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# In Vitro and Preclinical Characterization of Novel Selective Melanocortin-4 Receptor Agonists

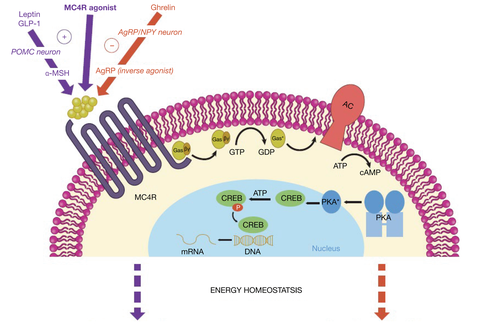
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## BACKGROUND

- Obesity results from an inability to maintain energy homeostasis by balancing energy intake, expenditure, and storage[1-4]
- The central melanocortin pathway is a principal regulator of this balance
  - Proopiomelanocortin (POMC) neurons in the hypothalamic arcuate nucleus release α-melanocyte-stimulating hormone (α-MSH), which activates the GPCR melanocortin-4 receptor (MC4R) on downstream neurons to suppress food intake and increase energy expenditure (**Figure 1**)[4]

**Figure 1. Melanocortin-Mediated Regulation of Gene Expression for Energy Homeostasis[5-7]**




α-MSH stimulation of MC4R leads to activation of the G protein, Gαs, and the subsequent activation of AC, which converts ATP to cAMP. cAMP-mediated activation of PKA leads to the dissociation of the catalytic subunit of the PKA complex. Upon translocation of the active PKA catalytic subunit (PKA*) into the nucleus, PKA phosphorylates the transcription factor CREB. When bound to upstream consensus DNA sequences (CRE), CREB-P facilitates transcription of a gene by interaction with the core transcriptional machinery. AC, adenylate cyclase; AgRP, agouti-related protein; α-MSH, α-melanocyte-stimulating hormone; cAMP, cyclic adenosine monophosphate; CRE, cAMP response elements; CREB, cAMP response element binding protein; GLP-1, glucagon-like peptide-1; GTP, guanosine triphosphate; MC4R, melanocortin receptor 4; NPY, neuropeptide Y; PKA, protein kinase A; POMC, proopiomelanocortin. Adapted from Gonçalves et al 2018 and Palmer et al 2017.[2,6]

- Loss-of-function mutations in MC4R cause hyperphagia and early-onset obesity, and are the most common monogenic cause of severe human obesity[1,4,7]
- Conversely, MC4R agonism increases satiety, reduces food intake, and reduces body weight in animal models and in patients with melanocortin pathway defects[1,2,7]
- MC4R is 1 of 5 melanocortin receptors
  - Pan-melanocortin receptor agonism leads to off-target effects, notably hyperpigmentation associated with MC1R agonism[2]
- A highly MC4R-selective agonist could treat obesity while minimizing MC1R-mediated off-target effects[9]

## OBJECTIVES: Development of Novel Peptides

- Palatin is developing differentiated, next-generation MC4R agonists designed to deliver meaningful weight-loss efficacy, substantially reduce or potentially eliminate hyperpigmentation, and provide more convenient dosing regimens. By addressing key limitations of existing MC4R therapies, Palatin's approach seeks to improve long-term treatment tolerability and usability for patients with rare neuroendocrine obesity disorders, including hypothalamic obesity, Prader-Willi syndrome, and Bardet-Biedl syndrome
- To extend the biological half-life of our peptides to support QW dosing, two approaches were taken. The first was the development of selective cyclic peptides (series PL1000) that can be easily loaded into erodible polymers or mini pumps. The second involved the development of a novel and proprietary peptide lipidation technology that allows for the development of lipidated peptides (series PL2000) that maintain selectivity and potency for the MC4R. A further advantage of lipidated peptides is the ability to be stable against gastric and intestinal breakdown, thereby supporting oral dosing

## METHODS

### In vitro: Functional activity

- Activation of human MC1R and MC4R was measured by second messenger cyclic adenosine monophosphate (cAMP) accumulation levels

### In vitro: Radioligand binding

- Binding activity was evaluated in Chinese hamster ovary cells expressing human MC1R
- Percent inhibition was assessed to derive the half-maximal inhibitory concentration ($IC_{50}$) and inhibition constant ($K_i$), where feasible

