THE ROCKEFELLER UNIVERSITY HOSPITAL
CENTER FOR CLINICAL AND TRANSLATIONAL SCIENCE

Summer 2020

Center for Clinical and Translational Science
e-Newsletter

Center News

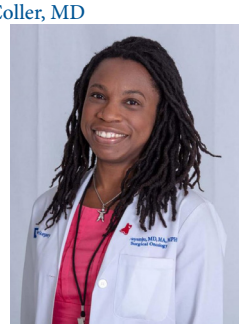
The Rockefeller University Hospital, IRB, and Center for Clinical and Translational Science All-Hands-On-Deck Response to the COVID-19 Pandemic

By Barry Coller, MD

In response to the COVID-19 pandemic, all members of the Rockefeller University clinical research enterprise came together to re-engineer processes and procedures to support exciting clinical and translational research to both better understand the nature of the infection and develop effective therapies. In this issue of the CCTS eNewsletter, articles highlight the efforts by the Research Facilitation Office, the Nursing Department, and the IRB, but every program and department participated in a heroic effort to keep the Hospital open and functioning, despite the closure of the University, during the height of the pandemic in New York City. This made it possible to arrange for the visits and blood collection from approximately 160 volunteers who recovered from COVID-19 as part of Michel Nussenzweig's lab's important project to isolate B lymphocyte cells making broadly neutralizing antibodies to SARS-CoV-2 for therapeutic development. Dr. Christian Gaebler, a Clinical Scholar in Dr. Nussenzweig's lab, describes his role in the research in an article in this eNewsletter as well. The success of that project is a tribute to the dedication and bravery of the entire staff.

Oluwadamilola "Lola" Fayanju, MD Leads Off Seminars in Clinical Research Initiative Focusing on Health Disparities

By Barry Coller, MD



Oluwadamilola "Lola" Fayanju

Dr. Oluwadamilola "Lola" Fayanju, Assistant Professor of Surgery, Division of Surgical Oncology at Duke University delivered the first in a series of seminars on health disparities on August 3rd, entitled *Beyond Us and Them: Eliminating Disparities among our Patients and the Doctors Who Treat Them*. Dr. Fayanju serves as Associate Director, Disparities and Value in Healthcare, Duke Forge, and Director of the Breast Clinic at the Durham Veteran's Administration Medical Center. Her presentation focused on the impact of race on health and her rigorous scholarship on the complex relationship between race and socioeconomic status on participation in surgical studies of breast cancer treatment. Dr. Fayanju's publications span the fields of basic advances in breast cancer therapy, health disparities, and population health. Her 2019 commentary in the Journal of the American Medical Association, *Hiding in Plain Sight*, recounts her experience as a woman physician of color and her penetrating insights call attention to the challenges we face as a nation in addressing systemic racism. Dr. Fayanju trained in the Duke CTSA KL2 program and now is pursuing her studies under an NIH K08 grant. She has received many honors and is currently a National Academy of Medicine (NAM) Emerging Leaders in Health and Medicine (ELHM) Scholar. The next speaker in the series will be Dr. Chibuzo Enemchukwu, a graduate of the Rockefeller University Center for Clinical and Translational Science Clinical Scholars program, whose research focuses on the use of pre-exposure prophylactic therapy of HIV in vulnerable, at-risk populations

$2.7M Award to Streamline Collecting Participant Feedback and Drive Improvement to the Clinical Research Enterprise

By. Rhonda G. Kost, MD

In May, the National Center for Accelerating Clinical Translational Science (NCATS) granted a $2.7 Million award to Rockefeller University to develop new infrastructure facilitating collection of research participant feedback for widespread adoption: **"Empowering the Participant Voice: Collaborative Infrastructure and Validated Tools for Collecting Participant Feedback to Improve the Clinical Research Enterprise (PAR-19-099, 1-U01-TR003206)**. Principal investigator Dr. Rhonda G. Kost, Associate Professor in the Center for Clinical Translational Science (CCTS), will lead a 6-site collaboration to leverage the Rockefeller-developed Research Participant Perception Survey (RPPS) into a new low-friction informatics and analysis platform to support rapid collection of actionable participant feedback. Dr. Roger Vaughan, head of biostatistics at the Rockefeller CCTS, will collaborate on analysis methods and program evaluation. Collaborating CTSA hubs for this award are Vanderbilt University, Johns Hopkins, Duke, University of Rochester, and Wake Forest University.

Why survey participants?

Partnering with patients and research participants, including those from communities disproportionately affected by health disparities, is essential to conducting clinical translational research.

continued on Page 16

The Clinical and Translational Research Facilitation Office Support of Rockefeller COVID-19 Research

By Donna Brassil, MA, RN, CCRC

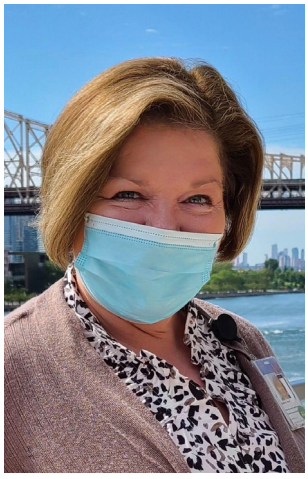
The Clinical and Translational Research Facilitation Office (CTRFO) supported the development and operationalization of COVID studies under conditions of University closure. We assisted numerous investigators in developing both clinical and basic human research protocols and helped to guide them through rapid Advisory Committee for Clinical and Translational Science (ACCTS) and Institutional Review Board (IRB) reviews. We would like to highlight two of these studies.

Arlene Hurley, MA, ANP-BC, CCRC conducted Protocol Development Navigation of Davide Robbiani's study, Peripheral Blood of Coronavirus Survivors to Identify Virus-Neutralizing Antibodies. This COVID-related study was the one that saw the most participants on campus during the University closure. Christian Gaebler, MD, a 3rd year Clinical Scholar, is the Principal Investigator of this study. There have been many study amendments since initial approval which have included the addition of 15 RU investigators from additional Labs on campus to share data and samples. To meet the enrollment goals of the study team, the four Facilitators joined the research team to participate in study implementation and conduct of this study by remote screening of the prescreened volunteers, and to conduct telephone consenting. We were assigned to contact 193 potential participants for remote screening, which included obtaining a medical history, including COVID-19 symptoms. We also obtained telephone consent and collectively conducted 63 of the 166 participant visits to Rockefeller University Hospital for the study (~38% of the screening visits). Arlene coordinated the study by preparing the medical records for each participant's outpatient visit, coordinating with the Nursing Department on projected participant enrollment to ensure an adequate supply of equipment needed to collect the research samples, and arranging for campus parking for the study participants through coordination with the Hospital Facilities Specialist and University Security Department. Arlene performed internal monitoring of the 166 enrolled participants' medical records, including monitoring data regarding the participants' permission to share their research samples. This information was provided to Technology Transfer Office and Office of General Counsel to aid in their completion of a Material Transfer Agreement between the Nussenzweig Lab and a start-up company developing a Neutralizing Antibody assay.

The CTRFO Facilitators also guided Ohad Bentur, MD, a 3rd year Clinical Scholar in Dr. Coller's Lab, through the Translational Navigation Process to rapidly develop and implement his study, Phase I Randomized Double Blind Placebo Controlled, Single-Dose, Dose Escalation Study to Evaluate the Safety, Tolerability, and Pharmacokinetics of Orally Inhaled Hydroxychloroquine Sulfate in Healthy Adult Volunteers. The time period from the initiation of Protocol Development Navigation to ACCTS/IRB approval and FDA review was less than 2 months, which is extraordinary for a Phase I study. Numerous experts within the Center for Clinical and Translational Science (CCTS), Hospital, and University participated in this Navigation process. IRB approval was granted on June 20th, the first participant was screened on June 24th, and enrollment was completed on August 10th. Richard Hutt, RN, BA, CCRC is coordinating this study, which includes strategizing goals with the sponsor, Pulmoquine Therapeutics, Inc., and the Contract Research Organization, Cliantha Research Ltd. Richard has been preparing for weekly external monitoring, which is being conducted virtually. This has necessitated the need for secure electronic platforms in which Richard has been uploading all source documents and essential regulatory documentation in addition to completing electronic Case Report Forms and answering data queries. Richard has also been performing Internal Monitoring. Dr. Bentur has been exemplary as Principal Investigator of this complex study, demonstrating outstanding team leadership.

Donna Brassil, MA, RN, CCRC

Arlene Hurley, MA, ANP-BC, CCRC



Kathleen Dowd, BSN, RN, CCRC

Richard Hutt, RN, BA, CCRC

Challenges of Staffing the Nursing Department During the COVID-19 Pandemic

By Rita K. Devine, RN, MPA

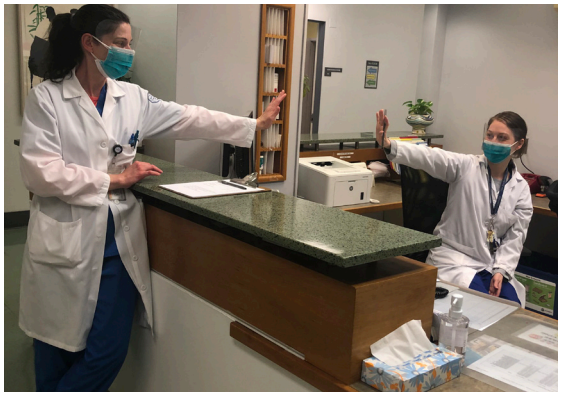
The great coach Vince Lombardi once said "Build for your team a feeling of oneness, of dependence upon one another and of strength to be derived by unity." The nursing staff of Rockefeller University Hospital has always worked as a team but the COVID pandemic and the requirements and restrictions that came with it presented new challenges to our very small team.

The urgency to start new COVID protocols did not allow the usual luxury of preparedness. Staffing, equipment, education and discussion seemed to happen overnight. Adhering to Rockefeller University Hospital's essential personnel policy required limited staff on site. Daily communication between the research teams was required to determine how many research participants would be scheduled in addition to the length and complexity of each visit. Precision communication among the nursing staff was required each day to determine the staffing required to maintain safe participant care and protocol demands, while adhering to our essential personnel only policy.

