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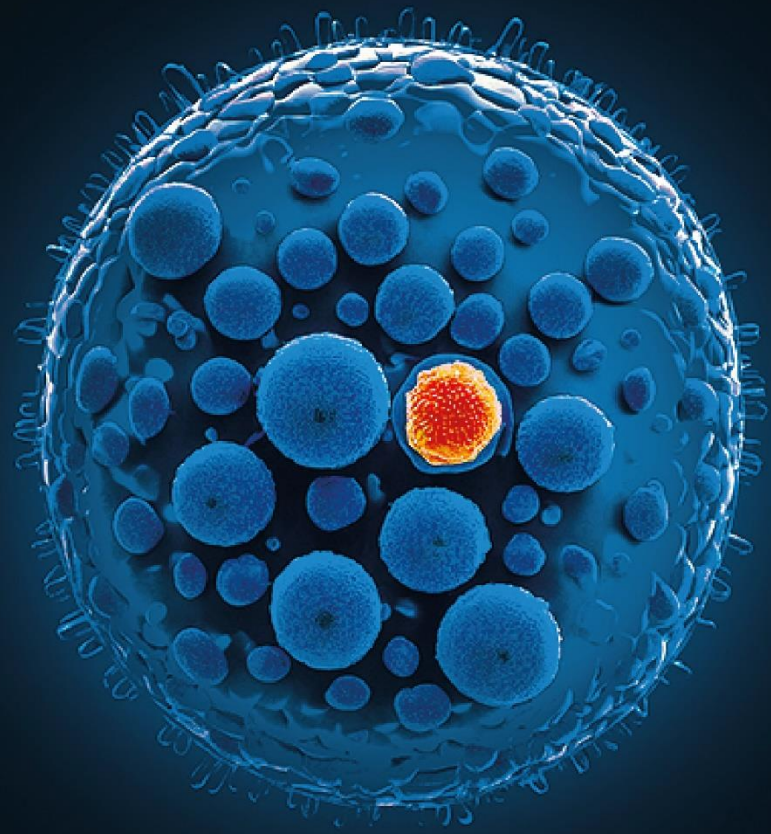
Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

HEAL ITALIA



FORUM NAZIONALE SULLA MEDICINA DI PRECISIONE

Il Modello HEAL ITALIA e il contributo della Ricerca al Sistema Sanitario del Futuro

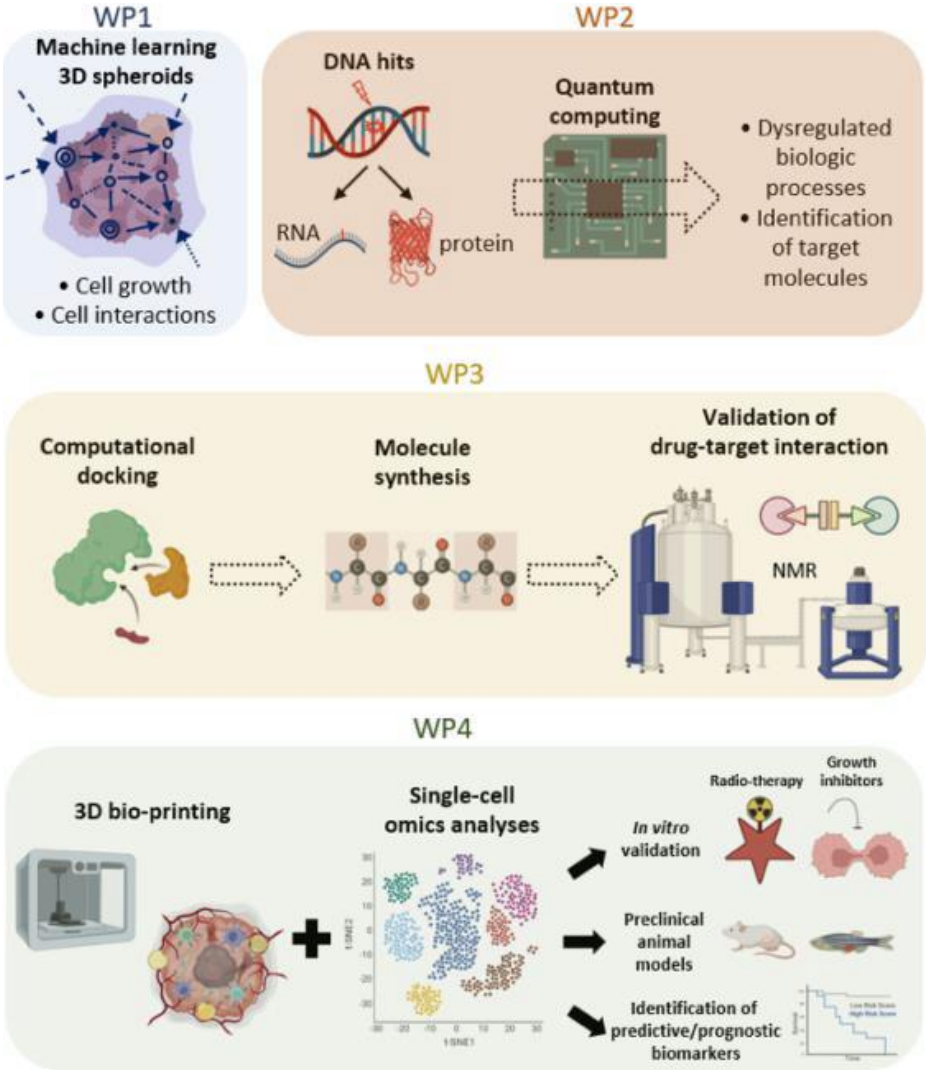
PALERMO
13 · 14 · 15
GIUGNO 2024

SPOKE 3
Prediction Models

n. of researchers: 60+

4 PhD students

Spoke Leader UNIPA
Affiliates
BIREX
IFO-IRE
IOM
ISS
M. NEGRI
SAPIENZA
SIT
TOR VERGATA
UNIBO
UNICA
UNICT
UNIFG
UNIMIB
UNIMORE
UNIPI
UNIVPM



PREDICTION MODELS (UniPA)

Development of advanced prediction models for prognosis and therapeutic response based on comprehensive data treatment

The realization of this activity will be facilitated by the already established protocol for the isolation and purification of organoids and model recapitulating the complex evolution of a cell even following an action of an external agent (drug, radiation, etc.). Organoids, fibroblasts, adipose, mesenchymal, endothelial and immune cells will be 3D bioprinted. This 3D structure, which will also be simulated through existing analytical tissue growth codes, will be investigated by evaluating the action of specific compounds selected by the consortium and radiotherapy. Its development following the external action will be monitored and the "physiopathology" will be analyzed and simulated with machine learning approaches capable of reproducing the complex mechanisms of cellular communication.

WP 1: Integrated experimental and computational models of 3D cultures of human cells with specific gene mutations or biogenesis alterations of RNA/Proteins;

WP 2: Simulation of mutated proteins and complex structures through quantum computing and AI;

WP 3: Pharmacophoric dynamic docking simulations of genetic altered molecules;

WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies.

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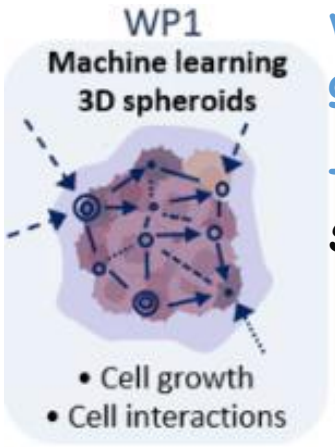
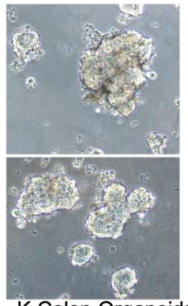
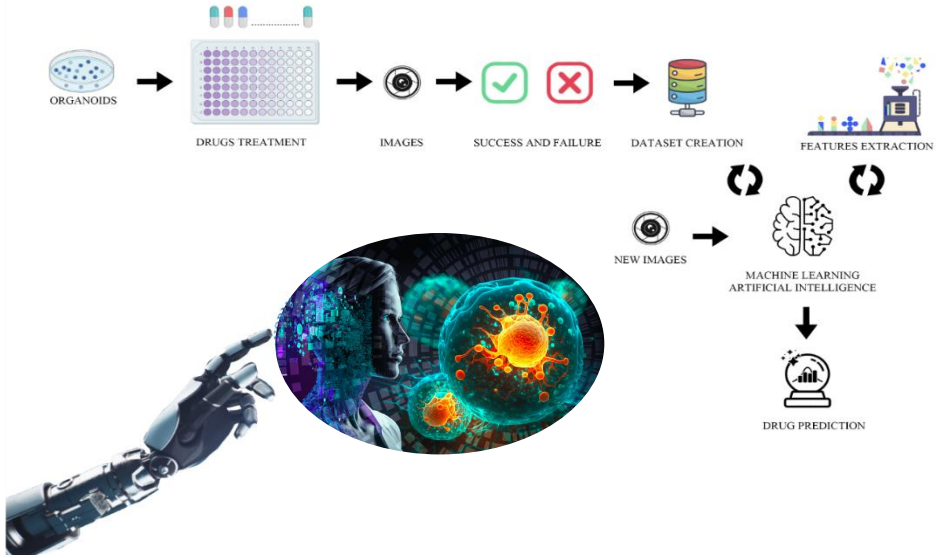


WP 1: Integrated experimental and computational models of 3D cultures of human cells with specific gene mutations or biogenesis alterations of RNA/Proteins

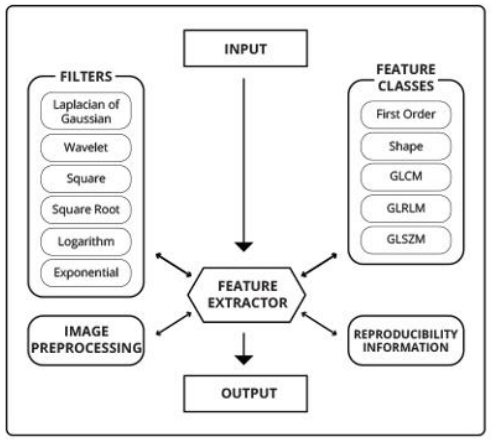
Task 1.1: 3D simulation of spheroid structures through machine learning (UNIPA: G. Raso, D. Tegolo, S. Vitabile, G. Cicceri, S. Di Bella; BIREX: D. Mascolo)

A benchmarking of deep learning models for automatic classification of intestinal organoids

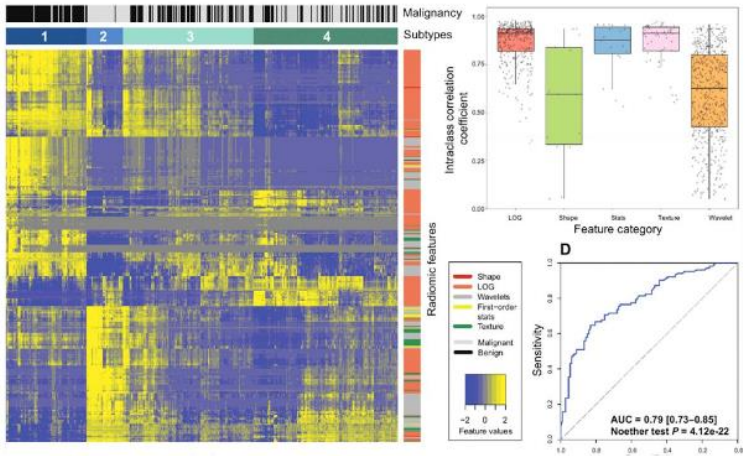

K Colon Organoids



Radiomics: All feature classes, with the exception of shape can be calculated on either the original image and/or a derived image, obtained by applying one of several filters.



