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No crops without seeds: the risks in declining support for fundamental research

Benjamin M. Hogan, Mark L. Kahn & Natasha L. Harvey

Over recent decades, shifts toward translational or applied research in many countries have come at the expense of fundamental discovery research. Here we discuss the historical importance of basic science in the cardiovascular field, the risks in its decline and the ongoing need for a strong foundation in fundamental discovery research.

Experience in the past century has proven that biomedical research leads to improved health, well-being and productivity. Research is often a progressive endeavor, whereby fundamental research (also called basic or pure research) generates essential new knowledge that underpins further translational research and development. Thus, the stronger our fundamental research sector, the more knowledge and the more beneficial health and economic outcomes are generated. Accordingly, developed nations maintained vibrant fundamental research sectors throughout the second half of the twentieth century. However, recent decades have seen a growing emphasis on translational or applied research, and away from fundamental research, in many countries. In adopting this position, the goal is to generate shorter-term outcomes for patients and society.

Recent data and frequent commentaries have highlighted this shift, often coupled with reduced funding for fundamental research or shifts in areas of research emphasis. For example, in Canada, government investment has stagnated and researchers have faced a challenging decline in investigator-led grants for fundamental research[1]. Similarly, Australian spending on fundamental research decreased 23% overall between 1992 and 2018, in conjunction with a shift toward applied research and targeted funding schemes[2]. In the United States, the public share of fundamental research funding dropped in recent decades, but this was driven largely by new investment from industry and higher education[3]. The US National Institutes of Health (the world's largest funder of basic science) has reiterated the central importance of fundamental research[4]. Yet, although NIH funding has remained steady, there has still been a worrying reduction in fundamental applications[4,5], in part associated with the perception by scientists that more basic work is less appreciated and with an underlying trend towards more applied areas. Such shifts away from fundamental research might seem to make sense when the immediate needs of patients are in focus, but they ignore the fact that scientific progress often occurs over decades. Major new leaps forward (as opposed to incremental gains) often come off the back of unpredictable breakthroughs that generate fundamental, deep new understanding.

The inherent value of fundamental research is well documented in areas such as oncology and immunology, but it is no clearer anywhere than in modern cardiovascular medicine. The way that physicians treat patients with cardiovascular disease today reaps the rewards of extensive new knowledge from fundamental research, often undertaken by international teams spanning generations of researchers. A collective effort at discovery has transformed the treatments that are delivered to millions of patients every day.

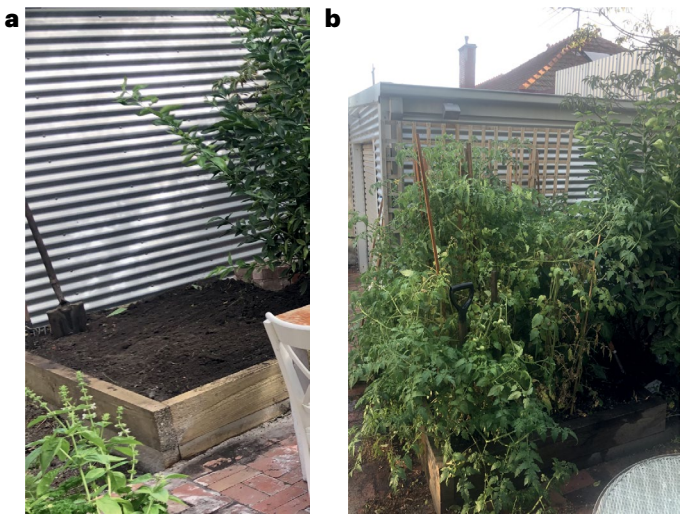

Fig. 1 | The Hogan/Smith suburban vegetable patch in Melbourne, Australia. Unseeded (**a**) versus seeded and largely left to its own devices (**b**). Rampant growth and a delicious crop of salad tomatoes are observable at right, belaboring the metaphor that seeds (basic science) inevitably deliver crops (outcomes and impact).

To explore just a few examples with profound impact in cardiovascular disease, we first look back about 50 years. In 1985, Brown and Goldstein were awarded the Nobel Prize in Physiology or Medicine for their discoveries regarding the regulation of cholesterol metabolism. Although their discoveries have revolutionized the way that hypercholesterolemia is treated, their initial questions originated with, "Why do families with familial hypercholesteremia have circulating cholesterol levels so high that they suffer heart attacks"? The answer turned out to be that these patients harbor mutations in genes encoding proteins that affect the function of the low-density lipoprotein receptor, the cell surface receptor important for binding and internalizing cholesterol that circulates in the form of low-density lipoprotein particles. The result of these mutations is that cholesterol cannot be taken up into cells and therefore circulating levels remain high, leading to accumulation within arterial plaques and subsequent stroke or heart attack[6]. The question posed by Brown and Goldstein was a fundamental scientific question, not one rooted in a search for new treatments for familial hypercholesterolemia. Even though the question was of

a fundamental 'seed' nature the knowledge generated was essential for the development of statins, the first of which was identified by Akira Endo[7], thereby providing effective therapies for cholesterolemia to the millions of people worldwide affected by this condition.

