The **Ph.D program in Pharmaceutical Sciences** is part of the efforts that the Department of Pharmaceutical Sciences constantly pursues and devotes to promote Ph.D. students. It offers rigorous grounding in a broad range of disciplines related to drug discovery and nutraceuticals, that are critical to **shaping successful next-generation scientists**. Four *curricula* of choice are currently structured in the program: (i) Medicinal Chemistry and Pharmacoinformatics, (ii) Organic and Bioorganic Chemistry, (iii) Pharmaceutical Technology, and (iv) Nutraceuticals. Talented Italian and foreign students are trained in a highly collaborative atmosphere using multidisciplinary and interdisciplinary approaches to develop expertise and gain skills that will enable them to excel in later career paths of choice, including academic, industrial and regulatory sectors. Features of the Ph.D program in Pharmaceutical Sciences include a close collaboration with international Universities and pharmaceutical companies, and a special emphasis on enhancing communication and leadership skills. Doctoral students actively participate in research stages abroad and deliver seminars. They also benefit from regular workshops and thematic courses, which facilitate exchange of information and building of knowledge. Collectively, these activities provide them with the opportunity to address their research topic from different perspectives. Several research projects of the Ph.D. program in Pharmaceutical Sciences are currently supported by European, National, and private funding organizations. **Applications to the following open positions are welcome for the Academic Year 2018/2019!**

Research Topic 1: Design and Synthesis of Type II NADH dehydrogenase inhibitors as innovative anti-TB agents.

Abstract: Tuberculosis (TB) caused by Mycobacterium tuberculosis (Mtb) is a major global health problem with significant morbidity each year. With the emergence of multidrug resistant (MDR) and extensively drug resistance (XDR) TB, the need for new treatments has never been greater.

The identification of mechanistically distinct anti-Mtb drugs could be the best way to circumvent resistance. In this context, type 2 NADH dehydrogenase (NDH-2), which is involved in the production of respiratory ATP, and is absent in the human counterpart, is emerging as an innovative target. The present project aims at identifying small molecules able to inhibit NDH-2 and active against MDR-TB and XDR–TB. The collaboration with Scott Franzblau (Director of Institute for Tuberculosis Research, University of Illinois, Chicago), Gregory Cook (Department of Microbiology and Immunology, University of Otago, New Zealand), and Michal Kolar (Laboratory of Genomics and Bioinformatics, Prague, Czech Republic) will grant the feasibility of the project.

Curriculum: Medicinal Chemistry and Pharmacoinformatics.

Supervisor: Prof. Oriana Tabarrini (oriana.tabarrini@unipg.it)

Research Topic 2: Discovery and development of chemical probes for understudied biological targets.

Abstract: The proposed research activity is focused on the discovery and development of new chemical entities to be used as chemical probes for understudied biological targets. In particular, the project will be directed towards the design, synthesis and characterization of lead-like compounds libraries useful to define the structural determinants and molecular basis of activation of steroid-responsive nuclear receptors, as well as to identify leads compounds for in vitro and in vivo appraisals. The doctorate student will learn on how to design lead-like libraries, to set-up novel chemical methods and systems for library preparation, to assess structure-property/structure-activity relationship insights, to optimize lead synthesis for large scale preparations. The student will have the opportunity to interact with supervisor experimental coworkers and industrial collaborators in a multidisciplinary environment. The suitable candidate should be interested in acquiring a deep knowledge of medicinal chemistry, organic synthesis with an emphasis on enabling technologies.

Curriculum: Medicinal Chemistry and Pharmacoinformatics.

Supervisor: Prof. Antimo Gioiello (antimo.gioiello@unipg.it)

Research Topic 3: Discovery and development of allosteric modulators of IDO.

Abstract: Indoleamine 2,3-dioxygenase (IDO) catalyzes the first and rate-limiting step of the Kynurenine pathway along the major route of Tryptophan catabolism. The scientific interest in the enzyme is high due to its involvement in mechanisms of immune tolerance and tumor immuno-editing process. Inhibitors of IDO are sought as promising small molecule immunotherapies to enhance the efficacy of current chemotherapeutic agents. The enzyme, however, features complex molecular functions, including catalytic and non-catalytic signaling functions, that make difficult the development of drug candidates with optimal pharmacological efficacy. Very recent studies have unveiled the presence of allosteric binding sites in the enzyme that may be instrumental to develop novel approaches to design small molecule modulators of IDO-mediated catalytic and non-catalytic signaling functions. The aim of the present project is to study the interaction between some in-house lead compounds and allosteric pockets in IDO, and then use the generated knowledge to design and synthetize novel modulators of catalytic and non-catalytic signaling functions. During the project, the candidate will learn computational approaches and biophysical methods for the study of ligand/target interaction, as well as develop skills in synthetic medicinal chemistry. The student will have the opportunity to work in a high multidisciplinary environment and use state-of-the art equipment such as Microscale Thermophoresis and Sirius-T3 instruments.

