Unlocking the potential of innovative medicines

Photochemical internalisation (PCI) – light-induced endosomal escape for enhancing nucleic acid delivery in vitro and in vivo.

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OTS Meeting
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PCI – Light induced endosomal release -enabling drugs to reach intracellular targets

STEP 1:

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

STEP 2:

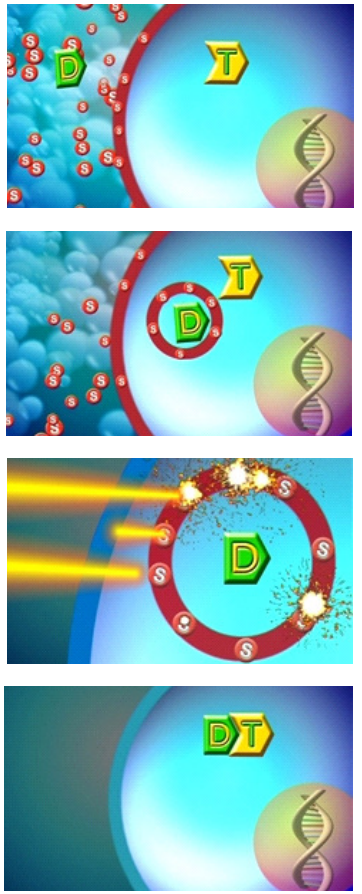
- $TPCS_{2a}$ (S) and the active molecule (D) are taken up by the cell, but D is unable to reach the target (T), as it is encapsulated in an endosome
- S is washed away from the cell membrane, but trapped in endosomes

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

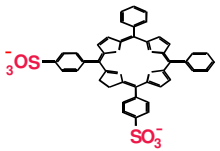


D

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

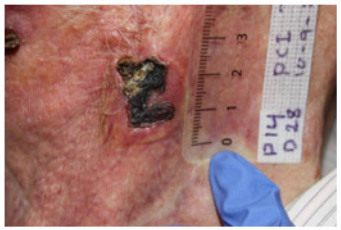
The target
- Target for the active molecule
- E.g. DNA, mRNA, enzyme, microtubuli

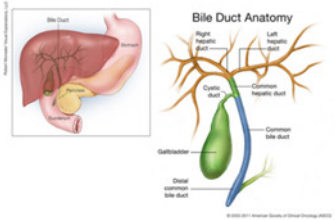
PCI mechanism of action – triggered endosomal escape through illumination

PCI Biotech AS - three focus areas

Local cancer treatment

- gemcitabine in bile duct cancer

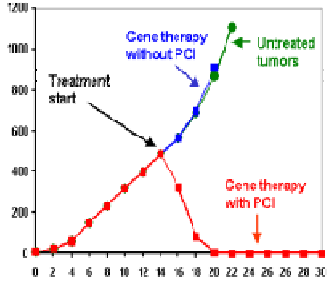




Systemic administration

PCI macromolecule delivery

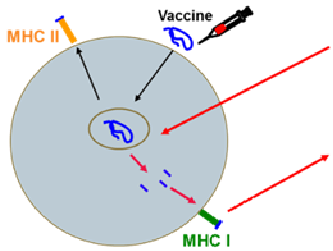
- immunotoxins
- siRNA & other oligo
- gene therapy



