The Catalyst – Engaging the General Public in RNA Science GoldLab Symposium, May 17, 2024



Thomas R. Cech, Distinguished Professor of Biochemistry, BioFrontiers Inst., CU Boulder Investigator, HHMI Disclosures: Storm Tx, Eikon Tx, SomaLogic

Why is it so hard for scientists to explain their science to the general public?



Why is it so hard for scientists to explain their science to the general public? Jargon – the technical language that facilitates research discussions impairs conversations with non-scientists

Telling people they had to get vaccinated against COVID-19 didn't work well, at least in the U.S.

Fully vaccinated as	<u>of March,</u>	2023
Australia	85%	
Canada	84%	
Brazil	83%	
UK	76%	
Botswana	71%	
India	70%	
Switzerland	70%	
U.S.A.	68%	

Josh Holder, *The New York Times* (March 13, 2023), data from U. of Oxford

The 21st Century is the AGE of RNA

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People are generally comfortable with DNA –

- Inherited traits
- Family history
- Genetic diseases
- Solving crimes



Image: Dzu-Doodles

RNA carries the same information as DNA, but in a single strand



Image: Dzu-Doodles

By now, most people have heard about mRNA



Lipid Nanoparticle mRNA Vaccine



Image: BOC Sciences

Many magazine articles, books, social media

"mRNA is a medicine" "mRNA is a drug"

Image: Clipart Library

mRNA is natural

It's in every cell in our body and It's in all the food we eat



Image: McLean Meats

Do you get my message?

We've known for 60 years:

DNA code \rightarrow messenger RNA \rightarrow Protein



Image: Australian Academy of Science

How to make the protein for vaccine

(Spike protein)



Messenger RNA vaccines take a shortcut!

DNA mRNA Drotein (Spike protein) mRNA Drotein



••• Covid-19 mRNA vaccines are not perfect

- Protect against hospitalization and death, but reinfection occurs
- Virus mutates \rightarrow immune escape
- Cold storage frustrates broad dissemination

O Major advantages of mRNA vaccines

- Adaptable: quick to respond to variant viruses
- Save a million chicken eggs per year



Image: Oliver Bunic/Bloomberg/Getty Images

What will the future hold?

Too early to tell if mRNA vaccines will catalyze a paradigm shift in medicine

- Hopefully, mRNA will provide more effective flu vaccines
- Personalized cancer vaccines are in clinical trials and look promising
- Therapeutic mRNA to replace proteins mutated in genetic diseases?

The 21st Century is the AGE of RNA

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Beyond a message: noncoding RNAs!

1. RNA can be a catalyst – Ribozymes

2. RNA can bestow immortality – Telomerase

3. RNA can guide genome editing – CRISPR







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Tetrahymena thermophila

10,000 copies of a gene that makes RNAs that form part of the protein-synthesis machinery



The functional DNA sequences were interrupted by an intron



Intron removed at RNA level by splicing



Intron removed at RNA level by splicing



RNA splices in the test tube



RNA splices in the test tube – but surprisingly doesn't require extract of nuclei (1980)



What was *catalyzing* Tetrahymena RNA splicing?

There had to be an enzyme, and we knew that

"All enzymes are proteins"

James B. Sumner, Nobel Prize in Chemistry, 1946

It's a Protein, or It's Not ?



Primordial Soup



RNA both carries information and is the copying machine, so at the beginning, an "RNA World"



Image: R. J. Davenport, AAAS 2001

1989 Nobel Prize in Chemistry





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The ends of our chromosomes are vulnerable – they need protection!



Just like the plastic tips on shoelaces.





Telomere DNA shrinks as cells divide, and when short, cells stop dividing. Most human cells (brain, heart, bone) are happy to stop dividing, but stem cells need to proliferate – so they need to extend their telomeres.

