SECRETARÍA NACIONAL DE EDUCACIÓN SUPERIOR, CIENCIA TECNOLOGÍA E INNOVACIÓN

PROYECTO PROMETEO

RESEARCH PROPOSAL FORM

Researcher's name	Gerasimos	Researcher's last name	Rassias
Area of research	Synthetic Organic Chemistry		
Title of PhD.	Chemistry	University that awarded the Ph.D.	Loughborough University UK
Host institution (MAIN)	Technical University at Machala	Name of the counterpart in the host institution	Wunster Favian Maza Valle
Higher Education Institution		Name of the counterpart in the host institution	
Name of research with which the research contributes	Investigación de moléculas a partir de plantas nativas de la provincial de el Oro y su aplicación contra el virus del dengue		
Objective of the research	The development of drug discovery capability at Technical University at Machala		
Starting date of activities	1 PERIOD 09/08/13 2 PERIOD 01/09/2014	End of activities	1 PERIOD 9-Oct-2013 2 PERIOD 15/10/2014
Total months of linkage	4 Months, 10 days		

Researcher Profile
I have received my education in the UK and USA. I have served as lieutenant in the Greek Army for two years. I worked for 10 years at GlaxoSmithKline's process chemistry department where I was involved with the development of drugs for various diseases. In several cases I was the lead chemist including the development of trametinib, a medicine for metastatic melanoma recently approved by the FDA. I have a significant record of publications, presentations at international conferences and awards for my research. Currently I teach organic chemistry and drug design and development at the University of Patras in Greece.

- In a concise way and no more than two thousand (2,000) words, please specify the following elements of your research proposal:

1. **Research Question and their delimiting spatial, temporal**

The problem: According to the World Health Organization (WHO), dengue is now a leading cause of

hospitalization and death among children in endemic regions, such as Asia and South America, and is now considered a major international health concern. After malaria, dengue is the most significant mosquito-borne human pathogen and is transmitted by the Aedes family of mosquito, infecting 50-100 million people each year, year, resulting in approximately 22,000 deaths annually. Currently there is no successful treatment available and and therefore research in this area for effective drugs can save the lives of thousands of people and improve the the quality of life of many more. Universities in Ecuador can contribute to the development of potential treatments for dengue but first must ensure that the appropriate infrastructure, capabilities and human resources resources and academic/industrial collaborations are in place.

The proposal: concerns primarily the development of treatments for the dengue virus through collaboration with a leading expert in the field and the development of drug discovery capability at the Technical University at Machala which, in the future, will help Ecuador fight similar diseases that affect Ecuadorian/South American people.

1st Phase of work: concems the selection of a core team 6 scientists with the following skills:
Two synthetic organic chemists preferably with experience in complex natural product synthesis and coupling reactions . Experience in array/parallel synthesis would be an advantage.
Two analysts with experience in HPLC method development, NMR spectroscopy, MS spectrometry and structural characterization.
One scientist with experience in molecular modeling, software for theoretical estimations of pharmacokinetic parameters and QSARs and possibly cheminformatics.
One project leader preferably with experience in medicinal chemistry or synthesis.

Prof. Rassias and Prof Vasudevan will help with the selection process.
The first phase of work includes the familiarization of the team with the research status on treatments for the dengue virus, assess the existing capabilities and determine the objectives of the work to be conducted at the Technical University at Machala. Prof Dr Vasudevan, a leading expert in the field will be in charge of this aspect. In parallel, the team and the collaborators will consult with the Technical University at Machala to upgrade and align existing courses, particularly from the department of Chemical Sciences and Health department to support future research in this and similar areas. Prof Rassias will work closely with the academics of the Chemical Sciences and Health department at the Technical University at Machala towards this effect. This phase is proposed to start late August/ beginning of September 2013 and should complete by the end of 2013.

2nd Phase of the work: concems the synthesis of compound libraries in order to identify molecules with appropriately balanced PK/PD properties. This work will connect with the already established research of Prof Dr Vasudevan and therefore will start from an advanced point. Prof Dr Vasudevan will be coordinating this effort at the Technical University at Machala and the biological testing of the compounds prepared will be conducted as appropriate at the laboratory of Prof Dr Vasudevan at Duke-NUS University in Singapore.
Prof Dr Vasudevan and Prof Rassias may decide when/if additional work is required to support the progression of Celgosivir, a candidate drug at advanced clinical trials.
This phase is proposed to start from January 2014 until the end of the project. Depending on the results, extension of the project may also be requested.

Long term objectives

Developed countries possess strong chemical industry. This is because the knowledge of chemistry is essential for the production of a wide range of goods that address diverse needs of a nation's population and constitutes a platform of growth, exports, jobs, commerce and collaboration with other nations.

Medicines are a key area for a government to invest as it can offer substantial growth and revenue opportunities. In addition, If a government encourages the development of pharmaceutical industry in its country, it may negotiate, influence or subsidize the types of drugs produced so that they are aligned with the medical needs of the population.

