



*Unlocking the potential of innovative medicines*

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## ***PCI Biotech***

*PCI – Unlocking the true value of innovative oncology therapies: from therapeutics to vaccines*

*SACHS, Basel, September 2014*

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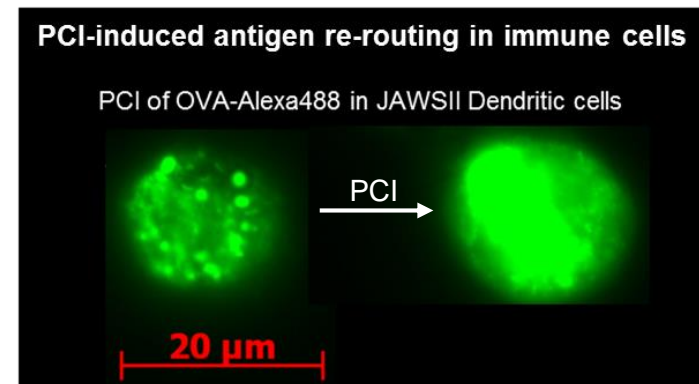
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# PCI Biotech at a glance

- 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<sub>2a</sub>) and light to induce the endosomal escape of active molecules trapped in endosomes

## PCI induces triggered endosomal escape by illumination

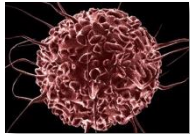


# PCI technology – enable drugs to cover additional areas of unmet medical need

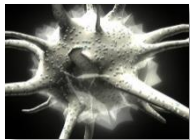


## Existing & innovative treatments

### Cells



Cancerous cell



Dendritic cell

### Active ingredient (trapped in endosome)

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



## PCI enhancement technology

### Photosensitiser (Amphinex)



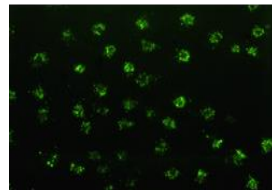
### Light source



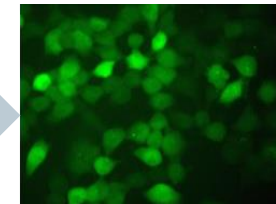
Red light



Blue light



Endosomal escape  
Release of drug in cells



# PCI technology – enabling drugs to reach intracellular therapeutic targets

## STEP 1:

- TPCS<sub>2a</sub> (S) and the active molecule (D) are injected into the body and carried by the blood stream to the cell



## STEP 2:

- TPCS<sub>2a</sub> (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<sub>2a</sub> (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



### The active molecule

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



### The PCI component

- Light sensitive component
- Amphinex - TPCS<sub>2a</sub>



### The target

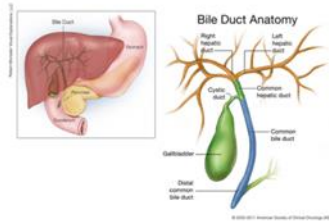
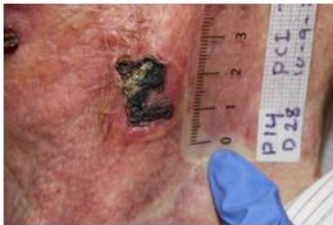
- Target for the active molecule
- E.g. DNA, mRNA, enzyme, microtubuli

*PCI mechanism of action – triggered endosomal escape through illumination*

# PCI Biotech is leveraging PCI (TPCS<sub>2a</sub>) in three distinct areas

## Local cancer treatment

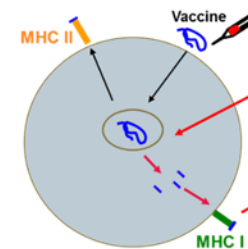
- bleomycin in head and neck cancer
- gemcitabine in bile duct cancer



*Systemic administration*

## PCI vaccination technology

- therapeutic vaccination



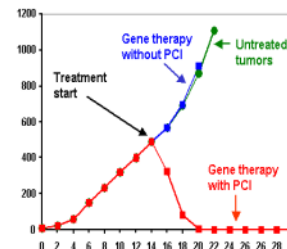
PCI – induce presentation on MHC class I

- 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*

# Clinical Programs

# Amphinex (TPCS<sub>2a</sub>) induced PCI of bleomycin Phase I summary

## Summary of design

- Amphinex dose-escalation study
- Bleomycin and light dose were fixed
- Patients with cutaneous and/or subcutaneous tumours
- 22 patients treated across 5 dose groups
- Majority of patients were squamous cell carcinoma of the head & neck

## Key findings

- Strong tumour response across all doses
- Apparent selectivity for cancer in several patients
- Well tolerated with appropriate analgesia and anesthesia
- Dose limiting toxicity at highest dose due to skin photosensitivity



