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Original Article

Preclinical and Clinical Demonstration of Immunogenicity by mRNA Vaccines against H10N8 and H7N9 Influenza Viruses

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Recently, the World Health Organization confirmed 120 new human cases of avian H7N9 influenza in China resulting in 37 deaths, highlighting the concern for a potential pandemic and the need for an effective, safe, and high-speed vaccine production platform. Production speed and scale of mRNA-based vaccines make them ideally suited to impede potential pandemic threats. Here we show that lipid nanoparticle (LNP)-formulated, modified mRNA vaccines, encoding hemagglutinin (HA) proteins of H10N8 (A/Jiangxi-Donghu/346/2013) or H7N9 (A/Anhui/1/2013), generated rapid and robust immune responses in mice, ferrets, and nonhuman primates, as measured by hemagglutination inhibition (HAI) and microneutralization (MN) assays. A single dose of H7N9 mRNA protected mice from a lethal challenge and reduced lung viral titers in ferrets. Interim results from a first-in-human, escalating-dose, phase 1 H10N8 study show very high seroconversion rates, demonstrating robust prophylactic immunity in humans. Adverse events (AEs) were mild or moderate with only a few severe and no serious events. These data show that LNP-formulated, modified mRNA vaccines can induce protective immunogenicity with acceptable tolerability profiles.

INTRODUCTION

Several avian influenza A viruses (H5N1, H10N8, H7N9, and H1N1) have crossed the species barrier, causing severe and often fatal respiratory disease in humans. Fortunately, most of these strains are not able to sustain person-to-person transmission.[1] However, lessons learned from these outbreaks demonstrated that new approaches are needed to address potential future pandemic influenza outbreaks.[2]

Two major glycoproteins, crucial for influenza infection, are hemagglutinin (HA) and neuraminidase (NA); both are expressed on the surface of the influenza A virion.[3] HA mediates viral entry into host cells by binding to sialic acid-containing receptors on the cell mucosal surface and the fusion of viral and host endosomal membranes.[4]

The segmented influenza A genome permits re-assortment and exchange of HA (or NA) segments between different influenza strain subtypes during concomitant host-cell infection. Generation of novel antigenic proteins (antigenic shift) and sustainable person-to-person transmission are hallmarks of pandemic influenza strains.[5] Such strains can spread quickly and cause widespread morbidity and mortality in humans due to high pathogenicity and little to no pre-existing immunity. Recent cases (2013) of avian-to-human transmission of avian influenza A virus subtypes included H7N9, H6N1, and H10N8.[6–8] The case-fatality rate in over 600 cases of H7N9 infections was ~30%.[1,9] Most recently, the World Health Organization reported another 120 cases since September 2016 resulting in 37 deaths.[10] To date, H10N8 infection in man has been limited; yet, of the three reported cases, two were fatal.[11]

The limited efficacy of existing antiviral therapeutics (i.e., oseltamivir and zanamivir) makes vaccination the most effective means of protection against influenza.[12] Conventional influenza vaccines induce protection by generating HA-specific neutralizing antibodies, the major correlate of protection, against the globular head domain.[13–15] Such vaccines utilize the HA protein, administered as a subunit, split virion, inactivated whole virus, or live-attenuated virus. A majority of approved influenza vaccines are produced in embryonated chicken eggs or cell substrates. This process takes several months and relies on the availability of sufficient supplies of pathogen-free eggs and adaptation of the virus to grow within its substrate.[16,17] The 5–6 months required to produce enough vaccine to protect a substantial proportion of the population consumes much of the duration of the often-devastating first wave of a pandemic.[18] This mismatch between the speeds of vaccine production and epidemic spread drives the search for vaccine platforms that can respond faster.[19]

Using mRNA complexed with protamine (RNActive, Curevac), Petsch et al.[20] demonstrated that intradermal (ID) vaccination of mice with RNActive encoding full-length HA from influenza virus H1N1 (A/Puerto Rico/8/1934) induced effective seroconversion and

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virus-neutralizing antibodies in all vaccinated animals. Immunity was long lasting and protected both young and old animals from lethal challenge with the H1N1, H3N2, and H5N1 strains of the influenza A virus.[20] Efficacy of these RNActive vaccines was also shown in ferrets and pigs.[21]

