2021 ACS GCI Pharmaceutical Roundtable Research Grant for Solvent Minimization in Flow Chemistry

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 Continuous Processing/Flow Chemistry initiative. The focus of the R&D will be toward implementing solutions to minimize the use of organic solvents in Flow Chemistry. 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. Note that this award will be exclusively for R&D; no portion of this grant will go to institutional overhead. Interested PIs 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 by **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

Organic solvents are used at every stage of a typical drug manufacturing process to solubilize reaction components, separate and purify chemical mixtures, and isolate products, and it has long been recognized that solvent-use represents the largest contributor to analyses of green chemistry metrics such as process mass intensity (PMI). However, increased regulatory scrutiny along with growing awareness of the environmental burden and risks to the health and safety of workers posed by organic solvent use have prompted the pharmaceutical industry to begin seeking more sustainable solutions regarding the amount and nature of solvents being employed. In recent years, flow chemistry and continuous processing have been promoted as emerging sustainable technologies for chemical

synthesis. They also offer significant benefits in process intensification and distributed manufacturing capabilities due to their inherently smaller footprints and tunable scale, making them well suited to "just-in-time" manufacture of pharmaceutical intermediates and APIs. However, one disadvantage which is often over-looked is that often reactions tend to be run under relatively dilute conditions in order to ensure homogeneity, leading to increased usage of solvents and increased quantities of chemical waste. A further challenge in the scaling of processes in flow is represented by the fate of the solvent on completion of the reaction with recycling (if implemented) typically carried out in a separate off-line manner.

This call for grant proposals is intended to look at strategies to reduce solvent use in flow chemistry with two suggested approaches being through either miniaturization of screening, optimization, or reaction systems; or through investigating approaches to solvent-recycling or recovery "on-line" in continuous flow. It is stressed that while proposals are not limited to these, they should embrace the over-arching theme of "reducing solvent use in continuous flow" and the principles of Green Chemistry and Engineering.

While solutions have been previously been advanced in these both these areas (lab-on-a-chip, nano-screening, nanofiltration and the use of membrane technology to facilitate separations), there is a continued need for further work to be done, and to specifically enable developments to be implemented in a diverse range of laboratories (academic or industrial) in a facile and cost-effective manner. In addition, consideration of mixing, mass-transfer, and heat transfer is critical to the submitted proposals, most notably for those involving proofs-of-concept in which reproducing results on large scale is a core goal of the proposed technology.

Key Considerations:

- New Synthetic Technologies in Flow: Addressing engineering, screening, and scale-up challenges by implementing emerging synthetic technologies in flow (chemistry in water, electrochemistry, high-throughput experimentation, mechanochemistry, nanofiltration, oscillating bed reactors, photoredox chemistry) and their impact on solvent usage are considered to be within the scope of this RFP.
- Solvents: Judicious selection of solvents and reagents based on the twelve principles of green chemistry is highly encouraged (see below). For any reactions exemplified, green solvents and reagents should be explored in order to remove reliance on unsustainable compounds including dichloromethane, dioxane, NMP, and DMF. Reactions operating under high concentration or neat conditions, as well as the usage of non-traditional solvent systems such as supercritical carbon dioxide are considered within the scope of this RFP. Additionally, consideration should be paid to the handling of solids or slurries in flow where relevant—especially under high concentration conditions or conditions involving reactive crystallization. For further guidance, please see the Roundtable's solvent selection tool.
- Scale-up: Reduction of overall solvent burden in flow chemistry is the overall purpose of this RFP, but demonstrations of possible scale-up to multi-gram scales would be an important direction to consider, notably in allowing quantitative benchmarking of the new methodology. Establishing line-of-sight to larger scales (kilograms) often informs on

considerations down the road of development (for example, life-cycle considerations), and can facilitate crucial "batch versus flow" discussions for future manufacturing campaigns.

