Biophysics and systems biology of cellular responses to perturbations.

Gastone.Castellani@unibo.it

Castellani G.C., Remondini D., Giampieri E., de Oliveira L., Sala C.,
Menichetti G., Virelli A., Zironi I.

Dipartimento di Fisica e Astronomia, Università di Bologna

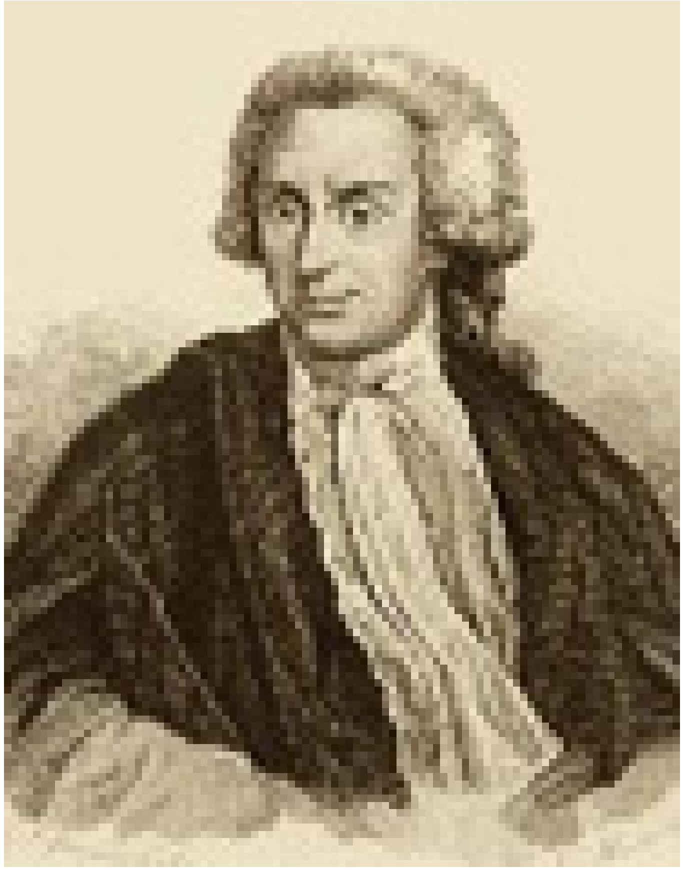
Dipartimento di Fisica Università di Bologna,and INFN
Galvani Center for Biophysics, Bioinformatics and Biocomplexity
via B.Pichat 6/2 ,Bologna, 40127, Italy
IBNS & Physics Department Brown University Providence RI USA

Trieste 27-09-2013

ALMA MATER STUDIORUM
UNIVERSITÀ DI BOLOGNA

BROWN

Centro Interdipartimentale “L. Galvani” (CIG)
Università di Bologna
Italy



DNA as the tree of knowledge.

Bologna Center for Biocomplexity

2000: L. Galvani Center for integrated studies of Biophysics Bioinformatics and Biocomplexity (http://www.centrogalvani.unibo.it) including Systems Biology, Genomics of Longevity and Laser-Plasma Physics.

Bio-immuno-pathological group: expertise in cell culture, sorting and omics measurements: is one of the leading laboratory in Europe and in the World for the study of Aging and senescence in humans, including the centenarians;

Biophysics group: decennial activity in the field of complex cellular function modeling and advanced data analysis, and recently is developing biophysical measurements as patch clamp and fluorescence microscopy.

An intriguing aspect of **Radiation** effect is the **sharing of mechanisms** with **cellular senescence**, **organismic aging** and **LDR-induced carcinogenesis** in humans as: e.g. the **Free radical theory (FRT)**.

Harman in the 1950s, .

1) the rate of living theory, which holds that lifespan is an inverse function of metabolic rate. In turn, this is proportional to oxygen consumption,

2) hyperbaric oxygen toxicity and radiation toxicity could be explained by the same underlying phenomenon: oxygen free radicals.

Perspectives

Anecdotal, Historical and Critical Commentaries on Genetics

Edited by Adam S. Wilkins

The Szilard Hypothesis on the Nature of Aging Revisited

Henrik Zetterberg,[*,1] Magnus Båth,[†,‡] Madeleine Zetterberg,[§,] Peter Bernhardt[†,‡] and Ola Hammarsten[††]**

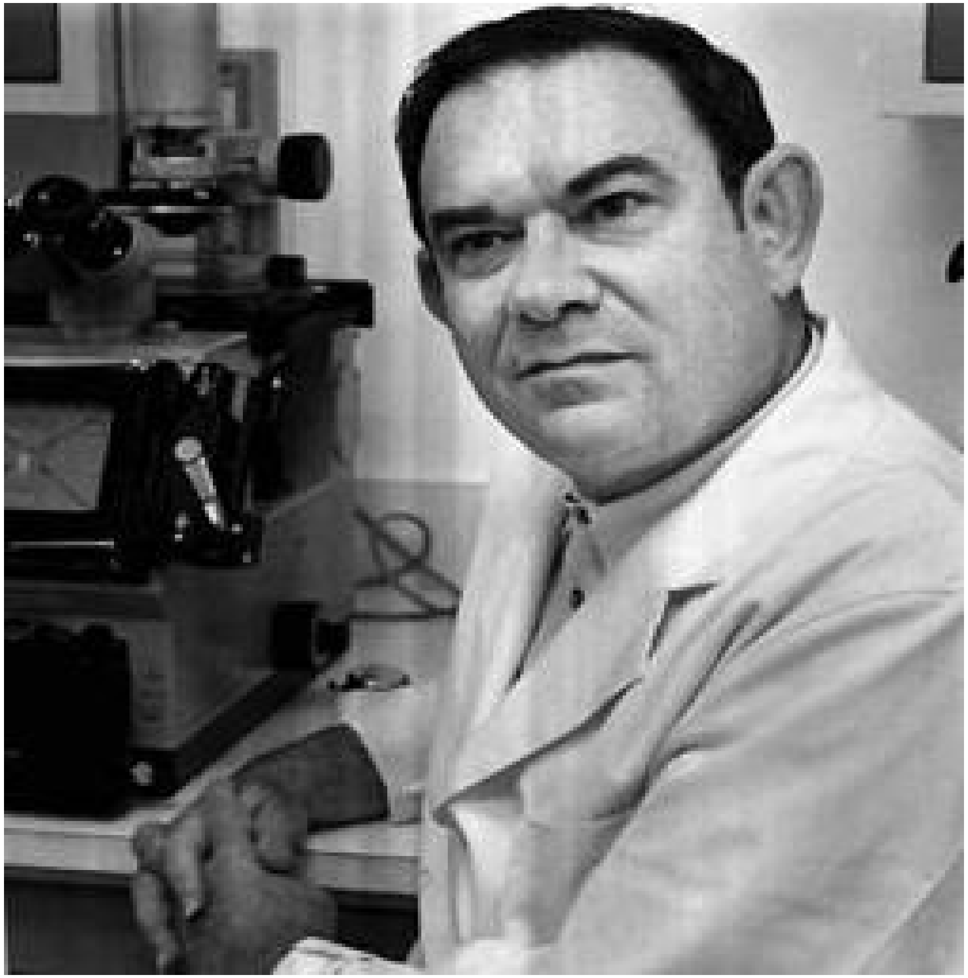
1 aging is the accumulation of damaged chromosomes or genes

2 a certain species is characterized by a certain aging hit rate:

3 aging hits are random events and do not vary interindividually

4 the surviving fraction of functional somatic cells determines the biological age of an individual:

Cellular senescence



Normal diploid cells cease to divide, normally after about 50 cell divisions in vitro.
This phenomenon is also known as **"replicative senescence"**, the

"**Hayflick phenomenon**",

or the **Hayflick limit** in honour of Hayflick, 1961.

Senescence is a multiscale and stochastic process:

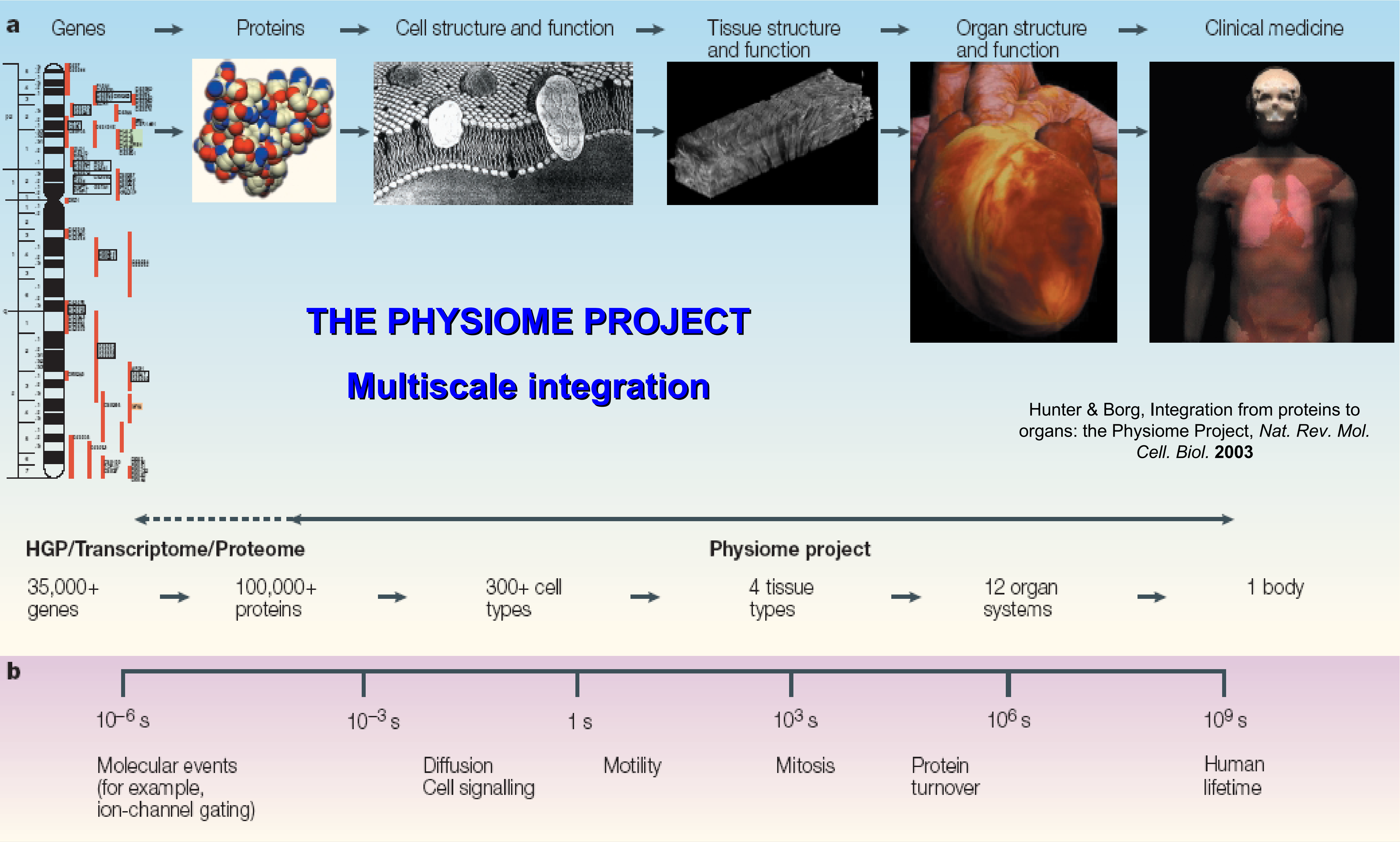
level of the whole organism
(organismal senescence)

level of its individual cells
(cellular senescence).

The relations between these two processes are still not clear

THE PHYSIOME PROJECT

Multiscale integration



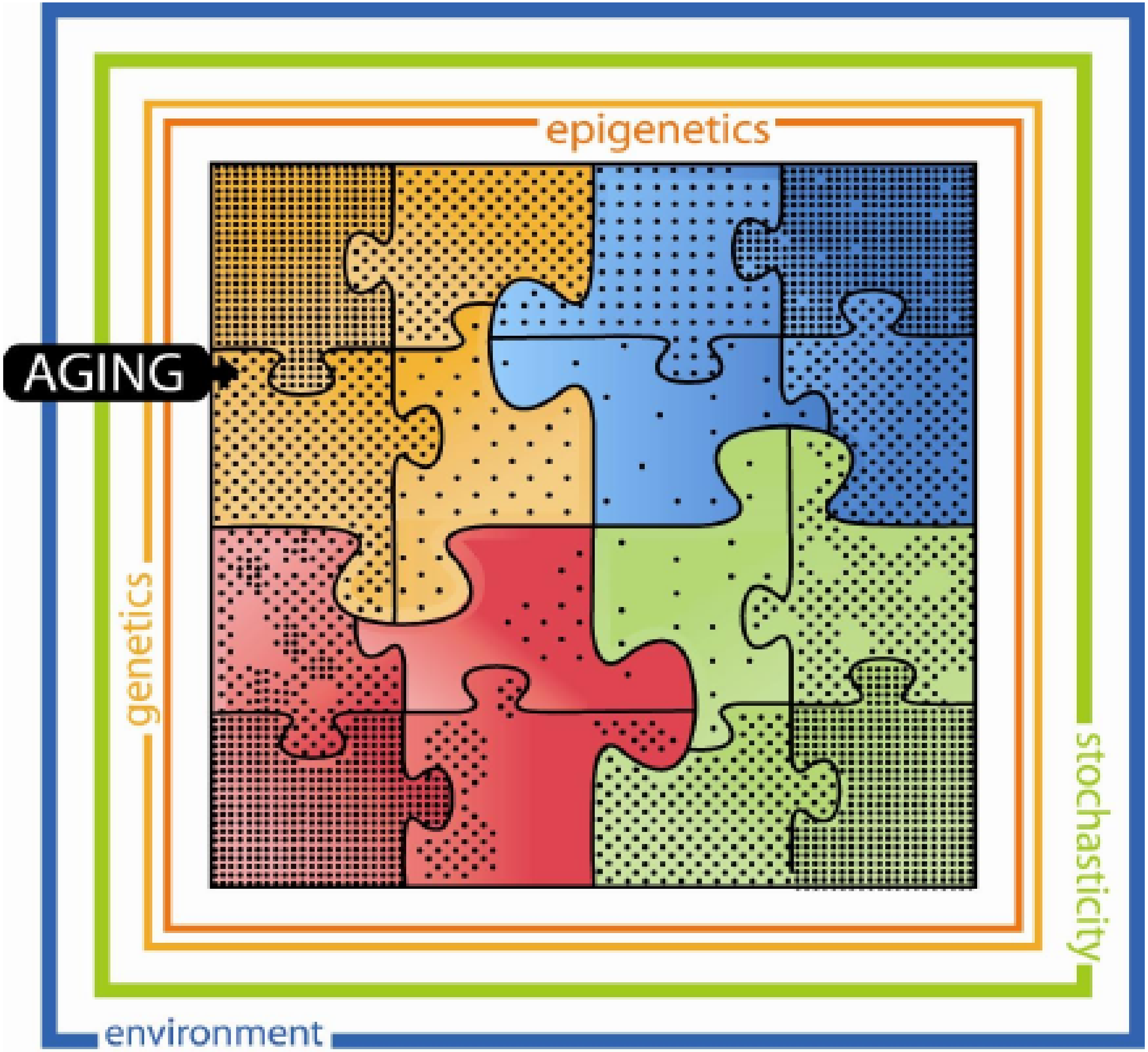
Hunter & Borg, Integration from proteins to organs: the Physiome Project, *Nat. Rev. Mol. Cell. Biol.* **2003**

L'organizzazione a livelli multipli di scale spaziali (da 1 nm per le proteine a 1 m per l'intero corpo) e temporali (da 10^{-6} s a livello molecolare a 10^{9} s per l'intero corpo) richiede una gerarchia di modelli

The mosaic of aging

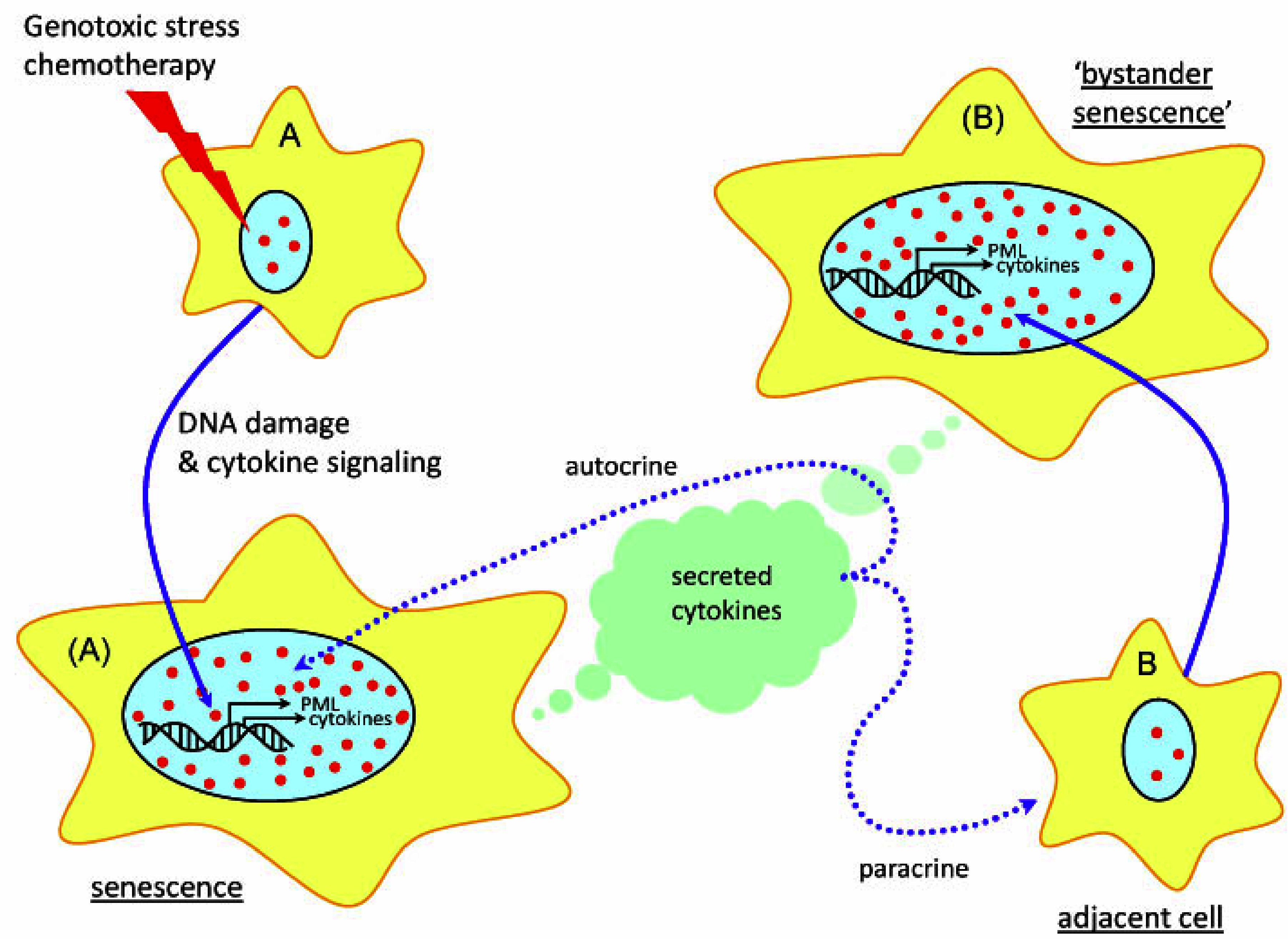
great variability at all levels of biological organization:

