European Cooperation in Science and Technology

COST 844: “Apoptosis and programmed cell death: molecular mechanisms and applications in biotechnology”

2000-2005

Laszlo Fesus (Hungary) - Coordinator

Boris Zhivotovsky

Swedish National Coordinator

FP5

Interplay among mitochondria and p53 family proteins during apoptosis induced by DNA damage – A new strategy for cancer therapy (Acronym: IMPALED – to kill with a sharp object)

2003-2005

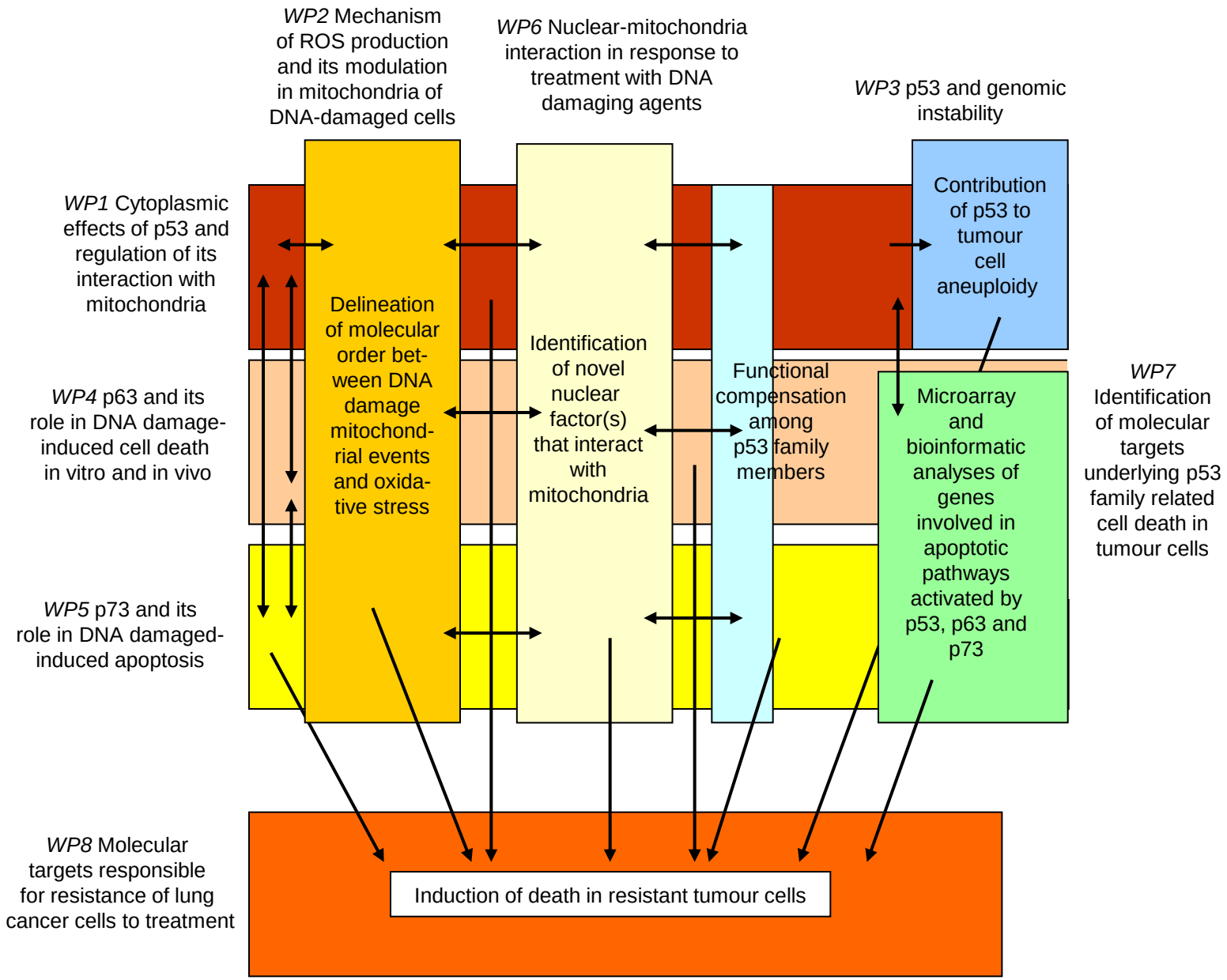
COORDINATOR: Boris Zhivotovsky

1.1 M Euro

This project aims to elucidate the mechanisms accounting for tumour cell resistance to death and to identify and verify the molecular targets responsible for resistance of tumour cells to DNA damaging drugs

“Academic partners”-1-4,
Karolinska Institutet, Sweden (Prof. Boris Zhivotovsky),
Institute Gustave Roussy, France (Prof. Guido Kroemer),
Weizmann Institute of Science, Israel (Prof. Moshe Oren),
University of Rome Tor Vergata (Prof. Gerry Melino);
“Clinical partner” – 5,
Karolinska Hospital, Sweden (Prof. Rolf Lewensohn) and
“Biotechnology company”-6, I
EIRX Therapeutics Ltd, Ireland (Prof. Tom Cotter)

Overall project layout



FP5

Apoptosis pathways in cancer and AIDS

2004-2006
1.6 M Euro

Sweden
France
Italy
Germany
Denmark

7 March 2007
Brussels

Descartes research prize 2006

Excellence in
scientific collaborative research

Laureate

We, the 2006 Descartes Prize Grand Jury, hereby certify that the research project entitled

