Expert Interview with David Reese, MD, on cancer prevention and precision medicine

Dr. David Reese is Executive Vice President, Research and Development (R&D) at Amgen. In his current role, he oversees Discovery Research, Global Development, Global Regulatory Affairs and Safety, and Global Medical. Prior to his position as head of R&D, he was the Senior Vice President of Translational Sciences and Oncology where he oversaw translation of Amgen's drugs from the lab to the clinic and guided Amgen's overall oncology strategy. He started his career as a clinical oncologist and was involved in a multitude of clinical trials that tested the safety and efficacy of cancer drugs, including trials for Herceptin/Trastuzumab, one of the first targeted therapies to be developed and which is used to treat certain types of metastatic breast and other cancers. He did his undergraduate studies at Harvard College and received his medical degree from the University of Cincinnati College of Medicine. In this interview, Dr. Reese shares his career path, views on the opportunities and challenges to developing cancer prevention drugs, and thoughts on precision medicine. This article represents Dr. Reese's personal views as an individual and cannot be attributed to Amgen.

Will you briefly describe to us your background and career path?

I am currently the head of research and development (R&D) at Amgen. I have been at Amgen for almost 17 years now. I was trained as a medical oncologist. After medical school, I did my training at University of California, Los Angeles (UCLA). I was a fellow and postdoc in the laboratory of Dennis Slamon, MD, PhD (1, 2) when the antibody that became Herceptin/Trastuzumab was going through preclinical work and then being developed. Following my tenure at the Slamon lab, I became a faculty member at UCLA, then at University of California, San Francisco (UCSF), and back at UCLA again, mostly doing translational research. My niche was early phase drug development. I moved to Amgen in 2005.

I have had a variety of roles in research and development at Amgen, initially running drug development programs in oncology, then the early oncology portfolio, then the entire early development portfolio across therapeutic areas – we focus on oncology, inflammation, and cardiometabolic disease. Then I ran what we call translational sciences, which had early development plus various other arms – toxicology, pharmacokinetics, metabolism, etc. I was part of the R&D leadership team, and then became head of R&D about four years ago. In my current role, I am responsible for crafting our research and development strategy and guiding those efforts.

Tell us a little more about the development of Herceptin/Trastuzumab.

HER-2 is a protein that is overexpressed, amplified, or, more rarely, mutated in a number of human cancers including breast, ovarian, and lung cancer. Overexpression or activation of HER-2 contributes to the increased proliferation and survival of cancer cells. At the Slamon lab, we were working on a mouse antibody (antibody 4D5) that could bind to HER-2 and block it, inhibiting its cancer promoting functions. This mouse antibody was later humanized and developed into Herceptin. UCLA was pivotal in the clinical trials and in addition to the pre-clinical studies, my colleagues performed the early combination trials for Herceptin/Trastuzumab as well.

In those days, platinum was not thought to be an effective agent against breast cancer. However, the team at Slamon lab had developed evidence that there was a synergistic interaction between Herceptin and platinum agents (3). Long story short, the effects of combinatorial treatment with Herceptin and chemotherapeutic agents were established in the phase III trial results in 1998 (4).

Remarkably, a patient from this trial who had metastatic breast cancer and was treated with platinum plus Herceptin remained alive and in complete remission for many years.
Obviously, a large number of people worked on this over many years, and I had my very tiny little piece.

What are your thoughts on prevention or early interception of cancer?

The first question for me is in determining which tumors are clinically relevant within the context of early detection. Prostate cancer in a 90-year-old male is not something to intervene on, but acute leukemia is a different story and needs attention.

The second big issue is in detection. Do we have the technologies to detect tumors at the very early stages? There are several companies now sequencing circulating tumor DNA in the blood to detect tumors. Some of these tests are clearly detecting existing tumors. The technologies that allow for the early detection of cancer are coming. In the future, we are clearly going to screen for a full panel of cancers. On the molecular level, we can divide breast cancer into discrete diseases, and the same can be said for lymphoma and some other malignancies. Ultimately, where we want to get is to be able to screen using a blood-based assay for molecular signatures that can precisely detect or predict tumors. But we are still in the basic stage of this technology.

Right now, we've got a bunch of observational data from these tests. To me one real question with many of these data is in the validation of them. A really important question is, if you get a positive result, what does it mean? What if the imaging studies are negative, which they may well be because the number of cells may be well below the limit of detection. What do you do? How many of those patients with positive results will develop clinically evident cancer, and over what period of time? I don't know whether there are any ways to answer these questions, except for doing very long longitudinal studies. I would love to hear of other approaches, but it is hard to get beyond the logic that you will need these big studies.

Are you optimistic that we are going to improve on current cancer detection methods?

That is another question: Are the new tests any better than the current methods? How do they compare with standard screening? But we're not even equipped to answer that question yet. We need to take the first step before we take that second step.

You are taught as an intern, "Don't order a test unless you're going to do something with the results." Because otherwise, you're just going to create grief for everyone. So, for me this is a philosophical issue. If you are the "we have to do everything as early as possible and I want to know everything" kind of person, you are going to say "test." If you are at the other end of the spectrum, you might say "I'll do the standard stuff and I'll wait to see how this technology evolves." Given the gap in knowledge, these are both perfectly rational approaches right now. It's no one's fault, it is just the state of the art. To me we must address those big buckets; without that I don't see a way forward.

