Program Evaluation Report
NCI Innovative Molecular Analysis Technologies (IMAT) Program
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Panel Members:

H. Shelton Earp, III, MD
Lineberger Professor of Cancer Research
Director, Comprehensive Cancer Center
University of North Carolina

Peggy Farnham, PhD
Chair and Professor
Biochemistry and Molecular Medicine
Vice Dean, Keck School of Medicine
University of Southern California

Katherine Ferrara, PhD
Professor of Radiology
Division Chief, Molecular Imaging Program
Stanford University

Trey Ideker, PhD, Panel Chair
Professor, Human Genomics & Precision Medicine, Department of Medicine
University of California San Diego

Wendell Lim, PhD
Professor, Cellular & Molecular Pharmacology
School of Medicine
University of California San Francisco

David Tuveson, MD, PhD
Professor of Cancer Research
Director, CSHL Cancer Center
Cold Spring Harbor Laboratory

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Summary of the IMAT Program

The Innovative Molecular Analysis Technologies (IMAT) program was established by the National Cancer Institute (NCI) to spur highly innovative technology development efforts addressing critical needs in cancer research. The program was initiated in 1998 and has been renewed roughly every 3 years; it was last renewed in 2020.

The IMAT program supports early-stage development of novel and potentially transformative technologies through an approach of balanced but targeted innovation relevant to the full breadth of the cancer research spectrum. The IMAT program is housed in NCI's Center for Strategic Scientific Initiatives (CSSI) and its management team is composed of representatives from all extramural divisions of NCI and members of the Office of the Director. The trans-divisional, multidisciplinary nature of the IMAT program management team is designed to promote a consolidated yet balanced representation of technology interests and needs across NCI. In support of its mission, IMAT employs a variety of investigator-initiated research project grant mechanisms while retaining a strong commitment to diversity and training of scientists and clinicians across disciplines.

The IMAT program has adjusted its structure and budget over time to match institutional and environmental conditions. Starting in 2003, the program terminated the use of Program Announcements (PAs) to solicit applications and started using Request for Application (RFA) solicitations, which allowed for unique application and review arrangements, as well as a set-aside budget guaranteeing a minimum investment by NCI in these awards to the community. During that same period, it was decided that the IMAT program would no longer support bioinformatics technologies or *in-vivo* or whole-body imaging tools, as those particular areas were beginning to receive support from emerging separate funding opportunities being offered by NCI. Instead, in 2005 the IMAT program added a new series of funding opportunities for proposals focused on improved sample-preparation technologies.

In 2008, the program adapted the R21 mechanism to allow larger awards for a 3-year award period and discontinued use of the "phased award" mechanism that allowed for a linked R21 and R33 award to applicants. In 2017, the program launched a series of Competitive Revision funding opportunities that seek to encourage the incorporation of IMAT-supported technologies into ongoing hypothesis-driven research efforts (e.g., active R01, U01, and P50 grants). In 2021, the program replaced the R21 award with the R61 award, to ensure the earlier-stage grant mechanism would continue to offer support for 3 years with a higher budget than NIH was allowing for the R21. The program is currently supported through 10 funding opportunities (2 R61s, 2 R33s, and 6 competitive revision RFAs), with the R61 and R33 awards covering 2 tracks: Molecular/Cellular Analysis Technologies (MCA) and Biospecimen Science Technologies (BST).

Authority for issuance of IMAT funding opportunities extends only until September 2023.

The 2023 Review Process

In support of a renewal request to continue offering the IMAT funding opportunities, NCI requires an independent evaluation of the program. CSSI convened a panel of esteemed scientists to engage in an evaluation of the IMAT program by the end of 2022. The panel includes the following individuals: *Trey Ideker* (University of California San Diego, Panel Chair), *Shelton Earp* (University

of North Carolina), *Peggy Farnham* (University of Southern California), *Katherine Ferrara* (Stanford University), *Wendell Lim* (University of California San Francisco), and *David Tuveson* (Cold Spring Harbor Laboratory) (see **Appendix 1** for biographies of the panelists). The main objectives of the evaluation panel were to assess the merits of the IMAT program and to make recommendations to the NCI should the program continue. These recommendations are intended to assist NCI's leadership in making a final determination about the path forward for the IMAT program.

