CURE NEWSLETTER N. 1
Issue Winter 2019

CURE
Eubiosis Reinstatement Therapy

Dear reader,

WELCOME

to the exciting world of CURE!

Did you know that there are 30 million Europeans suffering from asthma and that its control remains suboptimal despite treatment? Despite recent advances in research, a cure for asthma is still far from reality, and patients still need new treatment approaches to better manage the disease.

Some years ago, we found that bacterial viruses, also known as phages[1], are reduced in people with asthma. This unexpected finding within the EU-funded project PREDICTA revealed the significant role that phages have within the respiratory track, their ability to control bacterial populations and, presumably, bacterial imbalance and inflammation. In the CURE project we are looking at how to reinstate a healthy microbial ecology in the lungs (eubiosis), as an opportunity to fight asthma back.

Phage therapy is used routinely in other parts of the world, and it is just appearing as a novel treatment against microbial resistance in Europe. However, phage therapy has never been used for rebalancing dysbiosis[2] in humans. The European Medicines Agency is digging into the use of a stable specific phage mixture[3] to start with, but an efficient treatment will need to be more flexible and 'personalised', which is not allowed under the current rules.

Nikos Papadopoulos, CURE Coordinator

CURE in brief

CURE, a research project funded by the EU programme Horizon 2020, proposes a phage therapy to rebalance the structure of the microbiome[4] in the airways, with the hypothesis that this may also control the immune dysregulation[5] of asthma and eventually even cure it. To achieve this, researchers at CURE will need to predict with accuracy and repeatability the microbiological, immunological and clinical effects of adding several types of phages to the microbiological environment of the airways and design appropriate interventions.

Through CURE, we will first determine the characteristics and dynamics of the human respiratory microbiome in healthy subjects and in people with asthma, by describing in detail the currently unexplored virome[6], the viral-bacterial interactions network and their perturbations in time, as well as evaluating and quantifying interactions between the respiratory metagenome[7] composition, host responses[8] and clinical activity. This first step will allow us to develop a predictive model on the impact of phage interventions on microbial environments and clinical activity, thus guiding the design of well-characterised phages collection, clinically relevant to potentially treat asthma.

[1] Phages are also known as bacteriophages. A bacteriophage is a type of virus that infects bacteria; in fact, it literally means "bacteria eater". Source: https://www.nature.com/scitable/definition/bacteriophage-phage-293

[2] Dysbiosis is the condition of having imbalances in the microbial communities either in or on the body. Dysbiosis is associated with many diseases, such as inflammatory bowel disease and chronic fatigue syndrome. Source: https://www.nature.com/subjects/dysbiosis

[3] A phage mixture consists of multiple "bacterial viruses" types, also called phages or bacteriophages, in order to kill several clinical strains of triggering bacteria. Source: https://www.ncbi.nlm.nih.gov/pubmed/23701332

[4] The microbiome comprises all of the genetic material within a microbiota (the entire collection of microorganisms in a specific niche, such as the human gut). This can also be referred to as the metagenome of the microbiota. Source: https://www.nature.com/subjects/microbiome

[5] The immune system functions to prevent and decelerate the local establishment or systemic dissemination of bacteria, viruses, fungi, and protozoa. When there are abnormalities of immune regulation, we talk about immune dysregulation. Source: https://www.sciencedirect.com/topics/immunology-and-microbiology/immune-dysregulation

[6] The human virome is composed by the set of all viruses, eukaryotic and prokaryotic, present in the human body; as each body compartment constitutes a different microenvironment, the virome varies with the body part.
Source: https://www.sciencedirect.com/science/article/abs/pii/S0188440918300262

[7] Metagenome refers to the collective genome of microorganisms from an environmental sample.
Source: https://www.nature.com/subjects/metagenomics

[8] Host response refers to the process by which the host interacts with, and responds to, triggering agents that colonize or infect it. This includes defense mechanisms such as the immune response. Source: https://www.nature.com/subjects/bacterial-host-response

6
work packages

9
partners

1
objective: *set the ground to find a way to cure asthma*

The CURE project is structured in 6 work packages addressing current challenges and bottlenecks that need to be surpassed to take our hypothesis forward.

