

R&D Briefing

December 11, 2008

Agenda

December 2008 R&D Briefing

- Sign in and coffee
- Welcome Mark Dehring
- Introduction and Highlights Andrew Cuthbertson
- 'Flu Vaccine Update
- Plasma Replacement Therapies Stefan Schulte
- rCoagulation Products
- Q&A Andrew Cuthbertson
- Break
- ISCOMATRIX® Adjuvant Andrew Cuthbertson
- Therapeutic Proteins Overview
- Pre-clinical /Early Clinical Projects Andrew Nash
- Earlier Research Projects
- Summary Highlights, Q&A and Wrap Up Andrew Cuthbertson

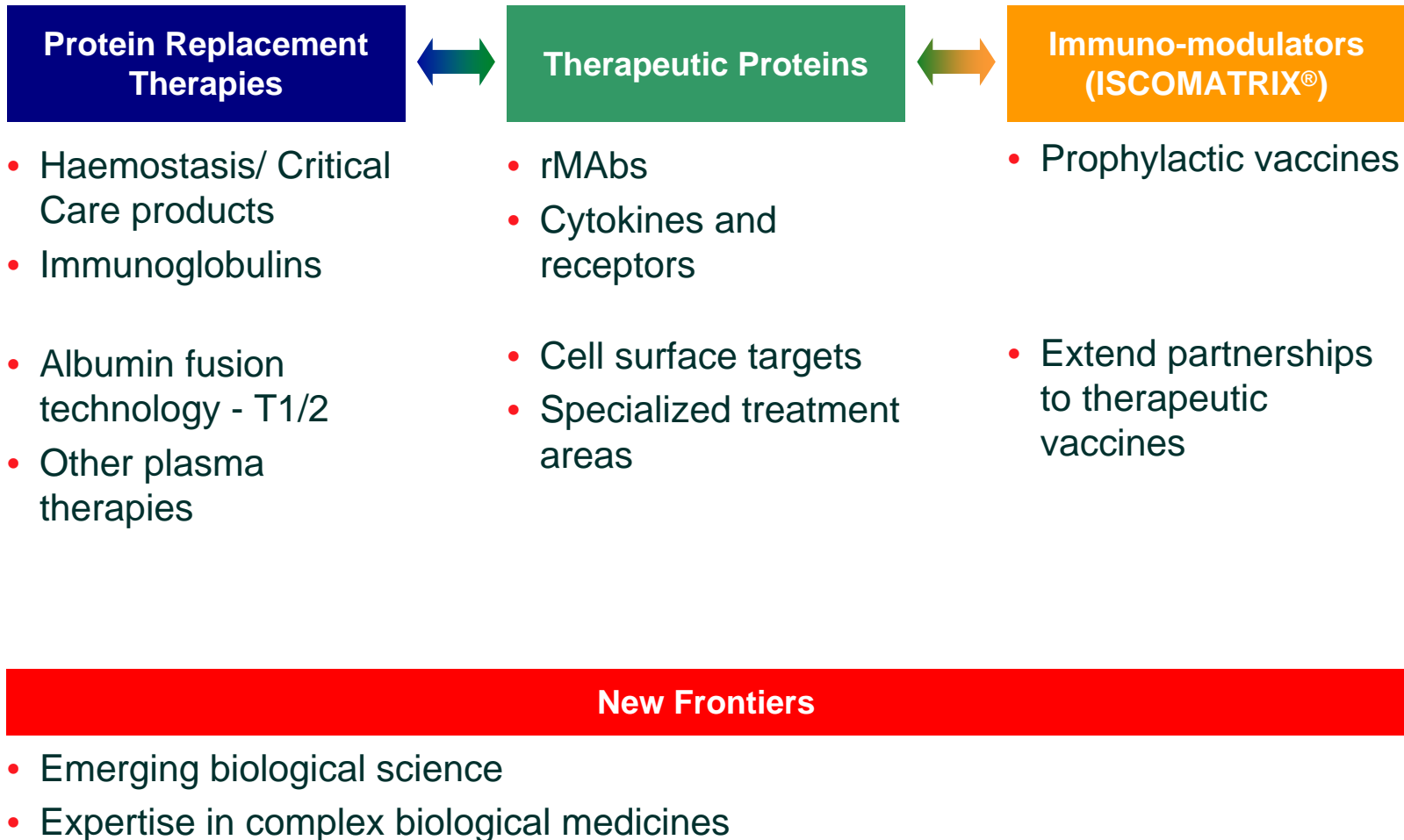
R&D Strategy

- 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

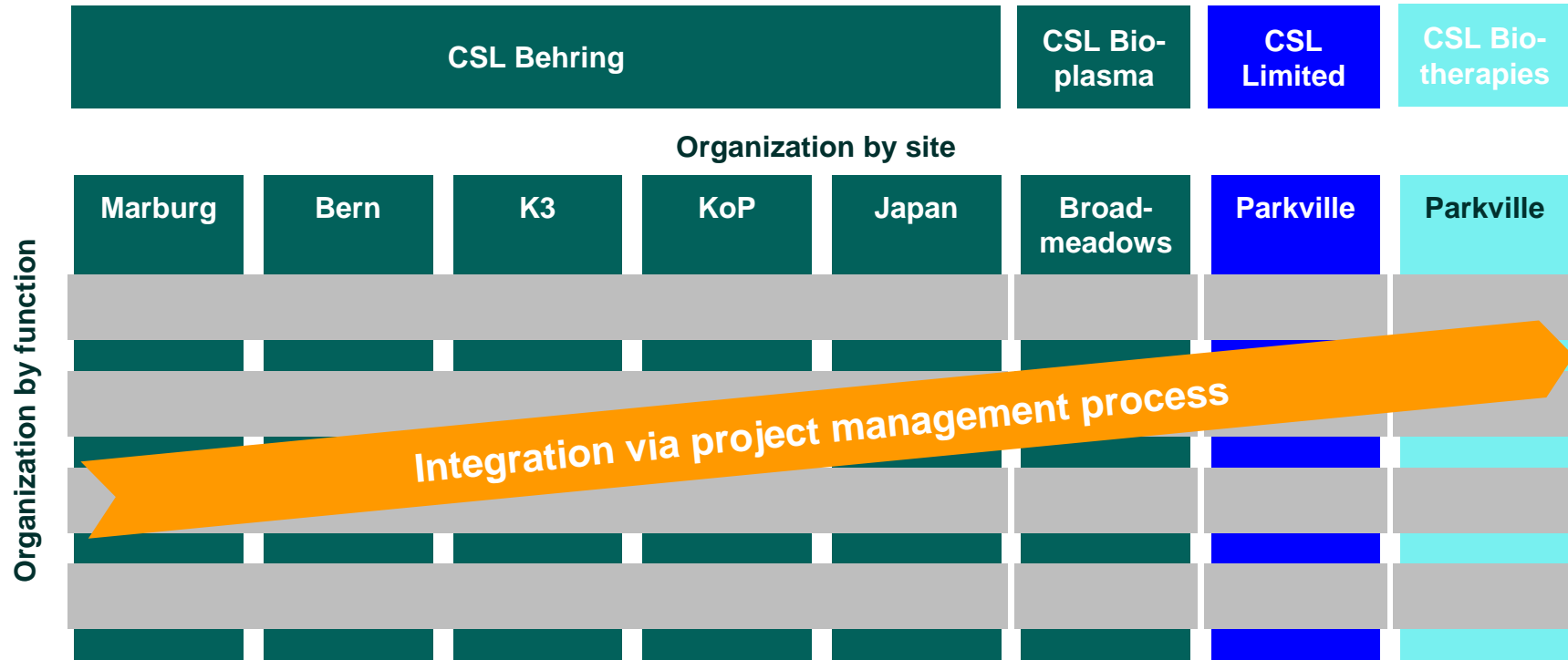


Karelle Rochecoute, Maria Mylonas and Darren Moulton discussing assay results of CSL influenza antigen

R&D Core Capabilities and Focus Areas



Leveraging Global Capabilities



Global project management to ensure access to best capabilities



Global R&D Pipeline

December 07

	Research	Pre-clinical	Phase I	Phase II	Phase III	Registration	Commercial/ Phase IV
Life Cycle Management					CSL718 SCIg 20%		Humate® P Zemaira® US Privigen® IVIG 10% GARDASIL® *
					Zemaira® EU	Beriner®	Rhophylac® ITP US
						Beriplex® EU Fluvax® China	Afluria® US Afluria/Enzira® EU
Market Development							
New Product Development	Rec coag factors	Rec coag factors	Vaccines– Merck*				
	Novel plasma proteins						
	Vaccines– Merck*	Vaccines– Merck*			Partnered Vaccine Programs*		
	Vaccines – Wyeth*	Vaccines– Wyeth*			CSL412 ISCOMATRIX® Flu		
	Beta common (Bion1/2)	CSL444 Pandemic ISCOMATRIX® Flu				CSL401 Pandemic Flu	
	Discovery projects	CSL111 reconstituted HDL	CAM3001* GM-CSFR - CAT/AZ				
		MK6105 IL-13R Merck *					
			CSL360 for AML				

Core Capabilities Plasma Therapeutics Vaccines ISCOMATRIX® Adjuvant Recombinant Proteins

