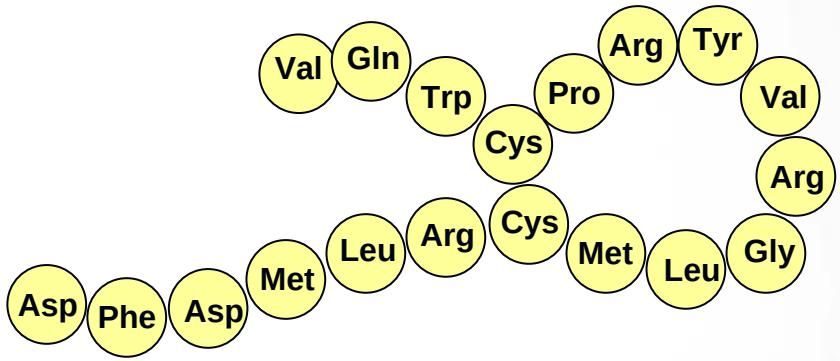
Melanin Concentrating Hormone Receptor-1 (MCH_1) antagonists for the treatment of obesity

July 20, 2010

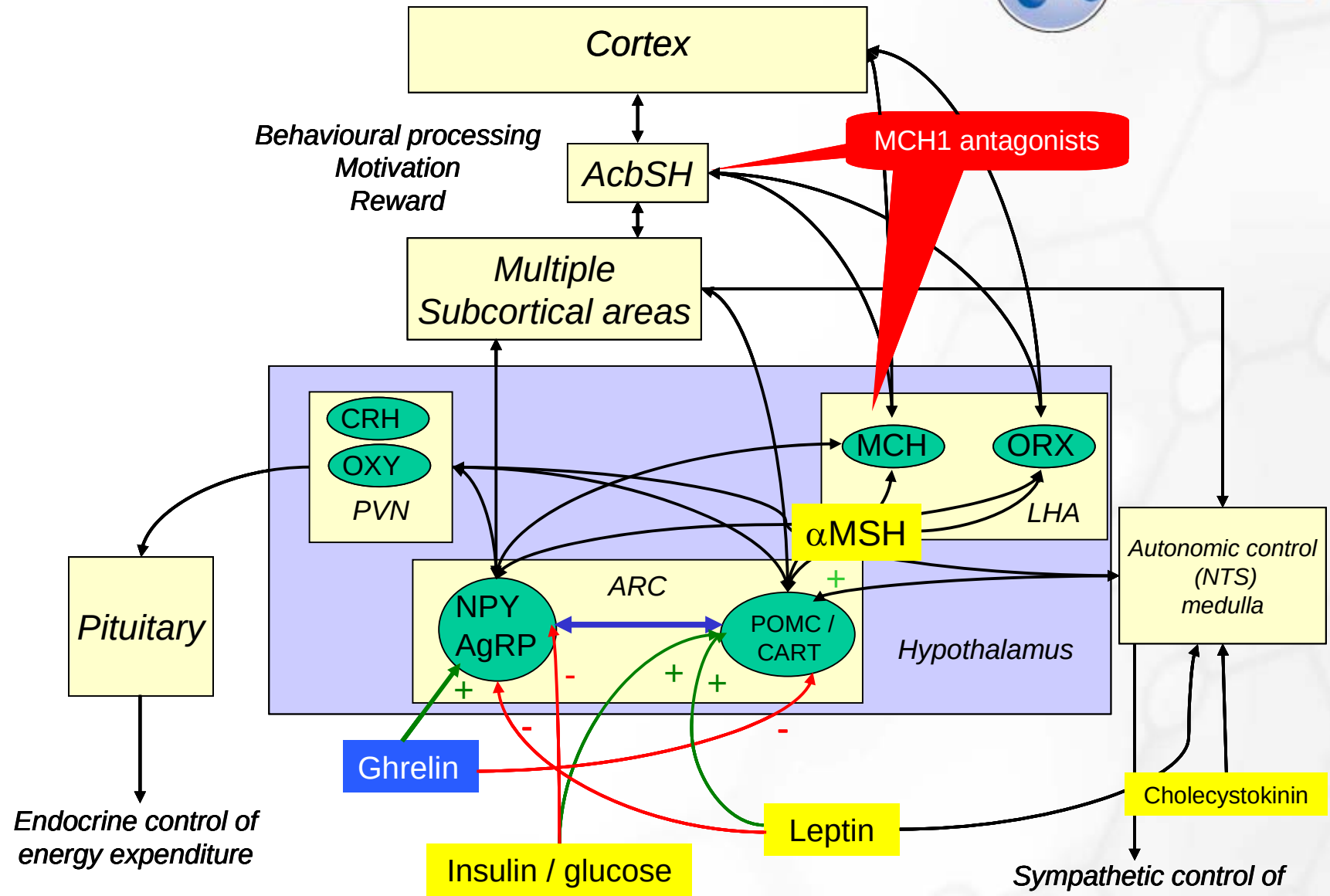
MCH_1 Antagonists for Obesity

Biology Overview



- Melanin Concentrating Hormone (MCH) is a 19 amino acid peptide (identical in rat and man). MCH_1 is a GPCR expressed primarily in the CNS. MCH plays an important role in energy balance and body weight.
- Mice overexpressing MCH develop obesity due to stimulation of food intake.
- MCH (-/-) mice are lean with normal body mass, reduced fat mass and resist obesity development due to hypophagia and increased metabolic rate.
- Chronic MCH_1 antagonists studies in rodents have shown slow onset of weight-loss but a large cumulative effect. No tolerance to the hypophagic effect of MCH_1 antagonists have been observed, unlike monoaminergic anti-obesity drugs.

Central Pathways Involved in Feeding and Energy Utilization



Sargent, BJ; Moore, NA *Br J Clin Pharmacol* 2009, 852.

Competitor MCH_1 Programs

- **3 Companies entered Phase I clinical trials (discontinued):**
  1. **Tularik/Amgen AMG-076 or T-71**
  2. **GSK 8564643**
  3. **Neurogen NGD 4715**

- **Toxicities observed preclinically:**
  - **hERG and QTc prolongation rampant!!**
  - **Abbott found cardiovascular toxicity across several structural classes: MAP and heart rate lowering as well as QTc**
  - **Others found random toxicity**
  - **GPCR selectivity, etc…**

MCH_1 Screening Strategy

Primary target assays + Key liability assays

Acute *in vivo* Exposure Profiling

Sub chronic *in vivo*

Candidate Selection Chronic models Tox & liability

Candidate Compound Profile
ALB-127158(a)
In Vitro Data

Property	ALB-127158(a)
MCH_1 Binding[1] (K_i, nM)	7.0 ± 1.5
MCH_1 Funct. Ant.[1] (IC_{50}, nM)	47 (n=2)
Molecular Weight	<410
tPSA	57
CLogP	2.62
LogP[2]	1.58
$LogD_{7.4}$	– 0.20
pK_a[2]	9.17, 3.16
Solubility in PBS (pH 7.4) (μM)	>500

[1]Human receptor; [2]Determined by potentiometric titration.

