“’til death do us part” Long term oral therapies that control cancer without cure

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Introduction

- There have been some incredible advances in our understanding of the genetic and cellular mechanisms by which cancers develop

- As this understanding improves, who have recognised the ability to develop therapies that specifically “target” some of the specific aberrations that underlie carcinogenesis

“Traditional therapy” for haematologic cancer

Bone marrow transplantation

What we really want

Ideal cancer therapy

- A pill
- Cures the disease
- No side effects

Ideal cancer therapy

A pill

- Nobody likes needles

Cures the disease

No side effects

Ideal cancer therapy

A pill

Cures the disease

- Recurring theme = they often don’t
- Patients remains on them “indefinitely”

No side effects

Ideal cancer therapy

A pill

Cures the disease

No side effects

- This drug does not exist

? GP perspective

- As more of these therapies are developed, you will see increasing numbers of patients in your routine practice
- An understanding of their “specific” toxicities would be useful
- You are potentially more capable of managing these toxicities and long term risks than us
  - eg agents associated with increased risk of cardiovascular events -> control of cardiovascular risk factors (hypertension, diabetes, smoking)

TODAY

- CML - “tyrosine kinase inhibitors”
- Myeloma - “immunomodulatory agents” (thalidomide + derivatives)
- CLL – ibrutinib and idelalisib

CHRONIC MYELOID LEUKEMIA (CML)

- Traditionally placed within the group of disorders referred to as myeloproliferative
  - implying inappropriate overproduction of “mostly normal” blood cells

- Diseases within this group
  - CML (“white cells”)
  - Polycythemia vera (“red cells”)
  - Essential thrombocytosis (“platelets”)
  - (Myelofibrosis)

CHRONIC MYELOID LEUKEMIA (CML)

- CML is genetically distinct from the other members of this oversimplified category

- Represents the first example of a disease for which a specific drug was designed and developed once the genetic basis of the disease was understood

CML - Diagnosis

- Most commonly diagnosed after an FBC is performed because of nonspecific symptoms such as fatigue, or abdominal discomfort (? Splenomegaly)

… FBC shows an elevated WCC

CML – Distinguishing features

- What would make a diagnosis of CML more likely in a patient with an elevated WCC?
  - No other infective / inflammatory cause (= most common cause of leucocytosis)
  - Splenomegaly on clinical examination
  - Elevated WCC is persistent, progressive and “excessive” (<- ? definition)
  - **Basophilia** (and to a lesser extent, eosinophilia <- broader DDx)
  - Presence of “slightly immature” white cells such as myelocytes, metamyelocytes)
    … but not blasts = more likely to represent acute leukemia (/ myelofibrosis)
  - Other blood count abnormalities
    - Elevated platelet count – not uncommon, but not specific
    - ? Low platelet count (+/- anaemia) - more likely to represent either something “more serious” or a more advanced stages of disease (“accelerated phase” or “blast crisis”)

Leukocytosis that is “not leukemia”

- When to consider an elevated WCC as “not leukemia”
  - Not persistent +/- progressive
  - Clear “reactive” aetiology – infection, drugs (eg steroids), inflammatory conditions eg inflammatory arthropathis, smokers with chronic bronchitis
  - Variable lineage – eg neutrophils / monocytes vs lymphocytes
    - Conversely if the differential consistently shows a single lineage to be elevated (eg (basophils = CML; lymphocytes = CLL) take more notice
  - “ Isolated” ie other counts normal (esp platelets … anemia is nonspecific)
  - ? Stable at low “low level” (<- ?? definition)

CML – Definitive diagnosis

- Based upon demonstration of a specific and unique acquired genetic abnormality within blood / bone marrow cells

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- Based upon demonstration of a specific and unique acquired genetic abnormality within blood / bone marrow cells

1960

- CML was known as “Chronic granulocytic leukaemia” (CGL)
- 2 scientists (Nowell + Hungerford) examined the chromosomes of patients with CGL and consistently found a abnormal shortened or “minute” chromosome
    - We now refer to this is the “Philadelphia chromosome”, based on where these 2 scientists worked and presented these preliminary findings

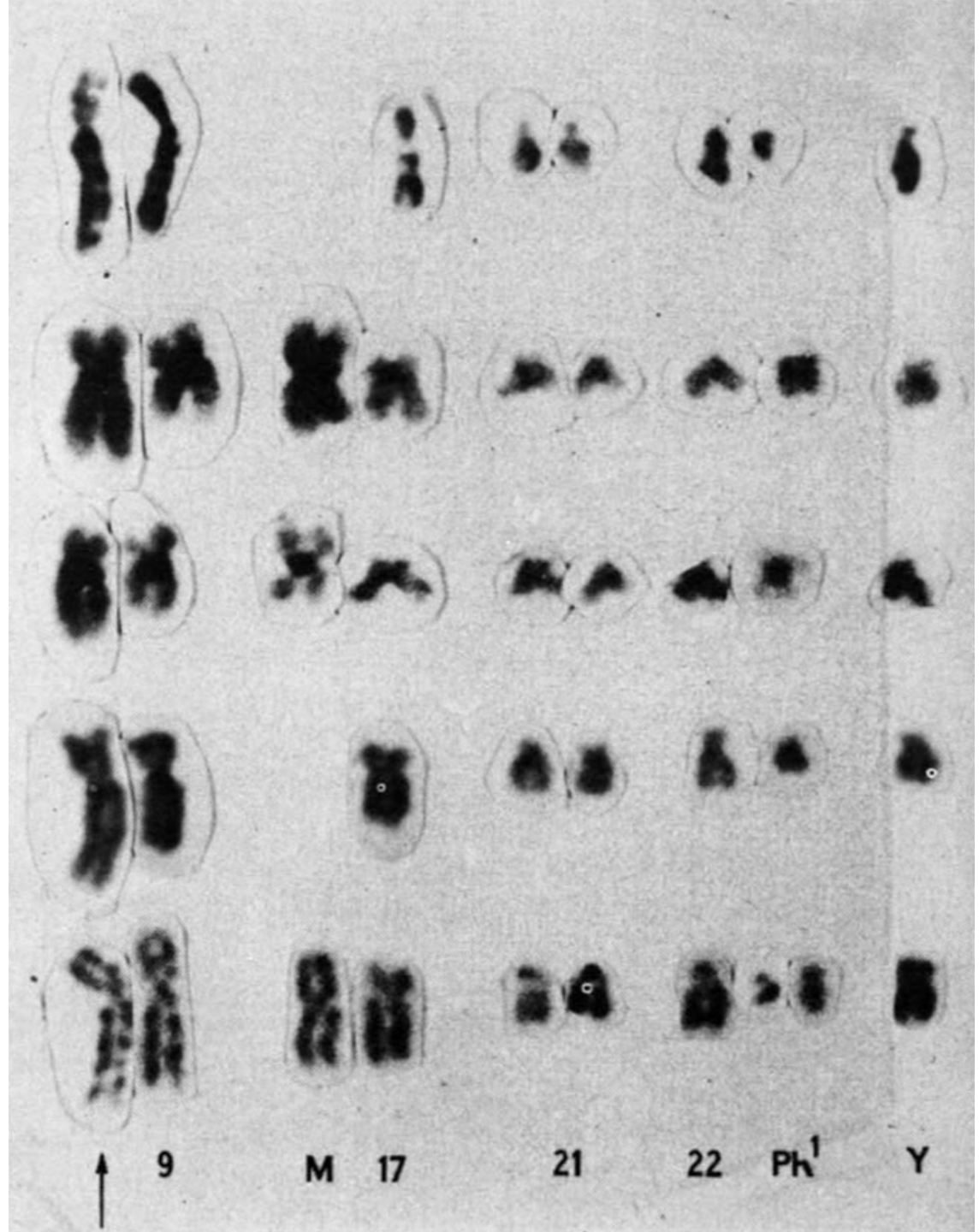
… at the time they had no idea what this mini chromosome represented

Science 18 Nov 1960:Vol. 132, Issue 3438, pp. 1497 - "MINUTE CHROMOSOME IN HUMAN CHRONIC GRANULOCYTIC LEUKEMIA" Nowell PC, Hungerford DA

1973

- Janet Rowley describes “A New Consistent Chromosomal Abnormaity in Chronic Myelogenous Leukemia …”
  - Using a new staining technique, showed that in addition to having the Philadelphia chromosome which by now was recognised as a “shortened” chromosome 22, chromosome 9 was too long

