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A training program in cardiovascular cell-based therapy: from the NHLBI Cardiovascular Cell Therapy Research Network

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Abstract

Stem/progenitor cell-based therapies offer novel treatment for many prevalent diseases. However, most physicians are not trained or introduced to cell therapy. We describe a model of a training program aimed at empowering physician–scientists with the knowledge and skills necessary for advancing the field of cardiovascular cell therapy. To date, five full-time scholars have completed this training program, obtained a full-time academic appointment in Cardiovascular Disease, and continue to actively contribute to the advancement of cell therapy applications. Another has returned to his parent institution to complete his PhD and several part-time scholars have continued in scholarly activities in other academic programs.

Keywords

cardiovascular; fellowship training; physician training; regenerative medicine; stem cell

Background

Stem/progenitor cell-based therapies offer novel treatment for diseases of the cardiovascular (CV) system that remain suboptimally treated. For example, the medical treatment of postmyocardial infarction left ventricular dysfunction has not changed recently, yet the healthcare burden of heart failure remains outstanding [1]. Many studies have demonstrated that cell therapy is safe in patients with CV disease and resulted in improved clinical outcomes [2]. Yet most physicians are not trained or introduced to cell therapy. This is, in part, explained by the inability of traditional didactic medical training to keep up with the rapid pace of discovery in this field. For example, the pioneering work of Yamanaka *et al.* that demonstrated the ability to reprogram adult fibroblast into pluripotent stem cells was published in 2006 [3]. Therefore, most clinician scientists would not have been introduced to this work during their formal training. Additionally, most physicians do not have the

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requisite vascular and stem cell biology knowledge required for optimal application and investigation of cell therapies. Furthermore, the heavy regulation of cell therapy and the false impression that cell therapy is dependent on the use of embryonic cell lines intimidates many clinicians and scientists from participating in the advancement of this important field.

Some have suggested that formal training in cellular and regenerative medicine would help clinician scientists to understand the appropriate use of cell therapy and improve the clinical applications of this treatment [4]. The Cardiovascular Cell Therapy Research Network (CCTR) was established by the National Heart, Lung and Blood Institute (NHLBI) in 2007 to develop, coordinate and conduct multiple collaborative protocols testing the effects of stem/progenitor cell therapy on CV disease. The CCTR is achieving this mission, having conducted multiple studies evaluating the safety and clinical impact of cell therapy in patients with ischemic left ventricular dysfunction [5–7]. Fortunately, the NHLBI Project Office recognized the need for training in this field and the CCTR includes a dedicated Clinical Research Investigator Skills Development Program (CRISDP). The University of Florida also recognizes the importance of cell therapy training and currently supports the salaries of two training scholars annually.

The purpose of this paper is to describe the CRISDP, at the University of Florida Regional Center (UFRC) of the CCTR, as a model for postgraduate training in cell-based therapies for CV disease that could be used to advance the field.

Mission

The intent of the UFRC-CRISDP is to empower young physician–scientists with the knowledge and skills necessary for conducting preclinical research and early-phase clinical trials in regenerative CV medicine through a structured training program. The UFRC-CRISDP focuses on postdoctoral fellows and junior faculty committed to clinical research careers and has three articulating aspects. The first is to select appropriate young physician–scientist candidates whose development is likely to result in the advancement of the field of cell therapy. The second is to provide selected candidates basic didactic training in stem cell biology, regenerative medicine, biomedical ethics, regulatory issues and trial design. The third aspect is application of this knowledge to selected projects requiring candidates to directly apply these educational experiences in well-designed mentored research studies. Specific training for clinicians also includes developing skills to master novel cell delivery techniques for CV disease patients.

Program structure

The training program structure is centered on: first, attracting appropriate applicants; second, the trainees; and third, the faculty. It also includes the program directors and UFRC-CRISDP Advisory Committee. The latter are responsible for selection of trainees, their course direction and evaluation, maintaining a high-quality faculty, and evaluation of the trainees as well as the overall program.

Applicants

The UFRC-CRISDP recruits individuals who are Cardiovascular Medicine fellows, Cardiothoracic Surgery fellows, and trainees or junior faculty from other CV-related clinical disciplines (Vascular Surgery, Vascular Medicine, Pediatric Cardiology and Pharmacology, among others). These individuals are targeted for recruitment because we believe that their clinical training in CV disease will contribute significantly to the development of clinically relevant translational experiments. At present, each year two full-time funded positions are available and two additional part-time positions funded by the candidates' resources (usually Department) are available each year.

The members of the UFRC-CRISDP Advisory Committee are actively involved in the recruitment and evaluation of applicants and have an opportunity to identify those with a proven interest in academic medicine and cell-based therapy. The Advisory Committee reviews each applicant's personal statement discussing their career goals and a one-page research plan outlining specific aspects of CCTRN or related cell therapy projects the applicant aims to work on. The Committee then interviews potential candidates, and those candidates who have demonstrated a clear commitment to an academic career are recruited.

