LIFE SCIENCES

HUMAN CHALLENGE TESTING

ADVANCED CLINICAL RESEARCH SOLUTIONS

SGS

Faced with increasing pressures on timelines and budgets, clinical research practices aimed at developing influenza vaccines need to continuously evolve in order to ensure effective and efficient pipeline development. Influenza replication kinetics and pathogenesis of highly laboratory adapted viruses in animal models is significantly different from infections occurring in humans, further complicating translation of vaccine efficacy, correlates of protection and outcome measures from animal models to human field trials.

To meet the demand for improved prognostic value, SGS has set up a unique, European-based, Controlled Human Infection Model (CHIM) with a benchmark containment facility within its Antwerp Clinical Pharmacology Unit (CPU), thus enhancing its existing service offering for clients in the field of infectious diseases and vaccine development.

CHIM studies have been proven to:

- **reduce costs through accelerated development of pipelines**
- **provide early efficacy data, enabling rapid candidate selection**
- **prospectively translate animal performance data to human endpoints and healthy volunteer data to outcomes in the field**
- **define correlates of protection and outcome measures related to vaccine efficacy to be carried through in the further development enhancing chance of success of field trials**

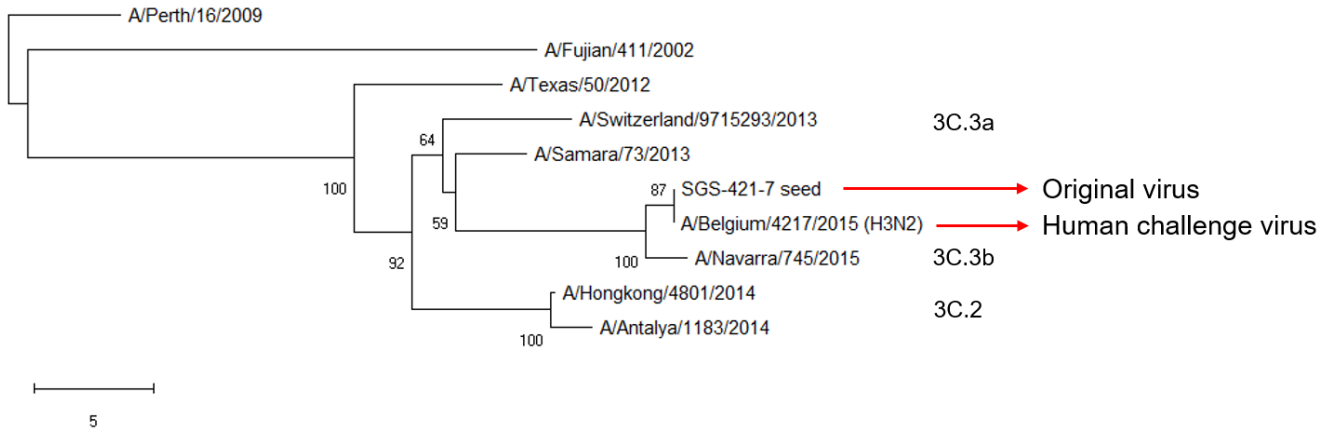
NEW, DRIFTED INFLUENZA A VIRUS AS EXPERIMENTAL CHALLENGE AGENT MEETING INTERNATIONAL GUIDELINES

SGS has developed a wild-type influenza A H3N2 strain for use as a challenge agent in healthy volunteer studies. A/Belgium/4217/2015 [H3N2] has been manufactured to (c)GMP and is approved for use as a challenge agent in CHIM studies with proven ability to demonstrate early efficacy for novel influenza drugs and vaccines. Challenge agent manufacture was undertaken by SGS in conjunction with an international CMO and a world leading academic institute to ensure compliance with regulatory guidelines, including:

- GMP / GLP
- ICH-GCP
- US IND (FDA) and EU IMP (EMA))

Phylogenetic Lineage (NJ analysis)

- Phylogenetic analysis of the SGS A/Belgium/4217/2015/ [H3N2] challenge virus has shown it to have retained 100% homology to the original wild-type isolate
- A/Belgium/4217/2015/(H3N2) = Clade 3C.3b – with no adaptive changes evidenced, following a single production round in embryonated eggs, relative to original virus HA sequences



EARLY CLINICAL TRIALS EXPERTISE

SGS has built up a unique experience in infectious diseases with over 40 years of providing industry with early phase clinical trial solutions, including First-In-Human studies, QT/QTc prolongation, human challenge testing, biosimilars and complex PK/PD studies.

