



# Mapping the Human Transcription Factor Landscape for the AI-Guided Design of Potent Muscle Promoters

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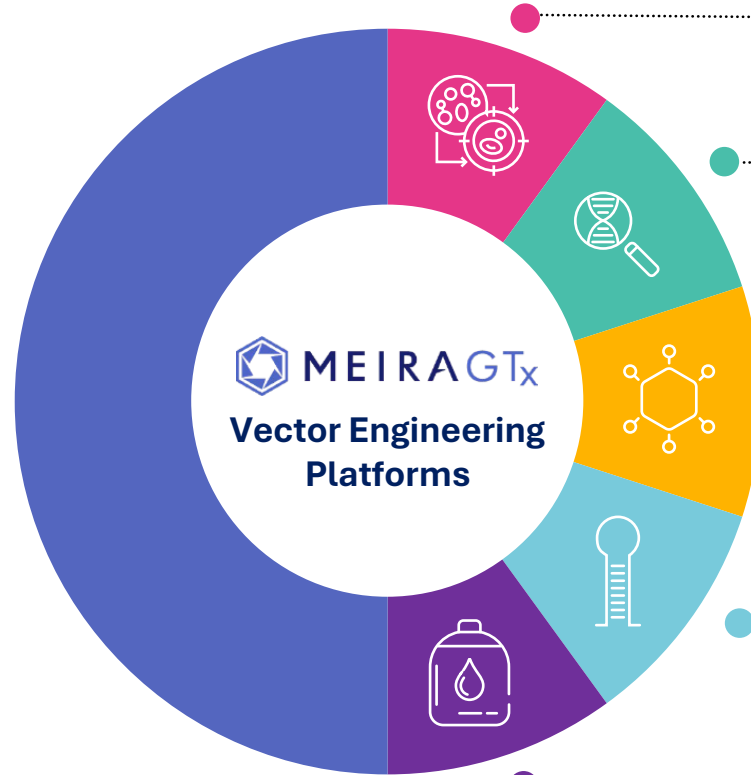
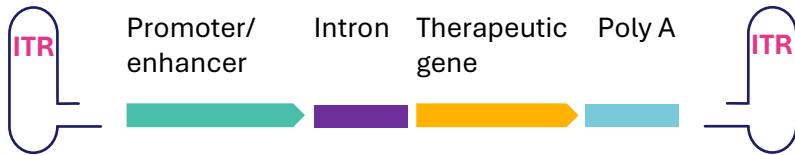
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# Comprehensive vector engineering technologies

Potency & safety optimization and precise control of gene expression

## In-house vector engineering platforms

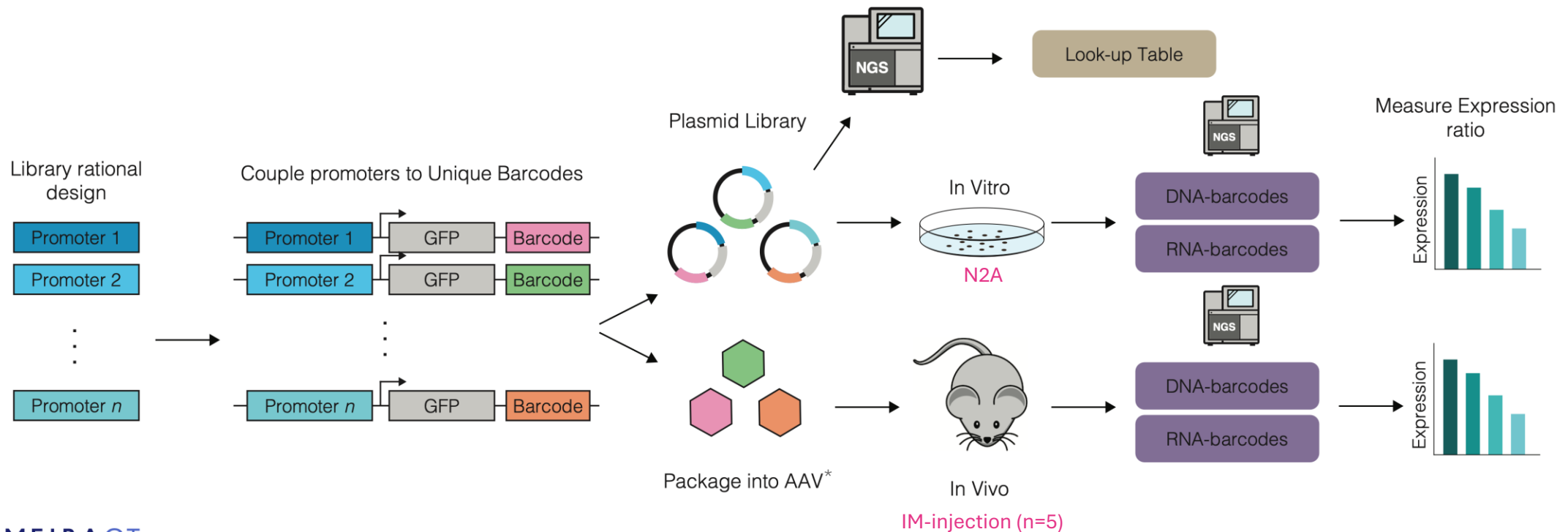
Extensive in-house vectorology capabilities addressing each element of the vector genome sequence



# SynProm – High-throughput platform for screening small potent promoters

Leveraging Oligo synthesis and Deep Sequencing to screen thousands of regulatory elements in any tissue, cell, model and condition.