A New Consistent Chromosomal Abnormality in Chronic Myelogenous Leukaemia identified by Quinacrine Fluorescence and Giemsa Staining.Nature 243, 290 - 293 (01 June 1973)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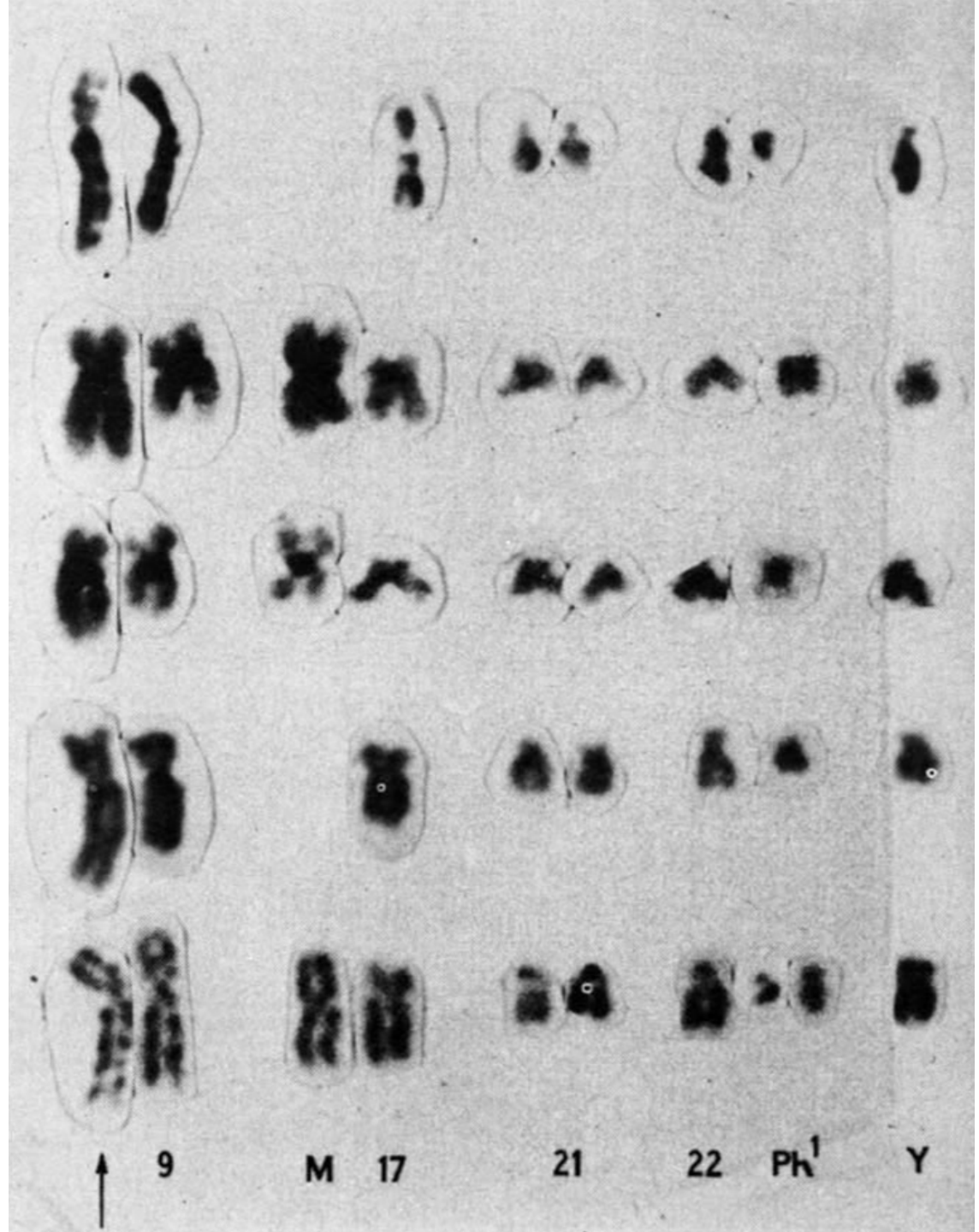
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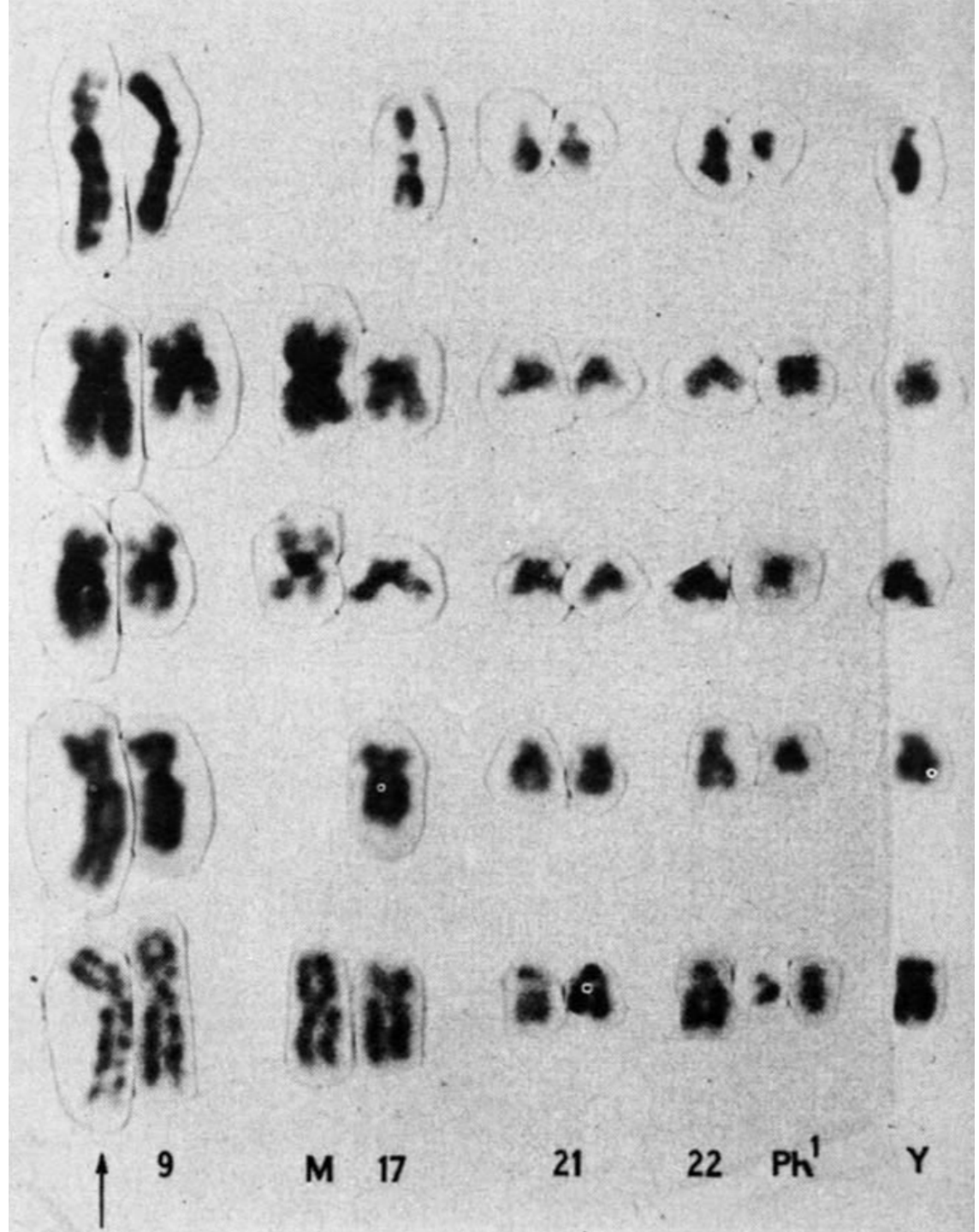
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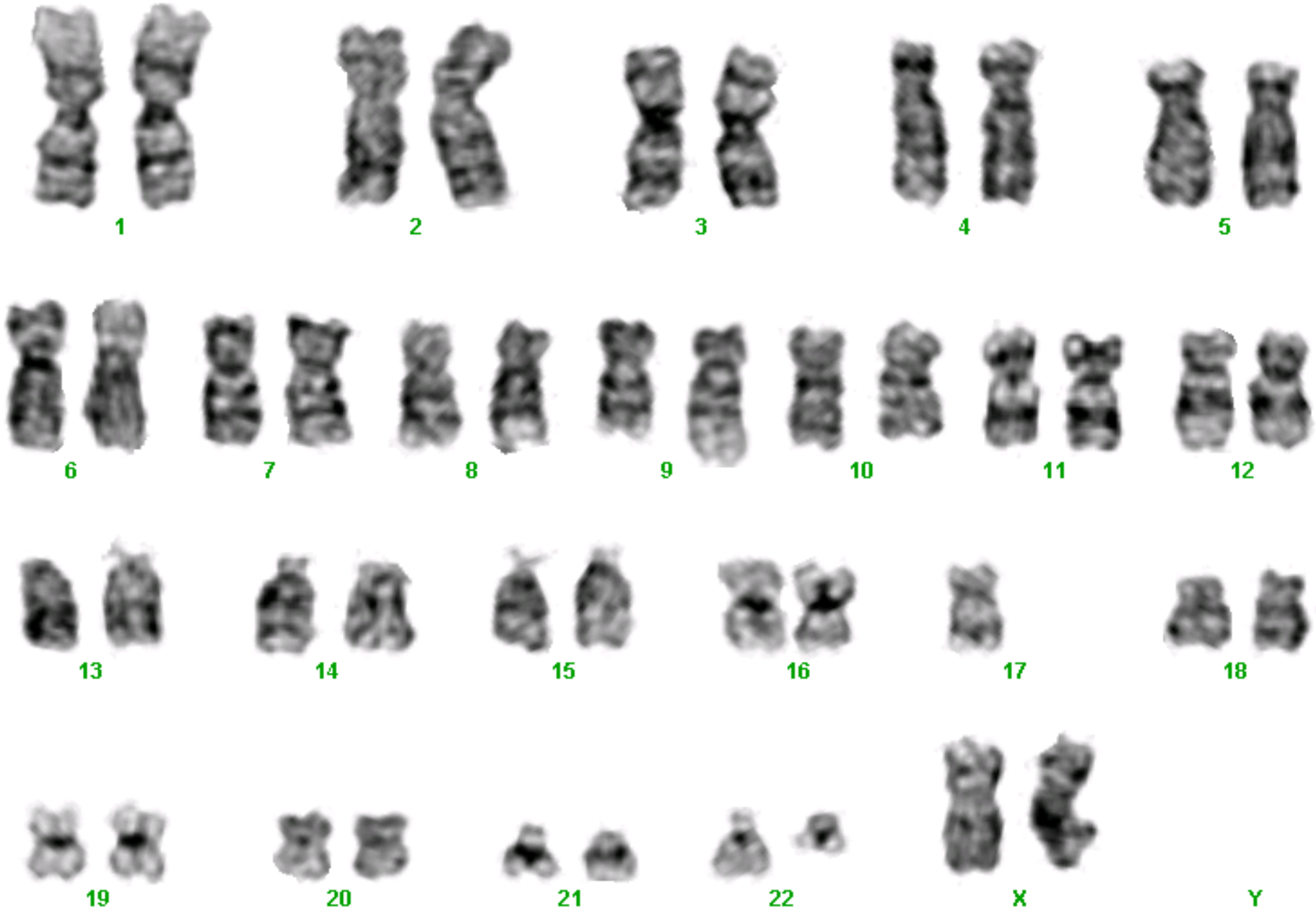
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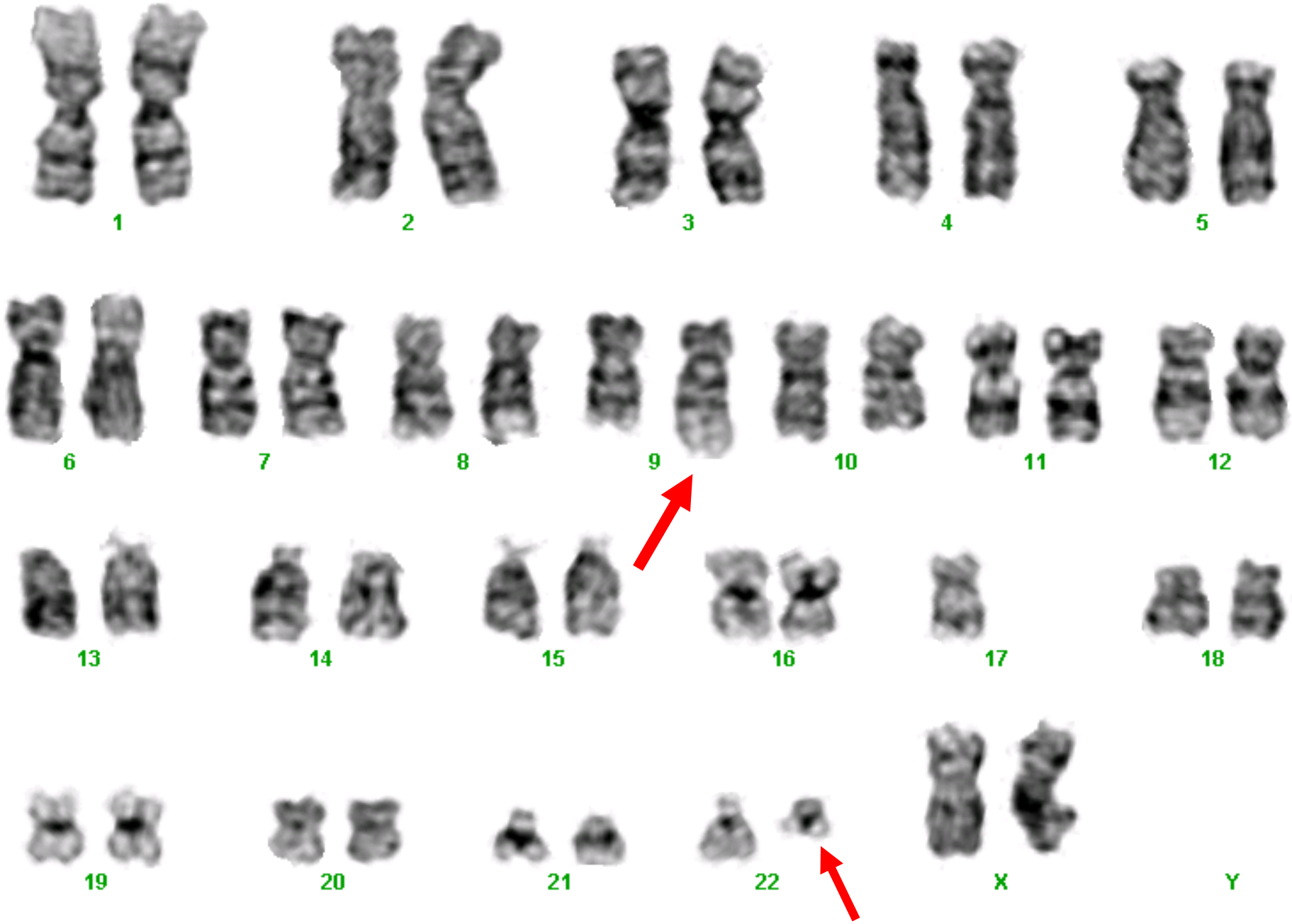
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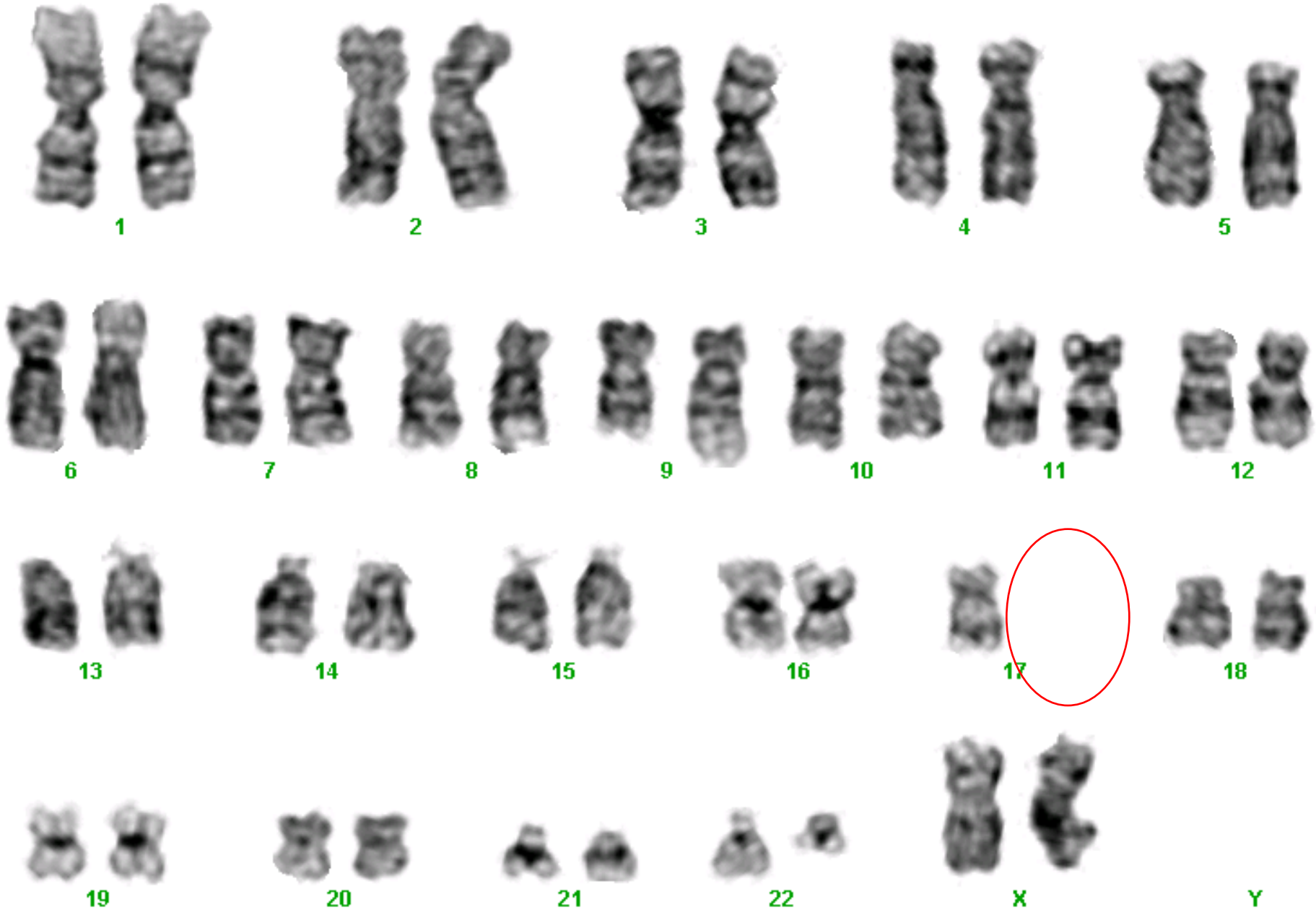
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CML – molecular pathogenesis