Candidate Compound Profile
In Vitro Data (continued)

Assay	ALB-127158(a)
CYP Inhibition[1] (IC_{50}, μM)	>30
hERG[2] (IC_{50}, μM)	18 (n=3)
Receptor Selectivity Panel[3]	No significant activity
CL_{int} (HLM) (μL/min/mg)[4]	2.3 (n=3)
CL_{int} (MLM) (μL/min/mg)[5]	2.4 (n=3)
CL_{int} (RLM) (μL/min/mg)[6]	1.8 (n=3)
Human PPB[7] (%)	85.3 (n=3)
Mouse PPB[7] (%)	58.2 (n=2)
Rat PPB[7] (%)	84.2 (n=3)
Dog PPB[7] (%)	65.5 (n=2)

[1]CYP isoforms tested, 1A2, 2B6, 2C9, 2C19, 2D6, 3A4; [2]Mini Patch Clamp; [3]Panel of 80 receptors, mostly GPCRs including MCH_2, tested at 1 and 3 μM; [4]Intrinsic clearance in Human Liver Microsomes; [5]Intrinsic clearance in Mouse Liver Microsomes; [6]Intrinsic clearance in Rat Liver Microsomes; [7]PPB = Plasma Protein Binding

Candidate Compound Profile
In Vitro Data (continued)

Assay	ALB-127158(a)
CYP Induction[1] (1A2 and 3A4)	Negative up to 100 μM
Reactive Metabolites (human liver microsomes)	No conjugates formed with glutathione or semicarbazide
Metabolic Profile (human, mouse, rat, dog, monkey liver microsomes and hepatocytes)	High metabolic stability in all species (95% parent remains); Human, rodent and monkey profiles similar
CYP Phenotyping (six human CYP isoforms[2])	Multiple CYP isoforms (1A2, 2B6, 2C9, 2C19, 2D6, 3A4) involved in metabolism
Time Dependent CYP Inhibition (six human CYP isoforms[2])	No observed formation of metabolism- or mechanism-based inhibitors
Mini-Ames (TA98 and TA100, +/- S9)	Negative up to 500 μM

[1]Human hepatocytes; [2]human 1A2, 2B6, 2C9, 2C19, 2D6, 3A4 isoforms

Design of an *Ex Vivo* Receptor Occupancy Assay Using [^{3}H]AMR-MCH-1[1]

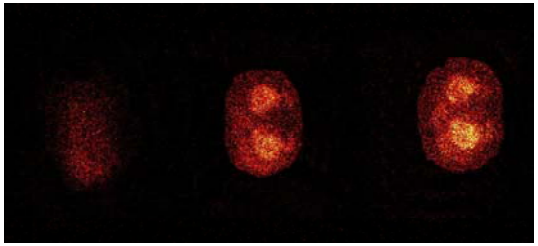
- Previously iodinated peptide ligands used to label MCH_1 receptors[2]
- Iodinated peptide ligands suffer from high non-specific binding
- Specific binding of [^{3}H]AMR-MCH-1 was high in the caudate putamen with low levels of non-specific binding
- Levels of *ex vivo* binding for previously reported compound (SCH-A[2]) were in good agreement with previous method

Ref: 1. Viggers, J.A. et al. Society for Neuroscience Annual Meeting 2008, Abstract 584.27/SS8.
2. Kowalski et al Eur. J. Pharmacol. 2006, 535: 182-191.

[^{3}H]AMR-MCH-1 *Ex Vivo* Autoradiography in Caudate Putamen of DIO Mice Following Oral Dosing of SCH-A (10 mg/kg and 30 mg/kg)

