MISSIONE 4
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Ministero dell'Università e della Ricerca

Italiadomani
PIANO NAZIONALE DI RIPRESA E RESILIENZA

Development of a third party-accessible, enabling platform for efficient preclinical drug discovery

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Campus Mattei

Università degli Studi di Urbino
23 Maggio 2024

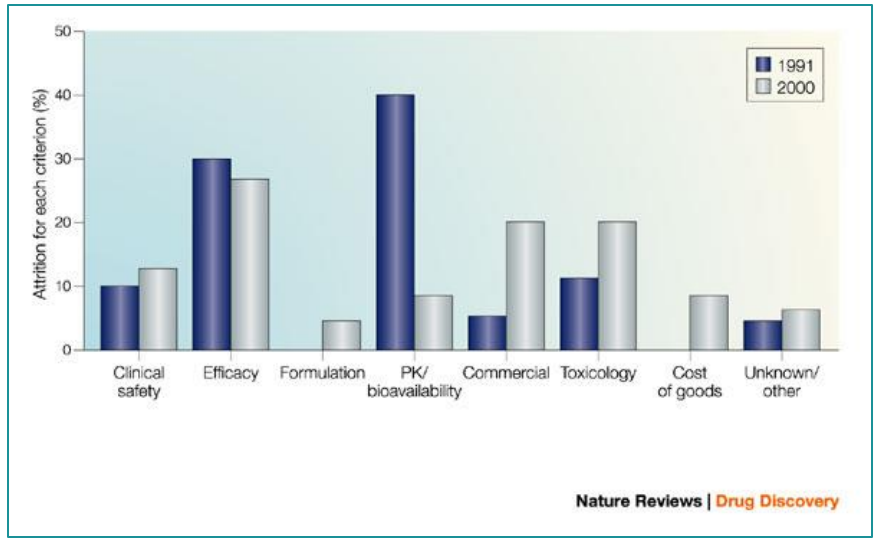
WP1 – Overall Goal

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

Lead optimisation is traditionally considered the place where academic drug discovery projects go to die a slow and painful death

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

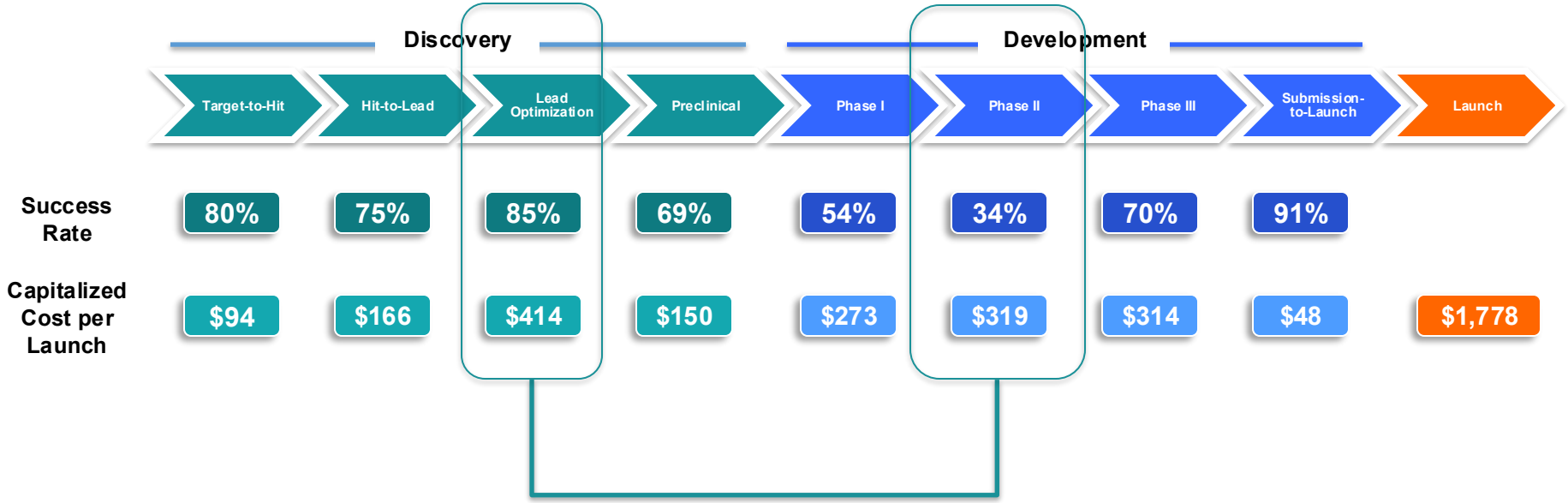
	Discovery				Development				
	Target-to-Hit	Hit-to-Lead	Lead Optimization	Preclinical	Phase I	Phase II	Phase III	Submission-to-Launch	Launch
Success Rate	80%	75%	85%	69%	54%	34%	70%	91%	
Capitalized Cost per Launch	$94	$166	$414	$150	$273	$319	$314	$48	$1,778



