



Trip Report for
“Targeting Diabetes with Novel Therapeutics,”
October 22-23, 2008

Alan J. Henderson, Ph.D.

December 4, 2008

AMRI Memorandum

TO: Barnes, Keith; Earley, Bill; Gauuan, Joli; Geiss, Bill; Guaciaro, Michael; Herr, Jason; Molino, Bruce; Reilly, John; Schaffer, Malissa; Voss, Matthew; Yang, Zhicai; Sargent, Bruce; Guzzo, Pete; Michels, Pete; Carr, Grant; Manning, Dave; Surman, Matthew; Henderson, Alan; Wolf, Mark; Liu, Shuang; Luche, Michele; Mocek, Ursula; Chase, Matthew; Khmelnitsky, Yuri; Cotterill, Ian

FROM: Alan J. Henderson, Ph.D.

DATE: October 22-23, 2008

RE: "Targeting Diabetes with Novel Therapeutics"

Abstract: The inaugural "Targeting Diabetes with Novel Therapeutics" Conference was held in Boston, MA as part of the CHI 'Discovery on Target' series running from October 21-23, 2008. The conference was attended by a relatively small (50 or so) group of scientists and clinicians and focused exclusively on diabetes. The presentations were quite varied, ranging from cutting-edge research involving stem cells to late-stage clinical trials of promising new therapies.

"FGF-21 for the Treatment of Type 2 Diabetes,"

Jesper Gromada, (Novartis).

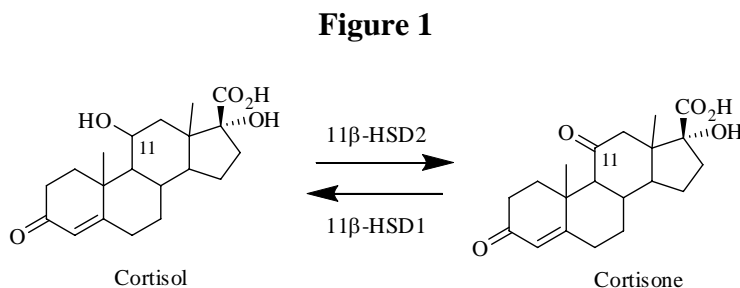
Fibroblast growth factor 21 (FGF-21) is a recently discovered metabolic regulator expressed in the liver, pancreas and thymus. It has been shown that serum levels of FGF 21 are regulated by fasting and re-feeding. The factor has an *in vivo* half life of 30-60 minutes in man, appears to be stable and has been shown to be highly variable regarding measured levels in healthy individuals. FGF-21 may elicit highly favorable antidiabetic properties, some of which are summarized below:

- Dose-dependently stimulated glucose uptake in adipocytes.
- Improved glucose tolerance and insulin sensitivity in normal C57BL/6 mice.
- Increased insulin sensitivity and normalized blood glucose levels in *ob/ob* mice.
- Chronic treatment with FGF-21 in diet-induced obese (DIO) mice resulted in a reduction in glucose, insulin, plasma lipid and non-esterified fatty acid (NEFA) levels.
- Chronic treatment with FGF-21 in DIO mice resulted in a reduction in body weight and increase in energy expenditure. Body temperature lowering and torpor induction was also noted in fasted mice.
- Improved glycemic control and lipid profile in diabetic monkeys.
- Reduced LDL cholesterol levels which was accompanied by a significant increase in HDL cholesterol levels.

FGF-21 also showed promise in improving the β -cell function in db/db mice. It was shown to stimulate insulin release to levels 50% above that of the non-treated animals. Additionally, insulin secretory capacity and glucose tolerance was improved, and there was evidence of enhanced β -cell survival with treatment. All of this evidence led to the hypothesis that Type 2 Diabetics and obese individuals may be FGF-21 resistant, and treatment with the factor could offer a promising new therapeutic approach to Type 2 Diabetes.

