

2015 American Society for Clinical Investigation Presidential Address Advancing the mission

Mukesh K. Jain

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ASCI Presidential Address

Introduction I have been honored to serve as president over the past year and as a member of the Council since 2012. The opportunity to work with my fellow Council members, distinguished colleagues across the country, and superb administrative team constitutes one of the great privileges of my professional life. I would happily conclude my tenure by enjoying our annual meeting's scientific sessions and then quietly returning home. But the burdensome tradition of delivering a presidential address carries on. Many past presidents have shared my consternation, perhaps best expressed by Dr. Holly Smith in his 1970 presidential address when he noted, "This rather strange custom is not embedded in the Bylaws of the American Society for Clinical Investigation. Furthermore, casual perusal of the past fails to reveal any firm mandate transmitted from a grateful membership for this form of gratuitous pontification" (1). I would add to Dr. Smith's trenchant remarks that the only firm mandate from the membership is that this address end in a timely fashion, and I intend to do so. Having succumbed to the power of tradition, I set out to develop thoughtful remarks. Over the past few weeks, my children, who are both here today, watched me struggle at the keyboard. They observed with amusement but not surprise as I attempted to illuminate previously unappreciated philosophical [...]

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I would add to Dr. Smith's trenchant remarks that the only firm mandate from the membership is that this address end in a timely fashion, and I intend to do so.

Having succumbed to the power of tradition, I set out to develop thoughtful remarks. Over the past few weeks, my children, who are both here today, watched me struggle at the keyboard. They observed with amusement but not surprise as I attempted to illuminate previously unappreciated philosophical insights. I say "without surprise" because like most young people they concluded some years ago that their father lacks a deep understanding of frankly anything, a view reaffirmed for them by my continued struggle.

I sought inspiration by reading previous presidential addresses. As I reviewed, it became clear that, while the elocutionary approach varied, recurrent themes dominated the discussion — reflective of

the importance of some issues across generations. David Ginsburg, in his 2002 presidential address, provided quantitative data that the most common topics include (a) the future of the physician-scientist, (b) clinical investigation, (c) ASCI state of the union, (d) research funding, and (e) education/mentoring (2).

and forth various potential initiatives to address opportunities and challenges facing our community, we did rely at times on Article II of our bylaws, which offered a thoughtful discussion of objectives. But we increasingly realized that a concise mission statement would serve us best in thinking through our varied ideas. Hap-

The ASCI's mission is to support the scientific efforts, educational needs, and clinical aspirations of physician-scientists to improve human health.

I found reading these previous addresses, and many, many more, to be simultaneously inspiring and disheartening. For everything I wished to say had been stated by others, more eloquently, and with more depth and insight than I could ever hope to achieve. This appreciation coupled with the recognition of myself as a utilitarian phenotype, unabashedly so, led me to abandon the well-stated, philosophical discourse as an approach. Rather, I chose to focus on three strategies that my colleagues and I have undertaken during my tenure. While each strategy may represent a modest advance, collectively they unite as a considered set of measures consonant with "Advancing the Mission" of the Society.

Strategy number 1: creating our mission

When I joined the Council three years ago, I felt it would be proper to understand the ASCI mission in greater depth. I realized that in order for us to understand the mission, we needed to have a stated mission. As my colleagues and I volleyed back

pily, after several robustly discussed iterations, we agreed upon a mission statement for our Society: The ASCI's mission is to support the scientific efforts, educational needs, and clinical aspirations of physician-scientists to improve human health.

This mission isn't new in its ideas, but it's new as a stated mission that implicitly addresses the career opportunities and environmental challenges we face, the latter of which includes diminishing support at each stage of our career life cycle, declining funds for discoveries, and inadequate infrastructure to translate (Figure 1).

I used the term "career life cycle" purposefully because it accurately conveys that our careers have multiple phases and it allows us to acknowledge that each phase features its own opportunities and challenges. Using this career life cycle as our guide, we can better anticipate, help others anticipate, and then collectively adapt to the features characterizing each phase.