Intervening in the discovery phase is the best way to reduce attrition rates down the line

Adapted from Paul *et al.*, Nat Rev Drug Discovery **2010. All costs are in million 2008 USD**

Kola and Landis, Nat Rev Drug Discovery **2004**.

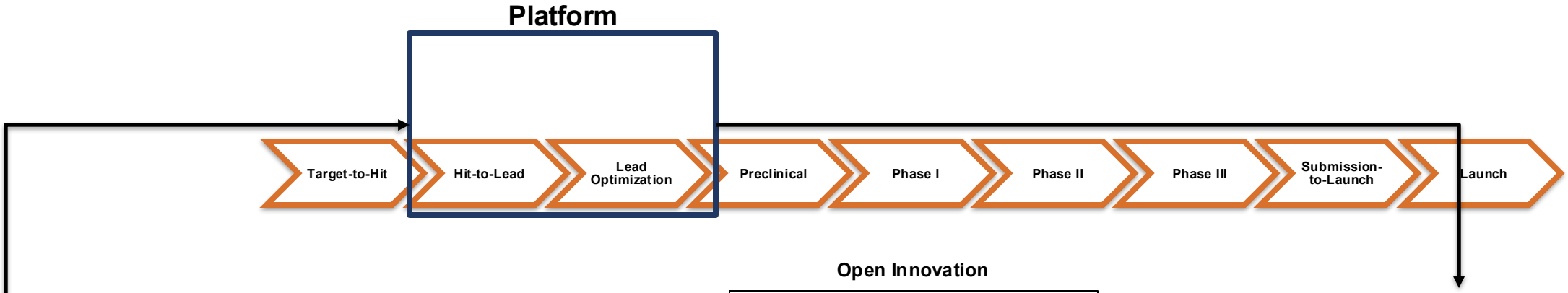


A parametric sensitivity analysis indicates that improving the lead optimization step provides the greatest beneficial effect on the progression rate in Phase II and on the total cost per launch

Waring et al., Nat Rev Drug Discovery **2015**.

The Open Innovation Paradigm

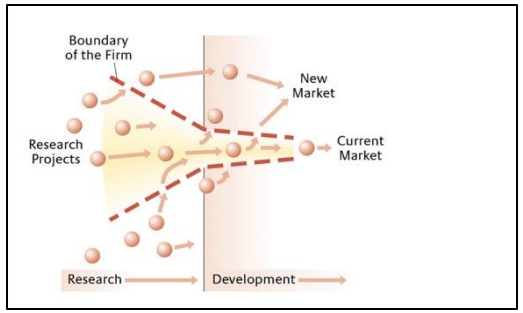
*"Open innovation is the use of purposive **inflows** and **outflows** of knowledge to accelerate internal innovation, and expand the markets for external use of innovation."* Henry Chesbrough



