Metabolic Franchise: Multiple Approaches to Metabolic Disease

INTRODUCTION

>60% of Type 2 Diabetes Patients Do Not Achieve Adequate Glucose Control

- 10-20% of the two most common drug classes (SU & metformin) either do not work initially or stop working after some time
- More than 50% of patients cannot get to desired glucose levels & end up on insulin therapy
  - >50% of those on insulin therapy are inadequately controlled because they are resistant to insulin action, which requires an increase in insulin dose
  - Inability to administer high doses of insulin because of hypoglycemia leads to suboptimal glucose control
- Obesity exacerbates diabetes, yet many diabetes drugs lead to weight gain
- Lipid abnormalities are common in diabetes leading to increased cardiovascular risk
- Available therapies are associated with many unwanted side effects including:
  - Hypoglycemia
  - Weight gain
  - Gastrointestinal disturbances
  - Exacerbation of congestive heart failure
  - Increased cardiovascular risk

Type 2 Diabetes
Significant Unmet Medical Need for New Therapies

- >220 million people worldwide
  - 366 million people worldwide by 2030
- 7th leading cause of death in US
- 1.1 million deaths from diabetes worldwide in 2005
  - 50% increase in mortality expected in next 10 years

Significant Need for New Therapies

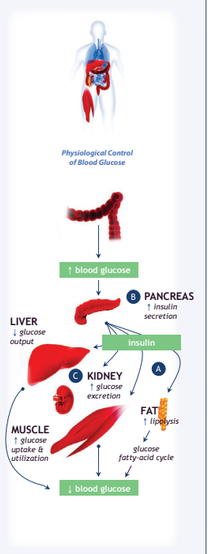
Metabolic Diseases
Why Antisense Drugs?

- Rationale
  - Many targets undruggable with traditional approaches due to issues with:
    - Target specificity (difficulty developing specific small molecules without altering other targets in the gene family)
    - Tissue specificity (difficulty inhibiting targets in specific tissues such as liver & fat without affecting tissues such as brain/adrenals)
    - Specificity results in drugs with more attractive safety profiles
  - Many important targets expressed in liver & fat cells
    - Antisense drugs have excellent distribution to these tissues

Antisense technology has the potential to yield many novel, first-in-class therapies to treat type 2 diabetes & other metabolic disorders

Isis' Metabolic Franchise
Distinct Novel Complementary Approaches to Diabetes

METABOLIC FRANCHISE OPPORTUNITIES



POTENTIAL STRATEGIES FOR NEW ANTISENSE DRUGS FOR METABOLIC DISEASES

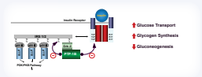
A — Insulin Action Enhancers: ↑ insulin sensitivity; insulin mimetic action → **ISIS-PTP1B$_{Rx}$**

B — Circulating Factors: ↓ action of insulin antagonists (e.g. glucagon); ↓ blood lipids (correct glucose-fatty-acid cycle) → **ISIS-GCGR$_{Rx}$**

B — Circulating Factors: ↓ action of insulin antagonists (e.g. glucocorticoid); ↓ blood lipids (correct glucose-fatty-acid cycle) → **ISIS-GCCR$_{Rx}$**

C — ↑ Glucose Excretion → **ISIS-SGLT2$_{Rx}$**

Protein Tyrosine Phosphatase-1B is a Brake on Insulin Signaling
Reduced PTP-1B Activity Amplifies Insulin's Effects



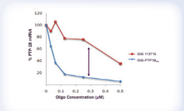
- PTP-1B inactivates the insulin receptor & acts like a brake on insulin signaling
- PTP-1B inhibition also reduces LDL-C, thus potentially reducing cardiovascular risk

PTP-1B – A Validated Target in Humans
Proof-of-Concept Demonstrated With ISIS 113715

- Two positive Phase 2 studies with ISIS 113715 completed
  - Meaningful reductions in glucose by multiple measures
    - Consistent effect on glucose & other short-term/intermediate-term indices of glucose control, such as fructosamine & glycated albumin
  - Broad therapeutic profile with positive effects beyond glucose control
    - In both studies, treatment with ISIS 113715 produced statistically significant lowering of LDL-C
  - PTP-1B inhibition was safe & well tolerated
    - No hypoglycemia or drug-drug interactions

Measurement	Monotherapy	Sulfonylurea Combination
Self-Monitored Blood Glucose	-23 mg/dL (p=0.01)	-24.8 mg/dL (p=0.06)
LDL-Cholesterol	-13 mg/dL (p=0.01)	-11 mg/dL (p=0.06)

