Biotech Showcase 2017

9 January, 2017

Per Walday, CEO

PCI BIOTECH

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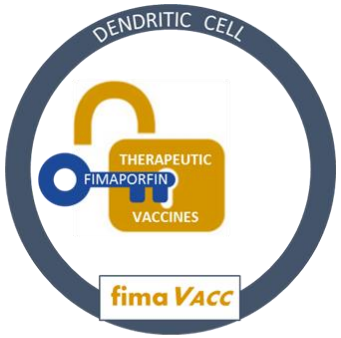
PCI BIOTECH AT A GLANCE

► Unlocking the potential of innovative medicines

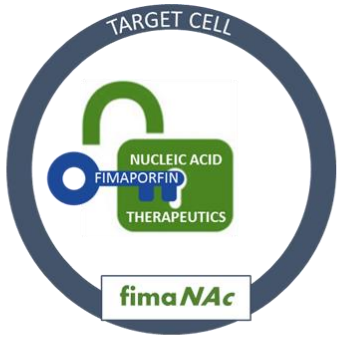
- A listed (PCIB:NO) cancer-focused biotech company
- Photochemical internalisation ("PCI") technology, originating from the Norwegian Radium Hospital
- Clinical programmes
  - **fima CHEM** – fimaporfin (Amphinex®) for the orphan indication inoperable bile duct cancer, Phase I completed
  - **fima VACC** – Vaccination technology that provides strongly enhanced cellular immune responses, Phase I initiated
- Pre-clinical programme
  - **fima NAc** – Efficient intracellular delivery of nucleic acid therapeutics, with four active research collaborations

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

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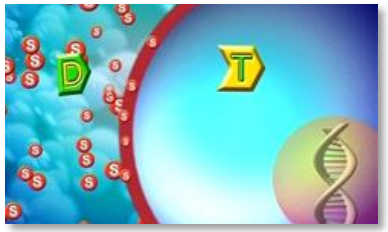
PHOTOCHEMICAL INTERNALISATION

► Triggered endosomal release through illumination

STEP 1:

- Fimaporfin (S) and the active molecule (D) are injected into the body and reaches the target cells



STEP 2:

- Fimaporfin (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 fimaporfin (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

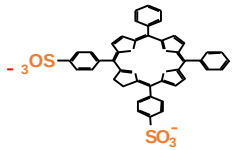
The active molecule

- 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
- Fimaporfin - Amphinex®



T

The target

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

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CHEMOTHERAPEUTICS

- A cornerstone in current cancer therapy

Chemotherapeutics will remain a **CORNERSTONE** in cancer treatment for the foreseeable future

PCI may enhance approximately **20%** of relevant approved chemotherapies

Niche indications may allow for **ORPHAN DRUG** applications

- **fima CHEM** may enable approved drugs to fulfil unmet local treatment needs
- First-in-man study published in Lancet Oncology*, with independent expert commentary
- Ready for Phase II in bile duct cancer with promising early signs of efficacy
- Opportunity for development in further niche indications

* **Lancet Oncology** (2016) **17**(9): p1217–1229

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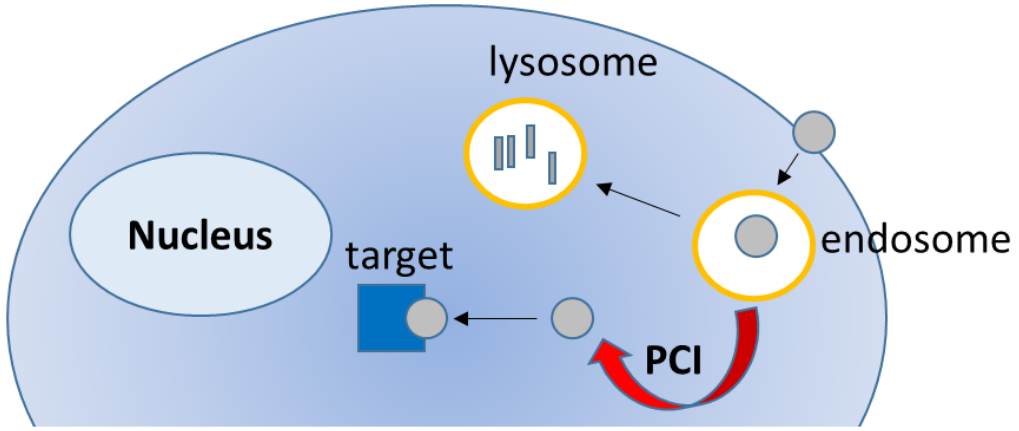
PCI TECHNOLOGY

▶ fimaCHEM – mode of action

Cancer cell



chemotherapeutic

Chemotherapeutics

Endocytosis

fimaCHEM

Release into cytosol

Lysosomal Breakdown

E.g.

- **Cytotoxic antibiotics** → DNA intercalation; free radical formation; etc.
- **Anti-metabolites** → DNA /RNA synthesis inhibition; DNA damage
- **Anti-microtubule agents** → Cell cycle arrest

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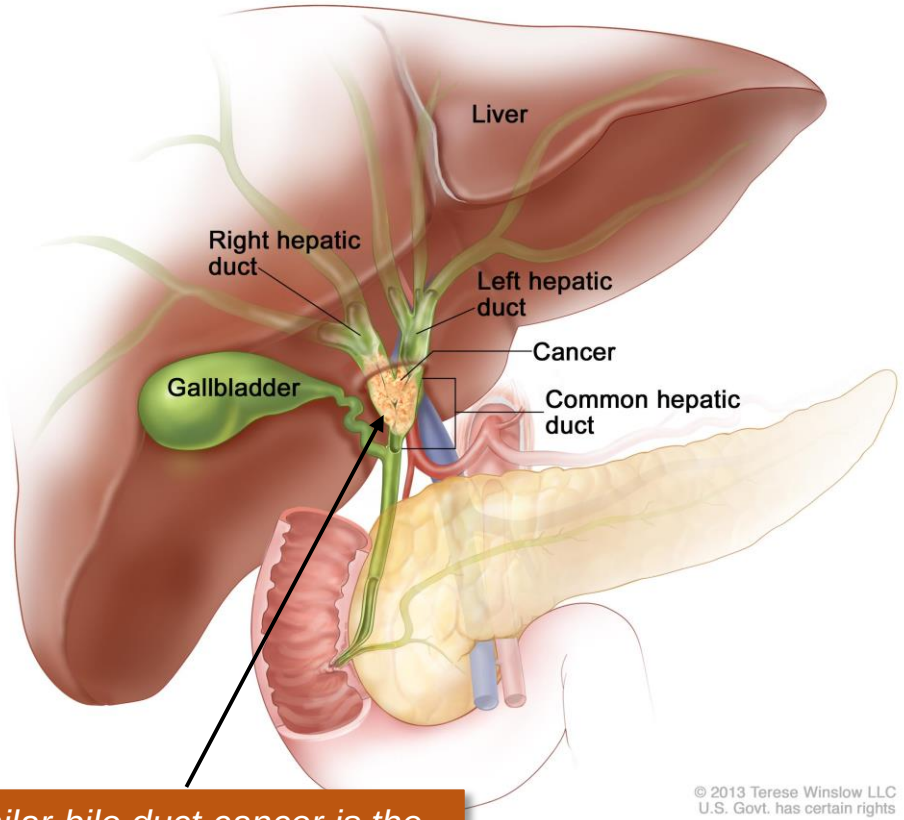
BILE DUCT CANCER

