Unlocking the potential of innovative medicines

PCI Biotech

An innovative and versatile platform technology for therapeutic enhancement and vaccination

Biotech Showcase
14 January 2015

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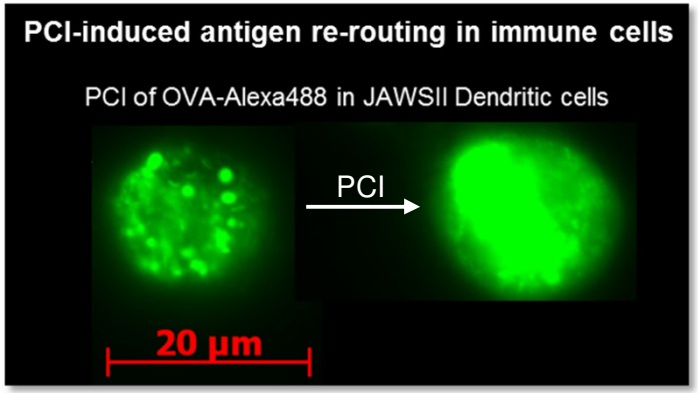
PCI Biotech at a glance

- A listed cancer-focused biotech company entering clinical Phase II for two indications; head & neck and bile duct cancer
- Pre-clinical program on therapeutic vaccination, with promising results showing substantial enhancement of the important cytotoxic T-cell response
- Technology based on photochemical internalisation ("PCI"), originating from the Norwegian Radium Hospital, using a small molecule photosensitizer ($TPCS_{2a}$) and light to induce the endosomal escape of active molecules trapped in endosomes

PCI induces triggered 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 carried by the blood stream to the cell

STEP 2:

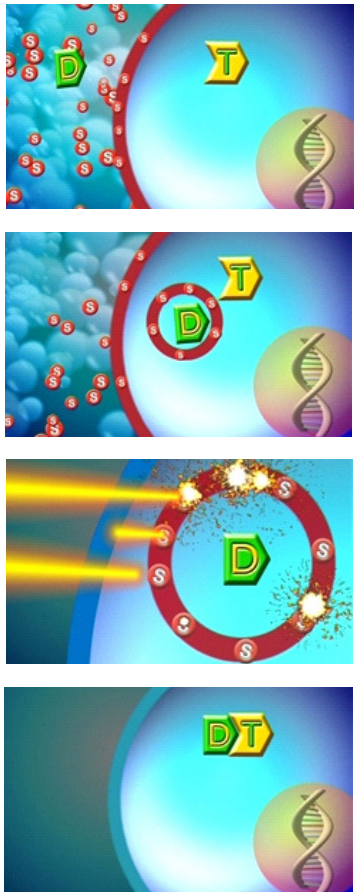
- $TPCS_{2a}$ (S) and the active molecule (D) are taken up by the cell, but D is unable to reach the target (T), as it is encapsulated in an endosome
- S is washed away from the cell membrane, but trapped in endosomes

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

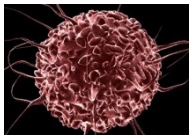
The target
- Target for the active molecule
- E.g. DNA, mRNA, enzyme, microtubuli

PCI mechanism of action – triggered endosomal escape through illumination

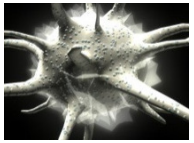
PCI technology – enable drugs to cover additional areas of unmet medical need

Existing & innovative treatments

Cells



Cancerous cell



Dendritic cell

Active ingredient
(trapped in endosome)

- Small molecules
- siRNA/mRNA
- Antibody targeted drugs
- Peptides
- Antigens

+

PCI enhancement technology

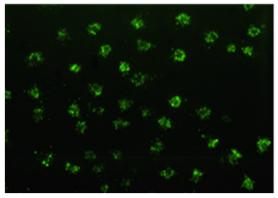
Photosensitiser
(Amphinex)

$TPCS_{2a}$

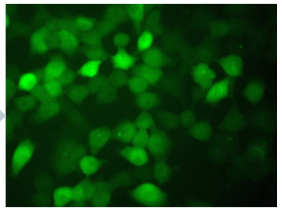
Light source

Red light

Blue light

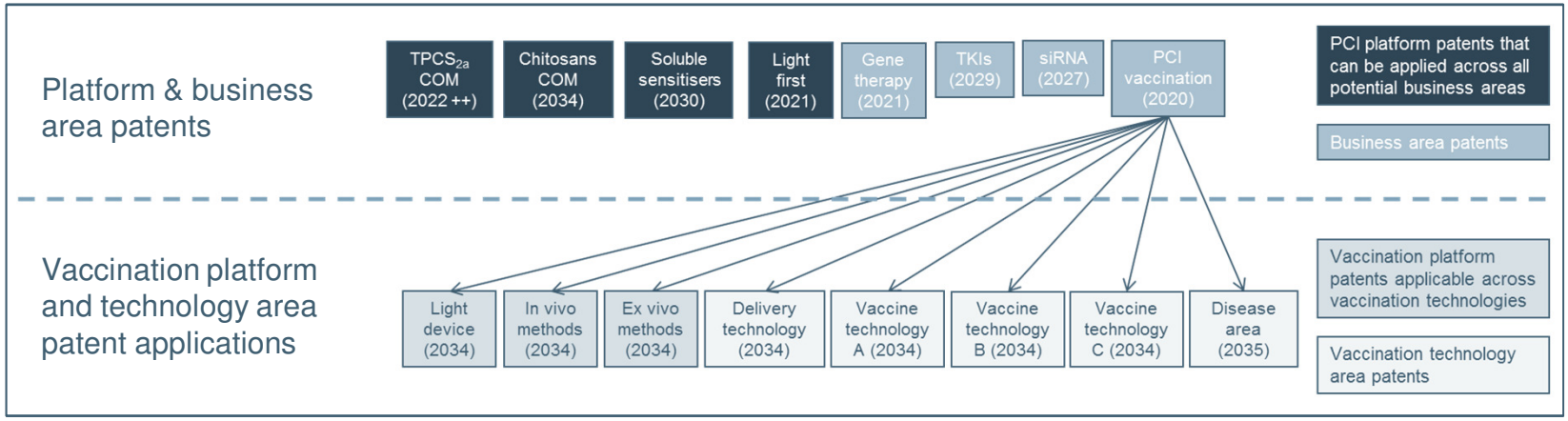


Endosomal escape
Release of drug in cells



PCI technology and IPR

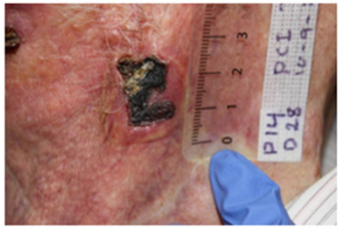
- PCI Biotech is the world leader in photochemical internalisation – an innovative technology platform for localised targeted endosomal escape
- PCI Biotech has several patents covering all potential business areas across the PCI platform, as well as business area specific technology and use patents
- The company follows an active patenting strategy to solidify and enhance the proprietary PCI platform, including all interesting and potentially valuable medical applications
- PCI Biotech is currently particularly active in the emerging field of immunotherapy, where several new patent applications have been filed the last years to build a robust IP estate for PCI as a powerful CTL-induction technology for therapeutic vaccination