MEDICAL UNIVERSITY OF LODZ

HELLENIC REPUBLIC
National and Kapodistrian University of Athens

Since the beginning of the project the **National and Kapodistrian University of Athens (N.K.U.A) and the Medical University of Lodz (MUL)**, clinical partners of CURE, have been cooperating to track in time variations in respiratory symptoms, microbiome imbalances and its perturbations from patients with asthma and healthy subjects, in order to unravel clinical phenotypes in relation to the microbiome. The patients involved in the project will be followed during a year, using questionnaires and physiological measurements including lung function, inflammation, responsiveness and immune status. All the data collected from the healthy subjects and asthma patients will serve as a baseline for the subsequent metagenomics analysis, host status and bacterial cultures[9] and phage isolation.

SIAF

BRFAA
BIOMEDICAL RESEARCH FOUNDATION ACADEMY OF ATHENS

Biomedical Research Foundation Academy of Athens

The **Swiss Institute of Allergy and Asthma Research (SIAF)** and the **Biomedical Research Foundation, Academy of Athens (BRFAA)** are focused on evaluating the immunological reactions of our body in relation to the microbial composition and diversity of our respiratory track as well as to understand the body's response caused by the immune system, from a mechanical point of view, into the effects of phages introduction on asthmatic patients. Particularly, at SIAF researchers are testing the effects of phages on epithelial barrier integrity and BRFAA is examining the effect of direct exposure of mononuclear cells to phages.

MANCHESTER 1824
The University of Manchester

The **University of Manchester (UMAN)** will define the respiratory microbial ecology (classification of species, diversity, richness and abundance), function (microbial gene expression, signalling pathway and gene ontology enrichment), genetic composition, evolution and interactions (correlation matrices and topology of co-occurrence networks) from the data collected of the patients participating in the project, using metagenomics. The work carried out by UMAN will bring to the project an overall insight of the microbial ecology and how it evolves in time.

[9] A microbial culture refers to a technique used in microbiology, letting microorganisms reproduce under controlled laboratory conditions, used to determine a type of organism and/or its abundance in a sample.
Source: https://en.wikipedia.org/wiki/Microbiological_culture

Institute ELIAVA

The **Georgi Eliava Institute of Bacteriophagy, Microbiology and Virology (ELIAVA)** and the **ELIAVA Bio Preparations LTD (ELIBIO)** are working together in order to generate a well-characterised collection of bacteriophages able to target bacteria relevant in asthma. In this sense, ELIAVA will be working, specifically, on identifying, isolating and characterising phages to tackle 'bad' respiratory bacteria, enabling ELIBIO to construct prototypes of phage mixtures relevant to different phenotypes of asthma.

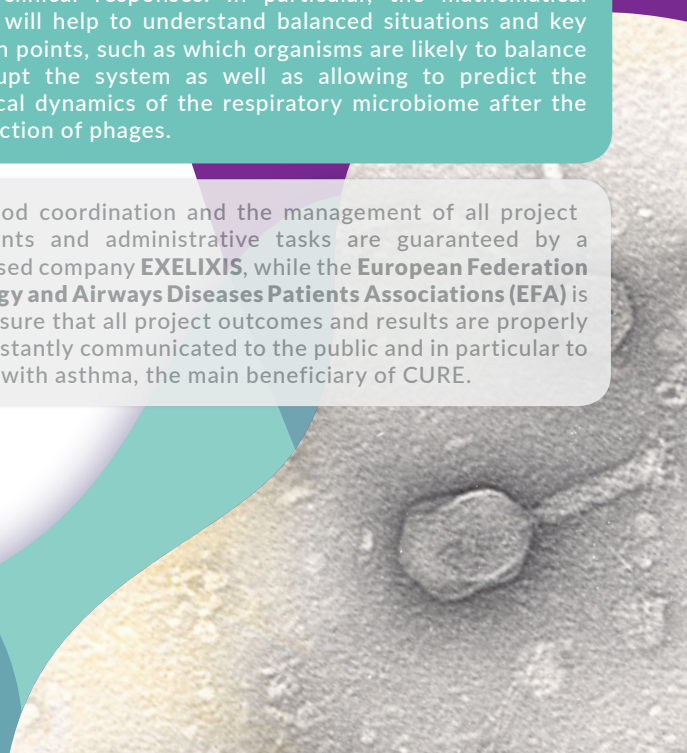
MANCHESTER 1824
The University of Manchester

All the work developed by the partners will enable the **University of Manchester** to develop and fit mathematical models to predict the microbiome ecological changes and design clinical responses. In particular, the mathematical models will help to understand balanced situations and key common points, such as which organisms are likely to balance or disrupt the system as well as allowing to predict the ecological dynamics of the respiratory microbiome after the introduction of phages.

