2021 ACS GCI Pharmaceutical Roundtable Research Grant for Technology-Enabled Late-Stage Functionalization (LSF) of Pharmaceuticals

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 Pharmaceuticals, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, F. Hoffmann-La Roche Ltd., Gilead, GlaxoSmithKline, Ipsen, Johnson & Johnson, Merck & Co., Neurocrine, Novartis, Novo Nordisk, Pfizer, Takeda, UCB Pharma, Vertex, and the ACS Green Chemistry Institute. Associate members are Ampac Fine Chemicals, Asymchem, Bachem, CatSci, Codexis, Hikal, Hovione, InnoSyn, Pharmaron, Polypeptide, Porton, Sai Life Sciences, Solara Active Pharma Sciences Ltd., and WuXi AppTec. Corteva Agriscience and EnzyTag are affiliate members.

The ACS GCIPR is seeking a one-year R&D commitment to assist the Roundtable's medicinal chemistry initiative. The focus of the R&D will be toward overcoming practical challenges associated with the late-stage functionalization of pharmaceuticals. Proposals are invited from public and private institutions of higher education worldwide. This 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 $50,000 for a grant period of 12 months. Interested PI's are required to provide a written proposal describing the investigator's capability to carry out the Roundtable's proposed research. The deadline for receipt of proposals is **May 15, 2021 at 5 p.m. EDT**. Proposals must be received by the deadline to be considered. Submissions must be a single PDF file submitted to gcipr@acs.org. GCIPR will notify the selected PI by **September 1, 2021**. It is expected that research will commence in the Principal Investigator's lab no later than **October 1, 2021** and last approximately 12 months.

Requirements for Submission

Proposals will 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 the appropriate institutional office for external funding. For international submissions, if there is no comparable office, submit a pdf of a letter signed by an appropriate university official recognizing the terms of the grant.

Detailed Project Description

The ability to reliably and rationally functionalize complex bioactive compounds at a late-stage is of significant value to medicinal chemists. On one hand, catalytic approaches to diversification often suffer from poor functional group compatibility and are ineffective in the direct modification of nitrogen-rich frameworks of interest to the industry. In contrast, stoichiometric approaches are predictable and broad in scope (e.g., palladium oxidative addition complexes, aryl phosphonium salts) but are unsustainable on large scales.

The purpose of this RFP is to encourage the development of novel approaches to late-stage diversification of pharmaceuticals that are either catalytic and broad in scope, or stoichiometric and rely on sustainable reagents. To accomplish this goal, the use of technologies may be accelerating and enabling, including but not limited to electrochemistry, photoredox catalysis, flow chemistry, or biocatalysis.

Key Considerations:

- Substrates: One key gap in today's synthetic chemistries is the lack of reliable reactions to allow for broad functionalization of complex bioactive compounds at a late-stage. Heterocycles, in particular, are ubiquitous in drug discovery. A variety of nitrogen-rich heterocycles (including those containing unprotected N–H and O–H bonds) are expected to be an important emphasis in proposals. In the substrates of interest themselves, reactions at C–H or C–X bonds, among others, are of equal strategic importance to the medicinal chemist and hence will not be prioritized one over the other. Instead, rapid diversification will be a particular focus.

- Type of bond construction: One of the most convenient features of cross-coupling reactions is the broad types of bond constructions that are possible, mostly using ligand-supported palladium catalysts and (hetero) aromatic halides as building blocks. Reactions capable of forging C–C, C–N, and C–O bonds are thus of tremendous value. As it relates to LSF, breadth of reactivity will be prioritized over ones that will examine a limited set of reaction types.

- sp2 vs sp3: Given the importance of 3D-rich architectures in drug discovery, a focus on sp3-functionalizations should be considered. In particular, methodologies that enable control of stereochemistry (either stereospecific or stereoselective) would bring significant value to the industry.

