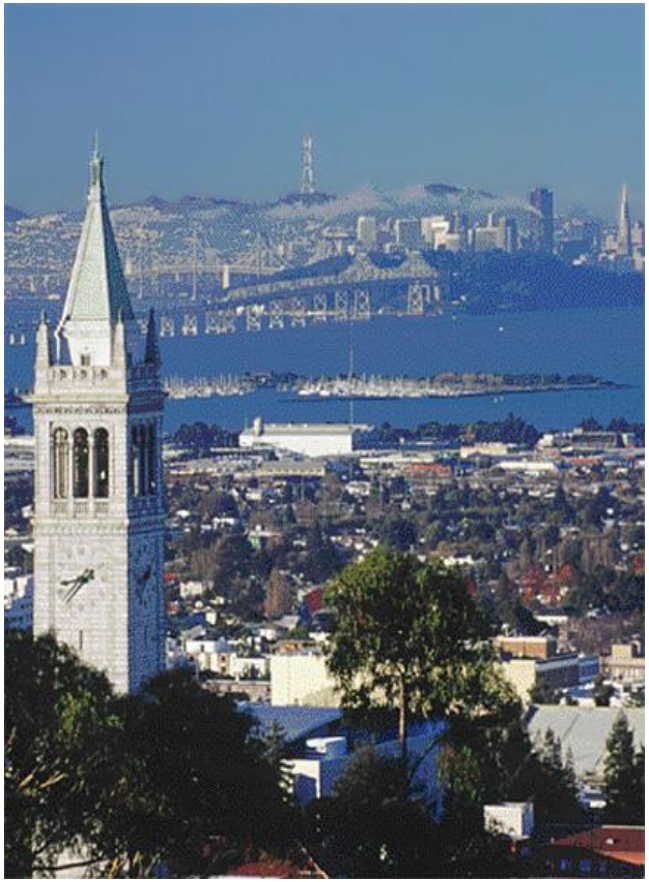
XMetD

XOMA Overview

XOMA background

- **Established 1981**
- **Headquarters: Berkeley, CA**
- **Publicly traded**
  - NASDAQ: XOMA
- **~ 170 employees**



XOMA's Vision

To be a leading bio-pharmaceutical company by

- **discovering** unique therapeutic antibodies using our world class expertise
- **developing** innovative products which improve patients' lives
- **commercializing** to specialty markets

Achieving this vision will provide significant returns for our stakeholders and rewarding opportunities for our employees

XOMA's Business Strategy

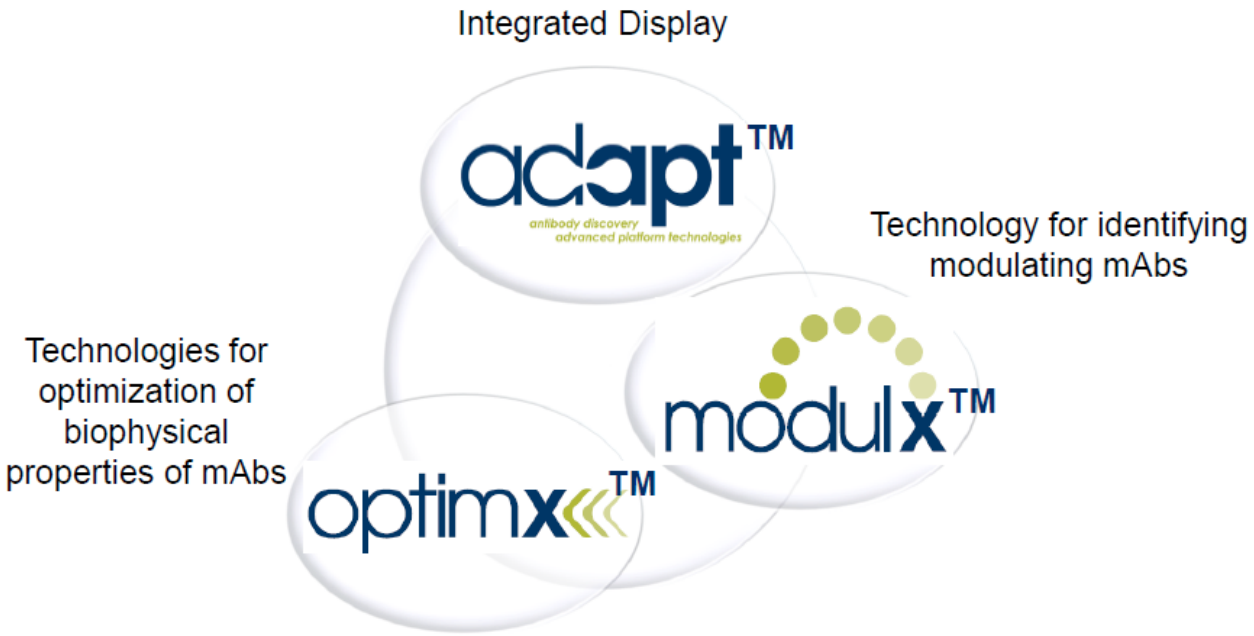
1. **Advance gevokizumab in collaboration with Servier**
   - XOMA retains all rights in U.S. and Japan for all indications except cardiovascular and diabetes with option rights to these
   - Phase 3 NIU program initiated Q2 2012
   - Multiple Phase 2 POC program to identify next Phase 3 program, expected to be developed jointly
2. **Commercialize gevokizumab and future products in the U.S. to Specialty markets and for orphan indications to capture greater value**
3. **Invest in differentiating discovery & development capabilities for pipeline and partnering**

