R&D Briefing

December 7, 2010

Agenda December 2010 R&D Briefing

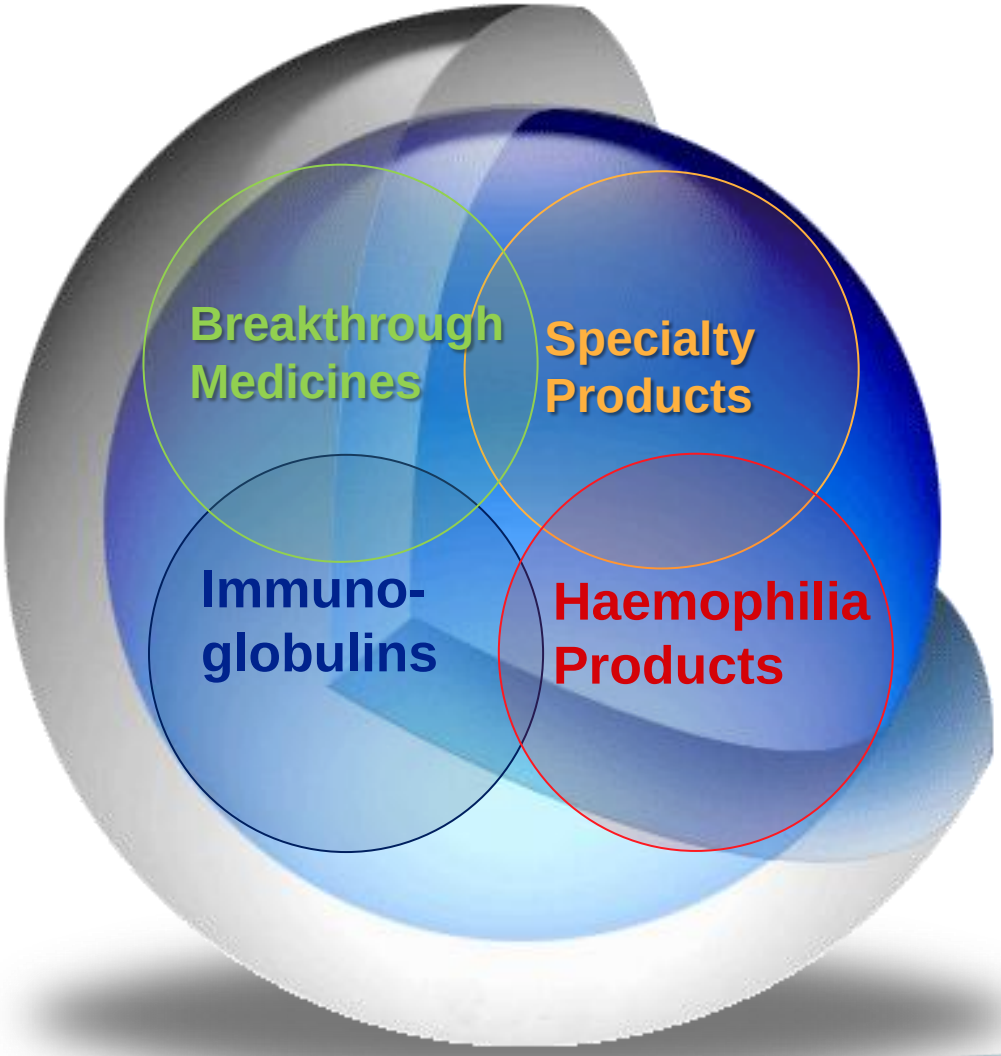
8.30am: Sign in and coffee

• Welcome	Mark Dehring
• Introduction and Highlights	Andrew Cuthbertson
• Immunoglobulins	Andrew Cuthbertson
• Specialty Products	Russell Basser
• Q&A	
• 20 Minute Break	
• Rec Coagulation Program	Simon Green
• Breakthrough Medicines	Andrew Nash
• Licensing	Andrew Cuthbertson
• Summary highlights, Q&A	

Noon: Finish

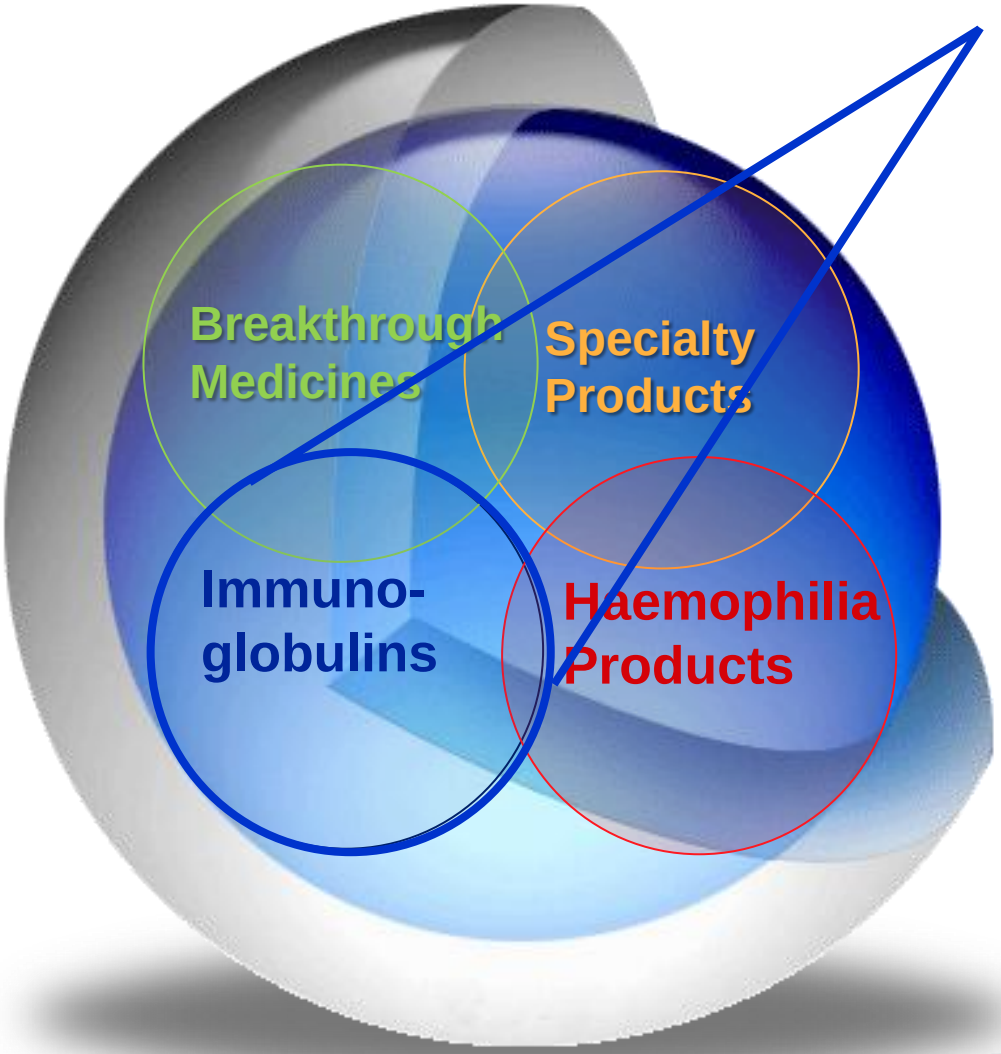
Introduction and Highlights

CSL R&D Strategy



- Maintain commitment to extracting maximum value from existing assets and supporting and improving current products
- Develop new protein-based therapies for treating serious illnesses focusing on products that align with our technical and commercial capabilities

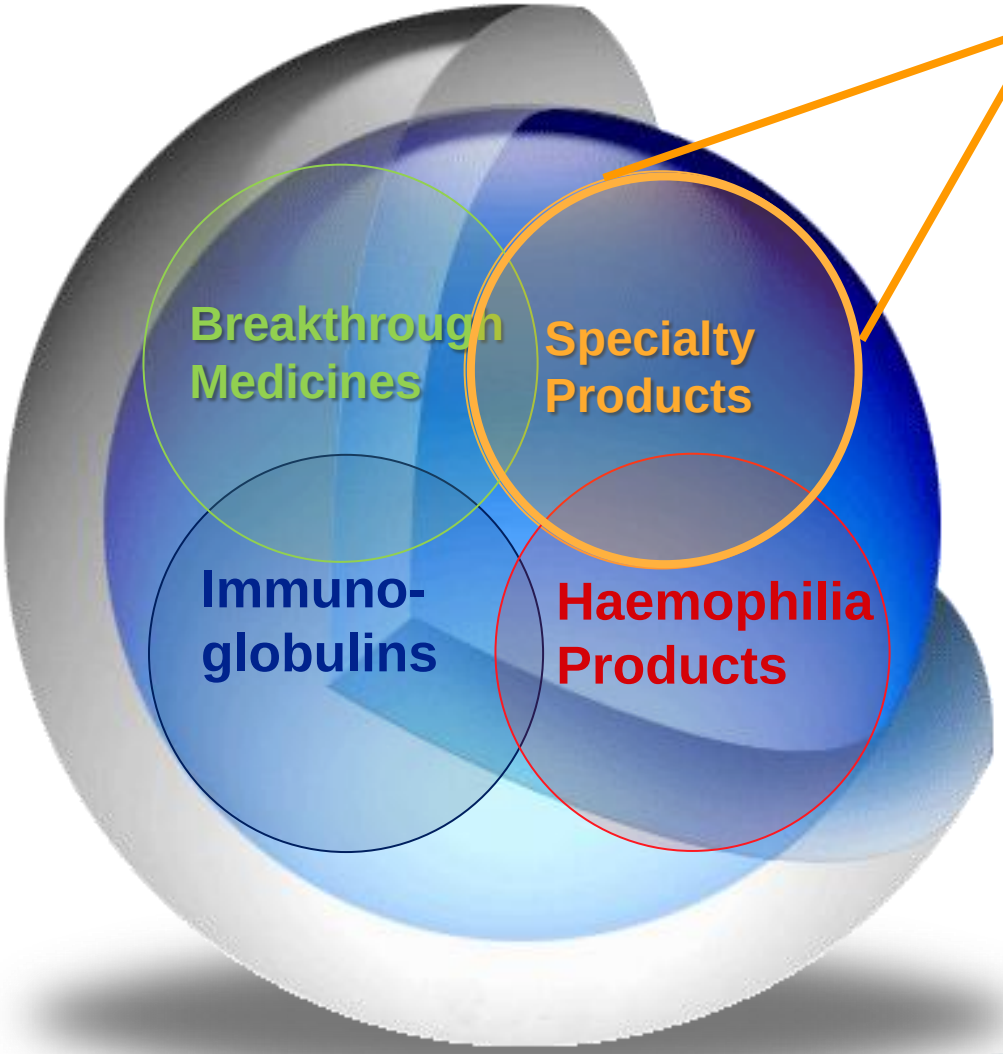
Immunoglobulins Strategy



Supporting and enhancing current portfolio and developing new products

- **Yield**
- **Label**
- **Formulation science**
- **Patient convenience**

Specialty Products Strategy

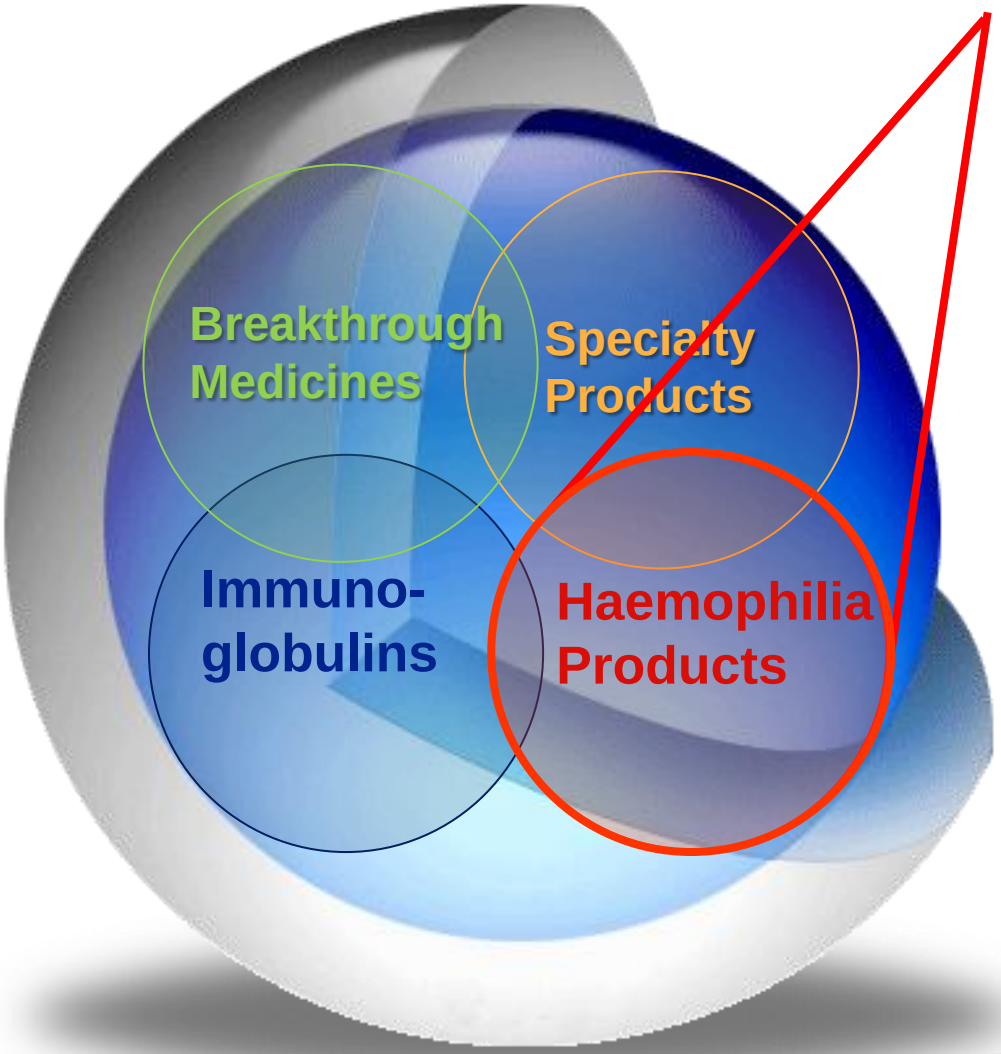


Expanding use through new markets, novel indications and/or modes of administration

e.g.

- **Berinert**
- **Beriplex**
- **Fibrinogen**

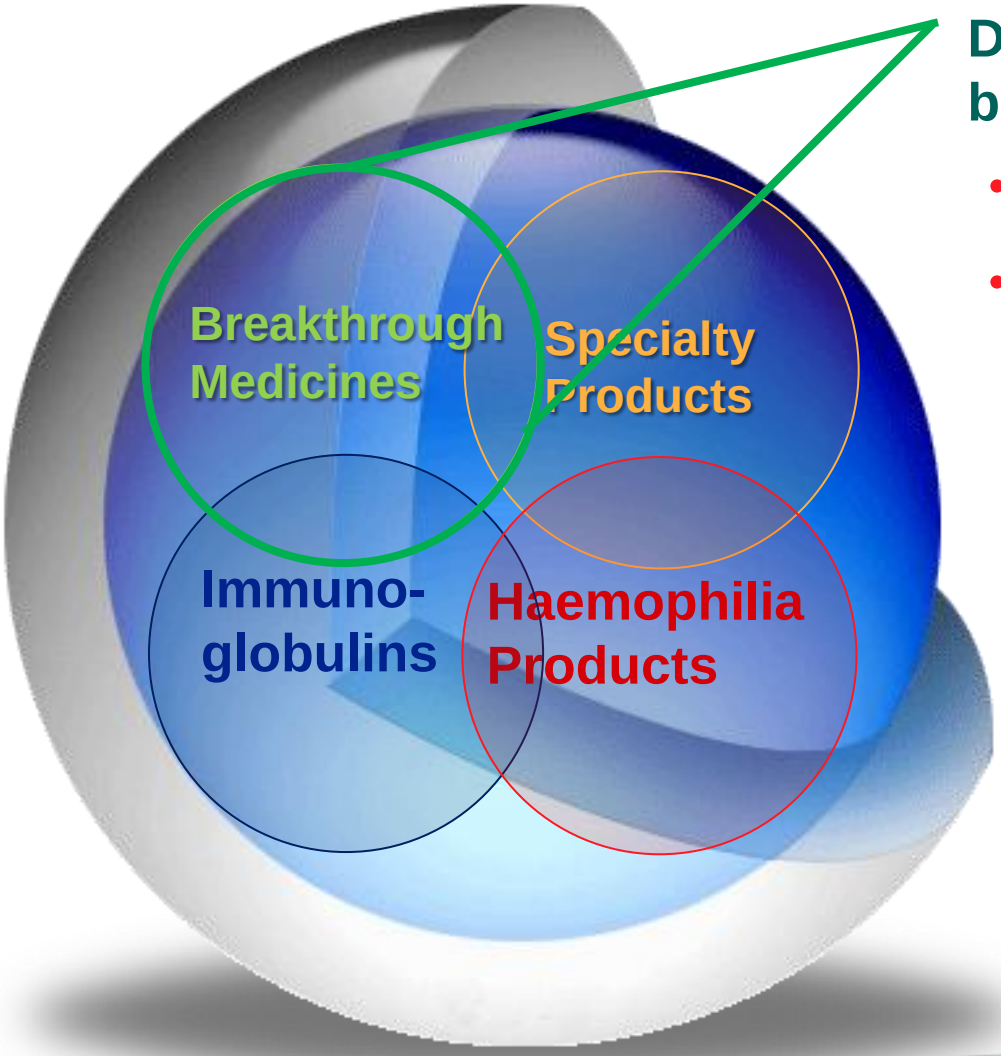
Haemophilia Strategy



Supporting and enhancing portfolio and developing new products

- **Plasma products**
- **Long acting rIX & rVIIa**
- **Patient convenience**
- **Coagulation research**

