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Title: SimCells: genome-free bacterial cells as vaccines against Pseudomonas aeruginosa infections

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Pseudomonas aeruginosa is a significant contributor to global pyogenic infections, constituting a substantial 23% of all infections acquired in intensive care units, with respiratory sources being predominant. Annually, England experiences around 13,000 cases of P. aeruginosa infections (PAIs), posing a 47% higher mortality risk to the 1.7 million individuals diagnosed with chronic lung diseases in the UK. Globally, P. aeruginosa ranks as the fifth most lethal pathogen, leading to approximately 559,000 deaths. The absence of new antibiotics discovered since the 1980s severely restricts treatment options for PAIs, highlighting the urgent need for alternative strategies such as vaccine development to address antimicrobial resistance. However, an approved vaccine targeting P. aeruginosa is yet to exist.

SimCells, generated by enzymatically shearing the bacterial genome, incapacitate bacterial replication while retaining immunogenic cell-surface features, making them an ideal whole-cell bacterial vaccine. This study presents a proof-of-principle investigation using P. aeruginosa SimCells as a whole-cell inactivated vaccine against pathogenic P. aeruginosa. Clinical strains of P. aeruginosa were converted into SimCells by inducing endonuclease expression using a chemical inducer, arresting the growth of host cells as their genome undergoes fragmentation and degradation by native cellular mechanisms. Lab-scaled production yielded SimCells with a purity of <1 viable cell per 1 billion SimCells. Nucleic acid staining revealed significantly reduced DNA content in SimCells compared to their wild-type counterparts. Cytometric analysis and immunofluorescence assays showed that the genome-shearing process in SimCell production effectively preserves cellular proteins and surface features. Animal studies demonstrated the safety and efficacy of P. aeruginosa SimCells. Mice tolerated doses of up to 2 x 10^9 SimCells and showed a significant reduction in lung bacterial burden after receiving these SimCells, surpassing the efficacy of chemically inactivated P. aeruginosa using paraformaldehyde. This study underscores SimCells' potential as vaccines against antimicrobial-resistant pathogens, particularly when effective antibiotic treatments are scarce. It sets the stage for the development of a human P. aeruginosa vaccine, addressing a crucial gap in combating this lethal pathogen.