At Work: Geneticist Raju Chaganti

Raju Chaganti

Geneticist Raju Chaganti studies genomic instability in cancer cells and its implications for clinical behavior of tumors and normal cellular developmental pathways. We spoke to him in 2008.

I come from a family of physicians, including my father, my brother, and two of my sisters. I, myself, was slated to be a physician, but through guile, I managed to avoid applying for medical school.

Even at a fairly young age, when I was ten or 12 years old, I was fascinated by plants. I wanted to learn more about them, which lead me to the field of botany. I received both a bachelor's and master's degree in the field from the Andhra University, in Waltair, India, where I also started to pursue a doctoral degree.

In 1956, after I'd finished my master's and was working as a research assistant in plant genetics at Andhra, I came across a paper in *Nature* written by two Englishman, Charles Ford and John Hamerton, showing that humans had 46 chromosomes. I was unaware that the number of human chromosomes had been previously unknown. I was a plant biologist, and plant genetics had advanced much further.

I became fascinated by this discovery. It seemed like a new field was emerging, and I thought that someday I should look into it. Being a part of a family of physicians, we received many medical journals at our home, including British titles like *The Lancet*. In these, I saw a set of papers by Charles Ford, in which he showed that individuals with Down syndrome and Klinefelter syndrome had extra chromosomes. That sealed my interest in this new field.

As a PhD student at Andhra, I was growing disappointed in my program, which was part of the old British system. In this system, you received your bachelor's and master's degrees, which were followed by two or three years of research and a thesis, after which you would be awarded a doctorate. I didn't feel that this provided me with the appropriate background in the field in which I was trying to specialize —genetics.

Studying Corn Genetics at Harvard

As a result, I applied in 1959 for graduate school at three American universities. The first program was at Harvard University with Paul Mangelsdorf, who was a renowned corn geneticist. The second was at California Institute of Technology (Caltech) with George Wells Beadle, a Nobel Prize-winning corn and Neurospora geneticist. And the third was at the University of Illinois at Urbana.

I was accepted at Harvard, conditionally accepted at Caltech, and rejected at Urbana. I joined Harvard where I spent five years studying corn genetics and where I received my PhD degree. Outside of my graduate school studies, I followed the advances in the emerging field of human genetics, especially cytogenetics and the study of the chromosomal basis of abnormal human development.

After receiving my PhD, I returned to India to teach at Andhra University, where I very quickly became

terribly unhappy. It seemed to me like a good time to try to contact Dr. Ford to ask if I could get an opportunity to train and work with him at the Medical Research Council (MRC) labs at Harwell, outside of Oxford.

After being offered a position by the MRC, I went to the Ford lab intending to stay a year, but ended up staying for four. During that time, I was trained in human genetics and mouse transplantation genetics. At the time, human cytogenetics was mainly clinically oriented and had little research basis, so that's what I worked on, using my experience from experimental plant genetics.

Back to top ^

Precursors of Human Bone Marrow Transplantation

Back then, there was an argument about which factors, cellular or humoral, provided protection from sub-lethal irradiation of mice. A series of experiments were devised by Ford and his colleagues at the MRC using chromosomally marked donor bone marrow cells, which showed unequivocally that this protection was due to repopulation of donor cells (or hematopoietic stem cells, as we say now). These discoveries were the precursors for human bone marrow transplantation.

When I finished my postdoctoral research with Dr. Ford, I did not want to return to India. I traveled to New York City in 1971 to take up a position with James German, a renowned pioneer in human genetics. I spent five years with Dr. German, working on what were then called the chromosome breakage syndromes, such as Bloom syndrome, which predisposed individuals to cancer, and on sex-chromosome disorders in humans.

At the end of my five years in the German lab, I learned that Memorial Sloan Kettering was looking for someone to start a diagnostic cytogenetics laboratory in their Department of Pathology. There were two reasons why this lab needed to be created.

The first was that the field of human cancer cytogenetics was evolving and the hospital needed someone to provide patients with a diagnosis on the cytogenetic level of their cancers. The second reason was that a team of doctors — Robert Good, Richard O'Reilly, John Hansen, and others — was just then setting up a bone marrow transplantation program to treat patients with certain cancers and immunodeficiencies.

They needed someone to track the cells that were engrafted into these patients, and at the time chromosomal tracking, along with HLA typing, was thought to be the best way to do that. My exposure to mouse transplantation work in the Ford lab was familiar to Dr. Good, so I was brought into the team in 1976. It was an exciting project to be a part of, and a pleasure to be a member of such a close-knit team led by Dr. Good.

