Executive Highlights

This document contains our coverage of novel therapies at ADA 2016. Immediately below, we enclose our themes on the category, followed by detailed discussion and commentary. Talk titles highlighted in yellow were among our favorites from ADA 2016; those highlighted in blue are new full report additions from our daily coverage.

Themes

- **It is becoming increasingly clear that future type 2 diabetes drugs will need to offer additional benefits beyond glucose lowering to be successful.** We can even imagine a future in which new type 2 diabetes drugs will have to demonstrate a positive effect on cardiovascular and/or renal outcomes in order to succeed now that two agents in different classes have already done so. We are also encouraged to see interest in evaluating such benefits with older generic drugs like pioglitazone in the IRIS trial and metformin in the planned GLINT trial. Demonstrating benefit in additional indications like obesity, type 1 diabetes, and NASH is potentially another way for type 2 diabetes drug manufacturers to differentiate their products. We saw results of several such efforts at this year's ADA, including data on semaglutide, exenatide/dapagliflozin, and canagliflozin/phentermine in obesity and data on canagliflozin and dapagliflozin in type 1 diabetes. New drug classes like the GLP-1/glucagon dual agonist class promise benefits on weight and other cardiovascular risk factors in addition to reductions in glucose. The bottom line is that we see little room in the current landscape for new drugs that offer nothing more than incremental glucose-lowering benefits, or those (other than insulin) that carry a risk of weight gain or hypoglycemia.
- **We saw a substantial amount of promising new data on GLP-1/glucagon dual agonists in type 2 diabetes and obesity at ADA 2016.** Most notably, we saw expanded phase 1 data for Sanofi's SAR425899, demonstrating significant reductions in weight, "clear" improvements in A1c and fasting plasma glucose, and a similar safety/tolerability profile as GLP-1 single agonists. A phase 1, randomized, blinded study of AstraZeneca's MEDI0382 GLP-1/glucagon receptor dual agonist found that the candidate was well tolerated overall, with reduced postprandial glucose levels and daily food intake at doses of 5, 10, 30, 100, 150, and 300 micrograms. Further, a preclinical study demonstrated that a single subcutaneous dose of MEDI0382 reduced fasting glucose levels by 42%, glucose AUC by 53%, and food intake by 18% in wild type but not GLP-1 receptor KO mice. We were also interested in a poster presentation of new data on the cholesterol-lowering effect of Janssen/Hanmi's phase 1 dual agonist HM12525A. As a class, GLP-1/glucagon dual agonists have generated some of the most buzz and industry investment out of any classes in the early-stage diabetes drug pipeline. Much of the recent Keystone Symposia on Novel Therapeutics for Diabetes and Obesity focused on this class and other polyagonists involving GLP-1 agonists. The promise of a winning combination of glucose-lowering, weight reduction, and even potentially cardioprotection has led several pharmaceutical companies to add these candidates to their early-stage pipelines - see our competitive landscape for more.
- **We heard several key diabetes clinical care experts speak to the importance of treating the right patients with the right medications at the right time.** During the 10th annual TCOYD/The diaTribe Foundation Diabetes Forum, Drs. Steve Edelman (UCSD, San Diego, CA), Rury Holman (University of Oxford, UK), Anne Peters (USC, Los Angeles, CA), Jeremy Pettus (UCSD, San Diego, CA), and John Anderson (The Frist Clinic, Nashville, TN) spoke eloquently on

the need to improve access and adherence to maximize the efficacy of currently available diabetes drugs. As Dr. Edelman put it, "One of the biggest challenges is getting the right drug to the right person. The second big part is getting people to be adherent and persistent and make diabetes higher on their priority list." Dr. Holman suggested that part of the problem is that clinicians don't have all of the information they need to offer truly personalized, tailored therapeutic options to their patients. He suggested enriching the clinical trial process so that trials yield more information useful for personalized therapeutic recommendations. During the ADA meeting itself, the highly respected Dr. Judith Fradkin offered an update on the NIH's plans for rolling out its Precision Medicine Initiative (PMI) Cohort Program and noted that diabetes will be one of the most highly represented conditions in the cohort, with an estimated 135,658 cases at baseline.

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MEDI4166: A PCSK9 AB-GLP-1 FUSION MOLECULE THAT ELICITS ROBUST ANTIDIABETIC AND ANTIHYPERLIPIDEMIC EFFECTS IN RODENTS AND NON-HUMAN PRIMATES (35-LB)

J Trevaskis, A Suckow, T Hummer, M Chodorge, A Celeste, D Hornigold, J Naylor, L Jenkinson, M Feigh, D Fairman, M Agoram, C Lee, S Coats, J Grimsby, C Rondinone, and A Konkar

AstraZeneca presented preclinical data for its PCSK9 inhibitor/GLP-1 agonist combination MEDI4166 demonstrating improvements in glucose, body weight, and LDL cholesterol in rodents and non-human primates. First, MEDI4166 was proven to be an effective GLP-1 agonist based on cAMP production after transfection of Chinese hamster ovary cells with a series of mammalian GLP-1 receptors. Second, ELISA

assays indicated that MEDI4166 inhibited PCSK9 and restored LDL uptake in HepG2 hepatoma cells. Third, single subcutaneous injections of 0.1, 1, and 10 mg/kg MEDI4166 into diet-induced obese (DIO) mice improved glucose tolerance, measured by glucose excursions seven days after the injection. Two- and six-hour fasting blood glucose levels also decreased in a dose-dependent fashion. Repeated weekly injections of either 3, 10, or 30 mg/kg MEDI4166 also reduced body weight of DIO mice over a 28 day period and prevented diabetes progression in db/db mice. Lastly, single injections of either 10 or 100 mg/kg MEDI4166 into healthy male cynomolgus monkeys showed that the higher dosage produced greater reductions in LDL cholesterol. AZ is currently conducting a two-part phase 1/2 trial of MEDI4166 in patients with type 2 diabetes that is expected to complete in November 2016 - see our AZ 1Q16 report for more details. This combination could have enormous potential given how many patients with type 2 diabetes are at high risk for cardiovascular disease, particularly if the GLP-1 agonist and PCSK9 inhibitor classes are eventually both established as cardioprotective.

