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BIO Leipzig
‹INFORMATICS›

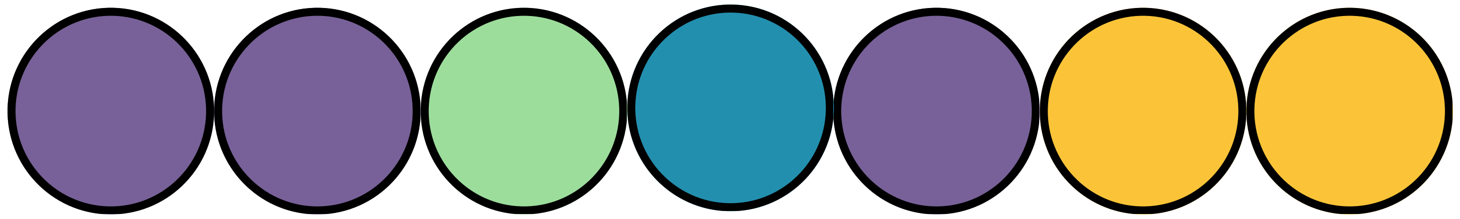
tRNA pools as key regulators of translation in melanoma

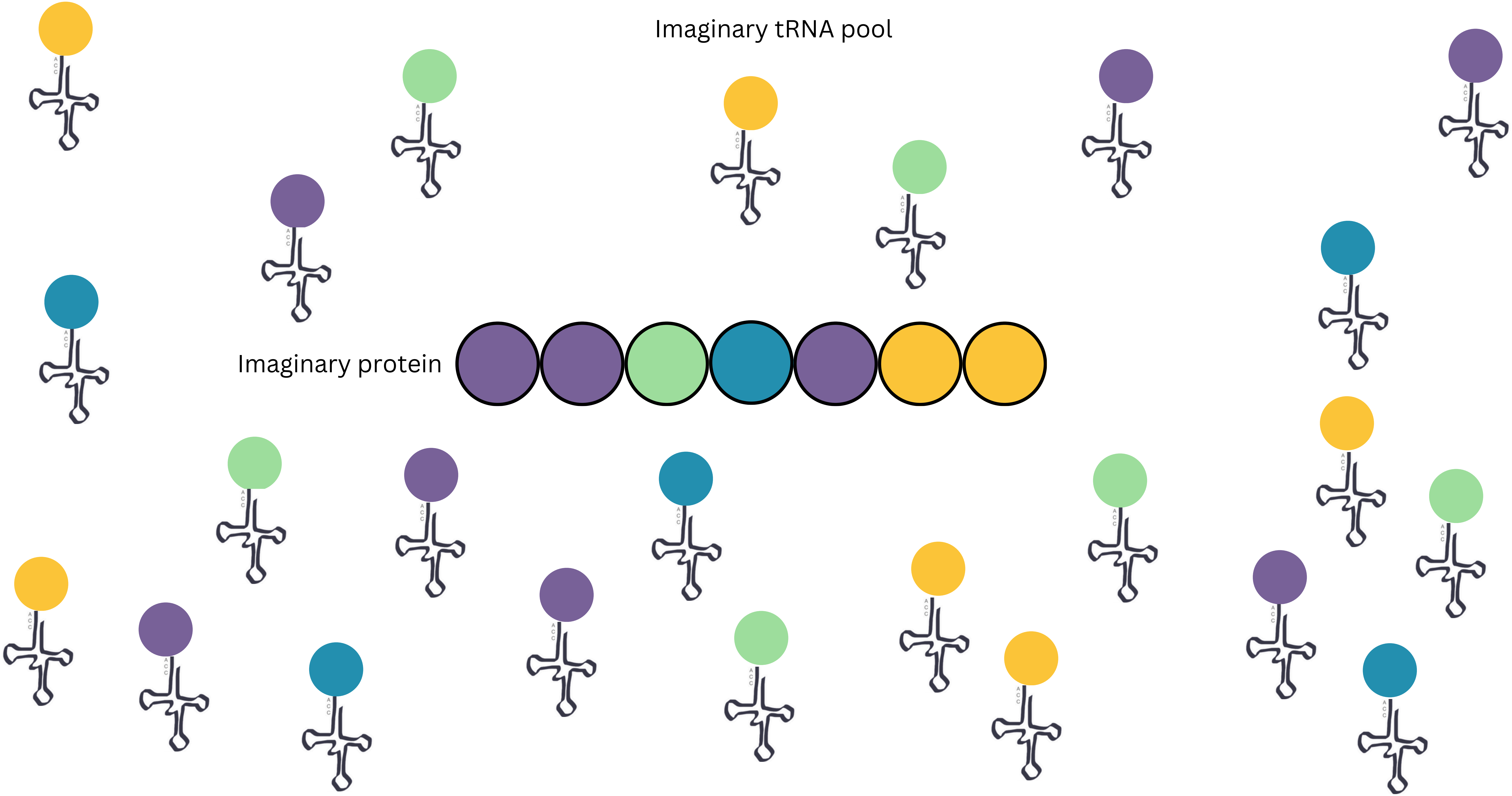
Dulce I. Valdivia

Joint work with: *Josefine Gnauck, Carolyn Schultz, Manfred Kunz, Mario Mörl &* **Peter F. Stadler**

