

## **Super-resolution Microscopy as a Novel Diagnostic Approach in Renal Pathology**

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In contrast to most other pathology subspecialties, in which light microscopic studies form the basis of a diagnostic work-up, ultrastructural examination by electron microscopy and immunofluorescence microscopy are indispensable tools in kidney pathology. Particularly injury to the nanometric structure of the kidney filter, the morphologic hallmark of proteinuria, to date can only be definitively confirmed using electron microscopy. We identified B7-1, a T cell costimulatory molecule, as a novel biomarker in the glomeruli of a subgroup of patients with nephrotic syndrome. B7-1 is targeted by a specific inhibitor, Abatacept, which reduced proteinuria in patients suffering from therapy-resistant or recurrent nephrotic syndrome. This breakthrough finding poses new diagnostic challenges to the field. In a subset of human biopsies from patients with proteinuric kidney disease, we observe disparate B7-1 staining patterns in the glomerulus, which vary by disease. This suggests differences in localization of B7-1 within the kidney filter as well as different pathogenic pathways, which cannot be resolved using conventional immunofluorescence microscopy methods. Therefore, this exposes a need for high-resolution immunofluorescence imaging. This proposal outlines the use of super-resolution microscopy on fresh frozen human kidney biopsies positive for B7-1, aimed at discerning the exact localization of B7-1 in the glomerulus. Results from this study will refine our understanding of the role of B7-1 in mediating proteinuria and contribute to a new diagnostic classification of proteinuric kidney diseases, with the ultimate goal to streamline our therapeutic efforts in patients suffering from resistant and thus difficult-to-treat kidney diseases.