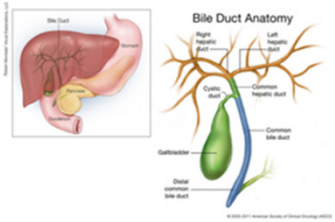


PCI Biotech is leveraging PCI ($TPCS_{2a}$) in three distinct areas

Local cancer treatment

- bleomycin in head and neck cancer
- gemcitabine in bile duct cancer

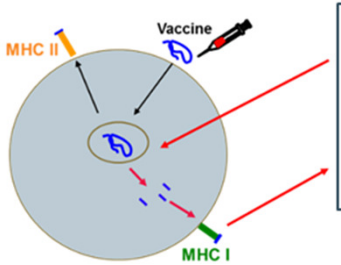




Systemic administration

PCI vaccination technology

- therapeutic vaccination



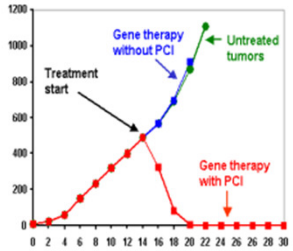
PCI – induce presentation on MHC class I

- Make it possible to achieve cytotoxic T-cell response with protein/ peptide vaccines
- Can solve a key challenge for many vaccine approaches

Local administration

PCI macromolecule delivery

- immunotoxins
- siRNA & other oligo
- gene therapy



Local or systemic administration

An innovative localised cancer treatment concept

Clinical programs:

Head & neck cancer

Bile duct cancer

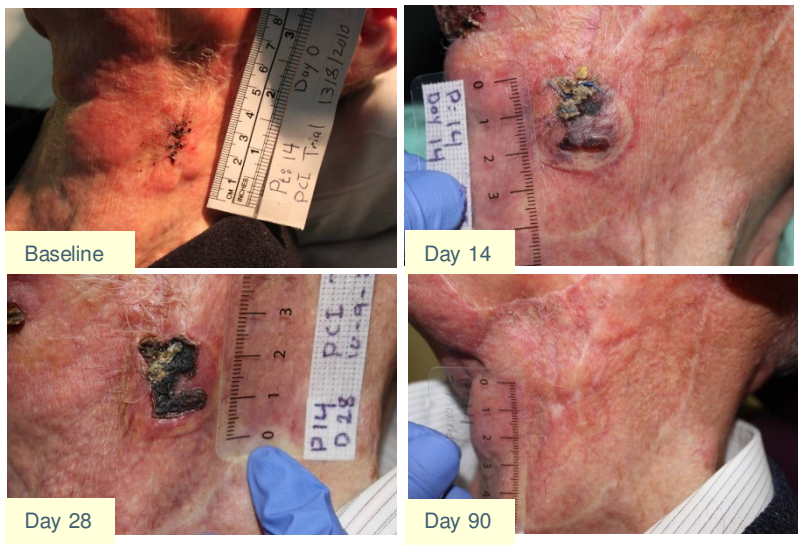
Amphinex ($TPCS_{2a}$) induced PCI of bleomycin
Phase I summary

Phase I study

- Amphinex® dose escalating study (0,25 mg/kg - 1,5 mg/kg)
- Patients with recurrent/metastatic cutaneous and/or subcutaneous tumours
- Total 19 patients included, majority being HNSCC
- DLTs at the highest dose (photosensitivity)
- Strong tumour response across all dose groups
- Apparent tumour selectivity in several patients

Phase I Extension study

- To study a lower dose of Amphinex® (0,125mg/kg)
- Three patients included – all HNSCC
- Tumour response starting to diminish



Complete Response following treatment of skin adnexal tumour

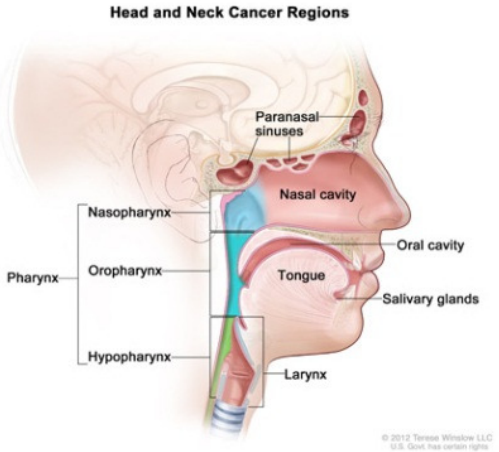
Overall conclusion Phase I studies

- Same safety conclusion for all 22 patients; Well tolerated with appropriate analgesia and anesthesia
- Amphinex® dose selected for further studies: 0,25 mg/kg

Amphinex ($TPCS_{2a}$) induced PCI of bleomycin Phase II study in head & neck cancer

Summary of design

- Patient inclusion: 2012-2015
- Target population: recurrent head and neck squamous cell carcinoma, unsuitable for radiotherapy and surgery
- Both cutaneous/subcutaneous and interstitial tumours
- Study design: single arm, open label multi-center study in up to 80 patients to assess safety and efficacy of a single treatment with Amphinex induced PCI of bleomycin
- Primary endpoint: progression free survival at 6 months

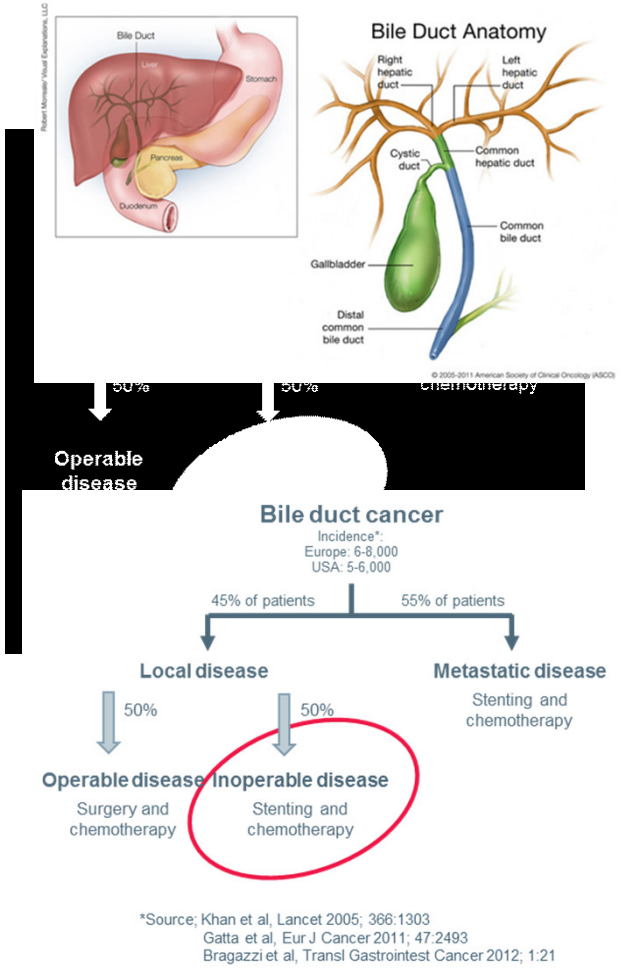


Preliminary findings

- Stronger effect with intra-tumour treatment than seen with surface illumination in Phase I
- Intra-tumour illumination is optimized in separate light dose escalation part of the study, running in parallel to open inclusion of patients for superficial illuminations
- Included an interim PoC analysis when 12 patients have been treated with intra-tumour illumination at the selected light dose

