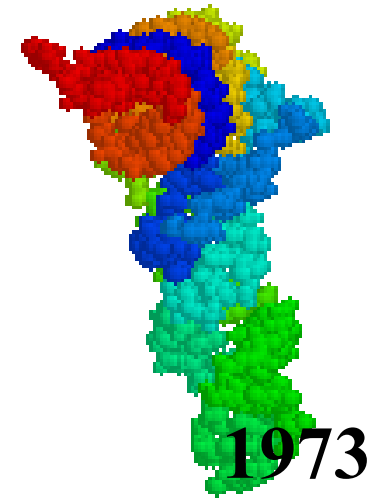
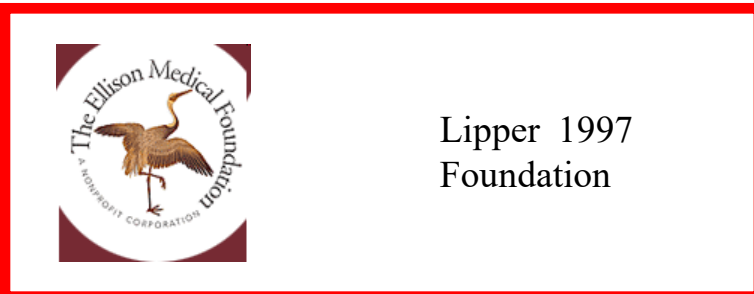


NASEM Semi-synthetic Cells

Applications and Insights Session 1

22-Jun-2025 12:35–1:20 EST George Church (7 minutes)



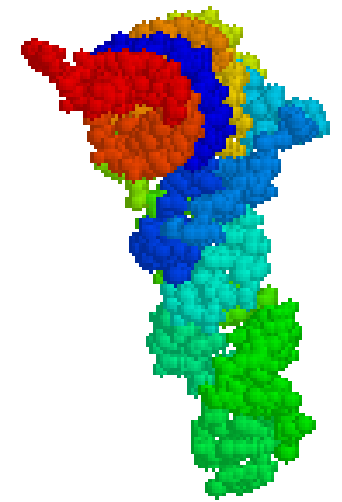
Lynn Rothschild, NASA
John Glass, JCVI
George Church, Harvard
Elizabeth Strychalski, NIST

arep.med.harvard.edu/t
full pfCOI list

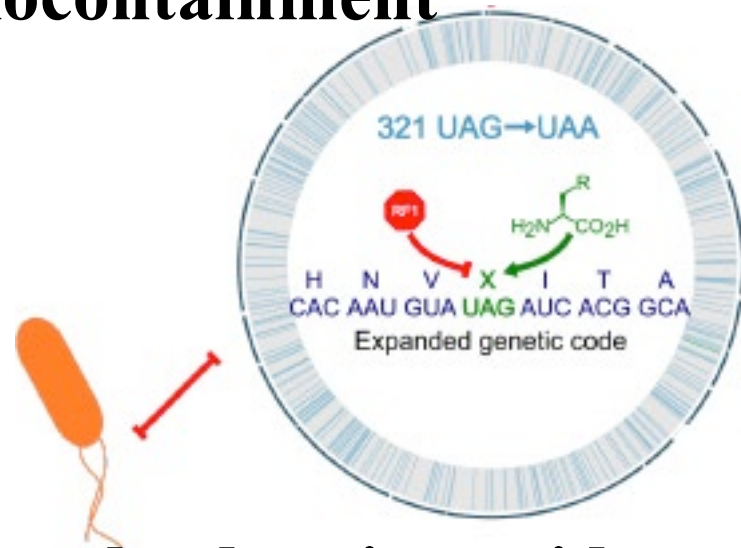
Multiplexed Genome Engineering (MAGE) 90-mers

4 Million bp Recoding

321 → 18,214 → 62,214 codons 1→3→7 of 64 codons



1. Biocontainment



2. Virus resistance

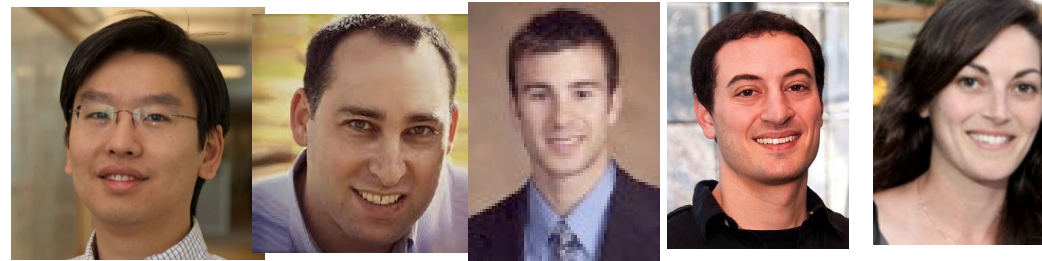


3. Non-standard amino acids

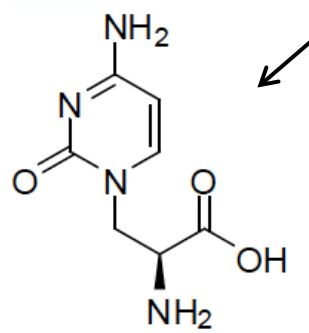
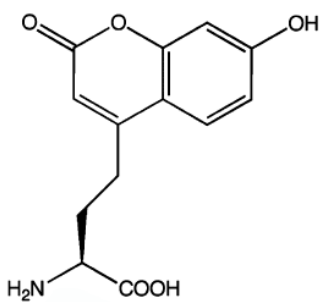
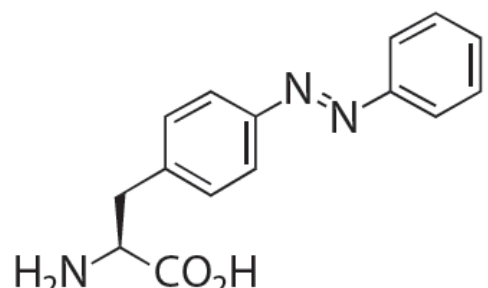
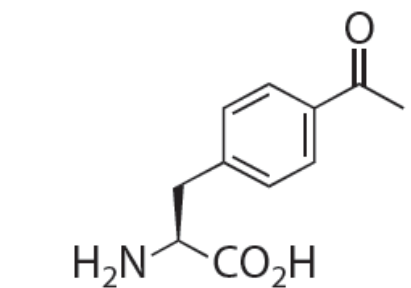
Immune tolerance
& Stability