Current Pipeline

Compound	Indication	Pre-clinical	Phase 1	Phase 2	Phase 3	Marketed
Gevokizumab	Non-infectious uveitis	→	→	→	→	
	Moderate-to-severe acne	→	→	→		
	Erosive osteoarthritis of the hand	→	→	→		
	Scleritis	→	→			
XMetA	Type 1 & 2 diabetes mellitus	→				
XMetS	Type 2 diabetes mellitus	→				
XMetD	Potential orphan indications	→				
TGF-β	Ophthalmology indications	→				
Discovery programs	Orphan indications	→				

XOMA's Ab Platform Includes Multiple Technologies that are ADAPTed to Specific Antibody Design Goals

- **XOMA mAb discovery program capable of rapid interrogation of receptors and discovery of novel allosteric binder**



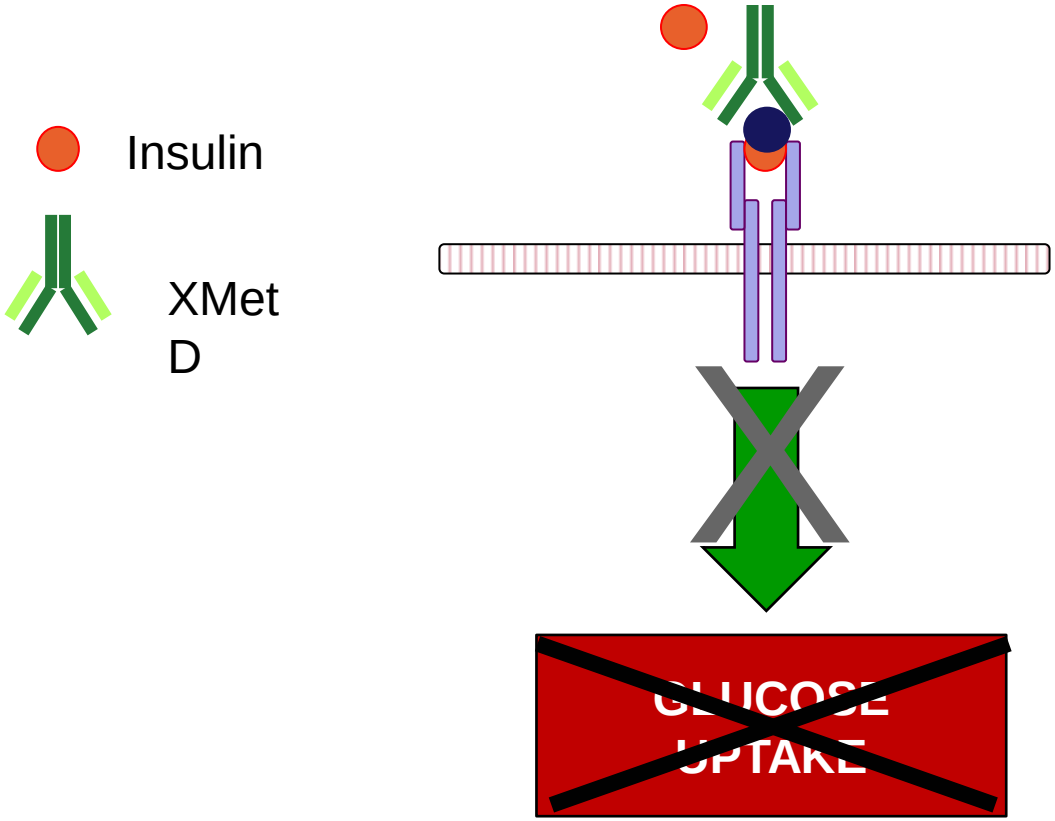
XOMA mAb Discovery: XMet Program

- **The XMet program uncovered three apparently novel classes of insulin receptor allosteric binders**
  - Activators of the INSR (e.g. XMetA)
  - Enhancers of the insulin-receptor complex (e.g. XMetS)
  - Deactivators of the INSR (e.g. XMetD)
- **XMetA and XMetS programs are in research**
  - XOMA intends to seek collaboration partners for global development for XMetA and XMetS
- **Within XMetD class molecules, a lead has been identified for development by XOMA to treat CHI and potentially other hyperinsulinemic hypoglycemic conditions**

