DEPARTMENT OF HEALTH AND HUMAN SERVICES
NATIONAL INSTITUTES OF HEALTH

219th Meeting of the
NATIONAL DIABETES AND DIGESTIVE AND KIDNEY DISEASES ADVISORY COUNCIL

DIVISION OF DIGESTIVE DISEASES AND NUTRITION SUBCOMMITTEE
Meeting Summary

Thursday, May 12, 2022
Zoom Video Conference

Open Session

1) Dr. Stephen James opened the meeting by welcoming everyone.

2) The minutes of the January 27, 2022 subcommittee meeting were approved.

3) In addition to the three DDDN Initiative Concept Clearances that were presented during the Open Session of the Full Council on Wednesday, May 11, 2022, four more Concept Clearances were presented during the DDDN subcommittee (more details on the clearances can be found in the appendix). The discussion included the following questions and responses:
   a) Ingestible Gastro-Intestinal Sampling, Monitoring and Delivery tools/devices for Advancing Microbiome Research (New)
      - **Question:** If using an R21 mechanism for this concept, is the objective to beta test existing engineered devices and not develop new ones?
      - **Answer:** Correct; the previously advertised FOA was for an R21/R33 where the R21 phase was for proof of concept for new devices and the R33 was a more expansive development stage for trials in humans. The new FOA may not encompass this same mechanism for development of trials in humans.
      - **Question:** How does this FOA differ from the previous one? What was learned from the previous set of applications?
      - **Answer:** The current FOA will differ from the previous FOA as the phased approach of an R21 to an R33 may not be used. We learned that phasing from an R21 to an R33 was difficult to establish.
   b) The Liver Tissue and Cell Resource Center (LTCRC) (New)
      - **Question:** In the past, has this always been a competitive renewal contract**?**
      - **Answer:** It is and has been a competitive renewal contract since 1986; every five years, the contract was competed.
      - **Question:** Is the amount of clinical metadata associated with the liver tissue and organoid cell lines limited? Can it be expanded?
      - **Answer:** The specimens come from cadavers or discarded livers at the time of surgery, therefore, the clinical information provided is limited to basic clinical information and demographics. There is an opportunity to provide both normal and diseased livers, and the amount of clinical data could possibly be expanded.

- **Question:** In recent years, it has been challenging to get access to normal healthy human tissue, particularly for hepatocyte isolation as transplants have top priority; has this been a challenge observed for LTCRC as well?
- **Answer:** Yes, the LTCRC has had the same limitations. Fortunately, the investigator involved is motivated and has a team who has ready access to livers that are not found suitable for transplantation. The NIDDK is aware that the primary competition is pharma and biotech companies who can pay top dollar for normal tissue.

c) A Consortium for Gut-Brain Communication in Parkinson's Disease (New)

d) Nonalcoholic Steatohepatitis Clinical Research Network (NASH CRN)

- **Question:** Has the information published in the White Paper put out by the American Gastroenterological Association in 2021 affected recruitment and enrollment in the NASH CRN?
- **Answer:** No trends have been recognized impacting recruitment and enrollment since the release of this White Paper.
- **Question:** Will ancestry data be available as part of the genome sequencing work? Is ethnicity self-reported by Hispanics?
- **Answer:** With the genetic testing involved in NASH CRN, we will have more accurate ancestry data available. All ethnicity is self-reported.
- **Question:** NASH and NAFLD seem to be the central hub for metabolic disorders; are there opportunities to collaborate with other agencies?
- **Answer:** Formally, we have interacted with NIEHS in children, looking at environmental exposures; we have also worked with the Foundation for the NIH for industry sponsored projects. Currently, we do not have any formal collaborations with other agencies or institutes, however at the site level, there is involvement with endocrinologists, cardiologists, and other impacted specialties.

e) Automated Self-Administered 24hr Recall (ASA-24)

- **Comment**: This is an incredibly important resource for the scientific community that should be advertised more broadly.
- **Question:** Is the dietary recall tool being used smart phone adapted?
- **Answer:** Yes; in 2019 an update was made to make the recall tool available on smartphones and tablets, both Android and Apple.
- **Question:** Is the recall tool user initiated or do alerts go out to prompt the user?
- **Answer:** Reminders are sent through the recall tool to the participants. The researcher will also remind the participant to look out for an invitation to complete the recall. Researchers can assist participants if necessary to overcome issues with literacy, numeracy, and other issues.
- **Comment:** Diet information is going to be important in studying the microbiome and the metabolites they produce. Collecting diet information should be considered in conjunction with noninvasive monitoring tools such as the ingestible GI sampling and monitoring devices discussed earlier in the meeting.
- **Response:** The Office of Nutrition Research is looking into this. And it is being considered as a component of the Precision Health Initiative.
- **Question:** Has the NIDDK reached out to the NHLBI regarding using this tool in their large cohorts?
- **Answer:** The NHLBI is very interested in dietary assessment, and they are part of the current ASA-24 implementation working group.
- **Question:** Is this tool available in different languages?
- **Answer:** It is currently available in English and Spanish.

