JOURNAL OF CHEMICAL EDUCATION

pubs.acs.org/jchemeduc Article

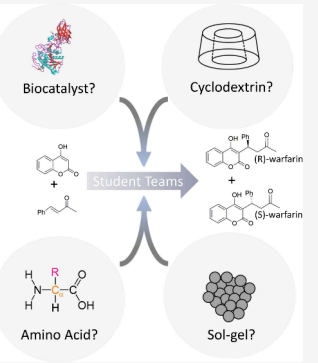
Evolution of a Biocatalysis CURE for Organic Chemistry Students

Anna I. Wurz, Clark I. Andersen, Joi P. Walker,* and Robert M. Hughes*

Cite This: *J. Chem. Educ.* 2024, 101, 3163−3170 Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information

ABSTRACT: Course-based undergraduate research experiences (CUREs) are increasingly recognized as valuable tools for engaging students in authentic research, for removing barriers to participation in research, and for the retention of students in STEM disciplines. Recently, we developed a CURE sequence for organic chemistry students in which they conducted self-directed investigations into bio- and organocatalytic approaches to the asymmetric synthesis of warfarin, a commonly prescribed anticoagulant with the potential for serious side effects. In this CURE, students worked on a chemistry problem with implications for modern medical practice while learning fundamental techniques in organic synthesis, chromatography, and spectroscopy. While engaging students in creative research activity, this CURE also emphasized working in scientific teams, an approach that prepares students for current practices in academic and industrial research settings. Publications on the design and implementation of CUREs have increased considerably in the past decade, but the benefits to faculty research are not well-documented. This article describes the evolution of this CURE from a screening-based approach to the identification of biocatalysts for the synthesis of warfarin to a more targeted approach using small biologically inspired catalysts. The most recent iteration of the biocatalysis CURE generated results that are included in an original research pre-print publication with student coauthors (Wurz, A. I.; et al. *ChemRxiv* **2024**, 10.26434/chemrxiv-2024-krf7h).



KEYWORDS: *Upper-Division Undergraduate, Organic Chemistry, Chirality, Enantiomers, Collaborative/Cooperative Learning, Undergraduate Research*

INTRODUCTION

Recent innovations in science education have reconceptualized traditional undergraduate research experiences (UREs).[1,2] These traditional approaches, in which students perform novel research, either in a faculty research group or through internship-style experiences, are effective at developing scientific skills and retaining students in scientific majors and careers.[3−6] However, accessing UREs can present challenges for students due to limited spaces or students not understanding the benefits of undergraduate research.[7−11] Different approaches have been proposed to broaden student access to research, including embedding science research directly into the undergraduate curriculum.[6,8−10,12,13] This approach, known as Course-based Undergraduate Research Experiences (CUREs), allows students to participate in authentic science research within their standard coursework.[12,14−16] CURE researchers have identified principles that define a CURE, which include discovery of new knowledge, broad relevance, and collaborative projects, emphasizing the iterative nature of science and laboratory skills.[9,17]

CUREs have the potential to shift the institutional culture and expectations for both instruction and research, realizing the research-scholar model of academic faculty. The research-scholar model in modern academic institutions is characterized by a steadfast belief in the mutually beneficial relationship between research activities and the ability to teach the subject to students.[18,19] In this model, research informs the content that is taught, exposing students to cutting-edge information.[20] Quantitative studies, however, have repeatedly demonstrated zero, or even negative, correlation between the various teaching and research measures employed at the individual academic level.[20,21] This suggests a fundamental disconnect in traditional teaching-research modalities, with an emphasis on one or the other but not both research and teaching synergistically. Given that these two aspects of academia not only inform each other, but exist in synergy, resolving this disconnect provides a very real benefit to science education. The data suggests that CUREs offer a mechanism by which faculty can merge these often-disparate aspects of academics and scholarship.[21] However, a recent review focused on CUREs in chemistry evaluated sixty-eight publications between 2016 and 2022. The majority of these articles (55, 81%) described the development of a specific CURE, while only 36% reported dissemination of student research beyond the class or institution.[2]

Realizing the 2-fold goal of CUREs, engaging undergraduates in research and obtaining reliable data, can be

Received: February 1, 2024
Revised: July 9, 2024
Accepted: July 19, 2024
Published: July 30, 2024

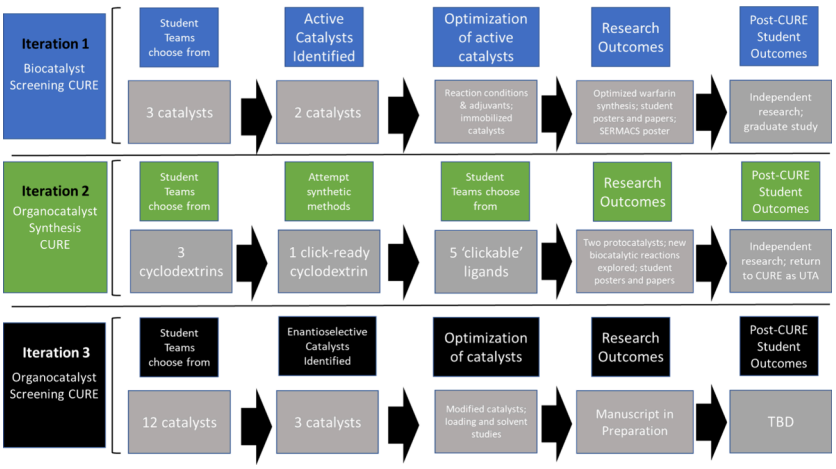


Figure 1. CURE trajectories and outcomes. Top: An initial one-semester CURE focused on screening and optimization of biocatalyst-based approaches to the synthesis of warfarin. Middle: A second two-semester CURE sequence built on the first but focused on the synthesis of cyclodextrin-derived organocatalysts. Bottom: A third two-semester CURE returned to the screening strategy of the first but focused on small molecule organocatalysts.

