A Graduate-Level Interdisciplinary Curriculum in CAR-T Cell Therapy

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Abstract

Objective: To evaluate the impact of a novel interdisciplinary graduate-level course in chimeric antigenic receptor-T cell therapy on students' knowledge and interests in translational science.

Materials/Participants and Methods: The course ran November 12 to 16, 2018. Students were surveyed before and after the course. The survey included questions regarding background, self-perceived knowledge/confidence in skills, and interests/predicted behaviors. Students were assigned to work in collaborative interdisciplinary teams to develop a research proposal.

Results: A total of 25 students taking the course for graduate-level credit were surveyed. Of these, all 25 (100%) completed the surveys. Students came from variable backgrounds and were at different stages of graduate training. After completion of the course, there was a statistically significant increase in self-perceived knowledge of immunotherapy (mean score of 3.6 postcourse vs 2.6 precourse, on a 5-point Likert scale; $P<.001$), knowledge of the bench to clinic translational process (3.7 postcourse vs 3.0 precourse; $P<.001$), confidence in critical reading skills (4.3 postcourse vs 4.0 precourse; $P=.008$), confidence in immunotherapy-focused grant writing skills (3.6 postcourse vs 2.8 precourse; $P<.001$), and interest in working in interdisciplinary teams (4.8 postcourse vs 4.6 precourse; $P=.02$).

Conclusion: The structure of this innovative and comprehensive course serves as a platform for educational courses in interdisciplinary translational research and helps trainees build knowledge and interest in the fields of chimeric antigenic receptor-T cells, regenerative sciences, and immunotherapy.

Translating scientific discoveries from the laboratory to the clinic has become increasingly important in ensuring that biomedical advances benefit patients in need of novel therapies.[1] The field of complex T-cell immunotherapies is one such area that is dependent on effective translation. Reliance on interdisciplinary teams that involve basic scientists, translational investigators, clinicians, regulatory experts, industry specialists, and manufacturers that communicate and work effectively with each other to collectively discover, translate, navigate US Food and Drug Administration (FDA) approval, and implement new treatments in the clinic is a core need of successful translation.[2] Consistently, interdisciplinary teams increase the success and efficiency of the workflow.[3,4] However, medical and graduate training has traditionally been organized along disciplinary lines to facilitate focused education. As a consequence, basic science and medical trainees often have few opportunities to directly interact during their training, limiting interdisciplinary proficiency.[2,5]

Interdisciplinary interaction is especially important in the development of increasingly complex T-cell therapies, which require extensive expertise, collaborations, and team science. One such area is the development of chimeric antigenic receptor-T (CAR-T) cell therapy for the treatment of cancer. T Cells are critical mediators of adaptive immunity that not only defend their hosts from foreign pathogens but also inhibit abnormal host cells from accumulating to help prevent and even fight diseases such as cancer.[6] CAR-T cells are engineered T cells that are redirected

against a specific tumor antigen. These CAR-T cells are stimulated and expanded *ex vivo* for a period of 1 to 2 weeks and then reinfused into patients, where they proliferate, produce cytokines, and exhibit their antitumor activity.

CAR-T cell therapy has recently emerged as a potentially revolutionary and curative therapy in the treatment of cancer.[7] Treatment with CAR-T cell therapy has resulted in unprecedented outcomes in B-cell malignancies in clinical trials, resulting in 2 FDA-approved constructs in 2017.[8,9] The discovery and engineering of T-cell therapies relies on expertise and collaboration across the fields of molecular biology, immunology, and virology. Clinical translation requires expertise in translational science, FDA regulation, and good manufacturing practices (GMPs). Successful delivery incorporates providers in multiple medical specialties, including oncology, critical care, neurology, and laboratory medicine.

Given the complexity of such an undertaking, comprehensive training for basic scientists, biomedical engineers, translational investigators, and clinician investigators is needed to ensure that experts from these distinct disciplines are able to work together to harness new discoveries and effectively bring them into the clinic in an efficient and timely manner. The development and implementation of this course, entitled "Regenerative T-Cell Immunology in the Treatment of Cancer," provides a blueprint of how to develop interdisciplinary curricula.