“11 β -HSD1 Inhibition as an Entrée to Cardio-Metabolic Benefit in Type 2 Diabetes,”

Reid Huber, (Incyte Corporation).



11 β -HSD1 and 11 β -HSD2 catalyze the tissue-specific interconversion of cortisone and cortisol via reduction and oxidation at the 11-position (figurefigureFigure 1). Cushing’s Syndrome, which is caused by high levels of cortisol in the blood, is characterized by a number of symptoms in common with human metabolic syndrome such as obesity, hypertension, insulin resistance, dyslipidemia and increased cardiovascular risk. Thus, if blood cortisol levels could be reduced via inhibition of 11 β -HSD1, the potential for treating Type 2 Diabetes exists.

INCB013739 is a potent 11 β -HSD1 inhibitor with favorable properties (IC_{50} = 1.1 nM in cells; >1000-fold selectivity over 11 β -HSD2, mineralocorticoid receptors and glucocorticoid receptors; good oral bioavailability with plasma $T_{1/2}$ = 11 hours in man; pharmacodynamically active in rhesus monkey adipose tissue after oral dosing). This compound was taken into a Phase I clinical trial of lean volunteers to assess its safety, tolerability, PK, and PD profile. The compound was found to be safe and well tolerated at the target blood levels although the maximum tolerated dose (MTD) was never achieved. Indirect measurement of urinary biomarkers allowed for assessment of the inhibitory activity of the compound in vivo. INCB013739 was found to dramatically reduced the cortisol: cortisone ratio in the liver, whilst having no effect in the kidney in a 9-day study at all doses tested (25 mg-200 mg). Sampling of human adipose tissue and concomitant ex-vivo analysis showed highly significant inhibition of 11 β -HSD1 activity at 200 mg over 24 hours. The compound also abolished hepatic 11 β -HSD1 activity during an oral cortisone challenge.

A 28 day Phase IIa study (n=9 placebo, n=22 drug) was then conducted in patients with Type 2 Diabetes using a 100 mg/kg bid dose. The patients were mildly obese (BMI 32-34.2) and had baseline fasting plasma glucose (FPG) levels of 170-190 mg/dL. The drug was well tolerated throughout the study, with no major adverse effects and no instances of hypoglycemia. Treated patients showed a mean 20-point reduction in blood glucose levels, as well as a mean 27-point reduction in cholesterol levels and a mean 13-point reduction in triglyceride levels. Systolic and diastolic blood pressure was also reduced.

Overall, INCB013739 successfully progressed through a phase IIa study where it was shown to be safe and well tolerated. The drug showed improvements in hepatic insulin sensitivity, plasma LDL-cholesterol and plasma total-cholesterol. A 3-month phase IIb dose range study (n=300) is planned in Type 2 Diabetic patients looking at similar markers as the phase IIa study, but extended to include HbA1c levels and body weight effects. The results are expected mid-2009.

“Antidiabetic Effects of Glucokinase Activators: From Benchside to Bedside,”

Joseph Grimsby, (Hoffmann-La Roche Inc).

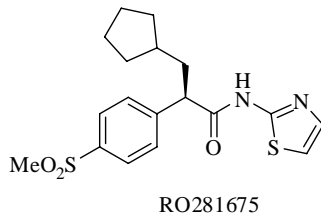
Glucokinase (GK) is a hexokinase that plays a key role in glucose homeostasis by controlling the rate of glucose metabolism in many tissues. In pancreatic β -cells, GK acts as a molecular sensor for glucose-stimulated insulin release and in hepatocytes it catalyses the first step of glucose metabolism (phosphorylation). Thus, there is a strong rationale for activation of the GK enzyme leading to improved insulin sensitivity and glucose tolerance amongst Type 2 Diabetics.

GK activators work by binding to an allosteric site located in the hinge region, approx. 20 Å from the glucose binding site. These compounds act as non-essential mixed type enzyme activators that increase the V_{max} and decrease $[S]_{0.5}$ to augment glucose metabolism and lower the threshold of glucose-stimulated insulin release in both normal and Type 2 human islets. Animals treated acutely and chronically with GKA's show improvements in basal and post-prandial glucose levels, which is thought to be mediated via a dual mechanism of suppressing hepatic glucose levels and increasing plasma insulin levels.

