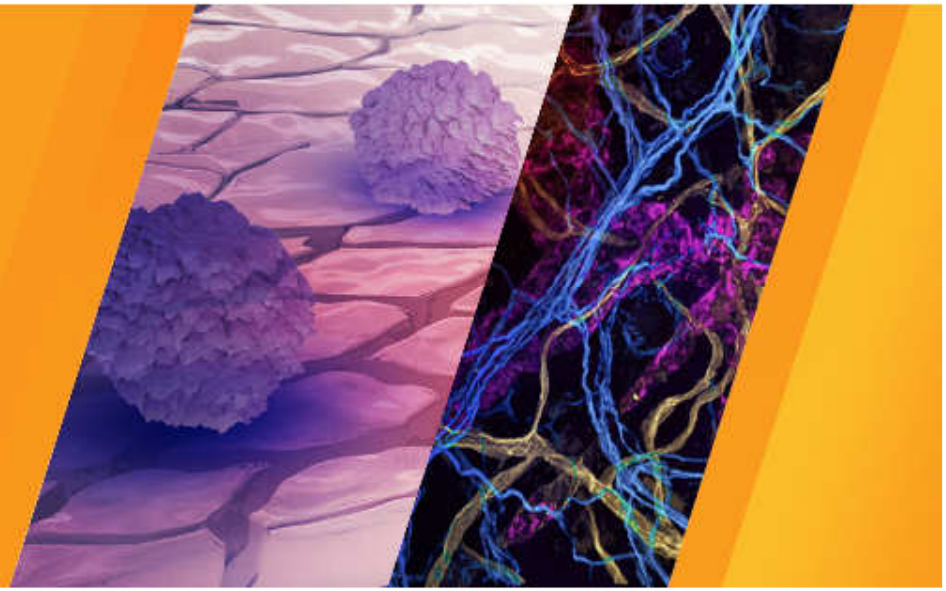
FARON
Pharmaceuticals

# SME AS A CENTRAL LINK BETWEEN BENCH AND BED SIDE



Markku Jalkanen, CEO

November 6, 2015


NASDAQ
WELCOMES
BIOTIE THERAPIES CORP.
BIOTIE
THERAPIES
Nasdaq
NJIT
#LOVEISON

# BASIC RESEARCH AS A VALUE DRIVER FOR NEW INNOVATIONS

Knowledge always beats guessing

## NEW KNOWLEDGE AND DATA ON PHYSIOLOGY OF MAN

- Glucose metabolism and GLP-1 agonists
- Cancer and PD-1 inhibitors

## DETAILED ANALYSIS OF (NEW) PATHWAYS

- New development targets (e.g. receptors)
- New actions of existing compounds (IFN-beta)

## NEW DISCOVERY METHODS

- Computer aided designs
- Robust screening systems

# INDUSTRY INTEREST IN BASIC RESEARCH

Majority of new information is created outside of industry facilities

## CO-OPERATION SAVES MONEY AND TIME

- Access to research methods and reagents
- Provides human resources

## NEW PROPRIETARY DEVELOPMENT PROJECTS

- Possibility for intellectual property rights
- Access to non-public knowhow and technologies

## RISK CONTROL

- Early analysis of data and concepts
- Exit possibility before major commitments

# BUSINESS REQUIREMENTS

Innovation is not yet a product

## PRODUCT IDENTIFICATION

- NCE, Biologics, Peptides, Nucleotides, etc.
- Manufacturing

## BUSINESS OPPORTUNITY

- Exclusivity (IP, regulatory, others)
- Target group optimization (biomarkers)

## PRODUCT RISKS

- Route of administration
- Safety
- Development plans

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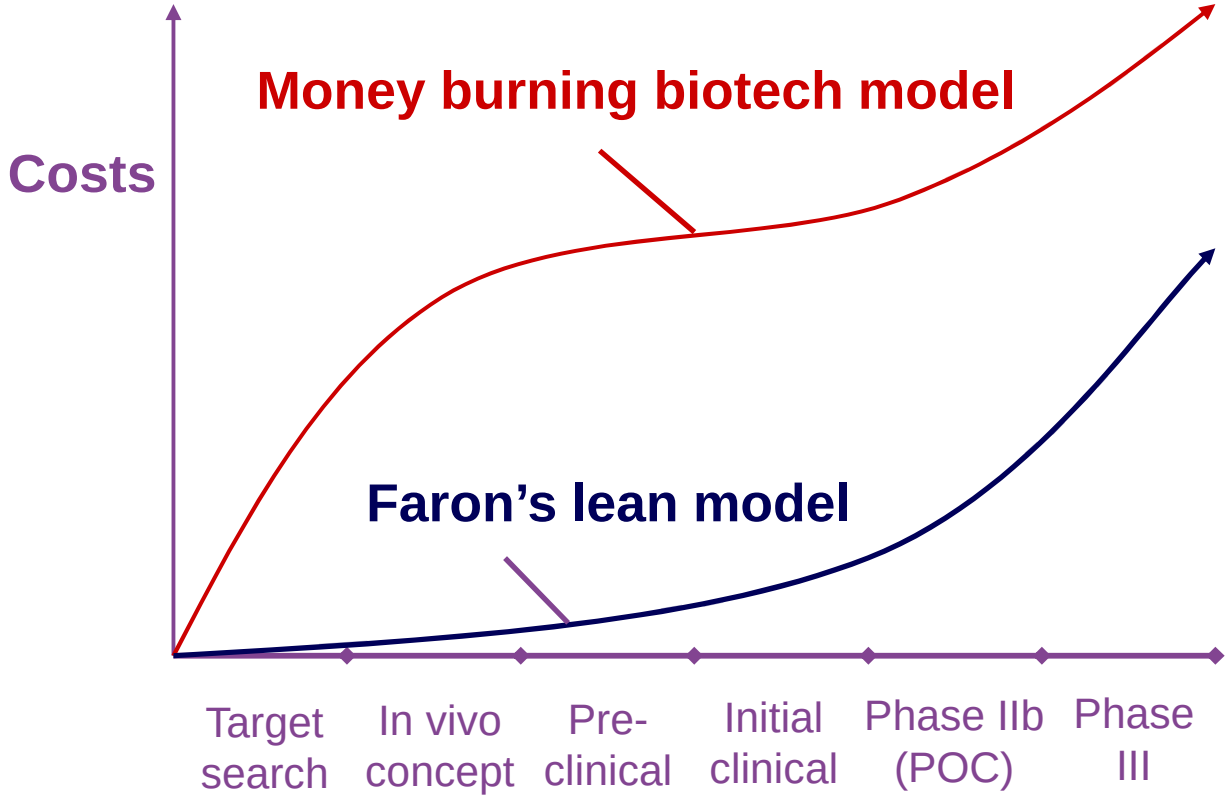
# CONQUERING ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS) AND CANCER