* Partnered Projects



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Life Cycle Management					CSL718 SCIg 20%		Humate® P Zemaira® US Privigen® IVIG 10% GARDASIL® *	
	Market Development		Fibrinogen New Indications Beriplex® New Indications		Zemaira® EU Beriplex® US	Beriner® Beriplex® EU Fibrinogen Congen Deficiency Fluvax® China	Rhophylac® ITP US Afluria® US Afluria/Enzira® EU	
		New Product Development	Rec coag factors	CSL689 rFVIIa-FP	Vaccines- Merck*			
			Novel plasma proteins	CSL654 rFIX-FP		Partnered Vaccine Programs*		
	Vaccines- Merck*	Vaccines- Wyeth*		CSL412 ISCOMATRIX® Flu				
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	G-CSF							
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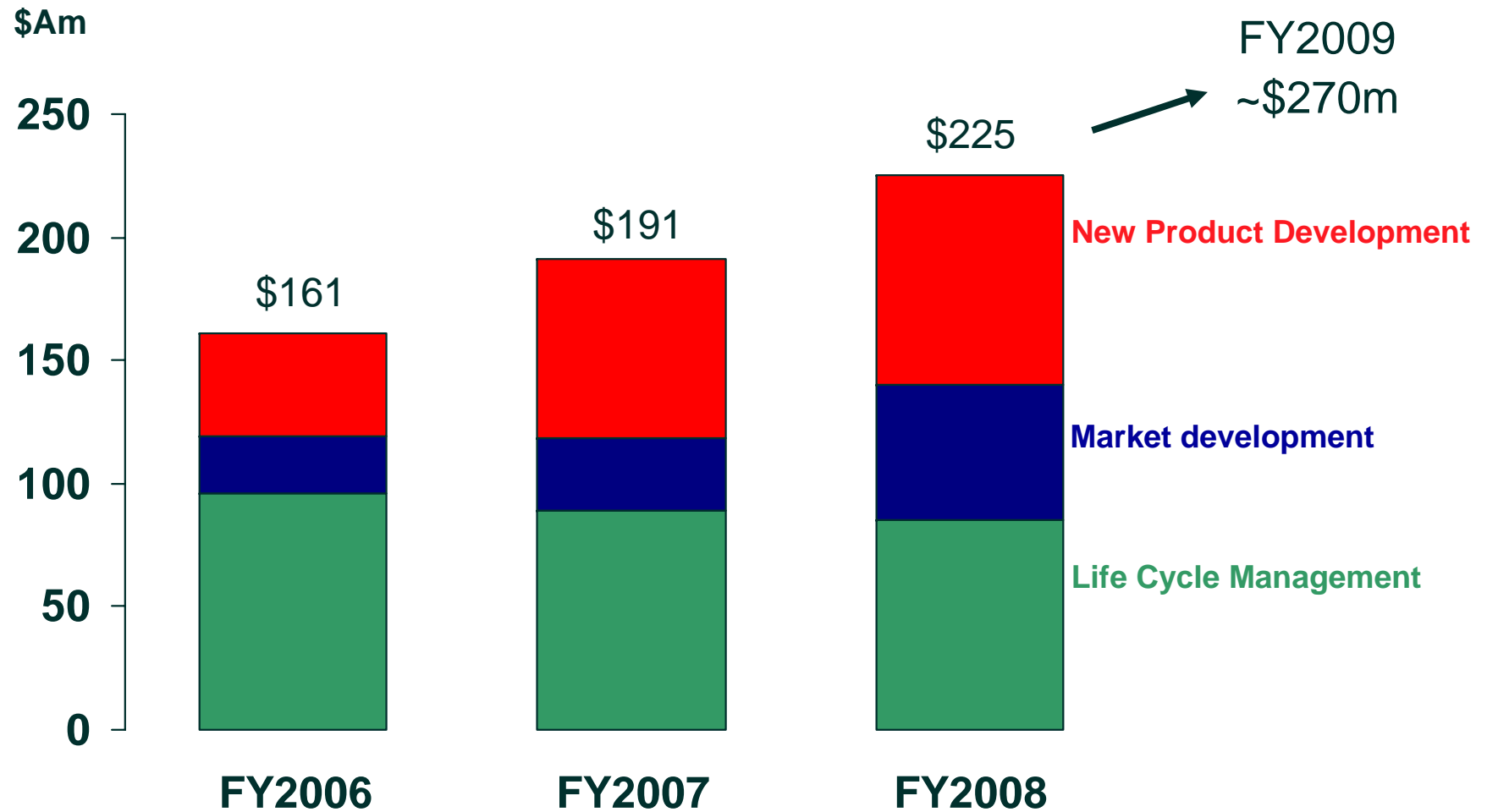
Core Capabilities Replacement Therapies Vaccines ISCOMATRIX® Adjuvant Therapeutic Proteins

* Partnered Projects



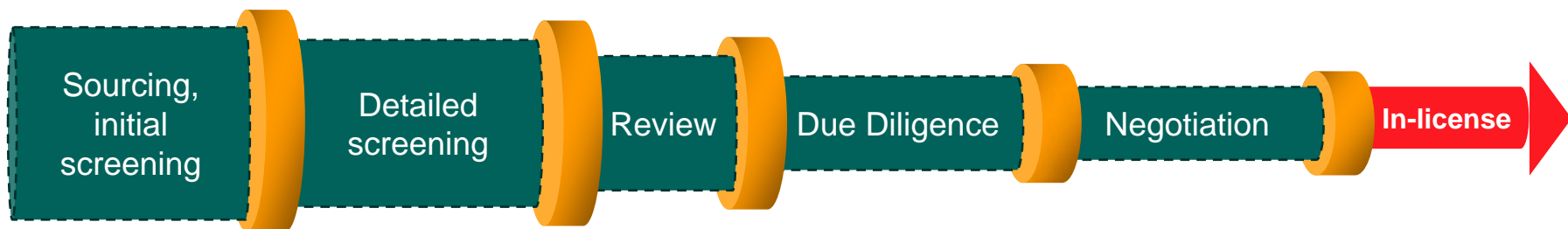
R&D Investment

Growth in new product and market development

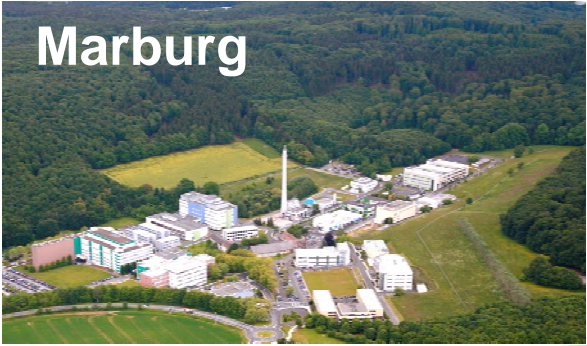


Building the R&D Pipeline

- Opportunities in current economic environment
- Process: high quality ideas in focus areas, efficient evaluation
- Integrated process across CSL Group to leverage full potential of networks



R&D Infrastructure and Facilities



GARDASIL®

Continued Growth Through Merck Life Cycle Management

- 2008: New indications and long-term evaluation
 - Approved new indication for prevention of vulvar and vaginal cancer
 - Ph 2 extension data with no breakthroughs through 5 years added to label
- 2008: new indications submitted for FDA review
 - Efficacy in adult women to 45 years
 - Efficacy in males
 - On target for submission to FDA in December 2008
- R&D - V503: 9-Valent HPV Vaccine
 - 5 additional HPV types
 - Cover 87% cervical cancer
 - Ph 3 trial underway
 - Anticipate filing BLA in 2012



