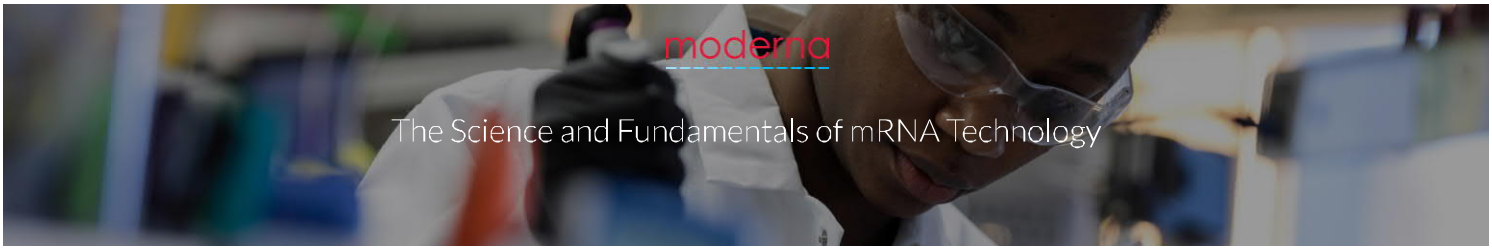


What does mRNA do? mRNA produces instructions to make proteins that may treat or prevent disease

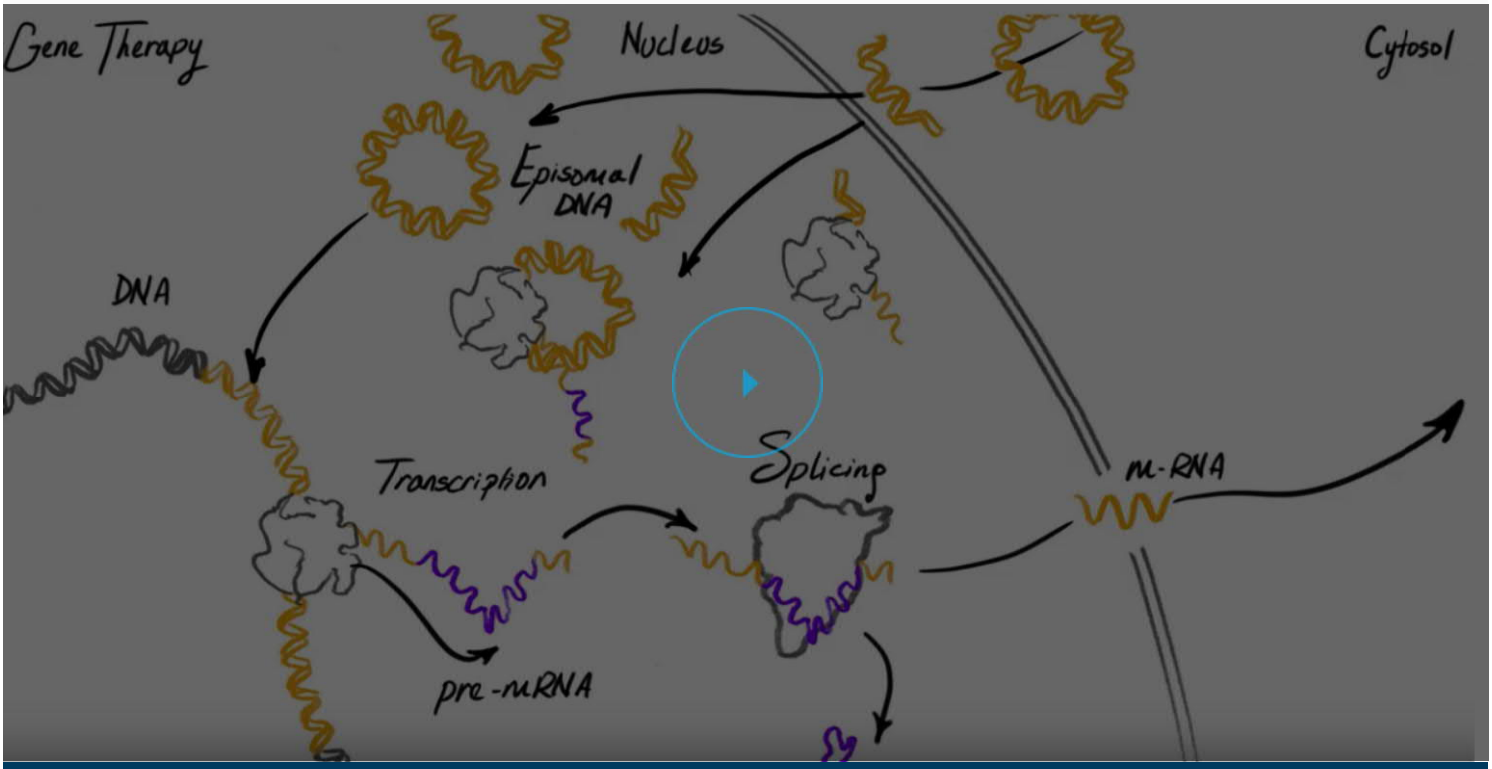
mRNA medicines aren't small molecules, like traditional pharmaceuticals. And they aren't traditional biologics (recombinant proteins and monoclonal antibodies) – which were the genesis of the biotech industry. Instead, mRNA medicines are sets of instructions. And these instructions direct cells in the body to make proteins to prevent or fight disease.

