

2011 American Society for Clinical Investigation Presidential Address

Lost — and found — in translation

Paul S. Mischel

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ASCI Presidential Address

Supplement

Valued colleagues and friends, thank you for the extraordinary privilege of serving as the 101st ASCI president. To stand before this distinguished group of physician-scientists without a PowerPoint presentation full of data slides is a deeply uncomfortable position. I do not stand before you with the data of graphs, charts, and models, but rather with the data of experience acquired through a journey from the clinic to the lab, and with the hope of fulfilling a promise. As you have probably guessed from the title, this talk will focus on the challenge of translational medicine: what it means (or doesn't) and the inadvertent obstacles we may have in fact created, including an assessment of the roadblocks that lie ahead. I can think of no topic more important to address in front of this audience than to ask what is the ASCI's role and responsibility in guiding the transformation of medicine through science to improve the lives of patients. This society is not about "establishment" or orthodoxy. The ASCI was founded on noble principles: insistence on excellence, skepticism, impatience with status quo, and the belief that science can and must transform the lives of patients. These are the very attributes that make us uniquely suited to guide this transition in medicine. It is true ASCI membership, because of its honorific status, [...]

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In Joel Howell's beautifully written history of the ASCI (1), we learn that the phy-

sician-scientists who gathered for the first ASCI meeting considered themselves to be colleagues, friends, and fellow revolutionaries with the shared goal of "moving clinical research towards a scientific basis grounded . . . in new more progressive sciences." Is there a more appropriate definition for translational medicine and a clearer delineation of ASCI's role in fostering it? In an era where genomics, genetics, epigenetics, and proteomics are transforming our landscape of disease, is it not crystal clear that the very DNA and spirit of the ASCI lie in using these new tools towards better understanding disease and improving the diagnosis and treatment of patients?

Please permit a short personal detour, which I hope will place the rest of this talk in context. I am the son of a philosophy professor, Theodore Mischel, who lived in a library of 3,000 books that he constructed in our home; I wanted to live in that library with him. When he was 51 and I 14, he developed severe stomach pain. Before I could grasp what was happening, I watched as my formerly robust father was transformed into a stomach cancer patient and a dying man. Perhaps the most painful part was the fallacy of hope that chemotherapy offered — we all spoke with optimism about how this would make him better, while watching him writhe in pain, shrink in form, and struggle to keep his dignity.

I recently read Abraham Verghese's brilliant novel *Cutting for Stone* (2). If you haven't read it, I urge you to do so. In the middle of the book, the main character, a 15-year-old boy, a twin like me, who had suffered the loss of his parents, wanders through the medical library of his adoptive father taking comfort in the medical volumes on the shelf. I read these words with disbelief. How could Dr. Verghese have gotten it so right? The medical library of my Uncle Charles (a medical student at the time) brought order, comfort, and hope. Harrison's textbook of internal medicine *Principles of Internal Medicine* was a balm to my soul. I made myself a promise to become a physician-scientist to try to help people with cancer. Do not most of us in this room share similar stories, motivations, and promises?

Lost in translation — a flawed construct?

We are not alone in our belief and hope that the lives of patients will be directly improved through science, much of it done by the people in this room. The NIH has devoted considerable resources to establishing translational research centers; medical schools and universities have developed translational research training programs. New medical journals specifically designed to cover translational science are arising at an astonishing pace. Yet clear and coherent definitions of translational medicine are lacking. Translational medicine means different things to different people. To molecularly based scientists, it means bridging the gap between basic and clinical sciences, i.e., transforming knowledge derived through basic science investigation into improved diagnosis and treatment of patients in a bench-to-bedside flow of information. To health care delivery scientists, it means translating knowledge about individuals into populations, to close the gap in the access and delivery of new treatment options.

The lack of clarity regarding translational medicine is not just an issue of semantics. The constructs we use, i.e., the conceptual elements by which we define things, have broad impact on how we judge them. Our current construct of translational medicine creates two specific unintended and serious problems.

(a) *The novelty/creativity problem:* In an increasingly competitive scientific landscape, novelty is an essential ingredient for publishing in high-impact journals, including our own journal, the *JCI*. Elite physician-scientists, like the ones in this room, aim to do work that is creative, original, and not derivative. By defining translational medicine as bridging the gap between basic and clinical, are we not relegating it to a derivative status? It sounds more like moving preestablished goods along a conveyer belt to their next destination than it does participating in exciting, open-ended discovery. Who in this room really wants to spend their time translating stuff that has already been done by others, simply moving it into

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the clinical setting? If we define translation as validating knowledge that is uncovered in basic investigation into clinical settings, are we not missing the critical opportunity for discovery? Isn't translational science supposed to be about the bidirectional flow of information between patients and models, integrating insights obtained from patients studied in well-designed molecularly guided clinical trials with knowledge obtained in well-controlled model systems? Can we not make room for a living, breathing dynamic science that incorporates the bidirectional flow of information between the patient and the models? Is that not the next frontier of experimental medicine. the place from which discoveries that are likely to transform clinical practice are most likely to arise? The work of our Korsmeyer awardees, Drs. Druker and Sawyers, and our other speakers, exemplifies what translational medicine can be at its best — illuminating about mechanism and transformative in its impact on patients' lives.

