

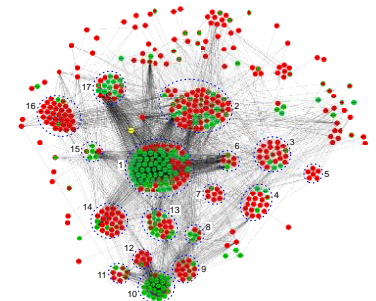
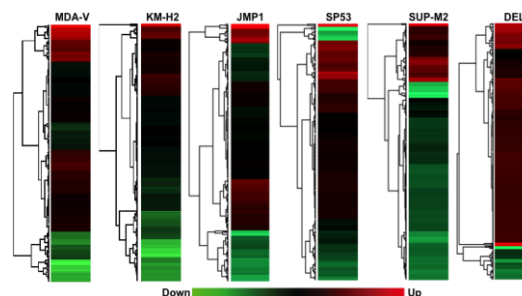
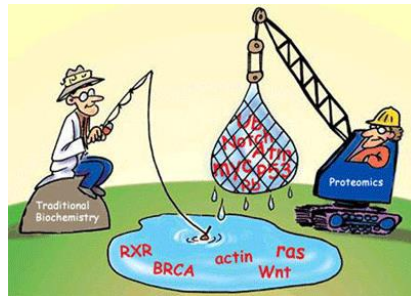


11 April 2022 - Thessaloniki

«Applied Nutrition and Health Promotion»

# Functional and clinical (nutri)proteomics in the era of precision medicine

## Nutrition and Health



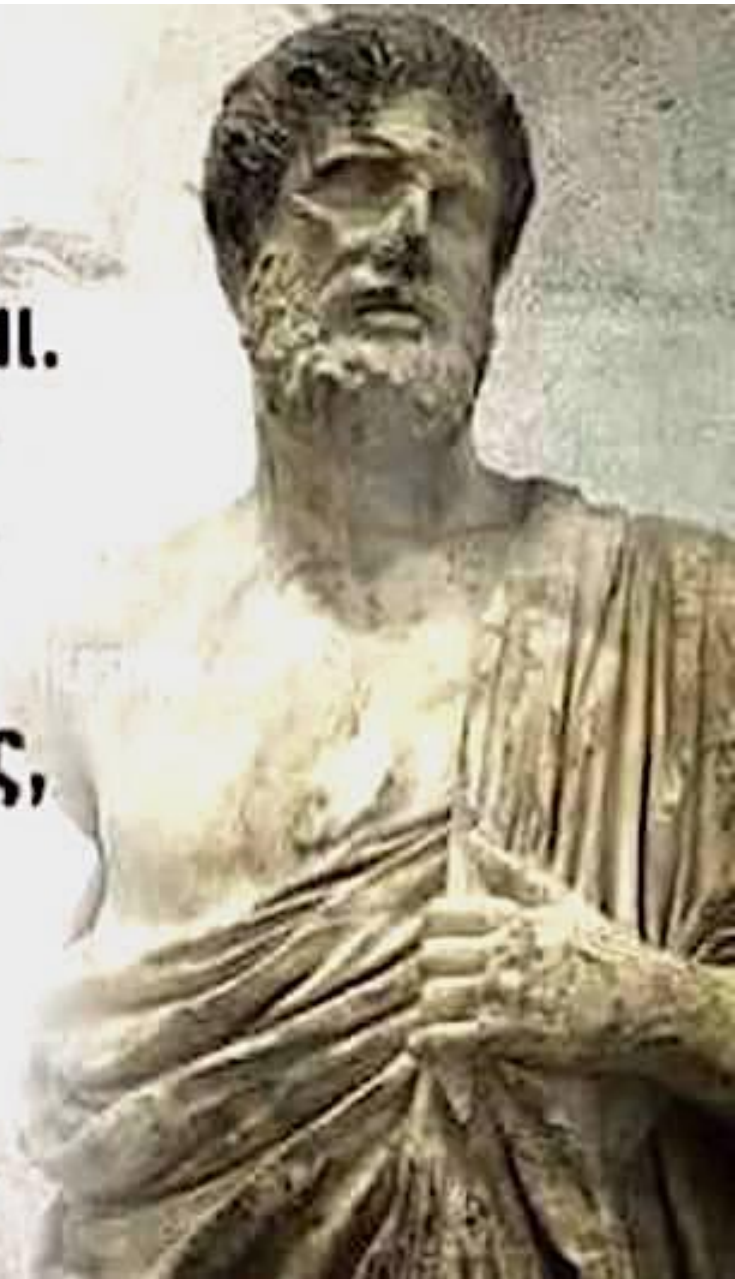
Assoc. Prof. Michalis Aivaliotis, Dep. of Medicine, AUTH

**Το σώμα μας έχει τη  
δυνατότητα να αυτοθεραπεύεται.**

**Ύψιστη σημασία έχουν:**

**Η διατροφή, η κίνηση,  
το περιβάλλον, ο τρόπος ζωής,  
ο τρόπος σκέψης.**

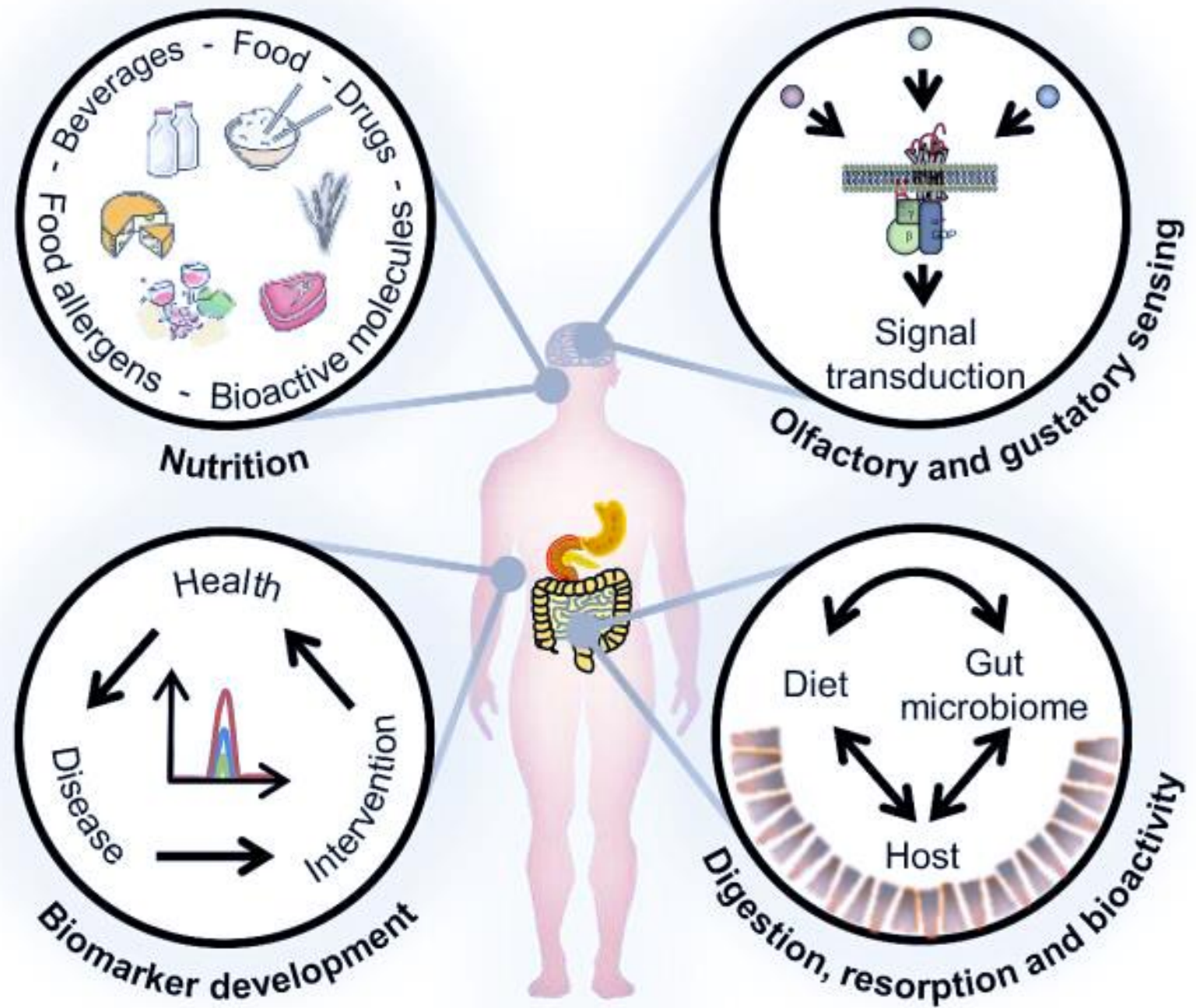
**Ιπποκράτης 460-377 π.Χ.**



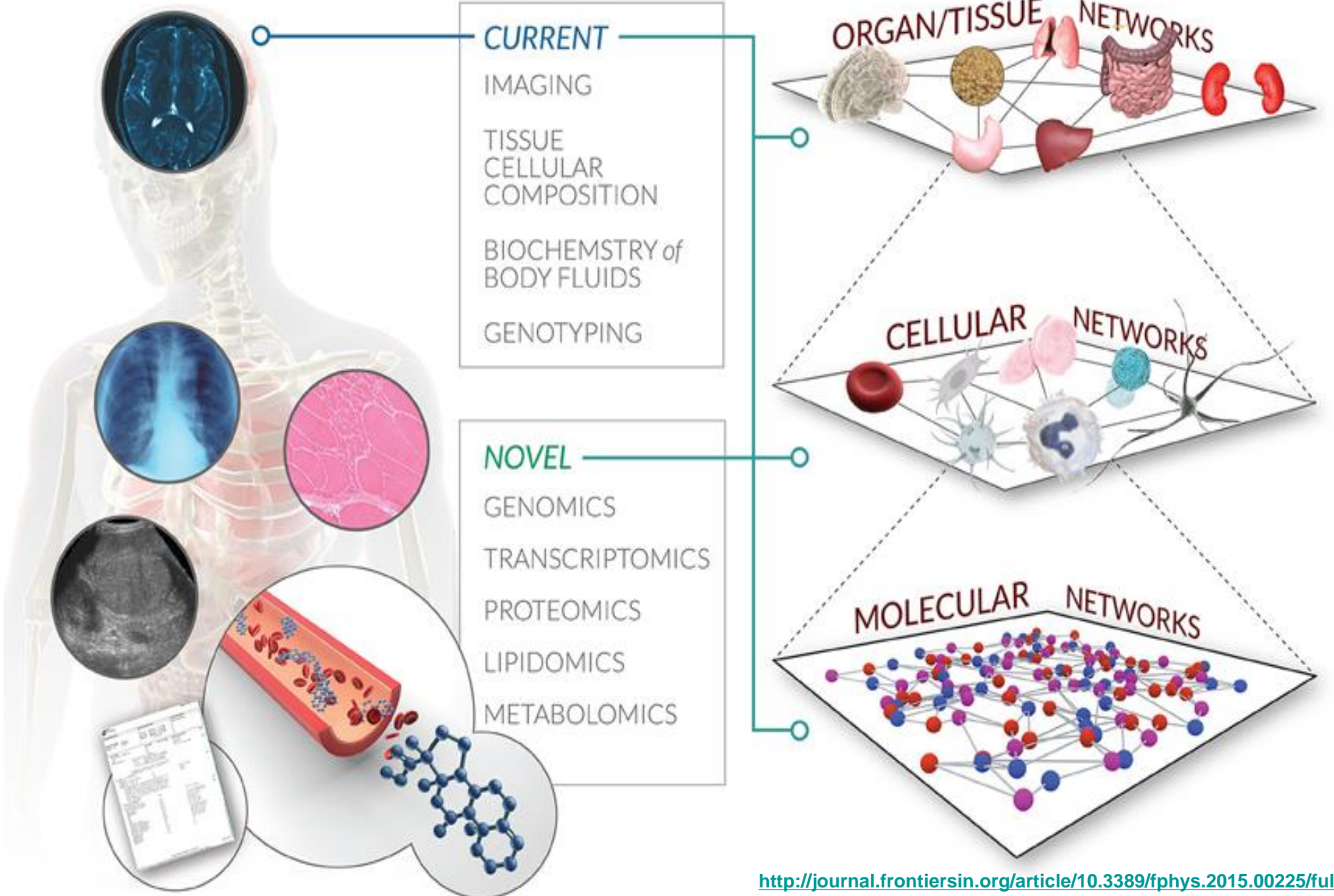
# Important Definitions

*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**.*

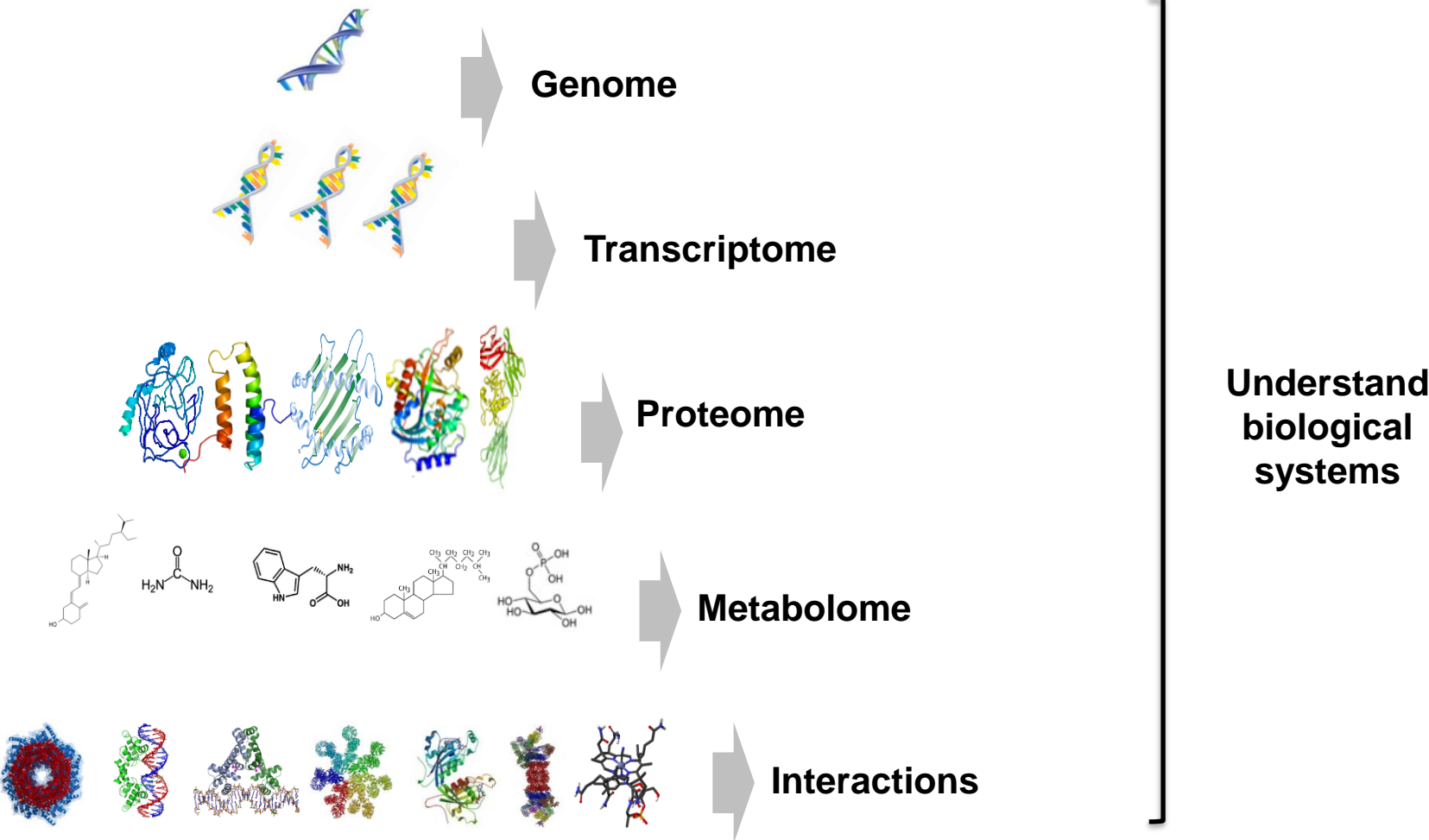
# Nutrition-based disease prevention or/and treatment



