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Active delivery of Zinc Fingers for *in vivo* enhancement of gene regulation

Summary

We have developed a universal method to enhance control of gene expression *in vivo* with artificial gene-regulatory transcription factors (**TFs**). In recent years, there are many examples of designer gene-specific TFs being used to up- or down-regulate target disease genes; the new method promises a significant increase the control of somatic gene expression. The key concept in this example is **active delivery** of zinc finger peptides (ZFs) by active gene expression, secretion and cell-penetration of designer transcription factors (TFs) such as ZFs. This is demonstrated in cells and is applied in vivo, for example in mouse or humans, using AAV-secretion/penetration ZF constructs.

Technology

The present invention provides new zinc finger peptides and encoding nucleic acid molecules that can be used for the modulation of gene expression *in vitro* and/or *in vivo*. The new zinc finger peptides of the invention may be particularly useful in the modulation of target genes associated with expanded GGGGCC hexanucleotide repeats or CGG trinucleotide repeats, and more specifically the targeted repression of such genes.

Applications

Current ZFP therapies are working well for months on end but the expression levels at 6 months and beyond are lower than after initial injection. Typically, only about 25-30% of whole-brain gene targets are repressed beyond 6 months, with standard constructs. Our Active delivery constructs will improve this situation by continuing 'drip-feeding' secreted cell-penetrating factors to bystander cells in the brain and other tissues by exploiting ZFs' intrinsic cell penetrating properties. These cell-penetration properties have not been coupled before to secretion *in vivo*, nor delivery with AAVs, and this is what is unique about this active delivery concept.

Intellectual Property

This technology is subject of a Priority patent application.

Benefits

- This invention provides new zinc finger peptides and encoding nucleic acid molecules that can be used for the modulation of gene expression *in vitro* and/or *in vivo.*
- This invention has therapeutic applications for clinical diseases where altered expression of genes is a key part of the disease aetiology.

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