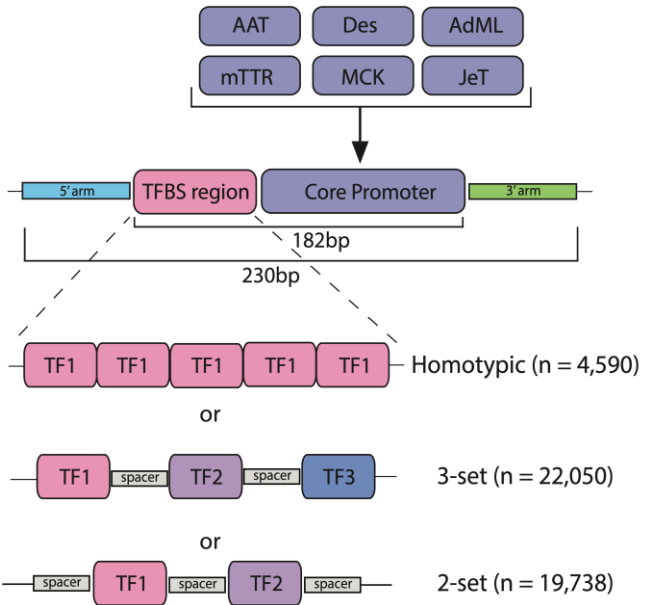
- Compact cis-regulatory elements are crucial for gene therapy, allowing larger payloads, fine regulation of expression and minimize off-target effects.
- Computationally designed library of **200,000+ small promoters (182bp long)** to screen and achieve potent and specific expression in desired tissues.
- Screens inform on which promoter in which tissue with which transcription factors are worth focusing our designing efforts



# MPRA Designs to Inform TFBS Regulatory Grammar

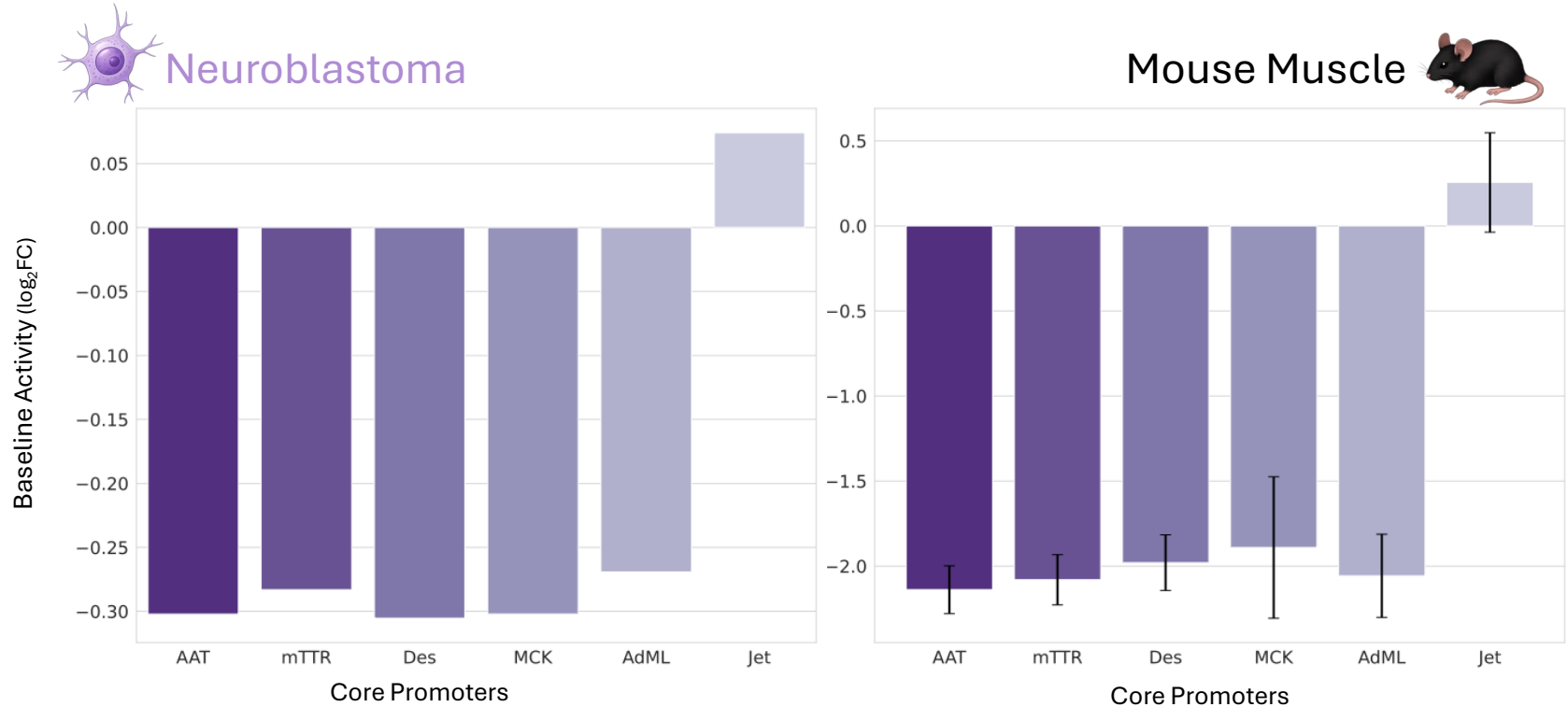
Synprom identifies the impact of each transcription factor binding site on promoter activity

