PCI applications

IPA - July 2019

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PCI BIOTECH

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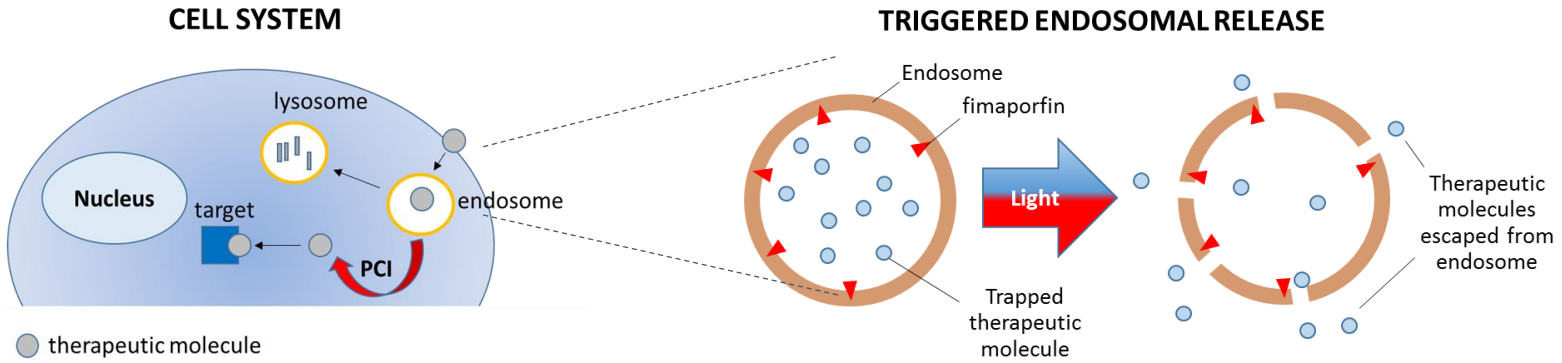
PCI Biotech at a Glance

- Unlocking the potential of innovative medicines

- A listed (PCIB:NO) cancer-focused biotech company
- Photochemical internalisation ("PCI") technology, originating from the Oslo University Hospital
- **Fima**porfin ($TPCS_{2a}$) proprietary photosensitiser

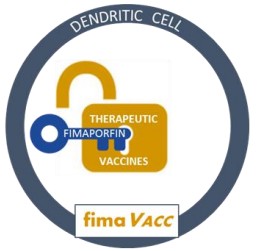
Mode of action



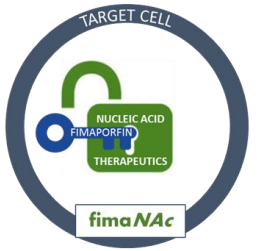
Broad application

PCI – the solution to a key challenge for several modalities

Enabling approved drugs to fulfil unmet local treatment need



Enhancing cellular immune responses important for therapeutic effect



Providing a delivery solution for nucleic acid therapeutics

PCI CAN BE USED FOR KILLING CELLS - BUT ALSO FOR GIVING LIVING CELLS NEW PROPERTIES

- Killing cells (**fima*CHEM***):
  - Photochemical (i.e. PDT) effect
  - Enhancing the effect of cytotoxic drugs

  } Local effect in illuminated area (except immunogenic cell death)

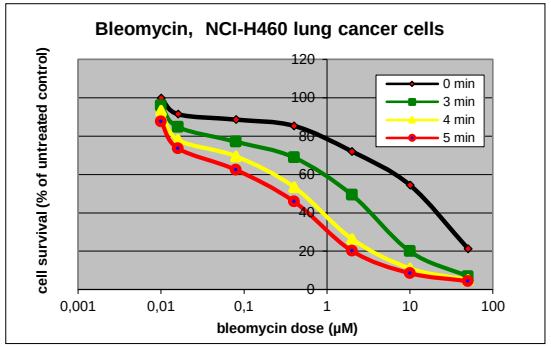
- Inducing new properties in living cells (**fima*NAc*** and **fima *VACC***):
  - Knock-down of gene expression e.g. by various types of oligonucleotides
  - Expression of proteins encoded by nucleic acids delivered by PCI (genes, mRNA)
  - Enhance antigen presentation by delivering protein or peptide antigens
  - Induce gene expression by photochemical effects, e.g. inflammatory cytokines