AMRI

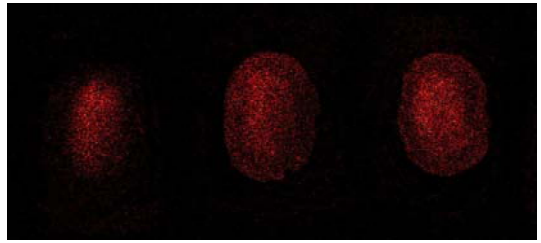
Vehicle 6H



Non-specific Binding | Total Binding | Total Binding

Sample 7a
Specific Binding =0.95 cpm/mm^2

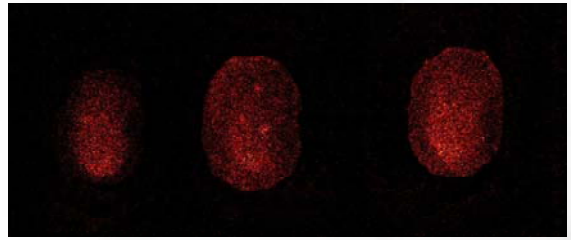
SCH-A (10 mg/kg po) 6H



Non-specific Binding | Total Binding | Total Binding

Sample 8b
Specific Binding =0.04 cpm/mm^2

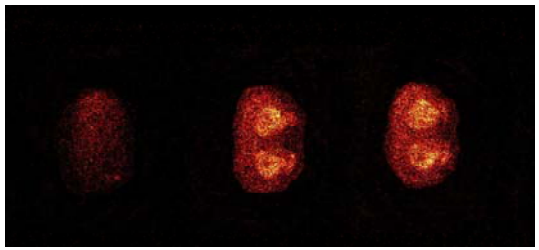
SCH-A (30 mg/kg po) 6H



Non-specific Binding | Total Binding | Total Binding

Sample 9c
Specific Binding =0.01 cpm/mm^2

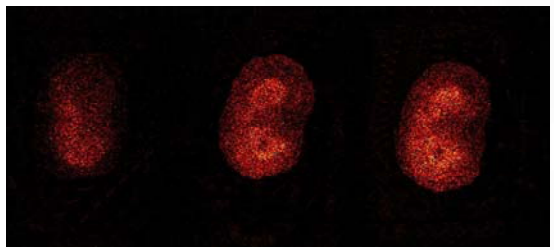
Vehicle 24H



Non-specific Binding | Total Binding | Total Binding

Sample 10d
Specific Binding =0.96 cpm/mm^2

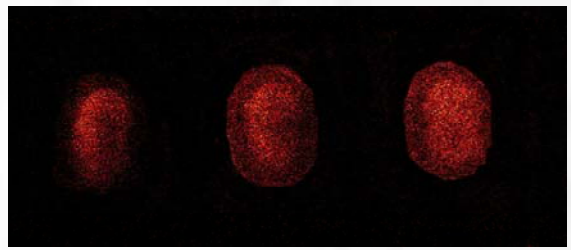
SCH-A (10 mg/kg po) 24H



Non-specific Binding | Total Binding | Total Binding

Sample 11e
Specific Binding =0.49 cpm/mm^2

SCH-A (30 mg/kg po) 24H

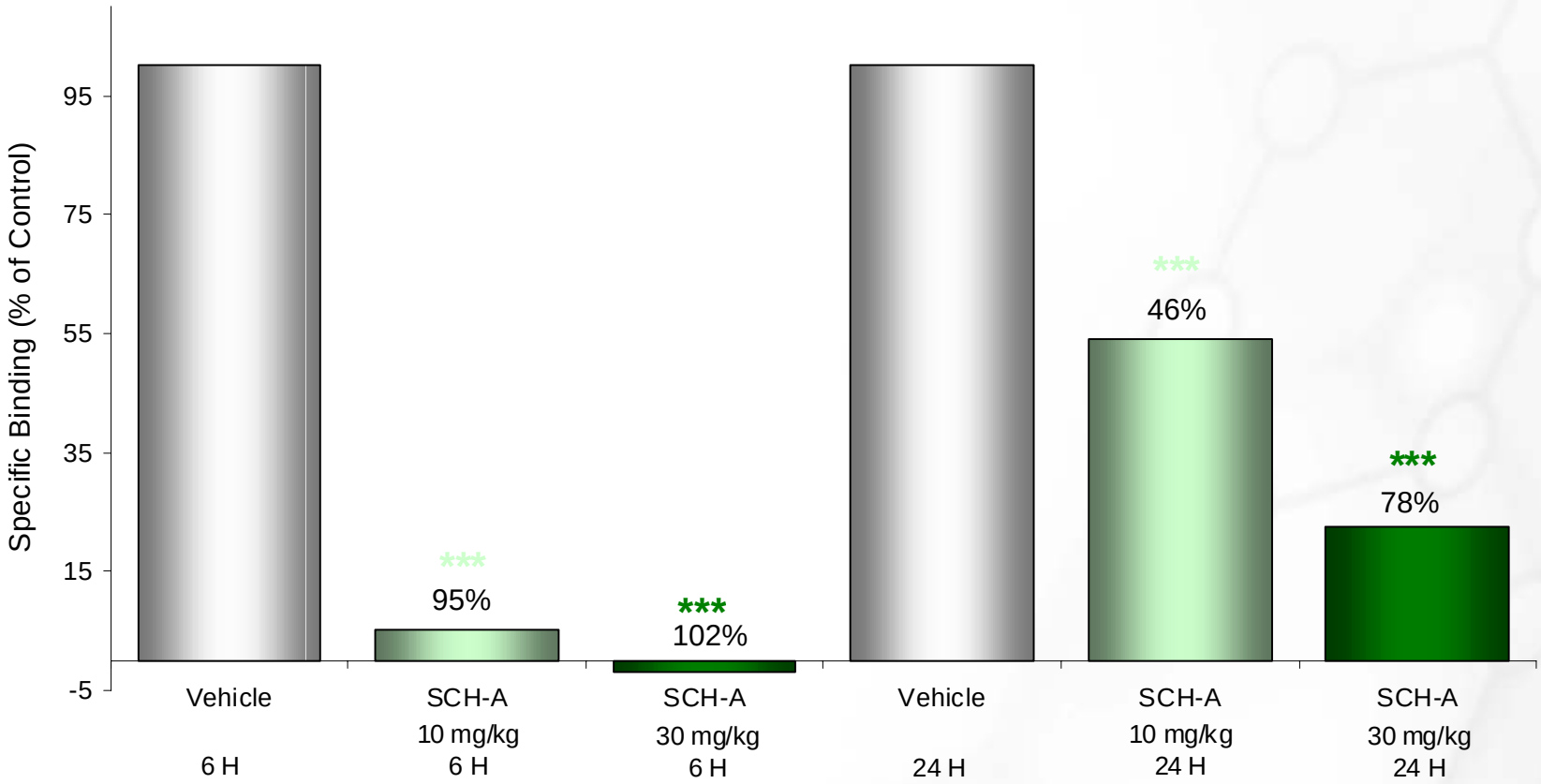


Non-specific Binding | Total Binding | Total Binding

Sample 12f
Specific Binding =0.18 cpm/mm^2

Images represent individual samples from each experimental group

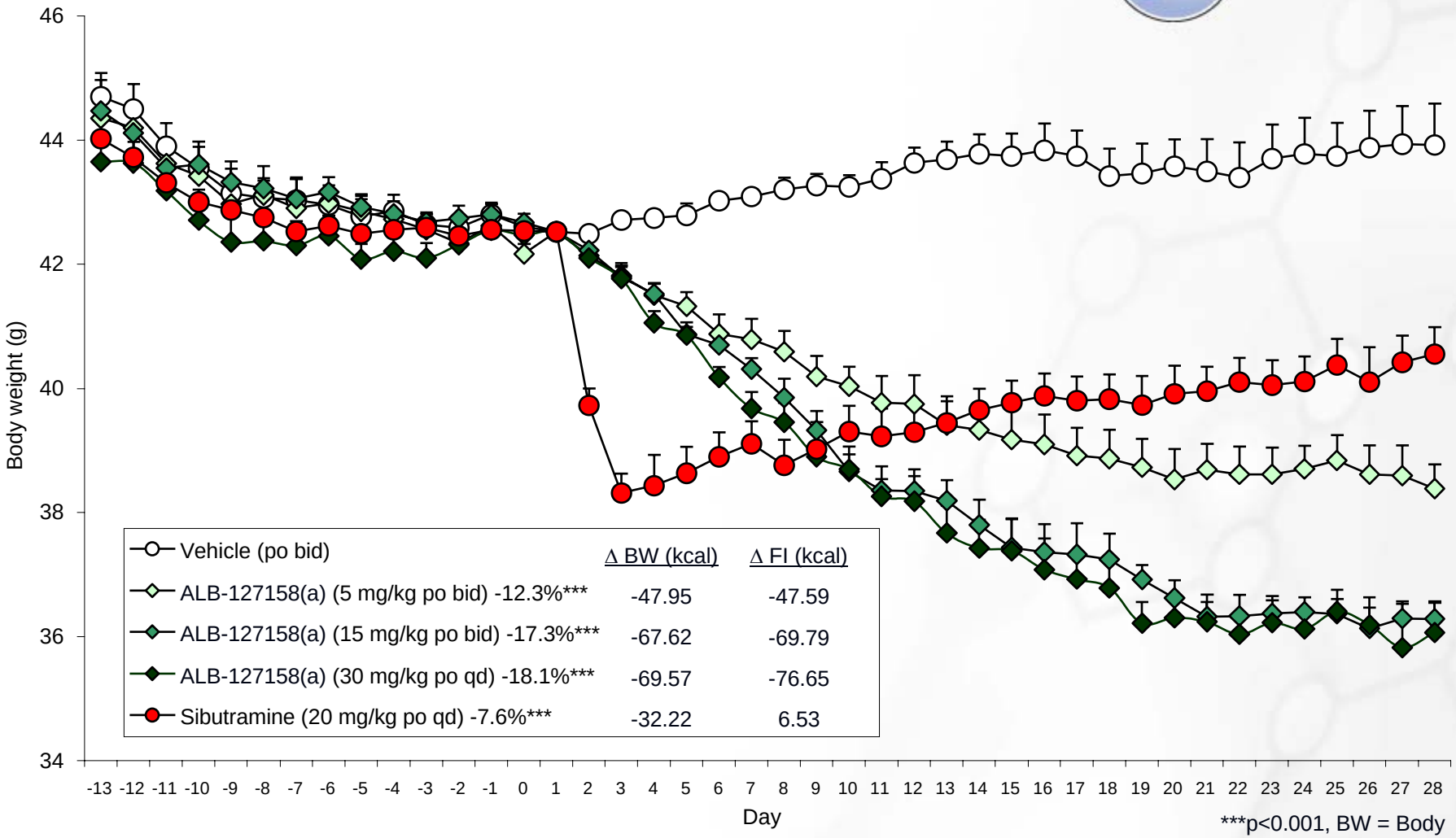
[^{3}H]AMR-MCH-1 *Ex Vivo* Autoradiography in Caudate Putamen of DIO Mice Following Oral Dosing of SCH-A (10 and 30 mg/kg)



Results are expressed as mean specific binding as a percentage of vehicle control taken as 100% (n = 5). Comparisons against the appropriate vehicle-treated group were by Williams' test. Significant differences are denoted by ***p<0.001

