LYMPHOMA CANADA

SAVE THE DATE RESEARCH
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AID CONFERENCE FORUM
ON LYMPHOMA SUPPORT
CAREGIVERS EDUCATION
SEPTEMBER 15 - 16, 2017
SURVIVORS MONTRÉAL, QC
THERAPIES SIDE EFFECTS

# AGRESSIVE LYMPHOMAS - FUTURE

Dr Stéphane Doucet
CHUM

# What are clinical trials?

Clinical trials are carefully planned research studies where the most-promising discoveries and results from laboratory studies are tested with patients.

Trials may look at:

- new treatments, tests or procedures
- lifestyle choices
- the impact of cancer on you and your family

# Importance of Clinical Trials

Preclinical Studies

## Phase I

- Few patients
- What's the highest/best dose that we can achieve
- Outcome: Toxicities

## Phase II

- Slightly more patients
- What's the effect at the best dose
- Outcomes: Efficacy & Toxicity

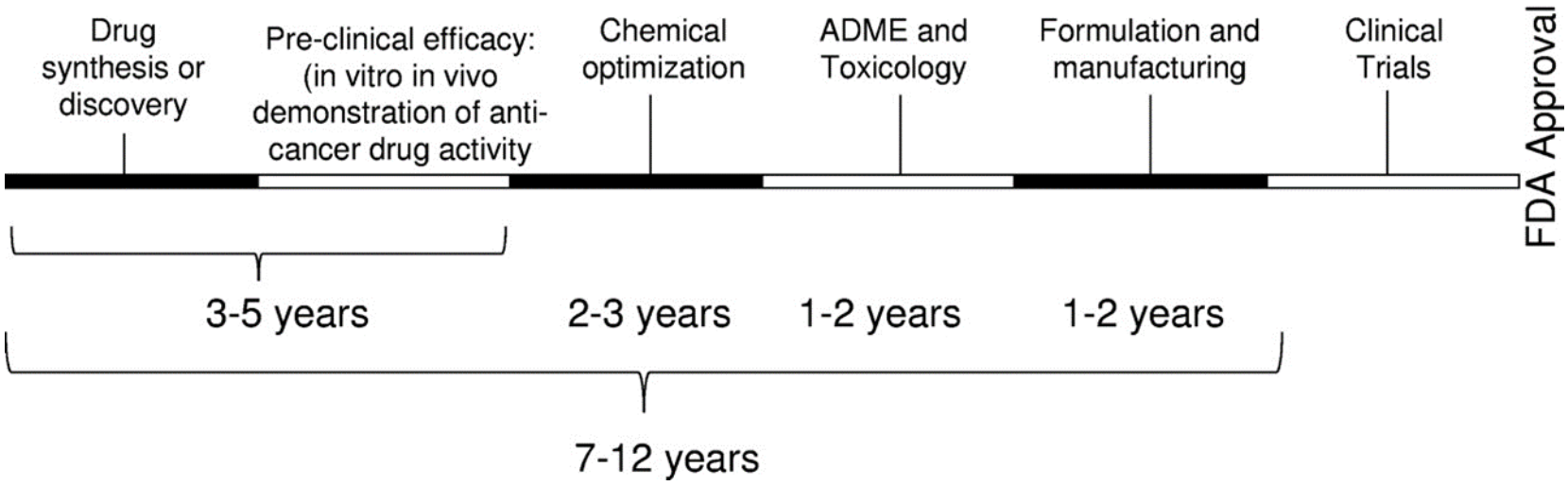
## Phase III

- Large number of patients
- Comparative trial – 2 or more treatments
- Outcomes: Survival, disease control

## Phase IV

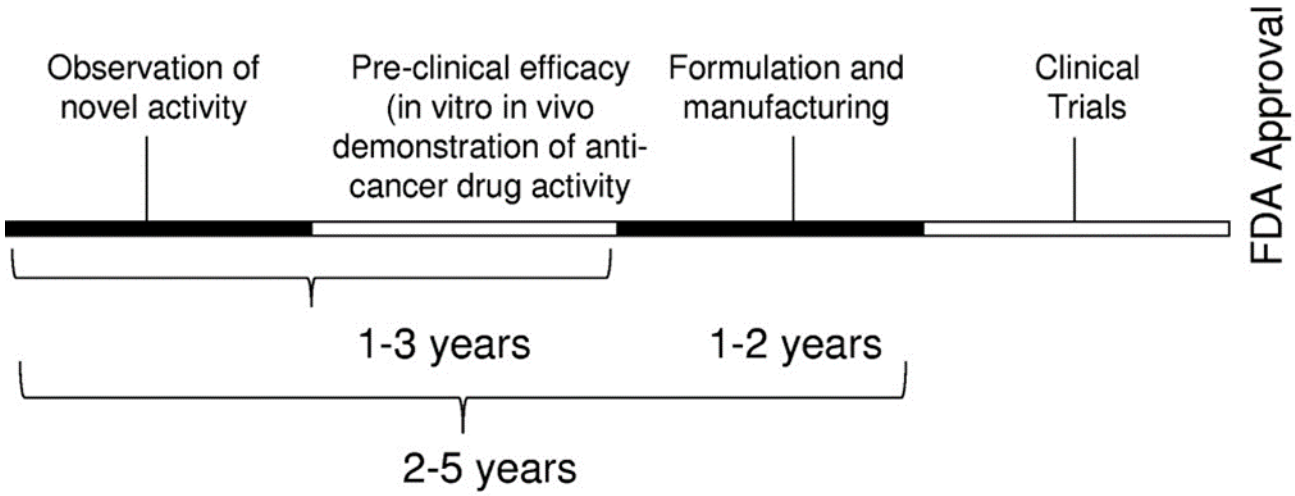
- Post marketing surveillance
- Huge numbers
- Outcomes: Unusual toxicities