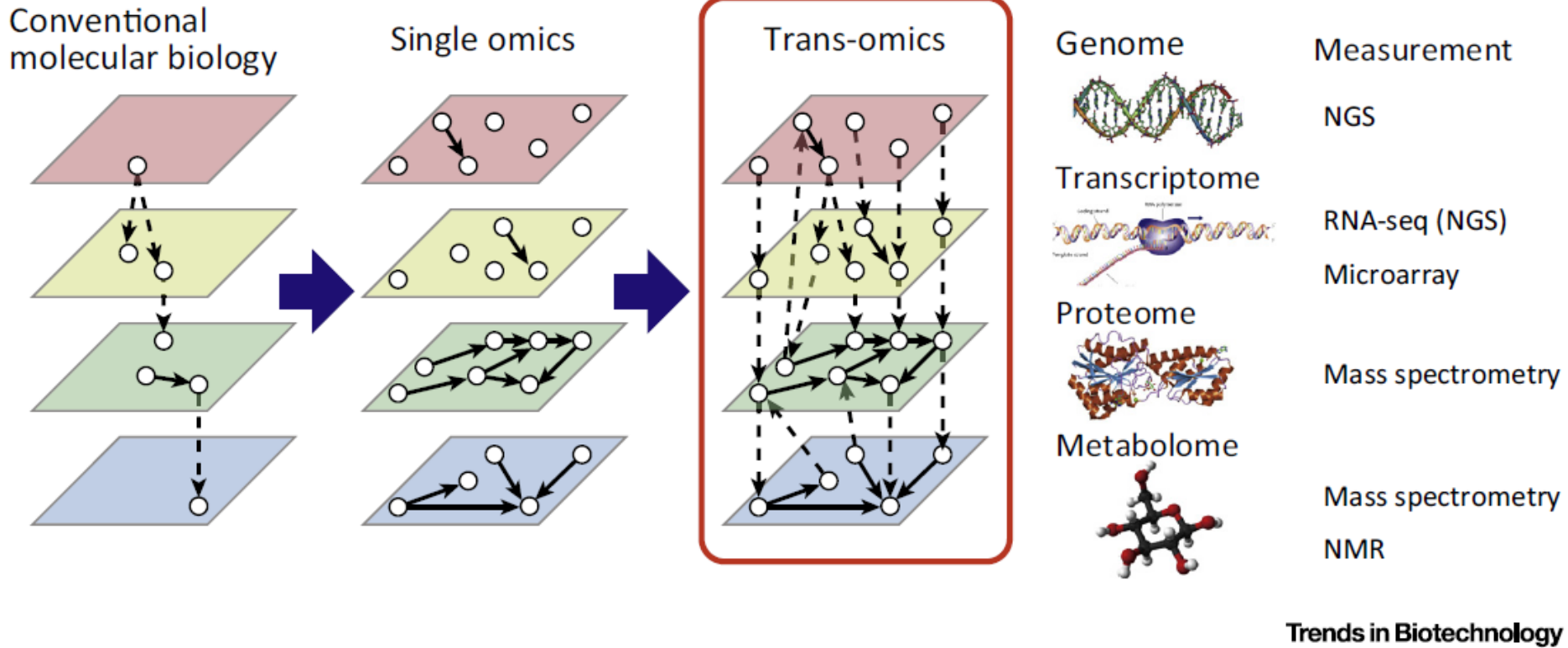
# The era of -omics and Systems Biology -The New Biology



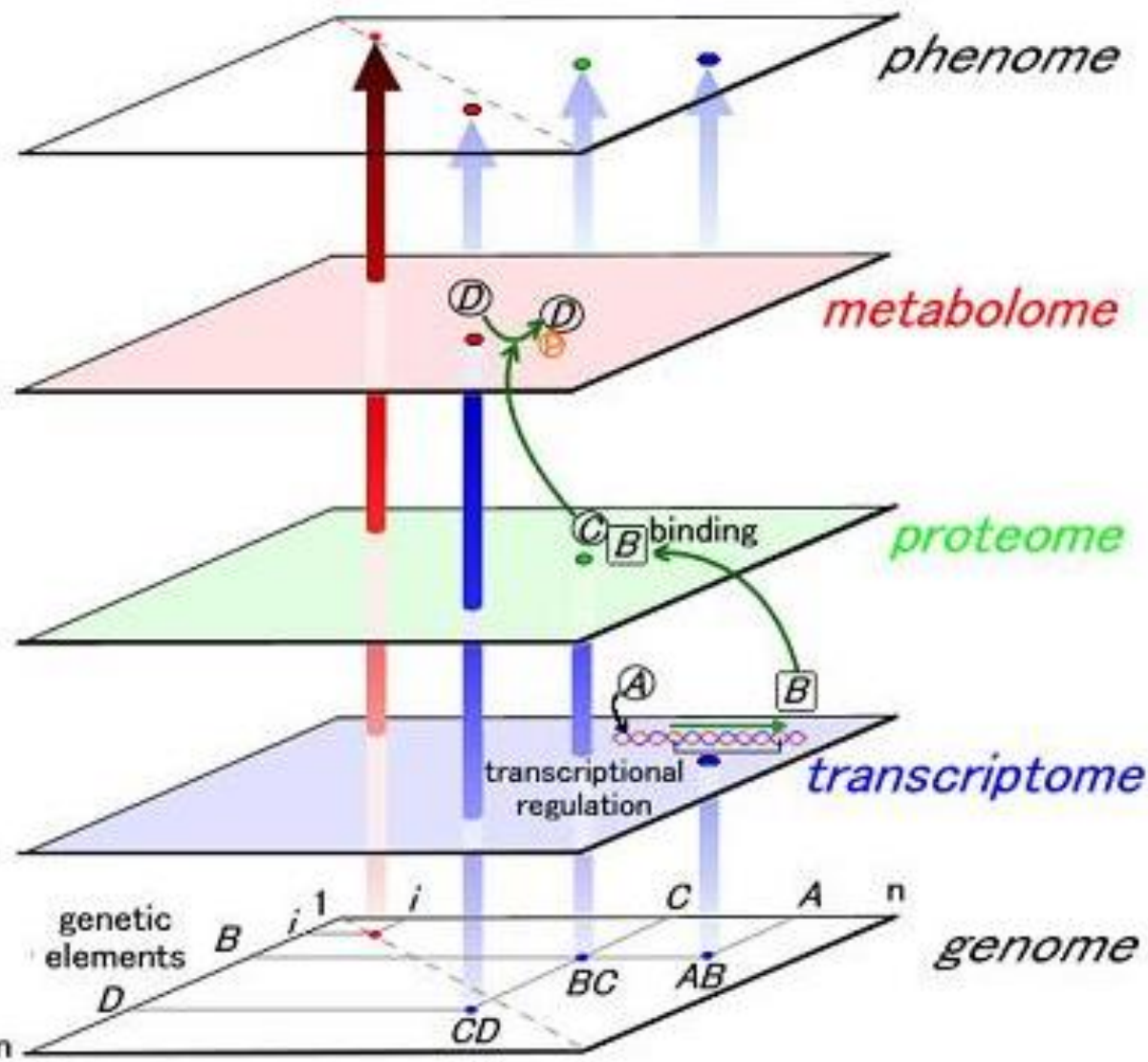
# The era of –omics and Systems Biology -The New Biology



# The era of –omics and Systems Biology -The New Biology



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



Differential omics is the beginning of Systems Biology

↓  
molecule  
cell  
tissue  
organism  
...



**Table 1.** Nutrigenomics core competencies and their relevance

Competency	Relevance
Genomics	Studies of genomes and functional and regulatory elements
Genetic variation	Studies of genome variations
Epigenomics	Studies of hereditary marks in chromatin (histones, DNA)
Transcriptomics	Studies of transcripts, including noncoding RNA and micro RNA
Proteomics	Studies of proteins, including their structure
Metabolomics	Studies of metabolites in cells, tissues, and body fluids
Systems biology	Holistic analysis of the cellular biochemical interaction networks

# Why to focus on proteome?

*Same genome, different proteome*



DNA

mRNA

Proteins

tells what **possibly**,

what **probably** and

what **actually** happens.

# *Proteins are flexible multi-tools*

## *The MVPs of cell*

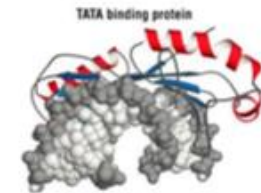


### **Binding**

### **Catalysis**

### **Switch (regulation)**

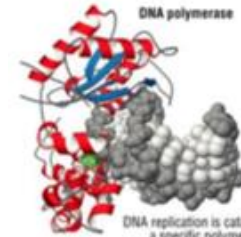
### **Structure**



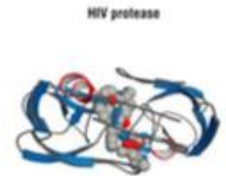
The TATA binding protein binds a specific DNA sequence and serves as the platform for a complex that initiates transcription of genetic information. (PDB 1tgh)



Myoglobin binds a molecule of oxygen reversibly to the iron atom in its heme group (shown in grey with the iron in green). It stores oxygen for use in muscle tissues. (PDB 1afb)



DNA replication is catalyzed by a specific polymerase that copies the genetic material and edits the product for errors in the copy. (PDB 1pbx)



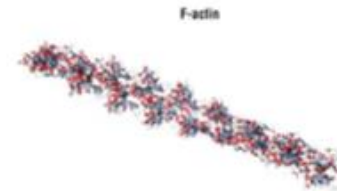
Replication of the AIDS virus HIV depends on the action of a protein-cleaving enzyme called HIV protease. This enzyme is the target for protease-inhibitor drugs (shown in grey). (PDB 1ahk)



The GDP-bound ('off'; PDB 1pfi) state of Ras differs significantly from the GTP-bound ('on'; PDB 121p) state. This difference causes the two states to be recognized by different proteins in signal transduction pathways.

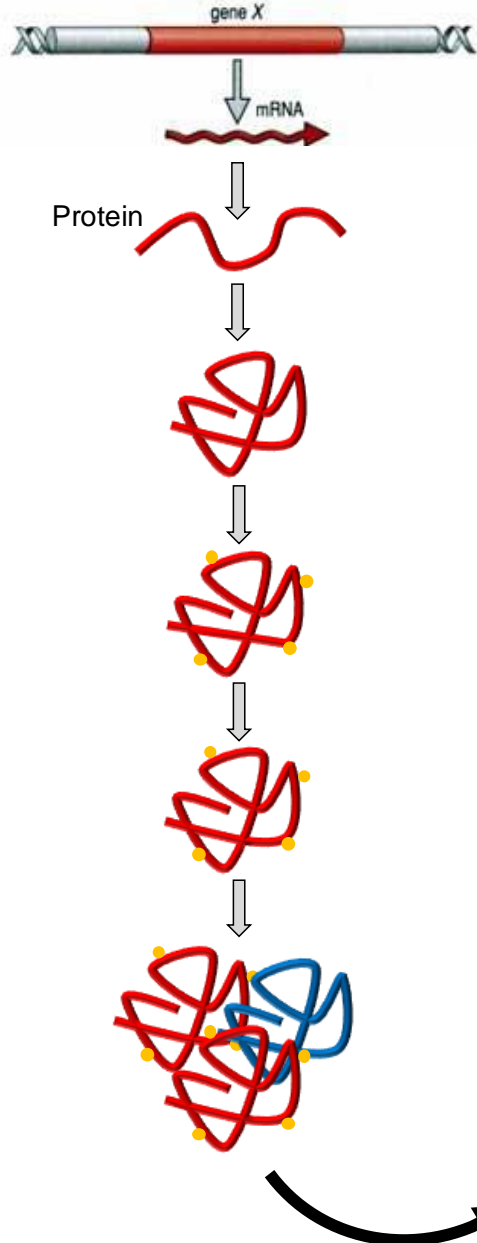


Silk derives its strength and flexibility from its structure: it is a giant stack of antiparallel beta sheets. Its strength comes from the covalent and hydrogen bonds within each sheet; the flexibility from the van der Waals interactions that hold the sheets together. (PDB 1s1k)



Actin fibers are important for muscle contraction and for the cytoskeleton. They are helical assemblies of actin and actin-associated proteins. (Courtesy of Ken Holmes)