- **macromolecules**
- **organelles**
- **cells**
- **organs**
- **individuals**
- **populations**

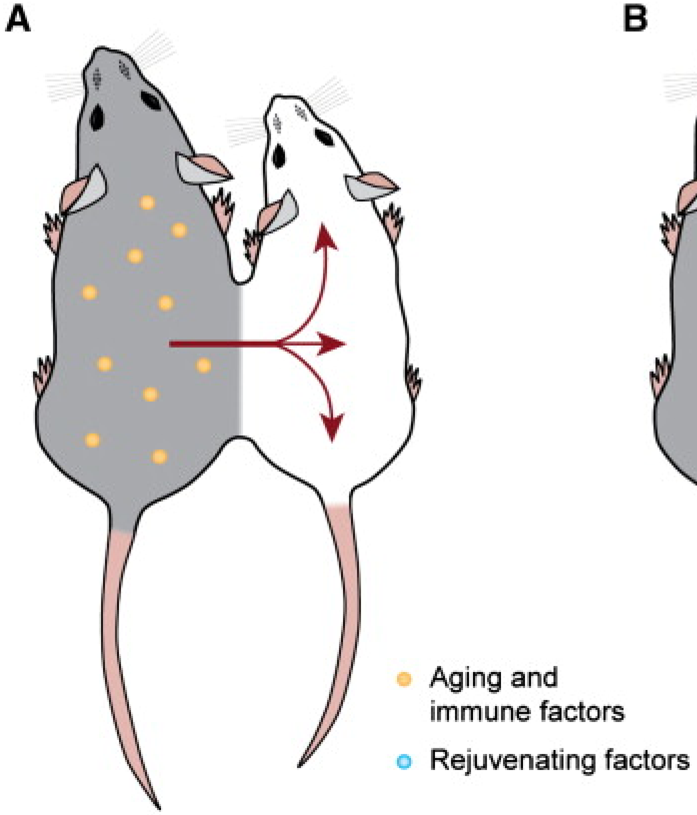


Cevenini et al., *Expert Opin. Biol. Ther. (2008) 8(9):1393-1405*

Ionizing Radiations



Parabiosis experiment



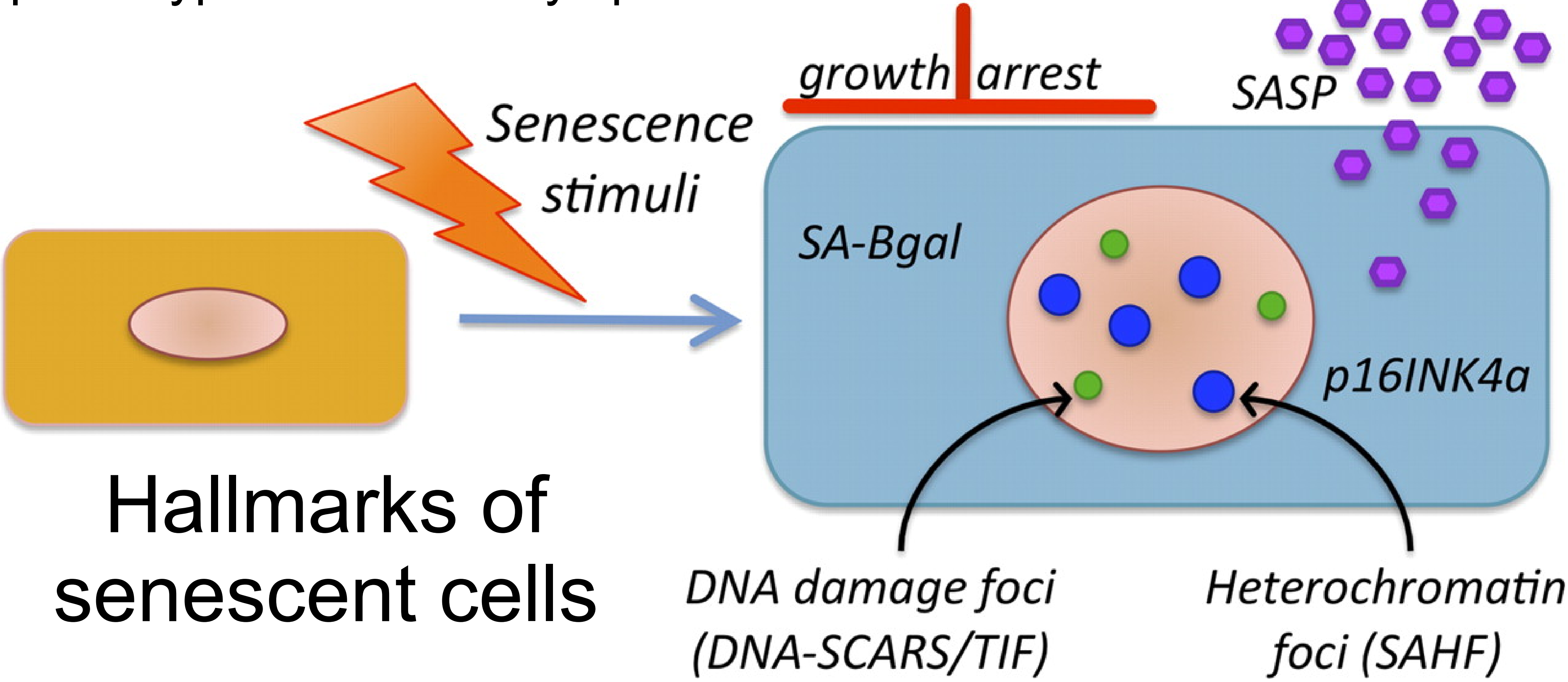
Aging

- Decreased neurogenesis
- Impaired synaptic plasticity
- Impaired cognition

Rejuvenation

- Increased neurogenesis
- Unknown effect on synaptic plasticity?
- Unknown effect on cognition?

Senescent cells differ from nondividing (quiescent, terminally differentiated), even if no single feature of the senescent phenotype is exclusively specific.



Hallmarks of senescent cells

Irreversible growth arrest; Expression of SA-Bgal and p16INK4a; Robust secretion of numerous growth factors, cytokines, proteases, and other proteins (SASP);
Nuclear foci containing DDR proteins (DNA-SCARS/TIF) or heterochromatin (SAHF).

Systemic character of Radiobiology

Radiation causes "mutation, cancer and aging":

Oxygen free radicals produced during normal respiration would cause cumulative damage which would eventually lead to organismal loss of functionality, and ultimately death.

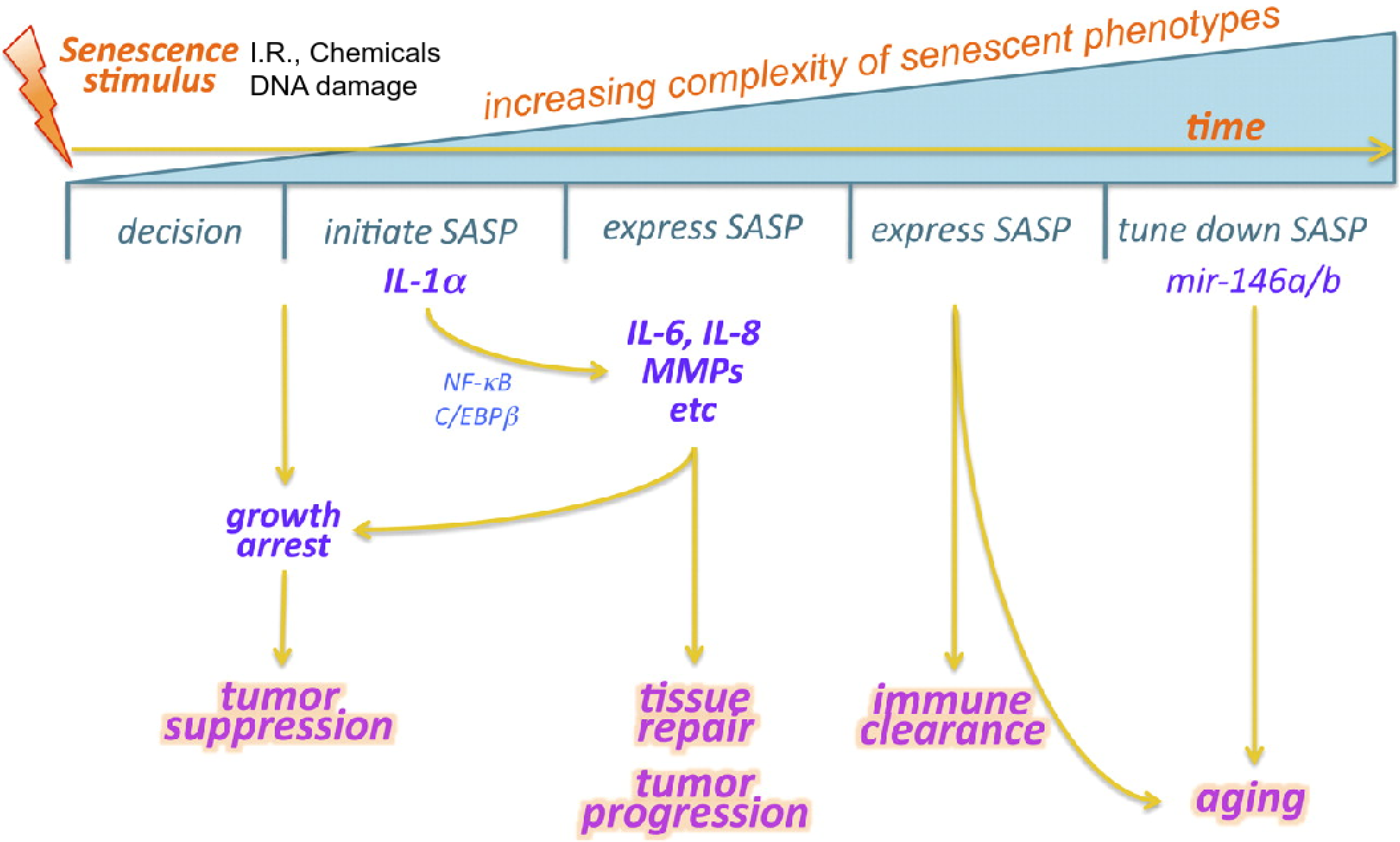
Free radical damage within cells has been linked to diseases as: cancer, atherosclerosis, Alzheimer's disease, and diabetes.

Free radicals play an important role in cellular processes such as phagocytosis, inflammation, and apoptosis.

Diffusible factors induce the spreading of damage to the other cells/tissues/organs

Ionizing Radiations can induce senescence and Radiation Associated Secretory Phenotype (RASP) than can be the mechanism of the Bystander effect

J Gerontol A Biol Sci Med Sci. 2013 May 20.
Ionizing Radiation Promotes the Acquisition of a Senescence-Associated Secretory Phenotype and Impairs Angiogenic Capacity in Cerebromicrovascular Endothelial Cells: Role of Increased DNA Damage and Decreased DNA Repair Capacity in Microvascular Radiosensitivity.
Ungvari Z, Podlutsky A, Sosnowska D, Tucsek Z, Toth P, Deak F, Gautam T, Csiszar A, Sonntag WE.



Senescence stimulus I.R., Chemicals
DNA damage

increasing complexity of senescent phenotypes

time

decision

initiate SASP

express SASP

express SASP

tune down SASP

IL-1α

mir-146a/b

NF-κB
C/EBPβ

IL-6, IL-8
MMPs
etc

growth arrest

tumor suppression

tissue repair

tumor progression

immune clearance

aging

Ionizing radiation act as a multiscale and stochastic process:

level of the whole organism
(organismal effect)

level of its individual cells and molecules
(cellular and molecular effects).

The relations between these two processes are still not clear

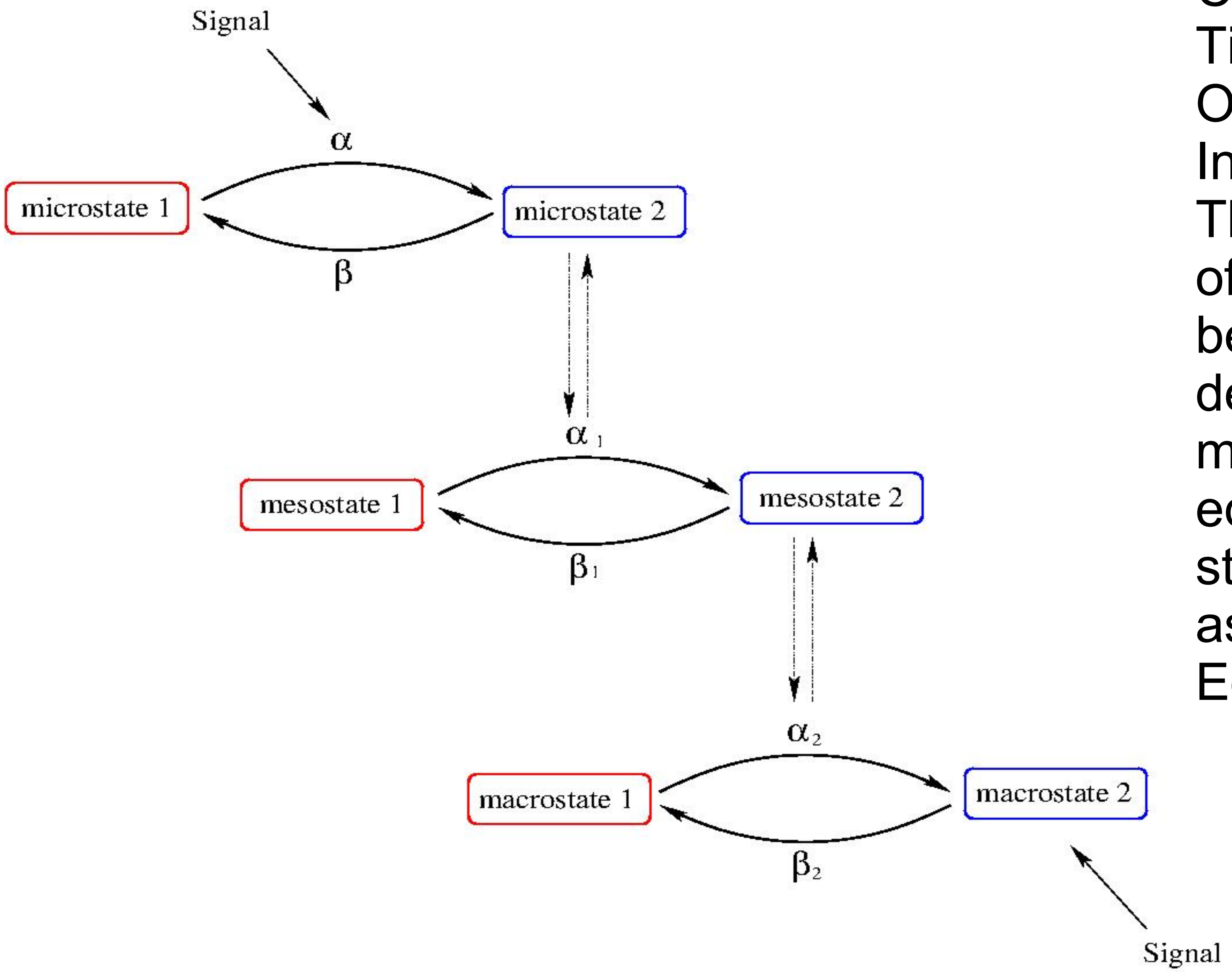
Radiat Environ Biophys (2008) 47:3–4
DOI 10.1007/s00411-008-0157-0

EDITORIAL

The first international workshop on Systems Radiation Biology: a new approach to solve old questions

Herwig G. Paretzke

Cascade of switches can be the mechanism for micro-macro transition and vice-versa



Senescence can take place at various levels:
Cells
Tissues
Organs
Individuals
This cascade of switches can be implemented by deterministic methods (differential equation) and stochastic methods as Chemical Master Equation (CME).

Cells can also be induced to senescence by signals such as

toxins, irradiation, or the activation of certain oncogenes.

In response to DNA damage (including shortened telomeres), cells either age or undergoes apoptosis, if the damage cannot be easily repaired.

How we can study complex phenomena such as

Aging and Radiation Biology?

Systems Biology!!!

