IMMOBILIZATION COMBINED WITH CALORIC RESTRICTION AS TRANSLATIONAL MOUSE MODEL FOR SARCOPENIA EXPRESSING KEY PATHWAYS OF HUMAN PATHOLOGY

Jelle C.B.C. de Jong[1,2], Lars Verschuren[3], Martien P.M. Caspers[3], Nanda Keijzer[1], Nicole Worms[1], Joline Attema[1], Christa de Ruiter[1], Simone van der Drift-Droog[1], Arie G. Nieuwenhuizen[2], Jaap Keijer[2], Aswin L. Menke[1], Robert Kleemann[1] and Anita M. van den Hoek[1]

1. Department of Metabolic Health Research, The Netherlands Organization for Applied Scientific Research (TNO), Leiden, The Netherlands
2. Human and Animal Physiology, Wageningen University, Wageningen, the Netherlands
3. Department of Microbiology and Systems Biology, The Netherlands Organization for Applied Scientific Research (TNO), Zeist, The Netherlands

TNO innovation for life

J.dejong@tno.nl

INTRODUCTION

- The prevalence of sarcopenia is increasing, and effective interventions are required to prevent or reverse age-related muscle loss. However, it often is challenging, expensive and time-consuming to develop and test the effectiveness of such interventions and translational animal models that are adequately mimicking the underlying physiological pathways of sarcopenia are scarce.
- Malnutrition and a sedentary lifestyle are strong predictors for the incidence of sarcopenia and possibly (de-)activate pathways underlying sarcopenia.

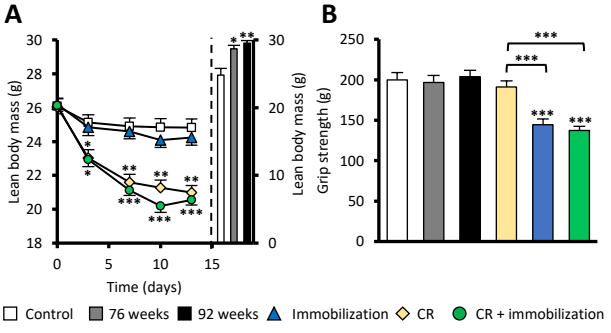
AIM

To investigate the translatability of three potential mouse models, in which sarcopenia was modelled by means of caloric restriction (CR) to mimic malnutrition, immobilization to mimic a sedentary lifestyle, or a combination (CR & immobilization) thereof.

METHODS

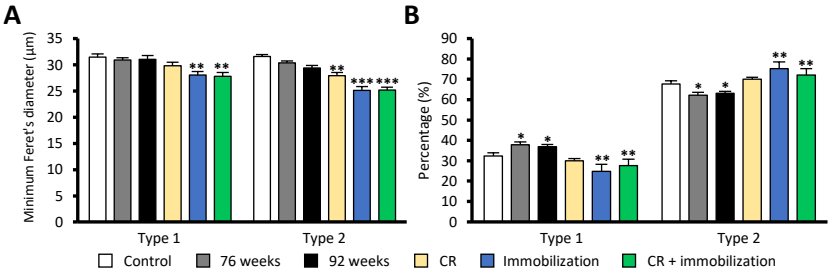
- C57BL/6J mice were calorically restricted (40%) and/or one hindleg was taped and immobilized for two weeks to induce muscle atrophy.
- Muscle mass, function and fiber type composition and type 1 and 2 myofiber diameters were compared to those of age-matched control (16 weeks) and aged mice (76 and 92 weeks).
- Transcriptome analysis of *quadriceps* muscle was performed to identify the underlying pathways and were compared with those of human aged *vastus lateralis* muscle biopsies using five different human studies.

CALORIC RESTRICTION INDUCES LOSS OF LEAN BODY MASS AND IMMOBILIZATION LOSS OF MUSCLE STRENGTH



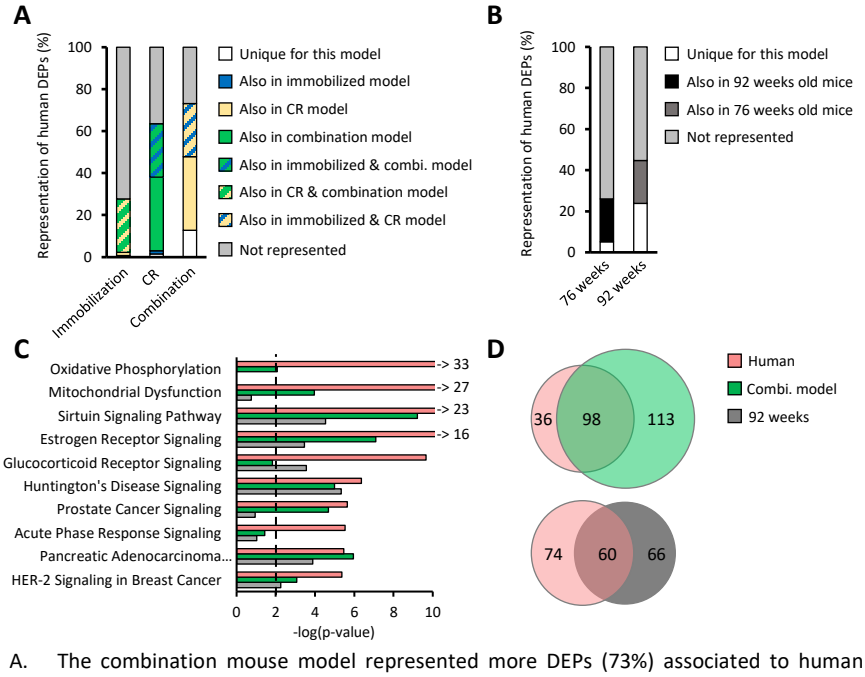
A. Total lean body mass decreased in models exposed to CR and did not change in immobilized mice. In aged mice, total lean mass was increased compared to control mice.
B. Grip strength decreased in models exposed to immobilization and did not change in aged mice or the CR group.

MOUSE MODELS RECAPITULATE TYPE 2 MYOFIBER ATROPHY AND DISPLAY LOSS OF TYPE 1 MYOFIBERS



A. Diameter of type 2 myofibers decreased with ageing and in all other models. Diameter of type 1 myofibers decreased in models exposed to immobilisation and was not decreased in aged models.
B. Percentage of type 2 myofibers decreased with ageing and increased in models exposed to immobilisation.

THE COMBINATION MODEL RECAPITULATES MORE PATHWAYS OF HUMAN MUSCLE-AGEING THAN THE AGED MODEL



A. The combination mouse model represented more DEPs (73%) associated to human muscle-ageing than the single-immobilisation (28%) or CR treatment (63%).
B. The aged mouse models represented less human DEPs (45%) compared to the combination model (73%).
C. Top 10 regulated pathways reveal lack of regulation of mitochondrial pathways in aged models in comparison to the combination model.
D. Venn-diagrams comparing overlap of combination and aged model with human DEPs.

CONCLUSIONS

We demonstrate that a two-week period of CR is an effective way to induce muscle atrophy, while immobilization is required to induce loss of muscle strength as well. The combination model exhibited loss of both muscle mass and function and illustrated substantial similarity with the pathways underlying human sarcopenia. We conclude that the combination model can be a suitable model for testing the effectiveness of muscle-ageing related interventions.

Acknowledgements: dietician Berbée, Calico Life sciences, HistoIndex and InHolland University of Applied Sciences