Didactic training

Scholars are enrolled in a series of courses that are taught by stem cell biology and regenerative medicine program faculty (Box 1). Not all scholars with an MD degree will have had basic science courses considered critical for a good knowledge base in cell therapy. The UFRC-CRISDP Committee determines if a scholar should take additional courses to supplement core knowledge. Additionally, scholars have the option to enroll in selected UF courses offered in the General Medical Sciences or Advanced Postgraduate Program in Clinical Investigation (APPCI), or complete a Master of Science degree in Clinical Investigation (MSCI), through participation in the APPCI. The recommended APPCI courses include Biostatistics, Grant Writing, Manuscript and Abstract Writing for Clinician Scientists, and Ethical and Policy Issues in Clinical Research.

Scholars also participate in weekly laboratory meetings, weekly CCTRN team meetings, and attend the CCTRN Steering Committee conference calls and one face-to-face meeting as observers. The team meetings commonly include contributions from cardiologists, hematologists, physiologists and cell biologists. This interdisciplinary approach to cell therapy provides the Scholars insight into the important collaborations required for success in this field. Furthermore, we feel that this collaborative environment promotes enhanced social capital, which some have defined as a set of relationships and shared values created and used by multiple individuals to solve collective problems, which is known to lead to productive clinical and academic effort [8].

Mentored laboratory experience

Practical research training consists of direct participation in the laboratory of a mentor. When additional skills are needed to fully participate, individual training with technical mentors or additional coursework is offered. The University of Florida, with its T-28 Training Core in Stem Cell Biology, Network Center grant in the NHLBI Bone Marrow

Transplant Network, Cellular Reprogramming Center, Gene and Cell Therapy Center, and other programs, has extensive expertise and activity in many areas related to cell therapy. These resources provide extensive research training options for Scholars. Potential preceptors include scientists with expertise in cardiac stem cell biology, bone marrow cardiac cell precursors, hematopoietic stem cells, liver stem cells, mesenchymal stem cell progenitors, and novel devices for cell delivery (Box 2). Scholars with training in interventional cardiology are also given the opportunity to participate in research aimed at cell therapy delivery techniques. They may use large animal models available in Animals Resources Center or the UF School of Veterinary Medicine for skills development (e.g., direct intramyocardial injections). Scholars also have the unique opportunity to interact with scientist at the UF supported Florida Biologix® biopharmaceutical company, which is a unit of the Center of Excellence for Regenerative Health Biotechnology. Florida Biologix has a 23,000 square-foot manufacturing and testing facility within a 30 min drive from the main University of Florida campus.

Mentors

Eligibility for mentoring in this training program at University of Florida includes having expertise in a scientific area related to cell-based therapy and dedicated research time, along with the desire to be a primary research mentor. Mentors are expected to help scholars to define roles and expectations, communicate with other scholars and balance priorities among their needs for academic advancement, publication, leadership skills and grantsmanship.

The scholar's primary mentor is expected to have the greatest knowledge about the scientific area that the mentee plans to investigate, is readily available for consultation and advice, helps with writing, guides the reading program, and helps to resolve technological problems. A scholar's initial research often begins with a project of considerable interest to the mentor, usually part of the mentor's funded research program. The scholar's research is expected to gradually evolve over time into projects of primary interest to the scholar. The overall aim is to advance the scholar in experience and knowledge in the cell therapy field of interest so that the primary mentor is needed less and less and eventually not at all.

Measures of success

Scholars

Measures of success of the scholars include completion of their required course work, presentation of scientific progress to CCTRN faculty, presentations at Department of Medicine and Clinical and Translational Science (CTSI) local, regional and national meetings, publications, approved (IRB or IACUC) project protocols, grant applications submitted, grant applications awarded, and academic positions acquired.

Results

To date, all of the full-time scholars accepted into the program remain in the program or have completed the program. Five of the full-time scholars who have completed the training program at the University of Florida have sought out and obtained a full-time academic

appointment and continue to actively participate in the CCTRN. One full-time MD scholar completed the year of training and returned to Italy to complete a PhD. Several PhD scholars from multiple medical fields have worked in the training program part time and contributed to research. Graduated scholars have had 55 presentations at national or international meetings. Of these, 15 were directly related to work completed or initiated as UFRC-CRISDP scholars. They have had 48 peer-reviewed publications, 11 of which were directly related to work completed or initiated as CRISDP scholars. These scholars have submitted 15 grant applications. Table 1 highlights the expertise of the scholar's mentor, the scholar's current position, and the areas of cell therapy that the scholar is continuing to contribute to.

