

# Computational Problems in Cancer Combination Therapy

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# Computational Problems in Drug Combination Therapy

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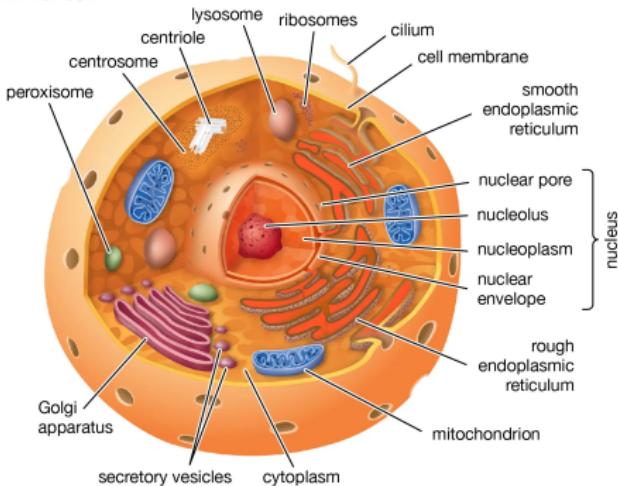
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# Cell: Components

**Cell:** the basic building block of living creatures

Animal cell



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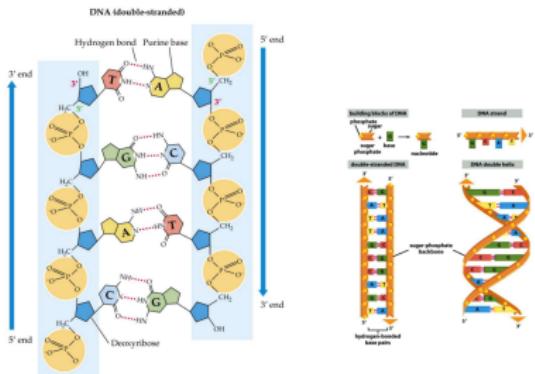
**1 Nucleus:** The structure in a cell containing the chromosomes. The nucleus has a membrane around it, and is where RNA is made from the DNA in the chromosomes

**2 Cell membrane:** Layer separating the inside of the cell from the outside. It regulates transport of materials from inside and outside the cell. It contains receptors that allow drugs to bind to it and provide a path to target the cancerous DNA in the nucleus.

# Genetic Material in a Cell

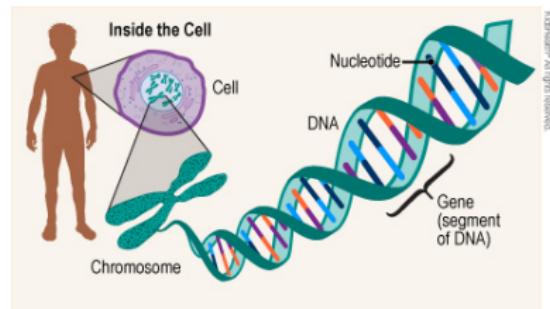
**DNA** is the main genetic material in eukaryotes and can be found in the nucleus and mitochondria

DNA is made up of Adenine, Guanine, Cytosine, Thymine and is double stranded



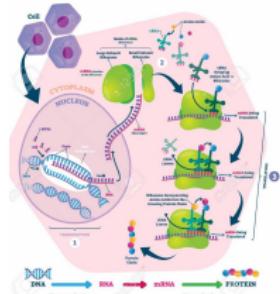
**Genes** on the other hand are basic units of inheritance that are made out of DNA. They are found on the chromosome. There are 2 types of genes:

- 1 Protein encoding Genes
- 2 Non-coding genes

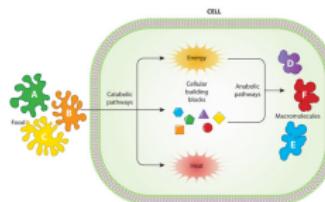


# Functions of a Cell

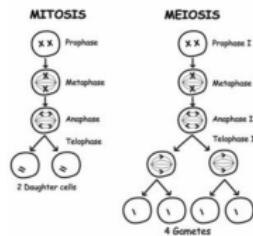
## 1 Protein Synthesis: Creating new proteins.



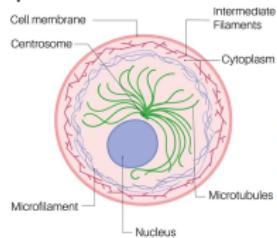
## 3 Metabolism: Break down nutrients for energy in an organism.



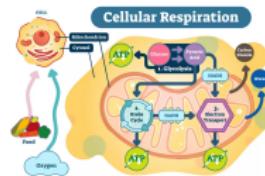
## 5 Reproduction: Cells can multiply by way of mitosis and meiosis.