Local or systemic administration

PCI vaccination technology

- therapeutic vaccination

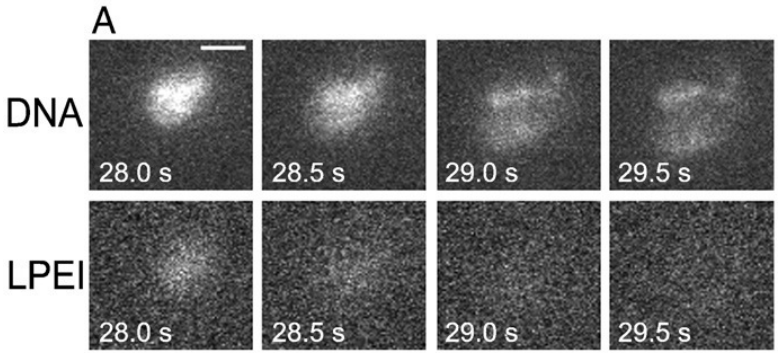


PCI – induce presentation on MHC class I

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

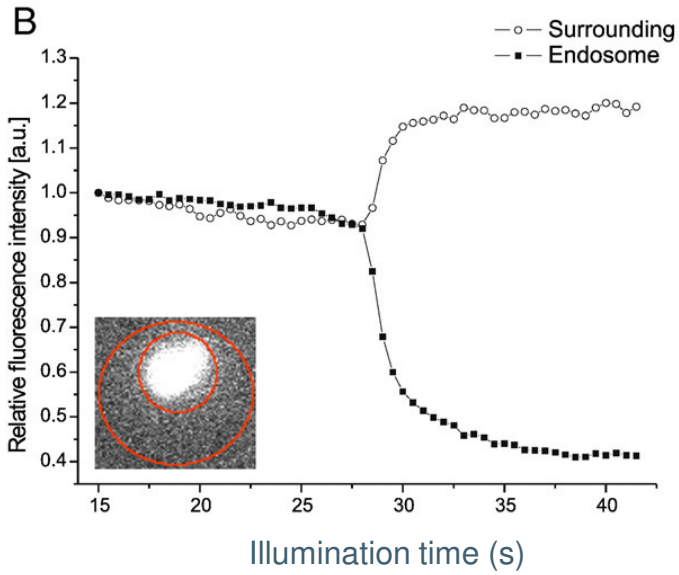
Local administration

PCI induces endosomal release of DNA (in PEI complex)



