The SMEs' role in the area of systems biology approaches for medical applications

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geneXplain

We aim to provide a comprehensive platform

of bioinformatics, cheminformatics

and systems biological tools

for personalized medicine and pharmacogenomics

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COOPERATION

The team participated in projects funded by EU Health – FP6, FP7

- **EuroDia (FP6: 01.03.2006-28.02.2010) - Diabetes**
  - Functional genomics of pancreatic beta cells and of tissues involved in control of the endocrine pancreas for prevention and treatment of type 2 diabetes. (BIOBASE)
- **VALAPODYN (FP6: 01.10.2006-30.03.2010) – Epilepsy**
  - Validated Predictive Dynamic Model of Complex Intracellular Pathways Related to Cell Death and Survival. (BIOBASE)
- **Net2Drug (FP6: 01.02.2007-31.07.2010) - Cancer**
  - From gene regulatory networks to drug prediction. (BIOBASE, ISB)
- **SysCo (FP6: 01.09.2007-27.02.2011) - Infection**
  - Systematic Functional analysis of Intracellular Parasitism as a model of genomes conflict. (BIOBASE,ISB)

...

The team*) participated in projects funded by EU Health – FP6, FP7

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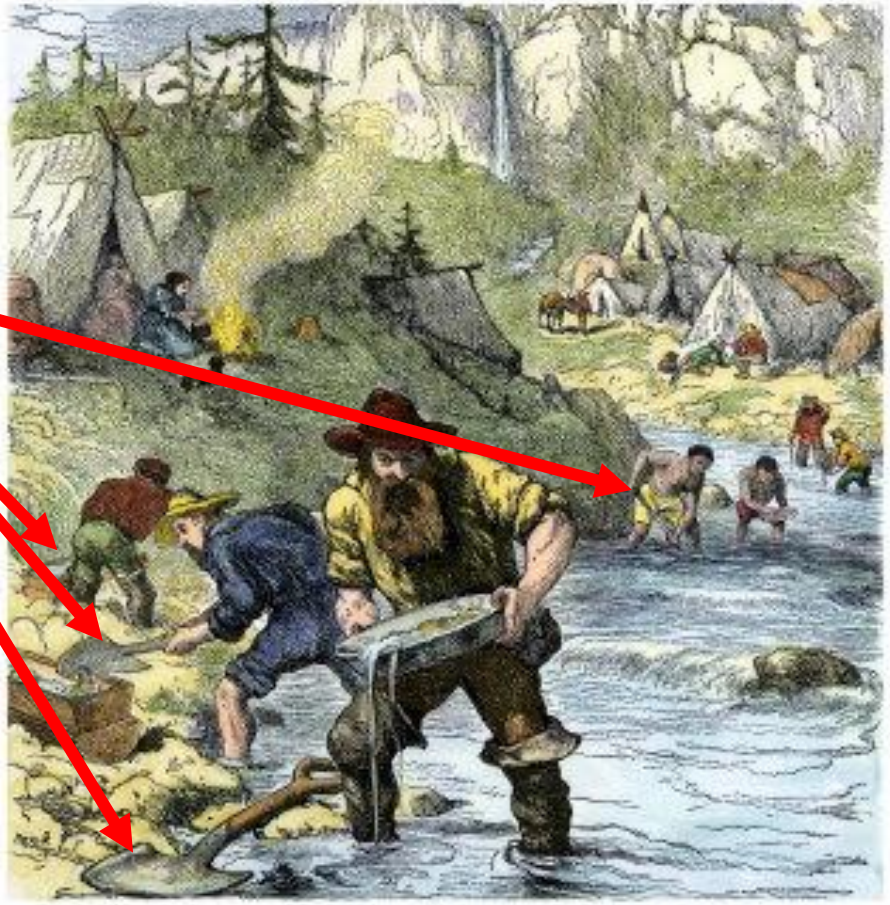
- **Gen2Phen (FP7: 01.01.2008-31.12.2012) - SNPs**
  - Genotype-To-Phenotype Databases: A Holistic Solution (BIOBASE)
- **LipidomicNet (FP7: 01.05.2008-30.04.2012) – Obesity**
  - Lipid droplets as dynamic organelles of fat deposition and release. Translational research towards human disease. (BIOBASE, ISB)
- **SysCol (FP7: 01.01.2011-31.12.2015) - Cancer**
  - Systems Biology of Colorectal Cancer (geneXplain)

*) The R&D team working in different time periods in SMEs: BIOBASE GmbH, ISB (Institute of Systems Biology, Russia) and geneXplain GmbH

Drug discovery – the Gold Rush

Tools



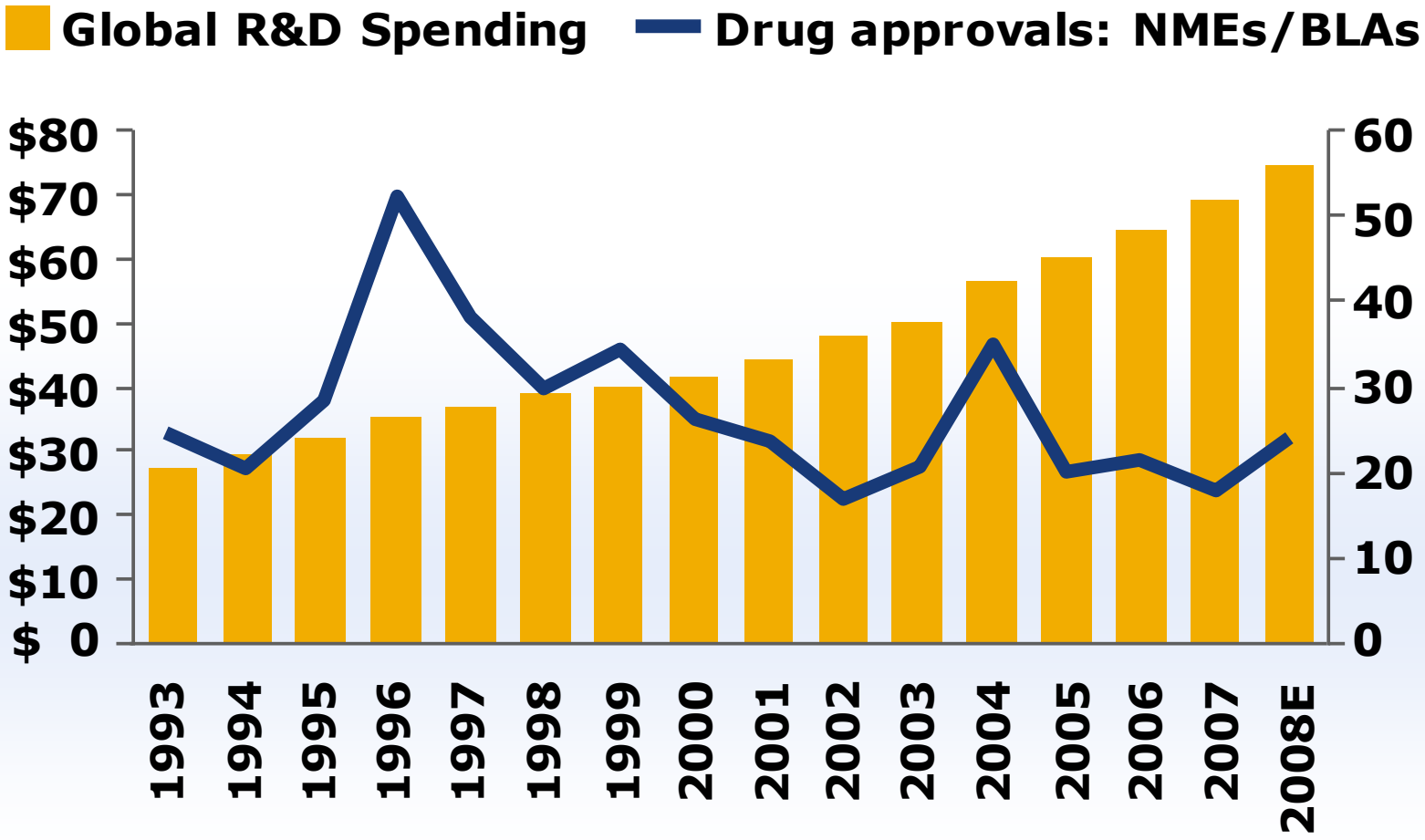
Drug discovery – should become a technology

Disease →  → **Therapy**

↑

Patient

R&D Pipeline


Global R&D Spending
Drug approvals: NMEs/BLAs
$80
$70
$60
$50
$40
$30
$20
$10
$ 0
60
50
40
30
20
10
0
1993
1994
1995
1996
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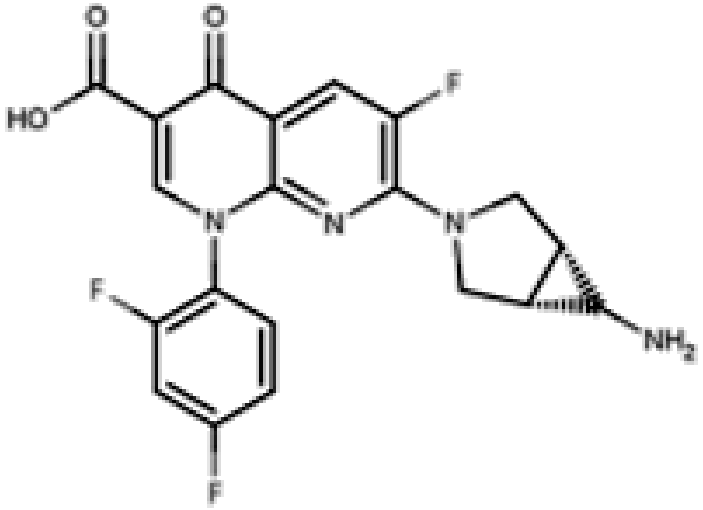
2007
2008E

Trovafloxacin - antibiotic



Withdrawn from market due to risk of idiosyncratic hepatotoxicity in 2001.

