

**PHARMACOLOGY-III**  
**UNIT-IV**  
***TOPIC: TARGET DRUGS TO ANTIGE***



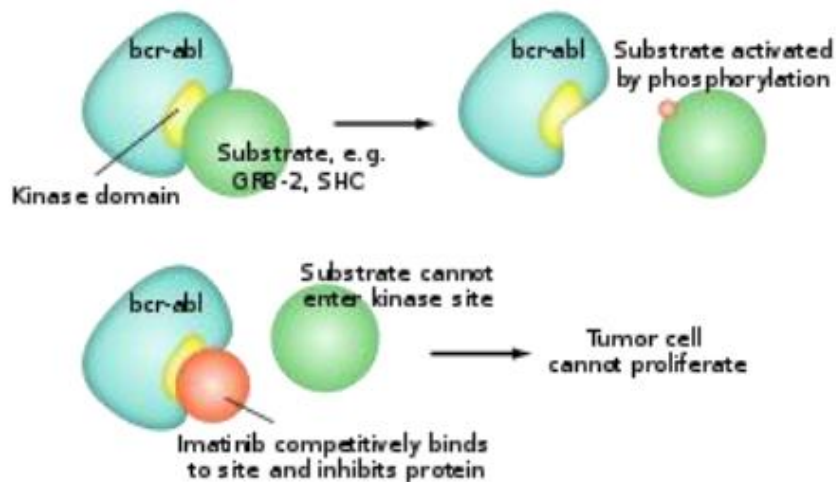
**Centurion**  
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*Shaping Lives...*  
*Empowering Communities...*

**Prepared By**  
**Sucharita Babu**  
**Assistant Professor**  
**School of Pharmacy and Life Sciences,**  
**Centurion University of Technology and Management**

The main categories of targeted therapy are currently small molecules and monoclonal antibodies.

### Small molecules



### Mechanism of imatinib

Many are tyrosine-kinase inhibitors.

**Imatinib (Gleevec, also known as STI-571)** is approved for chronic myelogenous leukemia, gastrointestinal stromal tumor and some other types of cancer. Early clinical trials indicate that imatinib may be effective in treatment of dermatofibrosarcoma protuberans.

**Gefitinib (Iressa, also known as ZD1839)**, targets the epidermal growth factor receptor (EGFR) tyrosine kinase and is approved in the U.S. for non small cell lung cancer.

Erlotinib (marketed as Tarceva). Erlotinib inhibits epidermal growth factor receptor, and works through a similar mechanism as gefitinib. Erlotinib has been shown to increase survival in metastatic non small cell lung cancer when used as second line therapy.

Because of this finding, erlotinib has replaced gefitinib in this setting.

Sorafenib (Nexavar)[13]

Sunitinib (Sutent)

Dasatinib (Sprycel)

Lapatinib (Tykerb)

Nilotinib (Tasigna)

Bortezomib is an apoptosis-inducing proteasome inhibitor drug that causes cancer cells to undergo cell death by interfering with proteins. It is approved in the U.S. to treat multiple myeloma that has not responded to other treatments.

The selective estrogen receptor modulator tamoxifen has been described as the foundation of targeted therapy.

- Janus kinase inhibitors, e.g. FDA approved tofacitinib
- ALK inhibitors, e.g. crizotinib
- Bcl-2 inhibitors (e.g. obatoclax in clinical trials, navitoclax, and gossypol.
- PARP inhibitors (e.g. Iniparib, Olaparib in clinical trials)
- PI3K inhibitors (e.g. perifosine in a phase III trial)
- Apatinib is a selective VEGF Receptor 2 inhibitor which has shown encouraging antitumor activity in a broad range of malignancies in clinical trials. Apatinib is currently in clinical development for metastatic gastric carcinoma, metastatic breast cancer and advanced hepatocellular carcinoma.
- Zoptarelin doxorubicin (AN-152), doxorubicin linked to [D-Lys(6)]- LHRH, Phase II results for ovarian cancer.
- Braf inhibitors (vemurafenib, dabrafenib, LGX818) used to treat metastatic melanoma that harbors BRAF V600E mutation
- MEK inhibitors (trametinib, MEK162) are used in experiments, often in combination with BRAF inhibitors to treat melanoma
- CDK inhibitors, e.g. PD-0332991, LEE011 in clinical trials
- Hsp90 inhibitors, some in clinical trials
- salinomycin has demonstrated potency in killing cancer stem cells in both laboratorycreated and naturally occurring breast tumors in mice.
- VAL-083 (dianhydrogalactitol), a “first-in-class” DNA-targeting agent with a unique bifunctional DNA cross-linking mechanism.
- NCI-sponsored clinical trials have demonstrated clinical activity against a number of different cancers including glioblastoma, ovarian cancer, and lung cancer.
- VAL-083 is currently undergoing Phase 2 and Phase 3 clinical trials as a potential treatment for glioblastoma (GBM) and ovarian cancer. As of July 2017, four different trials of VAL-083 are registered.

### **Small molecule drug conjugates**

Vintafolide is a small molecule drug conjugate consisting of a small molecule targeting the folate receptor. It is currently in clinical trials for platinum-resistant ovarian cancer (PROCEED trial) and a Phase 2b study (TARGET trial) in non-small-cell lung carcinoma (NSCLC).

Serine/threonine kinase inhibitors (small molecules)

- Temsirolimus (Torisel)
- Everolimus (Afinitor)
- Vemurafenib (Zelboraf)
- Trametinib (Mekinist)

□ Dabrafenib (Tafinlar)

### Monoclonal antibodies

Several are in development and a few have been licensed by the FDA and the European

Commission. Examples of licensed monoclonal antibodies include: Pembrolizumab (Keytruda) binds to PD-1 proteins found on T cells. Pembrolizumab blocks PD-1 and help the immune system kill cancer cells.[23] It is used to treat melanoma, hodgkin's lymphoma, non-small cell lung carcinoma and several other types of cancer.

- Rituximab targets CD20 found on B cells. It is used in non Hodgkin lymphoma
- Trastuzumab targets the Her2/neu (also known as ErbB2) receptor expressed in some types of breast cancer
- Alemtuzumab