Build Better mAbs with Machine Learning and Synbio

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ATUM

ATUM

Quantitative Biology

- Founded in 2003
- Based in SF Bay Area
- ~100 Employees

- Genes/Proteins/Cell lines
- Acquired Migs 2016
- Rebranded to ATUM 2016

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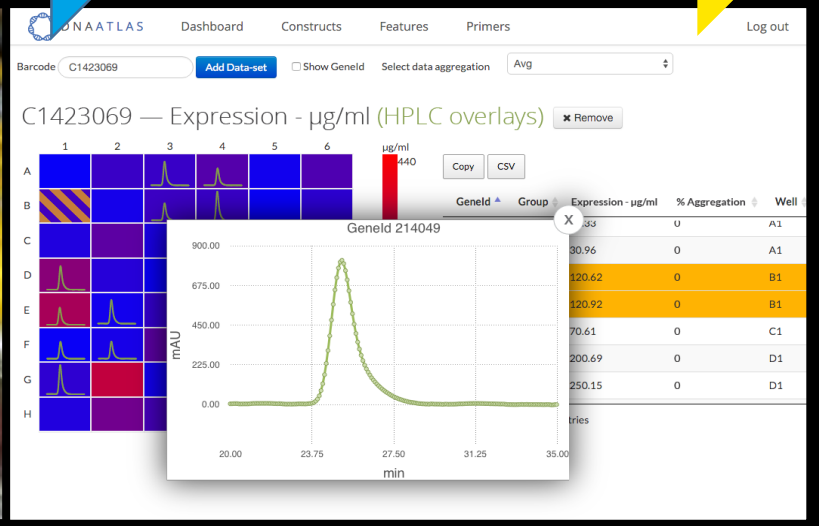
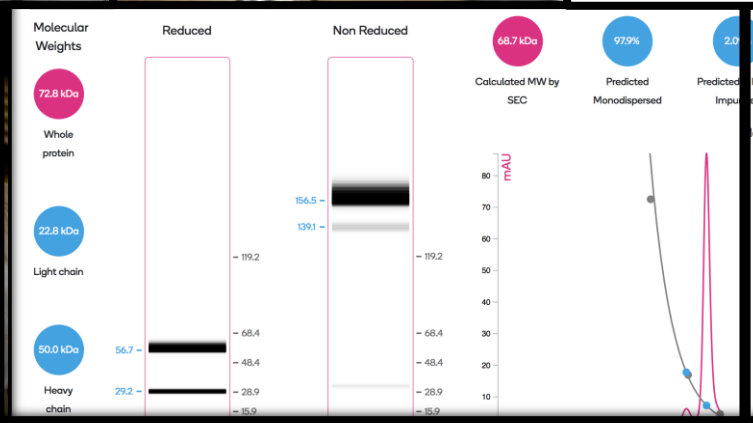
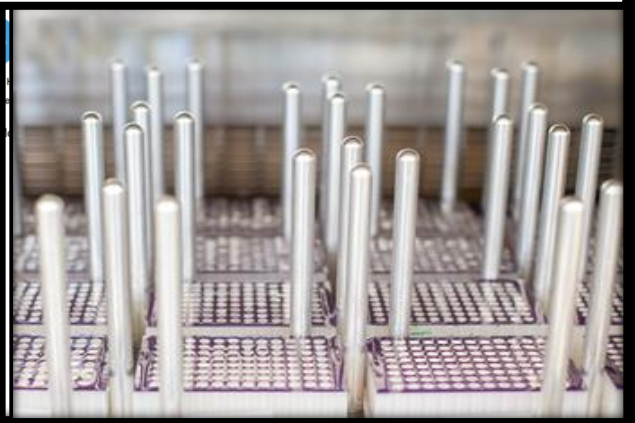
High Throughput Biologics Production

Genes → Proteins → Cell lines







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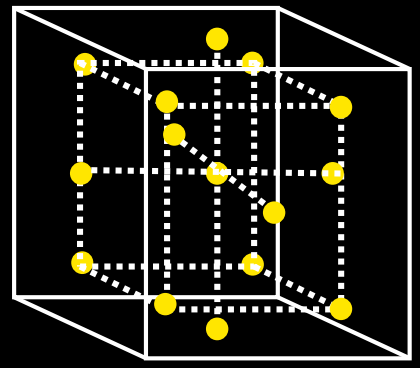
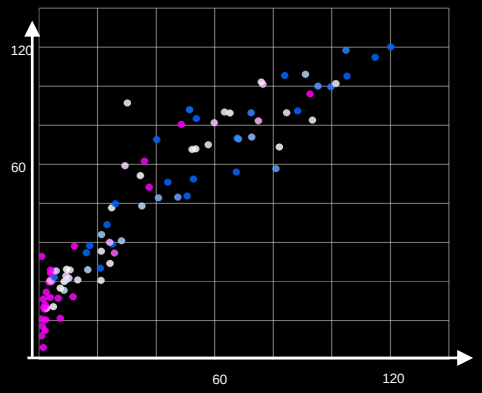
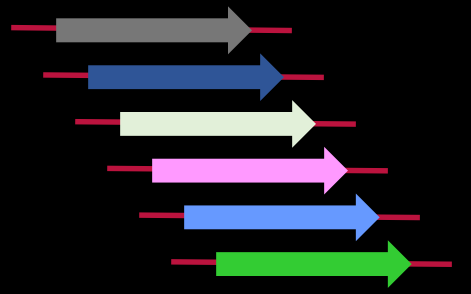
Design of Experiment



Genomic Data

Machine Learning





Synthetic Biology

Biology

Drug Candidate

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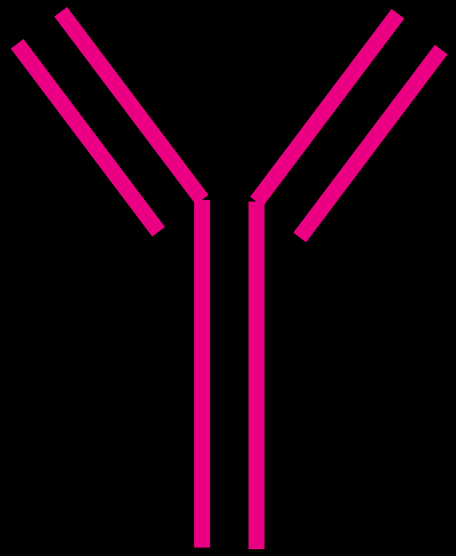
Testing 184 Variants To Capture the Space of 10^{23} Variants

Total available space:

VH = 2^{41} (~10^{12})

VL = 2^{36} (~10^{10})