## 2 Providing structure and support: Through the cytoskeleton of the cell its shape is maintained.



## 4 Energy Production: Produce energy for the cell and hence the host organism.



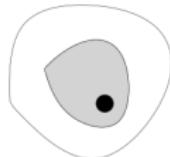
## Normal vs cancer cells

Cancer is a group of diseases characterized by uncontrolled growth (cell proliferation) and spread of abnormal cells

- 1 These cells can invade surrounding tissues and organs, leading to the formation of tumors and the disruption of normal bodily functions
- 2 Cancer can arise from almost any type of cell in the body and can occur in any organ or tissue via a process called metastasis

### Normal Cells

- 1 Small uniform shaped nucleus, and large cytoplasmic volume
- 2 Demarcated cell boundaries
- 3 Proliferate normally



### Cancer Cells

- 1 Large variable shaped nucleus
- 2 Cell boundaries poorly defined
- 3 Over-expressed proto-oncogenes causing uncontrolled cell growth



# Types of Cancer

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## Carcinomas

- Originate in epithelial cells that line surfaces of organs and tissues
- Most common type of cancer, occurs in skin, lungs, breast, prostate, colon
- e.g adenocarcinoma, basal cell carcinoma, squamous cell carcinoma

## Sarcomas

- Originate in connective tissues such as bone, muscle, cartilage, or fat
- e.g osteosarcoma (bone cancer), rhabdomyosarcoma (muscle cancer), and liposarcoma (fat cancer)

## CNS Tumors

- Originate in the brain or spinal cord
- Can be benign or malignant
- e.g. gliomas, meningiomas

## Leukemias

- Cancers of blood-forming tissues, including bone marrow
- It is where abnormal white blood cells proliferate and interfere with normal blood cell production
- Types: acute lymphoblastic leukemia (ALL), acute myeloid leukemia (AML), chronic lymphocytic leukemia (CLL), and chronic myeloid leukemia (CML)

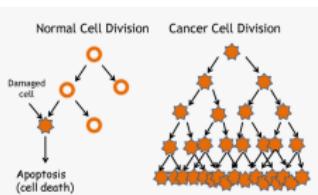
## Lymphomas

- Cancers of the lymphatic system, part of the body's immune system
- e.g Hodgkin and non-Hodgkin lymphoma

# What happens in cancer?

Essentially in Cancer, some genes are mutated, causing abnormal biological activity

**1 Apoptosis:** process of programmed cell death. Used during early development to eliminate unwanted and damaged beyond repair cells. In Cancer Apoptosis is inhibited and damaged cells remain and proliferate

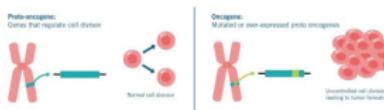


**2 Metastasis:** The cancer cells spread to different body parts from source

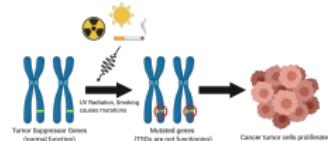


**3 Homeostasis:** A self-regulating process of organisms maintaining stability. In Cancer, these processes are inhibited and cells cannot maintain stability

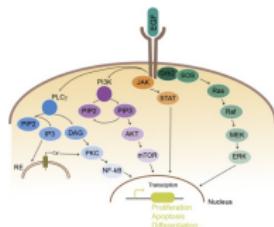
**4 Oncogene Activation:** Oncogenes control cell growth and division. Mutated oncogenes cause uncontrolled growth & tumorigenesis



**5 Tumor Suppressor Inactivation:** Tumor suppressor genes help in inhibiting cell cycle progression, promoting apoptosis, maintaining genomic stability. Their Inactivation contributes to cancer development and inhibition of apoptosis



**6 Dysregulated Growth Factor Signaling:** Growth factors like cytokines influence cell processes. Dysregulation causes cancer. e.g., EGFR leads to hyperactivity of downstream signaling pathways, causing cell proliferation and migration. And IGF-1R which signals cell growth and resistance to apoptosis in cancer cells



# Cancer Cell Lines

- Cancer cells extracted from patients and kept in a laboratory under certain conditions so they can proliferate and maintained for long periods.
- Used in research to study cancer biology and drug development

## Examples of Commonly Used Cell Lines

- NCI-60: Includes leukemia, melanoma, and cancers of the lung, colon, kidney, ovary, breast, prostate, and brain

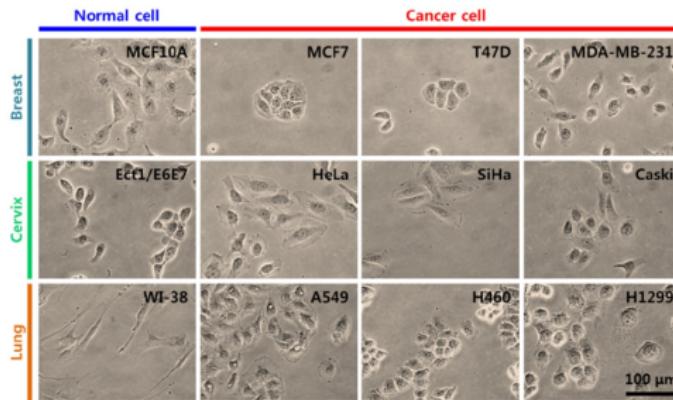


Figure: Example of Cancer Cell lines

# Cancer Signaling Pathways

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Signaling pathways transmit signals from cell surface receptors to internal cellular targets.

