Innovations in Small Molecule Cancer Therapy

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Drug Discovery

• **Natural Products**: From soil, plants, marine organisms; bioassay-guided fractionation; structure determination (NMR, X-ray); target and mode of action.

• **Hit Modification**: SAR (structure–activity relationships), combinatorial libraries, ADMET (absorption, distribution, metabolism, excretion, transport).

• **Rational Drug Design**: Known receptor, validated target, X-ray of complex, modify to optimize binding.

• **De Novo Design**: Known receptor and active site, computer model (docking studies), synthesis, hit identification, modification.
Preclinical Drug Development

- Target identification and validation, develop protein and cellular assays, animal models.

- High-throughput screening of small molecules (natural products, compounds from other projects).

- Identify hits, optimize lead for potency and ADMET properties.

- Identify candidate, file IND (Investigational New Drug Application), optimize synthesis (pilot scale: 1–10 kg, process scale: 100 kg).

- 5–10 year timeframe.
Clinical Trials

- **Phase I:** Small groups of healthy people (20–25, then 50–75) for safety, safe dosage range, side effects, ADMET in humans. 3–6 months, 70% success rate.

- **Phase II:** Larger groups of patients (20–200, then 50–500), both safety and efficacy evaluated, dosage refined. 6 months–2 years, 35% success rate.

- **Phase III:** Largest group of patients (250–1000), different locations, ethnic groups, ages, Adverse Drug Reactions (ADR) identified, rigorous statistical evaluation. Up to 5 years, 25% success rate.

- **Phase IV:** Post-Marketing Surveillance; conducted after approval is given, collects more data on ADR (Vioxx), can result in larger market for drug (Crestor).

- Once approval is given, average drug has 12 years remaining on patent.

Cell Cycle

- **G₀** (resting)
- daughter cell
- **G₁**
  - cell growth
  - signaling
  - days
- **S**
  - DNA synthesis
  - 1 day
- **G₂**
  - RNA synthesis
  - tubulin
  - 3 hrs
- **M**
  - mitosis
  - microtubule
  - 1 hr

Drugs:
- imatinib
- sunitinib
- cyclophosphamide
- cisplatin
- capecitabine
- bleomycin
- irinotecan
- vinblastine
- taxol
- ixabepilone
Mustard Gas and Cyclophosphamide

Mechlorethamine (Mustargen™)
The first chemotherapeutic agent

Cyclophosphamide (Cytoxan™)
Cisplatin (Platinol™)

DNA crosslink G–G DNA repair inhibited apoptosis

bladder ovarian testicular

K₂PtCl₄ + KI → K₂PtI₄ + NH₃

K₂PtCl₄ + NH₃ → K₂PtCl₃ + NH₄Cl

K₂PtCl₄ + AgNO₃ → 2KCl + PtCl₃ + NH₄NO₃

K₂PtCl₄ + H₂O → PtCl₃ + H₂O + NH₃

K₂PtI₄ + KCl → PtCl₃ + K₂I + NH₃

Carboplatin (Paraplatin™)

BMS, 1989 less toxic also leukemia, lung cancer

Oxaliplatin (Eloxatin™)

water solubility FOLFOX combination (5FU) colorectal cancer
Sanofi-Aventis 1994

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5-Fluorouracil

Pharmacia, 1962
Inhibits thymidylate synthase (dU → dT)
Breast, colon cancer

FdUMP

Presence of F instead of H prevents elimination of S–Enz
Enzyme is covalently modified, depleted
Related Drugs

Capecitabine (Xeloda™)
1998, Hoffmann–La Roche
Prodrug of 5-FU

Cladribine (Leustatin™)
1993, Ortho BioTech
hairy cell leukemia, also MS
- Purine (A) nucleoside analog
- Adenosine deaminase inhibitor
- Metabolized by normal cells
- Few side effects
- Morris J. Robins - BYU
Bleomycin (Blenoxane™)

1973 BMS  Strep. verticillus (Japan) 1962

Hodgkin's lymphoma
head, neck cancer
testicular cancer

DNA cleavage
$O_2 + Cu, Fe$-chelate

Side effects:
lung function
alopecia, ototoxicity

Synthesis, Mode of Action:
Boger *ACIE* 1999, 38, 448
Mode of Action

Scheme 1. Primary mechanisms for DNA cleavage induced by bleomycin A₂.
B = nucleobase, BLM = bleomycin A₂.

