**Macrocyclization of Site-Specific Protein-Poly(α-amino acid) Conjugates**

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Cyclization and polymer conjugation are two commonly used approaches for enhancing the pharmacological properties of protein drugs. However, cyclization of parental proteins often only affords a modest improvement in biochemical or cell-based *in vitro* assays. Moreover, very few studies have included a systematic pharmacological evaluation of cyclized protein-based therapeutics in live animals. On the other hand, polymer-conjugated proteins have longer circulation half-lives but usually show poor tumor penetration and suboptimal pharmacodynamics due to increased steric hindrance. We herein report the generation of a head-to-tail interferon–poly(α-amino acid) macrocycle conjugate *circ*-P(EG3Glu)20-IFN by combining the aforementioned two approaches. We compared the antitumor pharmacological activity of this macrocycle conjugate against its linear counterparts, *N*-P(EG3Glu)20-IFN, *C*-IFN-P(EG3Glu)20, and *C*-IFN-PEG. Our results found *circ*-P(EG3Glu)20-IFN to show considerably greater stability, binding affinity, and *in vitro* antiproliferative activity toward OVCAR3 cells than the three linear conjugates. More importantly, *circ*-P(EG3Glu)20-IFN exhibited a longer circulation half-life, remarkably higher tumor retention, and deeper tumor penetration *in vivo*. As a result, administration of the macrocyclic conjugate could effectively inhibit tumor progression and extend survival in mice bearing established xenograft human OVCAR3 or SKOV3 tumors without causing severe paraneoplastic syndromes. Taken together, our study provides until now the most relevant experimental evidence in strong support of the *in vivo* benefit of macrocyclization of protein–polymer conjugates and for its application in next-generation therapeutics.

**References**

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**Biography**

Prof. Hua Lu is an assist professor in the College of Chemistry and Molecular Engineering, Peking University. He obtained his B.S. from Peking University in 2006 and PH.D. from the University of Illinois at Urbana-Champaign in 2011. He worked as a Damon Runyon Cancer Research Foundation postdoctoral fellow at The Scripps Research Institute (TSRI, La Jolla, CA) before he started his independent research at Peking University in 2014. His research focuses on the development of methodologies for the controlled synthesis and medical application of poly(α-amino acid)s, sustainable polymers, and protein-polymer hybrids. He is a recipient of ACS AkzoNobel Award for Outstanding Graduate Research in Polymer Chemistry (2013), Excellent Young Investigator Grant of NSFC (2017), and Young Investigator Award of the Chinese Chemical Society (2017).

