Università degli Studi di Messina
Dipartimento di Scienze Chimiche, Biologiche, Farmaceutiche ed Ambientali

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Dipartimento Amministrativo Ricerca ed Internazionalizzazione

Università di Messina

Oggetto: Selezioni proposte per assegni di ricerca CRUI-Go for IT

Si comunicano le proposte per assegni di ricerca relativi al bando CRUI - Go for IT selezionate dal Dipartimento, tra quelle presentate dai docenti dell'Ateneo. Per entrambe le proposte, l'attività degli assegni sarà svolta presso il soggetto ospitante estero per un periodo tra 9 e 12 mesi. La procedura di selezione ed i dettagli della stessa sono inoltrate a parte.

AREA BIOLOGICA

Titolo del progetto: **Bioinorganic hybrid bacteriophage for specific antibacterial activity in the modulation of intestinal microbiota**
Soggetto Ospitante estero: Institut Pasteur, Parigi
Ricercatore Ospitante di Riferimento: David Bikard

AREA CHIMICA

Titolo del Progetto: **Dynamic covalent chemistry: exploration of selective imine formation with synthetic and biological molecules and macromolecules**
Soggetto Ospitante Estero: Université de Strasbourg
Ricercatore ospitante di riferimento: Jean-Marie Lehn (Nobel Laureate)

Le proposte selezionate sono riportate in dettaglio nelle prossime pagine.

distinti saluti,

Prof. Sebastiano Campagna

Direttore del Dipartimento Chibiofaram

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SEZIONE PROGETTO DI RICERCA PER ASSEGNO N. 1

AREA: 05 (Biological Science)

A**. DENOMINAZIONE PROGETTO DI RICERCA**

Bioinorganic hybrid bacteriophage for specific antibacterial activity in the modulation of intestinal microbiota

Tema della ricerca *(max 1000 characters):*

Phage display technology has successfully been established for discovery of epitope/mimotope peptides against pathogenic bacteria. The current project provides the use of engineered phages, selected by phage display technology, for the development of biohybrid complexes based on coupling of target agents and noble metal nanoparticles for the design of a new nanostructured system against bacteria diseases. This approach was recently successfully used to target cancer associated Fusobacteria in an animal model, highlighting the potential of this approach to easily target any bacterial species of interest. The aim of this project is to further evaluate the approach against different bacterial species with a specific focus on establishing its efficiency, specificity and safety.

The project includes four operational steps: (i) selection of M13 clones by phage-display technology with ability to selectively and specifically bind to molecular target of bacterial cell; ii) functionalization of the most responsive phage clones with antibacterial nano-materials (like Ag particles (AgNps)); iii) *in vitro* bactericidal evaluation of the phage/AgNps biohybrid system; iv) in vivo screening in mice using either infection or gut colonization models to evaluate efficiency and safety.

B. ATTIVITÀ ALL'ESTERO

I. Attività di ricerca da svolgere all'estero (max 2000 caratteri)

Phage libraries available at Microbiological Lab of UniME (prof Guglielmino) will be screened by biopanning against single bacteria species to isolate phage clones able to selectively and specifically recognized cellular target. Target bacteria will include pathogenic strains of E. coli, Klebsiella pneumoniae, Fusobacterium and Bacteroides. The selected phages will be amplified by growth in

Escherichia coli host. The binding affinity and specificity of phage clones will be evaluated through ELISA test against the target bacteria as well as a panel of other bacteria species. The selected clones will be subjected to DNA sequencing, in order to determine the amino acid sequences of the expressed peptides. Phages clone of interest will then be functionalized with antibacterial nano-materials (like AgNps) using electrostatic and chemical protocols. The complexes will then be evaluated by the Institut Pasteur in collaboration with Eligo Bioscience for their ability to kill target bacteria using classic microbiology techniques. The specificity of the phages will be further validated by testing their ability to kill the target bacteria within a mixed population without affecting the growth of non-target bacteria. These initial in vitro steps will be used to select good functionalized phages for in vivo testing in murine models. Gut colonization or infection models using E. coli, K. pneumoniae, F. nucleatum and B. fragilis will be established. The phage biohybrid will be administered either orally in the case of gut colonization of through intravenous injection in the case of infection models. The pharmaco-kinetics and pharmaco-dynamics of the phages will be evaluated using ELISA as well as microbiological readouts. Safety of the phages will be evaluated *in vitro* on cell cultures as well as *in vivo* through blood chemistry to evaluate liver functions and renal functions with escalating doses. Altogether the project should lead to a much better understanding of the potential of the phage biohybrid approach thanks to the strong and complementary expertise of the different partners.

II. ***Denominazione del soggetto ospitante all'estero*** *(Università, ente di ricerca pubblico o privato):*

Institut Pasteur

III. ***Sede legale del soggetto ospitante all'estero*** *(denominazione soggetto ospitante, città, nazione):*

28 rue du Dr Roux, 75015 Paris, France

IV. ***Sede presso cui si prevede di svolgere l'attività di ricerca all'estero****:*

Institut Pasteur

V. Denominazione dell'impresa coinvolta nell'attività da parte della sede estera:

Eligo Bioscience

VI. ***Documentazione comprovante gli accordi esistenti fra l'Università proponente e il soggetto ospitante all'estero individuato (ad es. lettera di impegno, accordo o altro), che si allega alla presente domanda****:*

Letter of commitment for a collaborative project between University of Messina, Institut Pasteur and Eligo Bioscience

Institut Pasteur

Synthetic Biology Group
Microbiology Department

Paris, August 28, 2020,

RE: Letter of commitment for a collaborative project between University of Messina, Institut Pasteur and Eligo Bioscience

With this letter I would like to support the application of a project in collaboration between Univesity of Messina, the Institut Pasteur and Eligo Bioscience in Paris, France, with a focus on the evaluation of a novel antimicrobial strategy based on the use of phage nanoparticles biohybrids. The Synthetic Biology laboratory at the Institut Pasteur has a long standing relationship with Eligo Bioscience in the development of novel antimicrobial strategies providing a complementary expertise to that of the Microbiological Lab of UniME (prof Guglielmino) in the generation of phage nanoparticles biohybrids. Within this project the Synthetic Biology lab at Institut Pasteur will be happy to host an Italian researcher to conduct the proposed work.