Back to top ^

Building a Lab at Memorial Sloan Kettering

I developed the lab, starting with one technician. At the time, there was only one chromosomal marker in cancer to track, the Philadelphia chromosome, which was a diagnostic marker of chronic myelogenous leukemia (CML). Barney Clarkson was using this marker to evaluate his new CML treatment protocols, and he and I worked extensively on this for a number of years.

I wanted to start a research program to discover more chromosome markers, which I was fortunately able to do. I, along with several other researchers from around the world, published a great deal of groundbreaking work on the chromosomal basis of cancer development.

We were helping to define the newly emerging field of cancer genetics. During this time, there wasn't a single day that wasn't scientifically exciting for me.

Back to top ^

Asking Basic Questions About Cancer

I had my clinical appointment at Memorial Hospital and an appointment at Sloan Kettering Institute doing basic science research, both of which I continue to hold in the Department of Medicine and the Cell Biology Program. Earlier, as a member of the Department of Pathology, I had a great deal of exposure to cancer pathology.

Back in the late 1970s and 1980s, I was looking for a cancer type to study using genetic techniques. I gravitated towards two types of cancer: lymphoid neoplasms and germ cell tumors. I picked these because I knew they were cancers arising in developmental lineages. It seemed to me that these would be cancers for which I could ask some basic questions.

That proved to be very rewarding work. Just as I was beginning my work studying lymphomas, the *MYC* translocation in Burkitt lymphoma was discovered. What we were eventually able to do was to identify many new translocations and identify their genes in other lymphomas.

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>
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In this work, we collaborated with Riccardo Dalla-Favera, who is now Director of the Cancer Center at Columbia University. The most significant of the genes we discovered was *BCL6*. In 1992, we described the translocation of the chromosome region and the gene the following year.

By the mid-1990s, the emphasis of the lab switched from lymphoid tumors to germ cell tumors, the genetics of which we had been studying for a number of years by then, in collaboration with George Bosl, current Chairman of Medicine at Memorial Sloan Kettering. One of the questions we were asking was how do these cells retain their memory of pluripotency (the ability of a cell to develop into any cell lineage) and how do they reactivate it in the tumors. We didn't have many clues.

Back to top ^

New Technologies Allow New Insights

But then, in the 1990s, high-throughput gene expression profiling technology using microarrays was developed, which allowed the expression pattern of all the genes in the genome to be scanned in one experiment. I thought we could use this technology to see how lineages were forming in germ cell tumors based on changes in gene-expression patterns. I wanted to learn how to use this technology at the bench myself, which is unusual for a senior researcher, which, by that time, I was.

In six months, with the help of friends at Columbia and Albert Einstein College of Medicine, I was able to set up the assays in my laboratory. This was long before SKI's Genomics Core Facility and the High-Throughput Screening Facility.

Today, we know there are three kinds of pluripotent cells: embryonic stem cells, induced pluripotent cells, and embryonal carcinoma cells. Embryonal carcinoma, deriving from germ cell tumors, is our system of study. With the new data that we acquired, we had some good clues as to how lineages were put together. However, the data were so vast that the traditional methods of data analysis would not work satisfactorily.

We needed to reduce these data to hypotheses that could be tested. My interest is transcription factors, specifically how to reverse engineer transcription factor networks from gene-expression profiling data. This would require advanced computational biology techniques, which were beyond my knowledge or capability. I needed help and found it in Andrea Califano, a leading expert in this field who heads the

Computational Biology Center at Columbia University.

Back to top

The Arc of a Career in Science

In 2006, Dr. Califano and I began working together, and we now have an exciting program trying to reconstruct transcriptional networks that regulate pluripotency and lineage development. This has led us to stem cell biology, which has become one of the main focuses of my lab at this time. We have recently discovered some new transcription factor modules that regulate pluripotency, which is very gratifying.

Looking back over my 30-plus years at Memorial, which has spanned my entire independent scientific career, it is interesting to reflect on the sea changes that have taken place both in the institution and in science. During this time, SKI became a world-class research institution, matching the world-class quality of the hospital. And entire new fields of scientific investigation were born.

It has been an exciting and humbling experience for me to personally witness and be part of the tremendous advances in both clinical and basic science research here at Memorial Sloan Kettering.

I am a scientist and my policy has always been to pursue what excites me. At present, I am punch-drunk with excitement for the research I am conducting. We are still making significant discoveries. If for some reason I no longer am able to be excited or to contribute, I will be the first person to acknowledge this and walk away, heading for the hills.

I am in my mid-70s and people have asked when I plan to retire. I tell them that I don’t feel any different intellectually than when I was 40. Physically, is another matter!

Back to top