Basic science under threat: lessons from the Skirball Institute

Agnel Sfeir[1*], Gord Fishell[2*], Alexander F. Schier[3*], Michael L. Dustin[4#], Wen-Biao Gan[5#], Alexandra Joyner[6#], Ruth Lehmann[7#], David Ron[8#], David Roth[9#], William S. Talbot[10#], Deborah Yelon[11#], Arturo Zychlinsky[12#]

1- Molecular Biology Program, Sloan Kettering Institute, MSKCC, New York, NY
2- Harvard Medical School, Boston, MA
3- Biozentrum, University of Basel, Basel, Switzerland
4- Kennedy Institute of Rheumatology, University of Oxford, Oxford, United Kingdom
5- Institute of Neurological and Psychiatric Disorders, Shenzhen Bay Laboratory, Shenzhen, China
6- Developmental Biology Program, Sloan Kettering Institute, MSKCC, New York, NY
7- Whitehead Institute, Department of Biology, MIT, Cambridge, MA
8- Cambridge Institute for Medical Research, Cambridge University, Cambridge, United Kingdom
9- Department of Pathology and Laboratory Medicine, Raymond and Ruth Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA
10- Department of Developmental Biology, Stanford University, Stanford, CA
11- Division of Biological Sciences, University of California, San Diego, La Jolla, CA
12- Max Planck Institute for Infection Biology, Berlin, Germany

* Correspondence to Agnel Sfeir: sfeira@mskcc.org; Gord Fishell: Gordon_Fishell@hms.harvard.edu and Alex Schier: alex.schier@unibas.ch

[#] Authors listed in alphabetical order

Support for basic science has been eclipsed by initiatives aimed at specific medical problems. The latest example is the dismantling of the Skirball Institute at NYU School of Medicine. Here, we reflect on the achievements and mission underlying the Skirball to gain insight into the dividends of a basic science vision within the academic enterprise.

Basic science across the world is under threat. Biological science as an enterprise is increasingly aimed toward solving specific medical problems such as Alzheimer's disease, cancer, and diabetes. These important health issues represent serious challenges facing society, but are they best addressed by solely focusing our efforts at correcting single diseases? Repeatedly, the solutions to medical challenges have rested on the foundation built by curiosity-driven basic science, with human health benefits only emerging over decades. There would be no statins had it not been for the foundational studies that unraveled the cholesterol biosynthetic pathway and LDL receptor function (Brown and Goldstein, 1974). Who would have guessed that restriction enzymes and CRISPR systems that protect bacteria from foreign DNA would transform the biotech industry and open the prospect of precision gene therapy? Most recently, disparate lines of research in virology, structural and RNA biology that seemed interesting mostly to basic scientists have now become the foundation of SARS-CoV-2 vaccines that are saving millions of lives. Can we afford to abandon such efforts? With the closing of institutes and departments that are devoted to broad-based discovery research, we urge the scientific community to reflect on the value of such endeavors. Here we share our experience and lessons from the Skirball Institute, an incubator that fostered three decades of basic science discovery, but unfortunately came to a close.

For the past twenty-seven years, the Skirball Institute for Biomolecular Medicine has served as a home for basic research at New York University (NYU) School of Medicine. Distributed across four thematic programs – Molecular Neurobiology, Developmental Genetics, Structural Biology and Molecular Pathogenesis – the institute established a reputation for scientific excellence and a nurturing environment for launching the careers of hundreds of young scientists, many of whom now populate top universities, medical schools, and institutes across the US and abroad. As scientists who were lucky enough to have been a part of this three-decades long adventure, we pause to reflect on its lasting legacy and discuss three key tenets that defined the Skirball mission, a focus on cross-disciplinary basic science, a highly collegial and collaborative environment, and being a training ground for future scientists (Figure 1). These principles represent shared commonalities with other basic science institutes embedded within academic institutions and form the backbone for the development of scientific talent and capital in the US and abroad.

