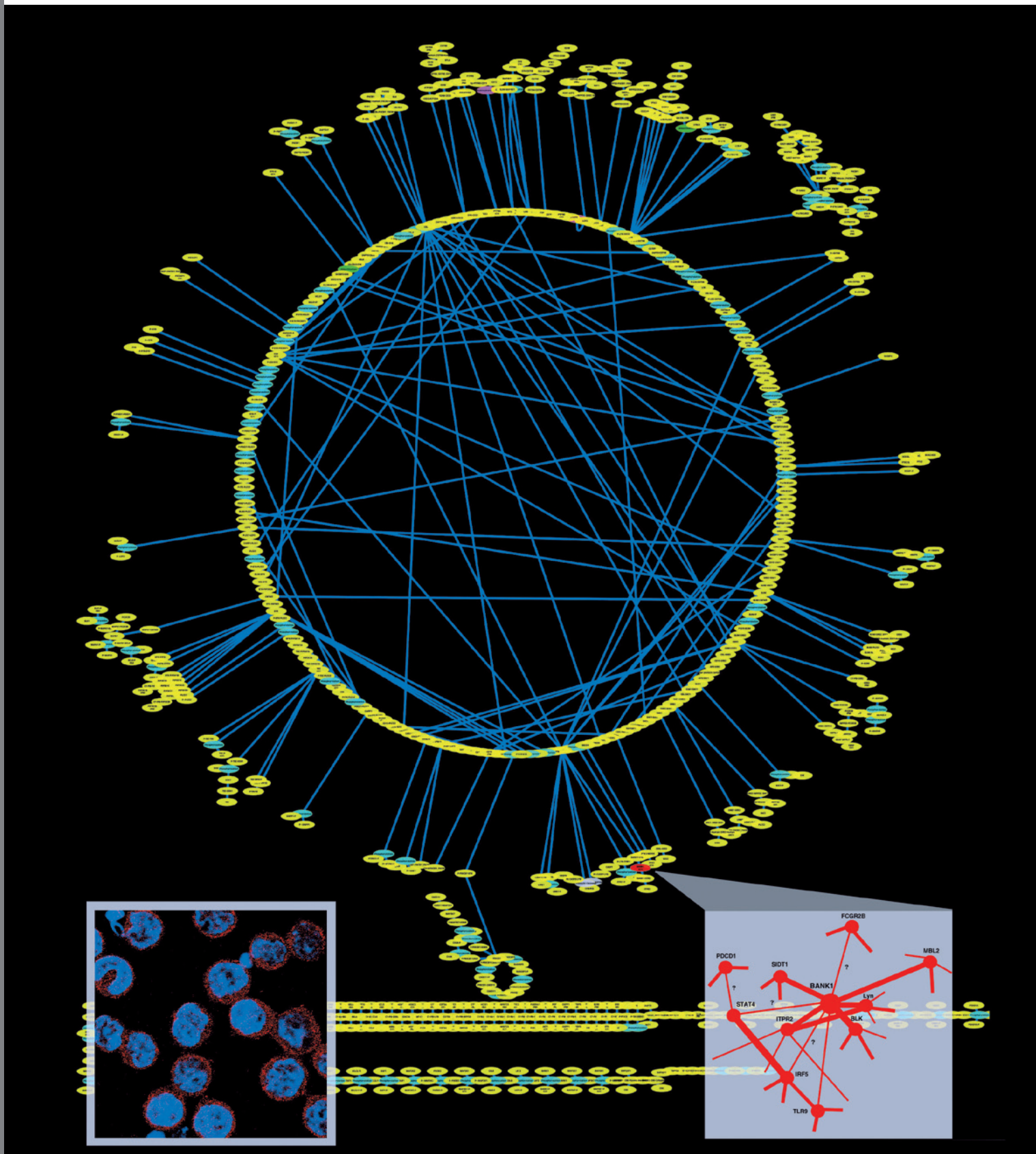
EUROPEAN SCIENCE FOUNDATION

SETTING SCIENCE AGENDAS FOR EUROPE

RESEARCH NETWORKING PROGRAMME

THE IDENTIFICATION OF NOVEL GENES AND BIOMARKERS FOR SYSTEMIC LUPUS ERYTHEMATOSUS (BIOLUPUS)

Standing Committee for the Medical Sciences
(European Medical Research Councils, EMRC)



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Introduction

The European Science Foundation (ESF) is an independent, non-governmental organisation, the members of which are 79 national funding agencies, research-performing agencies, academies and learned societies from 30 countries.