And everyone pitched in! Our largest study required obtaining half-a-pint of blood from each of more than 150 participants, so to scale up we needed to obtain samples from more than one participant at a time. When we realized that we did not have enough scales to measure the amount of blood being drawn, the Rockefeller University Hospital Bionutrition department loaned us their scales, along with the Krueger Lab, which also provided equipment to mix the blood with the anticoagulant as it was being drawn.

As New York City was hit hard by COVD-19, the nursing staff was also affected. Several staff members required quarantine and self-isolation and some could not return from abroad because of travel restrictions. Despite the limited availability of staff, all scheduled COVID-19- related study visits were completed as per the protocols. Several non-COVID studies could not be stopped because they required visits to assess the safety of already enrolled participants.

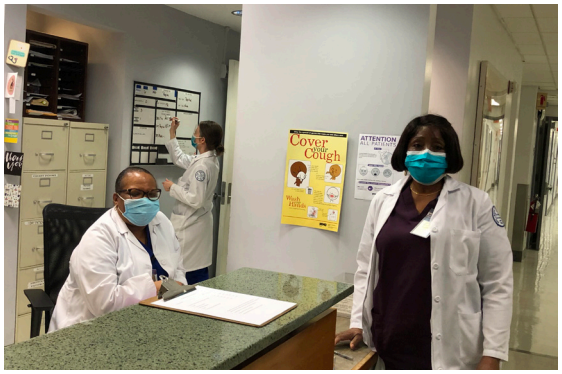
As the COVID pandemic in New York City evolves, we continue to function with the flexibility required to maintain equilibrium between safe care of the research participants and fidelity to the research protocols while adhering to requirements and restrictions as mandated from the University and New York City. The dedication of the nursing staff members, who bravely put their own health at risk in order to fulfill the University's mission and perform important studies to better understand and treat this terrible disease, reflects their professionalism, and is an inspiration for us all.



Kari Bovee CRN & Tia Gareau CRN

Micahel Dyer, Hospital Facilities Specialist

Jane Rodriguez CRN (OPU Charge Nurse) & Moz Murphy NA



Regina Butler CRN (IPU Charge Nurse), Tia Gareau CRN & Sonia Legister NA

Jill McCabe CRN, Nursing Clinical Operations Manager & Rita Devine MPA, R N, Director of Nursing & Patient Care Services

CRN - Clinical Research Nurse
IPU - Inpatient Unit
NA - Nursing Assistant
OPU - Outpatient Unit

Recruitment of Research Participants During the Height of the COVID-19 Pandemic

By. Rhonda G. Kost, MD

The Recruitment Core of the Clinical Research Support Office (CRSO) provided the strategy, services, and operations to support recruitment for COVID-19 studies at the Rockefeller University Hospital. In March, the first study was from the Laboratory of Molecular Immunology, led by Dr. Michel Nussenzweig, which required blood donations from individuals who recovered from COVID-19. An initial challenge in planning recruitment was the need for flexible eligibility criteria as the team sought to identify which clinical course (severe? moderate? asymptomatic?) might predict a strong immune response.

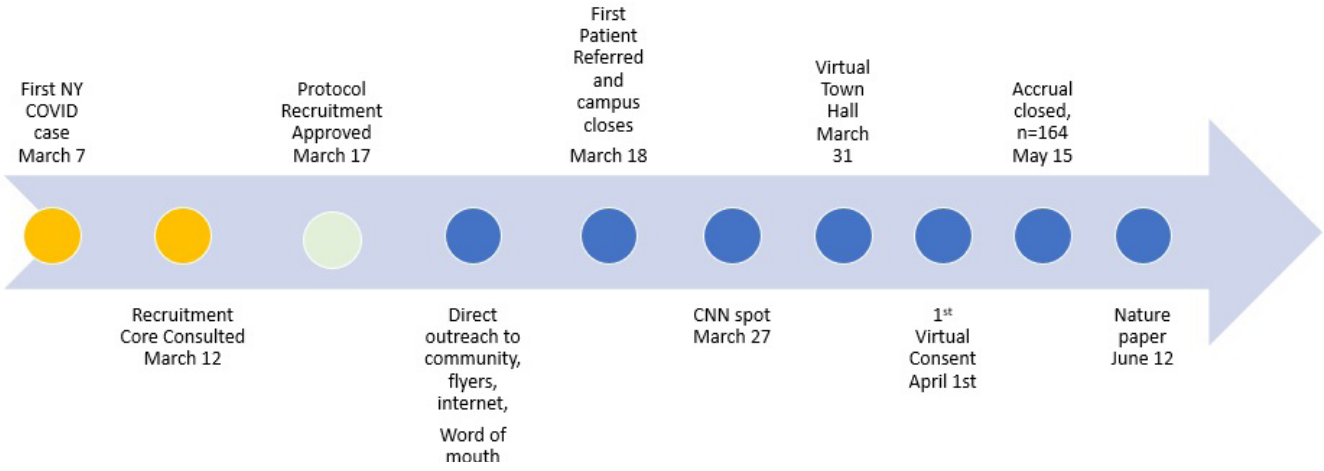
Recruitment specialist Kadija Fofana, MPH, drafted advertisements for social media, the internet, Rockefeller platforms, and hard copy distribution in communities that were affected early by the virus. Dr. Nussenzweig appeared on CNN, triggering inquiries from all over the country.

The research team hosted a Zoom Town Hall meeting to engage the index community of New Rochelle and many inquiries followed. Word of mouth was a powerful recruitment tool across communities and the study unearthed an enormous surge of altruism from people hoping to help find a treatment or cure for COVID-19. The geographic distribution of the more than 900 volunteers who responded and were pre-screened by the Recruitment core before referral to the Nussenzweig team for further screening spanned Westchester, the Bronx, Manhattan, Queens, Brooklyn, Long Island, New Jersey, and Connecticut. Volunteers were aged 18-80, with most in their 40-60s, and roughly balanced between the sexes. The Recruitment team creatively and rapidly built surge capacity to handle the call volume by training staff from other cores as pre-screeners. This required training in Human Subjects Protections and the scripts of recruitment and the Research Volunteer Repository, providing secure Zoom phone lines with Rockefeller caller id for remote workers, and creating REDCap intake forms and workflow to integrate with other applications. The surge capacity staff included: Lisa Sacerio, Sharon Adams, Maritza Sanchez, Robert Hanson, Andrea Ronning, Glenis George-Alexander, Dacia Vasquez, Kimberly Vasquez, Anthoneth Jeffrey, and Marlyn Appleton.

Driven by the CRSO leadership and the Hospital Information Technology (IT) group, with support from University IT, Office of General Counsel, and the IRB, new infrastructure was vetted and rapidly put into place to allow volunteers to self-prescreen through an online weblink hosted on a HIPAA-compliant, secure Amazon web Services/REDCap platform. This is one of multiple examples of the COVID-19 crisis accelerating the adoption of new processes. Hundreds of volunteers calling the 800RUCARES line and RUCARES elected to use the weblink and were able to quickly determine whether they were eligible, thus supplementing the hundreds of calls and conversations provided by the recruitment team. This platform opened the door for hosting other on-line activities requiring a HIPAA-compliant and secure platform.

In addition to the logistical challenges, pre-screening under COVID identified a number of additional issues: some individuals called seeking research enrollment as a means to obtain scarce COVID testing, some volunteers were eager to donate convalescent plasma for therapeutic purposes as well as participate in research and were concerned about the timing of contributing to multiple medical efforts, many callers were eager to recount their experience with COVID-19 infection in case the clinical history would help scientists, and some recounted a dramatic clinical course consistent with COVID but because of the lack of testing could not enroll. Ultimately, there were many more eligible responders than could be studied, a tribute to the desire of so many New Yorkers to come to the aid of others . Between March 17th and April 30th, approximately 1000 volunteers contacted the recruitment team through the RUCARES voicemail or email; more than 650 met initial prescreen eligibility, and about 160 were enrolled into the study.

The recruitment core also helped Clinical Scholar Dr. Ohad Bentur successfully accrue the 10 healthy volunteers needed for his Phase I study of inhaled aerosolized hydroxychloroquine. Recruitment for this study was readily achieved using campus advertising and the Research Volunteer Repository.



IRB Operations in the Time of COVID-19

By Vanessa Smith, MPS, CIP

The Rockefeller University Institutional Review Board (RU IRB) reviews the ethical suitability of all research investigations in the University that involve human participants. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects. This includes all proposals for research as well as ongoing or long-term clinical research protocols. The RU IRB meets in person monthly to review and to approve, modify, or disapprove all research projects involving human participants.

When the University began scaling down in-person operations on campus, the IRB Office responded by putting procedures in place to operate remotely under the skilled leadership of Thomas P. Sakmar, MD, Human Research Protection Program (HRPP) Director and Sarah J. Schlesinger, MD, IRB Chair. Working together, the IRB Office, Clinical Research Support Office, and Clinical Research Facilitation Office promptly issued guidance to the research community and IRB members to confirm HRPP operations would remain fully functional via remote procedures during the pandemic. To support the transition to remote procedures, IRB Specialists, Vanessa Smith, MPS, CIP and Dale Miller, BA, CIP reviewed guidance issued by the Office of Human Research Protections and Food and Drug Administration to become informed about recommendations for IRB review of research during the pandemic.

The Rockefeller University Institutional Review Board

Consultations were also had with industry experts to assist the HRPP in responding as flexibly as possible while observing applicable regulations.

The IRB Office continues to operate remotely and will do so for the duration of the pandemic to expeditiously review protocol submissions for current research and assist with any new COVID-19 related clinical protocols. As seen in the above photograph, monthly IRB meetings are being held via Zoom and will continue until guidance is issued that it is safe to resume these activities on campus. IRB Leadership and Staff continue to work in close liaison with the Clinical Research Support Office, Clinical Research Facilitation Office, Hospital Informatics, University IT, and many other key individuals within the HRPP to maintain open lines of communication. The IRB Office is sincerely grateful for the teamwork and dedication shown by all members of the Rockefeller Research Community to support the ethical conduct of research. We are also very thankful to our IRB members, many of whom have been members for over a decade, who responded kindly to efforts of IRB Staff to hold virtual meetings. As always our first responsibility is the protection of Human Research Participants, but closely following is our mandate to advance the University's research. The critical nature of this work is especially important now and it could not be done without the excellent teamwork and dedication of the Rockefeller Research Community

Update on Implementation of the Cerner Electronic Health Record at The Rockefeller University Hospital

By Prasanth Manukonda, MS, MA & Maija Neville Williams, MPH

The Rockefeller University Hospital is continuing implementation of Cerner CommunityWorks as our Electronic Health Record (EHR). Unfortunately, when the COVID-19 pandemic hit the nation in March, our go live date was pushed back from April 2020 to February 2021. Hospital staff are working diligently with Cerner during this difficult time, continuing departmental training and competency review in preparation for our next Integration Testing event. The goal of this event is to validate the solution build and additional integration points like Powerplan, Registration and Scheduling, Analytics, and integration of iRIS and Cerner.

