Unlocking the potential of innovative medicines

PCI Biotech

Photochemical Internalisation (PCI) – An Innovative CTL-induction Technology

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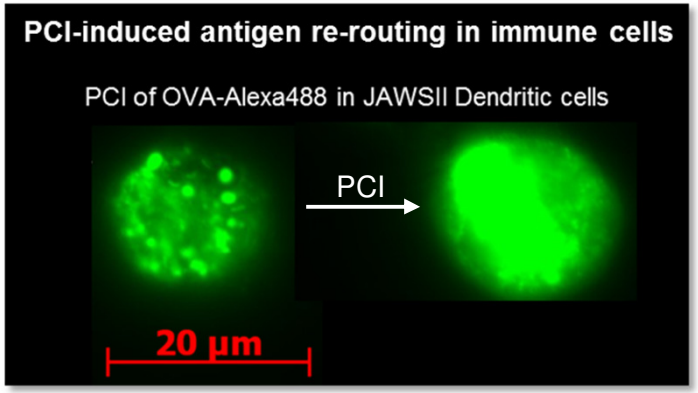
PCI Biotech at a glance

- A listed cancer-focused Norwegian biotech company
- Photochemical internalisation ("PCI"), - light-induced enhancement of the effect of drugs.
- Phase II clinical studies with cytotoxic drugs in two indications; head & neck and bile duct cancer
- PCI is also very good technology for delivery of oligonucleotides and other nucleic acids
- Pre-clinical program on therapeutic vaccination, with promising results showing substantial enhancement of the important cytotoxic T-cell response

PCI induces endosomal escape by illumination



PCI technology – enabling drugs to reach intracellular therapeutic targets

STEP 1:

- $TPCS_{2a}$ (S) and the active molecule (D) are injected into the body and reaches the target cells

STEP 2:

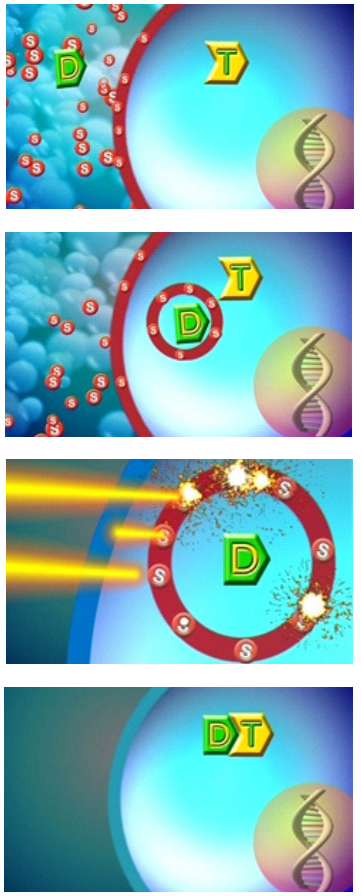
- $TPCS_{2a}$ (S) and the active molecule (D) are taken up by the cell, but D is unable to reach the target (T), as it is encapsulated in an endosome
- S is washed away from the cell membrane, but trapped in endosomes

STEP 3:

- Light activates $TPCS_{2a}$ (S) in the membrane of the endosome
- The membrane integrity is affected and the active molecule released

STEP 4:

- The active molecule (D) can now bind to its target (T) and initiate the therapeutic response

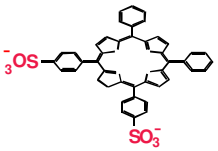


D

The active molecule
- Anticancer agent, e.g. bleomycin, gemcitabine
- Oligonucleotide, e.g. siRNA
- Protein, e.g. antibody-drug conjugate
- Peptide: e.g. antigen

