Replicon mRNA Vaccine: Japan Approves World's First Self-Amplifying mRNA Vaccine

New nightmare hits the market. What now? What are the problems? What about shedding?

By Dr. William Makis
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Nov. 27, 2023 – Japan's Ministry of Health, Labour and Welfare Approves CSL and Arcturus Therapeutics' ARCT-154, the first Self-Amplifying mRNA vaccine approved for COVID in adults

- "historic approval of the world's first Self-Amplifying messenger RNA (sa-mRNA) COVID-19 Vaccine"
- CSL and Arcturus Therapeutics announced Japan's Ministry of Health, Labor and Welfare (MHLW) granted approval for ARCT-154, a self-amplifying mRNA (sa-mRNA) COVID-19 vaccine for initial vaccination and booster for adults 18 years and older.
- "Self-amplifying mRNA technology has the potential to be an enduring vaccine option," said Nobel laureate Dr. Drew Weissman,"I look forward to seeing this next generation mRNA technology protect many from COVID-19 and possibly other harmful infectious diseases."
- The approval is based on positive clinical data from several ARCT-154 studies, including an ongoing 16,000 subject efficacy study performed in Vietnam as well as a Phase 3 COVID-19 booster trial, which achieved higher immunogenicity results and a favorable safety profile compared to a standard mRNA COVID-19 vaccine comparator. Initial study results have been published in MedRxiv and are expected to be published in a peer-reviewed journal by the end of the year.
- CSL's vaccine business, CSL Seqirus, one of the largest influenza vaccine providers in the world, partnered exclusively with Meiji Seika Pharma for

distribution of the sa-mRNA COVID vaccine, ARCT 154, in Japan.

- "We are proud of the role that Arcturus has played in this collaboration to develop and validate the first approved sa-mRNA product in the world," said Joseph Payne, Chief Executive Officer of Arcturus Therapeutics (San Diego, CA)

What Are Self-amplifying mRNA Vaccines?

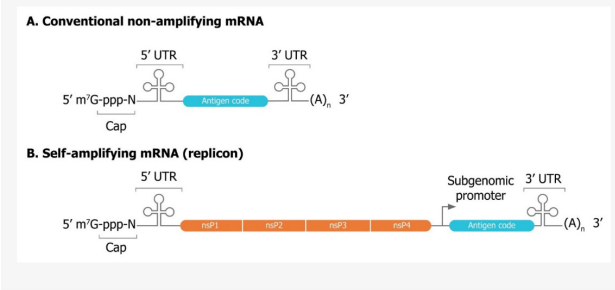


Figure 4. A comparison of mRNA vectors. Both conventional (**A**) and self-amplifying (**B**) mRNAs share basic elements including a cap, 5′ UTR, 3′ UTR, and poly(A) tail of variable length. Self-amplifying RNA (saRNA) also encode four non-structural proteins (nsP1–4) and a subgenomic promoter derived from the genome of the alphavirus. nsP1–4 encode a replicase responsible for amplification of the saRNA that enable lower doses than non-replicating mRNA.

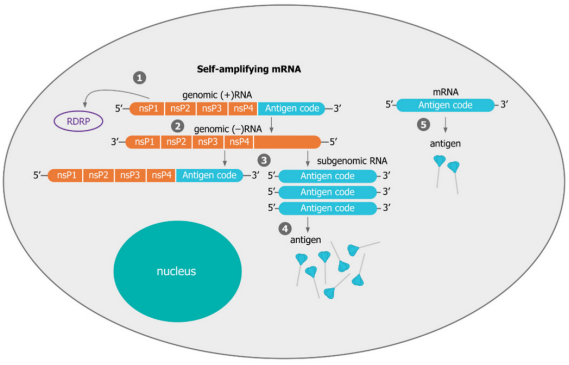


Figure 5. Mechanism of self-amplifying mRNA. (**1**) Following delivery to the cytoplasm, translation of the saRNA produces the non-structural proteins 1–4 (nsP 1–4) that form the (RDRP). (**2**) RDRP is responsible for replication of the saRNA producing copies of the saRNA. Multiple copies of the subgenomic RNA (**3**) are hence produced from each saRNA originally delivered. This leads to translation of many more copies of the antigen (**4**) when compared to a non-amplifying RNA (**5**).