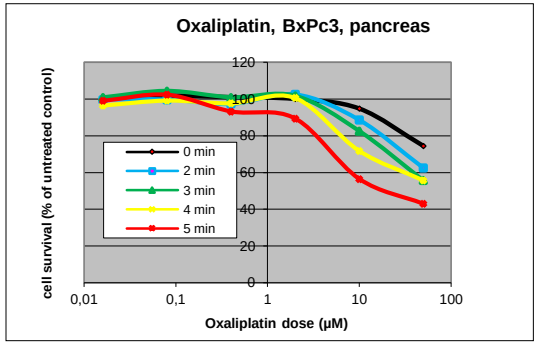
  } Local and/or systemic effect

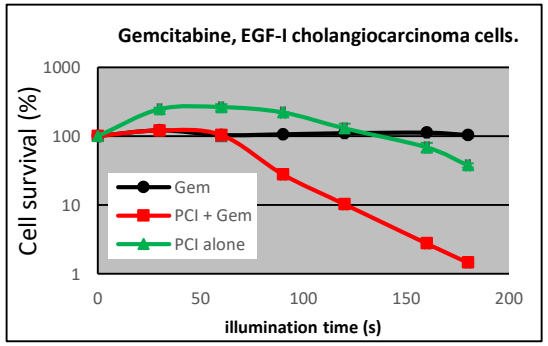
fimaCHEM – PCI WITH CHEMOTHERAPEUTIC DRUGS

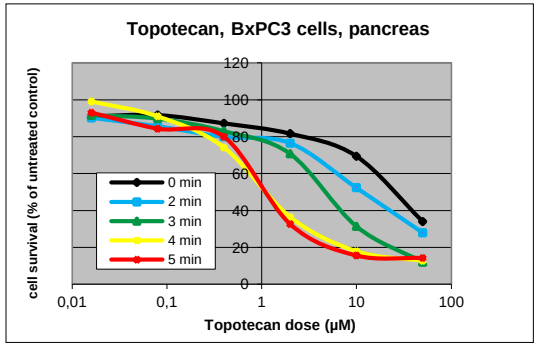
- Enhancing the cell killing effect of small molecule chemotherapeutics

- *In vitro* PCI can enhance the effect of ≈ 20% of the chemotherapeutic drugs tested; in various cancer cell lines
- So far bleomycin and gemcitabine have been employed in clinical studies









- Drugs testing positive *in vitro* / *in vivo*:
  - Bleomycin
  - Gemcitabine
  - Docetaxel
  - Erlotinib
  - Topotecan
  - Oxaliplatin
  - Vincristin
  - Doxorubicn
  - Imatinib
  - Nilotinib

fimaCHEM – PCI WITH CHEMOTHERAPEUTIC DRUGS

- PCI for enhancing the effect of small molecule chemotherapeutics

- First clinical study with bleomycin in cutaneous and sub-cutaneous tumours (mainly head and neck) (Sultan *et al*. Lancet Oncol. 2016;17(9):1217-29) – Colin Hopper, later talk
- Phase I study with gemcitabine in cholangiocarcinoma finished - Hans Olivecrona, later talk
- Pivotal study with gemcitabine in cholangiocarcinoma just started

- fimaCHEM very well suited also for other cancer indications where a better local treatment is needed
- Increase the effect of the drug at the site of disease, without increasing systemic side effects
- Large repertoire of chemotherapeutic drugs that can be used
- Many tumour types can be illuminated on the outside of the body or inside the body with optical fibres
- Animal studies indicate that PCI can induce abscopal effects, leading to anti-tumour effects also on non-illuminated tumours