challenging for faculty. Wolfe and Steed recently outlined the obstacles to publishable data from CUREs, noting the lack of reproducibility of data generated by novice students and the need for follow up work by the faculty or graduate students.[22] Survey data found that faculty reported that supplemental work was necessary to obtain publishable results.[22] The faculty survey also revealed that obtaining publishable results typically requires multiple iterations of the CURE. Based on these results and experiences, Wolfe and Steed identified several "best" practices for maximizing positive outcomes for both students and faculty regarding CURE design.[22] They described how three iterations of a CURE progressed from allowing students to have complete intellectual freedom to a more limited approach with an explicit goal of generating publishable results.[22]

The biocatalysis-focused Organic Chemistry CURE sequence described in this manuscript was recently added to the existing selection of organic CUREs. In this CURE, students work in teams to characterize biologically derived catalysts for carbon−carbon bond forming reactions, with a specific emphasis on the asymmetric synthesis of pharmaceutical compounds. This CURE sequence introduces students to biocatalysis and organocatalysis chemistry concepts that might not be covered in a traditional two-semester organic chemistry lecture course, provides hands-on experience with carbon−carbon bond forming reactions such as aldol and Michael additions, and enables students to synthesize biologically active molecules with direct links to modern medical practice. Three successive iterations of this CURE have been completed (Figure 1). Here we describe the evolution of this CURE

from a screening-based approach to the identification of biocatalysts for the synthesis of warfarin to a more targeted approach using small biologically inspired catalysts. Along the way, students used self-guided explorations of the chemical literature to guide their investigations, leading to alternative approaches to solving problems in biocatalysis. The recent iterations of the biocatalysis CURE are generating publishable results which is consistent with the process described by Wolfe and Steed.[22,23]

METHODOLOGY

A Warfarin-Focused CURE Sequence

Warfarin (Coumadin) is a drug currently used as an anticoagulant and commercially manufactured as a racemic mixture of its enantiomers, (R)- and (S)-Warfarin.[24] Warfarin enantiomers are metabolized through different pathways in the body; (S)-Warfarin is 3−5 times more potent than (R)-Warfarin, but (R)-Warfarin may be more effective for some patients with genetic variations in CYP29.[25] Stereoselective synthesis of warfarin is one pathway to providing enantiomerically pure warfarin to those patients who could benefit from a nonracemic administration of the drug. An enantioselective approach to warfarin synthesis could be achieved through biocatalysis, which is a promising alternative to conventional techniques with the possibility of high selectivity and low environmental impacts.[26] While organocatalysts such as DPEN (R,R or S,S Diphenylethylenediamine) have been identified for enantioselective synthesis of Warfarin,[27,28] the synthetic potential of biocatalysts for this reaction, including protein- and nucleic acid-derived catalysts for synthesis of Warfarin and similar pharmaceutical compounds remain underexplored. For example, Porcine Pancreatic Lipase (PPL) has been used for (R)-Warfarin synthesis[29] but the biocatalytic potential of other lipases and commonly used biocatalytic entities for warfarin synthesis, including promiscuous proteins such as α-amylase, are unknown or less well characterized.

These biocatalytic entities were investigated through a CURE format in which students select and screen biocatalysts for their ability to catalyze warfarin synthesis from simple substrates at small scale, with subsequent optimization of reactions for solvent composition, catalyst loading, and reaction temperature. In addition, students were invited to investigate the effects of catalyst immobilization and the inclusion of adjuvants for their effects on reaction yield, enantiomeric excess, and catalyst reusability. The experimental protocols the students used are included in the Supporting Information (SI).

Participants

This study was performed at a large, primary residential four-year, doctoral degree granting institution designated R2 by the

https://doi.org/10.1021/acs.jchemed.4c00118
J. Chem. Educ. 2024, 101, 3163−3170

Carnegie classification of institutions of higher education across all three iterations.[30] Participants were chosen from a pool of students who indicated interest in the CURE using a web-based form. For the first iteration of the CURE, Organic Chemistry I students were invited to join the Biocatalysis CURE for the following semester, with the CURE taking the place of the standard Organic Chemistry II laboratory course. For the second and third iterations of the CURE, General Chemistry II students preparing to enter Fall Organic Chemistry I were invited to join the Fall CURE. These students had the option to continue the CURE for the Organic Chemistry II laboratory course as well. While chemistry and biology majors comprised most of the students selected for the CURE, students from other disciplines (Neuroscience, Nutrition, Physical Therapy, Biomedical Engineering) were additionally selected to participate. Previous publications established that the CURE students were not significantly different from the selection pool based on sex, GPA, and ethnicity.[31,32] This study was approved for exempt Human Subject Research UMCIRB 20−000808.

CURE Facilities

The organic chemistry CURE classes were housed in a dedicated laboratory specific for CURE instruction. The facility had six workstations that accommodated up to four students for each team. Shared stations include a fume hood, a center bench, and bench space on the peripheral walls housing instrumentation such as two rotary evaporators, a lyophilizer, and an HPLC. Other required instrumentation was available in the PI's laboratory, including a centrifuge and a UV−vis spectrometer, or in dedicated rooms for NMR and mass spectrometry.