ALB-127158(a)
Efficacy Data

Effect of ALB-127158(a) on Body Weight in Male DIO C57BL/6J Mice

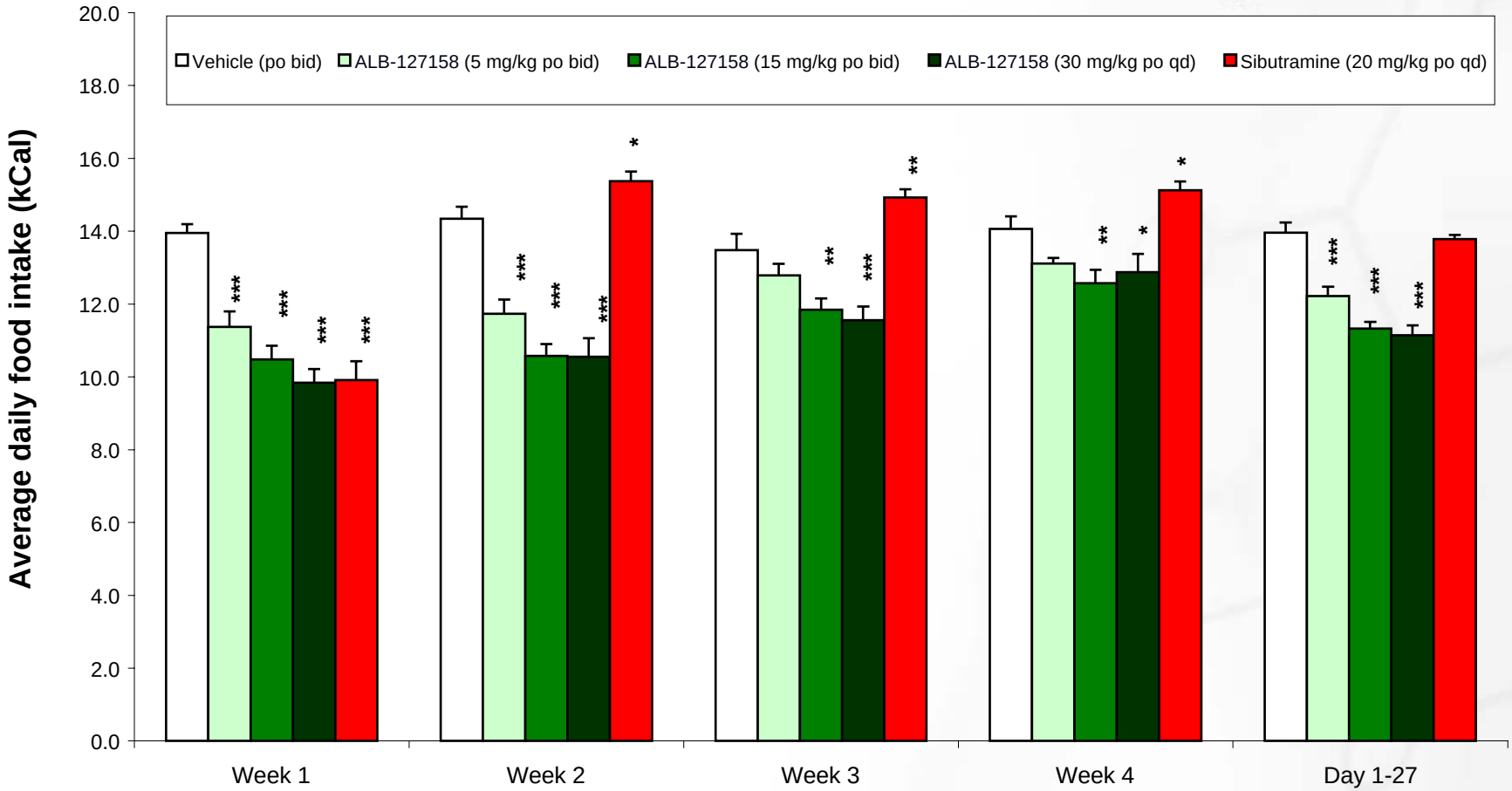


	Δ BW (kcal)	Δ FI (kcal)
ALB-127158(a) (5 mg/kg po bid) -12.3%***	-47.95	-47.59
ALB-127158(a) (15 mg/kg po bid) -17.3%***	-67.62	-69.79
ALB-127158(a) (30 mg/kg po qd) -18.1%***	-69.57	-76.65
Sibutramine (20 mg/kg po qd) -7.6%***	-32.22	6.53

***p<0.001, BW = Body Weight, FI = Food Intake

- **ALB-127158(a) caused sustained weight loss over the 4 week study**

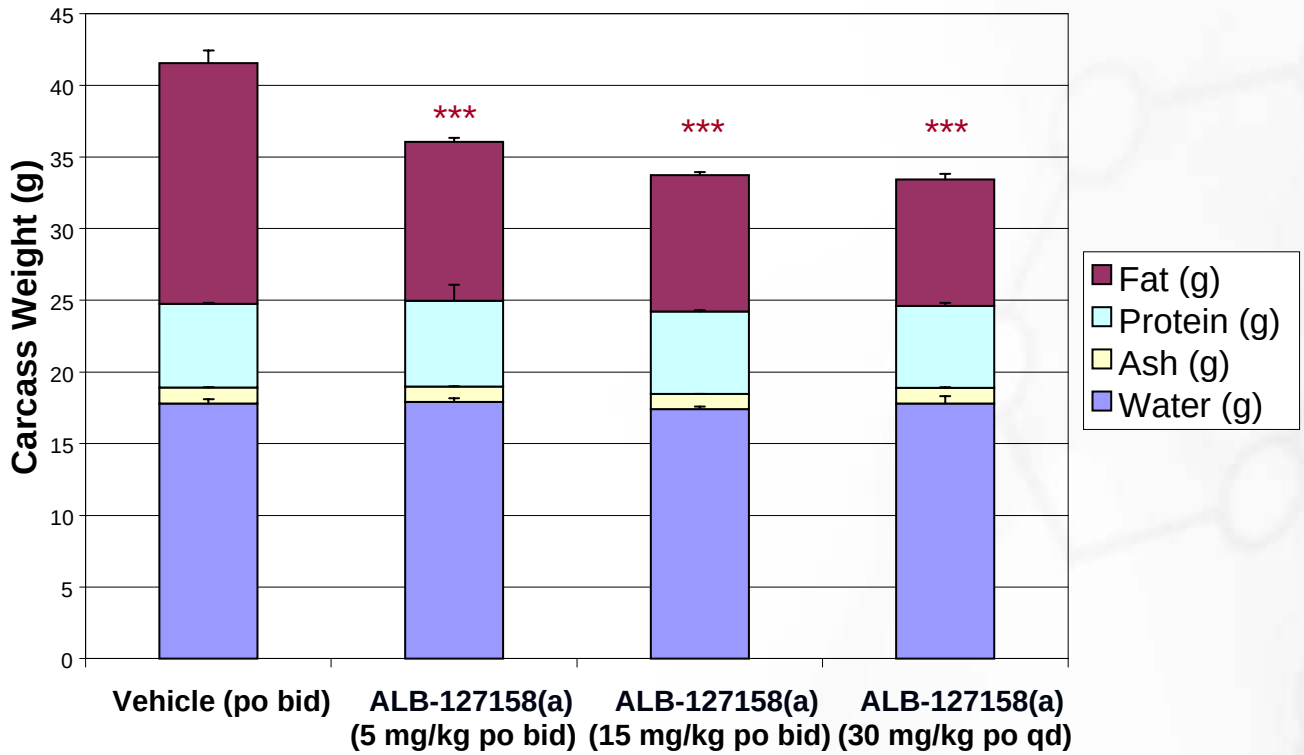
Effect of ALB-127158(a) on Food Intake in Male DIO C57BL/6J Mice



Data are adjusted means (n = 9) SEMs are calculated from the residuals of the statistical model. Data analysed by ANCOVA with body weight on Day 1 as covariate. Multiple comparisons against the obese vehicle group are by Williams' test (ALB-127158(a) bid) and multiple t-test (ALB-127158(a) qd and sibutramine): * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$.

