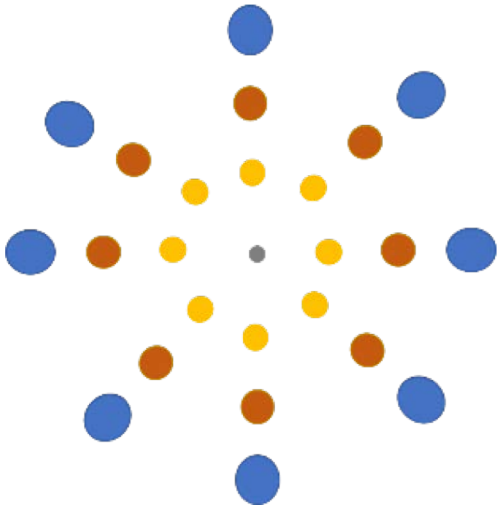
FLAG-ERA

Joint Transnational Call (JTC) 2016

for Flagship-proof-of-concept projects on

Digital Medicine for Cancer



ITFoC – IT Future of Cancer (Treatment)

Nora Benhabiles, Ph.D. EMBA
CEA
ITFoC Coordinator

The IT Future of Cancer Challenge …

THE FLAG-ERA ITFoC - A TRANSNATIONAL PARTNERING PROJECT

17 Partners

Research Organisations & Networks, Univerisities, Univeristy Hospitals, SMEs, Industry

6 countries

France, Italy, Turkey, Romania, Latvia & Germany (unfunded partner)

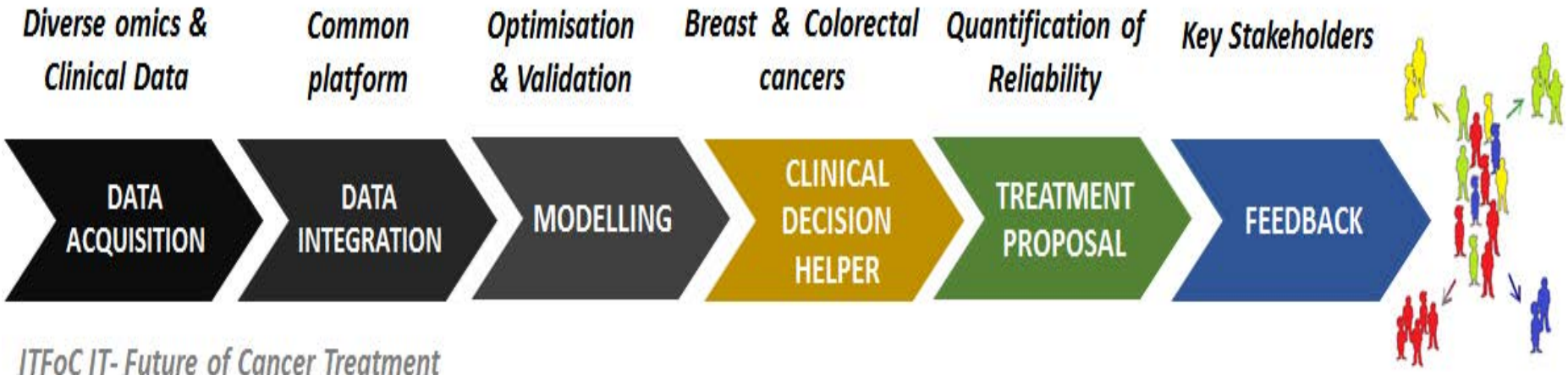
Full value chain of expertise

Information Technology, bioinformatics, mathematics, systems biology modelling, High Performance Computing, Artificial Intelligence, functional genomics, metabolomics and cancer research, biology and medicine, regulatory, ethics.

Experimental, computational, clinical and networking aspects

Participating countries for DMC : BE, EE, FR, IT, LV, RO, TR

ITFoC OVERVIEW : IMPACTS IN THE HEALTH VALUE CHAIN



THE PROJECT STRUCTURE

FLAG-ERA

Xenograft models (WP2)
model ID, source, location, reference patient

Primary cell lines (WP2)
model ID, source, location, reference patient

Clinical data (WP3)
staging, treatment, nutrition, medical history, chemotherapy, blood tests etc.

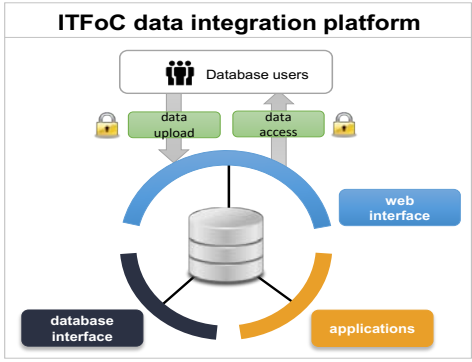
OMICS data (WP2, 3 & 4)
ITFoC generated & relevant public/consortium associated datasets

In silico modelling (WP6)
Patient ID, model type, drugs and concentrations tested, response

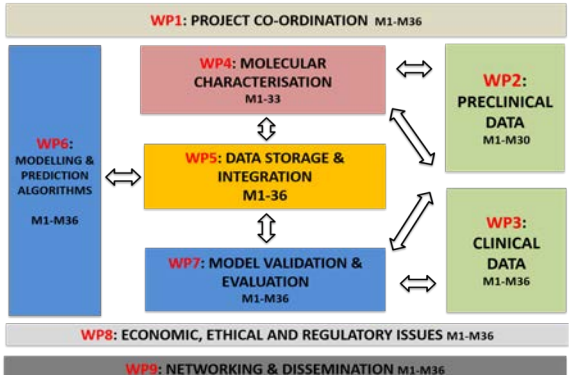
Semantic resources for data integration (WP5)
Information models and domain ontologies and Terminologies

Drug response data (WP3)
Pre-clincial /Clinical drug response testing

ITFoC
Data Integration



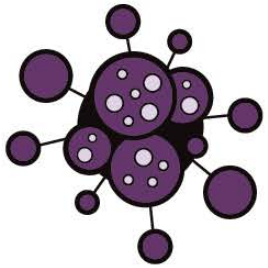
ITFoC data integration platform



XOSE FERNANDEZ
PhD.
Chief Data Officer – Institut Curie

Triple negative breast cancer : the challenge

CANCER IN FRANCE TODAY

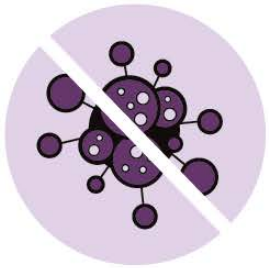


58,459

new breast cancer cases in France in 2018

+ 3 million

cancer survivors today



30.1%

breast cancers could be **avoided** by just following a healthier lifestyle

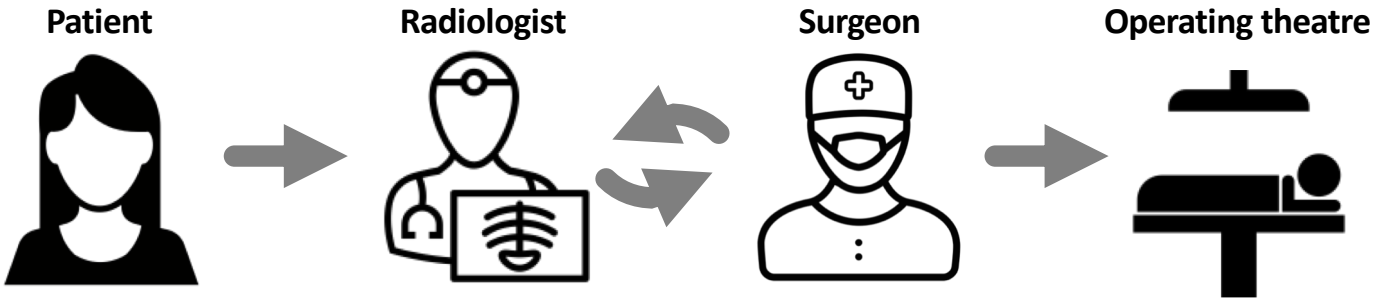
Source: *INCa* (2019)

