

## Professor Andrew Roberts

**Partnerships to develop novel drugs: Not always easy, but essential**

*The Walter + Eliza Hall Institute of Medical Research  
The Royal Melbourne Hospital  
The University of Melbourne  
Victorian Comprehensive Cancer Centre*

# Declaration of Conflicts of Interest and Disclaimers

## I have the following financial relationships to disclose:

Employment / Advisor: Nil

Speaker's Bureau for: Nil

Grant/Research support: AbbVie, Genentech/Roche, Janssen, Beigene, Servier

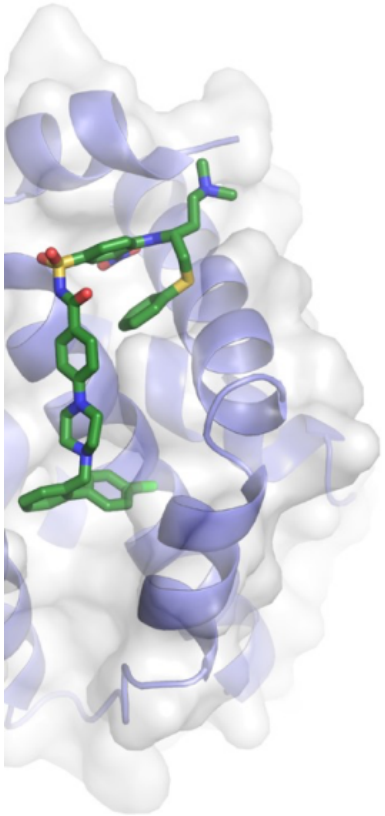
Stockholder in: Nil

Honoraria from: Nil

Employee of: Walter & Eliza Hall Institute which receives milestone & royalty payments related to venetoclax from Genentech/AbbVie

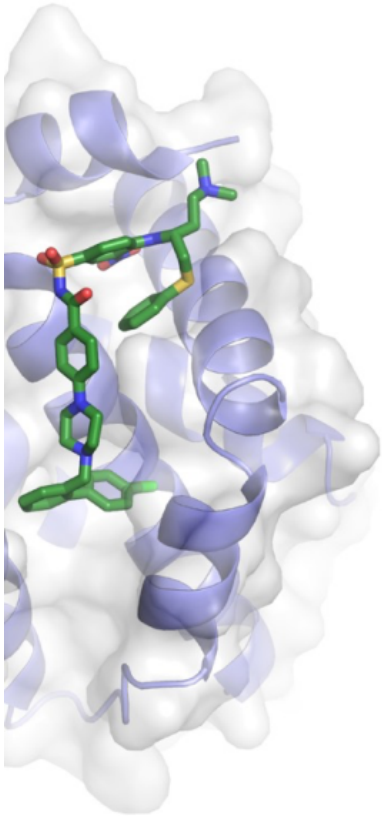
## Disclaimers:

- The drug being used as an exemplar, venetoclax, is not approved for routine clinical use in Singapore
- I am speaking as an academic, not as an agent for any pharma company or my employers

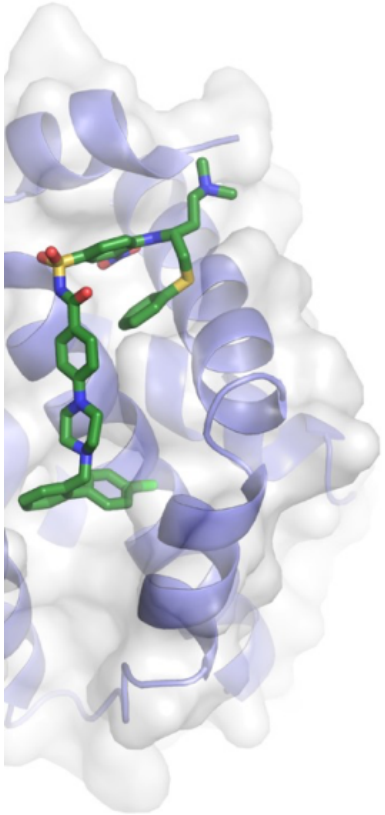


# How to make a big difference in cancer outcomes

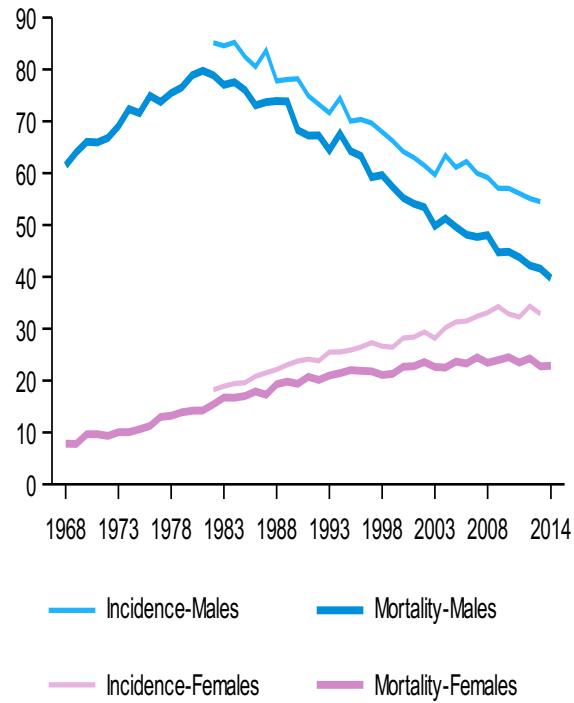
- Prevention
- New therapies
- Both based on research



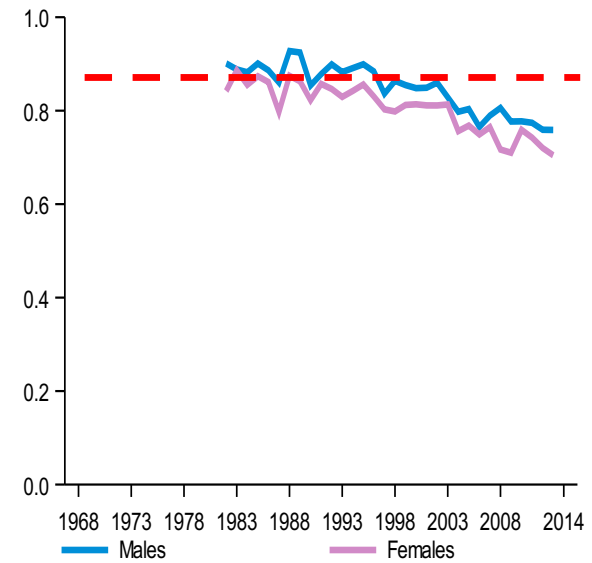
# Tobacco control – the major cause of reduced mortality from lung cancer