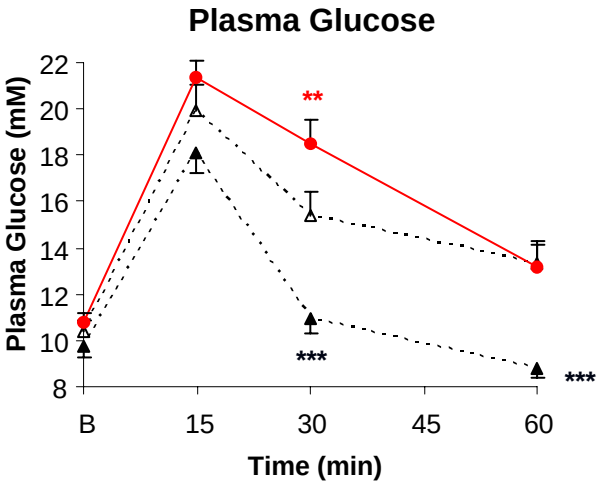
- **Body weight reduction correlates to a reduction in food intake**
- **ALB-127158(a) did not have a significant effect on water intake**

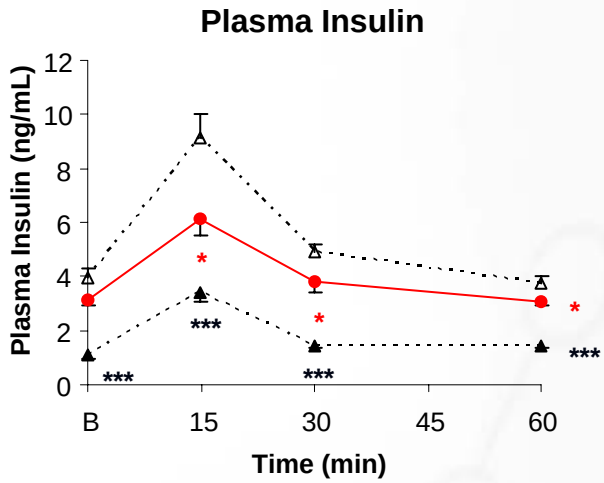
Effect of Chronic Administration of ALB-127158(a) on Body Composition in Male C57BL/6J DIO Mice



- Body weight reduction associated with exclusive loss in fat mass

Oral Glucose Tolerance Test (2 g/kg po) From Chronic DIO Mouse Feeding Study

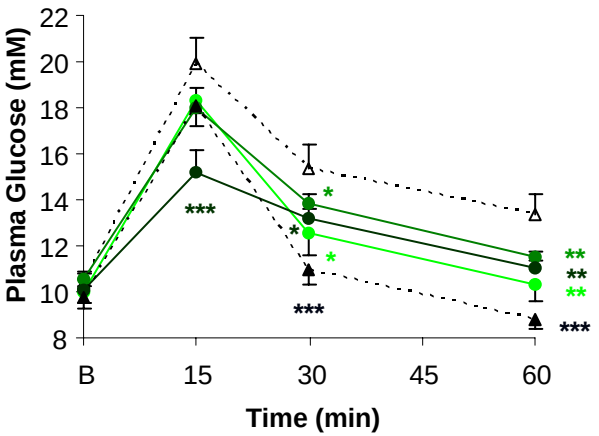


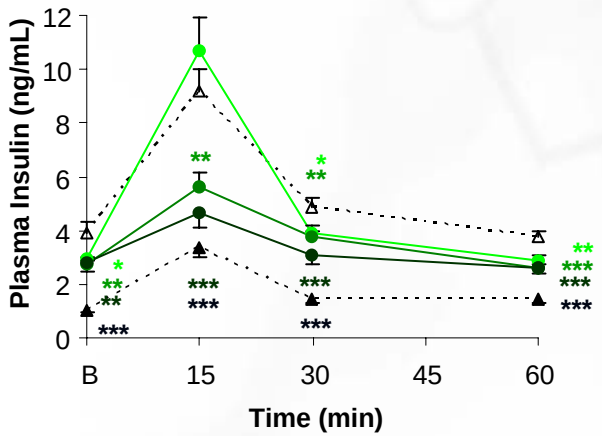


sibutramine

- DIO Vehicle
- 20 mg/kg qd
- Lean Vehicle

*p<0.05, **p<0.01, ***p<0.001





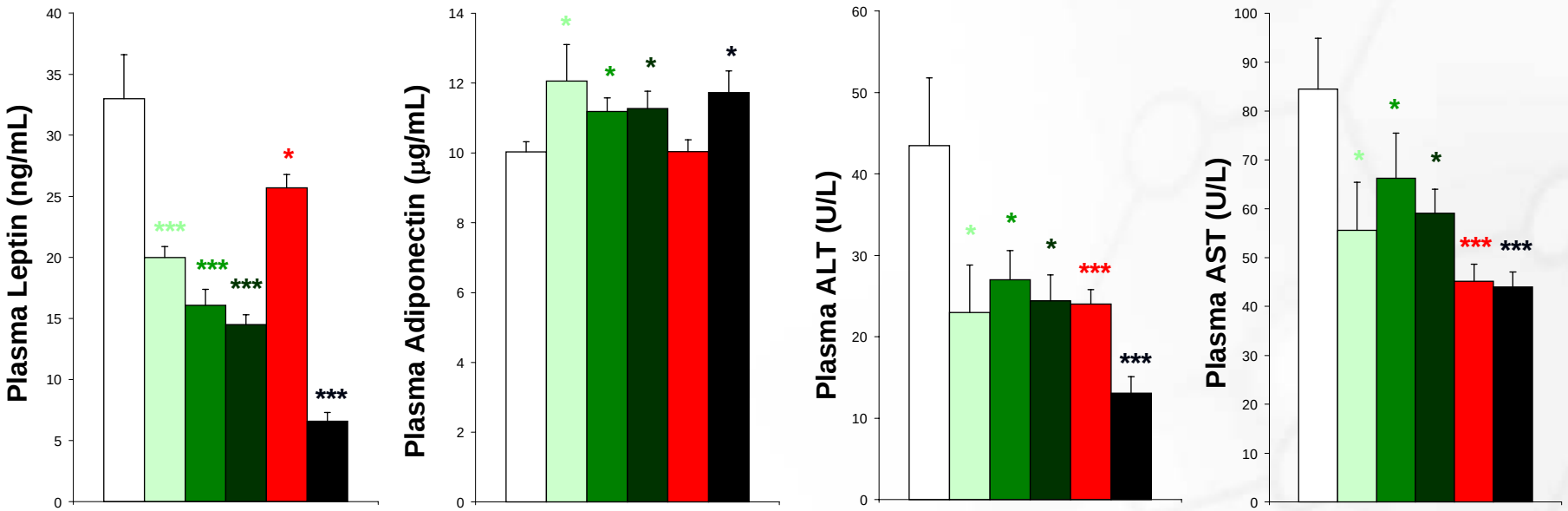
ALB-127158(a)

