2) INTERFERON REGULATED IMMUNOPROTEASOMES IN CLINICAL AND PATHOLOGY FEATURES OF PATIENTS WITH IGAN. GENETIC AND PHENOTYPIC STUDY

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Rationale

In a recent GWAS, we localized five IgAN susceptibility loci on Chr.6p21 (HLA-DQB1/DRB1, PSMB9/TAP1, and DPA1/DPB2 loci), Chr.1q32 (CFHR3/R1 locus), and Chr.22q12 (HORMAD2 locus) (Gharavi A. et al., Nat Genet. 2011 and PLoS Genet. 2012). One of these loci contain the PSMB8 and PSMB9 genes, which encode immunoproteasome units that were found to be upregulated in peripheral blood mononuclear cells from individuals with IgA nephropathy (Coppo, R. et al. Kidney Int. 2009: 75, 536–541). Immunoproteasomes (IPs) containing the interferon-inducible subunits β1i (LMP2), β2i (MECL-1), and β5i (LMP7) alter proteasomal cleavage preference, optimise the generation of peptide ligands of MHC class I molecules, alter cytokine profile, influence T-helper cell differentiation, and play a role in T-cell survival. Interferons elicited by pathogens are potent modulators of Toll-like receptors (TLR). We found an increased expression of TLR4 on peripheral blood mononuclear cells from patients with IgAN (Coppo, R. et al. Clin Exp Immunol. 2009).

In the present proposal, we hypothesize that other IgAN risk loci are associated with additional sequential hits in the immune system that influence the development and progression of IgAN (Suzuki et al., JASN 2011). For example, we hypothesize that a switch to an immuno-proteasome in peripheral blood mononuclear cells of patients with IgA nephropathy results in increased efficiency of antigen processing and presentation, leading to increased production of immune complexes.

Protocol
We would like to combine genetic, immunobiology and clinico-pathological data starting from VALIGA cohort to test these hypotheses. We will measure the following parameters and test association with Oxford scores:

1- *PSMB8* and *PSMB9* genes transcript levels from PBMCs
2- Serum levels of serum IgA-1 and Galactose deficient IgA1
3- Serum Levels of anti-IgA1 autoantibodies
4- Terminal complement activation
5- Genetic polymorphisms at five loci associated with risk of IgAN by GWAS

**Logistics**

We only require a one-time collection of whole blood that will be collected in specials tubes that will enable isolation of serum, plasma, DNA and RNA. We will provide all participating enters with tubes and supplies for collecting and shipping the samples. The shipment can be billed to our Fedex account.

detailed instruction for Project 1 and 2
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