ANNOUNCEMENT OF FINAL ORAL EXAMINATION
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

CANDIDATE: Nicolae Sandor

DEPARTMENT OR PROGRAM: Molecular and Translational Medicine, Cell & Molecular Biology

TITLE OF DISSERTATION: “A Murine Model of Glucocorticoid Myopathy and Alleviation Using Androgen Therapy”

DATE, TIME, AND PLACE: Monday, July 13, 2015 at 11:00 a.m.
Boston University School of Medicine
72 E. Concord Street (Room L 210)
Boston, MA 02118

EXAMINING COMMITTEE

FIRST READER: Dr. Monty Montano
SECOND READER: Dr. Shalender Bhasin
THIRD READER:
CHAIRMAN OF THE EXAMINING COMMITTEE: Dr. Caroline Apovian Email: capovian@bu.edu

ADDITIONAL COMMITTEE MEMBERS: Dr. Konstantin Kandror
Dr. Isabel Dominguez

Members of the committee are asked to confirm attendance by replying directly to the Chairman of the Examining Committee.

ALL MEMBERS OF THE SCHOOL OF MEDICINE FACULTY ARE INVITED TO ATTEND.
A MURINE MODEL OF GLUCOCORTICOID MYOPATHY ALLEVIATION USING ANDROGEN THERAPY

NICOLAE LUCIAN SANDOR

Boston University School of Medicine, 2015

Major Professor: Monty Montano, Ph.D., Assistant Professor of Medicine

ABSTRACT

Glucocorticoids (GC) are used widely for the treatment of a large number of inflammatory conditions. A loss in muscle mass and increases in muscle weakness are common complications of GC therapy. Androgen therapy has been suggested to reverse GC-associated muscle loss (GAML), but evidence of its effectiveness is inconsistent. Herein, I established a mouse model of GAML. Young adult male mice receiving 0.25 mg/kg/day of the GC dexamethasone (D) s.c. daily, for a week, lost 3% of their total body weight. Based on NMR lean body mass quantification and muscle dissection, more than 10% of their muscle mass was lost. More than half of the D-induced muscle loss could be reversed by co-administration of 0.7 mg/kg/day of testosterone (T). To my knowledge, this is the first mouse model of GAML demonstrating alleviation by T.

D-upregulated intramuscular atrogene expression and proteasome catalytic activity were suppressed by T co-administration. D downregulated cathepsin L enzymatic activity and beclin expression, indicating that lysosome was not a major effector of GAML. Changes in calpain 1 and in translation factors 4E-BP, eIF3f and eIF2, following T treatment, were inconclusive. The changes in proteasome activity and atrogene
expression were correlated with changes in expression of Foxo 1, 3a, and 4. Pro-catabolic factors REDD1 and Klf15 were repressed by T co-administration.

C2C12 differentiated myotubes were used to model GAML in vitro. Myotube diameter and total protein were reduced by D, and restored by T co-administration. Changes in C2C12 total protein were correlated with changes in protein degradation. D-induced proteolysis was inhibited by the proteasome inhibitor MG132.

In vivo, D reduced intramuscular IGF-I expression, an effect reversed by T co-administration. In C2C12, inhibition of IGF-1R signaling with picropodophyllin did not modify T protective effect. Mechanisms potentially explaining these observations are discussed.

In summary, my model demonstrates that T protective effect in GAML is mainly anti-catabolic, through the reversal of proteasome upregulation induced by D. In vivo, T stimulates a potentially protective intramuscular IGF-I response. The roles of protein synthesis and IGF-I in anabolic myoprotection could not be addressed in these models, and require further investigations.