S

The PCI component
- Light sensitive component
- Amphinex® - $TPCS_{2a}$

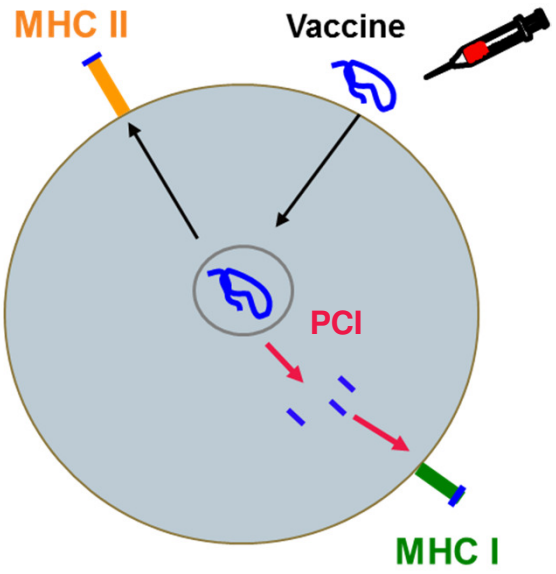


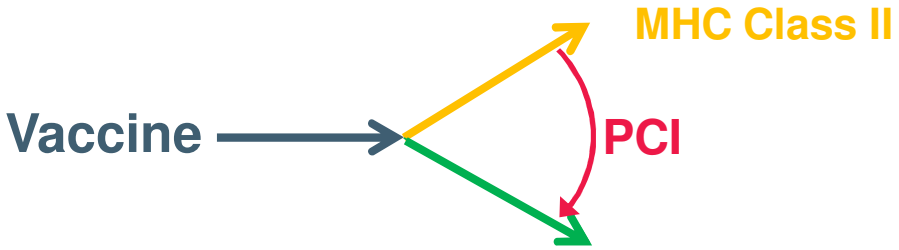
T

The target
- Target for the active molecule
- E.g. DNA, mRNA, enzyme, microtubuli

PCI mechanism of action – triggered endosomal escape through illumination

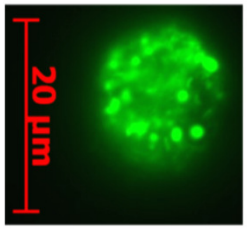
PCI for vaccination – enhancing cytotoxic T-cell response by light-induced cross presentation