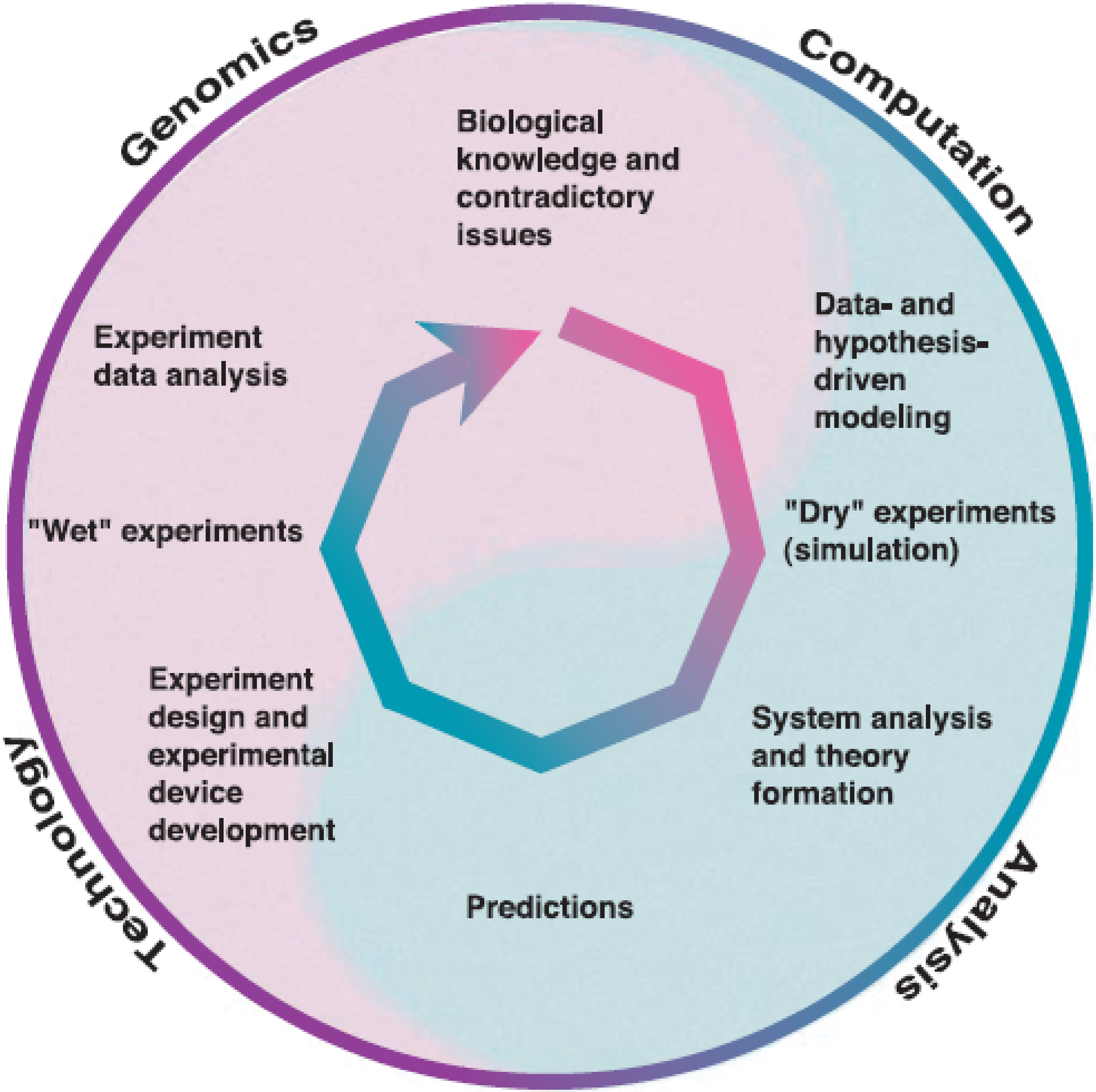
What is Systems Biology?
Classical definition (Kitano et al 2002)

Omics data-Computation-Modeling

Not a new idea (Von Bertalanffy)

Even older
scientific method (Galileo)

Hypothesis-Experiments-Model



Genomics

Computation

Biological knowledge and contradictory issues

Data- and hypothesis-driven modeling

"Dry" experiments (simulation)

System analysis and theory formation

Predictions

Experiment design and experimental device development

"Wet" experiments

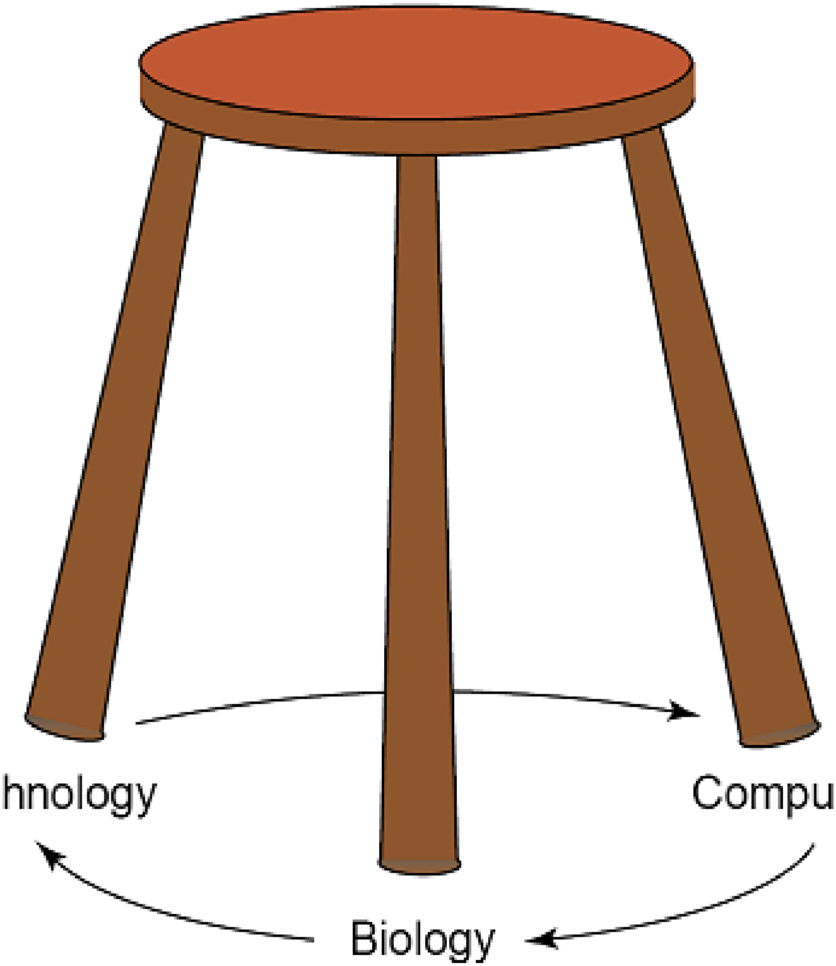
Experiment data analysis

Technology

Analysis

Kitano H, Systems Biology, a brief overview, *Science* 2002

The interdisciplinary character of Systems Biology



Systems biology

Technology
- "Omics" Methods
- Molecular Biology
- Imaging

Computation
- Mathematical Modeling
- Parallel and GRID Computing
- Statistics – Data Mining

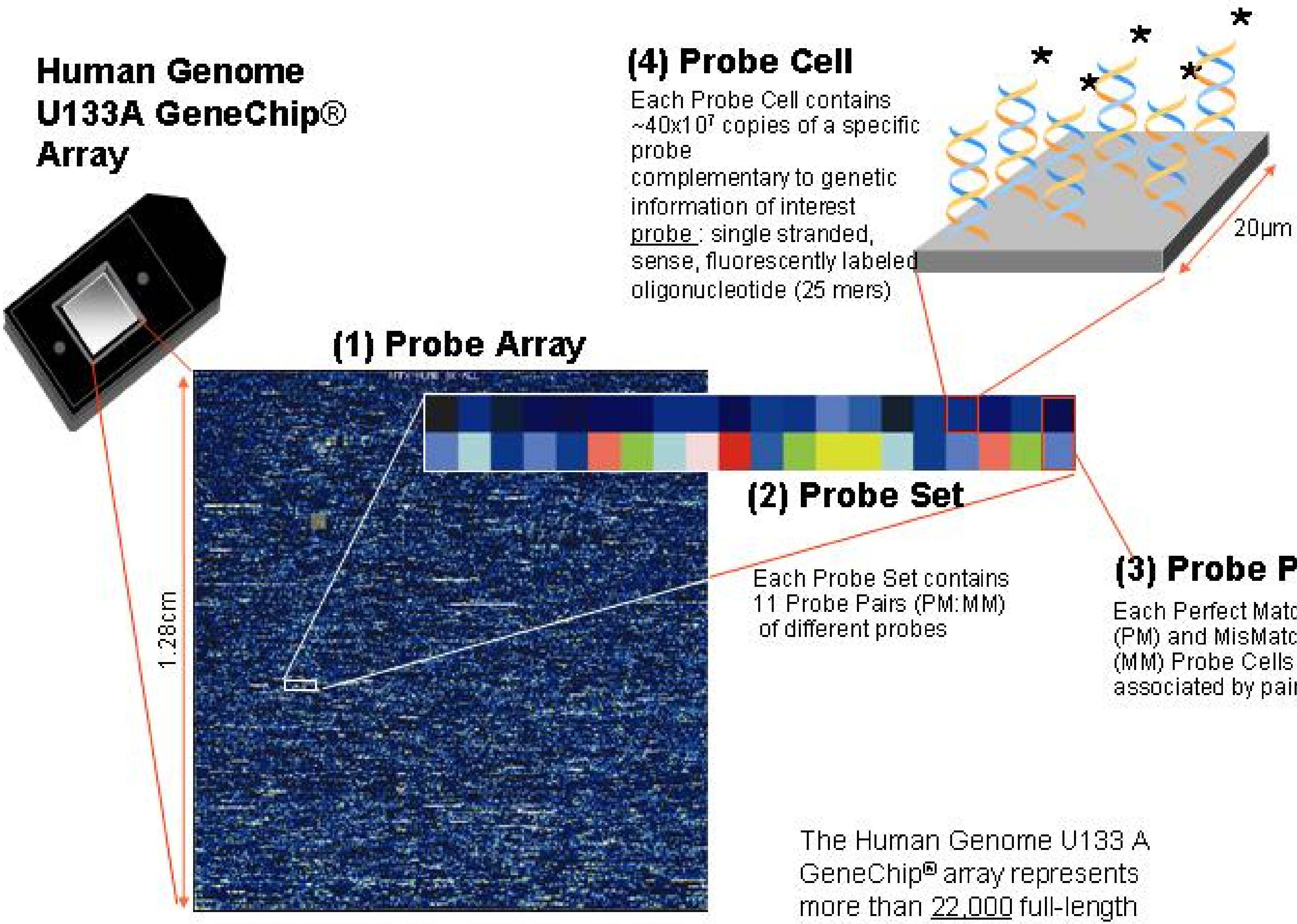
Biology
- Evolution Theory – CellularTheory
- Cellular Phenotypes – GeneExpression
- Emergent Properties – Diseases

Genomics Comparative Genomics:
Functional genomics:
Metagenomics:

Epigenomics:
Transcriptomics:

Proteomics: Immunoproteomics:
Nutriproteomics: Proteogenomics:
Metabolomics:
Metabonomics:

Chips and Features



Human Genome U133A GeneChip® Array

(1) Probe Array

(2) Probe Set

Each Probe Set contains
11 Probe Pairs (PM:MM)
of different probes

(3) Probe Pair

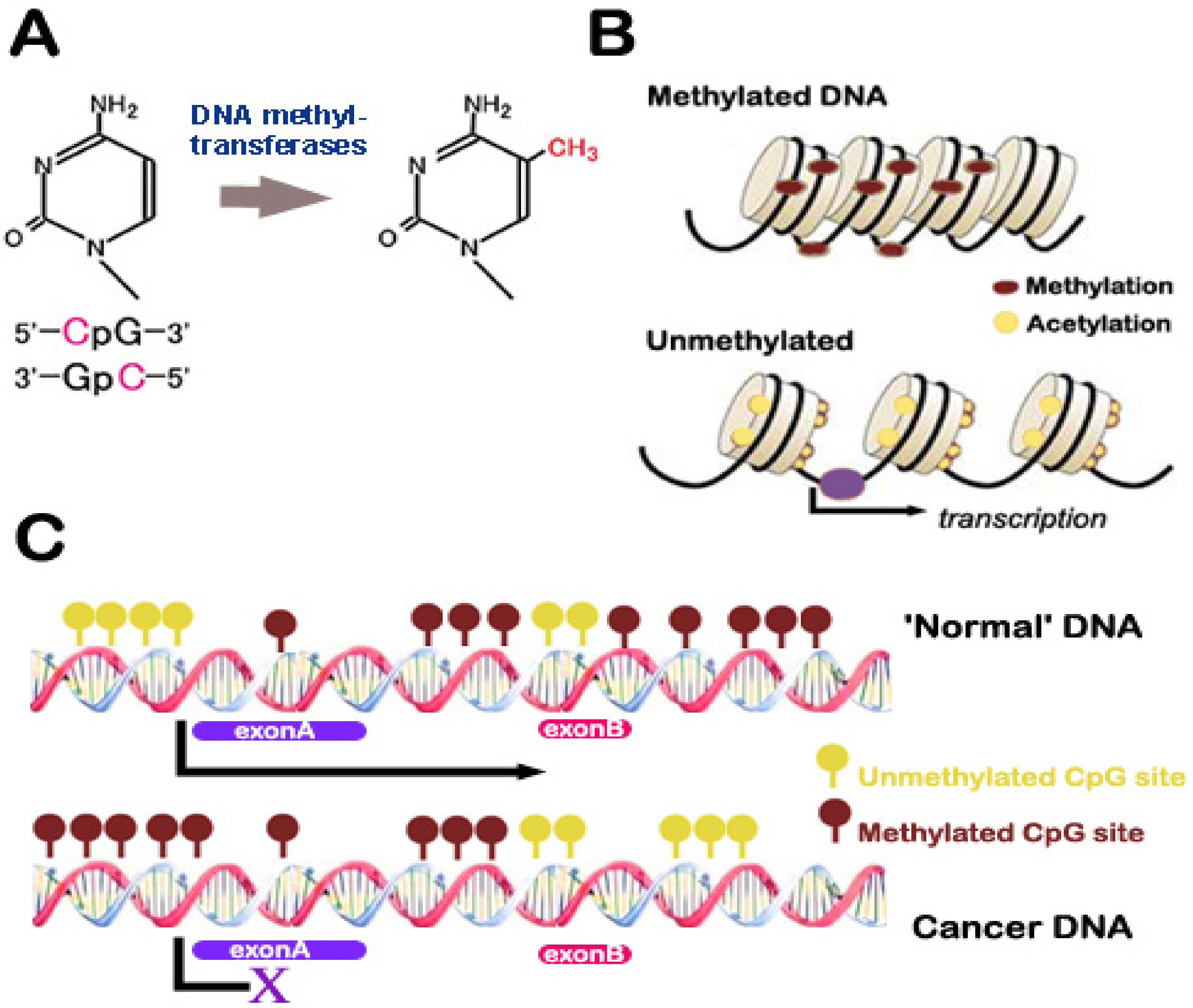
Each Perfect Match (PM) and MisMatch (MM) Probe Cells are associated by pairs

(4) Probe Cell

Each Probe Cell contains ~40x10^7 copies of a specific probe
complementary to genetic information of interest
<u>probe</u> : single stranded, sense, fluorescently labeled oligonucleotide (25 mers)

The Human Genome U133 A GeneChip® array represents more than <u>22,000</u> full-length genes and EST clusters.

DNA methylation pattern



A key ingredient to understand
cellular response to “perturbation”
such as ionizing radiation
is the notion of

BIOLOGICAL(BIOCHEMICAL)
PATHWAY

Krebs 1930

What is a biological Pathway ?

We can have at least two good definitions:

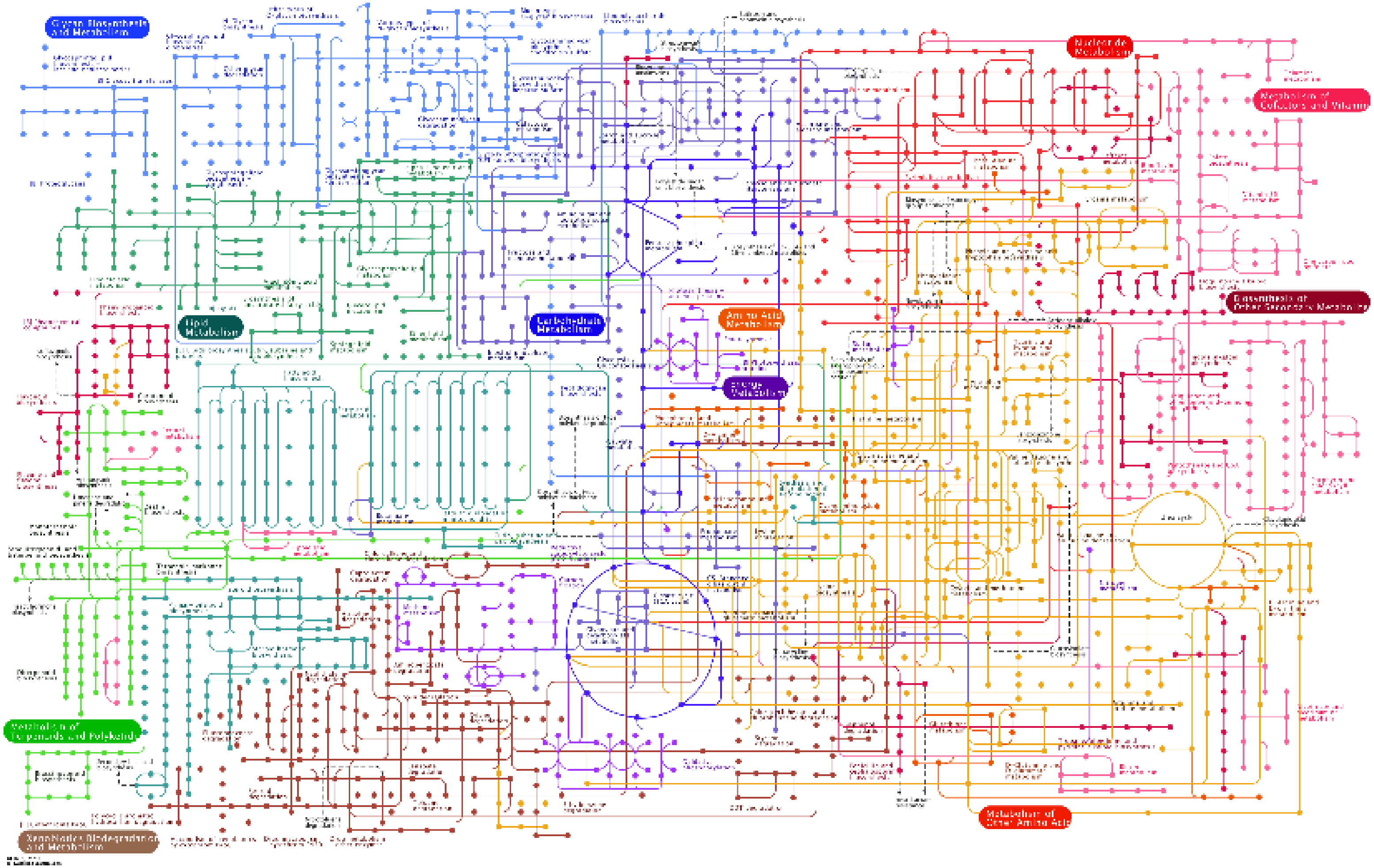
Biological

Biochemical Pathway: interacting molecules (proteins) that perform a biological function