Such efforts are essential in ensuring the viability of the physician-scientist, whose presence in biomedical research is critical — a view underscored in Dr. Donald Seldin's 1966 ASCI presidential address in which he stated, "Because I do not believe that, in the nature of things, powerful explanations for macroscopic

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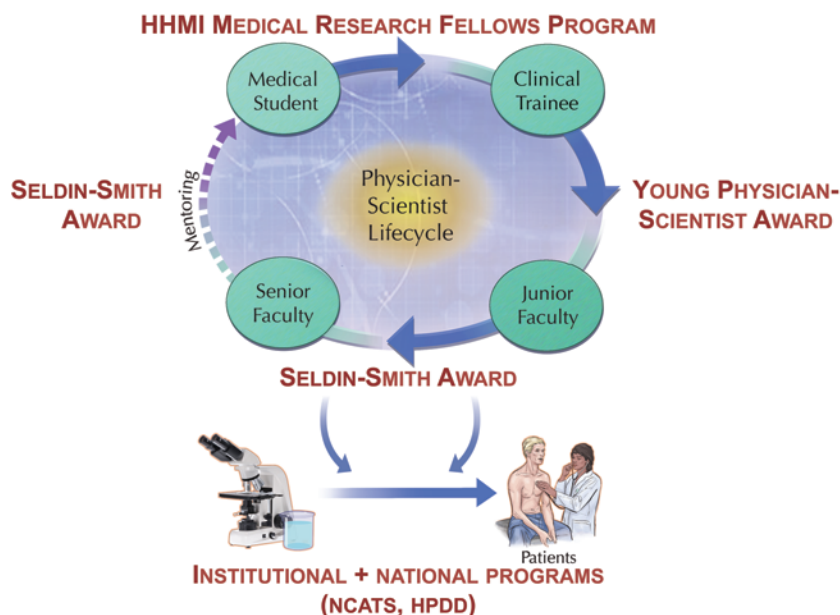


Figure 1. Advancing the mission. The life cycle of a physician-scientist. NCATS, National Center for Advancing Translational Sciences; HPDD, The Harrington Project for Discovery and Development.

clinical problems will ever be available by a complete reduction to chemistry and physics, I feel it essential, for this reason as well as others, to cultivate clinical investigation as a basic research activity of practicing clinicians and teachers” (3).

Strategy number 2: support physician-scientists’ scientific efforts and educational needs

The Council’s reflections on career life cycle dynamics led us to forge initiatives that support the physician-scientist’s scientific efforts and educational needs. We focused in large part on the earlier phases of the life cycle — from medical student to junior faculty, where (to continue the analogy) birth rates are low and fall out is high. I will highlight three specific initiatives related to Strategy number 2.

Howard Hughes Medical Institute Medical Research Fellows Program. The first is a collaboration with the Howard Hughes Medical Institute (HHMI) and relates to the medical student phase of the life cycle (Figure 1). The recruitment and retention of aspiring medical trainees in research has been and remains a constant challenge. Evidence has suggested that early exposure to research enhances a rising physician’s interest in pursuing a research career. A major effort to address this issue began decades ago in the 1950s with the establishment of dual degree MD-PhD pro-

grams. *Additionally*, prestigious fellowship programs instituted by the HHMI, Sarnoff Cardiovascular Research Foundation, NIH, and the Doris Duke Charitable Foundation have been effective. A 2003 review of the effect of two HHMI programs concluded that “one-year intensive training offered an effective imprinting experience on medical student research careers” (4).

Knowing this, the American Physician Scientists Association (APSA) and ASCI/AAP forged an important partnership nearly a decade ago. In addition to enhancing the vitality of the meeting, this partnership has strategically engaged dual-degree students and provided them an opportu-

nity to interact with and learn from role-model physician-scientists.