We modelled multiple TFBS domains in combination with six commonly used promoters



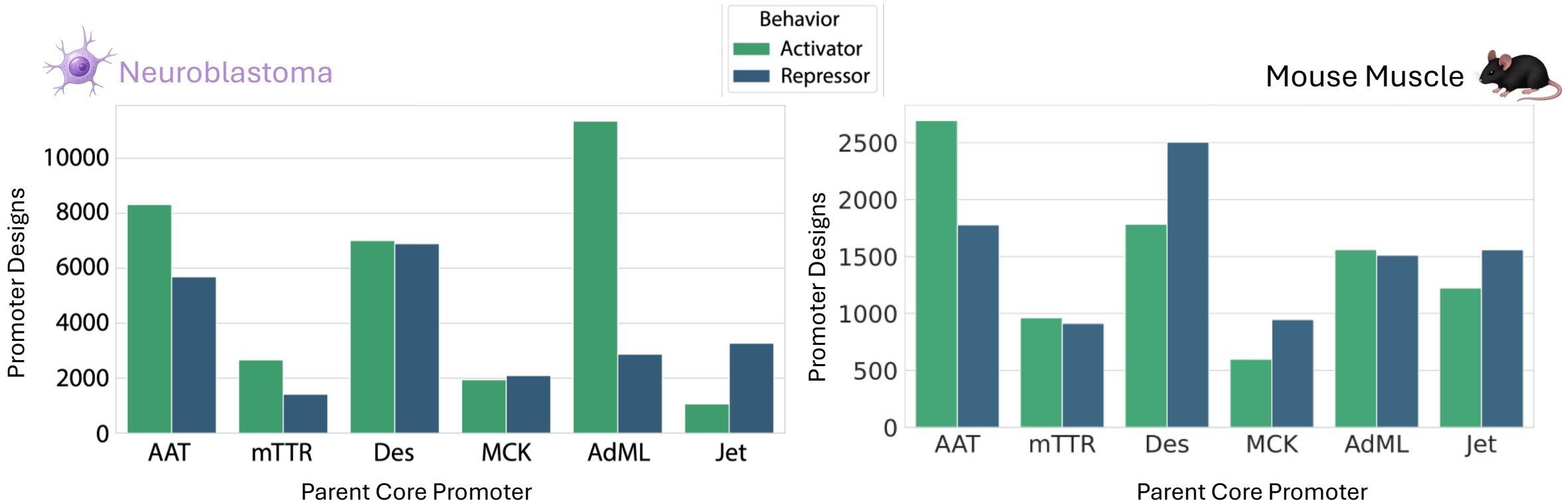
## Activity of un-enhanced (no TFBS) Core Promoters

Baseline core promoters have similar activity in different contexts (same directionality)