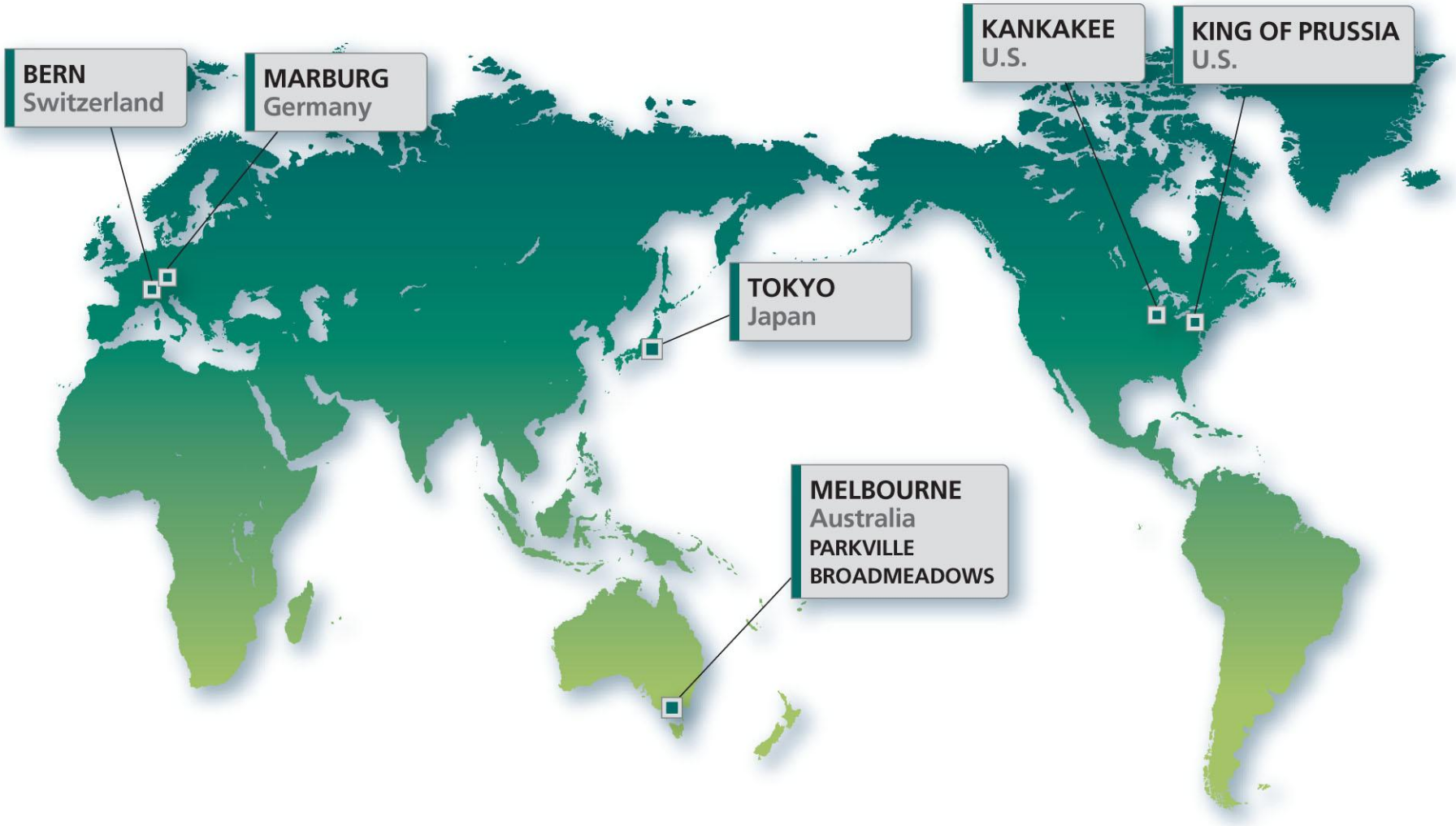
Breakthrough Medicines Strategy



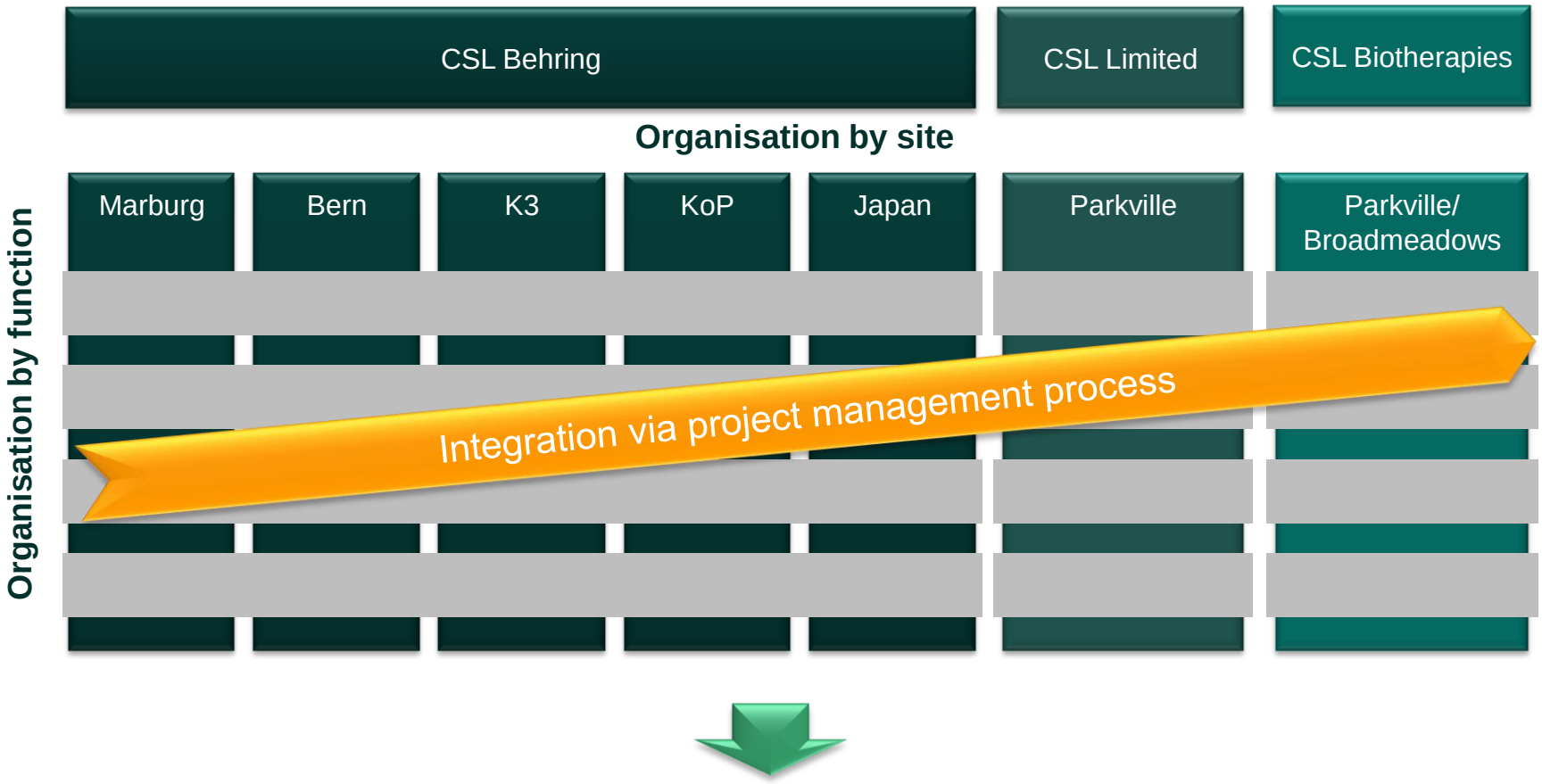
Developing new protein-based therapies

- **Significant unmet need**
- **Multiple indications, e.g.**
  - **Reconstituted HDL**
  - **Anti IL-3Rα mAb**
  - **Anti G-CSFR mAb**

Global R&D: Integrated R&D Facilities

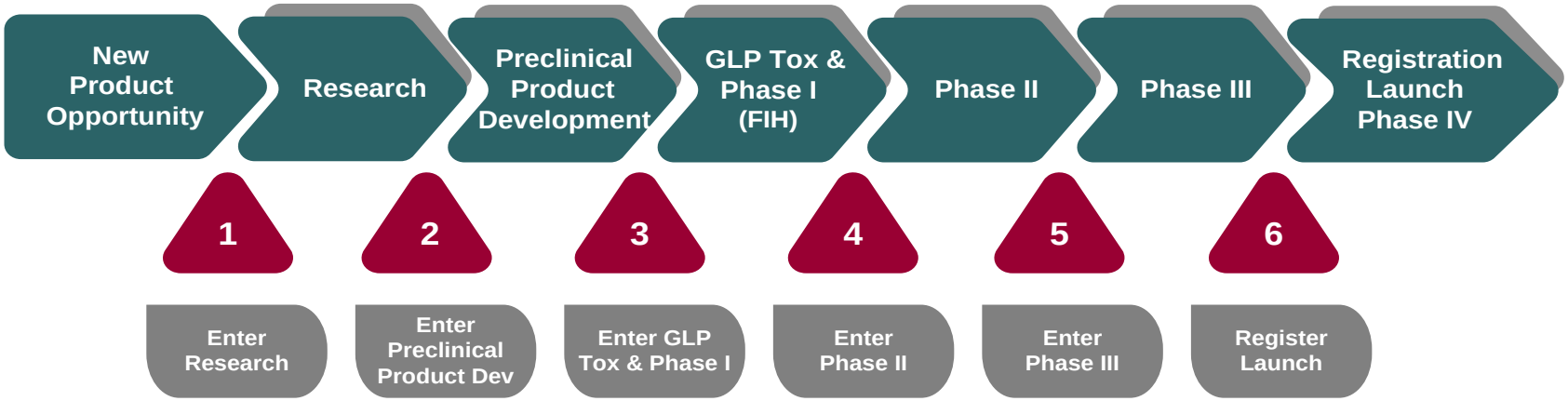


Leveraging Global Capabilities



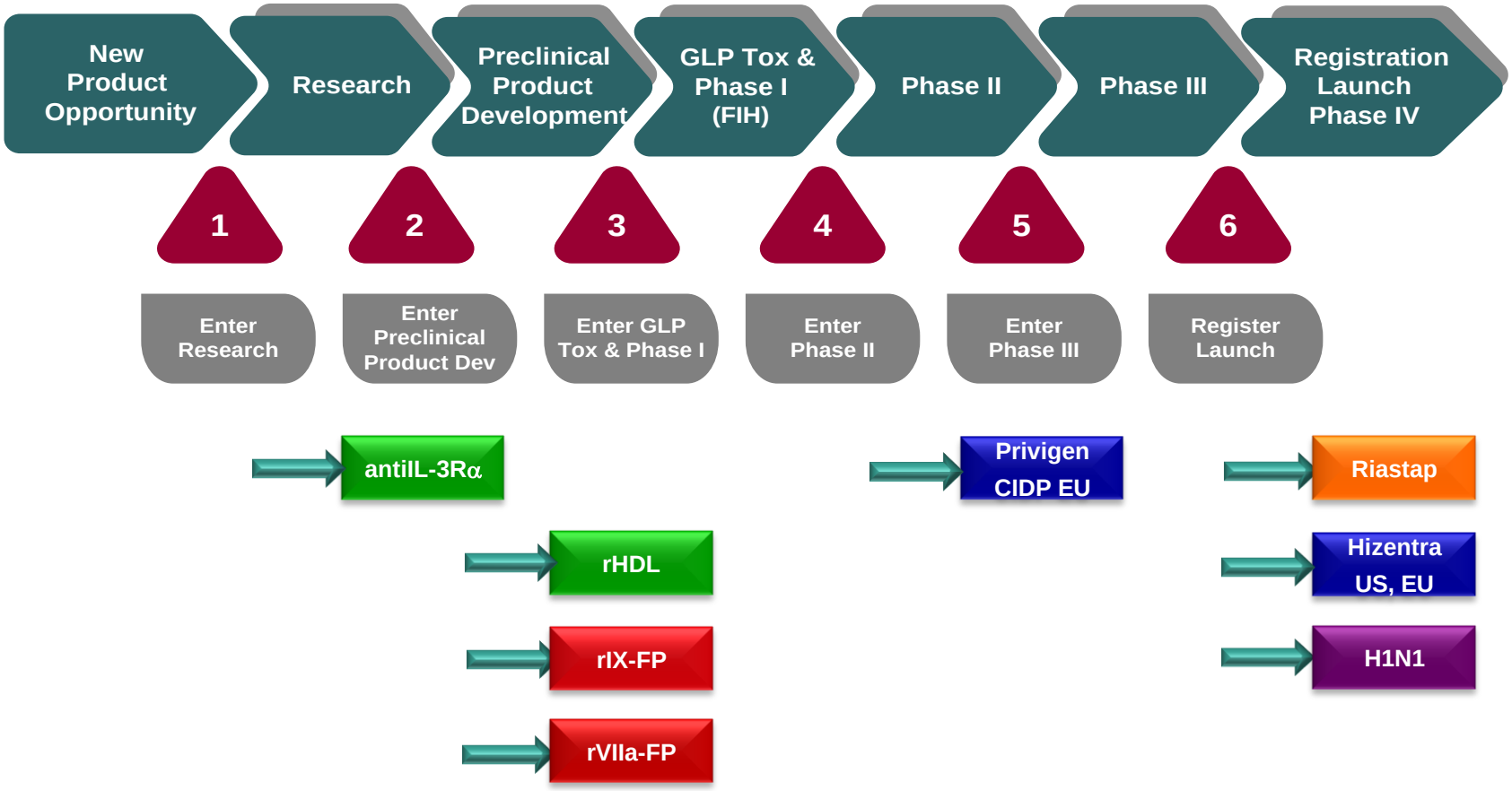
Global project management to ensure leverage of best capabilities

Stage Gate Decision System

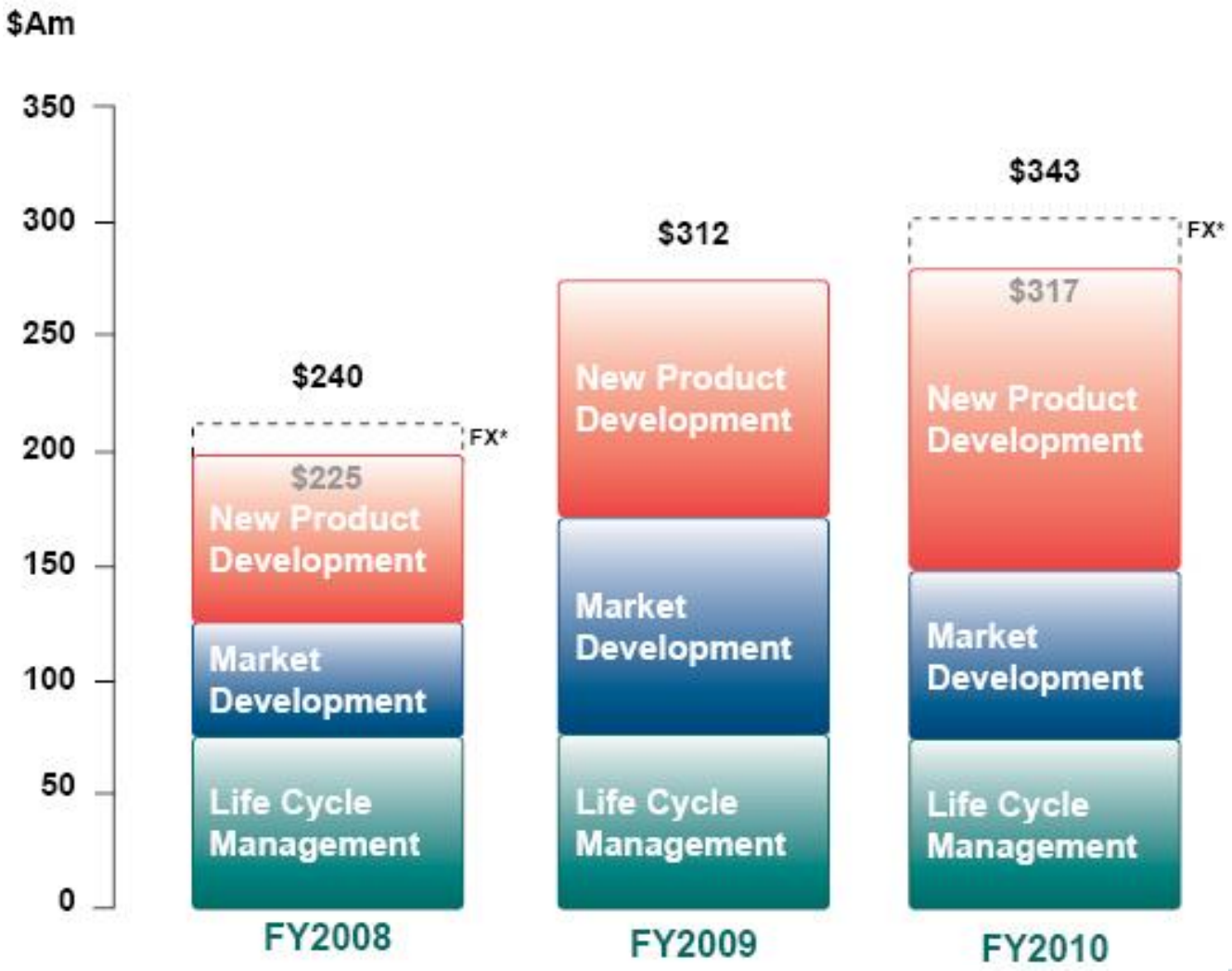


- Robust process to support high quality investment
- Provides clarity around key criteria and deliverables
  - Market environment
  - Data relative to Target Product Profile
  - Capabilities, capacity, ability to execute

