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Silvio O. Conte Digestive Disease Research Core Centers – Connecting People, Creating Opportunities, Developing Careers

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The Silvio O. Conte Digestive Research Core Center (DDRCC) program is an initiative funded by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). The program is named after long-serving Massachusetts congressman Silvio O. Conte who sponsored legislation to establish the centers that are designed to bring together basic and clinical investigators to enhance research related to digestive and/or liver diseases and their complications.

There are 17 DDRCCs (<https://www.niddk.nih.gov/research-funding/research-programs/digestive-disease-centers>), each organized around a central theme. The theme may reflect the digestive or liver disease research interests and expertise of Center members for example, inflammatory bowel disease. Other themes reflect unifying processes such as cell signaling or host-microbe interactions. Representative themes include: homeostasis, injury and repair, inflammation in the digestive tract or liver, GI injury and infection. These themes link investigators within a Center to foster collaborations, enhance multi-, inter- and trans-disciplinary research, and create synergies. The present report was proposed Dr. Stephen James, Director of the NIDDK Division of Digestive Disease and Nutrition following the recent Center Directors' meeting on February 26, 2021. The report is intended to describe and highlight the successes and challenges for DDRCCs as well as to increase awareness of DDRCCs in the general community.

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Promote collaborations

Centers employ several strategies to promote collaborations. All the Centers feature regular enrichment seminars that meet weekly or monthly. Most centers have annual symposia or retreats that feature national or international thought leaders in digestive and liver disease or in fundamental basic or clinical science. Other events include research and poster competitions, affinity group events such as journal clubs and theme-specific works in progress meetings, visiting professors, workshops, and named lectureships - all of which help to enhance the environment for digestive and liver research on campuses across the country.

Collaboration among existing members.

Centers provide technologies and expertise that advance investigation in digestive and liver disease. Centers actively promote the availability of these services to members through seminars, workshops and retreats and through member surveys. Workshops devoted to new technologies serve as a venue for members whose interests may overlap. In addition, many centers offer seed funding for development of new technologies through cores, an initiative that further promotes collaborations among existing members. Several centers are organized around intersecting thematic areas, with themes involving investigators whose interests have coevolved. Journal clubs, shared lab meetings and co-mentorship of trainees within this overarching structure all foster interactions among members and promote new initiatives and collaborations.

Collaboration to attract new members.

A key metric of success of the DDRCCs is the extent to which core services, technology and expertise remove barriers and attract new investigators. Outstanding DDRCC cores draw investigators new to the field of digestive and liver research, typically because they offer high quality services not routinely available in most individual investigators' laboratories. DDRCCs further attract new members by encouraging collaboration with existing members; this effort not only advances the research portfolio of new members, but enriches research programs for existing members.

Collaborations to enrich and nurture junior investigators.

All centers place great emphasis on promoting careers of junior investigators. Centers approach this objective through formal and informal mentoring programs and workshops as well as through their individual pilot and feasibility programs, many of which encourage ongoing mentorship meetings to guide programmatic development. In addition, some centers offer targeted pilot and feasibility awards to new investigators with the explicit requirement that the award include a new collaboration with an established investigator.

Collaborations with other centers.

As part of the big picture of success of the DDRCC program, many programs have exploited geographic or thematic proximity to promote collaborative interactions. A visible example of such collaborative efforts is the Midwestern Alliance (MWA), which represents six regional DDRCCs (University of Chicago, Cincinnati, Cleveland, University of Michigan,

Mayo and Washington University). An alliance was initially crafted with the goal of promoting interactions among members, sharing of expertise and expanded mentoring opportunities for junior faculty. Over the last decade, the MWA has expanded to include a pan-institution material transfer agreement (MTA) whereby samples or reagents generated by a member at one center can be shared by investigators at other centers with a simple, durable MTA. The centerpiece of the MWA is an annual retreat held at each of the host centers on a rotating basis where two selected pilot and feasibility awardees from each center give an oral presentation of their work in progress to an audience of ~150 faculty, postdoctoral trainees and graduate students, including all 6 center directors as well as National Institutes of Health program leaders. Additional regional alliances, one within California DDRCCs and another among Eastern DDRCCs are evolving and are expected to be similarly successful. Centers have also exploited overlapping interests in technology or unique core resources (for example organoids or inducible pluripotent stem cell technology) to promote cross-center collaboration.