Amphinex ($TPCS_{2a}$) induced PCI of gemcitabine – phase I/II cholangiocarcinoma

- **Patient population with high medical unmet need**
  - **Patient inclusion**: 2014/15
  - **Target population**: patients with inoperable bile duct cancer
  - **Study design**: open label, multicenter study in up to 45 patients to assess safety and efficacy of a single treatment with Amphinex induced PCI of gemcitabine, followed by systemic cisplatin/gemcitabine
    - Phase I: dose escalation study to assess the local tolerance
    - Phase II: randomized double-arm phase II study



*Source; Khan et al, Lancet 2005; 366:1303
Gatta et al, Eur J Cancer 2011; 47:2493
Bragazzi et al, Transl Gastrointest Cancer 2012; 1:21

Unlocking the potential of new treatment paradigms

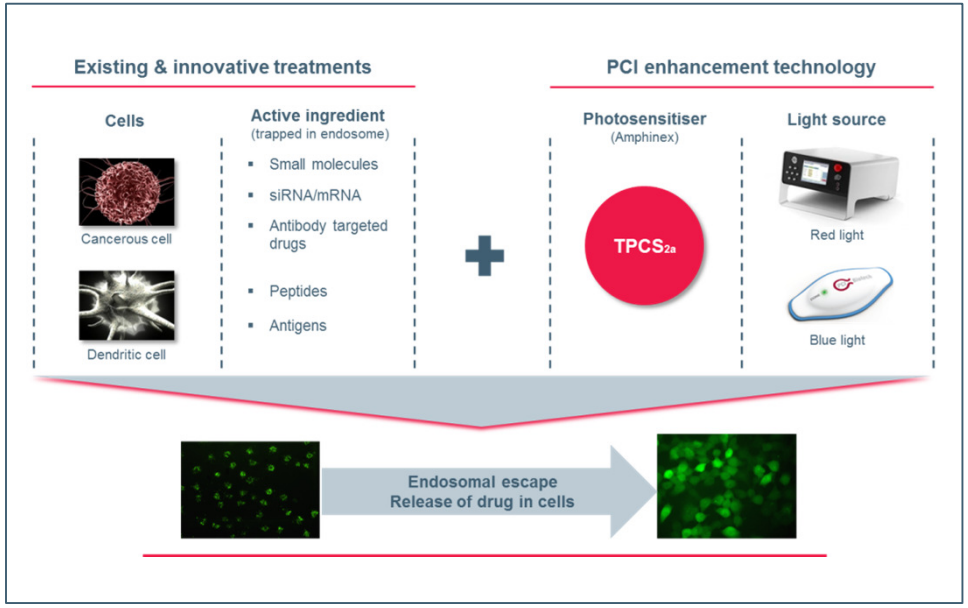
Pre-clinical programs:

Macromolecular delivery

CTL induction in vaccination

Unlocking the true potential of new treatment paradigms

Enhancement of therapeutic vaccination and delivery of macromolecules

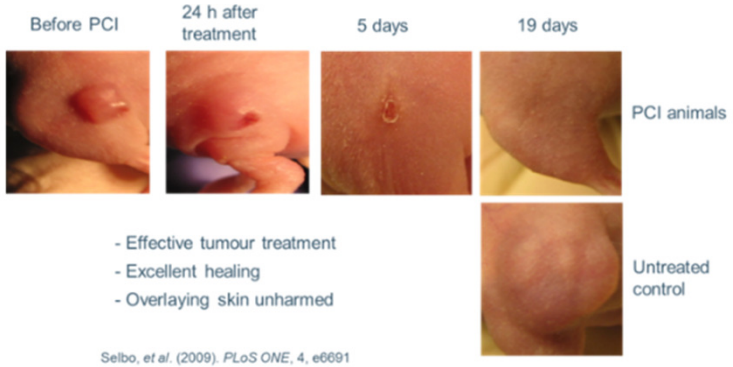


- PCI is a clinically proven endosomal escape technology that may realise the true therapeutic benefit of innovative medicines
- Strong preclinical efficacy evidence
  - Potentiation of responses considered key for effective **therapeutic vaccination**
  - Effective localised delivery of a range of **macromolecules**
    - **siRNA**

PCI may realise additional therapeutic potential of innovative medicines and increase their coverage of unmet need in certain disease areas

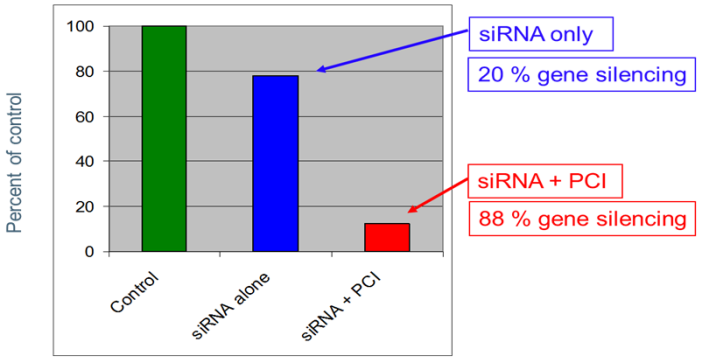
Macromolecules – endosomal escape of a range of products, pre-clinical data

1 Intracellular delivery of immunotoxin – *in vivo*



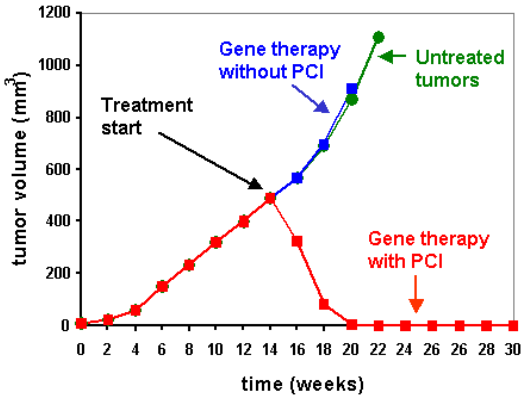
Selbo, *et al.* (2009). *PLoS ONE*, 4, e6691

2 Intracellular delivery of siRNA



Bøe, S., Longva, A.S. and Hovig, E. (2007). *Oligonucleotides* 17, 166-73

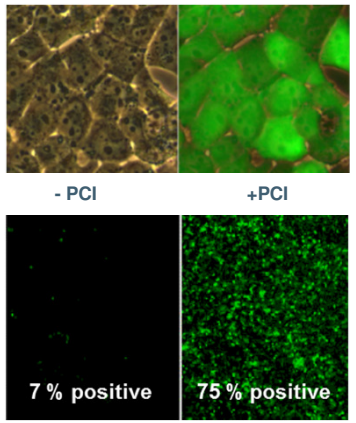
3 Intracellular delivery of gene therapy – *in vivo*



