系统生物学课程文献

学 院：生命科学技术学院

专 业：基因组学

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学 号：2016304110164

TRANSPARENT PROCESS

OPEN ACCESS

Pervasive isoform-specific translational regulation via alternative transcription start sites in mammals

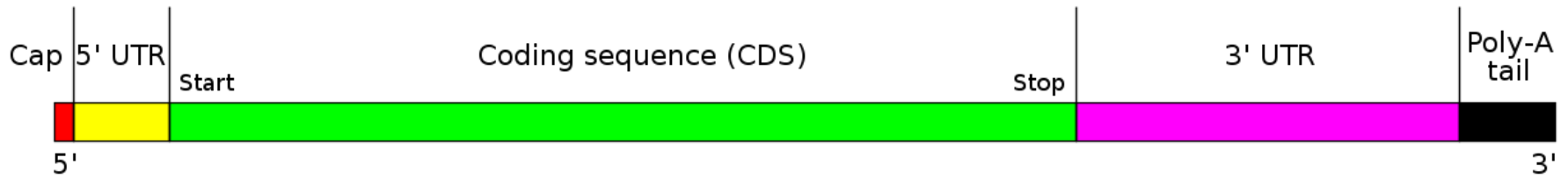Xi Wang[1,†], Jingyi Hou[1,†], Claudia Quedenau[1] & Wei Chen[1,2,*]

Background

陈 炜

- **1993年毕业于厦门大学生物化学专业。**

- **2002年于四川大学华西医学院获得医学遗传专业硕士学位。**

- **2002－2006年在德国柏林马普分子遗传学研究所师从国际著名人类医学遗传学家H.HILGER ROPERS教授攻读博士。**

- **2015年通过全球招聘成为德国马科斯•德尔布吕克分子医学中心兼柏林夏洛蒂医学院终身正教授。**

- **2016年入选中组部第十二批千人计划（创新人才）。**

- 现为南方科技大学生物系讲座教授。

➢ 研究领域：

　　主要从事**系统生物学及基因组学研究**，研究领域包括基于系统生物学的基因调控研究、非编码RNA的鉴定及功能研究、人类疾病遗传学研究、癌症基因组学研究等几个方面。自2007年独立领导实验室以来，作为第一作者或通讯作者发表论文30篇，总共发表论文96篇，总被引用次数8181，H-index达到41。

Background

The structure of a typical human protein coding mRNA including the untranslated regions (UTRs)

| Cap | 5' UTR | Coding sequence (CDS) | 3' UTR | Poly-A tail |

Start — Stop

5' ... 3'

➢ Translational regulation:

- Alternative TSS isoforms

- UTRs

- Cis-elements

    1. uORFs (upstream open reading frames)

    2. stable RNA secondary structures near 5′ cap

    3. 5′-terminal oligopyrimidine (5′ TOP)

