

FZC18

EmergenceBio2008



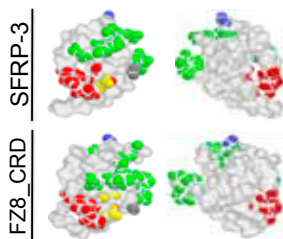
Preclinical study of FZC18, an anti-tumor polypeptide for colon and liver cancers.

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INSERM UMR-991: Liver, Metabolisms and Cancer - Rennes

Background

The Wnt/ β -catenin pathway controls cell fate through regulation of cell proliferation and death, migration, differentiation and metabolism. Extracellular Wnt proteins interact with specific *frizzled* membrane receptors and induce a cascade of events resulting in the translocation of β -catenin to the nucleus which in turn activate the transcription of genes involved in cell proliferation and tumor growth. When Wnts are quenched by extracellular inhibitors, the pathway is inactivated, β -catenin is degraded, cells stop proliferating and finally die. Wnt signalling is naturally controlled by extracellular molecules modulating the access of Wnts to the Frizzled receptors, such as DKKs (Dickopffs) and the SFRP (secreted frizzled related protein) families. We previously identified the function of the *frizzled* domain of collagen 18 (FZC18) which carries structural identity with the extracellular Wnt-binding domain of the *frizzled* receptors. The main bottleneck of the program was the production of bioactive recombinant FZC18_CRD (117 amino-acids). The function of the *frizzled* CRD containing 10 cysteines relies on its compact structure where disulfide bond formation and glycosylation play a crucial role.



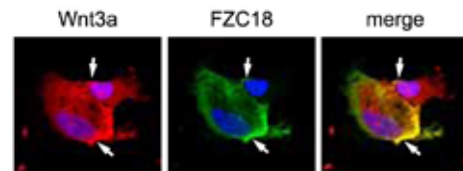
Structural model of FZC18_CRD using SFRP3 and FZ8_CRD crystal structures as templates (PloS One, 2008). Blue, N-terminal, grey, C-terminal, red, green and yellow are solvent exposed surfaces putatively involved in interaction with Wnts.

Aims

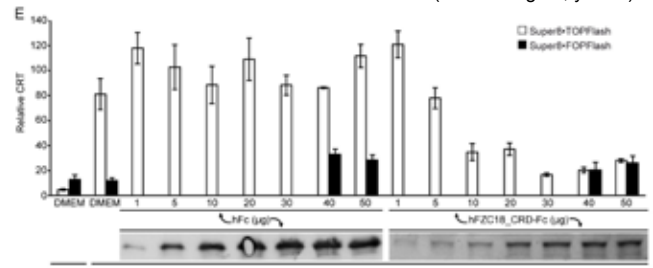
To demonstrate the efficacy of FZC18 as a new bio-drug for cancer treatment in a pre-clinical context. The main objectives of the project were: a) the definition of the best conditions to produce recombinant bioactive FZC18, b) the *in vitro* and *in vivo* validation of its efficacy

Salient Results

Production of conditioned media containing soluble FZC18 and partial affinity purification of FZC18_CRD showed that FZC18 inhibits Wnt/ β -catenin signaling by interacting with Wnt3a and the Receptors Frizzled 1 and 8.



FZC18 colocalizes with Wnt3a at the cell surface (see « merge », yellow).



FZC18_CRD inhibits Wnt3a-induced β -catenin signaling.

Conclusions and Perspectives

FZC18 acts a potent anti-cancer drug in tumor cells. Thus, partially purified FZC18_CRD showed to be biologically active *in vitro*. Optimization of the production and purification conditions should yield enough amounts of biologically active protein for *in vivo* pre-clinical studies in mice bearing human tumors. This will be achieved within a framework program between the Gyeonggi Institute of Science & Technology Promotion (Seoul, South Korea) and Inserm-Transfert.

-Patent : Use of FZC18-containing collagen 18 polypeptides for the treatment, diagnosis and outcome prediction of diseases (PCT/EP2008067779).

-Main publications: Lavergne et al. Oncogene 2011; 30(4):423-33 ; Quélard et al. PLoS One 2008; 3(4):e1878.

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