- <http://www.merck.com/newsroom/webcast/>

Influenza Vaccine Program

Global Influenza Vaccine Program

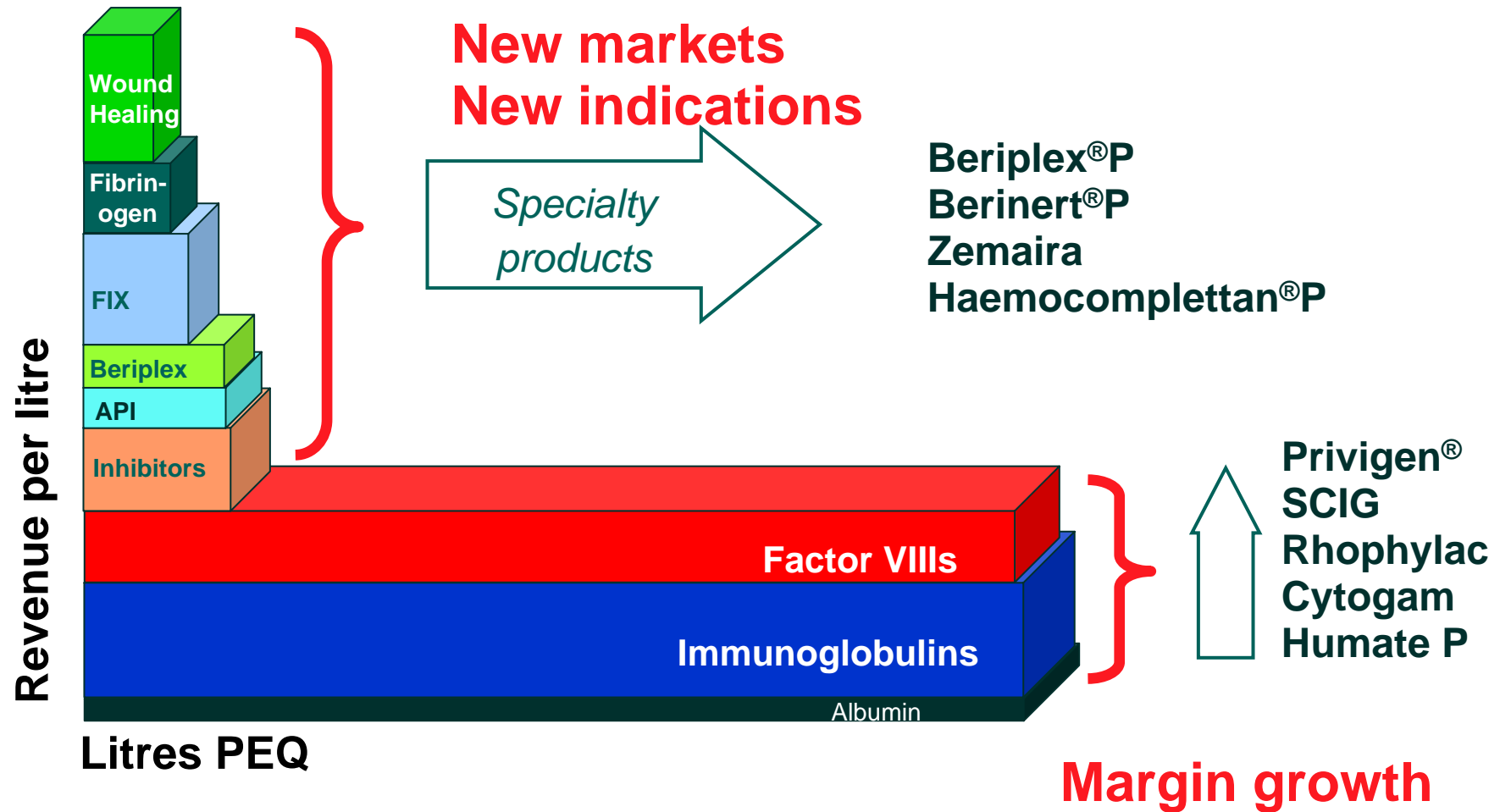
- Competitive advantages
- Expand influenza business
 - Licensure obtained in Germany and Ireland in 2008
 - Seeking additional registrations in Europe
 - Regulatory dossier submitted to China SFDA
 - US product launched October 07
 - Post-marketing clinical commitments
- Continued analysis of data and commercial opportunity for improved flu vaccine for elderly

Pandemic Vaccine Development

- Panvax® (avian influenza vaccine) approved June 2008 by Australian TGA
 - Approval of paediatric indication expected Q2 2009
- Core Pandemic Dossier approved November 2008 by Singaporean HSA
 - Adult, elderly and paediatric indications approved

Protein Replacement Therapies

Profitable Litre Objective for Margin Expansion



Privigen®



- Only Room Temperature Stable IVIG
- **Approved in key markets**
 - Licensed by FDA – July 2007
 - Licensed by Health Canada - Jan 2008
 - EMEA approval – April 2008
 - Licensed by SwissMedic - April 2008
- **New Manufacturing Facility**
 - SwissMedic Filed – October 2008
 - FDA Filed – October 2008
- **Additional capacity in construction**



IgPro20 – 20% Immunoglobulin for SC Treatment

- Minimal Dosage Volume for patient tolerance and convenience
- US trial is complete
- Submit US BLA mid-2009
- **Currently running 3 Phase III trials**
 - Extension of US Pivotal Phase III
 - European Phase III – Enrolment is complete
 - Extension of European Phase III



Specialty Products – Market Expansion

Beriplex® P/N – Market expansion

- PCC indicated for acute coagulation reversal
- **Expansion into 16 new EU markets**
 - MRP completed in Jan 08
 - Launch in UK (Mar 08), SE (May 08), NL (Sept 08), ES (Oct 08)
- **Expansion into US market**
 - Clinical studies initiated in the US
- **Production capacity enhancement**
 - Utilize plasma from other manufacturing sites
 - Stable and transportable intermediate identified
- **Evaluate potential new clinical indications**



Specialty Products – Market Expansion

Beriner[®] P

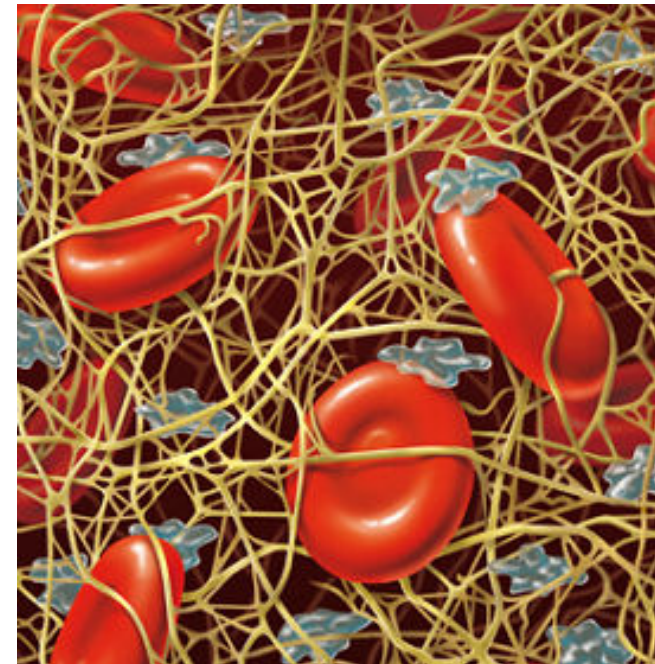
- C1 esterase inhibitor indicated for treatment of acute attacks of hereditary angioedema (Germany)
- **Seek additional licenses in EU**
 - MRP procedure started in Sept 08
 - Completion anticipated in Dec 08
- **Canada**
 - BLA submitted April 08
- **US**
 - BLA submission in Mar 08
 - Pre-approval inspection in May 08
 - FDA response received



Specialty Products – Market Expansion

Haemocomplettan® P/(Fibrinogen)

- Indicated for congenital fibrinogen deficiency
- **Market expansion in Europe and USA**
 - BLA submission July 08
 - Phase III/IV efficacy study initiated Oct 08
 - BPAC hearing in Jan 09
 - EU submission Feb 09
- **Production capacity enhancement**
 - Batch size & Freeze dry capacity increase
- **Evaluate potential new clinical indications**



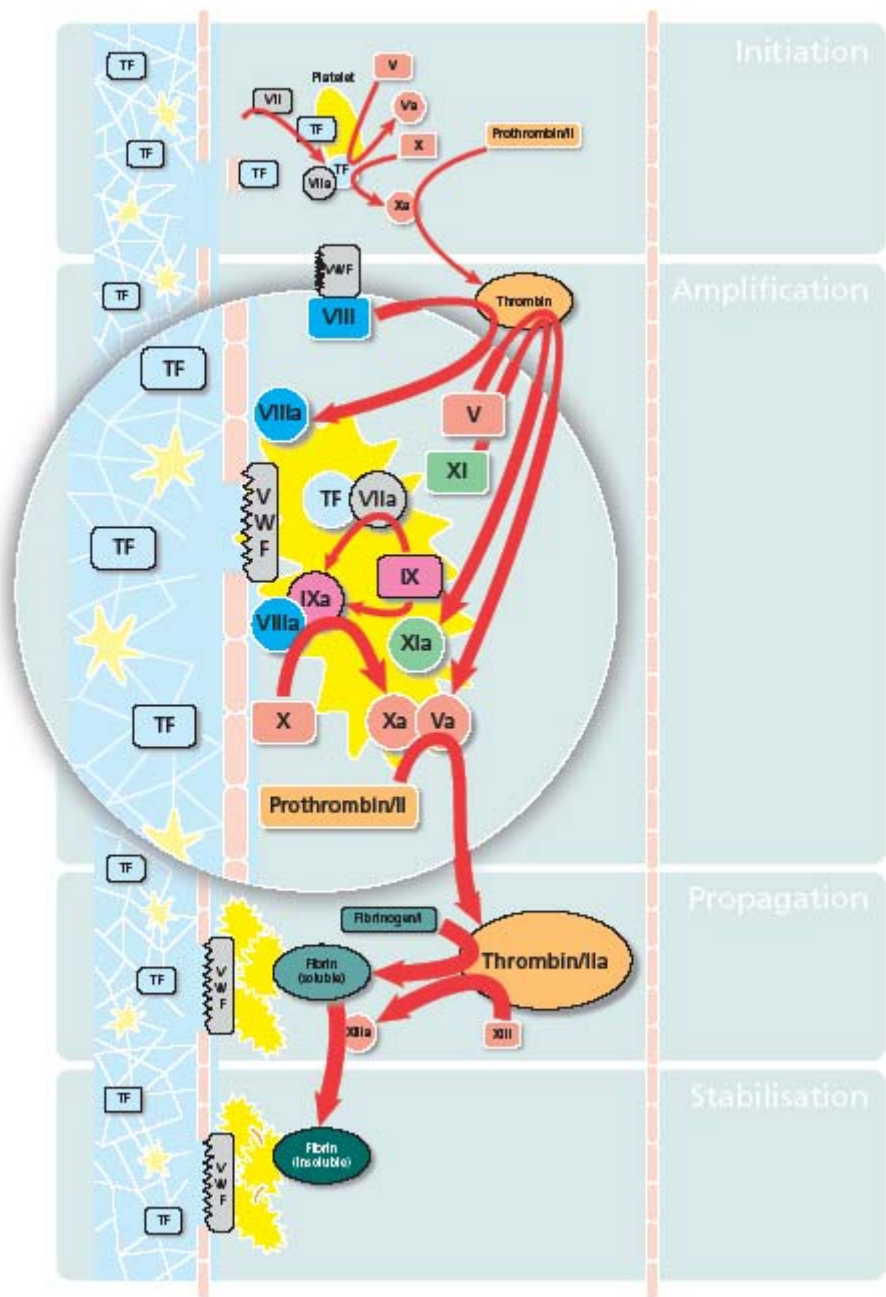
Progress in the Last Year on Other Projects

