

# Hamlet Biopharma

# This is Hamlet Biopharma

Innovative pharmaceutical company listed on Spotlight Stock Market



## Ground breaking discoveries

Cancer and Infections



## Recent clinical update

Data analysis of Alpha1H studies  
Strong treatment effects against  
bladder cancer



## Strategic merger

Hamlet Pharma with  
SelectImmune (Aug 2023)



## Drug development

Broader project portfolio &  
lower risk



## Patents

15 patent families  
60 individual patents

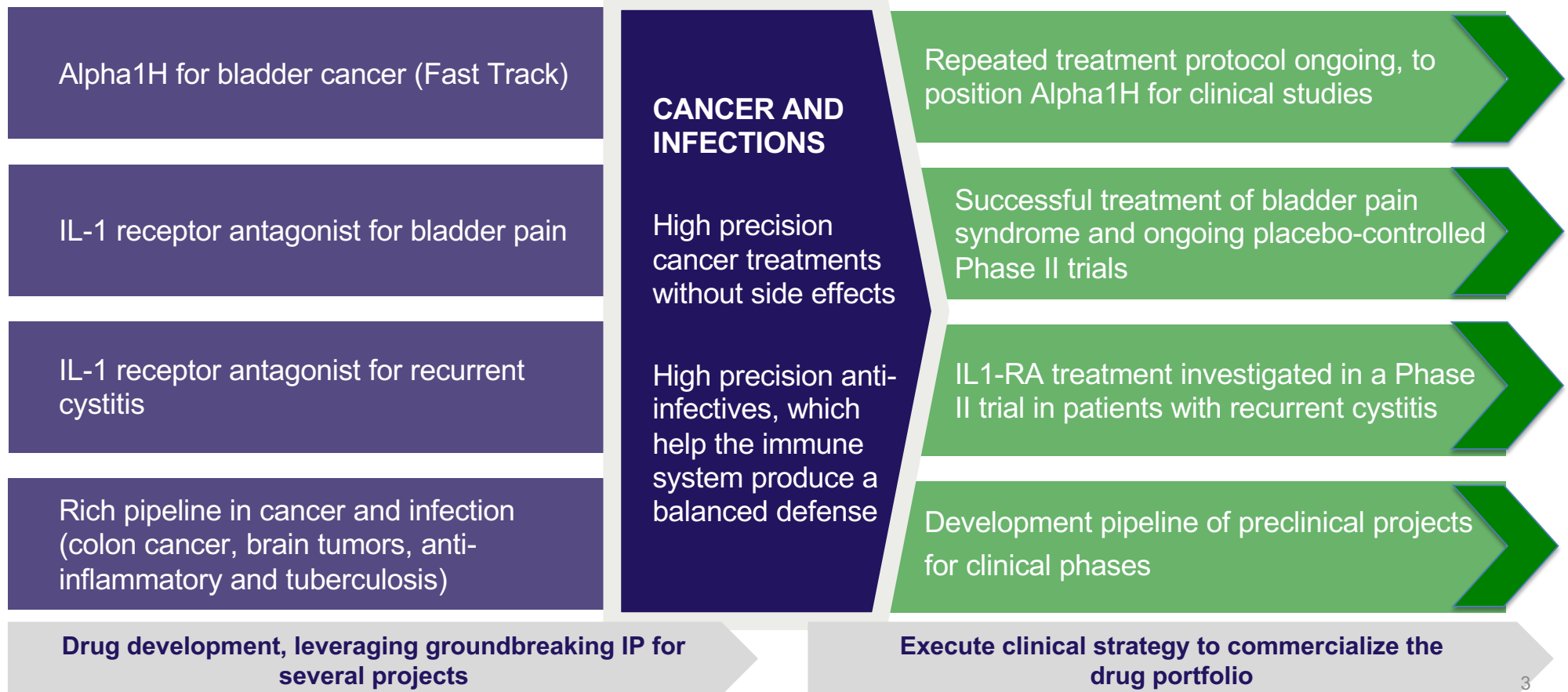


## Publications

Ranked in the top 1 % world-wide  
(Stanford ranking)