Apoptosis pathways in cancer and AIDS

Janez Potočnik
Commissioner for Science and Research

Claudie Haigneré
President of the Grand Jury 2006

CAPACITIES

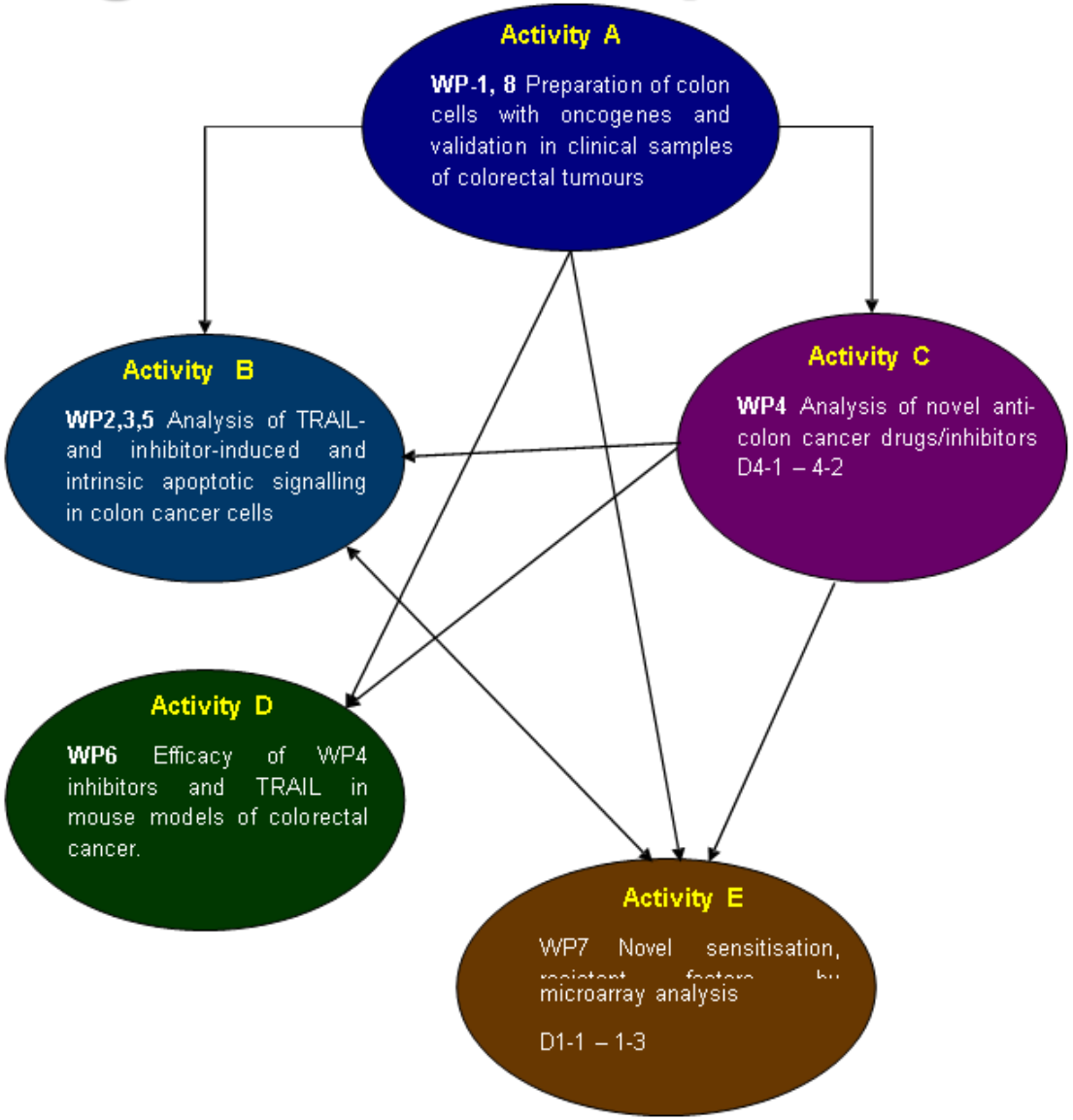
FP6

Sensitization of (colon) cancer cells to death receptor related therapies

Acronym: ONCODEATH
(2006-2009)
2.1 M Euro

Coordinator: Dr Alex Pintzas (Greece)
Prof Boris Zhivotovsky (Sweden) - Responsible for basic research
Partners: Dr Ladislav Andera (Czech Republic) – production of Ab
Prof Jean-Claude Martinou (Geneva Switzerland) – Mitochondrial function
Dr Spiros Linardopoulos (London U.K) - Cell cycle regulation
Dr Sylvie Robine (Paris France) – Animal model
Prof Paul Workman (Cancer Therapeutic Center, UK) - Clinical partner:
Prof Juan Carlos Lacal (Madrid Spain) – Industrial partner
Dr George Nasioulas (Athens Greece) - Diagnostic and Therapeutic Center

Graphical presentation of the components showing their interdependencies



Obtained results

1. Panel on new cell lines with up- and down-regulated colon cancer-related oncogenes.
2. Map of TRAIL-induced proximal signalling pathways per system.
3. Determinants of caspase-2 activation and Bax in TRAIL-induced apoptosis of tumour cells.
4. Assessment of a role of mitochondrial fission and fusion in TRAIL-mediated apoptosis.
5. Selection of PI3 kinase and Aurora inhibitors that cooperate with TRAIL in inducing apoptosis of colon cancer cells.
6. Assessment of sensitivity of tumours induced by activated oncogenes in transgenic mice and in mouse xenografts
7. List of apoptotic genes in response to individual oncogenic signalling in colon cells by microarray analysis
8. Validated sensitisation and resistant mechanisms in clinical samples

FP6

CHEMORES
TUMOUR CHEMOTHERAPY RESISTANCE

Molecular mechanisms underlying chemotherapy resistance, therapeutic escape, efficacy and toxicity (2008-2013)
7 M Euro

18 partners from 9 countries

*APO*ptosis *SYS*tems Biology Applied to Cancer and AIDS

www.apo-sys.eu

(2009-2012)