► Location and classification

- Often referred to as cholangiocarcinoma
- The cancer cells originates from the cells inside the bile duct (called cholangiocytes)
- Cholangiocarcinoma includes:
  - Intrahepatic tumours (10%*)
  - Perihilar tumours (60-70%*)
  - Distal tumours (20-30%*)
  - Different incidence, pathobiology and management



Perihilar bile duct cancer is the initial target for PCI treatment

* Bile duct cancer, Am Cancer Soc, 10/30/2013

BILE DUCT CANCER

▶ The unmet need

- Rare disease, yearly incidence rate of 1-2 per 100,000 in the western world – higher incidences in Asia
- Five-year survival rate of less than 5%, and 0% when inoperable – average approx. 12 months survival
- Current management
  - Surgery
    - Only potentially curative treatment
    - Less than ⅓ are resectable at presentation
  - Stenting
    - **Endoscopic** stenting for palliative biliary drainage
  - Chemotherapy
    - No approved chemotherapy
    - Recommended chemotherapy: **gemcitabine** and cisplatin

Excellent technology fit with PCI

Targeted illumination is done using standard endoscopic procedure

The active chemotherapy gemcitabine is significantly enhanced by fima CHEM

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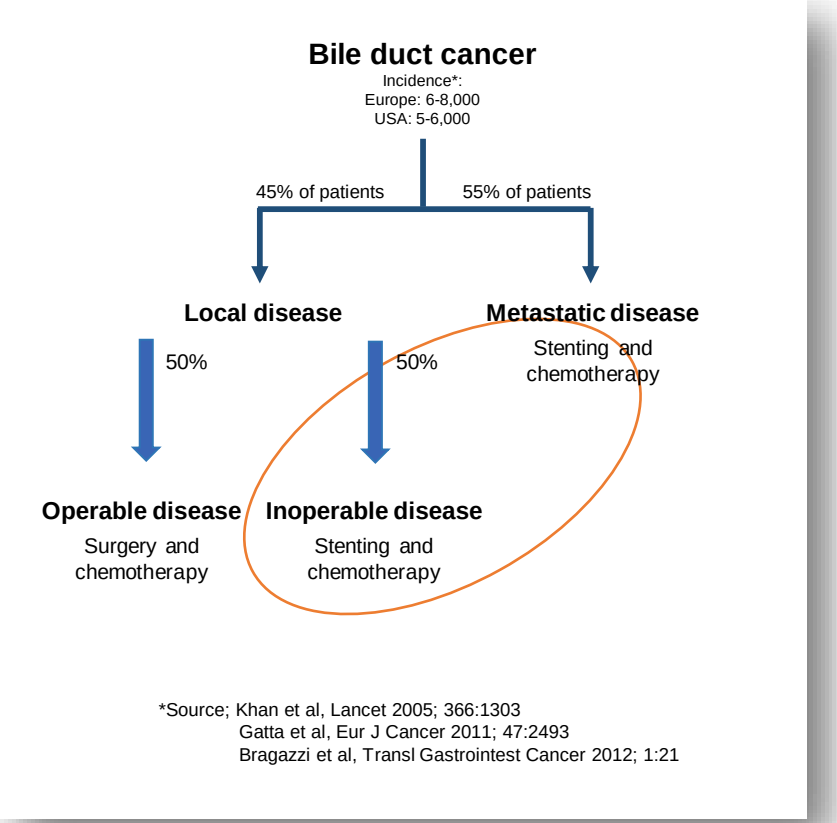
Bile Duct Cancer

A sizeable orphan market potential

- **Immediate target market is as first line treatment**
  - Incidence is close to 15,000 across Europe and the US
  - Immediate target is inoperable patients with primary hilar disease
  - Approximately 3,000 assumed to be eligible for fimaCHEM
  - Possible upside in distal and more advanced metastatic disease
  - Higher incidences in Asia
- **Attractive price potential**
  - Lack of approved medicinal treatment options
  - Diseases with <10,000 in US support annual pricing >$100,000[1]
- **Potential significant majority share of the market**
  - Anticipated benefits
    - No competing marketable treatment alternatives
    - Greater efficacy due to local chemotherapy boost
    - Easy light access through established standard procedures