BREAST CANCER TREATMENT TODAY

+2M Annual diagnoses globally

58K Annual diagnoses in France

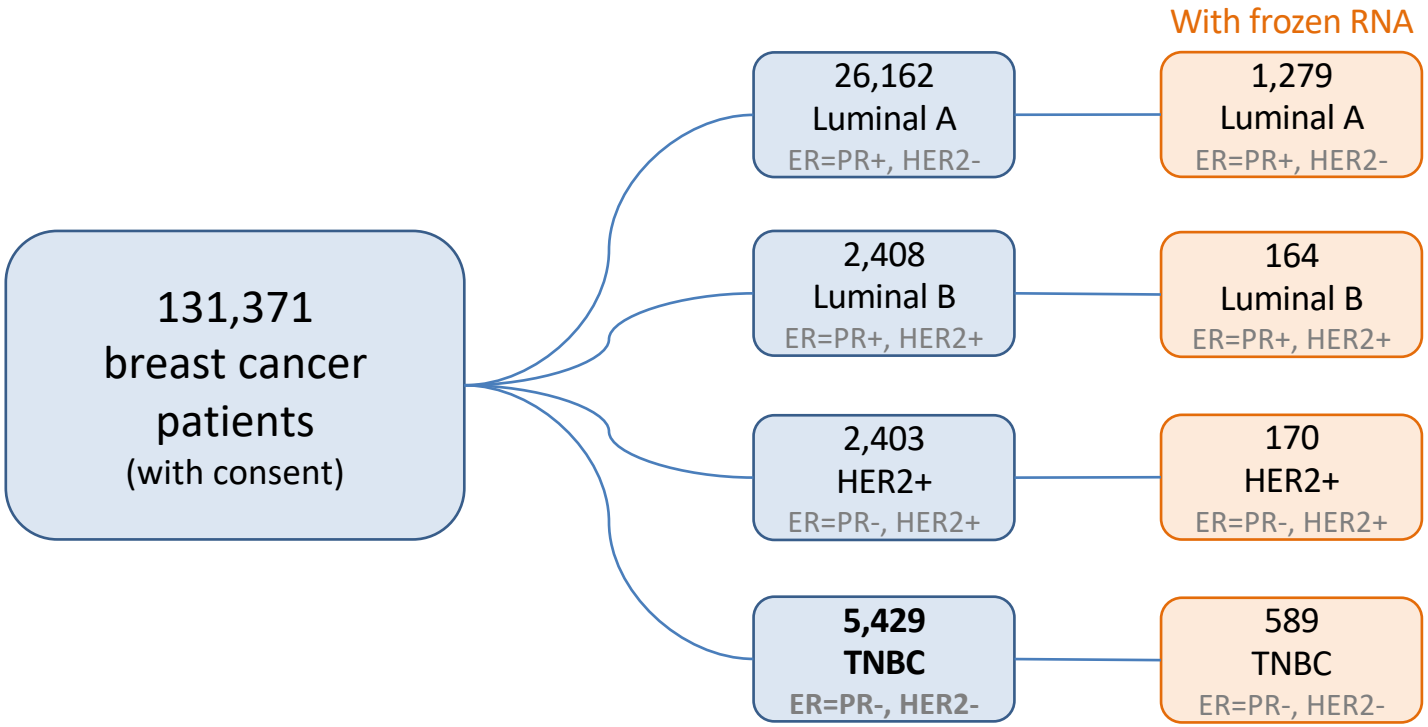
Surgical treatment in **93%** of cases



- **~ 40%** Mastectomies
- **~ 60%** Lumpectomies
- Reconstructive Surgery
- Revision Surgery (**15-30%**)

Source: *INCa; American Cancer Society 2017, World Health Organisation*

THE CURIE EXAMPLE : HOW TO TARGET POPULATION ?



WHY TRIPLE NEGATIVE BREAST CANCER?

- Despite being the rarest form, it accounted for 15-20% of the over 2 million new breast cancer cases in 2018
- **TNBC** is more commonly diagnosed in women who
  - Are **under** the **age of 40 or 50**
  - Have a mutation in the ***BRCA1*** gene
- Compared with other forms of breast cancer, TNBC
  - Is **more aggressive** and causes more rapid progression and **shorter overall survival**
  - Can be more **difficult to diagnose**, as younger women have denser breast tissue and **standardised** mammograms are **not yet recommended**
  - **Reduces the likelihood** of **surviving** the first **5 years** after diagnosis
  - Has an **increased likelihood of returning** to other areas of the body, with the lungs and brain being the most likely sites of distant recurrence.

FLAG-ERA

Inserm
Institut national
de la santé et de la recherche médicale

ANITA BURGUN
MD, Ph.D. Professor of Biomedical Informatics

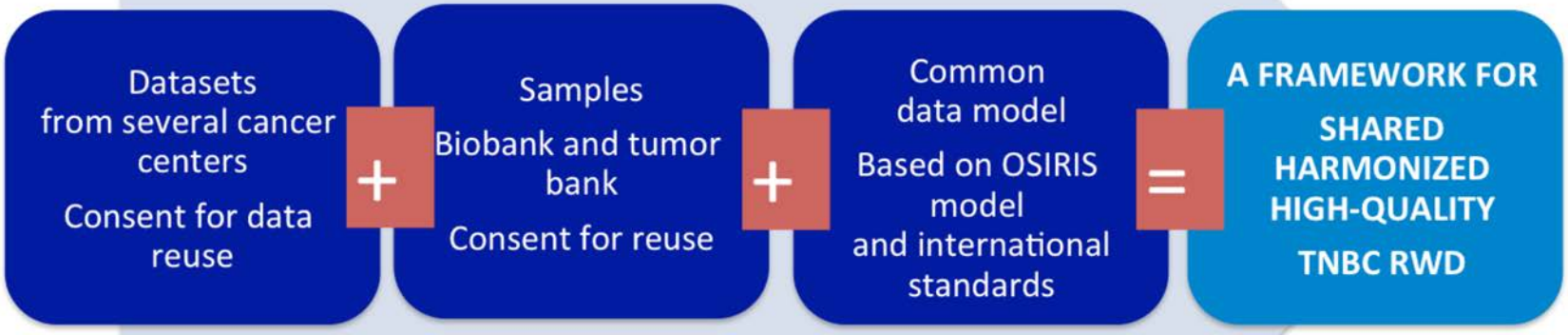
A Complex journey :

- *Heterogeneity of clinical cases*
- *Heterogeneity of data*
- *Heterogeneity of models…*

ADDRESS HETEROGENEITY ISSUES

A sample of 9 patients from HEGP
40 to 80 years old

- $T_1N_1M_0$ *(1 patient)*
- $T_2N_0M_0$ *(2 patients)*
- $T_2N_1M_0$ *(2 patients)*
- $T_2N_2M_0$ *(1 patient)*
- $T_3N_3M_0$ *(1 patient)*
- $T_4N_0M_0$ *(1 patient)*
- $T_4N_1M_1$ *(1 patient)*
- $T_4N_1M_1$ *(1 patient)*



Several cancer centers
Adoption of a common model

PATIENT SAFETY IN AI DEVELOPMENT AND CLINICAL DECISION SUPPORT SYSTEM

FLAG-ERA

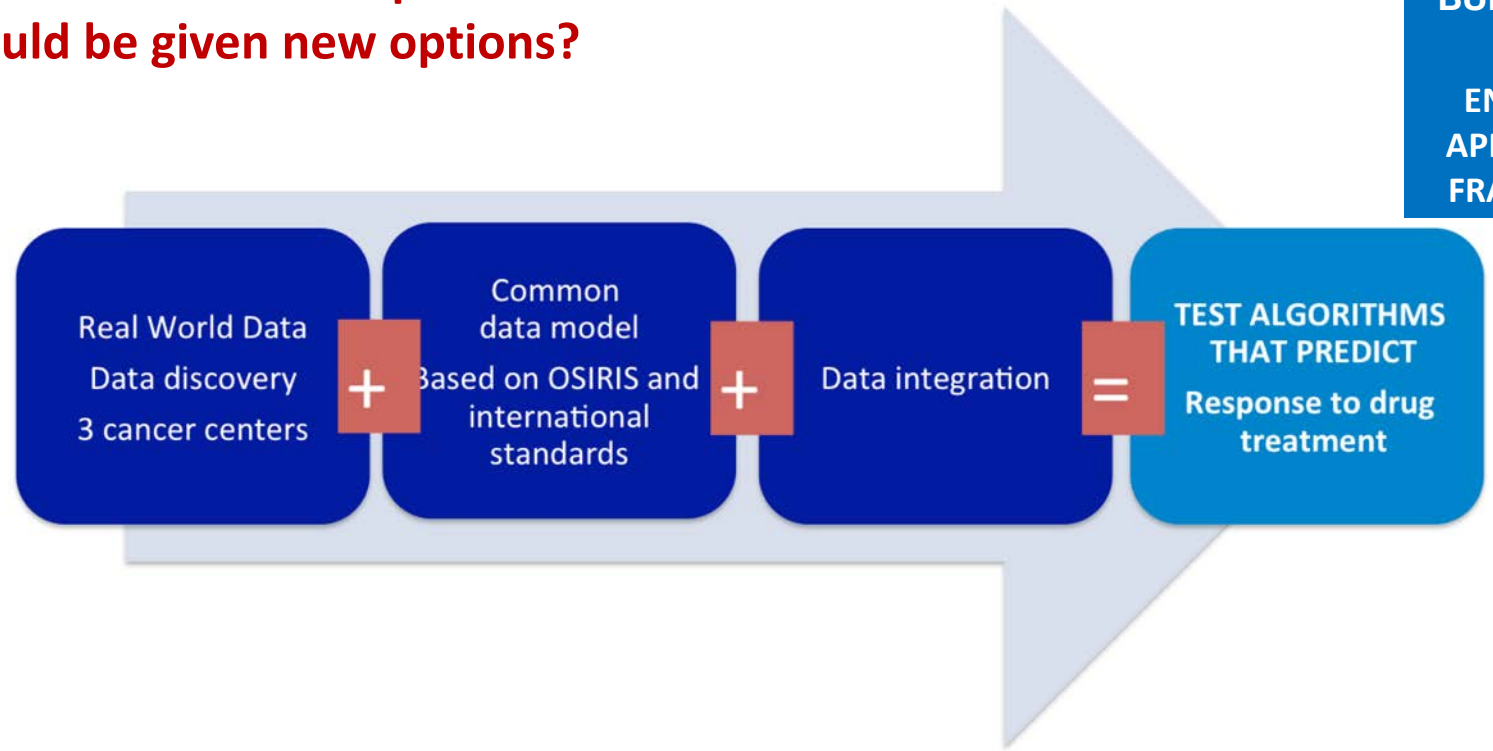
[AI] shaping Europe's digital future

PREPARE FOR CHANGES

BUILD TRUST

ENSURE AN APPROPRIATE FRAMEWORK

What patients will not respond to standard treatment?
And should be given new options?



Tsopra R, et al. submitted Artificial Intelligence in Medicine 2020.