MEDI0382, A GLP-1-GLUCAGON DUAL AGONIST, MEETS SAFETY AND TOLERABILITY ENDPOINTS IN A SINGLE-DOSE STUDY IN HEALTHY VOLUNTEERS (107-LB)

P Ambery, S Klammt, M Petrone, W Pu, S Dicostanza, L Jermutus, and C Rondinone

This poster presented the findings of a phase 1 randomized, blinded study of GLP-1/glucagon dual agonist MEDI0382, which demonstrated that the candidate met safety and tolerability endpoints. The study was conducted in six cohorts of healthy participants in Germany; each cohort included eight participants, six of whom received one dose each of MEDI0382 at 5, 10, 30, 100, 150, and 300 µg, and two of whom received placebo. Blood pressure, pulse, food intake, and adverse events were monitored for 28 days. At the end of this study period, larger doses of MEDI0382 showed decreases in daily food intake and plasma glucose levels as compared to placebo. Specifically, doses of 30, 100, 150, and 300 µg respectively showed 96%, 82%, 60%, and 23% of daily food intake compared with placebo. Post-meal glucose level peaks decreased in all patients receiving doses of MEDI0382 compared to the placebo. Heart rate over the 28-day observation period did not statistically differ from the pre-dose baseline, except in the 300 µg dosing group. In addition, MEDI0382 was found to be well-tolerated, although vomiting, increased pulse rate, and blood pressure were observed at the higher doses, establishing a tolerability window for future studies in patients with diabetes (doses starting at 100 µg caused episodes of vomiting; 1 patient with 1 total episode of vomiting, 4 patients with 9 episodes, and 5 patients with 30 episodes at 100, 150 and 300 µg of MEDI0382, respectively). Otherwise, gastrointestinal disorders were the major reported adverse event (33.3% of participants). On the pharmacokinetic side, MEDI0382 showed a maximum concentration between 4.5-9 hours, as the data showed to be consistent with a profile indicating once-daily dosing. This candidate remains early in development, but we find this combination approach potentially promising, as it has clear benefits in both glycemic control and weight management. Next question - how cardioprotective or renal protective is it?

A LEUCINE, METFORMIN, AND SILDENAFIL COMBINATION REGRESSES NONALCOHOLIC STEATOHEPATITIS (NASH) IN MICE (260-LB)

M Zemel, A Bruckbauer, and O Flores

NuSirt presented data from a dose-finding study of its leucine/metformin/sildenafil combination in a mouse model of nonalcoholic steatohepatitis (NASH). This study builds on previous work showing that leucine allosterically overexpresses Sirt1, that leucine/metformin combination therapy reverses non-alcoholic fatty liver disease (NAFLD) in mice, and that the triple combination with sildenafil provides even greater efficacy. In this study, mice (n=90) were fed either a low-fat diet (10% calories from fat) or a high fat/ atherogenic diet (1.25% cholesterol by weight and 60% of calories as saturated fat) for eight weeks and then randomized to one of nine treatment groups for an additional eight weeks. Treatment groups included two control groups (low-fat diet and high-fat diet) and seven active treatment groups involving 24 g/kg leucine paired with different doses of metformin (either 0.5 or 1.0 g/kg) and sildenafil (either 12.5, 25, 50 or 100 mg/kg). Treatment with the drug combination resulted in, on average, a 43% reduction in steatosis, a 55% reduction in inflammation, and a 50% reduction in fibrosis after the eight-week treatment period. These data confirmed previous results demonstrating that the appropriate dose for metformin is 0.5 g/kg in mice,

with no additional benefit seen with higher doses. Sildenafil produced dose-dependent effects up to a dose of 25mg/kg, at which point there was no additional benefit. The optimal human equivalent doses were determined to be 2.2 g/day of leucine, ~500 mg/day of metformin and 2mg/day of sildenafil. NuSirt is currently conducting a phase 2a trial of the combination (also referred to as NS-0200) in patients with NAFLD-NASH that is expected to complete in 4Q16; see our interview with management earlier this year for more updates on the company's plans.

ANTIDIABETIC EFFECTS OF NOVEL, LONG-ACTING AMYLIN ANALOGUE ZP4982 IN ZDF RATS (283-LB)

J Skarbaliene and R Just

This study aimed to explore the anti-diabetic impact of Zealand's long-acting amylin analog ZP4982, which improves glycemic control by inhibiting food intake and gastric emptying and suppressing glucagon secretion. Over the course of four weeks, Zucker Diabetic Fatty (ZDF) rats were subcutaneously administered either vehicle, ZP4982 (30 nmol/kg, dosed every fifth day), or liraglutide (40 nmol/kg, dosed twice daily). ZP4982-treated rats showed significantly lower non-fasting blood glucose levels after two weeks and significantly lower non-fasting and fasting blood glucose levels at the end of the study ($p < 0.001$ vs. vehicle for all; p-value vs. liraglutide not given). ZP4982 also resulted in significantly lower A1c levels compared to both vehicle- and liraglutide-treated rats after four weeks ($p<0.001$ vs. vehicle; $p<0.05$ vs. liraglutide). Additionally, ZP4982 significantly increased insulin levels and lowered blood glucose levels during an intra-peritoneal glucose tolerance test ($p < 0.001$ vs. vehicle; p-value vs. liraglutide not given). This is the first data we have seen for this candidate, and we are excited to see continued early-stage activity in diabetes from Zealand despite the company's stated shift toward specialty disease areas. We imagine that weight loss could be a key advantage for this candidate compared to existing type 2 diabetes drugs and look forward to seeing data on this endpoint in future studies.