XMetD Rationale

XMetD mechanics

- Allosteric antagonist that inhibits insulin dependent activation of the INSR



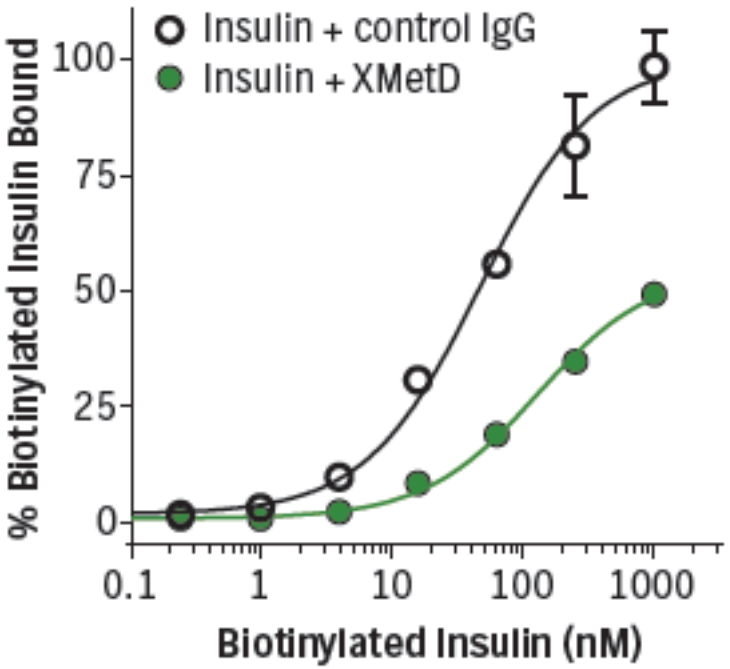
XMetD In Vitro Profile

XMetD In Vitro Profile

Antagonism	• Inhibits binding of insulin to the INSR • Inhibition of INSR auto-phosphorylation • Inhibition of INSR signaling via Akt
Specificity	• Does not affect IGF-1R mediated Akt signaling

Assay to analyze inhibition of binding of insulin to the INSR

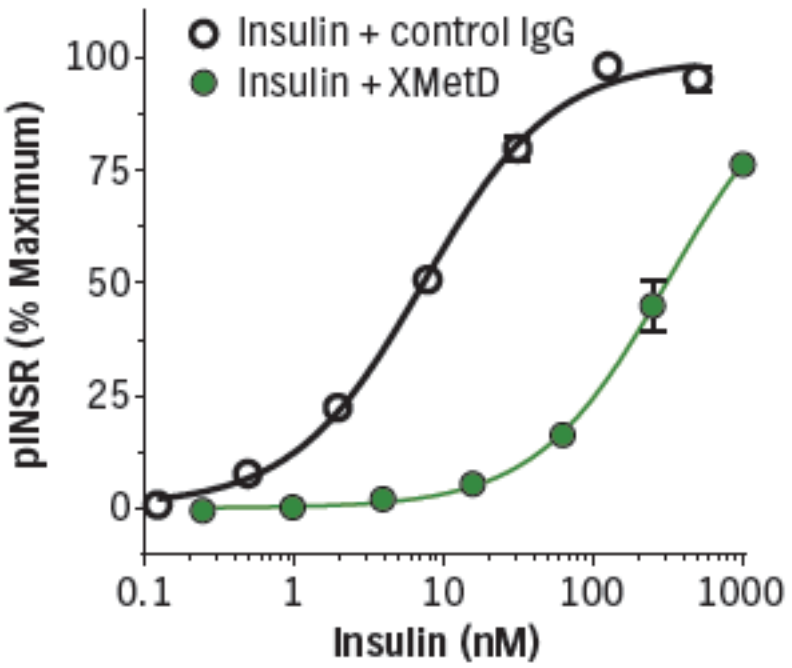
- Cells expressing hINSR preincubated with XMetD or control IgG
- Cells were then challenged with increasing concentrations of insulin
- Biotinylated insulin binding to INSR measured by FACS



- **XMetD appears to inhibits the binding of insulin to the INSR by ~3x**

Assay to analyze attenuation of INSR auto-phosphorylation

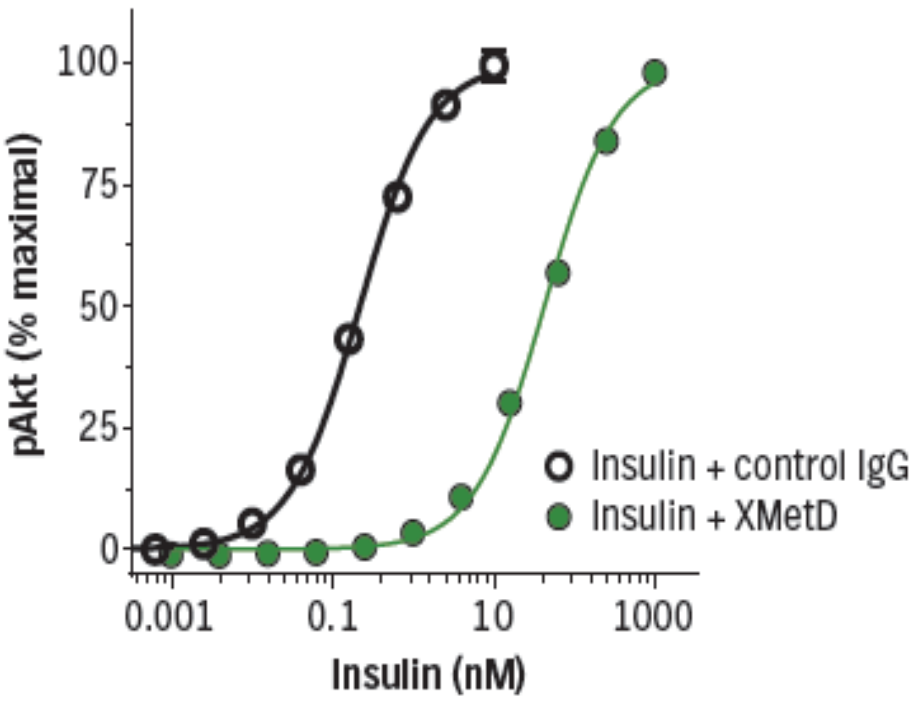
- Cells expressing hINSR preincubated with XMetD or control IgG
- Cells were then challenged with increasing concentrations of insulin
- INSR autophosphorylation was determined by ELISA