11 M Euro

Boris Zhivotovsky

Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden

Karolinska Institutet

SEVENTH FRAMEWORK PROGRAMME

APO-SYS Consortium

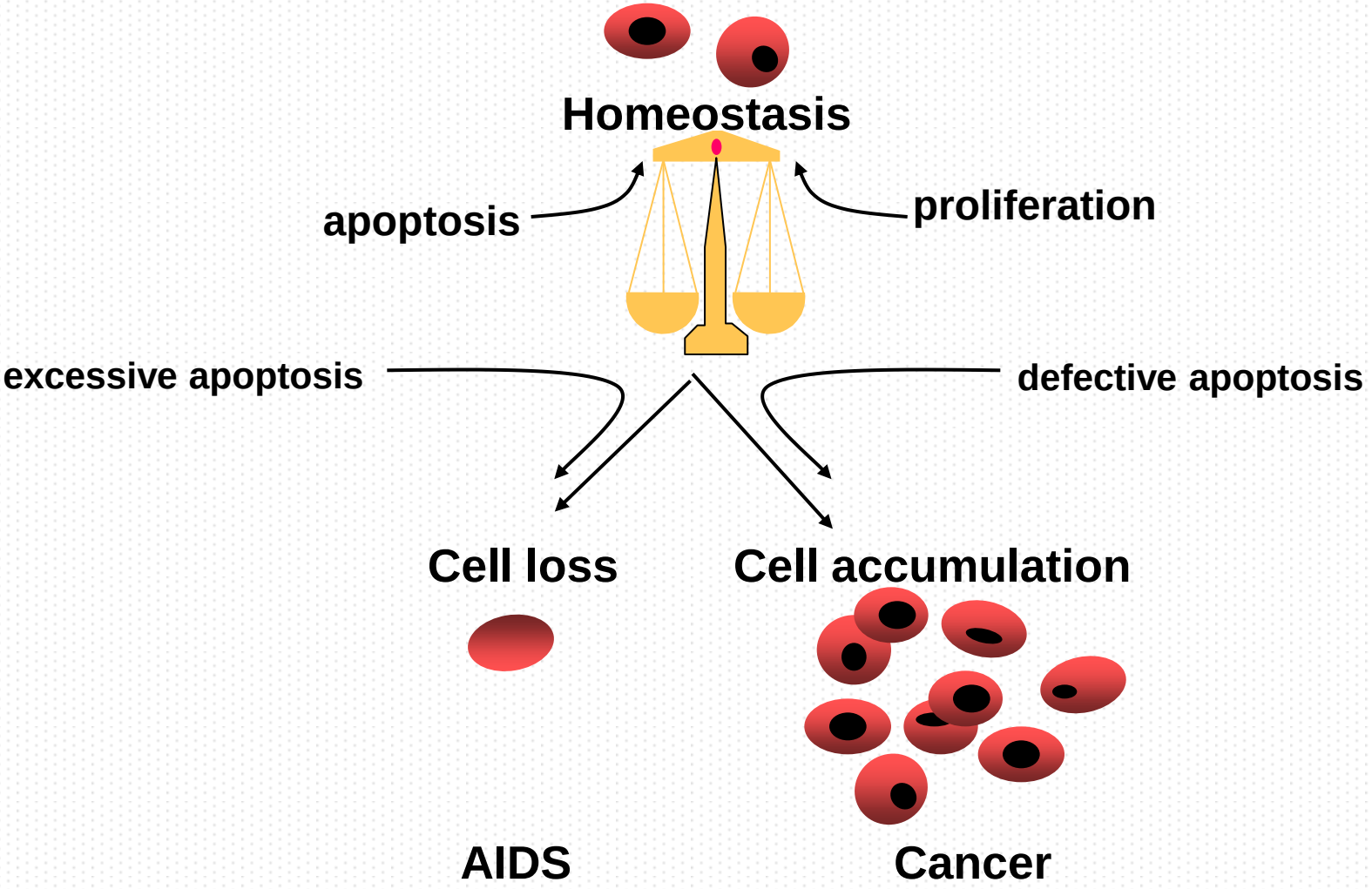
Partners: **23 laboratory groups from 12 different countries**

Basis: **Extension of a 2006 Descartes Prize-winning EC Project "Apoptosis" and EC project on systems biology of cancer "ESBIC-D" plus new groups**