GK activators (unlike other antidiabetic approaches such as TZD's) are lipid neutral, and studies were carried out to see exactly where the glucose actually goes. Using a ^{13}C glucose tracer in DIO mice (single dose), it was found that glucose disposal occurs primarily via increases in CO_2 and H_2O production, with increased ^{13}C levels detected in the plasma, palmitate synthetic pathway and liver/adipose tissue.

Clinical data was presented on one of the Roche compounds (RO281675 – Figure 2) in 48 males at a single ascending dose (25 mg – 400 mg).

Figure 2



The compound showed a dose-dependant reduction in fasting and post-prandial glucose levels with an excellent pharmacodynamic effect. However, hypoglycemia was reported at the highest dose (400 mg). RO281675 was then progressed to a multiple ascending dose in 59 patients who had a BMI in the 22-37 range and had been diabetic for 0.7-29 years. The compound was dosed at 10, 25, 50, 100 and 200 mg qd and 200 mg bid in a 5.5 day study. Dose related increases in plasma insulin levels and decreases in plasma glucose levels were noted, and at the highest dose normalization of blood glucose levels occurred. However, hypoglycemia was reported at the 200 mg qd and 200 mg bid doses. Nevertheless, the 100 mg bid dose did not cause significant hypoglycemia and had a robust efficacious effect.

In conclusion, glucokinase activators were shown to offer a promising new therapeutic approach to treat Type 2 Diabetes, although hypoglycemia may be an adverse effect requiring close control.

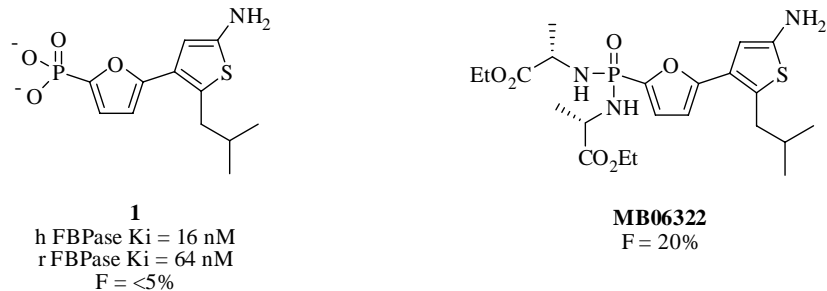
“Discovery of a Second Generation FBPase Inhibitor, MB07803, with Reduced Metabolism, Improved Oral Bioavailability and Clinical POC in Type 2 Diabetic Patients,”

Max Dang, (Metabasis Therapeutics).

Fructose-1,6-bisphosphatase (FBPase) is a hormone regulated enzyme that converts fructose 1,6-bisphosphate to fructose-6-bisphosphate. FBPase is involved in the gluconeogenesis process, which is a pathway resulting in the synthesis of glucose via metabolic intermediates. As FBPase plays a key role in this process, inhibition of the enzyme could be beneficial in treating Type 2 Diabetes. Furthermore, patients who have genetic defects relating to loss of FBPase function lead normal lives without hypoglycemia (as long as they eat regular meals).

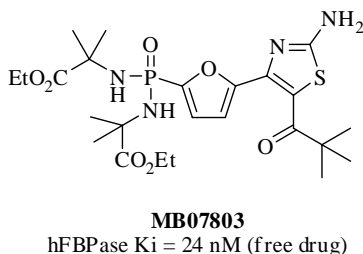
Metabasis’ strategy to uncover FBPase inhibitors centered on inhibition of the AMP binding site. Starting with AMP as the lead molecule, they developed a furan-based compound **1** which had very good activity against human and rat FBPase, but suffered from poor bioavailability. This was significantly improved upon using a prodrug strategy to deliver MB06322 (figurefigureFigure 3).