The strength of ESF lies in the influential membership and in its ability to bring together the different domains of European science in order to meet the challenges of the future.

Since its establishment in 1974, ESF, which has its headquarters in Strasbourg with offices in Brussels and Ostend, has assembled a host of organisations that span all disciplines of science, to create a common platform for cross-border cooperation in Europe.

ESF is dedicated to promote collaboration in scientific research, funding of research and science policy across Europe. Through its activities and instruments ESF has made major contributions to science in a global context. The ESF covers the following scientific domains:

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Cover picture:
B cell receptor signalling pathway (partial) analyzed with Cytoscape software. Pathway details are available at http://www.netpath.org/.
On the left: B cells stained with antibodies against B cell specific adaptor molecule BANK1 (kindly provided by Dr C. Castillejo-López).
On the right: BANK1 gene-gene interactions found in SLE patients (modified from Castillejo-López C. *et al*, submitted).

Systemic lupus erythematosus (SLE) is a chronic inflammatory disorder considered a prototype of autoimmune diseases and inflammation. Its clinical manifestations are variable and sometimes cannot be distinguished from other apparently more frequent inflammatory diseases such as rheumatoid arthritis, Sjögren's syndrome and many others (Table 1). SLE is more frequent in women of child-bearing age than in men, and is also associated with a higher frequency of thrombotic events, spontaneous foetal loss and cardiovascular disease. Around 30% of lupus patients develop renal inflammation that can lead to renal failure – one of the most severe complications of SLE – while others may have only mild skin manifestations. Without effective therapy SLE causes serious morbidity in about 1 in 2000 women between 20 and 50 years of age and represents a considerable socioeconomic burden on European society. A large number of individuals live with an undiagnosed lupus, leading to a higher risk of early death.

Table 1.

Organ-specific manifestations	
Dermatological manifestations	malar rash, discoid lupus, alopecia, mouth, nasal, vaginal ulcers
Muscoloskeletal	arthritis, increased risk for bone fractures
Hematological	anaemia
Cardiac	pericarditis, myocarditis, endocarditis
Pulmonary	pleuritis, pleural effusion, lupus pneumonitis
Renal	proteinuria, glomerulonephritis
Neuropsychiatric	cognitive dysfunction, psychosis, headache, mood disorder, anxiety
Systemic	fatigue, depression, pain, sleeping problems, fitness
Other rare manifestations	gastroenteritis, menstrual disturbances, pancreatitis, systemic vasculitis, cystitis, myeloid malignancies

The BIOLUPUS Research Networking Programme has a long-term objective to apply genomics, proteomics and the use of translational databases to the identification of new disease genes and pathways and consequently to define new biomarkers of clinical importance allowing for a more precise diagnosis at early stages of disease development. The cost of treatment of a lupus patient is higher than for patients with any other rheumatic disease, mainly because lupus patients require, at least every three months, close follow-up of their aggressive treatment and their disease activity that has to be assessed by laboratory tests each time. Strict follow-up is required in particular of lupus patients who

become pregnant as a syndrome related to the presence of antibodies anti-Ro/La in the newborn child can lead to heart block (neonatal lupus).

Given the diversity of symptoms and organs affected, it is very difficult to diagnose SLE, so there is a need for new disease biomarkers. At present, no definite biomarkers for lupus are available with the exception of anti-dsDNA antibodies. Such antibodies are mainly used to estimate disease activity, are imprecise, and cannot be used as a tool to diagnose SLE. The lack of biomarkers for lupus has also impeded the realisation of clinical trials for new drugs.

The identification of susceptibility genes for lupus has been very successful but their clinical usefulness still needs to be tested and this can only be done with the availability of very detailed clinical information in a large number of patients with long-term follow-up. Such large numbers of individuals can only be obtained through well-organised networks across all of Europe.

Thirty-five participants from ten European countries, including clinicians, immunologists, bioinformaticians and geneticists, are involved in the BIOLUPUS initiative. The network will serve as a basis for the creation of a Pan-European biobank and a database with clinical, environmental and demographic information that can be used for genetic studies as well as clinical trials of new drugs.