The Skirball Institute was established in 1993 through a gift from the Skirball Foundation. The founding director, the late Lennart Philipson, was a visionary leader. Having made EMBL (European Molecular Biology Laboratory) a key training ground for future leaders in molecular biology in Europe, he was recruited to NYU with the goal of creating a collaborative environment for interdisciplinary basic science. His vision offered the opportunity to bridge molecular biology and medical research without the constraints imposed by traditional boundaries. Breaking from the top-down structure of medical school departments, the institute embraced a flat administrative structure, where at any given time ~30 faculty members jointly made decisions on new recruitment and the overall direction of the institute. Faculty and trainees were supported by administrative staff who were equal partners in this adventure. The atmosphere at Skirball was aspirational, without being elitist. The institute championed collegiality, and a deep sense of camaraderie was shared by cohorts of junior faculty along with a group of more senior colleagues and mentors. The junior faculty among us felt we had something to prove but were too fresh out of the gate to

worry much about our legacy. Most of all, we had terrific fun, often finding ourselves late at night at Skirball poring over each other's grants and with a wry smile, encouragingly retorting "still needs work".

Embedded within a medical school, Skirball focused on attentive mentoring for its trainees in their journeys of discovery. Graduate students, physician scientists, and postdocs received personalized guidance that shaped the growth of their scientific careers; some young technicians who did their first experiments at Skirball are now faculty at Stanford University and the University of Chicago. Career development for junior faculty was always a high priority shared across the institute. New investigators were supported not only by close colleagues in their area of interest, but also by faculty with different scientific and career stage perspectives. These features added value to being a junior PI at Skirball compared to traditional departments and more thematically focused research institutes.

The leadership of Skirball, from Lennart Philipson to Ruth Lehmann, always advocated for blue sky science and oversaw recruitment of outstanding junior faculty from emerging fields regardless of their research theme. The juxtaposition of diverse science and cross-fertilization across disciplines created an intellectually rich environment fostering creativity and attracting independent investigators in pursuit of opportunity over security. The unique setup inspired us to follow our science wherever it led us and to pursue exciting research areas at their most fundamental level. If there was a battle cry it was to "take risks and the rest will follow" and for many of us it indeed did. Anyone who attended the yearly Skirball retreat walked away energized. All of molecular biology was our playground. The breadth of the intellectual landscape was immense, broadly ranging from how organisms assemble during development to the maternal parenting of newborns. It spanned genome packaging and stability to organellar function, membrane protein structure and onto synapse formation (Figure 2). Our focus on basic discovery meant we were free to take advantage of a combination of model organisms including bacteria, *C. elegans*, *Drosophila*, *Xenopus*, zebrafish and mice, comprising an amazing menagerie. We worked hard and were so entrenched in the effort that we have only recently begun to fully appreciate what a remarkable nexus in biology we were straddling.

Throughout its tenure, the institute's *esprit de corps* was tangible, and many of the discoveries made under Skirball's roof resulted from interdisciplinary collaborations. The institute recognized and incentivized breaking down walls between areas of research, as exemplified through the annual Philipson Prize for the best interdisciplinary paper published within a given year. Among the many stellar honorees, the Philipson Prize recognized the interdisciplinary work that led to the first live imaging of microglial processes (Davalos et al., 2005). Skirball scientists developed ultrasound backscatter microscopy to gain unprecedented spatial resolution of the embryonic mouse heart and neural tube (Turnbull et al., 1995). Collaborations across disciplines also led to finding the missing link controlling the neuromuscular synapse (Kim et al., 2008) and the discovery of how growth factors function as morphogens, bringing to life the brilliant concept first proposed by Alan Turing (Schier and Talbot, 2005). More recently, seminal discoveries led by Skirball scientists shed light on how gut microbes train the immune system (Ivanov et al., 2009) and uncovered a critical role for the neuro-immuno circuit in regulating tissue homeostasis (Talbot et al., 2020).

This brief summary illustrates how the Skirball Institute embodied the vision laid out by Vannevar Bush, an influential policymaker who headed the U.S. Office of Scientific Research and Development (OSRD) during world war II. In his "Science, the Endless Frontier" report to the US president (web resource 1), he argued that "The most important ways in which the government can promote industrial research are to increase the flow of new scientific knowledge through support of basic research, and to aid in the development of scientific talent." The implementation of Bush's vision made the US the leader in basic

sciences and laid the foundation for remarkable improvements in human health and prosperity. But with the closure of basic science institutes, including the Skirball Institute, this vision is under threat.