40th TBI Winter Seminar
Bled, Slovenia
February 10th, 2025

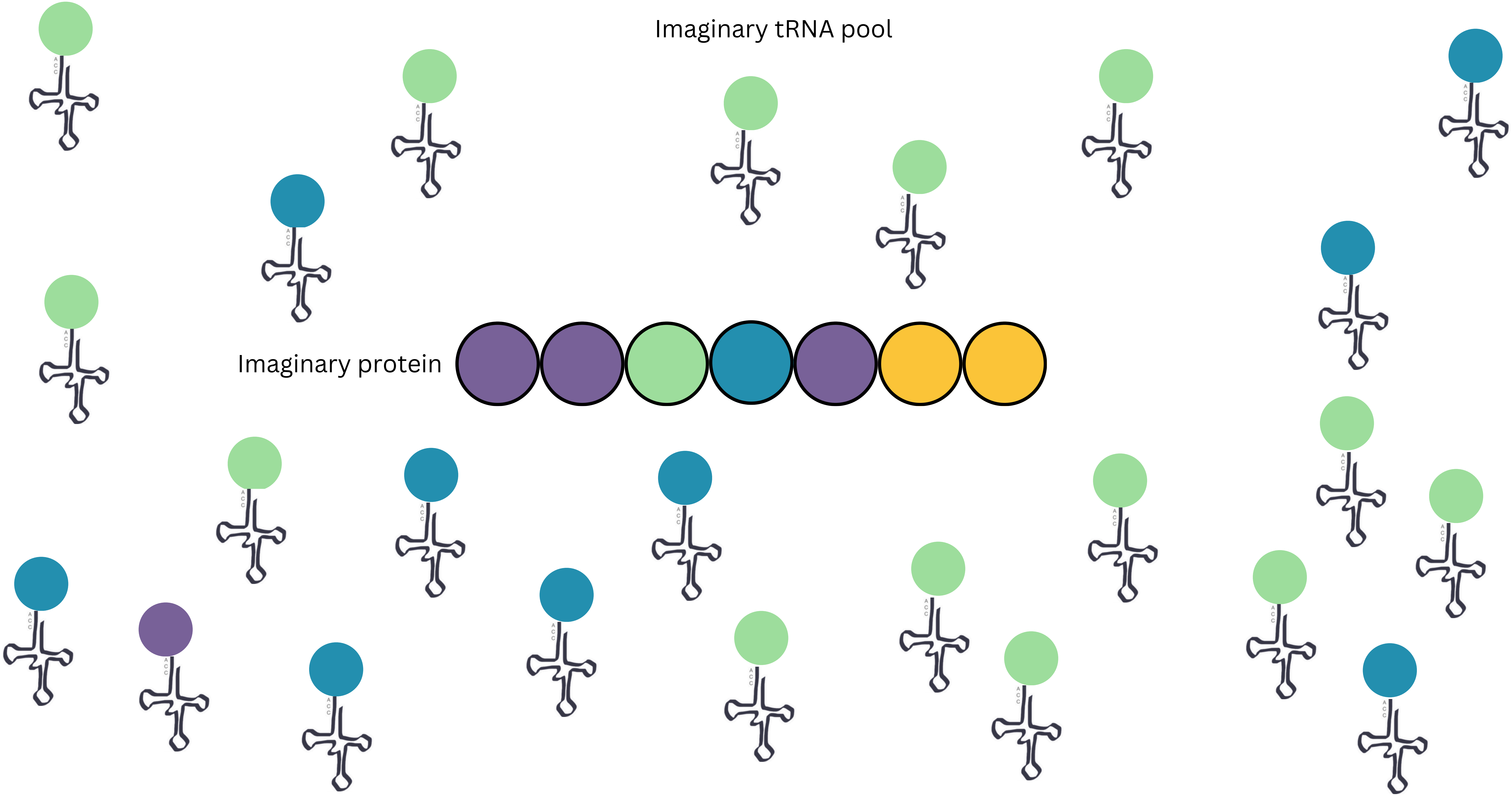
Imaginary protein





Imaginary tRNA pool

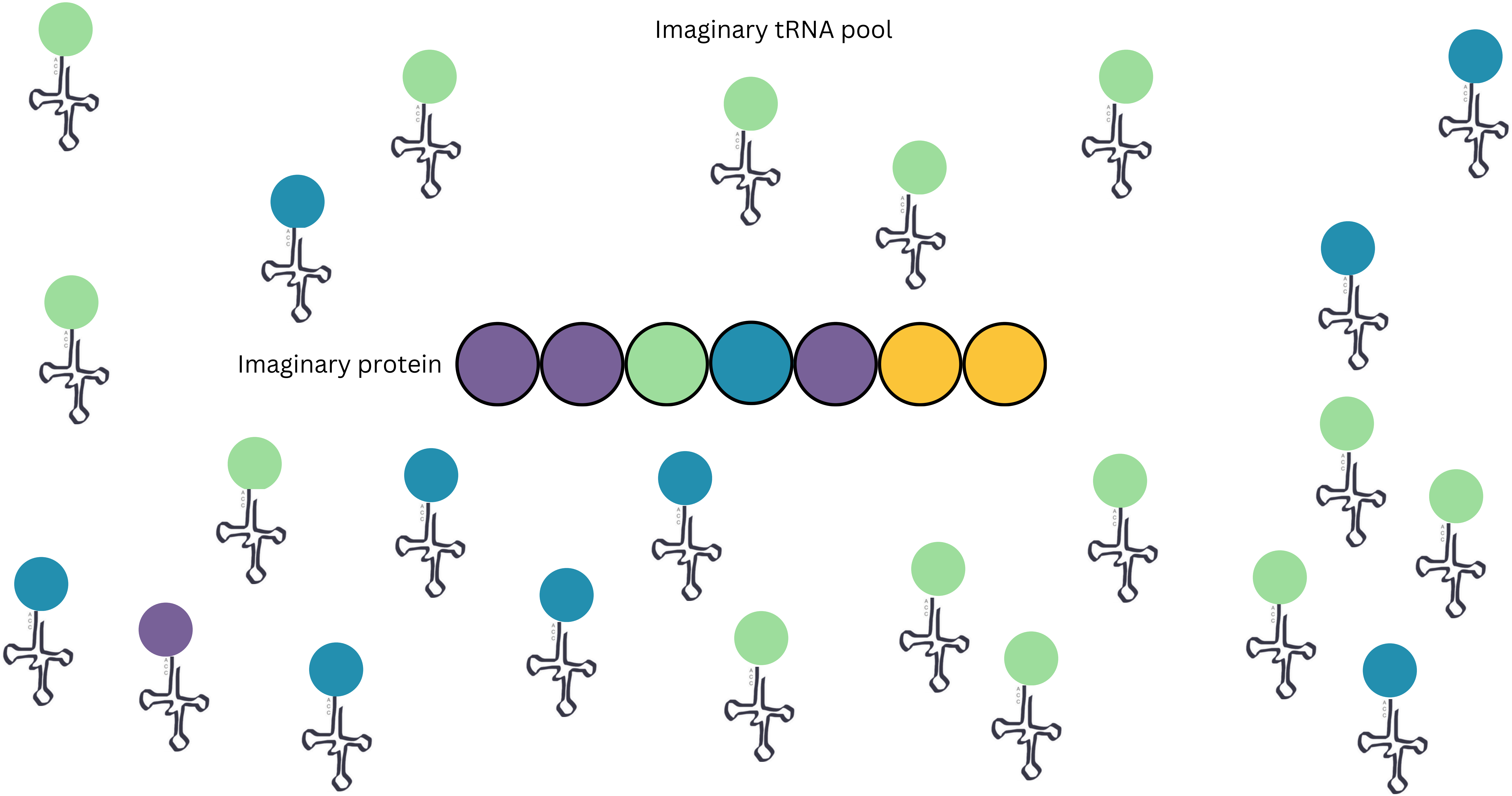
