Functional and clinical proteomics in the era of precision medicine

Michalis Aivaliotis
Important Definitions

Biomedical research

• The area of science devoted to the study of:
  - the processes of life
  - the prevention and treatment of disease
  - the genetic, lifestyle and environmental factors related to disease and health
Important Definitions

Basic research

• Research conducted to increase fundamental knowledge and understanding of the physical, chemical and functional mechanisms of life processes and disease
• Not necessarily directed toward solving any particular problem in humans or animals

3. Provides the foundations of other types of research (e.g. applied, clinical, translational)
If we don’t know how a life process functions normally, we won’t know how to recognize and treat it when it functions abnormally.
Precision Medicine
Personalized Medicine
From **Basic Research** to Precise Personalized Medicine and Improved Health

[Image of a diagram showing the process of translation from basic research to clinical research and improved health]

- **BASIC RESEARCH**
- **CLINICAL RESEARCH**
- **IMPROVED HEALTH**

**Translation**
- From basic science to human studies
- Of new knowledge into clinical practice

[Link to the original source: https://www.sydneyvital.org.au/our-research/translational-research-diagram/]
From Basic Research to Precise Personalized Medicine and Improved Health

Model System
- Basic Science
  - Hypothesis-Driven Targets
  - Hypothesis-Generating Targets (e.g., Genomics)

Basic Human Clinical Research
- Epidemiology
- Imaging
- Genetics
- Pathology

Drug/Treatment Development and Clinical Trials
- Costs
- Complexity
- Phenocopy

Full Clinical Implementation
- Costs
- Toxicity
- Response Heterogeneity
- Disease Aversion
- Lack of Information

Basic to Translational
- Systems Biology
- Cross-Species Validation
- Bioinformatics
- Repositioning
- Innovation

Translational to Clinical
- Education
- Information Technology
- Personalized Medicine
- Cost Management

https://www.arcr.niaaa.nih.gov/arcr371/article01.htm
From Basic Research to Precise Personalized Medicine and Improved Health

From **Basic Research** to Precise Personalized Medicine and Improved Health

![Diagram showing the process from basic research to patient bedside care](https://surgery.duke.edu/research/shared-resources/substrate-services-core-research-support)
The era of ‒omics and Systems Biology ‒The New Biology
The era of -omics and **Systems Biology** -The New Biology
The era of –omics and Systems Biology - The New Biology

Collection and integration of multi–omics date

The era of *-omics* and **Systems Biology** - The New Biology

<table>
<thead>
<tr>
<th>Competency</th>
<th>Relevance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genomics</td>
<td>Studies of genomes and functional and regulatory elements</td>
</tr>
<tr>
<td>Genetic variation</td>
<td>Studies of genome variations</td>
</tr>
<tr>
<td>Epigenomics</td>
<td>Studies of hereditary marks in chromatin (histones, DNA)</td>
</tr>
<tr>
<td>Transcriptomics</td>
<td>Studies of transcripts, including noncoding RNA and micro RNA</td>
</tr>
<tr>
<td>Proteomics</td>
<td>Studies of proteins, including their structure</td>
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<tr>
<td>Metabolomics</td>
<td>Studies of metabolites in cells, tissues, and body fluids</td>
</tr>
<tr>
<td>Systems biology</td>
<td>Holistic analysis of the cellular biochemical interaction networks</td>
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</tbody>
</table>
Biological Interaction Networks
The era of –omics and Systems Biology - The New Biology

• Integrative systems biology
  Extracting biological knowledge from the -omics through integration

• Predictive systems biology
  Predicting future of biosystem using ‘omics knowledge, e.g. in-silico biosystems

Functional Omics

Biological System/Pathway/Process/Condition

Directly relevant sub-ome
- genes
- DNA methylation
- transcripts
- proteins
- metabolites
Functional Omics

Health/Disease/Pathobiology/Mechanisms
(Humans, animals, microorganisms, viruses)

Directly relevant sub-ome

- genes
- DNA methylation
- transcripts
- proteins
- metabolites
Biomolecule changes in:

- Abundance
- Localization
- Modification
- Structure (primary, quaternary)
- Interaction (binary, complexes)
Functional stimulation, perturbation, comparison

Metabolic state
Drug
Culture conditions
Stress
Gene KOs
Proteome
Interactions
Temperature