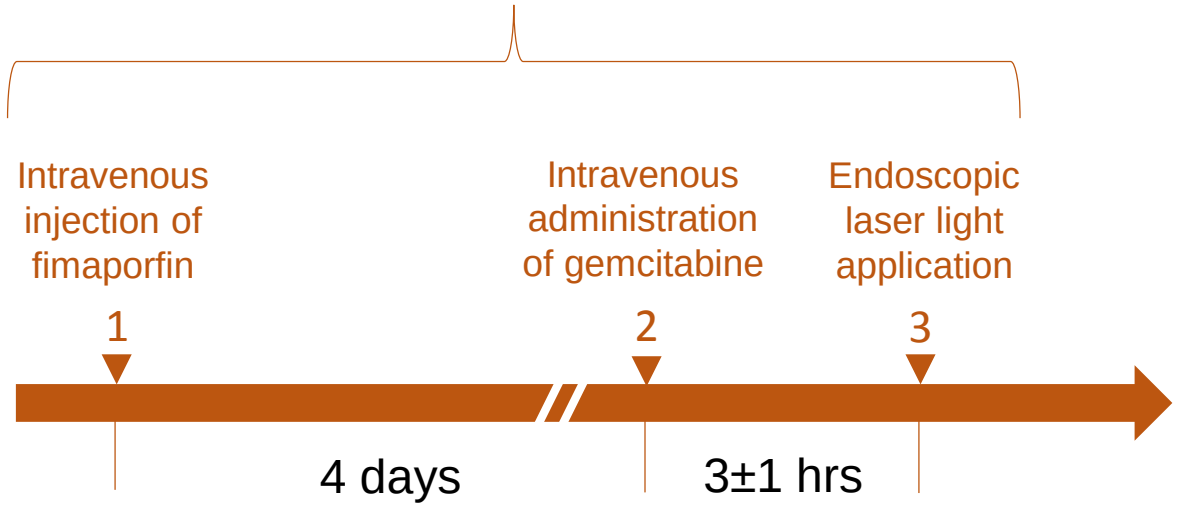
[1] LifeSciCapital, OD Market Sector Analysis 2016

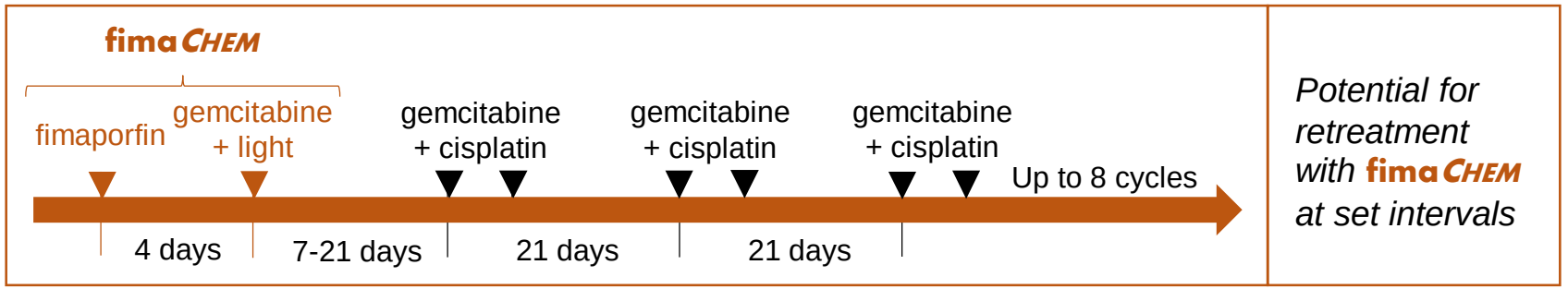
BILE DUCT CANCER

- A proven technology with excellent fit to standard procedures

fima CHEM

A three step treatment procedure





Potential for retreatment with fima CHEM *at set intervals*

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BILE DUCT CANCER – CLINICAL PHASE I/II STUDY

- Early promising signs of durable response in Phase I

- **6 months radiology data from all dose cohorts – local read**

RECIST*	PD	SD	PR	CR	NA**
Cohort IV***	1		2	1	2
Cohort III		1	1	1	
Cohort II		1			2
Cohort I	1	1			1

PD: Progressive disease (>20% growth)

SD: Stable Disease

PR: Partial Response (>30% shrinkage)

CR: Complete Response (no visible tumour)

* Response Evaluation Criteria In Solid Tumours (rules defining when cancer patients improve, stay the same or worsen during treatments)
** Not measurable / Not radiologically evaluable
*** Cohort IV expanded; Four radiologically evaluable patients at 6 months

- Subjects are in the study for 6 months after PCI treatment
- After 6 months patients are followed for survival only
- Commissioned central independent radiological expert evaluation of Cohort III & IV, as this is an expected requirement from regulatory authorities

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BILE DUCT CANCER – CLINICAL PHASE I/II STUDY

- Early promising signs of durable response verified by independent expert evaluation

- **6 months radiology data: Cohort III & IV – local vs. central**

RECIST	PD	SD	PR	CR	NA
Local	1	1	3	2	2
Central	2	1	2	2	2

- Central radiological RECIST evaluation of all patient images from Cohort III and IV
- All images evaluated by two study-independent radiologists with expertise in RECIST and bile duct cancer
- Tumour response verified at central evaluation
  - Progressive disease due to appearance of new lesions (one missed at local read)
- **More than 50% response rate** – far above expected with standard treatment

BILE DUCT CANCER – CLINICAL PHASE I/II STUDY

- Convincing response at target tumour level

- **6 months radiology data: Cohort III & IV – response at single lesion level**

Measurable lesions	Lesion shrinkage		Stable lesion	Lesion growth
19 (total number of targets selected across the two independent readers)	**17**	**12** (lesion undetectable)	**1** (<20% reduction & <10% increase)	**1** (>10% mass increase)
		5 (>20% mass reduction)		

- Independent radiological evaluation of all patient images from Cohort III and IV
- All images evaluated separately by two radiology experts
- **Shrinkage of almost 90% of selected target lesions, with more than 60% being undetectable at 6 months**
- "*Change in tumor size by RECIST correlates linearly with overall survival in Phase I oncology studies*" [1]

[2] ***"Maintenance of biliary drainage is critical in patients with advanced biliary cancer… …response in tumor bulk may therefore have a greater effect on survival than would be the case for other cancers."***

[1] Jain et al 2012 – JCO 30:2684-90 (analysis of 24 phase I studies)
[2] Valle et al 2010 – NEJM 362:1273-81 (landmark publication for cis-gem treatment in bile duct cancer)

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BILE DUCT CANCER

► The opportunity

High unmet medical need

- Overall survival of inoperable disease is ~12 months
- Five year survival of inoperable disease is close to 0%
- Tumour response may be more critical than for other cancers
  - tumours tend to block the bile duct
  - biliary drainage is key for patient treatment and survival

