What is the main focus of your lab?
Understanding the molecular mechanisms that drive cancer and using that info to develop better treatments for patients.

What lead your lab to investigate ecDNA and its possible links to cancer?

For years our lab has been studying the most common genetic alterations that occur in brain cancer and a particular gene in brain cancer. We were trying to understand why drugs targeting that gene didn't help and why it was so difficult for drugs treatments to be effective. Cancer has strong heterogeneity and we speculated that the heterogeneity contributes to the difficulty in development and designing of drugs to target it. Cancers develops over time but people found that it develops at the speed that is much to rapid.

They sought to understand the cancer genome and looked at the chromosomes. It was discovered that the gene of interest was on ecDNA, and when being treated, the ecDNA was disappearing and reappearing after the treatment had stopped. Copy number of ecDNA and tumors can change which suggested a very important role in cancer.

In the 1970s people noticed but didn't understand the importance of ecDNA. Plus the technology wasn't in place to allow them to interrogate it. Single cell organism such as bacteria have circular DNA. For example plasmids. Eukaryotic cells have chromosomes, not plasmids. The circular DNA was thought to be something only 1.4% of call cancer have.

I talked to people who studied oncogene amplification. Everyone recognized the gene of amplification but didn't understand them. They showed me maps of the genome of where they were amplified but didn't ask how does it happened and the molecular mechanism. I was beginning to think about how genome maps are made. The Human genome map was made and scientist were able to use sequencing to identify where genes were. High spatial recognition but not a lot of genome recognition. Spatial recognition is lost when genome recognizing was large. An assumption was made that a gene in cancer cell was in same place as normal genes. Like Ptolemy's presumed map of solar system Copernicus's map had the same variables in different positions. The changes in the sun's position explained changes that couldn't be explained before. This is why we thought where things were in the genome may play a huge role.

How do you think this discovery will affect the way people approach cancer research in the future?
What it will do is raise questions and create new challenges. It encourages the field to think about new research and help us understand why cancer evolves and becomes resistant to treatment.

What challenges have you faced while working with ecDNA?
A practical concern is that [working with ecDNA] is not easy to do. DNA is not arranged in an easily recognizable fashion. Normally you can't tell where anything is. There is a very small window where chromosomes line up. That is also when the cell is most vulnerable. One must find ways to examine the cell to allow routine detection in patients with cancer.

Is there a possibility that targeting ecDNA could become a form of cancer treatment?
Trying to understand of this creates vulnerability. And yes, we are using science to understand and develop treatments.

How have people reacted to the discovery?
My experience so far in integrated analysis of genome sequences and localizing gene have led us to find evidence of ecDNA in every cancer and that ecDNA can jump on chromosomes. Difference [between ecDNA and chromosomal DNA] comes from how genes are inherited. Daughter cells gets same chromosomal DNA but ecDNAs are randomly parceled out to daughter cells. Each daughter cell receives partial chromosome but ecda have random and dramatic variation. This fuels genetic variation and explains how cancers develop so rapidly. The response has been favorable. There has been an increasing amount of evidence people confirming that maybe important genes are not on chromosomes. Recognizing this, one is very important, two approaches cancer treatment in a very different way. Gene mutated on chromosomes respond better to treatments. Suggesting there's a lot to be learn including better treatment options. In general there has been no resistance. Initial surprise but acceptance and a lot of questions of how you can stop it.

Are there any ethical concerns about working with ecDNA based off the ever present debate of human cells and CRISPR?
Not that I know of because we're not using anything to manipulate DNA [in humans]. We're trying to figure out how to help patients.