## Low cost approach

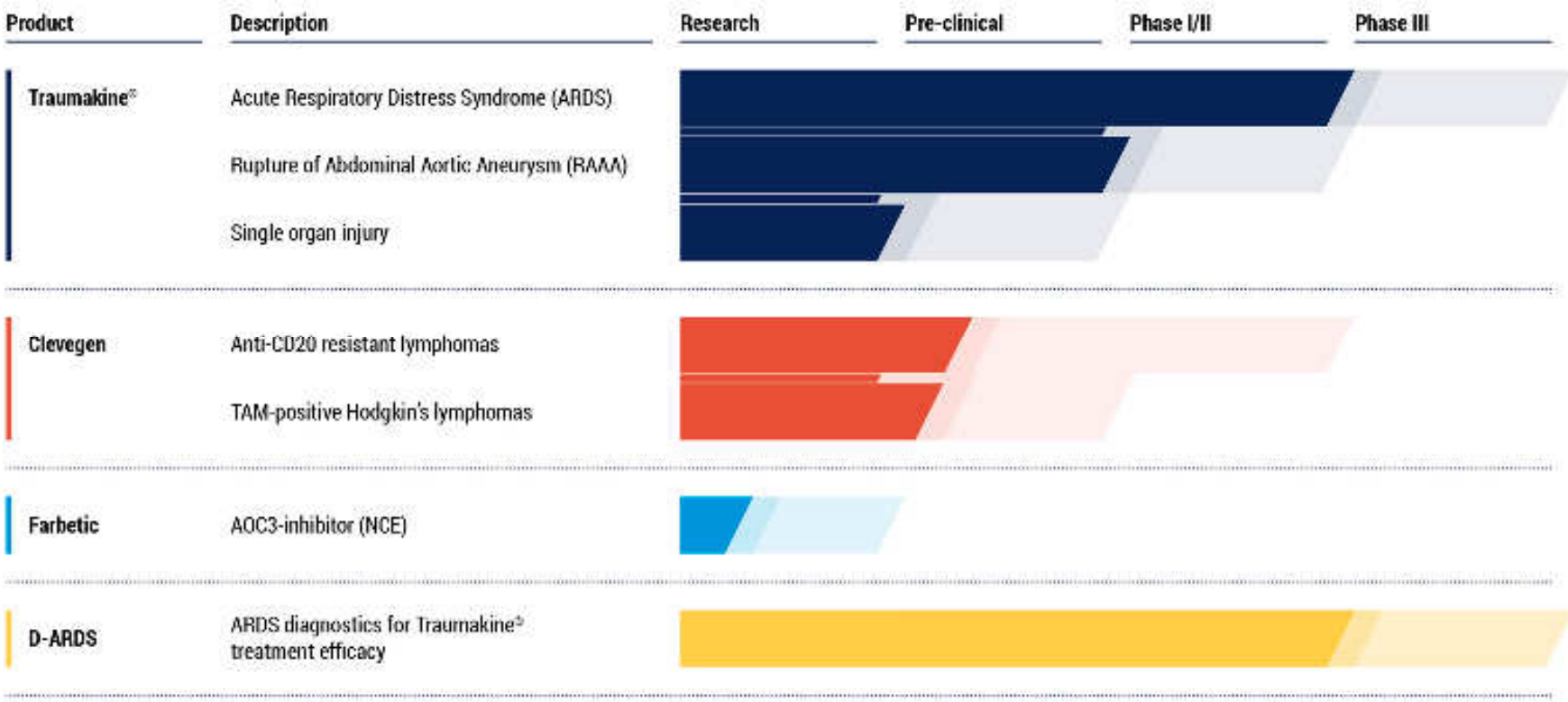
# LOW COST BUSINESS MODEL

Stepwise investment strategy with outsourcing network



# FARON SNAPSHOT

- Lean drug development company based in Turku, Finland about to be listed at London AIM
- Founded in 2007. €20+ million invested to date plus network support
- Faron's innovations are largely sourced from academia; it has developed strong links with Turku University in Finland, and arrangements with several world class laboratories and clinics




Solid bars describe current situation and shadowed parts anticipated progress with proceeds

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# ACUTE RESPIRATORY DISTRESS SYNDROME (ARDS)

## Traumakine®

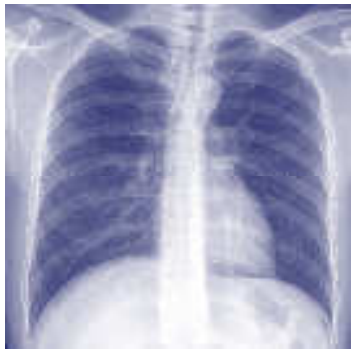
# ACUTE RESPIRATORY DISTRESS SYNDROME

## Orphan Lung Disease with No Available Drug Treatment

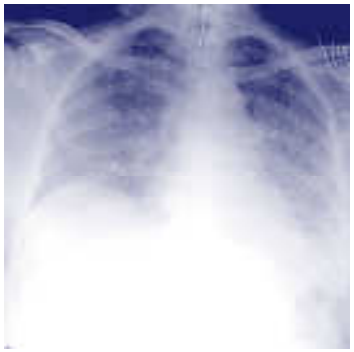
**ARDS is a rare disease characterised by vascular leakage and inflammation of the lungs and acute but persistent loss of lung function**