# Timeline for new drug discovery



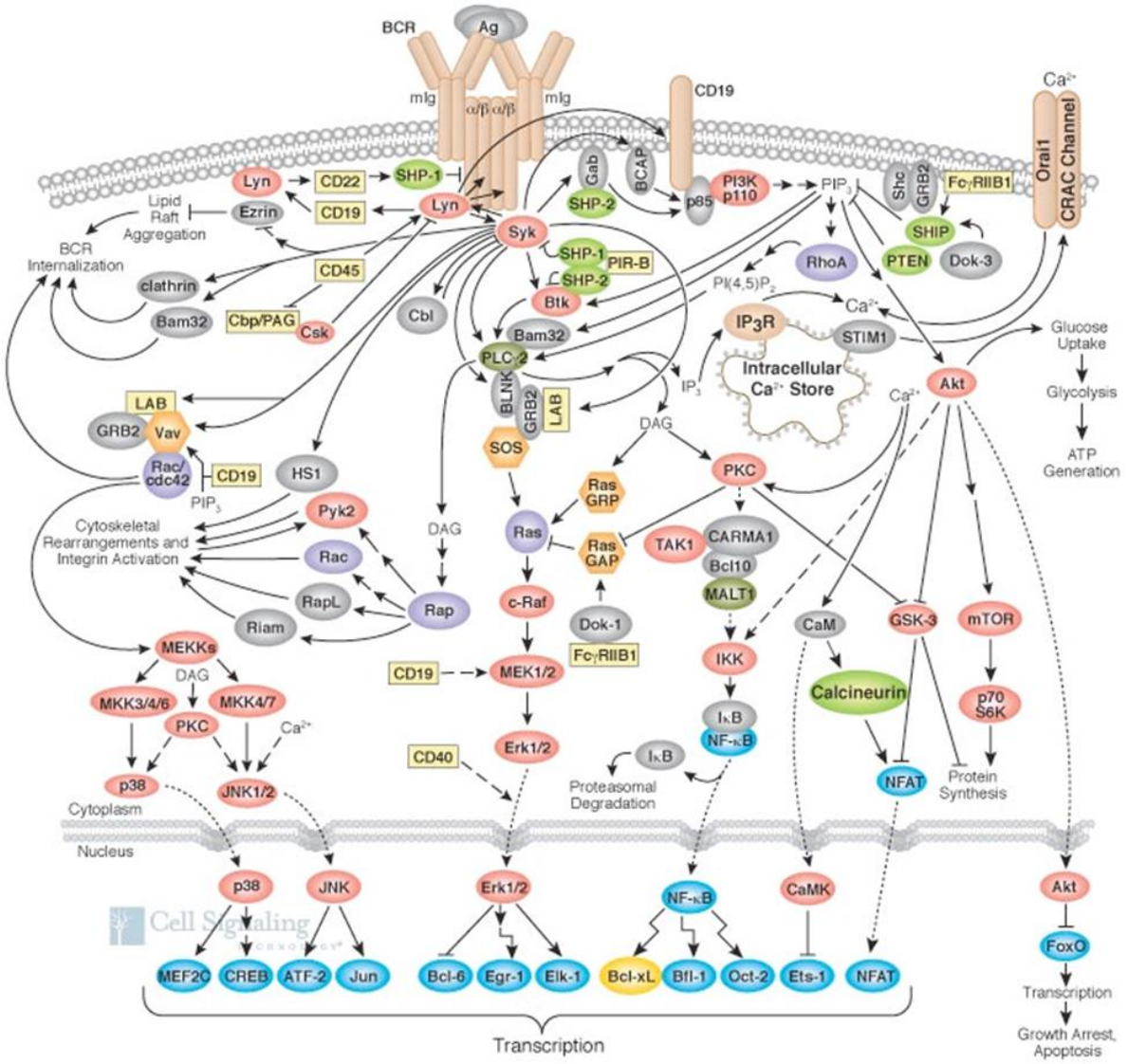

Sukhai M A et al. Blood 2011;117:6747-6755

# Timeline for drug repurposing

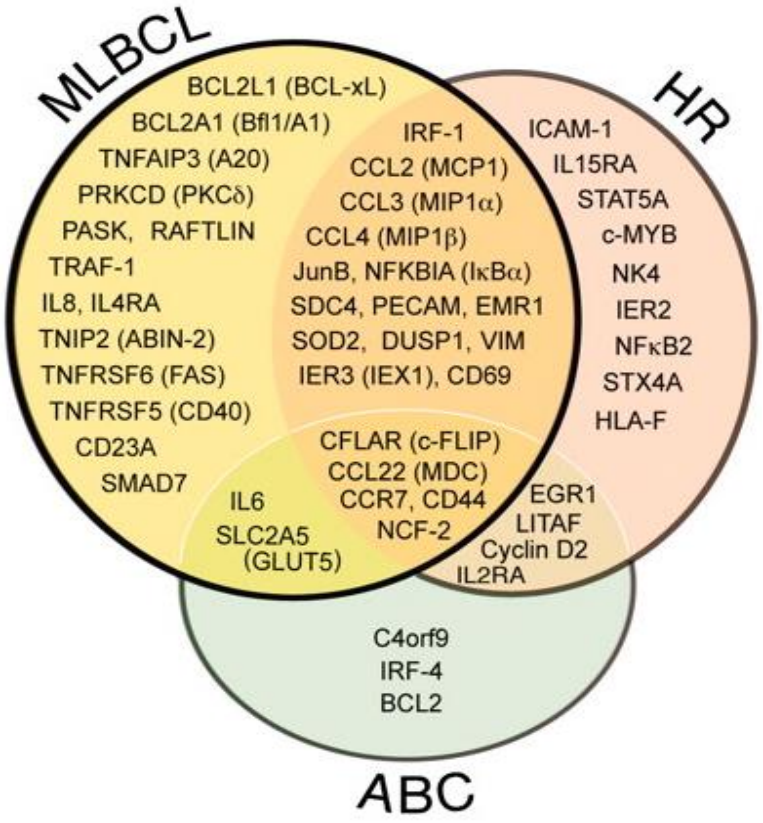



**Sukhai M A et al. Blood 2011;117:6747-6755**

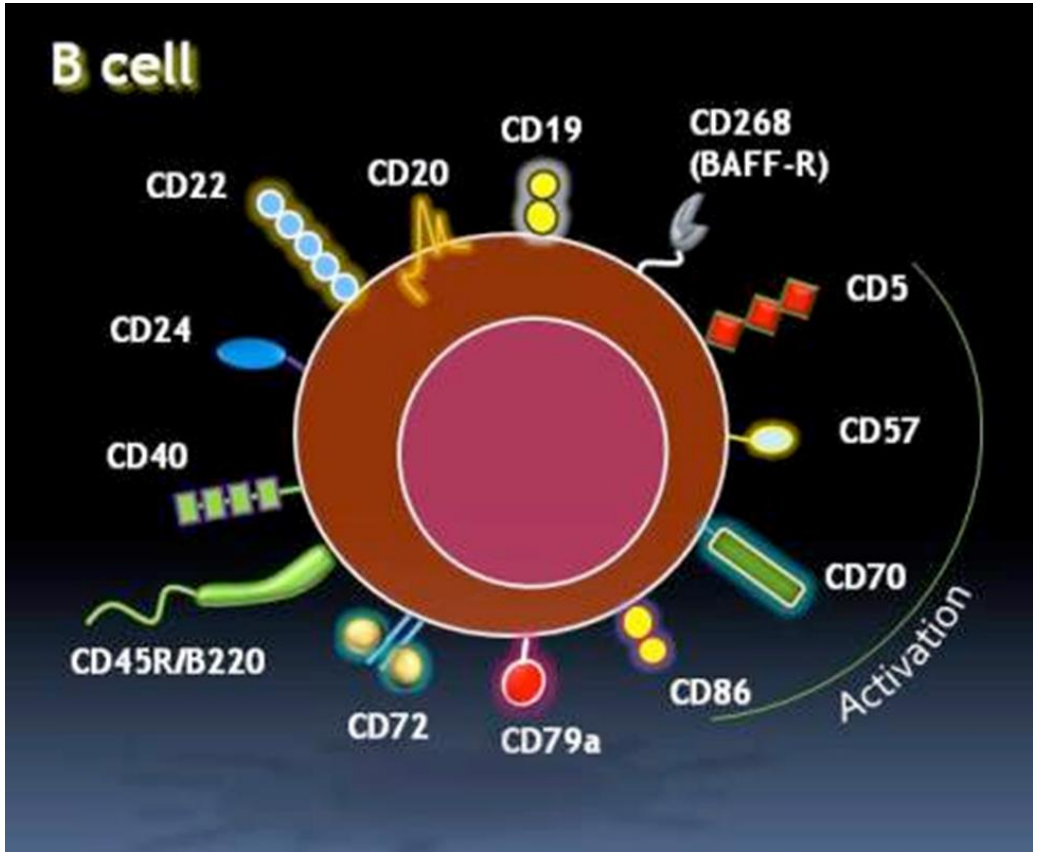
Many targets…



# Genetic Characterization of NHLs



# Cell surface targets




- CD20 is a good target
- Expressed on >90% B cell lymphomas

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# Immuno-oncology

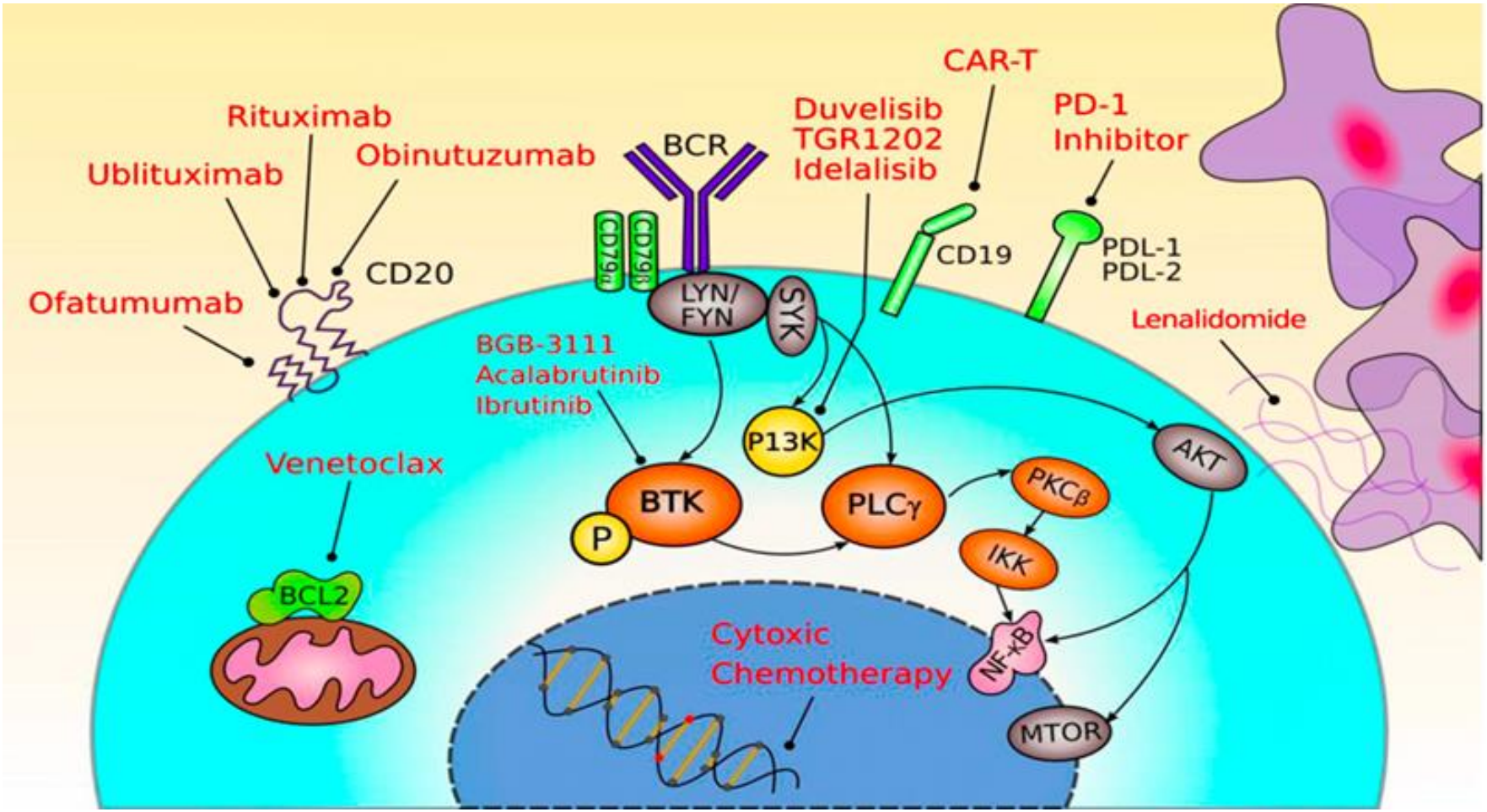
"Immuno" in Immuno-Oncology (I-O) refers to your immune system.

