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AAV Reference Material Working Group-Submission for donation of plasmid production and QC testing

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To: Members of the AAV Reference Material Working Group

Aldevron, LLC (Fargo, ND) wishes to be considered as a potential production site for the reference pDG Helper plasmid (400 mg) and the AAV plasmid pTR-UF11 (150 mg). These deliverables along with initial pilot lots will be accompanied by the appropriate release forms and documentation (physically and/or electronically). Aldevron has completed multiple lots of the pDG plasmid and ITR-bearing vectors for use as ancillary reagents for various manufacturing processes. A redacted Manufacturing Summary Report (MSR) is available upon request that gives a more comprehensive overview of the processes used in production. The lot numbers of all raw materials and the Certificates of Analysis or Origin can be incorporated as into the final documentation if desired.

Facilities and Equipment

The plasmid production unit is located in approximately 5500 square feet of laboratory space in the 7500 square foot primary facility. The area is serviced by four independent air-handling units and also includes an isolated circuit that supports the class 1000 space. Within this clean room is a class 100 production suite. Two fermentor's (16 L and 20 L) along with shake flask capacity of approximately 120 L are located in an area separated by three doors from plasmid purification rooms. All the chromatographic and associated purification hardware necessary to complete the production of pDG and pTR-UF11 are currently on-site. Vacuum, steam, large scale centrifuges, micro-incubators, freezers (-10°C to -80°C), refrigerators, sterile hoods, spectrophotometers and sundry requisite QC equipment are also available.

Growth and Purification

Starting with MCB material a WCB of 50 vials will be generated. The bank(s) will be qualified which will include the small scale isolation of plasmid DNA to be used for sequencing and to serve as a source of reference material for QC tests (e.g. restriction digests). Growth will be undertaken in the 20 L fermentor using a proprietary animal component-free medium. A Ribonuclease-free process that utilizes GRAS kosmotropes is employed during bacterial lysis and anion exchange chromatography is used as the primary capture step. The plasmid bearing fraction will then undergo a diafiltration/ultrafiltration step to prepare it as a suitable feedstock for the polishing step (reversed phase chromatography). All growth, processing and primary capture/concentration steps will be undertaken in areas that are documented to have been cleaned and isolated (temporally and spatially) from other processes in the building.

Polishing and final formulation will occur within the clean room and production suite respectively if this level of quality is required.

Quality Control

Tables 1 and 2 of RFP 6.0 correspond exactly to the release specifications and test modes used by Aldevron. In addition a bicinchoninic acid assay for residual protein impurity is undertaken. Samples for USP sterility testing are outsourced to a third party. All vials of final product will feature a unique number (e.g. 5 of 60) along with the Aldevron Lot #, concentration and plasmid name.

Shipping

Pending confirmation of final product sterility all dispensed aliquots of plasmid will be held in a -80°C freezer. When released the DNA will be shipped priority overnight on dry ice to the final site. In order to minimize the potential loss of product shipments can be broken up over a series of days. Accompanying each shipment will be a letter indicating the disbursement of material indicating what has shipped (if appropriate), what is in the current shipment and what has yet to be shipped (if appropriate).

Aldevron routinely ships DNA to biopharmaceutical organizations from around the world.

Personnel

The following will be involved in the production of both plasmids:

John Ballantyne (CSO) will have an overview role in either project.

Donald Klocke (Production Manager, Scientist) will control all day-to-day aspects of the production and will manage the tracking and batch record use of all steps.

Jeffery Jensen (Fermentation Technician) will be responsible for the preparation, isolation, sanitizing and harvesting of all growths.

Natasha Petry (Microbiologist) will be responsible for the manufacture and testing (in conjunction with QC personnel) of the WCB's, fermentor inoculum and fermentor product.

Brandee Godfrey (QC Director) will be responsible for all final product testing and release.

Cynthia Biffert (Microbiologist, QC Scientist) will assist Miss Petry and Mrs. Godfrey with materials receipt, control and release and aspects of QC.

David Larson (Buffer Technician) will be responsible for the manufacture of all processing and chromatographic buffers.

Michelle Berg (Client Relations, Sales and Marketing) will be the point of contact for the project(s).

Fred Donovan (Production Technician) will be responsible for lysis, capture and generation of polishing feedstock.

Matthew Bickel (Production Technician) will assist Mr. Donovan.

Karen Beckman (Production Technician) will assist Mr. Donovan and Mr. Klocke with polishing and final product preparation.

All personnel have worked on at least two clinical source production lots with the exception of Mr. Bickel who will be under the supervision of Mr. Klocke or Mr. Donovan at all times.

Estimated Project Length

Because of the relative stability and past experience with **pDG** we would expect the minimum length of time to complete the production, release and shipping of this plasmid would be six weeks from an initiation point. The pilot material excluding sterility testing will take approximately two weeks to generate.

Since the stability and hence the yield of the **pTR-UF11** will be subject to some experimentation it is likely the initial pilot lot will take up to four weeks to deliver. A more accurate time frame for the production of the final 150 mg lot will be determined based on the findings of the pilot study.

Estimated Value of Donation

Based on the pricing structures used for similar works that Aldevron has undertaken we estimate the value of the production of both lots to be \$51,000. The value of the pDG being \$36,000 and for the pTR-UF11 being \$15,000.

Summary

Thank you for the opportunity to submit a bid to donate reference material for this important project. Aldevron is the leader in the production of preclinical DNA and we are confident in our ability to meet and exceed your expectations. Please feel free to contact us at your convenience if you have any questions or concerns.

Contact Information – RFP 6.0

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