**Standardised Rates / 100,000**

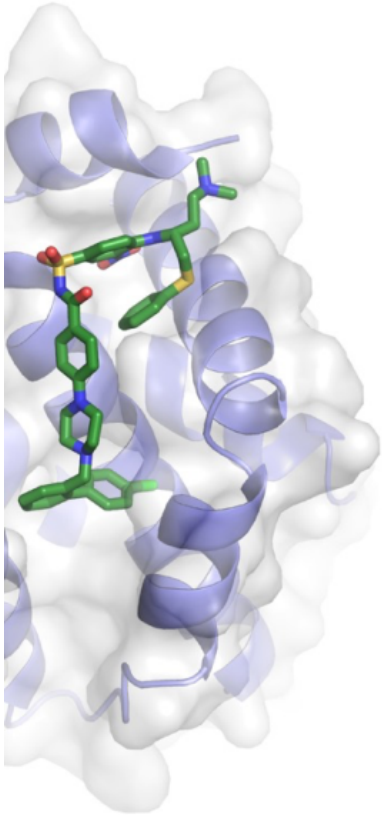


**Ratio Incidence: Mortality**

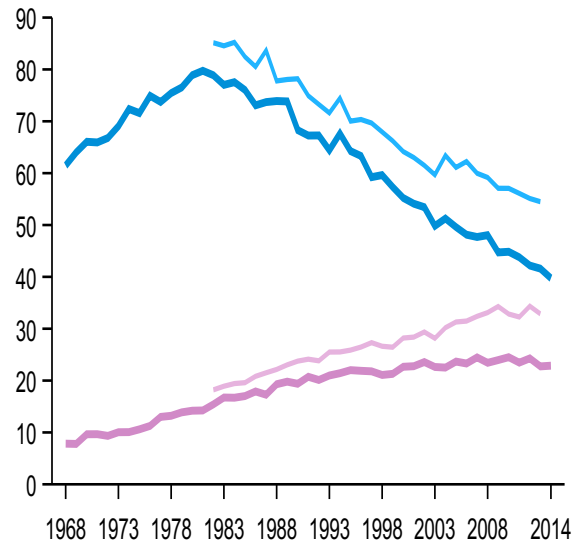


AIHW Data

# Tobacco control – the major cause of reduced mortality from lung cancer

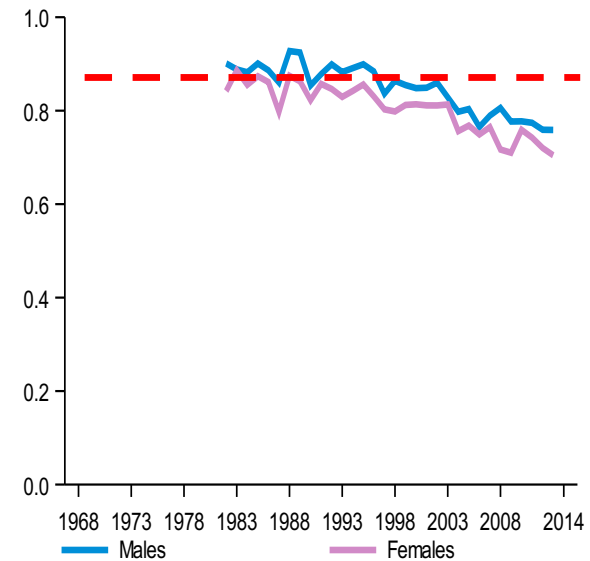


**Standardised Rates / 100,000**



**50% reduction in incidence & mortality (males)**

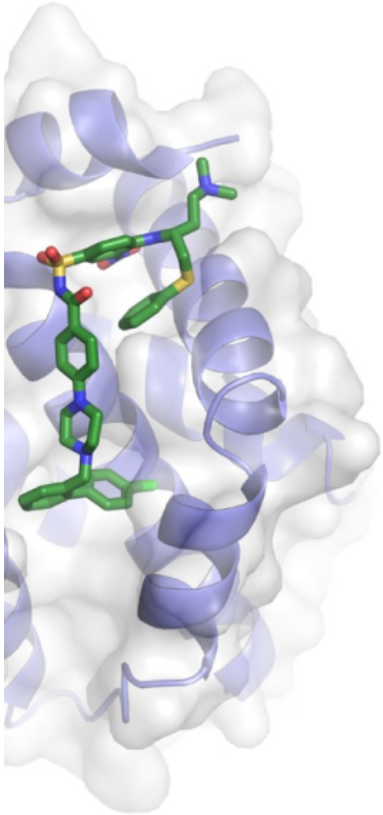
**Ratio Incidence: Mortality**



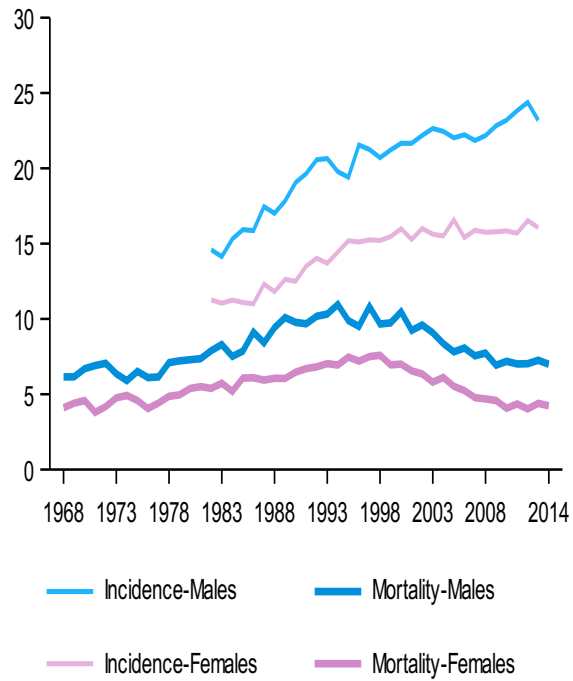
**< 10% increase in "cure" fraction**

AIHW Data

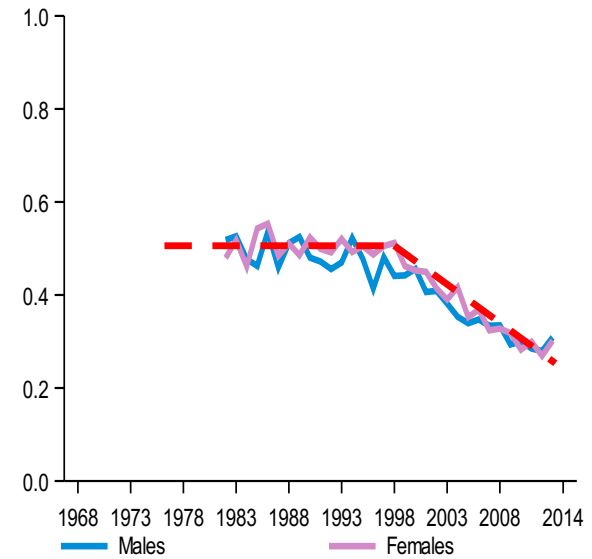
# Rituximab – turning the tide of lymphoma



Standardised Rates / 100,000

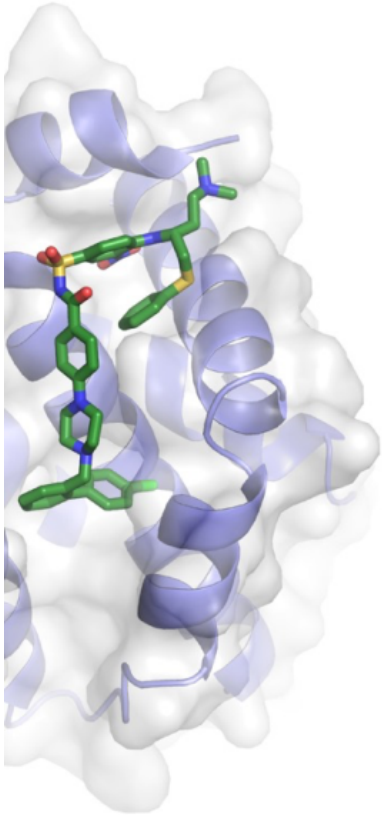


Ratio Incidence: Mortality

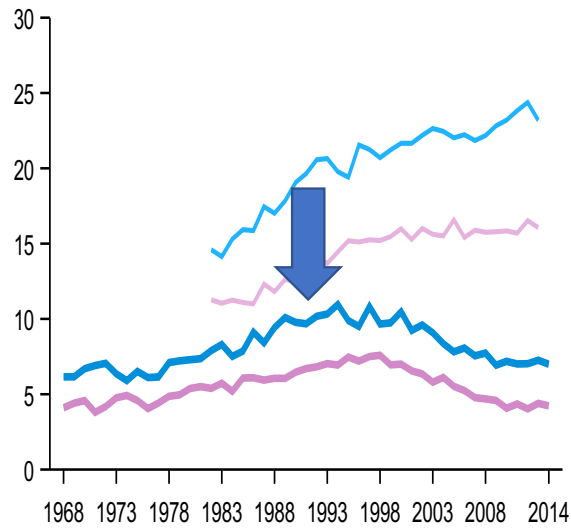


AIHW Data

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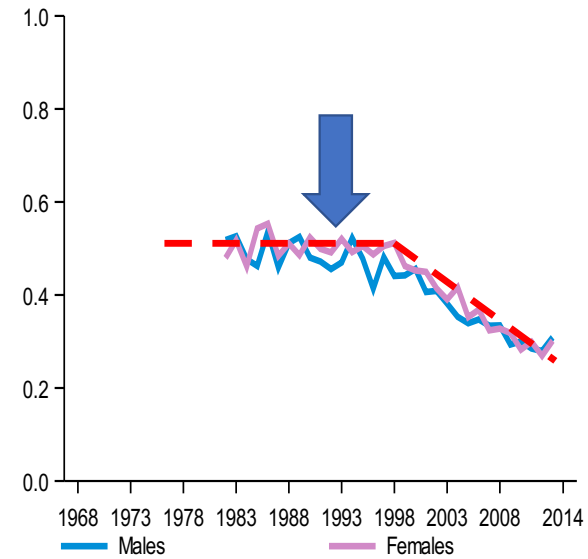


