Benchmarking Human Tissue Culture Systems that Mimic the Tumor Microenvironment

Cancer of the mouth and throat, also called head & neck cancer, is difficult to cure. Patients often do not respond to the radiation therapy that is used as a treatment or develop resistance. Similarly, patients frequently fail to respond to anticancer drugs, especially those used against the more aggressive forms of cancer. Part of this problem relates to the "difficult" and aggressive nature of the tumor cells themselves. Clinicians find it difficult to select which patients may benefit from which of these treatments, because they do not have any tools that could predict if a patient will respond or not. There are no clear diagnostic signals that would predict that a patient's tumor may be likely to respond or not, and how long a certain therapy may be efficient before the patient tumor develops resistance. Similarly, it is difficult to predict if radiation may be beneficial, and for which patients. If clinicians had access to reliable methods that help them making better "informed" decisions, more patients would get more effective treatments, more patients might be cured, and useless therapies could be avoided. In addition, for head and neck cancers, there are only 3 or 4 drugs used for chemotherapy: Clinicians do not have many options to choose from. Therefore, it is also important to develop and test new concepts, such as drugs targeting the immune system.

It has been found that only a fraction of patients benefit from these novel and very costly drugs. Like in other treatments, it is unclear why some patient's tumors are shrinking, while others do not respond at all. The concept of "personalized medicine" aims to change this difficult situation for both patients and doctors. The basic idea is that the response of a tumor to any therapy should be tested BEFORE a decision is made. Only such treatments will then be used for therapy, which are predicted by the test to be effective. For this purpose, we need more informative and better models, that are closer to the original tumor. And we need better tests, that reflect what happens in real tumor tissues. Such "in vitro" assays also have the advantage that combinations of drugs, or with radiation can be tested. However, the problem with this concept is that although such tests are currently developed by many research groups, none of them have yet been successfully used for guiding treatment decisions. Currently, not any of these tests is officially recommended for clinical use. Before these can be used in the clinic, it is required to fully understand how informative, predictive, and reliable these tests really are.

We do know that not only the tumor cells alone are critical for how well a tumor responds to a certain therapy. Other cells, which are always present in tumors, may be even more important for therapy response. However, their numbers as well as their functions can be quite different between patients – which is called "tumor heterogeneity". For example, there are many different types of immune cells in these tumors, which are not usually included in any tests for drug sensitivity. In most models, only the tumor cells themselves are present. These cells may tell us a lot about the genetic changes such as mutations found in a tumor. But this may not be enough to predict how these tumor cells respond to therapies, or if the tumor cells are aggressive and spread to other organs (= invasion and metastasis). Most definitely, the tumor cells alone will not tell us anything about the response of a patient to drugs that target the immune systems. We will address the composition of the different models with each other, and with the primary tumor, to find out how well these systems may be suitable to answer the complex questions related to drug response and therapy.

We will also try to optimize those tests in which important cells like the immune cells are not lost, and which effect they may have on the response of the tumor on immune therapies or other treatments. We can then use the improved models to analyze which cellular and molecular processes may be involved when a tumor becomes resistant to a therapy. Such studies are not possible with tumor tissues themselves, and difficult to study in animal models. This information about the function of cells and genes from experimental studies may be especially important for improving future therapies. It may guide us to find genes that could be the target of new drugs. We can also use the same models to test such new, experimental drugs. This information may also help us to identify groups of patients that respond or do not respond to therapies – and suggest alternative drugs.