One new feature we have been working on during the pandemic is the integration of laboratory tests from Memorial Sloan Kettering Cancer Center (MSKCC) and LabCorp. Once the system is live, we will be able to order labs from MSKCC and LabCorp through Cerner. We will also be ready for data sharing with Healthix, the New York Health Information Exchange, the national CTSA consortium, and other national data sharing initiatives.

Once Cerner CommunityWorks is fully implemented it will improve quality and efficiency internally, streamlining operations and promoting national patient safety initiatives. Below is the revised implementation schedule.

Event	Date
Project Kickoff	9/25/2019 (Completed)
Workflow and Integration	10/14/2019 (Completed)
Train the trainer	12/09/2019 (Completed)
Integration Testing 0.5	11/2/2020
Integration Testing 1	12/7/2020
Integration Testing 2	1/4/2021
Conversion	2/1/2021
Conversion Week 2	2/8/2021
Leadership Assessment	3/8/2021
Health Check	4/12/2021

Rockefeller Clinical Scholars to Evaluate New Interactive Web-based Individual Development Plan Platform

By Editorial Staff

An individual development plan (IDP) is a tool to assist trainees with establishing and achieving their career goals, both in the short and long term. By providing an opportunity for reflection and an analysis of one's strengths and weaknesses, as well as one's interests and aspirations, it can help build pathways to success and professional satisfaction.

The Clinical Scholars program has used the American Association for the Advancement of Science (AAAS) IDP. Since it was designed for use by postdoctoral fellows in the sciences, it does not address all of the topics and competencies of interest to Clinical Scholars. To address this shortcoming the Clinical Scholars program leadership has partnered with the University of Pittsburgh's Clinical and Translational Science Institute by participating in a cluster-randomized study they are leading comparing the AAAS IDP to the KL2 Customized Career Development Platform (CCDP) they have developed to assist Scholars in developing their careers. Unlike the AAAS IDP, which is a single questionnaire, the CDDP is an online platform that enables trainees to document competency-based goals, objectives, and milestones related to research and career progress. This allows the scholars to map out their career plans, generate timelines and Gantt charts, and communicate effectively with their mentoring teams to ultimately achieve their goals. Trainees, mentors, and program administrators have access to the interactive CCDP, thus serving as an efficient communication tool. Thus, the online format makes the CDDP a dynamic tool, enabling real-time accessibility for the Clinical Scholar to modify the CCDP as plans change. Scholars are currently enrolling in the CDDP and we look forward to their feedback and their mentors' feedback on using this exciting new educational tool.

Heilbrunn Family Center for Research Nursing Heilbrunn Scholar Symposium

By Bernadette 'Candy' Capili, PhD, NP-C

Each year, the Heilbrunn Family Center for Research Nursing hosts a symposium at Rockefeller University to showcase the research conducted by the Heilbrunn Nurse Scholar awardees. The Scholars meet virtual each month during their award period, but the symposium provides an opportunity for the Nurse Scholars to meet each other in person and share their research and professional development experiences.

Due to the COVID-19 pandemic, we held two separate virtual 2020 symposia on May 7 and May 21. Attendees included members of the Rockefeller University Hospital, Rockefeller nurses, nursing faculty from the Tri-State Area, Nurse Scholars' mentors, and the Nurse Scholars' study team members.

The topics for the symposium ranged from primary care provider burnout to aromatase inhibitor adherence. On May 7, Drs. Norful, Knisely, and Jennings-Mathis presented. Dr. Allison Norful, an assistant professor from Columbia University, discussed the impact of primary care providers (physicians, nurse practitioners, and physician assistants) co-managing patients with other clinicians on rates of burnout, job satisfaction, and intention to leave their current position. Results from her cross-sectional survey (n=333) showed that burnout was significantly associated with job satisfaction, and effective co-management of patients with a colleague reduced provider burnout.

Dr. Mitchell Knisely, an assistant professor at Duke University, discussed his on-going research characterizing the genetic pain profiles of participants with sickle cell disease. He is determining whether functional polymorphisms in candidate genes (i.e., IL-1B, IL-6, & TNF-α) are associated with pain subgroup membership. Dr. Karen Jennings-Mathis, an assistant professor at the University of Rhode Island, presented her on-going research to investigate the relationship between early-life adversity, adipokine status, dietary intake, and physical health among adults.

On May 21, 2020, Drs. Casida and Xavier and Ms. McCall presented. Dr. Jessie Casida, an Associate Professor at Johns Hopkins University, described the development of a self-care app for a left-ventricular assist device (LVAD). He aims to evaluate the effect of using the app on patients' self-efficacy, adherence to medical therapies, LVAD-related complications, and health care utilization. Dr. Rose Mary Xavier, an Assistant Professor at the University of North Carolina-Chapel Hill, discussed her work on leveraging novel tools from network science, bioinformatics, and integrating multiplex high-dimensional data types (genetics, imaging, cognitive, and symptom data). Her goal is to identify neuro-biologically informed psychosis and schizophrenia symptom profiles among adolescents. Ms. Maura McCall, a doctoral candidate from the University of Pittsburgh, discussed her project to identify temporal patterns and relationships of aromatase inhibitor (AI) adherence and symptoms among postmenopausal women with early-stage breast cancer. She will also explore the role of genotypic variation in temporal patterns and relationships for AI adherence and symptoms.

In closing, the discussions were robust and engaging. The virtual platform was well-received by nurse scholars and attendees.

CTSA Discussion Forum for Nurses in Translational Research

By Bernadette 'Candy' Capili, PhD, NP-C

In March 2020, Dr. Capili, Director of the Heilbrunn Family Center for Research Nursing, led the creation of a Discussion Forum (DF) for nurses in translational research, under the auspices of the CTSA Program Steering Committee. The purpose of the DF is to provide a mechanism for nurses at CTSAs to connect, communicate, and collaborate. The goals of the DF include discussing emerging topics related to translational nursing and addressing gaps in training and education by developing collaborative projects across CTSA hubs. Inaugural members of the group include Dr. Chris Kovner from New York University, Dr. Margaret Barton-Burke from Memorial Sloan Kettering, and Dr. Olga Jarrin-Montaner from Rutgers University.

Rockefeller Tops International Ranking of Scientific Research Publication Impact

The Rockefeller University website

The Centre for Science and Technology Studies Leiden rankings of over 1100 universities from 65 countries ranked Rockefeller number one, with the highest percentage of frequently cited scientific publications as a proportion of the total number of its publications. The Leiden Ranking's methodology accounts for differences between scientific fields in citation and collaboration practices. The Leiden group found that 33.3 percent of Rockefeller publications were among the top 10 percent most widely cited of all scientific publications during the time period studied, 2015 to 2018. Rockefeller was also ranked first when measuring the proportion of publications in the top one percent. In fact, 5.5 percent of Rockefeller publications were considered extremely high impact by this metric. The figure for the other institutions in the top-five group range from 4.3 to 3.3 percent.

All Sciences

	University	P	P(top 10%)	PP(top 10%)
1	Rockefeller Univ	933	311	33.3%
2	MIT	10563	2587	24.5%
3	Princeton Univ	5322	1256	23.6%
4	Stanford Univ	16161	3560	22.0%
5	Harvard Univ	33722	7268	21.6%

Biomedical and Health Sciences

	University	P	P(top 10%)	PP(top 10%)
1	Rockefeller Univ	788	270	34.3%
2	MIT	2196	668	30.4%
3	Princeton Univ	721	192	26.7%
4	Caltech	529	137	25.9%
5	Univ California - Berkeley	2240	488	21.8%

Re-imagining Biostatistical Education – A Combined Course in Critical Thinking, Biostatistics, Scientific Writing, Leadership and Team Science, and Rigor, Reproducibility, and Reporting (R3)

By Roger Vaughan, MS, DrPH

For over a decade, Rockefeller has taken a novel approach to biostatistical education in the Clinical Scholars program, by presenting information "from the driver's seat" perspective rather than through a traditional "bottom up" statistical approach. The biostatistics educational program is ready to pivot again, in content and approach, to acknowledge the simultaneous skill sets necessary to do great science.

CAPITALIZING ON COMPLEXITY

It is becoming increasingly clear that the hard and soft skills necessary to conceptualize, operationalize, design, manage, lead, analyze, communicate, and replicate – just a sampling of the skills sets necessary to interrogate a hypothesis, are not applied serially across the life of a project – they are spherical, you need them all, and all at once, at all phases of an investigation, and in a successful research career. The new approach to biostatistical education attempts to respect that reality. As a sphere, there is no "starting point", but we use the elements of biostatistics as a jumping in point, and an articulated hypothesis as a scaffold, through which we can develop, experience, and practice the other skills, including critical thinking, team science and leadership, principles of replicability, and clear reporting.

Rather than creating multiple discrete courses to attend to these related and critical skill sets, the re-imagined biostatistics course will employ some proven "flipped classroom" methodology to keep all elements alive as the course progresses. We will first ask the incoming Clinical Scholars to do some basic review over the summer to refresh them on the fundamentals of design and methodology. We will then do a three-day intensive concentrated review of the elements of the inferential method and the bases of statistical tests. At the conclusion of the review, each Scholar will articulate a hypothesis, perhaps one they came to Rockefeller to study, perhaps a practice placeholder. Using this hypothesis, we will then use an ongoing series of individual sessions to: take a deep dive into designs appropriate for their hypotheses; develop a suite of analytic tools necessary to interrogate their hypotheses; understand limitations and meaning of results; describe the results in a way suitable for the Peer Review process, Study Section, or oral communication. We will periodically convene as a group to present to each other our progress, new methodology, results, challenges, and next steps. These will also serve as mock Peer Review and Study Section sessions (better to get beaten up by friends…). Each step will be infused with principles of Rigor, Reproducibility and Team Science.