- Zemaira[®]
 - Met enrollment target for Ph III/IV study
- Cytogam[®]
 - Assure market supply
- Rhophylac[®]
 - US approval of ITP study
- Vivaglobin[®]
 - Completed R&D activities
- Humate P[®]
 - Completed R&D activities



Next generation Anti-D – pure & simple





Recombinant Coagulation Factors with extended half-life

Half-life Improvement for Coagulation Products

Products with improved half-life will be beneficial to patients

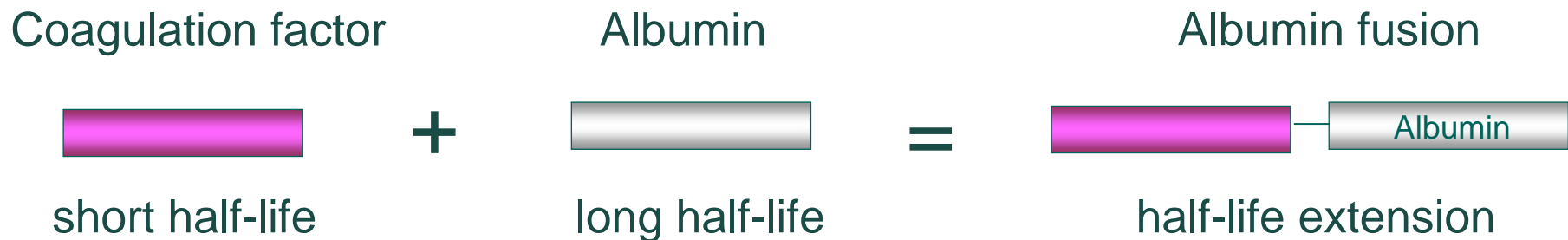
- Less frequent injections
- Improved compliance
- May enable prophylaxis

Several technologies to extend half-life of proteins

- Sustained delivery
- Chemical modification
- Genetic mutation
- Fusion with carrier proteins (Fc fusion, Albumin)

Albumin as a Carrier Protein

- Albumin has a naturally long half-life (~20 days)
- Highly abundant protein
- Molecular structure is known
- Proof of principle data for FVIIa and FIX

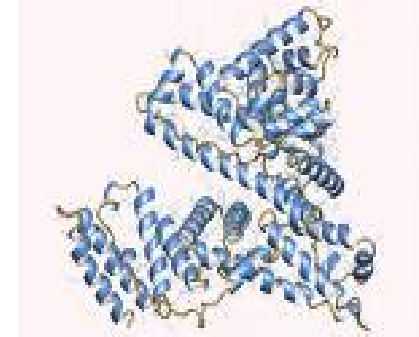


Half-life Extension of FVIIa and FIX

- **FVIIa** – indicated for treatment of inhibitor patients

- Half-life ~2.4 h
- Several infusions required for treatment:
 - Joint bleeding: ≥ 2
 - Surgery: every 2 – 3 h for ≥ 2 days

=> Goal for half-life extension: One infusion per bleeding event



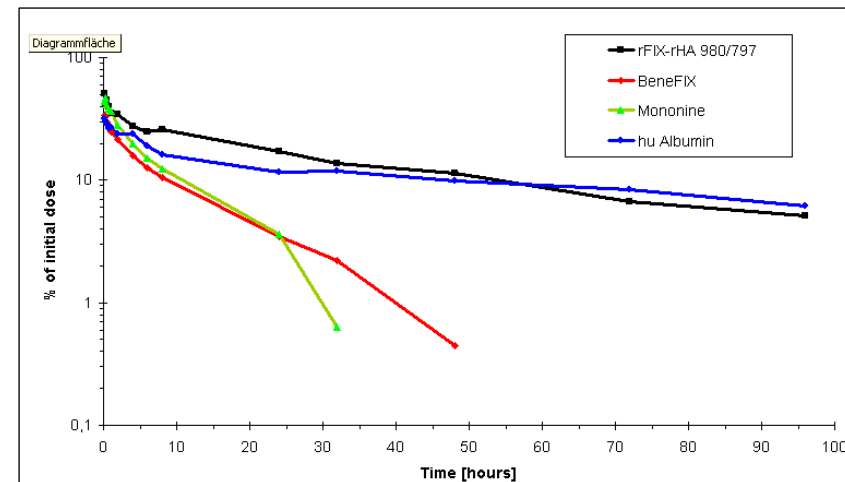
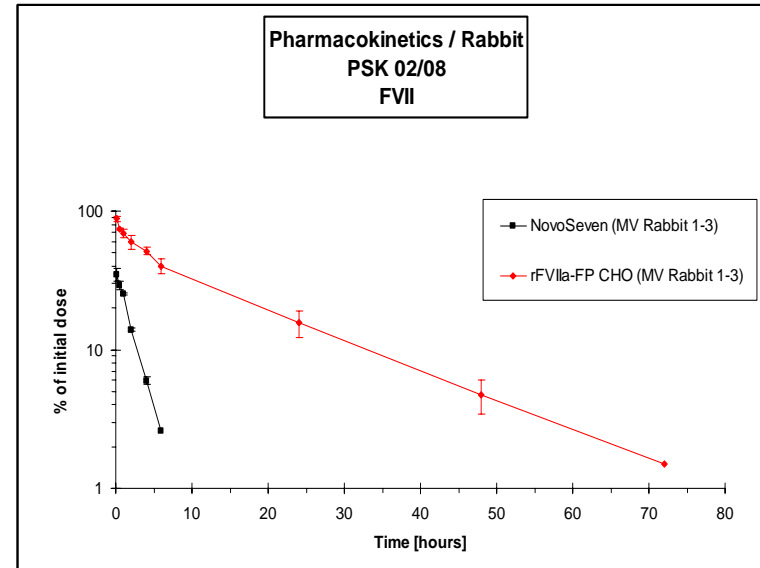
- **FIX** – indicated for treatment of Hemophilia B

- Half-life ~20 h
- ~ 3 infusions required per week

=> Goal for half-life extension: One infusion per week

rFVIIa/ FIX - Albumin Fusion Proteins – Current status

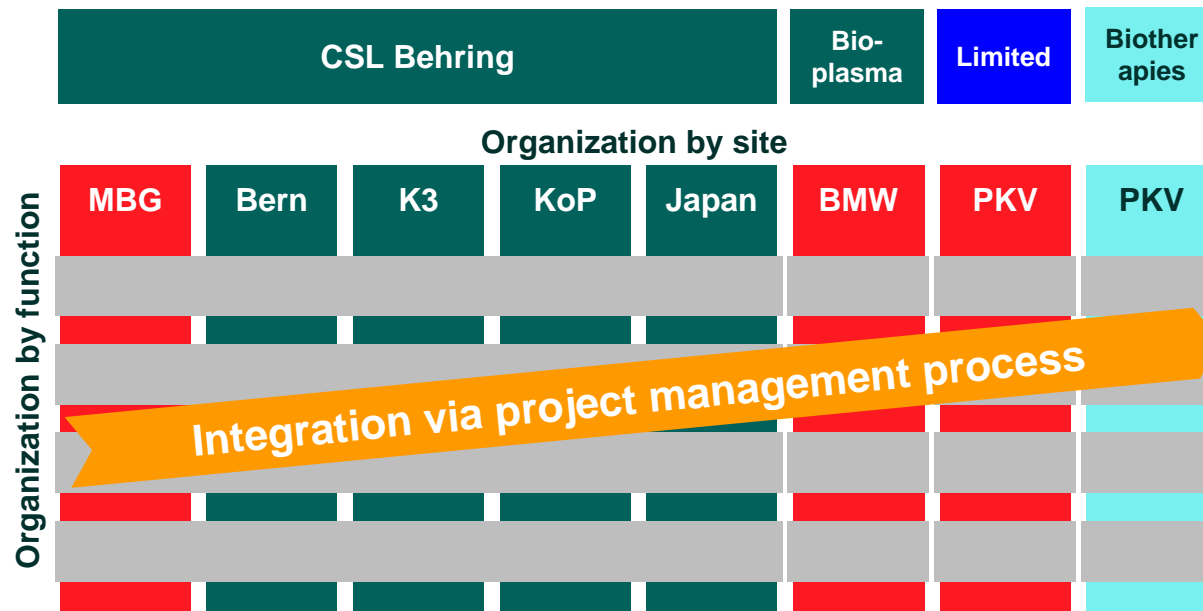
- Preclinical target validation completed
 - Significant Half-life extension in various animal models
 - rFVIIa: 5 to 9-fold
 - rFIX: 2 to 4-fold
 - Comparable biological activity
 - In vitro
 - In vivo
 - Construct for development defined
- Exclusive license from Novozymes



rFVIIa/ FIX – Albumin Fusion Proteins – Next Steps

- Using R&D capabilities across CSL Group

- Cell line development
- Process development
- Analytical method development
- GMP Material production
- Pharma/Tox program
- Clinical studies
- Regulatory submission



