BENCH-TO-BEDSIDE DRUG REPURPOSING IN PANCREATIC CANCER
&
METABOLOMIC SIGNATURES AS INNOVATIVE LIQUID BIOPSY BIOMARKES

***Alfredo Budillon**, MD, PhD*
Scientific Director
Istituto Nazionale Tumori IRCCS G. Pascalle
a.budillon@istitutopascale.na.it

Fondazione IRCCS
Policlinico San Matteo, Pavia
Venerdì 8, Maggio 2026

ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

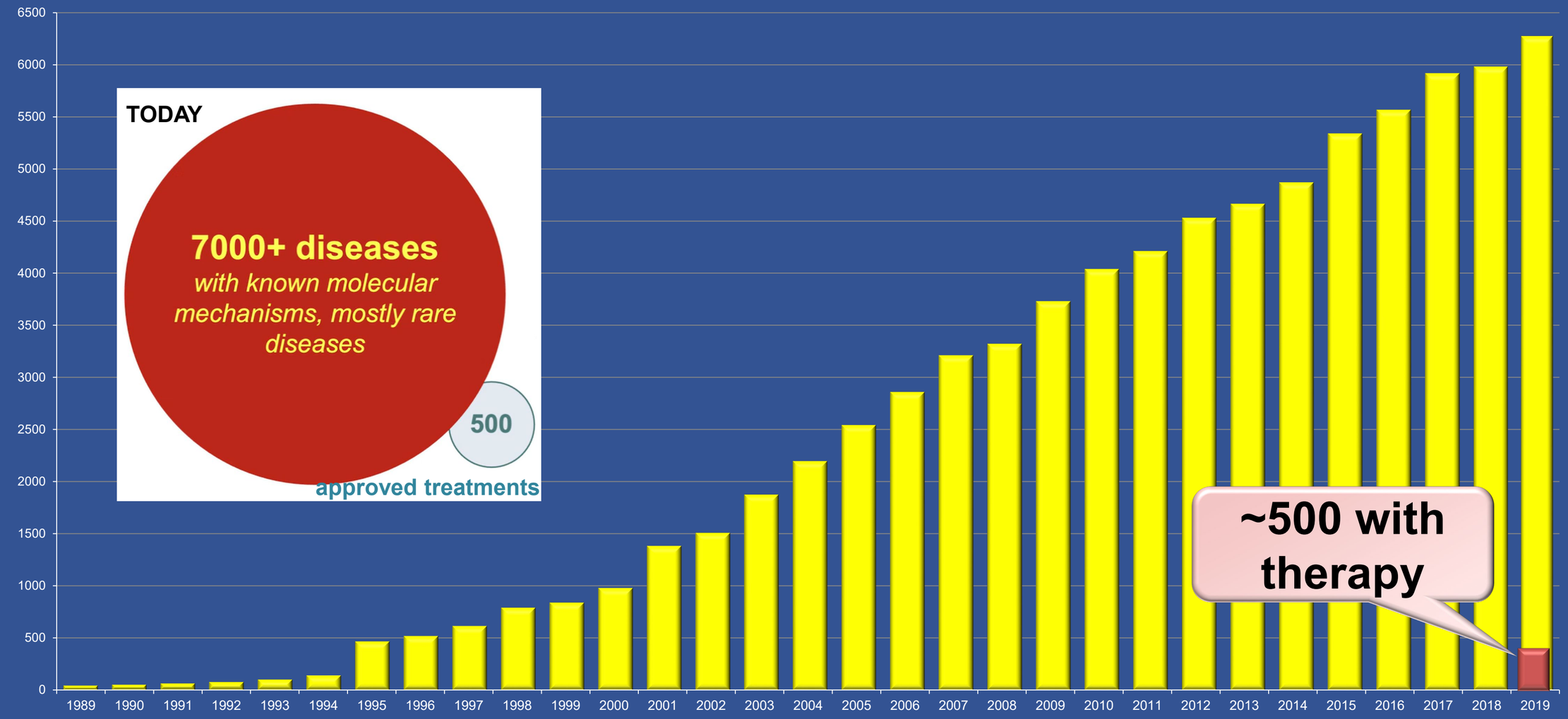
- Drug Repurposing/Repositioning: what, why, when
- REMEDI4ALL European Project
- Pancreatic cancer project – VESPA trial
- Metabolomic biomarkes in liquid biopsy

- ***Drug Repurposing of an approved drug / Repositioning of an investigational drug*** *(DR): a strategy in which existing drugs with a known efficacy, pharmacokinetic and safety profile are tested and validated for use in new therapeutic applications outside of their original clinical indication(s) …..*

- *"**Repurposing" or "repositioning**" an approved drug (under IP coverage) or generic*
- *Drug "**rescue**" (used in previous clinical studies but not further developed and submitted regulatory agency for approval).*
- *Drug "**re-engenering**" new formulation (?)*

- *DR has demonstrated **high utility to serve unmet patient needs** in a broad variety of disease areas (i.e Covid 19)….*

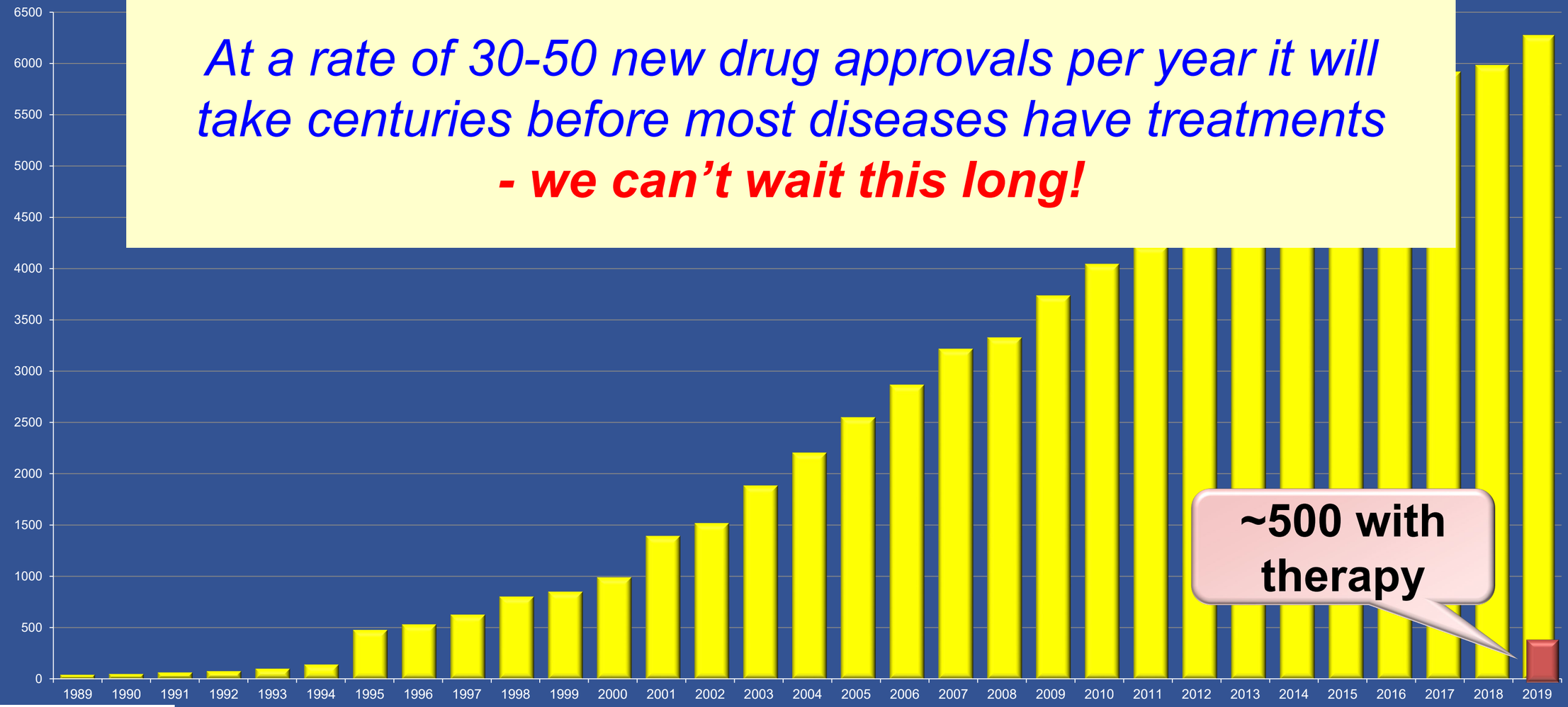
Disorders with known molecular bases



Donald Lo, #iDR24 - borrowed from Chris Austin, NCATS/NIH

Disorders with known molecular bases

At a rate of 30-50 new drug approvals per year it will take centuries before most diseases have treatments
- we can't wait this long!



Donald Lo, #iDR24 - borrowed from Chris Austin, NCATS/NIH

What if we stay with the status quo?

7000 diseases

out of which

500 have treatments

~50 new medicines
approved per year

~1.1 billion[1]

average cost of development per medicine

=

To treat all diseases

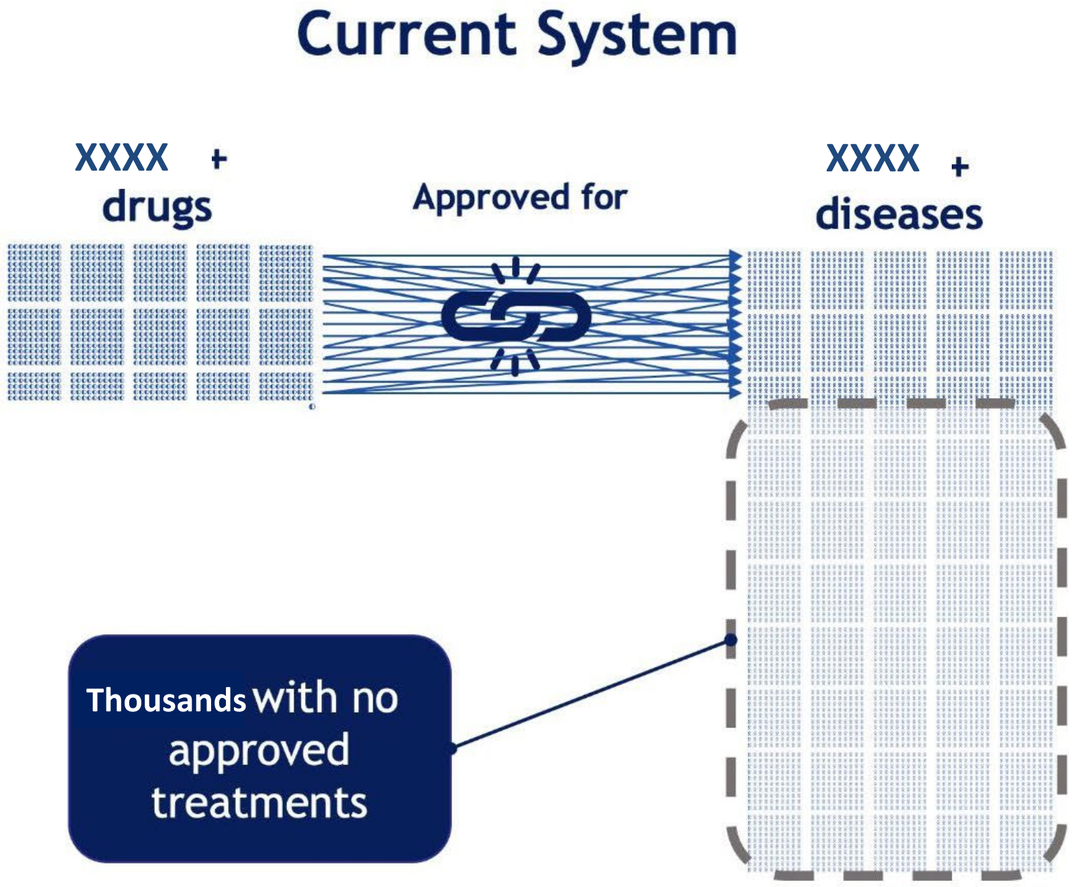
130 years & $ 7.1 TN*

(or twice the GDP of Germany)

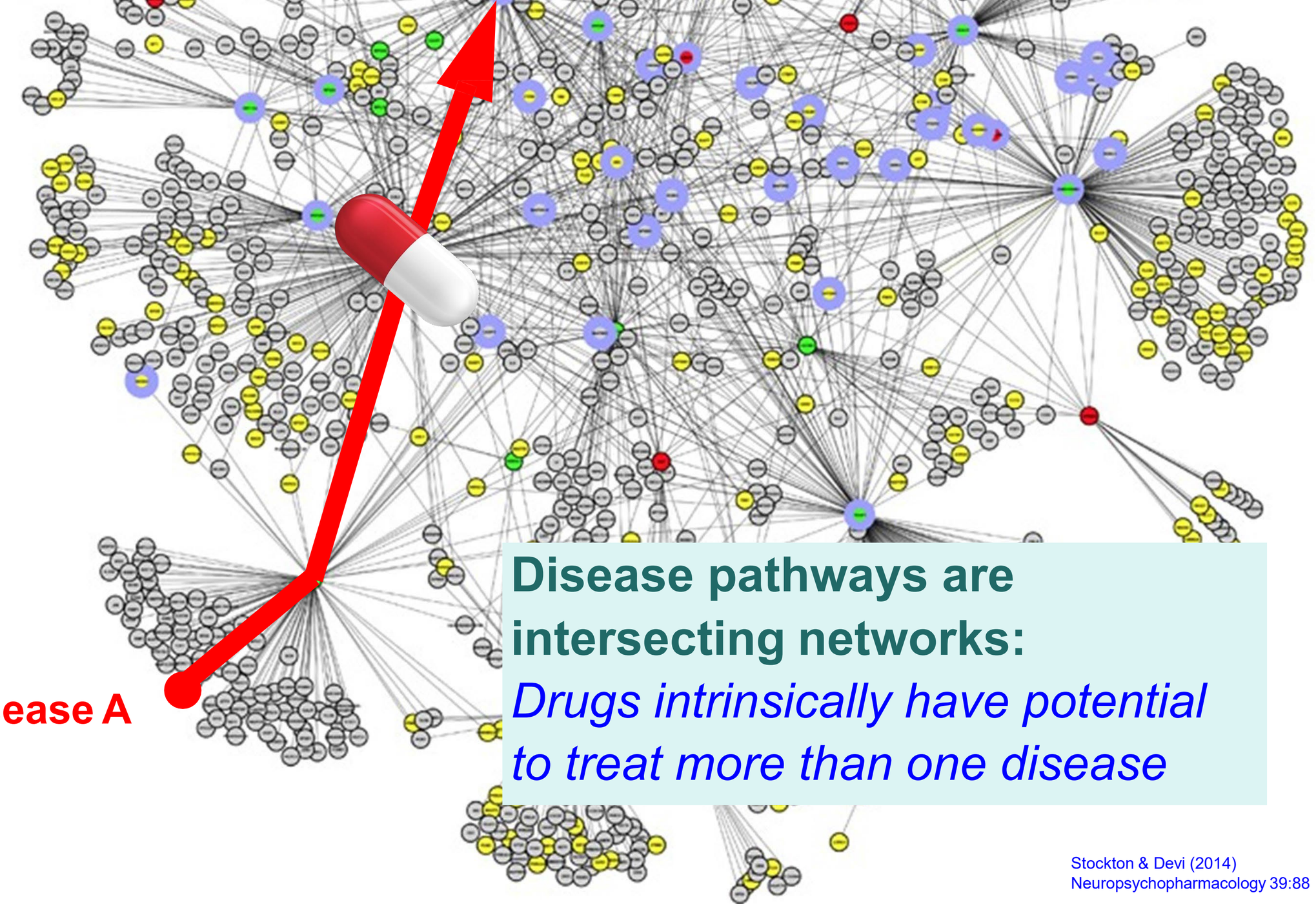
*if each new approved medicine was targeted at one of the diseases lacking treatments

1. Wouters OJ, McKee M, Luyten J. Estimated Research and Development Investment Needed to Bring a New Medicine to Market, 2009-2018. *JAMA.* 2020;323(9):844–853. doi:10.1001/jama.2020.1166

There is tremendous untapped potential within our EMA and FDA-approved medicines



Promise of drug repurposing is to help fill this gap FASTER, CHEAPER, and SAFELY

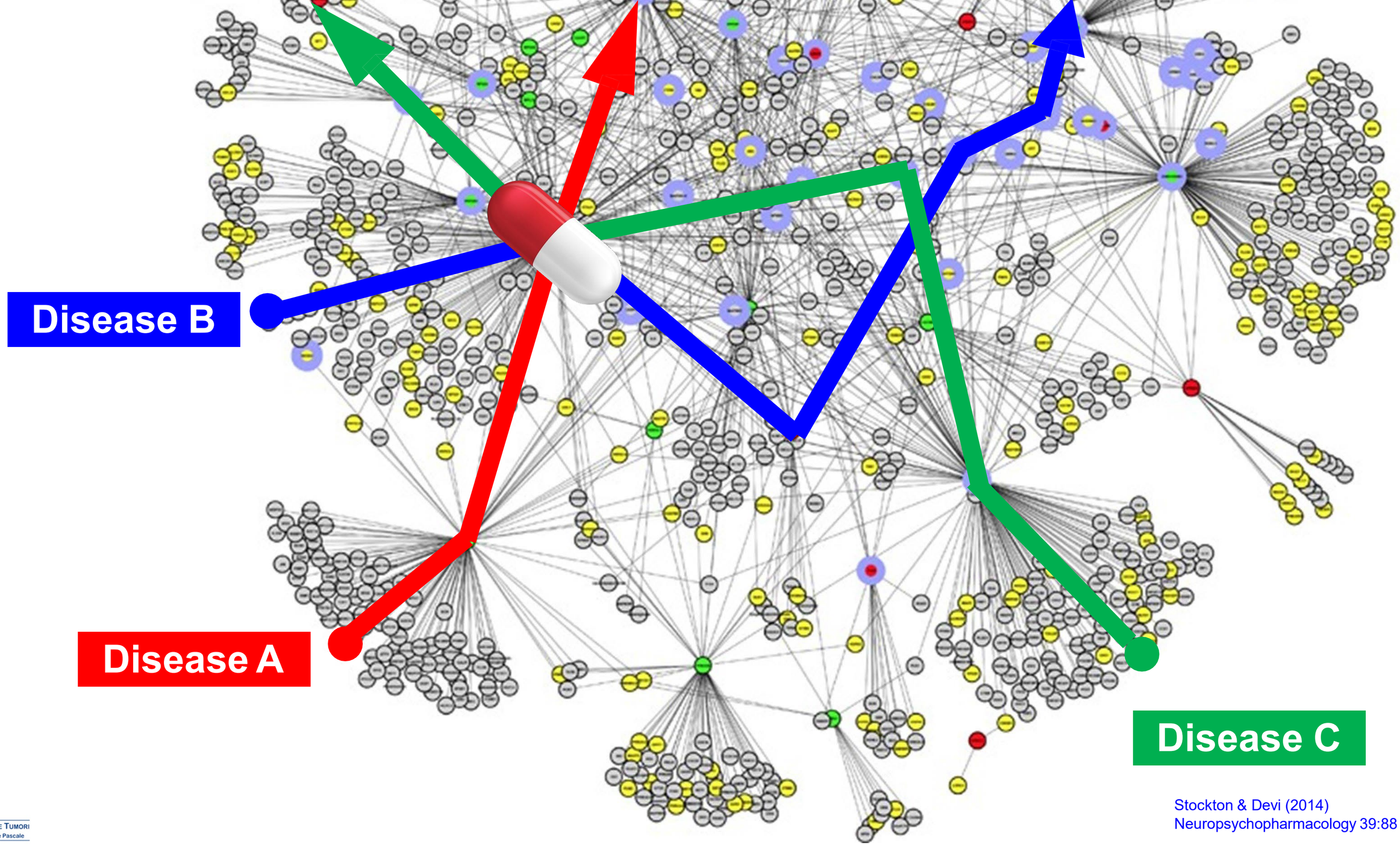


Disease A

Disease pathways are intersecting networks:

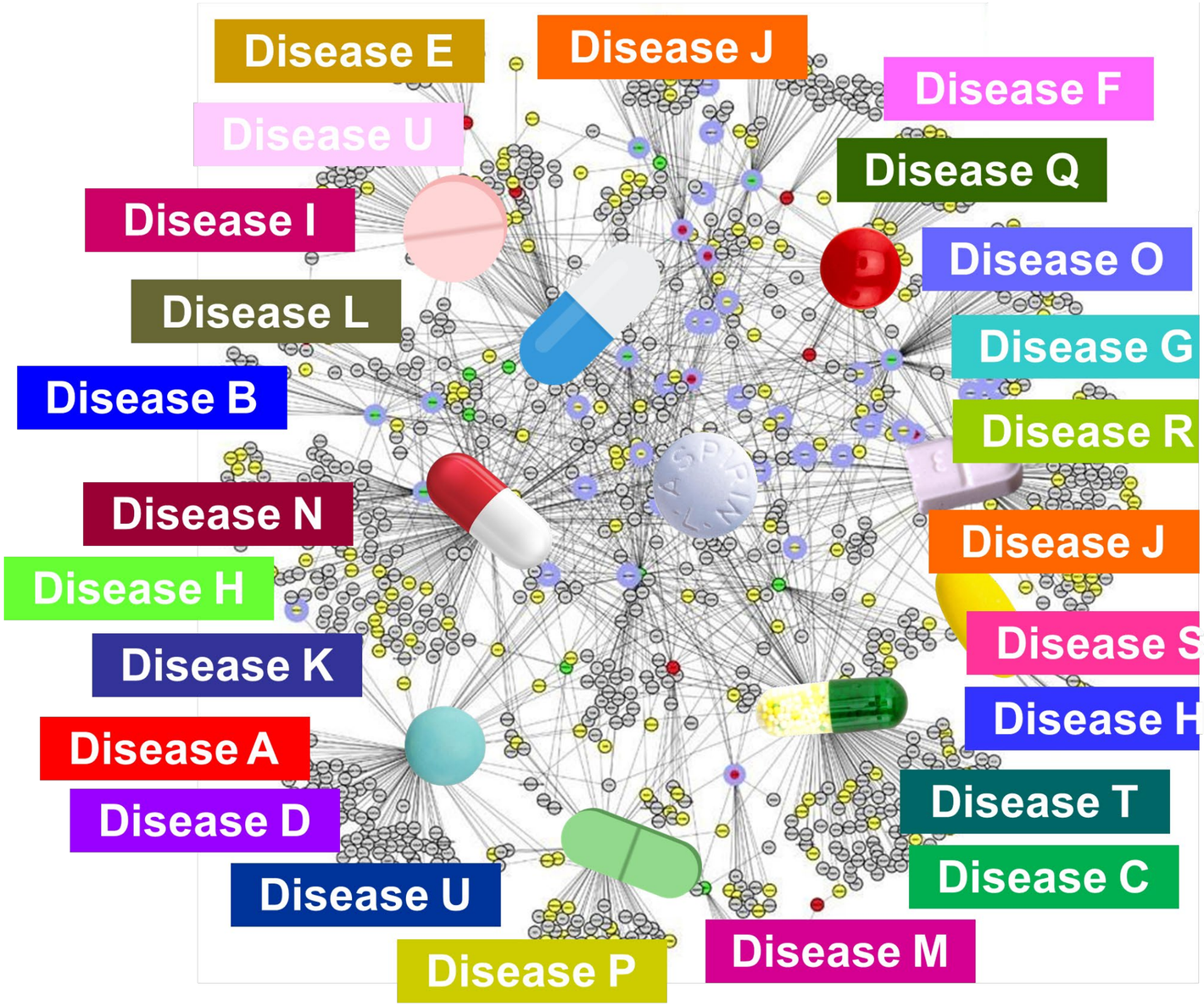
Drugs intrinsically have potential to treat more than one disease

Stockton & Devi (2014)
Neuropsychopharmacology 39:88



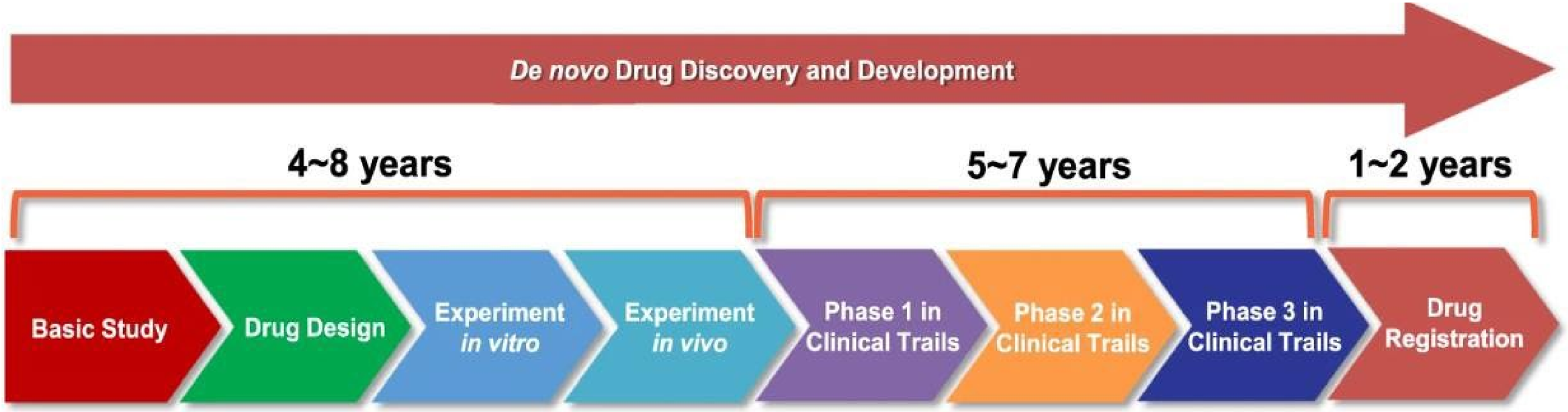
Stockton & Devi (2014)
Neuropsychopharmacology 39:88

Drug repurposing:
Making better use of the drugs we already have



Stockton & Devi (2014) An integrated quantitative proteomics and systems biology approach to explore synaptic protein profile changes during morphine exposure. Neuropsychopharmacology 39:88

Stockton & Devi (2014)
Neuropsychopharmacology 39:88



The rationale behind DR is clear, with **development times and costs** estimated to range from 30-75% lower than that of developing a new chemical entity from scratch.

Drug Repurposing vs. De Novo Drug Development

www.fda.gov

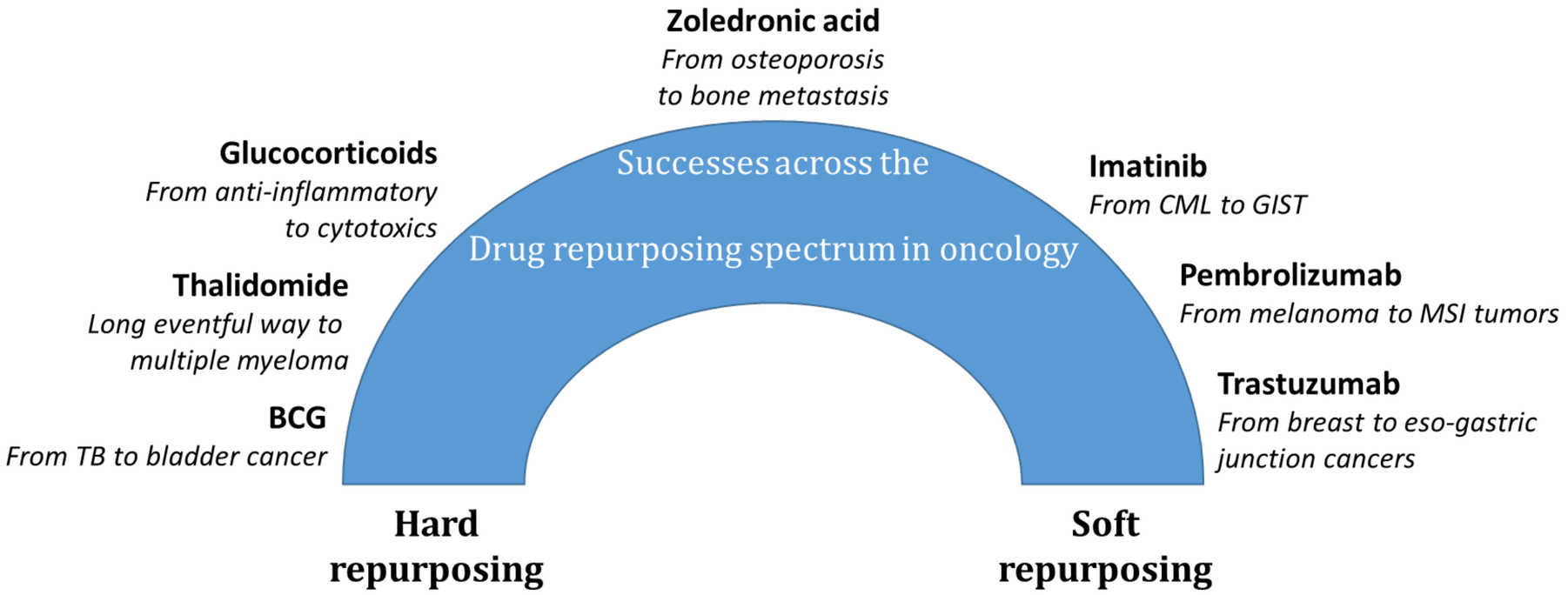
Source: https://www.cureswithinreach.org/

Examples such as **Thalidomide and Sildenafil**, yielded by clinical insight, retrospective clinical analysis and deep understanding of the (poly)-pharmacology, are illustrative of effective repurposing strategies.

Drug	Original use	Today use in clinical practice
Thalidomide	Morning sickness (1950's)	Leprosy, multiple myeloma
Sildenafil	Angina and Hyperetension (1989)	Erectile dysfunction, pulmonary hypertension

blockbuster drug!!!

Drug Repurposing in oncology



Medicines: improving outcomes and value
Repurposing medicines in the NHS in England
Regional Medicines Optimisation Committees Advice
Items which should not be routinely prescribed in primary care
Chief Professions Officers' medicines mechanisms programme
Medicines Value and Access
Innovative Medicines Fund
Guidance on conditions for which over the counter items should not routinely be prescribed in primary care
Medicines optimisation
Support for prescribers

Repurposing medicines in the NHS in England

Did you know?

Repurposed medicines have been used as effective treatments for COVID-19. An example of this is tocilizumab, originally an arthritis drug, that has been shown to support recovery from COVID-19 pneumonia in hospitalised patients and to cut the relative risk of death from the virus by 14%. It is typically used in addition to dexamethasone, another repurposed drug with significant life-saving benefits in the treatment of COVID-19.

Medicines Repurposing programme

The Medicines Repurposing programme identifies and progresses opportunities to use existing medicines in new ways.

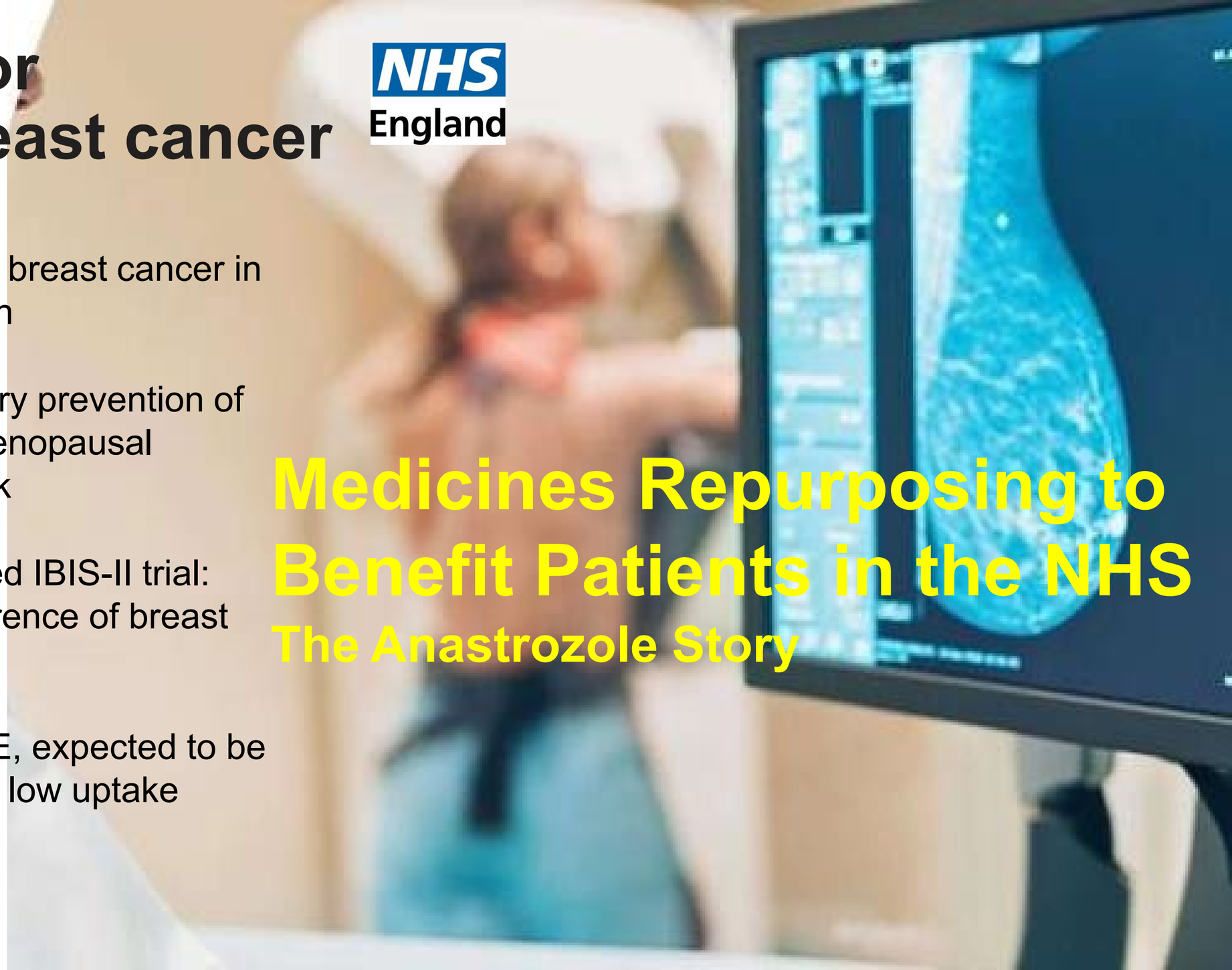
The programme aims to:

- identify and develop opportunities to repurpose prioritised medicines to improve outcomes, patient experience and value for money
- support and advance innovative research into medicines that might be repurposed and adopted into the NHS.

Anastrozole for preventing breast cancer

NHS England

- Initially licensed to treat breast cancer in postmenopausal women
- Repurposed use: primary prevention of breast cancer in postmenopausal women at increased risk
- Double-blind randomised IBIS-II trial: 49% reduction in occurrence of breast cancer
- Recommended by NICE, expected to be cost saving, but historic low uptake



Medicines Repurposing to Benefit Patients in the NHS

The Anastrozole Story

Istituto Nazionale Tumori IRCCS - Fondazione Pascale

MHRA licence variation

Primary prevention of breast cancer in postmenopausal women at moderate or high risk

BBC NEWS

Home UK World Business Politics Tech Science Health Family & Education

Anastrozole: Thousands to be offered drug to prevent breast cancer in England

Lesley Ann Woodhams said she's grateful for every day she gets to take the drug

sky news Home › UK

'Repurposed' drug that could prevent breast cancer to be offered to nearly 300,000 women

The NHS estimates 2,000 cases would be prevented if 25% of eligible women in England take up the offer - and half of those take the drug for the recommended five years.

The new 'remarkable' breast cancer pill (Image: Getty Images/Science Photo Library RF)

NEWS POLITICS FOOTBALL CELEBS TV CHOICE ROYALS

Breast cancer drug Anastrozole costing just 4p a day halves the risk for women

Last call from Italian drug agency (AIFA) on rare disease clearly mentioned drug repurposing …..

L'Agenzia Italiana del Farmaco (AIFA) ha annunciato l'approvazione del nuovo **bando di ricerca indipendente per il 2025**, interamente dedicato alle malattie rare.

L'attenzione sarà rivolta alle patologie a bassa incidenza, che spesso non attraggono investimenti commerciali significativi, e l'obiettivo principale sarà pertanto quello di sviluppare terapie farmacologiche efficaci per le malattie rare, migliorando la salute e la qualità di vita dei pazienti.

IL NUOVO BANDO AIFA DI RICERCA INDIPENDENTE 2025 DEDICATO ALLE MALATTIE RARE

Il bando, deliberato dal Consiglio di Amministrazione dell'Agenzia, prevede un finanziamento complessivo di 10 milioni di euro.

Le aree di intervento rispecchiano le priorità del Piano nazionale malattie rare 2023-2026, ponendo l'accento su innovazione terapeutica, medicina personalizzata, e integrazione tra ricerca clinica e bisogni assistenziali. Nello specifico, il bando AIFA riguarderà **due principali linee di ricerca**:

- Studi preclinici e clinici finalizzati allo sviluppo di **terapie farmacologiche per patologie prive di trattamenti specifici**, inclusi progetti di riposizionamento di farmaci esistenti per nuove indicazioni terapeutiche nelle malattie rare;
- studi preclinici e clinici mirati allo **sviluppo di farmaci orfani derivati dal plasma**.

Il bando sarà pubblicato a giugno nella sezione dedicata alla ricerca indipendente del sito AIFA.

The EU Pharmaceutical legislation – repurposing now and in the future

The Pharmaceutical Package is going to replace:

1. The basic pharmaceutical legislation
   - Directive 2001/83/EC

   and

   - Regulation (EC) 726/2004

2. The specific orphan and paediatric regulations
   - Regulation (EC) 141/2000 concerning orphan medicinal products

   and

   - Regulation (EC) 1901/2006 concerning medicinal products for paediatric use

The proposed package can be found here and contains:

- The **Directive 2023/0132**

Contains all the requirements for authorisation, monitoring, labelling and regulatory protection, placing on the market and other regulatory procedures for all medicines authorised at EU and national level.

- The **Regulation 2023/0131**

Sets specific rules (on top of the ones in the Directive) for medicines authorised at EU level, in particular the most innovative ones. It sets out the rules on coordinated management of critical shortages and security of supply of critical medicines. It also sets out the rules governing the European Medicines Agency (EMA) and includes the provisions on orphan and paediatrics

- **Council Recommendation** on antimicrobial resistance (AMR)

What are the proposed provisions specifically on repurposing?

Article 84 of the Directive:
Data protection for repurposed medicinal products

- Aims to get companies to **invest in repurposing** of generic medicines and generate the evidence needed for repurposing by creating a case for it
- Grants 4 years of data protection for the **additional data** a company generates for certain repurposing projects concerning new indications
- Strictly for **off patent medicines** and cannot be applied to prolong other exclusivities

What are the proposed provisions specifically on repurposing?

Article 48 of the Regulation:
Scientific opinion on data submitted from not-for-profit entities for repurposing of authorised medicinal products

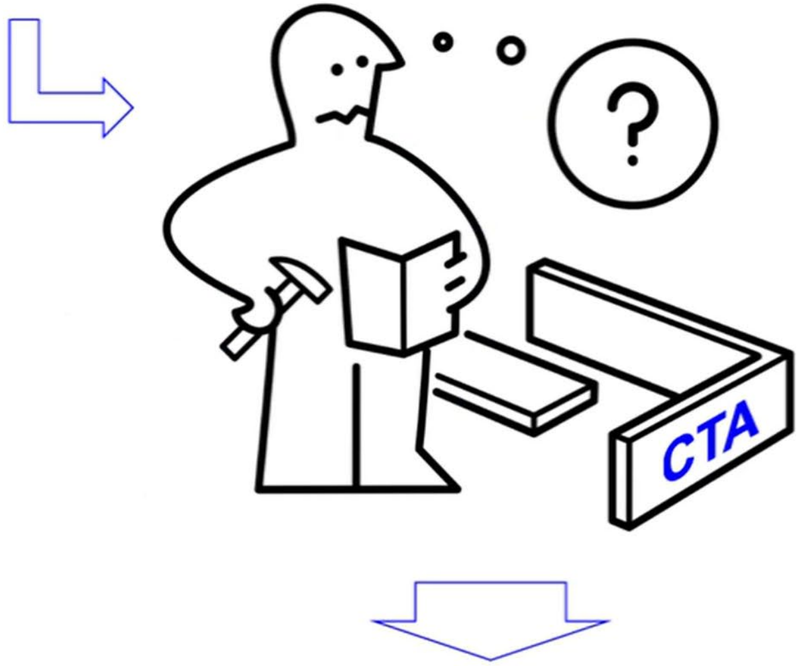
- Allows **not-for-profit entities to submit evidence for a new indication** to EMA or National Competent Authorities for certain products, provided that it fulfils an **unmet medical need** (Definition as per Art 83 of the Directive)
- The EMA will evaluate **all available evidence** and if a decision is **favourable**, then marketing authorisation holders will need to submit a variation and bring it **on-label**
- In contrary to article 84, this does not only apply to off-patent medicines

Problem:

No shortage of hypotheses, but ***most projects never reach patients!***

Why?

Most DR hypotheses generated by people/groups who are undertaking drug development ***for the very first time***…



REPURPOSING OF MEDICINES 4ALL

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

EUROPEAN MEDICINES AGENCY

FDA U.S. FOOD & DRUG ADMINISTRATION

- **Drug Repurposing (DR) is a complex endeavour requiring expertise from multiple disciplines to align for success**.

