From Gene to Therapy and Back Again

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Interviewee: Benjamin Izar, MD/PhD, Vivian and Seymour Milstein Family Associate Professor of Medicine, Department of Medical Hematology and Oncology, Columbia VP&S

Stepping out of the elevator into Dr. Benjamin Izar's laboratory, I'm immediately greeted by the sights and sounds of science- carts full of beakers rushing by to be cleaned, pipettes hanging from workbenches, and machines seemingly from science fiction whirring along. Working my way through the maze, I find Dr. Izar in his office, white coat on, the interplay between clinician and scientist on full display as he discusses an experiment with a student. After a few minutes, he welcomes me, and we begin our exploration of the world of cancer immunotherapy- through his eyes.

What would become one of the most exciting fields within medicine started off as quite the opposite. While experiments conducted by Dr. William Coley at the turn of the 19th century found that introducing a bacterial infection into hosts with cancer paradoxically shrunk their tumors, few scientists rushed to conclude the immune system could be the key to the long-sought cure for cancer. Research continued to favor the emerging and exciting fields of radiation as means of wiping away cancer alongside traditional surgical practice.

Yet some remembered and continued to be fascinated by Coley's observations. With the increasing knowledge and legitimacy of the field of immunology, the science of the immune system, new generations of scientists began to wonder if this system- so talented at identifying non-self infections- could in fact be used to target the body's own cells gone haywire.

These questions led to an explosion of research in labs across the world, culminating after decades of research in the advent of checkpoint inhibitors in the early 2010s- monoclonal antibodies that block key proteins on the surfaces of our immune cells that promote a "standing down" of the immune system. In these drugs, the message to cells is clear- fight on. What once had been a fringe element on the frontiers of cancer treatment seemed to be its newest salvation.

While checkpoint inhibitors have indeed revolutionized the treatment of some cancers- like melanoma, where administration of checkpoint inhibitors can literally melt tumors away, effectively achieving long-term disease remission in metastatic patients- other cancers remain unresponsive. It is in these observations that the age-old question arises: why? It is this question, and these drugs, that Dr. Izar has spent much of his career investigating.

He walks me through the latest approaches his lab has taken to solve this mystery, including cutting-edge technologies like single-cell sequencing, where complex machinery allows researchers to map the transcriptome and genotype of a singular cell- a feat once thought impossible and only mere decades after the completion of the Human Genome Project. This approach has allowed Dr. Izar and his colleagues to gather deep information on all the different

cells within a tumor, subclassifying them into populations that may be causing disease- or preventing it.

These advances are impressive in their own right, but it's Dr. Izar's most recent project that particularly catches my attention- Inborn Errors of Immunity, or IEI. These diseases involve single-nucleotide variants, meaning single erroneous letter alterations in a patient's genomic code that result in diseases of the immune system. Patients born with these variants often suffer from a variety of immune disorders, including some that suppress the immune system and others that enhance its activity, either of which predispose to illness, and indeed, cancer.

Dr. Izar's team set out to learn from what he described as these "experiments of nature" to improve current cellular therapies, such as chimeric antigen receptor (CAR) T cells (genetically engineered immune cells designed to recognize specific proteins on the surface of tumor cells and kill them). The idea of introducing the smallest possible change in these cells – just one single letter – is a stark departure from current approaches, which are characterized by increasingly more complex types of engineering. "We found ourselves thinking – we need to understand IEIs better to better inform development of cancer therapies", Dr. Izar tells me, "and there is great precedence in medicine learning from rare disorders to make major advances."

In a recent 2025 paper published in *Cell* by the lab, Dr. Izar and his team inch closer to this goal. They looked at one specific IEI: Activated PI3K Delta Syndrome, or APDS, an illness classically caused by one gain-of-function mutation that leads to an intense overactivation of the body's immune cells. This disease results in patients developing frequent infections and lymphomas, a type of cancer affecting white blood cells.

The team set up a robust experimental strategy using CRISPR, a gene editing technology that has cracked open the world of molecular biology. Using small RNAs designed to scan for regions in the genome specific to the abnormalities present within the genes of patients with APDS, the lab was able to deduce many different subvariants of APDS depending on differences within the genetic code. Paired with functional analyses within the paper that looked at factors such as immune cell activation, this work demonstrated clearly the benefit of continuing to catalogue the many different variants of disease patients have- with the hopes of not only better understanding the underlying mechanism, but targeting it in a therapeutic approach.

I'm amazed by the creativity inherent within Dr. Izar's approach, and find myself drawn more into the circumstances and journey that could create such an out-of-the-box approach. As the Vivian and Seymour Milstein Family Associate Professor of Medicine and a 2024 Seldin-Smith Award for Pioneering Research awardee from the American Society for Clinical Investigation- one of the youngest inductees in recent history- Dr. Izar in many ways stands as a changemaker within the field. One of his biggest pieces of advice? "Pick the mentor over the project."

His advice is rooted in his own personal experiences with mentorship. Earning his medical degrees at Justus Liebig University in Germany, Dr. Izar continued his training at Massachusetts

General Hospital, Beth Israel Deaconess Medical Center and Dana-Farber Cancer Institute in Boston, where he describes the immense impact two of his post-doctoral mentors had on his professional development- in particular, the ability to be “creative without fear”.

It’s that creativity and daring that drives the Izar Lab forward- a glance at the lab’s website shows a burgeoning cohort of MD/PhD, PhD, and MD candidates with a variety of unique scientific experiences, underscoring the multidisciplinary approach to the lab’s work. In recruiting these students, Dr. Izar explains, “I try to recruit people who can teach me.” I’m taken by the humility- that a scientist at the apex of his field with so many accolades remains rooted in a mindset of lifelong learning from both mentor and mentee.

That mindset isn’t just constrained to work within the Izar Lab- one only needs to look at Dr. Izar’s publication history to see multiple collaborations with his peers, both at Columbia and other institutions from around the world. Dr. Izar recounts many of his meetings with collaborators, from recommendations by colleagues and mentors to chance encounters at conferences or even cold emails. In teaming up with other scientists, Dr. Izar highlights the immense benefit in not only the exchanging of ideas, but the formation of a stronger scientific community, something he attributes to “being generous” with credit and sharing resources.

And being at an institution like Columbia certainly facilitates those relationships. “It feels like an immense place of opportunities,” he tells me. From access to biobanks for patient samples to clinical care to world-renowned peers and colleagues, Dr. Izar shares that at Columbia you can “be the expert” in whatever field you choose.

Winding down our conversation, I find myself amazed at the ground Dr. Izar has covered not just in our conversation, but already in his career- with no signs of slowing down. And as for the field of cancer immunotherapy itself? “There’s never been a greater time of opportunity in understanding the immune system and how we can leverage it to improve lives than there is now,” he shares.

As I make my way back through the scientific labyrinth, I am quickly replaced by another student, the rhythm of the lab quickly returning to plans for more experiments and the flow of new ideas. From checkpoint inhibitors to IEIs, it’s clear with collaborative and innovative investigators like Dr. Izar leading the future of immunotherapy, we may yet sooner understand ways to unlock the power harnessed within each of our own immune systems. One letter, one gene, one treatment at a time- and, perhaps one day, one cure.

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