- "Replicons encode their own replication machinery to boost their copy numbers directly after administration in target cells"
- "Replicon RNA additionally encodes viral replicase genes. These genes allow the rapid amplification of the mRNA. The self-amplifying viral genes originated from viruses, for example, alphaviruses and flaviviruses"

The 16 Centre Vietnamese "Safety Study" Japan Government Used for Approval

- VACCINE: "ARCT-154 consists of a replicon based upon Venezuela equine encephalitis virus in which RNA coding for the virus structural proteins has been replaced with RNA coding for the full-length spike (S) glycoprotein of the SARS-CoV-2 D614G virus, an early variant of the ancestral strain containing a single point mutation, encapsulated in lipid nanoparticles. 100 µg active ingredient, stored in vials at -20°C or lower, was dissolved in 10 mL sterile saline immediately before use and 0.5 mL doses containing 5 µg were administered by intramuscular injection in the deltoid."
- "allows host cells to make copies of the vaccine mRNA, increasing the amount of protein produced with lower doses of administered mRNA"
- "accelerated approval" = we initiated the present accelerated, integrated phase 1/2/3a/3b study, designed following EMA, FDA and WHO guidance, to evaluate the safety, reactogenicity, immunogenicity, and efficacy of ARCT-154.
- We present the first study results up to three months after the first vaccination of human volunteers with this novel vaccine
- 90% had at least one adverse event after 1st dose (most mild)
- "overall systemic AEs and local reactions were less frequent in recipients of

ARCT-154 than licensed mRNA vaccines”

- “A parallel study in Japan has shown that in adults fully immunized with mRNA vaccines, mainly BNT162b2, as primary vaccine, the immune response to a booster dose of ARCT-154 was superior to that of a booster dose of BNT162b2 when measured as neutralizing antibodies”
- “ARCT-154 is most likely to be used as a booster dose, rather than for primary immunization, to enhance and broaden the level of immunity against circulating variants”

The Dec. 20, 2023 Japanese Study by Oda, et al

- Enrolled 828 participants ages 18 to 64.
- 3x mRNA vaccinated (Pfizer or Moderna) were given 4th booster shot of either ARCT-154 or Pfizer.
- better immune response 28 days after jab to ARCT-154 compared to Pfizer
- “both boosters were equally well tolerated”

The Dec. 13, 2022 Study by Low, et al

- 169 volunteers, Phase I/II
- ARCT-021 was generally well tolerated up to the 7.5 µg dose.
- The 10 µg dose was associated with more local and systemic solicited AE, including grade 3 severity
- There appeared to be a dose-related trend for ≥grade 2 lymphopenia with 0%, 25%, 26.5%, 30.0%, and 40.0% of participants affected at the 1.0, 3.0, 5.0, 7.5, and 10 µg dose levels, respectively. Onset of lymphopenia occurred within 24 h after injection and resolved uneventfully, generally within a day.

The “Benefits”

- ARCT-154 (5 µg) requires one-tenth to one-sixth as much vaccine per person as other RNA-based COVID-19 boosters
- Reducing the amount of vaccine administered in each injection should result in “lower production costs”
- Because of its virus-like nature, saRNA interacts with the immune system in distinctive ways
- With the approval for ARCT-154 secured in Japan, its developers are now seeking authorization in Europe; a regulatory decision is expected next year.
- Last August, the Coalition for Epidemic Preparedness Innovations (CEPI) announced that it was committed to providing up to $3.6 million for the development of self-amplifying saRNA platforms
- “Once administered, the expression of these molecules can last for a longer period.” Therefore, companies can expect to save costs by manufacturing lower volumes, while also reducing the dose burden for patients. Lower doses could also translate to fewer potential side effects.
- The production of RNA vaccine candidates is fast and an influenza vaccine candidate was reported to have been produced in only 8 days [8].
- “there is no risk of mRNA integrating into the host genome [9]. mRNA is non-infectious and only transiently present in cells due to its degradation by host cell RNases”

- "sa-mRNA vaccine facilitates durable COVID-19 immunisation"
    - maintain elevated immune response through 12 months post-vaccination