I-O uses drugs known as immunotherapies that target your body's immune system to help fight cancer.

# Dr David Porter

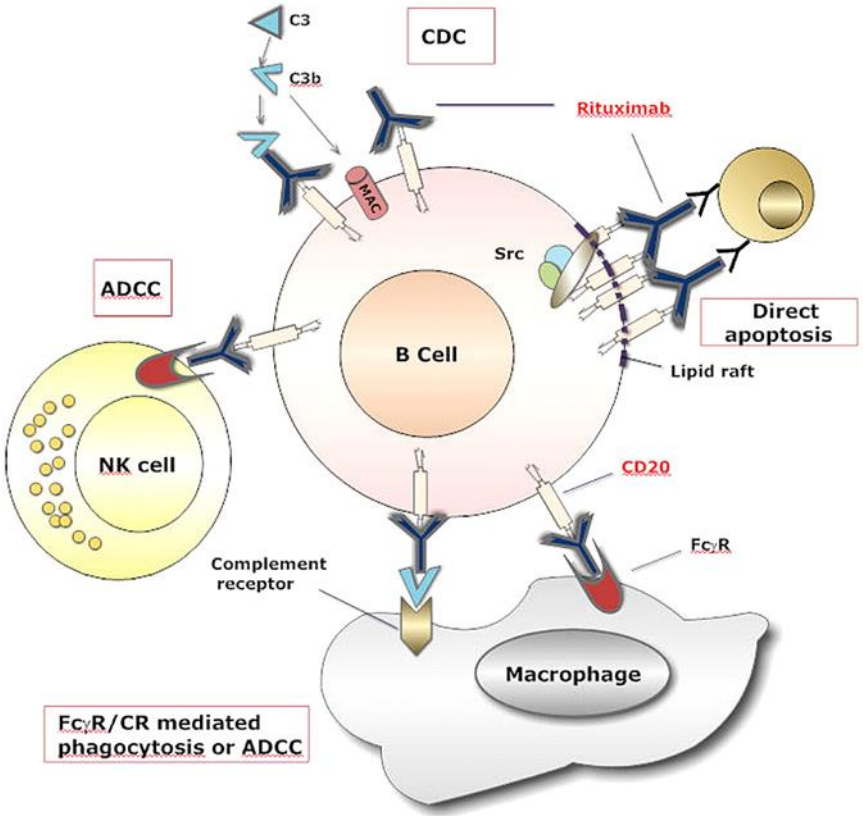
“Immunotherapy is revolutionizing cancer care. We are now using completely new approaches in the treatment of the disease. It took a long time to get here, although it seems so logical to try stimulating and manipulating the immune system to attack cancer cells. The potential in oncology right now is enormous and seemingly limitless. Some of the issues we are grappling with are how to control the immune system and how to target it to go after specific types of tumors.”

