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Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

Innovation, digitalisation and sustainability for the diffused economy in Central Italy

Università degli Studi di Urbino
4 novembre 2022

Finanziato dall'Unione europea
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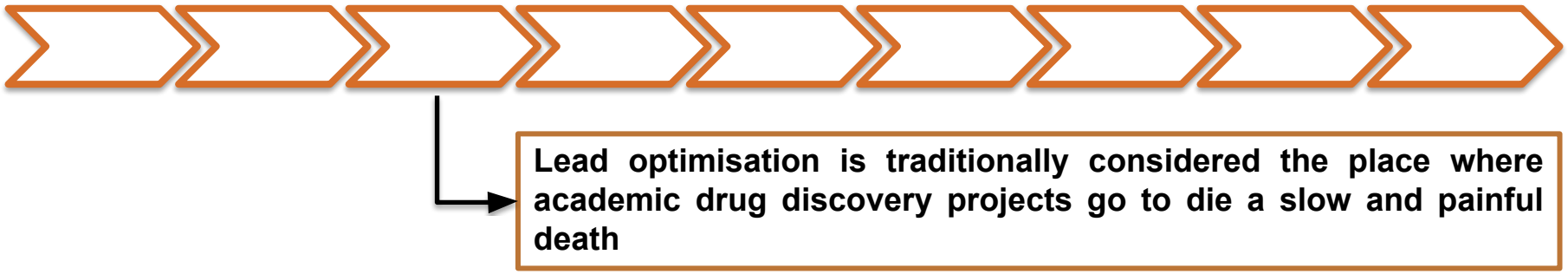
Kick-off meeting "SPOKE 8"

Introduction to WP 1
Development of a third party-accessible, enabling platform for efficient preclinical drug discovery

Giovanni Bottegoni

WP1 – Overall Goal

Enabling platform for the delivery of **optimised leads** at an **accelerated pace**

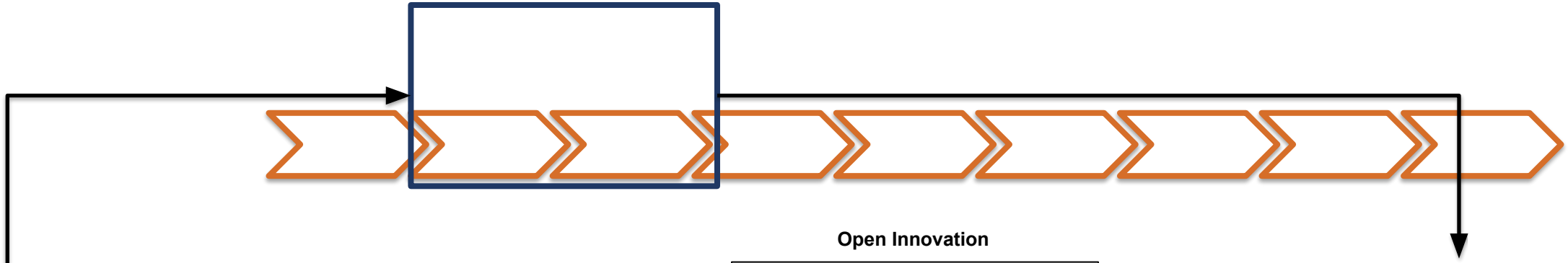


- **Deployment of an actual platform of general applicability**
- **Identification of optimised leads**

The Open Innovation Paradigm

*"Open innovation is the use of purposive **inflows** and **outflows** of knowledge to accelerate internal innovation, and expand the markets for external use of innovation."* Henry Chesbrough

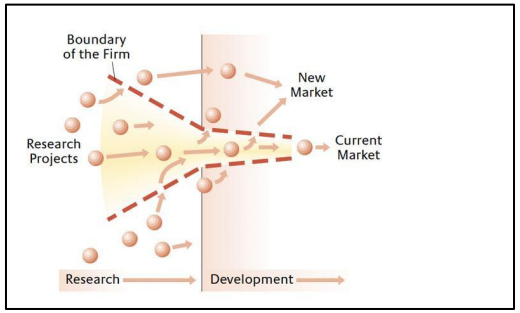
Platform



Attract external partners interested in:

- developing leads with activity at *their* targets
- test leads they already have for new activities
- optimise promising scaffolds
- etc.