Program

The success of the UFRC-CRISDP is measured by the strength of the scholars. The program continuously reviews the success of recruitment by evaluating the strength of enrolled scholars relative to the potential of targeted recruits. Additionally, the program strives to announce the program to women and under-represented minority groups and the program evaluates their ability to recruit scholars from these groups. To date, three of the University of Florida scholars are women and two scholars are from under-represented race/ethnic groups. Success of the research program is also determined by the ability of its scholars to overcome methodological obstacles, establish technically feasible projects, generate hypothesis-driven high-quality data, and assemble their findings into presentable work at meetings and in publications. Finally, the program measures success in its ability to maintain core senior staff on its Advisory Committee and as mentors to enrolled scholars.

Limitations

The relative short duration of the UFRC training program and the relative small number of scholars to date make it difficult to conclude that this training program has already significantly impacted CV cell therapy. We recognize the importance of tracking measures of success in the years to come. The program will follow graduated scholar progress.

Conclusion

Stem cell-based therapies offer novel treatment for diseases of various organ systems, yet most physicians in training are not trained in or even introduced to clinical application of cell-based therapy. The UFRC of the CCTRN offers a dedicated training program in cell science for CV clinician scientists. The training includes didactic and laboratory experiences. Five scholars have completed the training program, obtained an academic appointment, and actively contribute to the advancement of cell therapy applications.

Future perspective

Stem/progenitor cell-based therapy for the treatment of CV disease will require ongoing collaboration between cardiologists, hematologists, physiologists and cell biologists. Efficient collaboration will require that physicians have basic science training critical for a good knowledge base in cell therapy. This training is likely to be more commonly offered as a formal fellowship.

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Box 1. Cell therapy fellowship core courses†

- Mouse Genetics
- Human Genetics I
- Human Genetics II
- Applications of Bioinformatics to Genetics
- Autoimmunity
- Molecular Immunology
- Advanced Cellular & Molecular Immunology
- Stem Cell Biology

†All courses are 1 credit/1 h per week.

Box 2. Examples of preceptors for cell therapy scholars**Preceptor expertise**

- Resident cardiac stem cells
- Bone marrow cell precursors
- Endothelial cell function
- Vascular injury/stem cells
- Hematopoietic stem cells
- Neural stem cells
- Liver stem cells
- Pancreatic stem cells
- Cell enhancement with small molecules
- Muscle stem progenitors
- Mesenchymal stem progenitors
- Germ cells
- Enhanced myoblasts
- New devices of cell delivery
- Cellular reprogramming

Executive summary

Background

- Most physicians are not trained or appropriately introduced to cell therapy.

Mission

- The Cardiovascular Cell therapy Research Network (CCTRN) includes a dedicated Clinical Research Investigator Skills Development Program (CRISDP) that aims to: first, select appropriate young physician–scientist candidates whose development is likely to result in the advancement of the field of cell therapy; second, provide selected candidates basic didactic training in stem cell biology, regenerative medicine, biomedical ethics, regulatory issues and trial design; and third, allow trainees to directly apply these educational experiences in well-designed mentored research studies.

Program structure

- The University of Florida CRISDP includes didactic training and mentored laboratory experiences.

Measures of success

- University of Florida CRISDP scholars have had many presentations at international meetings, peer reviewed publications, and multiple grant applications. Many graduated scholars have obtained full-time academic appointments and continue to contribute to the CCTRN.

Table 1

Scholar’s ongoing contribution to cell therapy.

Scholar	UFRC-CRISDP training period	Scholar’s primary degree	Number of primary mentors; mentor’s expertise	Scholar’s current position, expertise	Ongoing contribution to cell therapy
1	2008–2009	MD	2; clinical trials, imaging	Assistant Professor, imaging	Advances in imaging after regional ventricular therapy
2	2009–2011	MD	1; clinical trials	Assistant Professor, imaging	Clinical trial design
3	2009–2011	MD	2; clinical trials, delivery of biologics	Assistant Professor, interventional cardiology	Developing invasive methods of evaluating ventricular function and delivering biologics
4	2009–2010	MD	2; clinical trials, advanced heart failure	Assistant Professor, advanced heart failure	Clinical trial design
5	2011–2012	MD, PhD candidate	2; cellular scaffolding, animal models, clinical trials	Cardiology Fellow	Developing new cellular scaffolding models
6	2011–2012	MD	2; clinical trials, advanced heart failure	Assistant Professor	Clinical trial design
7	2012–2013	MD	2; clinical trials, advanced heart failure	Cardiology Fellow	Protocol development
8	2014–Present	MD, PhD	3; cardiac physiology, cell enhancement, clinical trials	Assistant Professor	Pharmaceutical techniques of cell enhancement

CRISDP: Clinical Research Investigator Skills Development Program; UFRC: University of Florida Regional Center.