Jodi Fisher Horowitz Professor in Leukemia Care Excellence and Director of Blood and Marrow Transplantation at the Abramson Cancer Center of the University of Pennsylvania

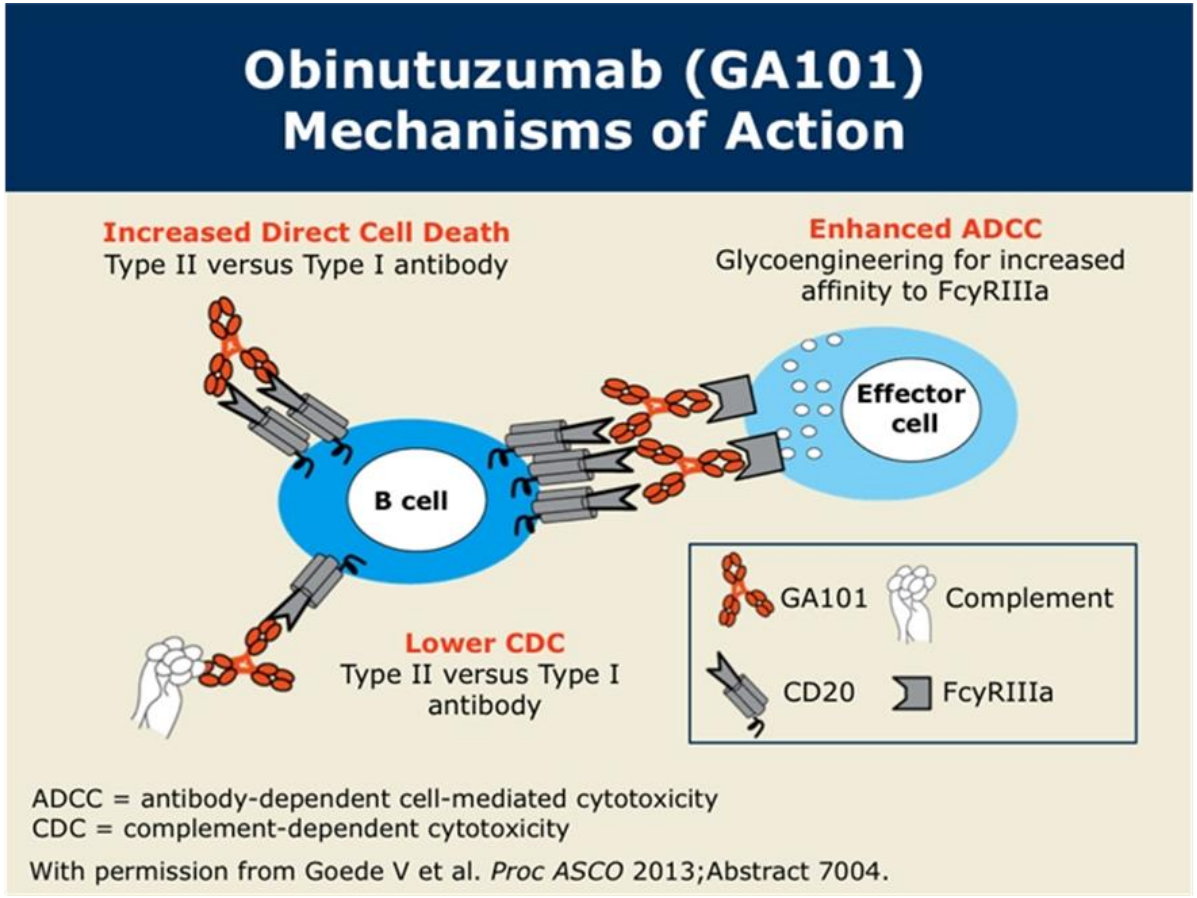

CAR-T
Rituximab
Duvelisib
TGR1202
Idelalisib
PD-1
Inhibitor
Ublituximab
Obinutuzumab
BCR
CD79α
CD79β
CD19
PDL-1
PDL-2
CD20
Ofatumumab
LYN/
FYN
SYK
Lenalidomide
BGB-3111
Acalabrutinib
Ibrutinib
P13K
AKT
Venetoclax
BTK
P
PLCγ
PKCβ
IKK
BCL2
Cytoxic
Chemotherapy
NF-κB
MTOR

# Monoclonal antibodies

- Mimicking the immune system
- Rituxan
- Development of novel anti-CD20 MAbs with activity in rituximab-resistant disease



# Obinutuzumab



# Targeted Therapies

Targeted therapies are drugs or other substances that block the growth and spread of cancer by interfering with specific molecules ("molecular targets") that are involved in the growth, progression, and spread of cancer.