- Key roles in regulating cell proliferation, survival, and apoptosis
- Dysregulation in Cancer
  - Oncogene Activation
    - Oncogenes drive uncontrolled cell growth
    - Examples: RAS, MYC, ERBB2 (HER2)
    - Mutations in the KRAS (a type of RAS) gene are common in pancreatic, colorectal, and lung cancers
  - Tumor Suppressor Inactivation
    - Tumor suppressors inhibit cell growth and promote apoptosis
    - Examples: TP53, PTEN, RB1
- Key Pathways
  - PI3K/AKT/mTOR
    - Regulates cell growth, proliferation, and survival
    - Frequently activated in cancers due to mutations in PI3K, AKT, mTOR
    - Commonly observed in breast, prostate, and endometrial cancers
  - MAPK/ERK
    - Controls cell division, differentiation, and apoptosis
    - Activation often occurs through mutations in RAS or BRAF

## Drug Interaction with Cancer Cells

Drug mechanisms involve complex interactions with cancer cells, affecting signaling pathways and cellular processes

### **Target Binding**

- Drugs interact with specific molecular targets on or inside cancer cells.
- Examples include receptors, enzymes, and DNA.

### **Modulation of Biological Pathways**

- Drugs can alter cellular signaling pathways.
- This can inhibit cell proliferation or induce apoptosis.

### **Pharmacokinetics and Pharmacodynamics**

- Pharmacokinetics (PK): How the body absorbs, distributes, metabolizes, and excretes drugs.
- Pharmacodynamics (PD): The effects of the drug on the body, including mechanisms of action.

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## Steps in Drug interaction with Cancer Cells

- 1 Drug Delivery** First the drug is delivered to the tumor site through the bloodstream or directly through injection. Drug delivery systems such as nanoparticles, liposomes, or conjugates may enhance drug stability, solubility, and tumor targeting.
- 2 Cellular Uptake** Drugs should enter the cancer cells through Cellular uptake which is done according to the drug's physiochemical properties. Passive diffusion, facilitated transport, endocytosis, or receptor-mediated uptake may facilitate drug entry into cancer cells.

**3 Target Engagement** When the drug enters the Cancer cell it targets cellular components that are propagating the cancer, such as receptors, enzymes, signalling proteins or nucleic acids. The drug will bind to receptors and can perform many actions such as:

- 1 Allosteric Modulation:** Inhibit or decrease a receptors action on Cancer progression.
- 2 Enzyme Inhibition:** Prevent Enzyme activity.
- 3 Nucleic Acid Interference:** Prevent translation to harmful Proteins.

# Properties of drugs

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Key Properties of Drugs are

- 1 Molecular Weight:** Sum of atomic weights of all atoms in the drug.  
The unit is (g/mol).
- 2 Lipophilicity:** The degree at which a drug dissolves in oil or fats.  
Cell membranes are made of lipids(fats), therefore highly lipophilic drugs can be absorbed by cells easily. It is given by the LogP or the LogD value and it has no units.
- 3 Hydrogen Bonding Capacity:** Hydrogen bonds are important for drug-binding to target. It's unit is KJ/mol.
- 4 Three Dimensional Shape:** Important for drug PK, visualised using molecular modeling software and encoded in Protein Data Bank (PDB) files or molecular graphics formats (e.g., MOL, SDF).
- 5 Affinity:** Strength of interaction between drug molecule and target
- 6 Binding kinetics:** Rate at which drug binds and dissociates from target. Dissociation constant ( $K_d$ ), association rate constant ( $K_{on}$ ), and dissociation rate constant ( $K_{off}$ ) can be used to characterize drug-target interactions.

# Drug Resistance in Cancer

Drug resistance is a major challenge, driven by genetic mutations, alternative pathway activation, and other factors

## Genetic Mutations

- Cell Mutations causes resistance
- e.g., Mutations in the BCR-ABL gene in chronic myeloid leukemia (CML) confer resistance to imatinib

## Activation of Alternative Pathways

- Cancer cells may activate compensatory pathways to survive
- e.g activation of PI3K/AKT pathway when MAPK pathway is inhibited

## Altered Drug Metabolism

- Changes in drug uptake, efflux, or metabolism reduce drug effectiveness
- e.g., Overexpression of drug efflux pumps like P-glycoprotein

## Epigenetic Changes

- Epigenetic modifications can affect gene expression and drug response
- e.g., DNA methylation changes that silence tumor suppressor genes

## Tumor Heterogeneity

- Different cell populations within a tumor respond differently to therapy
- e.g., Subclonal populations with different mutations

## Immune Evasion Mechanisms

- Cancer cells can evade immune detection and destruction
- e.g., Upregulation of PD-L1 to inhibit T-cell mediated killing

## Drug Repurposing

Using existing drugs, originally developed for other diseases, for cancer treatment

### Benefits

- Shorter development time and lower costs
- Known safety profiles

### Examples

- Metformin (diabetes drug) for various cancers
- Thalidomide (originally developed as a sedative) for multiple myeloma