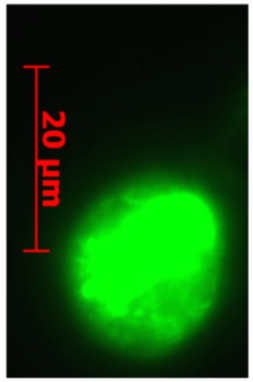


Generate more disease specific cytotoxic T-cells

Attack cancer and virus-infected cells more efficiently



Without PCI

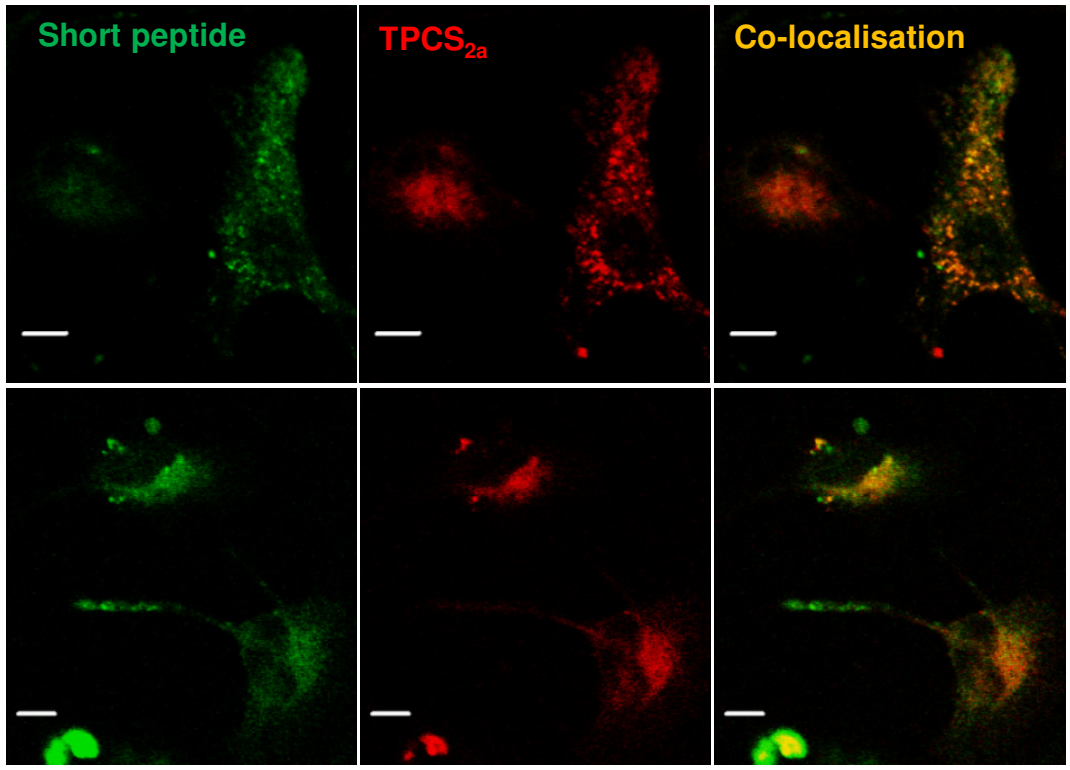


With PCI

Ovalbumin antigen in JAWSII dendritic cells

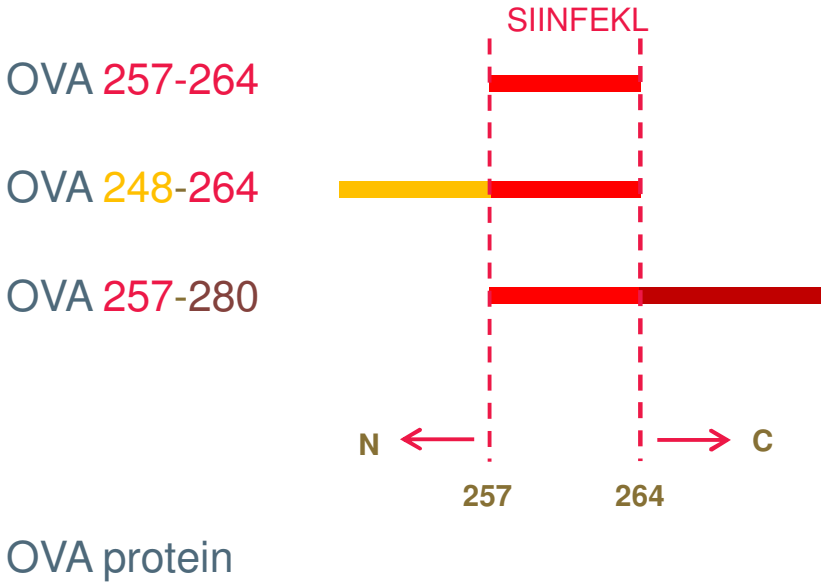
Mechanism of action – peptide antigens are taken up in endosomes and co-localize with $TPCS_{2a}$

Both short and long peptides are taken up by endocytosis, co-localises with $TPCS_{2a}$ in endosomes and are re-localised upon illumination

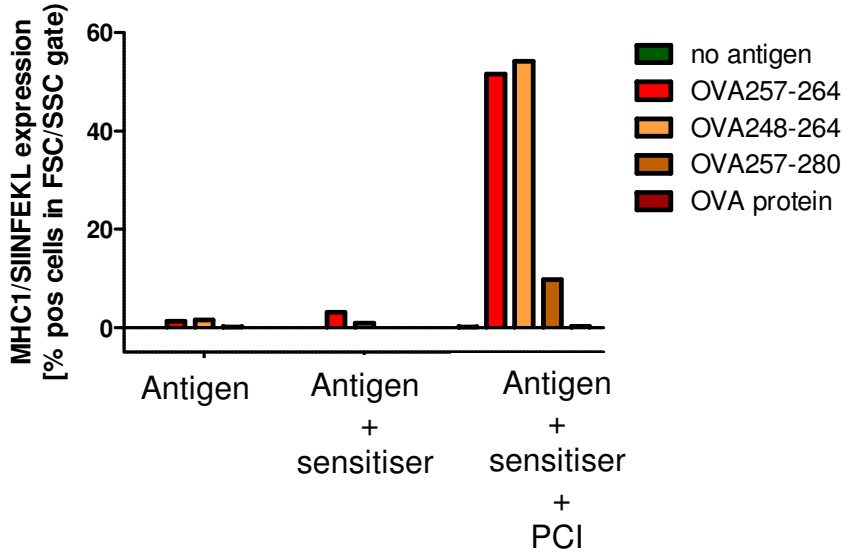


Mechanism of action - PCI increases MHC I presentation of SIINFEKL (OVA) peptide and N- and C-terminal extentions

