

A Systems Biology View to Diabetes

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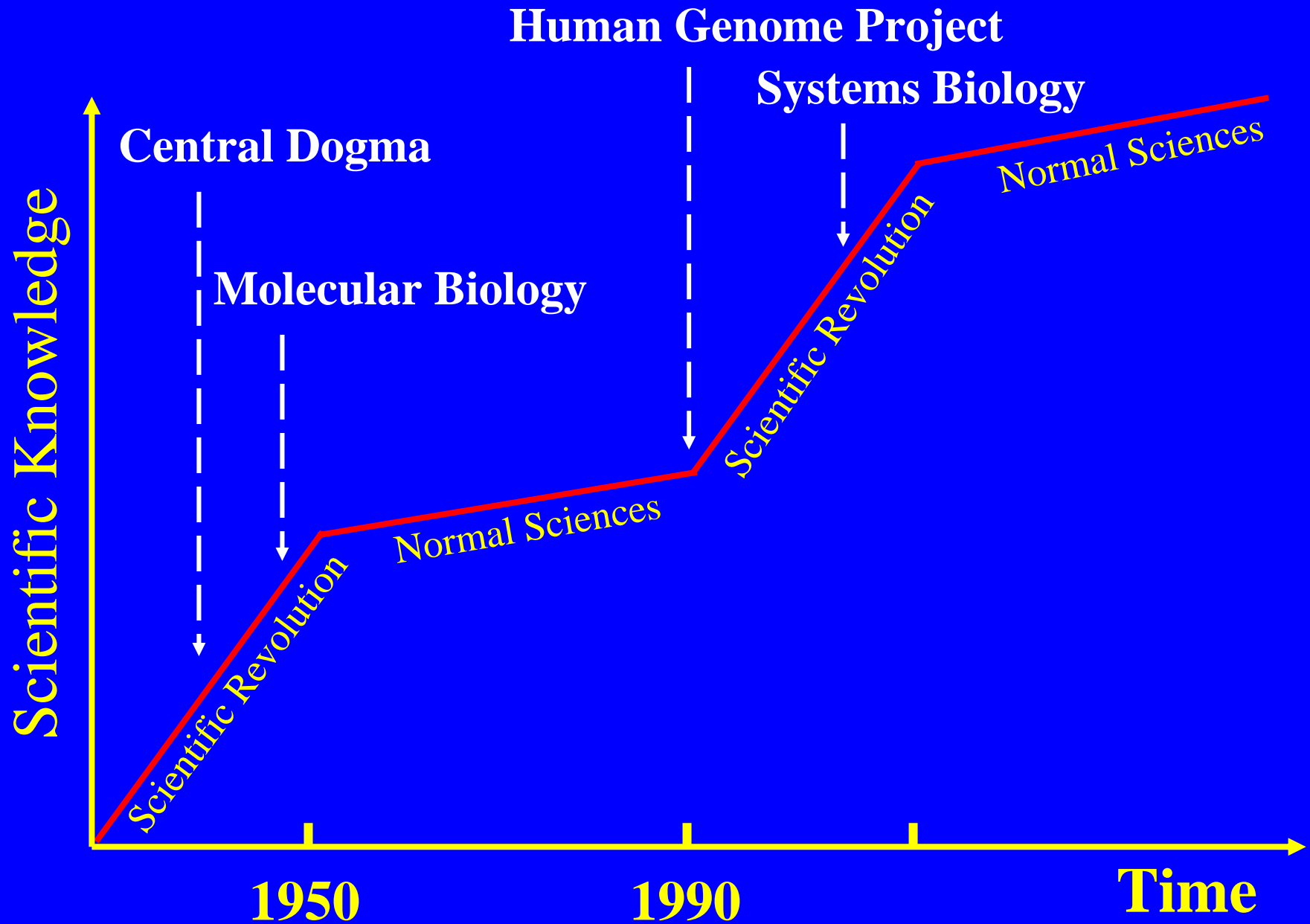
Department of Systems Biology, USTC

Part I

New Trends in Life Science in 21th Century:

Systems Biology

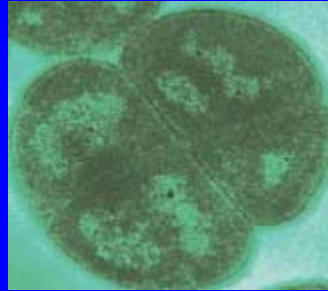
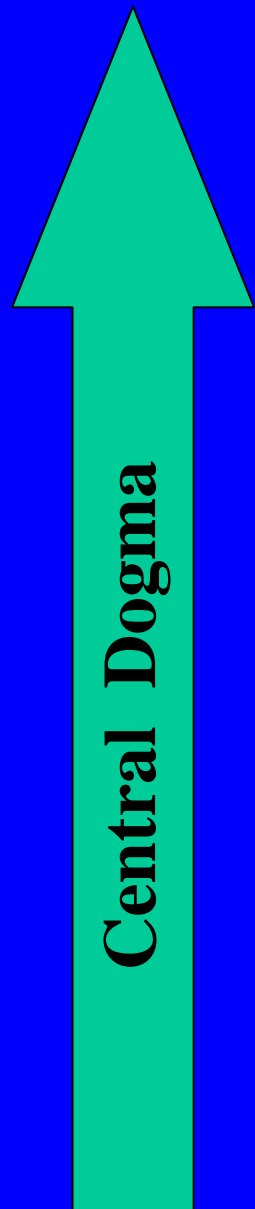
Scientific Revolution in Life Science in 21th



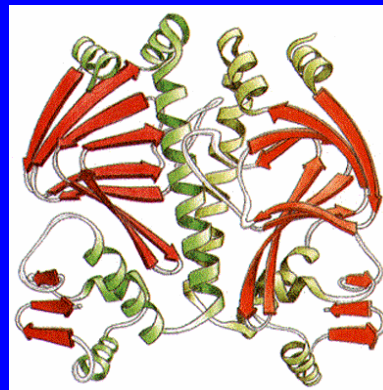
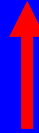
First Scientific Revolution

Change the View of Life

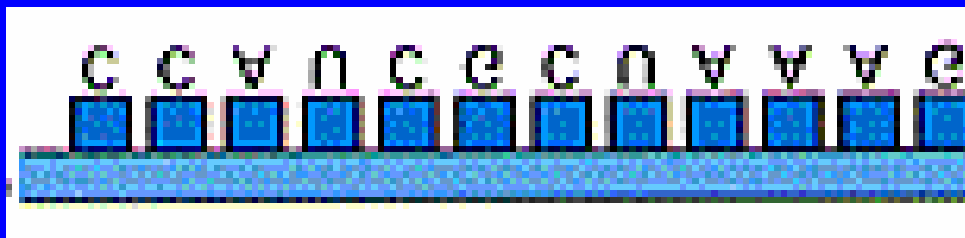
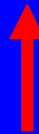
Philosophy for Biologists in 20th Century: **Reductionism**



Function



Protein



Gene

Classic View of Life: Simple System

One gene



One protein



One function

RESEARCH ARTICLE

Structural Basis for Double-Stranded RN

III (fig. S1). Although previous bacterial RNase III crystal structures revealed a single catalytic metal ion in each RNase III domain (21), subsequent studies implicated two metal ions in the

**nature
cell biology**

2005, 7,
1167

A schizo
cerebral

ARTICLES

Vol 438|15 December 2005|doi:10.1038/nature04225

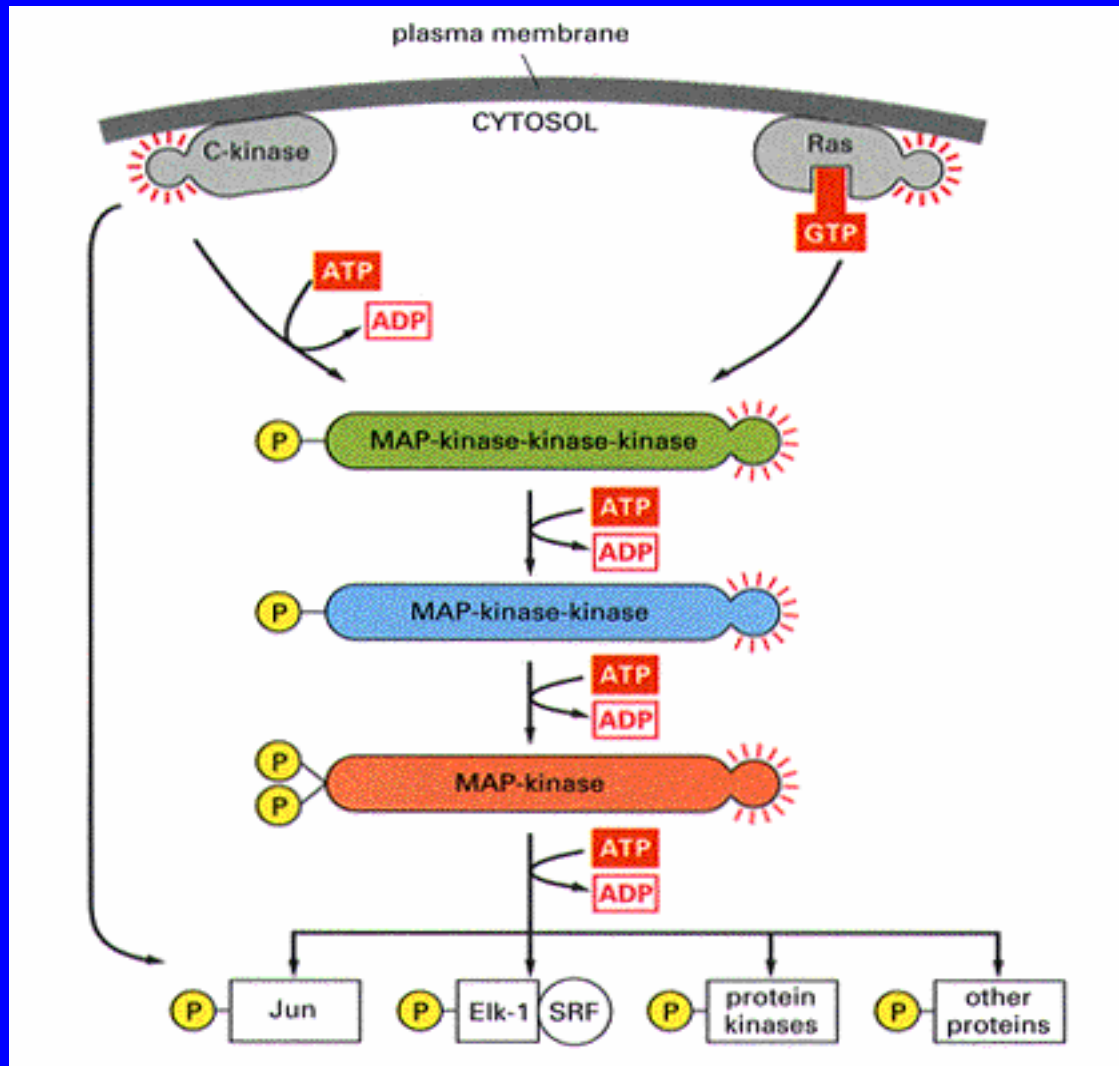
nature

ARTICLES

**Hypomethylation-linked activation of
PAX2 mediates tamoxifen-stimulated
endometrial carcinogenesis**

Research limited in individual gene or protein

Classic View of Life: Simple System



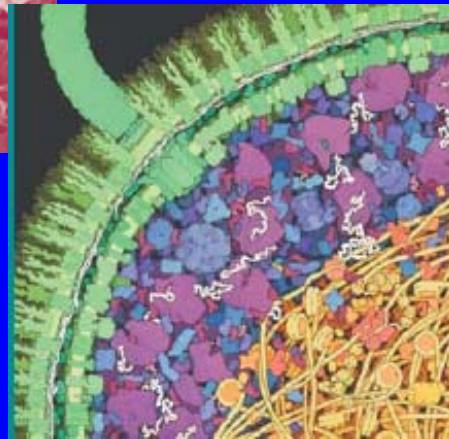
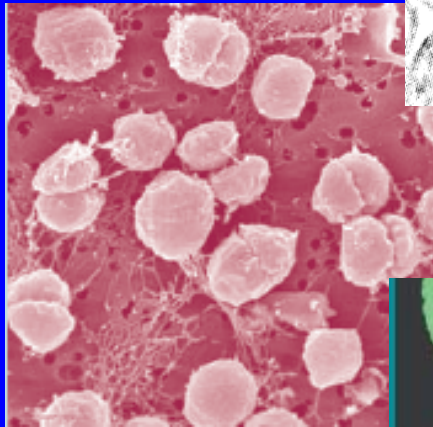
Research based on linear interaction

