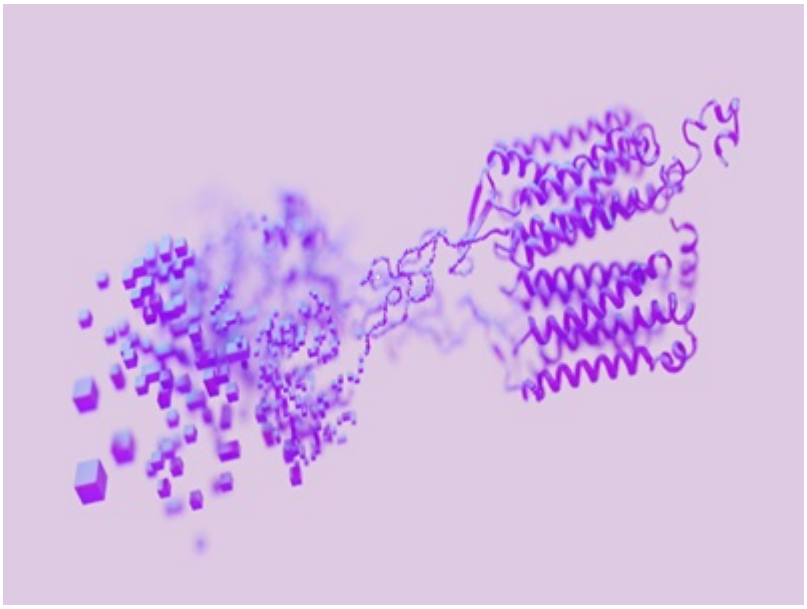
De Novo Designed Oligomeric Proteins that Modulate Fibroblast Growth Factor Signaling and Vascular Differentiation

The solution is a cyclic homo-oligomeric fibroblast growth factor (FGF) receptor binding module with tunable geometric properties that modulates activity of isoform-specific FGF signaling.



Technology ID

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Category

Selection of Available Technologies

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What is the Problem?

Growth factors and cytokines bind to the extracellular domains of cell surface receptors, initiating downstream signaling cascades. The clustering of cell surface receptors enhances and sustains activation of signaling pathways. As a result, there is an interest in designing protein assemblies to drive receptor clustering and thus enhance activation of signaling pathways of interest.

Fibroblast growth factor receptors (FGFR) are tyrosine kinases that play critical roles in vascular differentiation, but the complex pathways with which FGFRs mediate proper tissue differentiation is not well understood. The design of a tunable oligomeric protein that binds to FGFRs is necessary to better understand the role of FGFRs in vascular differentiation.

What is the Solution?

The solution is a cyclic homo-oligomeric FGFR binding module with tunable geometric properties that modulates activity of isoform-specific FGF signaling. The oligomeric protein can be designed with up to eight subunits of repeat protein building blocks that can be modularly extended. The de novo designed FGFR minibinders targeting two FGFR isoforms allow for tunable outcomes in vascular cell fate upon isoform-specific FGFR activation. Activation of the C-isoform favors arterial endothelial cell formation while activation of the B-isoform induces pericyte differentiation.

What is the Competitive Advantage?

The competitive advantage of this technology lies in its ability to modulate FGFR isoform activity to control bifurcation of endothelial and mesenchymal cell fate during vascular development. The de novo designed FGFR binding modules have geometry- and valency-dependent activity for tunable outcomes in vascular cell fate. The designed scaffold presented here can incorporate other receptor binding domains to study and manipulate many different cellular signaling pathways.

References

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