PyRadiomics Toolbox



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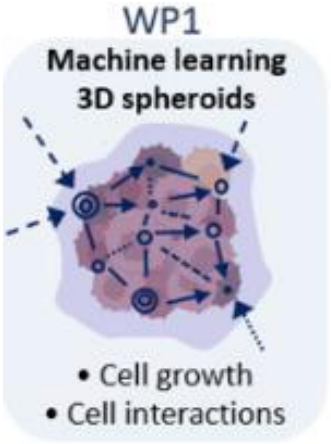
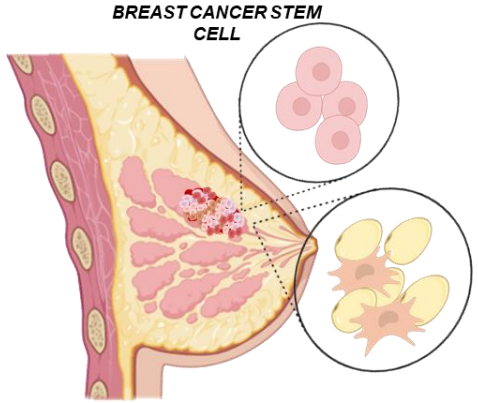


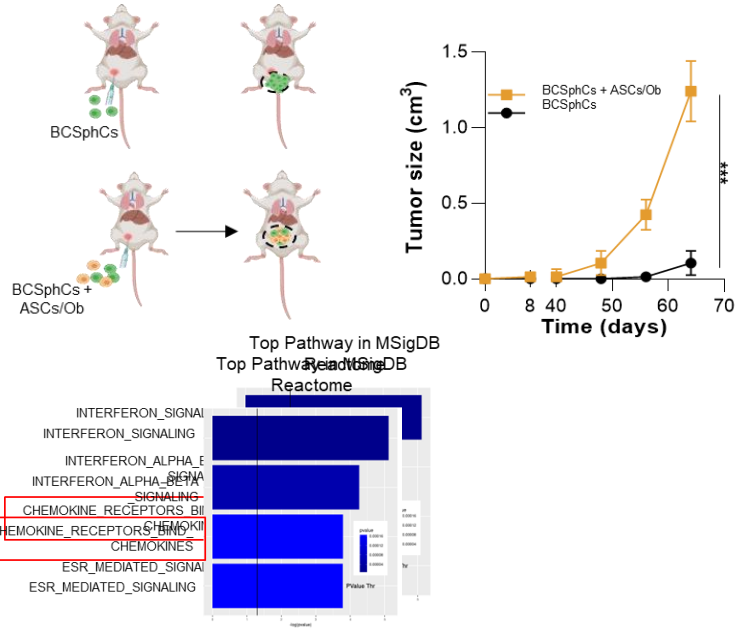
WP 1: Integrated experimental and computational models of 3D cultures of human cells with specific gene mutations or biogenesis alterations of RNA/Proteins

Task 1.2: Regulatory molecular circuits of 3D cell growth affecting physio-pathological cell phenotypes

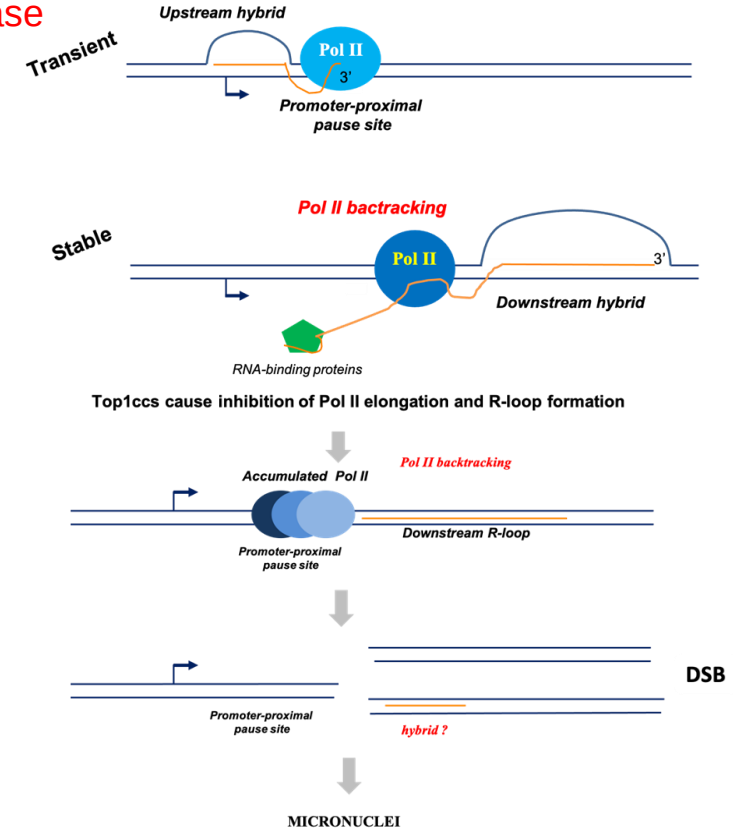
*(**UNIPA**: M. Todaro; **UniBO**: G. Capranico)*

How does the adipose tissue in obese patient influence the development and progression of breast cancer?





Topoisomerase I-DNA cleavage complexes (Top1ccs) cause genome instability through **Transcription-Replications conflicts (TRCs)** increase



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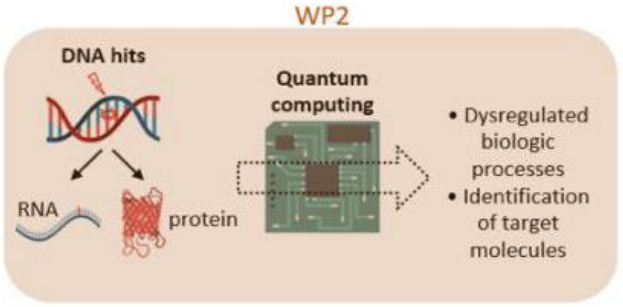
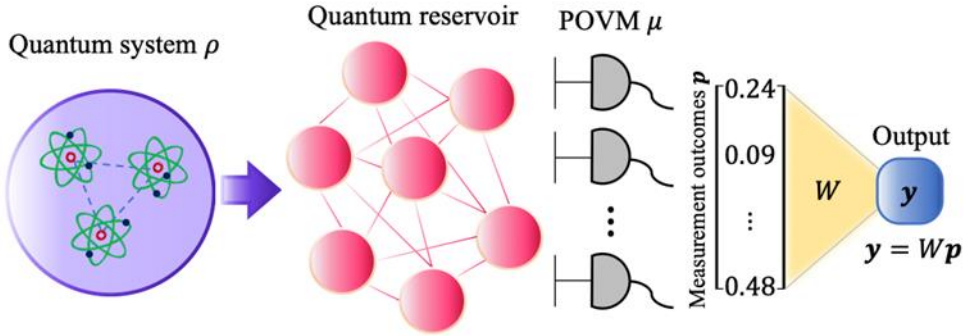


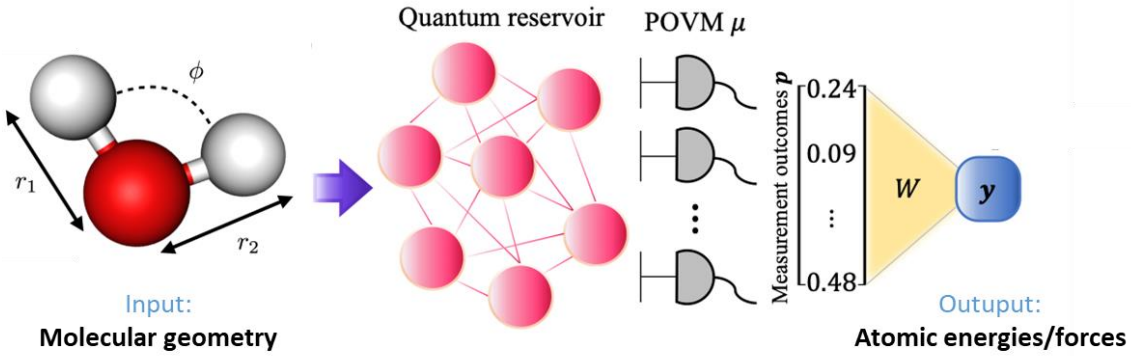
WP 2: Simulation of mutated proteins and complex structures through quantum computing and AI

Task 2.1: Quantum computing techniques applied to biochemical systems, molecular biology and organic chemistry (***UNIPA:*** *G.M. Palma)*

Quantum Extreme Learning Machine (QELM)



The paradigm: **Supervised quantum machine learning**.
The quantum devices is "trained" to learn the functional relation between provided input and output. The data are encoded in the device as quantum states of some qubits interacting with a reservoir. The output is obtained measuring the reservoir plus classical post-processing.



New efficient ways to establish if the dynamics of a reservoirs is suited to a QELM algorithms.

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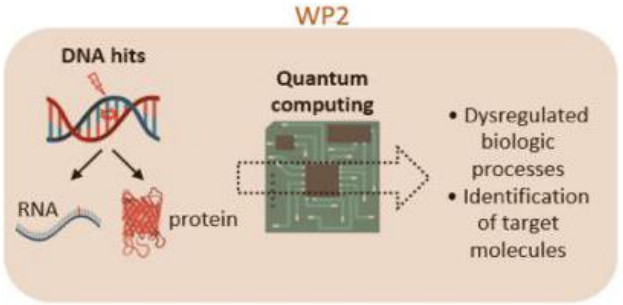
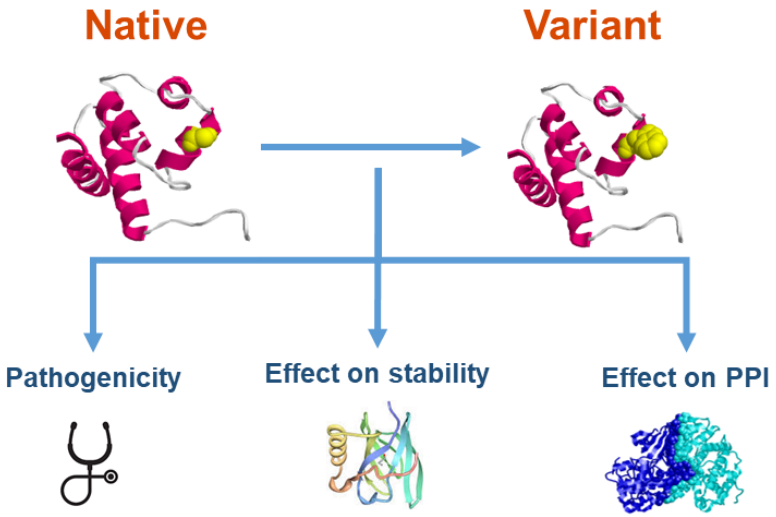


WP 2: Simulation of mutated proteins and complex structures through quantum computing and AI

Task 2.2: Integrative in silico assessment of the impact of mutations on protein structure, function, and interactions (***UniTOR VERGATA:*** *L. Stella;* ***UniBO:*** *C. Savojardo)*

Providing ML models for the prediction of the overall effect of mutations on characteized proteins

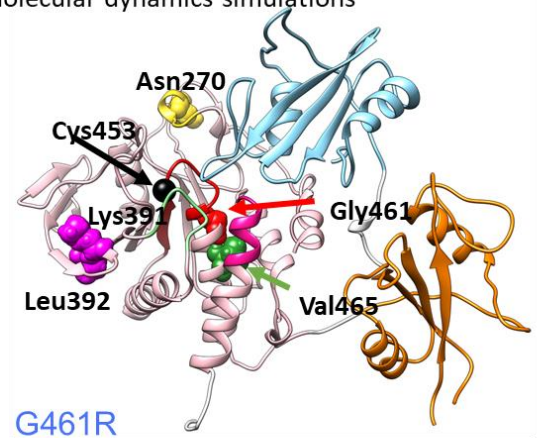
The problem: Given a mutated protein, is it possibile to use machine-learning to predict the effect of the mutation?