Starting from commercial molecule

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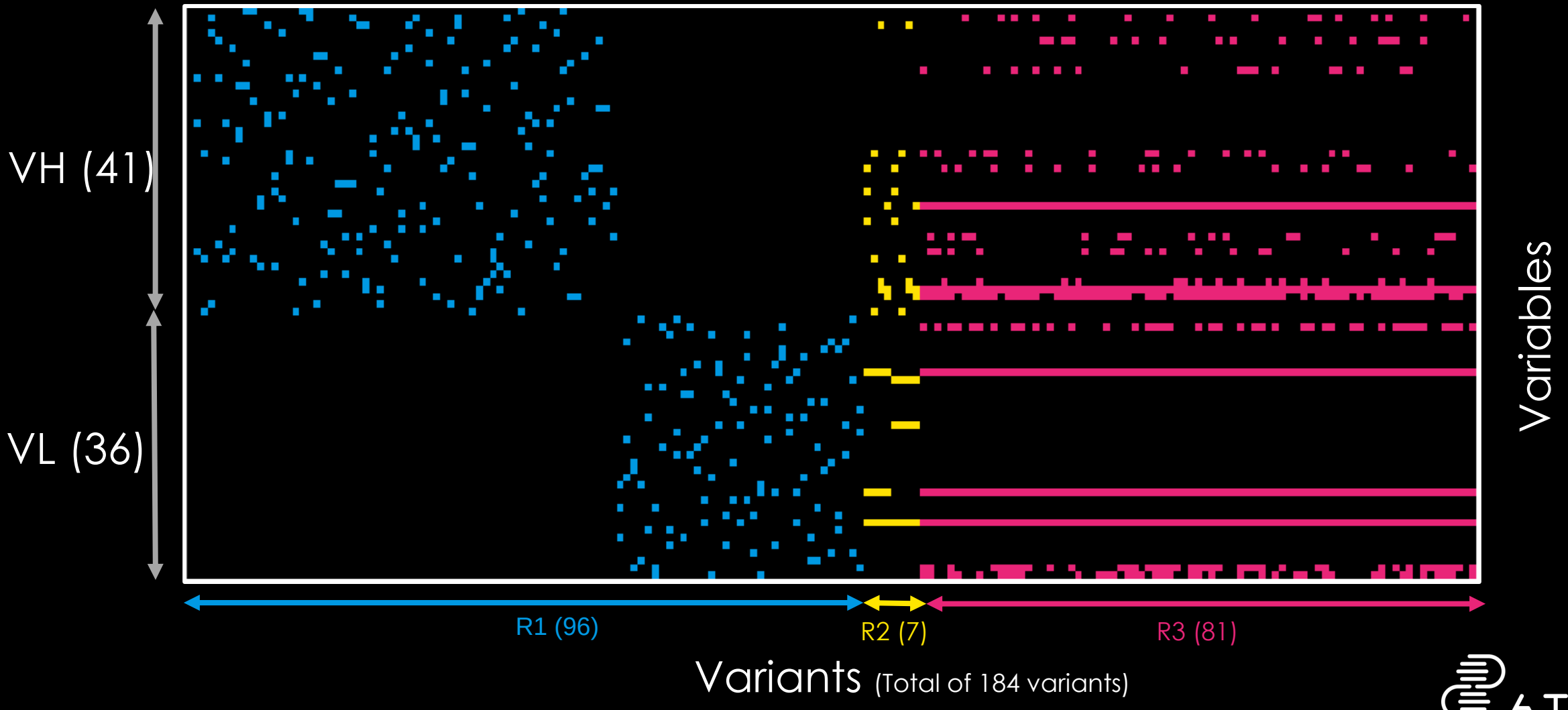
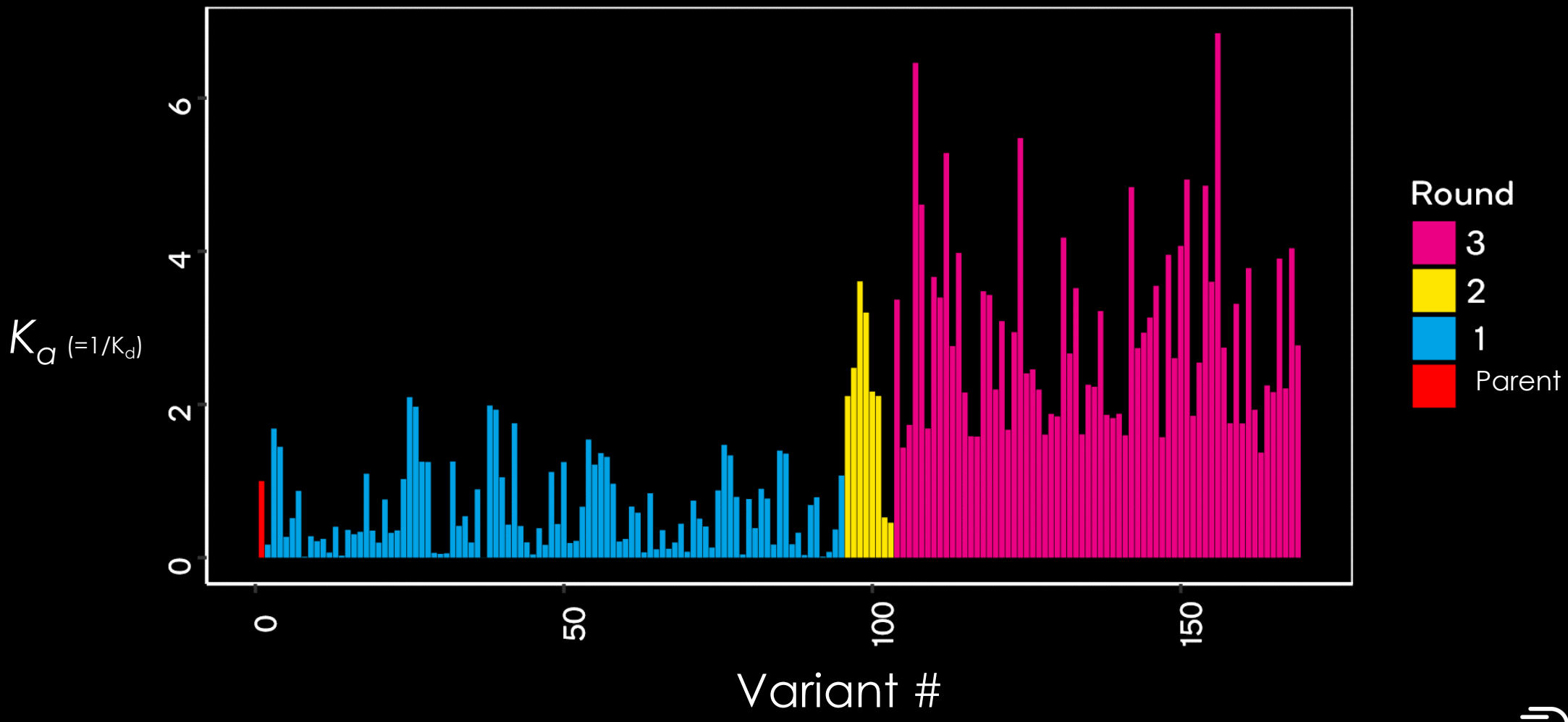
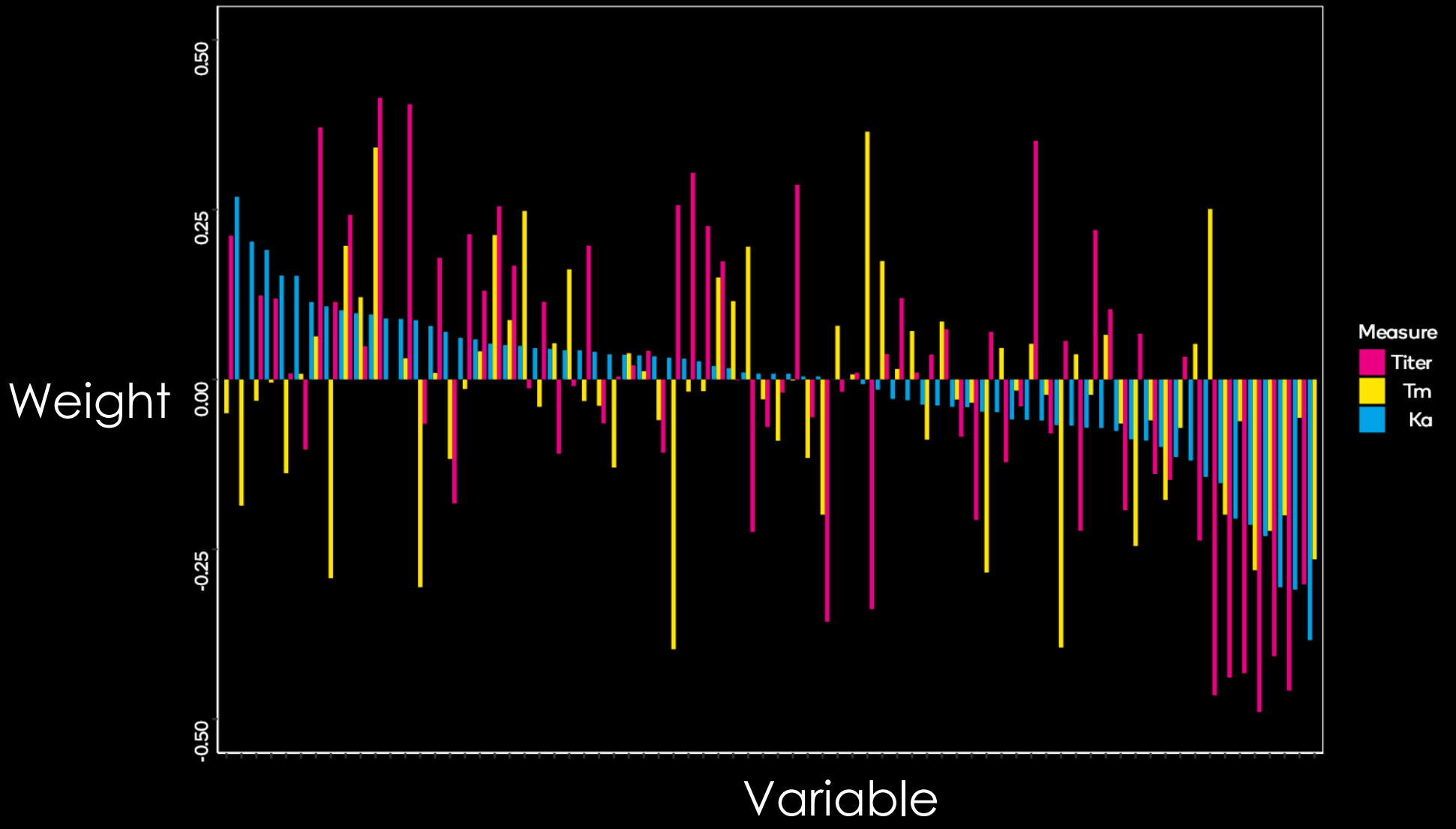
Variable Matrix