The Council recognized the value of such engagements and sought to develop a complementary new program that helps increase the supply of physician-scientists. I am very pleased to announce the establishment of a collaboration with the HHMI Medical Research Fellows Program that will provide talented MD students who have scientific aspirations with an opportunity to engage with the ASCI/AAP (Figure 1). This new program is spearheaded by ASCI Vice President and HHMI investigator, Dr. Vivian Cheung, in close collaboration with Melanie Daub, Program Officer for the HHMI Medical Research Fellows program, who has kindly joined us today. This year, a small contingent of students from the program is attending our meeting, and participation will expand in future years. We are excited about this program, and we hope these talented students benefit from the program and engagement.

Young Physician-Scientist Award Program. Another critical phase of the life cycle is the junior faculty phase. Members of this group are vulnerable for manifold reasons, some of which include a long training path, stagnant or declining federal funding, the demands of delivering health care, and dual-occupation families. The fact that we lose highly trained, talented, and committed individuals when they are most productive poses problems not only for the future of science but also for our economy and society.

In the mid-1990s, Dr. David Nathan led an NIH-sponsored committee to evaluate

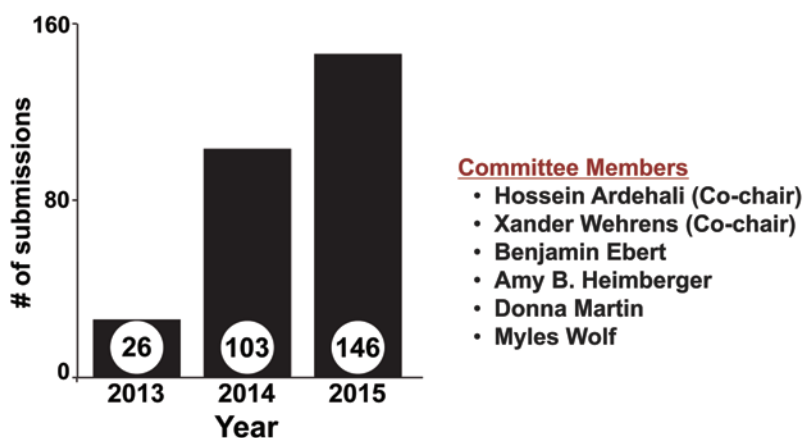


Figure 2. ASCI YPSA program and committee members. There has been early growth in the number of applicants since the program’s inception in 2013.



DONALD W. SELDIN



LLOYD H. ("HOLLY") SMITH JR.

Figure 3. Seldin-Smith Award for Pioneering Research. Donald W. Seldin (left) and Lloyd H. (Holly) Smith Jr. (right).

the shortfall of clinician-scientists, and its members arrived at and instituted remedies. More recently, in 2014, the “Physician-Scientist Work Force Working Group Report” revisited the topic. Led by Drs. David Ginsburg, Susan Mills, and Sherry Shurin, the working group recommendations focused on the supply of physician-scientists. Additional suggestions have been provided by Ronald Daniels (5), president of Johns Hopkins University, in a commentary in the *Proceedings of the National Academy of Sciences* as well as by a rising physician-scientist, Dr. Dania Daye (6), and colleagues in a recent “Perspective” piece in the *JCI*. I highlight a few suggestions that I believe will be particularly impactful: (a) redirecting funds to young physician-scientists — whether it be through a shift in postdoctoral grants to physicians, conditional R01s, or K99/R00 just for MDs; (b) investing in the individual and across a scientific career — whether it be the particularly promising young investigator or support for senior investigators to mentor the next generation; (c) expanding loan repayment programs and support for family care; and (d) supporting training of “late bloomers,” i.e., those that develop an interest in the physician-scientist career path during residency or fellowship.

This latter issue resonates for me, as it was after medical residency when my first serious research experience changed my career trajectory. While the future physician-scientists identified here may not be large in number, they are likely to be committed.