Complete Response following treatment of skin adnexal tumour

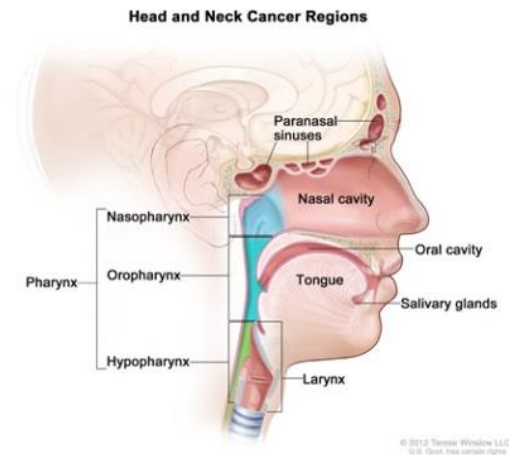


# Amphinex (TPCS<sub>2a</sub>) induced PCI of bleomycin Phase II study in head & neck cancer



## 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

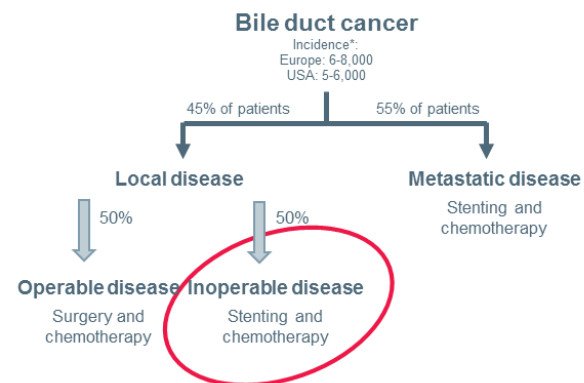
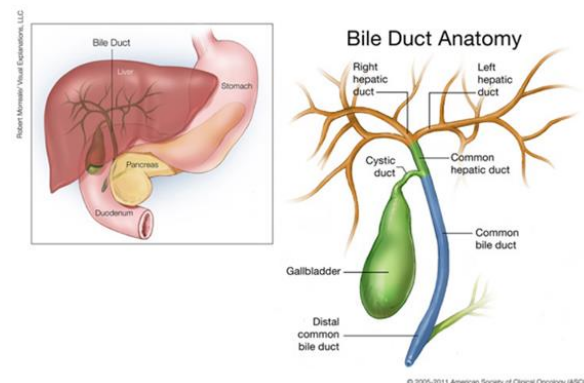


## Preliminary findings

- 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; started in Q3 2013
- Included an interim PoC analysis when 12 patients have been treated with intra-tumour illumination at the selected light dose

# Amphinex (TPCS<sub>2a</sub>) induced PCI of gemcitabine – phase I/II cholangiocarcinoma

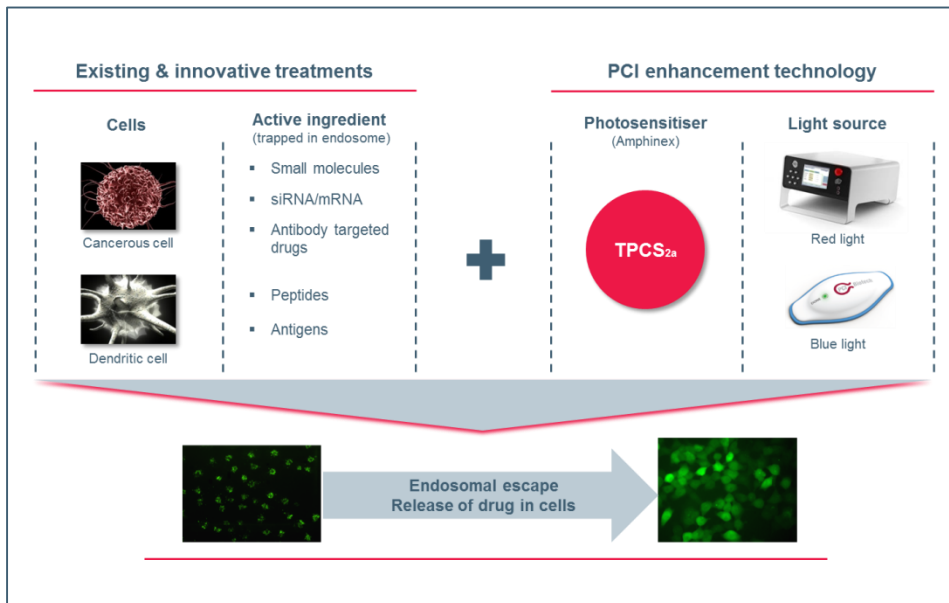
- **Patient population with high medical unmet need**
  - **Patient inclusion:** 2014/15
  - **Target population:** patients with inoperable bile duct cancer
  - **Study design:** open label, multicenter study in up to 45 patients to assess safety and efficacy of a single treatment with Amphinex induced 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 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