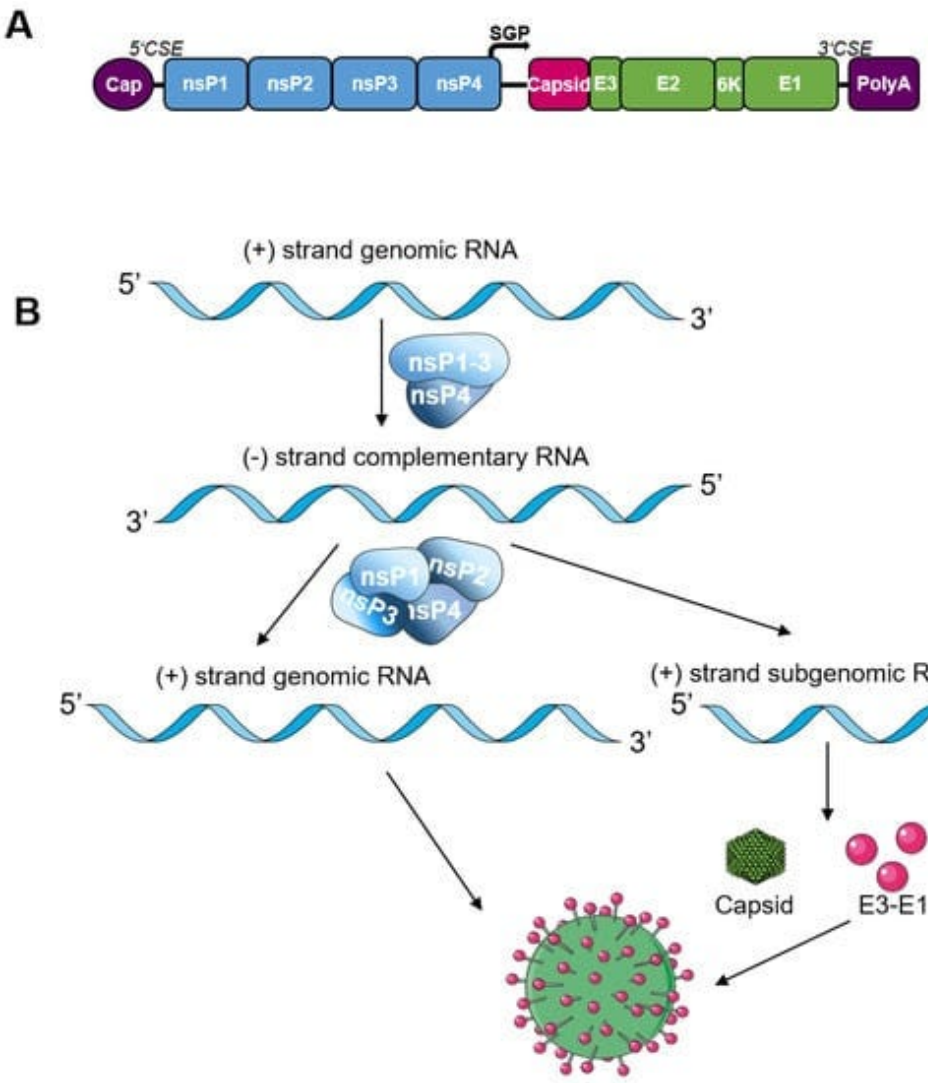
The "Problems"

- Arcturus Uses its own "lipid nanoparticles" – not much detail available, claims they are similar to Pfizer & Moderna LNPs

