3) The role of the complement system in determining outcome in IgA-nephropathy

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Background
Complement analyses such as C3, C4 or CH50 usually reveal no abnormalities in patients with IgA-nephropathy (IgAN). However, we and others have shown that using very sensitive techniques, systemic complement activation can be demonstrated in such patients (Zwirner 1997; Smailhodzic 2011). The prognostic relevance of such systemic complement activation, however, is unknown. In addition, it has now been demonstrated that IgA in IgAN can activate the MBL-pathway in addition to the alternative pathway of complement (Roos 2006). MBL exhibits a functionally relevant polymorphism, which, for example, determines the risk for infections following liver transplantation (de Rooij 2010). Again, the role of this polymorphism in IgAN is unknown.

As part of the STOP-IgAN study (Eitner 2008), we have established an extensive clinical database, a prospective biobank and have repetitively obtained serum samples. These samples so far have never been thawed and thus allow in-depth analyses of the complement system. The study currently comprises almost 450 patients with prospective 2-3 year follow-up.

We propose to measure C3, its catabolic fragment C3d and MBL in these samples. Additionally, since it has been shown recently that IgAN is associated with a novel N-terminal mutation of H (Schmitt 2011), we will assess H and its variant as well.

References


**Research Plan**
We plan to first generate data in the above STOP-IgAN population. In the meantime we have already measured the C3d/C3 values of all the sera. Based on these findings we can conclude that there is complement activation in the IGAN patients.

The following is to establish the pathways that are involved meaning:

1. The measurement of the activity of the alternative, classical and lectin pathways, including the levels of MBL and Ficolins using sensitive ELISA methods that have been established earlier. In particular given hints for a genetic role of factor H, we will assess H and H variants.
2. Measurement of C3a and C5a (to be done via the Gharavi-group in New York).
3. Depending on the outcome of C3a and C5a we will decide whether to measure the levels of soluble C5b-9.

If we can identify novel markers, we then plan to validate our findings in independent populations such as the VALIGA cohort.

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