***Causes include: pneumonia (bacteria/virus), sepsis, aspiration of fumes, food or stomach contents into the lung and trauma (e.g. accidents)***

**Chest X-ray of ARDS patient i.e. "white lung"**



Normal Lung



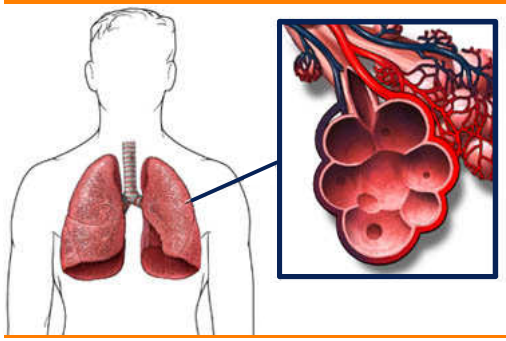
ARDS Patient Lung

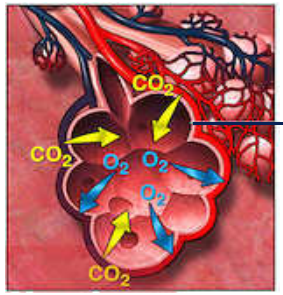
- ARDS is the leading cause of respiratory failure in ICU patients who require mechanical ventilation
- Annual ARDS incidence in Europe is 170,000 and in the US is nearly 200,000 patients
- High mortality rate of 35 to 45% and survivors suffer long term mental and physical problems
- Significant unmet medical need – currently no approved drug treatment

# TIME COURSE AND CHARACTERISTICS OF ARDS PHASES

## Prolonged Condition Ultimately Leads to Multiple Organ Failure and Death

### ALI/ARDS impacts the alveoli



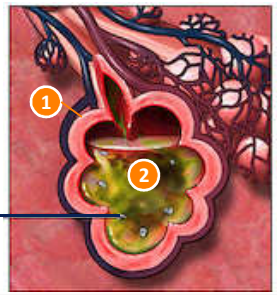



**Normal alveoli**

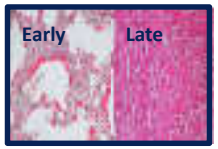
Normal gas exchange across thin alveolar walls allowing the uptake of fresh oxygen and the release of carbon dioxide

**ARDS alveoli**

Protein rich fluid from capillaries filling the alveolar space and preventing gas exchange




### Time course and characteristics of ALI/ARDS phases

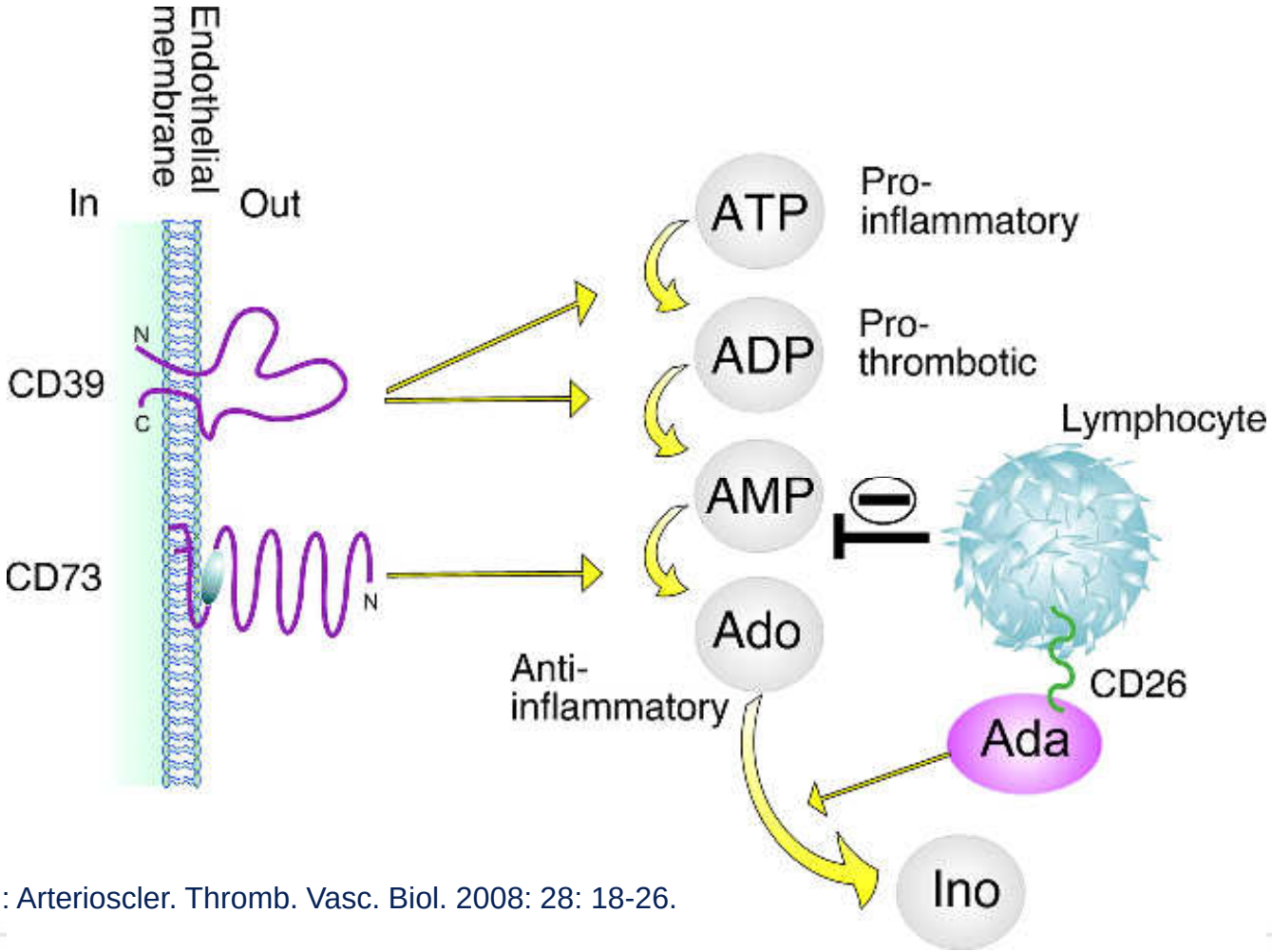
| | Timing | Micrograph | Characteristics |
|---|---|---|---|
| Exudative | < 48h |  | Characterised by accumulation in the alveoli of excessive fluid, protein and inflammatory cells that have entered the air spaces from the alveolar capillaries due to endothelial and pulmonary vascular endothelial damages. This results in refractory hypoxia and respiratory damage |
| Proliferate | ~1-2 weeks |   | Connective tissue and other structural elements in the lungs proliferate in response to the initial injury. Under a microscope, lung tissue appears densely cellular. Also, at this stage, there is a danger of pneumonia, sepsis and rupture of the lung causing leakage of air into surrounding areas |
| Fibrotic | ~2-3 weeks |  | If the proliferative stage is not resolved, the condition might evolve to a chronic phase whereby the lung is completely molded by sparsely collagenous and fibrous tissue. The surface area for gas exchange is significantly reduced. Pulmonary hypertension results from pulmonary vascular destruction |