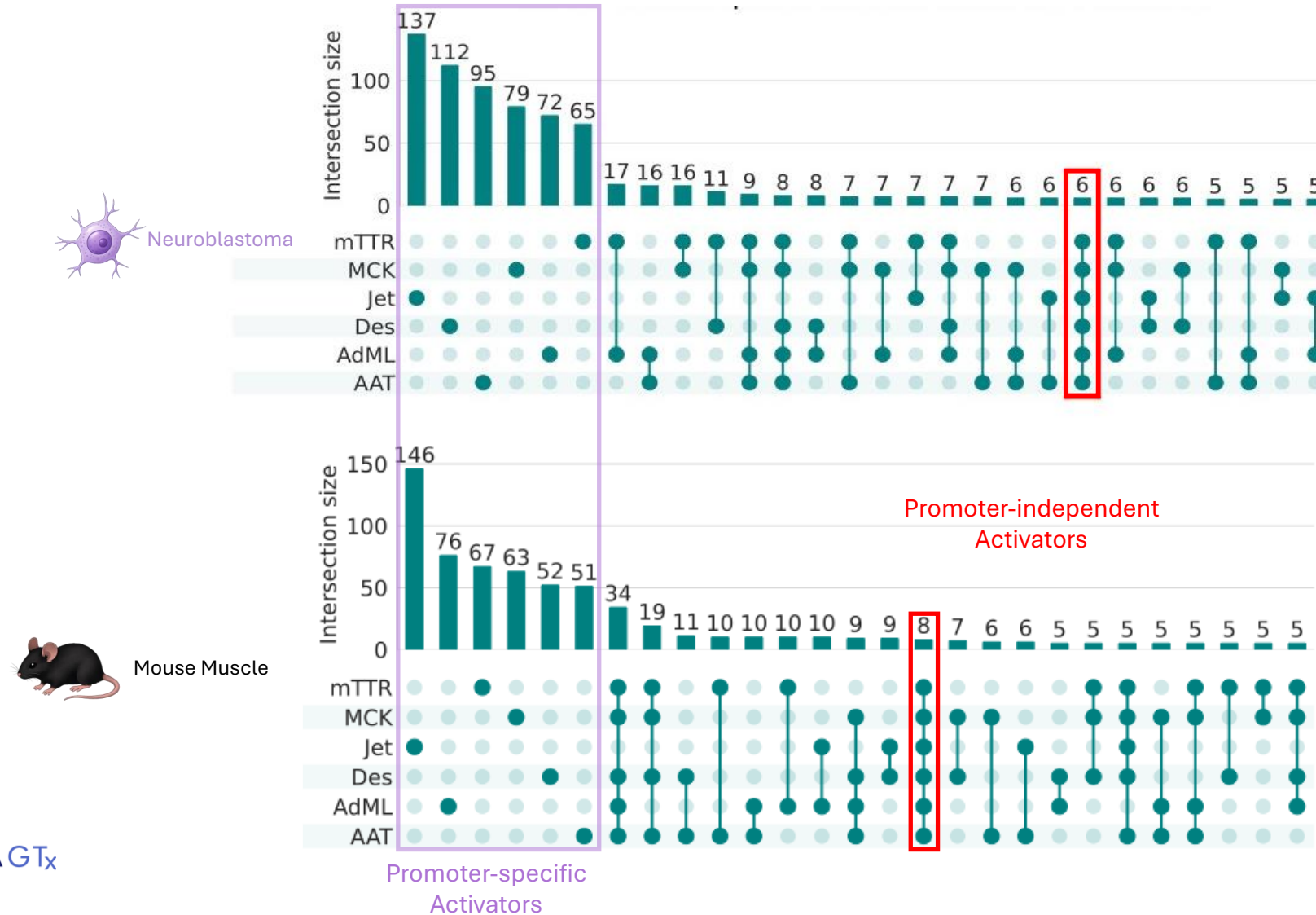
# TFBS–Promoter interaction is influenced by target tissue and molecular ceilings

- Core promoters' activity is increased and repressed by different TFBS combinations.
- Different magnitude but same directionality across tissues
- Weak promoters (e.g. AdML and AAT) are more prone to activation with the addition of TFBS domains.
- Already-strong core promoters (e.g Jet) can be boosted only with a limited number of TFBS