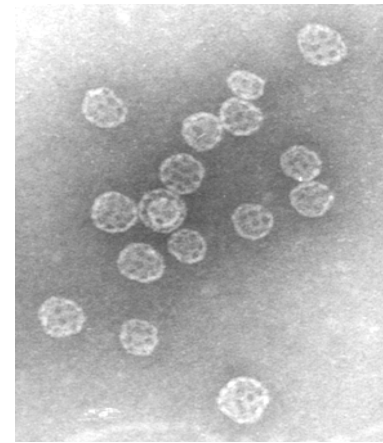
Q&A

Break

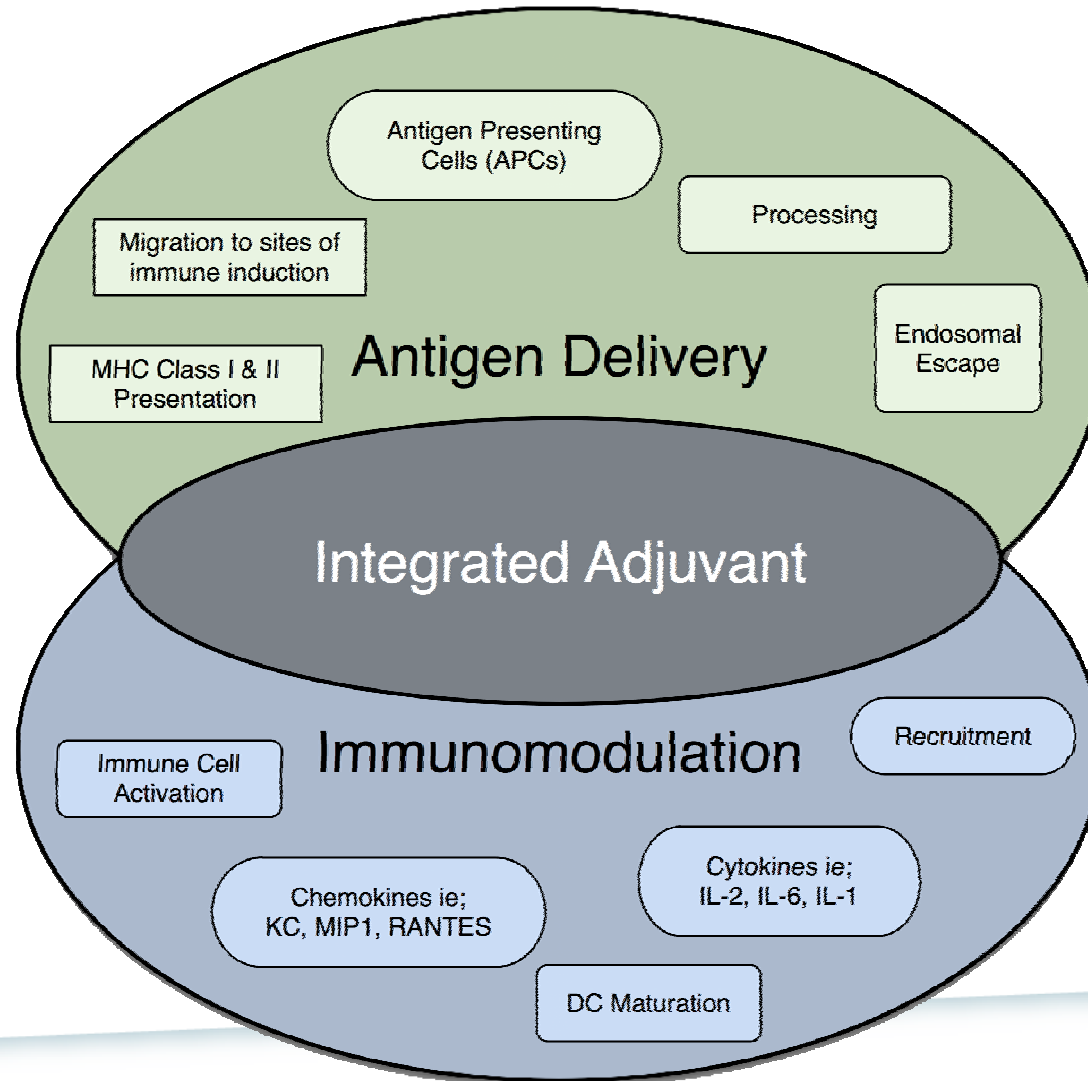
ISCOMATRIX® Adjuvant Technology

ISCOMATRIX® Adjuvant

- Proprietary biological adjuvant for use in humans
- Complex of ISCOPREP® saponin, cholesterol and phospholipid



Integrated Mechanism of Action of ISCOMATRIX® Adjuvant



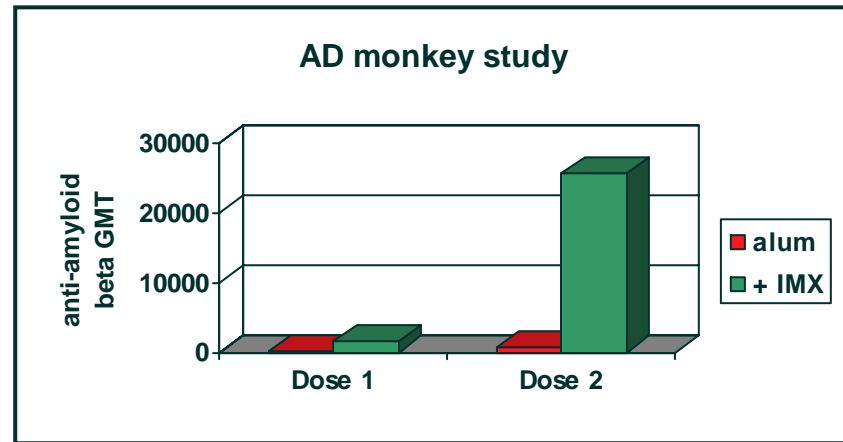
Manufacture of ISCOPREP® Saponin and ISCOMATRIX® Adjuvant at Industrial Scale

- Developed pilot processes at Parkville
- Transferred to Kankakee, USA
- Scale-up at Kankakee
 - ISCOPREP® saponin
 - ISCOMATRIX® adjuvant



Merck & Co. Inc. Recruiting Alzheimer's Disease Vaccine Study

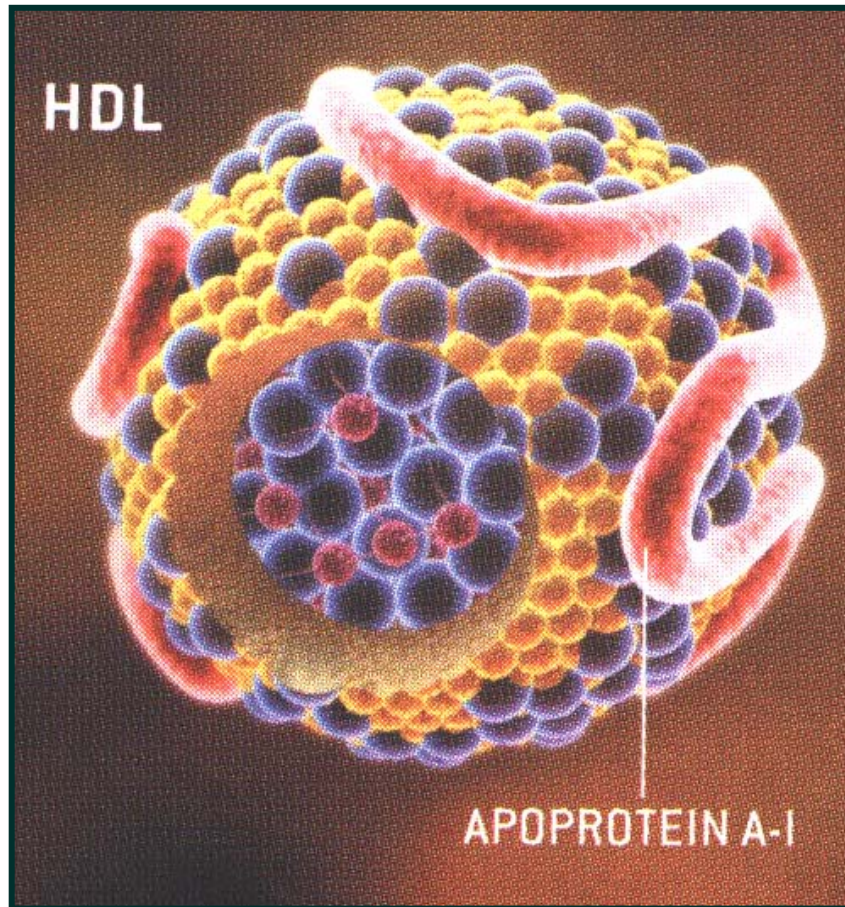
- Beta-amyloid vaccine formulated in aluminium with or without ISCOMATRIX® adjuvant
- Phase I study in patients with Alzheimer's Disease
- Broad agreements in infectious diseases
- Evaluations continuing



