Cancer Therapy

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Therapy – Curative or Palliative?

- Is cancer "curable"?
  - "Cancer" is not a single disease; a collection of hundreds of diseases – no single cure possible
- Cancer therapy aims at
  - Complete cure (rare)
  - Prolonging the survival
  - Alleviation of the worst symptoms
  - Rehabilitation
- Three major approaches (with various combinations)
  - Medical (chemotherapy)
  - Surgical
  - Radiation

Issues to be considered in anticancer therapies

- ## Specificity
  - How do we selectively target cancer cells that are almost identical to normal cells? For example, many anti-cancer drugs target rapidly proliferating cells. But they do not distinguish between rapidly dividing cancer cells and other normal high-turnover cells like bone marrow, epithelia etc. (hair loss and bone marrow depletion are two very common side-effects of anti-cancer therapy)

- ## Toxicity
  - Side effects of anticancer drugs are a result of lack of specificity
  - What is the maximum dose tolerated by the patient? – A balance has to be struck between side effects tolerated and maximum efficacy of the drug
  - Second-site tumor

- ## Resistance

The Ideal Anticancer Drug
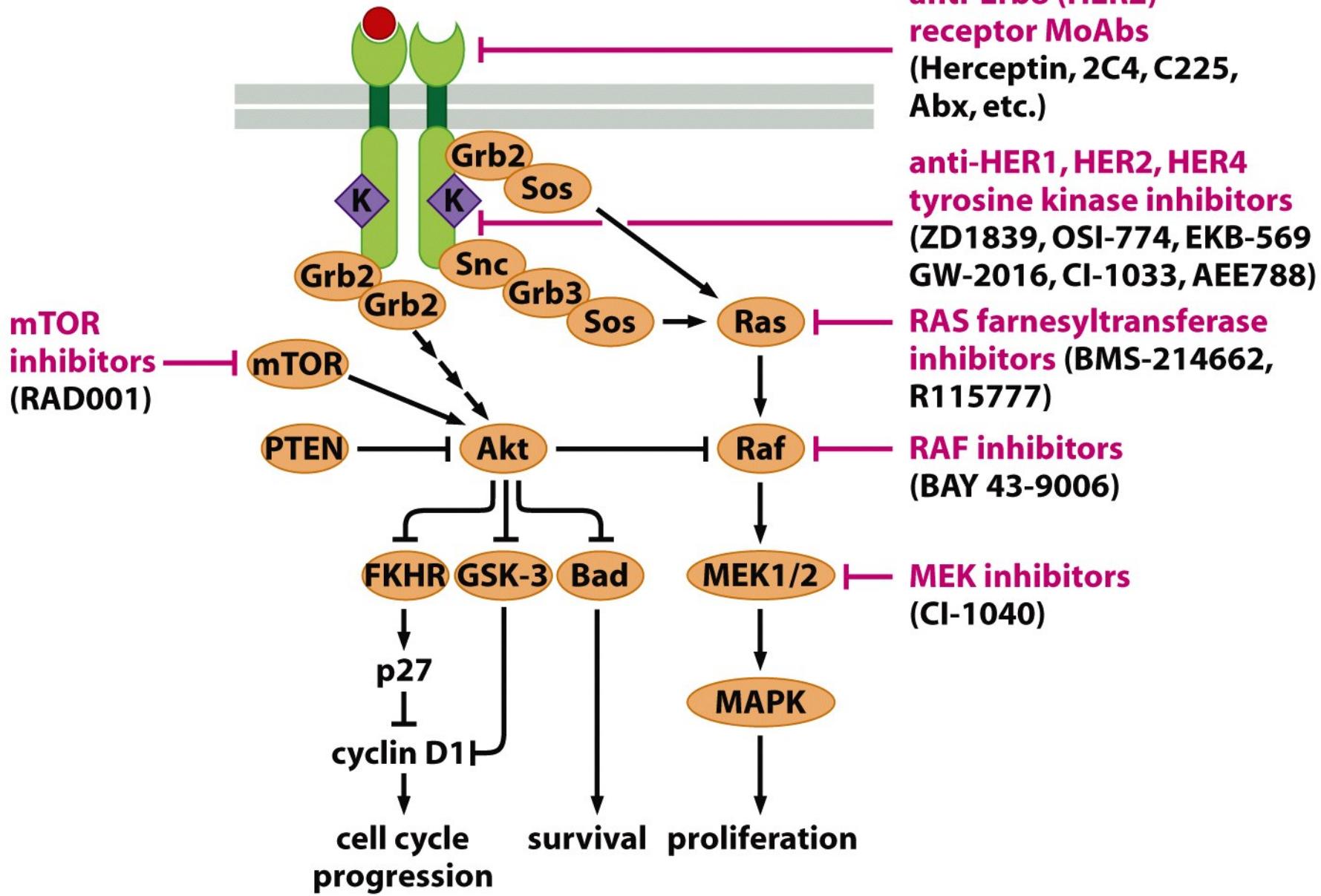
- Should kill all cancer cells
- Should be able to target cancer stem cells and quiescent cancer cells
- Should target multiple pathways
- Should not kill normal cells, including the high-turnover cells
- Should have no toxicity and side effects
- Should have good bioavailability

