



PhD in INGEGNERIA DELL'INFORMAZIONE / INFORMATION TECHNOLOGY - 38th cycle

Research Area n. 1 - Computer Science and Engineering

PNRR_352 Research Field: COMPUTATIONAL GENOMICS FOR REPURPOSING VALPROIC
ACID AND SIMVASTATIN IN PANCREATIC CARCINOMA

Monthly net income of PhDscholarship (max 36 months)

€ 1400.0

In case of a change of the welfare rates during the three-year period, the amount could be modified.

Context of the research activity

**Motivation and objectives of the research
in this field**

The process of repurposing of medicinal products 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 indication(s) has demonstrated high utility to serve unmet patient needs in a broad variety of disease areas. Policy, funding and research attention in the area has been steadily growing since the early 2000s, with systematic computational approaches augmenting the serendipitous DR successes. 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. A large-scale analysis of drug development pipelines between 2012-2017 showed that almost 170 repurposed drugs entered development stages across a range of indications. Of these, some 72% were in Phase II clinical development. Of particular interest is that almost 70% of the Phase I and II trials for repurposed drugs were sponsored by academia, indicating the key role this sector has in promoting DR as a solution to unmet patient needs. However, DR is a complex endeavour requiring expertise from multiple disciplines, including Engineering and Computer Science, to align for success.

The research will address some of the systemic



	<p>inefficiencies that hamper the pace and effectiveness of DR from the computational biology point of view. 1) The heterogeneous availability and quality of computational tools, as well as scattered and non-standardised datasets and other resources, to support effective rational DR utilising machine learning (ML) and artificial intelligence (AI) methods. 2) The siloeing of the in silico area, often with little understanding of the reliability of the tools available to the DR community, while later preclinical projects are often advanced with little evidence of mechanism of action.</p> <p>The creation of a platform of tools for in silico DR will be exploited for a specific clinical case. In particular, this research will assess the synergistic antitumor interaction between valproic acid and simvastatin, and its potentiation of gemcitabine/nab-paclitaxel doublet chemotherapy in patients with metastatic pancreatic carcinoma (mPDAC). Preliminary results will be confirmed by determining minimum effective dose for synergism and toxicity by in silico and in vitro drug screening. Confirmation of in vivo efficacy will be done in patient-derived xenografts and immunocompetent models. Preclinical mechanistic insight studies include in silico drug interaction prediction and multi-omics evaluation in vitro and in vivo models. A patient-centric randomized multinational PoC phase-2 study will test prolongation of progression-free survival by experimental combination vs. standard chemotherapy alone as first-line treatment in mPDAC patients, and exploratory biomarkers on tumor tissue and blood samples will be studied.</p>
<p>Methods and techniques that will be developed and used to carry out the research</p>	<p>A first step in the activity will be to create a repository of AI open-source tools and open-access datasets for supporting user-driven in silico discovery applications. Starting with a state of the art analysis, the identified resources will be evaluated, ranked and classified according to specifications such as clinical/preclinical applications, disease-specific/agnostic, pre/post-screening, open source/proprietary data, technical robustness against attack and security, and general safety, accuracy, reliability and reproducibility. Tools promoting the FAIR principles (Findability, Accessibility,</p>



Interoperability, and Reusability) will be promoted. A secondary stage gap analysis will form the subsequent addition of computational tools. Instead of implementing novel AI algorithms, the focus will be on modification or extensions of existing open-source methods for in silico discovery. Tools supporting FAIR will be promoted, such as supporting standardised data formats; being available as software containers for easy deployment on high-performance computing (HPC) systems and exposing application programming interfaces (APIs) to facilitate integration in pipelines. AI models will be properly validated and documented according to emerging standards. These tools will then be used to contribute to the specific study of the repurposing of valproic acid combined with simvastatin to potentiate first line gemcitabine/nab-paclitaxel chemotherapy regimen in metastatic pancreatic cancer preclinical models and patients. The research will study the possible interaction between valproic acid and simvastatin, as well as their possible interactions with the standard chemotherapy agents by performing a pathway analysis of transcriptomic perturbations afforded by the single drugs. The pathways with anti-oncogenic potential that are similarly affected or the pro-oncogenic that are regulated in opposite ways are possibly responsible for the synergistic effects. Useful data to be used for this purpose are provided by the LINCS portal (<http://lincsportal.ccs.miami.edu/>), where these treatments were performed in several cell lines, including the pancreatic cancer cell line YAPC. These results will be complemented with the transcriptomics analysis of the experimental combination treatments performed in cell lines and in patient-derived xenografts. In addition, the research will use the genomic and basal transcriptomic profile together with the sensitivity to the drugs provided by the DepMap portal (<https://depmap.org/portal/>) for a broad collection of cell lines, to find determinants of sensitivity. This will provide information on the subsequent study of the possible variability of the therapeutic response in the clinical trial. Finally, the stratification parameters discovered in the cell lines will be tested in the basal tumor samples collected from the patients.