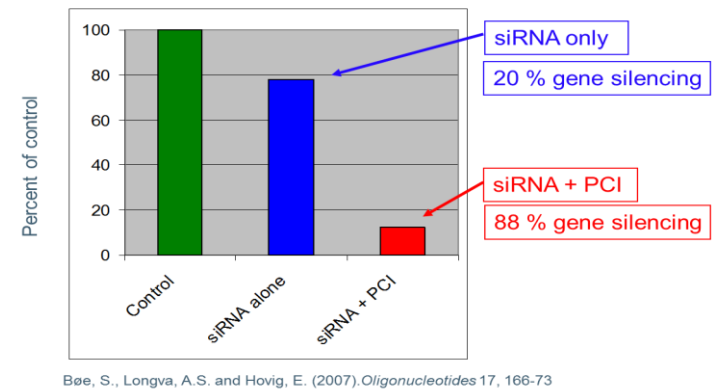
*PCI may realise additional therapeutic potential of innovative medicines and increase their coverage of unmet need in certain disease areas*

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

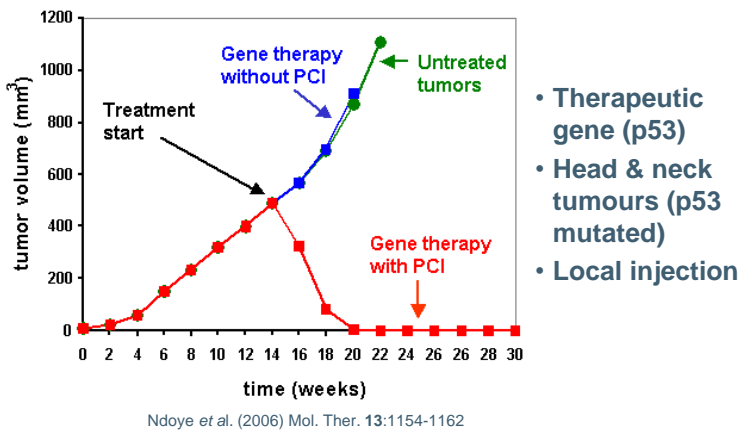
## 1 Intracellular delivery of immunotoxin – *in vivo*



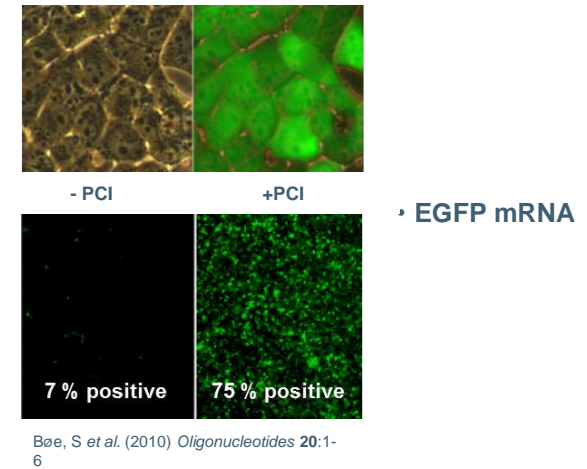
## 2 Intracellular delivery of siRNA



## 3 Intracellular delivery of gene therapy – *in vivo*



## 4 Intracellular delivery of mRNA

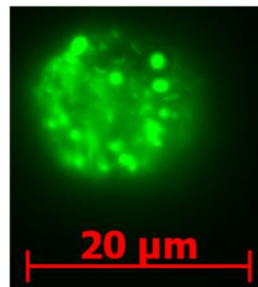


## CTL-inducing technology

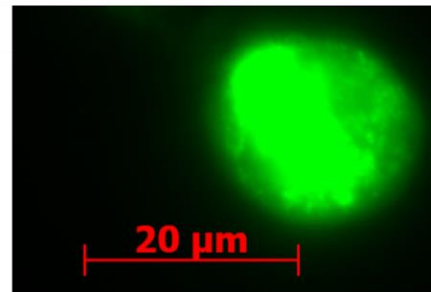
PCI can induce escape of antigens from endocytic vesicles in antigen presenting cells, thereby enhancing MHC class I antigen presentation

