Dr. Chirag R. Parikh is Professor of Medicine and Director of the Program of Applied Translational Research (PATR) at the Yale School of Medicine. He also holds the title of Professor in the Clinical Epidemiology Research Center through the VA Connecticut Health Care System. After receiving his medical degree in Mumbai, India in 1996, Dr. Parikh completed residency training in Internal Medicine at Nassau University and the State University of New York (SUNY) in Stony Brook, New York. Subsequently, he pursued a fellowship in Nephrology and Hypertension at the University of Colorado Health Sciences Center in Denver. He also completed a PhD in 2003 at the University of Colorado where he was the first student to complete the Clinical Investigation and Translational Research program. Dr. Parikh is board-certified in Internal Medicine and Nephrology and continues to practice medicine in addition to directing the PATR.

At the PATR, Dr. Parikh oversees numerous patient-oriented research programs studying the translational and epidemiological aspects of acute kidney injury (AKI) and other kidney diseases, with a special interest in developing novel kidney injury biomarkers to aid clinical decision-making and drug development. He has won numerous awards for this work, including the Outstanding Investigator Award from the Society of Clinical Investigation. Dr. Parikh is a prolific writer and speaker, having published more than 250 peer-reviewed manuscripts, 50 book chapters and reviews, and having given more than 50 invited presentations at academic centers and scientific conferences worldwide. As a leader in translational kidney research with a strong interest in drug development, he answered questions recently about what his research group is currently investigating, how he became interested in translational research, and his advice for young scientists interested in translational work and drug development.

**Dr. Parikh, what is your group working on right now? Could you please provide a brief description of what your group does and how this work aids drug development?**

At the PATR, most of the work we do is related to biomarker development to facilitate early disease diagnosis and risk stratification, and to provide more comprehensive information with which to make patient care decisions. Our projects mainly involve the evaluation of a specific type of kidney disease known as acute kidney injury (AKI). AKI is common – between 5 and 10 percent of hospitalized patients will develop it. It is especially common after cardiac surgery and in ICU patients, and it is associated with a very high mortality rate. Serum creatinine (sCr) is the current paradigm for AKI diagnosis, but this measurement is rather imprecise and nonspecific. Furthermore, this test has remained relatively unchanged for 60 to 80 years. Thus, we are...
working on developing better AKI biomarkers.

Most nephrologists such as myself perceive sCr as inadequate, especially because it is only a marker of filtration. Filtration is indeed one of the kidney’s main roles, but this organ has many additional functions beyond that, including maintaining the body’s acid-base balance and appropriate levels of minerals like potassium and calcium. Thus, since sCr does not capture all the different functions of the kidney, its use as a sole diagnostic test may delay disease recognition especially if the filtration function of the kidney is intact. A patient has to lose significant kidney mass before filtration changes. This leads to a period of time when disease starts before we can detect it using sCr. Ideally, a kidney disease detection tool would be a structural marker which could be measured as soon as injury begins. For example, a biomarker like this exists in the field of cardiology, namely troponin as a structural marker for the heart. For the last several years, our group has focused on making similar advances in the field of nephrology. By studying patients who develop AKI after cardiac surgery, we have identified a few proteins in blood and urine that could be diagnostic and supplement sCr. By detecting a disease immediately at its onset, physicians can broaden the treatment window. Thus, our biomarker work is an opportunity for drug development: if these novel proteins are elevated sooner, we can then enroll patients in trials to treat AKI earlier in their course of injury.

These new markers could also aid in drug development in other ways. For example, in current drug trials for chronic kidney disease, outcomes manifest only after many years. For example, in the field of diabetic kidney disease, a typical study will have 2000 to 3000 patients who are followed for 3 to 5 years, with the main endpoints of the study being doubling of serum creatinine levels and the need to start dialysis. If we could use biomarkers to better identify patients who would likely have a more rapid course of disease, we could primarily enroll these patients in trials, thereby reducing trial duration and size. In the drug development field, biomarkers that help identify patients likely to get clinical events are called prognostic biomarkers.

We at the PATR are also interested in developing pharmacodynamic (PD) biomarkers. These are biomarkers used to observe the immediate effect of a drug. Essentially, when a patient receives a drug, a physician can measure the PD biomarker and determine if the drug had an effect or not – then the physician can make a decision to continue using the drug or try a different regimen or dose. We are trying to identify PD biomarkers linked to the drugs’ mechanisms of action, which can then become surrogate endpoints to help with Phase 2 and 3 clinical trials. So instead of waiting months to years, we could use these PD biomarkers to decrease trial time.

