ACS Green Chemistry Institute
Pharmaceutical Roundtable

ACS GCIPR Key Research Areas Grant – TFA Alternatives

2026 ACS Green Chemistry Institute Pharmaceutical Roundtable Research Grant for Identification of alternatives to trifluoroacetic acid (TFA) in peptide couplings/cleavages

The ACS Green Chemistry Institute Pharmaceutical Roundtable (GCIPR) is a partnership between the ACS Green Chemistry Institute® and pharmaceutical-related corporations united by a shared commitment to integrate the principles of green chemistry and engineering into the business of drug discovery and production. Current members are Abbvie, Amgen, Astrazeneca, Bayer, Biogen, Biohaven, BMS, Boehringer Ingelheim, Ferring, Gilead, GSK, Ipsen, J&J, Lilly, Merck, Merck KGaA, Neurocrine, Novartis, Novonordisk, Pfizer, Roche-Genentech, Sanofi, Takeda, UCB, Vertex and the ACS Green Chemistry Institute. Associate members are Asymchem, Axplora, Bachem AG, ChemExpress, Codexis, Dr. Reddys, EuroAPI, Hongene Biotech, Hovione, InnoSyn, Nitto Avecia, Olon, PharmaBlock, Pharmaron, Polypeptide, Porton, Sai Life Sciences, Sk Pharmteco, ST Pharm, Syngene, Veranova, and Wuxi AppTec. Affiliate members are Corteva Agriscience, Aralez Bio, FMC, Phlow Corp, PHT, USP, and Zoetis.

The ACS GCI Pharmaceutical Roundtable is seeking a one-year R&D commitment to assist the Roundtable's green chemistry initiative to develop strategies to obviate/reduce the need to use trifluoroacetic acid (TFA) for the removal of protecting groups and/or cleavage from resins (in SPPS and/or LPPS mode) in peptide chemistry by devising suitable and sustainable replacement protocols/conditions/reagents.

Proposals are invited from public and private institutions of higher education worldwide. This collaborative project is intended for a student within the selected Principal Investigator's research group. One grant is planned to be awarded and the total award is limited to $80,000 for a grant period of 12 months. Interested PIs are required to provide a written proposal describing the investigator's capability to carry out the Roundtable's proposed research. Deadline for receipt of proposals is **May 1, 2026, at 5 p.m. EST**. All submissions must be made in our application portal: https://gci.acs.org. The Principal Investigator with the selected proposal will be notified by **October 1, 2026.** It is expected that research will commence in the principal investigator's lab no later than **Q4 2026** and last 12 months.

Requirements for Submission

Proposals will only be accepted from public and private institutions of higher education. The grant is not limited to institutions in the United States. Proposals must be submitted through our application portal at https://gci.acs.org, and applicants must provide the contact information for the grant officer who will process the grant if selected. For institutions without a grant office or a

comparable administrative office, applicants must upload a PDF letter signed by an appropriate university official acknowledging the terms of the grant and accepting the role of financial officer for the grant.

Detailed Project Description:

Although a historical mainstay of synthetic organic chemistry, recent innovations and discoveries in oral peptide therapeutics have rendered peptide chemistry as an area of intense interest. Bolstered by an ever-growing arsenal of unnatural amino acids and computational models to aid in design, peptide-based therapeutics are positioned to revolutionize drug development, providing sorely needed alternatives to conditions where biologics dominate. Indeed, their unique balance of enhanced binding affinity paired with diminish immunogenicity and, in some cases, significantly lower production costs is very attractive to the pharmaceutical sector and is reflected in their growing percentage (>8%) of all drugs approved in the last decade. Although alternatives are in development, large-scale peptide synthesis is predominantly achieved by solid-phase peptide synthesis, a highly successful but decades old technology which relies heavily on the use of orthogonal protecting groups and the strong acid, trifluoroacetic acid (TFA) in deprotection and resin cleavage phases. Although wholly suitable for these tasks, TFA is a well-known PFAS "forever chemical" whose removal from water supplies is challenging and its thermal decomposition generates greenhouse gases (CO_2, HCF_3) as well as sources of HF (upon hydrolytic decomposition).

As such, many regulatory agencies have moved to monitor and regulate the use of TFA, with some proposing to designate it as a reproductive toxin. Given its clear negative impact of our environment and uptick in its use catalyzed by interest in peptide therapeutics, a clear and present need for reliable, sustainable alternatives to TFA exists. With this in mind, the ACS GCI is seeking creative solutions for the development of sustainable platforms to reduce the use of or wholly replace TFA in operations relating to peptide chemistry, broadly defined. Representative key areas include (but are not limited to): 1) Identification of suitable conditions/reagents for direct replacement of TFA 2) Alternative novel protecting groups and/or resins that do not require TFA 3) Methods to use ultra-low loadings of TFA for cleavage operations 4) Methods for TFA recovery and recycling 5) Replacement for TFA in UPLC operations and/or preparative LC while maintaining separation efficacy. Emphasis should be placed on elimination of TFA rather than reduction but proposals will be considered on both fronts.
Based on a need for innovation in this area, this RFP seeks proposals that fall within the following general framework of enhancing the sustainable profile of cleavage operations and peptide synthesis/purification: *Direct replacements for TFA; Alternative novel resins/PG; TFA minimization, recycling, and recovery; Alternatives to TFA in purification; Novel peptide assembly strategies that avoid PGs and/or TFA completely.* Proposed areas of research should be practical in nature and have some definable metric for scoring efficacy against traditional TFA approaches. Further, submissions should make clear how the developed processes can be used to advance peptide drug discovery and/or agrochemical efforts and its amenability to scale up.