POTENT CHOLESTEROL LOWERING EFFECT OF THE NOVEL LONG-ACTING GLP-1/ GLUCAGON DUAL AGONIST HM12525A (1026-P)

SY Jung, YJ Park, JS Lee, EJ Kim, YM Lee, YH Kim, M Trautmann, and S Kwon

This poster presented preclinical data suggesting a range of metabolic benefits for Janssen/Hanmi's long-acting once-weekly GLP-1/glucagon dual agonist HM12525A. This study investigated HM12525A's effects on levels of total cholesterol, HDL cholesterol, LDL cholesterol, liver LDL cholesterol receptor expression, serum cholesterol, serum PCSK9, hepatic triglycerides, NAFLD scores, PPAR-α and CPT-1, and ketone bodies in mice, hamsters, and rats. Previously studies had shown that HM12525A produced greater weight loss compared to GLP-1 agonist liraglutide (Novo Nordisk's Victoza). In this study, HM12525A was found to lower serum cholesterol levels, decrease LDL cholesterol levels, and decrease the LDL/HDL ratio more than liraglutide. HM12525A treatment was associated with a 68% reduction in total cholesterol and a 48% reduction in LDL cholesterol, compared to 12% and 2% reductions, respectively, with liraglutide. HM12525A had little effect on increasing HDL cholesterol levels (and we've seen from CETP trials that increasing HDL cholesterol may not translate into positive cardiovascular effects). Mechanism of action studies showed that the use of HM12525A leading to decreases in levels of cholesterol and the LDL/HDL ratio may be attributed to its ability to increase hepatic β-oxidation, decrease the hepatic LDL receptor clearance by decreasing PCSK9 expression, inhibit hepatic cholesterol biosynthesis, and increase HDL cholesterol. These results suggest that HM12525A may have therapeutic potential to treat hyperlipidemia. Combined with previous mouse studies indicating greater reductions for HM12525A vs. liraglutide in terms of A1c (-1.4% vs +1.2%) and body weight (-31% vs. -17%), the efficacy profile of this dual agonist appears particularly promising. The GLP-1/glucagon dual agonist class has been the focus of significant industry interest and investment for some years and we're intrigued by the possibility of a once-weekly drug that can offer a winning combination of A1c, body weight, and cholesterol reductions. We certainly hope these impressive results translate into human studies and into positive effects on cardiovascular outcomes down the line.

LONG-ACTING GLP-1 AND GLUCAGON RECEPTOR DUAL AGONISTS FOR THE TREATMENT OF TYPE 2 DIABETES (1049-P)

S You, M McDonald, M Case, D Steiner, T Tat, C Jenkinson, R Pick, J Hart, V Moreno, J Parise, W Yan, R Camacho, R Swanson, E Chi, K Demarest, and J Leonard

Janssen introduced a new preclinical GLP-1/glucagon dual agonist, JNJ-54728518 candidate in this poster. The candidate is a PEGylated derivative of oxyntomodulin with an increased half-life (18 hours in lean mice) and retained potency for both the GLP-1 and glucagon receptors. Diet-induced obese (DIO) mice treated with JNJ-54728518 were found to be much more tolerant of glucose associated with greater secretion of glucose-dependent insulin. Compared to 10 nmol/kg of GLP-1 agonist liraglutide (Novo Nordisk's Victoza), administration of 10 nmol/kg of JNJ-54728518 produced lower glucose levels (59 vs. 118 mg/dl), lower daily food intake (0.04 vs. 0.07 g/g body weight, more fat loss (12.3 vs. 6.0 g), and greater body weight loss (-27% vs. -7%). Janssen also shared that JNJ-54728518 "markedly" reduced cholesterol levels. Late last year, Janssen acquired Hanmi's phase 2 GLP-1/glucagon dual agonist, which has a similarly promising efficacy profile in terms of A1c-lowering, body weight reduction, and cholesterol-lowering. We'll be curious to see how this preclinical candidate fits into Janssen's pipeline and wonder if Janssen may be "hedging its bets" by including multiple GLP-1/glucagon agonists in its pipeline in case one doesn't quite meet the increasingly high efficacy bar for new diabetes drug.

EFFECTS OF LEUCINE-METFORMIN COMBINATIONS ON GLYCEMIC CONTROL IN TYPE 2 DIABETES (1144-P)

K Niswender, O Kolterman, M Kosinski, and M Zemel

NuSirt BioPharma presented results from their phase 2a head-to-head study of a leucine/metformin combination compared to 850mg metformin BID. After a washout period, a fixed dose of leucine was combined with different levels of metformin (125mg, 250mg and 500mg) and administered twice daily. The control, 500mg metformin, was administered twice daily for two weeks then titrated up to 850mg twice daily for an additional two weeks. Meal tolerance tests were conducted at day 0 and day 28 to analyze changes in glucose area under the curve (AUC). Fasting plasma glucose and insulin, A1c, and 24-hour glucose tests were also undertaken. In a per-protocol analysis, the metformin control arm exhibited greater improvements in fasting glucose ($p<0.05$) and average daily glucose ($p<0.05$) and non-significantly greater improvements in total, but not incremental, glucose AUC. An intention-to-treat (ITT) analysis demonstrated comparable glucose improvements between leucine/metformin and the metformin control. The authors attributed the lackluster results partly to the metformin control arm exhibiting markedly greater improvements in glucose and glucodynamics than expected (from previous trials). The metformin control arm had an ~two-fold greater loss of glycemic control during washout ($p<0.05$) resulting in poorer baseline control and a larger potential improvement with treatment compared to the other arms. Adjusting for this difference resulted in comparable effects of leucine/metformin and the control.

Oral Presentations: Obesity and Related Conditions

SAFETY, PHARMACOKINETICS, AND PHARMACODYNAMICS OF THE NOVEL DUAL GLP-1/ GLUCAGON AGONIST SAR425899 IN HEALTHY SUBJECTS AND DIABETES PATIENTS

Joachim Tillner, PhD (Sanofi, Paris, France)

Dr. Joachim Tillner (Sanofi, Paris, France) presented positive phase 1 data for Sanofi's GLP-1/glucagon dual agonist SAR425899 demonstrating a reassuring safety/tolerability profile, a half-life consistent with once-daily dosing, and improvements in glycemia and body weight. We saw some of this data at the Keystone Symposia on Molecular and Cellular Biology meeting in April demonstrating significant reductions in weight (-5.5 kg [~12 lbs] vs. -2.4 kg [~5.2 lbs]; p<0.001) and "clear" (p-value not specified) reductions in A1c (-0.59% vs. +0.06%) and fasting plasma glucose (-55 mg/dl vs. -22 mg/dl) with SAR425899 vs. placebo after four weeks in 36 patients with type 2 diabetes. In this presentation, Dr. Tillner also shared data from the other two parts of Sanofi's phase 1 program for the candidate: a single ascending dose study in 32 healthy males and a three-week multiple ascending dose study in 40 healthy males. The

three studies together demonstrated a safety/tolerability profile for SAR425899 that was comparable to GLP-1 single agonists. GI side effects were the most prominent adverse events (nausea was the limiting factor for dose escalation in the single ascending dose study) and the drug produced an increase in heart rate in the same range as previously studied GLP-1 agonists. Based on these results, Dr. Tillner expressed confidence that GLP-1/glucagon dual agonism works, despite his initial incredulity at the idea of a diabetes treatment that stimulates glucagon production. He stated that Sanofi's goal for SAR425899 is to equal GLP-1 agonists in terms of glycemic control and surpass them in terms of weight reduction. We assume the company is planning to pursue a type 2 diabetes indication for the candidate, but we wonder whether there could be any potential in obesity or prediabetes as well. GLP-1/glucagon dual agonists have attracted a significant amount of industry interest and we will be curious to see how the various candidates can differentiate themselves - see our competitive landscape page for an overview of the current field.