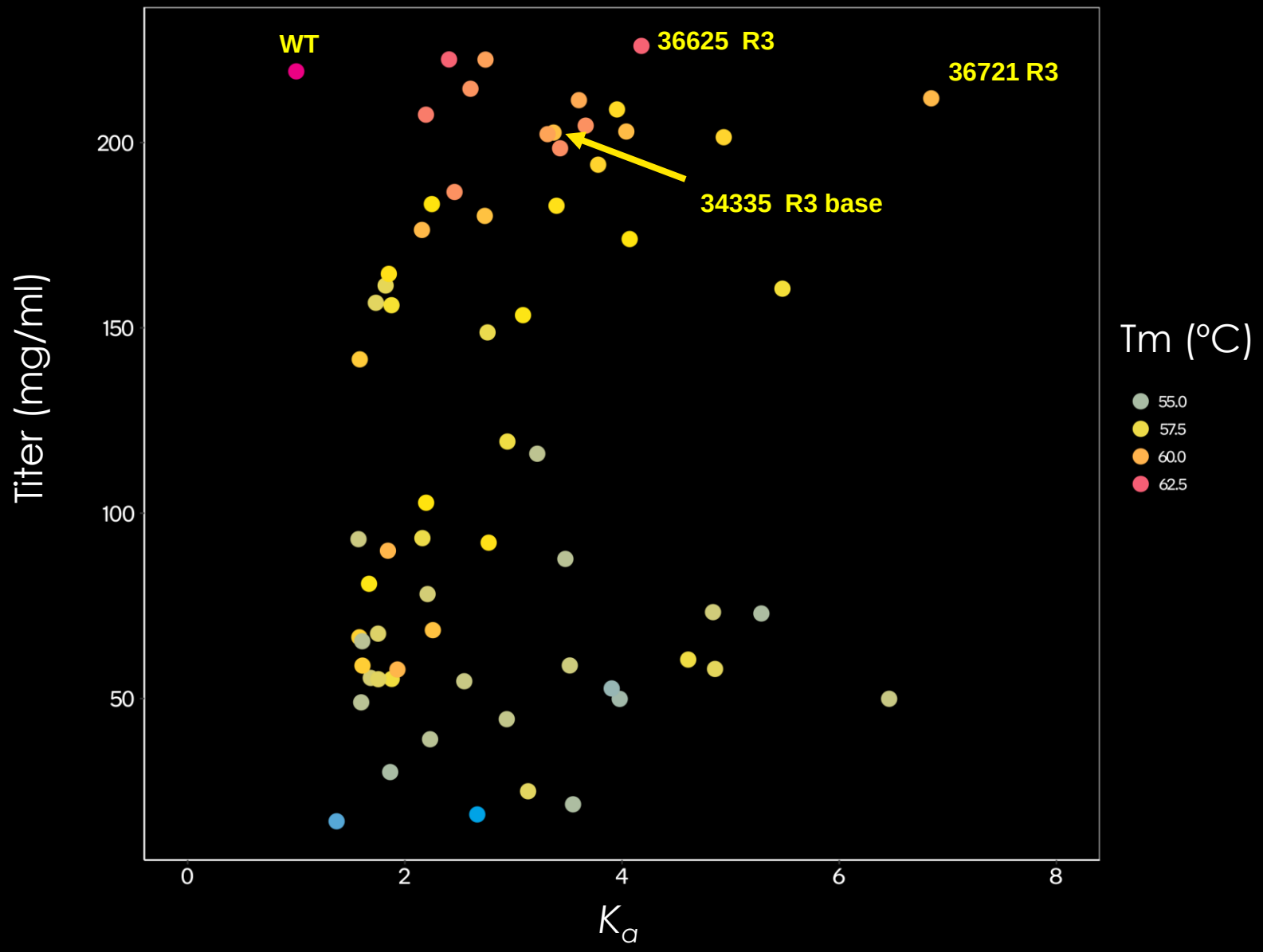
K_a Improvement by Round



Multidimensional Variable Weight Plot

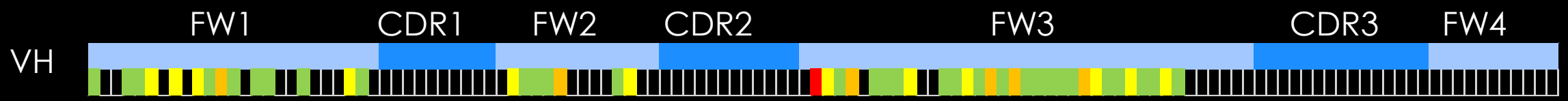


Multi-Dimensional Improvements(R3)



Clone	Titer (mg/L)	Tm (°C)	Kd (nM)
36721	212	59.8	0.16
36625	226	62.4	0.25
Parent	219	63.8	0.98

mAb Framework Protein Engineering



2 options, 3 options, 4 options, 5 options on 2 leads: FW1, FW2

Total explored diversity: ~2x 10^{19}.
Total number of genes made: 96 – The Power of DoE

