



# **CSL Research - Investor Site Tour @ Bio21 Institute**

30 April 2018

# CSL Research

- Bio21 / Parkville, Marburg, Bern
- Protein, gene & cell based therapies

Immunoglobulins

Haemophilia

Specialty  
Products

Breakthrough  
Medicines

Transplantation

- ~200 staff
- Molecular Biology, Protein Biochemistry,  
Cell Biology & Physiology, Bioinformatics,  
Research & Clinical Analytics, Pharm/Tox  
Plasma Protein Science & Discovery



# Global Hub for Research & Translational Medicine

- New laboratories being constructed on the Bio21 site, 3628m<sup>2</sup>
- CSL space from 1470m<sup>2</sup> to 3500m<sup>2</sup>
- Capacity to increase from 75 FTE's to 165 (relocation from PKV)
- University of Melbourne to fund construction
- CSL to fund fit-out of CSL space
- Construction commenced Q3 2016 with fit-out completed Q3 2018



Aerial Site Plan/Architectural Perspective View Looking East



# Melbourne / Parkville Biomedical Precinct

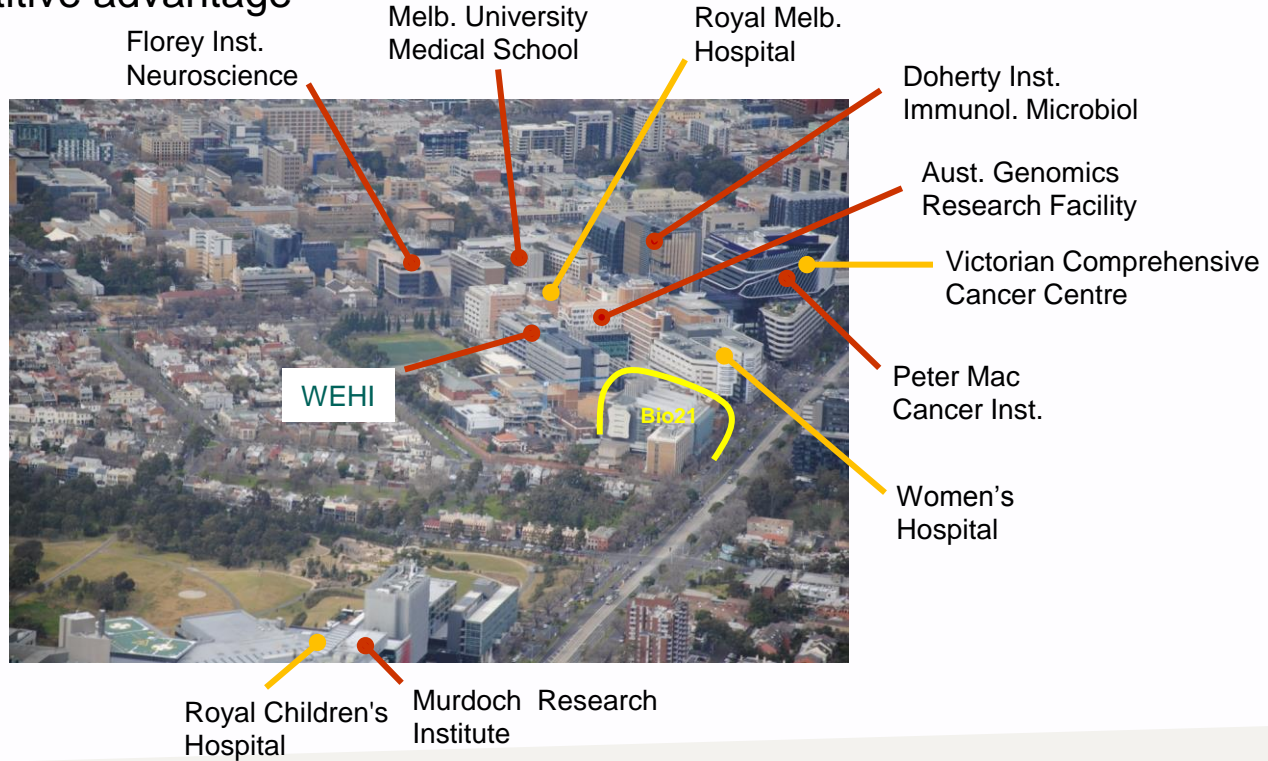
- a CSL competitive advantage





# Melbourne / Parkville Biomedical Precinct

- a CSL competitive advantage



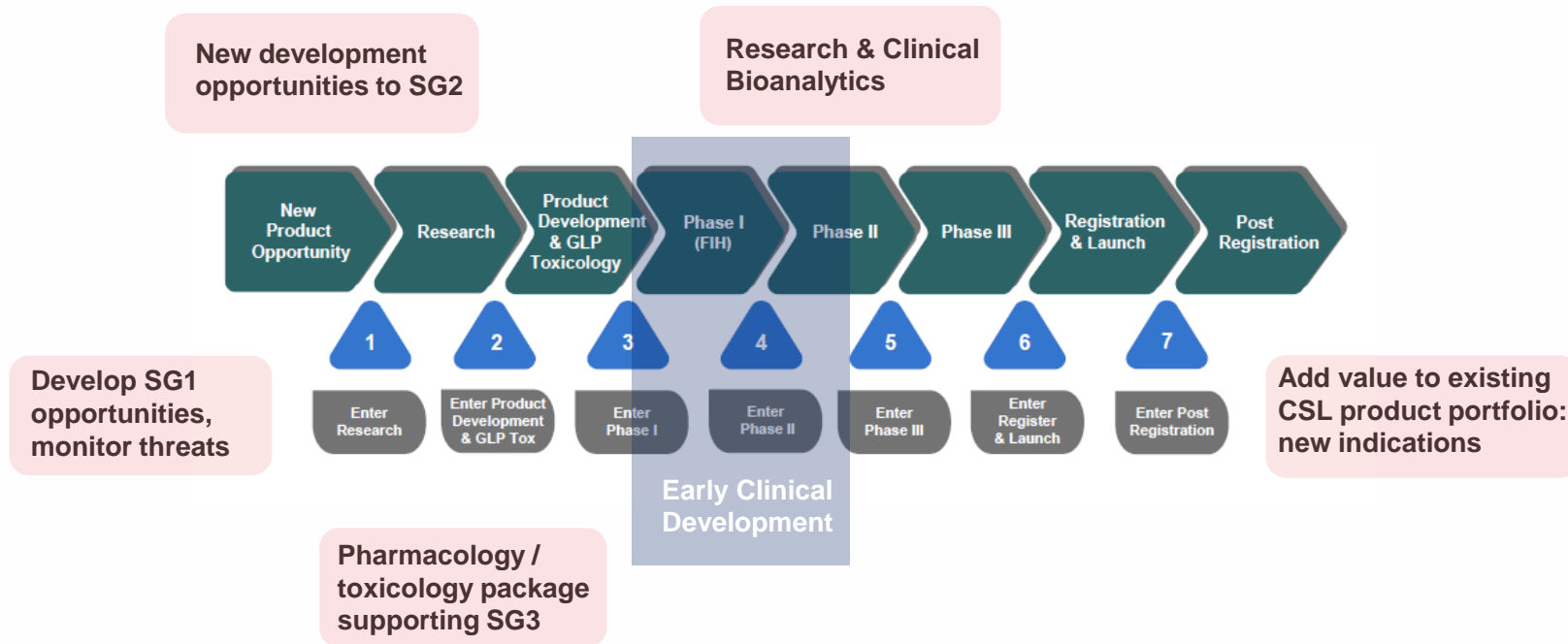
# WEHI / CSL Bioinformatics Alliance

WEHI - world leaders in bioinformatic software development

- By research specialty
  - differential expression
  - regulation of gene expression
  - cancer genome analysis
  - statistical genetics
  - molecular epidemiology
- By technology
  - DNA-seq, RNA-seq (population and single cell), ChIP-seq, Microarray
- By disease area
  - cancer, auto-immune diseases, neurological disorders, malaria
- By people
  - 9 computational labs
  - ~ 90 computational researchers (including post-docs, RAs and students)
  - underpinned by strong, ongoing investment in IT support and infrastructure