Open Innovation



Attract external partners interested in:

- acquire intellectual property
- partecipate in joint ventures

Incorporate start-ups and spin-offs

Henry Chesbrough, *Open Innovation. The New Imperative for Creating and Profiting from Technology*. HBR Press 2003

WP1 – General Outline

WP leader: UNIURB
Participants: Ud'A, UNIPG
Duration: 36 M

Encompasses 3 Tasks

Milestones	M1.1a Computational backbone deployment (Y1)	M1.1b Screening libraries (Y2)	M1.1c Enhanced synthesis of selected compounds (Y2)	M1.1d Prospective validation of the infrastructure (Y3)
	M1.1e Facilitated scale-up (Y3)	M1.2a Implementation of in silico polypharmacology (Y1)	M1.2b in vitro characterisation of multi-target compounds (Y2)	M1.2c Multi-target lead optimisation (Y3)
	M1.3a Activity against metastatic cancer: in vitro testing (Y1)	M1.3b Activity against metastatic cancer: in vivo testing (Y2)	M1.3c Simultaneous detection of molecules in multiple biological tissues (Y2)	M1.3d Identification of novel small organic molecules (Y3)
Outputs	D1.1b Virtual screening platform and library (Y2)	D1.1c Flow technology and automation implementation (Y2)	D1.1d Actual active molecules identified (Y3)	D1.1e Scale-up of selected leads (Y3)
	D1.2b Selected in vitro binding and functional assays implemented (Y2)	D1.2c Optimized multi-target leads identified (Y3)	D1.3a Array of in vitro assays purposely conceived and validated (Y1)	D1.3b 3R-compliant animal models conceived and validated (Y2)
	D1.3c Analytical protocols to quantify molecular concentrations (Y2)		D1.3d Lead compounds with potential anticancer activity identified (Y3)	

WP1.1: Computationally-driven, Integrated Infrastructure for Lead Identification and Optimisation

General Description of Task 1 (UNIURB, UNIPG)

Creating an **integrated platform** that streamlines the **identification of hits** (simulative- and AI-based virtual screening tools), their **efficient synthesis** (flow chemistry and automation), characterisation (array of **biophysical assays**), **optimisation**, and preliminary **de-risking** (**lipidomics** and **organoids**);

Setup of an **externally accessible**, confidentiality-compliant, computationally-driven **platform** for the **screening** of commercial and/or in house generated libraries and for the subsequent **optimization** and **characterization** of identified hits