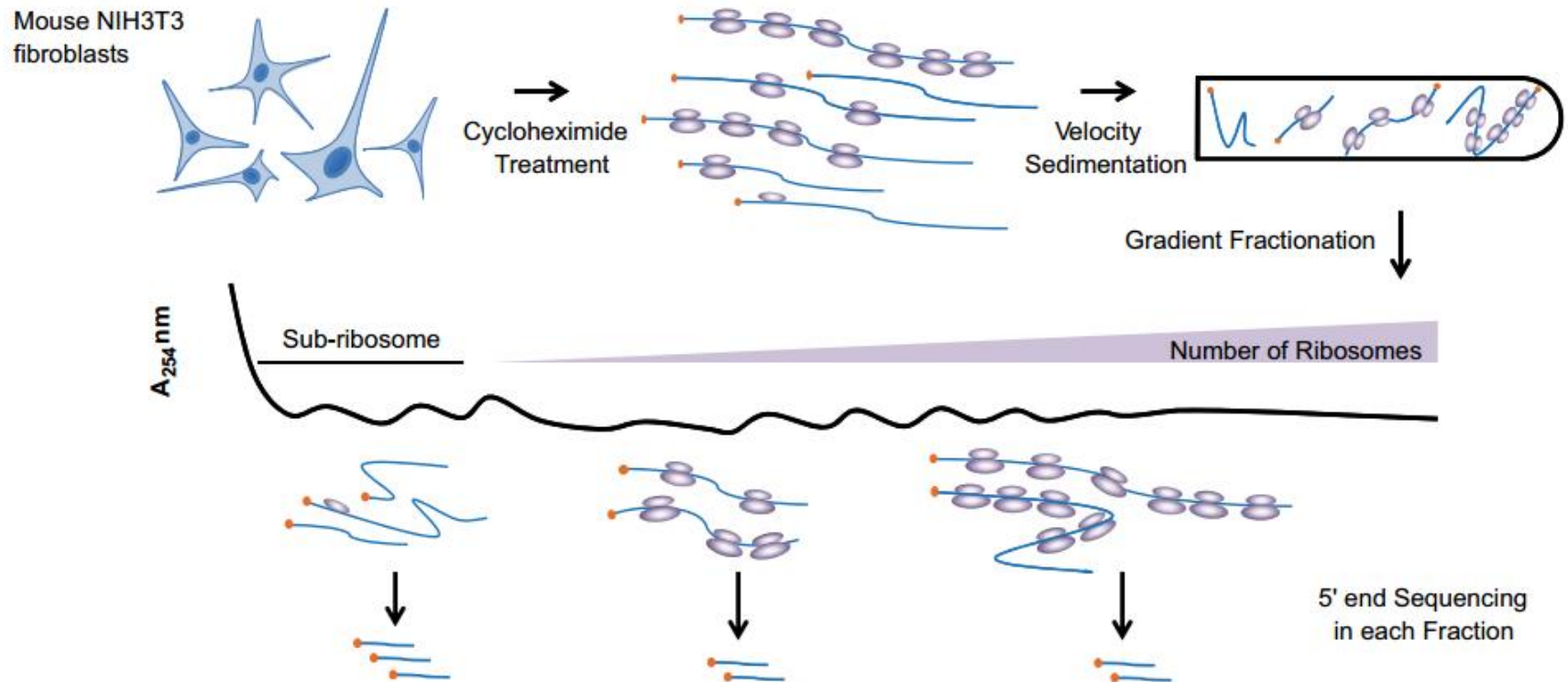# Genome-wide assessment of translational efficiency Associated with distinct TSS isoforms

Methods:

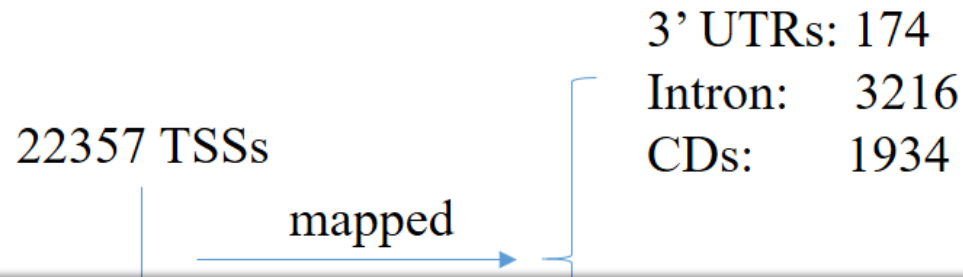   Polysome profiling

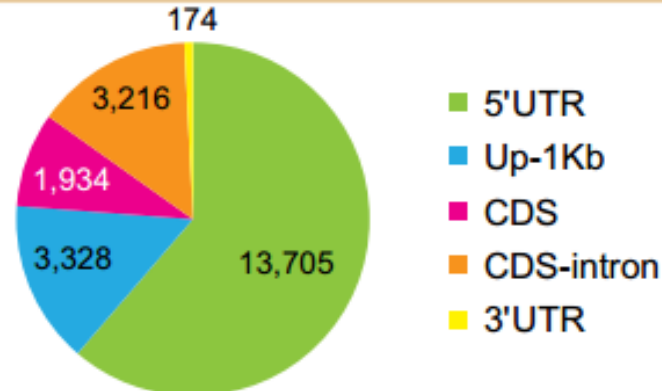   mRNA 5′ end sequencing

Material:

    NIH3T3 mouse fibroblasts

Genome-wide assessment of translational efficiency
Associated with distinct TSS isoforms

22357 TSSs

mapped →

3' UTRs: 174
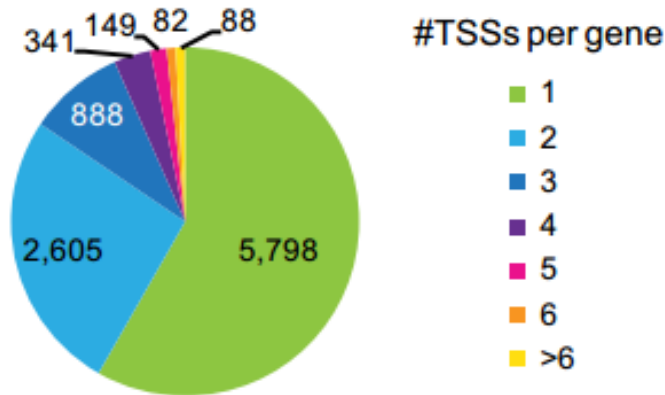Intron: 3216
CDs: 1934

TE (translational efficiency):

calculating the averaged numbers of its associated ribosomes based on their normalized sequencing read counts from different fractions.

