

# ***Examples of Innovation and Risk Management: Perspective from University and Industry***

***EUFEMED Conference 2017***

***Professor Alan Boyd PFPM***

***18<sup>th</sup> May 2017***

Faculty of Pharmaceutical Medicine  
of the Royal Colleges of Physicians of the United Kingdom

*Advancing the science and practice of pharmaceutical medicine for  
the benefit of the public*



# Topics for Discussion

- Innovation – what is driving it and why it's needed
- Innovation Examples from Universities and Industry and how risk has been managed during Development
  - Gene Therapy Based Products
  - Repurposing Medicines
  - Immunotherapy

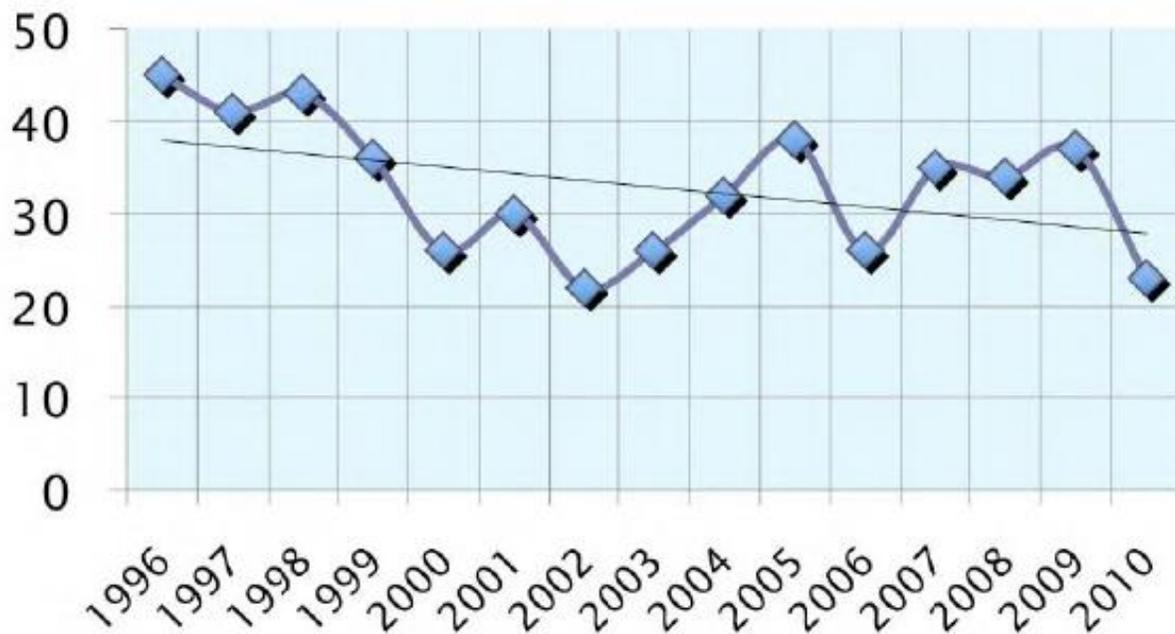


# Drug Development – Innovation and What Drives It

- Discoveries about the molecular basis of disease provide unprecedented opportunities to translate research findings into new medicines.
- BUT developing a brand-new drug takes an enormous amount of time, money and effort.
- Translation of a promising molecule into an approved drug takes between 10-12 years on average and estimated to cost around US\$2,870million (Tufts 2016)
- Crucial to advance strategies to reduce this time frame, decrease costs and improve success rates.



# NME\* Applications to CDER (Last 15 Years)



Calendar Year	Applications Filed
1996	45
1997	41
1998	43
1999	36
2000	26
2001	30
2002	22
2003	26
2004	32
2005	38
2006	26
2007	35
2008	34
2009	37
2010	23

In fact, except for 2002, the 23 NME applications to CDER filed in 2010 is the lowest number filed in more than 15 years.

\*2004-2010 represents applications for New Molecular Entities (NMEs) filed under New Drug Applications (NDAs) and therapeutic biologics filed under Original Biologic License Applications (BLAs). 2001-2003 represents NMEs but not therapeutic biologics.



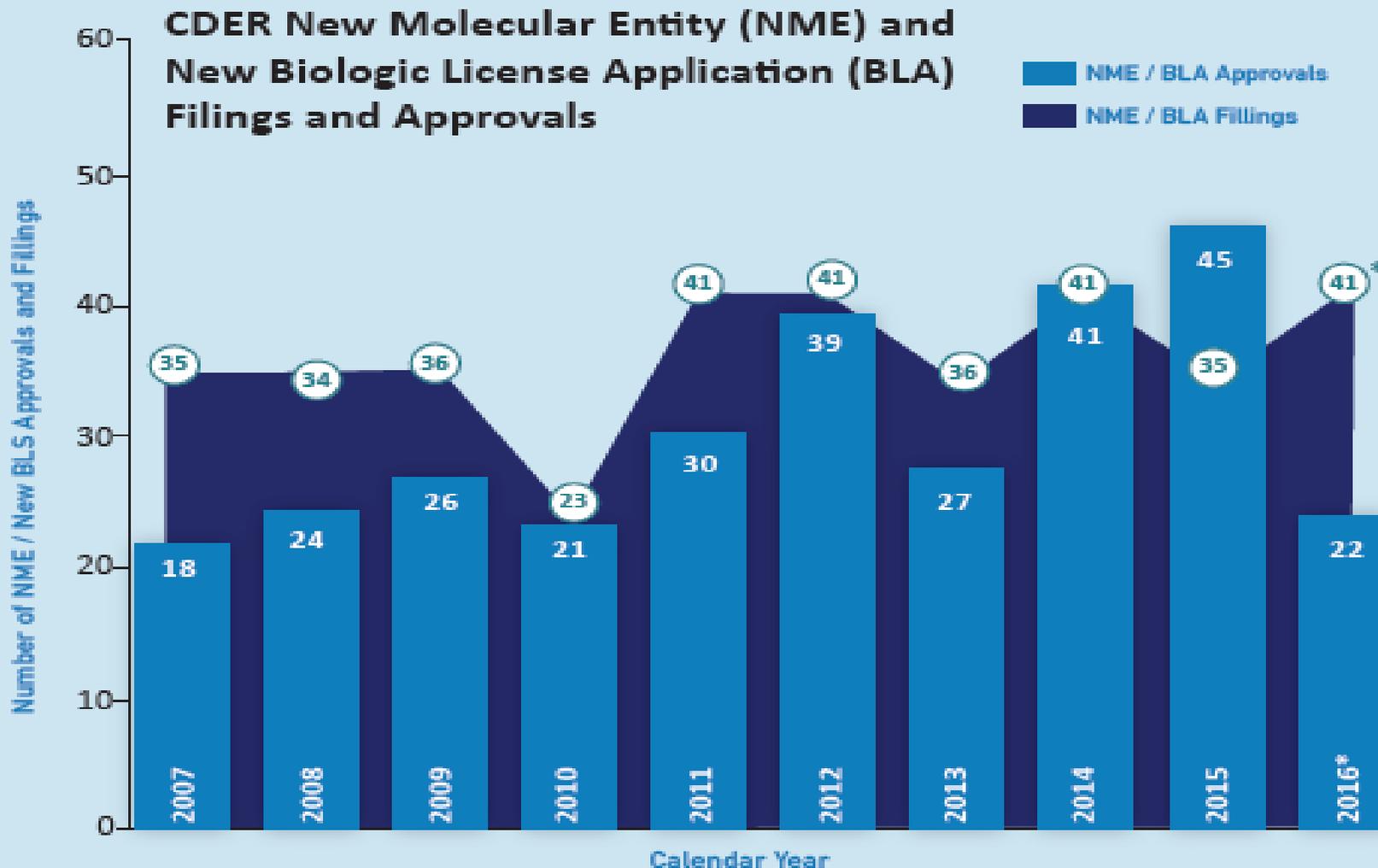
# 22

novel drug approvals in CY 2016 is less than the average number approved annually during the past decade

