COVID-19
due anni dopo

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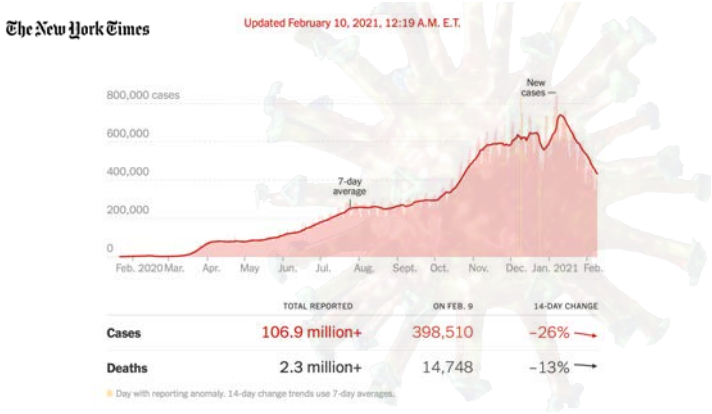
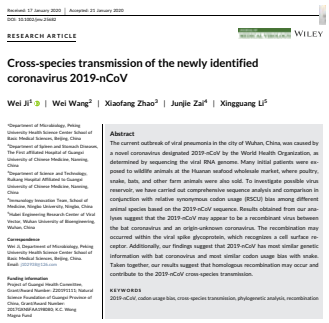


Origin of COVID19 epidemics

- First cases in December 2019
- Origin in Wuhan city market
- From animal reservoir to inter-human transmission
- January 30 WHO declaration of PHEIC (Public Health Emergency of International Concern)

Cross-species transmission relies on genetic mutations



RESEARCH ARTICLE

WILEY

Cross-species transmission of the newly identified coronavirus 2019-nCoV

Wei Ji[1] | Wei Wang[2] | Xiaofang Zhao[3] | Junjie Zai[4] | Xingguang Li[5]

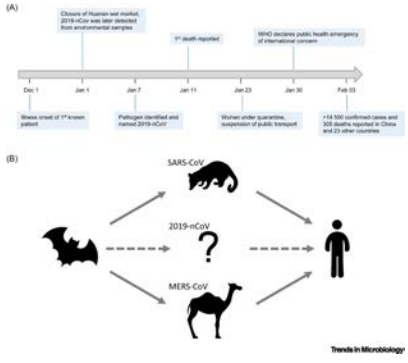
Abstract

The current outbreak of viral pneumonia in the city of Wuhan, China, was caused by a novel coronavirus designated 2019-nCoV by the World Health Organization, as determined by sequencing the viral RNA genome. Many initial patients were exposed to wildlife animals at the Huanan seafood wholesale market, where poultry, snake, bats, and other farm animals were also sold. To investigate possible virus reservoir, we have carried out comprehensive sequence analysis and comparison in conjunction with relative synonymous codon usage (RSCU) bias among different animal species based on the 2019-nCoV sequence. Results obtained from our analyses suggest that the 2019-nCoV may appear to be a recombinant virus between the bat coronavirus and an origin-unknown coronavirus. The recombination may occurred within the viral spike glycoprotein, which recognizes a cell surface receptor. Additionally, our findings suggest that 2019-nCoV has most similar genetic information with bat coronavirus and most similar codon usage bias with snake. Taken together, our results suggest that homologous recombination may occur and contribute to the 2019-nCoV cross-species transmission.

KEYWORDS

2019-nCoV, codon usage bias, cross-species transmission, phylogenetic analysis, recombination

Origin of SARS-CoV-2



The New England Journal of Medicine

BRIEF REPORT

A Novel Coronavirus from Patients with Pneumonia in China, 2019

Na Zhu, Ph.D., Dingyu Zhang, M.D., Wenling Wang, Ph.D., Xingwang Li, M.D., Bo Yang, M.S., Jingdong Song, Ph.D., Xiang Zhao, Ph.D., Baoying Huang, Ph.D., Weifeng Shi, Ph.D., Roujian Lu, M.D., Peihua Niu, Ph.D., Faxian Zhan, Ph.D., Xuejun Ma, Ph.D., Dayan Wang, Ph.D., Wenbo Xu, M.D., Guizhen Wu, M.D., George F. Gao, D.Phil., and Wenjie Tan, M.D., Ph.D., for the China Novel Coronavirus Investigating and Research Team

SUMMARY

In December 2019, a cluster of patients with pneumonia of unknown cause was linked to a seafood wholesale market in Wuhan, China. A previously unknown betacoronavirus was discovered through the use of unbiased sequencing in samples from patients with pneumonia. Human airway epithelial cells were used to isolate a novel coronavirus, named 2019-nCoV, which formed a clade within the subgenus sarbecovirus, Orthocoronavirinae subfamily. Different from both MERS-CoV and SARS-CoV, 2019-nCoV is the seventh member of the family of coronaviruses that infect humans. Enhanced surveillance and further investigation are ongoing. (Funded by the National Key Research and Development Program of China and the National Major Project for Control and Prevention of Infectious Disease in China.)

This article was published on January 24, 2020, and updated on January 29, 2020, at NEJM.org.

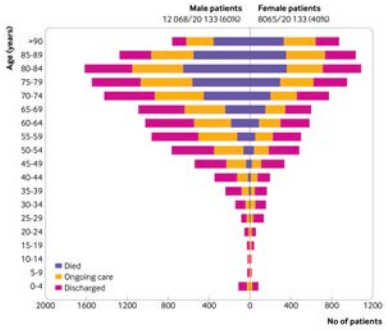
N Engl J Med 2020;382:727-33.
DOI: 10.1056/NEJMoa2001017

Technology & Ideas

It's Still Hard to Predict Who Will Die From Covid-19

The complicated ways in which the coronavirus interacts with human immune systems.

- Viral dose
- Genetics
- Route (inhaling droplets vs. touching surfaces and face)
- Virulence of the virus (?)
- Immune and inflammatory response



COVID-19: The many unknowns

- Why men more than women? Why obese people? Why black people?
- Why older people more affected?
- Why the *happy hypoxia* feature?
- Why lung thrombosis?
- Why intense sweating?
- Why loss of sense of smell and taste?

Understanding the pathology underlying the disease can provide answers to some of these questions

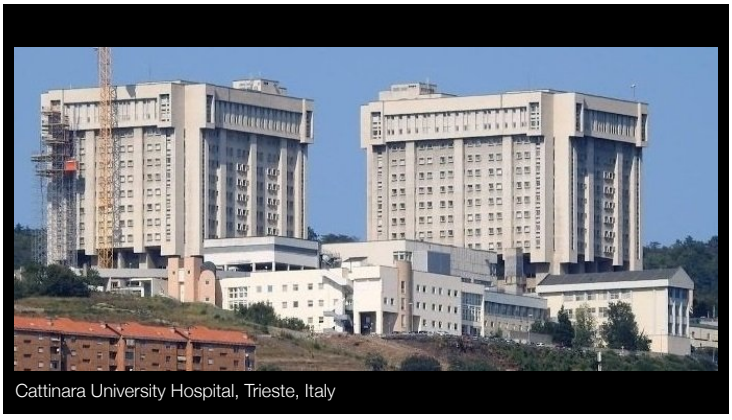
Diagnostic tests

Swab

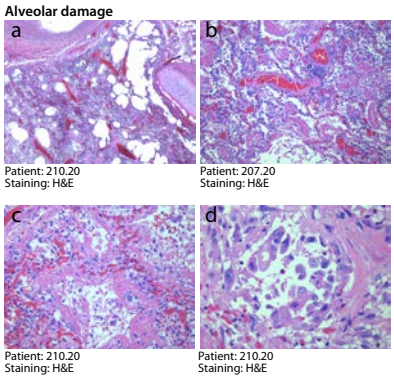
- Detection of viral genome - RT PCR ("molecular test")
- Detection of viral proteins - lateral immunochromatography ("antigenic test")
- Detection of viral genome - new CRISPR/ Cas9 tests

Blood

- Antibodies

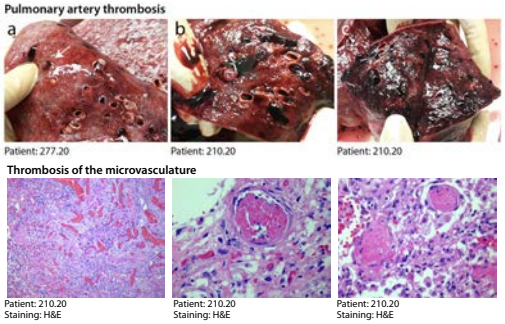

Cattinara University Hospital, Trieste, Italy

Diffuse alveolar damage and extensive fibrotic tissue substitution



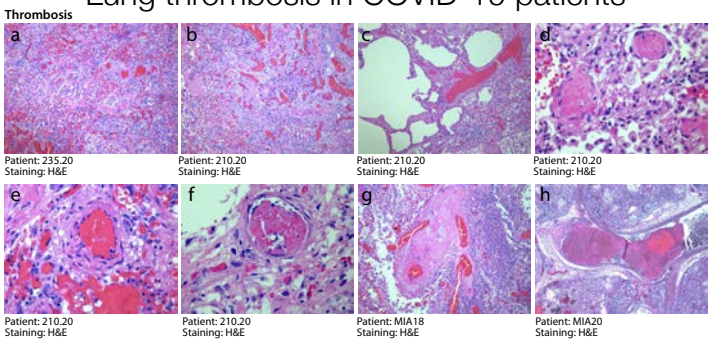
Bussani et al. 2020. Lancet EBioMed 61, 103104