- **XMetD appears to attenuate autophosphorylation of the INSR in the presence of insulin by ~40x**

Assay to analyze attenuation of INSR signaling via Akt

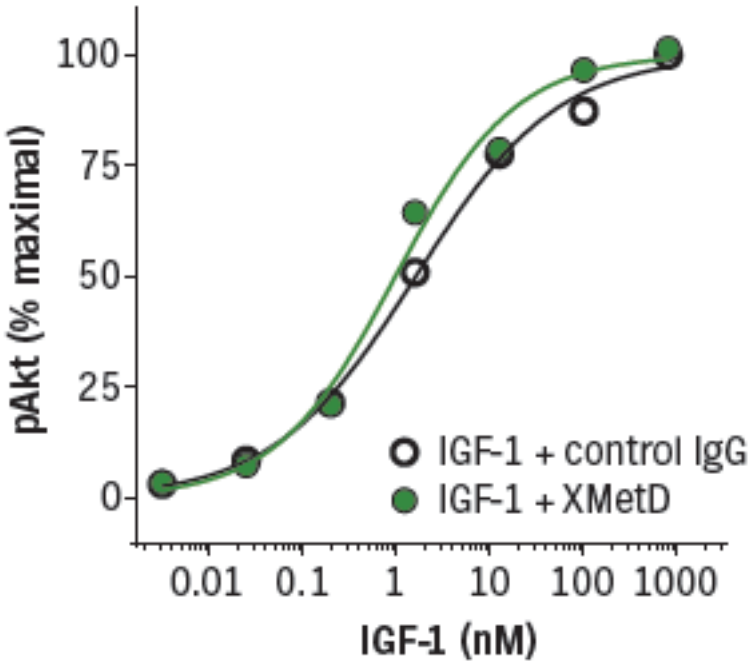
- Cells expressing hINSR preincubated with XMetD or control IgG
- Cells were then challenged with increasing concentrations of insulin
- Phosphorylation of Akt determined by electrochemiluminescence



- **Akt signaling via INSR appears to be effectively attenuated in the presence of XMetD by ~100x**

Assay to demonstrate lack of antagonism of IGF-1R via Akt

- Cells expressing hINSR preincubated with XMetD or control IgG
- Cells were then challenged with increasing concentrations of IGF-1
- Phosphorylation of Akt determined by electrochemiluminescence



- **XMetD is selective for the INSR and does not appear to affect Akt signaling via the IGF-1R**
- **Theoretically should permit normal IGF-1 response**

