SETTORE SCIENTIFICO-DISCIPLINARE: AGR/16 MICROBIOLOGIA AGRARIA

ASSEGNO DI RICERCA DI DURATA: annuale, rinnovabile.

TUTORE: Prof. Daniele Generali

ASSEGNISTA: Dr.ssa Maria Valeria De Bonis

TITLE OF THE RESEARCH PROJECT: The "omics" technologies for the study of food-drug interactions in oncology

AREA OF THE RESEARCH PROJECT: Among the factors contributing to the success of a single therapy, in addition to the clinical features, the interactions of a specific drug with other drugs, supplements, herbal products and foods are of not negligible importance in oncology. Foods and food supplements, therefore, can affect the absorption, metabolism, bioavailability and excretion of the drug, could it ineffective, enhance its toxicity or a particular side effects or create even serious undesirable effects. It therefore becomes necessary to determine:

- the *in silico* study of drug interactions between medicines, herbal supplements and foods
- the nutrigenomic and metabolomics basis of individual products (drugs, foods, etc.)
- the interactions between oral and/or intestinal microbiome and drugs, herbal supplements and foods

The research work will tentatively stem into 3 sub-projects.

Sub-Project 1

Title: Food and Drug Interactions in Oncology

Background: the simultaneous intake of food and drugs can have a strong impact on drug release, absorption, distribution, metabolism and/or elimination and consequently, on the efficacy and safety of pharmacotherapy. As such, food-drug interactions (FDIs) arise when nutritional/functional dietary consumption regulates biochemical mechanisms involved in drug metabolism, and are one of the main challenges in oral drug administration. Every intake of food or drink changes the physiological conditions in the human gastrointestinal tract; furthermore, the growing use of food supplements and functional food requires urgent attention in oral pharmacotherapy. Therefore, a precise understanding of how different foods and drinks affect the pharmacodynamics as well as formulation performance is important in order to be able to predict and avoid such interactions.

To advance the pharmaceutical arena, a better knowledge of the food induced changes affecting drug activity is required to understand whether the design of a formulation which overcomes the overall food effect could represent a successful strategy for future drug development in oncology.

Hypotesis: during oncotherapy, the administration of food or drink affects

1. drug release (volume and composition of luminal fluids transit times, motility),
2. drug absorption (uptake and efflux transporters),
3. drug distribution (lymphatic transport, lipoprotein and plasma protein binding),
4. drug metabolism and elimination (metabolising enzymes and transporters).
5. Moreover, the microbiome can be another integral factor for oral drug bioavailability and pharmacokinetics.

Aim: a tentative, modular *in silico* mechanistic study will be initiated incorporating the physical and functional lag to at least one of multiple compartments involved, as listed above, for a meaningful patient cohort.

Experimental design: following a literature scrutiny which will highlight the boundaries and realistic potential of the research at stake, a model encompassing one or more of the above compartments will be tried based on Ordinary Differential Equations, by using the COMSOL Multiphysics and/or MATLAB platforms.

Expected results: based on the availability of *in vitro*/*in silico* data pertinent to the research at stake, and consistently with the available literature, a working mathematical platform leading to analytical correlations will be initiated to implement a generalistic study on FDIs in oncology.

Sub-Project 2

Title: Metabolomics as a Tool for Oncotherapy Optimization

Background: nutrition and food sciences are bound to collaborate to develop and implement metabolic assessment technologies and to assemble annotated databases of metabolite profiles in humans, thus building the knowledge needed to link metabolism to diet and health. Biochemical and physiological research must be guided to define the mechanisms by which diet interacts with metabolism in different individuals, as people are metabolically, physiologically, and genetically different and therefore have different responses to food compounds.

Integrating metabolism with the genetic and dietary variables that affect health is the role of nutrition science. Integrating personal nutritional value with food's other key values of safety, quality, comfort, delight, convenience and affordability is the role of food science. These two fields need to address a common problem, metabolic health, with coordinated solutions in the field of personalised oncotherapy.