There are likely no better real world vehicles than following a manuscript through the Peer Review process, or shadowing a grant through the study section process, to practice, hone, and appreciate how important Team Science and Leadership skills are, how essential clear articulation and presentation skills are, and how rock solid methodology and critical thinking is, to advancing science. We are very excited about the upcoming year.

New Clinical Scholars Join the Center for Clinical and Translational Science

By Editorial Staff

On July 1, 2020 five new Clinical Scholars joined the Rockefeller University Clinical Scholars Program. They are Drs. Yelina Alvarez, Charlie Buffie, Katherine Knorr, Mira Patel, and Rashid Rumah.

New Scholar orientation takes place the first Wednesday in July. The orientation is usually in-person for the Scholars and the Clinical Scholars program leadership meet and get to know each other as the curriculum and goals for the Scholars are reviewed and discussed. This year's orientation was virtual to adhere to the social distancing requirements, but the engagement and interest in the program and for each other was just as interactive as past orientation. Please join us in welcoming the incoming Clinical Scholars.

Yelina Alvarez, MD, PhD
Mentors: Daniel Mucida, PhD
Laboratory: Laboratory of Mucosal Immunology

Research Interest: Dr. Yelina Alvarez's research focuses on understanding the mucosal immune system and how it communicates with the rest of the resident cells and microbiota and how dysfunctional interactions can lead to human diseases such as functional disorders and inflammatory bowel disease.

Bio: Dr. Alvarez received her MD and PhD from the New York University School of Medicine. She completed her internal medicine residency at New York University and gastroenterology fellowship at the Hospital of the University of Pennsylvania.

Charlie Buffie, MD, PhD
Mentors: Sean Brady, PhD
Laboratory: Laboratory of Genetically Encoded Small Molecules

Research Interest: Dr. Charlie Buffie uses a variety of in vitro screening approaches and animal model systems to elucidate the identity and function of genetically-encoded small molecules made by native intestinal bacterial populations, with special attention to the prevalence and abundance of these metabolites in human subjects.

Bio: Dr. Buffie received his PhD from Weill Cornell Graduate School and his MD from Weill Cornell Medical College. Dr. Buffie completed his internal medicine residency and is completing his Gastroenterology & Hepatology Fellowship at New York-Presbyterian Hospital/Weill Cornell Medicine.

Katherine Knorr, MD, PhD
Mentors: Jeffrey Ravetch, MD, PhD
Laboratory: Leonard Wagner Laboratory of Molecular Genetics and Immunology

Research Interest: Dr. Katherine Knorr's research focuses on research involves defining patterns of aberrant spliceosome protein snRNP500 expression on the surface of malignant myeloid cells. Expression of this protein correlates with durable responses after allogeneic stem cell transplantation in patients with acute myeloid leukemia and myelodysplastic syndrome. The proposed mechanism of response involves formation of antibodies against the snRNP500 protein.

Bio: Dr. Knorr received her MD and PhD from the University of Minnesota. Dr. Knorr completed her internal medicine residency at New York-Presbyterian Hospital/Weill Cornell Medicine and is completing her Oncology Fellowship at Memorial Sloan Ketterin gCancer Center.

continued on Page 9

New Clinical Scholars Join the Center for Clinical and Translational Science

By Editorial Staff

continued from Page 8

Mira Patel, MD
Mentor: Dr. Sohail Tavazoie
Laboratory: Elizabeth and Vincent Meyer Laboratory of Systems Cancer Biology

Research Interest: Dr. Mira Patel studies the role of immunosurveillance in mechanisms of cancer progression and metastasis, particularly as it relates to germline genetic variants that may predispose to metastatic disease.

Bio: Dr. Patel received her MD from Johns Hopkins University School of Medicine. Dr. Patel completed her Otolaryngology-Head and Neck Surgery at Washington University in St. Louis/ Barnes-Jewish Hospital and is completing her radiation oncology residency at Memorial Sloan Kettering Cancer Center.

Rashid Rumah, MD, PhD
Mentors: Vincent Fischetti, PhD
Laboratory: Laboratory of Bacterial Pathogenesis and Immunology

Research Interest: Dr. Rashid Rumah's research focuses on how the gut-brain axis contributes to serious neurological diseases of unknown origin, including multiple sclerosis (MS) and Sudden Infant Death Syndrome (SIDS).

Bio: Dr. Rumah received his MD from Weill Cornell Medical College and his PhD from the Rockefeller University.

CCTS Biostatistics Group Supports a Broad Range of Rockefeller Scholarship

By Roger Vaughan, MS, DrPH

The mission of the Rockefeller University Center for Clinical and Translational Science (CCTS) is to support high quality, translational science, and educate outstanding translational scientists in the Clinical Scholars program.

One of the outcome metrics of the research support is peer reviewed publications enabled by the CCTS. To that end, the CCTS Biostatistics Group, directed by Dr. Roger Vaughan, and including senior biostatistician Caroline Jiang and statistical programmer Neha Singh, have recently co-authored or been acknowledged on a series of important publications, as listed below, in high impact journals. While members of the biostatistics group may have been included or acknowledged, it took the entire CCTS Team to support each publication.

As part of its educational program, the Biostatistics group reinforces the importance of Team Science and emphasizes the value of including a methodologist as early as possible during research protocol development. This is coupled with a major emphasis on Rigor, Reproducibility, and Reporting (R3), a new CCTS initiative, to insure the integrity of the research and its reporting. It is gratifying, therefore, that so many of the papers have a current of former Clinical Scholar first authors.

Many of the collaborations between the Biostatistics group and investigators began as a result of revision requests from the peer review process, where reviewers rated the quality of the science as high, but had concerns about the analytic approach or methods. As data becomes more complex, as journals become more highly aware of reproducibility and validity issues, and as reviewers become more analytically sophisticated, it is increasingly important that the analytics be of the highest quality and follow the R3 principles.

The CCTS Biostatistics group remains eager to assist with grant and manuscript preparations, so please feel free to contact Dr. Vaughan at roger.vaughan@rockefeller.edu

Select publications:

Becher T, Palanisamy S, Kramer D, Eljalby M, Marx S, Wibmer A, Butler S, Jiang C, Vaughan R, Schöder H, Mark A and Cohen P. Brown adipose tissue is associated with improved cardiometabolic health in humans. Nature Medicine, 2020, in press.

Pressl C, Jiang C, Correa Da Rosa J, Friedrich M, Vaughan R, Freiwald W, Tobin J. Interrogating an ICD coded electronic health records database to characterize the epidemiology of prosopagnosia. J Clin Trans Sci., In Press.

Orange D, Yao V, Sawicka K, Fak J, Frank M, Parveen S, Blachere N,
Hale C, Zhang F, Raychaudhuri S, Troyanskaya O, Darnell R. RNA Identification of PRIME Cells
Predicting Rheumatoid Arthritis Flares. N Engl J Med 2020;383:218-28.

Khodursky S, Svetec N, Durkin S, Zhao L. The evolution of sex-biased gene expression in the Drosophila brain. Genome Res. gr.259069.119. Published in Advance June 18, 2020

Meet the Graduate: Tukisa D. Smith, MD, MS

By Editorial Staff

Tukisa Smith

Dr. Tukisa Smith joined the Clinical Scholars program at the Rockefeller University in 2018. Dr. Tukisa Smith received her M.D. from Saint Louis University and completed her internal medicine residency at SUNY Downstate. She completed her Allergy and Immunology fellowship at the Icahn School of Medicine at Mount Sinai and is a diplomate of the American Board of Allergy and Immunology.

Dr. Smith's interest in research peaked during her junior year in college. As a double major in business and science, while working as an Organic Chemistry teaching assistant, she realized that the laboratory environment was a welcome contrast from the business school, as it provided an exciting opportunity for exercising precision in experimental design and, execution. There were ritualistic aspects of maintaining a laboratory and the demand for perfection and order was appealing. Her interest in research was further developed when she prepared for experiments that related to the biochemistry of disease mechanism.

Since Dr. Smith was not a traditional premed or biology major, she was not aware of a career path in which one could become a researcher focused on disease mechanism. Given her deepened interest in research, she joined the NIH Postbaccalaureate Intramural Research Training program at Johns Hopkins in the Division of Infectious Diseases and matriculated into the graduate program in molecular biology with an emphasis in biotechnology. She had a natural knack at bioassay development and was fascinated with microorganism drug resistance mechanisms. She recalls her growing concern about the dangers of antibiotic resistance when she studied the minimal inhibitory concentrations of antibiotics for various bacterial strains isolated from patients. It was at that moment that Dr. Smith knew her career path would be in the field of understanding host immune responses against microorganisms rather than antimicrobial development. It was this pathway that lead her to medical school and subsequently into the field of Allergy and Immunology. Throughout her training she was consistently drawn to translational research focused on understanding disease outcomes in patients with immunodeficiencies and immune dysregulation.

During her final year in fellowship, her mentor, Dr. Charlotte Cunningham-Rundles at Mount Sinai, encouraged her to think outside of the box and take time off to conduct translational research. Coincidentally, Dr. Barry Coller had sent her an email regarding the KL2 Clinical Scholars program. Dr. Smith applied to the Clinical Scholars program, and after interviewing with various heads of lab, she was invited to join the Laboratory of Biochemical Genetics and Metabolism headed by Dr. Jan Breslow. Dr. Smith was also co-mentored by Dr. Manish Ponda, Assistant Professor in the Breslow Laboratory and a graduate of the Clinical Scholars program. It was a unique opportunity to work with scientists outside of her area of expertise and learn new approaches to understanding immune responses related to the coagulation factor XII contact system, which is a part of the innate immune system with a role in adaptive immune responses.

Dr. Smith's research has focused on a rare autosomal dominant disease called Hereditary Angioedema (HAE), clinically characterized by attacks of swelling involving the subcutaneous tissue and mucous membranes. HAE attacks are unpredictable, often extremely painful or disfiguring; when they occur in the neck they can lead to asphyxiation and death. Most patients have either a quantitative or qualitative abnormality in the major inhibitor of the contact system, C1 esterase inhibitor. Dr. Smith is particularly interested in the group of patients with HAE who have normal C1 inhibitor level and function, also known as HAE-nl-C1INH, since in most cases, the mechanism is not known. She is also interested in therapeutic development related to the bradykinin pathway, which is involved in HAE, since it is also thought to contribute to various immune mediated diseases.