- Catalysis or stoichiometric: Existing tools to accomplish LSF are often not applicable to pharmaceutical agents. In one instance, catalytic strategies do not typically perform well in complex settings. On the other hand, stoichiometric approaches using palladium or phosphorus are powerful but unsustainable. In this RFP, applicants are encouraged to consider either approach. That is, can we render catalytic strategies more broad through novel catalyst design, for example? Or alternately, can stoichiometric approaches be rendered more green using sustainable metals and/or reagents?

- Technologies: To overcome the intrinsic challenges of LSF, the strategic inclusion of new technologies may be an important avenue to examine. Given that most pharmaceutical agents are complex, containing chiral centers and nitrogen heterocycles, high temperatures would be expected to be incompatible. We therefore encourage applicants to consider electrochemistry, photoredox catalysis, flow chemistry, or biocatalysis as enabling.

- Solvents, additives, oxidants, reductants: Traditional approaches to LSF have included solvents and reagents that do not necessarily fit the twelve principles of green chemistry (https://www.acs.org/content/acs/en/greenchemistry/principles/12-principles-of-green-chemistry.html). For instance, many C–H functionalizations employ stoichiometric silver salts as terminal oxidants. Increasingly green solvents and reagents should be explored in

attempt to remove reliance on unsustainable compounds including dioxane, NMP, and DMF. For more information, please see the Roundtable's solvent selection tool: https://www.acsgcipr.org/tools-for-innovation-in-chemistry/solvent-tool.

- Scale-up: Breadth of reactivity is the primary objective of this RFP, but demonstrations of possible scale-up to multi-gram scales would be an important future direction to consider. In medicinal chemistry, enabling pre-clinical evaluation is an important area of focus, and establishing line-of-sight to larger scales (kilograms) often informs on considerations down the road of development (for example, life-cycle considerations).

Project Goal

To develop new and broadly applicable methods to achieve the late-stage diversification of pharmaceuticals agents employing sustainable catalysts and reagents.

Project Timeline

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

Proposal Format (Maximum 3 pages as described below + CVs)

All of the information below must be submitted as a single PDF file. All components described in sections A, B, and C must be included in the same PDF file to assure the proposal is reviewed in its entirety.

A) Title Page (*1 page, 12 pt. font, 1-inch margins*)

1. Project Title:
2. Principal Investigator:
3. Title / Position(s):
4. Telephone Number(s):
5. Fax Number(s):
6. Postal Mailing Address:
7. Email Address:
8. Research Group Website:

B) Proposed Plan of Work *(2 pages, 12 pt. font, 1-inch margins)*

1. Objectives: Briefly state the project objectives
2. Project Approach: Include specific aims and investigations planned
3. Proposed milestone deliveries with brief description of the manner in which the researcher intends to achieve them
4. 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
5. 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.

C) Detailed Estimated Budget: The total amount requested would include all direct costs, student assistantships, etc. The total award is limited to $50,000 for a grant period of up to 12 months. This does not count toward your page limit.

1. Institutional overhead costs (indirect costs) should not be more than 10% of the total budget.
2. Post-doctoral associate salary and benefits are supported.
3. Student stipend and benefits are supported. Proposals for support of advanced graduate students are highly favored.
4. PI salary supplements will not be supported.
5. Laboratory supplies and instrument use charges are supported.
6. No funds may be allocated for travel, equipment purchase or repair, or administrative support.

D) Curriculum Vitae of Project Team Members: Please submit a curriculum vitae of each project team member (up to two pages per team member). 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 the ACS GCIPR Research Grant shall make acknowledgement in the following manner: "This manuscript was developed with the support of the American Chemical Society Green Chemistry Institute Pharmaceutical Roundtable (www.acsgcipr.org). The ACS GCI is a not-for-profit organization whose mission is to catalyze and enable the implementation of green and sustainable chemistry throughout the global chemistry enterprise. The ACS GCI Pharmaceutical Roundtable, composed of pharmaceutical and related industries, was established in 2005 to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry. The activities of the Roundtable reflect its member's shared belief that the pursuit of green chemistry and engineering is imperative for business and environmental sustainability.
- 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
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