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(54) Title of the Invention: **Engineering CRISPR CAS9 immune stealth**
Abstract Title: **Engineering CRISPR CAS9 immune stealth**

(57) Described herein are methods of avoiding an immune response in a subject being administered a regimen requiring Cas9 in order to optimize and broaden the application of CRISPR based therapeutics comprising administering immune orthogonal Cas9. Also described herein are methods to modify a Cas9 protein by swapping highly immunogenic peptides or amino acids with less immunogenic counterparts. These methods are particularly useful to enable the application of Cas9 arsenal for repeat treatments. Further provided are Cas9 proteins modified to reduce immunogenicity.