- It logically followed that the typical chromosomal changes in CML are due to a reciprocal translocation of genetic material between chromosomes 9 + 22

- In time : 2 specific genes involved in the translocation were determined and given names : BCR + ABL
  - BCR = “breakpoint cluster region” [function uncertain]
  - ABL = “Abelson murine leukemia viral oncogene homolog 1”
    - Encodes for a tyrosine kinase = enzyme that transfer phosphate residues from ATP to tyrosine amino acids on various signalling molecules with cells that that tell it to **GROW + PROLIFERATIVE**

CML – molecular pathogenesis

BCR-ABL translocation

↓

BCR-ABL fusion protein

↓

“constitutive tyrosine kinase”

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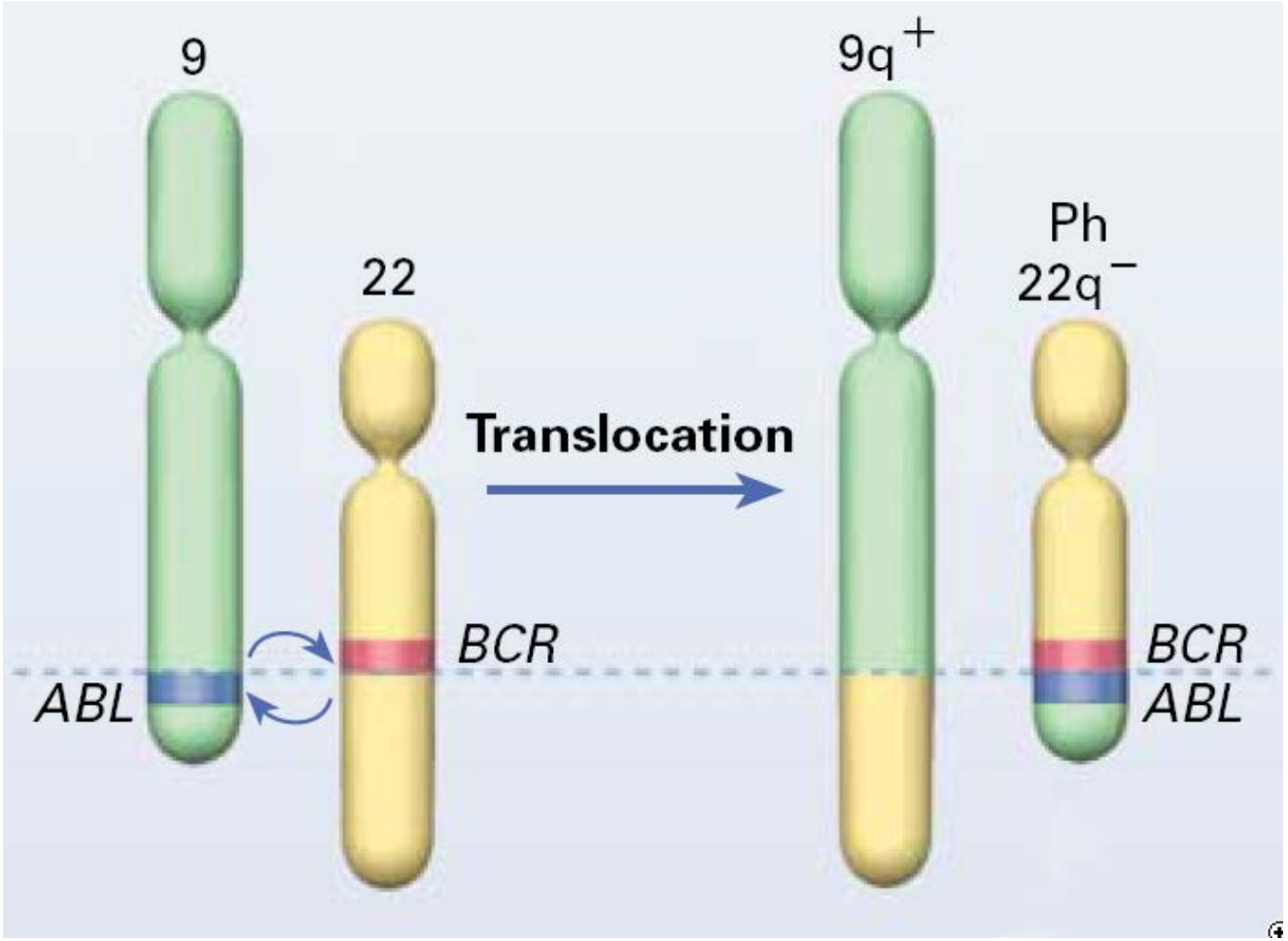
inappropriate activation of multiple downstream signal transduction pathways

