



UniversityHospital Zurich



URPP Translational Cancer Research



UZH - URPP Translational Cancer Research - Messenger RNA Platform

Swiss Public Health Conference

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mRNA vaccines

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COVID-19 vaccines



Production of synthetic (ivt) mRNA



Pascolo. Messenger RNA: The Inexpensive Biopharmaceutical. JMEST. Vol. 4 Issue 3, March - 2017

mRNA vaccines: Natural (long used) and synthetic (newly approved)



Facts on synthetic (ivt) mRNA vaccines

- > mRNA IS VERY STABLE (in the abscence of RNases!)
- > RNA-liposome formulations may not be stable (aggregate, change size/form over time or by freeze/thaw)
- RNA in liposome is already an approved drug: Onpattro (Patisiran). Up to 30 mg i.v. every 3 weeks. siRNA. Treatment of polyneuropathy in people with hereditary transthyretin-mediated amyloidosis.
- ivt mRNA vaccines are vegan
- > <u>1 million doses in 6 L and few hours</u> (viruses require 5000 L and few days/weeks for 1 million doses)

1869: In the kitchen of the castle of Tuebingen (Germany), Friedrich Miescher (1844-1895) isolates from the nuclei of human blood cells a new biological phosphate-rich substance that he names Nuclein.

1871: Back in Basel (Switzerland), he re-isolates it from salmon sperm. From such samples DNA and RNA were later on characterized

1889 Altman names the phosphate-rich product nucleic acid

1901 Kossel discovers nucleotides (A, C, G, T, U)

1929 Levene and Jacobs dissociate RNA and DNA

1943 Avery finds that DNA is the genetic material

1953 Complementarity of bases and structure of DNA: Watson and Crick



From the Portrait Collection of the University of Basel

Discovery of mRNA: 1961



Artist: Caroline Schupbach

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Martinon et al use mRNA in liposomes to vaccinate mice against Influenza



Martinon....Meulien. European Journal of Immunology 1993 "Induction of virus-specific cytotoxic T lymphocytes in vivo by liposome-entrapped mRNA"

Martinon et al use mRNA in liposomes to vaccinate mice against Influenza



Artist: Caroline Schupbach

Martinon et al use mRNA in liposomes to vaccinate mice against Influenza



Probst....Pascolo. Gene Therapy 2007 "Spontaneous cellular uptake of exogenous messenger RNA in vivo is nucleic acid-specific, saturable and ion dependent"

Martinon et al use mRNA in liposomes to vaccinate mice against Influenza



Probst....Pascolo. J Immunother 2008 "Results of the first phase I/II clinical vaccination trial with direct injection of mRNA"

11/20

Martinon et al use mRNA in liposomes to vaccinate mice against Influenza



Ozlem Tureci CMO and Ugur Sahin CEO/CSO BioNTech

ivt mRNA vaccines against SARS-CoV-2

In liposomes, intramuscular, coding Spike

Moderna: <u>PseudoU</u> mRNA. Started March 16 > 25 μ g, 100 μ g, or 250 μ g.

BioNTech/Pfizer: <u>PseudoU (BNT162b) and U (BNT162a)</u> mRNA. Started April 23 > 1µg up to 100µg

CureVac: <u>U</u> mRNA. Started June. > 2µg up to 12µg

Safe and well tolerated although there were some side effects

ALL VOLUNTEERS SEROCOVERTED – NEUTRALISING ANTIBODIES AFTER BOOST

Approved: 100 μ g for Moderna and 30 μ g for BioNTech/Pfizer. CureVac failed with 12 μ g

Over 95% protection against COVID-19 and 94% protection against infection by SARS-CoV-2 (BioNTech/Pfizer results in Israel)

Variants: "With the BNT162b2 vaccine, the effectiveness of two doses was 93.7% among persons with the alpha variant and 88.0% among those with the delta variant. With the ChAdOx1 nCoV-19 vaccine, the effectiveness of two doses was 74.5% among persons with the alpha variant and 67.0% among those with the delta variant.

Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant | NEJM July 2021

ivt mRNA vaccines against SARS-CoV-2

BioNTech/Pfizer. https://www.nejm.org/doi/full/10.1056/NEJMoa2027906 October 14, 2020



mRNA platform @ URPP since January 2017

https://www.cancer.uzh.ch/en/Research/mRNA-Platform.html





mRNA platform @ URPP Production & Optimisation of mRNA (coding luciferase)





4.0\$10

mRNA platform @ URPP Production & Optimisation of mRNA (coding luciferase)

in vitro

HEK



in vivo









mRNA platform @ URPP

https://www.cancer.uzh.ch/en/Research/mRNA-Platform.html

Swiss National Science Foundation NRP78 "An optimised prophylactic mRNA vaccine against coronavirus disease 2019"

> EU grant «NEWmRNA» Monique Dornonville de la Cour Stiftung UZH URPP «Translational Cancer Research» UZH Stiftung für wissenschaftliche Forschung



Synthetic mRNA: Tomorrow

- Vaccines against (all) viruses
- > Vaccines against cancer (shared tumor antigens or individualised vaccines against mutations)
- Vaccines against allergies
- > Expression of therapeutic proteins: erythropoïétine, antibodies, bispecifics, etc
- Regeneration: blood vessels, retina, skin, muscles, neurones...
- Reprogramming cells: iPSC, CAR-T cells
- Modifying genomes (Meganucleases, TALEN, CRISPR/CAS)

CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis Gillmore, et al. Lebwohl. N Engl J Med 2021; 385:493-502



> Tolérisation spécifique du système immunitaire

<u>A noninflammatory mRNA vaccine for treatment of experimental autoimmune encephalomyelitis.</u> Krienke, et al. Sahin. Science. 2021 Jan 8;371(6525):145-153.

Thanks for your attention

Synthetic Messenger RNA-Based Vaccines: from Scorn to Hype. Pascolo S. Viruses. 2021 Feb 9;13(2):270. doi: 10.3390/v13020270.

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