- Therapeutic gene (p53)
- Head & neck tumours (p53 mutated)
- Local injection

Ndoye *et al.* (2006) Mol. Ther. **13**:1154-1162

4 Intracellular delivery of mRNA



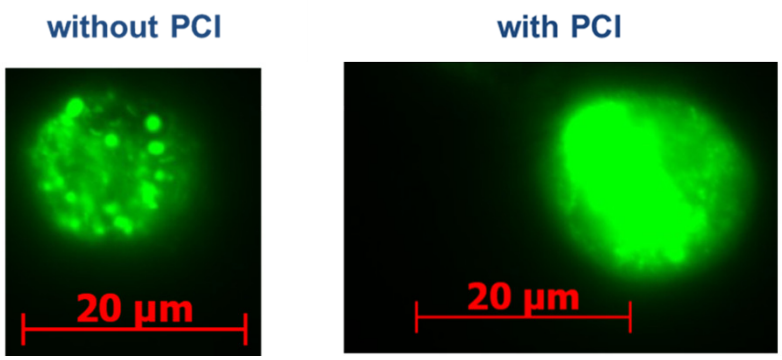
- EGFP mRNA

Bøe, S *et al.* (2010) *Oligonucleotides* **20**:1-6

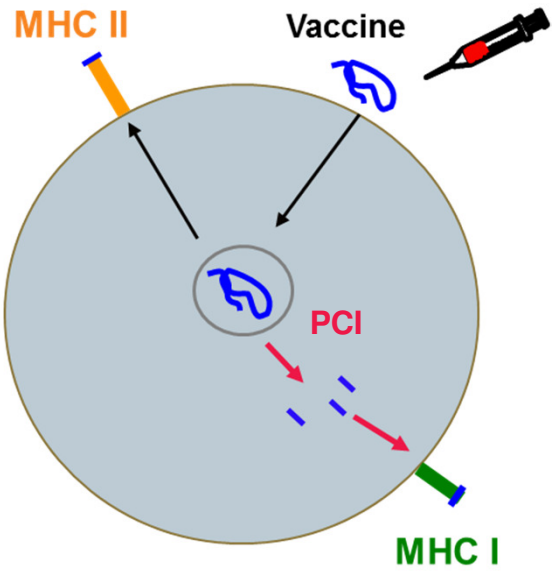
PCI – an effective CTL-induction technology

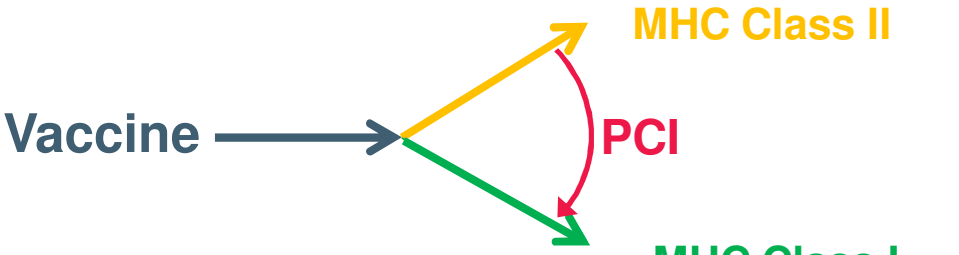
PCI can induce escape of antigens from endocytic vesicles in antigen presenting cells, thereby enhancing MHC class I antigen presentation

PCI of OVA-Alexa488 in JAWSII Dendritic Cells



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



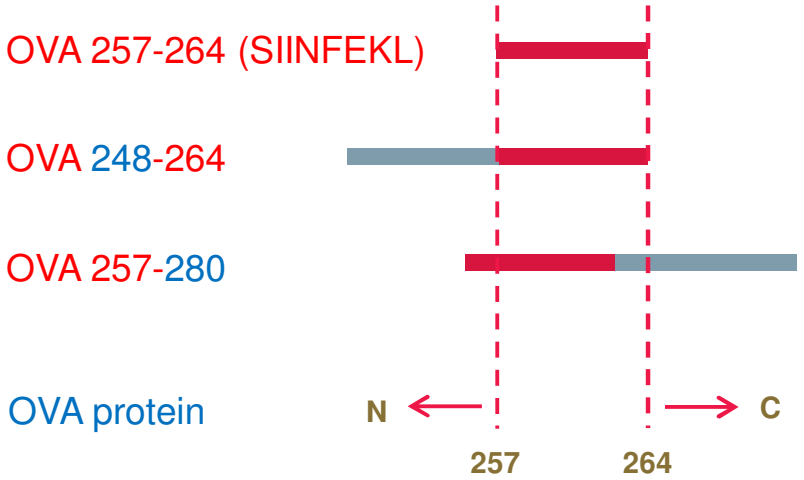


Generate more antigen specific cytotoxic T-cells

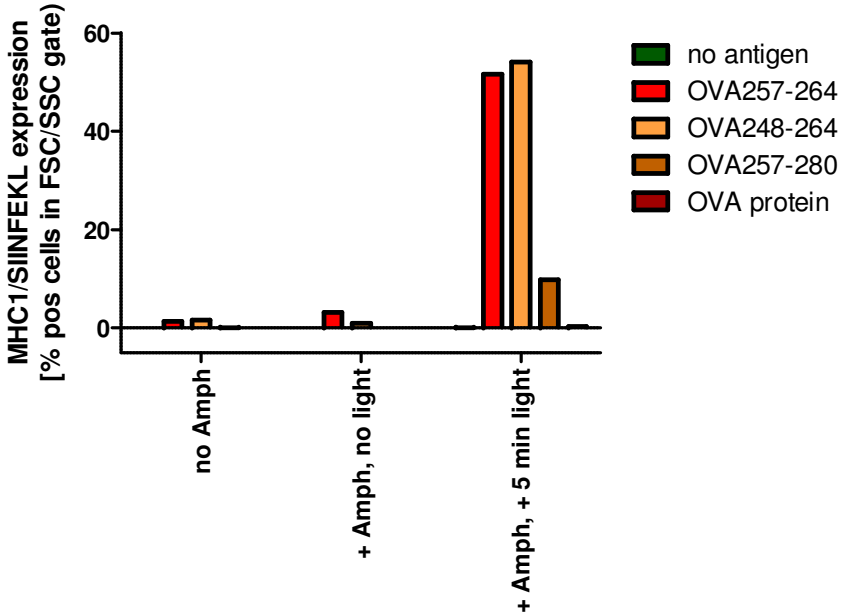
Attack cancer and virus-infected cells more efficiently

PCI with N- and C-terminal extended SIINFEKL (OVA) peptides increases MHC I presentation in macrophages

Cells stained with antibody specific for SIINFEKL/MHC I complex



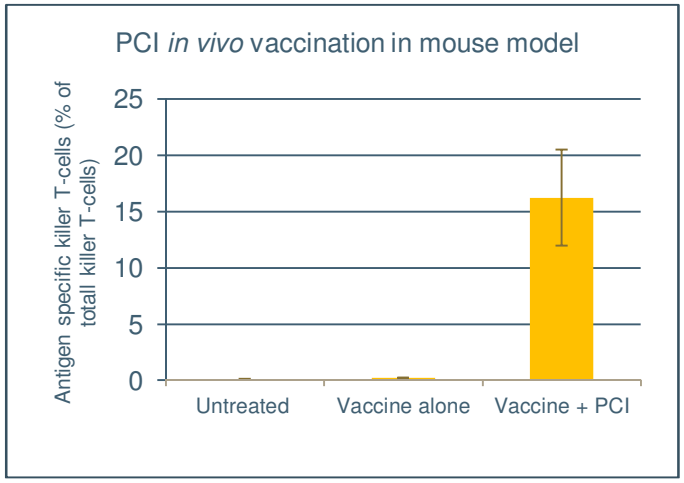
MHC1/SIINFEKL expression in B6 macrophage cell line, OVA peptides and proteins, concentrations of all antigens corresponds to 3 µg/ml of SIINFEKL