The panelists, led by Dr. Ideker, participated in four virtual meetings between December 2022 and March 2023. Drs. Kelly Crotty and Tony Dickherber (program co-directors) provided information to the panel drawn from analysis of IMAT funding from 1999–2022. The information spanned diverse measures, including bibliometric measures (publications and citations from IMAT-funded projects), examples of "success stories" with significant impact developed out of IMAT-funded projects, and information about IMAT applicants and awardees compared to other programs. The panel also requested, considered, and discussed unique aspects of the IMAT program in the context of the broader NCI investment in technology development. Panelists did not review confidential materials such as applications or review documents.

Panel Assessment

Overall, the panelists appreciated the clear importance of the IMAT program and its contributions to the portfolio of NCI-funded research. The program has funded an impressive array of technology development projects for cancer research, both historically and currently, and this success has undoubtedly helped launch other, subsequent, NCI technology programs. ***Panel opinion was unanimously in favor of program continuation***, with a focused set of recommendations for program structure and emphasis moving forward. In what follows, we document the panel's overall assessments of the IMAT program across distinct areas, followed by its major suggestions for the future.

<u>Track record of impactful technology development</u>

The IMAT program boasts an impressive track record of funding impactful technologies for cancer research, some of which have been simply transformative. Anecdotal, but nonetheless striking, early examples include the BeadChip and BeadArray platforms, which launched Illumina (Chee, 1999); rolling circle amplification, now a standard method in molecular biology and especially used in biosensing (Lizardi, 1999); the PROTACS protein degron method, presently being adopted and furthered by dozens of cancer drug companies (Crews, 2006); and multiple grants that catalyzed the era of shotgun proteomics (Aebersold, Smith, Yates, all circa 2000). More recent IMAT grants are already showing appreciable impact, including microfluidic platforms for 3D cell culture (Kamm and Jacks, 2012), which was subsequently spun out into AIM Biotech; Conditionally Reprogrammed Cell technology which led to a Georgetown University biobank that is widely used by the cancer research community including many intramural researchers at NCI (Schlegel, 2013); and duplex sequencing, which has now been commercialized by TwinStrand Biosciences (Loeb, 2014). A separate collection of recent IMAT awards (2014-2018) has catalyzed the emerging area of spatial -omics technology, including SlideSeq (Chen), Multiplexed

Imaging of Nucleosome Architecture (MINA, Wang); and Multiplexed Ion Beam Imaging (MIBI, Nolan/Angelo). One challenge with assessing technology impacts in this anecdotal manner is that not enough time has passed to assess all of the most recent IMAT awards in the current funding portfolio. Regardless, the panel was impressed not only by the fundamental contributions of IMAT-funded programs, but also by the repeated historical examples of transfer of technology to industry.

Interest in the IMAT program and competitive outlook

The panel noted that the IMAT program had shown sustained competitive funding rates, with approximately 13% of submitted applications being funded each of the past several years. This funding rate was slightly lower than the standard funding rates of NCI R01 applications, which historically have hovered around 15%. Consistent with these statistics, the IMAT program officers reported a sizable tranche of high quality grant applications with review scores just slightly worse than the funded applications (i.e. those at 14 percentile and above), meaning that many worthy applications were consistently being passed over for funding. Thus, the IMAT program has been, and continues to be, quite competitive.

The program officers did report that the number of applications had fallen somewhat in recent years (by approximately 25% over the past 10 years, accompanied by an increase in funding rates from 10 to 13%). This point generated much discussion among panelists and led to committee recommendations (see next section below). The panel did note, however, that while IMAT was one of the original means of funding technology development at the NCI, it was no longer unique in this respect. More recent NCI efforts, such as the Cancer Imaging Program, Informatics Technology for Cancer Research (ITCR), Small Business Innovation Research (SBIR), and others are now also attracting large numbers of biotechnology and bioengineering grant applications. When all of these NCI programs were considered together (IMAT included), the total number of grant applications in biotechnology/bioengineering had not fallen. In fact, the total value of NCI investment in technology-focused grants had increased in recent years by >50% (period 2014 to 2022). Thus, the panel concluded that the modest decrease in IMAT applications was likely related to the recent multiplication of mechanisms offered by NCI for funding novel technology development. The panel also suggested that the recent move from the R21 to the R61 funding mechanism may result in an increase in IMAT applications.