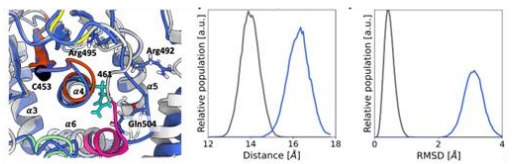


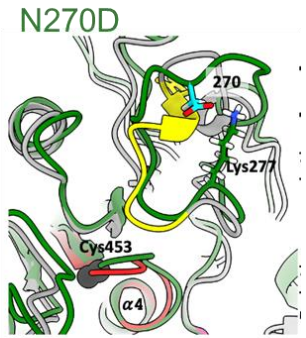
Mutation effects can be measured at different molecular levels

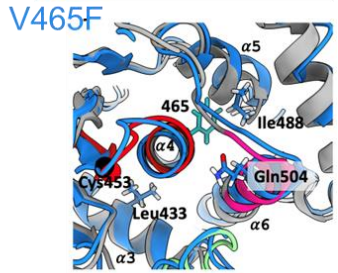
SHP1 mutants

Structural and dynamic effects of pathogenic mutations affecting the SHP1 phosphatase (the closest homologue of SHP2) were identified by modelling and molecular dynamics simulations









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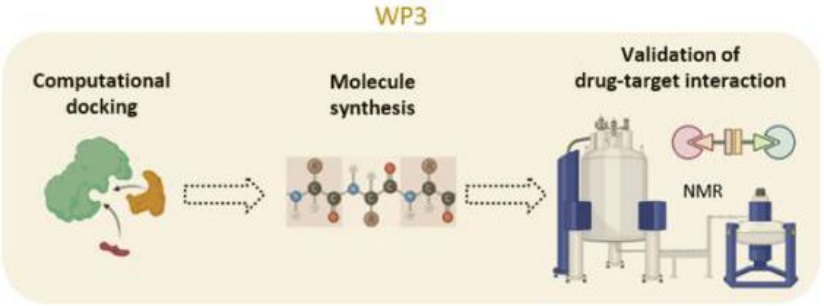
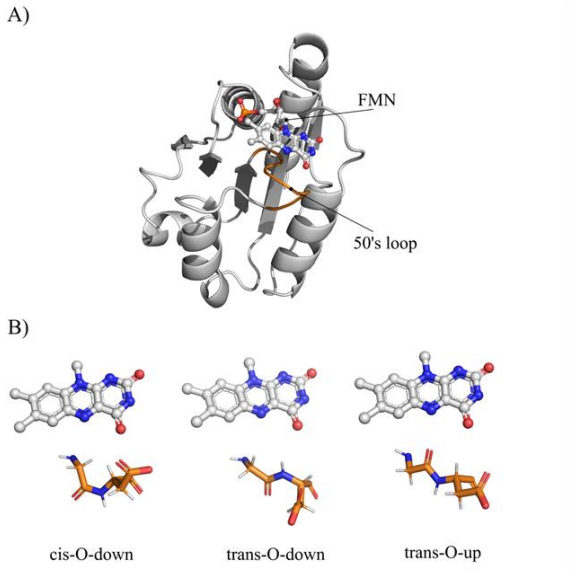


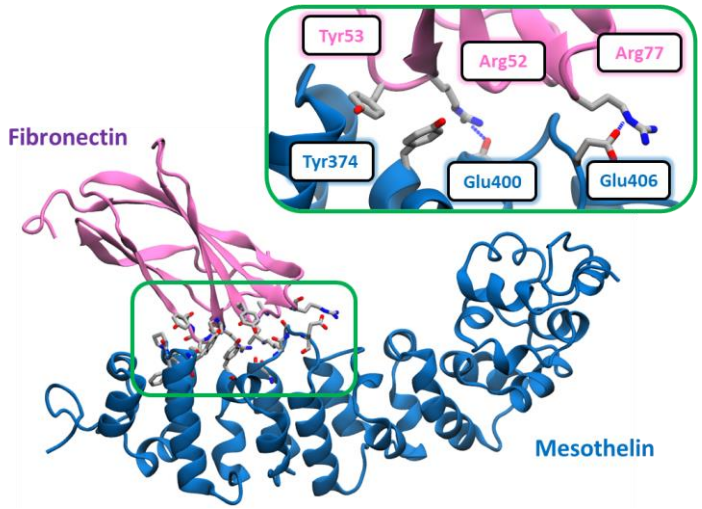
WP 3: Pharmacophoric dynamic docking simulations of genetic altered molecules

Task 3.1: Computation of molecule bearing genetic alterations able to bind to the target in the most effective way possible (docking) and with the greatest affinity (search for the best scoring) (***UNIPA:*** *A. Barone, G. Spinello;* ***BIREX:*** *M. Pulvirenti;* ***UniMIB: L. De Gioia***)

Activity:	**Outcome:**
We have carried out Thermodynamic Integration calculations on wild type and single-point mutant flavodoxins, evaluating results (cofactor binding affinity and redox potentials), and comparing them to available experimental data. Results have been published.	Computed thermodynamic properties to be compared with corresponding experimental data, to validate the computational protocol



Activity:	**Outcome:**
We are carrying out *in silico* site-directed mutagenesis to predict single-point hot spot mutations that are able to increase the binding affinity of novel engineered variants of the Fibronectin protein (in collaboration with the UNIPI unit)	The best-identified mutants will be expressed and purified by our collaborators at Unitrento for experimental validation.



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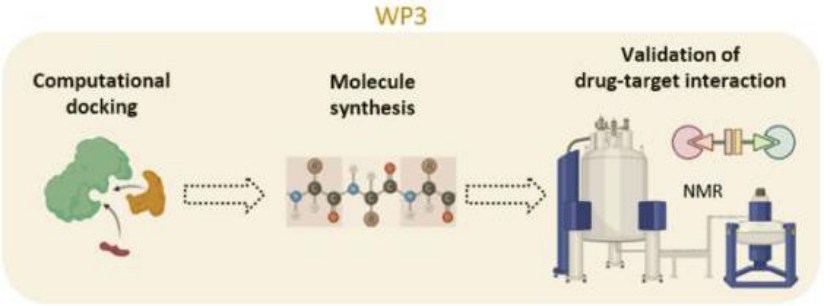


WP 3: Pharmacophoric dynamic docking simulations of genetic altered molecules

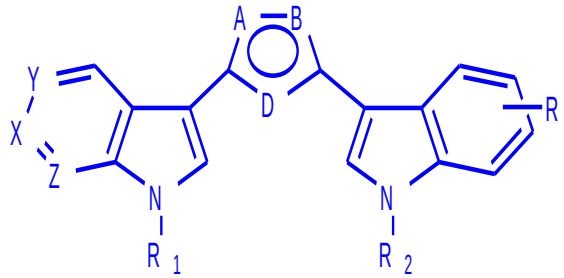
Task 3.2: Molecular synthesis for the experimental validation of computation models (***UNIPA:*** *P. Diana;* **UniBO:** *C. Savojardo)*

Non-Equilibrium Thermodynamic Integration in drug design: inhibitors of proteins

Activity:	**Outcome:**
We have carried out the computational investigation of the binding of a set of small-molecules (in collaboration with the UNIPA unit) to the GSK3 target, using a non-equilibrium thermodynamic approach. We have also tested different force-fields, to validate results.	Poses and binding energies of small molecules to the pharmacologically relevant kinase target GSK3.

Molecular synthesis for the experimental validation of computation models

Activity:	**Outcome:**
We have carried out the molecular synthesis of a new library of small molecules endowed with different substitutions, as potential kinase inhibitors (such as GSK3)	Library of small molecules inhibitors for the experimental validation of computational results obtained in the previous activity of the same task.



X or Z or Y = N, CH
A or B or D = CH, S, N, O
R = H, OMe, Br, F, Cl
R1 and/or R2 = H, Me, alkyl chains

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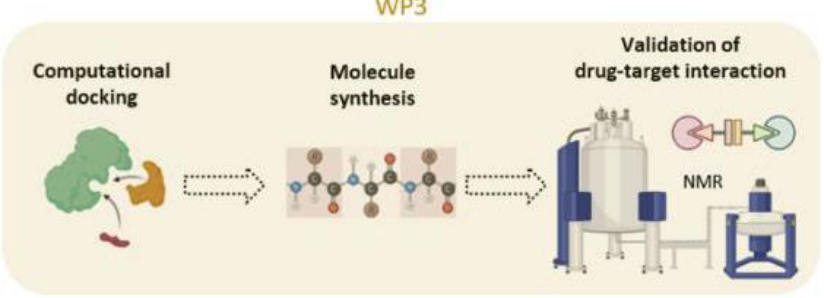
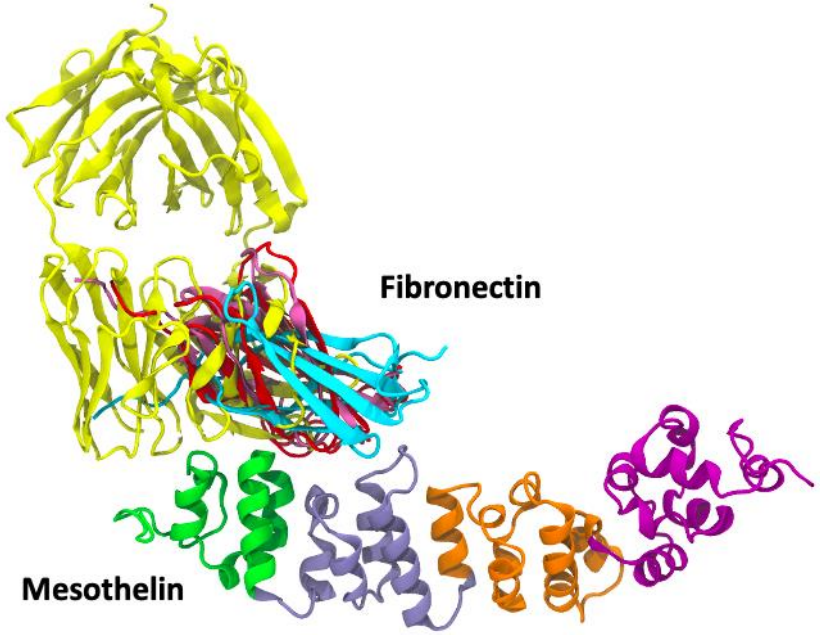


WP 3: Pharmacophoric dynamic docking simulations of genetic altered molecules

Task 3.3: Fight the enemy before you can see it: moving tools for early diagnosis from bench to bedside (***UniPI:*** *F. Minutolo, S. Landi)*

Establishment of the optimal conditions for the immunostaining of the MSLN-overexpressing with Fn3, an anti-His-tag and an anti-MSLN antibody. For these preliminary experiments we employed only MSTO_clone_1. Further investigation of the "three-component" reaction as a better strategy compared to the Sonogashira coupling to obtain the desired probes.



