

» On-Conversation with Lynda Chin, MD, Associate Professor of Dermatology & Chair of the Glioblastoma Disease Working Group of The Cancer Genome Atlas (TCGA), Dana-Farber Cancer Institute and Harvard Medical School



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The National Cancer Institute partnered with the National Human Genome Research Institute and has recently embarked on the initial phase of an effort called The Cancer Genome Atlas (TCGA). This pilot project will assess the feasibility of the larger, all-encompassing endeavor—that being the systematic exploration of the entire gamut of genomic aberrations in the landscape of human cancers. TCGA will use cutting-edge

genomic technologies of high-throughput DNA/RNA sequencing, microarray profiling, and computational biology to document, and eventually characterize all that is not well in a cell that has cancer. The program, which will discern the genetic fingerprints for lung, ovarian, and glioblastoma tumors, will validate the overall approach to what is, by any assessment, a Herculean undertaking.

Lynda Chin, chair of the Glioblastoma Disease Working Group, gives OBR some of her thoughts on the project thus far.

OBR: Why a pilot program—why not just jump right in??

LC: At the onset of the TCGA there were skeptics. People thought that the cancer genome was simply too noisy, and that because cancer is inherently unstable there would be lots of things that happened that were not relevant to developing therapeutics, or diagnostics, and that we would never be able to make sense out of all the complex changes to figure out what's really important. The pilot program is to determine—one way or the other—whether the cancer genome is too complex to be useful or if something really can be learned. So far, the early results have far exceeded the expectation.

OBR: What are the immediate challenges of the project?

LC: Well, we call it a pilot because we need to figure out the process. It's the first time anyone's attempted this scale of multi-dimensional characterizations on a very large cohort of tumors, so, every step is new—the number of centers, the network that's involved, and we're attempting the integration of two

cultures: those from genomics and those from cancer biology—so I think a pilot needs to work out how all of this can work together.

The demands of the work will also necessarily drive technological development. Just as with the human genome project, the scientific goal of the data was driving a lot of the new technology. Just think, when we started out a year and a half ago next generation sequencing wasn't even something anybody considered, now, it's a technology that's likely to displace all the other platforms.

OBR: You work with the glioblastoma team, but you're not a neuro-oncologist.

LC: I trained as a dermatologist, and through that I developed an interest in cancer genetics. I had a specific disease focus on melanoma which led me to glioblastoma—it's a little hard to see the connection but they are related. A melanocyte is a known neuro-epithelial derivative, and melanoma is one of the four tumor types that most commonly metastasize to the brain. Fifty percent of metastatic melanoma patients die of brain mets. Glioblastoma is a primary

tumor, of course, but it is related to melanoma on the genetic level.

OBR: How did you come to this project?

LC: I started out in genetics and mouse modeling—developing mouse models to study melanoma and other tumor types. One of the challenges of that is how to compare mice to humans and how to show how mice are reflecting human disease. On the pathology level, the morphology can be compared, but that's very superficial; on the molecular level, genes and pathways are typically examined, but that is rather subjective...so one of the things that I began doing was to compare the levels of global copy number alterations that are spontaneously emerging in a mouse tumor as well as in humans.

To do this, we developed our own technology (at Harvard). At that time, (end of 1990s and early 2000), expression profiling was the focal point of work in this area and technologies for copy number profiling were rather limited, particularly ones that worked for both species. We also ended up developing

home-brew algorithms to assess our data, and that's really how I came to be connected with cancer genomics. When the Atlas project was announced and proposals were requested, we joined forces with the computational group at Harvard Partners and went into that competition.

OBR: Can you give us an idea of the scale of the project?

LC: It's a pretty large collaboration. The Atlas' research network probably has over 100 investigators. There are three sequencing centers involved, and there are seven genome characterization centers that include DNA profiling, RNA profiling, microRNA, and methylation profiling. Then there's the biospecimen core resource (BCR). Basically, all the tissue goes in there and the DNA and RNA come out from this centralized BCR facility, so, everybody gets the same quality, standardized biomolecules.

On the analysis side, when the project was designed there were several microarray platforms included for cross-platform comparisons, as well as multiple platforms for copy number, expression profiling, and so on. The purpose of all this was to arrive at very high confidence data—and let me say, each data set is very high quality, more than anything else I have seen out there by individual investigators. The data is amazing.

OBR: What short-term practical applications do you see coming out of this work? Biomarkers? Genetic testing?

LC: I think this will be the foundation for all of those things because what we are talking about here is a “parts list”. If, for example, you want to diagnose a problem with your car, you need to know what parts are in there and what parts are affected.

Knowing what parts of the cell or parts of the body are affected gives us the foundation for developing diagnostics or therapeutics...some of this will come in a relatively short time as some discoveries will be quick to translation, but some will take longer.

In the end what we're looking to get at is what has been labeled ‘personalized medicine’. My definition of that is: A patient is diagnosed with cancer, the tumor is biopsied and genomic tests are performed. Based on what the results are, the right drug is then prescribed. But to get to that point you have to know not just what the cancer genomic changes are, but also what they mean. In other words, you have to make the connection to function. So that's the next step. The “parts list” is the first step; the second is to know what each part does.

OBR: You don't seem to doubt the availability, or eventual development of the technology, is there something else you might need help with?

LC: The front end and the back end of the project is where we need clinicians. The Atlas project is not possible without them. In fact, they are the ones that have to convince the patients that they should consent and participate in this

study. On the front end we need the samples from their patients. Clinicians are the ones who have the samples as they have the patients.

We also need the clinicians' input to analyze the data, and we've set up the Disease Working Group to that end. We can crunch the data, or treat the data as a generic set, but the value comes from asking important clinical questions using that data set. And those questions are known to the clinicians. If the clinicians don't interact with the genome people, the Atlas people, the computational biologists...then people won't know what the right questions are to ask. **OBR**



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