

## **PCL/23/04 - The effect of DNA damage on PARylation and extrachromosomal DNA (ecDNA) dynamics**

Glioblastoma (GBM) is the most common type of brain cancer and is particularly aggressive with limited treatment options. Extrachromosomal DNA (ecDNA) are small circles of genetic code that exist separately to the rest of our DNA, and can contain cancer information, known as oncogenes. Whereas we normally have only two copies of each piece of our genetic information (one from each parent) in each of our cells, ecDNA can exist in much higher numbers. As a result, there are many more oncogenes per cell in many cancers, but particularly GBM.

Radiotherapy, which creates damage in DNA, is used to treat most GBM. My work has shown that ecDNA are affected by DNA damage. I have shown, using molecular scissors, that making a cut in an oncogene present on ecDNA completely removes ecDNA. However, when cuts were created elsewhere - not on ecDNA - ecDNA were unexpectedly affected. Radiotherapy creates random, non-specific DNA cuts, and initial experiments show this also affects the number of ecDNA.

This project aims to develop these initial observations to explore how ecDNA respond to DNA damage caused by existing cancer treatments, and by directly targeting the ecDNA themselves. It will use new methods that can measure how much of each oncogene is left after DNA damage, and how they are organised. This will explain the mechanism by which these genetic changes evolve and how they can be targeted by new treatments.