It's actually basic human biology.

DNA (deoxyribonucleic acid) is a double-stranded molecule that stores the genetic instructions your body's cells need to make proteins. Proteins, on the other hand, are the 'workhorses' of the body. Nearly every function in the human body – both normal and disease-related – is carried out by one or many proteins.

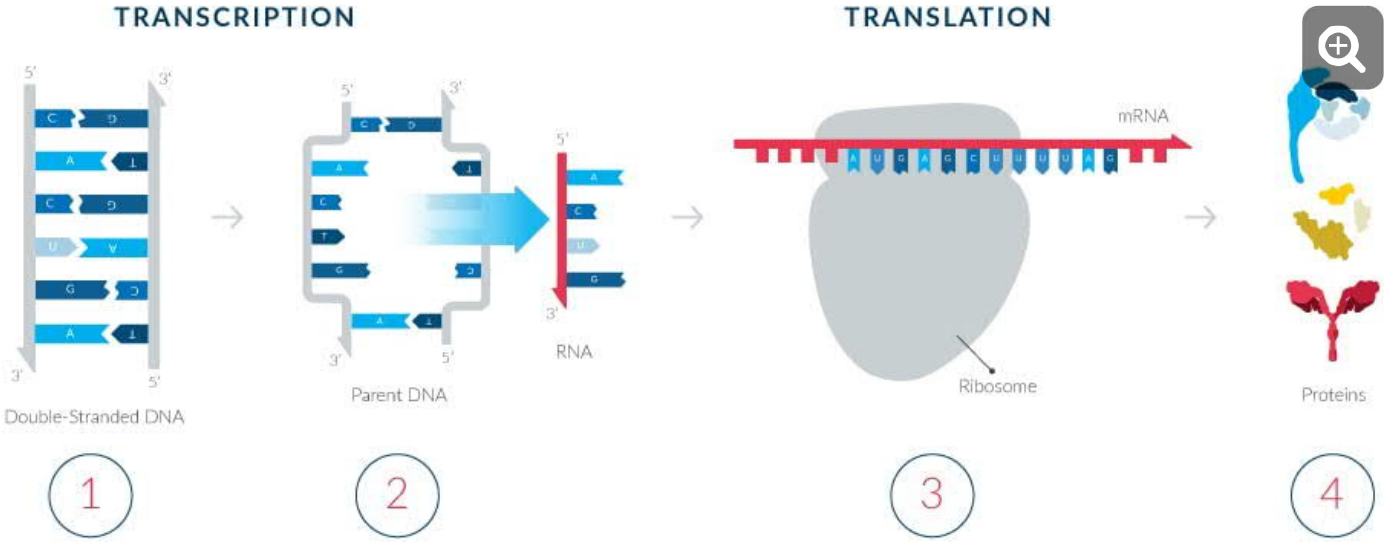
mRNA is just as critical as DNA.