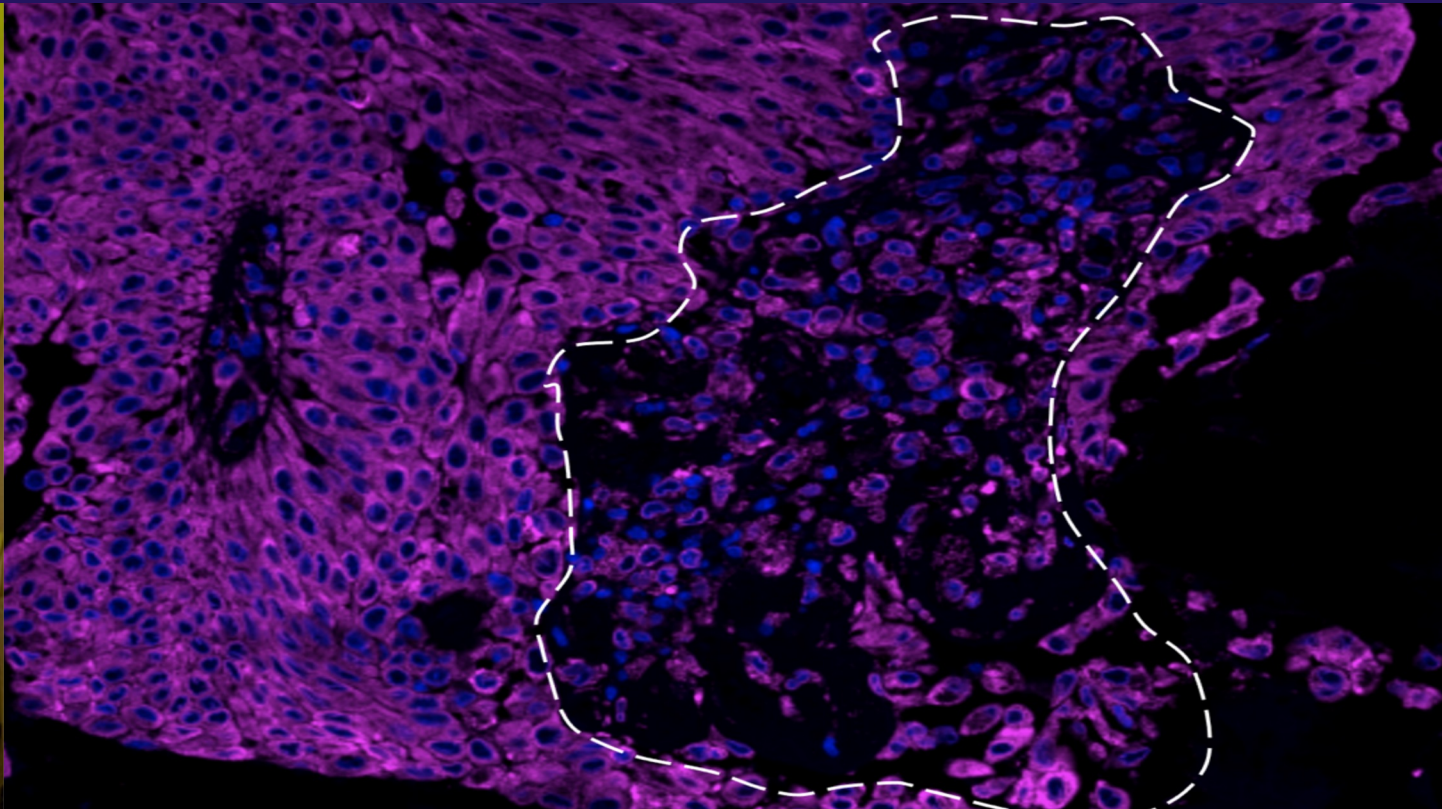
# Pipeline – Indications and studies

## Cancer and infections: Addressing unmet medical needs in large patient groups

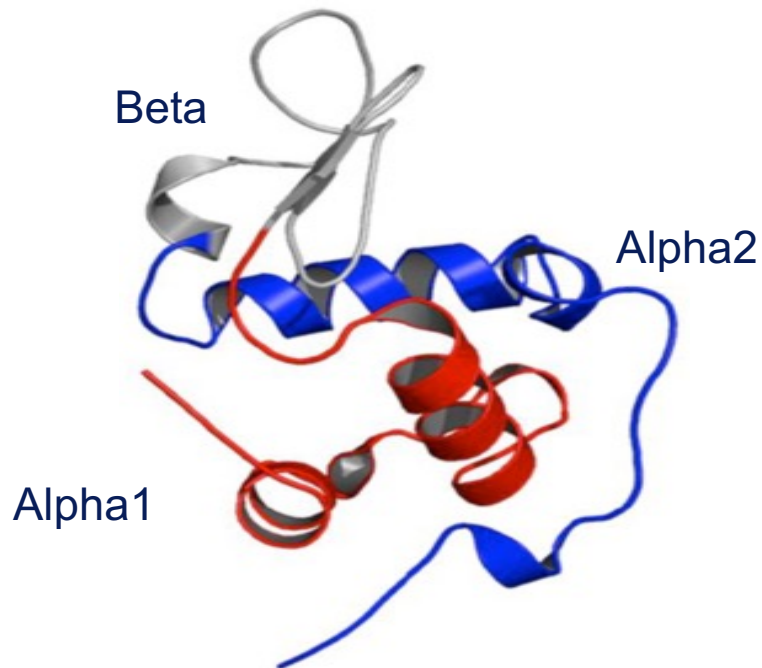


# Alpha1H: Bladder cancer

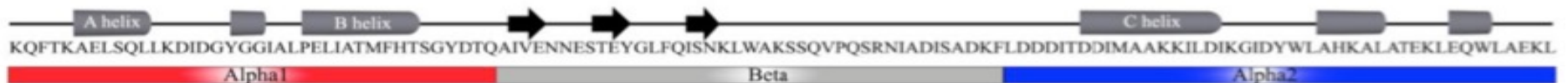
A groundbreaking anti-cancer technology based on the synthetic Alpha1H peptide complex



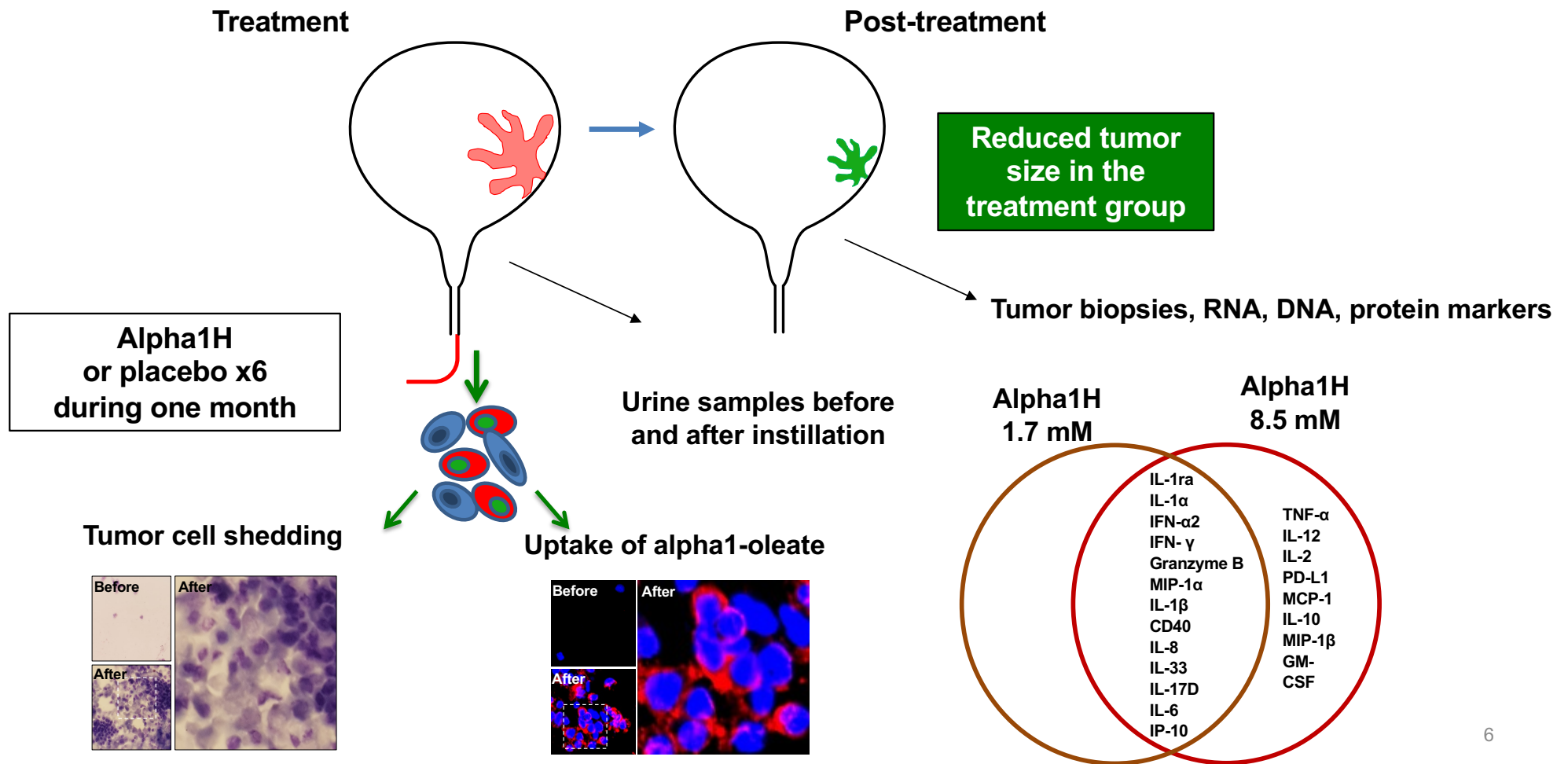
# Alpha1H – the synthetic peptide-based drug