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

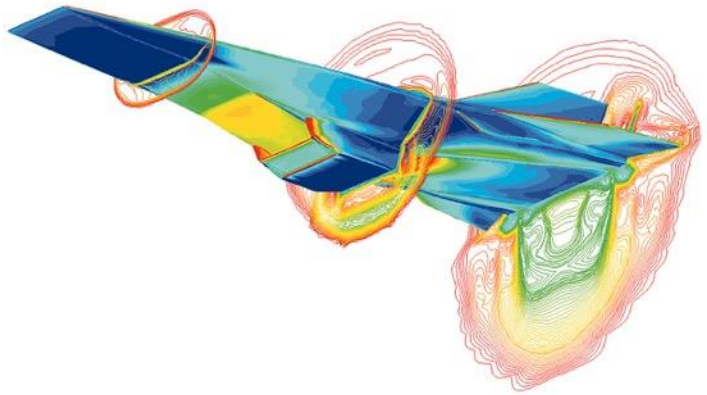
Henry Chesbrough, *Open Innovation. The New Imperative for Creating and Profiting from Technology*. HBR Press 2003

WP1 – 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

Of Drugs and Airplanes

"Many **major aerospace projects** require a decade or more of R&D along with over a billion dollars in investment to get a single new product to market."



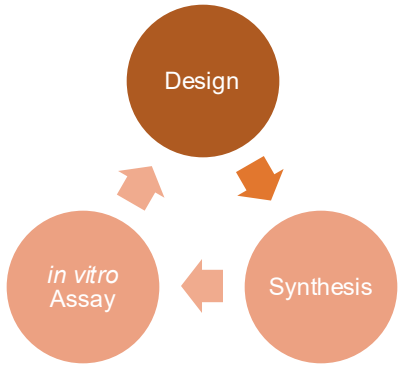
Why do not we approach drug discovery the same way?

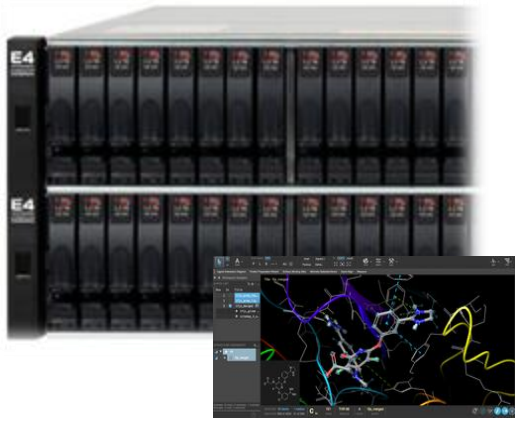
- Biology is involved
- Limited accuracy of the input
- Multi-disciplinary Effort
- Information is largely incomplete

"All models are wrong, some are useful" G. Box

WP1 - Development of a third party-accessible, enabling platform for efficient preclinical drug discovery

Target-to-Hit → Hit-to-Lead → Lead Optimization → Preclinical → Phase I → Phase II → Phase III → Submission-to-Launch → Launch





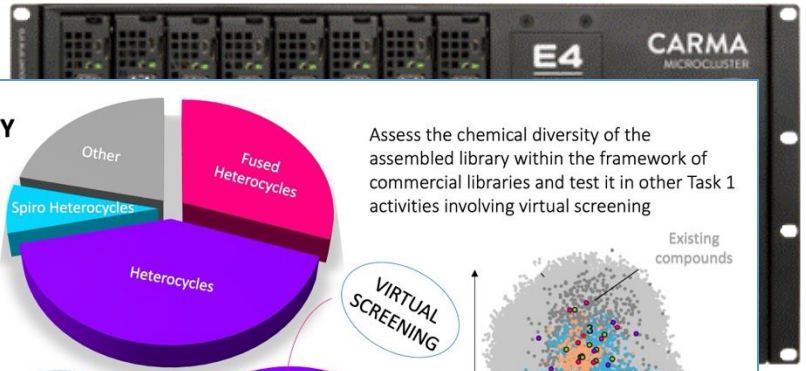
Compound Prioritization by Computational Means (10^2)