XMetD In Vitro Summary

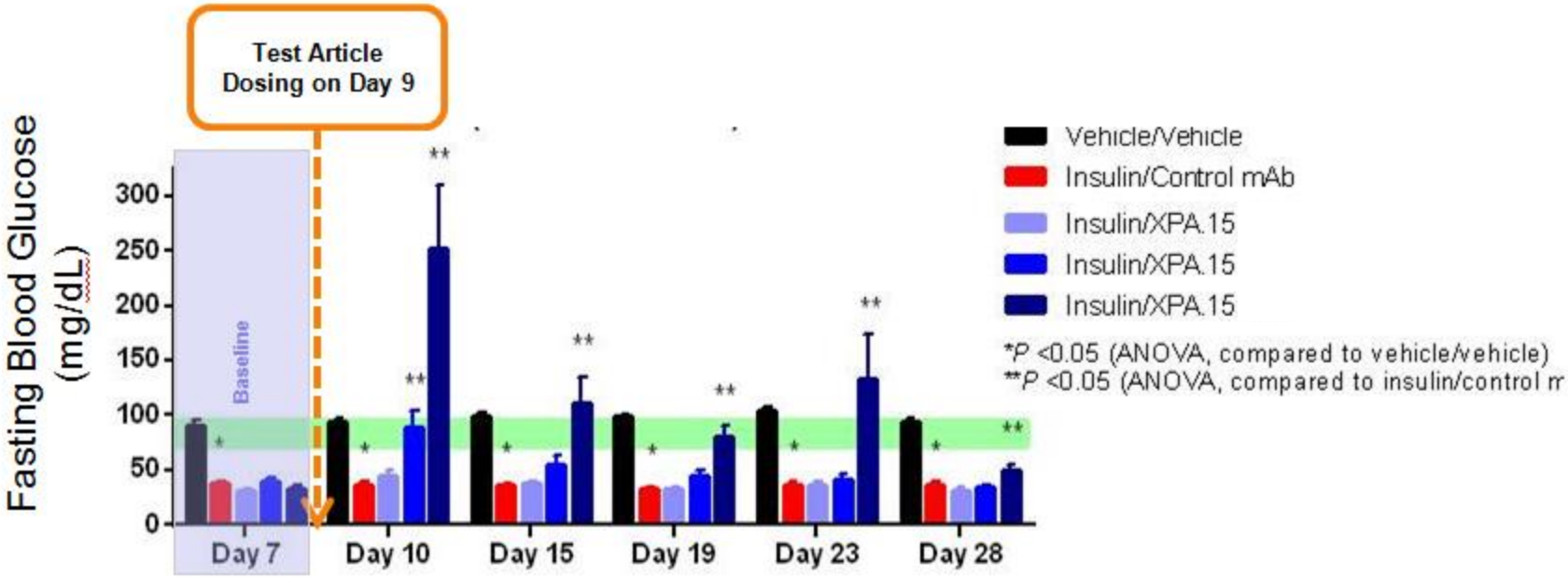
- XMetD antagonism can be measured via insulin binding inhibition, INSR autophosporylation, and Akt signaling
- Antagonist activity of XMetD is selective for the INSR

XMetD Pharmacology

Pharmacology models and studies

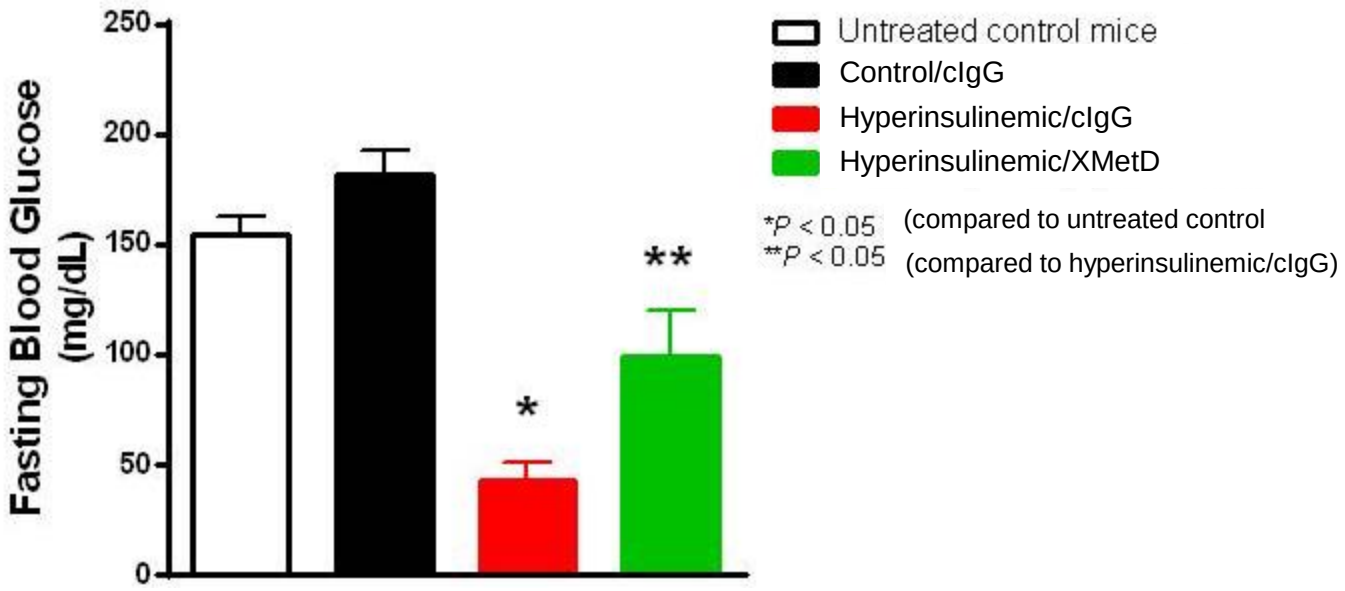
- **Objective for pharmacology models to use XMetD to restore FBG in hypoglycemic animal models**
- **XMetD was tested in rodent models of hyperinsulinemia-induced hypoglycemia:**
  - Rat model of hyperinsulinemic hypoglycemia
  - Mouse model of hyperinsulinemic hypoglycemia
  - Sur1 -/- mouse model (Deleon @ CHoP)
- **Primary PD endpoints for efficacy evaluation**
  - Fasting and fed glucose levels
  - Fasting and fed insulin levels

Single dose, rat hyperinsulinemic model to demonstrate efficacy on FBG



- XMetD has a dose dependent effect on hypoglycemia in a single dose study
- At higher doses, duration extends through Day 28