Systems medicine

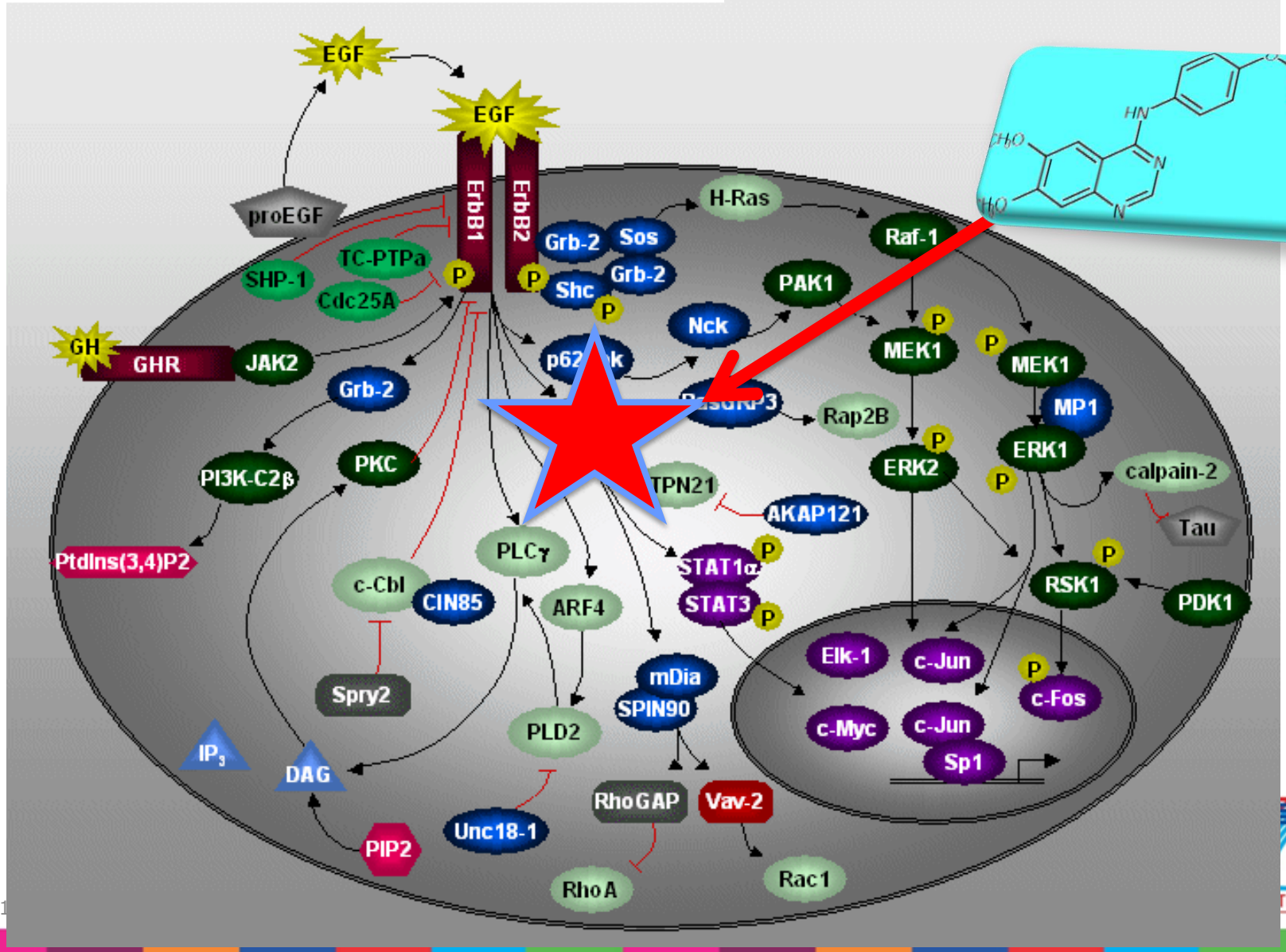
Systems approaches will transform the way drugs are developed … that will target multiple components of networks and pathways perturbed in diseases.

They will enable medicine to become predictive, personalized, preventive and participatory

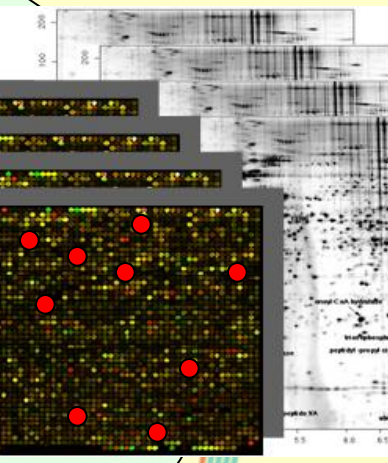
Systems medicine: the future of medical genomics and healthcare
Charles Auffray[1]*, **Zhu Chen**[2] and **Leroy Hood**[3]
Genome Med 2009, **1**:2

COOPERATION

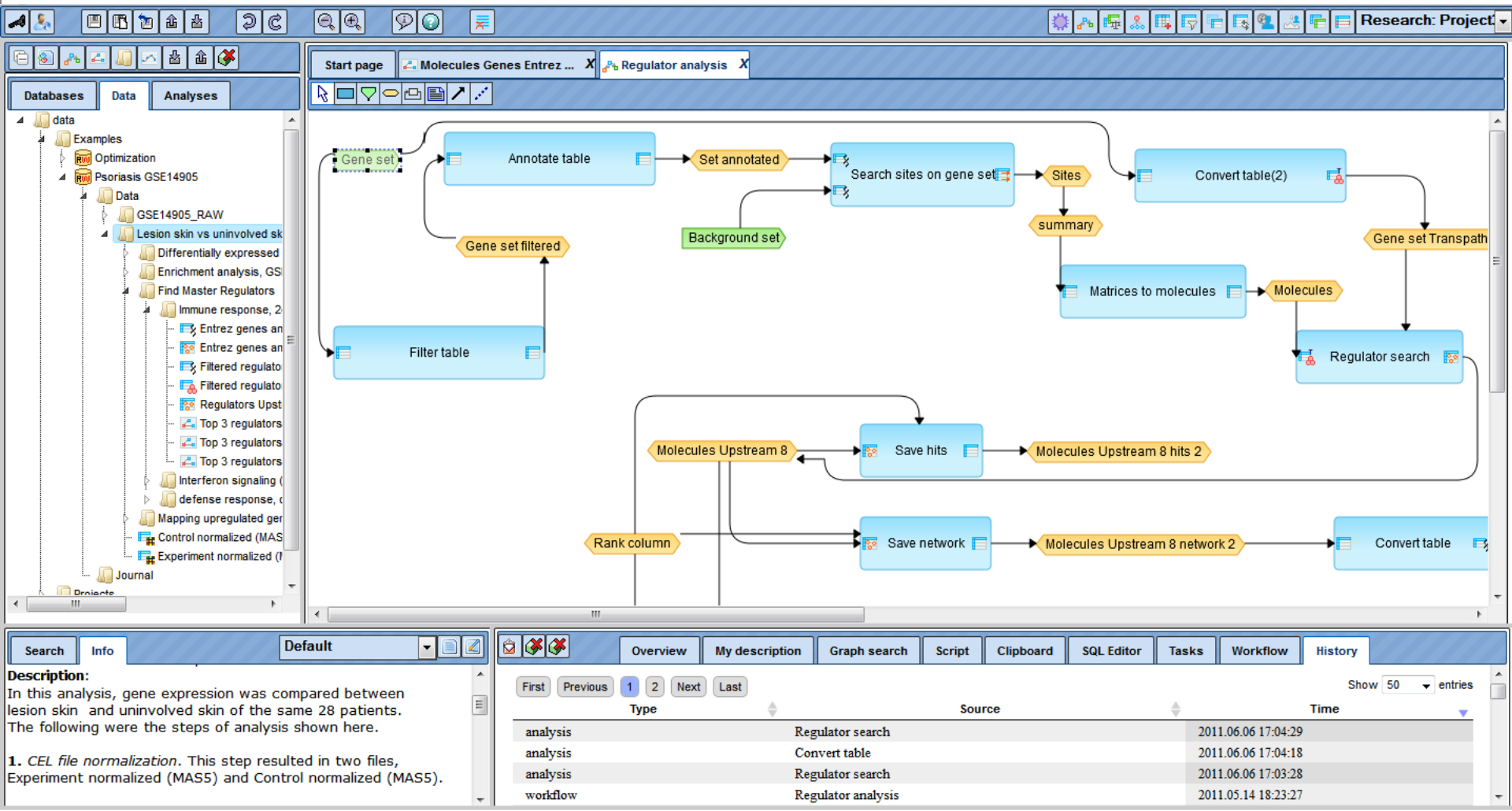
We should find a key pathway of a disease, select a good target and inhibit it.