For a faster, targeted patient recruitment across the Americas and Europe, clients can rely on SGS for:

- extensive database of investigators, subject matter experts and key opinion leaders with in-depth knowledge of infectious disease pathologies and access to relevant populations
- specific skill-sets to successfully execute studies in anti-influenza, RSV, HIV, HBV/HCV as well as malaria drug and vaccines plus delivery devices
- discovery team and expertise in a wide range of respiratory diseases (asthma, COPD)
- a favorable regulatory environment in Belgium with very short Phase I trial approval timelines (14 working days)

BENCHMARK CLINICAL PHARMACOLOGY FACILITES

SGS's clinical pharmacology unit is located in Antwerp, Belgium and has a total of 88 hospitalization beds. The Clinical Pharmacology Unit (CPU) has successfully completed several US FDA, FAMHP inspections and numerous client audits over the past 5 years.

For optimized early phase clinical trials, SGS features:

- biosafety Level 2 quarantine facility
- GMP pharmacy for on-site formulation
- GCLP laboratory within the unit for rapid sample processing e.g. PBMC preparation
- full eSource clinic automation (EDC) including sample tracking for safety lab data

Specialist R&D quarantine facilities

SGS's hospital-embedded, Human Challenge Unit (HCU) is a 20-bed quarantine facility that is certified to Biosafety Level 2 (BSL2). The quarantine unit is HEPA-filtered and operates under negative pressure (HVAC) as well as being equipped according to international, benchmark standards with the latest technologies for remote monitoring.

Volunteers are provided with either individual, en-suite or ward-style cubicles according to study requirements. The challenge facility is served by a dedicated clinical trial laboratory equipped with PCR, cell-counters, a flow cabinet, acid cabinet and with dedicated systems and workflows to safely handle infectious samples. The laboratory has HEPA-filtered exhaust systems and an airlock to prevent cross-contamination or accidental release of agents.

CONTROLLED HUMAN INFECTION MODELLING EXPERTISE AND CAPABILITY: OPTIMISING DECISION MAKING IN DRUG DEVELOPMENT

CHIM or Human Challenge Testing (HCT) is an increasingly recommended route to obtaining proof of concept data relating to the efficacy of anti-virals and vaccines during early phase development. While statistically meaningful data can be obtained in animal models, such models are inherently unreliable predictors for efficacy in humans due to the absence of prior exposure and thus pre-existing immunity and most animal species demonstrate substantial anatomical and immunological dissimilarities. The use of highly adapted laboratory strains in animal models with essential differences in replication kinetics may further complicate defining efficacy outcome measures and correlates of protection. Following on from initial safety and PK/PD assessments, CHIM can give early, statistically meaningful performance data, leading to faster well-informed Go / No-Go decisions. Due to their exploratory nature CHIM studies can be flexible in design and in exploratory outcome measures (ICH_E9-Statistical guidance on clinical trial design chapter 2.1.3) which may aid in obtaining solid performance data to aid in design of later field trials.

HUMAN CHALLENGE TRIAL VERSUS TRADITIONAL MODEL

CHALLENGE STUDY

- Small cohorts (40-60)
- Controlled environment
- High attack rate
- Known inoculation date
- Short duration (28d)
- Early kill / no kill decisions
- May predict field trial
- Design / performance

PHASE II FIELD STUDY

- Large cohorts (250-300)
- Uncontrolled environment
- Low attack rate (prevalence)
- Unknown inoculation date
- Long duration (>1yr)
- High cost
- Restricted window for enrolment
- Extensive data analysis required for decisions
- Noise / data ratio

DEVELOPMENT BENEFITS

Smaller sample size requirements to obtain statistically meaningful data

Facilitates the development of prophylactic and therapeutic small / large molecule drugs and vaccines, as well as providing early safety data in healthy volunteers

Predictions of effectiveness in later field studies (de-risking)