PCI – a simple and effective procedure for both modes of therapeutic vaccination

In vivo vaccination

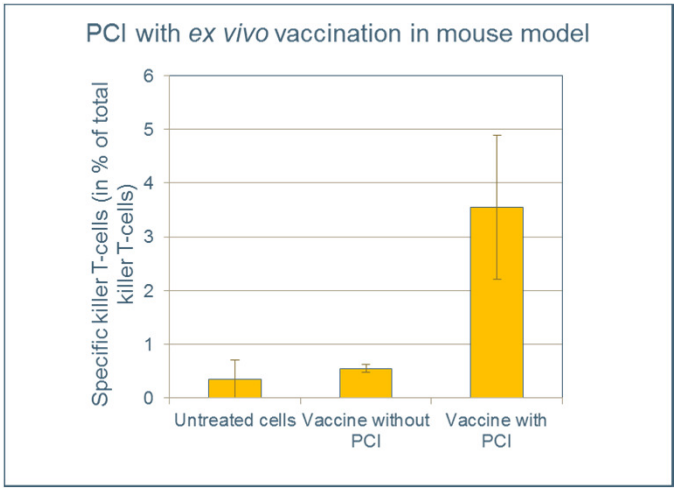
- Inject vaccine (+ adjuvant) into patient, e.g. in or under the skin
- PCI: add photosensitiser and illuminate
  - > *PCI induced increase in antigen specific CD8⁺ T-cells >100 times has been seen*
  - > *Further optimisation of* in vivo *PCI vaccination method ongoing*



(collaboration with NTNU & University Hospital Zurich)

Ex vivo vaccination

- Remove immune cells from patient
- Give vaccine + adjuvant treatment to the cells in laboratory; PCI: performed on cells in laboratory
- Return the treated cells to the patient
  - > *PCI induced increase in antigen specific CD8⁺ T-cells up to 16 times has been seen*
  - > *Further optimisation of* ex vivo *PCI vaccination method ongoing*

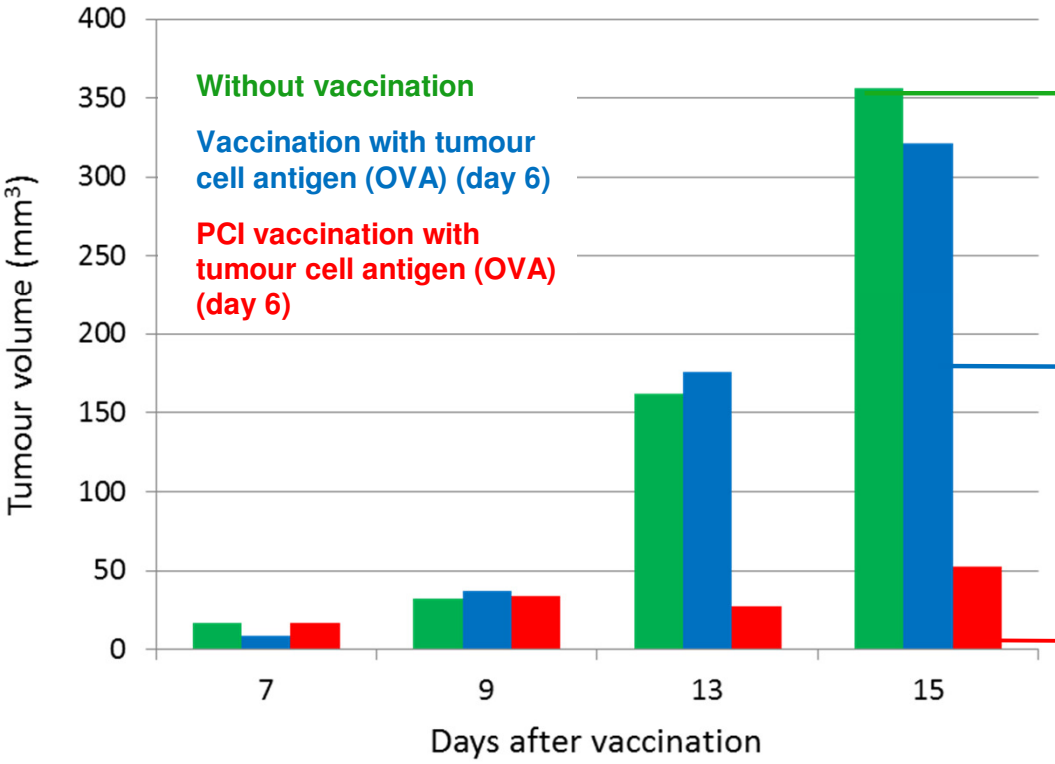


(collaboration with NRH & University Hospital Zurich)

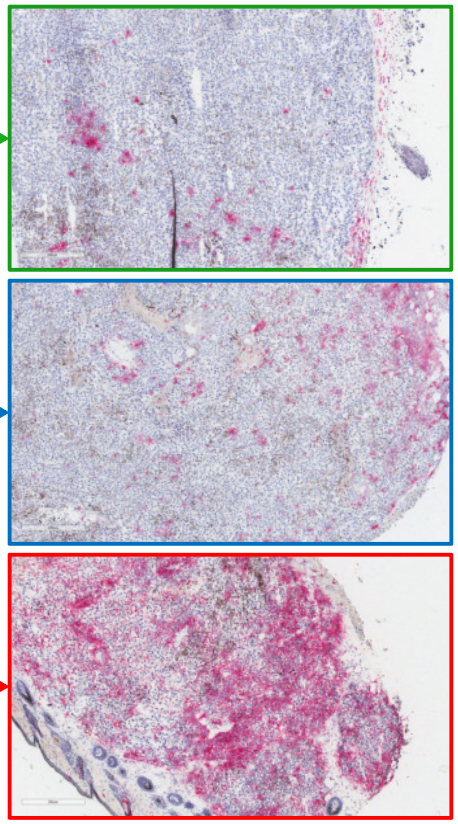
PCI induced immune response translates into therapeutic effect in animal tumour model (B16-F10-OVA melanoma/OT-1)

Tumour volume at different time points after inoculation

(mean values; n=5/group)