PCI of OVA-Alexa488 in JAWSII Dendritic Cells

without PCI



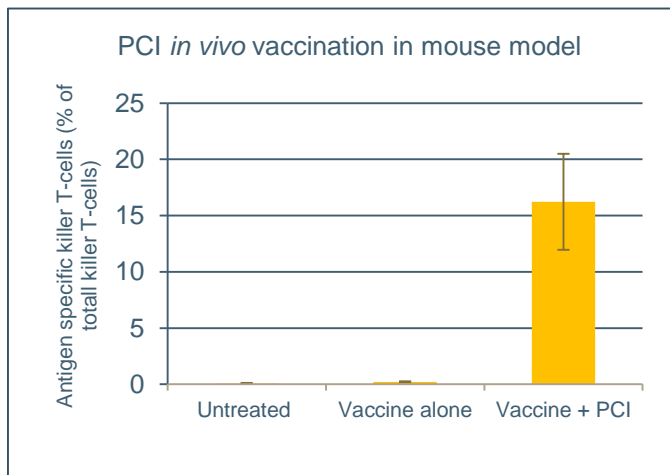
with PCI



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

## In vivo vaccination

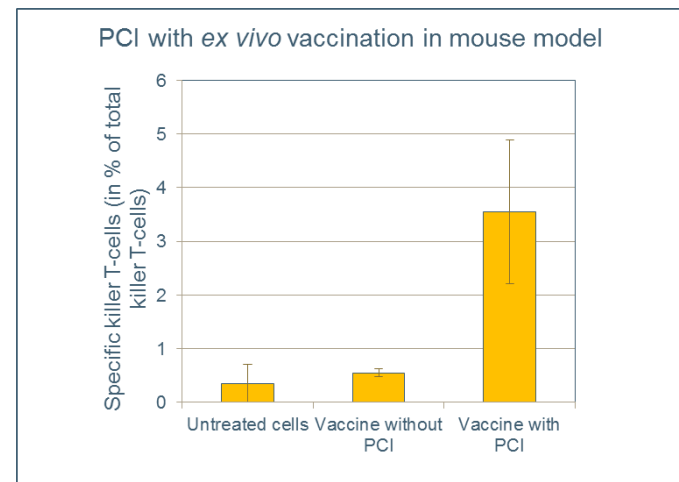
- Inject vaccine (+ adjuvant) into patient, e.g. in or under the skin
- **PCI: add photosensitiser and illuminate**
  - > *PCI induced increase in antigen specific CD8<sup>+</sup> T-cells >50 times has been seen*
  - > *Further optimisation of in vivo PCI vaccination method ongoing*



(collaboration with NTNU & University Hospital Zurich)

## Ex vivo vaccination

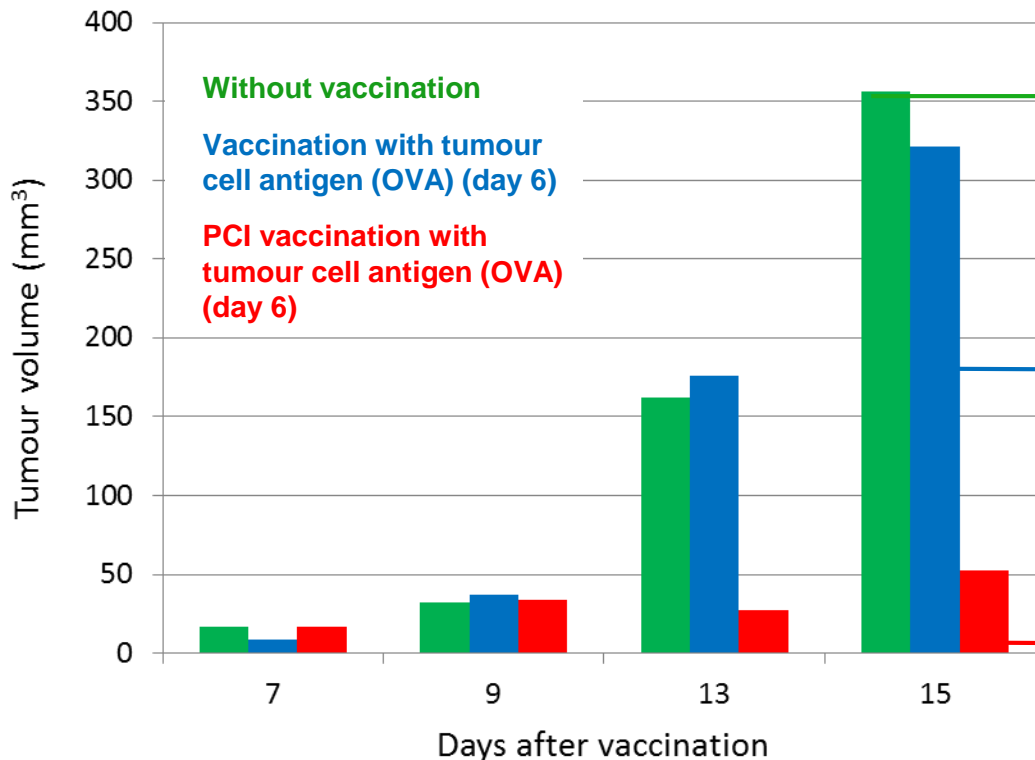
- Remove immune cells from patient
- Give vaccine + adjuvant treatment to the cells in laboratory; **PCI: performed on cells in laboratory**
- Return the treated cells to the patient
  - > *PCI induced increase in antigen specific CD8<sup>+</sup> T-cells up to 16 times has been seen*
  - > *Further optimisation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