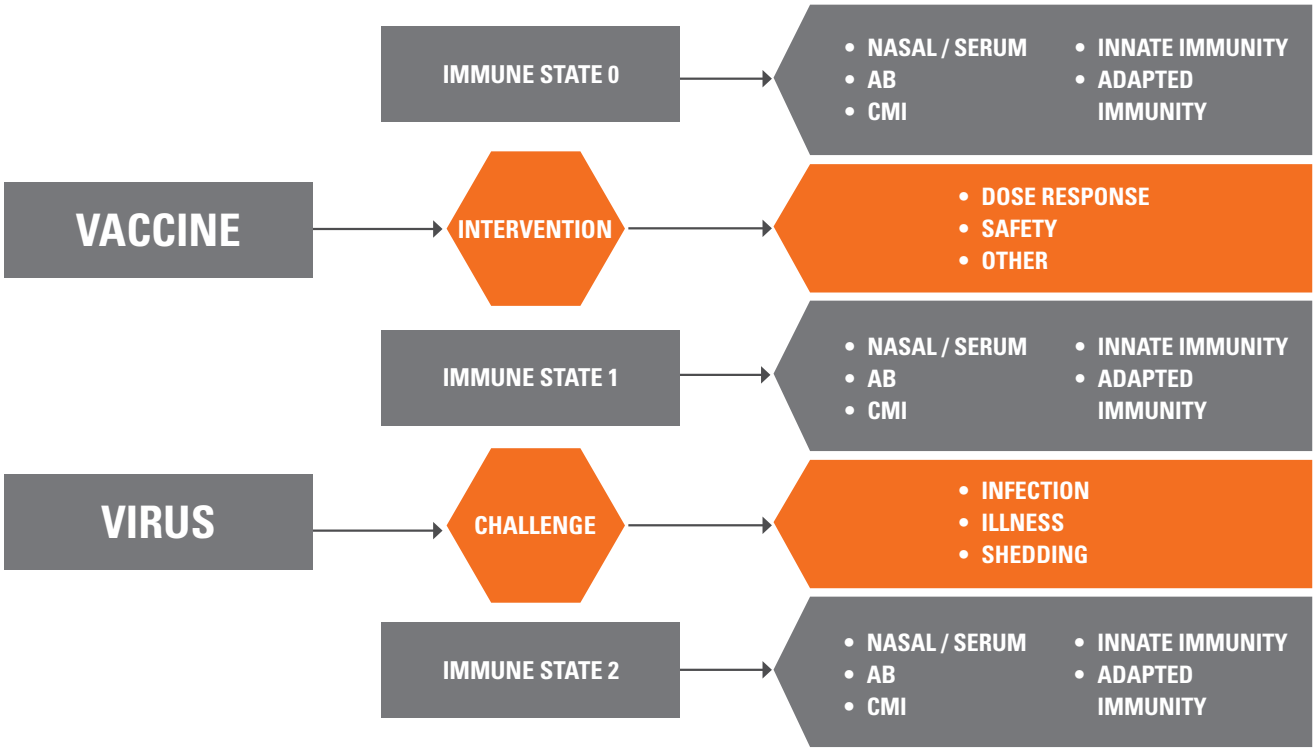
Collection of data in controlled environments

Reduced need for extensive Ph2a trials, shortening timelines and associated costs as well as avoiding the necessity for high prevalence seasons for influenza and RSV

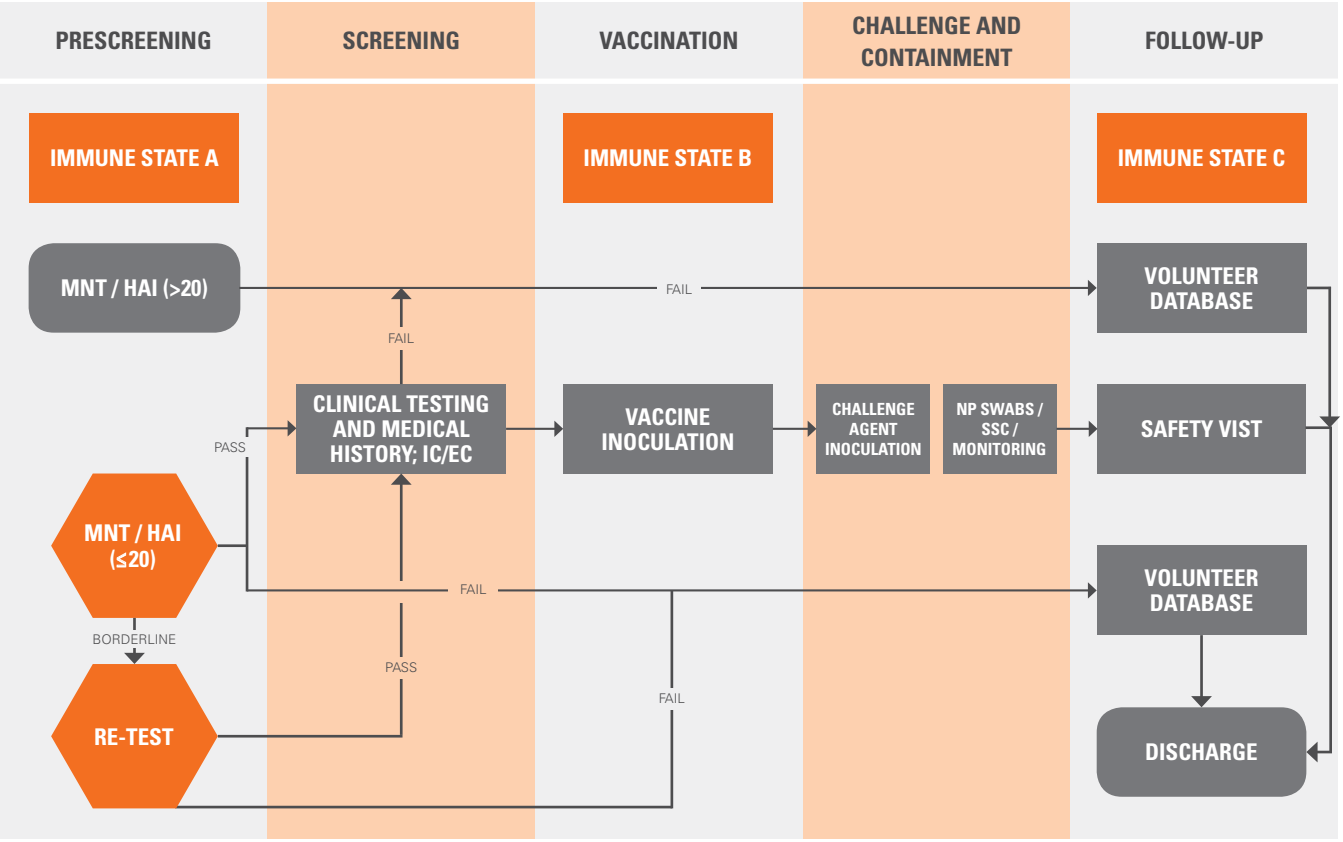
HUMAN CHALLENGE MODELLING (VACCINE)