The use of a delivery system can dramatically reduce the doses needed to generate potent immune responses, without an additional conventional adjuvant. Lipid nanoparticles (LNPs) have been used extensively for the delivery of small interfering RNA (siRNA), and they are currently being evaluated in late-stage clinical trials via intravenous administration.[22]

Exogenous mRNA can stimulate innate immunity through Toll-like receptors (TLRs) 3, 7, and 8 and cytoplasmic signal-recognition proteins RIG-I and MDA5.[23,24] The adjuvant effect of stimulating innate immunity may be advantageous for purified protein vaccines, but indiscriminate immune activation can inhibit mRNA translation, reducing antigen expression and subsequent immunogenicity.[25,26] This can be overcome by replacing uridine nucleosides with naturally occurring base modifications, such as pseudouridine and 5-methylcytidine.[27–29] Recently, we[30] and others[31] have shown how LNP-encapsulated modified mRNA vaccines can induce extraordinary levels of neutralizing immune responses against the Zika virus in mice and nonhuman primates, respectively.

In this study, we evaluated the immunogenicity of two LNP-formulated, modified mRNA-based influenza A vaccines encoding the HA of H10N8 (A/Jiangxi-Donghu/346/2013) and H7N9 (A/Anhui/1/2013) in animals and H10N8 HA mRNA in humans from an ongoing trial. In the animal studies, we show that both vaccines generated potent neutralizing antibody titers in mice, ferrets, and cynomolgus monkeys (cynos) after a single dose. Additionally, a single dose of H7N9 HA mRNA protected mice from an autologous lethal challenge and reduced lung viral titers in ferrets. Encouraged by these findings, a first-in-human, dose-escalating, phase 1 trial is ongoing, with interim results reported here that confirm the observed, preclinical immunogenicity data with a safety profile consistent with other non-live vaccines.

RESULTS

H10N8 and H7N9 HA mRNA Immunogenicity in Mice

In vitro protein expression for both H10N8 HA (H10) and H7N9 HA (H7) mRNA vaccines were confirmed by transfection of HeLa cells. Western blot of resulting cell lysates demonstrated a 75-kDa band for both constructs using the corresponding HA-specific antibodies (Figure S1), consistent with previous reports for other HAs.[22] Due to a lack of glycosylation, both H10 HA and H7 HA protein controls had a molecular weight of 62 kDa.

Hemagglutination inhibition (HAI), IgG1, and IgG2a titers were measured after a single 10-μg dose of either formulated H10 or H7 mRNA in BALB/c mice immunized ID. HAI titers were below the limit of detection (<10) at day 7 but increased well above baseline by day 21 (Figure 1A). Unlike HAI, both anti-H10 and anti-H7 IgG1 and IgG2a titers were detected on day 7 (Figures 1B and 1C). For H10, IgG1 and IgG2a titers continued to increase until day 21 and were maintained at day 84. For H7, both IgG1 and IgG2a antibody titers increased 10-fold between day 21 and day 84 (Figure 1C). IgG2a titers were greater than IgG1 titers at all time points following formulated H10 or H7 mRNA immunization, suggesting a TH1-skewed immune response. For H10, these differences were significant at day 84 ($p = 0.0070$) and for H7 at day 7 ($p = 0.0017$) and day 21 ($p = 0.0185$). A 10-μg H10 mRNA-boosting immunization (21 days post-prime) resulted in a 2- to 5-fold increase in HAI titers, compared to a single dose at all time points tested ($p < 0.05$) (Figure 1D). Titers remained stable for more than a year, regardless of the number of doses.

While most vaccines are delivered via an intramuscular (IM) or subcutaneous administration,[32] the ID route of administration has the potential to be dose sparing. Therefore, to examine the effect of administration route on immunogenicity, BALB/c mice were immunized ID or IM with formulated H10 or H7 mRNA at four different dose levels. All animals received a boosting immunization on day 21, and serum was collected 28 days post-boost (day 49). Immune responses were observed for both vaccines at all dose levels tested (Figures S2A and S2B). Titers were slightly higher following IM administration at 2 and 0.4 μg for H10, but this difference was only significant at the 2-μg dose ($p = 0.0038$) (Figure S2A). The differences in H10 HAI titers were significant between some of the dose levels following IM administration: 10 versus 0.4 μg, $p = 0.0247$; 10 versus 0.08 μg, $p = 0.0002$; 2 versus 0.08 μg, $p = 0.0013$; and 0.4 versus 0.08 μg, $p = 0.0279$. HAI titers following H7 immunization trended higher as the dose increased although no significance was detected. In addition, there was no significant difference between IM and ID immunization (Figure S2B). T cell responses, as measured by IFNɣ ELISpot, were observed for both H10 and H7 at all doses tested (Figures S2C and S2D). Similar to H7 HAI titers, T cell responses trended higher following IM administration, especially for H7. However, significance could not be established due to pooling of the samples by group. Overall, after two doses, immunization with either H10 or H7 mRNA elicited an immune response at all doses tested with both ID and IM administration.