Therapeutic Protein Portfolio

Pre-clinical / early clinical projects

rHDL: Potential Long Term Value



JAMA-EXPRESS

Effects of Reconstituted High-Density Lipoprotein Infusions on Coronary Atherosclerosis

A Randomized Controlled Trial

Jean-Claude Tardif, MD; Jean Grégoire, MD; Philippe L. L'Allier, MD; Reda Ibrahim, MD; Jacques Lespérance, MD; Therese M. Heinson, DVM; Simon Kouz, MD; Colin Berry, MD; Russell Basser, MD; Marc-André Lavoie, MD; Marie-Claude Guertin, PhD; Josep Rodés-Cabau, MD; for the Effect of rHDL on Atherosclerosis-Safety and Efficacy (ERASE) Investigators

JAMA. 2007; 297:1675-1682.

Therapeutic Proteins

- **CSL research at the Bio21 Institute**

- capabilities, focus

- **Project updates**

- Preclinical / early clinical projects***

- CSL360, anti-IL-3R α , acute myeloid leukemia
 - anti-GM-CSFR α , rheumatoid arthritis
 - G-CSF antagonists, inflammatory disease
 - anti-IL-13R α antagonists, asthma

- Research projects***

- IL-11 antagonists
 - EphA4
 - VEGF-B antagonists
 - β common antagonists

Therapeutic Proteins

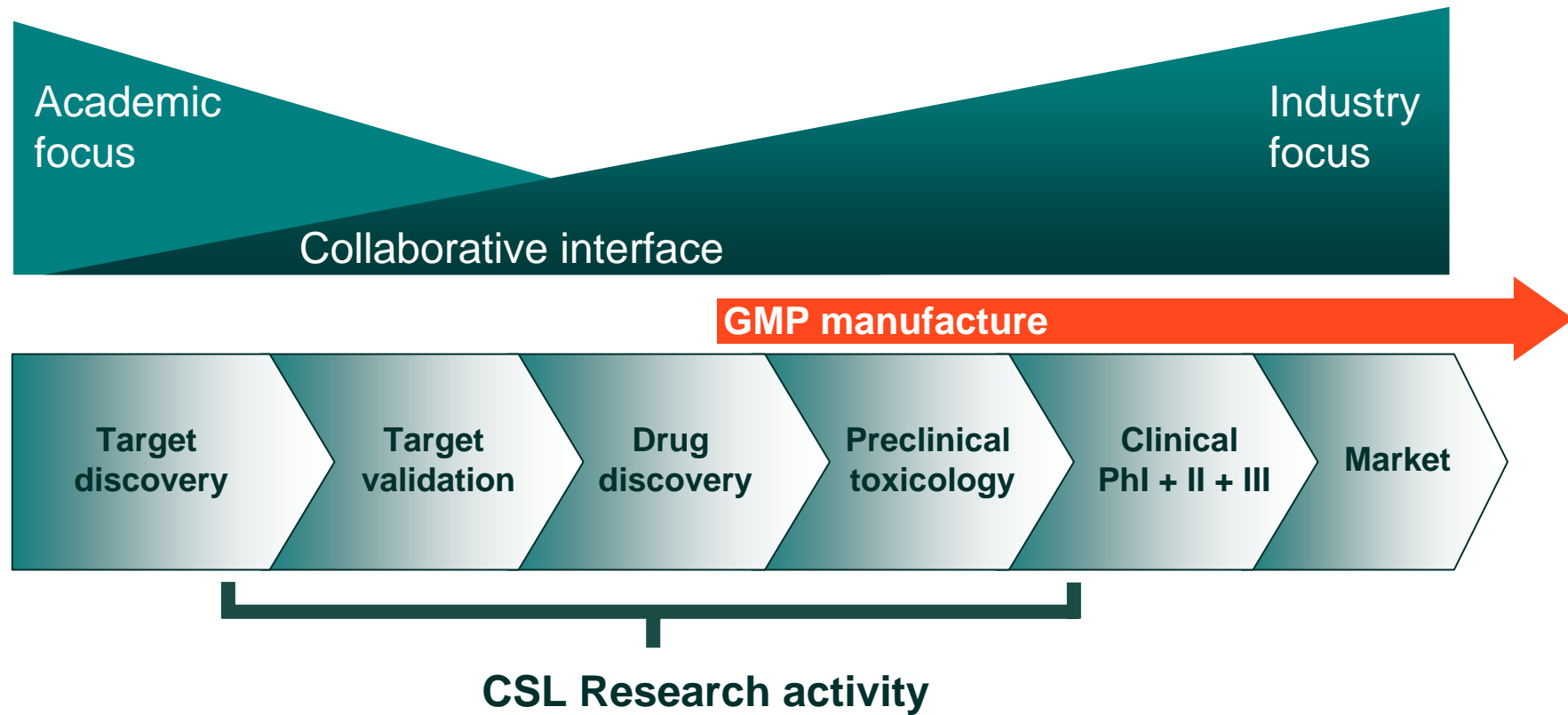
CSL Research at the Bio21 Institute

- research activity consolidated within a state-of-the-art facility located in the heart of Australia's premier medical research precinct
- focus on cytokines and cytokine receptors
- 65 staff with research groups specializing in Cell Biology/ Physiology, Molecular Biology and Protein Biochemistry
 - "in-house" and Bio21-based platform technologies
- leverage research activities through collaboration with leading academic groups



Therapeutic Proteins

CSL Research at the Bio21 Institute



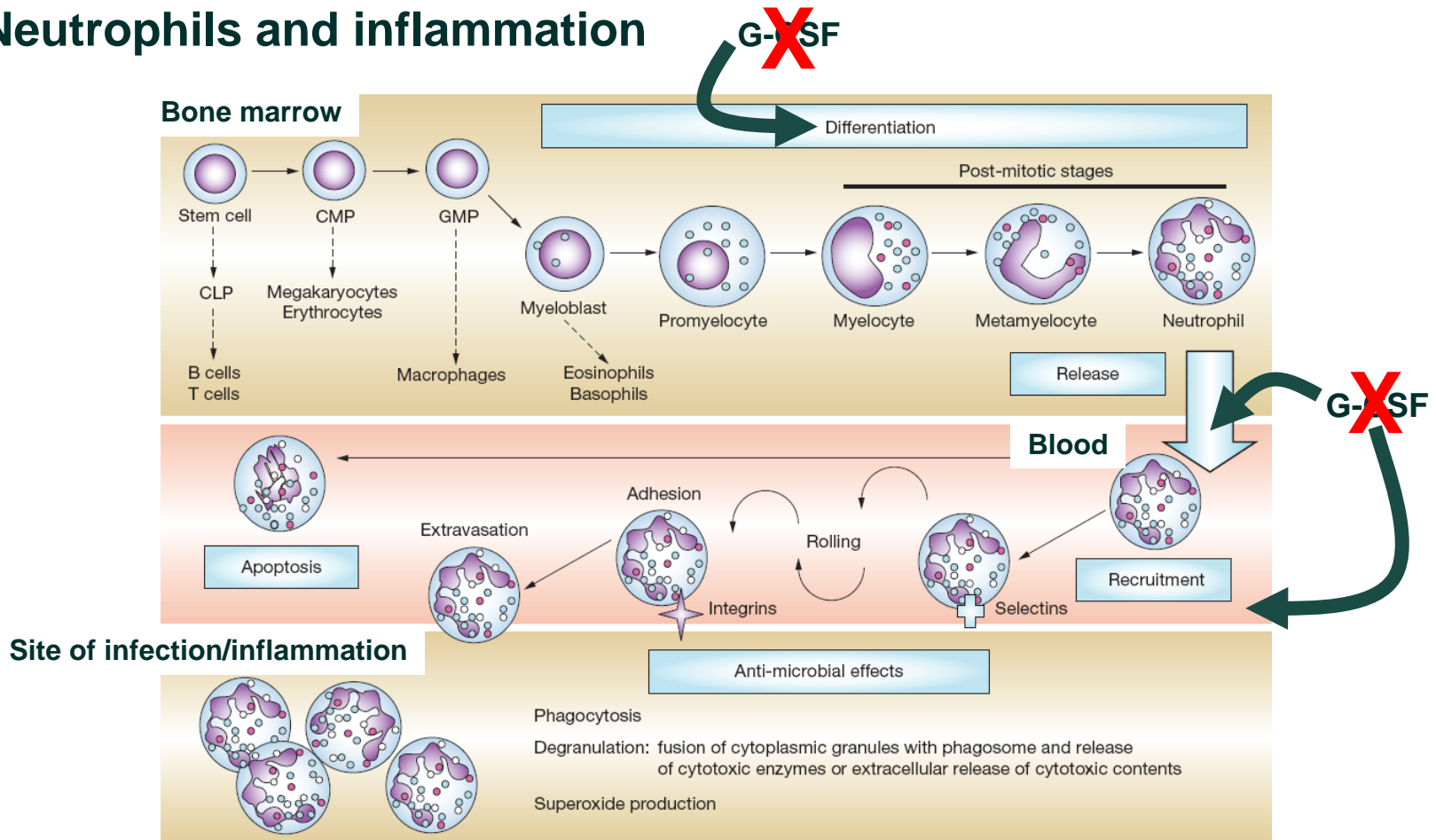
CSL360 (IL-3R α) - AML

CSL360 for acute myeloid leukemia

- Acute myeloid leukemia
 - cancer of immature blood cells
 - no major changes in treatment for last 20 years
 - outcome depends on number of factors
 - < 50yrs old: 5yr survival 30-40%
 - > 60yrs old: 1yr survival 10-20%
- CSL360 Phase I clinical trial
 - Phase I study in patients with relapsed, refractory or high-risk AML
 - dose-escalation study (5 dose levels 0.1mg/kg -10mg/kg)
 - multi-dose at weekly intervals (at least 4)
 - study is continuing with 20 evaluable patients to be accrued and treated at 10mg/kg weekly

