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At the request of MaartenMemorial, Dr Luider, Head of Research of the Maarten van Sten Laboratory | Erasmus MC Rotterdam wrote a scientific research proposal especially for the 18th edition. This project proposal focuses on research of Multiple Myeloma (Kahler's disease), mammary carcinoma, viruses such as HPV and identification of antibodies using mass spectrometry.

In 2024, MaartenMemorial chooses to use the funds raised to co-fund the position appointment and investment of a:

- 1 Postdoc / Senior Biomedical Scientific Researcher
- 2 Mass spectrometer (Astral TFS)

#### **Description scientific project proposal:**

Since the last century it is possible to identify proteins with two techniques i.e. crystallography of a pure protein completed with NMR information of this pure protein and since 2000 a complete other identification technology has been developed with mass spectrometry directly on tissues and body fluids, this has been named proteomics. This development has revolutionized the research field. It was in 2000 only possible to identify a dozen of proteins, today it is possible to identify thousands of proteins in one sample within one hour. The sequence analysis of the human DNA in 2002 has strengthened the protein identification via database dependent analyses. Besides this milestone in DNA sequencing, the technology development of mass spectrometers was impressive the last two decades. The identification of proteins with Orbitrap and Time of Flight mass spectrometers online coupled to nano liquid chromatography devices was very successful. Also developments in sample preparation, improvements in resolution and different fractionation methods even within the mass spectrometer has facilitated the improvements in protein identifications, quantitation and the determination of modification in proteins.

In 2023 a new design mass spectrometer was launched by Thermo Fisher Scientific. This device called ASTRAL is able to identify in tissues and body fluids significant higher numbers of proteins than in current mass spectrometers. Except for this improvement it is also able to identify large numbers of proteins in a single cell ("single cell proteomics"). This gives the most intriguing possibility to monitor at the single cell level accurately tumor progression at the protein level in combination with genetic analysis. Per cell thousands of cellular proteins can be detected including their post translational modification.

We like to apply for the new ASTRAL mass spectrometer: Four examples are listed below that would benefit from this new technology

1. In *multiple myeloma* after treatment a relative small number of tumor cells remain in the body. This minimal residual disease will give eventually a relapse of cancer. Better understanding of protein expression with combined genetic information can lead to a better personalized treatment and will possible diminish the number of remaining cancer cells resulting in a prolonged period without relapse or even the possibility to cure the disease.
2. In serum samples of hereditary *breast carcinoma* carriers with genetic differences in BRCA1 and BRCA 2 we have found that a small number of proteins change longitudinally in serum of patients that

develop breast carcinoma in contrast to patients that do not develop this cancer. The ASTRAL gives the possibility to measure these differences more accurately because much more data will be available per sample, subtle differences in quantities of identified proteins can be recorded in a significant improved way and opens ways to perform statistical analysis in large numbers of samples obtained from a cohort study.

3. Viruses such as HPV can initiate cancer for instance *cervix carcinoma* but also head and *neck cancer*. Why one patient infected with HPV will develop cancer and another infected patient do not develop cancer is unknown. Using smear cervix samples we have found that the presence of specific proteins involved in replication predict if a patient will develop cancer or not. HPV is involved in the dysregulation of modifications in DNA and proteins. We found that phosphorylation in specific proteins are associated to initiate cervix cancer. The ASTRAL gives significant improvements in the identification and phospho-modification of proteins involved in cancer initiated by HPV.

4. In many diseases including cancer, *antibodies are produced* that are specific for certain proteins. Increased concentration of certain proteins in the bloodstream or changes in their structure compared to the normal situation can trigger the humoral immune system. Sometimes these autoantibodies can visualize the cancer tissue and even these antibodies could be foreseen to be part of a therapeutic treatment. The ASTRAL gives the possibility to sequence these autoantibodies in combination with genetic information. The ASTRAL technology in combination with genetic information gives a way to sequence antibodies in serum that recognize tumor tissue and can be applied in cancer treatment.

#### How can we realize the exploitation of such an investment?

The purchase value of the ASTRAL is approx. 1.5 million euro and the cost of operation is estimated at 500.000 euro (total 2 million euro). Such investments are in regular national funding too large. Therefore collaboration is needed to realize such large investments. Collaboration between Maarten Memorial and other partners could result in the installation of this device in the Maarten van Sten laboratory for the research described above and other cancer related research. To realize such an initiative carrying capacity is needed. The Maarten van Sten laboratory has all facilities to house the device and the research team has the experience to operate and maintain mass spectrometers used for proteomics.

In collaboration with MaartenMemorial,

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*Disclaimer:*

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