First Person Profile: Matthew L. Meyerson, MD, PhD

Pioneering scientist leads key discoveries in cancer genomics

Born just a few hundred yards away from Boston's Dana-Farber Cancer Institute (DFCI), Matthew L. Meyerson, MD, PhD, likes to joke that, of all of his colleagues, he has traveled the shortest distance from where he started.

That anecdote belies Dr. Meyerson's long and accomplished scientific journey, one that has been paved with major discoveries and numerous accolades in the field of cancer genomics. That journey continues today.

"Clearly, we don't know enough about cancer yet," says Dr. Meyerson, director of the Center for Cancer Genomics at DFCI and a professor of genetics and medicine at DFCI and Harvard Medical School. "There's still a big knowledge gap in the genome. If we knew enough, we could treat every cancer."

Dr. Meyerson leads a broad research portfolio aimed at achieving that ambitious goal. Additionally, he serves as a senior associate member of the Eli and Edythe L. Broad Institute of MIT and Harvard, a research collaboration between the Massachusetts Institute of Technology (MIT) and Harvard that seeks to better understand the genetics of human disease and to develop potential treatments.

Additionally, Dr. Meyerson cochaired the executive committee of The Cancer Genome Atlas (TCGA), which is supervised by the National Cancer Institute's Center for Cancer Genomics and the National Human Genome Research Institute. Last year, Dr. Meyerson was honored along with 5 fellow DFCI researchers with the American Association of Cancer Research Team Science Award for the team's groundbreaking efforts on the TCGA project. Among his many other awards are his election to the National Academy of Medicine in 2018, the National Cancer Institute's Knudson Award in Cancer Genetics in 2019, and his naming as the second most influential scientist in the world in all fields of science by Thomson Reuters Corporation in 2014.

Dr. Meyerson is widely recognized for his early and ongoing discoveries in cancer genomics. Among other things, he and DFCI colleagues have discovered: (1) mutations in the *EGFR* gene that cause certain types of lung cancers; (2) mutations in the gene *HLA-A* that can cause it to lose function in lung cancer and potentially help the cancer to evade the body's immune system; and (3) the connection between the bacterium *Fusobacterium nucleatum* and colon cancer.

The discovery of *EGFR* mutations was the result of collaborations with fellow DFCI scientists William R. Sellers, MD; Pasi A. Jänne, MD, PhD; and Bruce E. Johnson, MD. "Matthew is willing to take big risks without fear, and in our collaboration on sequencing kinases, his confidence was instrumental in getting us going," says Dr. Sellers, Dr. Meyerson's long-time colleague and collaborator who serves both as senior advisor to the DFCI president on experimental therapeutics and as a core member of the Broad Institute, where he is director of the cancer program. "Without Matthew's enthusiasm, we would never have embarked on these larger-scale projects."

Raised in Philadelphia, Pennsylvania, Dr. Meyerson felt drawn to science at a young age. Rather than focusing on people and medicine, however, he was first interested in rocks and minerals. "My mother used to take me rock hunting," he recalls. "We would go to mineral dumps and other places where one could find interesting rocks and minerals."

Eventually, however, a wonderful ninth-grade biology teacher sparked his curiosity for human science through the creative use of sliced potatoes. "They turned out to make a great medium for microorganisms," Dr. Meyerson explains. "It allowed you to do streaking as a way to purify the organisms and to study the natural world in a really simple way."

Finding a Career Path

Dr. Meyerson observed the ravages of disease firsthand through his sister, who had both Crohn's disease and a mental illness. Watching her suffer from these chronic conditions played a major role in Dr. Meyerson's decision to pursue a medical career. Graduating from Harvard in 1985 with a

bachelor's degree in chemistry and physics, he later earned both his MD and his PhD in biophysics from Harvard as well. He served in many clinical rotations before moving on to research, and he recalls one patient in particular who influenced the ultimate direction of his career.

"In the late 1980s, a patient of mine had been losing weight and coughing up blood, but he kept delaying medical care," he says. "His diagnosis turned out to be lung cancer, and there was almost nothing we could do for him. I thought that, on the one hand, there was so little we could do for patients like him, but, on the other hand, there was so much we *could* learn about cancer through molecular biology. It seemed to be one disease area where we could really make an impact on patients' lives."