Progress through Stage Gates in 2010

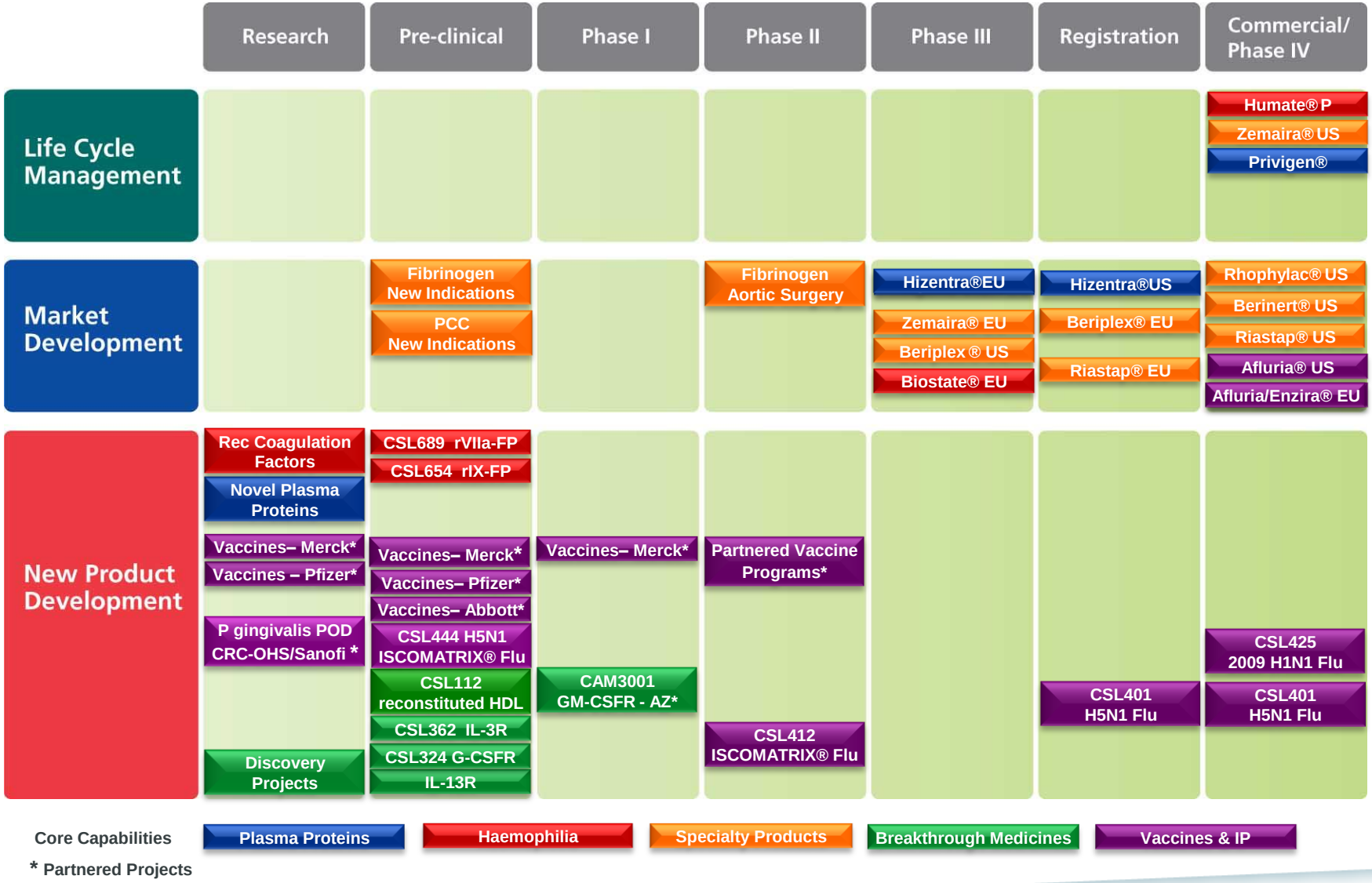


R&D Investment



* *Foreign currency impact using FY2009 exchange rates*

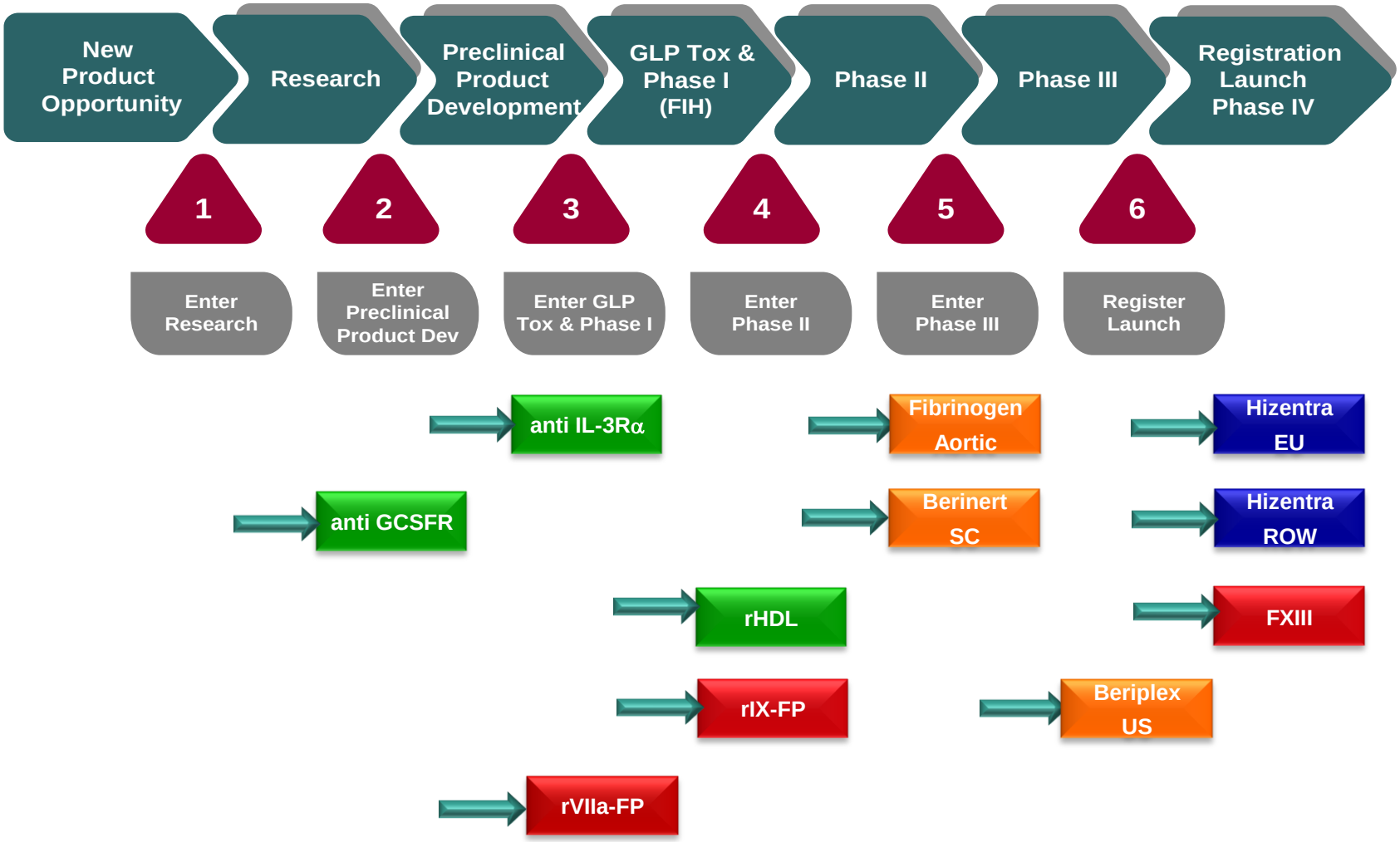
Global R&D Pipeline December 2009



Global R&D Pipeline — December 2010

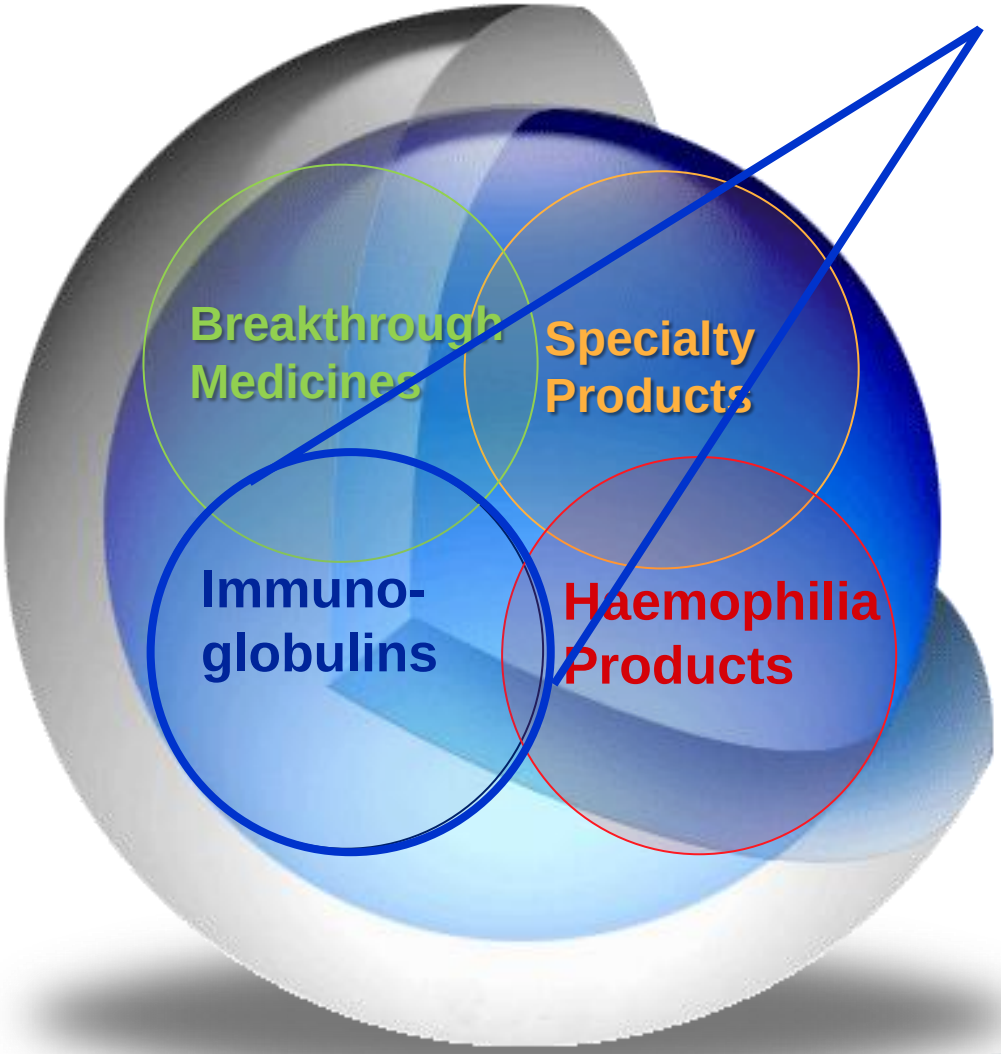
* Partnered Projects

Expected Progress in next 12 months



Immunoglobulins

Immunoglobulins Strategy



Supporting and enhancing current portfolio and developing new products

- **Yield**
- **Label**
- **Formulation science**
- **Patient convenience**

Privigen®

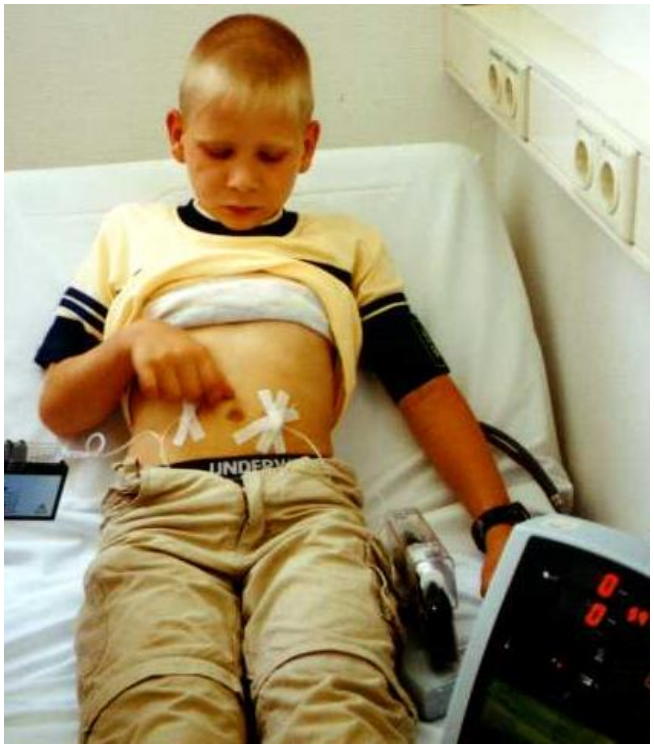
- Only room temperature stable IVIG (36 months)
- IgLab Module2 comes on-line 2011 (submitted to the FDA 25 Nov)
- Privigen approved and launched in US, Europe, Australia, Canada and other countries, with additional registrations underway
- European Phase III study in CIDP initiated

CSL™

Hizentra®

- First 20% SCIg launched in US
  - FDA approval March 2010
- Expected to be the first 20% SCIg launched in Europe, Canada, Switzerland, Japan and other geographies
  - Review in progess: EMA, Switzerland, Canada
  - Launches expected in 2011
- Japan Phase III study initiated Sept 2010

Hizentra™
Immune Globulin Subcutaneous (Human)
20% Liquid



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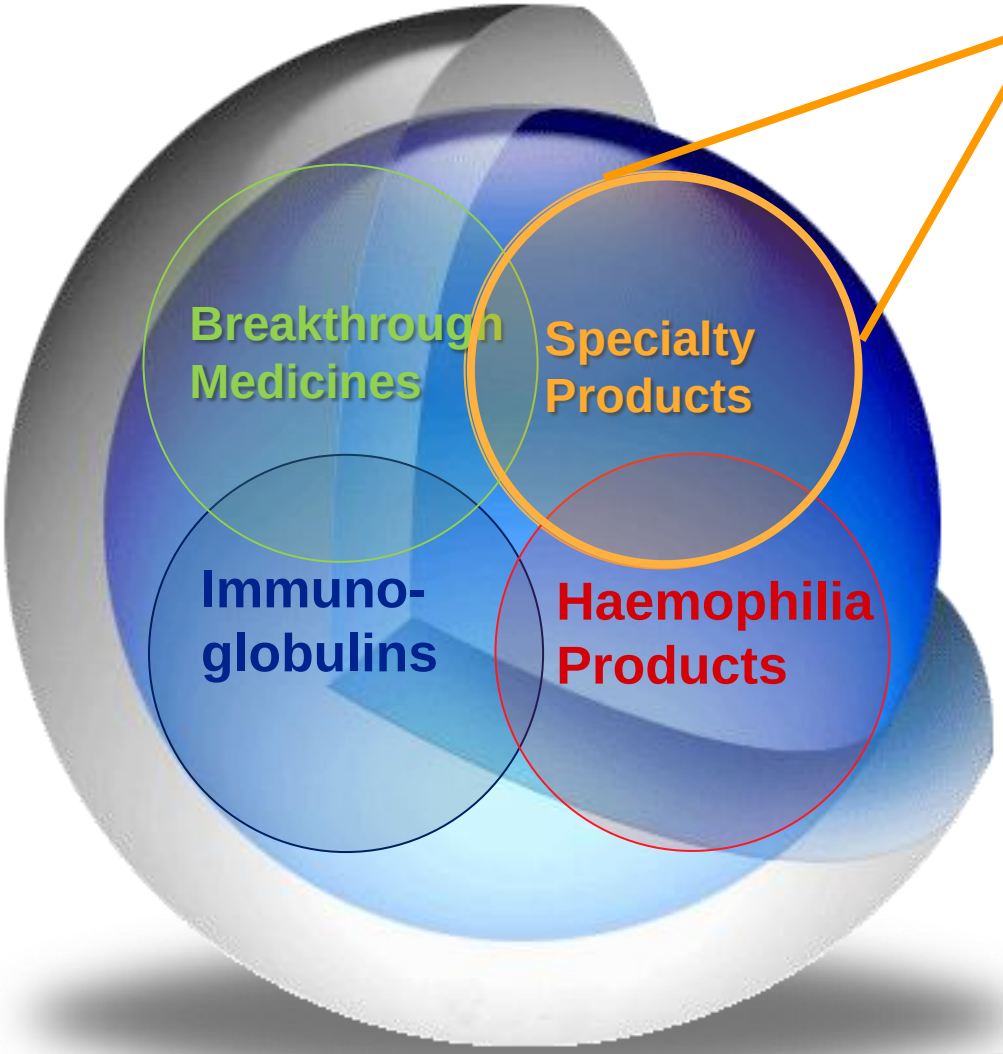
Specialty Products

Specialty Products Strategy



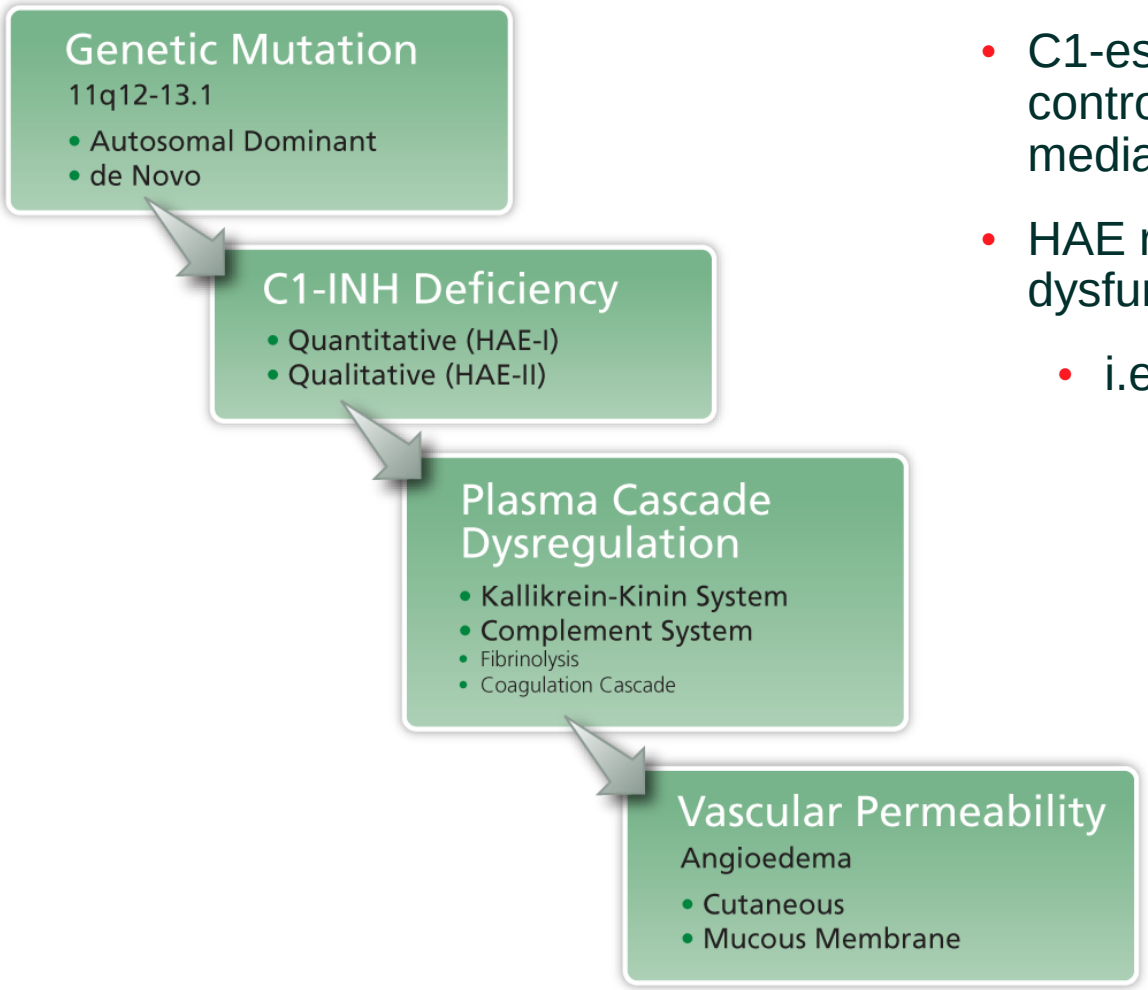
Expanding use through new markets, novel indications and/or modes of administration e.g.

- **Berinert**
- **Beriplex**
- **Fibrinogen**

Improving Treatment for Hereditary Angioedema

Berinert® Program

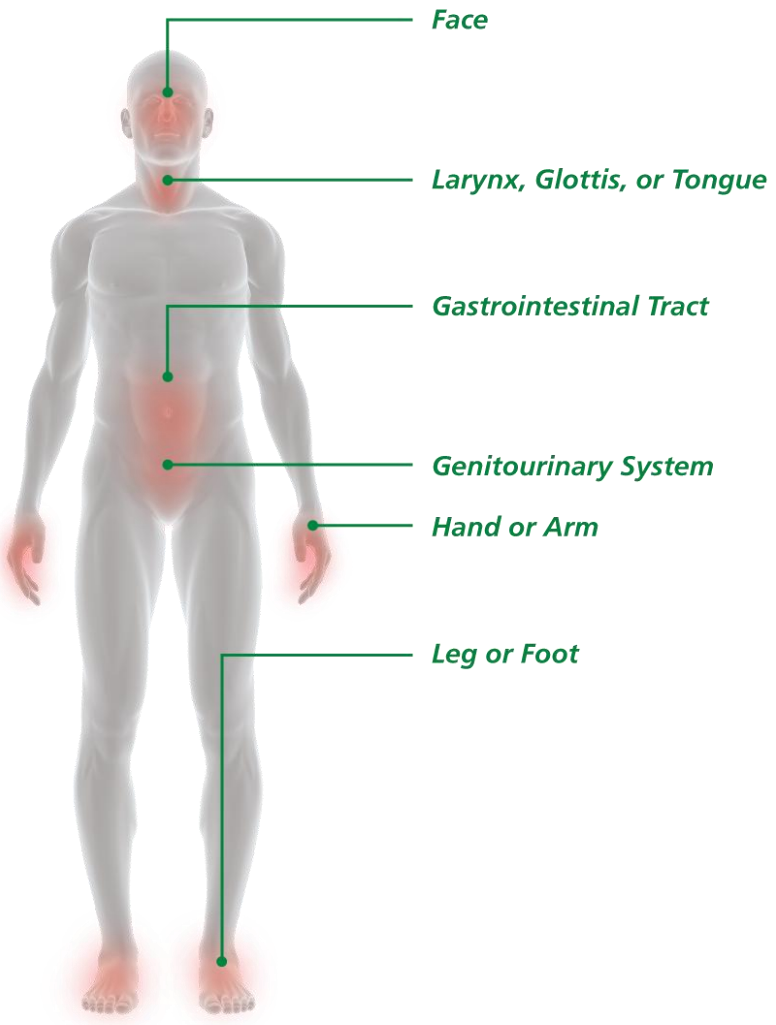
Hereditary Angioedema (HAE)



- C1-esterase inhibitor is the primary control protein of activation of mediators of vascular permeability
- HAE results from deficiency or dysfunction due to gene mutation
  - i.e. life-long condition

What Happens to Patients?

- Recurrent episodes of swelling, sometime with a rash
- Unpredictable and occur anywhere in the body
- Life-threatening if laryngeal swelling
- Attacks caused by stress, infection, menstruation, some drugs, unknown causes



HAE Treatment Guidelines

The Canadian Hungarian International Consensus Algorithm for HAE[1]	UK C1 Inhibitor Deficiency Guidelines[2]
C1-INH concentrate is the first-line therapy in severe attacks of HAE	C1-INH concentrate should be given in cases of laryngeal and severe abdominal edema
Home care with C1-INH concentrate should be offered	Home care with C1-INH concentrate should be offered
C1-INH supply for personal use at home or with travel should be offered for self-administration	Long-term C1-INH prophylaxis may be necessary where steroids are not effective, not tolerated, or contraindicated
C1-INH prophylaxis for Danazol-resistant patients should be considered	Short-term prophylaxis with C1-INH is to be preferred as it is more physiological and more reliably achieves normal C1-INH levels

1. Bowen , et al, *Ann Allergy Asthma Immunol.* 2008
2. Gompels et al, *Clin Exp Immunol*. 2005

Berinert® - Effective Treatment for HAE

- Long clinical use in Europe
- Orphan drug status for treatment in US in 2009
- Currently given via intravenous administration
  - A&E or self-administration
- High quality manufacturing process
- Strong safety record

BERINERT®
C1 Esterase Inhibitor, Human
Reliable Relief. On-Demand.

