Nephroprotective and antifibrotic potential of microRNA-21 in the COL4A3 knockout mouse model of Alport syndrome

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Awarded 2013

Dr. Gross' research will focus on two hypotheses:

1. Anti-miR-21 therapy might be able to target the proinflammatory, profibrotic program of tubular cells to calm down progressive tubulo-interstitial fibrosis in AS

2. Anti-MiR-21 therapy might be able to modulate the malfunctioning cellular program of the podocyte, caused by its genetic inability to produce intact α3/4/5 (IV) collagen

Dr. Gross' project takes four crucial points into account while addressing the nephroprotective potential of anti-microRNA-21 therapy (miR-21) in COL4A3 -/- mice:

1. MiR-21 is elevated in interstitial kidney fibrosis. It targets the redox metabolic and lipid metabolism pathway – both correlating with oxidative and fibrotic kidney damage. It effects kidney fibrosis and is a candidate target for antifibrotic therapy. Preliminary data in mice presented at the Congress of the Am. Soc. of Nephrology 2012 make anti-miR-21 to a potential therapy in Alport syndrome.

2. Dr. Gross's 14-year long experience in the COL4A3 -/- mice as animal model for Alport syndrome will enable a thorough evaluation of the potential of anti-miR-21 therapy.

3. The anti-miR-21 compounds will be supplied by Regulus Therapeutics. However, the ASF Macquarie KFOC funding program will ensure that the study will be performed and interpreted independently as autonomous researchers.

4. Preliminary data indicate that miR-21 acts different and independent from RAAS. Therefore, this project will identify the way of action of anti-miR-21 in COL4A3 -/- mice and possible synergistic, beneficial effects on top of ACE-inhibition.

These four goals will be the assessed using experience from 15 original research publications in COL4A3 -/- mice: analysis of untreated vs. anti-miR-21 treated vs. ACE+anti-miR-21 treated mice will include but will not be limited to lifespan of until death from end stage renal fibrosis, proteinuria, kidney function tests, histology, electron-microscopy, immunohistochemistry, immunoblots and RT-PCR-techniques. Comparison with previous data will help define the optimal target and starting-point of anti-miR-21 therapy, both points are crucial for future therapy in humans. Only the profound knowledge about the potential risks, benefits and targets of anti-miR-21 in mice might allow translation of this basic science project into therapy in humans within the next years. For example, if it is known what to look for, prescreening can be done of urine samples from human Alport-patients (originating from ASTOR or the EARLY PRO-TECT Alport trial) for miR-21 of interest. By this, the design and potential beneficial outcome of future clinical trials with anti-miR-21 compounds in patients with Alport syndrome can be optimized – as done previously with ACE-inhibitors.