(b) *The review problem — limbo*: The second problem is an inadvertent consequence of our narrow definition of translational medicine.

“Midway on our life's journey, I found myself in dark woods, the right road lost.”

— Dante Alighieri, *The Divine Comedy*

So begins Dante's journey into the nine rings of hell. So begins the experience of submitting “translational studies” to grant and journal review panels. The first stop along Dante's journey is limbo — typically a sticking point for translational studies. At first glance, Dante's limbo looks like a lovely place: green meadows filled with scholars leisurely talking and teaching. A place populated by Horace, Homer, Ovid, Socrates, and Hippocrates all enwrapped in erudite transdisciplinary discussion. An ideal sabbatical perhaps! However, limbo is not quite the real thing — terrific people who don't quite fit into the right camp. In Dante's case, it was nonbelievers who couldn't gain admittance to the real show because the correct belief system wasn't in place yet. They didn't have the right badge. Have we inadvertently created a “limbo” of translational medicine by labeling it “translational”? Have we created an environment that looks beautiful and compelling on the outside, but which lacks legitimacy?

To their credit, the NIH has placed great emphasis on translational science. This

is enlightened, wise, and in line with the demand of the citizens of this country. The challenge lies not in the spirit, intent, or even the letter of the translational mechanisms. Rather, the problem lies in construction of review panels for translational studies consisting of basic scientists and clinicians, in which the proposals fall right between the cracks. In particular, it is the most innovative science that falls right in the gap. Oddly enough, by creating a mechanism designed to bridge a gap and populating the panel with reviewers that sit on either side, we have oddly reinforced the gap. In short application formats, the basic scientists often find that not enough attention has been paid to the basic mechanisms, while the clinicians often find that the clinical aspects, particularly clinical trial designs, have not been adequately fleshed out. Are we not the right people to have a voice here?

The same is often true of manuscript reviews, particularly many of the high profile journals that have strict figure and word limits. One consequence is the type of paper we are all familiar with — a fundamentally mechanistic study with one immunohistochemical image thrown in at the end to show translational relevance. Those papers can be wonderful, but if we are to take advantage of the remarkable influx of new information and the power of new technologies to transform the lives of patients, then we need to realign the construct of translational medicine to broaden our horizons. Do we not have a responsibility here as well?

Found in translation — the ASCI as a leading voice in the transformation of medicine through science

The ASCI has three main instruments of influence: (a) its selection of new members; (b) its journal, the *JCI*; (c) the shared value system that influences all that we do in our roles as physicians, scientists, mentors, article writers and referees, and grant seekers and reviewers. My experience of participating in the selection of new ASCI members for the past three years has provided a window into the integrity of this process and the seriousness by which the council members address the challenge. It is something that the ASCI can be proud of. We have again this year inducted a remarkable group of individuals who exemplify the spirit of the ASCI in their accomplishments. Welcome to ASCI; we are honored to have you as its members.

Finding our voice

The *JCI*, our journal, is the embodiment of our spirit and our principals. As you know, this is a year of editorial transition for the *JCI*. We are grateful to editor-in-chief Dr. Larry Turka and his editorial team at the University of Pennsylvania for their remarkable service over the past five years. Your stewardship has built on the advances of previous editorial teams in delivering an outstanding journal that is universally held in high esteem. As this is a period of editorial transition, much of my presidential year has been occupied with the process of selecting a new editorial team. We have worked very hard to bring together a balanced, fair, and wise committee to carefully consider and recommend the next editor. I am delighted that the ASCI council has recommended Dr. Howard Rockman and the team from Duke and UNC to edit the *JCI*.

In every transition, there is an opportunity, one that I hope will not be missed. The flawed construct of translational medicine, by relegating it into a derivative role, creates a misleading misperception of lack of novelty. If we redefine translation as discovery through the bidirectional flow of information between patients, especially through clinical trials and models, do we not have the opportunity for publishing creative, novel, and important work in the *JCI*? Is this not the right journal in which to help foster a living, breathing, dynamic science? Do we not have the opportunity to both do elegant science and to change the course of patients' lives? The work of our Korsmeyer recipients, Drs. Druker and Sawyers, provides an exemplary model of how we can embrace science that is elegant and rigorous, including studies that provide new insights through the bidirectional flow of information through molecular analyses of patients in clinical trials integrated with rigorously defined model systems. It is my hope that we will focus on what is enduring and important, not necessarily on what is trendy. It is my hope that the *JCI* will lead the way towards a more thoughtful and illuminating translational medicine that has the capacity to improve lives.

This attitudinal shift has an important corollary. It means that the *JCI* must not define itself in comparison to other high profile journals or even adopt their metrics for success. The very act of defining a competitor journal distracts us from our primary goal. More importantly, there is not any other group of individuals that I



am aware of that is more uniquely qualified to address the challenge of improving patients' lives through rigorous mechanistic science than the ASCI, and no journal more appropriate than the *JCI*. The *JCI* has the opportunity to build on its previous success and to transform this rapidly changing scientific landscape.