Physico-computational

Molecules that can be clusterized together or that show high correlation (spatial or temporal)

Pathways definition:http://www.genome.jp/kegg/ " a priori biological knowledge"

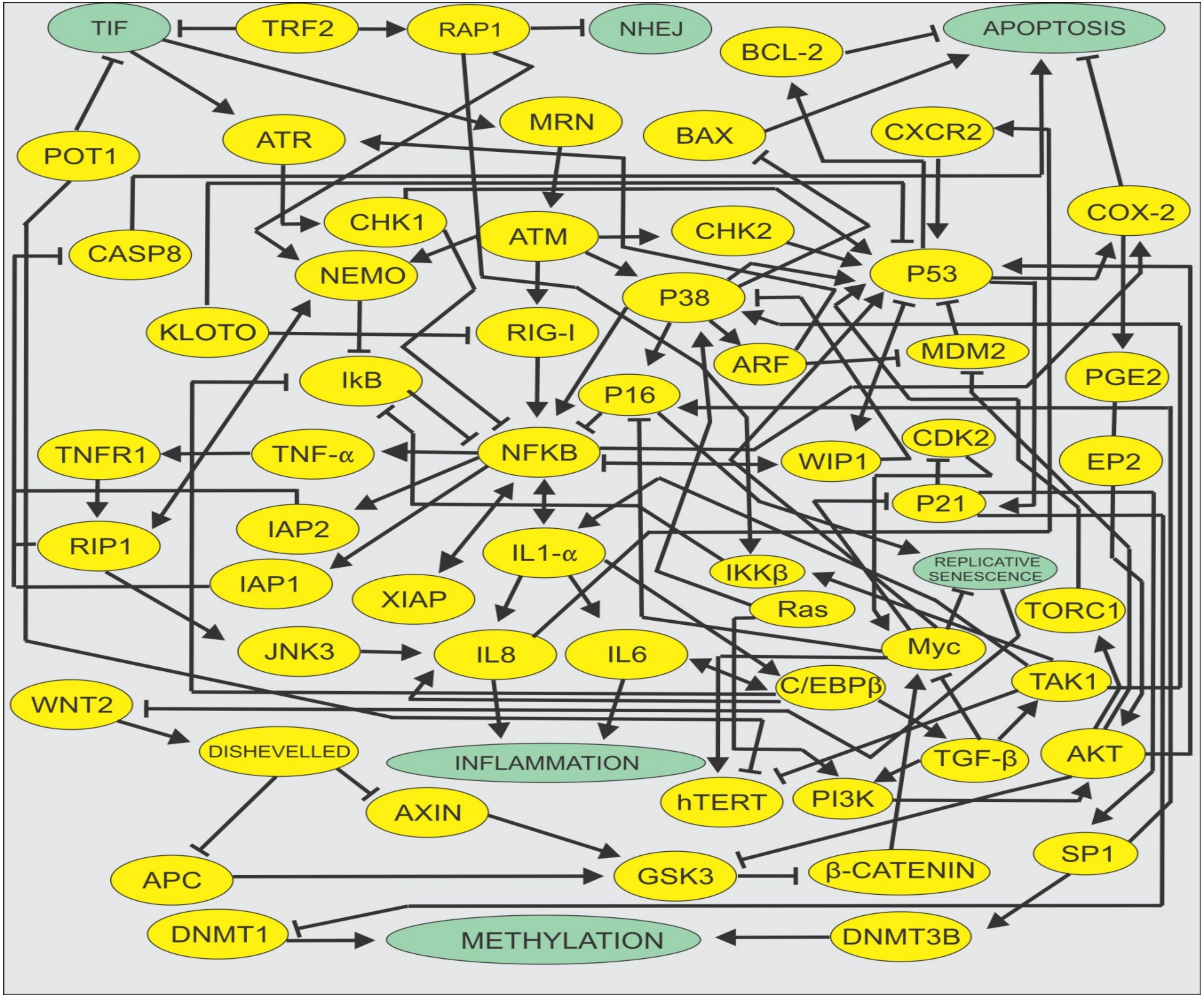


The biological definition of pathway is based on biological knowledge

A biological pathway is a series of reactions among molecules in a cell that leads to a certain product or a function in a cell.

Pathways can be involved in:

assembly of new molecules (biosynthesis)
degradation of molecules
signaling
etc...


TIF
TRF2
RAP1
NHEJ
APOPTOSIS
BCL-2
MRN
BAX
CXCR2
ATR
POT1
COX-2
CHK1
ATM
CHK2
CASP8
NEMO
P53
P38
KLOTO
RIG-I
MDM2
ARF
IkB
PGE2
P16
CDK2
TNFR1
TNF-α
NFKB
WIP1
EP2
P21
IAP2
RIP1
IL1-α
REPLICATIVE SENESCENCE
IKKβ
IAP1
XIAP
TORC1
Ras
Myc
JNK3
IL8
IL6
C/EBPβ
TAK1
WNT2
DISHEVELLED
INFLAMMATION
TGF-β
AKT
hTERT
PI3K
AXIN
SP1
APC
GSK3
β-CATENIN
DNMT1
METHYLATION
DNMT3B

Pathways identification: Networks-unsupervised

<u>Keywords</u>:

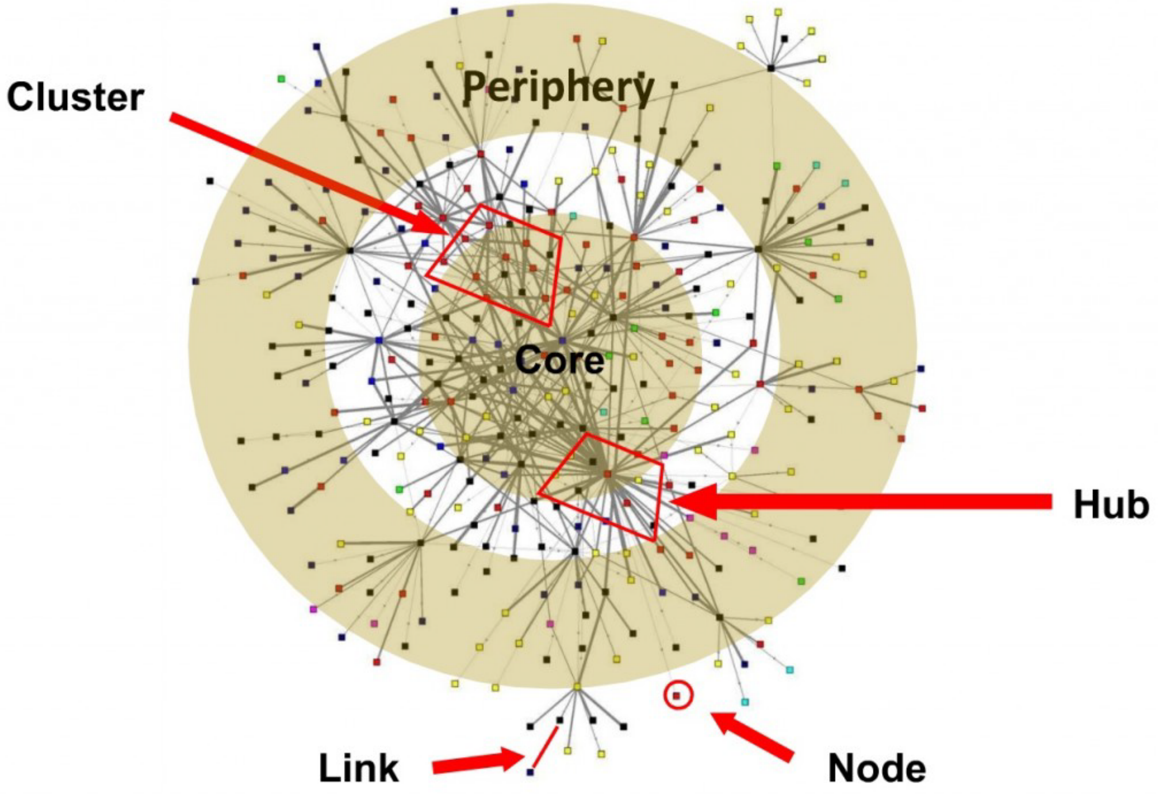
Node

Link

Connectivity

Data driven

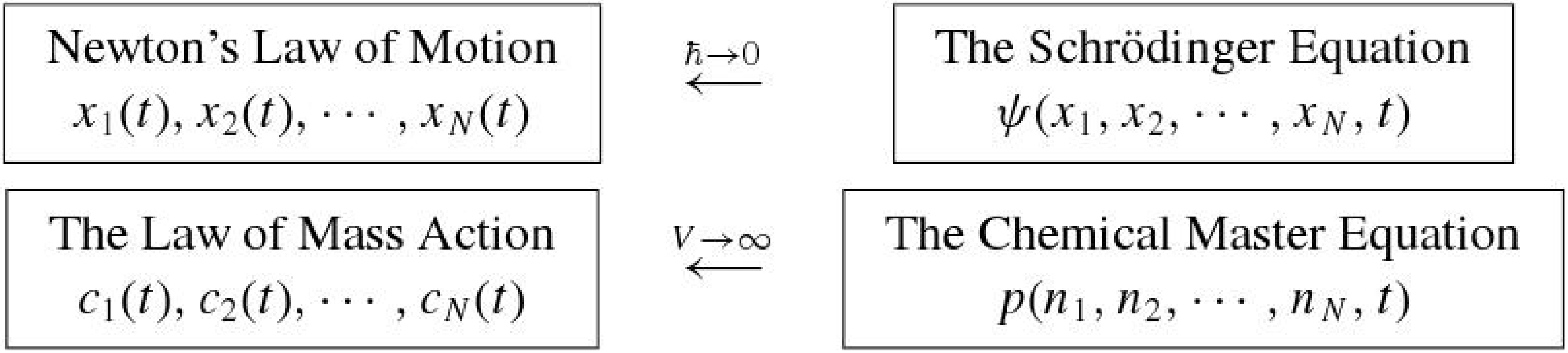
Degree distribution



Main structure
in <u>complex</u>
<u>systems</u>

- ✓No central control
- ✓Collective behavior
- ✓Appearance of emergent properties

Pathways Modeling:
Deterministic vs Stochastic description



Newton's Law of Motion
$x_1(t), x_2(t), \cdots, x_N(t)$

$\xleftarrow{\hbar \to 0}$

The Schrödinger Equation
$\psi(x_1, x_2, \cdots, x_N, t)$

The Law of Mass Action
$c_1(t), c_2(t), \cdots, c_N(t)$

$\xleftarrow{V \to \infty}$

The Chemical Master Equation
$p(n_1, n_2, \cdots, n_N, t)$

$$\frac{dp_m(t)}{dt} = \sum_{\ell \neq m} Q_{lm} p_l - \sum_{\ell \neq m} Q_{ml} p_m$$

Castellani GC, Bazzani A, Cooper LN. Toward a microscopic model of bidirectional synaptic plasticity. Proc Natl Acad Sci U S A. 2009

Correlation method

1) Temporal correlation between genes

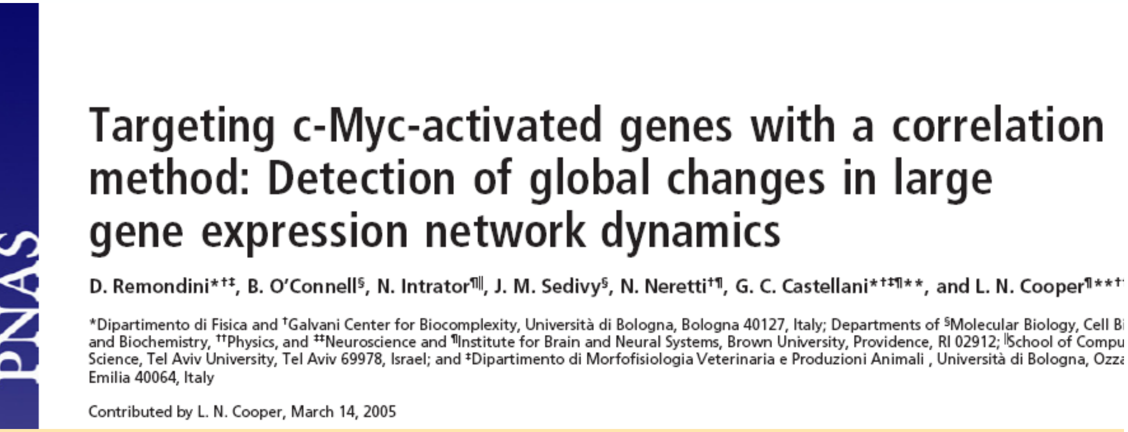
2) Correlation between genes over replicas (cell lines)

3) Grouping the correlation for pathways or functional groups

4) Discretization of the correlation matrix →

Visual representation of interactions (graphical model)

Connectivity map: Correlation method

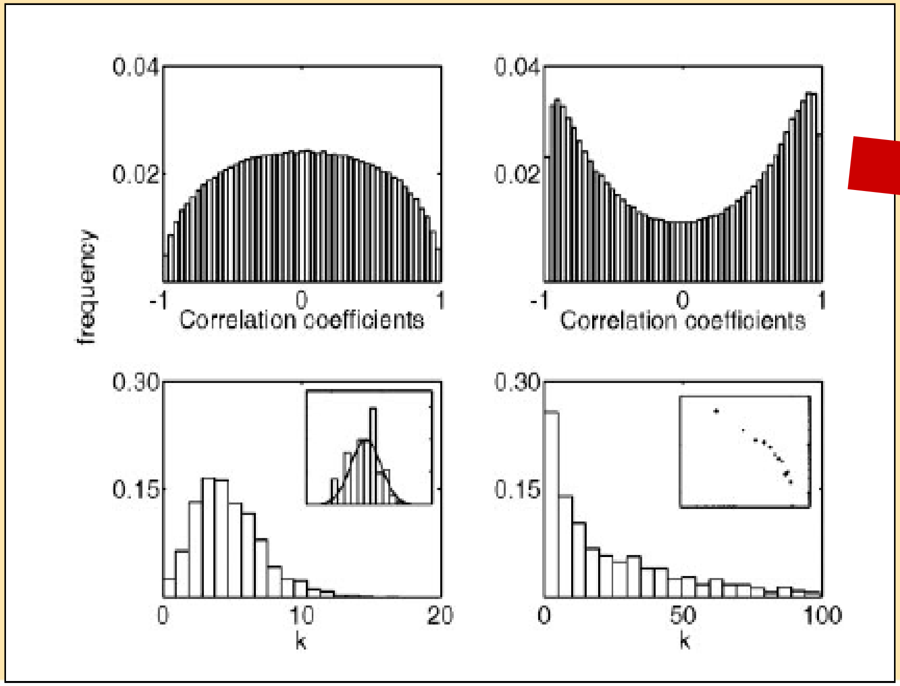


Targeting c-Myc-activated genes with a correlation method: Detection of global changes in large gene expression network dynamics

D. Remondini[*,††,‡], B. O'Connell[§], N. Intrator[¶,||], J. M. Sedivy[§], N. Neretti[†,¶], G. C. Castellani[*,†,‡,¶,**], and L. N. Cooper[¶,**,†

[*]Dipartimento di Fisica and [†]Galvani Center for Biocomplexity, Università di Bologna, Bologna 40127, Italy; Departments of [§]Molecular Biology, Cell Bi and Biochemistry, [††]Physics, and [‡‡]Neuroscience and [¶]Institute for Brain and Neural Systems, Brown University, Providence, RI 02912; [||]School of Compu Science, Tel Aviv University, Tel Aviv 69978, Israel; and [‡]Dipartimento di Morfofisiologia Veterinaria e Produzioni Animali , Università di Bologna, Ozza Emilia 40064, Italy

