Abstract citation ID: bvac150.1829

Tumor Biology

PMON51

A Single Multipurpose FSH–Blocking Therapeutic for Osteoporosis, Obesity and Alzheimer's Disease

Funda Korkmaz, MD, Tan-Chun Kuo, MS., Sakshi Gera, PhD, Damini Sant, PhD, Victoria DeMambro, PhD, Anisa Gumerova, MD,PhD, Kathayani Sudha, MD, Ashley Padilla, MS, Jessica Netto, BS, Farhath Sultana, PhD, Sari Miyashita, PhD, Eleanor Shelly, BS, Pushkar Kumar, MD, Jocoll Burgess, PhD, Hasni Kannangara, MS, Valeriia Muradova, MD, Susan Hutchison, BS, Mansi Saxena, PhD, Vitaly Ryu, PhD, Se-Min Kim, MD, Marcia Meseck, MS, JD, Ki Goosens, PhD, Cliff Rosen, MD, Daria Lizneva, MD, PhD, Tony Yuen, PhD, and Mone Zaidi, MD, PhD

Pharmacological and genetic studies over the past decade suggest that FSH is an actionable target for diseases affecting millions, notably osteoporosis, obesity and Alzheimer's disease (AD). Blocking FSH action prevents bone loss (1, 2), fat and energy metabolism (3) and AD–like features in mice (4). We recently developed a first–in–class, humanized, epitope–specific FSH blocking antibody that binds to a 13–amino–acid–long sequence of FSHβ—"MS-Hu6"—with a KD of 7.52 nM (5). We showed that MS-Hu6 bound specifically to FSHβ and its different glycosylated forms, namely FSHβ21/18 and FSHβ^{24}, without binding to LH and TSH. Here, using a GLP–compliant platform, we report the efficacy of MS-Hu6 in preventing obesity, osteoporosis and AD in mice. Notably, MS-Hu6-treated mice showed lower body weight and fat mass, increased lean mass (qNMR) and evidence of beiging in ThermoMice (IVIS

imaging) compared with IgG–treated mice. Consistent with this, the thermogenic genes Ucp1 and Cidea were upregulated, whereas Pparg expression was attenuated in fat depots. Treatment of ThermoMice for 8 weeks also increased bone mineral density (BMD), improved microstructure (micro-CT), elevated bone formation (dynamic histomorphometry), and upregulated the osteoblastic genes Alp and Col1a1. The increase in bone mass and improved microstructure were replicated in C.J.R's lab using female mice 24 weeks post–ovariectomy. Preliminary testing using AD mice, namely APP/PS1 mice, showed that MS-Hu6 prevented the impairment in recognition and contextual memory. Biodistribution studies using 89Zr–labelled, biotinylated or unconjugated MS-Hu6 in mice and monkeys showed localization to bone, bone marrow and fat depots. MS-Hu6 displayed a β phase t½ of 13 days (316 hours) in humanized Tg32 mice, and bound endogenous FSH. In monkeys, an acute single injection of MS-Hu6 did not affect vitals, and biochemical parameters remained within the normative range. We tested 215 variations of excipients using the protein thermal shift assay to generate a final formulation that rendered MS-Hu6 stable in solution upon freeze–thaw and at different temperatures, with minimal aggregation, and without self–, cross–, or hydrophobic interactions or appreciable binding to relevant human antigens. MS-Hu6 showed the same level of "humanness" as human IgG1 in silico, and was non–immunogenic in ELISPOT assays for IL-2 and IFNγ in human peripheral blood mononuclear cell cultures. In conclusion, MS-Hu6 is efficacious, durable and manufacturable, and is therefore poised for future human testing as a multipurpose therapeutic for obesity, osteoporosis, and perhaps for AD.References: [1]Sun et al., Cell, 2006, PMID: 16630814; Ji et al, PNAS, 2018, PMID: 29440419; [3]Liu et al., Nature, 2017, PMID: 28538730; [4]Xiong et al., Nature (In press); [5]Gera et al., PNAS, 2020, PMID: 33127753

Presentation: Monday, June 13, 2022 12:30 p.m. - 2:30 p.m.