Recognizing the need to enhance engagement of individuals at this phase of their career life cycle, we established the Young Physician-Scientist Award (YPSA)

program in 2013 (Figure 1). This program recognizes young investigators who at the time of their nomination are supported by an NIH K award or equivalent, are early in their first faculty appointment, and have made notable achievements in their research. The ASCI set aside funds to support up to 40 of these individuals to attend the annual meeting. Since inception, the number of applicants has increased beautifully (Figure 2). Because these young investigators are so critical to the future of ASCI, we are delighted to see such growth.

Seeing the success of the program, we established in 2014 a committee of ASCI members to evaluate YPSA applicants and to help plan this annual meeting (Figure 2). The committee established a separate poster session for YPSA on Saturday night and invited Dr. Griffin Rodgers, Director of the National Institute of Diabetes and Digestive and Kidney Diseases, to share reflections prior to launching the inaugural Young Physician-Scientist



SELECTION COMMITTEE	ADVISORY COMMITTEE
 Mukesh K. Jain (Chair)	 Joseph L. Goldstein (Chair)
 Vivian Cheung	 Michael S. Brown
 Stuart H. Orkin	 Stanley B. Prusiner
 Charles L. Sawyers	 Arthur Weiss
 Elizabeth McNally	 Robert Lefkowitz

Figure 4. Seldin-Smith Award for Pioneering Research. Seldin-Smith Award Selection Committee (left) and Advisory Committee (right).



*San Francisco, CA
August 25, 2014*



*Dallas, TX
February 20, 2015*

Figure 5. Seldin-Smith celebrations. Left: taken August 25, 2014 in San Francisco, California; from left to right, Margaret and Holly Smith, Mukesh K. Jain, and Vivian G. Cheung. Right: taken February 20, 2015 in Dallas, Texas; from left to right, Mukesh K. Jain, Donald W. Seldin, Vivian G. Cheung, and John Hawley.

poster session. We believe this dedicated session will enhance the experience of YPSA awardees and increase participation. I hope many of you here will consider attending, especially if you are a newly elected member. We believe this represents an exceptional opportunity to encourage and inspire our YPSA awardees, many of whom will undoubtedly be future members of our Society.

Donald Seldin-Holly Smith Award for Pioneering Research. The Council recognized that our efforts to target and support various phases of the physician-scientist life cycle were part of a continuum that began with many before us. As such, we felt it proper to connect physician-scientists with significant achievements throughout long careers to those who are early in their careers.

You heard beautiful remarks a few minutes ago from Drs. Michael Brown and Warner Greene about two paragons of academic medicine. Drs. Donald Seldin and Holly Smith have for decades provided exemplary leadership in science, medicine, and education. Both shepherded once fledgling institutions to greatness and in so doing left an indelible mark on hundreds of trainees and faculty, their respective institutions, and the profession as a whole. Both also served as ASCI presidents and remain staunch supporters of this Society, as exemplified by their attendance at nearly every meeting over the past half-century, including today (Figure 3).

I am pleased today to officially announce the establishment of the Donald Seldin-Holly Smith Award for Pioneering Research (Figure 1). For this award, the ASCI will call for nominations of physician-scientists who are early in their faculty appointments and who are on a particularly promising trajectory in their research careers. From these nominations, a panel of ASCI presidents, guided by a senior advisory board, will select the recipient (Figure 4).

The recipient will (a) receive an unrestricted award to advance her or his academic efforts, (b) be provided with a mentoring team to advise on career development, and (c) have an opportunity to speak at the Joint Meeting.

Through this award we hope to recognize the country's most promising young physician-scientists, connect them to later-phase physician-scientists mentors, hear about their accomplishments, and celebrate the legacies of Drs. Seldin and Smith.

The Society has set aside \$1.2 million, and we will seek over the next several years to build a multimillion-dollar endowment to support the country's most promising young individuals. We have high hopes that the individuals selected and supported by this program will become the next physician-scientist leaders in academic medicine.

