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REVIEW

UAB-UCSD O'Brien Center for Acute Kidney Injury Research

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Abstract

Acute kidney injury (AKI) remains a significant clinical problem through its diverse etiologies, the challenges of robust measurements of injury and recovery, and its progression to chronic kidney disease (CKD). Bridging the gap in our knowledge of this disorder requires bringing together not only the technical resources for research but also the investigators currently endeavoring to expand our knowledge and those who might bring novel ideas and expertise to this important challenge. The University of Alabama at Birmingham-University of California-San Diego O'Brien Center for Acute Kidney Injury Research brings together technical expertise and programmatic and educational efforts to advance our knowledge in these diverse issues and the required infrastructure to develop areas of novel exploration. Since its inception in 2008, this O'Brien Center has grown its impact by providing state-of-the-art resources in clinical and preclinical modeling of AKI, a bioanalytical core that facilitates measurement of critical biomarkers, including serum creatinine via LC-MS/MS among others, and a biostatistical resource that assists from design to analysis. Through these core resources and with additional educational efforts, our center has grown its investigator base to include >200 members from 51 institutions. Importantly, this center has translated its pilot and catalyst funding program with a \$37 return per dollar invested. Over 500 publications have resulted from the support provided with a relative citation ratio of 2.18 ± 0.12 (iCite). Through its efforts, this disease-centric O'Brien Center is providing the infrastructure and focus to help the development of the next generation of researchers in the basic and clinical science of AKI. This center creates the promise of the application at the bedside of the advances in AKI made by current and future investigators.

acute kidney injury; acute renal failure; core; kidney disease; O'Brien Center

INTRODUCTION

Established in 2008, the University of Alabama at Birmingham (UAB)-University of California-San Diego (UCSD) O'Brien Center for Acute Kidney Injury (AKI) Research (UAB-UCSD O'Brien Center) is an interdisciplinary center of excellence in AKI-related research. It is one of eight National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)-funded O'Brien Centers in the nation and the only O'Brien Center that connects two distinct universities under a common and integrated framework with a singular, disease-centric research focus (1). Preexisting strengths in research at each institution have been brought together to reciprocally enhance each other but also provide this breadth and depth of expertise to the larger research community in the United States and beyond. The natural collaborative spirit at each institution has enhanced the ability of the UAB-UCSD O'Brien

Center to sustain and integrate seamlessly as a unit, leveraging institutional commitments at both academic medical centers to further propel the development of a preeminent center of excellence for AKI-related research. Our mission is as follows:

“To provide shared core facilities to enhance collaborations and further investigations in kidney-related research, foster interactions among investigators from different backgrounds and disciplines, and provide intellectual resources and infrastructure to attract new and established investigators to AKI research.”

HISTORICAL BACKGROUND

The UAB-UCSD O'Brien Center began from an idea to combine the individual strengths of UCSD in clinical



research and UAB in basic science research in AKI, thereby enhancing the research capabilities of both institutions. As this collaboration grew and the UAB-UCSD O'Brien Center became a reality, our vision matured to not only include enhancement of the research depth of our respective institutions but especially to foster national and international research in AKI beyond these institutions. By supporting new young investigators and facilitating incorporation of established investigators with new research efforts in AKI, the impact of the center was amplified. The UAB-UCSD O'Brien Center uses biomedical research cores to facilitate conduct of unique experimental techniques and to train investigators in their use. In addition, a resource for biostatistical analysis provides early and continuing statistical support to investigators doing AKI research. As an added benefit, these resources have assisted research efforts beyond AKI to include studies in chronic kidney disease (CKD), a known long-term consequence of AKI. Collaborative efforts with institutional centers at UAB, funded by the National Institutes of Health (NIH)/NIDDK, in hereditary and genetic causes of kidney disease, such as polycystic kidney disease, have also broadened the reach of the UAB-UCSD O'Brien Center. As the center has matured, a continued focused effort to facilitate AKI-related research and efforts to allow for translational studies to be accomplished by the investigator base has been directed in the key thematic areas of 1) AKI in the intensive care unit and transplant setting, 2) renal vascular dysfunction and hemodynamic alterations, 3) oxidative stress and metabolism, and 4) genetic susceptibility. The aims illustrate the integrated approach to enhancing AKI research (Table 1).

CENTER STRUCTURE

This center uniquely has a disease-oriented approach and provides both preclinical and clinical core resources for investigators pursuing AKI-related research. However, although the program resides under one AKI "umbrella," there is research latitude to assist investigators with other kidney-related research activities. This is in recognition that AKI is on a continuum between normal kidney

function, progressive CKD, and kidney failure and transplantation. A strength of the UAB-UCSD O'Brien Center is the translational nature of the contribution across the life-cycle of an investigation by the three major cores, providing expertise in design and implementation of technical approaches for the NIH nomenclature of T₀-T₄ research (Fig. 1). For T₄ research, we leverage resources within the Centers for Clinical and Translational Science (CTSA) at our respective institutions. In addition, the incorporation of training opportunities for the entire research investigator base, including graduate and medical students, research fellows, and faculty through the Enrichment Program (discussed below), provide opportunities to accomplish research on AKI at any level.

The administrative core of the UAB-UCSD O'Brien Center is guided by Dr. Anupam Agarwal at UAB and codirected by Dr. Ravindra Mehta at UCSD and Dr. Paul W. Sanders at UAB. The administrative core provides overarching resources to the center, maintains a robust Enrichment Program, Pilot and Feasibility Grants Program, and Biostatistical Resource, which provides statistical support to users of the facilities. The administrative core coordinates the diverse activities of the center, facilitates interactions and collaborations among the researchers, maintains communications through our website, video conferences, and newsletters, and promotes scientific development through pilot grant funding and education initiatives. It also links cross-cutting activities of the three Biomedical Cores: the Clinical Studies of AKI (Core A), the Preclinical Studies of AKI Core (Core B), and the Bioanalytical Core (Core C). Investigators can access the services of the cores through our website by completing a core usage request (<https://www.uab.edu/medicine/obriencenter/core-usage-request-form>) with a response from the core personnel within 1–2 days.