# *Protein Life Cycle and maturation*



***Primary and Secondary***

***Tertiary***

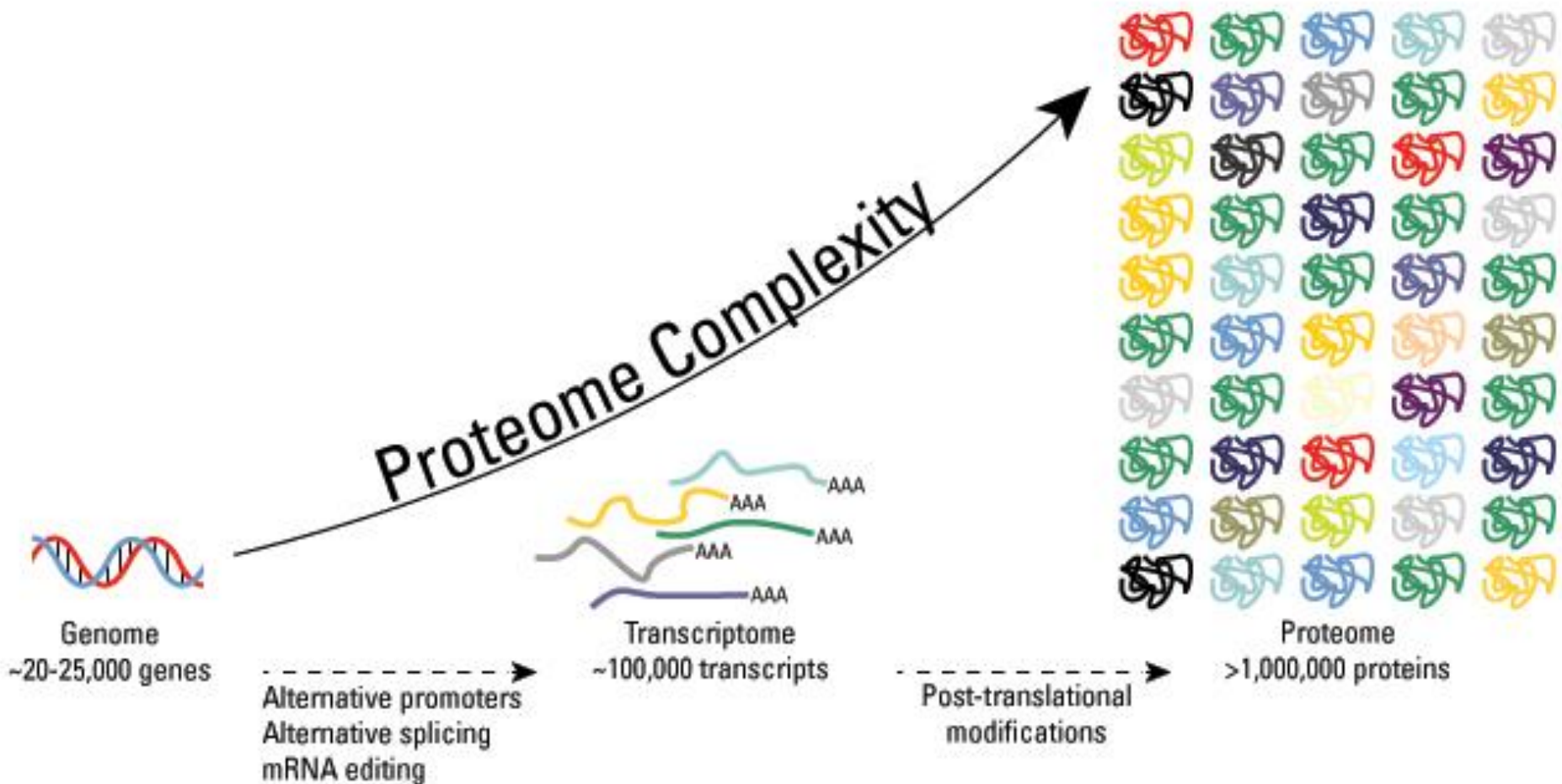
***Modifications***

***Localization***

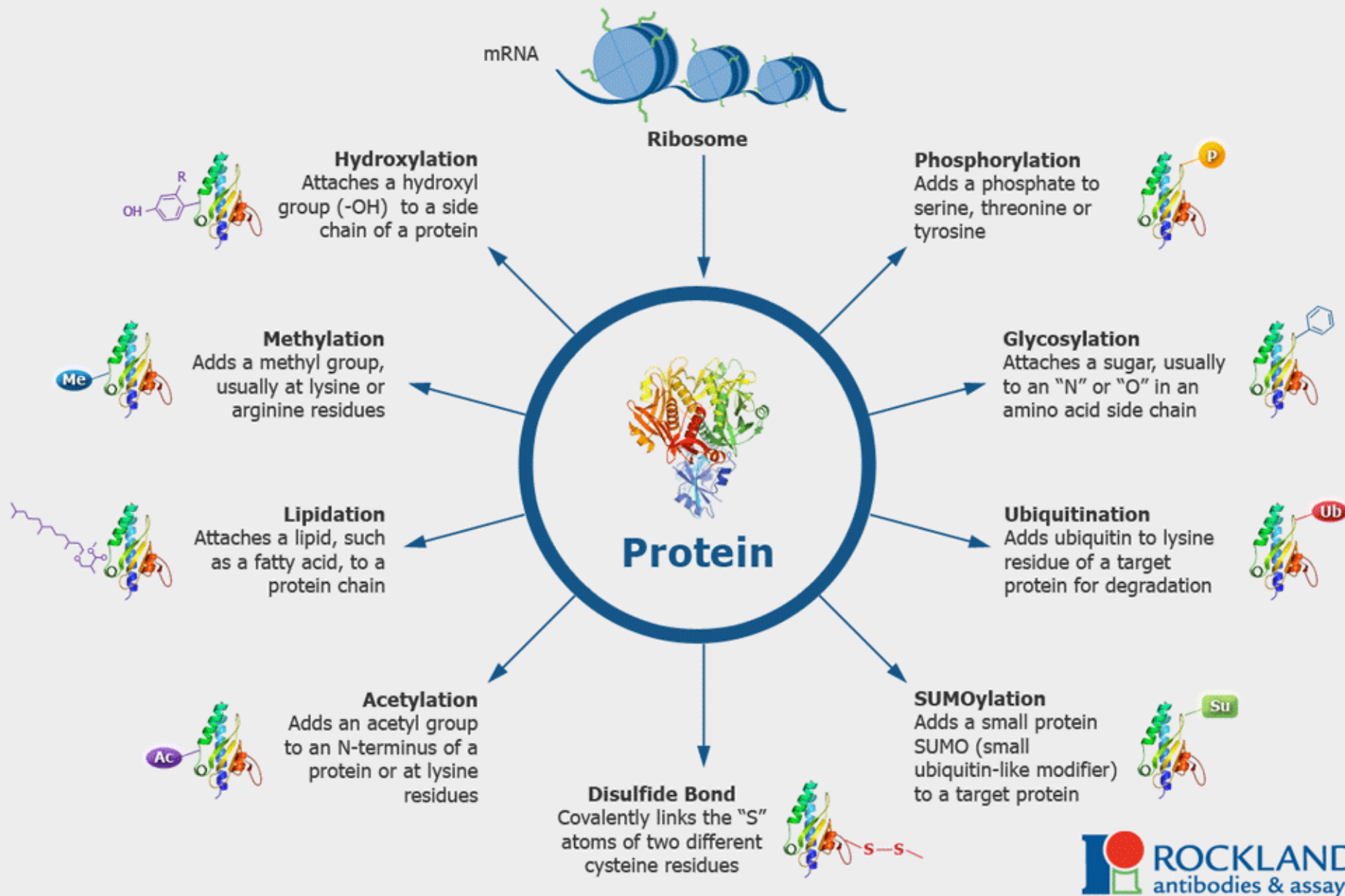
***Quaternary (Protein Complex)***

***Interactions / Regulation/Death***

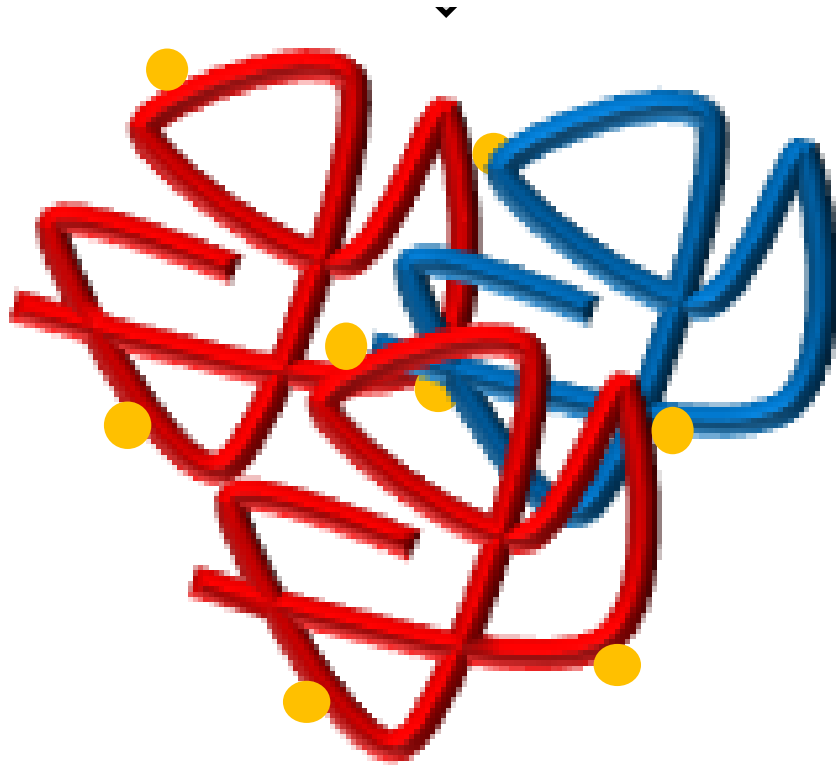
# Protein “Characters” through Modifications



# Protein Modification ~ 200 known PTMs



# Proteins are never alone: Protein Complex

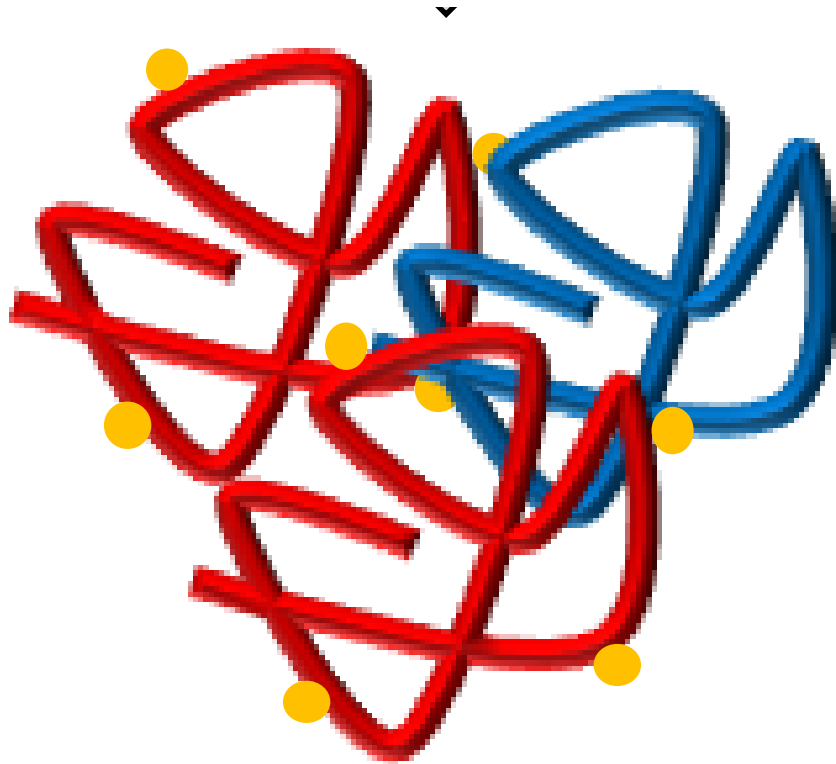


$\geq 2$  polypeptide chains

Non-covalent interactions

- Hydrogen bonds
- Electrostatic
- Hydrophobic
- Van der Waals

# Proteins are never alone: Protein Complex

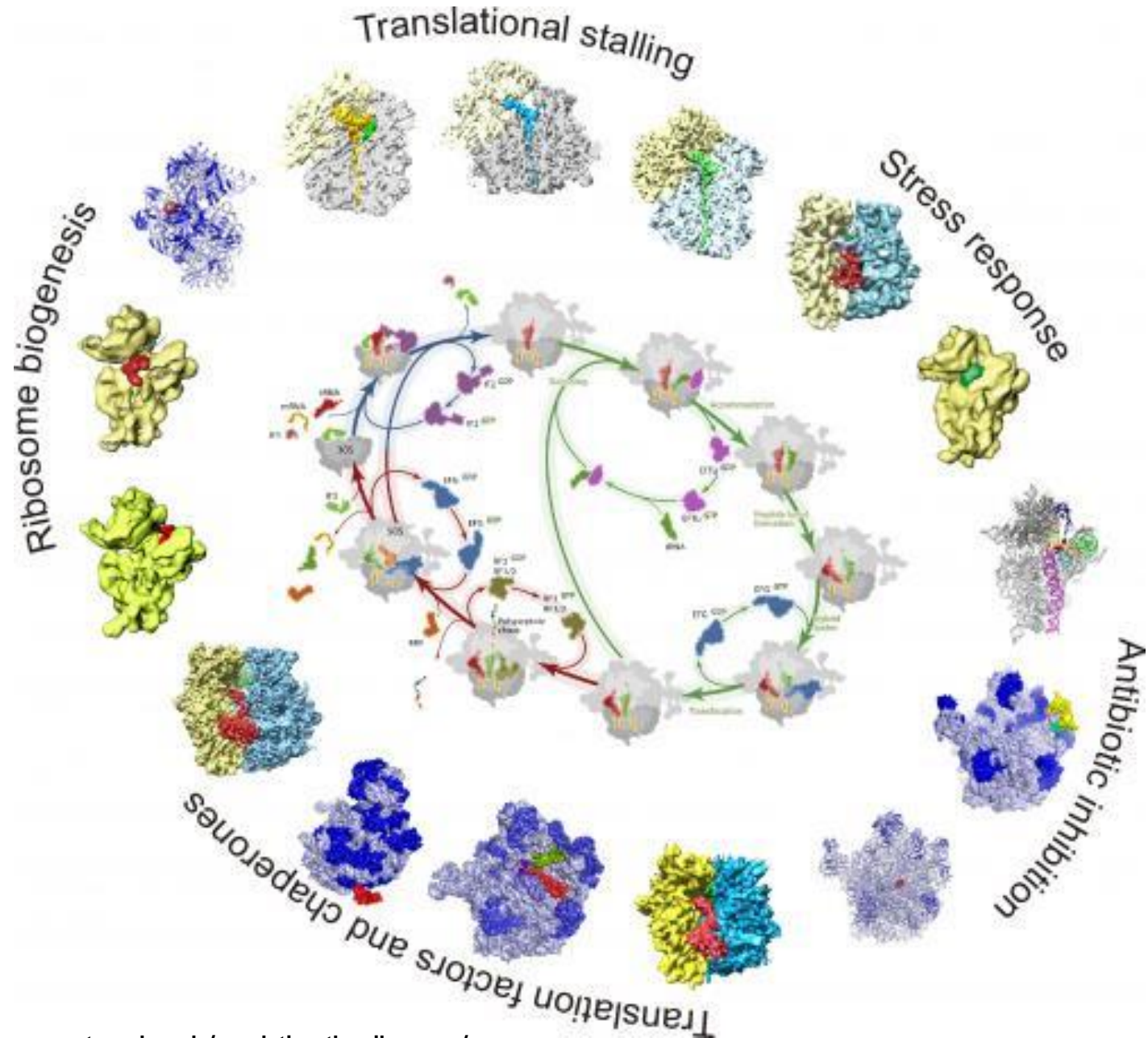


## Highly dynamic

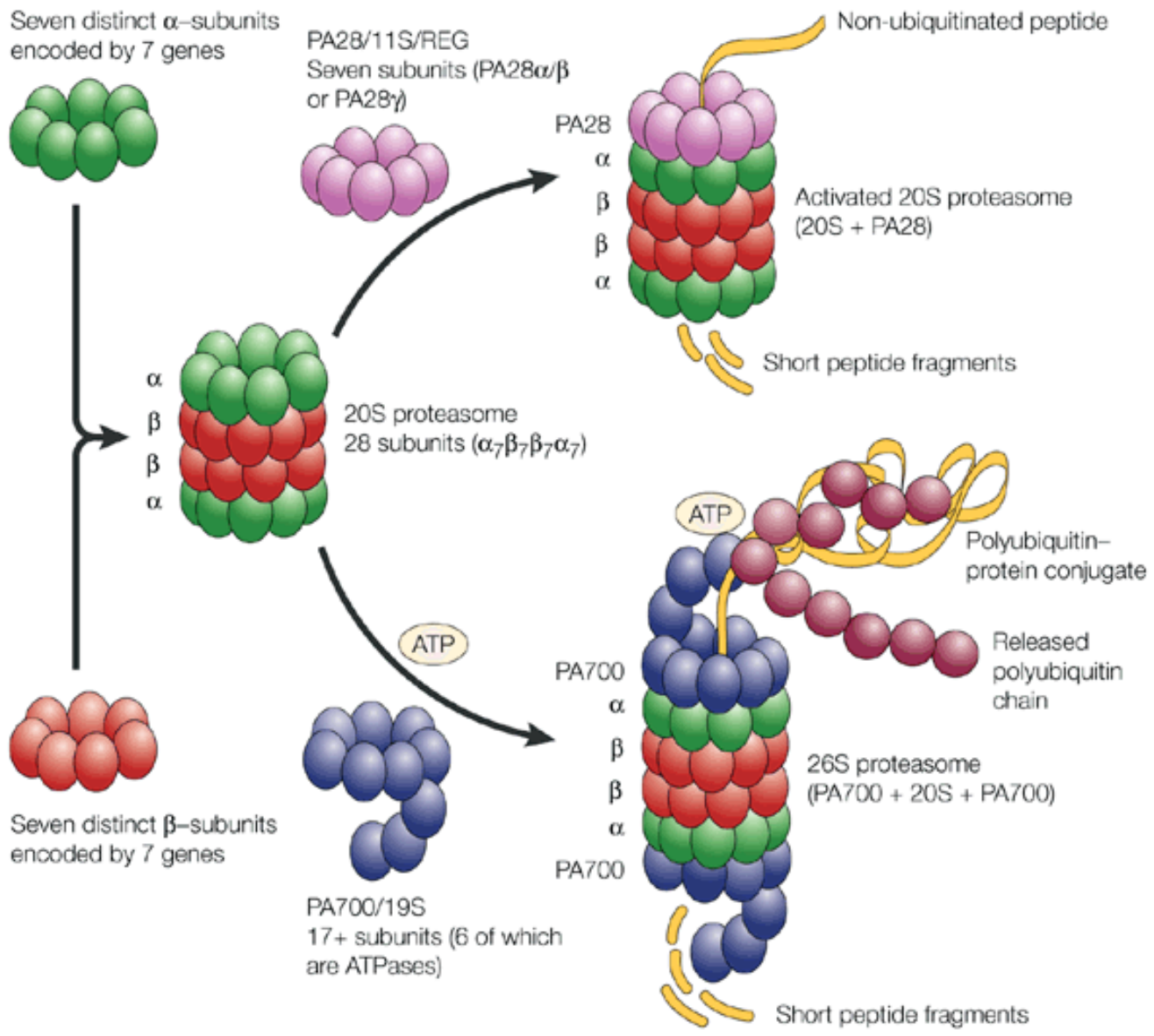
- Size
- Shape
- Interacting partners
- Localization
- Stability
- Abundance
- Properties



