



## **2023 ACS GCI Pharmaceutical Roundtable Research Grant for Overcoming Practical and Engineering Barriers for the Application/Scale-up of Electrochemistry in Flow**

The [ACS Green Chemistry Institute Pharmaceutical Roundtable](https://gci.acs.org) (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, Boehringer-Ingelheim, Bristol-Myers Squibb, Eli Lilly and Company, F. Hoffmann-La Roche Ltd., Gilead, GlaxoSmithKline, Ipsen, Johnson & Johnson, Merck & Co., Merck KGaA, Darmstadt, Germany, Neurocrine, Novartis, Novo Nordisk, Pfizer, Sanofi, Takeda, UCB Pharma, Vertex, and the ACS Green Chemistry Institute. Associate members are Aexplora, Ampac Fine Chemicals, Asymchem, Bachem, CatSci, Codexis, Hikal, Hovione, InnoSyn, Kaneka, PharmaBlock, Pharmaron, Polypeptide, PHT International Inc., Porton, Sai Life Sciences, Solara Active Pharma Sciences Ltd., STPharm, and WuXi AppTec. Affiliate members are Corteva Agriscience, FMC and Zoetis.

The ACS GCIPR is seeking a one-year R&D commitment to assist the Roundtable's Continuous Processing/Flow Chemistry initiative. 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 \$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 15, 2023, at 5 p.m. EDT**. All submissions must be made in our application portal: <https://gci.acs.org>. The Principal Investigator with the selected proposal will be notified by **September 1, 2023**. It is expected that research will commence in the principal investigator's lab no later than **October 2023**, and last approximately 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 in our application portal <https://gci.acs.org> 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**

There is a current resurgence in the development of electrochemistry to mediate synthetic transformations with the merits of this technology from a sustainability perspective well recognized. However, while the advantages of flow technology to control such processes is acknowledged (improved mixing, better heat exchange, reproducibility, and selectivity), there remains significant challenges with translating electrochemical processes from batch to flow to exploit these benefits. Most notably herein is the ability to construct a set-up to get sufficient current through the electrodes. As such, we are seeking proposals for flow set-ups that can be easily implemented/constructed and will enable the robust performance and/or scale-up of electrochemical reactions in an economical and sustainable manner.

From an environmental perspective, the case to adopt electrochemistry as a core methodology are highly compelling most notably with the fact that one is replacing potentially harsh/toxic reagents simply with electrons, which have a minimal footprint, generate no waste, and have negligible cost. From a big picture, the latter point is further emphasized by a global drive to more sustainable and economical sources of electricity. In addition, electrochemical reactions are conducted under mild conditions typically at room temperature and atmospheric pressure. While these reasons have led to a shift in to increased uptake in academia most notably in adopting electrochemistry as a preferred methodology specifically for oxidation/reduction reactions, this trend has not been as not been mirrored within industry where the barrier to invest in what is professed to be a newer technology (though in fact is >150 years old in organic synthesis) is raised owing to a known substitute chemical reagent being well established for the same transformation.

One of the commonly cited reasons for the lack of uptake of electrochemical processes is the belief that these reactions tend to be non-selective, though this perception highlights the bigger issue in that the use of electrochemistry to mediate organic reactions is still very much thought to be a “black box”. The issue of selectivity can in many cases be mitigated through judicious choice of electrode materials, the nature of the electrolyte or through controlling the potential of the working electrode. Better understanding of the role of the electrode’s composition would be beneficial to the community though cost of these materials is also a key area of concern, and proposals around the development of novel, easily accessible substituents as well as innovations in 3D-engineering of cells/electrodes are welcomed. In addition, electrochemical reactions often work best under aqueous conditions owing to the conductivity of the solution allowing facile transport of ions between the two electrodes. Given that organic reactions are not typically conducted in water, biphasic aqueous/organic mixtures can be utilized or organic solvents containing supporting electrolytes though solutions to enable better translation of conventional solution phase chemistry to an electrochemistry setting are welcomed.

Interestingly there are several commercialized electrochemical processes that are operated on multi-ton scale though these are for commodity/low-cost chemicals (adiponitrile) in which marginal increases in efficiency and cost-savings are amplified through the scale of the process. In the commercial manufacture of specialty high-value chemicals, the default option is still to employ well-understood

chemical process to provide the molecules of interest. The multistep nature and complexity of the final compounds coupled with the need for selectivity can represent barriers for utilization of electrochemistry though one advantage of the technology here is that “significant” productivity gains can be obtained (yield, PMI) if a single step of a multistep sequence is carried out with electrochemistry as given the lack of additional reagents required, the product obtained can ideally be telescoped into a subsequent step. Furthermore, transitioning an electrochemical process on scale from batch to flow provides numerous other benefits such as lower energy costs through minimization of the inter-electrode gap which also leads to faster reactions at higher current with lower concentrations of the supporting electrolyte as well as the cells offering high electrode surface area to reaction volume ratios. Challenges do exist with fouling of the electrodes, buildup of gases within the cell, as well as the fact that the reactions are “heterogeneous” in nature, which is often highlighted as the major flaw in flow-based technologies. One area that would potentially see a shift in the adoption of electrochemistry within the pharmaceutical industry is development of new methodologies that highlight the use of cheap, renewable feedstocks and their facile conversion to high-value, functionalized building blocks (heterocyclic, chiral).