CSL™

Berinert® Development Program

- Improving Convenience
  - Developing a high concentration, low volume formulation
  - More rapid and easier subcutaneous administration
- Improving Options
  - Program to gain indication for prevention for sufferers with frequent attacks
  - Launch when prevention indication for Berinert® is available in US
- Expanding Indications
  - Exploring opportunities for new medical uses

Treating the Bleeding Patient

Acquired Bleeding Disorders

- Coagulation factor deficiencies can occur because of multiple factors
- Current treatment options
  - Donated blood products – platelets, fresh frozen plasma (FFP), cryoprecipitate
  - Specific products such as those in CSL portfolio
- Problems with donated blood products
  - Sensitivity reactions
  - Large volume
  - Time taken to administer
  - Storage not straightforward
  - Consume a lot of donated blood
  - Limited lifespan

Beriplex® to reverse anti-coagulation with Vitamin K antagonists (e.g. warfarin)

Challenges with Anti-Coagulation

- Vitamin K antagonists are the most commonly prescribed oral anti-coagulants to prevent clotting for people who are at risk, i.e. previously had a clot, artificial heart valves, etc

- Potential problems
  - Over anti-coagulation can be a consequence of other medications, illness, other factors
  - Need to urgently reverse if trauma, surgery immediately required

What is Beriplex®?

Beriplex® P/N

- Highly purified preparation containing vitamin K-dependent coagulation factors
  - FII, FVII, FIX, FX
  - 2 viral inactivation steps
- Specific antidote to vit K antagonists (anti-coagulants)
  - provides rapid normalisation of clotting
- Used in Europe for >10 years with excellent safety record
- Current program to expand geographical usage

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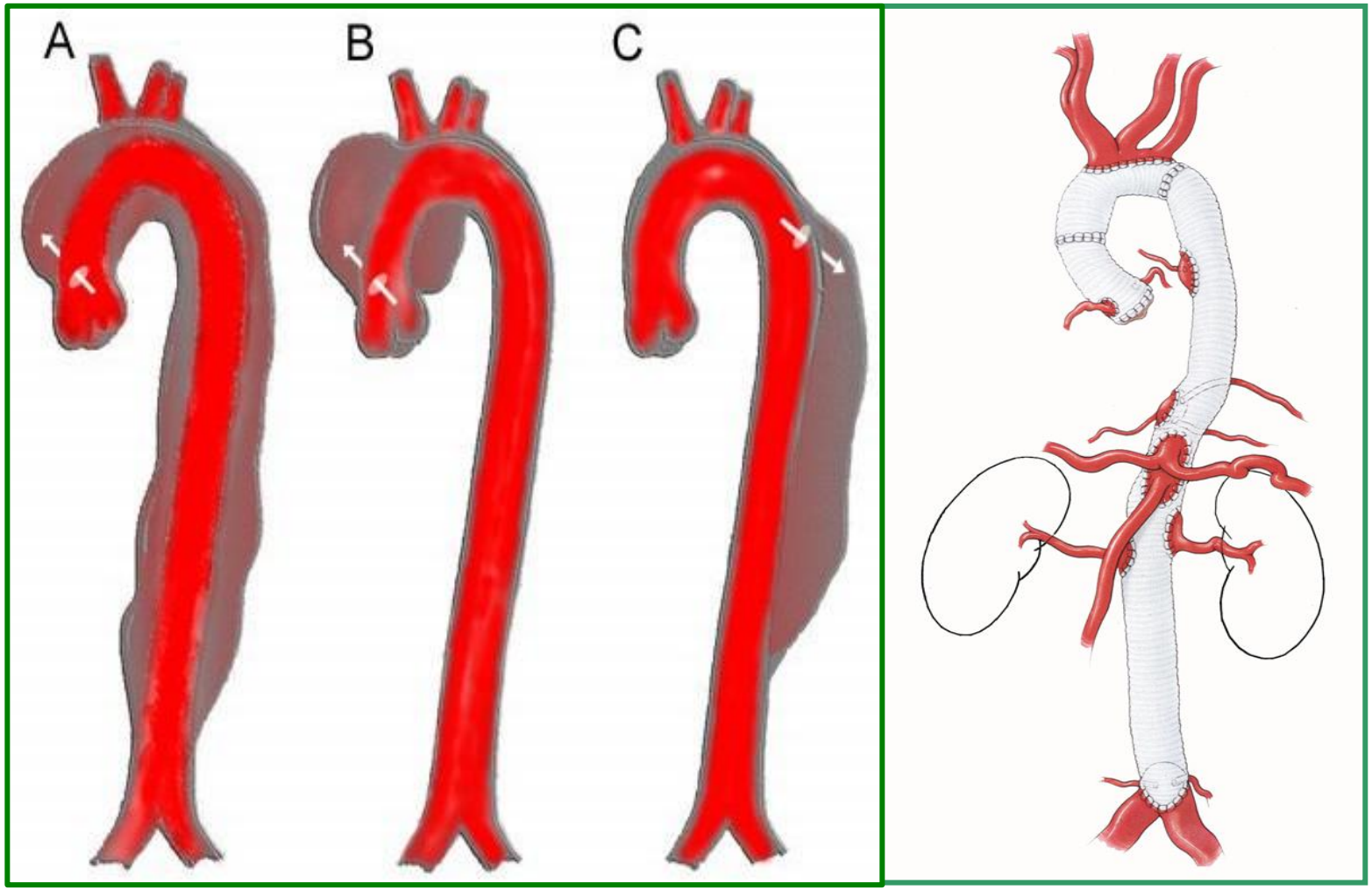
Program to licence Beriplex® in US

- Seeking approval for use of Beriplex® to reverse the effects of vitamin K antagonists for
  - Bleeding related to over-anticoagulation
  - Patients needing surgery
- 2 large randomised, controlled clinical trials
- Bleeding study completed and analysis currently underway
  - BLA submission planned for 2011

Fibrinogen Concentrate for Major Cardio-Aortic Surgery

Aortic Aneurysm – a Potentially Lethal Problem



Fibrinogen in Aortic Surgery

- Patients go on cardiopulmonary bypass and coagulation factors are consumed → bleeding
- Concept – a quickly administered, fast acting, low volume medicine to microvascular bleeding that will substantially reduce the need for donated (allogeneic) blood products

RIASTAP™
Fibrinogen Concentrate
Strengthens clots. Speeds haemostasis.

CSL™

Pilot Experience in Hannover

British Journal of Anaesthesia **102 (6):** 785–92 (2009)
doi:10.1093/bja/aep089 Advance Access publication May 2, 2009

BJA

CRITICAL CARE

Bleeding management with fibrinogen concentrate targeting a high-normal plasma fibrinogen level: a pilot study

N. Rahe-Meyer[1]*, M. Pichlmaier[2], A. Haverich[2], C. Solomon[1], M. Winterhalter[1], S. Piepenbrock[1] and K. A. Tanaka[3]

[1]Department of Anaesthesiology and [2]Department of Cardiac, Thoracic, Transplantation and Vascular Surgery, Hannover Medical School, Carl-Neuberg-Str. 1, D-30625 Hannover, Germany. [3]Department of Anesthesiology, Emory University, School of Medicine, Atlanta, GA, USA

**Corresponding author. E-mail: rahe-meyer.niels@mh-hannover.de*

British Journal of Anaesthesia **104 (5):** 555–62 (2010)
doi:10.1093/bja/aeq058 Advance Access publication March 26, 2010

BJA

Recovery of fibrinogen after administration of fibrinogen concentrate to patients with severe bleeding after cardiopulmonary bypass surgery

C. Solomon[1 4]*, U. Pichlmaier[1], H. Schoechl[3], C. Hagl[2], K. Raymondos[1], D. Scheinichen[1], W. Koppert[1] and N. Rahe-Meyer[1]

Thromboelastometry-guided administration of fibrinogen concentrate for the treatment of excessive intraoperative bleeding in thoracoabdominal aortic aneurysm surgery

Niels Rahe-Meyer, MD, MSc, PhD,[a] Cristina Solomon, MD,[a] Michael Winterhalter, MD,[a] Siegfried Piepenbrock, MD,[a] Kenichi Tanaka, MD, MSc, PhD,[b] Axel Haverich, MD,[c] and Maximilian Pichlmaier, MD[c]

J Thorac Cardiovasc Surg 2009;138:694-702

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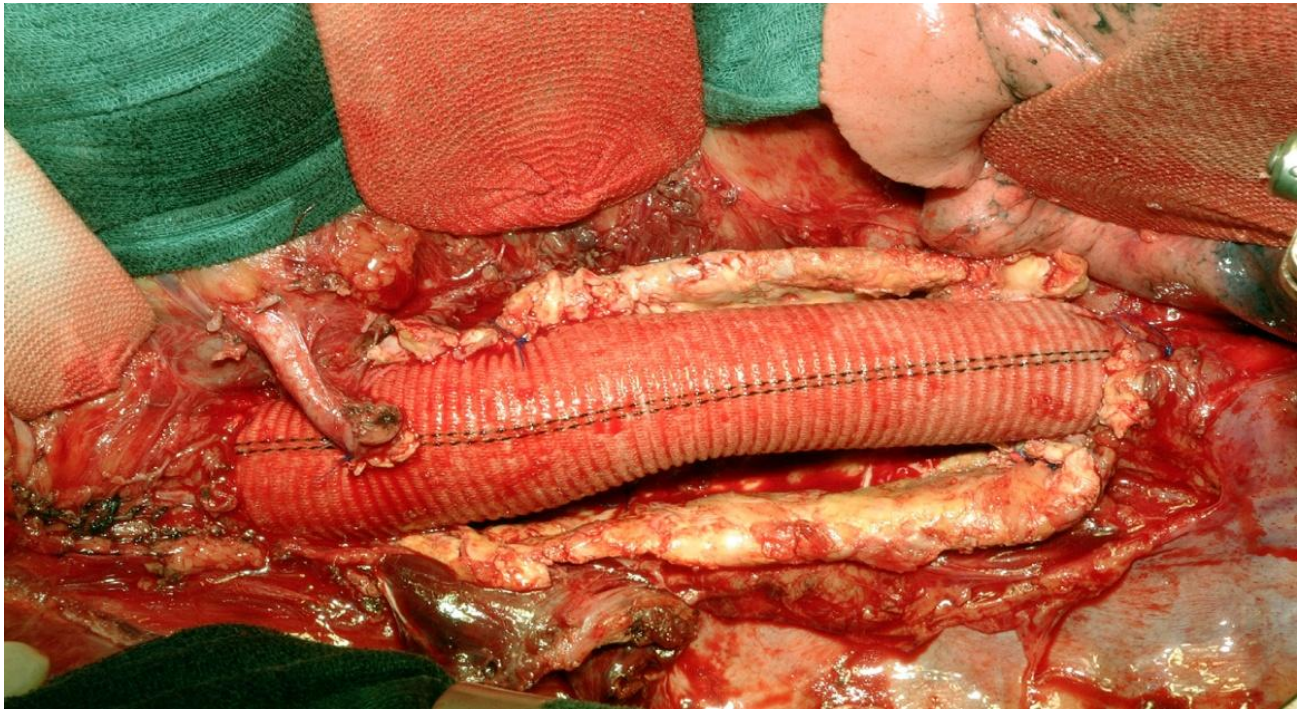
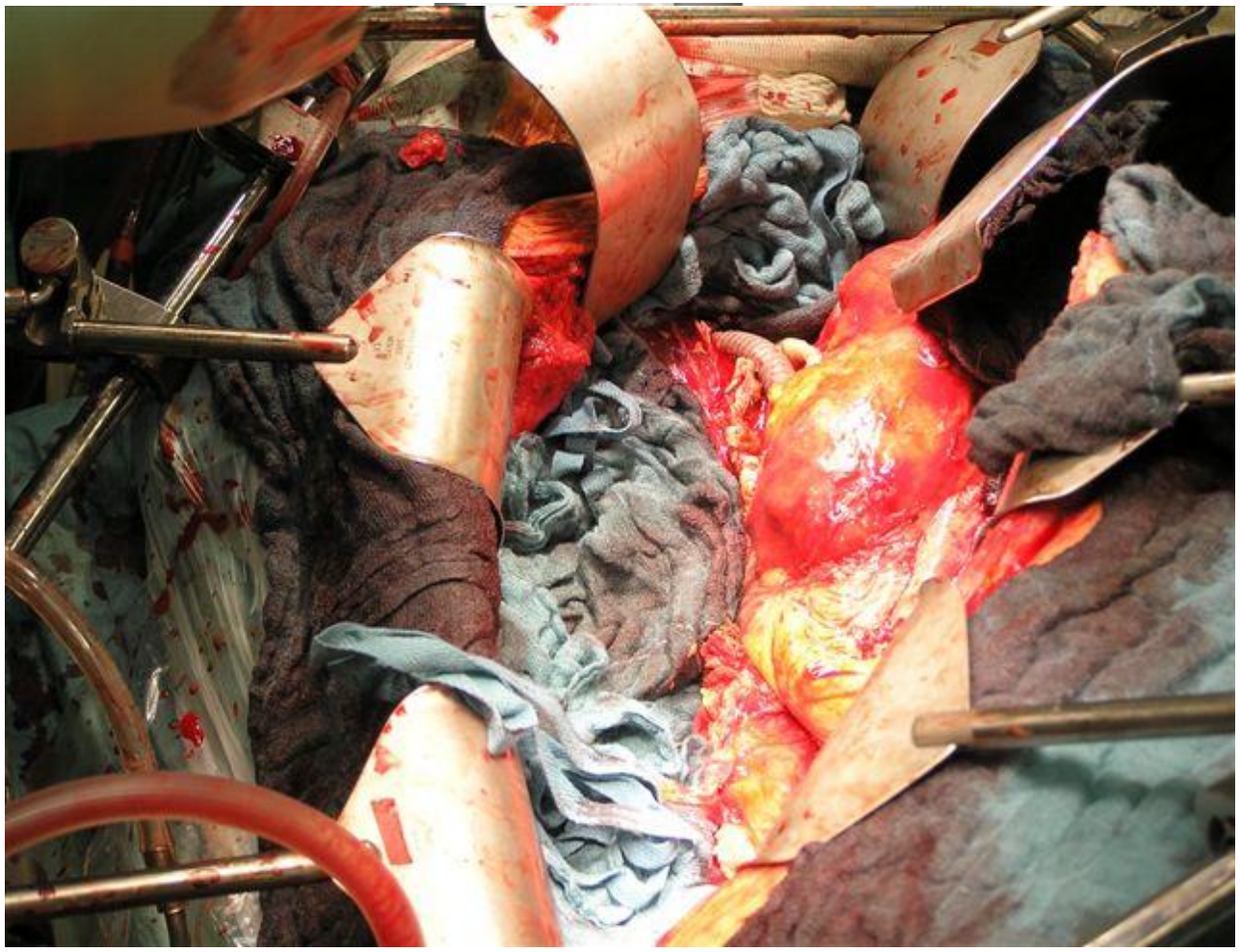
Proof-of-Concept Study in Aortic Repair

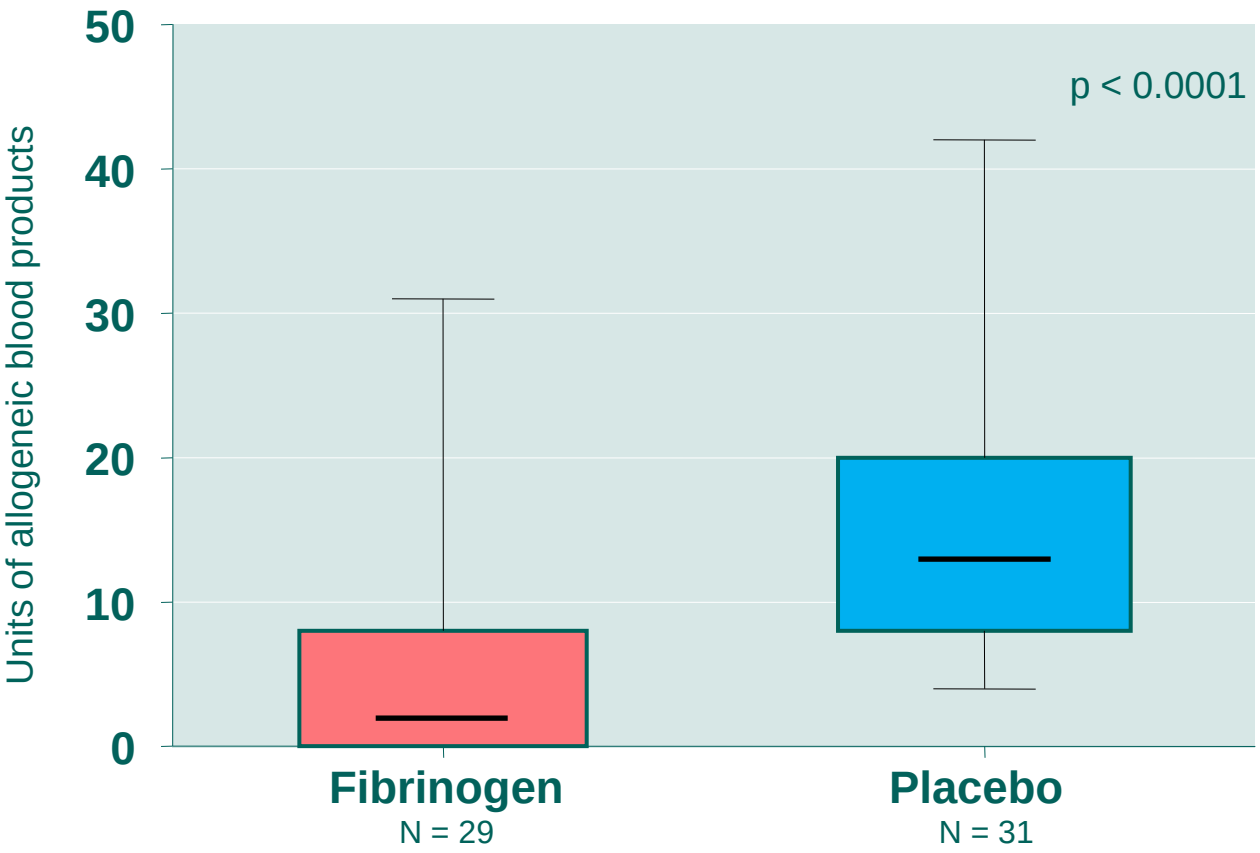
- Prospective, randomized, double-blind, placebo-controlled, single-center study



Standardised Approach



Fibrinogen Reduced Amount of Blood Transfused



Fibrinogen Reduced Proportion of Patients Requiring Transfusion

Administration of donated blood products	Proportion of subjects		
	Fibrinogen (N = 29)	**Placebo** (N = 31)	
No	45%	0%	
Yes	55%	100%	p<0.0001

Fibrinogen in Aortic Surgery Program

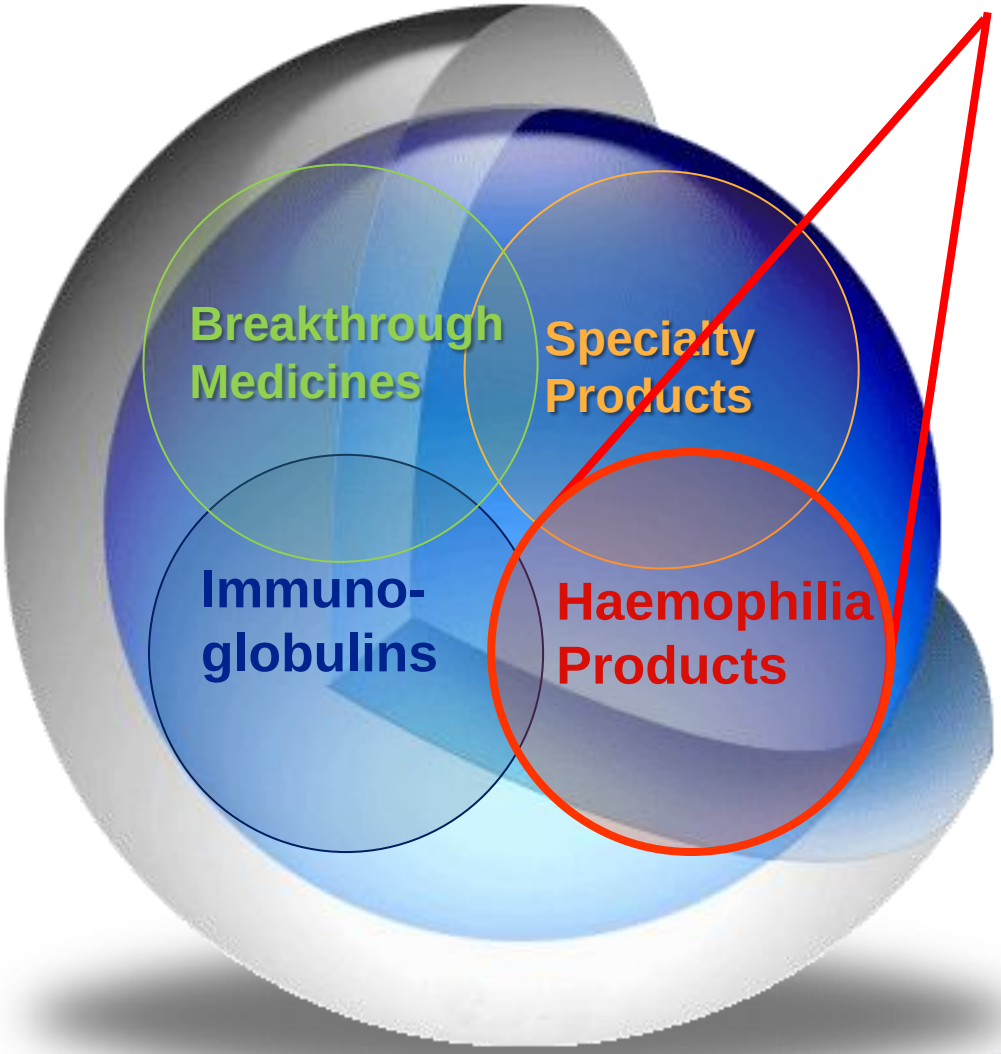
- Next 12 months
  - Confirm findings in multi-centre trials in Europe to commence in 2011
- Longer term Outlook
  - Obtain extended approvals in EU
  - Obtain indication approval in US