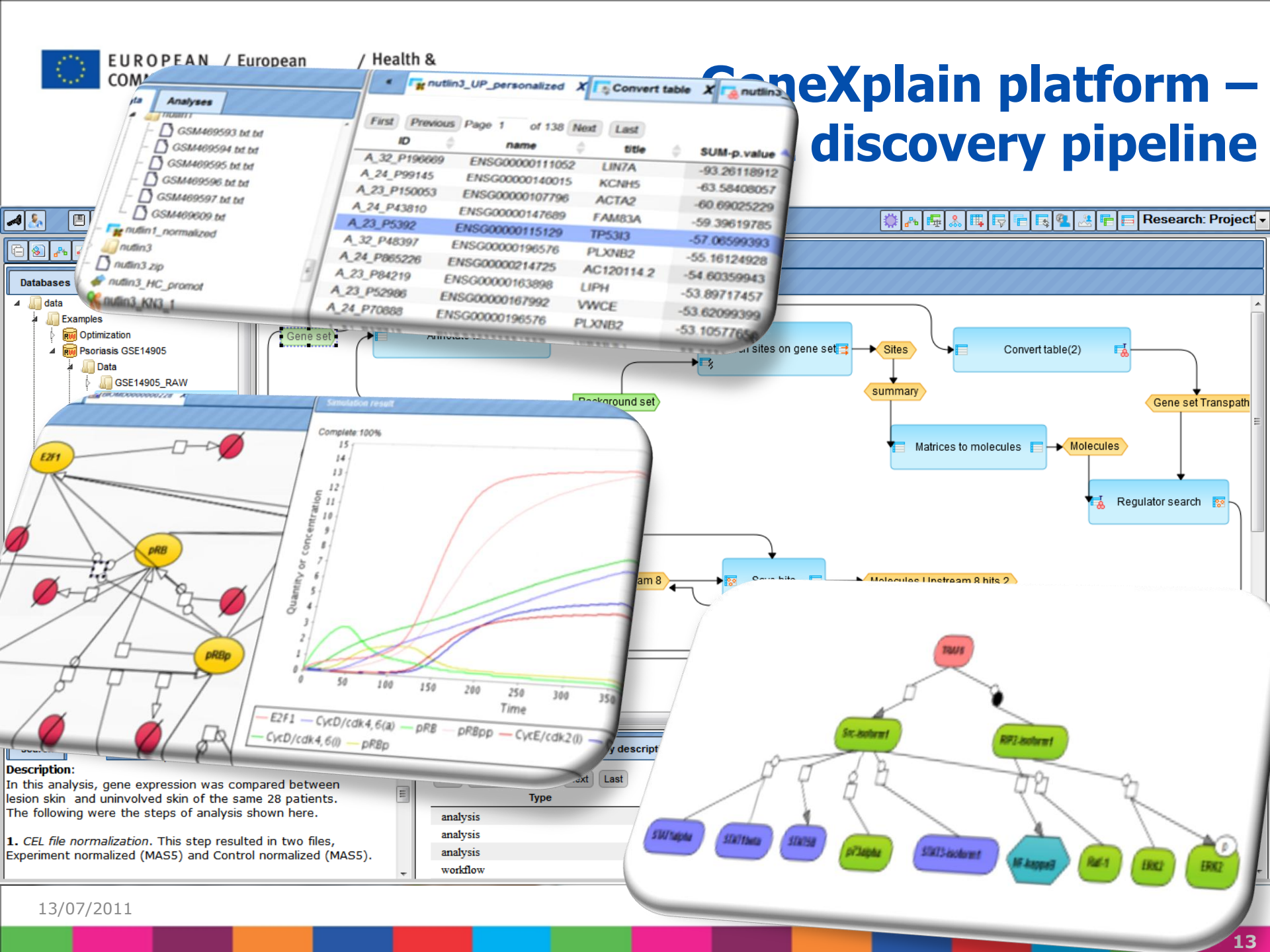
Master regulator



GeneXplain platform – drug target discovery pipeline

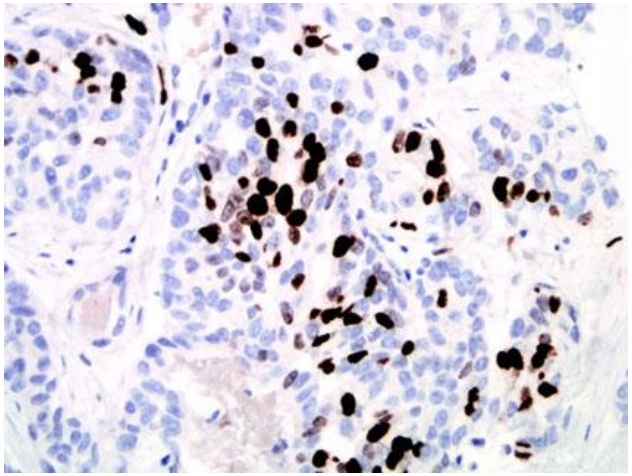


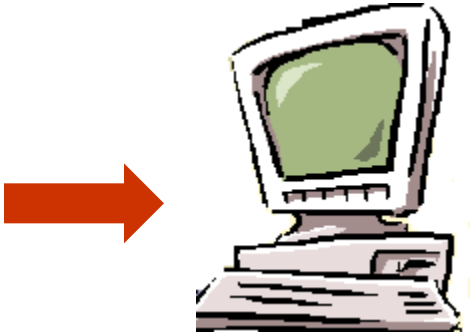
GeneXplain platform – discovery pipeline



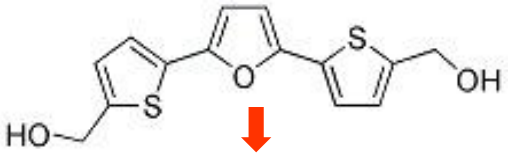
Cancer projects: Net2Drug, SysCol

Cancer





Apoptosis versus survival of cancer cells



1μM RITA

p53

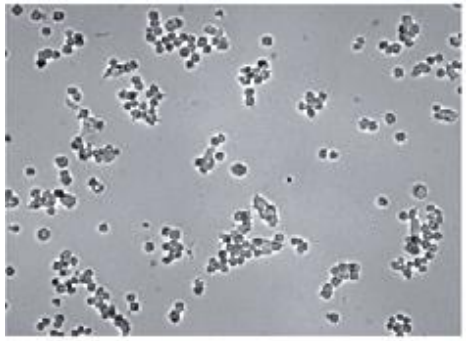
PRO-APOPTOTIC

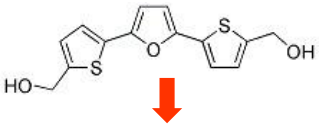
Noxa, PUMA, Bax, Fas

PRO-SURVIVAL

IGF-1R, p110α, p110β, eIF4E, c- Myc, survivin, Bcl-2, Mcl-1

APOPTOSIS





0.1μM RITA

?

p53

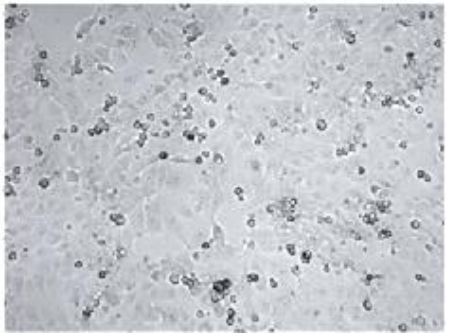
PRO-APOPTOTIC

Noxa, PUMA, Bax, Fas

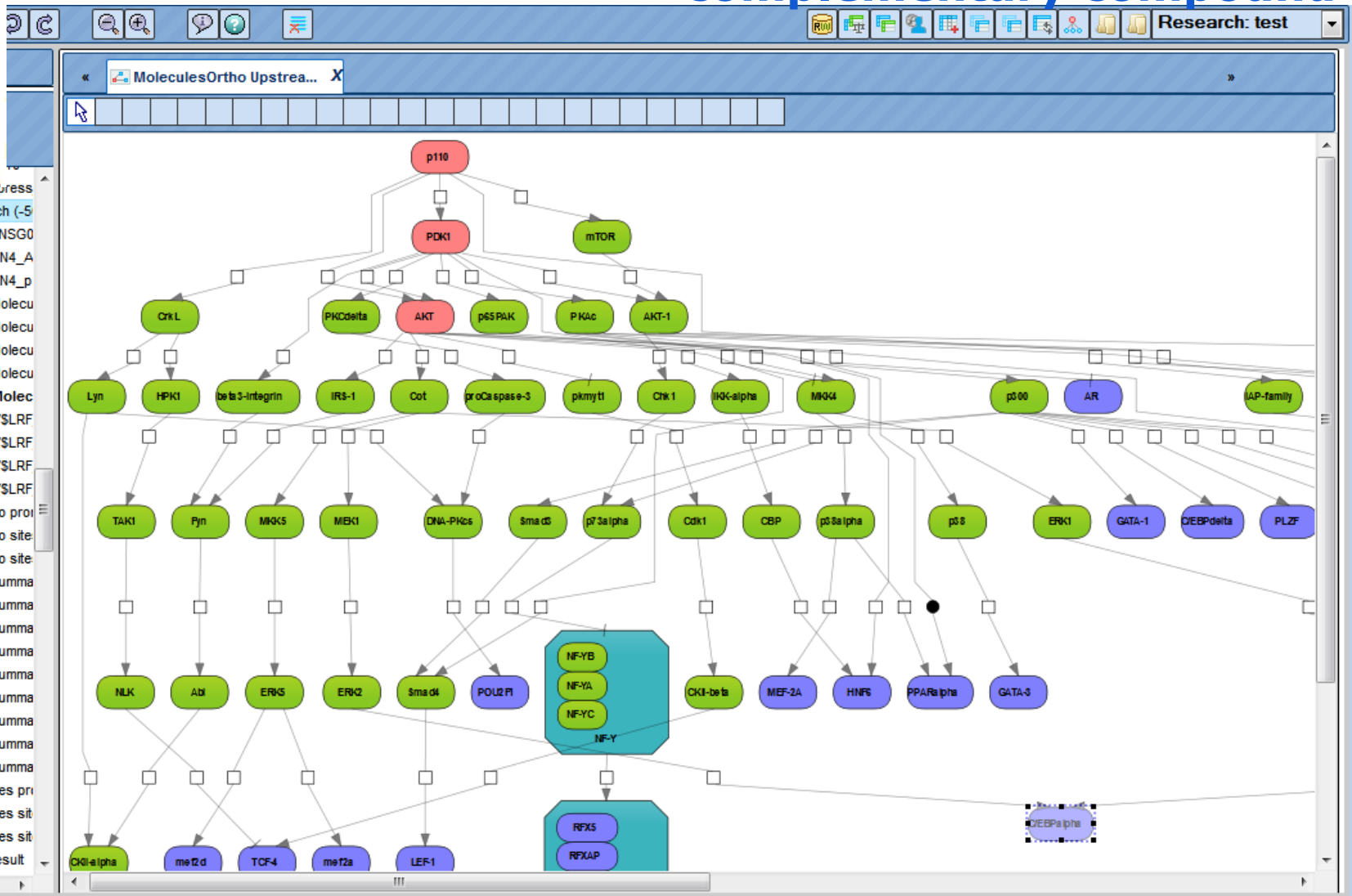
PRO-SURVIVAL

IGF-1R, p110α, p110β, eIF4E, c- Myc, survivin, Bcl-2, Mcl-1

APOPTOSIS



Survival mechanisms of cancer cells upon RITA treatment and potential target proteins for a complementary compound



