NIMBL NEWS

EDITION 1

NIMBL PROJECT ONLINE: www.nimbl.eu

JUNE 2011

WELCOME TO NIMBL!

NIMBL is a 3 year EU-funded study, investigating the causes and progress of Nuclease Immune Mediated Brain and Lupus-like conditions, including;

- Aicardi-Goutières Syndrome (AGS),
- Retinal Vasculopathy with Cerebral Leukodystrophy (RVCL)
- Familial Chilblain Lupus (FCL)
- ...and some cases of Systemic Lupus Erythematosus (SLE).

The study is a collaboration between geneticists, neurologists, immunologists and clinicians from the UK, the Netherlands, Italy, Spain and the USA.

The project is led by Prof Yanick Crow, at the Manchester Academic Health Science Centre, Manchester, UK.

THE NIMBL INVESTIGATORS

Top row (left to right): Yanick Crow, Arn van den Maagdenberg, Taco Kuijpers, Luis Francisco Santamaria, Dan Stetson, Gillian Rice, David Bonthron
Bottom row (left to right): Adeline Vanderver, Ivana Olivieri, Simona Orcesi, Johanna Loewenstein

NIMBL CONDITIONS....

- AGS, RVCL and FCL are rare with a total of only about 750 diagnosed cases world-wide
- Children with the more severe forms (e.g. AGS) usually show symptoms during the first few months of life, often after a period of apparently normal development
- Currently there are five genes implicated in NIMBL conditions: TREX1, RNASEH2A, RNASEH2B, RNASEH2C, and SAMHD1
- At present there are no cures. Current treatments manage or alleviate the symptoms rather than treating the underlying cause

THE AIMS OF THE PROJECT....

These conditions are rare. The purpose of the NIMBL consortium is to share information about these rare cases, and thus increase our knowledge of these disorders. This can only benefit affected families, both now and in the future.

The NIMBL research study aims to gain a greater understanding of:

- the normal progress of these illnesses, including the biochemical changes
- the underlying cause (genetic and biochemical)

This should help to:

- give an earlier, faster and more accurate diagnosis in the future
- suggest and investigate potential new treatments and therapies
- provide insight into other autoimmune conditions

The investigation of NIMBL diseases hopefully will not only improve the health and well-being of NIMBL patients and their families, it is also expected to lead to better treatments of much more common autoimmune disorders including systemic lupus erythematosus.

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NIMBL STUDY DESIGN...

Affected individuals and their relatives will be invited to provide biological samples to understand and monitor the progress of the condition. These can also be used to measure the effect of any new treatments in the future.

NIMBL investigators will:

- Investigate the underlying cause of the conditions by examining the genetic material (DNA) to try to identify the exact change that has occurred and the exact location in the genome; this can help with future diagnosis of the condition both in the families already identified, and also in other cases yet to be identified
- Study the function of the genes that are involved, and how the gene products are modified in the affected individuals; this will help to identify potential new treatments
- Use cell-lines and genetically modified mice to investigate the biochemical changes in cells as the condition progresses; these animal models will be able to show changes affecting, for example, the brain, which are difficult to test in affected children
- Use cell-lines and genetically-modified mice to investigate potential drug targets and test the effectiveness of new treatments.

NB: All information and samples will be kept confidentially and securely, and identified by a code.

Information (identified by the code) may be shared with members of the consortium.

NIMBL NEWS AND EVENTS...

A patient conference was held in Washington DC on 30 April 2011, and a video of this will be available on the NIMBL website soon; another conference is being planned in Manchester. Pavia have enrolled 28 new AGS patients from across Europe.

RECENT NIMBL PUBLICATIONS...

- Serra M., et al. (2011) Characterization of Trex1 Induction by IFN-γ in murine macrophages. *J Immunol* 186(4):2299-2308

39 Repair exonuclease (Trex1) is the most abundant mammalian 39→59 DNA exonuclease with specificity for ssDNA. Trex1 deficiency has been linked to the development of autoimmune disease in mice and humans, causing Aicardi-Goutières syndrome in the latter. In addition, polymorphisms in Trex1 are associated with systemic lupus erythematosus. On the basis of all these observations, it has been hypothesized that Trex1 acts by digesting an endogenous DNA substrate. In this study, we report that Trex1 is regulated by IFN-g during the activation of primary macrophages. IFN-g upregulates Trex1 with the time course of an early gene, and this induction occurs at the transcription level. The half-life of mRNA is relatively short (half-life of 70 min). The coding sequence of Trex1 has only one exon and an intron of 260 bp in the promoter in the nontranslated mRNA. Three transcription start sites were detected, the one at 2580 bp being the most important. In transient transfection experiments using the Trex1 promoter, we have found that two IFN-g activation site boxes, as well as an adaptor protein complex 1 box, were required for the IFN-g–dependent induction. By using EMSA assays and chromatin immune precipitation assays, we determined that STAT1 binds to the IFN-g activation site boxes. The requirement of STAT1 for Trex1 induction was confirmed using macrophages from Stat1 knockout mice. We also establish that c-Jun protein, but not c-Fos, jun-B, or CREB, bound to the adaptor protein complex 1 box. Therefore, our results indicate that IFN-g induces the expression of the Trex1 exonuclease through STAT1 and c-Jun.

- Ravenscroft JC., et al. (2011) Autosomal dominant inheritance of a heterozygous mutation in SAMHD1 causing familial chilblain lupus. *Am J Med Genet* 155A(1):235-237

Although the function of the 626 amino-acid protein SAMHD1 remains unknown, evidence suggests that, like TREX1, it has an important role in innate immunity and inflammation . Following on from our recent description of progressive arthropathy with distal joint contractures and painful mouth ulcers in association with bialleic SAMHD1 mutations, and of a large vessel intracerebral vasculitis in patients with SAMHD1-associated AGS, this current report further highlights the variable inflammatory phenotypes which can arise due to mutations in SAMHD1. Moreover, by analogy with TREX1, our findings suggest a possible role for SAMHD1 in the pathogenesis of SLE.

- Briggs TA., et al. (2011) Tartrate resistant acid phosphatase deficiency causes a bone dysplasia with autoimmunity and a type I interferon expression signature. *Nat Genet* 43(2):127-131

We studied ten individuals from eight families showing features consistent with the immuno-osseous dysplasia spondyloenchondrodysplasia. Of particular note was the diverse spectrum of autoimmune phenotypes observed in these individuals (cases), including systemic lupus erythematosus, Sjögren's syndrome, hemolytic anemia, thrombocytopenia, hypothyroidism, inflammatory myositis, Raynaud's disease and vitiligo. Haplotype data indicated the disease gene to be on chromosome 19p13, and linkage analysis yielded a combined multipoint $\log_{10}$ odds (LOD) score of 3.6. Sequencing of *ACP5*, encoding tartrate-resistant acid phosphatase, identified biallelic mutations in each of the cases studied, and *in vivo* testing confirmed a loss of expressed protein. All eight cases assayed showed elevated serum interferon alpha activity, and gene expression profiling in whole blood defined a type I interferon signature. Our findings reveal a previously unrecognized link between tartrate-resistant acid phosphatase activity and interferon metabolism and highlight the importance of type I interferon in the genesis of autoimmunity.

FOR MORE INFORMATION... Please contact us at: nimbl@manchester.ac.uk