Bio-resource for Biomarker Development for Rare Cancer: Issues and Solutions

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Cancer biomarker discovery has been the major subject in proteomics. The biomarker for early detection in ovarian cancer considerbaly determined the direction of cancer proteomics (Petricon III EF et al, Lancet 2002), and at the same time, the detection limits of proteomics modalities of those dsays were clearly pointed out by the meta-analysis of plasma biomarkers (Anderson NL et al, Mol Cell Proteomics 2002). Since then, the cancer biomarker discovery and the modality development are the drving force for proteomics. Many biomarker candidates were reported, and the level of proteomics modalities was improved to find more candidates. However, there are few biomarkers which were discovered by proteomics and proven to be clinically useful for cancer patients. We may need to solve the issues, which are not prominent but essentially important for biomarker study.

We have been focusing on rare cancers, which defined as maligincies with extremely low incidende. As the number of patients with rare cancers is quite small, there are many challenging issues in the rare cancer studies. For example, the samples for research are always hard to obtain, and the clinical applications are difficult to achieve because the market size is too small to expect enough rewards for for-profit-company. Through our experience, we discuss the issues and solutions of biomarker discovery.

We found that while the performance of proteomics modalities were highly improved and considerably large numbers of proteins can be detected nowadays, the fundamental research resources are still under development, especially rare cancers. One inherent difficulty of biomarker study is that the number of samples is always too small to obtain conclusive results, and it is hard to convince the people to launch a large-scale validation. To compensate for a small number of samples, we need a possible theory of biomarkers and attract the sample providors, such as physicians. The *in vitro* data that the predictive or prognostic biomarkers significantly influence the malignant phenotypes of cancers in a reasonable way are mandatory to start biomarker validation. To reveal the function of biomarker candidates, we need cancer models such as xenografts and cell lines. However, they are quite limited and hard to obtain from public biobanks especially for rare cancers. With this notion, we started the project to develop the patient-derived cancer models in 2014. We have challenged tumor tissues from 400 sarcoma cases, and established 40 xenografts and 60 cell lines. A lack of proper models hinders the progress of research, and our models will change the future of rare cancer studies.

Biobanking of clinical materials are essentially required to perform biomarker studies. There are many biobanks, and their samples have been utilized for proteomics studies. The biobanks will remain one of the most important system for cancer proteomics. However, the underutilization of biobanking resources is the issue to challenge for many years, and the samples of rare cancers are not always prioritized for banking. To address this issue, we launch a novel biobank, Tochigi Cancer Biobank (TCB), in 2021. TCB will function as a unique biobank for biomarker studies by its four characters. Firstly, it focuses on rare cancers and intractable cancers. Secondly, it functions as living biobank, which preserve tumor tissues in a special preservation solution, so that the tumor tissues can grown after long term storage at the extreme low temperature. Thirdly, it allows the users to access the bioresources with ease, asking them adequate handling fees. Fourth, it will provide high-end contract analysis.

The difficulties we encounter in rare cancer studies are common subjects in cancer research, and what we learn here will be applicable to the studies of other cancer types. At the dawn of cancer proteomics, the technological limitation seemed to be the only obstacle. However, the biomarker study has realized us many challenging issues in the clinical application of proteomics. And what we have learned from the biomarker development should be applicable to the other subjets of cancer research.