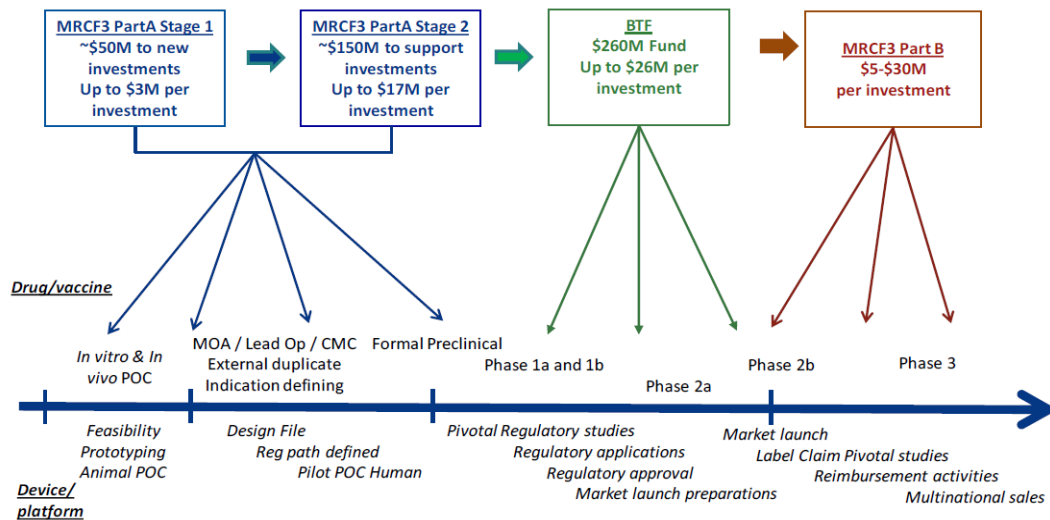


# CSL Research



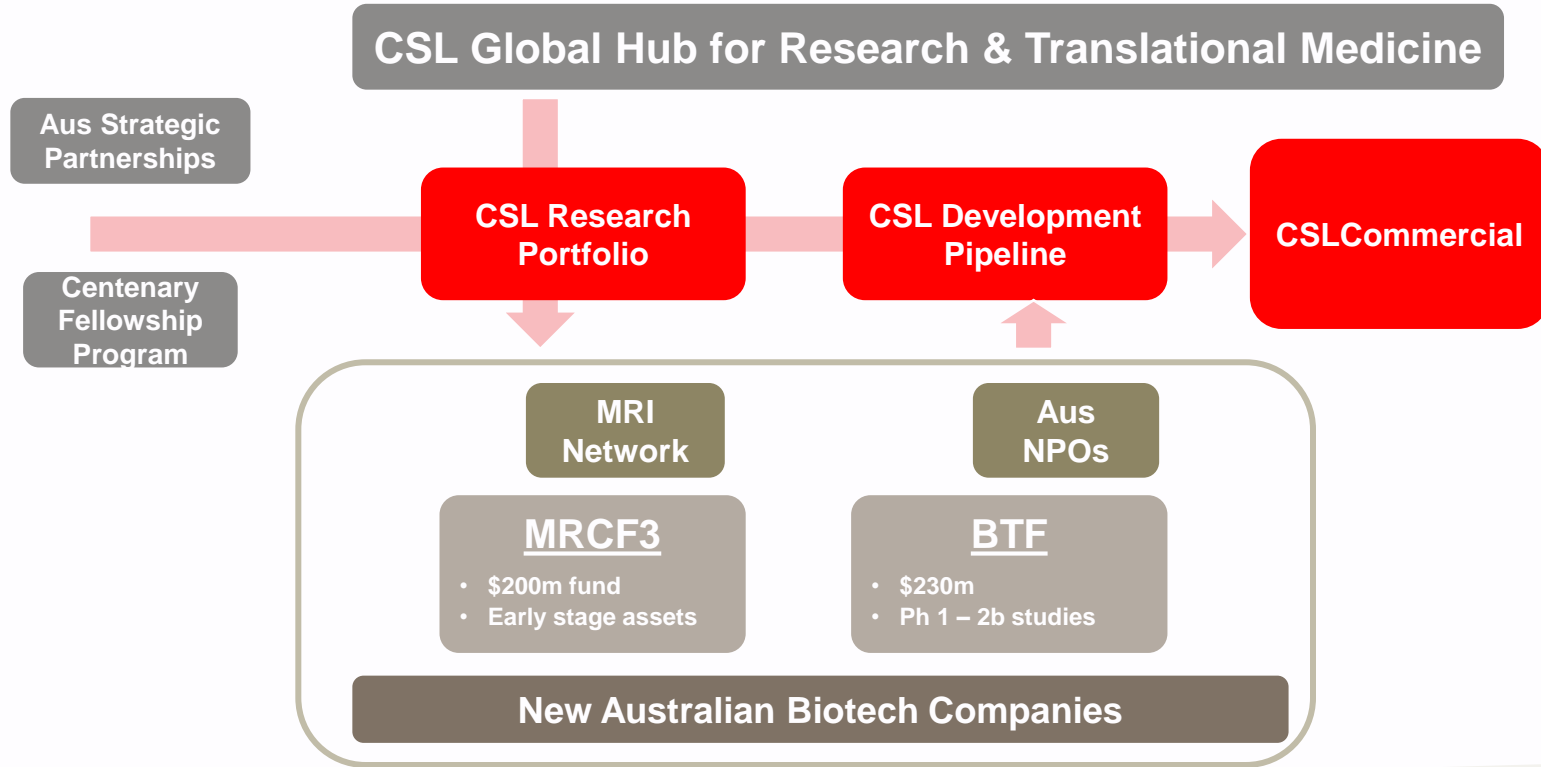
# MRCF BTF

- Partnership with Brandon Capital
- Medical Research Commercialisation Fund Network
  - \$200M MRCF3 and \$230M MRCF BTF
- Four super funds, CSL and the Aus Govt (BTF only)