Her latest research project is focused on understanding whether patients with HAE are at increased risk of COVID-19-related complications, some of which may also involve the bradykinin pathway. Some have speculated that HAE patients who are treated with drugs to counteract the bradykinin pathway may be protected from COVID-19 complications.

When asked to share her expectation and experiences in the Clinical Scholars, Dr. Smith replied:

"I entered the program expecting that I would learn new skillsets as a clinical researcher. I left the program transformed. I learned the various ways by which I could fashion my career where I can wear multiple hats including that of a physician, translational researcher, biotechnologist and entrepreneur, patient advocate, and policy influencer. I learned the most from my fellow Clinical Scholars, who are some of the greatest minds in a wide range of disciplines. Active dialogue with my colleagues allowed me to become inspired and passionate about my research and I would often gain inspiration from their work, commitment, and drive.

The best part of the program was the opportunity to engage with world experts in various fields and to hear about their stories and career trajectories. Dining with such individuals was truly a privilege that most are not afforded and those are moments I will always remember. I would describe the program, specifically at Rockefeller University, as one of a kind."

As a recent graduate of the program and now Assistant Professor of Medicine at the University, San Diego, Dr. Smith was asked for her advice to current Clinical Scholars:

"I would say take advantage of all opportunities afforded through the program. Various seminars and workshops might not directly coincide with your research interests; however, you will be surprised how keeping an open mind will impact your research and approach to problem solving. I have taken away many learning points that have equipped me in my present role as a professor, physician, and clinical and translational researcher."

Meet the Scholar: Christian Gaebler, MD

By Editorial Staff

Christian Gaebler

Dr. Christian Gaebler joined the Clinical Scholars program at the Rockefeller University in 2018. He received his MD from the Charité-Universitaetsmedizin in Germany and completed his internal medicine and infectious disease residency at the same distinguished institution. He currently is a third year Clinical Scholar and serves as Co-chief Clinical Scholar.

As a medical student, Dr. Gaebler quickly realized how little is known about the pathophysiology of disease and in many cases even less about the mechanism of successful treatments. He found this disappointing but intriguing which inspired him to learn the pathophysiology of disease with the intent of discovering new treatments.

Complex systems, such as the nervous system and the immune system, especially fascinated Dr. Gaebler and so he was attracted to immunology research in Dr. Michel Nussenzweig's Laboratory of Molecular Immunology at Rockefeller University. He interviewed with Dr. Nussenzweig and was invited to join his lab. Dr. Gaebler's current research focuses on the HIV latent reservoir and how the treatment with anti-HIV broadly neutralizing antibodies developed by Dr. Nussenzweig's lab impacts the HIV-reservoir. Recently, he shifted some of his efforts to studying SARS-CoV-2. In fact, since April 1, his lab has recruited more than 150 COVID-19 convalescent individuals and studied the SARS- CoV-2 specific immune responses in these individuals. He and his colleagues have also identified distinct antibodies that neutralize the virus very potently and several of these are being further developed as therapeutic and preventive drugs. (https://www.rockefeller.edu/news/28079-covid19-antibody-response/)

With his shift to SARS-CoV-2 research came challenges and opportunities. When asked to reflect on theses, Dr. Gaebler responded:

"The pandemic required us to shift our focus on a completely new research subject and work with unprecedented urgency and speed. At the same time, the difficulties outside of the lab and especially the abrupt shortfall of any support system, especially with regard to child care, were overwhelming. The challenge of my wife and I both being essential workers and working full time (and often more intensely and longer than ever) while also taking care of our 2-year-old toddler at the same time was physically and psychologically extremely tough."

The highlights were the experience of everyone coming together and working towards one goal. The motivation and dedication of everyone, including our research participants was beyond impressive!"

Dr. Gaebler was asked to describe his experience in the Clinical Scholars program, focusing on his expectations when joining the program, what he is looking forward to as Co-chief Scholar this year, and his plans for when he graduates the program.

"I was hoping for a stimulating and well-mentored research environment in a group of peers with the same background, concerns, and career planning questions. My expectations were met a thousand times, and I am extremely grateful for the opportunity that this program has given me. Often I have to remind myself that this is real and pinch myself when we are for example eating lunch and having scientific discussions with an expert of his field. The whole program is a learning opportunity. It is hard to point out specific occasions.

As Co-chief Scholar I am hoping to give back and contribute to the program in a way that we make the best of the current challenges and create a curriculum that is valuable for all current Scholars. The recent months and the challenges of COVID-19. have been the most educational.

The most valuable aspects of the Clinical Scholars program are the protected time, the endless teaching and learning opportunities, and the strong mentorship.

After I graduate, I hope to stay a bit longer in New York and at Rockefeller to keep working on our clinical trials on COVID-19 and HIV. "

R3 Enhancing Scientific Rigor, Reproducibility, and Reporting Series

The R3 Enhancing Scientific Rigor, Reproducibility, and Reporting Methodology Series will start September 24, 2020 and Roger Vaughan, MS, DrPH, Director of Biostatistics will be the first speaker of the series. In a joint effort between the CCTS, University IT, and the Markus Library, The Rockefeller University has created the "R3 -Enhancing Scientific Rigor, Reproducibility, and Reporting" seminar series designed to help improve reproducibility in science, by presenting advances across a range issues including, Data Storage and Repositories, Statistical Analysis, Pipeline Documentation, and Drug Formulation. The series will be via Zoom from 2:00 PM - 3:00 PM

Methodology Series dates

September 24, 2020
October 22, 2020
November 19, 2020
December 17, 2020
January 21, 2021
February 18, 2021
March 18, 2021
April 15, 2021
May 20, 2021

How The Kidney Reacts to Nutritional Changes

By Dana Bielopolski, MD, PhD

Hypertension is a disease of the westernized world, as it stems from lifestyle habits: salt and alcohol consumption, lack of physical activity, smoking, and obesity. Since publication of the original Dietary Approach to Stop Hypertension (DASH) diet study in 1997 many additional controlled studies have demonstrated the clinical efficacy of the DASH diet to meaningfully lower blood pressure.

The DASH diet emphasizes fruits, vegetables, and low-fat dairy products and is reduced in fat and cholesterol. It is exceedingly unlikely that a "magic nutrient" can explain its additive effect over simply a low salt diet. Rather the impressive BP reductions reported are best interpreted as a combined effect from multiple dietary factors rather than the effects of a single factor. Lower salt consumption reduces blood pressure, but the DASH diet is much more effective, lowering blood pressure as efficiently as one anti-hypertensive drug.

Certain dietary patterns have been associated with low BP. Observational studies and clinical trials have associated vegetarian diets with lower BP, yet the nutrients responsible for the BP-lowering effects of these diets have remained uncertain. Attention has focused on macronutrients (particularly the type and amount of fat), micronutrients (potassium, magnesium, and calcium), and fiber. However, data from observational studies and small-scale trials have been extremely inconsistent.

The precise mechanism through which DASH achieves its effect is not understood. The overall goal of my project is to learn more about its mechanism. One hypothesis is that the additive affect is attributed to the increasing the consumption of potassium.

Observational studies highlight the role of potassium in preventing stroke, reducing blood pressure and cardiovascular morbidity, and protecting the kidneys from damage caused by hypertension. But how does potassium exert its beneficial effect? Potassium is the trigger for release of aldosterone, a hormone, from the adrenal glands that results in excretion of the additional potassium. Potassium excretion obligates sodium excretion, so, potassium acts like a diuretic drug, but without drug side effects. To assess whether the DASH diet results in aldosterone-induced changes in ion channel composition in the kidneys' epithelium, we will monitor urine exosomes, which contain epithelial cell membranes.

Traditionally, adherence to the DASH diet has been evaluated using questionnaires, but we have learned that patients commonly underreport the amount of sodium they consume. One of the great strengths of the Rockefeller University Hospital staff's extensive experience in conducting long-term, in-hospital nutritional studies with research volunteers, is that we can monitor carefully food intake and collect biologic samples to independently assess dietary adherence, outcomes, and mechanisms.

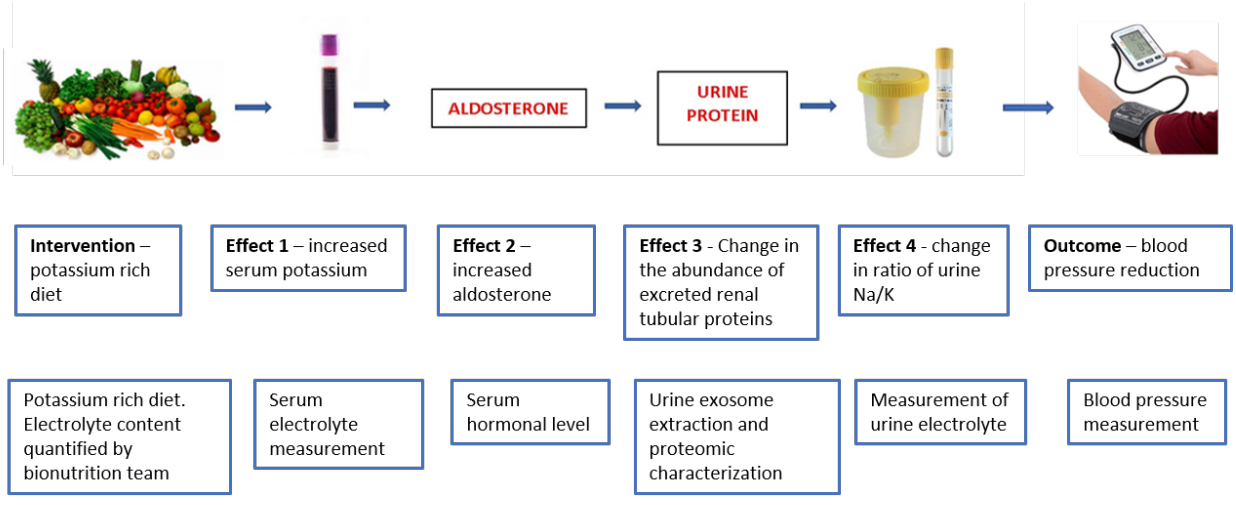
We hypothesize that exposing stage 1 hypertensive volunteers to a high potassium and low sodium DASH diet will change the composition of renal ion channel in an aldosterone-dependent manner, leading to excretion of both sodium and potassium and a reduction in blood pressure.