Without mRNA, your genetic code would never get used by your body. Proteins would never get made. And your body wouldn't – actually couldn't – perform its functions. Messenger ribonucleuc acid, or mRNA for short, plays a vital role in human biology, specifically in a process known as protein synthesis. mRNA is a single-stranded molecule that carries genetic code from DNA in a cell's nucleus to ribosomes, the cell's protein-making machinery.



Learn about messenger RNA's role in human biology, the instructions it provides that direct cells in the body to make proteins, and why we believe mRNA medicines may have the potential to treat a broad array of diseases.

mRNA's role in protein synthesis



1 Through a process known as transcription, an RNA copy of a DNA sequence for creating a given protein is made.

2 This copy – mRNA – travels from the nucleus of the cell to the part of the cell known as the cytoplasm, which houses ribosomes. Ribosomes are complex machinery in the cells that are responsible for making proteins.

3 Then, through another process known as translation, ribosomes 'read' the mRNA, and follow the instructions, creating the protein step by step.

4 The cell then expresses the protein and it, in turn, carries out its designated function in the cell or the body.

Using mRNA to develop a new category of medicines.

At Moderna, we are leveraging the fundamental role that mRNA plays in protein synthesis. We have developed proprietary technologies and methods to create mRNA sequences that cells recognize as if they were produced in the body. We focus on diseases where enabling targeted cells to produce – or turn 'on' – one or more given proteins will enable the body to fight or prevent a given disease.

- We start with our desired sequence for a protein.
- We design and synthesize the corresponding mRNA sequence – the code that will create that protein.
- Before synthesis, we also engineer that mRNA sequence to optimize the mRNA's physical properties, as well as those of the encoded protein.
- We deliver the mRNA sequence to the cells responsible for making that protein via one of several modalities. Reaching different types of cells requires different delivery methods.
- And, once the mRNA – the instructions – are in the cell … human biology takes over. Ribosomes read the code and build the protein, and the cells express the protein in the body.