Extensive thrombosis



Bussani et al. 2020. Lancet EBioMed 61, 103104

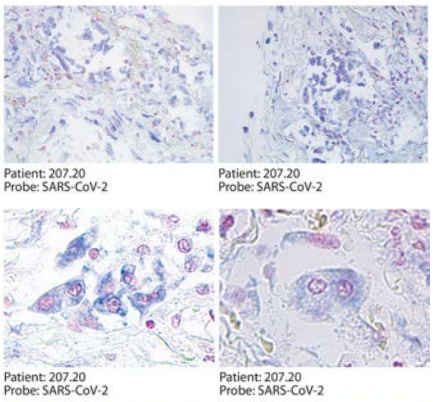
Lung thrombosis in COVID-19 patients

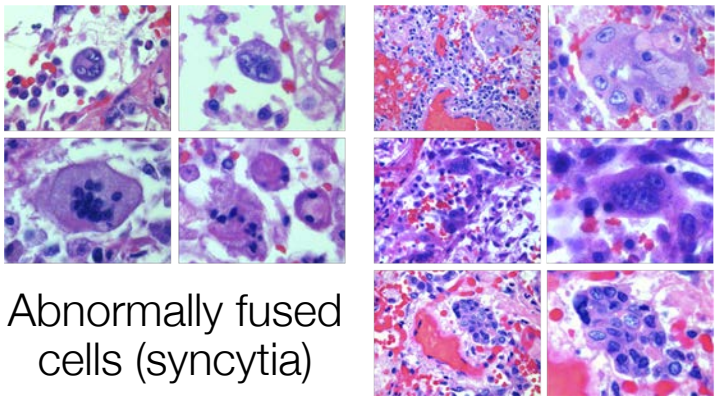


Bussani et al. 2020. Lancet EBioMed 61, 103104

Prolonged virus persistence

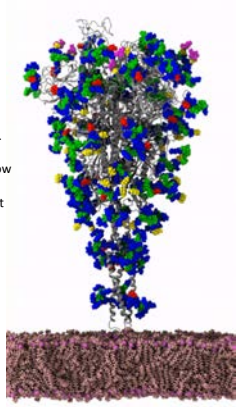
In situ hybridisation for SARS-CoV-2 RNA





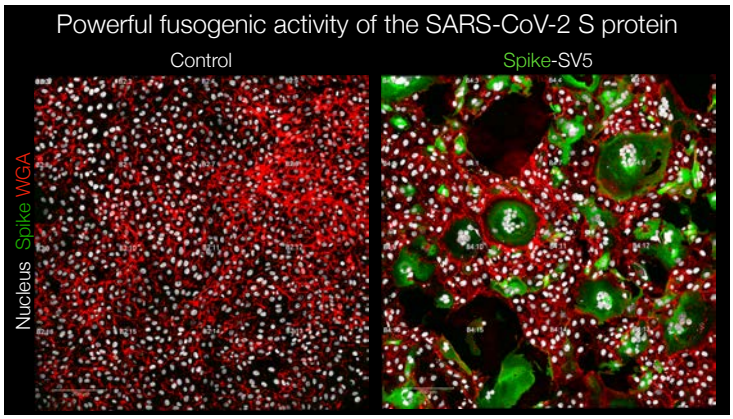
Abnormally fused cells (syncytia)

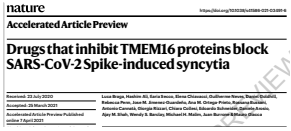
SARS-CoV-2 spike protein (gray) with glycans scattered around on its surface. The structure jiggles, which might affect how antibodies or other molecules bind with it



SARS-CoV-2 S protein

Lorenzo Casalino, Zied Gaieb, and Rommie Amaro, UC San Diego





COVID-19 is far more complex than a disease due to a virus that “simply” kills lung cells

Therapies attempted (with no or little success)

Antiviral

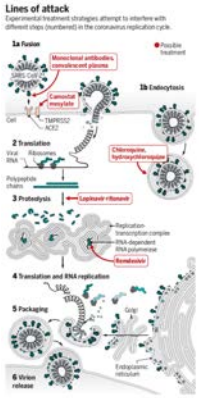
Chloroquine/Hydroxychloroquine
Lopinavir/ritornavir (protease inhibitor)
Remdesivir (nucleoside analogue RdRp inhibitor)
Favipiravir (nucleoside analogue RdRp inhibitor)

Anti-cytokine storm

Antibodies against Il-6 receptor (tocilizumab, sarilumab)
IL-1 receptor inhibitor (anakinra)

Anti-spike monoclonal antibodies

casirivimab/imdevimab (Regeneron)
bamlanivimab (Eli Lilly)



Scientifically unfounded therapies

Lactoglobin
Ozone therapy
Adenosine
Ivermectin

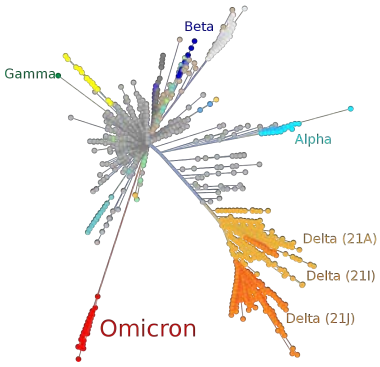
… several others

Is SARS-CoV-2 mutating?

WHO Variants of Concern

Five out of many variants of interest and variants to be monitored

WHO Variants of Concern

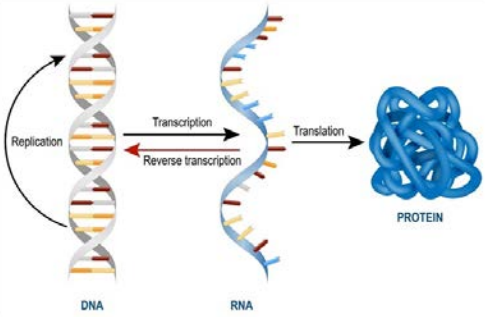


The principal concerns about omicron include whether it is more infectious or severe than other VoCs and whether it can circumvent vaccine protection. Although immunological and clinical data are not yet available to provide definitive evidence, we can extrapolate from what is known about the mutations of omicron to provide preliminary indications on transmissibility, severity, and immune escape. Omicron has some deletions and more than 30 mutations, several of which (eg, 69–70del, T95I, G142D/143–145del, K417N, T478K, N501Y, N655Y, N679K, and P681H) overlap with those in the alpha, beta, gamma, or delta VoCs. These deletions and mutations are known to lead to increased transmissibility, higher viral binding affinity, and higher antibody escape. Some of the other omicron mutations with known effects confer increased transmissibility and affect binding affinity. Importantly, the effects of most of the remaining omicron mutations are not known, resulting in a high level of uncertainty about how the full combination of deletions and mutations will affect viral behaviour and susceptibility to natural and vaccine-mediated immunity.

The Lancet, December 3, 2021

Vaccines

Flow of genetic information

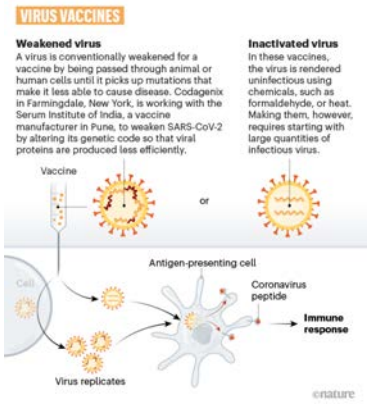


THE RACE FOR CORONAVIRUS VACCINES

Sinopharm and Sinovac (CoronaVac) (China)
Covaxin (India)

sinovac

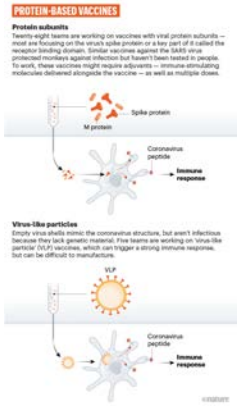
Nature **580**, 576-577 (2020)



THE RACE FOR CORONAVIRUS VACCINES

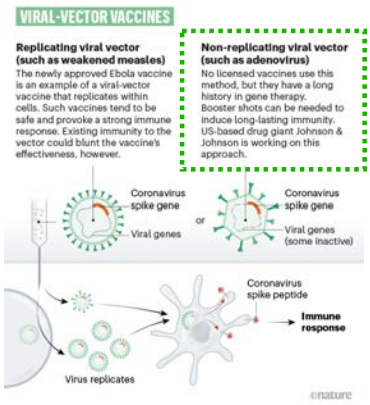
Novavax
Clover Biopharmaceuticals
University of Queensland
Sanofi/GSK

Nature **580**, 576-577 (2020)