- Macrophage cell line
- Stained with antibody specific for SIINFEKL/MHC I complex



MHC1/SIINFEKL expression in B6 macrophage cell line, OVA peptides and proteins, concentrations of all antigens corresponds to 3 µg/ml of SIINFEKL

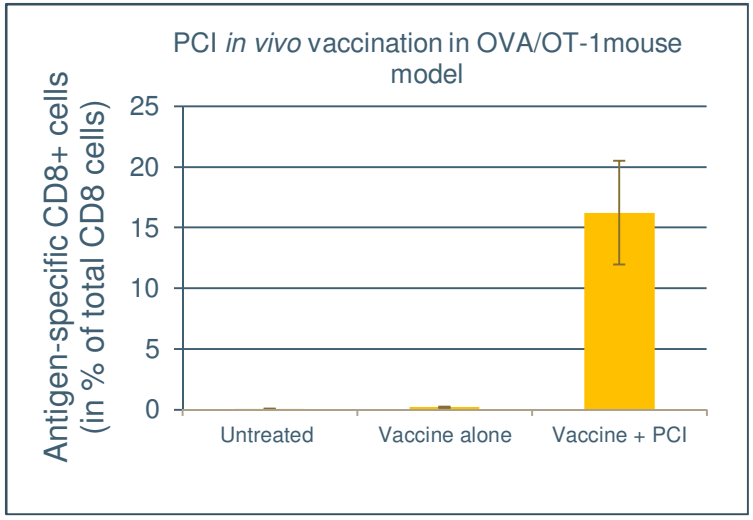


PCI enhances *in vivo* vaccination with protein antigen in mice (collaboration University Hospital Zurich)

- Mice were vaccinated with an intradermal injection of a mix of protein antigen (OVA) and photosensitiser

