would give rise to a tumor with low EGFR levels, whereas a tumor arising from a cell with high levels of EGFR would give rise to a tumor with high EGFR levels.

In 2012, in a project spearheaded by a graduate student in my lab named David Nathanson, who is now an associate professor at the University of California, Los Angeles, we set out to understand why. We wanted to see where copies of EGFR were located. Typically when we sequence cancers, we grind up a tumor and "read" all of the genes present, looking for mutations and copy number variations, and then we assign the location of these genetic alterations to the chromosomes where those genes are in the human reference genome. But when we looked at a cell getting ready to divide—the only time when it’s possible to tell where a specific piece of DNA is located—we were surprised to find that EGFR was not where we’d predicted. In fact, it was not sitting on a chromosome at all. Rather, all of the amplified oncogenes were found on circles of extrachromosomal DNA (ecDNA). We could see these extra pieces of DNA near the chromosomes inside the nucleus of cancer cells.

When we removed the treatment with the EGFR inhibitor from cultured tumor cells, EGFR copy number quickly rebounded, but again, not on chromosomes. When we saw this, we realized that ecDNA might explain why some cancers can become resistant to treatment so quickly, allowing tumors to evolve at a rate that far exceeds anything that could be accounted for by classical genetics. We published our results in Science in 2014, but they were not immediately accepted by the community. Although we had only studied one tumor type, glioblastoma, we began to wonder whether this might be the tip of the iceberg.

Without realizing it, this study led us, and now others, to a series of discoveries that have changed the way that researchers view cancer in general, revealing frightening ways that tumors can evolve. We have learned that ecDNA is central to the behavior of some of the most aggressive forms of cancer, enabling remarkably elevated levels of oncogene transcription, creating new gene regulatory interactions, and providing a powerful mechanism for rapid change that can drive very high oncogene copy numbers or allow cancer cells to resist treatment.

Along the path of discovery, we found that we were not the first to have seen these extrachromosomal particles. But with new tools in hand, and new questions in mind, we saw them in a very different way. And when we took the time to peer deeply into the nucleus of cancer cells, we saw ecDNAs in abundance. We eagerly pursued studies to understand their importance in cancer progression and drug resistance, and even founded a biotech company, Boundless Bio, to identify and develop new ways to treat patients whose cancers are driven by ecDNA.