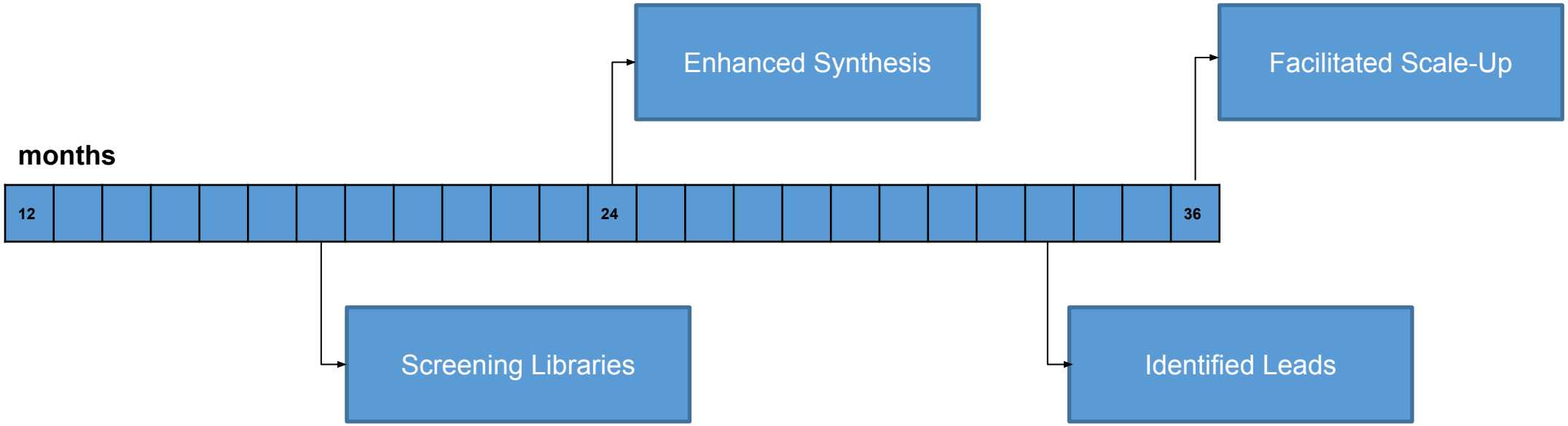
WP1.1: Milestones

Milestone No	Milestone Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
M1.1a	Computational backbone deployment	UNIURB	Deployment and **retrospective testing** of the commercial hardware and software computational backbone	M12	Replication of results from publicly available benchmarks
M1.1b	Screening libraries	UNIURB, UNIPG	The computationally-driven virtual screening platform is ready	M18	Commercial virtual libraries can be stored and/or accessed In house virtual libraries deployed
M1.1c	Enhanced synthesis of selected compounds	UNIPG	Sustainable methodologies and innovative tools such as flow technology and automation to complement conventional synthesis are deployed	M24	Compounds throughput can be increased

WP1.1: Milestones

Milestone No	Milestone Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
M1.1d	Prospective validation of the infrastructure	UNIURB, UNIPG	New molecules that turn out to be active in wet experiments can be identified thanks to the facility	M33	Experimental activities and mechanistic, kinetic, thermodynamic and structural information on compound–target interactions of novel compounds can be determined and turn out to be in line with the predictions
M1.1e	Facilitated scale-up	UNIURB, UNIPG	Synthetic optimization of selected leads for pharmacological appraisals (see also **WP3** - **T3.1**) through green methodologies and automated flow chemistry approaches	M36	Planned synthetic routes are simple, environmentally friendly, low cost and highly efficient in terms of yield

WP1.1 – Deliverables



WP1.1 – Deliverables

Output No	Output Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
D1.1b	Screening Libraries	UNIURB, UNIPG	The computationally-driven virtual screening platform is ready	M18	Total number of available compounds
D1.1c	Enhanced Synthesis	UNIPG	Flow technology and automation work at full capacity	M24	(Compounds)/(time) = (Synthetic Throughput)
D1.1d	Identified leads	UNIURB, UNIPG	Actual active molecules identified by computational means and subjected to hit-to-lead optimisation	M33	Computational predictions are validated in wet experiments
D1.1e	Facilitated scale-up	UNIURB, UNIPG	Overcoming issues in traditional synthesis, the scale-up of selected leads is facilitated	M36	n. of compounds synthesized in the hundreds of milligrams scale

WP1.2: Development, validation and application of tools for rational polypharmacology

General Description of Task 2 (UNIURB, UNIPG)

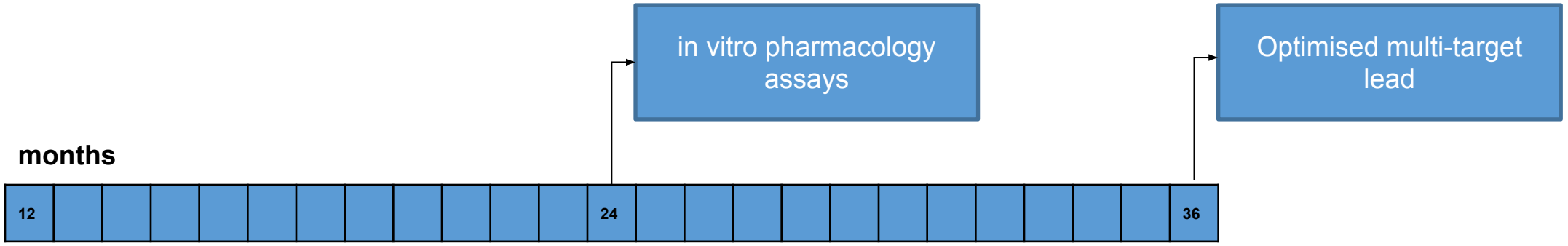
Adopting the now **established** multitarget-directed ligand approach, i.e., **rationally engineering activity at multiple targets**, as a way to rapidly exploit actionable knowledge coming from genomic and electronic medical records analysis

Create an **integrated pipeline** for **engineering**, **testing** and **optimizing activity** at multiple targets in a single molecule. Proof of concept (poc) compounds will be initially generated for target combinations selected based on in house expertise (e.g., nicotine addiction and bipolar disorder).