The Clinical Studies of AKI Core (Core A) is directed by Dr. Ravindra Mehta at UCSD and codirected by Dr. Michael Seifert at UAB. This core offers support in the design and conduct of clinical research in AKI, access to comprehensive data sets of well-characterized patients with and without AKI from multiple sources for epidemiological studies evaluating risk factors and consequences of AKI and outcomes research (Table 2). A biorepository that includes human kidney biopsy tissue, blood, DNA, and urine is linked to an accessible deidentified clinical database of patients with and without AKI and enables translational research studies (Table 3). The kidney biopsy repository includes 196 biopsies from patients with a top-line diagnosis of AKI. The repository also has >15,000 archived kidney biopsies from various kidney diseases and is managed by renal pathologist Dr. Frida Rosenblum at UAB. In response to the coronavirus disease 2019 (COVID-19) pandemic, this core is also operating a global registry to understand the natural history of COVID-19-related AKI, identify risk factors that could lead to modification of therapy in high-risk individuals, and understand the course and outcomes of patients with kidney dysfunction from COVID-19 (Clinical Trials Registration No. NCT04491227). At UAB, in collaboration with our CTSA, we have an ongoing collection of urine samples (>450 samples as of November 15, 2020) from hospitalized patients with COVID-19 with and without AKI.

Table 1. Mission and aims of the UAB-UCSD O'Brien Center

<p>Mission: We support shared core facilities to enhance collaborations and further investigations in kidney-related research, foster interactions among investigators from different backgrounds and disciplines, and provide intellectual resources and infrastructure to attract new and established investigators to AKI research.</p>
<p>Aims</p> <ul style="list-style-type: none"> • Facilitate hypothesis-driven research through the support of shared core facilities and to leverage these core technologies into new projects, interactions, and collaborations in AKI-related research while ensuring rigor and reproducibility for the core services • Foster interactions among UAB-UCSD investigators and extend these to include investigators from regional, national, and international institutions—an extended research base • Provide a Pilot and Feasibility Grants Program to attract new and established investigators to AKI research • Administer an Enrichment Program that delivers outstanding opportunities for training and education

AKI, acute kidney injury; UAB, University of Alabama at Birmingham; UCSD, University of California-San Diego.

UAB-UCSD O'Brien Center for AKI Research

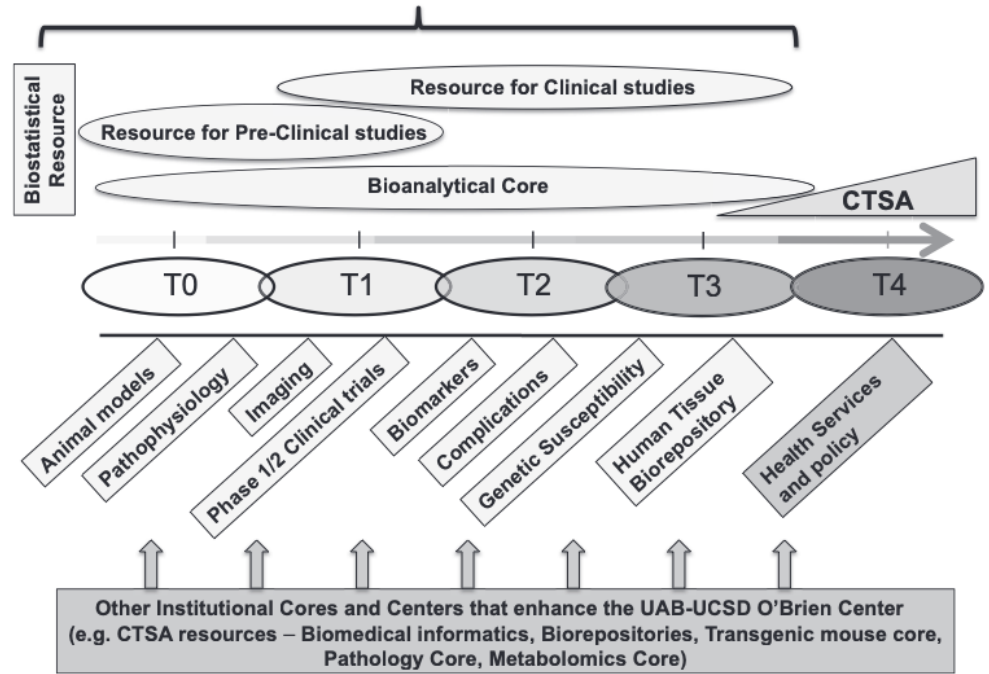


Figure 1. Diagram of the integration of resources across the translational science spectrum. The core resources of the University of Alabama at Birmingham (UAB)-University of California-San Diego (UCSD) O'Brien Center for Acute Kidney Injury Research provide infrastructure across the spectrum of research from basic science investigations (T₀) to translation to patient care (T₄). These resources include a variety of approaches to facilitate research in each realm and leverage additional available resources at each academic medical center, including those of the Centers for Clinical and Translational Science (CTSAs) of each institution. AKI, acute kidney injury. [Modified from Zarjou et al. (81).]

As part of the educational mission, the Clinical Studies of AKI Core sponsors the Workshop on Healthcare Data Analytics. This new workshop began in 2020 and provides a hands-on learning opportunity to 10 people/year to grow and enhance skills in large data set analysis. This program has been well received by the kidney community.

The Preclinical Studies of AKI Core (Core B) is directed by Dr. Paul W. Sanders at UAB, with codirectorship by Dr. James George at UAB and Dr. Volker Vallon at UCSD. This core provides three subcores that focus on individual robust experimental modalities for animal studies of AKI. The Small Animal Microsurgical Core Facility, directed by Dr.