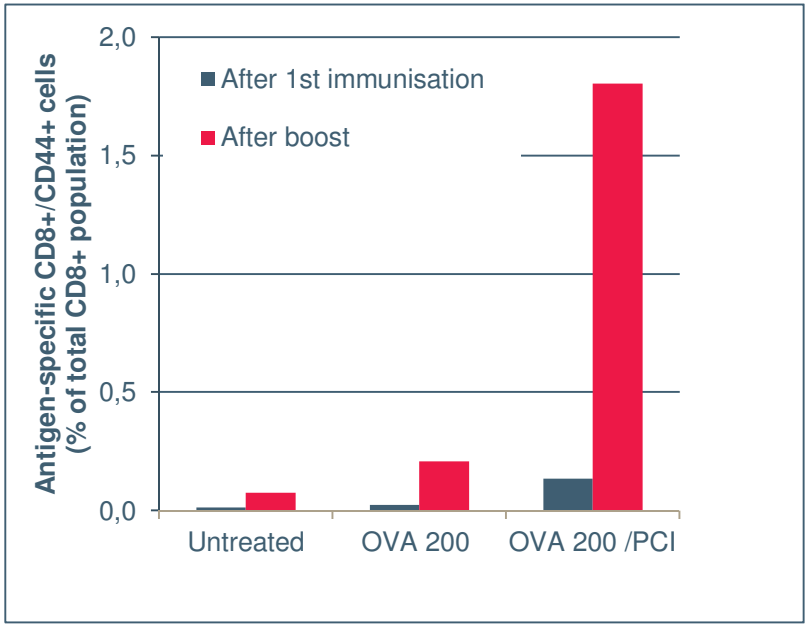
Tumour infiltration of CD8⁺ T-cells



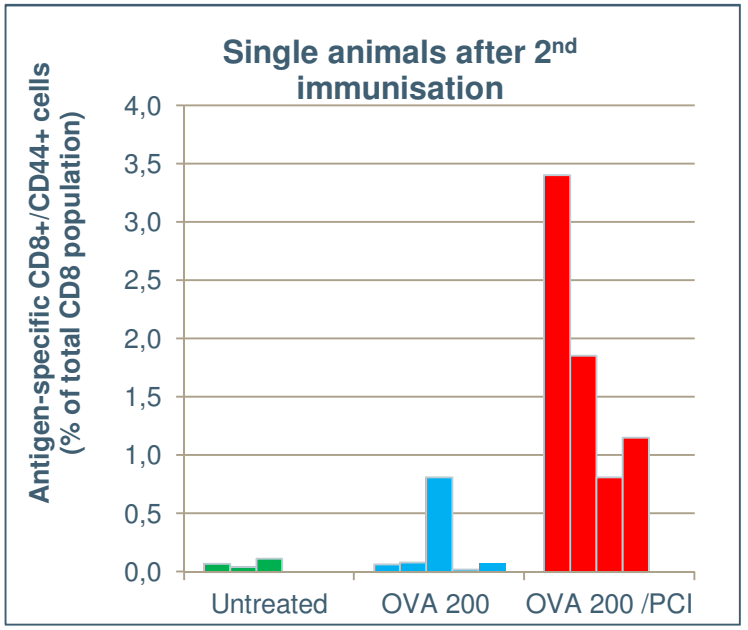
Håkerud, Selbo et al., Manuscript in prep.

With OVA antigen PCI induces antigen-specific CD8 cells also from mouse endogenous T-cells

- Mice immunised with 200 µg OVA +/- PCI at days 0 and 14, blood samples analysed on days 7 and 21

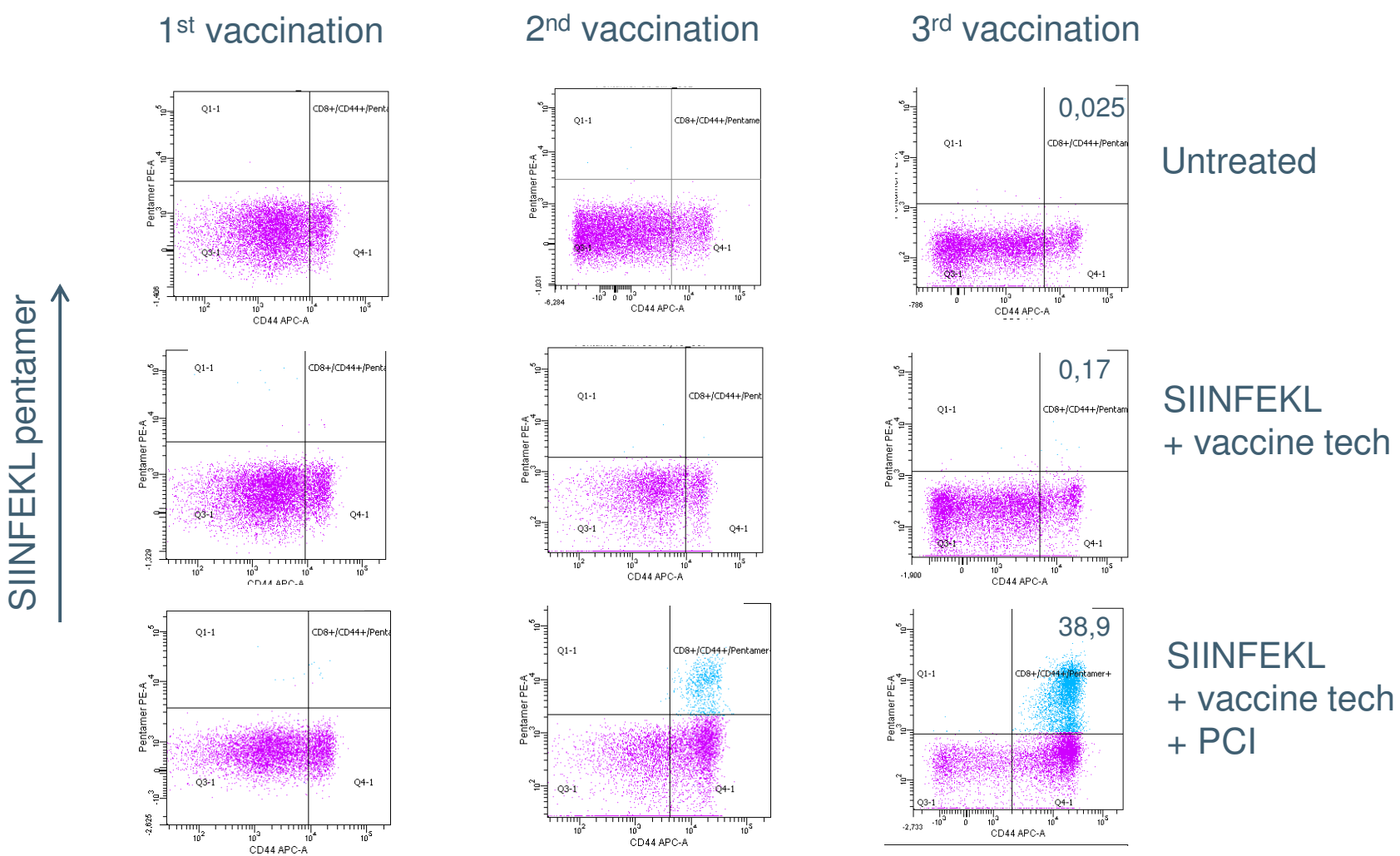


- PCI enhances CD8 response both after 1st immunisation and 2nd immunisation.