WP1.2: Milestones

Milestone No	Milestone Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
M1.2a	Implementation of ***in silico*** polypharmacology	UNIURB	Traditional single-target in silico methods for hit identification are optimized to return multi-target hits	M12	Retrospective comparison with publicly available data (e.g., extracted from ChEMBL)
M1.2b	*in vitro* characterisation of multitarget compounds	UNIURB, UNIPG	Assays in multiple cell lines designed and realized to carry out polypharmacological profiling of compounds (and biologics, see also **WP2** - **T2.1** and **T2.2**).	M24	*in vitro* activity profile can be determined
M1.2c	Multitarget lead optimisation	UNIURB, UNIPG	**Organoid models** will be designed for polypharmacological profiling of compounds (and biologics, see also **WP2** - **T2.1** and **T2.2**). **A lipidomics-based approach** to evaluating the risk of clinical hepatotoxicity potential will also be applied to the most promising compounds.	M36	The compounds' ADMET and PK preliminary profiles is sufficiently optimized to selected which compounds to progress to translational assays or *in vivo*

WP1.2 – Deliverables



WP1.2 – Deliverables

Output No	Output Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
D1.2b	in vitro pharmacology assays	UNIURB, UNIPG	Selected in vitro binding and functional assays are up and running. **Given the multitarget nature of sought compounds, throughput is key.**	M24	(Activity points measured)/(time) = (throughput of the assays)
D1.2c	Optimized multitarget leads	UNIURB, UNIPG	Optimized multitarget leads **ready to progress** toward project-specific translational or in vivo models are identified	M36	n. of compounds characterized in terms of ADMET and PK preliminary profiles

WP1.3: Test bed for preclinical compounds against innovative targets for metastatic cancer

General Description of Task 3 (UNIURB, Ud'A)

Development of a complete set of **primary** and **secondary assays** to **accelerate the development of NCEs**, both **internally developed** (see task 1.1 and task 1.2) or **externally provided**. Innovative techniques for the extraction of samples from biological fluids and tissues and recovery of molecules at low concentration will also be implemented.

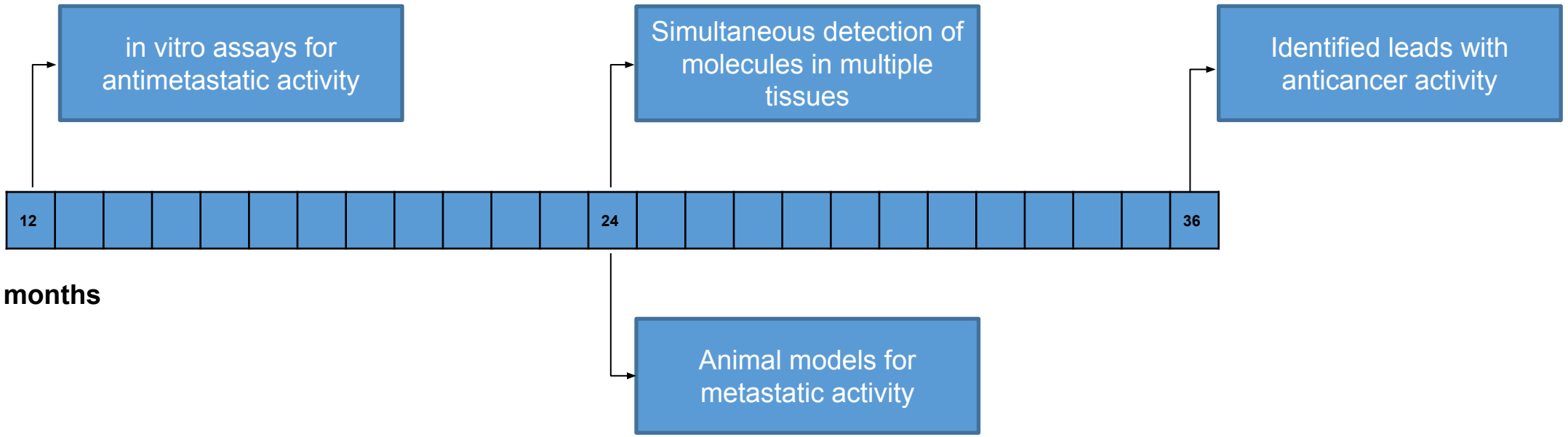
WP1.3: Milestones

Milestone No	Milestone Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
M1.3a	Activity against metastatic cancer: *in vitro* testing	UNIURB	*ad hoc* Cell systems to test the effects of target compounds on cell growth and migration are up, running and validated	M12	Replication of results from publicly available benchmarks and comparison with standard of practice assays (e.g., Boyden chamber)
M1.3b	Activity against metastatic cancer: *in vivo* testing	UNIURB	Setting of preclinical mouse models to test small molecules effects on cancer growth and dissemination	M24	Animal models can demonstrate the antineoplastic activity of tested compounds