- the **European DR** eco-system remains at an early stage of development, with **several systemic inefficiencies that hamper the pace and effectiveness of DR**.

- Indeed DR is a common drug development approach in Academia.

Horizon Europe commitment to drug repurposing (DR):

Two major new initiatives launched end 2022/2023

50 Million Euros on two projects !

REPURPOSING OF MEDICINES 4ALL
The European Platform for Medicines Repurposing

RePo4EU

- Complete and accessible DR platform from preclinical develop to approval and clinical practice
- Transform the broader DR ecosystem

- Online platform for precision drug repurposing
- Data hub for key information, training resources, matchmaking and collaboration

These projects have received funding from the European Union's Horizon Europe research and innovation programme

REPURPOSING OF MEDICINES 4ALL

***VISION**: An EU research and innovation ecosystem that facilitates fast, cost-effective and **patient-centric** development and implementation of **repurposed medicines**, meeting high unmet medical needs in any disease area*

Supporting the full value-chain to have maximal impact on the drug repurposing ecosystem

Basic Research → Preclinical development → Clinical trials → Regulatory/ approvals → Marketing/ reimbursement

- WP4 Research data, tools and *in silico* discovery
- WP7 Clinical development & implementation
- WP5 *In vitro* discovery
- WP11 Business planning and communication
- WP8 Market access
- WP6 Preclinical development & validation
- WP9 Funders network & policy

WP1 Patient engagement
WP2 Demo and User Project operations
WP3 Training & capacity building
WP10 Demonstrator projects
WP12 Internationalisation & Networking
WP13 Project Management

25 Partners
25 millions EUR

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442.
Views and opinions expressed in this presentation are those of the author(s) only. They do not necessarily reflect those of the European Union who cannot be held responsible for the information it contains.

REPURPOSING OF MEDICINES 4ALL

Therapeutic Hypothesis **for repurposing a specific drug**

Implement a complete and accessible drug repurposing platform

Demo and User projects

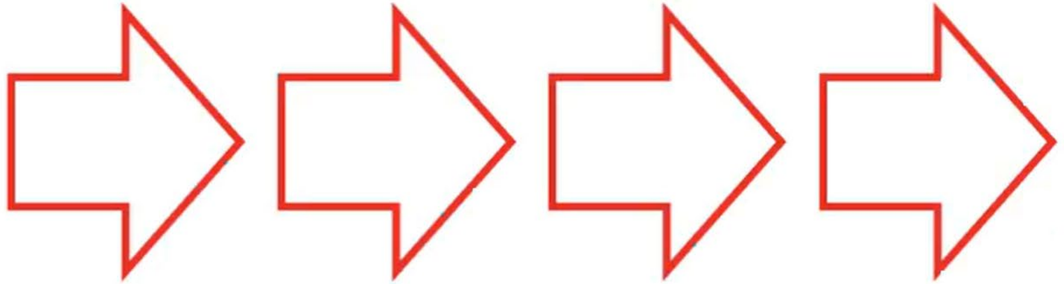
New treatments for patients

25 Partners
25 millions EUR

This project has received funding from the European Union's Horizon Europe research and innovation programme under grant agreement No 101057442.
Views and opinions expressed in this presentation are those of the author(s) only. They do not necessarily reflect those of the European Union who cannot be held responsible for the information it contains.

REMEDi4ALL infrastructure as a "one-stop shop" for drug repurposing

Therapeutic Hypothesis



Regulatory approval and clinical implementation

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Tools and Approaches Supporting the Drug Repurposing Ecosystem

Funded by the European Union

REPURPOSING OF MEDICINES 4ALL

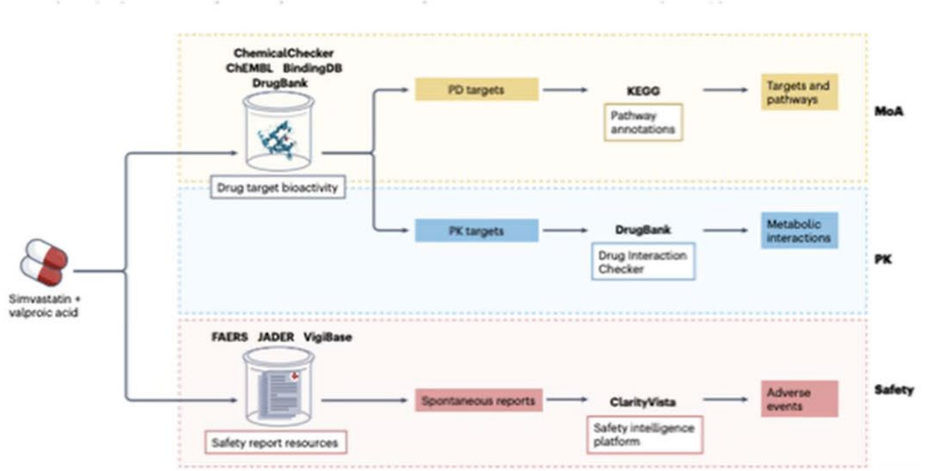


Fig. 4 | Characterizing the simvastatin and valproic acid combination in metastatic pancreatic ductal adenocarcinoma. Pharmacodynamic (PD) and pharmacokinetic (PK) data for both drugs were extracted from drug–target bioactivity databases. Targets that affect drug PD were annotated using KEGG to explore potential pathways and mechanisms of action (MoAs). Targets that affect drug PK were analysed with the Drug Interaction Checker to evaluate potential PK interactions. Concurrently, the ClarityVista safety intelligence platform was used to assess spontaneous reports and anticipate adverse event signals associated with the combination. Supplementary Fig. 10 provides more detailed analyses and results from this case study. FAERS, FDA Adverse Event Reporting System.

Nature Reviews Drug Discovery | Volume 24 | July 2025 | 521–542

Target Validation

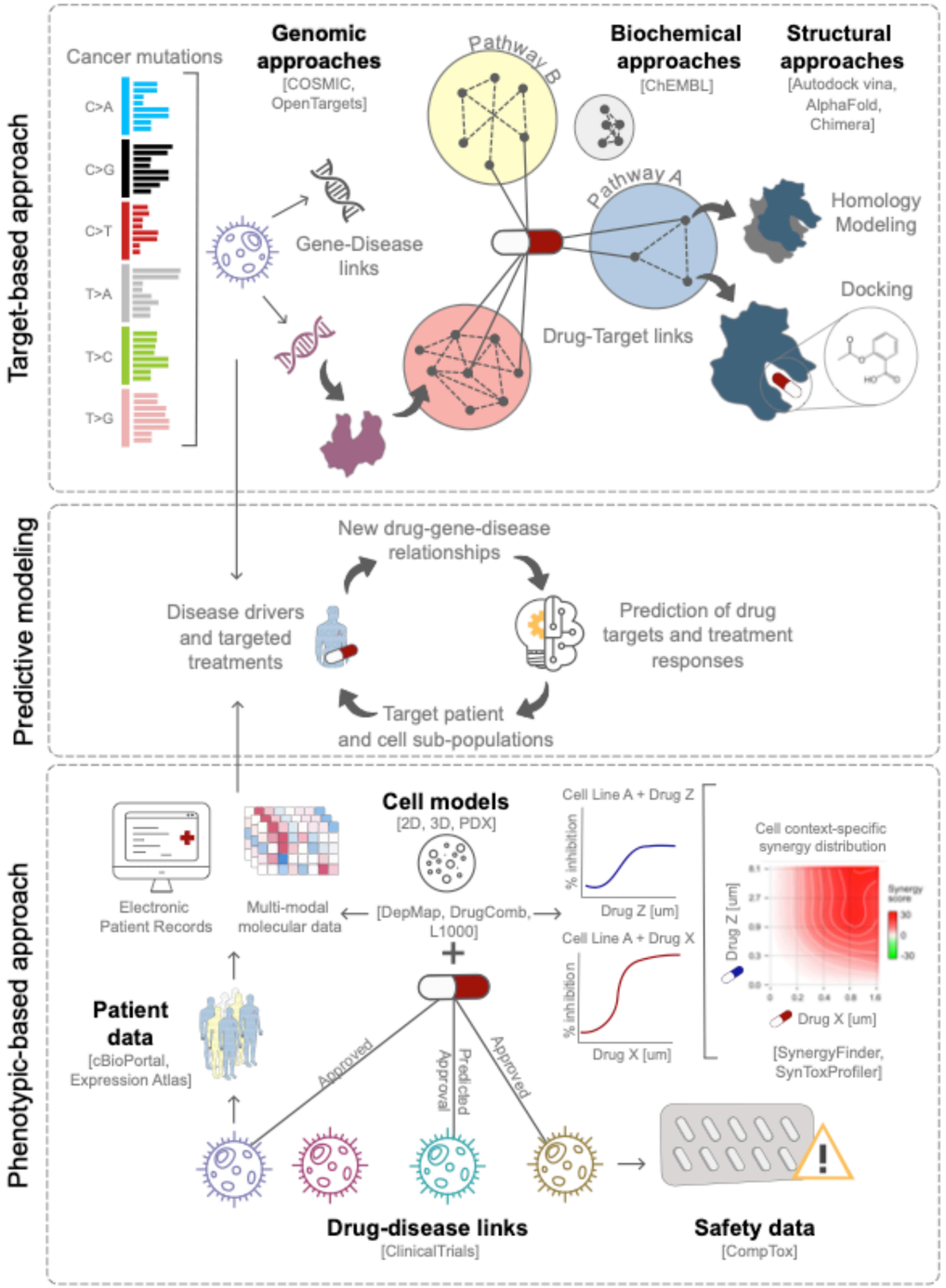
- Integrates in-silico and experimental data
- Confirms target engagement and mechanism
- Supports mechanistic plausibility
- De-risks translation to clinical studies

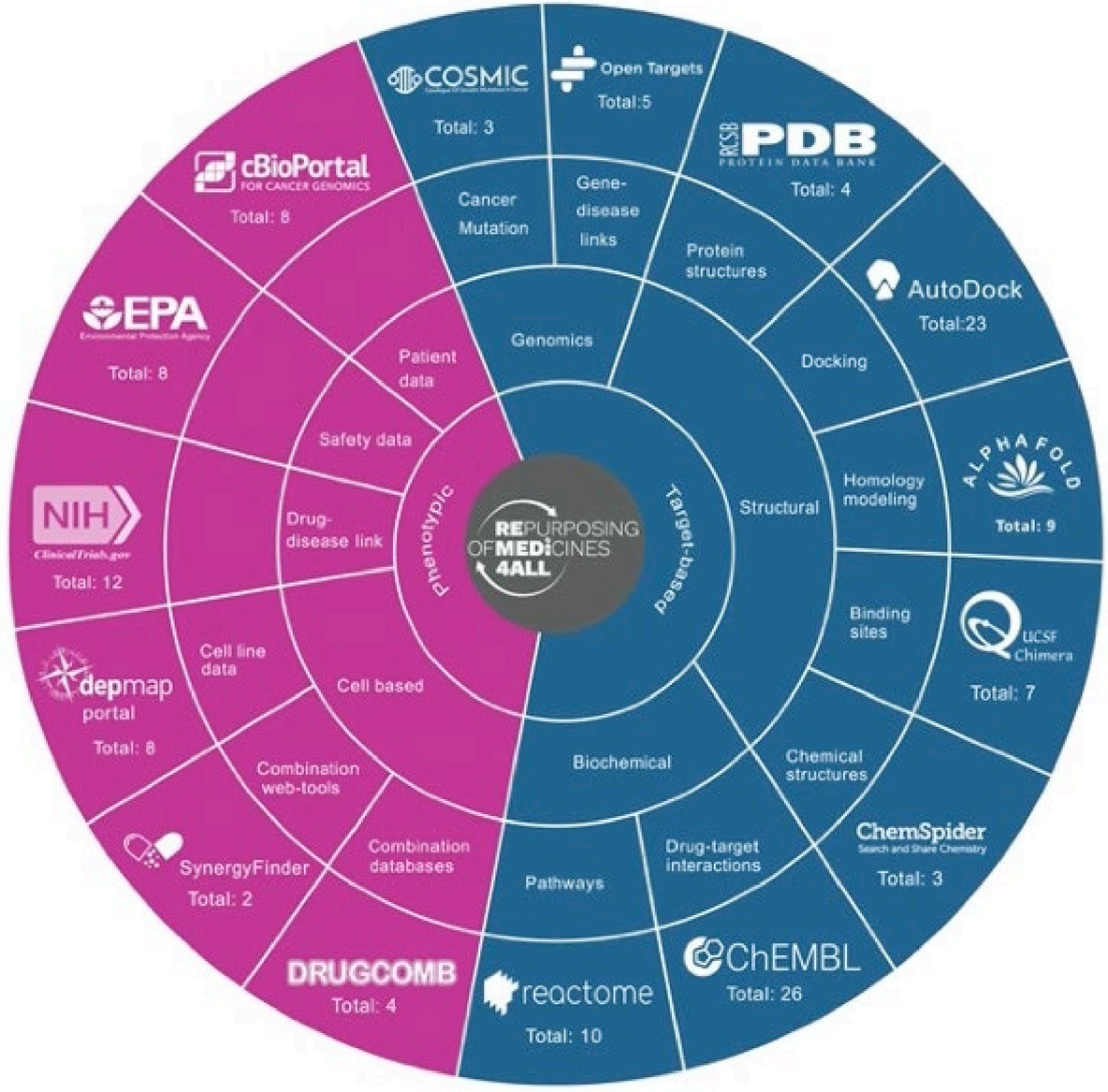
AI and Data Integration

- Computational repurposing catalogue
- Integration of ChEMBL/PubChem/other databases
- Annotation pipelines for compound libraries
- Machine learning models for prioritisation

Reproducibility Framework

- Independent validation of key findings
- Multi-centre experimental confirmation
- Standardised workflows and SOPs
- Improves reliability of repurposing evidence





Tanoli Z. et al, Nat Rev Drug Discov. 2025 Mar 18. doi: 10.1038/s41573-025-01164-x

REMEDi4ALL Tools: Critical Path

- **Target Product Profile (TPP)**
- **Repurposing Development Plan (RDP) template**
- Go/No-Go Milestone Framework
- Target Validation Framework
- Risk Management Plan (RMP)
- Clinical Master Protocol Guidance
- Early HTA Support Service
- Framework for Patient Engagment
- Code of Conduct RDTs
- Catalogue of experimental standards/ workflows
- Dashboard REMEDi4ALL expertise
- In silico DR tools catalogue
- Funding calls database
- Patient Engagement Plan (PEP) template
- Reproducibility framework
- .....
- .....
- .....
- .....
- .....
- .....

30+ preclinical, translational and clinical tools, guidances, frameworks

D10.9 Progress report on implementation of REMEDi4ALL Drug Repurposing tools

Istituto Nazionale Tumori IRCCS - Fondazione Pascale

Funded by the European Union

Repurposing Development Plan

Structured roadmap from hypothesis to implementation

Repurposing Development Plan Template

This **Repurposing Development Plan (RDP)** summarises the development strategy and key studies and decision points to support the repurposing of *<please insert product name>* for the treatment of *<please insert indication>*.

As such, the RDP serves as a reference document that captures the discussions and decisions made by the **Repurposing Development Team (RDT)** as the project is implemented and facilitates timely and effective planning as well as interactions with potential public or private (e.g., commercial) partners.

The RDP is a living document that is reviewed and updated at critical project milestones and decision points. The document history for this project shown below:

Document version	Date signed off	Comments
1.0		First version

1. **Repurposing hypothesis** *(Lead author: project PI, max. 3 pages)*

1.1. Therapeutic hypothesis

Describe the therapeutic hypothesis for the candidate drug to be repurposed and summarize the key studies and data that support this hypothesis.

1.2. Clinical unmet need

Describe the unmet need from the clinical as well as patient perspectives. Summarize engagement that has been done with the clinical and patient community to understand the biggest challenges to treating the disease and to the daily living of patients, and the impact of the proposed drug repurposing strategy on disease management and patient's lives.

1.3. Current therapeutic landscape for the indication

- Identifies gaps and critical studies
- Defines go/no-go milestones
- Guides regulatory and clinical strategy

The RDP template sections:

1. Patient Engagement
2. Scientific Approach
3. Clinical and regulatory approach
4. Project planning and timelines
5. Risk mitigation plan
6. Intellectual property (IP)
7. Early Health Technology (eHTA)
8. Market uptake and clinical practice

Funded by the European Union

Our first four "Demo" customers...

REPURPOSING OF MEDICINES 4ALL

SciLifeLab

Karolinska Institutet

NIH National Center for Advancing Translational Sciences

DNDi

UNIVERSITÄTSMEDIZIN GÖTTINGEN UMG

Fraunhofer

Demo1: COVID/ Pandemic Preparedness

Platform developed and validated

Demo3: Oral tazarotene For MSD

abbvie

Preparing CTA filing

The University Of Sheffield.

UNIVERSITY OF HULL

SERVIZIO SANITARIO REGIONALE EMILIA - ROMAGNA
Istituto Ortopedico Rizzoli di Bologna
Istituto di Ricovero e Cura a Carattere Scientifico

Demo4: Losartan for *osteogenesis imperfecta*

>70% enrolled

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

SaludMadrid

vespa trial

Demo2: Valproate and simvastatin for pancr. cancer

>80% enrolled!

Our first four "Demo" projects...

SciLifeLab

Karolinska Institutet

National Center for Advancing Translational Sciences

DNDi

REPURPOSING OF MEDICINES 4ALL

Demo1:
COVID/
Pandemic
Preparedness

Platform developed and validated

3 out of 3 clinical trials on track to finish on time and within budget

Demo3:
Oral tazarotene
For MSD

abbvie

Preparing CTA filing

SERVIZIO SANITARIO REGIONALE
EMILIA - ROMAGNA
Istituto Ortopedico Rizzoli di Bologna
Istituto di Ricovero e Cura a Carattere Scientifico

Demo4:
Losartan for
osteogenesis imperfecta

>70% enrolled

dMadrid

vespa trial

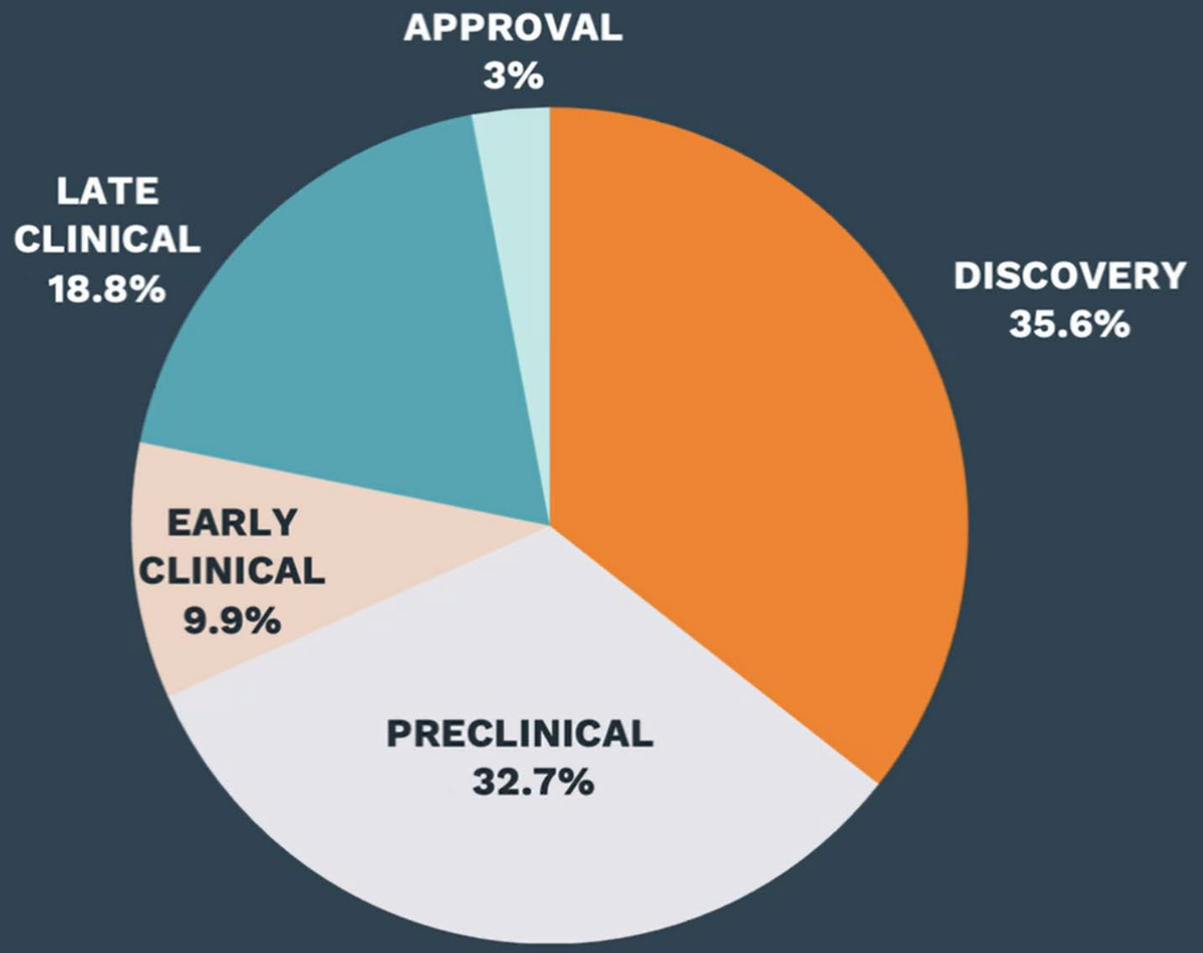
Demo2:
Valproate and
simvastatin for
pancr. cancer

>80% enrolled!

ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

REMEDi4ALL CONCIERGE:

covering all development stages



Slide credit: Alicia Soler

R4ALL PIPELINE: Frontburner projects

	Indication [C] = Confidential	Discovery	Preclinical	Phase 2/ Phase 1-2	Phase3/ Phase 2-3	Approval/ label extension	Reimbursement
Demos	Pandemic preparedness						
	Pancreatic cancer						
	Multiple Sulfatase Deficiency						
	Osteogenesis imperfecta						
Concierge miniprojects	Colchicine – Heart disease						
	Etoposide – HLH syndrome						
	Sorafenib – FLT3 ITD+ AML						
	Metformin – Tuberculosis						
	Tacrolimus - HHT						
	Compound A – Cavernoma [C]						
	Ravicti – SLC6A, STXBP1, SYNGAP						
	Ultra-rare neurodevelopment [C]						
	Ph2 drug – Kv7 encephalopathies						
	Lead ID – MDD [C]						
	Lead ID – Glioblastoma [C]						
	Mucolipidosis II & III						
	YWHAG syndrome						

Funded by the European Union

Doing research with patients, not just to patients.

REMEDi4ALL Patient Engagement framework

REMEDi4ALL is positioning **the patient's voice and experience at the heart of every repurposing project** and empowering them as true co-creators.

Patient Champion

- Offers **unique insight** into a specific disease and the disease community
- **Core stakeholder**
- Represent their community
- Actively participate in our RDTs

Patient Advocacy Groups

- Group of **patients, relatives, carers** or **individual experts**
- **Additional source** of patient insight
- Help **access a more representative** selection of patient experience

Multi-stakeholder meetings

- **Sharing information** and advance learning, promoting dialogue and constructive interaction
- **Facilitating collaborations** between all stakeholders
- **Patient centricity** running as the core narrative

Funded by the European Union

REPURPOSING OF MEDICINES 4ALL
The European Platform for Medicines Repurposing

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Patient co-creation is key for effective drug repurposing

REPURPOSING OF MEDICINES 4ALL

The MOI-A Study: Improving Quality of Life for people living with Osteogenesis Imperfecta

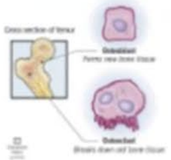
The MOI-A study hopes to:

- Reduce pain
- Reduce fatigue
- Strengthen bone

SCAN TO LEARN MORE

THE MOI-A STUDY AIMS TO:

- Improve **Quality of Life** for people with Osteogenesis Imperfecta (OI)
- Assess if a **repurposed drug** can **reduce bone turnover** in people with OI
- Assess if reducing bone turnover **reduces pain and fatigue**
- Assess if reducing bone turnover **changes bone density**



WHAT IS BONE TURNOVER?

Bone is constantly renewing itself in the body. Special cells called osteoclasts break down old bone allowing another type of specialised cell, osteoblasts, to form new bone and repair broken bone. This cycle of breakdown and repair is called bone turnover.

WHY DOES THIS MATTER IN OI?

In OI a genetic mutation means there is an **imbalance in bone turnover** which results in bone being broken down too fast and not being properly formed. This improper formation and fast breakdown means **bone is fragile and fractures easily**.

It is thought that this change in bone turnover leads to **increased bone pain and increased fatigue** where the body is working harder to repair and replace bone.

People living with OI tell us that pain and fatigue are the symptoms that affect quality of life most, so it is important that we look for treatments that target causes of these symptoms.

- Bisphosphonates are **the only treatment targeting bone turnover** for OI.
- They **reduce the action of osteoclasts**, meaning bone is broken down more slowly.
- Bisphosphonates **aren't right for everyone**, so it is important we explore different treatments.

THE MOI-A STUDY: DRUG REPURPOSING FOR OI

The MOI-A study aims to see if **Losartan**, a drug **usually used to reduce blood pressure**, can help **slow down bone turnover**.

This is called drug repurposing.

Drug repurposing means finding **new ways to use medicines that already exist**; using a drug in a way that was not its original purpose.

Repurposed drugs, like Losartan, are **already used in the clinic**, so are **often safer to use** than a completely new drug.

LO STUDIO MOI-A MIRA A:

- Migliorare la qualità della vita delle persone affette da osteogenesi imperfetta (OI)
- Valutare se un farmaco riposizionato può ridurre il turnover osseo nelle persone con OI
- Valutare se la riduzione del turnover osseo riduce il dolore e l'affaticamento
- Valutare se la riduzione del turnover osseo modifica la densità ossea

Ridurre il dolore

un farmaco solitamente usato per ridurre la pressione sanguigna, può aiutare a rallentare il turnover osseo.

I farmaci riutilizzati, come il Losartan, sono già utilizzati in clinica, quindi sono spesso più sicuri da usare rispetto a un farmaco completamente nuovo.

SCAN TO LEARN MORE

Patient champion facilitates data donation

Alan Finglas

- Original Tazoral® data package
- Preclinical development (safety, toxicity, pharmacokinetics)
- Phase I-III raw data from 1.500 adult probands
- Right-of-reference for regulatory affairs and licensing

Slide credit: Alicia Soler (EATRIS)

International Drug Repurposing Meeting

Funded by the European Union

The REMEDi4ALL project has received funding from the European Union's Horizon Europe Research & Innovation programme under grant agreement No 101057442.

Views and opinions expressed in this presentation are however those of the author(s) only and do not necessarily reflect those of the European Union. Neither the European Union nor the granting authority can be held responsible for them.

REMEDi4ALL Digital Academy

Open-access online learning platform covering drug repurposing from early research through to patient access. For patients, researchers, clinicians, industry, regulators, and policymakers, with a **particular focus on researchers and patient groups.**

The content is organised into ten modules, split into:

- **Core modules, which cover the essential steps** of a repurposing project
- **Foundation modules, which provide additional skills and context**

Each module is broken down into submodules and topics, with:

- **Clear, introductory explanations** to topics, including why the topic matters and what users will learn
- **Practical, accessible language, overall.**
- **"Learn more" sections** that link to useful external resources from other organisations.

>1200 **Total users**

69 **Countries**

Top 5 site visiting countries: **UK**, **Netherlands**, **Spain**, **USA** and **France**.

The REMEDi4ALL project has received funding from the European Union's Horizon Europe Research & I programme under grant agreement No 101057442.
Views and opinions expressed in this presentation are however those of the author(s) only and do not n reflect those of the European Union. Neither the European Union nor the granting authority car responsible for them.

REMEDi4ALL Bootcamps

REMEDi4ALL Bootcamps are **short, in-person focused training events** that provide the chance to meet others in the repurposing field, engage with experts and discuss vital repurposing topics. Carefully targeted to specific audiences, bootcamps provide **focused and intense learning.**

Patient Bootcamp (June 2025 and Autumn 2026)

- **dedicated to empowering patients with the knowledge and tools to actively participate in drug repurposing research**
- **2025 edition:**
  - **35 students** representing 18 different countries and more than 23 different diseases
  - **96%** of attendees would recommend the bootcamp
  - **93%** said that the bootcamp met their expectations
  - **71%** of survey respondents met all their learning objectives

Academic Bootcamp (March 2025 and March 2026)

- **designed to help academic teams navigate the full repurposing pathway and accelerate promisi ideas towards patient impact**
- **2025 edition (2026 data under analysis)**
  - **16 students** including PhD students, postdoctoral researchers, PIs, group leaders, a clinical academic and research coordinator.
  - **100%** of attendees would recommend the bootcamp
  - **93%** said that the bootcamp met their expectations
  - **Average** increase of **1.61** in knowledge scores on a 5-point scale after bootcamp

REMEDi4ALL Hackathons

The REMEDi4ALL Repurposing Hackathon is designed to help early career researchers **learn by doing**. International trainees with an interest in drug repurposing work in small teams in a week-long residential course **to plan the development of a repurposing candidate for a specific patient community**.

3 editions held near Barcelona, Spain:

September 2026: applications open this week

October 2025: 14 early career researchers from 9 countries – overall experience **4.82/5**

May 2024: 15 early career researchers from REMEDi4ALL institutions across Europe (8 different countries) – overall experience **4.58/5**

> "The most valuable aspects of the Hackathon were the **collaborative energy and the diversity of perspectives.** Working alongside people from different disciplines really **broadened my understanding of how complex health challenges can be tackled creatively.**"
> **2025 attendee**

> "Intense, inspiring, enjoyable"
> **2024 attendee**

COMING SOON

REMEDi4ALL FOUNDATION

+

eatris

=

Full infrastructure support for both academic and commercial drug repurposing to bring more treatments to more patients cheaper and faster

Our DR experience……

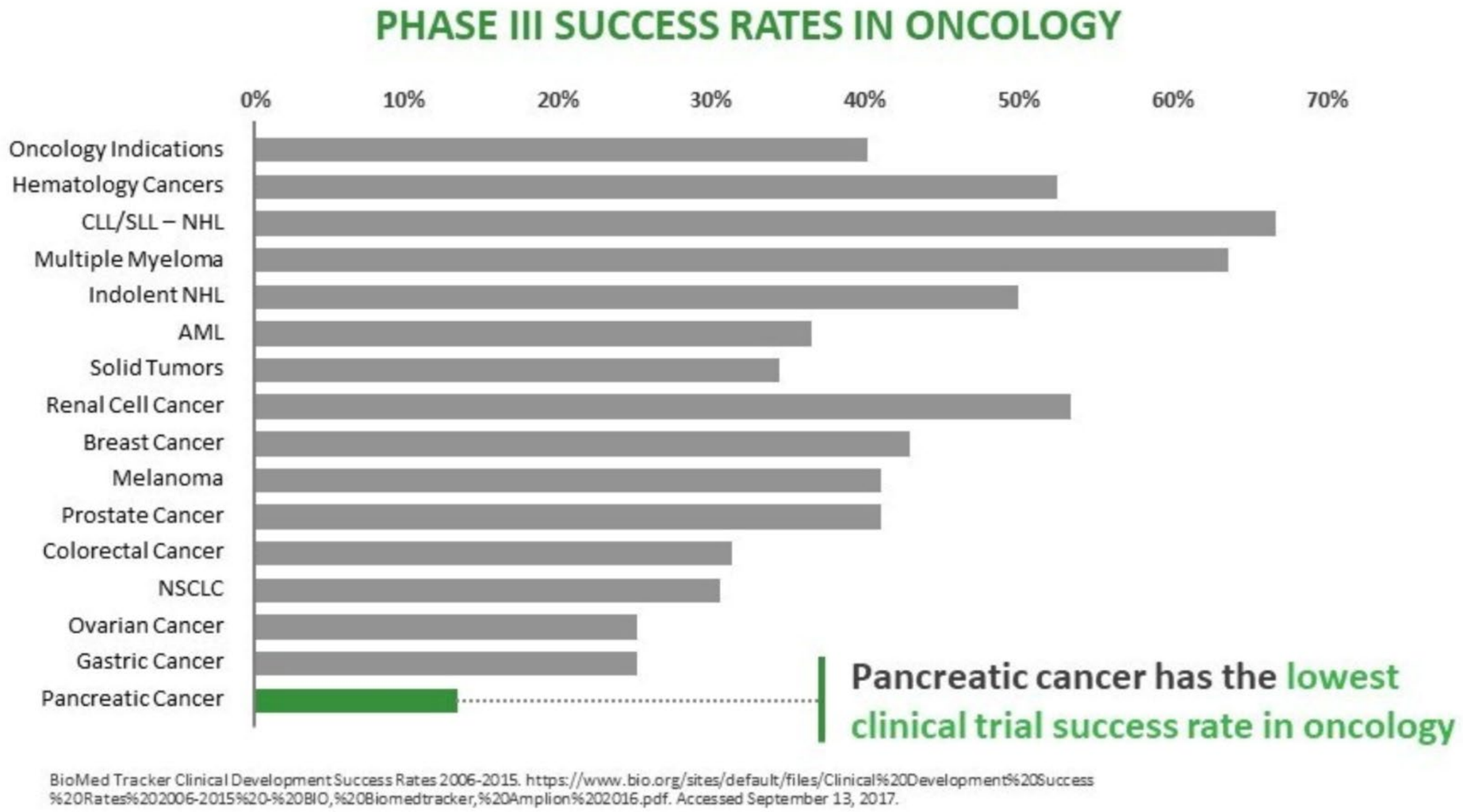
Drugs development : Probability of Phase 1 → Market

Oncology <5%

Table 3: Sucess-% by discipline	Phase I → Phase II	Phase II → Phase III	Phase III → application	Application processing → marketing authorization	All phases
	Success-%	Success-%	Success-%	Success-%	
Hematology	69.6 %	48.1 %	76.8 %	93.1 %	23.9 %
Metabolism	61.8 %	45.0 %	63.6 %	87.5 %	15.5 %
Infectious diseases	57.8 %	38.4 %	64.0 %	92.9 %	13.2 %
Other	63.6 %	38.6 %	60.0 %	88.4 %	13.0 %
Ophtalmopathy	71.6 %	35.5 %	51.2 %	91.1 %	11.9 %
Autoimmune diseases	55.2 %	31.4 %	65.3 %	94.1 %	10.7 %
Allergy	56.4 %	28.3 %	64.7 %	100.0 %	10.3 %
Gastroenterology	46.7 %	34.2 %	57.1 %	90.9 %	8.3 %
Diseases of the respitory system	55.9 %	21.9 %	64.5 %	95.6 %	7.5 %
Psychiatry	52.7 %	26.8 %	56.3 %	91.2 %	7.3 %
Endocrinology	43.3 %	26.6 %	66.2 %	86.3 %	6.6 %
Neurology	47.7 %	26.8 %	53.1 %	86.7 %	5.9 %
Cancer	48.8 %	24.6 %	47.7 %	92.0 %	5.3 %
Cardiovascular diseases	50.0 %	21.0 %	55.2 %	82.5 %	4.8 %
Urology	40.9 %	15.0 %	69.2 %	84.6 %	3.6 %
Median	54.0 %	28.6 %	61.8 %	91.0 %	8.1 %

Source: Thomas et al, 2021: Clinical Development Success Rates and Contributing Factors 2011–2020

Drugs development : Probability of Phase 1 → Market
Oncology <5%



BioMed Tracker Clinical Development Success Rates 2006-2015. https://www.bio.org/sites/default/files/Clinical%20Development%20Success%20Rates%202006-2015%20-%20BIO,%20Biomedtracker,%20Amplion%202016.pdf. Accessed September 13, 2017.

Success rate even lower in PDAC

Original Investigation

April 4, 2024

Clinical Value of Molecular Targets and FDA-Approved Genome-Targeted Cancer Therapies

Ariadna Tibau, MD, PhD[1,2]; Thomas J. Hwang, MD[1,3,4]; Consolacion Molto, MD, PhD[5]; et al

» Author Affiliations

JAMA Oncol. 2024;10(5):634-641. doi:10.1001/jamaoncol.2024.0194

Key Points

Question What is the validity of the molecular targets and clinical benefits of US Food and Drug Administration–approved genome-targeted cancer drugs based on the results of pivotal clinical trials?

Findings In this cohort study, 50 molecular-targeted drugs covering 84 indications were identified. Using an international grading system to evaluate molecular targetability strength (European Society for Medical Oncology Scale for Clinical Actionability of Molecular Targets) and a scale to assess clinical benefit in genome-targeted cancer therapies (European Society for Medical Oncology Magnitude of Clinical Benefit Scale), 24 indications (29%) supported high-benefit genomic-based cancer treatments.

Meaning The therapeutic benefit grading frameworks used in this study can help stakeholders identify therapies with the greatest clinical potential.

…among recently approved genomic based cancer treatments, fewer than one-third demonstrated substantial patient benefits at approval !

quotidianosanità.it

Spesa farmaceutica. Nei primi 10 mesi del 2025 tocca quota 21 miliardi (+6,9%). La diretta sfonda il tetto di 4,2 mld. Il nuovo monitoraggio di Aifa

È quanto emerge dal “Monitoraggio della spesa farmaceutica Nazionale e Regionale gennaio-ottobre 2025” curato dall’Aifa. La convenzionata invece è in avanzo di 461 mln. L’Agenzia: “Trend di crescita in linea con quello osservato negli altri Paesi a economia avanzata dotati di sistemi sanitari pubblici”. IL REPORT

La spesa dei medicinali dispensati attraverso le farmacie aperte al pubblico risulta pari a 7.208,8 milioni di euro (6,39% del FSN), invece, quella relativa ai medicinali acquistati direttamente dalle strutture sanitarie pubbliche risulta pari a 13.605,9 milioni di euro (12,06% del FSN).

Tale spesa è al netto della spesa per farmaci innovativi e per gli antibiotici per il trattamento di infezioni da germi multiresistenti che risulta pari a 654,9 milioni di euro, nonché della spesa per gas medicinali (212,6 milioni di euro).

È quanto emerge dal “Monitoraggio della spesa farmaceutica nazionale e regionale gennaio-ottobre 2025” presentato al Consiglio di Amministrazione dell’AIFA.

In totale la spesa farmaceutica (acquisiti diretti + convenzionata) nei primi 10 mesi dell’anno si attesta a 21 miliardi e 27 milioni di euro, con uno scostamento dal tetto programmato pari a 3,77 miliardi di euro. Rispetto ai primi 10 mesi del 2024 la spesa cresce di 1,36 miliardi (+6,9%).

AIFA
AGENZIA ITALIANA DEL FARMACO

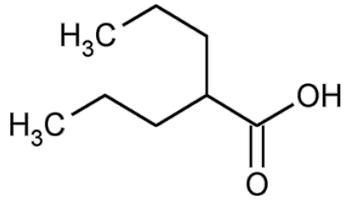
22.04.2026

Monitoraggio della Spesa Farmaceutica Nazionale e Regionale Gennaio-Ottobre 2025

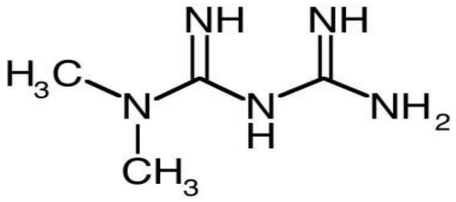
Adempimento AIFA ai sensi della Legge 222/2007 e della Legge 135/2012, successivamente modificata dalla L. 232/2016 e dalla L. 145/2018 condotto sulla base dei dati di spesa convenzionata e delle DCR acquisite dalle Regioni, nonché dei dati acquisiti dall’NSIS del Ministero della Salute, relativi alla tracciabilità del farmaco (DM 15 luglio 2004).

DR-ongoing studies

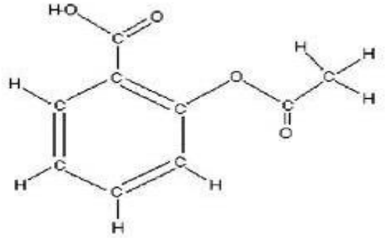
- There is a clear rationale for seeking combinations of agents—both repurposed and standard oncological drugs—which together work to attack multiple aspects of the tumour, and the microenvironment.
- We decided to repurpose generic drugs (also based on epidemiology evidences) to add to existing regimens and protocols to improve clinical efficacy with lower toxicity and at lower cost.



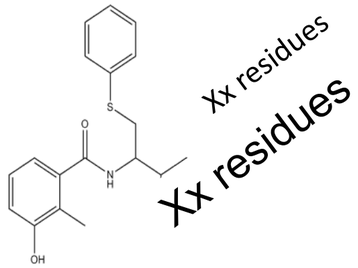
Valproic acid (antiepileptic)



Dimethylbiguanide (metformin, antidiabetic)

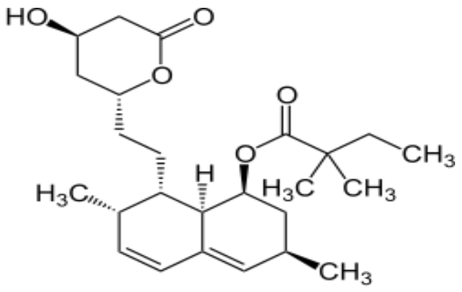


Acetylsalicylic Acid (Aspirin)

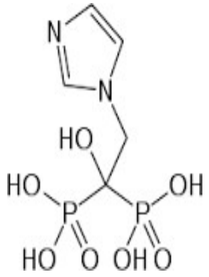


Xxx antiviral

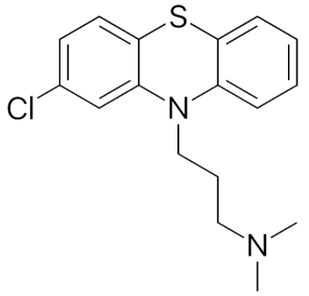
& .....