**Generalisation of the core pathology underlying ARDS**

- The damage to the endothelium and epithelium results in the creation of an open interface between the alveoli air space and capillary (#1 on the bottom picture to the left)
- Protein rich fluid and micro-organism fills the alveoli air space and reduces the normal gas exchange needed to maintain respiration (#2 on the bottom picture to the left)
- Prolonged inflammation and destruction of pneumocytes leads to proliferation, hyaline membrane formation and lung fibrosis. The longer the condition evolves the smaller the chances of survival with the main cause of death being multiple organ failure

# EXTRACELLULAR PURINES REGULATE VASCULAR HOMEOSTASIS

## The battle of good and bad

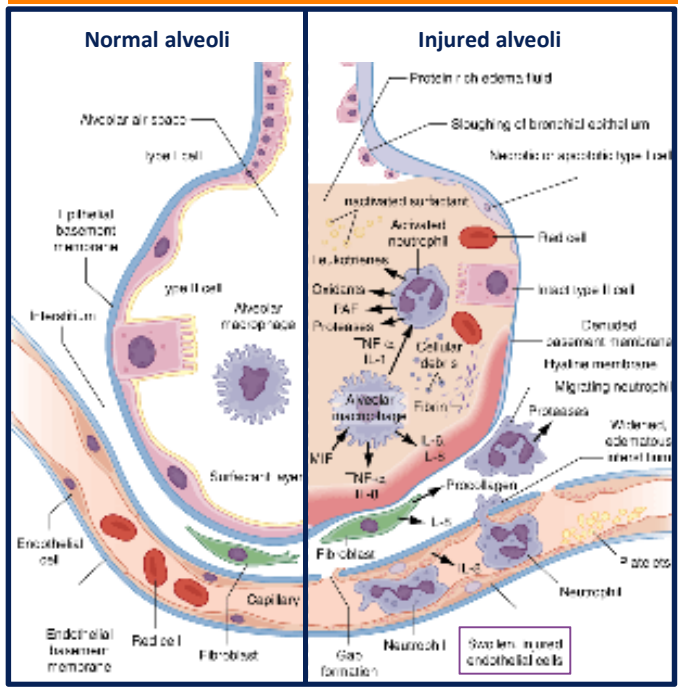


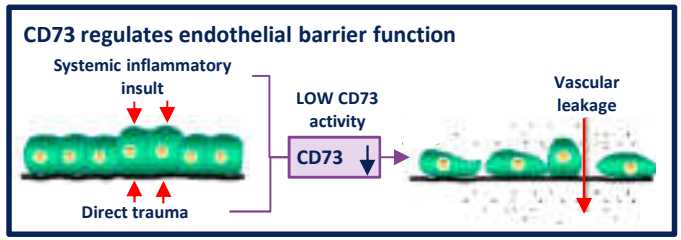

Jalkanen & Salmi: Arterioscler. Thromb. Vasc. Biol. 2008: 28: 18-26.

# TRAUMAKINE® – ENHANCES CD73 ACTIVITY

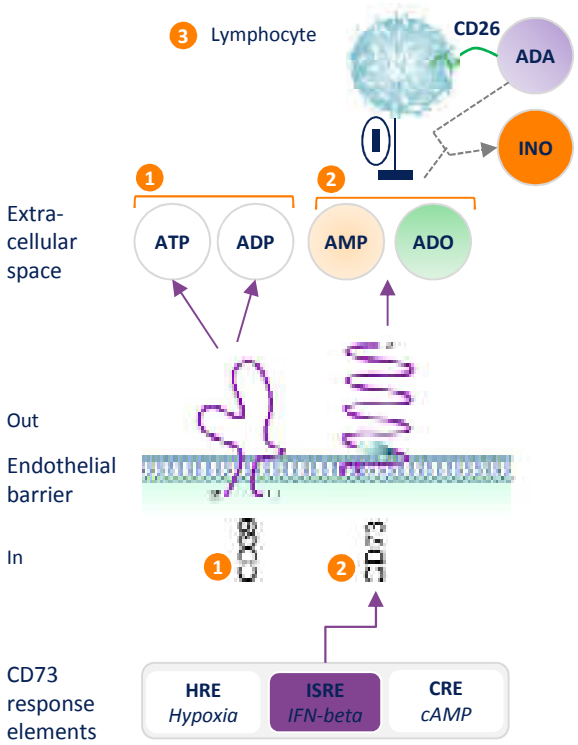
## FP-1201-lyo Prevents Early Vascular Leakage and Escalation of Inflammation

### ARDS – endothelial barrier damage




### Any compound that can increase CD73 presence is beneficial




**Adenosine production is crucial**

1. **CD39** hydrolyzes **ATP** (Adenosine-5' triphosphate) and **ADP** (Adenosine diphosphate) to **AMP** (Adenosine monophosphate)