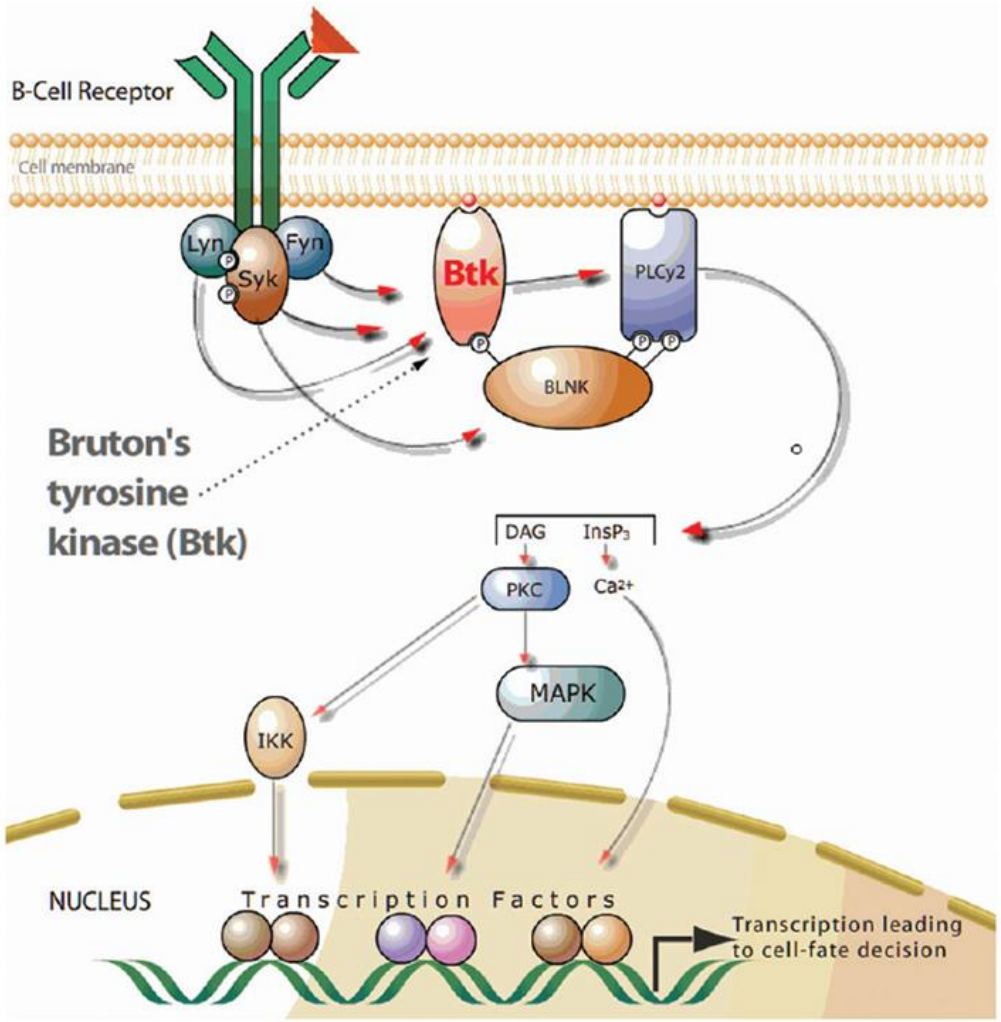
- B cell focus in lymphoma
- T cells largely unaffected by targeted therapies so patients stay healthier during treatment

# Bruton's Tyrosine Kinase (BTK) Inhibitors

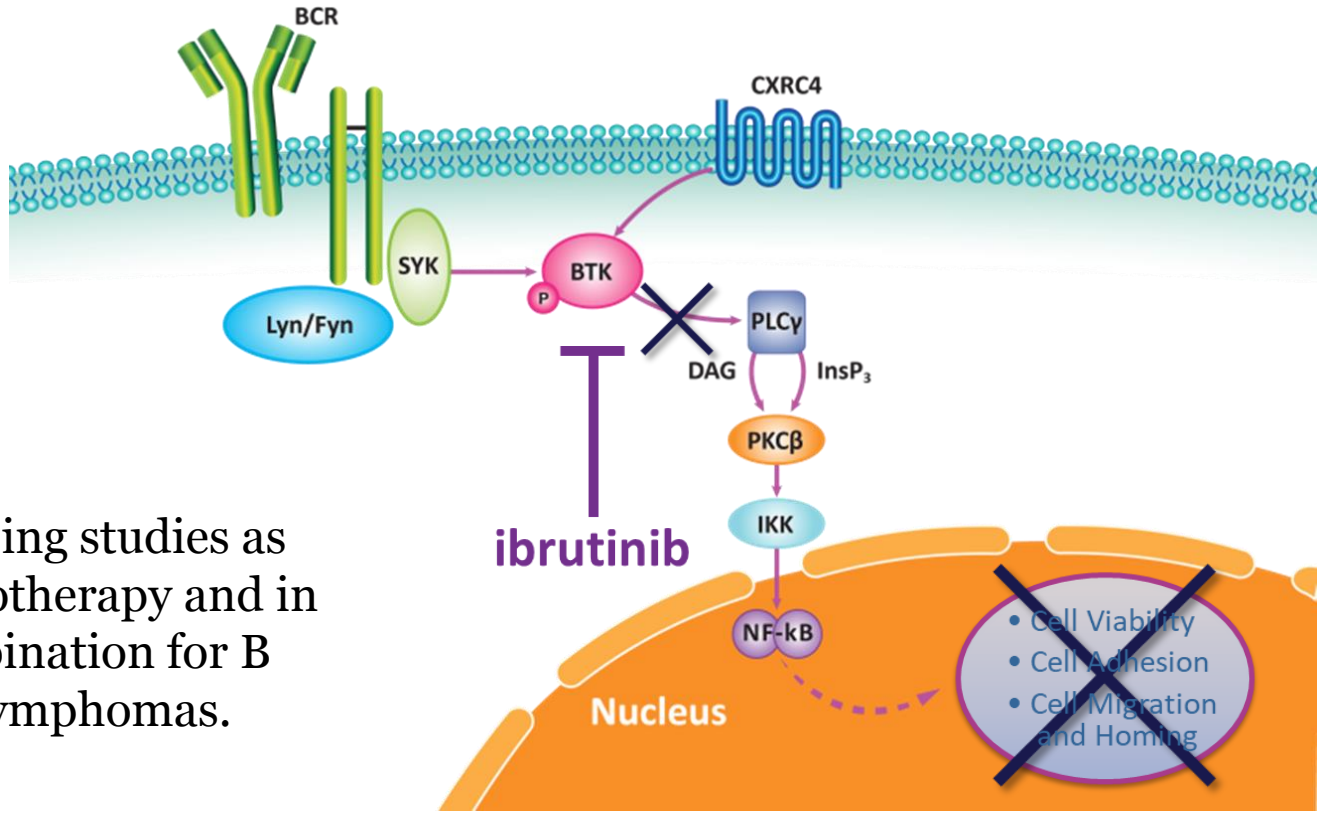
- BTK is a protein that plays a critical role in the growth and survival of B-cells
- New therapies stops BTK from working, killing the malignant B-cells
  - Ibrutinib
- More selective and potent BTK inhibitors are being investigated.
  - ACP-196
  - ONO/GS-4059
  - BGB-3111, CC-292

# Ibrutinib

- First in class, potent, irreversible BTK inhibitor
- Many trials in combination with other drugs