- DIO Vehicle
- 5 mg/kg bid
- 15 mg/kg bid
- 30 mg/kg qd
- Lean Vehicle

*p<0.05, **p<0.01, ***p<0.001

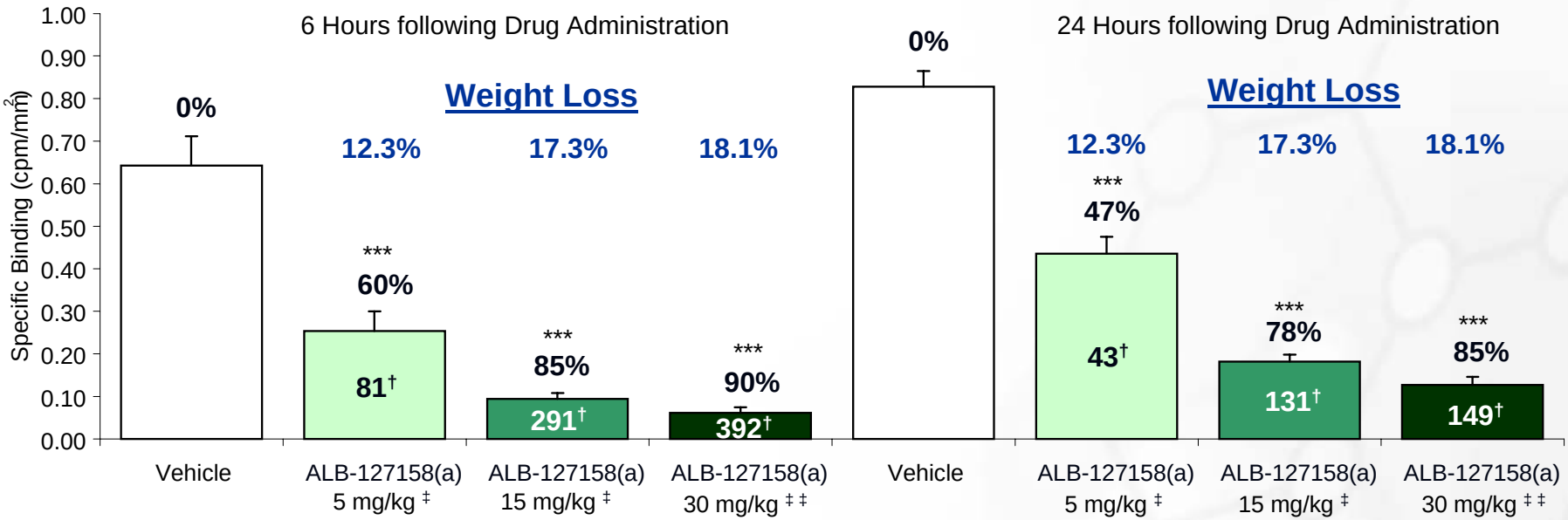
- **ALB-127158(a) improves glucose tolerance and insulin sensitivity following an OGTT**

Plasma Parameters Following Chronic DIO Mouse Study on ALB-127158(a)



- Significant improvements were found in plasma leptin, adiponectin, ALT and AST.
- No significant effects were seen in freely fed glucose or insulin levels or in cholesterol, NEFA, glycerol, TAG or BUN.
- No drug related changes observed in gross necropsy.

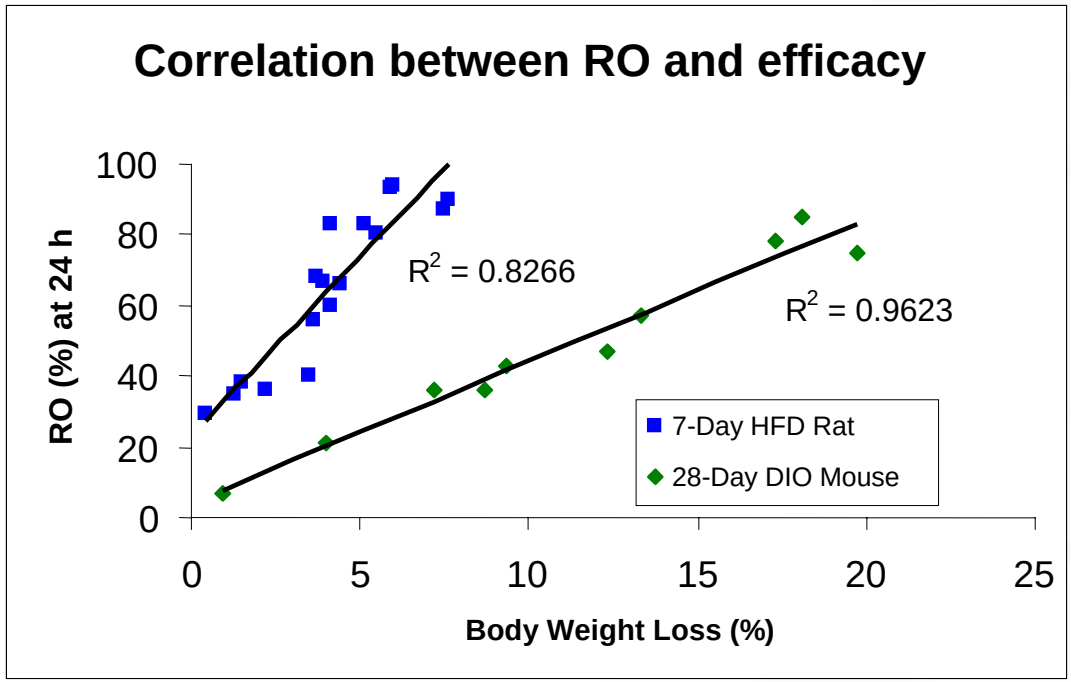
Ex Vivo MCH_1 Receptor Occupancy Following Chronic Administration of ALB-127158(a) in DIO Mice



†Concentration (ng/g) of ALB-127158(a) in the brain
‡MCH_1 receptor occupancy was measured 6 or 24 h following a single dose subsequent to 36 days of twice daily dosing;
‡‡Subsequent to once daily dosing

- **Body weight reduction correlates to MCH_1 receptor occupancy**

Good Correlation of AMRI Compound Efficacy with Receptor Occupancy at 24 h



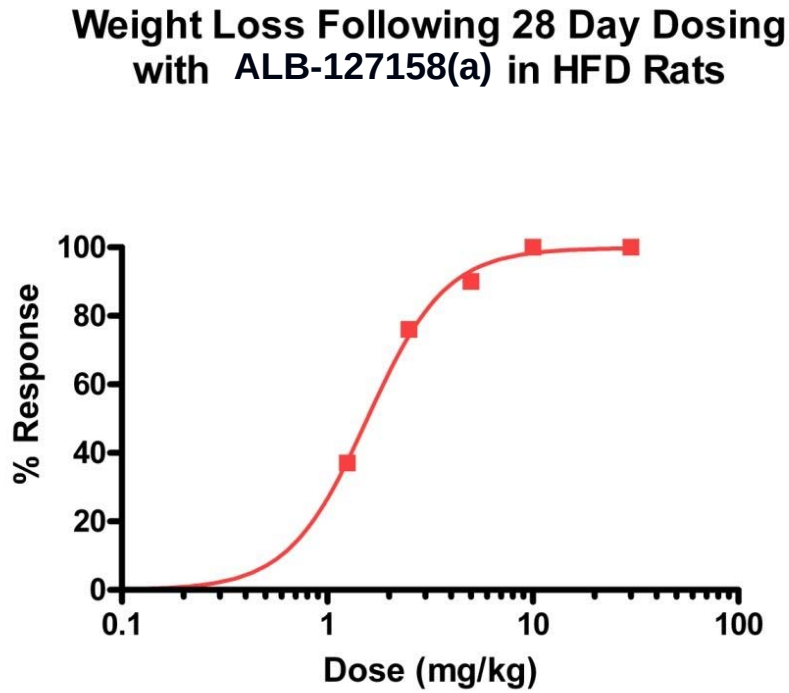
Ex Vivo MCH_1 Receptor Occupancy Following Administration of ALB-127158(a) to HFD Rats