- Substrates and Reactions: The pharmaceutical industry prominently features heterocycles and highly polar materials. Substrates and reactions of study should be selected based on a pharmaceutically relevant profile.
- Processing: Standard pharmaceutically relevant operations such as liquid-liquid extractions, distillations, crystallizations, precipitations, and membrane separations have proved to be somewhat challenging in flow and have often increased the burden in terms of the amount of solvent employed. Consideration should be given to understanding, improving, and generalizing purification or separation methodologies to obtaining high purity isolated materials with appropriate physical properties (i.e. crystal form, particle size, etc.) upon scale-up or in the context of high-throughput screening.
- Life-Cycle Considerations: Advances concerning solvent recycling or maximizing disposal of process waste as non-hazardous are also within the scope of this grant. In the case of solvent recovery or recycling, demonstration of the purity and reusability of the recovered material is a key concern. Quantitative evaluation of the advantages of a newly developed system or method (e.g. through formal calculations such as life cycle analysis, process mass intensity, and the green innovation scorecard) should be included. For further information please see the Roundtable's list of tools for innovation in chemistry.
- Greenness: To ensure that flow chemistry continues to stay at the frontier of sustainability, applications should be reflective of the key research areas described by the ACSGCIPR:
    - https://www.acsgcipr.org/advancing-research/
    - https://pubs.acs.org/doi/abs/10.1021/op100327d

  And of the twelve principles of both green chemistry and green engineering, as well as the design principles for sustainable and green chemistry and engineering:

    - https://www.acs.org/content/acs/en/greenchemistry/principles/12-principles-of-green-chemistry.html
    - https://www.acs.org/content/acs/en/greenchemistry/principles/12-design-principles-of-green-engineering.html
    - https://www.acs.org/content/acs/en/greenchemistry/principles/design-principles-booklet.html

  Additional selected recent review perspectives/reviews on flow chemistry include:

    - Guidi, M.; Seeberger, P. H.; and Gilmore, K. How to approach flow chemistry. *Chem. Soc. Rev*., **2020**, *49*, 8910-8932.
    - Baumann, M.; Moody, T. S.; Smyth, M; Wharry, S. A Perspective on Continuous Flow Chemistry in the Pharmaceutical Industry. *Org. Process Res. Dev*., **2020**, *24*, 1802-1813.

- Gioiello, A., Piccinno, A., Lozza, A. M. and Cerra, B. Medicinal Chemistry in the Era of Machines and Automation: Recent Advances in Continuous Flow Technology. *J. Med. Chem.*, **2020**, *63*, 6624-6647.
- Cole, K.P. What Elements Contribute to a High-Quality Continuous Processing Submission for *OPR&D*? *Org. Process Res. Dev.* **2020**, *24*, 1781-1784.

Project Goal

Promote innovation at the interface of chemistry and engineering to develop practical solutions to minimize use of organic solvents either through miniaturization, or through recycling approaches with continuous flow chemistry.

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. Summarize the student's (undergraduate, graduate student and /or postdoc) capabilities to perform the Roundtable's proposed work.
2. Brief description of the PI's research facilities.
3. Proposed milestone deliveries (primary project and side project) with brief description of the manner in which the researcher intends to achieve them.
4. 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.

5. References (does not count toward your page limit).

C) Curriculum Vitae of Project Team Members: Please submit a curriculum vitae of each project team member (two pages per team member). Note that this does not count toward your page limit.

Report Requirements

- Progress reports are due at one-month intervals from initiation of research and discussed in arranged monthly teleconferences.
- 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.
- Reports must be submitted as a PDF document electronically to gcipr@acs.org. Reports will be shared with the member companies of the Roundtable. In addition, the content of the report will 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 (https://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 and engineering throughout the global chemistry enterprise and across the Society. The ACS GCI Pharmaceutical Roundtable is composed of pharmaceutical and biotechnology companies and was established to encourage innovation while catalyzing the integration of green chemistry and green engineering in the pharmaceutical industry. The activities of the Roundtable reflect its members' 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
Email: gcipr@acs.org