Promising early signs of efficacy

- Strikingly high (4/7) durable tumour response rate (CR+PR)
- Two CR among seven evaluable pts in highest dose cohorts
- RECIST evaluation confirmed by independent experts
- Good overall safety and tolerability

fimaCHEM for bile duct cancer

Well-defined market

- First-line treatment in a rare disease with limited pipeline
- Approx 3,000 pts in US + Europe eligible for treatment
- Potential upside: metastatic disease & Asia (high incidence)
- Orphan Designation (OD) in EU; US in planning
  - provides development & commercialisation benefits
  - OD drugs have higher probability of success and price

Proven technology with excellent fit

- First-in-man Phase I study published in Lancet Oncology
- Easy light access through standard endoscopic procedure
- Significantly enhancing the active standard-of-care drug
  - boosting effect where most needed – inside the bile duct
  - potential for local re-treatment

BILE DUCT CANCER

► Status and strategy going forward

- **Phase I completed with good tolerability and very promising early signs of efficacy**
  - No serious unexpected safety findings and no apparent increase in adverse reactions with increasing doses
  - Very promising early signs of efficacy – significant tumour shrinkage observed radiologically
  - Results verified at central evaluation by study-independent external radiological experts in RECIST
- **Orphan designation**
  - Granted Orphan Drug Designation in EU
  - Open IND in US – Orphan Drug application in process
- **Regulatory interactions with EU and US authorities, to determine fastest way to market**
  - Promising signs of efficacy in a life threatening orphan indication without approved treatment alternatives
  - May allow for marketing authorisation based on restricted data, e.g. a pivotal phase II study

IMMUNOTHERAPY

- A new hope for millions of patients

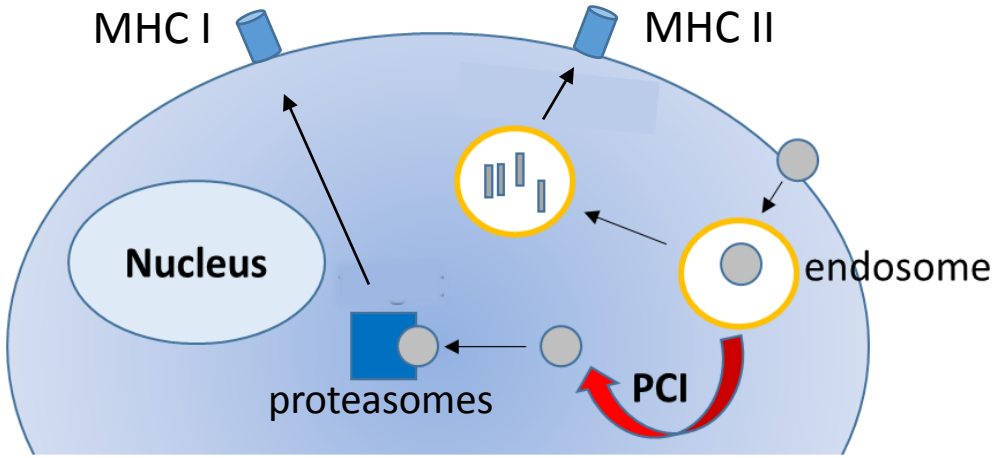
- fima VACC enhances cellular immune responses important for therapeutic effects
- Initiated Phase I study in healthy volunteers for clinical validation
- Aim is to out-license the technology on non-/semi-exclusive basis
- Opportunity to develop own therapeutic vaccination products

* Citi Research "Immunotherapy – the beginning of the end for cancer". Baum, May 2013
** Clinicaltrials.gov. Therapeutic cancer vaccines, PCIB analysis, August 2016
*** CPI: Checkpoint inhibitors