Provide high-quality Real World standardized datasets to validate the algorithms

NEW CHALLENGES IN TRANSLATIONAL RESEARCH

FLAG-ERA

[AI] shaping Europe's digital future

PREPARE FOR CHANGES

BUILD TRUST

ENSURE AN APPROPRIATE FRAMEWORK

Algorithm DEVELOPMENT (internal)

External clinical validation
(early phase trial)

First on external RWD

Retrospective high-quality data
Several cancer centers

Predict response to treatment
(non response to standard treatment)

Data
Samples
Follow-up
Consent (data reuse + samples)

Safe enough?
Make decision about further CT

Prospective study (phase III)

Surveillance (phase IV)

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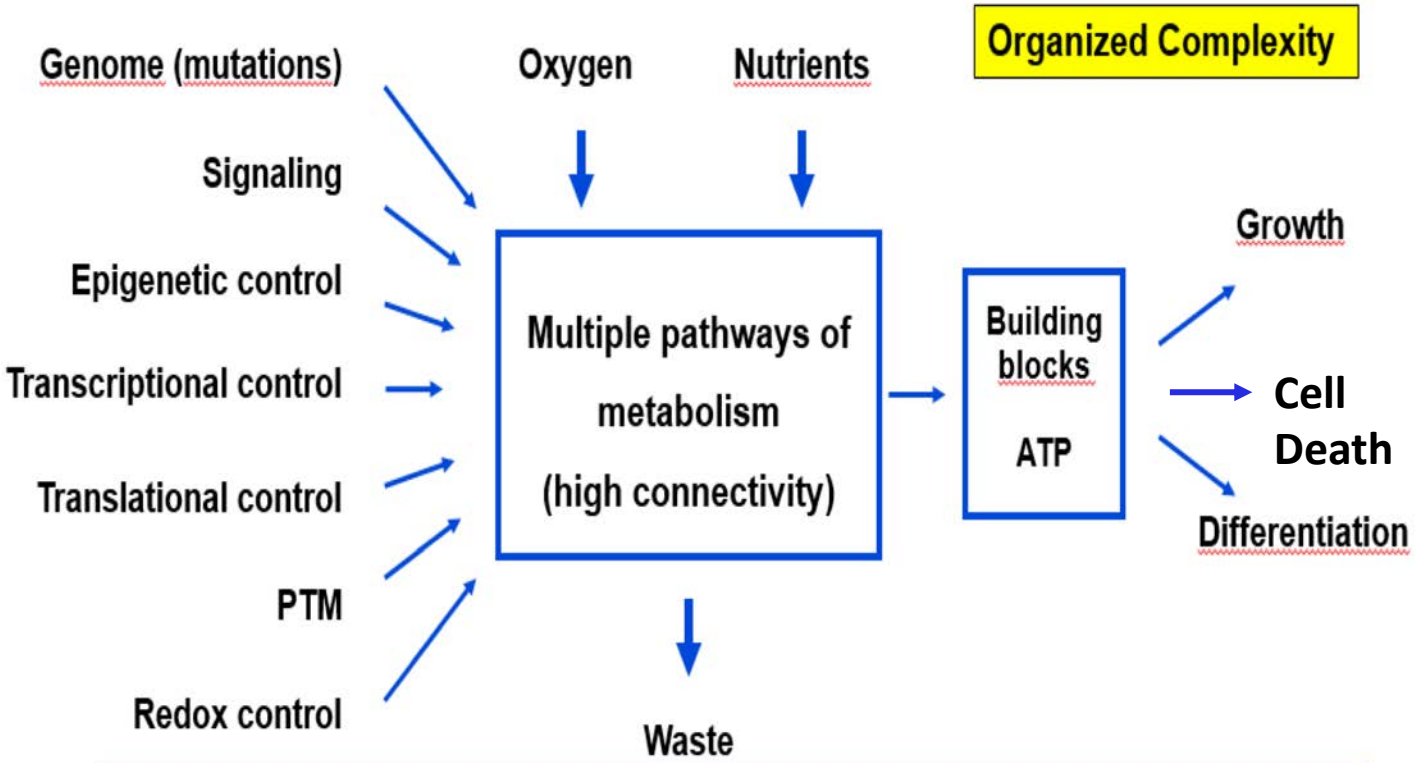
Marco VANONI
Lilia ALBERGHINA

SYSBIO
CENTRE OF SYSTEMS BIOLOGY

The central role of metabolism in triple negative breast cancer

THE CENTRAL ROLE OF METABOLISM IN CELLULAR LIFE



*"…any perturbation of cellular physiology will have a **metabolic fingerprint**, i.e., changes in a certain part of metabolism, and this may be quite specific. It further means that with the high degree of connectivity in metabolism, it is difficult to analyze changes in metabolism without the use of **mathematical models**."*

J. Nielsen, Cell Metabolism 25, 575, 2017

THE RULES GOVERNING CANCER METABOLIC REWIRING

Boundary conditions for Cancer Metabolic Rewiring (CMR)

- Increased utilization of Glucose and Glutamine
- Oxygen availability less than that required for complete Glucose utilization

Characteristic profile of CMR:

- Glutamine utilization ⇒ branched TCA cycle
- Glucose oxidation ⇒ Lactate (even in presence of O2)
- Glutamine may be converted to Lactate
- A large number of different Redox controlled metabolic routes may generate CMR
- Yields maximal growth rate

Damiani et al. PLoS Comp. Biol. 2017

PRE-CLINICAL STUDIES

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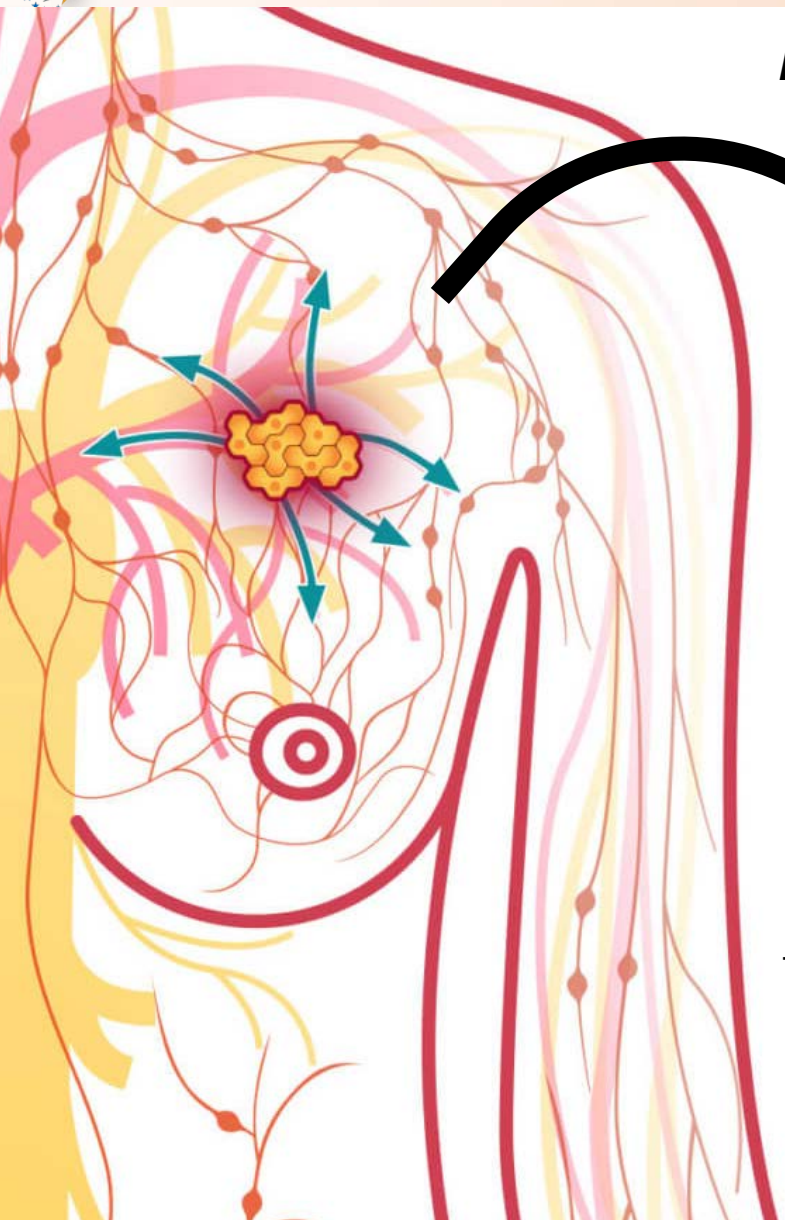
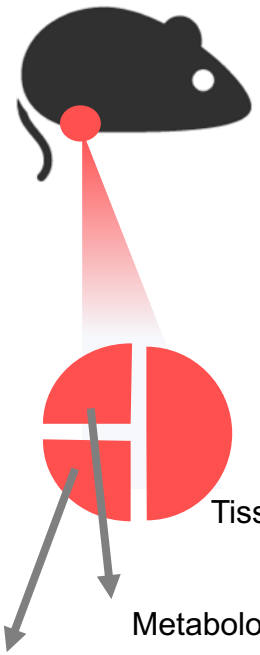