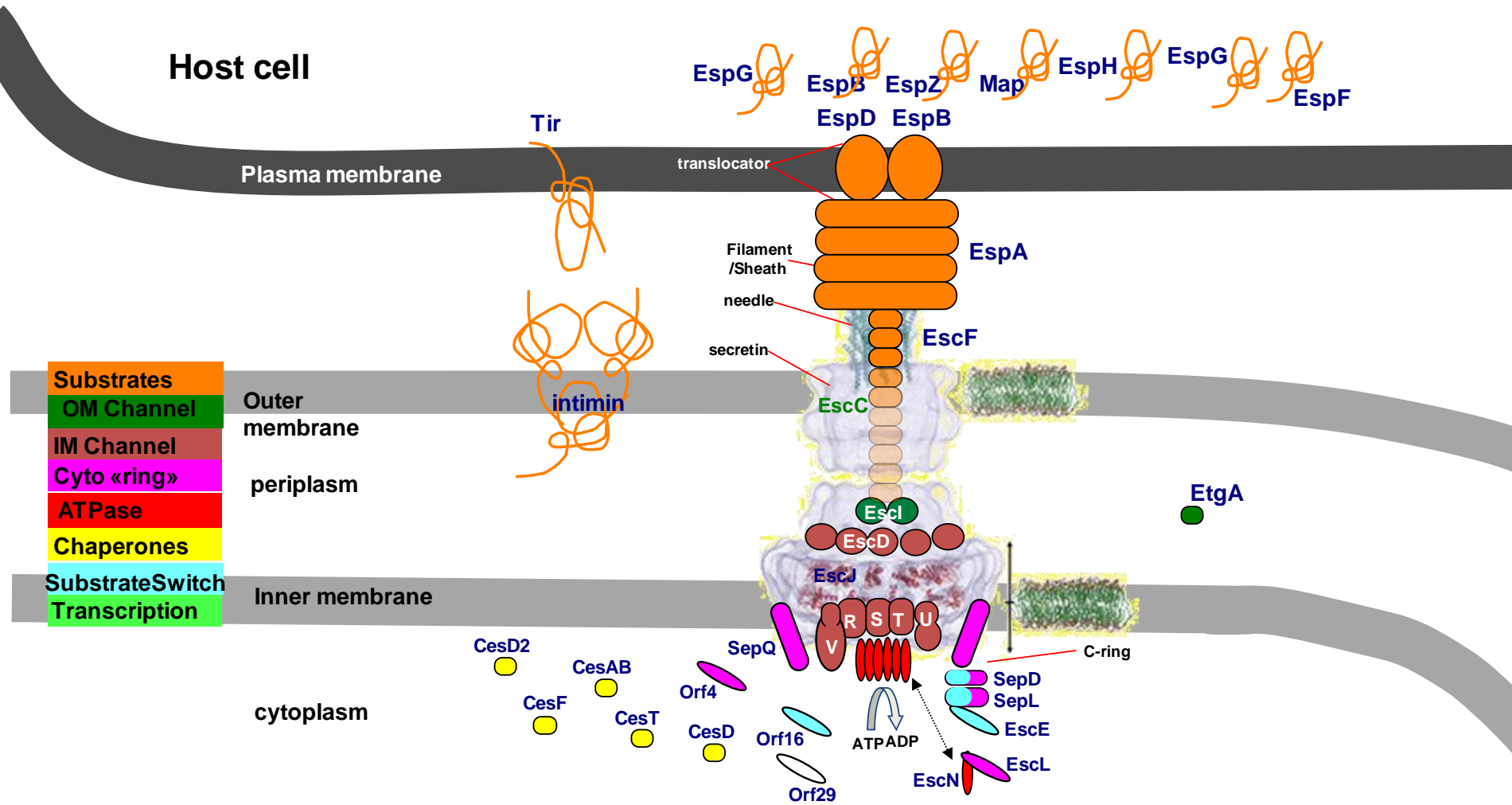
# Protein Machineries – Ribosome –Protein Maker



