ in combination with bleomycin)

Bile duct cancer (phase I)

($TPCS_{2a}$ in combination with gemcitabine)

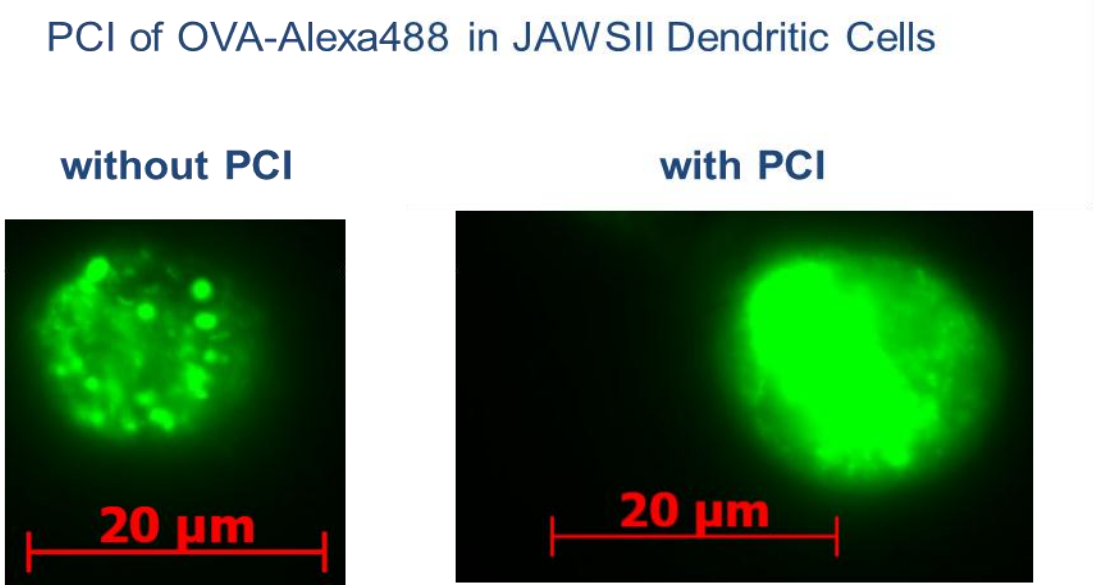


PCI with macromolecules:

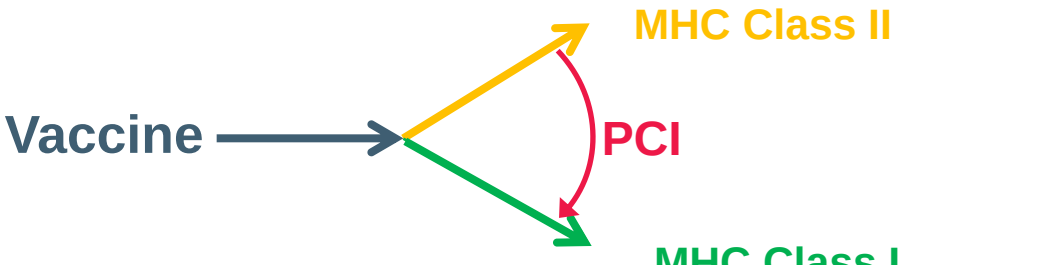
- antibody-drug conjugates
- siRNA and other oligos
- gene therapy
- nano

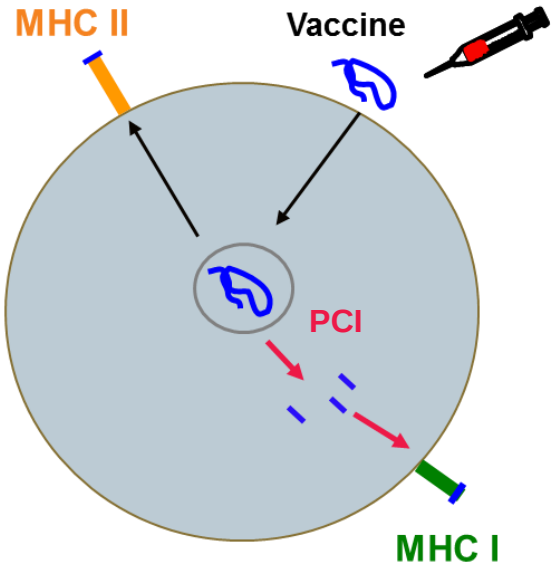
PCI / $TPCS_{2a}$ as a vaccination technology

