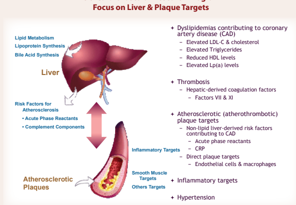
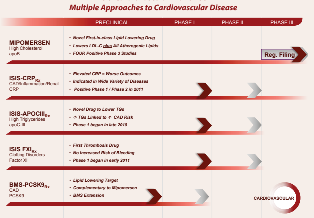
Cardiovascular Franchise: Multiple Approaches to Cardiovascular Disease

CARDIOVASCULAR FRANCHISE OVERVIEW

Isis' Cardiovascular Research Program Focus on Liver & Plaque Targets



Isis' Cardiovascular Franchise
Multiple Approaches to Cardiovascular Disease

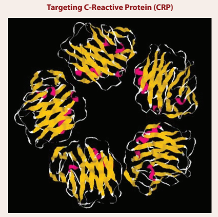


Cardiovascular Franchise Strategy

- Building diverse portfolio that attacks targets & processes contributing to cardiovascular disease & atherosclerosis
  - Creating a lipid-lowering franchise
    - Mipomersen most advanced
    - Advancing others (PCSK9; Lp(a); apoC-III)
- Expanding program to inflammation in cardiovascular disease
  - ISIS-CRP$_{Rx}$ in Phase 1; initiating Phase 2 program in rheumatoid arthritis & multiple myeloma
  - Advancing other programs
- Further expanding into thrombosis
  - ISIS-FXI$_{Rx}$ most compelling target – currently in Phase 1 development
  - Advancing other factors in same pathway

TARGET: C-REACTIVE PROTEIN (CRP)

Targeting C-Reactive Protein (CRP)



- CRP is elevated in many inflammatory diseases & diseases with inflammatory components, such as cardiovascular disease
- Elevated CRP levels associated with worse outcome in many diseases
- CRP is a complex glycoprotein & it has been very difficult to develop a small-molecule drug to inhibit it

The Importance of CRP

Diseases & conditions with an inflammatory component, such as cardiovascular disease

- Acute Coronary Syndrome
- Atrial Fibrillation
- Heart failure
- Restenosis
- Stroke
- Thrombosis
- Hypertension
- Peripheral Arterial Disease
- Crohn's Disease /IBD
- Insulin Resistance, Diabetes, Metabolic Syndrome
- Multiple Myeloma
- Rheumatoid Arthritis
- Cachexia
- Chronic Kidney Disease (CKD)
- End-Stage Renal Disease (ESRD)
- Fibromyalgia
- Multiple Sclerosis
- Periodontal Infections
- Retinopathy
- Dementia
- Organ Transplant/Graft vs. Host Disease
- *C. Difficile* in Inflammatory Bowel Disease (IBD)

- So if you can reduce CRP in a disease where it is elevated, you should provide therapeutic benefit to these patients, creating an enormous commercial opportunity

What's the question?

- In what diseases will reducing elevated CRP result in benefits to patients?
- Our drug should be the first to answer this question

ISIS-CRP$_{Rx}$ Statistically Significant Reductions in Phase 1

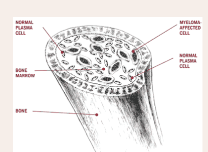
- Completed a Phase 1 clinical study
  - ISIS-CRP$_{Rx}$ produced statistically significant reductions in CRP
    - Subjects with elevated CRP levels had an average reduction of >70% compared to baseline
  - ISIS-CRP$_{Rx}$ was well tolerated at doses up to 600 mg/week

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

- Evaluate the effects of reducing CRP in diseases with well established clinical endpoints
  - Evaluate in diseases with chronically elevated CRP
  - Evaluate in diseases with acutely elevated CRP
- Initiate Phase 2 Program in 2011
  - ISIS-CRP$_{Rx}$ will be evaluated in Phase 2 proof-of-concept studies that are expected to begin mid-2011
    - Rheumatoid arthritis – evaluate in patients with stable chronically elevated CRP
    - Multiple myeloma – evaluated prior to & after patients receive autologous stem cell transplants
- Expand Phase 2 Program to explore the impact of CRP reductions in other diseases in which CRP is elevated, such as:
  - End Stage Renal Disease (ESRD)
  - Atrial fibrillation
  - Secondary prevention of heart attacks