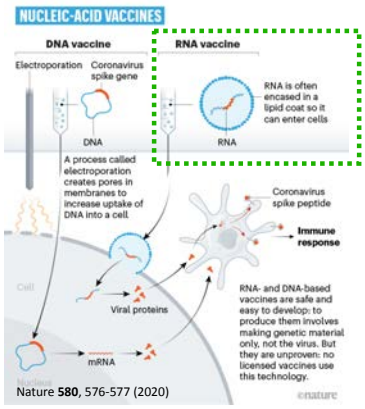


Oxford/AstraZeneca
Cansino
J&J/Janssen
Sputnik V

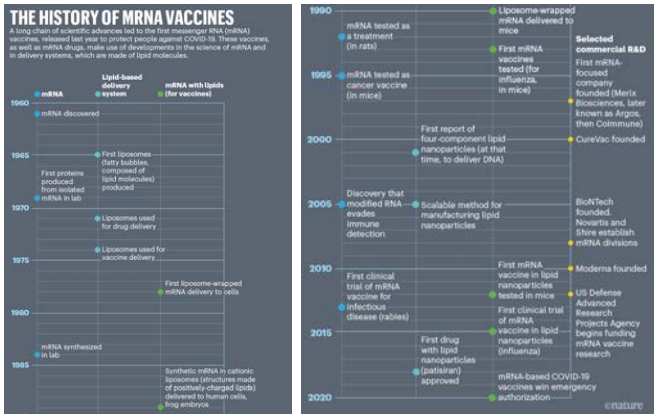
Nature **580**, 576-577 (2020)



Moderna
Pfizer/BioNTech
CureVac



Nature **580**, 576-577 (2020)



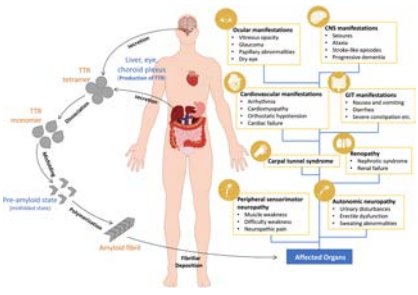
The NEW ENGLAND JOURNAL of MEDICINE
ESTABLISHED IN 1812 AUGUST 5, 2021 VOL. 385 NO. 6

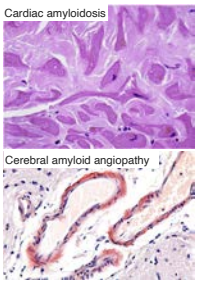
CRISPR-Cas9 In Vivo Gene Editing for Transthyretin Amyloidosis

Julian D. Gillmore, M.D., Ph.D., Ed Gane, M.B., Ch.B., Jorg Taubel, M.D., Justin Kao, M.B., Ch.B., Marianna Fontana, M.D., Ph.D., Michael L. Maitland, M.D., Ph.D., Jessica Seitzer, B.S., Daniel O'Connell, Ph.D., Kathryn R. Walsh, Ph.D., Kristy Wood, Ph.D., Jonathan Phillips, Ph.D., Yuanxin Xu, M.D., Ph.D., Adam Amaral, B.A., Adam P. Boyd, Ph.D., Jeffrey E. Cehelsky, M.B.A., Mark D. McKee, M.D., Andrew Schiermeier, Ph.D., Olivier Harari, M.B., B.Chir., Ph.D., Andrew Murphy, Ph.D., Christos A. Kyratsous, Ph.D., Brian Zambrowicz, Ph.D., Randy Soltys, Ph.D., David E. Gutstein, M.D., John Leonard, M.D., Laura Sepp-Lorenzino, Ph.D., and David Lebwohl, M.D.

ATTR amyloidosis

Progressive fatal disease (death within 2-6 from diagnosis in case of cardiac involvement)
Accumulation of amyloid fibrils composed of misfolded transthyretin protein





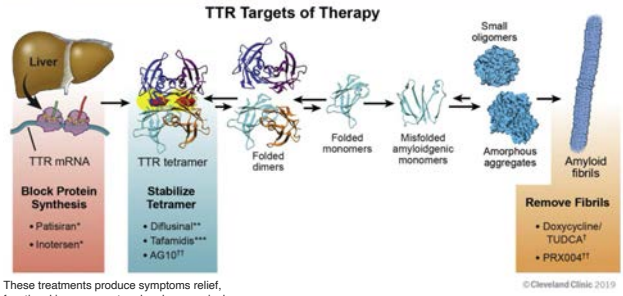
ATTR amyloidosis

1) Acquired
2) Hereditary: due to >100 different pathogenic mutations in TTR
   50,000 patients worldwide
   autosomal dominant inheritance
   clinical phenotype dominated by a combination of cardiomyopathy and polyneuropathy

Mutation	Sensory neuropathy	Motor neuropathy	Gastrointestinal symptoms	Cardiac complications
V30M	707 (89.5%)	305 (38.6%)	547 (69.3%)	212 (26.9%)
V122I	35 (60.3%)	11 (19.0%)	16 (27.1%)	57 (96.6%)
S50R	26 (89.7%)	16 (55.2%)	19 (65.5%)	13 (44.8%)
E89Q	21 (95.5%)	10 (45.5%)	13 (68.4%)	13 (65.0%)
T60A	16 (80.0%)	5 (25.0%)	8 (40.0%)	19 (90.5%)
F64L	18 (90.0%)	11 (55.0%)	10 (50.0%)	7 (35.0%)
S77Y	16 (94.1%)	8 (47.1%)	12 (70.6%)	9 (52.9%)
I68L	7 (46.7%)	6 (40.0%)	2 (13.3%)	13 (86.7%)
I107V	10 (83.3%)	9 (75.0%)	7 (58.3%)	8 (66.7%)
G47A	8 (72.7%)	2 (18.2%)	2 (18.2%)	1 (9.1%)
L111M	1 (10.0%)	0 (0.0%)	1 (10.0%)	7 (70.0%)

Mutations carried by ten individuals or more listed in a descending order.

Current therapies for ATTR amyloidosis



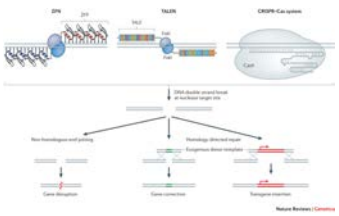
These treatments produce symptoms relief, functional improvement and prolong survival, but require long-term administration and are fraught by major side effects

What is gene editing?

Gene editing technology

- zinc finger nucleases (ZFNs)
- transcription activator-like effector nucleases (TALENs)
- clustered regularly interspaced short palindromic repeat (CRISPR)/Cas system

Protein:DNA RNA:DNA



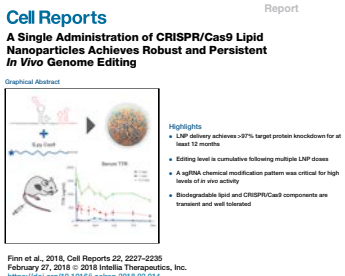
Nature Reviews Genetics **15**, 541–555 (2014)

Why gene editing?

- More extensive TTR knockdown is associated with greater improvement
- Monogenic, dominant disease
- Limited and specific normal function of TTR (thyroxine and vitamin A transport)
- >99% TTR produced by the liver, for which targeting LNPs are available and effective

NTLA-2001, an in vivo gene editing for i.v. infusion

Single dose NTLA-2001 results in > 95% reduction in serum TTR in mice and non human primates



Cell Reports

Report

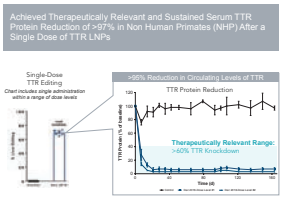
A Single Administration of CRISPR/Cas9 Lipid Nanoparticles Achieves Robust and Persistent *In Vivo* Genome Editing

Graphical Abstract

Highlights

- LNP delivery achieves >97% target protein knockdown for at least 12 months
- Editing level is cumulative following multiple LNP doses
- A sgRNA chemical modification pattern was critical for high levels of in vivo activity
- Biodegradable lipid and CRISPR/Cas9 components are transient and well tolerated

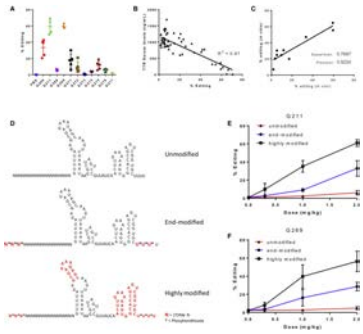
Finn et al., 2018, Cell Reports 22, 2227–2235
February 27, 2018 © 2018 Intellia Therapeutics, Inc.
https://doi.org/10.1016/j.celrep.2018.02.014



Liver editing was determined by NGS from a core needle liver biopsy and circulating serum TTR concentration was determined by an LC-MS/MS assay specific for the TTR protein.

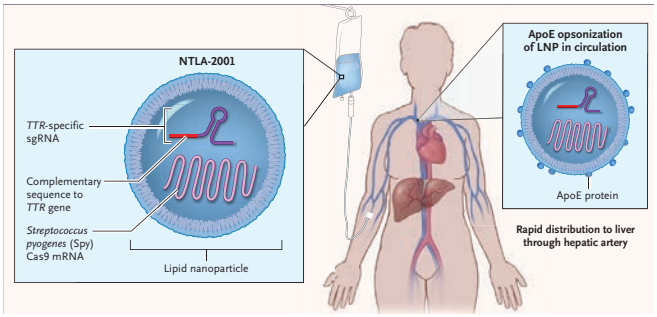
Presented at the Second European Congress for ATTR Amyloidosis, Berlin, September 1–3, 2019.

Optimisation of TTR specific guides

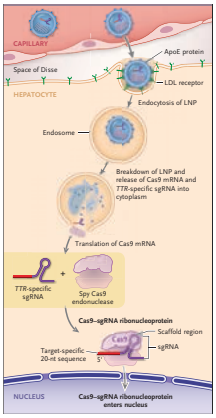


The carrier system for NTLA-2001 is a LNP based on a proprietary ionizable lipid, combined with a phospholipid, a pegylated lipid, and cholesterol, formulated in an aqueous buffer for intravenous administration. The active components are a human-optimized messenger RNA (mRNA) molecule encoding Streptococcus pyogenes (Spy) Cas9 protein and a single guide RNA (sgRNA) molecule specific to the human gene encoding trans- thyretin (TTR). These components form the cargo of the LNP for drug administration.