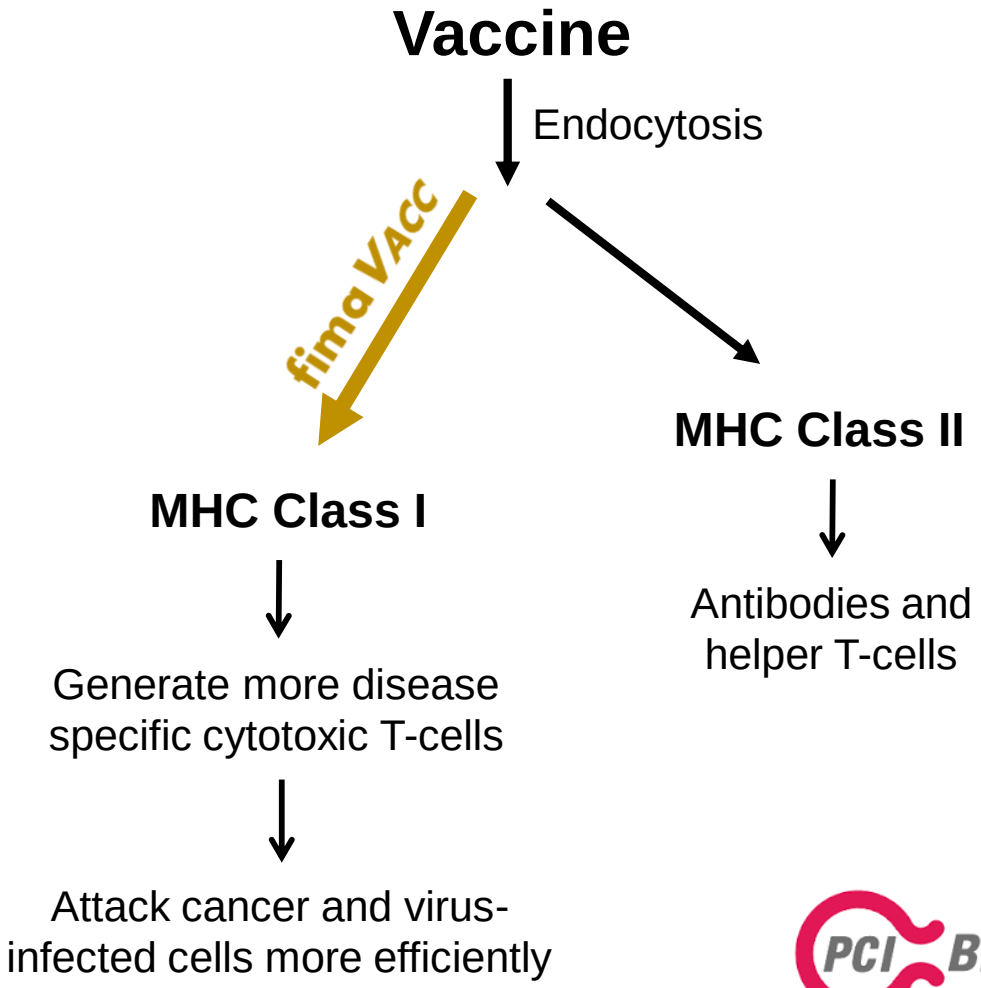
PCI TECHNOLOGY

▶ fima VACC – mode of action

Dendritic cell



vaccine antigen



THERAPEUTIC VACCINATION WITH fima VACC

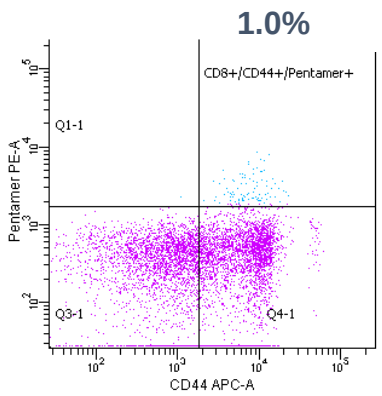
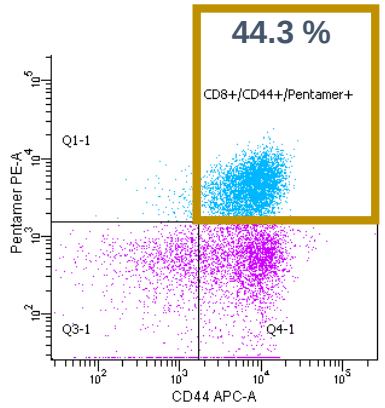
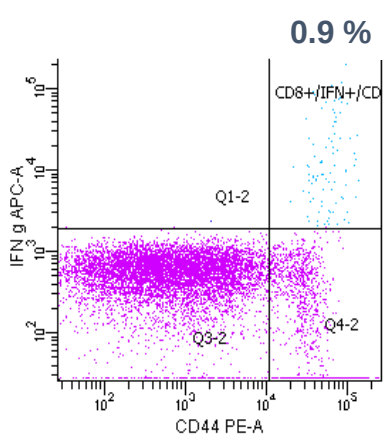
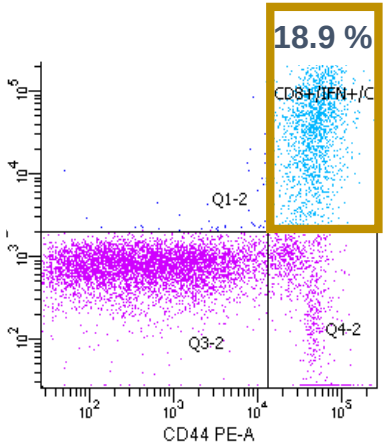
- Opportunity to play a key role in second generation immunotherapy

Patented disposable "band-aid-like" device for user-friendly illumination of the vaccination site

- Unique mode of action
  - induction of antigen specific cytotoxic T-cells by MHC class I antigen presentation in dendritic cells
- Broad applicability
  - peptide and protein antigens
  - particulate antigen formulations
  - prophylactic & therapeutic vaccination
- Safety of fimaporfin confirmed in Phase I studies
- Excellent stability
  - stable at room temperature
  - stable in solution
  - can be autoclaved
- Cost effective synthesis

fima VACC STRONGLY ENHANCES VACCINATION EFFECTS

- Impressive effects with clinically relevant HPV therapeutic vaccine in mice

	Vaccination without fima VACC	Vaccination with fima VACC
Amount of activated antigen-specific CD8 T-cells in blood		
Amount of activated antigen-specific CD8 T-cells in spleen		

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

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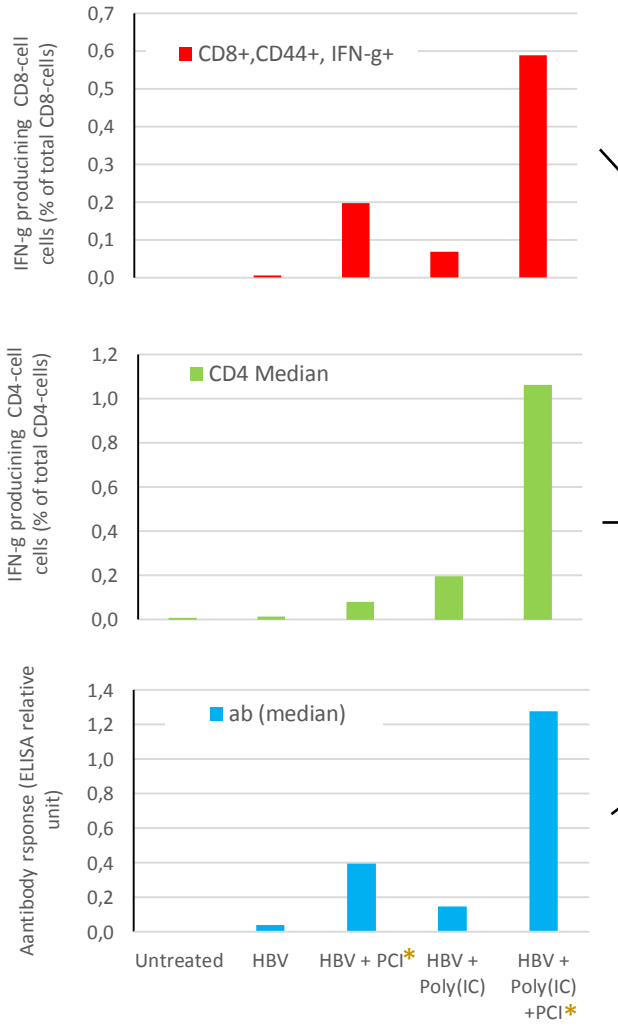
HBV SURFACE ANTIGEN

► **fima VACC** enhances both CD8, CD4, and antibody responses



Immune response with fima VACC

Type of immune response	Fold increase compared to HBV alone	Fold increase compared to HBV + poly(IC)
CD8	110x	9x
CD4	75x	5x
Antibody	33x	9x