Imaginary protein



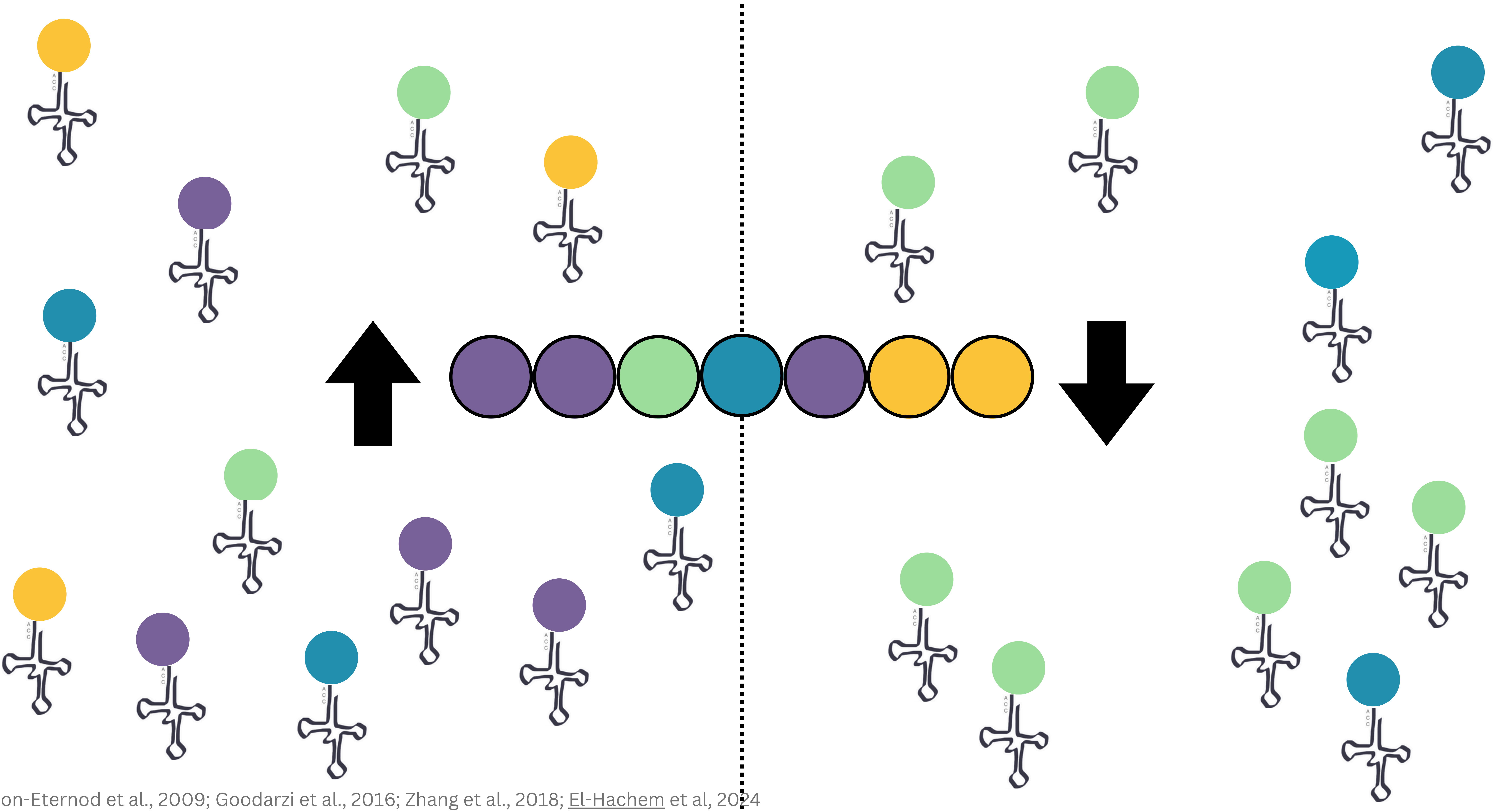
Imaginary tRNA pool

Imaginary protein

How do the changes in tRNA pools could affect protein synthesis?