Contributed by L. N. Cooper, March 14, 2005



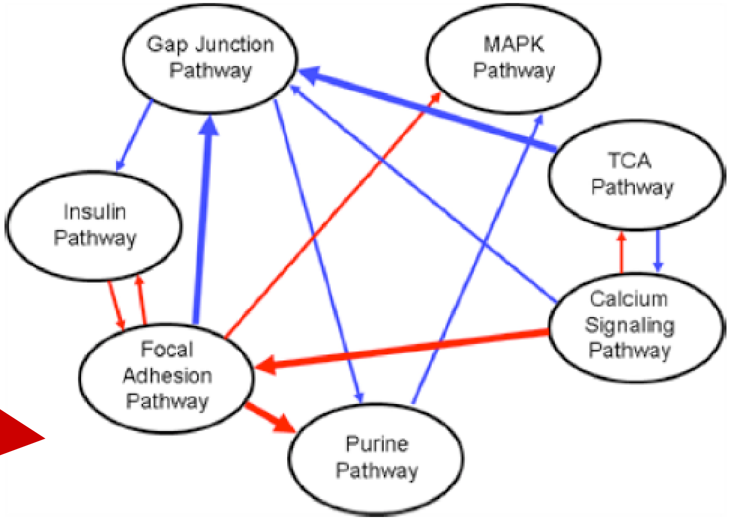
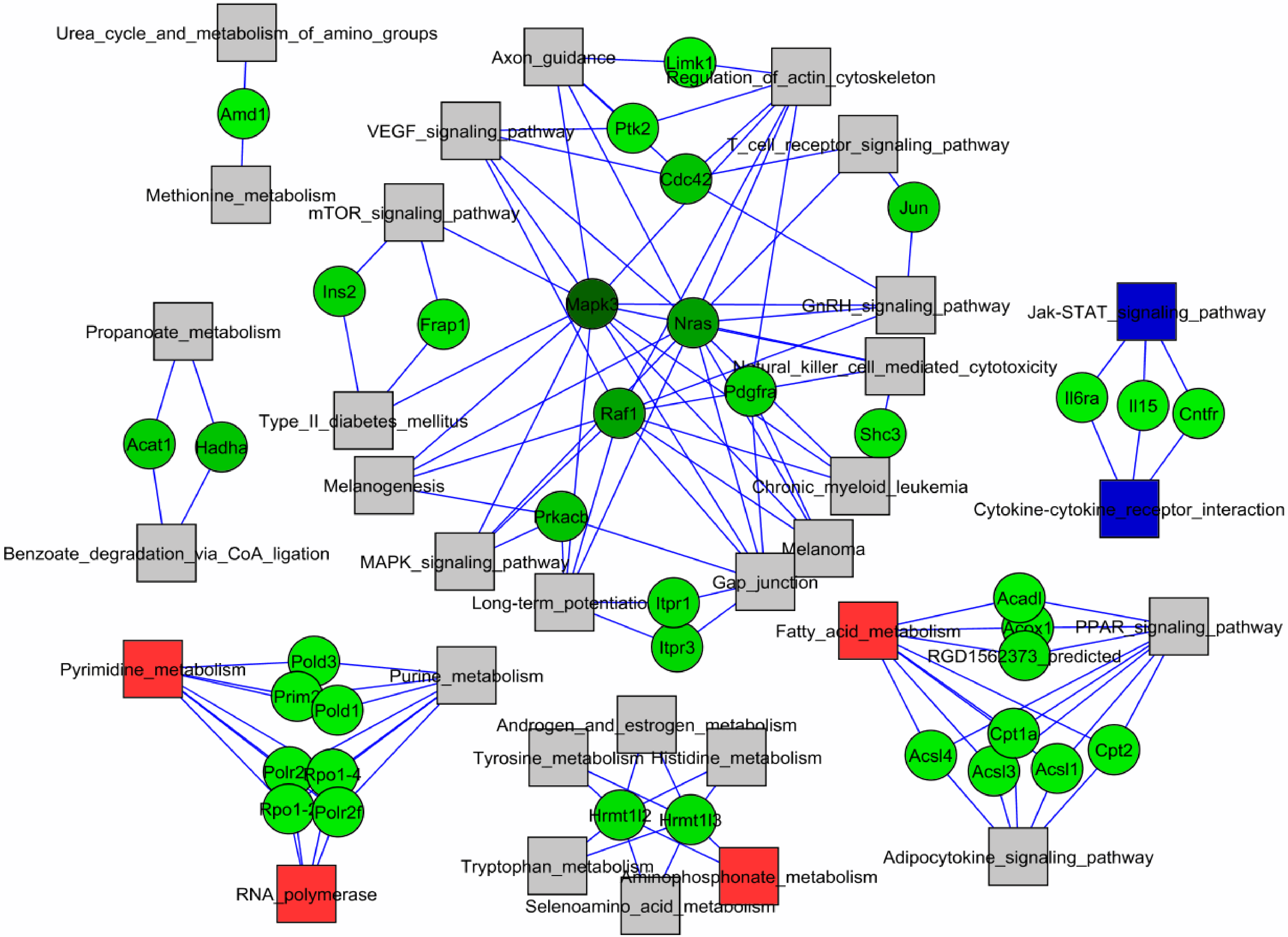
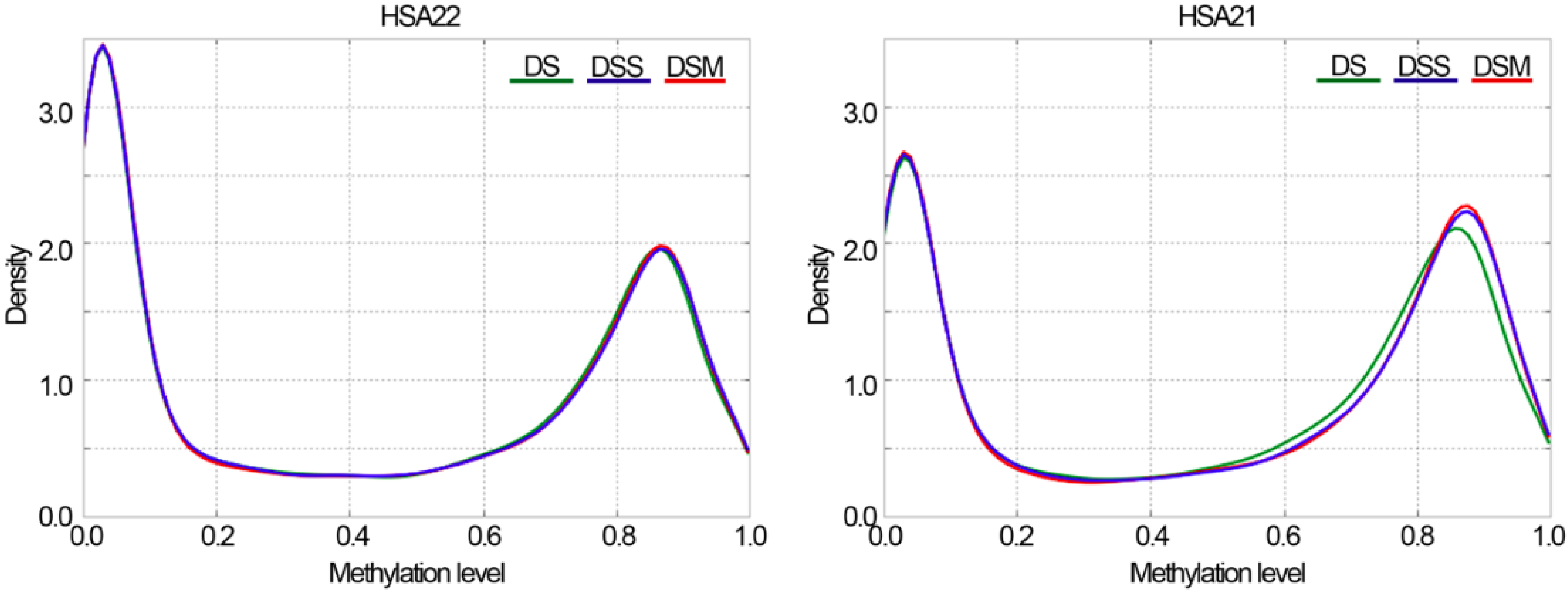


Fig. 3. Network of selected Myc-influenced pathways showing positive and negative correlations. The red and blue arrows denote positive and negative co-regulation, respectively. The thickness of the arrows is proportional to the magnitude, or absolute value, of the co-regulation. A network with these properties is called a weighted directed graph.


Urea_cycle_and_metabolism_of_amino_groups
Amd1
Methionine_metabolism
Axon_guidance
Limk1
Regulation_of_actin_cytoskeleton
VEGF_signaling_pathway
Ptk2
T_cell_receptor_signaling_pathway
Cdc42
mTOR_signaling_pathway
Jun
Ins2
Frap1
Propanoate_metabolism
Mapk3
Nras
GnRH_signaling_pathway
Jak-STAT_signaling_pathway
Natural_killer_cell_mediated_cytotoxicity
Pdgfra
Raf1
Il6ra
Il15
Cntfr
Type_II_diabetes_mellitus
Acat1
Hadha
Shc3
Melanogenesis
Chronic_myeloid_leukemia
Prkacb
Cytokine-cytokine_receptor_interaction
Benzoate_degradation_via_CoA_ligation
MAPK_signaling_pathway
Melanoma
Gap_junction
Long-term_potentiation
Itpr1
Acadl
Fatty_acid_metabolism
Acox1
PPAR_signaling_pathway
Itpr3
RGD1562373_predicted
Pyrimidine_metabolism
Pold3
Purine_metabolism
Prim2
Pold1
Androgen_and_estrogen_metabolism
Tyrosine_metabolism
Histidine_metabolism
Cpt1a
Cpt2
Acsl4
Acsl3
Acsl1
Polr2k
Rpo1-4
Rpo1-1
Polr2f
Hrmt1l2
Hrmt1l3
Tryptophan_metabolism
Aminophosphonate_metabolism
Adipocytokine_signaling_pathway
RNA_polymerase
Selenoamino_acid_metabolism

Overall DNA Methylation

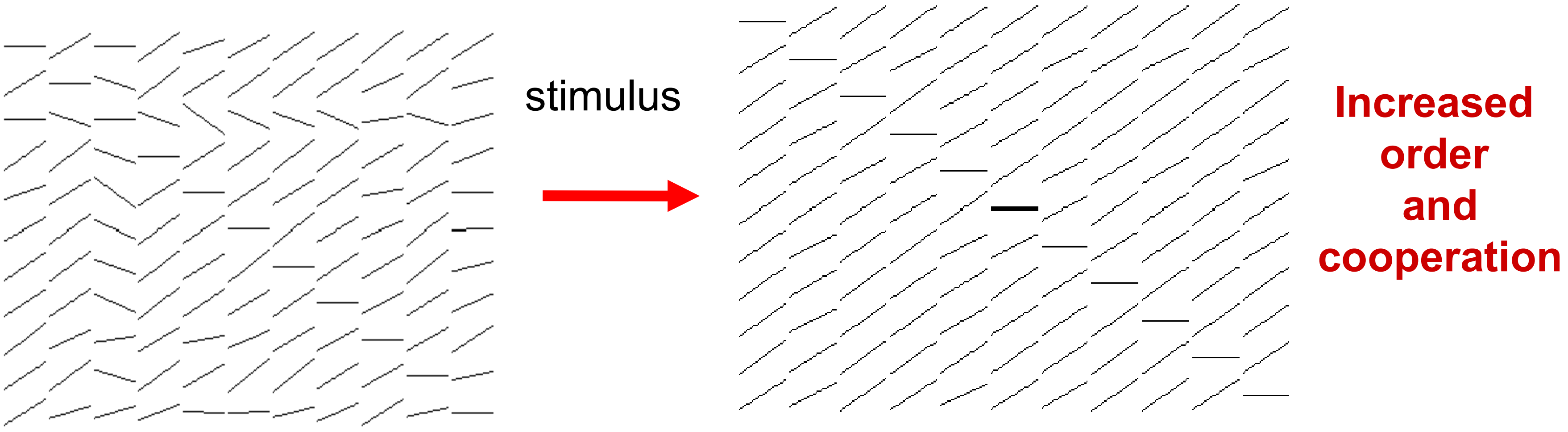


Perturbation approach

Many experiments can be conceptualized as **"perturbation"** of a "basal state" (cell growth, metabolism, young or healthy phenotype,)

"External perturbations" like temperature in physical systems are realized by gene activation via physical, chemical or biological signals (ionizing radiations, transcription factors, aging, infections etc..)

•Emergent properties arising in the context of perturbation theory are the so called **"phase transitions"**



Gene expression measurements

We analyzed gene expression measurements from the GEO Omnibus, The analysis are based on the methods described in [Francesconi et al. 2008, Neretti et al 2007]. P53 is the first pathway influenced by ionizing radiations, as coded by KEGG (www.genome.ad.jp/**kegg/**) followed by steroids biosynthesis and cell cycle.

1: Neretti N, Remondini D, Tatar M, Sedivy JM, Pierini M, Mazzatti D, Powell J,Franceschi C, Castellani GC. Correlation analysis reveals the emergence of coherence in the gene expression dynamics following system perturbation. BMC Bioinformatics. 2007 Mar 8;

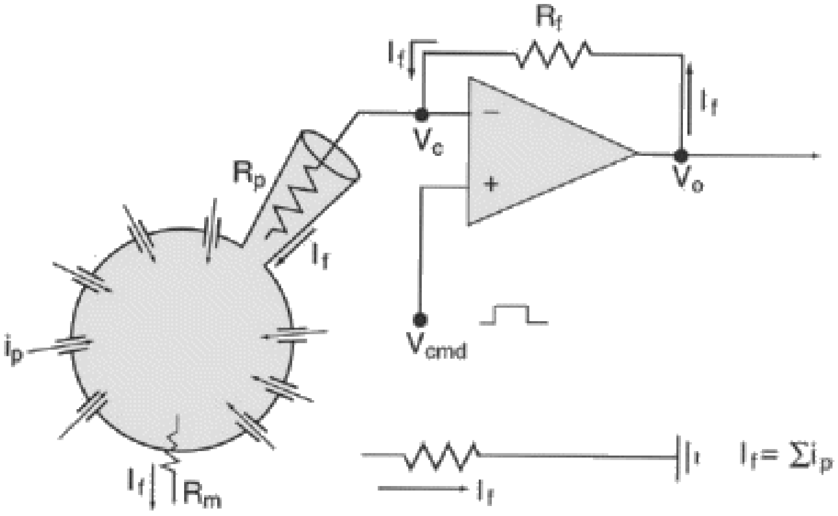
2: Francesconi M, Remondini D, Neretti N, Sedivy JM, Cooper LN, Verondini E,Milanesi L, Castellani G. Reconstructing networks of pathways via significance analysis of their intersections. BMC Bioinformatics. 2008 Apr 25;9

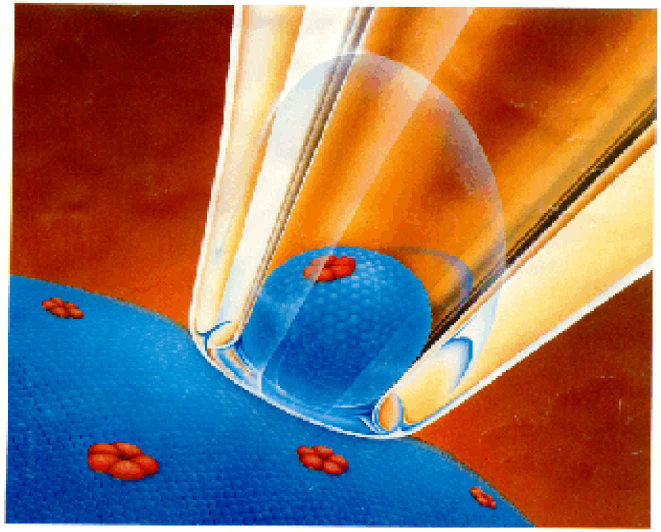
Pathways	pval	U/D
p53 signaling pathway	6.35E-17	1
Biosynthesis of steroids	1.00E-10	1
Cell cycle	1.06E-08	1
Neuroactive ligand-receptor interaction	1.42E-07	-1
Aminoacyl-tRNA biosynthesis	7.63E-07	1
Cell Communication	8.92E-07	-1
Terpenoid biosynthesis	1.72E-06	1
Apoptosis	1.06E-05	1
T cell receptor signaling pathway	0.00039307	1
Polyunsaturated fatty acid biosynthesis	0.000875007	1
Natural killer cell mediated cytotoxicity	0.002964111	1
Ribosome	0.00480522	-1
Small cell lung cancer	0.005294056	1
B cell receptor signaling pathway	0.005519981	1
Calcium signaling pathway	0.006255598	-1
Amyotrophic lateral sclerosis (ALS)	0.006301049	1
Tight junction	0.008687461	-1

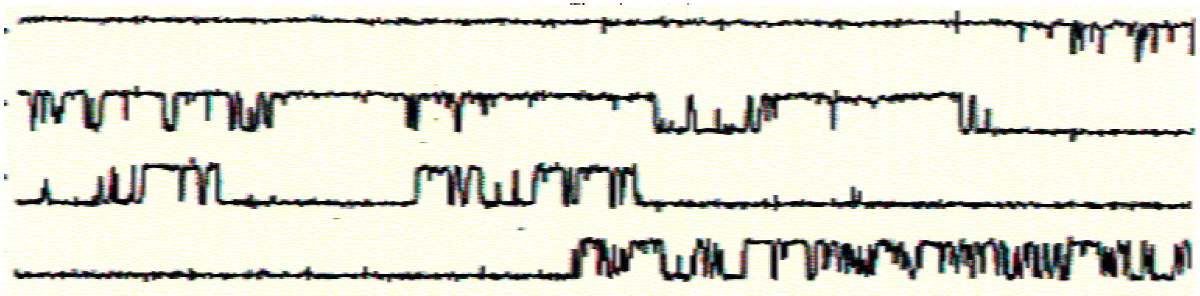
Pathways	pval	U/D
Cyanoamino acid metabolism	0.0088605	1
Pancreatic cancer	0.010856689	1
Reductive carboxylate cycle (CO2 fixation)	0.01565399	1
Valine, leucine and isoleucine biosynthesis	0.02007625	1
Folate biosynthesis	0.020348718	1
Starch and sucrose metabolism	0.028190214	1
Focal adhesion	0.028564124	-1
Glycerolipid metabolism	0.028731531	-1
Adherens junction	0.029670313	-1
Phenylalanine metabolism	0.030074211	-1
Dentatorubropallidoluysian atrophy (DRPLA)	0.030910646	-1
Phenylalanine, tyrosine and tryptophan biosynthesis	0.033487807	1
Pathogenic Escherichia coli infection – EHEC	0.044350053	-1
Pathogenic Escherichia coli infection – EPEC	0.044350053	-1
One carbon pool by folate	0.044827933	1
Maturity onset diabetes of the young	0.045306449	-1
Metabolism of xenobiotics by cytochrome P450	0.046093339	-1

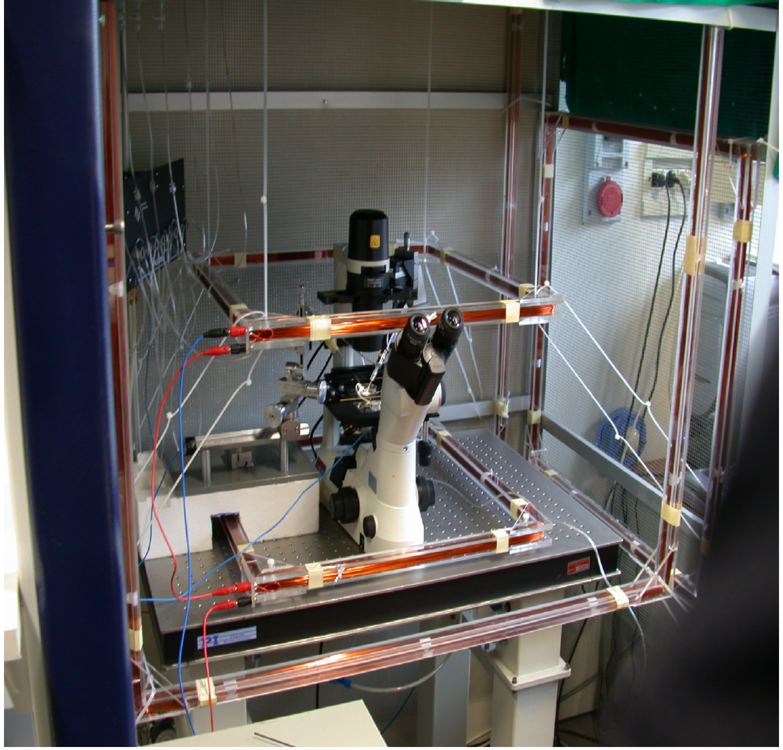
espressione genica in 3 linee di fibroblasti umani γ irraggiati (1.5Gy)su vari intervalli di tempo.(2,6 e 24h) (GEOD7075 www.ebi.ac.uk). e a 6h non irraggiate