Figure 3



When dosed in vivo (humans), MB06322 was rapidly cleaved to the mono-deprotected intermediate, but took much longer to release the actual drug. During this process, very high levels of the *N*-acetyl metabolite of MB06322 were generated (NAT2 acetyl CoA mediated); this was thought to be due to the long timeframe required for release of the drug from the prodrug. Thus, Matabasis embarked on a program to increase the bioavailability, efficacy and half life of this compound, whilst eliminating formation of the *N*-acetyl compound. SAR development was undertaken, and introduction of a ketone into the thiazole ring was found to negate *N*-acetylation of the drug. A subtle change to the pro-drug resulted in MB07803 (Figure 4) which was assessed preclinically.

Figure 4



In ZDF rats, MB07803 was found to significantly lower blood glucose levels in both six hours fasted and fed animals. It was also efficacious in an oral glucose tolerance test. In a 28 day food-administered study, the drug was efficacious at 30 mg/kg qd although there was no effect on food intake or body weight. In the cynomolgous monkey, a 3 mg/kg and 10 mg/kg dose lowered blood glucose levels by 15% and 45% respectively. Furthermore, in the rhesus monkey, the minimum efficacious dose (MED) was found to be 10 mg/kg (vs 30 mg/kg for MB06322) and the bioavailability was 50% (vs 9% for MB06322).

This compound was then taken into a Phase I clinical trial, initially looking at the in vivo conversion of the prodrug into the drug. At a 50 mg dose, the prodrug was rapidly metabolized, and the intermediate mono-deprotected form was detected in much lower levels than for MB06322. Furthermore, the active metabolite (drug) was detected in high levels consistent with qd dosing in man. In addition, no *N*-acetyl metabolite was detected

until the dose was increased to 600 mg. The compound had a half life of approx. 18 hours and a bioavailability of 26-29% in man. It also showed effective proof of concept in this trial. A phase IIa study is planned

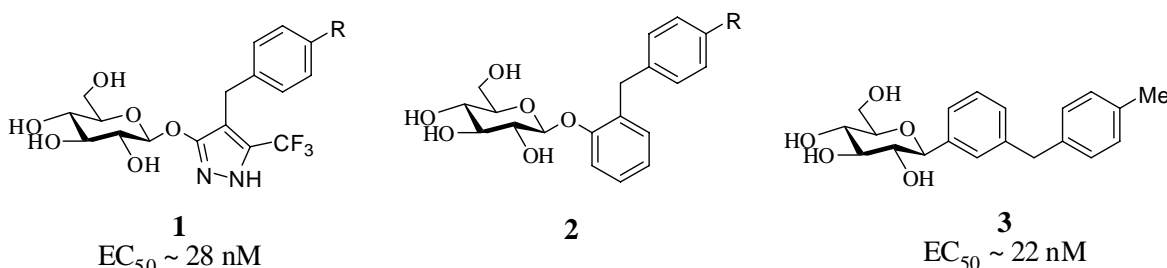
“SGLT2 Inhibition: A Novel Approach to the Treatment of Type 2 Diabetes,”

Jean Whaley, (Bristol-Myers Squibb).

Inhibition of the renal sodium-glucose cotransporter 2 (SGLT2) promotes the excretion of glucose into the urine and represents a new therapeutic approach to treat hyperglycemia. The non-selective SGLT inhibitor phlorizin has been shown to improve insulin sensitivity and reduce endogenous glucose production in diabetic animal models by the correction of glucotoxicity. Genetic mutations resulting in deficiency of SGLT2 (Familial Renal Glucosuria) results in individuals who exhibit benign glucosuria (up to 100 g of glucose excretion/day) yet have normal glucose levels and no health risks. However, individuals with SGLT1 mutations suffer from a glucose-galactose malabsorption syndrome.