This graduate course was designed for medical, master's, and predoctoral students, as well as postdoctoral fellows, staff, and faculty. Its aim was to provide necessary investigational skills across biomedical, regulatory, and translational sciences. An inaugural 3-day version of this course was piloted in 2017 and was expanded to 5 days in 2018. In addition, the 2018 course offered continuing medical education (CME) credit for attending physicians. The goals and objectives of this course are based on core competencies as outlined by Mayo Clinic Graduate School of Biomedical Sciences (MCGSBS) and Mayo Clinic Regenerative Sciences Training Program.[10,11] This course is one approach to enhance interdisciplinary investigational skills of scholars in training and faculty, and we recommend that similar efforts be widely implemented in developing T-cell immunotherapy programs.
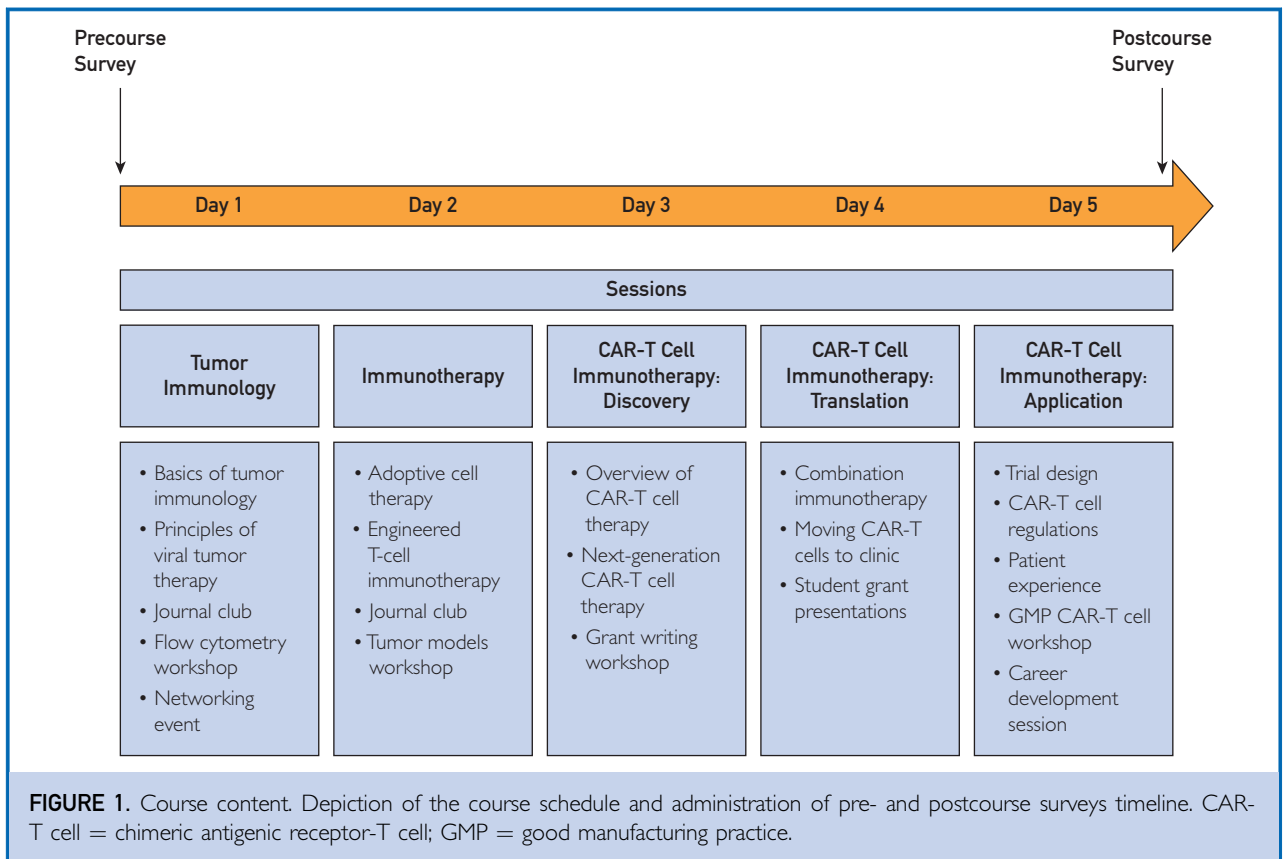
The primary goals for this first-of-its-kind course were to: (1) provide basic science and medical trainees a knowledge base and increase their interest in translational T-cell therapeutics; (2) foster interdisciplinary interactions, including vertical integration (working with others at different levels of training) and horizontal integration (working with others from different training backgrounds); and (3) help trainees begin to master skills critical to sustain careers in translational science, including grant writing and critical analysis of primary literature.