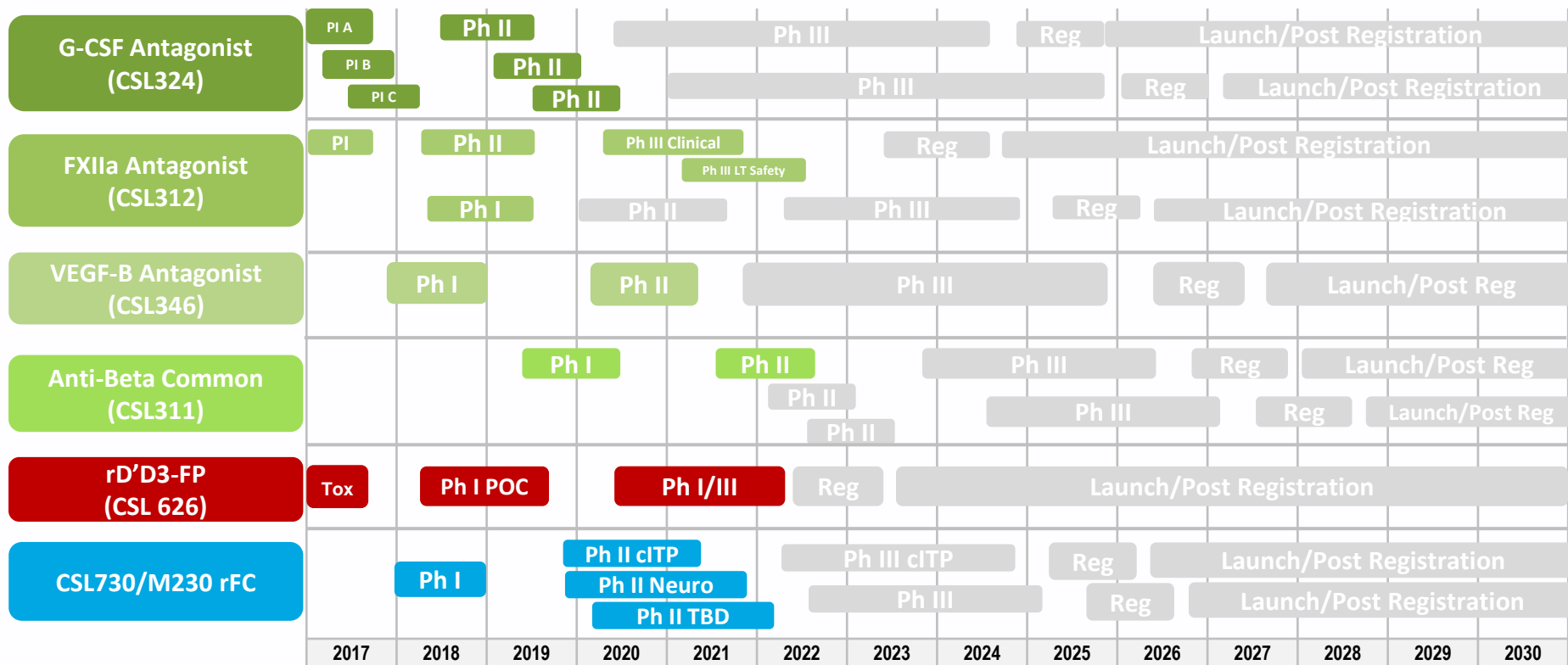




# Australian R&D Pipeline Model



# Early Development Pipeline Examples



# CSL312

Targeting Factor XIIIa for HAE and other indications

# Hereditary Angiodema

- Hereditary angioedema (HAE) is a disorder that results in recurrent attacks of severe swelling
- All body sites are associated with impairment and patients are impacted during and between attacks
- Most severe are laryngeal attacks which can require emergency interventions to protect the airway



Berinert – intravenous, on-demand

HAEGARDA – subcutaneous, prophylactic (2x/week)

CSL312 – subcutaneous, prophylactic (1x/2 weeks, 1x/month?)



