Sethera Therapeutics Releases New Paper Introducing Enzymatic Macrocyclization Platform to Upgrade GLP 1 Peptides

SALT LAKE CITY, UT, UNITED STATES, October 14, 2025 /EINPresswire.com/ -- Sethera Therapeutics, a biotechnology company advancing next-generation polymacrocyclic peptide therapeutics, today announced a published study that outlines a new biocatalysis platform that installs precise C-terminal thioether macrocycles on peptide therapeutics—rapidly, at a late stage, and without the leader tags typically required by peptide-modifying enzymes. The core catalyst, PapB, is a radical S adenosyl L methionine (rSAM) maturase that cleanly macrocyclized therapeutically relevant GLP-1 pathway analogs in vitro. The work, accepted in the journal, ACS Bio & Med Chem Au, demonstrates leader-independent activity and broad sequence tolerance, including compatibility with non-canonical residues already used in marketed incretin drugs.

Sethera's enzymatic step functions as a "finishing" operation on pre-optimized peptides: it adds a compact ring that can (i) protect C termini against proteases, (ii) rigidify segments to improve receptor binding or bias signaling, and (iii) serve as a modular handle to tune pharmacokinetics or targeting. Because the key constraints of the enzyme can be reduced to a local Cys–X^n–Asp/Glu motif and do not require bespoke leader tags, Sethera can apply the same catalyst across families of peptides, compressing timelines and de-risking manufacturing transfer.

The platform runs in aqueous, mild conditions using standard cofactors, supporting straightforward scale-up and integration with solid-phase peptide synthesis workflows. In head-to-head enzyme tests, the Sethera process modified leaderless and leader-swapped substrates, underscoring its robustness and reducing the engineering burden typically associated with RiPP enzymes. Sethera is actively applying the platform to GLP-1, GIP, and glucagon pathway peptides and exploring broader classes where late-stage macrocyclization could unlock stability, selectivity, or tissue targeting.

The underlying research was conducted at the University of Utah and led by first author Jacob ("Jake") Pedigo, a researcher in the Bandarian Lab (Department of Chemistry). Sethera co-founders Vahe Bandarian, PhD (CSO), and Karsten A. S. Eastman, PhD (CEO), are co-authors on the study. The University of Utah holds patent interests in the findings, and Sethera Therapeutics has been formed to translate this enzymology into pipeline and partnership programs. This work was supported in part by the National Institutes of Health (R35 GM126956; T32-GM122740).

About Sethera Therapeutics
Sethera Therapeutics is revolutionizing peptide-based drug development with its cutting-edge enzymatic cross-linking technology. Their platform enables the synthesis of highly stable, polymacrocyclic peptides designed to engage with single targets or multiple targets simultaneously, offering unparalleled precision in therapeutic design. Sethera has a PolyMacrocyclic peptide (pMCP) Discovery Platform that helps partners discover and engineer MCPs with unique architectures and chemistries for targets of all kinds. The technology was first developed at the University of Utah with NIH funding and licensed exclusively to Sethera Therapeutics. By collaborating with industry leaders and research institutions, Sethera aims to unlock new possibilities in drug discovery and development, providing tailored solutions for a wide array of therapeutic needs. For more information about partnering with Sethera, please visit https://setheratx.com/.

Forward Looking Statements:
This press release contains forward-looking statements regarding development plans and potential applications. Actual results may differ materially due to risks and uncertainties in R&D, manufacturing, regulatory review, market adoption, and other factors.

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