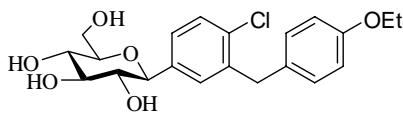
BMS instigated an SGLT2 inhibitor program aiming to identify inhibitors that were selective over SGLT1. Compound **1** had good activity against SGLT2, yet in vivo it was efficacious in mice but not in rat. This was attributed to cleavage of the O-glycoside in rat, resulting in generation of the inactive hydroxyl-pyrazole. A second generation of analogs were prepared (**2**) with a central phenyl ring, which resulted in good SGLT-2 activity (particularly when R was a lipophilic group). Furthermore, during the preparation of one of the analogs in this series, a side product (C-glycoside) was isolated, and SAR development around this led to the potent SGLT2 inhibitor **3** that was significantly more stable than the O-glycosides (Figure 5).

Figure 5



Further elaboration of compound **3** led to Dapagliflozin, which ultimately became the clinical candidate. This compound had excellent potency against SGLT2, exquisite selectivity over SGLT1 and a very good PK profile in all species tested (Figure 6).

Figure 6



Dapagliflozin

| | Human EC ₅₀ | Rat EC ₅₀ |
|-------|------------------------|----------------------|
| SGLT2 | 1.1 nM | 3 nM |
| SGLT1 | 1200 nM | 200 nM |

| | Rat | Dog | Monkey |
|-------------------------|-----|-----|--------|
| Cl (mL/min/kg) | 4.8 | 1.5 | 6.4 |
| F% | 84% | 83% | 25% |
| V _{dss} (L/kg) | 1.6 | 0.8 | 0.8 |
| T _{1/2} (h) | 4.6 | 7.4 | 3.0 |

Preclinically, dapagliflozin showed a dose dependant reduction in blood glucose levels (ZDF rat) at 0.01, 0.1 and 1 mg/kg doses. There was also a dose dependent increase in urine volume (10-fold over 6 h, 2-fold over 24 h). In a sub-chronic 14 day study, there was a significant dose-dependant reduction at day 8, with no reduction in body weight noted after day 14. This compound had a superior profile to all competitor compounds, not because of its potency but because of the extended half-life and stability of the C glycoside. In a 28 day study for body weight effects (DIO rat), dapagliflozin caused a 6% weight reduction even though food intake actually increased. This effect was enhanced when the animals were pair fed.

Results for the phase IIa clinical trial for this compound were disclosed. In a 47 naive patient population with Type 2 Diabetes and fasting serum glucose levels of <240 mg/dl, dapagliflozin dose-dependently reduced the glucose levels (5, 25, 100 mg doses; 14.5, 17.3 and 21% reduction respectively) on day 13 (placebo 6.3%). Additionally, an oral glucose tolerance test resulted in a 19.2, 22.9 and 18.8% reduction respectively (placebo 5.7%). All subjects dosed with the drug had increased glucose excretion via the urine on days 5 and 13. To date there have been no major adverse effects with this compound. It is currently in Phase III clinical trials.

“Managing Diabetes with an Amylin Mimetic: A Step Closer to Restoring Normal Physiology,”

Elaine Chiquette, (Amylin Pharmaceuticals).

Amylin is a 37 amino acid peptide that is co-located and co-secreted with insulin from pancreatic β -cells. It is deficient in patients with Type 1 and late stage Type 2 Diabetes. Whereas insulin helps to regulate glucose disappearance, amylin helps to regulate glucose appearance. Amylin Pharmaceuticals has developed a synthetic amylin analog,

Pramlintide, in order to overcome human amylin's propensity to aggregate, adhere to surfaces and form insoluble particles.