Primary and metastatic breast carcinoma grown in immunocompromised mice



Tissue culture

Metabolomics

Transcriptomics

Molecular subtypes	Triple negative (ER−, PR−, HER2−)	HER2+	Luminal B	Luminal A

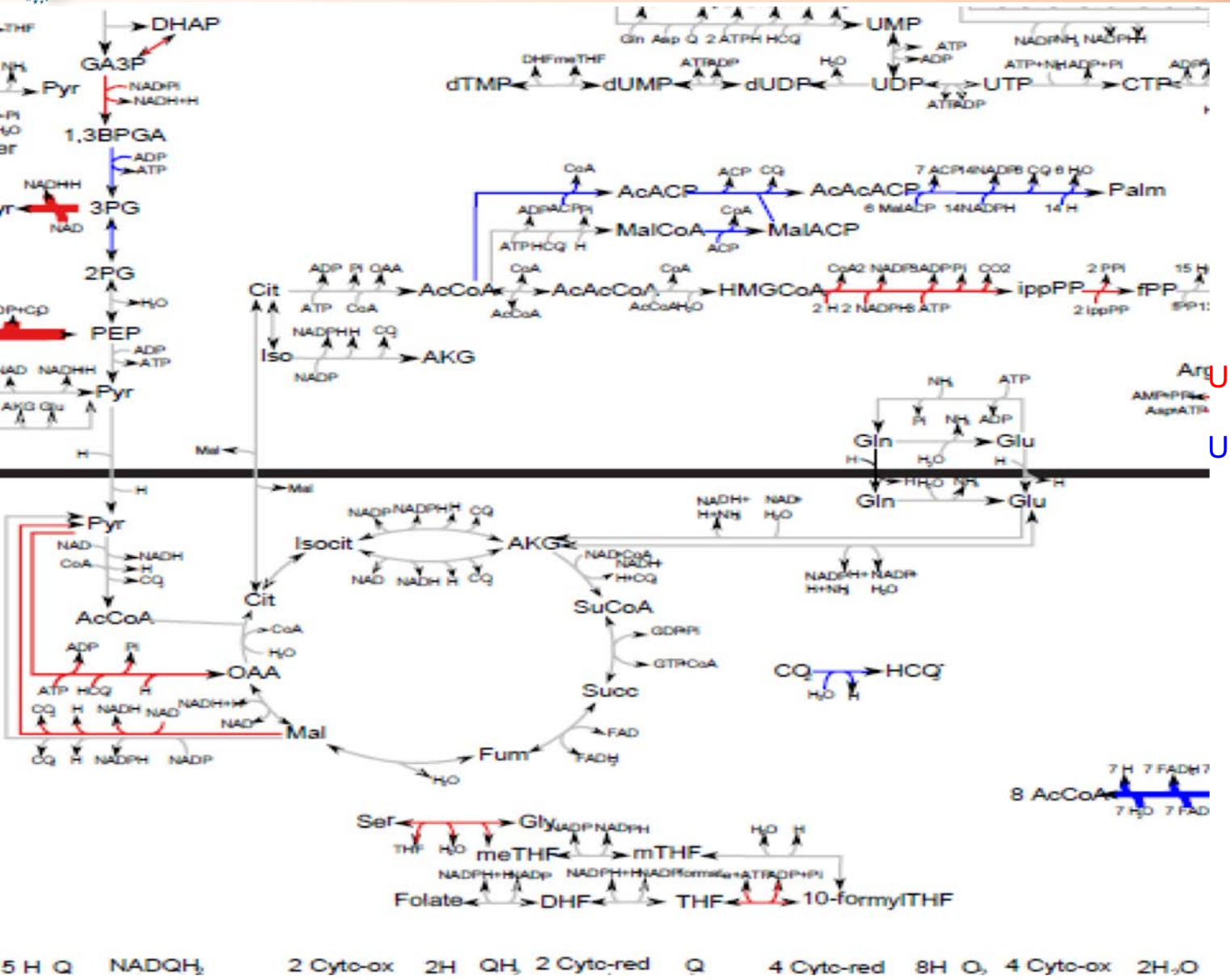
Legend	Acronym	Numerosity
Basal-like1	BL1	10
Basal-like2	BL2	2
Immunomodulatory	IM	1
Mesenchymal	M	3
Mesenchymal stem-like	MSL	2
Luminal androgen receptor	LAR	2
Unclassified	N.A.	1
Luminal	LUM	6

EurOPDX
Translating Knowledge in Oncology

European Institute of Oncology (Milan)
Institute Curie (Paris)

CENTRAL METABOLISM MODULATION IN DIFFERENT BREAST CANCER SUBTYPES

FLAG-ERA



Up-regulated in BL1

Up-regulated in NOT BL1

FLAG-ERA

PAOLA TURANO
CLAUDIO LUCHINAT

C.I.R.M.M.P.
Consorzio Interuniversitario
Risonanze Magnetiche di
Metallo Proteine

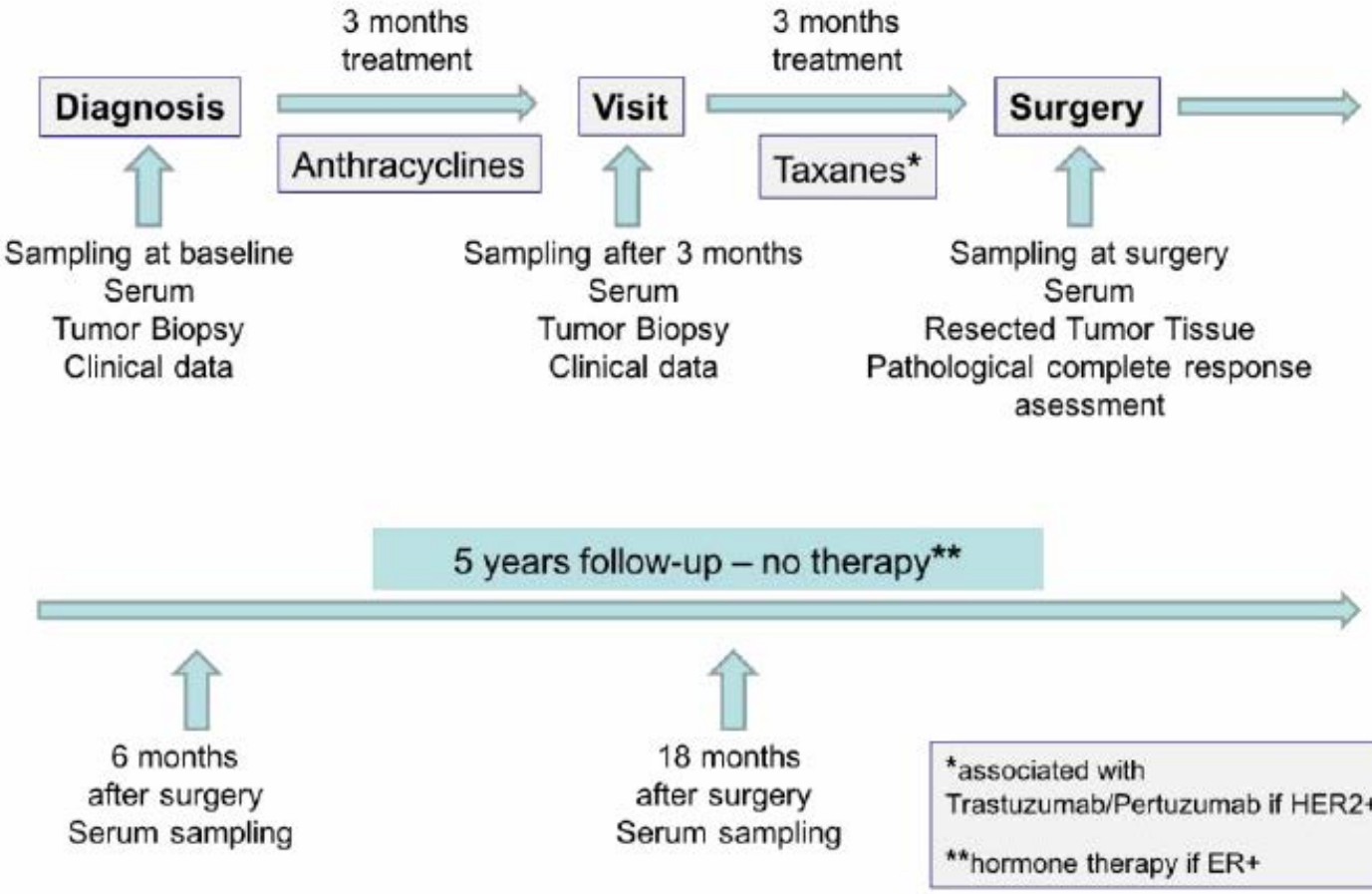
Clinical aspects and metabolomics (Done with the Aviano biobank so far)

ITFoC CLINICAL TRIAL IN ITALY : STUDY DESIGN

FIAG-FRA

Overview of sampling regime within the ITFoC clinical study of 60 patients:

Patients with triple negative (HER2-/ER-/PR-), or luminal (HER2-/ER+), or HER2+ non-metastatic primary invasive carcinoma of the breast who are candidate to sequential primary (neoadjuvant) chemotherapy with anthracyclines and taxanes according to the centre clinical practice.