DNA – Cy5 labelled

LPEI – A488 labelled



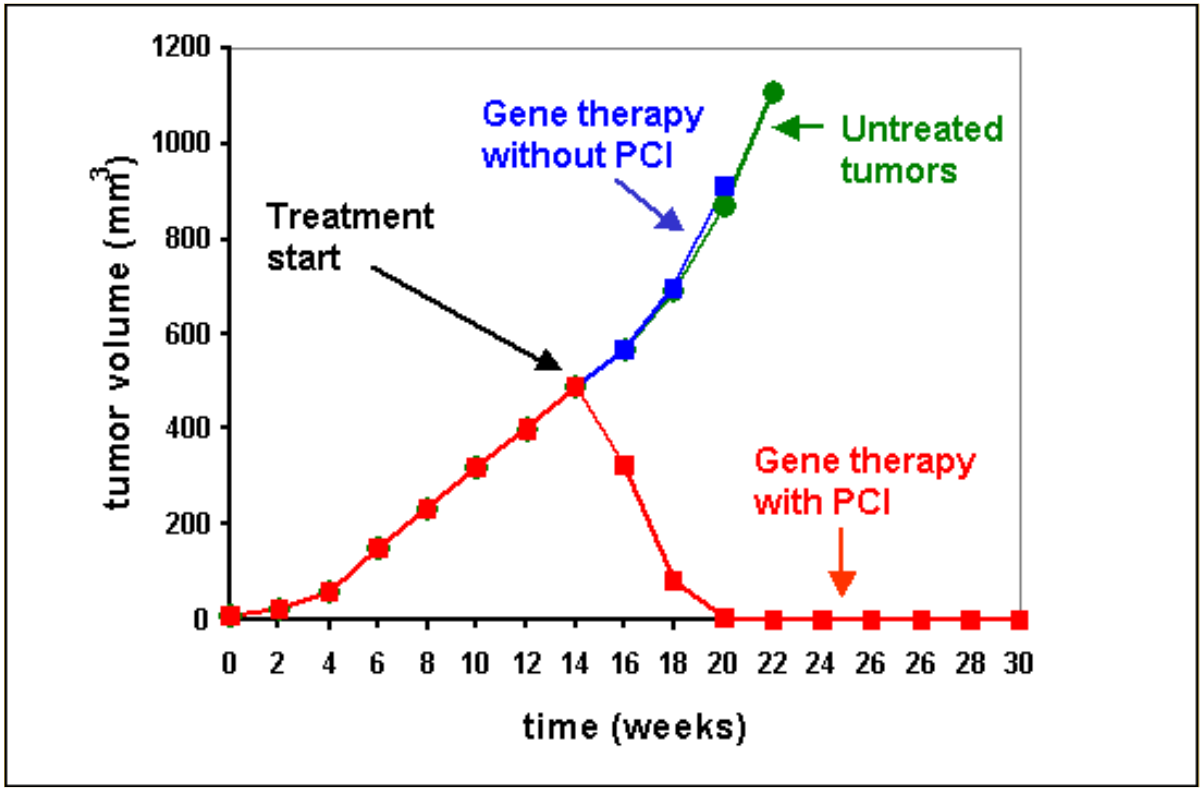
DNA outside endosome

DNA in endosome

de Bruin et al. J. Control. Rel. 130 (2008) 175

PCI-enhanced gene therapy can eradicate human head and neck tumours in mice.

- Therapeutic gene (p53) delivered by polymer (PEI-based) vector
- Head and neck tumours (p53 mutated), subcutaneous in mice

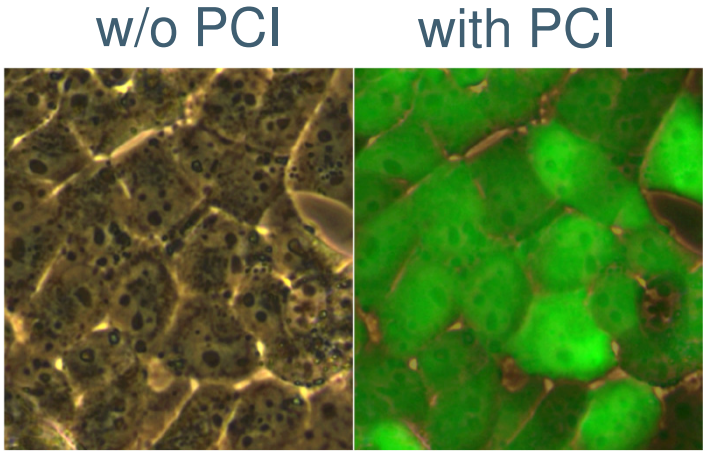


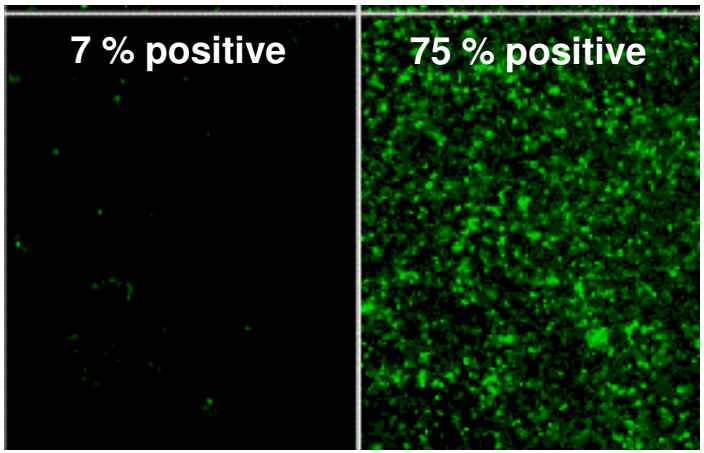
- Local injection of gene and photosensitiser
- Weekly injection for 7 weeks
- Induction of apoptosis in tumour cells