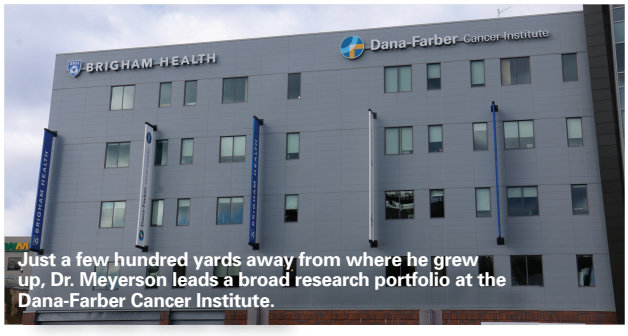
Watching the experiences of his father and his father-in-law, both of whom were diagnosed with metastatic cancer, further solidified his interest in oncology research. At Harvard, Dr. Meyerson joined the laboratory of cancer microbiologist Ed Harlow, PhD, where he worked to identify genes that control cell division in the cell cycle. Conducting experiments using yeast, he and his colleagues cloned the cyclin-dependent kinase genes and identified 18 genes in the family as key drivers of cell division, most prominently *CDK4* and *CDK6*. (Today, *CDK4* and *CDK6* have become the targets of major breast cancer drugs, including palbociclib, ribociclib, and abemaciclib.) He calls the work "a wonderful, exciting, and challenging experience."

Dr. Meyerson completed his residential training in clinical pathology at Massachusetts General Hospital in Boston, which was followed by a postdoctoral fellowship with Robert A. Weinberg, PhD, at MIT's Whitehead Institute for Biomedical Research.

During his postdoctorate, Dr. Meyerson collaborated with fellow researcher Christopher A. Counter, PhD, to clone the human telomerase protein catalytic subunit gene.[1] "We knew it was activated as cells became immortalized, and that it was an important factor in cancer cell survival," he says, noting that it is now recognized as one of the most common genes affecting multiple types of cancer.

Joining the DFCI faculty in 1998, Dr. Meyerson continued his collaborative efforts to further elicit and understand the genomic mechanisms of cancer. "I've always enjoyed working closely with colleagues," he says. "Bringing my mind together with others is a lot of fun."

In Dr. Meyerson's case, it also proved to be a highly successful strategy as he worked toward a better understanding of the genomics of lung cancer, on which he chose to focus because of its prevalence and very poor outcomes. "That was when the human genome was being sequenced, and I thought it was a great opportunity to study lung cancer," he says.



Just a few hundred yards away from where he grew up, Dr. Meyerson leads a broad research portfolio at the Dana-Farber Cancer Institute.

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—Matthew L. Meyerson, MD, PhD

A fellow faculty member questioned Dr. Meyerson's choice at the time, telling him it was better to start with a biological hypothesis rather than focusing on a specific disease. Still, Dr. Meyerson pursued his plan, working closely with Dr. Sellers, Dr. Johnson, and a number of other colleagues on sequencing research. Ultimately, their work led to the discoveries of mutations in the *EGFR* and *BRAF* genes in lung cancer and resulted in the development of many new targeted therapies—specifically, protein kinase inhibitors—for treating the disease.

A Lifetime of Research

Dr. Meyerson and Dr. Sellers also worked with Eric S. Lander, PhD; Bruce Stillman, PhD; and others to develop the concept of the TCGA program as a systematic approach to cancer genomics. As part of that effort, Dr. Meyerson developed an algorithm for understanding which types of genes were important for cancer pathogenesis.

Dr. Meyerson and his colleagues have made many more significant discoveries along the way. For example, along with chemist Heidi Greulich, PhD, Dr. Meyerson and his colleagues identified a genome-inspired method of drug discovery involving a compound that kills cancer cells expressing *PDE3A* and *SLFM12* proteins. The researchers described their use of predictive chemogenomics in small-molecule discovery in a study published in *Nature Chemical Biology*.[2]

More recently, Dr. Meyerson's team published findings online in *Cancer Discovery* indicating that patients who have lung cancer and are from Latin American countries that have a higher percentage of Native Americans are more likely to have the *EGFR* mutation than patients who have lung cancer and are from Latin American countries with fewer Native Americans.[3] One possible reason is that Native Americans are believed to have crossed the Bering Strait from Asia some 20,000 years ago. Asians who have lung cancer also have a high rate of *EGFR* mutation, whereas patients with lung cancer who are of European and African descent are more likely to have the *KRAS* mutation.