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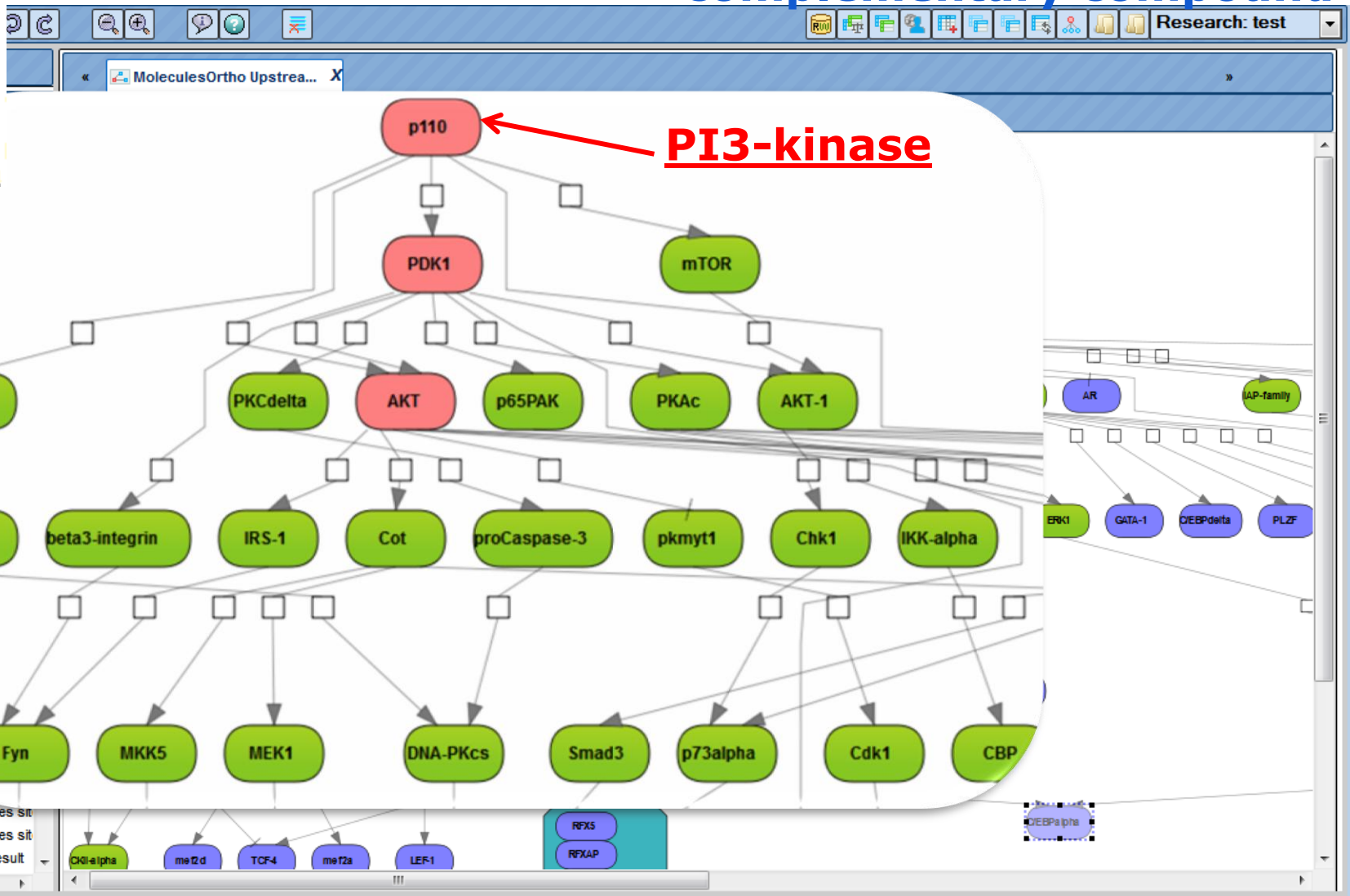
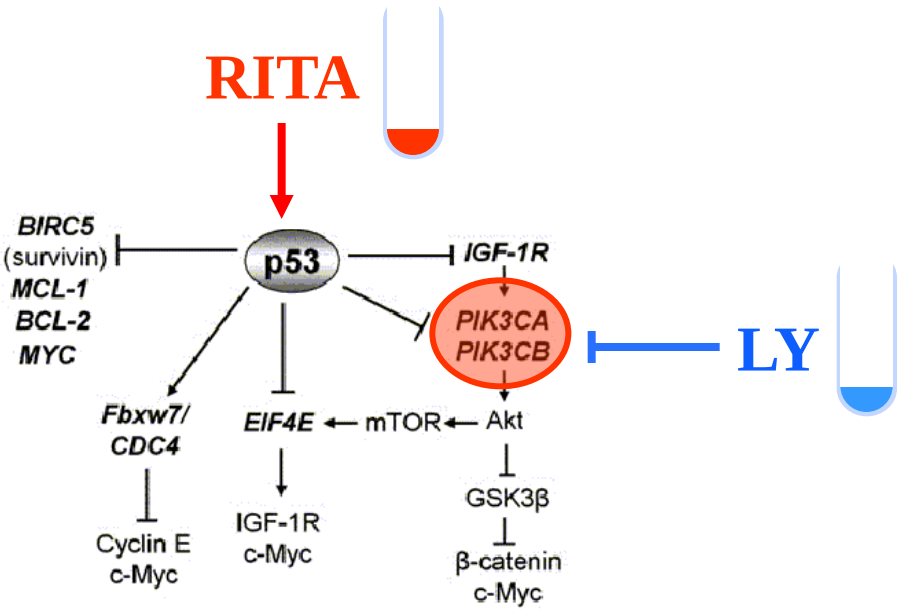
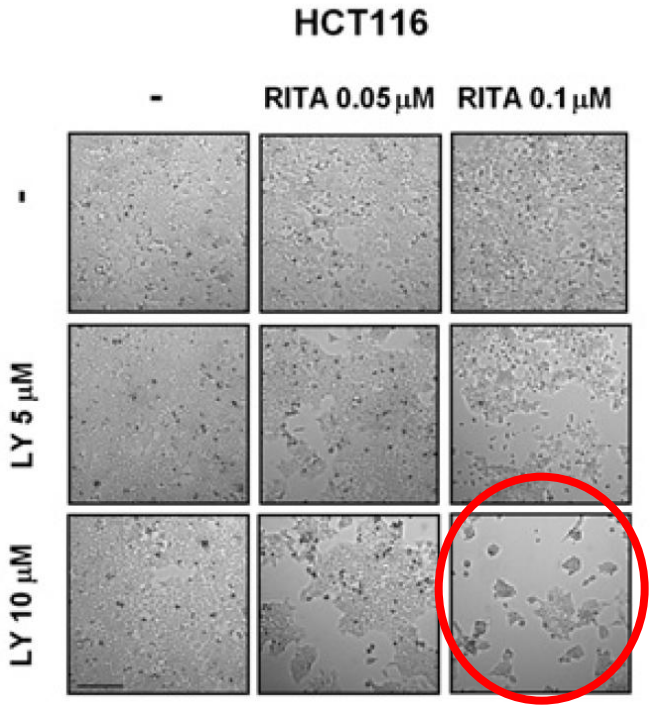
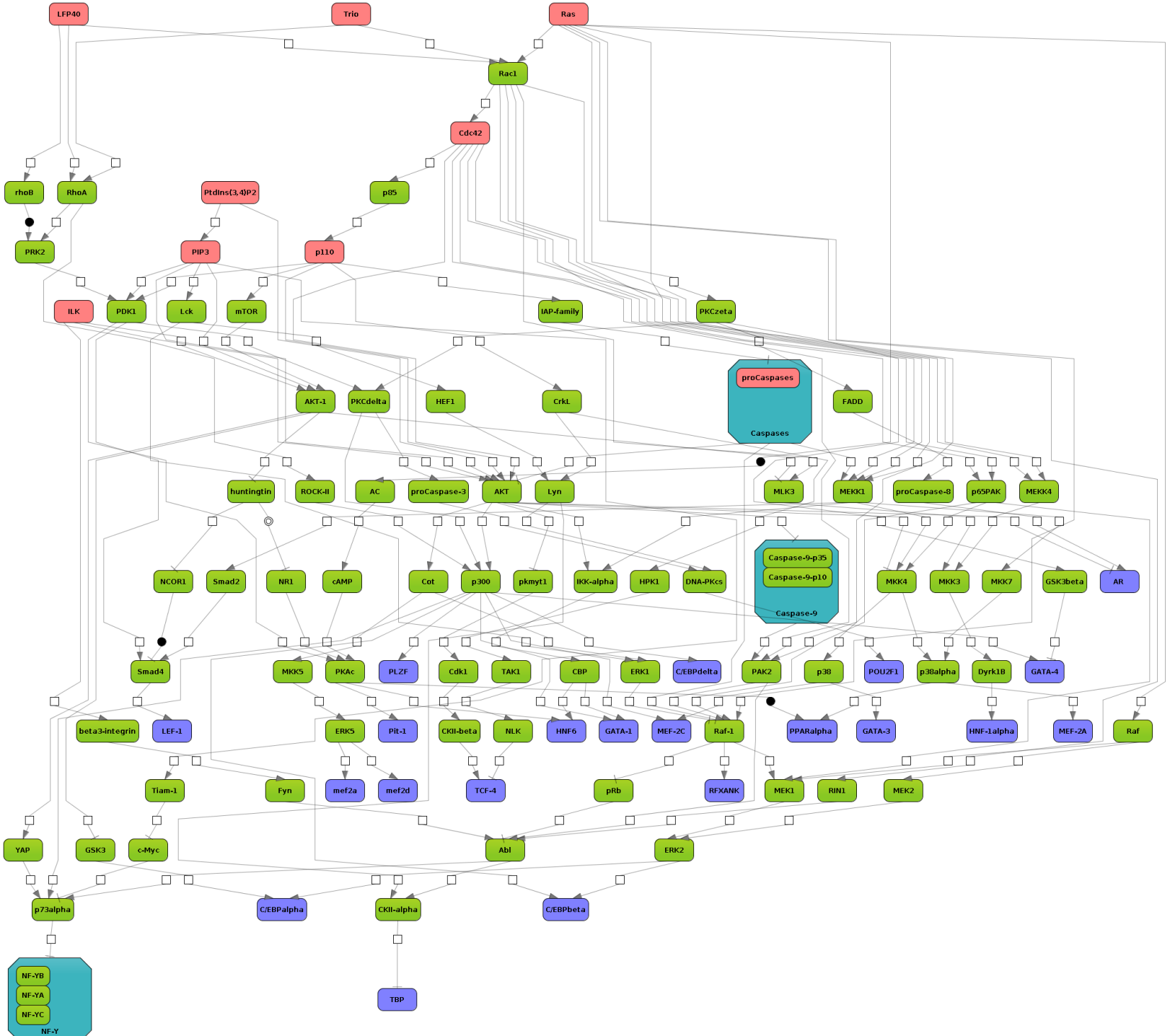
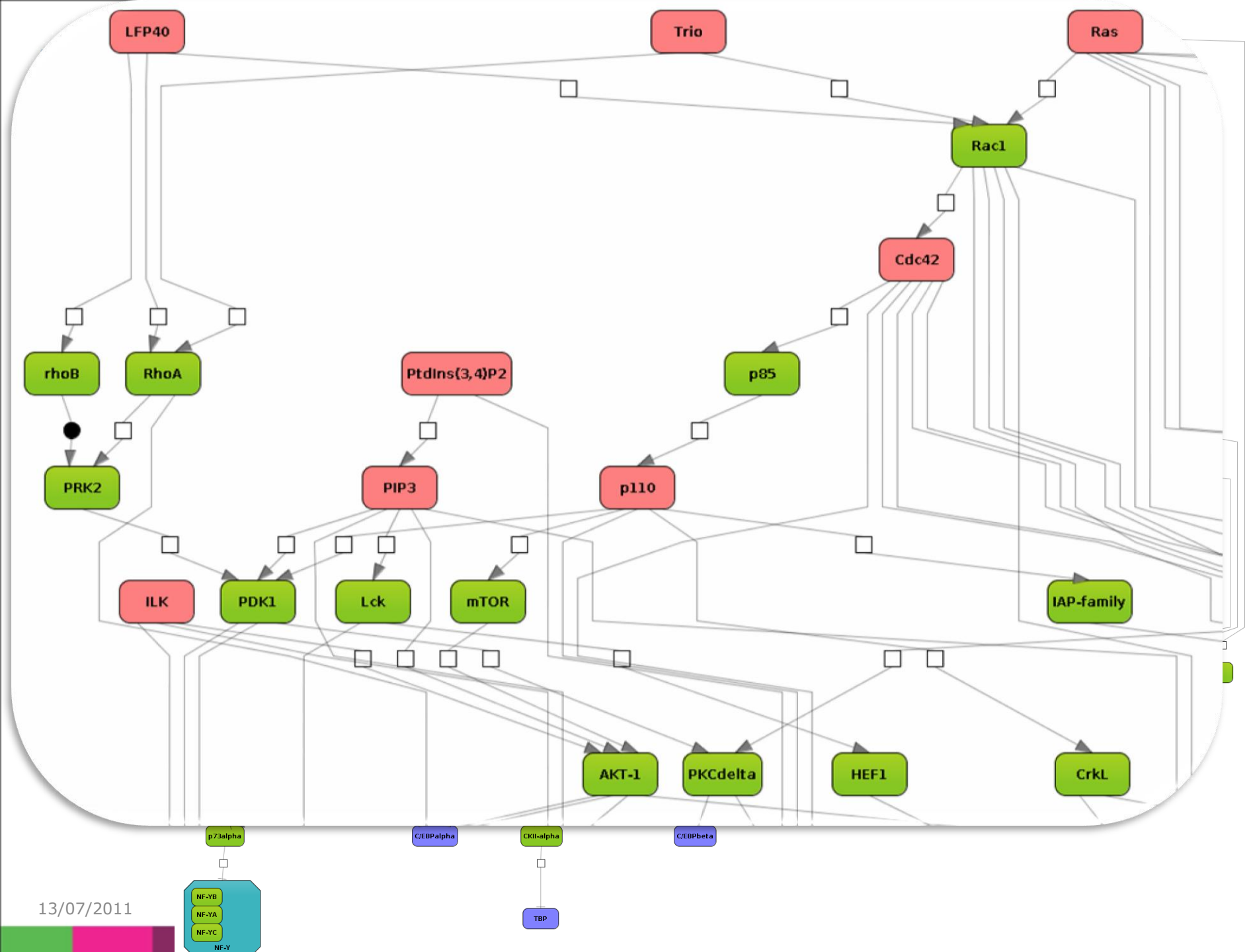