Team Science

An important feature of the CURE was to provide training in developing a productive team. At the outset of the CURE project, students were instructed on Team Science principles, which would inform how their teams could function successfully.[33,34] The student teams were tasked with creating key elements needed for team function - communication plans, research plans, and conflict resolution strategies.[35] Students received instruction in Team Science concepts within the framework of Team Knowledge, Team Skills, and Team Attitudes adapted from Enhancing the Effectiveness of Team Science.[34] These competencies are listed in Table 1 and students were encouraged to use these elements to facilitate experimental design and data collection and analysis.

Using the Team Science principles allowed the CURE to progress as a research group, with students preparing to work with their teams long-term. They were encouraged to exchange phone numbers and email with their teammates. This was done to build trust and cohesion with each other and to emphasize collective efficacy in the project thereby creating a safe place to discuss ideas and to use failure as a method of improvement and learning.

Table 1. Team Science Competencies

Knowledge	Skills	Attitudes
Task Understanding	Communication	Team Orientation
Shared Mental Models	Assertiveness	Team Trust
Role Knowledge	Conflict Resolution	Team Cohesion
Teammate Characteristics	Providing Teammate Guidance	Value of Conflict
Team Objectives and Resources	Problem Analysis	Collective Efficacy
Understanding Group Dynamics	Project Particular Analysis	Interdisciplinary Appreciation

The goal with Iterations 2 and 3 were for the teams to remain consistent throughout two-semesters, however, some attrition was inevitable. This presented a challenge to the remaining team members to bring new students into the team and up to speed on the progress of the research, but with the implementation of Team Science principles in the CURE (Table 1), students new to the research were easily incorporated into the team. At the conclusion of each iteration, and at the end of each semester in Iterations 2 and 3, some students participated in a focus group where they were encouraged to share what they've learned or skills they've developed regarding research and Team Science.

CURE Design and Implementation

Each organic CURE lab is a substitute for the conventional organic laboratory course and must be taken as a corequisite to the corresponding lecture course. The lab met twice a week, Monday and Tuesday, for 1.5 h each day (total 3 h per week; 1 credit hour). For each semester, teams of 2−3 students were given semester-long projects involving the synthesis, purification, and characterization of pharmaceutical compounds such as warfarin. Students' performances throughout the semester were graded based on the assignments listed in Table 2; all assignments, except for the individual writing prompt, were completed and submitted as a team. Designated time to work on assignments was provided during class; however, teams were encouraged to collaborate outside of class as needed using the team's agreed-upon communication plan. To facilitate regular communication between team members, each team drafted a communication plan discussing preferred modes and frequency of communication, conflict resolution strategies, and course or project specific situations.

Table 2. CURE Graded Assignments

Assignment	Percentage
Research Paper:	
Introduction	10%
Experimental	10%
Results and Discussion	10%
Team Science Elements:	
Communication Plan	5%
Research Plan	5%
Individual Writing Prompt	10%
Literature Meeting (2)	10%
Notebook Check (3)	30%
Poster and Presentation	10%

The students were introduced to research plans within the first week of class. Using an online discussion board associated with the course Web site, teams initially detailed a short description of the research project, along with the intended final product. Then, they reflected on their progress regularly during the semester, adjusted what tasks needed to be done considering where they were in the research process, and identified how those steps were expected to help them accomplish their project goals. Where possible, teams designated specific individuals to take on specific responsibilities for the project. Students were given time in class to complete their plans, but if more time was needed, teams

https://doi.org/10.1021/acs.jchemed.4c00118
J. Chem. Educ. 2024, 101, 3163−3170

communicated outside of class hours to discuss their results and formulate a plan. This document helped each team progress more efficiently through the research process and better take advantage of working in a team. Other assignments throughout the semester were group literature meetings, a discussion of two instructor-approved peer-reviewed papers relevant to the research topic, in addition to three notebook checks to ensure proper documentation of experiments and compliance with record keeping standards. During the second half of the semester, teams submitted sections of their final research paper: Introduction, Experimental, and Results and Discussion. Each student within the team participated as a lead author or a coauthor for at least one of the sections. The last day of class each team gave a final presentation using a conference-style poster of their research and future directions with questions and discussion after each poster.

Individual writing prompts were due a week after the poster presentations. The purpose of the prompt was to promote further investigations into the research topic by reading research articles and formulating a new project to fill a gap in scientific knowledge. Students were instructed to create a proposal for the design and synthesis of a biocatalyst or organocatalyst that could be used in the asymmetric synthesis of a pharmaceutical compound (other than warfarin) that is currently provided/administered in its racemic form. The proposal needed to include synthetic methods for making the catalyst, selection of a target pharmaceutical compound, methods for evaluating catalytic activity, an assessment of the environmental impacts of the proposed synthesis, in addition to a description of a team-based approach that will achieve these research goals. A summary of the timeline of assignments is detailed in Figure 2, and the instructions provided to the students to complete the writing prompt is found in the SI.