# Strongest TFBS Activators are Tissue and Promoter Dependent

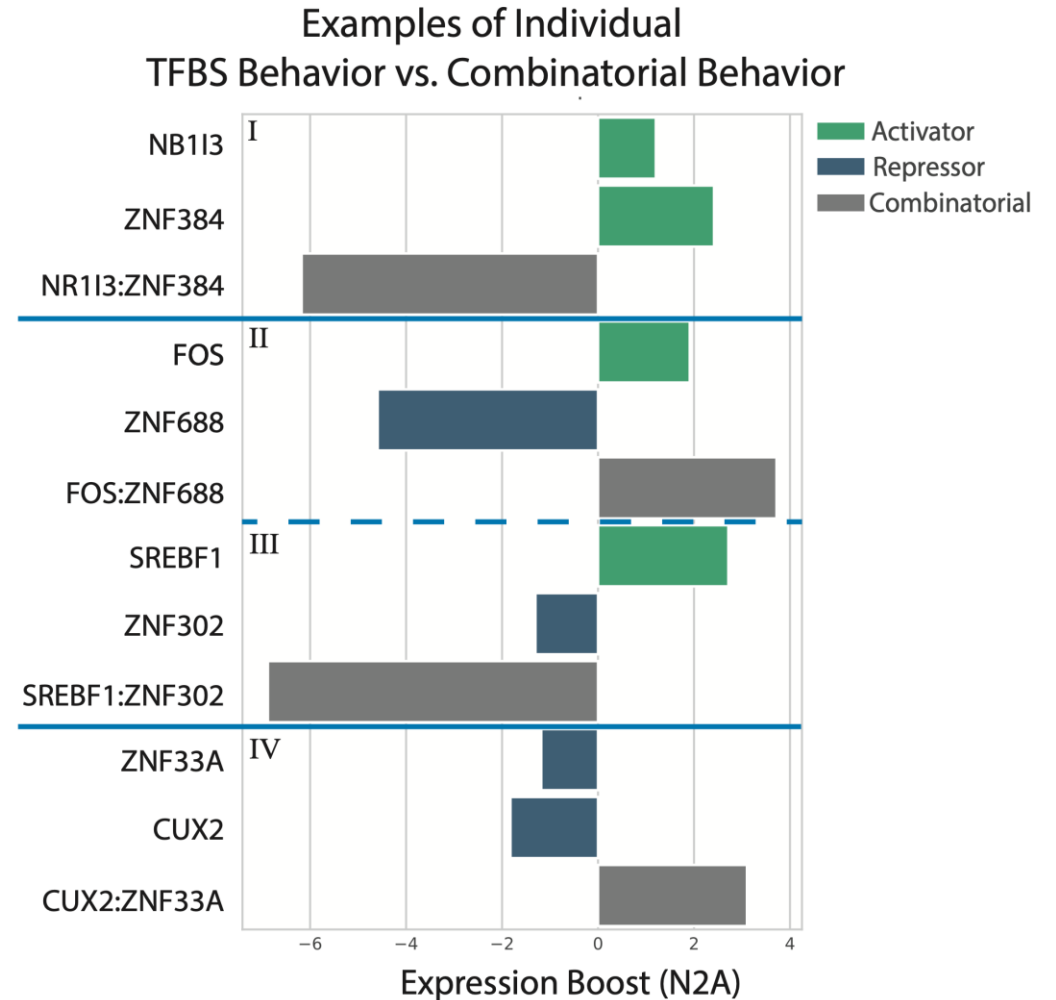
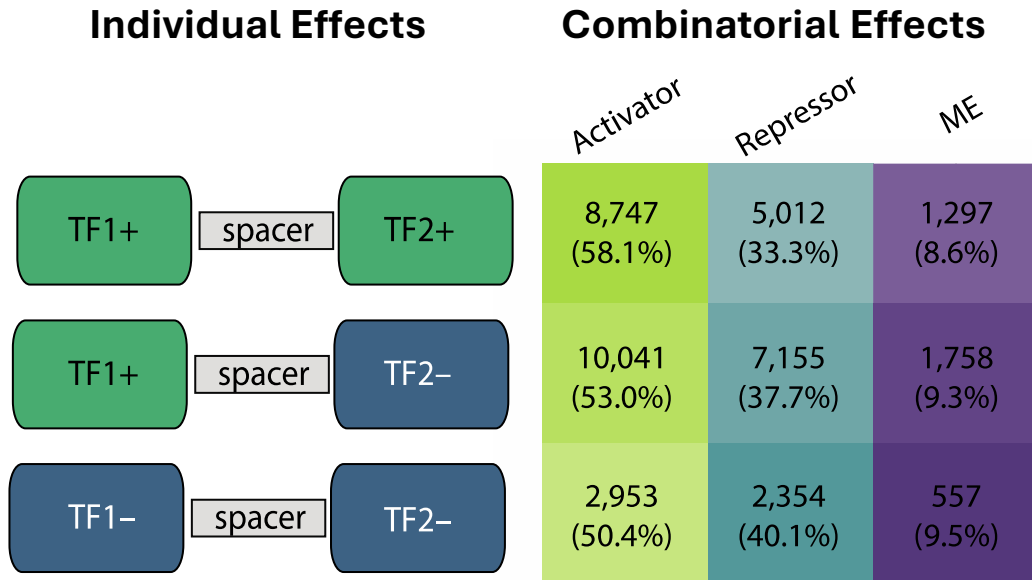
Minimal overlap of TFBS effect across tissue suggest a strong context dependency. Promoter behavior cannot be generalized without modelling tissue/cell of action and core promoter element.

