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CANCER IMMUNOTHERAPY

STINGing systemically

> A safe and efficacious intravenous STING agonist has the potential to transform the success of cancer immuno-therapy

Agonists of stimulator of interferon genes (STING), a receptor that triggers an immune response when stimulated by pathogen DNA, have recently attracted interest as cancer immunotherapies, with several agents now in clinical trials. However, these are all modified cyclic dinucleotides (CDNs) that are delivered intratumorally, and so a report on a new class of synthetic small-molecule STING agonists suitable for systemic administration by Ramanjulu, Pesiridis, Yang et al. in *Nature* is exciting.

Tumour-derived DNA can activate cyclic GMP–AMP synthase (cGAS) to produce cGAMP, the endogenous ligand of STING. Downstream signalling results in production of type I interferon (IFN) and other pro-inflammatory cytokines that stimulate cross-presentation of tumour antigens and mobilization of tumour-specific $CD8^+$ T cells. Therefore, STING agonists have the potential to enhance the immunogenicity of tumours and induce an antitumour adaptive immune response.

In the search for STING modulators, the authors carried out a high-throughput screen to identify ligands that compete with cGAMP for STING binding to modulate STING activity. This approach discovered two amidobenzimidazole (ABZI) compounds that inhibited cGAMP binding to STING. Crystal structures of each compound in complex with the STING carboxy-terminal domain revealed that both compounds bind to the cGAMP binding pocket, with two bound molecules of compound per STING dimer. The authors added a linker between the two compounds to create a single dimeric ABZI (diABZI), which had enhanced binding to STING. Further optimization yielded compound 3, a more potent diABZI.

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Importantly, previous structural and mechanistic studies of STING concluded that conformational changes in the 'lid' loop in STING to a closed or protected conformation were necessary for activation of the pathway. However, studies with the ABZI STING agonist demonstrated that conformational changes in the lid are dispensable for pathway function, and activation can occur in an open conformation. "The ABZI series of STING agonists bring in a new chemical class with completely different physicochemical properties than the CDN class of the STING agonists. This enriches the chemical space for activating STING and provides more options for the clinical development of STING agonists," explains Ramanjulu.

In vivo, subcutaneous administration of compound 3 activated secretion of IFNβ, IL-6, TNF and other cytokines in wild-type C57Blk6 mice but not in *Sting*$^{-/-}$mice, confirming the STING-dependent activation of compound 3. Intravenous injection every 3 days of compound 3 in doses as low as 1.5 mg/kg induced durable tumour regression in a mouse model of colorectal cancer. Depletion of $CD8^+$ T cells suppressed the antitumour activity, suggesting that compound 3 inhibits tumour growth by activating the adaptive immune response.

These intravenous ABZI STING agonists are now being progressed to the clinic. "Intravenous delivery of a STING agonist opens treatment options for a much larger group of cancer patients, as current intratumoural delivery is limited to accessible tumours or relies on complicated image-guided technology that limits the number of injections that can be given practically," says Pesiridis. "A safe and efficacious intravenous STING agonist has the potential to transform the success of cancer immunotherapy," concludes Yang.

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ORIGINAL ARTICLE Ramanjulu, J. M. et al. Design of amidobenzimidazole STING receptor agonists with systemic activity. *Nature* https://doi.org/10.1038/s41586-018-0705-y (2018)