HOKKAIDO UNIVERSITY

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Doctoral Dissertation Evaluation Review

Degree requested Doctor of Life Science　　Applicant's name YOGESH K V

Examiner :

Chief examiner	Professor Shin-Ichiro Nishimura
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Title of Doctoral Dissertation

Synthesis of Complex Glycopeptides Toward Novel Cancer Marker Discovery
（複雑な糖ペプチドの合成による新しい癌マーカーの探索）

Results of Evaluation of the Doctoral Dissertation (Report)

Recently, MRM (Multiple Reaction Monitoring) analysis has been explored as a potential method for a quantitative proteomics and glycoproteomic study. However, specific synthetic glycopeptide as an internal standard are essential to establish a new method for characterization and quantitation of glycopeptides using MRM analysis. Thus, it is possible to realize absolute quantitation by its combination with target synthetic glycopeptide as an internal standard.

In this study, based on the status of prior studies on large-scale glycomics of over 3,500 human serum samples, which revealed that serum glycoproteins of cancer patients often bear dominantly specific glycoforms, namely branched tri- and tetra-antennary *N*-glycans, beyond cancer species when compared with normal control groups. Hence, the author has conducted research on developing a SRM-based targeted absolute quantitation method using synthetic glycopeptide fragment of AGP (alpha-1-acid glycoprotein) carrying complex type tri-antennary *N*-glycan, which is assumed to be derived through direct tryptic digestion of human serum AGPs aiming at biomarker discovery required for an early diagnosis of diseases including cancer.

In conclusion, the author has demonstrated for the first-time high potentials of quantitative glycoproteomics targeting serum tryptic glycopeptides as new class biomarkers that can be directly monitored without any enrichment process of the parent glycoproteins. Remarkably, a use of structure-defined synthetic glycopeptides as a calibration standard in SRM assay allowed for the absolute quantitation of the focused glycopeptides elaborated during a tryptic digestion of the whole serum glycoproteins. The present versatile chemoenzymatic protocol using locust bean gum galactomannan as abundant materials would enable the synthesis of a variety of branched *N*-glycoforms both triantennary and tetra-antennary *N*-glycans when combined with a series of enzyme-assisted modifications. Particularly, *trans*-glycosylation activities of engineered *endo*-glycosidases to the GlcNAc-peptides as acceptors using preformed oligosaccharide oxazolines as donor substrates might be a key to improve the feasibility of this approach. Our extensive efforts to construct a library of such structure-defined glycopeptides will provide nice tools, which can contribute not only to discover novel disease biomarkers but to understand the significance and molecular mechanism in the dynamic and site-specific protein glycosylations. Therefore, we acknowledge that the author is qualified to be granted a Doctorate of Life Science from Hokkaido University.