# CSL312 – targeting FXII

Clot occluding  
ECMO system



Heparin

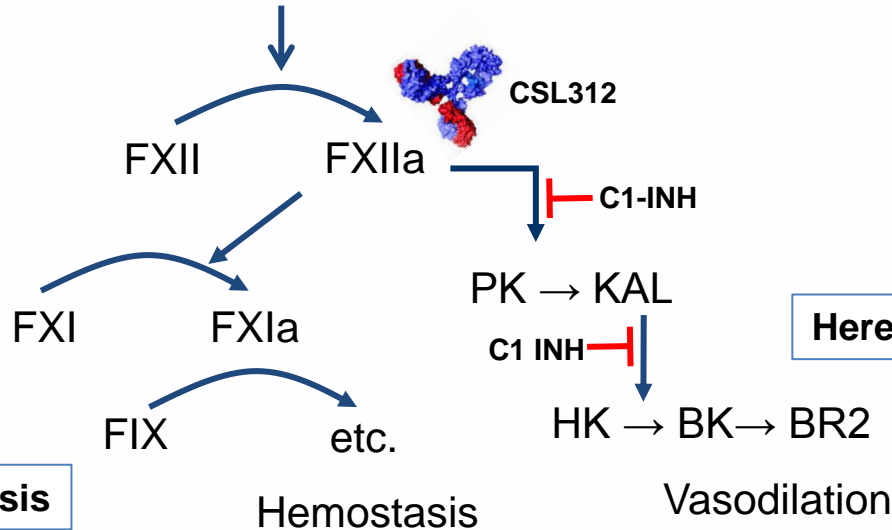


Heparin induced bleeding

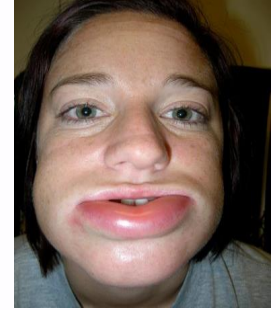
Thrombosis

## FXII activation

Damaged / negatively charged surface



HAE attack



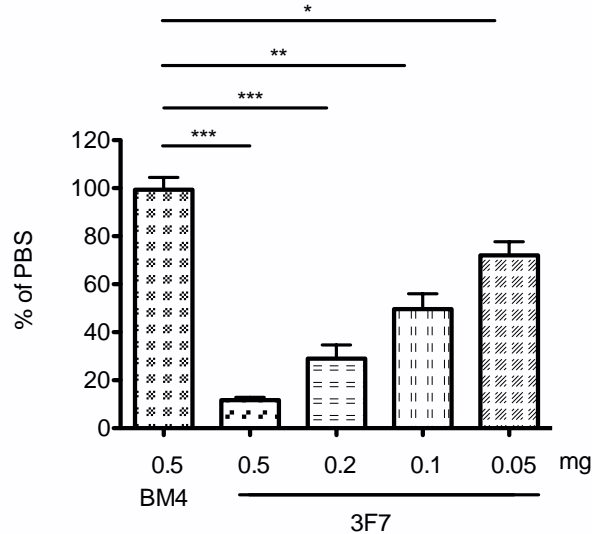
Hereditary Angioedema



# CSL312 – targeting FXII for HAE

Percutaneous anaphylaxis, a mouse model of HAE

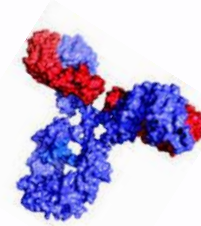
- anti-FXIIa mAb inhibits edema



Ctrl



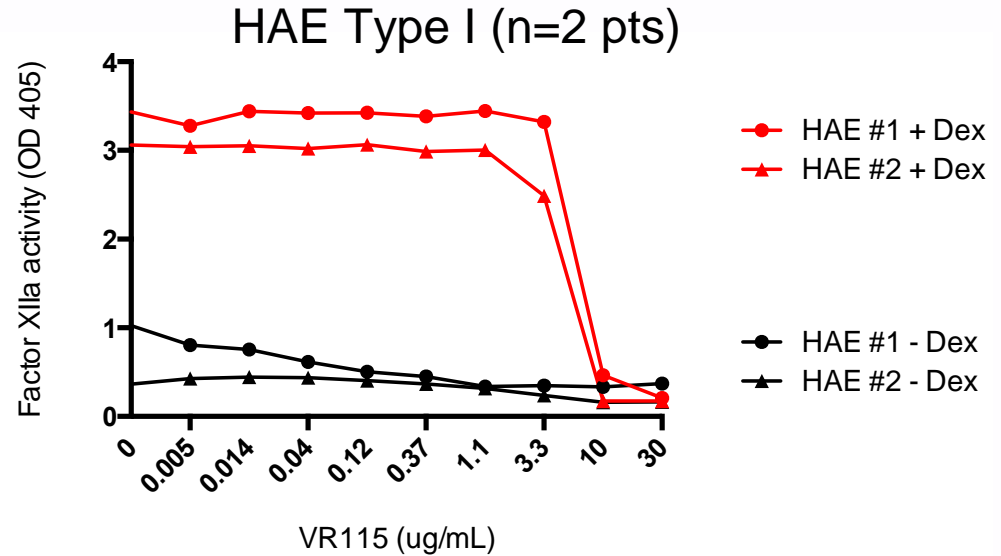
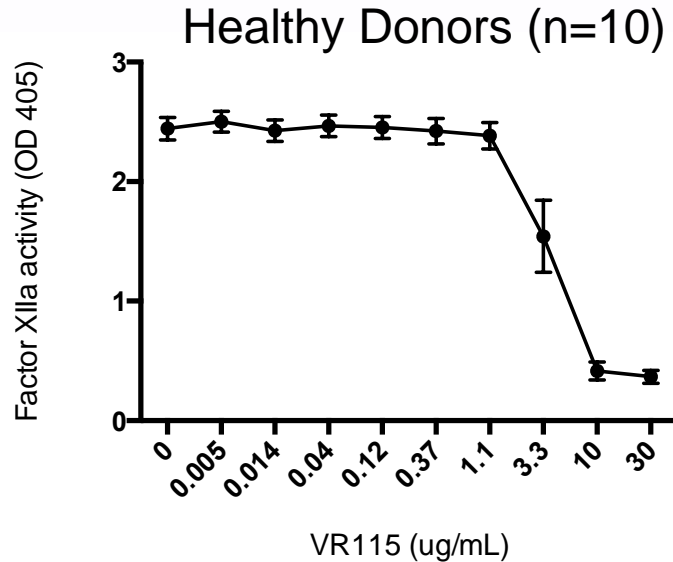
ANTI-FXIIa



CSL312 – Fully human mAb targeting Factor XIIa

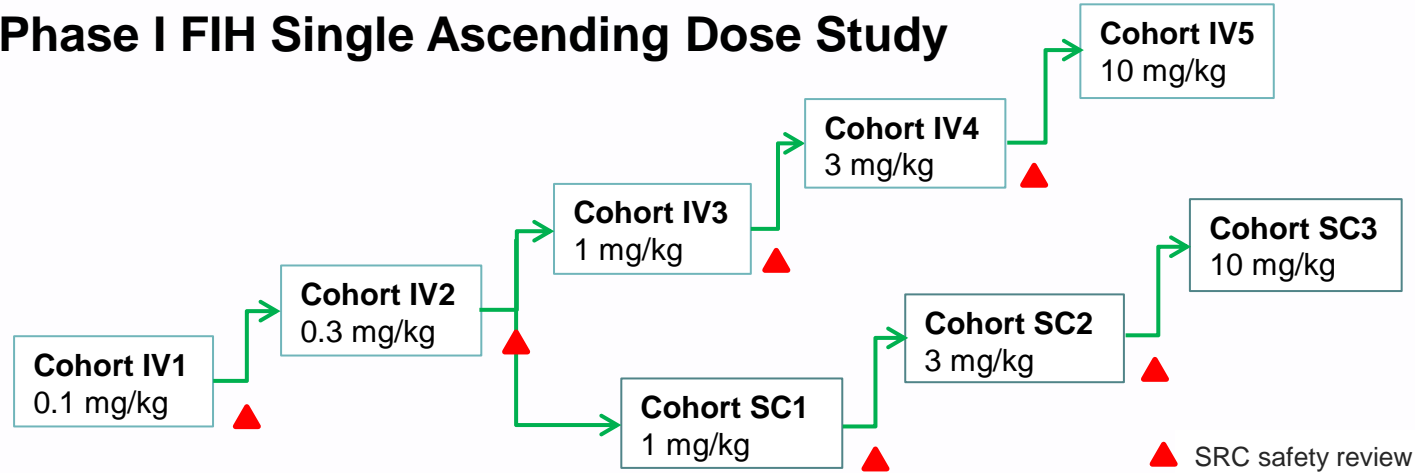
# CSL312 – targeting FXII for HAE

- CSL312 inhibits Factor XIIa activity in human plasma



# CSL312 – targeting FXII for HAE

## A Phase I FIH Single Ascending Dose Study



- Randomised, double blind, placebo controlled
- 48 healthy male subjects
- 4 active subjects and 2 placebo subjects per cohort
- Successfully completed, Phase II planning in progress

# CSL312 – targeting FXII for ECMO

## RCH ECMO Collaboration

- *Translational science collaboration (Prof. Monagle)*

Part 1. Evaluation of plasma from healthy children.

Part 2. Evaluation of plasma from children on ECMO

Part 3. Evaluation of plasma from children on CPB

FXII and the kallikrein-kinin system in infants on ECMO, bradykinin production, FXII antigen levels, FXII activity and CSL312 inhibitory potential

Clot occluding  
ECMO system



Heparin



Heparin induced bleeding

# CSL Gene Therapy

## Strategy for Calimmune Technology



# Calimmune GT Technologies

*Expertise/Know-how*

## VECTOR DESIGN



Ability to design and make efficient therapeutic vectors

*In vivo Selection Tool*

## SELECT+™



Genetic cassette to render stem cells protected against purine analogues to drive in-vivo selection

*Cell Processing*

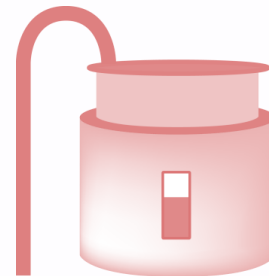
## PROPRIETARY METHODS



Novel SOPs to achieve high cell yields and standardization of cell product

*Lenti Manufacturing*

## CYTEGRITY™

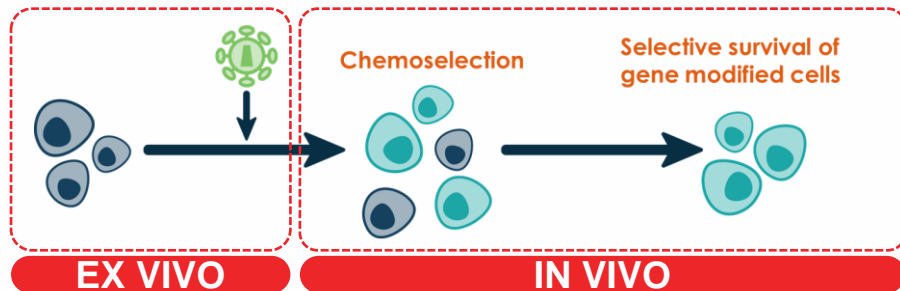


Only large-scale, stable vector production system used clinically

# Select+

Reduces conditioning, increases engraftment and enables out-patient treatment

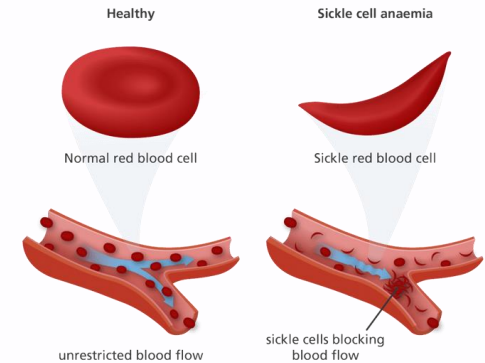
Hypoxanthine-  
guanine  
phosphoribosyltran-  
sferase (HPRT)  
knockout to confer  
resistance to 6-  
Thioguanine (6TG)