Pie chart legend:
- 5'UTR — 13,705
- Up-1Kb — 3,328
- CDS — 1,934
- CDS-intron — 3,216
- 3'UTR — 174

Alternative TSSs lead to differential TE in 745 out of 4153 multi-TSS genes
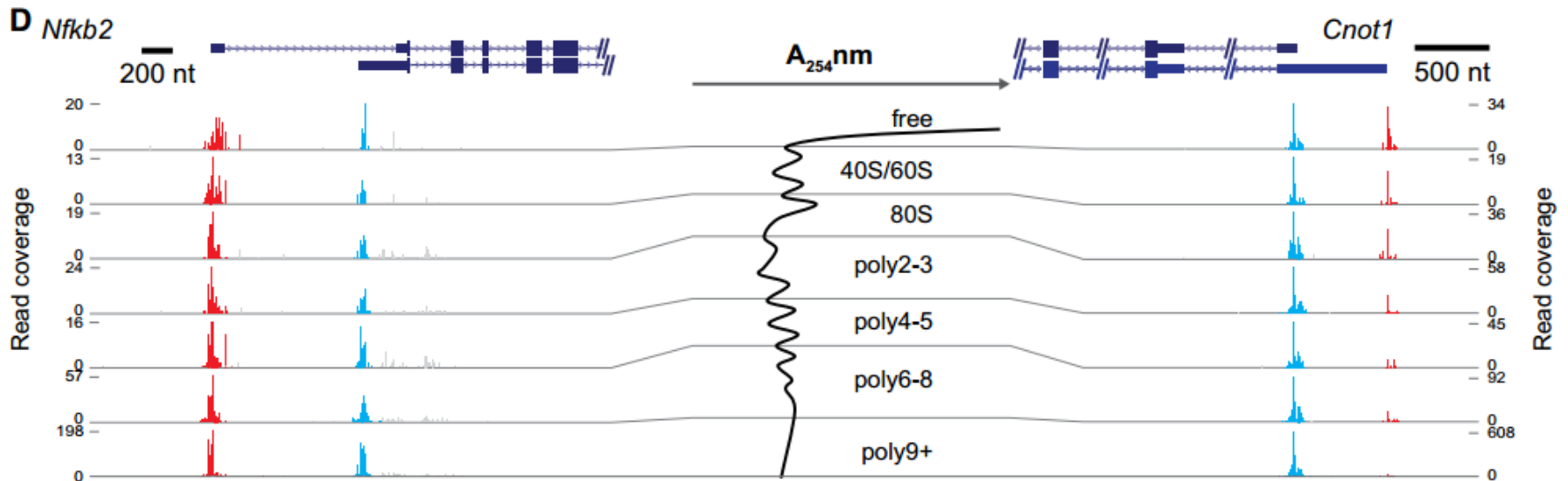