   ATP and ADP have strong pro-inflammatory and pro-thrombotic activities

2. AMP is converted to adenosine (**ADO**) by **CD73**, which also produces adenosine locally

   Adenosine is anti-inflammatory in its effect and therefore helps to maintain the endothelial barrier

   Adenosine production can be reduced if CD73 activity is low, which occurs in ARDS and ultimately damages the endothelial barrier and leads to vascular leakage

3. Furthermore, certain leukocytes like **lymphocytes** are capable of removing adenosine through the production of **ADA** (adenosine aminohydrase) – end product **INO** (Inosine)

4. Any increase in CD73 expression can, therefore, aid the production of adenosine and reduce both vascular leakage and inflammation

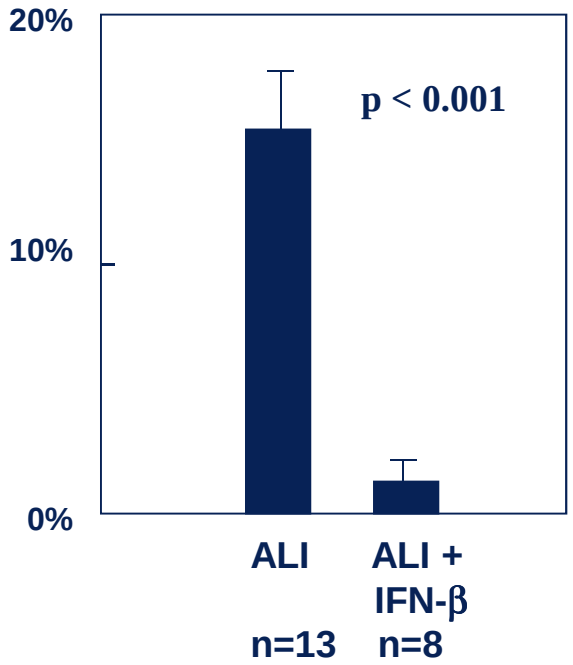
   These can be cAMP, Hypoxia and **IFN-beta**, which activate the CD73 gene

**Interferon-beta 1a (Traumakine®) enhances CD73 (5'-nucleotidase) expression and adenosine production, which inactivates pro-inflammatory and pro-thrombotic purines. This prevents both early vascular leakage and escalation of inflammation, which are the two early patho-physiological events leading to ARDS**

# PROOF OF CONCEPT STUDY IN MICE

## Vascular leakage as a surrogate marker

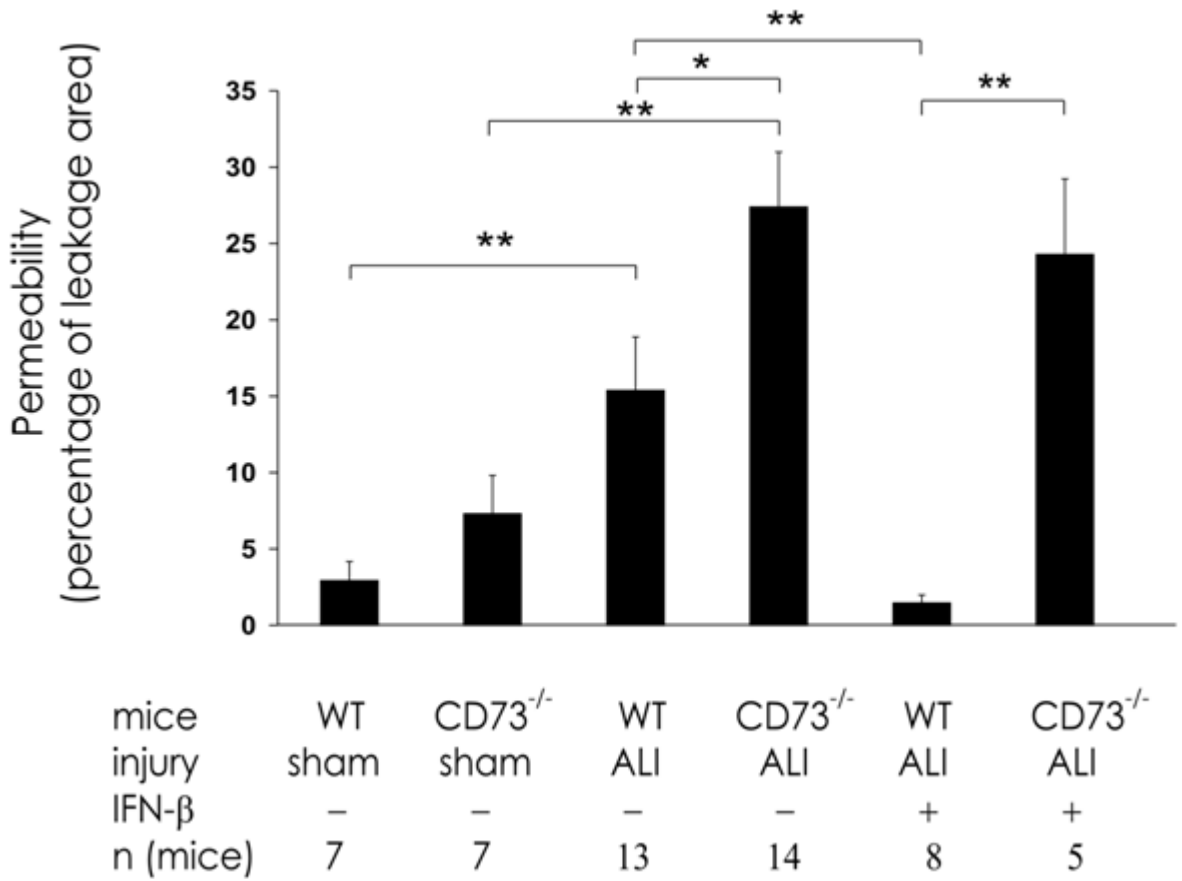
Mice were induced acute lung injury by closing mesenteric artery for 30 minutes. Simultaneously with reperfusion initiation for 4 hours, mice were given IFN-beta iv (20.000 units). Five minutes prior euthanasia mice were given FITC-dextran and leakage to lungs were measured as percentage of leakage area (n=8-13±SEM).