In some cancers, tRNA pool variation disrupts translation in codon biased mRNAs



Pavon-Eternod et al., 2009; Goodarzi et al., 2016; Zhang et al., 2018; El-Hachem et al, 2024

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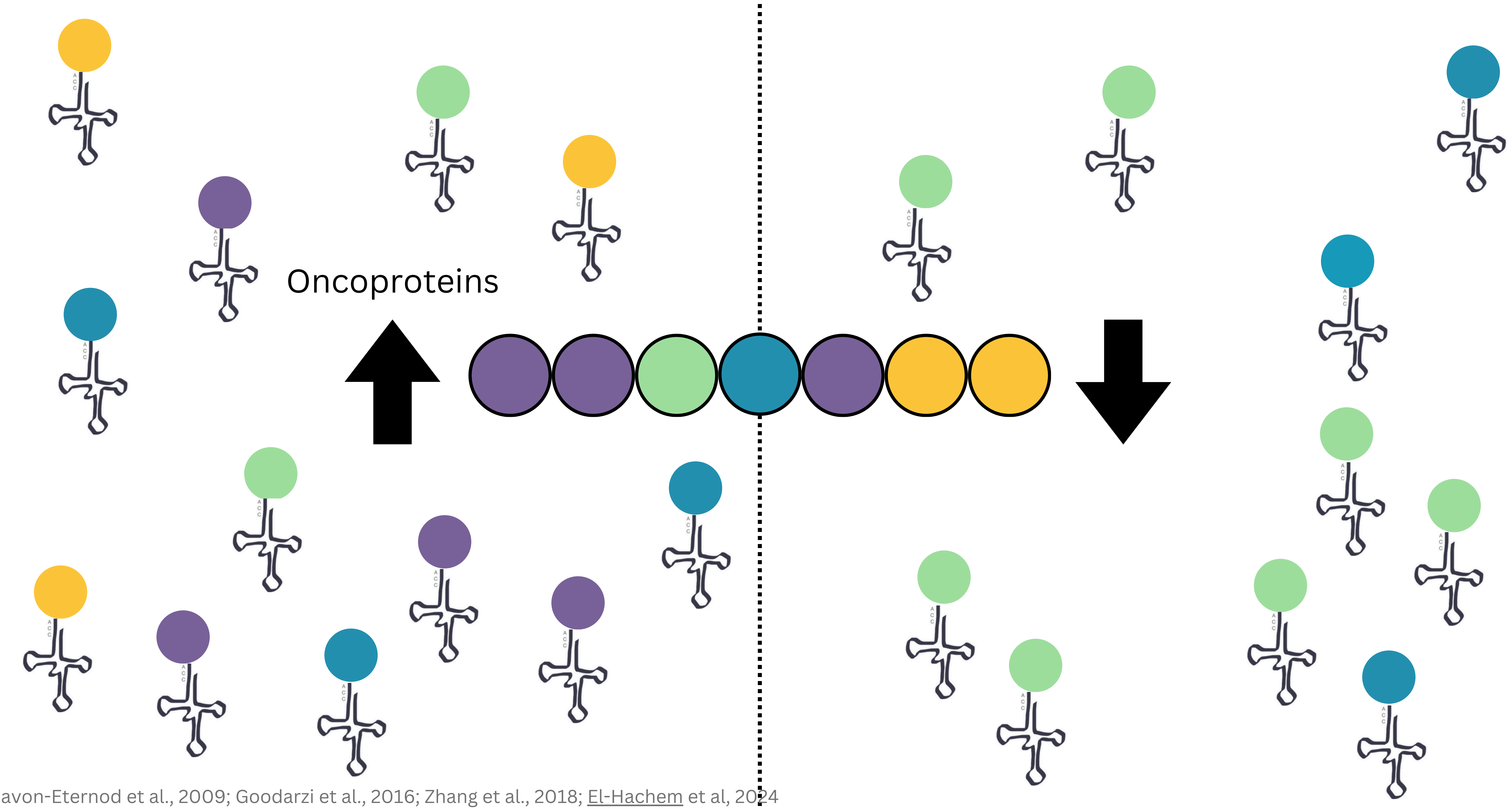

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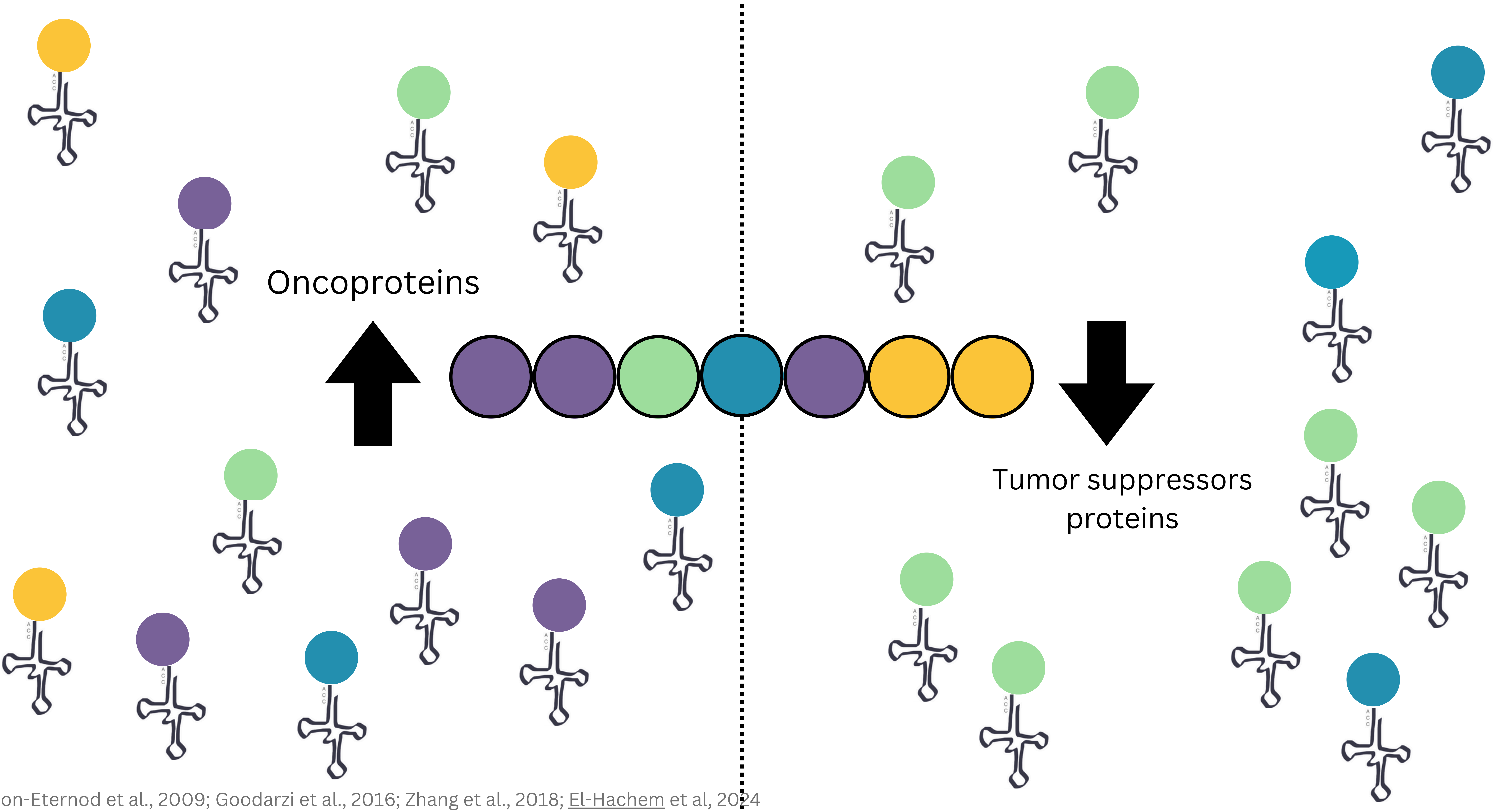