From Boger Angew. Chem., Int. Ed. 1999, 38, 448
DNA Binding (Minor Groove)

From Boger Angew. Chem., Int. Ed. 1999, 38, 448
Camptothecin Derivatives

**Camptothecin**

- NCI 1966 Wani, Wall
- Topoisomerase I inhibitor
- DNA unwinding, 1 strand cleaved, religates
- Toxic (cystitis)
- Poor pharmacokinetics
- Low water solubility
- *Camptotheca acuminata*
- China-India

**Irinotecan - (Camptosar™)**

- Yakult Honsha (Japan), Pfizer - 1994 prodrug, colorectal cancer
- Urethane cleaved to 7-Et-10-OH-camptothecin

**Topotecan - (Hycamtin™)**

- GSK 1996 ovarian, lung complex X-ray
- Diarrhea
- Myelosuppression
- Infection
Topotecan Complex X-ray

topoiso merase I

single strand break

HO
NMe₂
HO
DNA
Paclitaxel (Taxol™)

Isolated from the bark of the Pacific yew tree (*Taxus brevifolia*)
Paclitaxel Semisynthesis

10-Deacetylbaccatin
Isolated from the needles of the Himalayan yew tree
(*Taxus baccata*)
Binding of Taxol to Tubulin

From Molecules and Medicine, p. 190
Ixabepilone (Ixempra™)

**Epothilones**

- **Ixabepilone**
  - **Chemical Structure:**
    - A $R = H$
    - B $R = \text{Me}$
  - **Activity:**
    - HCT-116 (colon) 0.32 nM
    - PC-3M (prostate) 0.52 nM
    - MCF7 (adr) 2.9 nM
  - **Properties:**
    - Active against MDR resistant cells
    - Higher water solubility than taxol
    - Less active in vivo (ester hydrolysis)
    - Total synthesis, analogs

- **Origin:**
  - *sorangium cellulosum* 1996
  - Höfle, Merck
  - Myxobacteria 30mg/L

- **Pharmacological Effects:**
  - Microtubule stabilizer and polymerization promotor
    - 0.7 μM
    - Interphase microtubule dynamics 10 nM

**Ixabepilone**

- **Chemical Structure:**
  - BMS 2008
    - 128 nM MCF7(adr)
    - Metastatic breast cancer
    - Enhanced stability
    - Semisynthetic
Semisynthesis

Epothilone B

\[ \text{Pd(PPh}_3\text{)}_4 \, 10 \text{ mol\% NaN}_3, \text{THF-H}_2\text{O} \]

\[ \text{Ph}_3\text{Pd} \]

S-retained (double inversion)

Ixabepilone

\[ \text{DPPA NaHCO}_3 \text{ DMF} \]

Vinca Alkaloids

Vinblastine (R=Me)
Velban™
Eli Lilly 1964
Rose Periwinkle
Madagascar 1950s

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Tubulin Binding α/β interface
Microtubule assembly inhibited
M-phase prevented

ABVD Therapy
adriamycin-bleomycin-vinblastine-dacarbazine
Hodgkin’s lymphoma
non-small cell lung
breast, testicular
vincristine: acute childhood leukemia

Vincristine (R=CHO)
Oncovin™

Vinpocetine

alopecia
GI
myelosuppression
allergic reaction
neuropathy
lung, heart
Kinase Signaling

Signal

ATP → Kinase → ADP

Protein - OH

OFF

Phosphatase

Protein - OPO₄⁻

ON

Ser/Thr: PKC
Tyr: Abl (Bcr-Abl)
Imatinib (Gleevec™)

Novartis, 2001
chronic myelogenous leukemia (CML)
gastrointestinal stromal tumors
selective, negligible side effects

PKC-α Random Screen

2-aminophenyl-4-(3-pyridyl)-pyrimidine
- Non-natural, heterocycles, optimal ADMET
- Screening, rational design
- no stereocenters, simple synthesis

Imatinib

6-methyl
No PKC-α activity

piperidylmethyl benzamide

Selective Bcr-Abl tyrosine kinase inhib. 30 nM
PDGFR, c-Kit
Imatinib–Bcr-Abl Complex

From Molecules and Medicine, p. 195
Sunitinib (Sutent™)

Pfizer (Sugen), 2006

indolone-pyrrole

GIST
Renal cell carcinoma

angiogenesis inhibitor:
PDGF-R
VEGF-R