Questions and Answers

Q: What kind of ratio are you expecting between GLP-1 and glucagon? Are you seeing evidence of glucagon target engagement?

A: Target engagement is something we discussed from the beginning. Glucagon increases blood glucose, so the idea is that if you increase the dose you'll see a U-shaped curve of blood glucose. We haven't seen that so far. We've thought about biomarkers like FGF21 and have measured them but seen no real effect. We've measured blood lipids hoping that glucagon might have an effect on lipid metabolism. For me the results are not absolutely clear. They don't confirm that there's no effect. We've measured ketone bodies and seen a change but that data is still in discussion. There's no clear answer. Our plan is to go to the target of energy expenditure and do dedicated studies to see if glucagon does what it needs to do.

Oral Presentations: Preclinical Therapeutic and Signaling Regulation of Insulin Sensitivity

ACUTE METABOLIC EFFECTS OF MEDI0382, A GLP-1/GLUCAGON DUAL AGONIST, IN WILD TYPE AND GLP-1 RECEPTOR KNOCKOUT MICE

Sarah Will (MedImmune, Gaithersburg, MD)

Ms. Sarah Will provided a rapid-fire summary of data characterizing the acute effects of AstraZeneca's GLP-1/glucagon receptor dual agonist MEDI0382 for diabetes and obesity. Results showed that a single subcutaneous dose of MEDI0382 reduced fasting glucose levels, glucose AUC, and food intake in wild type but not GLP-1 receptor knockout (KO) mice. Specifically, in wild type mice, MEDI0382 (3 nmol/kg) reduced fasting glucose levels by 42% ($p<0.01$) compared to vehicle, while an equimolar dose of liraglutide did not. Further, MEDI0382 reduced glucose AUC (area under the curve) levels to a greater degree than did liraglutide following an intraperitoneal glucose challenge (53% vs. 26%). In addition, MEDI0382 reduced food intake in overnight fasted mice by 18%, while an equimolar dose of liraglutide reduced food intake by 34%. These effects were completely blocked in GLP-1 receptor KO mice for both MEDI0382 and liraglutide; further, MEDI0382 elevated glucose levels in GLP-1 receptor KO mice but did not do so in wild type mice. In contrast, treatment with IUB118 (a selective glucagon-receptor agonist) significantly elevated glucose levels and failed to inhibit food intake in both wild type and GLP-1 receptor KO mice. Ms. Will noted that taken together, these data indicate that MEDI0382 engages both GLP-1 and glucagon receptors, though the acute effects of glucose tolerance and food intake are mediated solely by GLP-1 receptors. We have high optimism for dual agonists, and these results do not disappoint - however, greater research is required to determine the safety, efficacy, and durability of MEDI0382 in human participants.

Oral Presentations: Lipid Mediators

TREATMENT OF TYPE 2 DIABETES THROUGH HEPATIC INSULIN SIGNALING

Rongya Tao, PhD (Harvard Clinical and Translational Science Center, Cambridge, MA)

Dr. Rongya Tao presented data on the role of hepatic insulin signaling in metabolic homeostasis with the goal of unearthing possible treatment options for type 2 diabetes that target insulin resistance. Specifically, insulin receptor substrates 1 and 2 were investigated in liver-specific knockout mice (LDKO), a diabetic

mouse model. Studies showed that insulin regulation of hepatic glucose production was disrupted in LDKO mice, but this was corrected when Foxo1 was deleted in triple knockout mice (LTKO). Therefore, hepatic insulin signaling is independent from the liver's reduction of glucose production, and Foxo1 is necessary to maintain hepatic glucose production at regular levels. LDKO mice also had deregulated metabolic homeostasis in fat, but this was normalized in the LTKO mice. The LDKO mice also showed greater oxygen consumption and energy use and remained resistant to high fat diet-induced obesity, while the LTKO mice consumed oxygen normally. Insulin also did not inhibit lipolysis in LDKO mice, which suggests higher lipid synthesis and secretion. A further RNA microarray revealed more than 20 secreted proteins that are different in the livers of LDKO mice, which may contribute to diabetes. This research should shed more light on the role of hepatic insulin signaling in the pathogenesis of type 2 diabetes and hopefully lead to the discovery of new therapeutic targets.

Oral Presentations: Clinical Therapeutic and Signaling Regulators of Insulin Sensitivity

DUODENAL MUCOSAL RESURFACING IMPROVES METABOLIC MEASURES IN TYPE 2 DIABETES: FIRST-IN-HUMAN STUDY, 6 MONTH DATA

Alan Cherrington, PhD (Vanderbilt University, Nashville, TN)

Dr. Alan Cherrington (Vanderbilt University, Nashville, TN) provided new details on the six-month data for Fractyl's Revita Duodenal Mucosal Resurfacing procedure for type 2 diabetes. The procedure, which recently received CE Mark approval, involves ablation of a portion of the duodenal mucosa via a technique that the company has characterized as similar to an upper endoscopy. Dr. Cherrington shared that significant A1c reductions occurred in both patients with a baseline A1c >10% (mean baseline A1c=~11%) and those with a baseline A1c of 7.5%-10% (mean baseline A1c=~9%) who had a "long" segment of more than 9 cm ablated (mean= ~9.3 cm). The procedure demonstrated peak efficacy at three months, with A1c reductions of ~3.5% in the higher baseline A1c cohort and ~2% in the lower baseline A1c cohort. However, the effect was substantially attenuated at six months, (much more so in the subjects who reduced their diabetes medications), resulting in a final six-month A1c reduction of 2.1% in the higher baseline A1c group and 1.0% in the lower baseline A1c group. These A1c reductions are not as strong as we might have hoped, given the high starting A1c and the relatively invasive procedure (as compared to a more traditional oral or injectable medication). We imagine that Fractyl will need to demonstrate sustained efficacy in order for the procedure to appeal to a large number of patients, and we hope future trials can provide more clarity on this point. Dr. Cherrington also shared that the Revita DMR procedure improved insulin sensitivity (as measure by HOMA-IR) and metabolomic analysis indicated improved insulin sensitivity, reduced oxidative stress, and improved mitochondrial function following the procedure.