Statins (cholesterol lowering)



Zoledronic acid (bone disease drug)



Chlorpromazine

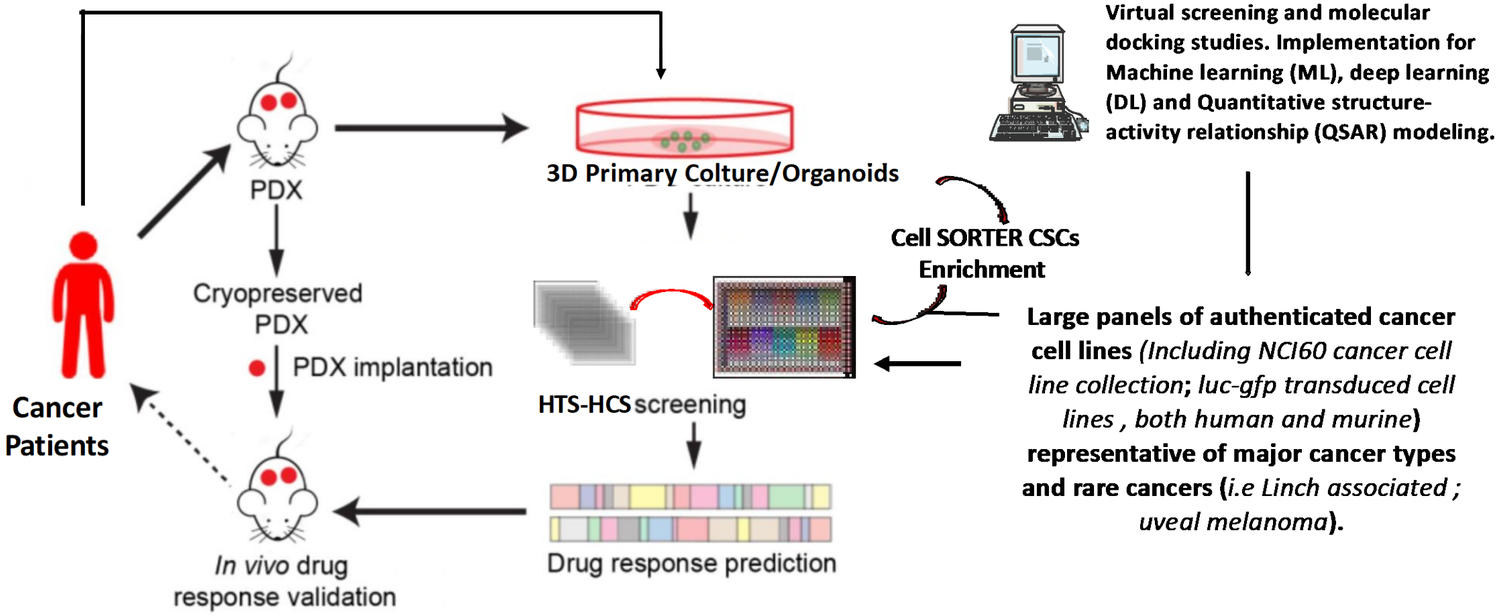
(schizophrenia, bipolar disorder, and acute psychosis)

& .....

High-throughput screening (HTS) & High-content screening (HCS) Platform

MERCOGLIANO LABORATORIES

DRUG DISCOVERY- DRUG REPURPOSING PROJECTS



Virtual screening and molecular docking studies. Implementation for Machine learning (ML), deep learning (DL) and Quantitative structure-activity relationship (QSAR) modeling.

Large panels of authenticated cancer cell lines *(Including NCI60 cancer cell line collection*; *luc-gfp transduced cell lines , both human and murine*) **representative of major cancer types and rare cancers (***i.e Linch associated ; uveal melanoma***).**

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

IEO Istituto Europeo di Oncologia

IMN ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI - IRCCS

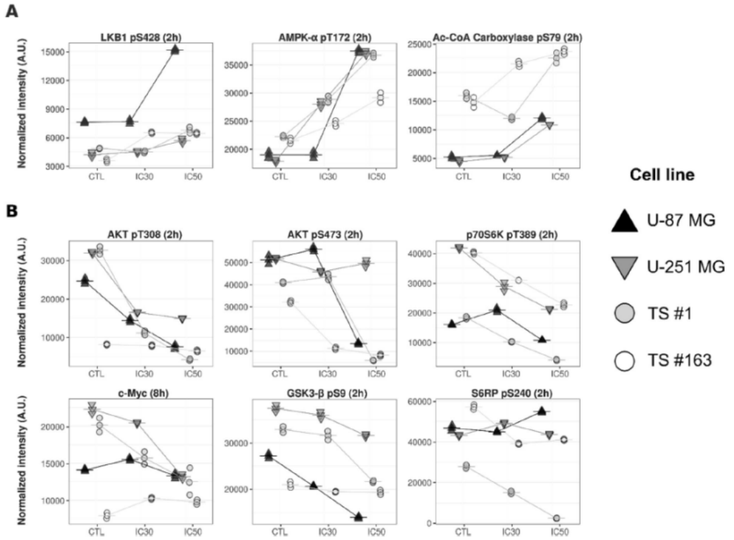
OSPEDALE SAN RAFFAELE

ALLEANZA CONTRO IL CANCRO

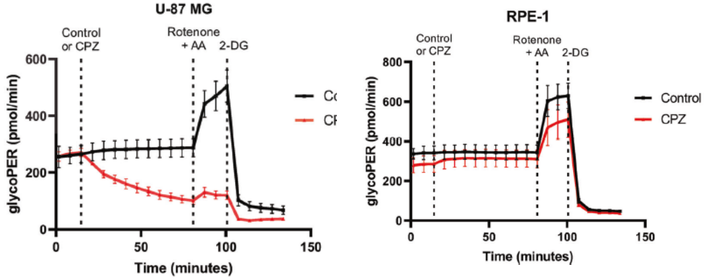
Chlorpromazine affects glioblastoma bioenergetics by interfering with pyruvate kinase M2

Cell Death and Disease (2023)14:821

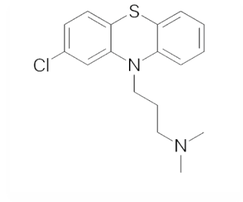
Claudia Abbruzzese[1,13], Silvia Matteoni[1,13], Paola Matarrese[2], Michele Signore[3], Barbara Ascione[2], Elisabetta Iessi[2], Aymone Gurtner[4,5], Andrea Sacconi[6], Lucia Ricci-Vitiani[7], Roberto Pallini[8], Andrea Pace[9], Veronica Villani[9], Andrea Polo[10], Susan Costantini[10], Alfredo Budillon[11], Gennaro Ciliberto[12] and Marco G. Paggi[1]✉

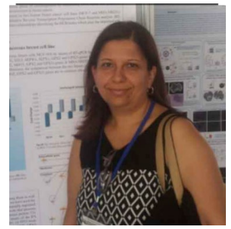


Reverse-Phase Protein microArrays (RPPA) showed that CPZ treatment led to a constant increase of the autophagic response and an inhibition at several levels of the PI3K/AKT/mTORC1 anabolic pathway

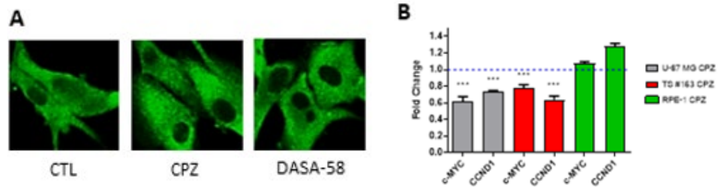


The extracellular lactate determinations (glycoPER) show that CPZ interferes with glycoPER and OCR in GBM cells (U-87 MG) while affecting the non-cancer RPE-1 cells to a lesser extent.

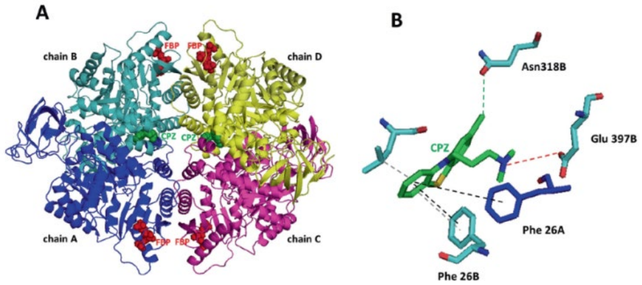




Susan Costantini



CPZ induces a drastic reduction of nuclear (dimeric) PKM2 amount in GBM cells but not in non-cancer RPE-1 cells and alters the transcriptional pattern downstream of nuclear PKM2



CPZ binds PKM2 tetramer in the same binding pocket used by other known activators

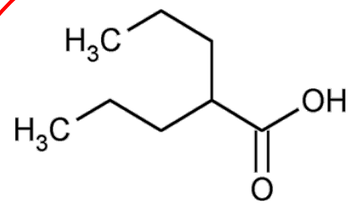
Proof-of concept RACTAC phase 2 Study . *A.Pace et al. Front Oncol. 2023 Dec 14:13:1320710. doi: 10.3389/fonc.2023.1320710. eCollection 2023*

Integrated Screening for Small Molecules Interfering with PKM2: A Drug Repurposing Strategy Against Glioblastoma

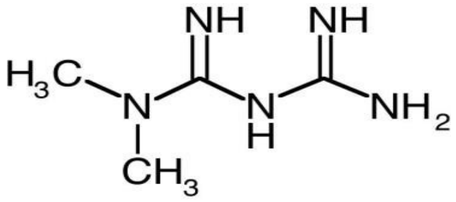
Costantini S et al. J Transl Med. 2025 Dec 8;23(1):1388

DR-ongoing studies

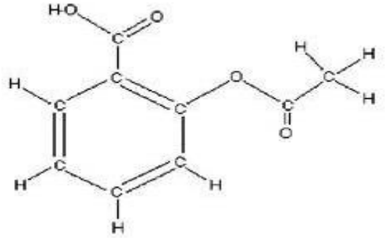
- There is a clear rationale for seeking combinations of agents—both repurposed and standard oncological drugs—which together work to attack multiple aspects of the tumour, and the microenvironment.
- We decided to repurpose generic drugs to add to existing regimens and protocols to improve clinical efficacy with lower toxicity and at lower cost.



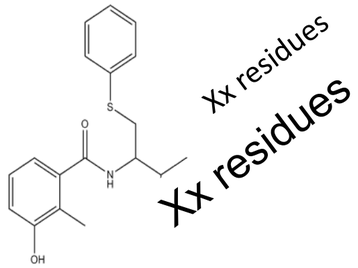
Valproic acid (antiepileptic)



Dimethylbiguanide (metformin, antidiabetic)

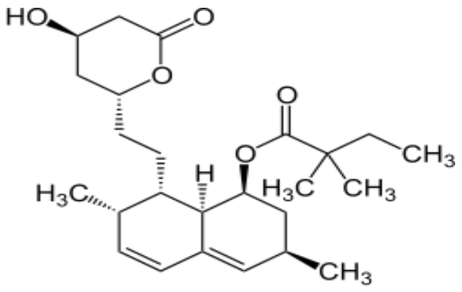


Acetylsalicylic Acid (Aspirin)

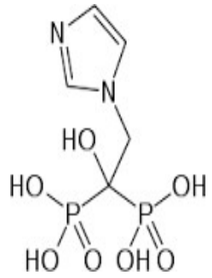


Xxx antiviral

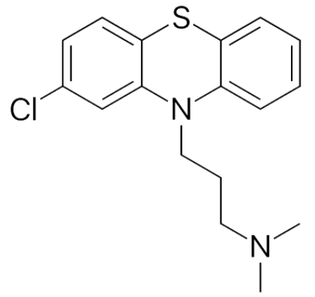
& .....



Statins (cholesterol lowering)



Zoledronic acid (bone disease drug)

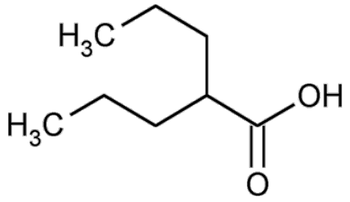


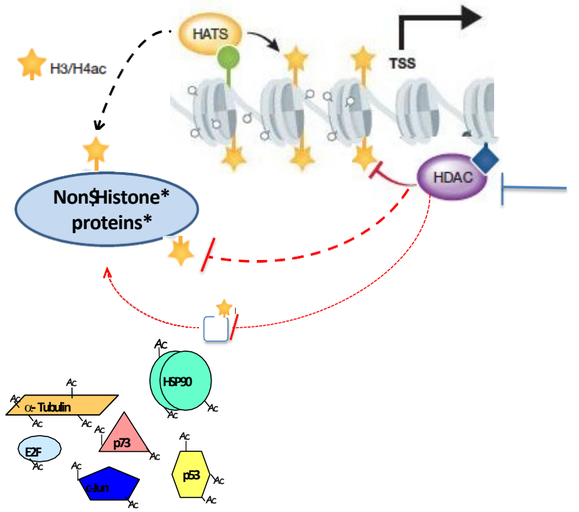
Chlorpromazine

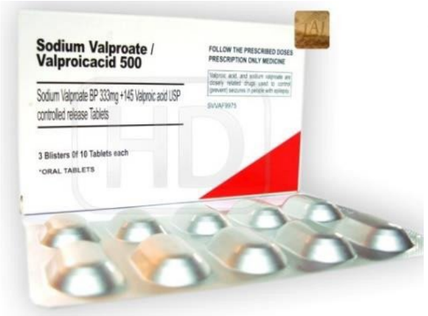
(schizophrenia, bipolar disorder, and acute psychosis)

& .....

- **Valproic acid** used (over 40 years) as an **anticonvulsant agent** and mood stabilizer -recommended plasma level 50-100 mg/ml (0.5 mM)- is a very inexpensive generic drug with **HDAC inhibitory activity** (less potent of other HDACi) and proven **antitumor effects**.



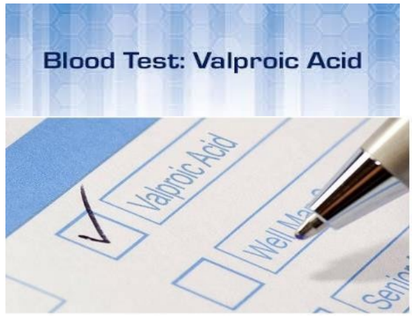




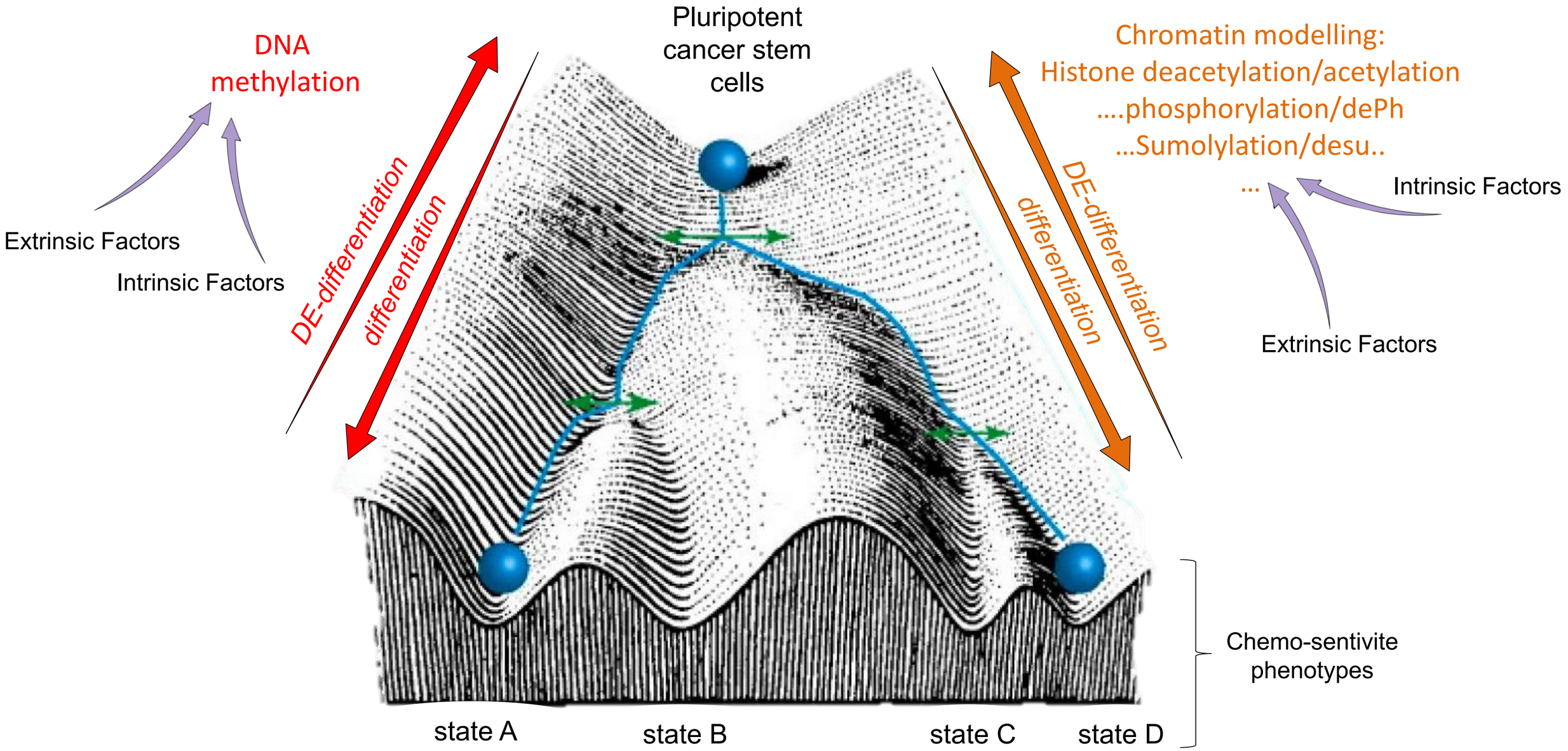
- VPA has a half-life of 9-18 hand can be **orally administered**.

- VPA has a **good safety profile** with somnolence and neovestibular symptoms (dizziness, confusion) as dose limiting toxicities (DLTs), rather than fatigue.

- **Cheap and easy blood test available** for VPA PK studies.

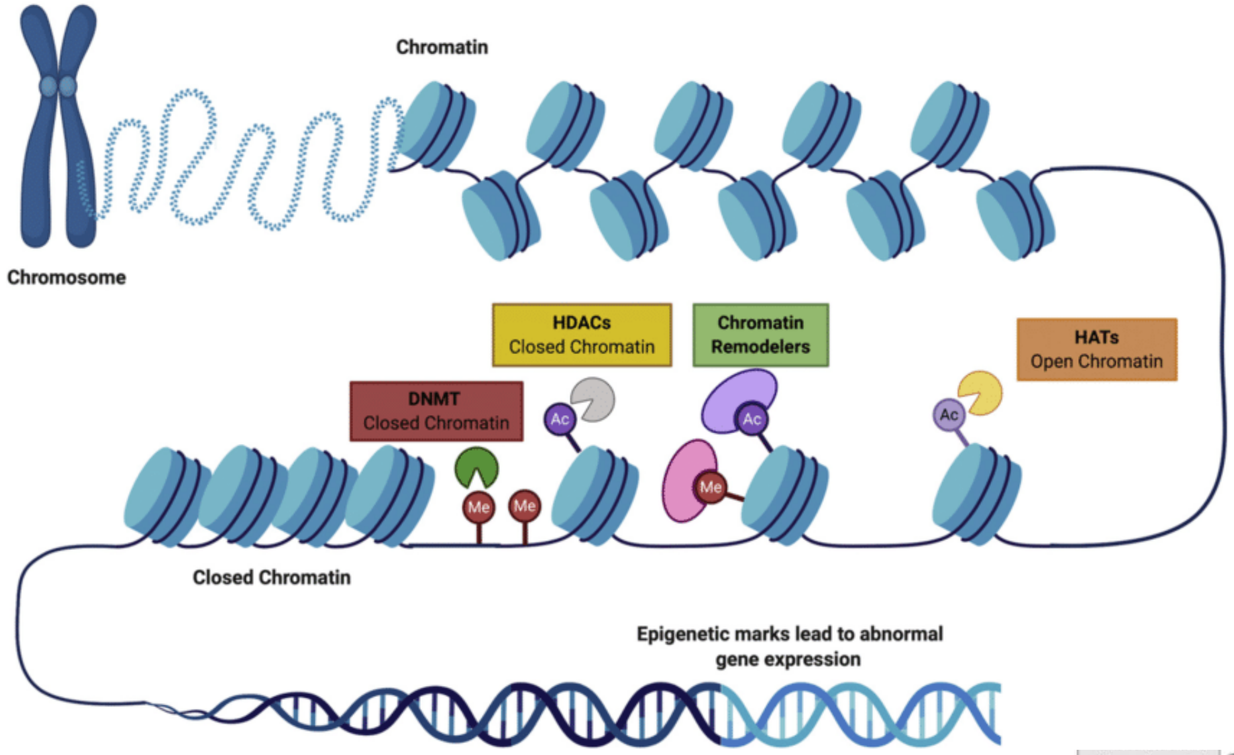


Epigenetic mechanisms are important mediators of cellular identity/plasticity

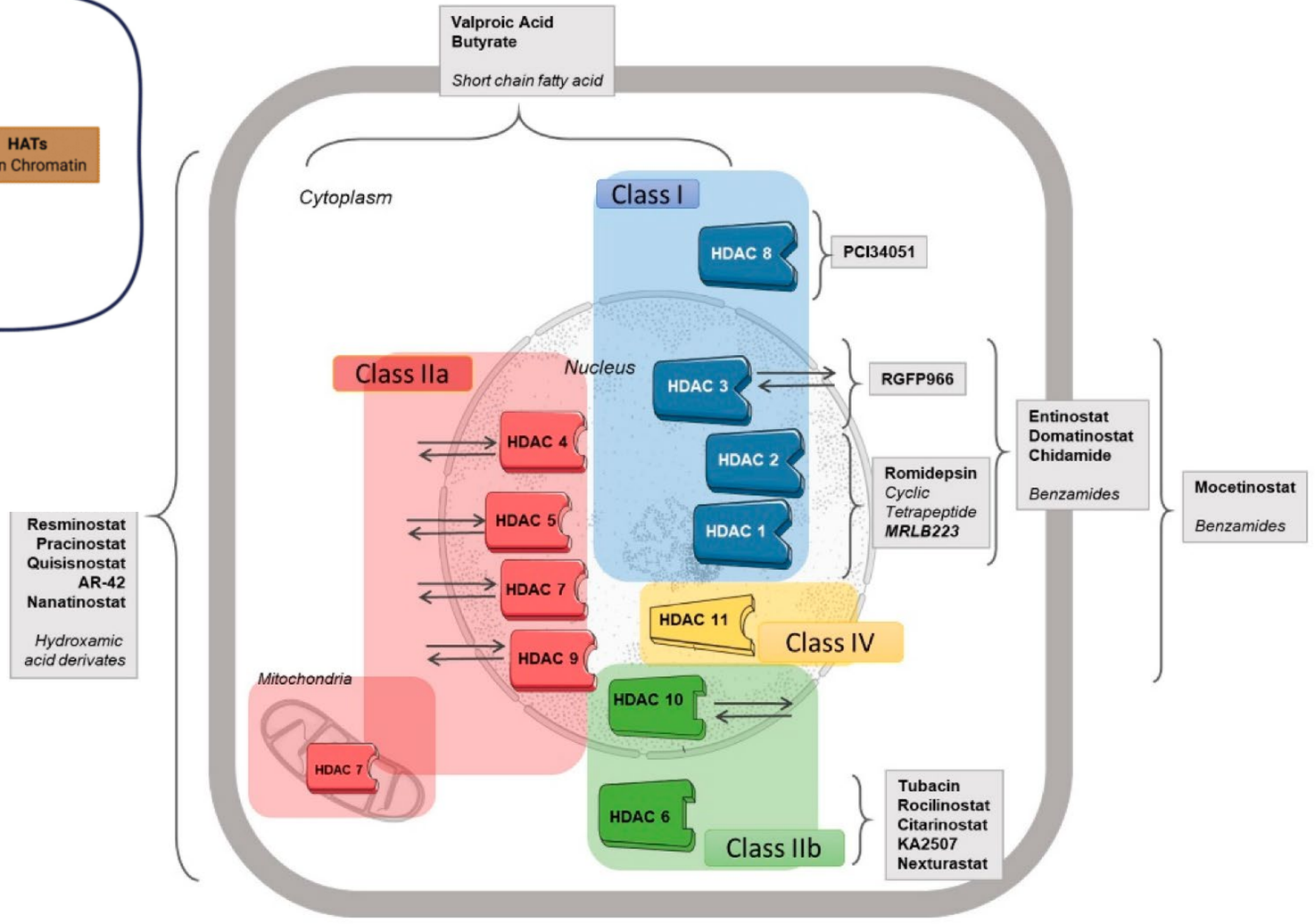


Srinageshwar B, Int J Mol Sci. 2016

Chromatin modeling and Histone deacetylase



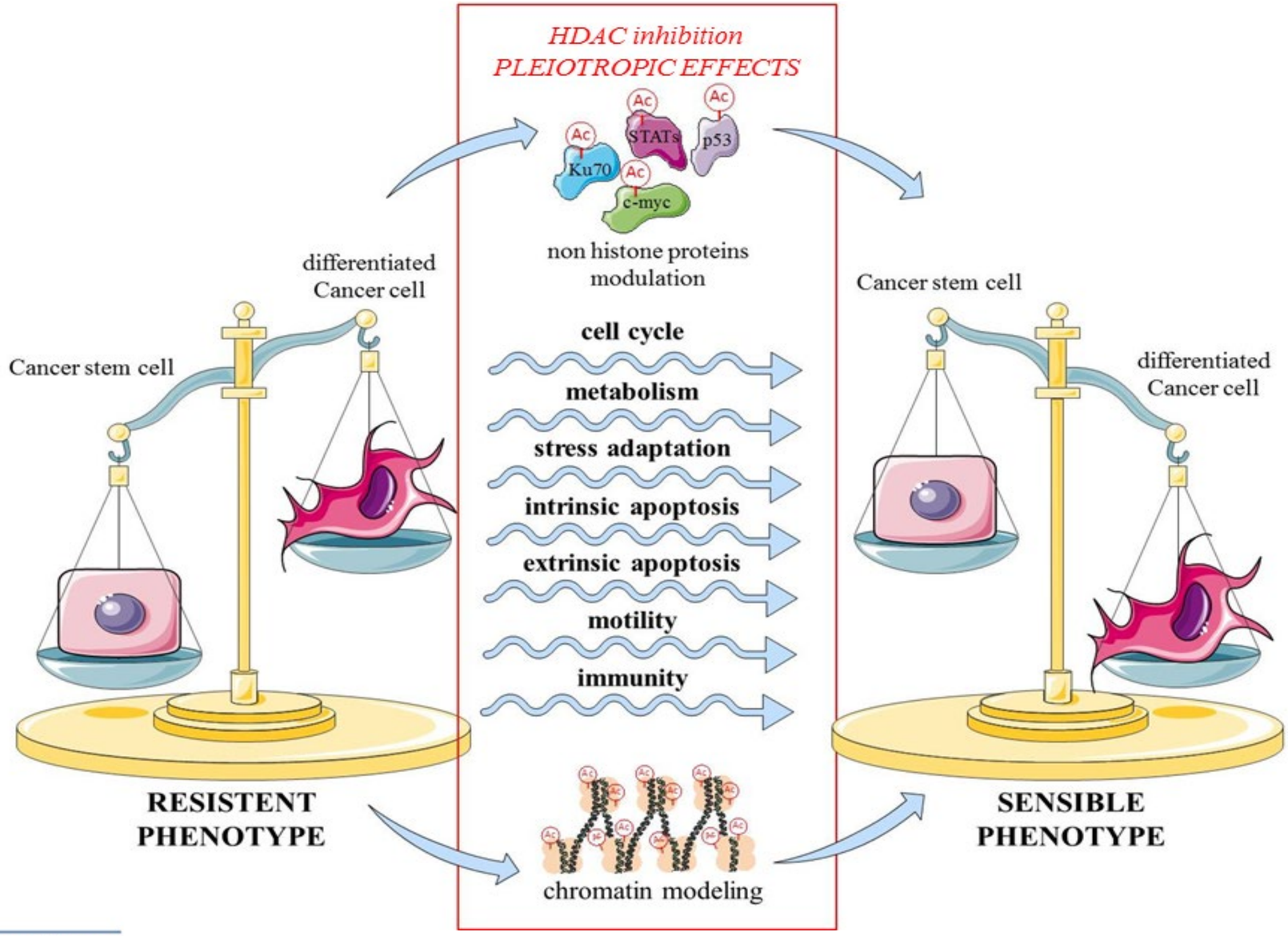
Conboy A et al. 2021



- HDACs act as **gene-silencing mediators.**
- Disruptions to the balance between HAT and HDAC activity can result in the aberrant expression of genes that ultimately leads to the **instability of chromatic structures and epigenetic diseases.**

Grumetti L. et al Cancer 2022

HDAC inhibition affects stemness balance



Adapted from Roca et al. Journal of Clinical Medicine 2019

HDAC inhibitors rather than pure anticancer drugs are, particularly at low doses, “biological modifiers”, able to modulate sensitivity of cancer cells to antitumor drugs

Anti-ErbBs drugs
EGFR-TKIs (gefitinib, erlotinib)
Anti-ErbB3 MoAb
Anti-EGFR MoAb (Cetuximab) (*plus Cisplatin*
Head & Neck cancer and NSCLC

Bianchi L., Bruzzese F. et al., ***Proteomics 2011***
Bruzzese F. et al, ***J Cell Phys 2011***
Leone A. et al. ***Free Rad Biol Med, 2015***
Ciardiello C, Roca S. et al. ***Oncotarget 2016***
Caponigro F. et al. ***BMC Cancer 2016 (CLIN TRIAL)***
Iannelli et al. Fron Dev Cell Biol 2022

Topo-I Inhibitors
(Camptothecin, Topotecan)
SCLC
Bruzzese F. et al., ***Mol Cancer Ther 2009***

Gemcitabine & Taxol
Fluoropyrimidines & Irinotecan
Pancreatic cancer
Roca et al. J Exp Clin Can Res 2022

Drugs Targeting Mevalonate Pathway
(Zoledronic Acid, Simvastatin)
Prostate cancer, Multiple Myeloma
Bruzzese F. et al. ***Cell Death Dis 2013***
Iannelli et al. J Exp Clin Can Res 2020

Grumetti L. et al.Cancers 2022 Jan 29;14(3):695

Immune Checkpoint Inhibitors
(anti-CTLA-4 & anti-PD-1)
Breast cancer
Terranova-Barberio M et al. ***Oncotaraet 2017***

Fluoropyrimidines
(5-Fluorouracil, Capecitabine)
Colorectal and Breast cancer
Di Gennaro E. et al. ***Cancer Biol Ther. 2009***
Di Gennaro E.et al. , ***British J Cancer 2010***
Terranova-Barberio M et al. ***Oncotarget 2015***
Avallone A. et al. ***BMC Cancer 2014 (CLIN TRIAL)***

Fluoropyrimidines & Oxaliplatin
Colorectal cancer
Roca MS et al. ***unpublished***

Fluoropyrimidines & Cisplatin
Head & Neck cancer
Piro G. et al. Mol Cancer Ther 2019
Iannelli et al. Fro nDev Cell Biol 2022

Fluoropyrimidines & Radiotherapy
Colorectal cancer
Terranova-Barberio M et al ***J Exp Clin Cancer Res 2018***

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

DR-ongoing clinical studies

- **Phase 1/2 study of Valproic acid and short-course Radiotherapy plus Capecitabine as preoperative treatment in low-moderate risk rectal cancer- V-shoRT-R3** *(NCT01898104).*
  (Phase 1 closed, 27 pts ; Phase 2 completed, 49 pts)

RF-2011-02346914

- **Phase II clinical study of Valproic Acid Plus Cisplatin and Cetuximab in Recurrent and/or Metastatic Squamous Cell Carcinoma of Head and Neck-V-CHANCE trial** *(NCT02624128).* *(completed, 14 pts)*

Intramural Funds (RC)

- **Randomized phase-2 study of Valproic acid in combination with Bevacizumab and Oxaliplatin fluoropyrimidine regimens in patients with ras-mutated metastatic colorectal cancer (REVOLUTION trial)** *(NCT04310176).* *(completed>200 pts)*

RF-2016-02363314

- **Valproic Acid/Simvastatin Plus Gemcitabine/Nab-paclitaxel Based Regimens in Untreated Metastatic Pancreatic Adenocarcinoma Patients (VESPA trial)** *(NCT05821556).* *(recruiting, >140 pts)*

RF-2021-12371995

EU Horizon GA101057442.

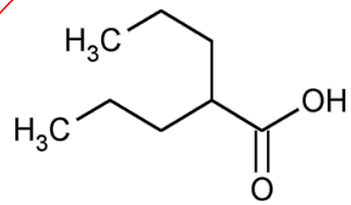
- **Valprolc aCid To pOtentiate anti-EGFR treatment efficacy and prevent/revert resistance In colorectal cAncer (VICTORIA)** *Recruitment started March 2025*

Finanziato dall'Unione europea NextGenerationEU

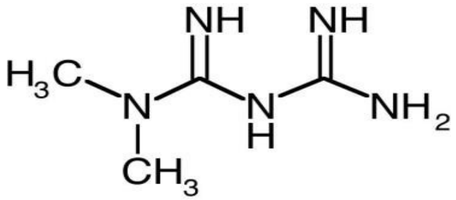
PNRR-MCNT2-2023-12377998

DR-ongoing studies

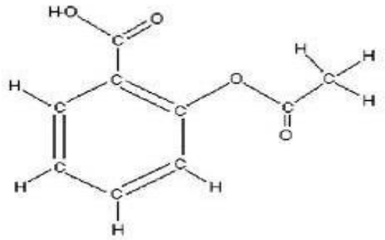
- There is a clear rationale for seeking combinations of agents—both repurposed and standard oncological drugs—which together work to attack multiple aspects of the tumour, and the microenvironment.
- We decided to repurpose generic drugs to add to existing regimens and protocols to improve clinical efficacy with lower toxicity and at lower cost.



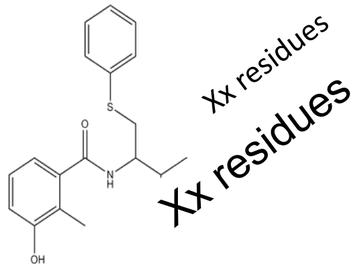
Valproic acid (antiepileptic)



Dimethylbiguanide (metformin, antidiabetic)

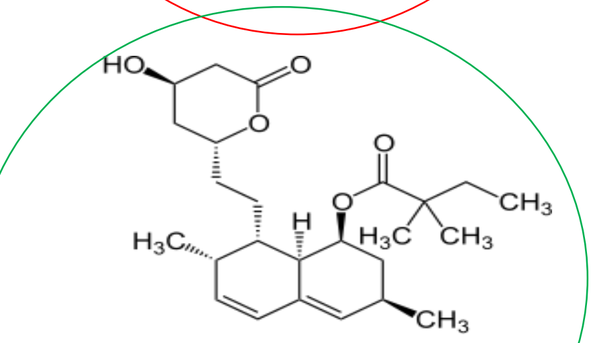


Acetylsalicylic Acid (Aspirin)

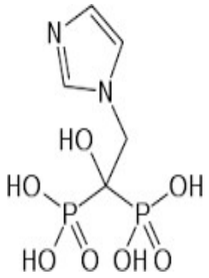


Xxx antiviral

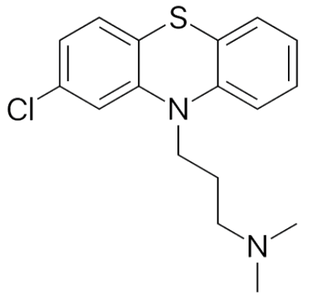
& .....



Statins (cholesterol lowering)



Zoledronic acid (bone disease drug)

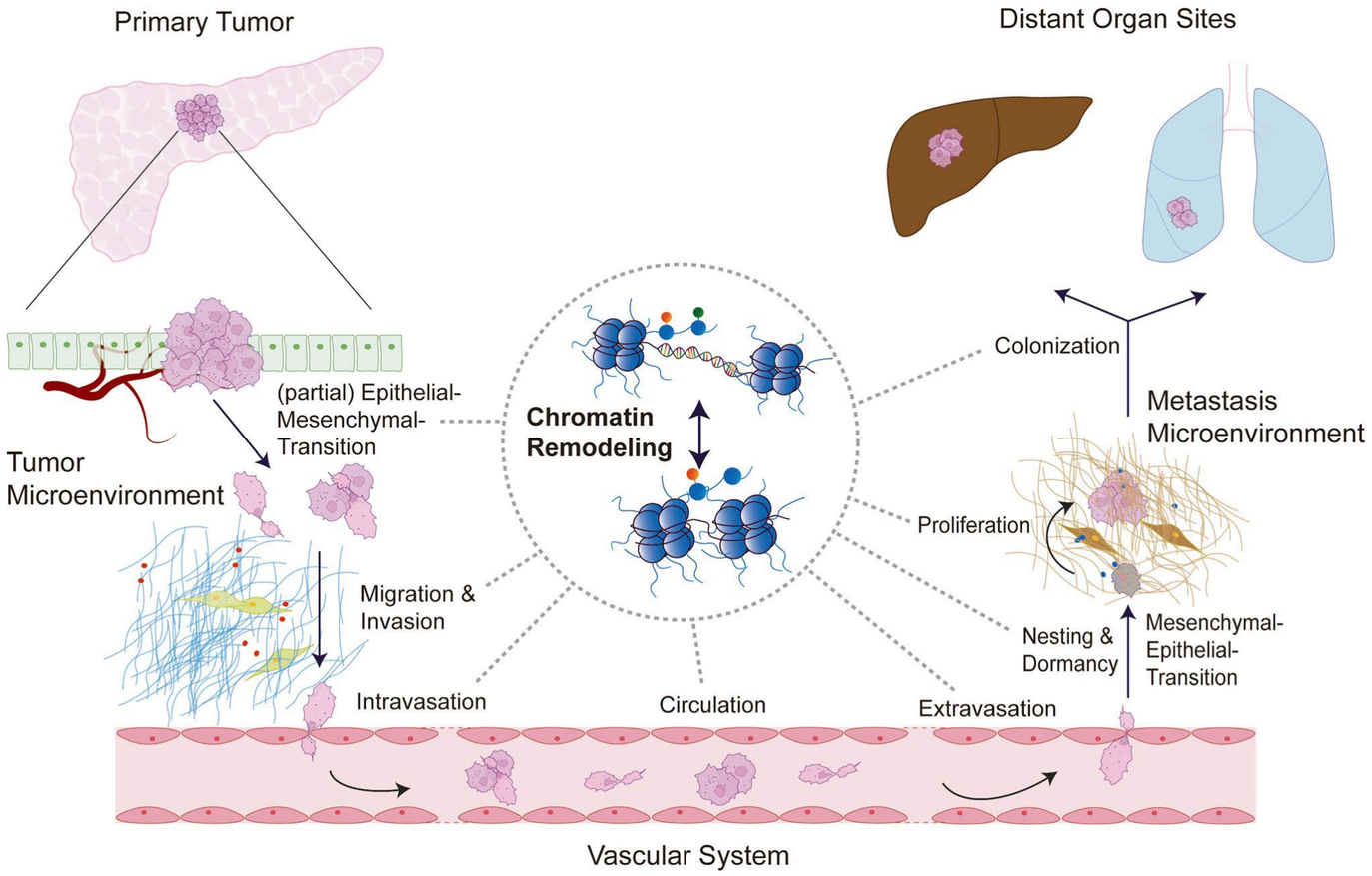


Chlorpromazine

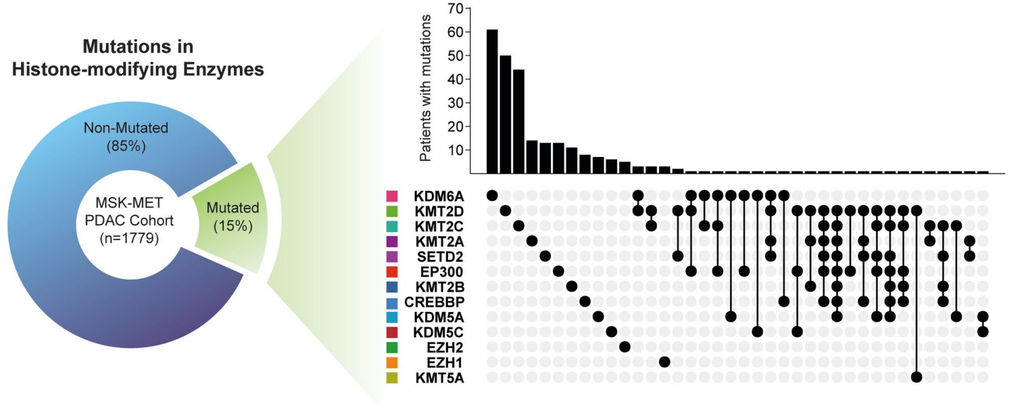
(schizophrenia, bipolar disorder, and acute psychosis)

& .....