- Injection site illuminated with blue light

- Blood and spleen analysed for antigen- specific CD8 cells by flow cytometry

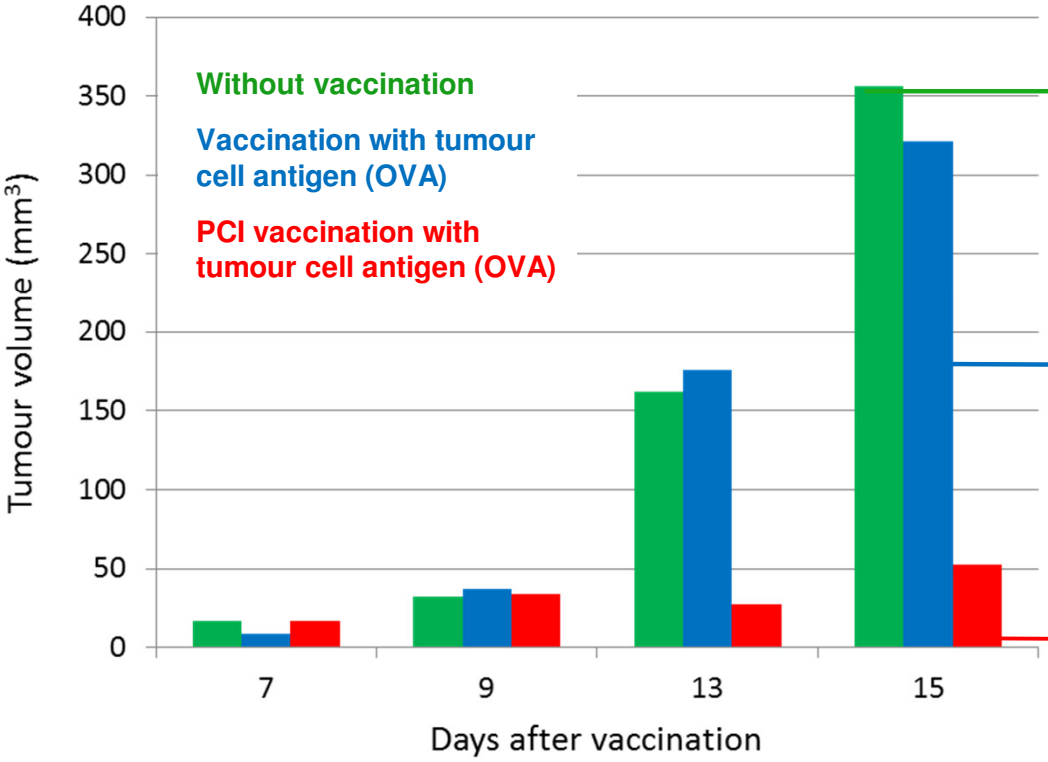


→ With PCI vaccination enhancement of up to > 100 can be achieved

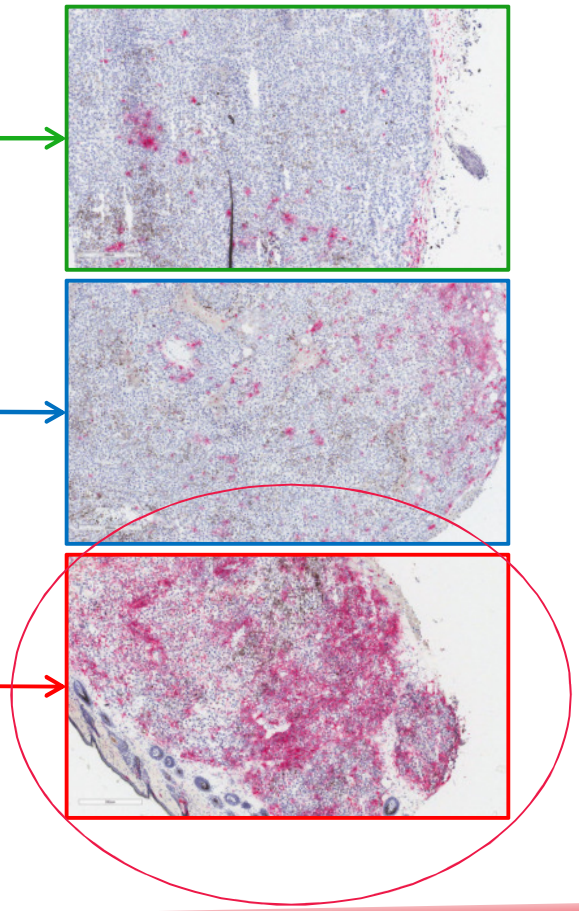
PCI induced immune response translates into therapeutic effect in animal tumour model with protein antigen (B16-OVA melanoma/OT-1)

Tumour volume at different time points after inoculation

(mean values; n=5/group)



Tumour infiltration of CD8⁺ T-cells

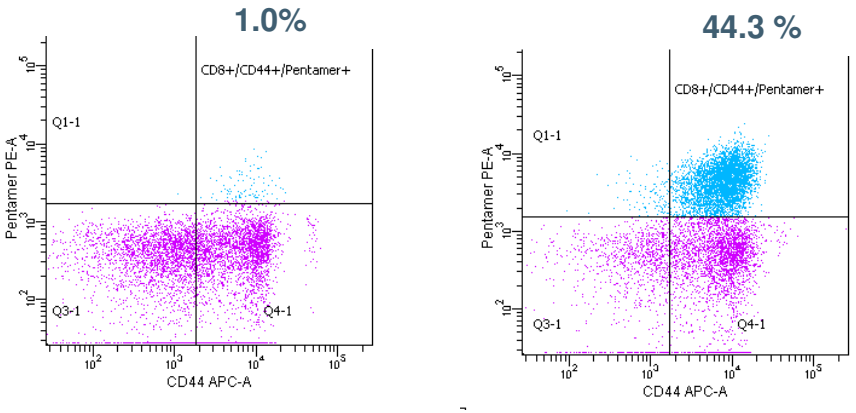


PCI strongly enhances CD8 cell proliferation and IFN-γ production after *in vivo* immunisation with HPV long peptide antigen