Alpha1 is the active domain of alpha-lactalbumin  
Alpha1H reproduces the effects of HAMLET  
Synthetic, GMP manufacturing, large quantities  
International patents valid >2038  
Therapeutic effects in animal models of cancer  
Therapeutic effects in clinical trials of  
bladder cancer



# Alpha1H: Bladder cancer – Treatment



# Alpha1H : Placebo-controlled study results, Part I

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## Safety

No drug related safety issues

## Efficacy

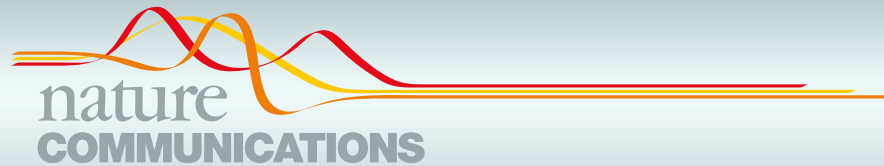
Uptake of the drug by tumor cells ( $p < 0.0001$ )

Reduction in tumor size ( $p < 0.04$ )

Increased shedding of tumor cells and tumor cell fragments ( $p < 0.0001$ )

Apoptotic cell death in the tumor and shed cells ( $p = 0.002$ )

# Alpha1H: Publication, placebo-controlled study










ARTICLE



<https://doi.org/10.1038/s41467-021-23748-y>

OPEN

## Bladder cancer therapy using a conformationally fluid tumoricidal peptide complex

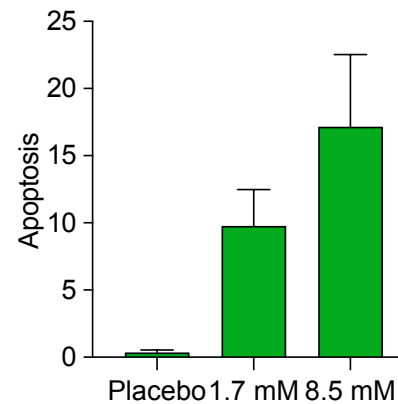
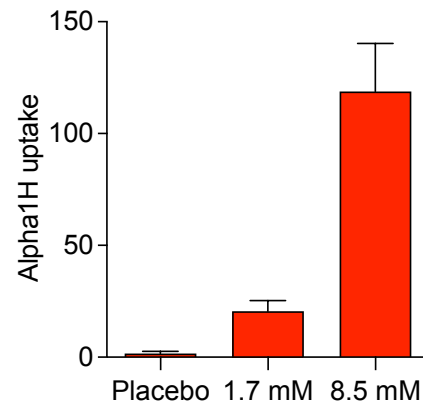
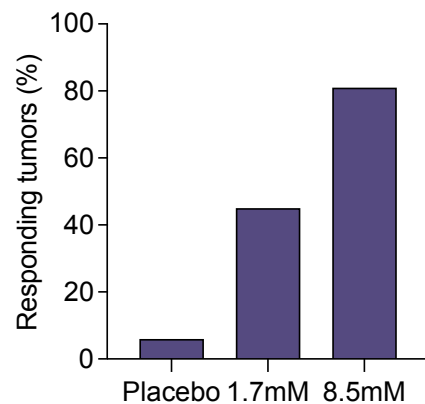
Antonín Brisuda<sup>1,7</sup>, James C. S. Ho <sup>2,6,7</sup>, Pancham S. Kandiyal<sup>3</sup>, Justin T-Y. Ng<sup>4</sup>, Ines Ambite <sup>2</sup>, Daniel S. C. Butler <sup>2</sup>, Jaromir Háček<sup>5</sup>, Murphy Lam Yim Wan<sup>2</sup>, Thi Hien Tran<sup>2</sup>, Aftab Nadeem<sup>2</sup>, Tuan Hiep Tran<sup>2</sup>, Anna Hastings <sup>3</sup>, Petter Storm<sup>2</sup>, Daniel L. Fortunati<sup>3</sup>, Parisa Esmaeili<sup>2</sup>, Hana Novotna<sup>1</sup>, Jakub Horňák<sup>1</sup>, Y. G. Mu <sup>4</sup>, K. H. Mok <sup>3</sup>, Marek Babjuk<sup>1,8</sup> & Catharina Svanborg <sup>2,8</sup>✉



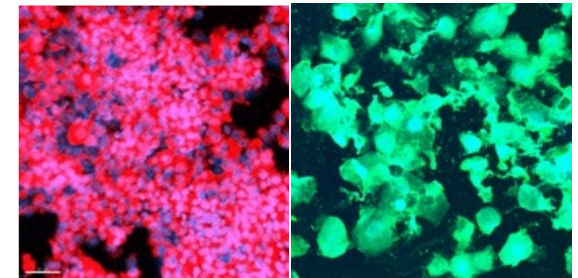
# Alpha1H: Bladder cancer – Dose-escalation study