ISIS-PTP1B$_{Rx}$ – A More Potent Inhibitor
Preclinical Studies Demonstrate up to Five-Fold Greater Potency



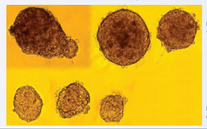
ISIS-PTP1B$_{Rx}$ – Advancing in Development

- Completed IND-enabling studies to support Phase 1 study
- Phase 1 Study – to begin in 2011
- Phase 2 Program – to begin in 2012
  - Initial studies will include combinations with metformin & insulin
  - 6 month studies

Glucagon Receptor (GCGR)
A Dual-Acting Target With Potential to be Disease-Modifying

- Glucagon is the hormone that opposes the action of insulin
  - The balance of glucagon & insulin controls normal glucose levels
  - In type 2 diabetes, this balance is disrupted in favor of glucagon action, resulting in high blood glucose levels
- Glucagon acts by binding to its receptor (GCGR) in liver cells
  - Reducing the level of GCGR will reduce glucagon action & restore the balance between glucagon & insulin action
- Traditional therapeutic attempts to antagonize glucagon signaling have not been very successful
  - GCGR is a difficult target for small molecules due to several reasons, one of them being that it has close homology to other glucagon-related peptides
- In contrast, GCGR can be specifically inhibited with antisense drugs without inhibiting other related peptides

GCGR Antisense Drug Improves Pancreatic Function: A Disease Modifying Effect



ISIS-GCGR$_{Rx}$ – Advancing in Development

- Dual mechanism of action
  - Reduces hepatic glucagon action, which lowers blood glucose levels
  - Increases GLP-1, which improves insulin secretion & leads to pancreatic regeneration
- Potential for disease modification
- Mechanism of action distinct & expected to be additive to most current therapies
- Expected to work well in a broad patient population, especially in severe diabetics, where the imbalance between glucagon & insulin is even greater & most therapies are ineffective
- Additional attributes
  - Weight neutral or may cause weight loss
  - May reduce triglycerides due to inhibition of fat breakdown in adipose tissue
- Status: Phase 1 study to begin in 2011

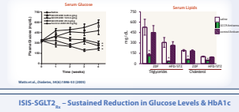
Glucocorticoid Receptor
A Validated Target for the Treatment of Diabetes

- GCCR is an intracellular receptor that mediates the action of glucocorticoids (GCs)
- Excessive GC action in liver & fat is involved in obesity, insulin resistance & glucose intolerance
  - In liver → GCs raise the level of blood sugar by increasing the amount of glucose released by the liver (gluconeogenesis)
  - In fat & muscle → GCs impair insulin action & also increase adiposity
- Attenuation of GC action through its receptor is a very attractive therapeutic approach
  - However inhibition of GCCR in tissues other than liver/fat (for example - in the brain) can lead to chronic steroid-related side effects
  - Several small-molecule inhibitors of the glucocorticoid pathway have failed because of inhibition of GC action in the brain

In contrast antisense drugs cause very selective inhibition in liver/fat tissues, providing a clear advantage vs. small molecules

GCCR Antisense Drug – Marked Reduction in Glucose & Lipids

- Highly effective in multiple animal models of type 2 diabetes
- No effect on glucocorticoid action in tissues other than liver & fat
- Reduced weight gain
- Reduced plasma triglyceride & cholesterol levels
- No evidence of hypoglycemia



Watts et al., Diabetes, 54(8):1846-53 (2005)

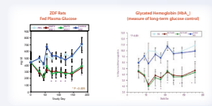
ISIS-GCCR$_{Rx}$ – Advancing in Development

- GCCR antisense drug key attributes
  - Robust glucose lowering
  - Anti-obesity effects
  - Cholesterol & triglyceride-lowering effects
  - No systemic glucocorticoid antagonism or CNS side effects
    - No symptoms of chronic steroid toxicity
    - No side effects due to distribution of drug to the central nervous system
    - Preclinical efficacy & safety superior to small molecules targeting the same pathway
- Therapeutic Opportunities
  - Patients with type 2 diabetes
  - Obese patients
  - Patients on chronic glucocorticoids who experience steroid-induced insulin resistance
- Status: Phase 1 study to begin in 2011

Sodium Dependent Glucose Co-Transporter 2 (SGLT2)