Create opportunities

A major mission of the DDRCCs is to provide an infrastructure to the Center members, recognizing that needs are dynamic due to evolving concepts, new technologies and changing membership, especially the new pool of members funded by the pilot and feasibility (P & F) program. To deliver this mission, NIDDK support helps establish scientific or clinical cores deemed useful as identified through periodic surveys. Table 1 includes the names of the scientific cores from each of the Centers and whether the Center includes a standalone clinical core. Details can be found on Center websites through this hyperlink: (<https://www.niddk.nih.gov/research-funding/research-programs/digestive-disease-centers>). Centers traditionally house between 3 and 4 scientific or clinical cores that either leverage existing institutional services or are created *de novo* based on available resources and member needs. Center cores must be used by at least two members, but in practice most cores are in high demand and used extensively. In fact, the extent of core usage by the center members serves as a valuable metric to rank and score a center during the peer-review process, and thus gauge the overall impact a Center.

DDRCC cores provide a tiered access. Typically, full members and P&F recipients have top-tier access to the core services in the form of priority, subsidized costs, and access to analytical pipelines, as applicable. Associate-members, non-members, and outside members have lower order of priority. Such tiered access incentivizes the needs to maintain center membership in good standing and promotes a high level of engagement by members.

Many cores are unique to a center, that is, the core is created *de novo* and does not exist in the parent institution. These unique cores may be located in the center space, staffed by center employees, and equipped with technologies purchased by the center, often subsidized or supported, in part, by institutional resources. The Center leadership (including core directors) decides on the services, policies, and priorities for the core. Many times, it is more efficient to leverage existing institutional cores. This allows members to have access to expensive technologies that would otherwise be out of reach. When institutional cores are leveraged to support DDRCC members, core directors negotiate with the institutional core to

provide Center members priority access and/or discounted services, in exchange for Center funds that support core personnel salary, equipment maintenance, and other relevant costs.

The range of core services across the 17 existing Centers is broad, although there are clear commonalities. Most Centers offer high-end cell and tissue imaging services; various “-omic” platforms and analysis at both single cell and tissue levels; animal models including gnotobiotic facilities; access to human and preclinical tissues and microbiota with appropriate annotations, and biostatistical support mostly through clinical component or cores; and more recently, innovative models to study disease such as human induced pluripotent cell lines, organoids, organ-on-chips, along with the use of gene editing tools.

DDRCC cores are dynamic, reflecting evolving needs and recent breakthroughs in science and technologies. Services offered by the cores are terminated or introduced based on member needs and cost-effectiveness. Centers also can sunset a core when the services being offered become cheaper, routine, and more readily available elsewhere. Core services may also be available to members at other DDRCCs. This strategy also allows collaboration between different Centers, which may yield an even greater impact and further fulfil the NIDDK’s mission of “integrating, coordinating, and fostering interdisciplinary cooperation between groups of established investigators that conduct high-quality research on digestive and/or liver diseases”.

Develop careers

One of the most important contributions made by DDRCCs is in the area of career development of junior investigators. Ideal career development for junior investigators requires a multifaceted approach, including appropriate mentorship, adequate financial support - including seed funding - and an environment conducive to outstanding science.

A critical role for DDRCCs is that they help create a rich and nurturing environment for digestive and liver disease research. All of the currently funded Centers have developed a robust community of investigators, providing an infrastructure for world-class gastrointestinal disease research. This infrastructure is vitally important to each institution because it helps create a culture that attracts others. All components of a DDRCC, including their scientific cores, facilities, enrichment programs and leadership play an important role in this effort. Whether it is a developing junior scientist drawn to a Center by an experienced investigator already at the Center, or a senior scientist interested in developing synergy through collaboration, DDRCCs provide an ideal nidus for the growth of digestive disease research.

Centers also provide other venues within their environment to promote careers. Many of these occur through dedicated enrichment programs, which are an integral part of all DDRCCs. Specific examples include academic skills workshops, dedicated career development sessions, focus group meetings for young investigators and graduate student career days. As highlighted above, in addition to providing unique and valuable services, DDRCC scientific cores also provide consulting and education that is valuable to early investigators.