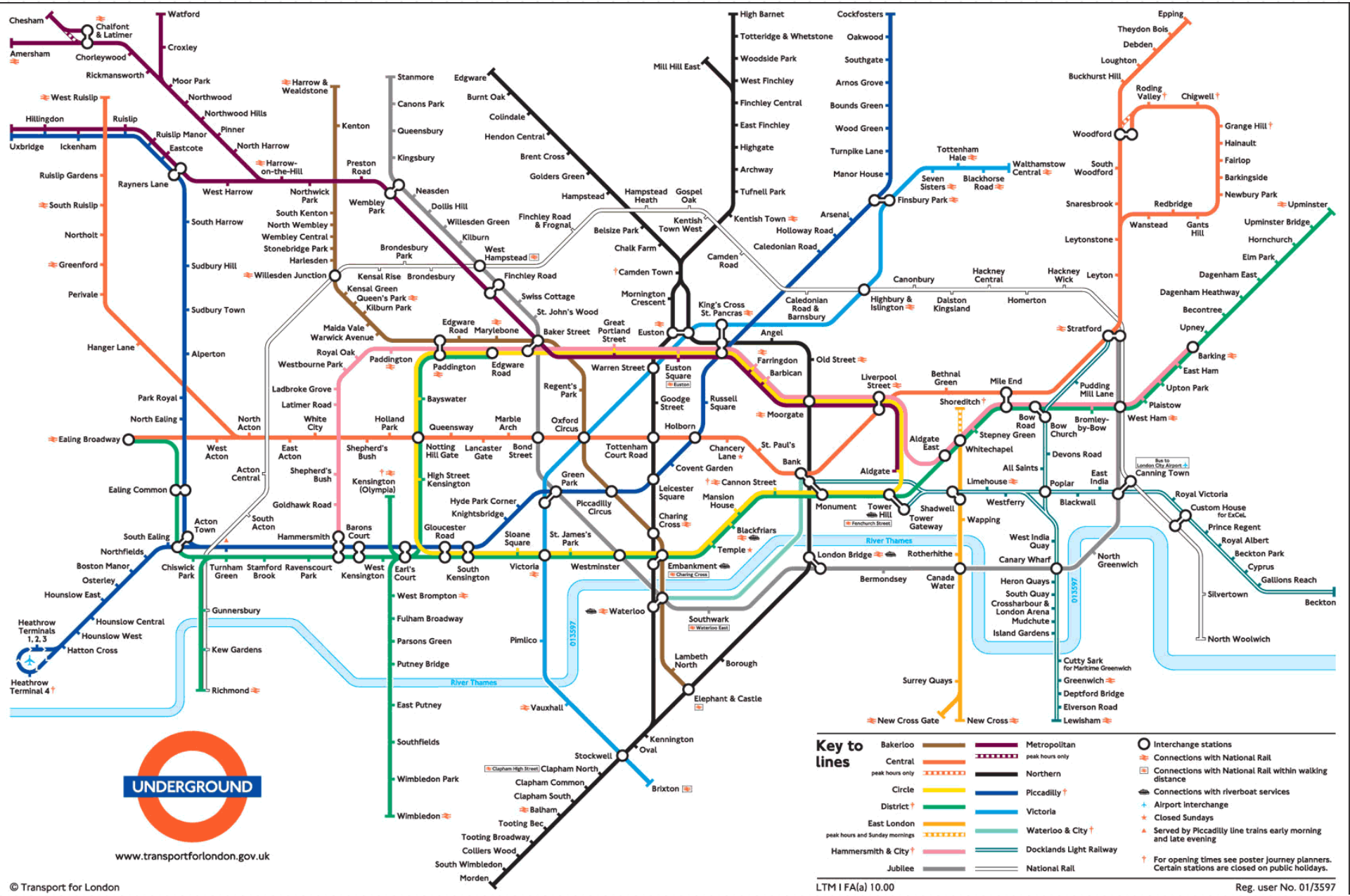
Involves: **experimental biologists, biomedicine/translational medicine bioinformaticians, biomathematicians, biostatisticians and clinical scientists**

Combines: ***in silico*** **systems biology,**
in vitro and in vivo **model organisms experimentation**
clinical input - tissue samples from patients with cancer and AIDS