↓

Proliferation and restance to apoptosis

↓

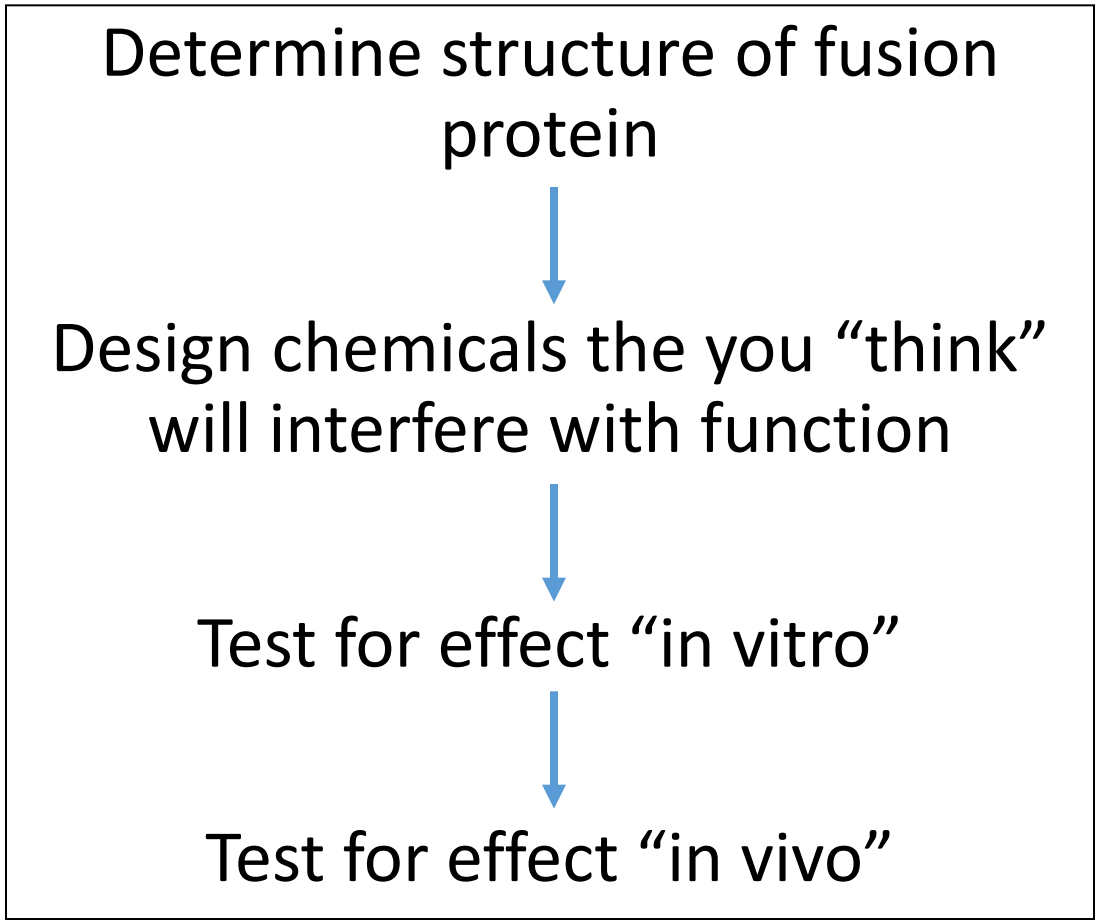
CML

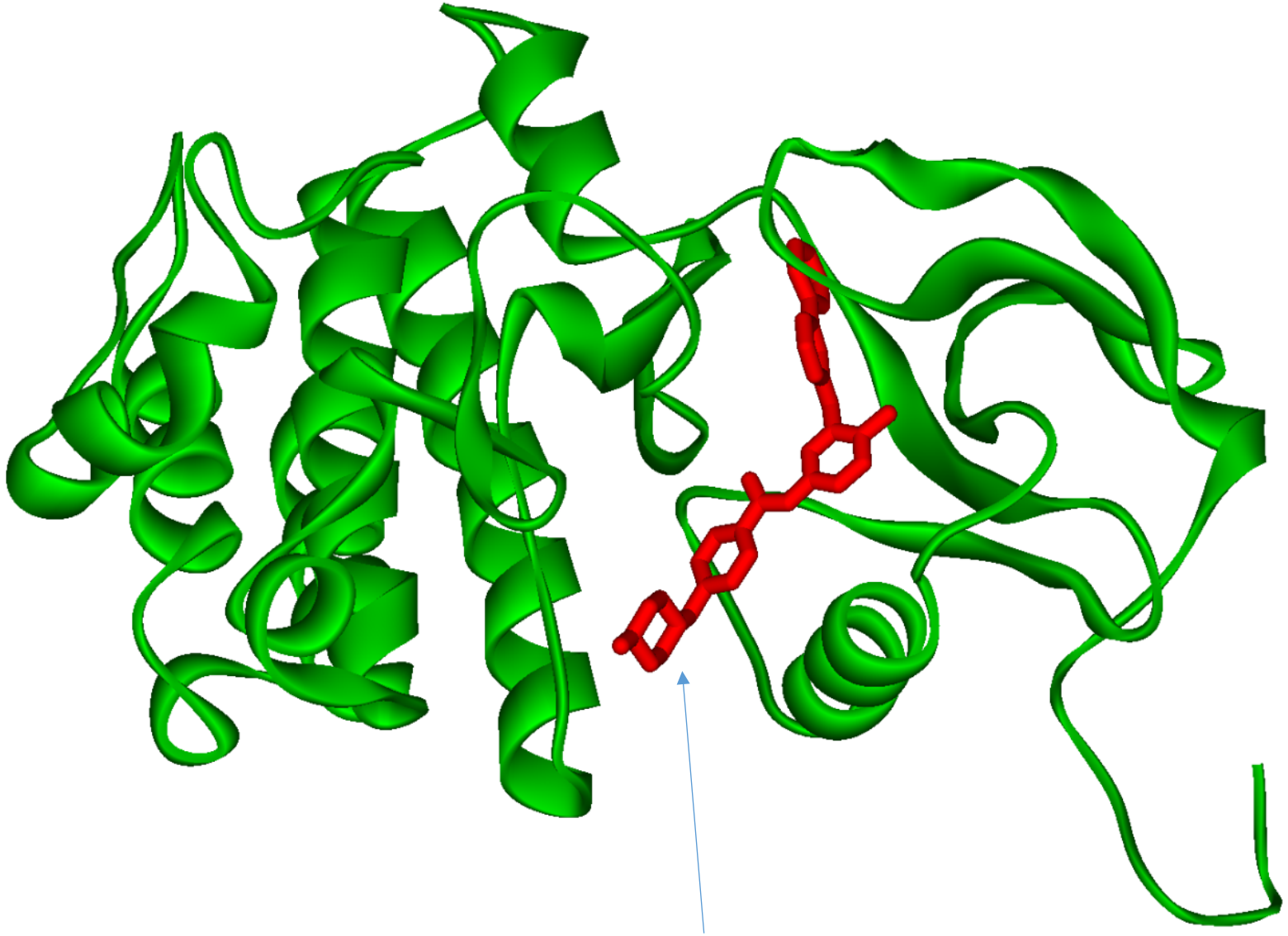


NEJM 2003

CML – molecular therapy

This understanding then leads clever scientists on a path to "design" a chemical that could inhibit BCR-ABL, and thus treat CML



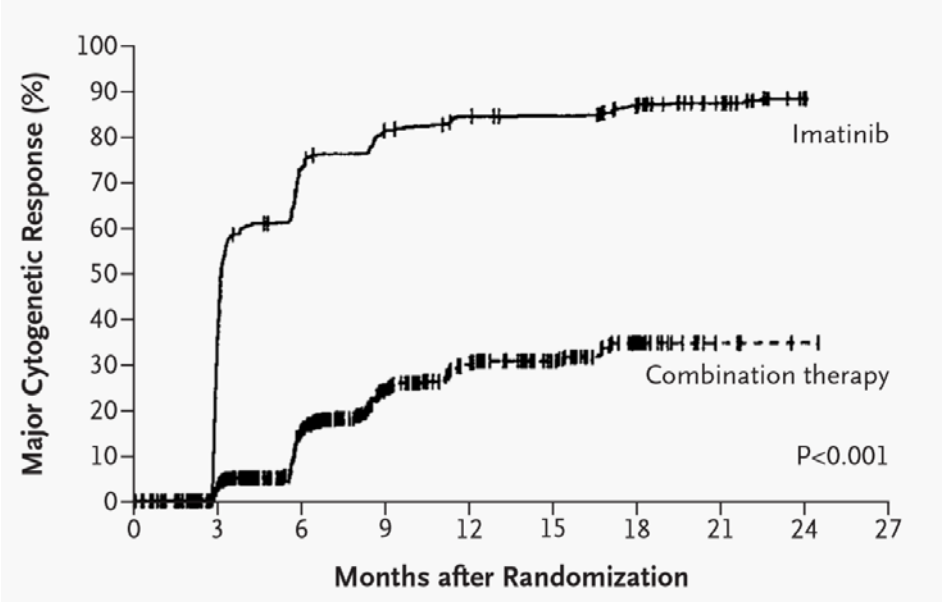


STI-571 / imatinib / Glivec

Salesse S, Verfaillie CM. BCR/ABL: from molecular mechanisms of leukemia induction to treatment of chronic myelogenous leukemia. Oncogene. 2002 Dec 9;21(56):8547–59

IRIS trial (NEJM 2003)

- Randomised comparison of “standard of care” (cytarabine + interferon) to monotherapy with imatinib
- Imatinib associated with
  - Better responses →
  - Improved freedom from progression to accelerated / blast phase
  - Better tolerated
  - (subsequent studies) > 90% survival beyond 5 years



1. O’Brien SG, Guilhot F, Larson RA, Gathmann I, Baccarani M, Cervantes F, et al. Imatinib Compared with Interferon and Low-Dose Cytarabine for Newly Diagnosed Chronic-Phase Chronic Myeloid Leukemia. New England Journal of Medicine. 2003 Mar 13;348(11):994–1004.

Glivec (Imatinib)

- Sounds “perfect” … but it’s not
  - Side effects
  - Treatment failure
    - ? Up to 30% of patients
  - It doesn’t usually cure
    - Majority of patients who stop the drug (in the absence of a deep molecular response) will relapse
  - (expensive)

Glivec (imatinib) - toxicities

- Gastrointestinal : nausea, diarrhoea
- fluid retention + **oedema esp periorbital**
- **rash**
- Neutropenia / other cytopenias (? Correlates to treatment effect)
- LFT derangement
- Fatigue, muscle cramps, myalgias

- (teratogenic)

How to improve on imatinib

- Higher doses = typically limited by toxicities
- Combination therapies (eg interferon) – not established
- **Design something better → "Second generation" molecules**
  - Niltoinib ("Tasigna")
  - Dasatinib ("Sprycel")

Nilotinib + Dasatinib

- Similar mechanism but structural differences = more “powerful” inhibitors of BCR-ABL
  - + differing susceptibility to BCR-ABL mutations that can cause resistance to Glivec

- Clinical studies show that you get more rapid, and potentially “deeper” response, with very low rates of transformation to advanced stages of disease

- BUT because the overall survival of CML is so good these days (> 90% at 5 years), very difficult to demonstrate a difference in overall survival

Imatinib, Nilotinib and Dasatinib

- All are available on PBS for initial therapy of CML in chronic phase

- Choice between imatinib and secondary generation agents remains a matter of debate, recognising lack of absolute survival benefit and “unique” individual toxicities of the three agents

Imatinib (“Glivec”)

- “First in class” but regarded as the “weakest” of the BCR-ABL inhibitors with regards to rapidity and depth of response
- Predictable toxicities, but usually manageable
- Haematologists are comfortable with it

Nilotinib (“Tasigna”)

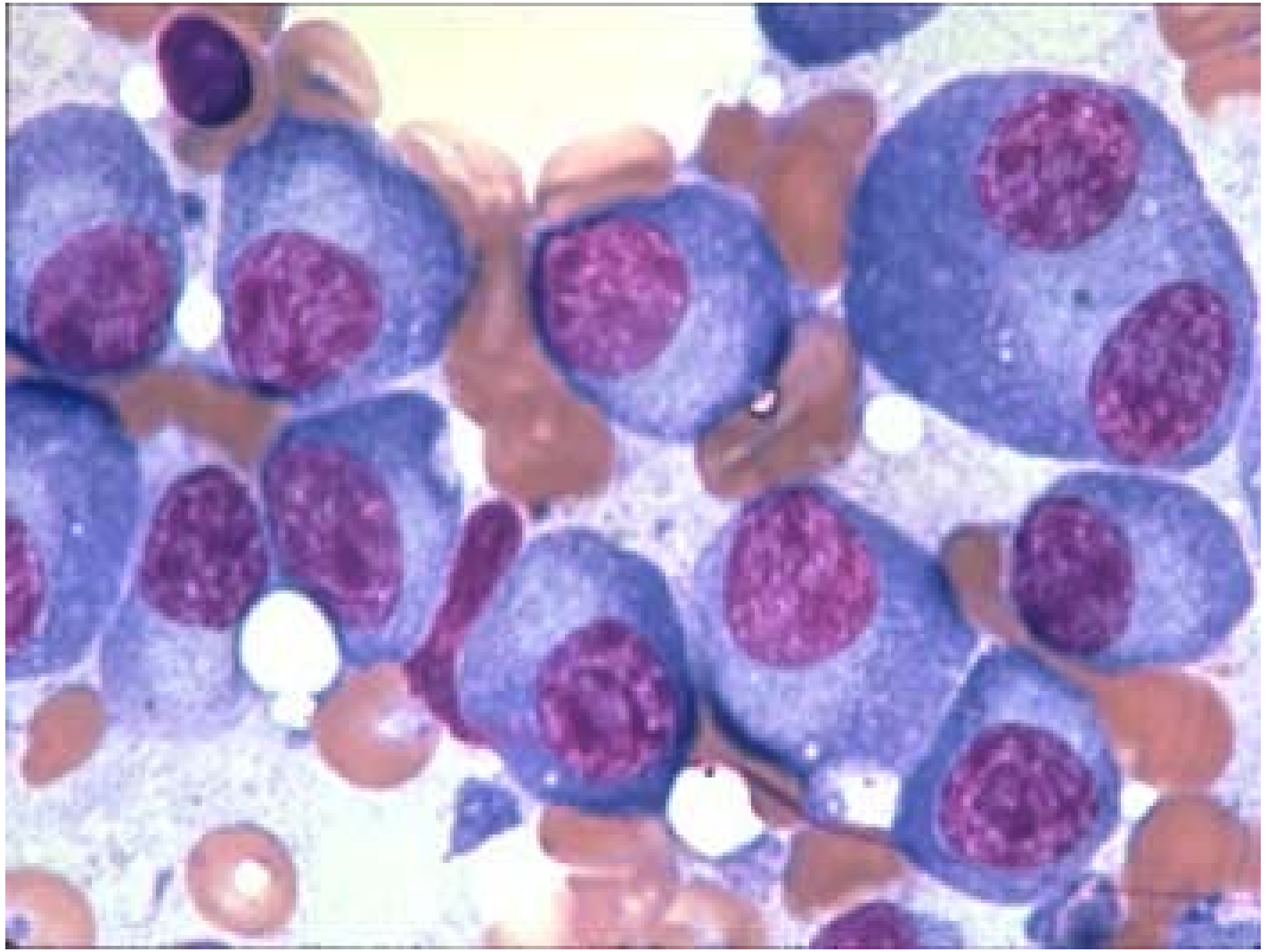
- More rapid, and overall “deeper” response compared to imatinib
- BUT issues
  - Must be taken on an empty stomach, twice a day ← compliance difficulties
  - Exacerbation of **diabetes**
  - LFT derangement, pancreatitis
  - ? Increased **risk of cardiovascular disease**

… patients who are on Tasigna can particularly benefit from a GPs expertise in monitoring and controlling these risk factors

Dasatinib (= “Sprycel”)

- More rapid, and overall “deeper” response compared to imatinib
  - (but nb no direct comparison to Tasigna ever likely to occur)
- Once day dosing, no dietary requirement (← ? better compliance)
- BUT as with nilotinib, significant toxicities
  - Pleural effusions – unpredictable, often late in course
  - Peripheral oedema
  - Pulmonary hypertension
  - Cytopenias

Myeloma and “immunomodulatory agents”



Thalidomide - history

- The history of thalidomide and myeloma is perhaps not as “clever” as imatinib and CML
- Broadly marketed in late 1950s as sedative and anti-emetic … in certain regions specifically promoted as highly effective treatment for morning sickness in prengnacy
- By 1961, clearly identified as teratogenic – causing limb deformities and amelia

Thalidomide - history

- Some years later, the teratogenic effects were attributed to inhibition of new vessel formation (… critical to embryonic lengthening of arms, legs, fingers and toes)

- In 1970s : new vessel formation (“angiogenesis”) established as important to the development of solid tumours

… leads to investigation of angiogenesis inhibitors as anti-cancer therapies

Bielenberg DR, D'Amore PA (2008). *Lymphat Res Biol.* **6** (3-4): 203–7

Thalidomide - history

- 1990s Folkman et al hypothesize that growth of blood cancers including myeloma are dependent of angiogenesis

- This leads to sequential clinical trials of thalidomide (= recognised angiogenesis inhibitor) that eventually culminate in several studies in the 1990s demonstrating superior clinical efficacy to “standard of care” therapies in myeloma patients

Folkman J (Dec 2001). "Angiogenesis-dependent diseases". *Semin Oncol* **28** (6): 536–42
Singhal S et al. Antitumor Activity of Thalidomide in Refractory Multiple Myeloma. New England Journal of Medicine. 1999 Nov 18;341(21):1565–71.