Docking algorithm	Binding affinity (kcal/mol)
Cluspro	**-22.9 ± 4.6**
Hdock	-5.4 + 4.0
pydock	-6.9 + 4.6

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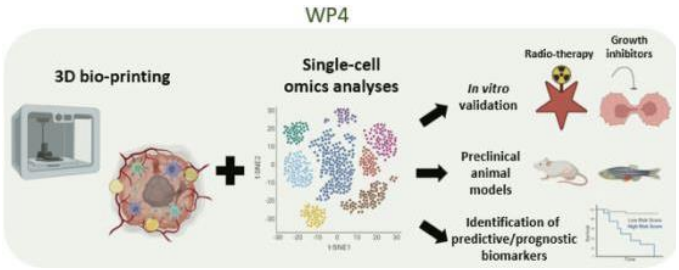
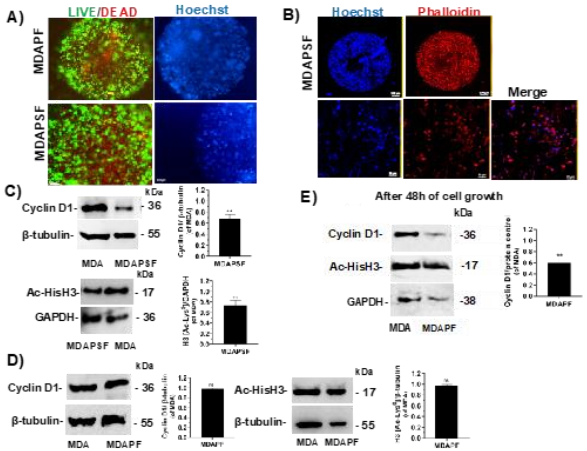


WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies *(UNIPA: G. Stassi)*

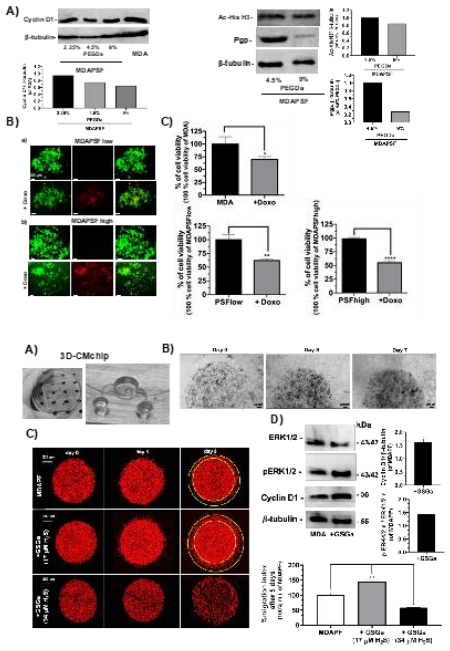
Task 4.1: Modeling of 3D approaches of multicellular spheroids structures for estimating the risk of disease initiation and progression ***(UNIPA: G. Stassi; IFO-IRE:*** *A. Bagnato, G. Blandino, D. Donzelli;* ***ISS:*** *E. Ambrosini, P. Picchieri, B. Serafini, A. Zeuner;* ***UniMIB:*** *R. Fruscio, A. L. Vescovi;* ***UniMORE:*** *V. Zappavigna;* ***UniPI:*** *S. Danti, F. Minutolo;* ***UniTOR VERGATA****: S. Melino)*

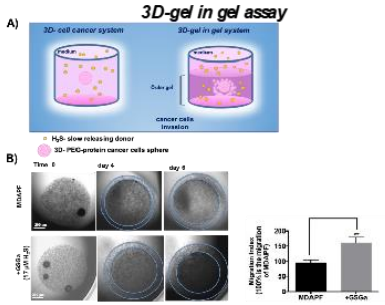
Optimization of 3D cell-culture models for studying cancer cell proliferation

Protein-Hydrogel based tumoroids represent a valid tuneable model for studying the **physically induced trans-differentiation (*PiT*)** of cancer cells and are a more reliable and predictive *in vitro* screening platform to investigate the effects of anti-tumour drugs.

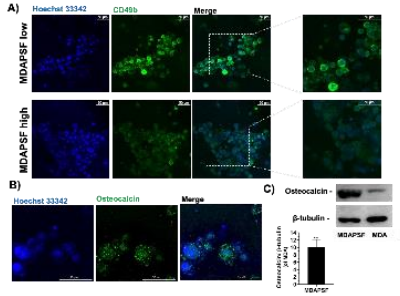


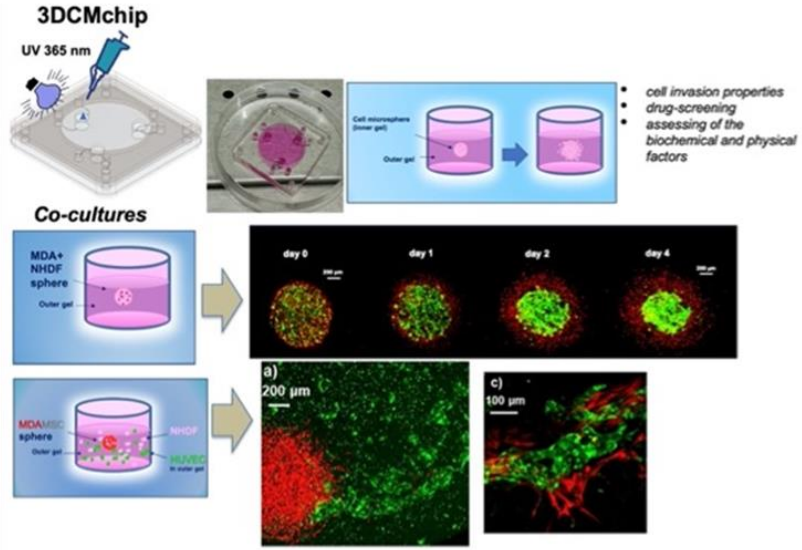
Effects of the tumoroid stiffness on the cyclin D1 expression and multi-drug resistance (MDR)





Effects of the stiffness on the trans-differentiation of MDA-MB 231 cancer cells into osteoblast-like cells





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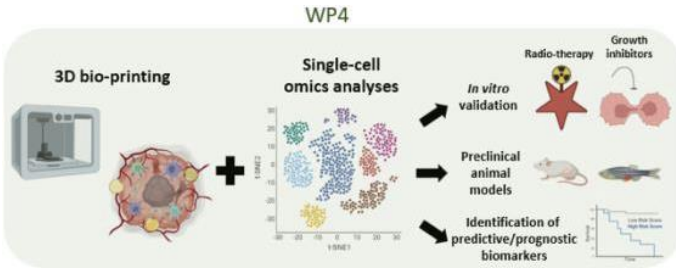
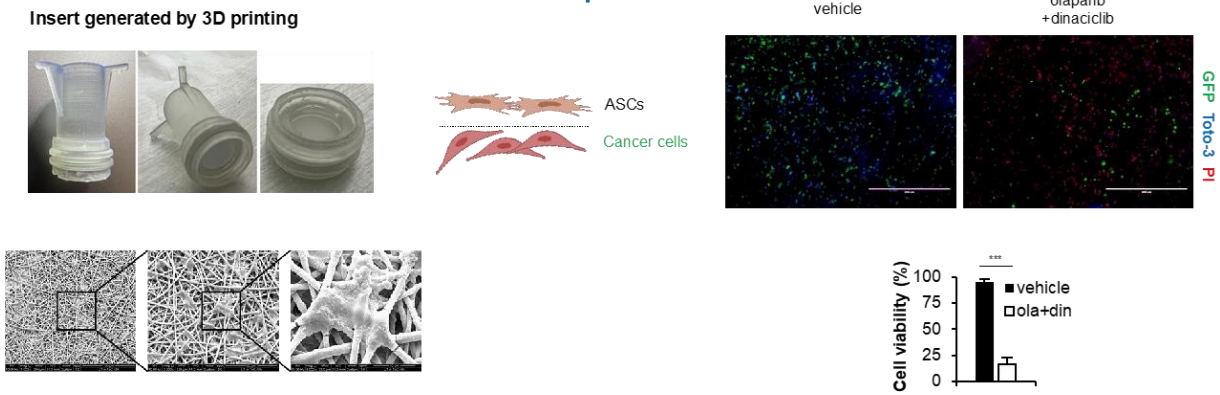


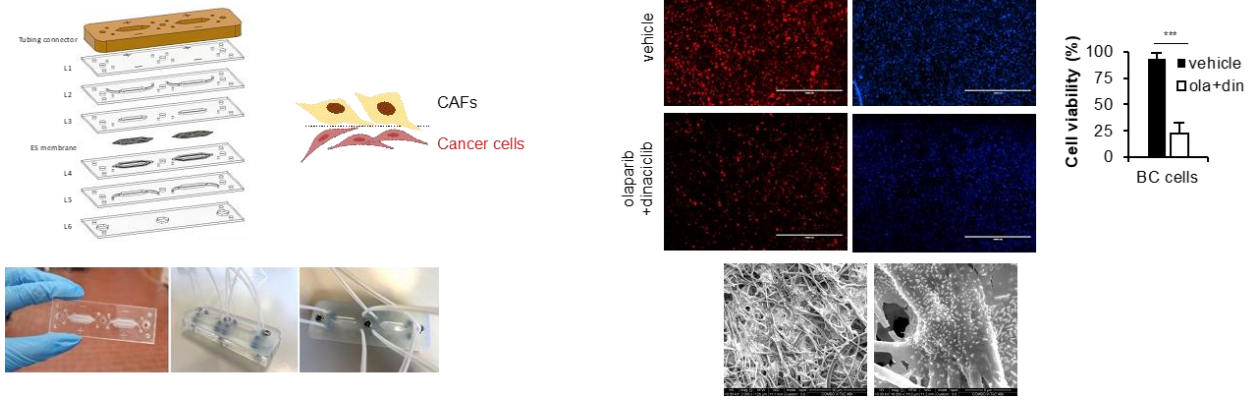
WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies *(UNIPA: G. Stassi)*

Task 4.1: Modeling of 3D approaches of multicellular spheroids structures for estimating the risk of disease initiation and progression ***(UNIPA: G. Stassi; IFO-IRE:*** *A. Bagnato, G. Blandino, D. Donzelli;* ***ISS:*** *E. Ambrosini, P. Picchieri, B. Serafini, A. Zeuner;* ***UniMIB:*** *R. Fruscio, A. L. Vescovi;* ***UniMORE:*** *V. Zappavigna;* ***UniPI:*** *S. Danti, F. Minutolo;* ***UniTOR VERGATA****: S. Melino)*

Validation of a static cell culture insert system to assess cellular viability following chemotherapic treatments



Validation of a Tumor-on-Chip (ToC) system in combination with microfluidic platforms to test the efficacy of innovative anticancer therapies



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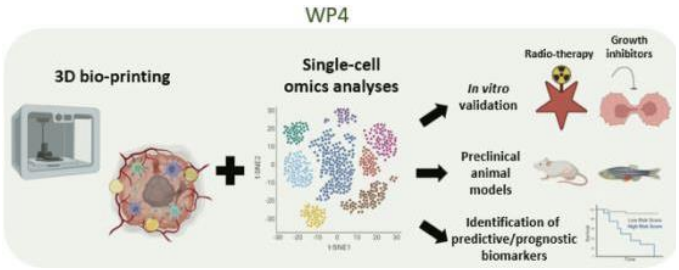


WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies *(UNIPA: G. Stassi)*

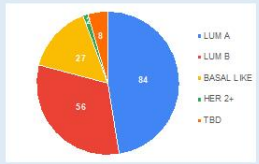
Task 4.1: Modeling of 3D approaches of multicellular spheroids structures for estimating the risk of disease initiation and progression ***(UNIPA: G. Stassi; IFO-IRE:*** *A. Bagnato, G. Blandino, D. Donzelli;* ***ISS:*** *E. Ambrosini, P. Picchieri, B. Serafini, A. Zeuner;* ***UniMIB:*** *R. Fruscio, A. L. Vescovi;* ***UniMORE:*** *V. Zappavigna;* ***UniPI:*** *S. Danti, F. Minutolo;* ***UniTOR VERGATA:*** *S. Melino)*

Generation of breast cancer organoids

- 16 breast cancer organoids generated

histotype	organoids
LUM A	7
LUM B	5
TNBC	4

- 177 breast cancer tissues available for organoids generation



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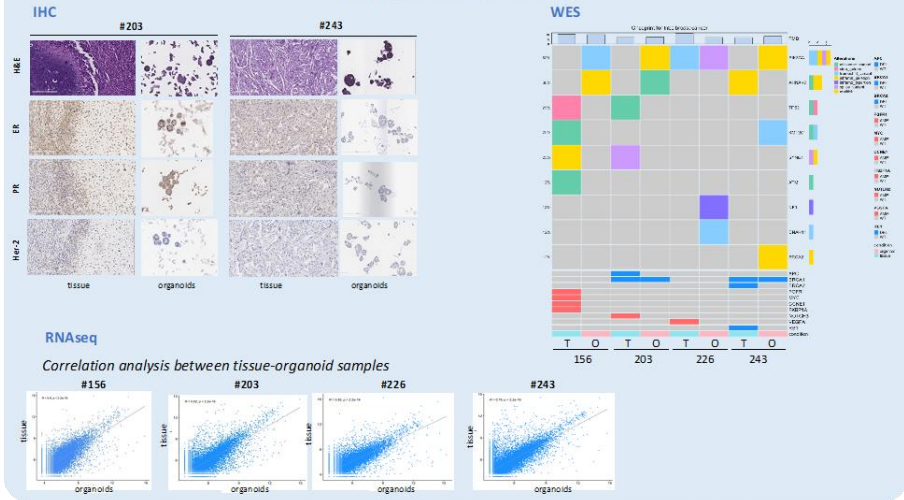
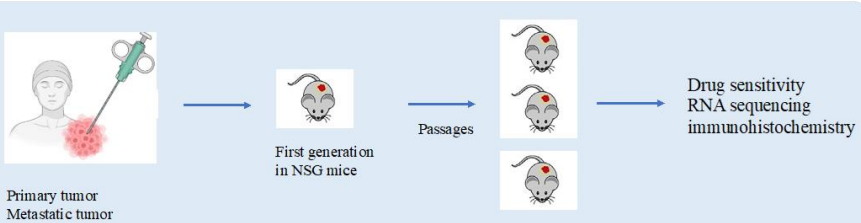
TNBC organoids characterization



Generation of PDX models from TNBC patients

Histotype	PDX implanted
TNBC	7



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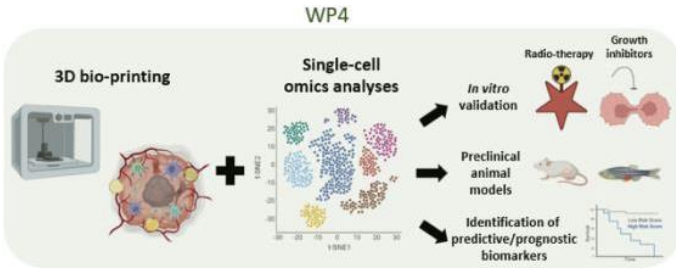

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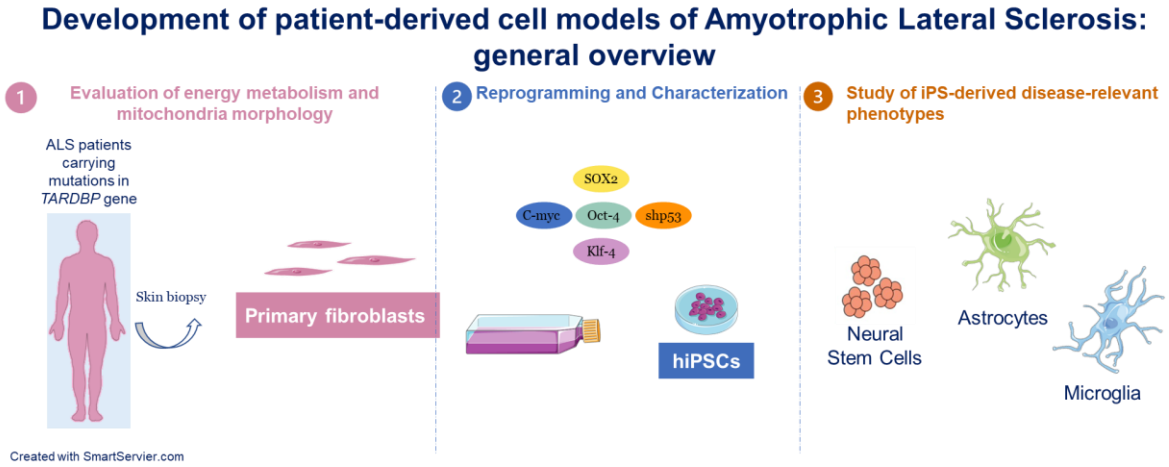

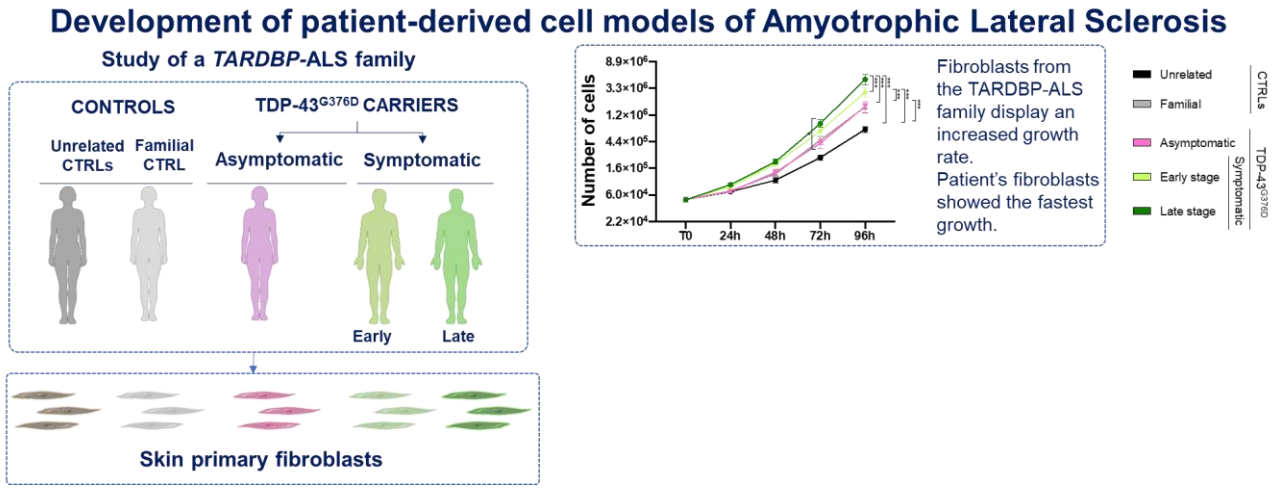

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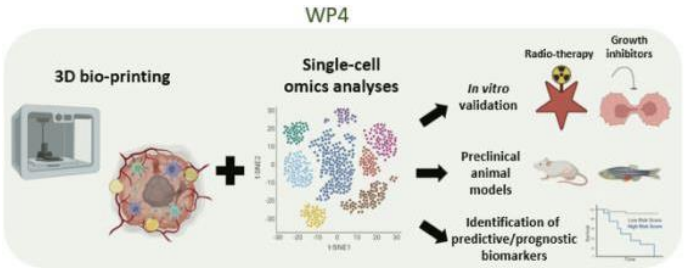

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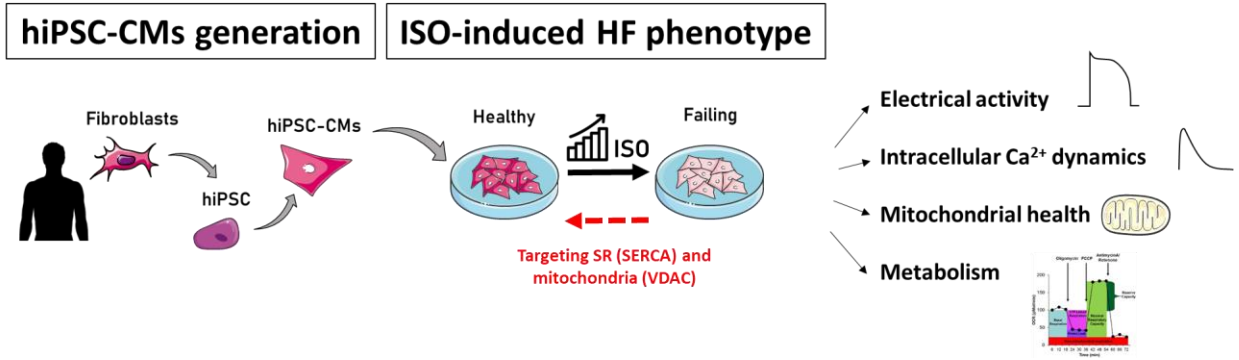
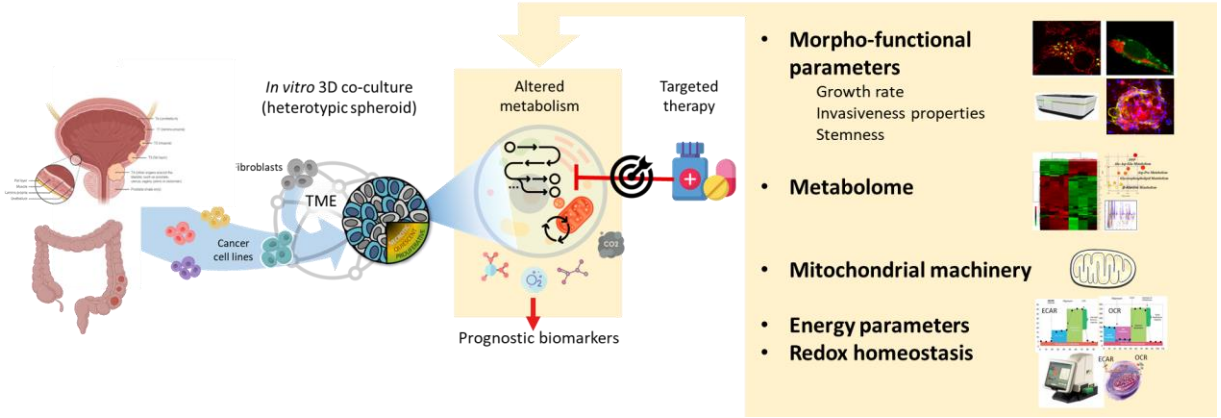
In vitro **platform of failing human induced pluripotent stem cell (iPSC) derived CMs to study new strategies targeting SR and mitochondria for the heart failure (HF) therapy**



In vitro platform of three-dimensional bladder and colorectal cancer cellular models to study metabolic prognostic biomarkers and therapeutic targets by multi-scale analysis