Death of Cancer cells treated with 0.1 μM RITA and PI3-kinase inhibitor LY294002



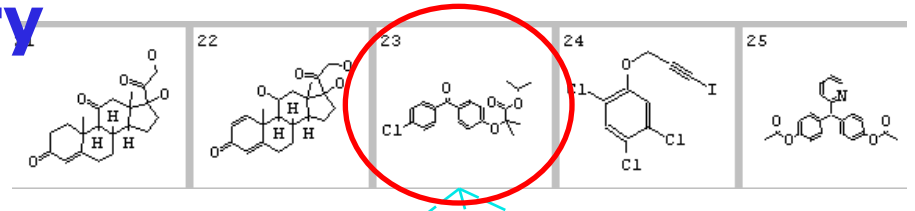


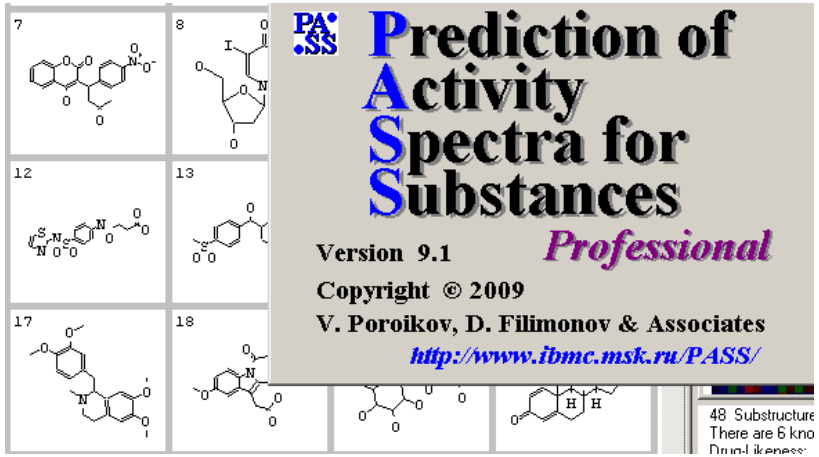

LFP40
Trio
Ras
Rac1
Cdc42
rhoB
RhoA
PtdIns(3,4)P2
p85
PRK2
PIP3
p110
ILK
PDK1
Lck
mTOR
IAP-family
PKCzeta
proCaspases
Caspases
AKT-1
PKCdelta
HEF1
CrkL
FADD
huntingtin
ROCK-II
AC
proCaspase-3
AKT
Lyn
MLK3
MEKK1
proCaspase-8
p65PAK
MEKK4
Caspase-9-p35
Caspase-9-p10
Caspase-9
NCOR1
Smad2
NR1
cAMP
Cot
p300
pkmyt1
IKK-alpha
HPK1
DNA-PKcs
MKK4
MKK3
MKK7
GSK3beta
AR
Smad4
MKK5
PKAc
PLZF
Cdk1
TAK1
CBP
ERK1
C/EBPdelta
PAK2
p38
POU2F1
p38alpha
Dyrk1B
GATA-4
beta3-integrin
LEF-1
ERK5
Pit-1
CKII-beta
NLK
HNF6
GATA-1
MEF-2C
Raf-1
PPARalpha
GATA-3
HNF-1alpha
MEF-2A
Raf
Tiam-1
Fyn
mef2a
mef2d
TCF-4
pRb
RFXANK
MEK1
RIN1
MEK2
YAP
GSK3
c-Myc
Abl
ERK2
p73alpha
C/EBPalpha
CKII-alpha
C/EBPbeta
NF-YB
NF-YA
NF-YC
NF-Y
TBP

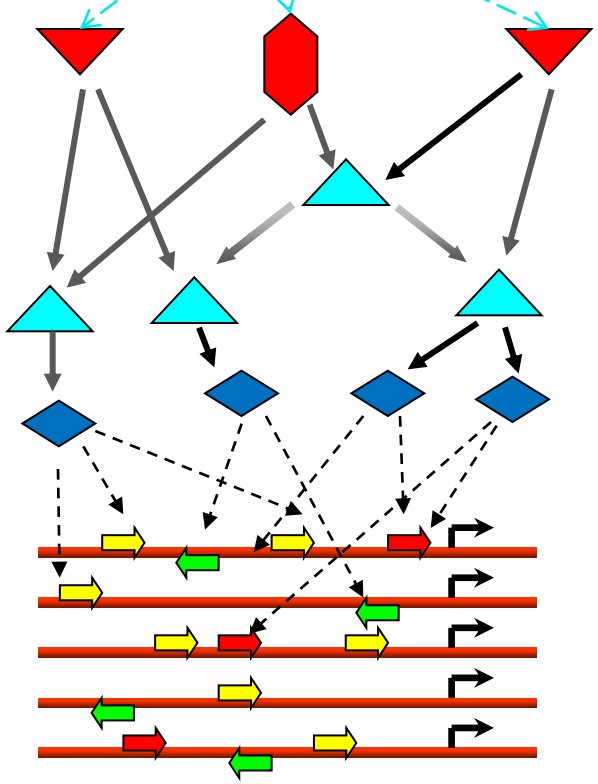

LFP40
Trio
Ras
Rac1
Cdc42
rhoB
RhoA
PtdIns(3,4)P2
p85
PRK2
PIP3
p110
ILK
PDK1
Lck
mTOR
IAP-family
AKT-1
PKCdelta
HEF1
CrkL
p73alpha
C/EBPalpha
CKII-alpha
C/EBPbeta
NF-YB
NF-YA
NF-YC
NF-Y
TBP

Identified 64 novel componds

ChemNavigator Library 24 million compounds







Tested 16 compounds in a panel of several cancer cell lines.