From 2007 through 2015 CDER averaged about

# 30

novel drug approvals per year



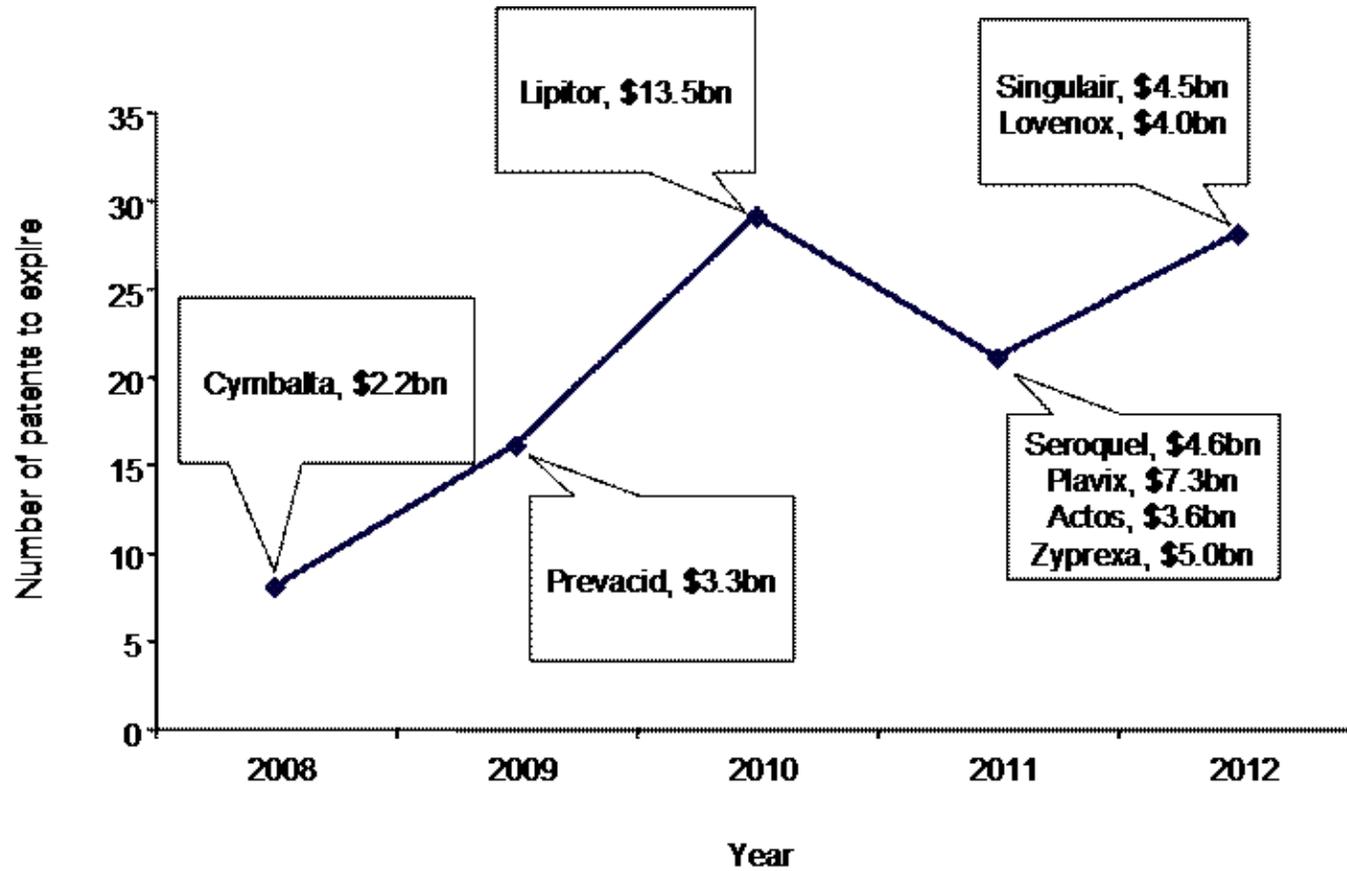
# In-Licensing Opportunities by Pharma

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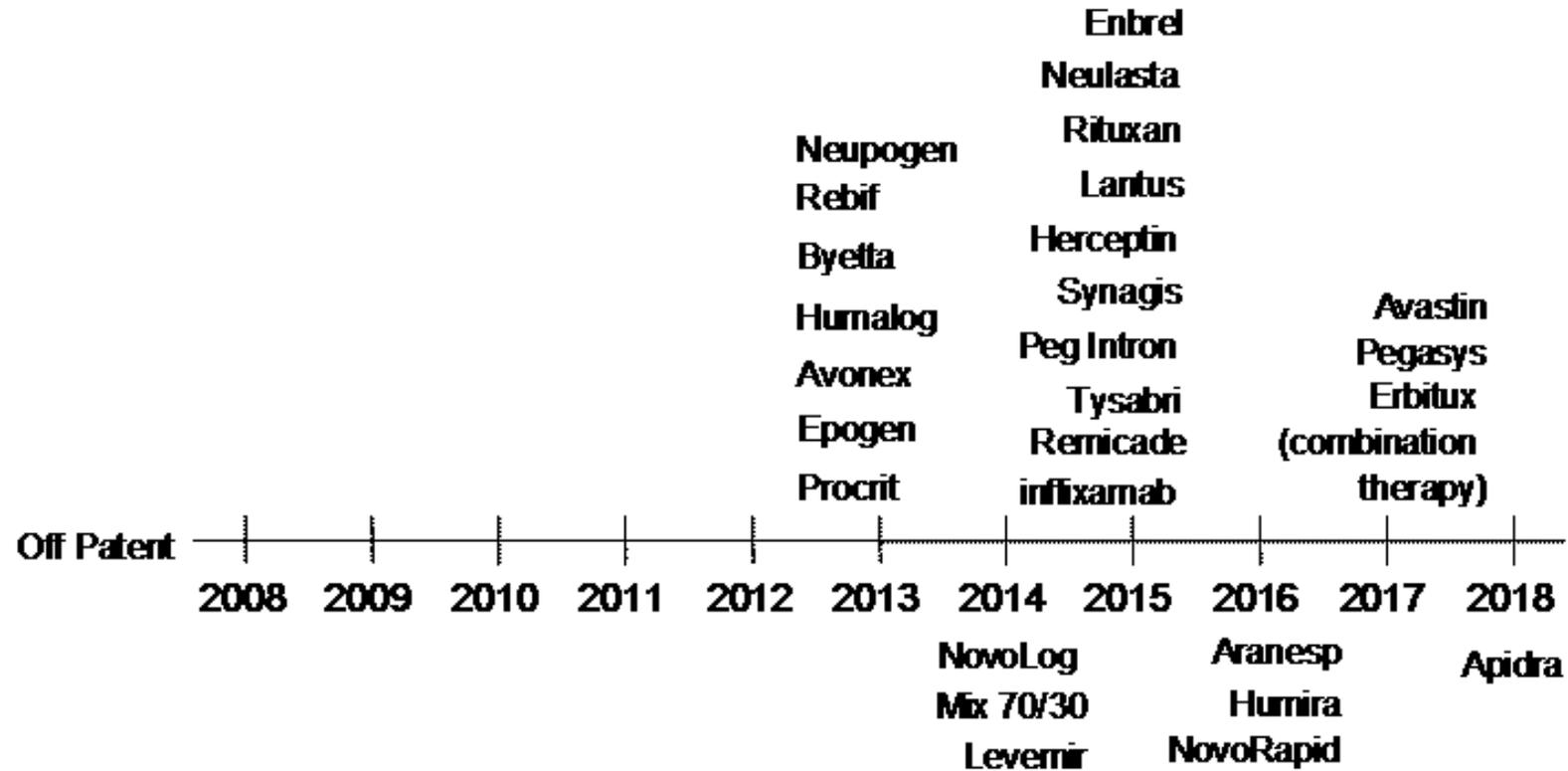
- In-licensing increasingly important as a way of filling 'product gaps'
- In-licensed products now make up about 25% of the total revenue of the top 20 Pharma
- Licensing deals increased significantly over past 10 - 15 years
- Pfizer & GSK – companies with largest sale forces are most active in-licensees.
  - In 2002 Pfizer generated U\$15.1 billion or 53% of total revenue from in-licensed products – Lipitor® – worlds best selling drug
  - AstraZeneca – 2015 – Total Sales U\$24.75 billion – Crestor® - Sales U\$5.0 billion – companies #1 product – 20% of sales



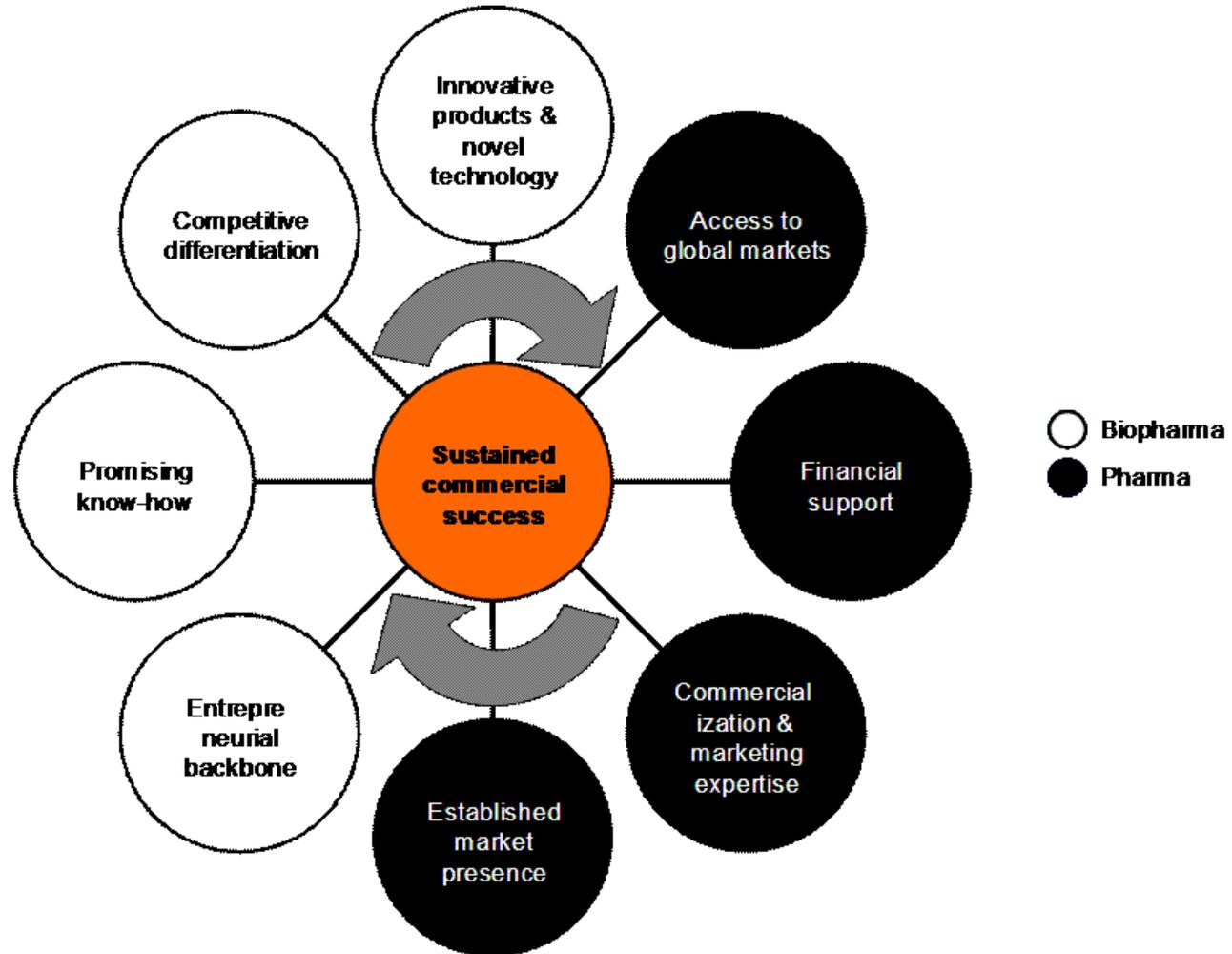
# Drug patent expiries in the US, 2008-2012



