



# AGRP-derived melanocortin receptor ligands

## Identifying a selective MC4R antagonist for appetite modulation

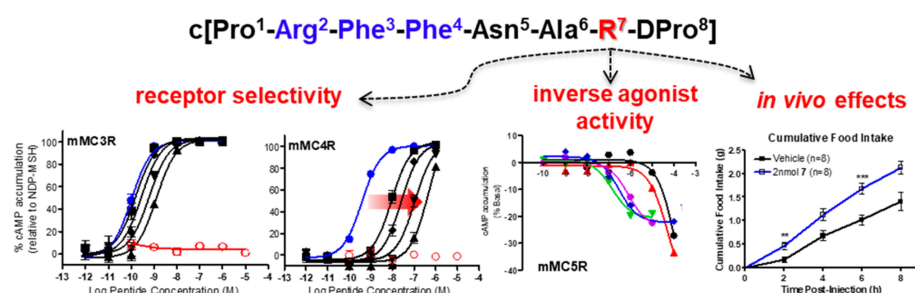


Fig. 1. MC4R antagonist affects food intake in mice (Fleming et al., 2018)

**IP Status:** Issued US Patent; **Issued Patent No.** 11,332,499

## Applications

- Treatment of anorexia-cachexia

## Key Benefits & Differentiators

- **Appetite modulation:** MC4R antagonist increases food intake in mice

## Technology Summary

In the US over 5 million people suffer from cachexia, a serious condition of extreme weight loss and muscle wasting common in people with cancer, chronic heart failure, HIV/AIDS, chronic obstructive pulmonary disease, chronic kidney disease and other chronic diseases. In cancer patients, cachexia increases hospitalization costs, length of stay and mortality. While many biological pathways control appetite and weight, the final step is controlled by two brain receptors, melanocortin receptors 3 and 4 (MC3R and MC4R, respectively). Activation of MC4R results in decreased food intake while blocking MC4R results in increased food intake. Therefore, MC4R offers a druggable target in the pursuit of treatments for anorexia-cachexia syndrome.

Researchers at the University of Minnesota leveraged the Agouti-related protein (AGRP), a potent orexigenic peptide that antagonizes MC3R and MC4R, to generate novel peptides that are highly potent and selective antagonists against MC4R. The AGRP-derived peptides were designed to mimic the active  $\beta$ -hairpin secondary structure that contains the hypothesized Arg-Phe-Phe pharmacophore. The most potent scaffold, c[Pro<sup>1</sup>-Arg<sup>2</sup>-Phe<sup>3</sup>-Phe<sup>4</sup>-Asn<sup>5</sup>-Ala<sup>6</sup>-Phe<sup>7</sup>-DPro<sup>8</sup>], comprised the hexa-peptide  $\beta$ -hairpin loop from AGRP cyclized through a DPro-Pro motif. However, this scaffold is 16-fold less potent than AGRP at the mouse MC4R (mMC4R) thus necessitating modifications to facilitate studies in mouse models. A more potent mMC4R antagonist was generated containing a Phe<sup>7</sup> to Nle<sup>7</sup> substitution. This peptide was equipotent

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20160310

## Category

Life Sciences/Human Health

Life Sciences/Pharmaceuticals

Life Sciences/Therapeutics

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to the lead ligand 200-fold selective for the mMC4R over the mMC3R and caused a significant increase in food intake when injected intrathecally into male mice (Fig 1). These compounds are a first step to developing MC4R antagonists for treating underweight conditions, including cachexia.

## Phase of Development

### TRL: 4-6

Food intake studies in mice

## Desired Partnerships

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## Researchers

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## References

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