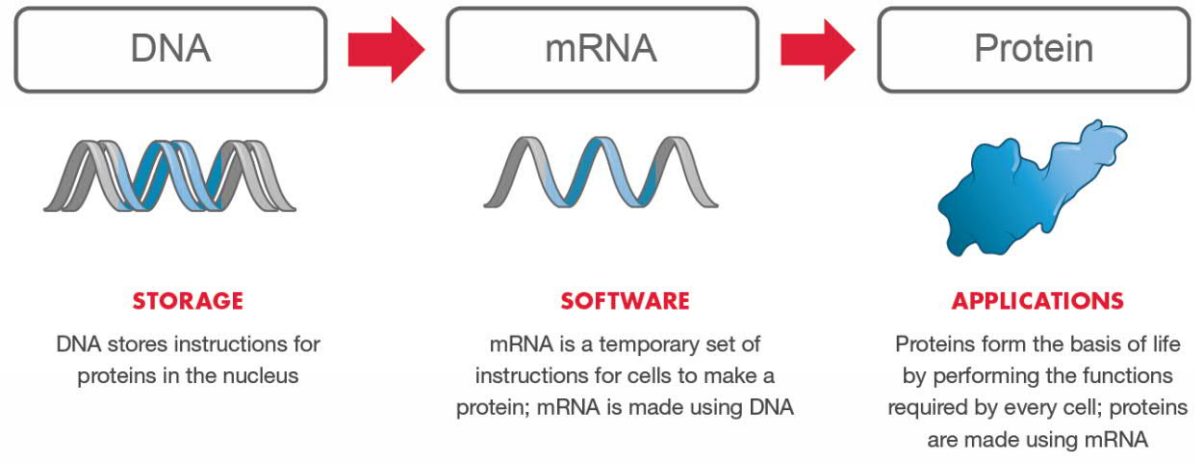
Enabling Drug Discovery & Development

We built Moderna on the guiding premise that if using mRNA as a medicine works for one disease, it should work for many diseases. And, if this is possible – given the right approach and infrastructure – it could meaningfully improve how medicines are discovered, developed and manufactured.

Our Operating System

Recognizing the broad potential of mRNA science, we set out to create an mRNA technology platform that functions very much like an operating system on a computer. It is designed so that it can plug and play interchangeably with different programs. In our case, the "program" or "app" is our mRNA drug - the unique mRNA sequence that codes for a protein.

We have a dedicated team of several hundred scientists and engineers solely focused on advancing Moderna's platform technology. They are organized around key disciplines and work in an integrated fashion to advance knowledge surrounding mRNA science and solve for challenges that are unique to mRNA drug development. Some of these disciplines include mRNA biology, chemistry, formulation & delivery, bioinformatics and protein engineering.

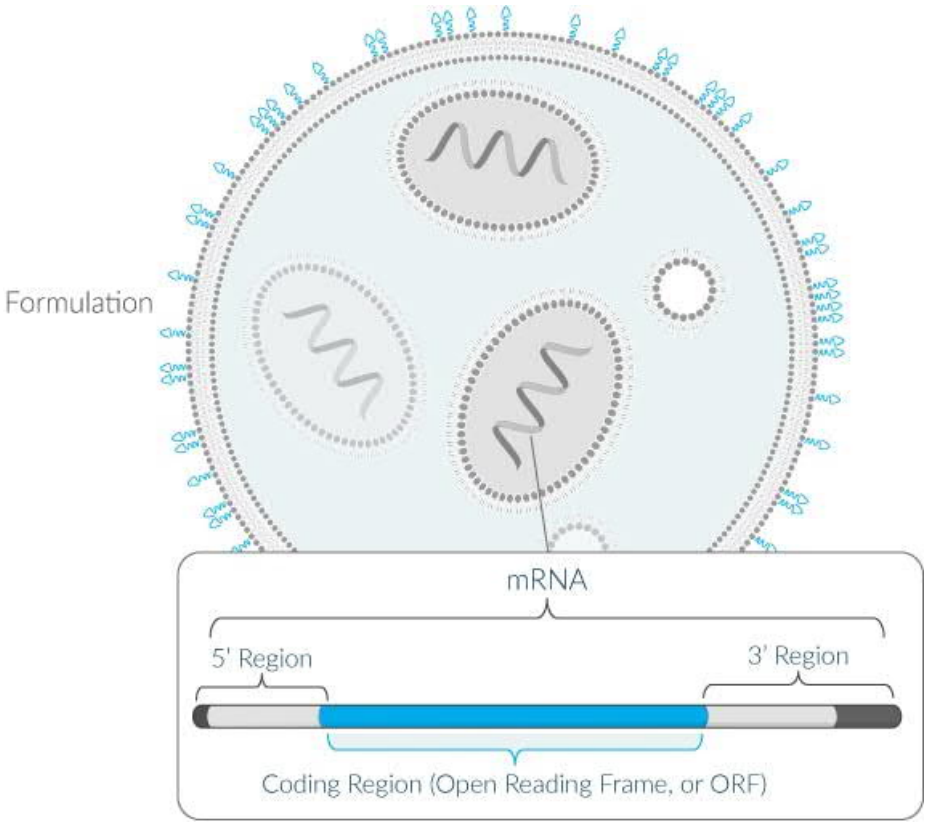


Our mRNA Medicines – The 'Software of Life'

When we have a concept for a new mRNA medicine and begin research, fundamental components are already in place.