Although today marks our official announcement, we celebrated the establishment of this award in San Francisco late last year and Dallas earlier this year

(Figure 5). All of us at ASCI are deeply grateful to Dr. Vivian Cheung and Dr. Helen Hobbs, who tirelessly contributed their time and effort to make these events and this award possible. We are also grateful to those friends, admirers, and colleagues of Drs. Seldin and Smith who gave generously to enhance the endowment. And finally, we are grateful to Drs. Seldin and Smith themselves for providing the inspiration that has spanned many academic generations and advanced our mission. Would you please join me in thanking Drs. Donald Seldin and Holly Smith?

Strategy number 3: advance the clinical aspirations of physician-scientists

Our third strategy related to the clinical aspirations of physician-scientists to translate fundamental discovery at the bench to impact patients by the bedside (Figure 1). In Dr. Smith's 1970 presidential address, which I referenced at the outset of my remarks, he identified a challenge connected to the "outflow pathway from medical science to its final application in health care" (1). He noted, "... the thrust of this criticism is that the biomedical scientist pursues his research as an intellectual game, hermetically sealed off from the real problems of society, indifferent to the ultimate utility, or even lack thereof, of his discoveries. The spin-offs may be there but they come grudgingly from a process with a rather low angular velocity."

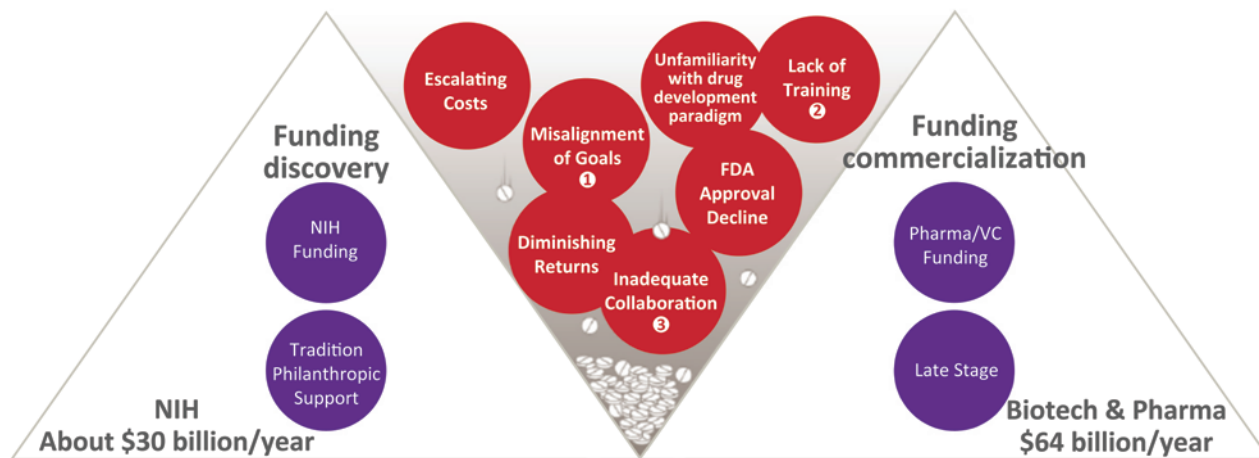


Figure 6. The Valley of Death. The gap located between fundamental discovery by the public sector and commercialization of that discovery by the private sector.

In the 45 years since these remarks, we have witnessed remarkable progress in basic biomedical research, fueled by powerful technologies and fundamental insights into the biologic basis for disease. Strikingly, despite this progress, we have not witnessed a correlative increase in the number of FDA-approved drugs in recent years. Many refer to this as the “Valley of Death” (Figure 6). This famed metaphorical chasm — this gap located between fundamental discovery by the public sector and commercialization of that discovery by the private sector — has clearly damaged a real core aspiration of the physician-scientist to change standard of care.

