Drug Discovery and Technology Capabilities at WEHI

Melbourne, Australia
History of WEHI

• Established 1915
• Focused on the fundamental principles of medical biology to mitigate disease
• Independent Research Institute affiliated with University of Melbourne, Royal Melbourne Hospital and the Victorian Comprehensive Cancer Center
WEHI Overview

90 laboratories working on 50+ diseases

120 Clinical trials currently underway

1200+ researchers and staff

> +30 million patients world wide have benefited from our research
WEHI performs influential basic and translational research focused on four key therapeutic areas:

- Cancer
- Immunology & Inflammation
- Infectious diseases
- Ageing and development
WEHI was ranked 19th in the 2019 Nature Index for global not-for-profit/non-governmental organizations.

Translating discoveries: Venetoclax = New targeted treatment for Chronic Lymphocytic Leukaemia approved by FDA in 2016.

Gender Equity in Research: WEHI is recipient of SAGE Athena SWAN Award + membership of Male Champions of Change.

Increased funding partnership with State government ➢ State government invests $18M in WEHI National Drug Discovery Centre (in addition to contributions announced by Federal government).
History of our Drug Discovery Centre

- First academic drug discovery infrastructure at an Australian research institute
  - High-throughput screening facility
  - Medicinal chemistry laboratories
- 2003-2019: Completed > 30 drug discovery projects

Victorian Government
$18M
Instrumentation
Compound management system
Protein production

Australian Government
$25M
Over 4 years
Subsidised screens for Australian researchers

WEHI & philanthropy
$35M
New laboratories & infrastructure
Unique Drug Discovery Capability Embedded Within a World-Class Medical Research Institute

- Established drug discovery infrastructure
  - Assay development
  - High throughput screening
  - Medicinal chemistry
  - Structural biology
  - Animal disease models
  - High containment PC3 animal facility for infectious work

- Track record of successful drug development with industry partners
Key Strengths

• Embedded within **world-class biology research**, thus delivering first-in-class innovative drug discovery projects

• Quality, capabilities & scale comparable to **pharmaceutical industry standards** with the flexibility & innovation of academia

• Active from **target discovery** to **preclinical candidate** stage
Drug Discovery at WEHI & Collaboration with Local Precinct Partners

WEHI

ACRF Chemical Biology Division
Medicinal Chemistry

Structural Biology Division
X-Ray/NMR structures
Biophysical assays

Advanced Technology & Biology Division
High-throughput screening
Assay support
Proteomics

External

DMPK
CDCO (Monash University)

Fragment based screening
MIPS (Monash University)
Bio21 (University of Melbourne)

Australian Synchrotron (ANSTO)
Collaborative Crystallisation Centre, C3 (CSIRO)
NMR (Bio21, University of Melbourne)
CryoEM (Bio21, University of Melbourne & Monash University)
High-Throughput Screening

Team

- Staff of 18 people and expanding
- >100 years combined experience
- Automation, engineering, data analysis and screening experts from industry and academia

- Small molecule screening libraries
- Lead-like diversity libraries (up to 440K compounds)
- Focused and FDA approved drug libraries
High-Throughput Screening
### Categories of assays

<table>
<thead>
<tr>
<th>GPCR</th>
<th>Enzyme</th>
<th>Ion Channel</th>
<th>Cell-based</th>
<th>Protein-Protein interaction</th>
</tr>
</thead>
</table>

### Types of assays

#### GPCR
- **Ca\(^{2+}\) flux**
- IP-One, cAMP measurement TR-FRET
- ATP/ADP consumption (luminescence/FP)
- Cleavage of tractable substrate
- Alpha reagent / FRET or TR-FRET assay
- Mass spectrometry

#### Enzyme
- Membrane potential measurement (fluorescent dye)
- Homogenous ELISA, TR-FRET / AlphaLISA
- Viability assay
- High-content imaging
- Flow cytometry

#### Ion Channel
- AlphaScreen / TR-FRET
- Fluorescent polarization (FP)

#### Basic technology
- Recently implemented
Data Acquisition Technologies

- **High Content**: Opera phenix (PerkinElmer)
  - confocal imaging with high throughput through simultaneous acquisition

- **Multimode reader**: PHERAstar FSX (BMG)

- **Flow cytometer**: iQue Screener PLUS (Intellicyt)

- **FLIPR Penta**: (Molecular Devices)