PCI FOR NUCLEIC ACID THERAPIES - fimaNAc

- Delivery is a main hurdle for all nucleic acid therapies

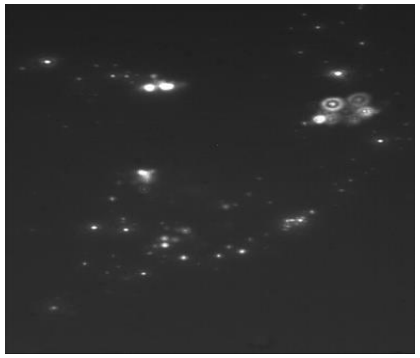
- Nucleic acid therapies (genes, mRNA, oligonucleotides, microRNAs) have a very large potential for the treatment of a variety of diseases
  - As yet only a few drugs on the market
- Nucleic acids are large and charged molecules – endocytosis only possible uptake mechanism
- Delivery vehicles (polymers/liposomes/viruses etc.) commonly used, but also these are generally taken up into endosomes

Endosomal release a main delivery barrier for nucleic acid delivery

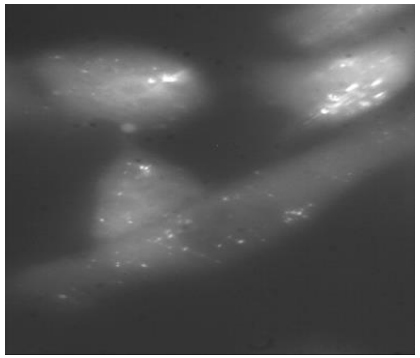
This barrier could be overcome by PCI

fimaNAc RELEASES OLIGONUCLEOTIDES FROM ENDOSOMES

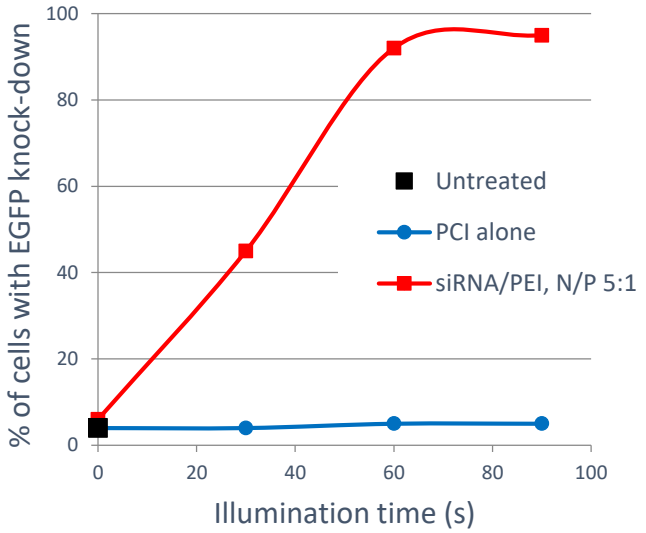
- Effect with many types of oligonucleotides



PCI



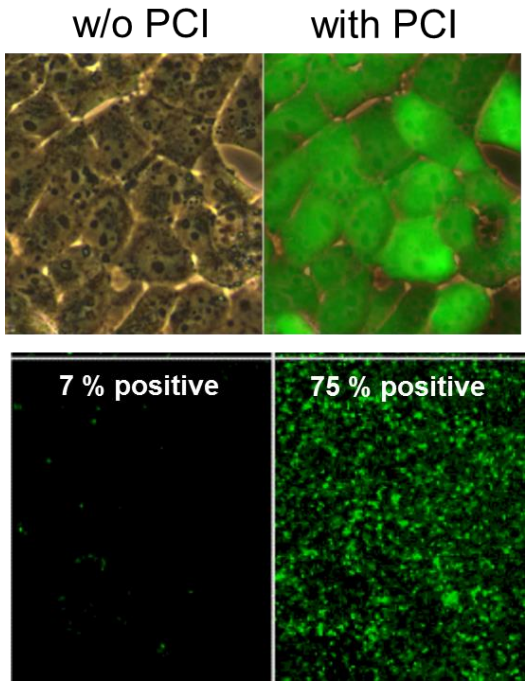
PCI with siRNA induces knock-down of target gene in ≈ 100 % of the treated cells



