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## **Immunomodulatory properties of human MuStem cells: assessing their impact on adaptive and innate immunity**

Judith Lorant, Nicolas Jaulin, Isabelle Leroux, Cindy Schleder, Céline Zuber,  
Marine Charrier, Blandine Lieubeau-Teillet, Yann Péréon, Armelle Magot,  
Antoine Hamel, et al.

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Lowering cardiac G protein-coupled receptor kinase-2 (GRK2) activity with bARKct expression, a peptide inhibitor of GRK2, has resulted in improvement of heart failure in several different animal models. Therefore, we investigated whether bARKct gene delivery using adeno-associated virus type 9 (AAV9), a more specific approach in preventing desensitization of the G protein-coupled receptor by displacing GRK2 from the plasma membrane than beta-blockers, could ameliorate development of cardiomyopathy in mdx and Sgcd<sup>-/-</sup> mice. We found that long-term treatment with AAV9- bARKct-cDNA with a cardiac-specific promoter could significantly improve left ventricular systolic function and ameliorate myocardial hypertrophy in mdx mice, whereas beneficial effects on cardiac function in Sgcd<sup>-/-</sup> mice were mild without protection from hypertrophy. Interestingly, in contrast to mdx mice neither GRK2 nor nuclear factor-kappaB (NFj B) were upregulated in Sgcd<sup>-/-</sup> mice, indicating the existence of distinct pathogenic mechanisms in these cardiomyopathic mouse models. Taken together, effectiveness of AAV-mediated bARKct therapy may vary between different genetic causes and presumably dependent on the state of adrenergic dysregulation mediated through the upregulation of GRK2.

## OR010

Therapeutic angiogenesis: novel insights in the mechanism of action of FGF-4

G M Rubanyi C Basilio

1: Angionetics Inc. 2: New York University, School of Medicine

Generx (Ad5FGF-4) is currently in Phase 3 clinical trial as a therapeutic angiogenesis product candidate for the treatment of patients with refractory angina. Experiments were performed in cultured cells to explore whether FGF-4 is capable to interact with the adenoviral vector and endogenous VEGF. The potential interaction with the Ad5 vector was tested in cultured RCS chondrocytes and 3T3 fibroblasts. Ad5GFP (M.O.I. 10vp/cell) was added to the cells, which were treated 24 hours later by FGF-4 (10ng/ml). FGF-4 stimulated gene expression 5-10 fold (GFP fluorescence and Western blot) in both RCS (growth inhibition) and 3T3 cells (growth promotion). This novel observation suggests a positive interaction between the Ad5 vector and the transgene of Generx, potentially leading to increased extent and duration of gene expression after Ad5FGF-4 administration. The interaction between FGF-4 and endogenous VEGF was studied in a co-culture system of human dermal fibroblasts (HDF) and human umbilical vein endothelial cells (HUVEC). FGF-4 (1-8 ng/ml) stimulated new vascular network formation, including tube elongation and branching, which was significantly inhibited by both anti-VEGF (4 ug/ml) and anti-VEGFR2 (30 ug/ml) antibodies. FGF-4 stimulated the release of VEGF from HDF, but not from HUVEC. These results demonstrate that FGF-4 stimulates the release of VEGF from non-endothelial cells and FGF-4 and VEGF act synergistically on endothelial cells in the formation of new vascular structures.

## OR011

Immunomodulatory properties of human MuStem cells: assessing their impact on adaptive and innate immunity

J Lorant<sup>1 2 3</sup> N Jaulin<sup>3 4</sup> I Leroux<sup>1 2 3</sup> C Schleder<sup>1 2 3</sup> C Zuber<sup>1 2 3</sup>  
M Charrier<sup>1 2 3</sup> B Lieubeau<sup>5</sup> Y Péréon<sup>6</sup> A Magot<sup>6</sup> A Hamel<sup>7</sup>  
O Adjali<sup>3 4</sup> K Rouger<sup>1 2 3</sup>

1: INRA UMR703 PAnTher, F-44307 Nantes, France  
2: LUNAM Université, Oniris, École nationale vétérinaire, agro-alimentaire et de l'alimentation Nantes-Atlantique, Nantes, F-44307, France  
3: Atlantic Gene Therapies, F-44000 Nantes, France  
4: INSERM UMR1089, Nantes University Hospital, F-44000 Nantes, France  
5: INRA, USC 707 Université, EA 4644 IECM, Nantes, F-44307, France  
6: Centre de Référence des maladies neuromusculaires rares Nantes-Angers, Service des Explorations Fonctionnelles, Centre Hospitalier Universitaire Hôtel-Dieu, Nantes, F-44093, France  
7: Service de Chirurgie Infantile, Centre Hospitalier Universitaire Hôtel-Dieu, Nantes, F-44093, France

Several preclinical approaches based on allogeneic stem cell delivery were shown to be attractive for the treatment of genetic muscular dystrophies. Nevertheless, a significant hurdle for their clinical translation is the immune rejection of donor cells. Immunosuppressive regimens are generally used to overcome host immunity and can allow the improvement of graft survival. Nevertheless, they are associated with a number of side effects, limiting their long term use. Recently, some tissue-specific adult stem cell populations were described to exhibit immunomodulatory properties that could increase their ability to engraft in an allogeneic recipient and improve their regenerative potential. We have previously demonstrated that allogeneic muscle-derived delayed adherent stem cells (that we called MuStem cells) are able to phenotypically and clinically correct the Duchenne dystrophic canine model (Rouger et al., 2011; Robriquet et al., 2015). Recently, we isolated human MuStem cells and assessed their immunomodulatory potential. We evaluated their ability to inhibit T cell proliferation and to modulate the complement pathway. Interestingly, our preliminary data showed that human MuStem cells were able to modulate allogeneic T cell proliferation and to express immunomodulatory molecules such as prostaglandin-E2, indoleamin-2,3-deoxygenase-1 and TGFb2. Moreover, MuStem cells were also able to secrete Factor H molecule suggesting a potential effect on the alternate pathway of the complement system. Overall, our study is critical for the understanding of the crosstalk between MuStem cells and the immune system, as well as the design of safe and efficient allogeneic stem cell-based therapy for the treatment of muscle dystrophies.

## OR012

Targeted genome editing in human long-term repopulating hematopoietic stem cells for the correction of SCID-X1

P Genovese<sup>1</sup> G Schirotti<sup>1 2</sup> A Conway<sup>3</sup> D Guschin<sup>3</sup> G Escobar<sup>1 2</sup>  
T Di Tomaso<sup>1</sup> V Marin<sup>4</sup> E Giuliani<sup>4</sup> C Firrito<sup>1</sup> P D Gregory<sup>3</sup>  
M C Holmes<sup>3</sup> B Gentner<sup>1</sup> C Bovolenta<sup>4</sup> G J Cost<sup>3</sup> A Lombardo<sup>1 2</sup>  
L Naldini<sup>1 2</sup>

1: San Raffaele Telethon Institute for Gene Therapy (HSR-TIGET) 2: Vita-Salute San Raffaele University  
3: Sangamo BioSciences, Inc. 4: MolMed S.p.A.

Targeted genome editing has brought gene correction within the reach of gene therapy. We recently showed that gene targeting in the most primitive hematopoietic stem/progenitor cells (HSPC) is constrained by gene transfer efficiency and a bias against the use of homology directed repair. By combining Integrase Defective Lentiviral Vectors (IDLV) for donor template delivery and mRNA transfection for ZFN expression and