Symposium 4

International Collaboration 1

Chairpersons

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The Catholic University of Korea, Korea

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Speakers

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Michael A. Nauck
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Gary Sweeney
York University, Canada

Sae Won Kim
ProGen Co. Ltd., Korea

Michael D. Jensen

Mayo College of Medicine, USA

Education

Period	Affiliation	Position
– **1982-1985**	Mayo Graduate School of Medicine	Fellow
– **1980-1982**	Mayo Graduate School of Medicine	Resident
– **1980**	St. Luke's Hospital of Kansas City	Resident
– **1979**	U.M.K.C. School of Medicine	Medical Student

Affiliations / Experience

Period	Affiliation	Position
– **1985-Present**	Mayo Clinic	Consultant

Committee Memberships

- North American Association for the Study of Obesity/The Obesity Society
- American Society for Nutrition
- NIH Integrative Physiology of Obesity and Diabetes Study Section
- NIH Clinical and Integrative Diabetes and Obesity
- NHLBI Expert Panel to Update the Report on the Identification, Evaluation and Treatment of Overweight and Obesity in Adults
- NIDDK DDK-E, beginning October

Publications

- Jensen MD, Haymond MW, Rizza RA, Cryer PE, Miles JM: Influence of body fat distribution on free fatty acid metabolism in obesity. J. Clin. *Invest*. 83:1168-1173
- Jensen MD: Gender differences in regional fatty acid metabolism before and after meal ingestion. J. Clin. *Invest*. 96:2297-2303
- Levine JA, Eberhardt NL, Jensen MD. Role of Non-exercise Activity Thermogenesis (NEAT) in Resistance to Fat Gain in Humans. *Science* 283: 212-214
- Nielsen S, Guo ZK, Johnson CM, Hensrud DD, Jensen MD. Splanchnic Lipolysis in Human Obesity. J. Clin. Invest. 113: 1582 - 1588
- Tchoukalova, Y, Votruba, SB, Tchkonia, T, Giorgadze, N, Kirkland, JL, Jensen, MD. Regional differences in cellular mechanisms of adipose tissue gain with overfeeding. *PNAS* 107(42):18226-31

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Sex Differences in Adipose Tissue Metabolism as It Relates to Risk of Diabetes

Michael D. Jensen (Mayo College of Medicine, USA)

From an epidemiological perspective, it is know that there are differences in insulin resistance, diabetes and CVD risk betweem males and females. Because obesity is a common denominatory risk factor, it is important to understand how adiposity difference between adult males and females. There are major sex differences in body composition/cellularity, and this is accompanied by significant sex differences in adipose tissue fatty acid release as well as adipose tissue fatty acid storage. Women have more body fat and more adipocytes than men at any given BMI.

Insuln resistance is a well-recognized risk factor for diabetes, but it is important to recognize that there are different measures of insulin resistance for different tissues. HOMA-IR, which is a composit of insulin and glucose concentrations, estimates whole body insulin resistance with respect to glucose metabolism. A low value indicates the individual is more insulin sensitive with respect to glucose metabolism. ADIPO-IR is a measure of adipose tissue insulin resistance with regards to lipolysis – it is the product of insulin and FFA concentrations; again, a low value indicates the individual is more insulin sensitive with respect to adipose tissue lipolysis. Except for plasma glucose concentrations, which statisticallys speaking cannot be employed as a predictor of diabetes, insulin resistance with respect to glucose metabolism (HOMA-IR) the best predictor of future Type 2 Diabetes. After adjusting for age, sex, family history of diabetes, ethnicity, physical activity, and smoking status, greater baseline ADIPO-IR predicts a greater risk of incident dysglycemia. Of interest, the normal values for ADIPO-IR are different in adult males and females.