Genome
Cell specific gene expression

Functional Hypothesis
Experimental Confirmation
Data Validation

Monitor proteome changes
Affected sub-proteome
Comparative Proteomics – Healthy vs Disease

Healthy

Disease

Monitor proteome changes

Affected sub-proteome

Experimental Confirmation

Functional Hypothesis

Data Validation
Comparative Proteomics: Disease 1 – Disease 2

Monitor proteome changes

AFFECTED SUB-PROTEOME

FUNCTIONAL HYPOTHESIS

DATA VALIDATION

EXPERIMENTAL CONFIRMATION
Comparative Proteomics: Disease (sub) stages

Monitor proteome changes

Affected sub-proteome

Experimental Confirmation

Functional Hypothesis

Data Validation

Early stage (Mild)

Late stage (Aggressive)

Nucleus
Comparative Proteomics – Diet/Nutrition/drug effect

Monitor proteome changes

Before

After

Nucleus

Experimental Confirmation

Functional Hypothesis

Data Validation

Affected sub-proteome

Monitor proteome changes
What is the proteome?

- **Genome:** 20,000 genes, static (?)
- **Transcriptome:** > 40,000 mRNAs, dynamic (other RNAs)
- **Proteome:** > 47,000 proteins, highly dynamic

Proteome variability: genomic variations, gene expression, alternative splicing, protein cleavage, modifications
Why perform proteomics?

*Same genome, different proteome*

**DNA**
- tells what possibly,

**mRNA**
- what probably and

**Proteins**
- what actually happens.
Proteins are flexible multi-tools

The MVPs of cell

- **Binding**
- **Catalysis**
- **Switch** (regulation)
- **Structure**
Protein Maturation/Regulation/Function

Primary and Secondary

Tertiary

Modifications

Localization

Quaternary (Protein Complex)

Interactions / Regulation/Death
Protein Modification

- Genome (~20-25,000 genes)
  - Alternative promoters
  - Alternative splicing
  - mRNA editing

- Transcriptome (~100,000 transcripts)
  - Post-translational modifications

- Proteome (>1,000,000 proteins)

https://www.thermofisher.com
Protein Modification ~ 200 known PTMs

- Hydroxylation: Attaches a hydroxyl group (-OH) to a side chain of a protein
- Phosphorylation: Adds a phosphate to serine, threonine or tyrosine
- Methylation: Adds a methyl group, usually at lysine or arginine residues
- Glycosylation: Attaches a sugar, usually to an "N" or "O" in an amino acid side chain
- Lipidation: Attaches a lipid, such as a fatty acid, to a protein chain
- Ubiquitination: Adds ubiquitin to lysine residue of a target protein for degradation
- Acetylation: Adds an acetyl group to an N-terminus of a protein or at lysine residues
- SUMOylation: Adds a small protein SUMO (small ubiquitin-like modifier) to a target protein
- Disulfide Bond: Covalently links the "S" atoms of two different cysteine residues
Protein Complex

≥2 polypeptide chains

Non-covalent interactions
- Hydrogen bonds
- Electrostatic
- Hydrophobic
- Van der Waals
Protein Complex

- Highly dynamic
- Size
- Shape
- Interacting partners
- Localization
- Stability
- Abundance
- Properties
gene -- m-RNA -- protein -- amount -- modifications -- localization -- interactions -- function
gene  -- m-RNA   -- protein – amount -- modifications  -- localization -- interactions --function
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Classical biochemistry

gene -- m-RNA -- protein -- amount -- modifications -- localization -- interactions -- function

Classical biochemistry
gene -- m-RNA -- protein -- amount -- modifications -- localization -- interactions -- function
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classical biochemistry
Classical biochemistry

gene -- m-RNA -- protein – amount -- modifications -- localization -- interactions --function

Classical biochemistry

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Classical biochemistry
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gene -- m-RNA -- protein -- amount -- modifications -- localization -- interactions -- function
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Omics - strategies
Transcriptomics

Gene --- m-RNA --- protein --- amount --- modifications --- localization --- interactions --- function

Omics - strategies
Proteomics

基因 -- m-RNA -- 蛋白 -- 数量 -- 改变 -- 定位 -- 交互 -- 功能

Omics - strategies
Omics - strategies

gene -- m-RNA -- protein – amount -- modifications -- localization -- interactions -- function