Although academic centers may be poised for interdisciplinary investigation and collaborations, strategies for training and preparation specifically in the field of engineered T-cell therapy are lacking. In this article, we describe the 2018 course design and content, faculty and staff, and participants and course survey design, distribution, and analysis of this innovative course. We plan to iterate on this offering to develop further curricula that will aid trainees in developing the skills necessary to form and work on strong translational teams to innovate and improve human health.

MATERIALS/PARTICIPANTS AND METHODS

Course Design and Content
The goals of the "Regenerative T-Cell Immunology in the Treatment of Cancer" course were to: (1) provide basic science and medical trainees a knowledge base and increase their interest in translational T-cell therapeutics, (2) foster interdisciplinary interactions, and (3) help trainees begin to master skills critical to sustain careers in translational science. The learning objectives were for students to: (1) discuss the current state of translational T-cell immunology and immunotherapy and (2) assemble into interdisciplinary teams to develop and present a research proposal. The course was hosted and funded by the Department of Immunology and Center for Regenerative Medicine at Mayo Clinic in Rochester, Minnesota. The 2018 "Regenerative T-Cell Immunology in the Treatment of Cancer" course was a 5-day course that ran November 12 to 16, 2018; took place at MCGSBS in Rochester, MN; and was available through videoconferencing to Mayo Clinic in Florida and Arizona sites. Participants were eligible to take the course for 3 credits through MCGSBS. Coursework was graded

FIGURE 1. Course content. Depiction of the course schedule and administration of pre- and postcourse surveys timeline. CAR-T cell = chimeric antigenic receptor-T cell; GMP = good manufacturing practice.

dichotomously as either satisfactory (S) or nonsatisfactory (N). Attendance and completion of the final project were required to achieve a passing "satisfactory (S)."

The course contained sessions on the basics of tumor immunology, principles of viral tumor therapy, adoptive cell therapy, engineered T-cell immunotherapy, overview of CAR-T cell therapy, next-generation CAR-T cell therapy, combination immunotherapy, moving CAR-T cells to clinic, trial design, and CAR-T cell regulations. The course also included 2 journal clubs; workshops on flow cytometry, tumor models, grant writing, and GMP CAR-T cell generation; a student grant presentation session; a networking event with students and faculty; a career development session; and a patient experience session (Figure 1; Supplemental Figure 1, available online at https://mcpiqojournal.org).

Faculty and Staff
To provide students with a broad team of expertise and model the importance of forming diverse interdisciplinary teams, we selected faculty from a variety of backgrounds. The faculty consisted of 1 doctoral-level basic scientist (immunology), 1 doctoral-level biomedical engineer scientist, 7 doctoral-level translational scientists (immunology, virology, and cellular therapy PhDs), and 13 MD/MD-PhD—level clinician-scientists (immunology, virology, hematology, and transplant medicine) from Mayo Clinic in Rochester. Staff consisted of a teaching assistant, who was an MD-PhD student, 2 MD-level hematology fellows to lead the journal clubs, and an upper-level clinical flow cytometry technician to teach the flow cytometry workshop. Faculty also included a translational physician scientist from Washington University, St. Louis, Missouri.

Participants
A total of 25 trainees participated in the course for MCGSBS credit and were from diverse backgrounds. Students were recruited to participate in the course through e-mail advertisements through MCGSBS, Mayo Clinic

Department of Immunology, Mayo Clinic Department of Molecular Medicine, Mayo Clinic Center for Regenerative Medicine, and Mayo Clinic Division of Hematology, as well as the MCGSBS course catalog. There were 2 postbaccalaureate students (Mayo Clinic), 4 MS students (Mayo Clinic), 1 PhD/MS student (Mayo Clinic), 1 resident physician pursuing an MS (Mayo Clinic), 1 fellow physician pursuing an MS ("other" institution), 1 attending physician pursuing an MS (Mayo Clinic), 11 PhD students (Mayo Clinic), 2 PhD/other educational category students (Mayo Clinic/ other institution), 1 MD-PhD student (Mayo Clinic), and 1 other educational category student (pharmacist pursuing MS; Mayo Clinic) who took the course for MCGSBS credit. All received a passing grade of "satisfactory (S)." The course was also CME accredited, and 4 MCGSBS registered students elected to take the course for CME credit as well.