Measured output:

- Titer post purification
- Tm
- Kinetic off-rate

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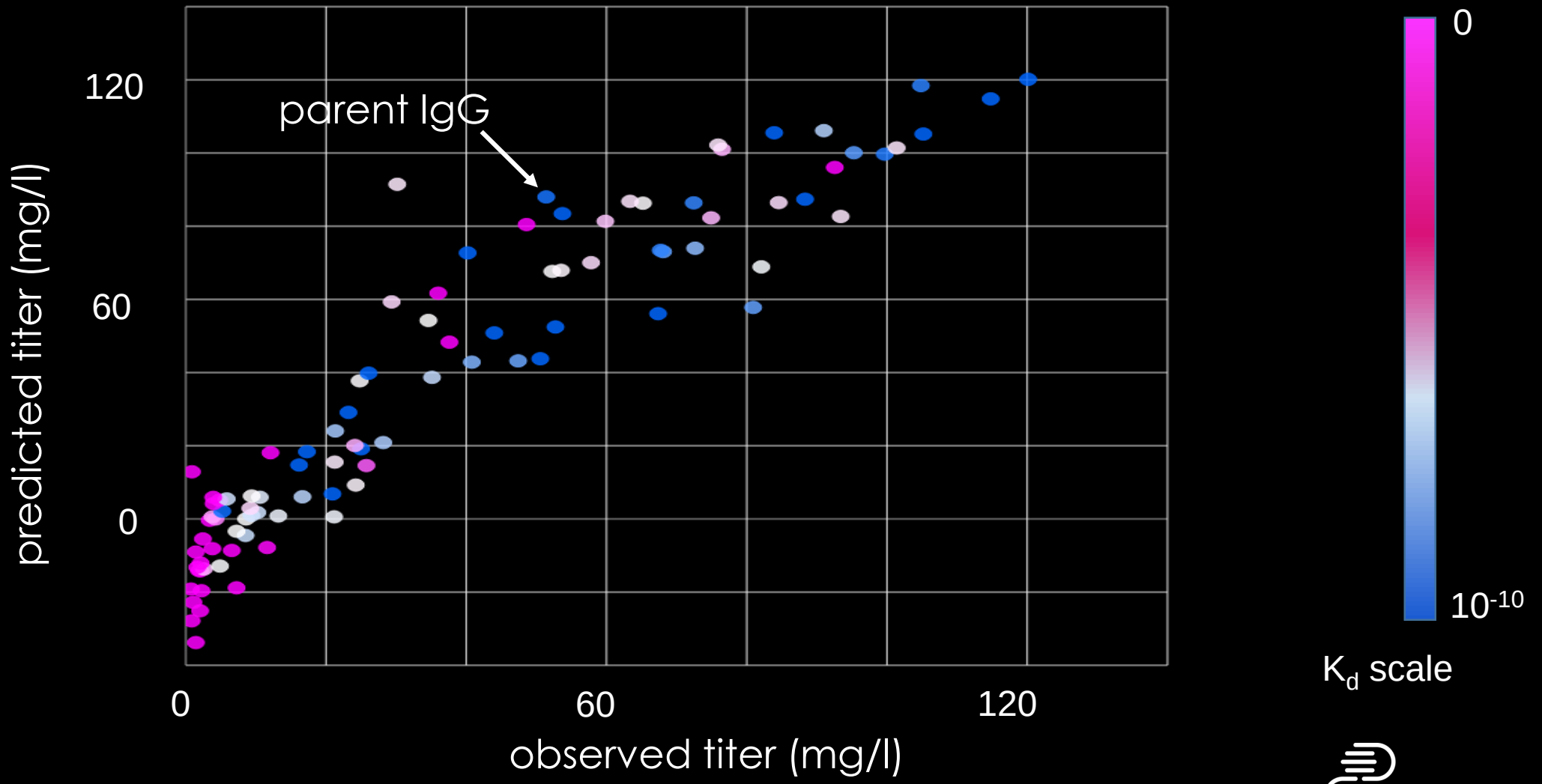
Modeling of Titer