# Ibrutinib

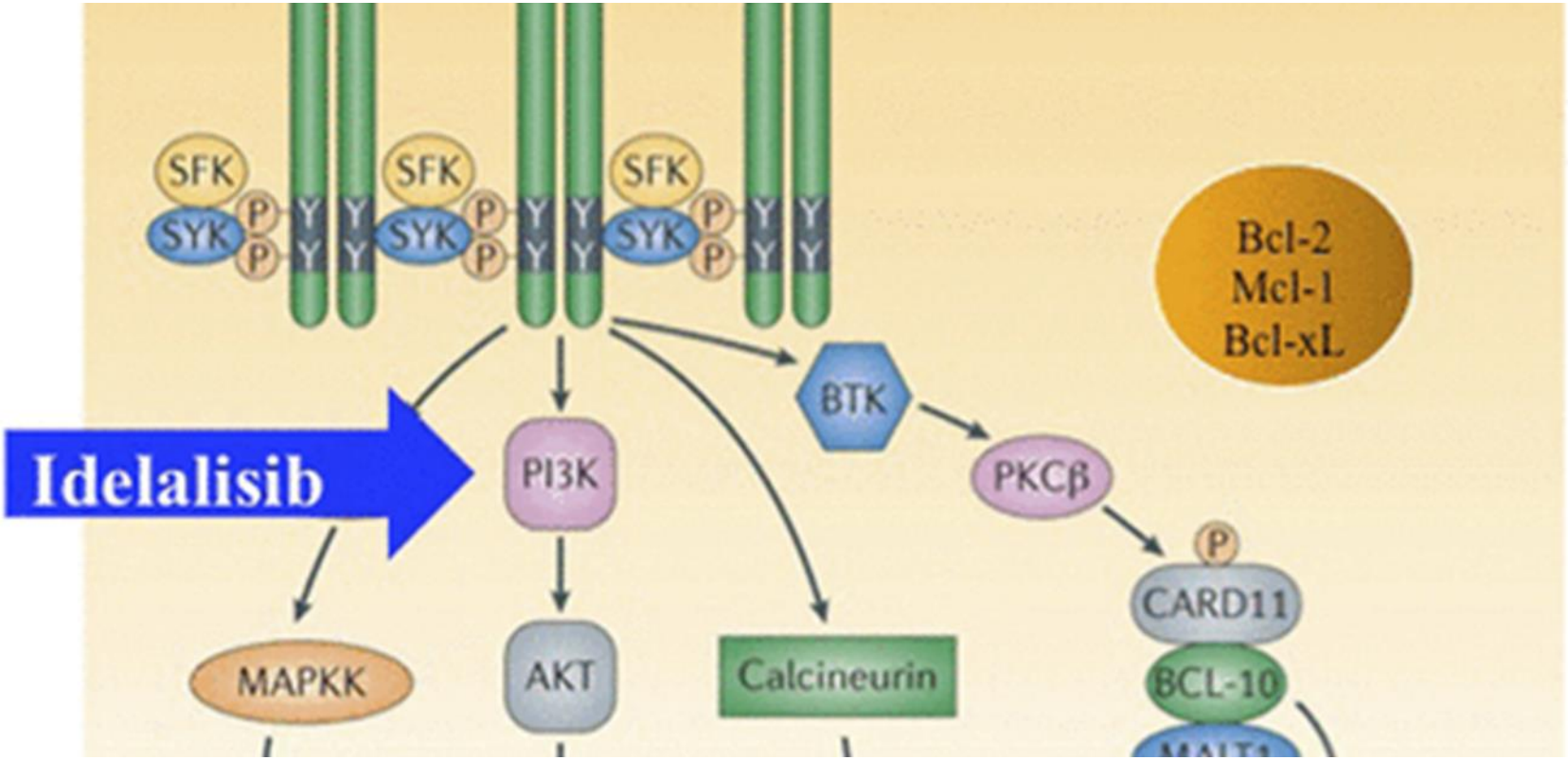



Ongoing studies as monotherapy and in combination for B cell lymphomas.

# PI3K inhibitor

- The PI3K pathway is important in regulating the cell cycle
- It is directly related to cellular inactivity, proliferation, cancer, and longevity.
- Combination therapies for DLBCL? Trials underway.

# Idelalisib

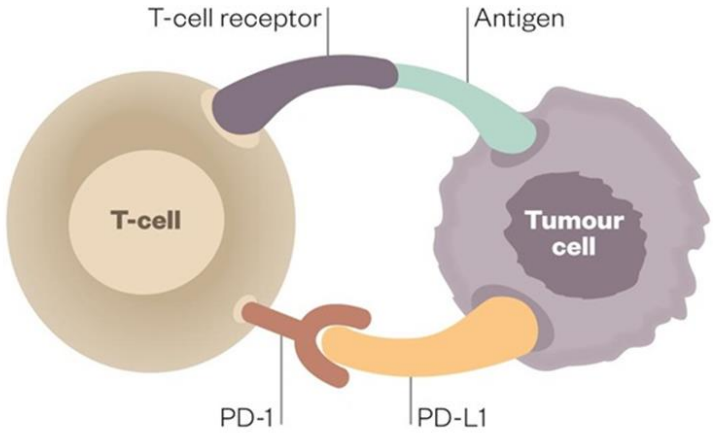

SFK
SYK
P
P
Y
Y
Bcl-2
Mcl-1
Bcl-xL
Idelalisib
PI3K
BTK
PKCβ
P
CARD11
BCL-10
MAPKK
AKT
Calcineurin

# Umbralisib (TGR-1202)

- Unique structure and improved tolerability
- Monotherapy, oral
- June 2017: combination of TG-1101 (ublituximab) and TGR-1202 (umbralisib), ‘U2 regimen', with bendamustine is a highly active and well tolerated treatment for patients with aggressive lymphomas. Combination being bought forward in the DLBCL arm of the UNITY-NHL program.

# Immune checkpoint inhibitors

- PD = Programmed Cell Death protein
- PD-1 and PD-L1 turn off T-cell activation, preventing T cells from attacking the cancer.
- PD-1/PD-L1 inhibitors achieve anticancer effects in the form of durable responses, improvements in survival, and less toxicity for patients.
- Binding of T-cells to PD-L1/2 inhibits T-cell function and blunts the normal immune response



# Pembrolizumab

- PD-1 inhibitor, used for many types of cancer
- 210 adult cHL patients enrolled in a multicenter, non-randomized, open-label clinical trial. Patients had refractory or relapsed disease after autologous stem cell transplantation and/or brentuximab vedotin (175 patients)
- ➢ With a median follow-up of 9.4 months (range: 1-15), the overall response rate was 69%, including partial responses in 47% of patients and complete responses in 22%
- Demonstrated antitumor activity in recurrent/refractory primary mediastinal large B-cell lymphoma (phase II KEYNOTE-170 trial)
- ➢ Objective response rate (ORR) was 41% based on 29 patients (95% CI, 24–61). Four patients (14%) showed complete response (CR) and 28% a partial response (PR).