Single :   housekeeping functions
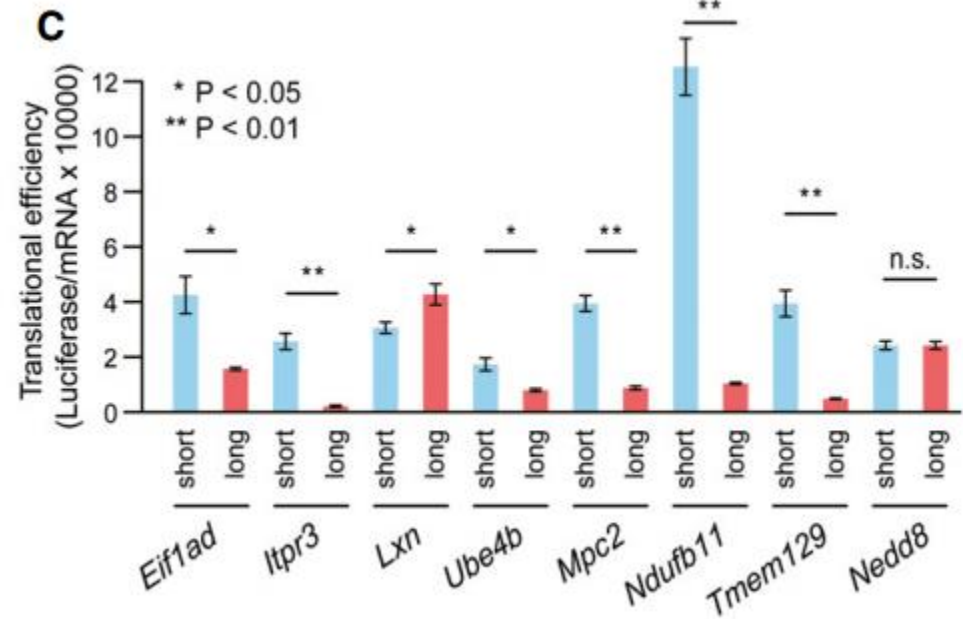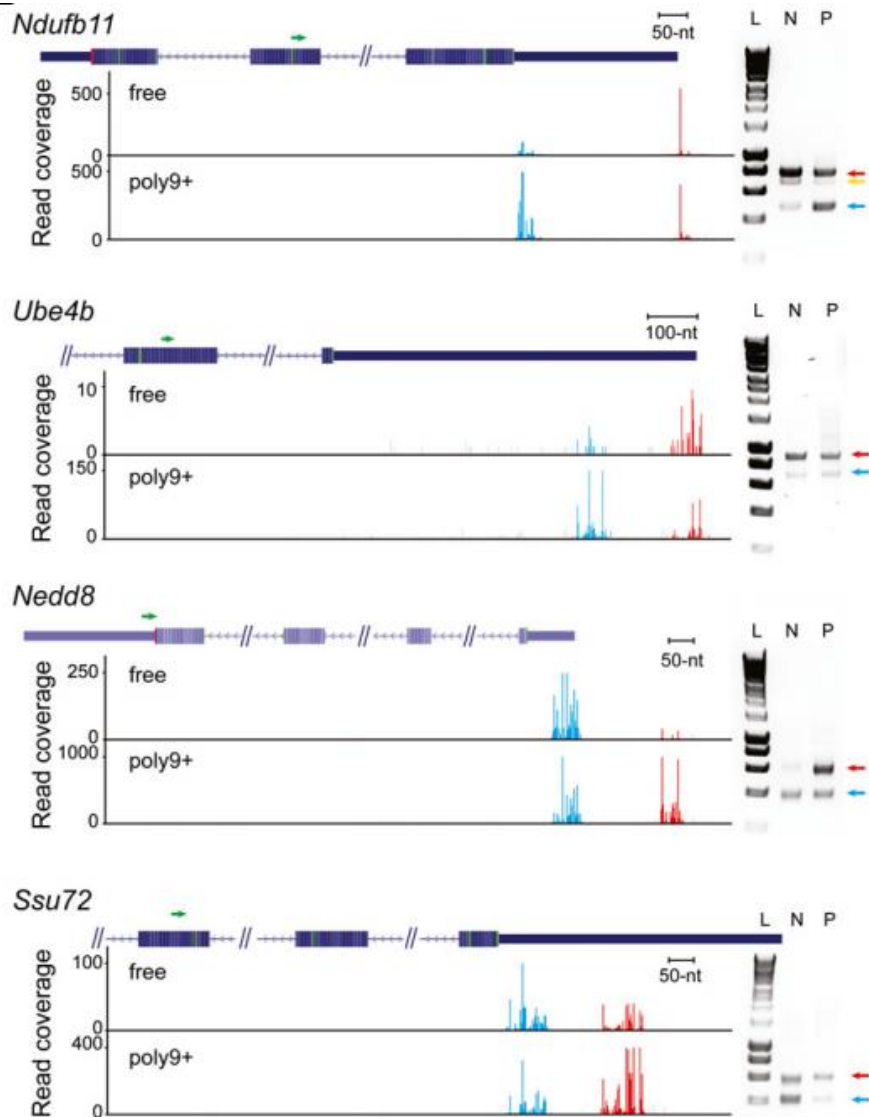
Multiple : regulatory pathways