f) Continuation of the Childhood Liver Disease Research Network (ChiLDReN)
- **Question:** How much of a precedence is there for a network to have a Bioinformatics Center? This seems like a very big opportunity.
- **Answer:** Other networks have turned to commercial enterprises for genomic and other omic analyses. It is very important that at least one of the ChiLDReN centers have bioinformatics expertise because of the large amount of omics data that will be accrued.
- **Comment:** Genomic data experts may be easier to find than other high-dimensional analytic area such as metabolomics or proteomics and try to integrate it with the genomic data, then it becomes much harder more difficult.
- **Response:**
  - Dedicated bioinformaticists are definitely needed. The Intestinal Stem Cell Consortium has incorporated bioinformaticists as part of the consortia projects to look across animal models and humans to try to understand commonalities.
  - The support of data science and informatics is a hot topic internally at the NIH. Everyone recognizes that trying to do this one study at a time is highly inefficient. Eventually we want to cross-fertilize different research areas, so the idea is to create moveable data and platforms that will be useable for several years. There is an NIH Associate Director for Data Science who is looking at multiple initiatives along this line.
  - Dr. Rodgers noted that storage and sharing of data sets, including genomic data, is a priority, DK-Net is largely focused on diabetes and endocrine conditions at the moment but also includes resources that are relevant to liver diseases and other digestive conditions.

g) Expansion of the Liver Cirrhosis Network (LCN)
- **Question:** Are the contrast MRIs proposed being used for diagnostic or follow up visual imaging? Is the novelty that you will be looking at elastography in addition to the imaging?
- **Answer:** Yes. They will also be assessing fat fractions and fibrosis, in addition to hepatocellular carcinoma.
- **Question:** Is there enough standardization across centers that the data will be comparable across sites?
- **Answer:** Yes, this is currently being worked on across centers by site radiologists and an imaging analysis center will be established for uniformity and rigor of review. The goal is to be able to look at progression of fibrosis.
- **Comment:** Image-derived phenotyping developed using artificial intelligence may be an option.
- **Response:** This is already being done in the NASH CRN and will be part of the LCN as well.

4) Dr. Saslowsky reminded everyone that current NIDDK funding opportunities can be found at https://www.niddk.nih.gov/research-funding/current-opportunities.

5) Dr. Saslowsky introduced the recently launched NIH Scientific Data Sharing website https://sharing.nih.gov where one can find out how to get help with data sharing, stay up to date on NIH data sharing policy-related statements, news and events, and look for training opportunities. Data sharing plans will be required starting with applications submitted to NIH for January 25, 2023 and subsequent receipt dates.
   a) **Question:** With the policies that are being put in place for data sharing, will there be a requirement for a centralized location for those data to be shared or will it remain acceptable to

store data and make it publicly available within one's own storage platform at their university/institute?

b) **Answer:** There is not going to be a hard rule that data has to be shared in one particular place; the important factor is that the data are fully publicly accessible. The proposed storage location and accessibility should be discussed between applicants, their program official before the award is made.
c) **Question:** Is there an opportunity to collaborate or synergize with journals? Most high and intermediate level journals have a data sharing requirement of their own.
d) **Answer:** Yes. However, the new policy requires establishment of a data sharing plan in advance of the data being collected, so the collaboration with journals will come much later in the research.
e) **Question:** Will there be a requirement to share unpublished data?
f) **Answer:** There is a requirement that any data that will be useful to the broader public and the broader research community must be shared, regardless of whether it is published. This includes negative findings that might not make it into a published manuscript. The challenge may be to determine what data will be "useful." The policy also describes the limitations on sharing human subject information. The policy is very broad and does not address requirements for specific types of data; this will need to be discussed with applicants as they develop their specific data sharing plans.
g) **Question:** Regarding journal publications, will there be any communication of whether the data has been retracted or changed in any form? Having this information would give a sense of the quality of the data set.
h) **Answer:** There is nothing in the current policy that touches on this point, but we will investigate further.
i) **Question:** Is there any effort to encourage the collection of health equity data that could help get at social disparities of health?
j) **Answer:** Yes, this intersects with the data sharing policy requirement.