CLINICAL TRIAL: ONGOING COLLECTION IN PRATO AND PISA

	Baseline serum	Baseline biopsy	3 months serum	3 months biopsy	Serum before surgery	Resected tumor at surgery	Serum 6 months after surgery	Serum 18 months after surgery	Serum at relapse
Prato Hospital									
1	yes	Yes (p)	yes	Yes (p)	yes	Yes (p)	no	no	no
2	yes	Yes (p)	yes	Refuse					
3	yes	Yes (p)	yes	Refuse					
4	yes	Yes (p)	yes	Refuse					
5	yes	Yes (p)							
6	yes	Yes (p)							
7	yes	Yes (p)							
Pisa Hospital									
1	yes	Yes (f)	yes		yes	No residual tissue	to be done 25/03/2020		
2	yes	Drop-out							
3	yes	Yes (f)	yes		yes	Yes (f)	to be done 10/04/2020		
4	yes		yes		yes	Yes (f)	to be done 16/04/2020		
5	yes	Yes (f)	Drop-out						
6	yes	Yes (f)	Drop-out						
7		Yes (f)			Yes	No residual tissue			
8	yes	Yes (f)							

IMMUNE-METABOLOMIC PROFILE OF BREAST CANCER

	Visit 1 – Diagnosis	Visit 2 – 12° week treatment	Visit 3 – 24° week treatment	Visit 4 – 2 months after surgery	Visit 5 – 6 months after surgery	Visit 6 – 1 year after surgery	Visit 7 – 2 year after surgery
N of samples	43	34	32	27	22	21	21

	Complete Responders	Partial Responders
N of patients	27	20

Available information:

- Age
- Type of surgery
- Pathological response
- Tumour size
- Lymph node involvement
- Stage
- Tumour histotype
- ER/PR status
- HER2
- Ki67
- Neoadjuvant CT toxicities
- Recurrence events
- Recurrence locations
- 3-year outcome (Alive/Dead)

- ER(+) and ER(-) are metabolomically different at baseline
- Their metabolic responses to NAT must be evaluated separately.

cancers MDPI

Article

Effect of Estrogen Receptor Status on Circulatory Immune and Metabolomics Profiles of HER2-Positive Breast Cancer Patients Enrolled for Neoadjuvant Targeted Chemotherapy

Alessia Vignoli [1,2,†], Elena Muraro [3,†], Gianmaria Miolo [4], Leonardo Tenori [1,2], Paola Turano [1,5], Emanuela Di Gregorio [3], Agostino Steffan [3], Claudio Luchinat [1,2,5,*] and Giuseppe Corona [3,*]

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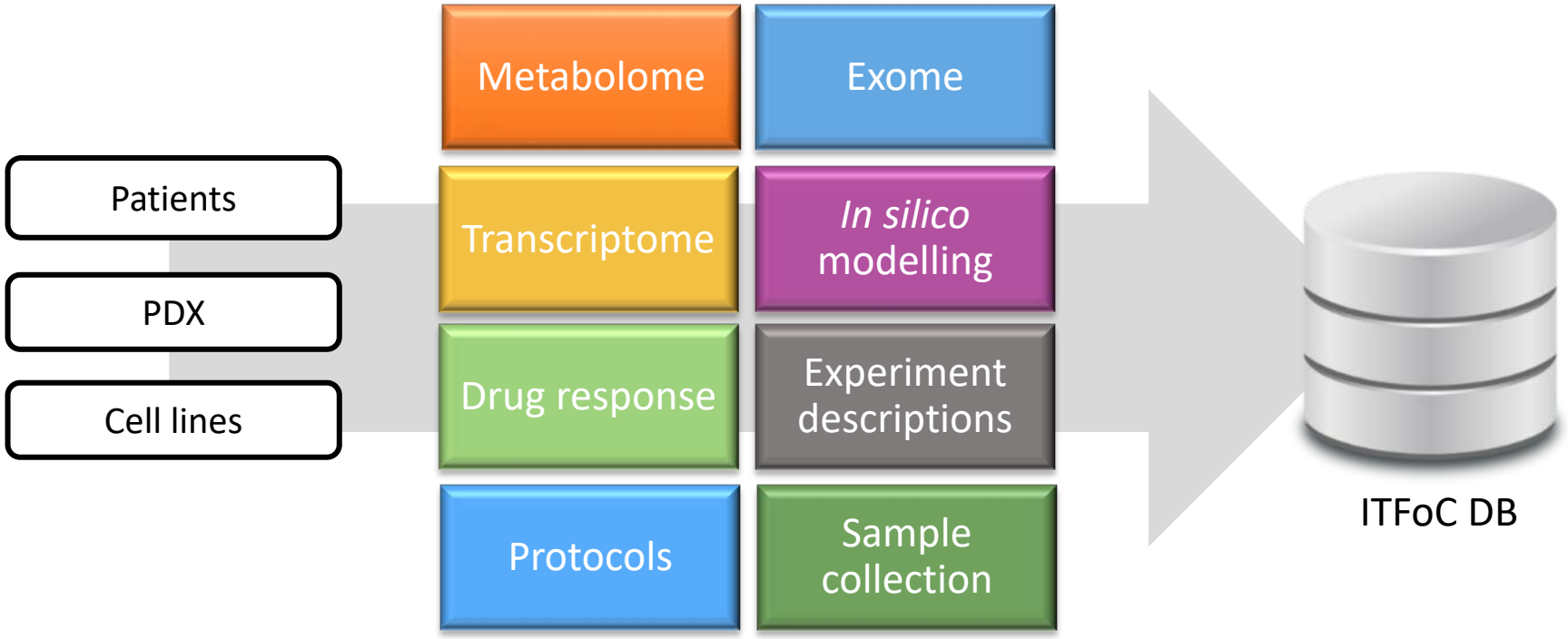
Nora BENHABILES

DATA

Oliver Hijano
Rosy Tsopra
Felix Dreher
Hans Lehrach
Lesley Ogilvie
Anita Burgun
Marc Cuggia
Unicancer
et *al.*

ALACRIS THERANOSTICS

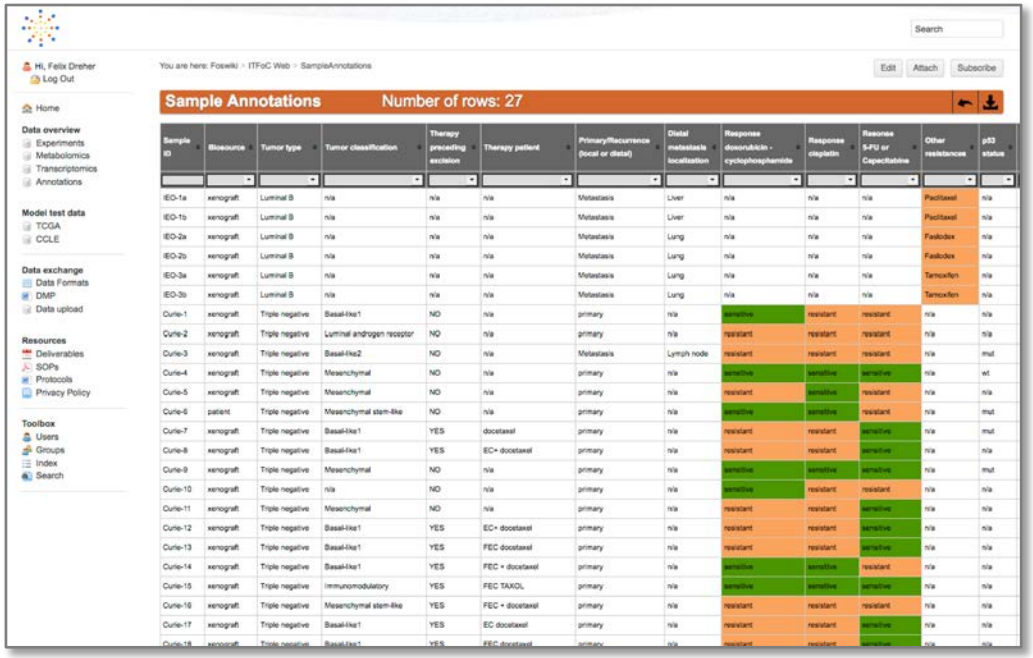
DATA GENERATION & INTEGRATION



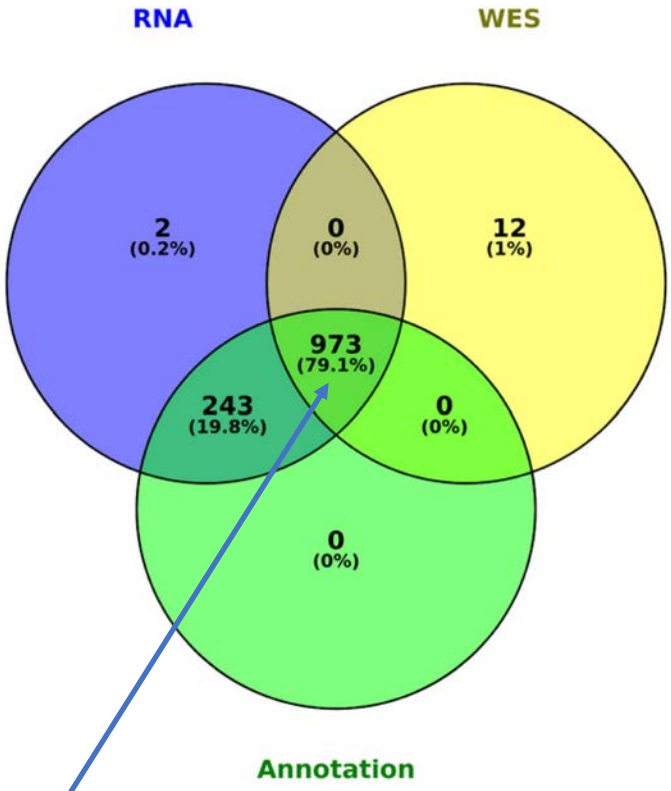
All omics data are mapped to **Ensembl version 91**