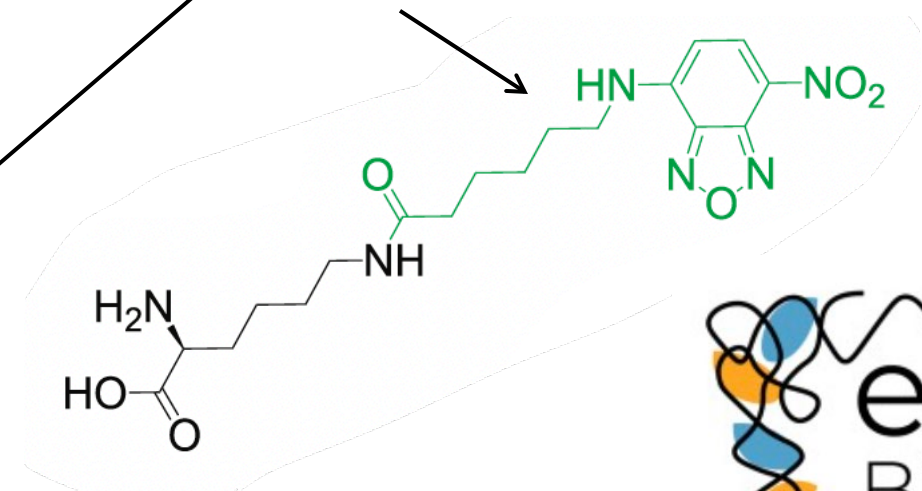
Nature 2023 Nyerges ...
COSB 2020 Ostrov, et al
Science 2016 Ostrov, et al
Nature 2015 **Mandell** et al
Science 2013 Lajoie et al
Science 2011 **Isaacs** et al
Nature 2009 Wang et al



Non-standard Amino Acids



AA	Side Chain #atoms(non-H)	Key AA Features	
Ketone	9	Orthogonal reactivity	
Azobenzyl	14	Photoisomers	
Coumarinyl	13	Redox	SelenoCys
Cytosinyl	8	Nucleopeptide	
NBD	25	Fluorogenic	

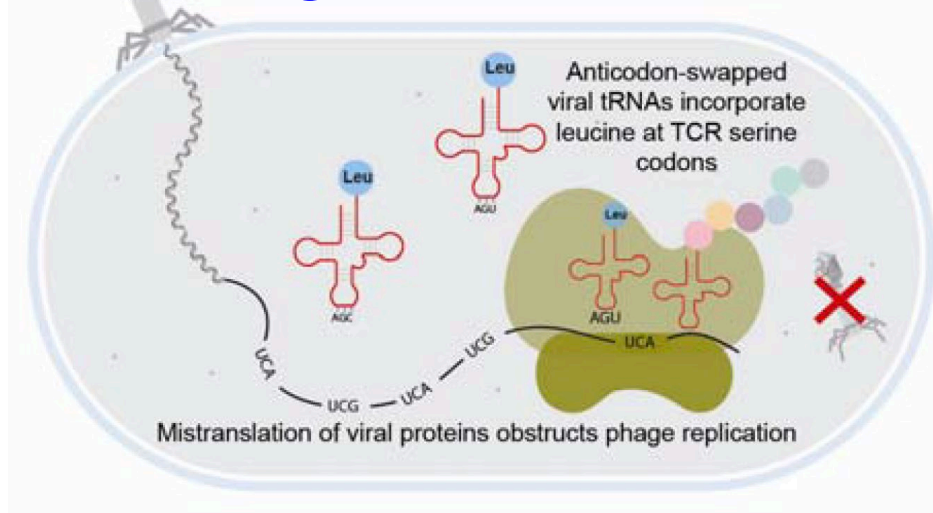


Moret,
de Puig

Kuru

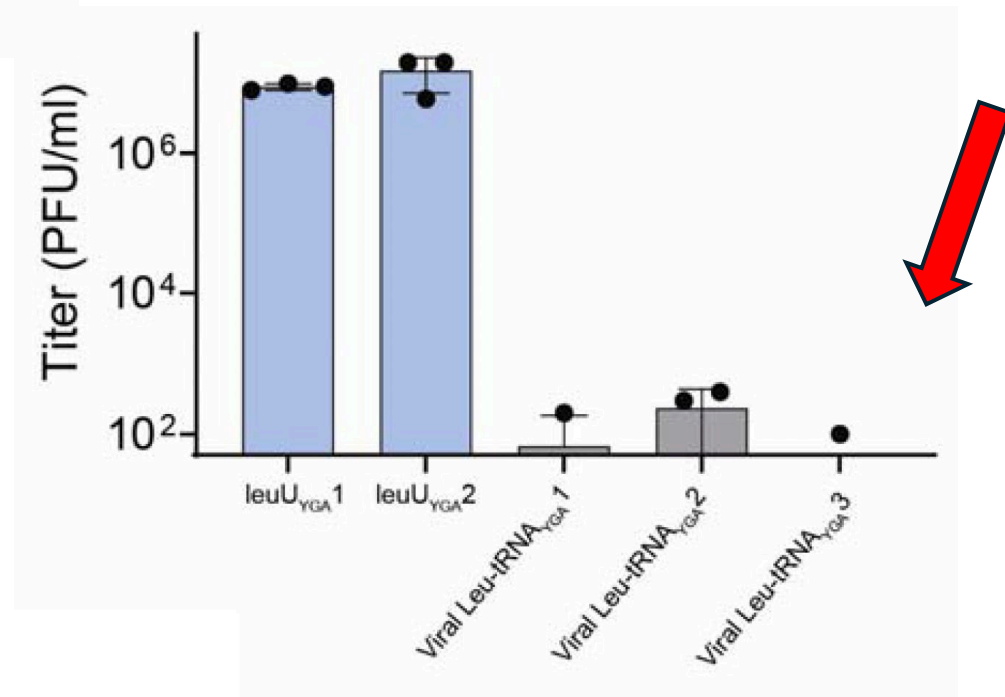
Resist all natural viruses:

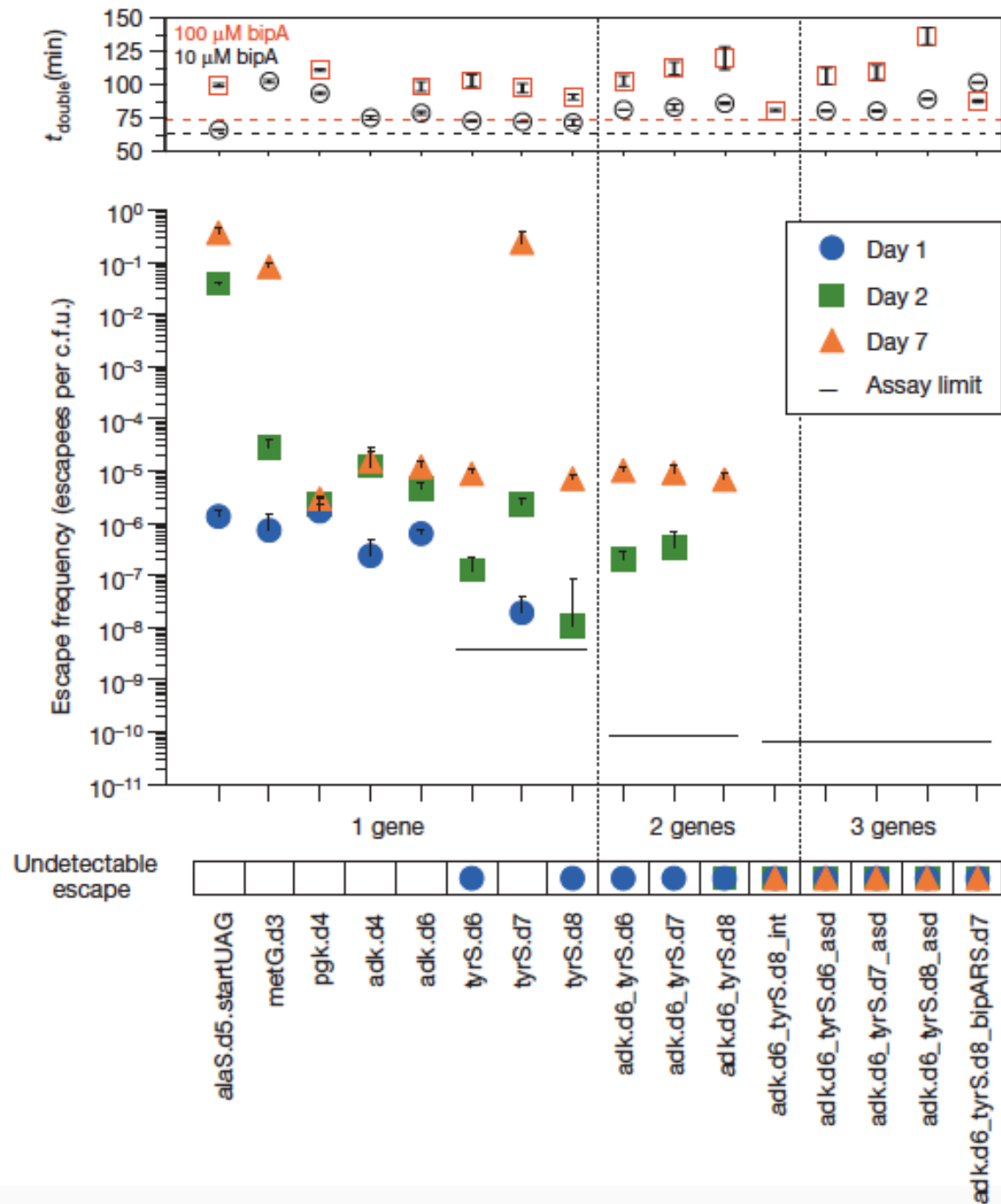
Recoding TCA TCG: Ser $\rightarrow$ null $\rightarrow$ Leu



$\rightarrow$ Resistant to ALL viruses
Tested with a **mixture of twelve** fresh environmental isolates of phages which escape Syn61 Δ 3 block (previous best)

Akos Nyerges, Svenja Vinke,
Regan Flynn...Church,
2023 Nature





Biocontainment:

Multiple essential proteins dependent on one AA not found in nature (BipA)

Undetectable escape rate (<1 per trillion)

Preventing escape & malfunction of recoded cells due to tRNA base changes
Biorxiv 2024 **Chiappino-Pepe**, et al.