Kiss et al. (2007)
*Eur. J. Immunol.* 37:3334

# VASCULAR LEAKAGE IS CD73 DEPENDENT

CD73 could become a valuable biomarker for ARDS severity and treatment efficacy

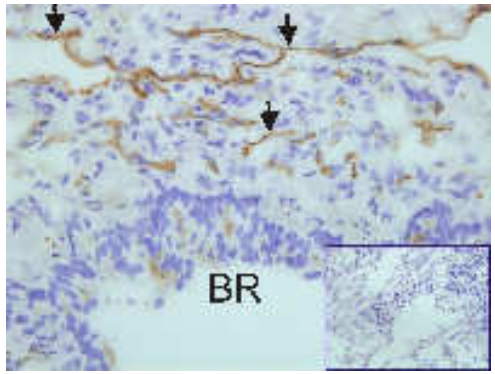


FARON Pharmaceuticals

# INTERFERON-BETA UP-REGULATES LUNG VASCULAR CD73

Repetition of animal findings with human tissues

A

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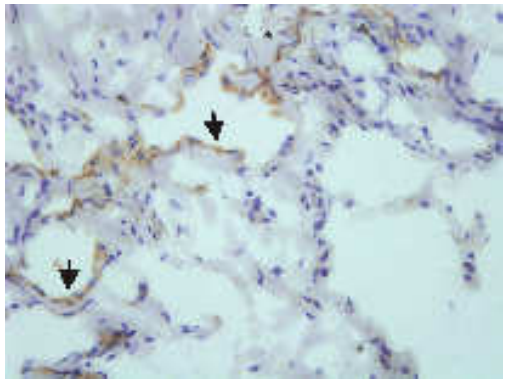

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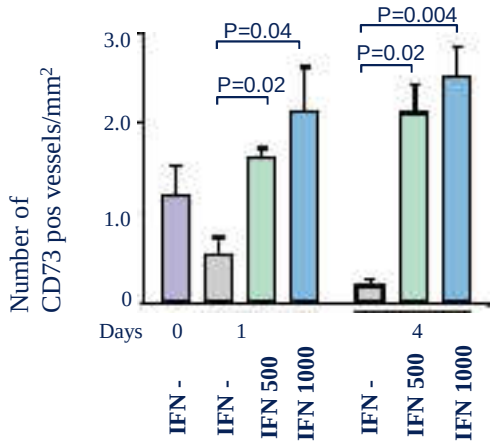


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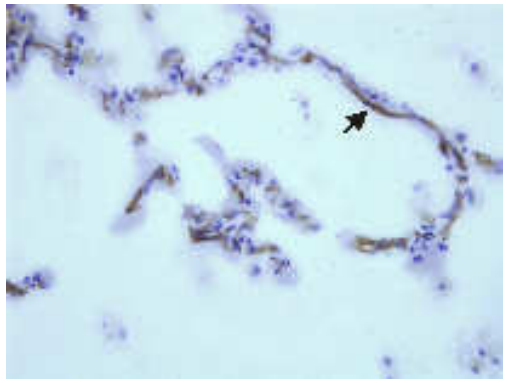

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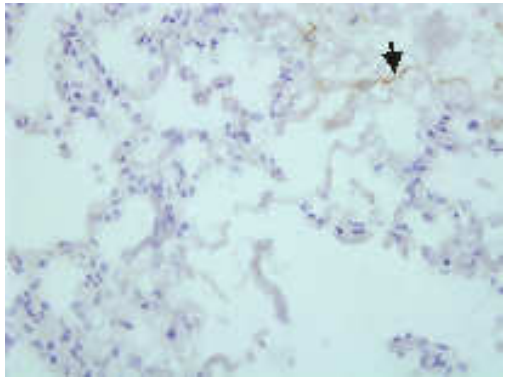
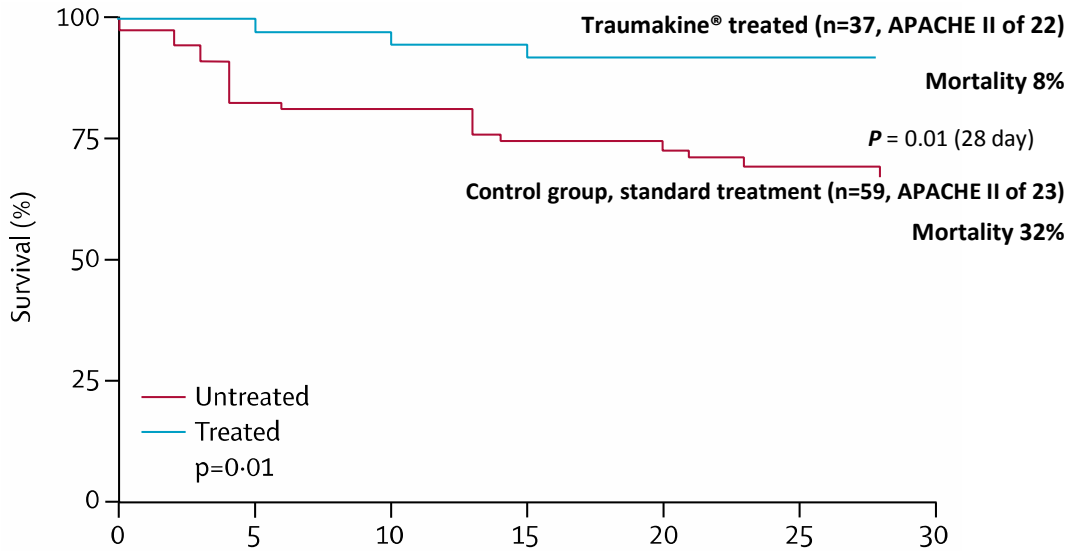