Success in funding young investigators

The panel was encouraged to find that the IMAT R21 funding mechanism had shortened the time from the Principal Investigator's (PI) initial university degree to receipt of a successful NCI award. In particular, the median time from degree to award was 15 years for IMAT R21 investigators, as compared to 20 years for the regular Clinical and Translational Science R21 (**Figure 1**). The panel viewed this short time to award as a distinguishing feature of the IMAT program and an important facet of technology-focused awards. The panel also discussed whether these statistics might ultimately be impacted by the recent move from the R21 to the R61 mechanism; however, panel opinion was that such a move was unlikely to affect time-to-award. Indeed, preliminary data from

the new R61s over the past year indicate continued interest and enthusiasm from young investigators.

Integration of IMAT awards with other NCI and NIH programs

An important measure of success for cancer technology development is whether that technology is widely adopted, leads to additional research awards or new capabilities in industry, and/or otherwise impacts the broader biomedical community. In this respect, the panel requested statistics to assess and document transfer of technology from IMAT grants; these were researched and provided by NIH program staff, focusing on IMAT awards made in FY2018. Among other figures, these statistics showed that of 29 IMAT awards total, 3 led to later IMAT grants, 8 to later NCI R01s, and 8 to spun-out companies. Thus, the panel found ample evidence of successful handoffs of early technology developed in IMAT to other NIH programs and/or industry.

Ensuring innovation and high-risk/high-gain projects in key focus areas

IMAT staff continuously seek input from multiple stakeholders to identify core areas of technology development where innovation is most needed. In response to the previous 2020 evaluation and its ensuing recommendations, IMAT staff developed best practices for polling the cancer research community to identify new technology needs and opportunities. As part of these best practices, priority areas for technology development are identified by internal NCI surveys and by outside investigators who send IMAT officers topics of special interest. Some of these intramural and extramural solicitations are judged sufficiently compelling to lead IMAT officers to release Notices of Special Interest (NOSI). NOSI are bulletins distributed widely to the biomedical research community to announce interest in receiving applications in a certain area; unlike RFAs, they are non-binding and similar to, but typically more specific than, the parent Program Announcement (PA). A recent example is the release in April 2022 of NOT-CA-22-083, Technologies and Informatics Tools for Cancer Metabolomics. In general, directing efforts of IMAT staff towards “idea intake” was considered to be a very positive development by the panel, leading to suggestions for even more extensive, active measures to identify and solicit areas for IMAT technology focus (see below).

On a related note, and further following the recommendations of the 2020 review panel, IMAT developed the “4-I” system to track different types and degrees of technology innovation. These 4 I’s are [1] Innovative new technology with high-risk/high-gain, [2] Improvement of existing technology, [3] Integration of previously separate siloed technologies, and [4] Implementation of existing technology among the biomedical research community. This system has been applied by IMAT over the past several years to evaluate the “4-I” categories relevant to each grant submission, thus allowing IMAT to ensure that at least some of its funded applications fall squarely in the first category of high risk/high gain projects. Of course, staff should not (and do not) expect innovative grants to be submitted only in solicited areas, since one might argue that topics of innovative grant applications may be, by nature, unpredictable.

Panel Recommendations

Align study sections with the core IMAT mission of funding innovative technologies

An overarching need for the IMAT program, stated by the program leaders and also clear to the committee from the evaluated data, is to ensure that the program solicits and funds highly innovative applications. Analysis of funded applications using the "4-I" system (see above) and the ratio of funded R21s to R33s suggests that reviewers are still tending to reject or provide lower scores to innovative applications. The consensus of the panel, which echoed comments of the 2020 panel also, was that the IMAT program should continue to use the 4-I system but seek to further emphasize the first and third categories (Category I: Innovative New Technologies; Category III: Novel synthesis of existing technologies). The committee had extended discussions relating to this concern leading to the **major recommendation**, as has been made in the past, that the IMAT program take additional measures to ensure it remains highly focused on innovation. In particular, the panel recommended that all study section participants should be made well aware of, and instructed in, the key criterion of innovation (e.g. include a pre-review Zoom session for all reviewers and provide guidance to the study section Chair). In addition to this specific measure, the panel noted it was making recommendations in other areas (see below) that may serve to **increase the number and innovativeness of IMAT applications**.

