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De Novo Design of Oral and Cell-permeable Peptides using Generative AI

Hans Melo[1], Elliott Dolan[1], Musa Ozboyaci[1], Patrick Finneran[1], Stephan Kudlacek[1], Vikram Mulligan[1,2]
Menten AI, Inc. San Francisco, CA 94111
Flatiron Institute, New York
hans@menten.ai

Up to 80% of drug targets remain beyond the reach of small molecules and biologics. Cyclic peptides contain the favorable selectivity and high affinity of proteins, and the beneficial features of small molecules, and could be capable of drugging many of those targets. However, key challenges remain including cell permeability and oral bioavailability. We present a physics-based Generative AI approach to design de novo cyclic peptides that exhibit passive permeability and high affinity. As an example, we discuss how Menten AI's generative AI platform was used to design cyclic peptides targeting a challenging PPI. Results show cyclic peptides achieved cell-permeability in PAMPA assays with Papp>10*-6 as well as functional inhibition of the target.