Table 2. Comprehensive databases accessible for AKI research (Core A)

Database	Data Source	Data Content
International ICU AKI Registry	33 centers worldwide	Comorbidities, risk factors for AKI, clinical and laboratory data, fluid balance status, severity of illness scores, dialysis requirements and outcomes through hospital discharge. Currently, 17,444 patients have been screened and 3,179 patients are enrolled.
Drug-Induced Renal Injury Consortium	42 centers worldwide	634 patients (adult, n = 493; pediatric, n = 141) with drug-induced kidney disease. Blood, urine, and DNA samples have been collected as well as the clinical course of injury and outcomes up to 90 days post event.
Global Snapshot of AKI	International Society of Nephrology 0by25 project	Phenotypic information on 4,018 patients (adult, n = 3,664; pediatric, n = 354) enrolled from 289 centers in 92 countries. Presenting symptoms, risk factors, course, and outcome over 7 days of patients with AKI.
UAB and UCSD Clinical Data Warehouse from EHR	UCSD Epic with Clarity and UAB Cerner Datasets	Clinical laboratory, medication, and administrative data for outpatient and inpatient encounters at UAB and UCSD.
UC Accrual to Clinical Trials	Administrative and EHR data from 5 UC medical centers	Detailed data on demographics, diagnosis, procedures, laboratory, medication, and vital signs.
COVID-19 Kidney Disease Global Study	Data from 74 centers across 25 countries	Clinical data on course and outcomes of patients with COVID-19 with AKI, chronic kidney disease, end-stage kidney disease, and transplant (>3,000 patients as of March 1, 2021).

AKI, acute kidney injury; ICU, intensive care unit; UAB, University Of Alabama at Birmingham; UCSD, University of California-San Diego; EHR, electronic health records; UC, University of California.

Table 3. Samples available in the Core A Biorepository

Patient Group	Sample Size	Blood	DNA	Urine
AKI Biorepository				
ICU AKI registry (UAB/UCSD sites)	87	211	127	1,275
Drug-Induced Renal Injury Consortium Study	631	733	276	973
Post-AKI followup	93	273		1,180
Normal healthy subjects	126	298	204	871
Kidney Tissue Biorepository				
Donor kidneys	68	34		34
Normal kidney tissues from nephrectomies	25			
Native and transplant kidney biopsies*	196†			

AKI, acute kidney injury; ICU, intensive care unit; UAB, University of Alabama at Birmingham; UCSD, University of California-San Diego. *Ongoing and includes >15,000 biopsies; †biopsies with a diagnosis of AKI.

James George, provides surgical expertise in a variety of surgical models of AKI in rodents (Table 4). Assistance in the development of additional, novel surgical models applicable for AKI research are available on an as-requested basis and leverage the significant precision of dedicated microsurgions. Assistance with nonsurgical models is also provided to individual investigators, as is access to state-of-the-art surgical facilities. The Small Animal Imaging Facility, codirected by Dr. Anna Sorace and Dr. Jason Warram at UAB, provides state-of-the-art molecular imaging of functional, structural, and metabolic parameters, including molecular ultrasound, microcomputed tomography (CT), single-photon emission CT/CT, magnetic resonance imaging, positron emission tomography/CT, γ -camera, and bioluminescence and fluorescence imaging in rodents. The Renal Physiology subcore, directed by Dr. Volker Vallon at UCSD and supported by Dr. Prabhleen Singh and Dr. Scott Thomson, provides expertise and training for studying function of the whole kidney, including renal oxygenation evaluation in preclinical models and at the single nephron level, and renal micropuncture. In addition, technical expertise in preclinical models of AKI and CKD as well as the isolation of primary renal and vascular cells in culture is available through this core. The innovation of Core B centers on provision of requisite skills and knowledge in the field and flexibility in the preclinical procedures that are made available to hone and test an investigator's hypothesis.

The Preclinical Studies of AKI Core provides hands-on education through workshops annually. The Rodent Kidney Physiology/Injury Workshop, now in its 11th year, is held at UCSD and offers a comprehensive demonstration and

Table 4. Surgical procedures in mice and rats (Core B)

Surgical Models for the Study of Kidney Disease
<ul style="list-style-type: none"> Bilateral and unilateral models of kidney ischemia-reperfusion 5/6th nephrectomy Unilateral ureteral obstruction Parabiosis Kidney transplantation in mice and rats
Other microsurgical techniques
<ul style="list-style-type: none"> Arteriovenous fistula Telemetry

hands-on engagement in a variety of animal handling and models as well as phenotype techniques to evaluate renal function. The Flow Cytometry Workshop has been held at UAB since 2017 as a 3-day hands-on workshop covering the basics of use of antibodies, preparation of kidney samples, mechanics, and scientific theory of FACS analysis as well as the analysis of data. These workshops bring together small groups each year (6–9 individuals/course) so that focused attention is provided to enhance skill development in the investigator base.

The Bioanalytical Core (Core C) is directed by Dr. Stephen Barnes at UAB and codirected by Dr. Victor Darley-Usmar at UAB and Dr. Sucheta Vaingankar at UCSD. This core provides state-of-the-art bioenergetics, oxidative stress analysis, metabolite analysis, and biomarker assays for AKI research

Table 5. Selected biomarker assays (Core C)

Biomarker
<ul style="list-style-type: none"> Albumin Activin A Adrenomedullin α_1-microglobulin Ammonium bio-ADM (SphingoTec) BSAP BUN Creatinine CRP Cystatin C Endothelin 1 FGF-23 Furosemide GST-α GST-π Hepcidin Hippurate, <i>p</i>-cresol sulfate IGFBP-7 IL-10 IL-18 IL-6 Iohexol KIM-1 L-FABP Lipocalin2/NGAL MCP-1 Parathyroid hormone Penenkephalin Phosphate penKid (SphingoTec) Procollagen type III NP TGF-β1 TIMP-2 TNF-α TRAP-5 Uric acid Uromodulin Vitamin D-binding protein

Bio-ADM, bioactive adrenomedullin; BSAP, B cell-specific activator protein; BUN, blood urea nitrogen; CRP, C-reactive protein; FGF, fibroblast growth factor; GST, glutathione S-transferase; IGFBP, insulin-like growth factor-binding protein; IL, interleukin; KIM-1, kidney injury molecule-1; L-FABP, L-type fatty acid-binding protein; NGAL, neutrophil gelatinase-associated lipocalin; MCP-1, monocyte chemoattractant protein-1; penKid, proenkephalin A; TGF- β 1, transforming growth factor- β 1; TIMP-2, tissue inhibitor of metalloproteinase-2; TNF- α , tumor necrosis factor- α ; TRAP-5, tartrate-resistant acid phosphatase-5.