After intravenous administration and entry into the circulation, the LNP is opsonized by apolipoprotein E (ApoE) and transported through the systemic circulation directly into the liver, where it is preferentially distributed.



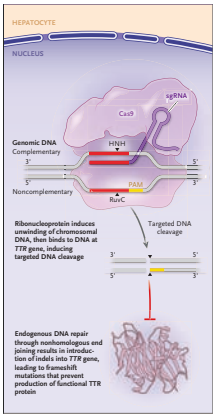
NTLA-2001 LNP uptake in hepatocytes through the low density lipoprotein receptor



Cleavage of DNA at TTR Gene Sequence by Cas9

An sgRNA targeting the TTR sequence AAAGGCUGCUGAUGACACCU (human genome build hg38, chromosome 18: 31592987–31593007) was selected for efficient knockout and specificity after a comprehensive off-target characterization workflow that applied a combination of both computational modeling and empirical approaches. To select for a high therapeutic index (i.e., the ratio of on-target to off-target edit- ing), we performed genomewide assays and targeted sequencing to identify and verify candidate sgRNA off-target sites.

The in vitro dose–response and gene-editing potency of NTLA-2001 were assessed in primary cell cultures of human hepatocytes. Candidate loci were validated for the detection of off-target insertions and deletions (indels) with the use of next-generation sequencing after NTLA-2001 treatment of primary human hepatocytes at concentrations up to 27 times as high as concentrations that achieved greater than 90% reduction in TTR protein (EC_{50}).



Sponsors: Intellia Therapeutics and Regeneron Pharmaceuticals

Intellia THERAPEUTICS

REGENERON SCIENCE TO MEDICINE

Intellia Therapeutics Announces First Patient Dosed in Phase 1/2 Clinical Trial of NTLA-2002 for the Treatment of Hereditary Angioedema

Dec 13, 2021

- *NTLA-2002 is the first single-dose genome editing therapeutic candidate designed to prevent angioedema attacks in patients with hereditary angioedema (HAE) to enter clinical study*

CAMBRIDGE, Mass., Dec. 13, 2021 (GLOBE NEWSWIRE) -- Intellia Therapeutics, Inc. (NASDAQ:NTLA), a leading clinical-stage genome editing company focused on developing curative therapeutics using CRISPR/Cas9 technology both *in vivo* and *ex vivo*, today announced that the first patient has been dosed with NTLA-2002, the company's *in vivo* CRISPR/Cas9 genome editing candidate being developed as a single-dose therapy to prevent attacks in people living with hereditary angioedema (HAE). NTLA-2002 is a systemically administered therapy designed to inactivate the target gene *kallikrein B1 (KLKB1)* to reduce plasma kallikrein activity and thus prevent HAE attacks.

"HAE is a genetic disorder that can cause painful and life-threatening inflammatory attacks, and currently available chronic therapies have a high treatment burden," said Intellia President and Chief Executive Officer John Leonard, M.D. "With the progress of our first-in-human clinical study evaluating NTLA-2002 for people living with HAE, we look forward to beginning clinical testing as we aim to develop a single-dose treatment for these patients."

Clinical study

Open-label, multicenter study
Single dose of NTLA-2001, total RNA dose of 0.1-0.3 mg per kilogram of body weight intravenously
Key eligibility criteria: age 18-80 years, a diagnosis of polyneuropathy due to hATTR amyloidosis (with or without cardiomyopathy), body weight of 50-90 kg, lack of access to approved treatments for ATTR amyloidosis.
Previous use of TTR stabilizers was permitted with a washout period (3 days for diflunisal).

No-observed-adverse-effect level (NOAEL): 3 mg per kilogram in monkeys, equivalent to 1 mg per kilogram in humans. In accordance with allometric scaling based on total body-surface area and application of a safety factor of 10, the maximum recommended starting dose was 0.1 mg per kilogram.

To mitigate against potential proinflammatory effects of intravenous LNP infusions, patients received glucocorticoid and histamine receptor type 1 and type 2 blockade before infusion.

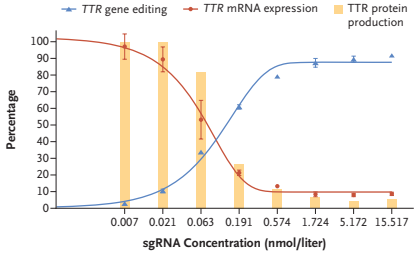
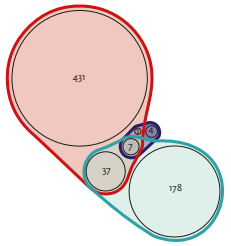
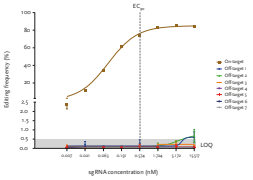


Figure 2. In Vitro Evaluations of the Potency of NTLA-2001.
Shown is the relationship between increasing concentrations of sgRNA and the consequent percentages of *TTR* editing, as well as *TTR* mRNA expression and TTR protein production in a single lot of primary human hepatocytes. The primary indel patterns were a single-nucleotide deletion or insertion at the cut site, inducing a frameshift mutation (data not shown).

Potential off-target effect

Potential off-target editing loci discovered for human single guide RNA (sgRNA), the CRISPR/Cas9 targeting sgRNA of NTLA-2001, during the discovery phase of off-target editing characterization. The on-target site is one of the seven loci identified with all three methods.





Site description	Annotation	PHH lot 1		PHH lot 2	
		Mean % Indel (%)	p value	Mean % Indel (%)	p value
On-target	On-target	93.97 ± 1.03	0.001	93.84 ± 0.10	1.91E-07
Off-target 1	Intergenic	7.47 ± 0.72	0.002	1.43 ± 0.13	1.99E-03
Off-target 2	Intronic	3.76 ± 0.13	3.40E-06	1.07 ± 0.15	4.71E-02
Off-target 3	Intergenic	0.47 ± 0.05	3.60E-04	0.04 ± 0.04	0.307
Off-target 4	Intergenic	1.88 ± 0.03	0.01	0.33 ± 0.06	0.001
Off-target 5	Intergenic	0.38 ± 0.10	0.02	0.13 ± 0.06	0.029
Off-target 6	Intronic	0.37 ± 0.05	0.01	0.10 ± 0.02	0.011
Off-target 7	Intergenic	0.37 ± 0.05	0.01	0.10 ± 0.02	0.001

Values in **bold** represent validated off-target indels. PHH denotes primary human hepatocytes.

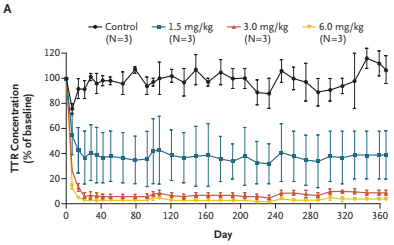


Figure 3. In Vivo Pharmacologic Properties of Cyn-LNP, the Nonhuman Primate Surrogate of NTLA-2001.

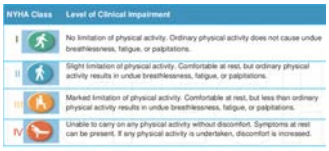
Panel A shows mean reductions in the serum TTR protein concentration as a percentage of the baseline concentration in cynomolgus monkeys (three per dose group) that received Cyn-LNP intravenously at doses of 1.5, 3.0, and 6.0 mg of total RNA per kilogram of body weight on day 0 and were followed up for 367 days. A control group that received no treatment is shown for comparison. I bars indicate standard deviations for the three animals in each group. Panel B shows the results of next-generation sequencing after administration of Cyn-LNP to cynomolgus monkeys. The sgRNA target sequence is indicated in blue next to the required PAM sequence, shown in red. [G/A] represents a naturally occurring single-nucleotide polymorphism in the cynomolgus monkeys used in the study. The nucleotide position of indels relative to the cynomolgus monkey genome (build mf5, chromosome 18) are +1: 50681549–50681550. The primary indel pattern was a single-nucleotide insertion at the cut site, inducing a frameshift mutation. An "N" at the insertion site indicates a multinucleotide insertion (e.g., AA or AGG), which in aggregate constituted 1.03% of all indels. The remaining fraction comprised deletions of various lengths.