6) Planned Workshops (more details can be found in the appendix):
   a) **Integrated Physiology of the Exocrine & Endocrine Compartments in Pancreatic Diseases Workshop** **https://www.niddk.nih.gov/news/meetings-workshops/2022/integrated-physiology-exocrine-endocrine-compartments-pancreatic-diseases-workshop** will be held at the Natcher Conference Center on June 29-30, 2022. The goal of this 1.5-day workshop will be to gather clinical and basic science investigators who are interested in diseases of the exocrine and/or endocrine pancreas and in achieving an understanding of how the two compartments interact in disease. This workshop will provide an opportunity for investigators in exocrine diseases to come together with those studying islets in diabetes as a means to foster interdisciplinary discussion and identify areas for advancement.
   b) **Clinical Trials in Pancreatitis: Opportunities and Challenges in the Design and Conduct of Patient-Focused Clinical Trials in Recurrent Acute and Chronic Pancreatitis Workshop** **https://www.niddk.nih.gov/news/meetings-workshops/2022/clinical-trials-pancreatitis** will be held at the University Club in Pittsburgh, PA on July 20, 2022. The objectives of this meeting are to identify gaps and recommendations; help attendees understand the principles and requirements of clinical trials for treatment approaches for Recurrent Acute and Chronic Pancreatitis; use workshop recommendations to inform possible future funding initiatives by NIDDK and to publish a conference summary.

Closed Session

Council members reviewed competing applications; two applicants with >$2M (the NIH recently increased the threshold from >$1M to >$2M) in NIH funding (direct costs), two foreign applications, and two budget restorations. There were no appeals or skipped applications to review. In all discussions, Council members concurred with NIDDK/DDDN.

Comments and critiques regarding discussion topics and initiatives from council members are welcome and should be emailed to Drs. James and Saslowsky in advance of the next meeting.

-Appendix-

National Institute of Diabetes and Digestive and Kidney Diseases

DDN Concept Clearances

May 2022 Advisory Council

National Institute of Diabetes and Digestive and Kidney Diseases

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National Institute of Diabetes and Digestive and Kidney Diseases

Ingestible Gastro-Intestinal Sampling, Monitoring and Delivery tools/devices for Advancing Microbiome Research

Lead Division / Office: DDN

Program Contact(s): Padma Maruvada

Executive Summary:
The gastrointestinal (GI) microbiota, and mucosal interactions play a critical role in homeostasis, energy metabolism, host immunity, permeability, and transmission of metabolic signals along the GI-brain axis. Altered microbial composition and metabolism have been implicated in a variety of both communicable (i.e., infectious diseases) and non-communicable diseases including diabetes, obesity, inflammatory bowel disease (IBD), and cancer. However, translating knowledge of microbiome research to impact health in humans remains largely an unmet goal in the field. The exact nature and overall biogeography of GI mucosal and microbial interactions are not well defined in humans, and analysis of feces as a proxy for microbial composition and function does not truly reflect the regional host-microbe community interactions. Limited studies on regional communities within the GI tract suggest unique microbial ecologies and metabolic impact on the host. Development of non-invasive, ingestible devices/tools for collection of samples and data for mechanistic exploration of GI microbiota interactions in clinical cohorts is needed to advance the field. Devices capable of monitoring disease and/or delivering therapies could advance microbiome research. This initiative seeks to support the development of ingestible tools/devices that enable sampling of luminal and mucosal contents (both host and microbial components), detecting and/or monitoring site-specific microbiome-host interactions.

The Need / Background:
The composition and function of the GI microbiota, including interactions within the GI mucosa, play vital roles in a variety of metabolic and physiological functions that affect the development and maintenance of innate and systemic immunity, inflammation, and energy homeostasis. Accumulating evidence indicates that chronic inflammation in the GI tract largely is driven by microbial dysbiosis (altered microbial composition) and appears to precede the development of both communicable and non-communicable diseases such as enteric infections, diabetes, obesity, cardiovascular disease, inflammatory bowel disease (IBD), mental disorders, and cancer (PMID: **31747581** DOI: 10.1016/j.immuni.2019.09.020*). Microbial dysbiosis and failure to establish and maintain an appropriate GI microbiota in early life may increase the risk for several pediatric diseases including type 1 diabetes, necrotizing enterocolitis (NEC), celiac disease, asthma, and allergies. In addition, aging *per se* may drive microbial dysbiosis and contribute to related metabolic alterations. Emerging evidence indicates that diet-microbiome interactions may also contribute to health disparities in disease progression including cardiometabolic diseases and colorectal cancer.

Mechanistic microbiome studies are predominantly limited to animal models, and despite some notable successes in using fecal-microbial transplants (FMT) and other microbiome-targeted therapies, the translation of these findings to clinical practice remains a major challenge in the field.

A better understanding of the molecular mechanisms of FMT efficacy, pre/probiotic supplements, and other microbiome targeted therapies would aid the development of novel strategies that modulate the gut microbiota to restore gut and systemic health.

Current microbiome research in large cohorts often relies on fecal analysis as proxy for characterizing microbial communities in the GI tract and does not necessarily reflect regional or mucosa-associated microbial communities. The abundance and variety of microbial metabolites that are biosynthesized in different regions of the GI tract is not well defined, therefore the exact nature of GI mucosal and microbial metabolite interactions is unknown. Endoscopy has been used previously to characterize mucosa-associated microbial communities in both the upper and lower gastrointestinal tracts. However, endoscopic preparatory procedures can disrupt microbial populations, making it difficult to interpret data from this sampling technique. In addition, these procedures cannot access many anatomical regions and fail to allow precise serial sampling for longitudinal characterization of host-microbe interactions and changes to microbial ecologies.