Generally, the only thing that changes from one potential mRNA medicine to another is the coding region – the actual genetic code that instructs ribosomes to make protein. Utilizing these instruction sets gives our investigational mRNA medicines a software-like quality. We also have the ability to combine different mRNA sequences encoding for different proteins in a single mRNA investigational medicine.

We are leveraging the flexibility afforded by our platform and the fundamental role mRNA plays in protein synthesis to pursue mRNA medicines for a broad spectrum of diseases.



Within a given modality, the base components are generally identical across development candidates - formulation, 5' region and 3' region. Only the coding region varies based on the protein/s the potential medicine is directing cells to produce.

Learn how our Research Engine and Early Development Engine are enabling us to fully maximize the promise of mRNA to meaningfully improve how medicines are discovered, developed and manufactured.

Overcoming Key Challenges

Using mRNA to create medicines is a complex undertaking and requires overcoming novel scientific and technical challenges. We need to get the mRNA into the targeted tissue and cells while evading the immune system. If the immune system is triggered, the resultant response may limit protein production and, thus, limit the therapeutic benefit of mRNA medicines. We also need ribosomes to think the mRNA was produced naturally, so they can accurately read the instructions to produce the right protein. And we need to ensure the cells express enough of the protein to have the desired therapeutic effect.

Our multidisciplinary platform teams work together closely to address these scientific and technical challenges. This intensive cross-functional collaboration has enabled us to advance key aspects of our platform and make significant strides to deliver mRNA medicines for patients.

US010703789B2

(12) **United States Patent**
De Fougerolles et al.

(10) **Patent No.: US 10,703,789 B2**
(45) **Date of Patent: *Jul. 7, 2020**

(54) **MODIFIED POLYNUCLEOTIDES FOR THE PRODUCTION OF SECRETED PROTEINS**

(71) Applicant: **ModernaTX, Inc.**, Cambridge, MA (US)

(72) Inventors: **Antonin De Fougerolles**, Waterloo (BE); **Justin Guild**, Framingham, MA (US)

(73) Assignee: **ModernaTX, Inc.**, Cambridge, MA (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **16/438,978**

(22) Filed: **Jun. 12, 2019**

(65) **Prior Publication Data**

US 2020/0017565 A1 Jan. 16, 2020

Related U.S. Application Data

(63) Continuation of application No. 14/987,328, filed on Jan. 4, 2016, now Pat. No. 10,385,106, which is a (Continued)

(51) **Int. Cl.**

A61K 48/00	(2006.01)
A61K 38/17	(2006.01)
A61K 47/54	(2017.01)
A61K 9/127	(2006.01)
C07K 14/535	(2006.01)
C12N 15/88	(2006.01)
A61K 9/50	(2006.01)
C07K 14/47	(2006.01)
A61K 31/7088	(2006.01)
C07K 19/00	(2006.01)
C12N 15/85	(2006.01)
A61K 38/18	(2006.01)
A61K 38/19	(2006.01)
A61K 38/48	(2006.01)
A61K 9/14	(2006.01)
A61K 47/10	(2017.01)
A61K 38/21	(2006.01)
A61K 38/36	(2006.01)
A61K 38/44	(2006.01)
A61K 39/395	(2006.01)

(Continued)