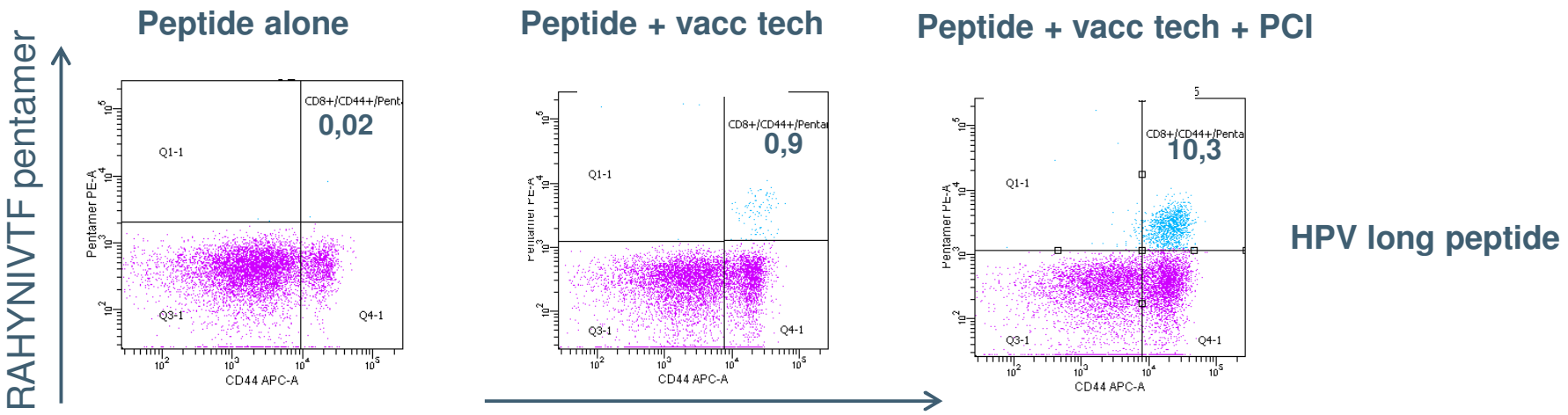


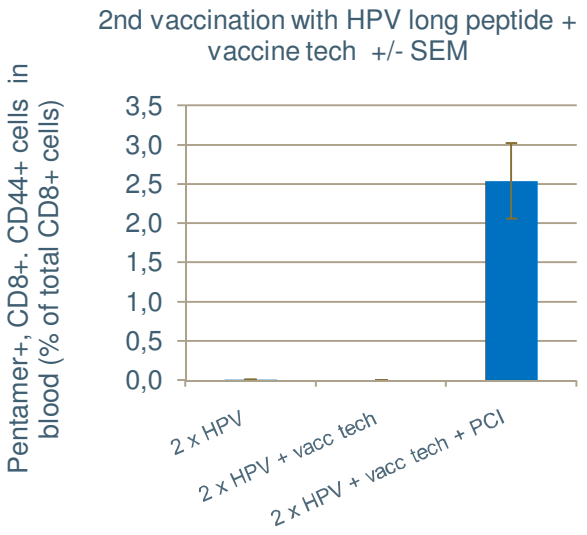
- 100% of PCI-treated animals give a CD8 response to the vaccine (both after 1st and 2nd immunisation), compared to only 20% in the antigen alone group (only after 2nd immunisation).

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



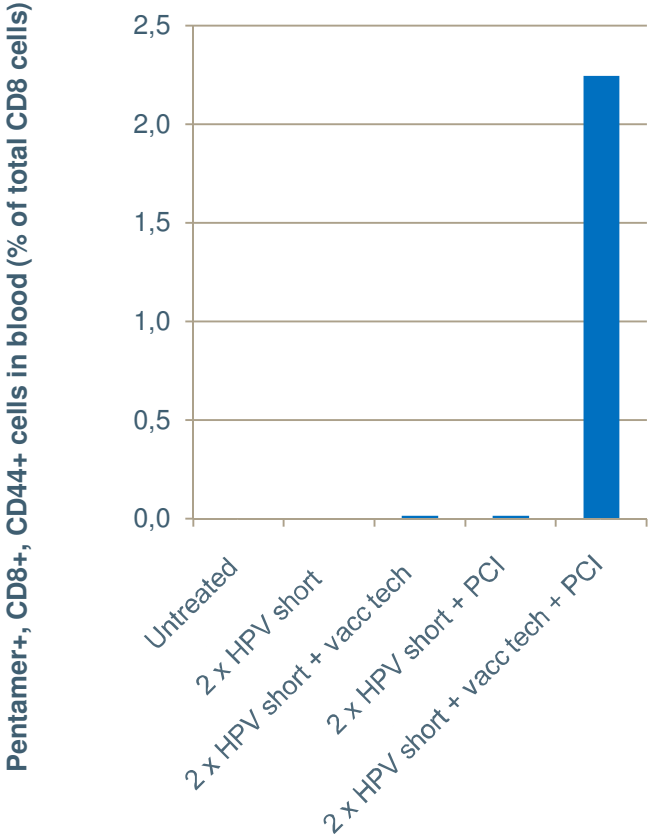
Two PCI vaccinations combined with state-of-the-art vaccine technology significantly enhance HPV long peptide antigen response



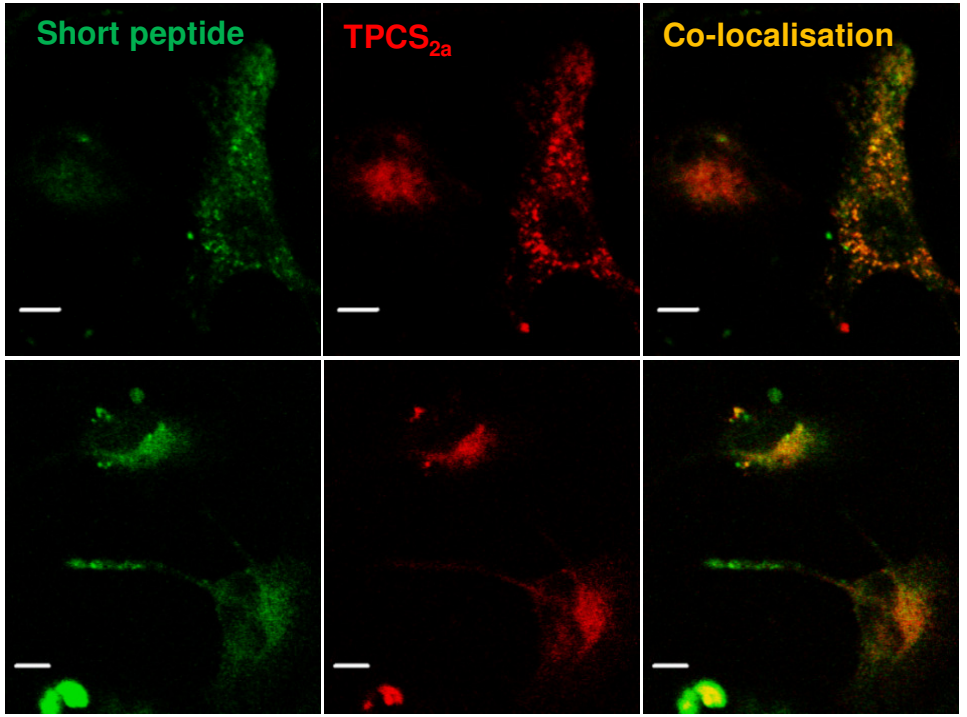


PCI combined with state-of-the-art vaccine technology strongly induces CD8+ response with HPV short peptide antigen