Improve integration of IMAT with other NCI and NIH technology programs

The panel recognizes that the IMAT program budget itself is not large, and the funding rate is already among the more competitive NCI grant opportunities (similar to that of other exploratory programs such as the general R21 pool). However, when one looks at the overall NCI-funded technology programs together, a much larger budget, approaching $200-300M, is revealed. Related to this observation, it would be reasonable to say that the IMAT program is an early discovery arm of NCI technology development and a point of entry to the wider pool of funding, some with higher funding rates (e.g. STTR and SBIR).

Therefore, the panel opinion is that it will be critical to "un-silo" these separate NCI technology programs, so that technology-focused investigators have a better overarching view of all relevant funding mechanisms. In particular, one way to attract attention from the NIH-funded research community, and thus more grant applications, is to seek synergy/combination with other NCI funding mechanisms for technology development, such as SBIR/STTR, Cancer Imaging Program, Academic/Industrial Partnerships, ITCR, Cancer Center Support Grants, and so on. It is realized that certain of these budgets are congressionally mandated and have their own review processes and program teams; however, if the IMAT program could be seen as a starting point, the panel believes this stance would increase its attraction and potentially add value.

Several additional ideas emerged from the panel towards this end. First, with respect to "marketing" the various NCI technology programs as conjoint development efforts, there could be a closer coordination among the various technology/engineering RFAs, for example using the same submission dates or including cross-referral of applications across programs. The IMAT program currently organizes an Annual Meeting which includes panels on commercialization and technology transfer, with information regarding relevant funding opportunities in the other NCI-

sponsored programs. These panels are clearly a step in the right direction and could seek to more specifically include officers from other NCI technology-related programs, positioning the annual IMAT gathering to facilitate an exploration of the next steps in NCI-funded efforts. Inclusion of "outside" funded investigators who have had success in turning IMAT grants into larger initiatives could also help transform the IMAT Annual Meeting into a central gathering place that would increase integration. An attempt to have the community place IMAT at the base for discovery – and thus entry into the wider world of NCI technology development – would promote the idea of integration. These steps, along with the new mechanism (R61 with three years of funding), should improve the visibility of the program among biomedical investigators.

Another fairly recent IMAT granting mechanism has been developed to allow competitive revisions that provide funding for non-IMAT investigators to validate an IMAT technology by incorporating it into their ongoing research. For this new mechanism to be highly successful, investigators will need to be made aware of the list of IMAT-funded technologies; perhaps a website, flyer or brief program presentation at various cancer conferences would help increase awareness of the technologies and this funding mechanism.

Increase efforts to market the IMAT program

Initial funding from the IMAT program has spurred development of a multitude of transformative approaches important in cancer research today, including small molecule-mediated protein degradation (PROTACS), rolling circle amplification, gene expression arrays, and quantitative proteomic methods. These IMAT success stories have become the basis of new therapeutic and diagnostic methods that are FDA-approved, and they have played a transformative role in founding or supporting major biotechnology and/or biopharma companies. Most of these IMAT ideas were considered too risky for support from traditional governmental, foundation, philanthropy or venture-funding mechanisms. It is success stories such as these that need to be more widely known by the scientific community.

Because most NCI-funded cancer research is conducted by scientists affiliated with NCI-designated Cancer Centers, the panel recommends that the IMAT program be advertised through the NCI Cancer Centers office, as a means for cancer centers to inform their members of the exciting opportunities offered by IMAT funding. IMAT funding could be linked to, or augmented by, developmental funding provided by Cancer Centers. Furthermore, with the expansion of initial funding for IMAT projects to the three-year R61 format of up to $150k/year, successful grants can count as an "R01 equivalent" for cancer center Programs. Cancer Center Directors should be made aware of this change and asked to encourage their most innovative faculty to apply for IMAT funding.

Other methods for increasing the community awareness of IMAT is to send systematic targeted emails to scientific leaders in specific technology development areas, or to hold monthly virtual research seminars with presentations by IMAT-funded investigators (but open to others in the scientific community and advertised to members by all Cancer Center Directors). Marketing needs could be assessed by back-evaluation of who is applying, and whether certain Cancer Centers are poorly represented in applications. It will be especially important to ensure that Cancer Center Directors, as well as the wider scientific community, realize that IMAT is generally

a better funding mechanism for highly innovative, non-hypothesis-driven awards than other current opportunities.