The Ideal Target

- Limitations in choosing targets for chemotherapy
  - Many drugs, often low-molecular weight organic compounds, almost always *inhibit* biochemical functions
  - Very few examples of drugs that can *restore* the function of tumor suppressors (compounds that can restore p53 function)
- Oncogenes and oncoproteins are hence the logical targets for most anti-cancer drugs
- The biochemistry of a protein also dictates its effectiveness as a target
  - Structural features of the target protein, eg. A catalytic cleft in an enzyme is an attractive target

anti-Erb8 (HER2) receptor MoAbs (Herceptin, 2C4, C225, Abx, etc.)

anti-HER1, HER2, HER4 tyrosine kinase inhibitors (ZD1839, OSI-774, EKB-569 GW-2016, CI-1033, AEE788)

mTOR inhibitors (RAD001)

RAS farnesyltransferase inhibitors (BMS-214662, R115777)

RAF inhibitors (BAY 43-9006)

MEK inhibitors (CI-1040)

Types of Anticancer Drugs

- Alkylating agents (Cyclophosphamide)
- Anti-metabolites (5-Fluorouracil)
- Cell cycle arrest
  - Interference with spindle assembly (Vincristine)
- Topoisomerase inhibitors (Irinotecan)
- Antibiotics (Doxorubicin)

The Drug Discovery Cycle

- Rational drug design
  - Computational
- Testing on cell models
  - Determination of selectivity
  - Therapeutic index
  - Solubility and other considerations
- Testing on animal models
  - *In vivo* action of the drug is tested
  - Pharmacokinetics and pharmacodynamics
- Clinical trials
  - Phase I – focus on toxicity; **Therapeutic Window** determined
  - Phase II and III – focus on efficacy, including indications, improvement over existing drugs etc.

Issues in Drug Screening in Cell Models
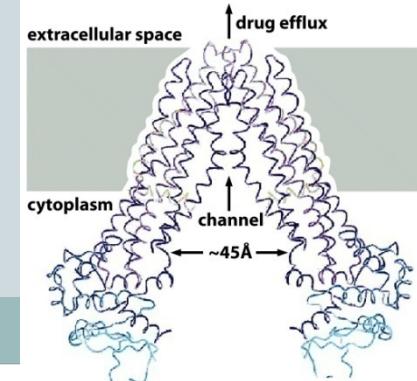
- In vitro conditions often do not reflect in vivo conditions
  - Metabolism and clearance of a drug in the body is rarely reflected in cell cultures
  - Radiation of cancer cells in culture is not a reflection of how tumors would behave on radiotherapy – other factors like blood supply play a crucial role
- Toxicity and side-effects are not often predictable at the cell model stage

