Basic Research in Clinical Medicine

Masayuki Amagai
Professor and Chair, Department of Dermatology, Keio University School of Medicine
Team Leader, Laboratory for Skin Homeostasis, RIKEN Center for Integrative Medical Sciences

Without the valuable research funding that Kakenhi provides, I would not be able to keep pursuing my research in a university setting—nor would I be in the field of basic research at all, for that matter. When I took charge of my own little laboratory as an instructor in the Department of Dermatology at Keio University's Graduate School of Medicine in 1996, the very first thing on my agenda was to apply for Kakenhi funding. I still remember filling out the application form, desperately racking my brain to explain how I would direct my research activities, what elements would make my approach original, and how my efforts would benefit society. That initial endeavor opened up an ongoing stream of support that continues to this day: After securing funding under the Grant-in-Aid for Scientific Research (C) program in 1997, I was fortunate enough to make good on my research objectives and later obtain funding under the programs of Grant-in-Aid for Exploratory Research, Grant-in-Aid for Scientific Research (B), Grant-in-Aid for Scientific Research (A), and Grant-in-Aid for Scientific Research (S). To me, Kakenhi's bottom-up research support system is a tremendous asset that gives scholars in every discipline phenomenal opportunities to tackle the pressing issues of the day.

As a dermatologist, I form my basic research process around identifying possible research topics in my clinical observations while treating patients and then looking for possible solutions to the issues through a fundamental approach. Professor Takeji Nishikawa, my predecessor at the Department of Dermatology, devoted a portion of his research to pemphigus, an autoimmune blistering disease. When I was studying under Dr. John Stanley at the NIH in the USA, I was lucky enough to be able to successfully identify desmogleins (cell-cell adhesion molecules in the cadherin family) as the target antigens of pemphigus. Upon returning to Japan, I produced recombinant desmogleins and developed serological diagnostic tools for pemphigus (1997), which are now used around the world. The next stage of my research focused on the mechanisms of autoantibody production, which I began to unravel by creating a mouse model for pemphigus via the novel approach of using autoantigen knockout mice (2000). I later analyzed autoreactive B cells and T cells, as well,

eventually finding that desmoglein-reactive T cells not only produced antibodies but also caused a different type of skin inflammation (2011). My other projects have included 3D imaging of epidermal tight junctions and Langerhans cells (2009), examining the roles of skin microbiome in atopic dermatitis (2015), and elucidating the mechanisms for epidermal tight-junction homeostasis with the shape of Kelvin's tetrakaidecahedron (2016). In addition to making further inquiries into pathogeneses of autoimmune diseases and allergic disorders, I also want to develop novel therapeutic strategies with less severe adverse effects. For most of my projects, I have relied on Kakenhi funding to drive my research forward.

Now, as I work on basic research in a department of clinical medicine, something is starting to worry me. I get the undeniable sense that the foundations of diversity in basic research—an integral part of research development—is starting to crumble. Not only are the challenges of sustaining basic research in a clinical medicine department mounting, but the process of training young researchers to carry on the effort is also an increasingly strenuous task. "Physician-scientists"—professionals who both see patients and do basic research—are gradually becoming an endangered species.

More and more up-and-coming clinicians are opting to focus on obtaining the board certification as a specialist instead of earning a PhD in medicine. Two-year junior residency programs and three- to five-year senior residency programs are vital in the training of capable clinicians, and there is nothing wrong in their approach per se. The problem, however, is that these programs can also deprive the physician-scientists—a small minority of the larger clinician population—of opportunities to maintain their research activities during their formal clinician training periods. They end up losing chances to pursue deep-probing basic research during their late 20s and early 30s, exactly the ages when they can make their biggest strides as physicians and researchers. The rise of clinical research is another factor. Recognizing the shortcomings of Japan's clinical research infrastructure, the Japan Agency for Medical Research and Development has spearheaded a resource-heavy effort to build a sturdier foundation for clinical research and promote initiatives in the field. It is undoubtedly important to conduct drug discovery research and medical device development in Japan with clear exit strategies in place. Young clinicians benefit, too, as clinical research not only provides opportunities to blend clinical work with research activities but also makes it easier to cultivate ideas for study. However, clinical research is an endeavor that emphasizes organizational teamwork—role-sharing arrangements,

collaborators, and support systems—over the aims and activities of individual researchers. The basic approach of clinical research can discourage projects that embrace individual imagination and originality, research into topics that might not necessarily grab headlines, and other efforts that, on the surface, could appear trivial. In the realm of clinical research, the point that concerns scientists more than anything else is whether they are doing the research *correctly*—a direct contrast to the central concern of basic research, an area where scientists actively try to do things differently from others. For many physicians, though, clinical research remains a higher-profile, more prevalent pursuit than basic research.

Despite the current challenges, basic researchers in clinical medicine still have some reasons to be optimistic. Thanks to technological innovations enabling single-cell analysis, scholars now have the ability to gather large amounts of data from small case populations and derive universal truths from those findings. Analyzing medical big data being generated from day-to-day clinical practice, meanwhile, has the potential to throw the doors of discovery wide open. Artificial intelligence is making inroads into the medical field, bringing with it the promise of revolutionary transformations in clinical practice. The fusion of basic research and clinical practice, too, will keep opening up new, exciting possibilities. Things are moving forward.

As a support system for basic research in clinical medicine, Kakenhi will continue to play a bigger role than ever before. The process of sustaining basic research through clinical insights is more than just a crucial element in nurturing the diversity of basic research—it also plays a pivotal role in forging a stronger foundation for the future of scientific technology. I sincerely hope that the next generation of researchers will continue to make pioneering contributions to the world’s scientific research.