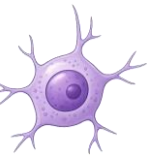




# Promoter potency can't be simply improved with "plug & play" TFBS

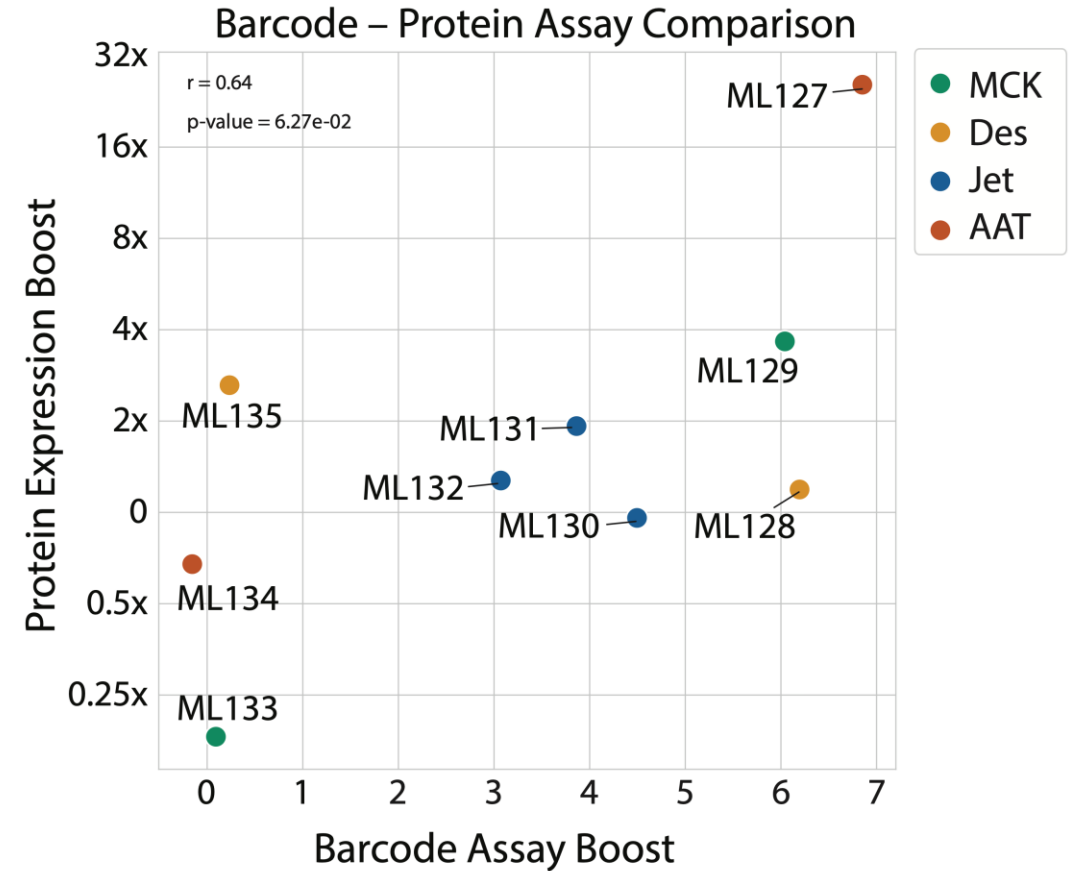
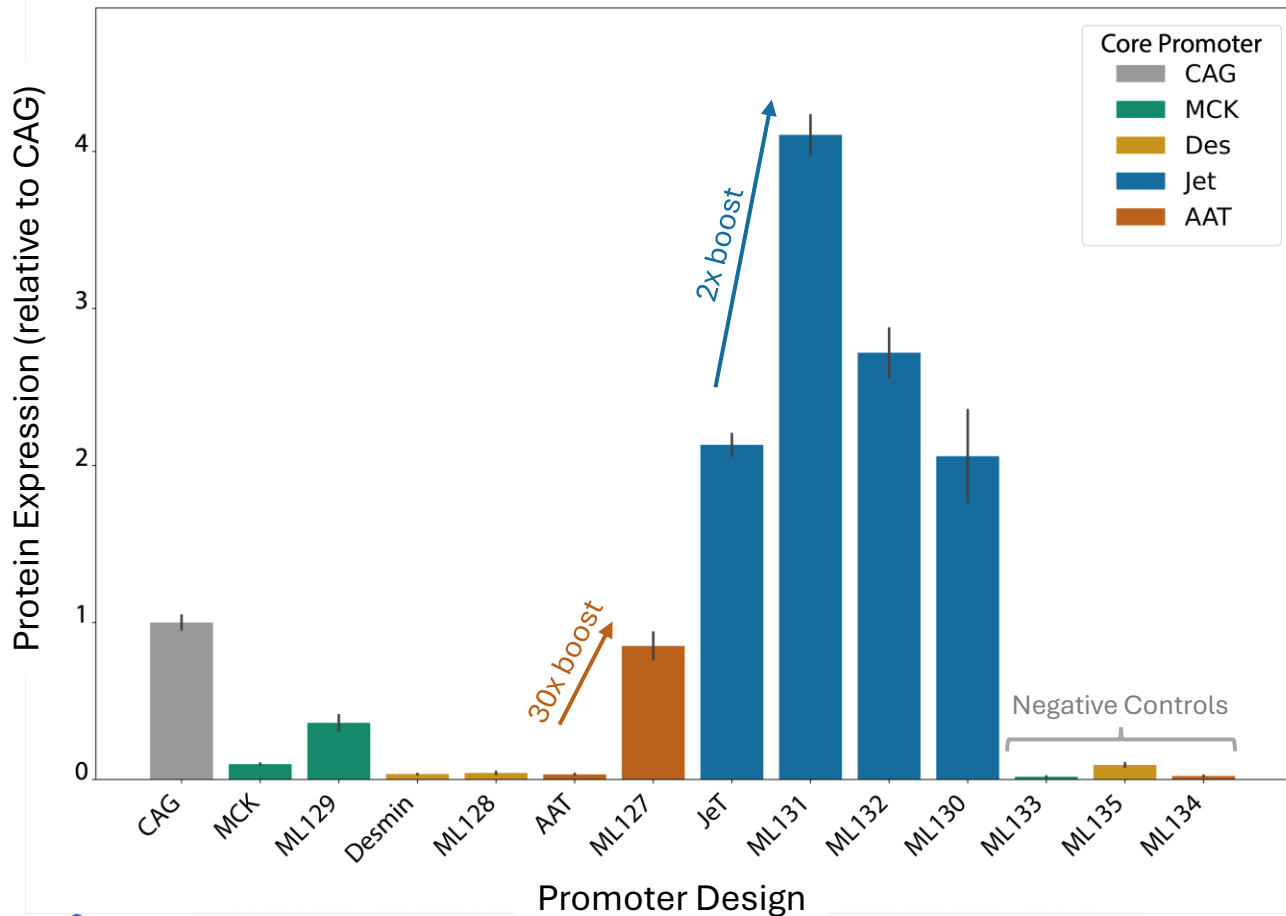
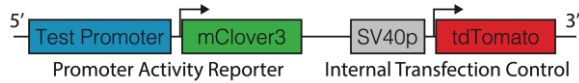
When combining multiple TFBS in promoter rational designs, the activity of an individual site is a poor predictor of its behavior in a composite context





