

Commentary

Completing the Great Unfinished Symphony of Cancer Together: The Importance of Immigrants in Cancer Research

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Recent changes in U.S. immigration policy are adversely affecting biomedical science, at a time when biomedical research is most sorely needed on multiple fronts. Here we discuss the immense contributions of immigrants to cancer research and the adverse impact that current administration policies will have on successful cancer research.

"America, you great unfinished symphony, you sent for me

You let me make a difference

A place where even orphan immigrants

Can leave their fingerprints and rise up ..."

—Leslie Odom, Jr. and Lin-Manuel Miranda, *Hamilton*

but in recent years, an anti-immigrant sentiment has rapidly burgeoned. This is manifesting itself not only in crackdowns on illegal immigration, but also in the thwarting of legal immigration, and the sciences are particularly vulnerable to this. In this commentary, we address the issues this anti-immigrant sentiment poses, specifically for cancer research.

grees than multi-generational native-born peers, and increasingly contribute to the U.S. economy overall. Nearly 50% of all Fortune 500 companies were founded by immigrants and their children (Fearnow, 2019), and since 2000 nearly 40% of U.S.-based winners of the Nobel Prizes in Physics, Chemistry, and Medicine have been immigrants (Anderson, 2018).

Introduction

America has always had a complex and checkered history of immigration. From the first colonists who set foot on its shores to the waves of immigrants that came after—some involuntarily, like African slaves so cruelly torn away from their homes, others seeking to voluntarily escape theirs, like Irish immigrants who fled the potato famine to come here; Italians who immigrated to Ellis Island to escape the unstable 1920s government of Italy; European Jews who flocked steadily here over the years, especially during the pogroms (1880–1914) and then again during the heinous reign of Nazi Germany; and more recently, refugees from Central and South America. Indeed, with the exception of the slaves brought here against their will, immigrants came to America to seek the American Dream and the solace offered by our Lady Liberty: "Give me your tired, your poor, your huddled masses yearning to breathe free..." America was the beacon for innovators, scientists, and pioneers,

Immigrants and the Economy

Immigrants are strong contributors to the U.S. economy. Data show that immigrants make up a high percentage of the essential workforce and are employed at far higher rates than their native-born counterparts (Sherman et al., 2019). Partly this may be due to the lack of "roots" in one particular geographical area, which allows immigrants to go where the work is, and this in itself contributes to the economy. In figures from 2009, the average foreign-born adult with an advanced degree was shown to pay over \$22,500 in taxes, including federal, state, FICA, Social Security, and Medicare, while receiving about a tenth of that back in government-sponsored benefits (such as unemployment, Medicare, etc.) (Zavodny, 2011). Compare that to American taxpayers who reap two to three times *more* than they pay into the system in Medicare, Social Security, and other benefits. Further, data show that children born to immigrant families are upwardly mobile, getting higher de-

Immigrants in Cancer Research: Current Status

The contribution of immigrants to the biomedical, and specifically cancer research, workforce cannot be overstated. A recent study looked at some of the top cancer research centers in the country, including MD Anderson, Johns Hopkins, and others, and found that the number of foreign-born cancer researchers at these institutions ranged from 40% to more than 70% (Neill and Avasthi, 2020). It is not clear if these figures include those working in internet technology, artificial intelligence, and bioengineering, all critical fields for the implementation of cancer research through the technologies they provide. Many of these immigrant workers are here on visas for highly skilled individuals (H1B), scholarly visas with a requirement to return home and provide service to their own countries (J-1), or student visas (F-1). In the past few weeks, we have seen two of these groups of visa holders suddenly



subjected to increased and draconian restrictions with paltry explanations provided. While the executive order restricting F visas was stopped through lawsuits brought by an array of public and private universities, processing of these visas at U.S. embassies abroad has slowed to a crawl. Further, researchers from specific countries—China, Iran, and others—are banned from entering the U.S. These restrictions, coupled with the abysmal failure of the U.S. response to COVID-19, will likely serve to drive away talented international researchers in droves, who might prefer to take their talents where they are welcomed and appreciated, and where healthcare systems provide affordable care, especially during a pandemic. This is particularly true now that the gap in scientific funding and excellence has been decreasing between the U.S. and other advanced and developing economies.