Redefining translational medicine through a community of shared values

I was asked by a senior and highly esteemed ASCI member, acknowledging that election into the ASCI is still an important rite of passage and acknowledgement of scientific achievement, "What is the utility and desirability of the much-attenuated annual meeting . . . MD fellows in my laboratory would much prefer to attend a specialized topical science meeting (i.e. Keystone meeting, ASH, AACR, Gordon Conference) to meet people who work in their area and get valuable feedback and networking." This member goes on to state, "I know that no President wants to be the person who turns out the lights and admits defeat but, if you have the time and inclination, I would love to know what you see as the intrinsic value of the current annual meeting for a young scientist. I have addressed to several other ASCI presidents who have tended to ignore it and push on."

Let me address this question head on, because I think it makes us ask what is important and enduring about the ASCI. First, we must not undervalue the importance of what it means to be inducted into the ASCI. It is indeed a critical rite of passage, a measure of achievement and something to which young physician-scientists aspire. More importantly, the ASCI provides models. At a time when young physician-scientists are fed a diet of discouraging news, low funding rates, difficult job markets, difficult journal review processes, the ASCI provides a model of what is achievable with hard work, perseverance, and focus. There is another aspect. I would assert that the biomedical world has ceded the responsibility of training the physician scientist to MD PhD programs. These are wonderful opportunities. However, simply put, that is not the only route towards a suc-

cessful career as a physician-scientist doing rigorous mechanistic work. If it were, I of course would not be here today, and neither would most of today's brilliant speakers, including our award winners. What about the clinically trained MD who is driven to do research because he or she has developed a belief that the current standards of practice are not good enough? Shouldn't the door be wide open for the talented and perseverant among that lot? Is not the ASCI precisely a model of shining examples of how it can be done? I would not be here before you today if it were not for the training I received from our ASCI dinner speaker Dr. Louis Reichardt, a spectacular basic scientist and formidable mentor who also happens to be a world-class mountaineer and a terrific person. He was willing to take on the responsibility of mentoring a clinically trained, scientifically novice physician who wanted to change medicine through science. It was certainly not easy, and the support of my wife, Dr. Deborah Kado, herself a physician-scientist, gave me the strength to meet the challenge. It changed the trajectory of my life. Similarly, Dr. Charles Sawyers helped me see that the pathologist was the key to linking molecular phenotype with treatment, and that as someone who had expertise in signal transduction and pathology, the door was wide open. You all know him as a brilliant scientist and as a most deserving winner of this year's Korsmeyer Award (along with Brian Druker). I am fortunate enough to know him as a teacher and friend. There are others.

In an increasingly specialized world, doesn't the broad perspective afforded by a general meeting, and a general journal, provide precisely the right stimulus for creativity? Bruce Alberts points out that the fundamental reason for the explosive growth of science is that 100 units of knowledge can be combined in 100 more ways than can 10 units of knowledge. The challenge comes in finding the right combinations. To paraphrase Henri Poincare, via Dr. Alberts, the true work of the inventor consists in choosing among these combinations so as to eliminate the useless ones. If we only attend specialist conferences where we are listening to much of what we already

know, we miss a profound opportunity to develop new combinations, potentially ones that could be transformative. Is not the ASCI, a gathering of physician scientists who share the same values of rigor and mechanism, particularly fertile soil for such interactions? We have clear examples in our midst of how we can transform the landscape. Let me give a personal example. I am engaged in an active collaboration with future ASCI president Peter Tontonoz. Peter has never worked in cancer or I in metabolic disease, yet this collaboration has brought our joint work to new, exciting, and highly unexpected places.

We are doctors, authors, and reviewers. We are teachers, grant reviewers, and grant seekers. We are leaders in academic medicine. But we are first and foremost, by virtue of our membership in ASCI, ambassadors and models for the physician-scientist. The very principles that formed the ASCI are still deeply relevant, and they in no small part help shape the way we interact with our patients, with each other, and with the rest of the world.

In closing, it has been a privilege and an honor to be ASCI president. Thank you for this rare opportunity. To the members of the ASCI council — thank you. You are a remarkable group of people. I also want to thank John Hawley, a thoughtful, talented, and devoted steward of the ASCI, and someone I am happy to call my friend. John, it is your work and that of Karen Guth as well that keeps the ASCI on track. To my colleagues at the AAP, it has been a pleasure working with you.

I would like to acknowledge a debt of profound gratitude to my uncle, Walter Mischel, my father's brother, an outstanding scientist, one of the pioneers of modern psychology and a member of the National Academy of Sciences, for helping me find my voice — in this speech and in life in general. Most importantly, to my wife, Dr. Deborah Kado, and my daughters, Anna and Sarah, thank you for being here; you mean more to me than you can ever know.

Thank you.

1. Howell JD. A history of the American Society for Clinical Investigation. *J Clin Invest.* 2009;19(4):682–697.
2. Verghese A. *Cutting for Stone*. New York, New York, USA: Knopf Publishers; 2009.