Table 6. Pilot and feasibility grant proposal submissions (2007–present)*

Type	Junior Investigator	Established Investigator	Total
Clinical research	96	25	121
Preclinical research	103	27	130
Total	198	52	251

*Although the O'Brien Center was funded by the National Institutes of Health in 2008, two pilots were funded in 2007 using institutional funds.

as well as consultation, training, and experimental design support. The core also offers assays for posttranslational modification of proteins and quantitative analysis of tricarboxylic acid cycle and bioenergetic metabolic intermediates by liquid chromatography with tandem mass spectrometry (LC-MS/MS). The techniques available through this core include LC-MS/MS-based assays for serum and urine creatinine as well as the quantitation of a variety of other

biomarkers of renal injury and repair (Table 5). Nano LC-MS for targeted and untargeted metabolomics and associated statistical and network analyses for clinical and animal model samples are available through this Core. This technical expertise builds on a funding investment provided by the NIH for a week-long Workshop on Metabolomics, held annually from 2013 to 2018. Determination of mitochondrial bioenergetics using the Seahorse platform provides an important technical resource for individual users as well as training in the use of this instrument. Innovations in the use of novel starting material for these measurements allow new opportunities to explore these measurements in archival material (2). As part of its educational mission, this core has offered a Mitochondrial Bioenergetics Workshop that provided real-world examples of the use of this technology as well as sessions dedicated to instruction on the use of the Seahorse instrument. The Biostatistical Resource is directed by Dr. Gary R. Cutter and codirected by Dr. Orlando Gutierrez, both at UAB. It provides statistical support to the

Table 7. Core workshops and symposia

Workshop/Symposium	Description	Details
Centerwide		
Annual Renal Symposium	Held in collaboration with the UAB Childhood Cystic Kidney Disease Core Center at UAB, this symposium presents basic and translational research on AKI and polycystic kidney disease. This symposium also includes the Dr. James Schaffer Lecture which honors his contribution to enhancing understanding of renal physiology.	Held on World Kidney Day. The 2020 and 2021 symposia were conducted virtually.
Annual AKI Symposium	Held in conjunction with the annual International CRRT meeting in San Diego, CA, this symposium covers several topics in basic science, translational, and clinical aspects of AKI. Video recordings of presentations are freely available on our website. Proceedings are published each year in <i>Nephron</i> .	Usually held in February with registration in concert with the International CRRT meeting. The 2021 symposium was held virtually.
Core A		
Workshop on Healthcare Data Analytics	This hands-on workshop helps investigators gain new knowledge and experience in conducting research using the increasingly available public and private biomedical data resources using robust methodologies.	Registration is limited to 10 participants. The workshop is usually held in January.
Core B		
Rodent Kidney Physiology/Injury Workshop	Held at UCSD, this program includes faculty from UCSD and UAB and is designed to provide hands-on practice in animal handling and phenotyping techniques for commonly used methods to study kidney function in rodents.	Limited to 9 participants for the maximum interaction and time for training. This workshop is usually held in the spring.
Flow Cytometry Workshop	Held at UAB, this program provides hands-on instruction on the use of flow cytometry to analyze cells from tissues and cell culture and includes instruction on the preparation of samples, selection of fluorophores, and analysis using FlowJo software.	Registration is limited to 6 individuals to allow for hands-on training with the FACS machine. Held as needed, this workshop has been held in early summer.
Core C		
Workshop on Metabolomics	Held in conjunction with the Targeted Metabolomics and Proteomics Laboratory led by Dr. Barnes, this workshop provides instruction and hands-on experience with metabolomic investigation.	Offered as needed
Mitochondrial Bioenergetics Workshop	Held in collaboration with Seahorse Bioscience and led by Dr. Daley-USmar, this workshop provides real-world examples and instruction on the use of Seahorse technology.	Offered as needed

AKI, acute kidney injury; ICU, intensive care unit; UAB, University of Alabama at Birmingham; UCSD, University of California-San Diego; CRRT, Continuous Renal Replacement Therapy.

research projects, pilot projects, and other Cores in the UAB-UCSD O'Brien Center with expertise for the planning, design, data management, and analysis of their research projects and specific expertise in clinical trials and epidemiological studies. This resource is available to the entire research investigator base, but it is particularly helpful to new investigators who are initiating projects. Pilot project applicants are particularly encouraged to discuss their projects with the biostatistical resource before submission for competitive funding. The support of this core from development to completion of research ensures a robust approach and analysis to all these studies of AKI.

The Pilot and Feasibility Grants Program is overseen by Dr. Paul W. Sanders at UAB and is offered across the investigator base to elicit novel research in AKI by new investigators around the nation. This program provides the intellectual resources and the research infrastructure to attract new and established investigators to AKI research. A Request For Applications is announced annually on our website and to members of the investigator base. Three to four pilot projects are provided seed funding to develop novel projects in AKI research (Table 6). All pilot awards are considered mentored projects, and even the senior investigators who are transitioning into AKI research are assigned an appropriate advisor who has interests in AKI. Pilot award recipients present their findings at quarterly video conferences.