We call on the government as well as philanthropists, and academic institutions to renew Bush's vision of science as an endless frontier and act in support of basic science institutes that foster fundamental discovery biology that embody the Skirball pillars (Figure 1). First and foremost, basic science needs funding agencies, including NIH and NSF to act. The NIH Director's fund was developed to instigate investigator driven and innovative science. This mechanism is a step in the right direction but is not enough, especially when the modular budget for R01 grants, designed to foster research in basic science, has seen no increase since 1999 (web resource 2). Various branches within NIH fund extramural program projects and centers, including a mechanism that supports NCI-designated cancer centers. One idea would be for the NIH to establish a similar funding program that recognizes basic science institutes that foster fundamental discovery without being defined or confined to a particular disease. Similar funding challenges are being faced abroad, as the Wellcome Trust has decided to increase its focus on global heath, including health impacts of climate change, and ERC has recently needed to weather political attacks on its basic science mission (web resource 3). Philanthropy also seems to be shifting away from endowment-based support for medical schools and universities in favor of launching theme-focused institutes that have minimal ties to academic institutions. While these new endeavors will certainly advance science, their dedication to specific diseases and therapies limits insights and cross-fertilization from other disciplines. Moreover, a serious knock-on effect is that their structures do not typically include a paired mission for graduate and postgraduate education and training. This last point highlights the need for medical schools and universities to strengthen their commitment to fundamental discovery biology, where science is pursued with no disease or even endpoint in sight. To that end, now and more than ever, academic institutions need visionary leaders who can navigate challenging funding climates while preserving curiosity-driven basic science.

In Lewis Thomas' classic "Lives of the Cell", he points out that medicine in most cases helps mask symptoms rather than solve the underlying problems. Enduring therapeutic advances often require an understanding of fundamental mechanisms of disease processes attained through basic research. History has shown that such answers inevitably come from unexpected places and odd juxtapositions that are based upon deep understanding of biology. In fact, analysis of 28 "transformative" drugs approved by the FDA between 1995-2009 revealed that 80% of these medicines are traced back to basic science discoveries, many of which took place decades before realizing that the work had implications for a medical breakthrough (Spector et al., 2018). While "Manhattan projects" to tackle cancer, aging, and neuropsychiatric disease are important, they should not come at the expense of academic basic science institutes that champion innovation at their core and train the next generation of scientists. Skirball was such a place. It is now ending, but if there is a lesson from this adventure, it is that science and the world need more Skirballs.

Web resource list

1- https://www.nsf.gov/od/lpa/nsf50/vbush1945.htm: “Science; The Endless Frontier” – A report prepared in July 1945 by Vannevar Bush – the Director of the Office of Scientific Research and Development – and submitted to the US president (United States Government Printing Office, Washington: 1945)

2- https://grants.nih.gov/grants/funding/modular/modular_11_09_1999.htm#:~:text=In%20the%20December%2015%2C%201998,as%20a%20modular%20grant%20application
this link indicates that NIH introduced the R01 modular grants with a budget of 250,000$ per year in 1999

3- https://www.science.org/content/article/new-strategy-wellcome-trust-will-take-global-health-challenges: Wellcome Trust implementing a strategic shift to focus on global health challenges: infectious disease, mental health, and global warming.

Declaration of interests

Agnel Sfeir is a co-founder, consultant, and shareholder in Repare Therapeutics. Gord Fishell is a co-founder, consultant, and shareholder in Regel Therapeutics. Alexander Schier, Michael Dustin, Wen-Niao Gan, Alexandra Joyner, Ruth Lehmann, David Ron, David Roth, William S. Talbot, Deborah Yelon, and Arturo Zychlinsky declare no competing interests.