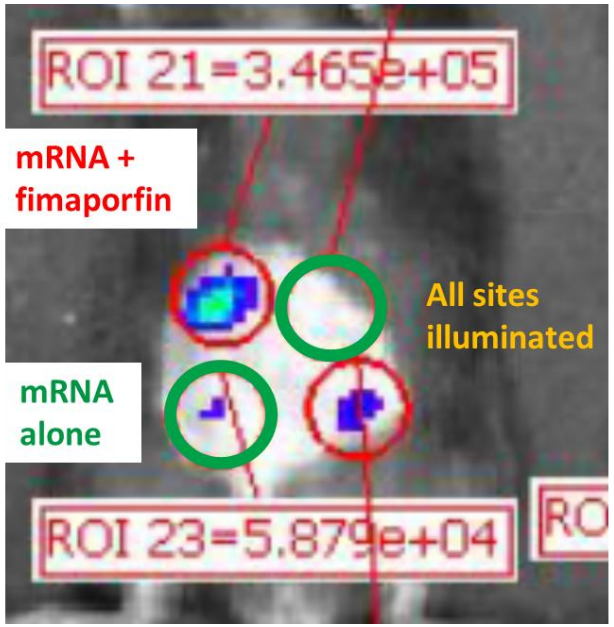
- Effect with all types of oligonucleotides tested (siRNA, DNA oligos, PNA)
- Works well both with naked oligoes and with oligos bound to delivery vehicles
- Works well also *in vivo*