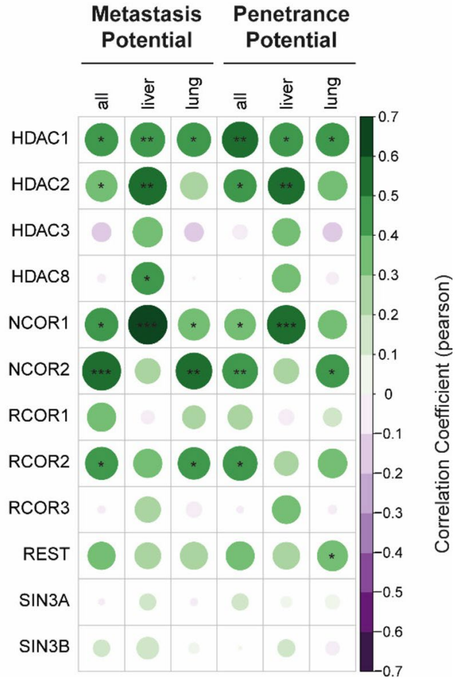
Non-mutational epigenetic reprogramming contribute to abberrant activities of cancer and TME cells, including PDAC



PDAC cells undergo chromatin remodeling during metastatic process



PDAC patients tumor samples display mutations in histone modifying enzymes



Pearson correlation between metastatic/penetrance. potential and RNA expression of class I HDACs

Lukas Krauß et al. , Cancer and Metastasis Reviews, 2023

Roca et al. J Exp Clin Cancer Res (2022) 41:83
https://doi.org/10.1186/s13046-022-02295-4

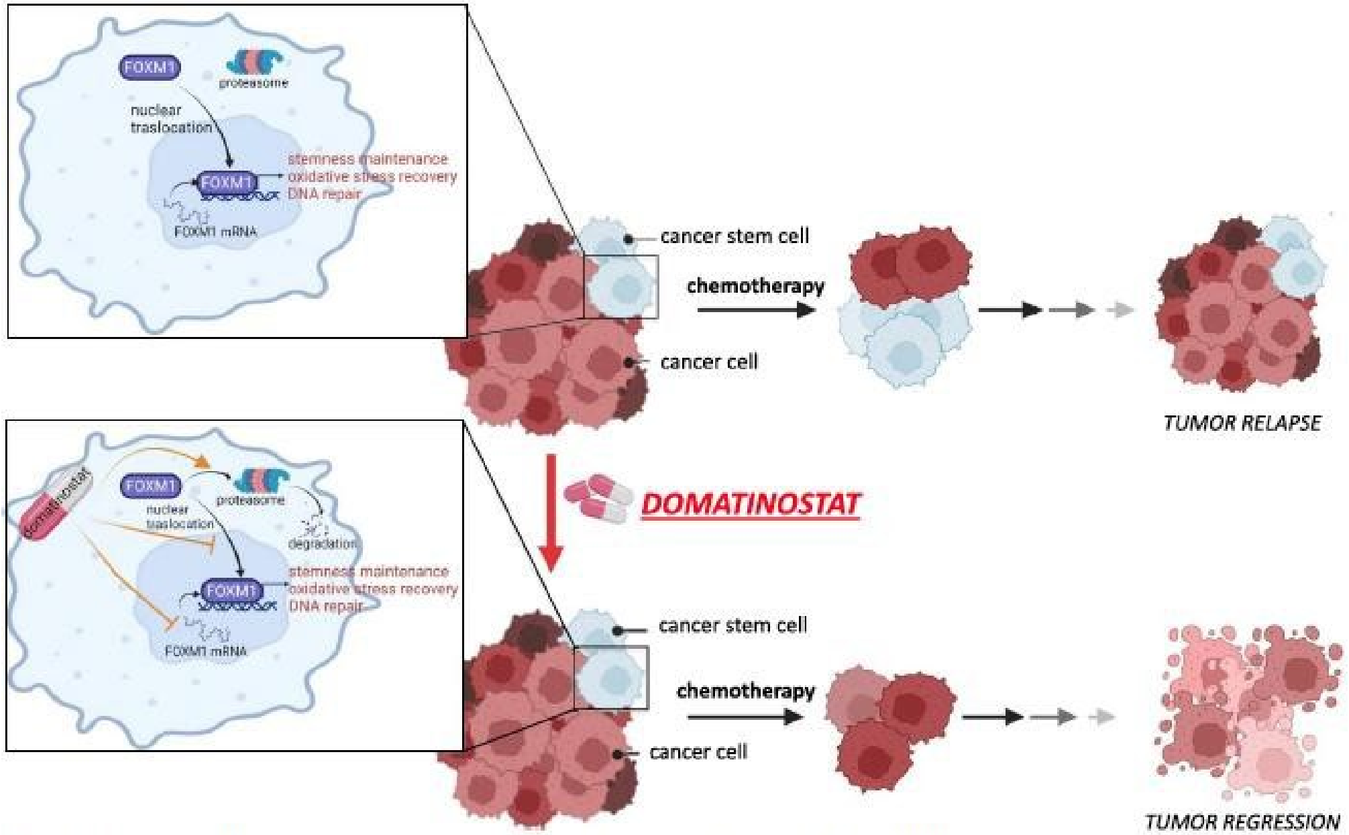
2022

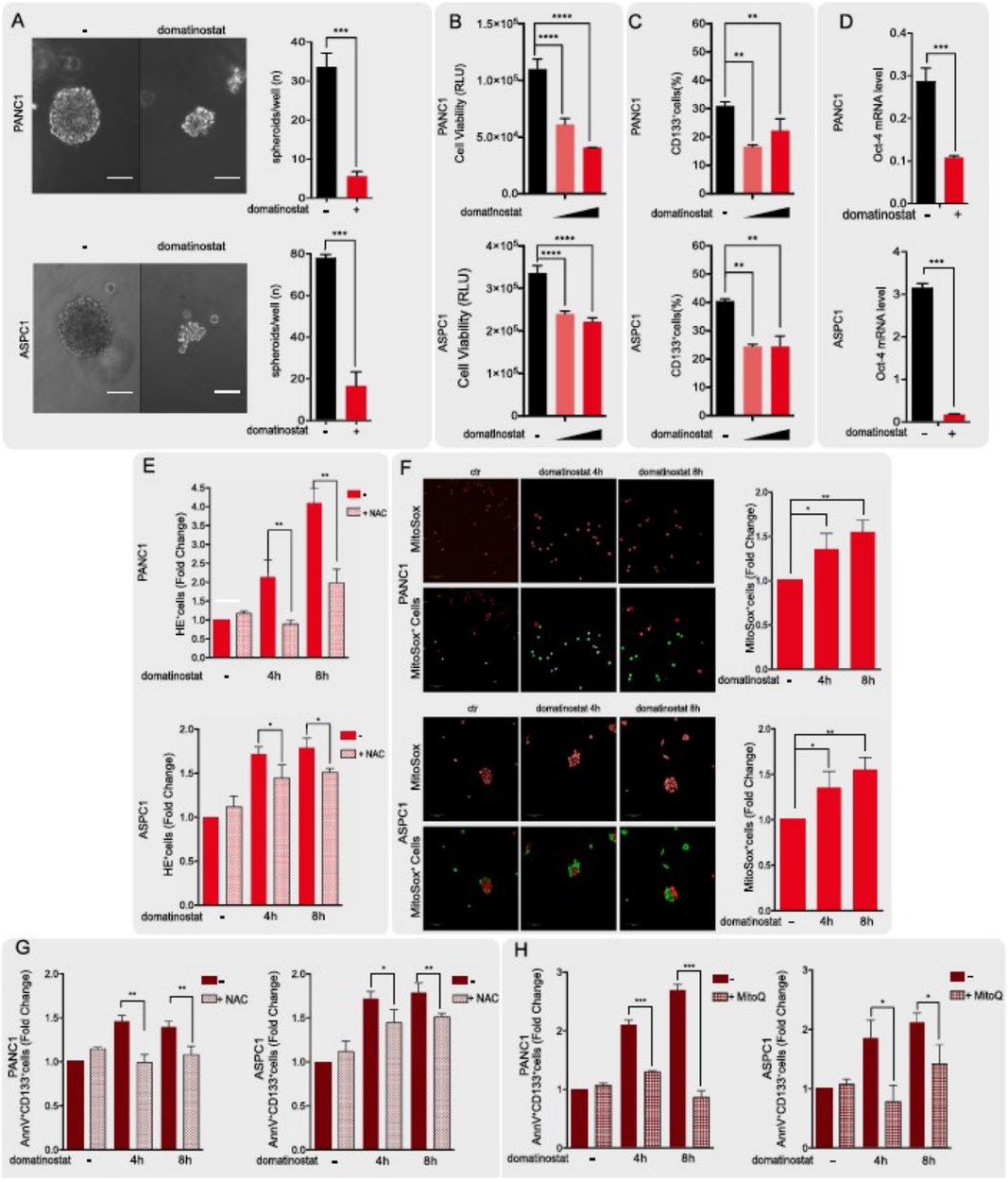
Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

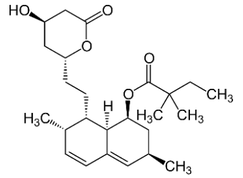
HDAC class I inhibitor domatinostat sensitizes pancreatic cancer to chemotherapy by targeting cancer stem cell compartment via FOXM1 modulation

Maria Serena Roca[1], Tania Moccia[1], Federica Iannelli[1], Cristina Testa[1], Carlo Vitagliano[1], Michele Minopoli[2], Rosa Camerlingo[3], Giulia De Riso[4], Rossella De Cecio[5], Francesca Bruzzese[6], Mariarosaria Conte[7], Lucia Altucci[7,8], Elena Di Gennaro[1], Antonio Avallone[9], Alessandra Leone[1†] and Alfredo Budillon[1*†]

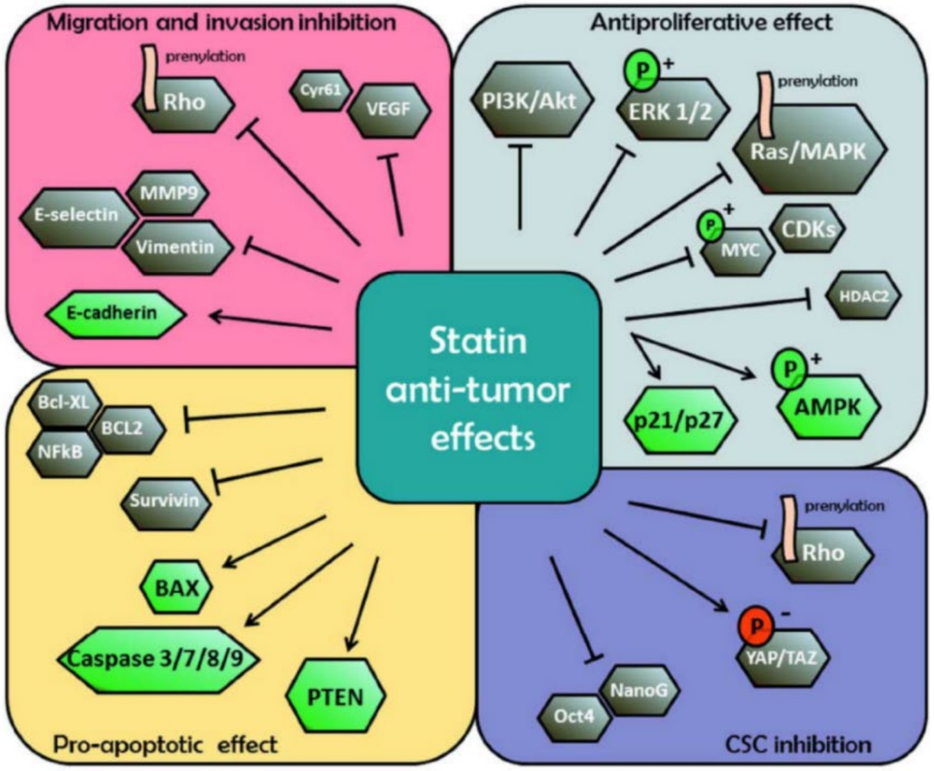




Simvastatin



Statins, developed as **lipid-lowering drugs**, inhibit HMG-CoA reductase (HMGCR), the first step of the **mevalonate pathway**, preventing cholesterol formation and the protein prenylation branch have demonstrated a **direct antitumor activity** in monotherapy or in combination with chemotherapy and target therapy in different tumor models



Iannelli et al. Recent Patents on Anti-Cancer Drug Discovery, 2018

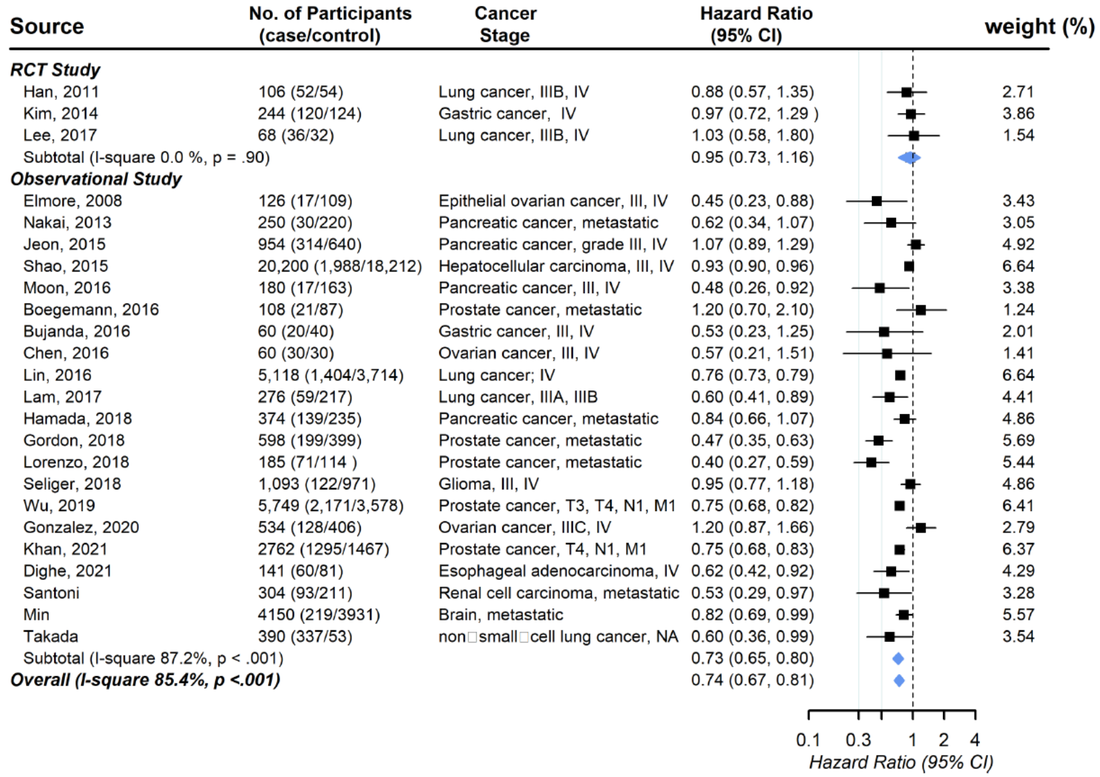


FIGURE 2
Pooled associations between statin and overall survival in patients with advanced-stage cancer.
Zhou Q, et al. Front. Oncol. 13:1234713, 2023.

JNCI J Natl Cancer Inst (2017) 109(5): djw275

doi: 10.1093/jnci/djw275
First published online December 31, 2016
Article

ARTICLE

Influence of Statins and Cholesterol on Mortality Among Patients With Pancreatic Cancer

Brian Z. Huang, Jonathan I. Chang, Erica Li, Anny H. Xiang, Bechien U. Wu

Conclusions: Statin use rather than cholesterol level was associated with **lower mortality risk** in patients with pancreatic cancer. **Statins appear to improve survival through a lipid-independent mechanism**

Cancer Prev Res (Phila). 2021 Jul 9;canprevres.CAPR-21-0123-A.2021.
doi: 10.1158/1940-6207.CAPR-21-0123. Online ahead of print.

Statin exposure and pancreatic cancer incidence: A Japanese regional population-based cohort study, the Shizuoka Study

Kohei Saito [1], Yoko Sato [1], Eiji Nakatani [2], Hideaki Kaneda [3], Seiichiro Yamamoto [4], Yoshiki Miyachi [1], Hiroshi Itoh [5]

Affiliations
PMID: 34244151 DOI: 10.1158/1940-6207.CAPR-21-0123

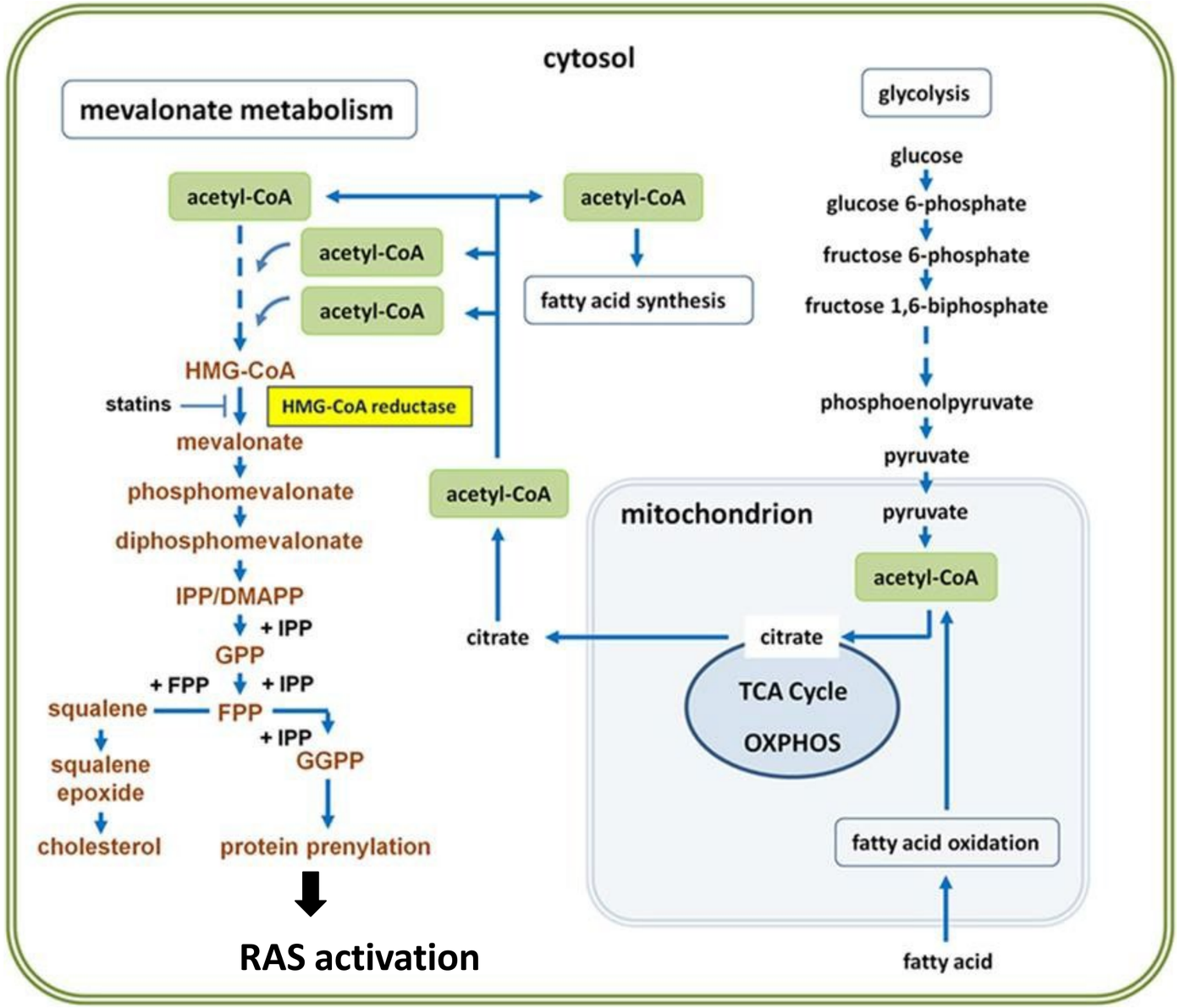
In conclusion, the present Japanese regional population-based cohort study shows that statin exposure was associated with a **lower incidence of pancreatic cancer**.

Statins and the risk of pancreatic cancer: A systematic review and meta-analysis of 2,797,186 patients

J Cardiology 2022 DOI: 10.5603/CJ.a2022.0014

Overall statins use is significantly associated with a **reduction in risk of pancreatic cancer**. However, these results were not confirmed for the randomized controlled trial subgroup (tot. 7000 pts). Further prospective studies are needed to confirm the current results.

- **Mevalonate pathway, might play a critical role in PDAC.**
- **HDAC inhibitors/Statins cross talk.**

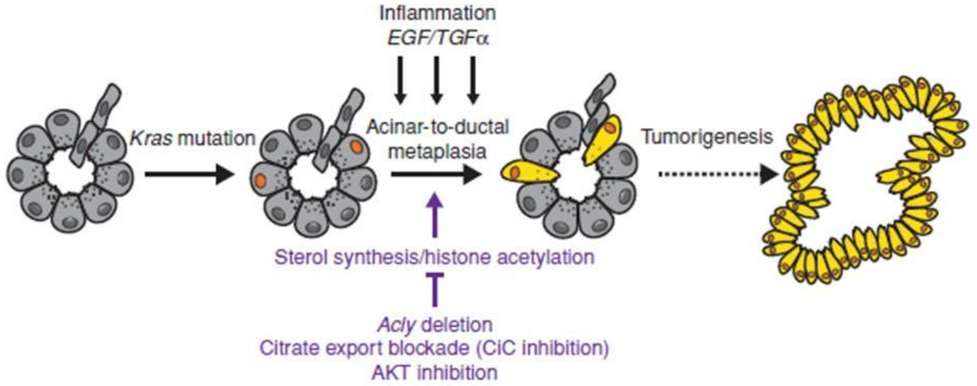


Published OnlineFirst January 9, 2019; DOI: 10.1158/2159-8290.CD-18-0567

RESEARCH ARTICLE

Acetyl-CoA Metabolism Supports Multistep Pancreatic Tumorigenesis

Alessandro Carrer[1], Sophie Trefely[1,2], Steven Zhao[1], Sydney L. Campbell[1], Robert J. Norgard[1,3], Kollin C. Schultz[1], Simone Sidoli[4], Joshua L.D. Parris[1], Hayley C. Affronti[1], Sharanya Sivanand[1], Shaun Egolf[1], Yogev Sela[3], Marco Trizzino[5], Alessandro Gardini[5], Benjamin A. Garcia[4], Nathaniel W. Snyder[2], Ben Z. Stanger[3], and Kathryn E. Wellen[1]



ELSEVIER
CrossMark
Cancer Genetics 208 (2015) 241–252
Cancer Genetics

Inhibition of the mevalonate pathway affects epigenetic regulation in cancer cells

Heidrun Karlic [a,*], Roman Thaler [b,1], Christopher Gerner [c], Thomas Grunt [a,d,e],

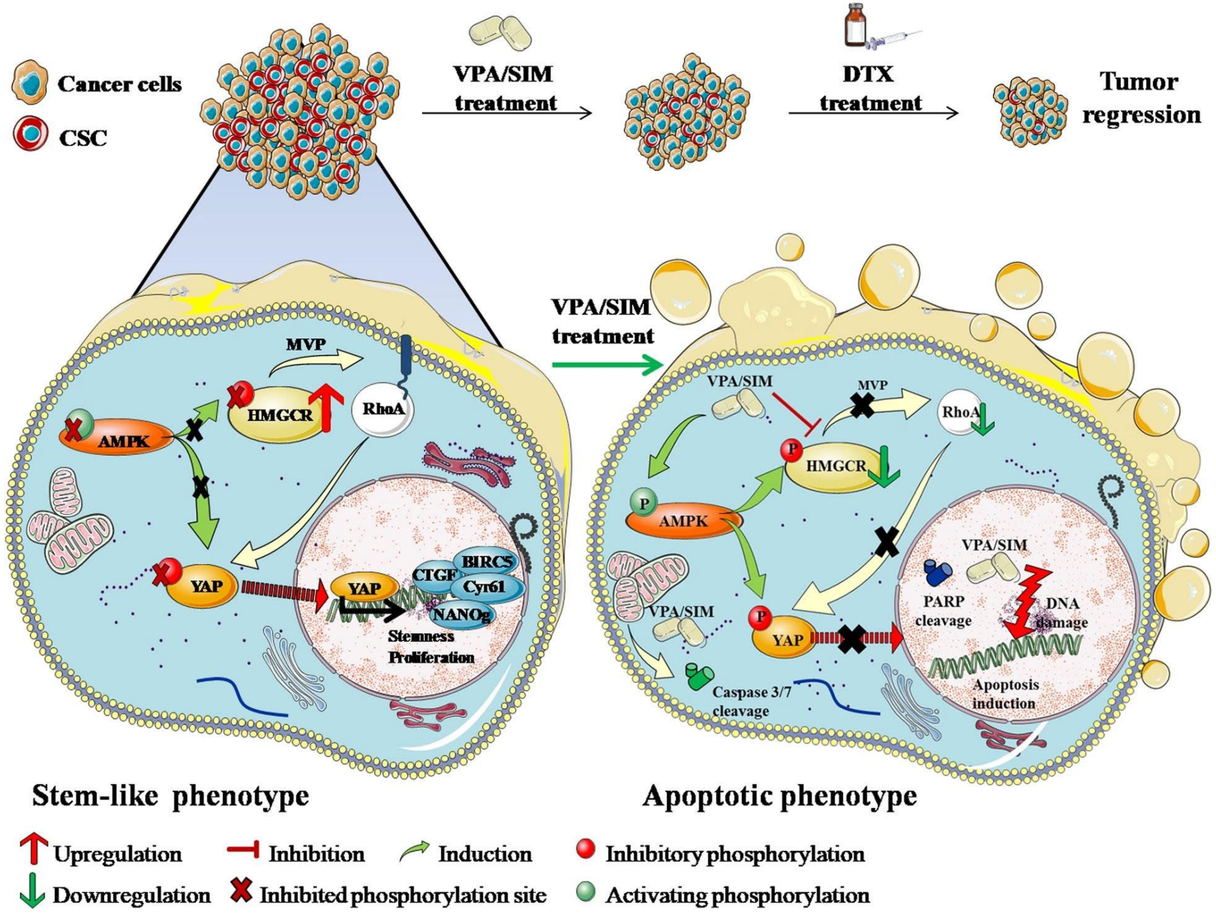
Iannelli et al. Journal of Experimental & Clinical Cancer Research (2020) 39:213
https://doi.org/10.1186/s13046-020-01723-7

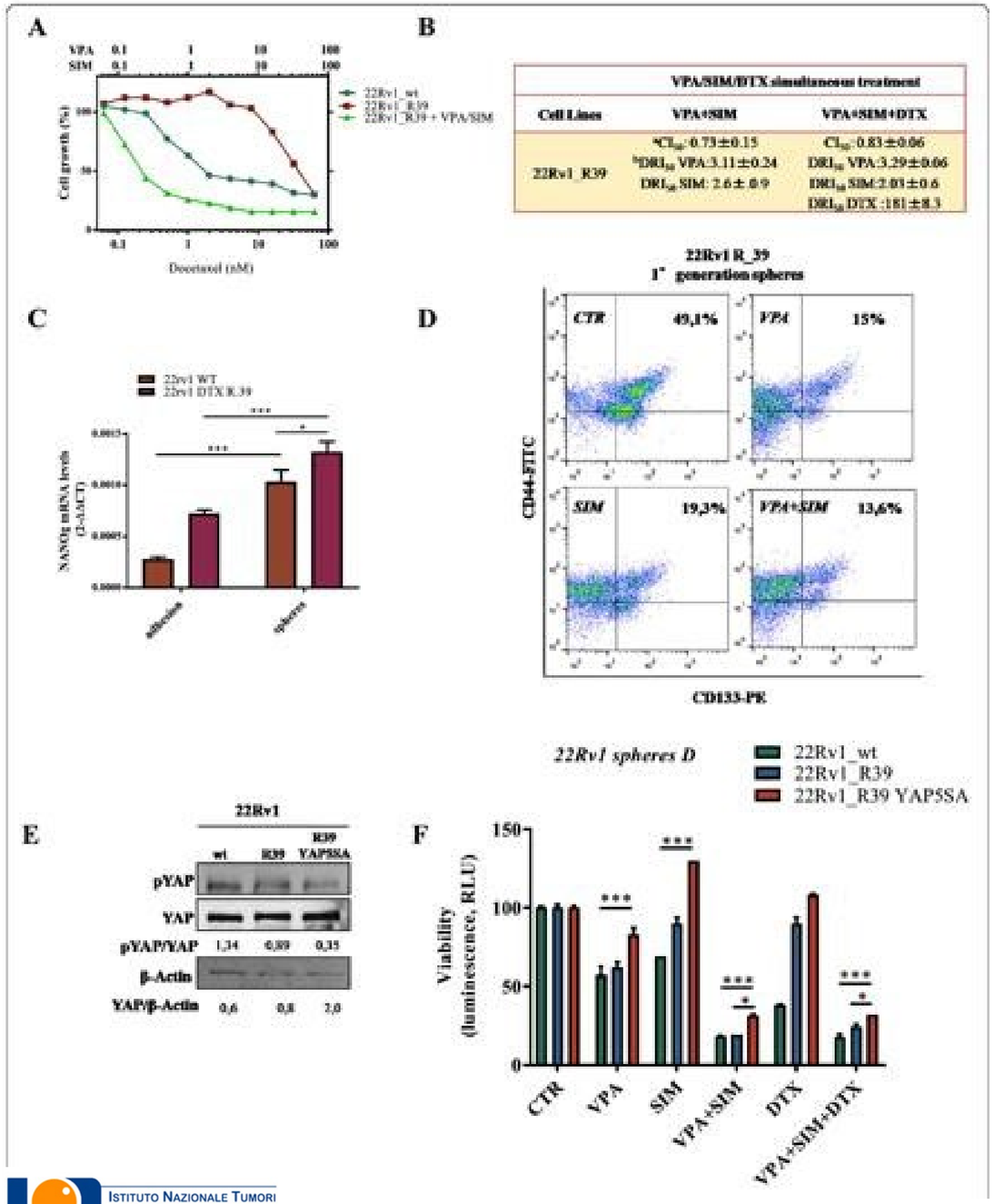
Journal of Experimental & Clinical Cancer Research

RESEARCH Open Access

Synergistic antitumor interaction of valproic acid and simvastatin sensitizes prostate cancer to docetaxel by targeting CSCs compartment via YAP inhibition

Federica Iannelli[1], Maria Serena Roca[1], Rita Lombardi[1], Chiara Ciardiello[1], Laura Grumetti[1], Simona De Rienzo[1], Tania Moccia[1], Carlo Vitagliano[1], Angela Sorice[1], Susan Costantini[1], Maria Rita Milone[1], Biagio Pucci[1], Alessandra Leone[1], Elena Di Gennaro[1], Rita Mancini[2], Gennaro Ciliberto[3], Francesca Bruzzese[1,4*†] and Alfredo Budillon[1*†]





Istituto Nazionale Tumori IRCCS - Fondazione Pascale

Integrated proteomics and metabolomics analysis reveals new insight into the synergistic antitumor effect of valproic acid plus simvastatin in prostate cancer xenograft models associated with downmodulation of YAP/TAZ signaling

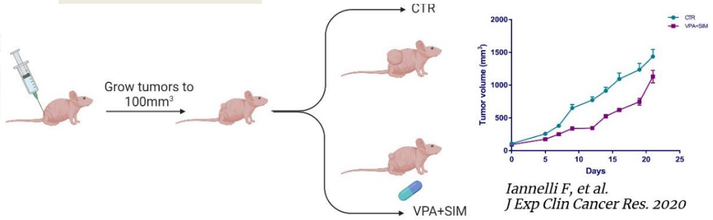
Iannelli *et al. Journal of Experimental & Clinical Cancer Research* (2020) 39:213
https://doi.org/10.1186/s13046-020-01723-7

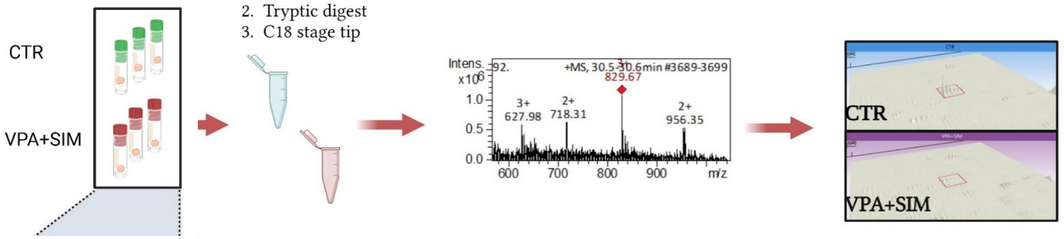
Journal of Experimental & Clinical Cancer Research

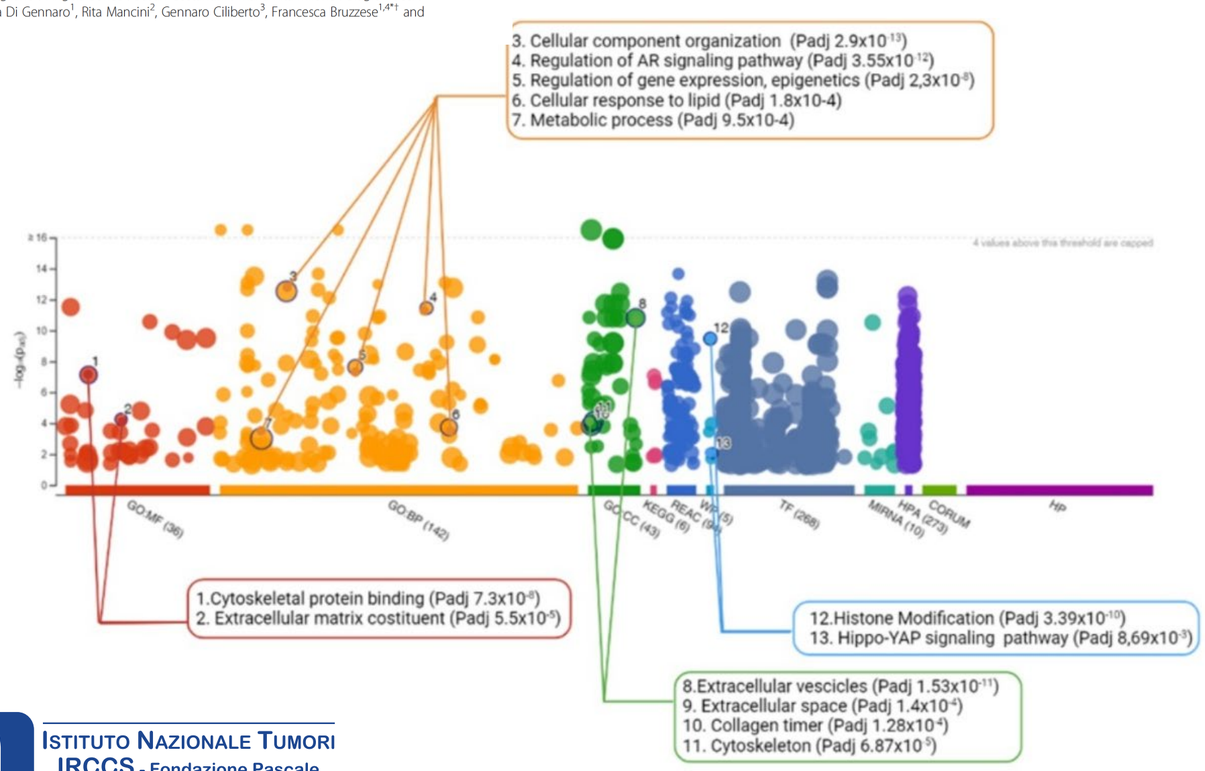
RESEARCH Open Access

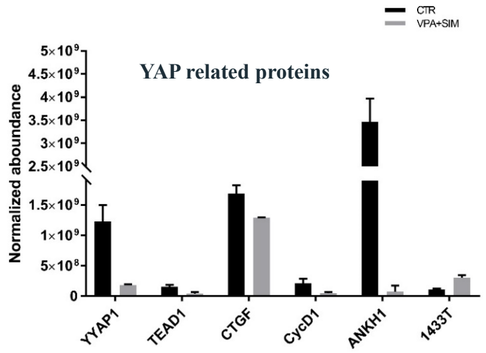
Synergistic antitumor interaction of valproic acid and simvastatin sensitizes prostate cancer to docetaxel by targeting CSCs compartment via YAP inhibition

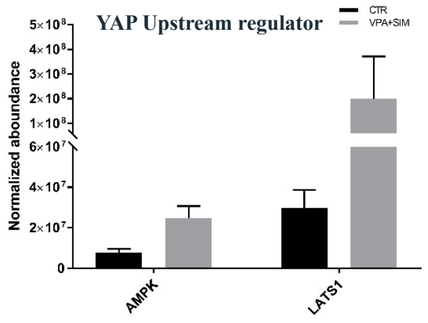
Federica Iannelli[1], Maria Serena Roca[1], Rita Lombardi[1], Chiara Ciardiello[1], Laura Grumetti[1], Simona De Rienzo[1], Tania Moccia[1], Carlo Vitagliano[1], Angela Sorice[1], Susan Costantini[1], Maria Rita Milone[1], Biagio Pucci[1], Alessandra Leone[1], Elena Di Gennaro[1], Rita Mancini[2], Gennaro Ciliberto[3], Francesca Bruzzese[1,4*†] and Alfredo Budillon[1*†]











Iannelli F, Lombardi R. Pucci … and Budillon Cancer Cell Int 2024.

ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

Europäisches Patentamt
European Patent Office
Office européen des brevets

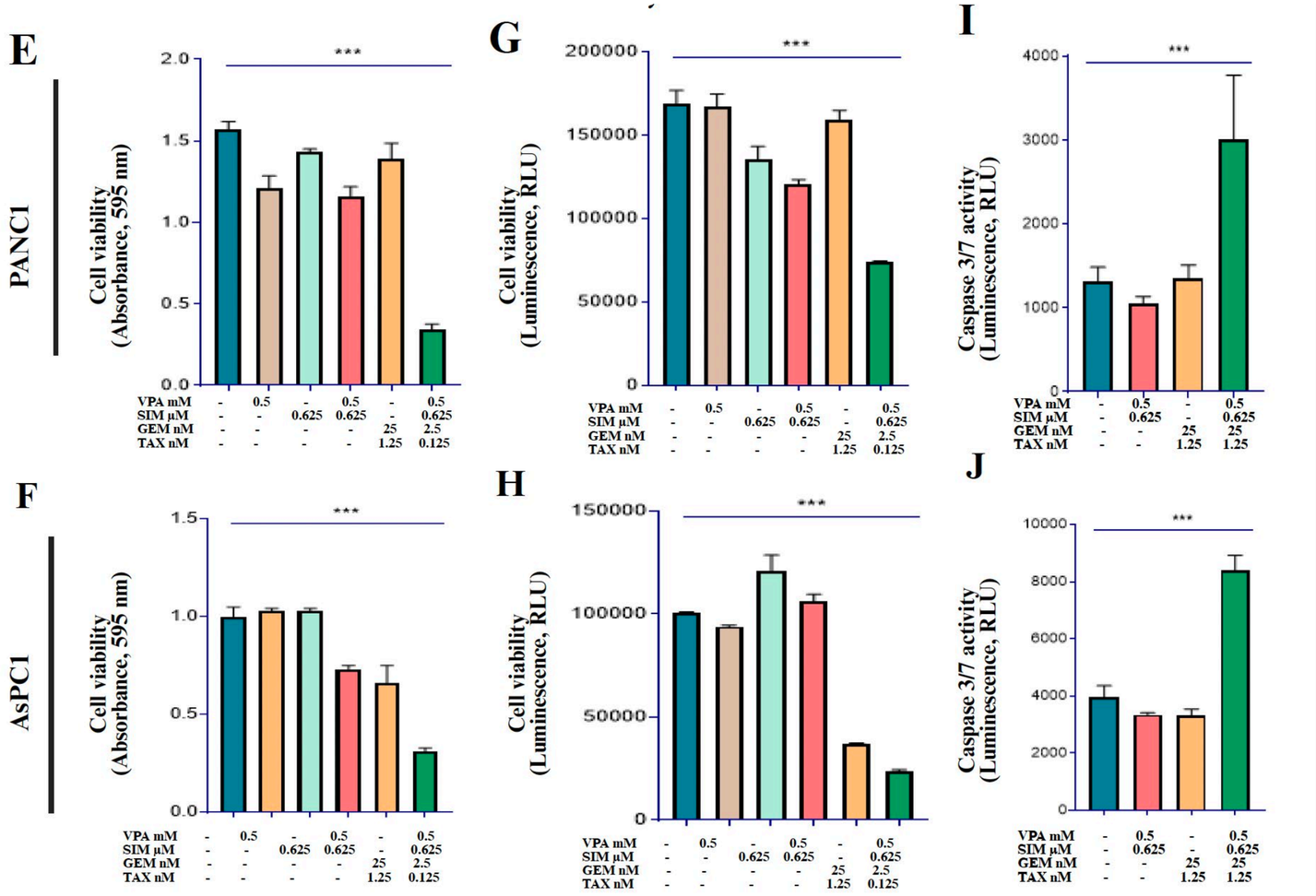
Acknowledgement of receipt

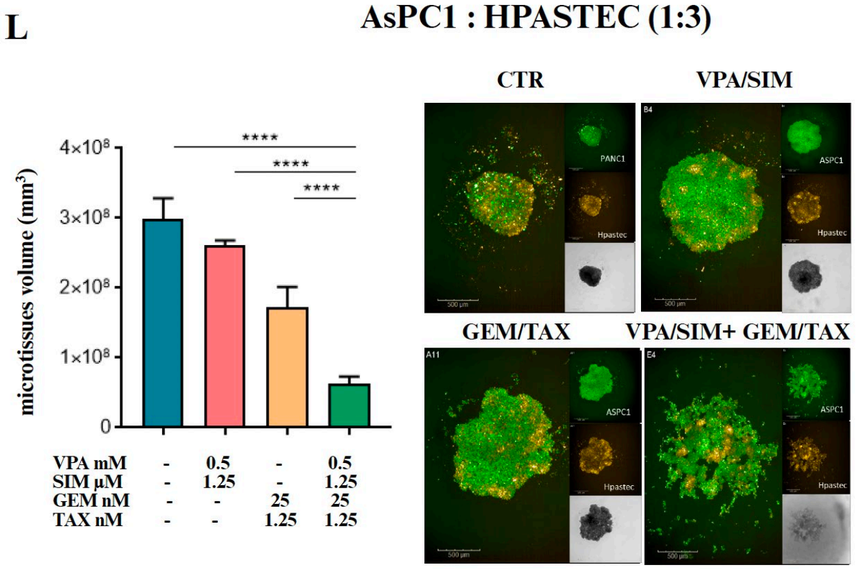
We hereby acknowledge receipt of your request for grant of a European patent as foll

Submission number	10827483
Application number	EP22166770.2
File No. to be used for priority declarations	EP22166770
Date of receipt	05 April 2022
Your reference	BE151127
Applicant	ISTITUTO NAZIONALE TUMORI IRCCS - FONDAZIONE G. PASCALE
Country	IT
Title	COMBINATION OF VALPROIC ACID AND STATINS FOR USE IN THE TREATMENT OF PANCREATIC CANCER

invention *relates to a combination of an* ***HDAC inhibitor and statins*** *for use in the treatment of* ***pancreatic cancer****. Preferably the invention relates to a combination of valproic acid (VPA) or any of its salts and simvastatin (SIM). The combination of the invention* ***synergistically improves the anti-proliferative and pro-apoptotic effect of conventional chemotherapy, as gemcitabine/taxol***

VPA/SIM combination sensitizes PDAC cells to chemotherapy





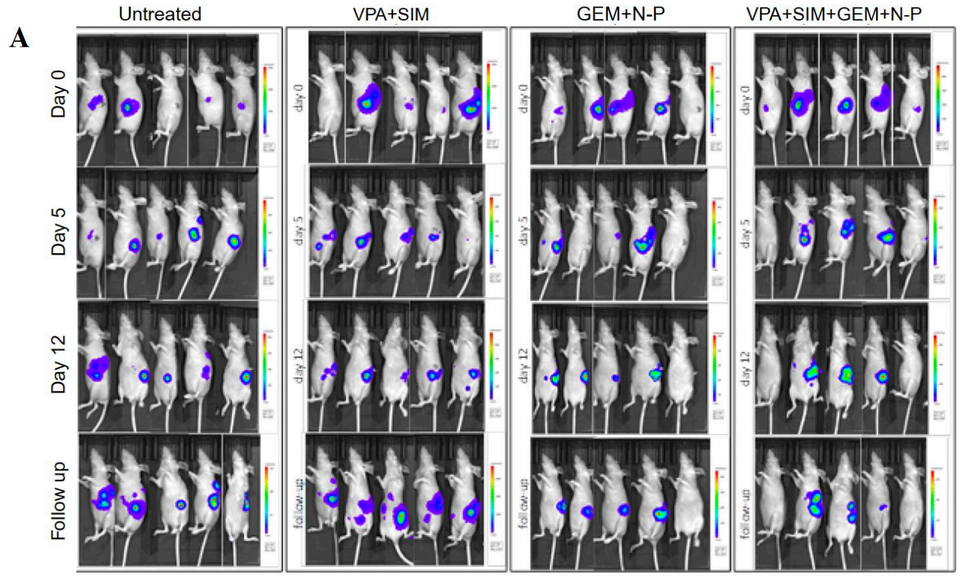
MS Roca et a. SUBMITTED

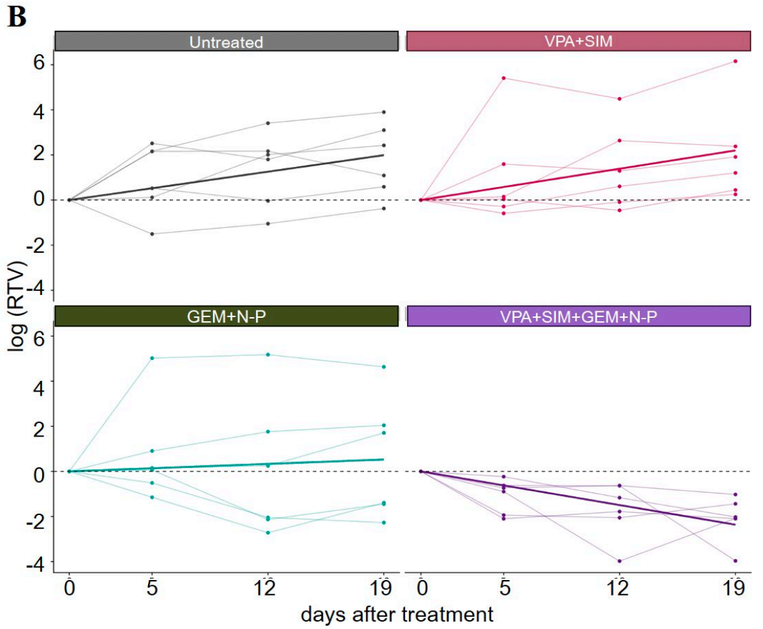
DO NOT POST

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

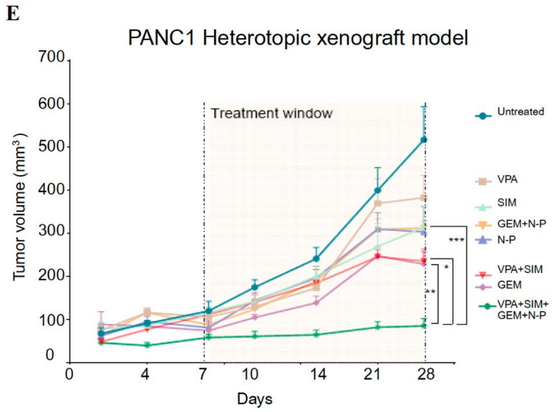
In vivo synergistic antitumor effect of VPA/SIM in combination with gemcitabine/Nab-paclitaxel.

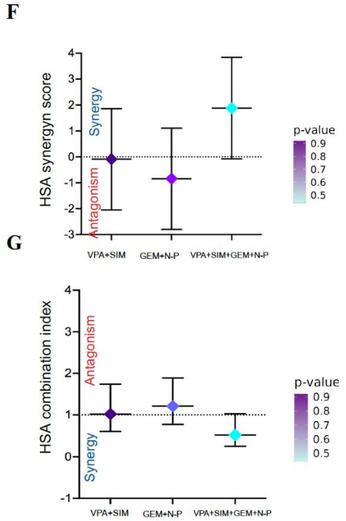
Orthotopic model





Heterotopic model



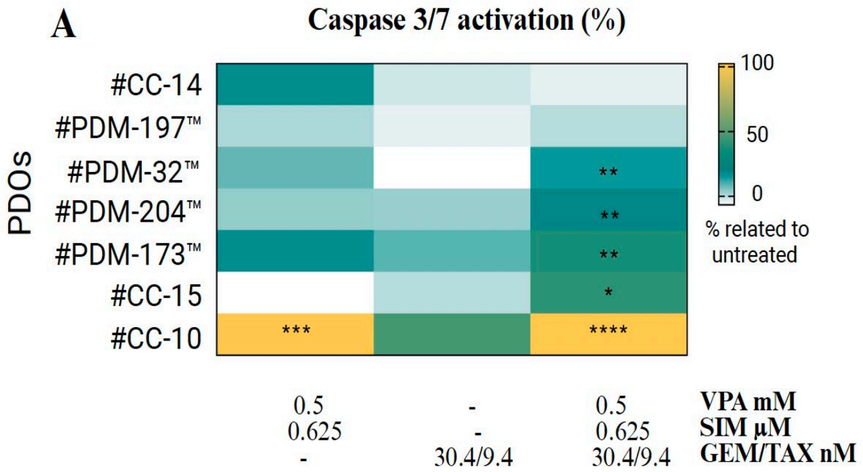


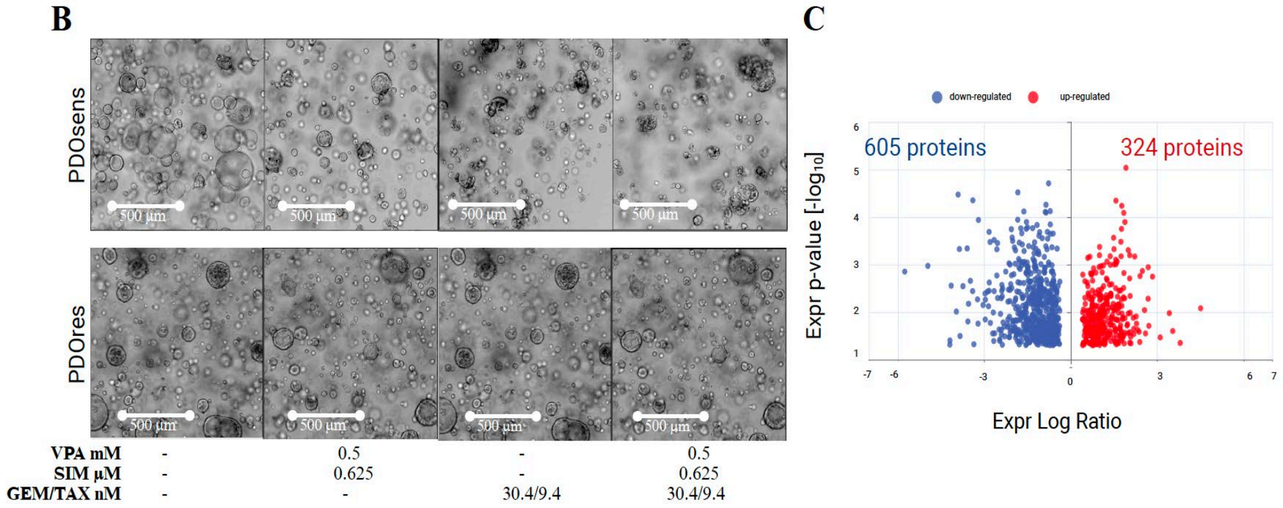
MS Roca et a. SUBMITTED

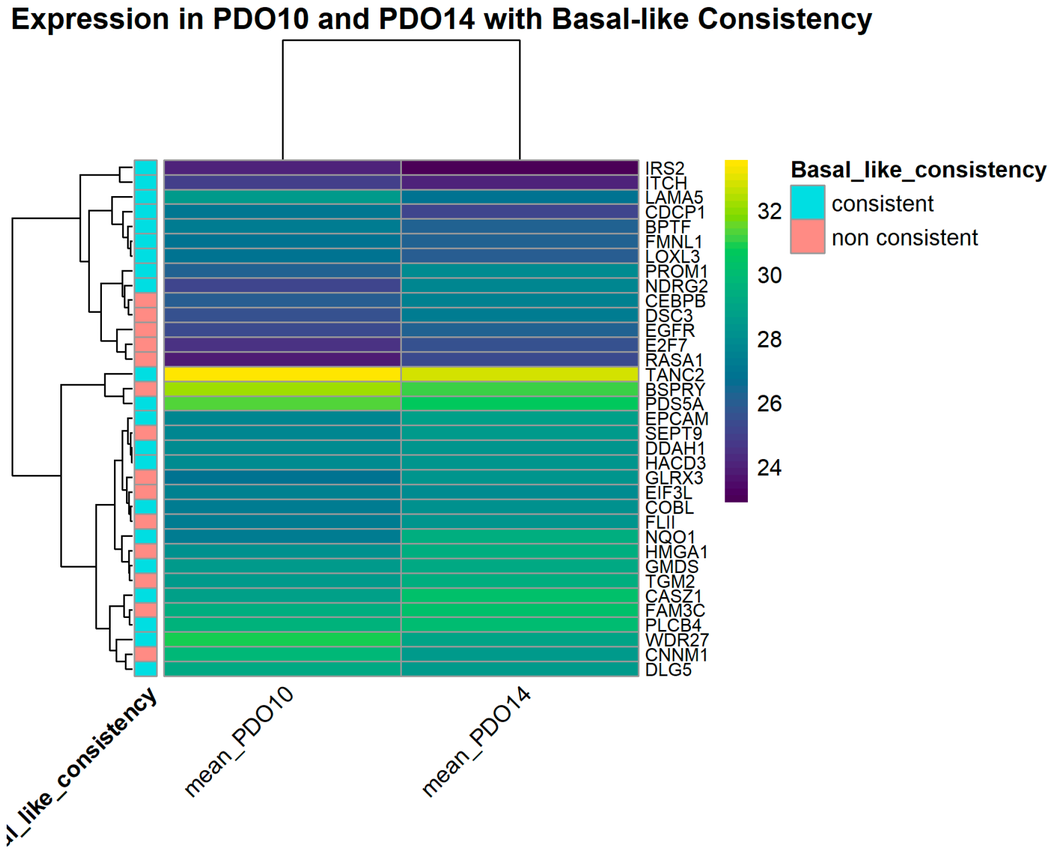
ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

DO NOT POST

Patient-derived organoids response to VPA/SIM combination plus chemotherapy reflects PDAC subtypes features : PDOsens better recapitulates basal-like transcriptional features, not in absolute expression levels, but relative to PDOres





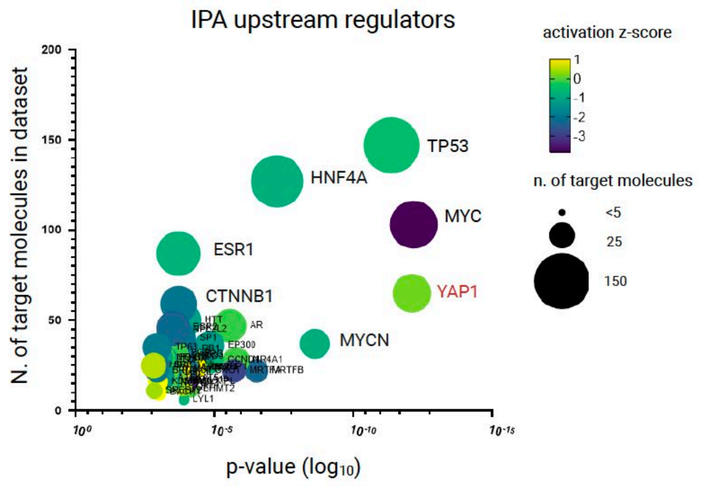


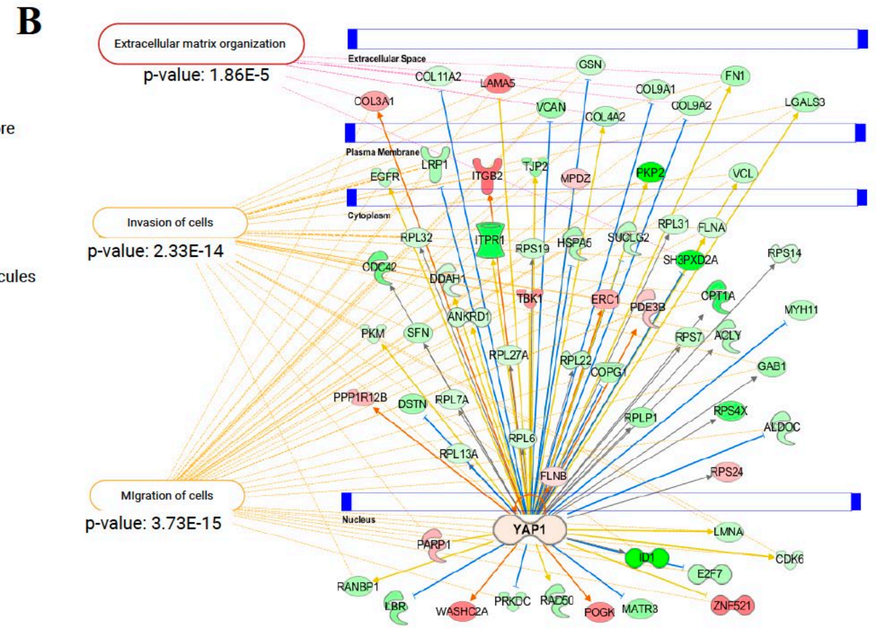
ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

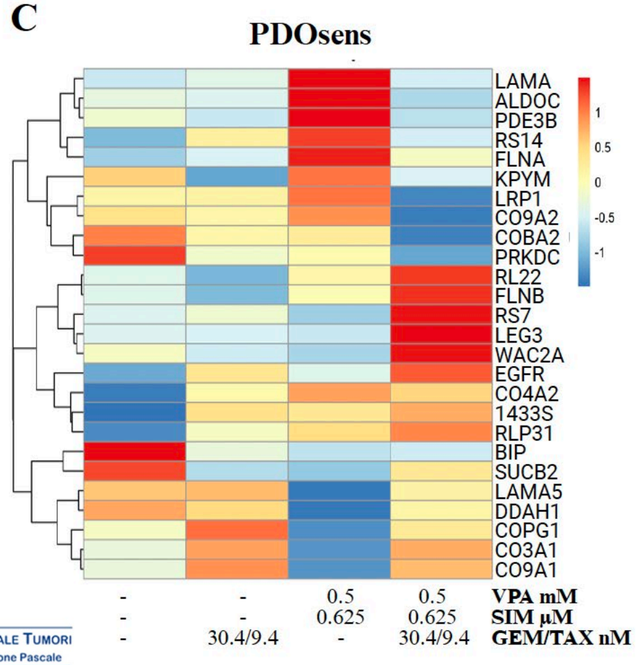
MS Roca et a. SUBMITTED

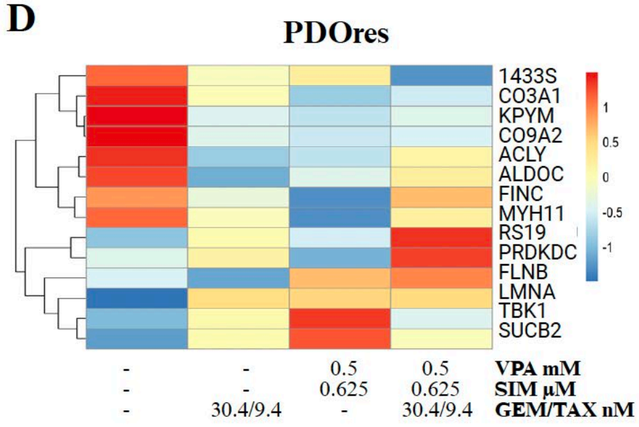
DO NOT POST

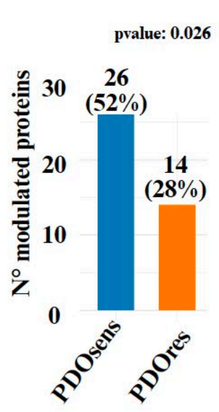
YAP1 came out as one of the major upstream regulators correlating with 65 of the modulated proteins and was also predicted as basally hyperactivated in PDOsens vs PDOres









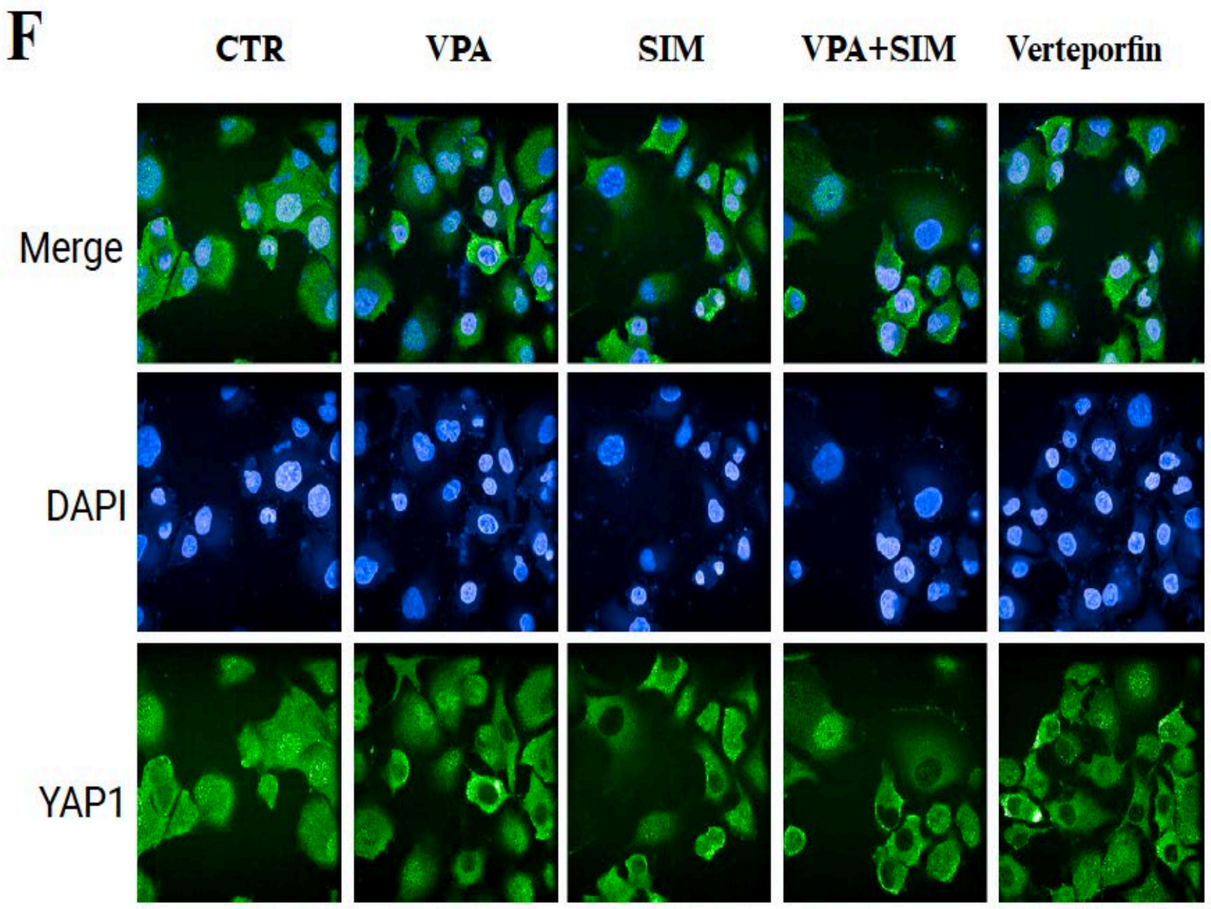


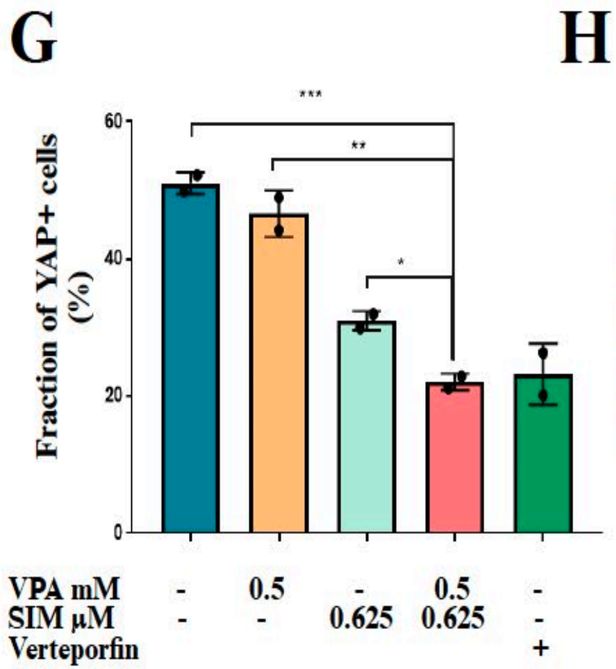
ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

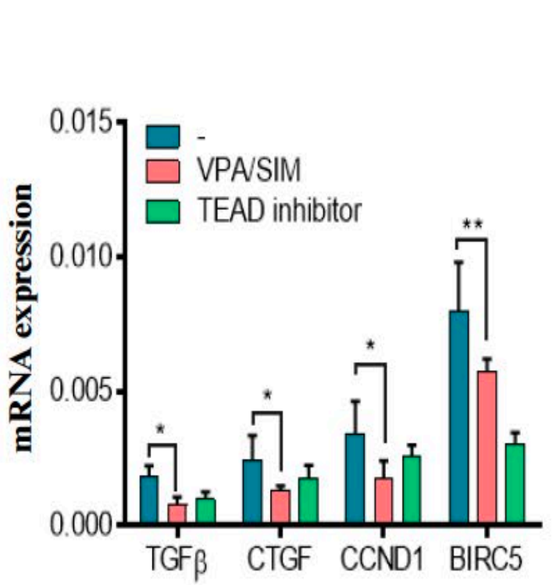
MS Roca et a. SUBMITTED

DO NOT POST

VPA/SIM reduces YAP1 activity by downregulating nuclear localization and transcriptional output





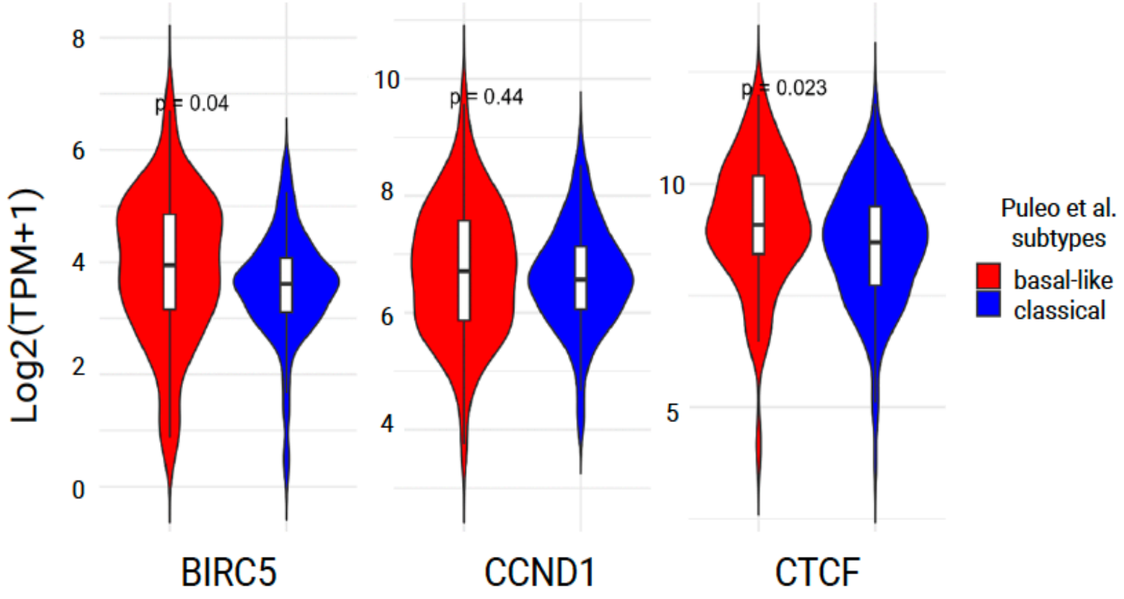


MS Roca et a. SUBMITTED

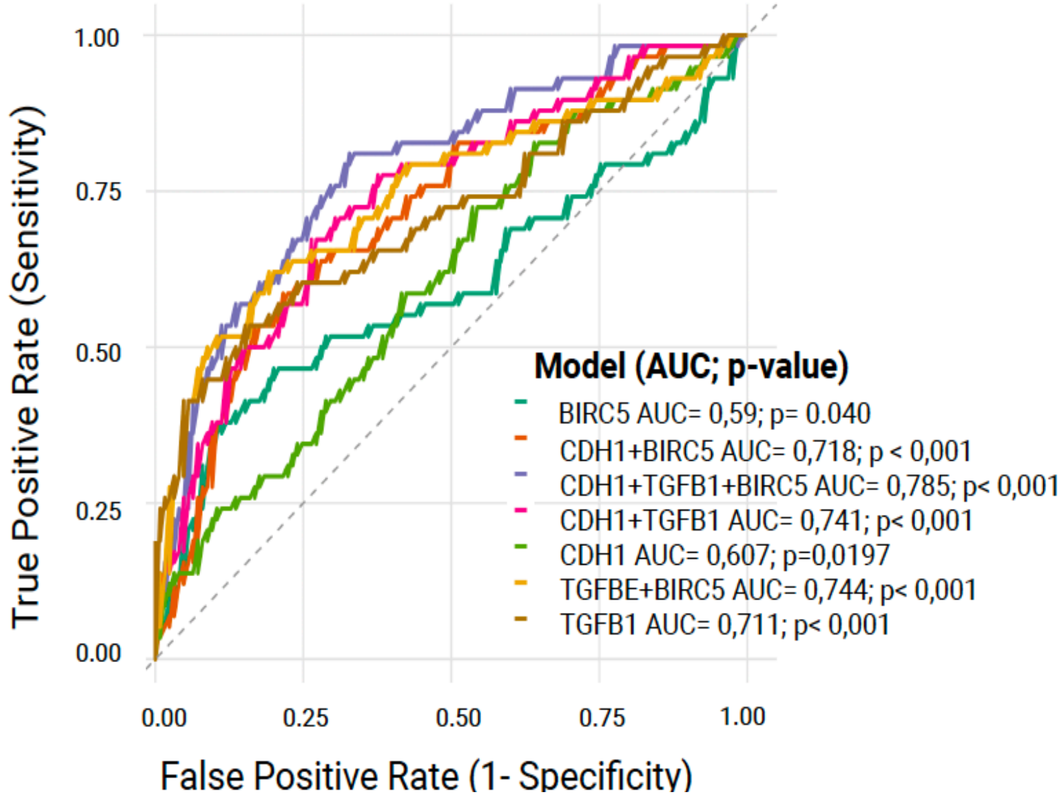
DO NOT POST

CDH1, TGFB1 and BIRC5 expression provides an initial proof of concept biomarker set to distinguish VPA/SIM-responsive basal-like PDAC from classical subtypes.

I



L



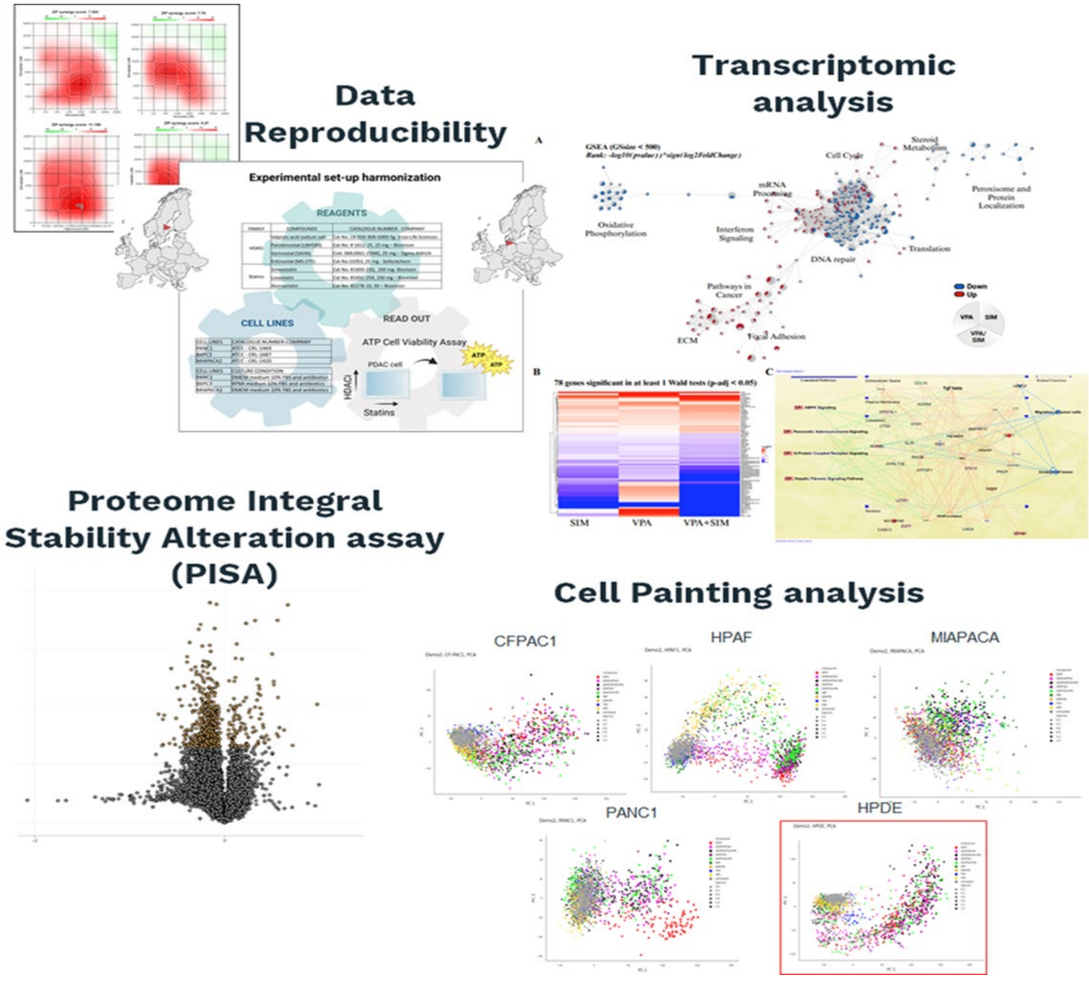
MS Roca et a. SUBMITTED

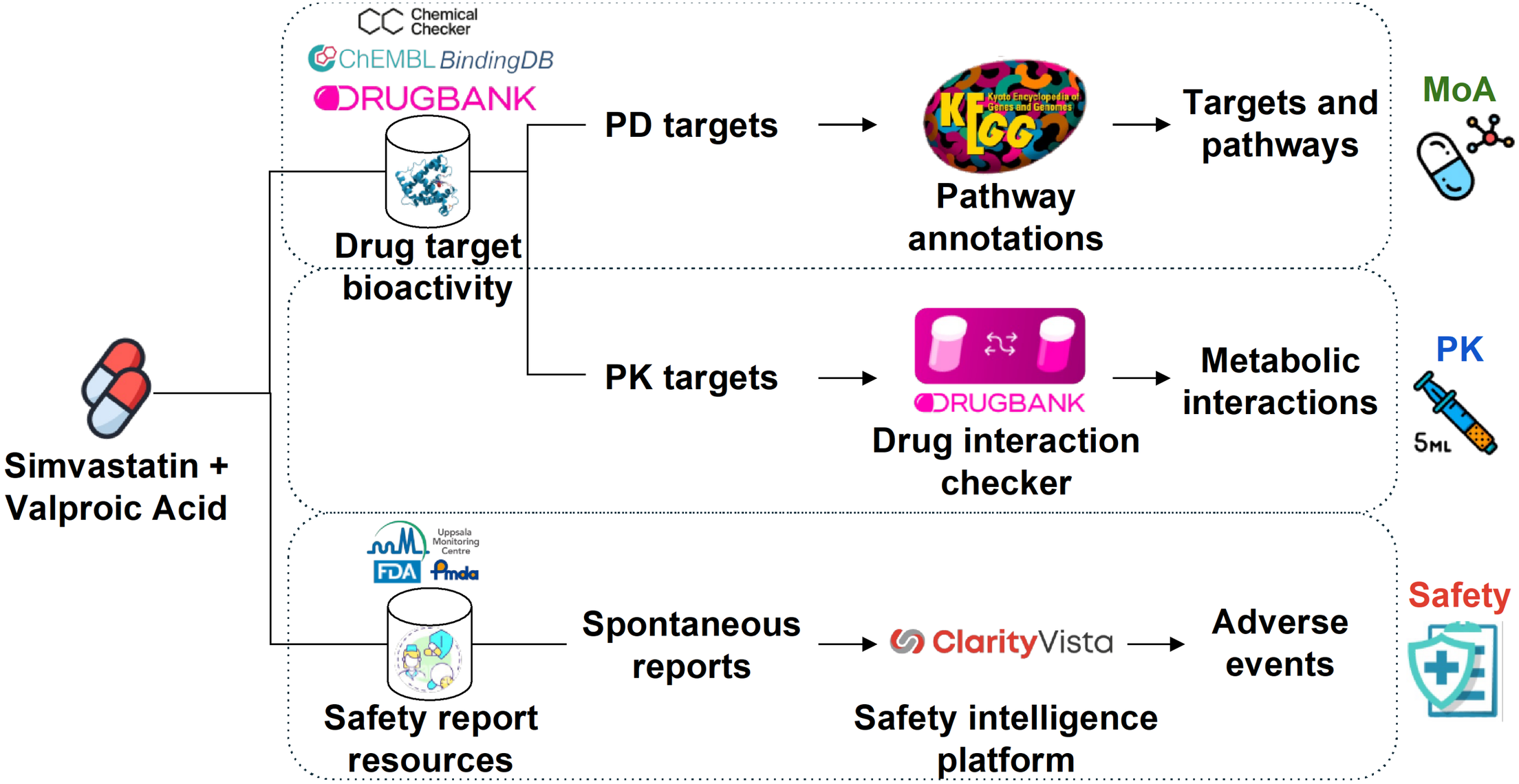
DO NOT POST

Multiomic studies: collaborative efforts within REMEDI4ALL

- *The integration of OMIC DATA from data could led to the identification of potential circulating biomarkers (e.g. miRNAs) to be validated in VESPA patients, which may prove useful in enhancing patient stratification and guiding treatment decisions.*

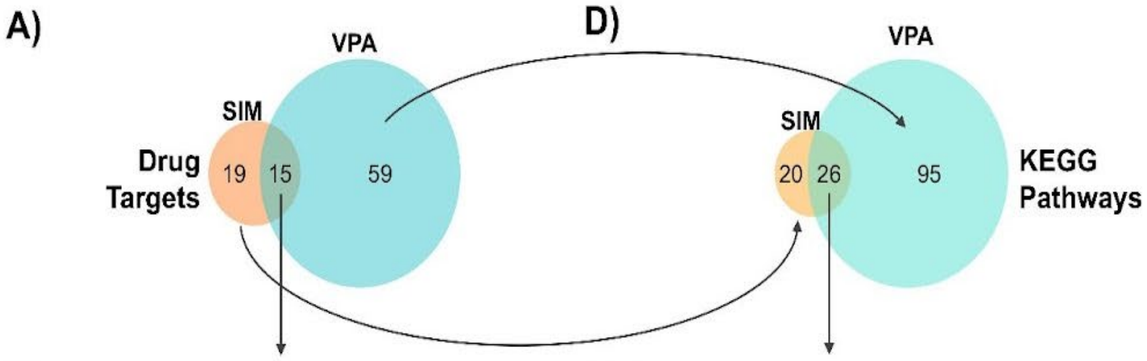
Institute	Type of analysis
INT-NA	Proteomic
Mario Negri	Transcriptomic
Mario Negri IRYCIS	Transcriptomic (RNA-seq, miRNA-seq)
IRE	Atac-seq
Karolinska	PISA
Uppsala	Cell Painting
INT-NA Karolinska Fraunhofer FIMM	Reproducibility





Tanoli Z. et al, Nat Rev Drug Discov. 2025 Mar 18. doi: 10.1038/s41573-025-01164-x

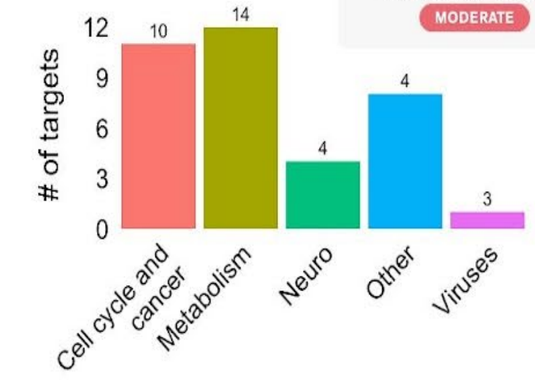
In silico identification of primary and secondary targets of Valproic Acid and Simvastatin and their pathways