The aims of the study are to 1) characterize urinary exosomes before and during the DASH diet, and 2) validate the urinary sodium/potassium ratio as a measure of DASH adherence. We are recruiting ten healthy volunteers with relatively mild (stage 1) hypertension and they will consume the DASH diet as inpatients at the Rockefeller University Hospital for two weeks. Participants will undergo daily blood pressure measurements, daily blood and urine sample collection, 24-h urine collection, and 24-h ambulatory blood pressure monitoring (ABPM).

The diagram below summarizes the causal pathway we propose to characterize the mechanism of the DASH diet, underscored by a list of performance indicators we will measure to test the hypothesis.

The menu was planned based upon the guidelines of the National Heart Blood and Lung Institute (NHBLI) of the National Institute of Health (NIH).

In designing the study, our challenges were to meet the diet requirements while making the menu palatable and appealing. The main differences from the American style diet are the low salt (2.3 grams of sodium recommended compared to more than



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How The Kidney Reacts to Nutritional Changes

continued from Page 12

4.5 grams in a typical American diet) and the high potassium. To achieve these goals, the DASH diet has an abundance of fruits and vegetables. To avoiding the potential confounding effect of weight reduction on blood pressure, we also had to calculate caloric intake to maintain weight stability throughout the study.

The clinical protocol was developed with assistance from many Rockefeller Center for Clinical and Translational Science (CCTS) and Hospital staff under the Translational Research Navigation process. Under the ongoing threat of COVID-19, the protocol was interrupted just as it began, and to resume, had to be re-Navigated to incorporate the new rules and challenges related to risk assessment, social distancing, SARS-CoV-2 testing, and staff and patient safety. These include asking participants to complete a symptom survey prior to arrival on campus and testing for the virus before admission.

The first participant was enrolled on June 14th, 2020. Below is an example of the impact the diet had on the participant's 24-hour ambulatory blood pressure. The most dramatic change is during sleep where the participant's blood pressure decreased from 120/74 to 109/67 mmHg. This enhanced "nocturnal dipping" is associated with improved cardiovascular health and reduced all-cause mortality.

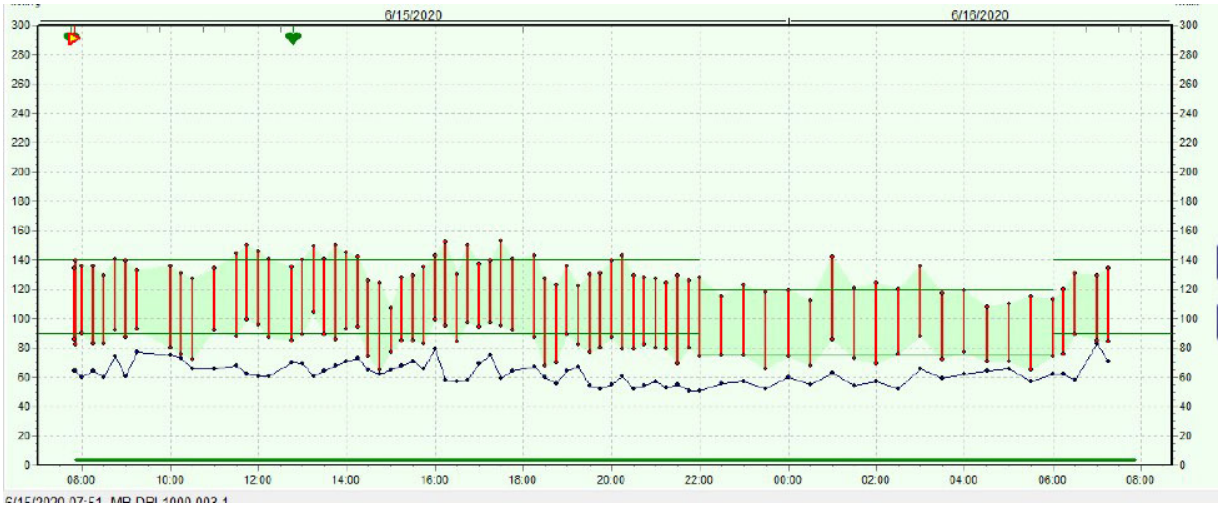
Understanding the mechanism underlying the DASH diet may shed light on the physiologic process by which nutrition influences blood pressure and potentially lead the way to new therapeutics that target ion channels.

We also hope that by introducing our participants to better nutritional choices we will be able to not only reduce their blood pressure during the intervention, but help them to carry the lessons home, modify their lifestyle, continuing eating a healthier diet after the study, and sustaining the lower blood pressure without requiring medication.

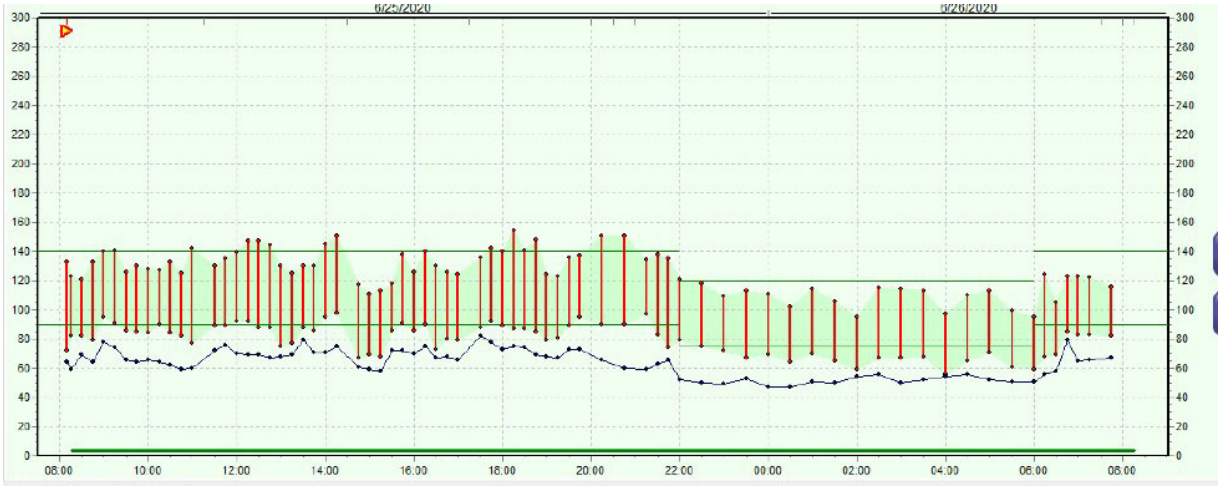
This article affords me a great opportunity to thank the great staff of the Rockefeller University Hospital, the Navigation team, and the Clinical Research Support Office headed by Dr Rhonda Kost, who made this trial come to life with the reopening of the University.

24-hour Ambulatory Blood Pressure Monitoring. A: Baseline, B: Day 11.

A



B



The Time-Restricted-feeding effects on Inflammation and Obesity (TRIO) Study

By José O. Alemán MD PhD

The impact of early time restricted feeding on metabolism and inflammation in obesity

Time Restricted Feeding (TRF) is a form of intermittent fasting that confines food intake to active daytime hours and involves fasting for 12 to 14 hours. Circadian misalignment caused by changes in sleeping and eating behaviors has emerged as having a detrimental impact on weight, glucose metabolism, and other cardiovascular disease-related outcomes. Feeding during active periods appears to be advantageous for weight, glucose metabolism and related outcomes whereas feeding during the inactive period confers deleterious effects on these outcomes. Therefore, TRF shows great promise as a novel intervention for addressing obesity and related cardiovascular outcomes. To address this potential, we are conducting a randomized 7-day isocaloric crossover feeding study titled "The Time-Restricted-feeding effects on Inflammation and Obesity" (TRIO), in humans with prediabetes and obesity. We will study the effect of restricting the timing of caloric intake to earlier in the day (TRF) versus later in the day (usual feeding pattern, UFP) on glucose levels and inflammation..

In the TRIO study Dr. Jose Aleman, a graduate fo the Clinical Scholars program who is now Assistant Professor of Medicine at NYU, will explore the impact of TRF on systemic inflammation and shifts in glucose metabolism over 1 week, as well as its effects on surrogate markers of diabetes and cardiovascular disease while weight remains stable. Dr. Jan Breslow, Head of the Laboratory of Biochemical Genetics and Metabolism, will serve as Co-PI.

Animal studies suggest that timing of feeding, including intermittent fasting or TRF, decreases inflammation and causes ketosis. We are unaware of any data in humans on these potential mechanisms. Dr. Aleman's independent work at NYU aims to understand the role of inflammation in fat towards causing the complications of excess weight. His team is pursuing this goal by obtaining detailed phenotyping of subjects with obesity undergoing bariatric surgery and observing how metabolic and inflammatory phenotypes change with one form of bariatric surgery called sleeve gastrectomy. The overall hypothesis is that obesity is associated with activation of inflammatory signaling pathways,

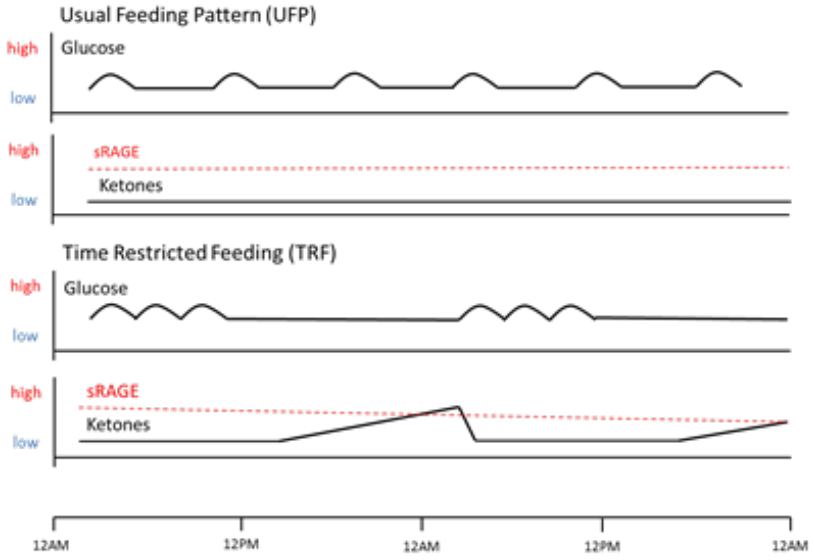


Figure 1: Schematic of Proposed measurements in the TRIO study. Under Usual Feeding Pattern (UFP), glucose levels alternate with meal consumption, preventing ketogenesis and contributing to stable soluble RAGE levels. Under Time Restricted Feeding (TRF), overnight fasting enables glucose depletion and ketogenesis, decreasing inflammation, soluble RAGE (sRAGE) over the length of the clinical study.

the most notable of which is the Receptor for Advanced Glycation End-Products (RAGE) signaling pathway, and treating obesity will decrease this form of inflammation. However, we lack interventions to decrease this form of systemic inflammation when weight is stable, such as when maintaining weight after bariatric surgery. Activation of the RAGE pathway can be assessed by measurements of soluble RAGE (sRAGE), an inhibitor of the pathway. We hypothesize that the downstream consequences of RAGE activation are reductions in energy expenditure and glucose tolerance, increased white blood cell (WBC) counts and inflammatory gene expression, and greater levels of circulating cytokines. Low levels of sRAGE are associated with long-term risk of diabetes, cardiovascular disease, and premature mortality.

