Amniotic Fluid Stem Cells (AFSC) and Alport Syndrome

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Alport Syndrome (AS) is characterized by a hereditary form of glomerulonephritis, wherein an abnormal level of glomerular basement membrane (GBM) is produced, gradually leading to interstitial fibrosis and eventual loss of renal function. At present, there is no definitive therapy to delay progression to ESRD for patients with AS.

Researchers have recently demonstrated that exogenous stem cell therapy can attenuate fibrosis in animal models of AS. Despite very encouraging results, the studies with bone marrow mesenchymal stem cells are hard to compare due to the use of mice with varying genetic backgrounds, each of which profoundly influences the progression of AS in a different way. In addition, the use of irradiation before injection (which was shown to be renal protective itself) coupled with varying time points of injection among studies, still leaves the open question on the beneficial effect of using exogenous stem cells to treat AS. But, most importantly, very little is known about the main mechanisms by which stem cells influence the progression of fibrosis in AS. In order to claim that stem cells can be used as an anti-fibrotic therapy it is crucial to understand the cellular mechanisms responsible for this effect. In this study we propose to use stem cells derived from amniotic fluid (AFSC) as a novel approach to reversing fibrosis in AS as a potential therapeutic approach, but also as a useful tool in understanding how stem cells modulate the molecular mechanisms that lead to reverse interstitial fibrosis in AS. We recently discovered evidence suggesting that a single injection of AFSC has the capacity to reduce the fibrotic process of AS accompanied with an overall improvement of renal function and lifespan of treated mice. We showed that the beneficial effect of the injected cells is evident through a regulation, present within the first days after injection, of genes involved in extracellular matrix deposition and in progression of fibrosis.

In this proposal we will focus our attention on investigating which molecular signaling pathways promoting renal fibrosis are modulated by injection of AFSC during the early phase of the disease, and which renal cells are targeted by this intervention. In addition we would like to investigate whether multiple injections of AFSC can have a potentiating effect on life span, renal physiology and renal morphology in treated mice compared to a single injection. Successful completion of this proposal will significantly improve our knowledge of how stem cells mediate their positive effects in AS. In addition, understanding how stem cells behave in an *in vivo* environment will strengthen the foundation for translating stem cell research into viable clinical therapies for the future and possibly significantly delaying or avoiding End Stage Renal Failure in AS patients.