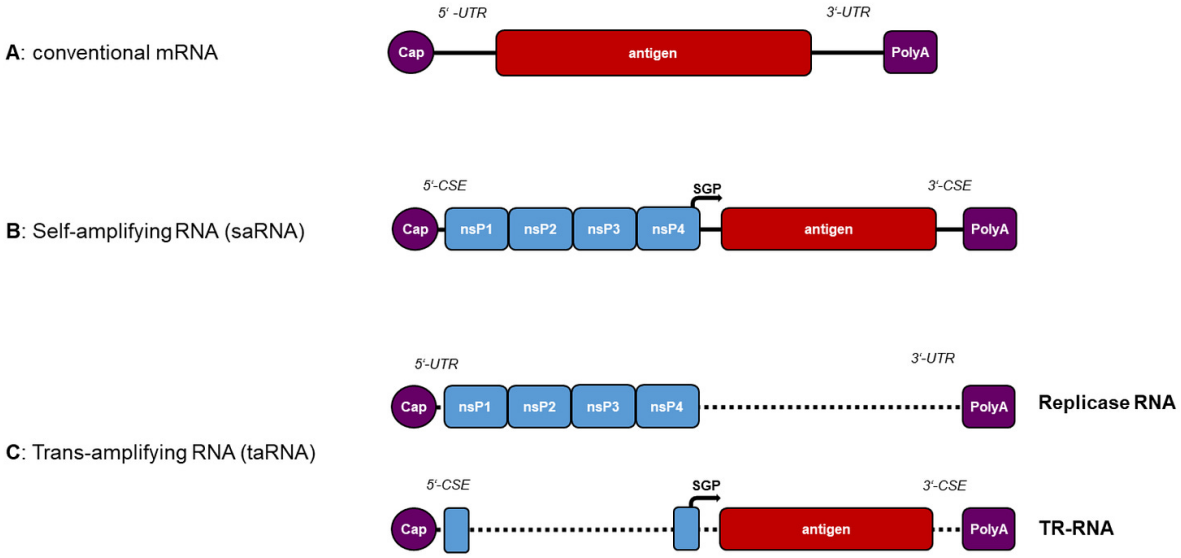
Lipid nano particle (LNP) formulations

	Particle Diameter	Polydispersity Index (PDI)	RNA Trapping Efficiency
Conventional mRNA	65 nm	0.10	92%
LUNAR-COV19	69 nm	0.11	90%

- No safety studies or biodistribution studies available for the Arcturus LNPs.
- sa-mRNA is much larger (due to the additional replication machinery sequences) up to 3 times larger.
    - "which leads to challenges during production, such as increased product-related impurities during synthesis and lower binding capacities in chromatography steps due to its larger size."
- any faulty sa-mRNA once injected, will be amplified in the cell, leading to higher concentrations of faulty proteins.
- most saRNA vaccines are based on the genome of the positive-sensed alphaviruses Venezuelan equine encephalitis virus (VEEV), Sindbis virus (SINV), or Semliki Forest virus (SFV)(shown below)



- For the construction of saRNA vaccines, the alphavirus structural proteins are replaced by the antigen gene (spike protein for COVID-19 Vaccines)



- no indication of how much "amplified mRNA" you're producing
- no indication of how much spike protein you're producing
- The viral replicase first uses the positive sense genome as template to synthesize complementary negative sense RNA which subsequently serves as

template for the synthesis of genomic and subgenomic plus-strand RNA.
        - The subgenomic RNA is produced in excess of the viral genome [24].
        - This process leads to high and sustained levels of antigen expression relative to conventional mRNA.
        - RNA self-amplification in transfected cells also leads to cellular exhaustion, immune stimulation through dsRNA intermediates and a host cell antiviral response leading to apoptosis.
        - In many ways, this process mimics a viral infection and leads to enhance antigen-specific B and T cell responses [75,88]
    - "it remains necessary to elucidate how long RNA amplification and antigen expression continues [70].
        - After administration of a luciferase saRNA, expression returned to baseline levels after one month [113].
        - Moreover, in theory, if the saRNA expresses budding-competent viral glycoproteins, it might be released in vesicles, leading to transfer of the saRNA to additional cells [114]. This should be taken into consideration for the safety evaluation of saRNA vaccines.
    - DNA Contamination? Yes please
        - "saRNAs and taRNAs are produced like mRNAs from a DNA template by in vitro transcription and the addition of a cap structure."
    - "several approaches to circumvent innate immune activation can be applied; however, for sa/taRNA vaccines, nucleoside modifications will be lost during the amplification step and will be of less benefit"
    - In contrast to mRNA vaccines, the intracellular RNA amplification results in dsRNA and thus a stronger activation of innate immune responses. RNA can be recognized by multiple pattern-recognition receptors including TLR3, TLR7, etc.
        - The resulting signaling cascades lead to the production of type I interferons (IFN) and pro-inflammatory cytokines [24].
        - Although the innate response has an adjuvant effect which can promote the specific immune response, it can also induce RNA degradation and thereby reduce antigen expression [132].
        - Strategies to reduce the IFN activation have been described for saRNA vaccines
    - LNP formulation also has adjuvant effects

Companies with sa-mRNA in Pipeline:

Table 1. Status of saRNA vaccine clinical trials against infectious diseases.