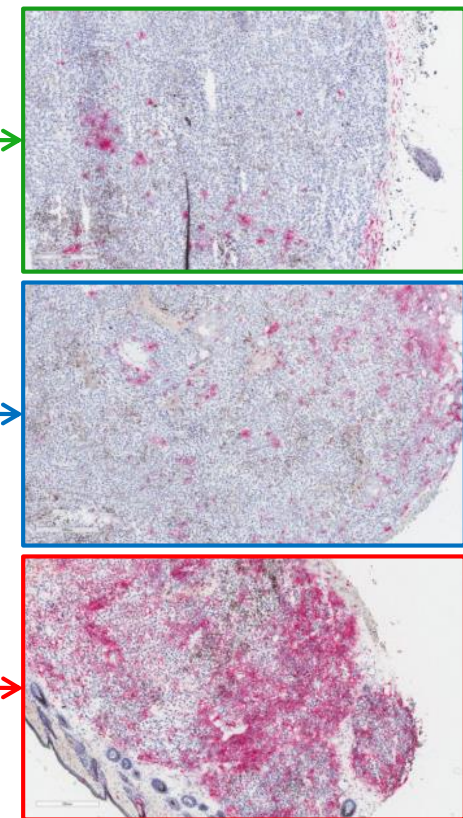
(collaboration with NRH & University Hospital Zurich)

# 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)

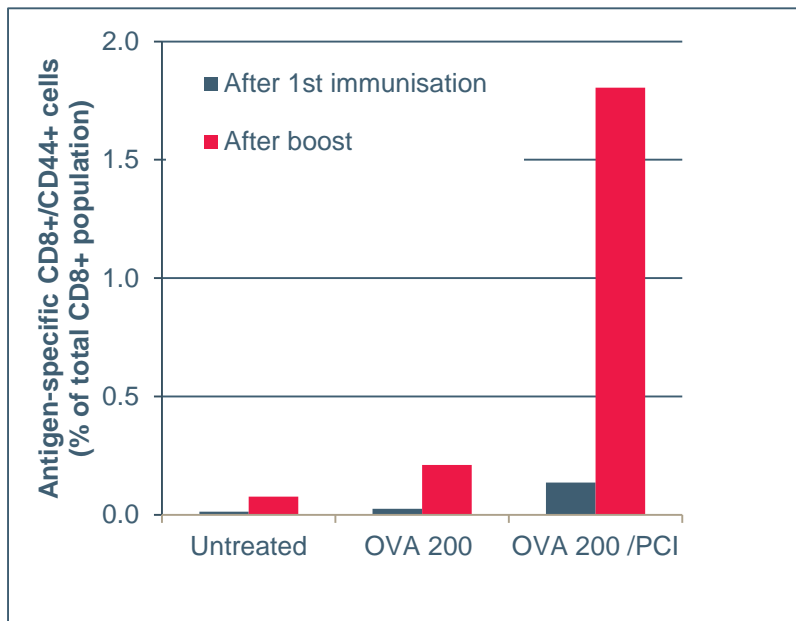


Tumour infiltration of CD8<sup>+</sup> T-cells

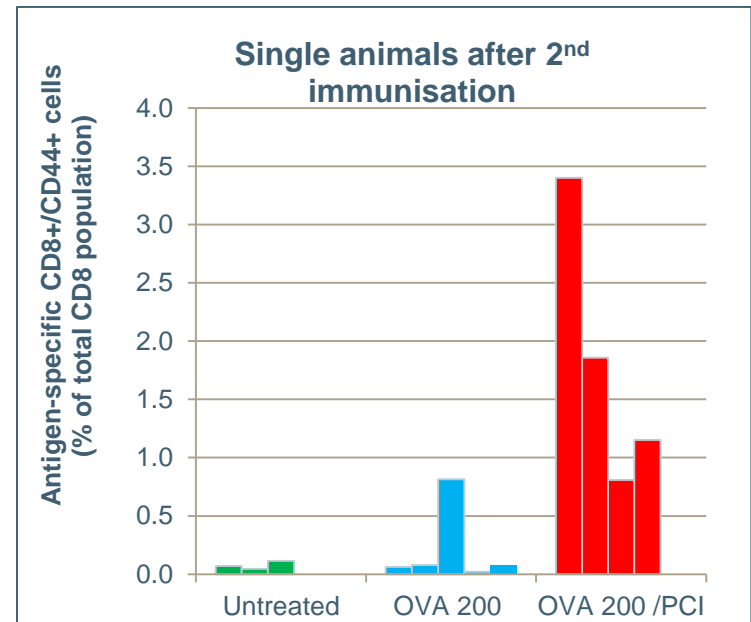


# With OVA antigen PCI induces antigen-specific CD8 cells also from mouse endogenous T-cells

- 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 1<sup>st</sup> immunisation and 2<sup>nd</sup> immunisation.



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



# PCI combined with immune stimulator enhances immune response with SIINFEKL (OVA) peptide antigen > 100 times in normal mice.