Drug discovery and development requires the collaboration of several sciences such as biology, biochemistry, synthetic chemistry, pharmacy, engineering, computer modeling, statistics and medicine, hence all of these disciplines may improve by participating in such programs. Drug discovery and development is complex process in which Ecuadorian Universities will have to collaborate with other universities, institutes and companies from abroad and this is an opportunity to learn the best practices in these fields and implement them in Ecuador. Therefore the greatest beneficiary in this initiative is the country, since it will gain highly trained professionals to support the health system. If the development of the pharmaceutical sector is in the government's agenda, supporting drug research is a key investment because companies tend to establish research and production facilities in countries where they can recruit well-trained professionals. Accordingly, University teaching and research in Ecuador should be aligned with the expectations of both the industrial and academic collaborators from abroad.

Short term objectives

The Technical University at Machala has an established Chemical Sciences and Health department with significant emphasis on biochemistry and pharmacy. At the heart of the drug discovery is medicinal chemistry which studies the design, modification and optimization of drug candidates in order to find the molecules with the best balanced pharmacokinetic and pharmacodynamic properties. Therefore the Technical University at Machala should enhance its medicinal chemistry and drug discovery direction either by modifying existing courses or by creating a new course dedicated to this purpose. Next, it would have to consider laboratory facilities and equipment to support this teaching and research.

A strong medicinal chemistry department at the Technical University at Machala would enable the university to to collaborate with experienced scientists from the academia and industry abroad and apply for funding outside outside Ecuador. From this interaction it will gain the knowledge and technology to conduct high quality research which will raise the University's international profile and ranking and consequently its graduates will be more successful in finding jobs in Ecuador and abroad. This provides the platform for achieving the long term term objective described above, namely attracting pharmaceutical industries in Ecuador. As a vehicle for this development opportunity, a project is needed which will help the staff at Machala capture the bigger picture of the task and identify areas of strengths and weaknesses and reorganize accordingly. For this reason we have chosen to work on a project for the treatment of Dengue virus and collaborate with the group of Dr. Subhash Vasudevan, Professor of Emerging Infectious Diseases Program in Duke-NUS Graduate Medical School in Singapore and one of the leading experts in this field. Currently Dr. Vasudevan is the project leader for Phase I/II clinical triais of the drug Celgosivir against dengue. if this progresses to the next phase, the governement may wish to support further clinical trials to be conducted in Ecuador and thus provide free access to a promising experimental drug for the people of Ecuador. Dr Vasudevan's goup is also working on other compounds that need further development before they are tested in humans. Chemists at the Technical University of Machala can synthesize derivatives with appropriate structural modifications that will be tested for

for their biological activity in Singapore in order to identify molecules that may be candidate selected for the next phase. They can also help develop a production method for Celgosivir.

2. **In this part mention clearly what will be the contribution of research knowledge in the respective area**

The scientific knowledge to be gained from this project will help understand which strategies that are most effective in fighting the dengue and similar viruses that cause major diseases and are also without satisfactory treatment. For example the dengue virus belongs to the wider family of the *Flavivirus* genus which includes the West Nile virus, tick-borne encephalitis virus, yellow fever virus, and several other viruses which may cause encephalitis. The dengue virus is an unmet medical need that affects the health and the economy of the affected counties therefore research for effective drugs can save the lives of thousands of people and improve the quality of life and working capacity of many more. Furthermore this project will help the Technical University at Machala to establish state-of-the-art facilities, skilled researchers and high profile collaborations to address other tropical diseases and therefore have a substantial impact in the health of the local population and other people in South America. Towards these goals, the Technical University at Machala can work together with several organizations that can provide funding for this work such as GlaxoSmithKlines's centre at Tres Cantos in Spain, Novartis's Institute for Tropical Diseases (NITD) in Singapore and the Drugs for Neglected Diseases Initiative (DNDi). These are potentially strategic partners for establishing a strong pharmaceutical sector in Ecuador.

3. **The methodology used in the investigation. This section should demonstrate the feasibility of the research.**

Developing a vaccine against the disease is challenging. With four different serotypes of the dengue virus that can cause the disease, the vaccine must immunize against all four types to be effective. Vaccination against only one serotype could possibly lead to severe DHS (Dengue hemorrhagic shock) when infected with another serotype due to Antibody-Dependent Enhancement. Additionally, vaccination is only effective for those inoculated before infection with the virus. Those that lack such prevention and succumb to infection have no options for care beside treatment of symptoms. Clearly, there is an urgent need for the development of antiviral drugs that will allow health professionals to cure, or at least diminish, these viruses after infection. After entering a human cell, the virus encodes for three structural proteins (capsid [C], pre-membrane [PrM], and envelope [E] proteins) and seven non-structural proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, and NS5). One strategy is to find molecules that interrupt the function of these proteins and limit virus replication. The most promising drug candidates today come from targeting the E, NS1, NS2bNS3 protease and NS5 proteins but toxicity, virus resistance and potency across all 4 genotypes of the virus are constant concerns. A second strategy is to investigate biological targets of the host (human) cell that enhance the defence mechanisms it uses to stop virus replication. In this battle, the Technical University at Machala can join forces with other academic departments and organizations which have ongoing programs for dengue in advanced stages. One such group is that of Dr. Subhash Vasudevan.
Regarding the first strategy that targets viral proteins Dr. Vasudevan may select the most effective molecules that inhibit E, NS1, NS2bNS3 protease and NS5 proteins from the literature and recommend structural modifications in order to improve their potency and overall PK/PD properties using standard medicinal chemistry techniques. The synthesis of these will take place at the Technical University at Machala and will be sent to the laboratory of Dr. Vasudevan for testing. Using standard medicinal chemistry techniques, this may take place in an iterative manner so that 2nd and 3rd generation of improvements are made.