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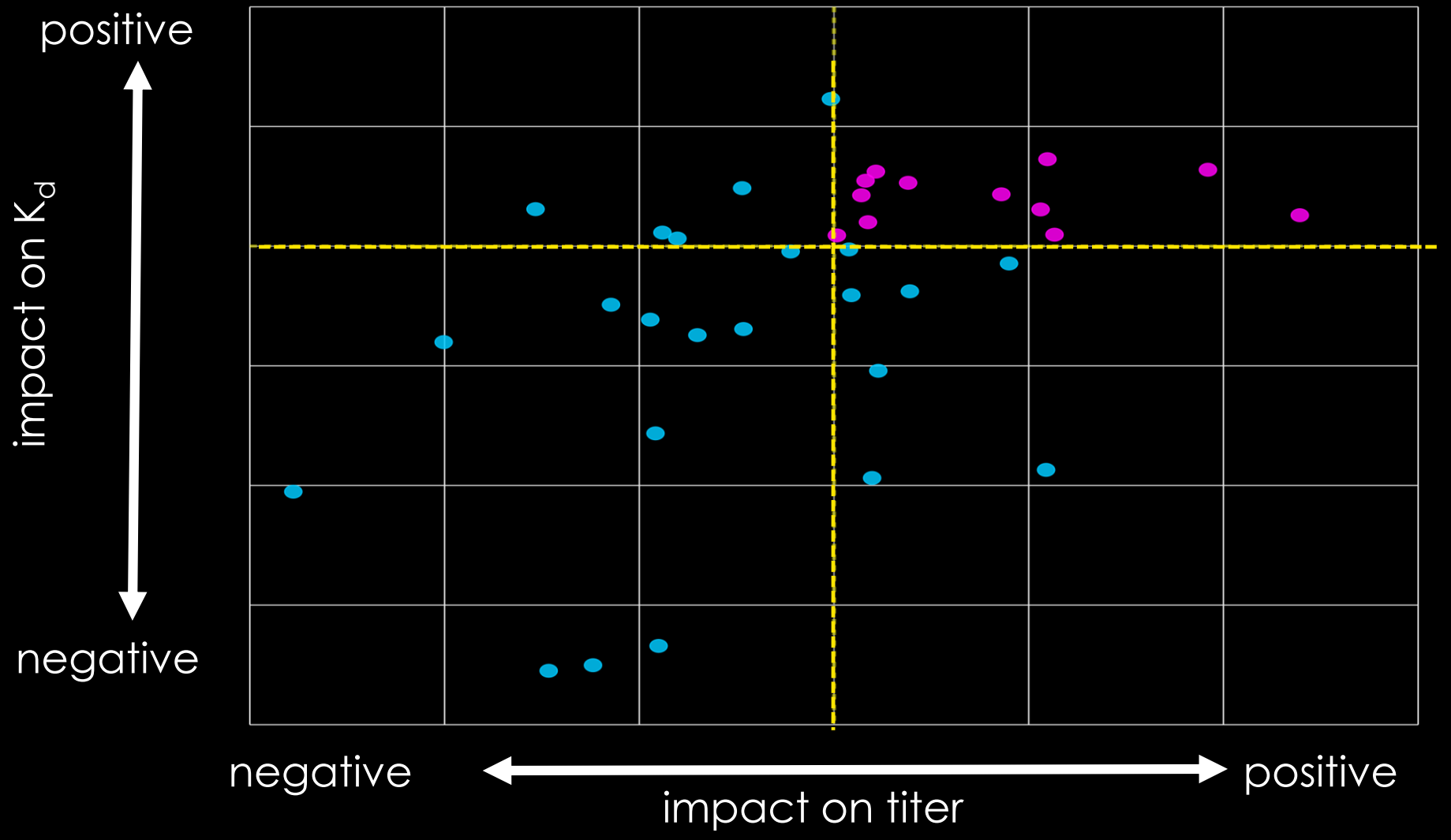
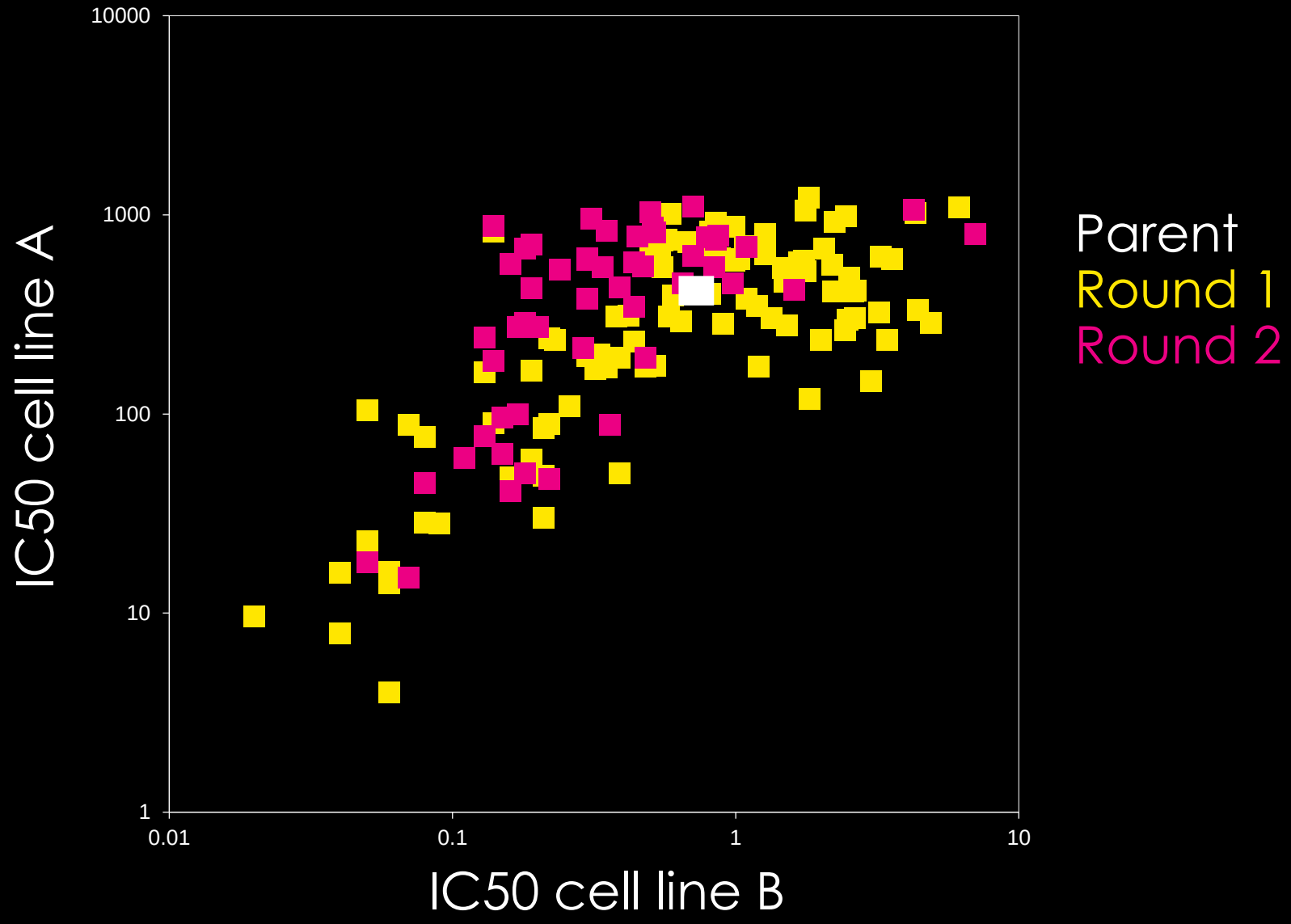
Impact of Sequence Variables



Cell Based Assay (log log)



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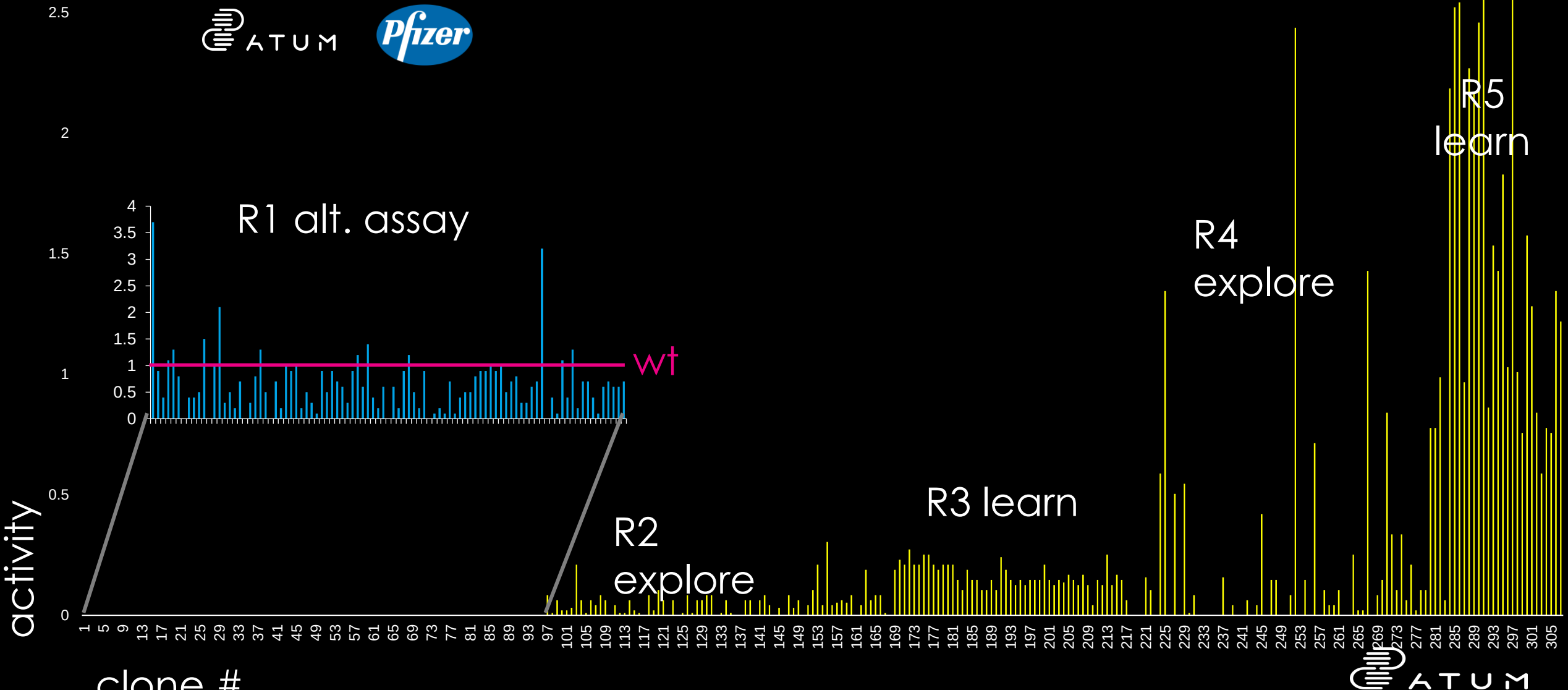
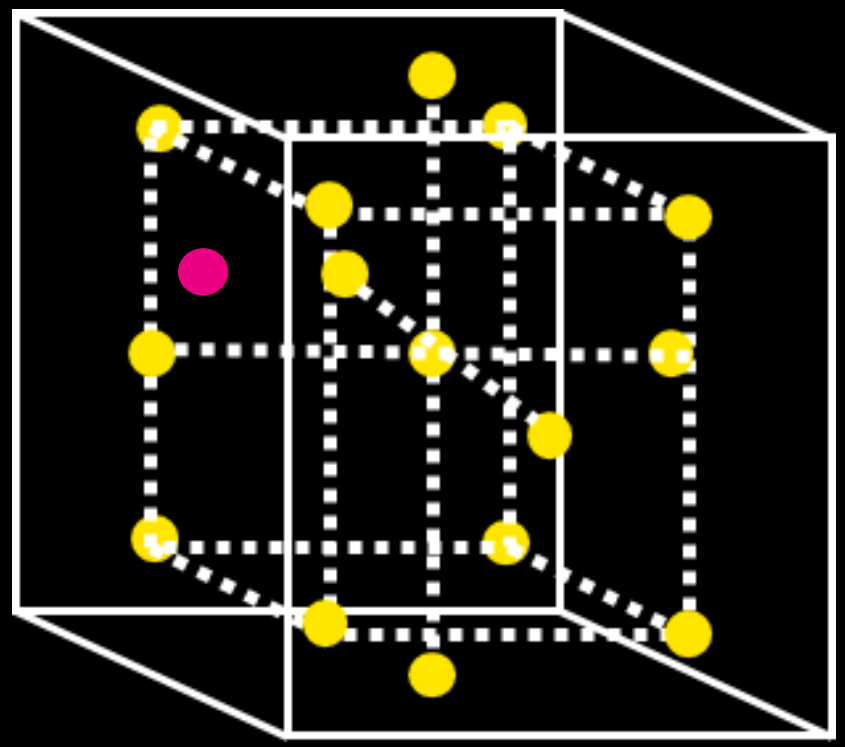
Case Study - Biocatalysis