- **We previously saw six-month data demonstrating a mean A1c reduction of 1.2% (p<0.001) at six months, as well as improvements in fasting glucose (non-significant, p=0.09), postprandial glucose (p<0.05), and weight loss (-1.8 kg, p<0.05) in the cohort of patients who had a "long" segment ablated.** Fractyl also recently presented data at the EASL International Liver Conference demonstrating improvements in hepatic transaminase levels (AST and ALT specifically, p<0.01) with the procedure.

Oral Presentations: Treatment and Management of Complications - Can a Dog Really Smell Hypoglycemia?

SUPERIOR EFFICACY OF A DUAL GLP-1/GLUCAGON RECEPTOR AGONIST IN REVERSING STEATOSIS AND IMPROVING INDICES OF NONALCOHOLIC STEATOHEPATITIS (NASH) COMPARED WITH GLP-1 RECEPTOR AND FXR AGONISTS IN A MOUSE MODEL OF NASH

James Trevaskis, PhD (MedImmune, Gaithersburg, MD)

Dr. James Trevaskis presented results, showing the superior efficacy of dual GLP-1/glucagon agonist G49 in the mouse model of nonalcoholic steatohepatitis (NASH) compared to GLP-1 agonist liraglutide and FXR agonist obeticholic acid (OCA). As background, the dual agonist G49 combines elements of glucagon and exenatide. The study stratified C57BL6 mice (who were maintained on a high fat, fructose, and cholesterol

diet) to liraglutide, OCA, G49, or placebo for 28 days. The findings demonstrated G49's superiority to both liraglutide and obeticholic acid (OCA) in lowering blood glucose, hepatic triglycerides and collagen, and overall NASH score. Specifically, hepatic triglycerides were decreased 52% by G49, and less so by liraglutide (32%) and OCA (23%), p<0.001. G49 reduced hepatic collagen by 40% (p=0.053 vs. placebo vehicle), with more modest reductions by liraglutide (29%) and OCA (19%). Body weight declined approximately 10% in mice treated with G49 or liraglutide, but not OCA, and the weight loss was driven by changes in fat mass without substantial changes in lean mass. Dr. Trevaskis attributed this superiority to the greater impact of G49 on fibrosis, since the drug's effect on steatosis was comparable to that of liraglutide. Dr. Trevaskis used this data to point out the promise of the dual agonist drug class, especially in treating NASH.

- **According to Dr. Trevaskis, the promise of G49 lies in its ability to work on three axes - reducing steatosis, reducing fibrosis, and improving metabolism.** He stressed that there is a critical, unmet need for effective NASH therapies and shared that parallel to ongoing clinical trials for liraglutide and Intercept Pharmaceutical's OCA, there is emerging interest in dual agonists like G49, which Dr. Trevaskis called a "magic drug" due to its multiple physiological targets.
- **Despite its pronounced effect on overall NASH score, G49 was less effective than liraglutide and OCA in reducing plasma ALT.** Liraglutide resulted in a 61% decrease in ALT. OCA resulted in a 43% decrease, while G49 resulted in a 38% decrease (p=0.052 vs. placebo).

Questions and Answers

Q: One of your intriguing findings was that improvement in ALT was better with liraglutide than with other drugs. Clinicians tend to use ALT as a dominant measure, but is it as good of a marker for fat or fibrosis in the liver?

A: ALT is not a specific liver damage marker for NASH, but it's how many patients come to realize that they have high liver fat. So ALT may indicate that there's something else impacting liver health.

Q: What is the exact contribution of glucagon-receptor activation?

A: Glucagon-receptor activation increases lipid oxidation quite dramatically in isolated hepatocytes. This gives us reason to believe that there's some kind of mobilization at the mitochondrial level, along with some links to lipid metabolism that are underappreciated at this point. The combined effect of glucagon-receptor activation and GLP-1 activation seems to override any negative effects of glucagon. The potency of the two compounds working together is very important. Too much glucagon alone will drive excessive weight loss.

Q: Have you looked at GLP-1 receptors in the pancreas, kidneys, or other organs?

A: A follow-up study is looking at the pancreas, but we haven't looked at any other tissues.

Symposium: Fifty Winks of Diabetes

CIRCADIAN TIMING OF METABOLISM IN MOUSE MODELS AND HUMANS

Charna Dibner, PhD (University of Geneva, Switzerland)

Dr. Dibner presented a series of studies from her lab on rhythmic insulin and glucagon release. She opened with a broad view on peripheral clocks, noting that they control body metabolism in nearly all tissues, including the pancreas. She reviewed experiments that confirmed the presence of cell-autonomous, functional clocks in islet cells. A key component of this mechanism is the transcription factor CLOCK, which regulates rhythmic gene expression. Dr. Dibner showed that basal insulin secretion is circadian in nature, and is altered by disruptions in CLOCK. She then turned to studies comparing oscillation properties in alpha vs. beta cells. RNAseq data show that several important genes in these cells - including insulin and glucagon - are regulated in a circadian manner, with similar and distinct characteristics between the two cell types. Notably, under constant in vitro glucose conditions, both hormones are secreted in a rhythmic manner, though the glucagon peak appears to lag behind that of insulin (per Dr. Dibner, this is to be confirmed with

future data). Circadian timing has also been shown as a potential contributing factor to obesity, as this work likely has broad implications across the metabolic disease spectrum.

Questions and Answers

Q: Do you think that if you use an inhibitor against glucagon in your mice, that you will block the glucagon signal on beta cells and thus disrupt the circadian rhythm?

A: That's a good question. We are doing this study. It is difficult to get glucagon knock-out mice, but we are blocking glucagon with siRNA. We are on the way to showing it. That is a very good point.