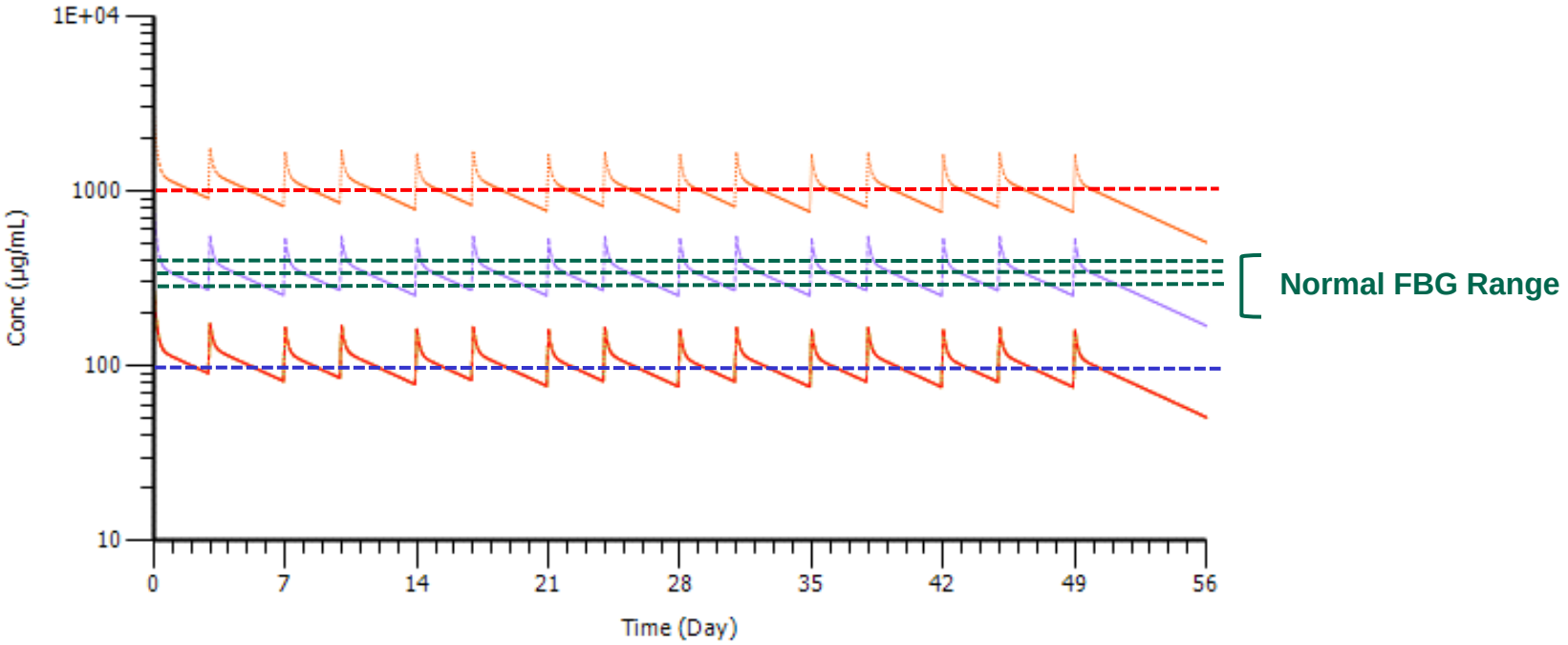
Single dose, mouse hyperinsulinemic model to demonstrate efficacy on FBG



- XMetD restores FBG in mice with elevated insulin levels

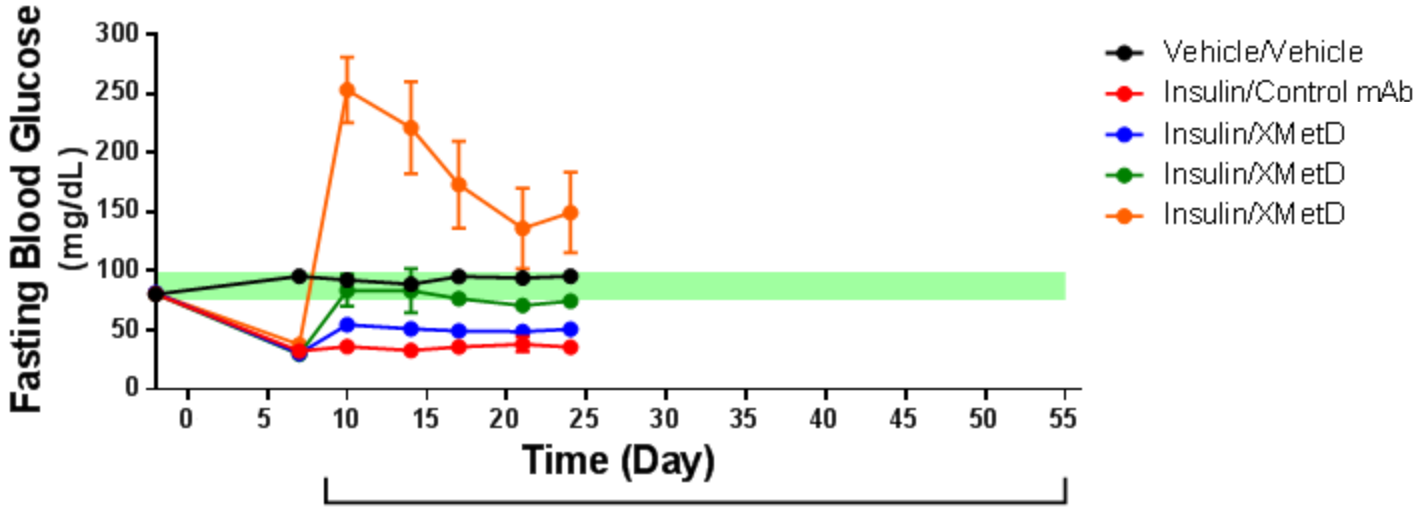
Demonstration of prolonged FBG control with a repeat dosing in a rat hyperinsulinemic model