Prolteomics

bioinformatics

Omics - strategies
gene -- m-RNA -- protein – amount -- modifications -- localization -- interactions -- function

Proteomics

bioinformatics

Classical Biochemistry

Transcriptomics

Genomics/Epigenomics
Complexity of Proteome and proteomics

- Metabolic state
- Interactions
- Temperature
- Drugs
- Stress
- Mutations/gene KOs
- Genome
- Cell specific gene expression
- Culture conditions
Zoom-in and Zoom-out is required

One protein
(Classical protein biochemistry)
(~150 yrs)

Many proteins
(Modern protein biochemistry/Proteomics)
(~40 yrs)
Quantitative Proteomics – Experimental Workflow

[Diagram showing a workflow for quantitative proteomics, starting with biological samples (cell lines, tissues, biological fluids) leading to protein extraction, sample fractionation, and finally MS-based quantitative proteomics with subcategories such as comparative proteomic profiling, interactomics, modificomics, and targeted analysis.]
Quantitative MS-Data Analysis

Mueller LN. et al. JPR (2008) 7:51
Biological Sample

Cell lines

Tissues

Biological fluids

2DE

Sample A

Sample B

DIGE

Sample A

Sample B

combine

Image analysis

Protein Relative Quantitation of differentiated in abundance proteins

Spot excision

Digestion

LC-MS/MS analysis

Protein Identification

Procedure

Alternative procedure

Light labeling

Heavy labeling

Fluorescence dyes
Measuring protein dynamics using SILAC

Relative changes in protein levels

Relative changes in protein production

Protein turnover

(Ong et al., 2002) (Schwanhaeusser et al., 2009) (Doherty et al., 2009)
SILAC vs Label-Free

Hubner NC et al. J Cell Biol. 2010
Evidence of PTMs

2-DE

Radioactive labeling/phosphoprotein specific AB
Enrichment of Phosphopeptides

Phosphopeptides are often of low abundance and give bad MS response.

**SCX:**
- Non-phosphorylated peptides
- 100% B: phosphorylated peptides
- 15% B: phosphorylated peptides

**IMAC:**
1. Load/wash
2. Elution

Net charge 2+:
\[\text{NH}_2-\text{Ala-Thr-Asp-Ser-Pro-Lys-COOH} \quad \text{Net charge 2+}\]

Net charge 1+:
\[\text{NH}_2-\text{Ala-Thr-Asp-Ser-Pro-Lys-COOH} \quad \text{Net charge 1+}\]

**Poros 20MC**
- Me: Fe(III), Ga(III)
- Me: 3+
- Enriched phosphopeptides
Neutral Loss dependent MS/MS/MS

Neutral Loss of phospho-Ser and phospho-Thr sides

Phosphopeptide - 80 Da
Phosphoproteome Quantitation: triple SILAC time-resolved analysis

State A: Light Arg0, Lys0
State B: Medium Arg6, Lys4
State C: Heavy Arg10, Lys8

Mix lysates 1:1:1 and digestion
Phosphopeptide enrichment
nLC-MS/MS

Double triple SILAC – time course

0 min EGF
Light
Arg0, Lys0

5 min EGF
Medium
Arg6, Lys4

20 min EGF
Heavy
Arg10, Lys8

1 min EGF
Light
Arg0, Lys0

5 min EGF
Medium
Arg6, Lys4

10 min EGF
Heavy
Arg10, Lys8

Protein/phosphorylation profile

Fold change/activation

Time (min)

Src-substrate Cortactin

TQpTPPpSPAPQPTTEER

Targeted Proteomics – Detection/Monitoring/Quantitation

Target protein lists, candidate biomarkers

Target peptides and MRM transitions

Isotope labelled internal standards

Mass spec analysis

Quantitative results for hundreds of proteins

Principle of SRM/MRM assays for targeted proteomic analysis:

- Q1: Peptide Selection
- Q2: Fragmentation
- Q3: Fragment Selection

Intensity

www.mrmatlas.org
Biomarker development

Emerging proteomic strategies in the clinic

Sampling and discovery in the clinic

Data integration

Network information:
- Pathways
- Protein – protein interactions
- Co-expression
- Other “omics” data
- Analysis of expression changes in conjunction with the underlying molecular architectures of networks and pathways