B) Common Targets

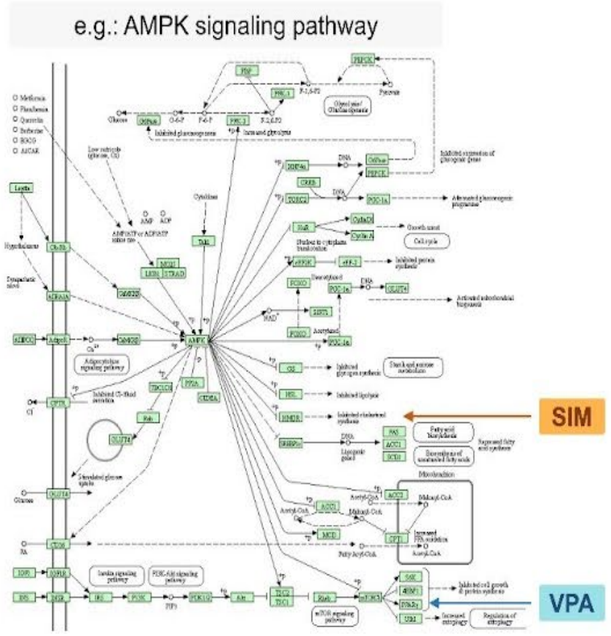
CES1	CES2	CYP1A2	CYP2B6	CYP2C19
CYP2C8	CYP2C9	CYP3A4	CYP3A5	HDAC2
SLCO2B1	TDP1	UGT2B7	UGT1A3	UGT1A1

C) Pathways categories



E) Common Pathways

e.g.: AMPK signaling pathway



Postmarketing reports of adverse events from four databases standardized and de-duplicated in CLARITY PV

Tanoli Z. et al, Nat Rev Drug Discov. 2025 Mar 18. doi: 10.1038/s41573-025-01164-x

In silico studies on Valproic Acid and Simvastatin interaction

ISTITUTO DI RICERCHE FARMACOLOGICHE MARIO NEGRI · IRCCS

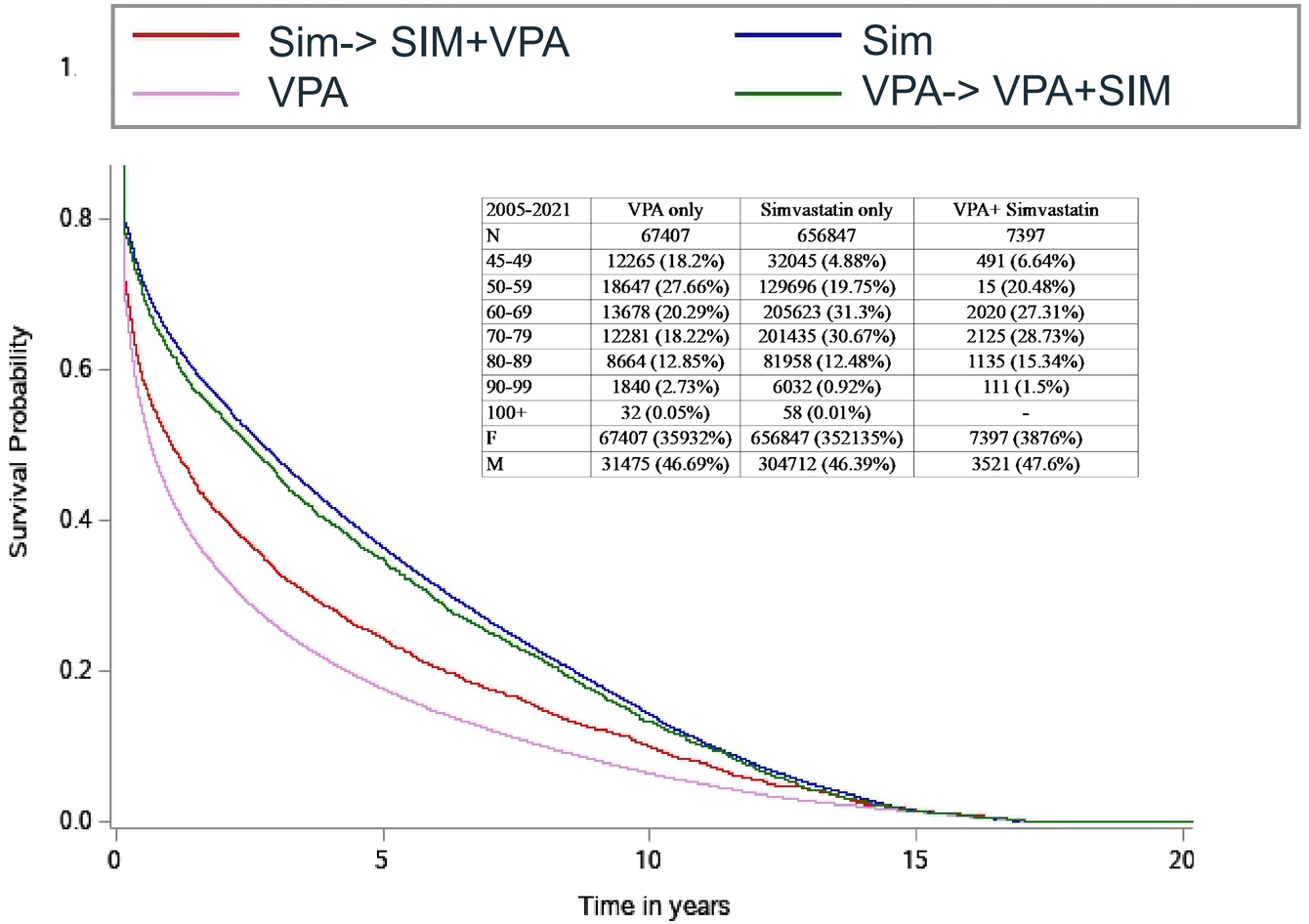
Lombardy Region (Italy) Dataset on valproic acid and/or Simvastatin use

Drug discontinuation

(Cox model)

HR(95% C.I.)	unadjusted	Sex and age adjusted	Sex, age and DDCI(no C10) adjusted
Simvastatin → +valproic acid vs valproic acid alone	0.85 (0.82; 0.88)	0.78 (0.76; 0.81)	0.77 (0.74; 0.79)
Valproic acid → + simvastatin vs simvastatin alone	1.04 (1.00; 1.08)	1.07 (1.03; 1.11)	1.05 (1.01;1.09)

DDCI: parameter based on the number of drugs used in the previous year as a proxy of global disease status



2005-2021	VPA only	Simvastatin only	VPA+ Simvastatin
N	67407	656847	7397
45-49	12265 (18.2%)	32045 (4.88%)	491 (6.64%)
50-59	18647 (27.66%)	129696 (19.75%)	15 (20.48%)
60-69	13678 (20.29%)	205623 (31.3%)	2020 (27.31%)
70-79	12281 (18.22%)	201435 (30.67%)	2125 (28.73%)
80-89	8664 (12.85%)	81958 (12.48%)	1135 (15.34%)
90-99	1840 (2.73%)	6032 (0.92%)	111 (1.5%)
100+	32 (0.05%)	58 (0.01%)	-
F	67407 (35932%)	656847 (352135%)	7397 (3876%)
M	31475 (46.69%)	304712 (46.39%)	3521 (47.6%)

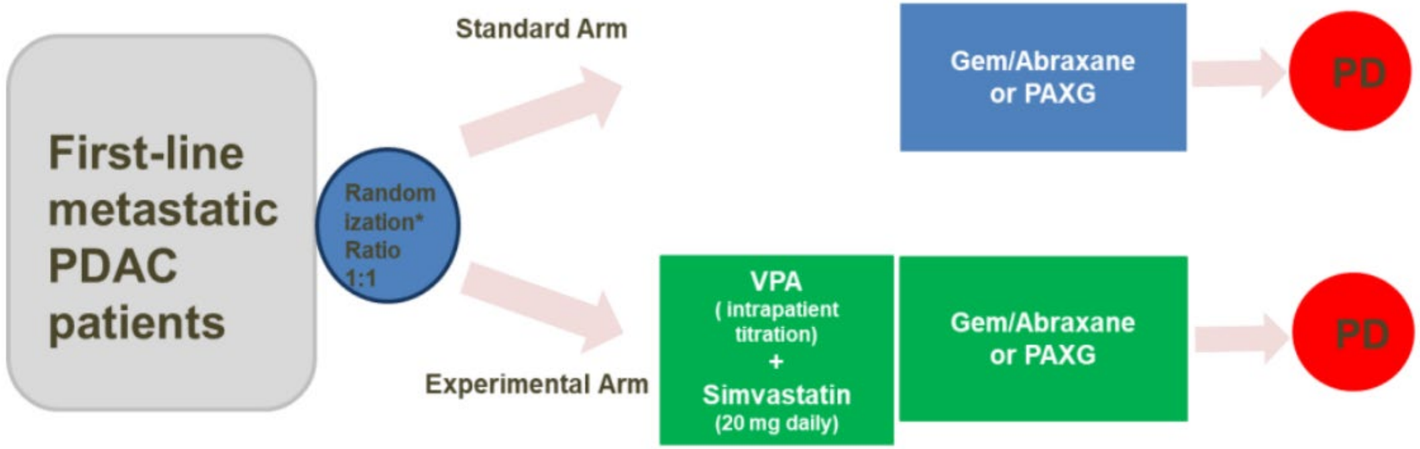
Unpublished data please do not post !

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Laura Fiorenza et al….& Maddalena Fratelli, Manuscript to be submitted

Randomized phase 2 study of Valproic acid combinEd with Simvastatin and gemcitabine/nab-paclitaxel-based regimens in untreated metastatic Pancreatic Adenocarcinoma patients - vespa trial

NCT05821556; EudraCT number 2022-004154-63; EU CT Number: 2024-518710-11-00



Primary endpoint: progression free survival **(PFS)**

Secondary endpoints:
objective tumor response rate **(ORR),** duration control rate **(DOR),** disease control rate **(DCR),** overall survival **(OS),** overall toxicity rate and quality of life **(QoL).**

Exploratory objectives: Biomarkers studies on Tissue and Blood samples

Randomization will be stratified by center, PS (0 vs 1) and by treatment of chemotherapy backbone (GEM/ABRAX vs PAXG).

A total of 170 patients, 85 for arm, will be enrolled

Ministero della Salute
RF-2021-12371995

***BMC Cancer* 24, 1167 (2024).** https://doi.org/10.1186/s12885-024-12936-w

Standard of Care in metastatic PDAC

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO OPEN SCIENCE FOR OPTIMAL CANCER CARE

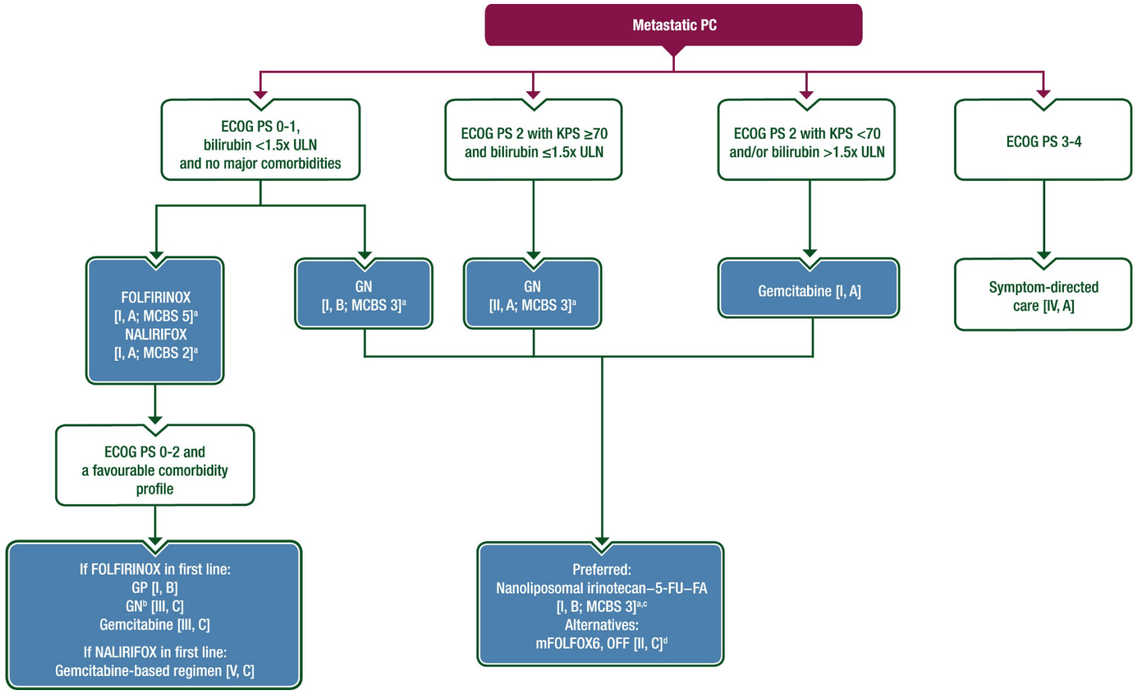
SPECIAL ARTICLE

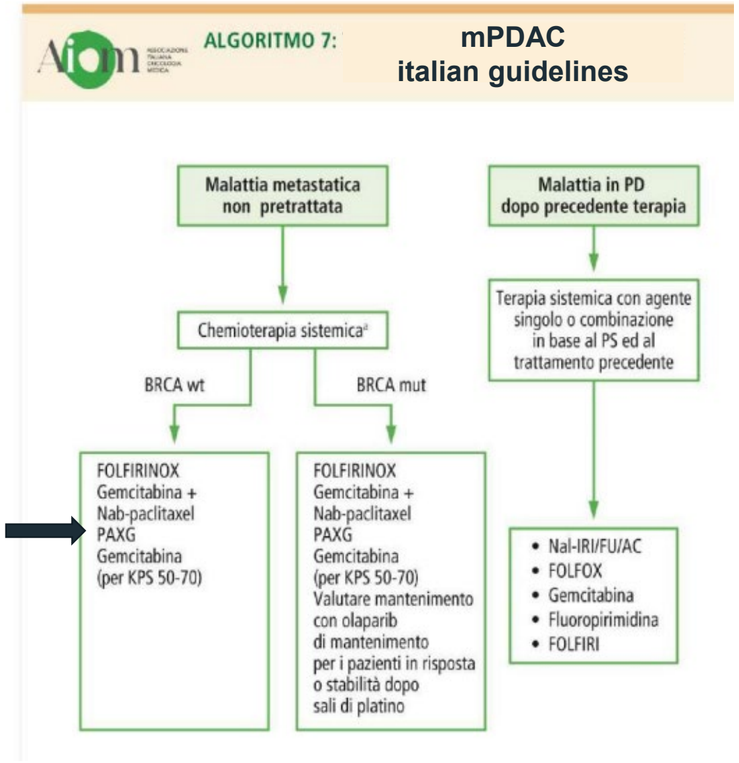
ESMO Clinical Practice Guideline Express Update on the management of metastatic pancreatic cancer

T. Conroy[1,2] & M. Ducreux[3,4], on behalf of the ESMO Guidelines Committee*

[1]Department of Medical Oncology, Institut de Cancérologie de Lorraine, Vandoeuvre-lès-Nancy; [2]Université de Lorraine, INSERM INSPIIRE, Nancy; [3]INSERM U1279, Université Paris-Saclay, Villejuif; [4]Department of Cancer Medicine, Gustave Roussy, Villejuif, France

Available online 9 April 2025





Nab-paclitaxel plus gemcitabine with or without capecitabine and cisplatin in metastatic pancreatic adenocarcinoma (PACT-19): a randomised phase 2 trial

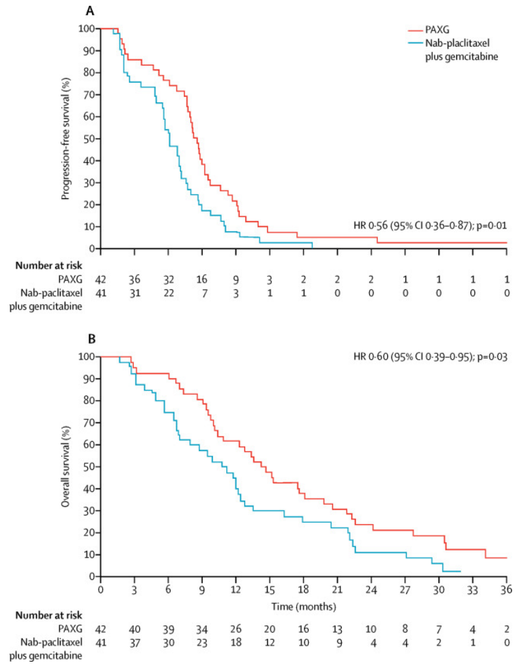
Michele Reni, Silvia Zanon, Umberto Peretti, Marta Chiaravalli, Diletta Barone, Chiara Pircher, Gianpaolo Balzano, Marina Macchini, Silvia Romi, Elena Gritti, Elena Mazza, Roberto Nicoletti, Claudio Doglioni, Massimo Falconi, Luca Gianni

Lancet Gastroenterol Hepatol 2018; 3: 691–97

Published Online July 6, 2018

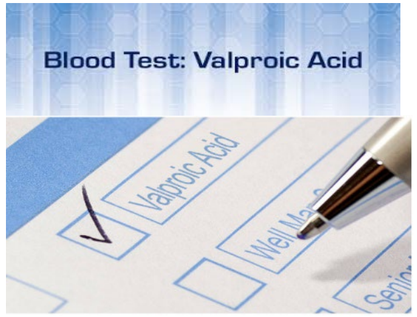
Summary

Background Current treatment for metastatic pancreatic ductal adenocarcinoma includes combination chemotherapy, such as FOLFIRINOX or nab-paclitaxel plus gemcitabine. We investigated the activity of a novel four-drug regimen, consisting of cisplatin, nab-paclitaxel, capecitabine, and gemcitabine, compared with nab-paclitaxel plus gemcitabine, in the PACT-19 trial.



Median progression-free survival was ***8,3*** months (95% CI 1·5–36·3) in the **PAXG** group and ***6,1*** months (1·1–18·7) in the nab-paclitaxel plus gemcitabine group (HR for progression 0·56, 95% CI 0·36–0·87; p=0·01). After a median follow-up of 30·9 months (range 22·1–34·9), median overall survival was 14·4 months (95% CI 2·7–37·4) in the PAXG group and 10·7 months (1·7–31·9) in the nab-paclitaxel plus gemcitabine group

VPA titration



Days	morning dose*	midday dose*	evening dose*
-7	0	0	500
-6	300	0	500
-5	500	0	500
-4 & -3	500	300	500
-2 & -1	500	500	500
* the interval between doses will be 12 hours on days -7 to -5 and 8 hours from day -4			

Valproic acid (VPA) will be administered in each patient with a **titration strategy** to improve the compliance for the treatment, looking for a target **serum level between 50 and 100 µg/mL** that represents the **recommended values for the treatment of epilepsy** and also a useful concentration to produce the desired synergistic effect with chemotherapy based on preclinical studies.

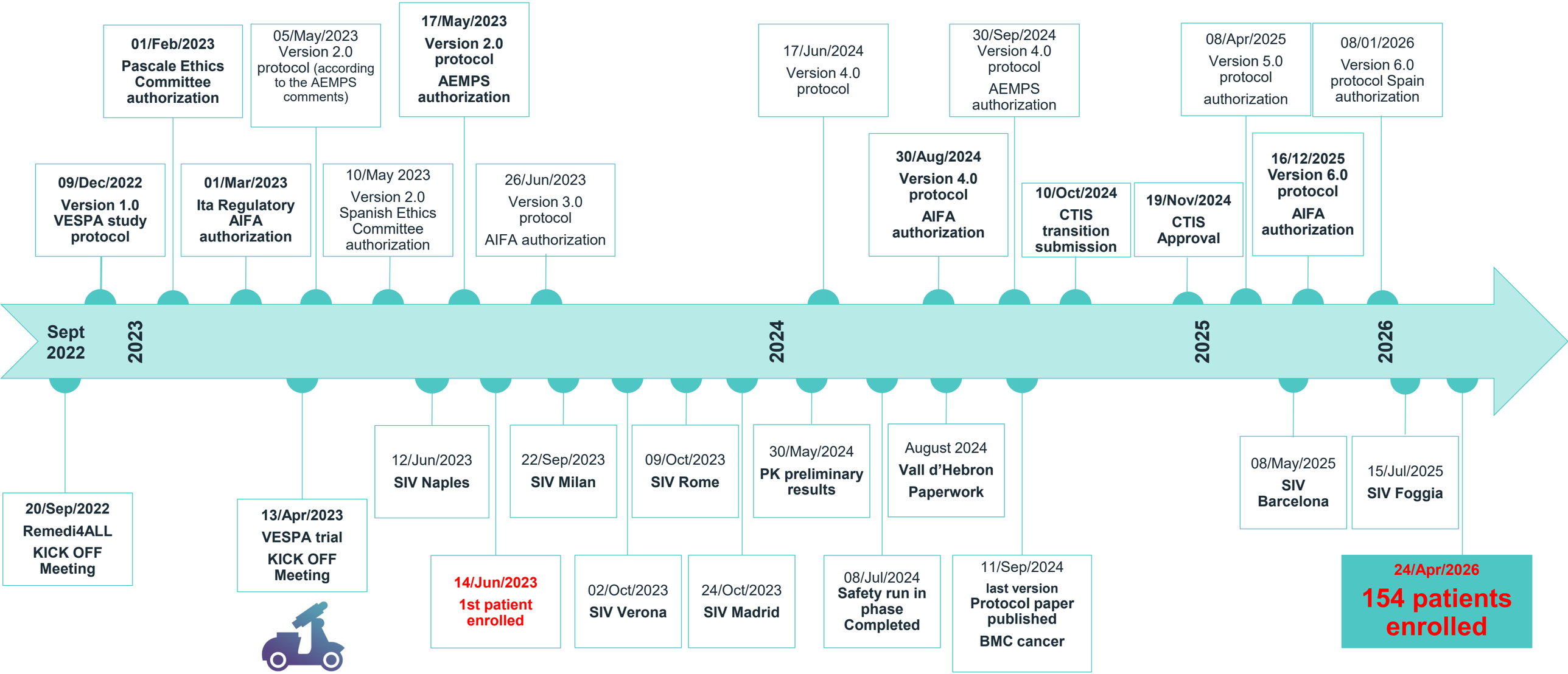
Serum level of VPA will be checked by drawing a blood sample within 2 hours after taking the morning dose using a commercially **available valproate test**, available in the Pathology Unit of each center involved in the trial. Consequently, the dose of VPA will be adjusted depending on the reached steady level. Simvastatin and valproic acid will be administered until the end of treatment.

A diary containing details about the home administration will be dispensed by the Investigator to the patient.

Randomized phase 2 study of Valproic acid combinEd with Simvastatin and gemcitabine/nab-paclitaxel-based regimens in untreated metastatic Pancreatic Adenocarcinoma patients

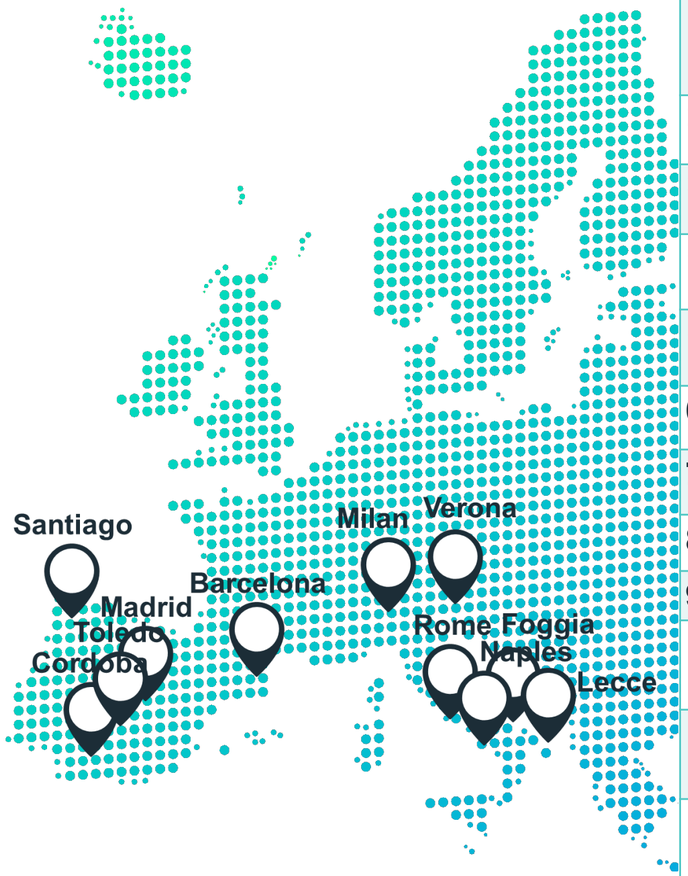
ISTITUTO NAZIONALE TUMORI
IRCCS - Fondazione Pascale

vespa trial



Participating sites

vespa trial



n. site	Principal Investigator(s)	Institution	Location
1	Dr. Antonio Avallone; Dr. Alfredo Budillon	IRCCS Fondazione G. Pascale- UOC Oncologia Clinica Sperimentale	Naples, Italy
2	Prof. Michele Milella	University of Verona Hospital Trust, Department of Oncology, Pancreas Center	Verona, Italy
3	Prof. Michele Reni	University Vita e Salute, IRCCS San Raffaele, Department of Oncology Pancreas Institute	Milan, Italy
4	Prof. Giampaolo Tortora	University Cattolica del Sacro Cuore, IRCCS Fondazione Policlinico Universitario Gemelli- Medical Oncology	Rome, Italy
5	Dr. Rodriguez Garrote Mercedes	Ramon y Cajal Hospital and Health Institue (IRYCIS)	Madrid, Spain
6	Dr Jaume Capdevila	Hospital Universitari Vall d'Hebron	Barcelona, Spain
7	Dr. Guido Giordano	Ospedali Riuniti, Azienda Ospedaliero Universitaria	Foggia, Italy
8	Dr. Emiliano Tamburini	Azienda Ospedaliera Pia Fondazione Card. G. Panico, Tricase (LE)	Lecce, Italy
9	Dr Silvana Leo	ASL Lecce - P.O. Vito Fazzi	Lecce, Italy
10	Dr. Maria Teresa Cano Osuna	Univ. Hospital Reina Sofía Córdoba (IMIBIC)	Cordoba, Spain
11	Dr. Ana Belén Ruperez Blanco	Univ. Hospital Toledo	Toledo, Spain
12	Dr. Elena Maria Brazos Vazquez	Univ. Hospital Santiago de Compostela (IDIS)	Santiago De Compostela, Spain
13	Dr. Katia Bruna Bencardino	Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan	Milano, Italy
14	Dr. Ilario Giovanni Rapposelli	Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST S.r.l. IRCCS, Meldola (FC)	Meldola, Italy

Amendment 03 – Version 4.0 protocol_17 Jun 2024
Amendment 04 – Version 5.0 protocol_06 Feb 2025
Amendment 05_Mod Sostanziale VHIO
Amendment 06 – Version 6.0 protocol_23 Oct 2025

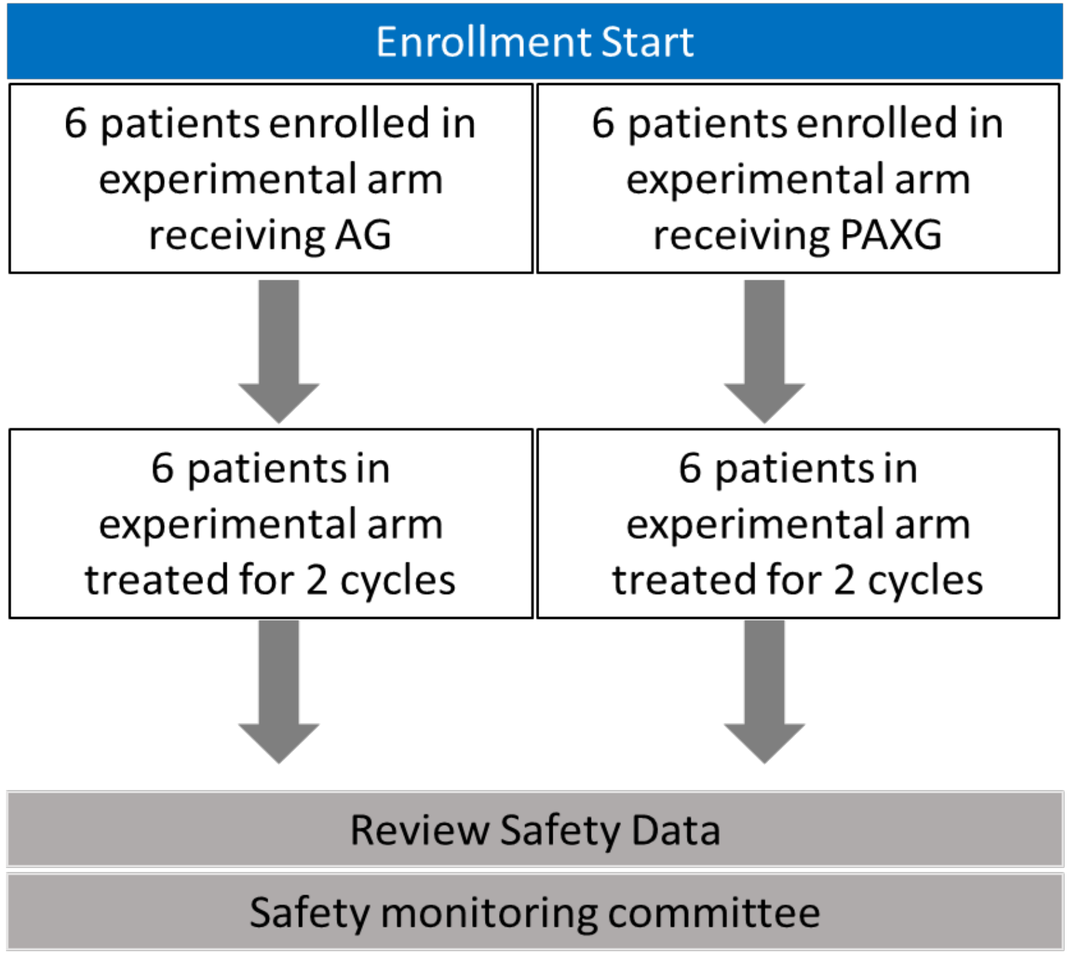
Recruitment progress

vespa trial

Patients	In Screening	Enrolled	Treated	ARM A	ARM B
	156	154	141	70	71

Principal Investigator(s)	Institution	Location	SIV	Enrolled pts	Treated pts
Dr. Antonio Avallone; Dr. Alfredo Budillon	IRCCS Fondazione G. Pascale- UOC Oncologia Clinica Sperimentale	Naples, Italy	12/06/2023	55	54
Prof. Michele Milella	University of Verona Hospital Trust, Department of Oncology, Pancreas Center	Verona, Italy	02/10/2023	15	12
Prof. Michele Reni	University Vita e Salute, IRCCS San Raffaele, Department of Oncology Pancreas Institute	Milan, Italy	22/09/2023	40	38
Prof. Giampaolo Tortora	University Cattolica del Sacro Cuore, IRCCS Fondazione Policlinico Universitario Gemelli- Medical Oncology	Rome, Italy	09/10/2023	22	20
Dr. Rodriguez Garrote Mercedes	Ramon y Cajal Hospital and Health Institue (IRYCIS)	Madrid, Spain	24/10/2023	8	6
Dr Jaume Capdevila	Hospital Universitari Vall d'Hebron	Barcelona, Spain	08/05/2025	8	3
Dr. Guido Giordano	Ospedali Riuniti, Azienda Ospedaliero Universitaria	Foggia, Italy	15/07/2025	4	4
Dr. Emiliano Tamburini	Azienda Ospedaliera Pia Fondazione Card. G. Panico, Tricase (LE)	Lecce, Italy	10/09/2025	3	3
Dr Silvana Leo	ASL Lecce - P.O. Vito Fazzi	Lecce, Italy	17/09/2025	0	0
Dr. Maria Teresa Cano Osuna	Univ. Hospital Reina Sofía Córdoba (IMIBIC)	Cordoba, Spain	30/01/2026	0	0
Dr. Ana Belén Ruperez Blanco	Univ. Hospital Toledo	Toledo, Spain	24/03/2026	0	0
Dr. Elena Maria Brazos Vazquez	Univ. Hospital Santiago de Compostela (IDIS)	Santiago De Compostela, Spain	10/04/2026	0	3
Dr. Ilario Giovanni Rapposelli	Istituto Romagnolo per lo Studio dei Tumori "Dino Amadori" - IRST S.r.l. IRCCS, Meldola (FC)	Meldola, Italy	24/02/2026	1	1
Dr. Katia Bruna Bencardino	Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milan	Milano, Italy	-		

Safety run in phase *completed*



"SMC recommend the trial to continue recruiting patients"

The Study included an initial 6-patients safety run-in phase in the experimental arm (both for AG and PAXG treatment)

Safety evaluation has been performed by an independent **Safety Monitoring Committee (SMC)**

Dr. Joaquin SÁEZ-PEÑATARO, MD
Clinical Pharmacology Specialist
Hospital Clinic Barcelona, Spain

Dr. Maria Carmela Piccirillo, MD
Medical Oncologist
Istituto Nazionale Tumori G. Pascale, Napoli, Italy

Dr. Federica Valsecchi, PhD
Pancreatic cancer patient advocate
Fondazione Nadia Valsecchi
Conta su di noi, sempre.
Memorial Sloan Kettering Cancer Center, New York, USA (suggested by Patient' Organization)

Trial continues until 170 patients enrollment

Independent Data Monitoring Committee Appointed (v.4 protocol)

SMC plus:

Dr. Paolo Chiodini
Full professor – Medical statistics
University of Campania – Luigi Vanvitelli, Naples, Italy