The issue of insulin resistance, and the sex differences surrounding it, is important because diabetes is more prevalent in men than in women, especially in middle-aged populations. Peak in diabetes prevalence occurs age 65-69 in men and 70–79 years of age in women. Women with diabetes have a greater relative cardiovascular disease risk than men with diabetes. Could this relate to the issue of lipotoxicity? It is known that fatty acids act as both a fuel for cells and as signaling molecules. Fatty acids in the circulation can arise from adipose tissue (FFA), from meals (chylomicrons) and in the form of lipoproteins (VLDL). Women have greater FFA release relative to energy needs, but very modestly greater plasma FFA concentrations. Both men and women with upper body/visceral obesity (which is more common in men) typically have subnormal suppression of FFA after meals; this can cause insulin resistance in other tissues via lipotoxicity. It has been reported that greater postprandial chylomicronemia are a risk factor for metabolic diseases and adipose a main site for meal fatty acid storage. There are differences in the adipose depot storage of both meal fatty acids and FFA, with women havning greater storage capacity than men, e.g. the efficiency of meal fat storage in subcutaneous fat is greater in women men. There are interesting adipose depot meal fat storage differences between the sexes, also. The greater clearance of chylomicrons by adipose tissue in women maintains lower postprandial triglyceride concentrations, which likely protects lean tissue from potentially lipotoxic effects of meal-derived fatty acids. We've also found that the efficiency of FFA storage in subcutaneous fat in women is greater than men.

This greater recycling of FFA back into adipose tissue allows increase lipolysis in women without as much of an increase in FFA concentrations. In summary, fat storage capacity is greater in women than men, probably related to both more body fat, greater numbers of adipocytes and (in leg fat) greater lipogenic machinery per adipocyte. Compared with men, adipose tissue in women appears to sequester fatty acids and serves as "overflow" storage site for non-oxidized fatty acids, serving to protect lean tissue.

Michael A. Nauck

Ruhr-University Bochum, Germany

Education

Period	Affiliation	Position
– **1975-1980**	University Freiburg	M.S
– **1973-1975**	Heinrich Heine University Düsseldorf	M.S

Affiliations / Experience

Period	Affiliation	Position
– **2015-Present**	Head of Clinical Research, Ruhr-University Bochum, St. Josef-Hospital	Research Position
– **2000-2015**	Diabetes Centre Bad Lauterberg	Head Physician
– **1993-2000**	Ruhr-University Bochum, Knappschafts-Krankenhaus	Consultant
– **1981-1993**	University Göttingen, Gastroenterology and Endocrinology	Physician in Training
– **1980-1981**	University Göttingen, Biochemisty	Scientist

Committee Memberships

- ADA/EASD Guideline Writing Group
- Working Group (ADA/EASD/Diabetes UK/ Endocrine Society) Diabetes Remission

Publications

- Drucker DJ, Nauck MA. The incretin system: glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase-4 inhibitors in type 2 diabetes. *Lancet*. 368:1696-705
- Nauck M, Stöckmann F, Ebert R, Creutzfeldt W. Reduced incretin effect in Type 2 (non-insulin-dependent) diabetes. *Diabetologia*. 29:46-54
- Nauck MA, Heimesaat MM, Ørskov C, Holst JJ, Ebert R, Creutzfeldt W. Preserved incretin activity of glucagon-like peptide 1 [7-36 amide] but not of synthetic human gastric inhibitory polypeptide in patients with type-2 diabetes mellitus. J Clin Invest. 91(1):301-7
- Nauck MA, Kleine N, Ørskov C, Holst JJ, Willms B, Creutzfeldt W. Normalization of fasting hyperglycaemia by exogenous glucagon-like peptide 1 (7-36 amide) in type 2 (non-insulin-dependent) diabetic patients. *Diabetologia*. 36(8):741-4
- Nauck MA, Müller TD. Incretin hormones and type 2 diabetes. *Diabetologia*

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The Role of GIP/or Glucagon Receptor Agonism in the Treatment of Obesity

Michael A. Nauck (Ruhr-University Bochum, Germany)

In recent years, GLP-1 receptor agonists (GLP-1 RA) have been characterized as highly effective weight loss agents for subjects with and without diabetes mellitus, and liraglutide, as well as semaglutide have been approved for the treatment of obesity. Currently, dual or triple agonists not only activating GLP-1 receptor agonists are under development or even have been approved (the dual GIP/GLP-1 receptor agonists tirzepatide). What is the contribution of stimulating GIP or glucagon receptors in addition to those for GLP-1?