Data interpretation

Analysis of “big data”
- Identification of disease specific groups of interconnected proteins
- Combination with individual patient information (age, gender...) and clinical picture
- Matching to similar cases

Diagnosis
- Individualised therapy plan
- Early stage detection of developing disease
- Intervention accompanying monitoring

S. Sauer and T. Luge Proteomics 2015,15, 997–1013
An emerging workflow for shotgun proteomic analysis of complex ecosystems such as the human or animal intestine

S. Sauer and T. Luge Proteomics 2015, 15, 997–1013
Our Approach

Multi-omics data
Comparative analysis
Network and pathway analysis
Integration
Drug-repurposing

Understanding (bio)pathology
Biomarkers/drug targets
Drugs/Therapy

Health Disease
Lymphoma

Haematological cancer
Derives from lymphocytes
Large heterogeneity
Deactivated wt-p53
Wt p53 deactivated due to MDM2 overexpression

Reproduced from KEGG database
Effect of Nutlin-3a in lymphoma

- Non-genotoxic activation of p53
  - Cell cycle arrest
  - Apoptosis
  - Tumor growth inhibition
But...

...it doesn’t work in all of the cases.
Comparative Transcriptomics and Proteomics

Different regulation in lymphoma sub-types

Network Analysis

Understand Lymphoma Pathobiology
N3a global proteome differential affect

Fig 1: Overview of the results from the comparative transcriptomics and proteomics analysis on model Lymphoma cell lines +/-N3a Psatha et al 2016

A) Lymphoma sub-types
- Transcriptomics
  - HL
  - MCL
  - ALC
- MS-based Proteomics
  - HL
  - MCL
  - ALC

Deregulated Transcriptome
- 675
  - MCL 440
  - HL 322
  - ALC 1310

Deregulated Proteome
- 3578
  - MCL 733
  - HL 2245
  - ALC 1489

B) Transcriptomic Signature
- ALC
- HL
- MCL

Proteomic Signature
- ALC
- HL
- MCL

Enrichment
- Apoptosis
- Cell Death
- Cell Cycle
- Metabolism
- Ribosome
- DNA metabolism
- Chromosome org.
- Protein localization
- Signal transduction Reg.
- Cell communication Reg.
- Cell differentiation
- DNA replication
- p53 signaling path.
- NER
- Cell proliferation
- MAPK signaling path.
- Proteolysis Reg.

C) p53 signaling
- Up
- Apoptosis
- Proteolysis
- OxPhos
- Mitochondrial translation
- Autophagy

Down
- Cell Cycle
- Biosynthesis
- Protein translation
- mTOR pathway
- Heat Shock Response
- Angiogenesis
N3a-affected Proteins and pathways
Common N3a-affected PPIs network analysis
P53 signaling pathway

Lymphoma-type dependent activation and rewiring of p53 signaling pathway

Fig04: Integrative visualization of the effect of N3a in p53 signaling pathway. Psatha et al. 2018
Hierarchical clustering and comparison of affected proteins per lymphoma type and biological process.

Autophagy

Mitophagy

Exosomes
Integrated protein network in MCL
Integrated PPIs network in ALCL
Integrated PPIs network in HL
N3a-affected signaling pathways
Proposed and tested novel therapeutic strategies

<table>
<thead>
<tr>
<th>substance</th>
<th>mode of action</th>
<th>targets</th>
<th>concentration</th>
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</thead>
<tbody>
<tr>
<td>Ly294002</td>
<td>PI3K/mTOR-inhibitor</td>
<td>ATP-competitive</td>
<td>10 nM</td>
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<tr>
<td>Rapamycin</td>
<td>mTOR-inhibitor</td>
<td>FKBP12</td>
<td>30, 50 μM</td>
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<tr>
<td>Nutlin-3A</td>
<td>p53-activator</td>
<td>MDM2 antagonist</td>
<td>1.5-6 μM</td>
</tr>
<tr>
<td>17-AAG</td>
<td>HSP90-inhibitor</td>
<td>ATP-competitive</td>
<td>0.25-1 μM</td>
</tr>
</tbody>
</table>