## Successful clinical trial program

### Clinical Results



### Alpha1H uptake and apoptosis



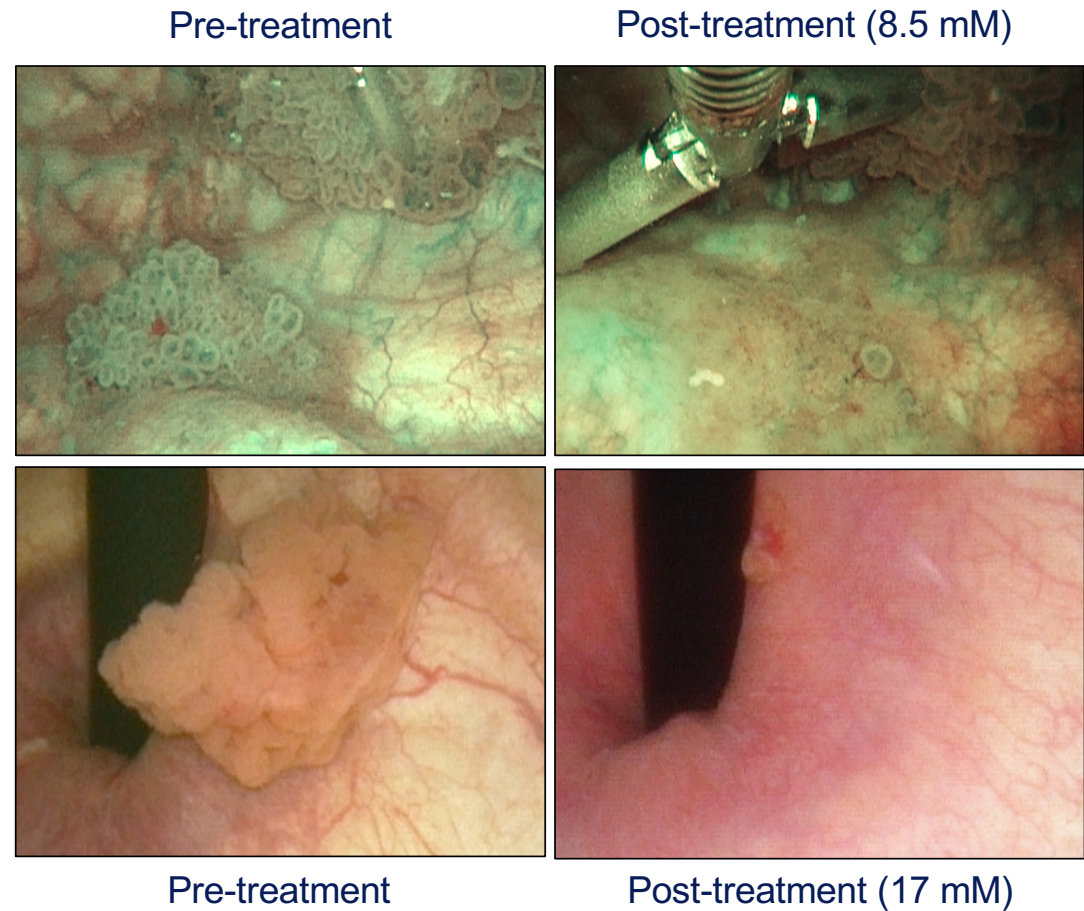
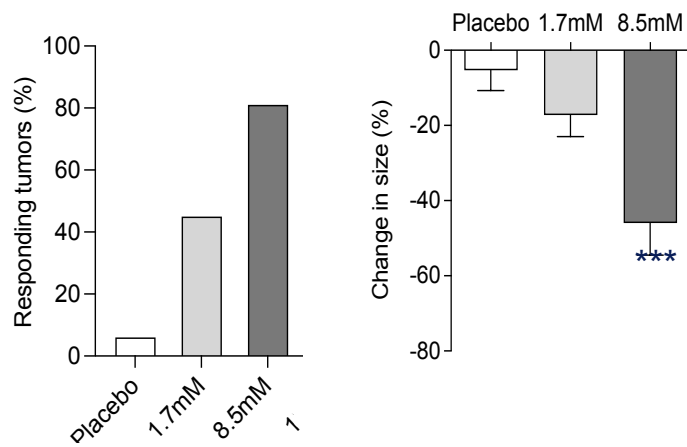
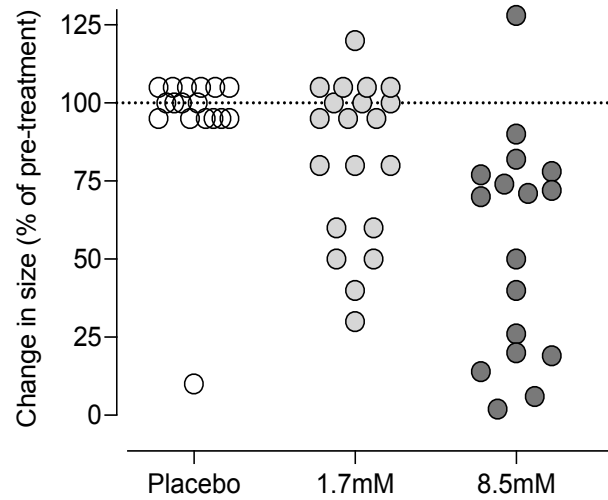
#### Efficacy & Safety:

- Reduction in tumor size and number
- Uptake of the drug by tumor cells
- Rapid shedding of tumor cells and apoptotic cell death
- Inhibition of cancer gene expression
- No drug related safety issues

#### Current Stage:

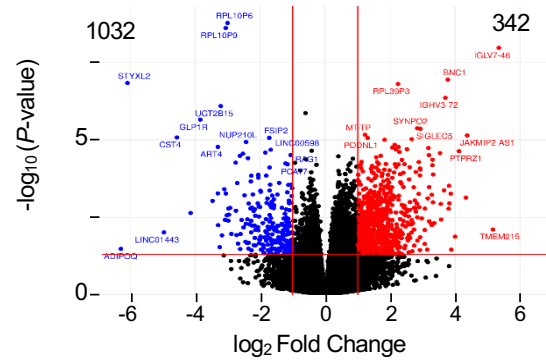
- Part I - A placebo-controlled study (completed) ✓
- Part II - A dose-escalation study (completed) ✓
- Part III - Repeated treatment protocol (ongoing)

# Alpha1H– tumor response in patients with bladder cancer

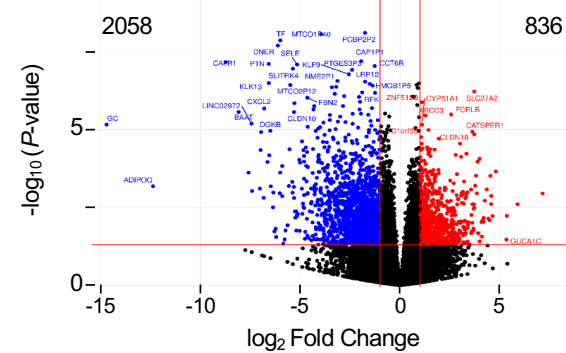


# Reprogramming of gene expression in Alpha1H-treated tumors

Volcano plot (Alpha1H 1.7 mM vs Placebo)

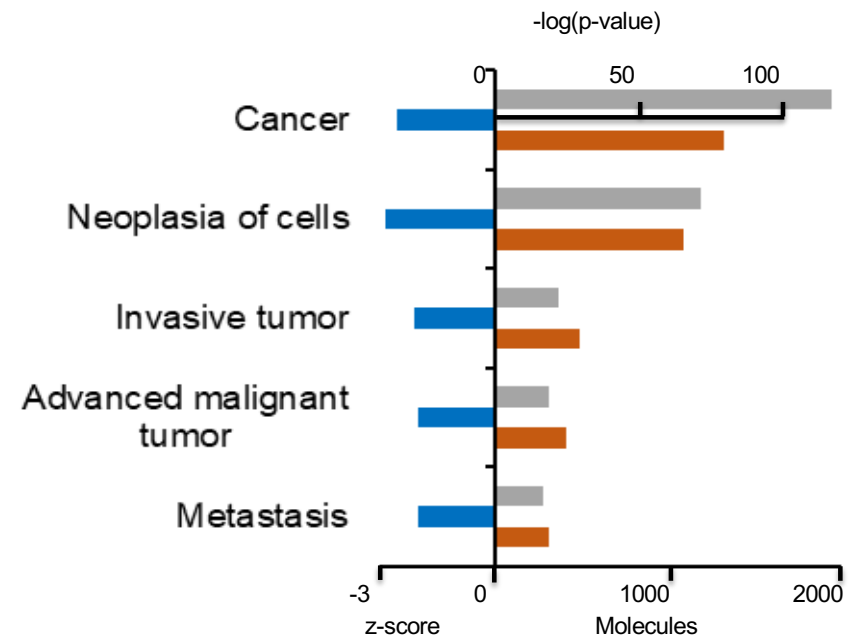


Volcano plot (Alpha1H 8.5 mM vs Placebo)



● Upregulated ● Downregulated ● Not regulated

Biofunctions (Alpha1H 8.5 mM)



# Alpha1H: Immune response with anti-tumor potential

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**Alpha1H triggers a strong immune response with anti-tumor effects.**

New analyses of clinical data from patients with bladder cancer treated with Alpha1H show a strong immune response with anti-tumor effects.