## Targeted Therapies

Drugs designed to specifically target molecular pathways involved in cancer growth and progression

### Mechanisms of Action

- Inhibition of tyrosine kinases (e.g., imatinib targeting BCR-ABL)
- Blocking hormone receptors (e.g., tamoxifen targeting estrogen receptors)

### Advantages

- Increased specificity for cancer cells
- Reduced side effects compared to conventional chemotherapy

# Strategies to Combat Cancer

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## Immunotherapy

Treatments that harness the body's immune system to fight cancer

### Types

- Checkpoint inhibitors (e.g., pembrolizumab targeting PD-1)
- CAR-T cell therapy (e.g., Kymriah for certain leukemias)

### Benefits

- Potential for long-term remission.
- Effective in cancers resistant to other treatments

## Adaptive Therapy

A strategy that adjusts treatment based on the evolutionary dynamics of the tumor

### Principles

- Maintaining a stable population of drug-sensitive cancer cells to suppress the growth of resistant cells
- Reducing the intensity of treatment to delay resistance

### Examples

- Adaptive dosing of vemurafenib in melanoma to manage resistance

# Strategies to Combat Cancer

## Personalized Medicine

Tailoring treatment plans based on the individual genetic and molecular profile of the patient's tumor

## Techniques

- Genomic sequencing to identify actionable mutations
- Biomarker testing to guide therapy choices

## Benefits

- Increased treatment efficacy
- Reduced risk of adverse effects

## ■ Overcoming Drug Efflux

- Inhibitors of efflux pumps (e.g., verapamil)

## ■ Combination of Chemo- and Radiotherapy

- Synergistic effects enhance treatment efficacy

## ■ Overcoming DNA Repair Mechanisms

- PARP inhibitors for BRCA-mutated cancers

## ■ Disrupting the Tumor Microenvironment

- Targeting angiogenesis (e.g., bevacizumab)

## Combination Therapy

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- Use of two or more drugs to achieve a therapeutic effect that is greater than the sum of individual effects
- Also known as polytherapy or multi-drug therapy

### Benefits

- Increases efficacy by targeting multiple pathways
- Reduces the likelihood of resistance developing.
- Allows for lower doses of individual drugs, reducing toxicity

### Examples of Successful Combinations

- Trastuzumab and paclitaxel in HER2-positive breast cancer
- Imatinib and chemotherapy in Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL)

# Synergistic Effects in Combination Therapy

**Synergy:** The interaction of drugs resulting in a combined effect that is greater than the sum of individual effects

## Synergy Models

- **Bliss Independence**
  - Assumes drugs act independently
  - Combined effect calculated as:  $E_{AB} = E_A + E_B - E_A \cdot E_B$
- **Loewe Additivity**
  - Assumes drugs with similar mechanisms
  - Combined effect based on dose-response curves
- **Chou-Talalay Method**
  - Quantitative analysis using combination index ( $CI$ )
  - $CI < 1$  indicates synergy,  $CI = 1$  indicates additivity,  $CI > 1$  indicates antagonism
- **Highest Single Agent:**
  - Assumes combined effect superior to single drug's effect
  - Combined effect calculated as  $S_{HSA} = E_{A,B,\dots,N} - \max(E_A, E_B, \dots, E_N)$ ,  
 $E_{A,B,\dots,N}$  is combined effect between  $N$  drugs &  $E_A, E_B, \dots, E_N$  are the measured responses of the single drugs

# Combination Therapy: Successful Examples

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## ■ Trastuzumab and Paclitaxel

- Used for HER2-positive breast cancer
- Trastuzumab targets HER2 receptor, Paclitaxel disrupts microtubule function

## ■ Imatinib and Chemotherapy

- Used for Philadelphia chromosome-positive acute lymphoblastic leukemia (ALL)
- Imatinib inhibits BCR-ABL tyrosine kinase, chemotherapy kills rapidly dividing cells

## ■ BRAF and MEK Inhibitors

- Used for BRAF-mutant melanoma
- Combined targeting of BRAF and MEK pathways reduces tumor growth and resistance

### Genomic Data: DNA Sequencing

- **Whole Genome Sequencing (WGS)**: WGS translates all of the 3 billion DNA base pairs that make up an entire genome into a file made up of base letters.
- **Whole Exome Sequencing (WES)**: WES translates only the protein-coding base pairs of the genome into a file made up of base letters. Gives insights into potential driver mutations and cancer pathways.
- Both methods Identify mutations, copy number variations, and structural variations
- This data is typically represented as variant call format (VCF) files or mutation annotation format (MAF) files

# Cancer Data Types: Genomic Data: RNA Sequencing

## Genomic Data: RNA Sequencing

- Transcriptome analysis to measure gene expression levels
- Identifies differentially expressed genes and alternative splicing events
- These data provide insights into dysregulated gene expression patterns and molecular subtypes of cancer.
- Represented as raw read counts, normalized expression values (e.g., fragments per kilobase of transcript per million mapped reads, FPKM), or transcripts per million (TPM) values.