This collaborative research project integrates the Rockefeller University Hospital's expertise in conducting sophisticated nutritional studies with Dr. Aleman's group's expertise in obesity, dietary interventions,.. exercise, and metabolic studies (Popp et al. 2016, Vanegas et al. 2017). Figure 1 details the timing of the TRF intervention within a 2-day period and the predicted changes in metabolic and inflammatory parameters.. Systemic and adipose tissue inflammation are known to decrease with long-term weight loss and maintenance, but the dynamics of sRAGE within each circadian rhythm are not well understood. We hypothesize that decreased glucose and AGEs would decrease signaling through the RAGE pathway, and over 7 days lead to a reduction in sRAGE with TRF, which has not been tested previously in the context of a detailed feeding study. Through the proposed metabolomic analysis, we will be able to measure AGEs in the context of this detailed dietary intervention, linking timing of feeding directly to RAGE signaling.

The study will enroll 10 persons with obesity (BMI>30 kg/m2) and prediabetes (HbA1c 5.7-6.4%) and randomize them TRF or UFP. In the TRF arm, participants consume all food between 8 am and 2 pm, producing a 16-hour fast each day, and eat 80% of their calories prior to 1 pm. In the UFP arm, participants consume their calories between 8 am and midnight and eat 50% of their calories after 4 pm. In both arms, participants consume diets with the same macro- and micronutrients based on their home diet, analyzed by Bionutritonists in the Rockefeller Bionutrition Department, using the validated Vioscreen Food Frequency Questionnaire (that captures the participants usual intake within the last 3 months). The study has crossover design, with subjects switching to the other intervention arm after completing the

continued on Page 15

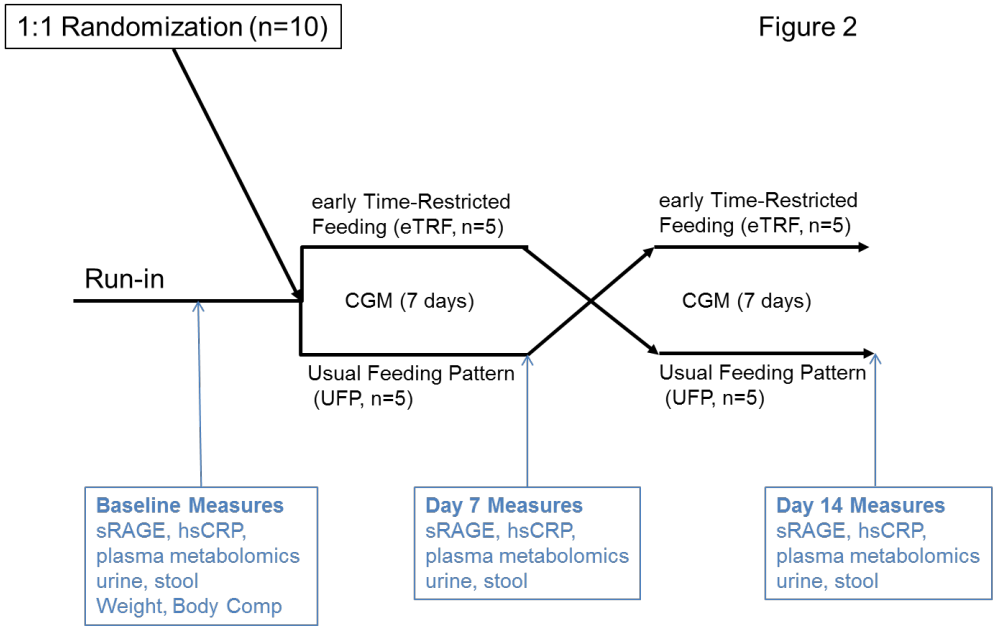
The Time-Restricted-feeding effects on Inflammation and Obesity (TRIO) Study

continued from Page 14

first 7 day intervention (Figure 2). Subjects will act as their own control, and we will be able to monitor compliance with the TRF intervention by monitoring continuous glucose monitoring (CGM) tracings. CGM technology is widely used in the care of patients with diabetes, and the TRIO study will be the first application of CGM at Rockefeller Hospital. We know that glycemic variation decreases with TRF interventions, but will test sRAGE, clinical markers of inflammation such as high sensitivity C-reactive protein (CRP), plasma metabolomic profiles by liquid chromatography/mass spectrometry, in addition to collecting urine and stool for future analyses. with the TRF intervention by monitoring continuous glucose monitoring (CGM) tracings. CGM technology is widely used in the care of patients with diabetes, and the TRIO study will be the first application of CGM at Rockefeller Hospital. We know that glycemic variation decreases with TRF interventions, but will test sRAGE, clinical markers of inflammation such as high sensitivity C-reactive protein (CRP), plasma metabolomic profiles by liquid chromatography/mass spectrometry, in addition to collecting urine and stool for future analyses.

As part of Drs. Aleman and Breslow's commitment to training the next generation of obesity and cardiovascular researchers, nutritionist clinical fellows from the NYU American Heart Association Obesity Center, Dr. Collin Popp and Dr. Sally Vanegass, will participate in the deployment and execution of the TRIO study in collaboration with Rockefeller Bionutrition Department. We hope the TRIO study will yield new connections between metabolism and inflammation, while testing for additional benefits of this creative dietary intervention in the clinical setting. with the TRF intervention by monitoring continuous glucose monitoring (CGM) tracings. CGM technology is widely used in the care of patients with diabetes, and the TRIO study will be the first application of CGM at Rockefeller Hospital. We know that glycemic variation decreases with TRF interventions, but will test sRAGE, clinical markers of inflammation such as high sensitivity C-reactive protein (CRP), plasma metabolomic profiles by liquid chromatography/mass spectrometry, in addition to collecting urine and stool for future analyses.

Figure 2: TRIO Study Design



$2.7M Award to Streamline Collecting Participant Feedback and Drive Improvement to the Clinical Research Enterprise

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Recruitment, retention, and representative sampling remain major challenges to research. Assessing participants' research experiences provides essential outcome data for improving the clinical research enterprise, yet those experiences go largely unmeasured. The paucity of direct participant experience data to support evaluation of research practices is a critical translational gap. This grant is directed at addressing this crucial need to improve clinical investigation.

To execute the project aims, the teams will collaborate in Year 1 to develop integrated RPPS/REDCap tools and dashboard and analytics modules, as wells as formalize the implementation framework to afford institutions flexibility in their specific deployments of demonstration cases, while preserving common elements and standards for future data integration and benchmarking. In Years 2 and 3, sites will implement use cases – study-level surveys, departmental aggregation of project surveys, and institutional level surveys – among different targeted populations and using various outreach platforms to demonstrate the usability and value of the infrastructure and make refinements. Key deliverables are the examples of actionable findings gleaned from participant feedback that institutions then use to drive measurable improvements to research experiences. In Years 3 and 4, the team will actively disseminate the infrastructure across the REDCap user community and CTSA Consortium hubs. The value proposition for different for different stakeholders – investigators, clinical research managers, department and institutional leadership,

Figure 1

and NCATS – will be refined in the path to widespread use. A key element of deliverable in dissemination is to gain the critical mass of users to support valid inter-institutional benchmarking.

Valid tools, good intentions, and persisting barriers

Through a series of multi-site projects from 2010-2018, Dr. Kost led the development of a suite of validated Research Participant Experience Survey (RPPS) tools in collaboration with investigators at 15 NIH funded academic health centers. The RPPS collects actionable data about study conduct, informed consent, trust, respect, education and communication. The RPPS tools - available in English and Spanish and in long, short and ultrashort versions - have been in use to drive improvements in research at Rockefeller since 2013, at Johns Hopkins University since 2017, , and in some form at up to 16 CTSA hubs in total. Requirements for infrastructure to support implementation, redundant across sites, have stalled uptake and collaboration related to participant outcomes. When collected, participant experience data can provide the evidence base to support the impact of innovative practices. Figure 1 shows the change in one measure of participant experience before and after a team implemented a video designed to enhance informed consent. Figure 1 shows the responses to the RPPS question "How well did the discussions and information provided before the study prepare you for your research experience?" The frequency of the response "completely" from participants in this study (blue), was 50-53% in the preceding years (2015-2017), but rose to 75% in the year after the new video (green) came into use inlate 2017. By comparison, the response scores for the same question for all studies at Rockefeller (orange) were unchanged in the same time frame. While limited by retrospective design and sample size, this example illustrates the kind of impact data that could be collected to via a streamlined RPPS/REDCap platform.

Despite the availability of the valid RPPS, institutions report persisting barriers to broad implementation, pointing to the need for a ready-to-use platform, standardized approach, low-cost institutional infrastructure, and plug-and-play visualization and analysis tools to streamline collection of participant feedback.