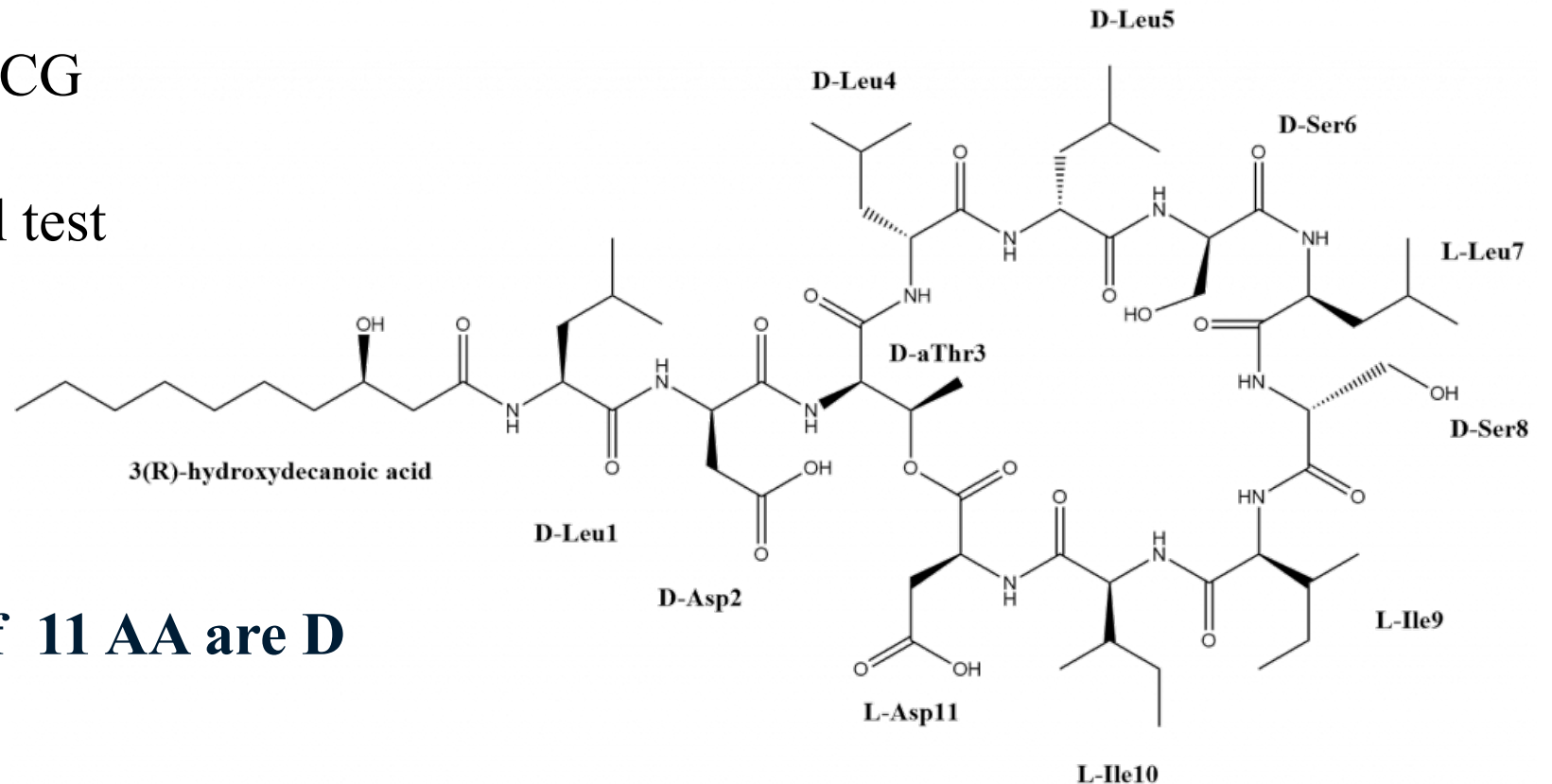
Biocontainment of genetically modified organisms by synthetic protein design.
Nature 2015 **Mandell** et al.



Non-Ribosomal Peptide Synthesis is hard to program since each AA requires a huge, bespoke (1100 AA) enzyme

All D-AA versions of the 20 standard AA are seen in NRPS

Pub.	Free codons
2013	1 TAG (in production)
2025	2 TAG , TGA
2023	3 TAG , TCA, TCG
2025	7 weak growth
2025	34 <i>in vitro</i> partial test

