# A 100% French nasal vaccine against COVID-19 yields positive pre-clinical results

**For a year now, the BioMAP research team, from the Infectiology and Public Health (ISP) joint research unit run by INRAE and the Université de Tours, has been involved with support of many collaborators, in the development of a 100% French nasal vaccine against the SARS-CoV-2 virus. This project is well in line with the commitment to partnership research promoted by the Institut Carnot's France Futur Élevage programme, of which INRAE and the university are co-directors.**
**The aim of BioMAP is to develop a candidate vaccine based on viral proteins that can be administered in the nose. Research is now gaining in momentum. Pre-clinical tests demonstrate the efficacy of the candidate vaccine after two nasal immunisations delivered three weeks apart, both in terms of the immune response and early neutralisation of the original virus and its variants, which would greatly decrease the risk of contamination by a vaccinated individual. The team obtained these results together with a consortium formed by the pharmaceutical group Recipharm, the Bio$^3$ Université de Tours – Groupe IMT and the biotech company Vaxinano, with financial support from the Agence nationale de la recherche (ANR), the Centre-Val de Loire Regional Council[1], the Université de Tours and INRAE.**
**Following these very positive results, development and production of vaccine batches will begin this autumn with the goal to moving into the clinical phase in 2022, and a market launch in 2023.**

In contrast to intramuscular vaccines, only nasal vaccines are able to block the virus in the nose by inducing local immunity in the nasal mucosa, i.e. the portal of entry and multiplication of the virus. The vaccine candidate, developed by the BioMAP team[2], would take position as the eighth nasal vaccine currently starting clinical testing in the world, and the only one based on viral proteins in France.

## This technology for nasal vaccine has already proven to be an efficient barrier against toxoplasmosis infection in primates

This SARS-CoV-2 protein vaccine candidate builds on the BioMap team's expertise in mucosal vaccine design. In partnership with the biotech company Vaxinano, the team has already successfully developed an effective candidate vaccine to protect monkeys from toxoplasmosis. This stable, non-toxic and adjuvant-free nasal vaccine is based on a total protein extract from *Toxoplasma gondii,* the infectious agent being produced by the team and further encapsulated in starch and lipid-based nanoparticles (Vaxinano technology). The SARS-CoV-2 nasal vaccine candidate is based on similar technology.

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1 ANR RA-COVID-19 funding and Centre Val de Loire Region funding for joint initiatives in the fight against COVID 19.
2 The BioMap team of the Infectiology and Public Health joint research unit is directed by Professor Isabelle Dimier-Poisson, at the university's department of medicine.

In a similar strategy, the SARS-CoV-2 vaccine protein component was designed and produced by the team, and then encapsulated by Vaxinano. The vaccine, consisting of the Spike protein with other viral proteins that are not prone to mutations, would protect vaccinated individuals regardless of the mutated circulating coronavirus variant strains.

This vaccine was first tested *in vivo* in a pre-clinical mouse model. Two nasal applications, three weeks apart, induced a strong humoral immune response – in particular of the mucosal compartment with neutralising Immunoglobulin A (IgAs[3]), which are polyspecific, i.e. more permissive against variation of the Sars-CoV-2 – along with a cellular response in the nasal cavities and lungs. The protective efficacy of the vaccine was also assessed in terms of survival and absence of clinical signs after infection on vaccinated animals, 100% of individuals survived with no clinical signs (respiratory distress, weight loss, etc.) unlike the unvaccinated control group. Second, the candidate vaccine was tested for contagiousness in the established Syrian hamster model, which mimics the human pathophysiology of COVID-19, again providing striking results with no viral detection in the lungs and nose of vaccinated/infected animals while unvaccinated/infected animals showed a high level of viral RNA in both lungs and nasal cavities. These results, highly predictive of the effectiveness of a vaccine in humans, allow us to predict that contagiousness between individuals is completely abolished.

## An easily administered, non-invasive vaccine as a first dose or a booster

Technically, the vaccine will be administered by means of a small adapter placed at the end of a needle-less syringe, allowing an ideal diffusion within the nasal cavity. Currently, a device developed for this vaccine specifically for humans is being evaluated in collaboration with the Recipharm/Resyca group. Non-invasive and requiring minimal logistics, this basic vaccination system would allow for a wider distribution to Europe and far beyond. Moreover, the vaccine is highly stable at room temperature and even longer at 4°C and thus would not require the strictlogistics mandatory to maintain cold chain integrity, unavailable in most countries of the world.