Given this innovative vaccine platform, we examined the biodistribution of the mRNA vaccines for both routes of administration. Male CD-1 mice received 6 μg formulated H10 mRNA either IM or ID. Following IM administration, the maximum concentration (C_{max}) of the injection site muscle was 5,680 ng/mL, and the level declined with an estimated $t_{1/2}$ of 18.8 hr (Table 1). Proximal lymph nodes had the second highest concentration at 2,120 ng/mL (t_{max} of 8 hr with a relatively long $t_{1/2}$ of 25.4 hr), suggesting that H10 mRNA distributes from the injection site to systemic circulation through the lymphatic system. The spleen and liver had a mean C_{max} of 86.9 ng/mL (area under the curve $[AUC]_{0-264}$ of 2,270 ng.hr/mL) and 47.2 ng/mL (AUC_{0-264} of 276 ng.hr/mL), respectively. In the remaining tissues and plasma, H10 mRNA was found at 100- to 1,000-fold lower levels.

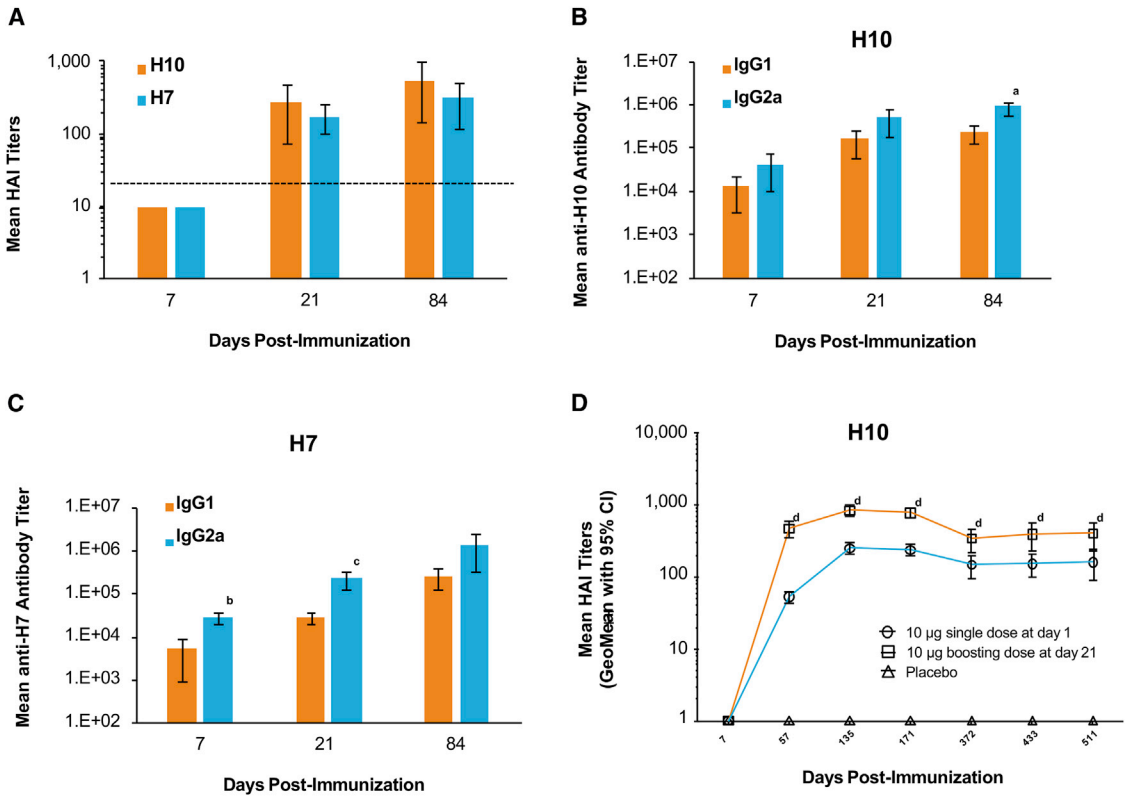

Figure 1. Mice Immunized with H10 or H7 mRNA Generate Robust and Stable Antibody Responses Consistent with a TH1 Profile

