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

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, 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 Axplora, 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. The focus of the R&D will be toward Overcoming Practical and Engineering Barriers to Enable the Broad Application and Scale-up of Photochemistry in Flow. 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

In recent years, photochemistry (and especially photoredox catalysis) has been embraced as a transformative synthetic method with reactions often taking place under very mild conditions. However, photochemical transformations are often perceived as complex in terms of reaction kinetics and scale-

up. We are seeking proposals that can facilitate the seamless implementation of photochemistry across a broad range of reaction scales while adhering to the key principles of Green Chemistry. In addition, the development of novel photocatalyzed flow-processes using earth-abundant metal complexes and/or organic photoredox catalysts are within scope of this topic as is the use of supported catalysts for photo-flow processes.

One cannot understate the growth of photochemistry/photocatalysis over recent years within the synthetic organic chemistry community with numerous novel synthetic methods being developed that typically operate under mild reaction conditions specifically at room temperature using visible light and often able to avoid undesirable toxic and/or hazardous reagents. To exploit these attributes, photo-mediated methods have been merged with numerous other synthesis platforms including transition-metal catalysis, biocatalysis, asymmetric methodologies and electrochemistry to enable the construction of chemical bonds from a versatile array of coupling partners.

However, despite the attractive attributes of photochemically-promoted processes, these transformations are often perceived to be very complex in terms of reaction kinetics and present challenges specifically in translating to scale-up. Given this, we believe the time has come for innovative breakthroughs to establish synthetic photochemistry as a core capability within both academia and industry across the full range of scales from milligrams through to kilogram and full commercial production scale. The rise of photocatalysis has been driven by both the evolution to LEDs (Light-Emitting Diodes) that reduce the effective cost of photons for photochemical applications as well as the emergence of various photochemical reactor technologies (several of which are commercially available) in the past several years.

With continuing growing environmental awareness and the potential impacts of emissions on climates and human health, the chemical industry strives to transition to develop more sustainable and efficient processes with reduced waste generation and minimal environmental impact with over-arching goals to drive towards carbon neutrality and/or becoming "net zero" in the coming years. Given the tangible benefits presented by photochemistry, increased adoption of such a reaction paradigm can play a pivotal role in this transition enabling the development of processes, which are aligned with the 12 Principles of Green Chemistry, and specifically focus on minimizing PMI, use of recommended solvents with consideration of health, environmental, safety and regulatory aspects, as well we the adoption of sustainable and affordable catalysts. With this latter point in mind, polypyridyl complexes of both Ru (II) and Ir(III) have become established as photoredox catalysts due to their ability to strongly absorb visible light facilitating their selective excitation over organic substrates for most reaction of interest. Their excited states are typically formed with 100% efficiency with lifetimes ranging from 300 ns – 6 ms, which is sufficient to allow them to engage in bimolecular reactions with the backbone ligand enabling tuning of the catalyst for the specific transformation under investigation. The complexes are generally stable with respect to either photochemical or thermal decomposition and are highly versatile owing to their reversible redox behavior though despite their proven ability to catalyze many distinct transformations, the high intrinsic cost and precious nature of the metals utilized presents a significant barrier to the adoption of the technology within industry.

The development of photocatalyzed flow processes using earth-abundant metal complexes and/or organic photoredox catalysts offering "metal-free" alternatives to transition metal catalysis are to be favored within the submitted proposals while innovations focusing on solid-supported catalysts for ease

of incorporation into flow systems enabling recycling/re-use of the systems, which while extensively utilized in the solar field, only limited examples of such heterogenization exist for photoredox-based systems. Innovations also in equipment to facilitate such processes will also be considered specifically on those which are easy to implement in a cost-effective manner in both academic/industrial labs and offer easy translation across a broad range of scales (mgs to kgs). Proposals describing new approaches to facilitate the screening for the discovery of novel and optimization of photoredox processes will also be considered, while proposals that focus on developing novel bond-forming transformations are encouraged most notably if they rely on feedstock renewable chemicals as starting materials.

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 photoredox-mediated reactivity, the focus should be on utilizing readily available feedstock chemicals as starting substrates.
- Innovative Equipment-Based Approaches to Implementing Photoredox Chemistry in Flow: Consideration here will be paid to the ease of implementation of new equipment not only across a range of scales but also in its feasible incorporation into different research settings (academic/industrial), Given this, the relative footprint and cost of the device are important considerations for many laboratories. Herein, proposals dealing with novel device-based approaches, integration with established equipment including PAT will also be considered.
- Scale-up: Establishing clear line-of-sight for any developed photoredox approaches across a range of scales to inform crucial "batch versus flow" decisions for future manufacturing campaigns.
- Life-Cycle Considerations: Advances concerning recycling and/or maximizing disposal of process waste as non-hazardous are also within the scope of this grant.
- 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 Photoredox Chemistry in Flow include:

- N. A. Romero and D. A. Nicewicz. "Organic Photoredox Catalysis". *Chem. Rev*., 2016, 116, 10075-10116.
- A. Y. Chan, I. B. Perry, N. B. Bissonnette, B. F. Buksh, G. A. Edwards, L. I. Frye, O. L Garry, M. N. Lavagnino, B. X. Li, Y. Liang, E. Mao, A. Millet, J. V. Oakley, N. L. Reed, H. A. Sakai, C. P. Seath, and D. W. C. MacMillan. "Metallophotoredox: The Merger of Photoredox and Transition Metal Catalysis". *Chem. Rev*., **2022**, *122*, 1485-1542.
- K. Donnelly and M. Baumann. "Scalability of Photochemical Reactions in Continuous Flow Mode". *J. Flow Chem*., **2021**, *11*, 223-241.
- R. Lindroth, K. L. Materna, L. Hammarström, and C-J. Wallentin. "Sustainable Ir-Photoredox Catalysis by Means of Heterogenization". *ACS Org. Inorg. Au*, **2022**, *2*, 427-432.
- M. González-Esguevilla, D. F. Fernández, J. A. Rincón, M. Barberis, O. de Frutos, C. Mateos, S. García-Cerrada, J. Agejas, and D. W. C. MacMillan. "Rapid Optimization of

Photoredox Reactions for Continuous-Flow Systems Using Microscale Batch Technology". *ACS Cent. Sci*., **2021**, *7*, 1126-1134.
- C. Yang, R. Li, K. A. I. Zhang, W. Lin, K. Landfester and X. Wang. "Heterogeneous Photoredox Flow Chemistry for the Scalable Synthesis of Fine Chemicals". *Nature Commun*., **2020**, *11*, 1239.

Project Goal

Promote innovation at the interface of chemistry and engineering toward overcoming barriers for the application/scale-up of photochemistry 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. 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