Some of the devices/tools supported for development through this initiative include but are not limited to:

- Development of non-invasive ingestible micro-robotic tools such as smart pills or other devices that can be used to facilitate monitoring, possibly with real-time telemetry, *in situ* metabolic signaling and host-microbiota interactions along the discrete regions of the GI tract
- Development of devices that integrate engineered live biosensors and/or theragnostic bacterial strains to allow interrogation, and/or visualization of unique regional host-microbe interactions
- Development of minimally invasive devices that enable delivery of dietary/drug constituents to a single site or multiple locations in the GI tract in humans
- Development of minimally invasive tools that allow single time or multiple sampling of gastric mucosa for reliable measurement of biochemicals
- Development of minimally invasive devices and tools that enable collection of microbial samples for cultivation from distinct regions of the GI tract

1. PMID: 31747581 DOI: 10.1016/j.immuni.2019.09.020 - https://www.sciencedirect.com/science/article/pii/S1074761319304169?via%3Dihub

The Opportunity:
There is a critical need for ingestible tools/devices that allow monitoring, interrogation *in situ* and

sampling of gut mucosal tissues at various anatomical regions of the gastrointestinal tract without disrupting normal GI physiology and associated microbial flora. Such tools may support mechanistic studies in humans, allow collection of luminal contents for single or repeated measures, and enable study of metabolic signaling and identification of potential biomarkers. Devices capable of delivering and/or monitoring dietary components, drugs or special probiotics strains will advance our knowledge on unique host-microbial interactions. Devices are also needed for collecting gut microbial samples from inaccessible anatomical sites without contamination and under proper pH and O2 conditions, to allow for subsequent isolation and culture. Regional sampling also may provide a better understanding of how the mucosa-associated microbiota triggers or sustained inflammatory events associated with aging, metabolic disease, obesity, IBD, hyperplasia and cancer and may contribute to health disparities.

Ingestible smart pills are emerging as non-invasive tools for GI research applications. These tools offer the ability to collect luminal contents, monitor in situ metabolic activities, deliver drugs/ dietary constituents, and collect mucosal material for exploring microbial communities. For example, an ingestible self-orienting millimeter-scale applicator (SOMA) that autonomously aligns itself to interact with GI tissue and deliver drugs to the GI mucosa (PMCID: PMC6430586*). Hydrogel devices ingested as pills withstand repeated mechanical loads in the stomach for up to one month enable long term collection of gastric contents (PMCID: PMC6353937*). Probiotic microorganisms can be designed to colonize specific regions of GI tract to allow for longitudinal monitoring by fluorescence imaging (PMID: 33545291 DOI: 10.1016/j.ijpharm.2021.120342*; PMID: 33448140 DOI: 10.1002/adhm.202001953*). In addition, there is a potential for harnessing novel strategies such as theragnostics that combine therapeutics with diagnostics into a single multifunctional microbial agent that can be used alone or combined with ingestible devices for targeted delivery to further explore host-microbiome interactions. However, many of these innovative applications are still in developmental phases and mostly confined to feasibility studies in large animal models. Supporting further development and optimization of these devices for clinical research is crucial to advance microbiome research and presents an excellent opportunity. PAR-20-133 has been successful in stimulating interest among researchers, initiating various collaborative interactions between biomedical engineers and gastroenterologists. Leveraging on this opportunity and additional support will advance microbiome research.

This initiative aligns well with the strategic goals of the NIDDK strategic plan namely 1.3: Develop innovative technologies and resources and expand data science to advance scientific progress and enhance health, and 2.1: Enhance the development and testing of diagnostics, therapeutics, and prevention strategies. For this reason, we believe this is a very timely effort for advancing diet-host-microbial interactions.

1. PMCID: PMC6430586 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6430586/
2. PMCID: PMC6353937 - https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6353937/
3. PMID: 33545291 DOI: 10.1016/j.ijpharm.2021.120342 -

https://www.sciencedirect.com/science/article/pii/S0378517321001460?via%3Dihub
4. PMID: 33448140 DOI: 10.1002/adhm.202001953 - https://onlinelibrary.wiley.com/doi/10.1002/adhm.202001953

The Proposed Approach:
Propose a PAR for soliciting applications under investigator initiated R01 mechanism. No pay-line funds will be requested. These applications support technology development of ingestible devices, followed by demonstration of optimization and feasibility of the device in appropriate animal models and further demonstrate the functionality of the device in a relevant cohort. Optimization and improvisation of an existing technology will also be supported in this initiative. Progress will be monitored by semiannual reports and initially negotiated milestones.

