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Design of target-seeking antifibrotic compounds

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Selective delivery of drugs and biotherapeutics to the site of disease (synaphic targeting) has number advantages. First, the enhanced accumulation of the therapeutic compound at the target tissue increases drug efficacy without increasing side effects. Alternatively, the dose of the drug can be lowered to reduce the side effects. On the practical level, when a drug is difficult or expensive to make, being able lower the dose may be the key to commercial viability. Certain targeting systems can change the distribution of the drug in beneficial way. Examples include wider distribution and deeper penetration of the drug in the target tissue, active intracellular targeting when desirable, and even targeting to a particular subcellular organelle. We illustrate these principles by describing the development a targeting system for an antifibrotic biotherapeutic, decorin. Decorin prevents tissue fibrosis and promotes tissue regeneration by inhibiting transforming growth factor- β (TGF-β) activity and by other regulatory activities. The system is based on vascular homing peptide (sequence: CARSKNKDC; referred to as CAR) that specifically recognizes angiogenic blood vessels in injured (regenerating) and inflammatory tissues and can deliver a systemically administered payload to such tissues with high selectivity. So far the CAR-targeted decorin has been shown to promote tissue repair with reduced scarring in a skin wound model, but this biotherapeutic can potentially be used other injuries and in various fibrotic diseases.

Key Words: Fibrosis, transforming growth factor- β, (TGF-β), scar, decorin, angiogenesis, inflammation.

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