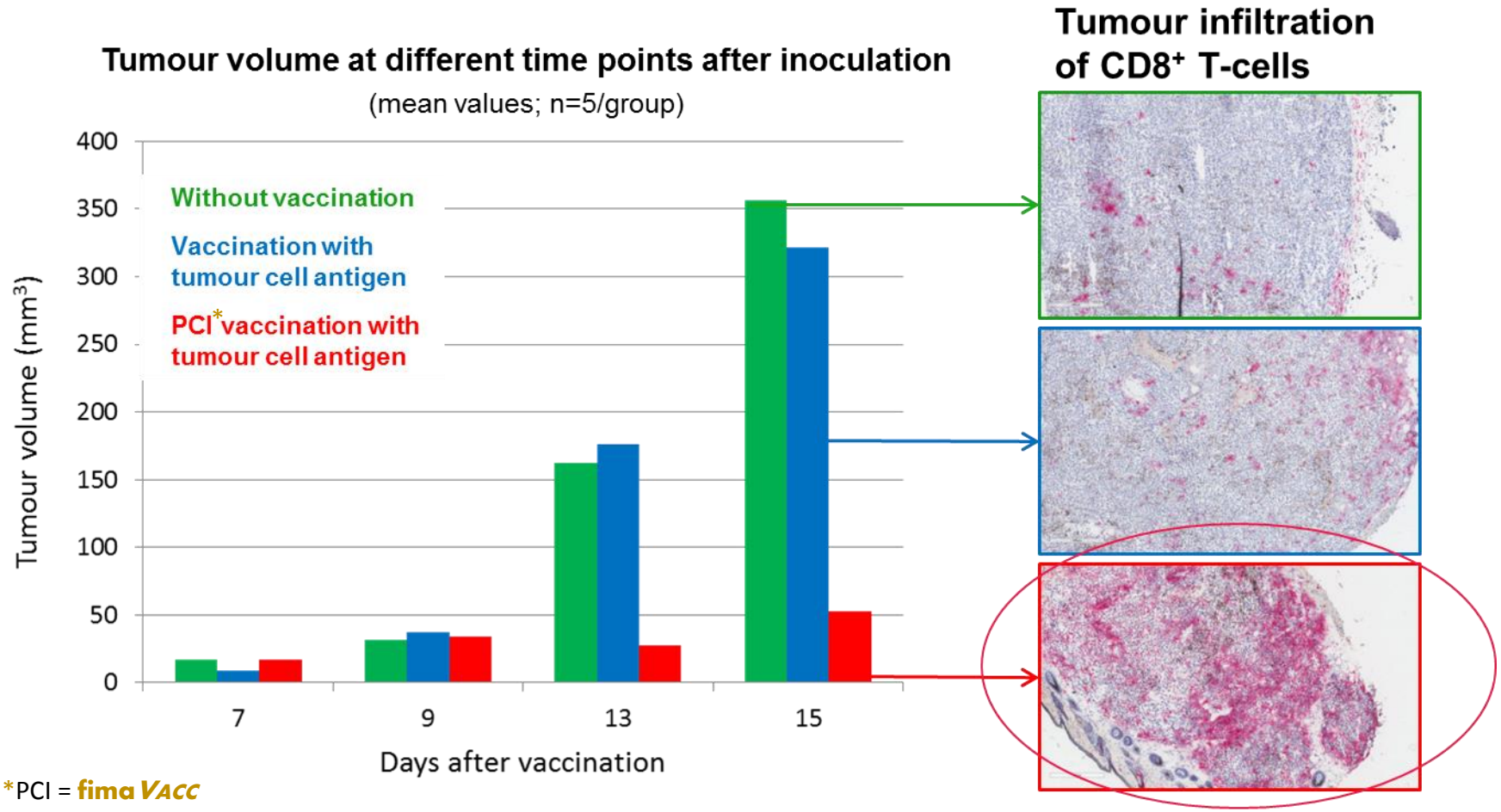
Elicit strong effects in all important aspects of immune response

*PCI = fima VACC

THERAPEUTIC VACCINATION IN TUMOUR MODEL

- **fima VACC** induces cytotoxic T-cells that infiltrate tumours

Therapeutic fima VACC vaccination with OVA in animal tumour model (B16-OVA melanoma/OT-1)



*PCI = fima VACC

THE fima VACC OPPORTUNITY

- Clinical validation targeting a huge market with limited investments

An Open-Label Phase I/Proof of Principle, Dose escalation Study to Assess Safety, Tolerability and Immune Response of Fimaporfin-induced Photochemical Internalisation (PCI) of Antigen/Adjuvant in Healthy Subjects

- **Improving immunogenicity of vaccines is a main priority in the immunotherapy industry**
- **Potential for quick clinical validation of concept with substantial upside at limited cost**
  - Open-label, antigen-adjuvant controlled study in up to 80 subjects
  - Initiated 3Q 2016 and expected completion 1H 2017
  - Dose escalation of light and fimaporfin, and investigating optimal timing of light application
  - Main objective is to determine safety, tolerability and vaccine induced immune responses
- **Establishing fima VACC as a clinical asset is a major milestone towards commercialisation**

NUCLEIC ACID THERAPEUTICS

- A treatment modality with huge potential

- fimaNAc may provide a delivery solution for many nucleic acid therapy applications
- Opportunistic collaborative approach
- Aim is to out-license the technology on non-/semi-exclusive basis

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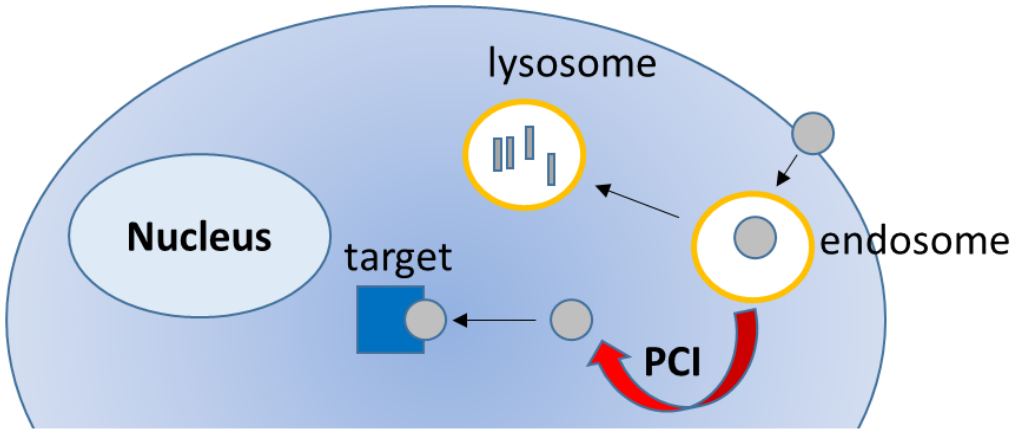
* Research and Markets “RNAi therapeutics market”. Dec 2015