### In vivo: DIO mouse and dog blood pressures

- Body weight was assessed in a diet-induced obesity (DIO) mouse model using male C57BL/6J mice
- Animals received either vehicle or the MC4R-selective peptide subcutaneously (n=6 per group), dosed twice daily for peptides and once on Day 0 for lipidated peptides
- Male beagle dogs were injected once SC with vehicle or PL1001 (n=3). Blood pressure was measured by tail cuff
- Procedures were approved by the IACUC and conducted in accordance with the USDA Animal Welfare Act and the Guide for the Care and Use of Laboratory Animals

## RESULTS

### In vitro: Functional activity at MC4R and MC1R

- Palatin's MC4R-selective peptides and lipidated peptides are potent agonists at human MC4R with minimal activity at human MC1R (**Table 1**)
- Ongoing optimization is focused on combining high MC4R potency with minimal or no MC1R activity to deliver a differentiated next-generation MC4R agonist without pigmentation effects

### In vitro: Radioligand binding at MC1R

- Across a concentration range of 3.9 nM to 2000 nM, PL1001 (representative peptide) produced ≤36% inhibition of specific binding at human MC1R (**Figure 2**)
- Because inhibition did not reach the 50% threshold at any concentration tested, $IC_{50}$ and $K_i$ could not be calculated

### In vivo: Body weight and food intake in DIO mice treated with a selective peptide

- Twice daily administration of PL1002 shows significant dose-dependent reduction of body weight and food intake in DIO mice (**Figure 3**)

### In vivo: Cardiovascular safety in dogs treated with PL1001 (representative) selective peptide

- PL1001 had no effect on heart rate or blood pressure at efficacious doses (**Figure 4**)

### In vivo: Body weight and food intake in DIO mice treated with a lipidated peptide

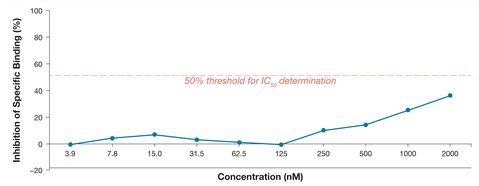
- Palatin's long-acting lipidated peptides have increased half-life compared to Palatin's selective peptides (**Figure 5**)
  - The half-life of selective peptides is about 2 hours while lipidated peptides have a half-life of 24 hours in rodent and >168 hours in dog
- A single dose of PL2001 on Day 0 showed a significant dose-dependent reduction of body weight and food intake (**Figure 6**)

**Table 1. Functional Activity (cAMP Accumulation) at Human Melanocortin Receptors**

| Agonist | MC1R $EC_{50}$, nM (mean) | MC4R $EC_{50}$, nM (mean) | MC4R Selectivity[a] |
|---|---|---|---|
| Bremelanotide | 0.23 | 5.0 | 0.05 |
| Setmelanotide | 0.4 | 0.66 | 0.61 |
| PL8905[b] | 30 | 0.5 | 60 |
| PL1001 | >10,000 | 1-50 | >200 |
| PL1002 | 50-100 | <1 | >100 |
| PL2001 | >10,000 | 1-50 | >200 |
| PL2002 | 100-1000 | 1-50 | >100 |

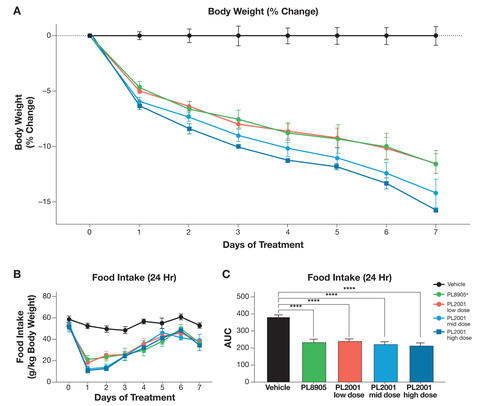
[a]Selectivity is defined as ratio of MC1R $EC_{50}$ to MC4R $EC_{50}$ (larger number is more MC4R selective relative to MC1R).
[b]PL8905 is a potent MC4R agonist used for comparison and indexing.
PL1001 and PL1002 are cyclic peptides, while PL2001 and PL2002 are lipidated peptides.
cAMP, cyclic adenosine monophosphate; $EC_{50}$, half-maximal effective concentration; MC1R/MC4R, human melanocortin-1/-4 receptor.