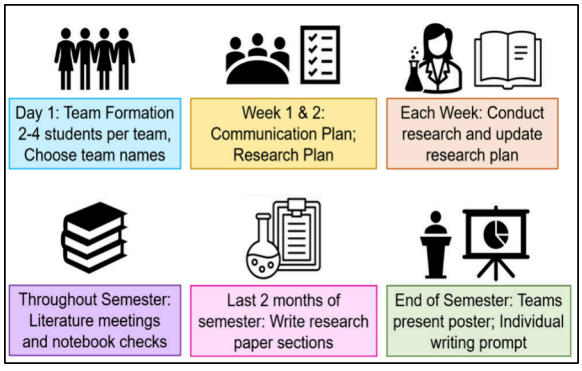


Figure 2. General timeline of CURE lab assignments and goals.

Students were trained in research skills such as thin-layer chromatography, HPLC, mass spectrometry, and NMR. Some skills (TLC setup and visualization methods, such as UV/vis and anisaldehyde staining; Chiral HPLC) were taught by instructor/TA demonstration in class; others were conducted by departmental staff (for instance, students attended an NMR training session with the instrument specialist and a training session with the manager of the Mass Spectrometer facility). These sessions took place during regularly scheduled class times.

Iteration 1: Biocatalyst Screening CURE. In the first iteration of the CURE, 17 students were divided into 6 teams of 3−4 students, and two teams worked with one of two potential protein biocatalysts (PPL or and α-Amylase) or an L-proline organocatalyst to synthesize warfarin from 4-hydroxycoumarin and benzylideneacetone (Figures 3 and S1). This project was based on previously published work from our laboratory conducted by graduate and undergraduate students, which explored biocatalytic approaches to synthesize the Wieland−Miescher ketone.[26] During the first course meeting, students are introduced to the concepts of biocatalysis and catalytic promiscuity, and introduced to their relevance to the principles of green chemistry. They were also provided a course pack that includes several literature examples of biocatalysts in organic chemistry. After initial investigation of their chosen catalysts under a standard set of reaction conditions, student teams were then encouraged to expand their investigations to explore other solvent systems, catalyst loading, reaction temperatures, reaction adjuvants, and immobilization methods. The weekly timeline for the research conducted is provided in Table S1.

Iteration 2: Organocatalyst Synthesis CURE. In its second iteration, the biocatalysis CURE was expanded to a 2-semester format, Organic Chemistry I and II laboratory course, in which an initial cohort of 19 students was divided into 6 teams of 3−4 students. The focus was also shifted from screening and optimization of protein biocatalysts to the synthesis and characterization of potential organocatalytic molecules. In this CURE, teams were tasked with the synthesis of cyclodextrin derivatives and investigate their organocatalytic potential (Figure 4). The student teams chose between three different cyclodextrins (α, β, and γ) and five different CuAAC (a Cu(I) catalyzed azide−alkyne cycloaddition)[36] ready amine-bearing alkyne ligands (Figure S2). Amine-bearing ligands were selected in order to investigate their ability to promote imine-formation in the warfarin reaction. The CuAAC reaction was introduced to students as a "click reaction", and the general utility and orthogonal properties of click reactions was emphasized throughout the course.

In the first semester of this two-semester sequence, students worked on the functionalization of cyclodextrins with azide components to enable click-type CuAAC reactions between azido cyclodextrins and alkyne ligands (Figure 4). In the second semester of the two-semester sequence, students investigated the organocatalytic potential of their reaction

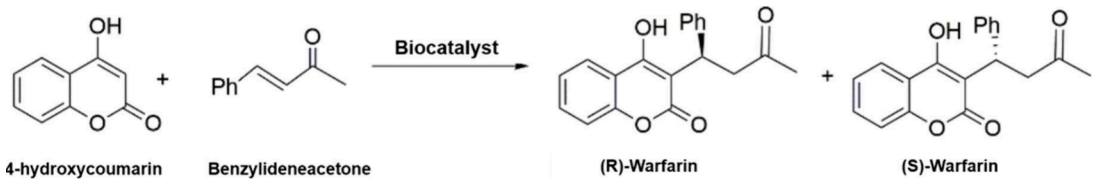


Figure 3. CURE-lab warfarin synthesis. Warfarin synthesis is used for all three biocatalysis/organocatalysis CUREs as a model reaction. This reaction is readily performed under small scale, room temperature conditions and amenable to a variety of solvent conditions.

https://doi.org/10.1021/acs.jchemed.4c00118
J. Chem. Educ. 2024, 101, 3163−3170

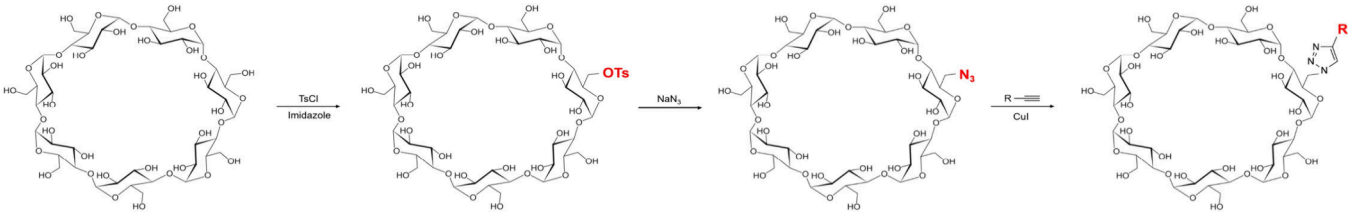


Figure 4. CURE-lab cyclodextrin derivatization strategy. The proposed route to potential organocatalyst-cyclodextrin hybrid molecules. Cyclodextrins can be monotosylated using various reaction conditions. In this CURE, students used tosylation of β-cyclodextrin with tosylimidazole to synthesize monotosyl β-cyclodextrin, followed by displacement of the tosyl moiety with azide and subsequent coupling to alkyne-bearing molecules using a click-type CuAAC reaction.

products in several different carbon−carbon bond forming reactions. At the start of the second semester, the number of teams decreased to 5 after a loss of 7 students for various reasons: some students were not required to take a second semester of organic chemistry for their majors (e.g., public health or engineering) and thus opted out of the second semester CURE laboratory; in at least one case, students were unable to advance in the CURE due to lack of academic success in first semester organic chemistry. The weekly timeline for the research conducted is provided in Table S2.