Immigrants in Cancer Research: Major Contributions

The contribution of foreign-born physicists to American physics is well documented, with luminaries such as Albert Einstein, Enrico Fermi, Leo Szilard, Hans Bethe, and many others helping America to become a leader in technology and, incidentally, playing a major part in the U.S. winning the space race via the successful 1969 moon landing. A similar argument can be made that immigrant scientists have played a major role in U.S. cancer research, working in laboratories across the nation and helping to unravel the basic mechanisms of oncogenesis and develop new innovative tools for cancer therapies. In fact, through the help of immigrant scientists, the U.S. has become one of the world leaders in cancer drug development, stimulated by the combination of strong basic academic laboratories and a large number of pharmaceutical and biotech companies. [Table 1](#) lists immigrant cancer scientists who have received Nobel Prizes or Lasker Awards. It is impossible to describe all the notable contributions of foreign-born scientists to the U.S. cancer research enterprise, which range from those of Salvador Luria (Italy) and Max Delbrück (Germany), who showed that mutations can be inherited from cell to daughter cell, to the birth of the tumor metabolism field, described by Carl and Gerty Cori. This

latter couple were both born in Prague, but because of scientific limitations and anti-Semitism came to the Roswell Park Cancer Institute in 1922 to pursue their studies on carbohydrate metabolism. While not focused specifically on cancer research, the Coris published an early paper on tumor metabolism in 1925, which together with the body of their work (including the Cori cycle, discovered in 1929) paved the way for the important research area known as cancer metabolism. In 1931, the Coris moved to Washington University, where they continued their groundbreaking work and won the Nobel Prize in 1947. At WashU, they built a leading department of biochemistry which included seven future Nobel laureates ([Rubin, 2019](#)), an immense contribution to cancer research and biomedical science.

Another area of groundbreaking research encompassing the outstanding work of multiple outstanding immigrant scientists is the crucial role of the microenvironment in cancer progression. This field became widely accepted due largely to the efforts of Mina Bissell, who was born in Tehran, Iran, and came to the U.S. in 1959 for college and later received her PhD from Harvard in 1969. Dr. Bissell then moved to Lawrence Berkeley National Laboratory, where she has been ever since. Her paradigm-shifting work has been crucial in demonstrating the role of the microenvironment in tumor progression, a role that had been controversial before her studies. In 1982, Bissell proposed the theory of dynamic reciprocity, which altered our view of how cancer cells affect their environment and vice versa ([Bissell and Aggeler, 1987](#)). Similarly, Isaiah Fidler, born in Israel in 1936, came to the U.S. to study veterinary medicine. In time he would play a major role in revisiting and proving the seed and soil hypothesis, demonstrating the crucial interactions between tumor cells (the seed) and the microenvironment of the metastatic sites (the soil). His work has paved the way for the development of novel approaches for therapy aimed at modulating the microenvironment (such as anti-angiogenesis therapy) ([Fidler, 2003](#)). Another important contributor to understanding of the roles of the microenvironment in disease progression was Zena Werb. Dr. Werb was born in the Bergen-Belsen concentration camp in Ger-

many in March 1945. After the war, her family emigrated to Canada. After obtaining her Bachelor's degree from the University of Toronto and her PhD from the Rockefeller University, Dr. Werb moved to the University of California, San Francisco, where she initiated her classic studies on the tumor microenvironment, focusing on the extracellular matrix ([Egeblad et al., 2020](#)). The tradition of outstanding immigrant scientists in the field of tumor microenvironment continues to this day with researchers such as Kornelia Polyak (Hungary), Rakesh Jain (India), Mikala Egeblad (Denmark), Yibin Kang (China), and many others. In addition, immigrant scientists have made huge contributions to cancer research fields such as epigenetics, e.g., Danny Reinberg (Argentina), Peter Jones (Zimbabwe), Jean-Pierre Issa (Lebanon); genomics and cancer genetics, e.g., Alan Ashworth (UK), Elizabeth Blackburn (Australia), Mario Capecchi (Italy), Edison Liu (Hong Kong); immunology, e.g., Antoni Ribas (Spain), Lieping Chen (China), Anjana Rao (India), Olivera Finn (Serbia), Francesco Marincola (Italy); and countless others.

The development of chemotherapy in cancer treatment certainly represents a watershed moment in cancer research. Before the 1950s the treatment of cancer was limited to surgery and radiation therapy, but a series of experiments at NCI in the 1950s and 1960s led to the development of modern chemotherapy. A crucial member of the team involved in the development of this new approach was Min Chiu Li, an immigrant from Shenyang, China, who had come to the University of Southern California in 1947 to pursue postgraduate education following his MD in China. Dr. Li was part of the NCI team that first successfully treated a solid tumor with chemotherapy. In addition, while treating choriocarcinoma with methotrexate, Dr. Li used serum hCG levels to assess treatment efficacy, continuing treatment even after clinical remission, an important insight which represents the first use of a molecular biomarker to assess therapy response. Dr. Li later moved to Memorial Sloan Kettering Cancer Center and shared the Lasker Award in 1972 for his enormous contributions to the field of cancer chemotherapy ([Freirich, 2002](#)). In fact, in oncology, basic and translational science are a critical

