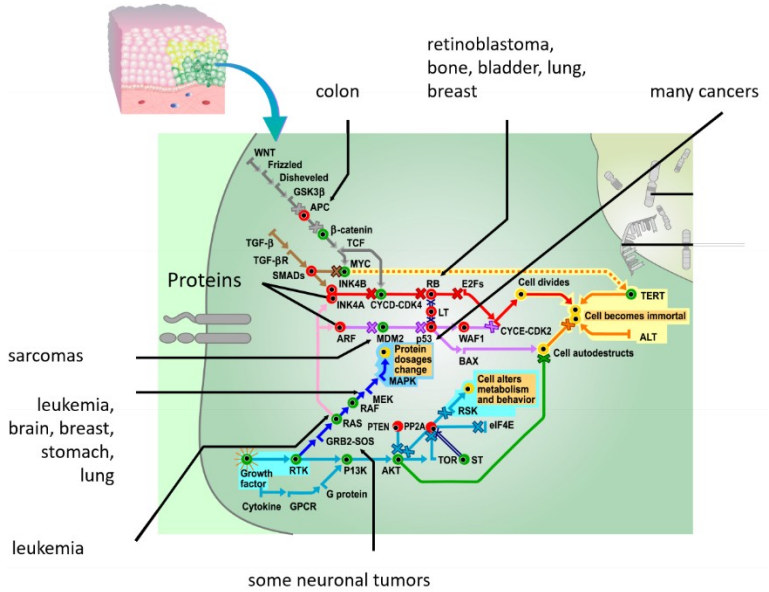
ONC 6 – Pharmacology of Kinase Inhibitors

Describe how new cancer therapies target tumor specific Signal Transduction Pathways

There are a variety of signal transduction pathways involved in cancerous cells (pathways that allow for actual communication to destination effector proteins/machinery). In cancer, a *loss of communication + regulation* is what → **abnormal growth** (hallmark of cancer).



The above diagram helps to illustrate how different cancers display different **mutations** along signal transduction pathways resulting in their abnormal growth.

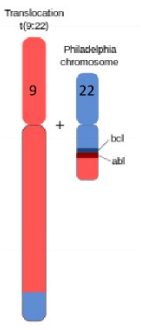
- Since different cancers affect different pathways, each type of cancer needs to have its drug target *individualized*.

Small-Molecule Kinase Inhibitors are used to help *stop* this abnormal growth signaling observed in cancerous cells.

- They *differ* from larger, antibody based therapies (antibody-mediated cytotoxicity or even immunotherapy) as they are *smaller* → ↑ *penetration* into tumors to which some antibodies may be too large to target.
- They have more predictable *PK and PD*
- They are cheaper and easier to manufacture than larger antibodies (think drugs vs biologics)

Discuss Philadelphia Chromosome Translocation and the Targeting of the BCR-ABL Signal Transduction Pathway

Philadelphia Chromosome is an *error* chromosome in that there has been inappropriate translocation of *Chromosome 9* and *Chromosome 22* onto one another.



Chromosome 9 and Chromosome 22 have been "cut and pasted" onto one another resulting in error.

This gene is responsbile for the transcription of **BCR-Abl**, a *Tyrosine Kinase* that is responsible for phosphorylation necessary for certain **growth pathways**.

This mutation results in the **loss of a negative, regulatory domain** leading to uncontrolled, overactive phosphorylation → **abnormal and excessive growth**. (*eg. In Myelogenous Leukemia*)

Explain the MoA, toxicities and resistance mechanisms of Imatinib. Name some of its congeners and how molecular knowledge of the drug target aid rapid drug development

Imatinib is a small-molecule kinase inhibitor that binds to the ATP binding site of **BCR-Abl** leading to inactivation of this overactive enzyme.

- ↓ Phosphorylation → ↓ Abnormal Growth
- Also a selective inhibitor of other Tyrosine Kinase enzymes (*PDGF* and *C-kit kinases*) which are also involved in other cancers

Extensive *molecular knowledge* of this binding interaction has been important because;

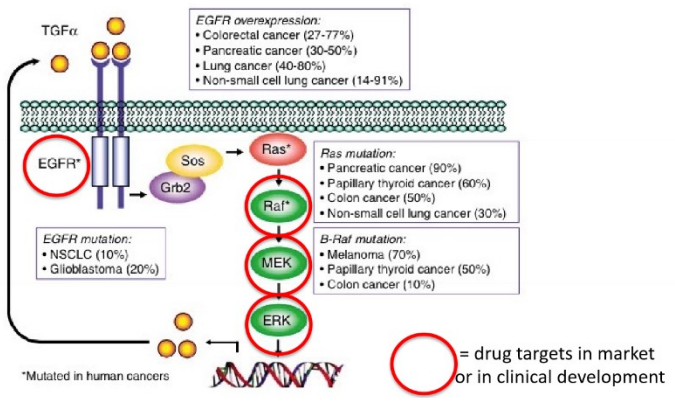
- Imatinib fits **too well** into the ATP binding site such that small changes (cancers mutate a lot!) lead to a **loss in binding affinity** between Imatinib and the ATP Binding Site.
- Other drugs such as *dasatinib*, *bosutinib*, *ponatinib* have been created with different physicochemical properties allowing their use in *Imatinib-resistant Cancers*.