Q: You showed the difference in phase in the synchronized alpha and beta cells. That suggests that there is a period difference. The only alternative explanation would be an autocrine resetting that is occurring with each cycle. Can you clarify this? Your studies separated alpha and beta cells, so autocrine signaling is unlikely.

A: I can see your point. We have to consider the viability of the cell. Here, we rarely did more than 2.5 cycles. I am careful with the period - I don't take the first period seriously. I think the alpha cells have a shorter period length, if you synchronize with forskolin.

Q: That would suggest that the composition of the clock mechanism is different in these two cell types. One explanation could be post-translational modification.

A: Right. I know you're trying to help, but that's difficult to imagine. It's not very clear because we're only doing 2.5 cycles. It's difficult.

Q: To understand the idea that the cycles are staggered - this has the implication that the beta cells and alpha cells are intrinsically expressing a different period, or that they are being re-entrained with each cycle.

A: My feeling is that this is more on the entrainment level; but yes, it has to be better thought out.

Q: Have you thought about testing insulin secretagogues such as SFUs to see whether treating beta cells with these agents leads to different insulin secretion at different times of day?

A: Yes, Dr. Bass has shown that.

Symposium: Novel Experimental and Therapeutic Strategies to Target the Central Nervous System (CNS)-induced Regulation of Metabolism

MULTI-AGONISM THERAPEUTIC STRATEGIES TO CNS REGULATION OF ENERGY HOMEOSTASIS

Brian Finan, PhD (Novo Nordisk, Indianapolis, IN)

While GLP-1/glucagon dual agonists are known to induce greater body weight loss due to reduction in food intake and increase in energy expenditure compared to GLP-1 agonists alone, the benefits of adding additional components to that co-agonist is less clear. Dr. Finan discussed preliminary data regarding the potential of a GLP-1/glucagon/GIP triple agonist, presenting rodent and primate studies that demonstrated superiority of the triple agonist to a GLP-1/glucagon dual agonist in increasing body weight loss while maintaining robust glycemic control. Adding GIP agonism to a GLP-1/glucagon dual agonist introduces anorectic effects and buffers from glucagon-induced hyperglycemia. Dr. Finan further argued that targeting thyroid hormone via GLP-1 powerfully reverses obesity via synergistic central nervous system actions, in a molecular "Trojan horse-like approach." Though the triple agonist is clearly still in its early stages of development, it's clear that the triple agonist approach is gaining traction among those in the diabetes field. In particular, Dr. Richard DiMarchi (Indiana University, Indianapolis, IN) is a big proponent of the triple agonist approach involving GIP. The significant interest in multi-agonists involving some combination of GLP-1, glucagon, and GIP was a clear theme of the recent Keystone Symposia on New Therapeutics for Diabetes and Obesity and it appears that the significant potential for weight loss benefits on top of glucose-lowering is a major attraction for this approach.

Questions and Answers

Q: Was thyroid stimulating hormone measured when combining the three agonists?

A: Yes, we measured circulating levels of thyroid stimulating hormone, but we didn't see any changes there.

Symposium: Genetic Analysis of Gut Flora in Diabetes and Metabolic Diseases

THE HUMAN MICROBIOME

George Weinstock, PhD (The Jackson Laboratory for Genomic Medicine, Farmington, CT)

Dr. George Weinstock spoke on one of the hottest areas of early-stage research in diabetes, the human microbiome. He explained that since its founding in 1998, research funding and publications on the microbiome field have grown exponentially. Characterizing microbial communities (e.g. salivary, gut) by next-generation or shotgun sequencing of 16s rRNA provides rich visual representations of the types of taxa within each body site, all of which are vastly distinct from each other. Stool sample analyses consistently show three microbe divisions: Ruminococcus, Prevotella, *and* Bacteroides. *However, the gut microbiome makeup is extraordinarily sensitive to environmental effects. Mice from different geographical locations can have distinct microbiomes, despite being controlled for genotype and diet - a crucial point for researchers to consider. Dr. Weinstock and Mike Snyder are currently pursuing a Personal "Omics" Profiling (POP) project for people with diabetes. They plan to document genomes, microbiomes, cytokines, and other measures for adults (n=300) with diabetes over three years in order to build integrated profiles that may provide markers for disease progression. Biochemical analyses are also profiling differences in microbiomes within household environments (e.g. dust vs. filter) to further develop the hygiene hypothesis. Scientists hope in the near future to harness microbiomes therapeutically, though that will likely be many years down the road in diabetes. It is particularly encouraging that fecal transplants from healthy individuals to those with* C. difficile *infections have proved more effective than antibiotic treatments.*

- **Dr. Weinstock presented data showing that compared to average healthy subjects, athletes have "golden" microbiomes.** A study of downhill bike racers show that *Prevotella* are significantly more abundant in athletes than otherwise normal people (40% v. <5%), as is *Clostridiales*. More notably, the main archaebacteria found in humans, *Methanobrevibacer smithii*, is more abundant in professional racers. One hypothesis suggests that *M. smithii* metabolizes bacterial waste products, providing nutrients and energy used by athletes' bodies.
- **One POP subject with prediabetes progressed to diabetes after an RSV infection**, which prompted Dr. Weinstock to sequence viral genomes in conjunction with the microbiome. The advent of human rhinovirus, for example, was shown to spike gut *Ruminococcaceae* and deplete *bacteriodetes*, which likely affects glucose levels and contributes to diabetes.

Questions and Answers

Q: How are you going about trying to functionalize the role of taxa in promoting health or disease, and how are you trying to distinguish species to the level of granularity needed? For example, E. coli are both pathogenic and non-pathogenic.

A: For bacteria, the action is not at the genus or species level - it's at the strain level. With shotgun sequencing, we can see everything; we can go down to the SNP level, we can see individual genes. Often, the analysis of shotgun is not at the taxonomical level, but rather at the individual and functional levels. With 16S, you can narrow it down to a species (we've done other papers where we look for polymorphisms within 16S genes that hit down to strain level) and look for associations that way.

Q: In the clustering of C57BL/6 mice at Bar Harbor v. West, was there a small group that was from Bar Harbor but had the microbiome equivalent to the JAX West site?

A: There could be some overlap. We didn't have as many mice from Bar Harbor as we had from JAX West.