B

Indel Size	Sequence	Indel Frequency %
Wild type	AGACACAAATACCAGTCCAGCGAGGCAGAG[G/A]AGGAGCAG	—
+1	AGACACAAATACCAGTCCAAGCGAGGCAGAG[G/A]AGGAGCAG	98.9
>+1	AGACACAAATACCAGTCCANGCGAGGCAGAG[G/A]AGGAGCAG	1.03

Patients

- Two study sites: Aukland, New Zealand and London, UK
- 6 patients
- Age: 46-64, 4M, 2 F
- Mutations: p.T80A (3), p.S97Y (2), p.H110D
- All had sensory polyneuropathy and HF NYA class I



Safety

Preferred Term	All patients receiving 0.1 mg/kg dose (n = 3)		All patients receiving 0.3 mg/kg dose (n = 3)		All patients	
	Related	Not related	Related	Not related	Related	Not related
Diarrhea	0	1 (33.3%)	0	0	0	1 (16.7%)
Nausea	1 (33.3%)	0	0	0	1 (16.7%)	0
Infusion-related reaction	1 (33.3%)	0	0	0	1 (16.7%)	0
Skin abrasion	0	0	0	1 (33.3%)	0	1 (16.7%)
Headache	1 (33.3%)	1 (33.3%)	0	0	1 (16.7%)	1 (16.7%)
Vertigo positional	0	1 (33.3%)	0	0	0	1 (16.7%)
Foreign body sensation in eyes	0	1 (33.3%)	0	0	0	1 (16.7%)
Catheter site swelling	0	1 (33.3%)	0	0	0	1 (16.7%)
Acute sinusitis	0	1 (33.3%)	0	0	0	1 (16.7%)
Thyroxine decreased	1 (33.3%)	0	0	0	1 (16.7%)	0
Rhinorrhea	1 (33.3%)	0	0	0	1 (16.7%)	0
Pruritus	0	1 (33.3%)	0	0	0	1 (16.7%)
Rash	0	1 (33.3%)	0	0	0	1 (16.7%)

For each preferred term subjects reporting more than one adverse event are counted only once using the closest relationship to study drug. Adverse events are coded to System Organ Class and Preferred Term using Medical Dictionary for Regulatory Activities, version 23.0. Related includes all events reported as possibly or probably related to study drug after investigator assessment.

Safety

Preferred Term	All patients receiving 0.1 mg/kg dose (n = 3)		All patients receiving 0.3 mg/kg dose (n = 3)		All patients	
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Skin abrasion	0	0	0	1 (33.3%)	0	1 (16.7%)
Headache	1 (33.3%)	1 (33.3%)	0	0	1 (16.7%)	1 (16.7%)
Vertigo positional	0	1 (33.3%)	0	0	0	1 (16.7%)
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Rhinorrhea	1 (33.3%)	0	0	0	1 (16.7%)	0
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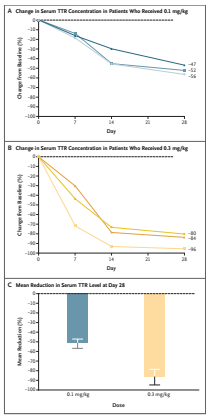
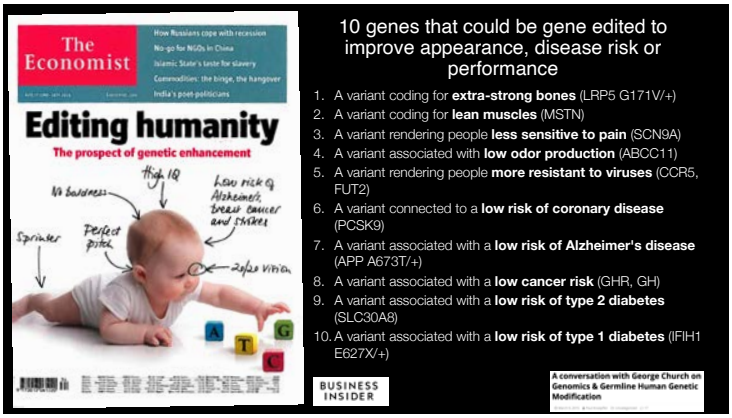
For each preferred term subjects reporting more than one adverse event are counted only once using the closest relationship to study drug. Adverse events are coded to System Organ Class and Preferred Term using Medical Dictionary for Regulatory Activities, version 23.0. Related includes all events reported as possibly or probably related to study drug after investigator assessment.

TTR protein reduction



https://www.nejm.org/doi/10.1056/NEJMoa2107454

Why is gene editing different from gene therapy?



10 genes that could be gene edited to improve appearance, disease risk or performance

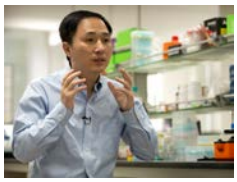
1. A variant coding for **extra-strong bones** (LRP5 G171V/+)
2. A variant coding for **lean muscles** (MSTN)
3. A variant rendering people **less sensitive to pain** (SCN9A)
4. A variant associated with **low odor production** (ABCC11)
5. A variant rendering people **more resistant to viruses** (CCR5, FUT2)
6. A variant connected to a **low risk of coronary disease** (PCSK9)
7. A variant associated with a **low risk of Alzheimer's disease** (APP A673T/+)
8. A variant associated with a **low cancer risk** (GHR, GH)
9. A variant associated with a **low risk of type 2 diabetes** (SLC30A8)
10. A variant associated with a **low risk of type 1 diabetes** (IFIH1 E627X/+)

BUSINESS INSIDER

A conversation with George Church on Genomics & Germline Human Genetic Modification

Germline gene editing

2018: announcement of the birth of twin girls with edited genomes



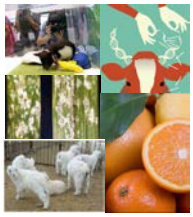
- Lack of definitive evidence
- Strategy: engineering mutations, inducing resistance to HIV (silencing of CCR5), into human embryos (requiring IVF)
- The major problem is not gene editing itself but lack of safety testing (other mutations, increased sensitivity to other diseases), lack of standard procedures for recruiting, HIV people should not undergo IVF

Gene editing vs GMOs

Process-based or product-based GMO regulations

Traceability

Reversibility



CRISPR on the farm

- petite pigs
- disease-resistant wheat and rice
- dehorned cattle
- disease-resistant goats
- vitamin-enriched sweet oranges

CRISPR and gene drive

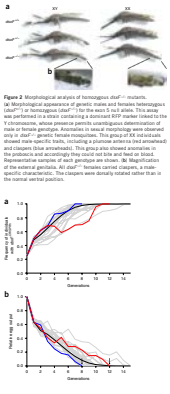
nature biotechnology
OPEN

A CRISPR–Cas9 gene drive targeting *doublesex* causes complete population suppression in caged *Anopheles gambiae* mosquitoes

Kyros Kyrou[1,2], Andrew M Hammond[1,2], Roberto Galizi[1], Nace Kranjc[1], Austin Burt[1], Andrea K Beaghton[1], Tony Nolan[1] & Andrea Crisanti[1]

In the human malaria vector *Anopheles gambiae*, the gene *doublesex* (*Agdsx*) encodes two alternatively spliced transcripts, *dsx-female* (*AgdsxF*) and *dsx-male* (*AgdsxM*), that control differentiation of the two sexes. The female transcript, unlike the male, contains an exon (exon 5) whose sequence is highly conserved in all *Anopheles* mosquitoes so far analyzed. We found that CRISPR–Cas9-targeted disruption of the intron 4–exon 5 boundary aimed at blocking the formation of functional AgdsxF did not affect male development or fertility, whereas females homozygous for the disrupted allele showed an intersex phenotype and complete sterility. A CRISPR–Cas9 gene drive construct targeting this same sequence spread rapidly in caged mosquitoes, reaching 100% prevalence within 7–11 generations while progressively reducing egg production to the point of total population collapse. Owing to functional constraint of the target sequence, no selection of alleles resistant to the gene drive occurred in these laboratory experiments. Cas9-resistant variants arose in each generation at the target site but did not block the spread of the drive.

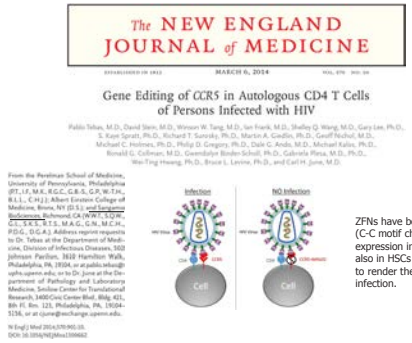
Received 6 April; accepted 3 August; published online 24 September 2018; doi:10.1038/nbt.4245



CRISPR and gene drive

State-of-the art of gene editing in humans?

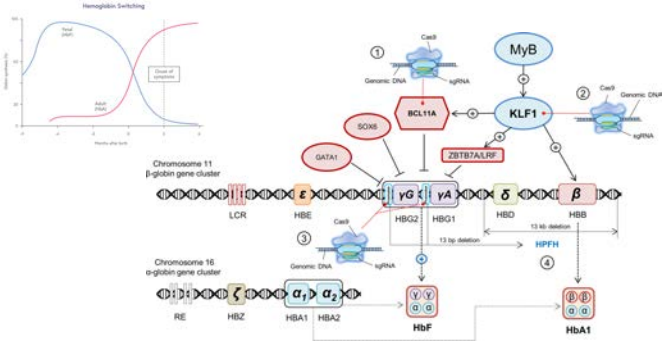
Genome editing for human therapy



ZFNs have been used to disrupt CCR5 (C-C motif chemokine receptor type 5) expression in human T cells, and later also in HSCs (phase I/II trial ongoing), to render these cells resistant to HIV infection.