Human disease can result from too much or too little apoptosis



London Tube's Map

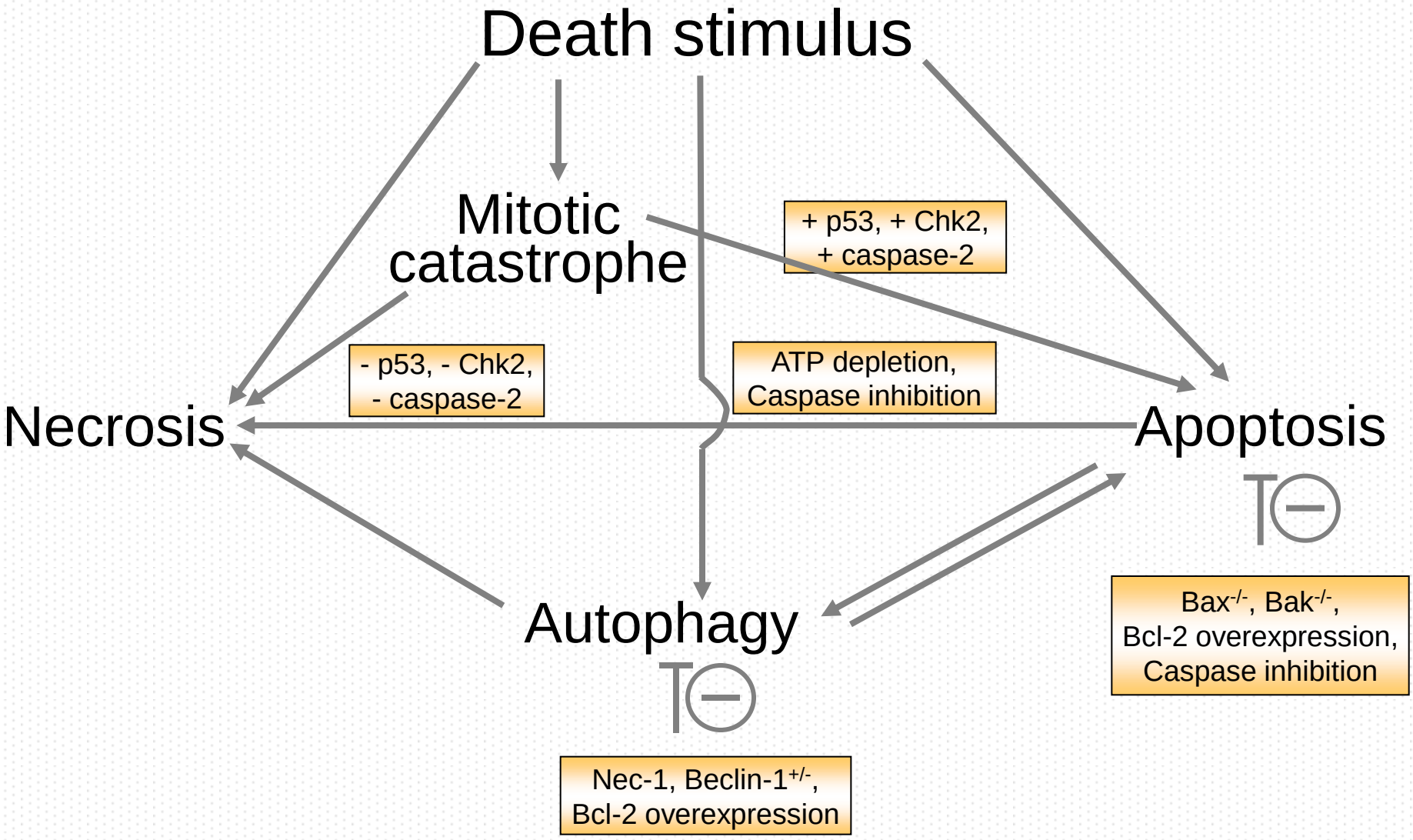


MOSCOW METRO & MONORAIL SCHEME

Modes of cell death

- Apoptosis
- Necrosis
- Anoikis
- Autophagic cell death
- Excitotoxicity
- Cornification
- Wallerian degeneration
- Mitotic catastrophe
- Paraptosis
- Pyroptosis
- Mitoptosis
- Senescence

Cross-talk between different modes of cell death



APO-SYS Consortium

The main Goal:

To understand the basic cell biology of apoptosis and to transform this knowledge into computer models of the relevant biological processes and to translate the resulting knowledge to two major pathological conditions, namely cancer and AIDS

APO-SYS Consortium

Objectives:

- **create a unique database integrating existing and accumulating knowledge** on lethal signal transduction pathways leading to apoptosis or non-apoptotic (necrotic, autophagic, mitotic) cell death;

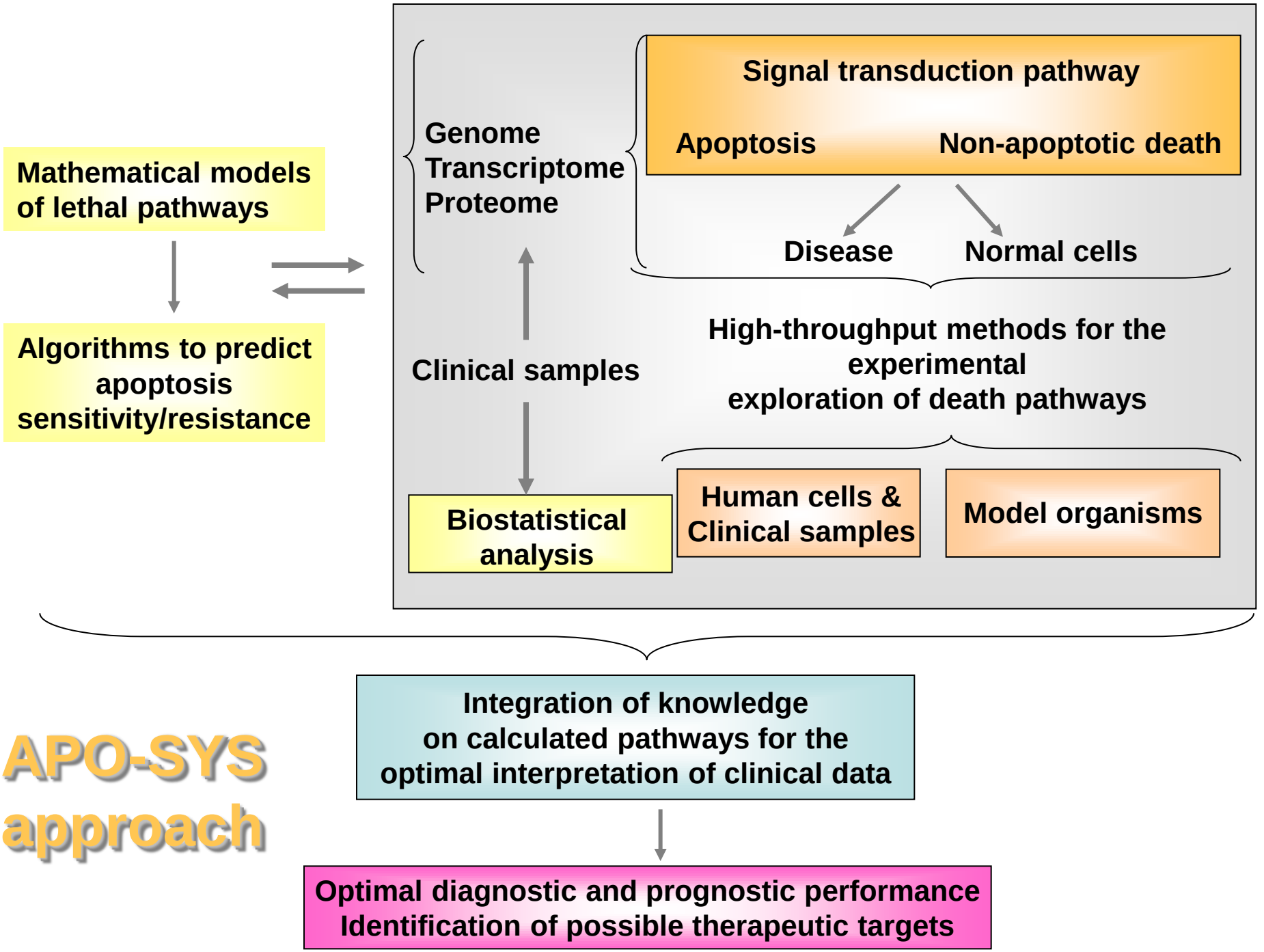
- **perform data mining to integrate system-wide analyses** on cell death (genome, epigenome, transcriptome, proteome, lipidome data);

- **use high-throughput methods** for the experimental exploration of death pathways in human cell lines *in vitro* and in relevant disease models (*in vitro* in human cells and *in vivo* in mice and Drosophila);