- Protein expression
  - Proteomics
  - Immunoblot
  - mTOR/HSPs

- Therapeutic strategy
  - PI3K
  - mTOR
  - MDM2
  - p53
  - HSP90

- Inhibition
- Activation
- Interaction

- Protein translation
  - Cell proliferation
  - Survival

- Apoptosis
  - Cell cycle arrest
  - Senescence
1. Hodgkin lymphoma (HL)
2. Non-Hodgkin lymphoma (NHL)

MCL:
- chromosomal translocation t(11;14)(q13;q32) (IgH/CCND1)
Network and pathway analysis
Integration
Drug-repurposing

GSE30189 (Stages):
1. Normal (N)
2. In Situ (IS)
3. Classical (C)
4. Intermediate (I)
5. Aggressive (A)

GSE45717
1. Healthy
2. Typical MCL
Differential expressed genes (DEGs)

Healthy vs Stage

Stage\(^{(t)}\) vs Stage\(^{(t+1)}\)

Comparative Analysis

Active Subnetworks

Pathway Enrichment

Pathway Clustering

Co-expression Networks

GEO

Array Express

Drugbank

GSE30189

GSE45717

MCL Stages

MCL vs Healthy

NtolS

IStoC

Ctol

ItoA

HtoMCL

Drugs

Drug Repurposing

protein-drug

pathway-drug

Co-expression Networks

up

down

DEGs
## Affected Biological Pathways

<table>
<thead>
<tr>
<th></th>
<th>pathfindR</th>
<th>PaintOmics</th>
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<tbody>
<tr>
<td>NtoIns</td>
<td>18</td>
<td>8</td>
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<tr>
<td>IStoC</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>CtoI</td>
<td>45</td>
<td>8</td>
</tr>
<tr>
<td>ItoA</td>
<td>71</td>
<td>12</td>
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<tr>
<td>HtoMCL</td>
<td>185</td>
<td>58</td>
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</table>
# Significantly affected pathways

<table>
<thead>
<tr>
<th>Pathways</th>
<th>Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>p53 and cell cycle</td>
<td>DLBCL</td>
</tr>
<tr>
<td>B-cell receptor (BCR) signaling</td>
<td>DLBCL, MCL, CNS</td>
</tr>
<tr>
<td>PI3K/Akt/mTOR signaling pathway</td>
<td>DLBCL</td>
</tr>
<tr>
<td>JAK-STAT signaling pathway</td>
<td>DLBCL</td>
</tr>
<tr>
<td>NF-κB pathway</td>
<td>MCL</td>
</tr>
<tr>
<td>Jak/STAT pathway</td>
<td>MCL</td>
</tr>
<tr>
<td>Wnt/β-catenin pathway</td>
<td>MCL</td>
</tr>
<tr>
<td>WNT pathway</td>
<td>cHL, MCL, CLL</td>
</tr>
<tr>
<td>p53 Pathway</td>
<td>MCL, ALCL</td>
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<tr>
<td>NF-κB prosurvival signals</td>
<td>CNS</td>
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<tr>
<td>PD-1/PD-L1 pathway</td>
<td>HL, nHL</td>
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<tr>
<td>HGF/c-MET signaling pathway</td>
<td>B cell lymphoma, T and NK cell lymphoma, Hodgkin lymphoma</td>
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<tr>
<td>Hippo pathway</td>
<td>Pancreatic cancer, Breast cancer</td>
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Novel findings

• There are “stage specific” deregulated biological pathways.

• *In Situ* stage show a distinct pathway enrichment phenotype.

• Basic cellular processes related to protein processing, translation and RNA processing are affected at the Classical stage.

• Signaling pathways related to apoptosis, cellular senescence and proliferation are affected at the Intermediate and Aggressive stages.
TP53 signaling pathway

1. Regulates cell cycle
2. Inhibits angiogenesis
3. Activates DNA repair proteins
4. Induce growth arrest
5. Initiate apoptosis
Pathways cross-talk

Intermediate

MAPK pathway

P53 pathway

In Situ

Aggressive

CtoI
IStoC
NtoIS ItoA

In Situ

Aggressive

Pathways cross-talk

Intermediate

MAPK pathway

P53 pathway

In Situ

Aggressive
Visualization of DEGs and enriched pathways

- Drug-target networks
- Drug-pathway-target networks
New potential treatments for MCL

NtoIS

IStoC

Protein  Drug  Biotech  Lymphoma  Enriched Pathway
Target  Enzyme  Transport  Carrier  Member of pathway
New potential treatments for MCL
New potential MCL-drugs categories