Myeloma and thalidomide

- Thalidomide becomes “first in class” of drugs that we new refer to as “novel agents” for the treatment of myeloma

Myeloma and thalidomide

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- Mirriam-Wester dictionary definition of novel :
  - “new and not resembling something formerly known or used”

http://www.merriam-webster.com/dictionary/novel

Myeloma and thalidomide

- Thalidomide becomes “first in class” of drugs that we new refer to as “novel agents” for the treatment of myeloma

- Mirriam-Wester dictionary definition of novel :
  - “new and not resembling something formerly known or used”

- My definition :
  - “we don’t really know how they work”

http://www.merriam-webster.com/dictionary/novel

Thalidomide – mechanisms of action

- Suppression of angiogenesis
- Interference with supportive microenvironment
  - Alteration of expression of cellular adhesion molecules
- **“ Immunomodulation”** (IMID)
  - Increase cell mediated cytotoxicity
  - Increased cytokines eg TNFa
- Inhibition of specific cellular pathways that are know to be aberrantly active in myeloma (eg NFKB)

Thalidomide – mechanisms of action

- Suppression of angiogenesis
- Interference with supportive microenvironment
  - Alter
- **“ Immunc**
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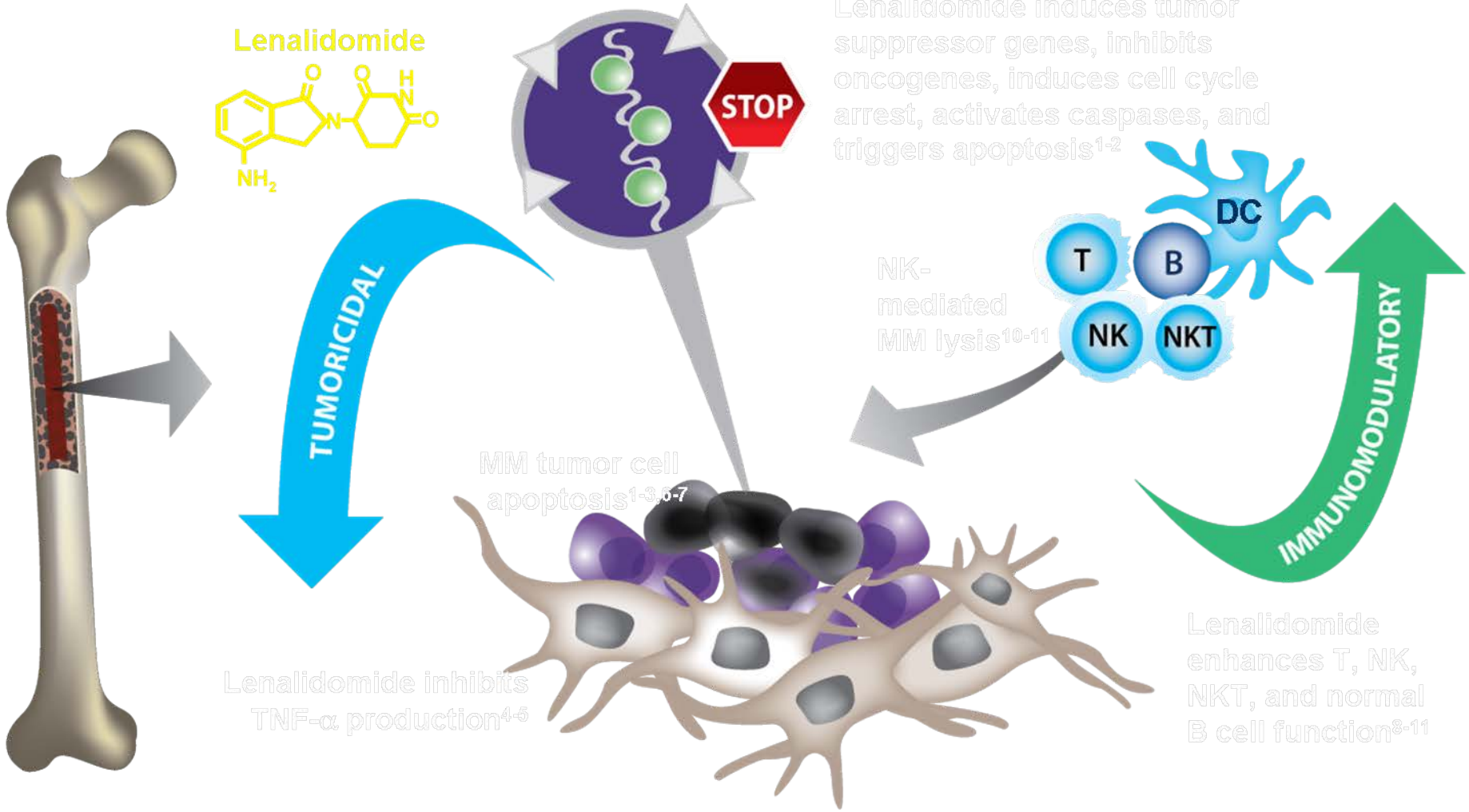
- Inhibition of specific cellular pathways that are know to be aberrantly active in myeloma (eg NFKB)

… We don’t really know how it works

Lenalidomide (“Revlimid”)

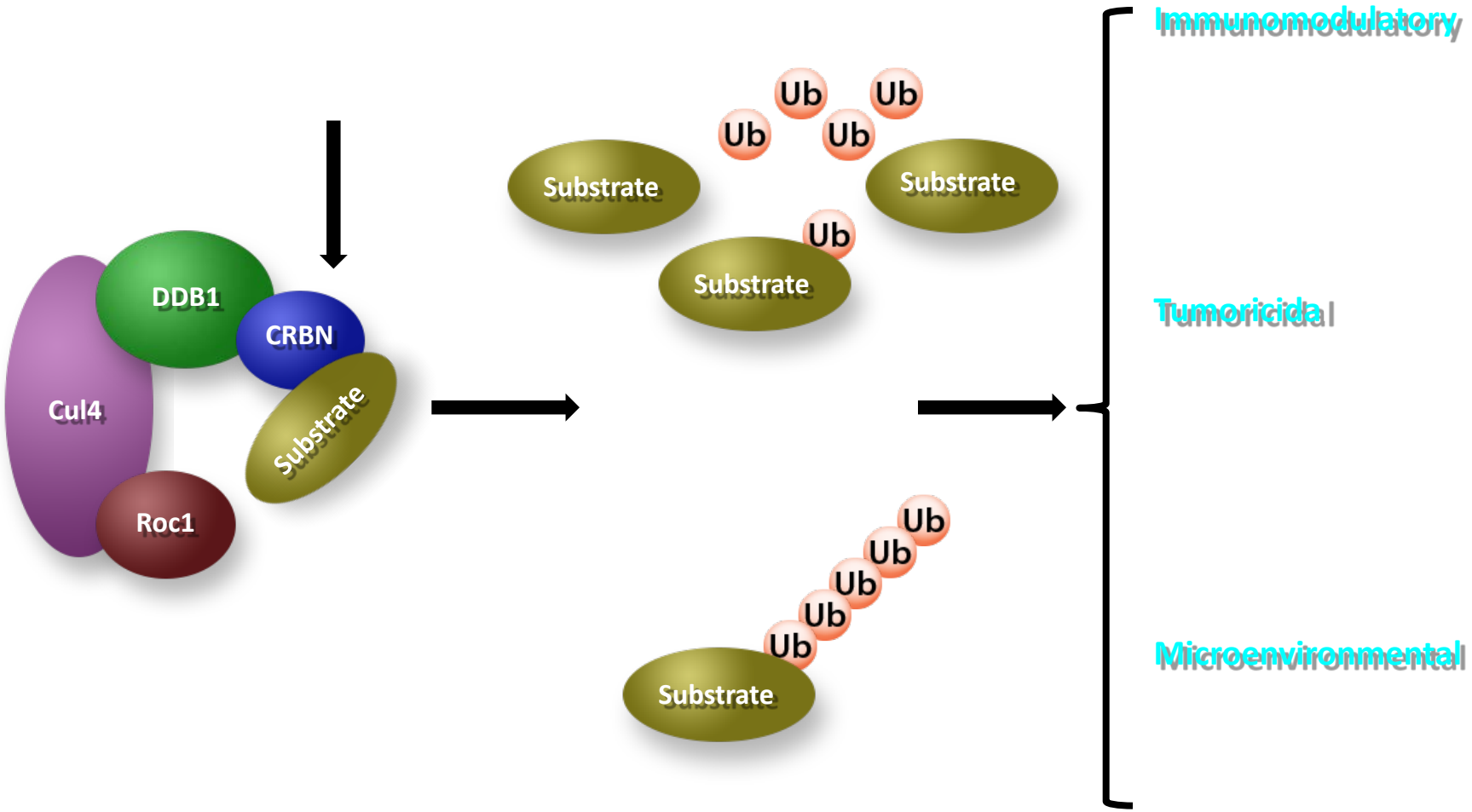
- “Next generation” of thalidomide
- designed to be “better, stronger, faster”, with less side effects
  - More potent “immunomodulation”
  - Less toxicity (esp neuropathy)



These events lead to tumor cell death and increased immune response[1-10]

1.Lopez-Girona A, Mendy D, Gaidarova S, Brady H. Lenalidomide inhibits the multiple myeloma cell survival factor IRF4/MUM1. *Clin Lymph Myeloma.* 2009;9:s135.
2.Gandhi AK, Kang J, Capone L et al. Dexamethasone synergizes with lenalidomide to inhibit multiple myeloma tumor growth, but reduces lenalidomide-induced immunomodulation of T and NK cell function. *Curr Cancer Drug Targets.* 2010; 10:155-167.
3.Hideshima T, Chauhan D, Podar K, et al. Novel therapies targeting the myeloma cell and its bone marrow microenvironment. *Semin Oncol.* 2001;28:607-612.
4.Corral LG, Haslett PA, Muller GW, et al. Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-α. *J Immunol.* 1999;163:380-386.
5.Jourdan M, Tarte K, Legouffe E, et al. Tumor necrosis factor is a survival and proliferation factor for human myeloma cells. *Eur Cytokine Netw.* 1999;10:65-70.
6.Weber DM, Chen C, Niesvizky R, et al. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N Engl J Med*. 2007;357:2133-2142.
7.Dimopoulos M, Spencer A, Attal M, et al. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N Engl J Med*. 2007;357:2123-2132.
8.Schafer PH, Gandhi AK, Loveland MA, et al. Enhancement of cytokine production and AP-1 transcriptional activity in T cells by thalidomide-related immunomodulatory drugs. *J Pharm Exp Ther.* 2003;305:1222-1232.
9.Haslett PA, Hanekom WA, Muller G, Kaplan G. Thalidomide and a thalidomide analogue drug costimulate virus-specific $CD8^+$ T cells in vitro. *J Infect Dis.* 2003;187:946-955.
10.Davies FE, Raje N, Hideshima T, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood*. 2001;98:210-216.
11.Chang DH, Liu N, Klimek V, et al. Enhancement of ligand-dependent activation of human natural killer T cells by lenalidomide: therapeutic implications. *Blood*. 2006;108:618-621.