Expected Annual Expenditures: >$1M to <$5M

National Institute of Diabetes and Digestive and Kidney Diseases

The Liver Tissue and Cell Resource Center (LTCRC)

Lead Division / Office: DDN

Program Contact(s): Jose Serrano

Executive Summary:
NIDDK supports clinical research on the diseases of internal medicine and related subspecialty fields as well as many basic science disciplines, including end-stage liver disease. To understand the pathophysiology of the diseases that lead to end-stage liver disease it is essential for researchers to have access to liver tissue and cells from a variety of liver diseases as well as normal livers. These specimens would not be available to researchers who work outside a liver transplant center. Moreover, these specimens are prohibitively expensive on the commercial market. To address the limitation imposed on liver research by the lack of suitable normal and pathologic human liver tissue and cells, NIDDK has supported the procurement and distribution of liver tissue since 1986 and this concept would continue this investment.

The Need / Background:
To address the limitation imposed on liver research by the lack of suitable normal and pathologic human liver tissue and cells, NIDDK established a contract for the procurement and distribution of liver tissue in 1986, the Liver Tissue and Cell Distribution System (LTCDS). Throughout the ensuing years the University of Minnesota has competitively procured continuation contracts in consortium with different institutions.

The objective continues to be the provision of human liver, both tissue and hepatocytes to help bridge the gap between animal research and human applicability. The service makes it possible to directly investigate the human hepatocytes and hepatic tissue in studies of cell biology, metabolism, gene regulation and disease conditions. Over the years, the LTCDS has provided human hepatocytes primarily in culture and human liver tissue (primarily pathologic) as quick frozen blocks taken in the operating room at the time of hepatic resection during orthotopic or living related donor liver transplantation. In addition, the LTCDS has increasingly provided "normal" human hepatocytes in culture or normal liver tissue (primarily frozen), slides, and tissue blocks.

Since the inception of the current contract in 1986, over 1,000 investigators in the field of liver research, mostly funded by NIH, have received liver tissue specimens and hepatocyte preparations. Pathological liver specimens have been sent to investigators interested in a broad range of liver diseases (hemochromatosis; hepatocellular cancer; hepatoblastoma; tyrosinemia; alcoholic steatosis and cirrhosis; nonalcoholic steatohepatitis; hepatitis C; hepatitis B; cirrhosis; primary biliary cholangitis; sclerosing cholangitis; Wilson’s disease; biliary atresia; autoimmune hepatitis and cystic fibrosis). Consistently over the years, 91% of investigators using LTCDS services have responded in annual queries “that their ongoing and future liver research would be compromised without this core resource”.

The Opportunity:
The service provided by the LTCDS has been a reliable source of high quality liver tissue as well

as isolated hepatocytes used by hundreds of investigators at a fraction of the cost of charged by commercial sources, significantly reducing the cost of NIH funded research as over 80% of LTCDS users are NIH funded investigators.

The Proposed Approach:
As the purpose of this initiative is to provide human liver tissue and hepatocytes as a research resource to the scientific community, the Resource-Related Research Projects (R24) grant, is an appropriate mechanism.

An R24 resource grant mechanism is a non-hypothesis-driven activity to provide data, materials, tools, or services that are essential to making timely, high quality, and cost-efficient progress in a field.

Expected Annual Expenditures: <$1M

National Institute of Diabetes and Digestive and Kidney Diseases

A Consortium for Gut-Brain Communication in Parkinson's Disease

Lead Division / Office: DDN

Program Contact(s): Terez Shea-Donohue

Executive Summary:
Parkinson's disease (PD) is the second most common and fastest growing neurodegenerative disorder, with approximately 60,000 Americans diagnosed annually. The incidence of PD increases with age regardless of gender and treatments target only symptoms as no therapies exist for the neurodegeneration in PD. More than 50% of patients who develop PD have a history of bowel complaints, predominantly constipation, gastroesophageal reflux, and nausea, which often precede the onset of motor symptoms. These findings indicate that gastrointestinal (GI) dysfunction may be an early manifestation of the disease and that the gut may be an unexplored diagnostic and/or therapeutic target. An NIDDK sponsored a workshop focused on the gut-brain axis in PD recognized progress in this area required an infrastructure to support a multidisciplinary approach between investigators in neurology and gastroenterology. In addition, research into the temporal relationship between GI symptoms and disease progression in PD needed larger and longitudinal collections of patient data and biospecimens. The goal of this initiative is to accelerate research progress by promoting partnerships across currently siloed clinical disciplines to investigate the role of the gut in the etiology and progression of PD. Given the evidence that gut health significantly impacts brain morphology and function, research in this area may be applicable to other neurodegenerative disorders that involve dysfunction of the GI tract.