Drug Resistance

- In a tumor, some cancer cells might escape the action of the drug – such cells can form a tumor again

- Mechanisms of resistance
  - Insensitivity to the drug (polyclonality of the tumor)
    - Quiescent cancer cells in Go phase escape the action of anti-proliferative agents
    - Mutations in the targeted protein may render the drug ineffective
  - Efflux of the drug
    - Cancer cells expressing channels that can pump out the anti-cancer drug can escape and proliferate
  - Tumor stem cells

Combinatorial Therapy
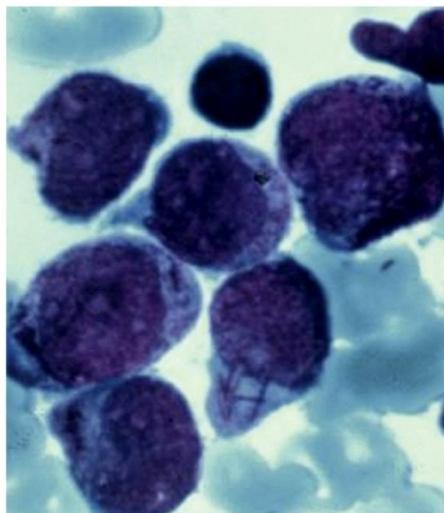
- Combinatorial therapy is a strategy aimed at maximizing the cure / survival rate and minimizing the side-effects and toxicity

- Large doses of one drug can cause unacceptable side-effects
  - Eg. Early use of cyclophosphamide in high concentrations for breast cancer therapy resulted in a 5.7 fold increase in risk of Acute Myelogenous Leukemia

- Instead, multiple drugs, targeting different pathways, at much lower concentrations may be more effective while reducing the side-effects to tolerable limits
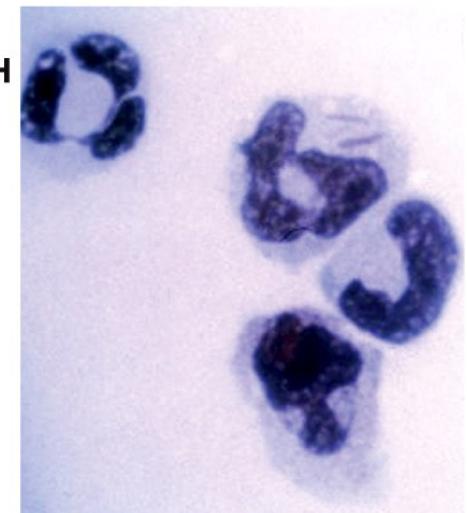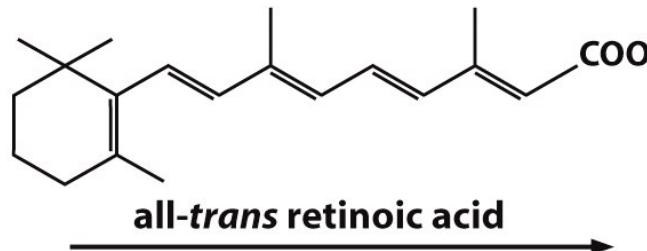
All-*Trans* Retinoic Acid

- A very successful therapy for Acute Promyelocytic Leukemia
- All-*trans* Retinoic Acid induces undifferentiated leukemic blast cells to differentiate into neutrophils
- Targets the PML-RAR fusion protein

promyelocytes

all-*trans* retinoic acid

COOH
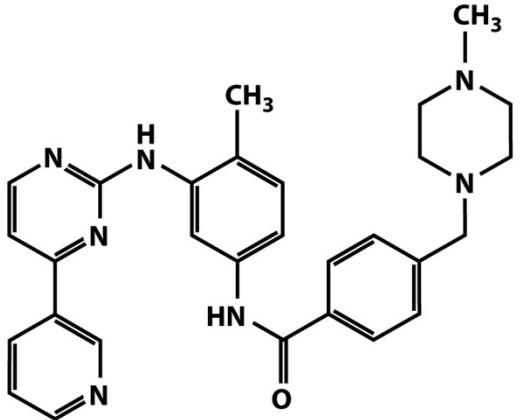
polymorphonuclear cells (neutrophils)