One of the most recognizable career development opportunities provided by DDRCCs surrounds the provision of seed funding for gastrointestinal disease research. All DDRCCs provide pilot and feasibility grants, funding between 3–5 pilot awards each year with budgets that range from \$25,000 – 50,000. Some institutions fund awards for two years (with the second year being a competing renewal). Money from the National Institutes of Health is often supplemented by institutional funds to increase the number or the size of awards. Pilot grants are provided to investigators in 3 categories: 1) new investigators; 2) established non-digestive disease investigators proposing a digestive disease project; and 3) established digestive disease investigators proposing a project that constitutes a significant departure from ongoing research. All Centers assign higher priority to new investigators in order to help young scientists at a vulnerable period in their careers. On average 80% of pilot and feasibility grants across all Centers are awarded to new investigators. All applications are rigorously peer reviewed. Both the process of developing the application and receiving feedback are important career development activities. The return on investment (measured by subsequent funded grants) from pilot and feasibility support by DDRCCs is exceptional, with a high rate of retention of awardees in digestive disease research. The success of these P & F programs reflects both the quality of applicants, as well as financial and educational support provided by DDRCCs.

Perhaps one of the most critical components of career development is mentoring. Mentorship in a DDRCC takes multiple forms. The traditional dyad-based mentor-mentee relationship is important, and DDRCC's support not only this style of mentorship through their various programs, but they also provide a wealth of additional mentorship. For example, enrichment programs and scientific cores play critical roles in mentoring. Additionally, the very nature of pilot and feasibility programs lends itself to mentoring. In particular, young investigators who obtain pilot and feasibility funding are exposed to an array of DDRCC members (who they otherwise would not be exposed to), and as such, benefit from the great knowledge and wisdom available in the Center. Most Centers also have created specific sessions within their enrichment programs (as above) specifically targeted to junior investigators. For example, works in progress sessions and academic skills sessions provide invaluable mentorship specifically targeted to young investigators. Finally, through interactions among each other, DDRCCs are providing opportunities for junior investigators to obtain critical mentorship from other Centers, beyond their own Center. Indeed, it has been proposed by the Midwestern DDRCC Alliance as well as the Eastern DDRCC Alliance to create junior investigator exchange programs, intended to specifically enhance mentorship across Centers.

Metrics of success of the DDRCC program

The DDRCC program has been operational for nearly 40 years. The longevity of the program provides face validity for the value to the NIH and institutions, but makes it difficult to assemble quantifiable metrics. One measure is the success of the pilot and feasibility programs. The pilot programs serve as an incubator for research faculty. Most pilot and feasibility recipients remain in digestive disease research and are promoted to full membership in their Centers where they mentor the next generation of scholars. In one longstanding center (UNC) half of the current Center members and nearly all of

the members of the executive committee were initially funded by a pilot award. Pilot and feasibility awardees obtain preliminary data that leads to successful future grant applications. Each \$100,000 invested by the NIH in the pilot program leads, on average, to \$1–2 million in subsequent awards. An additional measurable outcome is published research. An estimated 3,000 or more papers are published each year from the 17 centers in aggregate that are made possible by core services. Most institutions provide funds to support Centers through equipment grants, salary support, faculty recruitment and matching funds for the pilot program thereby amplifying the investment by the NIH. Perhaps the most important impact of the Centers program is the creation of a collaborative community of scholars dedicated to digestive disease research. Although that impact has no objective metric, it is clear that it is considerable.

Challenges

DDRCCs have been highly successful, but are not without challenges. Centers may support targeted recruitments, but are not able to make primary hiring appointments limiting the ability of DDRCC's to make their institutions more diverse. However, Centers have taken steps to help diversify their membership and to emphasize equity and inclusion. One approach has been to fund pilot and feasibility grants from applicants underrepresented in science as well as candidates from diverse backgrounds. Centers have also included training on implicit bias as part of their enrichment program. DDRCCs have further included a diverse group of individuals as members of executive committees, advisory committees and core directorships.