	Stem Cell Gene Therapy	Select+
Treatment setting	14-21 Day Hospitalisation	Outpatient
Scalability	Limited	Scalable
Conditioning	Higher toxic dose	Reduced intensity
Engraftment	Inconsistent	Ability to drive engraftment
Reproductive Impact	Causes sterility and infertility	None at anticipated dose
Post-infusion Selection	No	Yes, including re-dosing

# Sickle Cell Disease (SCD)

- SCD results from a single point mutation in the  $\beta$ -globin gene
- Hb tetramers (HbS) polymerise and deform the RBC shape (“sickle shape”)
- Sick RBCs obstruct blood flow causing vaso-occlusive crisis and pain
- Can be overcome by expression of fetal  $\gamma$ -globin



## Epidemiology and Health care costs of SCD

**4.4 million** incidence, most common in sub-Saharan Africa but SCD has a global footprint

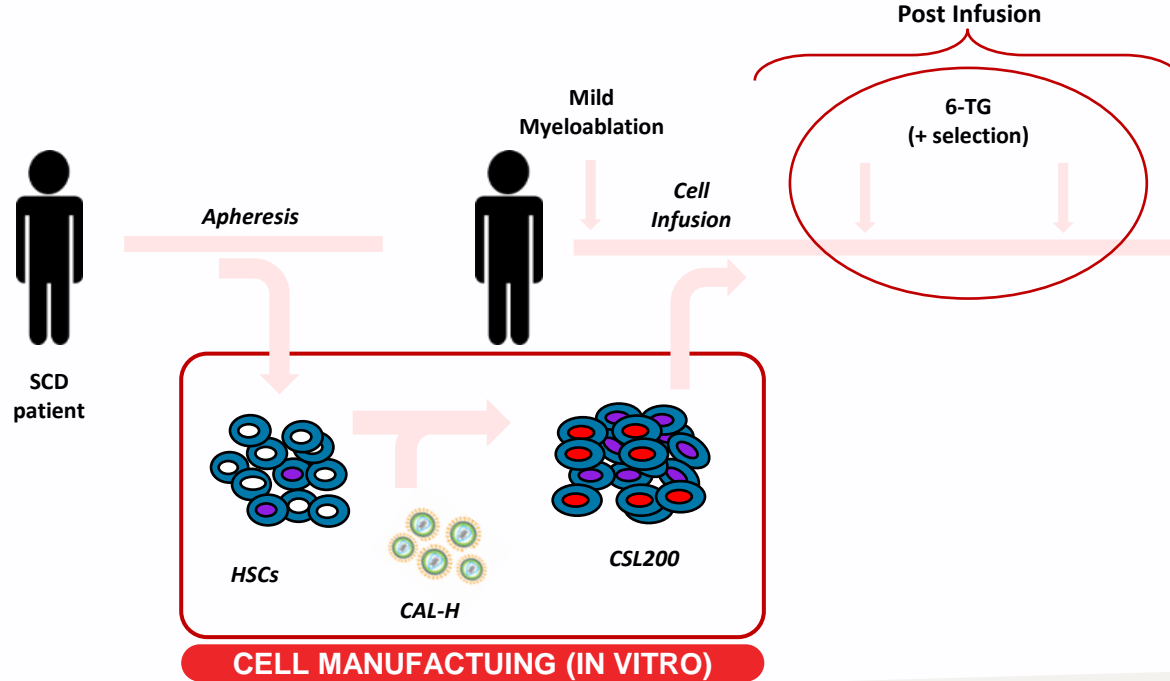
Estimated **100,000** people in US have SCD  
~1500/yr born in US (mandatory screening)

**>\$1.8b US** medical costs annually

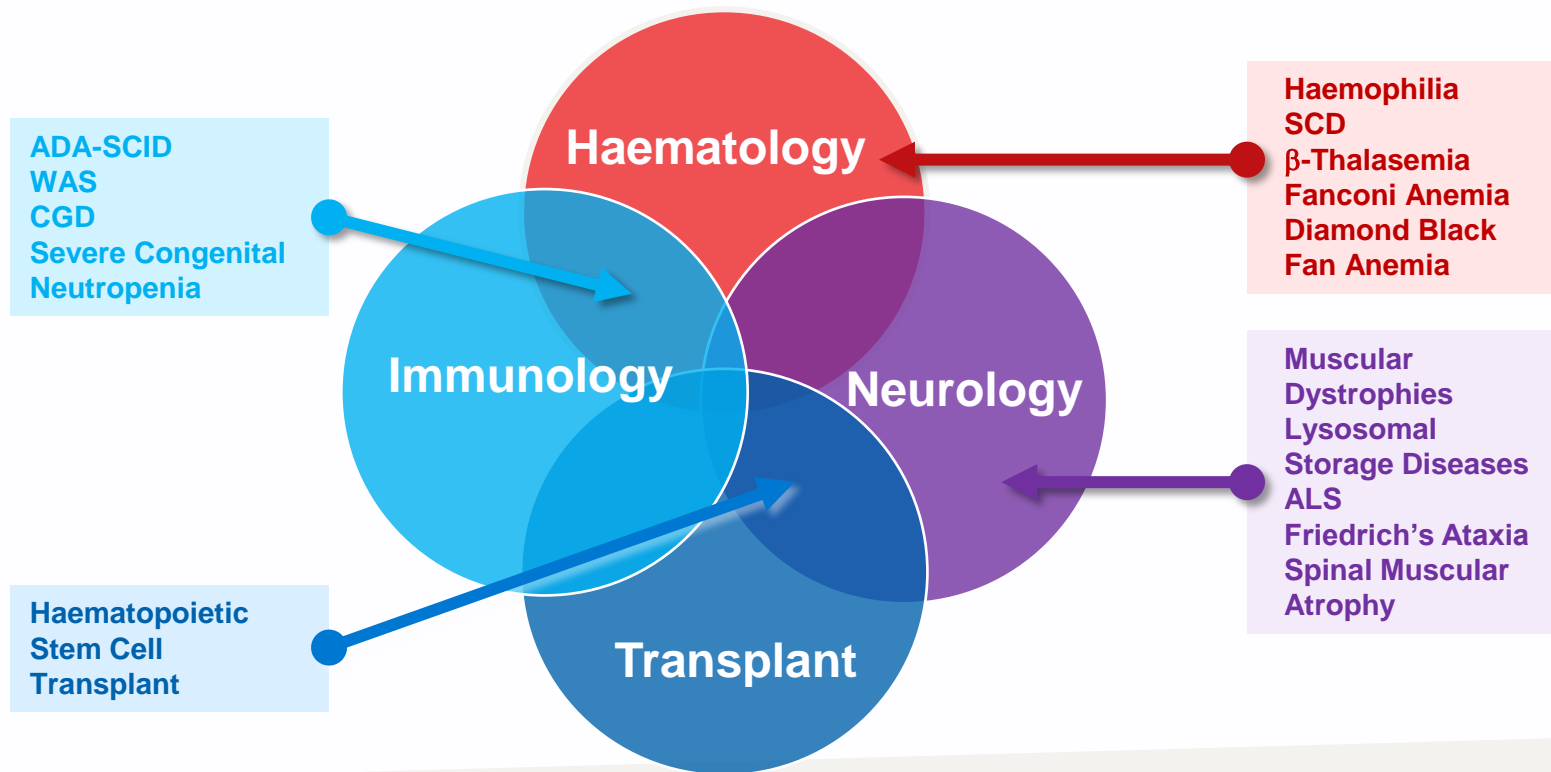
**>\$1m** lifetime cost to patient in US