- PCI can induce escape of antigens from endocytic vesicles in antigen presenting cells, thereby enhancing MHC class I antigen presentation



PCI for vaccination – enhancing cytotoxic T-cell response by light-induced cross presentation





Generate more disease specific cytotoxic T-cells

Attack cancer and virus-infected cells more efficiently

PCI enhances *ex vivo* vaccination in mouse OVA/OT-1 model

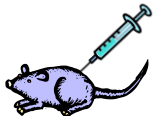
Waeckerle-Men *et al.* (2013). Eur. J. Pharm. Biopharm. 85:34-41

Dendritic cells isolated from mouse bone marrow

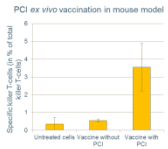
PCI

Treat cells with photosensitiser + antigen (OVA) + light

Treated cells stimulated to present antigen

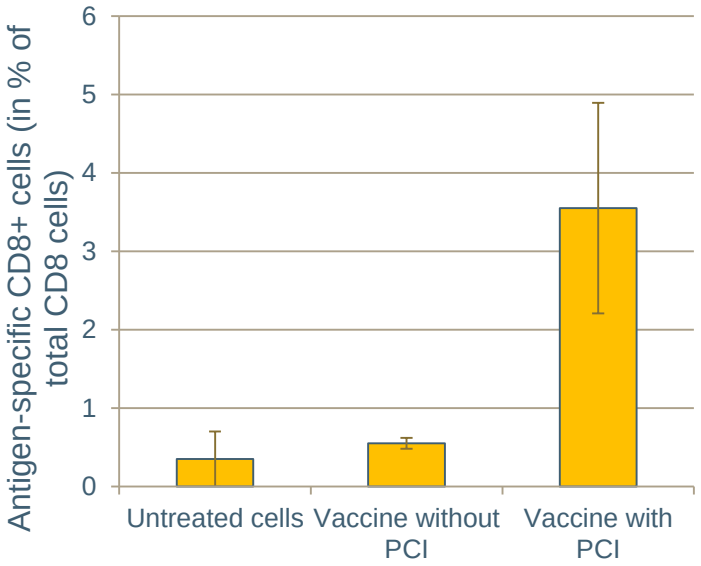


Inject treated cells into lymph nodes in mice



Analyse if antigen-specific T-cells in mouse are stimulated by treated cells

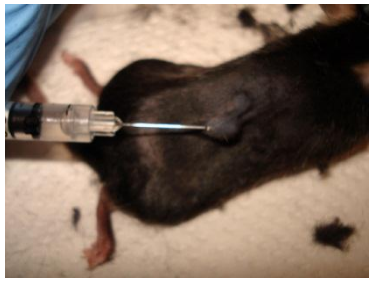
PCI *ex vivo* immunisation in mouse model

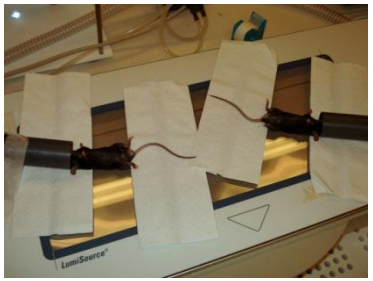
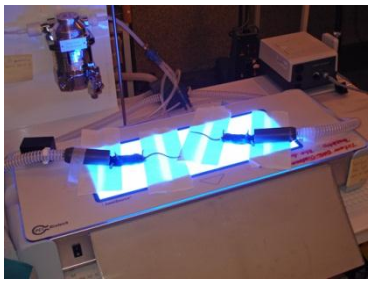