# Estimated last patent expiry dates of selected proteins



# Strengths of Biopharma and Pharma



# Gene Therapy Example



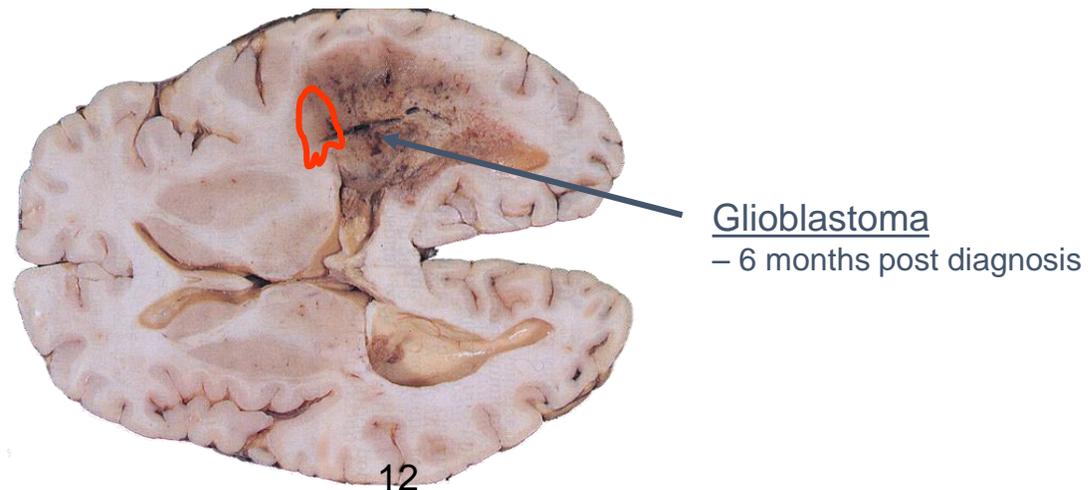
# Gene therapy delivering a therapeutic protein as a treatment modality

Ark Therapeutics & Cerepro<sup>®</sup>  
for  
Malignant Glioma



# Clinical Problem – Treatment of Malignant Glioma

- Malignant glioma - cancerous tumour confined to the brain
- c.38,000 cases p.a. (US and Europe)
- Standard care
  - Surgical removal of tumour with / without radio- and chemotherapy
  - Most recently licensed pharmaceuticals extend life by an average of 10 weeks
- Most patients die within one year of diagnosis



# CEREPRO™

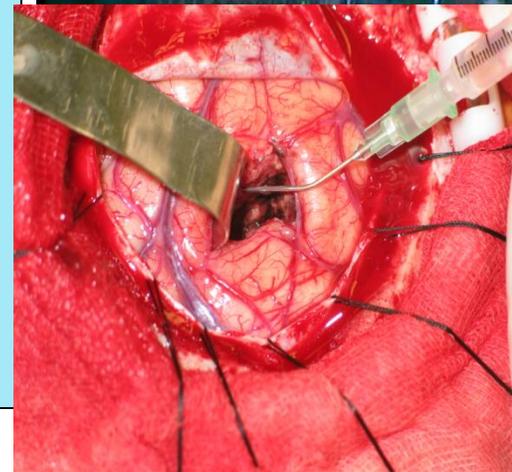
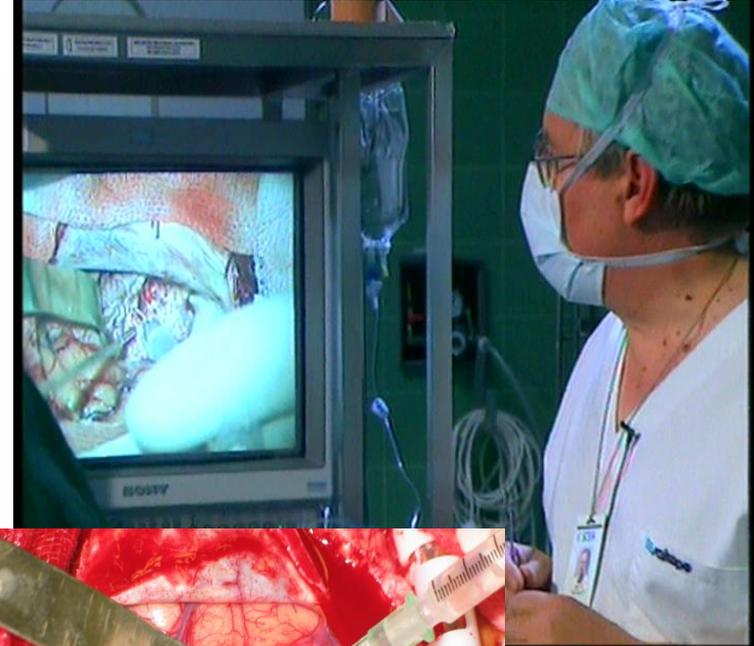


- Devastating disease - very poor prognosis
- Cerepro™ - developed for the treatment of operable primary & recurrent high grade glioma
  - Has survival benefits extending life on average by 7 months
  - Given in addition to Standard Therapy
- Orphan Drug Designation in EU & USA
- Marketing Authorisation was submitted to EMA for consideration