THEY NEED TELOMERASE



Image: Stem Cell Network.NRW, Dusseldorf

Telomerase – noncoding RNA + **TERT protein –** builds out chromosome ends, allows cells to proliferate continuously. **Immortality!**



You can lengthen your telomeres on Amazon.com



healthycell		TELOMERASE ACTIV
AGING HEALTHY		
TELOMERE LENGTH TELOMERASE ACTIVATORS NITRIC OXIDE BOOSTERS & CELL REPAIR NUTRIENTS+ SUPPORTS TELOMERES FOR A LO DIETARY SUPPLEMENT	NGER LIFESPAN [†] ³⁰ CAPSULES	DNA REPAR NOP THE NET CODE SCO ENTRY CODE SCO ENTRY COMPOSITIES COMPOSITIES SCORE REPAR REPAR

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Healthycell Telomere Length | Supplement for Lengthening Telomeres and DNA Repair, Anti... Capsule · 30 Count (Pack of 1) 4.3 ★★★★ (682)



Sponsored 🚯

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SRW Cel¹ Stability 60 Capsules | Stem Cell Supplement with 2-HOBA, Astragaloside & Rutin |... Capsule · 60 Count (Pack of 1) 4.9 ★★★★ × (17)



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No FDA approval required for food supplements No clinical trials

If cancer cells need telomerase for immortality, then how is it turned on?

--> Mutation in control region of TERT gene ANA-FARB

Levi Garraway, MD, PhD and his Harvard Med fellow Franklin Huang (2013)

The same mutation in the promoter of the *TERT* gene reactivates telomerase in cancers

- 80% of all melanoma tumors around the world
- 80% of glioblastoma
- 70% of bladder cancer
- 40% of liver cancer
- Absent in breast and colon cancers which still reactivate TERT

Huang et al., *Science* 2013 Horn et al., *Science* 2013

Beyond a message: noncoding RNAs!

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Genome editing is like text editing – but this text is part of 1 Million pages:

War is not the greatest evil, though it is an evil. The open struggle of the battlefield is not the greatest evil; worse is that chronic condition of society which mukes possible the violence of the stronger to the weaker.... Death is not worse than a dishonourable life which destroys its own soul as well as that of its neighbour. Tomáš Garrigue Masaryk

After editing:

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2020 Nobel Prize for CRISPR genome editing



NOBELPRISET I KEMI 2020 THE NOBEL PRIZE IN CHEMISTRY 2020





Emmanuelle Charpentier



Jennifer A. Doudna

"för utveckling av en metod för genomeditering" "for the development of a method for genome editing"



#nobelprize



Cech Lab reunion, 2007

CRISPR cleaves DNA – but not as simple as this!



CRISPR guide RNA finds the target sequence, Cas9 enzyme cleaves the DNA



Melanie de Almeida, LABIOTECH.eu (2018)

Then cellular repair machinery takes over: **Stitches the DNA** back together and can insert new sequences



Melanie de Almeida, LABIOTECH.eu (2018)

CRISPR credited with "the unthinkable power to control evolution," the awesome prospect of "editing humanity," the chance to direct "the future of the human race."

So, should we ban certain uses of CRISPR?

• What if it can be used to reduce pain and suffering? Note: first CRISPR therapy for Sickle Cell approved December 2023

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- What about CRISPR plants and animals in the environment?

CRISPR genome editing is already an outstanding research tool. Medical potential?

Deleting Bad Genes

• Limited uses

Repairing Faulty Genes

- Enormous potential
- Most diseases are genetic or have a genetic component
- Often the cause is clear, but we've had no way to fix it

Messenger RNA: in nature \rightarrow vaccines

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Wrought Studio™

My attempt to bring RNA science & medicine to the general public

Coming in June 2024

W. W. Norton, publisher





SCAN ME



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Dr. Samuel Ramsey

BioFrontiers Inst. hired Dr. Ramsey

- Research on honey bee parasitic mites
- Exceptional communicating science to general public
- Teaches graduate course on Science Communication