EXELIXIS
research management

EFA
European Federation of Allergy and Airways Diseases Patients' Associations

The good coordination and the management of all project documents and administrative tasks are guaranteed by a specialised company **EXELIXIS**, while the **European Federation of Allergy and Airways Diseases Patients Associations (EFA)** is making sure that all project outcomes and results are properly and constantly communicated to the public and in particular to people with asthma, the main beneficiary of CURE.



Highlights from Tbilisi

On September 24th 2018 the George Eliava Institute of Bacteriophage, Microbiology and Virology in Tbilisi, Georgia, hosted the 1st partner meeting of the CURE project after the kick-off meeting held in Greece in 2017.

A lot of progress has been made during the first year of project and really interesting results were presented in the meeting. To begin with, researchers are advancing with the identification of stable elements and oscillation patterns within the virome of the respiratory tract, through a clinical study which involved 40 asthma patients and 20 healthy subjects. This first step will permit to characterise the conditions causing microbial imbalances and identify its perturbations over the following 12 months.

Furthermore, positive progress was also achieved in the sequencing metagenomics analyses, allowing us to start defining the composition, interactions, function and evolution of the microbiological environment of the airways. Also, very exciting early findings had been found on the ways phages interact with the immune system, while some partners are struggling to isolate new phages against specific targeted bacteria.

CURE is just at the beginning of an amazing journey, exploring the ecology of the new world of human and microbe co-existence. While the first steps of the project are confirming our hypothesis of viral dysbiosis in asthma, we are just starting to understand how fast and under what circumstances this is able to change. Discovering how healthy and unhealthy microbiome states change over time will enable us to know how to control them and, therefore, we will be able to develop mathematical models and future intervention strategies in the upcoming months.

«We would like to show the effect of bacteriophages on the immune system»

Prof Mübeccel Akdis is head of the Immune dermatology department at the Swiss Institute of Allergy and Asthma Research (SIAF), a centre affiliated with the University of Zurich and located in Davos.

Question: What is your main field of research in your institute in Davos?

Professor Mübeccel Akdis: Our main area of research is the immunology and mechanisms of allergy and asthma. Davos is historically known as a place where people with tuberculosis were treated because of specific climate conditions and altitude that were beneficial for these patients. When the prevalence of tuberculosis in Europe drastically decreased, people realised that the climate in Davos and in particular the absence of house dust mites and low allergen concentrations were also favourable for people with asthma and allergy. For this reason our institute is located at the top of the mountains in Davos, where we study the mechanisms of development of allergic diseases and we assess the immune tolerance among patients having allergic immune responses to particular antigens.

How is SIAF contributing to the CURE project?

CURE is proposing a phage therapy to control the immune dysregulation of asthma. The role of our research group is to look at functional bacteriophages in the peripheral blood mononuclear cells (PBMC), in both asthmatic patients and healthy subjects, to understand the effect on the stimulation of the cells to particular antigens and the effect of bacteriophages on it. In addition, we are exploring the effects of bacteriophages on the epithelial cells in the nose and the airways and their barrier function.

Do we know already something about the immune responses to different viruses?

We don't know much about how the bacteriophages influence the immune system and the immune responses. There are several studies that demonstrate that viruses are the major causative agents that induce to asthma exacerbations and, even if there are different type of viruses involved, rhinoviruses in particular. Clinical studies show that in 80% of the children that have bronchiolitis, rhinoviruses are most of the time identified in the airways and nasal swabs during an asthma attack.

What do you expect to see from your research within CURE?

As an immunology research group, we would like to show the effect of bacteriophages on the immune system. We expect some improvements after treating the patients with bacteriophages. In CURE, there are already studies from other work packages aiming to show that bacteriophage treatment has a beneficial effect on asthma patients, so we would like to demonstrate molecular mechanisms of the effects of bacteriophages.

CURE

Eubiosis Reinstatement Therapy

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