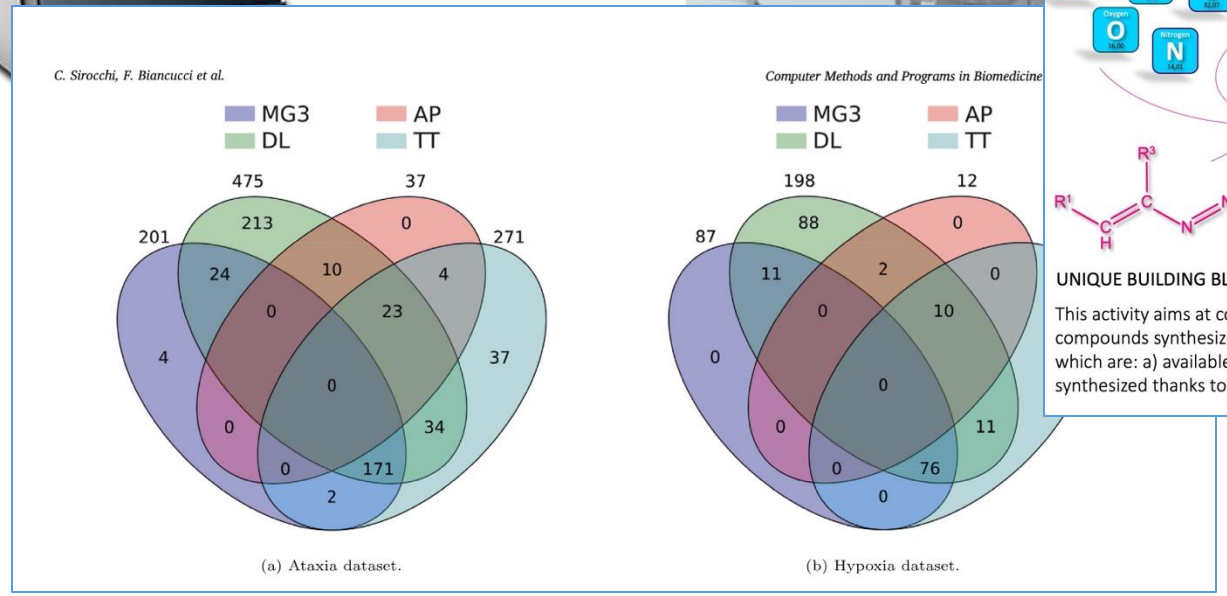
- Ultra Large Commercial Libraries (10^9)
- DL-generated Compounds (10^7)
- Combinatorial SAR Explorations (10^4)

Synthesis

Biophysical Assays

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





(a) Ataxia dataset. (b) Hypoxia dataset.

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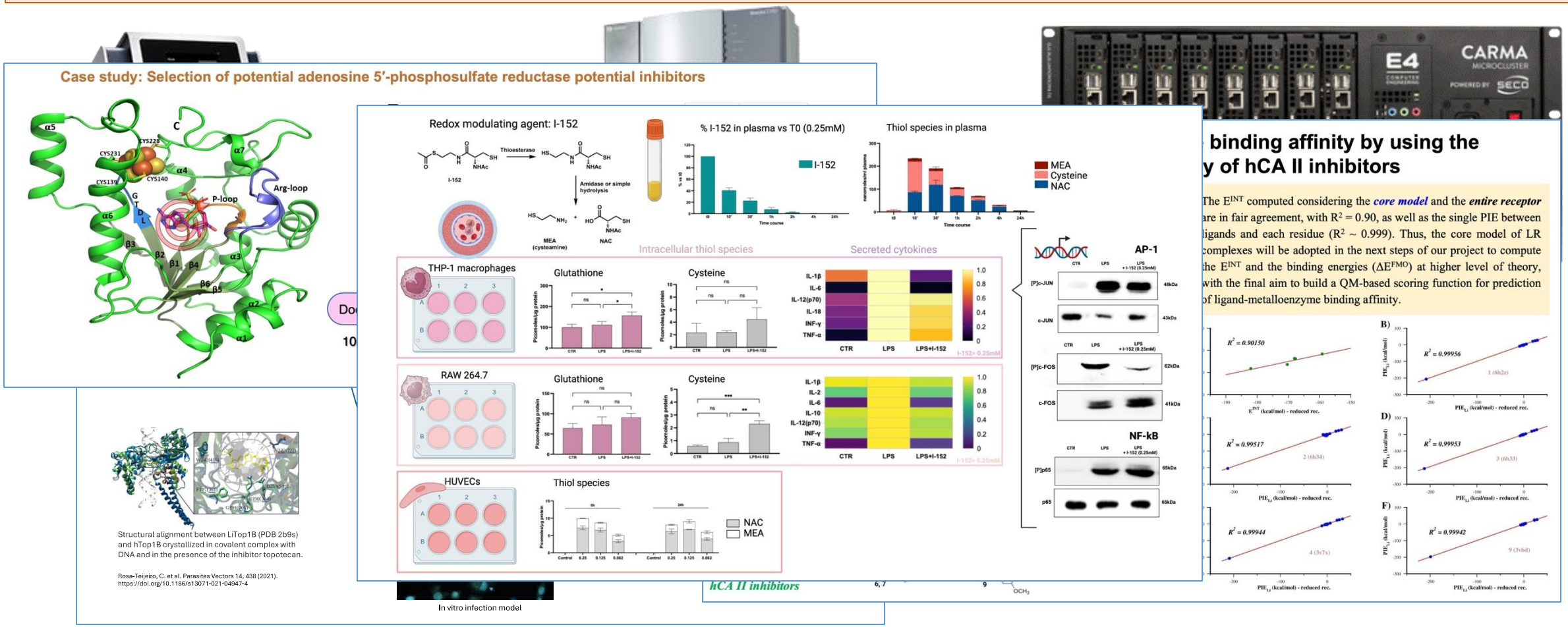
WP1.1: Computationally-driven, Integrated Infrastructure for Lead Identification and Optimisation