The reasons for this chasm are numerous. Major participants in the health care industry — the biomedical research enterprise in universities, the clinical research engine in hospitals, and drug development efforts in the pharmaceutical industry — face numerous challenges. Additionally, traditional partners, such as venture capital firms, have reduced their support of therapeutic products that lack demonstrated human clinical proof of concept. An Institute of Medicine report noted grimly that “... without mechanisms and infrastructure to accomplish this translation in a systematic and coherent way, the sum of data and information produced by basic research enterprises will not result in tangible public benefit” (7).

This translational productivity “gap” is a serious problem. Not to be misunderstood, I wish to emphasize my staunch advocacy for fundamental discovery —

this is the foundation on top of which all therapies rest. The purpose of my following comments is to emphasize that we may not be realizing the full promise of these discoveries. If we don’t leverage our scientific insights maximally, we risk a negative impact in public trust, economic growth, and most importantly human health. And I can think of no better group of individuals than members of this Society who ought to be at the forefront, leading efforts to address this productivity gap.

Fortunately, awareness of this issue has increased in recent years, with promising efforts at the local and national levels. Some institutions are dedicating significant energy and resources to support and

incentivize their faculty to traverse the so-called valley. These efforts typically involve assistance for lead optimization, preclinical development, and commercialization. I have seen a deep commitment to such efforts by leadership at my own university, and, happily, parallel efforts are developing or have been established across the land.

Further, leaders at disease-specific organizations, such as the Cystic Fibrosis Foundation and the Leukemia & Lymphoma Foundation, have increasingly focused their organizations on supporting translational opportunities in their respective areas of interest. These efforts have enjoyed palpable success.

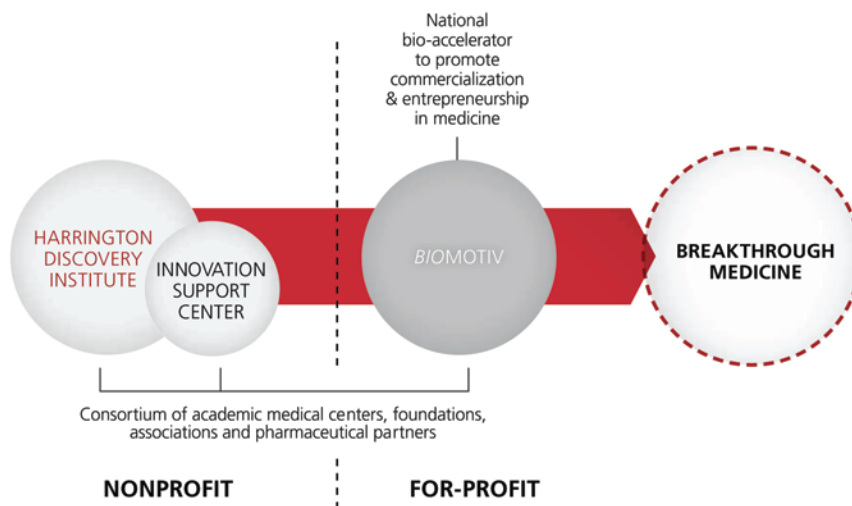
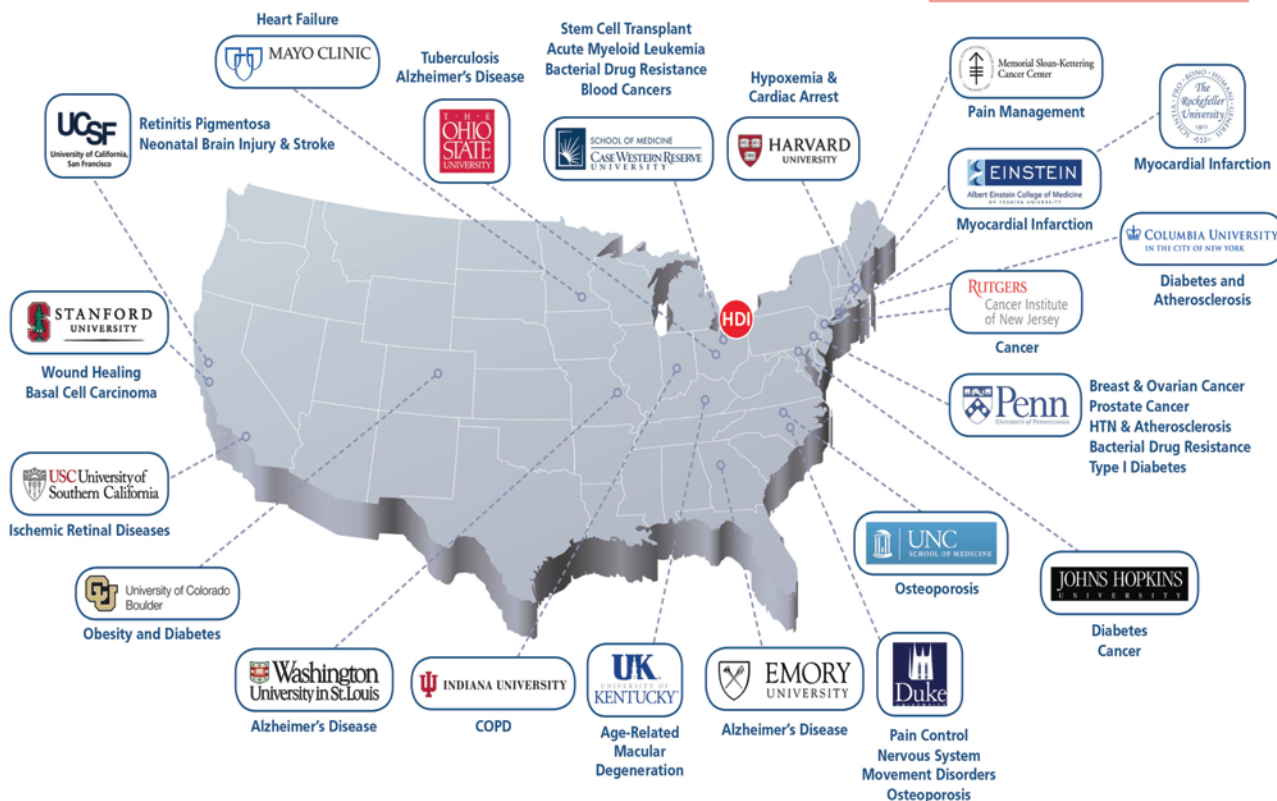