Life is Multidimensional



Winner

- ✓ Cell binding
- ✓ Antigen binding
- ✓ SEC HPLC
- ✓ Tm stable
- ✓ Humanized
- ✓ …And more

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Biology – Just a String of ACGT

Coding, Introns, motifs — Gene

+

Activity, Stability, Solubility — Protein

+

Promoters, order, RBS — Pathway

+

Chaperons, Copies, Locations — Genome

+

Temp, pH, O_2, Cell Line — Environment

Output

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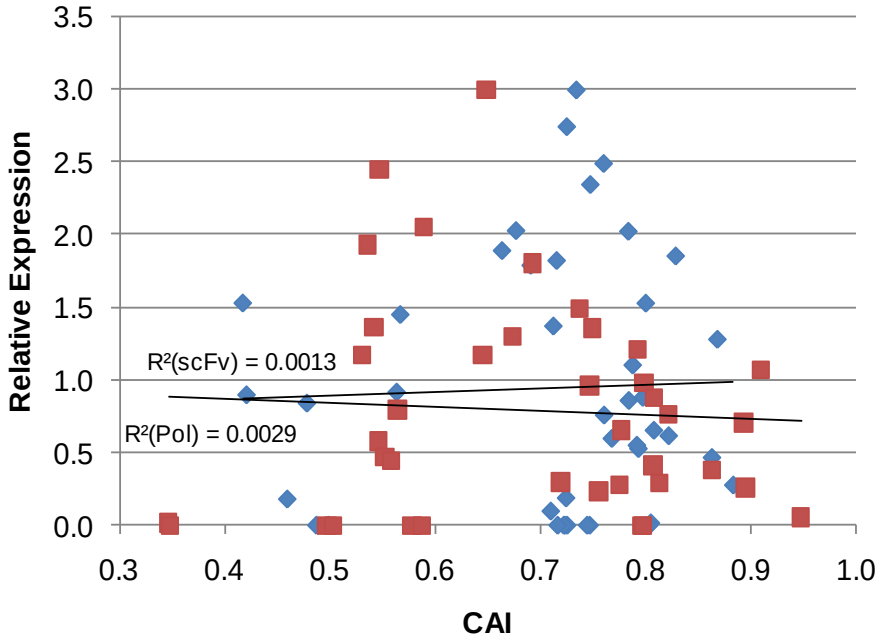
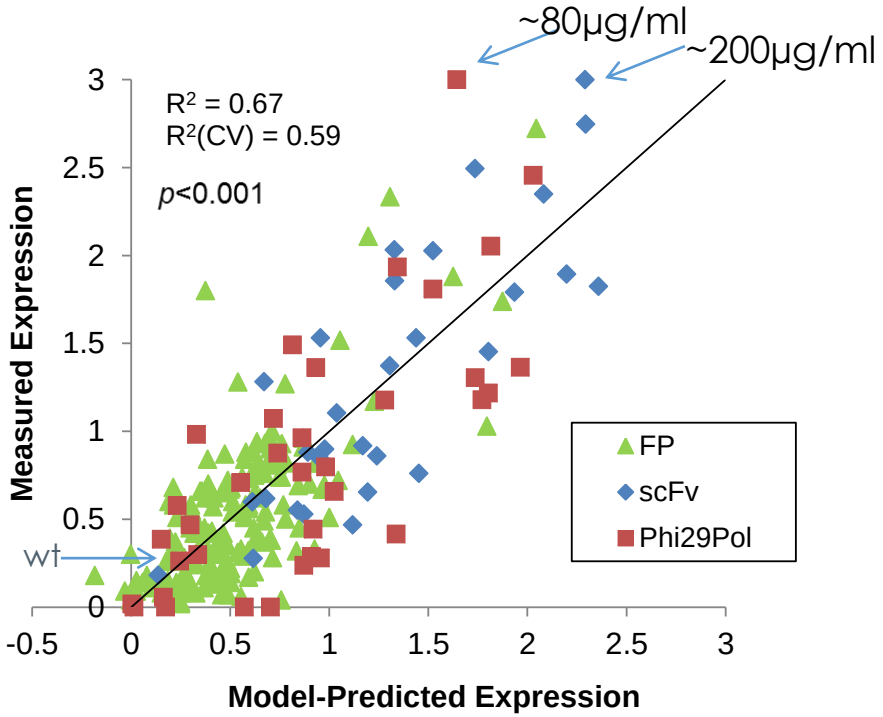
Case Study - Codon Optimization





- Prot Exp Purif 2012 83(1):37-46. Gustafsson, *et al.*
- PLoS ONE 2009 4(9):e7002. Welch, *et al.*