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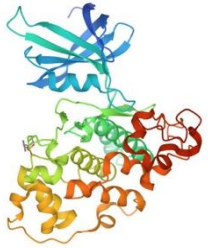
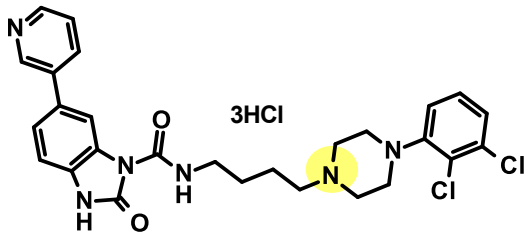
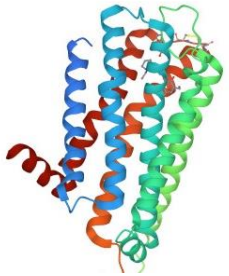
WP1.2: Development, validation and application of tools for rational polypharmacology







Target 2 **DTDL** **Target 1**

Manually curated dataset encompassing 158 DTDLs

```
from chembl_webresource_client.new_client import new_client
import json
import os
import pandas as pd

os.chdir('/common/users/vlembo/TESI/PYTHON_SCRIPTS/RETRIEVE_BY_ACTIVITY/TARGET_ACTIVITIES_JSON/')

target1_id = "CHEMBL1865"
target1_name = "HDAC6"
target2_id = "CHEMBL1827"
target2_name = "PDE-5A"
```

ChEMBL RDKit

Lembo and Bottegoni, **2024** J Med Chem, *just accepted*

- Targets are paired based on pre-existing independent validation at a given pathology. The promise of network pharmacology (Hopkins, Nat Chem Biol **2008**), that the druggable genome would have been greatly expanded by new target combinations, has yet to be fulfilled.
- DTDLs largely exploit known regions of the chemical space that the members of the target pair have in common
- Representative DTDLs never significantly depart from single target protype compounds

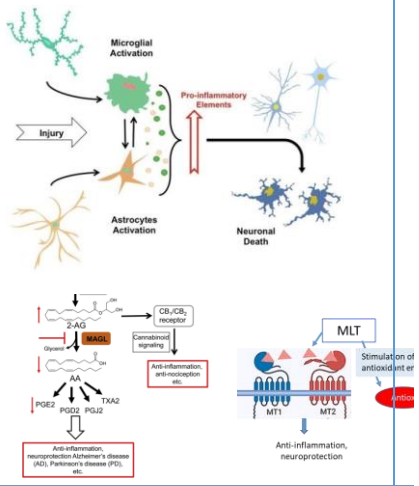
We have barely scratched the surface of what D/MTDLs have to offer to therapy and ultimately human health

