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Summary of Doctoral Dissertation

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A study on the effect of guanine-quadruplex topology on immunostimulatory properties of CpG oligodeoxynucleotides
(グアニン四重鎖構造のトポロジーが CpG オリゴ核酸の免疫活性化能に与える影響)

Synthetic cytosine-phosphate-guanine oligodeoxynucleotides (CpG ODNs) are promising candidates for vaccine adjuvants, as they activate immune responses through the Toll-like receptor 9 (TLR9) pathway. However, unmodified CpG ODNs are quickly degraded by serum nucleases, and their negative charge hinders cellular uptake, limiting their clinical application. The phosphodiester bond of CpG ODNs have been modified with sulfur to a phosphorothioate bond in order to stabilize CpG ODNs. The phosphorothioate modification has reported to have toxicity towards humans causing renal damages and non-specific protein binding. To overcome these complications, we use natural CpG ODNs with guanine-quadruplex (G-quadruplex or G4) as a scaffold to aid delivery into the cells and its nuclease resistance in serum. G4 structure has three topologies depending on their orientation and bond angles of guanine present in the G4 sequence. G4 topologies have different spatial specifications, their properties when used as a scaffold for CpG ODNs have been studied in this work. Also, a study has also been conducted to further improve the adjuvant potential of naked G4 CpG ODNs by conjugating G4 ligands that bind to its G-tetrad and stabilize the G4 structure.

In chapter one, we provide a background about general understanding of topics related to this study. We explain G-quadruplex, its structure and properties in detail, CpG ODNs and its uses also G4 ligands as well.

In chapter two, immunomodulatory properties of different topologies of G-quadruplex have been investigated.

In chapter three, we have tried to enhance the immune response induced by G4 CpG ODNs.

In chapter four, the key findings of this study have been summarized. For the first time, a meticulous study was conducted where the best performing topology was found in terms of immunomodulatory properties and its properties has been further enhanced to develop a molecule with potency of a vaccine adjuvant. This study as a whole provides information about cytokine profiles of different topologies of G4 CpG ODNs and insights about using G4 ligands in in vitro manner. Knowledge obtained from this study can be further optimized and used in development on natural CpG based vaccine adjuvants in future.