OncoMed PHARMACEUTICALS

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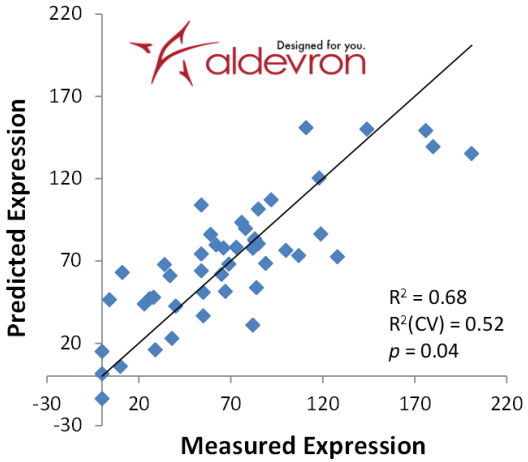
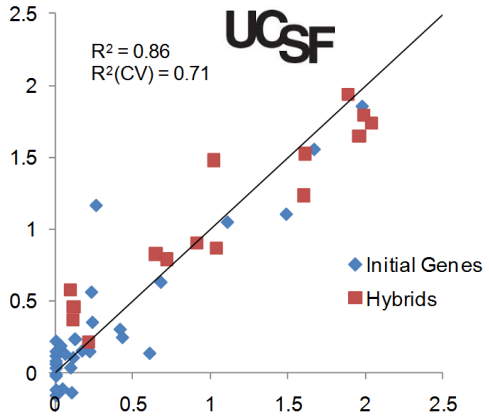
Custom Gene Design Algorithms

>50 host organisms interrogated to date

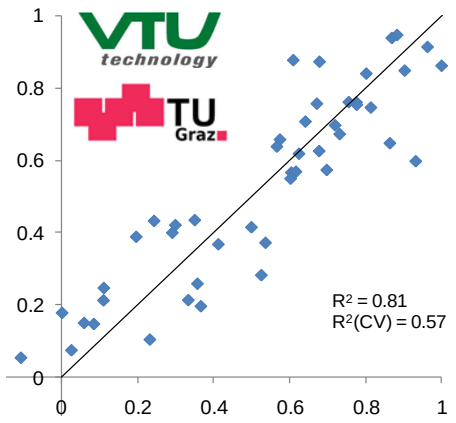
Baculovirus/*Sf9*



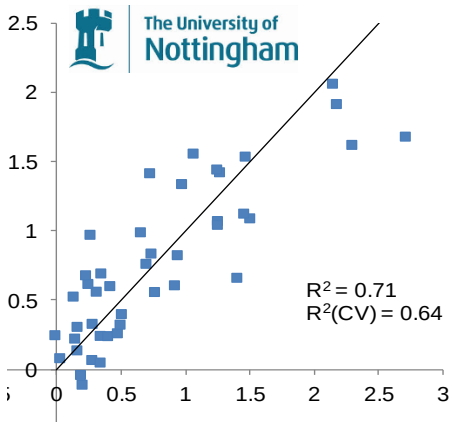
S. cerevisiae



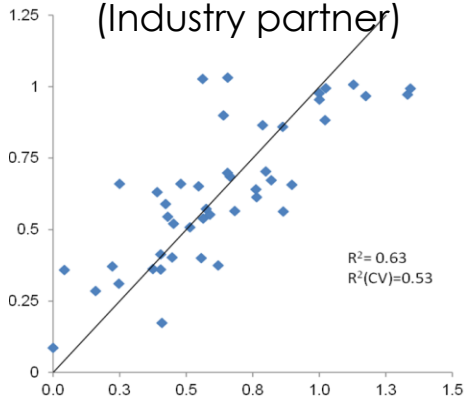
P. pastoris



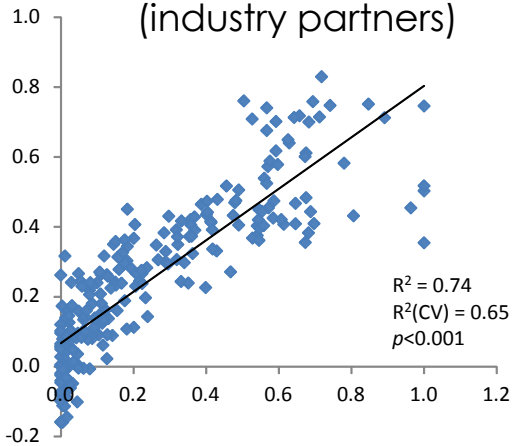
Clostridium sp.



Corn
(Industry partner)



Mammalian Cells
(industry partners)



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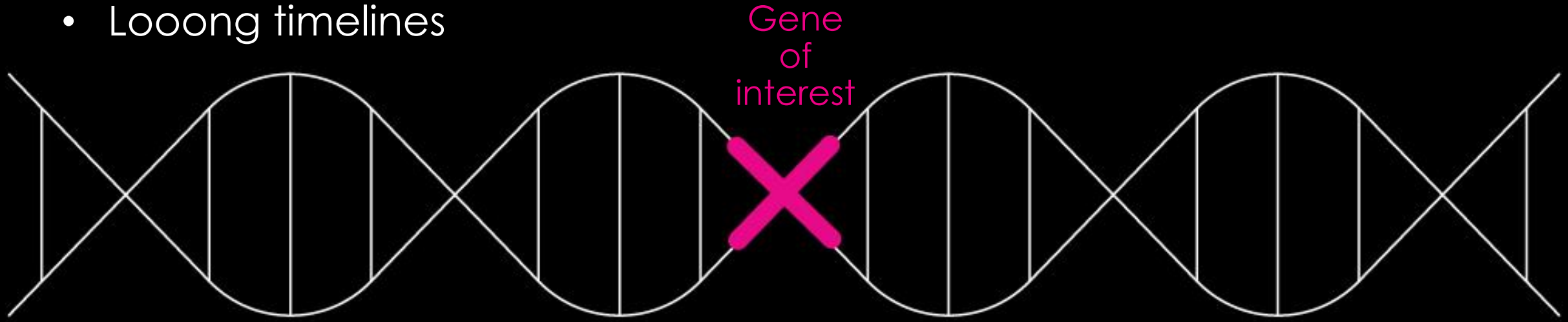
Making Stable Cell Line is Hard

Traditional technology

- Integration rate: <<1%
- Amplification often required
- Concatemer formation
- Transgene rearrangement
- Screening many clones
- Looong timelines



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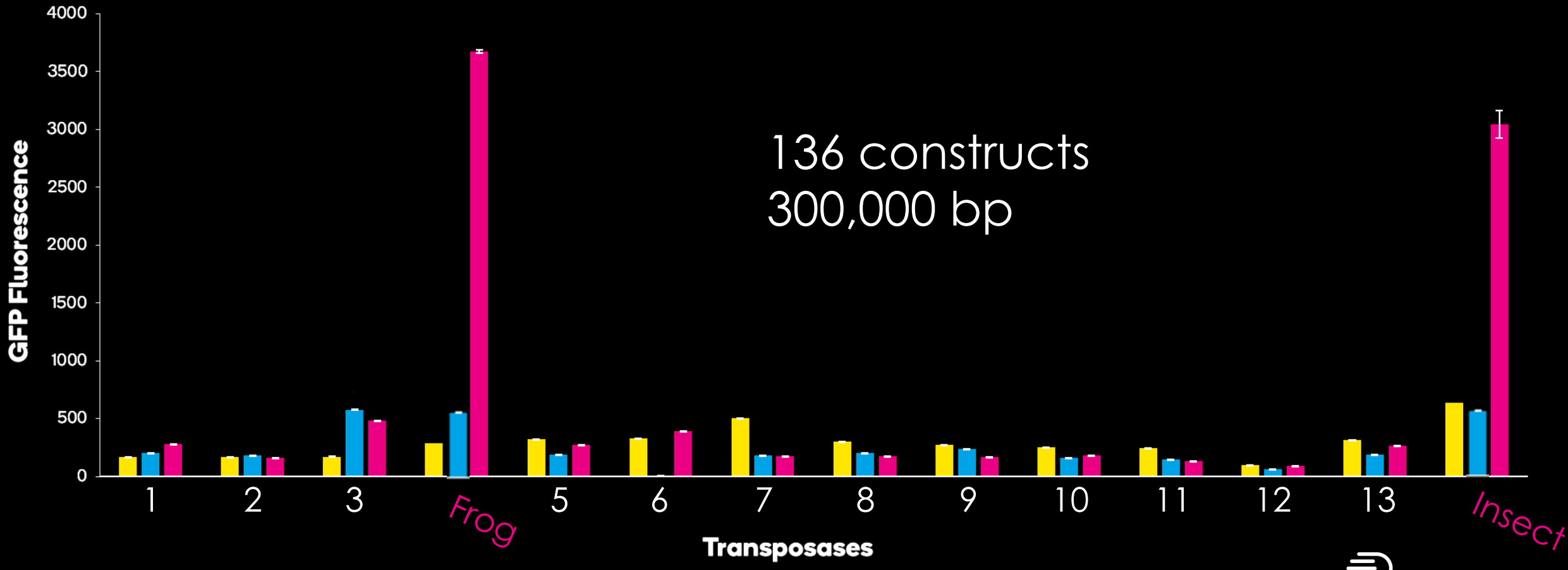
Two New Transposases - Leap In™

