Podcast Interview: Ira Mellman

**PNAS**: I’m your host Prashant Nair and welcome again to Science Sessions. After nearly a decade of disappointing results the field of cancer immunotherapy is slowly beginning to come of age. Encouraging results of a handful of antibody drugs for skin, kidney, and lung cancer in small groups of patients in Phase 1 clinical trials have sped up efforts to develop targeted immunological drugs to shrink tumors. At the South San Francisco-based biotechnology firm Genentech, cell biologist Ira Mellman, a recently elected member of the National Academy of Sciences, oversees the discovery and development of cancer drugs. After spending decades in academia at Rockefeller and Yale, Mellman moved to Genentech to practice what he calls people-focused science. I recently spoke with Mellman about the trials and triumphs of cancer immunotherapy.

**Mellman**: The process of drug discovery and development is a long one. I had made the assumption that when I came it was actually probably going to be closer to 10 years before I actually saw anything coming to fruition. But it actually turns out that the process, when it works well, can be a lot faster than that. Since just 2007, some projects have been initiated, have been taken through the validation process, and are now already entering into Phase 1 clinical trials.

**PNAS**: At the heart of one of these projects is a novel antibody against a protein called the epidermal growth factor receptor, which is widely implicated in a number of cancers. This antibody, says Mellman, has been engineered to target not only EGFR but another cancer-related protein called Her3 receptor, long known for its prognostic role in breast and ovarian cancers.

**Mellman**: We have this in patients, and some of the results that are coming out are just incredibly encouraging and very exciting.

**PNAS**: Another project is centered on an antibody that blocks a protein called PD-L1. This protein plays a role in protecting the body’s cells from potential autoimmune reactions with T cells of the immune system. Some cancer cells, however, subvert this protective mechanism by expressing PD-L1 on their surface and blocking interaction with killer T cells that would normally keep them in check. So Genentech has come up with an antibody that can specifically target PD-L1 in cancer cells.

**Mellman**: The idea was that we’d be able to reactivate the T cells that were entering tumor beds, and in fact even again very early stage trials are showing us that this is almost certainly going to turn out to be the case as well. What’s interesting about these two programs and the reason I point them out is that this was work that was really begun just a few years ago.

**PNAS**: The discovery of cancer immunotherapeutics may have received a boost in recent years, but challenges to their successful deployment in patients continue to loom large.
Mellman: There are really three elements to the process. One is the problem of immunosuppression, which is that even if you have a robust immune response to a cancer, when the mediators of that response, which, in most cases, are T lymphocytes enter into a tumor bed, the tumor turns them off. And this was part of the reason for wanting to develop an antibody that would block the PD-1-PD-L1 interaction, but there are a lot of other mechanisms of immunosuppression that tumors use to protect themselves. Second element is generating the T cells in the first instance. The third is how do you deliver the antigen? Do you just inject it? Do you inject it into the blood? Do you inject it into the skin? Do you inject it coupled to an antibody that targets to dendritic cells? Is one antigen enough? Should you do this multiple times? We don’t have the solutions to any of those problems, and as I look at the development path from not so much a biological point of view but a clinical point of view, it becomes a real long stretch of problems that you have to solve to go from conceiving of a vaccine to actually implementing one as part of a clinical regimen. Ultimately, it will be a very effective approach because we know what the candidates are, and it’s just a question of making the antibodies, the appropriate small molecules to actually get into it, and get right into the clinic, and see how this actually works in human patients.

PNAS: I asked Mellman whether his move from academia to industry has brought him closer to his goal of practicing people-centered science.

Mellman: It gives one a deep feeling of satisfaction that you’ve actually done science that’s meaningful to people’s lives – and not just interesting, which is what one normally does in the academic realm. You can be a terrific success if you’re serially interesting, and it doesn’t really matter if you’re particularly useful. Here, you really have to be both.

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