Q&A

Break

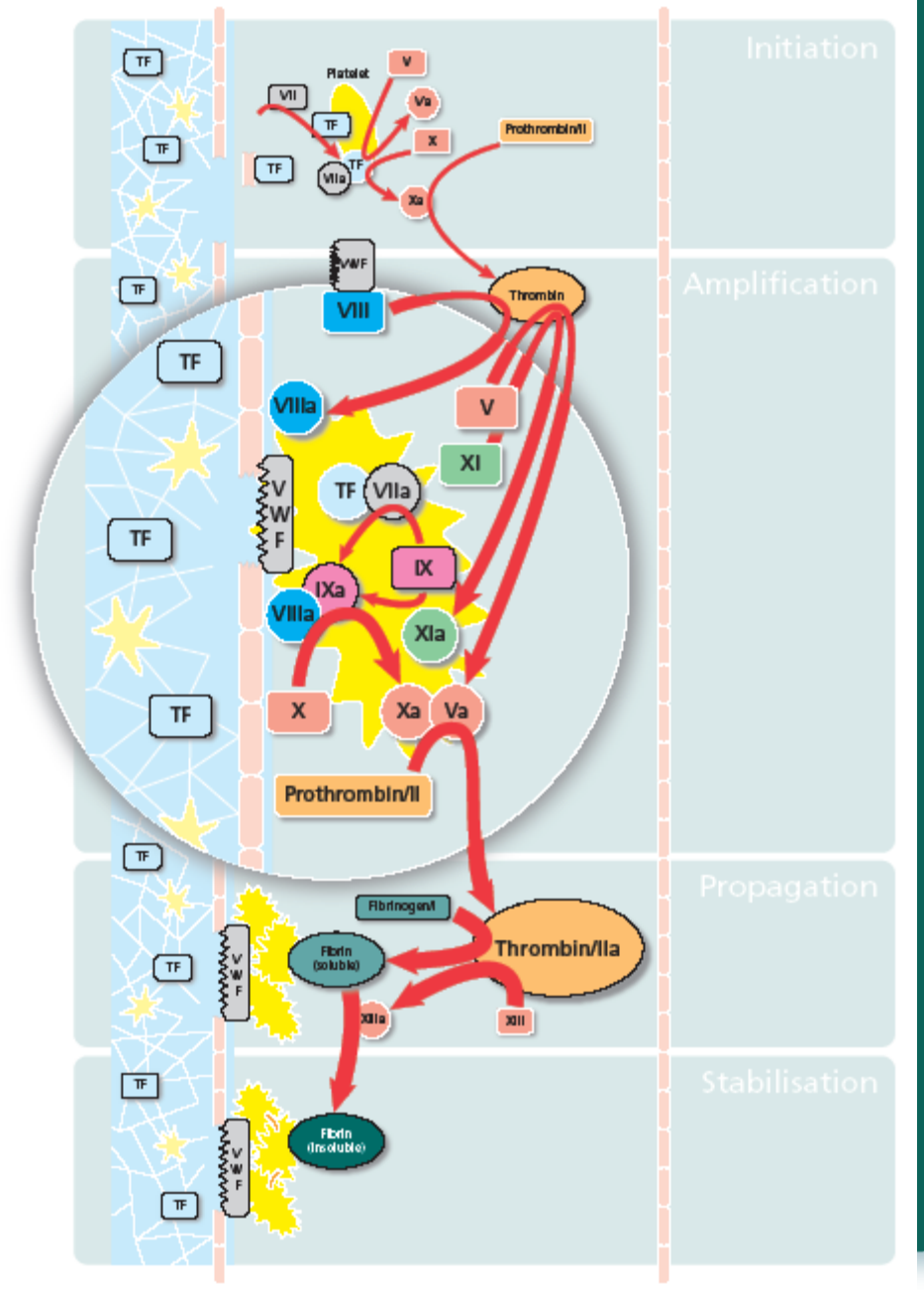
Haemophilia

Haemophilia Strategy



Supporting and enhancing portfolio and developing new products

- **Plasma products**
- **Long acting rIX & rVIIa**
- **Patient convenience**
- **Coagulation research**



Recombinant Coagulation Factors with extended half-life

CSL™

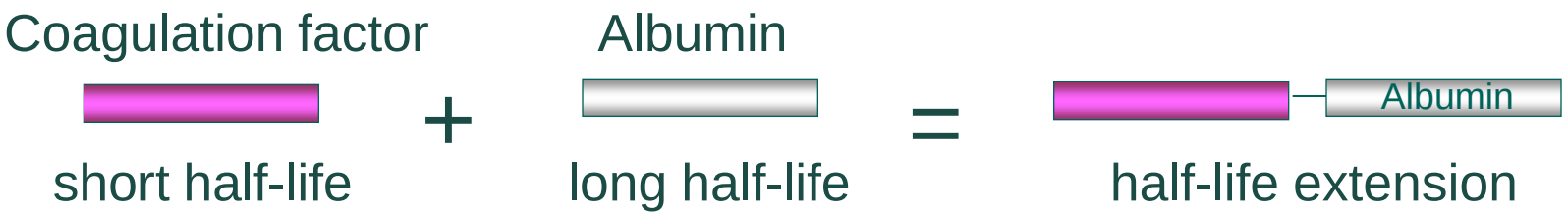
Half-life Improvement for Coagulation Products

Products with improved half-life will be beneficial to patients

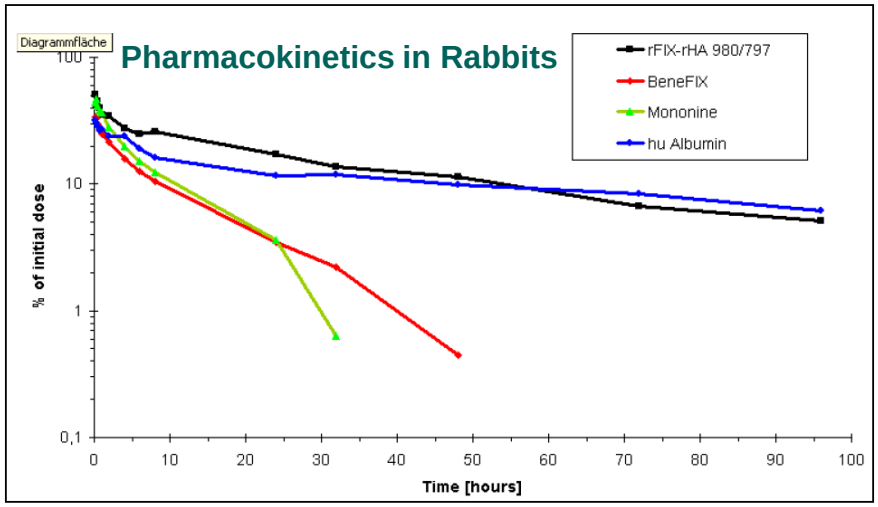
- Less frequent injections
- Improved compliance
- May enable prophylaxis

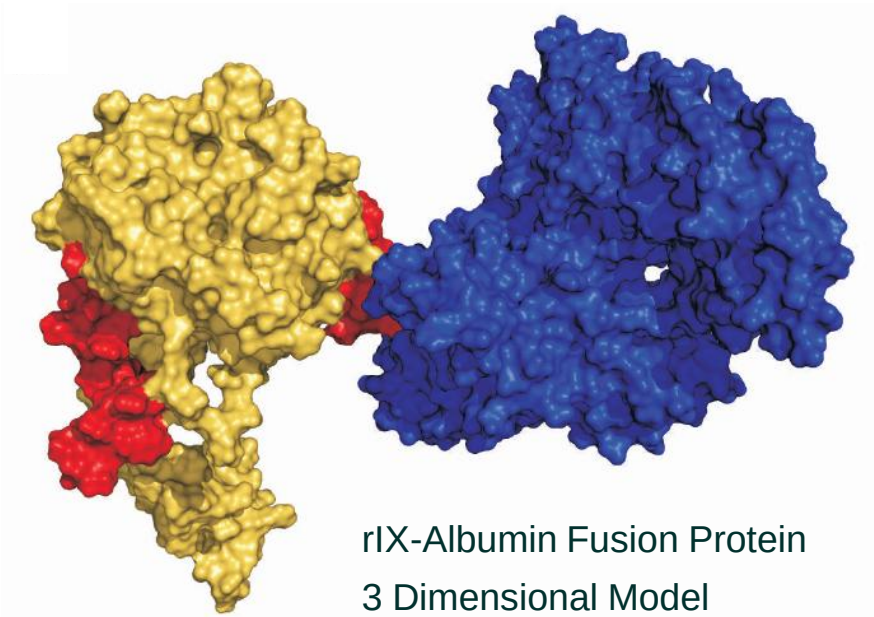
Albumin as a Carrier Protein

- Albumin has a naturally long half-life (~20 days)
- Proof of principle data for FVIIa and FIX

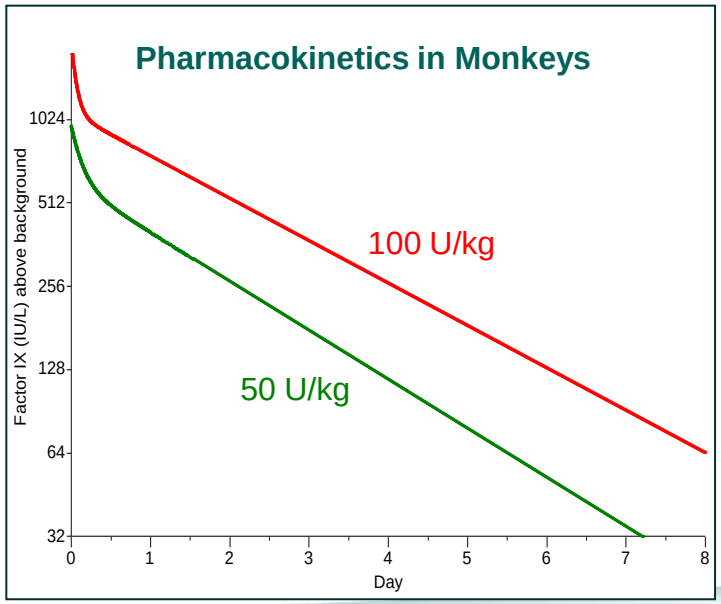


Albumin fusion extends the half life of rFIX





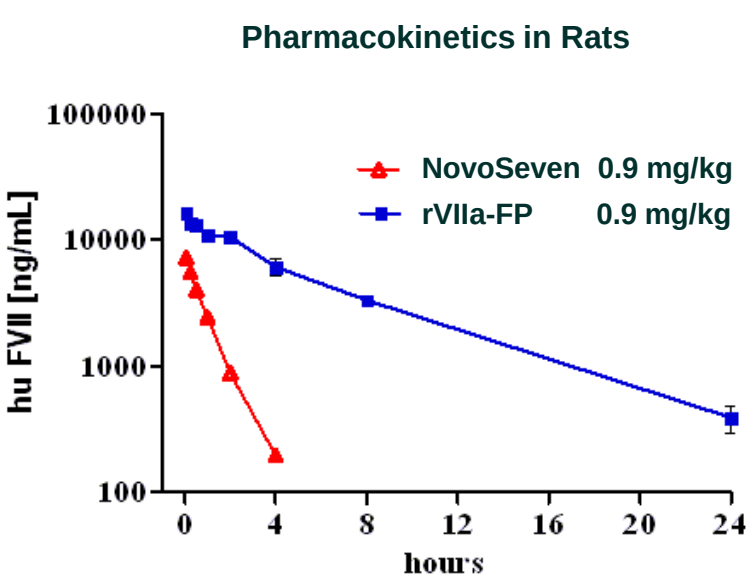
rIX-Albumin Fusion Protein
3 Dimensional Model

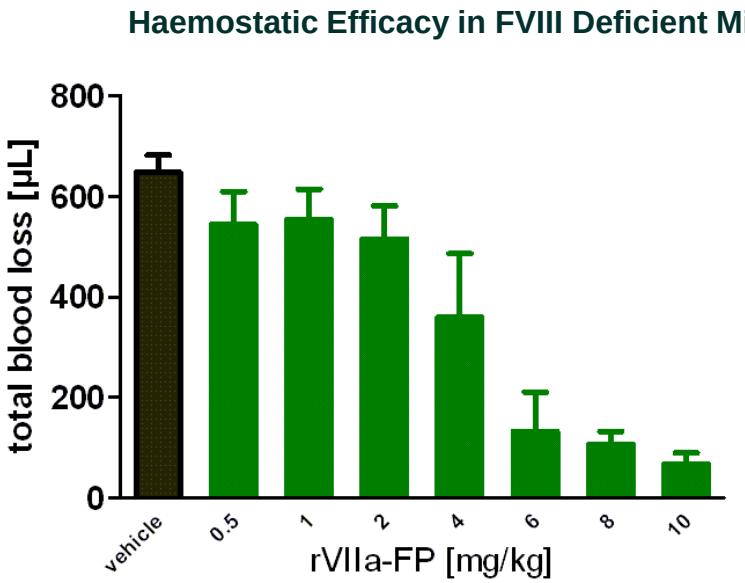


- Pre clinical toxicology completed
- Phase I commenced Oct 2010
- Data available in ~12 months

Extended half life suitable for once per week dosing

Albumin fusion extends the half life of rVIIa





- Pilot scale manufacturing process developed
- Proceeding to pre clinical toxicology, Q1 2011

Manufacturing for Rec Coagulation Products

Phase I / II

Process Development

GMP Manufacture

CSL

Parkville

Melbourne

Australia

Technical Transfer

Phase III & Launch

Contract Manufacturing

Cell Culture Intermediate

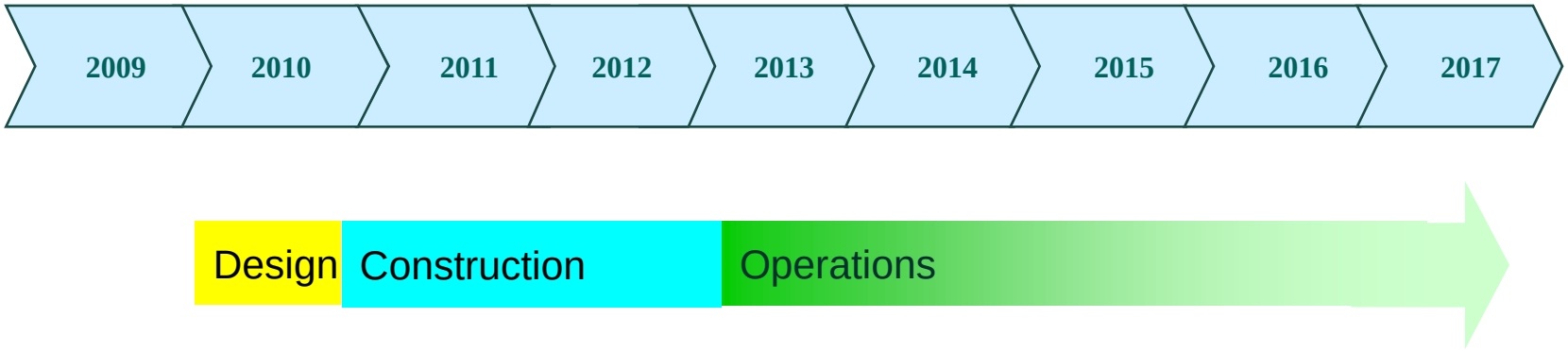
Intermediate

Transportation

CSL's purification expertise

Purification to Finished Product

Large Scale Biotech Facility



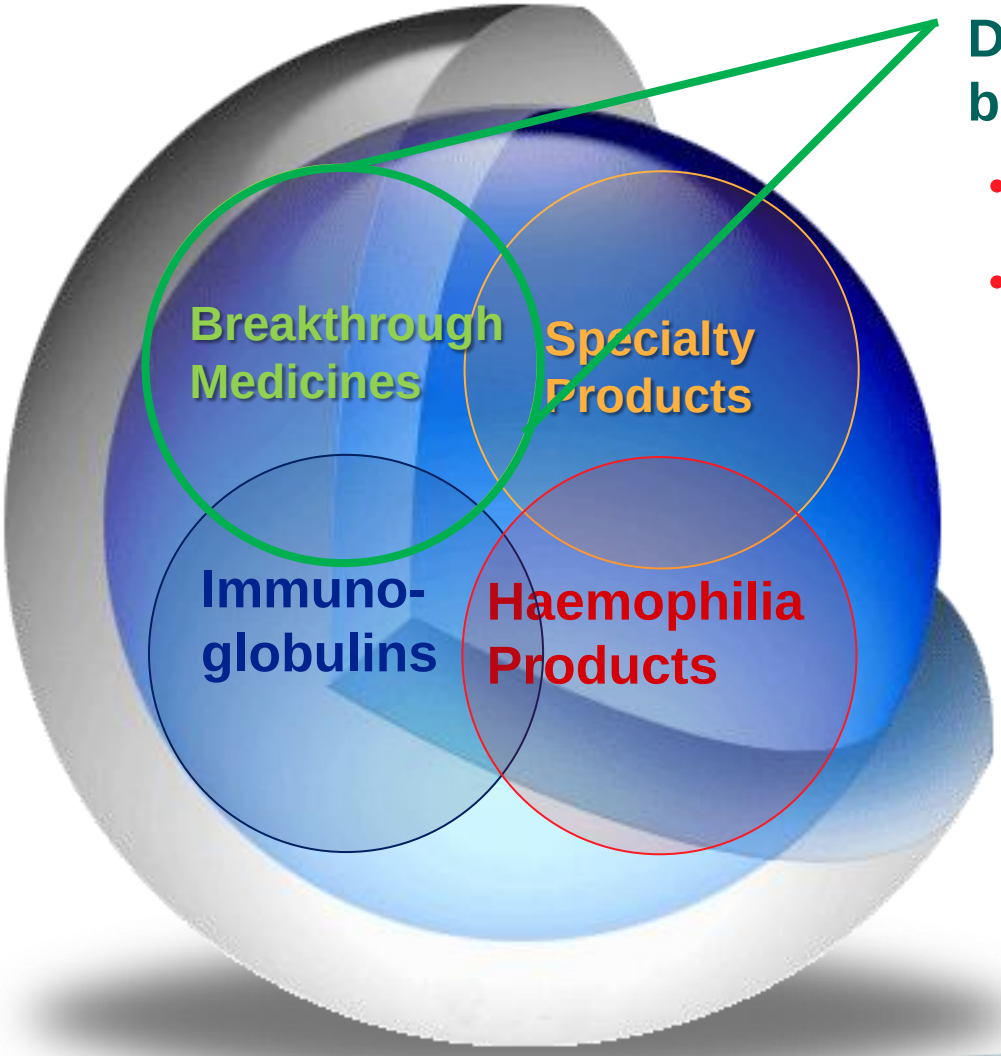
- Support large scale manufacturing for CSL's R&D portfolio
- Highly flexible to accommodate range of biotechnology manufacturing processes.
- Compliant to FDA, EMA and TGA requirements
- Construction commenced November 2010