SGS conducts human challenge studies to rapidly evaluate the efficacy of vaccines in safely breaking the cycle of infection and disease caused by problem pathogens including RSV, influenza and hRV. New approaches outside of large-scale field trials must be considered to provide early evidence of proof of principle in humans if the industry is to avoid costly failures in late phase.

Our human challenge testing facility provides the means for clients to explore these new options.



CONTROLLED HUMAN INFECTION PROCESS MAP



The challenge model is not only helpful as a proof-of-concept for effectiveness, but also as proof-of-mechanism for new targets e.g. in asthma and is increasingly being employed outside of academia.

A LARGE SCOPE OF INVESTIGATION

CHIM provides for a carefully controlled, systematic and efficient method of evaluating efficacy where outside variables may be substantially reduced or even eliminated. Subjects are pre-screened prior to being deliberately infected with a live challenge agent and are then continuously monitored for 2 weeks within a sequestered environment; eliminating the risks of co-morbidity and co-infection.

Subjects are swabbed to determine viral shedding and the data is utilized to construct a viral Area Under Curve (vAUC). Measurements of efficacy are related to reductions in the size of the vAUC as well as changes in cumulative symptom scores.

The challenge model also enables detailed assessment of immune parameters that may help in identifying correlates of infection and disease.

Due to the intense sampling scheme after vaccination and knowledge of the time of infection, the immunological parameters associated with disease may be translated into CoP and outcome measures.

SGS has extensive experience with a wide range of pharmacological techniques and interventions as developed over several decades. SGS and CPU / HCU specialist provisions include:

Different challenge techniques (e.g. virus, histamine, LPS) in both healthy volunteers and patient populations

Prolonged periods of quarantine and intense sampling regimens

Screening large volunteer populations for difficult IC/EC or other protocol criteria

Laboratory assays with complex sampling and/or preparation requirements for biomarker analysis (virus, protective antibodies, cellular immunity (PBMC), other)

PHASE 2A STUDY IN INFLUENZA

A Phase 2a Randomized, Double-blind, Placebo-controlled Trial to Evaluate the Safety, Immunogenicity, and Efficacy of a Vaccine Administered as a Single Intranasal Dose in Healthy Adult Volunteers Challenged with a Live, Antigenically Different Wild-type Influenza Type A Virus

DRUGS:

- Bris10 M2SR (H3N2 A/Brisbane/10/2007) Vaccine
- Challenge agent: Live, Antigenically Different Wild-type Influenza Type A Virus (A/Belgium/4217/2015 H3N2)

KEY CHALLENGES

- Serum prescreening of 547 HVs to enroll 99 serosusceptible (≤10MNT) subjects
- >100 nasopharyngeal swab assays (matrixed PCR) to exclude subjects with concomitant infection/s prior to isolation
- Intranasal inoculation of live vaccine and live challenge virus
- Intensive NP sampling schedule and SSC assessments
- 108 vaccinations and 99 subjects challenged in double-blind cohorts over 3 months

OUTCOMES:

- No adverse events associated with the novel, live IN vaccine
- Broad vaccine efficacy as evidenced by protection against a highly mismatched influenza challenge agent
- 62 percent reduction in vAUC compared to placebo
- 51 to 56 percent reduction in symptom scores
- Vaccine advanced to field trials based on significant CHIM results

Read about SGS's Infectious Diseases Clinical Trial Solutions
Join the scientific community, connect with SGS on LinkedIn: www.sgs.com/LinkedIn-Life

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