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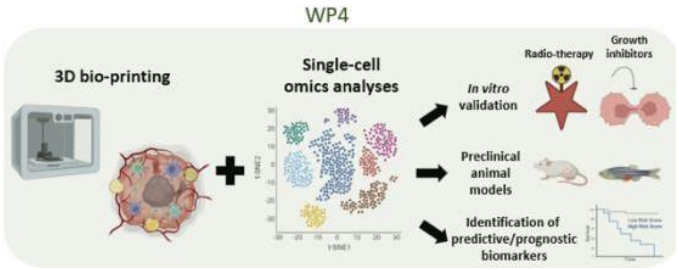

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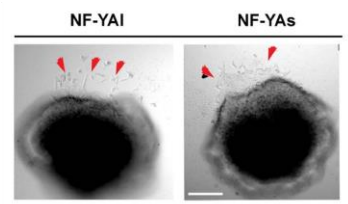
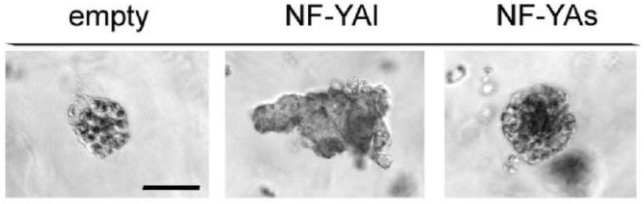
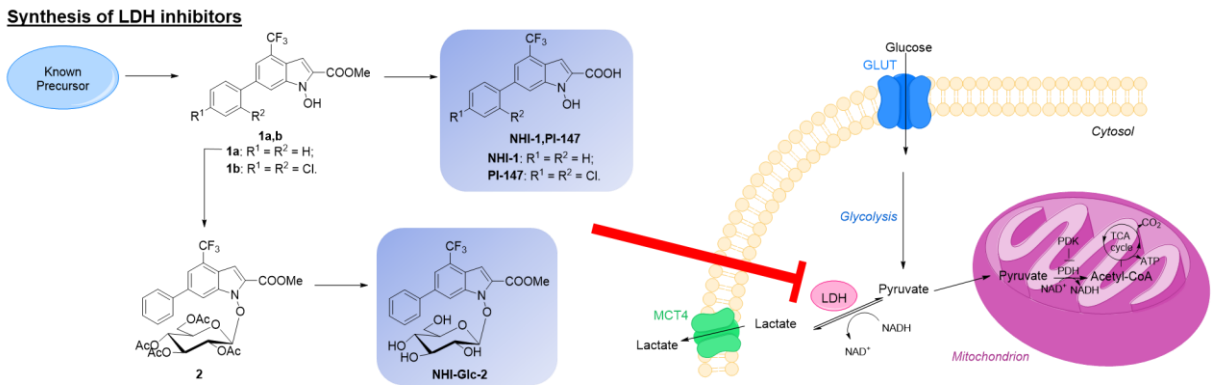
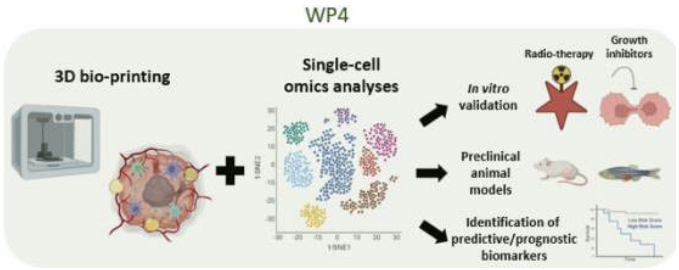
L'overespressione della isoforma NF-YAI in cellule tumorali HCT116 aumenta il potenziale invasivo. Colture 3D di cellule NF-YAI^{high} assemblate in Matrigel mostrano maggiore capacità migratoria e mimano un fenotipo tumorale aggressivo. Gli organoidi da singola cellula costituiti da cellule NF-YAI^{high} in Vitrogel assumono morfologia irregolare.









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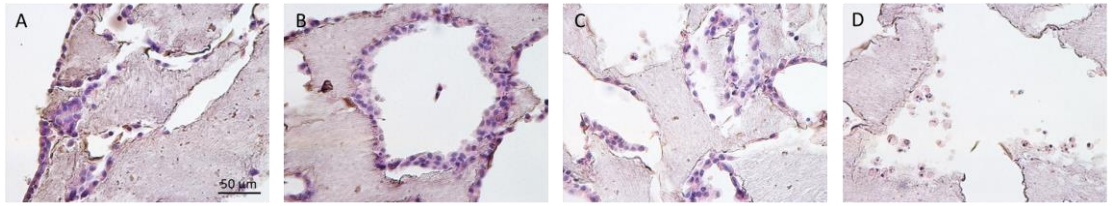
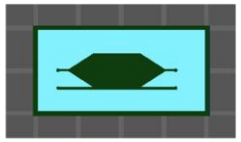
3D models of sinonasal cancer for testing new drugs



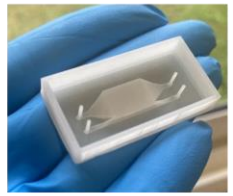
H&E staining of the **ITAC 3D constructs after 72 h treatment with different drugs:** (**A**) untreated; (**B**) treated with NHI-1; (**C**) treated with PI-147; (**D**) treated with NHI-Glc-2. The latter was the most effective in killing ITAC cells at **50 µM** concentration, single shot. Cell nuclei in violet, cytoplasm in pink. Original magnification 400×, scale bar 50 µm.

Design and fabrication of a nose-on-chip device

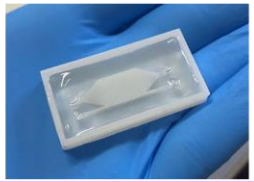
Design of the geometry with Computer-Aided Design (CAD) modelling in SolidWorks and export of the design in an STL file format to the Chitubox software.



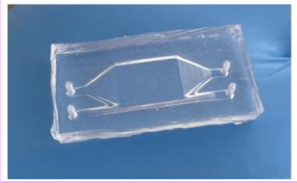
Fabrication of the mold with a digital light processing (DLP) 3D-printer (Anycubic Photon Mono X);



Treatment of the resin mold to prevent the PDMS from sticking to the 3D-printed mold and to remove uncured monomers and oligomers from the mold surface to allow PDMS curing process PDMS is then casted in the mold, degassed and cured in hot oven.



PDMS is gently removed from the mold and cut to desired shape, leading to inlets/outlets, channels, diffuser and chamber.



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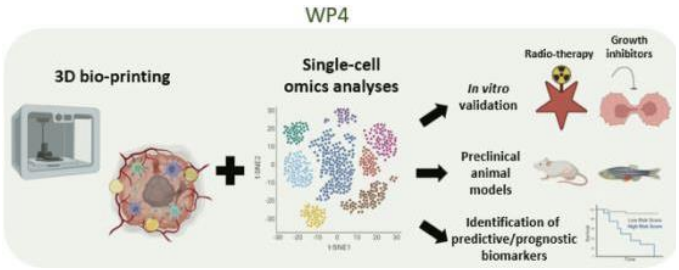
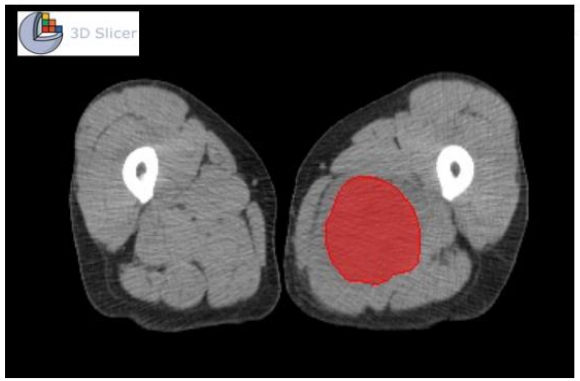
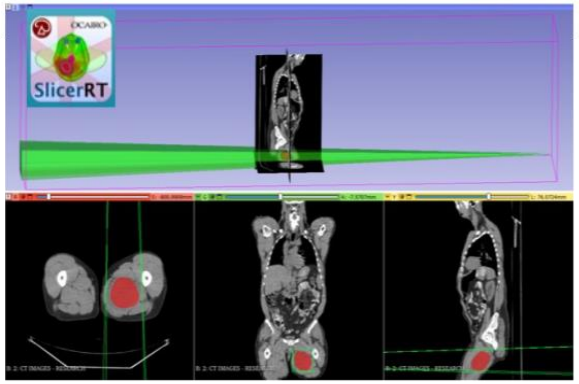


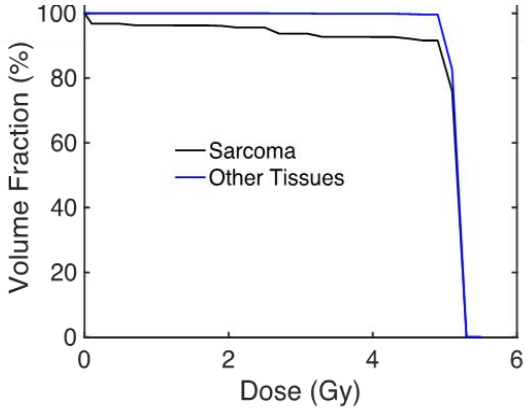
WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies *(UNIPA: G. Stassi)*

Task 4.2: Development of a powerful in vitro model for the response to radiotherapy in order to make clinical decisions more appropriate for treatment options (***UNIPA:*** *G. Stassi;* ***IOM:*** *L. Memeo;* ***UniBO:*** *M. L. Valentino;* ***UniCA:*** *A. Fanti)*

- The ***UniCA*** unit have worked to develop a multi-software framework for the investigation of hyperthermia treatment for radiotherapy enhancement.
- The processing of patient-specific images taken from available database (e.g., TCIA) has been carried out using the open-source software 3D Slicer [1].
- The software could be used to plan standard radiotherapy session by using the extension SlicerRT [2] and estimate the Dose volume histogram and Dose accumulation.







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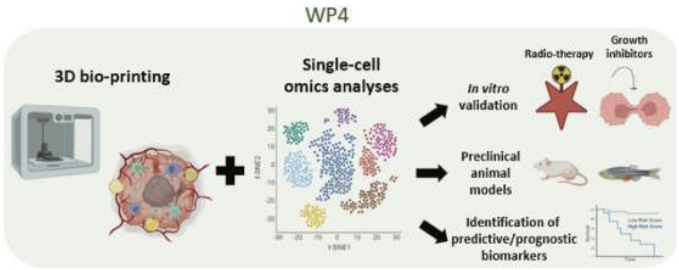
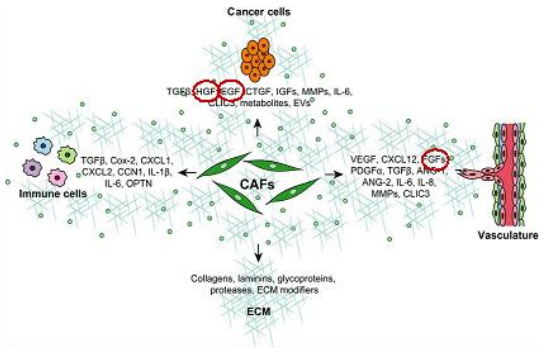
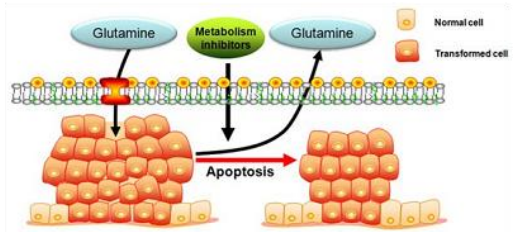


