Popular abstract

Lung cancer is by far the leading cause of cancer related death which poses an urgent need to better understand this disease and to improve treatments. Cancer is caused by normal human cells acquiring the capability to grow uncontrollably. This capability can be caused by different sets of molecules and mechanisms, making cancer not one but a group of diseases with a large range of variability.

Due to cancer's complexity and variability, research into finding the best cures can benefit from methods with high throughput. One class of methods, omics, is applied to study essential biological molecules such as DNA or proteins in their totality within a biological sample. These studies have predominantly been carried out on the gene level but there is clear evidence that proteins must be considered as well since they determine the characteristics of cells.

A lot of focus has been directed to develop therapies that can target these molecular drivers (i.e., targeted therapies). By gaining knowledge about which molecular drivers a certain patient might display, therapies can be tailored to benefit an individual patient (i.e., personalized medicine). These types of treatments have been effective in prolonging survival and quality of life for a subset of patients. A good example is a group of targeted therapies that is inhibiting aberrant growth signaling which has been explained to be one of the common hallmarks of cancer. Those therapies are now used as a standard of care for a subset of lung cancer patients based on mutations in one specific molecular driver. However, results from a clinical trial made it evident that some patients who lack this mutation might still benefit from this type of therapy. To find out why these groups of patients were responding Orre *et al*. tried to find measurable indicators (i.e., biomarkers) related to successful treatment. By doing so they were able to correlate mutations causing deletion of a specific gene to be associated with successful treatment in cell line models. In an attempt to further increase the effectiveness of this treatment, Orre *et al.* tried to combine targeted therapies against aberrant growth signaling with other types of targeted therapies, and the group was able to show that treatment against growth signaling could successfully be combined with another group of targeted therapy, which is combatting cancer cells capability of resisting cell death. By studying the proteome of cancer cells treated with this combination therapy they discovered that these cancer cells might alter their metabolism in order to resist the treatment.

In this master thesis, I have explored if the effects of this double combination of drugs could be further increased by adding a new, third drug with the aim of inhibiting the obtained altered metabolism. I compared triple combinations of these drugs with double combinations and monotherapies of these drugs. By performing drug sensitivity and resistance testing I was able to prove that the triple combination was more effective at high drug concentrations. Furthermore, I performed mass spectrometry-based protein-level molecular profiling to see how cancer cells responded to the triple combination compared to other combinations of the drugs. Thereby, I was able to detect an upregulation of one of the drug targets as a resistance response. Furthermore, the analysis indicated that cells treated

with the triple combination are switching to another type of cell. This response has previously been linked to the successful treatment response of one of the used drugs.

Taken together, these results indicate that the triple combination could be more effective than the two-drug combination and that lower doses of the included drugs could be used which hopefully would result in less severity of adverse events for patients.