Table 1. Immigrant Lasker and Nobel Prize Winners in the United States

Name	Country of Birth	Year of Prize	U.S. Institution	Research Area
Sidney Altman	Montreal, QC, Canada	Nobel, 1989	Yale University, Harvard University	Catalytic properties of RNA
Baruj Benacerraf	Caracas, Venezuela	Nobel, 1980	New York University, Columbia University, National Institutes of Health, Harvard Medical School, Dana-Farber Cancer Institute	Genetic basis of immunology
Elizabeth Blackburn	Hobart, Tasmania, Australia	Lasker, 2004; Nobel, 2009	University of California, Berkeley; University of California, San Francisco; Yale University; Salk Institute	Co-discovered telomerase
Günter Blobel	Niegostawice, Poland	Lasker, 1993; Nobel, 1999	Rockefeller University	Protein transport and localization in the cell
Mario Capecchi	Verona, Italy	Lasker, 2001; Nobel, 2007	Harvard School of Medicine, University of Utah	Gene targeting in mouse embryo-derived stem cells
Albert Claude	Brussels, Belgium	Nobel, 1974	Rockefeller University	Electron microscopy in biology
Gerty Cori	Prague, Austro-Hungarian Empire	Nobel, 1947	Roswell Park Cancer Institute, Washington University in St. Louis	Cell metabolism
Carl Cori	Prague, Austro-Hungarian Empire	Lasker, 1946; Nobel, 1947	Roswell Park Cancer Institute, Washington University in St. Louis	Cell metabolism
Max Delbrück	Berlin, German Empire	Nobel, 1969	Vanderbilt University, California Institute of Technology	DNA replication/genetic structure of viruses
Renato Dulbecco	Catanzaro, Italy	Lasker, 1964; Nobel, 1975	Indiana University Bloomington, California Institute of Technology, Salk Institute for Biological Studies	Found that certain animal cancer viruses can insert themselves into a cell's DNA
Hidesaburo Hanafusa	Osaka Prefecture	Lasker, 1982	The Rockefeller University	Genetics of RNA tumor viruses
Charles Brenton Huggins	Halifax, Nova Scotia	Lasker, 1963; Nobel, 1966	University of Michigan, University of Chicago	Use of hormones in cancer therapy
Har Gobind Khorana	Raipur, Multan, Punjab Province, British India (present-day Punjab, Pakistan)	Lasker, 1968; Nobel, 1968	University of Wisconsin-Madison, Massachusetts Institute of Technology	Deciphering the genetic code
Rita Levi-Montalcini	Turin, Italy	Lasker, 1986; Nobel, 1986	Washington University in St. Louis	Discovery of nerve growth factor (NGF)
Min Chiu Li	Mukden, China	Lasker, 1972	National Cancer Institute, Memorial-Sloan Kettering Cancer Center, Nassau Hospital	Solid tumor chemotherapy
Fritz Lipmann	Königsberg, Germany	Nobel, 1953	Massachusetts General Hospital, Harvard Medical School, The Rockefeller University	Bioenergetics
Salvador Luria	Turin, Italy	Nobel, 1969	Columbia University, Indiana University, University of Illinois at Urbana-Champaign, Massachusetts Institute of Technology	Genetic structure of viruses
Paul Nurse	Norwich, Norfolk, UK	Lasker, 1998; Nobel, 2001	The Rockefeller University	Cell cycle
Severo Ochoa	Luarca, Asturias, Spain	Nobel, 1959	New York University School of Medicine, Washington University School of Medicine in St. Louis	RNA polymerase discovery
George Emil Palade	Iasi, Romania	Lasker, 1966; Nobel, 1974	New York University; The Rockefeller University; Yale University; University of California, San Diego	Electron microscopy and cell fractionation
Georgios Papanikolaou	Kymi, Euboea, Greece	Lasker, 1950	Cornell University, New York-Presbyterian/Weill Cornell Medical Center	Early cancer detection; developer of the Pap smear