Iteration 3: Organocatalytic Screening CURE. The third iteration of the CURE continued with the two-semester format, this time with a focus on screening small molecules with organocatalytic potential. For the first semester, 18 students were divided into six teams of 3 students. In this project, students quantified reaction yields and the enantioselectivities of their catalysts in a warfarin synthesis. The weekly timeline for the research conducted is provided in Table S3.

RESULTS AND DISCUSSION

Iteration 1: Biocatalyst Screening CURE

After initial experiments to establish the baseline biocatalytic potential of PPL, α-amylase, and L-Proline in a standard warfarin synthesis, student teams organized a strategy to optimize these reactions. These optimizations included catalyst loading, solvent composition, and the addition of adjuvants selected based upon prior reports of their success in promoting catalysis and/or enantioselectivity in other biocatalytic reactions.[26,37,38] In particular, imidazole was selected as an adjuvant that promotes catalysis based on our prior work using PPL with imidazole to increase the yield of C−C bond forming reactions.[26] The teams analyzed their warfarin reactions for yield and enantioselectivity. Results from these experiments are described further in the SI (Iteration 1 results, Table S4 and Figure S2). Overall, Iteration 1 successfully established experimental protocols and analytical methodologies for small scale warfarin synthesis, identified promising biocatalysts and adjuvants, and explored several optimization strategies that could be carried forward to future CURE iterations.

Iteration 2: Organocatalyst Synthesis CURE

In addition to imidazole, multiple adjuvants for the biocatalytic reactions were investigated in the first CURE iteration (Table S4 and Figure S3) These results indicated that α-cyclodextrin might be a promising adjuvant (when combined with an L-proline organocatalyst) for promoting enantioselectivity in warfarin synthesis. As a result, iteration 2 of the CURE focused on the synthesis of cyclodextrin derivatives with organocatalytic potential. During the first semester, the main goal for the teams was to synthesize a cyclodextrin conjugate; during the second semester, the goal was to complete the synthesis and characterization and test the cyclodextrin conjugate activity toward catalysis of warfarin synthesis. Teams were assigned either α-, β-, or γ-cyclodextrin (two teams per cyclodextrin), with the end goal of creating an amine-functionalized cyclodextrin (Figure 4). Amine-bearing ligands were chosen with the idea that some of them might promote minimum ion formation with the benzylidene acetone substrate (as proposed for DPEN-catalyzed warfarin synthesis). Sequestration of substrates within the cyclodextrin bowl was proposed as a secondary mechanism for promoting catalysis. The teams each worked on their own synthesis of a "clickable" cyclodextrin, but the teams with the same type of cyclodextrin were encouraged to collaborate and compare results (Table S2).[39,40] We note that while all teams made considerable progress over the course of the semester, some ran out of time to complete their projects. For example, some teams struggled to purify and characterize their click reaction products. In hindsight, we realize that student teams may benefit from dedicating more effort to small-scale optimization studies before proceeding with larger scale coupling reactions and will make this adjustment in future CUREs. Overall, this two semester CURE cohort successfully identified a practical route to β-cyclodextrin functionalization that could be achieved within the time constraints of course-based academic research, created at least two proto-catalysts with promising initial results, and established new research directions that can be addressed in future CUREs. The results from this iteration are included in the SI.

Iteration 3: Organocatalyst Screening CURE

For the organocatalyst screening CURE, student teams selected amino acid and other amine-bearing small molecules from a 12-compound library and investigated their ability to catalyze the synthesis of warfarin, characterizing reaction yield and enantioselectivity. Promising results from this CURE led to publishable data. As a result, students in the second semester of this CURE, in addition to conducting additional synthesis of cyclodextrin conjugates (following optimized procedures developed in the second iteration of the CURE), assisted with the writing of a research manuscript that has be submitted for peer review and published online Project details are not provided in this manuscript due to pending publication.[23]

Limitations

The Organic Chemistry CURE was designed to last two semesters, and a limitation to this study is that, while the second iteration was indeed two semesters, the first iteration only included students for one semester. Research has suggested the greatest benefit to students in undergraduate

https://doi.org/10.1021/acs.jchemed.4c00118
J. Chem. Educ. 2024, 101, 3163−3170

research occurs with at least three semesters of experience[41] and there has been some work to maximize student research time by introducing multidisciplinary CURE projects which allow students to continue research within their undergraduate study.[42] While our Biocatalysis CURE project covers at most two semesters for participating students, this project has demonstrated that students gain important organic chemistry skills and team science competencies, even in a one semester format.