**Standardised Rates / 100,000**



**50% increase in incidence but 40% fall in mortality**

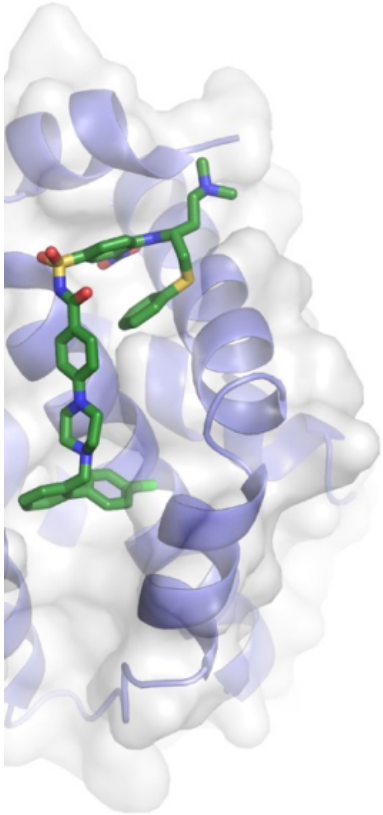
**Ratio Incidence: Mortality**



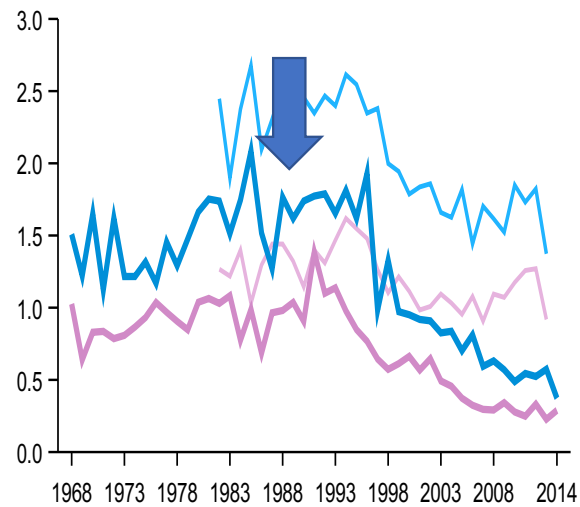
**~ 50% increase in "cure" fraction**

AIHW Data

# Imatinib & TKIs – revolutionised outcomes in Chronic Myeloid Leukaemia

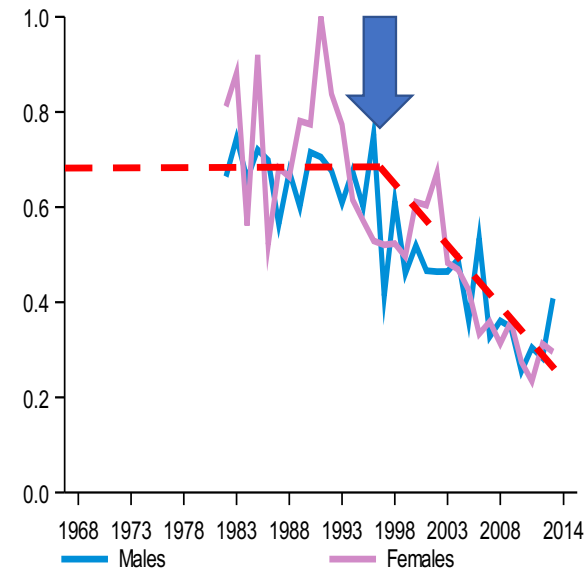


**Standardised Rates / 100,000**



**No change in incidence  
but 67% fall in  
mortality**

**Ratio Incidence: Mortality**



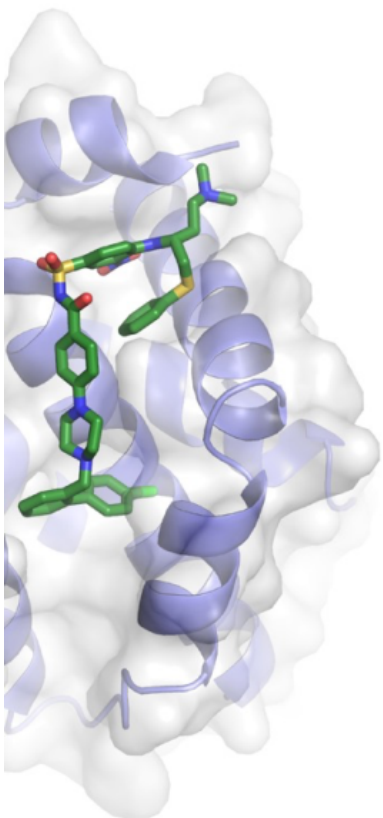
**~ 67% increase in  
"cure" fraction**

AIHW Data

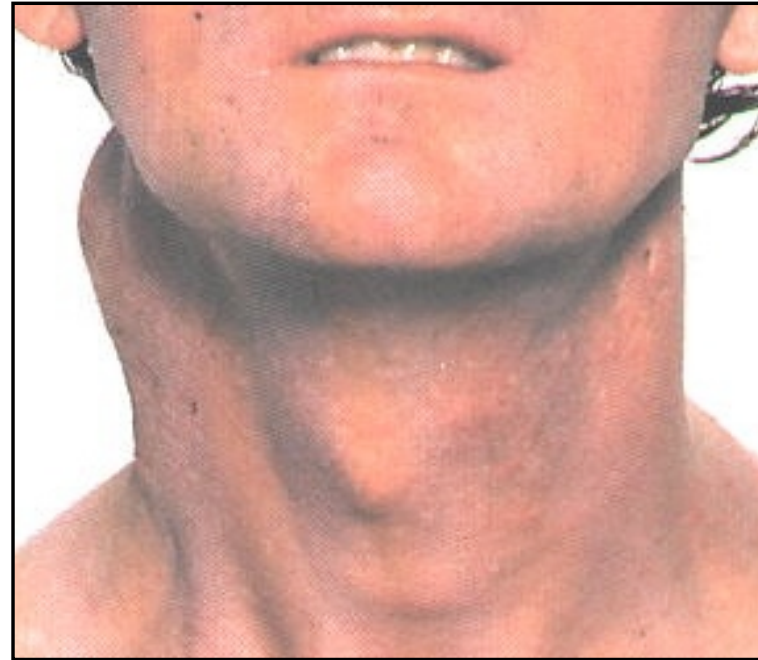
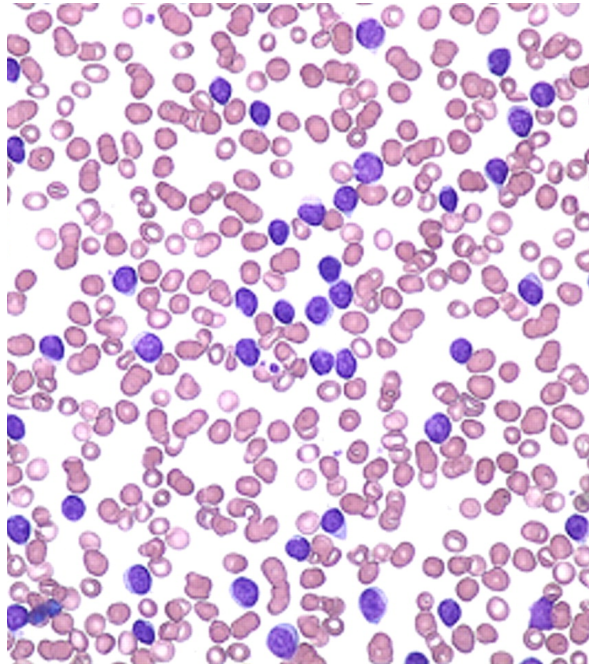
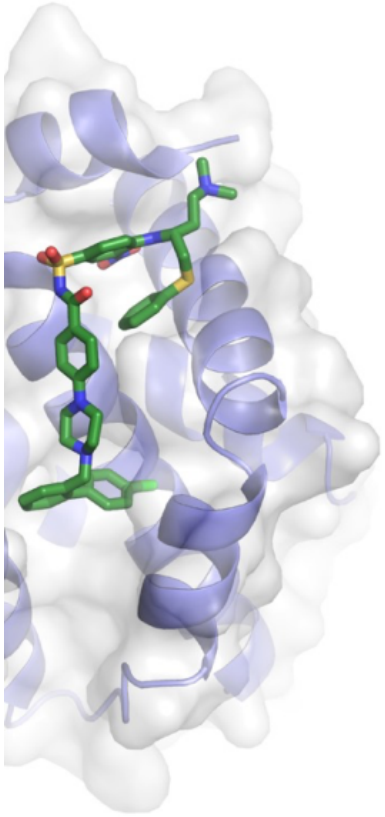


## Modern cancer treatments are targeted

- Cancer develops due to multiple abnormalities in genes that build up in a cell during life
- Cancer cells often depend on one or two of these genetic changes
- Modern cancer medicine seeks to
  - identify the Achilles' heel of a cancer cell
  - then target this “weakness”
- To design new therapies, first need to understand the biology of specific cancers