(52) **U.S. Cl.**

CPC ***C07K 14/535*** (2013.01); ***A61K 9/1271*** (2013.01); ***A61K 9/1272*** (2013.01); ***A61K 9/1277*** (2013.01); ***A61K 9/14*** (2013.01); ***A61K 9/5031*** (2013.01); ***A61K 31/7088*** (2013.01); ***A61K 38/1767*** (2013.01); ***A61K 38/1816*** (2013.01); ***A61K 38/1866*** (2013.01); ***A61K 38/191*** (2013.01); ***A61K 38/193*** (2013.01); ***A61K 38/212*** (2013.01); ***A61K 38/215*** (2013.01); ***A61K 38/36*** (2013.01); ***A61K 38/363*** (2013.01); ***A61K 38/44*** (2013.01); ***A61K 38/4833*** (2013.01); ***A61K 38/4846*** (2013.01); ***A61K 39/3955*** (2013.01); ***A61K 47/10*** (2013.01); ***A61K 47/54*** (2017.08); ***A61K 47/542*** (2017.08); ***A61K 48/0033*** (2013.01); ***A61K 48/0066*** (2013.01); ***A61K 48/0075*** (2013.01); ***C07K 14/47*** (2013.01); ***C07K 14/475*** (2013.01); ***C07K 14/505*** (2013.01); ***C07K 14/525*** (2013.01); ***C07K 14/56*** (2013.01); ***C07K 14/565*** (2013.01); ***C07K 14/745*** (2013.01); ***C07K 14/75*** (2013.01); ***C07K 16/2887*** (2013.01); ***C07K 16/32*** (2013.01); ***C07K 19/00*** (2013.01); ***C12N 9/0069*** (2013.01); ***C12N 9/644*** (2013.01); ***C12N 15/85*** (2013.01); ***C12N 15/88*** (2013.01); ***C12Y 113/12007*** (2013.01); ***C12Y 304/21005*** (2013.01); ***C12Y 304/21022*** (2013.01); *A61K 9/0019* (2013.01); *A61K 48/00* (2013.01); *C12N 2840/00* (2013.01)

(58) **Field of Classification Search**

CPC C07H 21/02; C12N 15/67; C12N 15/11

See application file for complete search history.

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Primary Examiner — Antonio Galisteo Gonzalez
(74) *Attorney, Agent, or Firm* — Clark & Elbing LLP

(57) **ABSTRACT**

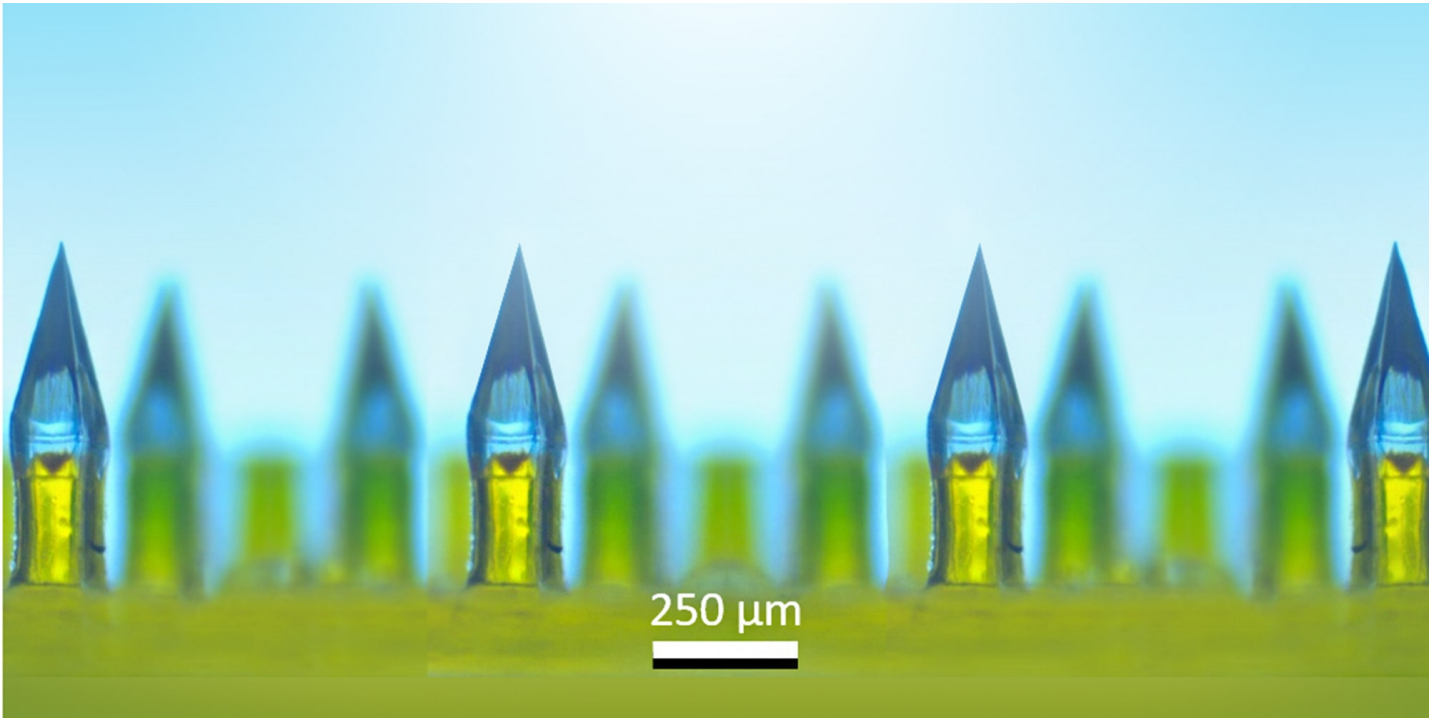
A pharmaceutical composition which has a plurality of lipid nanoparticles that has a mean particle size of between 80 nm and 160 nm and contains a modified mRNA encoding a polypeptide. The lipid nanoparticles include a cationic lipid, a neutral lipid, a cholesterol, and a PEG lipid. The mRNA contains a 5'-cap, 5'-UTR, N1-methyl-pseudouridine, a 3'-UTR, and a poly-A region with at least 100 nucleotides.