Iterations 2 and 3 took place over two successive semesters, and an effort was made to keep the teams intact. However, as noted in the Methodology section, several students did not to continue the second semester. This proved challenging for those students' teammates, as they had bonded with their teams from the prior semester and felt that their plans and the methods they had practiced would be impacted by having a teammate replaced with a new, inexperienced student. An aspect of the Team Science training imparted on the CURE students was developing a positive attitude toward working in teams, including appreciating team cohesion. Having their team disrupted tested the teams' communication, record keeping, and planning prowess. In interviews with students following Iterations 2 and 3, students who lost team members or who joined the CURE midway through the experience emphasized the transition was facilitated by utilizing the research and communication plans. In the end of semester focus group, a student that joined the project for the second semester remarked:

> *Yeah, as soon as I came in on the first day, [my team] ran through the entire notebook with me. They gave me like, a super quick rundown of what everything they had done the past semester, and then I just kind of jumped in. There might have been some points where I didn't necessarily know what I was doing, but they've been very good to like, clue me in on like, "Oh well, we're doing this because we did this last semester."*

While attrition can be expected in college courses there is little impact on peers and no impact on the outcome of the course. In contrast, losing a member of a research team could impact the research and as described in the limitations can be of concern to the CURE students. These cases are certain to occur in courses that emphasize team-based science, and we encourage faculty to emphasize the importance of team skills, such as communication and research planning to minimize disruption to the research project.

IMPLICATIONS

Three iterations of a biocatalysis/organocatalysis-focused CURE have been conducted, with the enantioselective synthesis of warfarin as a primary goal. All three CUREs were interconnected, with promising approaches carried forward from one iteration to the next. For example, promising adjuvants (cyclodextrins) identified in Iteration 1 were the basis for Iteration 2, while organocatalysts employed in both Iteration 1 and 2 prompted additional investigation of amine-bearing small molecules in Iteration 3. Notably, the approaches undertaken in Iteration 3 generated results that are included in peer-reviewed original research with student coauthors. In our estimation, multiple iterations of this CURE were critical for reaching the point where publishable results have been achieved.[23]

CUREs have the potential to merge the often-disparate aspects of academics and scholarship by bridging the teaching-research nexus.[21] Realizing the goal of publishable research may require iterative CUREs with research conducted by different student cohorts. We have described a three-year (four semester) CURE sequence that has achieved publishable data by using findings from each iteration to inform the research of the next. The iterative nature of research should distinguish CUREs from other types of laboratory experiences, however the point by Wolfe and Steed was that each iteration needs to be deliberate in focusing the research on the goal of publishable findings.[22] Wolfe and Steed identified "best practices" and the goal of this manuscript was to illustrate the efficacy of this process.[22]

In addition, each iteration of the biocatalysis-focused CURE resulted in direct outcomes for student participants. Several students elected to continue as independent researchers in either the PI's laboratory or in other laboratories at the university; some of these students have also returned to the CURE as "near-peer" mentors. For a subset of students continuing in research, this CURE has helped them identify future directions for independent research. Research products from this course have also been the basis for presentations at scientific meetings in which students have been acknowledged as key contributors.[43]

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available at https://pubs.acs.org/doi/10.1021/acs.jchemed.4c00118.

> Experimental protocols performed by the students in the biotcatalysis CURE sections; student instructions for completing the team science writing prompt; large figures detailing reaction schematics, chromatograms, mass spectra, molecular structures, and other information; experimental results and yields from Iterations 1 and 2; CURE timelines and descriptions of research (PDF)

AUTHOR INFORMATION

Corresponding Authors

Robert M. Hughes − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858-4353, United States;* orcid.org/0000-0002-4465-4212; Email: hughesr16@ecu.edu

Joi P. Walker − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858-4353, United States;* orcid.org/0000-0001-7783-4706; Email: walkerjoi15@ecu.edu

Authors

Anna I. Wurz − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858-4353, United States*

Clark I. Andersen − *Department of Chemistry, East Carolina University, Greenville, North Carolina 27858-4353, United States*

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.jchemed.4c00118

Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/acs.jchemed.4c00118
J. Chem. Educ. 2024, 101, 3163−3170

■ ACKNOWLEDGMENTS

This project was funded by the National Science Foundation (DUE 2013358).

■ REFERENCES

(1) Committee for Convocation on Integrating Discovery-Based Research into the Undergraduate Curriculum; Division on Earth and Life Studies; Division of Behavioral and Social Sciences and Education; National Academies of Sciences, Engineering, and Medicine. *Integrating Discovery-Based Research into the Undergraduate Curriculum: Report of a Convocation*; National Academies Press: Washington, DC, 2015.

(2) Watts, F. M.; Rodriguez, J.-M. G. A Review of Course-Based Undergraduate Research Experiences in Chemistry. *J. Chem. Educ.* **2023**, *100* (9), 3261−3275.

(3) Bixby, T. J.; Miliauskas, M. M. Assessment of the Short-Term Outcomes of a Semester-Long CURE in General Chemistry Lab. *J. Chem. Educ.* **2022**, *99* (12), 3849−3857.

(4) Blumling, D. E.; Hughey, C. A.; Boardman, B. M.; Judd, O. H.; Berndsen, C. E.; Boeckmann, D. M.; Paunovic, D. M.; Poe, T. M. Looking to Move Away from Expository General Chemistry Laboratories? We May Have a Cure for What "Ales" You. *J. Chem. Educ.* **2022**, *99* (12), 3858−3870.

(5) Kardash, C. M. Evaluation of Undergraduate Research Experience: Perceptions of Undergraduate Interns and Their Faculty Mentors. *J. Educ. Psychol.* **2000**, *92* (1), 191−201.

