RAPID, COST-EFFECTIVE AND SCALABLE GMP-COMPLIANT SIMIAN ADENOVIRUS-VECTORED VACCINE PRODUCTION FOR EARLY-PHASE CLINICAL TRIALS USING ENTIRELY DISPOSABLE PRODUCT-CONTACT COMPONENTS

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The Jenner Institute, University of Oxford, develops and produces a range of vaccines against emerging threats (such as Zika) and current global health challenges (including malaria, HIV and rabies). The Jenner Clinical Biomanufacturing Facility (CBF) manufactures multiple simian adenovirus-vectored vaccines for early phase clinical trials each year. Hitherto we have used shake flasks for upstream production and caesium chloride gradient ultracentrifugation for downstream purification. This process is robust and simple but also slow, human resource intensive and lacks scalability.

Here we report the development of a novel process using a 2 x 3L single-use stirred tank bioreactor system (MilliporeSigma Mobius®), coupled to a tangential flow filtration (TFF) and anion exchange chromatography (AEX)-based downstream process. The process also includes particle lysis and nucleic acid digestion inside the bioreactor, as well as clarification of cells and debris using depth filters. As our test case, we used a novel simian adenovirus-vectored rabies vaccine (ChAdOx2 RabG), which we will manufacture to GMP standards in the coming year. Each process run yields >$5x10^{13}$ ChAdOx2 RabG virus particles (approximately 1000 human doses), with residual host cell DNA, host cell protein and nuclease levels suitable for clinical trial use.
While similar processes have been previously reported for adenovirus manufacture, we will report a number of points of novelty. Firstly, we use single-use disposable product-contact components from beginning to end, greatly simplifying small-scale GMP manufacturing of multiple products. Secondly, we will report results of comparative testing with a range of modern ion exchange media (including resins, membrane adsorbers, monoliths and functionalized hydrogel formats). Thirdly, we will report the development and validation of novel quality control methods suitable for this process.

The resulting process will allow the CBF to increase production yield and produce more vaccines that transfer more easily to larger facilities.