Hypothesis: Binding of Lenalidomide and Other IMiD® Drugs to Cereblon E3 Ligase Alters the Protein Homeostasis of Myeloma Cells, Resulting in Pleiotropic, Clinically Relevant Effects



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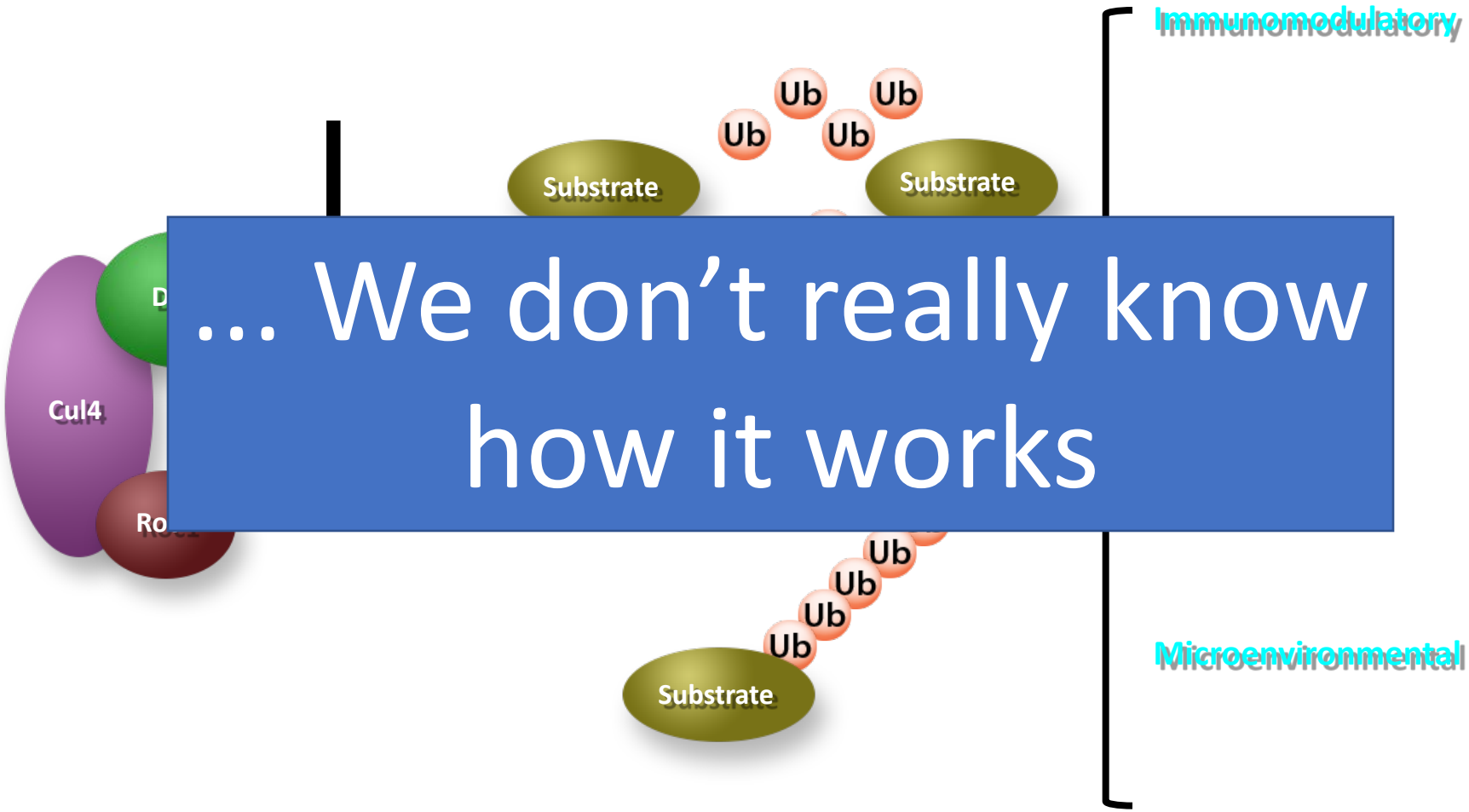


Thalidomide and Revlimid

- Whilst we may not entirely understand how they work, they are both effective, available on PBS, and widely used for treatment of myeloma

- An understanding of their unique side effect profiles is relevent

Thalidomide – side effects

- Sedation
  - This is amongst the effects is was originally marketed for in late 1950s
  - Always take dose at night
- Constipation
  - Usually manageable with simple aperients
- Peripheral neuropathy
  - Sensory, length dependent
  - Distal numbness followed by paraesthesia that progresses distal to proximal
  - Time and dose dependent
  - Most common adverse effect that leads to termination of therapy
- Increased risk of venous thromboembolism
  - all patinets must at least be on aspirin, and those at “high risk” (immobility, surgery, prior thrombosis) should be considered from LMWH prophylaxis

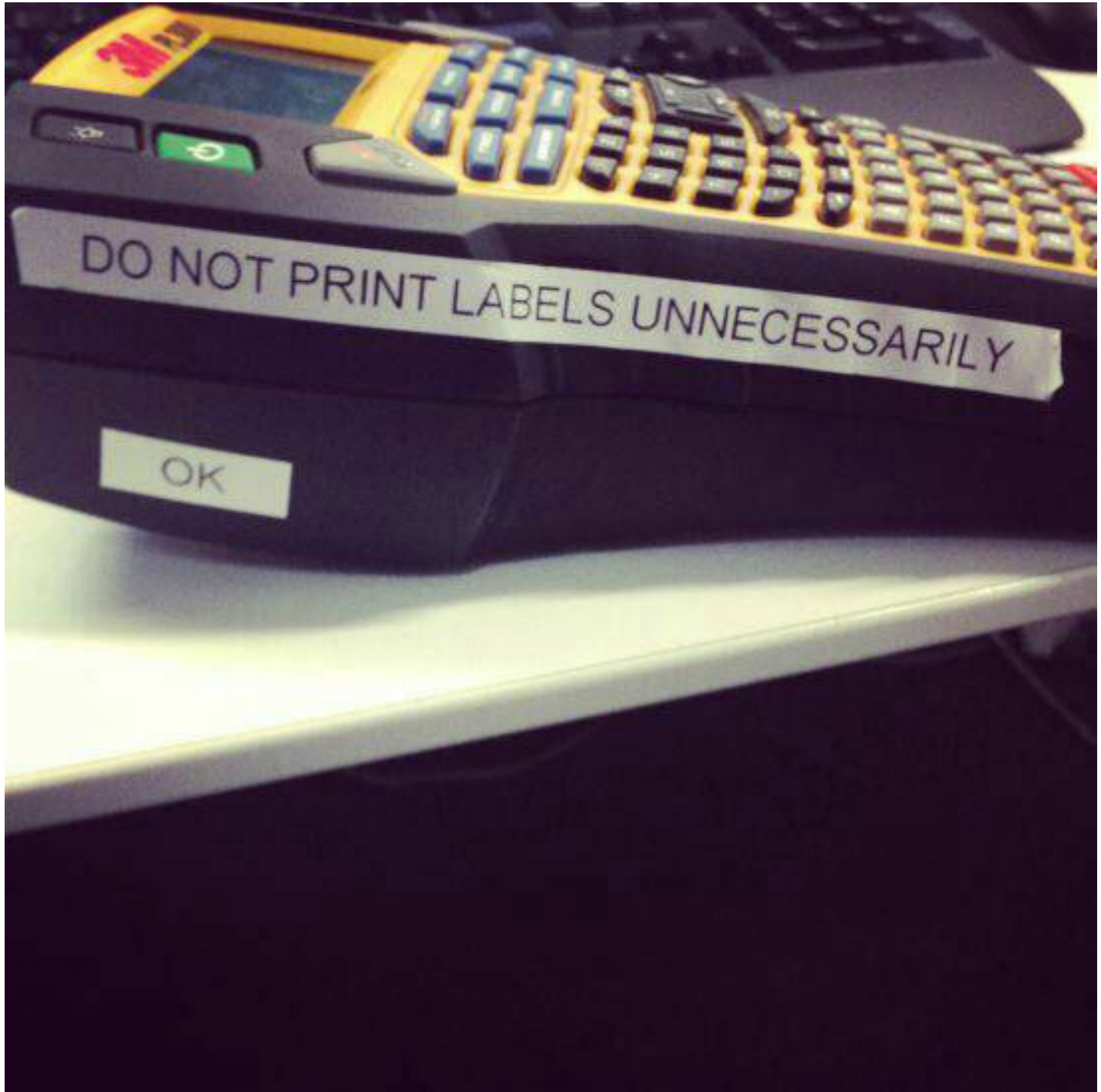
Lenalidomide vs Thalidomide

- Likely more potent anti-myeloma effect compared to thalidomide BUT hasn't been directly compared in up-front setting therefore currently only available on PBS for relapsed / refractory disease after failure of thalidomide

- Postulated difference in mode of action compared to thalidomide (? greater immunodulation vs anti-angiogenesis / microenvironmental) also equates to different toxicities

Lenalidomide (Revlimid) – side effects

- Compared to thalidomide
  - MORE cytopenias (esp neutropenia), ? rashes
  - LESS sedation, neuropathy
  - SIMILAR increased risk of venous thromboembolism
    - = all patients should at least be on aspirin +/- high intensity anticoagulation if risk factors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Chronic lymphocytic leukemia

CLL

- Most commonly diagnosed after FBC performed either as “routine” or for “nonspecific” symptoms such as fatigue, sweats

- FBC shows elevated lymphocyte count
  - +/- other cytopenias (anaemia, thrombocytopenia), due to :
    - marrow failure (= marrow “full” of CLL / more advanced stage of disease)
    - Splenomegaly -> increased consumption or normal cells esp platelets
    - Immunological disturbance causing accelerated destruction of “normal” blood cells

CLL - diagnosis

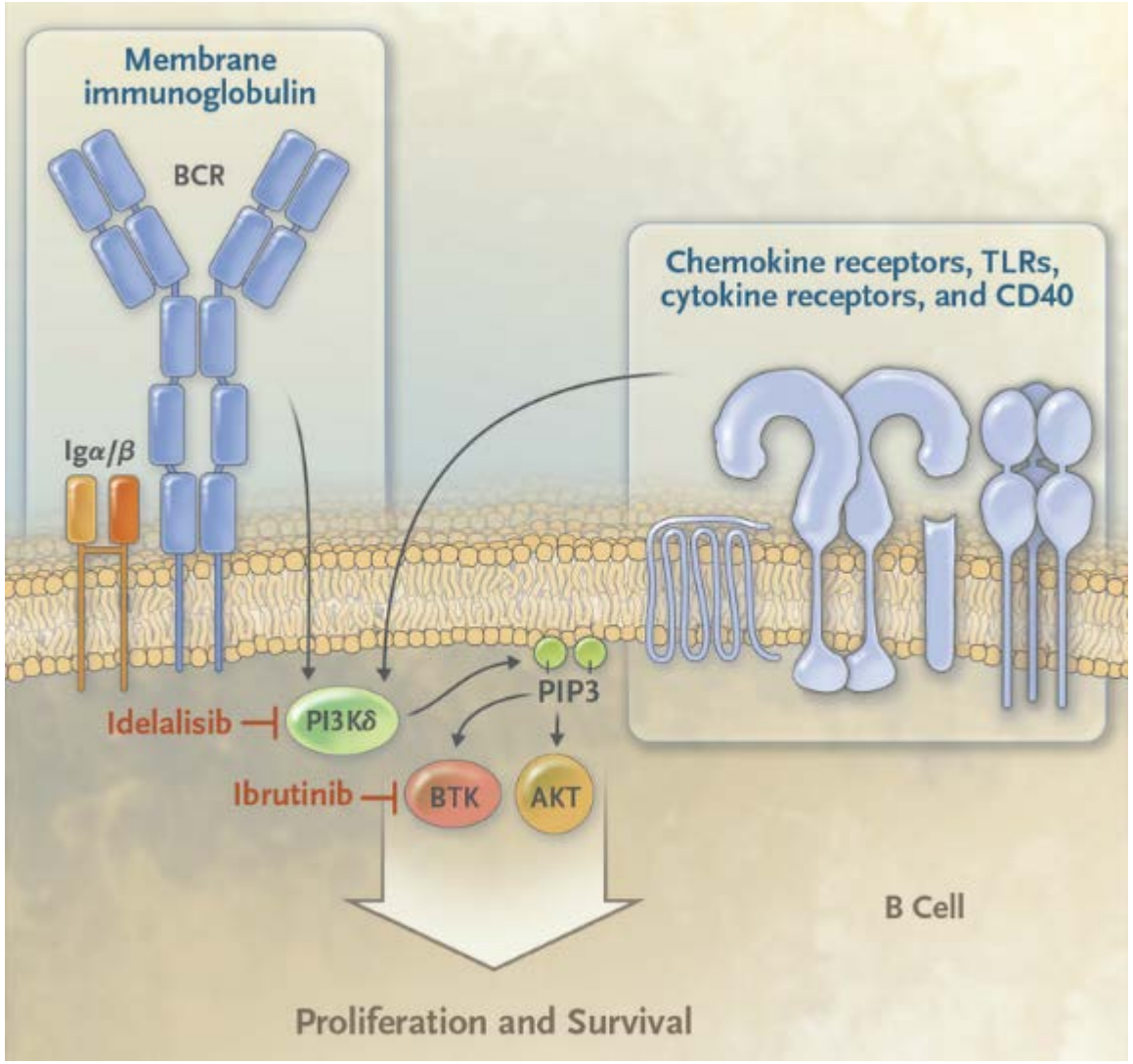
- Abnormal circulating lymphocytes have a somewhat characteristic profile of cell surface markers that can be identified by **flow cytometry**
  - A test that can be ordered through private laboratories
  - Analysis of proteins on the surface +/- inside cells to determine if they are :
    - clonal = all the same when they should all be different
    - Aberrant = demonstrating characteristics that aren't typical of normal immune cells
  - Considere if a patient has a persistence lymphocytosis not explained by other conditions (esp infection, inflammatory conditions)
    - And especially if associated with lymphadenopathy, splenomegaly, or other count abnormalities