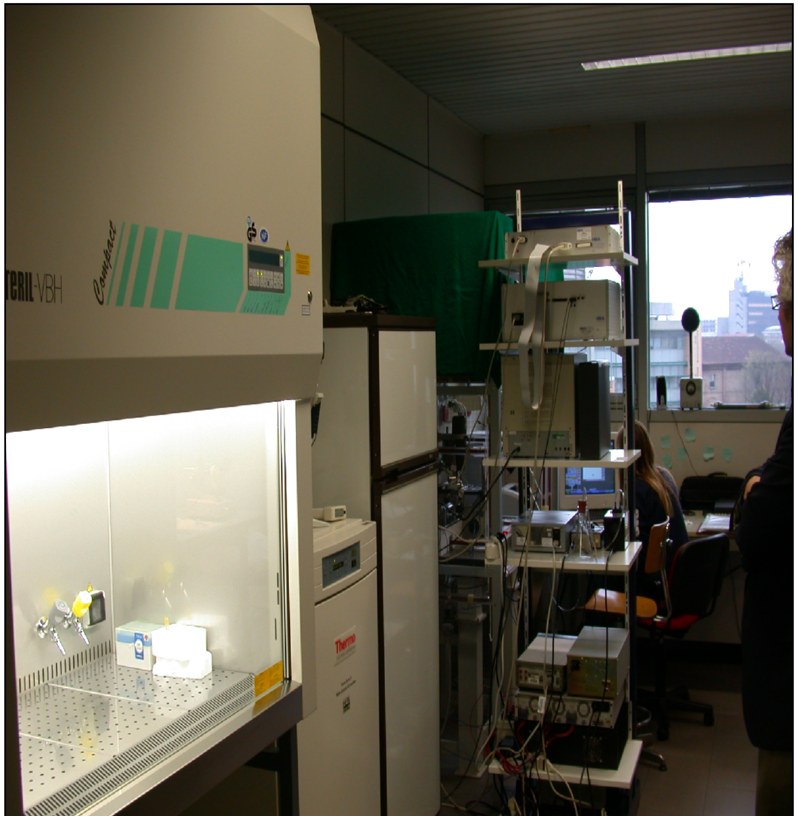
nome gene	P	descrizione gene
KCNJ5	0,000975	potassium inwardly-rectifying channel, subfamily J, member 5 (KCNJ5),
KCNK2	0,003001	potassium channel, subfamily K, member 2 (KCNK2), mRNA [NM_014217]
KCNQ2	0,006573	potassium voltage-gated channel, KQT-like subfamily, member 2 (KCNQ2),]
KCNK17	0,014396	potassium channel, subfamily K, member 17 (KCNK17), mRNA [NM_031460]
KCNK16	0,020902	potassium channel, subfamily K, member 16 (KCNK16), mRNA [NM_032115]
KCNB2	0,02129	potassium voltage-gated channel, Shab-related subfamily, member 2
KCNAB1	0,024799	potassium voltage-gated channel, shaker-related subfamily, beta member 1
KCNE1L	0,02737	potassium voltage-gated channel, Isk-related family, member 1-like (KCNE1L)
KCNAB1	0,027802	potassium voltage-gated channel, shaker-related subfamily, beta member 1
KCND3	0,036798	potassium voltage-gated channel, Shal-related subfamily, member 3 (KCND3),
KCNJ10	0,036905	potassium inwardly-rectifying channel, subfamily J, member 10 (KCNJ10),
KCNJ9	0,04971	potassium inwardly-rectifying channel, subfamily J, member 9 (KCNJ9),

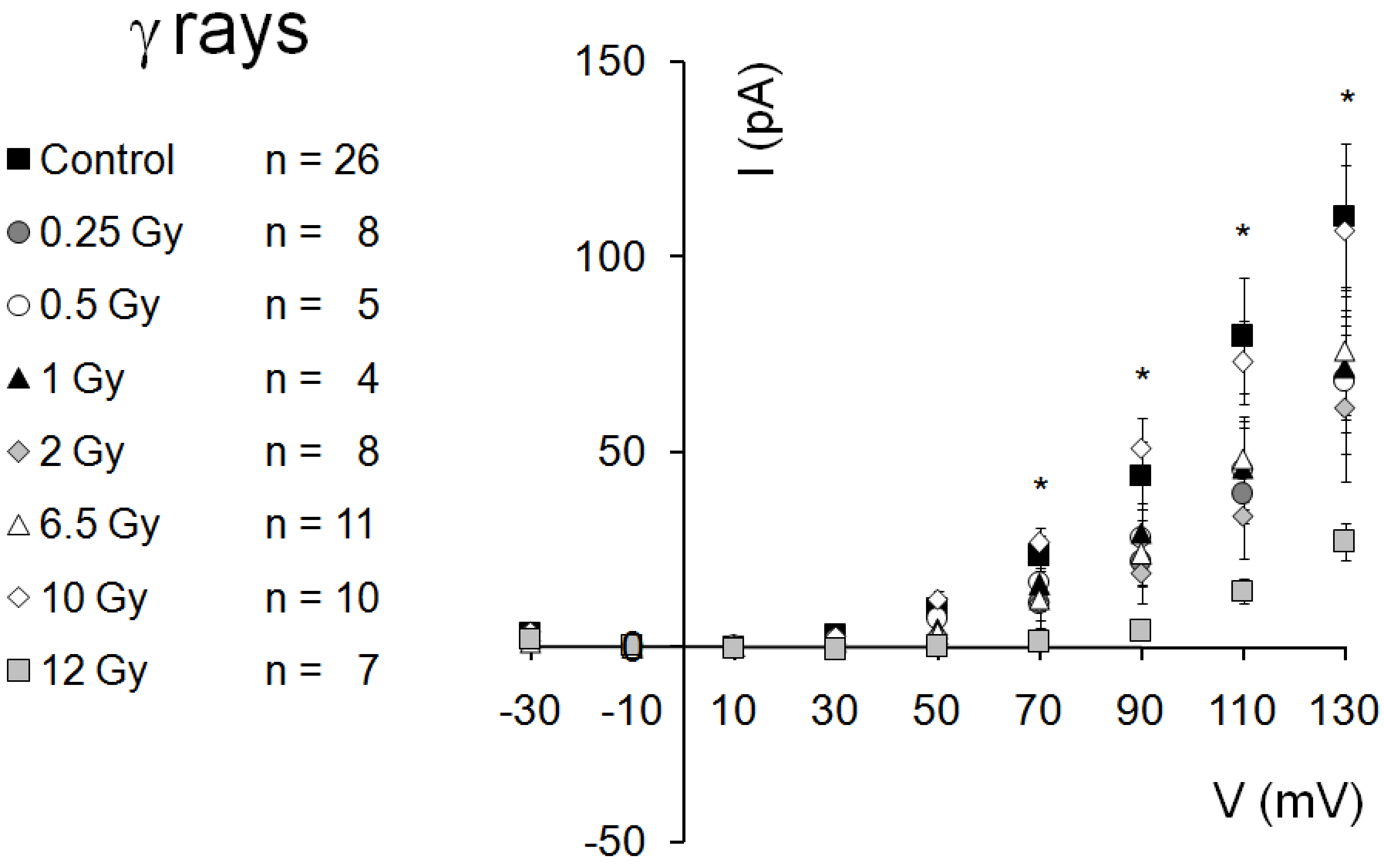

R_f
I_f
I_f
V_c
V_o
R_p
I_f
i_p
V_{cmd}
I_f
R_m
I_f
$I_f = \Sigma i_p$



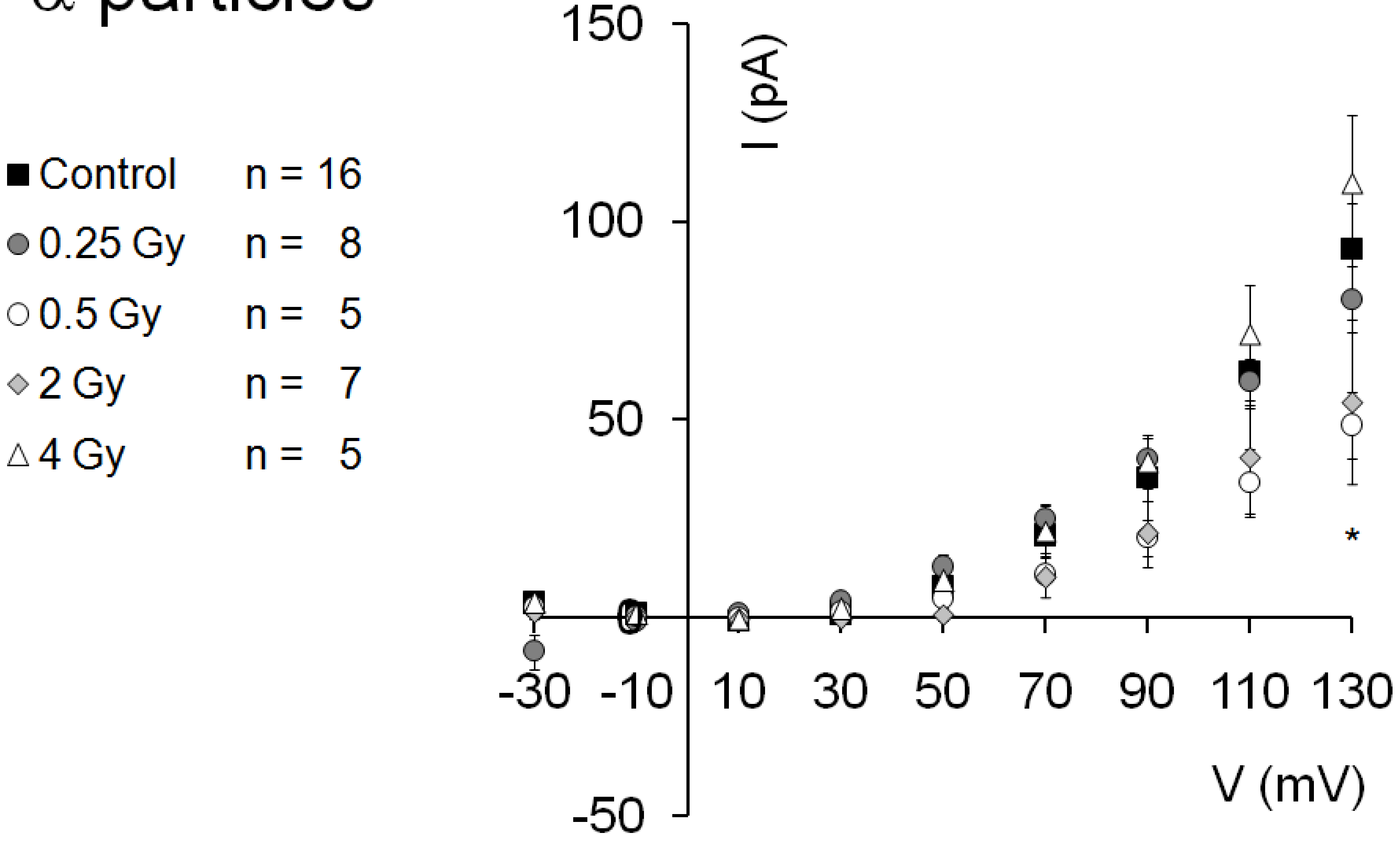


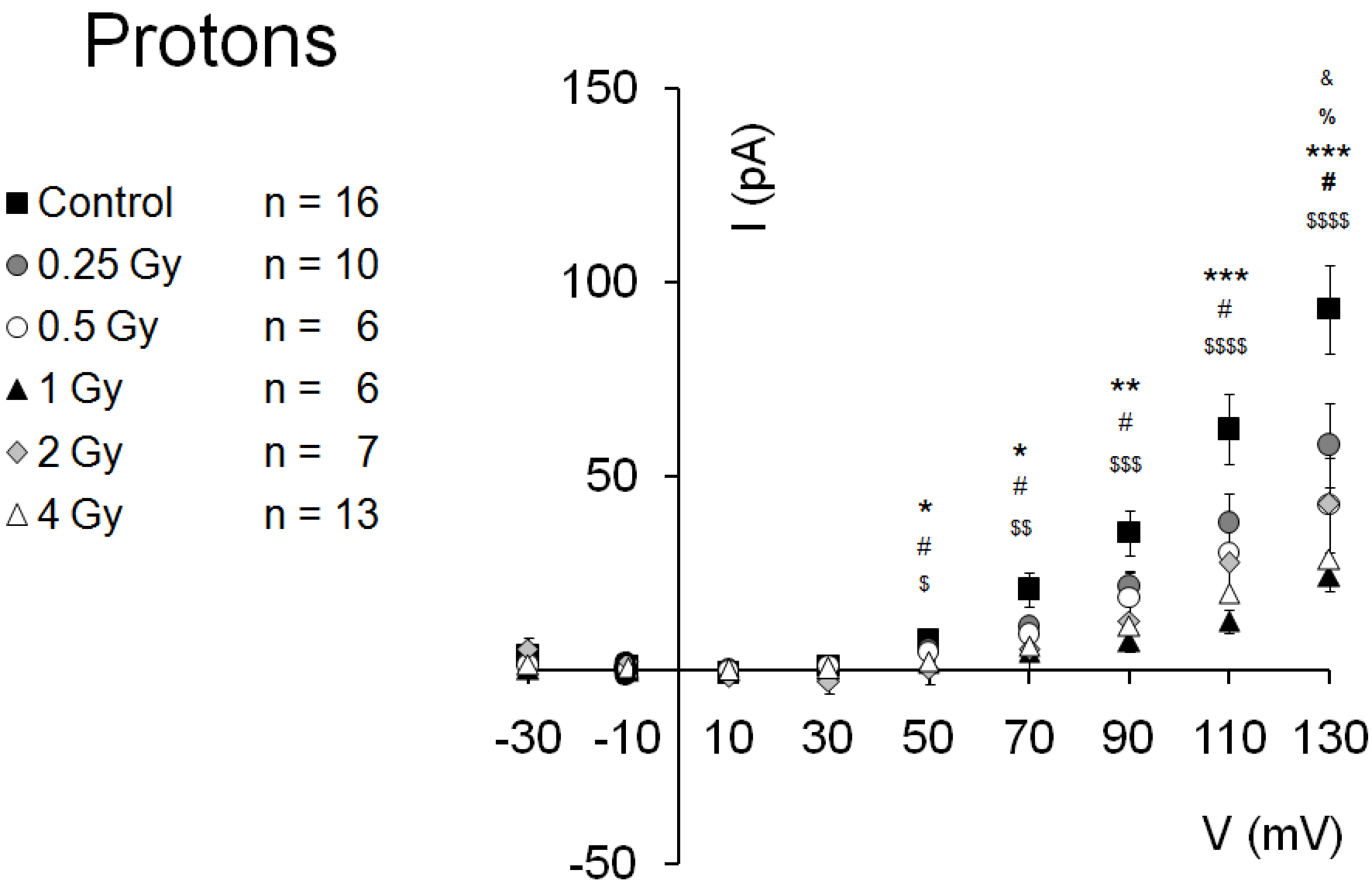



TERIL-VBH
Compact
Thermo


γ rays
■ Control n = 26
● 0.25 Gy n = 8
○ 0.5 Gy n = 5
▲ 1 Gy n = 4
◆ 2 Gy n = 8
△ 6.5 Gy n = 11
◇ 10 Gy n = 10
■ 12 Gy n = 7
I (pA)
150
100
50
-50
-30
-10
10
30
50
70
90
110
130
V (mV)
*
*
*
*

α particles


■ Control n = 16
● 0.25 Gy n = 8
○ 0.5 Gy n = 5
◇ 2 Gy n = 7
△ 4 Gy n = 5
I (pA)
150
100
50
0
-50
-30
-10
10
30
50
70
90
110
130
V (mV)
*