In addition to prognostic and PD markers, we are also studying predictive biomarkers. These biomarkers inform us if a patient is likely to respond to a given intervention. Development of predictive biomarkers is essential to realize the dream of precision medicine. Currently, most common interventions have a “number needed to treat” (NNT) of 20 to 30. This means that to find one responder to the drug, we have to treat 20 to 30 patients. To develop predictive markers, we are evaluating samples from completed clinical trials on diabetic kidney disease such as ACCORD or VA-NEPHRON-D. For example, if we could identify proteins that would predict response to an angiotensin receptor blocker (ARB) in the VA-NEPHRON D trial or patients who would benefit from tight glycemic control in the ACCORD trial, we could potentially target patients for treatment and prevent potential side effects in patients unlikely to respond. Predictive biomarkers have the ability to reduce NNT by enhancing efficacy and reducing harm.

In the field of oncology, predictive biomarkers have been very successful in targeting responses for breast cancer and melanoma. One of the biggest modern challenges is moving into an era of precision medicine where each person is given unique drugs based on his genetic make-up and lifestyle. Because the event rate in the general population for a certain drug is low, we currently have to give a drug to many individuals to see an effect without the help of biomarkers.

Lastly, we are interested in developing safety biomarkers which can identify drug toxicity to any tissue. We are using blood and urine samples from large national cohorts to evaluate kidney disease caused by the HIV drug tenofovir. Tenofovir can cause nephrotoxicity, specifically to the proximal tubule, so we are trying to identify biomarkers which could reveal months to years earlier than sCr when a patient has started to develop disease. Doing so would allow us to modify drug doses or change a patient’s antiretroviral regimen. Also, these biomarkers could potentially be used as safety endpoints for drug development of newer interventions for kidney disease.

How did you become interested in translational research, and how did you get to where you are today?

I went to medical school in India at one of the premier schools in the country, and I met a group of extremely smart physician-scientists who were involved in patient-oriented research. While there, I realized how much further medicine needs to advance to improve outcomes for most diseases – it was clear our knowledge in clinical medicine was sparse, and in some cases, incomplete. I
was involved in research during medical school, and I decided to become a physician-scientist. After coming to the US, one of my early mentors in residency was a nephrologist and critical care specialist, in addition to being a statistician. It was from him that I realized the power of numbers in medicine and statistical principles for testing hypotheses and generating evidence to help patients – this was in 1996. I saw the potential of large scale trials using precise statistical models to improve patient outcomes.

In 1999, I completed a nephrology fellowship at the University of Colorado, and there I was exposed to several groups which were involved in preclinical research using animal models. It was clear that there was a lot of valuable basic science work going on, but relatively less work was directly being applied to patient care – there was a bottleneck of information and lack of translation. There was a disconnect: the PhDs weren’t able to see patients, and the physicians weren’t exposed to all the tools of basic science research like mass spectrophotometry, microscopic and genetic techniques. Around this time, the NIH initiated a program to encourage translational research, and my research mentor Dr. Robert Schrier started a PhD program in Clinical Investigation at the University of Colorado. I was the first student to finish the program in 2003. The curriculum was divided so that trainees learned basic science techniques as well as epidemiological and statistical concepts. This background positioned me to become a physician-scientist in translational research. After a few years as faculty at the University of Colorado, I moved to Yale in 2005. Now, I conduct multi-center studies on kidney diseases with large numbers of patients, and each project I do has translational components such as biomarker development or investigating genetic risk factors; thus, we can uncover biological mechanisms of disease to improve patient outcomes. I spend about 75 percent of my time conducting NIH-funded research, and the remaining time with educational and clinical activities.

**Please talk a bit about how your role as a physician informs your work as a scientist as it concerns biomarker discovery, validation, and drug development.**

I have an advantage as a biomedical researcher because I get to see patients. I want to make healthcare efficient, effective, safe, equitable, and accessible. Unless you interact with patients, it is challenging to think about diseases from a patient’s perspective. For example, I just came from caring for patients who developed nephrotoxicity associated with some newly-approved drugs. My hypothesis is that these drugs reduce the tolerance of the kidneys and makes them prone to autoimmune reactions. So now that I’m off clinical service and back thinking about research, I am contemplating ways to prove this hypothesis. If I didn’t see patients like these, it would seem like I was working in a vacuum and my results would not as easily be put to meaningful use. The research would be knowledge-based but not necessarily outcome-based. I frequently get asked about the translational aspects of certain proteins and biological molecules. I get most interested in research hypotheses which have compelling biological mechanisms as well as potential for clinical use in patients.