- SGLT2 is a low affinity, high capacity glucose co-transporter
  - Expressed on the apical surface of S1 segment of kidney proximal tubule epithelial cells
  - Plays an important role in the reabsorption of glucose
- Humans with SGLT2 mutations
  - Result in excretion of glucose in urine without hypoglycemia
- Why Antisense?
  - Potentially greater efficacy expected as compared to small molecules
    - Small molecules only inhibit SGLT2 function by 50%
    - In contrast, SGLT2 antisense inhibition reduces SGLT2 expression by >80% across multiple species
  - Antisense drugs distribute preferentially to kidney & cause significant reduction of SGLT2 at low doses

ISIS-SGLT2$_{Rx}$ – Sustained Reduction in Glucose Levels & HbA1c



ZDF rats were administered two different antisense drugs that hybridize to distinct regions of the SGLT2 gene (SGLT2 ASO 1 & 2)
Dose: 1.6 mg/kg once a week for 26 weeks

ISIS-SGLT2$_{Rx}$ – Advancing in Development

- Multiple antisense oligonucleotides exhibited marked potency to inhibit kidney SGLT2 expression in multiple species
- SGLT2 inhibition in a rodent model caused a significant & sustained reduction in plasma glucose & HbA1c levels
  - Robust effects in extremely diabetic animals in which rosiglitazone was ineffective
- Well tolerated following 6 months of dosing; hypoglycemia was not observed in any of the models
- ISIS-SGLT2$_{Rx}$ is currently in Phase 1 clinical studies
  - Results expected in 2H2011

STANDARD TREATMENT PARADIGM FOR TYPE 2 DIABETES

Diagnosis: Type 2 Diabetes

↓

Diet & Exercise

↓

Combo Therapy with Oral Anti-Diabetic Drugs &/or GLP-1 Analogs

↓

>50% Need Insulin Therapy

→ >220 million people worldwide
$20 billion market in US

>50% of patients end up on insulin therapy

>50% of patients on insulin are still not adequately controlled

OPPORTUNITIES FOR ANTISENSE

OPPORTUNITIES IN OBESITY

The Obesity Epidemic

- Obesity has reached epidemic levels
  - >120 million people are overweight or obese in US & EU (BMI>30)
    - 85.8 million in the US; 39.2 million in EU
  - >5% of US adults are morbidly obese (BMI>40)
  - Co-morbidity: Diabetes, heart diseases, stroke, arthritis & some cancers
- Estimated annual cost: >$117 billion
- Very limited drug options
  - Only two FDA-approved drugs currently approved for long-term use; however gastrointestinal side effects limit utility
  - Cardiovascular risk has limited the number of drugs available
- Several CNS-acting drugs have failed recently (limited safety/efficacy)
- A non-CNS-acting anti-obesity drug has great commercial potential

Highly amenable to antisense targeting (Liver & adipose tissues)

Approach complementary to CNS-based drugs (Antisense Combination Therapy)

Potential to expand therapeutic opportunity: Prevent weight gain caused by anti-psychotics

Obesity

Largely Unexploited Market
>120 million obese people in US & EU
Annual cost estimate - $117 billion

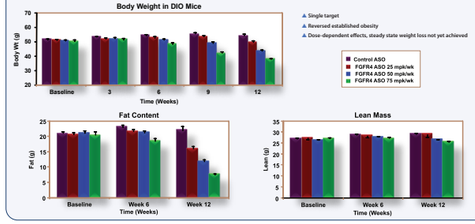
POTENTIAL STRATEGIES FOR NEW ANTISENSE DRUGS FOR METABOLIC DISEASES

Decrease Adiposity: correct energy balance (increase fat burning); decrease fat synthesis → **ISIS-FGFR4$_{Rx}$**

Developing ISIS-FGFR4$_{Rx}$ to Treat Obesity
An Exciting Preclinical Profile

- Dramatic reversal of established obesity in rodent models
  - Decrease in whole body fat content with small changes in lean mass
  - No ectopic fat accumulation
  - No effects on appetite
- Initial evidence of
  - Increased fat oxidation
  - Decreased lipid synthesis
- Distinct mechanism of action expected to be additive to diet, approved therapies & drugs in development
- Improvement of insulin sensitivity, glycemia, dyslipidemia & hepatic steatosis
- Status: IND-Enabling studies in progress to support clinical development

ISIS-FGFR4$_{Rx}$ – Reversed Obesity in Diet-Induced Obese Mice
Fibroblast Growth Factor Receptor 4 (FGFR4) - Novel Anti-Obesity Target



- Single target
- Reversed established obesity
- Dose-dependent effects, steady state weight loss not yet achieved