Real Picture of Life



Genes of Human

~ 300 00

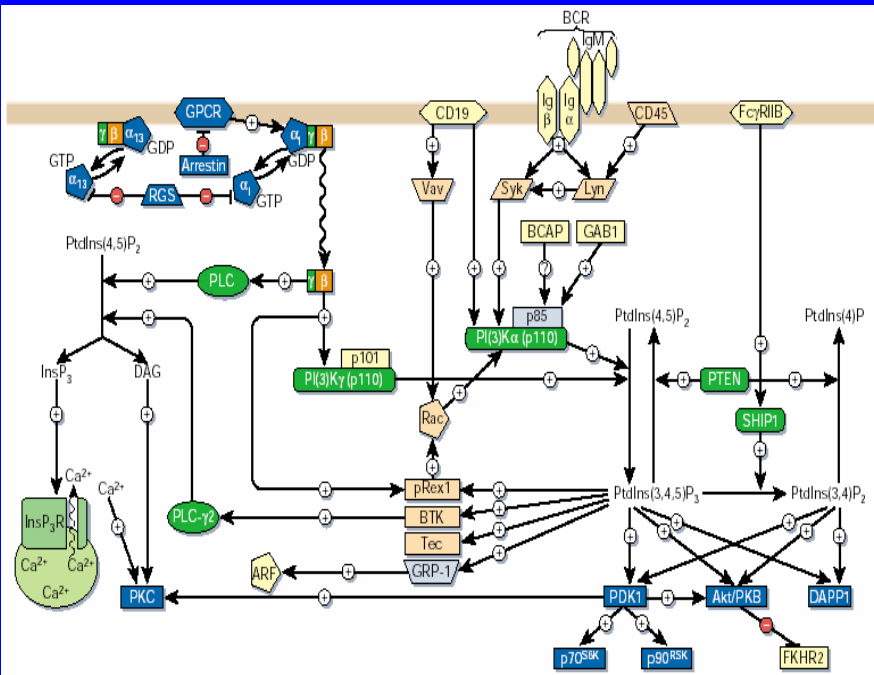


Proteins of Human

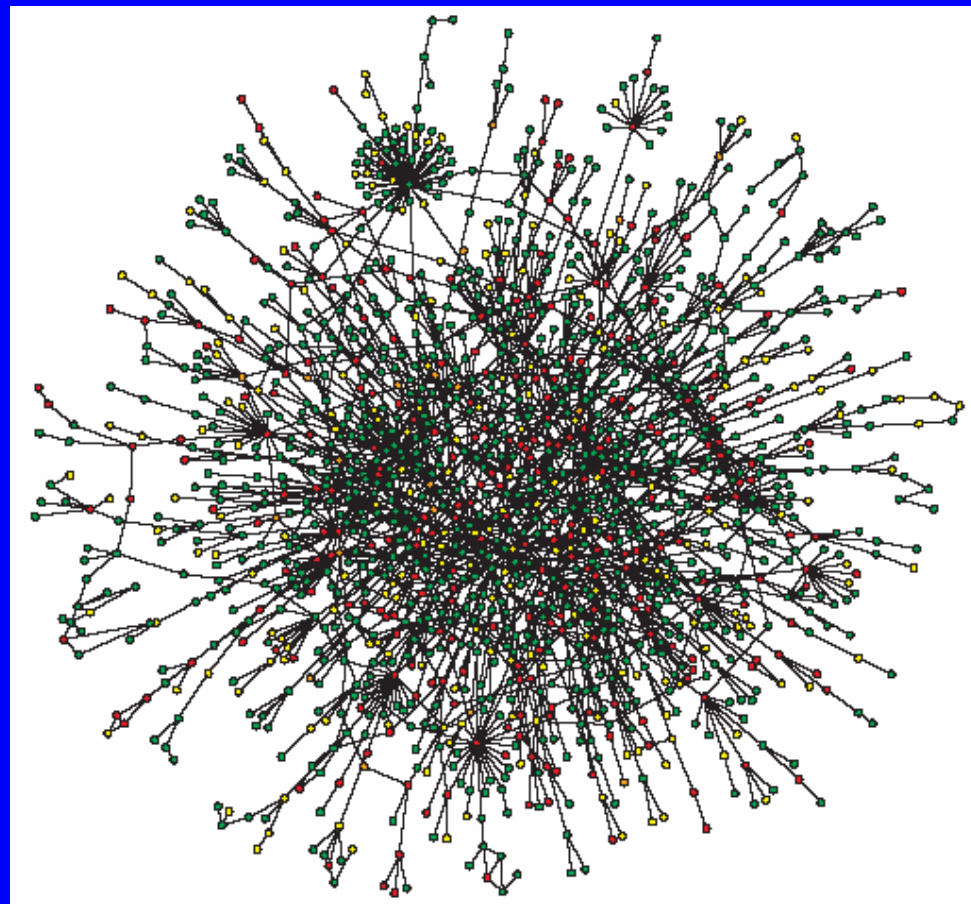
Millions

Real Picture of Life

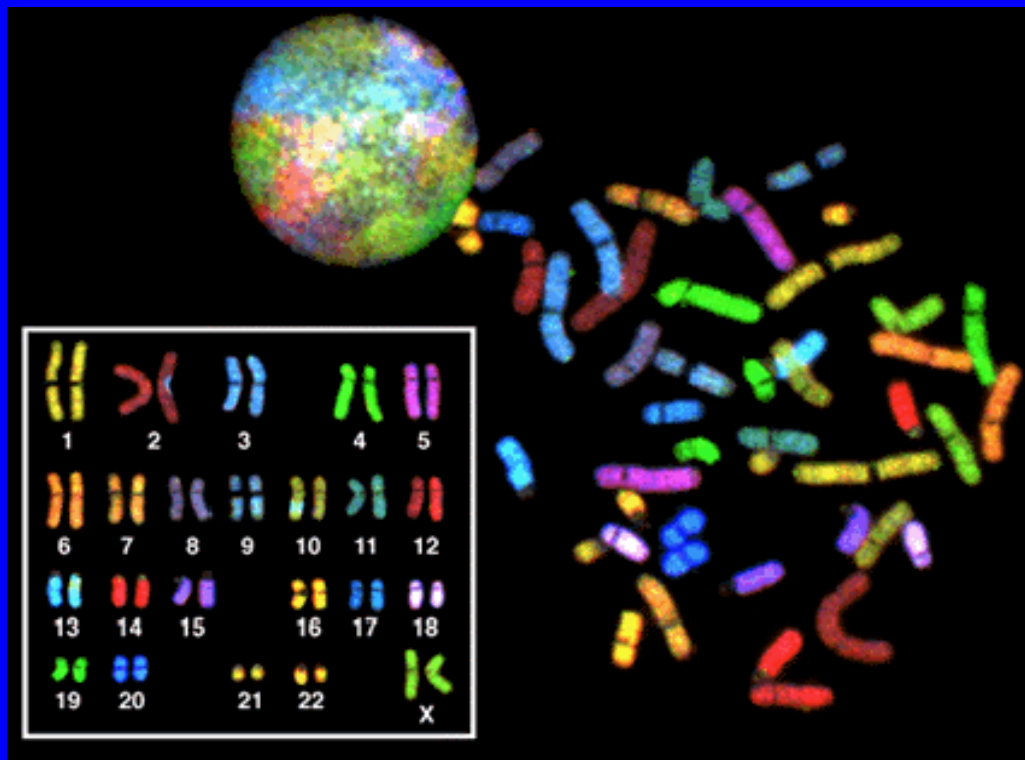
Signaling Network



Protein Interaction Network

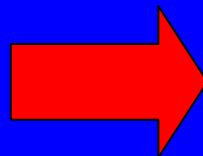
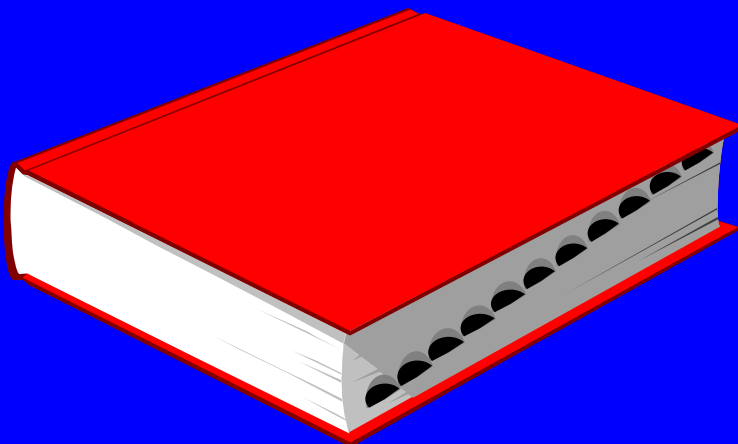


Human Genome Project



23 Chromosome
(3.3×10^9 bp)

Genes: ~ 30,000
~1.5% for coding protein



```
CTGCCGTTACTGCCCTGTGGGGCAAGGTGA  
ACGTGGATGAAGTTGGTGGTGAGGCCCTGG  
GCAGGTTGGTATCAAGGTTACAAGACAGGT  
TTAAGGAGACCAATAGAACTGGGCATGTG  
GAGACAGAGAAGACTCTTGGGTTTCTGATA  
GGCACTGACTCTCTCTGCCTATTGGTCTAT  
TTCCACCCTTAGGCTGCTGGTGGTCTAC  
CCTTGGACCCAGAGGTTCTTTGAGTCCTTT  
GGGGATCTGTCCACTCCTGATGCTGTTATG
```

Post-Genome Era

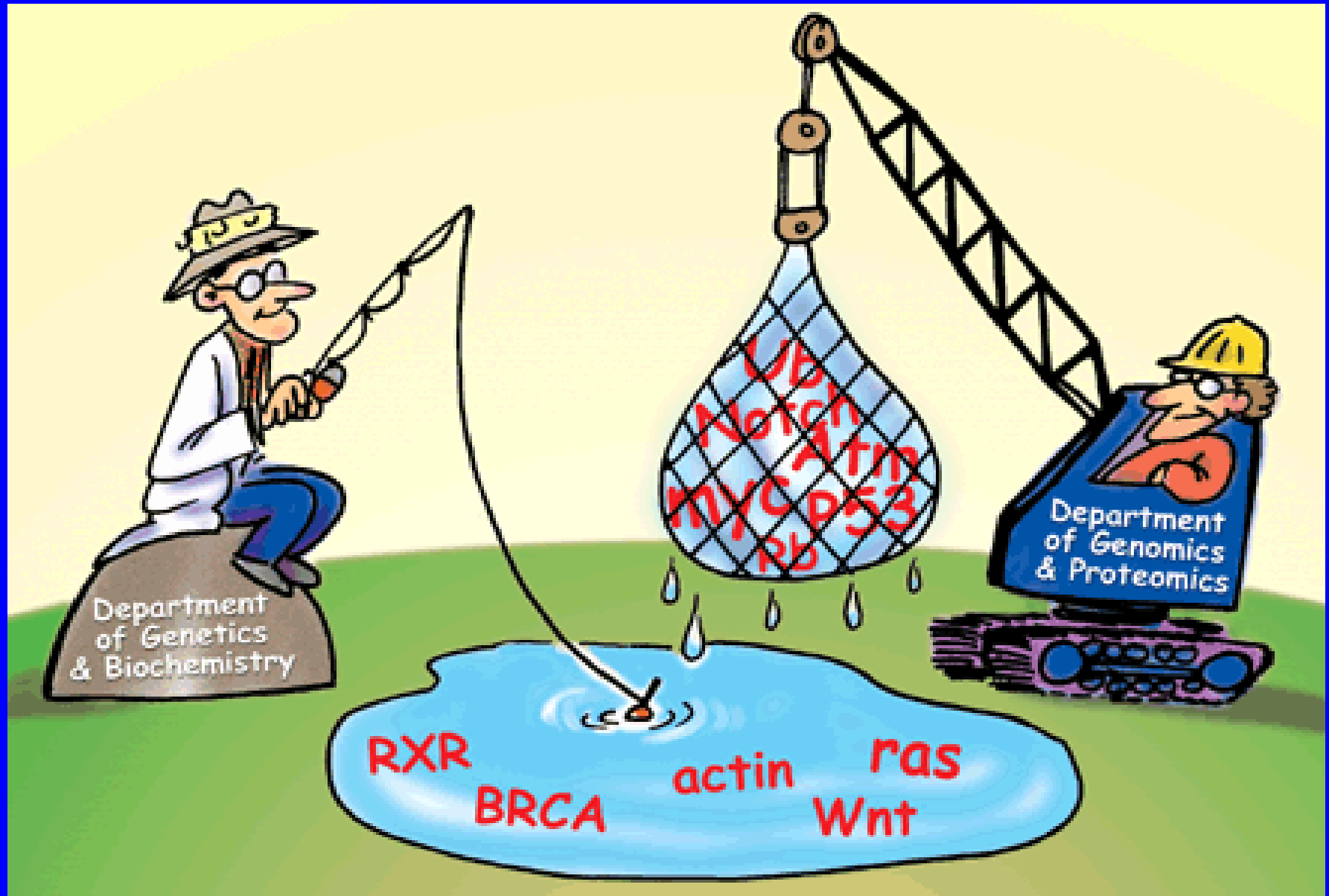
DNA Books



-Omics

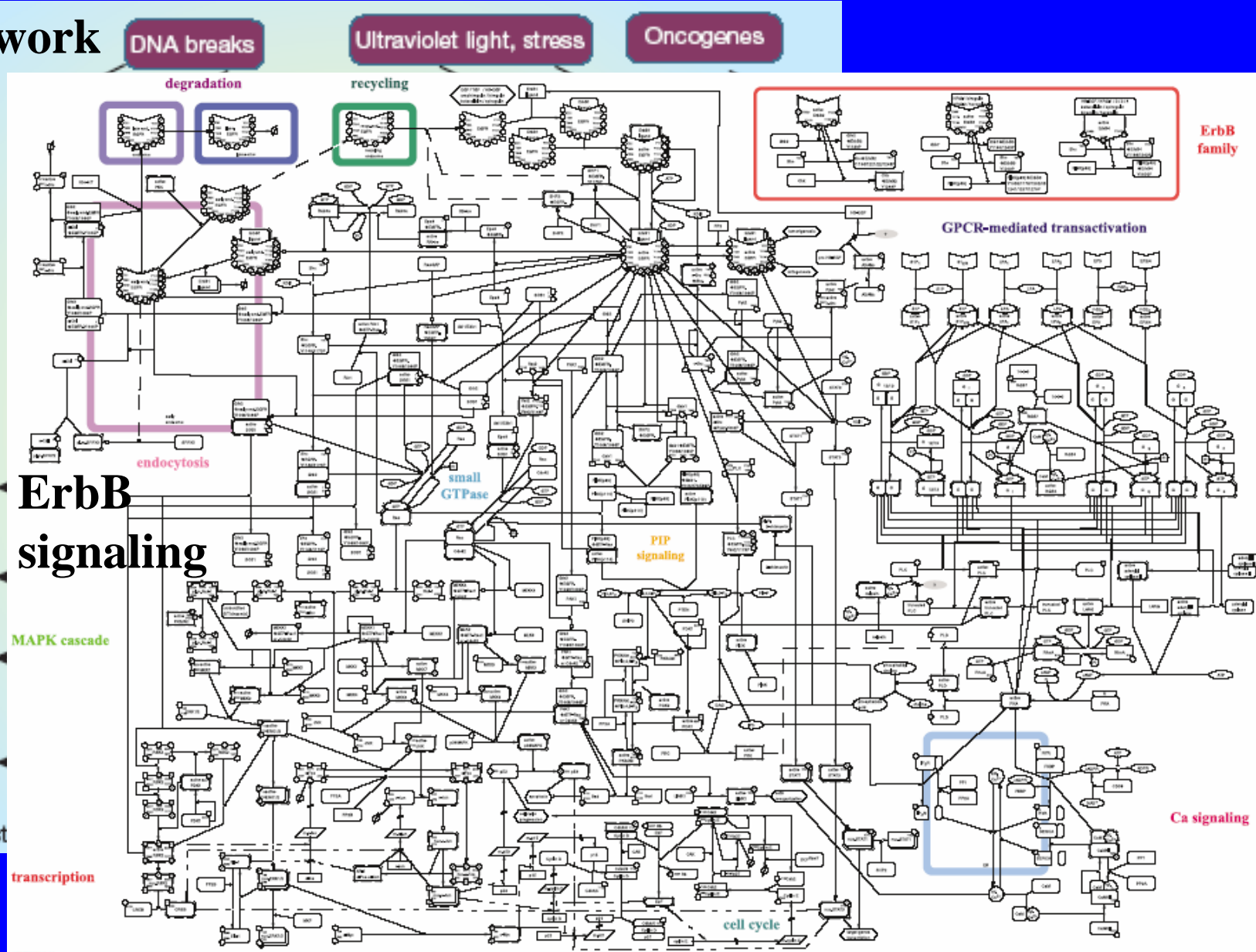
- Genomics
- Transcriptomics
- Proteomics
- Metabolomics