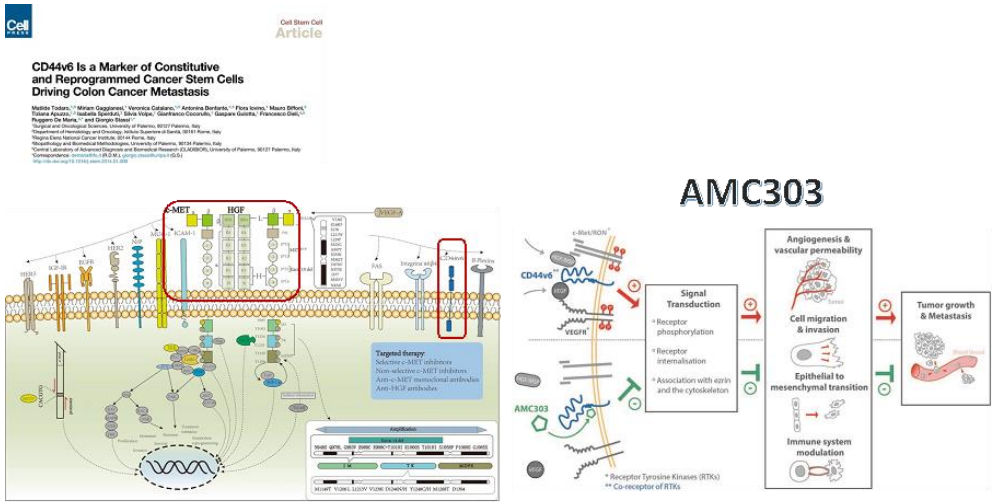
WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies *(UNIPA: G. Stassi)*

Task 4.3: Validation at single-cell level ***(UNIPA: G. Stassi; UniBO:*** *A. M. Porcelli;* ***UniCT:*** *C. Romano, P. Vigneri;* ***UniMIB:*** *R. Piazza;* ***UniSAPIENZA:*** *A. Zingoni;* ***UniPA:*** *S. Di Franco)*

Isolation and characterization of colon CSCs that can growth in absence of TME released factors (EGF, FGF, glutamine)







Targeting of specific TME-driven signaling pathways: CD44v6 and its partners in crime

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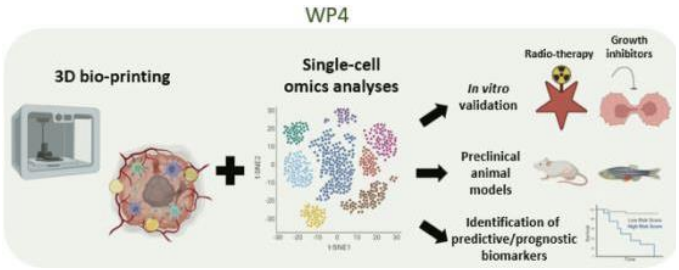
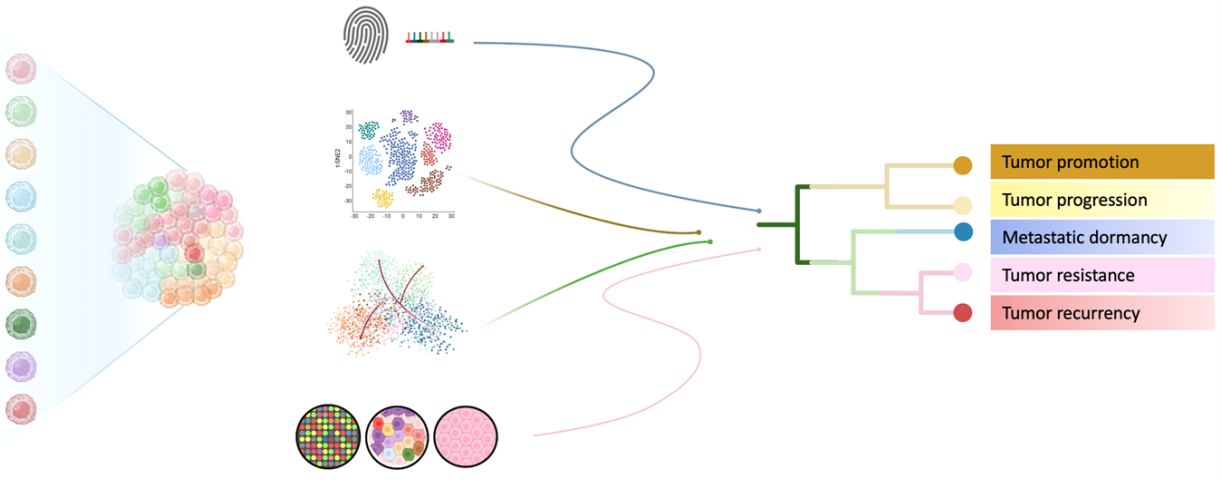


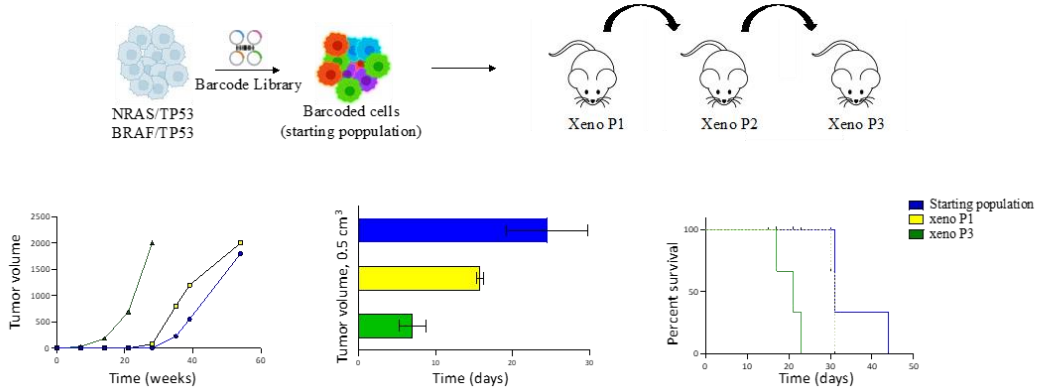
WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies

Task 4.4: Generation and optimization of preclinical animal models based on the use of organoids (***UNIPA: G. Stassi; IFO-IRE:*** *F. Ganci, M. Porru;* ***IOM:*** *C. Colarossi;* ***M. NEGRI:*** *G. Damia;* ***UniBO:*** *L. Ricciardello)*

Phylogenetic analysis of thyroid metastatic cell clones using barcoding technology



Generation of a highly aggressive thyroid cancer in vivo model



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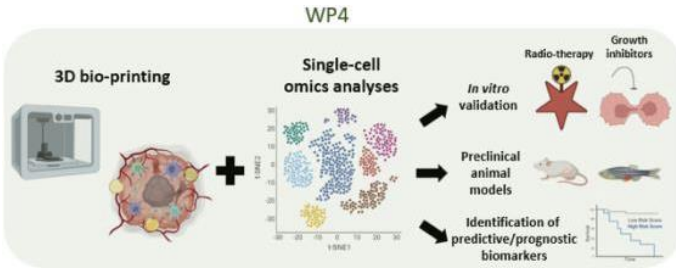

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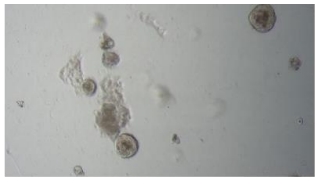
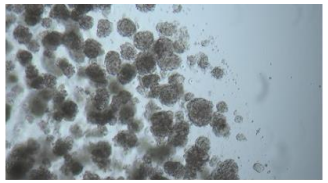
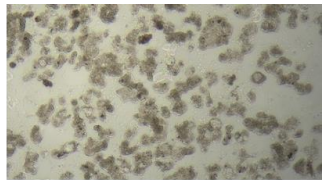
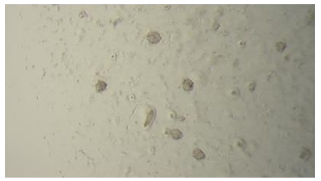
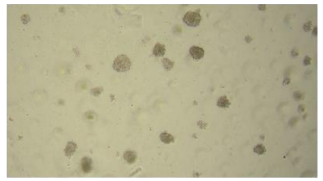
We set up the experimental conditions to obtain organoids from patients derived tumor xenografts (PDXs) of ovarian carcinoma available to undergoing histological examinantion, validation of functional DNA repair assays (i.e. RAD51 foci basal levels), and to investigate the stability of the replication fork (i.e. fiber assay) to better understand tumor response to treatments.

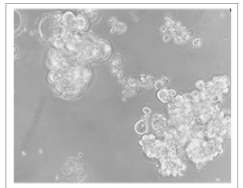

#154 (PDX BRCA1 mut)


#266 (PDX BRCA1 mut)


#316R (PDX BRCA1wt resistant to platinum)


#218 (PDX BRCA1 mut, olapib sensitive)


#218 (PDX BRCA1 mut, olapib resistant)


Isolated 3D cultures from ovarian cancer (OC) patient ascites.

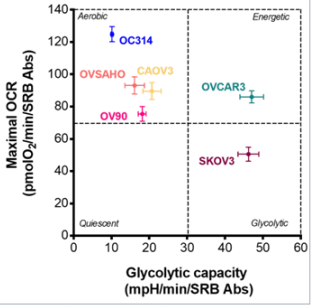
3D cultures (50%) from OC patients showed a *TP53* variant allele frequency (VAF) < 10%, indicating a poorly enriched cancer cell population in collected samples.

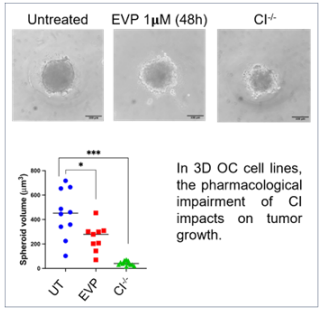
	TP53 WT (n=11)	P53 MUT (n=25)	VAF < 20%	VAF 20% - 60 %	VAF > 60 %
PRE-SCT	9	21	11	4	6
POST-SCT	2	4	1	0	3

Enrichment in cancer cell population of ascitic fluid 3D samples derived from three different patients showed a successful separation of cancer cells (VAF>50%). The enrichment was performed using Tumor Cells Isolation kit (Miltenyi Biotec).

Sample	*TP53* mutation	Pre-enrichment (VAF %)	Post-enrichment (VAF %)
Patient 1	p.Tyr163Cys	15	56
Patient 2	p.Glu204_Arg209del	18	72
Patient 3	p.Ile195Phe	8	66

A panel of different OC cell lines (OV90, OVSAHO, OC314, SKOV3, OVCAR3 and CAOV3) was selected as pre-clinical model of high-grade serous OC. The analyses of metabolic features of these cells, allowed clustering them into high (OC314), middle (OV90, CAOV3, OVSAHO) and low (SKOV3) OXPHOS. We selected cells with an intermediate OXPHOS status that may represent the cell population that likely activate different metabolic ways depending on their microenvironment to overcame potential metabolic therapeutics strategies.





In 3D OC cell lines, the pharmacological impairment of CI impacts on tumor growth.