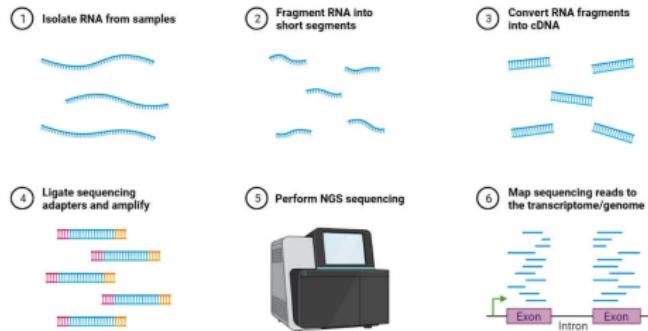


Figure: Process of RNA sequencing

### Epigenomic Data: DNA Methylation

- Methylation is a natural biological process that changes activity of DNA segment. Such data profiles can be obtained.
- Methylation patterns affect gene expression without altering the DNA sequence
- Analyzed using bisulfite sequencing
- Represented as  $\beta$  values that shows proportion of methylated cytosines at a particular location in a genome.
- They can be used to identify cancer-subtype, and possible targeted locations for treatment.

### Epigenomic Data: Histone Modification

- Many kinds of histone modifications cause tumor development.
- Histone proteins undergo post-translational modifications
- Analyzed using chromatin immunoprecipitation sequencing (ChIP-seq)
- ChIP-seq detects locations of histone-modification.
- This data can be found on Chip-Atlas aswell.

## Cancer Data Types: Proteomic Data

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### Proteomic Data: Protein Expression Data

- Give information of complete set of proteins expressed by humans at given time.
- Protein expression levels and post-translational modifications
- Techniques: Mass spectrometry (MS), Western blotting, and ELISA
- Represented in many forms, one being (pg/mL): concentration of target protein in sample.

### Clinical Data

- Patient demographics, medical history, treatment details, and outcomes
- Essential for correlating molecular data with clinical outcomes
- These data provide contextual information for interpreting molecular findings and evaluating treatment responses.
- Also contain survival data, including overall survival (OS) or disease-free survival (DFS) information, which allows for survival analysis and prognostic assessments.

## Cancer Data Types: Pathological Data

### Pathological Data

- Tissue samples, histological images, and pathology reports
- Pathological annotations help validate molecular findings

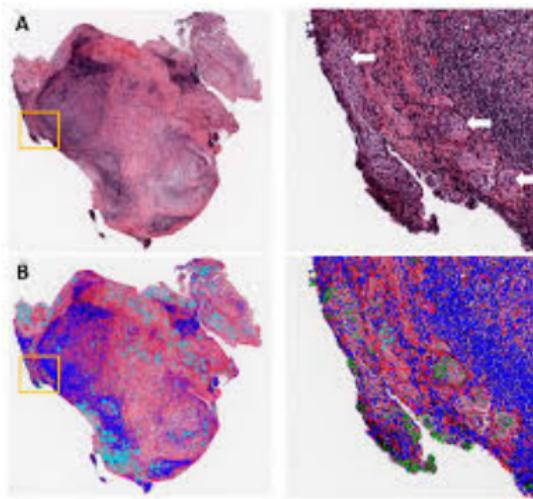


Figure: Lung Cancer Tissue Sample pathological data

# Data Sources for Cancer Research



The Cancer Genome  
Atlas (TCGA)



PubChem



DrugComb

## ■ The Cancer Genome Atlas (TCGA)

- Comprehensive molecular profiles of over 33 cancer types.
- Data available: Genomic, epigenomic, transcriptomic, and proteomic.
- Data types include: Aligned Reads, Allele-specific Copy Number Segment, Copy Number Segment, Gene Level Copy Number, Isoform Expression Quantification, and Masked Copy Number Segment.
- Data is available in JSON and TSV.
- There are a total of 265,021 files. Size of these files is 28.89TB.

## ■ PubChem

- Data available: Chemical information of drugs, BioAssays, Proteins, Genes, Pathways, and Cell lines.
- Data is available in JSON, XML, ASNT, and PNG.

## ■ DrugBank

- Information is given in section [Drug Data: Pharmacokinetic and Pharmacodynamic Data](#).

## ■ DrugComb

- Information is given in section [Cancer-Drug Interaction Data Sources](#).

# Drug Data: Chemical Structure Data

## Chemical Structure Data

- **Simplified Molecular Input Line Entry System (SMILES):**

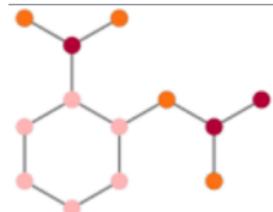
Textual representation of chemical structures using simplified notation. For example aspirin is represented as "CC(=O)OC1=CC=CC=C1C(=O)O"

- **International Chemical Identifier (InChI):** InChI

provide unique identifier for chemical compounds. They encode structural information like connectivity of atoms, stereochemistry, and tautomeric forms. For example, the InChI for aspirin is "InChI=1S/C9H8O4/c1-6(10)13-8-5-3-2-4-7(8)9(11)12/h2-5H,1H3,(H,11,12)".