Novel View of Life in 21st Century: Holism

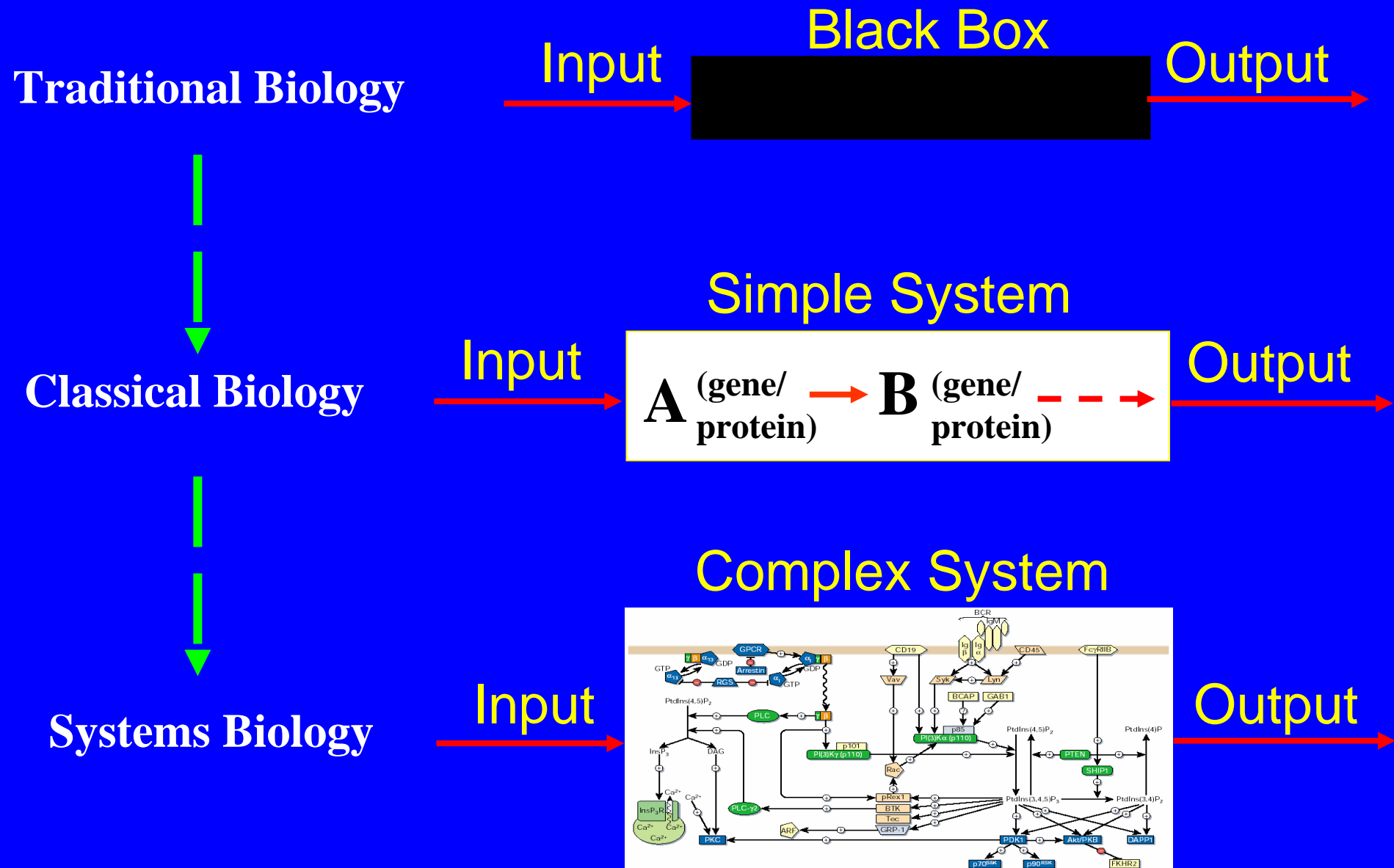


Novel View of Life : Complex System

p53 network



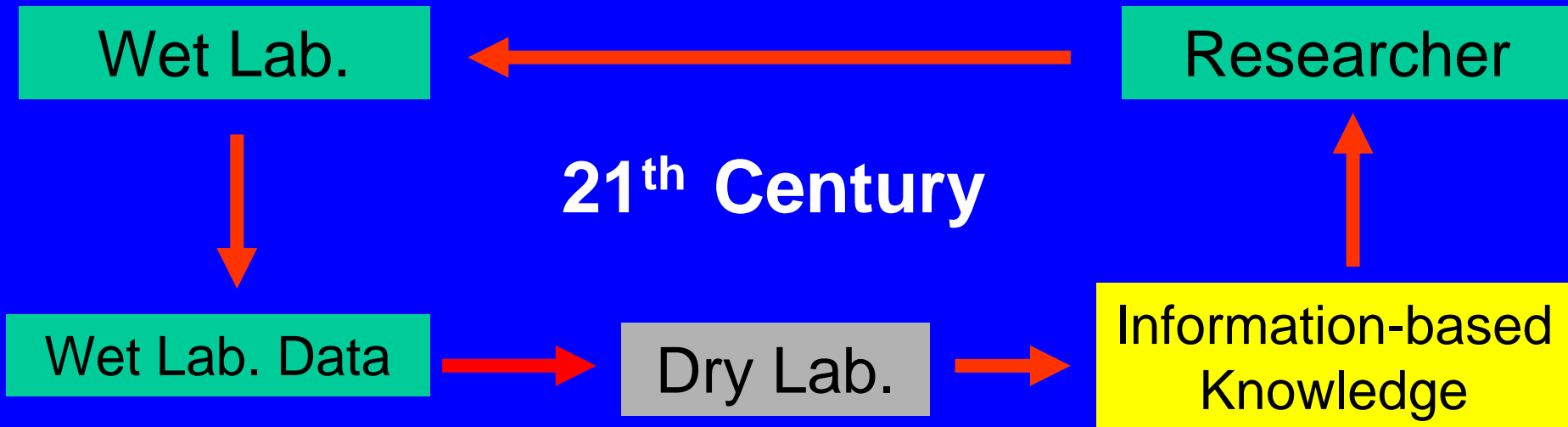
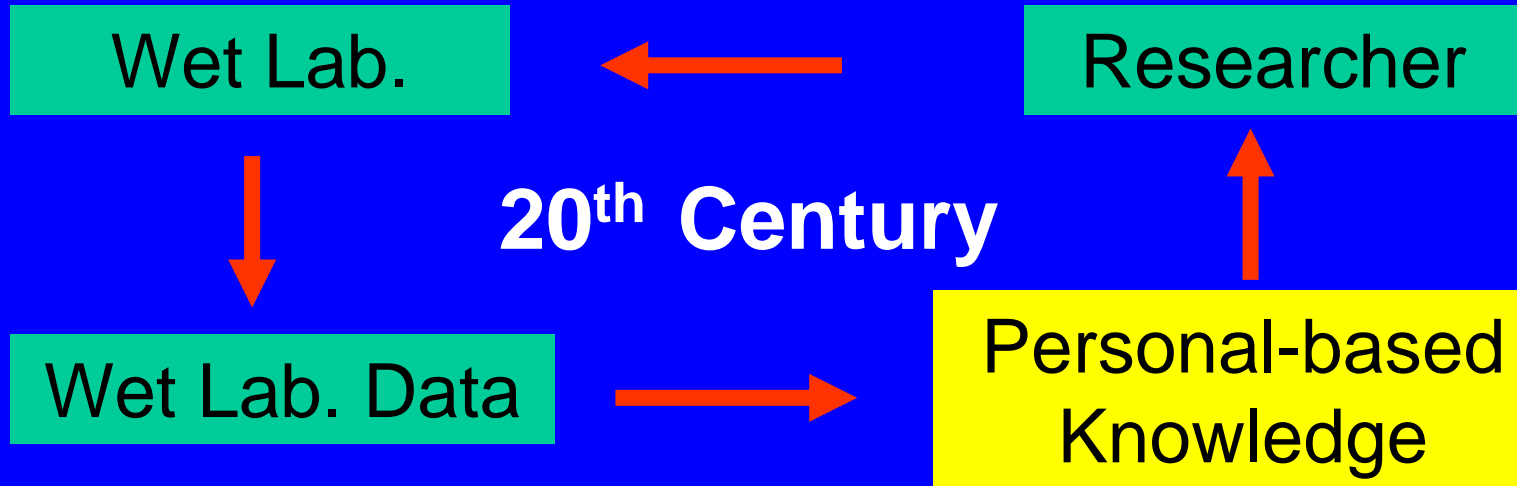
Systems Biology View of Life