Utilising Marburg's Coagulation Expertise

- Facility for purification and formulation of recombinant coagulation proteins
- Renovation of existing FDA compliant recombinant facility
- Utilise existing knowhow of plasma coagulation factors
- Opened November 2010

Breakthrough Medicines

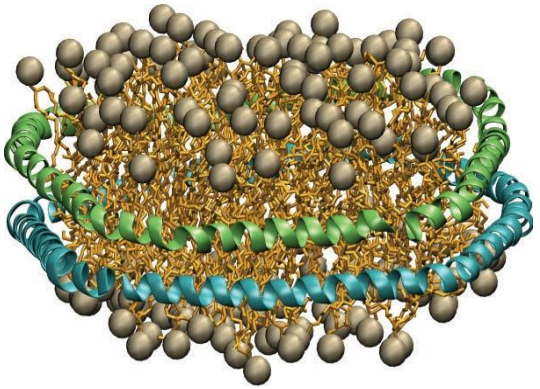
Breakthrough Medicines Strategy



Developing new protein-based therapies

- **Significant unmet need**
- **Multiple indications, e.g.**
  - **Reconstituted HDL**
  - **Anti IL-3Rα mAb**
  - **Anti G-CSFR mAb**

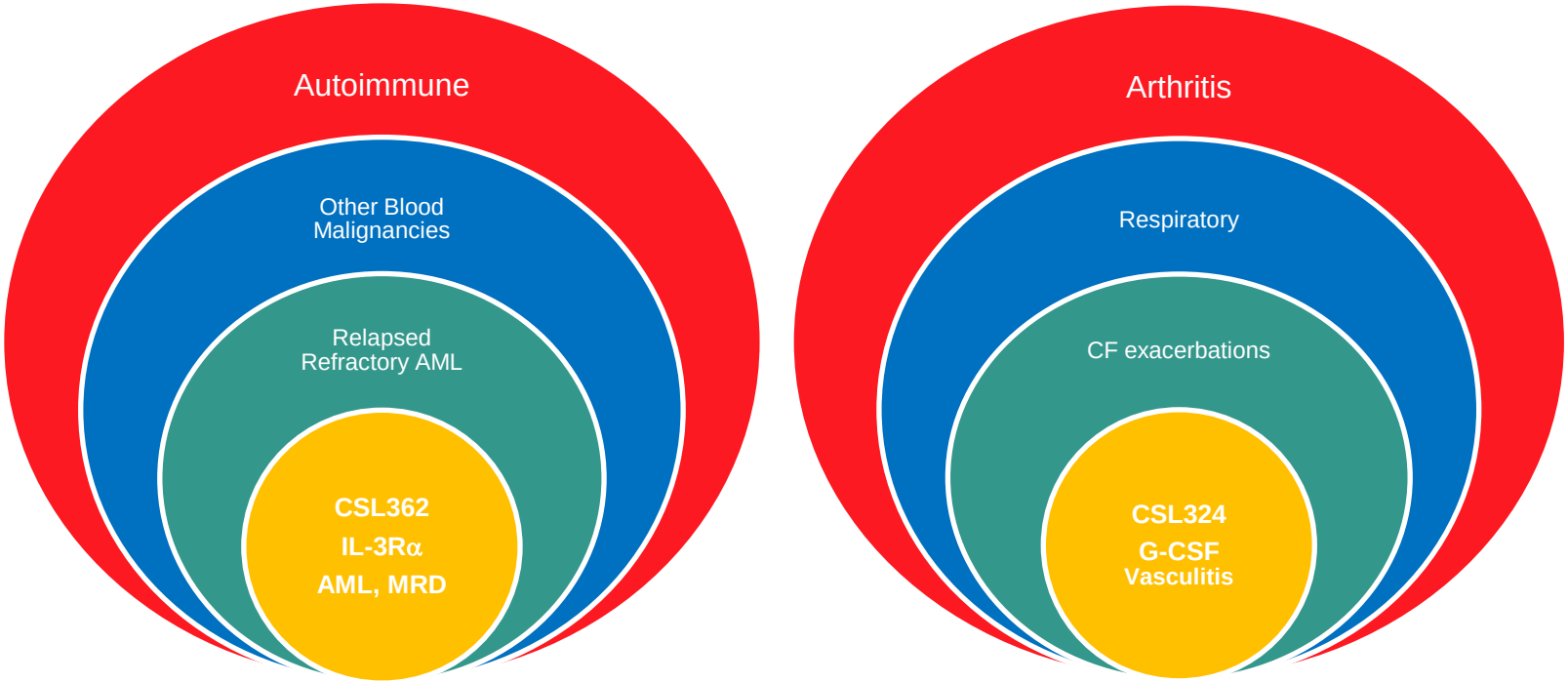
Reconstituted HDL (CSL112)



- Compelling opportunity
- Significant investment and risk in late stage development
- Phase I study progressing well
- Phase IIa to commence in 2011

Optionality of rMAb Programs

- Establish paradigm
- Opportunity for multiple medical indications



*Possible clinical indications only

CSL362

Acute Myeloid Leukemia

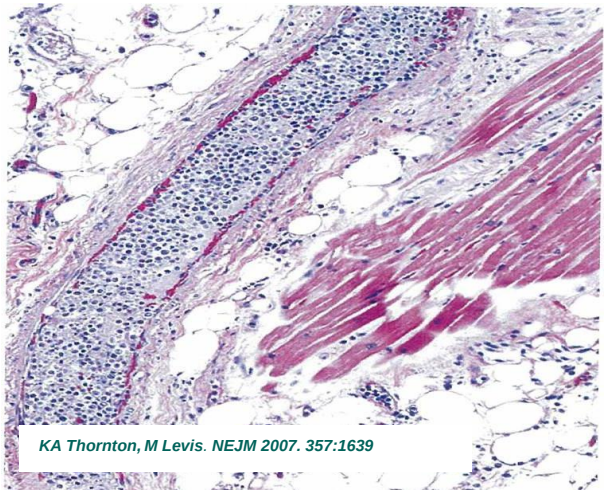
CSL362 - AML

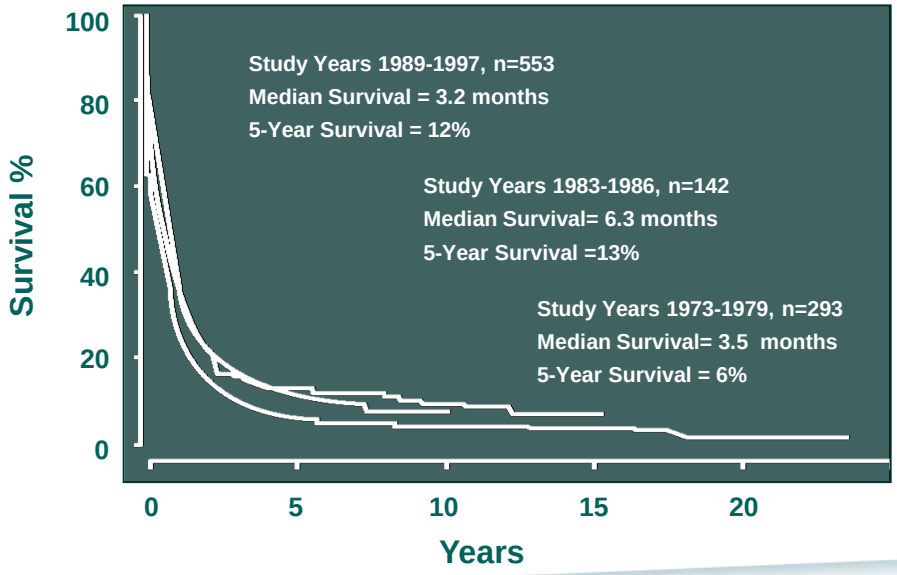
AML

- most common acute leukaemia in adults
- incidence increases with age
- untreated AML fatal: 3 - 4 mo

- chemotherapy → 50-75% CR
  ~70% will relapse

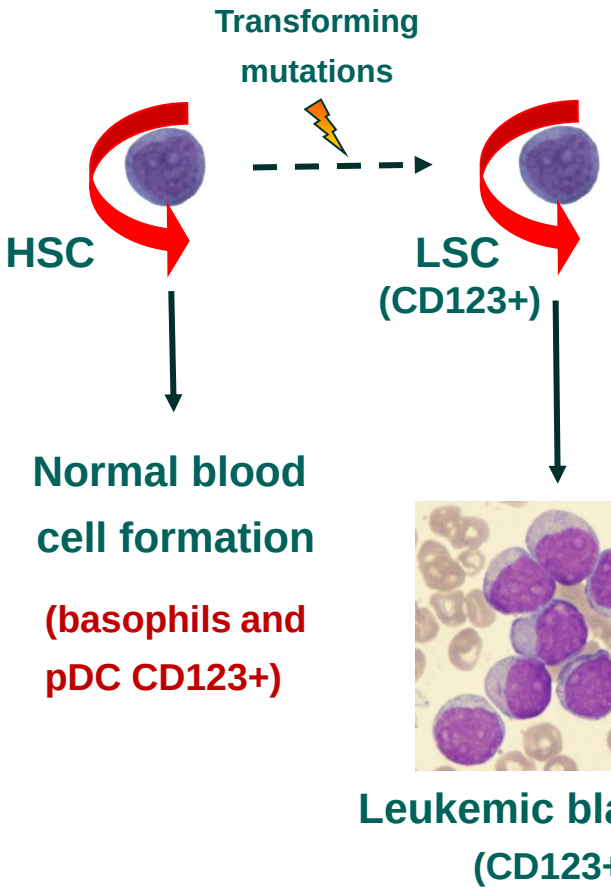
- 5-year OS = 21% (2008)
  < 55 yrs ~ 40%
  > 55-65 yrs < 10%
  > 65 yrs < 5%

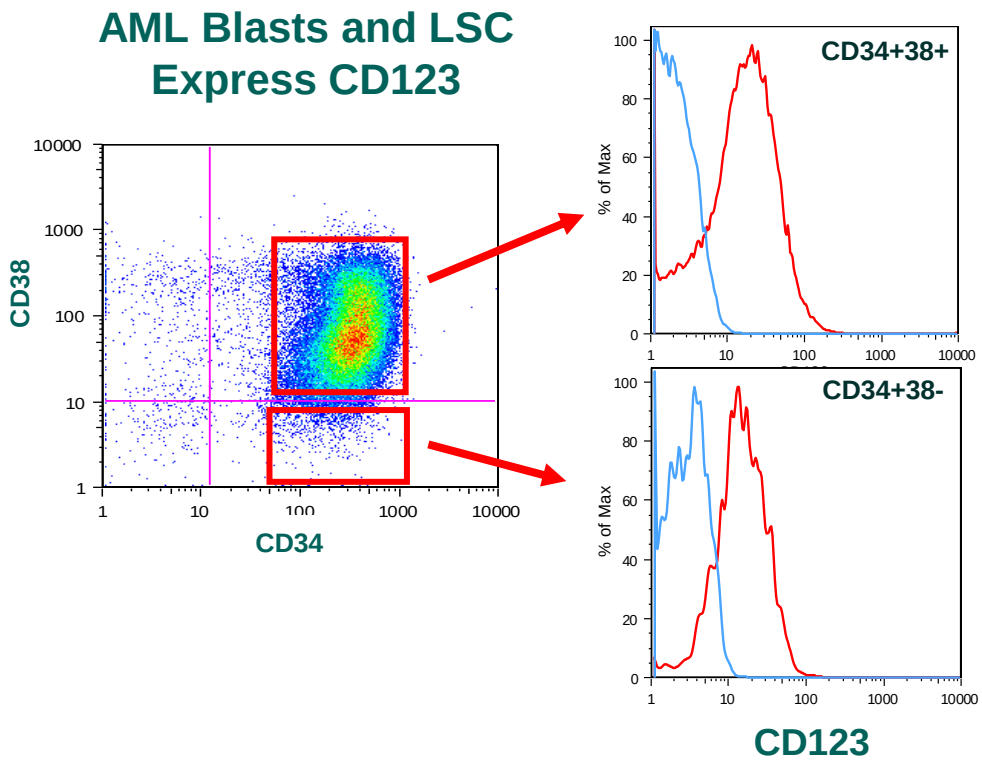




CSL362 - AML

CD123 is a target expressed on AML blasts and leukemic stem cells

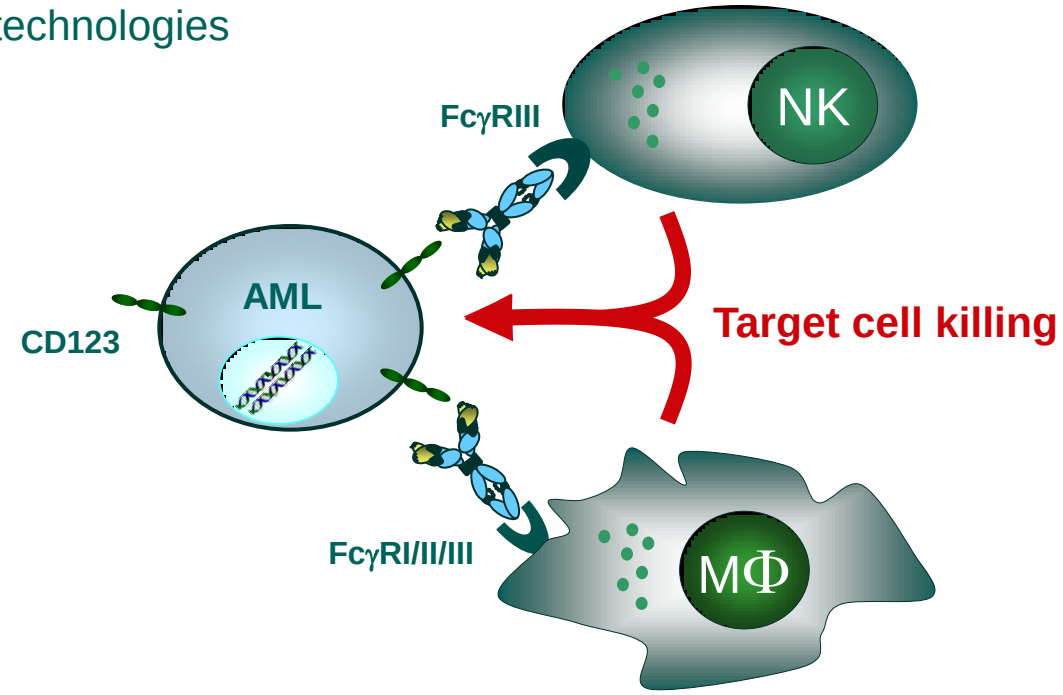




CSL362 - AML

CSL362 – a second generation mAb targeting CD123 (IL-3Rα)

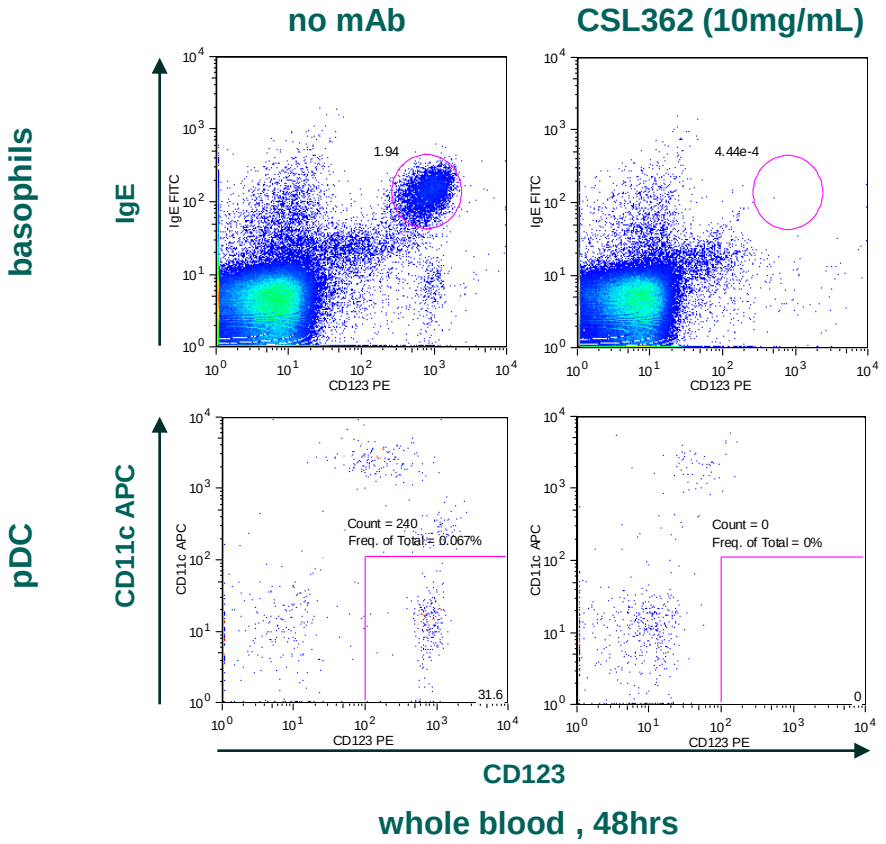
- retains (cf. CSL360) the ability to potently inhibit IL-3 activity
- humanised for reduced immunogenicity
- optimised for enhanced tumour killing activity
  - in-licensed proprietary technologies

