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Hellenic Foundation for Research & Innovation

Description of the funded research project

1st Call for H.F.R.I. Research Projects to Support Faculty Members & Researchers and Procure High-Value Research Equipment

Title of the research project: SMALLER crystals, FASTER experiments, BRIGHTER beams: Uprising methods for Drug Screening & Innovation.

Principal Investigator:

Irene Margiolaki, associate professor

Reader-friendly title:

CrystDRUG

Scientific Area:

Life Sciences (MEDICAL & HEALTH SCIENCES),
Molecular and Structural Biology and Biochemistry, Structural Biology

Institution and Country:

University of Patras, Department of Biology

Host Institution:

University of Patras, Department of Biology

Collaborating Institution(s):

1.European Synchrotron Radiation Facility (ESRF), Grenoble, France, 2.Universität Hamburg, Hamburg, Germany, 3.Architecture et Fonction des Macromolécules Biologiques (AFMB), Marseille, France, 4.Malvern PANalytical, X-ray diffraction instrumentation company, Almelo, Netherlands, 5. NanoMEGAS electron diffraction company, Brussels, Belgium, 6. TeraCrystal research, National Institute for Research and Technology, Romania, 7.CBL Pharaceutical company (Patras, Greece), 8. University of Limerick, Limerick, Ireland, 9.Paul Scherrer Institute, Swiss Light Source (SLS), Villigen, Switzerland, 10. Excelsus Structural Solutions, spin off company of Paul Scherrer Institute, PARK innovAARE, 5234, Villigen - Switzerland

Budget: 180.000€

Duration: 36 months

Project webpage(if applicable):
https://sites.google.com/view/margiolaki-biology-upat/funding

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Research Project Synopsis

CrystDRUG focuses on the structural characterization of nano/microcrystalline proteins and their complexes. Knowledge of the structure of biological macromolecules is a key element in the successful design of drugs. In this regard, the molecules studied in this program are either already components of pharmaceutical compounds for the treatment of diseases such as diabetes (insulin and its analogues) or are related to the development of drugs against viruses that are dangerous to public health. The structural characterization of proteins to date is carried out mainly using the single-crystal X-ray diffraction (SCXD) technique. Although highly efficient, the aforementioned technique has several limitations concerning the development of large crystals and the identification of a large number of polymorphs (crystalline and molecular configurations), while it is often not feasible to observe and record dynamic phenomena (time resolved studies). The research activity of the Principal Investigator (PI) and the research team of Biochemistry, Crystallography and Structural Biology at the Department of Biology of the University of Patras, has shown that protein structures can be extracted from nano/microcrystals via X-ray Powder Diffraction (XRPD) measurements. This approach allows for the study of low quality crystals, the immediate identification of polymorphs but also the observation of dynamic phenomena during their evolution. In addition to the XRPD method, the research activity is carried out in combination with methods such as electron diffraction (Electron Diffraction) and crystallography using X-ray Free Electron Lasers. Moreover, examination of “in solution” samples will be performed using Small Angle X-ray Scattering (SAXS). The synergy of techniques, the performance of which will be evaluated in various biological systems, is expected to allow more accurate extraction of information related to the structure and dynamic interaction of between molecules (eg proteins, ligands, etc.), thus leading to important observations, necessary for the design and development of new pharmaceutical compounds.

Project originality

The ground-breaking nature of CrystDRUG project is related to both the experimental protocols as well as the data collection and analysis strategies being developed, which will be made available to the scientific community at the end of the program, as well as to the molecules themselves: a) Pharmaceuticals for the treatment of diabetes: Insulin-binding complexes along with insulin analogues, in order to optimize the action of the drugs. (b) Virus proteins-targets for the design and production of antiviral drugs. The results of the program are expected to strengthen areas of pharmaceutical research such as the identification of new compounds (drug design) but also the optimization of existing ones to enhance their action (drug delivery). Enhancement of the second part (drug delivery) can be achieved in various ways:

- Improving the Absorption, Distribution, Metabolism & Excretion (ADME) characteristics of the drug, creating and detecting new crystalline polymorphs.
- Production of preparations in different forms (eg solutions of amorphous molecules or microcrystalline suspensions) and characterization of their action.

Along this axis, we will screen a large number of microcrystalline samples and unveil their structural characteristics upon variation of their physicochemical environment, examining the effect of pH, humidity, temperature and Oxidative Stress (OS) mimicking *in vivo* conditions.

Expected results & Research Project Impact

Please describe in short (max. 300 words) the expected results (TRL included, if available) and the scientific, social and/or artistic impact of your research project.

Within CrystDRUG program, the expression, isolation, crystallization and structural characterization of proteins and complexes of proteins-organic molecules are expected to be achieved, through a combination of biophysical methodologies. For the optimal exploitation of biophysical methodologies, new approaches for data collection and analysis are already being developed for some of them, with the aim of extracting structural information with maximum accuracy. Also, the novel protein-protein or protein-ligand complexes will be evaluated for their stability upon varying environmental conditions such as temperature, relative humidity and pH. The exported data in their entirety is expected to form the basis for the improvement of existing and the design of new pharmaceuticals.

The application of the proposed methodologies to selected protein targets related to diabetes as well as emerging viruses which can cause illnesses of epidemic magnitudes, is expected to actively assist in the identification of new bioactive molecules as potential candidates for the development of pharmaceutical preparations and consequently having a direct medical application in society. To this end, CrystDrug focuses on the creation of a knowledge and expertise platform for advancing drug innovation through ground-breaking research in biophysical methods, crucial for accelerating the “drug search” procedure, expecting to link academia with pharmaceutical industry and societal health care organizations. In addition, this grant will allow for the education and interaction of imaginative scientists with new ideas.

The importance of this funding

After a decade of fruitful research career abroad, I consciously decided to return to my homeland in order to contribute wholeheartedly to the research performed at the Greek University. This return coincided with the years of the deepest economic recession in our country, which led to a steady reduction of resources available for Research, making our daily lives unimaginably difficult. The establishment of EL.ID.EK. was the first significant and well-coordinated initiative to strengthen basic research and stop “brain-drain” phenomena that has plagued our educational institutions for the last decade. The financing of my research project by EL.ID.EK. was the most essential example of support from the Hellenic state, allowing me to considerably accelerate research activities which were often hindered due to lack of resources and at the same time to recruit my research team with talented young researchers.

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