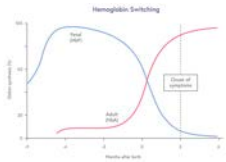
Ex vivo gene editing

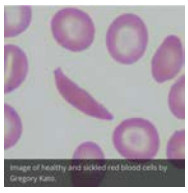
Ex vivo gene editing for haemoglobinopathies



Ex vivo gene editing for haemoglobinopathies

- CTX001 is an investigational ex vivo CRISPR gene-edited therapy for patients suffering from Transfusion-Dependent β-Thalassaemia (TDT) or severe Sickle Cell Disease (SCD).
- Haematopoietic stem cells are engineered to produce high levels of fetal hemoglobin (HbF; hemoglobin F) in red blood cells.
- Partnership between CRISPR Therapeutics and Vertex Pharmaceuticals Inc (Zurich and Boston).
- CTX001 was granted Fast Track Designation by the U.S. Food and Drug Administration for the treatment of SCD in January 2019.
- Two Phase 1/2 studies, one in β-thalassemia and one in Sickle Cell Disease, to assess the safety and efficacy of a single dose of CTX001 in patients ages 18 to 35. In both studies, the first two patients are treated sequentially and, pending data from these initial two patients, the trial will open for broader concurrent enrolment.
- Trial on β-thalassemia conducted at multiple clinical trial sites in Canada and Europe, with future addition of the United States. Trial on Sickle Cell Disease conducted at clinical trial sites in the United States.

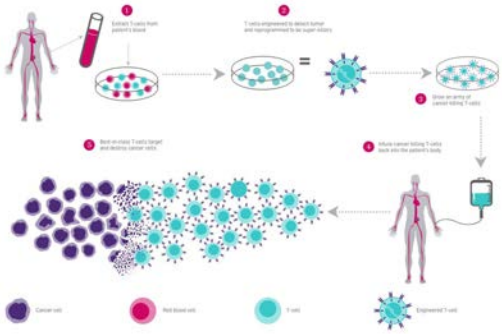




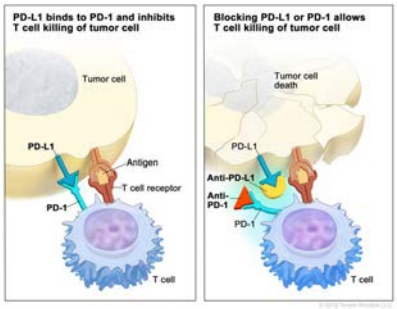
Victoria Gray, the first patient with SCD treated with CRISPR in July 2019

https://innovativegenomics.org/multimedia-library/meet-victoria-gray/

Immunotherapy for cancer



Immune checkpoint inhibitors to treat cancer



Approved checkpoint inhibitors

Name	Target	Approved
Ipilimumab	CTLA-4	2011
Nivolumab	PD-1	2014
Pembrolizumab	PD-1	2014
Atezolizumab	PD-L1	2016
Avelumab	PD-L1	2017
Durvalumab	PD-L1	2017
Cemiplimab	PD-1	2018

Chimeric Antigen Receptor (CAR)-T cells

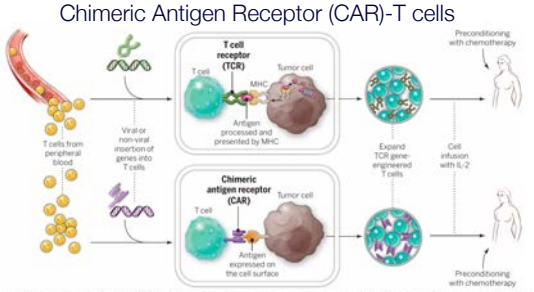


Fig. 4. Gene-modification of peripheral blood lymphocytes. In an attempt to broaden the reach of ACT to other cancers, techniques are being developed to introduce antitumor receptors into normal T cells that could be used for therapy. The top panel shows the insertion of a conventional TCR into a patient's T lymphocytes, followed by the expansion and infusion back into the patient. The bottom panel shows the insertion of a CAR into a patient's T cell, followed by the expansion of these cells and their re-infusion. TCRs and CARs are fundamentally different in their structures and in the structures that they recognize. TCRs are composed of one α chain and one β chain, and they recognize antigens that have been processed and presented by one of the patient's own MHC molecules. CARs are artificial receptors that can be constructed by linking the variable regions of the antibody heavy and light chains to intracellular signaling chains (such as CD3-zeta, CD28, 4-1BB) alone or in combination with other signaling moieties. CARs recognize antigens that do not need to be MHC-restricted, but they must be presented on the tumor cell surface.

THE CRISPR REVOLUTION

First U.S. Patients Treated With CRISPR As Human Gene-Editing Trials Get Underway

April 16, 2018 · 11:01 AM ET
Heard on All Things Considered

NY-ESO-1-redirected CRISPR (TCRendo and PD1) Edited T Cells (NYCE T Cells)
ClinicalTrials.gov Identifier: NCT03399448

- First CRISPR-based therapy trial that combines CAR-T and PD-1 immunotherapy
- University of Pennsylvania with the Parker Institute
- Autologous T cells transduced with a lentiviral vector to express a TCR with affinity to NY-ESO-1 and electroporated with CRISPR guide RNA/Cas9 to disrupt expression of endogenous TCRα, TCRβ and PD-1 (NYCE T Cells)
- Patients with late-stage cancers (multiple myeloma, melanoma, synovial sarcoma, myxoid/round cell liposarcoma) - 18 patients
- Two patients treated, one with relapsed multiple myeloma and one with relapsed sarcoma

NEWS

Genome editing seems safe suggests first study in US patients

11 November 2019

By Shaoni Bhattacharya

Seven active or recruiting trials in China are listed on the *ClinicalTrials.gov* clinical trial database.

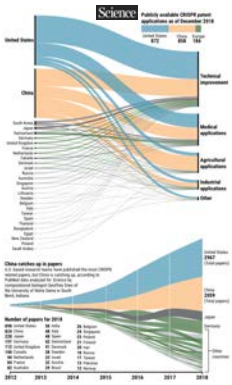
TREATMENTS

Doctors In China Lead Race To Treat Cancer By Editing Genes

February 21, 2018 · 5:00 AM ET
Heard on Morning Edition

With its CRISPR revolution, China becomes a world leader in genome editing

By Jon Cohen, Wenjie Dessai | Aug. 2, 2019, 8:00 AM



ARTICLES
https://doi.org/10.1038/s41591-020-0840-5

nature medicine

Check for updates

Safety and feasibility of CRISPR-edited T cells in patients with refractory non-small-cell lung cancer

You Lu[1,2,14] ✉, Jianxin Xue[1,14], Tao Deng[2,14], Xiaojuan Zhou[1,14], Kun Yu[2,14], Lei Deng[3], Meijuan Huang[1], Xin Yi[4], Maozhi Liang[5], Yu Wang[6], Haige Shen[4], Ruizhan Tong[1], Wenbo Wang[7], Li Li[7], Jin Song[4], Jing Li[8], Xiaoxing Su[9], Zhenyu Ding[1], Youling Gong[1], Jiang Zhu[1], Yongsheng Wang[2,12], Bingwen Zou[1], Yan Zhang[1], Yanying Li[1], Lin Zhou[1], Yongmei Liu[1], Min Yu[1], Yuqi Wang[4], Xuanwei Zhang[1], Limei Yin[1], Xuefeng Xia[4], Yong Zeng[2], Qiao Zhou[9], Binwu Ying[10], Chong Chen[10], Yuquan Wei[10], Weimin Li[11] and Tony Mok[13]

Clustered regularly interspaced short palindromic repeats (CRISPR)–Cas9 editing of immune checkpoint genes could improve the efficacy of T cell therapy, but the first necessary undertaking is to understand the safety and feasibility. Here, we report results from a first-in-human phase I clinical trial of CRISPR–Cas9 *PD-1*-edited T cells in patients with advanced non-small-cell lung cancer (ClinicalTrials.gov NCT02793856). Primary endpoints were safety and feasibility, and the secondary endpoint was efficacy. The exploratory objectives included tracking of edited T cells. All prespecified endpoints were met. *PD-1*-edited T cells were manufactured ex vivo by cotransfection using electroporation of Cas9 and single guide RNA plasmids. A total of 22 patients were enrolled; 17 had sufficient edited T cells for infusion, and 12 were able to receive treatment. All treatment-related adverse events were grade 1/2. Edited T cells were detectable in peripheral blood after infusion. The median progression-free survival was 7.7 weeks (95% confidence interval, 6.9 to 8.5 weeks) and median overall survival was 42.6 weeks (95% confidence interval, 10.3–74.9 weeks). The median mutation frequency of off-target events was 0.05% (range, 0–0.25%) at 18 candidate sites by next generation sequencing. We conclude that clinical application of CRISPR–Cas9 gene-edited T cells is generally safe and feasible. Future trials should use superior gene editing approaches to improve therapeutic efficacy.

NATURE MEDICINE | VOL 26 | MAY 2020 | 732–760 | www.nature.com/naturemedicine

- The treatment was safe to administer and had acceptable side effects like fever, rash, and fatigue.
- The desired edit was found in a median of 6% of T cells/patient before infusion back into the patient.
- Off-target effects — unwanted changes at various places in the genome — were observed at a low frequency and were mostly in parts of the genome that don't code for proteins. On-target effects — unwanted changes at the target site — were more common (median of 1.69%).
- Edited T cells were found in 11 out of 12 patients two months after the infusion, although at low levels. Patients with higher levels of edited cells had less disease progression.

In vivo gene editing

TheScientist
EXPLORING LIFE, INSPIRING INNOVATION

Man Receives First In Vivo Gene-Editing Therapy

The 44-year-old patient has Hunter syndrome, which doctors hope to treat using zinc finger nucleases.

Nov 15, 2017
KERRY GRENS

Hunter syndrome, or mucopolysaccharidosis II (MPS II), is a lysosomal storage disease caused by a deficient (or absent) enzyme, iduronate-2-sulfatase (I2S). When the enzyme is defective or missing, the sugars build up and can cause developmental delays, organ problems, brain damage, and early death.