Curriculum: Medicinal Chemistry and Pharmacoinformatics.

Supervisors: Prof. Emidio Camaioni (emidio.camaioni@unipg.it), Prof. Antonio Macchiarulo (antonio.macchiarulo@unipg.it)

Research Topic 4 (Application Reserved to Employees of Aboca SpA): Development of metabolomic methods to analyze selected classes of plant metabolites using broadband DIA Mass Spectrometry.

Abstract: It has been estimated that all plant species produces 90,000 - 200,000 different compounds, deriving from the transformation of organic raw materials into primary and secondary metabolites. The comprehensive qualitative and quantitative analysis of all these metabolites is a very ambitious goal and in the past few years several efforts have been devoted to define, in a systematic manner, the plants metabolome. If reference standards are available on the market, plants metabolites can be analyzed by comparison with the corresponding compounds. In case this is not possible, the development of LC-HRMS methods using broadband data independent acquisition (DIA) mass spectrometry [1] can be helpful to increase identification and quantification of plant metabolites. Using different broadband DIA algorithms (common to the modern high resolution mass spectrometers) the fragment ion of UHPLC eluted compounds is correlated to its precursor. Combining the MS/MS information with retention time, high resolution accurate mass and product/precursor ion intensity ratios, it is possible the identification and annotation of various compound increasing the knowledge level of the different natural complex matrices.

The aim of this project is to draw the workflow and criteria for target identification, annotation and quantification of various plant metabolites such as phenols, tannins, terpenes, polysaccharides. Data dependent acquisition (DDA) and/or broadband DIA will be used to characterize molecular complexes of different natural complex matrices (form raw vegetal extracts to formulated products). Data obtained will be also studied by multivariate statistical analysis, to achieve untargeted evaluation of elected classes of metabolites.

Curriculum: Medicinal Chemistry and Pharmacoinformatics.

Supervisors: Dr. Luisa Mattoli (LMattoli@aboca.it), Prof. Antonio Macchiarulo (antonio.macchiarulo@unipg.it)

Research Topic 5: C-H functionalization strategies for the synthesis of prenylated arenes and heteroarenes.
Abstract: The isoprene unit is a key feature in the structure of a wide array of bioactive molecules such as prenylated indole alkaloids, flavonoids, terpenoids. On the other hand the study and use of such molecules could be hampered by scarce availability from plants, for this reason the development of new efficient synthetic routes for their production is mandatory. The aim of the present project will be the application of C-H functionalization reactions for carbon-carbon bond forming in order to install the prenyl moiety on to the desired molecular scaffold. This methodology is considered an atom-economical alternative to classic cross-coupling reaction avoiding expensive and not sustainable pre-functionalization of reagents. Furthermore employment of benign solvents preferably derived from biomass and application of protocols in absence of any kind of solvent (solvent-free) will be evaluated.
Curriculum: Organic and Bioorganic Chemistry
Supervisors: Prof. Daniela Lanari (daniela.lanari@unipg.it), Prof. Massimo Curini (massimo.curini@unipg.it)

Research Topic 6: Unconventional treatment and control of problematic lung infectious diseases.
Abstract: The dramatic and troublesome worldwide scenario of bacterial resistance and the powerful raise of incurable infections may sign the end of the traditional antibiotic use as we know it. It is by now clear that antibiotics cannot be the only answer to the quest for effective control of pathologies like tuberculosis or aggressive nosocomial infections. A number of totally resistant bacterial strains are emerging as a result of decades of drug misuse and misconduct of antibiotic therapies. Therefore, the state of the art of antibiotic therapy demands a shift of current treatment strategies and rethinking of the way we see the fight against pathogens. This project will aim at investigating new ways of treatment that can give support to current antibiotic regimens and in some cases replace them. Strategies will be developed based on tolerance and control of infection rather than sole bacterial killing. This goal will be pursued by employing human microbiota metabolites together with the development of adequate lung delivery strategies and repurposing approaches for current available drugs. In this regard, indole derivatives produced by human commensals, particularly in the gut, could contribute to host's protection against infection by enhancing host's defenses as well as suppressing and/or normalizing imbalanced pathogen populations. In addition to the identification of potential novel treatment approaches, the information obtained could be extremely useful to address and understand novel targetable mechanisms for a safer control of lung bacterial infections.
Curriculum: Pharmaceutical Technology
Supervisor: Prof. Stefano Giovagnoli (stefano.giovagnoli@unipg.it)