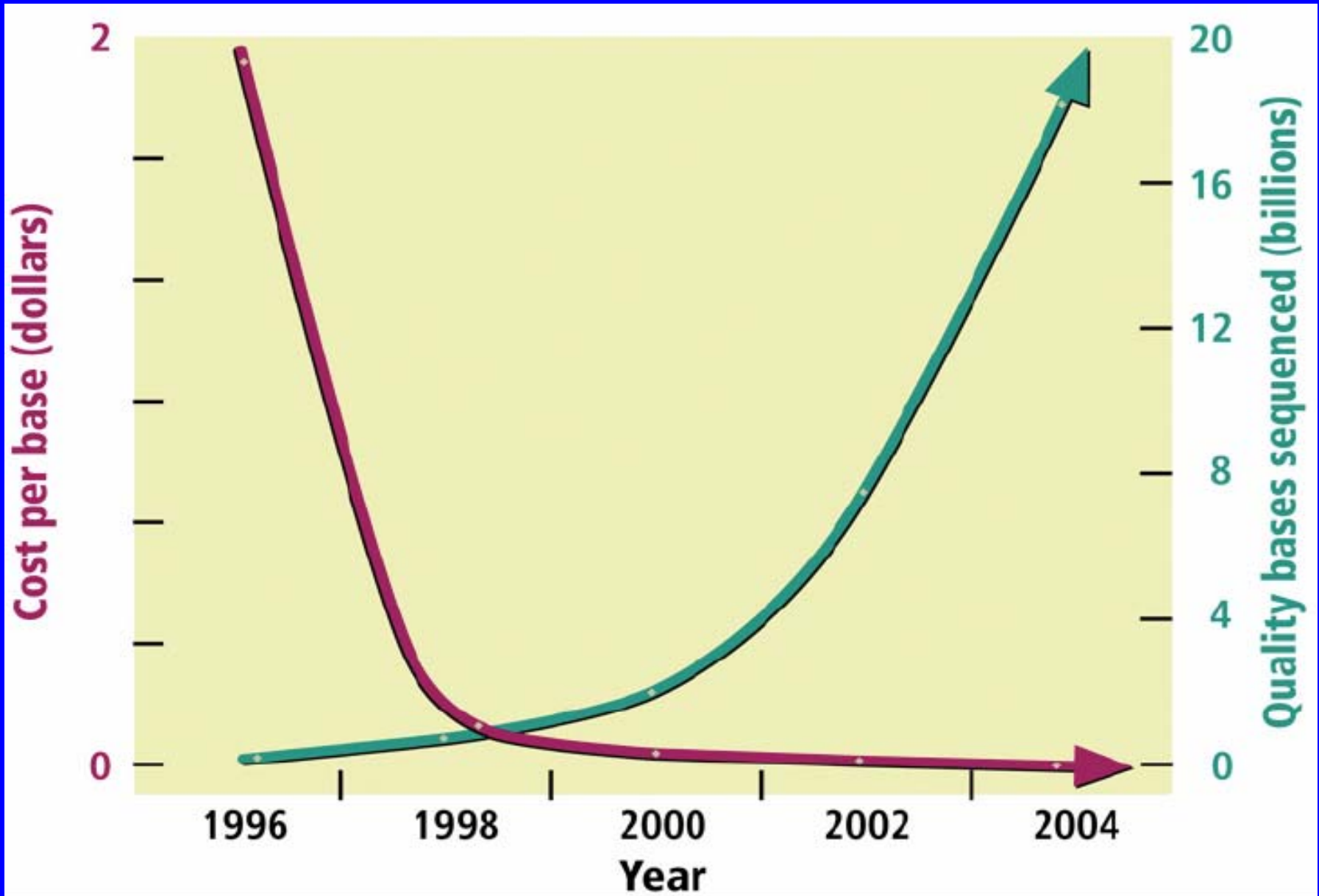
Second Scientific Revolution

Change the View of Life Science

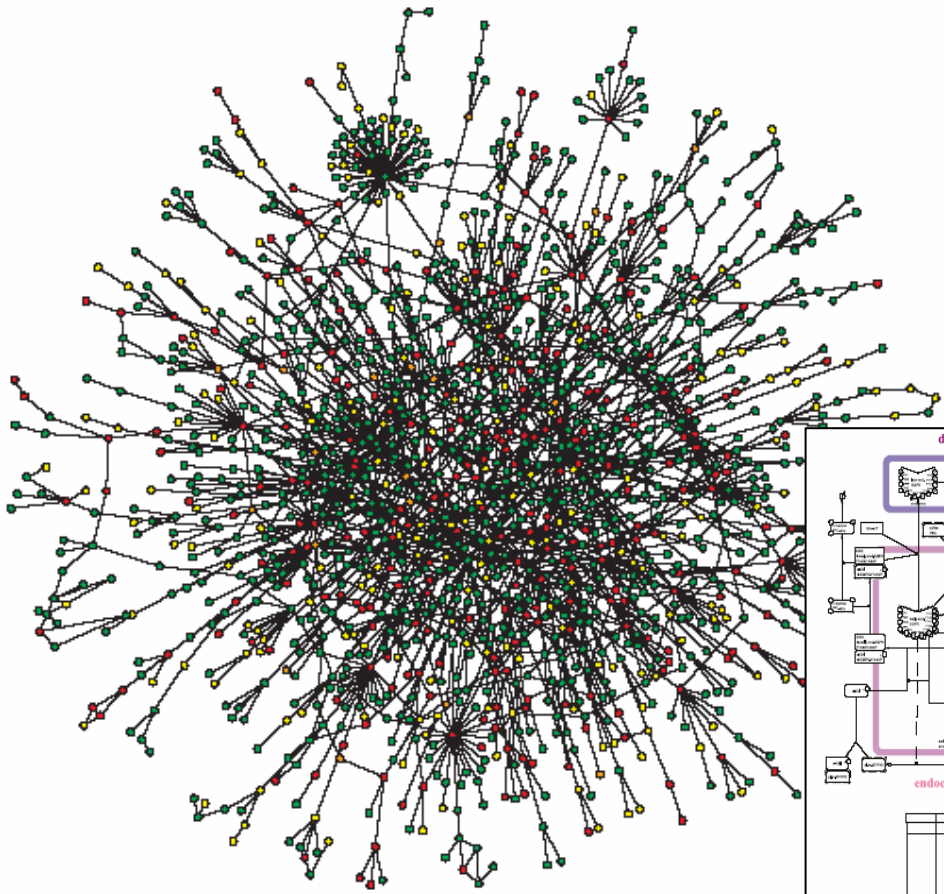
Process of Biological Knowledge Discovery



Huge amount of Experimental Date

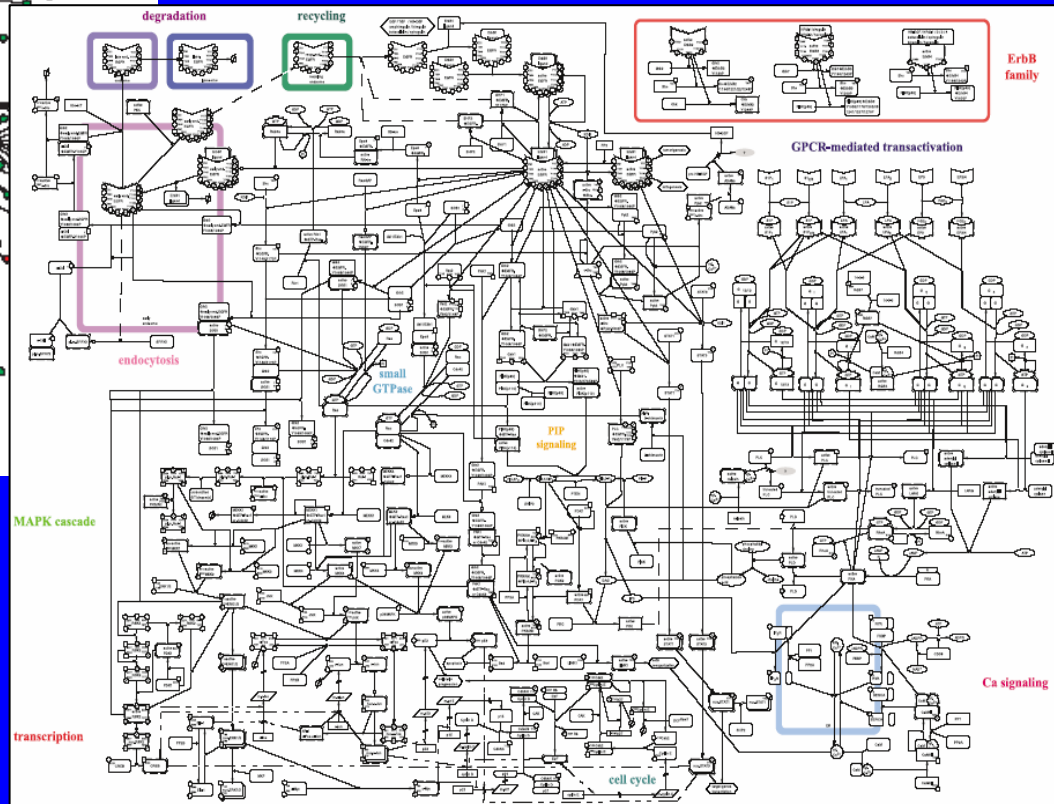


Complexity of Experimental Data

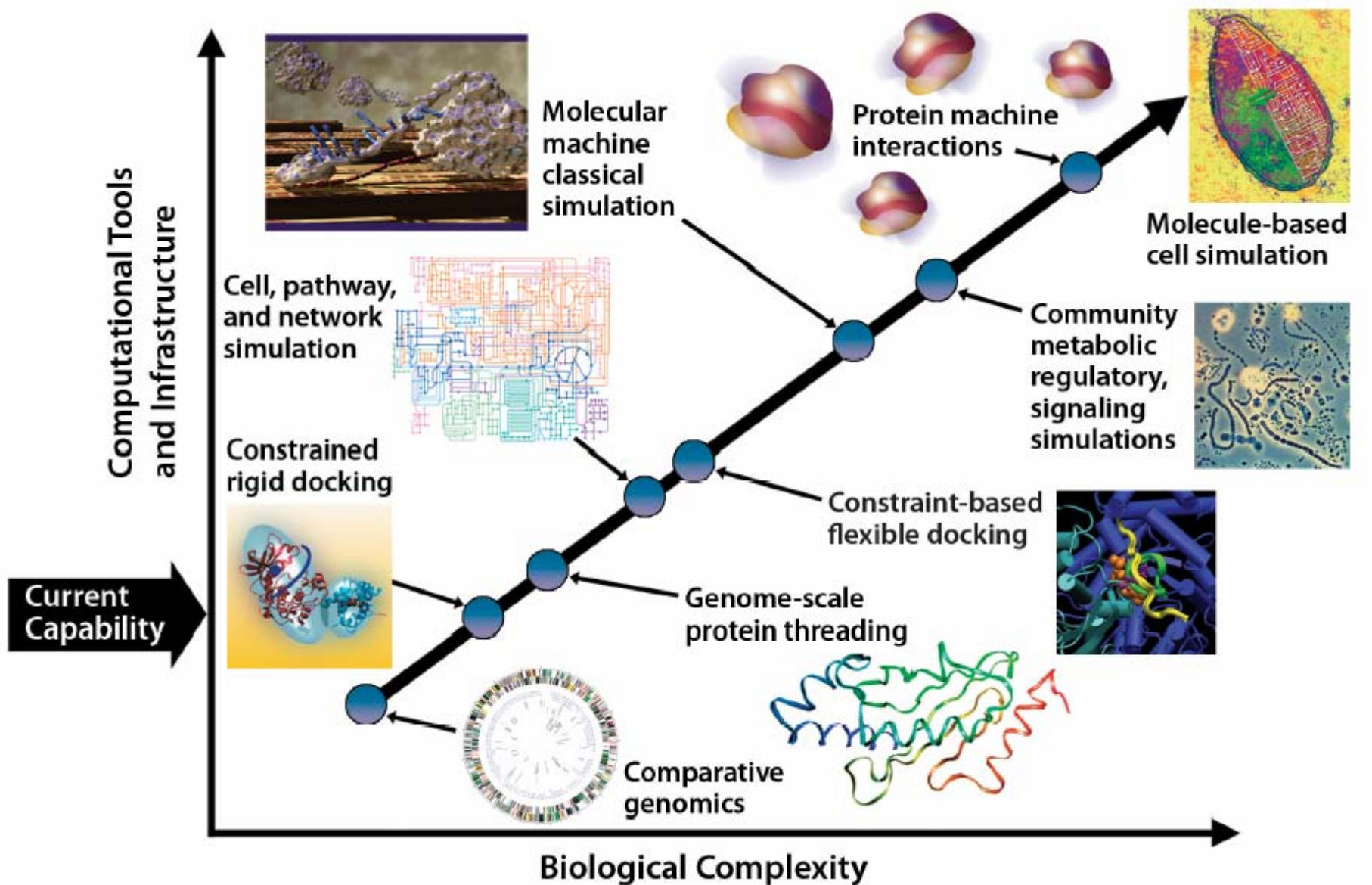


Protein interaction network

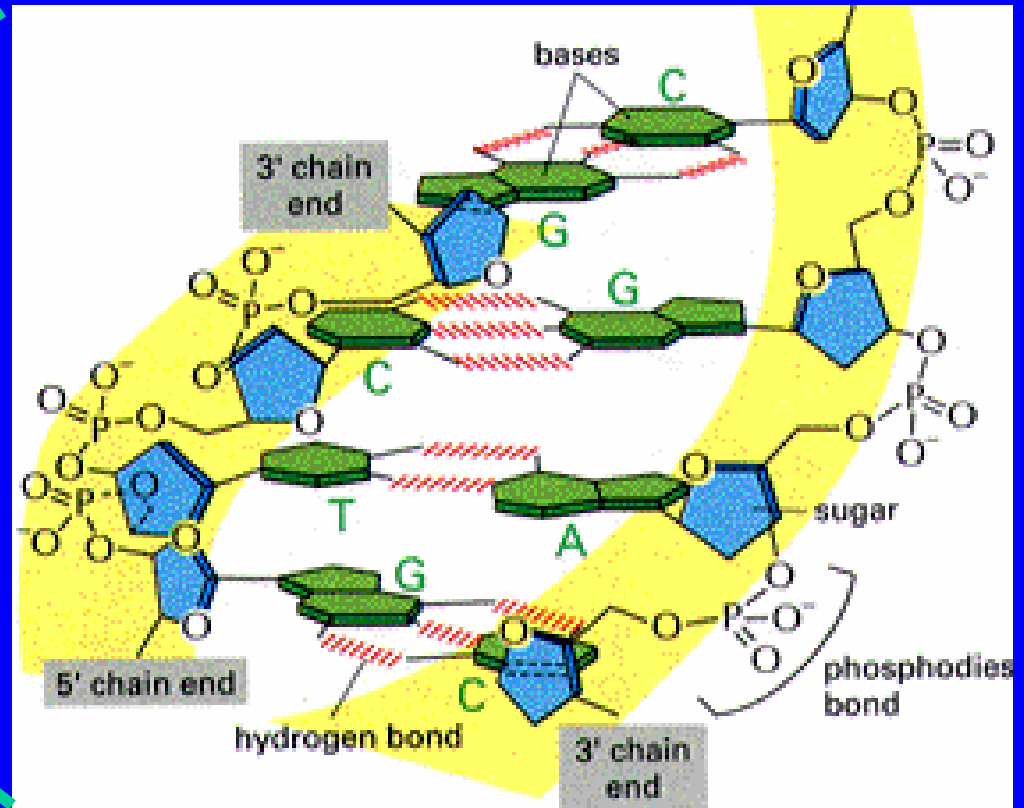
Cell signaling



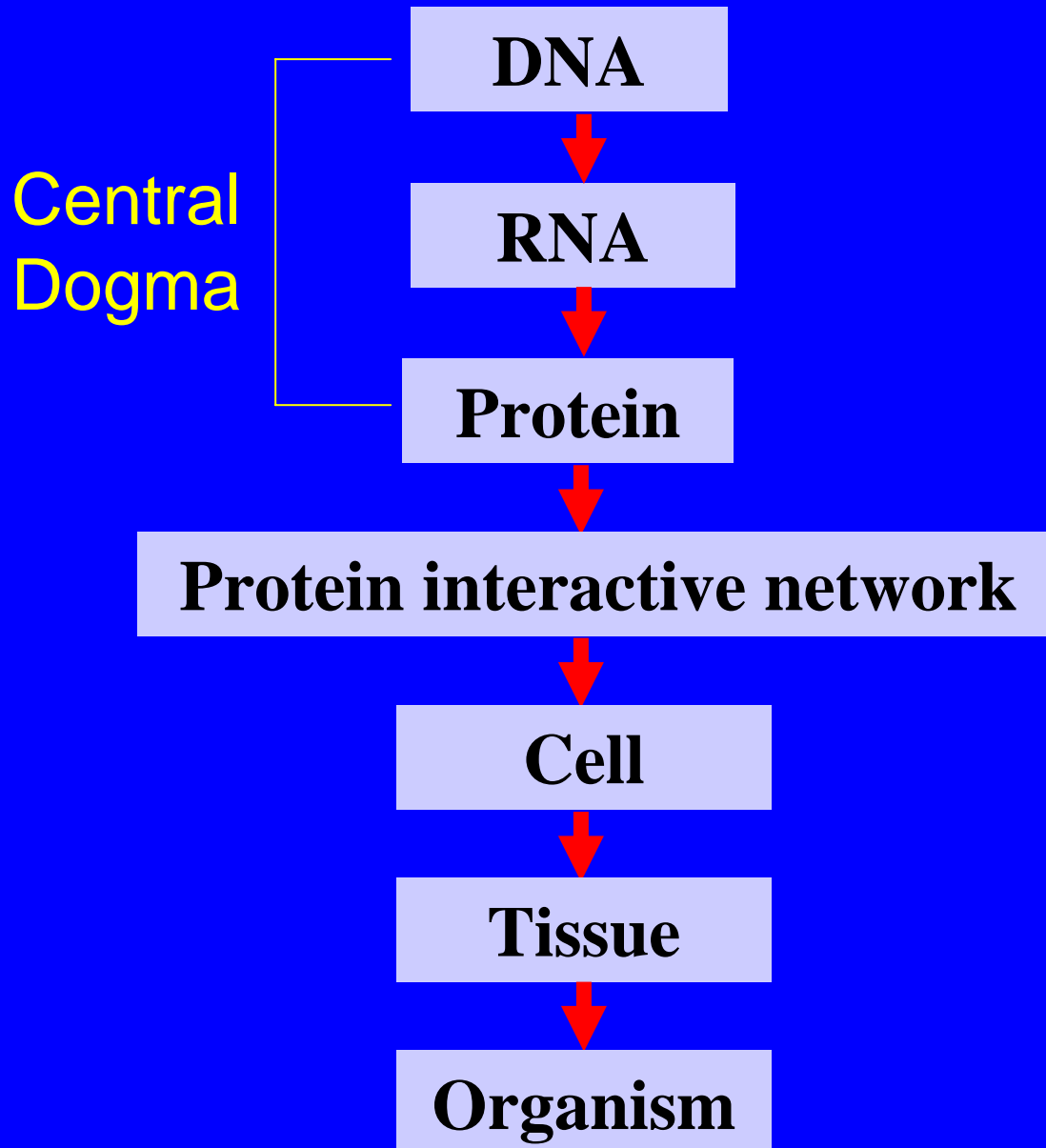
Computing capability decide understanding biological complexity



