Lay summary of research project grant application

1. Objective of the project

Despite existing therapies, systemic lupus erythematosus ("lupus") is still difficult-to-treat in many patients. The diagnosis is often delayed by several months, resulting in anxiety to the patients, repeated lab tests and referrals, and worse outcomes. Lupus begins several years before the actual time of diagnosis, when a person has no or very mild symptoms but her/his immune cells start malfunctioning and produce anti-nuclear ("ANAs") and other autoantibodies (so called "preclinical lupus"). This gives an opportunity for planning preventive strategies which could potentially restore immune system function and delay (or even, prevent) lupus. However, it is currently not possible to predict if a person with ANAs or other autoantibodies will eventually develop lupus or not.

Our study seeks to define the major clinical, environmental etc. factors that put someone at risk for lupus, especially the severe forms (e.g. kidney disease, neuropsychiatric lupus). These results will be complemented with the analysis of the genomic 'make-up' of individuals, which consists of several thousand genes ("transcriptome") and is responsible for the disease. Our previous studies have shown that the "transcriptome" can tell whether a person suffers from lupus or not, and therefore, we hypothesize that it can also be used to predict who will develop lupus.

2. Background (*short summary of what is already known and what this study will add to this*)

To date, it has not been possible to identify a group of individuals at high-risk for lupus in part due to the rarity of the disease. First-degree relatives of patients with lupus show increased risk but this is very low. ANAs and other autoantibodies are present in the serum many years before lupus is diagnosed, however, their predictive power is also very low. To address the need for identifying individuals who are at high risk for lupus, we will examine large patient registries and also, recruit individuals with autoantibodies or first-degree relatives of patients with lupus, who will be surveyed for several possible risk factors and observed for lupus development.

Furthermore, we will analyze their "transcriptome" and examine how well it can foresee lupus onset. If someone combines all previous data for a given individual, it may be more likely to determine her/his risk for lupus.

3. Methods and approach

First, patient registries of individuals with: autoantibodies but no disease, incomplete forms of lupus, and established lupus, will be reviewed to detect a first set of risk factors. Second, we will recruit healthy individuals with autoantibodies or first-degree relatives of patients with lupus (*inception cohort study*), to be surveyed for additional risk factors (including certain lifestyle factors) and observed for development of lupus. In these individuals, the blood "transcriptome" will be analyzed with the "RNA sequencing" technology, which provides a comprehensive analysis of all genes in an individual. We have previously used this technology to identify "gene signatures" that distinguish lupus versus healthy individuals. We will now test whether these "signatures" can predict who will develop lupus. All discovered risk factors will be coupled with these "transcriptome" results to develop a "*lupus risk prediction score*".

4. Primary and secondary outcome measures (if appropriate)

Individuals in the inception study will be monitored for lupus onset. The predictive ability of the "transcriptome" will be calculated. The effect sizes (i.e., how strong a parameter predicts lupus) of all identified risk factors will be converted into probabilities to enable the development of the "lupus risk prediction score".

5. Recruitment of participants (if appropriate)

All participating centres will actively recruit healthy individuals with autoantibodies or first-degree relatives of patients with lupus.

6. Inclusion and exclusion criteria (if appropriate)

The first part of the study involves analysis of registered cases of individuals with autoantibodies (free of disease), incomplete forms of lupus, and definitive lupus. The second

part includes healthy individuals with autoantibodies or first-degree relatives of patients with lupus.

7. Expected benefits for patients

Identification of risk factors that determine which individuals are at high risk for progression to lupus. Deeper understanding of the genes that account for the increased susceptibility to lupus.

8. Expected benefits for society

The results will facilitate the design and implementation of specific care plans and interventions that could potentially inhibit autoimmune inflammation and restore self-tolerance, thereby suspending lupus onset and/or lowering its burden.

9. Burden for patients participating in this study (if applicable: compare burden for intervention group and control group). What methods will be applied to carry out the project?

Inception study participants will undergo interview, physical examination, blood testing, and surveying by means of self-reported questionnaires, twice a year for up to five years. They will be asked to donate blood for "transcriptome" analysis. These constitute minor burden since this is a non-intervention study.

10. Patient involvement in the design and conduct of the study

The Arthritis Foundation of Crete participates in the consortium and has already been involved in the discussions and the design of the study. Its representatives will participate in all consortium meetings where the study details will be finalized and the results will be presented and discussed. In all phases, the patients' views will be incorporated as much as possible. Besides helping with patient recruitment and retention strategies (possible risk of the project), the Foundation will assist in the dissemination of the results.