Oncoproteins

Tumor suppressors proteins

Pavon-Eternod et al., 2009; Goodarzi et al., 2016; Zhang et al., 2018; El-Hachem et al, 2024

The goal

The goal is to identify candidate tRNAs for functional validation.

A tRNA candidate:

1. Shows a change in abundance associated with melanoma.
2. Could impact anticodon demand for *key proteins*.

The data

Three biological conditions

Bening nevus (*control*)

→

Primary melanoma

→

Left as an exercise to the reader

Metastatic melanoma

The data

Three biological conditions

Bening nevus (*control*)

Primary melanoma

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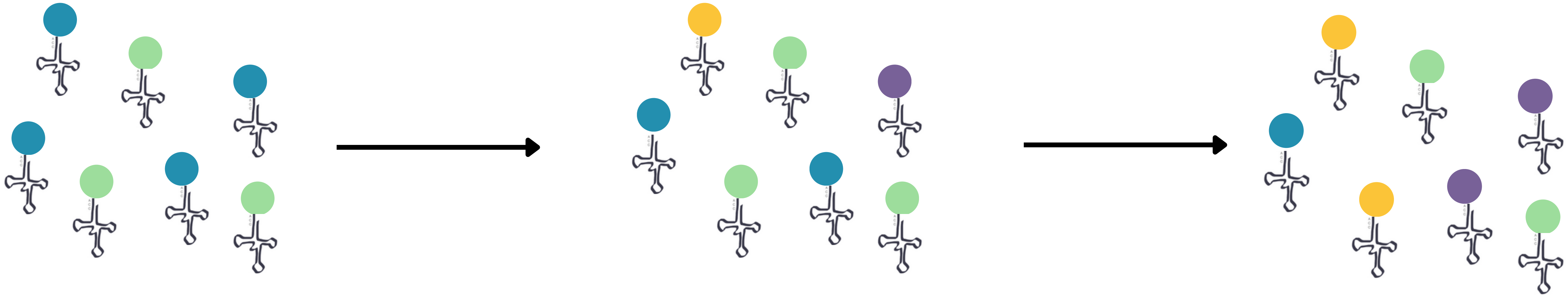
Metastatic melanoma

LOTTE-seq (v2.0)

+ AlkB treatment

Mature tRNAs

(x5 replicates)



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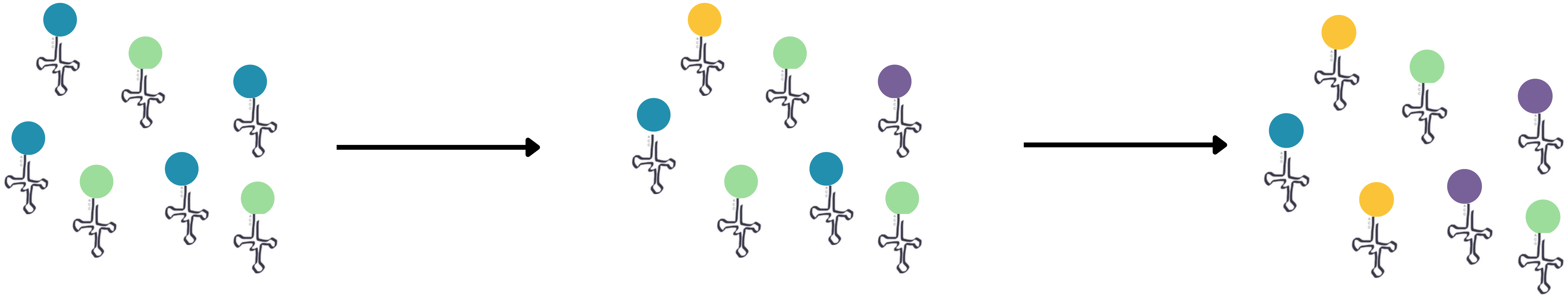

RNA-seq

(x3 replicates)