Kind regards,

David Bikard

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AREA

Area di ricerca 03

DENOMINAZIONE PROGETTO DI RICERCA

DYNAMIC COVALENT CHEMISTRY: EXPLORATION OF SELECTIVE IMINE FORMATION WITH SYNTHETIC AND BIOLOGICAL MOLECULES AND MACROMOLECULES

TEMA DELLA RICERCA

Supramolecular chemistry is defined as “chemistry beyond the molecule”, its entities being constituted of molecular components held together by non-covalent interactions. Supramolecular chemistry is intrinsically a dynamic chemistry in view of the lability of the non-covalent interactions connecting the molecular components. In the last times, the conjugation between the dynamic features and the robustness of the covalent structures led to the Dynamic Covalent Chemistry (DCC). In this field, the most versatile reversible reaction is the formation of imines between carbonyl and amino functional groups. The present project concerns the exploration of the use of imine formation, in particular in aqueous solution, focusing on the regioselective derivatization of synthetic and biological molecules for applications involving mapping the lysine distributions in monoclonal antibodies and tuning the activity of histones and retinal, eg. for regulation of gene expression.

ATTIVITÀ ALL’ESTERO

I. ATTIVITA’ DI RICERCA DA SVOLGERE ALL’ESTERO

The project involves three steps:

1) Exploration of aldehydes for high yield imine formation in aqueous medium

2) Application to synthetic polyamines

3) Application to biological molecules

The investigations along these three steps may not necessarily follow this sequence, but will be optimized depending on the results obtained.

1) Imine formation in aqueous medium

It is crucial to define the structural features of aldehydes that favour high yield imine formation with amino groups of both synthetic and biological interest. The lysine provides two amino groups to testing imine formation and plays very important roles in various bio-processes.

Starting with the important biological aldehyde pyridoxalphosphate, suitable aldehydes will be explored for imine formation with lysine and its derivatives.

On the other hand, 2-formyl-3-hydroxybenzoic acid and 2-carboxybenzaldehyde are able to form amino-lactones with secondary amines, thus providing the opportunity to explore the selective derivatization of polyamines.

2) Application to synthetic polyamines

The results obtained will serve for investigating selective imine formation with synthetic oligolysine compounds (which are models for lysine residues in biomacromolecules) in order to determine the factors influencing the regioselectivity of imine formation both kinetically and thermodynamically.

3) Application to biological (macro)molecules (in collaboration with Syndivia)

a) For instance, the terminal amino group of a lysine residue forms an imine with the aldehyde retinal, the key molecule in the light-sensitive receptor protein involved in visual phototransduction.

b) Derivatization of the lysine residues in the DNA binding proteins histones by acetylation or methylation plays a fundamental role in the regulation of gene expression.

c) Finally, another application would be mapping of the monoclonal antibody (mAb) lysine reactivity by reversible imine formation for analysing modified lysine distributions using various aldehydes.

II. DENOMINAZIONE DEL SOGGETTO OSPITANTE ALL'ESTERO:
Institut de Science et d'Ingénierie Supramoléculaires, Université de Strasbourg

III. SEDE LEGALE DEL SOGGETTO OSPITANTE ALL'ESTERO:
Université de Strasbourg, Institut d'études avancées de l'université de Strasbourg (USIAS); 5 allée du Général Rouvillois, F-67083 Strasburgo, Francia

IV. SEDE PRESSO CUI SI PREVEDE DI SVOLGERE L'ATTIVITA' DI RICERCA ALL'ESTERO:
Laboratory of Supramolecular chemistry (Prof. J.-M. Lehn), Institut de Science et d'Ingénierie Supramoléculaires (ISIS); 8 allée Gaspard Monge, F-67000 Strasburgo, Francia

V. DENOMINAZIONE DELL'IMPRESA COINVOLTA NELL'ATTIVITA' DA PARTE DELLA SEDE ESTERA:
Syndivia, 8 Allée Gaspard Monge, ISIS, Strasbourg, 67000, Francia

VI. DOCUMENTAZIONE COMPROVANTE GLI ACCORDI ESISTENTI FRA L'UNIVERSITA' PROPONENTE E IL SOGGETTO OSPITANTE A'ESTERO:
Lettera di impegno, in allegato alla presente proposta.

University of Strasbourg

Institute of Supramolecular Science and Engineering,
Laboratory of Supramolecular chemistry

8 allée Gaspard Monge, F-67000 Strasbourg

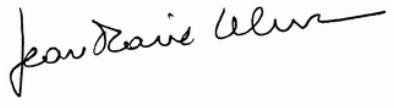
Jean-Marie LEHN, Professor
University of Strasbourg Institute of Advanced Study (USIAS)
Chair of Chemistry of Complex Systems

27/08/2020

Director of the Department of Chemical, Biological, Pharmaceutical and Environmental Sciences,

University of Messina

I herewith confirm that I will be glad to accept the proposal of the University of Messina to pursue in my laboratories the research activities following the project outlined.



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