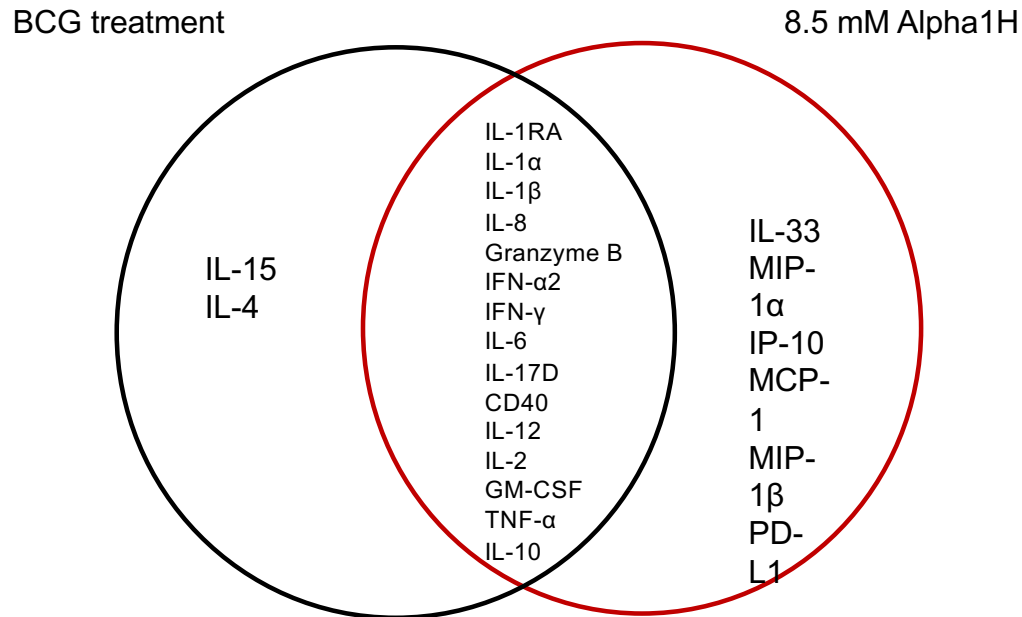
We have identified a broad immune response with robust anti-tumor potential in bladder cancer patients treated with Alpha1H.

Alpha1H triggers a similar response as BCG, the drug of choice for early bladder cancer, adding to the clinical potential of Alpha1H.

***In addition to killing tumor cells and inducing tumor cell shedding, Alpha1H activates a broad immune response, with a strong protective potential against bladder cancer.***

# Alpha1H: Bladder cancer – Alpha1H versus BCG

Immune response to Alpha1H treatment compared to BCG treatment reported in the literature



Immune response to Alpha1H treatment compared to placebo

Cytokines	8.5 mM	P-value
IL-1RA	▲	<0.0001
IL-1α	▲	<0.0001
IL-1β	▲	<0.0001
IFN-α2	▲	<0.0001
IFN-γ	▲	<0.0001
Granzyme B	▲	<0.0001
IL-8	▲	0.03
IL-12	▲	0.007
IL-2	▲	0.02
TNF-α	▲	0.0002
IL-17D	▲	<0.0001
CD40	▲	<0.0001
IL-6	▼	0.04
IL-10	▼	0.04
GM-CSF	▼	0.04
IL-4	▬	ns
IL-15	▬	ns
MIP-1α	▲	<0.0001
IL-33	▲	0.0005
PD-L1	▲	0.0009
IP-10	▼	0.0006
MCP-1	▼	0.006
MIP-1β	▼	0.04

Immune response to BCG treatment

Cytokines	BCG therapy
IL-1RA	▲
IL-1α	▲
IL-1β	▲
IFN-α2	▲
IFN-γ	▲
Granzyme B	▲
IL-8	▲
IL-12	▲
IL-2	▲
TNF-α	▲
IL-17D	▲
CD40	▲
IL-6	▲
IL-10	▲
GM-CSF	▲
IL-4	▬
IL-15	▬
MIP-1α	▬
IL-33	▬
PD-L1	▬
IP-10	▬
MCP-1	▬
MIP-1β	▬

▲ Activated ▼ Inhibited ▬ Variable

# Unlocking the power of Alpha1H- Advancing precision cancer therapy

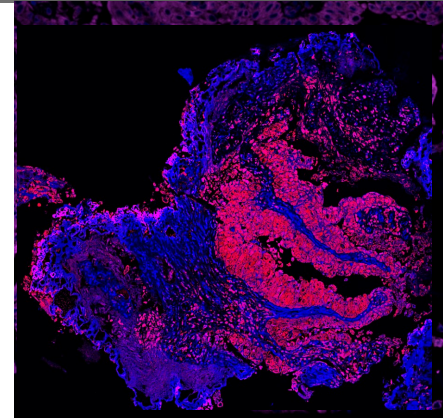
## Alpha1H - the anti-cancer discovery

Hamlet Pharma conducts drug development based on the drug candidate Alpha1H – a synthetic variant of HAMLET, with strong anti-tumor effects and a successful large-scale production method for clinical trials. The HAMLET family of molecules is a rich source of candidates with broad biological effects.

## Alpha1H for bladder cancer – the clinical breakthrough

- **Clinical stage:** Alpha1H has successfully passed Phase I/II and dose-escalation studies for the treatment of non-muscle invasive bladder cancer (NMIBC).
- **Clinical results:** Recent combined data analysis from the two clinical study parts showed **a significant reduction in tumor size – 82% reduction of tumors treated with the higher dose** and 45% reduction of tumors treated with the lower dose of Alpha1H.
- **FDA clearance of IND and Fast Track status. Continued trials towards Phase III in dialogue with the FDA**

**Strategy:** The primary commercialization strategy involves partnering/out-licensing of Alpha1H to a pharmaceutical company, for continued development and markets access. The strategy also involves partnering of the Alpha1H molecule for other cancer indications and exploring additional biological properties, such as effects on lipid metabolism.