# COMPELLING PHASE I/II TRIAL RESULTS

THE LANCET Respiratory Medicine

## Data Published in World Leading Medical Journal

### Primary endpoint: significant drop in mortality*




**Phase I/II trial showed a significant reduction in mortality with positive secondary endpoints**

**World leading peer reviewed article (Bellingan et al. (2014) The Lancet Respiratory Medicine 2: 98-107) has already reached the intensive care community**

### Positive secondary endpoints

- Mortality at six months was lower than expected
- Improvement in lung function and functional assessments aligned with improvement in lung function and general dysfunction
- Efficacy improvements are consistent with a reduction in vascular leakage

*Of the 37 patients treated with Traumakine®, 32 were diagnosed with ARDS (PaO2/FiO2 ≤200 mmHg) and 5 patients were diagnosed with ALI (PaO2/FiO2 ≤300 mmHg) 30% of the treated patients were diagnosed with sepsis and 41% with pneumonia. The study was carried out in 8 ICU centers in the UK

# INTEREST PAN-EUROPEAN PHASE III TRIAL

## Aiming at conditional MA in Europe

- Randomized, double-blinded, 300 moderate/severe ARDS patients in seven countries with 54 hospital sites
- Looking reduction of all cause mortality and days in ventilator
- Powered at 90 % with 50 % reduction in all cause mortality at D28
- Recruitment in 12 months plus 6 month follow-up and extended follow-up at 12 months
- Compelling results, based on EMA advise, will allow filing of conditional application for marketing approval

# TRAUMAKINE®

## Coordinated development roles for various Parties


### BASIC

- Discovery of the role of CD73 in endothelial barrier formation
- IFN-beta as an inducer of CD73 expression

### INDUSTRY

- Exclusivity (IP)
  - European Orphan Drug Designation status granted; 10 years market exclusivity from marketing approval +2 years subject to making a paediatric application
- Clinical
  - POC phase I/II study
  - Pivotal pan-European Phase III INTEREST trial
    - €6 million European Grant* for development of Traumakine® obtained together with academics
- Manufacturing arrangement secured by outsourcing

*EU/FP7 grant received by consortium, including Faron, University College London Hospital, University of Turku and University of Torino

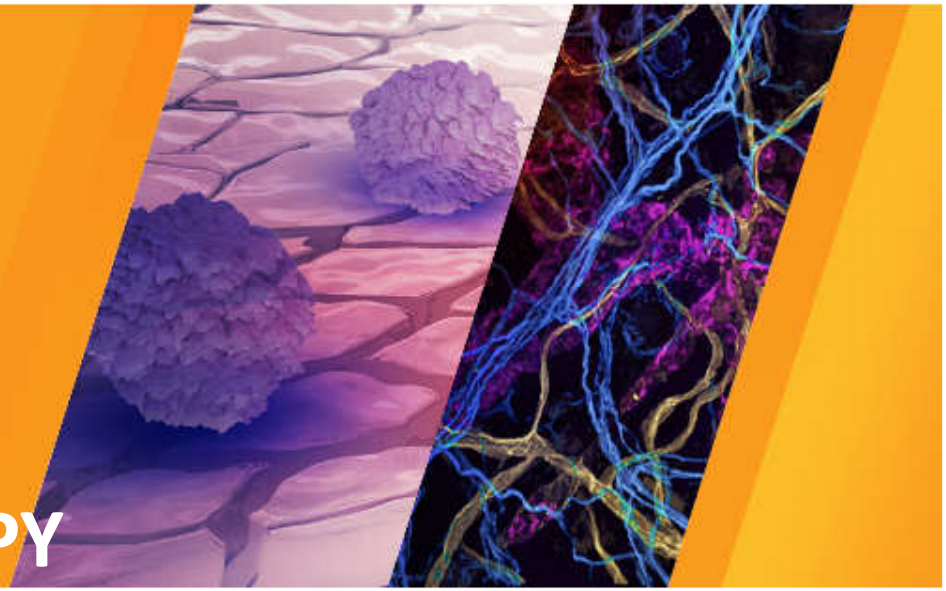
# MANUFACTURING ARRANGEMENT SECURED

## Production ramp-up with no Additional Significant Investment Expected

TRAUMAKINE Rentschler Biotechnologie

***Rentschler Biotechnologie is one of the biopharmaceutical industry's top contract manufacturing organisations and has significant experience in the production of interferon beta***


- The product is lyophilized (freeze-dried), which enables room temperature storage for up to 2 years
- Proprietary IV formulation
- Marketed as a daily administration kit readily available for bed side use
- CMC part is ready for CTA: Approved in Japan in October 2014
- Annual manufacturing capacity of more than a million treatments