As part of this program, access to the biostatistical resource ensures well-designed and robust studies. In addition to this funding, a catalyst program provides vouchers to highly meritorious applications that were not selected for full funding. This voucher program, which has supported 50 unique investigators to date, provides seed funding specifically for the use of core facilities, with the overall goal of catalyzing and encouraging continued advancement of these projects to facilitate garnering additional external funding in the future. Since its inception, the Pilot and Feasibility Grants program has supported 27 investigators (14 physician scientists and 13 PhD scientists) that include promising young investigators. Of these, 21 investigators (78%) are also new to AKI research and 83% have remained in kidney-related research. These pilot awards are given to investigators at UAB and UCSD as well as those in the extended research base. Since 2015, ~1/3 of investigators have been from outside UAB/UCSD, with the remaining approximately split across these primary institutions. For every dollar invested, the return on investment of these funds has been estimated at \$37.

The Enrichment Program, directed by Dr. Lisa M. Curtis at UAB with oversight by Dr. Joachim H. Ix at UCSD, includes cross-cutting initiatives to enhance collaborations, educate the research investigator base regarding unique technical approaches, and provide training for investigators throughout the workforce pipeline (Fig. 2). In addition to independ-

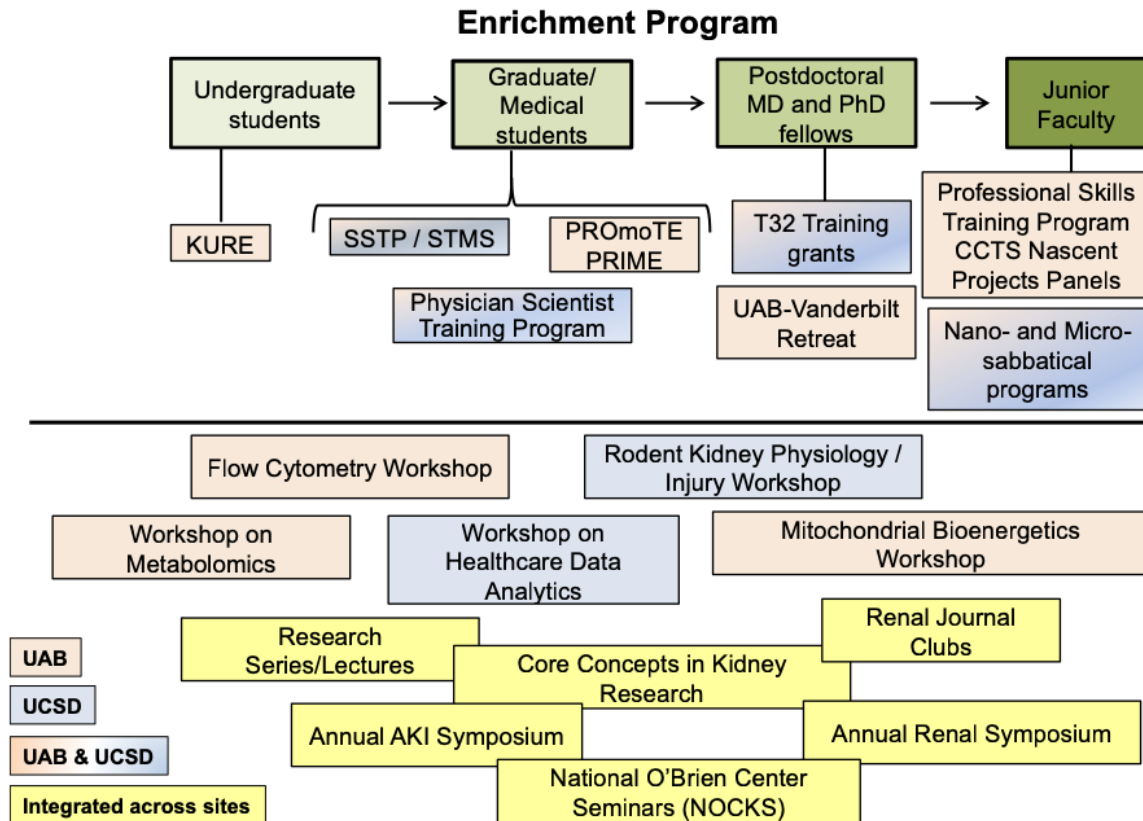


Figure 2. Enrichment program integration between the University of Alabama at Birmingham (UAB) and University of California-San Diego (UCSD). Training opportunities are provided across the range of levels from undergraduate students to postgraduate trainees to junior faculty at both UCSD and UAB as indicated by the coloring. These offerings are available to all research base investigators to foster development of renal scientists and enhance the retention of these individuals in the workforce pipeline, thereby increasing the numbers of individuals performing cutting-edge research in acute kidney injury (AKI). KURE, Kidney Undergraduate Research Experience; PRoMoTE, Predoctoral PhD and MD Research Training in Teams; PRIME, Predoctoral Interdisciplinary Training in Renal Physiology and Medicine.

Table 8. Pilot and Feasibility Program accomplishments (2007–present)*

	2007	2012	2013	2017	2018	Present
Pilot and feasibility investigators		12† (16 awards)		9† (12 awards)		7† (11 awards)
Young investigators, %		75		83.3		85.7
Investigators remaining in kidney-related research(since 2008), %		66.7		91.3		91.3
Subsequent extramural funding success (since 2008), %		63.2		66.7		66.7
O'Brien catalyst awards		9 (8 investigators)		35 (31 investigators)		21 (21 investigators)

*A list of the awardees and their project titles is provided at our website (<https://www.uab.edu/medicine/obriencenter/pilots/grant-recipients>). †Some recipients received a second year of support.

ent initiatives by each core (see Table 7), the Enrichment Program leverages offerings at each institution to provide cohesive value to the investigator base and integrates the center through cross-center offerings. Weekly Research Series/Lectures at both UCSD and UAB are used to incorporate discussions of AKI research and clinical care. These include traditional renal grand rounds as well as stand-alone seminar series that routinely serve 50–85 participants at each seminar and receive high satisfaction scores. In addition, journal clubs focused on kidney physiology and pathophysiology are conducted to enhance the training of students. The Core Concepts in Kidney Research, initiated and developed by Dr. Lisa M. Curtis at UAB, is an 8-wk seminar series that is conducted in late spring and cross-links clinical care and research initiatives in a broad discussion, often using tandem presentations by clinical and research faculty. Routinely, this latter offering reaches 80–90 participants at each session and routinely receives very positive evaluations (>90% positive measures). Each of these entities uses evaluations to rate the success of the programs and to improve and revise them. The recently started National O'Brien Centers Kidney Seminars (NOCKS) provide an additional opportunity for dissemination of research findings and core capabilities across each of the O'Brien Centers around the United States. These seminars are advertised to our investigator base to encourage a greater understanding of resources available to them.