CLL - treatment

- Regarded as incurable = treatment reserved for patients who have “symptomatic” disease
  - Progressive Lymphadenopathy / mass
  - Symptomatic splenomegaly
  - Bone marrow failure -> anaemia, thrombocytopenia
  - Constitutional symptoms (fevers, sweats, weight loss)

“Generation X” approach

B-cell receptor signalling pathway

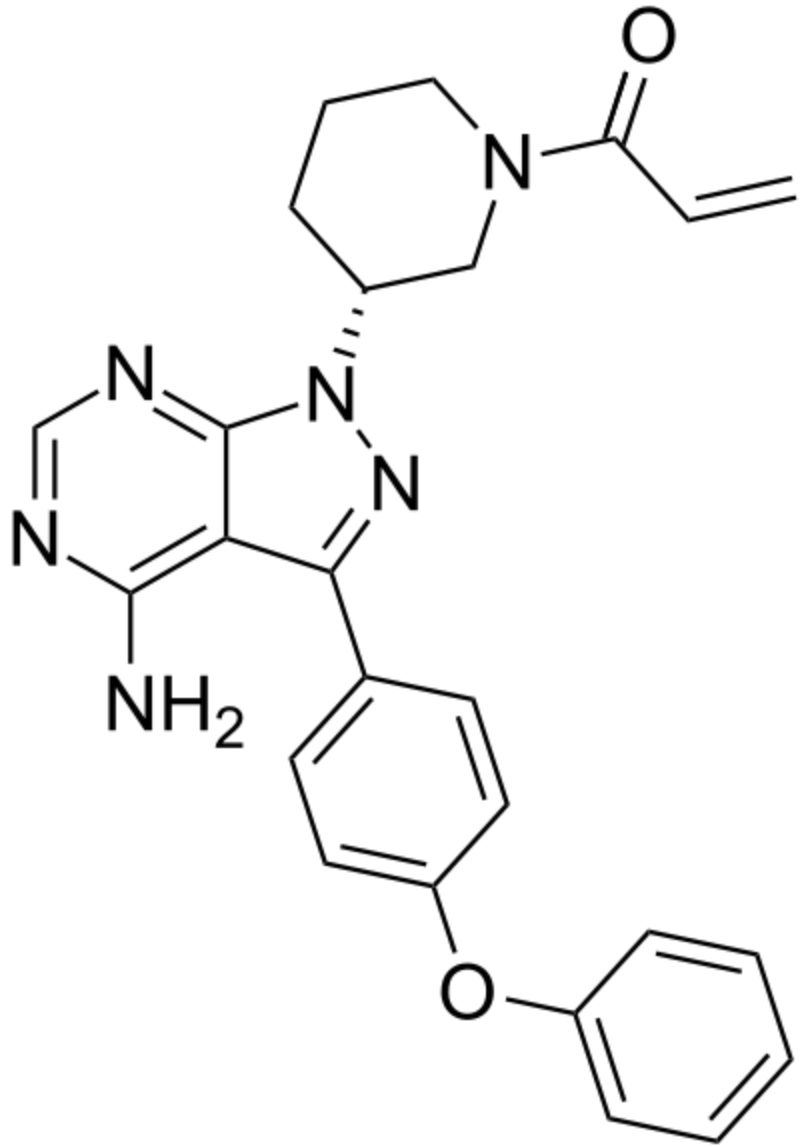


NEJM 2014:370(11):1061

CLL – “novel therapy”

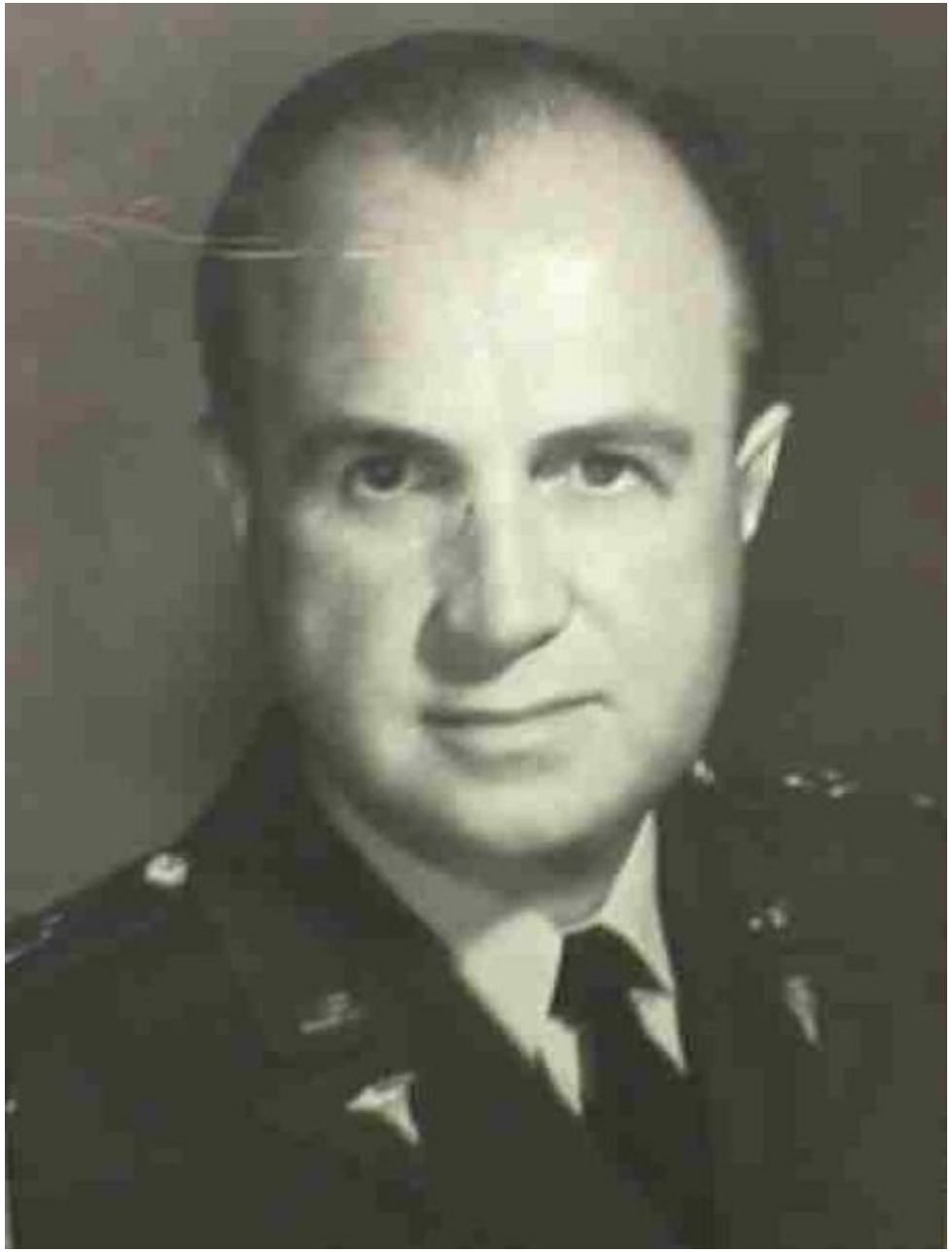
- There are currently 2 oral therapies that we have access to right now
  - Ibrutinib
  - Idelalisib

IBRUTINIB



Colonel Ogden Bruton

- Described agammaglobulinemia in a 7 year old boy with recurrent (predominantly sinopulmonary) infections
  - “Bruton’s syndrome”
  - “X-linked agammagloublinemia”
- Causative gene defect was discovered in 1993 in tyrosine kinase now know as BTK
  - Xq21.2



Bruton OC (1952). "Agammaglobulinemia". *Pediatrics* **9** (6): 722–8; Cell. 1993;72(2):279; Nature. 1993;361(6409):226

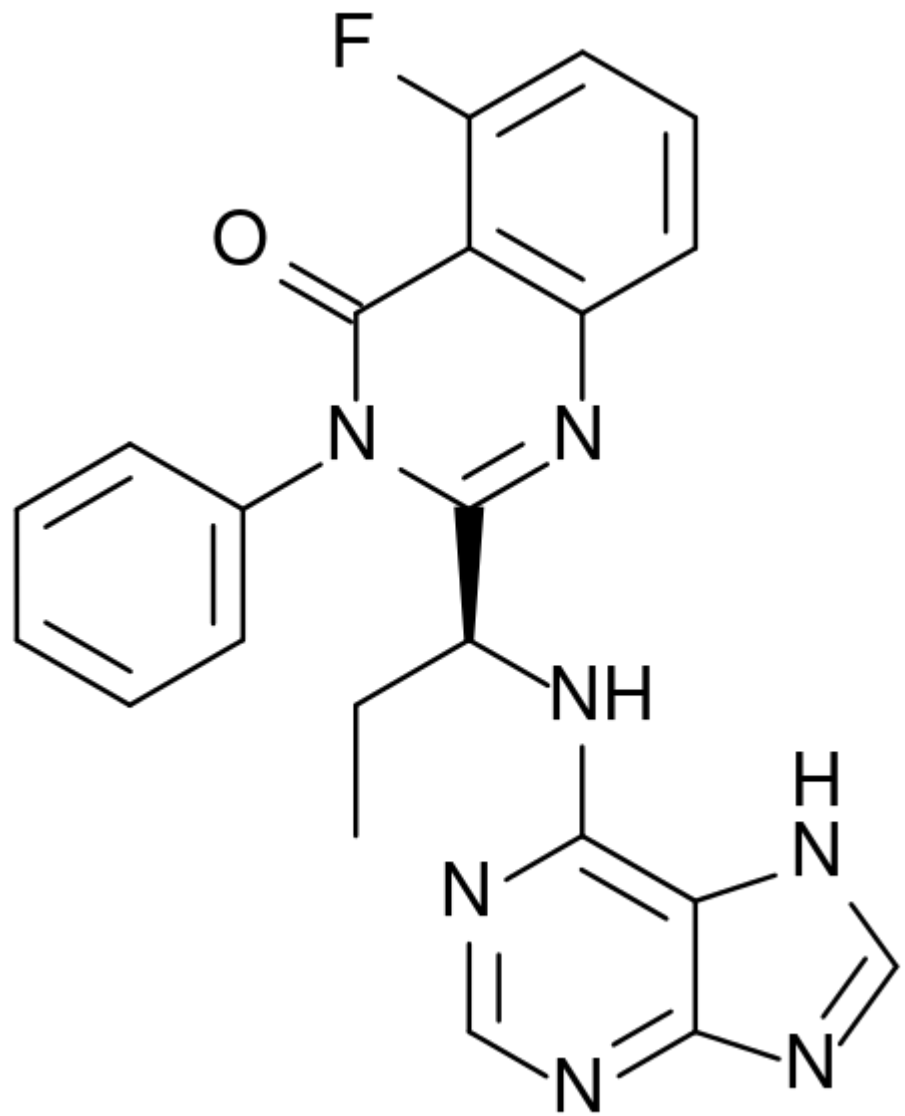
BTK and lymphoproliferative disorders

- BTK plays a central role in the constitutive activation of survival and proliferation pathways in CLL and other indolent lymphoma cells