Journal Clubs
Journal articles were assigned for participants to read before the journal clubs. These journal clubs occurred on days 1 and 2 of the 5-day course. The first journal club focused on engineered T-cell therapy for autoimmune diseases,[12] and the second journal club focused on regulatable engineered T-cell developments.[13] These sessions were led by hematology fellows.

Workshops
Four workshops occurred throughout the course. The workshops focused on flow cytometry (day 1), tumor models (day 2), grant writing (day 3), and generating a GMP CAR-T cell (day 5). Course participants learned practical skills for conducting translational research.

Networking Event and Career Development Session
On day 1, students had the opportunity to network and meet potential collaborators. On day 5, students and faculty engaged in a Career Development Session. Students participated in a faculty dinner and round table discussions about their career paths.

Final Project
Students worked in collaborative teams to construct a National Institutes of Health—style specifics aims page on a translational project relevant to T-cell immunology in the treatment of cancer. On day 1, objectives for the course and the project expectations were described. On day 3, expectations for the project were again reviewed and students worked on their projects in diverse teams. Students worked in teams of 2 to 5 students. Each group contained at least 1 student with bench research experience and at least 1 student with clinical experience. In addition, at least 1 person in the group had grant writing experience. With this approach, we hoped to foster collaboration between students at different levels of training (vertical integration) and from different training backgrounds (horizontal integration). During the day 3 grant writing session in which students could work on their projects, a clinician scientist (course director) and MD-PhD student (lead teaching assistant) were available to answer questions and help students. Students presented their projects on day 4. All student teams were able to successfully synthesize and defend novel specific aims pages that demonstrated the trainees' abilities to not only integrate the material that they learned but also meld the expertise from each of their group members into a unique cohesive project.

Patient Experience
Students interacted with a former patient with cancer to learn more about the patient perspective of cancer and cancer immune therapy. This patient was selected to participate in this session because she has participated in medical trainee education in the past. The session consisted of discussion with the patient and her family, the treating physician, and the students on the impact of hematologic malignancy and treatment on daily life.

Survey Design and Distribution
The survey was a series of questions regarding students' backgrounds, self-perceived knowledge/confidence in skills, and interests/predicted behaviors. Answer choices included a Likert scale with choices of strongly disagree (scored as 1), disagree (scored as 2), neutral (scored as 3), agree (scored as 4), and strongly agree (scored as 5). Students could also provide open-text field responses to elaborate on some questions. The final survey is available as Supplemental Figure 2 (available online at https://mcpiqojournal.org/). This study was

deemed by the Mayo Clinic in Rochester Institutional Review Board Wizard program to not require review because it fell under the area of quality improvement. The survey was distributed to students at the beginning (precourse survey) and end of the course (postcourse survey), filled out in class, and collected. The survey was distributed to and completed by all 25 students interested in taking the course for MCGSBS credit.

Statistical Analyses

The survey data were assembled and analyzed in Microsoft Excel and Prism Graph Pad. Figures were generated using Prism Graph Pad. Pre- and postcourse surveys were statistically analyzed using a paired t test and depicted in graphical form as mean ± SD. Values of mean ± SD and median are also displayed. Parametric testing was selected for Likert scale analysis with n=25 students.[14]

RESULTS

Participant Characteristics

Of the 25 trainees interested in taking the course for MCGSBS credit and to whom the survey was distributed, 100% (25 students) completed the survey. These 25 students were training in the following education tracks of MCGSBS: biochemistry and molecular biology (3 students), clinical and translational science (6 students), immunology (6 students), immunology plus other track (2 students), molecular pharmacology and experimental therapeutics (1 student), neuroscience (1 student), and virology and gene therapy (2 students). Of the 25 students, 6 (24%) self-described themselves as from "underrepresented" backgrounds, and 2 (8%) were self-described as from underrepresented and rural backgrounds. Of the respondents, 15 (60%) were women and 10 (40%) were men. The students self-reported themselves as the following: American Indian or Alaska native and white (1 student; 4%), American Indian or Alaska native and Hispanic or Latino (1 student; 4%), Asian (5 students; 20%), black or African American (1 student; 4%), Hispanic or Latino (1 student; 4%), Hispanic or Latino and white (2 students; 8%), white

(11 students; 44%), other (1 student; 4%), and no disclosure (1 student; 4%).