Continue to encourage applications from early-stage NIH investigators

The suggestions noted above for improving integration and marketing apply to all investigators. However, the review panel would also like to see additional efforts focused on applications from early-stage investigators (ESI). In terms of marketing, the panel suggested specifically targeting advertising to ESI investigators to increase interest, and thereby increase the numbers of ESI applicants. A key marketing point is that IMAT has long been very supportive of ESI (see above assessment), and the grants of these investigators have tended to perform very favorably with successful funding outcomes. Integration with other programs that are specifically focused on early-stage investigators could also be useful. For example, while the NIBIB Trailblazer award has been very successful, the program is not focused on cancer-specific applications and therefore may not be widely advertised in the cancer research community. It is also important that IMAT program staff communicate with NIBIB to ensure that reviewers realize that cancer-focused technologies are allowable under this funding mechanism. Such coordination with NIBIB, and other similar programs, may be productive in 1) ensuring that cancer-focused young investigators are not disadvantaged in other programs and 2) ensuring that early-stage cancer researchers are aware of the other programs.

Panel members also were enthusiastic about providing opportunities for IMAT young investigators to disseminate the results of their work and receive appropriate acknowledgement in an IMAT forum, as well as in larger groups of young investigators who have received prestigious awards. For example, although this may be out of the scope of this panel's purview, the group was enthusiastic about the potential for a cancer and technology-oriented K99/R00 award to further increase the momentum for the development of new technologies among young faculty.

The panel was encouraged to hear that the IMAT program staff have some flexibility in the funding of particularly innovative and important technologies and in the selection of applications from ESI applicants. Given that early-stage investigators can be disadvantaged in regards to having sufficient preliminary data, carefully constructing the review panel and criteria to ensure fairness to these young investigators is important. The IMAT program leadership team appears to have been very successful in this regard. There was a divergence of opinion on the panel as to whether further increased efforts should be made to preferentially fund applications from young investigators, or whether it is wiser to simply focus on increasing the number of applicants overall.

Expand efforts to identify and target technology development areas that need funding

The panel recognizes that the IMAT program leadership has made extensive efforts in engaging various groups to understand current gaps in technology and to prioritize tackling these specific technology challenges. For example, Branch Chiefs and Program Directors across the NCI Division of Cancer Control and Population Sciences held several joint meetings to identify specific technology gaps for the communities they support, leading to a new NOSI - NOT-CA-23-037. Regardless, the panel suggested that IMAT program leaders continue expanding their efforts in identifying technologies appropriate for their grant portfolio.

Emerging technology areas and concepts can be identified in diverse ways. IMAT staff should continuously seek to identify technology-related conferences they should attend, and they should seek to establish strong channels of communication with technology-oriented leaders, garnering their insights. To canvas a broader range of participants, IMAT staff should participate in the organization of Idea Lab or sandpit-style conferences on broad but provocative topics (in the past, this has been done with NSF and other organizations). A goal of such workshops should be to identify a focused list of key relevant emerging technology areas or needs. When attending such events, IMAT leadership should work hard to ensure that the attending audience also becomes well-educated about IMAT and considers collaborative IMAT grants as possible outcomes of workshop participation.

Once priority areas for transformative technologies are identified, IMAT leadership might participate in (and/or organize) focused workshops in this precise set of technology subjects. Examples include participation in the recent Seattle metabolomics workshop or the recent successful organization of the NIH Synthetic Biology Consortium. These meetings and groups are a strong venue to interface with potential IMAT applicants.

Finally, IMAT leadership should maintain close awareness of potential synergy with the new ARPA-H division (https://arpa-h.gov/research/#health-science). Although the mission of ARPA-H is still taking shape, it is at least partly intended to catalyze development of broad transformative health-relevant technology platforms that transcend specific diseases. Thus, there is great opportunity to work synergistically with ARPA-H on identifying critical technology areas of common interest.

Appendix 1: Panelist Biographies

Chair

Trey Ideker, Ph.D., is Professor of Medicine, Computer Science, and Bioengineering at UC San Diego, and former Chief of the Division of Genetics. He is the Director or Co-Director of the NCI Cancer Cell Map Initiative, the Bridge2AI CellMaps4AI Consortium, the NIGMS National Resource for Network Biology, and the UCSD Bioinformatics PhD Program. The mission of his laboratory is to enable a new era of cancer discovery and treatment based on the complete elucidation of the molecular networks underlying cancer. In 2006, Ideker was named one of the Top 10 World Innovators by MIT Technology Review and, in 2009, he was awarded the Overton Prize by the International Society for Computational Biology. Dr. Ideker serves on the Editorial Boards for *Cell*, *Cell Systems* and *PLoS Computational Biology*. He is a Fellow of the American Association for the Advancement of Science (AAAS), the American Institute of Medical and Biological Engineering (AIMBE), and the International Society for Computational Biology (ISCB), and he has served on the Boards of Scientific Advisors for the National Human Genome Research Institute and, presently, the National Cancer Institute.