BALB/c mice were vaccinated ID with a single 10-µg dose of formulated H10 or H7 mRNA. (A) H10 and H7 indicate mean HAI titers (limit of detection is 1:10). Dotted line indicates the correlate of protection in humans (1:40). (B and C) IgG1 and IgG2a titers were measured for both H10 (B) and H7 (C) via ELISA (n = 5/group). [a]p = 0.0070, [b]p = 0.0017, and [c]p = 0.0185 versus IgG2a at the same time point. (D) BALB/c mice were immunized ID with a single 10-µg dose of formulated H10 mRNA. A subset of these mice received a 10-µg boost on day 21. Serum was collected at the indicated time points, and neutralizing antibody titers were determined by HAI (n = 15/group). Placebo controls were also included. [d]p < 0.05 single dose versus boosting dose at the same time point. Error bars indicate standard mean error.

Following ID administration, C_{max} within the skin at the injection site was 18.2 µg/mL. Levels declined by 24 hr with an estimated $t_{1/2}$ of 23.4 hr, suggesting that the H10 mRNA likely dissipated to systemic circulation via the proximal draining lymph node, as seen for the IM dosing. Consistent with this, the spleen, with a C_{max} of 1.66 ng/mL (1,663.52 pg/mL; AUC_{0-96} of 114.25 ng.hr/mL), had the highest levels among distal tissues. Only trace amounts of H10 mRNA were found in the heart, kidney, liver, and lung. Overall, whether administered ID or IM, the biodistribution of this vaccine was consistent with that observed for other vaccines,[33] where a local deposition effect was observed followed by draining to the local lymph nodes and subsequent circulation in the lymphatic system (Table 1; Table S1).

To understand the expression profile of mRNA after IM and ID administration, BALB/c mice were injected on day 0 with formulated luciferase mRNA at four different dose levels (10, 2, 0.4, and 0.08 µg). Expression was found to be dose dependent. As the dose increased, expression was found in distal tissues, with peak expression observed 6 hr after dosing. There were no significant differences when comparing maximum expression and time of maximal expression across IM and ID routes (Figure S3A). The time course of expression was also similar with both routes (Figures S3B and S3C). However, the distribution of expression changed slightly when the two routes were compared. Expression outside of the site of administration was observed across all dose levels, but it was more pronounced following IM administration, which is consistent with the biodistribution data (Figures S4A–S4E; Table 1; Table S1).[34]

H7 mRNA Vaccine Provides Protection against Lethal Influenza H7N9, A/Anhui/1/2013, in Mice and Ferrets

To determine the time to onset and duration of immunity to influenza H7N9 (A/Anhui/1/2013) lethal challenge, BALB/c mice were immunized ID with 10, 2, or 0.4 µg formulated H7 mRNA. For negative controls, placebo and 10 µg formulated H7 mRNA deficient in expression, due to the removal of a methyl group on the 2′-O position of the first nucleotide adjacent to the cap 1 structure at the 5′ end of the mRNA (−15 Da cap), were included. Serum was collected on days 6, 20, and 83, and mice were challenged via intranasal (IN) instillation with a target dose of 2.5×10^5 tissue culture infectious dose ($TCID_{50}$) on days 7, 21, and 84. Changes in body weight and clinical signs of disease were monitored for 14 days post-challenge. A single vaccination was found to be protective against H7N9 challenge (2.5×10^5

Table 1. Biodistribution of H10 mRNA in Plasma and Tissue after IM Administration in Mice