Another example comes from research that focused on the fundamental nature of signaling through integrin receptors and the role of platelets in arterial thrombosis. By the 1950s the ability of aspirin to prevent myocardial infarction had been reported by a private medical practioner[8], but the mechanism by which it did so remained a mystery. Studies in the 1960s by Harvey Weiss, Sir John Vale, Phil Majerus and others demonstrated that aspirin was an anti-platelet agent, an insight that intersected with basic studies by David Phillips, Joel Bennett, Mark Ginsberg, Ed Plow, Richard Hynes and others in the 1970s and 1980s demonstrating that platelet aggregation was mediated by integrins, an ancient family of adhesion receptors[9]. These findings led to the discovery that platelet integrins are stringently regulated by 'inside-out' intracellular signals required to alter their extracellular structural conformation and enable ligand binding to form the shear-resistant arterial clots that underlie heart attacks and most forms of stroke. This work culminated in the development of agents such as the monoclonal antibody developed against GP IIb/IIIa by Barry Coller that block platelet aggregation and are used daily for coronary angioplasty[10].

Such breakthroughs from fundamental research might be easily thought of as historical. One might ask whether such big breakthroughs are less likely today, because we have accumulated so much new knowledge. However, this thesis is not one that stands the test of even the past few years. Fundamental research uncovered how clustered regularly interspaced short palindromic repeats (CRISPR) protect the prokaryote genome against bacteriophages as recently as 2007. This led rapidly to the demonstration that CRISPR–Cas9-mediated double-strand breaks could be directed with sequence specificity and the suggestion that this could allow efficient genome editing. The demonstration of CRISPR–Cas9 genome editing in mammalian cells came soon thereafter (for a useful summary, see ref. [11]). This fundamental research has revolutionized modern biomedical research, leading to the 2020 Nobel Prize in Chemistry and in a few short years to new therapeutic approaches in blood diseases including transthyretin amyloidosis[12], sickle cell disease and β-thalassemia[13]. The translation of this deeply fundamental science to the clinic has been heralded as the beginning of a new era of medicine.

All three of these examples (and there are many more) highlight research that started with simple, fundamental questions, and all demonstrate why such work is essential. They are emphatic examples of research that provided the 'seeds' of major new 'crops': new knowledge generation that led to permanent changes to medicine and clinical practice in cardiovascular disease (Fig. 1).

When it comes to the shift away from fundamental research, owing to reduced funding or increasing emphasis on applied research, we believe that there are substantial risks in favoring short-term demand for gains over investing in longer-term strategies. First, there is a compelling economic argument. Research from the International Monetary Fund has shown that policies that fund fundamental research foster the kind of innovation needed for economic growth and that basic research affects more sectors, has more international reach and achieves longer-lasting impact than applied research[14]. The investment in fundamental research by the NIH has delivered economic outcomes, with each US$1 put into public basic research leading to >US$8 of industry research and development investment return over 8 years[15]. Overall, NIH fundamental research is estimated to provide a positive return on public investment of ~43%, by fueling the entry of new drugs into the market[15]. It is clear that reducing funding in fundamental research comes with an economic cost. Second, there is risk in not diversifying the new knowledge that our national research programs generate. The top-down approach of selecting areas for research funding predicted to be 'translational' is a high-risk, short-sighted strategy. An excellent example arose from the COVID-19 pandemic, before which few would have considered understanding viruses in diverse animal species, or even mRNA vaccine technology, as essential translational research. Now, few would disagree with that premise. Diversity in research and in the new knowledge it generates is inherently valuable. Finally, the shift away from fundamental research will inevitably lead to changes in scientific training. In the authors' own institutions, postdocs and students are increasingly favoring applied research or planning alternative, non-academic careers. Anecdotally, this is a widely observed trend. In consequence, we are now training more postdocs and students with translational or applied projects that are often less exploratory, following predetermined translational pipelines. The risk is that if we stop training our students in the creative process of finding the questions no one else is asking, and in hunting down their own unique discoveries, what sort of scientists are we educating? What is the long-term cost to science and research leadership of such cultural change? And to positive health outcomes fueled by fundamental discoveries? This may well turn out to be the greatest cost of the current trend away from fundamental research.

For those of us who remain passionate about the importance of fundamental discovery research, the value of such work seems obvious. It is crucial that leadership is shown in promoting the importance of fundamental research. There is no question that outcomes for patients and new treatments are needed today, but a short-term goal does not have to come at the expense of a strong, complementary, long-term vision. We must promote a balanced and diverse research investment portfolio for society, in which fundamental, discovery science is an essential and secure component. We must better balance risk with reward as we look to the future. After all, if we stop sowing seeds today, where will the crops come from tomorrow?

Benjamin M. Hogan [1,2,3] ✉, **Mark L. Kahn** [4] ✉ & **Natasha L. Harvey** [5,6] ✉

[1]Peter MacCallum Cancer Centre, Melbourne, Victoria, Australia. [2]Sir Peter MacCallum Department of Oncology, University of Melbourne, Melbourne, Victoria, Australia. [3]Department of Anatomy and Physiology, University of Melbourne, Melbourne, Victoria, Australia. [4]Department of Medicine and Cardiovascular Institute, University of Pennsylvania, Philadelphia, PA, USA. [5]Centre for Cancer Biology, University of South Australia and SA Pathology, Adelaide, South Australia, Australia. [6]Adelaide Medical School, University of Adelaide, Adelaide, South Australia, Australia.
✉e-mail: ben.hogan@petermac.org; markkahn@pennmedicine.upenn.edu; natasha.harvey@unisa.edu.au

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Competing interests
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