PCI with HPV short peptide, 2nd immunisation



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

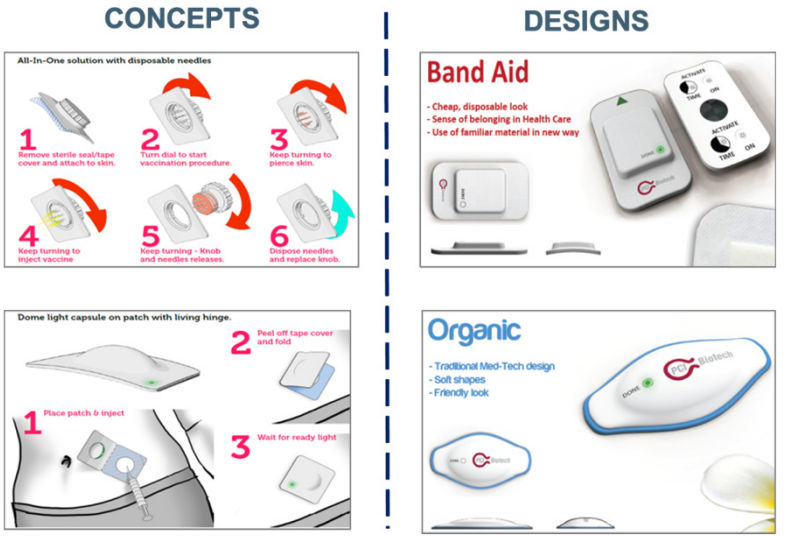


Cancer therapeutic vaccines – Competitive advantages and user-friendly solutions

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

Innovation – Unique mode of action; indication that $TPCS_{2a}$ induces MHC class I antigen presentation in dendritic cells and macrophages

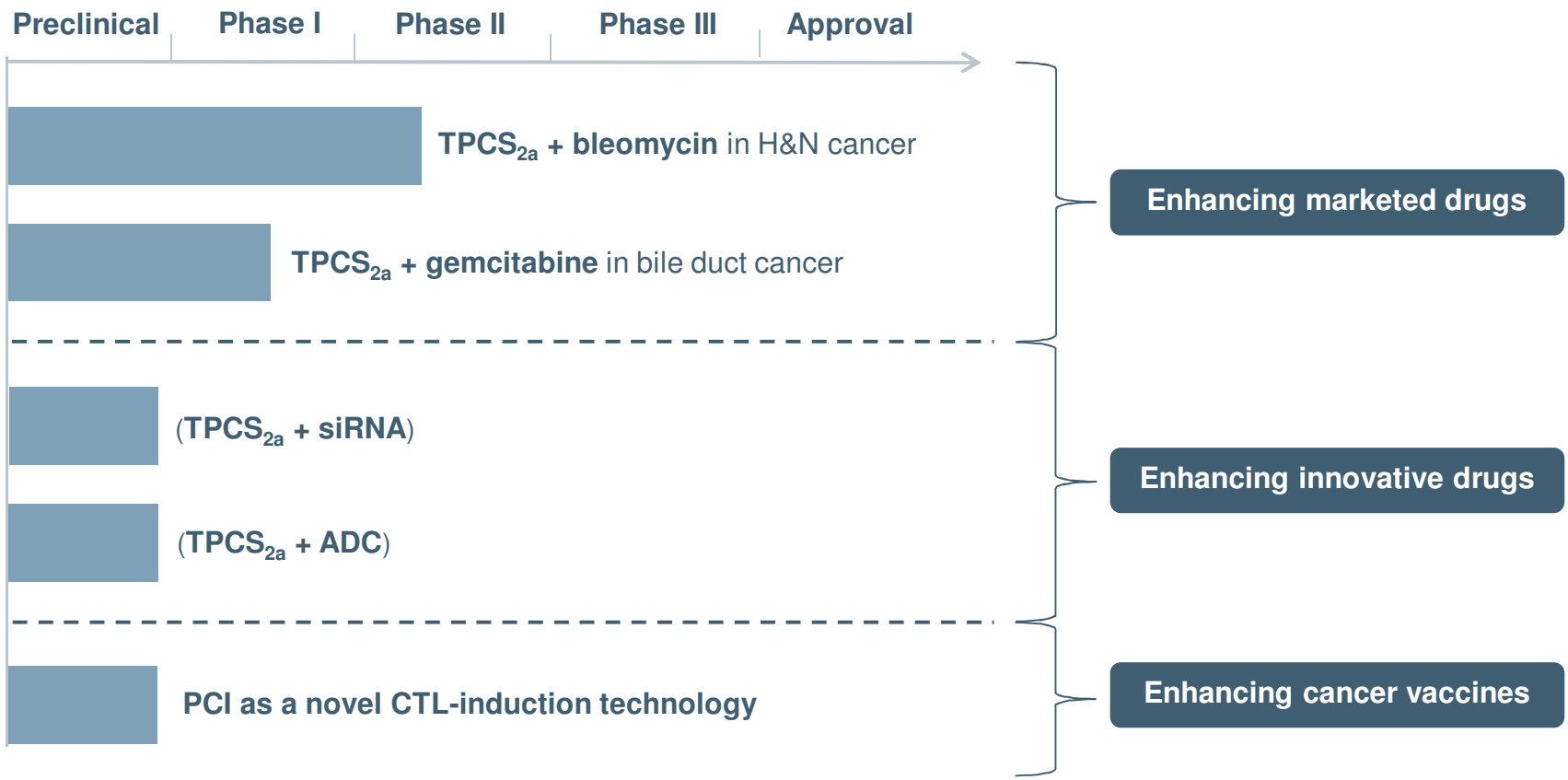


Cost effectiveness – Simple and cost effective synthesis of $TPCS_{2a}$

Broad applicability – Peptide and protein antigens as well as particulate antigen formulations; Prophylactic & therapeutic vaccination, *in vivo* & *ex vivo*

Clinical safety and preclinical efficacy evidence, combined with a comprehensive patent estate on PCI-mediated immunization (products, uses and devices)

PCI Biotech: versatile platform allows for diverse applications in the cancer field



Development and commercial strategy; Execution plan and future milestones

	2015	2016 - 2017
Head and neck cancer	➢ Complete proof of concept for intra-tumour illumination and initiate expansion of the Phase II ENHANCE study ➢ Open IND and initiate US sites	➢ Complete the Phase II ENHANCE study and initiate potential market approval process and/or licensing
Bile duct cancer	➢ Complete clinical Phase I dose-escalation part and initiate Phase II randomised study	➢ Orphan drug designation ➢ Complete bile duct cancer Phase II study and initiate licensing
Vaccines & Macromolecules	➢ Document immune-potentiation in relevant animal models and strengthen products/IP ➢ Position PCI in second generation cancer immunotherapy regimen ➢ Strategic R&D alliances and licensing	➢ Strategic collaboration to facilitate further vaccine product development in pre-clinical testing ➢ Enter clinical Phase I with partner

Focus on research leadership and licensing of the unique proprietary PCI technology

Enquiries

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