Jump-Starting Kidney Research

Fostering Disruptive Innovation to Advance Nephrology

Jenna M. Norton and Robert A. Star

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Introduction

Disruptive innovation in research is rare. Like a tornado, disruption lands abruptly and unexpectedly, injecting new ideas that may leapfrog stalled efforts and raze fixed constructs that impede scientific advances. Contrasting developmental research, which steadily builds and applies existing theories, disruptive research introduces novel approaches and concepts, pushing fields in new directions. Predicting and promoting such innovations may seem impossible. Often, cutting-edge research ultimately fails, and groundbreaking observations sometimes occur serendipitously during seemingly ordinary projects. But, as with tornadoes, early indicators and predisposing conditions exist. If we can identify and understand these predisposing conditions, we may be able to generate the "perfect storm" to promote disruptive advances in research.

The nephrology field is in particular need of disruptive innovation. Despite the laudable efforts of the nephrology research community, progress in recent decades to effectively address AKIs and CKDs has been largely incremental. AKI remains a therapeutic conundrum where a "bump" in creatinine results in the reflex nephrology consult. We lack deep pathophysiologic understanding of AKIs, such that our clinical management (advice on fluid intake and nephrotoxin avoidance, with watchful waiting and no specific therapy) is supportive and does not target the root cause of disease. A handful of Food and Drug Administration–approved biomarker tests for AKI exist, but they lack robustness and have not been sufficiently useful to affect therapies, prognosis, or subphenotyping. Hard outcomes—such as death, dialysis, and the newly recognized development of CKDs and later death from cardiovascular disease—occur long after AKI. In CKDs, the few available therapies that effectively slow progression are nonspecific, likely a reflection of our limited understanding of the pathophysiologic pathways of CKDs. Drug development in CKDs remains difficult given the heterogeneity of disease and slow rate of progression. Large sample sizes are needed to overcome the slow trajectory of CKDs, a relatively low rate of clinically important outcomes (*i.e.*, dialysis, death, clinically meaningful change in eGFR), and lack of valid surrogate outcomes. Although they were discovered in the midst of cardiovascular trials in people with type 2 diabetes, the recent addition of sodium-glucose cotransporter 2 inhibitors to our armamentarium of CKD treatments is disruptive, given their potential to change treatment paradigms and provide new insights on pathophysiology. Advances in molecular biology and genetics have enabled innovative discoveries, such as the contribution of APOL1 risk variants to CKD progression and racial disparities. We are finally looking for disease heterogeneity within both AKIs and CKDs to jump-start a personalized medicine approach.

To help trigger new momentum in kidney research, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) aims to build and learn from prior attempts to promote innovative research and development in a variety of fields to better understand, detect, and promote disruptive innovation in nephrology research. This may enable targeting limited research funds to the high-risk studies most likely to pay off (while still maintaining a healthy profile of developmental research) and building research infrastructure and networks that will promote disruptive findings.

Understanding and Creating Conditions that Foster Scientific Innovation

Research funders have long sought strategies to optimize research innovation. None have been a panacea. Expanding our view beyond the medical field and leveraging big data about science may provide new insights. Innovation, and factors that promote innovation, have been studied in the economic literature (1), and in an emerging "science of science" field (2). The former is typically case based, and the latter uses data on scientific inputs and outputs and computational modeling. Both fields aim to understand mechanisms, processes, factors, and challenges to innovation (2).

A significant challenge to disruptive research is the risk inherent to innovation. Only a small percentage of truly novel ideas succeed. Although innovation calls for risk takers, the science of science literature suggests researchers are often risk averse, preferring to conduct research well within their current expertise (2). In addition, traditional scientific funding infrastructure and peer-review processes—including within the National Institutes of Health—struggle to embrace risk.

Collaboration is a driver of innovation if the team can create synergy. The business literature focuses on

Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland

Correspondence: Dr. Robert A. Star, Division of Kidney, Urologic, and Hematologic Diseases, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, 6707 Democracy Boulevard, 6th Floor, Bethesda, MD 20817. Email: robert.star@nih.gov

random interactions in tight quarters (typified by the unique design of Massachusetts Institute of Technology Building 20, where acoustics and radar were developed; replicated in Google headquarters) (3). Business innovation efforts also include so-called "skunk works" or "swamp works," established away from corporate headquarters to remove small teams from the limitations and formalities of standard business policies and procedures and create a "start-up-like" environment more open to "out-of-the-box" ideas (3). Citation analyses suggest that high-impact science is associated with collaboration, particularly when collaboration occurs across research disciplines or with on-the-ground partners deeply invested in solutions (*e.g.*, businesses, governments, organizations) (4). Such diverse perspectives may foster innovation through generation of boundary-spanning ideas, bringing in principles from "outside" fields to catalyze innovation. For example, identification of *Helicobacter* as a gastrointestinal pathogen upended the surgical treatment of peptic ulcer disease, and oncology is undergoing a revolution with the introduction of checkpoint inhibitors borrowed from immunology.