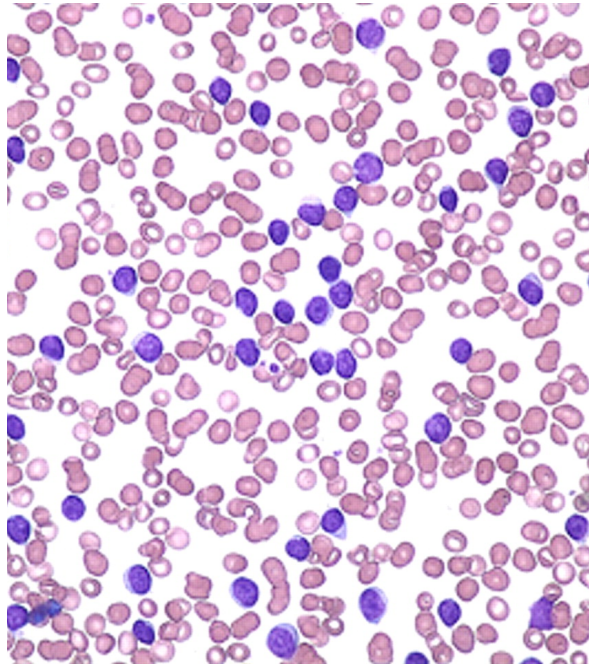
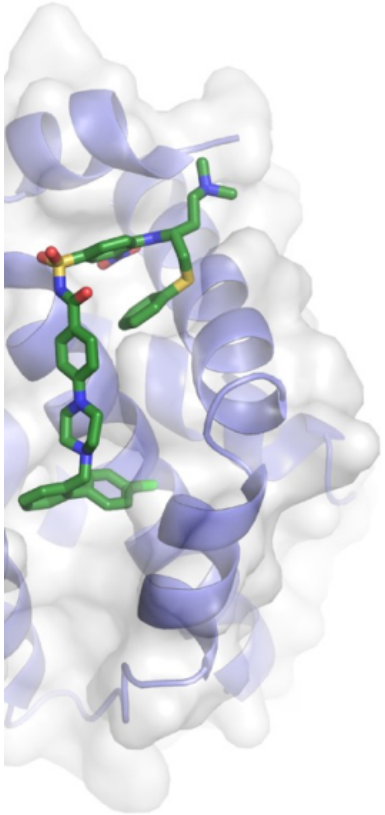


# Chronic Lymphocytic Leukaemia



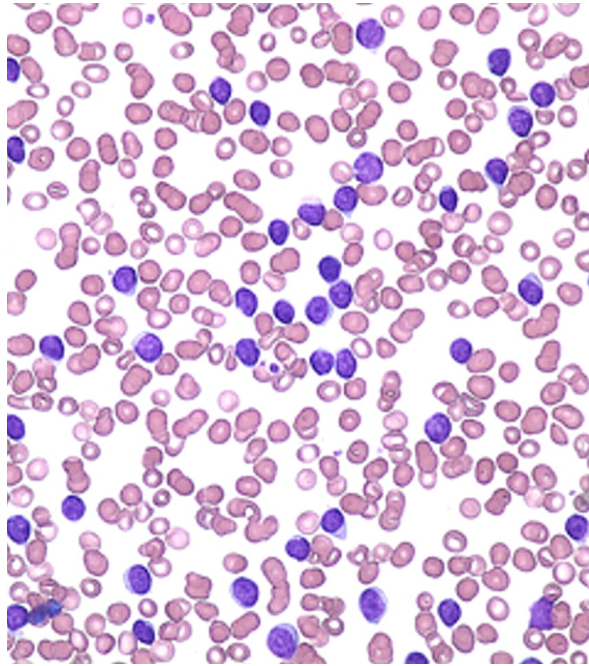
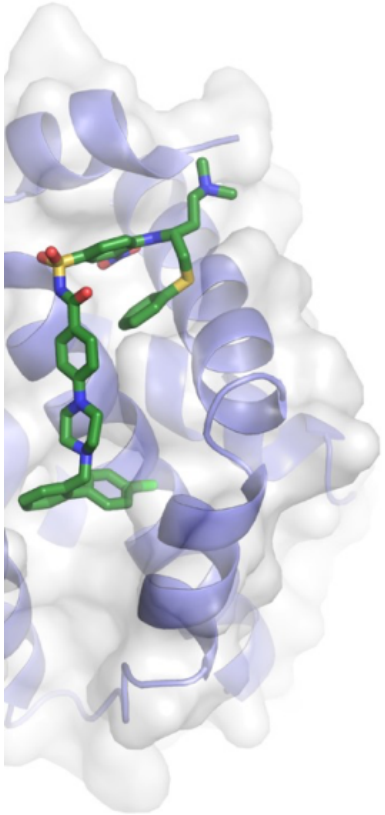
- Incurable disease, typically of older adults
- 40 - 50% of patients never need any therapy
- 20% pts have very poor prognosis

# Chronic Lymphocytic Leukaemia



- CLL cells are abnormally long lived and accumulate in large numbers
- Cells live longer than they should because of high levels of a protein inside them called BCL2
- The high levels of BCL2 are due to genetic changes that are seen in all CLL cells

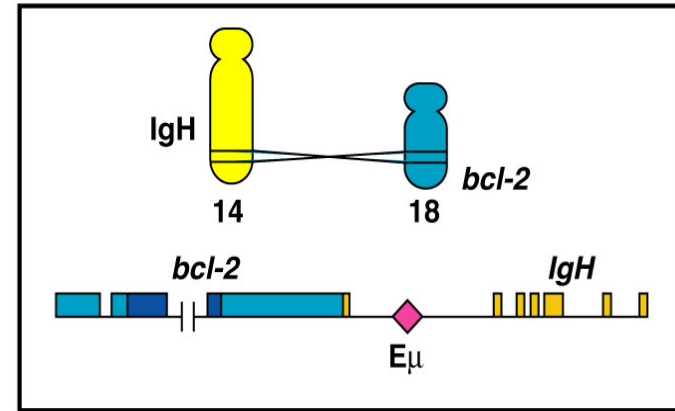
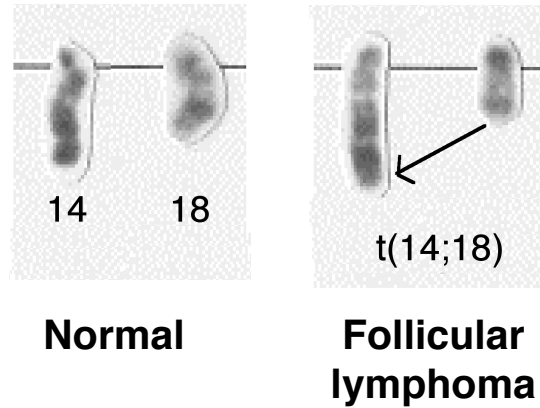
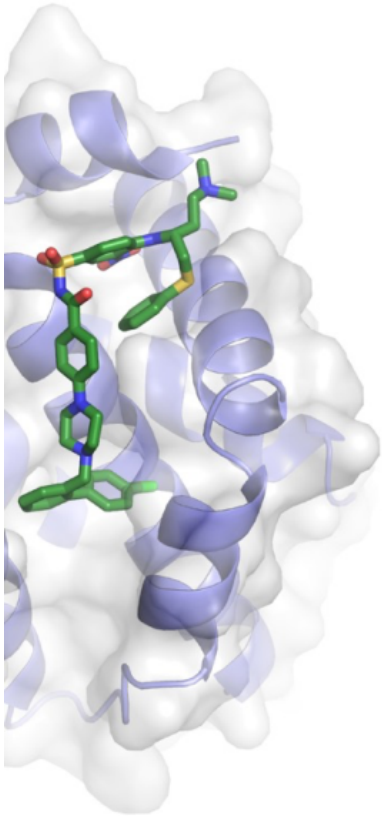
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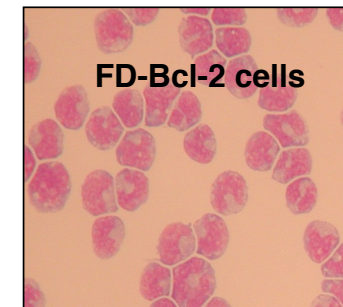
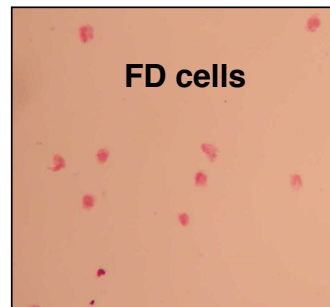
The function of BCL2 and its role in cancer was discovered at Walter + Eliza Hall Institute in 1988