In rodent animals, intracerebroventicular and peripheral administration of long-acting GIP agonists (not of the native GIP molecule) reduce food (energy) intake and body weight in animals expressing a functional GIP receptor (not in those without), indicating that GIP reduces body weight in a receptor-dependent manner. This is in contrast to the earlier findings that GIP receptor knock-out mice are protected from weight gain induced by high-fat feeding, indicating an obesogenic role for GIP. Along these lines, genetic studies indicate lower body weight in those with loss-of-function polymorphisms of the GIP receptor. In human studies, exogenous administration of GIP did not reduce ad libitum energy intake, a robust effect observed with GLP-1. Rather, the reduction in energy intake observed with GLP-1 alone was in part counteracted by the additional administration of GIP. To complicate matters more, GIP receptor antagonists have led to weight reduction in animal studies, especially in combination with GLP-1 receptor agonists. At present, it seems to be difficult to come up with firm conclusions regarding the role of GIP in regulating body weight in human subjects. GIP receptor agonism may mitigate nausea and vomiting elicited by GLP-1 RAs due to central nervous mechanisms.

Stimulation of the glucagon receptor has some limited effects reducing appetite and food intake, but also leads to increased energy expenditure. For subjects with diabetes mellitus, glucagon receptor agonism had been thought to potentially lead to deleterious rises in glycaemia. However, recent findings suggest intra-islet elevations of glucagon may stimulate insulin secretion and help lower plasma glucose.

As a consequence, dual agonists interacting with GLP-1 and glucagon receptors (e.g., survodutide) appear to provide more weight loss than selective GLP-1 receptor agonists do.

The GIP/GLP-1/glucagon triple receptor agonist retatrutide elicits the greatest weight loss (compared to single and dual agonists), and in animal experiments retatrutide-induced weight loss is not accompanied by a reduction in energy expenditure like weight loss associated with caloric restriction.

Gary Sweeney

York University, Canada

Education

Period	Affiliation	Position
– **1994**	University of Glasgow	Ph.D.
– **1990**	University of Glasgow	B.Sc

Affiliations / Experience

Period	Affiliation	Position
– **2001-Present**	York University Toronto	Professor
– **1996**	Hospital for Sick Children Toronto	Fellow

Committee Memberships

- Faculty search committee
- Innovation & Partnerships Working Group
- Heart & Stroke Foundation of Canada
- Canadian Institutes of Health Research

Publications

- *Molecular Metabolism* (2024) May;83:101921
- *Clinical and Translational Science* 2024 Mar;17(3):e13758
- *Diabetes* (2021) 70(1):51-61
- *EMBO Reports* (2019) 20(10):e47911
- *Proc Natl Acad Sci U S A.* 2018 115(7):1576-1581

Symposium 4

Treatment of Metabolic Syndrome Complications with Adiponectin Therapeutics

Gary Sweeney (York University, Canada)

A strong negative correlation between circulating adiponectin levels and cardiometabolic diseases has been well-documented. Research has shown that adiponectin has cardioprotective, insulin sensitizing and direct beneficial metabolic effects. Thus, therapeutic approaches to enhance adiponectin action are widely considered to be desirable and adiponectin mimetic drug discovery projects have been incorporated in pipelines of major pharma in recent years. The complexity of adiponectin structure and function means that recombinant adiponecitn itself is less than ideal as a therapeutic. This lecture will review our research on the physiological effects and molecular mechanisms of action of adiponectin in cardiometabolic tissues. Scenarios where enhancing adiponectin action would be of most clinical value will be reviewed. Recent progress on discovery of adiponectin-based therapeutics will be summarized and recent data to test the effects of the peptide ALY688 in cellular and preclinical animal models will be presented. Preliminary data indicate that ALY688, which will enter phase I clinical trials soon, is a promising new drug candidate for use in cardiometabolic disease and beyond.

Keywords: adiponectin, metabolism, signal transduction, autophagy, therapeutic.

Sae Won Kim

ProGen Co. Ltd., Korea

• Education

Period	Affiliation	Position
– **2007-2014**	Pohang University of Science and Technology (POSTECH)	Ph.D.
– **2003-2007**	Johns Hopkins University	B.S.