		C_{max} (ng/mL)		$AUC_{0-264\ h}$ (ng.hr/mL)		
Matrix	t_{max} (hr)	Mean	SE	Mean	SE	$t_{1/2}$ (h)
Bone marrow	2.0	3.35	1.87	NA		NC
Brain	8.0	0.429	0.0447	13.9	1.61	NR
Cecum	8.0	0.886	0.464	11.1	5.120	NC
Colon	8.0	1.11	0.501	13.5	5.51	NC
Distal lymph nodes	8.0	177.0	170.0	4,050	2,060	28.0
Heart	2.0	0.799	0.225	6.76	1.98	3.50
Ileum	2.0	3.54	2.60	22.6	10.8	5.42
Jejunum	2.0	0.330	0.120	5.24	0.931	8.24
Kidney	2.0	1.31	0.273	9.72	1.44	11.4
Liver	2.0	47.2	8.56	276	37.4	NC
Lung	2.0	1.82	0.555	12.7	2.92	16.0
Muscle (injection site)	2.0	5,680	2,870	95,100	20,000	18.8
Plasma	2.0	5.47	0.829	35.5	5.41	9.67
Proximal lymph nodes	8.0	2,120	1,970	38,600	22,000	25.4
Rectum	2.0	1.03	0.423	14.7	3.67	NR
Spleen	2.0	86.9	29.1	2,270	585	25.4
Stomach	2.0	0.626	0.121	11.6	1.32	12.7
Testes	8.0	2.37	1.03	36.6	11.8	NR

Male CD-1 mice received 300 μg/kg (6 μg) formulated H10 mRNA via IM immunization. Two replicates of bone marrow, lung, liver, heart, right kidney, inguinal- and popliteal-draining lymph nodes, axillary distal lymph nodes, spleen, brain, stomach, ileum, jejunum, cecum, colon, rectum, testes (bilateral), and injection site muscle were collected for bDNA analysis at 0, 2, 8, 24, 48, 72, 120, 168, and 264 hr after dosing (n = 3 mice/time point). NA, not applicable AUC with less than three quantifiable concentrations; NC, not calculated; NR, not reported because extrapolation exceeds 20% or R-squared is less than 0.80.

$TCID_{50}$; Figures 2A–2C). There was a significant increase in survival for animals in the three vaccine dose groups compared to the animals from the two control groups ($p < 0.0001$). Clinical observations in influenza-infected mice included rough coat, hunched posture, orbital tightening, and, in some cases, labored breathing. Weight loss (incidence and duration) was more prevalent for animals in the control groups and seen to a lesser extent in the low-dose vaccine group (Figures 2D–2F). HAI titers were below the limit of detection until day 20 for both the 10- and 2-μg dose groups (Figure S5). There was a 5- to 7-fold increase in HAI titers from day 20 to day 83 at all doses tested ($p < 0.0001$). Day-83 titers were dose dependent with mean titers of 224, 112, and 53 for the 10-μg dose, 2-μg dose, and 0.4-μg dose groups, respectively ($p < 0.0001$). Interestingly, despite complete protection to challenge at the 0.4-μg dose at day 21 (Figure 2B), a protective HAI titer (≥ 40) was not detected until day 83 at this dose, suggesting additional mechanism(s) of protection.

The negative mRNA control unexpectedly showed some delayed efficacy by day 21. However, this group of animals appeared to have received a dose lower than the day 7 and day 84 groups, based on back titer calculation (6.2×10^3 $TCID_{50}$ versus 3.8×10^5 and 6.1×10^5, respectively.), which was only ~3-fold higher than the LD_{50} of 1.88×10^3 (95% confidence interval [CI] = 8.02×10^2–5.51×10^3). Nonetheless, this group had comparable weight loss to the placebo group, and it was just above the threshold for euthanasia (30%) for some of the animals, thus confirming the significant protection observed in the positive vaccine groups. Additionally, it is not possible to rule out a low level of protein expression from the de-methylated cap of the negative mRNA control.[35]

Unlike mice, ferrets are naturally susceptible to human influenza virus isolates. Human and avian influenza viruses both replicate efficiently in the respiratory tract of ferrets, and numerous clinical signs found in humans following seasonal or avian influenza virus infection are also present in the ferrets.[36,37] Ferrets (n = 8/group) were vaccinated ID on day 0 with 200-, 50-, or 10-μg doses of formulated H7 mRNA. Formulated H7 mRNA with a −15 Da cap and placebo were included as negative controls. A subset of ferrets received a second ID vaccination on day 21. All groups were exposed to influenza H7N9 via IN challenge (1×10^6 $TCID_{50}$). The primary endpoint for this study was viral burden determined by $TCID_{50}$ in the lung at 3 days post-challenge, which is when the peak viral load is seen in control animals (data not shown). A reduction in lung viral titers was observed when ferrets were challenged 7 days post-immunization at all doses tested (Figures S6A–S6C). Ferrets immunized with 200 μg and challenged on day 49 had viral loads below the level of detection (Figure S6C). Antibody titers, as measured by HAI, increased significantly by day 21 for all dose groups ($p < 0.05$); as measured by microneutralization (MN), significant increases were observed by day 49 for all dose groups ($p < 0.05$) (Figures S7A and S7B). A second immunization increased titers but showed no statistical benefit compared to a single immunization, likely due to the two to four log reduction in viral lung titers seen in both the single- and double-immunization groups (Figures S7A–S7D). Two immunizations with 50-μg doses significantly increased HAI and MN titers compared to placebo ($p < 0.05$), and two immunizations with 200-μg doses generated significant HAI and MN titers versus placebo and all other doses ($p < 0.0001$) (Figures S7C and S7D).