# BCL2, the gene implicated in follicular lymphoma & chronic lymphocytic leukaemia regulates apoptosis

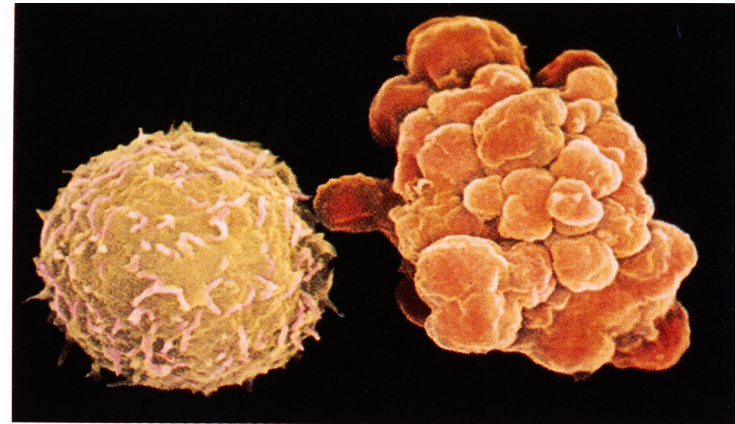
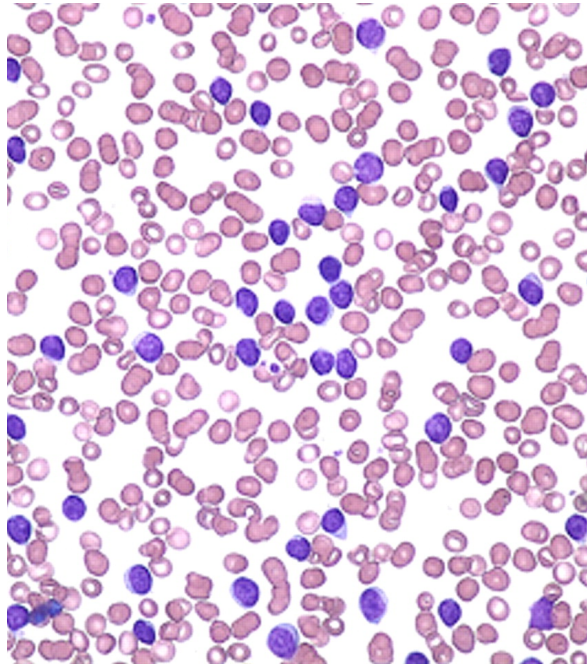
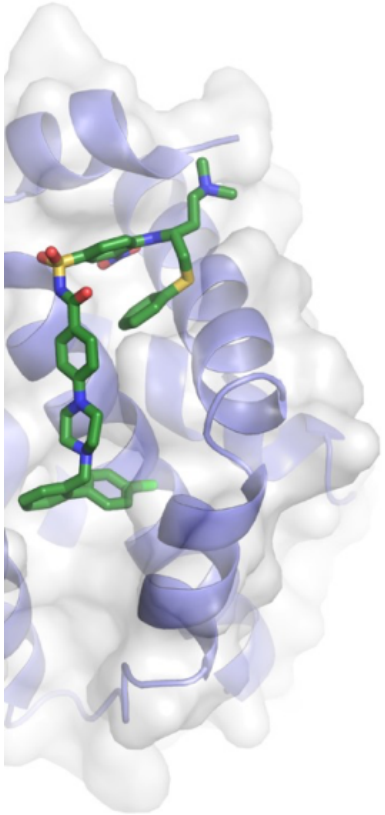


Tsujimoto *et al*, 1984: t(14;18) chromosomal translocation activates *BCL2*.

Vaux *et al*, Nature 1988: BCL2 enhances cell survival.



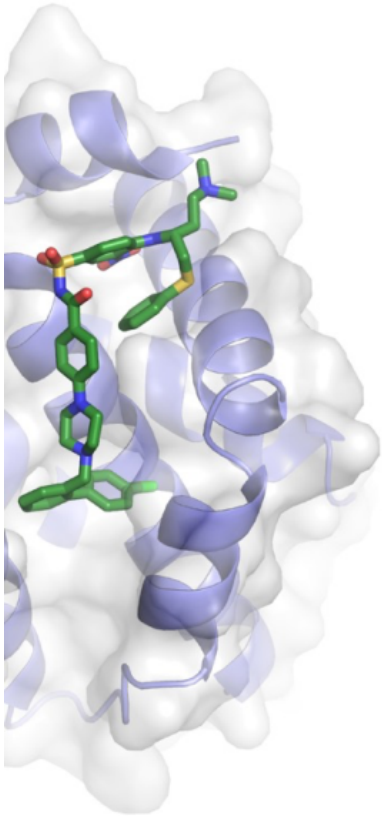
## Switching off BCL2 to treat cancer?



Will targeting BCL2 and turning it off, cause cancer cells to die?

## Concept of targeting BCL2 to treat cancers was not new

- First attempts by others in late 1980s
- Many failures
  - Difficult target
  - False leads through use of
    - Inefficient agents
    - Inexact models
  - Biology misunderstood
  - 15 years of frustration
- Breakthrough the result of:
  - Critical understanding of the biology of BCL2 in cells
  - Development of a new drug design technology



## Scientific Discoveries Paved the Right Way

**1984**

BCL2 gene discovered in cancer, but what it did and its relation to cancer unknown.

**1988**

Function of BCL2 protein discovered by Vaux, Cory & Adams.

*New field of cancer research into apoptosis born.*

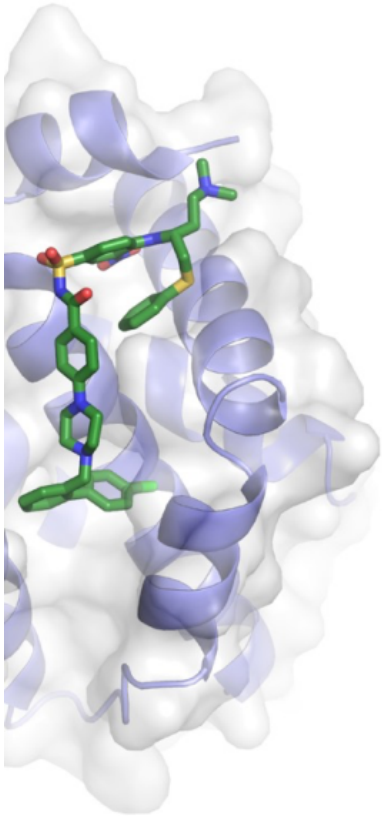
**1988-2005**

BCL2 family of proteins discovered.

Central importance to cancer understood.

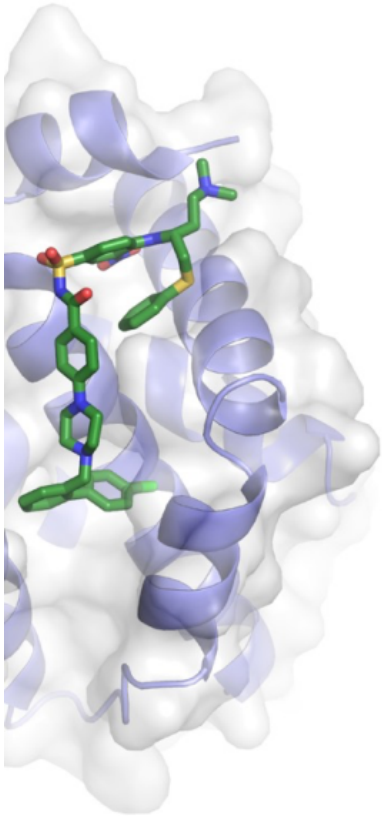
How cancer cells survive is defined.