*Cell shedding from bladder tumor biopsy: Tumor biopsy showing the shedding of cells from one region of the tumor in urinary bladder after treatment with Alpha1H (white line). The body of the cells are represented with magenta and the nuclei with blue.*



Hamlet Biopharma

# Alpha1H: Bladder cancer – An unmet medical need

## Bladder cancer: a global concern with high mortality and financial burden

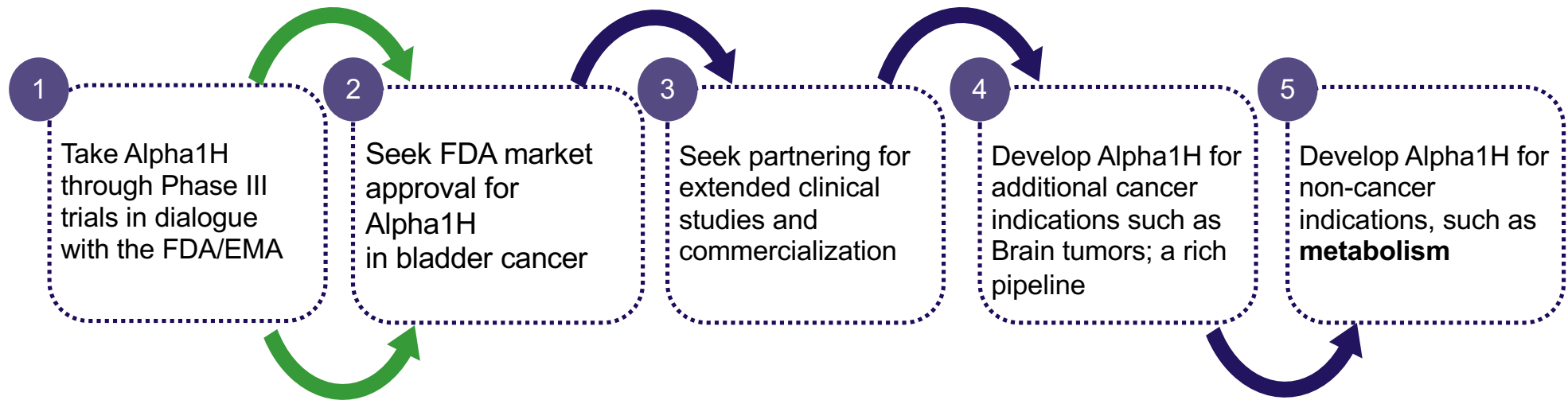


World:  
573,278 new cases  
ASR/100,000, 5.6

- The fourth most common malignancy in the United States and fifth in Europe.<sup>1,2</sup>
- The most expensive cancer indication in the US.
- More than 80% of patients with early bladder cancer recur after complete surgical removal of the first tumor.<sup>3</sup>
- Few efficient treatments. Great unmet need for new safe and effective treatments that prevent recurrences and stop disease progression.
- High mortality is mainly caused by the lack of effective therapies and the high recurrence rates.<sup>1-4</sup>
- Huge and growing market

1) [EUCAN. Bladder cancer statistics](#). 2) [NIH. Cancer Stat Facts: Bladder cancer](#). 3) [van Rhijn, \*Eur. Urol.\* \(2009\)](#). 4) [Globocan WHO](#).

# Alpha1H – Future strategy

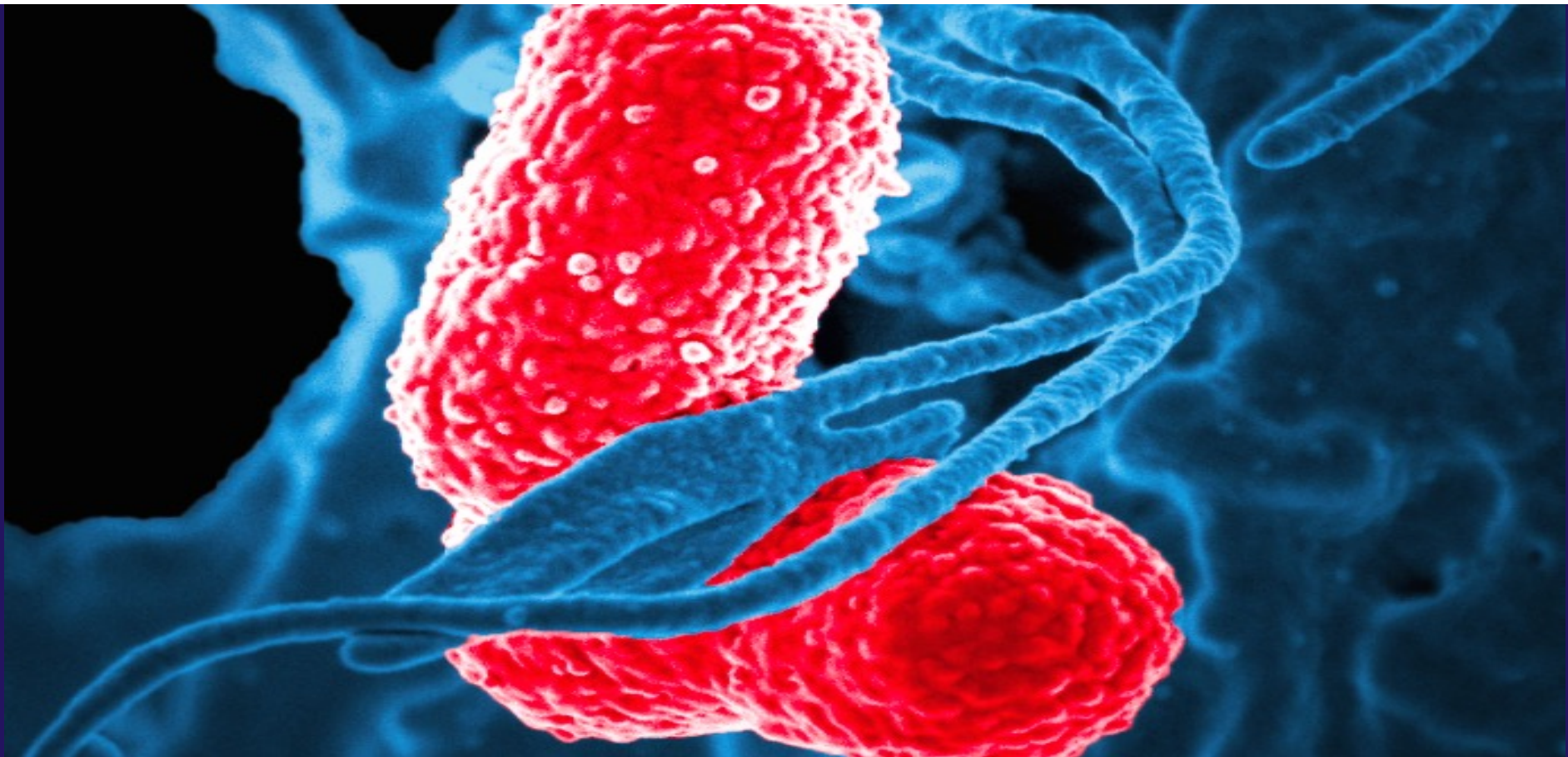


Strategic roadmap for the future development of Alpha1H family



## Immunomodulation– Bladder pain syndrome & acute cystitis

Alternatives to antibiotics are crucial, world-wide. Killing the bacteria is not enough!