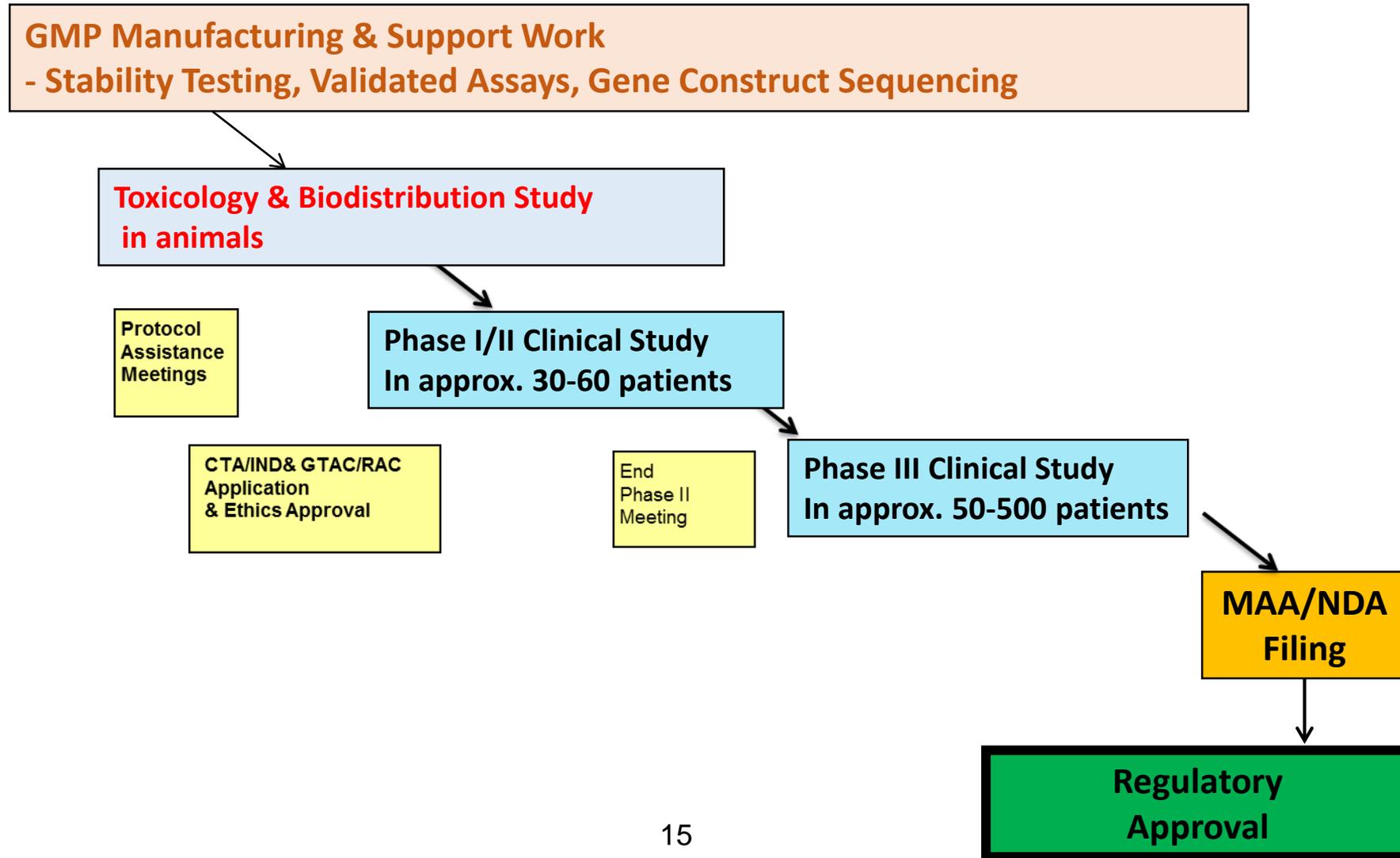


# Cerepro™ – High Grade Glioma Treatment

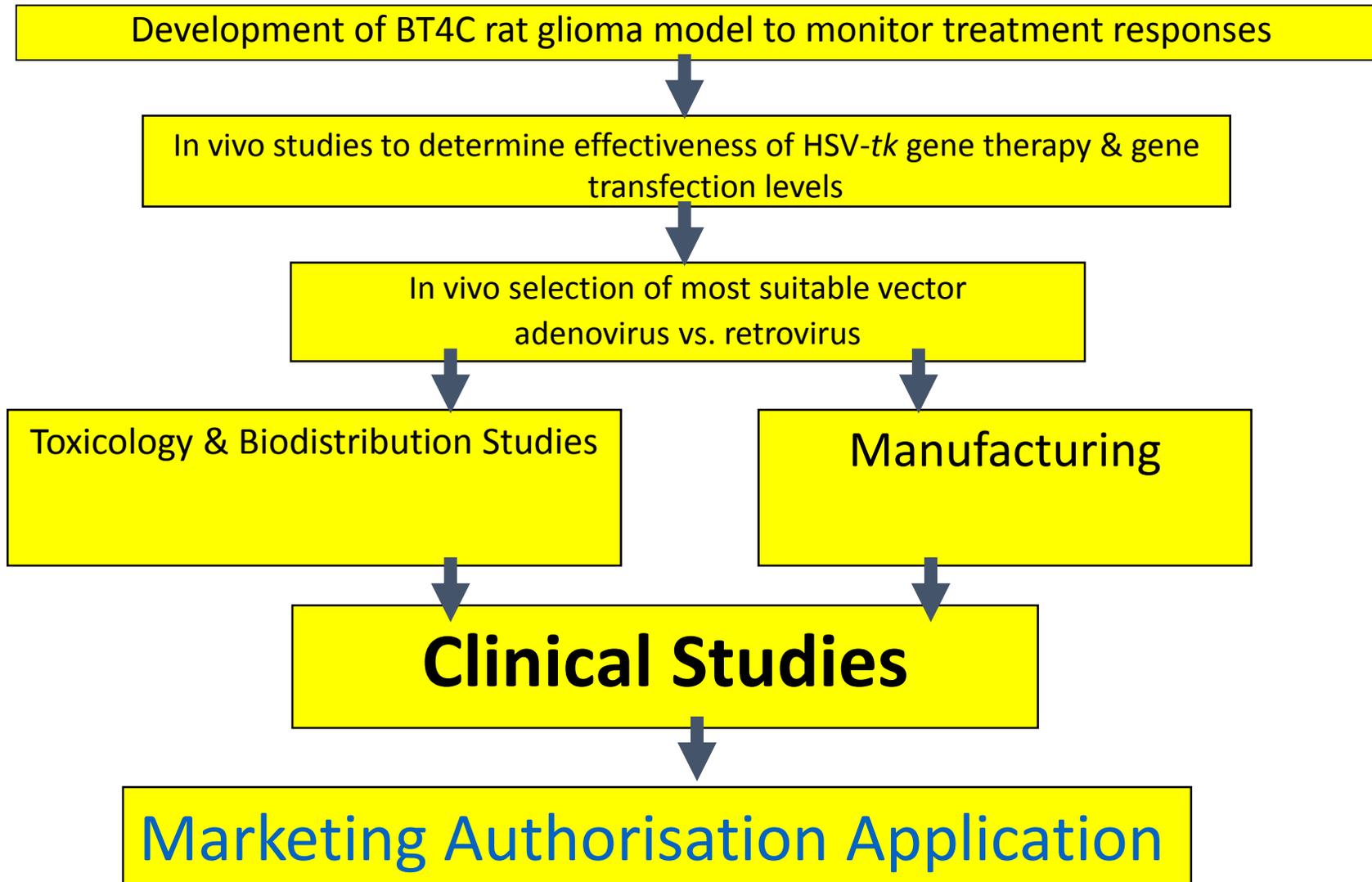
- Surgery to resect tumour mass
- Cerepro™ Adv.HSV-*tk* gene injected into wall of tumour cavity - underlying healthy neurones
- Ganciclovir given intravenously from 5 days post surgery for 14 days
- In brain Adv.HSV-*tk* gene protein product - thymidine kinase phosphorylates ganciclovir
- Phosphorylated ganciclovir kills any proliferating tumour cells. Does not harm healthy neurones



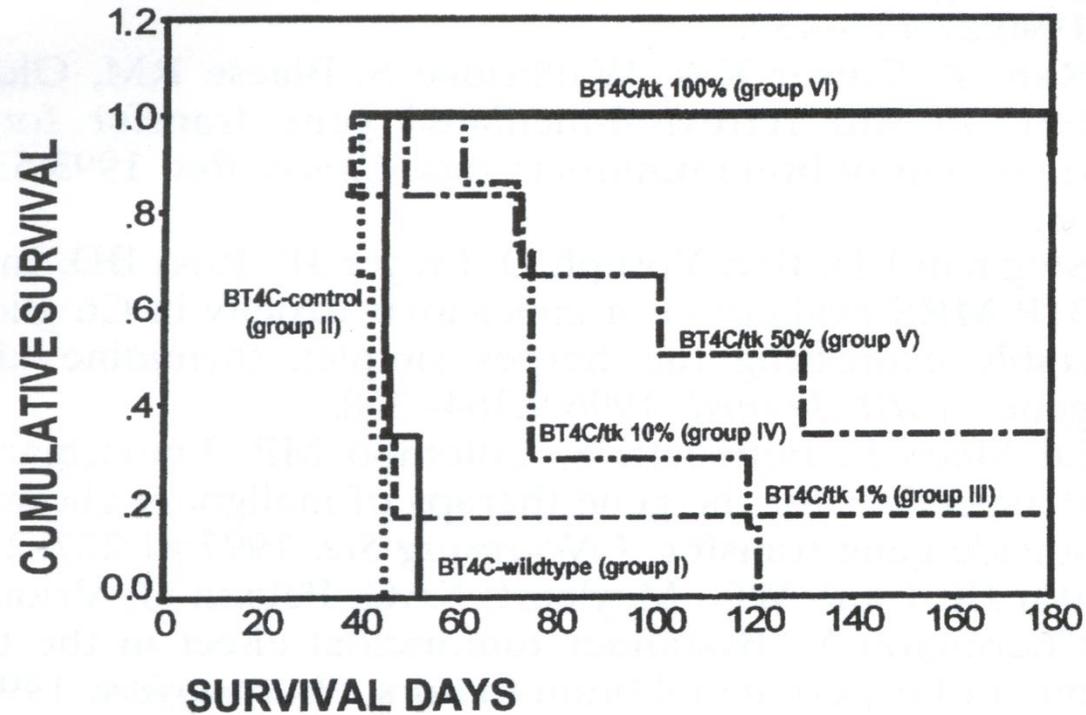
# Gene Therapy – Overall Development Process



# Cerepro™ - Development Pathway



# Survival of rats with BT4C Malignant Glioma



>10% transduction efficiency was needed for a successful therapeutic effect

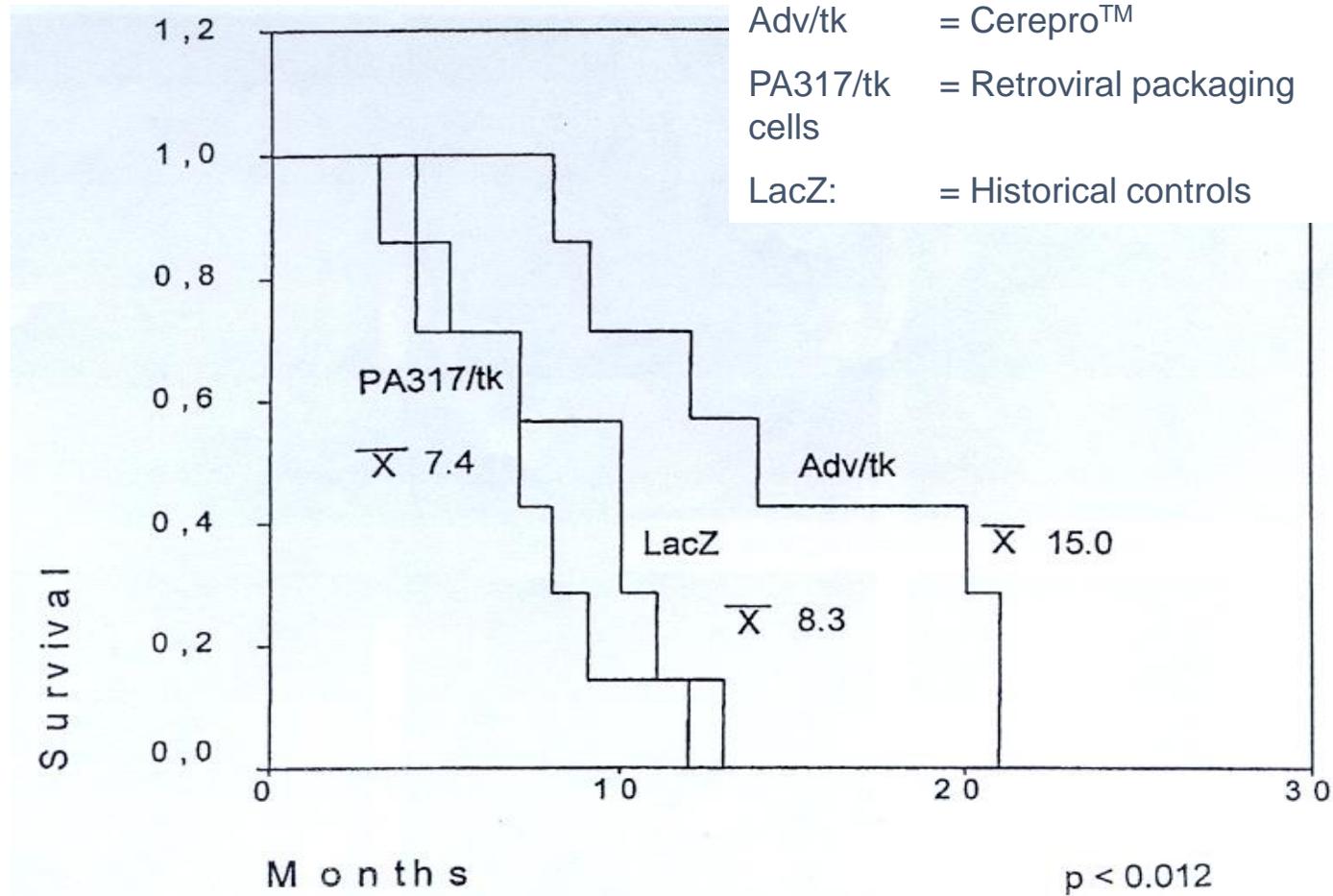
# Cerepro™ – Toxicology & Biodistribution Study in Rats



- Single Toxicology & Biodistribution Study to GLP in Rats
- Design agreed with EMEA
- Injection of Cerepro™ into the brain +/- GCV therapy
- Group also given Cerepro™ IV +/- GCV therapy
- Control Group
- Followed for up to 90 days
  