ITFoC-DB: CONSORTIUM DATA

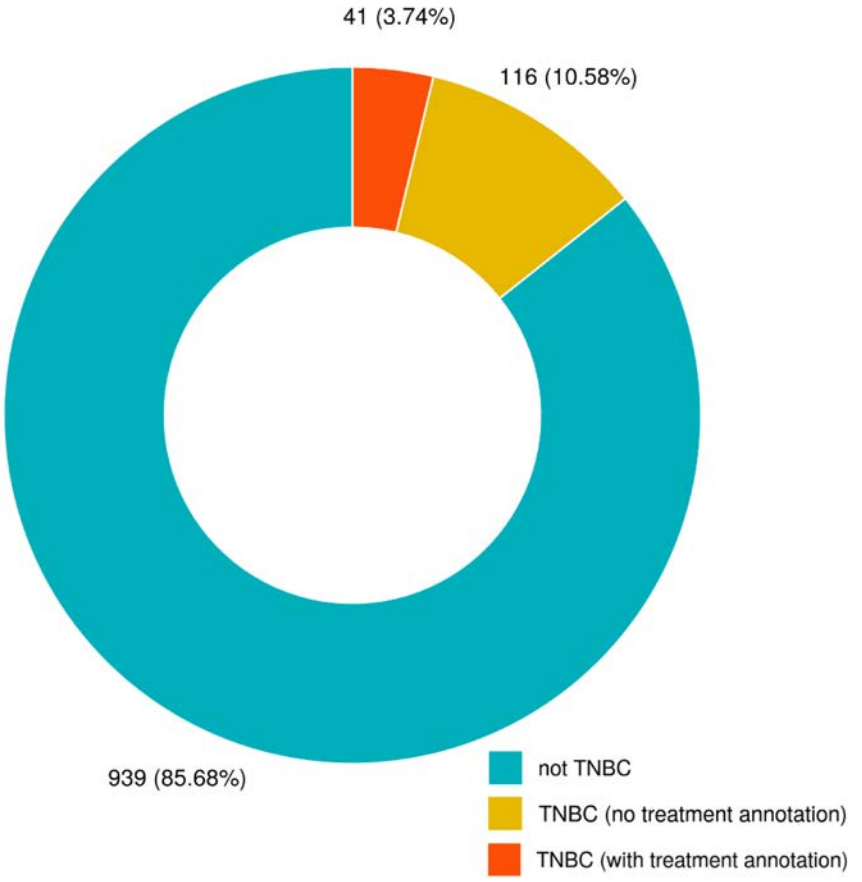
- 47 metabolomics patient samples (NMR, Firenze)
  - Files: full-spectrum and bucketed spectrum text files
- 27 xenograft samples (RNAseq, Riga)
  - 21 samples from Institute Curie, Paris
  - 6 samples from IEO, Milano
  - Files: FASTQ
- Sample annotation
  - Patient clinical variables
  - Tumor type, classification
  - Xenograft treatment response



PUBLIC OMICS DATA: TCGA BRCA SAMPLES



N=973 BRCA samples with transcripome, exome, and clinical annotation



N=41 TNBC samples (4%) with treatment response annotation

Targeted treatments:
Tamoxifen, Avastin, Denosumab, Faslodex

FLAG-ERA

Ugur SEZERMAN
Acibadem University
Biostatistics and Bioinformatics Dept.

ACIBADEM UNIVERSITY MMVII

epigenetiX

MODELLING

Hans Lehrach
Lucian Itu
Lesley Ogilvie
Giancarlo Mauri
Marco Vanoni

C.I.R.M.M.P.
Consorzio Interuniversita
Risonanze Magnetiche
Metallo Proteine

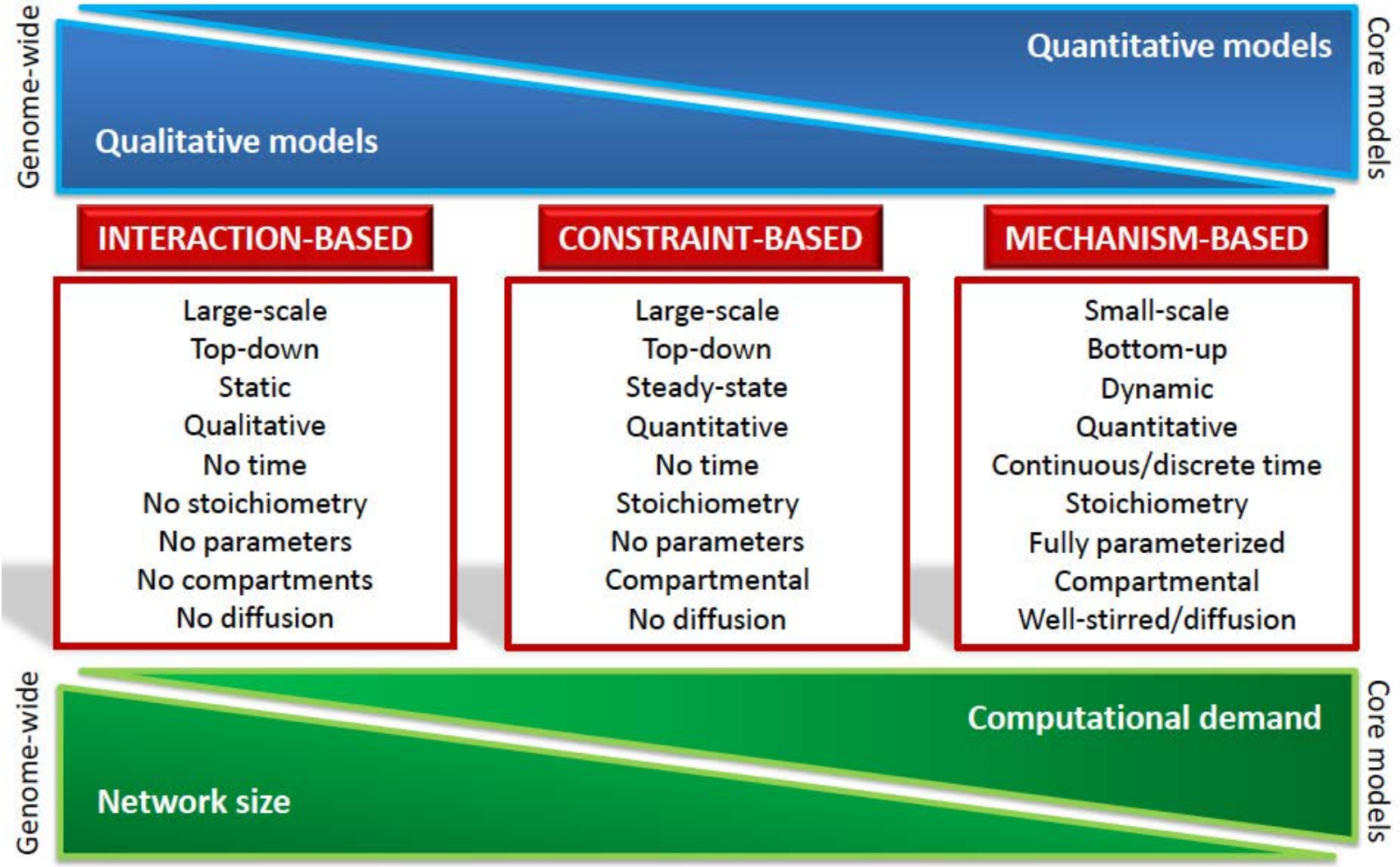
MAX-PLANCK-GESELLSCHAFT

SYSBIO
CENTRE OF SYSTEMS BIOLOGY

Universitatea
TRANSILVANIA
din Braşov

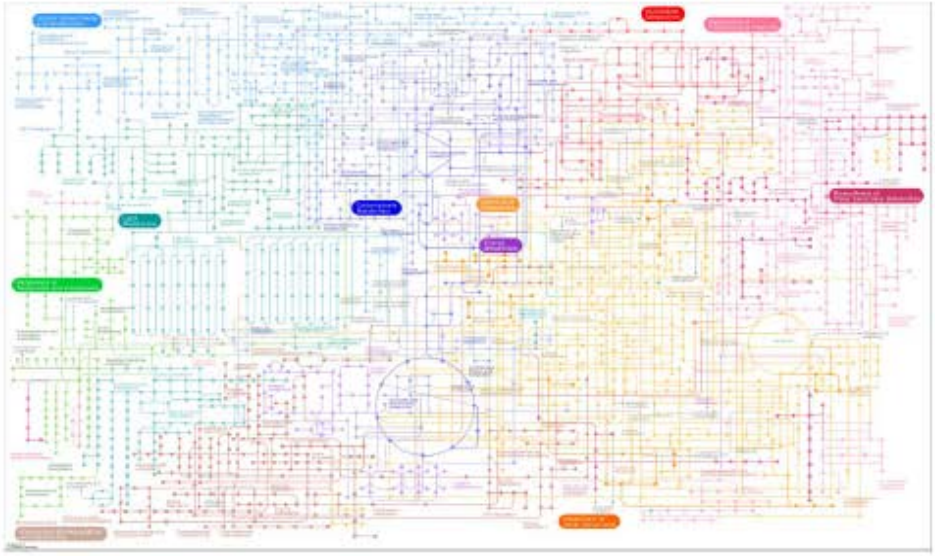
ALACRIS THERANOSTICS

DIFFERENT APPROACHES TO MODELLING

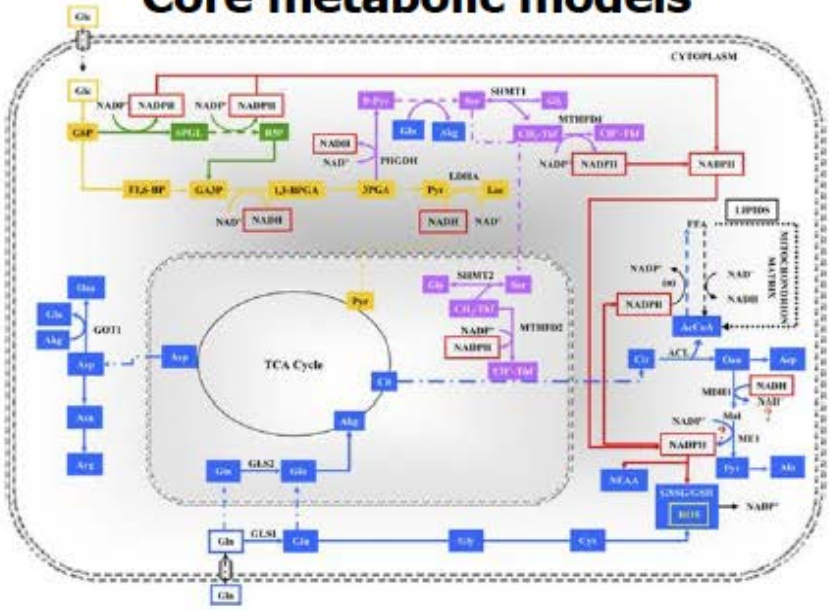


Genome-scale and core metabolic models

Genome-wide metabolic models



Core metabolic models



Alberghina, L., & Gaglio, D. (2014). Redox control of glutamine utilization in cancer. *Cell death & disease*, *5*(12), e1561.

