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Cover Story

Sustained delivery of antibodies *in vivo* by local retention

Local sustained delivery of protein drugs is becoming increasingly important in treating various diseases. This is driven in part by the expanding repertoire of monoclonal antibodies (mAbs) and other biologics populating the global drug pipelines. One advantage of local delivery by parenteral administration is the ability to bypass vascular barriers. Direct administration of recombinant proteins to diseased tissues circumvent the need for repeated infusion of the drug at a high dose to maintain therapeutic plasma concentrations for the duration needed. Raising local concentrations while reducing systemic exposure is desirable because many mAbs target endogenous factors with pleiotropic functions. A cytokine may confer divergent functions in different metabolic and cellular milieu.

Coinciding with the expanding use of mAb therapeutics are the advances made in peptide-based materials, in particular self-assembling peptides (SAPs). Physicochemical properties of SAP-based microstructures can be tuned by changing the peptides' sequences [1]. One of the early SAP platforms used as protein depots is the amphiphilic sequence (AEAEAKAK)2, commonly referred to as EAK16-II [2]. Upon injection, these peptides form fibrillar networks in an aqueous environment with high ionic strength. Such stimuli-response properties render fibrils to form *in situ*, thereby rendering structures that adapt and adhere to the contours of the surrounding tissues. The resultant water-filled networks are conducive for loading bioactive proteins. The rate of drug release, however, is difficult to control, and burst release is typically observed.

In this issue, Professor Wilson Meng and his colleagues report a local depot design in preventing the rapid loss of mAbs [3]. The fibrils are functionalized using a co-assembly method. Two SAPs are mixed and one of them is appended with an optically active bioaffinity property. By employing a bioaffinity mechanism, the release of mAbs is prolonged, losing only 6% in the first 6 h, compared to close to 20% without the mechanism. The optical module is unique, as a fluorogen-activating protein (FAP) embedded in the network self-reports the binding sites for mAb. Having very low background fluorescence incorporated into the fibrils, the module allows orthogonal monitoring of material stability independent of the model IgG drug. The use of protein A/G as IgG-binding sites is an interesting choice. The caveat here is immunogenicity, but it might not surpass those of recombinant chimeric proteins. Nevertheless, it remains to be seen if these Fc-binding proteins can advance to Phase III in clinical studies. It has gone through Phase I study already.

The SAP formulation serves to create a mAb depot in subcutaneous tissues, as evidenced by the increased amount retained at the injection site, and the reduced amount drained into proximal and distal lymph nodes as compared with free antibodies. Using computational modeling, the investigators elucidated the ratio of binding sites to mAbs as a key parameter critical for controlling the release rate. It appears that the bioaffinity is relatively stable. The Meng team's work contributes to the field by illustrating an application of an optically active bioaffinity mechanism. The molecular tools might help to enhance *in vitro-in vivo* correlations, leading to more robust optimization of sustained delivery systems for biologics.

The sustained drug delivery technology has advanced significantly over the last seven decades. Tens of thousands of sustained release formulations have been developed and used clinically. Most of them, however, are oral formulations. The long-term delivery of peptide and protein drugs after parenteral administration has been challenging, and there are only a handful of clinical formulations based on biodegradable poly(lactic-co-glycolic acid) (PLGA). The current limitations of PLGA formulations for peptide and protein drugs include high initial burst releases and difficult manufacturing processes, especially for protein formulations. The work by the Meng team presents an alternative approach of achieving sustained release of mABs with minimized initial burst release and without denaturing the mAbs. This approach can be modified to apply for sustained delivery of many other protein drugs.

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