(6) Nagda, B. A.; Gregerman, S. R.; Jonides, J.; von Hippel, W.; Lerner, J. S. Undergraduate Student-Faculty Research Partnerships Affect Studen Retention. *Rev. Higher Educ.* **1998**, *22* (1), 55−72.

(7) Desai, K. V.; Gatson, S. N.; Stiles, T. W.; Stewart, R. H.; Laine, G. A.; Quick, C. M. Integrating Research and Education at Research-Extensive Universities with Research-Intensive Communities. *Adv. Physiol. Educ.* **2008**, *32* (2), 136−141.

(8) Lopatto, D.; Alvarez, C.; Barnard, D.; Chandrasekaran, C.; Chung, H.-M.; Du, C.; Eckdahl, T.; Goodman, A. L.; Hauser, C.; Jones, C. J.; Kopp, O. R.; Kuleck, G. A.; McNeil, G.; Morris, R.; Myka, J. L.; Nagengast, A.; Overvoorde, P. J.; Poet, J. L.; Reed, K.; Regisford, G.; Revie, D.; Rosenwald, A.; Saville, K.; Shaw, M.; Skuse, G. R.; Smith, C.; Smith, M.; Spratt, M.; Stamm, J.; Thompson, J. S.; Wilson, B. A.; Witkowski, C.; Youngblom, J.; Leung, W.; Shaffer, C. D.; Buhler, J.; Mardis, E.; Elgin, S. C. R. Genomics Education Partnership. *Science* **2008**, *322* (5902), 684−685.

(9) Bangera, G.; Brownell, S. E. Course-Based Undergraduate Research Experiences Can Make Scientific Research More Inclusive. *CBE—Life Sci. Educ.* **2014**, *13* (4), 602−606.

(10) Barlow, A. E. L.; Villarejo, M. Making a Difference for Minorities: Evaluation of an Educational Enrichment Program. *J. Res. Sci. Teach.* **2004**, *41* (9), 861−881.

(11) Hurtado, S.; Eagan, M. K.; Cabrera, N. L.; Lin, M. H.; Park, J.; Lopez, M. Training Future Scientists: Predicting First-Year Minority Student Participation in Health Science Research. *Res. Higher Educ.* **2008**, *49* (2), 126−152.

(12) Goodwin, E. C.; Anokhin, V.; Gray, M. J.; Zajic, D. E.; Podrabsky, J. E.; Shortlidge, E. E. Is This Science? Students' Experiences of Failure Make a Research-Based Course Feel Authentic. *CBE—Life Sci. Educ.* **2021**, *20* (1), ar10.

(13) Denofrio, L. A.; Russell, B.; Lopatto, D.; Lu, Y. Linking Student Interests to Science Curricula. *Science* **2007**, *318* (5858), 1872−1873.

(14) Allen, W. E.; Hosbein, K. N.; Kennedy, A. M.; Whiting, B.; Walker, J. P. Embedding Research Directly into the Chemistry Curriculum with an Organic to Analytical Sequence. *J. Chem. Educ.* **2021**, *98*, 2188.

(15) Corwin, L. A.; Graham, M. J.; Dolan, E. L. Modeling Course-Based Undergraduate Research Experiences: An Agenda for Future Research and Evaluation. *Cell Biol. Educ.* **2015**, *14* (1), es1−es1.

(16) Satusky, M. J.; Wilkins, H.; Hutson, B.; Nasiri, M.; King, D. E.; Erie, D. A.; Freeman, T. C. CUREing Biochemistry Lab Monotony. *J. Chem. Educ.* **2022**, *99* (12), 3888−3898.

(17) Auchincloss, L. C.; Laursen, S. L.; Branchaw, J. L.; Eagan, K.; Graham, M.; Hanauer, D. I.; Lawrie, G.; McLinn, C. M.; Pelaez, N.; Rowland, S.; Towns, M.; Trautmann, N. M.; Varma-Nelson, P.; Weston, T. J.; Dolan, E. L. Assessment of Course-Based Undergraduate Research Experiences: A Meeting Report. *CBE—Life Sci. Educ.* **2014**, *13* (1), 29−40.

(18) Boyer, E. L. *Scholarship Reconsidered: Priorities of the Professoriate*; ERIC, 1990.

(19) Stappenbelt, B. The Effectiveness of the Teaching−Research Nexus in Facilitating Student Learning. *Eng. Educ.* **2013**, *8* (1), 111−121.

(20) Jenkins, A. *A Guide to the Research Evidence on Teaching-Research Relations*; The Higher Education Academy: Heslington, U.K., 2004.

(21) Gentile, A.; Oswald, A. M. The Oswald-Gentile Model of Instruction: A Holistic Approach. *IJTE* **2021**, *4* (2), 229−246.

(22) Wolfe, A. L.; Steed, P. R. Generating Publishable Data from Course-Based Undergraduate Research Experiences in Chemistry. *J. Chem. Educ.* **2023**, *100* (9), 3419−3424.

(23) Wurz, A. I.; Benson, N. R.; Carr, S. N.; Chamakura, K.; Chirinos, L.; Coll, S. P.; Franco-Gonzalez, A.; Ivory, K. F.; Jankowski, H. L.; Lamb, T. J.; LeBauer, S.; McPherson, G. L.; Nguyen, T.; Nolasco Guevara, J.; Parsad, L. N.; Pham, P.; Piner, E. G.; Richardson, K.; Bendjellal, A.; McRae, C.; Hughes, R. M. Beyond L-Proline: Investigation of the Properties of Other Natural Amino Acids in an Organocatalytic Warfarin Synthesis. *ChemRxiv* **2024**, DOI: 10.26434/chemrxiv-2024-krf7h.