WinNonLin Simulation of biwk x 7



- Data from Study 1 along with PK and TK data generated from prior studies were used to generate a dosing model for producing a euglycemic state
- Data derived from the model was used to design a multi-dose study
- Repeat study dosing study was done in the rat hyperinsulinemic model

Demonstration of prolonged FBG control with a repeat dosing in a rat hyperinsulinemic model *(contd.)*



- Preliminary data from Day 24
- Model accurate at predicting pharmacological dose response

Demonstration of efficacy in K_{ATP} CHI with Sur1 -/- mouse model

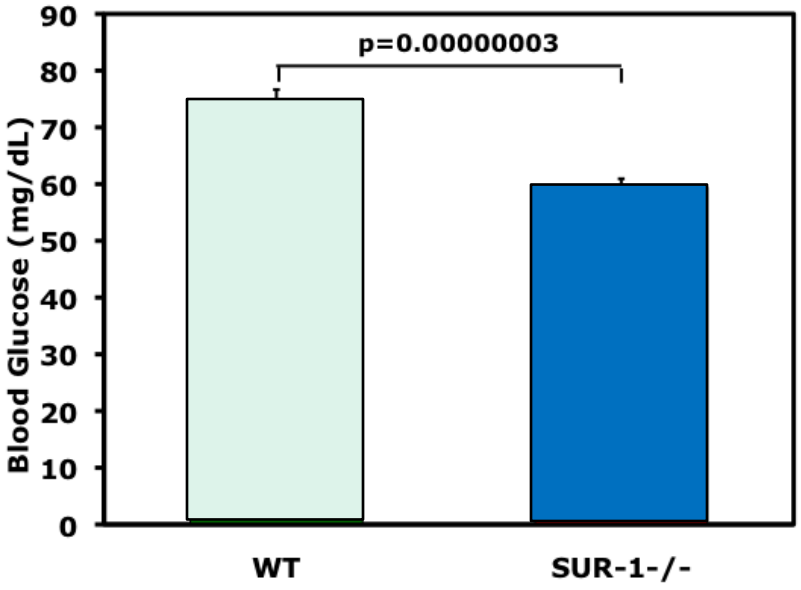
Background information on K_{ATP} CHI

- **K_{ATP} hyperinsulinism is a rare but devastating disease characterized by defects in the islet K_{ATP} channel**
  - The Sur1 -/- mouse model simulates one the most severe forms of this disease
- **Developed and run by Diva Deleon at CHoP**
  - XMetD experiments are run in collaboration with XOMA