In this framework, metabolomics (i.e. the measurement of small molecules in biofluids, tissues, and cells using spectroscopic analytical platforms) has been included in the National Institutes of Health roadmap as a core technology in the overall initiative to assist in delivering the therapeutic solutions. Metabolomics is not only concerned with the identification and quantification of metabolites, but also with relating metabolite data to biology and metabolism. As a result, metabolomics requires that whatever chemical information it generates must be linked to both biochemical causes and physiological consequences. This means that metabolomics must combine two very different fields of informatics: bioinformatics and cheminformatics. As such, metabolomics' techniques require electronically accessible and searchable databases, as well as software to handle data to predict or model properties, pathways, relationships and processes.

Hypotesis: one of the most recent technologies can be enforced to serve in the analysis of the footprints of nutrition and food sciences leading to metabolomics: stemming from the more general principles of Artificial Intelligence, Machine-Learning (ML) techniques offer an advantage in the analysis of large and complex clinical data sets, allowing for discovering of latent connections between data items and speculate on appropriate mapping functions, specifically useful in oncotherapy.

Aim: once a sample metabolite for a meaningful patient cohort is chosen, a ML framework, consisting of various techniques to allow algorithms to work better based on experience, is explored to detect patterns in retrospective clinical data sources, training the model in order to map flexible dependence functions of tumor malignancy and pharmacodynamics efficiency with personalised diet during oncotherapy.

Experimental design: Handling, processing, analysis and integration of the available data will be performed by using the Anaconda framework allowing for specific Python codes.

Expected results: With reference to the chosen metabolite, a flexible and robust pipeline is proposed for metabolomic data analysis. The ultimate goal of personalised nutrition is to enable each individual to be guided by predictive knowledge of their personal health to diets that prevent disease and maximize health potential.

Sub-Project 3

Title: Drug-Microbioma Interactions during Oncotherapy in Breast Cancer

Background: microbioma is considered a key 'metabolic organ'. Its metabolic activities play essential roles complementary to the host metabolic functions. The interplays between microbes and commonly used non-antibiotic drugs have garnered substantial attention in recent years. During oncotherapy, drugs can reshape the microorganism communities and, viceversa, the diverse microbes can affect pharmacodynamics by altering the bioavailability and bioactivity of drugs. The metabolism of drugs by microbial action or by microbioma's host co-metabolism can transform the drugs into various secondary metabolites, that may contribute to both the therapeutic benefits and the side effects. In view of the significant effect of the microbioma on pharmacodynamics and related clinical outcomes, it is important to explore their interactions during oncological treatments.

Hypotesis:. microbioma plays a role, as an example, in estrogen metabolism, strongly correlated to HR+/HER2-negative breast cancer development. Microbioma may also predict treatment response, chemotherapy resistance and development of side effects. Understanding how the microbes interact with drugs and influence the therapeutic efficacy will help discover novel directions in regulating the gut microbes to improve the therapeutic effects and clinical outcomes of a drug in precision oncotherapy.

Aim: A tentative, modular *in silico* mechanistic study will be initiated incorporating the above interactions and leading to joint pharmacodynamics and functional assessment.

Experimental design: following a literature scrutiny which will highlight the boundaries and realistic potential of the research at stake, a model describing the interaction of at least one oncological drug and the microbioma of a meaningful number of patients will be tried based on Ordinary Differential Equations, by using the COMSOL Multiphysics and/or MATLAB platforms.

Expected results: based on the availability of *in vitro*/*in silico* data pertinent to the research at stake, and consistently with the available literature, a working mathematical platform leading to analytical correlations will be initiated to implement a generalistic study on microbioma association impact on therapy, particularly drug efficacy and toxicity. In this way, a better understanding of these interactions in cancer will lead to potential therapy optimization.