Leveraging a platform in wide adoption

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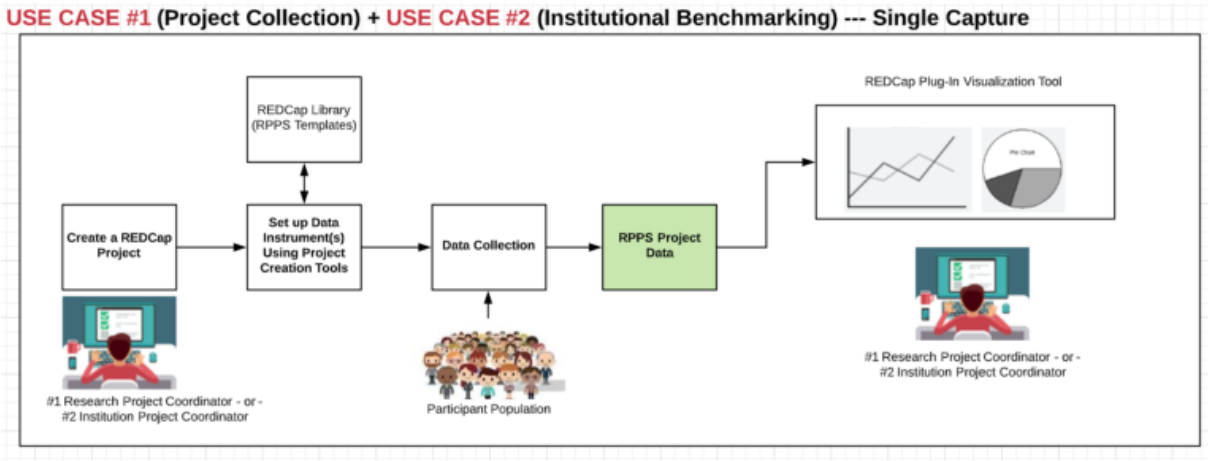

$2.7M Award to Streamline Collecting Participant Feedback and Drive Improvement to the Clinical Research Enterprise

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REDCap(https://projectredcap.org) is a secure, web-based application with workflow and software designed exclusively to support rapid development and deployment of data capture tools for research studies, with minimal training of the user. REDCap has security and usability features specifically designed to support participant-facing surveys and flexible deployment strategies. REDCap was developed at Vanderbilt by project collaborator Dr. Paul Harris, and has been used by over 970,000 users at more than 3,500 institutions to support more than 725,000 research projects. Virtually all of the CTSAs use REDCap. The REDCap Shared Data Instrument Library (SDIL) makes validated data collection instruments available to researchers , and supports technologies such as web services that allow integrated data collection through other platforms. When complete, the integrated RPPS/REDCap tools will be made available for direct download through the SDIL. A preliminary map of the data flow for a project level or institutional level survey, without inter-institutional integration is shown at the left.

Defining Success

With many deliverables along the way, both process-oriented and tangible, the ultimate measures of the success of the project will be: 1) the production of an Implementation Guide, RPPS/REDCap project tools, and infrastructure ; 2) outcome data from completed demonstration projects at the sites that illustrate the utility of the RPPS/REDCap to collect representative feedback from participant populations, and produce actionable findings to generate impactful improvements; and 3) embrace of the value proposition of RPPS/REDCap infrastructure evidenced by an expanded set of users, including REDCap users and institutional leadership, and participation in consortium benchmarking. The goal is to provide value to a range of stakeholders to sustain broad uptake and use of participant feedback to improve research.

The RPPS/REDCap project is also supported in part by an award to Rockefeller University from the National Center for Accelerating Tranlsational Science, 1U TR0001866.

Stakeholders and Anticipated Value Proposition

Stakeholder	Deployment	Value proposition
NCATS	• Consortium	• Benchmarks for Hub and for communities • Network potential for identifying best practices
Institutional leadership	• Institutional	• Internal and external benchmarking • Opportunity to test broad initiatives • Share data with leadership & communities
Human Research Protection Program	• Institutional • Investigator/project	• AAHRPP values RPPS approach • FDA values participant experience data • Tool & data to improve informed consent
Clinical Trial Management professionals	• Institution • Investigator/project	• Tool & actionable data to tailor practices • Ability to conduct comparative effectiveness • Tool for real-time feedback /correction
Investigators	• Study-level	• Direct participant feedback • Data speaks to investigators
Participants	• Consent • Study Milestones • End of study	• Being asked for feedback = Being valued • Respect • Teams are accountable • Opportunity to improve experience
Communities	• Consent • Study Milestones • End of study	• Being asked for feedback = Being valued • Sharing back data = Respect • Accountability of institution in response
Features: Confidentiality, Common Infrastructure, Dissemination, Dashboard, Ease-of-use, Free, Commitment to Quality improvement, Respect for Participants & Communities, Validity, Transparency, Standards for Benchmarking		

CCTS Biostatistics Group Supports a Broad Range of Rockefeller Scholarship

continued from Page 9

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Clinical Scholars Program Celebrates New Graduates

By. Michelle Romanick

On June 4, 2020, the Center for Clinical and Translational Science celebrated the graduation of 6 Clinical Scholars with a virtual celebration via Zoom. Despite the lack of physical proximity, the celebration was a wonderfully warm and inspiring event, with the Mentors speaking about their Scholars and Scholars sharing their experiences in the program. Dr. Sarah Schlesinger, Director of the Clinical Scholars program, welcomed the participants with inspiring words about the Scholars' achievements and the pride that the entire CCTS leadership has in the Scholars. Dr. Barry Coller, Co-Director of the program concluded the festivities by congratulating the Scholars and their families and emphasizing how the COVID-19 pandemic highlights the importance of translational scientists in addressing vital health needs.

Dr. Tobias Becher studied Brown fat dissipates energy as heat and is a promising therapeutic target against obesity and associated diseases in Dr. Paul Cohen's laboratory. His research explored the effects of brown fat on cardiometabolic health in humans. Dr. Becher accepted the position of Clinical Science Leader Cardiovascular at Roche Diagnostics, in Rotkreuz, Switzerland.

Dr. John Frew's research discovered novel inflammatory mediators in Hidradenitis Supppurativa providing the first descriptions of epithelialized tunnels as mediators of inflammation, as well as identifying novel mechanisms of therapy, sonographic and molecular Biomarkers of disease activity in Dr. James Kreuger's laboratory. Dr. Frew accepted the position of Staff Specialist and Associate Lecturer in the Department of Dermatology at the University of New South Wales, Sydney, Australia.

Dr. Krithi Irmady's research investigates the changes in gene expression and their regulation in Parkinson's disease patients to understand disease pathogenesis and identify potential new biomarkers and therapeutic strategies in Dr. Robert Darnell's laboratory. Dr. Irmady will continue as Instructor in Clinical Investigation in the Darnell Lab, while considering academic positions in Neurology.

Dr. David Knorr's research tested testing whether Fc-enhanced anti-CD40 antibody is safe to deliver intratumorally in patients with cancer. The studies are also looking for preliminary evidence of efficacy and include several corollary laboratory-based studies to define the effects of CD40 agonism in humans. Dr. Knorr was awarded a NIH National Cancer Institute Mentored Clinical Scientist Research Career Development K08 grant. Dr. Knorr is Assistant Attending in the Department of Medicine at Memorial Sloan Kettering Cancer Center. Dr Knorr will also continue as Visiting Assistant Professor in the Ravetch Lab.

Dr. Franck Rapaport's research investigates the inborn errors of immunity involved in the etiology of acute appendicitis, which will help improve our understanding of the disease and eventually contribute to the design of new clinical tests in Dr. Jean-Laurent Casanova's laboratory. Dr Rapaport will continue as Instructor in Clinical Investigation at Rockefeller University in the Casanova Laboratory.

Dr. Tukisa Smith's research focused on the contact system consists of a plasma protease cascade that has been suggested in the pathophysiology of various disease states in Dr. Jan Breslow's laboratory. Although increasing investigations have shown the contact system's role in host immune defenses against microbes, fewer studies have explored its role in regulating immune homeostasis and inflammatory response, which is the aim of Dr. Smith's research by characterizing this pathway's biomarkers in various inflammatory and immune-mediated diseases. Dr. Smith is Assistant Professor in the Department of Clinical Immunology at the University of California San Diego.

'Virtual' photo of the graduates and Clinical Scholar program leaders. Drs. Barry Coller, Sarah Schlesinger, Krithi Irmady, Tukisa Smith, Franck Rapaport, John Frew, David Knorr, Tobias Becher, and James Krueger

Rockefeller Historical Vignette: The Birth of Modern Virology

By Elizabeth (Betsy) Hanson

Rivers, Thomas
Courtesy of the Rockefeller Archive Center

In the 1920s virology was not an established discipline. Although researchers could study the effects of viral diseases in humans, animals, and plants, they had no criteria to describe viruses chemically--in fact, the very definition of a virus was a subject for debate! The best scientists could do was to say that, if an infectious agent passed through a fine porcelain filter that held back bacteria, then it was probably a virus ("a filterable agent"). In 1926, Thomas M. Rivers (1888-1962), director of the Rockefeller Hospital, made a bold statement about the essential nature of viruses that set the course of virology for decades to come. He said: "Viruses appear to be obligate parasites in the sense that their reproduction is dependent on living cells."

In stating that viruses needed living cells in order to replicate, Rivers was contradicting many workers in the field, including Simon Flexner, the director of the Rockefeller Institute, who claimed to have isolated and cultivated the polio virus in a cell-free medium. But Rivers had both laboratory and clinical experience on which to base his view. When, in 1926, the Society of American Bacteriologists invited him to organize a symposium on viruses, and deliver a lecture, he reviewed the body of knowledge on viruses. Several observations on the problem of growing viruses in the laboratory led him to his conclusion: the difficulty of cultivating viruses on artificial media could not be explained; although viruses were small, size should not prevent their cultivation; viruses were not particularly delicate or susceptible to destruction during laboratory procedures; nor had any viruses been found multiplying free in nature. His synthesis of the state of virology was published in a landmark book, Filterable Viruses, in 1928. Rivers' hypothesis led to many advances in the culturing and characterization of viruses that cause human disease.

Thomas M. Rivers received the BA from Emory College in 1909 and the MD from The Johns Hopkins University Medical School in 1915. After an internship and residency in pediatrics, he joined the Army in 1918, serving on commissions with the U.S. Army Medical Corps that investigated outbreaks of pneumonia and empyema. He returned to Johns Hopkins for a research appointment in 1919, and joined the Rockefeller Institute Hospital in 1922. In 1937 Rivers became director of the hospital, a position he held until 1953, when he became Vice President and Director of the Institute. He retired in 1955. Rivers was elected to the U.S. National Academy of Sciences. He served as president of the American Society for Clinical Investigation, the American Association of Immunologists, the Society of American Bacteriologists, and the Third International Congress for Microbiology, and received honorary degrees from Emory University, the University of Rochester, the University of Chicago, and the Rockefeller Institute.