ISIS-CRP$_{Rx}$ Phase 2 Study Populations

- Rheumatoid arthritis
  - Chronic immune-mediated inflammatory disease resulting in structural joint damage & functional disability
  - Increased risk of cardiovascular disease
  - CRP levels associated with worse outcomes
- Evaluating our drug in patients with rheumatoid arthritis chronically elevated CRP levels due to chronic inflammation
  - A well-understood clinical setting with well-established endpoints (i.e. global assessments of disease activity, pain & disability)
- Multiple myeloma
  - Blood cancer that develops in the bone marrow
  - CRP is believed to regulate tumor cell growth & protects myeloma cells from chemotherapeutic
  - Multiple myeloma patients undergo autologous stem cell transplantation, frequently incur an acute increase in CRP levels that lasts for several weeks to a month. These acute elevations are often associated with significant malaise & myalgia, serious symptoms – well established & measureable endpoints



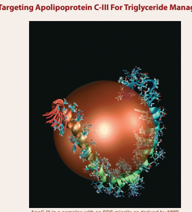
These studies will…

- Quickly demonstrate proof-of-concept & provide information opening up a wide range of disease opportunities for us to choose from for future development

"Each disease could represent a significant commercial opportunity of its own & any one of these could become a billion-dollar opportunity" - Stanley Crooke

TARGET: APOLIPOPROTEIN-CIII (APO-CIII)

Targeting Apolipoprotein C-III For Triglyceride Management

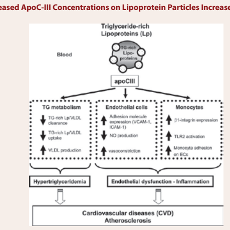

ApoC-III in a complex with an SDS micelle as derived by NMR

- ApoC-III is a glycoprotein synthesized principally in the liver
- Plays a key role in determining serum triglyceride levels
  - Inhibits clearance of triglycerides from the blood
- Difficult to specifically target using traditional therapeutics

Triglycerides in Lipid Management

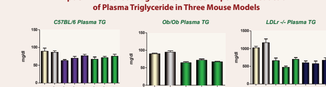
- Both NCEP & ADA recommend lowering triglycerides
  - Elevated triglycerides are recognized as an independent risk factor for coronary artery disease
  - High triglycerides have also been associated with increased risk of most strokes
- Genetically validated in humans
  - Humans with genetic loss of apoC-III have low triglyceride levels & low cardiovascular risk
  - An apoC-III drug will enhance clearance of triglycerides from the blood

Increased ApoC-III Concentrations on Lipoprotein Particles Increase CAD Risk

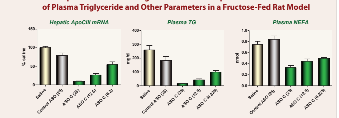


Circ Res. 2008 Dec 5;103(12):1348-50.

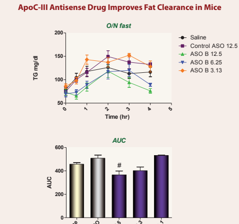
ApoC-III Antisense Drug Results in Dose-Dependent Reduction of Plasma Triglyceride in Three Mouse Models



ApoC-III Antisense Drug Results in Dose-Dependent Reduction of Plasma Triglyceride and Other Parameters in a Fructose-Fed Rat Model



ApoC-III Antisense Drug Improves Fat Clearance in Mice



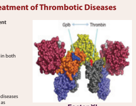
ISIS-APOCIII$_{Rx}$ – Advancing in Development

- Initiated Phase 1 in late 2010
  - Blinded, randomized, placebo-controlled, dose-escalation study in healthy volunteers
  - Designed to assess safety & pharmacokinetic profile; exploratory evaluation of effects on apoC-III & triglycerides
- Phase 2 proof-of-concept study to rapidly follow Phase 1
  - Blinded, randomized, placebo-controlled, dose-response study in patients with elevated apoC-III & triglycerides
  - Designed to provide evidence of clinical activity to lower apoC-III, & triglycerides & demonstrate safety in target population

TARGET: FACTOR XI

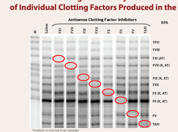
Targeting Factor XI for Treatment of Thrombotic Diseases

- Factor XI selected as target for first development candidate in thrombosis program
  - Decreases clotting without risk of bleeding
  - Genetically validated & safe target in humans
  - Broad market opportunity due to applications in both arterial & venous thrombosis
    - Can be used with anti-platelet agents
  - Patient convenience
    - Once per week or less frequent dosing
  - Coagulation factors have been linked to many diseases that go beyond thromboembolic disease such as inflammatory disease & cancer



Factor XI

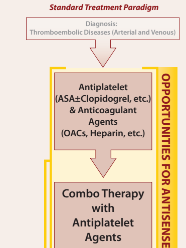
Antisense Drugs Selectively Reduce Levels of Individual Clotting Factors Produced in the Liver