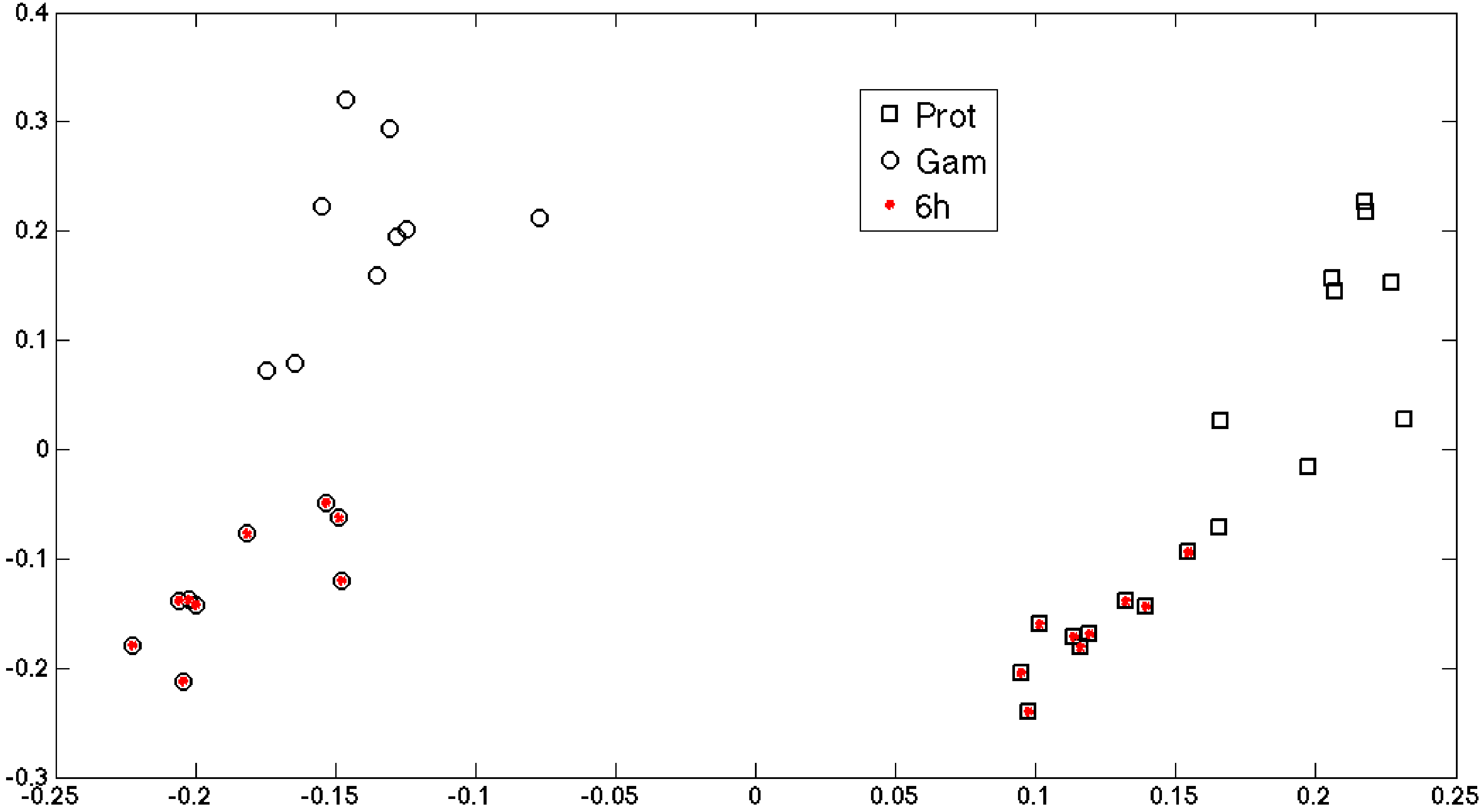

Protons
■ Control n = 16
● 0.25 Gy n = 10
○ 0.5 Gy n = 6
▲ 1 Gy n = 6
◇ 2 Gy n = 7
△ 4 Gy n = 13
I (pA)
150
100
50
0
-50
V (mV)
-30
-10
10
30
50
70
90
110
130
*
#
$
*
#
$$
**
#
$$$
***
#
$$$$
&
%
***
#
$$$$

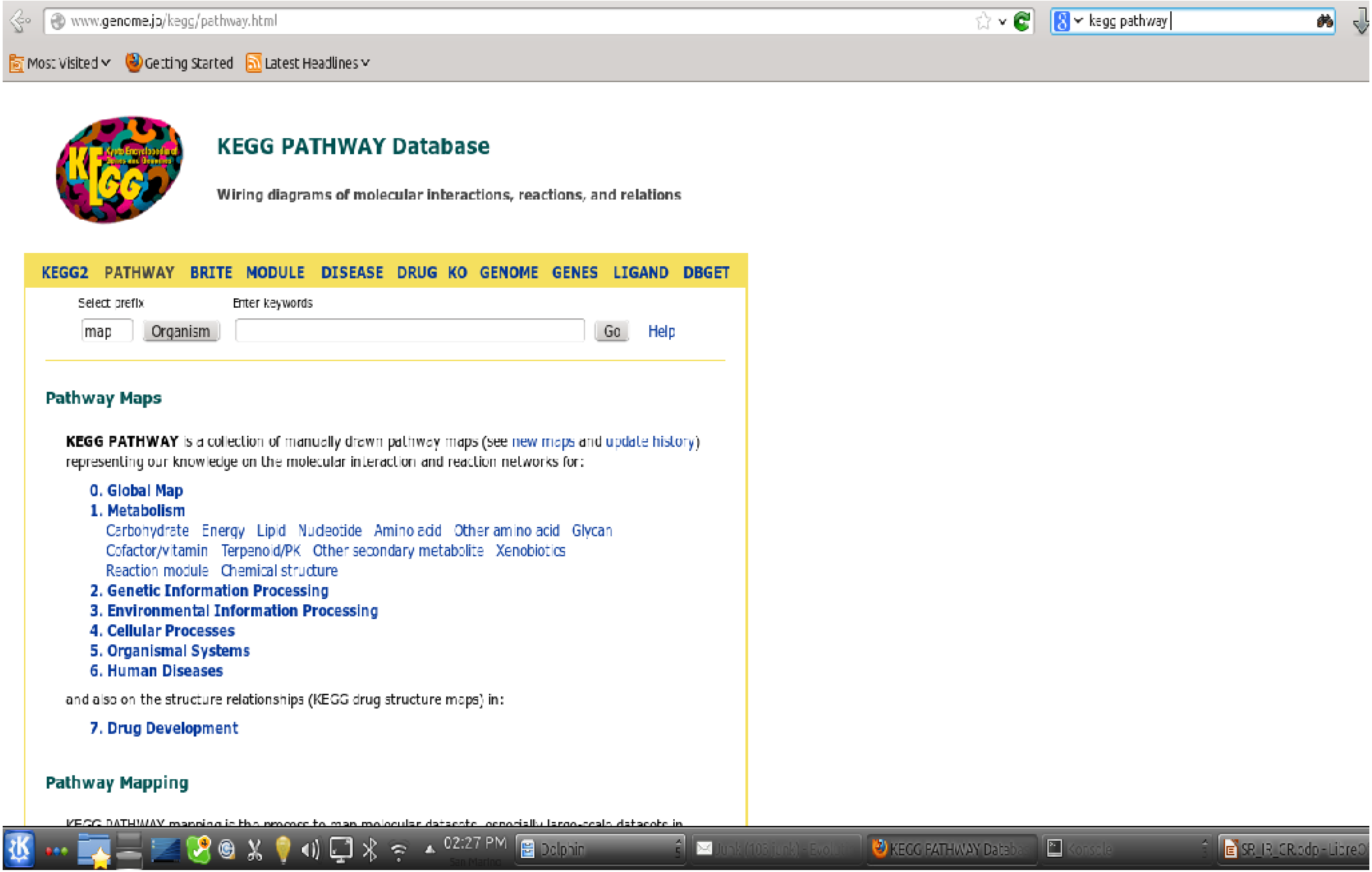
Esperimento INFN Excalibur

SampId	IR	DOSE	TIME
1	Protoni	0	6
2	Protoni	0	6
3	Protoni	0	6
4	Protoni	0.25	6
5	Protoni	0.25	6
6	Protoni	0.25	6
7	Protoni	2	6
8	Protoni	2	6
9	Protoni	2	6
11	Gamma	0	6
12	Gamma	0.25	6
13	Gamma	2	6
14	Gamma	0	6
15	Gamma	0.25	6
16	Gamma	2	6
17	Gamma	0	6
18	Gamma	0.25	6
19	Gamma	2	6

SampId	IR	DOSE	TIME
20	Gamma	0	24
21	Gamma	0.25	24
22	Gamma	2	24
23	Gamma	0	24
24	Gamma	0.25	24
25	Gamma	2	24
26	Gamma	0	24
27	Gamma	0.25	24
28	Gamma	2	24
29	Protoni	0	24
30	Protoni	0	24
31	Protoni	0	24
32	Protoni	0.25	24
33	Protoni	0.25	24
34	Protoni	0.25	24
35	Protoni	2	24
36	Protoni	2	24
37	Protoni	2	24

PCA analysis of the EXCALIBUR experiment





KEGG PATHWAY Database

Wiring diagrams of molecular interactions, reactions, and relations

Pathway Maps

KEGG PATHWAY is a collection of manually drawn pathway maps (see new maps and update history) representing our knowledge on the molecular interaction and reaction networks for:

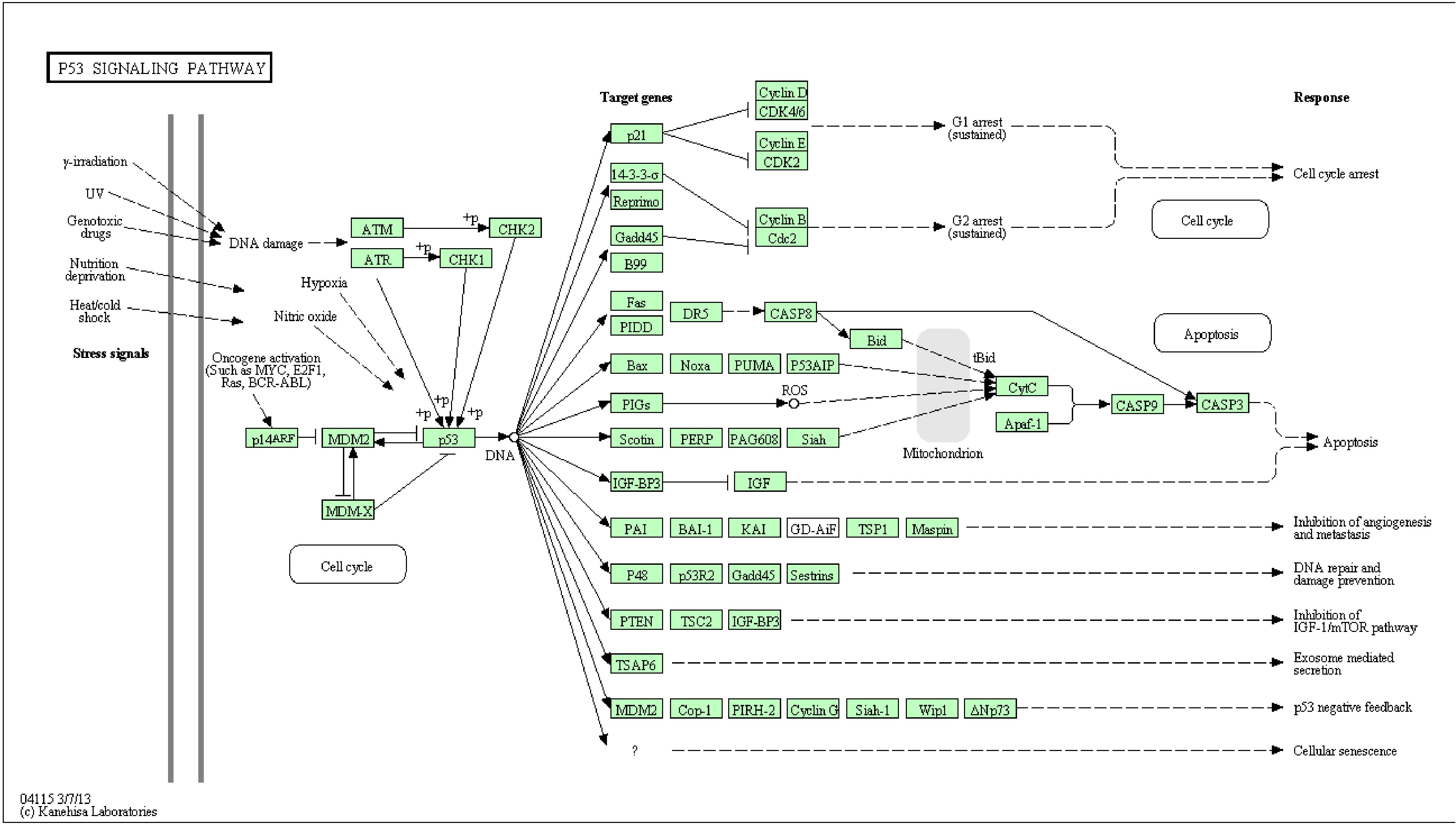
0. Global Map
1. Metabolism
Carbohydrate Energy Lipid Nucleotide Amino acid Other amino acid Glycan
Cofactor/vitamin Terpenoid/PK Other secondary metabolite Xenobiotics
Reaction module Chemical structure
2. Genetic Information Processing
3. Environmental Information Processing
4. Cellular Processes
5. Organismal Systems
6. Human Diseases

and also on the structure relationships (KEGG drug structure maps) in:

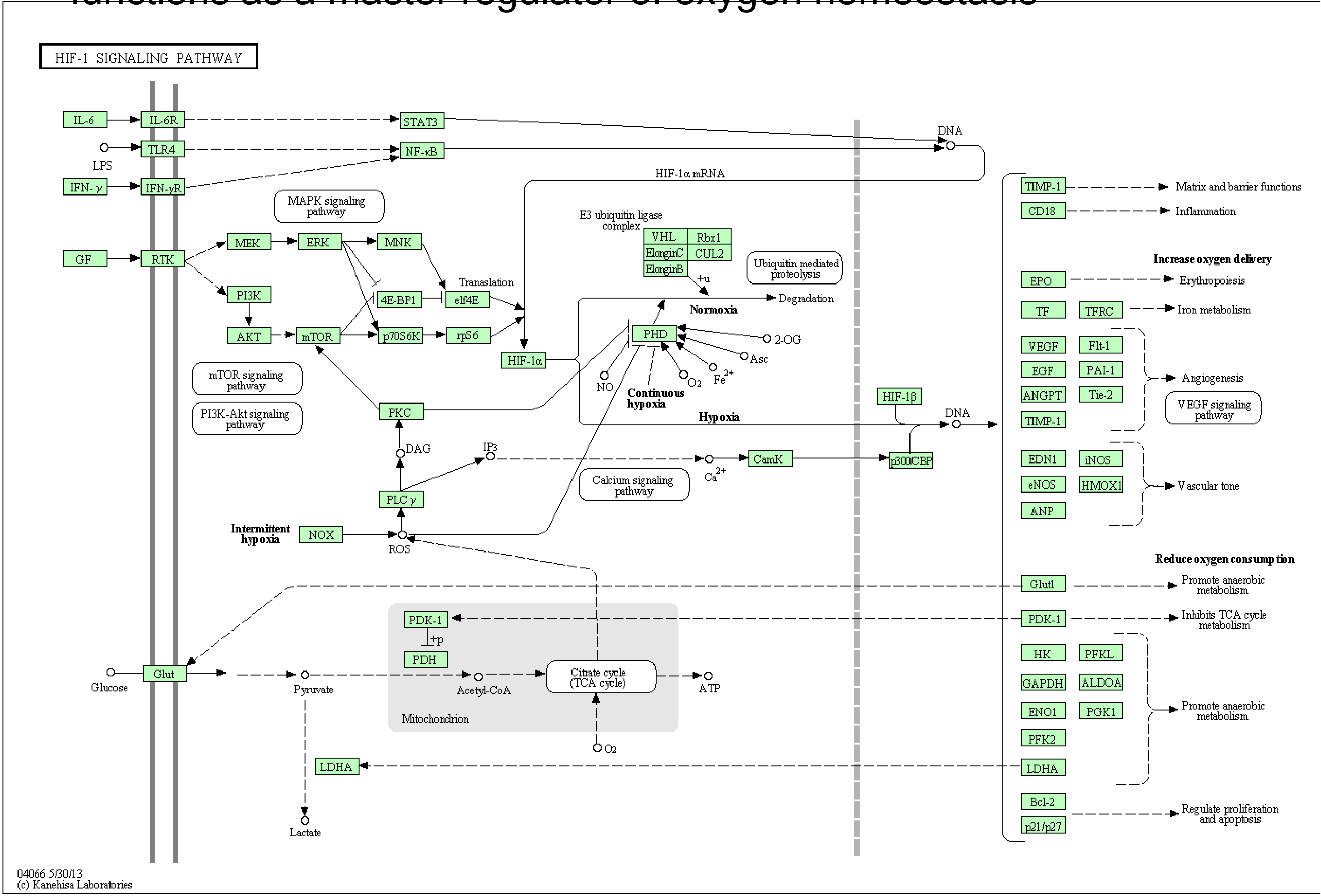
7. Drug Development

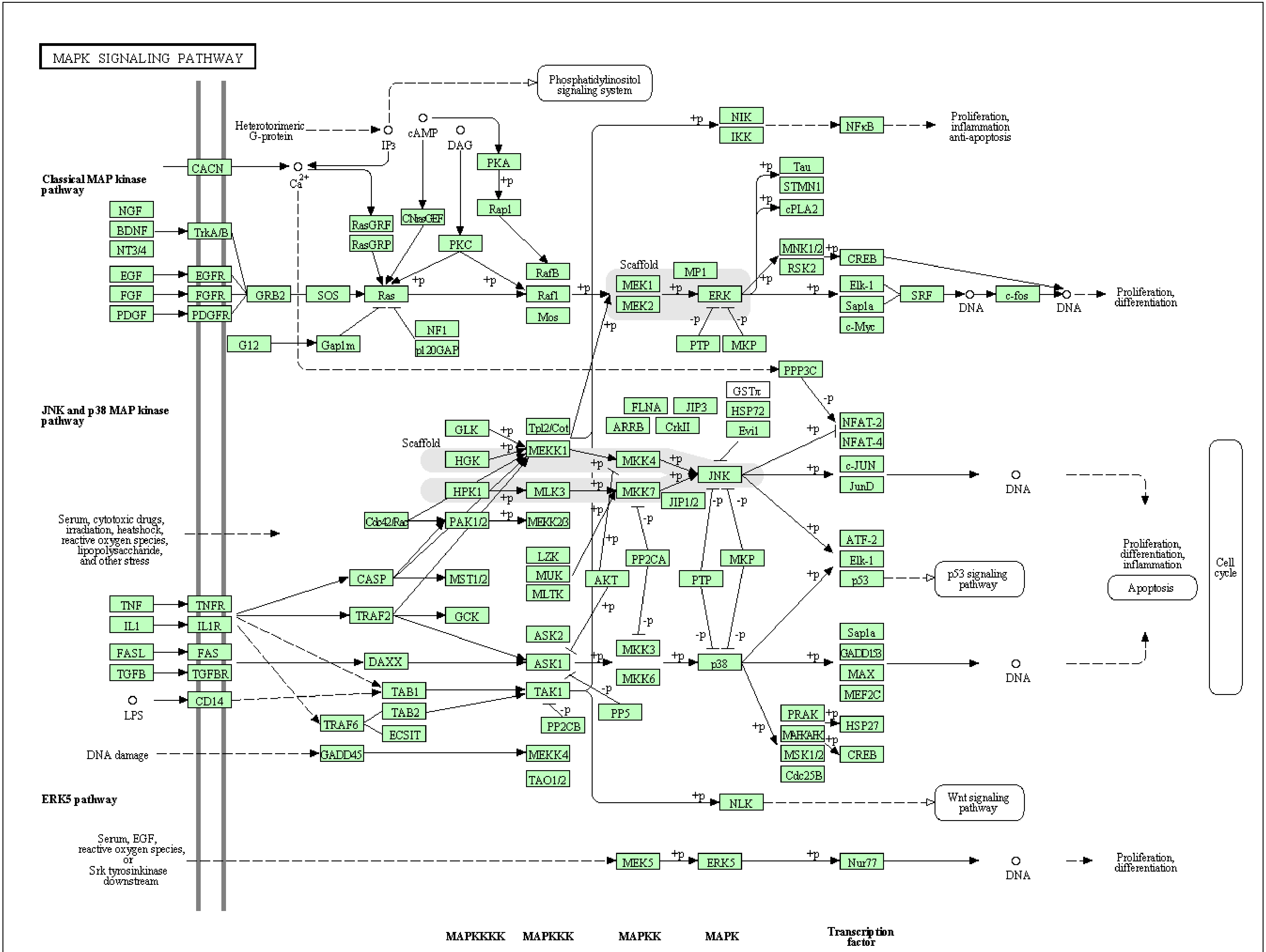
Pathway Mapping

KEGG PATHWAY mapping is the process to map molecular datasets, especially large-scale datasets in