# Inducing inactive promoters for expression in the brain

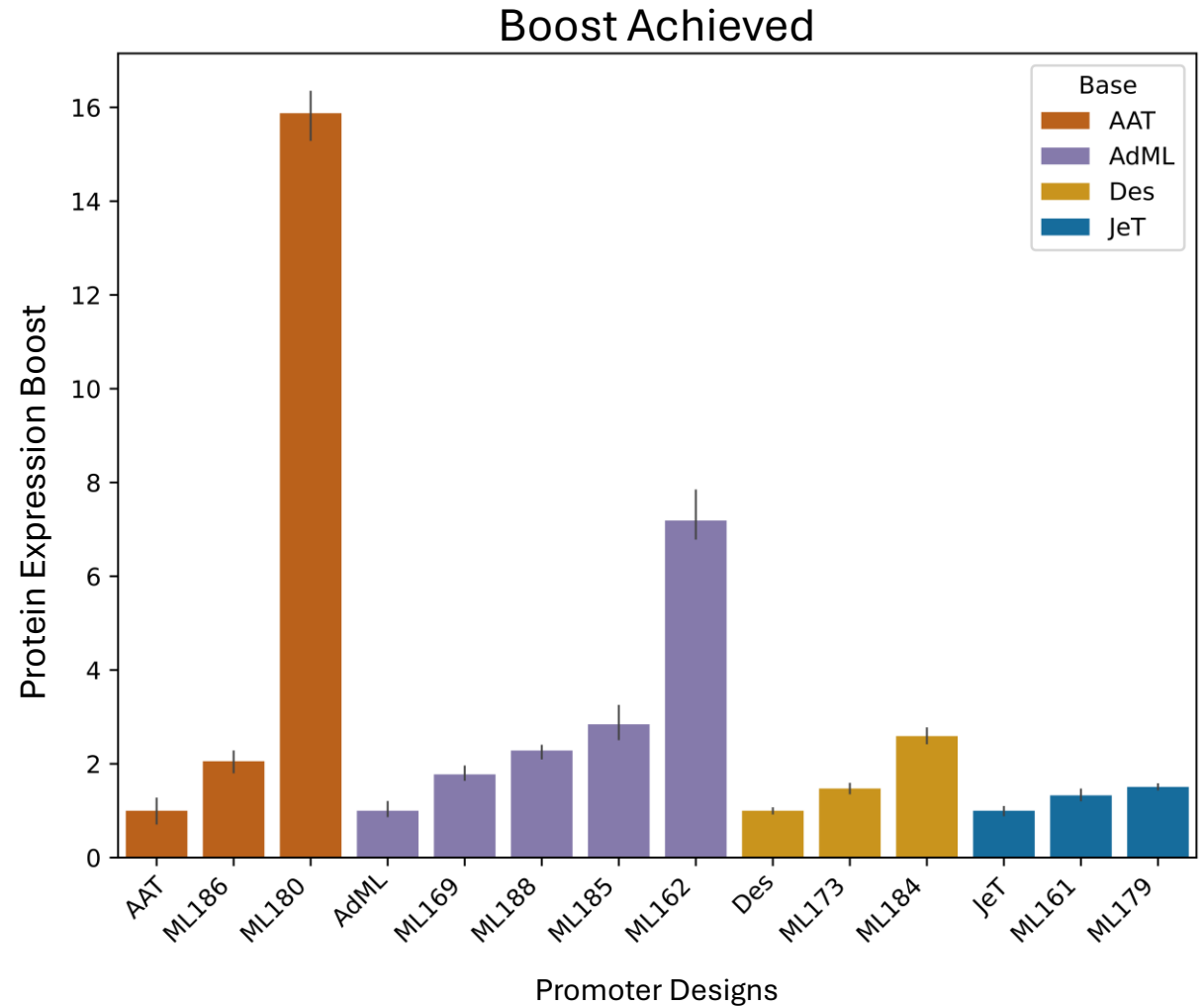
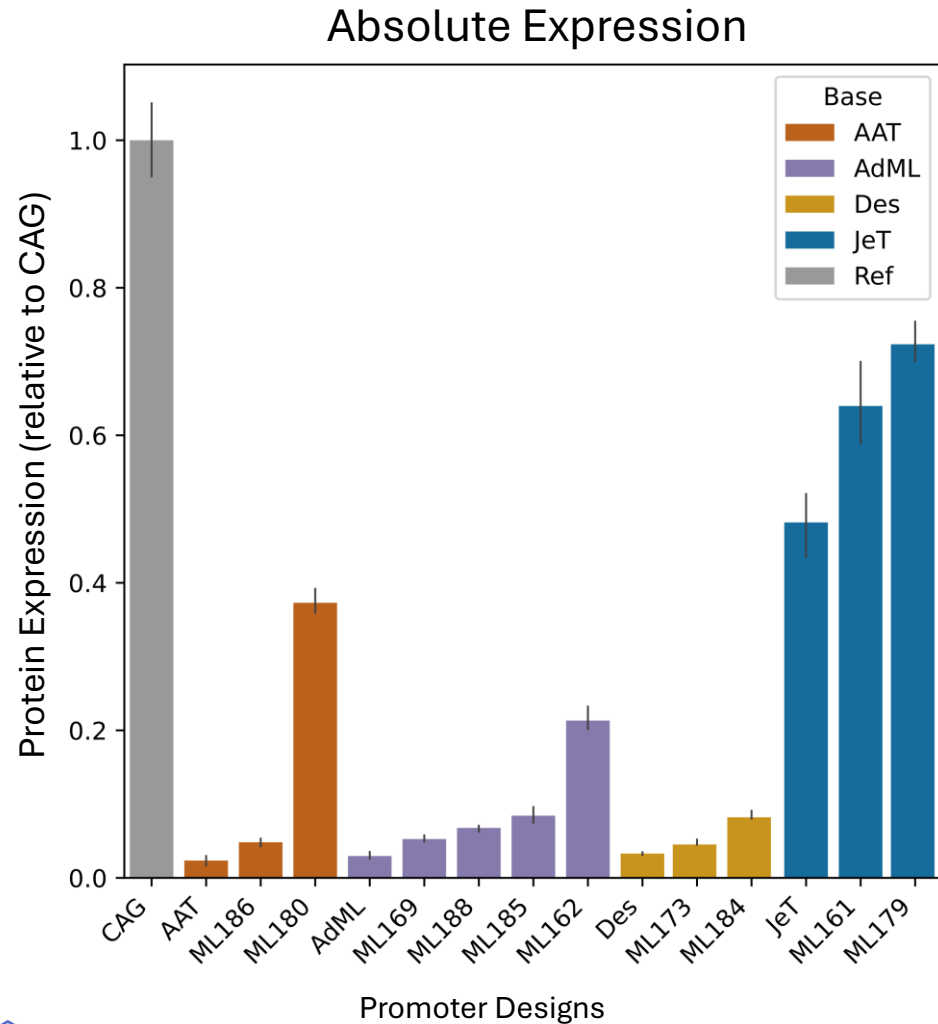
Liver-specific AAT, which is inactive in the brain, can be enhanced up to 30-fold and activated in the brain by incorporating selected transcription factor binding sites (TFBS). Already strong ubiquitous promoters like JeT can be boosted up 2x





# Boosted Muscle Promoters with ~CAG potency and 10% of its size

Core promoters were boosted up to 16x in mouse C2C12 cell lines achieving up to 80% of CAG activity with just 182bp



# TFBS Promoter Platform Delivers Small Potent Promoters

- TFBS-engineered synthetic promoters significantly **outperform gold-standard** promoters like CAG
- Drastically **reduced size** of the regulatory cassette, particularly suited for AAV-mediated muscle gene therapies
- **TFBS optimization** translates to larger payloads at lower viral doses with improved tissue restriction
- MGTX platform's is flexible and applicable to **any tissue/cell** of interest for the discovery of ad-hoc small and potent synthetic promoters
- High throughput screen with a **75% hit-rate** on selected candidates.
- The TFBS-Promoter dataset is a robust foundation for **machine learning-based modelling**.