- **Echo® MS System**: (SCIEX)
## Recent Screening Pipeline

<table>
<thead>
<tr>
<th>Indication</th>
<th>Assay type</th>
<th>Assay devel.</th>
<th>Primary screen</th>
<th>Hit validation</th>
<th>Hit to lead</th>
<th>Lead devel.</th>
<th>Collaborative model</th>
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</thead>
<tbody>
<tr>
<td>Cancer</td>
<td>Enzymatic</td>
<td></td>
<td>[116,000 cpds]</td>
<td></td>
<td></td>
<td></td>
<td>Pharma/Internal</td>
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<td>Cancer</td>
<td>Binding</td>
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<td>Inflammation</td>
<td>Enzymatic</td>
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<td>Cellular</td>
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<td>[115,000 cpds]</td>
<td></td>
<td></td>
<td></td>
<td>Internal</td>
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<tr>
<td>Prader-Willi Syndrome</td>
<td>Enzymatic</td>
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<td>[114,000 cpds]</td>
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<td></td>
<td>Internal</td>
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<tr>
<td>Cancer (AML)</td>
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<td></td>
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<tr>
<td>Inflammation</td>
<td>Cellular</td>
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<td>[120,000 cpds]</td>
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<td></td>
<td>Internal</td>
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<tr>
<td>Inflammation</td>
<td>Protein/protein</td>
<td></td>
<td>[115,000 cpds]</td>
<td></td>
<td></td>
<td></td>
<td>Internal</td>
</tr>
<tr>
<td>Cancer/antiviral</td>
<td>Enzymatic</td>
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<td></td>
<td>Internal</td>
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<tr>
<td>Malaria</td>
<td>Enzymatic</td>
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<td>[1300 cpds]</td>
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<td></td>
<td></td>
<td>Pharma/Internal</td>
</tr>
<tr>
<td>Malaria</td>
<td>Cellular</td>
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<td>[80,000 cpds]</td>
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<td>Pharma/Internal</td>
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<td>Neurodegeneration</td>
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<td></td>
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<tr>
<td>Cancer</td>
<td>Protein/protein</td>
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<td></td>
<td></td>
<td>Internal</td>
</tr>
<tr>
<td>Cancer (AML)</td>
<td>Protein/protein</td>
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<td></td>
<td>Academic/Internal</td>
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<tr>
<td>HIV</td>
<td>Reporter</td>
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<td>[114,000 cpds]</td>
<td></td>
<td></td>
<td></td>
<td>Academic/Internal</td>
</tr>
</tbody>
</table>
WEHI researchers are developing their own small and large molecule compounds against targets of interest, both as proprietary projects and in collaboration with industry.

WEHI has capability for advancing hit series through SAR analysis, structure-guided medicinal chemistry, target identification, binding mode analysis and mechanism of action assays.

**Chemistry labs:**
- Currently 28 chemists
- Proven capability to manage outsourced chemists
- Bundoora campus (16 fume-cupboards)
- Parkville campus (14 regular size + 2 large size fume-cupboards)

**Analytical Facilities:**
- HPLC-MS (2x Bundoora, 1x Parkville) & prep HPLC-MS (Bundoora)
- NMR 300 MHz (Bundoora and Parkville)
Structural Biology Capabilities

Crystallography
- Collaborative Crystallisation Centre, C3 (CSIRO)
- Australian Synchrotron (ANSTO)

Cryo-EM
- Centre for Cryo-EM (Monash University)
- Bio21 / WEHI Cryo-EM (under construction)

NMR
- 400, 500 & 600 MHz (Bio21)

Isothermal titration calorimetry

Surface Plasmon Resonance
- Biacore 4000 & S200
High Containment PC3 Animal Facility for Infectious Disease Models

Current animal models:
- *Mycobacterium tuberculosis*
- *Burkholderia pseudomallei, B. cepacia*
- HIV-1
- HTLV-1
- SARS-CoV-2

Technology in facility:
- Live cell IXM – Confocal imaging
- BD Aria Fusion – Flow cytometry analysis/sorting
- ID3 spectrophotometer plate reader
- Glascol - inhalation exposure system
- Technoplast animal unit – 1080 mouse capacity
- Beckman Coulter Ultracentrifuge

Dr Cody Allison – Imaging SARS-CoV-2 infected human cells
Track Record of Translation with Partners

Proven track record of translating basic research into clinical & commercial success, alongside our partners

Venetoclax
Anti-cancer medicine based on a discovery made at WEHI in the late 1980s

- 2004: HTS on BCL-2 family proteins
- 2006: Drug Discovery Collaboration and License Agreement with Genentech
- 2008: Tripartite Bcl-2 Research Agreement with Genentech and Abbvie
- 2016: Venetoclax FDA approval
Systems Biology at WEHI

Genomics

Bioinformatics

Proteomics
As a founding member of the Melbourne Genomics Health Alliance we also aim to integrate genomic medicine into everyday healthcare for the benefit of patients.

