A new technology for intracellular uptake of oligonucleotide therapeutics into cancer cells- A novel TRPC3/TRPC6 (Transient Receptor Potential C3/C6) channel selective activator L687 induces cellular uptake of antisense oligonucleotides -

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Abstract

In the field of oligonucleotide therapeutics including antisense oligonucleotides (ASO), it is a major challenge to deliver the ASO to the target tissues to be taken up selectively into the target cells, and this difficulty disturbs their implementations as drugs particularly for treating cancer. Based on our previous finding that Ca^{2+} enriched-medium enhanced intracellular ASO uptake, we focused on Ca^{2+} permeable TRPC3/C6 channels highly expressed in lung cancer cells and came up with the idea that activating these channels might enhance the intracellular ASO uptake. Indeed, we found that ASO uptake was largely increased by treating lung cancer cells with small molecule, L687 which we identified as a novel TRPC3/C6 activator. In animal model experiments, systemic administrations of ASO together with L687 to tumor-bearing mice increased the amount of ASO inside the tumor, resulting in decreased target gene expression and reduced tumor size, compared with administrations of ASO alone.

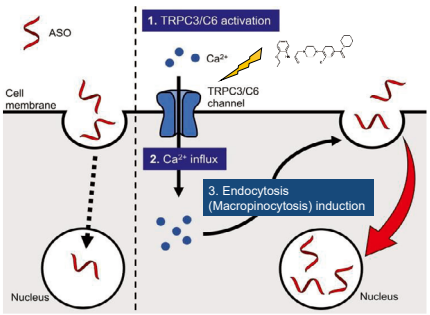
Background & Results

Unlike small molecule or antibody drugs, ASO can regulate the expression of disease-responsible proteins at the gene level and have been approved as therapeutic drugs for various intractable rare diseases. These characteristics are certainly applicable to cancer therapy and clinical trials of many oligonucleotides including ASOs as cancer therapy have been conducted. However, as of October, 2024, no oligonucleotides for treating cancer have been approved except for an ASO for treating low risk myelodysplasia and very few have advanced in late stage of clinical trials. One possibility will be the lack of an effective drug delivery system (DDS) that systemically administered oligonucleotides are delivered to tumor tissues to be taken up by cancer cells.

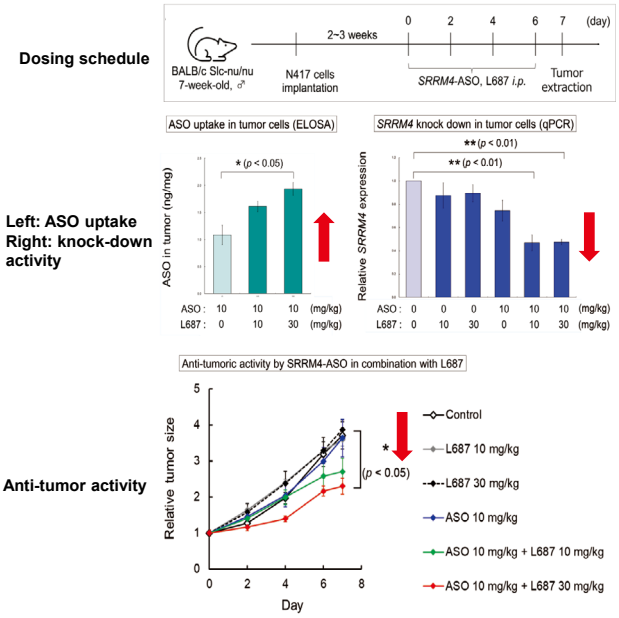
As mentioned above, we identified L687 that selectively activates TRPC3/C6 channels and promotes Ca^{2+} influx in TRPC3/C6 expressing cells. Along with L687, lung cancer cells were treated with ASO to evaluate its intracellular uptake and gene suppression activity. We found that the amount of ASO in the cells significantly increased in a L687 concentration- and incubation time-dependent manner, concomitantly with a decrease in target gene expression, compared to ASO treatment alone. In *in vivo* experiments, intraperitoneal administrations of ASO targeting tumor-growth responsible gene (*SRRM4*) together with L687 to xenograft mice harboring small cell lung cancer increased the amount of ASO inside the tumor, resulting in decreased *SRRM4* gene expression and significantly suppressed tumor growth, compared to ASO administrations alone.

Significance of the research and Future perspective

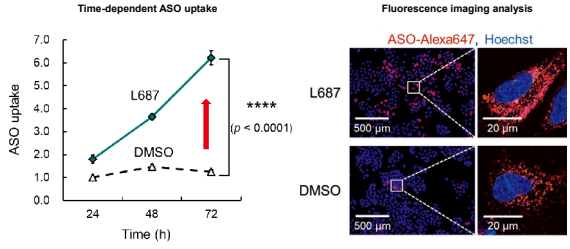
This research demonstrates that the method administrating L687 together with ASO targeting tumor-growth responsible gene against the TRPC3/C6 expressing tumor would be effective for treating cancer. So far, there has not yet been a small molecule that enhances intracellular ASO uptake and this research would be expected to take a new step in the development of a DDS for ASO.



Conceptual Diagram



Intrapenitoneal administration of L687 in combination with SRRM4 ASO on a tumor xenograft mouse model.



L687 induces intracellular uptake of oligonucleotides.

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