PERSONALIZED SYNTHETIC POLYPEPTIDE DNA CANCER VACCINES ENCODING A NOVEL PYROPTOTIC ADJUVANT TO GENERATE EFFECTIVE ANTI-TUMOR T CELL IMMUNITY

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Background As every tumor carries its unique set of neoantigens distinguishing it from healthy tissue, cancer vaccines need to be produced quickly and on an individual basis to swiftly induce a broad immune response targeting multiple antigens. DNA provides an ideal platform to achieve this, as a single polypeptide vaccine can encode multiple (>20) antigens. However, standard plasmid DNA vaccines take months to produce and tend to be poorly immunogenic in humans.

Methods To address the first issue, a GMP-compatible method (AmpliVax) was developed that allows the simultaneous production of milligram amounts of multiple DNA vaccines in single vessel reactions within two days. This method relies on a primer-free, isothermal, rolling-circle amplification using high fidelity DNA polymerase and RNA polymerase to amplify circular DNA templates into linear double-stranded concatemers. Concatemers are digested into single linear expression cassettes which are subsequently protected by nuclease-resistant caps. To improve DNA vaccine immunogenicity, two avenues were explored. First, neoantigen DNA vaccines were tested in a therapeutic setting together with a checkpoint inhibitor drug. Second, DNA vaccines were combined with a novel caspase-1-based genetic adjuvant (PyroVant) that induces pyroptosis by exploiting the inflammasome pathway.

Results Upon intradermal injection in mice, synthetic AmpliVax DNA vaccines matched plasmid DNA vaccines in terms of in vivo expression, immunogenicity and tumor protection. While treatment of mice carrying an MC38 colorectal tumor with either a polypeptide neoantigen DNA vaccine or anti-PD-1 did not significantly delay tumor outgrowth compared to untreated mice (0% survival), the combination of the neoantigen vaccine and anti-PD1 resulted in up to 70% tumor-free survival. PyroVant DNA accelerated and amplified antigen-specific CD8 T cell responses when administered simultaneously with a polypeptide DNA vaccine. What's more, subsequent challenge with melanoma cells revealed that PyroVant also significantly improved tumor-free survival.

Conclusions In conclusion, we have created a novel synthetic DNA vaccine platform suitable for the production of effective personalized cancer vaccines. Current efforts are aimed at testing combinations of therapeutic synthetic DNA vaccines, PyroVant and checkpoint inhibitors in multiple pre-clinical tumor models.

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