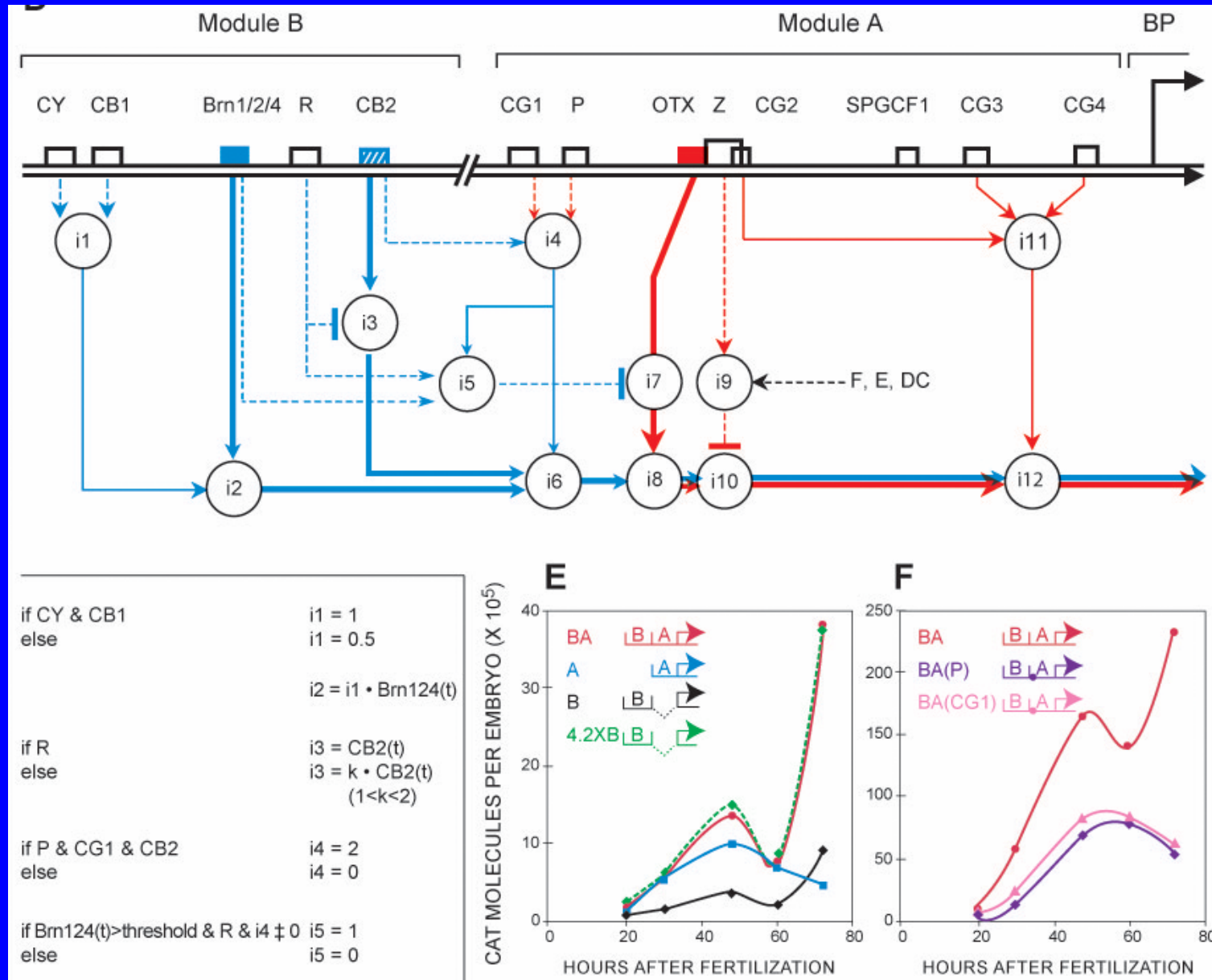
Life is information: Digital



Information Flow in Biological System



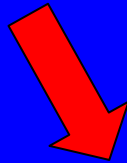
Computing in Biological System



Novel View of Life Science in 21th Century

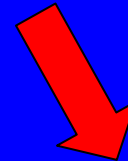
Traditional Biology Era

Life is vitalism



Molecular Biology Era

Life is machine



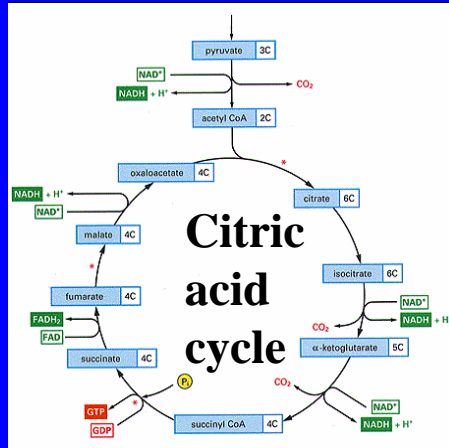
Post-Genome Era

Life is information

Systems Biology

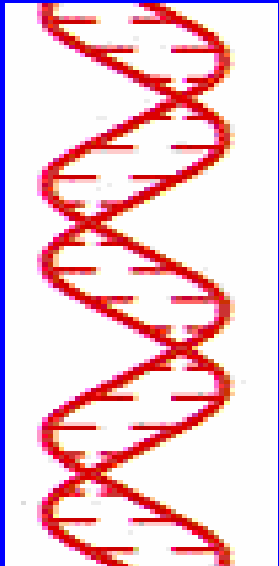
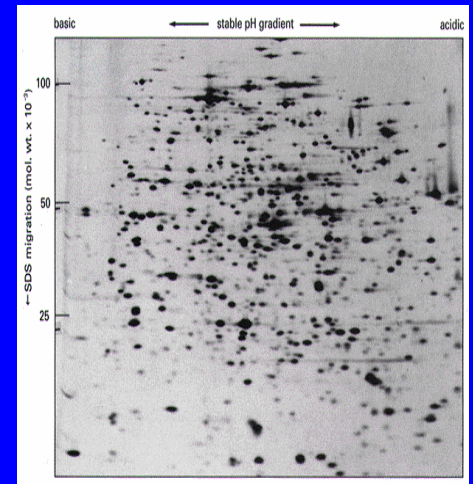
Integration Science

