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Neutralization of Autoantibodies directed against the Beta-1-Adrenoceptor and the Muscarinergic-2 Receptor treats Betacardiomyopathy

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Objective: Spontaneously hypertensive rats (SHR) with advancing age present with in addition to clinical signs of cardiomyopathy autoantibodies (AABs) directed to the beta1-adrenergic receptor (beta1-AAB) and in a minority with autoantibodies directed to the muscarinergic 2 receptor (m2-AAB). Under in vitro conditions, it has been demonstrated that well selected and identified aptamers among these the aptamer BC007 are able to neutralize rat beta1-AABs and m2-AABs. BC007 neutralizes also AABs found in humans with cardiomyopathy. Consequently, we used the model of AAB positive SHR to demonstrate the aptamers' potency for *in vivo* beta1- and m2-AAB neutralization.

Methods: For each tested aptamer, five SHR, age 30–32 weeks, with positive evidence for beta1-AABs and m2-AAB were treated with the aptamer. Control rats (n = 5) were not treated with aptamers but with 0.9 % saline solution (NaCl). Treatment was performed in a biphasic mode by bolus application of 2 mg/kg body weight dissolved in 0.9 % NaCl solution followed by an infusion of the same amount over 20 min. The treatment procedure was repeated five times at weekly intervals. For the application, chronic catheters (PhysioCath, DSI, St. Paul, MN, USA) were inserted under general anesthesia. The AAB titers were measured using a bioassay.

Results: SHR responded to aptamer treatment with a significant reduction in cardio-pathogenic AABs such as beta1-AABs and m2-AABs. With respect to the beta1-AAB reduction following application of a beta1-AAB specific aptamer, results has been recently published (Mol Cell Biochem. 2014;393:177-180). In case of the aptamer BC007 application, comparable results in AAB reduction have been seen that included also m2-AAB reduction. The AAB reduction was already visible at two days after the second aptamer application. Rats presented the lowest AAB level following the 5th aptamer application. Despite treatment finishing, thereafter, AABs did not substantially return within the study period. No signs for aptamer toxicity were observed by visual examination of the heart, liver, and kidney, or by measurement of plasma CK, ALT, and creatinine.

Conclusion: The aptamer BC007 is able to neutralize cardio-pathogenic AABs such directed to the beta1-adrenergic and muscarinergic 2-receptor *in vivo* without any detected negative side effect. Considering the comparable response (neutralization) to rat and human cardiopathogenic AABs following aptamer application *in vitro*, we suggest an aptamer based treatment concept for patients with positive evidence for cardio-pathogenic AABs such as in patients with dilated cardiomyopathy (betacardiomyopathy).

Biography

Dr. Mueller completed his MEng studies at the age of 24 years from the Technical University of Berlin and postdoctoral studies from the Free University School of Medicine Berlin, Germany. He was the CEO of several medical device companies. Right now is the CEO of Berlin Cures, a pharmaceutical company which develops aptamers against autoimmune diseases. He gave more than 200 talks at international conferences and has published more than 25 papers in reputed journals and is serving as a reviewer of renowned medical journals.

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