Dose (mg/kg, po, qd)		6 Hours Post Final Dose		24 Hours Post Final Dose		Weight Loss
		Receptor Occupancy	Brain Concentration	Receptor Occupancy	Brain Concentration	
Acute	1.25	5%	9.5 ng/g	14%	4.1 ng/g	N/A
	2.5	10%	19 ng/g	26%**	8.0 ng/g	N/A
	5	23%**	36 ng/g	40%**	17 ng/g	N/A
	10	49%***	82 ng/g	60%***	30 ng/g	N/A
28 Days	1.25	44%***	15 ng/g	35%***	6.4 ng/g	3.2%**
	2.5	56%***	27 ng/g	56%***	13 ng/g	6.5%***
	5	79%***	60 ng/g	66%***	27 ng/g	7.7%***
	10	89%***	146 ng/g	83%***	77 ng/g	8.6%***

**p<0.01; ***p<0.001.

- All dose groups showed statistically significant levels of *ex vivo* receptor occupancy upon chronic dosing.
- Multiple doses required to achieve maximal receptor occupancy.
- No receptor occupancy observed following 7-day withdrawal period.

Determination of the Predicted Clinically Efficacious Dose (Defined as the ED_{90})



- Identical weight loss was achieved at 10 and 30 mg/kg, therefore the ED_{max} = 10 mg/kg.
- The ED_{90} was determined to be approximately 5 mg/kg (corresponding to >70% receptor occupancy).

Candidate Selection Process

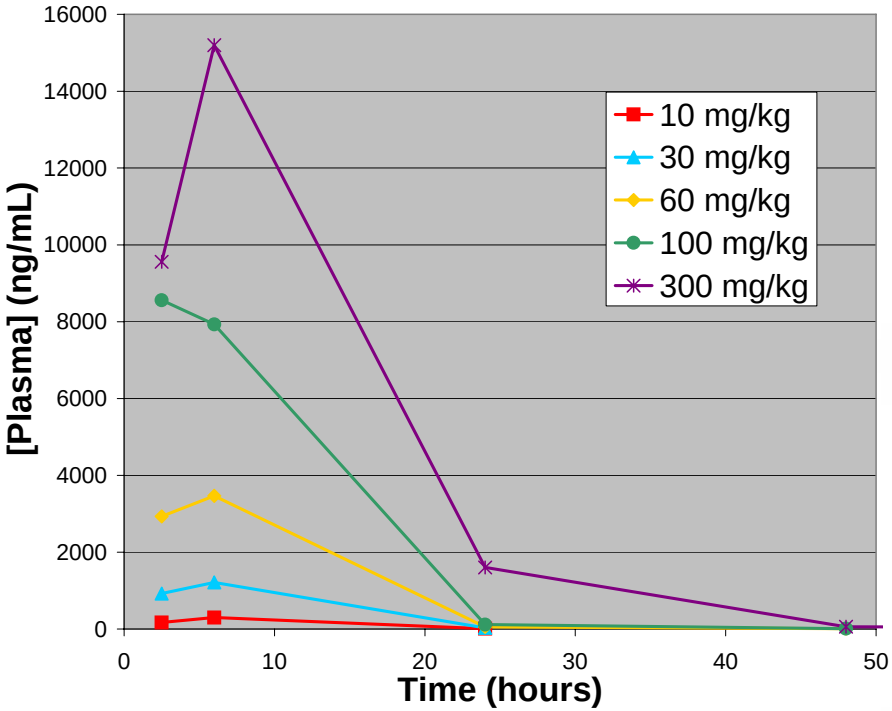
(Remember Toxicity Observed in other Programs)

- hERG functional mini patch clamp routinely run (1000X selectivity from MCH_1 binding desired)
- Necropsy and toxicity biomarkers (e.g. ALT, AST, BUN, etc…) completed after multi-dose and chronic studies
- Irwin profile in rat
- Single day versus multiple day PK to assess dose proportionality, accumulation
- CV parameters in telemeterized dog or monkey
- 5-day non-GLP toxicity study in rodents

ALB-127158(a)
PRE-CANDIDATE SAFETY & TOXICITY

ALB-127158(a) Showed No Significant Effects in Rat Irwin Behavioral Study

Plasma concentration of ALB-127158(a) following oral administration to rats



- ALB-127158(a) dosed orally at 10, 30, 60, 100 and 300 mg/kg
- Behavioral assessment took place 2 hours post dose; animals monitored daily out to 5 days
- No significant deviation from normal behavior observed
- ALB-127158(a) demonstrated dose proportional PK