Dr. Giuseppe Aprile
Medical Oncologist
Azienda ULSS8 Berica, Vicenza, Italy

Safety data

May 2025

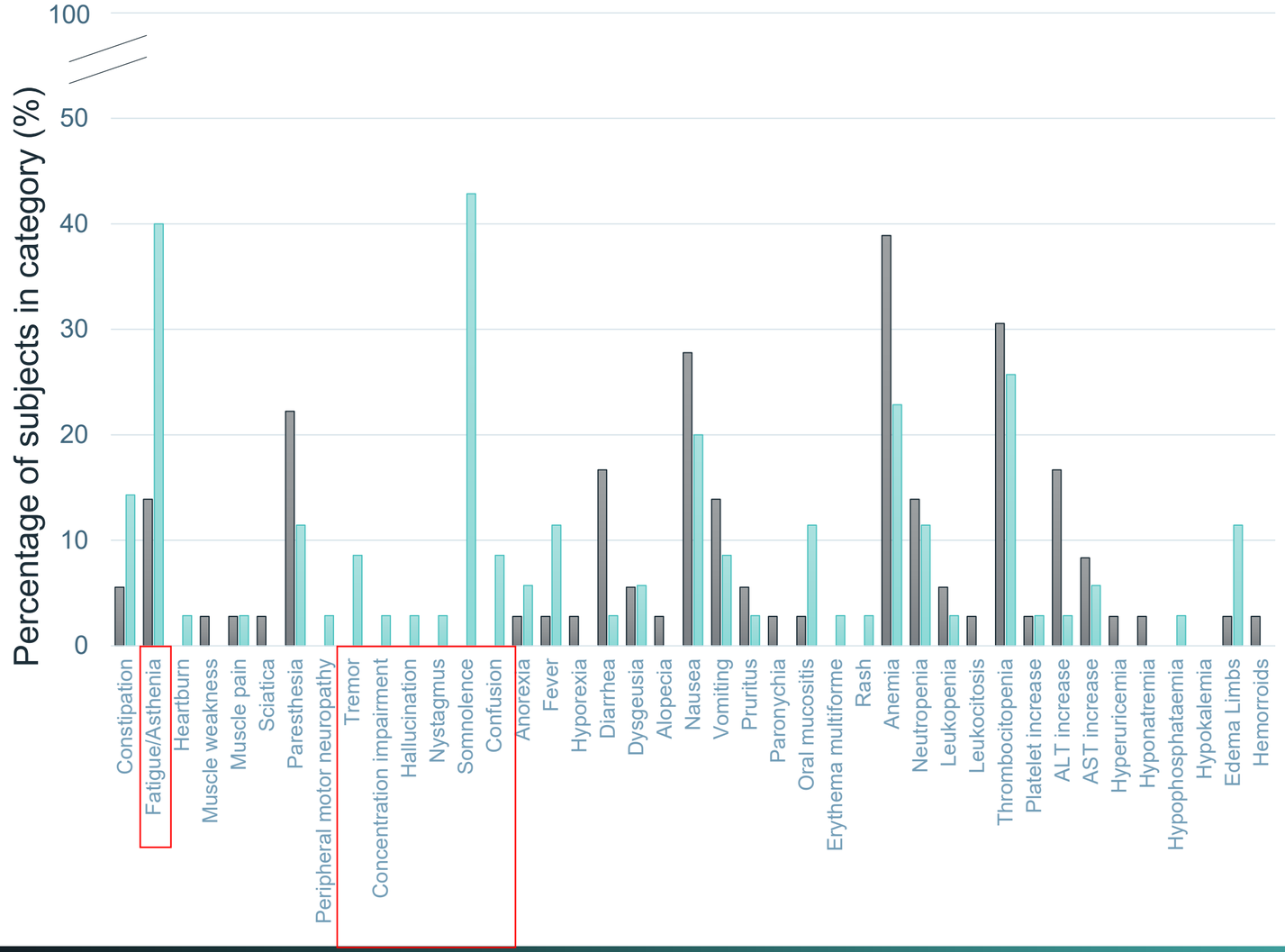
vespa trial

Arm A - standard

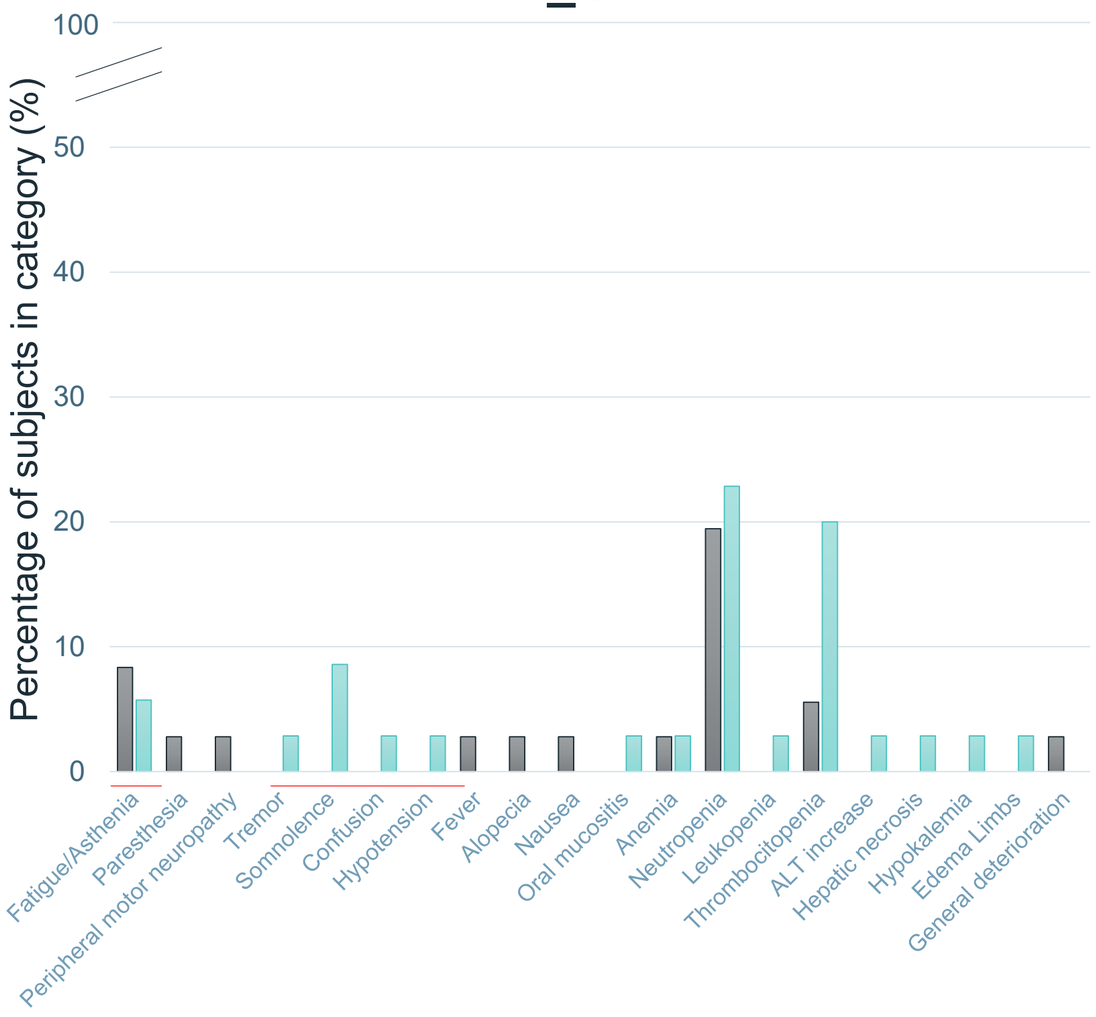
Arm B - experimental

Adverse Events (AE)_AG

AE_G1-G2



AE_G3



Safety data

May 2025

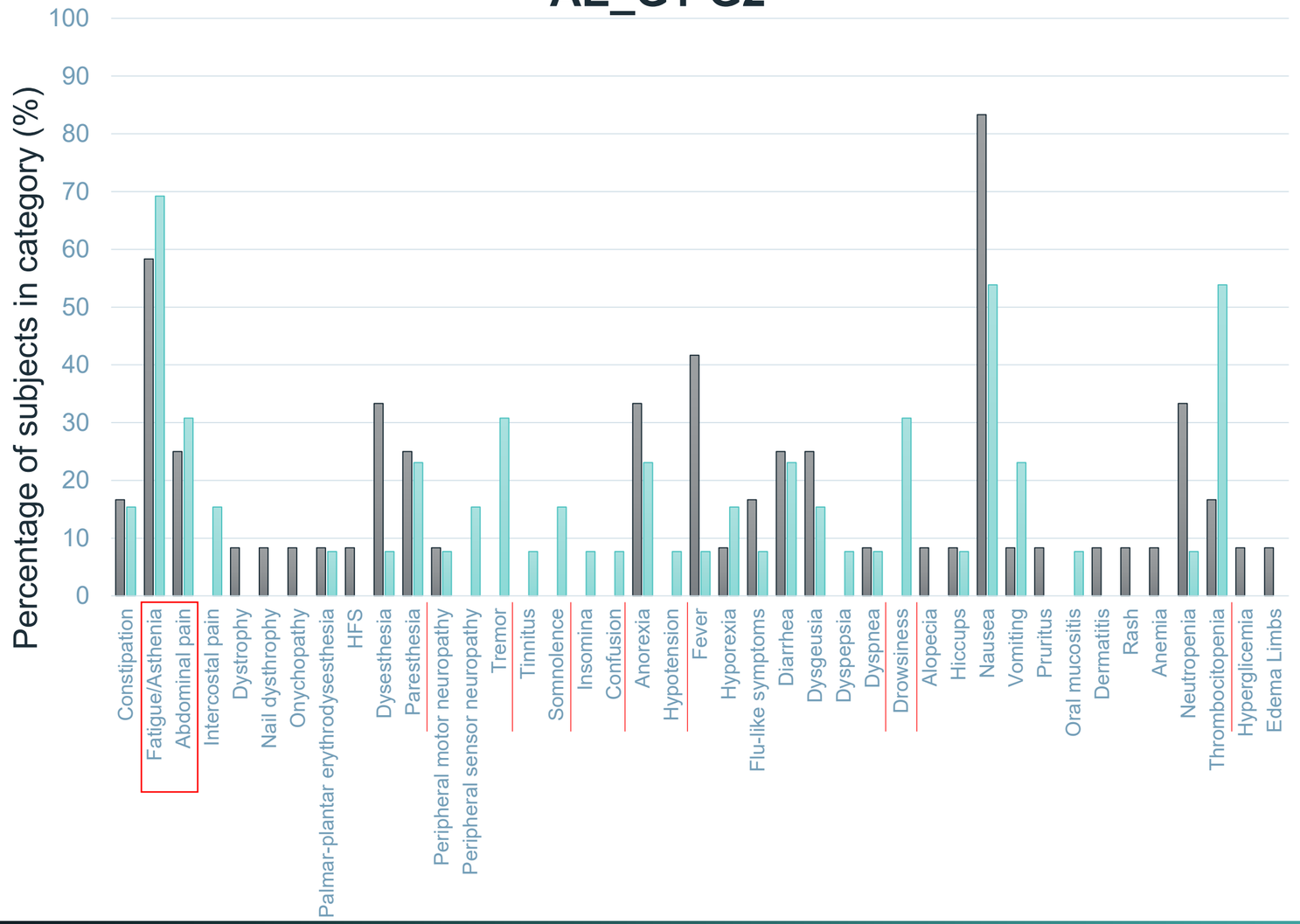
vespa trial

Arm A - standard

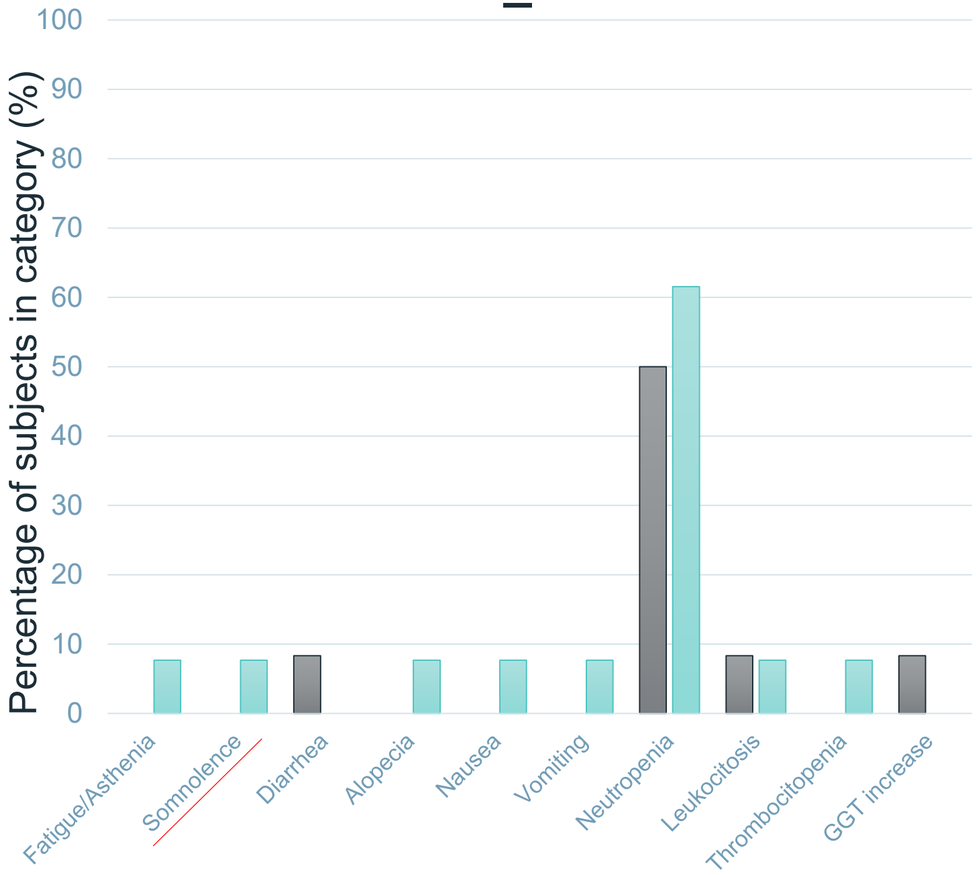
Arm B - experimental

Adverse Events (AE)_PAXG

AE_G1-G2



AE_G3

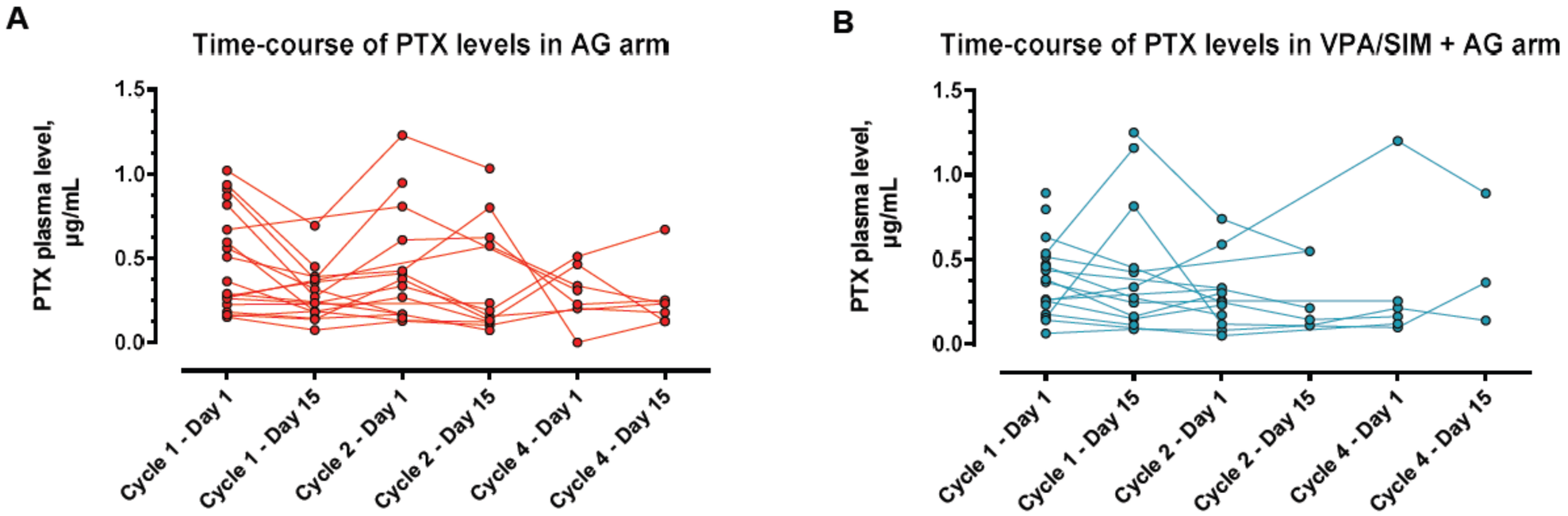


Preliminary Pharmacokinetics studies demonstrated no interference of experimental drugs on chemotherapy

(only AG regimen/Italian centers)

vespa trial

Paclitaxel plasma levels

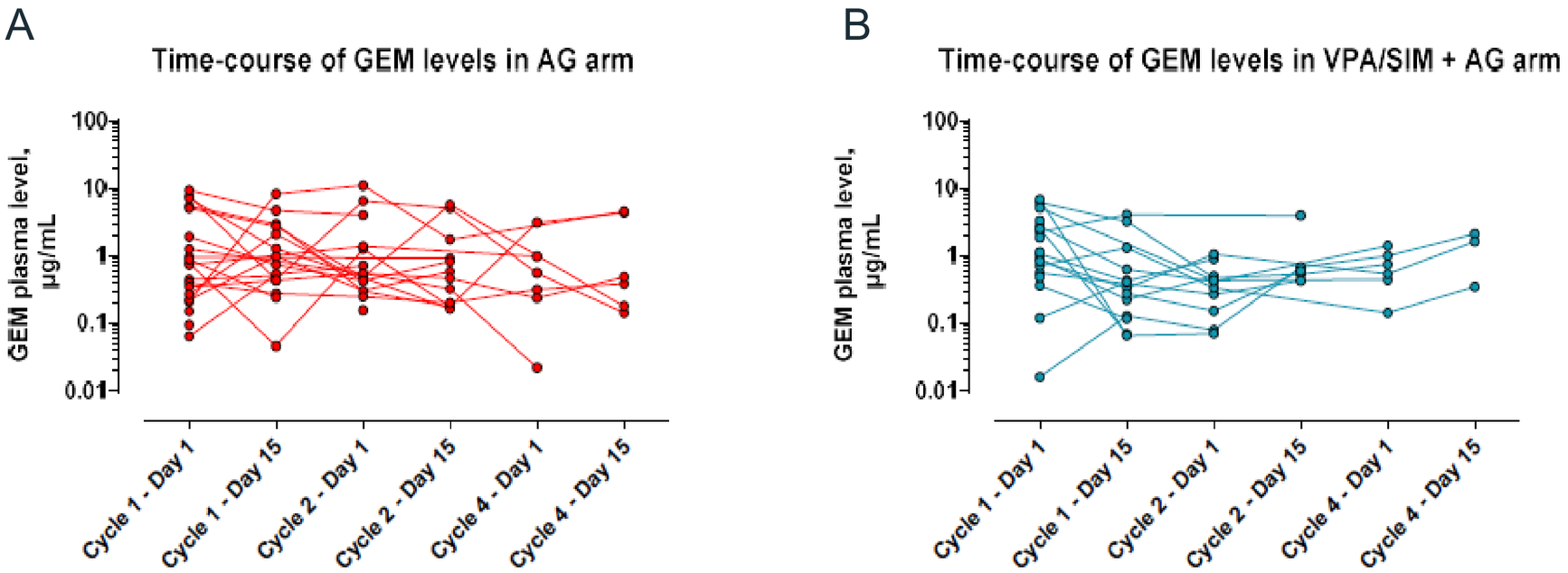


Intra-patient time-course profile of Paclitaxel (PTX) plasma levels over 4 cycles of treatment in AG arm (A) and VPA/SIM + AG arm (B). *Plasma were sampled whithin 1-1.5h from the end of Nab-PTX-infusion (125 mg/m^2 IV 30-min-infusion once a week)*

Preliminary Pharmacokinetics studies demonstrated no interference of experimental drugs on chemotherapy

(only AG regimen/Italian centers)

Gemcitabine plasma levels

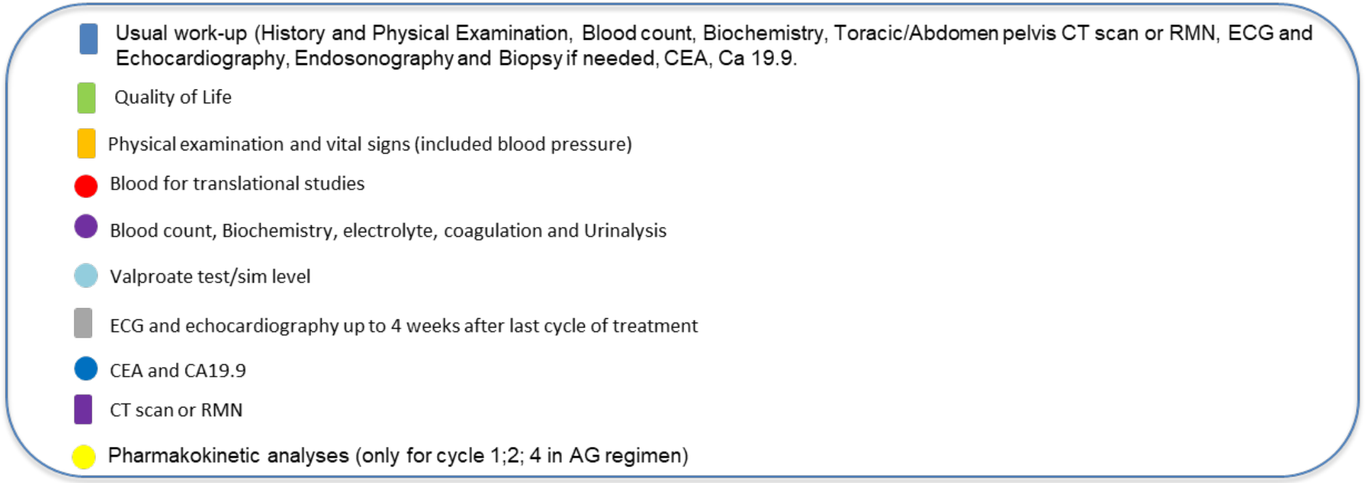


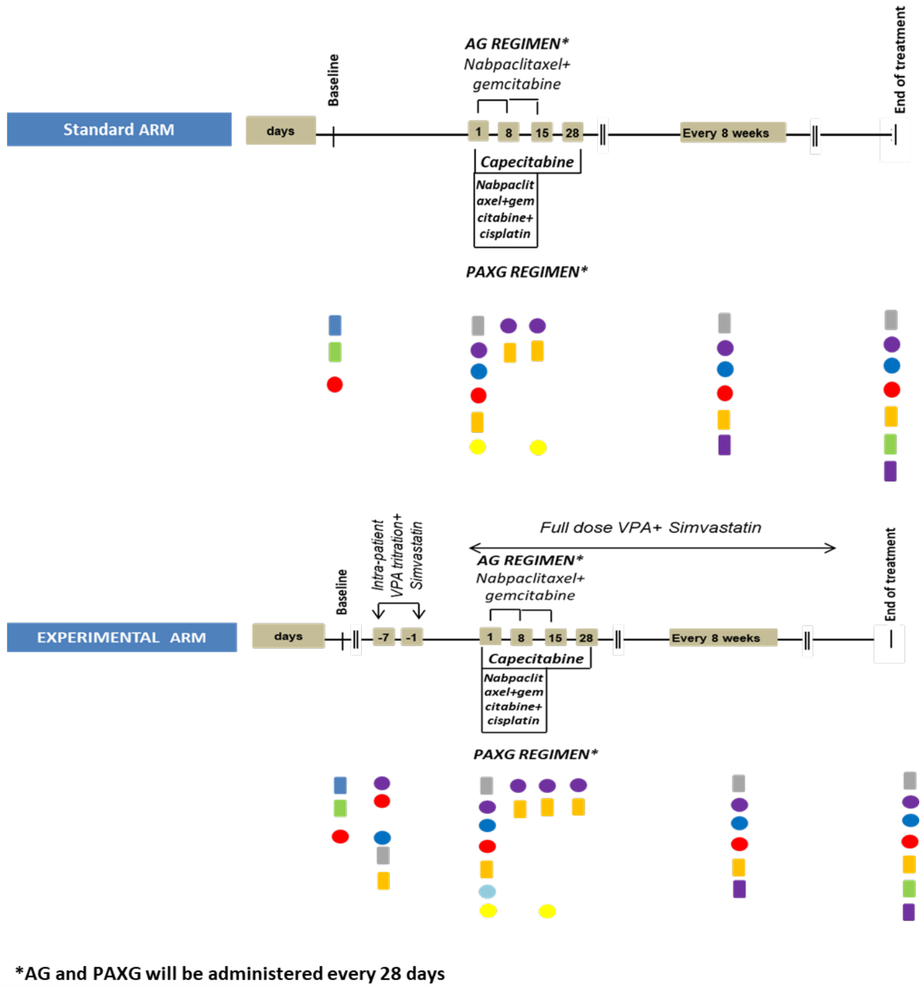
Intra-patient time-course profile of Gemcitabine (GEM) plasma levels over 4 cycles of treatment in AG arm (A) and VPA/SIM + AG arm (B).
Plasma were sampled whithin 30min from the end of GEM-infusion; 1000 mg/m^2 IV 60-min-infusion once a week).

Exploratory Secondary Objectives

- ***Peripheral blood samples*** for exploratory biomarker studies will be collected by any standard phlebotomy technique in EDTA tubes through 21 G needles and stored at -80°C as soon as possible (no later than 45 min). If a -80°C freezer is not available, samples contemporarily be kept at -20°C for a maximum of 3 months. Thereafter, samples need to be sent to the coordinator of translational studies for appropriate storage at -80°C.

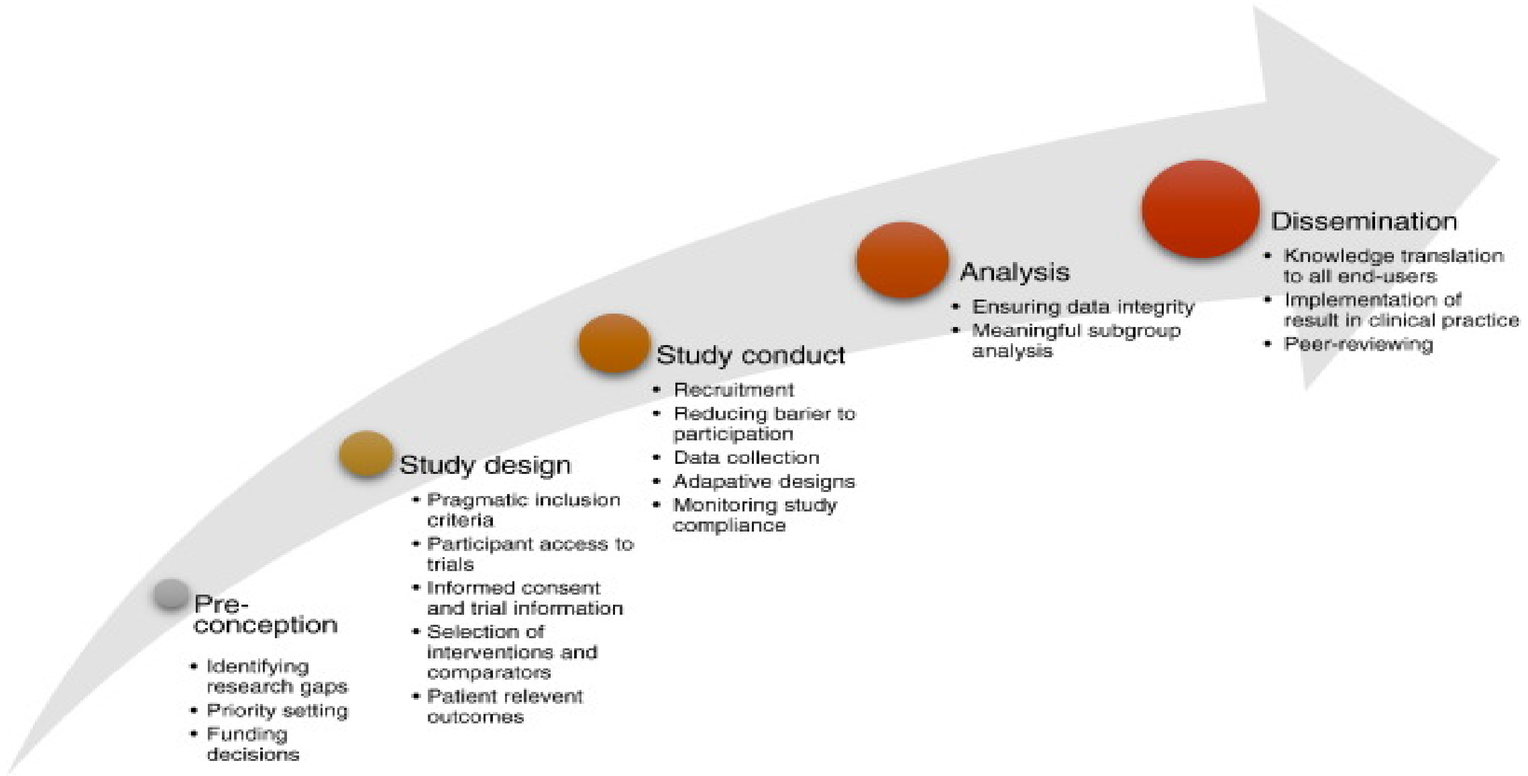
Blood samples will be collected:
- at *baseline* (BL)
- at *day 1* (after VPA intratritation), **only for first cycle of experimental arm**
- at *8 weeks*, the first day before drugs administration of a treatment
- every 8 weeks thereafter concomitantly with tumor assessment up to 40 weeks if not in progression
- at progression of disease (PD)





*AG and PAXG will be administered every 28 days

Patient Engagment Plan



«The active, meaningful, and collaborative interaction between patients and researchers across all stages of the research process, where research decision making is guided by patients' contributions as partners, recognizing their specific experiences, values, and expertise».

Rachel L.Harrington et al. ***VALUE HEALTH. 2020; 23(6):677–688***

The VESPA trial was planned as patient centric since the research design and patients contribute to each step of the study, being an active member of the study Steering Committee and Safety Monitoring Committee, to be sure to include patients' needs, as patient-oriented outcomes, design interventions, moral and ethical concerns and safety assessments.

REPURPOSING OF MEDICINES 4ALL

PATIENT FACT-SHEET

VESPA

Valproic acid combin**E**d wit
and gemcitabine/nab-paclitaxel ba
in untreated **P**ancreatic **A**denocarci

WHAT IS PANCREATIC CANCER?

The pancreas is a small but important digestive **organ.**

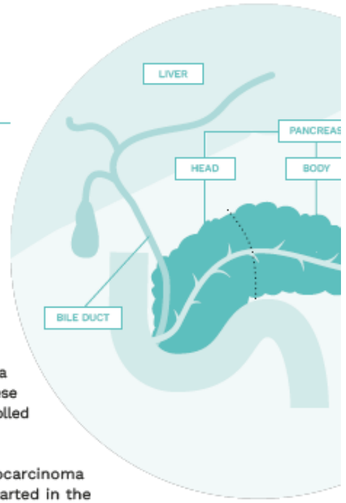
Special tubes or 'ducts' in the pancreas deliver digestive juices full of enzymes to other parts of the digestive system to help break food down into useful energy and nutrients.

Pancreatic Ductal Adenocarcinoma (PDAC) starts in the cells that form these ducts. The cells multiply in an uncontrolled way. This forms a tumor.

Metastatic Pancreatic Ductal Adenocarcinoma (mPDAC) means that your cancer started in the pancreatic ducts but has **spread to other parts of your body** such as your liver or lungs.

Currently, metastatic PDAC (mPDAC) cancer treatment remains chemotherapy-based but unfortunately, the outcome of this treatment is **not good as it is in other types of cancer.**

We need to do more research to find effective medications **to improve quality of life and prognosis of mPDAC patients.**



THE VESPA TRIAL AIMS T

- Assess if adding two repurpos to chemotherapy **improves h chemotherapy works.**
- **Slow down the spread** of dise
- Help **improve treatment optic** patients in the future.

WHAT IS DRUG REPURPOSING?

Drug repurposing means finding **new ways to use medicines that already exist;** using a drug in a way that was not its original purpose.

An example is **aspirin,** originally a **painkiller,** now used widely **to support heart health and prevent stroke.**

Using repurposed drugs means that a lot of important data already exists. This can **speed up** the clinical trial and approval process which means patients can access and **benefit from repurposed medicines faster** than newly developed medicines.

Repurposed drugs are **already used in the clinic,** so are **often safer to use** than a completely **new drug.**

All drugs have **more than one effect on the body.** Some of these can be unwanted side effects but some can be extremely **useful in treating diseases.** These are called **off-target effects.** We can **maximise the benefits** of off-target effects **through drug repurposing.**

THE VESPA TRIAL: DRUG REPURPOSING FOR PANCREATIC CANCER

240 patients in Italy and Spain who have been diagnosed with mPDAC and are about to start treatment will be invited to take part in VESPA.

In the lab there have been very promising results showing that a combination of Simvastatin + Valproic Acid can improve how well normal chemotherapy treatment works.

- Simvastatin—originally used to lower cholesterol
- Valproic Acid—originally used to prevent seizures and in some mental health issues

Both medications have been used by doctors around the world for many years. This mean we know they are safe and have minimal side effects.

PARTICIPATING IN VESPA

If you are **eligible and consent** to participate, a computer will **randomly assign you (randomise)** to one of two groups. Your **doctor cannot decide** which group you will be assigned to.

GROUP 1
Receive **standard treatment** for mPDAC (Abraxane based **chemotherapy)**

GROUP 2
Receive **standard treatment** for mPDAC (Abraxane based **chemotherapy)**
+ Simvastatin & Valproic Acid

Whatever group you are randomly assigned to, you are guaranteed to receive the same treatment that you would receive if you did not join the trial.

SCREENING

In the month leading up to your first treatment you will **undergo some tests** to make sure you are well enough to continue the trial. These are called **screening procedures** and help your clinical team determine if you are eligible for the trial.

Many of these tests will coincide with planned visits to clinic to limit the amount of hospital visits you will have to make.

Having additional tests is not a cause for concern and does not mean we think your cancer has progressed.

Screening tests include:
- A CT or MRI scan
- Some blood tests
- A scan of your heart (ECHO)
- A tracing of your heart (ECG)
- Vital signs (blood pressure, heart rate etc.)
- Physical examination
- A blood test to check thelevels of tumor markers (CA19.9 and CEA)
- A pregnancy test (where appropriate)
- A Quality of Life (QOL) questionnaire

Some of these tests will be **repeated throughout the course of your treatment** to ensure that you are not having any side effects to the medications and that they **are working as expected.**

Blood samples **before and during** treatment and a tissue sample **before starting** treatment will also be used for additional research to **improve our knowledge** on the disease and **assess the response** to the trial therapy.

TREATMENT

Each cycle of treatment will be **28 days.**

Both chemotherapy regimens in this trial contain **Nab-paclitaxel (Abraxane) + Gemcitabine: AG regimen or PAXG regimen.** Both regimens in the trial have been **proven to work for mPADC.**

These chemotherapy drugs **in the lab** show **promising enhanced antitumoral effects when combined** with **Simvastatin and Valproic Acid.**

You may be in hospital for **chemotherapy treatment 2 or 3 times** in this 28-day period **depending on which regimen** your doctor decides is best for you.

If you are randomized to the **experimental arm,** you will begin Simvastatin and Valproic Acid **7 days before chemotherapy starts** and continue taking them for the whole cycle. You can **take these tablets at home.** It is important to take these as scheduled and a **medication diary will be provided** to help ensure you are taking the correct amount and don't miss any doses.

Your **treatment on trial may be interrupted or stopped** if you have any **severe side effects.**

Your **treatment on trial will stop** if your **tumor grows or spreads** (disease progression).

You may experience side effects. **Side effects from chemotherapy, Simvastatin and Valproic Acid are often reversible and easily treatable.** If you are worried about side effects, please **talk to your doctor.**

Your **Patient Information Sheet** contains a list of *some* **common side effects.** You may experience **none, some, or all** of these, during your treatment.

Trial Schedule

DAY -28	DAY -28 TO 0	DAY -7	DAY 1	DAY 8	DAY 15	DAY 28	DAY 56
Consent	Screening Procedures	GROUP 2 Start Simvastatin + Valproic acid	Chemotherapy	Chemotherapy (AG regimen, nab-paclitaxel + gemcitabina only)	Chemotherapy	End of Cycle	+/- 7 days CT or MRI scan, Quality of Life Questionnaire

Communication **strategies to improve trial recruitment**

ISTITUTO NAZIONALE TUMORI IRCCS – Fondazione Pascale

EURORDIS RARE DISEASES EUROPE

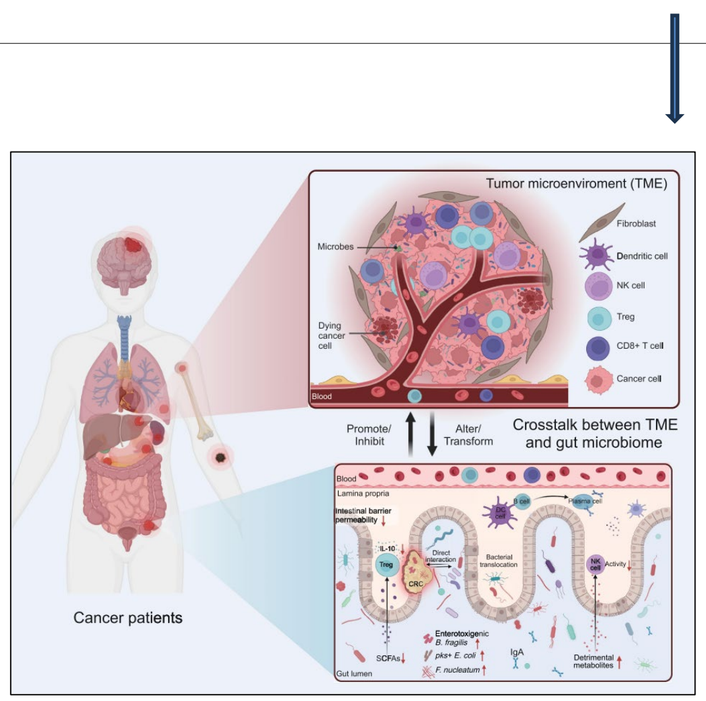
beacon for rare diseases
no rare journey alone

Fondazione Nadia Valsecchi
Conta su di noi, sempre.

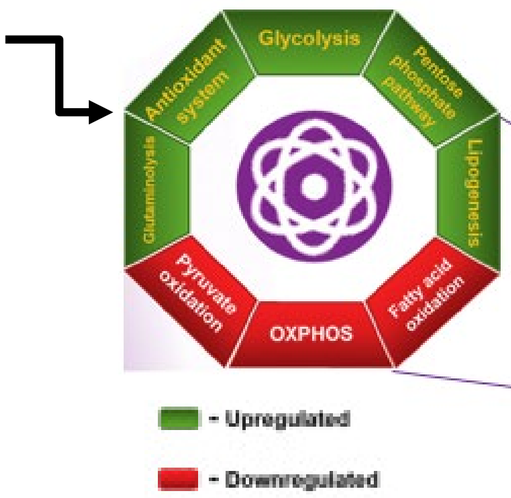
vespa trial

- Drug Repurposing/Repositioning: what, why, when
- REMEDI4ALL European Project
- Pancreatic cancer project – VESPA trial
- **Metabolomic biomarkes in liquid biopsy**

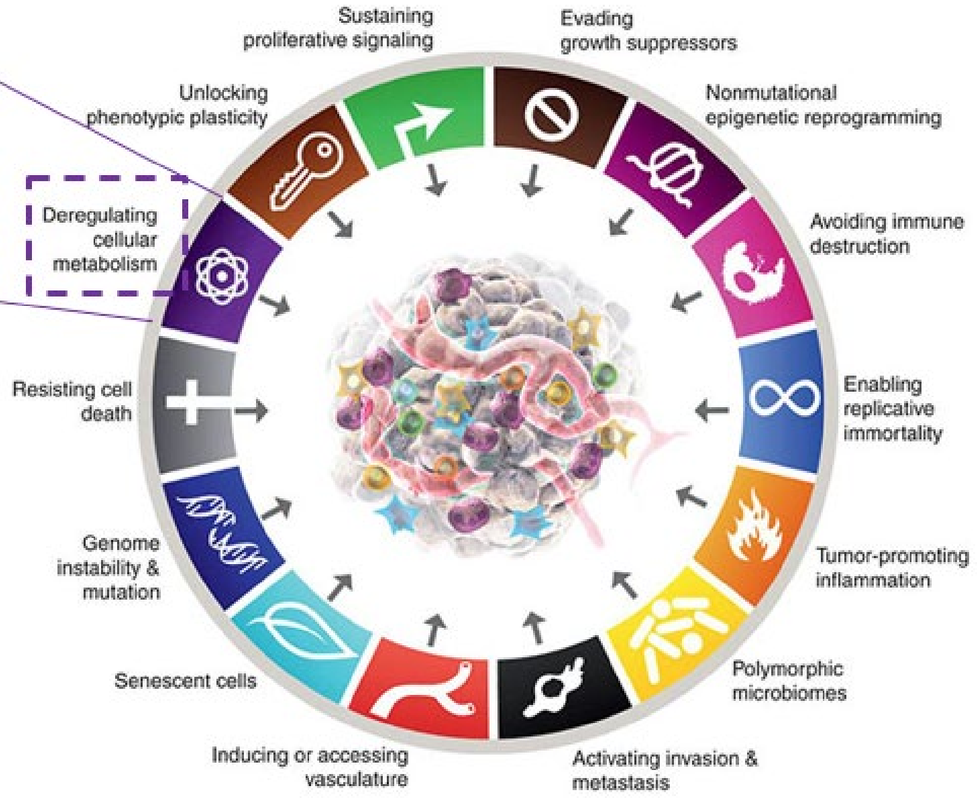
Deregulating cellular metabolism is a cancer hallmark



Jiang et al. Gut Microbes. 2024 Jan-Dec;16(1):2341717

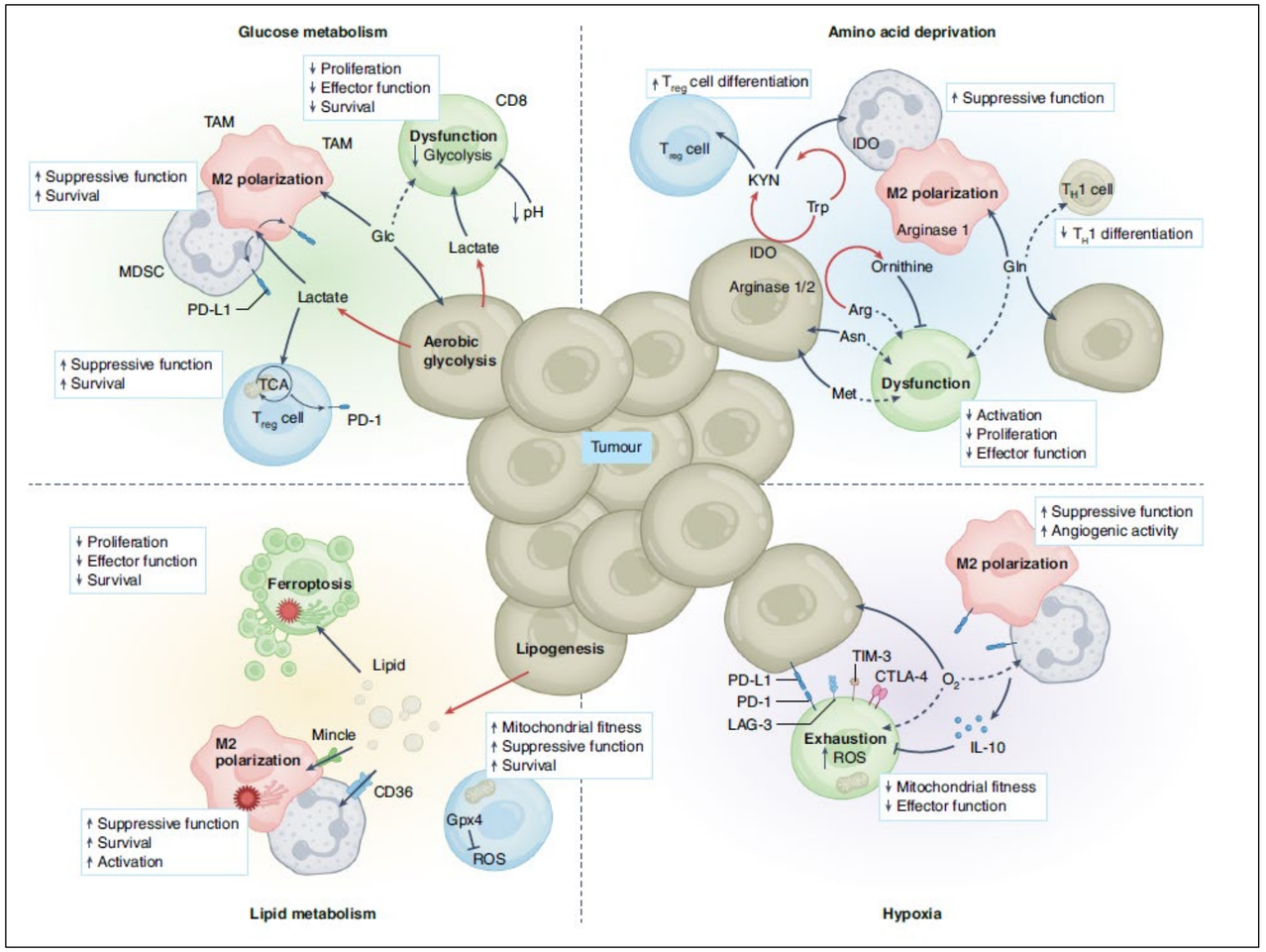


Metabolomics plays a critical role in recapitulating the interactions between cancer cells, TME and the systemic host environment (including microbiota)

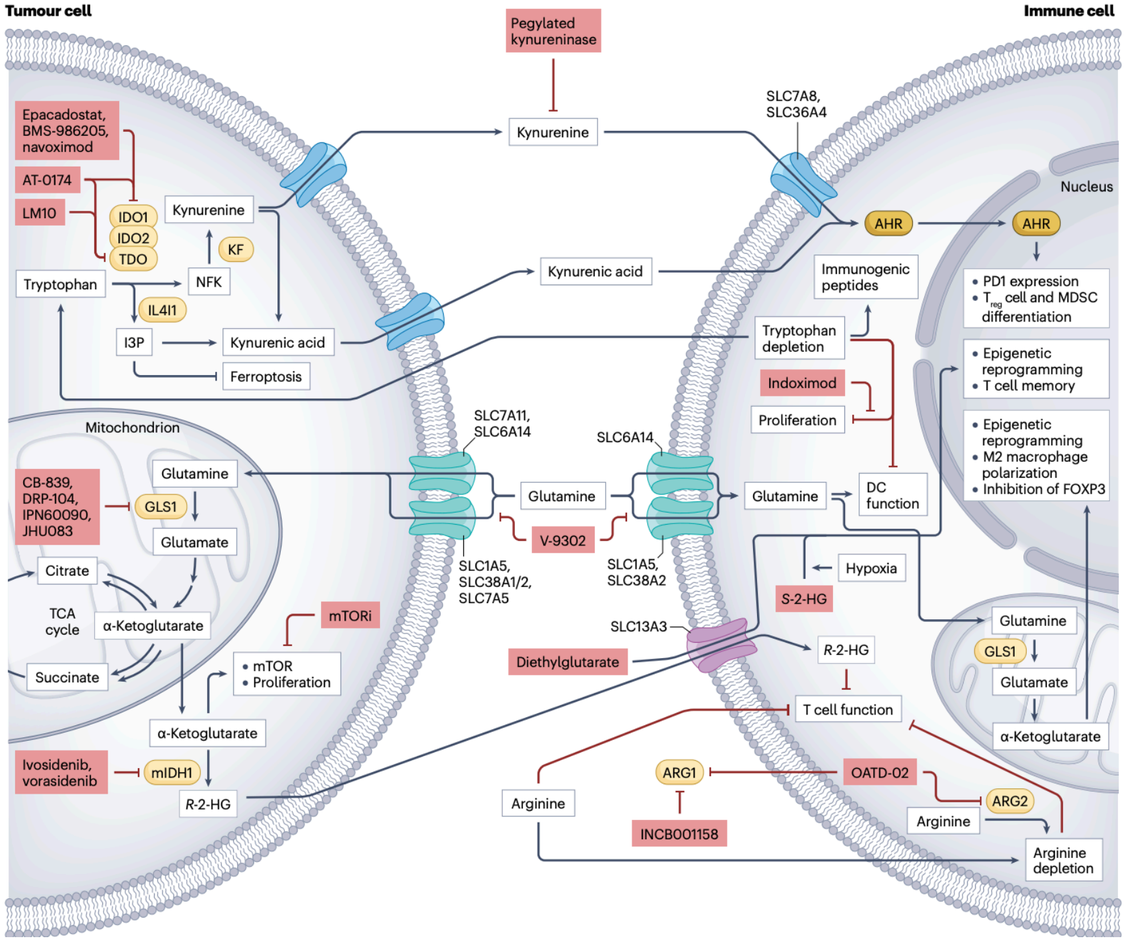


Hanahan D. Cell 2026 Jan 29:S0092-8674(25)01498-9
Hanahan D. Cancer Discov. 2022 Jan;12(1):31-46.