*Melbourne scientists lead the field*





# Critical understanding of regulation of apoptosis



## Cellular Stress

DNA damage  
Microtubule damage  
Cytokine deprivation  
Oxidative stress



## Intrinsic

Pro-apoptotic

BH3

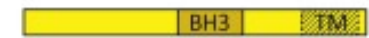
Pro-survival

Bcl-2

Bax/Bak

### Pro-apoptotic BH3-only proteins

BIM, BID, PUMA, NOXA, BAD, HRK, BME, BIK



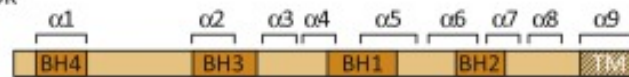
### Pro-survival guardians

BCL-2, BCL-X<sub>L</sub>, BCL-W, MCL-1, A1/BFL-1, BCL-B



### Pro-apoptotic effectors

BAX, BAK, BOK

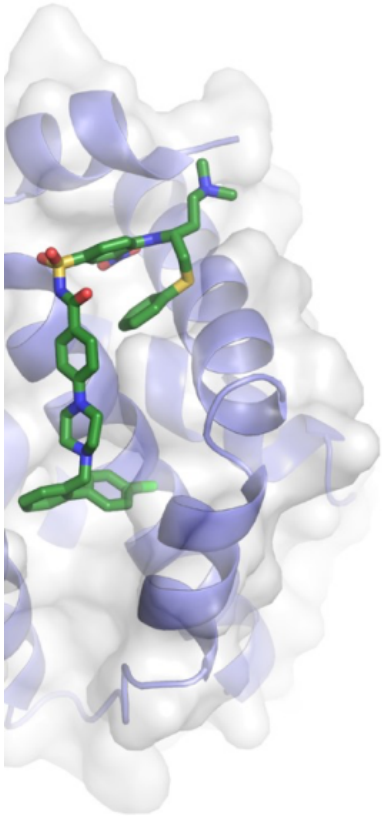


Caspase  
Activation

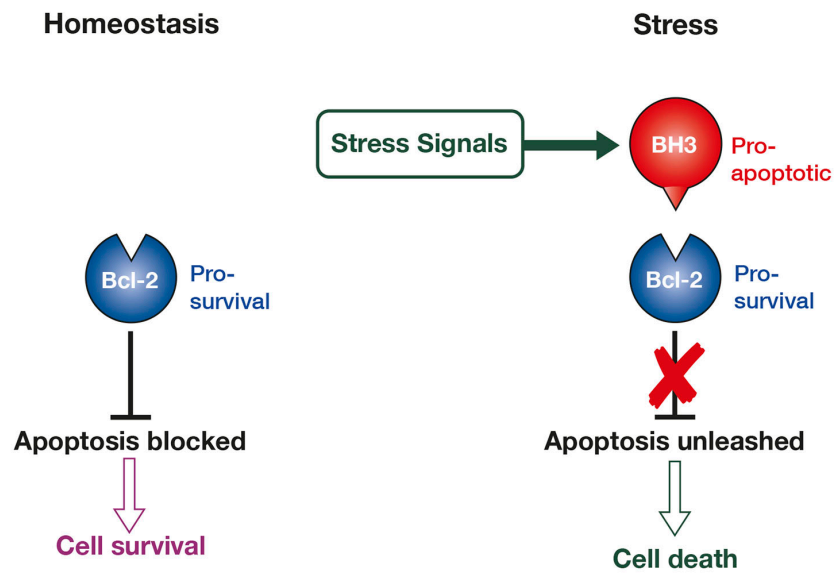
APOPTOSIS



# BH3 mimetics as inhibitors of BCL2

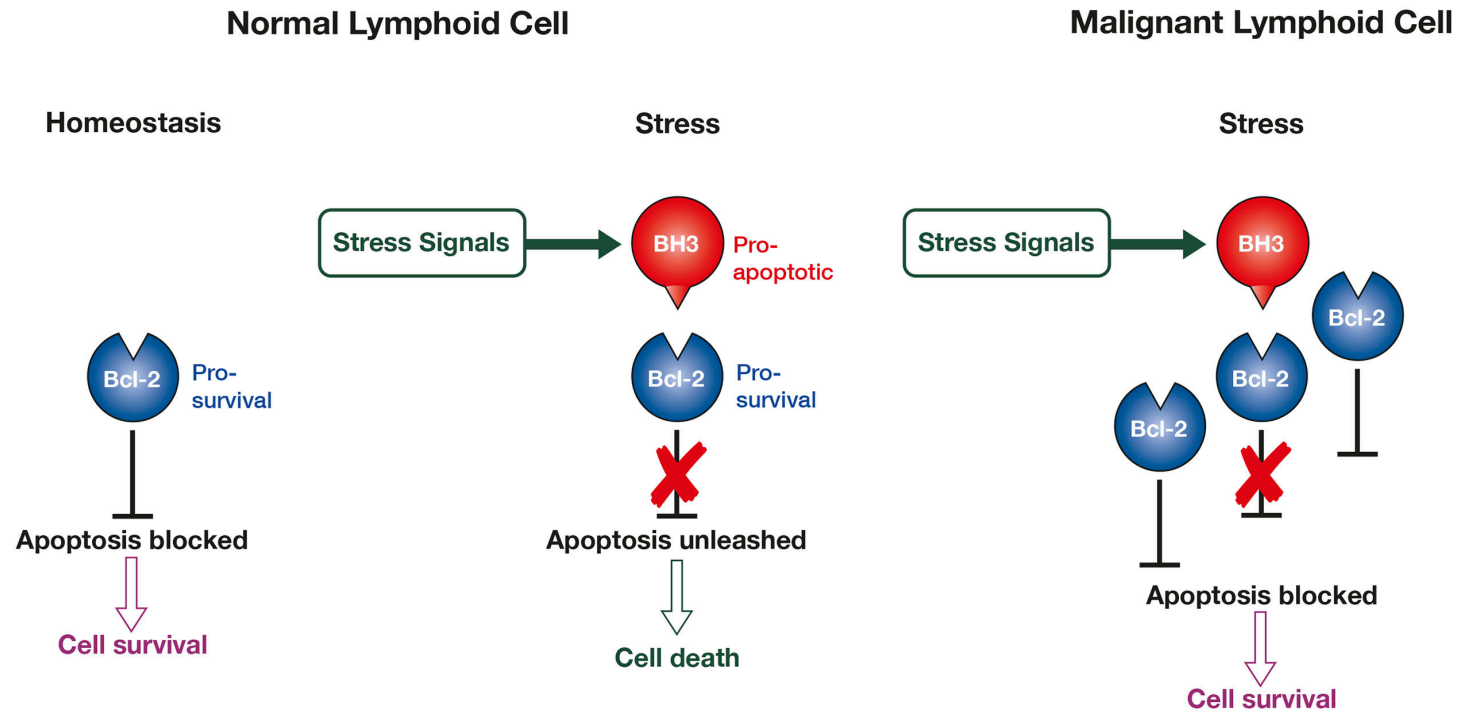
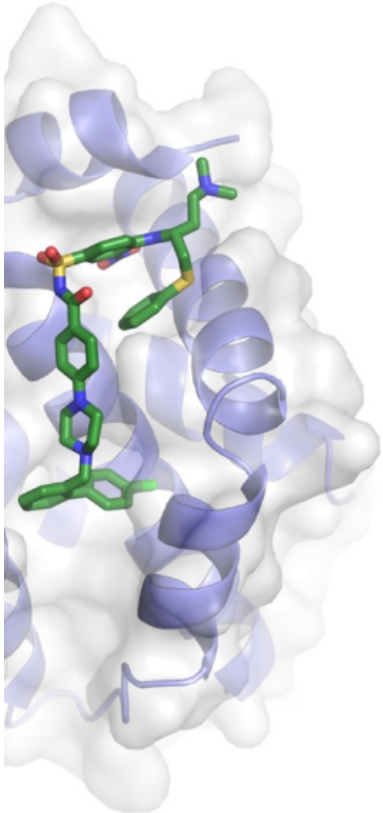


## Normal Lymphoid Cell

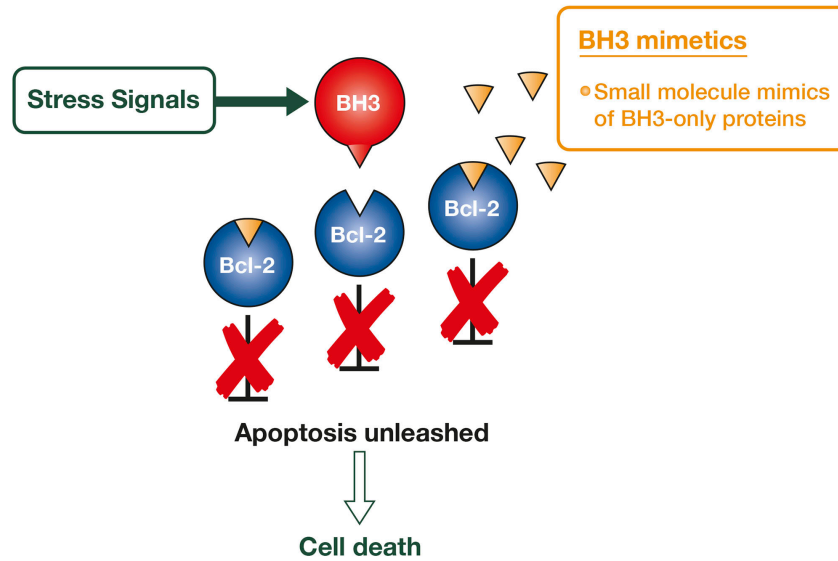
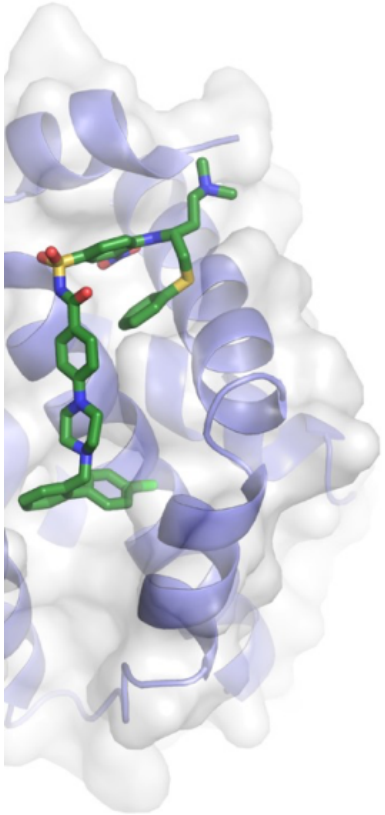


