Development of anti-aP2 therapeutics against diabetes and fatty liver disease

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Financial Disclosure

I don’t have any conflict of interest
Worldwide obesity gains 30%

70 Trillion $

Premature death

Obesity

Metabolic disease clusters

Insulin resistance
Type 2 diabetes
Fatty liver disease
Atherosclerosis
Hypertension
Stroke

Cancer
Asthma
Sleep apnoea
Osteoarthritis
Neurodegeneration
Gall bladder disease

Obesity recognized as a disease

Rosen, Cell 2014
Adipocyte Fatty Acid Binding Protein (FABP4-aP2)
Genetic deficiency of aP2 is protective in many diseases

aP2 -/-
aP2 deletion
aP2 & Diabetes

Deficiency of adipocyte FABPs protects against a variety of metabolic diseases

Maeda et al. 2005
Shum et al. 2006
Boord et al. 2004
Maekawa et al. 2002

Blood Glucose (mg/dl)

Maeda 2005 Cell Metabolism
aP2 & Atherosclerosis

Evidence that aP2 is important in metabolic disease

Hotamisligil Confidential

Boord 2004 Circulation
aP2 & Fatty Liver Disease

Evidence that aP2 is important in metabolic disease

Hepatosteatosis
Adipocyte Lipid Chaperone aP2 Is a Secreted Adipokine Regulating Hepatic Glucose Production

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http://dx.doi.org/10.1016/j.cmet.2013.04.012
Serum aP2 levels increased with obesity

Serum aP2 and BMI

- Male, r=0.41  p<0.001
- Female, r=0.46  p<0.001

Serum aP2 in genetic obesity in mouse and man

Cao & Hotamisligil, unpublished
Cardiometabolic Correlates and Heritability of Fetuin-A, Retinol-Binding Protein 4, and Fatty-Acid Binding Protein 4 in the Framingham Heart Study

Bernhard M. Kaess, Danielle M. Enserro, David D. McManus, Vanessa Xanthakis, Ming-Huei Chen, Lisa M. Sullivan, Cheryl Ingram, Christopher J. O’Donnell, John F. Keaney, Ramachandran S. Vasan, and Nicole L. Glazer
A genetic variant at the fatty acid-binding protein aP2 locus reduces the risk for hypertriglyceridemia, type 2 diabetes, and cardiovascular disease


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Communicated by Barry R. Bloom, Harvard School of Public Health, Boston, MA, March 15, 2006 (received for review December 15, 2005)

Promoter polymorphism results in decreased adipose aP2 expression

n: 7899
MVB

aP2

Lipolysis

β-adrenergic stimulation

Glucose Production

Other Organs?
Study Design

- Weekly Fasting Blood glucose
  Fed Body Weight
- Week 2 Glucose tolerance test
- Week 3 Insulin tolerance test
- Week 4-5 Clamp - SAC
- Histological and molecular tests from week 4-5 tissues.
The monoclonal anti-aP2 antibody CA33 improved glucose metabolism

**A.**

![Glucose levels comparison](image)

**B.**

![Insulin levels comparison](image)

**C.**

![Glucose response to insulin](image)

**D.**

![Glucose response to insulin](image)

* Burak et al. Science TM 2015
The monoclonal anti-aP2 antibody CA33 improved glucose metabolism.
CA33 effect is specific to aP2 and robust in different obesity models
Clamp Settings

Tissue collection

4 days recovery

H\textsuperscript{3}-glucose

+++ Insulin

+ Glucose

C\textsuperscript{14}-glucose

2 hr

2.5 hr

45 min

acclimatization

basal

Steady state

clamp

Tissue collection
CA33 decreased liver glucose production and increased peripheral insulin sensitivity.
CA33 treatment improved lipid metabolism and reversed hepatosteatosis in obese mice

Burak et al. Science TM 2015
CA33 treatment improved lipid metabolism and reversed hepatosteatosis in obese mice

Burak et al. Science TM 2015
CA33 prevented HFD induced weight gain and decreased BW
CA33 decreased fat mass

**A**
- Bar chart showing body composition (Fat mass (g) and Lean mass (g)) for Vehicle and CA33.

**B**
- Bar chart comparing Liver Weight and % Body Weight for Vehicle and CA33.

**C**
- Bar chart showing PGWAT Weight (g) for Vehicle and CA33.

**D**
- Bar chart showing BAT Weight (g) for Vehicle and CA33.

**E**
- Images of Vehicle and CA33 samples, indicating reduced fat mass.

*Burak et al. Science TM 2015*
CA33 accelerated oxidative metabolism and decreased fat mass

E

Activity counts (AU)

Vehicle
CA33

Light
Dark

F

Total food intake (g)

Vehicle
CA33

Light
Dark

G

VO2 (ml/kg/hr)

PBS
CA33

Light
Dark

H

RER

PBS
CA33

Light
Dark

Oxidation of a molecule of Carbohydrate

6 O2 + C6H12O6 => 6 CO2 + 6 H2O + 36 ATP

RER = VCO2/VO2 = 6 CO2/6 O2 = 1.0

Oxidation of a molecule of Fatty Acid

23 O2 + C16H32O2 => 16 CO2 + 16 H2O + 129 ATP

RER = VCO2/VO2 = 16 CO2/23 O2 = 0.7

Burak et al. Science TM 2015
Summary

- aP2 secretion increased with fasting.

- Serum aP2 levels increased with human obesity and contributes to hyperglycemia.

- Secreted aP2 can be effectively targeted by a monoclonal antibody to ameliorate diabetes and reduce fat mass and hepatic steatosis.

- CA33, as a potential preclinical molecule that lowered fasting blood glucose, improved glucose metabolism, increased systemic insulin sensitivity and reduced liver steatosis.

- These metabolic outcomes were;
  - reproducible in two independent models of obesity, genetic and dietary,
  - specific to aP2,
  - linked to the regulation of hepatic glucose output and peripheral glucose utilization.

- CA33 also decreased fat mass and increased oxidative capacity without any effect on physical activity and food intake.