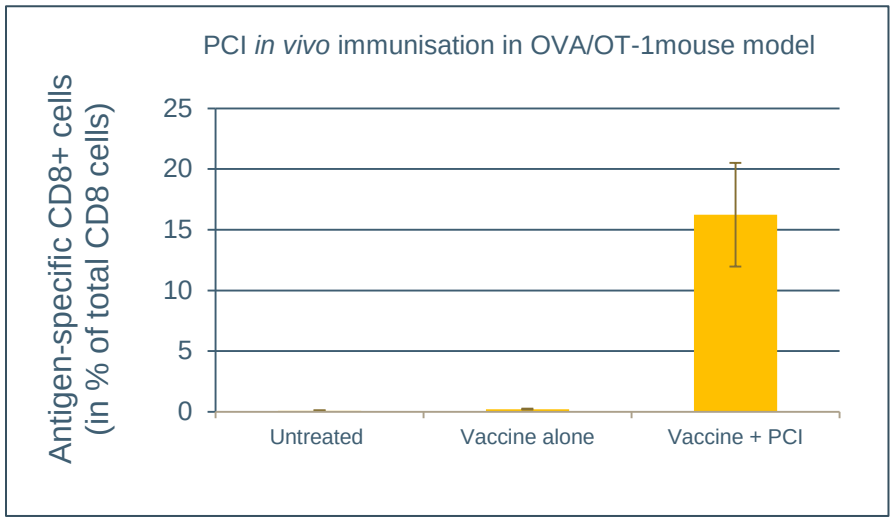
→ PCI enhancement of vaccination up to 16 times has been seen

PCI *in vivo* immunisation enhances CD8 immune response in mouse OVA/OT-1

Håkerud *et al.* (2014). J. Control. Release 174:143-50



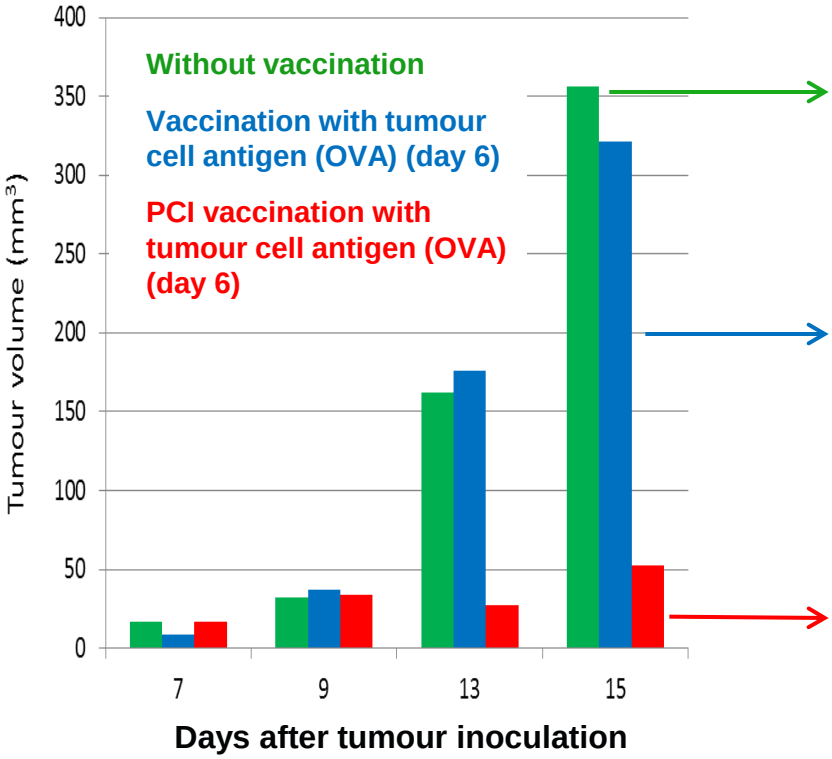


→ With PCI vaccination enhancement of CD8 immune response up to > 100 can be achieved