Coupled with the renaissance in interest in electrochemistry has seen the commercial availability of several lab-based systems enabling facile uptake either in a batch or flow mode. Proposals are welcomed that further this with a focus on modular, easy-to-construct hardware and user-friendly equipment with the capability to be implemented in both academic and industrial research labs. In addition, for such systems, scale is a critical consideration to enable facile translation of developed reaction conditions from “mg screening” through gram all the way to potential commercialization. In addition, proposals that seek to provide tangible, general solutions to flow electrochemical fundamental technical issues such as “clogging”, “dispersion of by-product gases” (gases do not conduct electricity hence hindering performance) and optimizing “single-pass” conditions are encouraged. Finally, general proposals that endeavor to promote the uptake and address the “stigma” of electrochemistry as a “niche” and/or “black-box” technology are highly sought after.

*Key Considerations:*

- Substrates and Reactions: The pharmaceutical industry prominently features heterocycles and highly polar materials often accessed through transient reactive intermediates. Specifically for proposals that explore new electrochemical methods that demonstrate the ability to rapidly build up molecular complexity from renewable, feedstock chemicals.
- Selectivity/Reactivity Innovations: Design/development of new electrodes focusing on novel materials and/or new orientations of these to probe selectivity within various reaction systems. Investigation of electroorganic reactions under “near-aqueous” conditions. Telescoping of electrochemical reactions into synthesis cascades for the assembly of complex bioactive molecules. Exploitation of electrochemistry in tandem with other technology paradigms such as photoredox-, metal-mediated, and/or bio-catalysis.

- Scale-up: Establishing clear line-of-sight for any developed electrochemistry across a range of scales to inform crucial “batch versus flow” decisions for future manufacturing campaigns and highlighting the sustainability benefits of such methodology when compared to conventional chemical approaches.
- Tools to Facilitate Uptake: Advances both in promoting the value and “simplicity” of flow electrochemistry as an emerging synthesis technology. Development of versatile hardware systems for easy implementation and use in a range of laboratory settings with innovations inherent to these devices that minimize well-known issues with electrochemistry in flow (clogging, electrode-fouling etc). Ability to incorporate PAT in a seamless manner, and rapidly optimize/screen conditions “on the fly” are considered to be a plus for novel systems though cost is also a key parameter in the design of new hardware.
- Greenness: To ensure that flow chemistry continue to stay at the frontier of sustainability, applications should be reflective of the key research areas and of the twelve principles of both [green chemistry](#) and [green engineering](#).

Additional selected recent developments/reviews on Electrochemistry in both Batch and Flow include:

- N. Tanbouza, T. Ollevier, and K. Lam. “Bridging Lab and Industry with Flow Electrochemistry”. *iScience*, **2020**, 23, 101720.
- T. Noël, Y. Cao, and G. Laudadio. “The Fundamentals Behind the Use of Flow Reactors in Electrochemistry”. *Acc. Chem. Res.*, **2019**, 52, 2858-2869.
- S. Maljuric, W. Jud, C. O. Kappe, and D. Cantillo. “Translating Batch Electrochemistry to Single-Pass Continuous Flow Conditions: An Organic Chemist’s Guide”. *J. Flow Chem.*, **2020**, 10, 181-190.
- F. Marken and J. D. Wadhawan. “Multiphase Methods in Organic Electrosynthesis”. *Acc. Chem. Res.*, **2019**, 52, 3235-3338.
- C. Kingston, M. D. Palkowitz, Y. Takahira, and P. S. Baran. “A Survival Guide for the ‘Electro-curious’”. *Acc. Chem. Res.*, **2019**, 53, 72-83.
- M. Atobe, H. Tateno, and Y. Matsumara. “Application of Microreactors in Electrosynthetic Processes”. *Chem. Rev.*, **2018**, 118, 4541-4572.
- D. S. P. Cardosos, B. Šljukić, D. M. F. Santos, and C. A. C. Sequeira. “Organic Electrosynthesis: From Industrial Practice to Laboratory Applications”. *Org. Process Res. Dev.*, **2017**, 21, 1213-1226.
- Y. Kawamata and P. S. Baran. “Electrosynthesis: Sustainability is Not Enough”. *Joule*, **2020**, 4, 701-704.
- M. Navarro. “Recent Advances in Experimental Procedures for Electroorganic Synthesis”. *Curr. Opin. Electrochem.*, **2017**, 2, 43-52.

## **Project Goal**

Promote innovation at the interface of chemistry and engineering toward overcoming barriers for the adoption/application/scale-up of electrochemistry in flow.

## **Project Timeline**

It is anticipated 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. Research Group website
5. 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.

6. 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.

7. 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 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](mailto: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](http://www.acsgcipr.org)

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