Integration of All Kinds of Molecules



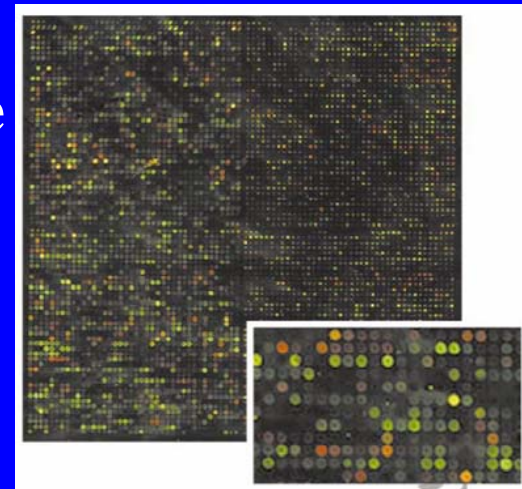
Metabolome

Proteome

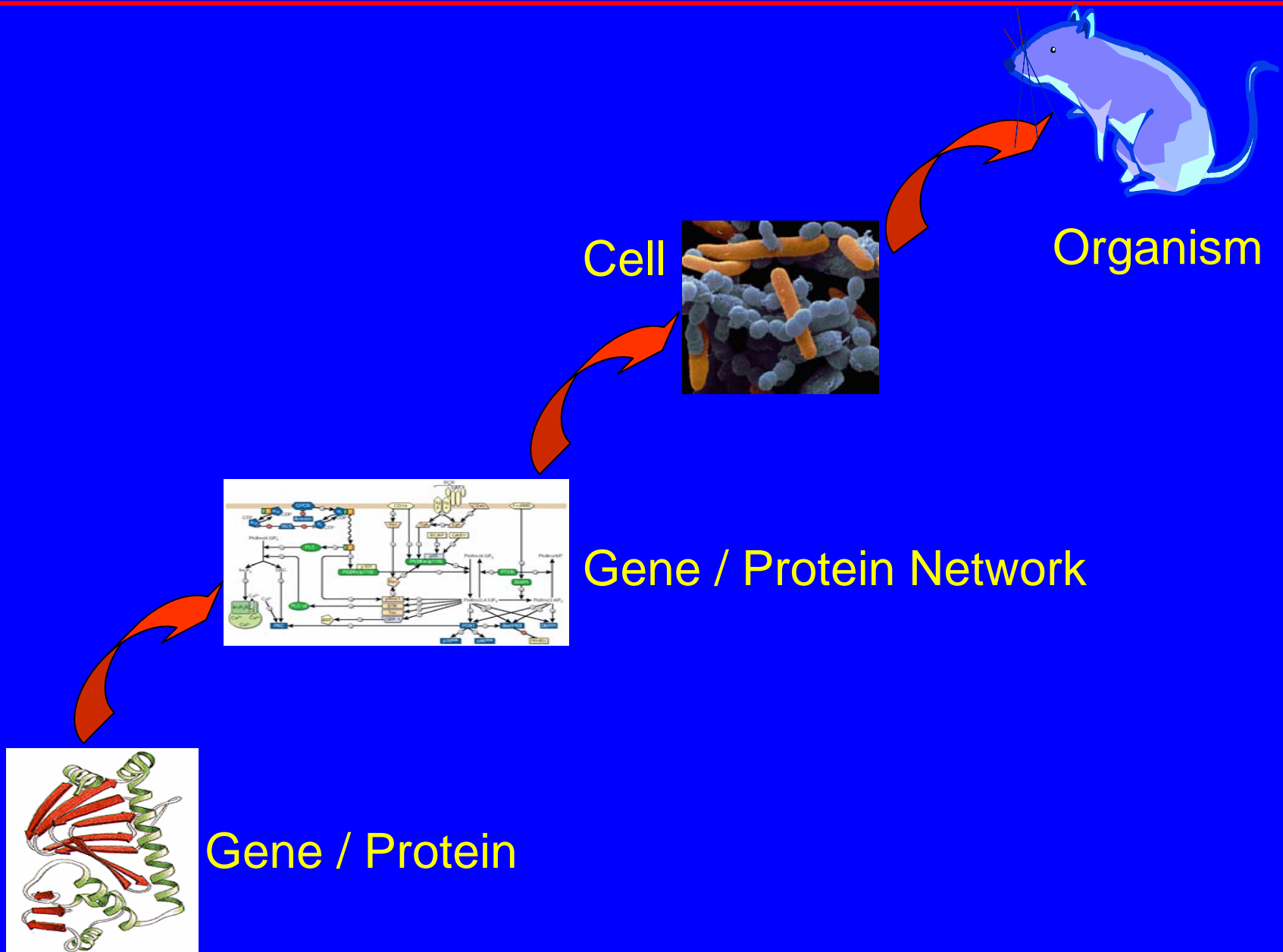


Genome

Transcriptome



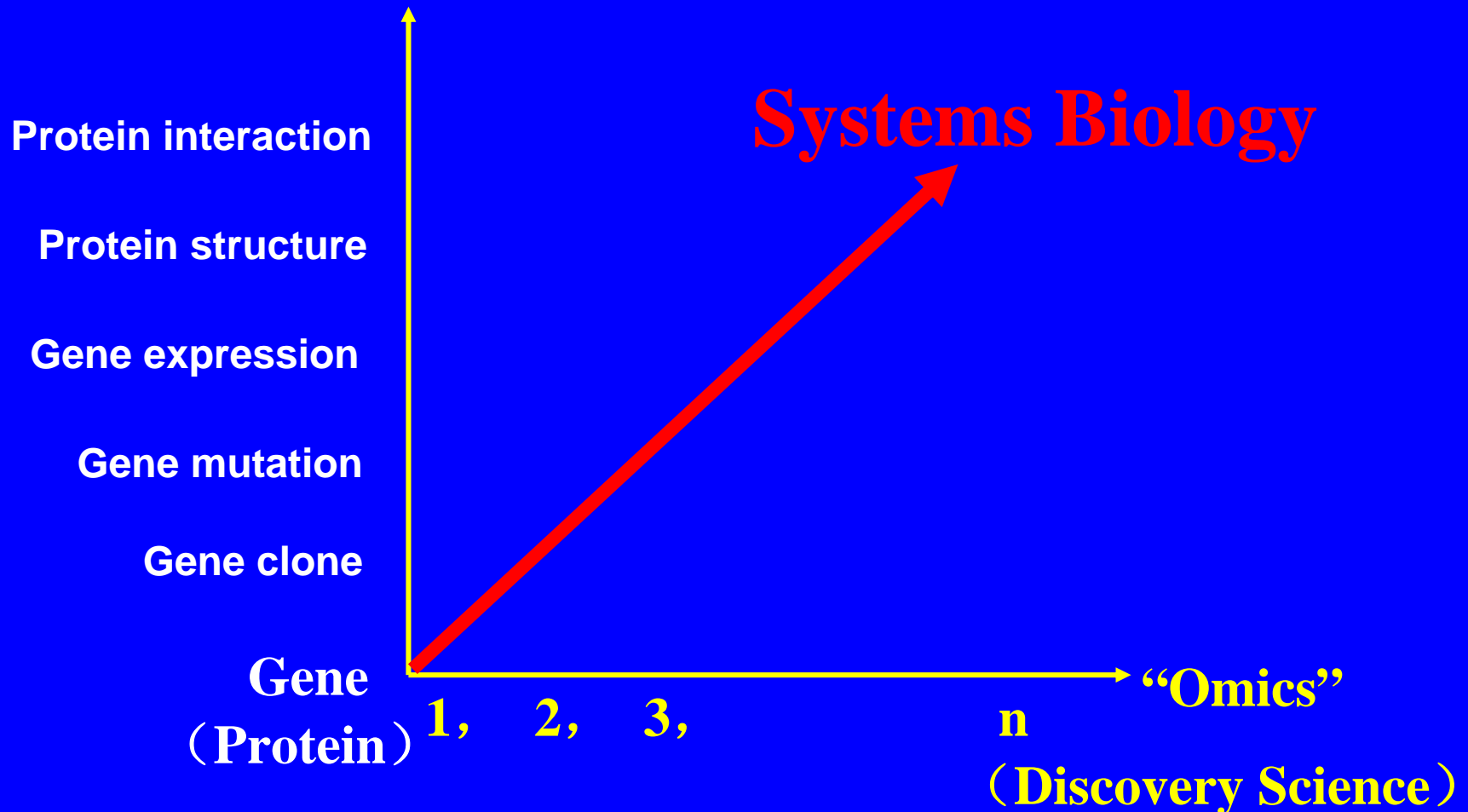
Integration of Different Levels



Integration of Small Science and Big Science

Experimental Biology

(Hypothesis-driven Science)



Integration of Wet Lab. and Dry Lab.

Wet Laboratory

- Molecular Biology
- Cell Biology
- Genomics
- Proteomics
- Metabolomics

Systems Biology

Dry Laboratory

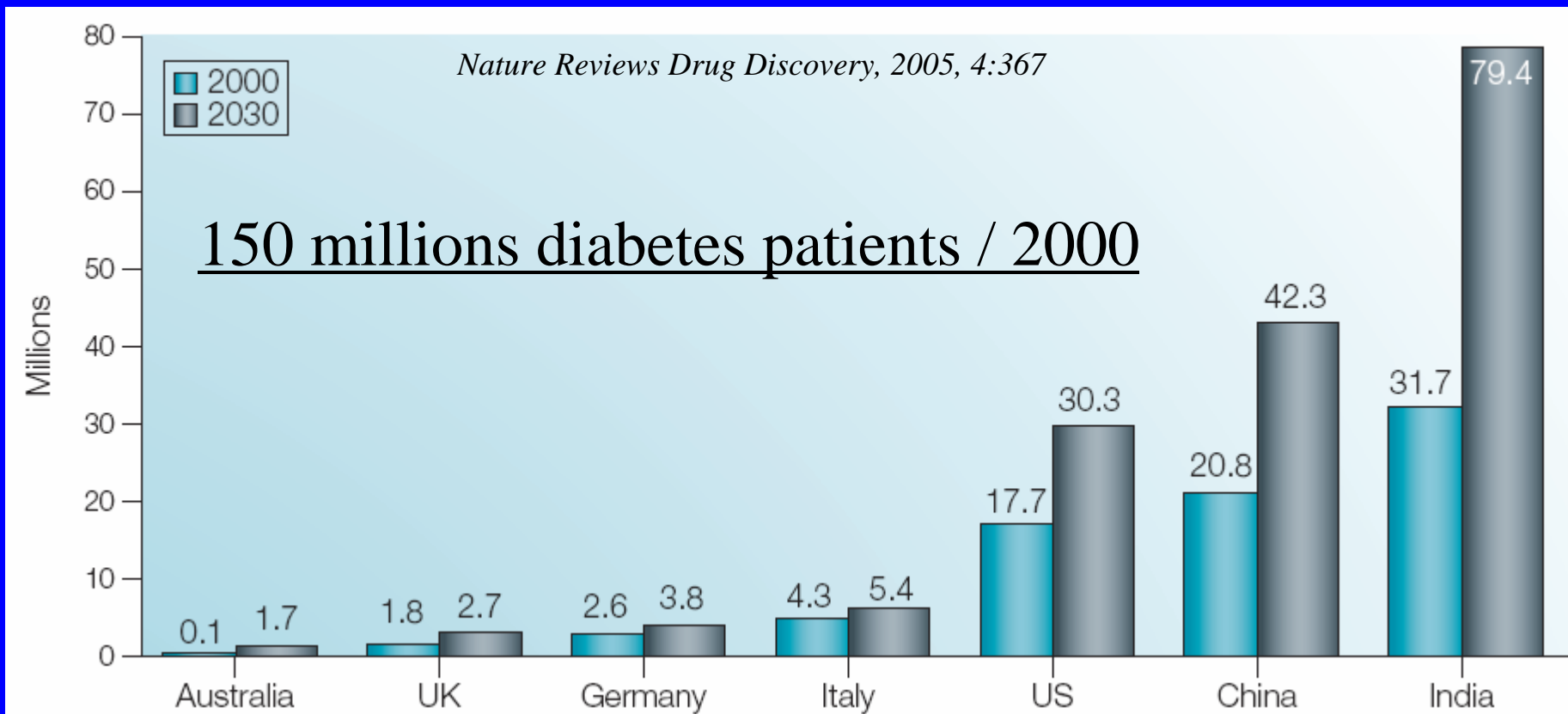
- Computing
- Informatics
- Modeling
- Mathematics

Part II

New Way against Diabetes:

Systems Biology

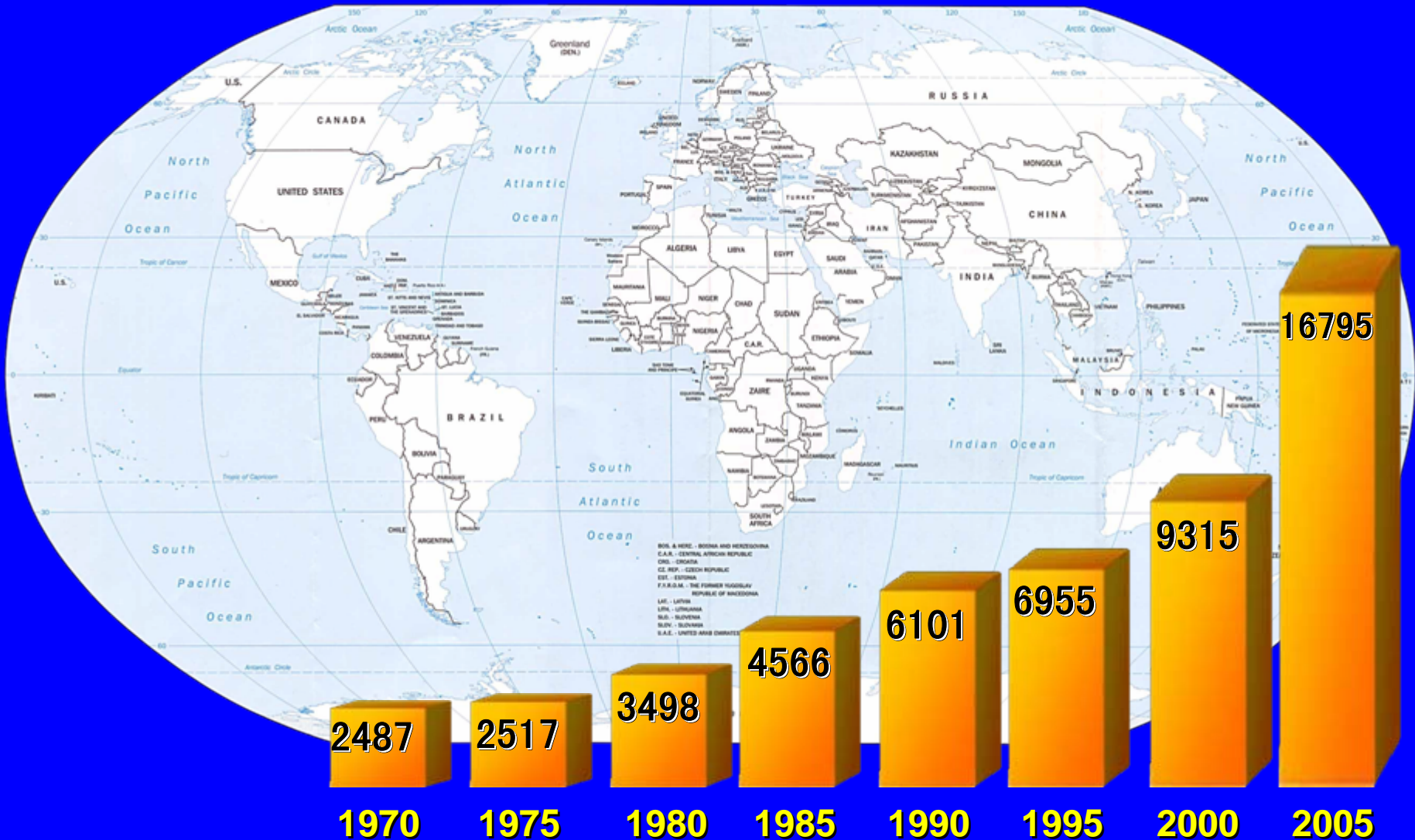
Diabetes in the World



2006-12-20, UN decided Nov. 14th of every year “World Diabetes Day” to be

“United Nations Day”

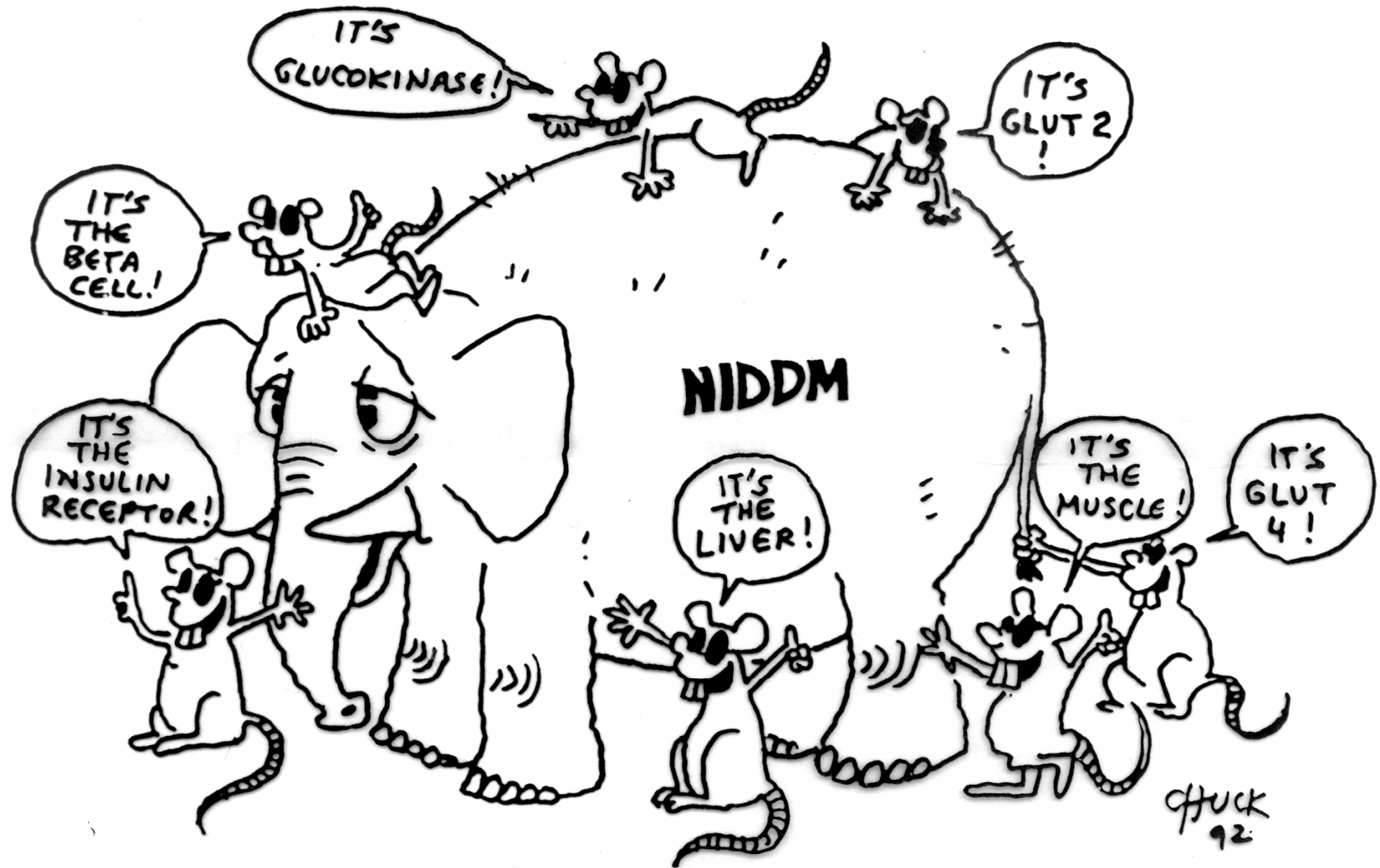
Answer Question or Solve Question ?