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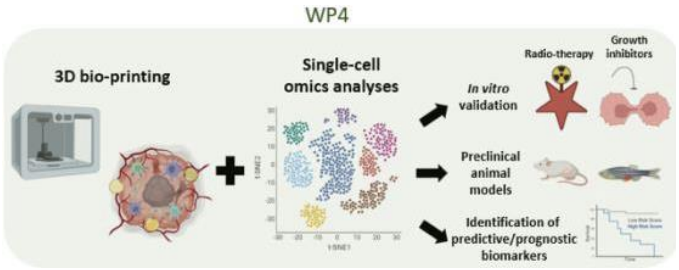
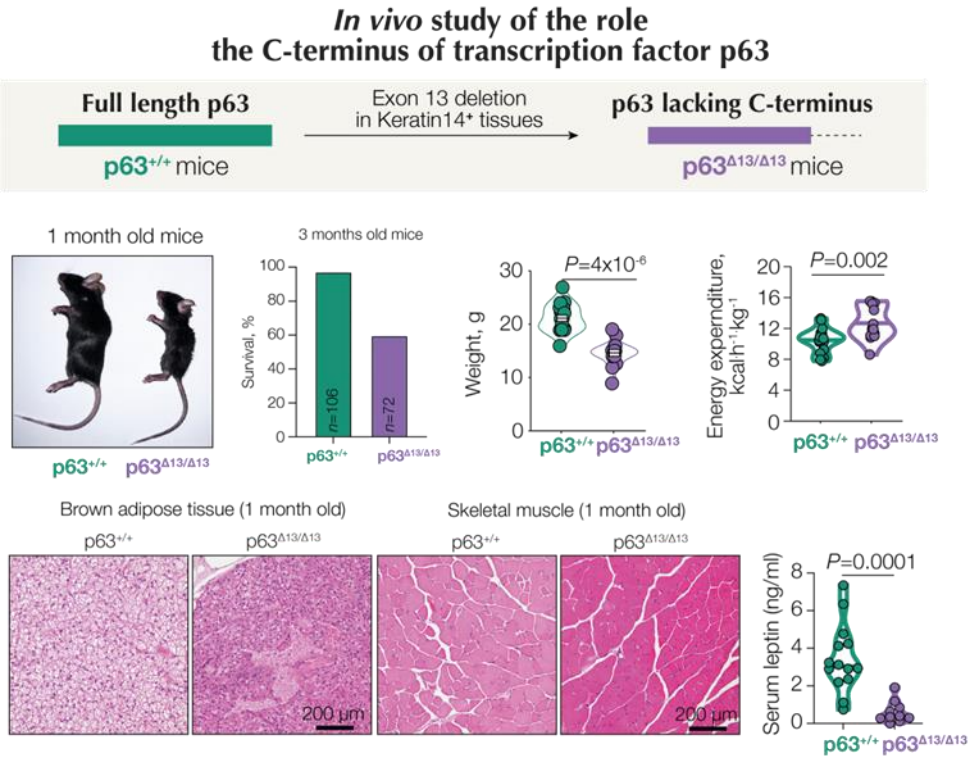


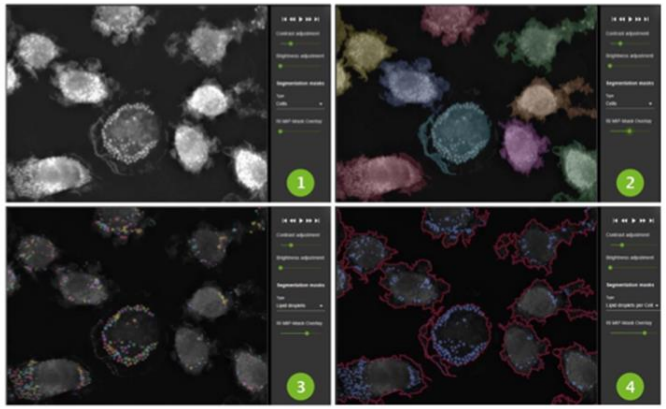
WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies *(UNIPA: G. Stassi)*

Task 4.5: Mouse models of mitochondrial metabolism (**UniTOR VERGATA:** E. Candi, G. Melino; **UniFG:** T. Cassano; **UniVPM:** S. Marchi)



Lipid droplets (LDs) detection through a **LABEL-FREE MODE** using a 3D-Cell Explorer-fluo (Nanolive SA, and quantification with the smart lipid droplets assay software (Nanolive), which provided several metrics, including morphological parameters, distribution and content, to **monitor and quantify LDs in live without staining**

TYPE OF METRIC	METRIC	LIPID DROPLETS	CELL	LD+ PER CELL
Quantitative	Count	✓	✓	✓
	Confluency (%)	-	✓	-
Morphological	Area (µm²)	✓	✓	✓
	Perimeter (µm)	✓	✓	✓
	Compactness	✓	✓	✓
	Eccentricity	✓	✓	✓
	Extent	✓	✓	✓
	Form factor	✓	✓	✓
Content	Granularity	✓	✓	✓
	Mean dry mass (pg)	✓	✓	✓
	Total dry mass (pg)	✓	✓	-
	Mean dry mass density (pg µm⁻³)	✓	✓	✓
	Mean RI	✓	✓	✓
Distribution	Distance to centroid of parent cell (µm)	✓	-	✓
	Ratio of total LD area to parent cell area (%)	✓	-	-



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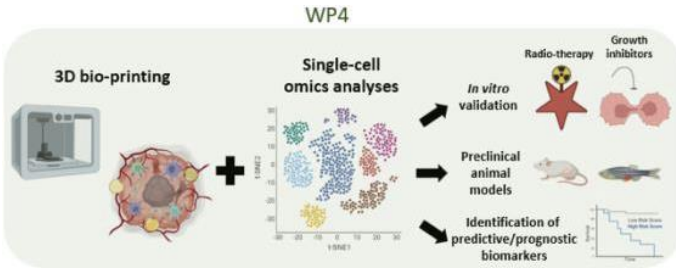
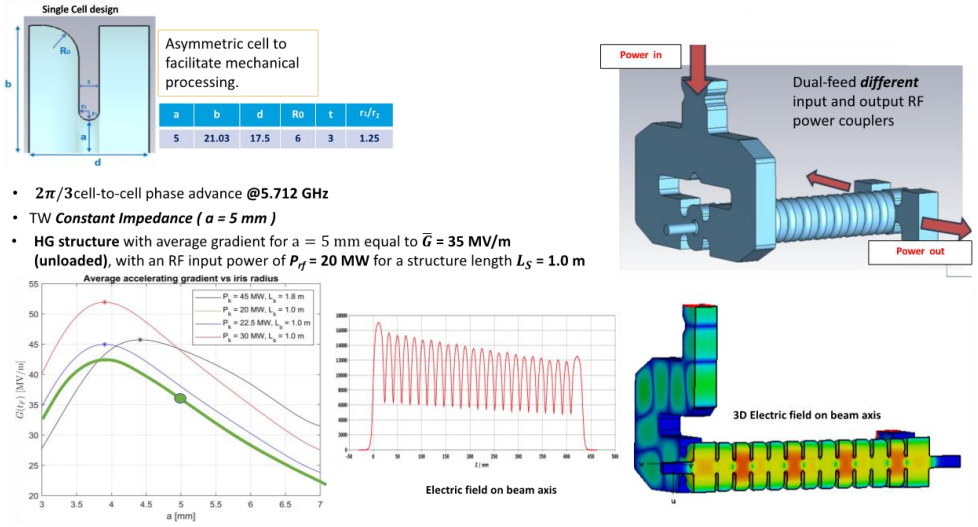
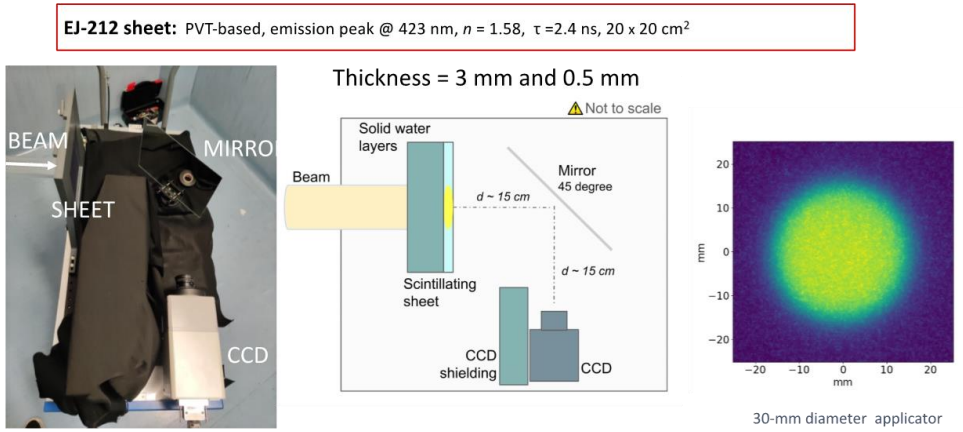


WP4: Preclinical models for precise therapeutic and diagnostic prevention strategies *(UNIPA: G. Stassi)*

Task 4.6: Innovative treatment planning system for electron FLASH radiotherapy from in silico modeling to preclinical validation in organoids and animal models for deep seated tumors (**IOM:** D. Giuffrida; **UniROMA SAPIENZA:** V. Patera; **SIT:** G. Felici; **UniPI:** F. Paiar, M. G. Bisogni)

Innovative system for electron FLASH radiotherapy from in silico modeling to preclinical validation in organoids and animal models for deep seated tumors





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Where are we going?

- **Integration of Multi-Omics Data:** Expanding the models to incorporate multi-omics data (genomics, proteomics, metabolomics, etc.) to enhance the accuracy and predictive power of the prognosis and therapeutic response;

- **Real-Time Data Analysis:** Developing capabilities for real-time data analysis to provide timely prognostic and therapeutic insights, allowing for more dynamic and responsive patient care;

- **Personalized Medicine:** Tailoring the prediction models to individual patients by including personalized health data, leading to more precise and effective treatment plans;

- **Machine Learning and AI Advancements:** Leveraging the latest advancements in machine learning and artificial intelligence to improve model performance and uncover new predictive biomarkers.

The CHALLENGE

- **Clinical Trials and Validation:** Conducting extensive clinical trials to validate the models in diverse patient populations, ensuring their robustness and generalizability;
- **Collaboration with Healthcare Providers:** Partnering with healthcare providers to integrate these predictive models into clinical workflows, facilitating their adoption and practical application in routine medical practice;
- **Ethical and Regulatory Considerations:** Addressing ethical and regulatory issues associated with the use of advanced predictive models in healthcare, ensuring patient privacy and data security;
- **Educational Programs**: Developing educational programs and tools to train healthcare professionals in the use and interpretation of these advanced prediction models, promoting widespread understanding and utilization.

Forecasts after project closure

- **Enhanced Prognostic Accuracy:** The development of sophisticated **prediction models** is expected to significantly improve the accuracy of prognostic assessments, enabling earlier and more reliable identification of disease outcomes;
- **Optimized Therapeutic Responses:** By predicting therapeutic responses with greater precision, **the models** will facilitate the customization of treatment plans, leading to more effective and targeted interventions for patients;
- **Data-Driven Decision Making:** Comprehensive data treatment will empower clinicians with robust, data-driven insights, enhancing decision-making processes in clinical settings;
- **Reduced Healthcare Costs:** Improved prognostic and therapeutic predictions will help in reducing unnecessary treatments and optimizing resource allocation, thereby lowering overall healthcare costs;
- **Patient-Centric Care:** The integration of personalized data **into prediction models** will promote patient-centric care, offering tailored treatment options that align with individual patient profiles;
- **Scientific Advancements:** The spoke 3 will contribute to the broader scientific understanding of disease mechanisms and treatment responses, paving the way for future research and innovation in the field of precision medicine;
- **Clinical Integration:** The successful implementation of **these models** in clinical practice will bridge the gap between research and real-world application, ultimately improving patient outcomes on a large scale.


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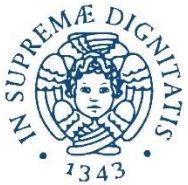
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