- Results supported progression into humans



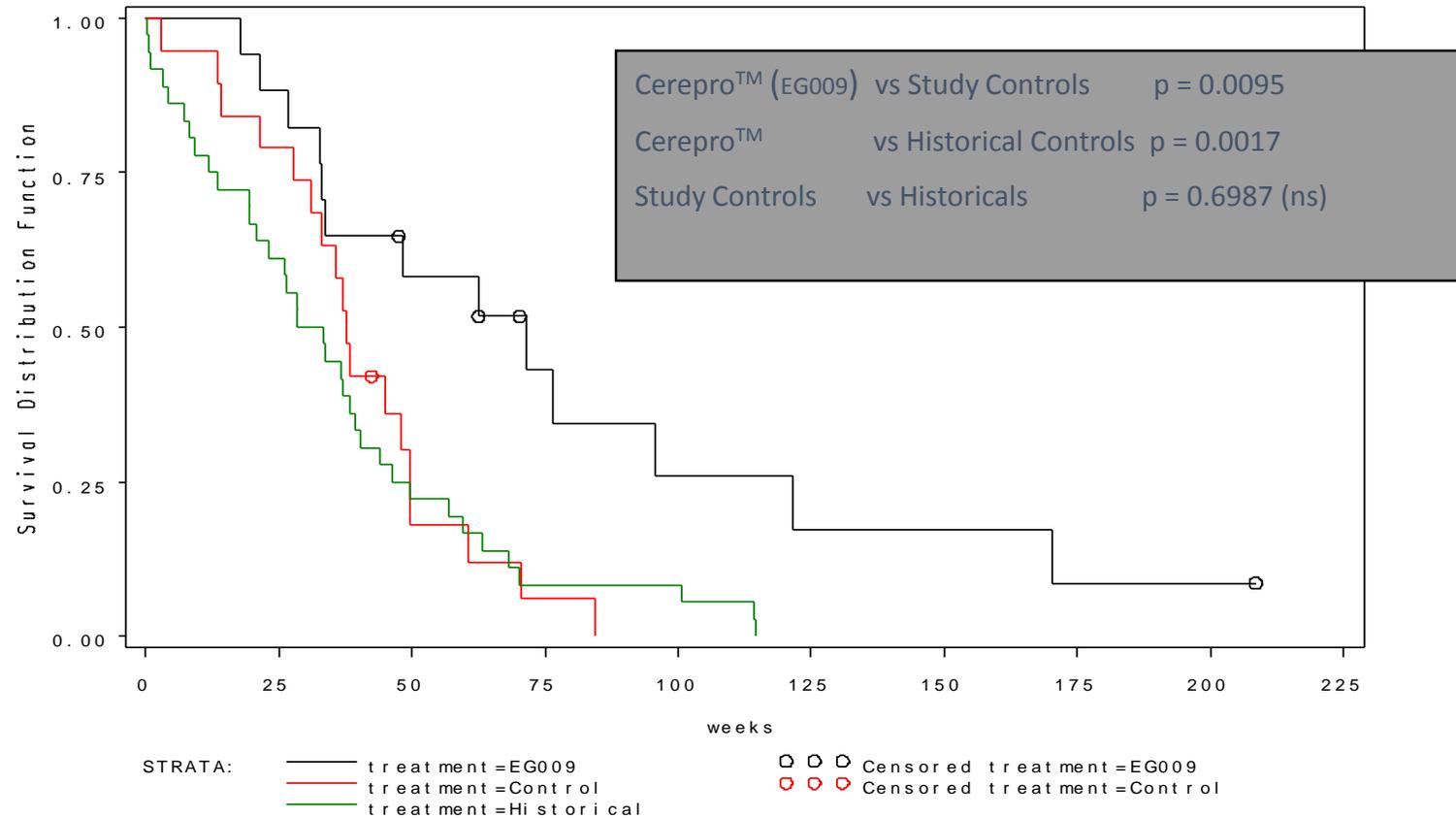
# Phase I & Phase II Study - CLINICAL EFFECTS



# PHASE III RESULTS – CEREPRO vs Standard Care vs Historical Controls



Primary Endpoint – All patients



*A Immonen et al, Molecular Therapy 2004,10; Nov(5): 967-972*





# Cerepro™ Conclusions

- Scalable Manufacturing Process to cGMP with fully validated potency and product release assays
- Efficacy of gene transfer established in humans
- Dose finding studies & vector selection performed in humans
- Patients treated with Cerepro™ had a survival advantage over those patients treated with standard care alone
  - Randomized, controlled study design, with significant improvement in survival ( $p > 0.0095$ )
- Cerepro™ was well tolerated and had an acceptable safety profile
- Quality of Life was maintained.
- Cerepro™ offered a promising advance in the treatment of operable high grade glioma in an area of unmet clinical need.

**Marketing Authorization Application Rejected**



# Drug Repurposing Examples



# A Different Approach to Drug Innovation - Drug Repurposing

- Drug repurposing as an Innovation solution.
- Many medicines approved for other uses - already been tested in humans, so detailed information available on pharmacology, formulation and potential toxicity.
- Repurposing builds upon previous research and development efforts, new candidate therapies ready for clinical trials quickly and do give a faster route to market and patients.



# Jump Start into Drug Development

## De novo drug discovery and development

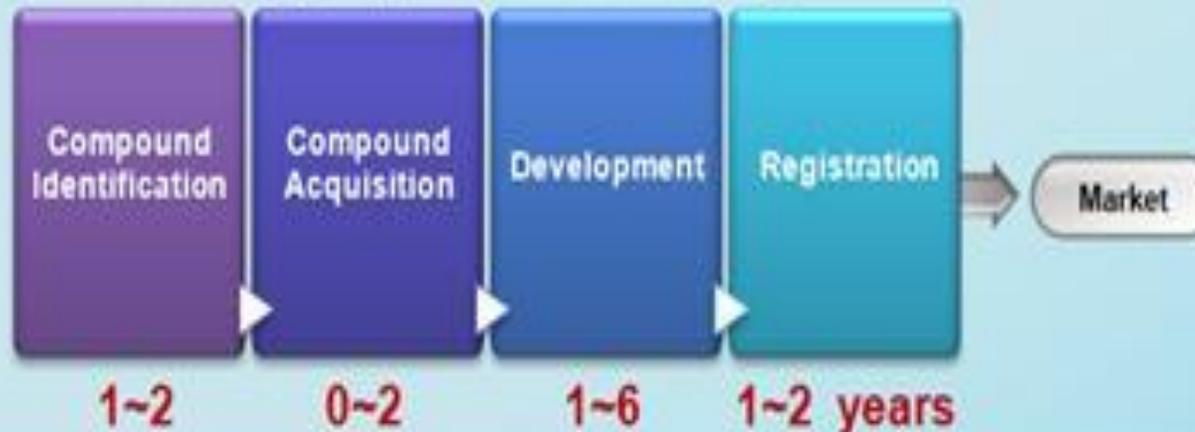
- 10~17 year process
- <10% overall probability of success



## Drug Repositioning

- 3~12 year process
- Reduced safety and pharmacokinetic uncertainty

# Drug Repositioning



# Case Histories

## Ark Therapeutics – ACE Inhibitors for Cancer Cachexia



# Cancer Cachexia



- Cancer cachexia is a devastating, multifactorial and often irreversible syndrome that affects around 50–80% of cancer patients
- Leads to substantial weight loss, primarily from loss of skeletal muscle and body fat.
- Account for up to 20% of cancer deaths.
- Mechanism believed to be related to activation of the inflammatory response and energetic inefficiency involving the mitochondria.
- No known treatment for this condition
- Cachexia also occurs with CHF, Respiratory Disease and HIV



# Use of ACE-Inhibitors

- Prof Hugh Montgomery at UCL
  - Identified that mitochondria in muscles in cachexia have an activated renin-angiotensin pathway
  - Suggested that ACE-Inhibitors could reverse the effects
  - Animal Models of Cachexia responded to ACE-Inhibition
  - Able to Patent this idea
- Ark Therapeutics – initiated a development programme to treat Cachexia with ACE-Inhibitors



# Use of ACE-Inhibitors – Risk Mitigation Steps

- Source of ACE-Inhibitor – Imidapril from Tanabe in Japan
  - Administered once daily 5 to 20mg/day
- Problems in giving an anti-hypertensive to patients with advanced cancer
- Utilised the Pharmacokinetic parameters to design a dosage regimen
- Resulted in a novel dosage regimen
- Divided daily dose with dose titration
- Manufactured capsules with different dose amounts than marketed product
- Commenced a Phase 2/3 Study



# ACE-Inhibitors in Cachexia - Result

Ark Therapeutics - News Announcement

## Ark Therapeutics Grp - Research Update

RNS Number:2905T

Ark Therapeutics Group PLC

28 October 2005

Preliminary Results of Vitor™ Study Show

Clear Therapeutic Effect in Cancer Cachexia

28 October 2005 - Ark Therapeutics Group plc ('Ark') announces today that the preliminary results of the Vitor™ study in 200 patients with cancer cachexia indicate that the product changes the pattern of weight loss in the three types of cancer (colorectal, lung and pancreatic) in the study.