ATGCGTACCTGACGTTGAGTA
TTAGGCTCCAGTACGGTG
ATGGCTGGAACGTTCCGATGA
TTAGGCTCCAGTACGGTG
TTAGGCTCCAGTACGGTG

ATGCGTACCTGACGTTGAGTA
TTAGGCTCCAGTACGGTG
TTAGGCTCCAGTACGGTG
ATGGCTGGAACGTTCCGATGA
TTAGGCTCCAGTACGGTG

ATGCGTACCTGACGTTGAGTA
TTAGGCTCCAGTACGGTG
ATGGCTGGAACGTTCCGATGA
TTAGGCTCCAGTACGGTG
ATGCGTACCTGACGTTGAGTA

The plan

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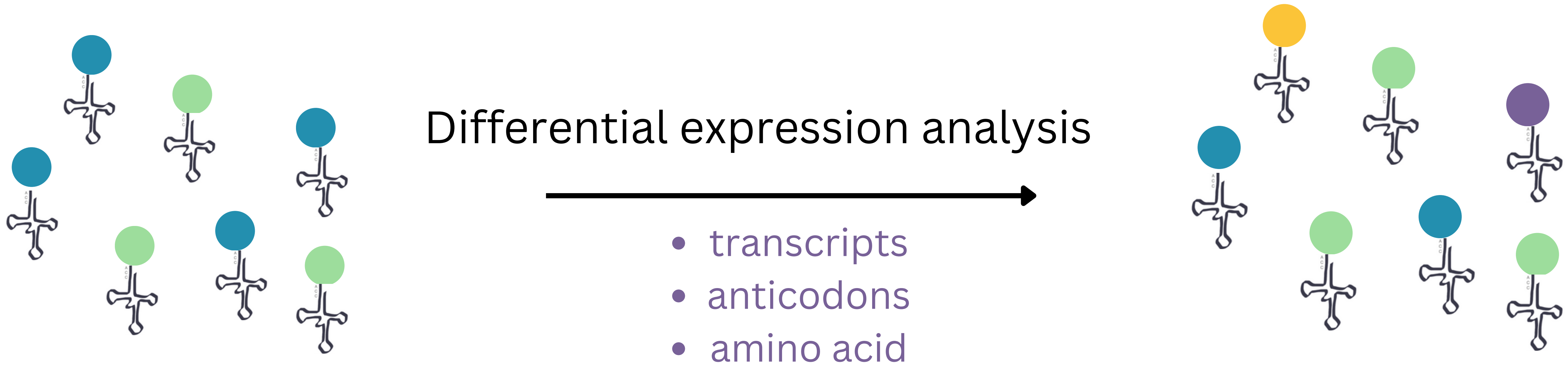


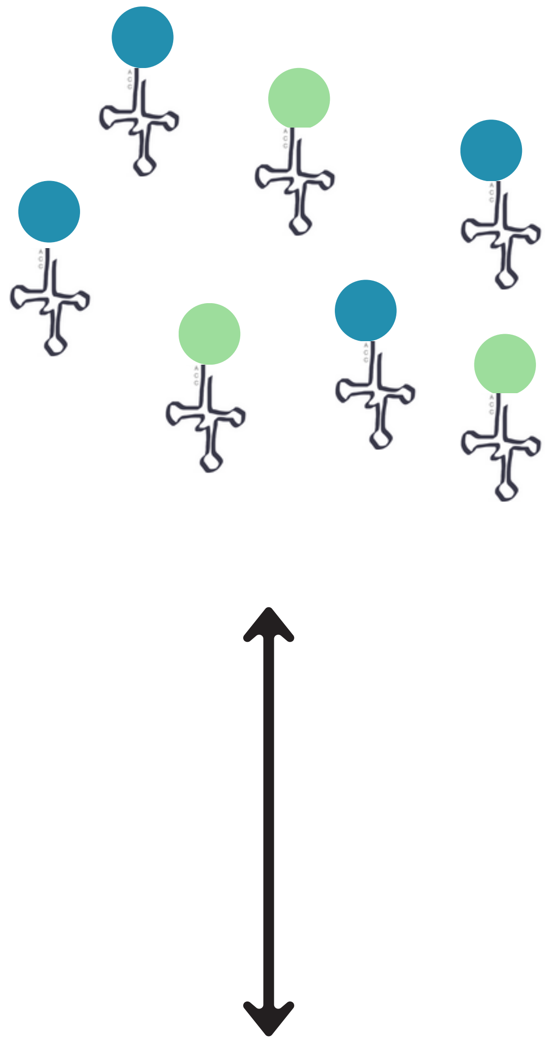
Differential expression analysis

- transcripts
- anticodons
- amino acid

The plan

1. Shows a change in abundance associated with melanoma.

2. Could impact anticodon demand for *key proteins*.



ATGCGT**ACC**TGA**CGT**TGA**GTA**

TTAGGC**TCC**AGT**ACG**GTG

ATG**GCT**GGA**ACG**TTC**CGA**TGA

TTAGGC**TCC**AGTACG**GTG**

TTAGGC**TCC**AGTACGGTG

Translational efficiency:

- tRNA **supply**: tAI - tRNA adaptation index

$$\mathrm{tAI}_g = \left(\prod_{k=1}^{l_g} w_{i_{kg}}\right)^{1/l_g}, \qquad W_i = \sum_{j=1}^{n_i} \underbrace{(1-s_{ij})}_{\text{Yeast/arbitrary}} tGCN_{ij}$$

- tRNA **demand**: Codon usage in mRNA

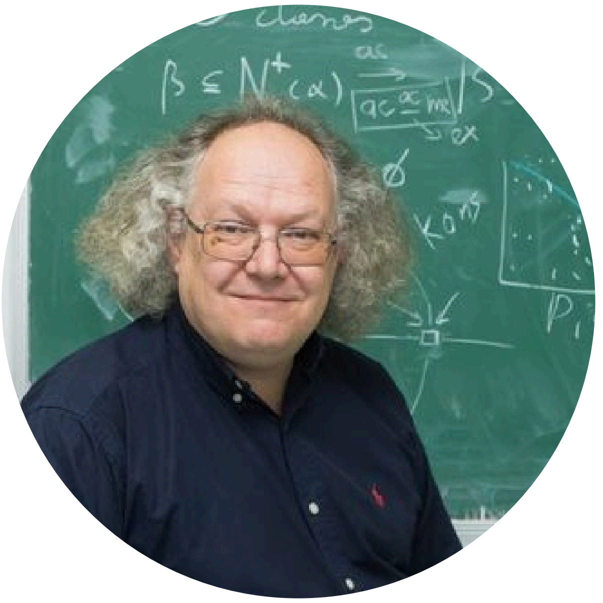
$$U_i = \sum_{j=1}^{g} a_j c_{ij}$$

* One isoforrm

dos Reis, Savva & Wernish, 2004; Pechmann & Frydman 2012; Hernandez-Alias et al. 2020

Thank you!