To enhance education center-wide, two symposia are held annually (Table 7). The annual AKI Symposium, now in its 11th year, is held in San Diego, CA, in conjunction with the annual International Continuous Renal Replacement Therapy (CRRT) meeting and focuses on advances in AKI research and clinical care. An annual Renal Symposium is held at UAB in conjunction with the Childhood Cystic Kidney Disease Core Center at UAB (Dr. Brad Yoder, Principal Investigator), a NIDDK-funded center that has a strong focus on cystic kidney disease. This symposium draws the investigator base together with onsite or virtual interfaces and allows for the dissemination of findings obtained through the resources provided by the center. Both opportunities are widely advertised and promoted among our investigator base.

A unique offering that can be used for any of the core activities is the Sabbatical Program, which allows investigators to focus on enhancing expertise by engaging in an on-site short-term instruction. These are offered as nanosabbaticals (1–2 days) and microsabbaticals (1–2 wk) depending on the time allotted to this training. Formal NIH-funded

training programs in AKI research are available at all levels of the workforce pipeline, from undergraduate, graduate, and medical students to established investigators at both primary institutions. These include summer research programs for graduate and medical students and training grant opportunities for graduate students and postdoctoral fellows. Although these programs are not housed within our O'Brien Center, they nonetheless leverage offerings at UCSD and UAB and are used to expand the reach of our O'Brien Center. A summer student supplemental program supports six to eight first-year medical students each summer, with three to four students at UCSD and UAB, respectively. In addition, a biannual 1-day retreat and 1-half-day research retreat are held between our O'Brien Center and the Vanderbilt O'Brien Center allowing trainees and junior investigators to present their work.

ACCOMPLISHMENTS

The accomplishments of the UAB-UCSD O'Brien Center include 1) serving as a vital catalyst in AKI research nationally, 2) disseminating research accomplishments of the investigator base, and 3) sharing data and resources to advance the understanding and management of AKI.

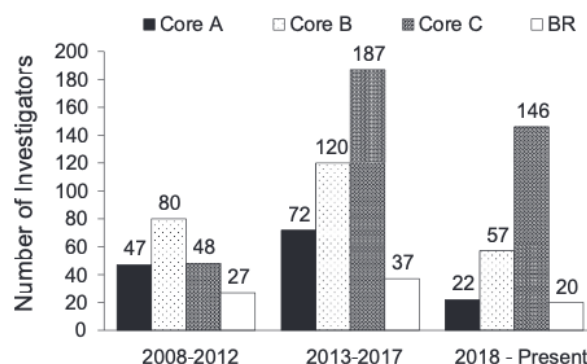


Figure 3. Utilization of the University of Alabama at Birmingham-University of California-San Diego O'Brien Center for Acute Kidney Injury Research Core Facilities. Core utilization has increased since 2008, demonstrating the relevance of these resources as well as the innovative approach to meeting the needs of the research base. The bars on the left and middle represent activity over 5-yr spans, whereas the bars on the right reflect usage in 3 yr, including 2020, when the COVID-19 pandemic resulted in shutdown at our institutions during the months of March to June. Core A, Clinical Studies of AKI Core; Core B, Preclinical Studies of AKI Core; Core C, Bioanalytical Core; BR, Biostatistical Resource.

Serve as a Vital Catalyst in AKI Research Nationally

The UAB-UCSD O'Brien Center has galvanized UAB and UCSD investigators around the study of AKI, raising the prominence of kidney-related research at our institutions, garnering the support and enthusiasm of the universities' leadership, fostering new collaborative interactions, and developing junior investigators via the pilot grants program (Table 8). The center has also catalyzed recruitment efforts and promoted research progress through its Biomedical Core Resources. These efforts have attracted new investigators to AKI research. The use of the UAB-UCSD O'Brien Center cores has grown extensively (Fig. 3) and, in turn, has facilitated new extramural funding. Over the 12+ years since the inception of the UAB-UCSD O'Brien Center, the leadership structure has been stable providing continuity and consistency while continually being responsive to the evolving needs of the investigator base. Importantly, the investigator base in 2020 has grown to include a total of more than 200 investigators, including an extended investigator base that provides support to nearly 100 investigators around the United States.

Disseminate Research Accomplishments of the Investigator Base

Investigators have used the core services and published several high-impact papers, including in the *American Journal of Physiology-Renal Physiology* among others (*Nature Medicine, Journal of Clinical Investigation, Kidney International, and Journal of the American Society of Nephrology*) (Table 9); a few are highlighted in the references (3–85), and a listing of all publications from our center is available on our website (<https://www.uab.edu/medicine/obriencenter/publications>). Research facilitated by the UAB-UCSD O'Brien Center has been presented at multiple scientific meetings, including at the annual meetings of the American Society of Nephrology and Experimental Biology. Notably, since 2008, over 500 papers have been published using the UAB-UCSD O'Brien Center Cores and/or Pilot/Enrichment support as of March 1, 2021. According to iCite (<https://icite.od.nih.gov/>), the average relative citation ratio (RCR) for our O'Brien Center publications is 2.18 ± 0.12 , with a median of 1.29 and a maximum of 27.86 (as of March 1,