Patients entering this study were all terminal cancer patients and had already lost an average of 15% of their body weight. A positive treatment effect with Vitor™ was observed across the treatment group, irrespective of cancer type. Whilst initially continuing to lose weight over the first four weeks of the study, colorectal and lung cancer patients then gained weight over the next eight weeks to study end (week 12) whereas placebo patients lost weight (Vitor™ daily rate of change +0.025lbs vs placebo -0.022lbs). Pancreatic cancer patients (the more aggressive of the cancers studied), whilst not gaining weight after the first four weeks of the study, exhibited a marked



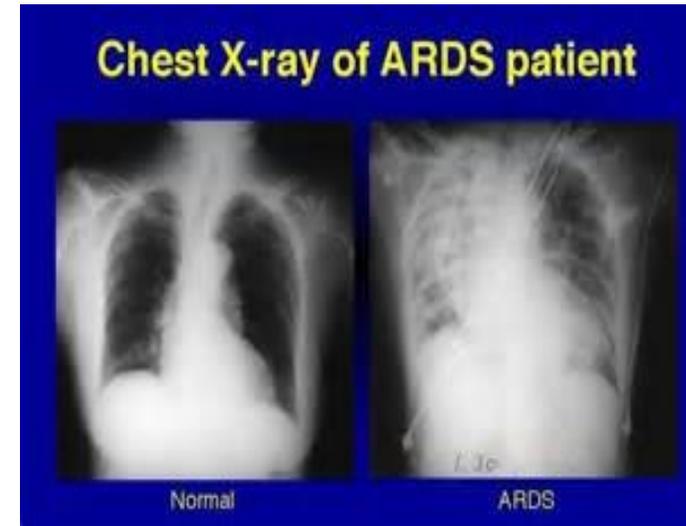
# Case Histories

## Faron Pharmaceuticals – IFN- $\beta$ for Acute Respiratory Distress Syndrome

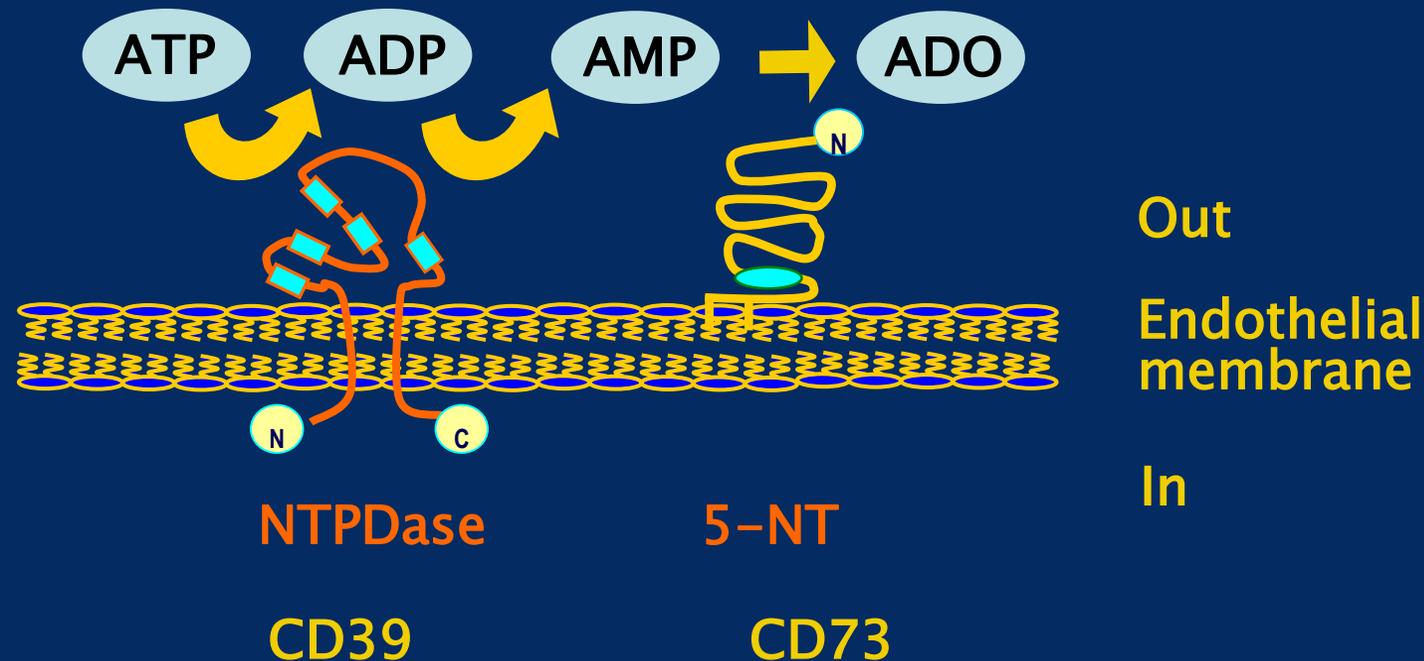


# Acute Respiratory Distress Syndrome

- **ARDS** is a medical condition occurring in critically ill patients characterized by widespread inflammation in the lungs.
- ARDS is not a particular disease, but it is a clinical syndrome triggered by various pathologies such as trauma, pneumonia and sepsis, trauma
- Hallmark of ARDS is diffuse alveolar damage to cells which form the alveolar barrier, surfactant dysfunction, activation of the innate immune response, and abnormal coagulation.



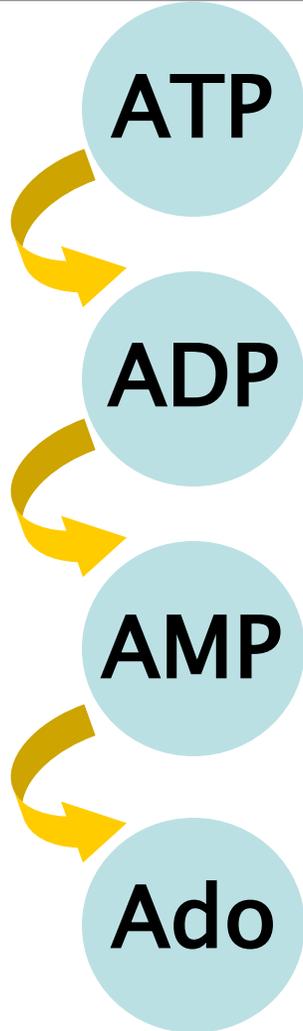
# Extra-cellular ATP/ADP/AMP inactivation by the vasculature leads to adenosine production



For further details see: *Salmi & Jalkanen, Nature Reviews Immunol 2005;5:760*  
*Jalkanen & Salmi, Arterioscler. Thromb. Vasc. Biol. 2008;28:xx*

# Purines in hemostasis and thrombosis

FARON  
Pharmaceuticals



## **Pro-inflammatory:**

- Recruitment of myeloid cells to the site of injury
- Facilitation of leukocyte adhesion to the endothelium

## **Pro-thrombotic:**

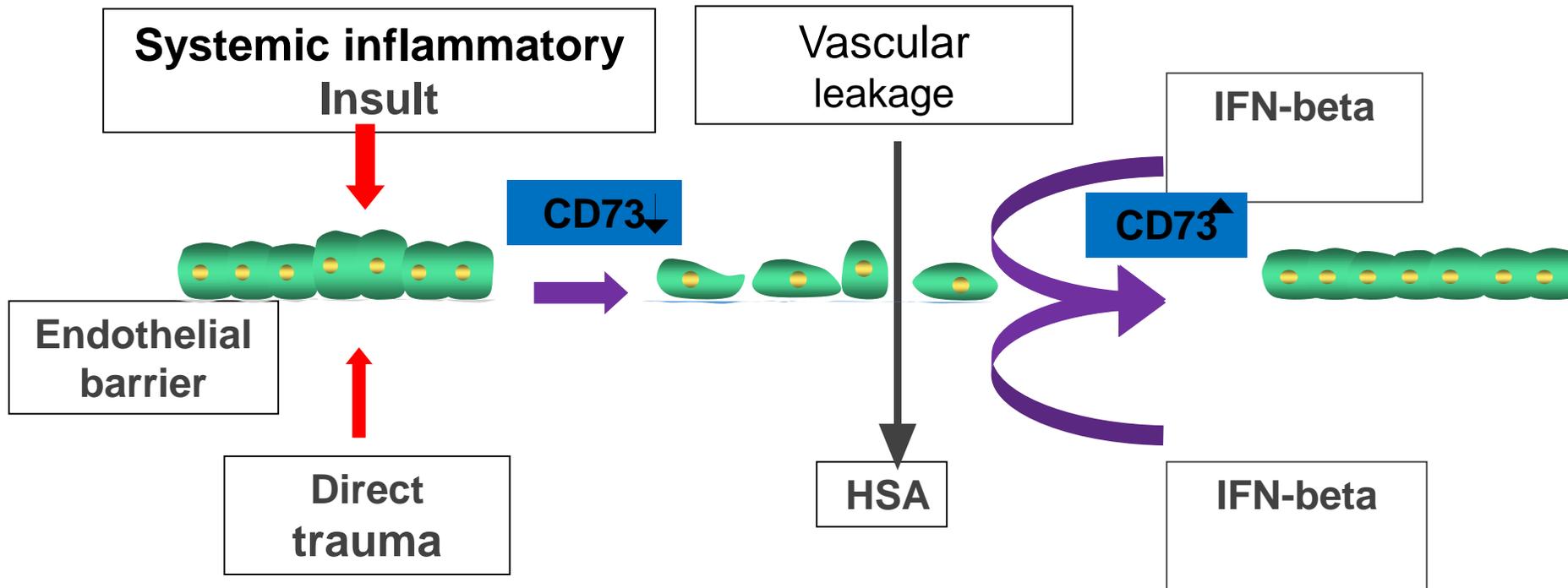
- Platelet activation and aggregation
- Potentiation of chemokine-mediated platelet function

## **Biologically neutral**

## **Anti-inflammatory:**

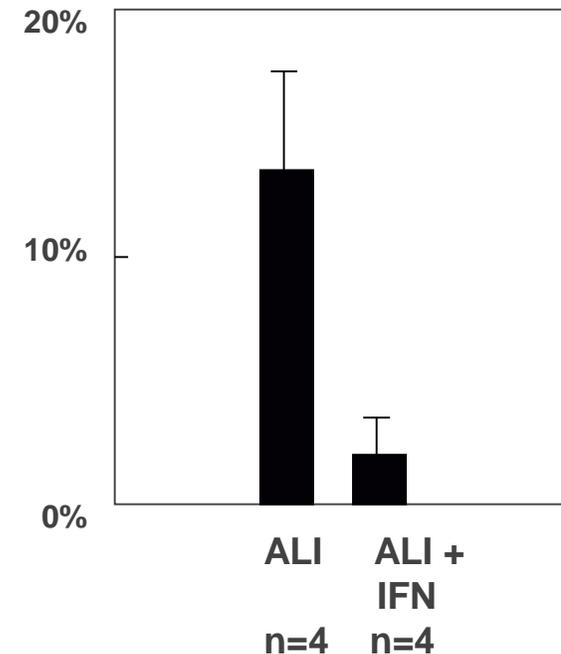
- Interferes with neutrophil-endothelial adhesion
- Inhibits the release of cytokines from the endothelium
- Maintains endothelial barrier function
- Other tissue and cell specific activities

# Interferon controls CD73 expression and thus leakage of vascular beds



# IFN-beta treatment prevents leakage of vascular beds in ALI

Mice were induced ALI 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=4,  $\pm$ SEM).