(24) Patel, S.; Singh, R.; Preuss, C. V.; Patel, N. *Warfarin*; StatPearls Publishing: Treasure Island, FL, 2023.

(25) Crader, M. F.; Johns, T.; Arnold, J. K. *Warfarin Drug Interactions*; StatPearls Publishing: Treasure Island, FL, 2023.

(26) Patel, M. P.; Green, N. T.; Burch, J. K.; Kew, K. A.; Hughes, R. M. Screening of Biocatalysts for Synthesis of the Wieland−Miescher Ketone. *Catalysts* **2020**, *10* (9), 1063.

(27) Wong, T. C.; Sultana, C. M.; Vosburg, D. A. A Green, Enantioselective Synthesis of Warfarin for the Undergraduate Organic Laboratory. *J. Chem. Educ.* **2010**, *87* (2), 194−195.

(28) Halland, N.; Hansen, T.; Jørgensen, K. A. Organocatalytic Asymmetric Michael Reaction of Cyclic 1,3-Dicarbonyl Compounds and α,β-Unsaturated Ketones—A Highly Atom-Economic Catalytic One-Step Formation of Optically Active Warfarin Anticoagulant. *Angew. Chem., Int. Ed.* **2003**, *42* (40), 4955−4957.

(29) Xie, B.-H.; Guan, Z.; He, Y.-H. Promiscuous Enzyme-Catalyzed Michael Addition: Synthesis of Warfarin and Derivatives. *J. Chem. Technol. Biotechnol.* **2012**, *87* (12), 1709−1714.

(30) *Carnegie Classification of Institutions of Higher Education: East Carolina University*. American Council on Education, 2023. https://carnegieclassifications.acenet.edu/institution/east-carolina-university/ (accessed 2023-05-02).

(31) Allen, W. E.; Hosbein, K. N.; Kennedy, A. M.; Whiting, B.; Walker, J. P. Design and Implementation of an Organic to Analytical CURE Sequence. *J. Chem. Educ.* **2021**, *98* (7), 2199−2208.

(32) Allen, W. E.; Hosbein, K. N.; Kennedy, A. M.; Whiting, B.; Walker, J. P. Embedding Research Directly into the Chemistry Curriculum with an Organic to Analytical Sequence. *J. Chem. Educ.* **2021**, *98* (7), 2188−2198.

(33) Fiore, S. M. Interdisciplinarity as Teamwork: How the Science of Teams Can Inform Team Science. *Small Group Res.* **2008**, *39* (3), 251−277.

(34) National Research Council. *Enhancing the Effectiveness of Team Science*; National Academies Press: Washington, DC, 2015.

(35) Hall, K. L.; Vogel, A. L.; Huang, G. C.; Serrano, K. J.; Rice, E. L.; Tsakraklides, S. P.; Fiore, S. M. The Science of Team Science: A Review of the Empirical Evidence and Research Gaps on Collaboration in Science. *Am. Psychol.* **2018**, *73* (4), 532−548.

(36) Castro, V.; Rodríguez, H.; Albericio, F. CuAAC: An Efficient Click Chemistry Reaction on Solid Phase. *ACS Comb. Sci.* **2016**, *18* (1), 1−14.

(37) Dogan, V.; Sayin, S.; Uyanik, A.; Yilmaz, M. Functional Group Effects of New Calixarene Derivatives on Catalytic and Enantioselective Behavior of Lipase. *Polycyclic Aromat. Compd.* **2019**, *39* (4), 318−331.
(38) Reetz, M. T.; Tielmann, P.; Wiesenhöfer, W.; Könen, W.; Zonta, A. Second Generation Sol-Gel Encapsulated Lipases: Robust Heterogeneous Biocatalysts. *Adv. Synth. Catal.* **2003**, *345* (6−7), 717−728.
(39) Tichá, I. C.; Hybelbauerová, S.; Jindřich, J. New α- and β-Cyclodextrin Derivatives with Cinchona Alkaloids Used in Asymmetric Organocatalytic Reactions. *Beilstein J. Org. Chem.* **2019**, *15*, 830−839.
(40) Pisaneschi, F.; Cordero, F.; Lumini, M.; Brandi, A. Click Chemistry: A Straightforward Route to Decorated Prolines. *Synlett* **2007**, *2007* (18), 2882−2884.
(41) Rodenbusch, S. E.; Hernandez, P. R.; Simmons, S. L.; Dolan, E. L. Early Engagement in Course-Based Research Increases Graduation Rates and Completion of Science, Engineering, and Mathematics Degrees. *LSE* **2016**, *15* (2), ar20.
(42) Allen, W. E.; Hosbein, K. N.; Kennedy, A. M.; Whiting, B.; Walker, J. P. Design and Implementation of an Organic to Analytical CURE Sequence. *J. Chem. Educ.* **2021**, *98*, 2199.
(43) Wurz, A. I.; Walker, J. P.; Hughes, R. M. Optimization of Warfarin Synthesis Using Biocatalysts and Adjuvants for Enantioselectivity: A CURE Approach. Presented at the 73rd Southeastern Regional ACS Meeting, San Juan, Puerto Rico, 2022; paper 983.

https://doi.org/10.1021/acs.jchemed.4c00118
J. Chem. Educ. 2024, 101, 3163−3170