Found active: Compound N15

Hypoxia inducible factor 1 alpha inhibitor	**Phosphatidylinositol 3-kinase beta inhibitor**

Targets

Showed growth suppression in 3 different breast cancer cell lines. The effect appears to be p53-independent (kills p53-null colon cancer cells) and it does not affect the growth of non-transformed mammary epithelial cells

Found active: Compound N6

Cyclin-dependent kinase 2 inhibitor	**Myc inhibitor**

Targets

Out of panel of 7 different cancer lines it killed only melanoma cells without any effects in other cell lines and on control non-transformed mammary epithelial cells.

Tested 16 compounds in a panel of several cancer cell lines.

Found active:

Hypoxia indu
factor 1 alpha

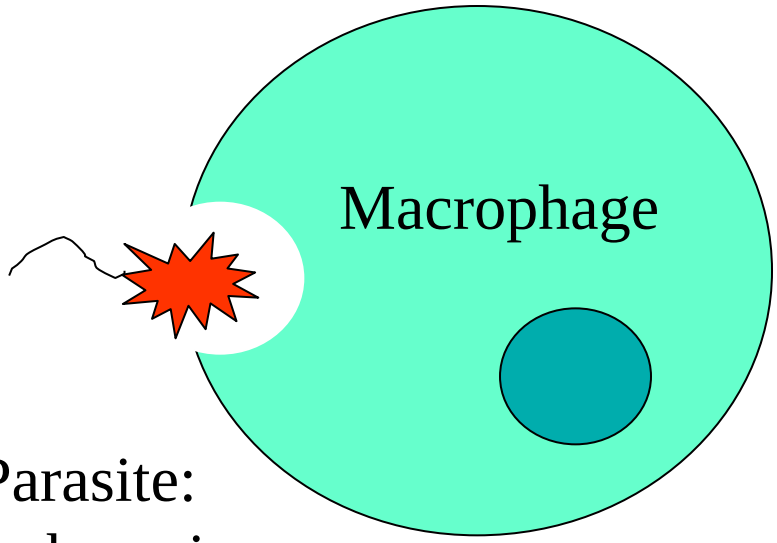
Showed growth supp
The effect appears tc
cancer cells) and it d
mammary epithelial c

Found active:

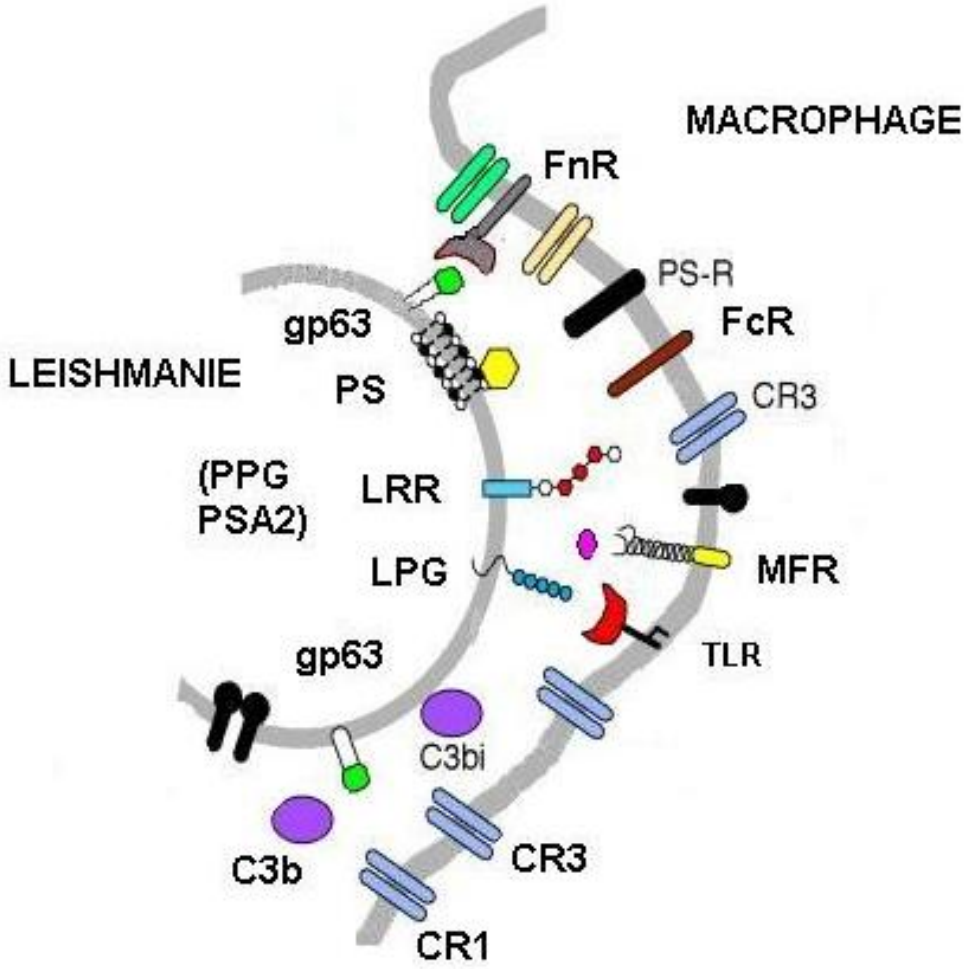
Cyclin-depend
kinase 2 inhibi

Out of panel of 7 diffe
without any effects in
transformed mamma

Infection project: SysCo

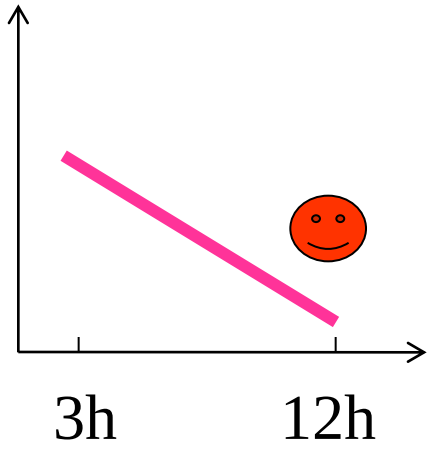


Parasite:
Leshmania

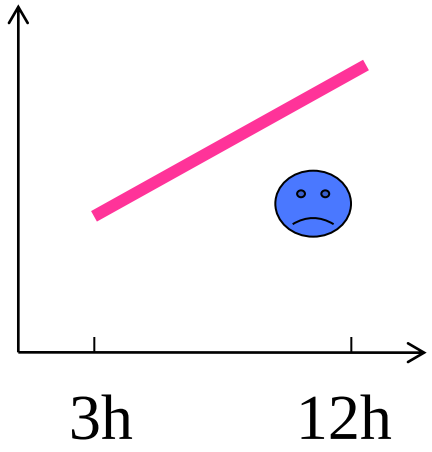


Parasite

Killed parasite

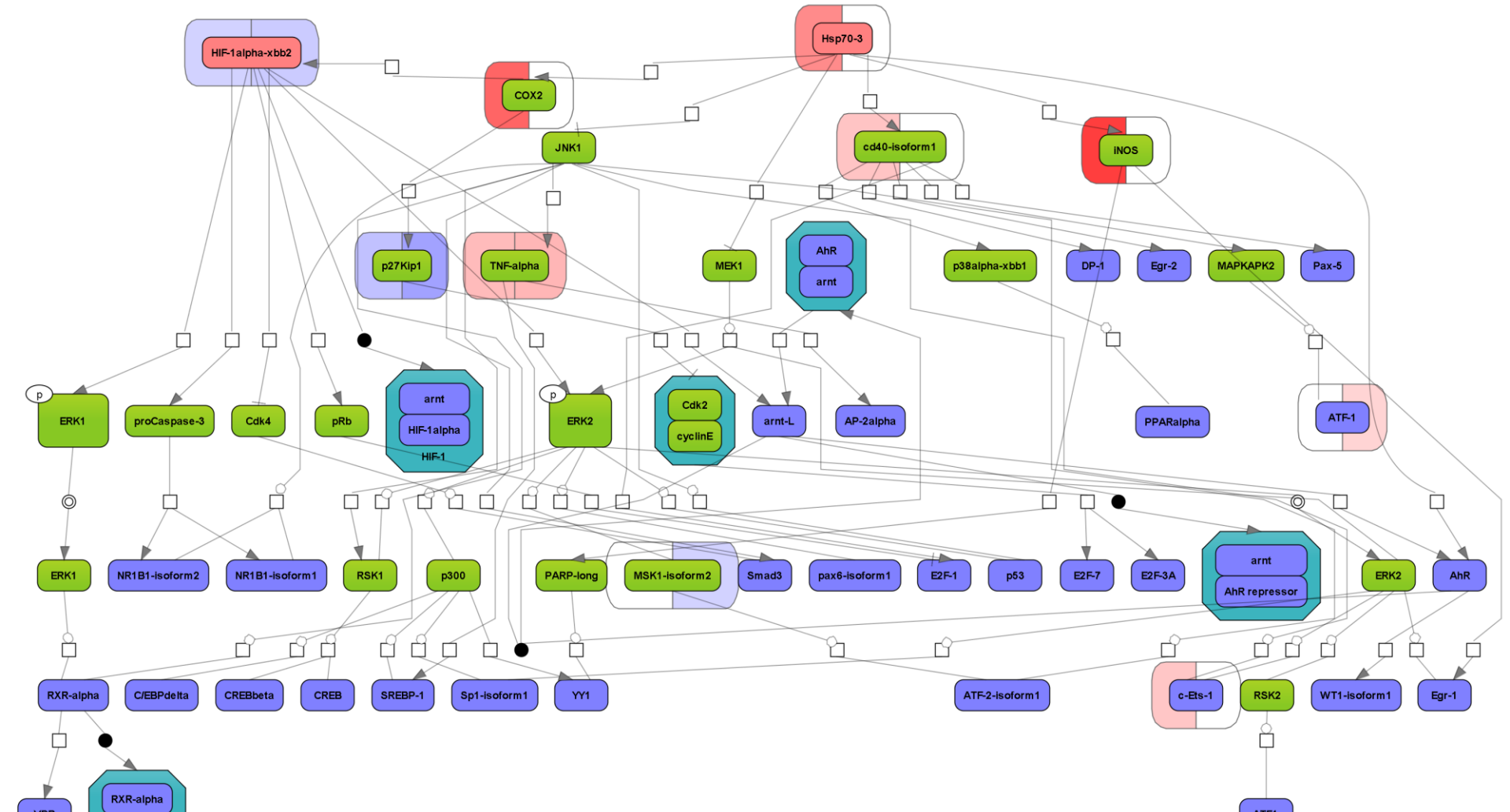


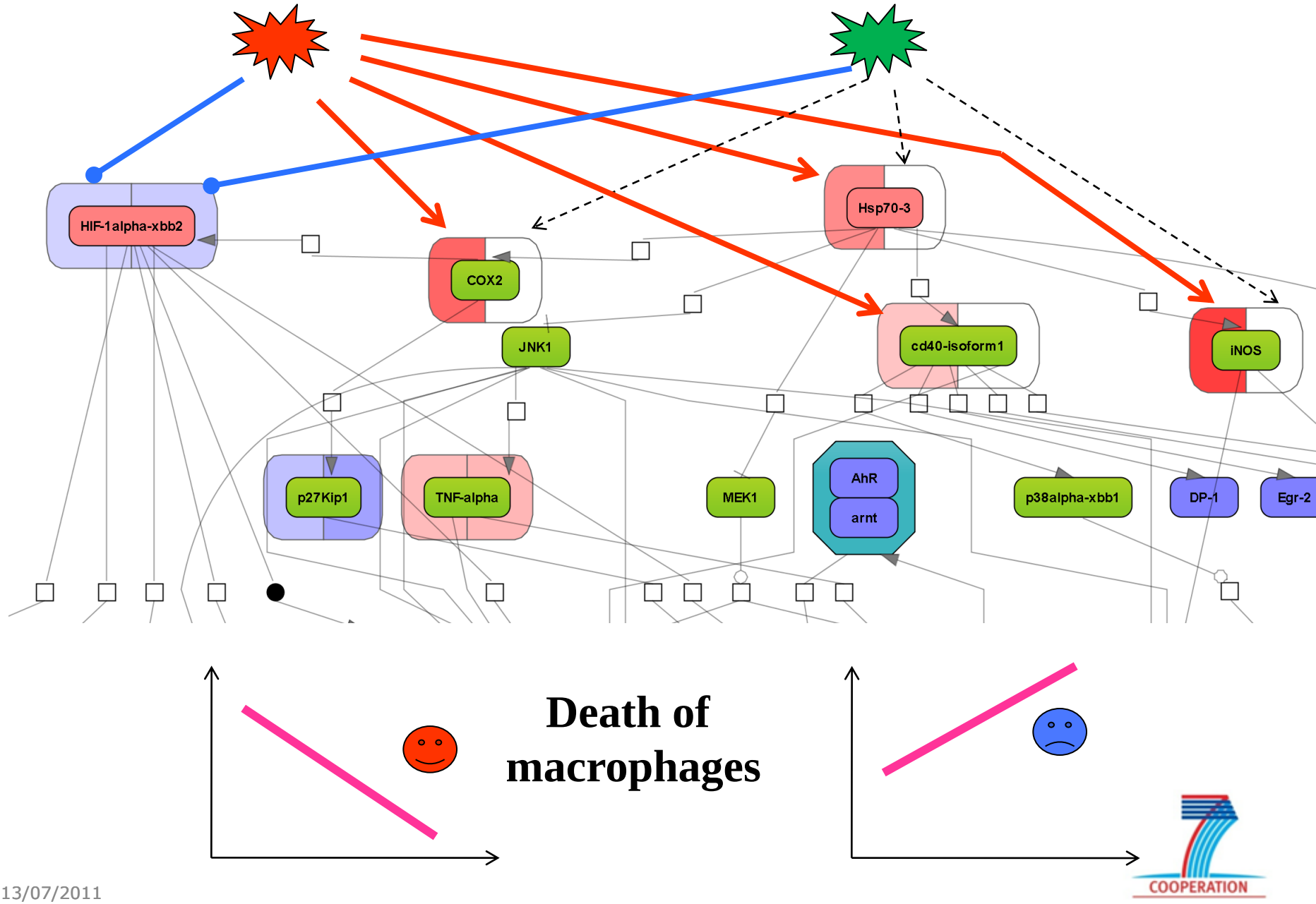
Death of macrophages by apoptosis



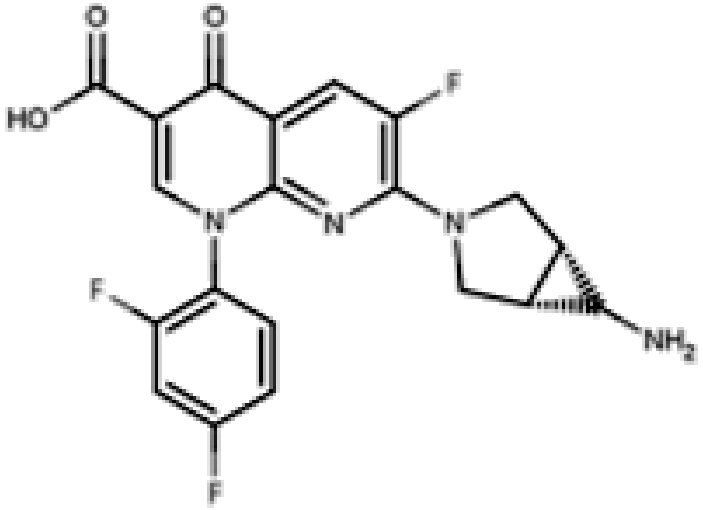
Parasite

Killed parasite



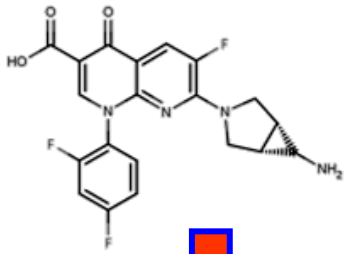

Parasite
Killed parasite
HIF-1alpha-xbb2
COX2
JNK1
Hsp70-3
cd40-isoform1
iNOS
p27Kip1
TNF-alpha
MEK1
AhR
arnt
p38alpha-xbb1
DP-1
Egr-2
Death of macrophages

Trovafloxacin - antibiotic

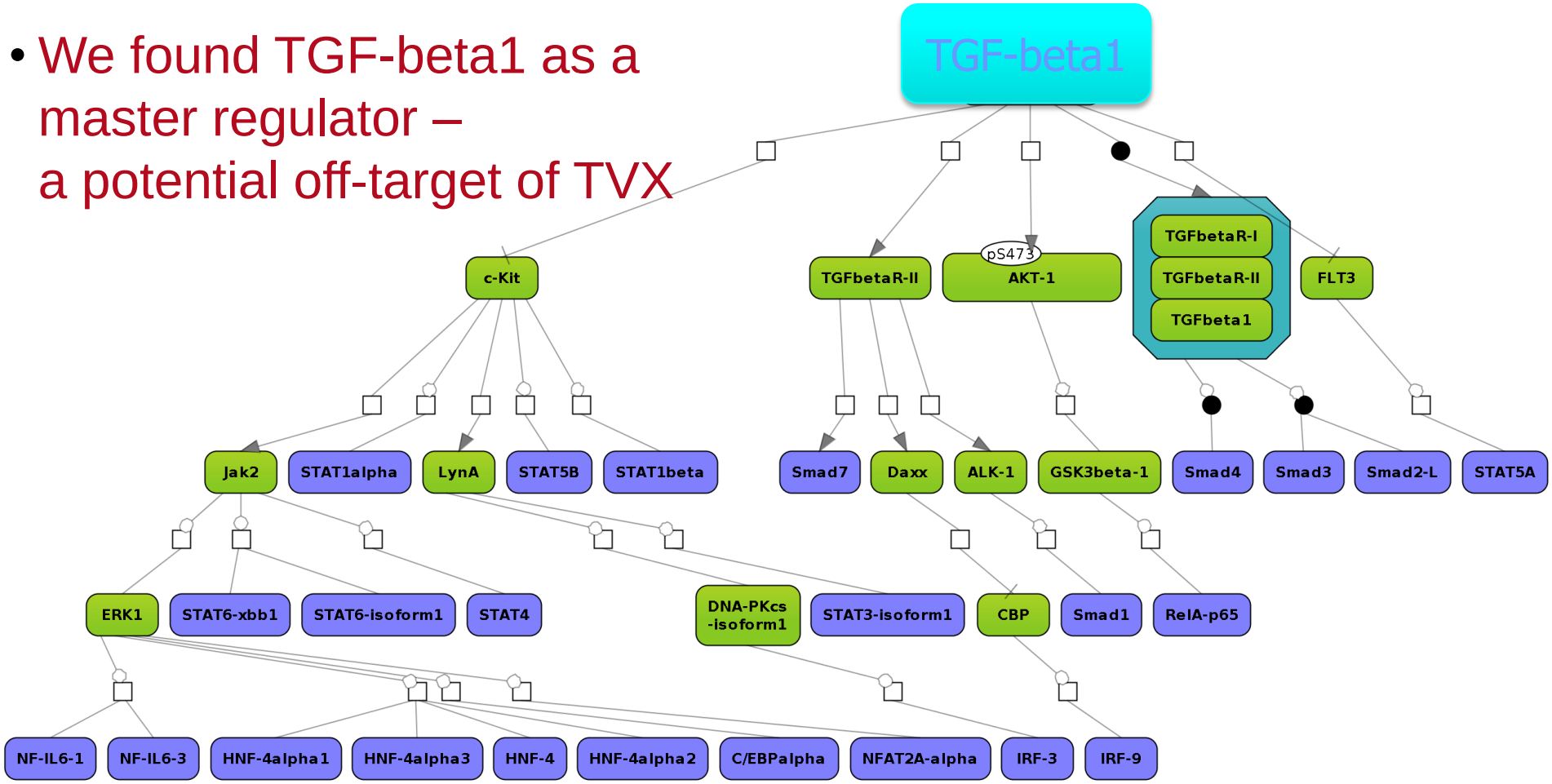


Withdrawn from market due to risk of idiosyncratic hepatotoxicity in 2001.