4153 gene ⟶ 13118 pairwise comparisons

TE value： log2-transformed fold changes spanned a range between 0.02 and 2.2
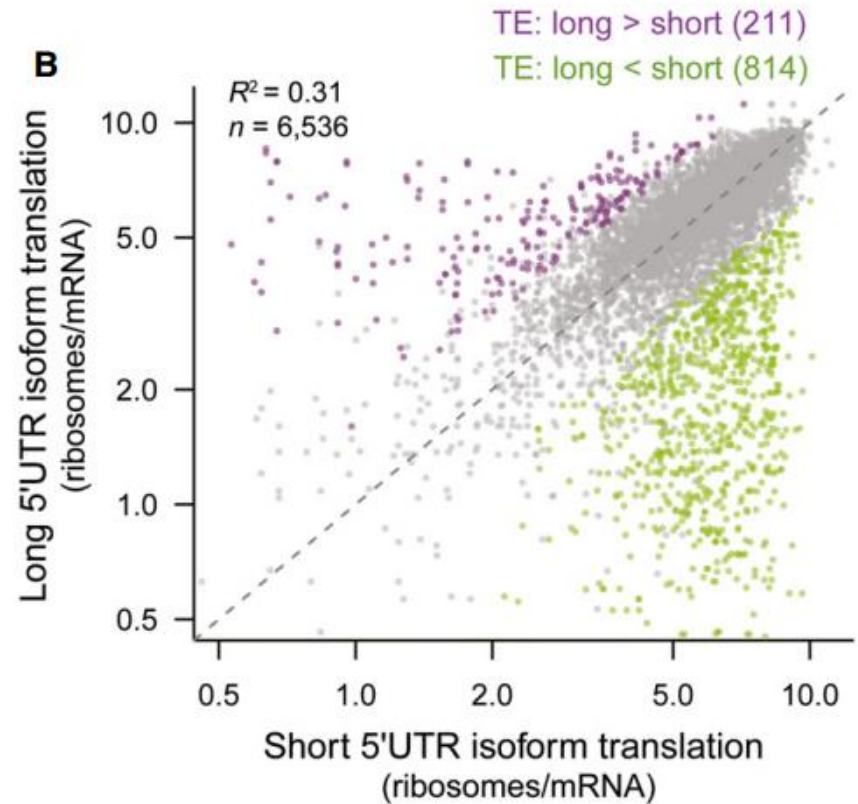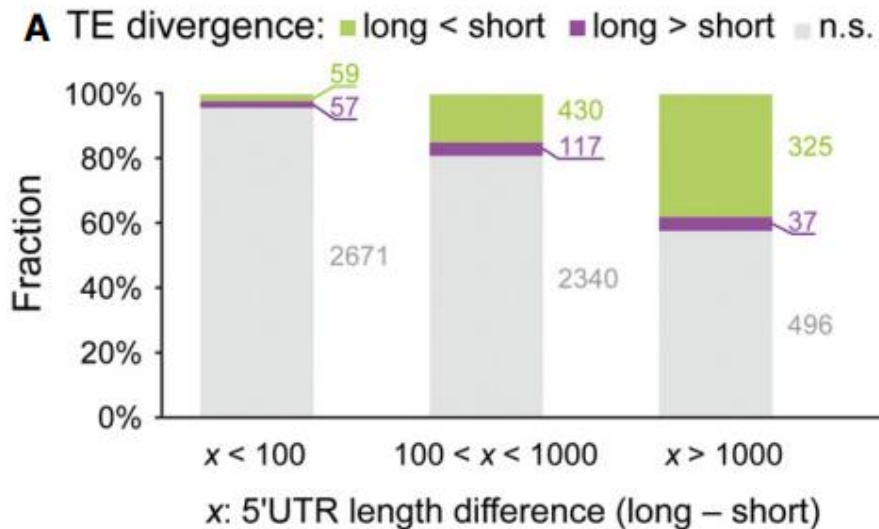
validation