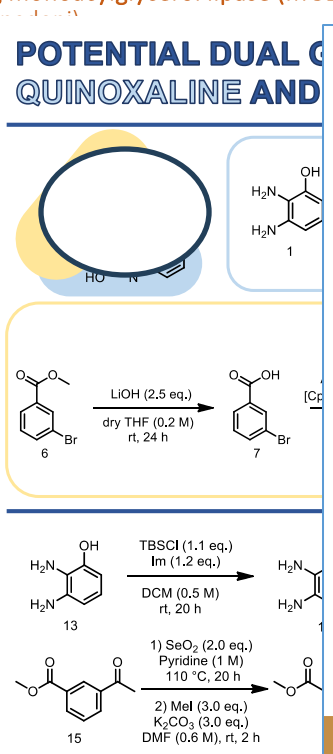
WP1.2: Development, validation and application of tools for rational polypharmacology

VITALITY – Spoke 8 – WP1 – Task2

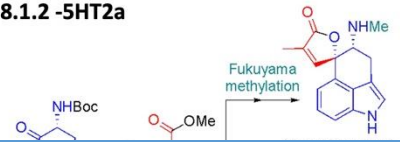
Title: Discovery of dual agents targeting monoacylglycerol lipase (MGL) and to promote neuroprotection (Gilberto S...)

Potential neuroprotection induced by MGL inhibithors and melatonin





Task **8.1.2 -5HT2a**



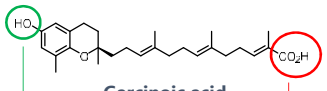
European Journal of Organic Chemistry **2022** (17), e202200315

- synthesis of all enantiopure rugulovasines

Garcinoic acid: A natual lead compound advanced to chemical optimization

Garcinia kola

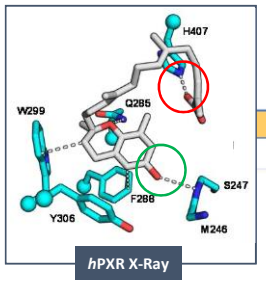
Extraction



Garcinoic acid

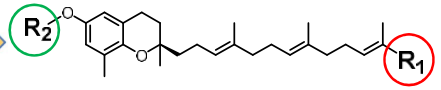
Key hot-spots

PXR activity
Off-target (selectivity): PPARa, 5-LO
Metabolism



*h*PXR X-Ray

Lead optimization



16 Novel derivatives

DSS - Colitis

- Synthesis of novel garcinoic acid analogs (n= 16) (*Gioiello - UniPg*) ✅
- *In vitro* screening of the novel derivatives as PXR ligands (*Tes Pharma*) ✅
- Computational analysis (structure-activity relationship) (*Bottegoni - UniUrb*)
- *In silico* e biophysical PK/PD profiling of best PXR ligands (*Goracci/Macchiarulo - UniPg*)
- *In vivo* validation of best PXR ligands (*Galli/Zelante - UniPg*)
- Scale-up optimization of preclinical candidates (*Gioiello/Vaccaro - UniPg*)

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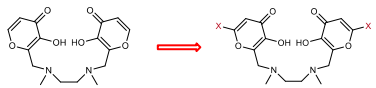
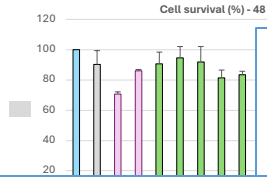
WP1.3: Test bed for preclinical compounds against innovative targets for metastatic cancer

Polyamino-bis-Maltol Compounds



Malten analyzed at both biological and molecular levels for its antiproliferative activity against cancer cells showed biological activities associated with the modulation of genes having k progression and apoptosis. Recently a new set of compounds) was synthesized by functionalizing the C6 units with different groups.