# Protein Machineries – Proteasome - Protein Recycler

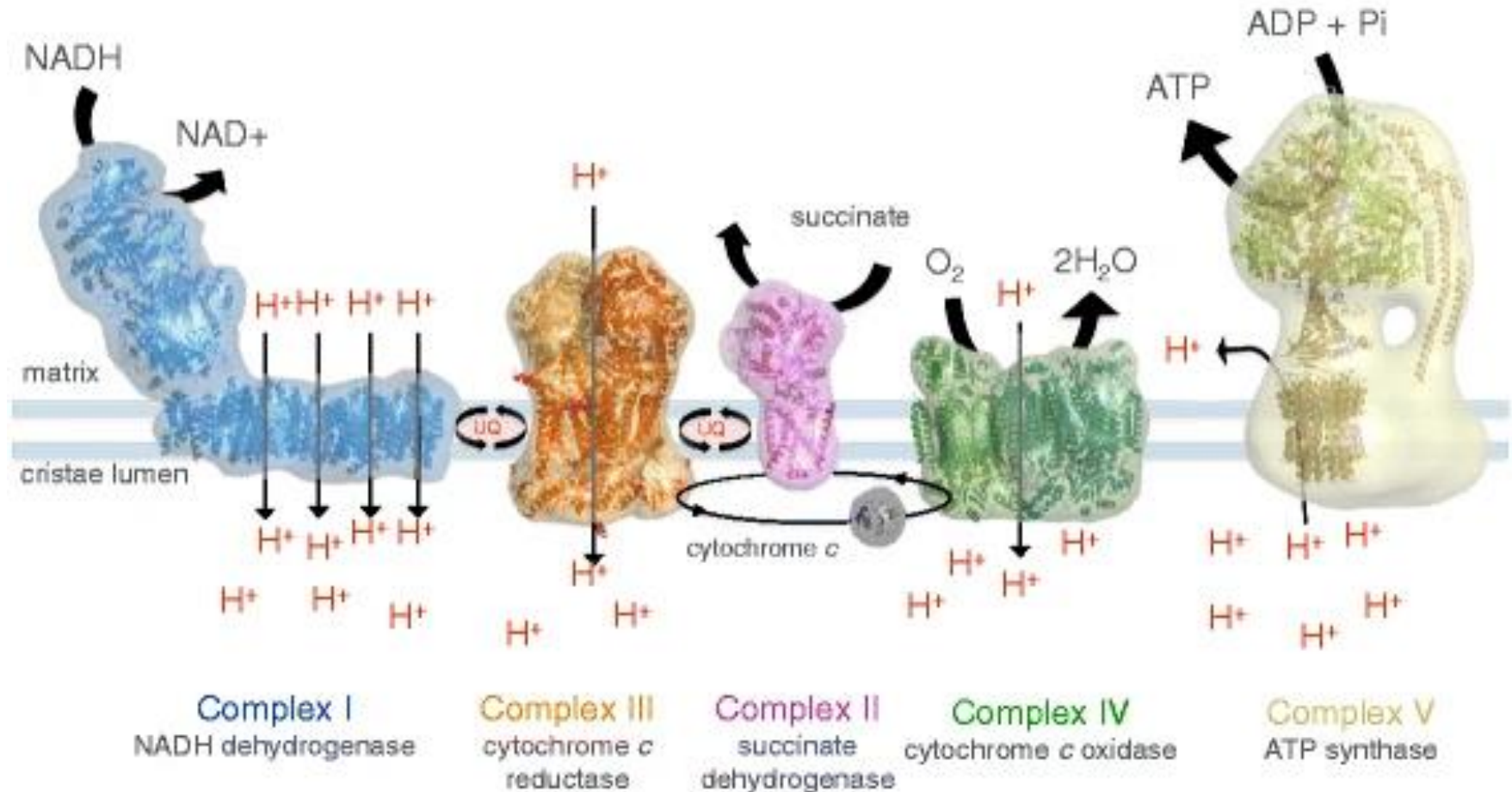


# Protein Machineries –T3SS “injectisome” -Pathogen

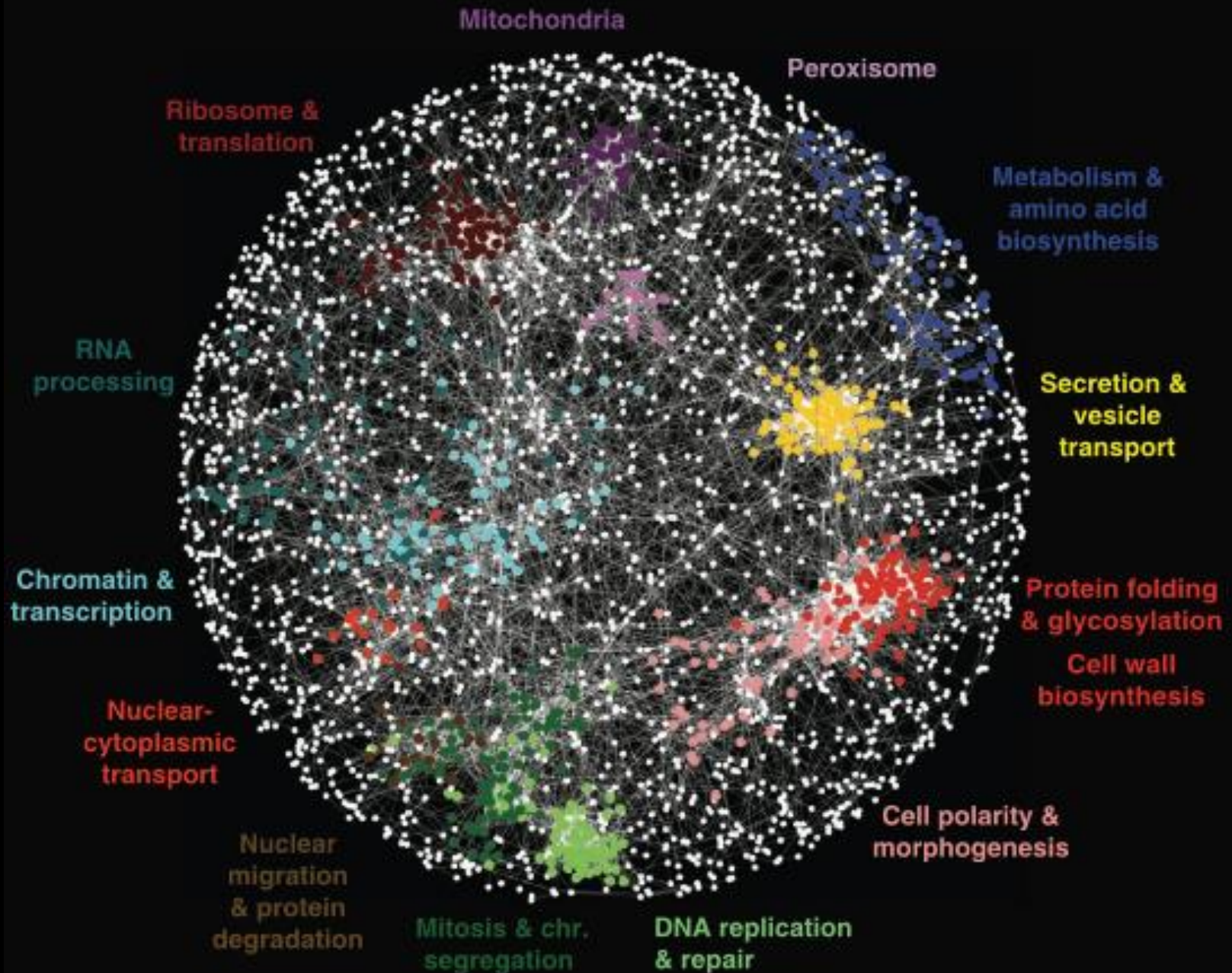


# Protein Machinerics – OxPhos – Energy production

## Mitochondrial respiratory chain complexes



# Protein Interaction Networks



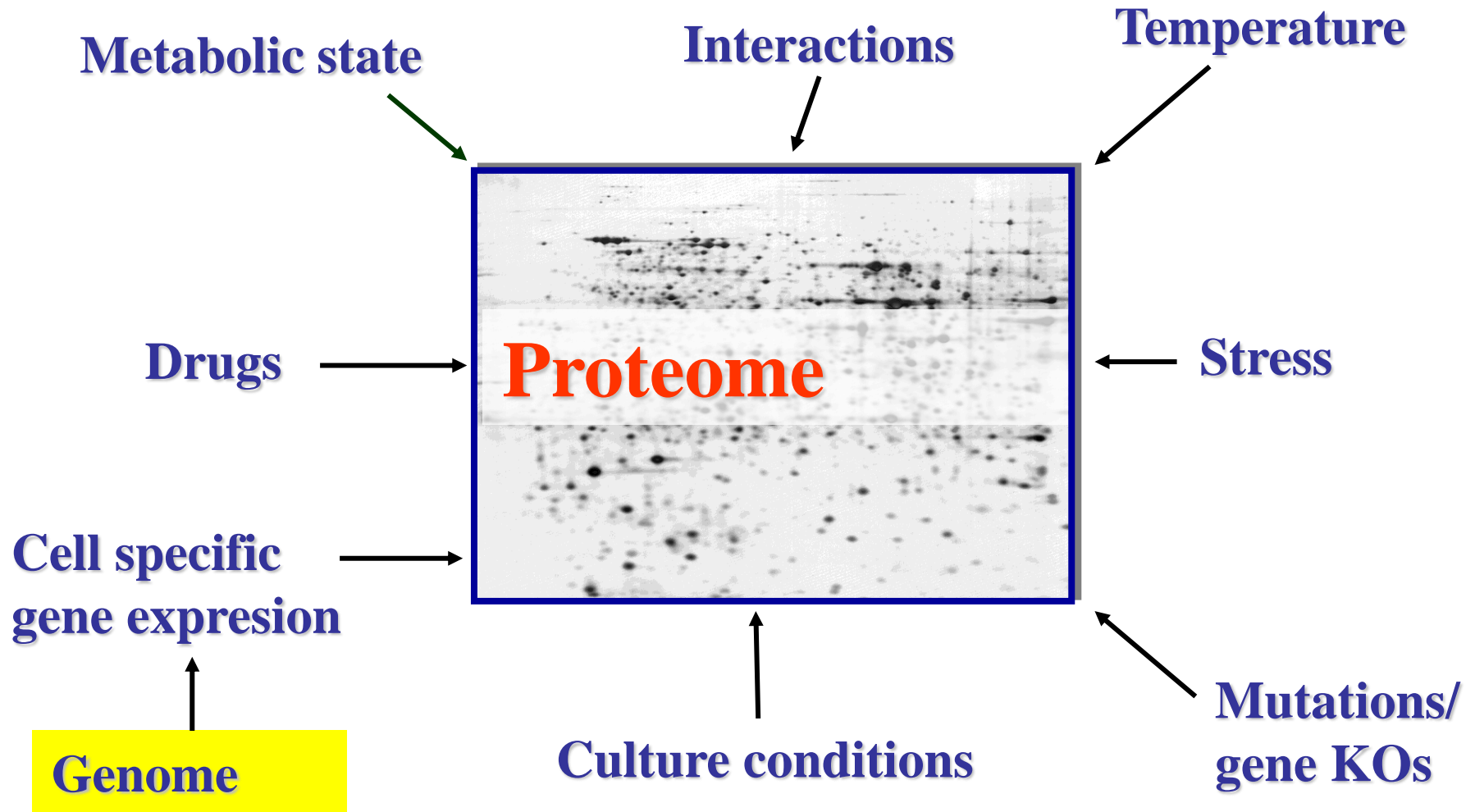
# ***Understanding the Cell function***

***We need to fully understand:***

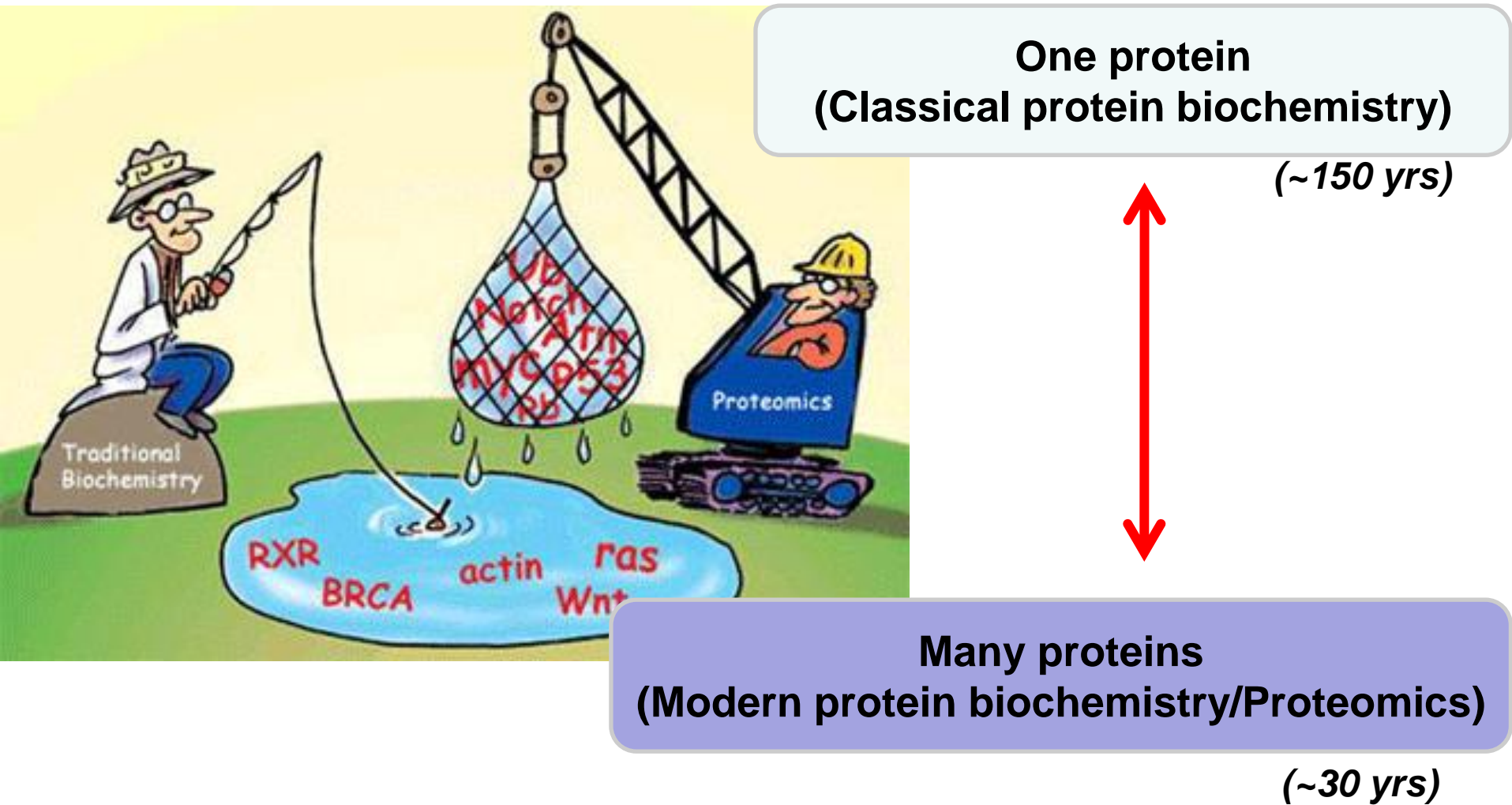
- 1. the function of <100 molecular machineries***
- 2. the interaction between molecular machineries***
- 3. the kinetics of the function of molecular machineries***

# ***Complexity of Proteome and proteomics***

## ***Proteins are very sensitive***



# What is proteomics?





# *Functional Proteomics*

**Biological Question/Pathway/Process/Condition**



**Directly relevant sub-proteome**

# *Functional Proteomics*

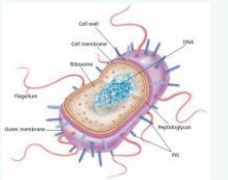
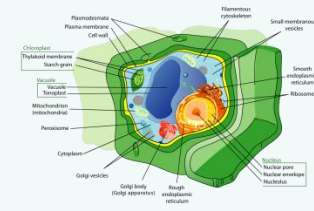
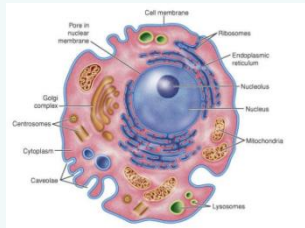
**Health/Disease/Pathobiology/Mechanisms  
(Humans, animals, microorganisms, viruses)**



**Directly relevant sub-proteome**

# Functional Proteomics

**Biological condition(s)**



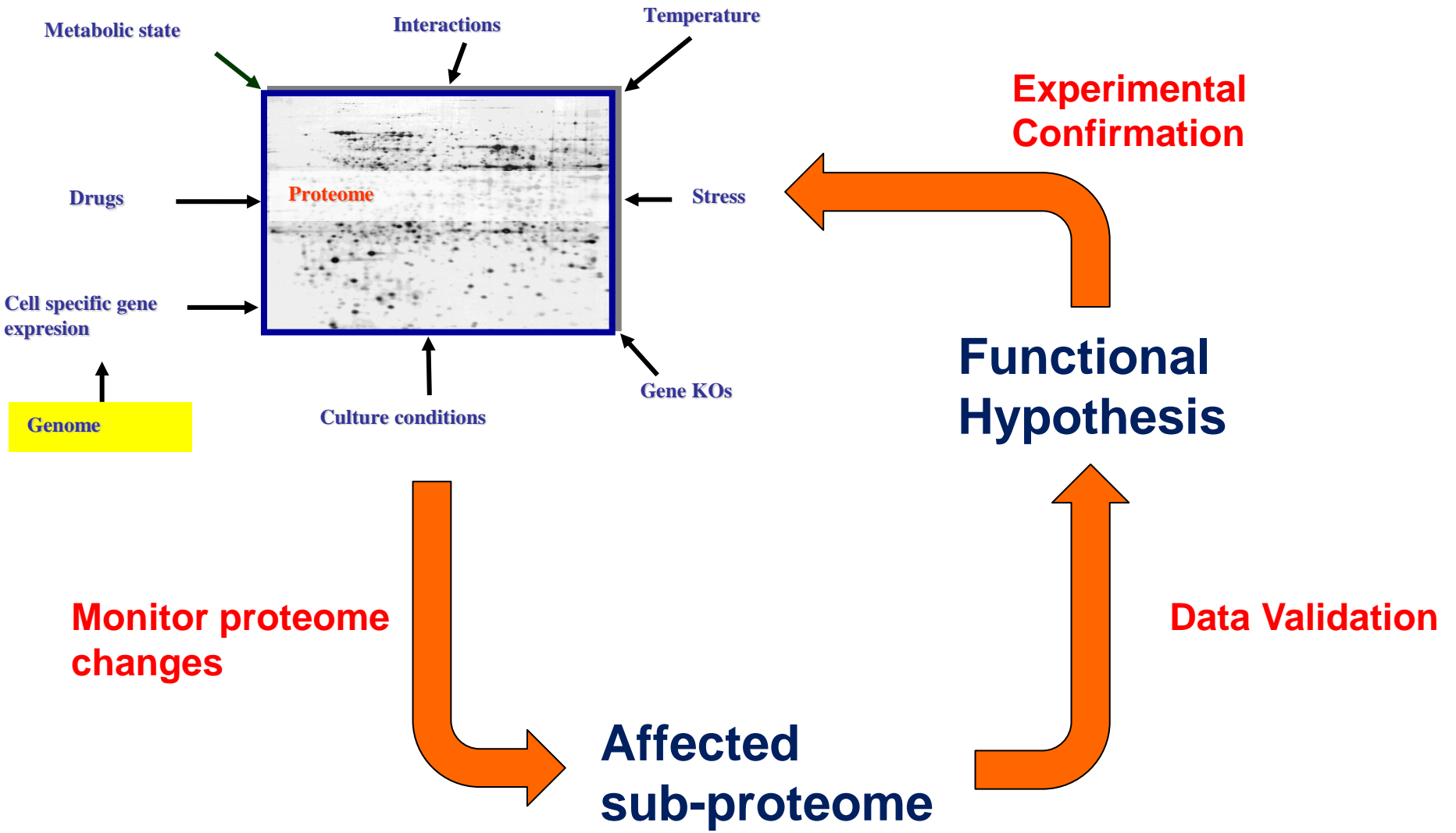
**Biological fluids**

**Protein(s)**

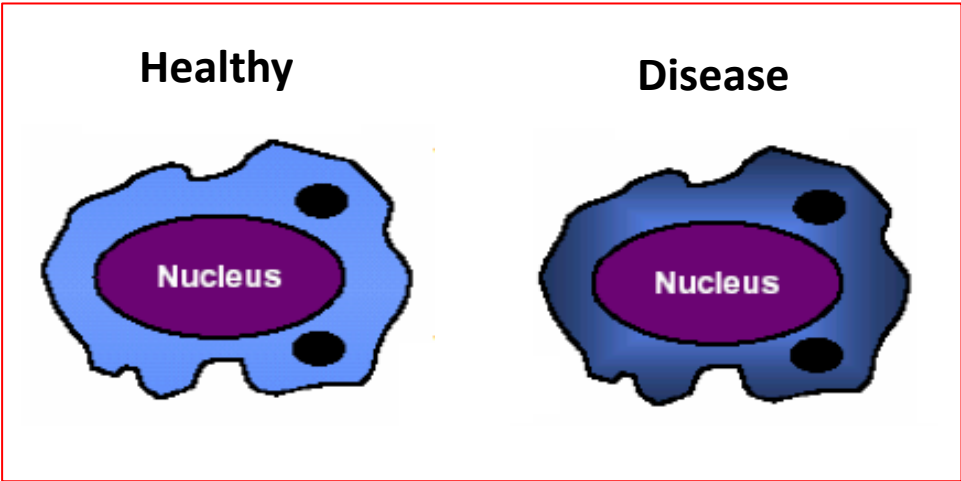
changes in:

- **Abundance**
- **Localization**
- **Modification**
- **Structure**  
(primary, quaternary)
- **Interaction**  
(binary, complexes)

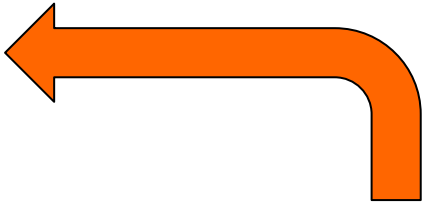
# Functional stimulation, perturbation, comparison



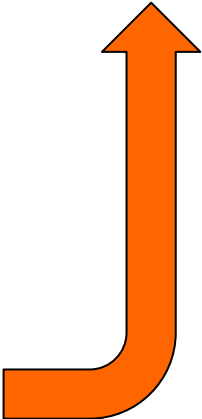
# Comparative Proteomics – Healthy vs Disease