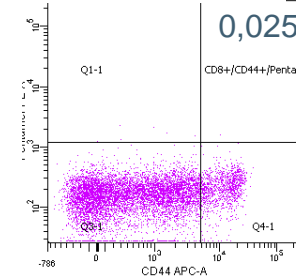
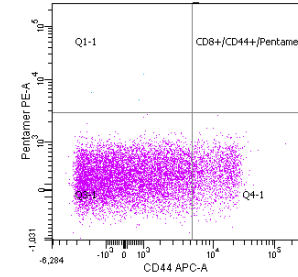
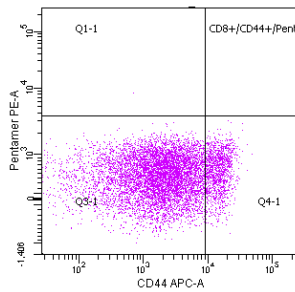


SIINFEKL pentamer

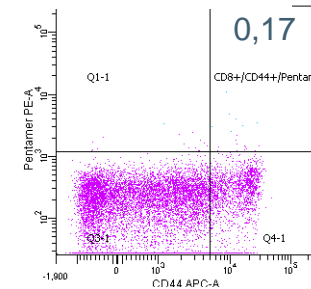
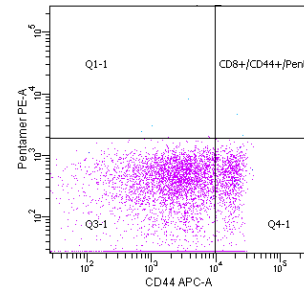
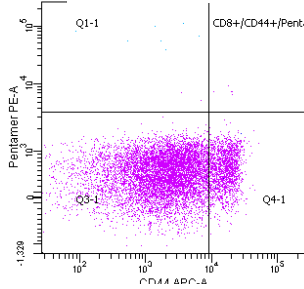
1<sup>st</sup> vaccination

2<sup>nd</sup> vaccination

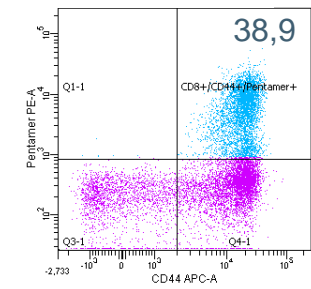
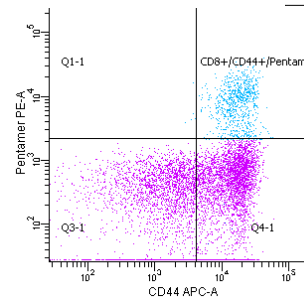
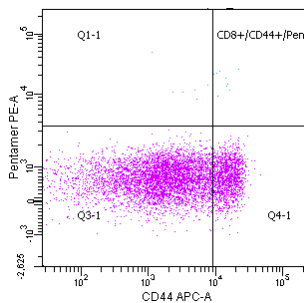
3<sup>rd</sup> vaccination