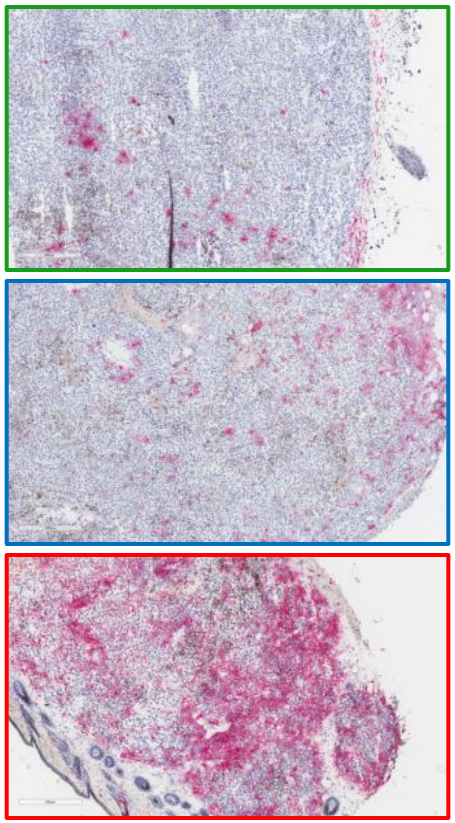
PCI induced immune response translates into therapeutic effect in animal tumour model (B16-OVA melanoma/OT-1)

Tumour volume at different time points after inoculation

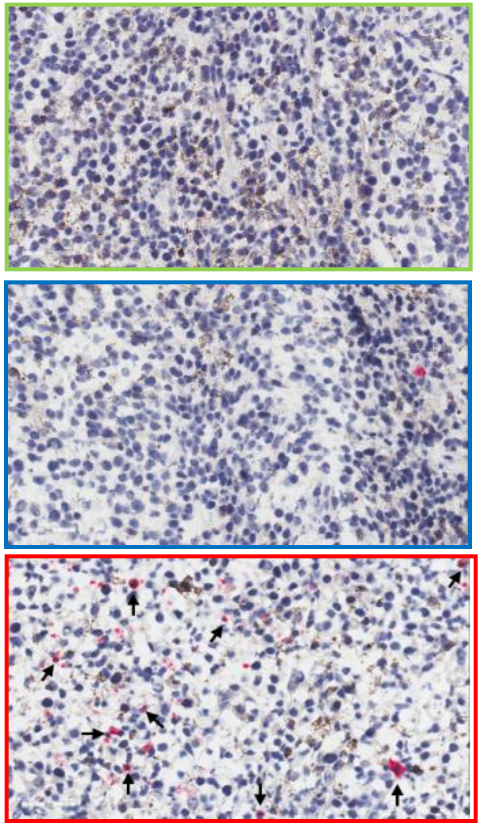
(mean values; n=5/group)