fimaNAc STRONGLY ENHANCES DELIVERY OF mRNA *IN VITRO* AND *IN VIVO*

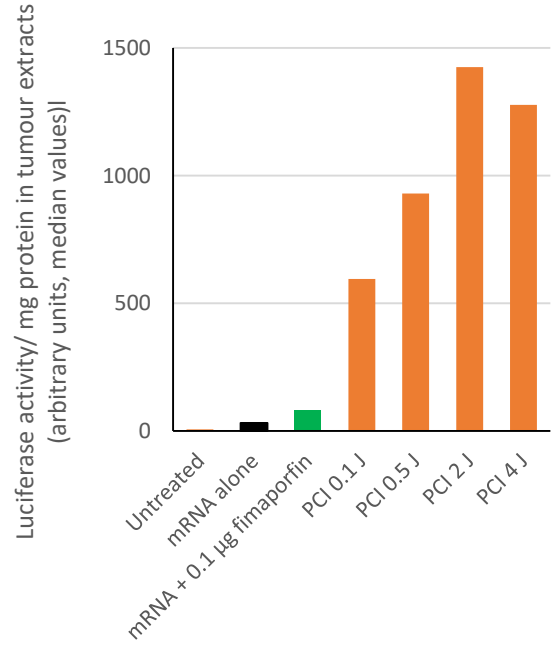
GFP mRNA – *in vitro*



Luciferase mRNA *in vivo* – intradermal administration



Luciferase mRNA *in vivo* – intratumoural administration

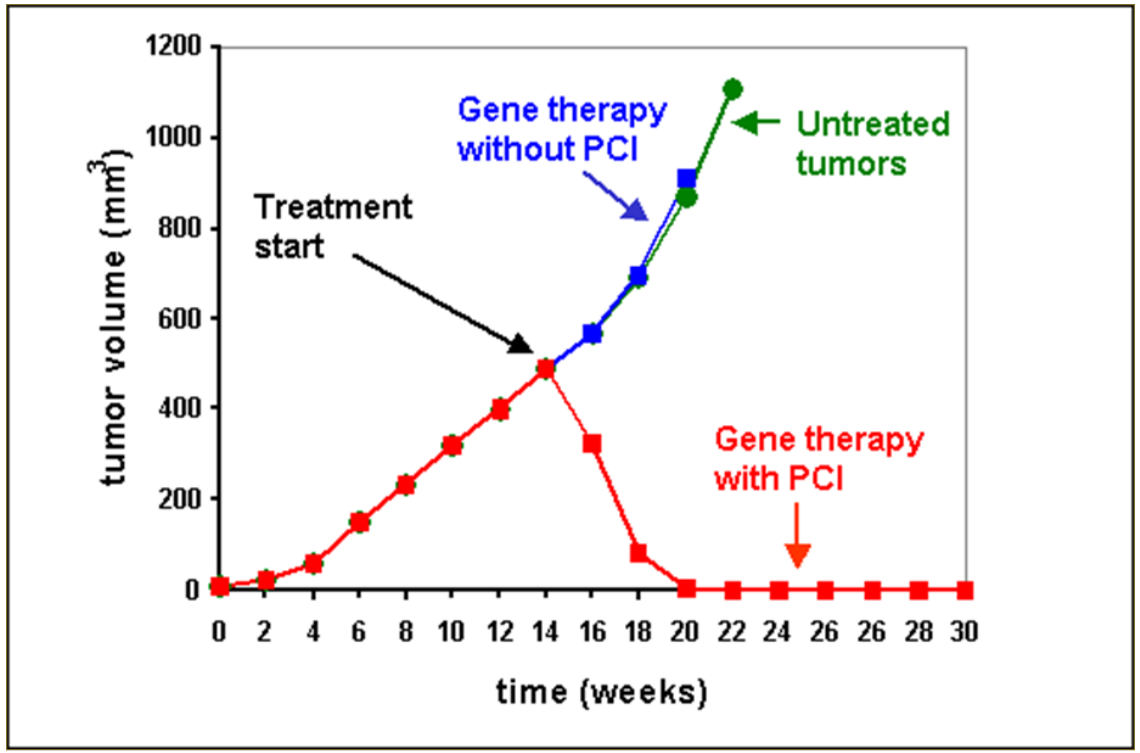


► At best light dose (2 J/cm^2) nearly 50 x enhancement as compared to naked mRNA alone

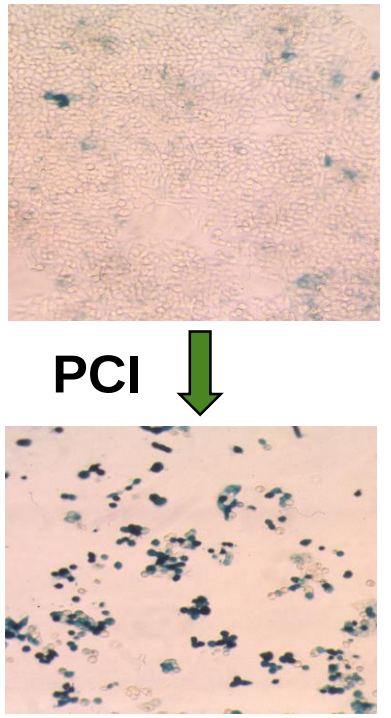
GENE THERAPY WITH fimaNAc

- Eradicates human head and neck tumours in mice

- Intratumoural delivery of plasmid with therapeutic gene (p53)
- 80 % of animals tumour free after PCI treatment