Vaccine	Target	Status	Sponsor	clinicaltrials.gov Identifier
ARCT-154-01	SARS-CoV-2	Phase 1/2/3 Active, not recruiting	Vinbiocare Biotechnology Joint Stock Company	NCT05012943
ARCT-165, ARCT-154, ARCT-021	SARS-CoV-2	Phase 1/2 Recruiting	Arcturus Therapeutics, Inc.	NCT05037097
saRNA-LNP based on VEEV	SARS-CoV-2	Phase 1 Active, not recruiting	National Institute of Allergy and Infectious Diseases (NIAID)	NCT04776317
LNP-nCOV saRNA-02 Vaccine	SARS-CoV-2	Phase 1 Recruiting	MRC/UVRI and LSHTM Uganda Research Unit	NCT04934111
GRT-R912, GRT-R914, and GRT-R918	SARS-CoV-2	Phase 1 Recruiting	Gritstone bio, Inc.	NCT05435027
GRT-R910	SARS-CoV-2	Phase 1 Active, not recruiting	Gritstone bio, Inc.	NCT05148962
CoV2 SAM (LNP)	SARS-CoV-2	Phase 1 Completed	GlaxoSmithKline	NCT04758962
AAHI-SC2, AAHI-SC3	SARS-CoV-2	Phase 1/2 Recruiting	ImmunityBio, Inc.	NCT05370040
ARCT-021	SARS-CoV-2	Phase 2 Terminated	Arcturus Therapeutics, Inc.	NCT04668339
PF-07852352, PF-07836391, PF-07836394, PF-07836395, PF-07836396, PF-07867246	Influenza	Phase 1 Recruiting	Pfizer	NCT05227001

My Concern…Shedding of Self-Amplifying mRNA

- Pfizer has admitted that its product sheds resulting in “environmental exposure” through inhalation or skin contact.

8.3.5.1. Exposure During Pregnancy

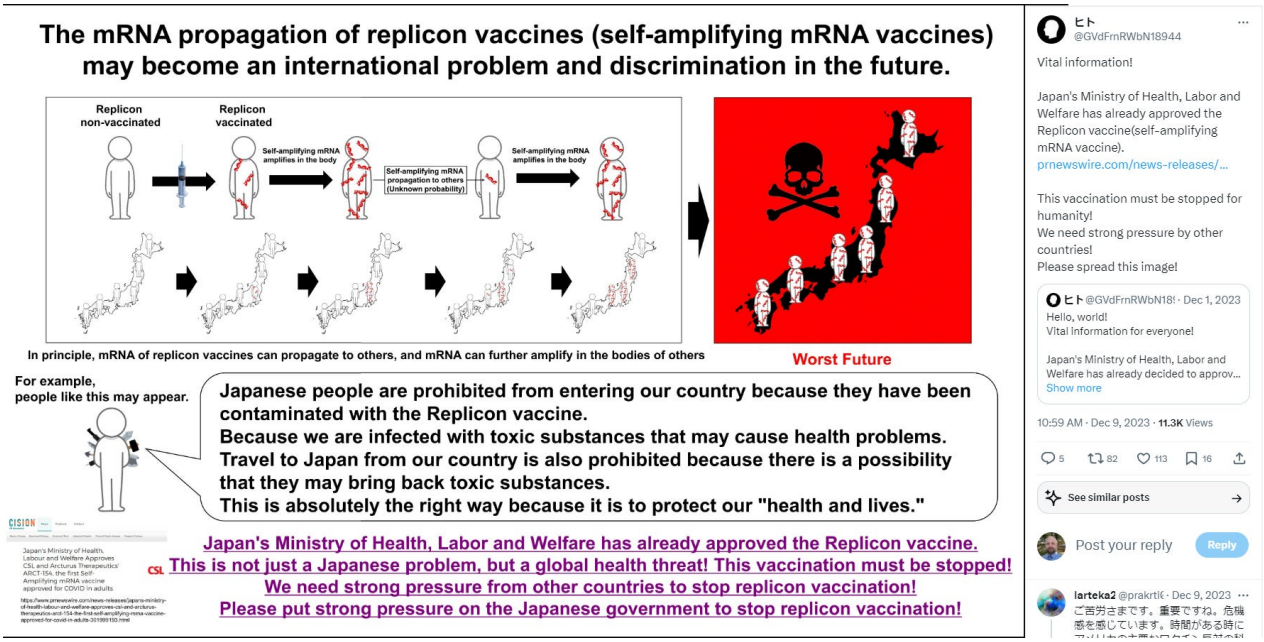
An EDP occurs if:

- A female participant is found to be pregnant while receiving or after discontinuing study intervention.
- A male participant who is receiving or has discontinued study intervention exposes a female partner prior to or around the time of conception.
- A female is found to be pregnant while being exposed or having been exposed to study intervention due to environmental exposure. Below are examples of environmental exposure during pregnancy:
  - A female family member or healthcare provider reports that she is pregnant after having been exposed to the study intervention by inhalation or skin contact.

  - A male family member or healthcare provider who has been exposed to the study intervention by inhalation or skin contact then exposes his female partner prior to or around the time of conception.

The investigator must report EDP to Pfizer Safety within 24 hours of the investigator's awareness, irrespective of whether an SAE has occurred. The initial information submitted should include the anticipated date of delivery (see below for information related to termination of pregnancy).

- But if you're exposed to a small quantity of Pfizer or Moderna COVID-19 mRNA Vaccine, via LNP/mRNA or exosome/mRNA, it will not vaccinate you.
- Your immune system destroys it.
- But what if you're exposed to shedding of a SELF-AMPLIFYING mRNA?
- Then theoretically, that mRNA could make unknown quantity of copies of itself in your body for an entire month, and that might be just long enough to cause permanent internal damage.
- This risk has not been studied.



Summary

Japan has approved the world's first COVID-19 self-amplifying sa-mRNA COVID-19 Vaccine.

Here are some of the problems with this technology:

- lower mRNA dose but higher amounts of spike protein and same side effect profile as Pfizer mRNA. The benefit? Lower production costs for big pharma.
- Arcturus uses its own Lipid Nanoparticles (LNPs), similar to Pfizer's – but there are no biodistribution or safety studies available.
- These LNPs will still deliver foreign pseudouridine modified sa-mRNA all over the body, across the blood-brain barrier and placenta barrier
- turns your body into a spike sa-mRNA & spike protein producing factory, instead of just spike protein factory
- You still also get DNA plasmid contamination
- sa-mRNA is 3 times as long as Pfizer mRNA (due to extra code for its own replication machinery), which means higher risk of impurities during manufacturing
- DNA contamination could be even more severe since purification will be even more difficult
- uses genome of the Venezuelan equine encephalitis virus (VEEV) for replication machinery
- increased risk of getting faulty sa-mRNA sequences which will then be amplified in your body, produce mutant proteins with unknown consequences.
- sa-mRNA is amplified inside cells to unknown quantities for up to a month (that's because the original sa-mRNA is pseudouridine modified but the copies made inside your cells are not)
- fidelity of the sa-mRNA amplification is unknown and untested
- you produce unknown quantities of spike protein
- you produce unknown quantities of mutated spike proteins and unknown non-spike proteins
- Japanese study by Oda shows same side effect profile as Pfizer COVID-19 boosters (this is a bad sign)

- they can produce RNA vaccine candidates rapidly, and an influenza vaccine candidate was reported to have been produced in only 8 days (also a bad sign)
- studies claim there is no risk of mRNA integrating into host genome with no evidence to back that up
- creates dsRNA intermediates which stimulate an immune response, the effects of which (and side effects) are not fully understood.
- SHEDDING becomes much more dangerous with a self-amplifying mRNA.
- Someone who is shed on may start producing unknown quantities of sa-mRNA for a period of around a month which could cause permanent damage.
- Finally, if an entire sa-mRNA is integrated into the genome, then you will be amplifying spike mRNA (and producing spike protein) indefinitely.
- No long term safety studies done.

This self-amplifying mRNA technology sounds like an even bigger disaster than what we've experienced with Pfizer & Moderna COVID-19 mRNA Vaccines.

Not interested.

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Dr. William Makis is a Canadian physician with expertise in Radiology, Oncology and Immunology. Governor General's Medal, University of Toronto Scholar. Author of 100+ peer-reviewed medical publications.

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