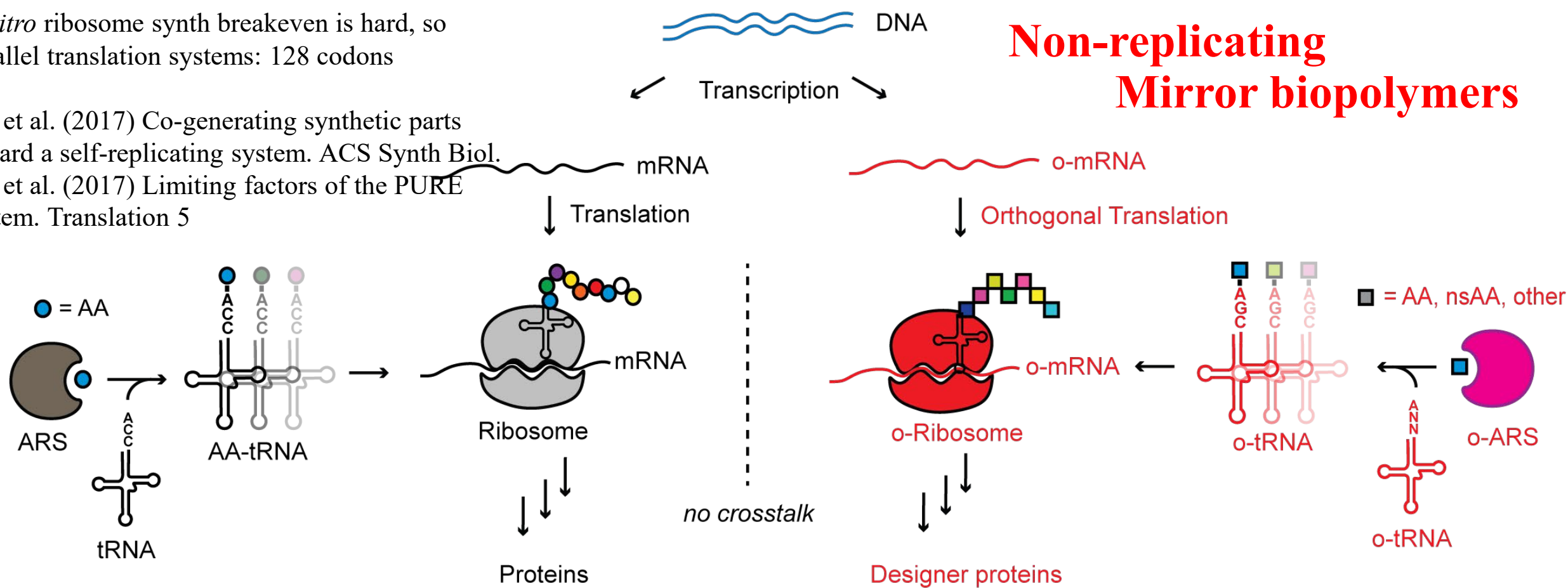


e.g. Arthrofactin 7 of 11 AA are D

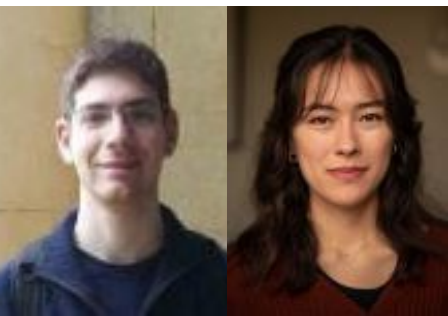
in vitro ribosome synth breakeven is hard, so
parallel translation systems: 128 codons

*Li et al. (2017) Co-generating synthetic parts
toward a self-replicating system. ACS Synth Biol.

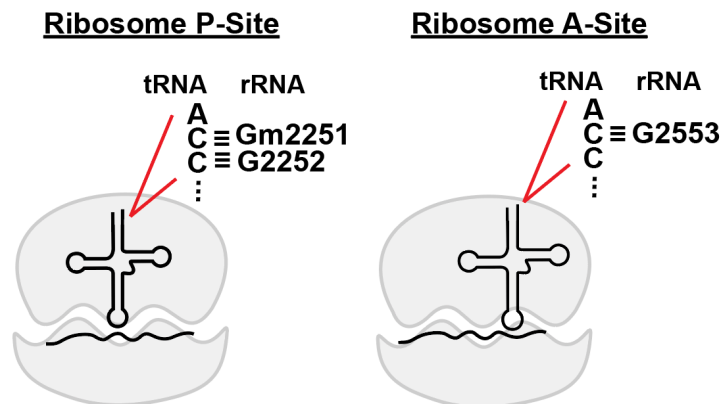
*Li et al. (2017) Limiting factors of the PURE
system. Translation 5



Felix Radford



Hana
Burgess

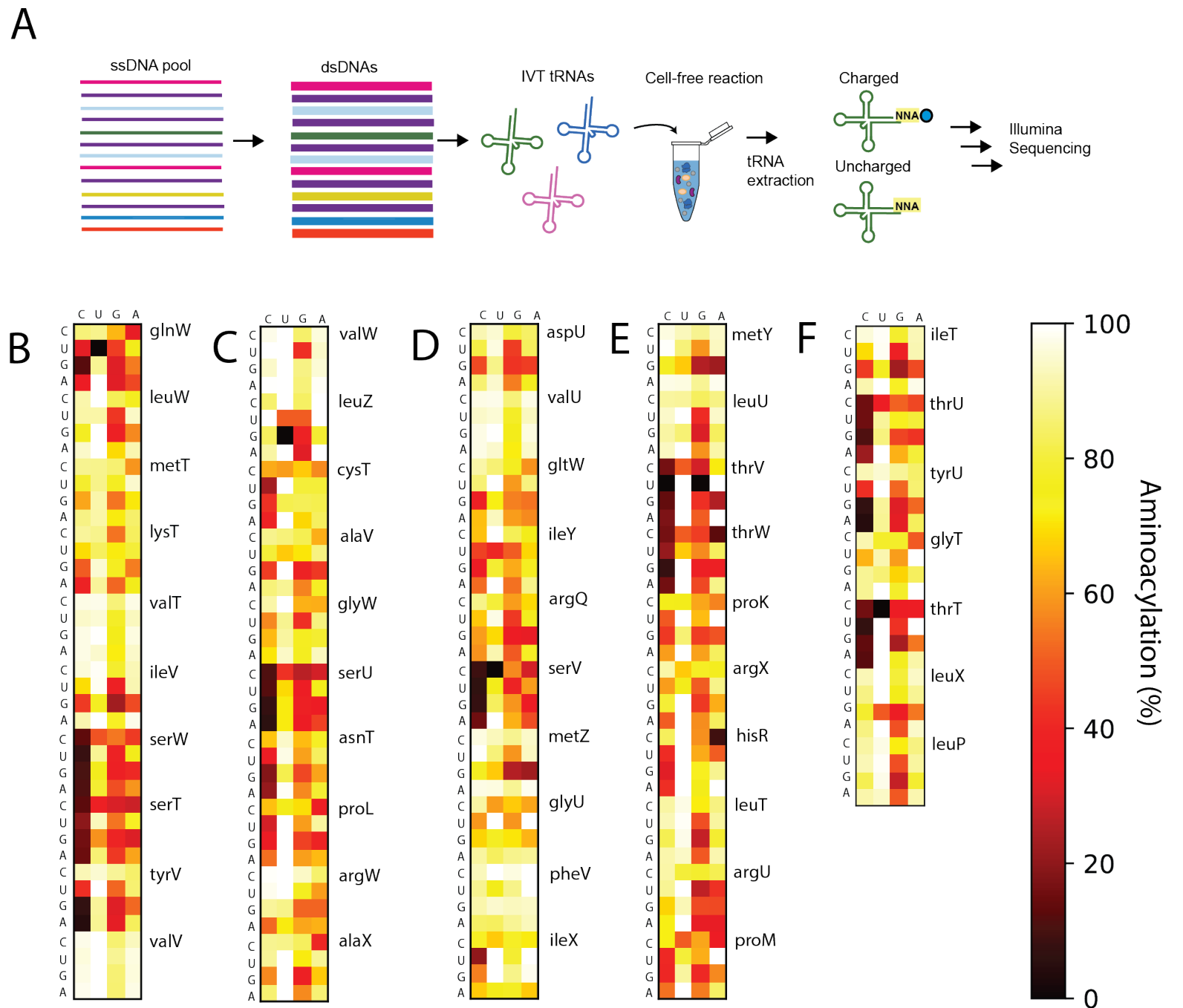
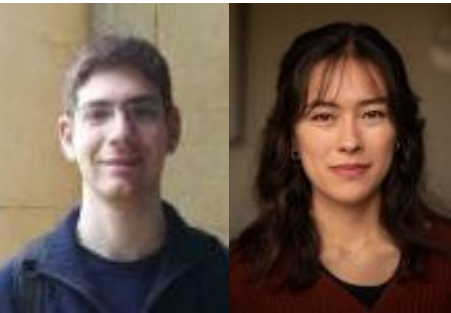