PCI enhances adenovirus gene transduction



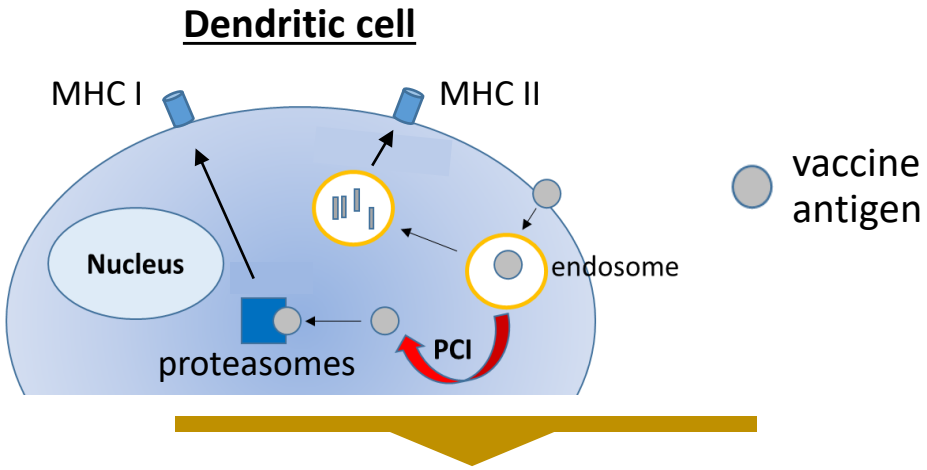
(Ndoye *et al.* 2006. *Mol. Ther.* 13, 1154-1162)

fimaNAc - POSSIBLE APPLICATIONS

- Oligonucleotides
  - Local gene expression knock-down
  - Skin conditions, scars, eye diseases, down-regulation of immunosuppresive mechanisms in tumours etc.
- mRNA
  - Vaccination (intradermal, intratumoral)
  - Modification of tumour microenvironment (combat immune suppression etc.) – e.g. mRNA encoding cytokines
  - Reprogramming of stem/progenitor cells (e.g. in the heart to help recovery from ischemia)
  - Production of therapeutic proteins (e.g. in inherited diseases). Local production, but may have systemic effect
- Plasmids
  - As for mRNA
  - DNA vaccination
  - Gene therapy
- Virus
  - As for mRNA
  - Gene therapy
  - Immunotherapy and vaccination

fima VACC - PCI FOR VACCINATION

- Enhancement of cytotoxic T-cell responses



Vaccine

fima VACC

MHC Class I

Generate more disease specific cytotoxic T-cells

Attack cancer and virus infected cells more efficiently

MHC Class II

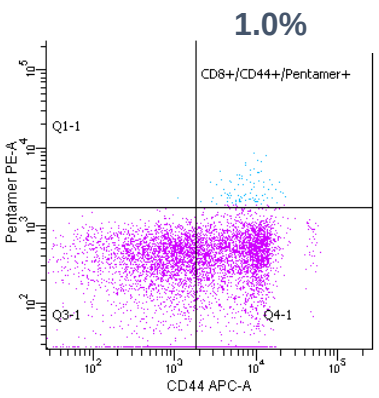
Antibodies and helper T-cells

fima VACC STRONGLY ENHANCES CYTOTOXIC T-CELL RESPONSE

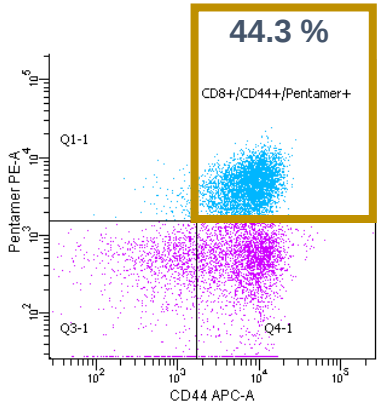
- Impressive effects with clinically relevant HPV therapeutic vaccine in mice