Anderson et al, 2014 Semin Hematol

# BH3 mimetics as inhibitors of BCL2

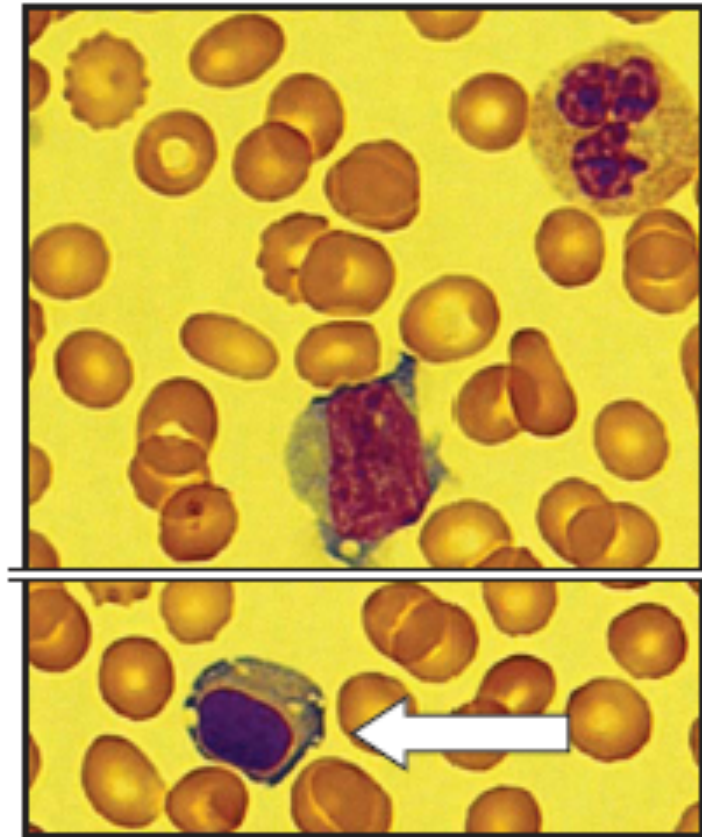
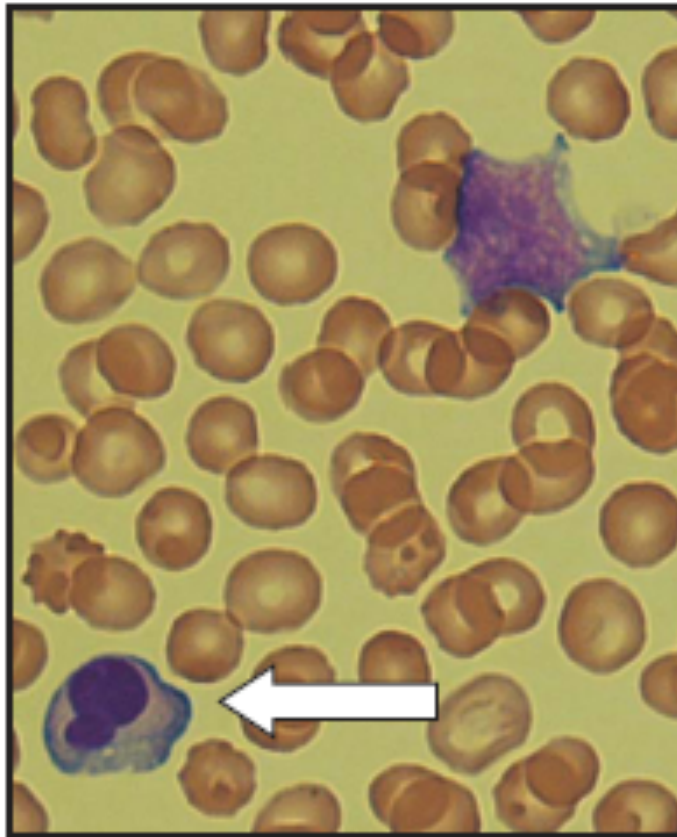
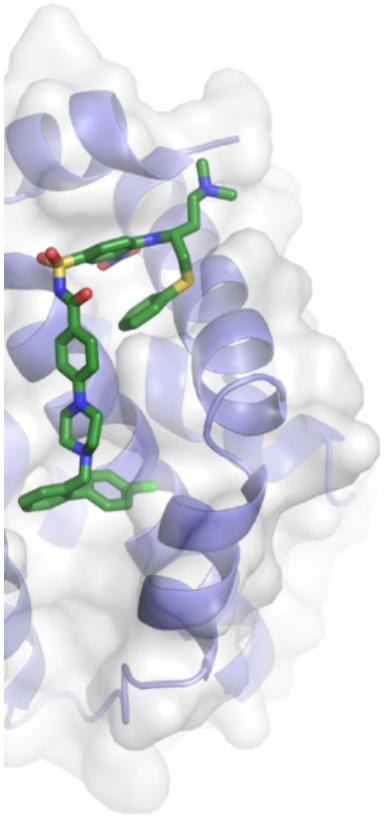


# BH3 mimetics as inhibitors of BCL2



Anderson et al, 2014 Semin Hematol

## Apoptosis of CLL in the Blood

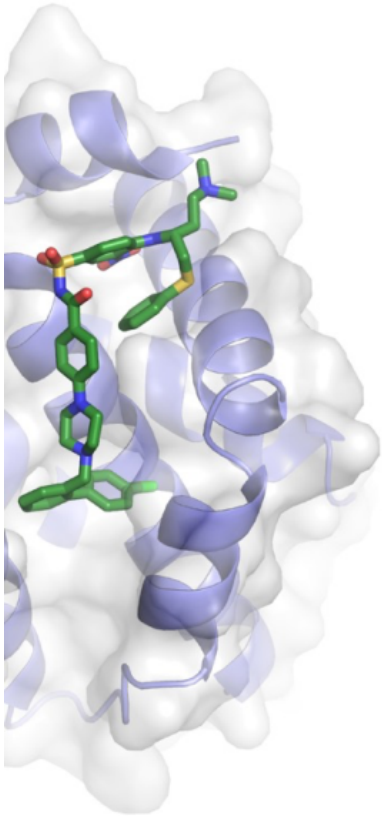


## Road to a novel cancer therapy

- 
- 2003-2010** Developing and assessing the first drugs designed to target BCL2 family.  
*Academic collaborations with pharma and hospitals*
- 2006-2011** Development of the first drug to specifically target only BCL2 – **venetoclax**.  
*Commercial partnership with Genentech & AbbVie*
- 2011-2015** First clinical trials of venetoclax. Melbourne leads the world – Royal Melbourne Hospital, Petermac, Walter + Eliza Hall Institute  
*Global collaborations*
- 2016-** Venetoclax approved in USA. Research is ongoing.