The Need / Background:
Neurodegenerative disorders encompass a spectrum of diseases including Alzheimer's disease, Parkinson's disease (PD), and PD-related disorders that all feature progressive degeneration and/or death of nerve cells. According to the Global Burden of Disease study, neurological diseases are currently the leading source of disability around the world. The second most common and fastest growing of these disorders is PD with approximately 60,000 Americans diagnosed annually. Regardless of gender, PD risk increases with age and the economic burden of PD is estimated to be $52 billion per year. There is little information on PD risk in underrepresented populations. Currently there are only symptomatic treatments for PD as there are no therapies that target the underlying neurodegeneration.

PD is emerging as a multisystem disorder associated with a heterogeneity of clinical changes, suggesting the existence of different subtypes, characterized by both motor and non-motor dysfunctions. For many decades, PD research focused on the brain; however, PD symptoms are not limited to motor dysfunction and more than 50% of patients who develop PD often have a history of bowel complaints affecting nearly all parts of the gastrointestinal (GI) system including the esophagus (dysphagia), stomach (nausea, gastroparesis), and colon (constipation), as well as

the rectum and anus (anorectal/defecatory dysfunction). Both the contribution of side effects of PD therapies on these GI symptoms and the impact of GI dysfunction on the efficacy of PD medications are poorly documented. The fact that GI symptoms may be present years before the appearance of motor symptoms gave rise to the hypothesis that the gut plays a key, but undefined, role in the initiation and/or progression of PD. Thus, gastroenterologists have the unique opportunity to be at the forefront of PD diagnosis and treatment.

The brain-gut axis in is a highly complex, bidirectional network that utilizes neural, neuroendocrine, metabolic, and immune pathways. There are two major neural influences that regulate GI function: the autonomic nervous system primarily via the vagus nerve, and the enteric nervous system (ENS). While the vagus is a proposed route for the ascending propagation of α-synuclein aggregates to the brain, the neural and possibly non-neural mechanisms of distribution of pathogenic factors between the brain and the gut in PD are unexplored. There are variations in α-synuclein accumulation along the gut that can affect propagation patterns and the relationship of these regional differences to gut symptoms is understudied. The strong focus on α-synuclein propagation and accumulation as critical to disease progression has also limited the search for other molecular signatures that that might serve as clinical diagnostic biomarkers of the GI pre-symptomatic phase of PD. There is little known about the role of pathogenic α-synuclein accumulation in the gut in GI dysfunction or its relationship to motor symptom duration or severity in PD.

There is increasing recognition that gut health has a significant impact on brain morphology and function. Prodromal GI dysfunction in PD has been linked to dysbiosis, enteric inflammation, enteric infection, and/or exposure to environmental toxins, all of which may contribute to the increased intestinal permeability reported in these patients. The scientific literature supports a close association between inflammation, neuroimmune interactions, and PD and retrospective studies suggest that there may be an increased risk of PD in patients with IBD. Differences in gut microbiota in PD patients have been linked to brain neurodegeneration and may correlate with severity and duration of motor symptoms. The therapeutic potential of targeting the prodromal phase of PD requires identification of the key gut-brain pathways and biomarkers that can be leveraged to develop diagnostic tools as well as therapies that impact disease progression in PD and potentially other neurodegenerative diseases.

The Opportunity:
There is a strong NIDDK interest in the impact of gut health on gut brain communication. NIDDK sponsored a mini-symposium and workshop in 2021 focused on the gut-brain axis in PD in collaboration with other NIH institutes. The published Meeting Summary of the workshop highlighted that research progress has been limited because there are few investigators who are experts in both the critical areas of neurology and gastroenterology and few collaborative interactions among scientists and clinicians in these fields. To move the field forward, there is an urgent need to incentivize interactions between investigators with complementary expertise in these two siloed disciplines. Integrated data from advanced techniques in brain-gut neuroimaging and assessment of autonomic dysfunction could be used to determine the role of the gut in the origins of PD as well as the mechanisms associated with progressive neurodegeneration in both the CNS and GI tract. Current and developing technologies that support repeated, non-invasive sampling of

luminal contents along the length of the gut in humans could be leveraged to study the microbiota and/or microbial products. The availability of patients and biospecimens is critical to the success of this initiative as few centers have sufficient information on GI dysfunction in patients with PD. Thus, critical to success is the collection of data and samples under a large-scale data sharing effort starting from the prodromal, non-motor GI phase to the overt motor phase. A multidisciplinary collaborative effort will provide the infrastructure needed to establish an annotated repository of biospecimens (e.g., blood, stool, and GI tissues) to allow for the identification and validation of developing innovative early-phase GI-based diagnostic tools and biomarkers for PD. Such an approach is also needed to overcome the practical hurdles that have precluded development of novel interventions based on gut-based targets that may be applicable to PD and potentially to the broader spectrum of neurodegenerative diseases.

