This project will use a laboratory culture of cancer cells to investigate how small differences between cancer cells cause chemotherapy to fail.

Cancer is a disease in which normal cells begin to proliferate in an uncontrolled way. While many cancers can be attributed to factors such as smoking, radiation, or UV exposure, more than half are thought to be “bad luck” caused by imperfect replication of animal cells.

One of the most common anticancer treatment is chemotherapy. Traditional chemotherapy works because cancer cells proliferate faster than normal cells. By carefully adjusting the dose of a toxic chemical, cancer cells can be eliminated while minimizing the effect on healthy cells. However, since the difference between a dose toxic to cancer and a dose toxic to healthy cells is small, a minor increase in resistance of cancer cells may be sufficient for treatment failure.

It is not fully understood why cancer comes back in some patients despite initial positive response to chemotherapy, and why its success rate varies greatly among different types of cancer. One possible reason is that cancer cells differ in their response to a chemotherapeutic drug even in a single person. This can be caused by mutations – small changes to the cell’s genetic make-up that affect the number of molecules of a specific protein produced by cells to resist the effect of the drug. Alternatively, non-genetic variations that naturally occur in most (not only cancer) cells in the level of the protein could be responsible.

To distinguish between these two possibilities, we will perform experiments in which cancer cells are cultured in a small transparent container, which makes it possible to observe the behaviour of cells using a special, automated microscope. The microscope will allow us to follow individual cells as they are being exposed to a drug. We will thus be able to see how the effect of the drug depends on how the cells behaved prior to exposure to the drug. We will also use special fluorescent dyes to look into what happens inside cells. Cells will also be screened for mutations; this needs to be done at the end of the experiment because it involves destroying the cells in order to extract their DNA.

These experiments will help to determine how much of chemotherapy failure can be attributed to genetic, and how much to non-genetic causes. This is very important for the future of chemotherapy. If non-genetic effects are very strong, sequencing DNA from cancerous tumours will not give us full information about what therapy would be best for a specific patient. Instead, it may be necessary to expose cells from a patient biopsy to a range of drugs and select the ones with best response.