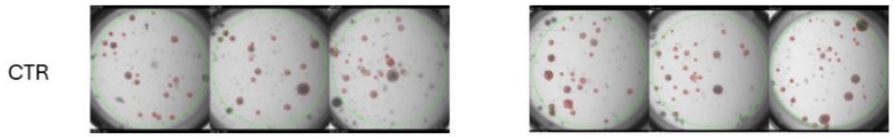
[British Journal of Cancer (2012) 103(2), 2



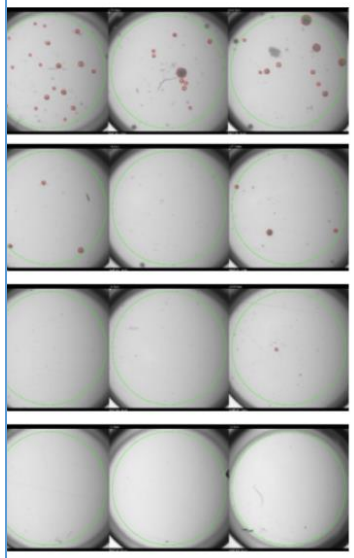
The new set of molecules in parallel with

Lead compound optimization o

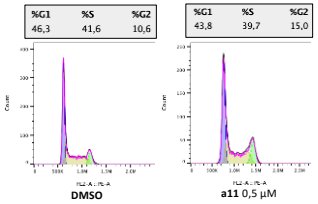
- Modification of three side chains
- Docking analysis



#36 – UR1286

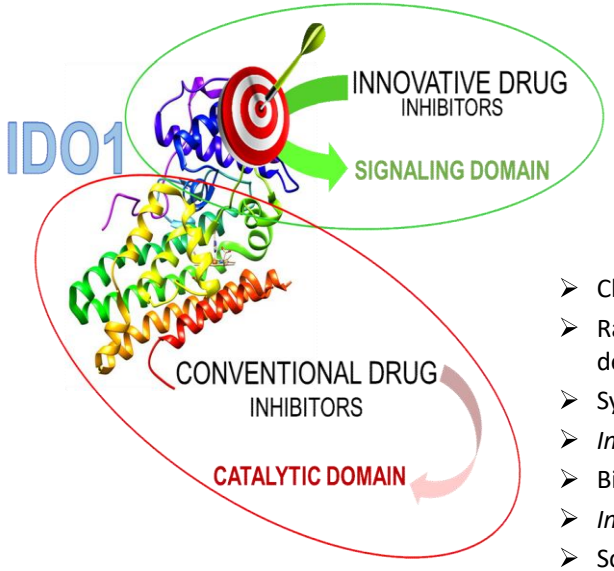


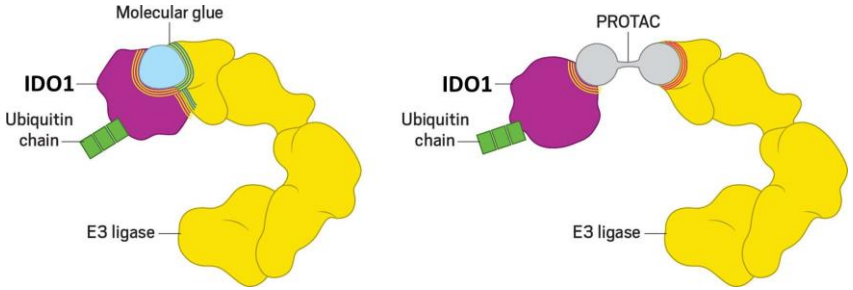
cell cycle 24 h



The biological activity of **a11** was deepened using the slight accumulation of cells in the G2/M phase of t percentage of hypodiploid cells starting from the co activity on U937 cells through the activation of the confirm this observation.

Design and development of IDO1 protein degraders (PI: Ciriana Orabona)





- Characterization of IDO1-mediated signaling in tumor cells (*Orabona – UniPg*) ✅
- Rational design of small molecules stabilizing IDO1 conformations suitable for the protein degradation (*DSF - UniPg*)
- Synthesis of IDO1 degraders (*UniPg + UniUrb?*)
- *In vitro* screening of IDO1 degraders (*Orabona – UniPg*)
- Biophysical PK/PD profiling of best IDO1 degraders (*Macchiarulo - UniPg*)
- *In vivo* validation of the best IDO1 degraders (*Orabona - UniPg*)
- Scale-up optimization of preclinical candidates (*UniPg + UniUrb?*)

Dose-dependent uptake of borono tryptophan derivatives. Both have been proposed to express LAT1

Grazie per l'attenzione