>80 % tumour free

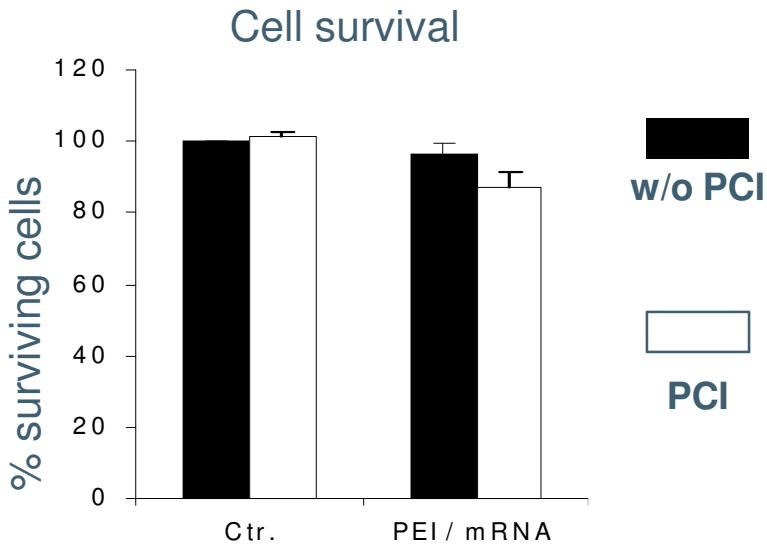
(Ndoye *et al.* 2006. *Mol. Ther.* 13, 1154-1162