➢ Isoform-specific TE
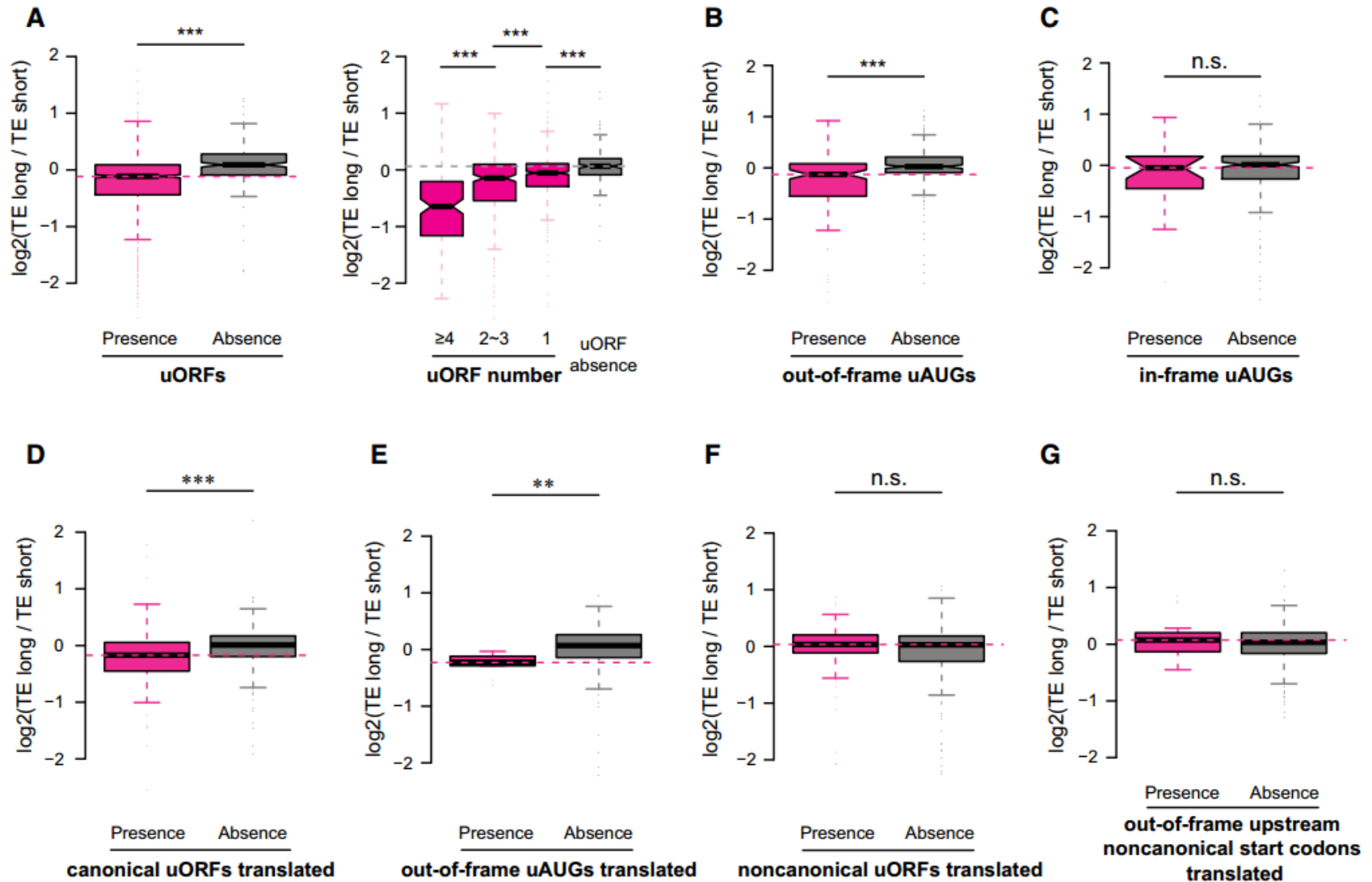
➢ Difference of alternative 5′UTRs