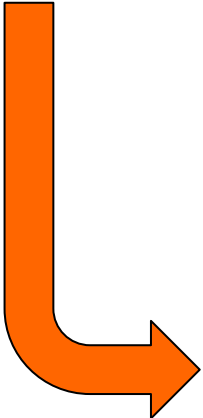
**Experimental Confirmation**



**Functional Hypothesis**



**Monitor proteome changes**

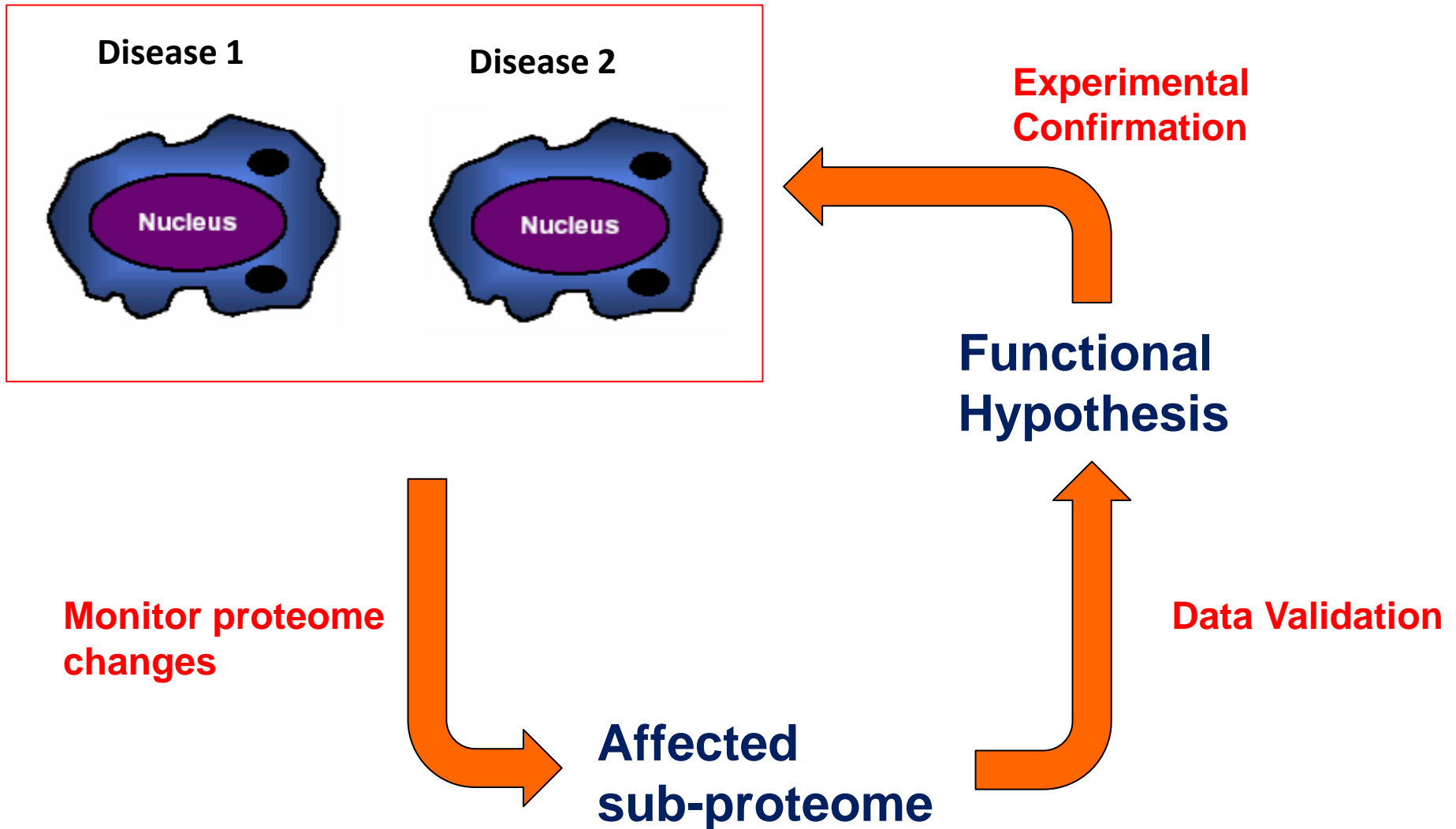


**Affected sub-proteome**

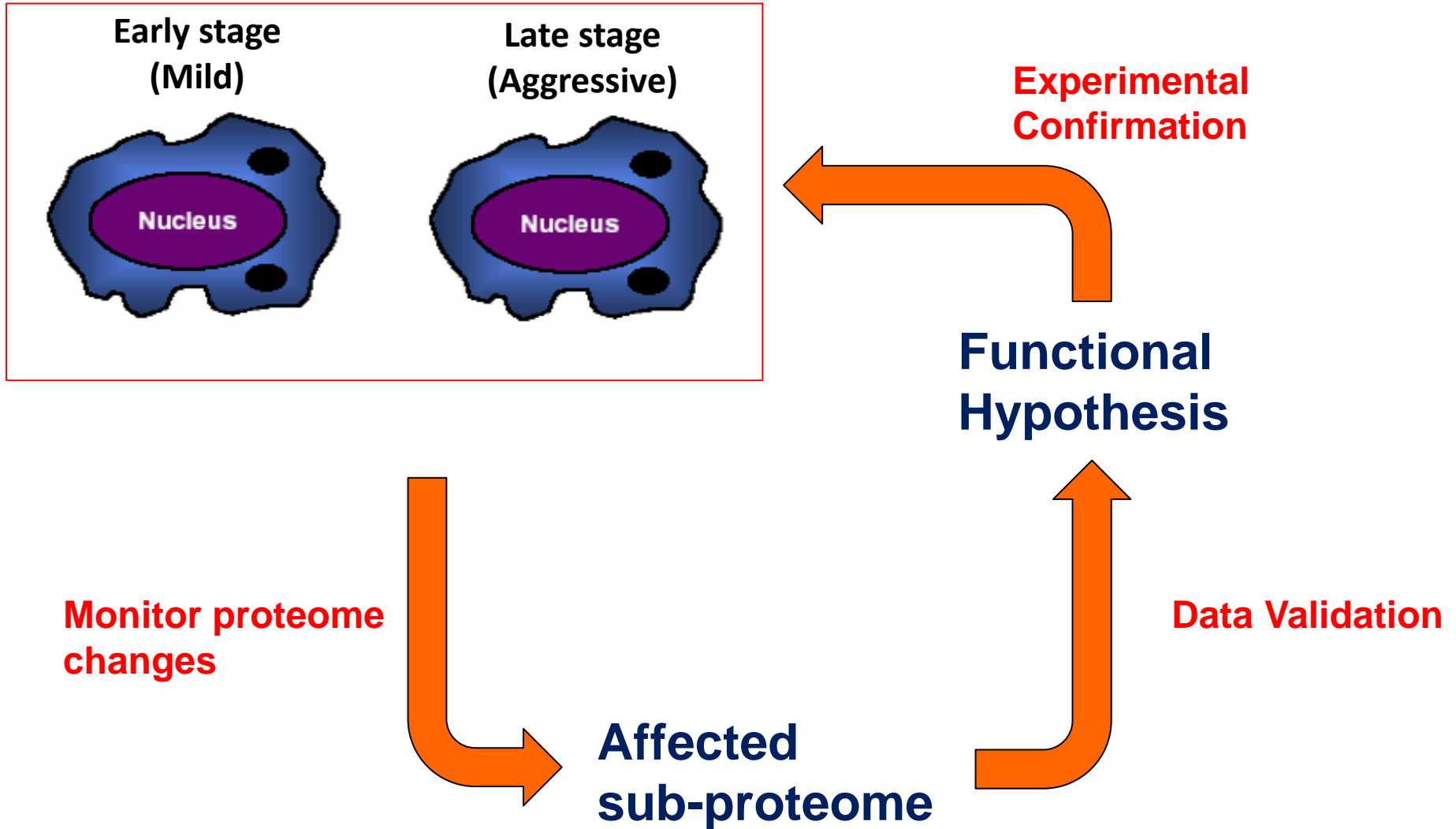
**Data Validation**



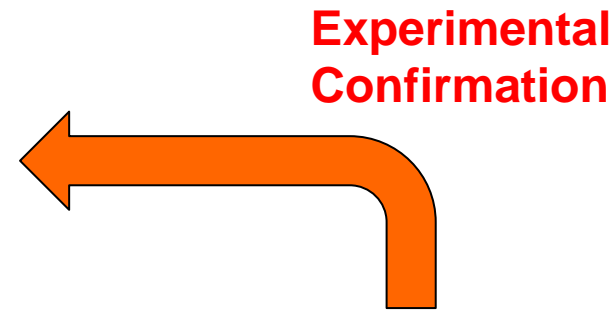
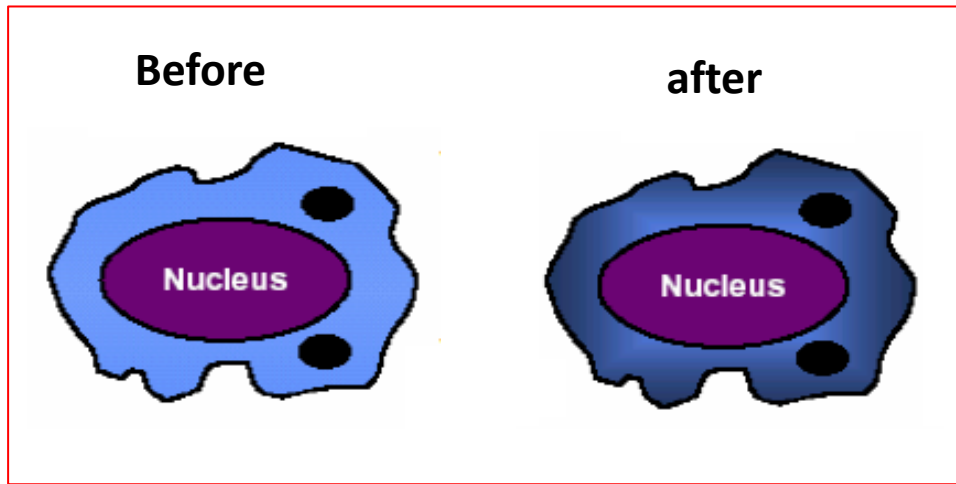
# *Comparative Proteomics: Disease 1–Disease 2*



# *Comparative Proteomics: Disease (sub) stages*

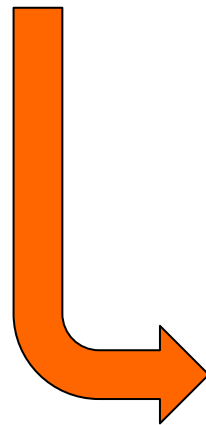


# *Comparative Proteomics – Diet/Nutrition effect*

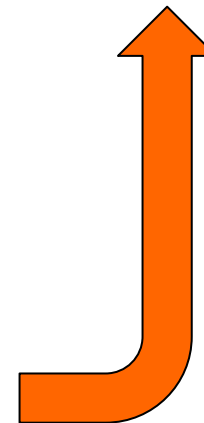


**Functional Hypothesis**

**Monitor proteome changes**



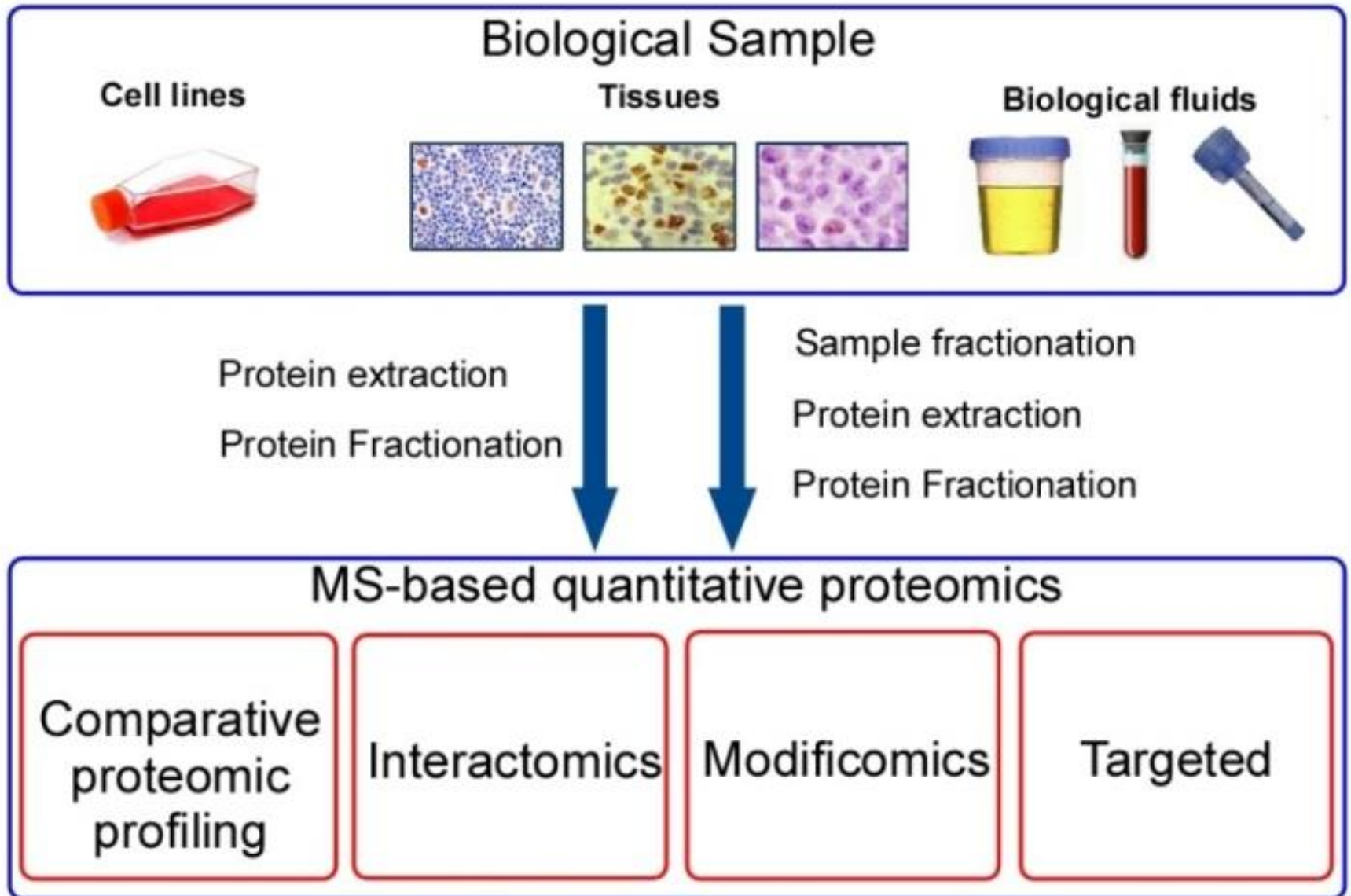
**Affected sub-proteome**



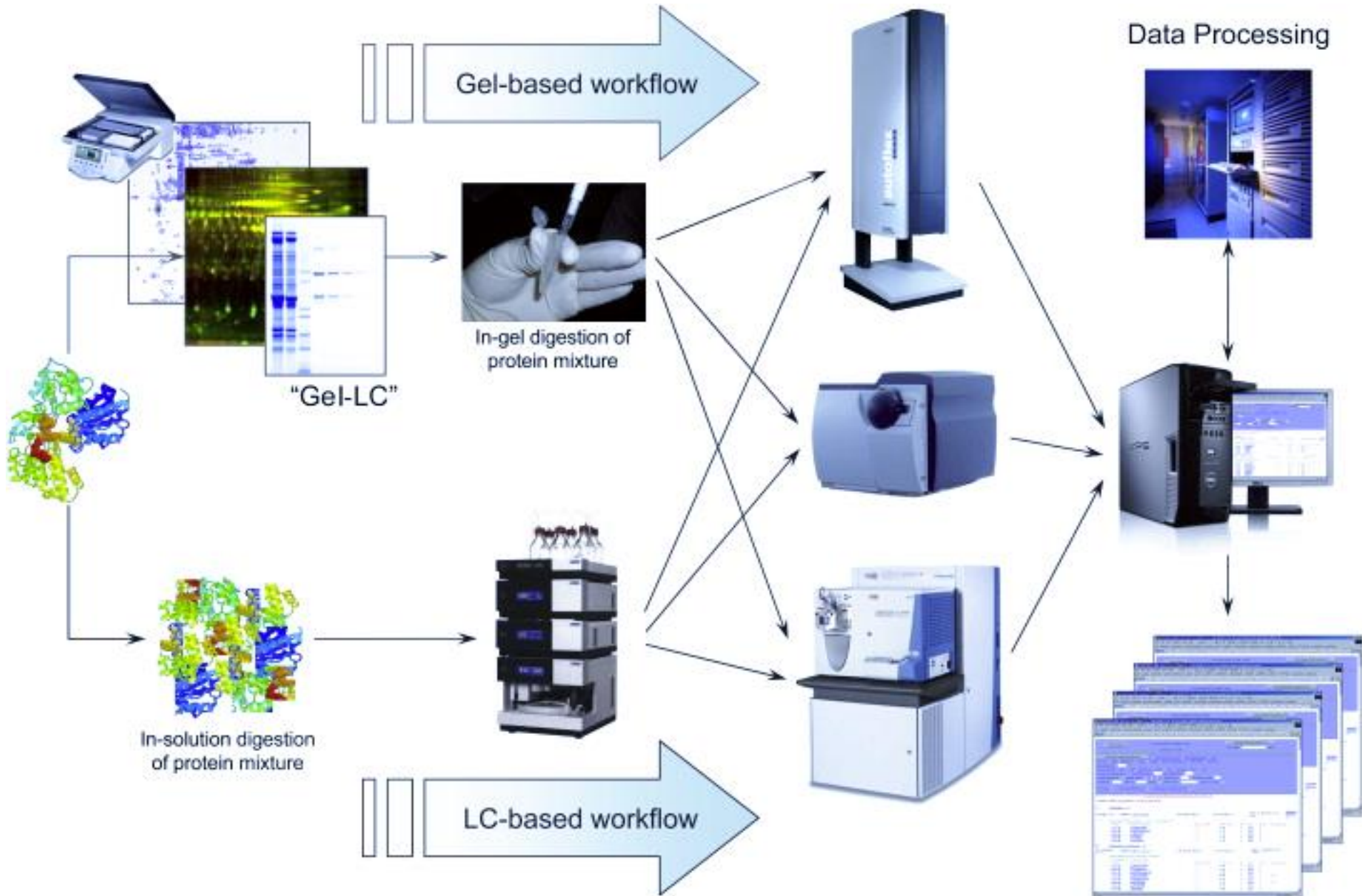
**Data Validation**



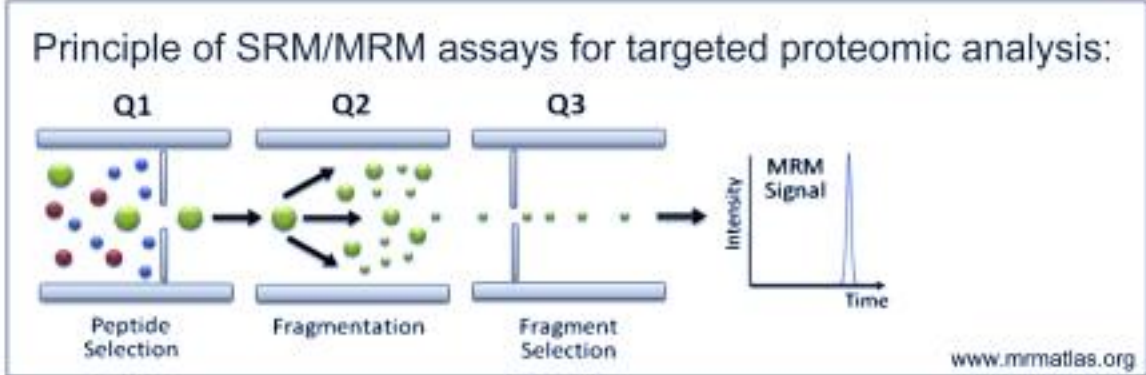
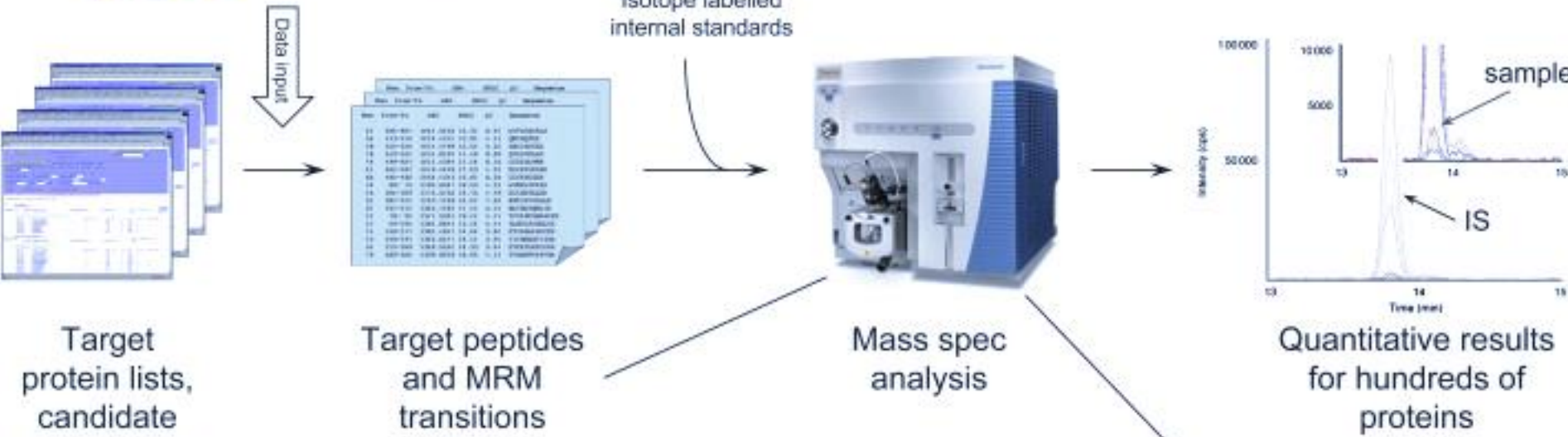
# *Quantitative Proteomics – Experimental Workflow*