PCI strongly improves mRNA delivery by a PEI vehicle

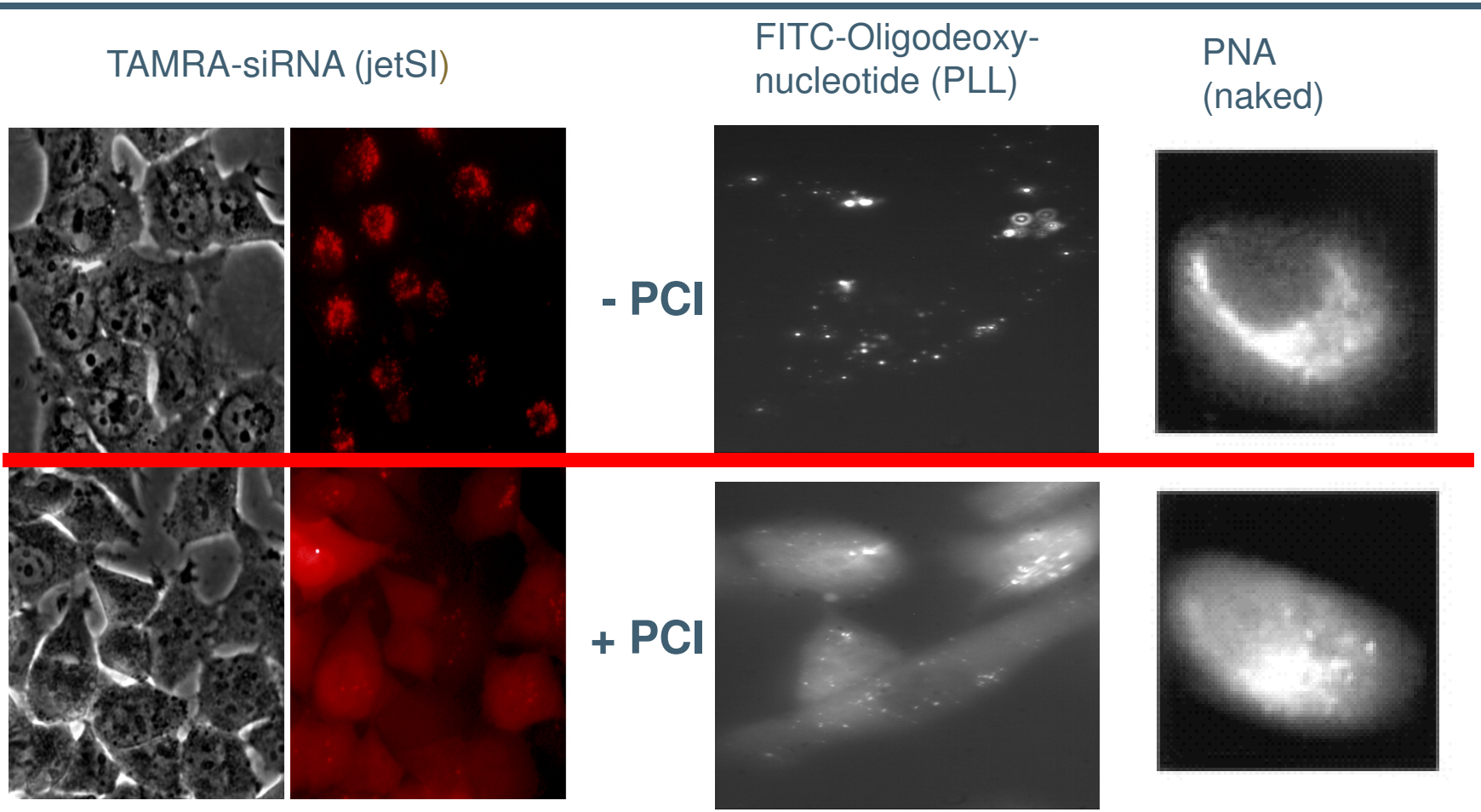




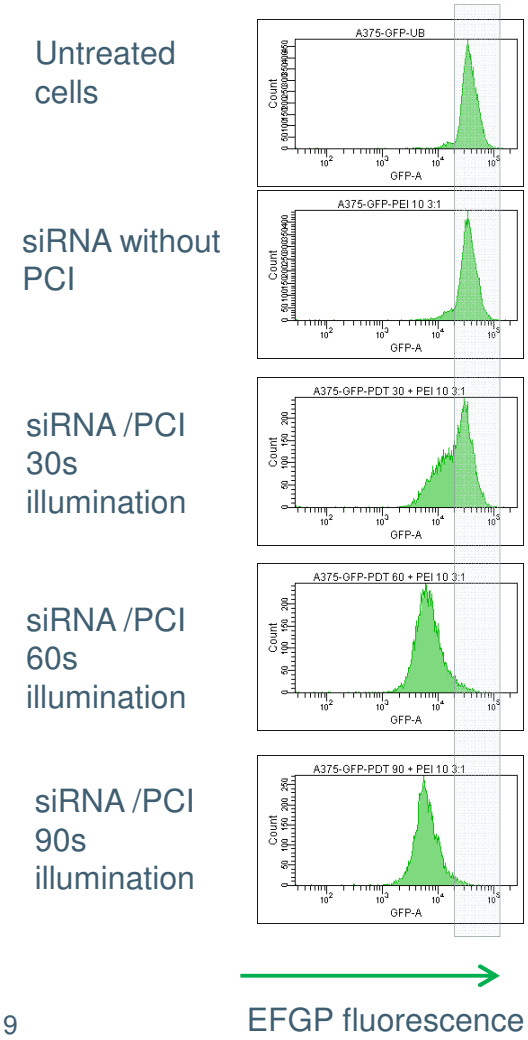
- EGFP mRNA
- Polyethylenimine (PEI) vehicle
- N/P ratio 2/1

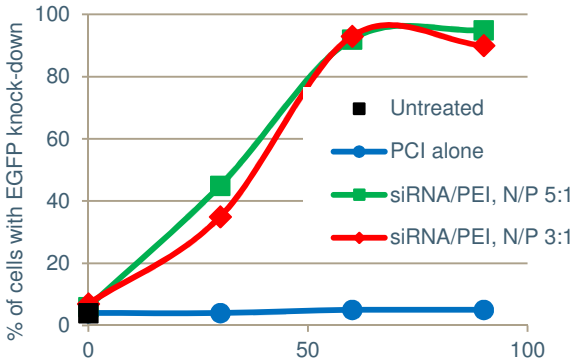


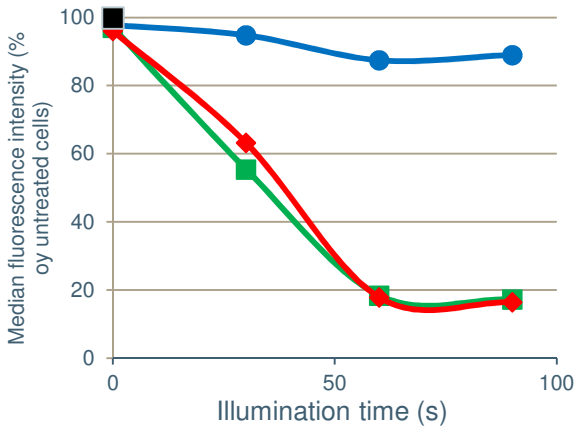
PCI induces endosomal escape of various types of oligonucleotides