Parameter	*Notes*
Efficacy	Small Molecule that binds to the overactive Tyrosine Kinase **BCR-Abl** decreasing its excessive phosphorylation → abnormal growth
Safety	Major Toxicities include; • Myelosuppression – no surprise here • Hepatic Disturbances – likely need to monitor LFTs • **HBV Reactivation** (unknown mechanism) – sometimes given **prophylactic anti-virals** • Edema due to *PDGF* inhibition (other Tyrosine Kinase) Polymorphisms in CYP 3A4 can lead to inter-individual variability
Resistance	As described with Imatinib, small Δ in binding site → large Δ in binding affinity ↑ **BCR-Abl Expression and Activity** – Will overpower our competitive antagonist

Discuss how the EGFR pathways are implicated in the development of various cancer types

Epidermal Growth Factor Receptors (EGFR) are *Tyrosine Kinase Associated Receptors* that when activated, activate the *Ras* pathway which will eventually lead to ↑ **transcription of growth factors** leading to uncontrolled growth (cancer).

- There are various targets along this signal transduction pathway including **EGFR itself, Raf, MEK and ERK**.



If we **block EGFR** (early in the pathway) that leads to a decrease of this signal cascade → ↓ growth

Cancer Cells can develop *resistance* to this by simply **mutating** something **further down** the pathway (*eg. Raf, MEK or ERK*)

That is why we have multiple targets along this pathway.

Explain the MoA, toxicities and resistance mechanisms of Gefitinib. Name other EGFR-TK inhibitors and their clinical use

Gefitinib is a small-molecule kinase inhibitor that blocks **EGF Receptors** at the ATP binding site.

Parameter	*Notes*
Efficacy	Small Molecule Kinase Inhibitor that blocks **EGF Receptors (HER1)** at the ATP binding site. *If* a cancer is due to mutated EGF-R, than there might be good response from this medication. • Overall clinical response has been low because it is common for cancers to **mutate targets further down the pathway** essentially bypassing EGF-R. • This is why we need multiple/combination therapy to multiple drug targets! (*eg. Raf, MEK, ERK*) Similar to Imatinib, also metabolized by CYP 3A4!
Safety	Major toxicities include; • N/V/D • QT Prolongation • Rare Interstitial Lung Disease
Resistance	Mutations **further down stream** (*eg. KRAS, Raf, MEK, ERK*) Mutation in **EGF-R** resulting in inability of Gefitinib to bind/block ↑ Drug Efflux

Afatinib, Erlotinib and **Osimertinib** are other common EGFR-TK inhibitors!

Discuss the concept of targeting mutated BRAF signaling pathway and the clinical applications

v-Raf Murine Sarcoma Viral Oncogene Homolog B1 (BRAF) is involved in the *Ras* pathway (see above) therefore it is further downstream from Growth Factors and EGF-Rs.

- It is a **Serine/Threonine Protein Kinase** that becomes **always active** in some cancer mutations → uncontrolled growth

Explain the MoA, toxicities and resistance mechanisms of Vemurafenib

Vemurafenib is a small molecule kinase inhibitor that binds *reversibly* to the ATP Binding site of mutated BRAF.

Parameter	*Notes*
Efficacy	Small Molecule that binds *specifically* to **Mutated BRAF** (V600E) and should only be used in this case • If used on **Wild Type BRAF** (normal), there is a paradoxical ↑ **Activity** → Uncontrolled Growth • This is due to a *loss of auto-inhibition* because the dimer BRAFs cannot phosphorylate each other (required for inhibition) and we just blocked phosphorylation! Similar to other Kinase Inhibitors, metabolized by CYP 3A4
Safety	Major toxicities: • QT Prolongation • Unrelated cutaneous skin cancers (bc of that loss in auto inhibition in WT BRAF)
Resistance	Switch to **other growth factors** (*PDGF, IGF and others*) instead of EGF Mutations **further downstream** (*MEK and ERK)* ↑ Drug Efflux

Name the ALK Kinase Inhibitors that are used in Lung Cancer Therapies

Anaplastic Lymphoma Kinase Receptors are involved in brain development but in *cancer*, they are constitutively active.

- Leads to Lung Cancers (Non-Small Cell LC), Melanoma, CNS Cancers and Retinoblastoma
- Small Kinase Inhibitors help to decrease this constitutive activity!