Facing Challenges

When he is not busy probing solutions to cancer genome challenges, Dr. Meyerson enjoys outdoor activities,

particularly hiking, with his wife, a pediatrician, and their 4 adult children. "We've spent a lot of time in the White Mountains of New Hampshire and the Green Mountains of Vermont, and we also climbed Colorado's Mount Elbert with our kids," he says.

Despite the progress in the field of cancer genomics, Dr. Meyerson says that many challenges still remain. Researchers need to continue the search for new drugs that target known mutations, such as those in the *P53* gene, which are implicated in approximately 50% of cancers and for which there is no targeted therapeutic, Dr. Meyerson notes. "We don't know the causes of all the alterations in the genome, and there are areas outside of the coding region that are completely dark matter to us," he says. "I see characterizing those regions of the genome as one of the biggest challenges in the future of cancer research."

References

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Supplemental Vitamin D May Reduce Advanced Cancer Risk

A team from Brigham and Women's Hospital in Boston recently published a secondary research analysis indicating that vitamin D supplementation was associated with an overall 17% risk reduction for advanced (metastatic or fatal) cancer.

The new analysis of the Vitamin D and Omega-3 Trial (VITAL) was published in November 2020 in *JAMA Network Open*.[1] Findings from the VITAL trial, which concluded in 2018, showed that vitamin D did not reduce overall cancer incidence; however, data hinted at a possible link to a reduction in cancer deaths. In this follow-up analysis, researchers also assessed participants with a normal body mass index (BMI) and found a 38% risk reduction in advanced cancers; this indicated that body mass may be tied to the relationship between vitamin D and the decreased risk.

Research interest in this area was originally generated by previous epidemiological studies showing that people who live near the equator have a lower incidence of developing cancer and dying of certain cancers. Because these residents have greater sunlight exposure and thereby produce more vitamin D, investigators have theorized that vitamin D could be tied to their lower cancer risks.

Paulette D. Chandler, MD, MPH, a primary care physician and epidemiologist in the Division of Preventive Medicine of Brigham and Women's Hospital, notes that vitamin D supplements are inexpensive and readily available and that the study provides important new information about its relationship with advanced cancer.

The VITAL study was a placebo-controlled trial conducted for more than 5 years. It involved 25,000 participants: men aged 50 years or older and women aged 55 years or older who did not have cancer at the beginning of the study. The group was racially and ethnically diverse. Researchers tested the independent effects of both vitamin D and omega-3 supplements as well as possible synergy between them. The study included 4 different groups: vitamin D (2000 IU/d) plus omega-3s, vitamin D plus a placebo, omega-3s plus a placebo, and placebos for both.

During the 5-year study period, 1617 participants were diagnosed with invasive cancer, including breast, prostate, colorectal, and lung cancer. Of the nearly 13,000 participants who received vitamin D, 226 were diagnosed with advanced cancer, whereas 274 who received the placebo were diagnosed with advanced cancer. Of the 7843 participants with a normal BMI (less than 25 kg/m^2) who were taking vitamin D, only 58 were diagnosed with an advanced cancer, whereas 96 participants who were taking the placebo were diagnosed with an advanced cancer.

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Researchers note that although the BMI connection could be coincidental, previous evidence does suggest a possible relationship between the two. Obesity and associated inflammation may reduce vitamin D's effectiveness as well as its receptor sensitivity, or it may alter vitamin D's signaling. Furthermore, randomized trials of vitamin D and type 2 diabetes have found evidence of vitamin D having a greater benefit for people at a normal weight while showing no benefit for obese patients.

Vitamin D deficiency is common in patients with cancer, researchers add. One study, for example, reported rates of vitamin D deficiency in patients with cancer as high as 72%.

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