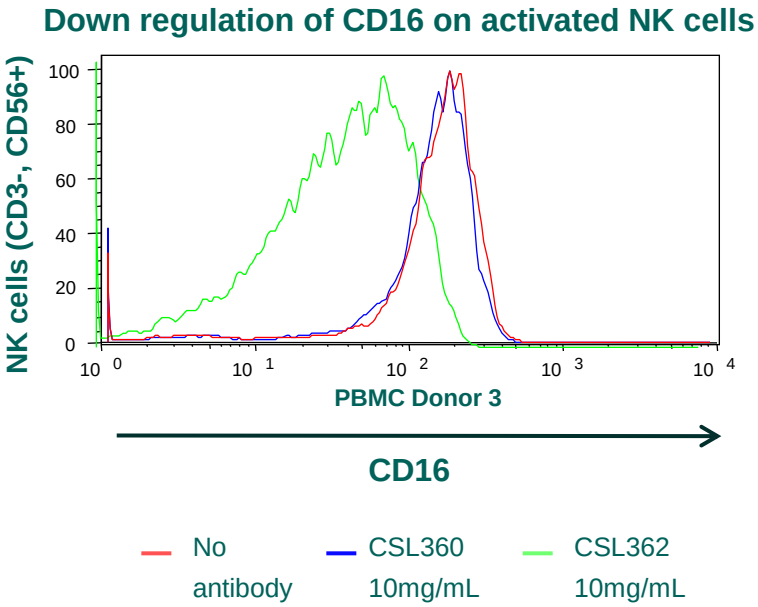


CSL362 - AML

CSL362 shows potent killing activity *in vitro* I

- blood basophils and pDC





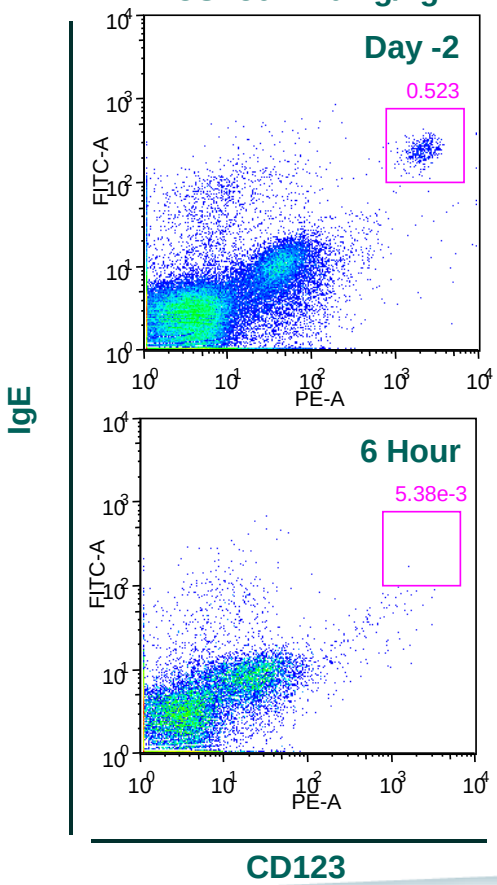
CSL362 - AML

CSL362 shows potent killing activity *in vivo* I

- basophils and pDC in non-human primates

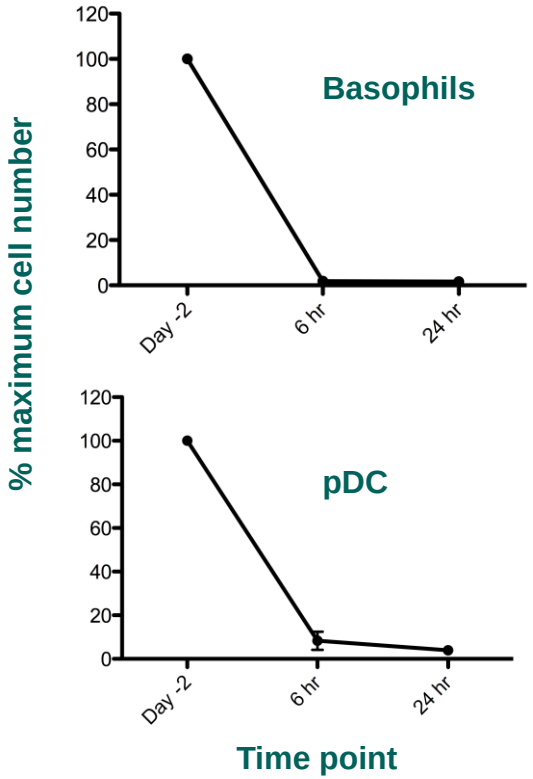
Basophil depletion

CSL362: 10mg/kg



Time course analysis of cell depletion

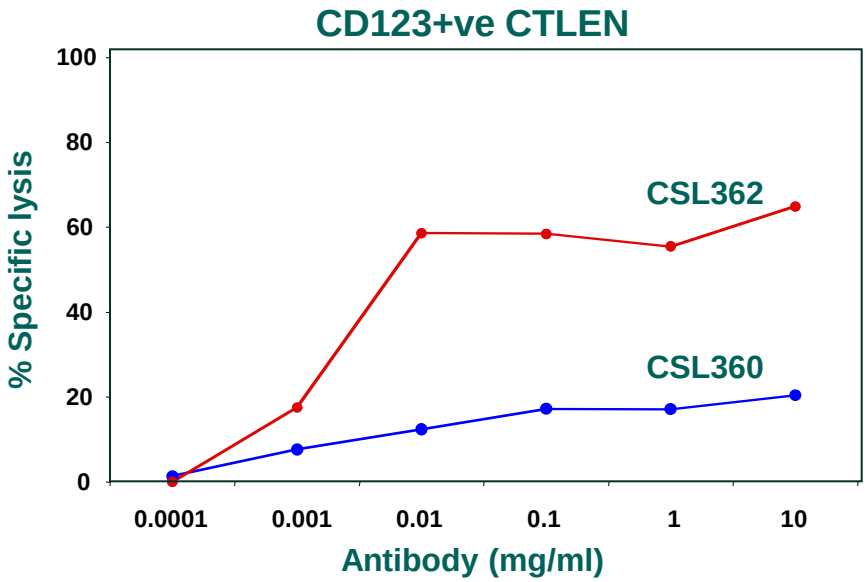
3 NHP's / grp, CSL362: 10mg/kg



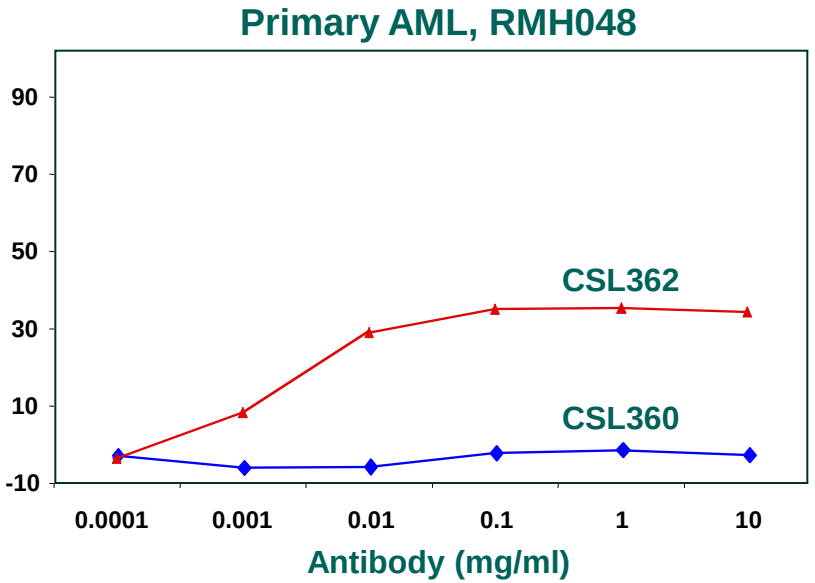
CSL362 - AML

CSL362 shows potent killing activity *in vitro* II

- tumour cell lines and primary AML cells



(Donor PBMC effectors, E:T = 100:1)

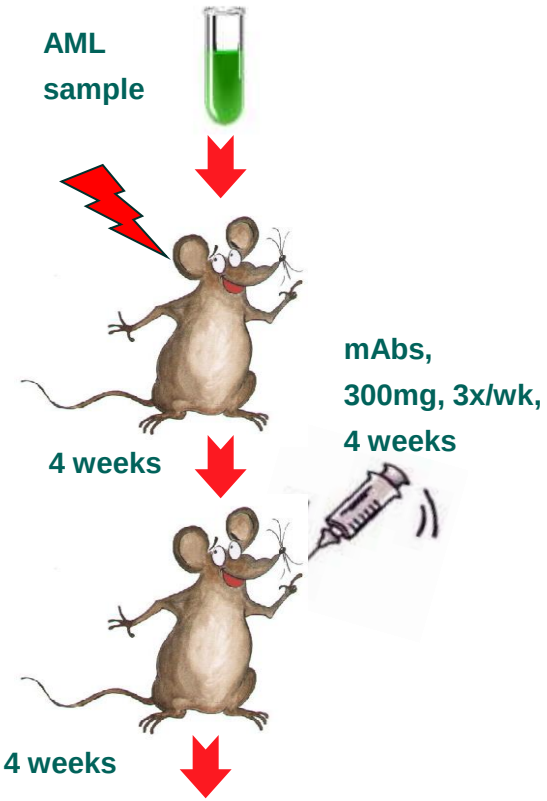


(Enriched NK effectors, E:T = 25:1)

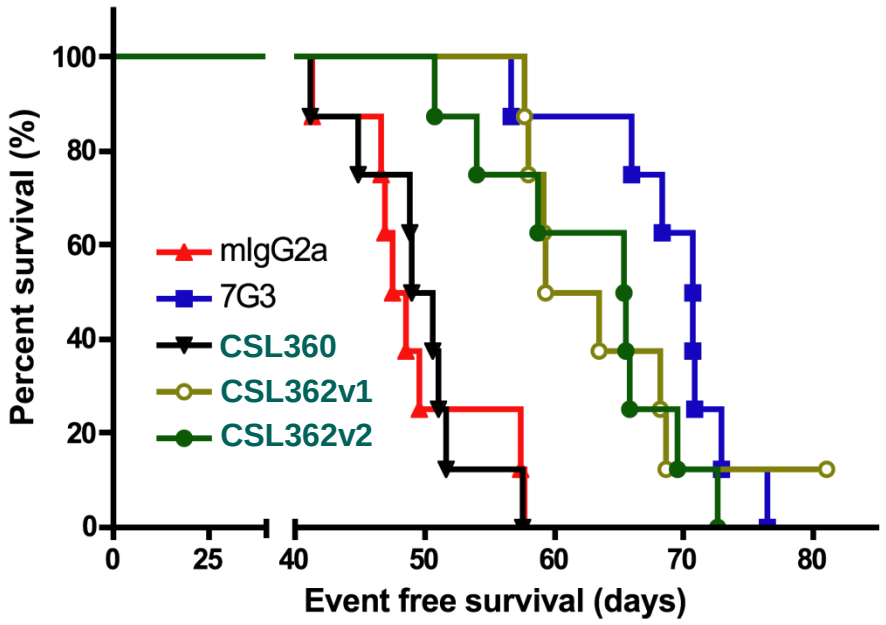
CSL362 - AML

CSL362 shows potent killing activity *in vivo* II

- primary AML cells in NOD/SCID mice



Engraftment measured by % human CD45+ cells in peripheral blood (>20% = event).



P= 0.0007 comparing CSL360 and CSL362 V1

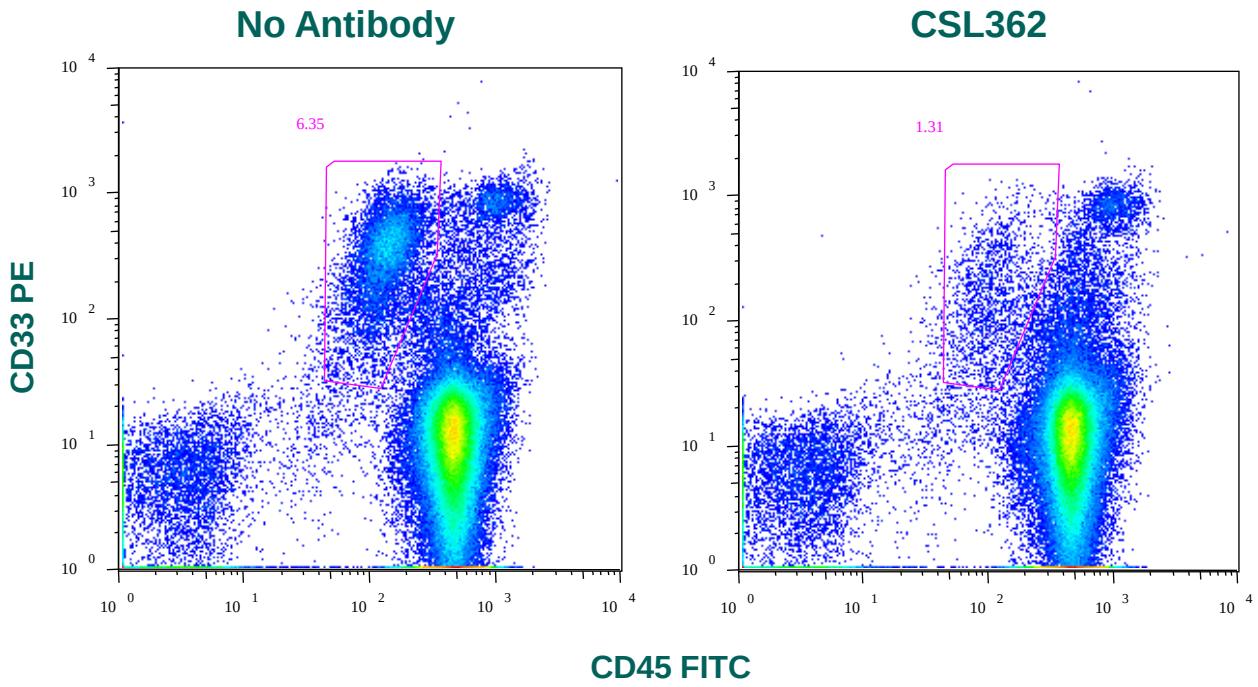
P= 0.0002 comparing CSL360 and CSL362

(LGD between these groups =12-15 days)

CSL362 - AML

CSL362 shows potent killing activity *in vitro* III

- primary patient AML blasts with autologous remission NK cells



NK and blast cells from RMH076 mixed at a ratio of 3:1. CSL362 added to a final conc. of 10ug/mL and the cultures incubated for 24h at 37ºC.

CSL362 – AML

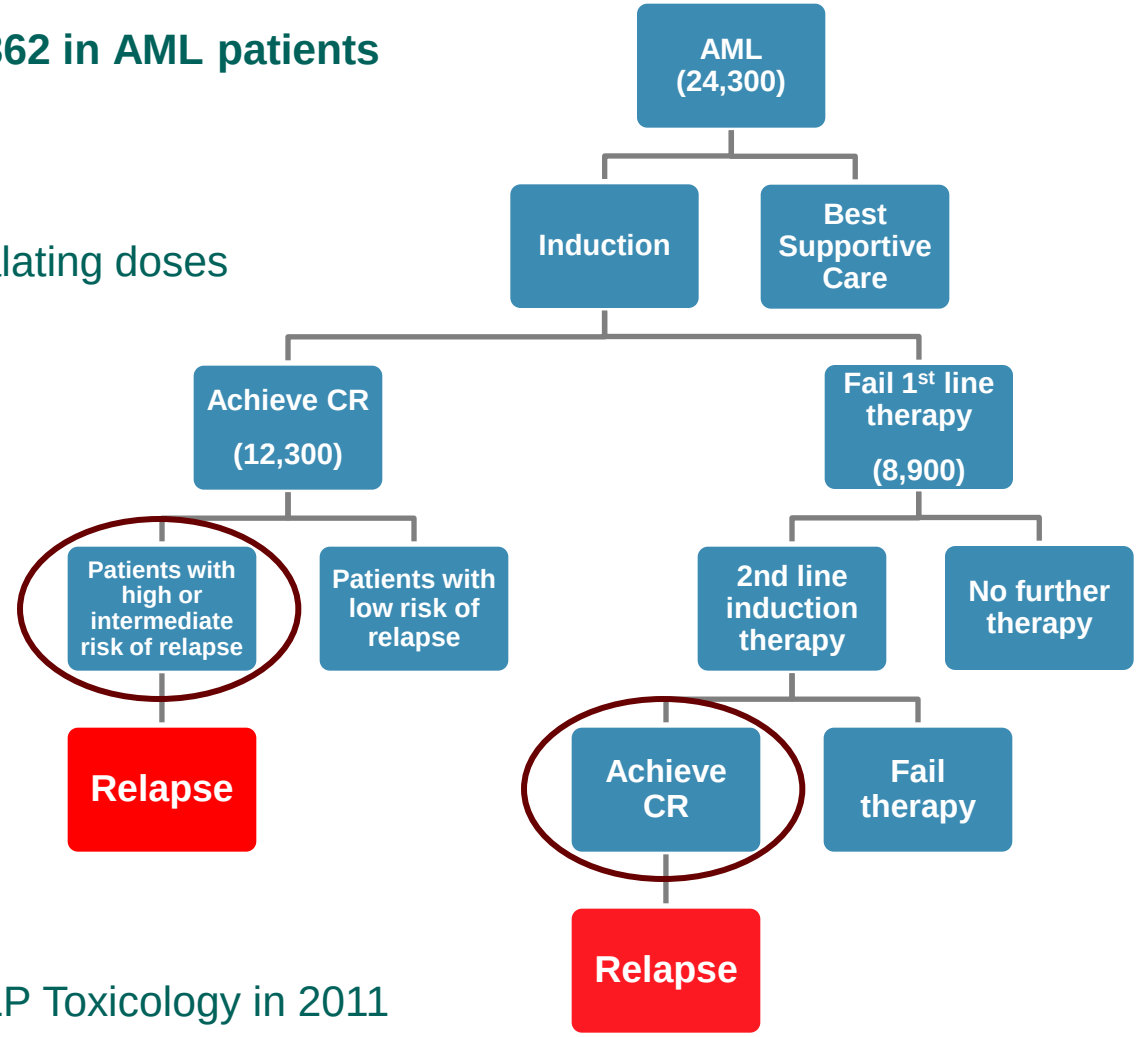
FIH, Phase I/IIa study of CSL362 in AML patients
- remission / early relapse

Primary objectives:

- safety and tolerability of escalating doses
- PK; immunogenicity

Secondary objectives:

- MTD (if exists within range)
- anti-leukaemic activity (clinical response rate)
- biological effect on CD123+ LSC and blasts
- biologically effective dose & schedule



Next milestone: commence GLP Toxicology in 2011

commence clinical studies early 2012

CSL362 – Longer Term Potential for SLE

pDC and basophils support the progression of SLE

- SLE is characterised by an IFNα signature and pDC are the major source of IFNα in SLE

Vol 465|17 June 2010|doi:10.1038/nature09102 nature

LETTERS

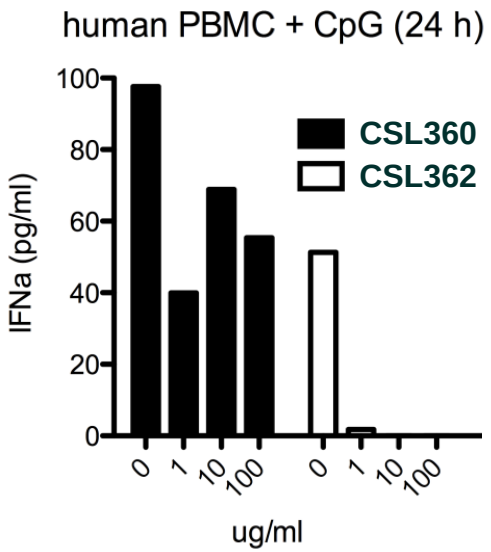
TLR recognition of self nucleic acids hampers glucocorticoid activity in lupus

Cristiana Guiducci[1], Mei Gong[1], Zhaohui Xu[2], Michelle Gill[2]†, Damien Chaussabel[2], Thea Meeker[1], Jean H. Chan[1], Tracey Wright[3,4], Marilynn Punaro[3,4], Silvia Bolland[5], Vassili Soumelis[6], Jacques Banchereau[2], Robert L. Coffman[1], Virginia Pascual[2,3] & Franck J. Barrat[1]

nature medicine

Basophils and the T helper 2 environment can promote the development of lupus nephritis

Nicolas Charles[1], Donna Hardwick[2], Eric Daugas[3], Gabor G Illei[4] & Juan Rivera[1]



- mAb added for 18 hr to deplete pDCs, CpG (5 uM) added for 24 hr to stimulate IFN-α production.

