2022 ACS GCI Pharmaceutical Roundtable Research Grant for Expanding Applications of Process Analytical Technology with 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, Kaneka, Novasep, Pharmaron, Polypeptide, Porton, Sai Life Sciences, Solara Active Pharma Sciences Ltd., and WuXi AppTec. Corteva Agriscience, EnzyTag, and PHT International Inc. 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 expand the applications of Process Analytical Technologies (PAT) within Flow Chemistry/Continuous Manufacturing. 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 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, 2022, 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 6, 2022**. It is expected that research will commence in the Principal Investigator's lab no later than **October 3, 2022,** 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 design, validation, and employment of analytical techniques to monitor processes and conduct quality control (QC) analyses represents a foundation for the batch manufacturing of pharmaceutical products and is a critical component for regulatory submissions. However, with the exponential growth in transitioning from batch to continuous methods for the synthesis of APIs, there exists a significant need to bridge the knowledge gap to develop innovative approaches to enable the efficient real-time analytical monitoring of such processes. To achieve this requires a paradigm shift in not only

the judicious selection of the appropriate technique for a specific process but also often in the consideration of sampling methodologies that can be utilized under extreme conditions (high temperatures and pressures), tolerate heterogeneous/viscous reaction media, and are compatible with a diverse range of chemicals (corrosives, reactives and unstable intermediates) without adversely affecting the desired analysis. From a sustainability perspective, efficient real-time monitoring of continuous processes allows the expedient discovery of the optimal conditions to maximize throughput (space-time-yield) while also providing an opportunity to rapidly highlight deviations from "steady state" enabling corrective actions to be taken "on the fly" thus preventing potential downstream waste. In addition, seamless integration of real-time analytics also provides the opportunity to develop AI/ML-based algorithms that can provide a feedback loop for the autonomous optimization and subsequent execution of flow chemistry processes.

This call for grant proposals is intended to solicit diverse proposals for the development of new process analytical technology (PAT) methods or systems in combination with continuous flow chemistry. Reductions in system footprint, and material/energy usage will be common themes making in-process faster and more efficient with flow chemical systems. Applications must leverage the benefits of both PAT and flow chemistry, and ideally highlight these with respect to their potential for more sustainable pharmaceutical chemical research, development, and manufacturing. Proposals may encompass in-line, on-line, at-line and off-line PAT tools, and those addressing gaps in sampling technologies are also welcomed. Submissions may include but are not limited to novel microLC systems (especially those allowing use with unusual process windows, and which allow at-line incorporation into flow chemical systems), systems/methods that allow inclusion of automated and/or self-optimizing platforms, and PAT methodologies for use with solid-state (or liquid/vapor) chemistry or continuous mechanochemistry. It is stressed that while proposals are not limited to these, they should embrace the over-arching theme of "implementing solutions to expand the applications of Process Analytical Technologies (PAT) within Flow Chemistry/Continuous Manufacturing" and the principles of Green Chemistry and Engineering.

While numerous advances have been reported in the innovative applications of PAT to flow chemistry/continuous processes over recent years (IR, Raman, NMR etc.), there is a continued need for work to be done, and to specifically enable developments that can be implemented in a diverse range of laboratory settings (academic or industrial) in a facile and cost-effective manner. In addition, consideration of the potential broader applicability of the proposals submitted both in terms of chemistries and scale as well as synergies with existing methodologies should be emphasized within the submissions.

Key Considerations:

- New Analytical Technologies in Flow: Addressing engineering, screening, and scale-up challenges with implementing emerging PAT in flow (sampling, high pressure, high temperatures, heterogeneous reactions, mechanochemistry, miniaturization etc.) and their impact on robust experimental outcomes are considered to be within the scope of this RFP.

- Analytical Methods/Devices: The dynamic nature of flow processes provides a major challenge for analytical methods with a balance often to be struck between the speed of data acquisition and the richness of the information obtained. Also, the relative footprint of the device is an important consideration for many laboratories while quantification of materials often presents a gap in many reported methods. Herein, proposals dealing with novel device-based approaches, extension of established methodologies as well as those exploiting synergies between analytical methods will all be considered.

- Sampling: Specifically, at-line and off-line PAT require removal of the samples from the reaction stream either in an automated or manual fashion and subsequent treatment (dilution/quench) prior to introduction to the analytical instrumentation. Challenges herein include the nature of the reaction stream (heterogeneity, viscosity), the processing conditions (temperature/pressure) as well as achieving this in a non-destructive manner. Further potential in novel sampling methodologies include space-time monitoring (and quantification-based) approaches utilizing either in-line or at-line PATs as well as new approaches to on-line sampling through new flow cell technologies.

- Self-Optimizing Systems: The development of AI/ML-based algorithms to embed feedback loops into flow-based reaction optimization platforms represents an area of significant research though gaps still exist in efficient machine-based approaches to interpreting the analytical data most notably for complex reactions in which multiple continuous and discrete variables contribute to the experimental outcome.

- Scale-Up: Establishing clear line-of-sight for a developed PAT application across a range of scales can inform discussion on down the road of development (for example, life-cycle considerations), and can facilitate crucial "batch versus flow" decisions for future manufacturing campaigns

- Substrates and Reactions: The pharmaceutical industry prominently features heterocycles and highly polar materials often accessed through transient reactive intermediates. Exemplification of new PAT methods should be selected to feature substrates and reactions of a pharmaceutically relevant nature.

- 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 PRT. In addition, comparison of methods can be achieved using the Analytical Method Greenness Score (AMGS):
    - https://www.acsgcipr.org/amgs

- https://pubs.acs.org/doi/abs/10.1021/op100327d
  Green Chemistry, 2019, 21, 1816-1826 (AMGS)

and of the twelve principles of both green chemistry and green engineering.

Additional selected recent review perspectives/reviews on flow chemistry and the applications of PAT include:

M. Guidi, P. H. Seeberger and K. Gilmore. "How to approach flow chemistry". *Chem. Soc. Rev.*, **2020**, *49*, 8910-8932.

M. Baumann, T. S. Moody, M. Smyth and S. Wharry. "A Perspective on Continuous Flow Chemistry in the Pharmaceutical Industry". *Org. Process Res. Dev.* **2020**, *24*, 1802-1813.

G. A. Price, D. Mallik and M. G. Organ. "Process Analytical Tools for Flow Analysis: A Perspective". *J. Flow Chem.*, **2017**, *7*, 82-86.

M. A. Morin, W. Zhang, D. Mallik and M. G. Organ. "Sampling and Analysis in Flow: The Keys to Smarter, More Controllable, and Sustainable Fine-Chemical Manufacturing". *Angew. Chem. Int. Ed.*, **2021**, *60*, 20606-20626.

Project Goal
Promote innovation at the interface of chemistry and engineering toward implementing solutions to expand the applications of Process Analytical Technologies (PAT) within Flow Chemistry/ Continuous Manufacturing.

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
Email: gcipr@acs.org