Figure 7. The Harrington Project for Discovery and Development. A dedicated initiative to ensure physician-scientists have the resources they need to accelerate the development of medical breakthroughs into medicines that benefit society.

ASCI/AAP MEMBERS WHO ARE GRANT RECIPIENTS



**Jayakrishna Ambati • Robert A. Bonomo • John Burnett • David Clemmons • Barry Collier
 Clark Distelhorst • Garrett FitzGerald • Roger Greenberg • Geoffrey Gurtner
 Richard Johnson • Richard Kitsis • Sanford Markowitz • Scott Oakes • Feroz Papa
 Irina Petrache • Geoffrey Pitt • Jonathan Powell • Daniel Simon • Ira Tabas • David Rowitch**

Figure 8. The Harrington Project for Discovery and Development. Names of all institutions and areas of research supported by HPDD. Names of ASCI/AAP members supported by HPDD from 2012 to 2015 are shown at the bottom.

And in government, the NIH launched in 2011 the National Center for Advancing Translational Sciences (NCATS) with the purpose of transforming the translational process so that new treatments and cures can be delivered to patients faster. This sweeping, disease-agnostic, early-stage, national initiative should make progress towards ensuring investigators can access appropriate resources for novel drug development.

My predecessor ASCI presidents amply offered examples and case studies

in their addresses and in deference to them I'll offer one of my own. I have elected to present this example of translational success because it is innovative, dedicated to physician-scientists, and already has established ties to our Society.