5-Day Rat Tox Study
Conclusions

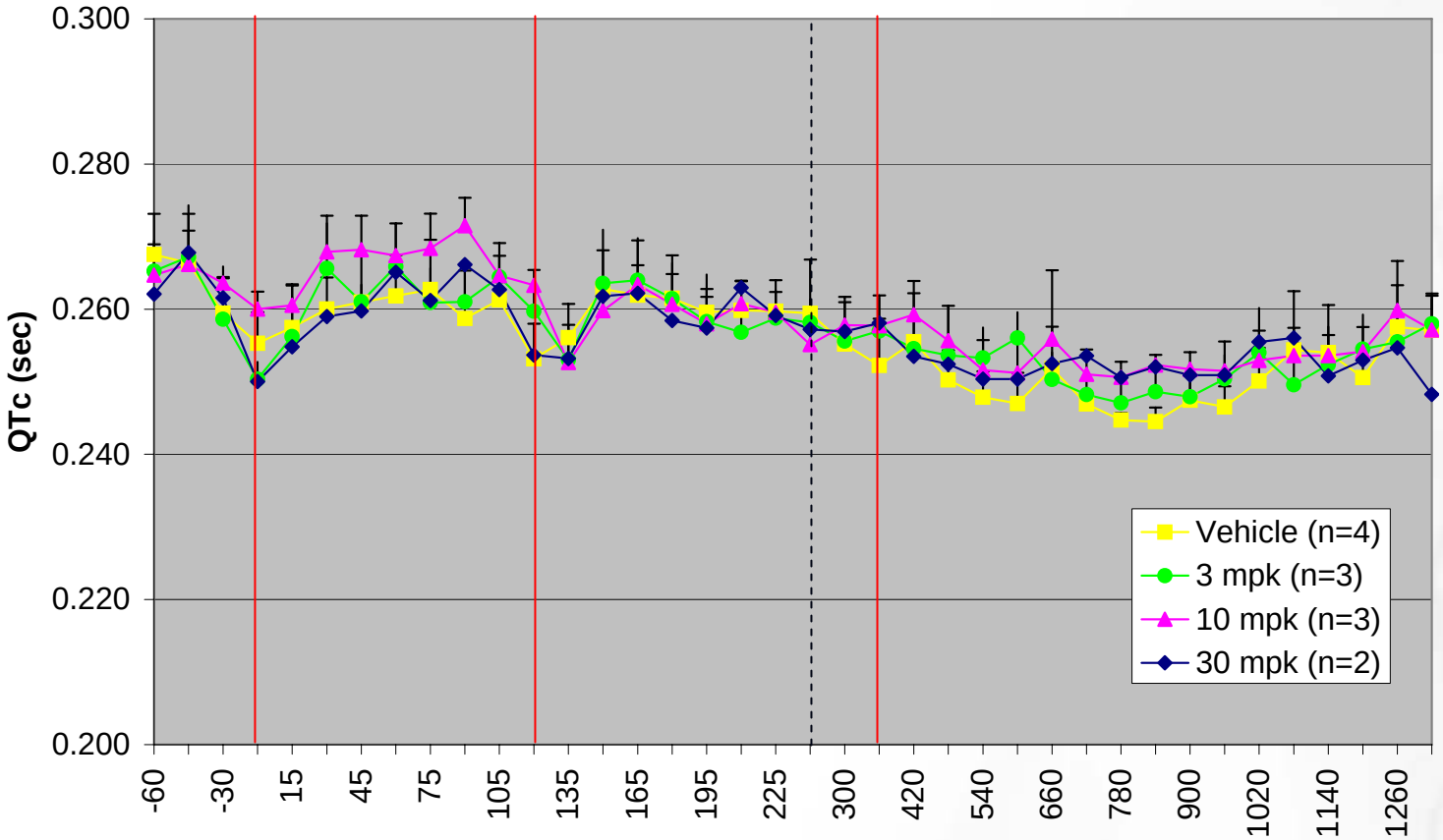
- Multiple doses examined above efficacious dose range
- Clinical observations, clinical chemistry/hematology, gross necropsy, organ weights, body weight and food intake monitored.
- NOEL > 20 fold separation from ALB-127158(a)'s efficacious dose and no evidence of adverse drug accumulation

Conscious Telemeterized Dog Cardiovascular Model

- Conscious, telemeterized dogs (n = 3) were dosed orally at 3, 10 and 30 mg/kg with a 1% methylcellulose vehicle.
- A minimum washout period of 72 hours was applied between doses.
- Following a 60 minute baseline period, the compound was given by oral gavage and blood pressure, heart rate and ECG were monitored for 24 hours.
- Blood was drawn predose and at 2, 6 and 24 hours post dose for TK analysis.

- Conclusion: No significant effect observed on systolic, diastolic, mean arterial pressure, heart rate or QTc following oral administration of ALB-127158(a)

No Significant Effect on QTc Observed with ALB-127158(a) in Telemeterized Dogs



- **Red lines = blood draws**
- **Dashed line = time scale change**

- **Conclusion: No significant effect observed on QTc following oral administration of ALB-127158(a)**

Comparison of Dog and Rat Plasma Levels of ALB-127158(a)

Species	Parameter	ALB-127158(a)
Dog	Dose (mg/kg po)	30
	C_{max} (ng/mL)	1446
	Free fraction[a] (ng/mL)	**499**
HFD Rat	Dose (mg/kg po)	5[b]
	C_{max} (ng/mL)	272
	Free fraction[a] (ng/mL)	**43**
	Weight Loss	7.7%

[a]Plasma protein binding for ALB-127158(a) : Dog = 65.5% (n=2), Rat = 84.2 ± 5.0% (n=3)
[b]Following a final dose subsequent to a 28-day study of qd dosing

- **No significant CV effects observed in dog at a plasma concentration 11.6-fold higher than an efficacious dose in rat**

Cross-Species Validation

- ALB-127158(a) is centrally-acting
- Efficacy is determined from rat models
- We know central/peripheral exposure in rats but not humans
- Studies conducted to determine CSF levels in primates to provide confidence on likely human central exposure prior to committing to a phase I study

Protocol Outline

Part 1: Rat plasma/brain/CSF
Doses of 3 and 10 mg/kg
(efficacious dose range)

Part 2: Monkey plasma/CSF
1, 3, 10 and 30 mg/kg
Single time point at expected CSF T_{max}

Rat/Monkey CSF Exposure

ALB-127158(a) 3 h Post Dose

- CSF is a very low protein fluid; drug in CSF considered to represent free fraction in brain

Rat Dose	Plasma FF (ng/mL)	CSF (ng/mL)	CSF/ Plasma FF	Monkey Dose	Plasma FF (ng/mL)	CSF (ng/mL)	CSF/ Plasma FF
				1 mg/kg	29 ± 9	3.4 ± 2.1	0.11 ± 0.04
3 mg/kg (>ED_{50})	25 ± 18	<1	ND	3 mg/kg	113 ± 23	19.1 ± 5.0	0.17 ± 0.03
10 mg/kg (ED_{MAX})	276 ± 91	11.9 ± 6.5	0.042 ± 0.013	10 mg/kg	589 ± 68	112 ± 32	0.19 ± 0.04
				30 mg/kg	954 ± 167	285 ± 56	0.31 ± 0.08

- Conclusion: greater drug exposure in monkey vs rat CSF predicts good CNS exposure for clinical use

CSF as a surrogate for assessing CNS exposure: Lin, J. H. Current Drug Metabolism 2008, *9*, 46.

Program Summary

- **ALB-127158(a) selected as first candidate compound**
- **Sustained, fat selective weight loss in a chronic DIO mouse and HFD rat models, positive effects on other metabolic parameters**
- **Weight loss correlates to reduction in food intake and *ex vivo* MCH_1 receptor occupancy (including *ex vivo* radioligand development)**
- **Safety margins suitable for progression**

Clinical Plans

- Regulatory genetox, safety / toxicology studies successfully completed
- Phase 1 plan accepted by MHRA in July and patient enrollment initiated
- Phase 1 design:
  - Single ascending dose study in lean subjects (BMI <25 kg/m^2)
  - Single dose fed / fasted study in overweight subjects (BMI >27 kg/m^2)
  - Multiple ascending dose study in overweight subjects (BMI >27 kg/m^2)
    - Includes feeding / hunger assessments on days 1, 7 and 14

MCH_1 Discovery Contributors

Chemistry (Albany)
Dustin Deering
Russell DeOrazio
Emily Freeman
James Grabowski
Cheng Guo
Mark Hadden
Alan Henderson
Gavin Guowei Jiang
May Xiao-Wu Jiang
Bruce Sargent
Matt Surman
Alex Usyatinsky
Lei Zhu

Chemistry (Singapore)
David Chan
Pearly Ng
Jagannath Panda
Suk Har Tiong
DJ Xie
Larry Yet

Lead Discovery (Bothell)
Michele Luche

In Vivo Biology (RenaSci)
Sharon Cheetham
Keith Dickenson
Simon Goddard
Steve Vickers
Jean Viggers

Development
Nick Moore

CADD (Albany)
Hélène Decornez
Douglas Kitchen
Jim Schermerhorn

ADMET (Albany)
Jiffry Ismail
Yuri Khmelnitsky
John Lindsay
Peter Michels
Vadim Mozhaev
Lyuda Mozhaeva
Julianne Zaremba
Boon-Keat Yew
Scott Tallman
Wei Yee Leong
Anne Payne