In the absence of an H10N8 (A/Jiangxi-Donghu/346/2013) challenge model, the onset and duration of immunity to formulated H10 mRNA in ferrets was tested by HAI. Groups of ferrets were immunized ID once, twice, or three times with 50 or 100 μg H10 mRNA. Immunization with a single dose of 50 or 100 μg resulted in significant and comparable increases in HAI titers at days 21, 35, and 49 ($p < 0.0001$; Figure 3). Immunization with a 100-μg dose resulted in only slightly elevated antibody responses on day 7 compared to day 0 ($p < 0.0001$), with minimal differences observed with the 50-μg dose on day 7 compared to day 0 ($p < 0.3251$). Subsequent boosts with either a 50- or 100-μg dose (delivered on day 21 or on both days 21 and 35) resulted in significant and comparable increases in HAI titers on days 35 and 49 ($p < 0.0001$). Overall, the H10 mRNA administered at a 50- or 100-μg dose yielded significant increases in HAI antibody titers as compared with prevaccination baseline values

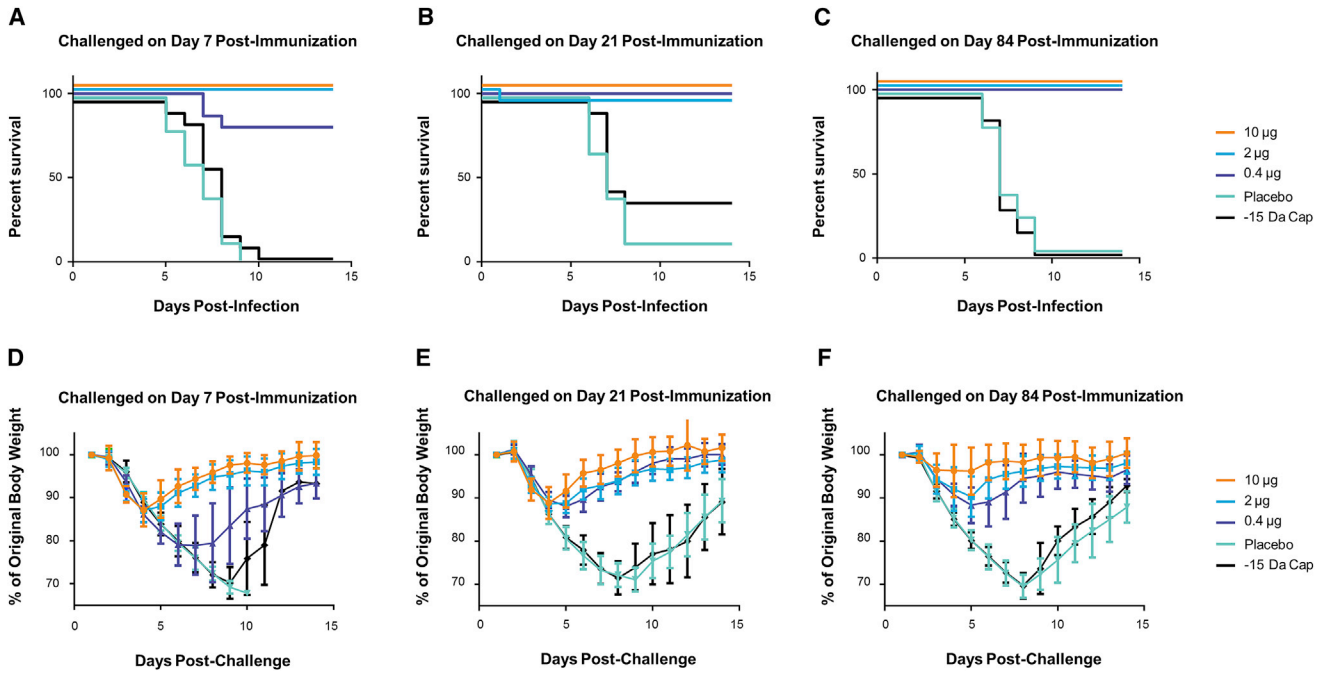

Figure 2. A Single Injection of an H7 mRNA Vaccine Achieves Rapid and Sustained Protection in Mice