**What advice do you have for physicians and scientists just starting out in their careers who are interested in translational research and drug development?**

This is a great era for students becoming physicians and physician-scientists. The number of research tools we have in these fields are proliferating, and health care providers are open to change. In addition, the NIH and FDA are facilitating research activities to ultimately advance translational science and lead to precision medicine. President Obama signed the Precision Medicine Initiative in 2016, under which one million individuals will be enrolled, with collection of biosamples and followed-up longitudinally. So in a few years, we will be able to investigate the biology, genetics, and pathways of many diseases in precise and meaningful ways. In 10 to 15 years, the diseases that we are studying today will likely be redefined. The classic example of such progress is breast cancer. When I was in medical school, classification systems for breast cancer included tumor size, axillary nodal status, and distant metastasis for diagnosis and prognosis. Now, we are able to perform genetic testing of tumors, looking for the presence of hormone receptors and other genes to more precisely classify the cancer. This will happen in the future with liver disease, kidney disease, dementia, and many other chronic conditions. For diseases that are more common, such as heart failure, dementia, and kidney disease, we will be able to identify particular genetic factors, biomarkers, and behaviors that are associated with likelihood of future disease.

As for specific advice, it is helpful to engage in some activities outside of your medical training if you are interested in a physician-scientist career. If you are studying for an MD, consider obtaining a PhD or master’s degree. If medical students don’t do this, they won’t know about opportunities available to them to engage in translational research – for example they won’t know about the use of mass spectrometry, advances with genetic studies, etc. At the same time, cataloging of big data – proficiency with bibliographic databases on genes, proteins, etc. – is becoming integrated in clinical practice. So medical students and trainees need to be
exposed to these technologies through formal or semi-formal opportunities. The opportunities are there, and the grants available for translational research are increasing. Funding agencies are encouraging proposals which combine biology and patient outcomes. For diseases like melanoma and breast cancer, because of advances in translational research, we have new drugs and new tools.

**What do you see as the future of translational research and drug development? What barriers remain in advancing our knowledge?**

My current journey has been very enjoyable – a significant amount of knowledge has emerged from my research projects. However, translating this knowledge into clinical use has been challenging. In general, we still need to figure out how to get newer biomarkers approved by the FDA and made available to patients and providers. Until recently, if a biomarker wasn’t strictly a diagnostic test, there was no mechanism for it to become approved by the FDA. For example, if a novel protein biomarker had intermediate performance but still gave some meaningful information, physicians didn’t know how to use it. It is challenging to patent these findings, make them available to the private enterprise, and reimbursable for physicians; so it was hard to put these markers into clinical use. Thus, we need to develop a better framework for clinical uptake for biomarkers, making them available to patients and without making clinical care very expensive.

There are also barriers to translation and drug development at other levels. For example, if you discover a new protein to be used in clinical care, how do you disseminate the assay for it so that physicians across the country can standardize it and benefit from it? How do you perform these assays in many hospital laboratories around the country? How do you interpret the results from these different labs and standardize reporting?

In addition, the majority of academic physicians do not currently participate actively in the FDA approval process – it is more commonly undertaken by private for-profit companies. Most doctors can only bring a biomarker to the level of a publishable manuscript by demonstrating its clinical efficacy. Also, whether we can use the biomarker in a clinical setting depends on other external factors, many of them financial. So if you end up creating a new test that isn’t for a disease with a large “market,” companies will be reluctant to disseminate this test due to the lack of financial incentives.

Other areas which need further progress include “-omics” technologies. We have the tools to generate large amounts of big data via measurements of proteins, genes, and metabolites. But standardizing these data, analyzing their functional significance, and exploring them with bioinformatic tools, can all be enhanced further to convert these findings into medical knowledge.

This process is far from perfect at the moment, and this is another barrier that we need to overcome in translational research.

Another barrier is around the availability of samples linked to clinical outcomes. Currently, a majority of hospitals and healthcare programs in the US don’t create their own sample biobanks. This is an issue because such biobanks are potential sources of patient information which could be studied as newer findings emerge from pre-clinical experiments. For example, if someone discovered a new protein today, it could take several years to create a large cohort of patients with this new disease to validate protein findings. But if we had these biobanks available already, translational research would significantly accelerate.

In addition, translational research is fundamentally a collaborative effort between basic scientists and clinical physicians. It often takes a group of skilled multi-disciplinary researchers and various stakeholders to advance results from bench to bedside. The majority of institutions currently reward a “single-laboratory” approach in terms of promotions, academic enrichment, etc. For translational research to succeed, we need to rethink how we reward people – we need to more effectively reward people conducting “team science” and who successfully translate the findings to the clinical world.

Lastly, more integrated training in translational research needs to take place within medical school curricula as well as in public health courses. The number of physicians engaged in translational research is still rather small. However, translational research is an up-and-coming field and has significant potential to shape the future of clinical medicine. Translational research is a powerful enterprise as it provides opportunities for realigning relations between patients, healthcare providers, pharmaceutical companies, and biomedical researchers.