Table 9. Major advances by our O'Brien Center

AKI in the ICU/Transplant Setting	
AKI Registry	Center members (Drs. Mehta, Tolwani, Cerda, Bouchard, and others) used Core A to develop a unique resource for well-phenotyped patients with AKI in a prospective multicenter, international registry of patients with AKI in the ICU. Biological samples are being collected on all patients developing AKI daily until recovery or discharge/death at UAB and UCSD sites.
CRRT	Center investigator Dr. Tolwani at UAB has provided new insights into the development and standardization of citrate as an anticoagulant in CRRT. This work was awarded a United States patent (US patent no. 8147698 B2) and has been licensed to Baxter worldwide.
Biorepository of human kidney tissues with AKI and healthy controls	Center investigator Dr. Roslyn Mannon and Dr. Michael Seifert have obtained >60 human kidney biopsies from heart beating deceased donors before implantation in addition to blood and urine samples from these donors. >65% of these biopsies display features of AKI and represent an innovative approach for obtaining human tissue to study AKI.
Global Snapshot of Kidney Disease in SARS-COV2 patients	Center members (Drs. Mehta, Macedo, and others) developed a new database customizing the CDC EPI-Info app for an ongoing international multicenter cohort of patients with AKI, chronic kidney disease, transplant, and end-stage kidney disease hospitalized with COVID-19 infection. This global registry will provide investigators with a unique resource for benchmarking epidemiology and outcomes of kidney disease in COVID-19.
Renal vascular dysfunction and hemodynamic alterations	
Molecular ultrasound imaging	Center investigators Drs. Hoyt, Warram, and Agarwal developed a novel ultrasound imaging technique for monitoring early inflammatory changes in AKI using P-selectin and VCAM-1 targeted microbubbles for Core B.
Intravital imaging	Center investigators Drs. Yoder, George, and Mrug, with the assistance of Core B, developed an intravital imaging system using an optical window to study vascular and tubular changes after AKI in live mice.
Computational modeling	Center investigators Dr. Vallon and Dr. Anita Layton (Duke University) are using computational modeling techniques and animal experiments to gain new insights into novel pathways in the pathogenesis of AKI and other kidney diseases (5R01DK106102, Principal Investigator: A. Layton).
Renal inflammation in ventilator-induced lung injury	Center investigators Dr. Singh and Dr. Crotty-Alexander at UCSD used Core B and demonstrated that ventilator-induced lung injury alters renal expression of vascular endothelial growth factor, VCAM-1, and angiotensin-2 in sepsis models.
Biomarkers	
Neonatal AKI	Center investigator Dr. Askenazi has demonstrated the significant negative outcomes in neonates with AKI using biomarkers analyzed by Core C. He has a National Institutes of Health multicenter planning grant to study sequelae of AKI in the neonatal ICU (U34DK117435).
Mass spectrometry- based imaging	Center investigator Dr. Kabarowski has optimized mass spectrometry imaging in kidney sections coupled with sequential window acquisition of all theoretical spectra-lipidomics to identify the role of lipids in AKI for Core C investigators.
Genetic susceptibility	
Drug-Induced Renal Injury Consortium	Center members (Drs. Awdishu, Mehta, Tolwani, and others) studied the genetics of drug-induced AKI and identified a rare variant, rs 117992092, on the MHC class 2 region of northern Europeans that associates with vancomycin nephrotoxicity.

AKI, acute kidney injury; ICU, intensive care unit; UAB, University of Alabama at Birmingham; UCSD, University of California-San Diego; VCAM-1, vascular cell adhesion molecule-1; MHC, major histocompatibility complex.

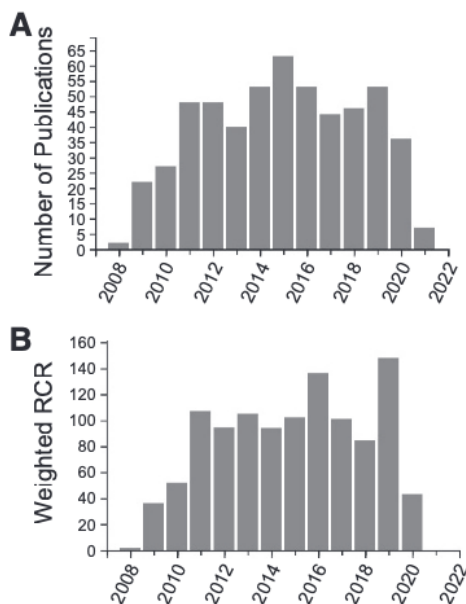


Figure 4. Publication metrics for the University of Alabama at Birmingham-University of California-San Diego O'Brien Center for Acute Kidney Injury Research (UAB-UCSD O'Brien Center). **A:** publications citing the UAB-UCSD O'Brien Center. These absolute numbers of publications indicate the productive impact of the Center. These publications have appeared in high-impact journals, including the *American Journal of Physiology-Renal Physiology*, *Nature Medicine*, *Science*, *Journal of Clinical Investigation*, *Journal of the American Society of Nephrology*, *Clinical Journal of the American Society of Nephrology*, *American Journal of Pathology*, *Journal of Biological Chemistry*, *Kidney International*, and others. **B:** weighted relative citation ratio (RCR) for center publications. Data were obtained from iCite [National Institutes of Health (NIH) Office of Portfolio Analysis]. To measure the impact of the publications from our center, we used the iCite tool from the NIH Office of Portfolio Analysis. This tool uses the RCR, which represents a citation-based measure of the scientific influence of articles. It is calculated as the cites/year of each paper, normalized to the citations per year received by NIH-funded papers in the same field and year. A paper with an RCR of 1.0 has received the same number of cites/year as the average NIH-funded paper in its field, whereas a paper with an RCR of 2.0 has received twice as many cites/year as the average NIH-funded paper in its field.

2021) for our O'Brien Center publications (Fig. 4). This RCR indicates a significant impact compared with other NIH-funded papers in the field. A paper with an RCR of 1.0 has the same number of cites/year as the average NIH-funded paper in its field, whereas a paper with an RCR of 2.0 has twice as many cites/year as the average NIH-funded paper in its field. The weighted RCR, which represents the sum of the RCRs for the articles in the group, was 1,104.33 for papers citing our O'Brien Center (as of March 1, 2021). A highly influential set of articles will have a higher weighted RCR than total publications, whereas a set of articles with below average influence will have a lower weighted RCR than total publications (<https://icite.od.nih.gov/>).