Challenge One

How to study molecular network

Tradition Way for Analyzing Diabetes



Knockout-mice used for diabetes research

Endocrinology (14)

COX-2	NOS
NPY	ACC2
apo E	p75(NTR)
p27(Kip1)	HSL
USF1	USF2
lfng	Orexin
SHIP2	HO-1

Beta cell (9)

Wfs1	TCF2
Pdx1	OGG-1
ARNT	Stat4
cyclin D1	
cyclin D2	
P58(IPK)	

Signaling (13)

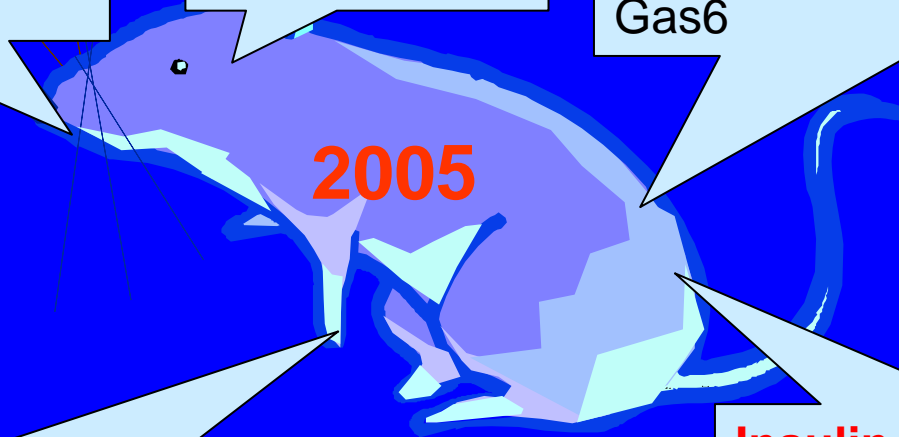
PTP1B	Meg1/Grb10
IR	Aging galectin-3
Insulin2	PAI-1
Socs7	SOCS1
IGF-I	CD
IRS1	IRS2
Gas6	

Insulin secretion (8)

HNF-4alpha	SGK1
P35	HNF-4alpha
Fem1b	PKClambda
IA-2	MafA

Insulin resistance (10)

MC4R	AR
GK	L-PGDS
GLUT4	PTEN
Alms1	ORP
Ikbkb	Acc2



Tissue-specific knockout insulin receptor

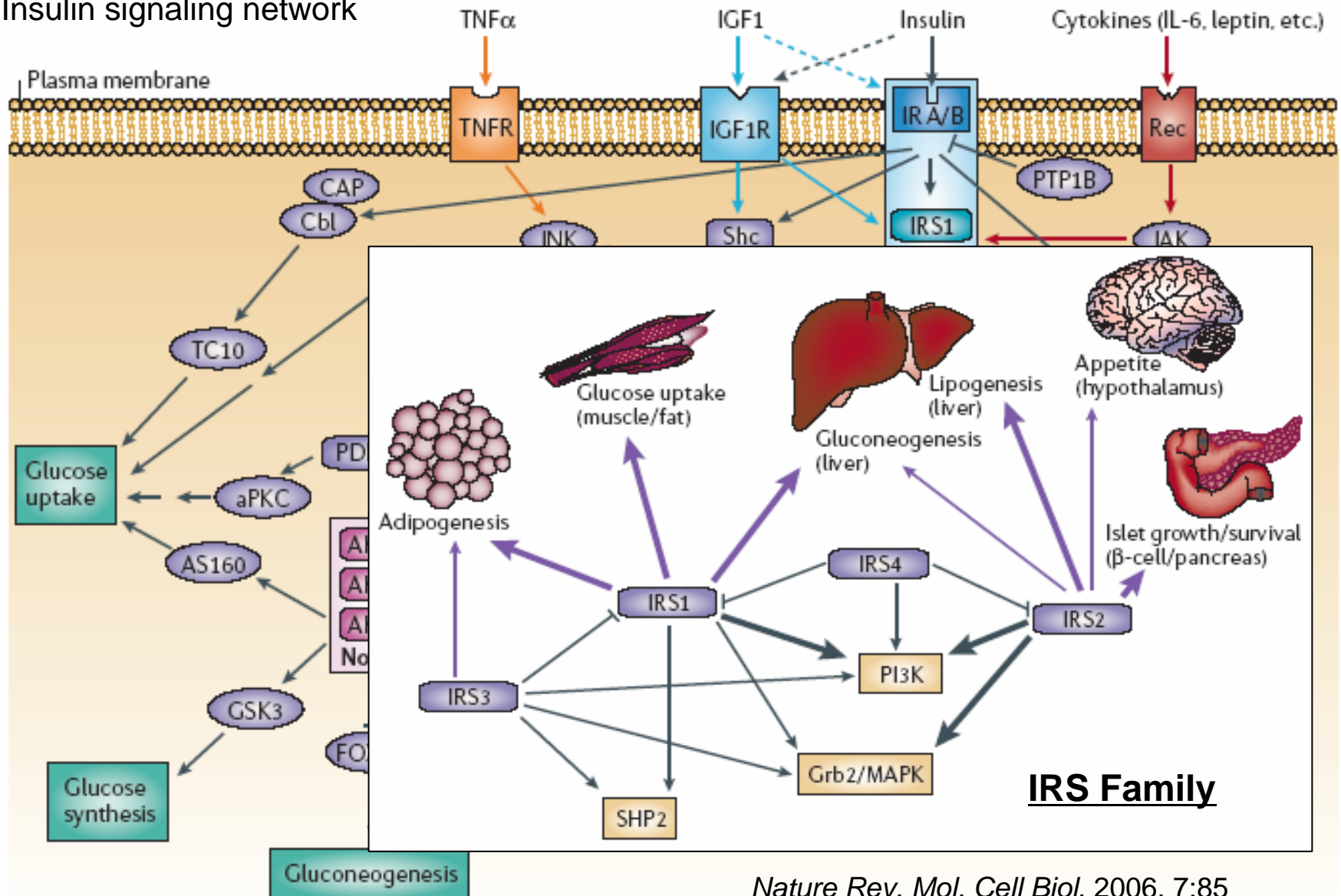
TABLE 1 Summary of phenotypes due to *Insr* knockouts

<i>Insr</i> knockout	Phenotype
Constitutive	Diabetic ketoacidosis
Muscle	Dyslipidemia
Muscle/adipose tissue	Impaired glucose tolerance
Adipocyte	Protection against obesity
Liver	Moderate insulin resistance, transient hyperglycemia
β -cell	Impaired glucose tolerance
Brown adipose tissue	β -cell failure
Central nervous system	Obesity, sub-fertility

[Annu. Rev. Physiol. 2003. 65:313](#)

Diabetes: a disease involving complex network

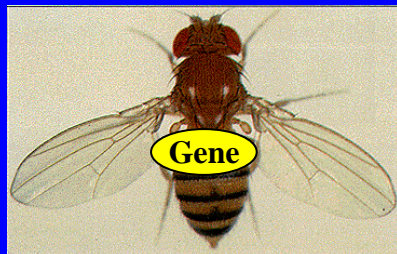
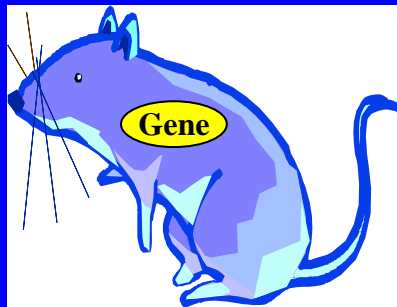
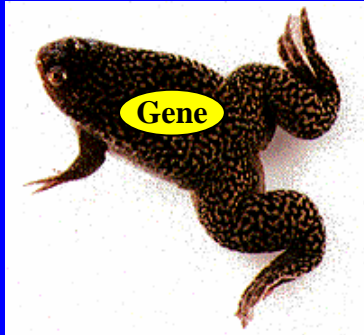
Insulin signaling network



Challenge Two

How to study complexity of systems

Tradition Way for Studying Diseases

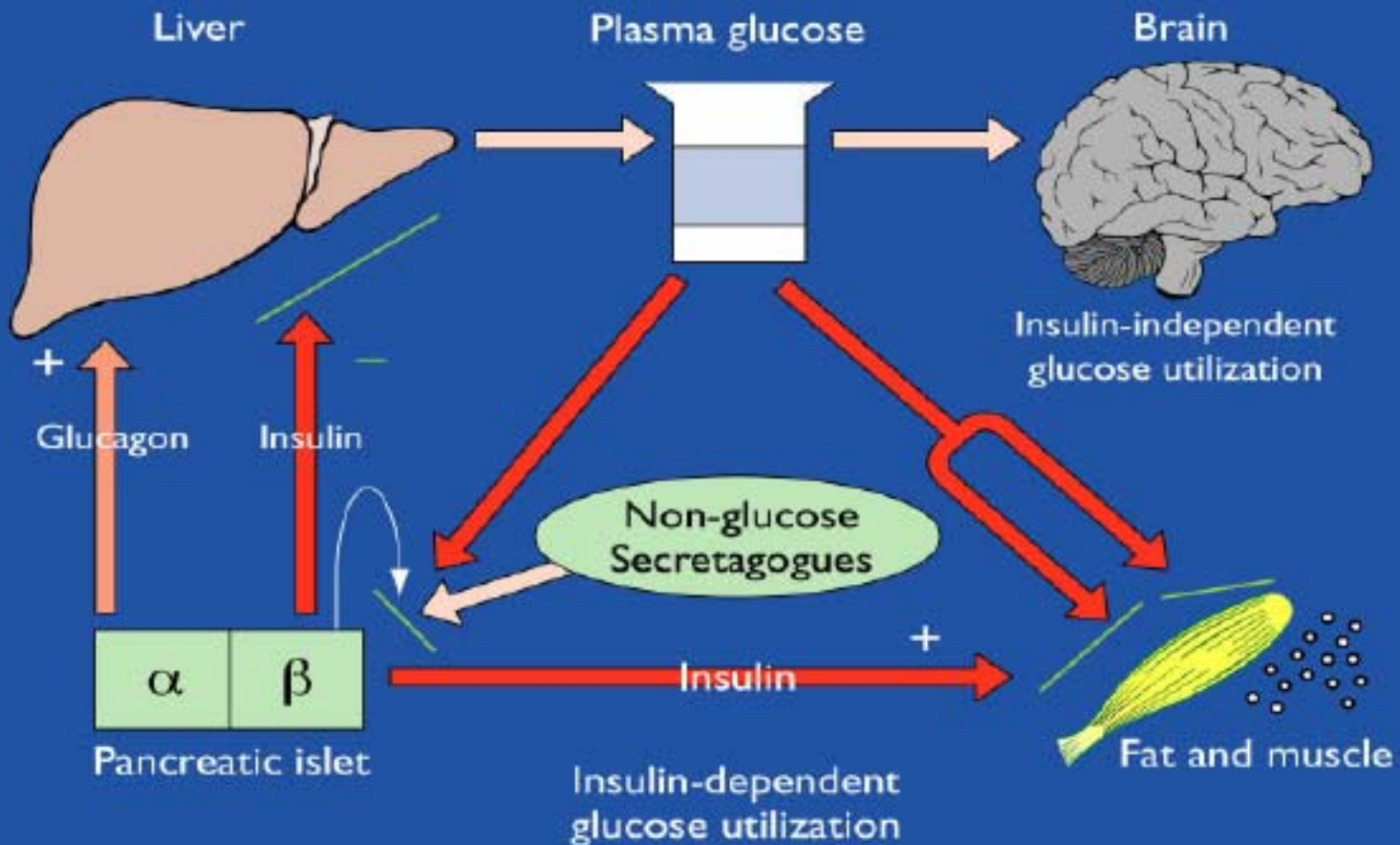


Linear deduction

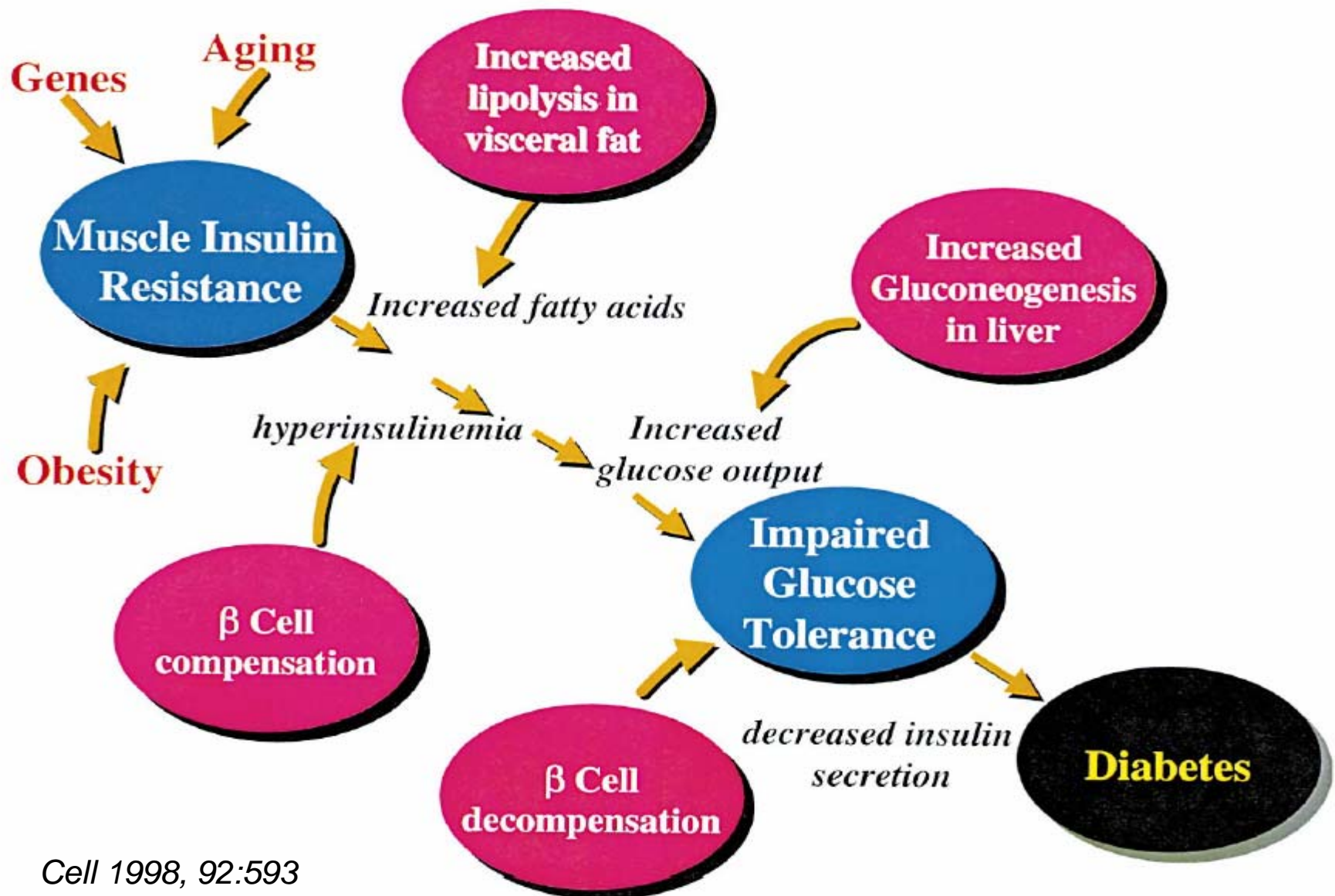


Metabolism is system work

Regulation of glucose homeostasis



Diabetes: dynamic development of systems



Animal System is different from Human System

Mouse	Human
MODY gene knockout ↓ Normal	MODY gene mutation ↓ Hyperglycemia
PPARγ-Pro467Leu mut ↓ Normal	PPARγ-Pro467Leu mut ↓ Insulin resistance

“when it comes to the control of intermediary metabolism and plasma glucose levels, there may sometimes be important differences between mice and humans.”