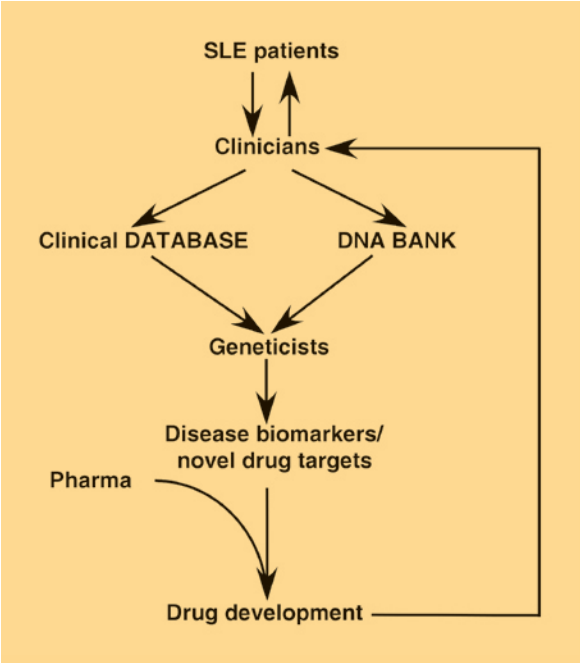

Figure 1. Flowchart on cooperation within the BIOLUPUS Programme

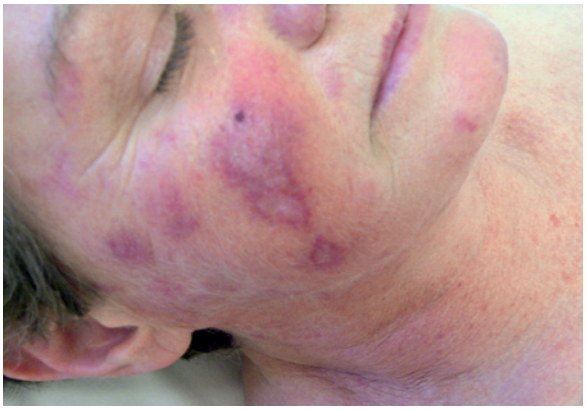

Figure 2. Discoid lupus affecting the face of a patient (Courtesy of Dr László Kóvacs)

Another aspect of the BIOLUPUS Programme is the organisation and coordination of training courses for PhD students and postdocs on genetic methods used in Genome-Wide Association Studies (GWAS), statistics of clinical data, epidemiology and functional analysis of the genes.

The running period of the ESF Research Networking Programme BIOLUPUS is five years from June 2009 to June 2014.

References

1. Castillejo-López, C. *et al.* (2010) Genetic interactions reveal a pathway of B-cell specific signalling proteins involved in SLE pathogenesis (submitted).
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4. Hom, G. *et al.* (2008) Association of systemic lupus erythematosus with C8orf13-BLK and ITGAM-ITGAX, *N. Engl. J. Med.* **358**, 900-9.
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Scope and Aims

SLE has a complex, polygenic inheritance, which makes genetic studies extremely difficult. Many genes with common variations that are normally present in the general population can make modest contributions to increased disease susceptibility. Moreover, multiple environmental factors, including lifestyle (diet, smoking, etc.), latent viral and bacterial infections, age and gender-related physiological changes could trigger the disease or lead it to progression and overt clinical expression.

Given the polygenic nature of lupus, each single susceptibility gene exerts only a modest effect on the disease. Complex epistatic interactions of multiple susceptibility genes can also impede the identification of the disease-related genes. Thus, despite the progress in genetics of SLE made recently, the real causative variants, and hence the functional effect, still remain to be identified for many genes. In order to be able to detect such marginal gene effects, large data sets and high-throughput techniques should be used along with stratification of patients for presence of diverse clinical symptoms, as the disease could have different manifestations. In addition, analysis of various populations of distinct origin is needed to find common and population-specific genes, and in this respect patient collections from different European countries are of great value to the Programme.