# Gene Therapy for Sickle Cell Disease

CSL's approach using CAL-H



# Opportunities for Select+







**CSL Behring Operations Investor Tour**  
**30-April 2018**  
**Val Romberg, EVP Manufacturing Operations and Planning**

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# CSL Overview

CSL is a global specialty biotherapeutics company that develops and delivers innovative biotherapies that save lives, and help people with life-threatening medical conditions live full lives

**30+**   
Countries  
Of operations around the world

**6.9+**  
US\$ Billion  
In annual revenue

**8**  
Manufacturing sites

 Australia  
 China  
 Germany  
 Switzerland  
 United Kingdom  
 United States

**19,000+**   
Employees around the world



**2.6**  
US\$ Billion  
In R&D investments in last 5 years  
advances exciting pipeline

**1,400+**   
R&D employees

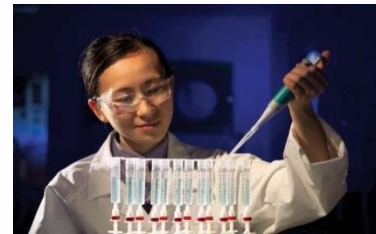
**170+**   
Plasma collection centres across  
Europe and North America

Global #1 in plasma therapies, #2 in influenza vaccines  
~US\$49bn market cap (Top #6 ASX-listing)  
A3 / A- credit rating (stable / stable)

**CSL**

# We are a global specialty biotechnology company

- Leading innovator and manufacturer in the ~US\$24bn plasma protein industry
- Largest plasma collector
- Major provider in ~US\$6bn\* influenza vaccine industry
- Major operations in U.S., Europe and Asia Pacific
- Providing medicines in 60+ countries
- Employs more than 19,000 people in over 30 countries
- \$645M R&D investment in 2016/17.



*\*Inclusive of seasonal  
and pre-pandemic sales.*

# Strategic Objectives



## Growth

Maximize portfolio value & deliver new product launches



## Efficiency

Be the most efficient, highest quality plasma player



## Influenza

Deliver on influenza strategy



## Innovation

Pursue new opportunities to diversify portfolio and enhance growth



## People & Culture

Create a culture that attracts, retains and develops the best talent

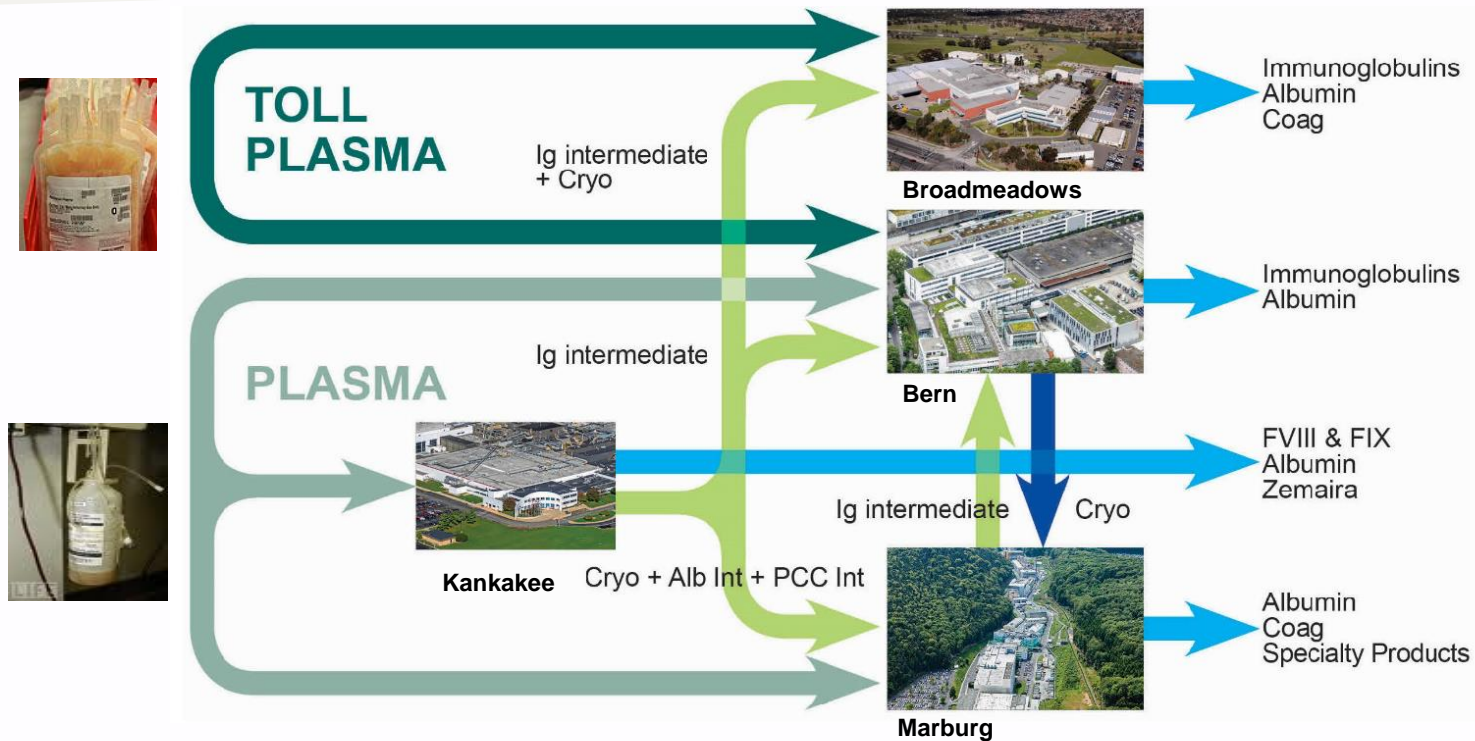


# STRATEGIC FOUNDATIONS



## RELIABLE SUPPLY

# CSL Behring Global Manufacturing Network



## MANUFACTURING OPERATIONS (1 of 2)

### **Bern, Switzerland** (1,400 employees)

- Core products: Immunoglobulins, Albumin
- Specialty products: anti-D-hyperimmune, cytomegalavirus-hyperimmune



### **Melbourne, Australia** (1,100+ employees)

- Toll plasma fractionation services for Australia, New Zealand, Hong Kong, Malaysia, Singapore and Taiwan
- Core products: Coagulation factors, critical care and immunoglobulins



### **Marburg, Germany** (2,400 employees)

- Core products: Coagulation factors and critical care
- Specialty products: hyperimmunes