Demonstration of efficacy in K_{ATP} CHI with Sur1 -/- mouse model *(contd.)*

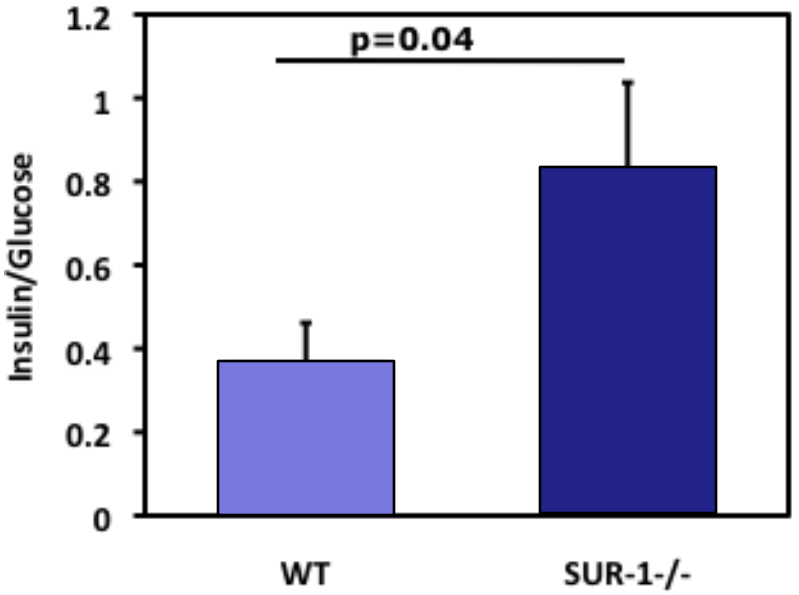
Sur1 -/- mouse model description

FBG glucose
WT vs. Sur1 -/-



- The Sur1 -/- model is characterized by lower FBG in relation to WT

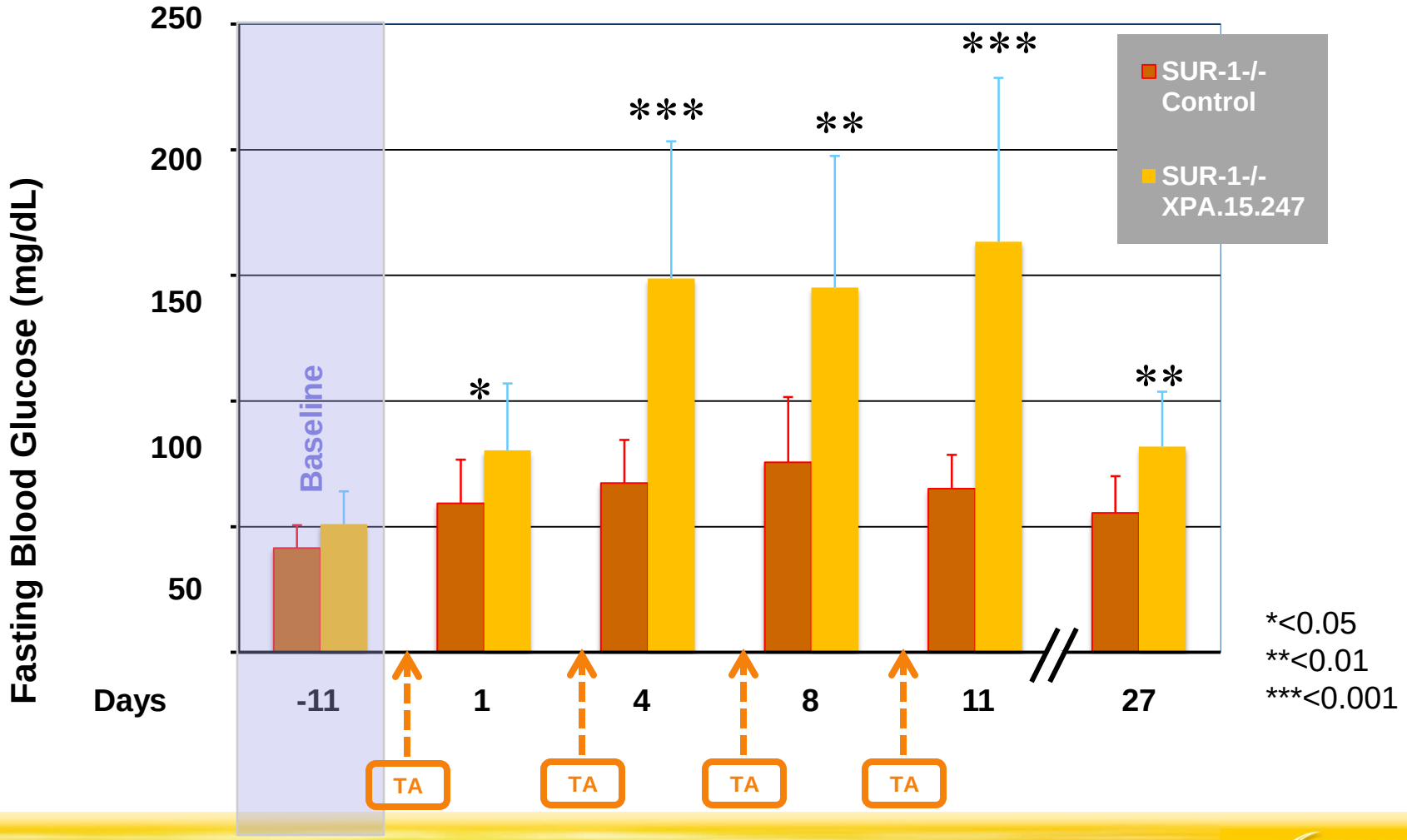
Insulin/glucose ratio
WT vs. Sur1 -/-



- The ratio of circulating insulin to FBG is significantly higher in the Sur1 -/- mouse

Demonstration of efficacy in K_{ATP} CHI with Sur1 -/- mouse model *(contd.)*

Efficacy and duration of 4 doses at 30mgs/Kg over a 28 days study



XOMA

Pharmacology Summary

- XOMA247 demonstrates the ability to normalize fasting glucose levels in both a hyperinsulinemic hypoglycemia and a CHI model of hypoglycemia in rodent models

XMetD Clinical Plans

Ph1: Study Design

- **Phase 1**
  - Design
    - Adult patients with CHI
    - Ascending single doses
  - Objectives
    - Safety
    - Pharmacokinetics
    - PK/PD relationship regarding hypoglycemia after a prolonged fast
    - Duration of activity
    - Optimal dose and dosing schedule