Science, 2005, 307: 370

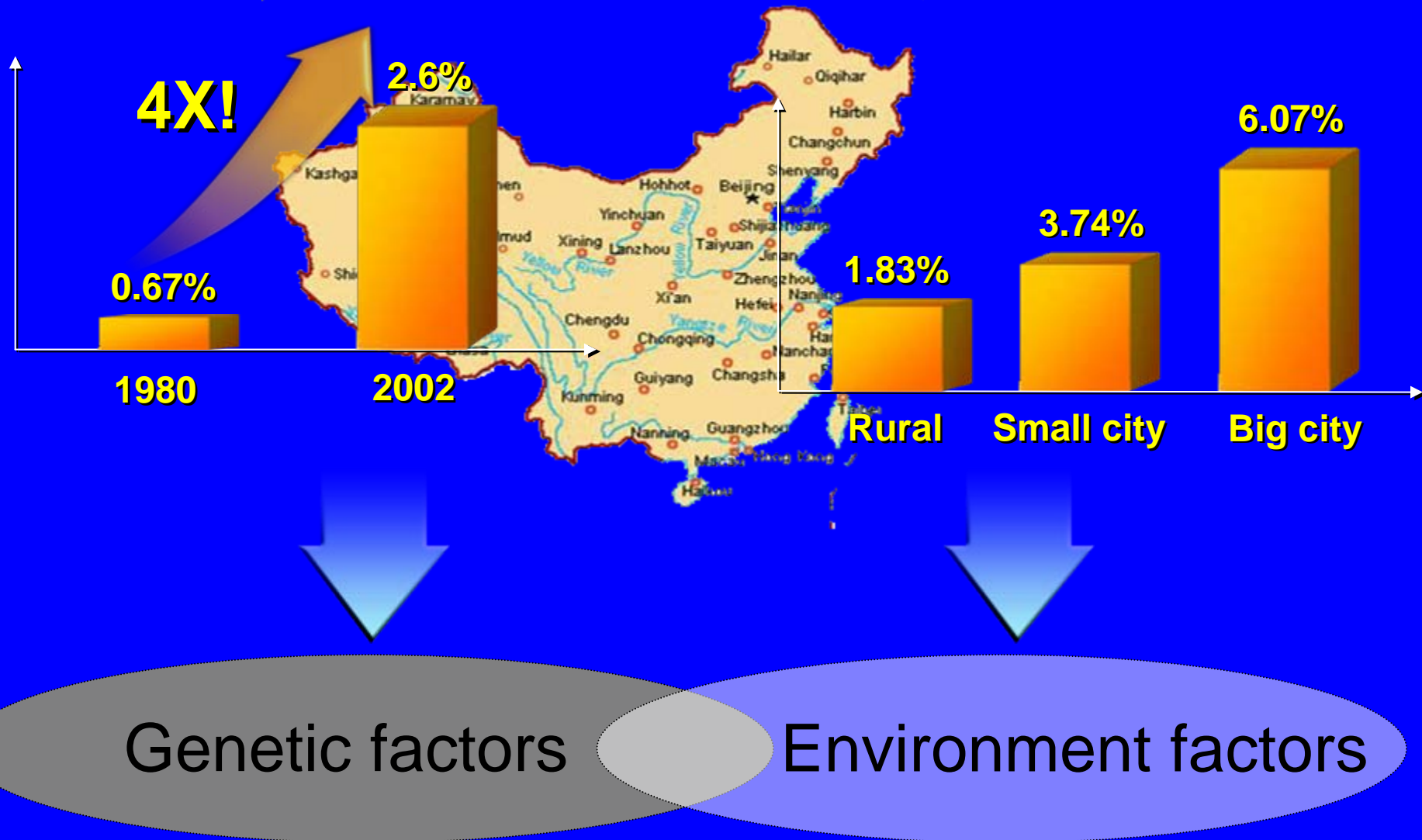
Diabetes: Personalized disease

**Genetic
factors**

Population grouping	Region	Percentage prevalence
Europeans	Britain	2
	Germany	2
	Australia (1981)	2
	Australia (2002)	8
	United States	8
Native Americans	Chile Mapuche	1
	US Hispanic	17
	US Pima	50
Pacific Islanders	Nauru (1952)	0
	Nauru (2002)	41
New Guineans	Rural	0
	Urban	37
Aboriginal Australians	Traditional	0
	Westernized	23

**Environ.
factors**

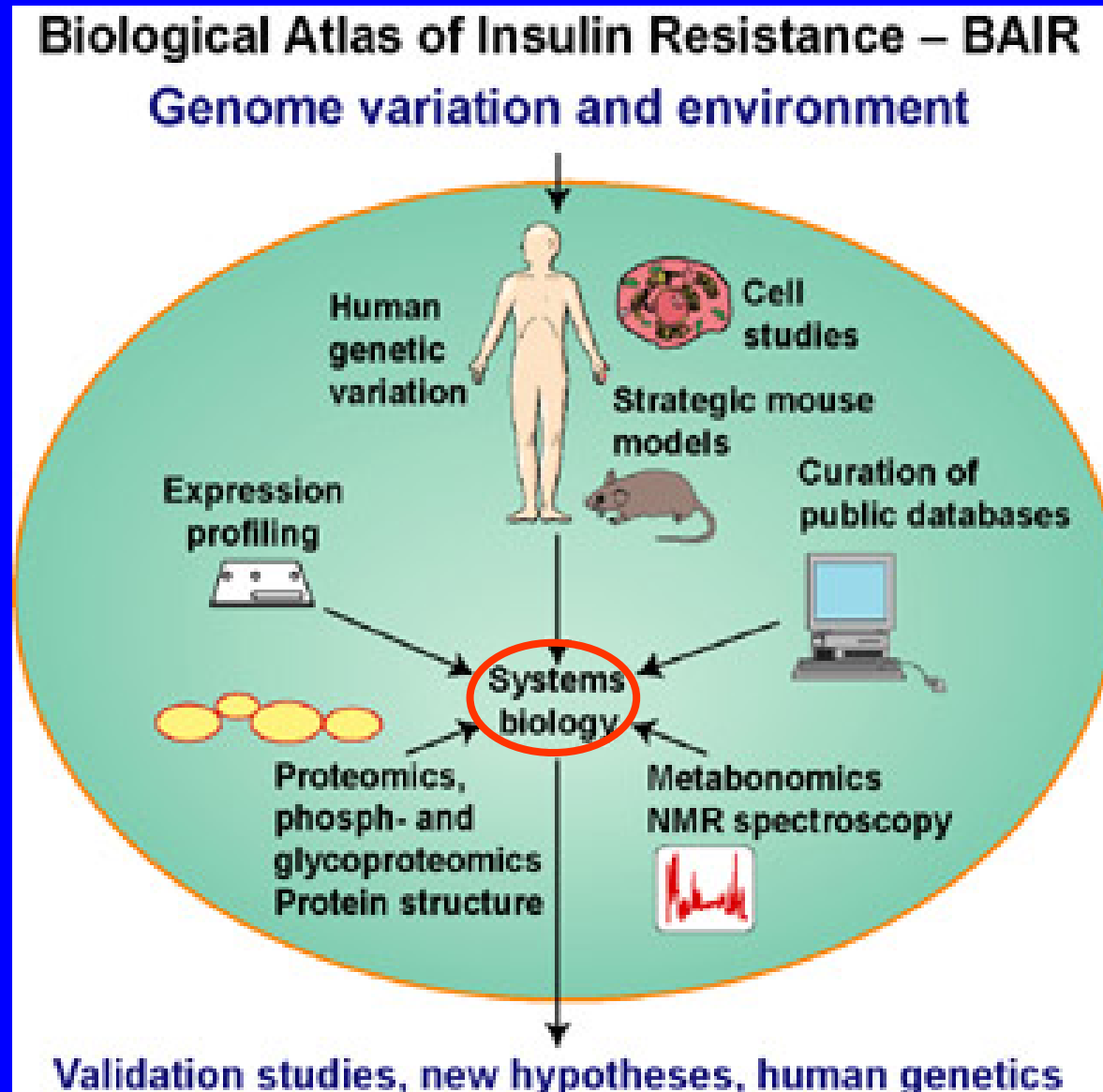
Factors involved in Chinese diabetes population



Solution against diabetes

Systems Biology

Biological Atlas of Insulin Resistance - BAIR



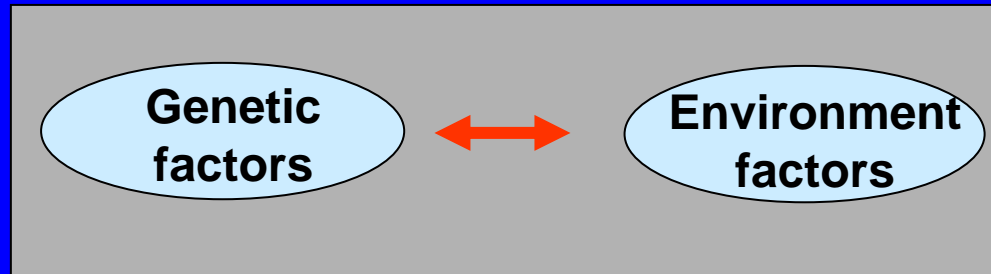
http://www.bair.org.uk/bair_organisation.html

Strategy of diabetes project in China

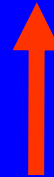
Type 2 diabetes of Chinese

clinic / population

Scientific
questions



Study



Systems for analysis

Clinic/population



Animal model



Cell model

Methodology

Mol. biology

Cell biology

Genetics



Genomics

Proteomics

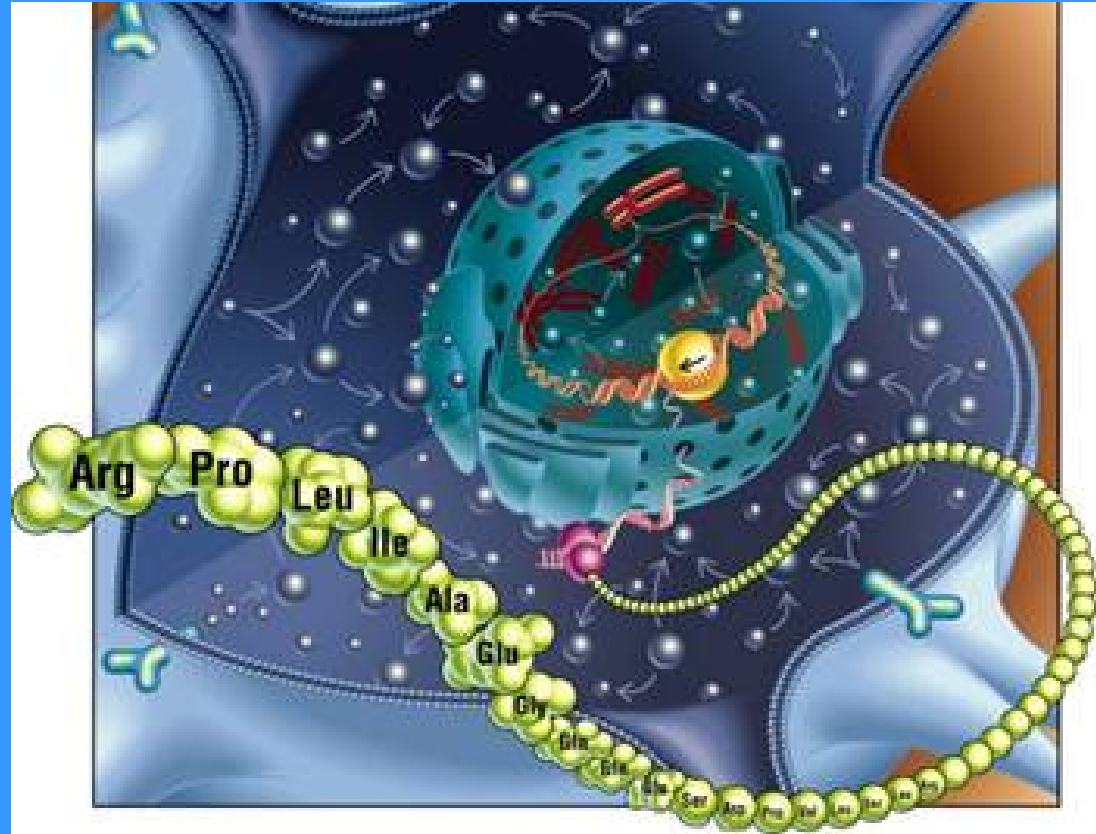
Metabolomics

Bioinformation

What is life?

Systems Biologist

- Components (Nodes)
- Interactions (Links)



Life is a statistical complex system rather than a determined simple system

Thank You!