Imatinib Mesylate (Gleevec)

- A success story of rational drug design
- Targets the BCR-ABL fusion protein (a product of the Philadelphia Chromosome) in Chronic Myelogenous Leukemia (CML)
- The structure of the compound Imatinib was optimized to improve binding to the catalytic cleft of the ABL tyrosine kinase domain
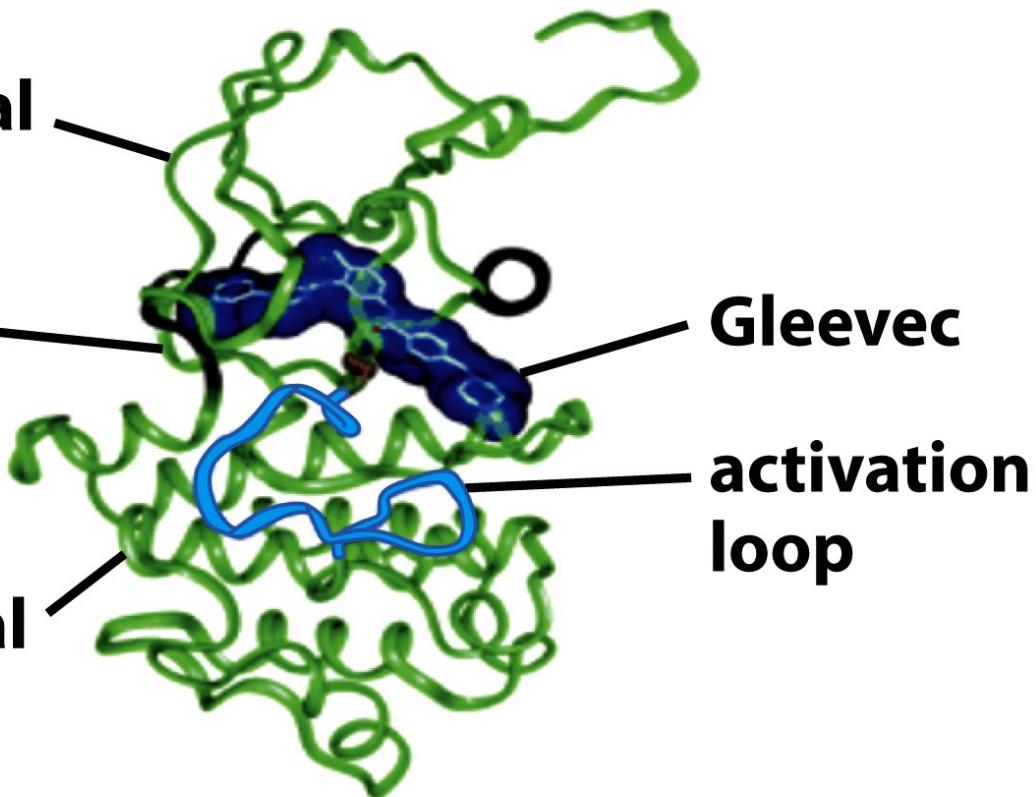
Gleevec®
(imatinib mesylate)