G-CSF Antagonists – Inflammatory Disease

Neutrophils and inflammation

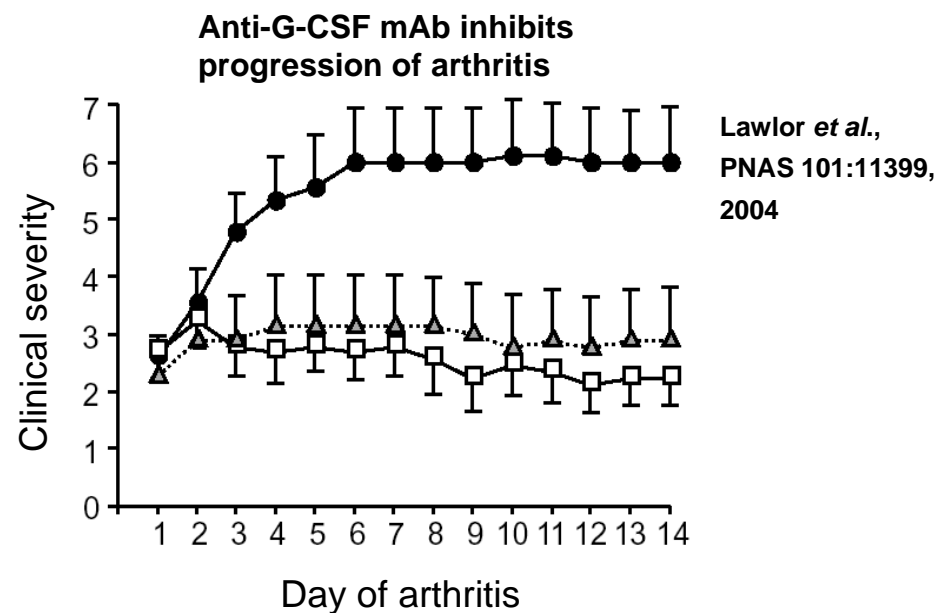
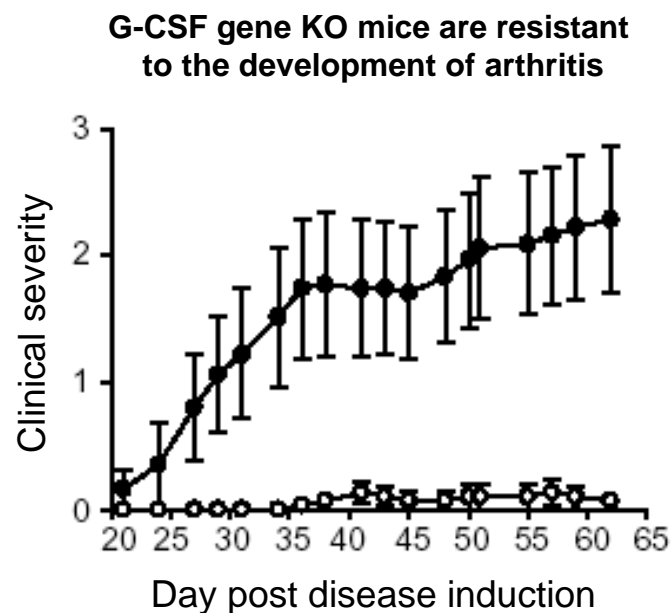


From: Eyles *et al* Nat Clin Prac Rheum 2006

G-CSF Antagonists – Inflammatory Disease

Does blockade of G-CSF impact on inflammation?

- G-CSF blockade in a mouse model of rheumatoid arthritis



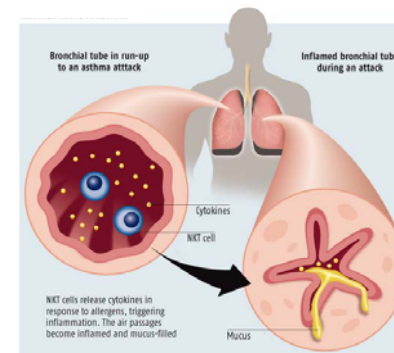
Current R&D activities

- lead antibody selection and optimisation in progress
- Phase I clinical studies currently being planned

Partnered Projects

- **anti-GM-CSFR α , rheumatoid arthritis**
 - licensed to MedImmune / AstraZeneca
 - CAM3001 Phase I study in RA patients is ongoing
 - Phase Ib safety, tolerability and efficacy with s.c administration to commence Q1 2009

- **anti-IL-13R α , asthma**
 - licensed to Merck & Co., Inc
 - lead selection and characterisation in progress

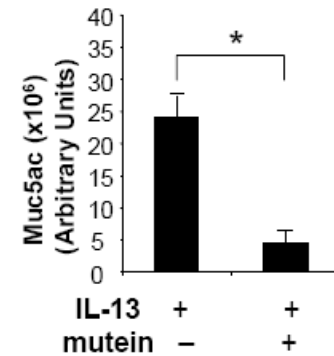
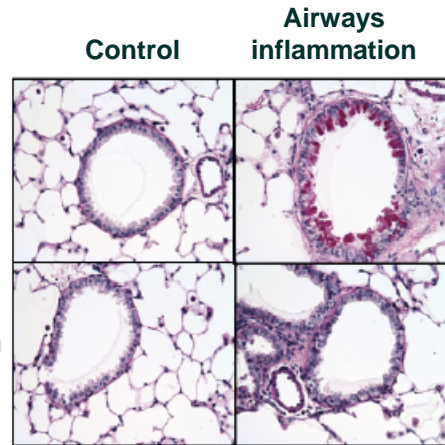
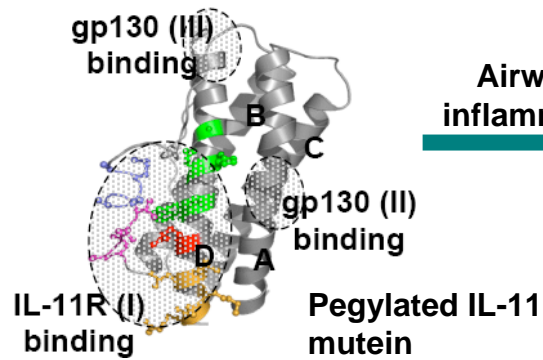


Therapeutic Protein Portfolio

Earlier Stage Research Projects

IL-11 Antagonists – Cancer and Airway Disease

IL-11 antagonists

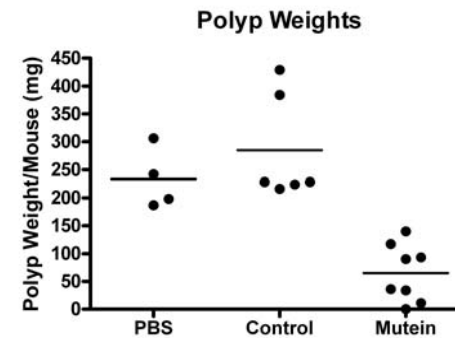


From: Lee *et al.*, Am J Respir Cell Mol Biol. 39:739, 2008

Gastric cancer

• Collaborators

- Yale University
- Ludwig Institute for Cancer Research



EphA4 Antagonists – Spinal Cord Injury

EphA4 antagonists

After spinal cord injury EphA4 knockout mice demonstrate:

