The tissue thin sections that Peter Wild uses in his work are robotically stained in the lab.

Personalized Precision Medicine (PhosphoNet PPM)

Unnecessary prostate operations could be avoided

Prostate operations can have unpleasant consequences, including incontinence and impotence. Researchers are working on new methods which should allow doctors to distinguish more precisely between insignificant and aggressive prostate tumors, meaning that in future, unnecessary operations will be minimized and fewer patients will have to expose themselves to the associated risks.

Most men over a certain age fall victim to prostate cancer. "At the age of 80, there is a roughly 80 percent chance of contracting the disease", says Peter Wild, head of the Systems Pathology & Clinical High-Throughput Genomics Laboratory at the University Hospital Zurich. "But fortunately not every tumor is aggressive nor must it be removed."

As with any other operation, removal of the prostate involves a likelihood of internal bleeding, infection and also particularly unpleasant side effects such as incontinence or impotence. "It's therefore very important to be able to clearly differentiate between the insignificant and aggressive cases", explains Wild, who leads one of the research groups involved in RTD Project PhosphoNet PPM. Diagnosis is based on a tissue sample, or biopsy, taken from the patient. A pathologist then examines the tissue under a microscope and assesses how severely it differs from healthy tissue. If the malignant tumor appears aggressive, it is surgically removed or irradiated. If clearly insignificant, it stays, and patients are actively monitored.

"The problem lies in those cases which are not so clear-cut, where the carcinoma appears neither unequivocally aggressive nor insignificant", explains pathologist Wild. Even nowadays there is no set of reliable criteria to aid the decision as to whether or not to operate. This means that in case of doubt, doctors as well as patients would rather decide in favor of an operation to be on the safe side. Wild is convinced that many prostate operations would be avoided if we could more accurately judge how aggressive a tumor is.

"In future every patient should be able to profit from a tailor-made therapy thanks to a personalized diagnosis."

This is exactly what the researchers involved in PhosphoNet PPM wish to address. The acronym PPM stands for Personalized Precision Medicine, the project's overarching goal. It is hoped that in future, patients will receive much more precise diagnoses and tailor-made treatments as a result of more individualized analyses on the level of proteins or genes. At this stage, the PhosphoNet PPM

Maja Schaffner

team is looking for characteristic features of the cancer that may aid evaluation in ambiguous cases. Based on these findings, they want to develop a test that allows the rapid and precise verification of a tumor's nature, so that patients must only undergo operation if the tumor is aggressive.

Large collection of prostate carcinomas

For their work, the researchers require a supply of cancerous tissues. "I've been collecting prostate tumors for years", says Wild. As part of the large-scale ProCOC study, the pathologist collected tissue and blood plasma samples, as well as the medical histories of around 450 consenting patients.

"The PhosphoNet PPM project could act as a template for further projects focusing on different types of cancer."

Every single prostate from this study will be dissected into various parts after removal. One such part will be rapidly "snap-frozen" and thus preserved for later examination. A large part will then be preserved in formalin and subsequently poured into paraffin blocks to enable it to be sliced. These wafer-thin slices will then be mounted onto microscope slides and stained.

"These thin sections contain a wealth of information", emphasizes Wild. "For example, we can see how much of the prostate tissue is affected, how much the tissue has changed and how heterogeneous the tumor is." Using certain staining methods or antibodies with colored markers, the researchers are able to identify particular proteins that the cancer produces. In a similar way, they are able to single-out individual genes and discern whether they are altered in different parts of the tumorous tissue. One such gene in which the researchers are particularly interested is *PTEN,* responsible for inhibiting tumor growth. Wherever this gene is lacking, the cancer is allowed to spread unchecked.

In order to analyze peculiarities in the tumor's genome and protein composition, the team uses tiny samples taken from either freshly extracted or conserved prostate tissue, subjecting these to cutting-edge high-throughput methods. One example of these is so-called next-generation sequencing, which is able to quickly deduce a sample's DNA and RNA sequences. Another example is a mass spectrometry-based technology developed by Ruedi Aebersold's group, which can identify a sample's entire protein profile.

Clever computing

The goal is to be able to use this new abundance of data, coupled with medical histories, in order to predict the further course of the disease in each individual patient. In time, pathologists will be sup-

ported in their work by a computer model. "We're developing a classifier in collaboration with IBM Research – Zurich", says Wild. "The model is currently learning how to differentiate between aggressive and insignificant tumors." It has the difficult task of sifting through countless variables for relevant information, identifying crucial patterns and indicators, known collectively as markers, in order to reveal the possible future progress of the tumor.