Bierinformatk Leipzig


Peter F. Stadler


Stephan Bernhart


Mario Mörl


Josefine Gnauck

Institute for Biochemistry, Uni-Leipzig

You, dear listener
@40th TBI-WS


Carolyn Schultz


Manfred Kunz

Department of Dermatology, Uni-Leipzig

DFG Deutsche
Forschungsgemeinschaft
German Research Foundation

tRNA adaptation index:

$$W_i = \sum_{j=1}^{n_i} (1 - s_{ij}) tGCN_{ij}$$

$$cTE = W_i / W_{\max}$$

Nelder and Mead algorithm,
on yeast microarray data

Since tRNA usage should be maximal for highly expressed genes, it would be natural to find the set of sij-values that maximize the correlation between expression levels and tAI values for any given organism

Codon usage

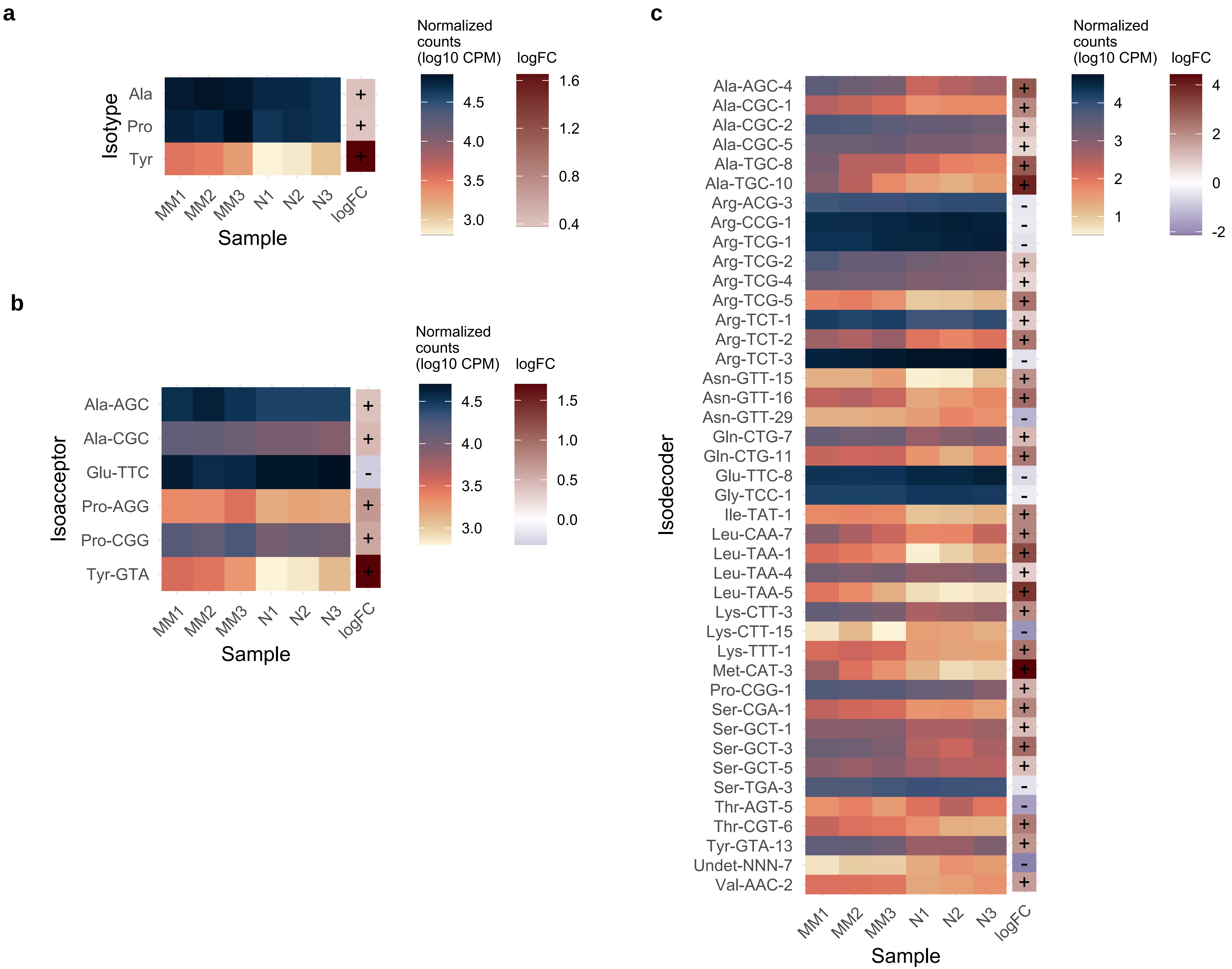
$$U_i = \sum_{j=1}^{g} a_j c_{ij}$$

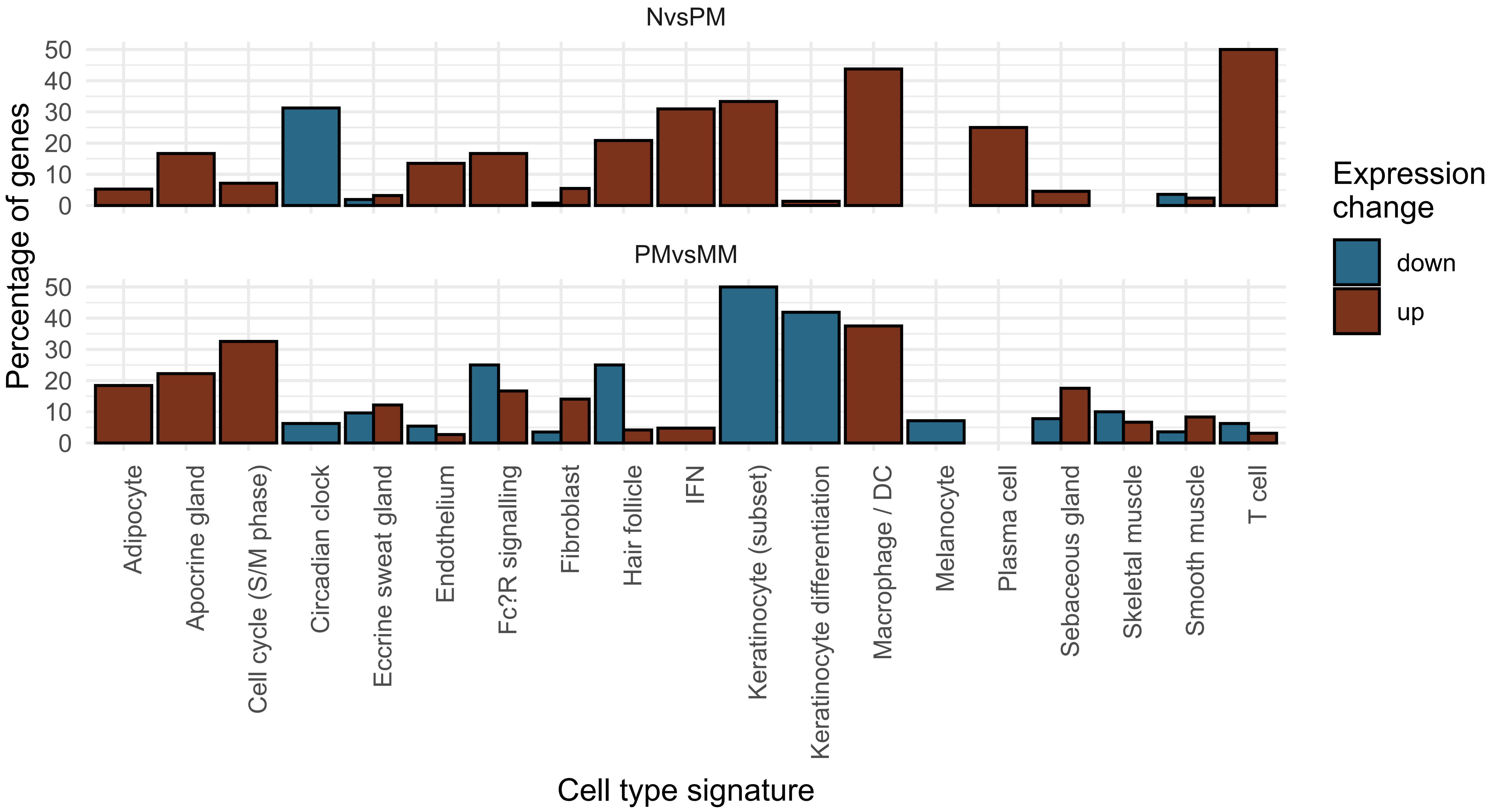
$$cu_i = U_i / U_{\max}$$

Transaltion efficiency/ SDA

$$nTE'_i = cTE_i / cu_i$$

$$nTE_i = nTE'_i / nTE'_{\max}$$


a
Normalized counts (log10 CPM)
logFC
Isotype
Ala
Pro
Tyr
+
+
+
MM1
MM2
MM3
N1
N2
N3
logFC
Sample
4.5
4.0
3.5
3.0
1.6
1.2
0.8
0.4
b
Normalized counts (log10 CPM)
logFC
Isoacceptor
Ala-AGC
Ala-CGC