P53 SIGNALING PATHWAY
Stress signals
γ-irradiation
UV
Genotoxic drugs
Nutrition deprivation
Heat/cold shock
DNA damage
Hypoxia
Nitric oxide
Oncogene activation (Such as MYC, E2F1, Ras, BCR-ABL)
ATM
ATR
CHK2
CHK1
+p
+p
+p
+p
+p
p14ARF
MDM2
p53
MDM-X
DNA
Cell cycle
Target genes
p21
14-3-3-σ
Reprimo
Gadd45
B99
Fas
PIDD
DR5
CASP8
Bid
Bax
Noxa
PUMA
P53AIP
PIGs
ROS
Scotin
PERP
PAG608
Siah
IGF-BP3
IGF
PAI
BAI-1
KAI
GD-AiF
TSP1
Maspin
P48
p53R2
Gadd45
Sestrins
PTEN
TSC2
IGF-BP3
TSAP6
MDM2
Cop-1
PIRH-2
Cyclin G
Siah-1
Wip1
ΔNp73
?
Cyclin D
CDK4/6
Cyclin E
CDK2
Cyclin B
Cdc2
G1 arrest (sustained)
G2 arrest (sustained)
tBid
CytC
Apaf-1
Mitochondrion
CASP9
CASP3
Response
Cell cycle arrest
Cell cycle
Apoptosis
Apoptosis
Inhibition of angiogenesis and metastasis
DNA repair and damage prevention
Inhibition of IGF-1/mTOR pathway
Exosome mediated secretion
p53 negative feedback
Cellular senescence
04115 3/7/13
(c) Kanehisa Laboratories

Hypoxia-inducible factor 1 (HIF-1) is a transcription factor that functions as a master regulator of oxygen homeostasis





04010 7/24/13
(c) Kanehisa Laboratories

The results show

1) Induction of secretory phenotype (production of inflammatory cytokines)

2) Activation of P53 pathway (genomic instability)

3) Involvment of cellular comunication and sugnal transduction(MAPK)

4) A clear discrimination between Protons and Gamma, as well as between time and doses

Senescence and IR Biological effects share a number of features including bystander effect and Secretory Phenotype

This is the basis of the systemic character of aging and Ionizing Radiation biological effects

A powerful method to study these complex phenotypes is the Systems Biology approach

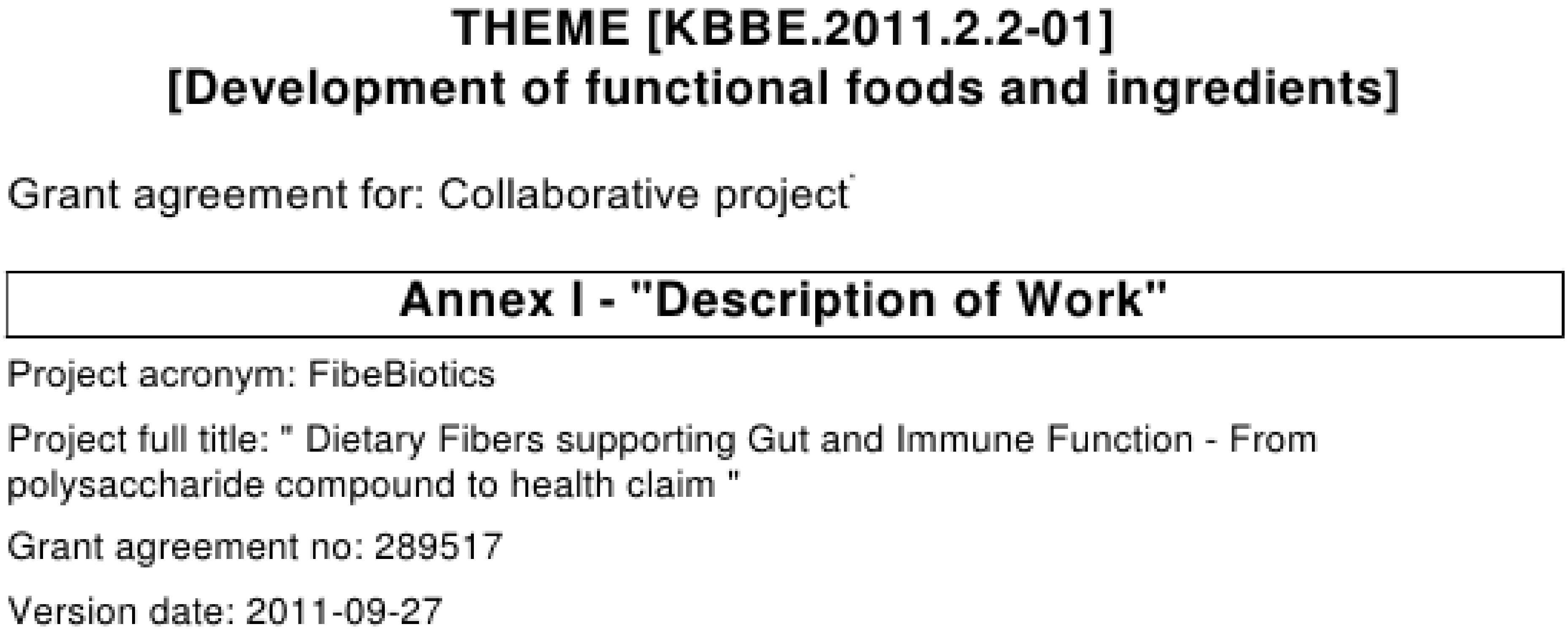
Systems Biology is just the scientific method in Biology with the help of computation and molecular biology (mainly high throughput technology)

Ionizing radiations (gamma and protons) are capable to induce RASP

Past EU projects

TCIA (T Cell In vitro aging) closed
GEHA Genetics of Healthy Aging closed
MARKAGE Markers of Aging (near to be closed)
NUAGE Nutrition and aging (in progress)

FibeBiotics



THEME [KBBE.2011.2.2-01]
[Development of functional foods and ingredients]

Grant agreement for: Collaborative project

Annex I - "Description of Work"

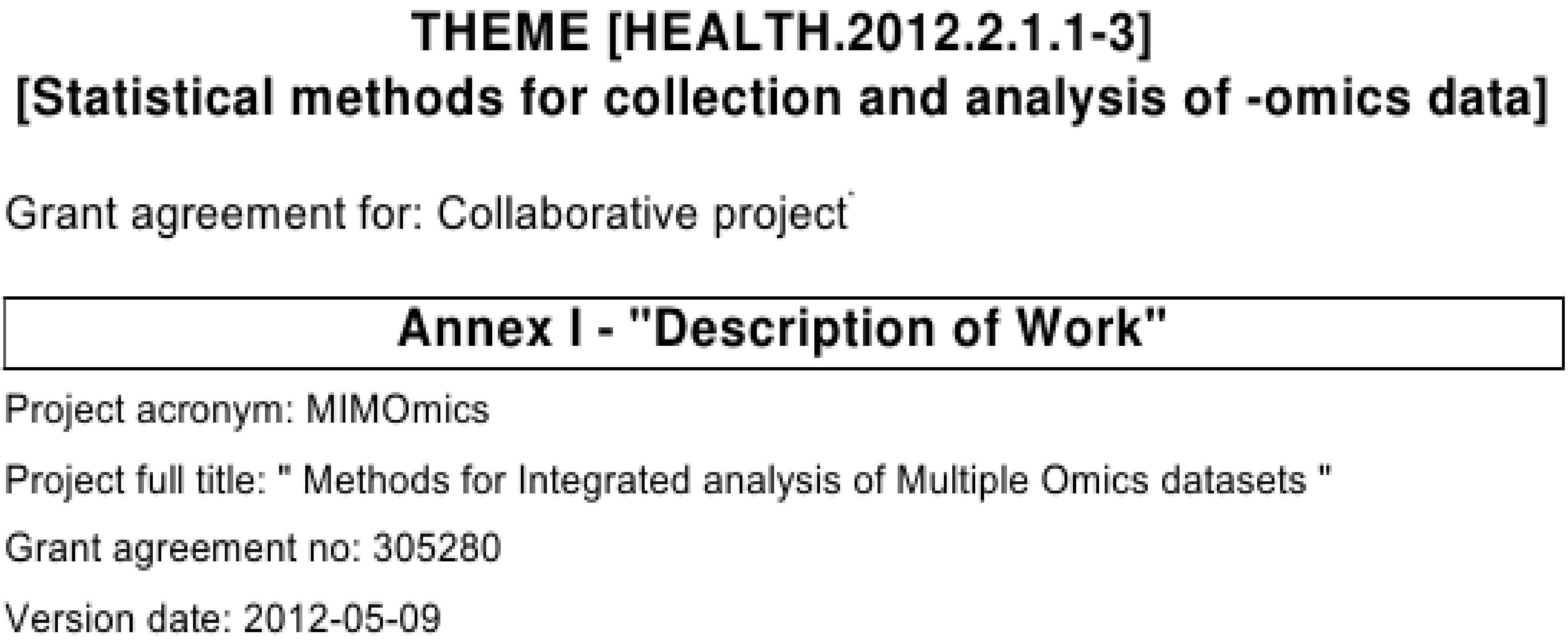
Project acronym: FibeBiotics

Project full title: " Dietary Fibers supporting Gut and Immune Function - From polysaccharide compound to health claim "

Grant agreement no: 289517

Version date: 2011-09-27

MIMOmics



THEME [HEALTH.2012.2.1.1-3]
[Statistical methods for collection and analysis of -omics data]

Grant agreement for: Collaborative project

Annex I - "Description of Work"

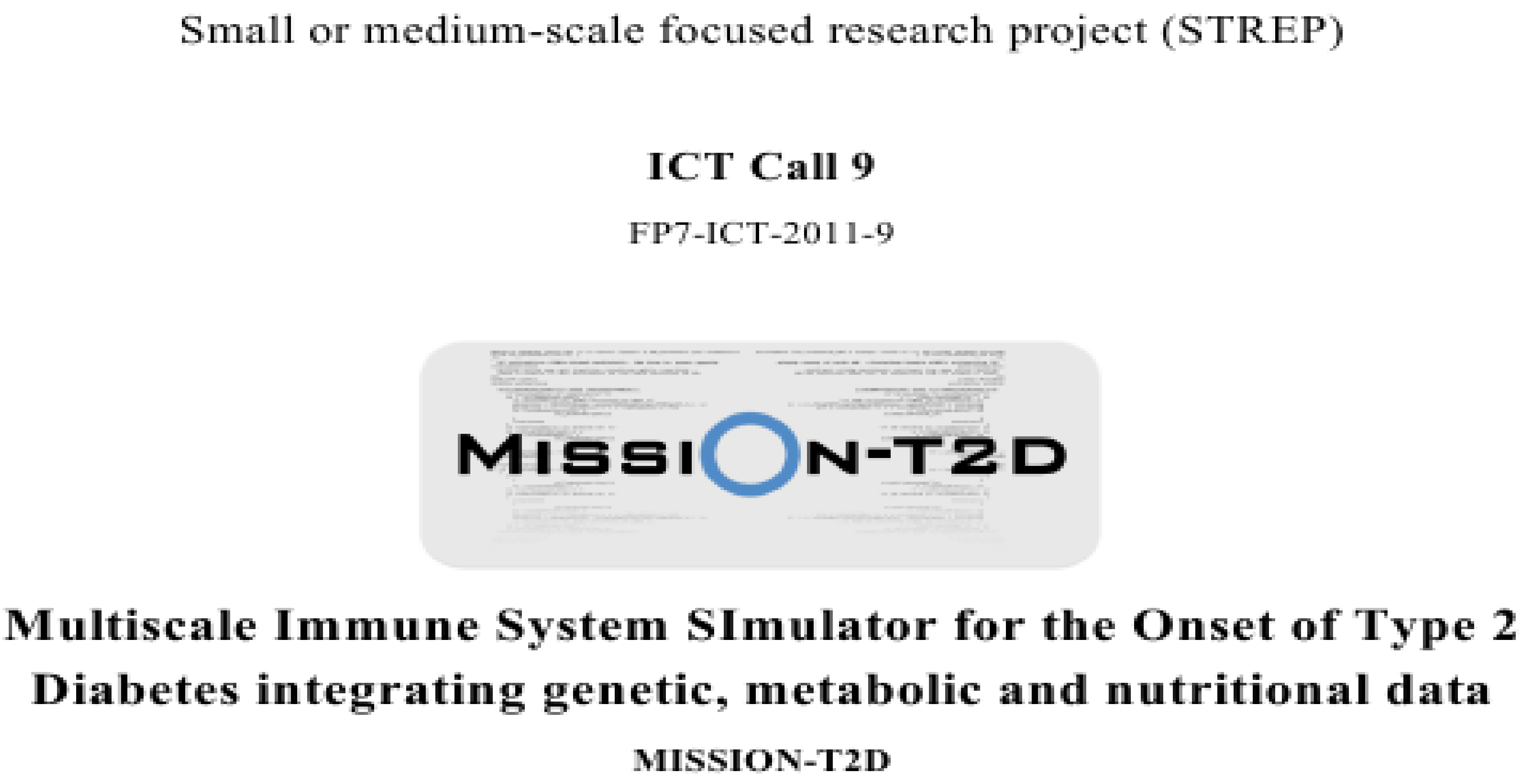
Project acronym: MIMOmics

Project full title: " Methods for Integrated analysis of Multiple Omics datasets "

Grant agreement no: 305280

Version date: 2012-05-09

Mission2D



Small or medium-scale focused research project (STREP)

ICT Call 9

FP7-ICT-2011-9

MISSION-T2D

Multiscale Immune System SImulator for the Onset of Type 2 Diabetes integrating genetic, metabolic and nutritional data

MISSION-T2D

Vianello D, Sevini F, Castellani G, Lomartire L, Capri M, Franceschi C. HAPLOFIND: A New Method for High-Throughput mtDNA Haplogroup Assignment. Hum Mutat. 2013 Sep;34(9):1189-94.

Garagnani P, Bacalini MG, Pirazzini C, Gori D, Giuliani C, Mari D, Di Blasio AM, Gentilini D, Vitale G, Collino S, Rezzi S, Castellani G, Capri M, Salvioli S, Franceschi C. Methylation of ELOVL2 gene as a new epigenetic marker of age. Aging Cell. 2012 Dec;11(6):1132-4.

Agarwal A, Adams R, Castellani GC, Shouval HZ. On the precision of quasi steady state assumptions in stochastic dynamics. J Chem Phys. 2012 Jul 28;137(4):

Bazzani A, Castellani GC, Giampieri E, Remondini D, Cooper LN. Bistability in the chemical master equation for dual phosphorylation cycles. J Chem Phys. 2012 Jun 21;136(23):235102.

Varani S, Rossini G, Mastroianni A, Tammik C, Frascaroli G, Landini MP, Castellani G, Söderberg-Nauclér C. High TNF-alpha and IL-8 levels predict low blood dendritic cell counts in primary cytomegalovirus infection. J Clin Virol. 2012 Apr;53(4):360-3.

Spazzafumo L, Olivieri F, Abbatecola AM, Castellani G, Monti D, Lisa R, Galeazzi R, Sirolla C, Testa R, Ostan R, Scurti M, Caruso C, Vasto S, Vescovini R, Ogliari G, Mari D, Lattanzio F, Franceschi C. Remodelling of biological parameters during human ageing: evidence for complex regulation in longevity and in type 2 diabetes. Age (Dordr). 2013 Apr;35(2):419-29.

Giampieri E, Remondini D, de Oliveira L, Castellani G, Lió P. Stochastic analysis of a miRNA-protein toggle switch. Mol Biosyst. 2011 Oct;7(10):2796-803. doi: 10.1039/c1mb05086a. Epub 2011 Jun 30.

Yap CS, Peterson AL, Castellani G, Sedivy JM, Neretti N. Kinetic profiling of the c-Myc transcriptome and bioinformatic analysis of repressed gene promoters. Cell Cycle. 2011 Jul 1;10(13):2184-96.

Bazzani A, Castellani GC, Cooper LN. Eigenvalue distributions for a class of covariance matrices with application to Bienenstock-Cooper-Munro neurons under noisy conditions. Phys Rev E Stat Nonlin Soft Matter Phys. 2010 May;81

Zironi I, Gaibani P, Remondini D, Salvioli S, Altilia S, Pierini M, Aicardi G, Verondini E, Milanesi L, Bersani F, Gravina S, Roninson IB, Franceschi C, Castellani G. Molecular remodeling of potassium channels in fibroblasts from centenarians: a marker of longevity? Mech Ageing Dev. 2010 Nov-Dec;131(11-12):674-81.

Remondini D, Salvioli S, Francesconi M, Pierini M, Mazzatti DJ, Powell JR, Zironi I, Bersani F, Castellani G, Franceschi C. Complex patterns of gene expression in human T cells during in vivo aging. Mol Biosyst. 2010 Oct;6(10):1983-92.

Milanesi L, Romano P, Castellani G, Remondini D, Liò P. Trends in modeling Biomedical Complex Systems. BMC Bioinformatics. 2009 Oct 15;10

Castellani GC, Bazzani A, Cooper LN. Toward a microscopic model of bidirectional synaptic plasticity. Proc Natl Acad Sci U S A. 2009 Aug 18;106(33):14091-5.

Lagomarsino MC, Bassetti B, Castellani G, Remondini D. Functional models for large-scale gene regulation networks: realism and fiction. Mol Biosyst. 2009 Apr;5(4):335-44.