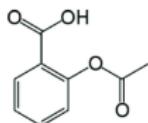
- **Molecular Graphs:** Molecular graphs represent chemical structures as graphs, where atoms are represented as nodes and bonds as edges. Molecular graphs can be represented in various formats, including

adjacency matrices, edge lists, or graph data structures.



- **Molecular Fingerprints:**

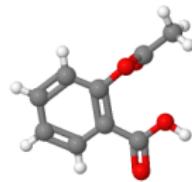
Binary/Numerical representation of Chemical structures. This is used for similarity searching and molecular characterization.



Aspirin Structure

Bit Position	Bit Substructure
0	$\geq 4$ H
1	$\geq 8$ H
2	$\geq 16$ H
3	$\geq 32$ H
4	$\geq 1$ Li
5	$\geq 2$ Li
6	$\geq 1$ B
7	$\geq 2$ B
8	$\geq 4$ B
...	...

Pubchem Molecular Fingerprint



### Pharmacokinetic and Pharmacodynamic Data

- **DrugBank:** Contains drug target information including structures, mechanisms, pharmacology, interactions, pathways, drug side-effects of approximately 16,558 drugs and 19,535 targets.
- It is a general Database so it is not specialised for Cancer Combination Therapy prediction however it contains data of individual drugs and targets.
- Structured in relational databases or XML files.
- Also contains detailed info on drug chemical structures, molecular weights, and systematic names.
- Data on drug pharmacokinetics (PK) and pharmacodynamics (PD), such as absorption, distribution, metabolism, excretion, and mechanism of action, are provided. Information about approved indications for each drug, including their use in cancer treatment, is available.
- Individual drug-target information is also detailed: proteins, enzymes, receptors, and nucleic acids, with which drugs interact.
- Also contains drug-target information such as binding affinities, binding sites, and modes of action. And drug-drug interactions, including synergistic, additive, or antagonistic effects when drugs are co-administered.

### DrugComb

- Database of drug combinations and their effects on cancer cells
- Provides synergy scores, response values and combination indices
- Contains over 400,000 drug combinations, covering 2800 drugs and 120 cancer cell lines.
- Displays Common top 5 target proteins in Drug Combination Section.
- Also gives molecular weight, chemical structure, SMILES and external links to STITCH and PubChem databases.
- The full common target proteins of the drug combinations, together with the confidence scores will be shown in tabular viewer at the bottom of the page
- Data is a relational database. Typically formatted as  $\langle DrugA, DrugB, Cellline, CSS/RI \text{ (A drug combination sensitivity score)}, S, Zip, Bliss, Loewe, HSA \text{ synergy scores} \rangle$
- Multiple sensitivity and synergy graphs of the drugs are available as well. Monotherapy curves for each drug in the drug-pair are also given.

### AstraZeneca-Sanger Drug Combination Dataset

- High-throughput screening data of drug combinations
- Includes response data for multiple cancer cell lines
- Contains 11576 experimentally tested drug combinations measuring cell viability over 118 drugs and 85 cancer cell lines.

### Kyoto Encyclopedia of Genes and Genomes (KEGG)

- Provides information on pathways, drugs, and diseases
- Useful for interpreting the impact of drug combinations on signaling pathways
- Provides Metabolic, Signaling, and disease Pathways and associated genes and molecules.
- Signaling pathway data are graphical diagrams (e.g. PNG, SVG)
- Machine readable data-files also available for analysis (e.g. KGML, KGML+XML)

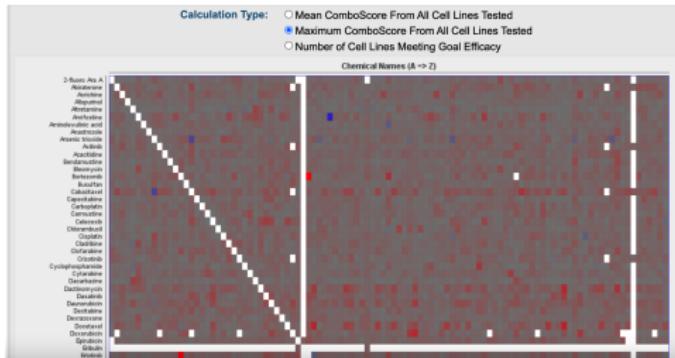
### **CancerRxGene or Cancer Therapeutics Response Portal (CTRP)**

- Drug response data for various cancer cell lines
- Includes information on cell viability and growth inhibition
- Provides information on the sensitivity of cancer cell lines to various anticancer drugs.
- Drug response profiles and genomic features of cancer cell lines.
- Drug response Profiles expressed as IC<sub>50</sub> values, Drug Efficacy profiles like dose-response curves, and Drug classification.
- Cancer Cell Line Data A total of 24 unique cancer target pathways are available which were tested against 621 compounds.
- The data of a total of 701 drugs is present in CTRP with its target signaling pathway.
- Data Format: Tabular/Relational DB