Educational objectives	<p>We are aimed at developing a highly qualified profile oriented to fulfill innovation needs in enterprises according to the PNRR guidelines, building specific competence, autonomy, research methodology and skills, in an interdisciplinary environment.</p> <p>Laboratory activity is an addition relevant aspect to complete the training and finalize the research. The strong connection with Istituto di Ricerche Farmacologiche Mario Negri makes one of the strength of our PhD research proposal.</p>
Job opportunities	<p>Career development of the trained innovation-oriented highly qualified profile is open both in research, academic and private institutions, and in production, both in Italy and abroad. Start-ups from research results are also highly possible. Employment in innovative computational genomics and pharmacology areas provides several opportunities.</p>
Composition of the research group	<p>0 Full Professors 2 Associated Professors 2 Assistant Professors 3 PhD Students</p>
Name of the research directors	Prof. Marco Masseroli / Maddalena Fratelli

Contacts	
<p>marco.masseroli@polimi.it 02-2399 3553 http://www.bioinformatics.deib.polimi.it/masseroli/masseroli.htm</p>	

Additional support - Financial aid per PhD student per year (gross amount)	
Housing - Foreign Students	--
Housing - Out-of-town residents (more than 80Km out of Milano)	--

Scholarship Increase for a period abroad	
Amount monthly	700.0 €
By number of months	6

National Operational Program for Research and Innovation	
Company where the candidate will attend the stage (name and brief description)	Istituto di Ricerche Farmacologiche Mario Negri IRCCS, settore attività: ricerca farmacologica, https://www.marionegri.it/
By number of months at the company	12



Institution or company where the candidate will spend the period abroad (name and brief description)	University of Helsinki (FIMM-UH), FI, Tero Aittokallio, settore attività: computational systems medicine, https://www2.helsinki.fi/en/researchgroups/computational-systems-medicine , https://researchportal.helsinki.fi/
By number of months abroad	6

Additional information: educational activity, teaching assistantship, computer availability, desk availability, any other information

Attinenza alla tematiche, alle missioni/componenti prescelte del bando PNRR v. D.M. 352, art.6

The proposed research is fully relevant to the education, innovation and research, and health missions of the PNRR. In particular, it will allow the training of a highly qualified figure, with advanced computational skills in data science and biomedicine. Furthermore, the results that will be achieved with the proposed research will provide important repercussions in the health sector, making it possible to make the health system and the access to pharmacological treatments more efficient, according to the PNRR guidelines.

Impresa, presso cui si svolgerà l'attività esterna

Istituto di Ricerche Farmacologiche Mario Negri IRCCS

mesi previsti: 18

descrizione sintetica attività: The activity will be performed as part of a large European project (REMEDI4ALL) that aims to build a European sustainable innovation platform to facilitate the repositioning of drugs. Specifically, the activity will concern the computational and machine learning development linked to one of the "demonstrator" projects of the platform, which will study the repurposing of valproic acid (a drug initially developed for the treatment of epilepsy and some disorders of mood) and simvastatin (a cholesterol-lowering drug used for the prevention of cardiovascular disease) for the treatment of metastatic cancer of the pancreas. We will test the hypothesis that the addition of these two drugs can enhance the effect of the first-line chemotherapy regimen with gemcitabine/nab-paclitaxel in preclinical models (cultured cells and "patient derived xenografts") and in patients with carcinoma metastatic pancreatic (mPDAC).

Ente, università, azienda, centro di ricerca presso cui si svolgerà il periodo di studio e ricerca all'estero.

University of Helsinki (FIMM-UH), FI Tero Aittokallio

mesi previsti: 6

descrizione sintetica attività: Also the activity abroad will be performed within the European project REMEDI4ALL, in collaboration with the group of Computational Systems Medicine leader of the work package of the REMEDI4ALL project dedicated to the creation of a collection of advanced tools for "drug repurposing" led by artificial intelligence (AI). The goal is to make available an archive of AI open-source tools and open-access datasets to support user-driven in silico applications.

All information regarding educational activities, personal funding, regulations and



**obligations of Ph.D. candidates are available on the
web site <https://dottoratoit.deib.polimi.it/>**