N-terminal lobe
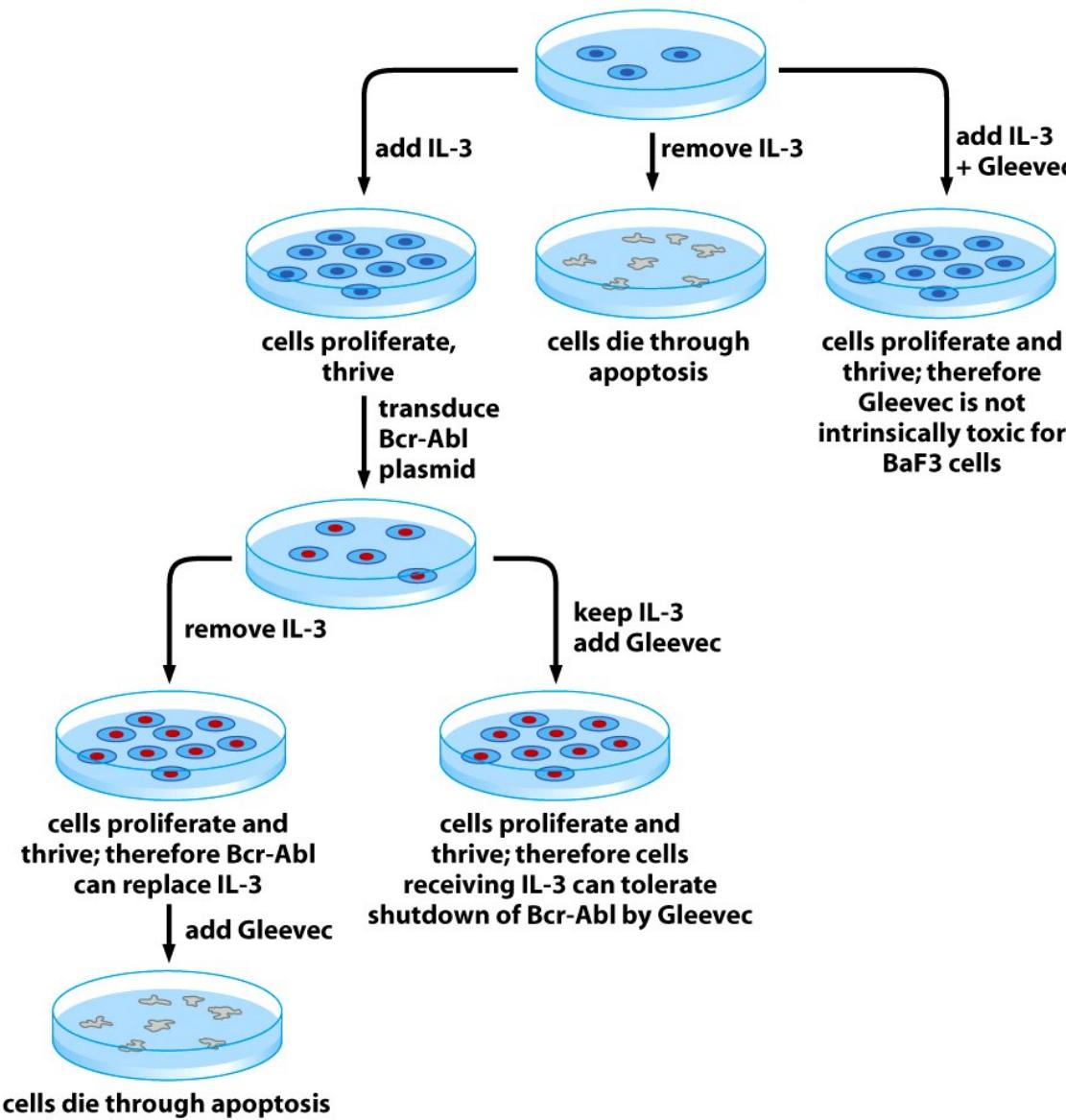
catalytic cleft

C-terminal lobe

Gleevec

activation loop

# Testing of Gleevec in Cell Models
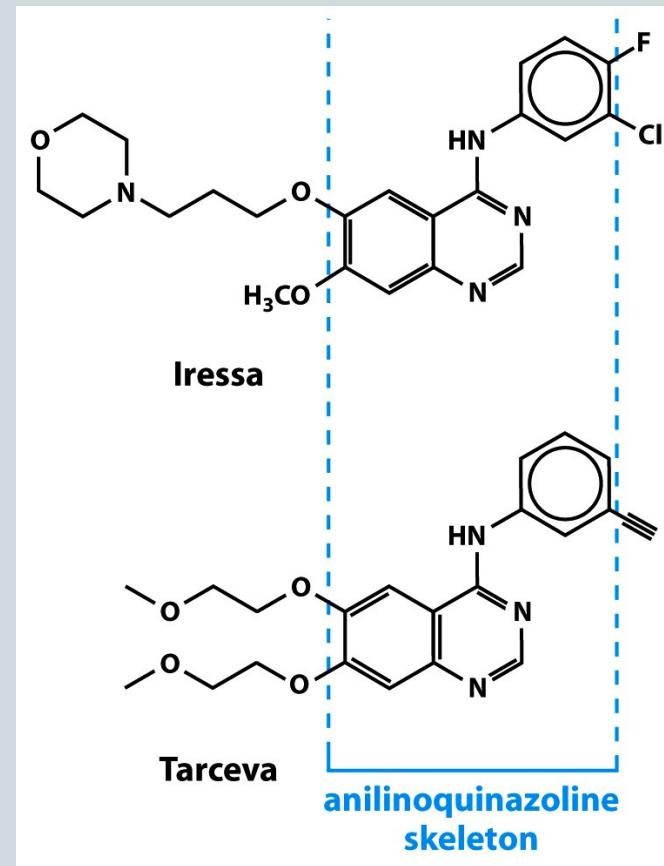
EGF Receptor Antagonists

- Iressa (Gefitinib) and Terceva (Erlotinib) are two famous examples of EGF-R inhibitors
- They are low-molecular weight tyrosine kinase inhibitors