PCI enhances gene silencing by siRNA-PEI complex (A375-EGFP cells)

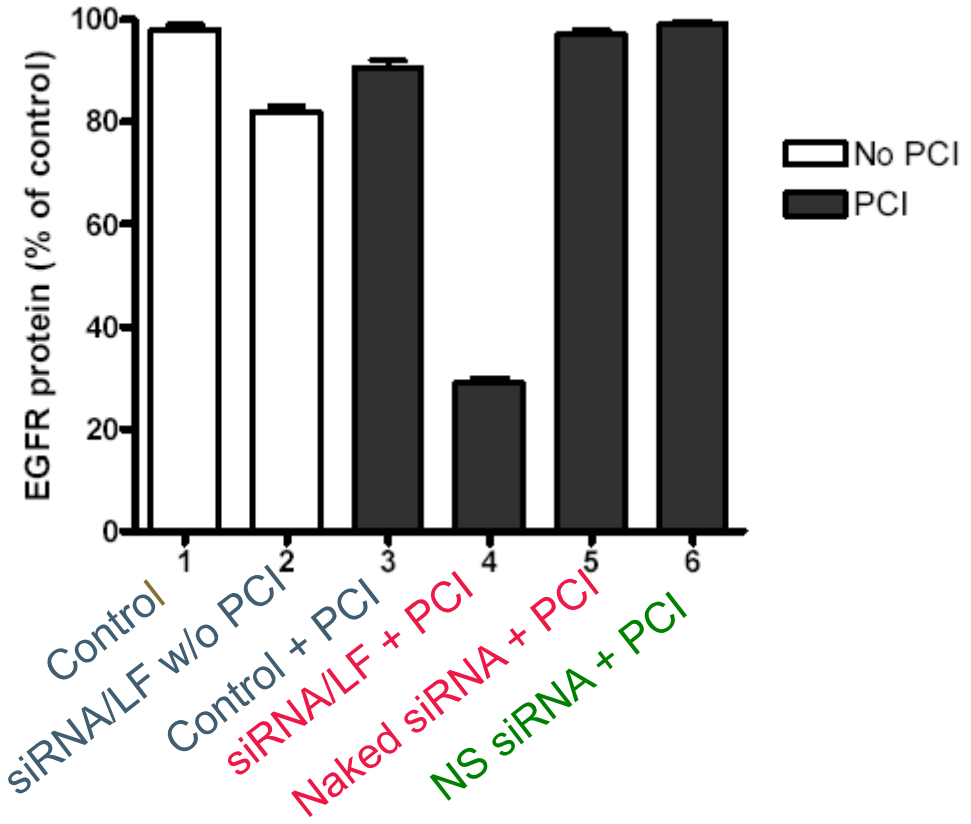






- PCI induces target gene knock-down in almost 100 % of the cells while siRNA-PEI alone has almost no effect
- > 80% knock-down of EGFP protein levels 3 days after treatment.
- 100 nM siRNA, PEI 10 000 (branched),

PCI can also enhance siRNA delivered by Lipofectamine (LF)



With Lipofectamine PCI can increase siRNA efficiency 10 X

siRNA dose, 50 % silencing:

- PCI: 340 pM

+ PCI: 35 -- ” --

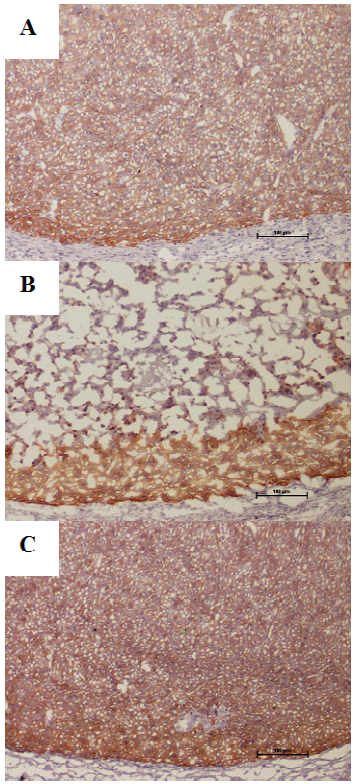
(Oliveira *et al.* 2007. *BBA,* 1768, 1211-7)

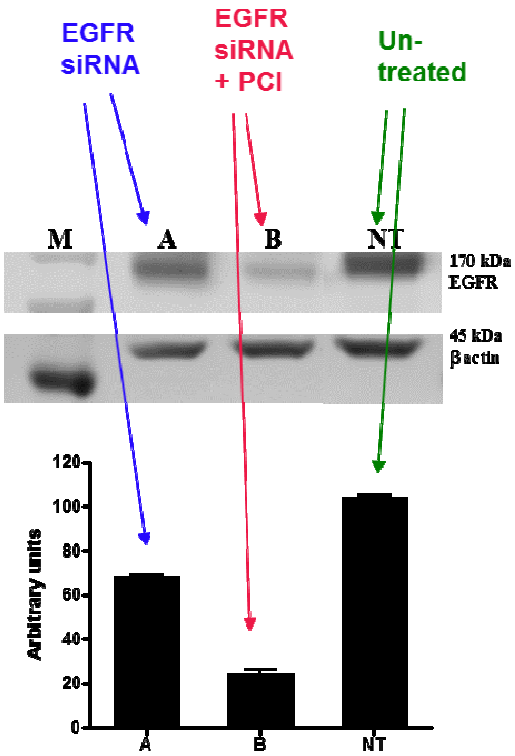
In vivo siRNA PCI – EGF receptor (EGFR) siRNA delivered with Lipofectamine

EGFR siRNA

EGFR siRNA + PCI

Non-specific siRNA + PCI





Oliveira, S. et al. (2008). Curr. Pharm. Design 14, 3686-97

- Intratumoural injection of photosensitiser and siRNA/Lipofectamine complex
- siRNA without PCI has only a modest effect on target gene expression, while siRNA with PCI induces almost 80% target gene knock-down.

PCI for nucleic acid delivery - summary

- PCI can improve delivery of many types of nucleic acids (plasmids, oliogonucleotides, mRNA, viral vectors).
- Most consistent improvement is seen with the use of polymeric delivery vehicles, but PCI can also improve delivery with:
  - Lipid-based vehicles
  - Naked oligos, provided they are stable to degradation and are taken up by the cells (e.g. peptide nucleic acids)
  - PCI is excellent for targeted vehicles (e.g. targeted to EGF receptor or transferrin receptors)
- The enhancement by PCI is best under conditions where the vehicles do not work well on their own
  - Low ratio of vehicle to nucleic acid
  - Low concentration of vehicle/nucleic acid complex
- This may be especially advantageous *in vivo*
  - Difficult to achieve a high concentration of vehicle/nucleic acid complex in target cells *in vivo*
  - Toxicity of the vehicle may be a problem, advantageous to use lower amounts of vehicle
- PCI Biotech is very interested in collaborations in the oligonucleotide area

Collaborators

- The Norwegian Radium Hospital – Oslo, Norway
  - Lina Prasmickaite
  - Kristian Berg
  - Eivind Hovig
  - Sigurd Bøe
- Utrecht University, The Netherlands
  - Sabrina Oliveira
  - Raymond Schifferlers
  - Gert Storm
- Alexis Vautrin Cancer Centre, Nancy, France
  - Alioune Ndoye
  - Gilles Dolivet
  - Jean-Louis Merlin
- Ludwig Maximillians Unversity, Munich
  - Ernst Wagner

Thank you