Panel Members

H. Shelton "Shelley" Earp, M.D., is the Lineberger Professor of Cancer Research and Director of the UNC Lineberger Comprehensive Cancer. His group has discovered and studied genes involved in a range of cancers, published over 200 biomedical-research articles and been continuously funded by NIH for over 40 years. Dr. Earp has received UNC School of Medicine teaching awards and chaired national review committees for the American Cancer Society and the National Cancer Institute. He has served as President of the American Association of Cancer Institutes, on the NCI Board of Scientific Advisors, and on the advisory boards of ten university cancer centers. His lab is supported by NIH grants, the Breast SPORE and the Breast Cancer Research Foundation.

Peggy Farnham, Ph.D., is the William M. Keck Professor of Biochemistry, the Chair of the Department of Biochemistry and Molecular Medicine, and the Vice Dean for Health and Biomedical Science Education at the Keck School of Medicine at the University of Southern California in Los Angeles, California. Dr. Farnham is an international leader in the study of chromatin regulation and its control of transcription factor binding and function. She has been a member of several international consortia of genomic scientists working on the ENCODE (Encyclopedia of DNA elements) and the PsychENCODE Projects and a participant in the NIH Roadmap Reference Epigenome Mapping Centers. Based on her contributions to biomedical research, she was elected as a Fellow of AAAS in 2010 and in 2012 she received the *ASBMB Herbert A Sober Award*, which recognizes outstanding biochemical and molecular biological research with particular emphasis on the development of methods and techniques to aid in research.

Katherine Ferrara, Ph.D., is a Professor of Radiology and the Division Chief for the Molecular Imaging Program at Stanford. She is a member of the National Academy of Engineering and a fellow of the IEEE, AAAS, the Biomedical Engineering Society, the World Molecular Imaging Society, the Acoustical Society of America and AIMBE. Following an appointment as an Associate Professor in the Department of Biomedical Engineering at the University of Virginia, Charlottesville, Dr. Ferrara served as the founding chair of the Department of Biomedical Engineering at UC Davis. Dr. Ferrara is known for work in the development of contrast agents and molecular imaging techniques and instrumentation. She has received the WMIS Gold Medal, IEEE Biomedical Engineering Award, IEEE Achievement Award and IEEE Rayleigh Award.

Wendell Lim, Ph.D., is the Byers Distinguished Professor in the Department of Cellular and Molecular Pharmacology at the University of California, San Francisco. He is Director of the UCSF Cell Design Institute. He obtained his bachelor's degree from Harvard University and his PhD from MIT. Dr. Lim's lab uses synthetic biology approaches to understand the logic of cell signaling systems and to enable engineering of next-generation precision therapeutic cells. He has served as chair of the Department of Cellular and Molecular Pharmacology, Director of the UCSF Center for Systems and Synthetic Biology. He served on the NCI Board of Scientific Counselors, is on the editorial board for Science and Cell, and serves on the Board of Directors for the Burroughs Wellcome Fund. He was the scientific founder of Cell Design Labs, a cell therapy startup acquired by Gilead in 2017.

David Tuveson, M.D., Ph.D., is the Roy J. Zuckerberg Professor of Cancer Research and the Cancer Center Director at the Cold Spring Harbor Laboratory. Dr. Tuveson is also the Chief Scientist for the Lustgarten Foundation for Pancreatic Cancer Research and is known for developing the first mouse and organoid models of pancreatic cancer. Dr. Tuveson was the President of AACR in 2021-22, and served on the NCI Board of Scientific Advisors from 2018-2022. He is a Rita Allen Foundation Scholar (2004), received the Hamdan Award for Medical Research Excellence - Pancreatic Diseases (2016), the 2022 Luminary Award, and was on Clarivate's list of the top-most cited researchers in 2022. Dr. Tuveson is a member of ASCI, AAP, and the National Academy of Medicine.