PCI TECHNOLOGY

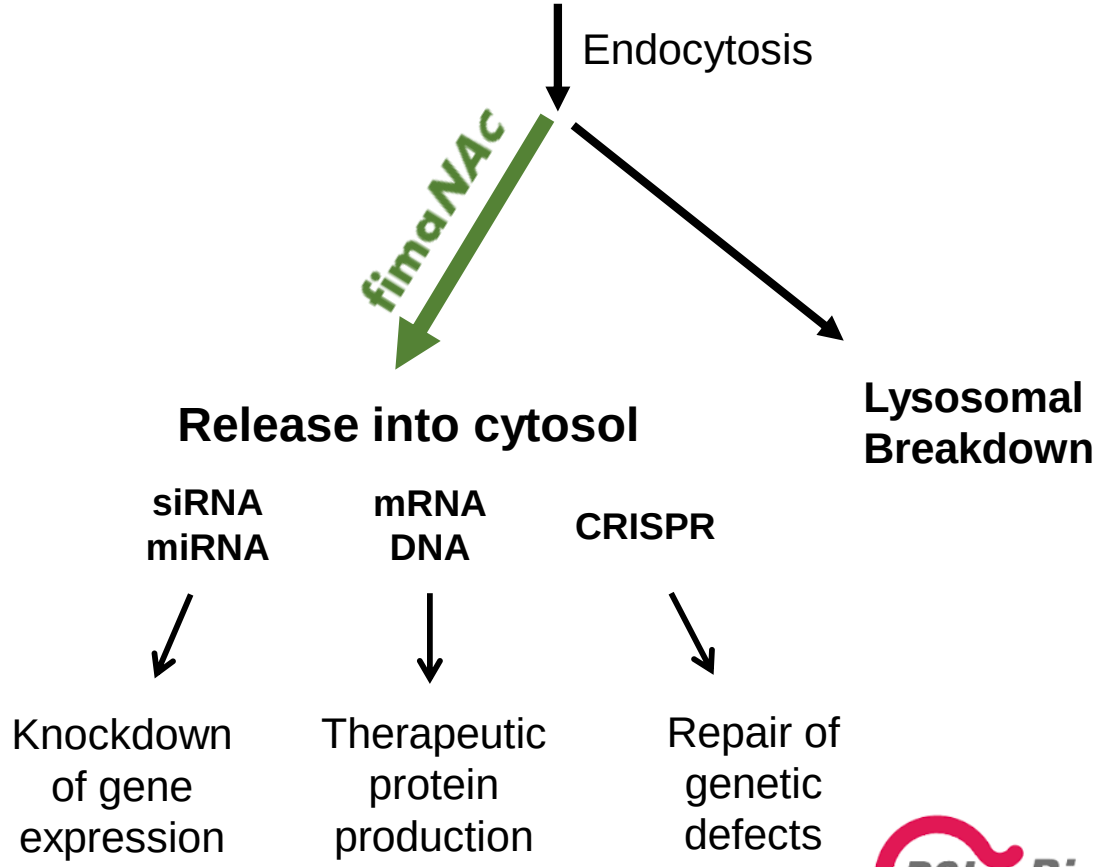
▶ fimaNAc – mode of action

Target cell



nucleic acid therapeutic

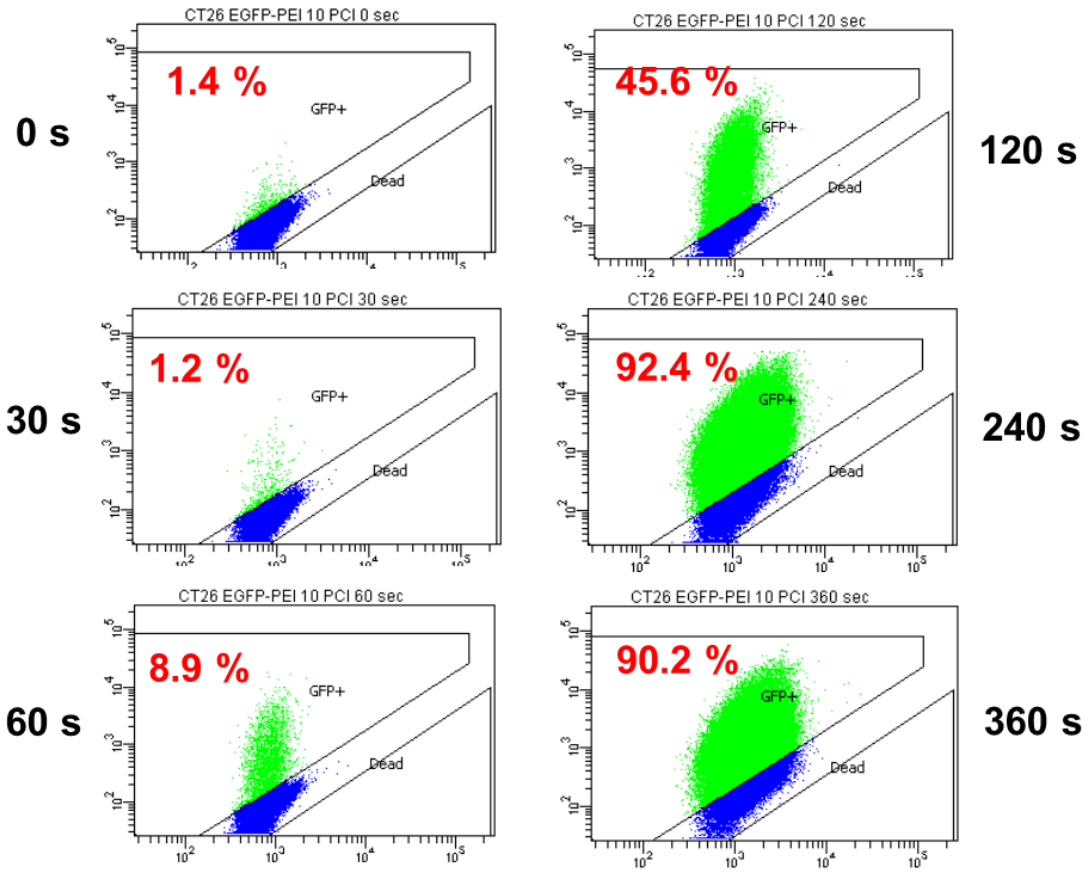
Nucleic Acid Therapeutics

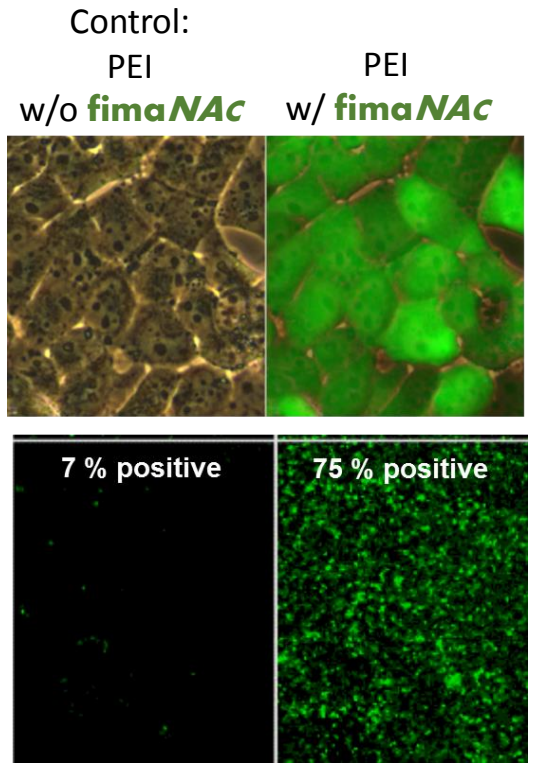


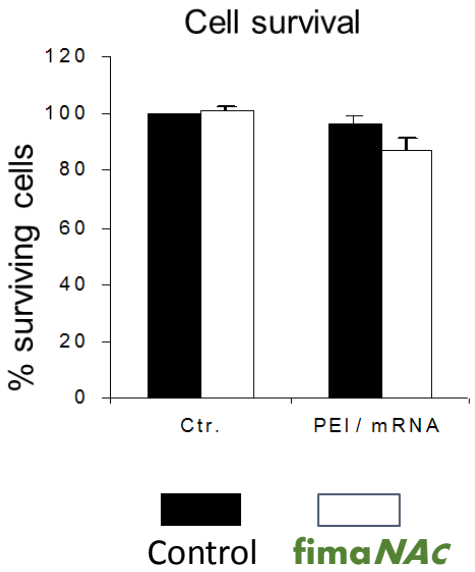
ENHANCING mRNA DELIVERY

- Strongly increased GFP synthesis with increasing light doses

fimaNAc with polyethylenimine (PEI) vehicle







VERSATILITY OF fimaNAc

- Delivery of many types of nucleic acid with many different vehicles *in vitro*

- **Main bottleneck in the field is delivery**
- fimaNAc can deliver many types nucleic acids
- Enhancement by fimaNAc is best under conditions favourable for vehicle safety
  - Low ratio of vehicle to nucleic acid
  - Low concentration of vehicle/nucleic acid complex
- Especially advantageous *in vivo*
  - Difficult to achieve a high concentration of vehicle/nucleic acid complex in target cells
  - Toxicity may limit the amount of vehicle used

Nucleic acids successfully delivered by fimaNAc

Type of nucleic acid	Delivery vehicle
Plasmids	PEI, cationic peptides, cationic lipids, polylysine ++ Targeting to EGF-R, transferrin-R
siRNA	PEI, cationic peptides, dendrimers, lipofectamine, DOTAP, nanogels, chitosan ++
PNA (peptide nucleic acids)	None, cationic amino acids attached
mRNA	PEI, Protamine
Adenoviral vectors	None, cationic polymers
AAV vector	None

Opportunistic approach – pursuing collaboration and partnering opportunities

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RESEARCH COLLABORATIONS

- Four active collaborations within nucleic acid therapeutics

fimaNAc

RXi Pharmaceuticals

- Initiated 2Q 2015
- Listed on Nasdaq
- Innovative therapeutic siRNA
- Clinical programmes in dermatology and ophthalmology

Top-10 large pharma

- Initiated 3Q 2015
- A global leader in nucleic acid therapeutics
- Collaborative research funded by partner
- Evaluate synergistic effects between companies' technologies