![Bar chart showing the number of drugs in different categories: Biotech Drug, Small Molecule Drug, Nutraceutical. The chart indicates a significant number in the Small Molecule Drug category.]
MCL – pathways and drugs

**BENIGN LYMPHADENITIS**

**PATHWAYS**
- Protein signaling pathway
- Hedgehog signaling pathway
- Frataxin R loading pathway
- p53 signaling pathway
- AGE-RAGE signaling pathway in diabetic complications

**DRUGS**
- Masoprostol
- Minocycline
- Metoprolol
- Bepridil
- Diltiazem
- Arsenic trioxide
- Tamoxifen
- Zeatin
- Betaxolol
- Fosfomycin
- Sulfinpyrazine
- Chloroquine
- Medroxyprogesterone
- Acetylsalicylic Acid
- alpha-Tocopherol succinate
- D-alpha-Tocopherol acetate

**IN SITU**

**CLASSICAL**

**PATHWAYS**
- Ribosome: Tight junction
- Proteosome: RNA transport
- Spliceosome
- Ubiquitin mediated proteolysis
- Ribosome biogenesis in eukaryotes

**DRUGS**
- Ibrutinib
- Acalabrutinib
- Bcl-xL
- Venetoclax
- Racemose
- Patelline
- Daratumumab
- Colchicine
- Lenalidomide

**INTERMEDIATE**

**PATHWAYS**
- Ribosome biogenesis in eukaryotes
- Cyclin D1
- MAPK signaling pathway
- Proteosome: Gap junction
- RNA degradation
- mTOR signaling pathway
- Cell cycle

**DRUGS**
- Ibrutinib
- Acalabrutinib
- Bcl-xL
- Venetoclax
- Racemose
- Patelline
- Daratumumab
- Colchicine
- Lenalidomide

**AGGRESSIVE**

**PATHWAYS**
- Apoptosis
- Endocytosis: Wnt
- Insulin: AMPK
- Hedgehog: NF-kappa B
- Mitophagy: FoxO
- Apelin: IGF-1
- IL-17
- T cell receptor: Circadian rhythm

**DRUGS**
- Ibrutinib
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**DRUGS**
- Ibrutinib
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**Abbreviations**

- MAPK: Mitogen-activated protein kinase
- mTOR: mammalian target of rapamycin
- ER: Endoplasmic reticulum

## FDA-approved drug for MCL

<table>
<thead>
<tr>
<th>Drug ID</th>
<th>Drug Name</th>
<th>Related MCL Stage</th>
<th>Pathway</th>
<th>Original Use</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>Fostamatinib</td>
<td>ALL</td>
<td>Ribosome Biogenesis</td>
<td>Rheumatoid Arthritis*</td>
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<tr>
<td>2</td>
<td>Aliqopa (Copanlisib Hydrochloride)</td>
<td>Classical</td>
<td>Leukocyte transendothelial Thyroid hormone signaling pathway</td>
<td>FL*</td>
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<tr>
<td>3</td>
<td>Lobeglitzazone</td>
<td>Classical</td>
<td>-</td>
<td>antidiabetic medication</td>
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<tr>
<td>4</td>
<td>Lenalidomide (Revlimid)</td>
<td>Classical</td>
<td>-</td>
<td>multiple myeloma, MCL</td>
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<tr>
<td>5</td>
<td>Arsenic trioxide</td>
<td>In situ</td>
<td>p53 signaling pathway prolactin pathway</td>
<td>Acute Promyelocytic Leukemia (experimental on MCL)</td>
</tr>
</tbody>
</table>

* tested on relapsed Lymphoma (MCL, DLBL, FL,HL)
Our Data

Bioinformatics and Functional analysis
Protein ID/Quant Comparison
GO terms Enrichment analysis
Pathway analysis
Protein Interactions network analysis

Public Data

Genomics
Transcriptomics
Metabolomics
Phenomics
Clinical Data

Integration

Wisdom

Personalized Medicine
Disease Mechanisms
Diagnostic/prognostic biomarkers
Novel therapeutic strategies
Novel Clinical tools
Integrated Multi-omics Repository
Future perspectives....

Current Medicine
One Treatment Fits All

Future Medicine
More Personalized Diagnostics
Acknowledgements
Thank you!!!