Research Topic 7: Industrial pharmaceutical processes and formulations for introducing innovations to improve quality, efficiency and capacity in Good Manufacturing Practices.
Abstract: The research project will cover the following areas of pharmaceutical processes and formulations: (a) real time release test development, pharmaceutical technology research (process and formulation) including RAMAN/NIR spectrophotometric use during pharmaceutical manufacturing for development and batch release purpose; (b) pharmaceutical legislation and regulations study, interpretation and research with the aim to analyze and/or propose data useful for introducing/enhancing innovations in pharmaceutical manufacturing; (c) process validation, as per EU GMP ANNEX 15 and related, including development and use of statistical tools for development and routine analysis of process performance; (d) pharmaceutical technology projects, with the aim to improve processes and formulations in order to increase quality and quality, efficiency and capacity; (e) development of suitable industrial processes and formulations. The above research activities will be carried out in collaboration with Menarini pharmaceutical company.
Curriculum: Pharmaceutical Technology
Supervisors: Dr. Michele Panzitta (mpanzitta@menarini.it), Prof. Maurizio Ricci (maurizio.ricci@unipg.it)

Research Topic 8 (Application Reserved to Employees of Aptuit): Factors affecting performance and stability of dry-powder inhalers (DPIs).

Abstract: Dry-powder inhalers (DPIs) are complex systems intended to consistently deliver a dose of drug substance with suitable aerodynamic characteristics to the lungs with local (topical) or systemic effect. The inhaled dry powders are primarily composed by a carrier and a micronized active pharmaceutical ingredient (API). These mixtures can be administered using different devices in single doses (capsules or blisters) or by multidose systems. The present PhD program will focus on the investigation of a number of variables that are known to have an impact on DPIs performance and stability including formulation, device, and manufacturing process. These will be assessed with the particular aim to achieve a better understanding of parameters affecting the behavior of powder blend formulations in capsule and related device. The study comprises the preparation of various DPI formulations based on a micronized API that will be characterized for chemical and physical properties and for aerodynamic performance. The following factors will be investigated: (a) Carrier (different grades of lactose and mannitol); (b) Single or dual excipient platform (carrier only vs addition of magnesium stearate); (c) Particle size distribution (PSD) of API and carrier; (d) Relative composition of powder mixture; (e) Type of capsule shell (gelatin vs HPMC); (f) Exposure of raw materials and formulations to different environmental conditions (temperature and relative humidity); (g) Powder blending procedure (high shear vs low shear, effect of screening, dilution and order of addition of components); (h) Capsule filling system ('pepper-pot' principle vs micro-dosator mechanism); (i) Device.

Curriculum: Pharmaceutical Technology

Supervisors: Dr. Cesare Di Palma (Cesare.DiPalma@aptuit.com), Prof. Maurizio Ricci (maurizio.ricci@unipg.it)

Research Topic 9: Study of plant secondary metabolite profile for food authentication and strategies for using food waste and by-products in the development of functional foods and nutraceuticals.

Abstract: The research deals with the development of innovative methods for the extraction and characterization of bioactive compounds from food and food processing wastes. The extraction of bioactive substances will be optimized to obtain high-efficiency and environment-friendly extraction methods. The chemical characterization of secondary metabolites will be performed by advanced chromatographic techniques hyphenated with highly selective detection systems. Qualitative and quantitative determination of secondary metabolite complex profiles offers the opportunity to identify new quality markers, which are of great relevance to reveal the origin or undeclared technological treatments of food products. The research will also address the enhancement of food processing wastes by identifying new strategies for their conversion in value-added products. Bioactive compounds isolated from food products represent valuable components of new functional foods and nutraceuticals.

Curriculum: Nutraceuticals

Supervisor: Prof. Lina Cossignani (lina.cossignani@unipg.it)

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