Baker D, Church G (2024)
Protein design meets
biosecurity. Science

Adamala et al.
(2024) Confronting risks of
mirror life. Science

The most
conserved
sequence
in the
biosphere:
CCA 3'
→ XYA 3'

Felix Radford
Hana Burgess



Semi-synthetic cells likely much faster than fully synthetic cells

Bioproduction, biocontainment and resistance to all viruses (2023)

Mirror proteins in the next 5 years via hybrid cells with ribosomal replacement of NRPS.

As with synthetic DNA in 2004, Gain-of-function virology in 2011, germline editing in 2017, we should be skeptical of mere consensus & moratoria. Instead:

- #1 Surveillance of all DNA synthesis requests
- #2 Checking stated/licensed use with actual DNA made (& AI use)
- #3 Recording each transaction for checking all unfavorable later outcome
- #4 Stiff (globally enforced) penalties
- #5 Encouragement of whistleblowers
- #6 Frequent tests of #1 to #5 with tough red-teams.

2024 Baker & Church (2024) Protein design meets biosecurity. Science

2009-2025 IGSC: [GeneSynthesisConsortium.org](https://www.genesynthesisconsortium.org/) [SecureDNA.org](https://www.securedna.org/)

2004 Church. A Synthetic Biohazard Non-proliferation Proposal.

**Biocontainment:
Non-standard AA
in essential proteins**

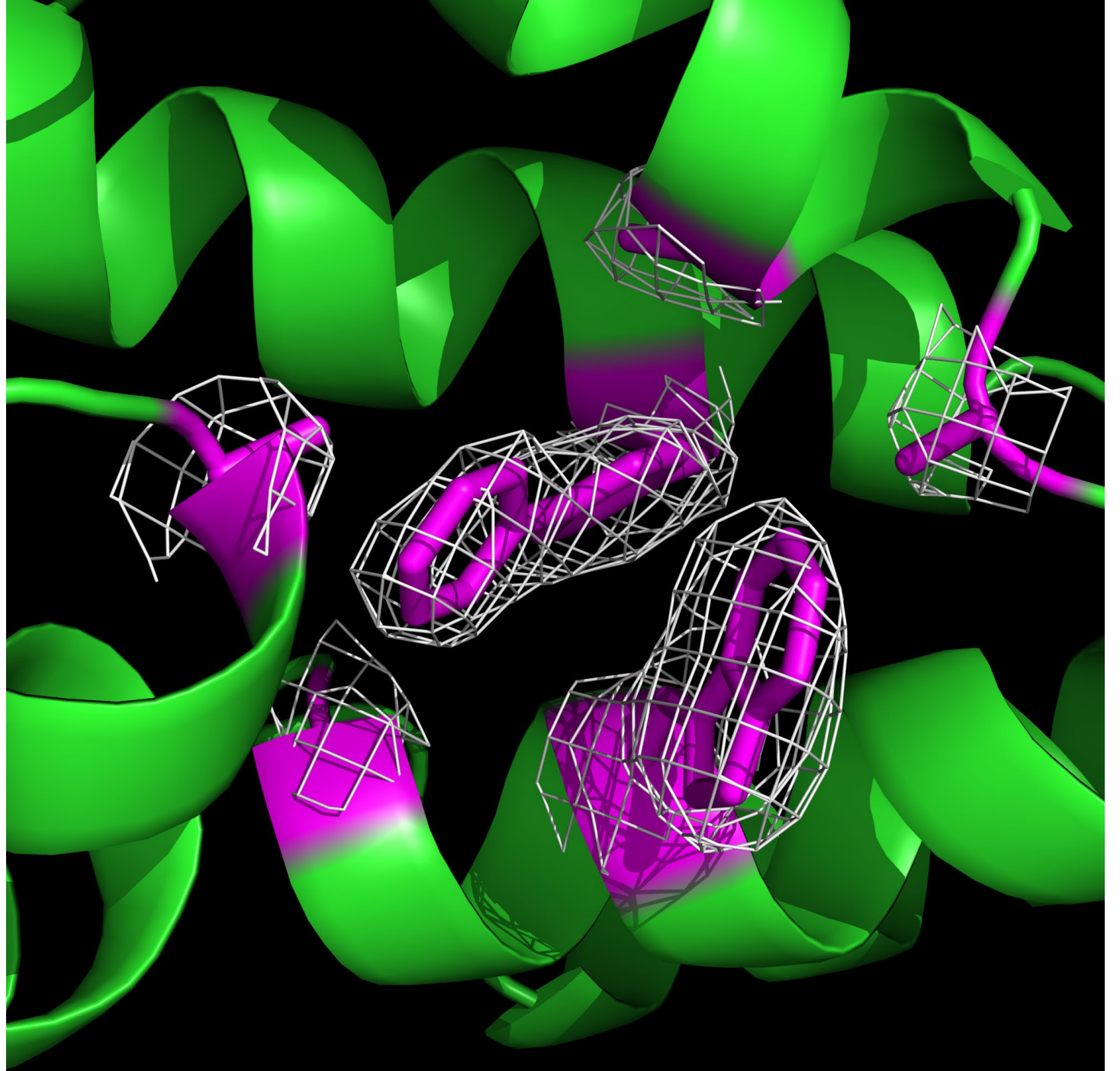
AA-tRNA synthetases

Eco_TyrS

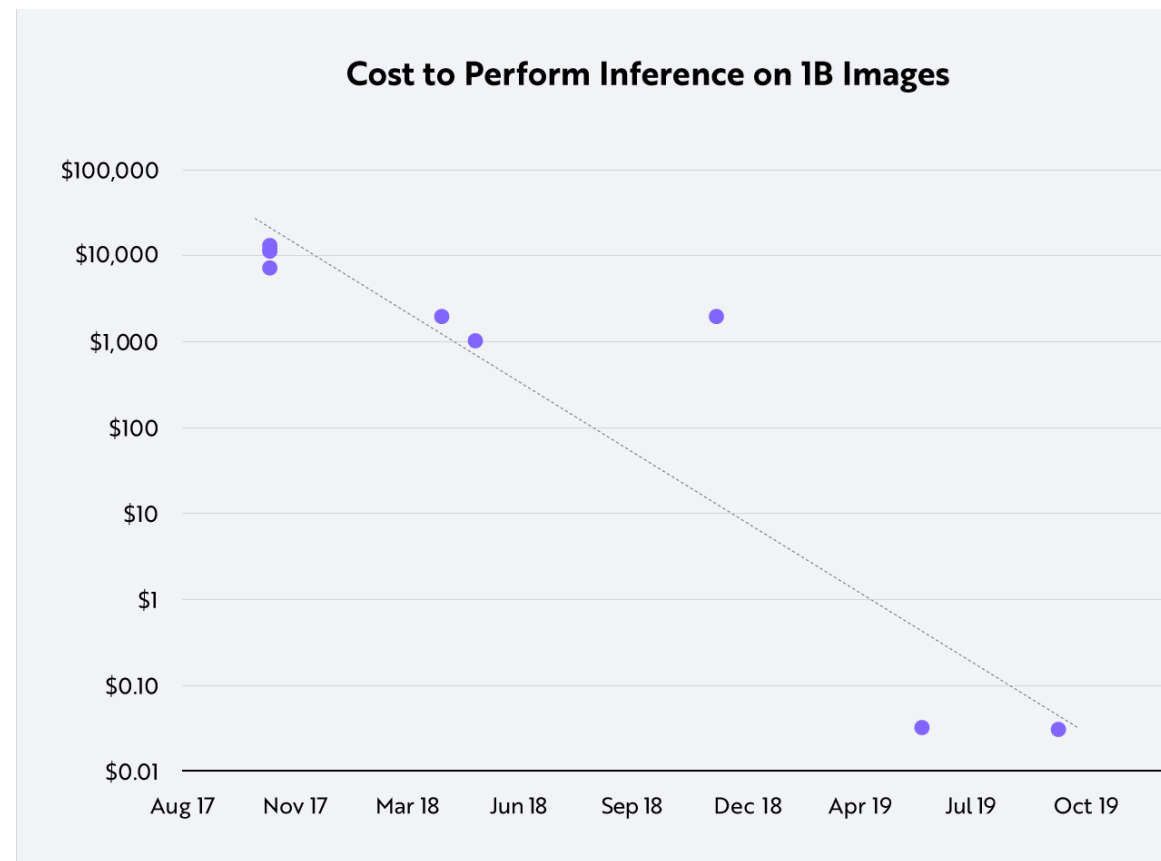
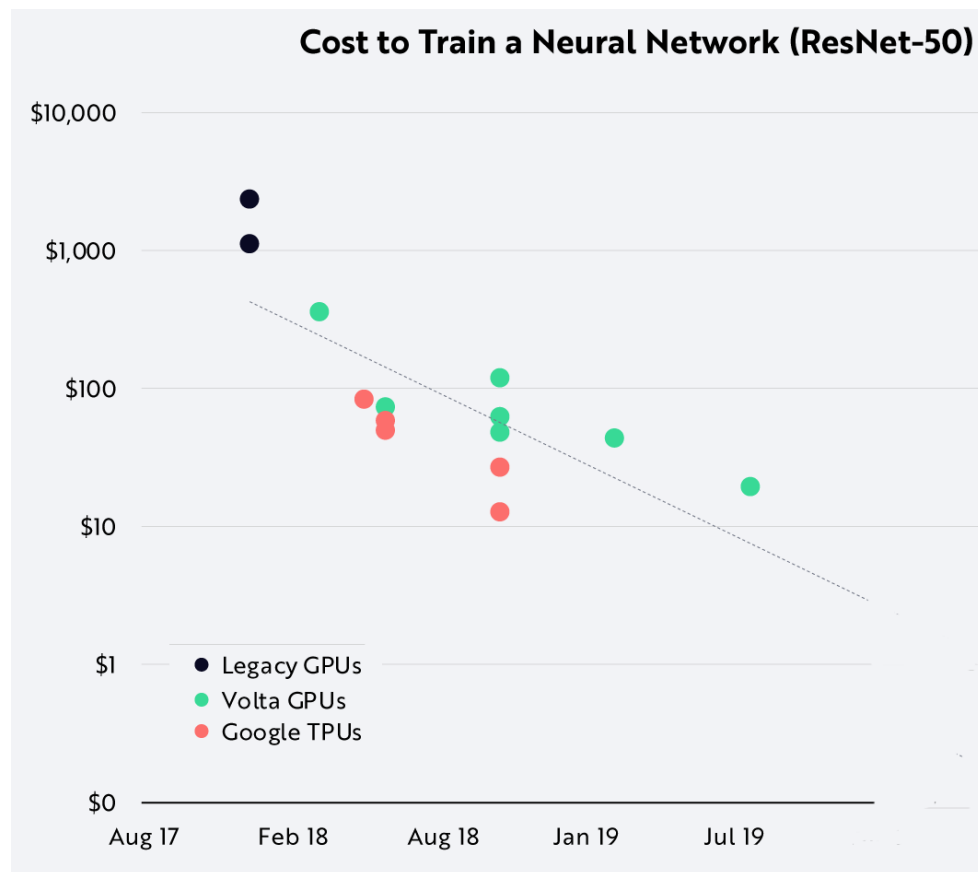
Mja_BipA