- Large scale (up to 8000 reactions)
- Automatically curated
- Less adapt to flux quantification
- Less control
- Need for less assumption

- Small scale
- High level of abstraction
- Need for more assumption
- Manually curated
- Easier to handle and control

CONSTRAINT-BASED MODELING STRATEGIES

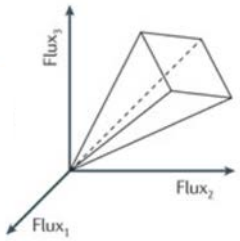
FLAG-ERA

Stoichiometric matrix
S

Steady state assumption
S*v=0

Enzyme capacity constraints
$v_{min} < v < v_{max}$

Feasible solutions space



new

Optimization

- Metabolic engineering
- Maximization of biomass by cancer cells

Monte Carlo Sampling

- Global Network Properties
- Significance of change for each flux between different conditions

Ensemble approach

- Comparison of different metabolic responses
- Analysis of cancer sub-phenotypes

A COMPUTATIONAL TOOL: POPFBA

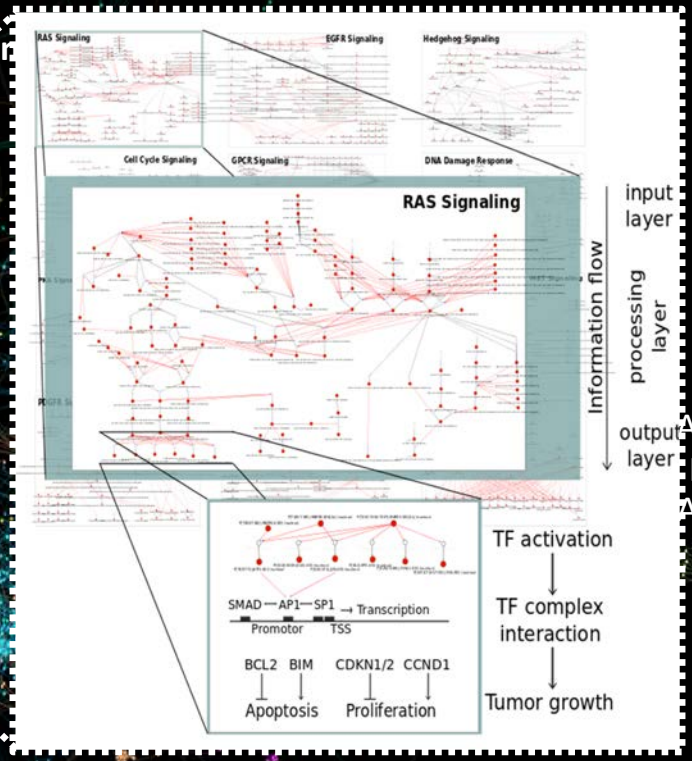
- Extension to classic Flux Balance Analysis, to explore how metabolic heterogeneity and cooperation phenomena affect the overall growth of cancer cell populations
- From a database of single cell RNA-seq data and with constraint based modeling it is possible to simulate flux distributions of a population of cells to analyse their metabolic interactions
- We can constrain the fluxes of metabolic reactions internal to cells on the basis of their activity level (RAS)

C. Damiani et al. popFBA: tackling intratumour heterogeneity with Flux Balance Analysis. Bioinformatics, 33, 2017, i311–i318

MODCELL- LARGE SCALE MECHANISTIC MODEL OF CELLULAR SIGNALLING

FLAG-ERA

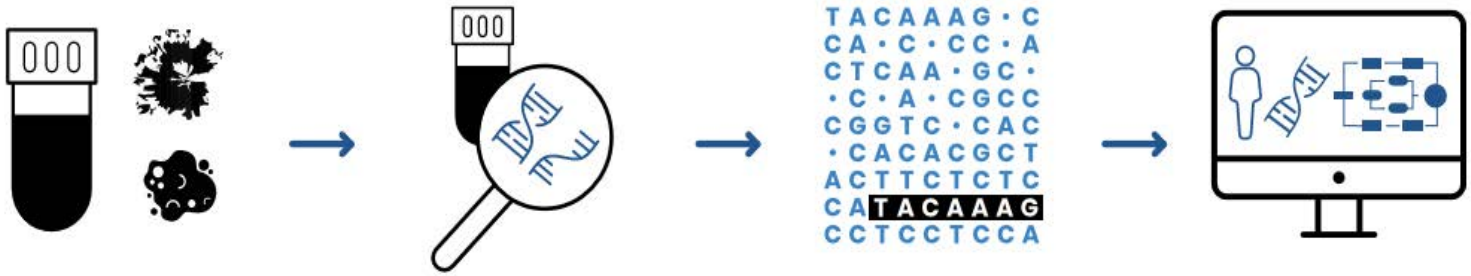
Visualisation of the ModCell cellular signalling network



> 50 signalling pathways (cancer associated)
> 800 genes
> 6000 biochemical species (e.g. protein complexes) interconnected by >9000 reactions
> 440 targeted drugs
> based on ordinary differential equations

MECHANISTIC APPROACHES

Individualise with personal data & drug target information



tumour exome & transcriptome

blood exome

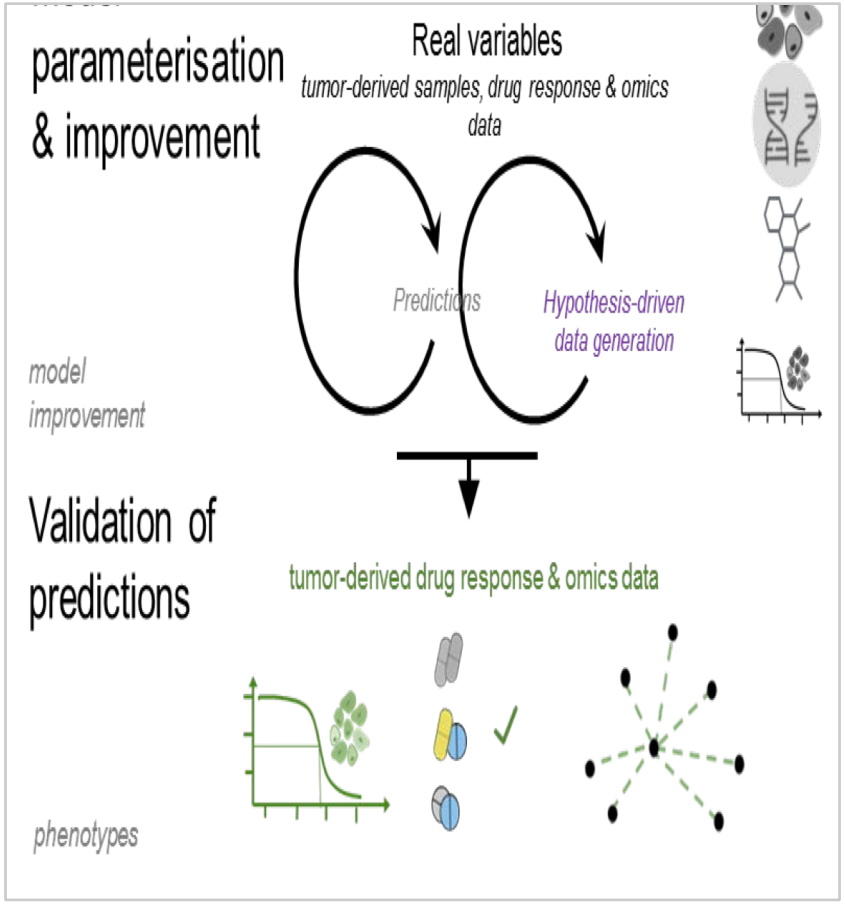
drug target information: **main target** and **binding affinity (K_D)** constants

Translate into systems of ordinary differential equations (ODEs)

Challenges & Next Steps

- Complex models generate a lot of unknown parameters.
- The systems of ODEs can only be solved if we have values for these parameters.
- Development of a parameter optimisation strategy as part of ITFOC

NEXT STEPS: Further development of the parameter optimisation strategy using ITFOC preclinical and clinical data



MACHINE LEARNING APPROACHES

MACHİNE LEARNİNG AND MODELLİNG İN PERSONALİZED CANCER TREATMENT

FLAG-ERA

- Big data coming from omics initiatives (genomics, transcriptomics, metabolomics, etc.) Integrated with clinical data facilitates development of methods to be used in personalized clinical decisions

- Using **machine learning approaches** (Deep Learning, Random Forests, SVMS, Feature Selection etc.) and **modelling approaches** (metabolic network models, ODE based models, mechanistic computer models)