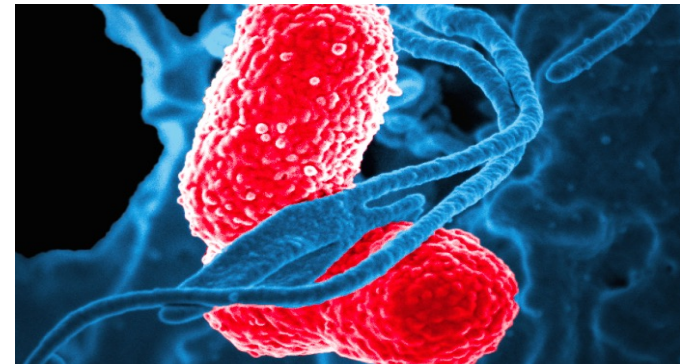


# The IL-1 receptor antagonist IL-1RA – Overview

## Immunotherapy has great potential

### In Phase II clinical trials: IL-1RA

- **Phase II projects:**
  - Indication I – Bladder pain syndrome
  - Indication II – Recurrent acute cystitis
- **Straight-forward regulatory process as the drug IL-1RA is in clinical use**



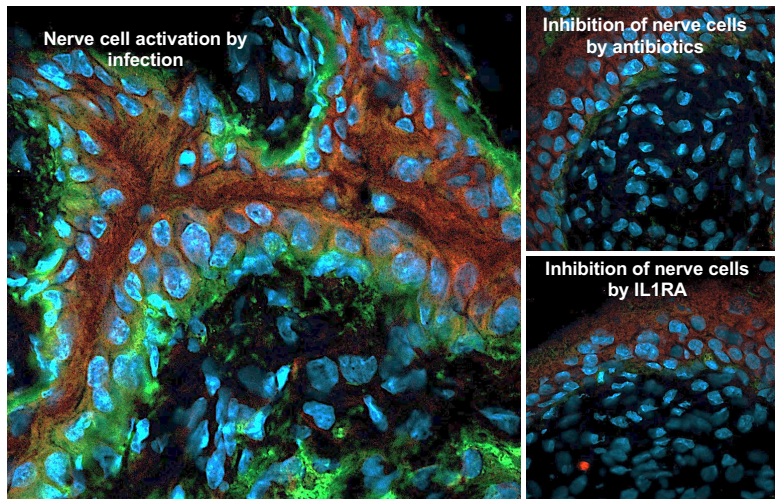
### Targeted medical problems

- **Bladder pain:** Affecting 0.1% of the global population, this disease causes severe, chronic lower urinary tract symptoms, socially and professionally debilitating. No long-term treatments available; morphine is the gold standard. Bladder removal surgery may cause lasting effects.
- **Recurrent acute cystitis:** Recurrent cystitis is usually defined as three episodes of urinary tract infection (UTI) in the previous 12 months, or two episodes in the previous six months.

# IL-1RA – Bladder pain syndrome treatment

## Indication I: Direct effects of infection on nerve cells - IL-1RA inhibits pain sensing

### Nerve cell activation and inhibition

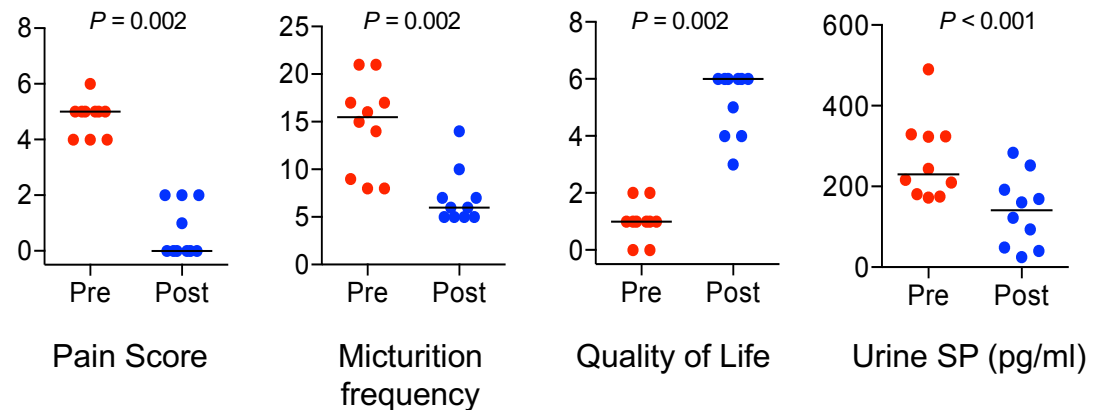


Substance P, NK1R, DAPI

### First clinical evidence of effect: Successful off label IL-1RA treatment in patients with bladder pain syndrome<sup>1</sup>

- Relief from severe symptoms
- Increased quality of life
- Laboratory findings confirm the effect

### IL-1RA - Patient response<sup>1</sup>

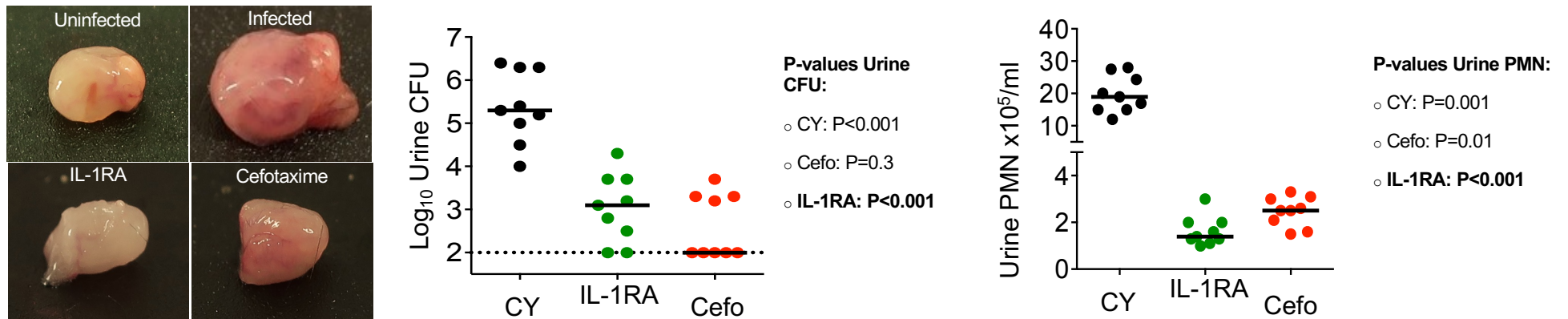


1) Wullt et al. 2021

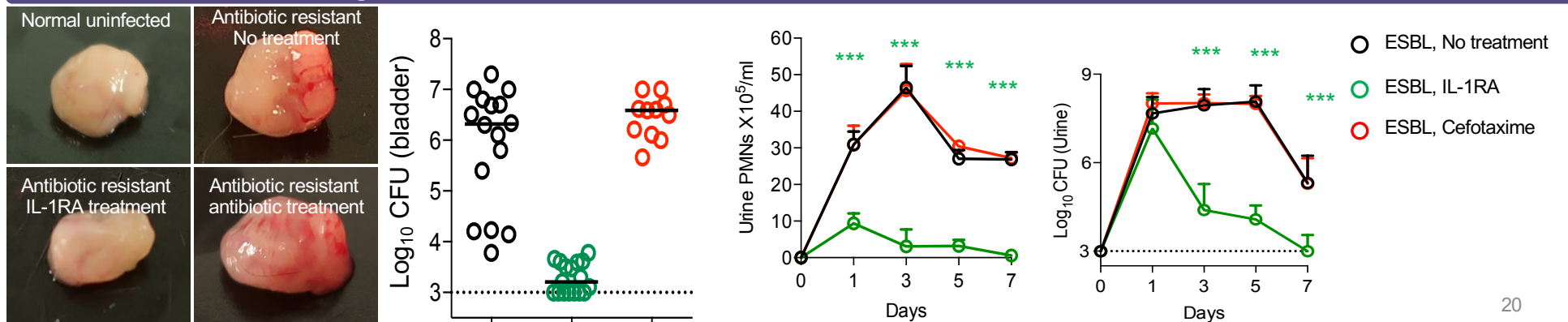
# IL-1RA – Effects on anti-biotic resistant bacteria