# Benefits of CD73 up-regulation in ALI

- **Inactivation of pro-inflammatory and pro-thrombotic purines**
- **Enhanced production of local adenosine,**
  - **an endogenous regulator of vascular permeability (reduced leakage of vascular beds) (JEM 1998:188:1433)**
  - **an enhancer of fluid clearance (activation of lung epithelial cells) (PNAS 2007:104:4083)**
  - **a suppressor of activated T cells (inhibition of inflammation) (JEM 2007:204:1257)**
- **Targeting a disease, which is currently without effective drug treatment**



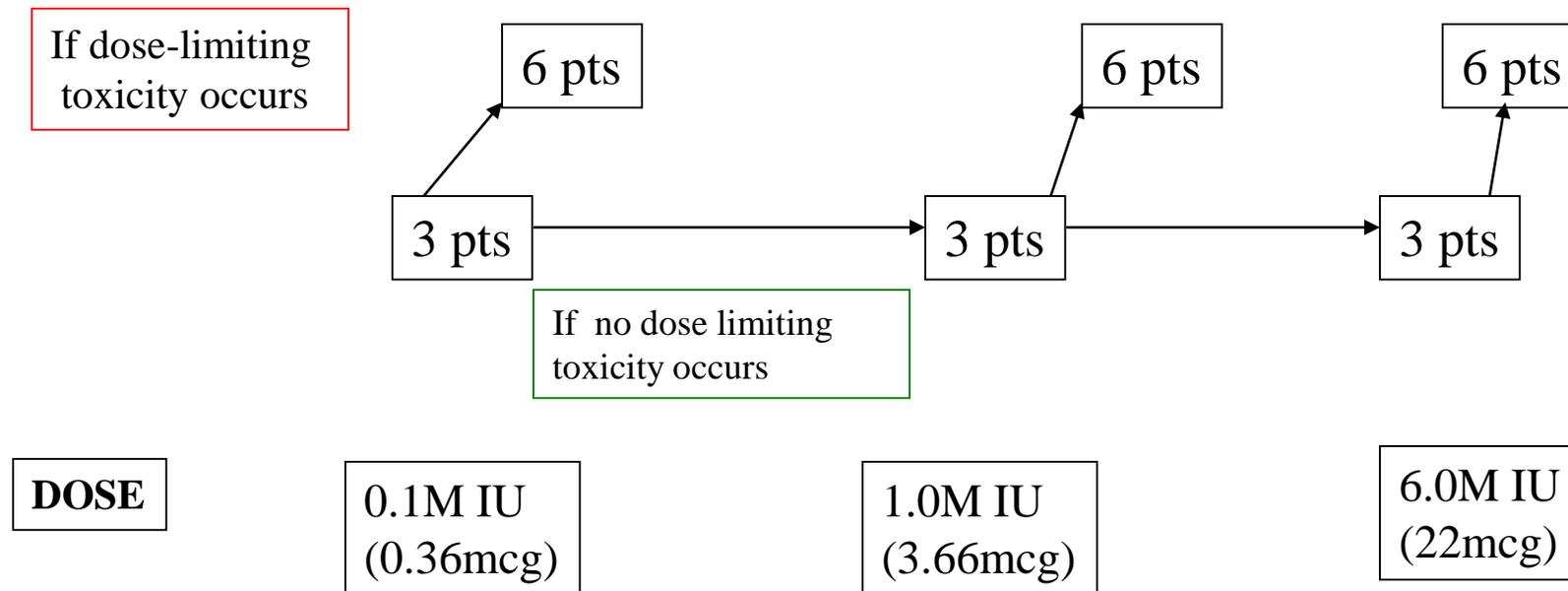
# Use of IFN- $\beta$ – a New Indication

- Source of IFN- $\beta$ –Rebif® from Merck – Treatment of MS
  - Administered three times a week by subcutaneous injection - available in three strengths: 8.8 micrograms, 22 micrograms and 44 micrograms in pre-filled syringes – dose is titrated due to adverse effects over 1 month with an antipyretic analgesic
- Problem in ARDs patients
  - In ITU – drug absorption from SC injection very poor
  - Due to lung leakage need to treat within 7 days or fibrosis in lung tissue develops
  - Therefore need to give by IV administration
- Utilised the Pharmacokinetic parameters to design a dosage regimen
- Resulted in a novel dosage regimen
- Divided total weekly dose administered IV daily for 6 days
  - Stayed within licensed dose range – 36M IU per week
  - (44 mcg (12M IU) given three times a week in MS)
  - Loading Dose given IV on day 1 - followed by 5 further IV doses given daily
- Commenced a Phase 1/2 Clinical Study – 2 Part Study - Dose Escalation (3+3 Design) up to 18 patient & Dose Expansion in 20 patients



## Phase I – Dose Escalation

Open-Label, dose escalation study of repeat doses of IFN-beta administered for 6 days IV in up to 6 patients per dose cohort



- Dose escalation will be continuous unless drug-related toxicity occurs
- Study will be terminated at a dose level at which 2 of 3 or 3 of 6 have DLT

## Phase II – Cohort Expansion

Open-Label, study of repeat doses of IFN-beta at the optimum tolerated dose, as established in Phase I, administered IV for 6 days in 20 patients

### Study Objectives

- **Primary Objectives**

- To evaluate safety and tolerability of IFN-beta in patients with ALI/ARDS
- To assess the safety, tolerability and preliminary efficacy of the optimum tolerated dose in patients who are likely to derive clinical benefit

- **Secondary Objectives**

- To establish appropriate dose(s) of IFN-beta for use in for future studies of patients with ALI/ARDS
- To determine PK parameters of IFN-beta when administered intravenously daily as a single injection for 6 days in ALI/ARDS patients
- To demonstrate the pharmacodynamic activity of IFN-beta in ALI/ARDS patients

- **Exploratory Objectives**

- To obtain peripheral blood samples for DNA extraction for future pharmacogenetic analysis and other potential correlative biomarkers of IFN-beta activity e.g CD73

# Results



## The effect of intravenous interferon-beta-1a (FP-1201) on lung CD73 expression and on acute respiratory distress syndrome mortality: an open-label study

*Geoff Bellingan, Mikael Maksimow, David C Howell, Martin Stotz, Richard Beale, Monika Beatty, Timothy Walsh, Alexander Binning, Alan Davidson, Martin Kuper, Sanjoy Shah, Jackie Cooper, Matti Waris, Gennady G Yegutkin, Juho Jalkanen, Marko Salmi, Ilse Piippo, Markku Jalkanen, Hugh Montgomery, Sirpa Jalkanen*

### Summary

*Lancet Respir Med* 2014;  
2: 98–107

Published Online  
December 23, 2013  
[http://dx.doi.org/10.1016/S2213-2600\(13\)70259-5](http://dx.doi.org/10.1016/S2213-2600(13)70259-5)

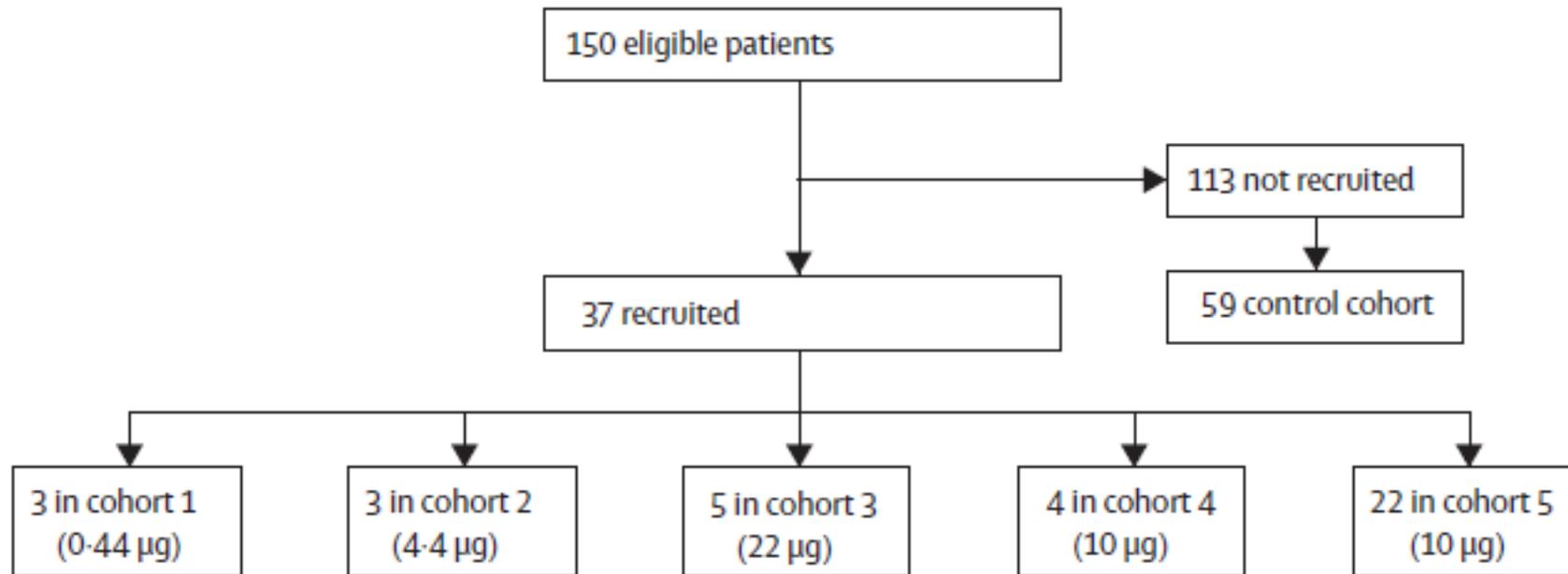
See [Comment](#) page 84

See Online for an audio

**Background** Pulmonary vascular leakage occurs early in acute respiratory distress syndrome (ARDS). Mortality is high (35–45%), but no effective pharmacotherapy exists. Production of anti-inflammatory adenosine by ecto-5'-nucleotidase (CD73) helps maintain endothelial barrier function. We tested whether interferon-beta-1a (IFN-beta-1a), which increases CD73 synthesis, can reduce vascular leakage and mortality in patients with ARDS.