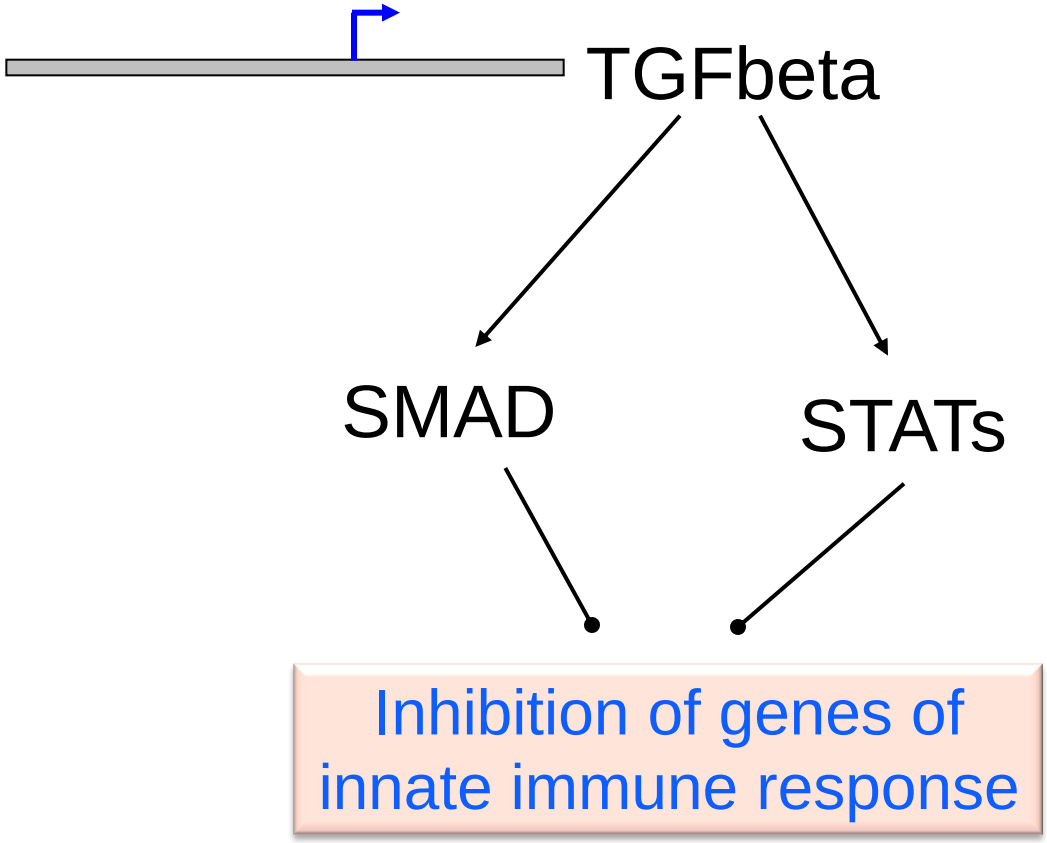
Trovafloxacin (TVX)



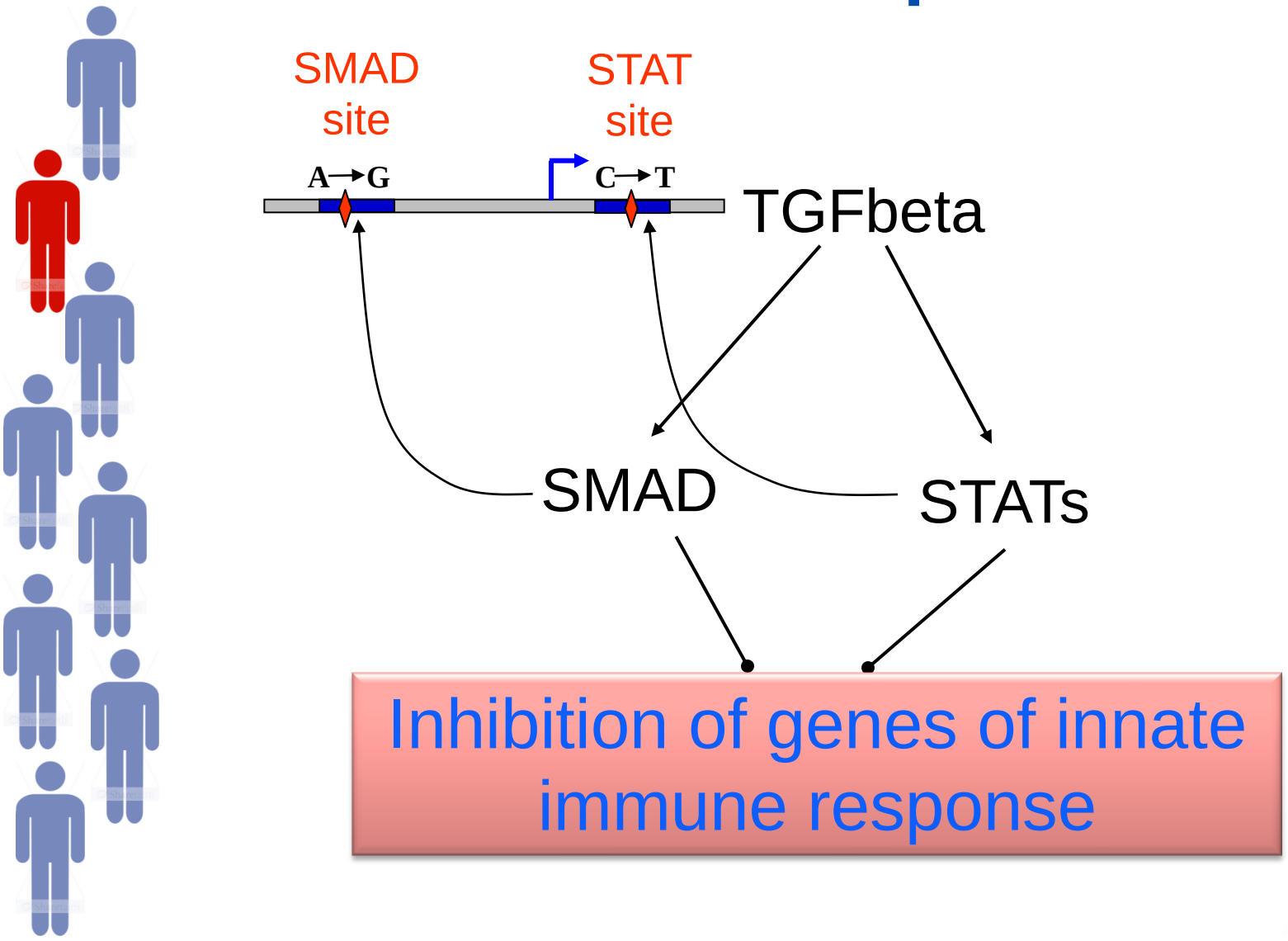
- We found TGF-beta1 as a master regulator – a potential off-target of TVX



TGF-beta dependent positive feedback



TGF-beta dependent positive feedback



The successes achieved so far by the SMEs as partner in EU Health collaborative projects, which would not be possible without the EU collaborative grants

- **Creation of innovative tools became possible**
  - Effective drug target search algorithms.
  - Upstream algorithm for microarray data analysis.
  - Support for creation of geneXplain platform.
- **World-wide recognition of the company**
  - In academia.
  - In pharma and biotech.
- **Generation of a portfolio of know-hows.**
  - Disease specific drug targets/biomarkers.
  - Effective computational algorithms.

Potential for exploitation of the results achieved so far by the SME in EU Health collaborative projects.

- **Bioinformatics and systems biology software (Algorithms are created with EU help)**
  - Global market value of about 500 Mio €.
  - GeneXplain platform share is about 50 Mio €.
  - Potential customers: 50 large pharmaceutical and biotech companies + 500 middle-sized and smaller biotech companies + 3000 academic work groups .
- **Services (Expertise is created with EU help)**
  - Data analysis services and consulting.
  - Creation of tailor-made solutions (software, models)
- **Exploitation of identified drug targets and lead compounds.**
  - Cancer leads compounds should be further validated.

The importance, benefits and impact of Health collaborative research funding for SMEs in the area of systems biology for medical applications.

- **EU funding is ultimately important for systems biology SMEs**
  - Supporting innovations/ideas that do not show yet return of investments history.
  - Help young companies to start up
- **Benefits**
  - Collaboration synergism
  - Inventor owns the IPs.
- **Impact**
  - Creation of new company was possible only upon EU grant
  - R&D in SMEs in Europe are directed towards innovations
  - Gives great competitive advantage in future.

What kind of research opportunities could attract Industry and in particular bitotechnology/healthcare SMEs in the field of systems medicine?

- **Creation of innovative tools – sustainable business**
  - Tools to support "omics" machines.
  - Tools to study disease mechanisms.
  - Tools for medical practice (virtual human/patient).
- **Participation in main stream research - marketing**
  - Learning from the best teams in the world.
  - Publications in the consortia – best marketing mechanism.
- **Opportunity to generate and co-own IPs on targets, biomarkers, drugs – opportunity business**
  - Various disease arias.
  - Increased chances due to synergy effect.

Explain genes to find new drugs

www. geneXplain .com