Tumour infiltration of CD8⁺ T-cells

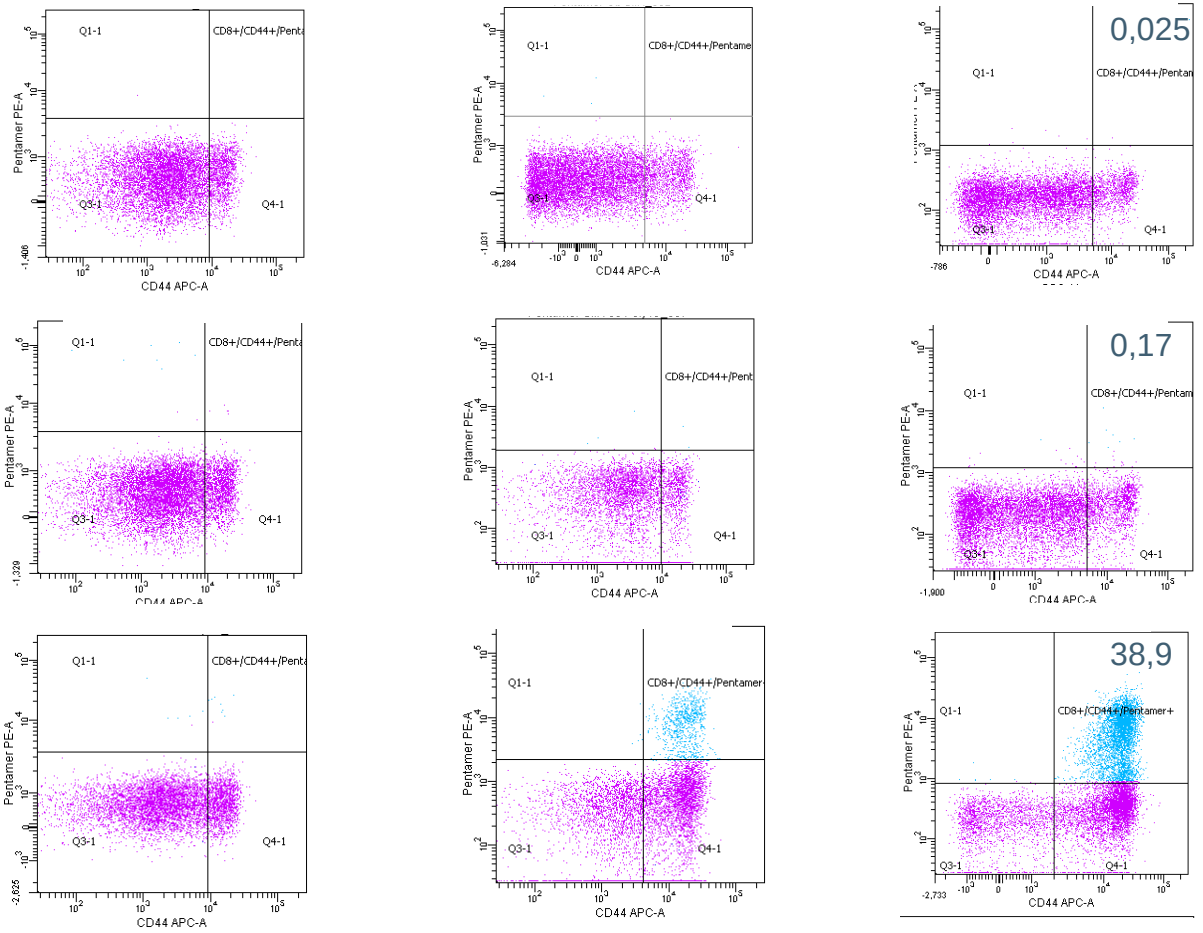


Apoptosis induction / Caspase-3



PCI combined with state-of-the-art vaccine technology enhances SIINFEKL (OVA) peptide response >100x in normal mice