BioNTech

- Initiated 3Q 2016
- German biotechnology company developing individualised cancer immunotherapies
- Clinical programmes in melanoma, head & neck, breast, ovarian and pancreatic cancer

eTheRNA

Boosting the human immune system to fight diseases

- Initiated 4Q 2016
- Belgian immunotherapy company
- Proprietary TriMix platform programming dendritic cells with synthetic mRNA
- Clinical programmes in melanoma and triple negative breast cancer

Research collaborations aim to evaluate synergies between the fima platform and partner technologies, with the potential for further partnerships

DEVELOPMENT PIPELINE

- Unlocking the true potential of innovative medicines

Programme	Therapeutic agents	Preclinical	Phase I	Phase II	Status
fimaCHEM	*Chemotherapeutics*				Phase I in the orphan indication bile duct cancer completed with promising early signs of efficacy
fimaVACC	*Therapeutic cancer vaccines*				Phase I study ongoing One active R&D collaboration
fimaNAc	*Nucleic acid therapeutics*				Four active R&D collaborations

An oncology focused company with three well differentiated assets

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Current Status and Strategy

► Strategic priorities for the three programmes

Programme	Strategy	
fimaCHEM	• Regulatory interactions with EU and US authorities on requirements for market approval (1H 2017) • Results have furnished increased external interest, which will be assessed in relation to various financing and partnering alternatives	***Seek regulatory clarity and assess development alternatives***
fimaVACC	• Expedite clinical validation with potential to significantly increase asset value (1H 2017) • Continued focus on partnering and explore internal product development	***Establish clinical asset***
fimaNAc	• Establish further research collaborations and convert to licensing deals	***Pursue out-licensing opportunities***

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