Q: If Bar Harbor were to buy a B6 from JAX West and import it, would the microbiome be impacted?

A: First, when a mouse comes to you from Bar Harbor or JAX West, it will change over time. Those experiments in Bar Harbor and JAX were not done at same time in the year. They were all fed the same monkey chow, but could be getting different grain at different parts of the year. Within JAX west, we did eight rooms that fell into two different groups. Groups of four were on different sides of the building and had different microbiomes. The microbiome is an extremely sensitive asset. You pick up things you otherwise didn't see. How important it is and how to manage it is not clear yet, but it is something we should be officially aware of.

Symposium: Diabetes and Precision Medicine - What Can We Learn about Diabetes with "Omics"?

MICROBIOMICS: UNDERSTANDING THE ROLE OF NUTRITION IN VASCULAR AND METABOLIC DYSFUNCTION

Nathalie Delzenne, PhD (Université Catholique de Louvain, Brussels, Belgium)

Dr. Nathalie Delzenne discussed the role of gut microbiota in metabolic diseases such as diabetes and obesity. Dysbiosis, the changes that occur in the gut microbiome due to diabetes, leads to a decrease in bacterial diversity and beneficial bacteria and an increase in potentially harmful bacteria. Therefore, the development of probiotics and prebiotics that target certain gut bacteria is an intriguing area of research in diabetes. Dr. Delzenne presented data showing that more than 100 microbial genes are modified after treatment with prebiotics; these modifications include an increase in bacteria correlated with intestinal L cells in mice, which is thought to be GLP-1 dependent. In addition, metabolic diseases often are associated with omega-3 polyunsaturated fatty acids depletion, which is considered to be linked to the gut microbiome; just three months of depletion in a low fat diet induces hepatic insulin resistance and vascular dysfunction in mic, and prebiotics improve the metabolic disorders in this context. Researchers are aiming to modify the gut microbiome to restore vascular function, which may have a positive impact on obesity and type 2 diabetes as well. Although there was plenty of buzz about the gut microbiome at this year's ADA, much more work is needed to solidify the associations between the microbiome and diabetes and to translate this early-stage research into viable treatments for patients.

Symposium: Microbiota, Inflammation, and Diabetic Cardiovascular Disease

PROBIOTICS AND MICROBIOTA MODULATION

Max Nieuwdrop, MD, PhD (University of Amsterdam, Netherlands)

A clear theme at ADA 2016 was a surge of interest in the effects of microbiota on diabetes and metabolic disease. Much of the research in this emerging field has been conducted in animals, but Dr. Max Nieuwdrop's work explores the human microbiome. He and his colleagues transplanted microbiota from lean individuals into individuals with obesity and type 2 diabetes using a procedure called fecal microbial transplantation (FMT). To their surprise, this procedure increased the patients' insulin sensitivity to a comparable extent as oral diabetes medications, suggesting that microbiota play a role in mediating insulin sensitivity. In future studies, Dr. Nieuwdrop hopes to determine which particular bacterial strains are responsible for these benefits. He foresees that engraftment with beneficial bacterial strains may soon be used in combination with diet, exercise, and drugs as a therapy for diabetes. Although studies like this clearly demonstrate that the microbiome meaningfully influences metabolic health, Dr. Nieuwdrop was quick to point out that science is still a long way from demonstrating a causal relationship between microbes and metabolism. This is a particularly relevant caveat to bear in mind when considering human microbiome studies, which, unlike rodent studies, do not control for age, diet, or genetic background and are thus far less reproducible.

Questions and Answers

Q: Could the success of the engraftment process be modulated by diet? In your fecal transfer experiments did you report HOMA?

A: We studied HOMA and oral glucose tolerance test. We did not see strong effects there; you need large groups or a clamp to pick up a signal. And yes, I believe that diet can improve the chances of engraftment. We are trying that with the Mediterranean diet. Of course, diet would only help the chances of bacterial engraftment if the system is unstable to begin with. A large effect may not be expected.

Q: You talked about the Mediterranean diet having probiotic effects. It is known to be beneficial to cardiovascular health. Could there be some magic bullet in this diet?

A: Yes, we are studying that. We are also studying the vegan microbiome. It is interesting to consider how strong the influence of the microbiome can be on a disease that has been developing for years.

Joint ADA/ASN Symposium-Innovations in Treating Inflammation for Diabetic Kidney Disease

THE MCP-1 INHIBITION STORY FOR DIABETIC KIDNEY DISEASE

Hermann Haller, MD (Hannover Medical School, Hannover, Germany)

Dr. Hermann Haller shared exciting preliminary data from a trial of Emapticap pegol (NOX-E36), a novel drug that decreased albumin/creatinine ratio (ACR) by 32% compared to control in patients with diabetic kidney disease. According to Dr. Haller, the drug targets inflammation, as it is strongly implicated in the development and progression of diabetic nephropathy. Researchers specifically zeroed in on MCP-1, a factor that recruits inflammation-inducing monocytes from bone marrow to the kidneys and is found at higher concentrations in the kidney in conjunction with proteinuria and kidney injury. They developed a small, stable left-handed RNA aptamer (a type of molecule known commercially as a Spiegelmer), Emapticap pegol, that selectively binds and neutralizes the function of MCP-1. An initial animal study in db/db mice offered encouraging results, demonstrating a robust reduction in glomerulosclerosis following Emapticap treatment. A subsequent small (n=75) double-blind, 24-week phase IIa clinical trial randomly assigned type 2 diabetes patients with albuminuria (ACR >100mg/g) to either an Emapticap treatment regimen (n=50) or a placebo (n=25). After 12 weeks, the Emapticap group saw a 32% reduction in ACR relative to the placebo group (p=0.014). Notably, this reduction persisted for at least 12 weeks after treatment termination, a phenomenon that Dr. Haller surmised was due to diminished monocytes in the kidneys leading to reduced inflammation and proteinuria.