# Nivolumab

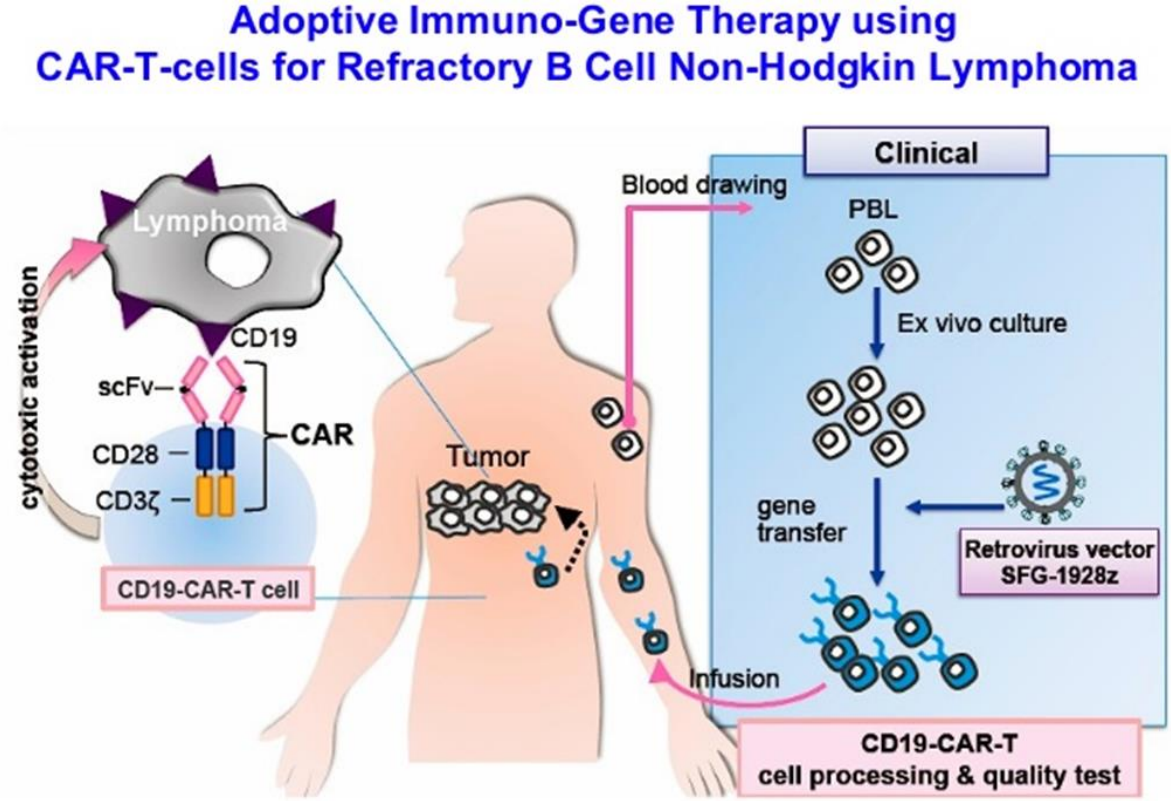
- PD-1 inhibitor
- Phase II CheckMate-205 trial, patients with relapsed/refractory Hodgkin lymphoma after autologous stem-cell transplant (ASCT)

➢ Overall response rate was 65% in brentuximab vedotin (BV)-naïve patients, 68% in patients BV after ASCT, and 73% in patients BV before and/or after ASC

- Phase 1 study (CA209-039), nivolumab well tolerated and exhibited antitumor activity in extensively pretreated patients with relapsed or refractory B- and T-cell lymphomas.

➢ 11 patients with DLBCL, ORR 36%; 23 patients with T-cell lymphoma, ORR 17%

# Chimeric antigen receptor gene therapy (CAR-T)



# Differences between small molecules and biologics

- Small Molecules:

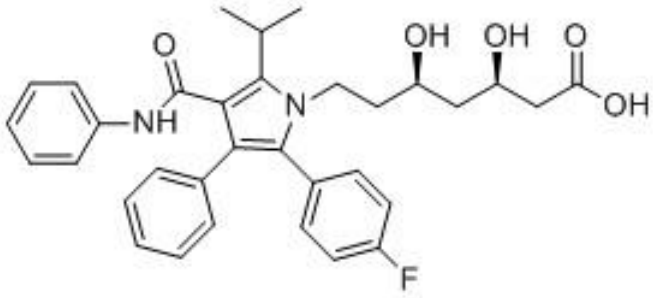
-made via chemical synthesis *in vitro*

-potentially made via different synthetic routes

**Synthetic route A** →

**Synthetic route B** →

**Synthetic route C** →




*Atorvastatin: lipid lowering agent*
Reference compound = Lipitor

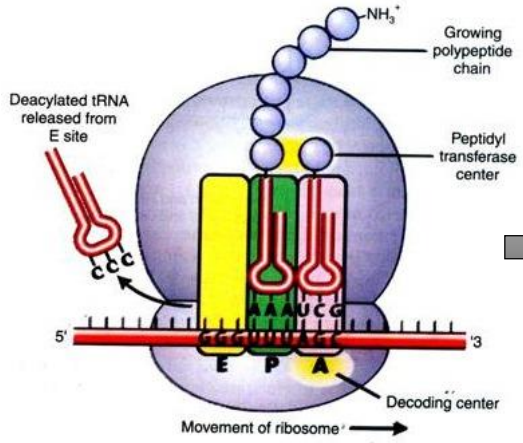
- Irrespective of the synthetic route, all compounds have the same chemistry/molecular weight **$C_{33}H_{35}O_5N_2F$ : 558.62g/mol**
  -<u>all generic small molecules have identical chemical formulas and structures</u>

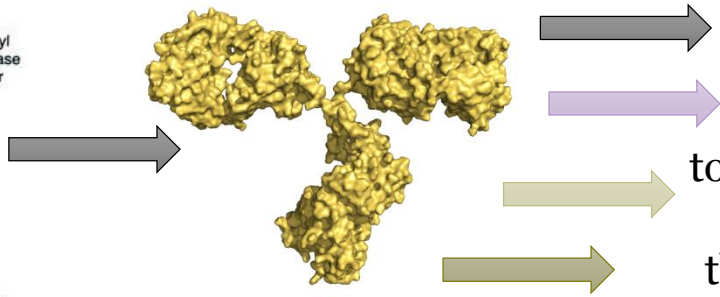
# Differences between small molecules and biologics

- Proteins

-made *in vivo* using a host organisms' cellular machinery

-template encoded by DNA-RNA and all molecules are synthesized identically by the ribosome