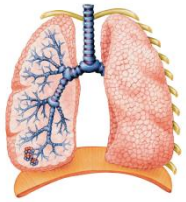
CSL 324

Acute and Chronic Inflammation

CSL324 – Acute and Chronic Inflammation

Neutrophils and inflammatory disease

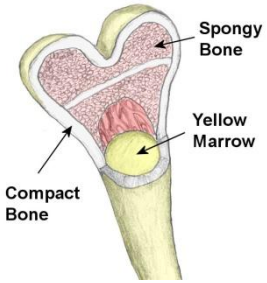
- most abundant WBC, ~10^9 cells / kg body weight leave the bone marrow (BM) per day
- key effectors of the innate response to infection *but...*
- excessive production and persistence within tissues leads to chronic inflammation and tissue destruction



COPD exacerbations

CF exacerbations

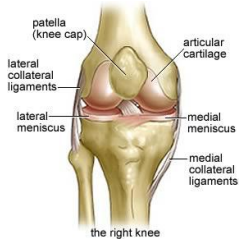
ARDS



G-CSF

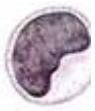
neutrophils

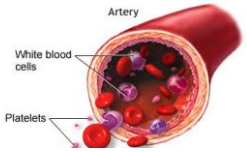
G-CSF



Rheumatoid arthritis

CSF's, cytokines





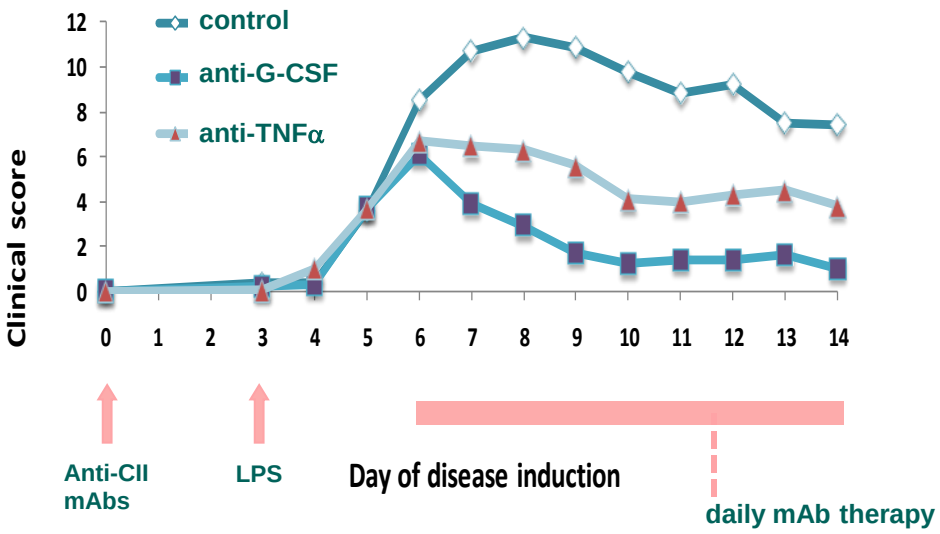
Vasculitis

CSL324 – Acute and Chronic Inflammation

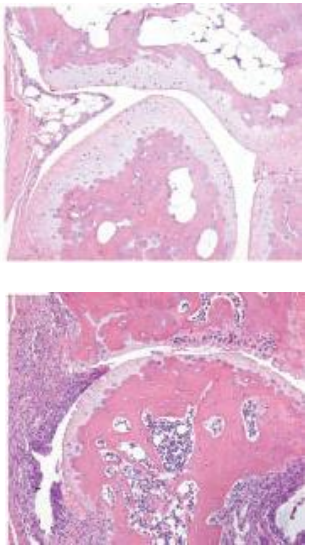
The role of G-CSF in mouse models of inflammatory disease

- anti-G-CSF mAb inhibits disease progression in mouse models of arthritis

Anti-collagen Ab – induced arthritis



Collagen-induced arthritis



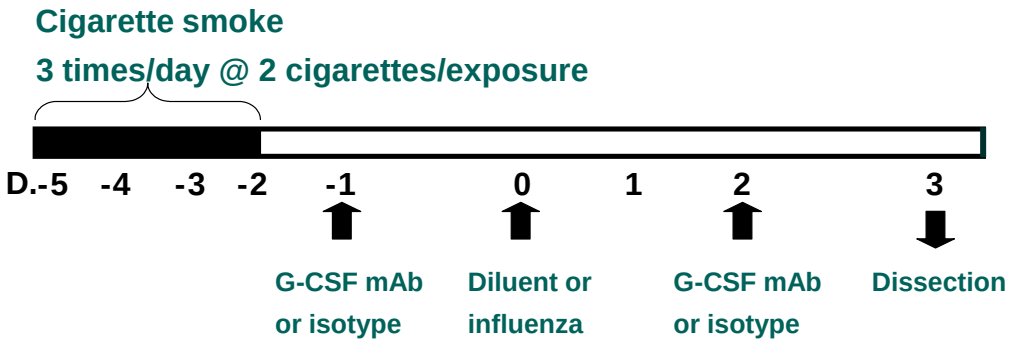
G-CSF gene knockout

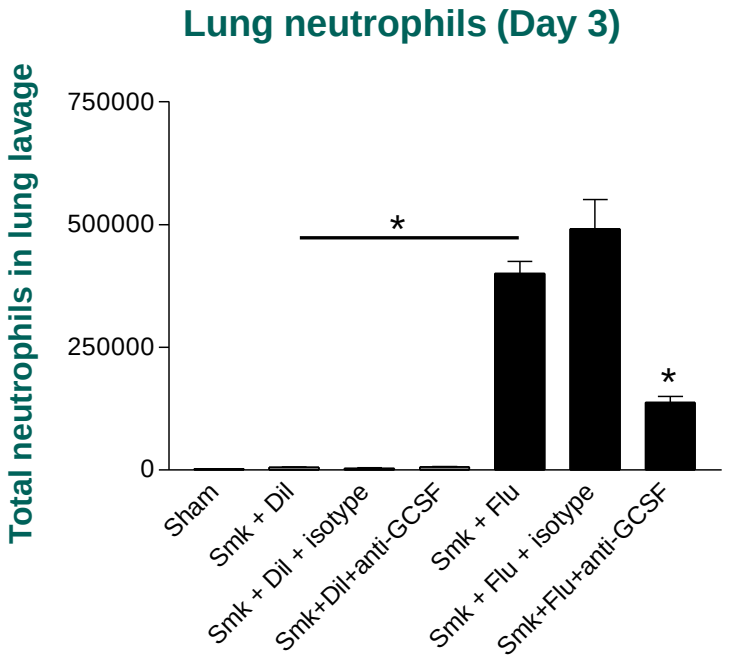
control

CSL324 – Acute and Chronic Inflammation

The role of G-CSF in mouse models of inflammatory disease

- anti-G-CSF mAb inhibits disease progression in a mouse model of COPD





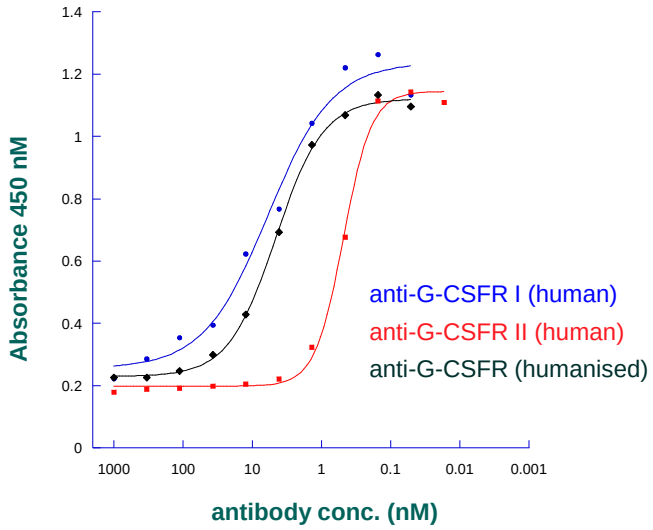
CSL324 – Acute and Chronic Inflammation

Identification and characterisation of a lead candidate mAb

- options available included:
  - humanisation of in-licensed mouse mAbs against the huG-CSGR
  - *de novo* generation of fully human mAbs utilising Dyax phage display technology (G-CSF and / or G-CSFR specific)

CSL324

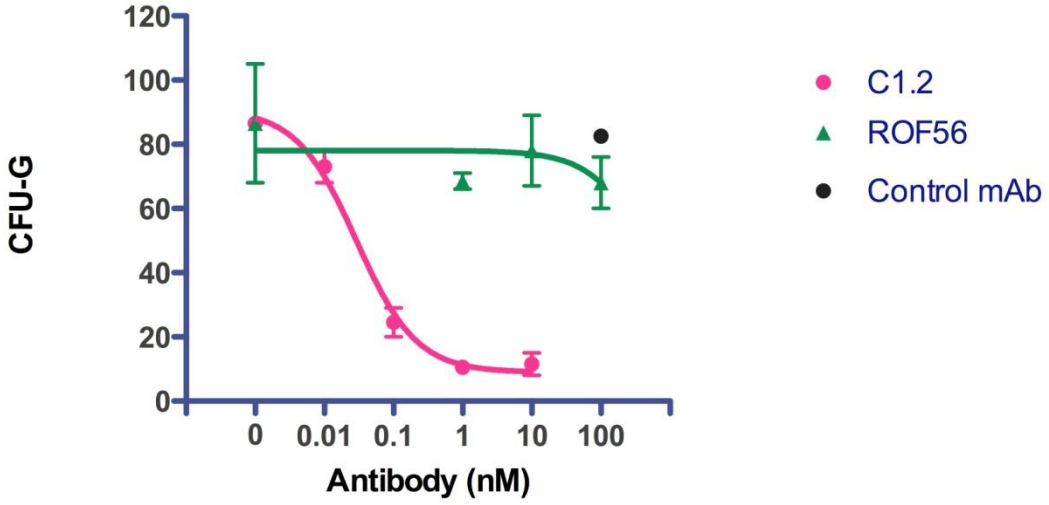
- fully human mAb directed against the human G-CSFR
- high affinity for target – 257pM at the cell surface
- potent antagonist of G-CSF activity in a variety of assay systems



CSL324 – Acute and Chronic Inflammation

CSL324 is a potent inhibitor of G-CSF action *in vitro*

- inhibition in of G-CSF mediated neutrophil production from HSC



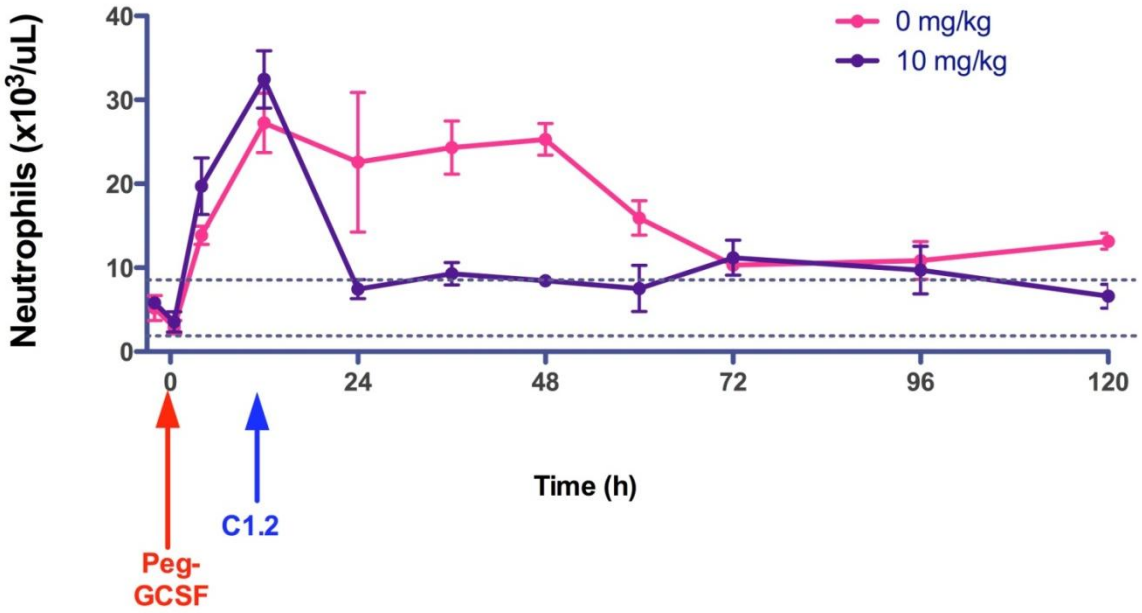
mAb	IC50 (nM)
C1.2	0.016
RO5F6	ND

Each point represents the mean +/- range of duplicate measurements

CSL324 – Acute and Chronic Inflammation

CSL324 is a potent inhibitor of G-CSF action *in vivo*

- inhibition of PEG-G-CSF induced neutrophilia in NHP's



- **2 groups (3 animals per group)**
- **s.c PEG-GCSF on Day 1**
- **single i.v infusion of CSL324 12 hrs later**

CSL324 – Acute and Chronic Inflammation

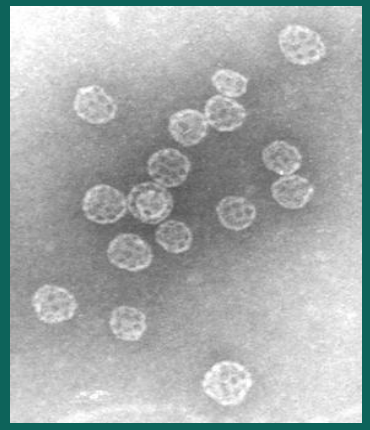
Concluding comments

- CSL324:
  - fully human monoclonal antibody directed against the G-CSFR
  - a potent antagonist of G-CSF activity in *in vitro* and *in vivo* assays systems
  - does not induce acute neutropenia in NHP's (role of G-CSF in homeostasis vs. acute or chronic inflammation)

- opportunities for clinical development in a number of inflammatory indications
  - potential for small parallel Phase IIa studies

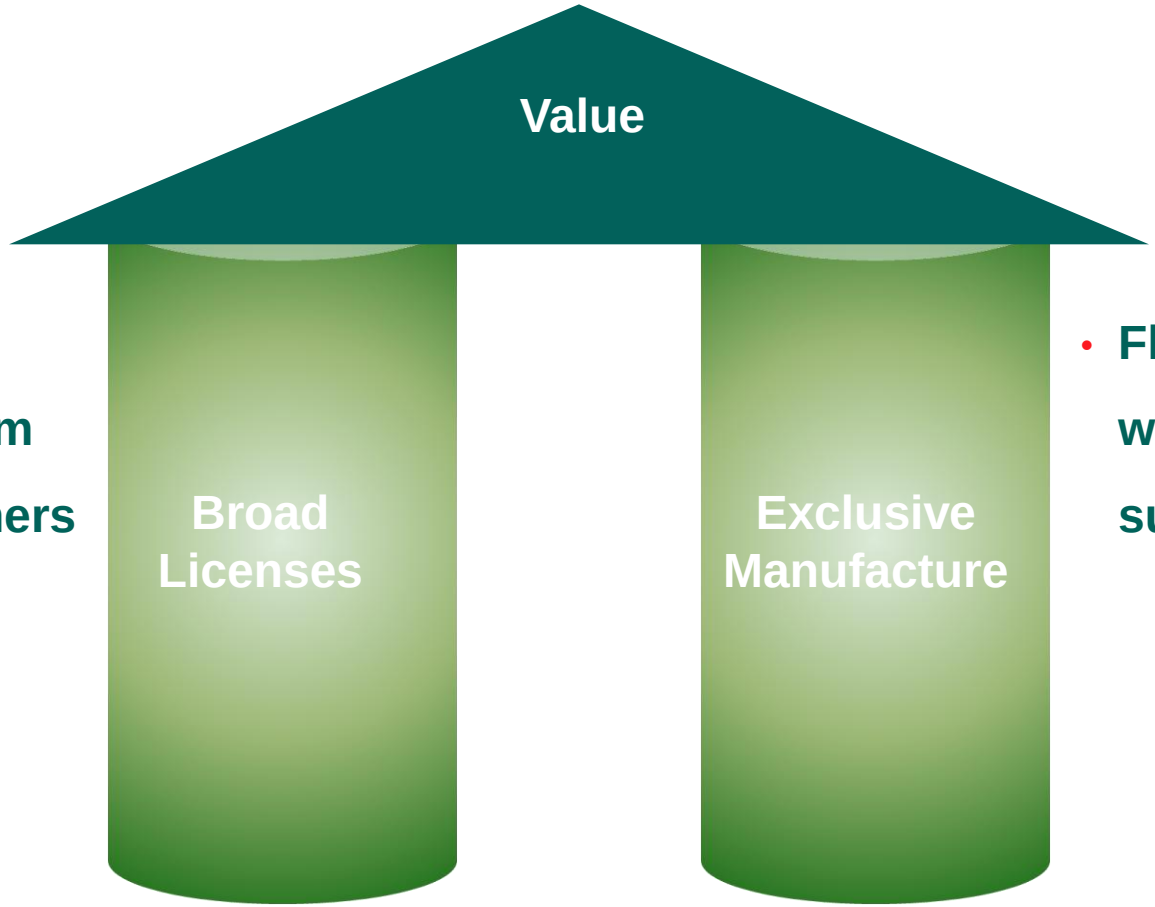
- **Next milestone:** commence preclinical tox studies late 2011

Licensing



ISCOMATRIX® Adjuvant

Business Plan: Pillars for Success



- Increased interest from major partners
- ~30 fields

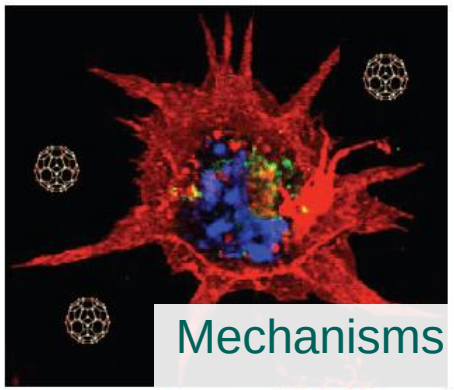
- Flexible capacity with long term supply

Merck Sharp & Dohme Corp.

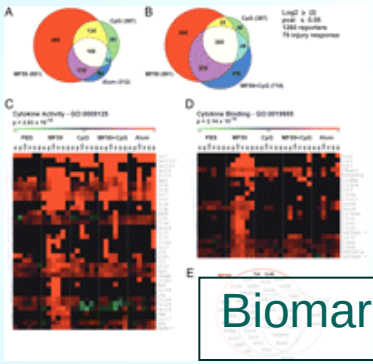
- Merck Sharp & Dohme Corp. continues to show confidence in ISCOMATRIX® adjuvant for vaccine development programs
- Additional Licences
- Broader research interest

High Quality Scientific Research

Internal research
Partners (Merck, Genentech)
High quality academics (WEHI)
FDA



Mechanisms



Biomarkers

Investigator led clinical studies (NCI)

Partnered Projects

Partnered Projects

CAM3001 (GM-CSFRα)

- Medimmume/AstraZeneca commenced Phase II study in Rheumatoid Arthritis Feb 2010

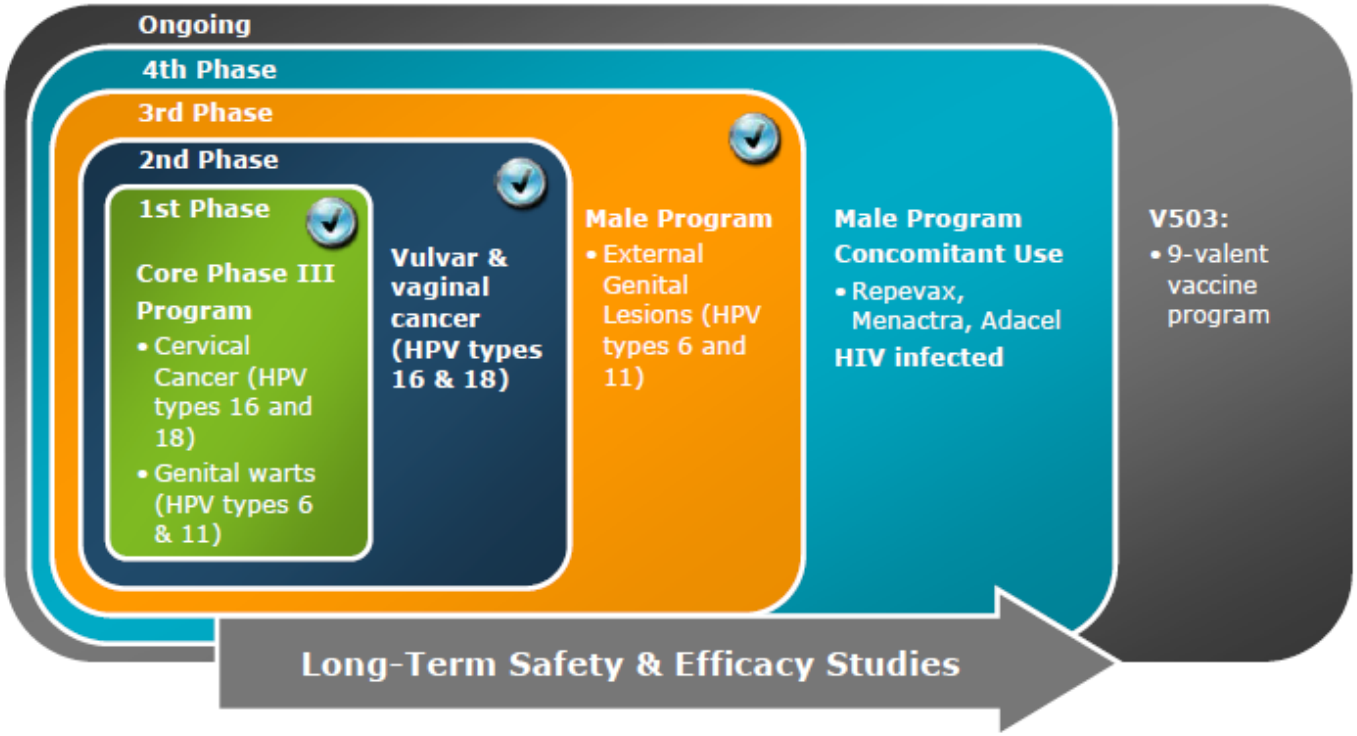
Periodontal disease vaccine

- Research agreement with Sanofi pasteur
- Option to an exclusive worldwide license

GARDASIL®

GARDASIL: Life Cycle Management Plan

GARDASIL
(Quadrivalent Human Papillomavirus (Types 6, 11, 16, 18) Recombinant Vaccine)



MERCK
Be well

CSL™

Summary

Global R&D Pipeline — December 2010

* Partnered Projects

Q&A