Amount of activated antigen-specific CD8 T-cells in blood

Vaccination without fima VACC



Vaccination with fima VACC

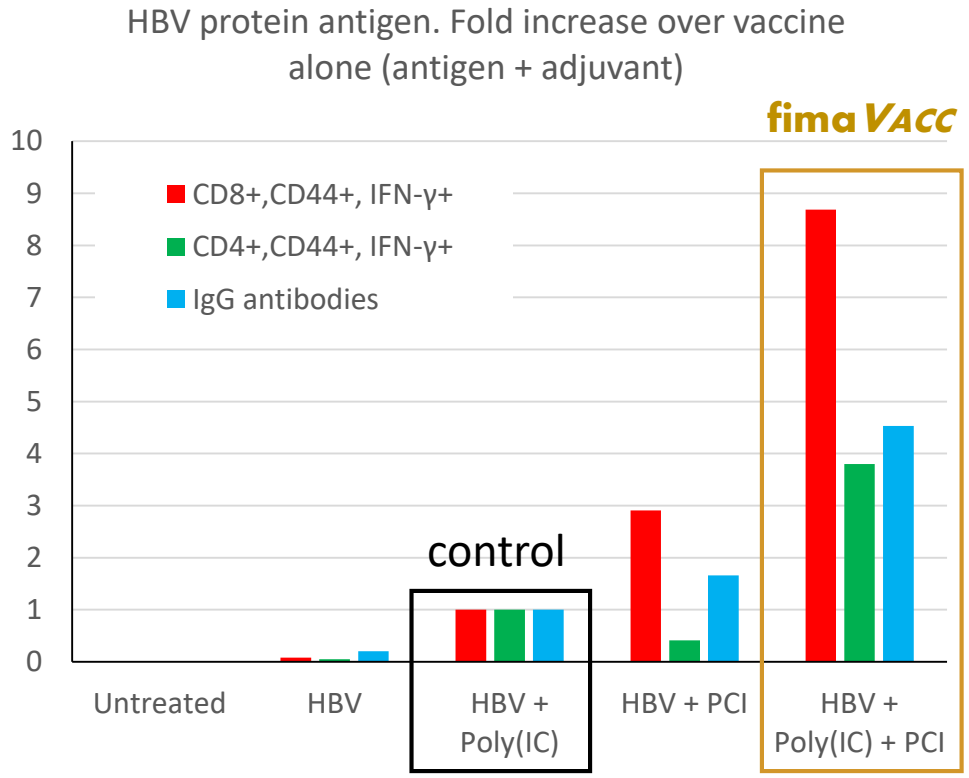


Cytotoxic (CD8) T-cells

- Most important immune cells to fight tumours
- Difficult to induce with vaccination
- fima VACC strongly enhances the ability of vaccines to induce CD8 T-cells:
  - >20 and >40 times enhancement seen in spleen and blood cells, respectively
  - Generation of immunological memory

fima VACC ENHANCES BOTH CD8 AND CD4 T-CELL; AND ANTIBODY RESPONSES TO AN INFECTION ANTIGEN

- HBV SURFACE ANTIGEN



- fima VACC enhances all branches of the immune response to a protein infection antigen
- Indicates that fima VACC has a large potential also in therapeutic and prophylactic vaccination against infectious diseases.