- **establish mathematical models** of lethal pathways to devise algorithms that predict apoptosis susceptibility and resistance;

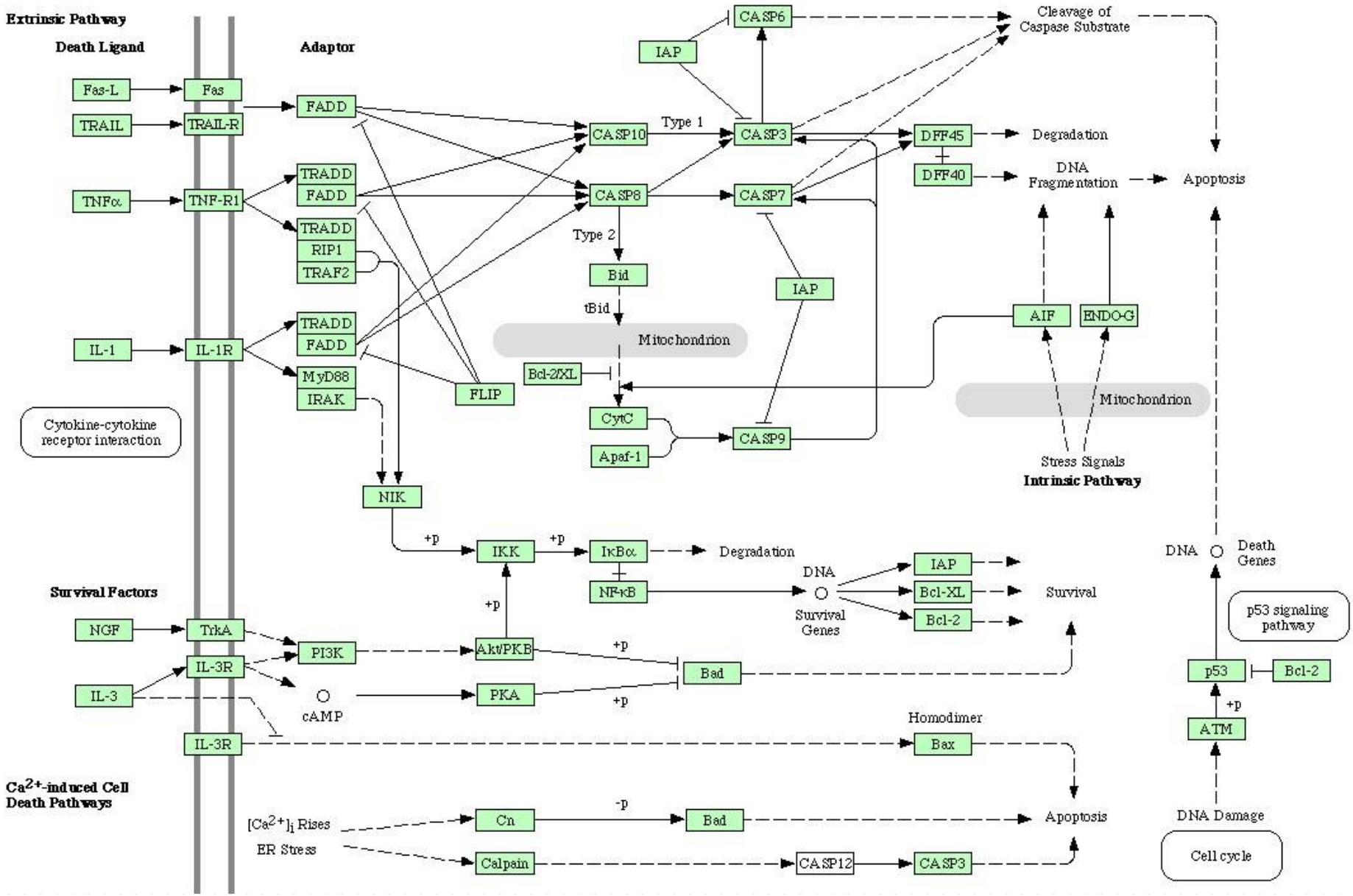
- **obtain data** (genome, transcriptome, proteome, lipidome) **on clinical samples** (cancer cell lines, cancer tissues, and serum and blood samples) and perform **biostatistical analyses** on them in order to demonstrate the contribution of apoptotic process in human cancers and AIDS;

- **integrate the knowledge into mathematical models** for the optimal interpretation of clinical data, aiming at optimal diagnostic and prognostic performance as well as at the identification of possible therapeutic targets for the treatment of cancer and AIDS.