Figures and legends

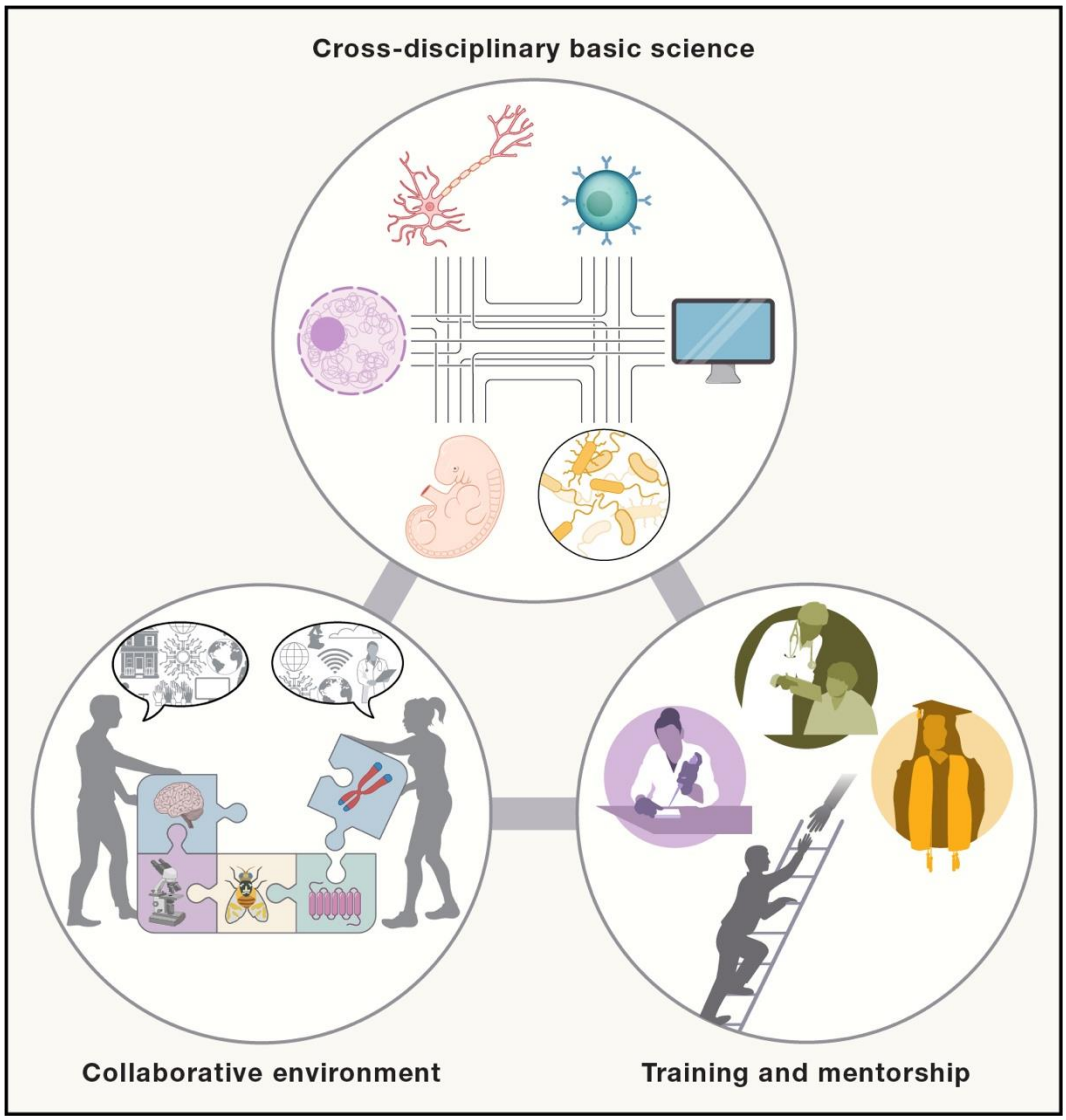

Figure 1: Organizing principles core to academic basic science institutes, including Skirball. Depicted are three ideals that constitute major benefits inherent to basic science institutes embedded within academic institutions, including cross-disciplinary basic science, a highly collaborative and collegial environment, and training the next generation of scientists. These pillars defined the mission of the Skirball Institute.