Selectively reducing individual clotting factors is important to reducing bleeding & enhancing safety in humans

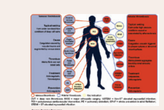
Thromboembolic Diseases & ISIS-FXI$_{Rx}$ Commercial Opportunity

Standard Treatment Paradigm



ISIS-FXI$_{Rx}$ has applications in both arterial and venous thrombosis & can be used with antiplatelet agents

ISIS-FXI$_{Rx}$ Has Potentially Broad Market Opportunities Due to its Applications in Both Arterial & Venous Thrombosis

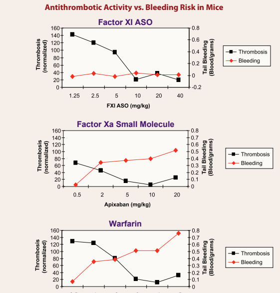


- Ideally, ISIS-FXI$_{Rx}$ will be used for prevention of CV outcomes (MI, recurrent ischemia, death & stroke) in post ACS patients receiving ASA & clopidogrel. Optimally, ISIS-FXI$_{Rx}$ will be used for prevention of ischemic stroke in AF patients
- Broad market opportunity
  - Anti-coagulant market to grow to over \$9.6 billion by 2014 (\$7.0 billion in 2008)
  - Anti-platelet market to decrease to \$8.2 billion due to expiring patents (\$10.9 billion in 2008)

ISIS-FXI$_{Rx}$ Phase 2 Study Populations

- Venous Thromboembolism (VTE)
  - High FXI levels associated with VTE
  - Low incidence of VTE found in humans with FXI-deficiency
  - VTE, encompassing deep vein thrombosis & pulmonary embolism, is a common but preventable disease
    - Associated with significant mortality & morbidity
    - Recurrent VTE is also associated with significant mortality & morbidity, & is fatal in about 4-9% of cases
- Atrial Fibrillation (AF)/Stroke
  - High FXI level is closely associated with incidence of stroke
  - Low incidence of stroke found in humans with FXI deficiency
  - AF patients have a five-fold risk of stroke
    - 30% mortality
  - Standard-of-care anticoagulants have a narrow therapeutic window & increased bleeding risk

Antithrombotic Activity vs. Bleeding Risk in Mice



Zhang H., unpublished

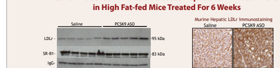
In preclinical studies, ISIS-FXI$_{Rx}$ demonstrated potent antithrombotic activity with no increase in bleeding compared with standard anti-clotting agents, including low-molecular weight heparin, warfarin & Factor Xa inhibitors, all of which increased bleeding

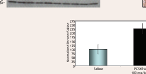
TARGET: PCSK9

Targeting PCSK9 for Lipid Management

- PCSK9
  - A novel approach to managing hypercholesterolemia, that is distinct from currently available therapies
  - Liver localized expression
  - Involved in cholesterol homeostasis
    - PCSK9 mediated LDL receptor degradation in the liver results in decreased plasma LDL clearance (i.e., higher plasma LDL)
    - Down regulation of PCSK9 results in increased LDL receptor expression in the liver, resulting in increased LDL clearance & lowering of plasma LDL
- Difficult to approach using traditional therapeutics
- ASO specificity allows targeting of PCSK9 without affecting closely related family members, thereby decreasing the potential for adverse events
  - Antisense therapeutic advantage: avoids adverse effects associated with mAb
- PCSK9 antisense drug will complement existing therapies in high-risk patient populations
- Potential commercial opportunity >1 million patients

PCSK9 Antisense Inhibitor Increases Hepatic LDLr Protein Levels in High Fat-fed Mice Treated For 6 Weeks

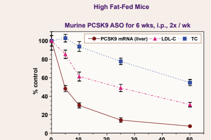


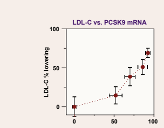


PCSK9 mRNA Reduction Correlates with LDL-C Lowering in Preclinical Studies

LDL-C lowering is proportional to PCSK9 mRNA knockdown in liver

High Fat-Fed Mice





CARDIOVASCULAR PROGRAM

Summary

- Cardiovascular program focusing on numerous targets that contribute to cardiovascular disease
- Diversified & growing program
  - Multiple drug opportunities
  - Novel mechanisms of action & areas
    - Hypertension
    - Orphan indications
- Four drugs in human clinical trials (mipomersen, CRP, FXI & APOC-III)
  - ISIS-CRP$_{Rx}$ to begin Phase 2 studies in 2011
- Multiple drugs in various stages of preclinical research & development
  - Lp(a) is an independent cardiovascular risk factor
  - Novel target to affect cells at vascular plaque site