The focus of most Centers is basic science. Thus, center budgets are not sufficient to support implementation science or community outreach. Additionally, DDRCC cores are primarily designed to serve the local membership. Increasing the visibility of these cores to a national audience could have a large impact on the field. The eligibility requirements for DDRCCs specify that at least 30 percent of the total funding contributing to the research base must be secured from the NIDDK. Many diseases of importance to gastroenterologists and hepatologists are not funded by NIDDK. For example, *C difficile* is largely funded by National Institute of Allergy and Infection Disease, alcoholic hepatitis is funded by the National Institute for Alcohol Use and Alcoholism and, and colorectal malignancy or Barrett's esophagus are funded by the National Cancer Institute. Patient oriented digestive disease research is often funded by PCORI or charitable foundations. Relaxing the 30 percent NIDDK requirement would focus attention on digestive and liver diseases rather than the funding agency.

Summary

Silvio O. Conte Digestive Disease Research Core Centers have had a major impact on the field for nearly 4 decades. Despite a relatively modest - and flat - budget, centers have had an outsized influence on their institutions by virtue of their high visibility, essential core services, small grants program, collaboration and mentoring opportunities and the important scientific advances made by their membership.

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Abbreviations:

DDRCC	Digestive Disease Research Core Center
NIDDK	National Institute of Diabetes, and Digestive and Kidney Disease
MTA	materials transfer agreement'
MWA	Midwestern Alliance
P & F	pilot and feasibility

Table 1.

NIDDK-funded digestive disease research core centers and their biomedical research cores

Center	Scientific Cores				Standalone Clinical * Core
Case-Western & Cleveland Clinic	Biorepository Core	Histology/Imaging Core	Mouse Models Core		No
Chicago	Multiparametric Host Cell Analysis Core	Integrative Clinical and Biospecimen Core	Tissue Engineering and Cell Models Core	Host-Microbe Core	Yes
Cincinnati Children's	Gene Analysis	Integrative Morphology Core	Pluripotent Stem Cell and Organoid Core		No
Harvard	Microscopy and Histopathology	Epithelial Cell and Mucosal Immunology	Gnotobiotic Mice, Microbiology, and Metagenomics	Clinical Translational Research Program	No
Massachusetts General Hospital	Human Genetics and Microbiome Core	Cell Circuits and Immunology Core	Cellular and In Vivo Models Core	Clinical Research Core	Yes
Mayo Clinic	Clinical Core	Epigenomics Core	Optical Microscopy and Microfluidics Core		Yes
Medical University of South Carolina	Analytical Cell Models Core	Advanced Imaging Core	Proteomics Core	Clinical Component	Yes
Michigan	Molecular Biology Core	Protein Localization, Identification and Folding (PLIF) Core	In Vivo Animal and Human Studies Core	Microbiome Core	No
Pittsburgh	Advanced Cell and Tissue Imaging Core	Clinical Biospecimen Repository and Processing Core	Genomics and Systems Biology Core	Human Synthetic Liver Biology Core	Yes
North Carolina	Biostatistics and Clinical Research	Advanced Analytics	Gnotobiotic Animal Core	Large Animal Models Core	Yes
Pennsylvania	Molecular Pathology and Imaging Core	Host-Microbial Analytic and Repository Core	Genetically Modified Mouse Core	Biomedical Data Sciences Core (BDSC)	Yes
San Diego	Human Translational Core	Preclinical Models Core	Microbiomics and Functional Genomics Core		No
San Francisco	Cell Biology Core	Immunology & Cell Analysis Core	Pathology & Imaging Core	Clinical & Translational Core	Yes
Southern California	Cell Separation and Culture Core	Cell and Tissue Imaging Core	Liver Histology Core	Analytical-Metabolic-Instrumentation Core	No
Texas Medical Center	Cellular and Molecular Morphology	Functional Genomics and Microbiome	Gastrointestinal Experimental Model Systems (GEMS) Core	Study Design and Clinical Research	Yes
Vanderbilt	Flow Cytometry Core	Mass Spectrometry Core	Imaging Core	Preclinical Models Core	No
Washington University	Advanced Imaging & Tissue Analysis Core	Biobank Core	Precision Animal Models and Organoids Core		No

* Centers are given the opportunity to have standalone clinical cores or to include a clinical component as part of the Administrative Core.