BALB/c mice were vaccinated ID with 10, 2, or 0.4 µg formulated H7 mRNA. Placebo and 10 µg formulated H7 mRNA with a reduced 5′ cap structure (−15 Da cap) were included as negative controls. On day 7, 21, or 84 post-immunization, mice were challenged via intranasal (IN) instillation with a target dose of 2.5×10^5 $TCID_{50}$ of influenza A/Anhui/1/2013 (H7N9). Serum was collected prior to challenge (days 6, 20, and 83). (A–C) Survival curves of mice challenged on day 7 (A), day 21 (B), or day 84 (C) post-immunization at the indicated doses. $p < 0.0001$ 10-, 2-, and 0.4-µg dose groups versus placebo or −15 Da cap at days 7, 21, and 84 post-immunization. (D–F) Weight curves of mice challenged on day 7 (D), day 21 (E), or day 84 (F) post-immunization at the indicated doses (n = 15/group). Error bars indicate standard mean error.

and controls ($p < 0.0001$). A single booster vaccination provided a significant increase in titers, but a second booster dose did not yield an additional increase (Figure 3).

H10 HA and H7 HA mRNA Immunogenicity in Nonhuman Primates

One of the major limitations with other nucleic acid-based technologies, such as plasmid DNA, has been translation to higher-order species, such as nonhuman primates. To evaluate the immune responses elicited in nonhuman primates, HAI titers were measured in cynos after two immunizations (days 1 and 22) at two dose levels (0.2 and 0.4 mg) of formulated H7 mRNA administered IM and ID (Figures 4A and 4B). Formulated H10 mRNA was tested with only the 0.4-mg dose delivered ID and IM with the same immunization schedule (days 1 and 22) (Figure 4C). Both H10 and H7 mRNA vaccines generated HAI titers between 100 and 1,000 after a single immunization (day 15). HAI titers of 10,000 were generated for both H10 and H7 at 3 weeks following the second immunization (day 43), regardless of dose or route of administration. At 0.4 mg, the cynos experienced some systemic symptoms, such as warm to touch pain at the injection site, minor injection site irritation, and, in some cases, decreased food consumption following either H10 or H7 immunization. All symptoms resolved within 48–72 hr. Overall, both ID and IM administration elicited similar HAI titers regardless of dose, suggesting that lower doses may generate a similar HAI titer.

H10 mRNA Immunogenicity and Safety in Humans

To evaluate the safety and immunogenicity of H10 mRNA in humans, a randomized, double-blind, placebo-controlled, dose-escalating phase 1 trial is ongoing (Clinical Trials Identifier NCT03076385). We report here interim results, obtained 43 days post-vaccination of 31 subjects (23 of whom received active H10 at 100 µg IM and eight of whom received placebo). Immunogenicity data show that 100% (n = 23) and 87% (n = 20) of subjects who received the H10 vaccine had an HAI $\geq$ 40 and MN $\geq$ 20 at day 43, respectively, compared to 0% of placebo subjects (Figures 5A and 5B). A total of 78% (n = 18) and 87% (n = 20) who received the H10 vaccine had an HAI baseline <10 and post-vaccination HAI $\geq$ 40 or HAI four or more times baseline, respectively, compared to 0% for placebo (Figures 5A and 5B). HAI geometric mean antibody titers of subjects given the H10 vaccine were 68.8 compared to 6.5 for placebo, and the MN geometric mean titers were 38.3 versus 5.0, respectively (Figures 5C and 5D).

The majority of adverse events (AEs) were mild (107/163 events; 66%) or moderate (52/163 events; 32%), using the Center for Biologics Evaluation and Research (CBER) severity scale.[38] AEs were comparable in frequency, nature, and severity to unadjuvanted and adjuvanted H1N1 influenza vaccines.[39] Twenty-three subjects who received 100 µg H10 IM reported 163 reactogenicity events with no idiosyncratic or persistent AEs observed. The majority of events were injection site pain, myalgia, headache, fatigue, and chills/common-cold-like symptoms

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