## Indication II: IL-1RA inhibits excessive inflammation in acute cystitis

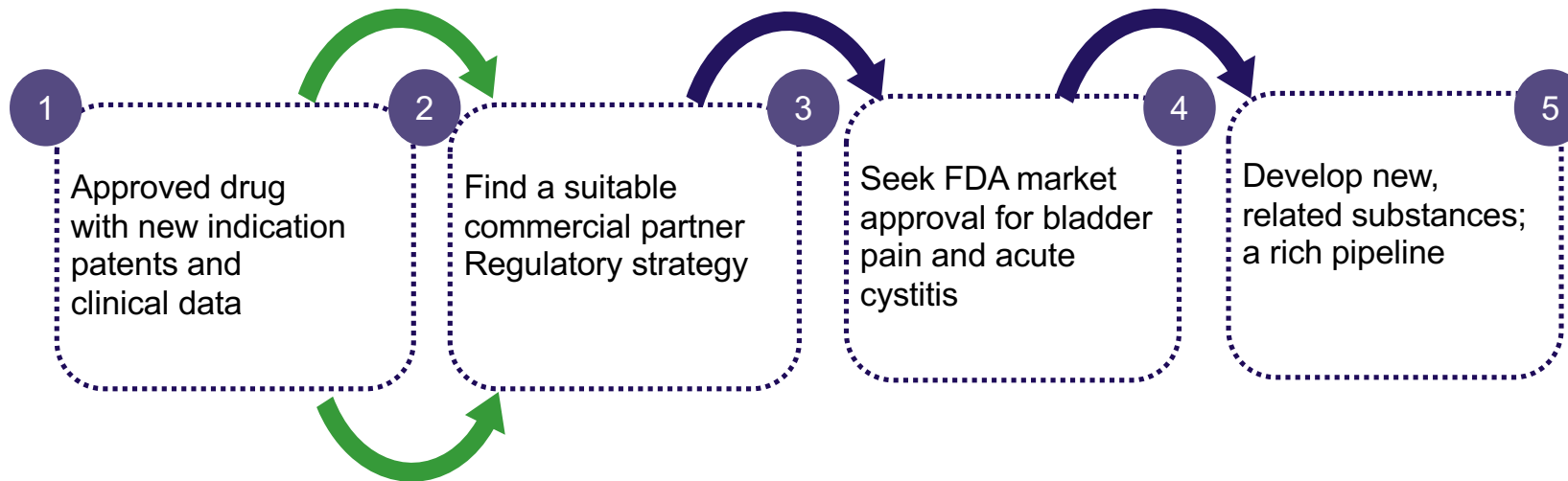
### Treatment of infection IL-1RA and the antibiotic Cefotaxime show similar efficacy



### Treatment effect of IL-1RA against antibiotic resistant bacteria



# IL-1RA – Future strategy



Strategic roadmap for the future development of the IL-RA family of therapeutics

# Pipeline – Overview of 15 projects, all with proven therapeutic efficacy in animal models

## Cutting-edge biotech pipeline: targeting cancer, infections and inflammation

Clinical		
Alpha1H	Bladder cancer	Phase II, Fast track, approaching Phase III
IL-1 receptor antagonist	Infection and inflammation	Phase II: a) Bladder pain syndrome b) Recurrent acute cystitis
Preclinical		
Alpha1H	Brain tumor	Positive data in animal model, development of technology
Hamlet	Colon and rectal cancer	Positive data in animal model
Hamlet	Oral cancer	Preclinical evaluation
NK1R-receptor antagonist	Pain and nerve activation inhibitors	Positive data in animal model, development of technology. Preparation of substance for clinical studies
RNA Pol II inhibitor - protein	Preventive anti-inflammatory and antibacterial effects	Positive data in animal model, development of technology. Preparation of substance for clinical studies
RNA Pol II inhibitor - bacteria	Prevention of inflammation and treatment of infection	Positive data in animal model, development of technology
IRF7 inhibitor, siRNA	Inhibits severe bacterial infections	Positive data in animal model, technology development. Data to support the development of drugs for clinical trials
Anti-TBC peptide	Pulmonary tuberculosis	Positive data in animal model, development of technology for drug production



Thank you  
for your  
attention

# Lead drug development projects

Name	Indication	Pre-clinical	Phase 1	Phase 2	Phase 3
<b>Alpha 1 H</b> Synthetic peptide, (N- term domain of $\alpha 1$ lactalbumin)	<ul style="list-style-type: none"> <li>Non-Muscle Invasive Bladder cancer (Placebo controlled, double blinded study + dose-escalation study)</li> </ul>				<b>Fast Track</b>
	<ul style="list-style-type: none"> <li>Brain cancer</li> </ul>				
<b>Hamlet</b> (Full size $\alpha 1$ -lactalbumin)	<ul style="list-style-type: none"> <li>Colorectal cancer</li> </ul>				
	<ul style="list-style-type: none"> <li>Oral cancer</li> </ul>				
<b>Anakinra</b> (IL-1 beta receptor antagonist) <i>New medical use</i>	<ul style="list-style-type: none"> <li>Bladder pain syndrome <i>(Placebo controlled study Phase II)</i></li> </ul>				
	<ul style="list-style-type: none"> <li>Recurrent, acute cystitis <i>(Placebo controlled Phase II)</i></li> </ul>				
<b>RNA Pol II bacterial inhibitor and other ip</b>	<ul style="list-style-type: none"> <li>Treatment of infection and prevention of inflammation</li> </ul>				



# Alpha1H: Fast track designation

## Fast Track designation for Alpha1H - treatment of bladder cancer

The U.S. Food and Drug Administration (FDA) has granted Alpha1H Fast Track Status for the treatment of bladder cancer.

This achievement builds on the momentum already gained from the FDA's earlier approval of the investigational new drug application (IND) for Alpha1H in July 2023.

This is a recognition of the potential of this innovative therapy to address bladder cancer, which is an unmet medical need.

# Hamlet Biopharma

Stock ticker: HAMLET   Spotlight Stock Market

[www.hamletbiopharma.com](http://www.hamletbiopharma.com)