We are collecting large amounts of observational data from these studies, and it is important. However, at a certain point these data are limited in what they can tell you. We need to prove that this technology is ultimately saving lives: that's the real goal.

Do you think these initial tests, where they are gathering data, are more informative in a high-risk population, like one with inherited mutations in cancer predisposition genes, compared to the population at large?

If we have patients with an inherited predisposition, whatever it might be, BRCA1 or one of the many other mutations, now we have (by definition) identified a very high-risk population. The risk-benefit ratio in a population with inherited cancer gene mutations is very different to what I started with, which is a general population. With a high-risk population, we need to be more aggressive in our responses; if we pick something up, we're going to do imaging every few months or other appropriate screening.

To me the high-risk populations are a proof of principle population in a way. It is an enriched trial population by definition. If the tests don't work in the high-risk population, forget it, the chances of them working in the general population are low to none.

Where are we with the development of cancer prevention drugs? What is the interest in pharma?

Right now, that's hard. Some of the the largest prevention studies to date (testing vitamins) gave us, in some instances, a contrary result in that those taking the preventive agent actually had higher rates of cancer. I think we will be much more keenly interested in prevention drugs once we feel that we have the right targets. We still have to solve many problems, such as accurately detecting cancer and validating and correctly interpreting the test results from detection tests.

What is your definition of precision medicine, and how can it influence cancer prevention and treatment?

From a drug developer's perspective, precision medicine can be described by the simple phrase "the right drug, for the right patient, at the right time, and at the right dose." It is obvious that oncology is where precision medicine has made the greatest inroads, because of molecular profiling of tumors and the advent of targeted therapies. I think we are just on the threshold of the era of human data that will lead to real precision medicine. It is part of our efforts to capitalize on the immense amounts of human data now available.

What do we mean by human data? At Amgen, we have sequencing data from hundreds of thousands of whole genomes. This is a huge increase from the couple of thousand we had a decade or so ago. But human data is not limited to genomics. We have genotypic data, combined with phenotypic data such as clinical information and demographic data, of two and a half million individuals. We also have total mRNA profiles (transcriptomics) and total protein profiles (proteomics) from tens to hundreds of thousands of individuals. So, this human data is not limited to genomics, it is multi-omic. This is more than 100 petabytes of data, even without including the real-life, clinical trial data we've got. This data will get richer in the future with biomarker work that will help predict disease progression and treatment outcomes.

The end game is not all these impressive amounts of data, but applying them to the individual patient, i.e., a true precision medicine. The folks who are able to ingest, aggregate, and critically analyze these large amounts of data are the ones who will push the field forward. We are in the early stages, but there are indications that this is coming fast. For example, it was known that the Artificial Intelligence (AI) company DeepMind was developing AlphaFold, a protein structure prediction program. But everybody thought it was still five or ten years off. Last July (2021), we went to bed one night and we woke up the next morning, and there were 350,000 predicted protein structures in a public database (5). The ability to predict the structure and function of a protein more quickly and efficiently using AI is an example showing that we are moving towards precision medicine very, very rapidly.

All this data and analysis will ultimately lead to precision medicine. I think it is sort of like the original motto of the United States “E Pluribus Unum”/ “from many, one,” meaning we will use the knowledge from large populations to help the individual patient.

What do you think are the biggest challenges in human data right now? Is it figuring out what to do with the data or is it figuring out how to cross-reference the data?

It is all the above. Of fundamental importance is the analytical engine. At a certain point the size of a dataset takes on a quality all its own, and we have reached that point and gone past that with our datasets. If you want to ship them somewhere, it takes two weeks over ultrafast pipes. It's not like you pop up an excel spreadsheet. So, we have an enormously rich resource there.

It is also enormously dangerous. There is so much data that anyone with some smarts and a statistical package can find out a large number of correlations. What I always ask my team is, “which ones are true?” In genetics literature, a good fraction of papers published is reporting correlations, not true findings. It is similar to when microarray technology came out in the mid to late 90s. Everybody got a machine and all these papers came out. Many terrible papers came out because quality control was bad and the field had to clean itself up. I think we're now at the moment in time with genetics data that, because of the ease with which you can do it, knowing what to do with it and how to correctly analyze it, is the challenge. It’s a smaller universe of folks that know how to do that accurately.

When it comes to cancer genomic data, aren’t most of what we have from late stage, malignant tumors? Aren’t genomic data from premalignant or early cancer stages still rare?

This is where I think some of the other technologies will be important because genomics in some ways is a starting point. We are looking at other areas such as cardiovascular disease, atherosclerotic cardiovascular disease. We have preliminary evidence, which I think almost certainly is going to pan out, that we can start to predict with a much higher degree of accuracy, which patients are going to have an event in the next few years based on changes in their proteome. Your genome is largely fixed. Your proteome varies over your lifetime. So, longitudinal sampling is critical here. What we're interested in creating is a real precision medicine that can say, “hey, your proteome changed. We now know you've moved into a very high-risk category to have a myocardial infarction in the next two years, so aggressive intervention is warranted.” That’s where I think all of this is heading.

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