WP1.3: Milestones

Milestone No	Milestone Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
M1.3c	Simultaneous detection of molecules in multiple biological tissues	Ud'A	Protocols based on innovative techniques for the extraction of samples from biological fluids and tissues and recovery of molecules at low concentration are deployed.	M24	Data collection and quantification on samples from animal models. Standardization of developed protocols.
M1.3d	Identification of novel small organic molecules exerting antimetastatic activity on selected forms of cancer	UNIURB	Identification, characterization, and test of proof-of-concept lead compounds (e.g., new molecules exerting activity interacting with reactive oxygen species and stress of the endoplasmic reticulum to treat multiple myeloma)	M36	At least one novel, patentable lead compound emerges from the pipeline with potential anticancer activity. Results in animal models are equal or superior to known antineoplastic compounds used as comparators

WP1.1 – Deliverables



WP1.3 – Deliverables

Output No	Output Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
D1.3a	*in vitro* assays to measure anticancer and potential antimetastatic activity of small organic molecules	UNIURB	Array of *in vitro* assays purposely conceived and validated (e.g., to assess activity on reactive oxygen species and stress of the endoplasmic reticulum of small organic molecules)	M12	Capacity of the assays: number of estimated activity values (IC50, EC50, etc.)
D1.3b	Suitable animal models to measure antimetastatic activity	UNIURB	3R-compliant animal models conceived and validated to assess the ability of small organic molecules to shrink tumor mass and prevent/reduce metastasis	M24	Antineoplastic activity of tested compounds can be clearly measured

WP1.3 – Deliverables

Output No	Output Name	Spoke/Affiliated	Description	Due Date (month number)	Means of Verification
D1.3c	Simultaneous detection of molecules in multiple biological tissues	Ud'A	Analytical protocols to quantify molecular concentrations in multiple tissues from models of metastatic cancer are deployed	M24	n. of data points collected
D1.3d	Lead compounds with potential anticancer activity	UNIURB	Lead compounds, either converging from an internal program (see also D1.1d) or from third parties, are identified	M36	n. of lead compounds identified

WP1 – Investments for Infrastructure Development

Investments for the infrastructure development for the implementation of WP	
Description	Spoke/Affiliated
T1.1-3 - Infrastructure for the biophysical characterisation of molecules in terms of mechanistic, kinetic, thermodynamic and structural information on compound–target interactions, thus equipped for performing **microscale thermophoresis** (MST), **surface plasmon resonance** (SPR), **circular dichroism** (CD) and **high resolution NMR**. High resolution NMR also enables quality control in medicinal chemistry. For recombinant protein expression and purification see **WP2**	UNIURB
T1.1 - Local **computational infrastructure** to be lodged in a dedicated environment with stabilized voltage and adequate cooling capacity. The project will be conceived to minimize carbon footprint.	UNIURB

WP1 – Impact

IMPACT	
Description	**Means of Verification**
In line with the tenets of **open innovation** (Chesbrough, 2006), we envision a bi-directional flow of people and ideas between UniUrb and companies, that is made possible by an agile and externally accessible platform that enables lead identification and optimisation. Encompassing advanced computational methods, synthetic chemistry skills, in vitro/vivo pharmacology and sound knowledge in key therapeutic areas, the **platform generates** value through:	
i) **Unique know-how**, made available to both **big players** and **local SMEs**, limiting the need for **massive infrastructural investments** (for example, for high-throughput wet screening), **shortening time to market**, and, thus, with clear potential for **attracting extramural funds and partnerships**.	• Number of research contracts involving the platform • Total amount of extramural funds attracted
ii) **Composition of matter patents**, claiming in house generated compounds active in key therapeutic areas such as oncology. This **IP** is instrumental to **incorporate spin-offs** and attract investments especially within the **emerging framework of portfolio-companies**.	• Number of patents granted • Number of patents out-licensed • Number of spin-offs incorporated

Grazie per l'attenzione