Removing cost barriers to scalable AAV manufacturing with TESSA®

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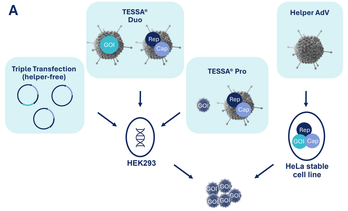
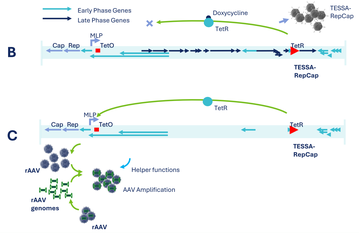
Poster

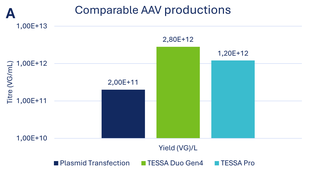
1. AAV Manufacture using TESSA® and other platforms

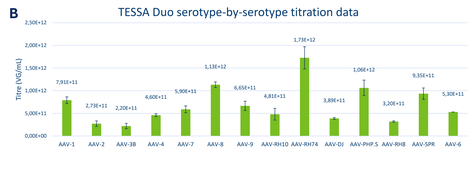
The manufacture of recombinant AAV (rAAV) is complicated by a requirement for AdV helper functions. Downstream removal of a helper adenovirus is technically challenging, and the risk of residual contamination may complicate regulatory acceptance. rAAV production in producer cells requires AAV repcap genes, helper functions, and AAV genomes. TESSA® (Tetracycline-Enabled Self-Silencing Adenovirus) supplies HEK293 producer cells with all three components in a manner analogous to triple transfection (A), using either TESSA Duo (TESSA® vectors for repcap genes, and the AAV genome) or TESSA® Pro (propagation of existing rAAV using a TESSA-repcap vector). In the presence of doxycycline (B), TESSA® vectors are propagated; in its absence (C), a TetR/TetO feedback loop silences adenoviral late genes while preserving helper function expression. This enables rAAV production without adenoviral contamination and removes the need for costly plasmids or stable cell lines. Using TESSA®, rAAV yields are up to 40-fold higher than triple transfection, with improved quality, including fewer partially encapsidated genomes and empty capsids. By addressing scalability and cost-of-goods limitations, TESSA® has the potential to transform rAAV manufacturing and improve patient access to AAV-based therapies.

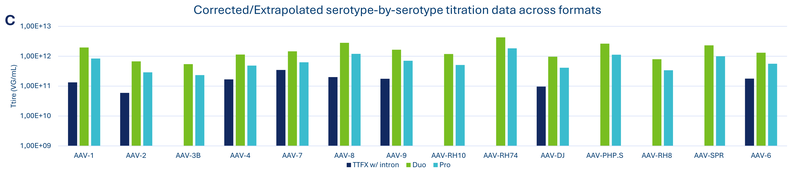




2. Comparable productions and serotype-by-serotype rAAV yield data

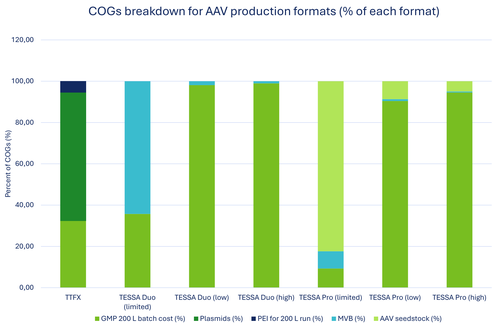






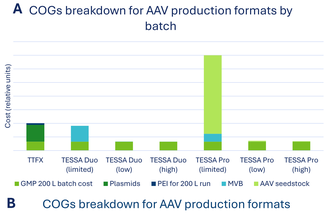
AAV yields for a consistent transgene and serotype (AAV8) were assessed using plasmid transfection, TESSA® Duo, and TESSA® Pro (A). For the same transgene, yields across a range of serotypes were evaluated using TESSA Duo (B), and for a different transgene using plasmid transfection (not shown). TESSA® Pro yields were extrapolated from TESSA® Duo data, based on the comparable production observed in (A), assuming similar relative yields between Duo and Pro. Yields were then corrected using the comparable productions to predict relative yields across the formats for multiple serotypes (C), where data were available.