Metabolites as agents and therapeutic targets in tumor-immune microenvironment



Kao et al. Nat Cell Biol. 2022 Nov;24(11):1574-1583.



Marcel P. Trefny MP Nat Rev Drug Disc 24, October 2025, 764–784

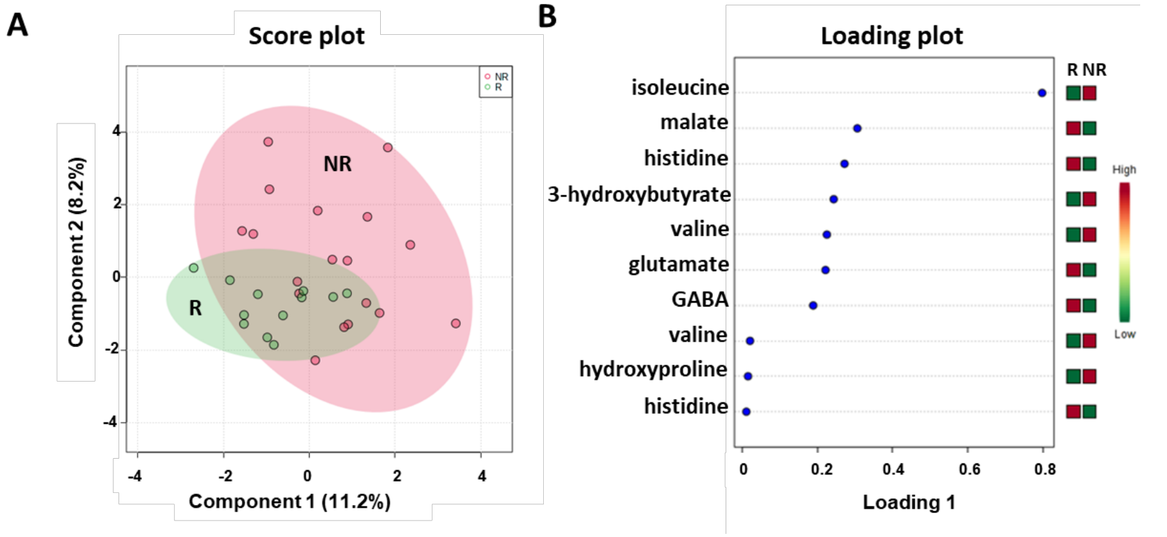
ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Plasma metabolomics, lipidomics and cytokinomics profiling predict disease recurrence in metastatic colorectal cancer patients undergoing liver resection

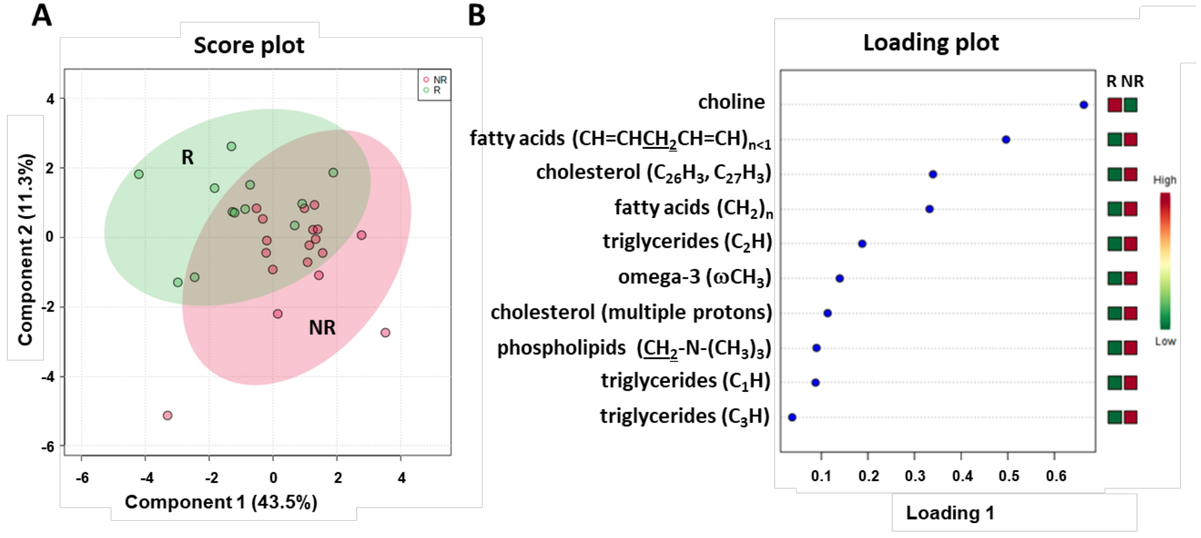
mCRC pts undergoing bevacizumab plus oxaliplatin-based induction chemotherapy before liver metastases resection, within the Obelics trial (NCT01718873) subdivided into responder (R) and non-R (NR) according to 1-year disease-free survival (DFS): ≥ 1-year (R) and < 1-year (NR).

We evaluate whether the **integration of plasma metabolomics, lipidomics and cytokinomics** can be used **to predict the risk of relapse and other patient outcomes after liver surgery, beyond or in combination with clinical morphovolumetric criteria**.

Metabolomics profiling



Lipidomics profiling



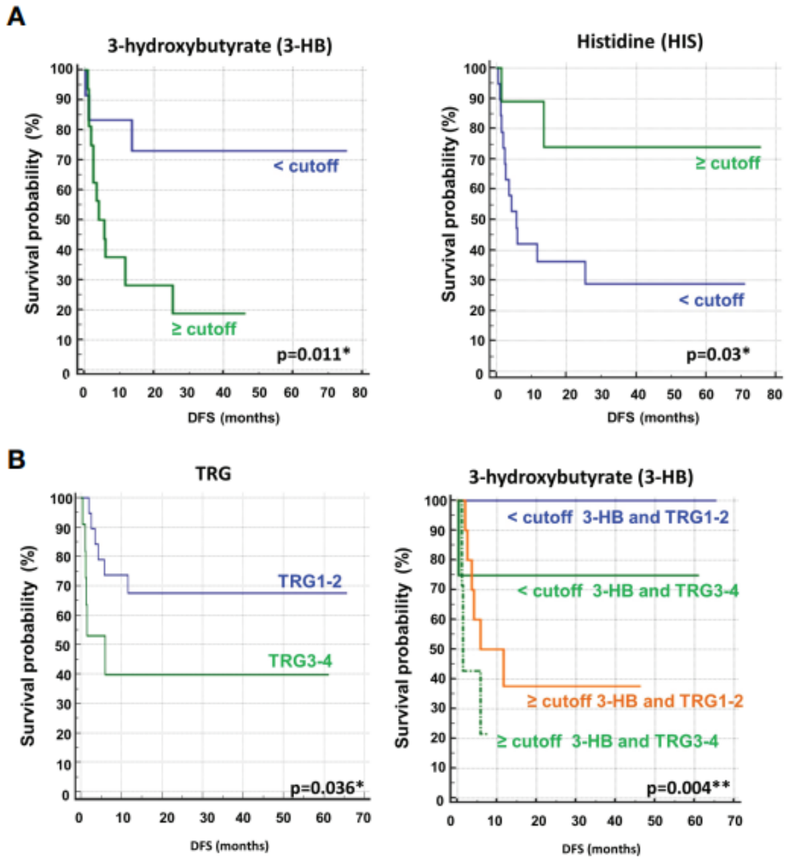
Small sample size: 30 pts

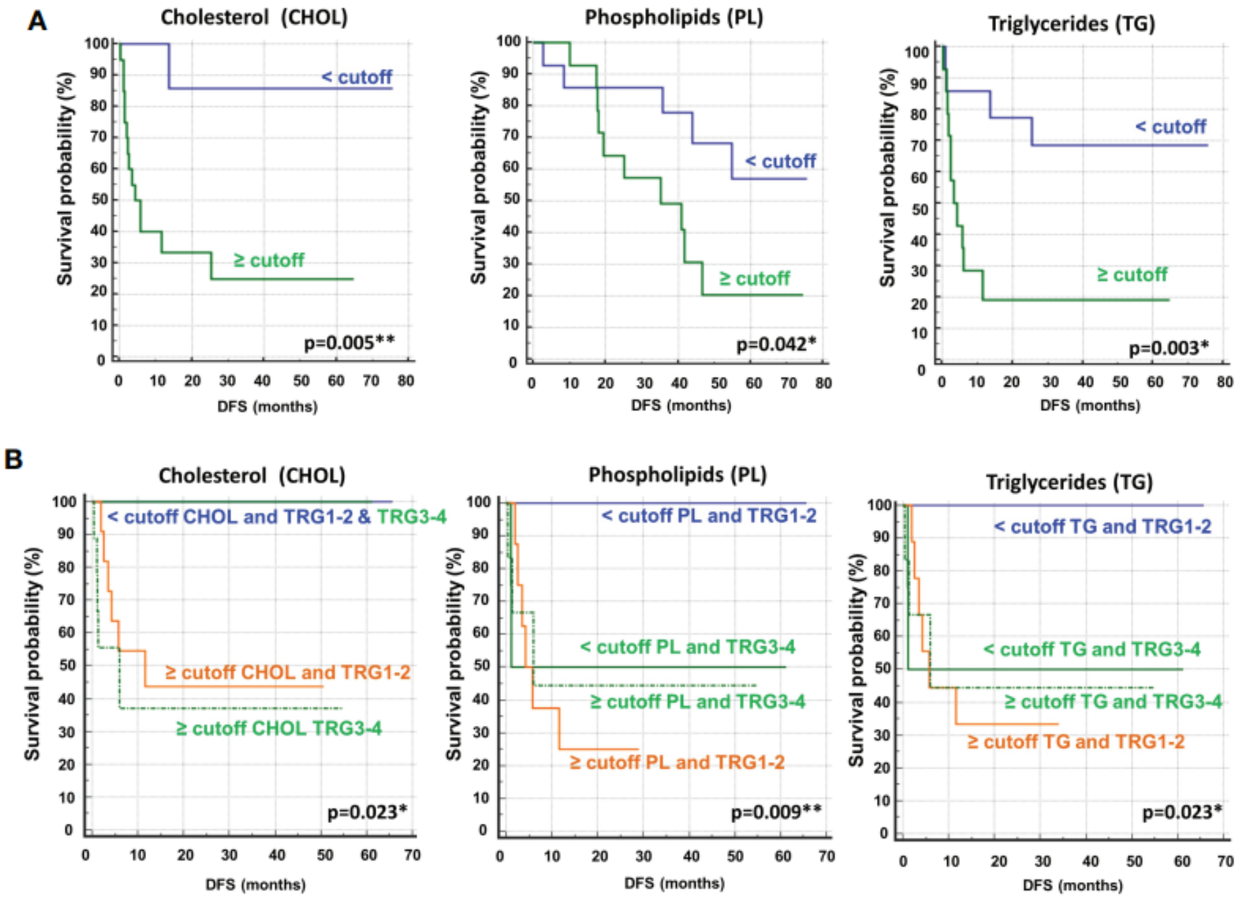
Costantini S ……Budillon A. Front Oncol . 2023 Jan 11:12:1110104

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Pathway analysis on the identified metabolites disregulated in Non-responmding patients (NR) patients

Metabolomics or lipidomics better predictors of DFS than tumor regression grade (TRG)

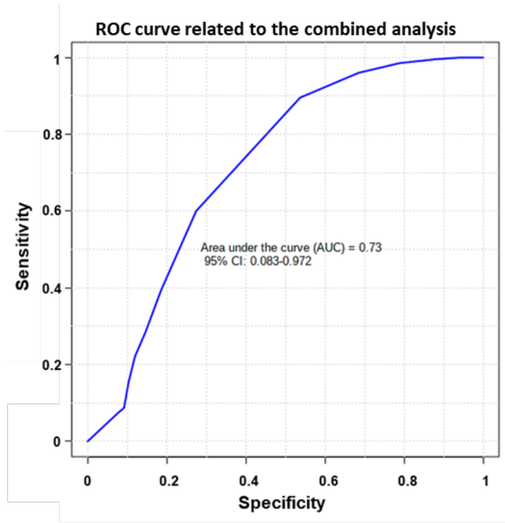


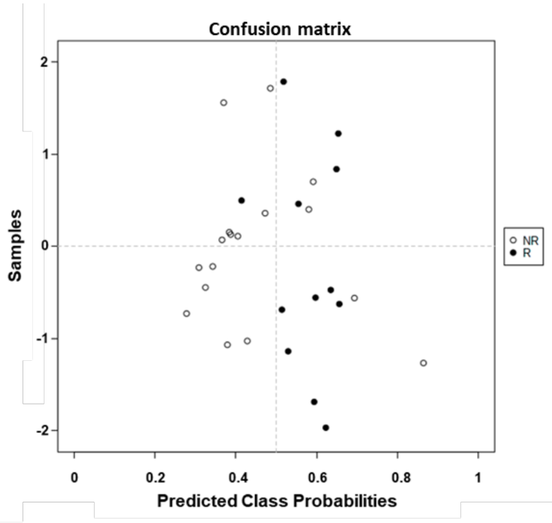


Costantini S ……Budillon A. Front Oncol . 2023 Jan 11:12:1110104

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Combined biomarker signatures (metabolomics, lipidomics, cytokinomics) using the support vector machine (SVM) algorithm increased predictive capacity





Accuracy: 83.3%

Positive predictive value: 73%

Negative predictive value: 93%

The combination of **3-hydroxybutyrate**, **cholesterol, phospholipids, triglycerides and IL-6** levels showed a significant predictive capacity .

Costantini S ……Budillon A. Front Oncol . 2023 Jan 11:12:1110104

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

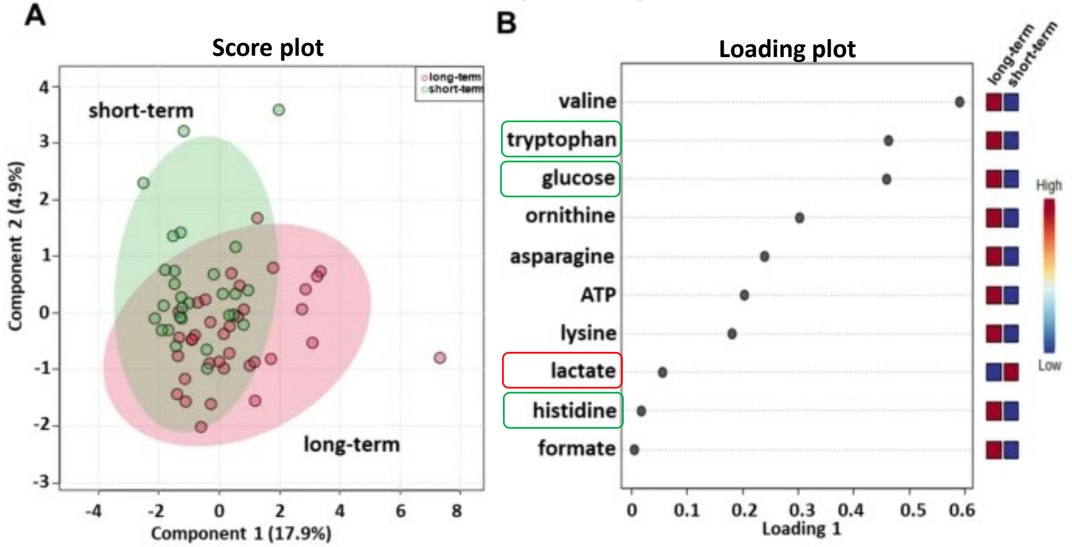
Metabolomic signatures in liquid biopsy are associated with overall survival in metastatic melanoma patients treated with immune checkpoint inhibitor therapy

Background: Immune checkpoint inhibitors improved the prognosis of metastatic melanoma patients. Some patients develop resistance to these treatments, leading to a poor prognosis.

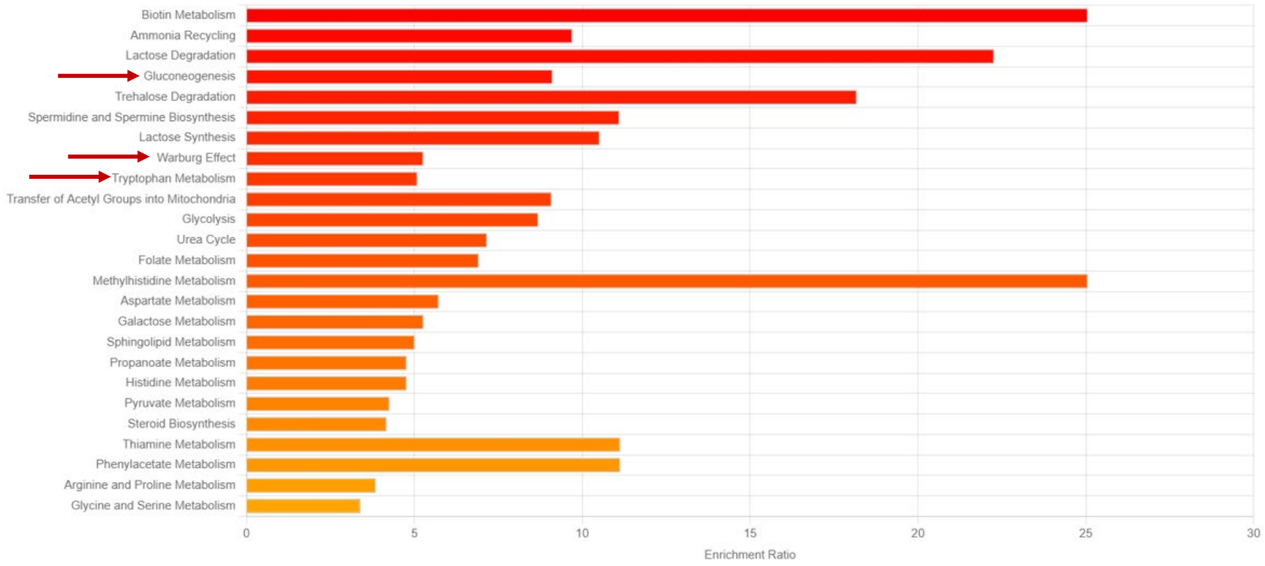
Aim: To identify potential non invasive and easy biomarkers to guide treatment strategies

- Untargeted plasma **metabolomics** profiling on patients with metastatic stage IV melanoma collected at baseline before first-line treatment with ipilimumab, nivolumab or the combination of ipilimumab plus nivolumab.
- The patients were classified into two groups on the basis of their 1-year overall survival (OS): those with good outcomes (long-term OS ≥ 1 year) and those with poor outcomes (short-term OS < 1 year).

Metabolomics profiling



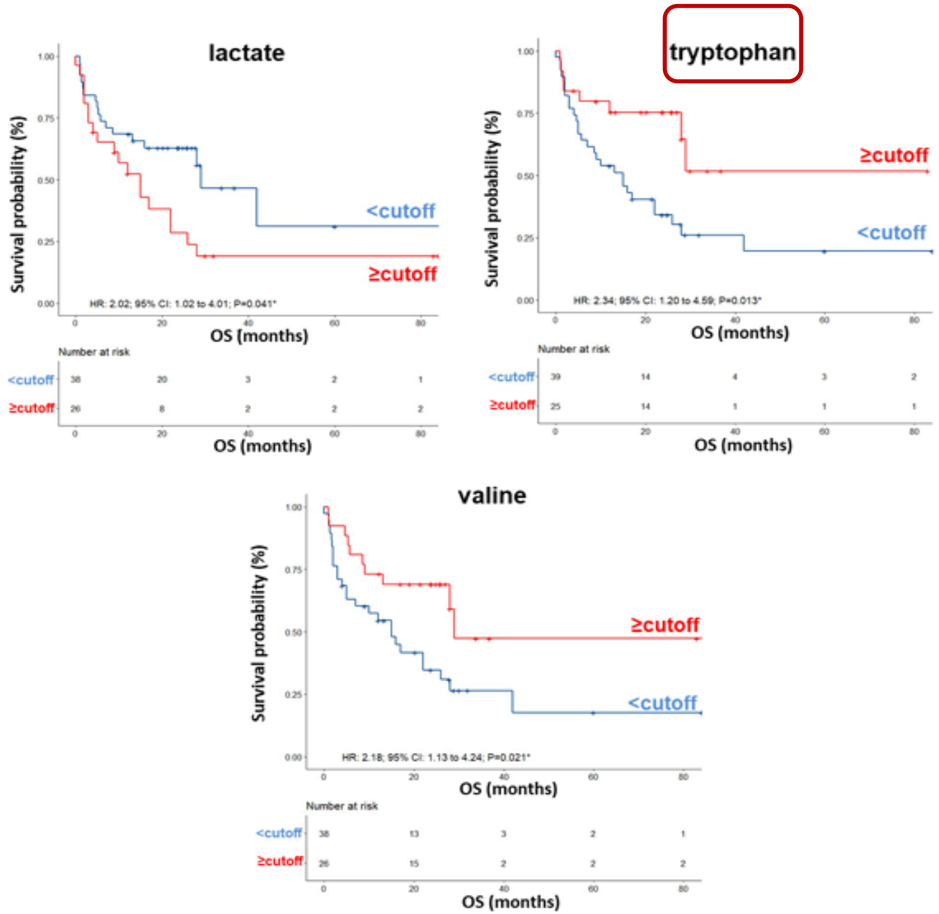
Enriched pathway analysis



ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Costantini S ….. Budillon A. J Exp Clin Cancer Res. 2025 Apr 10;44:119

Significant correlation between pretreatment levels of some metabolites and OS



	CR	PR	SD	PD	DCR(CR + PR + SD)	*p*-value; OR(95%CI)[§]
Patient number	6	13	14	31	33	
Asparagine level (<-0.97)		5	8	17	13	0.22
Asparagine level (≥-0.97)	6	8	6	14	20	
ATP level (<-0.0269)	3	4	8	17	15	0.45
ATP level (≥-0.0269)	3	9	6	14	18	
Formate level (<0.0883)	3	8	6	12	17	0.31
Formate level (≥0.0883)	3	5	8	19	16	
Glucose level (<-1.28)	2	4	8	19	14	0.13
Glucose level (≥1.28)	4	9	6	12	19	
Histidine level (<-1.49)	4	7	5	22	16	0.067
Histidine level (≥-1.49)	2	6	9	9	17	
Lactate level (<4.62)	5	10	8	15	23	0.082
Lactate level (≥4.62)	1	3	6	16	10	
Lysine level (<-1.19)	1	6	6	12	13	0.96
Lysine level (≥-1.19)	5	7	8	19	20	
Ornithine level (<-0.391)	2	5	5	10	12	0.73
Ornithine level (≥-0.391)	4	8	9	21	21	
Tryptophan level (<0.0555)	2	8	5	24	15	0.0088**; 4.11(1.39–12.19)
Tryptophan level (≥0.0555)	4	5	9	7	18	
Valine level (<0.602)	2	7	8	21	17	0.18
Valine level (≥0.602)	4	6	6	10	16	

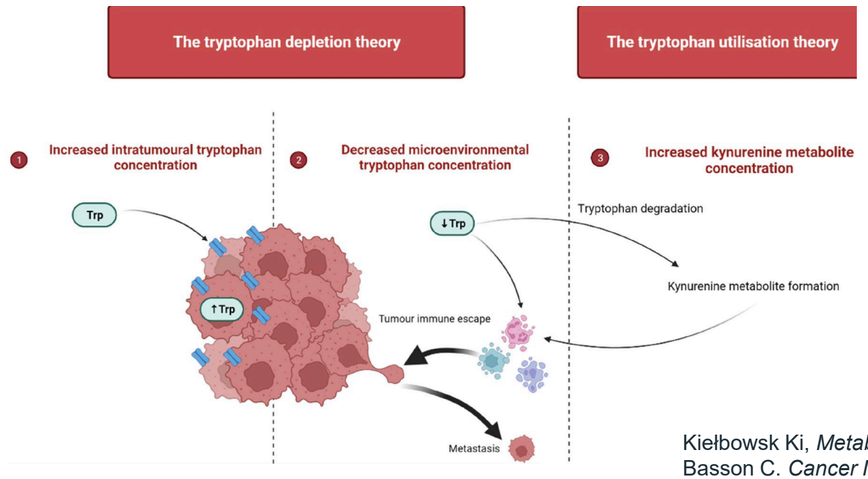
CR: complete response; PR: partial response; SD: stable response; PD: progression disease; DCR: disease control rate; [§]Association between the response and the metabolites levels was evaluated by chi square test. When the association is statistically significant (p-value < 0.05), we reported also odds ratio (OR) and 95% confidence interval (CI)

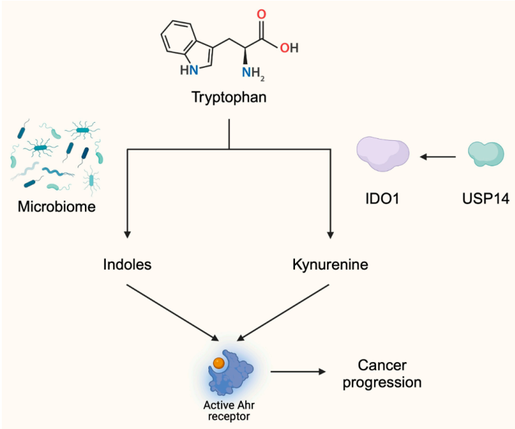
Total Pts of three coorts: 95

In the multivariate analysis, **tryptophan** was the only metabolite that **significantly predicted OS**

Association between **high levels of tryptophan and good response**

Costantini S ….. Budillon A. J Exp Clin Cancer Res. 2025 Apr 10;44:119



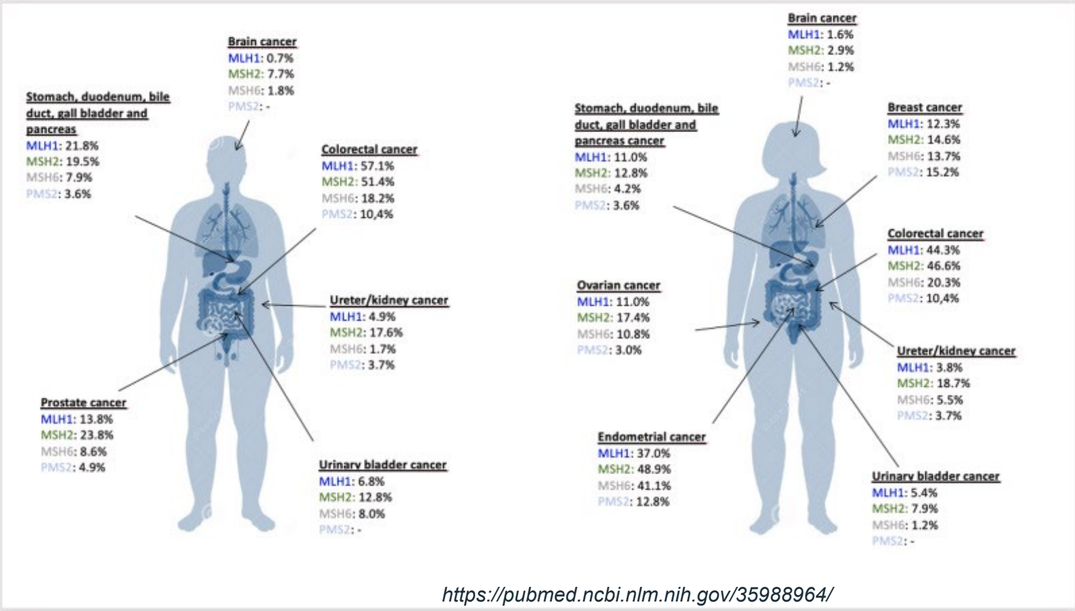


Kiełbowsk Ki, *Metabolites* 2025, *15*(3), 144
Basson C. *Cancer Med*. 2023;12:18691–18701

ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

Lynch syndrome (LS)

- It is one of the most prevalent hereditary diseases, **characterized by a high risk to develop cancer <u>even if Not all individuals with LS develop cancer</u>**
- Defective DNA mismatch repair (MMR)
- EPCAM deletion
- Heterozygous germline pathogenic variants in ATM, MLH1, MLH2, MSH2, MSH6, or PMS2
- **Lifestyle factors** can influence LS cancer risk, and actively shape systemic metabolism and induce the expression of inflammatory cytokines.



https://pubmed.ncbi.nlm.nih.gov/35988964/

Characteristics	Patients (#82)	Cancer-free (#42)	Cancer history (#40)	p-value
Gender n(%)				1
F	48 (59%)	25 (60%)	23 (58%)	
M	34 (41%)	17 (40%)	17 (43%)	
MMR n(%)				0.024*
ATM	1 (1.2%)	1 (2.4%)	0 (0%)	
MLH1	33 (40%)	21 (50%)	12 (30%)	
MLH1 - MSH2	2 (2.4%)	0 (0%)	2 (5.0%)	
MLH2	1 (1.2%)	0 (0%)	1 (2.5%)	
MSH2	28 (34%)	9 (21%)	19 (48%)	
MSH6	16 (20%)	10 (24%)	6 (15%)	
PMS2	1 (1.2%)	1 (2.4%)	0 (0%)	
BMI n(%)				**0.016***
Normal_weight	34 (45%)	22 (56%)	12 (32%)	
Overweight	27 (36%)	14 (36%)	13 (35%)	
Obesity	15 (20%)	3 (7.7%)	**12 (32%)**	
Smoking n(%)				0.076
NO	44 (54%)	27 (64%)	17 (44%)	
YES	37 (46%)	15 (36%)	22 (56%)	
Comorbidity n(%)				0.011*
NO	53 (65%)	33 (79%)	20 (50%)	
YES	29 (35%)	9 (21%)	20 (50%)	
Cancer site n(%)				
CCR	28 (34%)	-	**28 (70%)**	
Other	54 (66%)	-	12 (30%)	

AIM: ***identify significant metabolites, lipid signals and cytokines specific to cancer history in LS carriers and their correlation with or with lifestyle characteristics (BMI and smoking).***

DO NOT POST

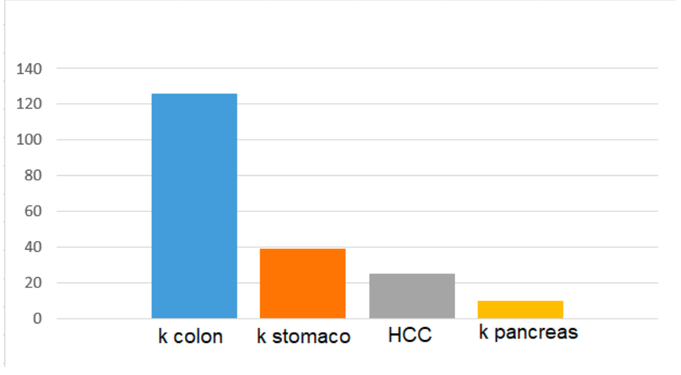
ISTITUTO NAZIONALE TUMORI IRCCS - Fondazione Pascale

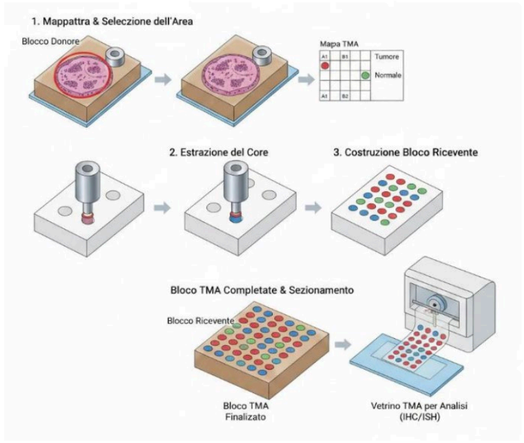
Costantini S, D'Angelo V… Budillon A and Di Gennaro E. Manuscript in prep 2026

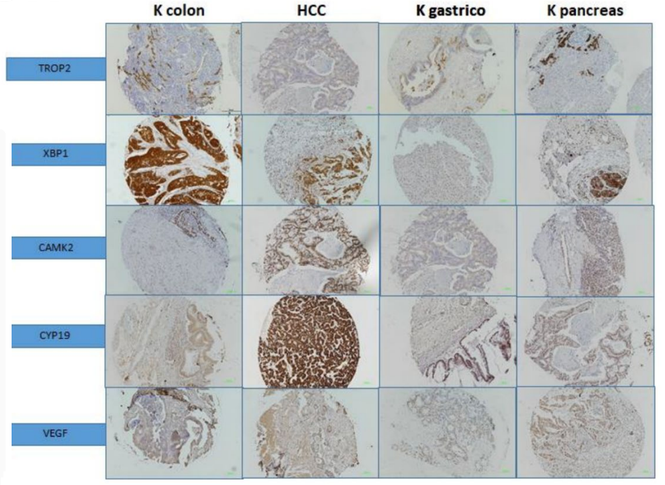
Correlation of Serum Metabolomics with Tumor Tissues Metabolic disregulation

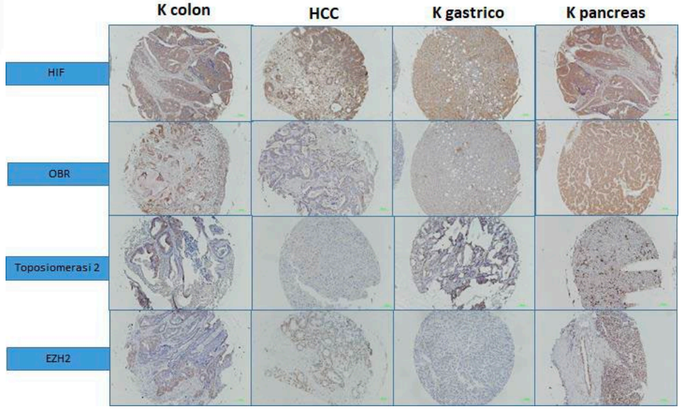
VIA METABOLICA PRINCIPALE	BIOMARCATORI	FUNZIONE PRINCIPALE
Glicolisi / Metabolismo del Glucosio	HIF1a	Fattore di trascrizione si attiva in ipossia e sovraregola quasi tutti gli enzimi della glicolisi (Effetto Warburg).
	Glucagone	Ormone che stimola la glicogenolisi e la gluconeogenesi
Metabolismo dei Lipidi e Acidi Grassi	RXR α, β, γ	Recettori nucleari che formano eterodimeri per regolare la trascrizione dei geni coinvolti nel metabolismo dei lipidi.
	SCD1	Stearoyl-CoA Desaturase 1 – Enzima cruciale per la sintesi degli acidi grassi monoinsaturi
	Cyp19	Aromatasi – Enzima chiave nella sintesi degli ormoni steroidei
	Cyp2R1, Cyp24, Cyp271a1	Citocromi P450 coinvolti nel metabolismo della Vitamina D e nei suoi precursori/metaboliti.
	OBR	Recettore della Leptina – influisce sull'omeostasi lipidica.
Metabolismo degli Amminoacidi	EZH2	Enhancer of Zeste Homolog 2 – Proteina coinvolta nell'alterazione epigenetica del metabolismo degli aminoacidi (es. Metionina)
Metaboliti Redox e Stress Ossidativo	Cyp1A1	Citocromo P450 1A1 Metabolismo di sostanze xenobiotiche e produzione di ROS (stress ossidativo).
	Angiogenina	Fattore di crescita che protegge le cellule dallo stress nutrizionale e dall'ipossia.
Regolazione Trasversale/Segnalazione (Hub Metabolico)	IGF1R	Promuove l'assorbimento di nutrienti (glucosio e amminoacidi) e la crescita cellulare.
	VEGF	Induce l'angiogenesi, fornendo nutrienti e ossigeno al tumore, sostenendo tutte le vie metaboliche.
	CD73	Metabolismo delle purine (via dell'adenosina), immunosopressore e promotore dell'angiogenesi.
	TROP2	Glicoproteina transmembrana coinvolta nella segnalazione della crescita e della proliferazione cellulare
	CAMK II	Calcio/Calmodulina dipendente chinasi II – regola indirettamente molte vie metaboliche in risposta ai segnali del calcio.
	FRAa	Recettore dell'Acido Folico Alpha – Importante per l'assorbimento del Folato(sintesi nucleotidi)
	XBP1	X-box binding protein 1 – Fattore di trascrizione per la risposta allo stress del reticolo endoplasmatico
	Topoisomerasi IIa	Enzima coinvolto nel mantenimento della struttura del DNA durante la replicazione cellulare.
	PEG-10	long non-coding RNA intermedio metabolico diretto che agisce come regolatore epigenetico alterando l'espressione degli enzimi e delle proteine direttamente coinvolte nelle vie metaboliche.

Tabella1. Elenco dei biomarcatori metabolici selezionati









Staff BBI INT PASCALE

Monica Cantile

Giosuè Scognamiglio

Istituto Nazionale Tumori IRCCS - Fondazione Pascale

Dept. of Translational Research
Experimental Pharmacology Unit LABS
Elena Di Gennaro
Alessandra Leone
Maria Serena Roca
Chiara Ciardiello
Federica Iannelli
Carlo Vitagliano
Tania Moccia
Laura Grumetti
Rossella Migliorino
Roberta Affatato
Eugenia Passaro
Barbara Mandriani

Lab-CROM
Susan Costantini
Federica Renza
Carmen Maccanico
Palmina Bagnara
Biagio Pucci
Laura Addi
Cristina Testa
Veronica Barile

Experimental Animal Studies Unit
Rita Lombardi
Francesca Bruzzese

Department of Abdominal Oncology
Experimental Clinical Oncology
Antonio Avallone
Alfonso De Stefano
Anna Nappi
Carmela Romano
Lucrezia Silvestro
Antonino Cassata
Rossana Casaretti
Claudia Cardone
Francesca Foschini
Valeria Vicario
Marco Borrelli

Surgery Units :
P. Delrio,
F. Izzo,
R.Palaia,
A. Belli,

Pathology
Gerardo Ferrara
Endoscopy
Mario De Bellis
Valentina D'Angelo
Radiology
Francesco Fiore
Antonella Petrillo
Luca Tarotto
Cinzia Granata
Clinical Pathology
Ernesta Cavalcanti

Department of Skin-Melanoma Experimental and Clinical Immunology and Innovative Therapies
Paolo Ascierto
Ester Simeone
Margaret Ottaviano
Maria Elena Capone
Domenico Mallardo
Gabriele Madonna

PDTA Hereditary Tumors
Valentina D'Angelo
GI Tumors
Matilde Pensabene
Breast Tumors
Jole Ventriglia
Gynecological Tumors

Istitutional BioBank
Monica Cantile
Giosuè Scognamiglio
Giovanna De Pietro
Anna Martorana
Emili Santella

ISTITUTO NAZIONALE TUMORI
IRCCS – Fondazione Pascale

Michele Milella, University of Verona
Michele Reni, San Raffaele Hospital
Giampaolo Tortora, Dian Gainnarelli, **Carmine Carbone**, Università Fondazione Policlinico A. Gemelli
Maria Laura Garcia Bermeyo, Mercedes Rodriguz Garrote, Bruno Sainz, Elisa Condem, IRYCIS (Spain)
Maddalena Fratelli, Mario Negri.

CRT – Clinical Research Technology
Paola Schiavo
Carmen Caruso
Giovanni Cucchiara

Patients partecipating in the VESPA trial, OBELICS Trial, and their families

Ministero della Salute
RF-2021-12371995

REPURPOSING OF MEDICINES 4ALL

European Union's Horizon Europe research and innovation programme under grant agreement No 101057442.

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

INNOVA Advanced Diagnostic Platform

cdp eatris
European infrastructure for translational medicine

AIRC

REGIONE CAMPANIA
DGR 180/2019

FSE POR CAMPANIA 2014 - 2020

Reproducibility:
Philip Gribbon, Maria Kuzikov
Fraunhofer Institute for Translational Medicine and Pharmacology ITMP, Hamburg, Germany
Annika Jenmalm Jensen, Weiyingqi cui
Department of Medical Biochemistry and Biophysics, Chemical Biology Consortium Sweden (CBCS), Science for Life Laboratory, Karolinska Institutet, Solna, Sweden.

In silico Analysis
Tero Aittokallio, Ziaurrehman Tanoli
Institute for Molecular Medicine Finland (FIMM), HiLIFE, University of Helsinki, Helsinki, Finland
Maddalena Fratelli, Laura Fiorenza
Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milan, Italy
Jordi Quintana
Chemotargets SL, Barcelona, Catalonia, Spain

Multiomics
Jordi Carreras Puigvert
Department of Pharmaceutical Biosciences and Science for Life Laboratory, Uppsala University, Sweden
Massimiliano Gaetani
Division of Physiological Chemistry I, Department of Medical Biochemistry and Biophysics, Karolinska Institutet, Stockholm, Sweden

Patient Derived Organoids
Carmine Carbone
Medical Oncology, Fondazione Policlinico Universitario Agostino Gemelli, IRCCS, Rome, Italy.

WP1 PATIENT ENGAGEMENT
Claudia Fuchs
Eve Hewitt
Rick Thompson

Donald Lo
Alicia Soler
Martin De Kort

Nadina Grosios

Christine Kubiak
Sareema JAVAID

Gauthier Bouche

All TEAMIT !!

And many many more


thank you