Iressa

Tarceva

anilinoquinazoline skeleton
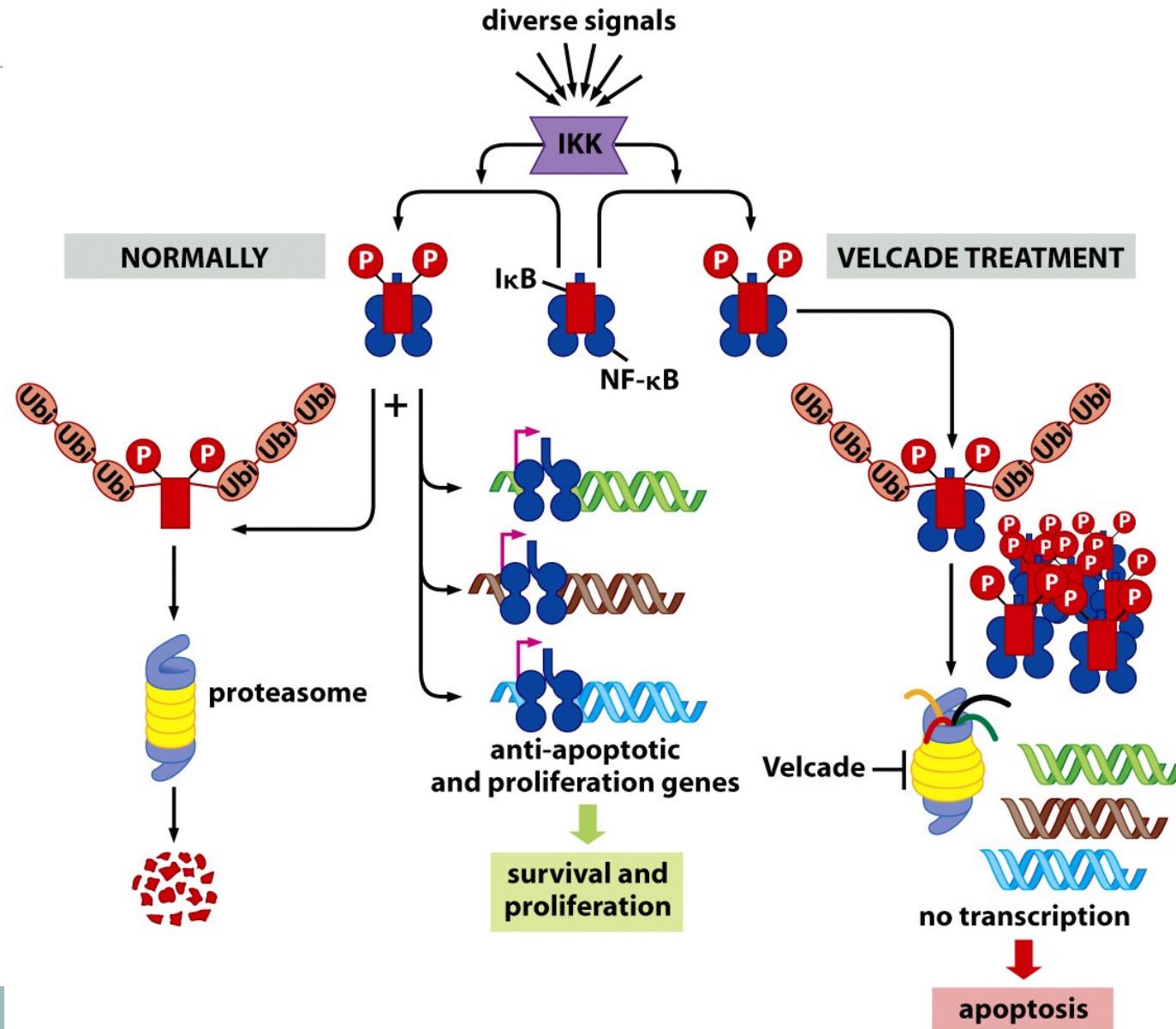
Proteasome Inhibitors

- Use of proteasomal inhibitors as anticancer drugs – a serendipitious discovery
- Originally intended to be a palliative, for **cancer cachexia**
- **Velcade** is an example

Mechamism of Action of Velcade
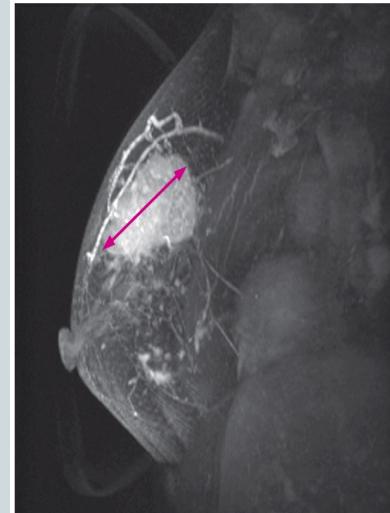
Gene Therapy

- siRNAs
  - Very specific targeting
- microRNA mimics
  - Targeting multiple pathways
- Use of viral vectors
  - Adenoviral vectors
  - Lentiviral vectors

Diagnosis

- An early diagnosis greatly improves the cure / survival rate of anticancer therapy

- Cancer screening and response-monitoring
  - Radiography
    - Mammaography for breast cancer
  - Tumor markers
  - Histopathology
    - The Pap smear for cervical cancer

pre-chemotherapy
longest dimension = 47 mm

post-chemotherapy
longest dimension = 16 mm

Tumor Markers

- Substances found only in cancer tissues or significantly elevated compared to normal tissues
- In blood, urine, stool etc.
- One of the most famous examples is PSA – Prostate Specific Antigen
  - Prostate cancer shows a many-fold increase of serum PSA levels; can be used as a screening test and also to monitor response to therapy
- Other markers
  - Carcino Embryonic Antigen (CEA) – stomach cancer
  - CA125 – Ovarian Cancer