# Cancer-Drug Interaction Data Sources

## NCI-ALMANAC

- It is a database of Drug combination screening data
- Data of Drug combinations against various cells is available as heat maps of "ComboScores" of the drug-pair against the targets.
- Tested against 60 human tumor cell lines.
- It contains over 5000 drug combinations, covering 104 drugs and 60 cell lines. It also provides growth inhibition data and synergy scores for each combination.
- Focuses on the efficacy of drug pairs in cancer treatment



**Figure:** Heatmap of Max "Comboscore" of all chemicals in the NCI-ALMANAC database

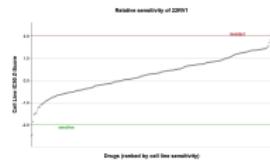
## Cancer-Drug Interaction Data Sources

## Genomics of Drug Sensitivity in Cancer (GDSC)

- Comprehensive resource for drug sensitivity and resistance data
  - Includes information on molecular markers of drug response
  - Tested for over 1000 cancer cell lines, covering over 250 drugs.
  - Also provides genomic, transcriptomic, and epigenetic data for each cell line and tools and resources to explore the data.

Asset	Serial Number	Description	Value	Location	Financial Type	Owner/Department
Laptop	DE00000001	DE00000001	1000	Office	Computer	HR
Laptop	DE00000002	DE00000002	1000	Office	Computer	HR
Laptop	DE00000003	DE00000003	1000	Office	Computer	HR
Laptop	DE00000004	DE00000004	1000	Office	Computer	HR
Laptop	DE00000005	DE00000005	1000	Office	Computer	HR
Laptop	DE00000006	DE00000006	1000	Office	Computer	HR
Laptop	DE00000007	DE00000007	1000	Office	Computer	HR
Laptop	DE00000008	DE00000008	1000	Office	Computer	HR
Laptop	DE00000009	DE00000009	1000	Office	Computer	HR
Laptop	DE00000010	DE00000010	1000	Office	Computer	HR

## Figure: GDSC cell line table



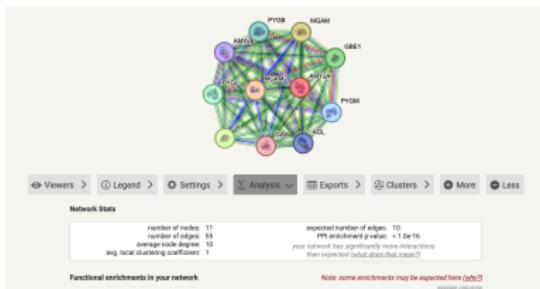
## Figure: GDSC sensitivity curve

## Figure: Drug ranks on cell lines

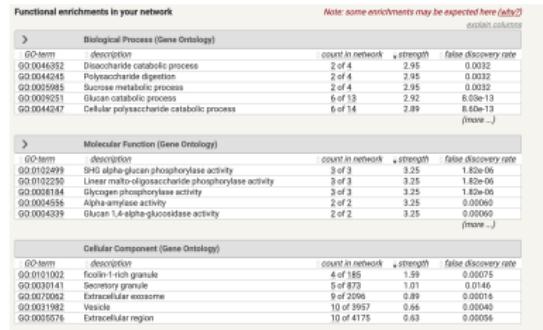
# Cancer-Drug Interaction Data Sources

## Search Tool for the Retrieval of Interacting Genes/Proteins (STRING)

- Database of known and predicted protein-protein interactions
  - Useful for understanding the impact of drug combinations on protein networks
  - Contains information on 9.6 million proteins.
  - Protein-Proteins links determined by many ways such as Co-expression and Neighborhood in the genome.
  - Data can be accessed in Tabular form, XML, or images.



**Figure:** Protein interaction network of Amylase with other proteins



## Figure: Example of Protein Analysis Details provided by STRING

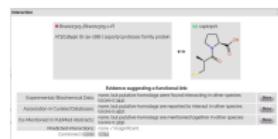
## Cancer-Drug Interaction Data Sources

# STITCH

- The database is very similar to STRING, but provides chemical interactions of proteins with small molecule
  - Provides insights into the molecular mechanisms of drug actions
  - It contains known and predicted interactions between chemicals and proteins based on text mining, experiments, databases, and prediction methods.
  - Covers 500,000 chemicals and 3.6 million proteins
  - Data also available in table format, XML, and images.



## Figure: STITCH example of chemical network



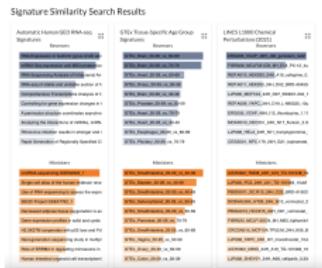
**Figure:** Example of Edge information (interaction)

## Figure: STITCH Tabular data example

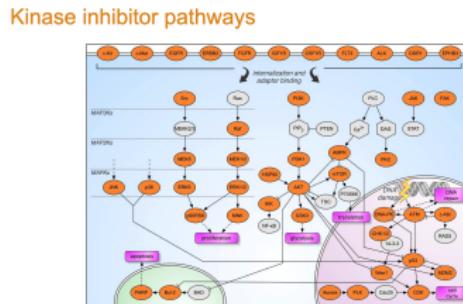
# Cancer-Drug Interaction Data Sources

LINCS

- Library of Integrated Network-Based Cellular Signatures
  - It is a collection of tools and data on cellular responses to various perturbations, including drugs
  - Contains tools like a Drug-Pathway browser tool to study various drug pathways, and tools that generate and analyze large-scale gene expression and drug response data to understand the effects of perturbations on cellular systems.