The Harrington Project for Discovery and Development was established through a generous gift from the Harrington family, impact philanthropists who are committed to using the resources created by their entrepreneurial success for social good (Figure 7). This interna-

tional initiative is dedicated to ensuring that inventive physician-scientists have the resources they need to accelerate the development of medical breakthroughs into medicines that benefit society. The project aligns the programs, resources, and structures of various nonprofits and for-profits into a new model of drug development in academia.

The effort has earned great interest from investigators around the globe — including many members of this Society (Figure 8) who are supported by Harring-

- **ASCI Council & Administrative Team, 2012-2015**
- **Scientific Mentors**
 - Edgar Haber
 - Mu-En (Arthur) Lee
- **Mentors & Colleagues (Boston & Cleveland):**

– Peter Libby	– Daniel I. Simon	– Fred C. Rothstein
– Patrick O’Gara	– Jonathan S. Stamler	– Jeffrey H. Peters
– Thomas M. Michel	– Marco A. Costa	– Pamela B. Davis
– Victor J. Dzau	– Richard A. Walsh	

Figure 9. Acknowledgments. A special thank you to the ASCI Council and administrative team and scientific mentors Edgar Haber and Mu-En (Arthur) Lee as well as mentors and colleagues from Boston and Cleveland over the years.

ton Project programs — as well as from prominent disease foundations, academic institutions, philanthropic thought leaders, countries, and global pharmaceutical companies.

Although this effort is housed at my home institution, I believe (and hope) this does not diminish the fact that the project offers a significant opportunity for our Society’s members to advance the mission. In fact, several years ago, the ASCI engaged with the Harrington Project in a specific way, namely through the ASCI-Harrington

Prize for Innovation in Medicine. This prize has allowed the Society to recognize annually a physician-scientist whose translation of a discovery has positively impacted human health. This year’s recipient, Dr. Douglas Lowy, is exemplary.

Conclusion

As I enter the blissful phase of retirement commonly referred to as past president, I am confident that the three strategies I have discussed — first, putting ASCI’s mission into words; second, programmatically

supporting the scientific and educational needs of our members throughout their life cycle; and third, advancing the clinical aspirations of our mission-driven and productive community — will advance to great success under the leadership of Drs. Levi Garraway, Vivian Cheung, and Benjamin Ebert and the entire ASCI Council.

Over the upcoming year, in my capacity as past president, I plan to cultivate interactions of the ASCI with like-minded organizations internationally. The Council made this request of me because it rightly believes that engagement with the broad ecosystem of physician-scientists across the globe will benefit us all. As one example, you may be aware that the UK has a parallel society to the AAP, namely the Association of Physicians of Great Britain and Ireland. Founded on the urging of Sir William Osler in 1909, this organization bears striking similarity to the ASCI/AAP. I am very pleased that the Association’s secretary, Professor Salim Khakoo of Southampton General Hospital, has joined us this year to learn a bit more about our meeting and Society. I will be attending next year’s Association of Physicians meeting in the UK with the hope of codifying transatlantic collaborations, perhaps initially in the areas of training and education.



Figure 10. Acknowledgments. (A) Jain family reunion July 2014. (B) From left to right, Nisha Jain (daughter), Mukesh K. Jain, Rachana Jain (wife), and Kavi Jain (son).

I wish to conclude by thanking you, our members, my colleagues on the Council, and our administrative team (Figure 9). It has been my great privilege to work with you over these three years. I wish also to thank the enormous number of individuals, organizations, and institutions that have provided support for this meeting and ASCI initiatives, in particular the Seldin-Smith Award. A complete listing of supporters can be found in the ASCI annual report. Finally, I would like to thank those people who have supported my personal efforts in my own career life cycle: (a) my scientific mentors (Figure 9), (b) institutional leaders and colleagues in Boston and Cleveland for their continued

and unwavering support (Figure 9), and (c) my own family, seen here in the Outer Banks at a recent reunion: two wonderful kids and my wife, who remains the wind beneath my wings (Figure 10).

Thank you.

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