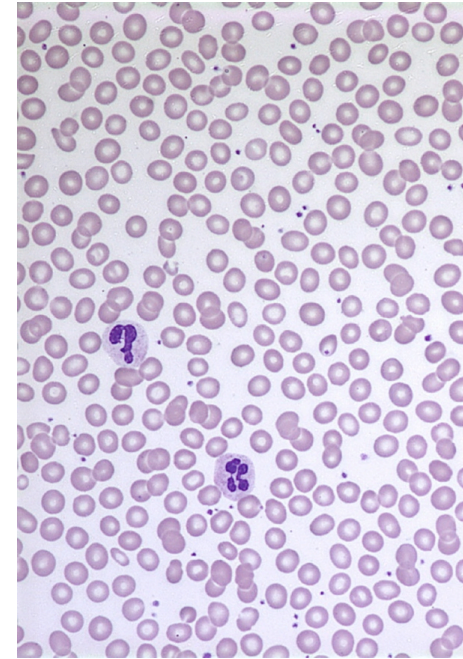
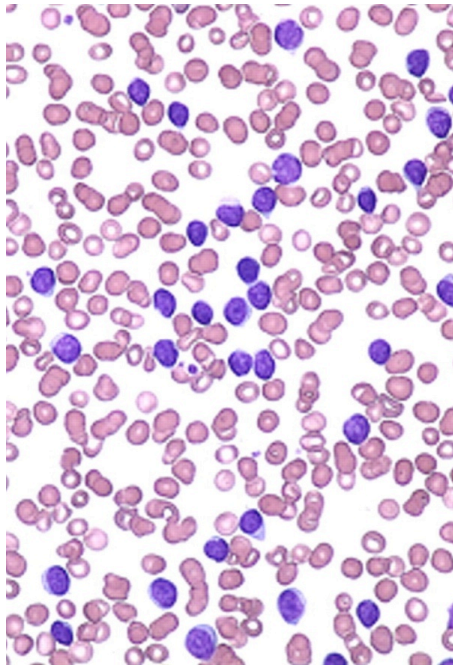
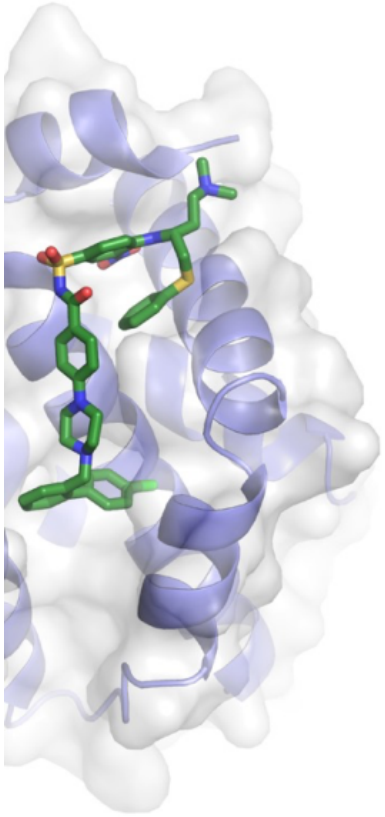
## 2016: Venetoclax, a new anti-cancer drug

- Venetoclax is the first drug that targets BCL2 approved for routine clinical use
  - First approved in April 2016 by US FDA
  - Now approved in several countries, including in Australia in Jan 2017
- Venetoclax is approved for use in specific subgroups of patients with previously treated Chronic Lymphocytic Leukaemia (CLL)
  - Deletion chromosome 17p
  - Mutation of *TP53* gene
  - Where other standard drugs have failed



## Outcomes of Collaborative Research

- A new class of drug
- A specific drug that can address unmet need in some patients with CLL

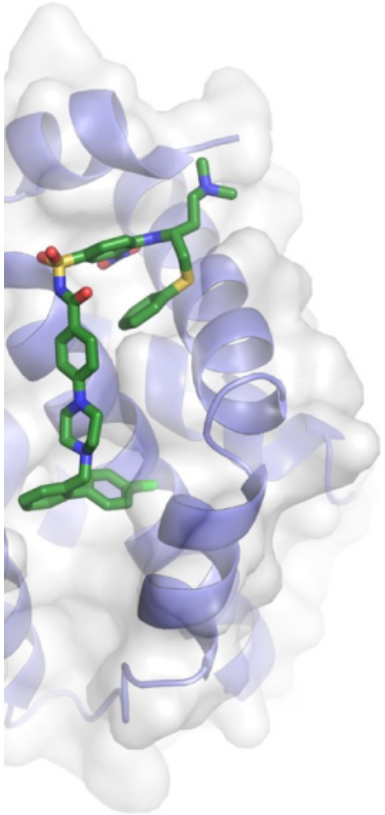




## Now and the Future

### Ongoing clinical trials (>40)

- Establish the place of this new therapy in other cancers where BCL2 is an Achilles' heel
- Combine venetoclax with other cancer drugs to increase the effectiveness of therapy



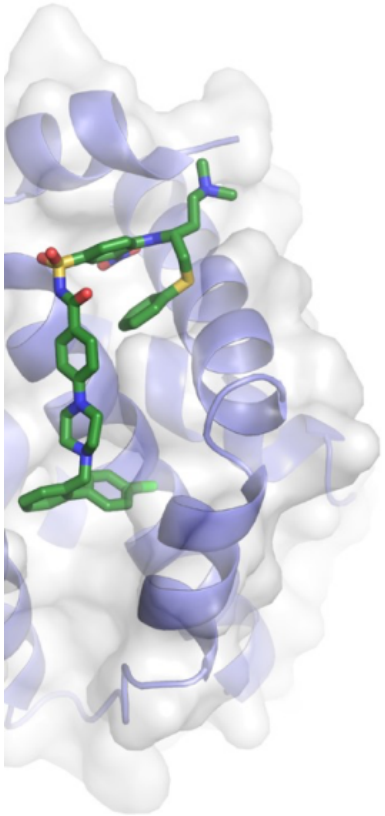
# Targeting BCL2 to treat blood cancers

## Scientific discovery in Melbourne has led to

- A new class of anti-cancer drug (BH3 mimetics)
- A drug that specifically targets BCL2 (venetoclax)
- World-first trials in Melbourne
- Ongoing research into how best to use BCL2 inhibitors in many leukaemias, lymphomas and other cancers

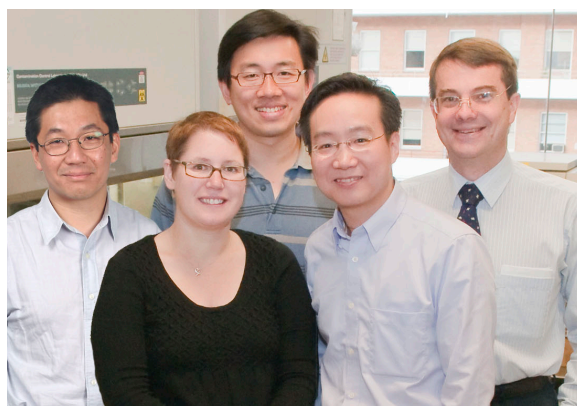
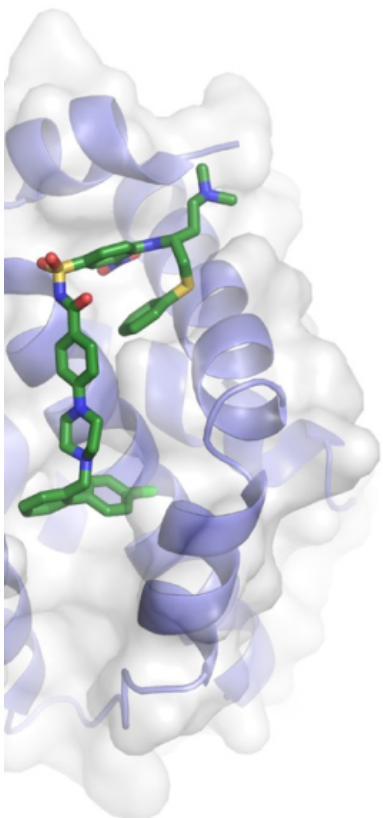
## Ongoing discovery and translational research

- Develop drugs that target other proteins similar to BCL2, & are an Achilles' heel of different cancers



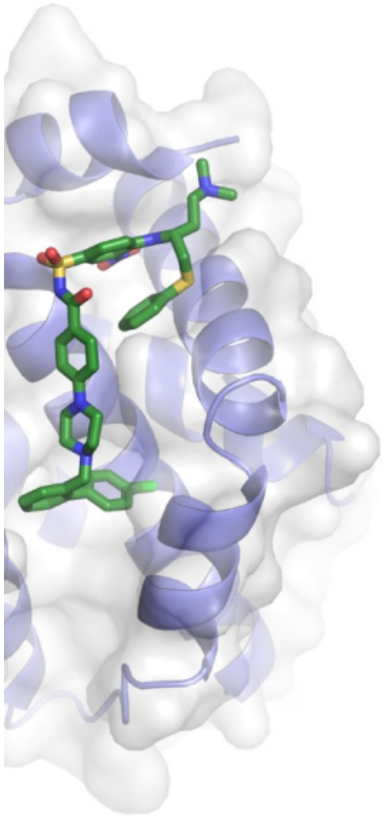
## The Power of Collaborative Research

- US pharma (AbbVie and Genentech) & Australian academia (WEHI)
- Research scientists with different expertise
  - Biology, Structure, Chemistry
  - Between and across organisations
- Basic scientists and clinicians scientists and clinical triallists
- Pharma, hospitals, research institutes, and patients



## Additional Outcomes of Collaborative Research

- Increased pharma clinical trial activity in early phase trials in Australia
- A burgeoning field of research in cancer biology & therapeutics, well beyond the targeting of BCL2
  - Both blue sky and applied
  - Supported by philanthropy and governments and industry
  - Feeding the cycle of continual advancement in science and improvement in care



# Acknowledgements

## Walter + Eliza Hall Institute

- >100 current and past scientists

## Royal Melbourne Hospital and Petermac; global clinical trial teams

## Partners

- AbbVie
- Genentech

## Patients and their families

## Funders of academic research

- NHMRC, Leukemia & Lymphoma Society, NIH, ACRF, LFA, CCV, VCA, and individual donors