Table 1. Continued

Name	Country of Birth	Year of Prize	U.S. Institution	Research Area
<i>(Continued on next page)</i>				
Oliver Smithies	West Yorkshire, UK	Lasker, 2001; Nobel, 2007	University of Wisconsin-Madison, University of North Carolina at Chapel Hill	Gene targeting in mouse embryo-derived stem cells
Ralph Steinman	Montreal, QC, Canada	Lasker, 2007; Nobel, 2011	The Rockefeller University	Dendritic cells
Jack Szostak	London, UK	Lasker, 2006; Nobel, 2009	Harvard Medical School	Telomeres and the enzyme telomerase
Susumu Tonegawa	Nagoya, Aichi, Japan	Nobel, 1987	Massachusetts Institute of Technology	Genetic mechanisms of antibody production

intermarriage, and a number of immigrant physician scientists have had a critical impact on bringing new treatments to the clinic. Waun Ki Hong (Korea), Carlos Arteaga (Ecuador), Olufunmilayo Olopade (Nigeria), Gabriel N. Hortobagyi (Hungary), Irene Ghobrial (Egypt), Chi Van Dang (Vietnam), Lieping Chen (China), Baruj Benacerraf (Venezuela), Azra Raza (Pakistan), Kristiina Vuori (Finland), and many, many others have all contributed enormously to translational and clinical cancer research. Of the 71 NCI-designated cancer centers in the U.S., at least 10 are led by foreign-born directors.

Given the history of contributions of foreign-born researchers in the United States to the understanding of cancer mechanisms, including five Nobel Prizes directly in cancer research, and to seminal discoveries that have led to improvements in cancer care, immigrants, to paraphrase Lin-Manuel Miranda in *Hamilton*, are getting the job done. With so far yet to go, however, depleting this critical resource of immigrant scientists is a dangerous path for U.S. science and medicine. The critical contributions of immigrants to cancer research, and the parallels between the increase in immigrant cancer researchers and physicians and ever-improving survival rates in cancer patients, are beautifully and comprehensively outlined in a 2013 report by the National Foundation for American Policy (Anderson, 2013). While the examples above provide an idea of the breadth of the impact foreign-born scientists have made on the U.S., it is impossible to fully acknowledge the contributions of immigrants to cancer research. Even in laboratories run by American-born scientists, immigrants make up a large proportion

of the trainee workforce, and while some of their names may go unnoticed, their efforts speak volumes. It is clear that without their contributions our country would not occupy its unique position in the world in terms of innovation and the development of new cancer therapies.

Dispelling Myths Regarding Immigrants

Finally, we feel it is incumbent upon us to dispel a couple of myths surrounding immigrant scientists. One of the most common complaints we hear is that immigrant scientists are “cheap labor.” In fact, the National Institutes of Health sets the same pay guidelines for all trainees, and nationality does not factor into pay rates. Another overriding concern is that immigrant workers “take American jobs” and that this could also potentially cause underrepresented minority U.S. scientists to get “pushed out” by international trainees, reducing their chances for positions in academia. In fact, a comprehensive study of the U.S. labor market from 2000 to 2007 showed that an increase in immigrant workers actually boosts American jobs, where for every 100 immigrant workers there is an increase of 262 jobs for American workers (Zavodny, 2011). If we look specifically at H1B visa holders, each 100 H1B visa holders result in 183 additional jobs among U.S. natives. It is only fair to assume that this increase in jobs is equally reflective of increased jobs for minority scientists as well. Given also that grants and fellowships targeted toward underrepresented populations by and large exclude foreign-born scientists, it is unlikely that it is truly the case that immigrants, rather than systemic failures, adversely affect minority scientists. And finally, having foreign-born scientists of

color increases representation among the ranks of scientists, which hopefully increases the recruitment and retention of minority scientists. Importantly, this commentary is not meant to devalue the incredible contributions of American cancer researchers, which are legion, but it is imperative to highlight the fact that there are more jobs than available U.S. workers in STEM. In a 2012 report by the President’s Council of Advisors on Science and Technology, it was projected that over the next decade the United States will need approximately 1 million more STEM professionals than it will produce at the current rate (PCAST, 2012), meaning that the immigration of highly skilled professionals is critical for the continued success of U.S. science.

Conclusions

In conclusion, the data overwhelmingly support the importance of immigrants for biomedical sciences and, in particular, cancer research. It is worth noting that all three authors of this commentary are immigrant scientists, cancer researchers, and, now, naturalized Americans. To beat a disease this deadly, we need the brightest minds, no matter from where they hail. We strongly propose that a diverse set of approaches, views, and backgrounds will work best to unravel the mysteries of cancer and point to important new avenues for therapy. Let us bring a diverse array of instruments to the floor so we can complete this great unfinished symphony.

ACKNOWLEDGMENTS

We dedicate this review to the thousands of immigrant trainees who have come to the U.S. to pursue cancer research, to the hundreds of well-recognized immigrant researchers we did not have room to mention, and to the U.S.-born cancer

research colleagues at every level who train (and train with) immigrants, who collaborate with immigrants, and who create safe spaces for immigrants to flourish. While this commentary has been U.S. focused, given the immigration policies that adversely affect research in this country, we also commemorate the native and immigrant researchers all over the world whose contributions to cancer research are invaluable. Together, we can make a difference in the race to cure cancer, and it will take a global effort.

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