## MANUFACTURING OPERATIONS (2 of 2)

### Kankakee, US (1,200 employees)

- Core products: Albumin, intermediate pastes,
- Specialty products: Coagulation factors,  $\alpha_1$ -proteinase inhibitor



### Lengnau, Switzerland (140+ employees)

- Core products: Idelvion, Afstyla
- New site under construction



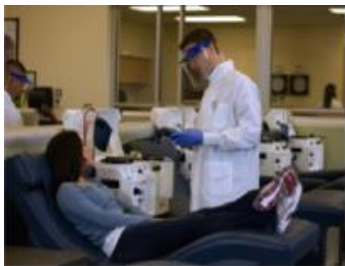
### Wuhan, China (300+ employees)

- Core products: Albumin, Immunoglobulins
- Serves the China market

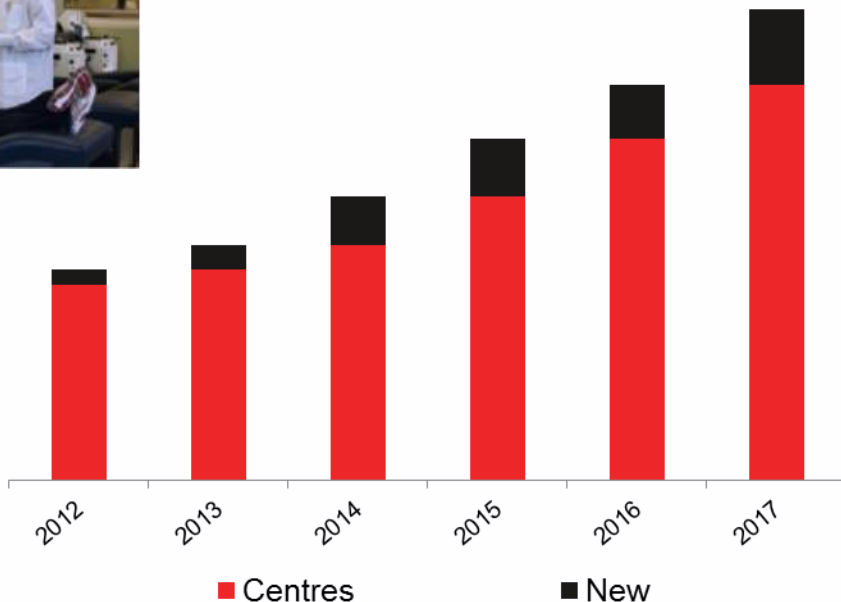


*Pre-pasteurization and filling*

# Large and Efficient Plasma Collection Network



*Plasma donor*



## As of April 2018

- Collection centres 194
- Unmatched rate of centre openings
  - 2-3 per month

## Outlook

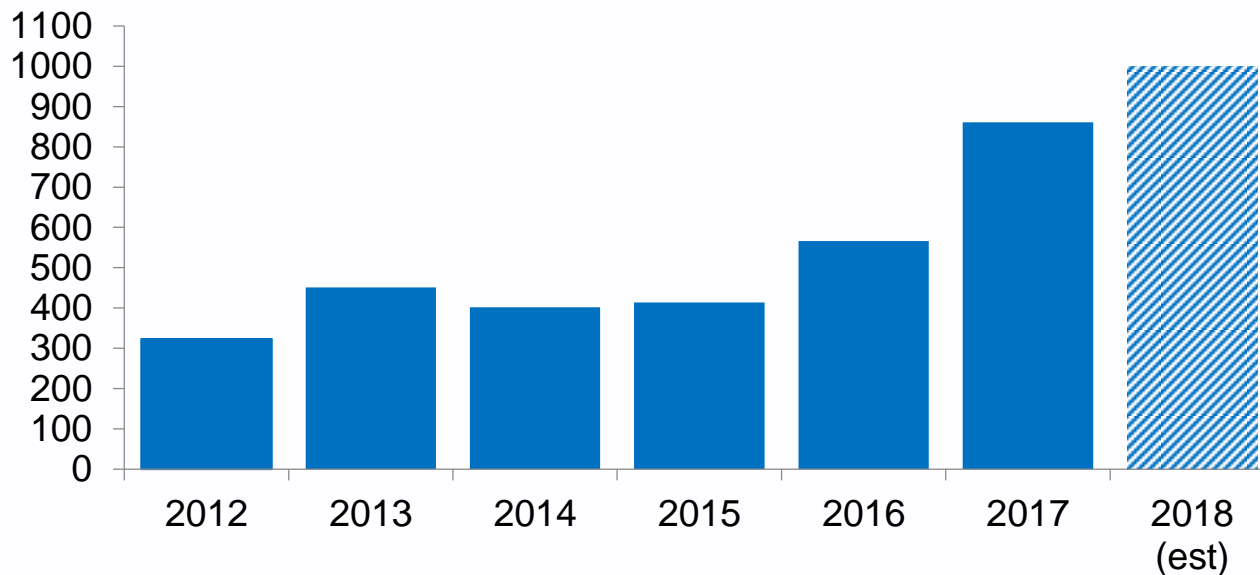
- ~25 to 30 centre openings in FY18
- CPL improves as more centres at peak efficiency
  - ~3 years from opening
- Replicating efficiencies in China over time

# Capital Spend

Capital spending 2012-present



Growth



# Growth in capital reflects three dynamics

- New products (Idelvion, Afstyl, Haegarda)
- Growth in existing products (Privigen/Hizentra, albumin, Haegarda/Beriner, Kcentra/Beriplex)
- Facilities that need modernization or replacement (K3 building 4, Marburg H67, Broadmeadows toll building)

# Investment

## Base Fractionation



Growth



**CSL**



# Investment



Growth

## Base Fractionation Capacity Additions/**Subtractions**

- Kankakee Building 30 New Bay – FY18
- Kankakee Building 33 (Everest) – FY18
- Broadmeadows Process Migration (Aurora) – FY 21
- Kankakee Building 33 Addition (BFX8)– FY22
- Marburg Base Frac (Phoenix)– FY 23
- **End Kankakee Building 4 – FY22?**
- **End Broadmeadows Chromatography – FY22**
- **End Marburg Building H67 – FY23**

# Investment



Growth

## Additional Large Capital Projects

- Protinus – additional Privigen/Hizentra modules in Bern
- Haegarda/Berinert capacity in Marburg and Kankakee
- Albumin expansion – Bern and Kankakee
- Serialization – BMW, K3, and Marburg
- New plasma collection centers
- Marburg R&D Building