1st vaccination | 2nd vaccination | 3rd vaccination



Untreated

SIINFEKL + vaccine tech

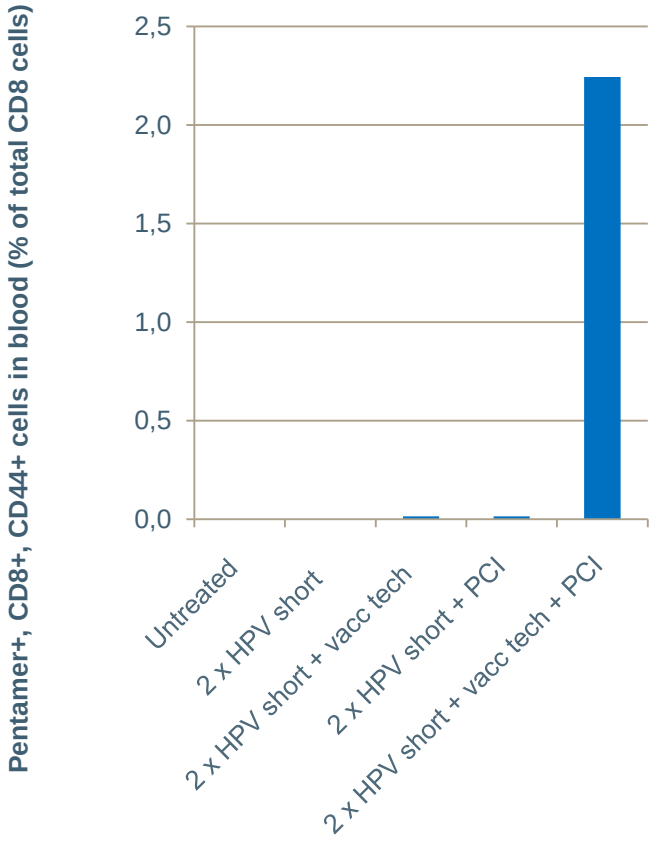
SIINFEKL + vaccine tech + PCI

SIINFEKL pentamer

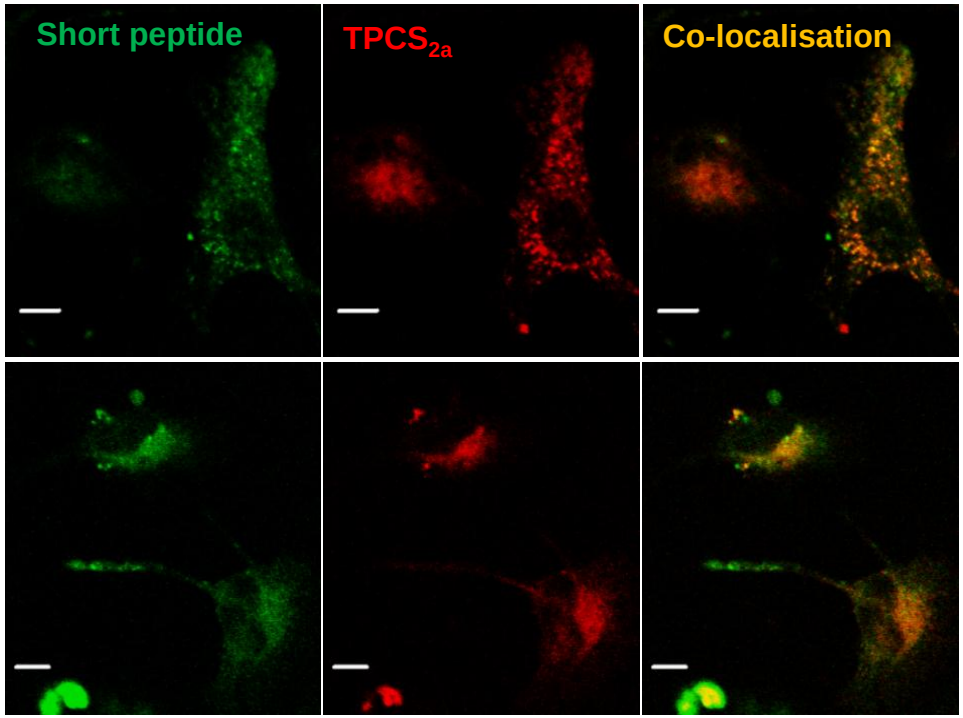
CD44

PCI combined with state-of-the-art vaccine technology strongly induces CD8+ response with HPV short peptide antigen