Glu-TTC
Pro-AGG
Pro-CGG
Tyr-GTA
+
+
-
+
+
+
MM1
MM2
MM3
N1
N2
N3
logFC
Sample
4.5
4.0
3.5
3.0
1.5
1.0
0.5
0.0
c
Normalized counts (log10 CPM)
logFC
Isodecoder
Ala-AGC-4 +
Ala-CGC-1 +
Ala-CGC-2 +
Ala-CGC-5 +
Ala-TGC-8 +
Ala-TGC-10 +
Arg-ACG-3 -
Arg-CCG-1 -
Arg-TCG-1 -
Arg-TCG-2 +
Arg-TCG-4 +
Arg-TCG-5 +
Arg-TCT-1 +
Arg-TCT-2 +
Arg-TCT-3 -
Asn-GTT-15 +
Asn-GTT-16 +
Asn-GTT-29 -
Gln-CTG-7 +
Gln-CTG-11 +
Glu-TTC-8 -
Gly-TCC-1 -
Ile-TAT-1 +
Leu-CAA-7 +
Leu-TAA-1 +
Leu-TAA-4 +
Leu-TAA-5 +
Lys-CTT-3 +
Lys-CTT-15 -
Lys-TTT-1 +
Met-CAT-3 +
Pro-CGG-1 +
Ser-CGA-1 +
Ser-GCT-1 +
Ser-GCT-3 +
Ser-GCT-5 +
Ser-TGA-3 -
Thr-AGT-5 -
Thr-CGT-6 +
Tyr-GTA-13 +
Undet-NNN-7 -
Val-AAC-2 +
MM1
MM2
MM3
N1
N2
N3
logFC
Sample
4
3
2
1
4
2
0
-2


NvsPM
PMvsMM
Percentage of genes
0
10
20
30
40
50
Cell type signature
Adipocyte
Apocrine gland
Cell cycle (S/M phase)
Circadian clock
Eccrine sweat gland
Endothelium
Fc?R signalling
Fibroblast
Hair follicle
IFN
Keratinocyte (subset)
Keratinocyte differentiation
Macrophage / DC
Melanocyte
Plasma cell
Sebaceous gland
Skeletal muscle
Smooth muscle
T cell
Expression change
down
up