X-ray

(electron density
at 1.0σ)

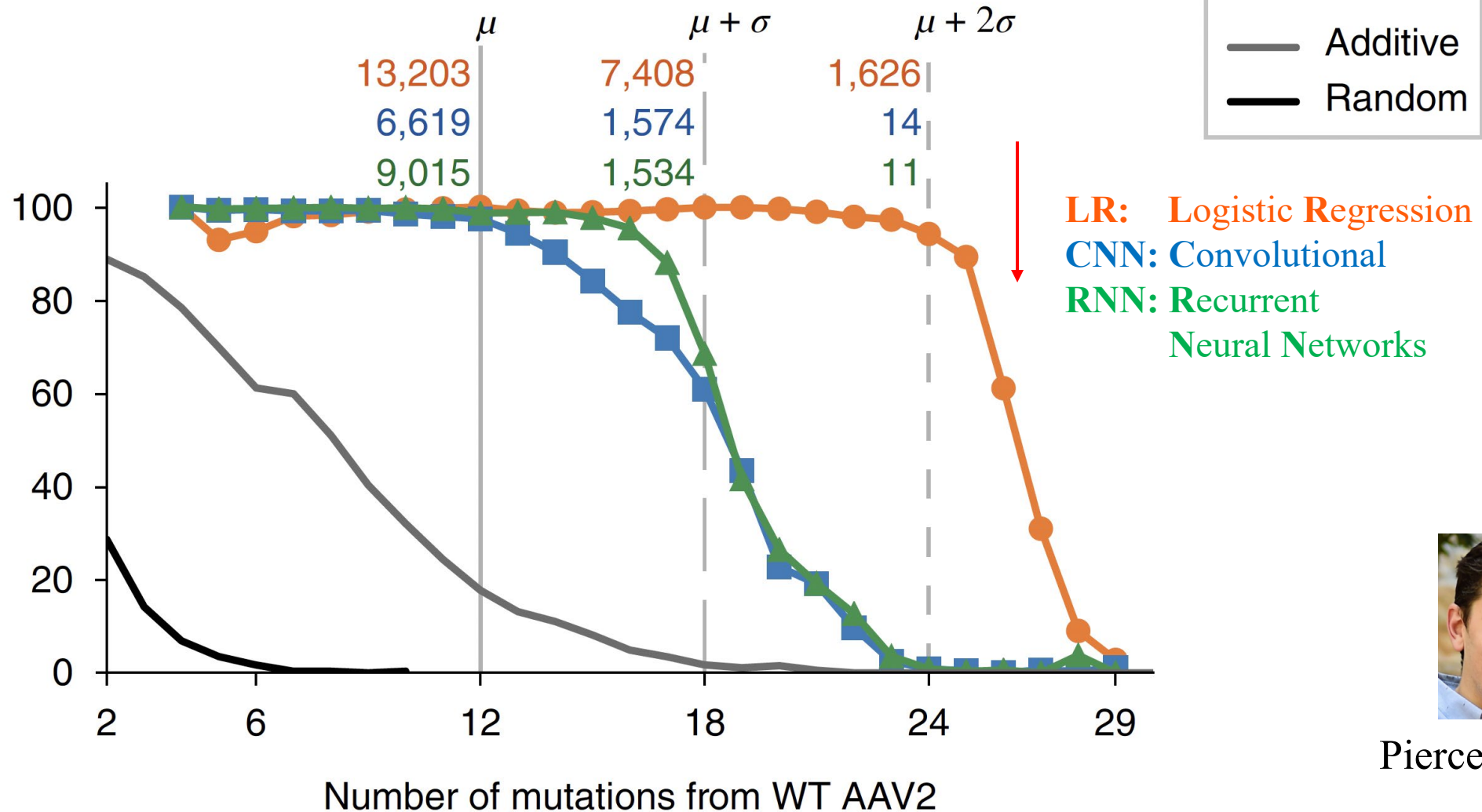


AI costs dropping 10X per year.



Deep diversification 28/28 via AI machine learning.

Bryant, et al. Nature Biotech 2020



Pierce Ogden

Eric Kelsic