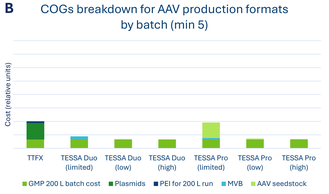
3. Cost breakdown for TESSA® formats versus Triple Transfection



- The costs involved in generating a 200 L GMP batch of rAAV were assessed for the different formats (left).
- For TESSA®, these costs depend upon the utilization of master viral banks (MVBs). 'Limited' assumes only one 200 L batch is made, rather than as many as are supported by an MVB.
- A TESSA® MVB supports between 98 (low) and 168 (high) 200 L AAV batches.
- Plasmid represent the largest cost component in triple transfection (TTFX), a cost that is eliminated in TESSA®.
- TESSA and AAV MVBs make up a large component of cost for TESSA® Duo and Pro where batches are limited, but this cost is amortized over a small number AAV GMP batches.

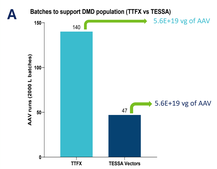
4. Batch cost amortized over multiple runs

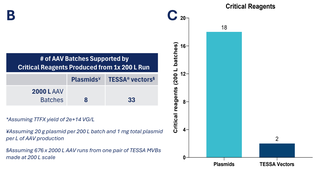




- Even with MVB utilization restricted to 1x 200 L AAV batch, TESSA® Duo is cheaper (per batch) that plasmid transfection (A).
- TESSA® Pro requires a GMP AAV seedstock, increasing initial costs. However, when that cost is spread over 5 runs (B) cost per batch is broadly equivalent to plasmid transfection, with cost falling further when spread over 10 batches (not shown).
- At higher batch number (low/high) cost is reduced even further with TESSA®.

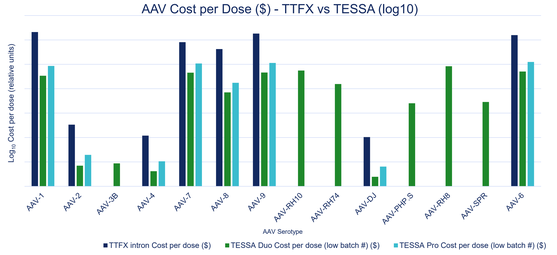
5. Critical reagent cost modelling for DMD





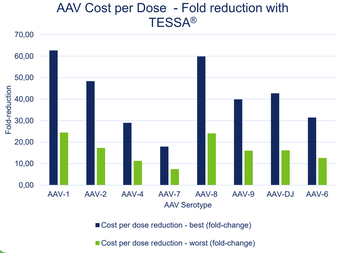
- Duchene muscular Dystrophy (DMD) requires high doses, with ~5.6e+19 VG of AAV needed to support the DMD population annually.
- Assuming a modest 3-fold yield improvement by TESSA® Duo reduces the number of 2000 L batches required to support this population annually from 140* to 47 (A).
- A 200 L production of TESSA® vectors versus a 200 L production plasmids support 8 and 33 2000 L AAV batches, respectively (B).
- A single pair of TESSA® MVBs support AAV manufacture for the DMD population, annually, versus 18 batches of plasmids (C).
- A TESSA MVB from a 200 L production is ~3-fold cheaper to produce than an equivalent production of plasmids.

6. Cost per dose modelling



Cost per dose depends upon the cost of critical reagents (plasmids, MVBs), how many AAV batches those reagents support, and how productive those batches are. TESSA is cheaper to make than plasmids, supports many more batches than plasmid transfection, and are more productive on a batch-by-batch basis. Relative cost per dose were estimated (above) for a range of serotypes across different formats (where data were available). Relative cost per dose were plotted on a Log_{10} scale due to the large differences between serotypes, and between TESSA formats and Plasmid Transfection.

7. Summary



TESSA® leads to large fold-reductions in cost per dose across serotypes

- Fold-reduction in cost between TESSA and Plasmid Transfection were calculated for different serotypes.
- A combination of cheaper critical reagents that support more AAV batches, and greater productivity in each batch leads to fold-reductions between 7-and 62 (left).
- Even where TESSA Pro batches have higher batch costs (with limited MVB utilization), cost per dose is lower. TESSA Duo is cheaper per dose and by batch, regardless.
- For indications with large patient populations and high doses, TESSA® addresses the need for scalable AAV manufacture with lower cost-of-goods, making otherwise costly AAV therapies affordable to healthcare providers, and accessible to patients.
- TESSA® is available evaluation. Request at www.minaris.com

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