**Methods** In ex-vivo studies, we first established that IFN-beta-1a induced CD73 up-regulation in cultured human lung tissue samples. We then tested the safety, tolerability, and efficacy of intravenous human recombinant IFN-beta-1a (FP-1201) in patients with ARDS in an open-label study (comprising dose-escalation and expansion phases)

## Results - Patients Treated

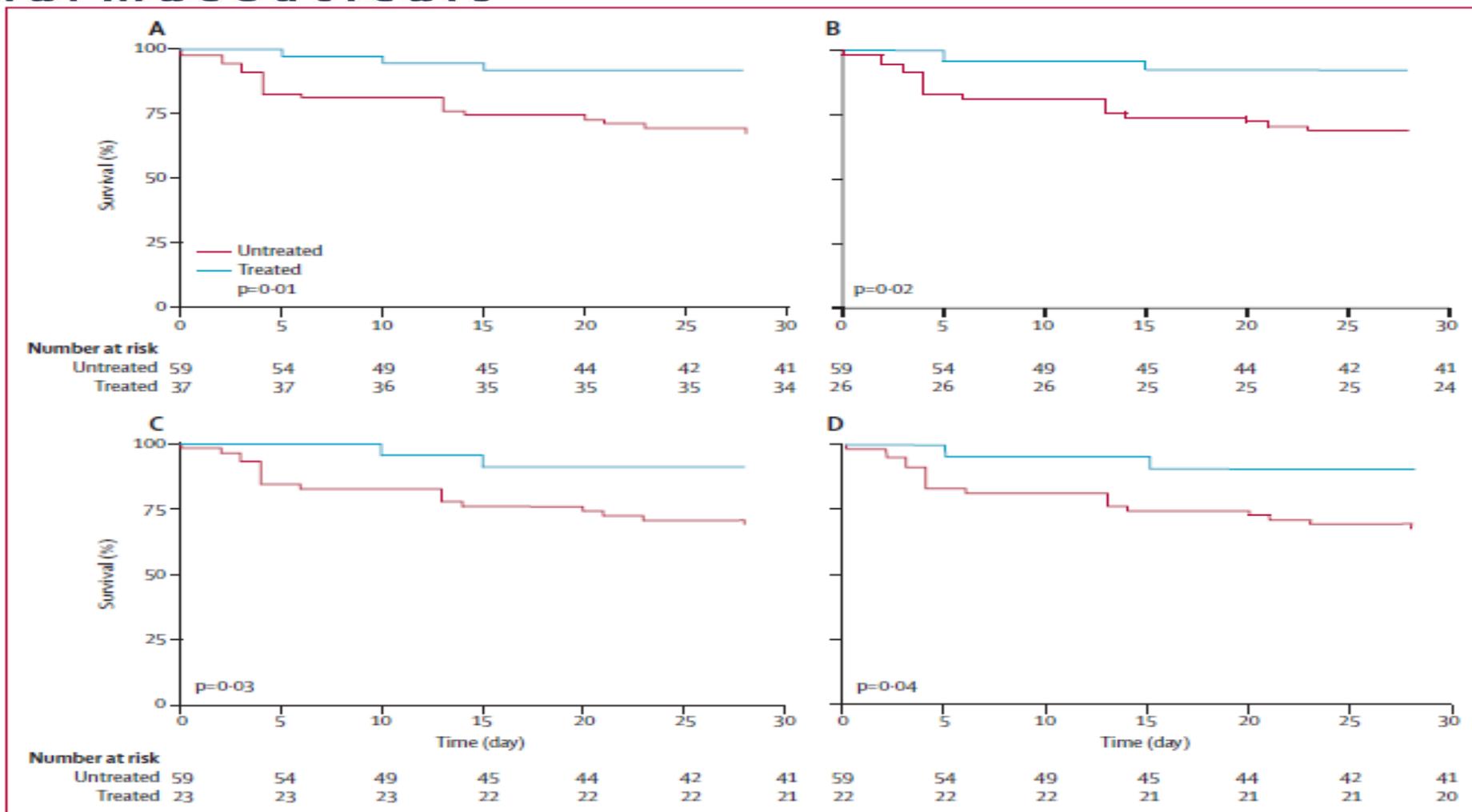


## Results - Efficacy

	All patients given optimal tolerated dose (10 mg)	All patients	Control cohort
n	26	37	59
Time to treatment	33 (25-43)	33 (26-44)	N/A
Day 28 mortality	2 (8%); p=0.02	3 (8%); p=0.01	19 (32%)
Month 6 mortality	3 (12%); p=0.004	4 (11%); p=0.03	24 (40%)
Days alive at day 28	28 (28-28); p=0.02	28 (28-28); p=0.008	28 (14-28)
Days alive and on intensive care at day 28	24 (10-28); p=0.17	21 (12-28); p=0.12	16 (7-28)
Days alive and off ventilation at day 28	6 (0-21); p=0.15	9 (0-19); p=0.11	0 (0-17)
Days alive and on vasoactive drugs at day 28	4 (0-6); p=0.44	3 (0-5); p=0.26	3 (2-7)

Data are N, median (IQR), or n (%); p value (when compared with the control cohort). N/A=not applicable.

**Table 2: Efficacy endpoints**



**Figure 4: Survival of FP-1201-treated patients compared with control patients**

Kaplan-Meier plots of (A) all-cause mortality at day 28 of all FP-1201 treated patients (n=37), (B) patients treated with the optimal tolerated dose (n=26), (C) patients treated at the same sites as control patients were enrolled (n=23), and (D) patients in cohort 5 (phase 2, n=22) versus eligible untreated control patients with ARDS (59 patients). All n values are for the log-rank test

## Recent Activities

- Raised Funds by IPO
- Commenced a Pan-European Phase 3 Study
- Developed Novel Formulation suited for use in ITU Setting

# Birmingham University – Recent Examples

- Idiopathic Intracranial Hypertension (Exenatide)
  - Dr Alex Sinclair
- Wolfram’s Syndrome (Sodium Valproate)
  - Professor Tim Barrett
- Use of Drug Screening Panel of FDA Approved Drugs

The screenshot displays the Selleckchem.com website, specifically the 'FDA-approved Drug Library' page. The page features a search bar at the top, a navigation menu, and a main content area with a table of drug listings. The table includes columns for 'Size', 'Price', and 'Quantity'. Below the table, there are links to download the library in XLS and ZIP formats, and a 'Cited by 42 Publications' and '22 Customer Reviews' section.

Size	Price	Quantity
Prepackaged (1000)		
1000 (1000) (1000)	1000 (1000)	U
200 (200) (1000)	200 (400)	U



# Summary of Case Studies from Repurposing

- Utilized what was known about the Original Products in terms of Safety and Pharmacokinetic Characteristics
- Worked within the Approved Dose Range for Humans
- Sought Regulatory Advice – MHRA, EMA, FDA early
- Worked with Key Opinion Leaders experienced in the disease
- Adopted a Problem Solving Approach to generate practical solutions



# Immunotherapy - IMMUNOCORE

IMMUNOCORE | ABOUT US | TECHNOLOGY & PIPELINE | PARTNERING | NEWS & EVENTS | CAREERS

## Breaking new ground in immuno-oncology

**LATEST NEWS**

**MAY 12, 2017**  
Abbas Hussain Joins the Board of Immunocore as Non-Executive Director

**MAY 08, 2017**  
Immunocore Identifies second novel ImmTAC® in the GSK collaboration

**FEB 28, 2017**  
Immunocore to Present at the Cowen and Company 37th Annual Healthcare Conference

VIPWA | NPWS >

**immunocore**

Immunocore is a world leading biotechnology company focused on the development of a new class of immunotherapeutic drugs, based on proprietary T cell receptor (TCR) technology. The Company is focusing its technology primarily in the area of immuno-oncology via the ImmTAC platform. The same underlying technology is being extended to address other hard to treat conditions including viral infections, through the ImmTAV platform, and autoimmune diseases. The scientific expertise at Immunocore spans the entire process of drug development, from the discovery and validation of

**Developing proprietary  
T cell receptor (TCR) technology  
For Oncology Indications**



# Immunotherapy - IMMUNOCORE

- Lead product – IMCgp100 for Treatment of Malignant Melanoma (unresectable stage III and stage IV)
- It is a bifunctional biologic comprising a soluble T cell receptor (TCR) fused to an antibody single chain variable fragment (scFv).
- The TCR functions to target and bind the drug to the melanoma associated antigen glycoprotein 100 (gp100) which is over expressed and presented on the surface of melanoma cells.
- The scFv component is designed to activate T cells in physical contact with the melanoma via cluster of differentiation 3 (CD3), which results in an immune response targeted towards the malignant tissue.
- Once administered, IMCgp100 binds to melanoma tissue and stimulates the immune system to attack the target tissue primarily via cytotoxic T lymphocyte (CTL) killing, but also via the stimulation of accessory immune mechanisms.



# Pre-Clinical Toxicology Issues

- Both the gp100-specific soluble TCR and the CD3 targeting moiety of IMCgp100 have been demonstrated to be highly selective and specific for the human HLA-A2-gp100 peptide complex and human CD3.
- Was demonstrated that the anti-CD3 scFv portion of IMCgp100 does not bind to T cells derived from cynomolgus macaque or mouse blood cells by flow cytometry.
- Therefore, binding and activation of IMCgp100 could not be demonstrated in non-clinical species, including non-human primates, despite non-human primate and human CD3 showing a relatively high degree of sequence identity.
- Based on these observations, it was concluded that no relevant non-clinical species for in vivo toxicology studies exists.
- In the absence of a relevant toxicology species, IMCgp100 was investigated for potential cross-reactivity to normal tissues other than target melanoma tissue in vitro. The results of these experiments were used to set a starting dose for the IMCgp100-01 clinical study and gain insights into potential adverse events (AEs) of the IMP.

**Clinical Development – Phase I Undertaken in Selected Oncology Units**



# *Examples of Innovation and Risk Management: Perspective from University and Industry*

- Innovation – what is driving it and why it's needed?
- Innovation Examples from Universities and Industry and how risk has been managed during Development
  - Gene Therapy Based Products
  - Repurposing Medicines
  - Immunotherapy



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