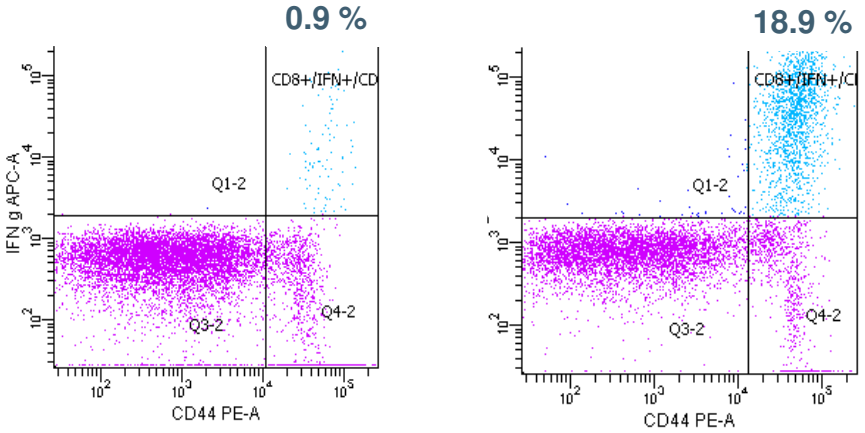
Vaccine

Vaccine with PCI

HPV pentamer in blood samples

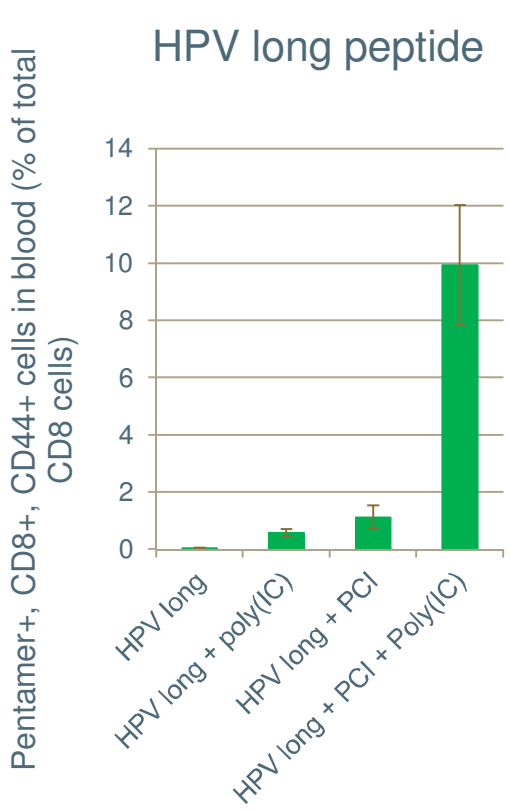


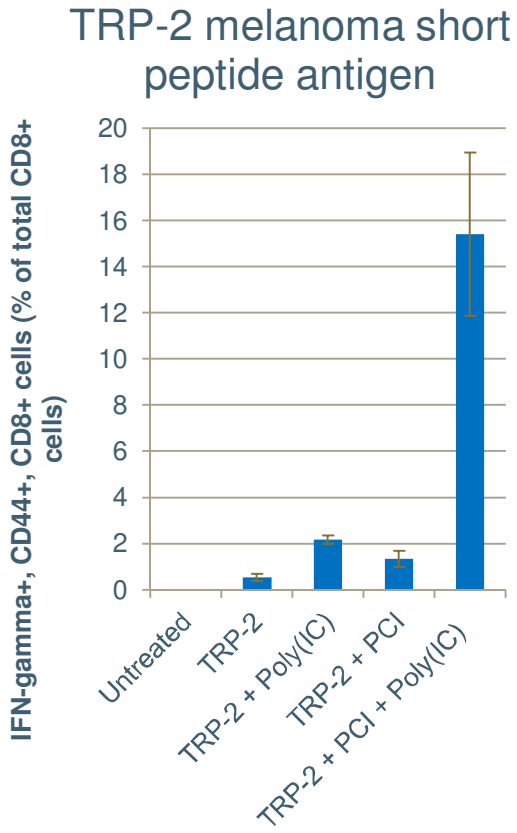
IFN-γ in spleen cells



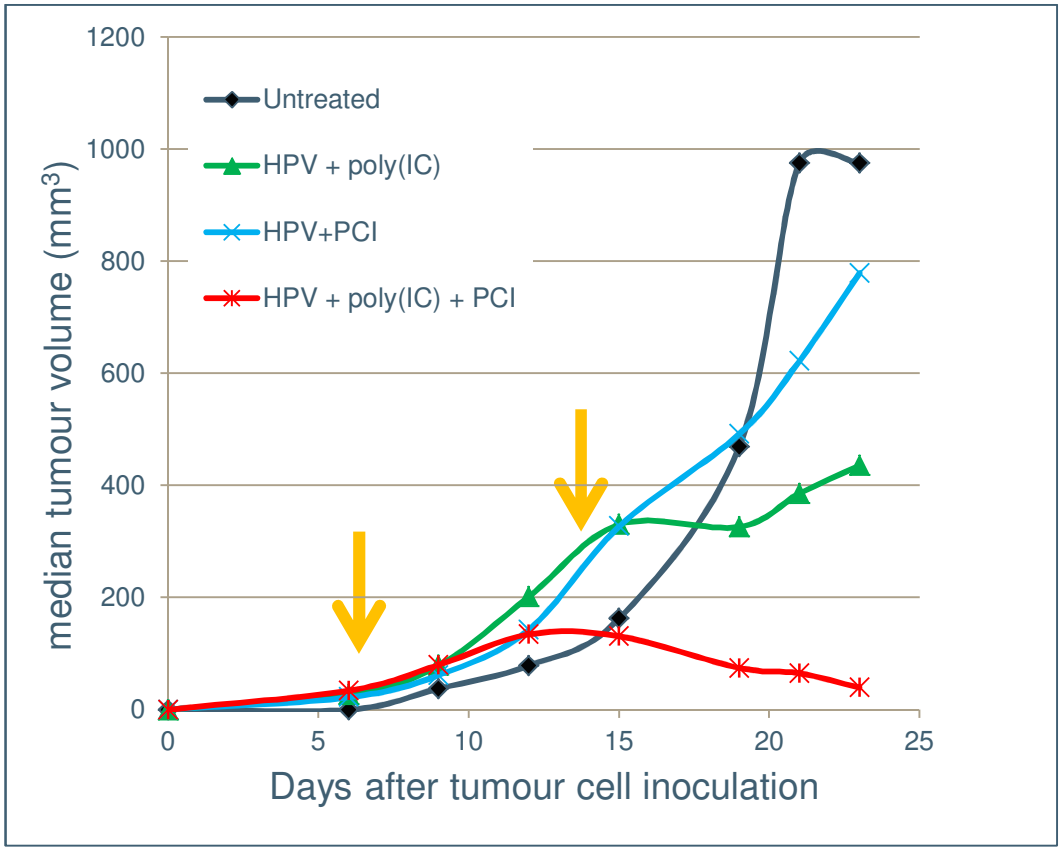
With peptide antigens PCI acts synergistically with other vaccination enhancement technologies.

- PCI acts synergistically with several commonly used vaccine adjuvants.
- PCI works with many different peptide antigens and stimulates both CTL proliferation and IFN-γ production





Therapeutic vaccination with HPV long peptide antigen in TC-1 mouse tumour model – PCI induces strong anti-tumour response



- Intradermal vaccination at days 6 and 13 after tumour cell inoculation
- 5 animals per group

Conclusions

- The PCI vaccination technology can enhance CD8-cell immune responses > 100 times.
- PCI acts by enhancing MHC class 1 antigen presentation by releasing antigens into the cytosol of antigen presenting cells
- The technology can be used with both protein, long peptide and short peptide antigens.
- PCI acts in synergy with other vaccination enhancing technologies
- The photosensitising compound used in PCI is already tested in clinical trials, has a good safety profile and is stable and easily produced.
- 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