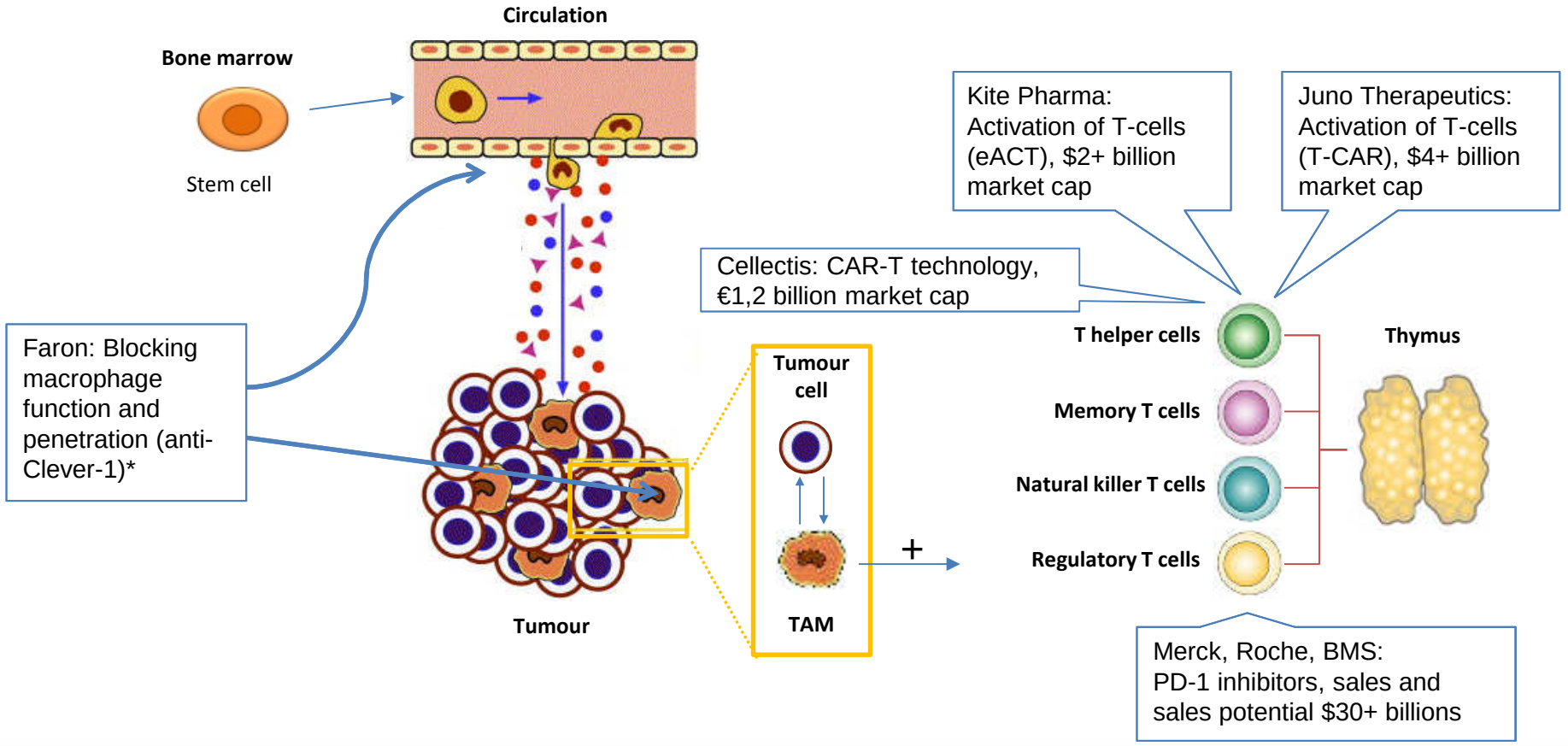
# CANCER IMMUNOTHERAPY

CLEVEGEN

# CANCER IMMUNOTHERAPY

## Promising Approaches to Intervene Tumour Immune Suppression

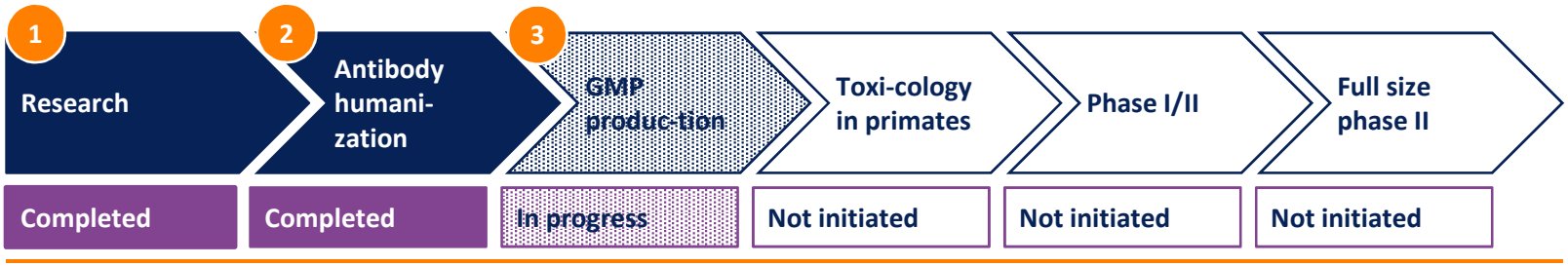
**Clevegen targets tumour activated macrophages (TAM), best known immune suppressive cells overruling also the T-cells**




*Karikoski et al. (2014) Clin. Cancer Res. 20:6452-64

# CLEVEGEN DEVELOPMENT PHASE

**Faron has carried out anti-Clever-1 antibody humanization – GMP next step**




**1**

- In 2003, the company entered into a collaborative relationship with inventors who had discovered Clever-1
- In December 2014, Faron's research network published a scientific paper. According to the in vivo research, Clever-1 is a central molecule for cell migration through vascular endothelia
- In experiments carried out on mice, anti-Clever-1 treatment has reduced primary tumors and metastases to 30 % compared to the control group. Anti-Clever-1 treatment has also shown to reduce the number of type 2 macrophages and regulatory T cells in experiments carried out on rabbits

**2**

- Faron has carried out anti-Clever-1 antibody humanization in collaboration with antibody technology company Antitope Ltd., based in Cambridge, UK
- Antitope's technology "Composite Human Antibodies" also provided de-immunization of the immunoglobulin backbone. This is important for humanized anti-Clever-1 antibodies as they are anticipated to remove immune suppression against tumor cells and removal of T cell epitopes will reduce possible reaction against them as well

**3**

- The fully humanized anti-Clever-1 antibody FP-1304 is ready for early GMP production and is currently in further mechanistic analysis

# FIRST TAM LICENSING DEAL BETWEEN BMS AND FIVE PRIME

*Commercial potential undisputed*

**TARGET**

- Global strategic immuno-oncology collaboration focused on development of Colony Stimulating Factor 1 Receptor (CSF1R) antibody program (FPA008) targeting TAM removal
- Combination therapy with the leading PD-1 inhibitor (Opdivo, nivolumab) in oncology indications
- Current development status in phase 1a/b (several small trials)

**DEAL VALUE**

- Total deal value of $1.74 billion including a $350 upfront payment
- Double-digit royalties on future sales plus co-promote right in the US

**MAJOR CONCERN**

- FPA008 blocks both M1 and M2 TAMs, which could result in removal of guardian macrophages from the draining lymph nodes promoting further cancer growth and spread.

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ENDOTHELIAL BARRIER IS EVERYTHING