The Proposed Approach:
There is interest from the other NIH Institutes who actively participated in the NIDDK sponsored activities that informed the rationale for this initiative concept proposal. To effectively advance the field, the approach of a cooperative agreement would be used to establish partnerships and collaboration between investigators with expertise in gastroenterology, neuroscience, microbiology, and immunology. A consortium of centers will allow recruitment of sufficient patients and use of standardized protocols to collect data and biospecimens relevant to both neurology and gastroenterology research. A cooperative agreement mechanism will also allow NIH program staff to facilitate the interactions between the clinical centers and coordinate the sharing of data and biospecimens needed to accelerate progress in this area. The consortium would include a coordinating center that would provide the infrastructure for the efficient design and conduct of multicenter clinical studies and creating a collection of patient samples that may be used for ancillary studies of etiology and pathogenesis.

Examples of scientific topics of interest include:

1. Longitudinal studies of disease progression in PD patients, including those from underrepresented populations, with temporally coordinated evaluations of GI and neurological functions. Priority should be given to GI function tests that might provide mechanistic insights relevant to mucosal barrier function, mucosal immunology, or motility/transit along the length of the GI tract.
2. Analysis of existing samples to identify and validate novel gut-based biomarkers that predict or contraindicate GI dysfunction in PD, correlate with specific symptoms of prodromal GI dysfunction, or associate with disease severity in PD. This can include validation of putative biomarkers such as pathogenic α-synuclein in the gut.
3. Recruitment, evaluation and continued follow up of PD patients to generate a multi-sample repository of tissues to perform multi-omic assessments of genetic, epigenetic and metabolomic profiles, including multi-modal single-cell analyses, with the goal of identification of novel gut-based biomarkers or other diagnostic tools and therapeutic targets.
4. Analyses of the composition and activities of the intestinal microbiome to identify

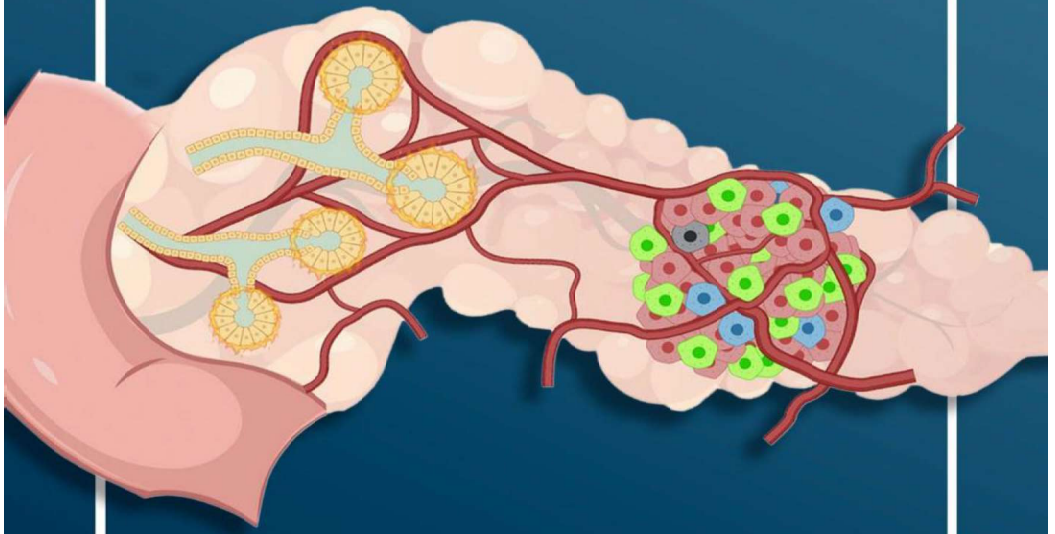
relationships among microbiome composition and the phenotype, onset, duration, and severity of GI dysfunction or of PD.

5. Characterization of gut-brain communication in PD using novel multimodal data from gut samples, brain and gut imaging, neurological or other relevant tests of neural and non-neural pathways with the goal of leveraging integrated data modalities to stratify PD patients. Analyses should consider the heterogeneity of PD patients with regard to occurrence of prodromal GI dysfunction, symptom onset, and disease progression.

Expected Annual Expenditures: >$5M

Planned Workshops

INTEGRATED PHYSIOLOGY *of the* EXOCRINE *&* ENDOCRINE COMPARTMENTS *in* PANCREATIC DISEASES WORKSHOP



JUNE 29–30, 2022

National Institute of Diabetes and Digestive and Kidney Diseases

Rationale for Workshop

- Investigations into the basic biology and pathophysiology of the endocrine and exocrine pancreatic compartments have largely avoided being informed by inter-compartmental interactions.
- The purpose of the 1.5 day workshop is to bring clinical and basic scientists together who are interested in diseases of the endocrine and exocrine pancreas to understand how the two compartments interact in diseases, to engage in interdisciplinary discussions and to identify areas for advancement.