Course Impact on Self-perceived Student Knowledge and Skills Confidence

Results are depicted in Figure 2 for students who received (25 students) and responded to the pre- and postcourse surveys (25 students). There was a statistically significant increase in self-perceived knowledge of immunotherapy ($P<.001$), self-perceived knowledge of the translational process ($P<.001$), self-perceived knowledge of the patient experience ($P<.001$), confidence in critical reading skills ($P=.008$), and confidence in grant writing skills ($P<.001$) postcourse compared to precourse. Data depicting the course impact on self-perceived student knowledge and skills confidence are summarized in Figure 2A.

Impact on Student Interest and Predicted Behaviors

In both the pre- and postcourse surveys, there was interest in cancer therapy and immunotherapy (precourse mean ± SD, 4.1±0.9; median, 4; postcourse mean ± SD, 4.4±0.7; median, 5), with a value of 4 corresponding to "agree," and a value of 5 corresponding to "strongly agree" in terms of being interested in cancer therapy and immunotherapy. There was also interest in translational research in the pre- and postcourse surveys (precourse mean ± SD, 4.5±0.5; median, 4; postcourse mean ± SD, 4.4±0.7; median, 5). There were statistically significant increases in interest in attending immunotherapy educational events ($P=.05$) and willingness to work in an interdisciplinary team including scientists, physician scientists, physicians, etc. to pursue a research question ($P=.02$) postcourse compared with precourse. Participants exhibited a desire to pursue a career in translational research in the pre- and postcourse surveys (precourse mean ± SD, 4.2±0.9; median, 4; postcourse mean ± SD, 4.4±0.9; median, 5). Data depicting the course impact on student interest and predicted behaviors are shown in Figure 2B.

DISCUSSION

The "Regenerative T-Cell Immunology in the Treatment of Cancer" course aimed to provide
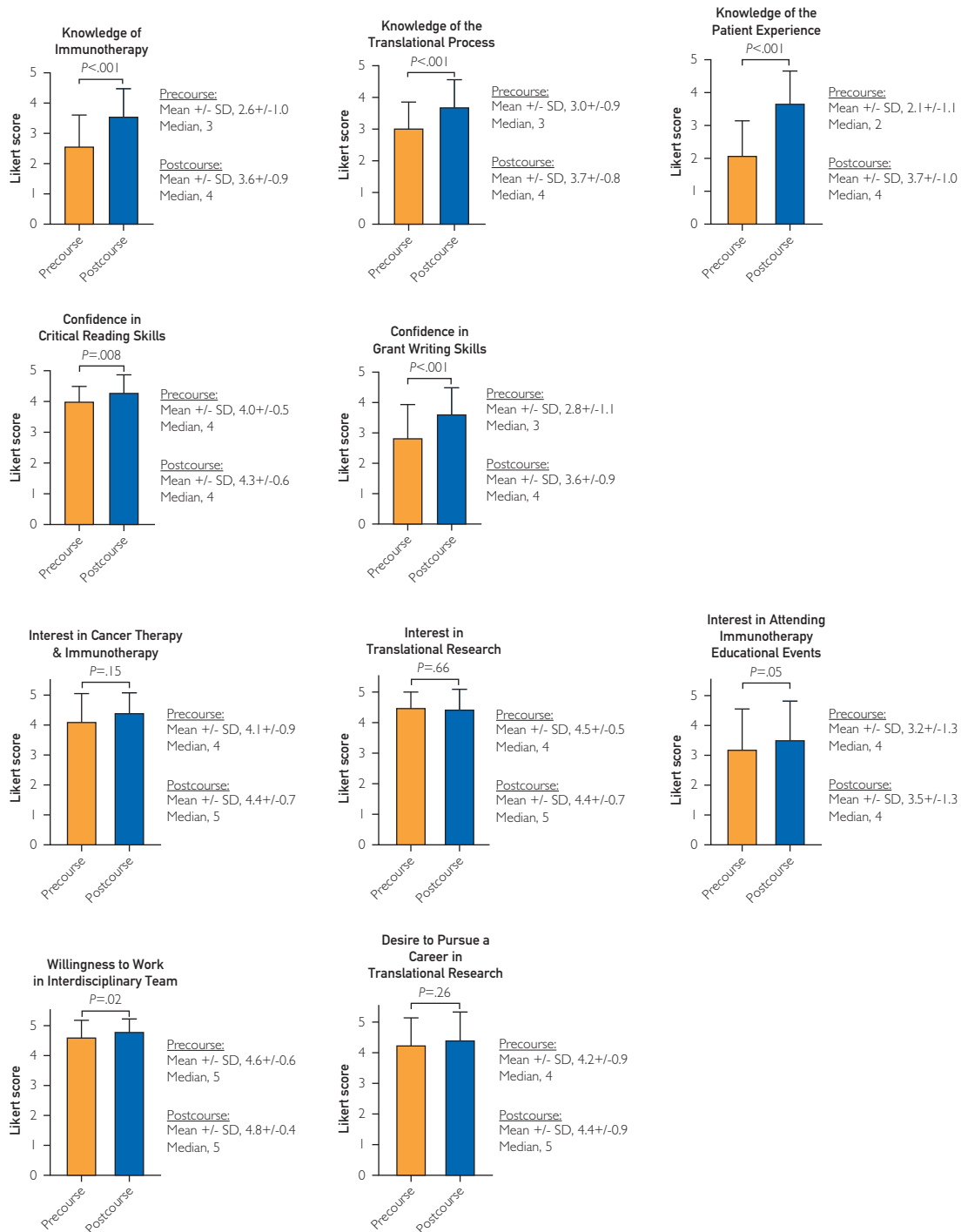
FIGURE 2. Course impact. Pre- and postcourse surveys were distributed to students taking the course for Mayo Clinic Graduate School of Biomedical Sciences credit (25 students) and were completed by 25 students. Students were asked to select whether they strongly agreed (score of 5), agreed (4), were neutral (3), disagreed (2), or strongly disagreed (1) with a given statement. Pre- and postcourse surveys were statistically analyzed using paired *t* test and depicted in graphical form as mean ± SD. Values of mean ± SD and median are displayed as well. A, Reflects impact on self-perceived student knowledge and skills confidence. B, Reflects impact on student interest and predicted behaviors.