PCI with HPV short peptide, 2nd immunisation

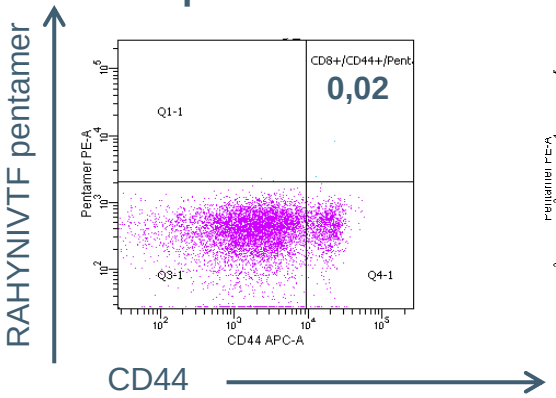


Also short peptides are taken up by endocytosis and co-localises with $TPCS_{2a}$ in endosomes

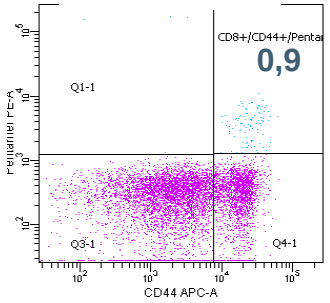


Two PCI vaccinations combined with state-of-the-art vaccine technology significantly enhance HPV long peptide antigen response.

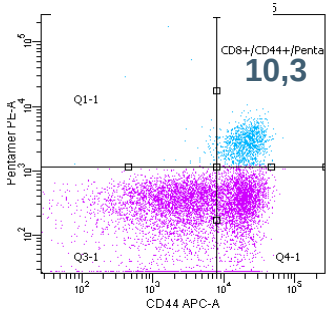
Peptide alone



Peptide + vaccine tech

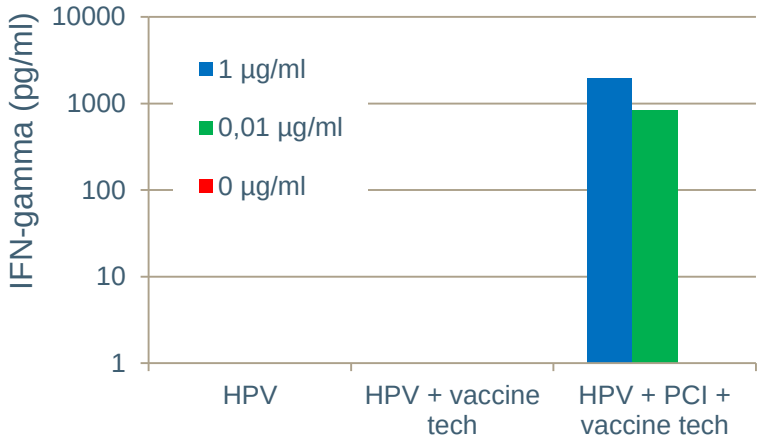


Peptide + vaccine tech + PCI



HPV long peptide

IFN-gamma production in spleen cells after restimulation with HPV peptide.



$TPCS_{2a}$ in therapeutic vaccination

Safety – $TPCS_{2a}$ tested in Phase I study (i.v. inj.) at much higher doses than what will be used for vaccination

Stability – $TPCS_{2a}$ can be autoclaved and is stable at room temperature, also in solution

Cost effectiveness – Simple and cost effective synthesis of $TPCS_{2a}$

Conclusions

- The PCI vaccination technology can enhance CD8-cell immune responses > 100 times.
  - Effects shown both in the OVA/OT-1 system and in normal mice.
- The probable mechanism for PCI vaccination is to enhance MHC class 1 antigen presentation by releasing peptide or protein antigens into the cytosol of antigen presenting cells
- The technology can be used with both protein, long peptide and short peptide antigens.
- The photosensitising compound used in PCI is already tested in clinical trials and have a good safety profile
- PCI is an innovative technology with an unique mechanism for enhancing the effect of many types of vaccines where a CD8 T-cell response is desired

Collaborators

- University Hospital Zurich
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