untreated



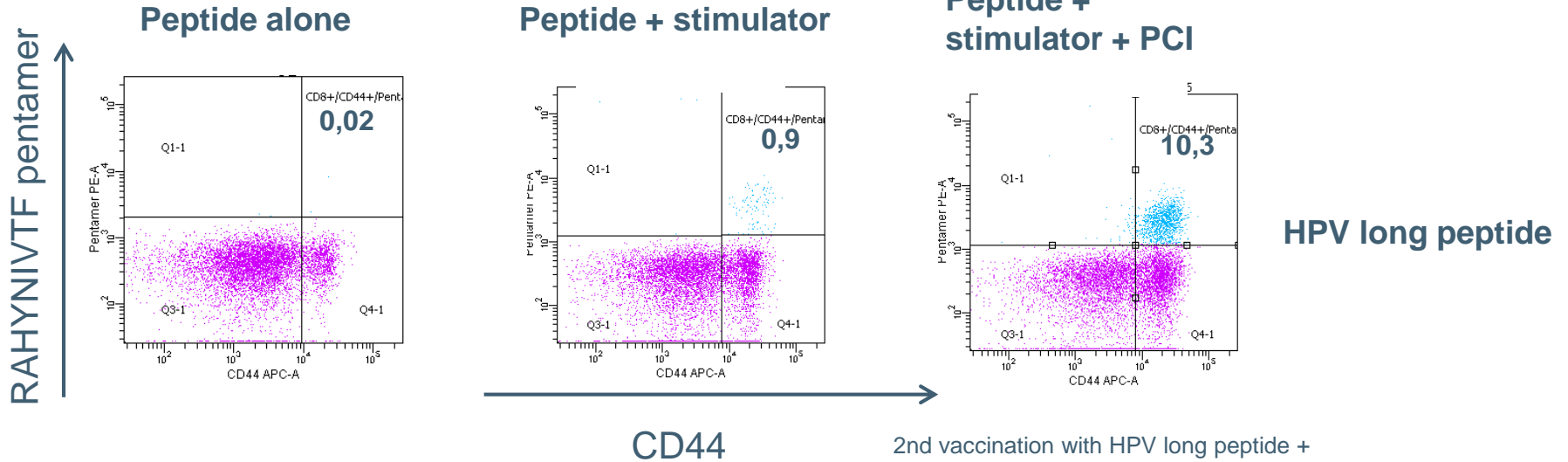
SIINFEKL + stimulator



SIINFEKL + stimulator + PCI

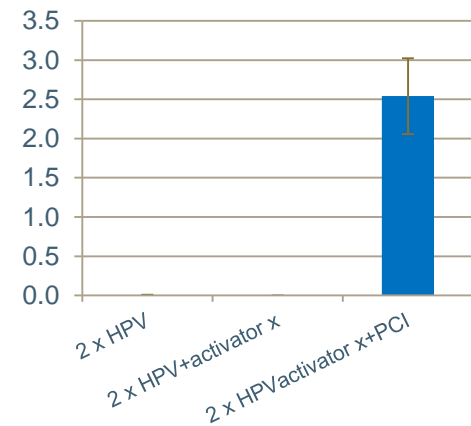


# 2 vaccinations with PCI/stimulator combination significantly enhance effect of a HPV long peptide antigen.



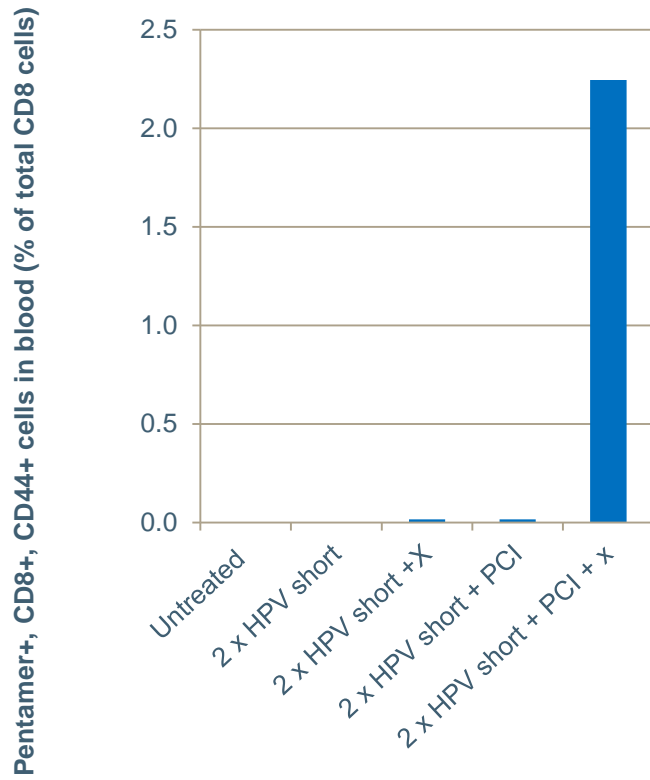
Pentamer+, CD8+. CD44+ cells in blood (% of total CD8+ cells)

2nd vaccination with HPV long peptide + stimulator . +/- SEM

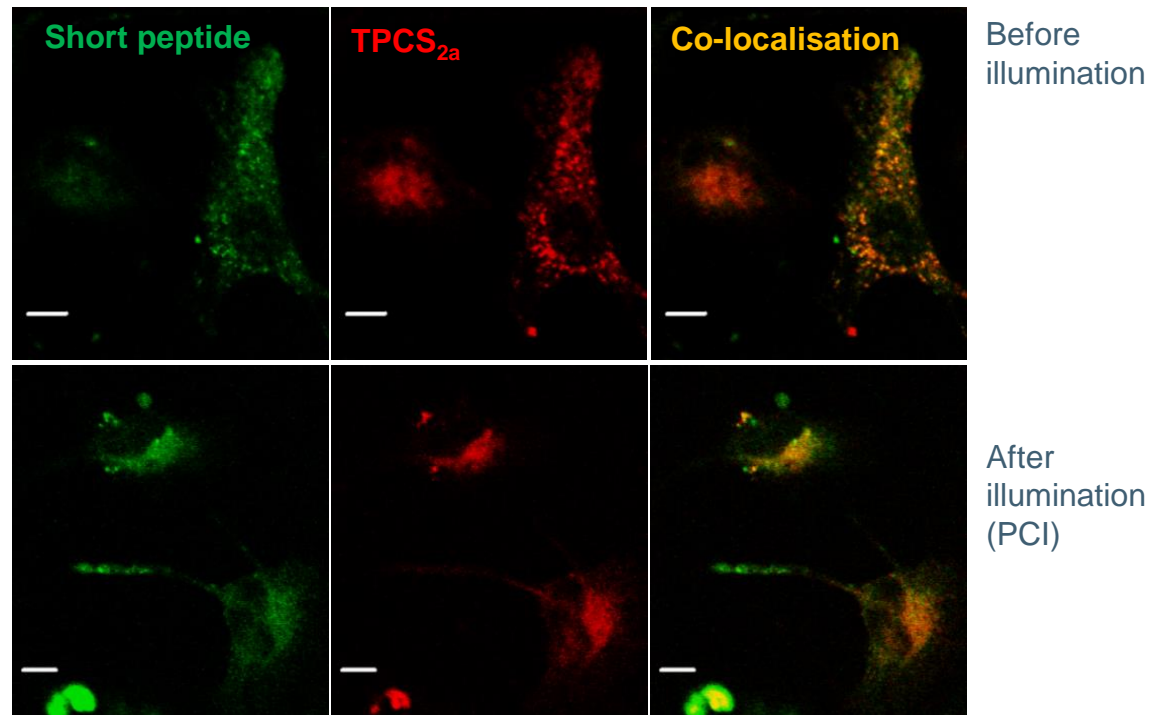


# PCI/X combination strongly induces CD8+ immune response also with HPV short peptide antigen.

PCI with HPV short peptide, 2<sup>nd</sup> immunisation



Also short peptides are taken up by endocytosis and co-localises with TPCS<sub>2a</sub> in endosomes