Isoforms with longer 5′UTR tend to have lower translational efficiency

5′UTR length ： **6 536 pairwise** comparisons between alternative isoforms with unambiguously determined 5′UTRs
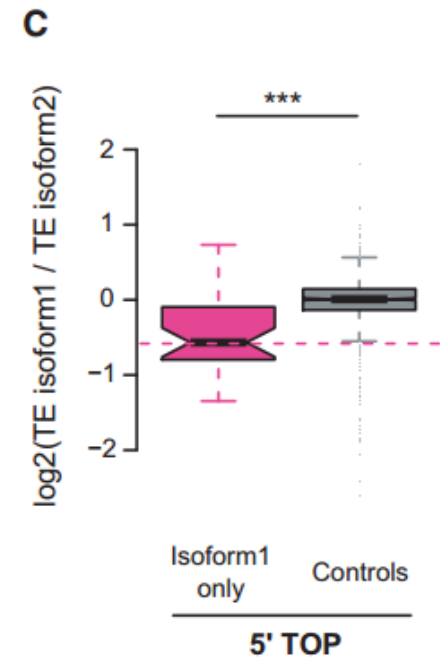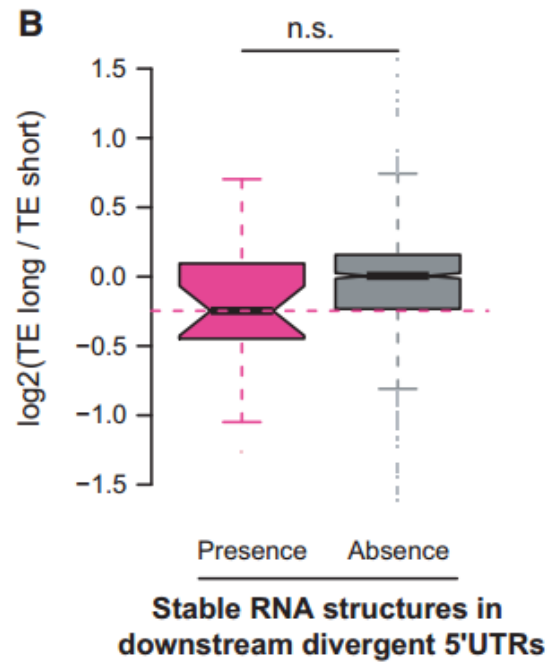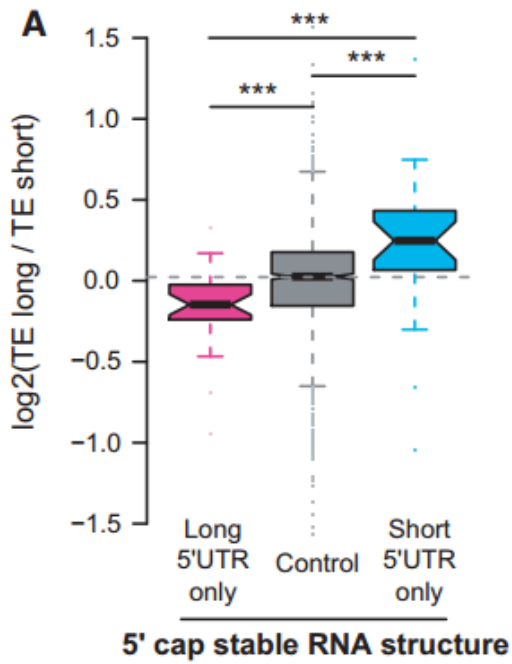

➤ **5′UTR sequences in general comprised of more translational repressive elements than enhancing ones.**

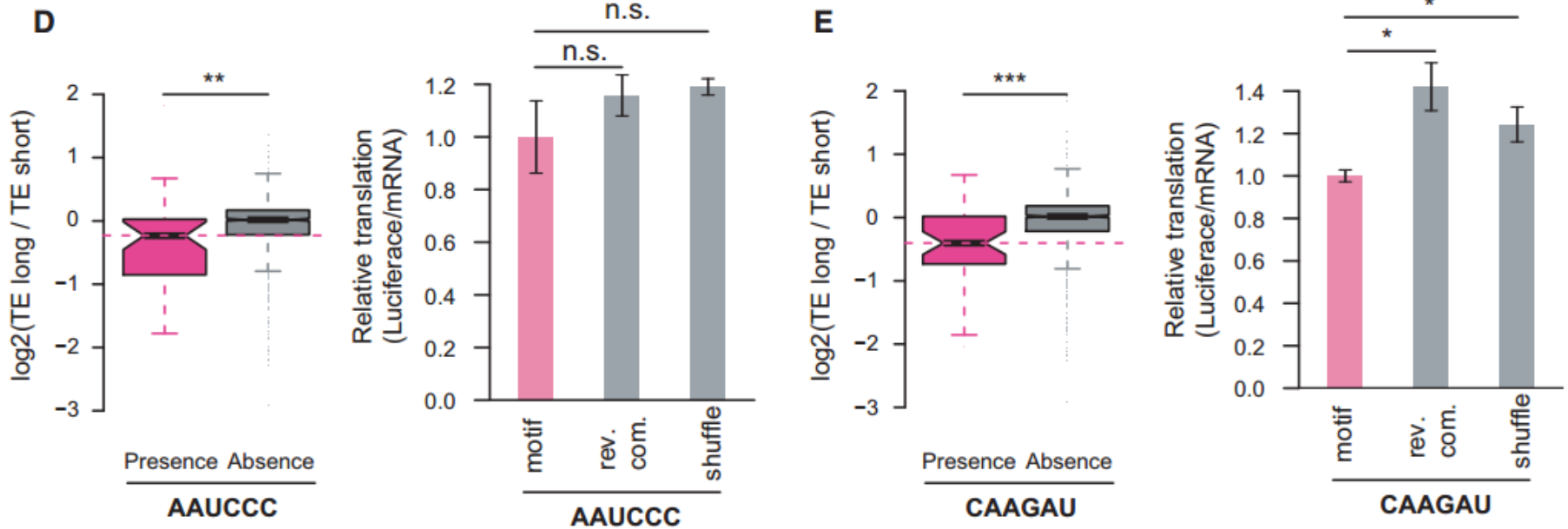# Upstream translation starting at AUG negatively affects the main ORF translation