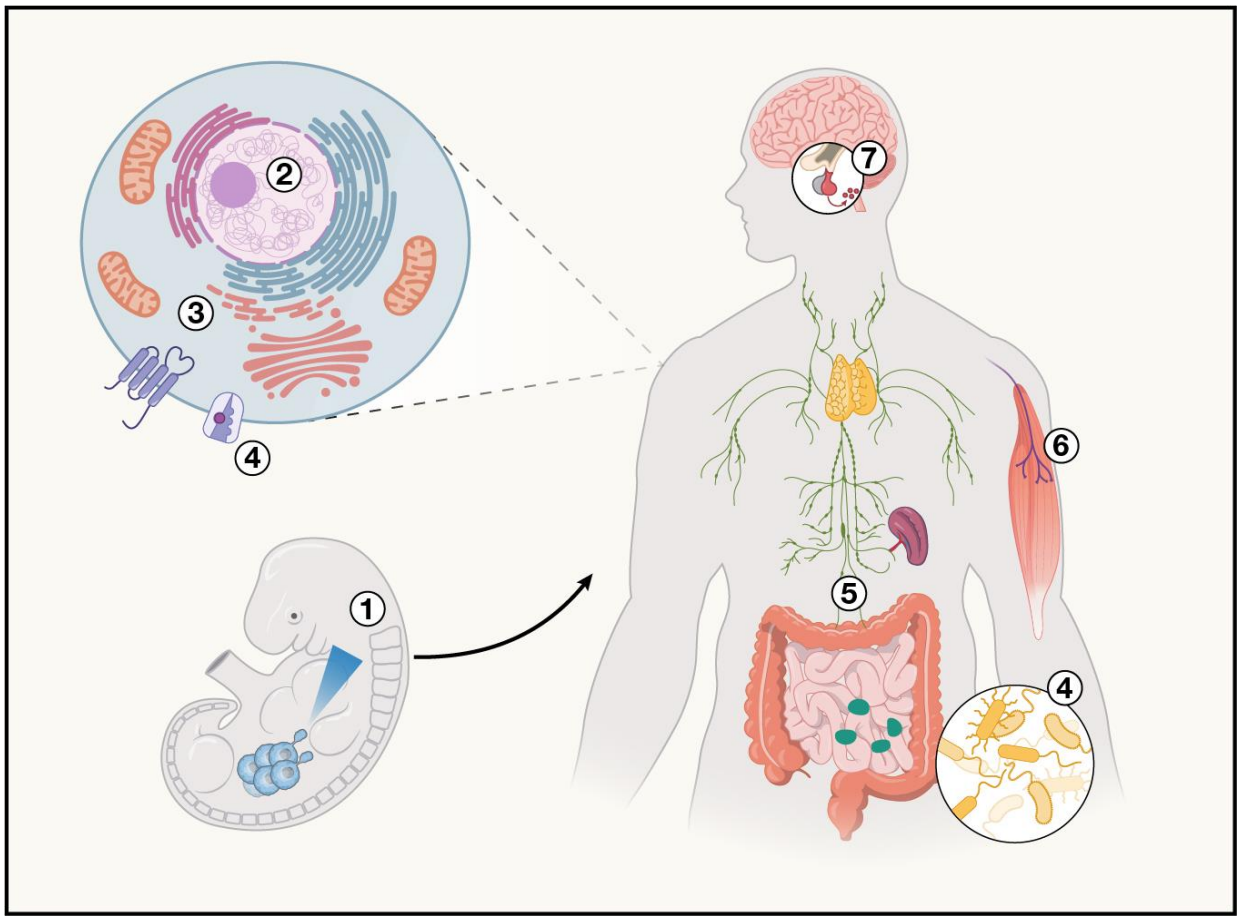

Figure 2: Summary of recent studies highlighting the breadth of recent discoveries led by Skirball scientists.

1- Developmental biologists observed in real time how a self-generated signaling gradient forms across a migrating tissue (Venkiteswaran et al., 2013). 2- Chromosome studies described a novel DNA repair machinery that has gone awry in cancer and provided structural insight into how genome packaging and histone modifications regulate transcription (Valencia-Sanchez et al., 2021). 3- At the organellar level, Skirball scientists identified how endoplasmic reticulum (ER) stress signals attenuate protein translation and showed that mitochondrial fragmentation drives the selective removal of deleterious mitochondrial genomes in germ cells (Lieber et al., 2019). 4- Structural biologists saw how alpha helices and beta sheets formed unique pores in proteins that selectively pass cations and lipids across cell membranes in human cells as well as bacteria (Isom et al., 2020). 5- New tools were developed to image cytokine gradients and define the mechanisms that control exit of immune cells from lymphoid organs (Mendoza et al., 2017). 6- Studying the neuromuscular synapses revealed the unexpected cause of Congenital myasthenia and provided a potential therapy for the debilitating disease (Oury et al., 2021). 7- Neuroscientists uncovered how oxytocin modulates neural circuits to foster maternal behavior (Carcea et al., 2021).

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