Organizing Committee

- Teresa Mastracci – Indiana Univ
- Stephen Pandol – Cedars Sinai
- Maike Sander – UC San Diego
- Ashok Saluja – Univ of Miami
- Melena Bellin – Univ of Minnesota
- Joana Almaca – Univ of Miami
- David Whitcomb – Univ of Pittsburgh
- Maren Laughlin – DEM/NIDDK
- Norann Zaghloul – DEM/NIDDK
- Jose Serrano – DDN/NIDDK
- Dana Andersen – DDN/NIDDK

Workshop Agenda

- Welcome – Griffin P. Rodgers NIDDK
- Overview of Pancreatic Anatomy, Physiology and Function – David Whitcomb
- New Insights into Anatomy and Physiology
  - Development and Maturation, Vascular Flow, Neuronal Innervation, and Stellate Cells
- Diabetes in the Setting of Exocrine Disease
  - Diabetes After Acute Pancreatitis, Diabetes After Chronic Pancreatitis, Cystic Fibrosis-related Diabetes, and Endocrine Effects of Exocrine Dysfunction

Workshop Agenda

- Metabolic Influences on the Exocrine Pancreas
  - Obesity and PDAC, Decreased Exocrine Mass in T1D, Insulin Effects on Exocrine Cells, and Acinar Cell Heterogeneity
- Genetic Drivers of Pancreatic Diseases
  - Genetic Drivers of Exocrine Disease, Diabetes, and Pancreatic Cancer
- Tools for Integrated Pancreatic Analysis
  - Histology and MRI Biomarkers, Organoids and Pancreas-on-a-Chip, Innervation Mapping, and Pancreas Slices
- Exocrine-Endocrine Cross-Talk
  - CFRDs, Beta-cell ER Stress, Inflammatory Signaling from Adipose Tissue, and Translational Regulation of Cross-talk

Workshop Logistics

- Date and Venue:
  - Natcher Auditorium, NIH Bethesda Campus
  - June 29-30, 2022
- Registration :
  - Attendance is Free but On-line Registration Required
  - See NIDDK Website (Meetings and Workshops)
- Deliverables
  - Conference Summary Manuscript
  - Recommendations to Inform possible future funding initiatives by NIDDK

CLINICAL TRIALS IN PANCREATITIS

Opportunities and Challenges in the Design and Conduct of Patient-Focused Clinical Trials in Recurrent Acute and Chronic Pancreatitis

July 20, 2022

NIH National Institute of Diabetes and Digestive and Kidney Diseases

The University Club
123 University Place,
Pittsburgh, PA

WITH THE ADDITIONAL SUPPORT OF THE NATIONAL PANCREAS FOUNDATION

Rationale for Workshop

- Recurrent acute and chronic pancreatitis are characterized by pain, disability and late-stage complications. No FDA-approved drugs currently exist to treat these conditions but interest in developing therapeutic strategies has increased.
- This one-day workshop will feature discussions to help attendees understand the principles and requirements of clinical trials for treatment approaches for these diseases.

Organizing Committee

- Co-chairs: Tonya Palermo (UW) and Phil Hart (OSU)
- Federal: Dana Andersen, Jose Serrano and Aynur Unalp-Arida (NIDDK) and Erica Lyons (FDA)
- Non-Federal: Vern Chinchilli (PSU), Zobeida Cruz-Monserrate (OSU), Evan Fogel (IU), Chris Forsmark (UFl), Linda Martin (Mission-Cure), Søren Olesen (Alborg Univ), Stephen Pandol (Cedars-Sinai), Emily Perito (UCSF), Anna Phillips (UPittsburgh), Hanno Steen (Harvard), Temel Tirkes (IU), David Whitcomb (UPittsburgh), Ying Yuan (MDAnderson)

Agenda

- Session 1: Introduction and Patient Perspectives
  - Keynote: Overview of key considerations in clinical trials – Robert Dworkin (URochester)
  - Patient perspectives on pancreatitis: The NPF/FDA Voice of the Patient Report, Considering participant burden to optimize recruitment and retention
- Session 2: Outcomes and Endpoints in Trials
  - Defining appropriate patient populations for inclusion in clinical trials in pancreatitis, Outcome measures and endpoint assessments in pancreatitis, and Selection of outcome measures for drug development in pancreatitis: a regulatory perspective

Agenda

- Session 3: Considerations for clinical trial design
  - Design and execution of proof-of-concept and feasibility clinical trials, Design of trials to assess efficacy of invasive treatments, and Approach to complex or innovative clinical trial design.
- Session 4: Additional Considerations
  - Design and conduct of clinical trials in children and adolescents, Public-private partnerships and foundations, Ethics in clinical trials: disease-specific applications, and Opportunities for investigators for conducting clinical trials in pancreatitis.

Workshop Logistics

- Date and Venue:
  - Wednesday July 20, 2022
  - University Club, Pittsburgh PA
- Registration:
  - Attendance is free and open to the public but advanced registration is required
  - See NIDDK Forthcoming Meetings for full info
- Deliverables:
  - A conference summary manuscript will be submitted for publication
  - Recommendations may inform possible future funding initiatives by NIDDK