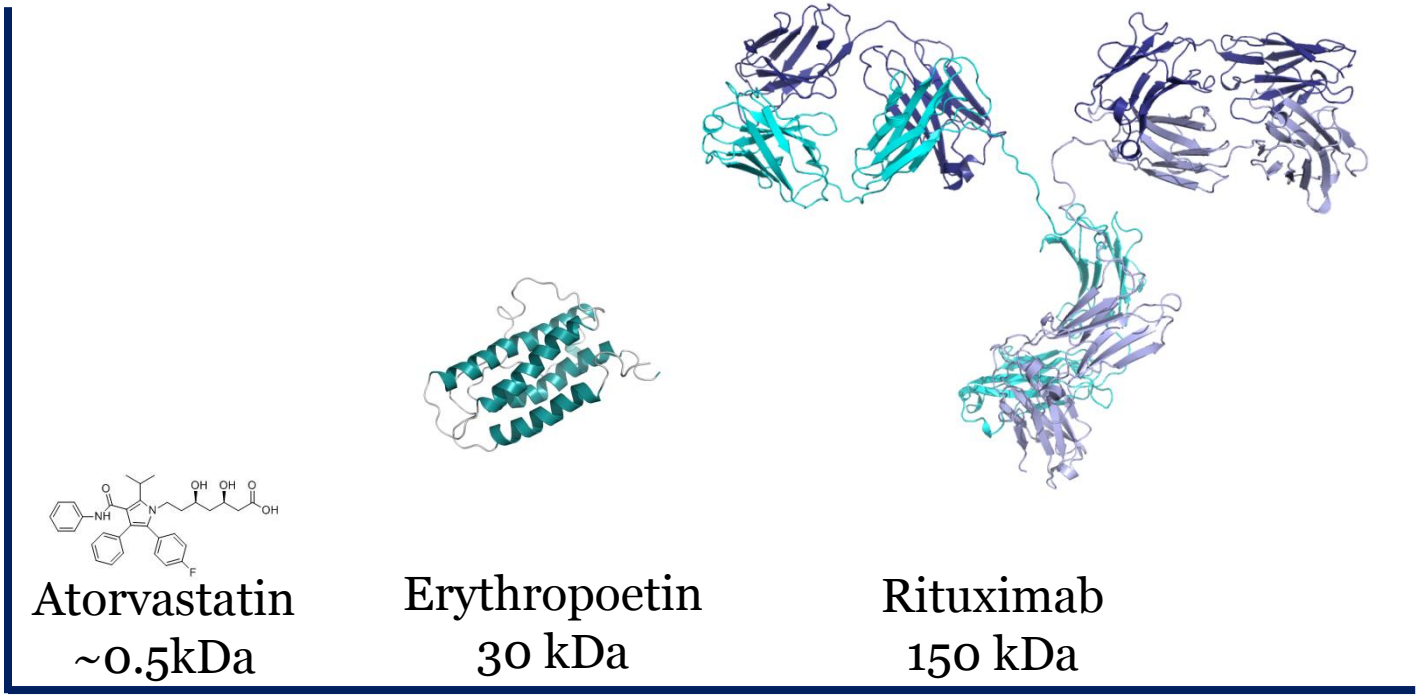


The final protein product may be subject to numerous post-translational modifications that can alter the chemistry of the molecule

*These modifications can have a number of important implications*

# Biologics and their inherent complexity




-a crucial difference between small molecules and biologics is that an increase in complexity and heterogeneity make it more difficult to accurately characterize the active pharmaceutical mixture.

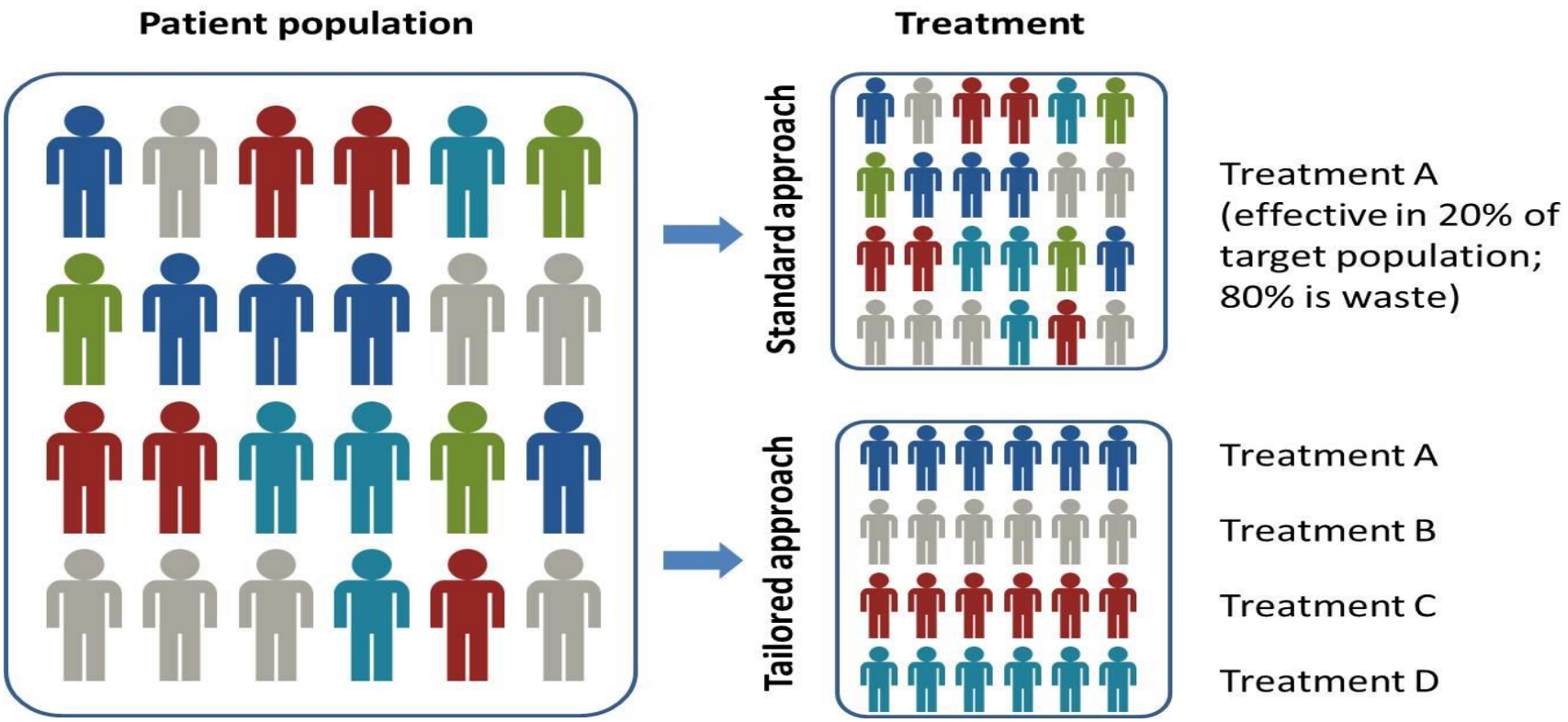
# The manufacturing processes influence biologics

- Details of the manufacturing process will affect the final product
- Manufacturing details and quality control are often proprietary and closely guarded company secrets

# Biosimilars in lymphoma

- SEBs currently used in supportive care (G-CSF, EPOs)
- Currently no approved SEB for lymphoma treatment in Canada
- ~13 SEBs in development for rituximab
- Market authorization for rituximab SEBs expected in Europe in 2017; expected to enter Canadian market in 2020
- Very limited awareness of SEBs in Canadian lymphoma patient community

# Precision Medicine



# Personalized medicine

- Personalized treatments
  - Not all people Are The Same
  - Match treatment to the patient's genetic profile
- Not all tumors are the same
  - Match treatment to the tumour's genetic profile
- Re-educate the patient's own immune system to attack the tumour

# Is research working?

- Yes!!!!
- Improved depth of remissions, longer remissions and improved survivals since introduction of rituximab
  - In combination with chemotherapy
  - As maintenance therapy
- Better understanding of cancer cell signaling and pathways
- Newer targeted agents

# Is research working?