J Clin Case Rep 2016, 6:2 (Suppl)
http://dx.doi.org/10.4172/2165-7920.C1.003

Biological therapies for conduction system disorders

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Gene based BioP were first described more than a decade ago; somatic gene transfer of various constructs (a dominant negative mutant of the inward rectifier channel [Kir2.1AAA], wild type HCN channels and a transcription factor [Tbx18]) have all been shown to create BioP activity. However, until recently, *in vivo* preclinical applications have been mostly limited to highly invasive open chest models. We have developed a clinically realistic minimally invasive delivery technique and used it to create BioP in a porcine model of complete heart block. Here, we propose to use this approach to compare two "finalist" therapeutic candidates with fundamentally different mechanisms of action. The first one is a wild type ion channel (HCN2) that artificially induces automaticity in ventricular cardiomyocytes by functional re-engineering. The goal is not to create a faithful replica of a pacemaker cell, but rather to manipulate a single component of the membrane channel repertoire so as to induce spontaneous firing in an excitable but normally quiescent cell. The active principle of the second therapeutic candidate, Tbx18, reprograms ventricular cardiomyocytes into sinoatrial node (SAN) like pacemaker cells (induced SAN [iSAN] cells). No one determinant of excitability is selectively overexpressed: The entire gene expression program is altered with resultant changes in fundamental cell physiology and morphology. The proposal utilizes the above mentioned percutaneous delivery method to reduce to refine and validate in a large animal model of bradycardia, the approaches required for translation to the clinic. We will characterize and compare the pacing efficacy and safety of HCN2 and Tbx18 derived BioP, testing the hypothesis that iSAN cells will provide superior chronotropic support as compared to HCN2. We will go on to perform long term efficacy, toxicology and bio distribution studies with the more promising therapeutic candidate and then prepare and obtain approval of an Investigational New Drug (IND) application for a first-in-human BioP trial. While the ultimate goal may be to render obsolete the electronic pacemaker, it is important to be realistic in thinking about potential first-in-human applications. Therefore, we have chosen to develop a bridge to device product that will temporarily provide hardware free chronotropic support in infected patients who are pacemaker dependent. To make BioP temporary, we deliver the genes in adenoviral vectors, relying on immunological clearance to limit bioactivity. Nevertheless, we will test catheter ablation of the BioP as a backup rescue strategy in case of persistent undesired BioP activity. This research proposal is designed to lay the groundwork for clinical testing of an optimized BioP in a needy patient population. Device related infections continue to rise in the USA. A temporary BioP could represent a future alternative hardware free "bridge" for those afflicted by device related complications.

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A chronic complex ulcerative colitis: Case report

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A 29-year-old male patient having eight-year history of ulcerative colitis with multiple ulcerative colitis exacerbations is on maintenance therapy. Colonoscopy established pancolitis extending from cecum to rectum with the presence of granularity, ulcers, hemorrhage and moderately active disease. It is also noted with hyperplastic mucosal nodules in the prolapsing rectum. This patient was diagnosed with ulcerative colitis only in 2001 treated in the past with mesalamine, azathioprine, adalimumab, infliximab, prednisone and hydrocortisone with antibiotic rifaximin and albendazole with an inadequate improvement in his condition. He is still suffering from multiple watery stools with blood and mucus sometimes and complains of abdominal distention with excessive flatus. Colonoscopy reconfirms active pancolitis with multiple small to medium size ulcers. He refused to go for colectomy advised by consultant. Therefore, it was recommended to change the current adalimumab to weekly infliximab with current azathioprine and mesalamine. Follow-up laboratorial investigation reveals that his hemoglobin, hematocrit, along with MCV, MCHC are lower than normal and random blood glucose, platelet count, RDW are higher than the normal. However, overall symptoms and quality of life of the patient have improved compared to earlier therapies. This case demonstrates and supports that combination of weekly infliximab infusion and oral azathioprine while maintaining remission with mesalazine may be beneficial in inducing remission rapidly, even in moderate cases of steroid-dependent ulcerative colitis.

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