RNA Rosetta Stone: RNA origami codes for exploring RNA diversity

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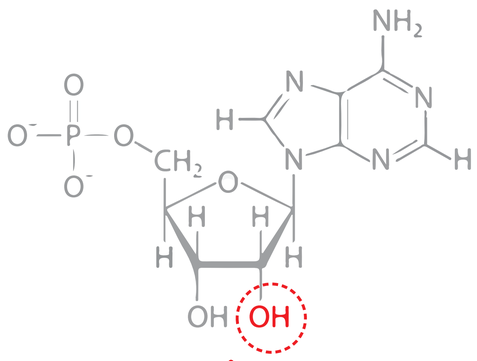
RNA - from genetics to cure

RNA or ribonucleic acid is one of the key biological molecules that bridges our genetic information (**DNA**) and molecular factories (proteins).
RNA is single-stranded in comparison to **DNA** helix.

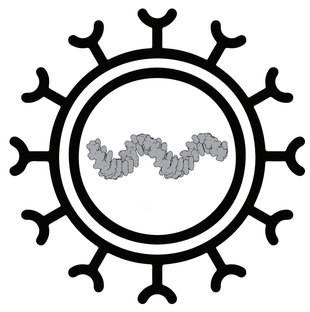
DNA
double-stranded

RNA
single-stranded

RNA differs in one 'letter' and a reactive group that cleaves it. This leads to a shorter RNA read length.



reactive group

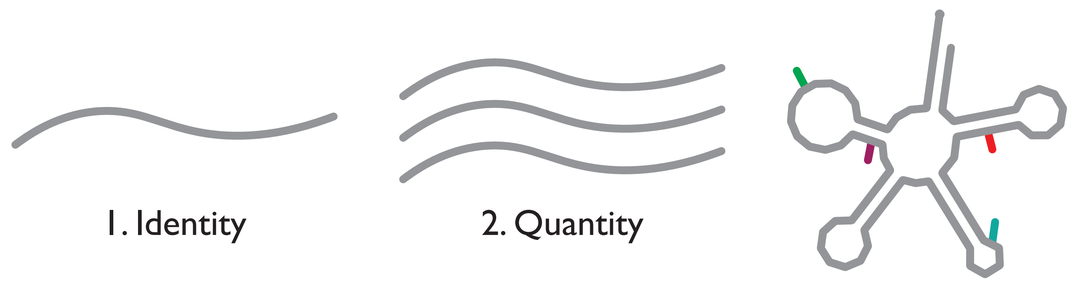


RNA is omnipresent from the genetic material of SARS-CoV-2 to RNA drugs and mRNA vaccines.

Beyond sequence - RNA fingerprint

AAUGCACAGUAGCUUA

RNA sequencing requires a lot of work and includes enzyme biases. Biases lead to the loss of native RNA information. In addition, we are unable to quantify full-length RNAs.
We cannot detect RNA makeup, i.e. chemical modifications, and shape.

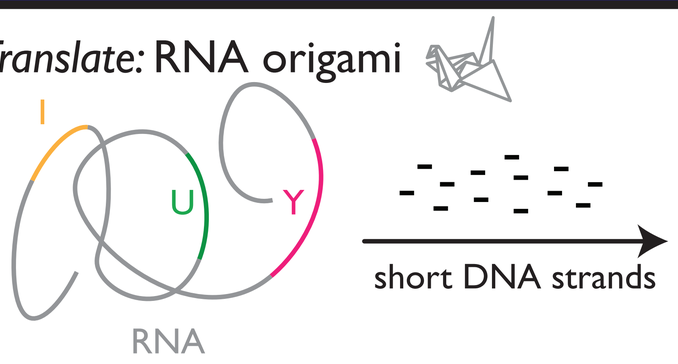


1. Identity
2. Quantity
3. Makeup

Sequence or order of letters does not tell us how RNA looks.
We are curious about identity (cancer and disease variants), quantity, and RNA makeup (RNA modifications that make mRNA vaccine more stable or RNA 3D structure as a target of antiviral drugs).