Pramlintide has similar PK and PD properties to human amylin, and has been shown to clinically suppress the rise in post-prandial glucagon levels seen in Type 1 and Type 2 Diabetic patients. It has also been shown to reduce gastric emptying, reduce calorie intake and significantly improve post-prandial glucose levels in Type 1 and Type 2 Diabetics when taken in combination with insulin (levels were improved over insulin alone). The potential problem with this approach, however, is hypoglycemia, as Pramlintide is co-administered with insulin to patients who fail to respond adequately to insulin alone. In order to better understand the effects, a clinical practice trial was conducted in patients with Type 1 (n=265) and Type 2 (n=166) Diabetes to assess the safety and efficacy in the clinical setting. The drug was dosed in combination with insulin over a six month period. In the Type 2 Diabetes population, HbA1c levels, body weight and insulin use were all significantly reduced (0.6%, 6.2 lbs and 6.4% respectively). In the Type 1 Diabetic group, HbA1c levels, body weight and insulin use were all significantly reduced (0.2%, 6.6 lbs and 12% respectively). There were also improvements in glucose fluctuations in both groups. Nausea was the main side effect which was mild to moderate, but could be controlled via dose titration. Hypoglycemia was found to be more common in Type 1 Diabetics, and careful patient selection, instructions and insulin dose adjustments are necessary to control such side effects.

Pramlintide (Symlin) has been on the market for three years, and was administered to more than 5,300 patients (pre-approval) in combination with insulin. It is indicated in both Type 1 and Type 2 Diabetics who have β -cell failure. It reduces postprandial hyperglycemia and glucose fluctuations, improves glycemic control and leads to a mean reduction in body weight. The drug does, however, contain a boxed warning outlining the potential risks for hypoglycemia.

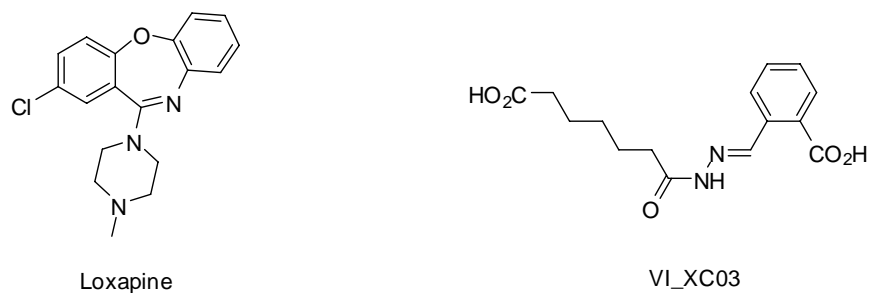
“Chemical Screening for Modulators of Beta Cell Differentiation and Proliferation,”
Julia Lamenzo, (Harvard University).

There are two potential sources of insulin producing β -cells which could potentially be used in transplant therapies for Type 1 Diabetics; beta cells derived through expansion of an existing beta cell population and beta cells derived through differentiation of embryonic stem cells.

Studies showed that through gene expression profiling there was a similarity between fresh and cultured whole and dispersed mouse islets, and that cultured mouse islets maintained characteristic β -cell expression. Subsequently, human islets dispersed and cultured in microtiter plates maintained characteristic β -cell expression. This allowed for an assay to be developed for screening of small molecules for β -cell expansion. 400 bioactive compounds were screened in a human islet study, using insulin as a biomarker for activity in the assay. This resulted in three hits that are being evaluated.

A study was undertaken to assess the transformation of stem cells to pancreatic beta cells via a small molecule-mediated process. Embryonic stem cells are converted to β -cells through a 5-step process. Key steps are the conversion of stem cells to endoderm SOX17 progenitors (via activin A) through pancreatic Pdx 10 progenitors (via FGF 10). However, natural production of Pdx cells declines after 3-4 days. Adding selected small molecules maintained Pdx levels by stopping degradation. Loxapine caused a 480% increase in SOX17 expression (over activin A) and a 10-fold increase in Pdx1+ cell expression vs DMSO in mouse embryonic stem cells. VI_XCO3 caused a 174% increase in SOX17 expression (over activin A) and a 2-fold increase in Pdx1 cell expression vs DMSO in mouse embryonic stem cells (Figure 7). Additional compounds are being screened.