Regarding the second strategy aimed at human cell mechanisms, α-glucosidase I and II are important targets because they the affect the formation and folding of N-glycosylated proteins. DENV proteins prM, E, and NS1 are all believed to be N-glycosylated and therefore α-glucosidase inhibitors are an important class of drugs. Dr Vasudevan is the project leader of Celgosivir a α-glucosidase inhibitor which is the most advanced drug candidate for dengue, currently in Phase I/II clinical triais. Under his direction, more analogues of this Celgosivir may be synthesised at the Technical University at Machala and Dr. Rassias can help with their synthesis. In the case where Celgosivir progresses and larger amounts of the drug is needed, Dr Rassias may also help chemists at Machala to identify a practical route of synthesis for larger production. The methodology for this will include evaluation of alternative routes and optimization with respect to sustainable raw materials, safety, cost, management of impurities and the overall quality of the product. Specialised software will be used for both the medicinal and process chemistry objectives. Based on the advanced stages of the dengue projects at Duke-NUS University in Singapore and the experience of Dr. Vasudevan and Dr. Rassias the proposed objectives are reasonable and feasible provided that The Technical University will commit equally to this collaboration.

4. Expectations

In this section, please fill out the following table. Please do not modify the components and must meet mandatory components 1, 4 and 7. If any component is not applicable, please put N / A

COMPONENTS		SPECIFIC OBJECTIVES	OBJECTIVE RESULTS
1	RESEARCH	Drug candidates for the treatment of dengue virus	At lest one candidate drug selected with the appropriate pharmacokinetic and pharmacodynamic properties
2	SCIENTIFIC TRAINING IN THE RELEVANT AREA OF THEIR SPECIALTY (theoretical training)	Generation of hits Lead optimization Route selection for large scale production	Familirisation of design and testing of small molecules in order to improve pharmacokinetic and pharmacodynamic properties with respect to biological targets Criteria for sustainable and economic manufacture of drugs at industrial scale
3	ADVICE ON THE DEVELOPMENT OF PUBLIC POLICIES	Enable exchange programs for foreign researchers to work in Ecuador and vice versa Ministry of Health to advice university research on treatments that require priority and provide relevant data on dengue and other tropical diseases If required, enable clinical trials with Ecuadorian population	Establish networking with potential collaborators and enable technology and knowledge transfer A well coordinated research centre that can attract external funding and collaborations with the pharmaceutical industry Enable development and access of experimental drugs to local population Minimize cost of treatment
4	TEACHING	Synthetic Organic Chemistry Medicinal Chemistry	Ability to design, synthesize, and modify organic molecules in order to identify lead drug candidates for the dengue virus

	COMPONENTS	SPECIFIC OBJECTIVES	OBJECTIVE RESULTS
		Process Chemistry	Aspects of large scale synthesis and production
5	CONSULTING AND DESIGN GRADUATE PROGRAMS	Master course in Medicinal Chemistry PhD and postdoctoral research in collaborative projects for tropical diseases	Understanding of how drugs are discovered and developed Training of young scientists in drug research for diseases relevant to Ecuador
6	MANAGEMENT NATIONAL AND INTERNATIONAL RESOURCES (administrative, human, economic, etc.)	Funding for appointment of skilled staff Funding for infrastructure and appropriate laboratory equipment and access to scientific journals	State of the art capabilities and competent staff that enable drug research at medicinal chemistry level. Alignment of knowledge and technology with collaborators
7	STRATEGIC RELATIONSHIP BETWEEN INSTITUTIONS NATIONAL AND INTERNATIONAL	Link with Dr. Rassias/University of Patras and collaborate on upgrading the teaching of chemistry for drug discovery and development. Organize workshops and student/academic staff exchange programs. Link with Dr. Subhash Vasudevan/ Duke-NUS University in Singapore and collaborate in the research for new drugs for dengue. Share knowledge in the field and establish mutual access to results and databases. Organize international conferences in the field.	Enable knowledge and technology transfer from Europe to establish state-of-the-art course and facilities in chemistry for drug discovery and development Establish appropriate networks with European and Asian universities and companies and collaborate on writing of proposals for external funding Enable knowledge and technology transfer from Singapore. Support celgosivir if it progresses to next phase. Candidate selection of new drug candidates for dengue. Support foundations for future work and communication of results to scientific community worldwide

SIGNATURE AND SEAL OF THE HOST INSTITUTION

UNIVERSIDAD TECNICA DE MACHALA RECTORADO El Oro - Ecuador

Date of proposal:_____