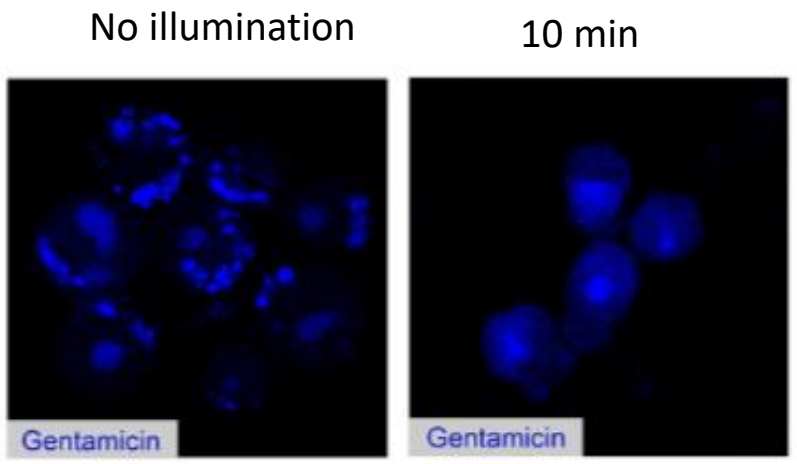
fima VACC - POSSIBLE APPLICATIONS

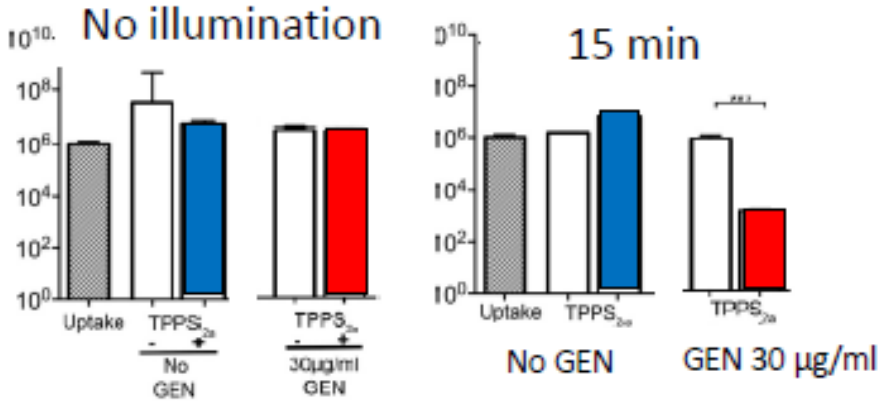
- Therapeutic and prophylactic vaccination where a better cytotoxic T-cell response is desired:
  - Peptide- and protein based therapeutic cancer vaccines
    - Intradermal vaccination
    - Intratumoural vaccination
  - Therapeutic vaccines against chronic viral infections (HBV, HCV etc.)
  - Prophylactic vaccines
    - Virus (influenza, hepatitis etc.)
    - Intracellular bacteria (e.g. tuberculosis)
    - Parasites (e.g. malaria)
- Phase I clinical study I heathy volunteers finalized - will be presented in more detail in later talk (session 16, 5:50 pm today)

OTHER POTENTIAL USES OF PCI

- PCI with antibody- or ligand-targeted drugs – up to 1000x enhancement seen in cell studies
  - Not yet tested in clinical studies, but has the potential to specifically kill tumour cells in a diseased area of the body without harming normal cells in the same area
    - Increase <u>efficacy</u> of treatment because of more efficient uptake of drug
    - Increase <u>specificity</u> by combining specificity of illumination with specificity of drug uptake into tumour cells
    - Eliminate infiltrating tumour cells in the tumour bed after surgery
    - Treatment of tumours in sensitive areas where extensive surgery is not possible or desired

- PCI for enhancing effect of antibiotics – treatment of intracellular bacterial infections





PCI induces gentamicin-mediated killing of *S. epidermidis* in infected macrophages

Zhang et al. J. Control. Release 2018; 283:214-222

PCI BIOTECH – DEVELOPMENT PIPELINE

- Unlocking the potential of innovative medicines

Programme	Indications / Therapeutics	Preclinical	Phase I	Phase II	Pivotal	Status
fimaCHEM	*Bile duct cancer / gemcitabine*					- Encouraging early clinical results - Orphan designation in Europe and USA - Pivotal registration study initiated
fimaVACC	*Therapeutic cancer vaccines*					- Phase I in healthy volunteers completed - Proof of concept in man achieved - Highly sought after vaccination features
fimaNAC	*Nucleic acid therapeutics*					- Six research collaborations

An oncology focused company with three well differentiated assets

Thank you