However, collaboration is not necessarily associated with scientific advances. As recently reported (5), innovation does not increase with the number of collaborators and, in fact, appears to decrease with increasing team size. The analysis of citation patterns for >65 million papers, patents, and software products from 1954 to 2014 found small teams were associated with citation patterns characteristic of disruptive innovation (*i.e.*, a novel citation node wherein future works cite the work in question, but not previous work upon which it was built), whereas large teams were associated with citation patterns characteristic of developmental research (*i.e.*, the work in question is referenced in future manuscripts, along with its predecessors) (5). The reduced disruptive capacity of large teams may be a consequence of democratic science, where the majority prevails. Science of science research has not yet explored how such patterns may differ in individual fields (*i.e.*, nephrology), given differences in culture, procedures, preferences, and other characteristics (2).

Learning from Recent and Ongoing Innovations in Nephrology

Nephrology researchers are using cutting-edge technologies and strategies—induced pluripotent stem cells, single-cell omics, molecular biology and genetics, model systems (tissue chips, organoids), machine learning, reimagined health information technologies, engaging patients as equal collaborators, novel clinical care delivery paradigms—that hold promise to drive advances in the field. Many of these are the subject of recent reviews published in this journal (6,7). We highlight one emerging area.

In 2017, the Kidney Precision Medicine Project (KPMP) merged efforts to understand the pathobiology of both AKIs and CKDs (https://kpmp.org/). Central to this effort is obtaining research kidney biopsy specimens and developing tools for a mechanistic understanding of kidney diseases. Kidney precision medicine studies, such as KPMP and Trident (8), that employ single-cell technologies and advanced molecular imaging will greatly improve our ability to interpret kidney histology (using objects rather than patterns of injury) and uncover distinct disease subgroups with specific pathways to target. However, we do not yet understand how to pathophysiologically phenotype participants enrolled in these studies (other than by performing a kidney biopsy), or how to use that information to better understand the wealth of omics data. Recently, cleavable optical probes were developed for real-time optical detection of the mechanisms of kidney injury (9). These probes are cleaved by superoxide and caspases, culprit molecules that cause tissue injury. The cleaved products can be detected by whole-animal imaging in mice and appear in the urine. They appear to be very early-stage biomarkers of AKI. Why is this useful? If replicated and translatable to humans, these or similar probes could be used to noninvasively detect kidney injury early, identify high levels of an injury molecule, and guide dose adjustments (as a drug-companion biomarker combination) (10). Because AKI caused by coronavirus disease 2019 appears to cause a variety of kidney injuries (cytokine storm, local thrombosis, direct viral invasion, rhabdomyolysis), we will need creative probes and biomarkers that can distinguish among these types of injury in patients who are sick and who cannot tolerate a kidney biopsy.

National Institute of Diabetes and Digestive and Kidney Diseases Efforts to Incentivize Innovation

To better support innovative, investigator-initiated science, NIDDK is exploring more flexible, less conservative funding opportunities. These opportunities will require less preliminary and feasibility data and employ novel review strategies, thereby encouraging high-risk, high-reward research ideas distinct from those that can be supported through the traditional R01 grant mechanism. Key areas of emphasis may include technologic innovation, proof-of-concept studies, and early prototyping research that present opportunities to break new ground. Because even the most forward-looking scientists and reviewers cannot predict with accuracy which studies will successfully shift paradigms, we anticipate many of these studies will fail. However, the considerable risk of failure will be balanced by the potential high influence on human-health and related research. For example, the recently released opportunity "Catalytic Tool and Technology Development in Kidney, Urologic, and Hematologic Diseases" calls for applications to develop novel tools and technologies that enable new lines of scientific inquiry and/or treatment, prevention, or diagnosis of kidney diseases (https://grants.nih.gov/grants/guide/pa-files/PAR-20-140.html). The Innovative Science Accelerator Program will provide seed funding through a flexible review process using a rigorous external peer review that will be instructed, educated, and encouraged to embrace a high-risk tolerance and establish a collaborative environment for idea and resource exchange (https://grants.nih.gov/grants/guide/rfa-files/rfa-dk-20-010.html). NIDDK aims to adopt successful strategies from the Innovative Science Accelerator Program review process to engender a frame shift among NIDDK-run review sections that will facilitate willingness by reviewers to take risks on potentially high-reward science. In addition, a Notice of Specialist Interest (NOSI)

on Advancing Polycystic Kidney Disease (PKD) Research through Catalytic Tool and Technology Development aims to facilitate development of novel tools and technologies that enable new lines of scientific inquiry and/or treatment, prevention, or diagnosis of polycystic kidney disease, with high likelihood to lead to scientific breakthroughs (https://grants.nih.gov/grants/guide/notice-files/NOT-DK-20-034.html).

People with kidney diseases and nephrologists need disruptive innovation. To help jump-start kidney research, the NIDDK aims to better understand, detect, and promote disruptive innovation, leveraging a growing body of literature on the origins and patterns of innovation from economics, business, technology, science, and other fields. Building on recent advances in kidney research, these efforts will encourage high-risk, high-reward science and transdisciplinary approaches to generate boundary-breaking ideas and improve kidney outcomes.

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