14 Claims, 14 Drawing Sheets

Specification includes a Sequence Listing.

Carnegie Mellon University

News



April 08, 2020

CMU-Developed Microneedle Patches Ready for COVID-19 Fight

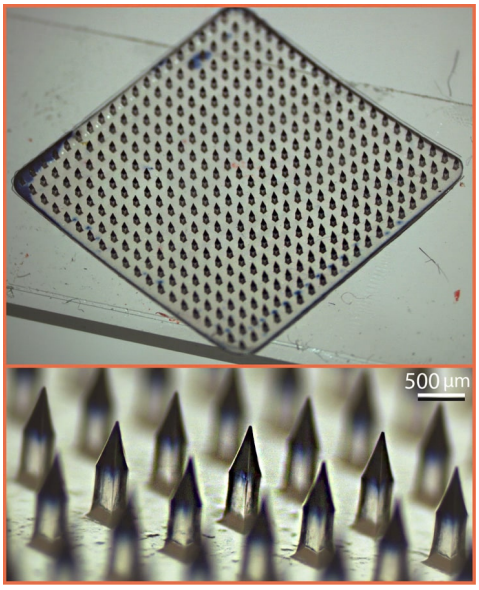
By Lisa Kulick Email (mailto:lkulick@andrew.cmu.edu)

Media Inquiries
Lisa Kulick

- *College of Engineering*
- *Email (mailto:lkulick@andrew.cmu.edu)*
- *412-268-5444*

As health care professionals battle the COVID-19 pandemic on the front lines, engineers are working behind the scenes with innovative technologies to tip the scales in this global fight.

Microneedle arrays contain hundreds of painless, dissolvable, tiny needles clustered on a miniature patch for delivery of vaccines or medications.