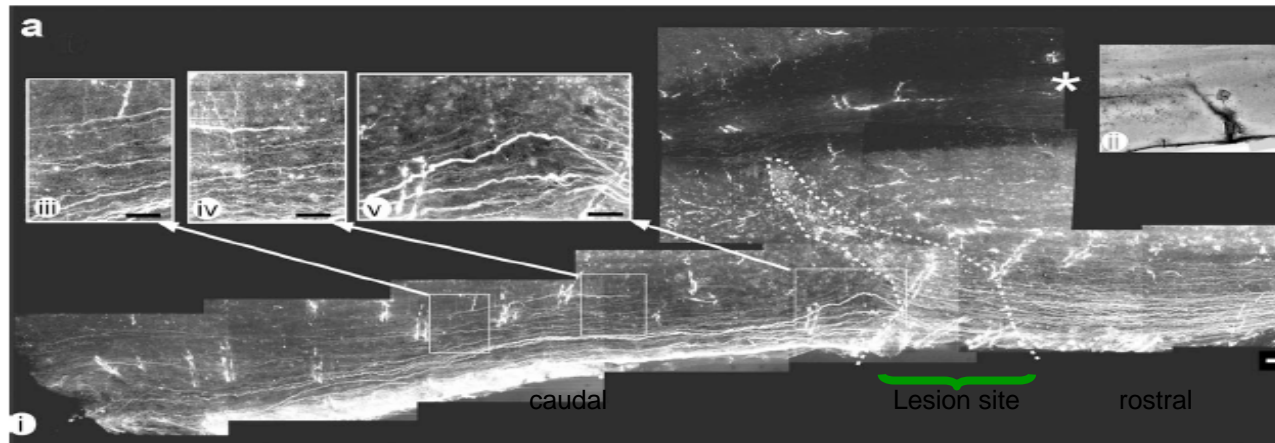
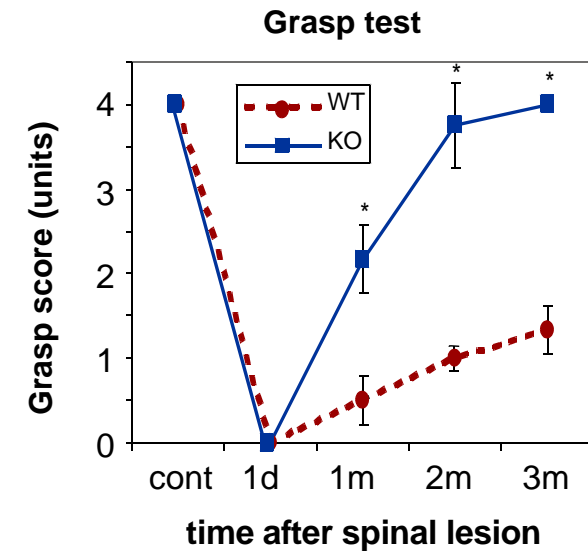
- reduced glial scarring,
- increased nerve regeneration
- improved motor function

Improved motor function

Axonal regeneration

• Collaborators

- The University of Melbourne
- The University of Queensland
- QIMR
- WEHI



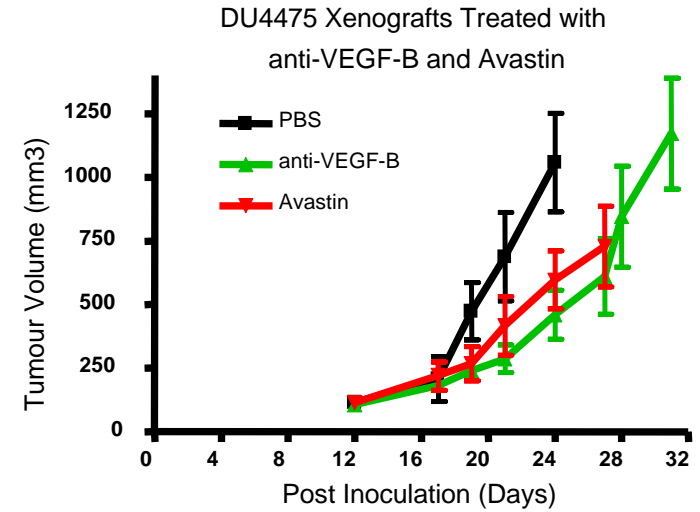
From: Goldshmit *et al.*, J. Neuroscience 24: 1064, 2004

VEGF-B Antagonists – Cancer and Eye Disease

VEGF-B antagonists

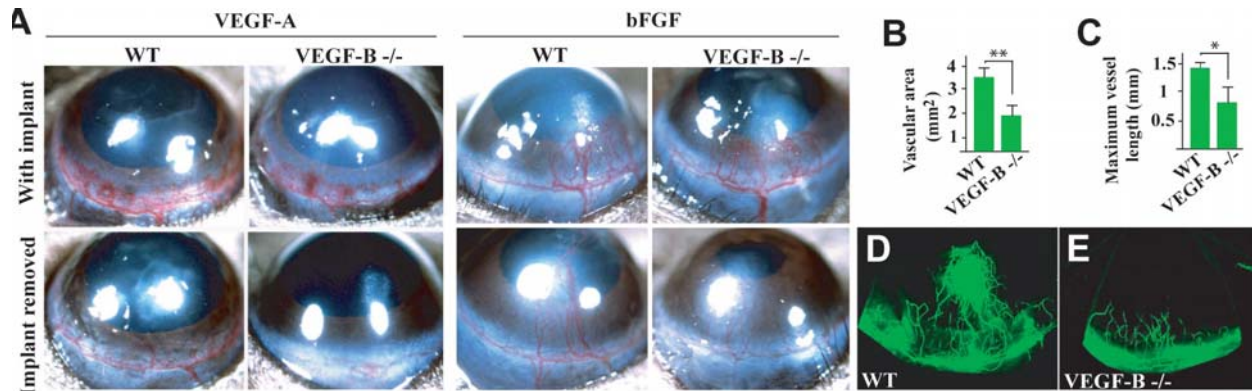
- VEGF-B antagonists inhibit:
- growth of breast carcinomas
 - survival of new vessels in the eye

Breast carcinoma
xenograft



Blood vessel
growth &
survival

- Collaborators
 - National Eye Inst., NIH (Xuri Li)
 - Ludwig Inst. For Cancer Research



Unpublished, presented with kind permission of Dr. Xuri Li, National Eye Institute, Bethesda USA

β -Common Antagonists – Cancer and Inflammation

β -common – a shared receptor used by the cytokines IL-3, IL-5 and GM-CSF

GM-CSF – neutrophils, macrophages – RA, AML, CML

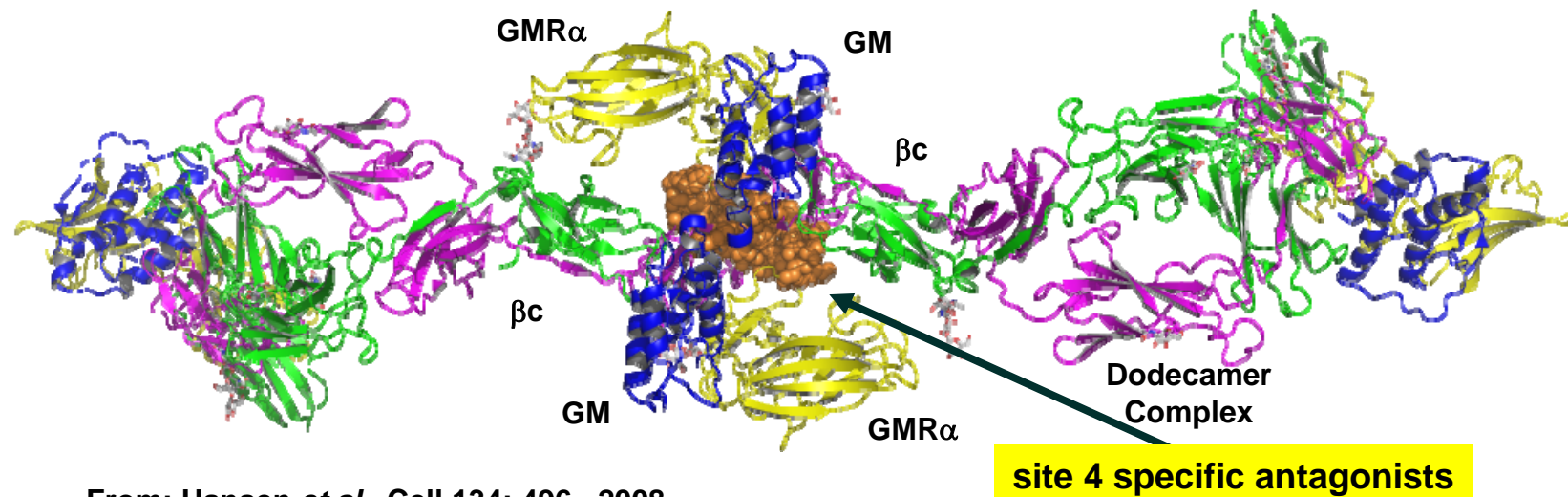
IL-5 – eosinophils – asthma, atopic disease

IL-3 – basophils, LSC & blasts - AML, asthma

- **Collaborators**

- IMVS, Adelaide

- St Vincent's Research Institute



From: Hansen *et al.*, Cell 134: 496, 2008

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	G-CSF							
	Discovery projects	IL-13R Merck *						
			CSL360 for AML					

Core Capabilities Replacement Therapies Vaccines ISCOMATRIX® Adjuvant Therapeutic Proteins

* Partnered Projects



R&D Investment Strategy

Continue to be fundamental to CSL's ongoing success

Support the core business and develop bio-therapeutic products for our global commercial organization

NPD increasing contribution to growth

Committed to investing in future portfolio and capabilities



Claudia Nerlich, laboratory technician in Marburg, preparing plasma fractions for potency test.

Q&A