Share Data and Resources to Advance the Understanding and Management of AKI

Research data generated by the UAB-UCSD O'Brien Center are available upon request to any member of our existing and any newly added investigator for noncommercial research uses. For investigators outside the research investigator base of the UAB-UCSD O'Brien Center, data are shared as

requested with any investigator or entity after appropriate assurances from the investigator and their institution that data will be used in a compliant manner as required by the NIH and federal entities. For human or animal subjects, all federally required assurances are requested and documented. Material transfers are made with no more restrictive terms than the Simple Letter Agreement (MTA) and any patented IP is widely available to the community in accordance with NIH guidelines. New techniques and methods are disseminated through the center's website and newsletters as well as in publications. After the conclusion of funding, we will adhere to the NIH Grants Policy on Sharing of Unique Research Resources, including making biological samples available to the NIDDK Biorepository, which may include urine, serum/plasma, tissue, or DNA.

INNOVATION

Innovations continue to be developed in technical and infrastructural aspects and frequently occur in response to the needs of the research investigator base.

Technical Innovations

Using competitive institutional funding at UAB, the UAB-UCSD O'Brien Center was able to renovate space and install a Bubble Room, a biological isolation room that is designed to permit surgical procedures on animals without the need to quarantine. The Bubble Room allows animals to be directly received for surgical procedures with a seamless return after recovery to the requesting investigator's institution for subsequent studies. Thus, investigators can send their unique animals for surgeries at the UAB Small Animal Microsurgical Facility of Core B. For experiments that involve clamping of the renal pedicle, we have found that the force applied by the clamp is an important cause of experimental variability in ischemia-reperfusion injury, particularly if the clamp is reused. We have therefore developed a quick and reliable method to determine the force applied by the clamp. This information is documented and tracked within the Small Animal Microsurgical Core Facility.

To enhance rigor and reproducibility and as a result of our quality control efforts, we have identified that different brands of plastics used can impact outcomes as protein adherence to the plastics can vary, particularly when analyzing small amounts of biological samples. In addition, not all antibodies to the same protein have the same affinity or specificity. Once an immunochemical reagent is used, the reagent is not changed without strong rationale and sufficient testing to ensure validity. For any set of samples that will require multiple gels or tubes, care is taken to use the same batch or lot to minimize variation at that level of analysis. All relevant information that is used in quality control, including vendors, brands, type of plastic, etc., is documented in the facility, and the information is available to investigators. To improve consistency in experimentation, the cores recommend and offer processing of samples or dissecting out the organ or tissue within the facility.

We have developed a web-based database that is accessible worldwide and is modular in nature to enable investigators to pursue AKI studies in different settings. The

database provides a systematic set of variables covering different aspects of AKI, for example, postcardiac surgery, intensive care unit, transplant, or contrast, that can be customized for individual research protocols and can additionally track biological samples. More recently, we have developed tools for direct extraction of data variables from the Epic electronic health record to populate case report forms, thereby reducing time spent by research coordinators to enter data. With the COVID-19 registry project, we have leveraged the CDC EPI Info database for a customized AKI data set for cloud-based data capture using cell phone technology. These enhancements further facilitate data acquisition for observational and interventional studies in AKI.

Infrastructural Innovations

In furtherance of a focus on patient care, a new patient advisory group was initiated to create opportunities for thoughtful communication and education strategies for patient groups. Likewise, a desire to broaden integration in research areas resulted in increased partnerships with industry, who have reached out to elicit our significant expertise in animal model generation as well as our bioanalytical methods. Such collaboration with industry has resulted in Small Business Innovation Research (SBIR)/Small Business Technology Transfer (STTR) grants. The combined thematic approach continues to facilitate AKI-related research at UAB and UCSD and beyond and allows for translational studies to be accomplished.

The intent of the UAB-UCSD O'Brien Center is to provide comprehensive support to investigators at every level, to foster development of entry-level investigators to support novel and innovative research programs, and to encourage the development of new lines of investigation by more experienced investigators, all in the support of AKI research and closely related diseases. The technical expertise and education infrastructure provide the tools, knowledge, and experienced technical support to advance AKI research in all facets from basic science exploration to clinical research in traditional and underserved populations and to innovations in the practice of clinical care of patients with AKI. The UAB-UCSD O'Brien Center has used the technology and tools of the cores along with the Pilot Grants Program and Enrichment Program to build a vibrant, interactive, interdisciplinary community of investigators facilitating fundamental and translational sciences related to AKI research. Unanticipated synergies and collaborations have emerged from the interactive and interdisciplinary faculty, which has been fostered by our center through its resources. Through this synergy of exploration, leveraging the strengths of UAB and UCSD, this O'Brien Center stands ready to push the frontiers of AKI research.

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DISCLOSURES

A.A. serves on the medical advisory boards of Akebia, Alpha Young LLC, Angion, Reata, and Dynamed; he also serves on the medical advisory board and has stock options for Goldilocks Therapeutics. R.L.M. has provided the following disclosures: consulting for Baxter, AM Pharma, Sanofi, Akebia, Intercept, Mallinckrodt, Biomerieux, Sphingotec, GE Healthcare, Indalo, and CHF solutions.

AUTHOR CONTRIBUTIONS

L.M.C. conceived and designed research; L.M.C. prepared figures; L.M.C. drafted manuscript; L.M.C., J.G., V.V., S.B., V.D.-U., S.V., G.R.C., O.M.G., M.S., J.H.I., R.L.M., P.W.S., and A.A. edited and revised manuscript; L.M.C., J.G., V.V., S.B., V.D.-U., S.V., G.R.C., O.M.G., M.S., J.H.I., R.L.M., P.W.S., and A.A. approved final version of manuscript.

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