Figure 7

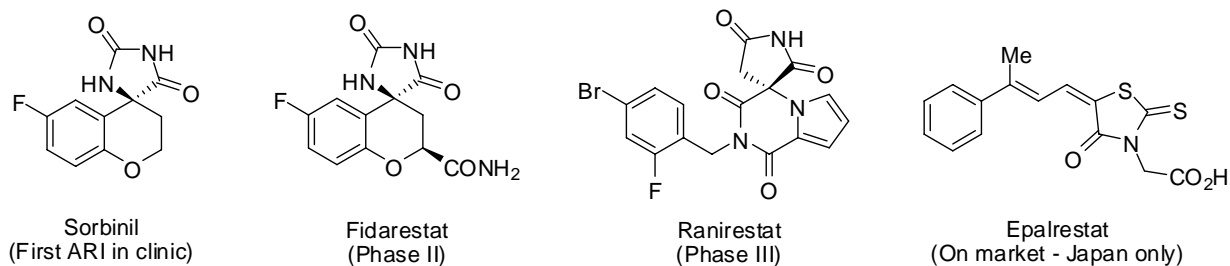


“Diabetic Complications and the Polyol Pathway: Lessons Learned and a New Paradigm,”

Peter Oates, (Pfizer).

Uncontrolled diabetes can lead to a number of dangerous conditions such as blindness (retinopathy and cataract), heart disease/stroke (atherosclerosis), kidney failure (damaged filtration system), high risk of infection and amputation (slow healing) and pain/loss of sensation (nerve damage). A leading pathway in the area of diabetic complications is the polyol pathway. This is a two-step process where glucose is converted to sorbitol (via aldose reductase) which is subsequently transformed into fructose (via sorbitol dehydrogenase). The hypothesis regarding the polyol pathway is that when sorbitol is generated in the cells, it cannot leave via osmosis, so the levels increase causing complications. This has been somewhat validated in rat models, where diabetic animals have cataracts. When dosed with an aldose reductase inhibitor (ARI), the sorbitol levels decrease and the cataract growth is reversed. Thus, ARI's were regarded as a good target for diabetic complications. A number of ARI's have made it to the clinic (representative compounds as shown in Figure 8) but the results of clinical trials have been disappointing.

Figure 8



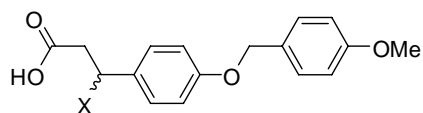
Recent findings, however, suggest the osmotic hypothesis is misleading, and that the sorbitol biomarker led to doses being used that were much lower than those needed for clinical efficacy, and the safety margins required had been overestimated. This was concluded from the fact that a) inhibition of sorbitol dehydrogenase increased sorbitol levels but did not cause a change in nerve conduction in either normal or diabetic rats and b) sorbitol constitutes only a small fraction of the total osmolytes, suggesting osmosis is not the issue. Further studies have suggested that oxidative stress is the link between ARI's and diabetic complications. Thus, a new paradigm for the polyol pathway now exists where tissue dysfunction and damage is caused by a reduction in oxidative defense (aldose reductase mediated) leading to oxidative stress. The use of ARI's at higher doses than previously administered should be a viable approach to treating diabetic complications. There is preclinical evidence in diabetic rodents to support this.





“GPR40 Agonists for the Treatment of Type 2 Diabetes,”

Daniel Lin, (Amgen Inc).

GPR40 is a GPCR that has been shown to be expressed in pancreatic β -cells and enteroendocrine cells. Stimulation of GPR40 in β -cells (by fatty acids such as linoleic acid) causes a glucose-dependant increase in insulin secretion. As the mechanism of action is glucose-gated, there is a reduced potential for hypoglycemia. Although agonism of the receptor appears to be the desired functional response (GPR40 KO mice are protected from HFD induced diabetes) there is still some debate as to whether agonism or antagonism is the desired outcome. Amgen initiated an HTS looking for GPR40 agonists (using an aequorin assay) resulting in the hit series (Figure 9).