**Figure 2. Inhibition of Specific Binding at Human MC1R**




$IC_{50}$, half-maximal inhibitory concentration; MC1R, melanocortin-1 receptor.

**Figure 3. Body Weight (A) and Food Intake (B and C) Change in DIO Mice Treated With PL1002 (Representative Peptide)**




****P<0.0001
*PL8905 is a potent peptide used for comparison and indexing.
AUC, area under the curve; DIO, diet-induced obesity.

**Figure 4. Cardiovascular Safety of Representative Peptide**

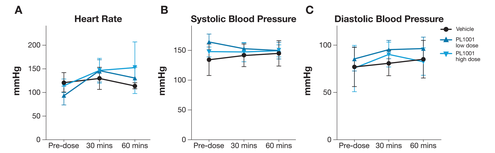



**Figure 5. Pharmacokinetics of Lipidated Peptides**

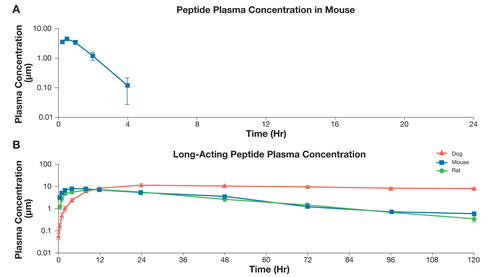
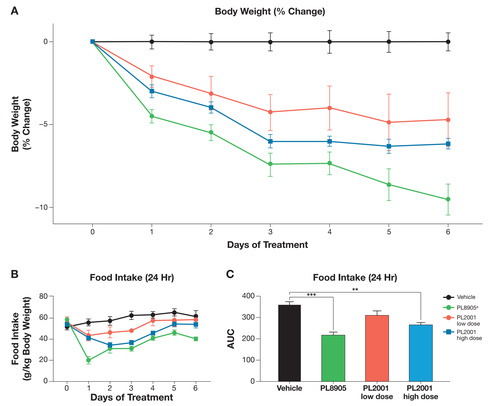



**Figure 6. Body Weight (A) and Food Intake (B and C) Change in DIO Mice Receiving Lipidated Peptide**




**P<0.01; ***P<0.005.
*PL8905 is a potent peptide used for comparison and indexing.

## CONCLUSIONS

- **Potent and highly selective MC4R agonism:** Palatin's novel peptide and long-acting lipidated peptide agonists demonstrated high potency at MC4R with minimal or no functional activity at MC1R in in vitro assays. This receptor selectivity supports the potential to substantially reduce or eliminate MC1R-mediated hyperpigmentation, a recognized limitation of currently approved MC4R agonist therapy.
- **Robust preclinical efficacy:** Both the selective peptide and long-acting lipidated peptide compounds demonstrated significant reductions in body weight and food intake in diet-induced obese (DIO) mice, providing evidence of biologically meaningful MC4R activation and supporting further development.
- **Differentiated long-acting peptide technology:** Palatin's novel, proprietary peptide lipidation technology substantially extended drug exposure while preserving MC4R potency and selectivity. The pharmacokinetic profile supports the potential for once-weekly or less frequent subcutaneous administration, offering a more convenient dosing approach compared with currently approved once-daily injectable MC4R peptide therapy.
- **Encouraging preliminary cardiovascular findings:** The representative selective peptide PL1001 demonstrated no observed effects on heart rate or blood pressure at efficacious doses in the preclinical model. Additional cardiovascular safety evaluations are planned.
- **Advancement toward clinical development:** PL2001, a novel long-acting, lipidated, MC4R-selective peptide agonist, has been selected as a clinical development candidate, with first-in-human studies targeted for the first half of 2027. Development of orally administered, highly selective MC4R peptide agonists is also ongoing.
- Collectively, these findings support Palatin's strategy of developing differentiated, next-generation MC4R agonists that combine potent weight-loss activity with minimal or no MC1R agonism, encouraging preliminary cardiovascular safety findings, and convenient, long-acting dosing. By addressing important limitations of existing therapies, particularly hyperpigmentation, cardiovascular safety concerns, and dosing frequency, Palatin's proprietary peptide platform provides a compelling foundation for advancing potentially best-in-class treatments for patients with rare neuroendocrine obesity disorders, including hypothalamic obesity, Prader-Willi syndrome, and Bardet-Biedl syndrome.

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