This vaccine would therefore target unvaccinated populations to protect against severe and moderate forms of COVID-19 and could moreover be a booster for already vaccinated populations to prevent transmission of the virus.

## A 100% French research and development consortium

Based on these results, the research team will rely on the skills of companies based in France, which have already been identified, to develop its vaccine for future clinical trials:
-Vaxinano, based in Lille,
-GTP Bioways, a CDMO[4] (Contract Development and Manufacturing Organisation) based near Toulouse,
-C.RIS Pharma, a CRO[5] based in Saint Malo,
-Recipharm, a manufacturer based in Monts, near Tours.
The transition to the clinical phase, supported by the ANRS/ Maladies infectieuses émergentes[6], is scheduled for the second half of 2022, with the perspective to bringing the vaccine to market in 2023.

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[3] Immunoglobulin A (IgA) is an antibody isotype that plays a crucial role in immune function of the mucous membranes. They are a first line of immune defence against toxins and infectious agents in the environment.

[4] CDMOs are pharmaceutical subcontractors whose core business is the manufacturing and packaging of medicines on an industrial scale.

[5] CROs are companies specialising in clinical trial organisation services for the pharmaceutical industry and for Public Scientific and Technical Research Establishments in France (EPST). CROs are involved in all phases of research and development particularly in the pharmacovigilance phase.

[6] Created on 1 January 2021, the ANRS/ Maladies infectieuses émergentes is the new autonomous agency of INSERM, created by the merger of the REACTing consortium and the National Agency for AIDS Research (ANRS) under the joint impetus of its two supervisory ministries, the Ministry of Higher Education, Research and Innovation and the Ministry for Solidarity and Health.

Made possible by the financial support of the ANR and the Centre-Val de Loire Regional Council, as well as by the commitment of all the partners mentioned, this project still involves a number of stages to be completed before the vaccine is brought to market. It is set to provide a major improvement in the protection of populations, in terms of prevention, contagiousness, effectiveness on current and future variants, and increasing the percentage of people vaccinated and thus collective protection.

**Laboratories involved in the pre-clinical studies**

*Achievement of experimental studies*: PFIE, INRAE Experimental Unit.
*In vivo studies*: Virology (VIRO), Joint Research Unit (ANSES/ENVA/INRAE); Molecular Virology and Immunology (VIM), Joint Research Unit (INRAE/Université Versailles Saint-Quentin-en-Yvelines)
*In-vitro studies*: Infectious Disease and Public Health (ISP), Joint Research Unit (INRAE/Université de Tours) : Teams BioMAp (Isabelle Dimier-Poisson) and BIP (Antoine Touzé); Morphogenesis and antigenicity of HIV and hepatitis viruses (MAVIVH), Joint Research Unit (INSERM/Université de Tours), Infectious agents resistance and chemotherapy (AGIR), Pathology Laboratory (Université de Picardie Jules Verne, CHU Amiens Picardie).

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**About INRAE**

Created on January 1, 2020, the French National Research Institute for Agriculture, Food, and Environment (INRAE) is a major player in research and innovation. INRAE carries out targeted research and resulted from the merger of INRA and IRSTEA. It is a community of 12,000 people with 268 research, experimental research, and support units located in 18 regional centres throughout France. Internationally, INRAE is among the top research organisations in the agricultural and food sciences, plant and animal sciences, as well as in ecology and environmental science. It is the world's leading research organisation specialising in agriculture, food and the environment. INRAE's goal is to be a key player in the transitions necessary to address major global challenges.

Faced with a growing world population, climate change, resource scarcity, and declining biodiversity, the institute is developing solutions that involve multiperformance agriculture, high-quality food, and the sustainable management of resources and ecosystems.

**About Université de Tours**

Multidisciplinary (Arts & Humanities, Law, Economics & Social Sciences, Literature & Languages, Medicine, Sciences & Technology, 2 Institutes of Technology (IUT), 1 Centre for Advanced Renaissance Studies, 1 Graduate School of Engineering), the University is located in the heart of Tours but also in Blois.
With over 36 research laboratories, it is the leading public research institution in the Centre Val de Loire region.

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