# Comparative Proteomics – Discovery



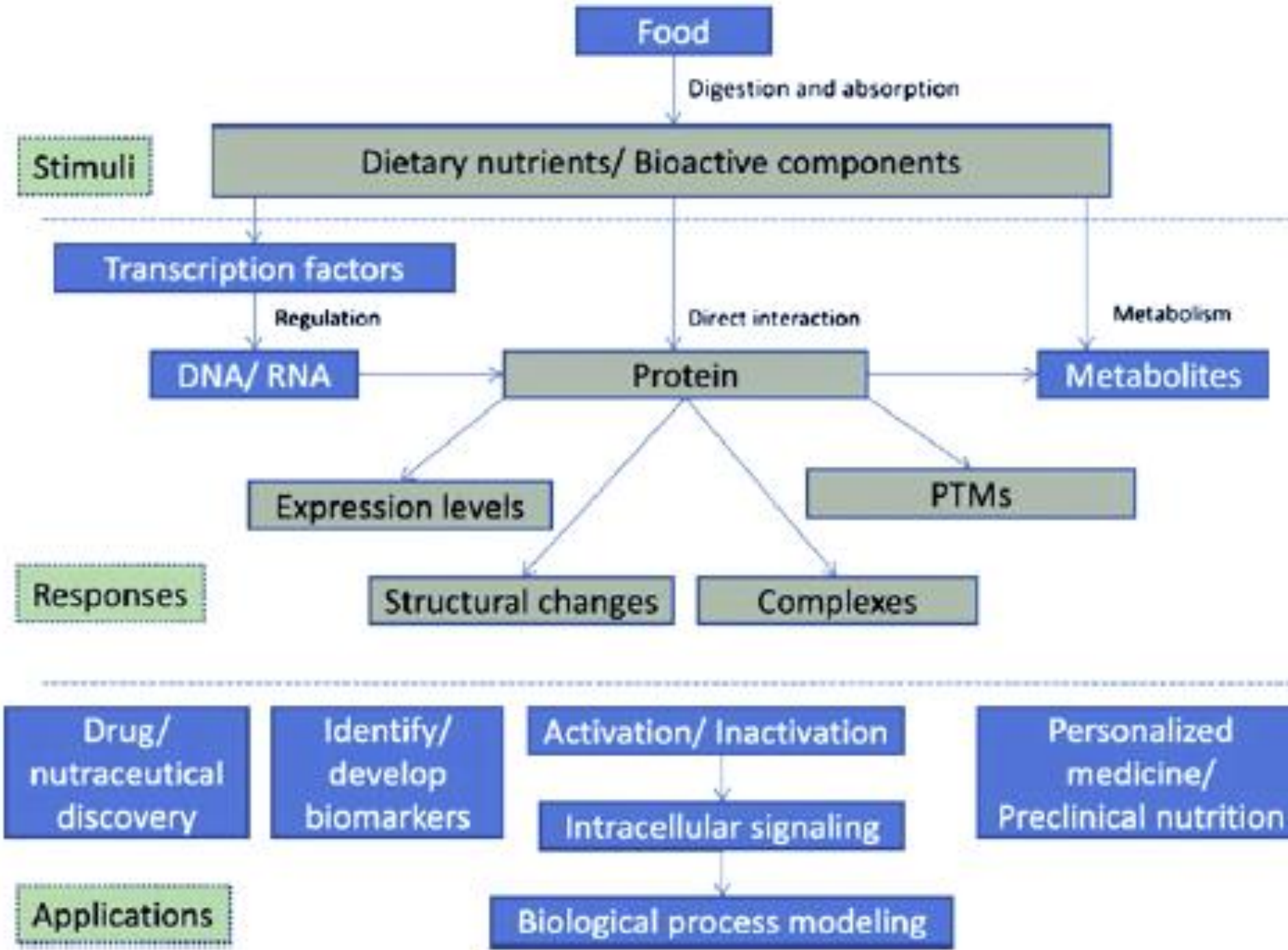
# Targeted Proteomics – Detection/Monitoring/Quantitation



# Nutritional proteomics or Nutriproteomics

Proteins and peptides derived from food and beverages can cause adverse allergic reactions but are in general required for multiple functions such as growth and homeostatic regulation.

Endogenously expressed human proteins and peptides can be used as biomarkers to monitor physiological deregulation and the effects of food consumption.



RESULTS BY YEAR

2,844 results

# Nutrigenomics: 240 articles 2021



1960

2022

RESULTS BY YEAR

25 results

# Nutriproteomics: 1 article 2021



2004

2021

# Nutrition AND proteomics: 541 articles 2021

RESULTS BY YEAR

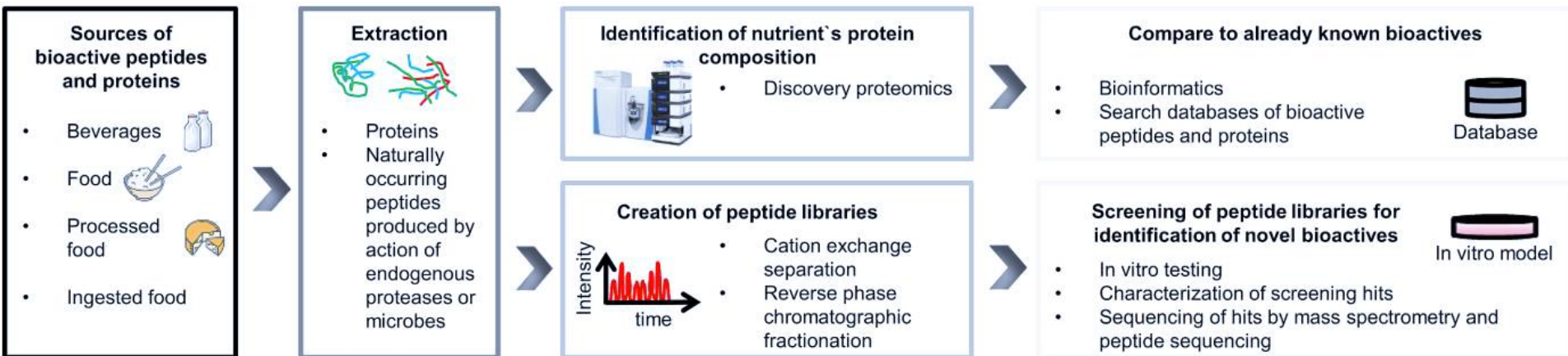
4,337 results



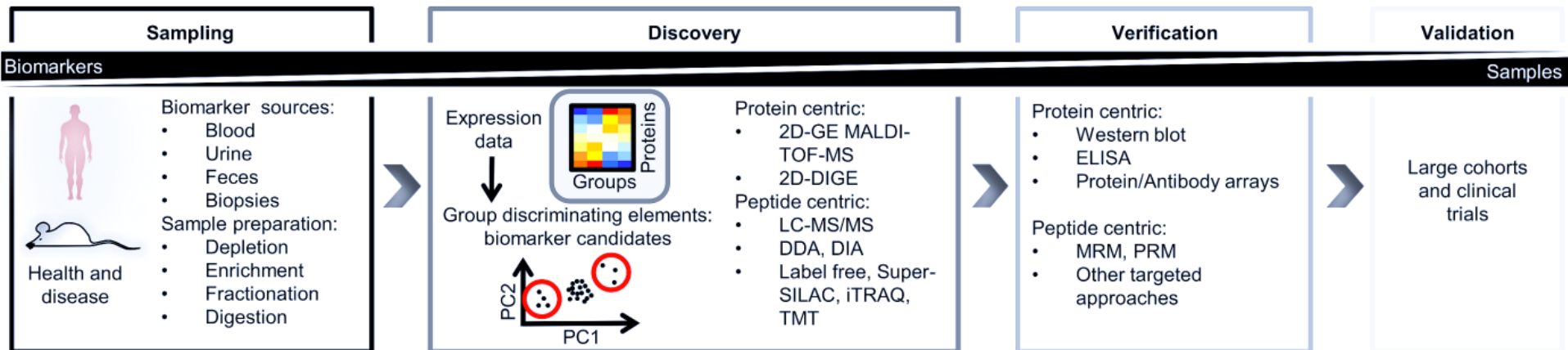
2000

2022

# Discovery of bioactive peptides and proteins from nutritional sources

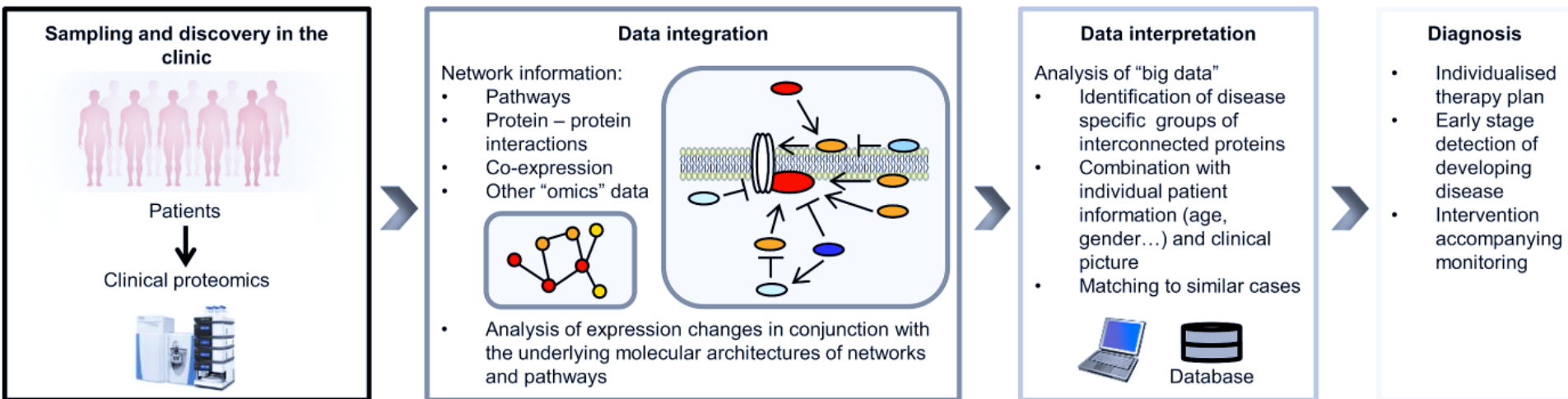


# Biomarker development in nutrition science

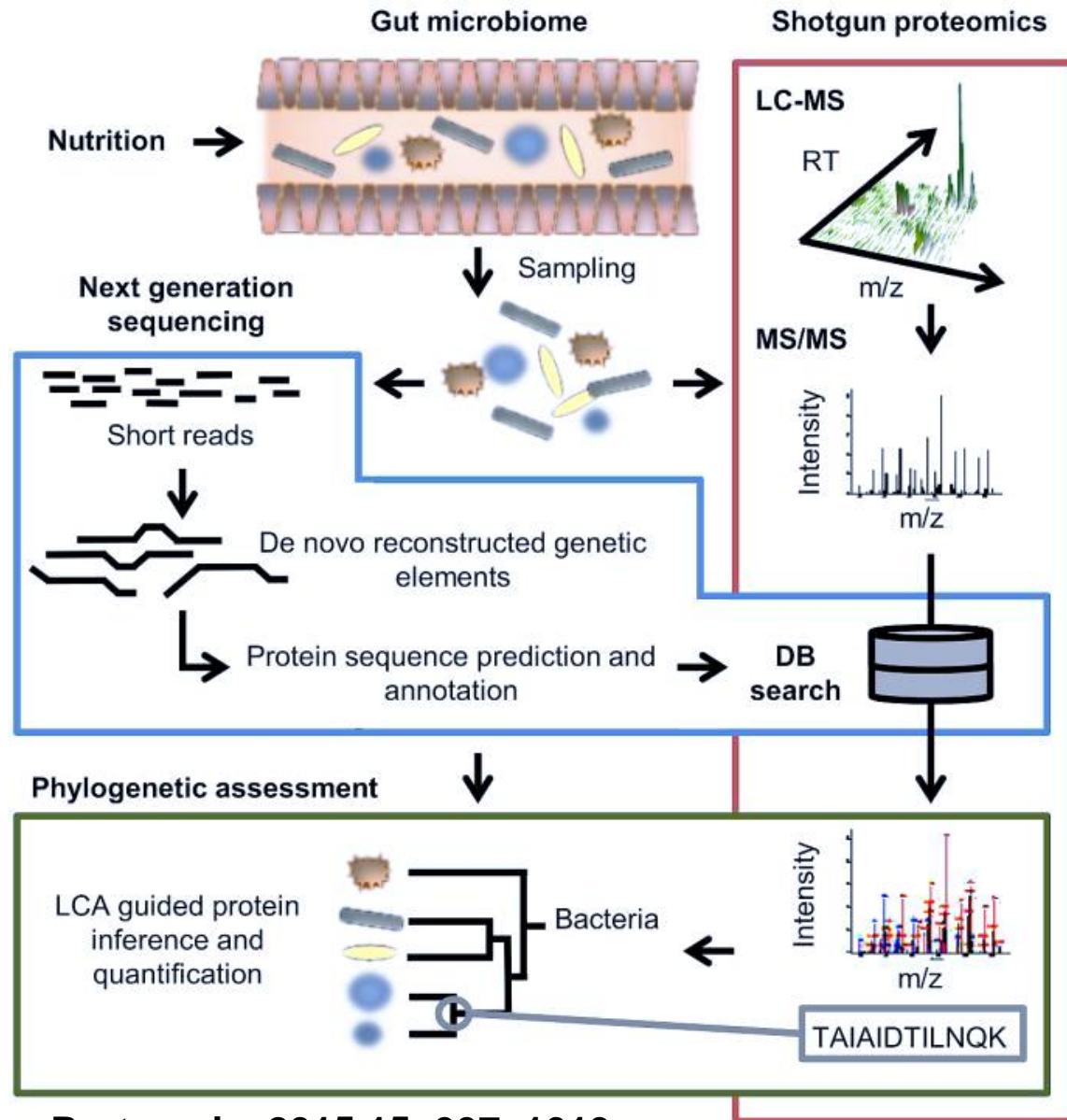




# Emerging proteomic strategies in the clinic



# An emerging workflow for shotgun proteomic analysis of complex ecosystems such as the human or animal intestine



# Understanding Nutritional Intervention for Cancer Treatment

## Phenotypic Interventions

Caloric Restriction

Fasting

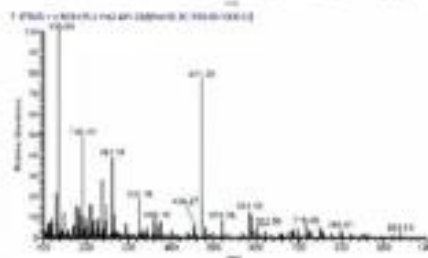
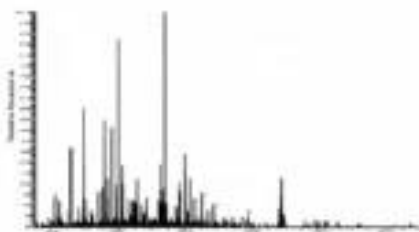
Ketogenic Diet