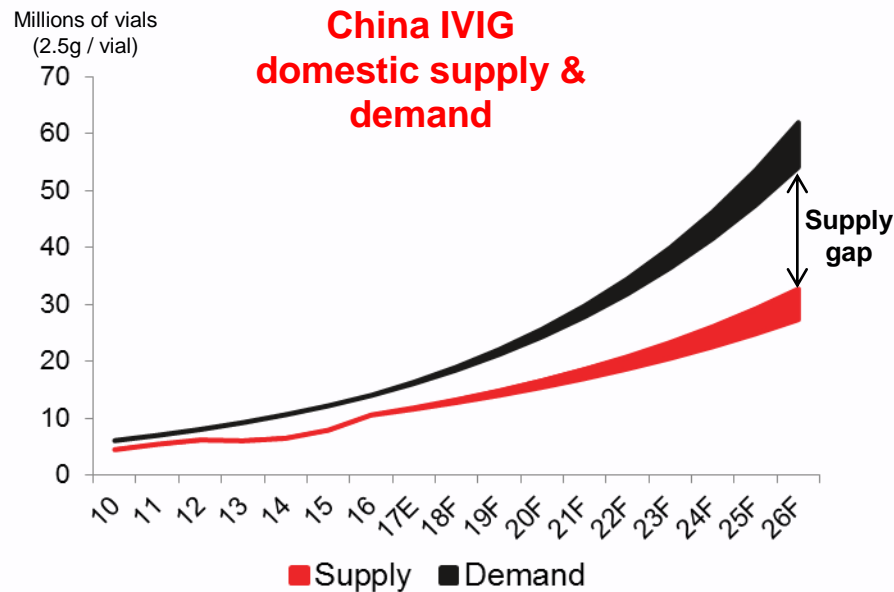
# Lengnau Facility



# Ruide JV - Presence in High Growth Market



Growth



- Acquisition of a majority stake in Chinese plasma fractionator Ruide:
  - Modest entry point to key market
  - CSL Behring has operational control
- Plasma products market in China:
  - ~US\$3.3b in 2016
  - 5 year growth rate ~15%
- China is the fastest Ig growth market:
  - Second in volume to the US
  - Demand forecasted to outstrip supply
- Planning for plasma centre expansion

# Investment



Growth

## Focused Efforts of CSL Behring Operations

- Reliable supply of life saving drugs to patients.
- Improve Margin
- Flexibility for Competitive advantage





# CSL Behring Australia



# CSL Behring Broadmeadows

- Facility established 1994
- Employs 1,100 staff
- Toll Fractionation model for APAC
- Large scale facility for Privigen
- Large scale facility for AlbuRx under construction
- Recombinant Manufacturing
- Formal integration with CSL Behring 2012



# Senior Australian Leadership Team (SaLT)



**Martin Schaeren**  
Senior Vice President &  
General Manager



**Greg Taylor**  
Senior Director Bulk  
Manufacturing



**Dr. David Hartley**  
Senior Director Filling,  
Packaging & Supply  
Chain



**Dr. Helmut Euler**  
Senior Director Quality



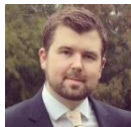
**Howard Wilton**  
Senior Director  
Engineering Services



**Dr. Robyn Elliott**  
Senior Director Strategic  
Expansion Projects



**Dr. Neama Baho**  
Snr Dir. Regional Head,  
AUNZ & International,  
Global Regulatory Affairs



**Adam Williams**  
Director  
Human Resources



**Jacqui Lomas**  
Senior Director Finance



**Dr. Germano  
Coppola**  
Senior Director, Plasma Product  
Development, R&D



**Viv Louzado**  
Business Technology  
Head Asia Pacific



**Metani Rooms**  
PACE AsiaPac Regional  
Deployment Lead



# CSL Behring Broadmeadows - Manufacturing



## Toll Facility

Contract manufacture of plasma for:

- Australia
- NZ
- Hong Kong
- Malaysia
- Singapore
- Taiwan

Partnerships with  
ARCBS and NBA



## Privigen Facility

Commercial IVIg  
Commenced production Nov 2015  
FDA/TGA approved



## AlbuRx Facility

Commercial albumin  
Construction started in June 2015  
Regulatory PAS submission by Q4 2018



## BMF Facility

(Biotechnology Manufacturing Facility)

Recombinant protein facility

Commenced production March 2013

Supports late stage clinical development

# Toll Manufacturing Product Range

- High yields and purity
- 2 dedicated VI steps
- Immunoglobulin -  
6% & 10% liquid IV & 16% liquid SC  
Low IgA & Procoagulants
- Ease of administration



- **ALBUMEX ALBUMIN**  
Critical care, shock, burns, respiratory distress, blood purification, plasma exchange.
- **INTRAGAM, EVOGAM IVIG / SCIG**  
Immune therapy autoimmune disorders, neurology.
- **BIOSTATE FACTOR VIII**  
Haemophilia A
- **BIOSTATE VON WILLEBRAND'S FACTOR**  
Von Willebrand's disease
- **MONOFIX FACTOR IX** Haemophilia B
- **PROTHROMBINEX PROTHOMBIN COMPLEX**  
Coagulation Disorders
- **THROMBOTROL ANTI THROMBIN III**  
ATIII Deficiency, Critical Care.
- **SPECIFIC IMMUNOGLOBULIN**  
Immune therapy for infections and transplants
  - Normal
  - Cytomegalovirus
  - Tetanus
  - Hepatitis B
  - Zoster
  - Rh(D)

# PRIVIGEN Facility (Turner Facility)

- Technology transfer from the CSL Bern facility
- Like for like processes and procedures
- TGA/FDA Compliant Facility
- Starting material – Precipitate A from Kankakee
- Batch size: ~13 kL PEQ with a starting paste mass of ~1100kg
- Finished Product Presentations:  
50, 100, 200 and 400mL



# ALBURX Facility

- Technology transfer from the CSL Bern facility
- Like for like processes and procedures
- Construction started in June 2015
- PAS submission by December 2018
- Formulations: 5%, 20% and 25%
- Formats: 50, 100, 250 and 500 mL



# Biotechnology Manufacturing Facility (BMF)

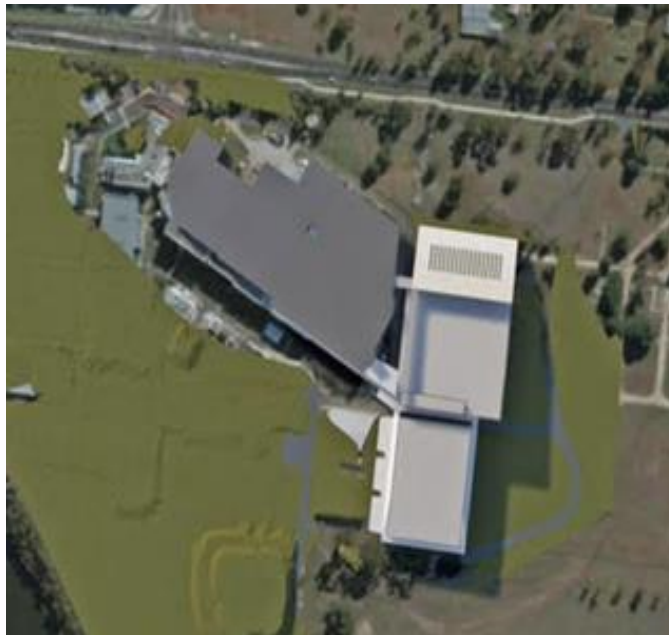
- Single use technology
- Capacity to support Phase III Clinical Trials & early commercial manufacture
- Accommodate a range of manufacturing processes including:
  - recombinant coagulation factors
  - monoclonal antibodies.



Bioreactor



# Project Aurora - New Broadmeadows Base Fractionation Facility





# Base Fractionation Facility

- Global Harmonized Design and process
- Additional space allowed within the building for further manufacturing expansion
- Early Works started in March 2018
- Construction of Module 1 to be completed by Dec 2020
- PAS submission for Module 1 by February 2022
- Base Fractionation intermediates will support the BMW AlbuRx and Privigen facilities allowing “end to end” manufacturing at BMW



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CSL has earned a reputation as a passionate, responsible company driven to care for patients and deliver on its commitments.

**At CSL, we are driven by our promise.**



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## CSL Limited

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