basic science and medical trainees with a knowledge base in the field of engineered T-cell immunotherapy for the treatment of cancer. It also focused on helping them begin to master skills necessary to sustain careers in translational therapeutics, including grant writing and critical analysis of primary literature and developing the ability to work collectively in situations that require vertical and horizontal integration. In investigating the impact of our course, there was a statistically significant increase in self-perceived knowledge of immunotherapy ($P<.001$), self-perceived knowledge of the translational process ($P<.001$), self-perceived knowledge of the patient experience ($P<.001$), confidence in critical reading skills ($P=.008$), and confidence in grant writing skills ($P<.001$) postcourse compared with precourse. In both the pre- and postcourse surveys, there was interest in cancer therapy and immunotherapy, interest in translational research, and a desire to pursue a career in translational research. There were statistically significant increases in interest in attending immunotherapy educational events ($P=.05$) and willingness to work in an interdisciplinary team ($P=0.02$). There was not a statistical change in interest in cancer therapy and immunotherapy, interest in translational research, or desire to pursue a career in translational research. However, this is likely due to the high level of preexisting interest in those taking the course and the relatively small number of participants, which is a limitation of the study.

The pilot course was 3 days long and occurred in 2017. The 2018 course was expanded to 5 days. The results presented here are from the 2018 course. The 2018 course not only offered MCGSBS graduate school credit, but also CME credit for physician participants. We hope to further grow the course by expanding the CME component to more participants and inviting more medical students to partake next year. Due to the success of this course, the Mayo Clinic Regenerative Sciences Training Program is aiming to implement similarly structured courses for other topics.

As there continue to be advances in basic science and clinical research, the need for a workforce that can participate in translational teams will need to continue to grow to ensure safe, efficient, and successful translation of findings from the laboratory to patient care. Therefore, coursework that allows students from a variety of levels of training to work as part of translational teams will be critical in helping trainees gather the skills they will need to be successful in these endeavors throughout their careers.

CONCLUSION

The structure of this course can serve as a platform for educational courses in interdisciplinary translational research and help trainees build knowledge and interest in the fields of CAR-T cells, regenerative sciences, and immunotherapy.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at https://mcpiqojournal.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

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