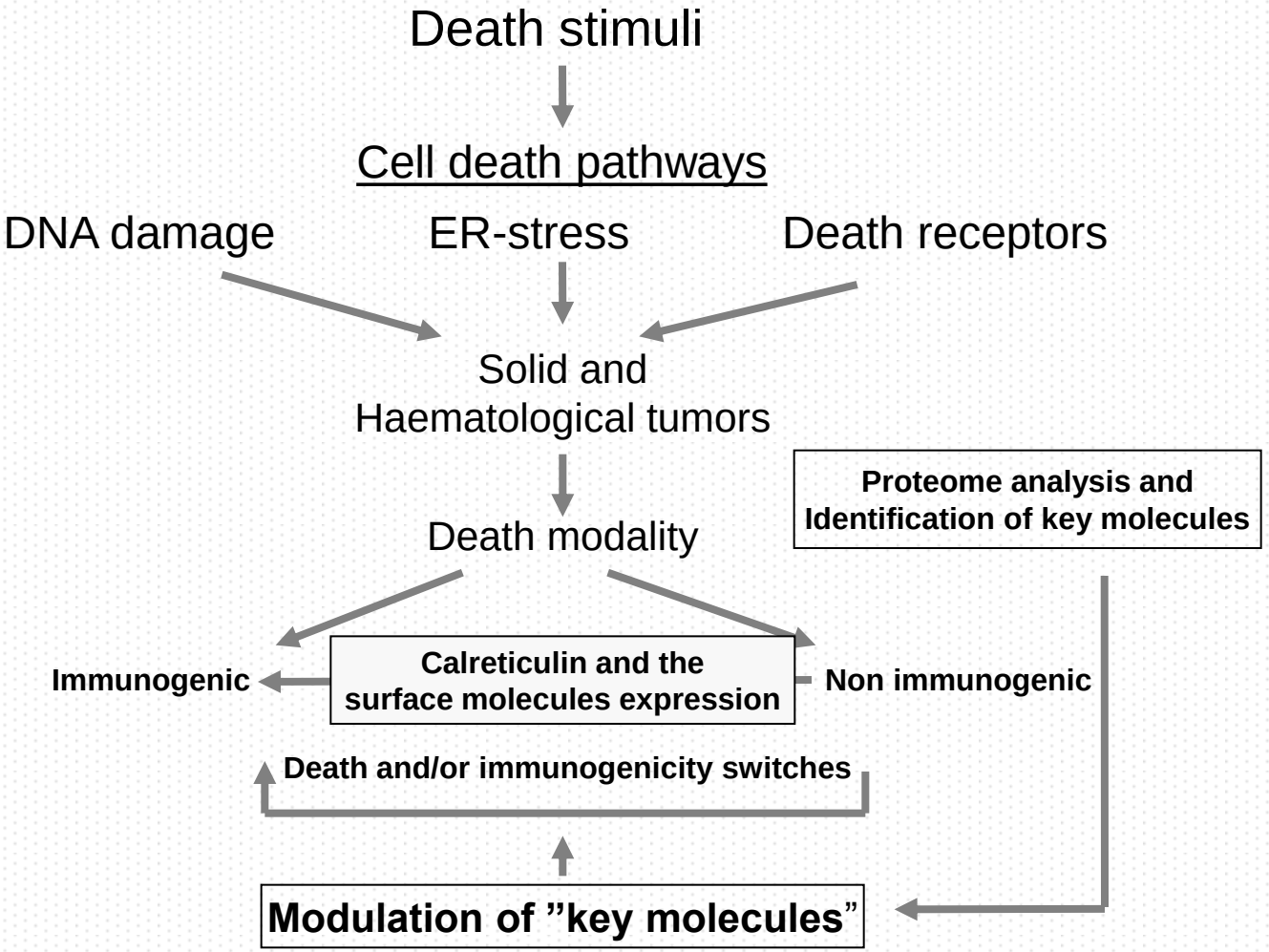


APO-SYS approach

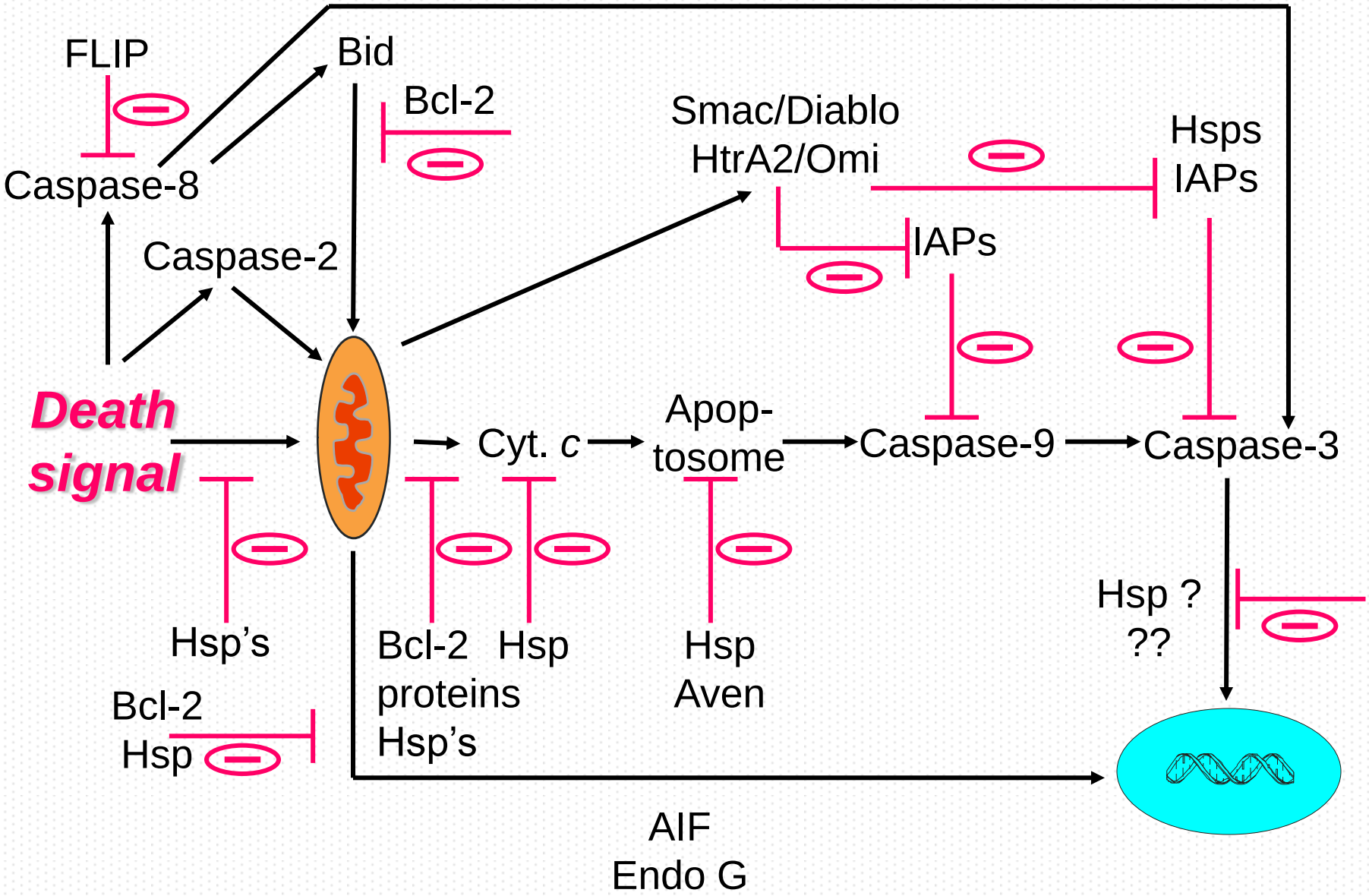
Apoptosis pathways



An experimental approach to target cancer therapy based on switches between cell deaths modalities

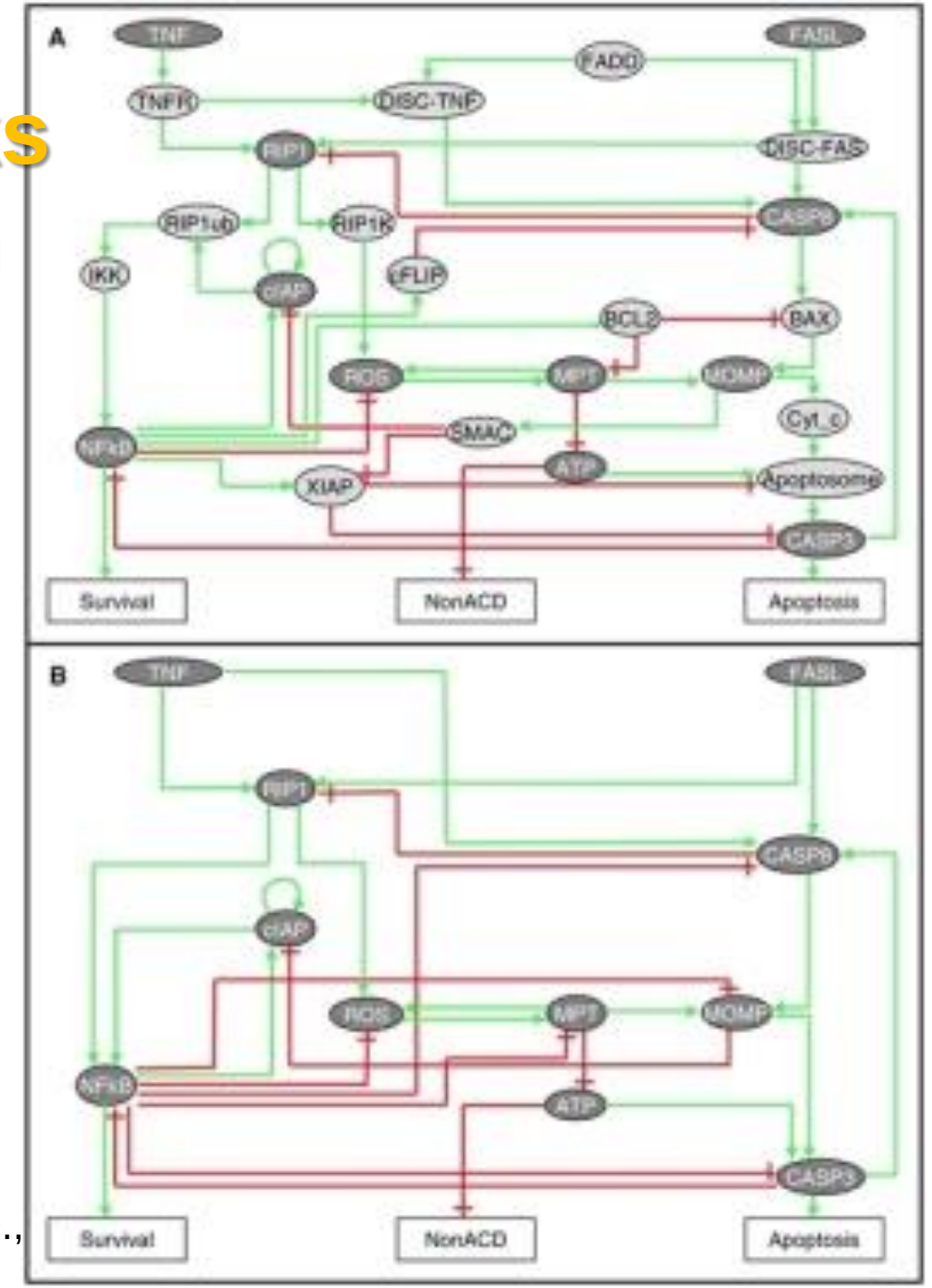


Therapeutic strategies based on modulation of apoptosis



Regulatory networks of cell-fate decision

Dynamical logical model of cell fate decision



Mathematical modelling of cell-fate decision in response to death receptor engagement. PLoS Comput. Biol. 2010; 6(3):e1000702.
Clazzone L., Tournier L., Fourquet S., Thieffry D., Zhivotovsky B., Barillot E., Zinovyev A.

Targeted Research Approaches

- One gene – one cancer paradigm
- Cancer is a systemic disease

Key milestones to judge how much we understand the system

- Understanding of structure of the system (gene regulatory and biochemical networks, as well as physical structure)
- Understanding of dynamics of the system (quantitative and qualitative analysis, as well as construction of theory/model with powerful prediction capability)
- Understanding of control methods of the system
- Understanding of design methods of the system

APO-SYS Consortium

More than 500 publications

The most successful project within FP7 in the field of Systems Biology