Sangamo

GENE THERAPY

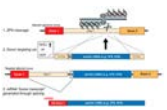
In vivo genome editing of the albumin locus as a platform for protein replacement therapy

Rajiv Sharma,[1,*] Xavier M. Anguela,[1,2,*] Yannick Doyon,[3,*] Thomas Wechsler,[3] Russell C. DeKelver,[3] Scott Sproul,[3] David E. Paschon,[3] Jeffrey C. Miller,[3] Robert J. Davidson,[1] David Shivak,[3] Shangzhen Zhou,[3] Julianne Rieders,[1] Philip D. Gregory,[3] Michael C. Holmes,[3] Edward J. Rebar,[3] and Katherine A. High[1,2]

[1]Division of Hematology, Children's Hospital of Philadelphia, Philadelphia, PA; [2]Howard Hughes Medical Institute, Philadelphia, PA; and [3]Sangamo BioSciences, Richmond, CA

Key Points

- AAV- and ZFN-mediated targeting of the albumin locus corrects disease phenotype in mouse models of hemophilia A and B.
- Robust expression from the albumin locus provides a versatile platform for liver-directed protein replacement therapy.



BLOOD, 8 OCTOBER 2015 • VOLUME 126, NUMBER 15

How does the treatment work?

Insertion of a replacement copy of the gene, using gene editing to snip the DNA helix of liver cells in a specific place near the promotor for the albumin gene - NOT GENE CORRECTION

The cells fix the damage by inserting the DNA for the new gene, supplied along with the ZFNs, and the gene's activity is then controlled by the powerful albumin promoter.

FDA has approved 3 clinical trials exploiting these modified liver cells into a factory delivering the factor IX gene for hemophilia B (NCT02695160), the a-L-iduronidase gene for mucopolysaccharidosis I (NCT02702115), and the iduronidate-2-sulfatase gene for mucopolysaccharidosis II (MPS II, Hunter syndrome) (NCT03041324).

This targeted approach should avoid the risks of insertional mutagenesis.
Because the body doesn't need much of the enzyme, modifying just a small fraction of the liver's cells should be enough to treat the disease.

Although Hunter syndrome patients often receive weekly infusions of the missing enzyme, their blood levels drop within a day. The hope is that the one-time gene-editing treatment—given as a 3-hour intravenous infusion—will allow the liver to keep making the enzyme at a steady rate for years.

Caveat: the I2S enzyme does not cross the blood-brain barrier, so the new treatment may not stop the brain damage that can occur in Hunter syndrome (as for replacement therapy).

A human has been injected with gene-editing tools to cure his disabling disease. Here's what you need to know

By Jocelyn Kaiser | Nov. 15, 2017 , 6:00 PM

Science

Brian Madeux, who has Hunter syndrome, has received a treatment aimed at editing the genome of his liver cells. AP PHOTO/DAN ROBERTS

SB-913: 3 AAV6 vectors

1. intact IDS gene
2. ZFN binding upstream of the target site
3. ZFN binding downstream of the target site

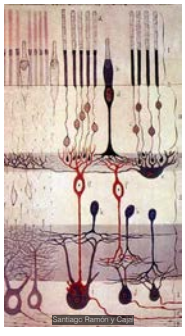
i.v. infusion

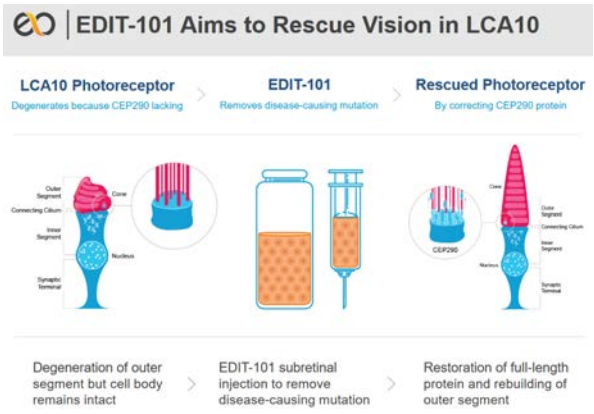
low dose is not effective:
represents a de facto placebo arm

approval upon efficacy demonstrated on clinical endpoints: six-minutes walk and lung function

In vivo gene editing LCA10 Leber Congenital Amaurosis

- Leber Congenital Amaurosis (LCA) is the most common cause of inherited childhood blindness. LCA10 is the most common form of LCA. It causes severe vision loss or blindness within the first few months of life.
- Due to mutations in the centrosomal protein 290 kDa gene (CEP290, MIM610142). Defects in this gene are also associated with Joubert syndrome and nephronophthisis. As of today, 35 different mutations in CEP290 are responsible for causing LCA.
- In the retina, CEP290 is mainly located to the connecting cilium of photoreceptors, where it plays an essential role in both cilium assembly and ciliary protein trafficking.
- Of the CEP290 mutations that result in LCA10, the most recurrent one, accounting for up to 15% of all LCA cases in many Western countries, is a deep intronic mutation (c.2991+1655A > G) in intron 26 of the CEP290 gene (hereafter referred to as "IVS26 mutation" or "IVS26 splice mutation").





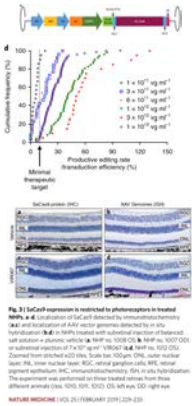
PERSPECTIVE

LCA10 trial of CRISPR genome editing treatment initiated

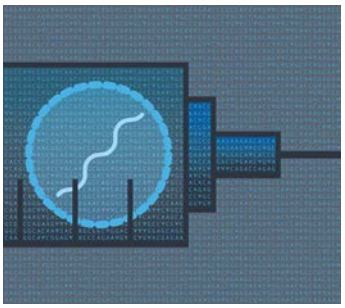
July 31, 2019

Single Ascending Dose Study in Participants With LCA10
ClinicalTrials.gov Identifier: NCT03872479

- First in vivo gene editing trial - the Brilliance trial
- AAV5 vector carrying *S. aureus* Cas9 and a guide targeting CEP290 intron 26.
- Patients receive a single subretinal injection in one eye following vitrectomy - 18 patients in up to five cohorts across three dose levels
- Editas Medicine in collaboration with Allergan - currently recruiting patients volunteers throughout the US.



The history of mRNA vaccines ?



The RNA sequence used in the COVID-19 vaccine developed by Pfizer and BioNTech (Ψ is a modified form of the uridine nucleotide, U)

1987 - The landmark experiment by Malone

Proc. Natl. Acad. Sci. USA
Vol. 86, pp. 6077–6081, August 1989
Biochemistry

Cationic liposome-mediated RNA transfection

[cationic lipid vesicles/*N*-[1-(2,3-dioleyloxy)propyl]-*N*,*N*,*N*-trimethylammonium chloride (DOTMA)/translation]

ROBERT W. MALONE*†‡, PHILIP L. FELGNER†, AND INDER M. VERMA*§

*Molecular Biology and Virology Laboratory, The Salk Institute, P.O. Box 85800, San Diego, CA 92138; †Department of Biology, University of California–San Diego, La Jolla, CA 92093; and ‡Vical Inc., 9373 Towne Centre Drive, Suite 100, San Diego, CA 92121

- He mixed strands of messenger RNA with droplets of fat
- He soaked human cells bathed in this genetic gumbo
- Cells absorbed the mRNA and began producing proteins from it

First applications in cancer

[CANCER RESEARCH 55, 1997-1400, April 1, 1995]

Advances in Brief

Characterization of a Messenger RNA Polynucleotide Vaccine Vector[1]

Robert M. Conry,[2] Albert F. LoBuglio, Marci Wright, Lucretia Sumerel, M. Joyce Pike, Feng Johanning, Ren Benjamin, Dan Lu, and David T. Curiel
Department of Medicine and Gene Therapy Program, Comprehensive Cancer Center, University of Alabama at Birmingham, Birmingham, Alabama 35294-3300

Dendritic Cells Pulsed with RNA are Potent Antigen-presenting Cells In Vitro and In Vivo

By David Boczkowski, Smita K. Nair, David Snyder, and Eli Gilboa

From the Department of Surgery, Duke University Medical Center, Durham, North Carolina 27710

- Main problems for large scale use of mRNA: unstable and expensive

CUREVAC
the RNA people®

CVnCoV
First-generation candidate
BAYER
CEPI
completed phase 3

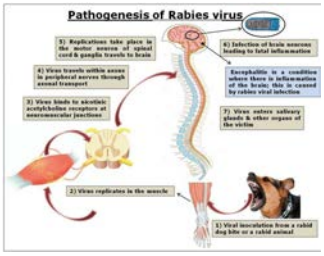
CV2CoV
Second-generation candidate
gsk
pre-clinical development

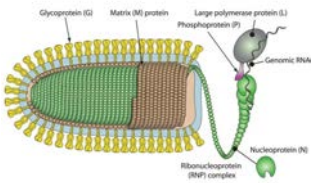
Ottobre 2021 - Interrotta la rolling review del vaccino anti-COVID-19 CVnCoV dopo il ritiro da parte di CureVac AG

La rolling review è uno strumento regolatorio di cui l'EMA si serve per accelerare la valutazione di un medicinale o vaccino promettenti durante un'emergenza sanitaria pubblica, come nel caso della pandemia da COVID-19. Di norma, tutti i dati sull'efficacia, la sicurezza e la qualità di un medicinale o di un vaccino e tutta la documentazione richiesta devono essere presentati all'inizio della valutazione nell'ambito di una formale domanda di autorizzazione all'immissione in commercio. Nel caso della rolling review, il CHMP provvede ad esaminare i dati non appena diventano disponibili dagli studi in corso. I dati sono valutati nell'ambito di cicli di rolling review: non esiste un numero predefinito di cicli, in quanto il processo dipende dai dati che diventano disponibili. Una volta che il CHMP stabilisce che vi sono dati sufficienti, l'azienda può presentare una domanda formale di autorizzazione all'immissione in commercio. Grazie alla possibilità di esaminare i dati quando diventano disponibili, il CHMP può formulare un parere sull'autorizzazione di un medicinale in tempi più brevi.