- Ibrutinib = potent, orally available inhibitor of BTK

Blood 2014:123(21):3215-3216

IDELALISIB



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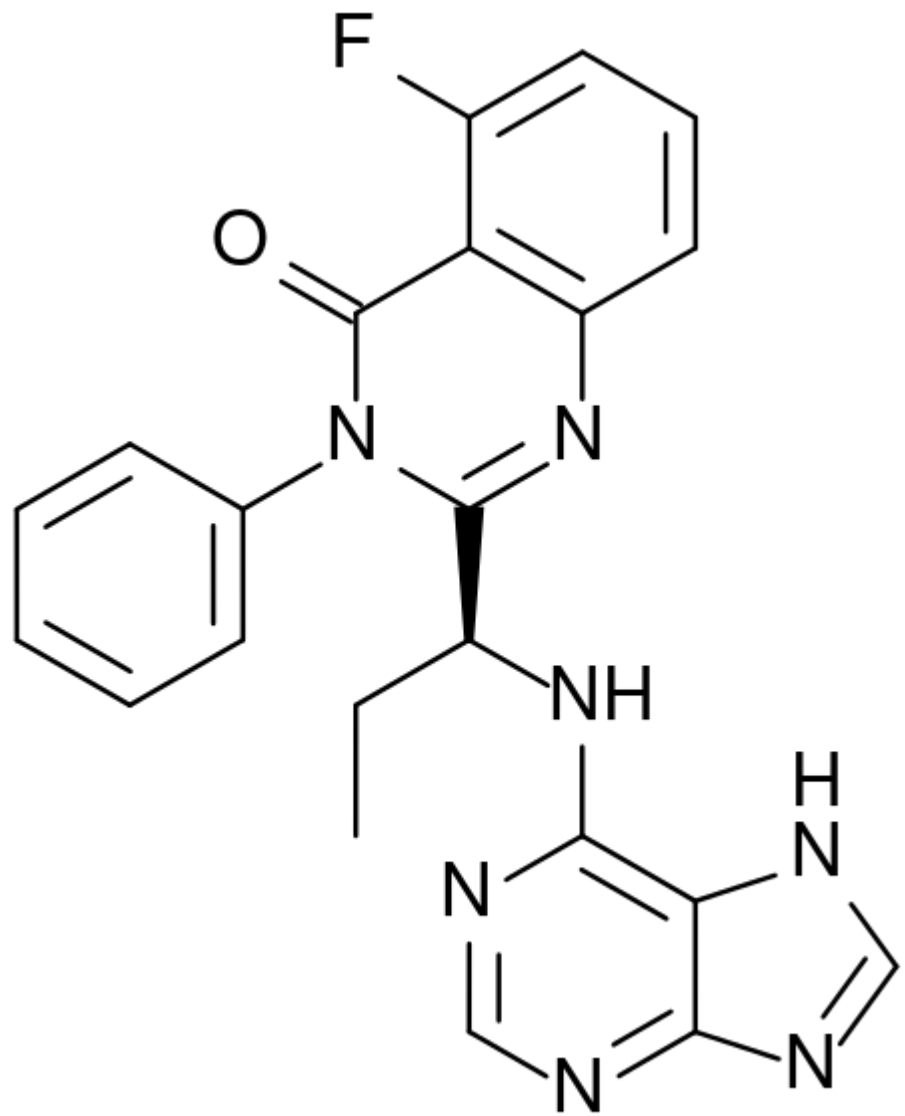
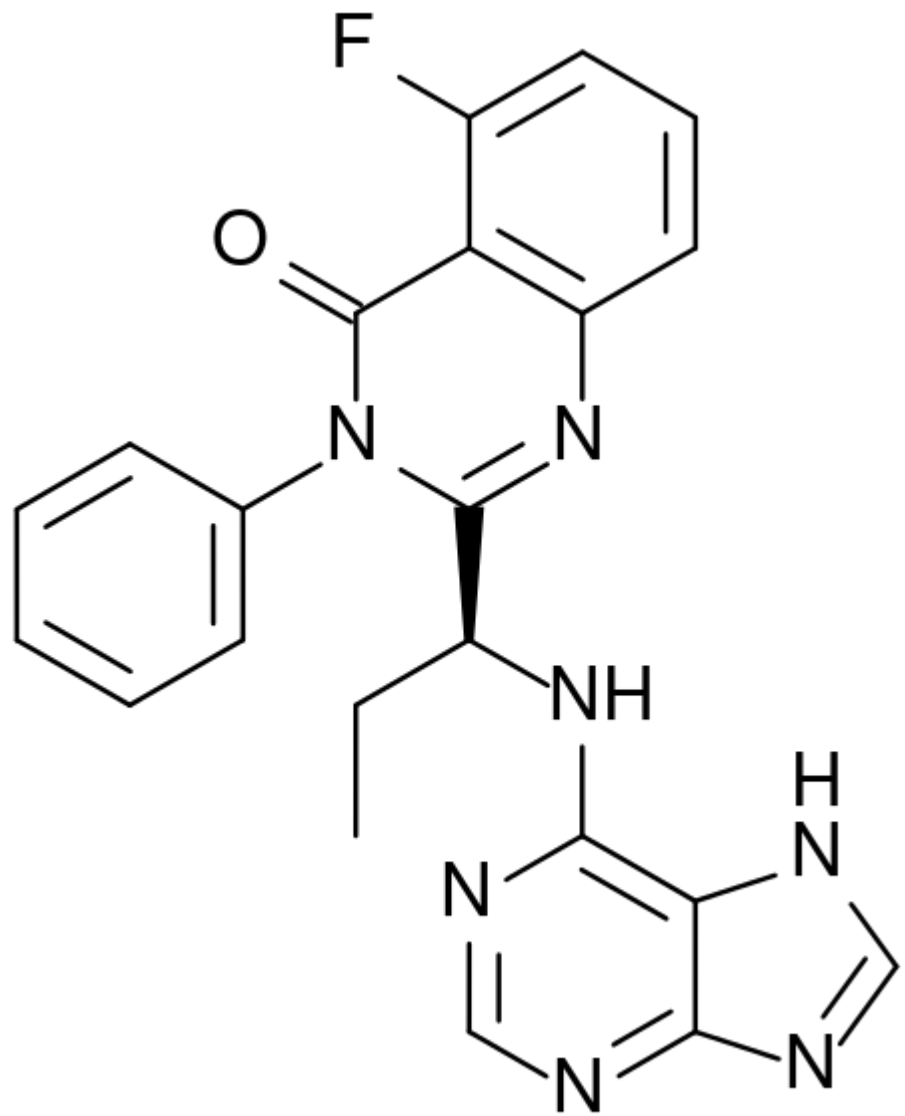


IDELALISIB



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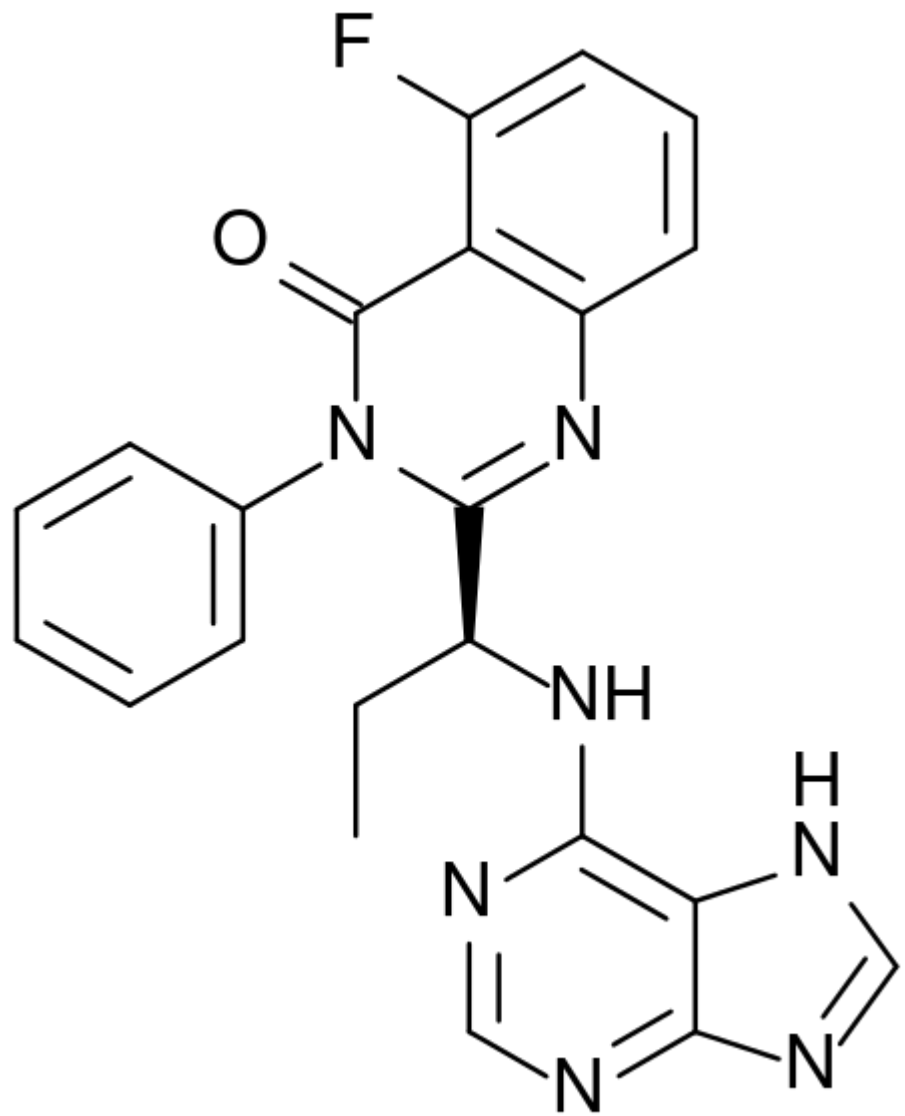

Idelalisib

- Potent, highly selective inhibitor of the delta isoform of phosphatidylinositol-3-kinase (PI3K)
- PI3K pathway is overactive in several malignancies including lymphoid + solid tumours
  - Delta isoform activation appears particularly important in CLL, indolent NHL, and mantle cell lymphoma

Blood 2014:123(22):3368-3369

Ibrutinib + Idelalisib

- Both drugs are being aggressively investigated in both relapsed / refractory and upfront therapy settings

- Common sides effects
  - Diarrhoea
  - Cytopenias
  - Immune suppression (by interfering with “normal” B-cell receptor pathway function)

Ibrutinib (“Imbruvica”) –specific issues

- Increased bleeding, especially gastrointestinal
  - Patients on warfarin not allowed to participate in clinic trials
- Atrial fibrillation
- Cytopenias
- Interactions with other drugs via CYP3A4 metabolic pathway

Idelalisib – specific issues

- Pneumonitis
  - Prophlaxis against Pneumocystis (with Bactrim) and monitoring for CMV is strongly recommended
- Colitis
  - Can result in profuse, watery diarrhoea that can be life threatening of not identified
  - Often “late” after commencement of therapy (not infreq > 12 months)
  - Treatment is with steroids +/- drug cessation

Ibrutinib + Idelalisib

- Both have “impressive” activity in relapsed / refractory patients who previously had limited therapeutic options

- Whilst initial response rates are good, we are not yet convinced about durability

  = to achieve our idea goal of “cure”, it is likely these therapies will need to be combined with other established treatments eg chemotherapy / monoclonal antibodies to improve the long term response rates

  … but at risk of increasing toxicity, especially immune suppression

- An awareness of toxicities is important as early recognition and management can prevent more serious / life threatening side effects