The first data sets from the ProCOC cohort have already been integrated into the model. These include parameters such as gene and protein composition, as well as information from medical histories like details of administered drugs or survival rates. Using cognitive computing technology, the model will continue learning using the remaining ProCOC data until it can reliably differentiate between aggressive and insignificant tumors. "We will then use data from a second cohort, where we already know the disease's outcome, in order to validate the model," explains Wild. "This will show us just how precisely our model predicts a cancer's development."

Understanding the cancer's tricks

Beside the classification of prostate carcinomas, the researchers involved in the PhosphoNet PPM project are also working on another unsolved problem, that of castration-resistant prostate cancers. "Sometimes the cancer has spread too far to be cured by surgery or radiation, and particularly aggressive prostate tumors that have been removed can still reoccur", clarifies Wild, "mostly in the form of bone metastases." These cases call for even more drastic measures. Since the tumor is driven by testosterone, this hormone's production must be halted with drugs or surgically hindered by the removal of the testes. This can lead to side effects like reduced libido, impotence, hot flushes, growth of breast tissue or weight gain in the affected men, but the hormone therapy is usually enough to cause the tumor to stop or even recede.

Unfortunately, this does not always work. After a while, castration-resistant tumors manage to circumvent even these proce-

Pathologist Wild marks the place where the tissue has been altered by cancer.

dures. They can, for example, form more androgen receptors in order to exploit even the smallest concentrations of testosterone left in the body. Or they can start stimulating production themselves, or simply switch to a different hormone to use as fuel.

The PhosphoNet PPM team wants to explore the mechanisms behind the tumor's ability to survive the withdrawal of testosterone. This knowledge will also have an impact on the choice of appropriate medication. Especially since we know that new, otherwise effective medicines can paradoxically stimulate a tumor's growth in some patients. "The more we know about the behavior of the tumor, the better we can predict which medication will be most effective in each case", explains Wild. "With this new-found knowledge, we might even identify novel drug targets."

Towards a more personalized medicine

The research work is in full swing and will continue even after PhosphoNet PPM finishes. "This project could act as a template for further projects focusing on different types of cancer", says Wild. The archiving of data and samples is something the pathologist is very passionate about. His goal is to digitize the thin sections and archive them, along with the gene and protein profiles, in a central, digital biobank. In future, researchers will be able to access and use this resource to extract relevant information, which will of course be anonymized.

One prostate can yield up to 70 thin sections.

Without doubt the most important facet for Wild is that the results coming out of projects like this are actually applied in hospitals. "The patients always come first. In future every patient should be able to profit from a tailor-made therapy thanks to a personalized diagnosis." The findings of the PhosphoNet PPM project will be an important step in this direction.


PhosphoNet PPM at a glance

Principal investigator: Prof. Ruedi Aebersold

Research groups:

- Prof. Ruedi Aebersold, Institute of Molecular Systems Biology, ETH Zurich – Proteomics
- Prof. Andreas Beyer, CECAD, University of Cologne – Systems and computational biology
- Prof. Bernd Bodenmiller, Institute of Molecular Life Sciences, University of Zurich – Imaging mass spectrometry and network analysis
- Prof. Manfred Claassen, Institute of Molecular Systems Biology, ETH Zurich – Computational biology
- Prof. Dr. med. Silke Gillessen, Department of Medical Oncology, Kantonsspital St. Gallen – Oncology
- Prof. Lucas Pelkmans, Institute of Molecular Life Sciences, University of Zurich – Image based transcriptomics
- Prof. Dr. med. Peter Wild, Institute of Surgical Pathology, University Hospital Zurich – Systems Pathology & Clinical High-Throughput Genomics Laboratory
- Prof. Christian von Mering, Institute of Molecular Life Sciences, University of Zurich – Bioinformatics

Total budget (2013–2016): CHF 7.1 million, including CHF 3.0 million from SystemsX.ch

Project type: Research, Technology and Development (RTD) Project
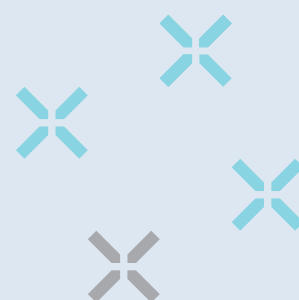
PhosphoNet PPM
Personalized-Precision Medicine