ID# 909834

Investigational, Live, Intranasal (IN) M2SR (M2-deficient Single Replication) H3N2 Influenza Vaccine Induces Serum HAI & Broad Immune Responses in High Proportion of Adults

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1. Introduction

- Currently available vaccines are relatively ineffective against drifted influenza strains, especially H3N2.
- To address the need for more effective influenza vaccines, FluGen is developing M2SR (M2 deficient Single Replication), an investigational, live influenza virus vaccine for intranasal administration. M2SR does not express the essential M2 virus protein and is therefore replication-restricted: no infectious virus is produced beyond the first cycle of antigen production.
- In a prior human influenza challenge study (EudraCT number: 2017-004971-30), a subset of adult vaccine recipients responded to a single intranasal (IN) dose of 10^8 $TCID_{50}$ M2SR by mounting a broad humoral immune response to both vaccine and drift strains. This response predicted subsequent protection against infection and disease following challenge with a highly drifted strain of influenza H3N2 (*Open Forum Infectious Diseases*, Volume 6, Issue Supplement_2, October 2019, Pages S967–S968).
- The current phase 1b clinical trial aims to evaluate safety and increases in responder frequency with higher dose levels following 1 & 2 vaccinations of H3N2 M2SR

Fig 1. M2-deficient Single Replication (M2SR) vaccine schematic

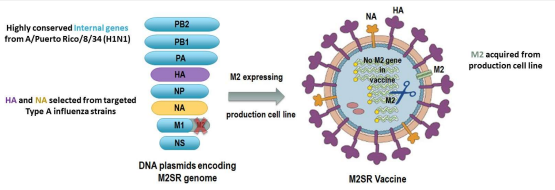
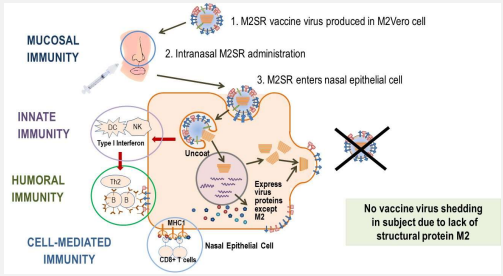


Fig 2. M2SR elicits broad immune responses similar to natural influenza infection



2. Methods

- A double-blinded, randomized, placebo-controlled study (NCT 03999554) was conducted with M2SR containing HA & NA from A/Singapore/INFIMH-16-0019/2016 (Sing2016) or A/Brisbane/10/2007 (Bris10) H3N2 virus.
- Healthy adults, 18-49 years of age, were screened for baseline microneutralization antibody titers (MNT) </=1:20 against A/Singapore/INFIMH-16-0019/2016.
- Subjects received 2 IN doses of either saline or 1 of 3 different dose levels of vaccine (10^8 – 10^9 $TCID_{50}$), administered 28 days apart.
- Solicited local and systemic reactions evaluated for 7 days after each vaccination.
- Adverse events (AE) followed for 28 days and serious AE (SAE) for 180 days.
- Serum and nasal swab samples were tested for influenza-specific antibodies.
- Serology assays were conducted at Viroclinics (Rotterdam, NL) and Southern Research (Birmingham, AL); mucosal IgA assays at VisMederi (Siena, IT).

Cohort (N=50 per cohort)	Vaccine	Dose ($TCID_{50}$)
1	Sing2016 M2SR	10^9
2	Sing2016 M2SR	$10^{8.5}$
3	Sing2016 M2SR	10^8
4	Bris10 M2SR	10^8
5	Placebo	Saline

3. Results

Study Demographics

- 71% female/29% male
- 81% White/17% Black
- 47% Hispanic
- Mean age 39 years

Safety Results

- **Favorable safety profile after first and second dose of M2SR**
- **No anaphylaxis, laryngospasms/bronchospasms**
- **No pattern of clinical pathology changes identified**
- **One SAE in placebo recipient**
- **No M2SR virus shedding**

Fig 3. AE Profile through 7 days post-vaccination

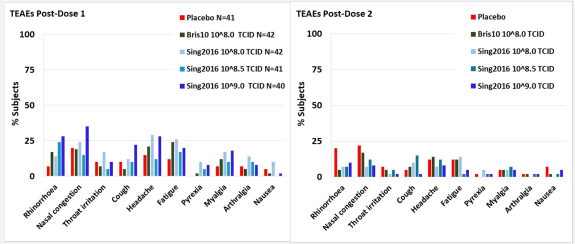


Fig 4. Single dose of intranasal 10^9 $TCID_{50}$ M2SR significantly increased seroprotective HAI Titers

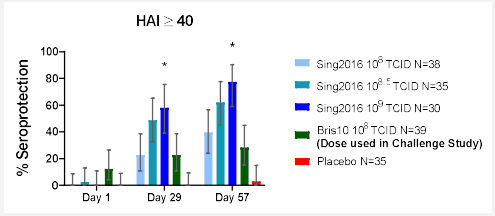


Fig 5. M2SR Significantly Increases NAI Seroconversion After First Dose

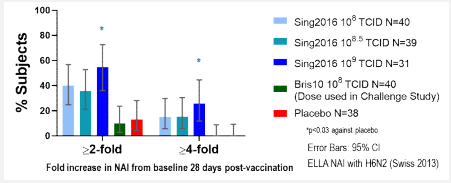


Fig 6. M2SR induced serum MNT against proximate and distant H3N2 drifted strains

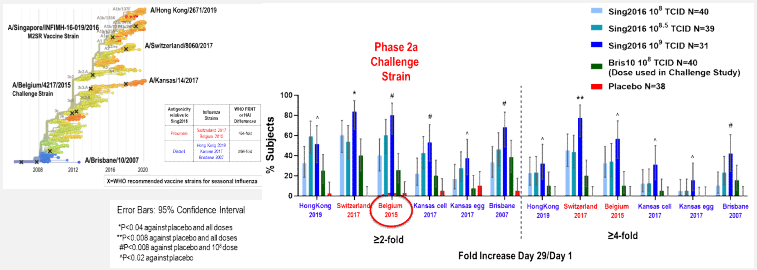
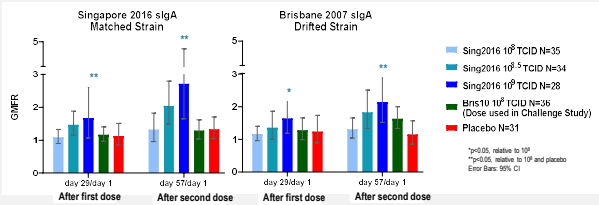


Fig 7. M2SR induces mucosal sIgA against matched and drifted strains



4. Conclusions

- **After 1 IN dose, 10^9 $TCID_{50}$ M2SR induced serum MNT response in 81% of subjects, compared to 28% response with 10^8 $TCID_{50}$ dose used in previous challenge study. These data indicate potential for greatly increased efficacy for the higher dose level.**
- **M2SR H3N2 vaccine well-tolerated after 1 & 2 IN doses**
- **Single M2SR dose 10^9 $TCID_{50}$ induced seroprotective serum HAI titers in 58% of serosusceptible adults, a result substantially greater than reported for licensed LAIV (Coelingh, 2014, Trials in Vaccinology 3:150).**
- **M2SR additionally induced Mucosal secretory IgA antibodies and Serum NAI antibodies**
- **Repeat M2SR dose increases immune response at all dose levels**