COVID-19 Response

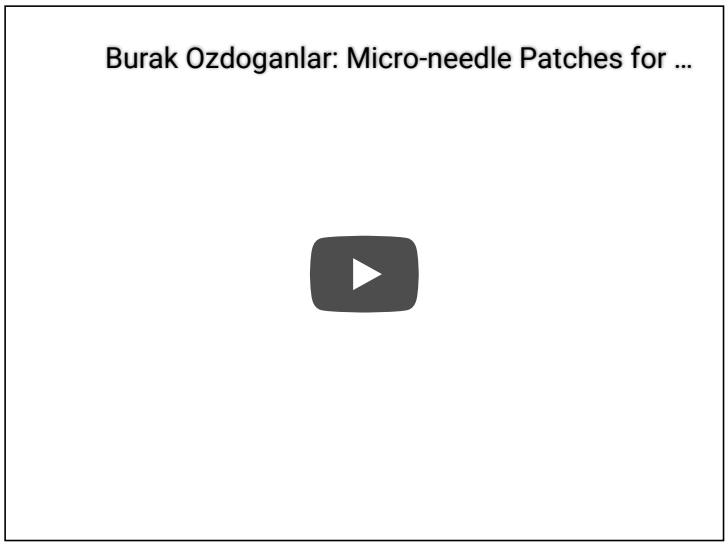
Carnegie Mellon University's Burak Ozdoganlar, who developed the manufacturing technique for dissolvable microneedle arrays, is offering to fabricate these patches for researchers working on potential vaccines and treatments.

These are the same microneedle patches co-developed by Carnegie Mellon University and the University of Pittsburgh Medical Center and recently announced for use with the PittCoVacc vaccine.

"I'm seeking researchers who are working on a vaccine against, or treatment for, SARS-CoV-2 to collaborate with me," said Ozdoganlar, a professor of mechanical engineering at Carnegie Mellon. "My lab can fabricate hundreds of microneedle arrays with your viable vaccine or antiviral drug very quickly for testing in your vaccine and drug development, and we can ramp up to thousands if needed.

"Furthermore, once a viable vaccine is identified, we can provide the necessary expertise, experience, and connections to scale up the manufacturing of the vaccine patches using Good Manufacturing Practice (GMP) guidelines to the levels that will effectively address the COVID-19 vaccination needs. We are here to do our part in providing support throughout this epidemic."

Ozdoganlar has been developing and innovating microneedle array drug delivery devices since 2006.



Burak Ozdoganlar discusses his work in microneedle array technology, an alternative to hypodermic needles or other oral drug delivery that provides significant advantages over traditional methods.

Microneedle arrays contain hundreds of tiny needles clustered on a miniature patch about the size of a contact lens. The microneedles are made from biodissolvable sugar-like natural materials, and the vaccine or drug to be delivered is mixed with this water-soluble material when fabricating the microneedles. When applied onto the skin, the microneedles quickly dissolve and deliver the medication. Due to the small size of the needles, the microneedle patch causes no pain or bleeding.

While the arrays are being tested on humans to deliver chemotherapy as a treatment for skin cancer, they also hold strong potential for use in vaccination and other treatments.

The technology is particularly promising for delivering vaccines or antibodies to fight pathogens since abrasions to the skin — even very tiny ones — produce an immediate and powerful response from the immune system. Traditional syringe vaccines that enter muscle tissue do not elicit quite as effective a response; they require a much larger dose of vaccine than microneedles do to achieve the desired immunity or treatment. Therefore, vaccination and treatment through microneedle array patches can be significantly more effective and faster than using hypodermic needles.

Ozdoganlar is eager to help researchers worldwide who are working to fight the coronavirus. Potential collaborators should send inquiries to: ozdoganlar@cmu.edu (mailto:ozdoganlar@cmu.edu).

Ozdoganlar is the Ver Planck professor in mechanical engineering and the associate director of CMU's Engineering Research Accelerator. He holds courtesy appointments in biomedical engineering and materials science and engineering. He is a Fellow of the American Society of Mechanical Engineers.

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Carnegie Mellon University
5000 Forbes Avenue
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