Nella lettera inviata all'EMA, CureVac AG ha motivato la decisione di ritirarsi indicando di voler concentrare i propri sforzi su un diverso programma di sviluppo di vaccini COVID-19. Come conseguenza del ritiro, l'EMA interromperà l'esame dei dati sul vaccino e non completerà la revisione. L'azienda si riserva il diritto di richiedere un'altra rolling review o di presentare una domanda di autorizzazione all'immissione in commercio in futuro.

mRNA vaccine for Rabies virus





Epidemiology of Rabies

All lyssaviruses have evolved closely with distinct natural reservoir hosts. The latter are animals species in which a pathogen of an infectious disease are maintained independently. For lyssaviruses, these are a wide range of mammalian species within the Carnivora and Chiroptera (bats) orders with a global distribution.

Of all carnivore host reservoirs the domestic dog is responsible for more than 90% of all human rabies fatalities worldwide.

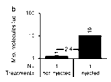
Because of the high fatality rate, the prevention of rabies infection is of utmost importance.

WHO strongly recommends discontinuation of the nerve tissue vaccine, and replacement with modern vaccines.

Source: WHO

CV7202

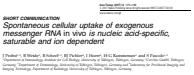
Prophylactic vaccine for rabies



CV7202 – Phase 1
CV7202 is a prophylactic mRNA-based vaccine encoding the rabies virus glycoprotein, RABV-G, formulated with next generation lipid nanoparticle (LNP).
CV7202 is currently being studied in a phase 1, dose-escalation, open-label clinical trial.

Study objectives:
- Primary: Safety, reactogenicity
- Secondary: Potential protective immune response, immunogenicity via geometric mean virus neutralization tests (VNT)

Rabies, a viral disease that causes inflammation in the brain, still occurs in more than 150 countries around the globe, with the infection responsible for more than 60,000 deaths every year, primarily in China and India.



SHORT COMMUNICATION

Spontaneous cellular uptake of exogenous messenger RNA in vivo is nucleic acid-specific, saturable and ion dependent

The company's chief scientific officer at the time, Steve Pascolo, was the first study subject: he injected himself,with mRNA and still has match-head-sized white scars on his leg from where a dermatologist took punch biopsies for analysis.

More information about the CV7202 study can be found at ClinicalTrials.gov (NCT03713086).

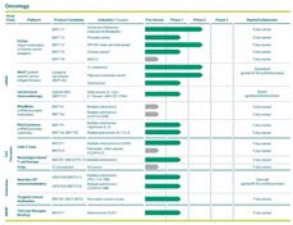
CV8102

Cutaneous melanoma, adenoidcystic carcinoma, squamous cell cancer of skin, head and neck

CV8102 (Study 1) – Phase 1
CV8102, a TLR7/8/RIG-1 agonist based on **noncoding single stranded RNA**, is designed to modulate the tumor microenvironment after intratumoral injection and to induce a systemic immune response to control injected as well as non-injected distant lesions.
CV8102 is currently being studied in a Phase 1, open-label, dose escalation and expansion study, which is enrolling patients with advanced melanoma, cutaneous squamous cell carcinoma, squamous cell carcinoma of head and neck, or adenoidcystic carcinoma, and superficially injectable tumor lesions.
The trial is testing escalating doses of single agent CV8102 and CV8102 in combination with licensed anti-PD-1 antibodies.

Study objectives:
- Primary: Safety, tolerability
- Secondary: Clinical efficacy, changes in various immune parameters in blood and tumor tissue

More information about the CV8102 study can be found at ClinicalTrials.gov.



Massive inflammatory reaction by mRNA-based vaccine for HIV/AIDS in mice

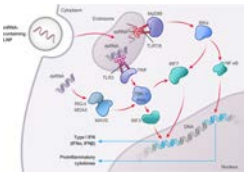
THE JOURNAL OF BIOLOGICAL CHEMISTRY Vol. 279, No. 12, Issue of March 26, pp. 12543–12550, 2004
© 2004 by The American Society for Biochemistry and Molecular Biology, Inc. Printed in U.S.A.

mRNA Is an Endogenous Ligand for Toll-like Receptor 3*

Received for publication, September 12, 2003, and in revised form, January 15, 2004
Published, JBC Papers in Press, January 16, 2004, DOI 10.1074/jbc.M310175200

Katalin Karikó‡§, Houping Ni¶, John Capodici¶, Marc Lamphier‖, and Drew Weissman¶
From the ‡Division of Neurosurgery and ¶Infectious Diseases, University of Pennsylvania, Philadelphia, Pennsylvania 19104 and the ‖Essa Research Institute, Andover, Massachusetts 01810

Toll-like receptors are immune sensors that act as first responders to danger signals from pathogens



From uridine to pseudo-uridine

Immunity, Vol. 23, 165–175, August, 2005, Copyright ©2005 by Elsevier Inc. DOI 10.1016/j.immuni.2005.06.008

Suppression of RNA Recognition by Toll-like Receptors: The Impact of Nucleoside Modification and the Evolutionary Origin of RNA

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Philadelphia, Pennsylvania 19104

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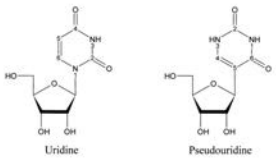

mRNA-based keratinocyte reprogramming into muscle and pluripotent cells

Highly Efficient Reprogramming to Pluripotency and Directed Differentiation of Human Cells with Synthetic Modified mRNA

Luigi Warren,[1,17] Philip D. Manos,[2,4,17] Tim Ahfeldt,[4,6,7,16] Yuin-Han Loh,[8,9,16] Hu Li,[11,12,16] Frank Lau,[4,13] Wataru Ebina,[1] Pankaj K. Mandal,[1] Zachary D. Smith,[14] Alexander Meissner,[4,8,15] George Q. Daley,[2,4,5,8,9,15] Andrew S. Brack,[4,8] James J. Collins,[11,12,16] Chad Cowan,[4,6,8,13] Thorsten M. Schlaeger,[2,4] and Derrick J. Rossi[1,2,4,10,*]
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Harvard Medical School, Boston, MA 02115, USA
[11]Department of Biomedical Engineering and Center for BioDynamics, Boston University, Boston, MA 02215, USA
[12]Wyss Institute for Biologically Inspired Engineering, Harvard University, Boston, MA 02115, USA
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[14]Broad Institute of MIT and Harvard, Cambridge, MA 02142, USA
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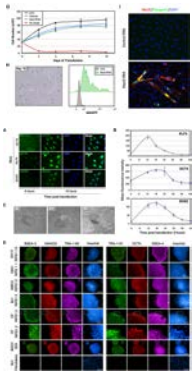
[17]These authors contributed equally to this work
[18]These authors contributed equally to this work
*Correspondence: rossi@rbi.harvard.edu
DOI 10.1016/j.stem.2010.08.012



HARVARD UNIVERSITY
HSCI HARVARD STEM CELL INSTITUTE

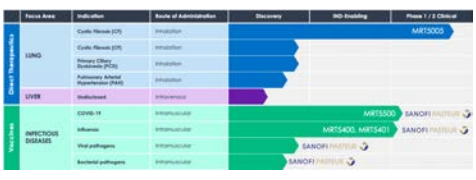
HSCI-supported research leads to new class of therapeutics

December 13, 2018

Biotech company Moderna, co-founded by HSCI scientist Derrick Rossi, is set to bring a new class of treatments to patients.

Translate BIO
A SANOFI COMPANY

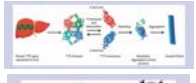
The pseudo-uridine debate

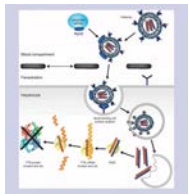


- Translate uses unmodified RNA
- Proprietary cap structure
- High RNA purity

Fat breakthrough

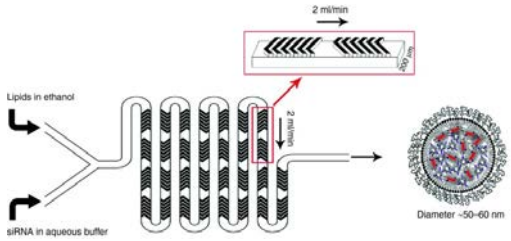
Pieter Cullis, a biochemist at the University of British Columbia in Vancouver, Canada, founded several companies, which pioneered LNPs for delivering strands of nucleic acids that silence gene activity.





One such treatment, patisiran (Onpattro), is now approved for the rare inherited disease hereditary transthyretin-mediated amyloidosis

LNP manufacturing



A T-connector apparatus combines fats (dissolved in alcohol) with nucleic acids (dissolved in an acidic buffer)

Inside a mRNA COVID vaccine