Cis-elements regulate the translational efficiency

➢ **5′ cap-adjacent stable RNA secondary structures inhibit translation**

➢ **TSS isoforms with 5′ TOP sequences are translated less efficiently**

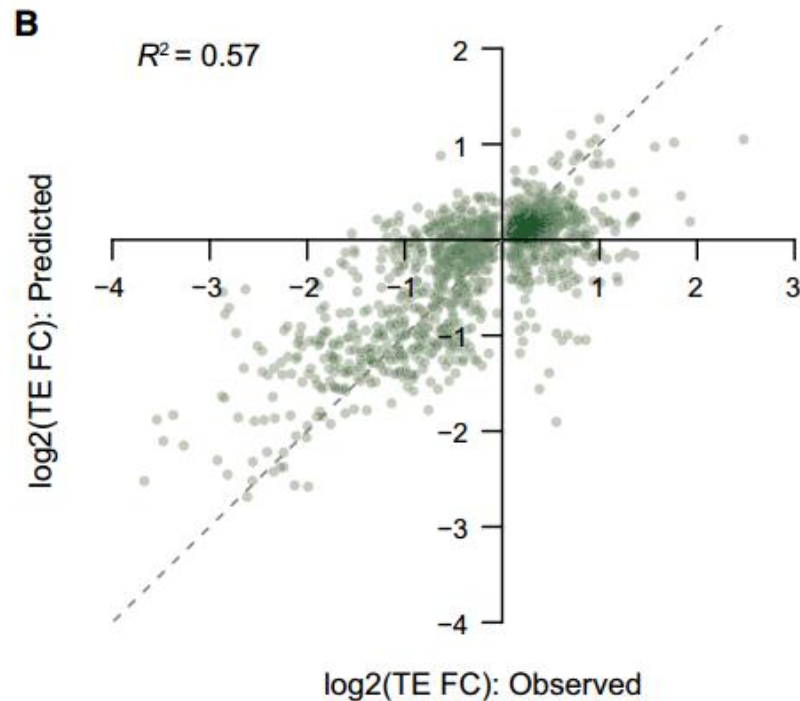# Novel sequence motifs associated with isoform specific translation

➢ **Identified 137 hexamers significantly correlated with the observed TE divergence, all of which acted negatively on translational regulation.**

Quantitative models explaining the TE difference between alternative TSS isoforms

A Contribution of sequence features in the models

Sequence Feature	Individual	Cumulative	Delta cumulative
uORF	35.6%	35.6%	35.6%
divergent 5'UTR length	35.1%	41.3%	5.8%
out-of-frame uAUG	3.7%	43.8%	2.4%
5' cap RNA structure	3.5%	43.9%	0.1%
downstream RNA structure	2.4%	45.7%	1.8%
5' TOP sequence	1.7%	46.5%	0.7%
Hexamers	* 23.2%	56.8%	10.3%

B

$R^2 = 0.57$

log2(TE FC): Predicted

log2(TE FC): Observed

Summary

1. 结论和创新点：

作者通过结合核糖体图谱和mRNA 5'高通量测序技术测量mRNA的实时翻译状态，定量分析可变TSSs和5'UTR对翻译调控的影响。

2. 启发：

结合多种研究方法系统分析揭示生物某一调控过程的发展。

3. 改进：

前人也对3'UTR进行了研究，认为3'UTR对翻译的调控作用可能大于5'UTR的作用，因此可以结合或者比较3'UTR与5'UTR对翻译调控的影响。

Thanks