At present, only a limited number of genes and biomarkers for overt lupus are used in the clinic, making the precise and early diagnostic of different forms of SLE a challenging task. BIOLUPUS aims at identifying new genes that can be useful as biomarkers in clinical trials of novel drug targets for lupus and in diagnostics based primarily on genetics. This will be accomplished by integrating experts from different fields with a common vision of achieving the well-being of SLE patients across Europe. The BIOLUPUS group will create a resource that will help in various types of research studies, ranging from studies on the genetics of SLE to proteomics and epigenetics.

BIOLUPUS is planning to put together three types of sample cohort:

a) an inception cohort of undifferentiated disease, of individuals not fulfilling the American College of Rheumatology (ACR) criteria for SLE but with manifestations suspected of being SLE or undifferentiated rheumatic disease, to be followed for four years;
b) an inception cohort of newly diagnosed individuals that do fulfil ACR criteria, also to be followed for four years;
c) a cross-sectional cohort of similarly confirmed SLE cases aimed at studying 5 000 cases.

The first two inception cohorts will be followed longitudinally for clinical assessment and frequent sampling in order to study genetic markers important for prediction of disease development and activity flares, while the cross-sectional collection will be used for association analysis of genetic variations with the broader clinical phases including disease activity, organ damage, and morbidity.

Additionally, a genome-wide scan using all 5 000 cross-sectional samples and 1 000 inception samples will be performed within the Programme. The possibility of having genome-wide data on all the patients together with detailed clinical information, in particular follow-up information, will be most useful for the advancement of the genetics of this disease.

As the identification of susceptibility genes for complex diseases advances, new methods are required to detect interactions between the numerous susceptibility genes and genes and environment. Bioinformatics analysis, cellular, biochemical and molecular biology assays will be applied to validate novel genes and gene networks. BIOLUPUS will offer training courses for clinical students on important clinical assessment tools (British Isles Lupus Assessment Group – BILAG and Systemic Lupus International Collaborating Clinics – SLICC), courses for doctoral students and scientists on statistical genetics and updates on lupus research.

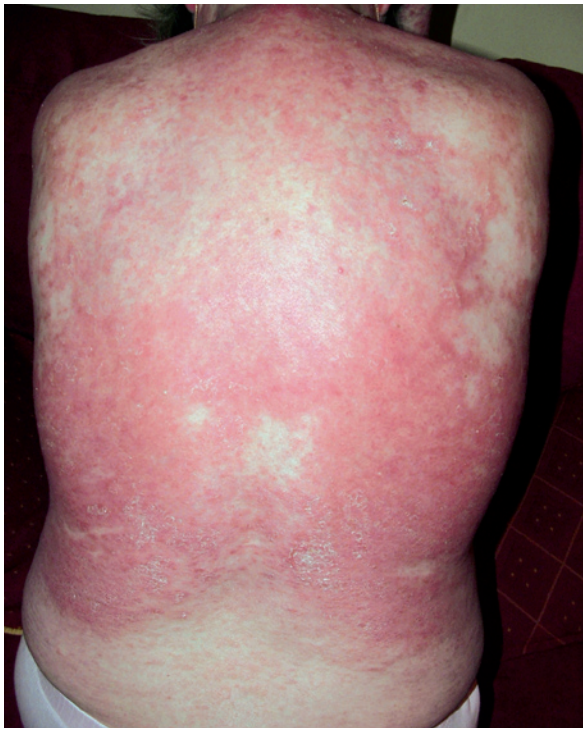

Figure 3. Cutaneous rash in a patient with severe lupus (Courtesy of Professor Carlos Vasconcelos)

Activities

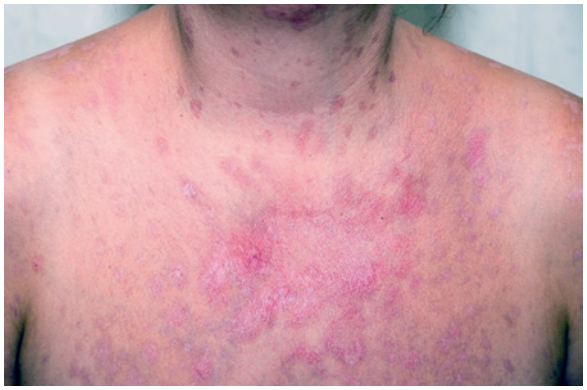

Figure 4. Chronic skin lesions in a female patient with lupus (Courtesy of Dr Emese Kiss)