Activity tested in CHO K1 and yeast



136 constructs
300,000 bp

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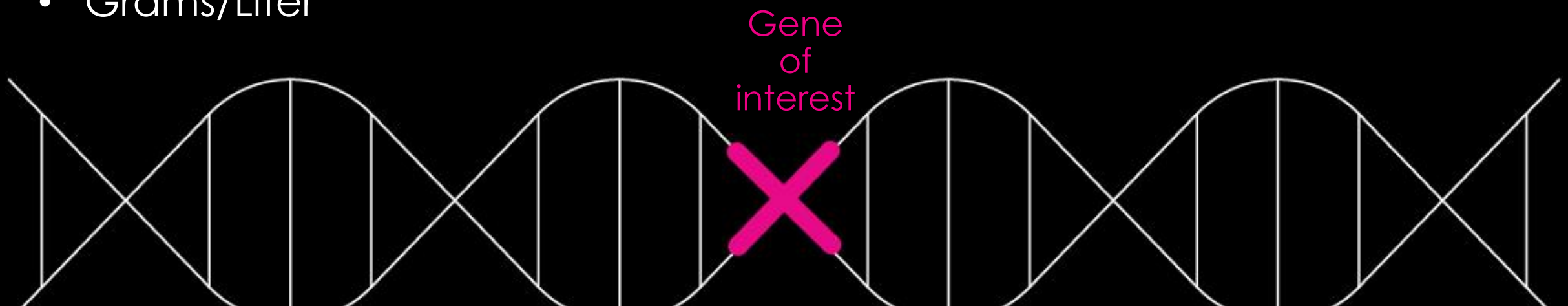
Transposase Advantages

Transposase technology

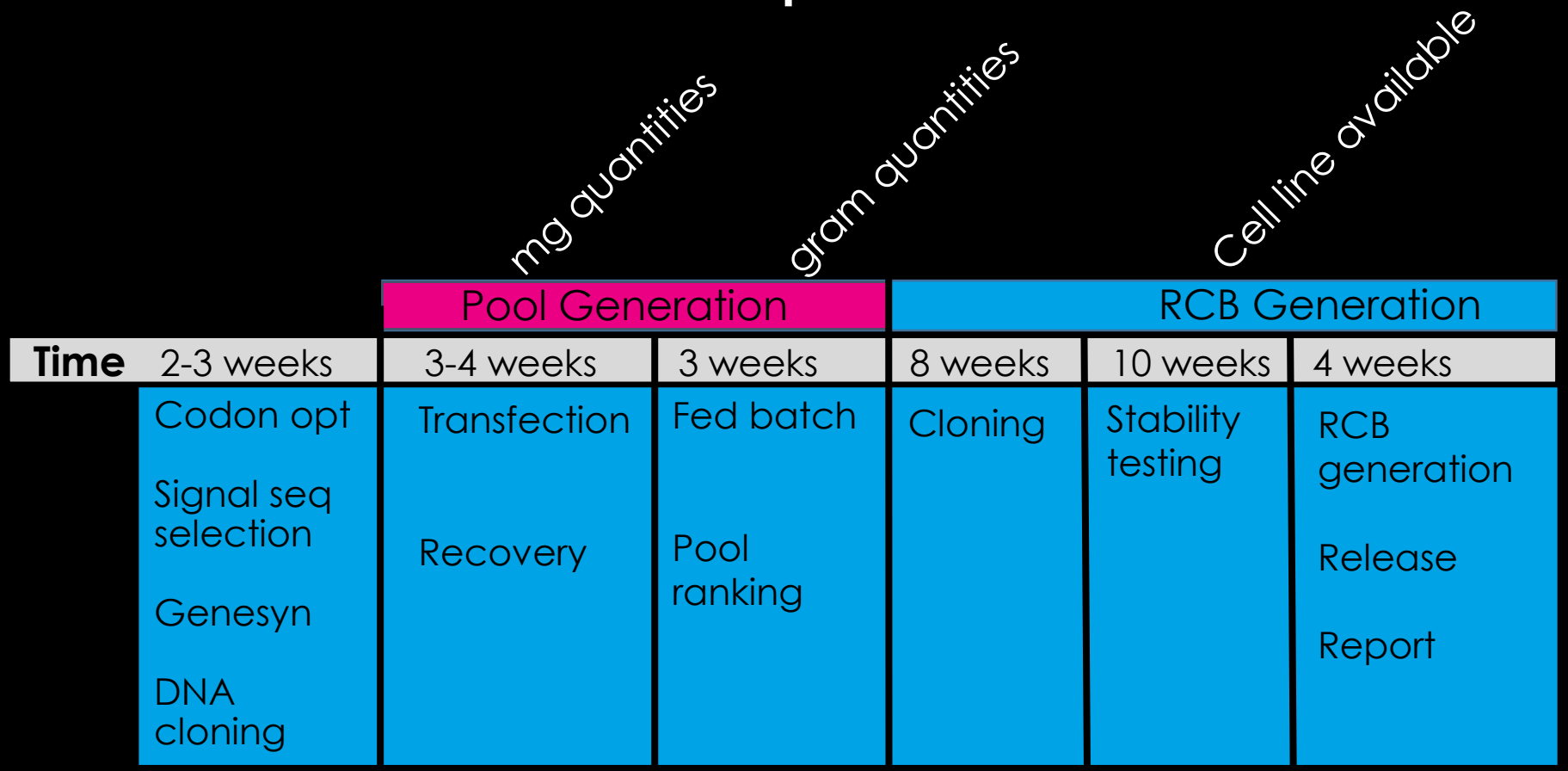
- Integration rate: >90%
- 2-40 copy integrations / genome
- Structural integrity
- Unlimited payload
- Unique locations
- Footprint-free excision
- 14 days from transfection to stable pool
- Grams/Liter

Traditional technology

- Integration rate: <<1%
- Amplification required?
- Concatemer formation
- Transgene rearrangement
- Loooong timelines



Cell Line Development



- HD-BIOP3 GS null CHOK1 (Horizon Discovery)
- DG44 (Columbia University)

Thank You

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