**Figure:** Sigcom LINCS: searches gene expression patterns for similar and reverse genes.



## Figure: LINCS pathway analyser tool

## ■ Pathway Analysis

- Identification of key signaling pathways involved in cancer
- Tools: KEGG, Reactome, Ingenuity Pathway Analysis (IPA)

## ■ Network Modeling

- Construction of interaction networks to understand molecular mechanisms via tools such as PathFX
- Types: Protein-Protein Interaction Networks (PPINs), Gene Regulatory Networks (GRNs), Metabolic Networks

## ■ Protein-Protein Interaction Networks (PPINs)

- Analyze interactions between proteins to identify potential drug targets.
- Tools: STRING, BioGRID

## ■ Gene Regulatory Networks (GRNs)

- Study regulatory relationships between genes.
- Tools: ARACNE, GENIE3

## ■ Metabolic Networks

- Explore metabolic pathways and their alterations in cancer.
- Tools: COBRA, MetExplore

## ■ Data Integration

- Integrating diverse data types: genomic, proteomic, clinical, and drug data
- Utilizing public databases: TCGA, ICGC, DrugBank, etc

## ■ Personalized Combination Therapy Selection

- Tailoring drug combinations based on patient-specific molecular profiles.
- Approaches: Precision Medicine, Personalized Oncology.

## ■ Drug Sensitivity Prediction and Biomarker Identification

- Predicting drug response using molecular data.
- Tools: Elastic Net, LASSO.

## ■ Optimization of Treatment Regimens and Dosing Schedules

- Developing optimal dosing strategies to maximize efficacy and minimize toxicity.
- Approaches: Evolutionary Algorithms, Reinforcement Learning.

## Predictive Modeling

- Build models to predict drug interactions and outcomes
- Leveraging historical clinical data and experimental results

### 1 Feature Extraction

- Using molecular features of drugs and genomic features of cancer cells
- Techniques: Graph-based features, molecular fingerprints

### 2 Model Training

- Training models on known drug combinations and their synergy scores
- Algorithms: Gradient Boosting, Deep Learning (e.g., Convolutional Neural Networks)

### 3 Model Validation

- Cross-validation and independent test sets to assess model performance
- Metrics: Precision, Recall, F1-score, Area Under the Curve (AUC)

Problem: don't provide interpretable outputs

## ■ **Pharmacokinetic (PK) Modeling**

- Describes how drugs are absorbed, distributed, metabolized, and excreted
- Tools: NONMEM, Simcyp

## ■ **Pharmacodynamic (PD) Modeling**

- Describes the effects of drugs on the body
- Models: Emax Model, Sigmoid Emax Model

## ■ **Synergy Scoring Algorithms**

- Quantitative measures of drug combination efficacy
- Methods: Bliss Independence, Loewe Additivity, Highest Single Agent (HSA), Chou-Talalay Method

## ■ Integrative Modeling

- Combining multiple types of data to build comprehensive models of cancer biology
- Tools: Cytoscape, NetworkX.

## ■ Systems Biology Approaches

- Studying the complex interactions within biological systems
- Approaches: Omics Integration, Dynamic Modeling

# Computational Methods in Cancer Combination Therapy

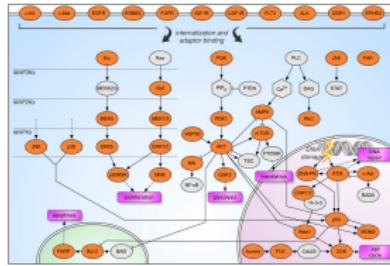
Method	Description	Examples/Tools
Network-Based Approaches	Construct and analyze networks to understand interactions	Cytoscape, STRING, PathFX, NetworkX
Machine Learning	Supervised and unsupervised learning to predict drug responses	Random Forest, SVM, Deep Learning
Pharmacokinetic Modeling	Modeling drug absorption, distribution, metabolism, and excretion	NONMEM, Simcyp
Pharmacodynamic Modeling	Modeling drug effects on the body	Emax Model, Sigmoid Emax Model
Synergy Scoring Algorithms	Quantifying efficacy of drug combinations	Bliss Independence, Loewe Additivity, Chou-Talalay
Systems Biology Approaches	Integrative modeling of biological systems	Cytoscape, Omics Integration

Table: Summary of Computational Methods in Cancer Combination Therapy

## Future Research Directions



**Figure: Sigcom LINCS:** searches gene expression patterns for similar and reverse genes.



One component of the HMS LINCS initiative is the creation of a highly curated library of kinase inhibitors. We are focusing on clinical compounds (FDA approved or undergoing trials) and tool compounds which are highly selective for important kinases.

## Figure: LINCS pathway analyser tool