## Analytical Methodologies

Nutritional Proteomics

Nutritional Metabolomics

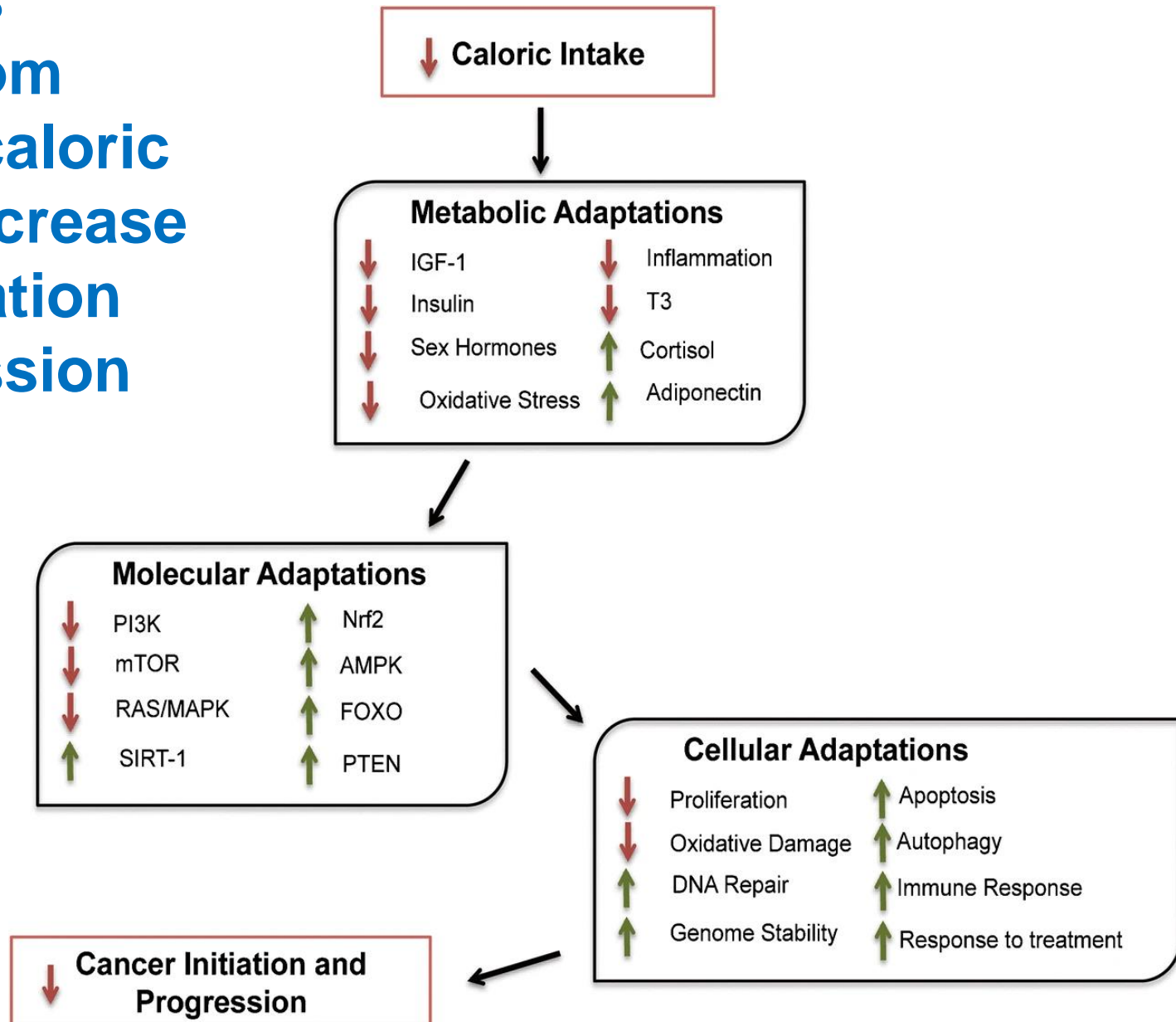


Application

Informed decision  
for treatment plan



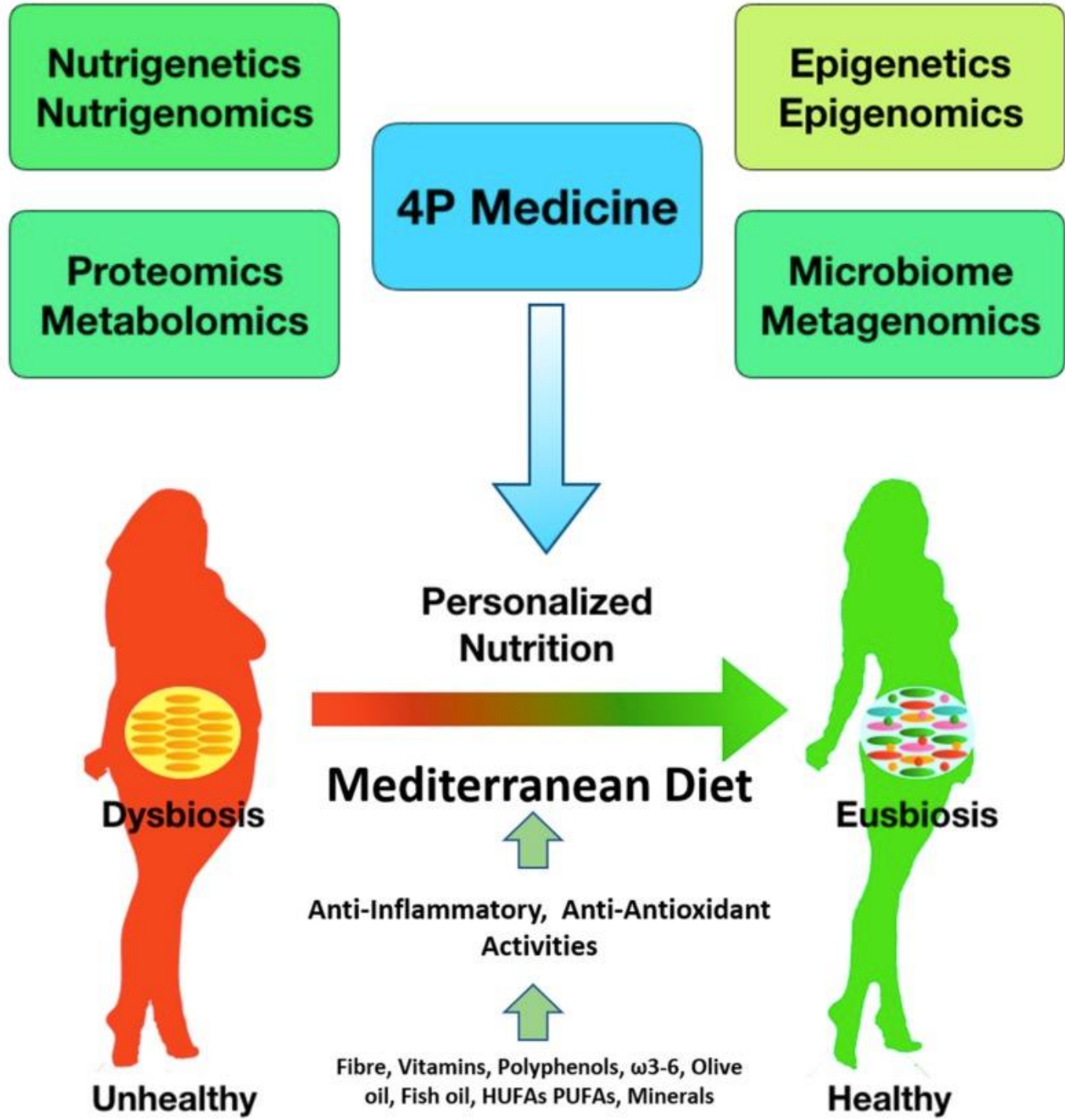
# Adaptations resulting from decreased caloric intake to decrease cancer initiation and progression



# Examples of proteomic studies in nutritional intervention in cancer

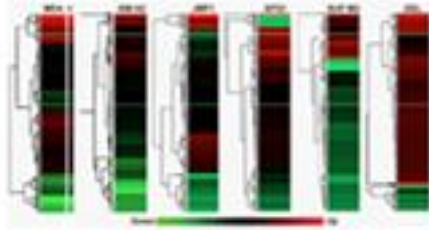
First author	Description	Sample type	Method	Reference
Dayon et al.	A scalable automated proteomic pipeline (ASAP <sup>2</sup> ), a sample preparation procedure that automates the depletion and general shotgun proteomics workflow for biomarker discovery	Serum	• Untargeted LC-MS/MS	[128]
Procházková et al.	Identify and quantify 16 protein biomarker candidates in complex breast cancer tumor samples to determine the tumor grade and lymph node status	Breast cancer tissue	• Untargeted LC-MS/MS • MRM LC-MS/MS	[133]
Shiromizu et al.	Determined annexin family of proteins are a prognostic marker for determining stage of colorectal cancer using global proteomics followed by targeted proteomics	Colon cancer tissue	• Untargeted LC-MS/MS • MRM LC-MS/MS	[134]
Sjöström et al.	A biomarker study on the N-glycosylated proteome of breast cancer	Breast cancer tissue	• Untargeted LC-MS/MS • MRM LC-MS/MS	[135]
Kawashima et al.	Determined proteomic changes in mice fed with high omega-3 versus high omega-6 diets	Murine liver tissue		[136]
Schroll et al.	A study on proteomic changes associated with serum or glucose starvation for 72 h in 3D cell culture	Colon cancer cell line (HCT 116)	• Untargeted LC-MS/MS	[53]
Schroll et al.	Global proteomic study to determine proteins that were deregulated when colon cancer 3D cell cultures were treated with glucose starvation, autophagy inhibition, and chemotherapy	Colon cancer cell line (HCT 116)	• Untargeted LC-MS/MS	[137]

# Role of Personalized Nutrition in Chronic-Degenerative Diseases

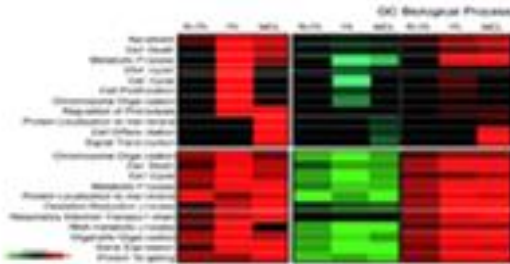


## Bioinformatics and Functional analysis

Protein ID/Quant  
Comparison



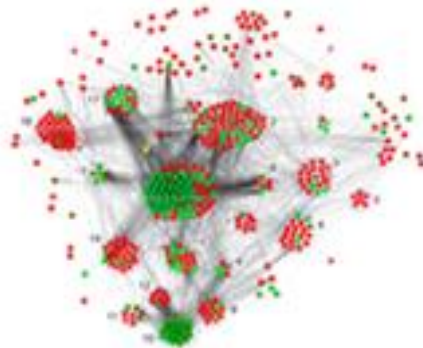
GO terms  
Enrichment analysis



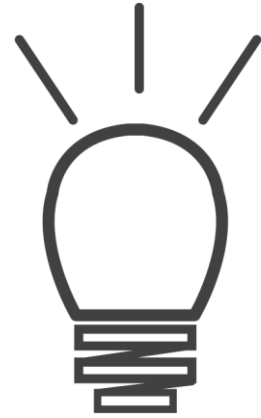
Pathway analysis



Protein Interactions  
network analysis



Gained  
Information



**WISDOM**

Personalized Medicine

Disease Mechanisms

Diagnostic/prognostic biomarkers

Novel therapeutic strategies

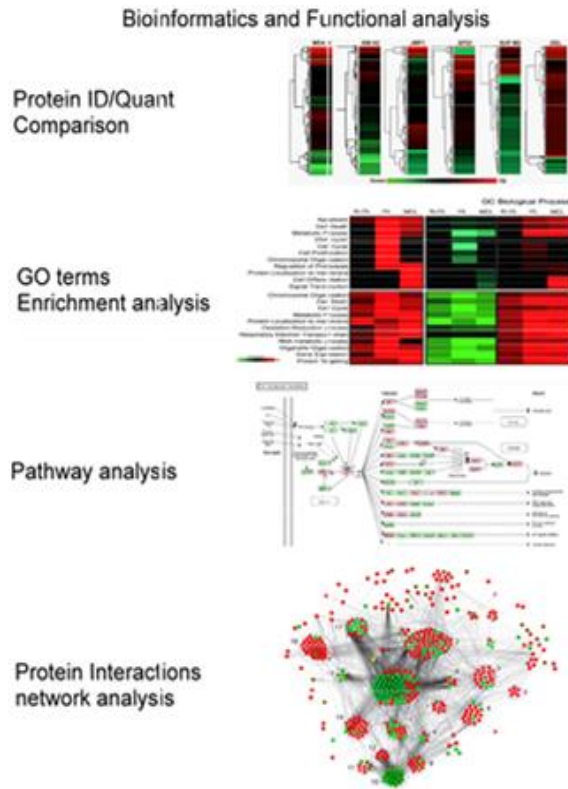
Novel Clinical tools

Integrated Multi-omics Repository

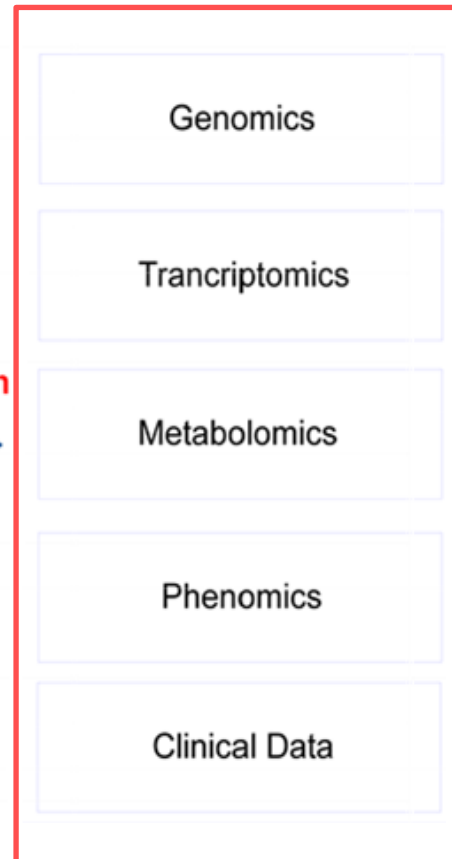
# Personalized Medicine

## Personal Protein Social Networks

### Our Data



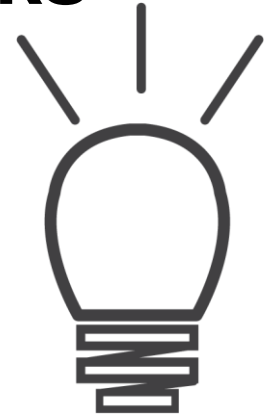
### Public Data



Integration



Gained Information



**W I S D O M**

Personalized Medicine

Disease Mechanisms

Diagnostic/prognostic biomarkers

Novel therapeutic strategies

Novel Clinical tools

Integrated Multi-omics Repository



# Current status in Nutriproteomics

Advances in nutriproteomics [Adapted from Wang et al. with permission] [14].

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Composition and characteristics of dietary proteins

Digestion and absorption of nutrients in the gastrointestinal tract

Nutrient metabolism (synthesis and catabolism) and its regulation

- Interorgan transport of nutrients
- Organelle-, cell and tissue-specific metabolism of nutrients
- Discovery of novel metabolic pathways and the mechanisms of their regulation

Functions of nutrients and phytochemicals in growth, reproduction, and health

- Signal transduction and cellular defense against oxidative stress
- Cell proliferation, differentiation and apoptosis
- Gene expression in response to nutrients and other dietary factors
- Fetal and postnatal growth, development and health
- Dietary prevention and intervention of disease

Protein profiles and characteristics in cells, tissues, and physiological fluids

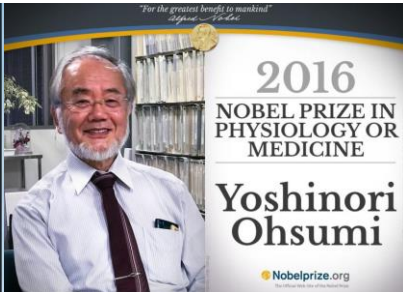
Biomarkers and individualized requirements of nutrients

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# More information



”Life is in an  
equilibrium state  
between synthesis  
and degradation of  
proteins.”

FUNCTIONAL PROTEOMICS AND SYSTEMS  
BIOLOGY RESEARCH GROUP

Aivaliotis Research Group

- About us
- Research
- Members
- Publications
- Tools
- Teaching
- Funding
- Photos
- Useful links
- ↓
- Awards and distinctions
- Collaborators
- Intranet
- Presentations
- Press Releases
- Contact us

<http://aivaliotis.webpages.auth.gr/>



**Thank you!!!**