# Cancer therapeutic vaccines – Competitive advantages and user-friendly solutions



**Safety** – TPCS<sub>2a</sub> tested in Phase I study (i.v. inj.) at much higher doses than what will be used for vaccination

**Stability** – TPCS<sub>2a</sub> can be autoclaved and is stable at room temperature, also in solution

**Innovation** – Unique mode of action; indication that TPCS<sub>2a</sub> induces MHC class I antigen presentation in dendritic cells and macrophages

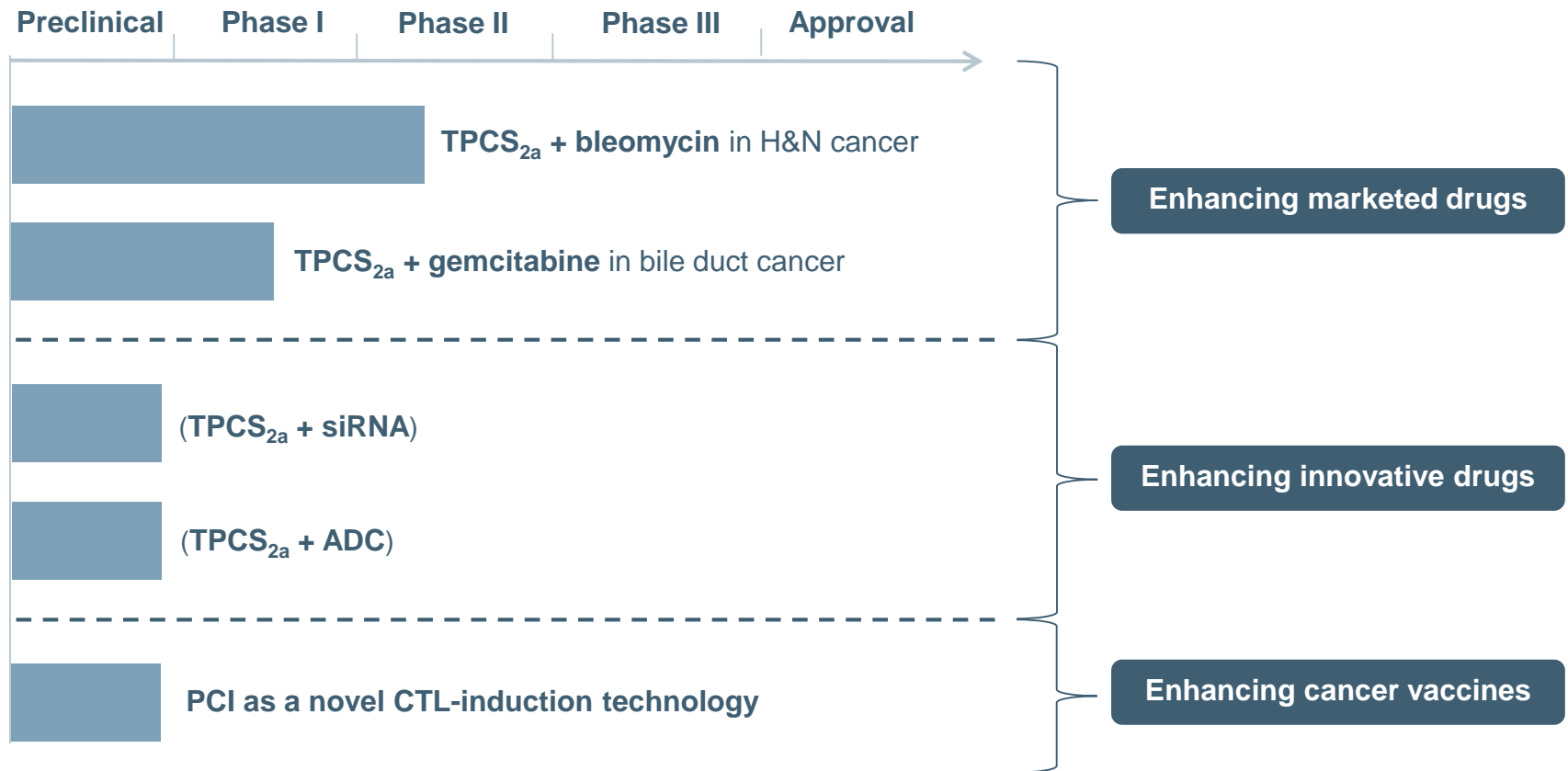
**Cost effectiveness** – Simple and cost effective synthesis of TPCS<sub>2a</sub>

**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



# Enquiries

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