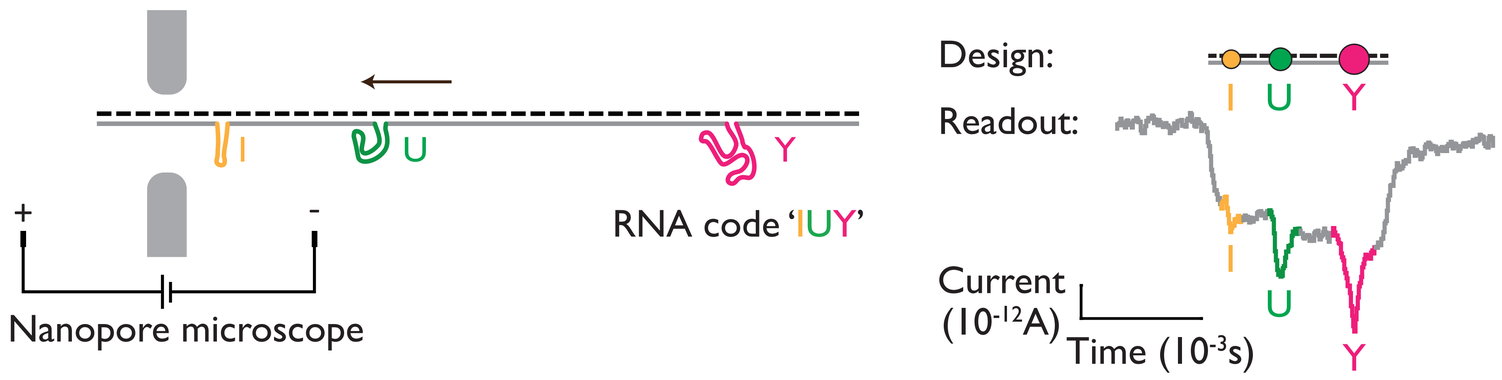
PROBLEM: identify, quantify and characterize innate RNA diversity

Translate: RNA origami



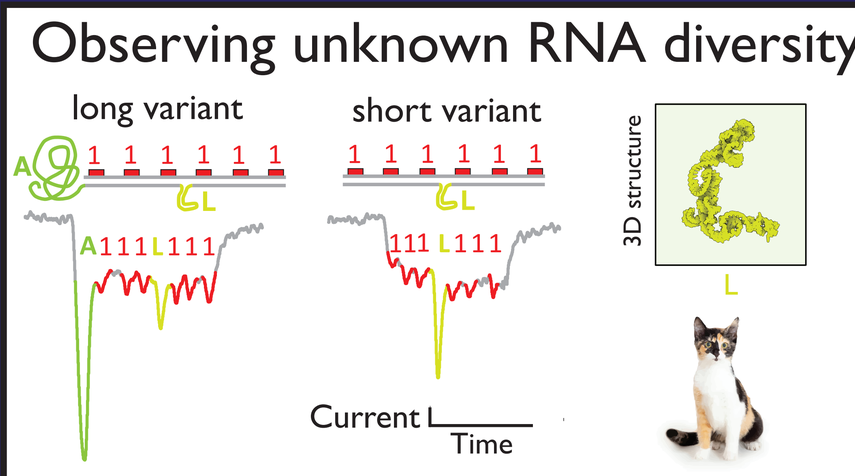
Target RNA is ***translated*** into RNA origami codes with designed sets of complementary DNA strands. Each RNA code has a set of bits (I, U, Y) that correspond to the size of uncomplemented RNA structures. Double-stranded RNA:DNA is stable and reactive group cleavage is absent.

Read: nanopores

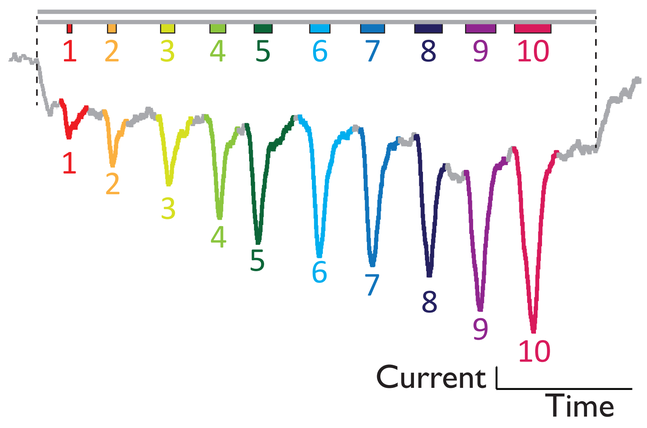


RNA codes are ***read*** with a nanopore microscope. that works via voltage-driven translocation of negatively charged RNA codes through a small orifice towards a positively charged electrode in an electrolyte solution. It translates RNA code into a current signal with 'super-resolution'.

Observing unknown RNA diversity



RNA that inactivates X sex chromosomes in females has two variants in humans (long and short), not only one! How does this variant affect cancer, color blindness, etc?



We can make up to 10 billion RNA codes!

SOLUTION: *translate* RNA sequence to RNA codes and *read* it with nanopores

Output and outlook

We introduce a platform to characterize innate RNAs with implications to chemistry, biology, and medicine.

Chemistry:
we can map RNA modifications and drug targeting RNA motifs.

Biology and Medicine:
we can detect vaccine byproducts that might lead to side effects.

Sustainability:
RNA-based energy-saving data storage and cryptography. RNA origami enabled materials can offer new ways of synthesis at the nanoscale.

Acknowledgments

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References

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[2] Boskovic F., and Keyser U.F., *Nature Chemistry* (revision)
[3] Boskovic F. et al., *medRxiv*, 2021