



2020 ACS GCI Pharmaceutical Roundtable Research Grant for *Increasing the Utility of Surfactant-Based Chemistry in Water Methodologies*

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, 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, Sanofi, 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, and WuXi AppTec. Chiral Technologies, Corteva Agriscience and EnzyTag are affiliate members.

The ACS GCIPR is seeking a one-year R&D commitment to assist the Roundtable's chemistry in water initiative. The focus of the R&D will be toward overcoming practical and engineering barriers to the broad application and scale-up of surfactant-based chemistry in water technology. 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. 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 **June 1, 2020 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 **August 15, 2020**. It is expected that research will commence in the Principal Investigator's lab by October 2020 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. 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 alternatives to organic solvents. In recent years, water has emerged as a promising alternative reaction medium. A growing body of research has demonstrated that a wide variety of organic reactions can be successfully adapted to aqueous media using nanomicelle-forming surfactants, often providing superior efficiency, selectivity, and productivity over conventional solvents.

Industrial researchers have expanded on this work, demonstrating that micelles in water can serve as the reaction space for certain transformations during drug substance manufacturing at multi-kg scales.

Although there has been progress in adapting organic chemistry to aqueous reaction conditions, replacing organic solvents with water during workup, purification, and isolation of reaction products has received comparatively little attention. The key problem lies in the physical properties of micellar reaction mixtures, which tend to be emulsions. When conventional solvents are used in drug manufacturing, emulsions are rare, and when they do occur, are often considered a barrier to scale-up and downstream processing. A handful of approaches have been developed to overcome the limitations of emulsions in aqueous micellar mixtures, including the use of an organic co-solvent to stabilize the emulsion and extraction of products using an immiscible organic solvent. However, in order to fully realize the environmental and safety benefits of conducting chemistry in water, there is a need for new techniques and approaches to scale-up and/or downstream processing of micellar mixtures that are broadly applicable and further reduce our reliance on organic solvents.

Key Considerations:

- **Processing:** Standard pharmaceutically relevant operations such as liquid-liquid extractions, distillations, crystallizations, precipitations, and membrane separations have limitations when operated in the presence of surfactants. Consideration should be given to understanding, improving, and generalizing the application of aqueous micellar methodology 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.
- **Surfactants:** TPGS-750-M and Brij-30 are two of the most widely used surfactants to enable chemistry in water. A variety of other surfactants have been reported in the literature tailored for specific purposes, such as reaction types, substrate classes, and stability. Development of new benign surfactants is within the scope of this grant if the new entity addresses a processing parameter. Surfactants designed to overcome chemical reactivity challenges are out of scope.
- **Substrates and Reactions:** The pharmaceutical industry prominently features heterocycles and highly polar materials. Substrates and/or reactions of study should be selected based on a pharmaceutically relevant profile.
- **Batch or Flow:** Addressing the engineering challenges of performing chemistry in water can be with respect to operations in batch, flow, or both.
- **Life-Cycle Considerations:** Advances concerning surfactant medium recycling and/or maximizing disposal of process waste as non-hazardous are also within the scope of this grant.
- **Greenness:** To ensure that chemistry in water and flow chemistry continue to stay at the frontier of sustainability, applications should be reflective of the key research areas described by the GCIPR:

<https://www.acsgcivr.org/advancing-research/>
<https://pubs.acs.org/doi/abs/10.1021/op100327d>

and of the principles of both green chemistry and green 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>

Additional references that provide an overview of the chemistry in water field include:

<https://onlinelibrary.wiley.com/doi/full/10.1002/chem.201705499>

<https://pubs.rsc.org/en/content/articlehtml/2016/gc/c5gc02371h>

Project Goal

Promote innovation at the interface of chemistry and engineering to overcome practical barriers to the broad application and scale-up of surfactant-based chemistry in water technology.

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—from section A through D—must be submitted as a single 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