MACHİNE LEARNİNG APPLİCATİONS AVAILABLE FOR PATIENT CARE

FLAG-ERA

Agendia

mammaprint

targetprint

cupprint

Clarient

CLARIENT

Prostate Gene Expression Profile

CLARIENT

Clarient Insight Dx Breast Cancer Profile

Prediction Sciences

PREDICTION SCIENCES

RapidResponse™ c-Fn Test

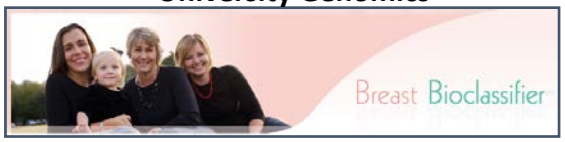
LabCorp

LabCorp

Laboratory Corporation of America

OvaSur

University Genomics



Genomic Health

oncotype DX

Breast Cancer Assay

Veridex

BioTheranostics

BIO THERANOSTICS

A BIOMÉRIEUX COMPANY

Theros CancerTYPE ID

BIO THERANOSTICS

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Breast Cancer Index

Applied Genomics

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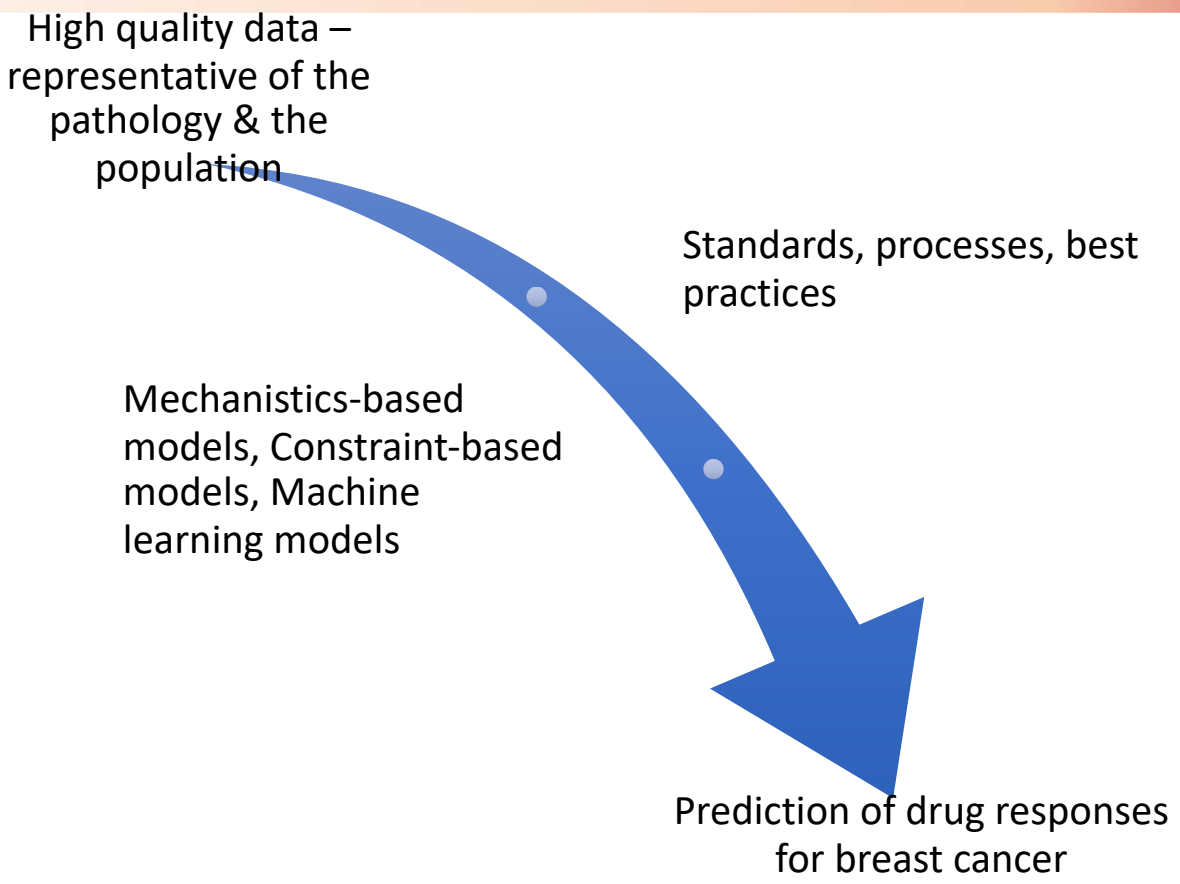
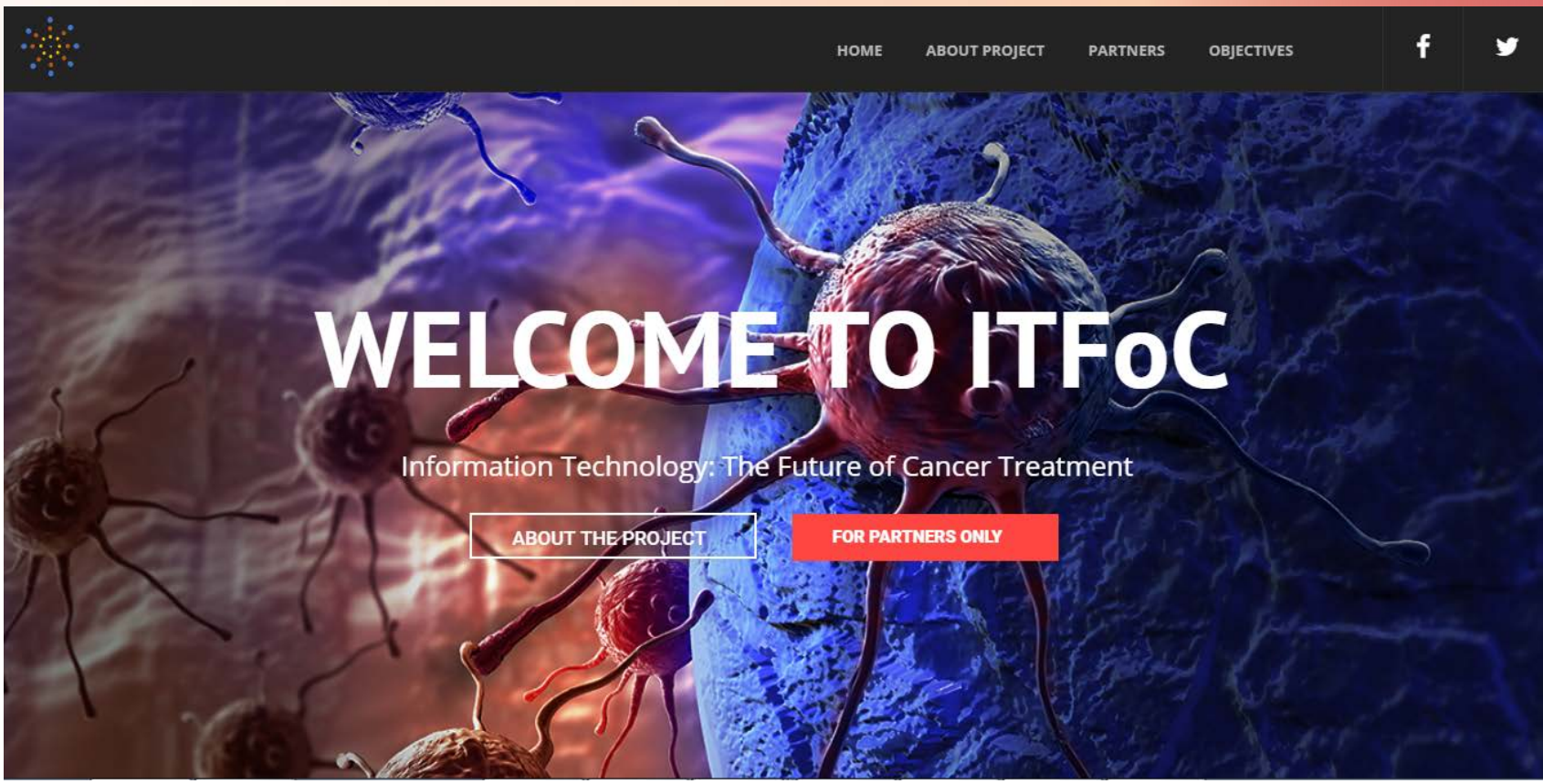
Nora BENHABILES

ITFoC CONTEST
The XTREM PREDICTION CHALLENGE

THE PREDICTION CHALLENGE



WORLD CONTEST OF DRUG RESPONSE PREDICTION, PINK OCTOBER 2021



- ITFoC Website Online : www.itfoc.eu online - public and partner only sections
- Social Media Accounts (Facebook &Twitter)
- Secure area for sharing documents and partner communication is fully functional

Coming soon: the organisation of the world contest on breast cancer drug prediction

- Despite the advances in therapy (approval of immunotherapies for triple negative breast cancer in 2019) many patients still experience an unmet need. New disruptive diagnostic and therapeutical approaches are mandatory in order to increase survival and quality of life
- ITFoC was part of the EU Agenda setting activities during Romanian Presidency of EU Council (2019). As a result, cancer is now a top priority for the European Union (EU Cancer Plan, Mission on Cancer)
- Vision paper in the context of "Value of Data in Oncology" high-level Conference (June 2019) - **"A new vision for cancer in the EU: data, technology and human touch"**

THE ITFoC TEAM
THANK YOU VERY MUCH FOR YOUR ATTENTION

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In particular thanks to the Flag Era secretary and our national research agencies, INCa, and our institutions for their constant support and advices