Department of Biomedical Sciences

presents seminar

香港城市大學
City University of Hong Kong

A permanent genetic treatment for spinal muscular atrophy using base editors

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(Meeting ID: 931 9736 8746 and Passcode: 623960)

Abstract

Spinal muscular atrophy (SMA) is a devastating neuromuscular disease caused by mutations in the SMN1 gene that reduce survival motor neuron (SMN) protein expression. Despite progress in the field that has resulted in therapies, there remains no permanent cure for SMA. SMN2 is a paralogous gene that mainly differs from SMN1 by a C•G-to-T•A transition in exon 7, resulting in the skipping of exon 7 in most SMN2 transcripts. Editing of the SMN2 exon 7 mutation should in principle offer a therapeutic strategy to restore SMN protein levels. Here, we developed a base editing approach to precisely edit SMN2 to revert the T•A to C•G mutation. We tested a range of different adenosine base editors (ABEs) and Cas9 variants, resulting in >80% intended editing in patient-derived fibroblasts with concomitant increases in SMN2 exon 7 and SMN protein levels. Delivery of these optimized ABEs via a dual adeno-associated virus approach resulted in precise SMN2 editing in an SMA mouse model. Moreover, we generated and characterized ABEs fused to high-fidelity versions of Cas9 variants which reduced potential off-target editing. These novel technologies may provide a long-lasting cure for SMA with several advantages compared to exogenous gene replacement.

About the Speaker

Dr. Christiano Alves is a junior faculty in the Department of Neurology and in the Center for Genomic Medicine at Massachusetts General Hospital (MGH) and Harvard Medical School, interested in the convergence between genome editing and applied physiology to make an impact on human health. His current research efforts focus on the development of genome editing technologies to treat muscular and neuromuscular diseases. Dr. Alves holds a Ph.D. in muscle physiology from the University of Sao Paulo, Brazil, with an internship at the Norwegian University of Science and Technology (NTNU), Norway. Before joining the Kleinstiver lab at MGH, he was a postdoctoral research fellow at Joslin Diabetes Center, Harvard Medical School (2017-2018), and at the Center for Genomic Medicine, MGH (2018-2021).

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All are welcome!