Figure 9



| X | Human EC ₅₀ |
|---|------------------------|
| H | 1.1 uM |
| Et | 3.2 uM |
| Ph | 0.66 uM |
| iPr | 0.12 uM |
|  | 1.2 uM |
|  | 0.26 uM |
|  (R) | 7.0 uM |
|  (S) | 0.06 uM |

The carboxylic acid was always preferable. Lead optimization of the above hit series resulted in a compound with interesting properties (hGPR40 EC₅₀ = 13 nM, structure not disclosed). This exhibited good PK properties (bioavailability greater than 67% in all species except rat, very low clearance, and good volume of distribution) and also showed favorable PD properties (dose dependant increase in glucose mediated insulin secretion in mouse islets, no effect in GPR40 KO mouse). In vivo studies (Sprague Dawley rats) showed a dose dependant reduction in blood glucose levels (IPGTT) and increase in insulin secretion.

In a Type 2 Diabetes mouse model (NONcNZ010/lt mice) compound 38 (10 mg/kg) was found to have improved efficacy over sitagliptin (3 mg/kg). Additionally, in ZDF rats, compound 38 significantly reduced glucose AUC and increased insulin AUC. In a 22 day study, treated animals showed improved glucose tolerance vs. vehicle. Finally, the compound was dosed at 100 mg/kg to fasted rats and was found to be glucose neutral (no hypoglycemia) in contrast to drugs acting via other mechanisms of action (such as glyburide).

Thus, GPR40 agonism offers a potential new treatment for Type2 Diabetes.

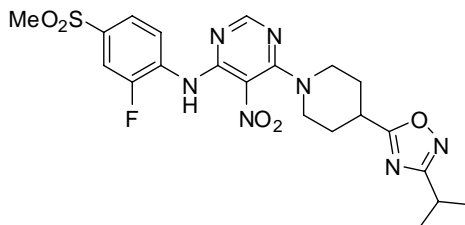
“GPR119 Agonists Mediate Glycemic Control via a Glucose Dependent Insulinotropic and Incretinotropic Action,”

Rob Jones, (Arena Pharmaceuticals).

GPR119 is a class A β -cell and GI restricted GPCR that stimulates cAMP and potentiates glucose sensitive insulin release (like GLP-1). Arena embarked on a GPR119 agonist

program and discovered AR 231453, a potent and selective agonist of GPR119 (Figure 10).

Figure 10



AR 231453
GPR119 EC₅₀ = 0.675 nM
Full Agonist
Mouse PK: Good exposure @ 10 mg/kg (T_{1/2} = 3.4 h, good C_{max})
Rat PK: Poor exposure

AR 231453 (20 mg/kg) was shown to have a similar effect to glyburide (30 mg/kg) when lowering blood glucose levels. However, unlike glyburide, AR 231453 did not cause hypoglycemia (dosed up to 100 mg/kg). AR 231453 also showed a significant increase in plasma insulin levels.

AR 231453 was subjected to an OGTT and IPGTT, where the compound was found to be more efficacious in the OGTT. This suggests the effect of the GPR119 agonist is gut mediated as well as pancreatic. The compound was also shown to stimulate release of the incretins GLP-1 and GIP at 10 mg/kg. Furthermore, when taken in conjunction with a DPPIV inhibitor, there was a cooperative effect on improving glycemic control.

A follow up compound (structure not disclosed) was also very potent against GPR119, but also showed very good rat PK at 10 mg/kg po (t_{1/2} = 4.3 h, F = 72%). This compound showed very promising sub-chronic effects in diabetic rodents, and was progressed to an eight week study in the ZDF rat. The compound exhibited dose-dependant protection against glucose tolerance (improved glucose handling as the dose increased) and also showed a statistically significant reduction in HbA_{1c} levels.

Thus, GPR119 agonism is a promising new approach towards targeting Type 2 Diabetics, which (unlike GLP-1 agonists) is amenable to the development of orally active small molecules.