• Affiliations / Experience

Period	Affiliation	Position
– **2023-Present**	ProGen Co., Ltd.	Director
– **2023-Present**	Yonsei University, College of Medicine	Adjunct Professor
– **2023-2023**	SL MetaGen, Inc.	Chief Business Officer
– **2014-2023**	SL BiGen, Inc.	Chief Scientist

• Publications

– Hwang I, Jin HT, Kang MC, Kim TY, Sung YC, Kim SW. Generation and functional characterization of a multigene-modified NK101 cell line exerting diverse mechanisms of antitumor action. *OncoImmunology* 2022;11(1):2014655

– Kim SW, Park HW, Kim H, Lee S, Choi SY, Park Y, Lee SW. Evaluating Antitumor Activity of Kiatomab by Targeting Cancer Stem Cell-Specific KIAA1114 Antigen in Mice. *Immune Network* 2019 Nov 19;19(6):e43

– Yang HG, Kang MC, Kim TY, Hwang I, Jin HT, Sung YC, Eom KS, Kim SW. Discovery of a novel natural killer cell line with distinct immunostimulatory and proliferative potential as an alternative platform for cancer immunotherapy. *Journal for ImmunoTherapy of Cancer* 2019; 7(1):138

– Kim SW, Yang HG, Kang MC, Lee S, Namkoong H, Lee SW, Sung YC. KIAA1114, a full-length protein encoded by the trophinin gene, is a novel surface marker for isolating tumor-initiating cells of multiple hepatocellular carcinoma subtypes. *Oncotarget* 2014; 5(5):1226-40

– Kim SW, Kim SJ, Park SH, Yang HG, Kang MC, Choi YW, Kim SM, Jeun SS, Sung YC. Complete regression of metastatic renal cell carcinoma by multiple injections of engineered mesenchymal stem cells expressing dodecameric TRAIL and HSV-TK. *Clinical Cancer Research* 2013; 19(2):415-27

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PG-102, a Bispecific GLP-1/GLP-2 Receptor Agonist for the Treatment of Obesity and Type 2 Diabetes

Sae Won Kim (ProGen Co. Ltd., Korea)

PG-102 is a first-in-class, 'heterodimeric' Fc-fusion protein dual agonist targeting GLP-1R and GLP-2R simultaneously. PG-102 has an experimentally optimized receptor potency balance with GLP-1-favored agonism suitable for obesity and type 2 diabetes (T2D) treatment and GLP-2, albeit with weaker activity, sufficient to reduce intestinal permeability and (gut-derived) chronic low-grade inflammation.

PG-102 is currently being investigated in phase 1b multiple ascending dose trial in Korea and has shown following benefits to date: (i) less frequent dosing; (ii) favorable safety and tolerability profile; (iii) avoidance of lean mass loss (in obesity); (iv) outstanding glucose-lowering effects (in T2D); and (v) amelioration of metabolic endotoxemia. First, the phase 1a single-ascending dose (SAD) trial investigating PG-102 in healthy volunteers revealed distinct pharmacokinetic (PK) profile with delayed Tmax (72-96 hours) and high area under the curve (AUClast). PK modeling projected potential for monthly dosing, proposing its capacity to increase patient compliance and adherence. Second, PG-102 demonstrated favorable safety and tolerability profile, as shown by lower incidence of gastrointestinal side effects compared to competing drugs in similar clinical settings (phase 1a in healthy volunteers). Third, in the preclinical model of diet-induced obese (DIO) mice, PG-102 exhibited more fat mass loss and less lean mass loss than semaglutide, while inducing similar degree of body weight loss. Of note, increasing PG-102 dose resulted in greater reductions in fat mass, but lean mass remained unchanged. Fourth, in obese, diabetic db/db mice, PG-102 exerted superior glucose-lowering effects than semaglutide, tirzepatide and retatrutide, due to its stronger capacity to protect pancreatic beta cells and enhance glucose uptake. Lastly, in both DIO and STAMTM mouse models (for metabolic dysfunction-associated steatohepatitis), PG-102 treatment lowered serum LPS and liver enzyme (ALT or AST) levels by increasing intestinal permeability. These results suggest PG-102 can control low-grade systemic inflammation which drives various types of metabolic comorbidities.

Based on above-mentioned patient-centric and efficacy-focused benefits, we believe that PG-102 can gain a footing in the highly competitive GLP-1 receptor agonist market. ProGen plans to further explore safety, tolerability and clinical efficacy of PG-102 in upcoming phase 2 obesity and type 2 diabetes trials.