- **Gene Expression Analysis**
- **Genome Comparison**
- **Next Generation Sequencing**
  - *illumina MiSeq*
  - *NextSeq*

**Single Cell Open Research Endeavour (SCORE):**
- Integrated program with a team to help you build a protocol best suited to your needs
- Pipeline from sample preparation to analysis with a mix of capable biologists, technologists and computational biologists
- Free consultation meeting
Single Cell Open Research Endeavour (SCORE)

Facility Capabilities

- Single cell whole genome DNA
- Single cell epigenetics
- Single cell proteomics
- Spatial technologies which allow the study of RNA in the context of the tissue/cell
- Single cell Multi-omics - a combination of methods to simultaneously detect two or more parameters (e.g. RNA + protein, DNA+RNA)
Proteomics

With high-resolution mass spectrometry technology our researchers are able to:

- Characterise protein identity and function
- Identify interactions between proteins and other molecules
- Quantify important biomarkers for disease diagnosis
- Study protein dynamics

Heavy labelling techniques allow precise quantification:

- SILAC
- HDX
Bioinformatics

• Integrated throughout WEHI applying mathematics, statistics and computer science to a number of research areas such as:
  – Genomics
  – Proteomics
  – Systems biology
  – Personalised medicine

• WEHI researchers have developed high-powered algorithms widely used around the world
  – *limma* and *edgeR* for analyzing RNAseq gene expression experiments
  – *Subread* sequence aligner
WEHI Centre for Dynamic Imaging

State-of-the-art equipment and renowned experts
State of the Art Imaging Equipment

**Confocal**
- Zeiss LSM 980 with Airyscan 2
- Leica SP8 Resonant Scanning Confocal
- Zeiss LSM 780 Confocal
- Zeiss LSM 880 Fast Airyscan Confocal
- Zeiss LSM 880 NLO Fast Airyscan Confocal

**Widefield**
- Nikon N-STORM 5.0 (super-resolution)
- Zeiss Axio Observer (Airlock)
- DeltaVision OMX SR (super-resolution)
- DeltaVision Elite

**Light sheet**
- Lattice light sheet
- Zeiss Lightsheet Z.1

**Preclinical**
- Bruker Skyscan 1276 Micro-CT
- IVIS Spectrum

**Multiphoton**
- Zeiss LSM 880 NLO Fast Airyscan Confocal
- Olympus FVMPE-RS Multiphoton
Bioimage Analysis

**Hardware**
- A range of interactive virtual machines hosted on WEHI’s High Performance Computing Cluster
- Access computing power from anywhere, including high-end graphics processing units (GPUs), large amounts of data storage and fast data transfer to and from network storage.

**Software**
- Fiji/ImageJ
- Bitplane Imaris
- Huygens
- Arivis
- Omero
- HALO

**Researchers**

**Imaging experts**
In-house Professional Histology Facility

- Guarantee professional histology services with qualities in a timely manner
- Digital pathology (virtual slides) and 2D fluoresces scanner
- Immunohistochemistry (IHC) auto-platforms up to IVD standard to access Multiplex IHC/IF and guarantee the quality and consistency
## Available Technologies

<table>
<thead>
<tr>
<th>WEHI</th>
<th>External</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live cell fluorescent imaging and high-content image screening – CDI</td>
<td>Cryo-EM Melbourne Advanced Microscopy – Bio21</td>
</tr>
<tr>
<td>Deep tissue or intravital imaging, observe cells in their natural environment – CDI</td>
<td>Cryo-EM The Ramaciotti Centre for Cryo-EM – Monash University</td>
</tr>
<tr>
<td>Anatomical/Digital Pathology, 2D Multiplex Immuno-labelling – Histology</td>
<td></td>
</tr>
<tr>
<td>4D images of sensitive samples at high speed – CDI</td>
<td></td>
</tr>
<tr>
<td>Perform non-invasive monitoring of disease progression over time – CDI</td>
<td></td>
</tr>
</tbody>
</table>
Our antibody facility services include

- Antibody production: 1-10 mg, 10-50 mg, 50-500 mg
  - Production of monoclonal antibodies
  - Production of polyclonal antibodies
  - *In vitro* production of monoclonal antibodies using bioreactor technology
- Purification of monoclonal antibodies from hybridoma or bioreactor supernatant
- ELISA assays for quantification of antibody titre
- Screening of antibodies using western blots
- Isotyping of monoclonal antibody supernatants
- Conjugation of monoclonal antibodies
- Nanobody production and purification
Nanobodies
- antibody fragments from camelids or cartilaginous fish
- small in size
- high-antigen binding affinity
- increased stability across temperature and pH range

immunization of alpacas with target protein

isolation of nanobody genes from plasma cells

cloning of nanobody library

screening of libraries for target-specific nanobodies

expression of resulting nanobodies in bacterial systems
Contact Us

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