Topical areas of interest include (but are not limited to):

- Identification of novel non-PFAS sustainable reagents/conditions/protocols that mimic the efficacy of TFA in cleavage of common acid-sensitive protecting groups to peptide work (e.g. Trt, Boc, tBu, Mtt, Mmt, THP, PMB etc). In particular, methods should employ solvents deemed by the ACI GCI as sustainable and avoid use of any fluorinated solvent system/reagents.
- Development of new amide or acid resins that allow for selective cleavage using non-reagent-based cleavage mechanisms (photochemical, electrochemical, mechanochemical), biocatalytic cleavage processes, novel protecting groups or protecting-group free chemistries. Reagent-based mechanism are welcome but must avoid use of any PFAS and following the solvent sustainability guidelines of the ACS GCI. Highly preferred are strategies that can be applied both to SPPS and LPPS (for fragments or full peptides).
- Development of catalytic methods involving the use of TFA at ultra-low loadings and proffer opportunities for TFA recovery. Alternatively, immobilized TFA-type reagents are welcome for in-solution selective and/or global deprotection.
- Methods or devices for the direct recovery and recycling of TFA from SPPS and/or LPPS cleavages/manipulations. Methods that employ continuous flow processing in support of these efforts are most welcome.
- Replacements of TFA for use in UPLC purification of peptidic material that retains its notable resolving power. Purification techniques/approaches can use novel solvent combinations and/or stationary phases that mimic the efficacy of TFA but metricing against TFA is required.

Project Goal

Render tools to reduce or eliminate the dependency on trifluoroacetic acid as a reagent for the cleavage, isolation, and/or purification of peptides by way of identification of new reagents/conditions or remediation of current platforms/strategies.

Project Timeline

It is expected that one year of research support will be sufficient to provide progress toward intended goals.

Proposal Format

Please be prepared to provide the following information in the application portal:

1. Name and email of grant officer
2. Name, title, phone, email and address of the Principal Investigator
3. Project Title

4. Abstract (200 words)
5. Research Group website
6. PDF of Proposed Plan of Work *(2 pages, 12 pt font, 1-inch margins)*
    - Objectives: Briefly state the project objectives
    - Project Approach: Include specific aims and investigations planned
    - Proposed milestone deliveries with brief description of the manner in which the researcher intends to achieve them
    - Brief description of the PI's research facilities and summary of the student's (undergraduate, graduate student and /or postdoc) capabilities to perform the proposed work
    - References (does not count toward your page limit)

Note: The PI should list any existing background intellectual property and/or collaborations they are aware of that might limit the freedom to operate any of the results arising from any research funded by ACS GCIPR. The priority of the Roundtable is to encourage research utilizing reaction conditions that are commercially available with the freedom to use.

7. PDF of Detailed Estimated Budget: The total amount requested would include all direct costs, student assistantships, etc. The total award is limited to $80,000 for a grant period of up to 12 months.
    - Institutional overhead costs (indirect costs) should not be more than 10% of the total budget.
    - Post-doctoral associate salary and benefits are supported.
    - Student stipend and benefits are supported. Proposals for support of advanced graduate students are highly favored.
    - PI salary supplements will not be supported.
    - Laboratory supplies and instrument use charges are supported.
    - No funds may be allocated for travel, equipment purchase or repair, or administrative support.
8. Curriculum Vitae of Project Team Members: Please submit a curriculum vitae of each project team member (up to two pages per team member, combined into one document). This does not count toward your page limit.

Report Requirements

- Progress reports or updates are due monthly or bi-monthly from initiation of research and will be discussed in arranged web-conferences. Reports will be shared with the member companies of the Roundtable.
- Reports are to include research milestones/significant outcomes, summary of progress to date noting any deviations from the proposal, and research plans for upcoming months.

- A final comprehensive report is due one month after the end of the grant period. This report must be submitted as a PDF document electronically to gcipr@acs.org. In addition, the content of the report should be targeted for publication in a peer-reviewed technical journal. The paper will be co-authored by the principal investigator and student(s) performing the work with the guidance of member companies of the ACS GCIPR.

Intellectual Property, Publication Acknowledgement, and Terms of the Grant

- The primary purpose of this grant is the public dissemination of research through publication.
- Every patent, United States or foreign, that results from research funded (in part or in its entirety) by the ACS GCIPR Research Grant shall be immediately dedicated to the public, royalty free.
- Publication of results is expected within 6 months of work completion.
- Each publication prepared in connection with an ACS GCIPR Grant shall make acknowledgement in the following manner: "This manuscript was developed with the support of the ACS Green Chemistry Institute Pharmaceutical Roundtable (https://www.acsgcipr.org), under Grant No. XXXXX. The ACS GCI Pharmaceutical Roundtable's mission is to catalyze green chemistry & engineering in the global pharmaceutical industry."
- Acceptance of a Roundtable Grant will be conditional upon agreement by the grantee institution that in the event the Principal Investigator is unable for any reason to conduct the research proposed, the funds, if previously paid by the Roundtable, shall, upon demand, be returned in full to the Roundtable, and further, that in the event the PI is unable for any reason to continue with the research after it has commenced, this grant shall be terminated forthwith and the unexpended and unencumbered balance of any funds theretofore advanced shall be returned to the Roundtable.
- The grantee institution, by acceptance of this grant, provides assurance that support normally provided by the institution for research of the faculty member will not be diminished.
- Applicants may have only one research grant with the ACS GCIPR at a time. In order to close a grant, the ACS GCIPR must receive and approve the required reports.

For additional information:

Website: www.acsgcipr.org
Email: gcipr@acs.org