- **Though theoretically promising, Emapticap pegol requires patients to self-administer sub-cutaneous injections twice daily**. This frequency and route of administration may be a barrier to use, and we wonder whether it would lead to sub-optimal regimen adherence.
- **The placebo group experienced decreases in ACR during the 12-week treatment period that closely mirrored the decreases in the treatment group.** To this point, one could argue that the improvements in ACR were solely due to behavioral and/or psychological changes. However, the placebo group returned to baseline ACR after the treatment period, while the experimental group's ACR was maintained at lower levels at 12 weeks post-treatment.
- **Though not specifically a glycemic control agent, Emapticap reduced patients' A1c by ~0.5% at the end of the 12-week treatment phase.** Dr. Haller explained that MCP-1 has been implicated in insulin resistance, so inhibiting it has the added benefit of decreasing blood glucose and A1c.
- **Dr. Haller was initially concerned about infections and serious adverse events in patients taking Emapticap, but observed none in the phase IIa trial**. Monocytes exist to fight infection, he stated, so using this drug "interferes with a system that is in place for a reason." However, inhibiting the recruitment of monocytes to the kidney did not result in a greater risk of infection.

Questions and Answers

Q: We need to work on the biomarker side of the equation. Do you think that phenotyping MCP-1 would be sufficient, or do you think other biomarkers should be in such a panel?

A: I think we should first focus on MCP-1, because there may well be differences amongst healthy and unhealthy individuals in this gene.

Q: If you were designing the next clinical trial, at what point do you think it would be the right time to introduce anti-MCP-1 therapy?

A: We have to rely on albuminuria for the time being. Traditionally, no albuminuria means no kidney disease, but we know this isn't always the case. The question is, can we define more phenotypic metrics? I'm a big proponent of biopsies, we need to do more of these to diagnose diabetic kidney disease.

Pathway to Stop Diabetes Symposium

SUMMARY

A high-powered group of researchers and industry representatives gathered in a closed session on Friday morning to hear presentations from the most recent recipients of the ADA's Pathway to Stop Diabetes grants. Introductory remarks by ADA President Dr. Des Schatz and Dr. C. Ronald Kahn (Joslin Diabetes Center, Boston, MA) emphasized the program's goals of promoting long-term, transformational change in diabetes care and encouraging collaboration. They also highlighted the selectiveness of the program: the 17 grant recipients selected thus far were chosen from a pool of 330 applicants, and as Dr. Kahn put it, "those 330 people were all pretty damn good." The introductory speakers also noted that there was a concerted effort to focus attention on this program at this year's ADA, with a dedicated poster session on Sunday and an oral presentation session on Monday in addition to this symposium. We remain very impressed with the Pathway initiative, which awards grants of up to $1.6 million over five to seven years to young diabetes researchers working on innovative projects focused on everything from neuronal regulation of feeding behavior to impaired wound healing. The program is supported by several heavy hitters in the diabetes industry, including Sanofi, Novo Nordisk, AstraZeneca, and Lilly, and we imagine this could make it easier for the researchers to eventually translate their findings into novel therapies. We think this program can play a major role in shaping the next generation of KOLs in diabetes. We also hope it can promote a more diverse group of leaders compared to the current crop (in a sign of some progress, 35% of the Pathway grant recipients are women compared to 26% of the mentors). See below for a more detailed overview of their work, though we unfortunately cannot provide specifics on the data presented at the symposium due to the closed nature of the session.

- **Dr. Praveen Sethupathy (University of North Carolina, Chapel Hill, NC) is exploring links between obesity and the gut microbiome.** His research aims to identify genetic factors that contribute to the intestine's response to microbes under normal conditions and in obesity and diabetes. Due to the intestine's crucial role in metabolism, Dr. Sethupathy is optimistic that this research could eventually reveal targets for future therapies.
- **Dr. Zachary Knight (UCSF, San Francisco, CA) is investigating neuronal circuits that regulate food intake.** While the field has a basic understanding of the mechanisms of weight regulation by the brain, Dr. Knight aims to delve deeper into the specific circuits that allow external cues to override normal regulation of feeding behavior. His research is focused on identifying the signals that activate the sensation of hunger and understanding how neural circuits promote food consumption. His goal is then to discover how these circuits are dysregulated in obesity, hopefully opening the door for new therapies.
- **Dr. Philip White (Duke University, Durham, NC) is using metabolomics to better understand the biochemical signatures of diabetes and obesity.** As compared to lean mice, the metabolome of obese mice is characterized by a disequilibrium in levels of enzymes involved in the breakdown of keto-acids in the liver. Dr. White hypothesizes that restoring homeostasis among these enzymes could be an effective strategy for improving glucose and lipid metabolism.
- **Dr. Andrew Scharenberg (Seattle Children's Hospital, Seattle, WA) is using gene editing to engineer stable regulatory T cells (Tregs) in patients with type 1 diabetes.** There is evidence suggesting that Treg dysfunction is one element of the immune imbalance in type 1 diabetes that leads to autoimmune attack on the beta cells. Dr. Scharenberg aims to edit genes in T

cells to engineer Tregs that will remain stable and protect beta cells from autoimmune attack, potentially preventing or reversing type 1 diabetes. Dr. Jeffrey Bluestone (UCSF, San Francisco, CA) is currently furthest along in the Treg field with a therapy in phase 1 trials, but this approach (while at a much earlier stage) could potentially produce even more stable and robust cells with greater efficacy.

- **Dr. Sui Wang (Harvard University, Boston, MA) is developing biological tools to dissect the gene regulatory networks (GRNs) mediating diabetic retinopathy**. Dr. Wang is interested in understanding the unique roles of different retinal cell types, with particular emphasis on the molecular events underlying the disease's early pathogenesis. She hopes that an understanding of these complex forces will leave researchers well-positioned to identify potential therapeutic targets to arrest the progression of retinopathy in its early stages.
- **Dr. Daniel Ceradini (New York University, New York, NY) is investigating whether restoring a key antioxidant pathway can reverse the impaired tissue regeneration associated with diabetes.** His research has previously demonstrated that this pathway is disrupted by hypoglycemia, and he aims to develop a therapy that can restore it and enable faster wound healing in people with diabetes. Wound healing is an area of particularly great unmet need in diabetes - the current standard of care consists of glycemic control and pressure off-loading - and we are very glad to see efforts to develop novel therapies.

-- Sadie Bronk, Shivani Chadrashekaran, Lucy Chu, Abigail Dove, John Erdman, Emily Fitts, Helen Gao, Varun Iyengar, Emily Reiger, Ava Runge, Nina Ran, Tony Thaweethai, Sarah Wilkins, and Kelly Close