Therefore the main objectives of the BIOLUPUS Research Networking Programme are:

- To initiate the use of a centralised clinical database for SLE for clinical, genetic and biomarker studies and subsequently for clinical trials on novel drugs;
- To coordinate the appropriate inclusion of data into the database and clinical assessment of the patients. To standardise the clinical evaluation of lupus patients across Europe and to train clinicians for the appropriate use of the assessment tools of most importance;
- To train students and postdocs in various statistical methods used in genome-wide association studies, statistics of clinical data, epidemiology and functional gene studies as well as methods for the assessment of outcome measures in clinical trials;
- To identify genes for lupus and use the database to help in understanding disease pathogenesis with the involvement of students from all throughout Europe.

Specifically, the activities of BIOLUPUS funded by the ESF will include:

- One- or two-day training courses on clinical assessment tools: we envisage a workshop each year of the Programme. These courses are directed at clinical practitioners and will include the use of a centralised database later in the Programme.
- A course on the latest statistical methods in genetics for genome-wide association studies, fine mapping and identification of gene-gene and gene-environment interactions. The identification of genes for lupus has been very successful, but we still need to investigate the interactions which underlie the majority of the genetic effects and which will help us in elucidating the specific characteristics that distinguish some lupus patients from others.
- A major lupus genetics conference (date to be announced) is planned towards the end of the Programme where the latest discoveries will be presented and discussed.
- Mobility of PhD students and postdoctoral scientists throughout Europe for short-term visits (3-6 months) to learn novel techniques. This is the major activity of the Programme to increase the availability of new techniques and methods across the participants of BIOLUPUS.
- Creation and initiation of the use of a centralised database for SLE for clinical, genetic and biomarker studies, subsequently to be of use in clinical trials on novel drugs. This is also a central activity of the Programme as it will allow the centralisation of clinical information that will become a Pan-European resource in lupus research.

In addition, BIOLUPUS will create a website with information on the Programme and will actively prepare state-of-the-art reviews on topics of interest for the general research community. Further, BIOLUPUS will create a map of the available resources regarding animal models of lupus, methodological techniques on several areas (proteomics, epigenetics, genomics).

Expertise available within BIOLUPUS

- All clinical groups will provide expertise on clinical medicine.
- Expertise and facilities for epidemiological studies including statisticians, epidemiologists and computer programmes.
- Availability of experts on the BILAG and SLICC indexes.
- Genetic data and computer facilities for statistical analyses.
- Expertise in mouse models of SLE, various KO and engineered models available for *in vivo* functional studies of genes, immunology expertise.

BIOLUPUS welcomes new participants with an interest in understanding the pathogenesis of SLE and in creating the necessary resources for the European Scientific Community to put European Lupus Research at the forefront.

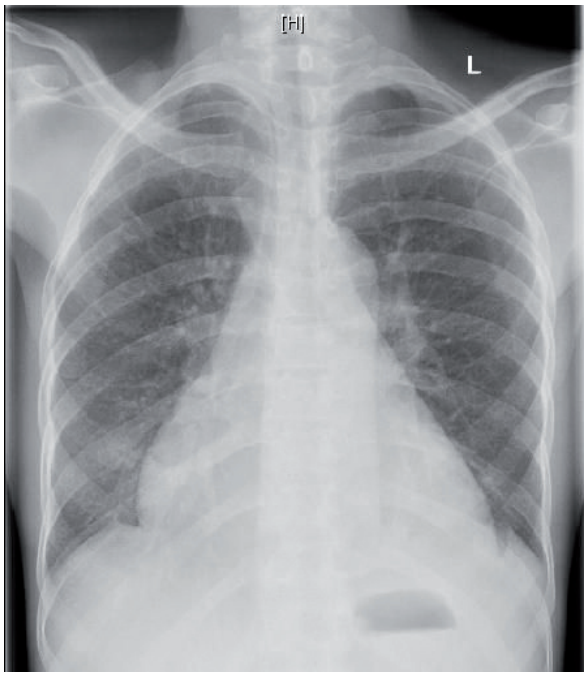

Figure 5. X-ray showing pericardial effusion in an SLE patient (Courtesy of Professor Torsten Witte)

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For the latest information on this Research Networking Programme consult the BIOLUPUS website: **www.esf.org/biolupus**

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