Cynbiose and the VirPath academic laboratory are teaming up in a collaborative research and development project to address the public health emergency related to the COVID-19 outbreak.

Marcy l'Etoile, France, June 8th, 2020 - Cynbiose, a service company specializing in the development of innovative preclinical models, in partnership with the academic laboratory VirPath of the International Centre for Research in Infectiology, announced today the launch of the COVIBIOSE project. This initiative is coordinated by the French cluster Lyonbiopôle and supported by the Auvergne-Rhône-Alpes region.

The COVIBIOSE project aims to **develop and characterize an innovative non-human primate (NHP) preclinical model** to study the pathophysiology of the infection by SARS-CoV-2[1] and evaluate the efficacy of therapeutic **or prophylactic candidates** in order to fast-track them to clinic trials.

As part of the race to discover and develop prophylactic or therapeutic candidates to fight against the Covid-19 outbreak, a critical step is the preclinical evaluation in clinically relevant animal models. In particular, this has been the case during major health crises linked to the emergence of new pathogens over the past 40 years (HIV, Prion, SARS-CoV, MERS-CoV, Nipah, Hendrah, etc.).
In the case of the last two coronavirus outbreaks (SARS-CoV-1 in 2003 and MERS-CoV in 2012), mice did not turn out to be a relevant animal model and required the development of transgenic lines, which have other drawbacks (price, immune system, availability). By comparison, the **phylogenetic proximity of non-human primates to humans** makes of these species **an asset to research on coronaviruses[2]**. All NHP species do not react identically to coronaviruses infection, and african green monkeys (AGM) have shown a higher viral load of

[1] Coronavirus 2 of Severe Acute Respiratory Syndrome

[2] Kuiken, T *et al.* Newly discovered coronavirus as the primary cause of severe acute respiratory syndrome. *The Lancet*, *362*(9380), 263–270.

SARS-CoV in the lungs than rhesus and cynomolgus macaques[3] as well as pronounced clinical symptoms following SARS-CoV-2 infection[4].

The COVIBIOSE project

Cynbiose and the academic **laboratory VirPath propose to** develop a **NHP model of SARS-CoV-2 infection on the african green monkey** *(Chlorocebus aethiops),* one of the well-known species of NHP used in biomedical research. The infectious challenge will be carried out thanks to a bank of **human** viral **strains** isolated from clinical samples of patients in France and produced by the laboratory VirPath from January 2020. The NHP model of infection by **SARS-CoV-2 will be characterized on several aspects:** clinical symptoms and pathology, viral load, pathophysiology, immune response, transcriptomics and histopathology.

As soon as the preclinical model is characterized and validated, VirPath will be able to validate the preclinical efficacy of its innovative therapeutic **strategies.** In particular, these studies will help define the optimal doses and strategies for the delivery of already available repurposed drugs, alone or in combination, to **treat COVID-19 patients.**

This unique and innovative **preclinical model will then be made available to biopharmaceutical companies** in order to quickly assess the efficacy of drug or vaccine candidates in a translational model.

"This context of major health crisis must give rise to a mobilization commensurate to the challenges we must face collectively, while maintaining a scientific approach that is both constructive and sustainable. Cynbiose is one of the only ***private CRO in Europe*** *able to implement studies in* ***primates*** *involving* ***infectious challenges warranting a biosafety level 3****, as required by SARS-CoV-2. Cynbiose* ***has more than 10 years of experience conducting studies on major infections*** *such as the Dengue or Zika virus for the biopharmaceutical industry and academic research. In addition, our company has developed specific* ***expertise in NHP model of infections by respiratory viruses*** *(hRSV and Metapneumovirus), notably in collaboration with the Mérieux Foundation, the VirPath laboratory (METABIOSE project) and the Laboratory of Immunobiology of Viral Infections (IBIV) of CIRI. All our teams are mobilized in this race against time,"* said Hugues Contamin, CEO of Cynbiose.

"*VirPath has been able to respond since January 2020 to the current health crisis of COVID-19. Within the framework of national coordination and the REACTing consortium coordinated by INSERM, the laboratory's researchers isolated* ***several strains of the SARS-CoV-2 virus*** *from clinical samples of the first COVID-19 patient in France, amplified and characterized them by sequencing on the UCBL1 ProfileXpert genomic platform, and established their own viral bank. The team has also developed and characterized cellular* ***models of infection*** *as well as a unique physiological model of reconstructed human respiratory epithelium infected* ***with SARS-CoV-***

[3] McAuliffe, J. *et al*. (2004) Replication of SARS coronavirus administered into the respiratory tract of African Green, rhesus and cynomolgus monkeys. *Virology*, *330*(1), 8–15**.**

[4] Woolsey, C., *et al.* (2020). Establishment of an African green monkey model for COVID-19. *BioRxiv*, 2020.05.17.100289.

2[45], *as well as all viral* ***quantification protocols*** *(infectious titer on cell lines and viral genome copy by molecular biology)****,*** *needed for the evaluation of* ***drug candidates.*** *Moreover, some* ***antiviral candidates*** *have already been validated by the laboratory and are currently undergoing clinical trials*", says Manuel Rosa-Calatrava, INSERM Research Director, co-director of the VirPath Laboratory.

*"****The implementation of the NHP model of SARS-CoV-2 infection on the african green monkey is naturally in line with our partnership with Cynbiose****. This model will effectively allow us to synergistically complement our preclinical capabilities for the assessment of therapeutic and prophylactic candidates against COVID-19",* adds Manuel Rosa-Calatrava.

A joint steering committee has been established, bringing together virologists, clinicians, experts in preclinical development and biosafety, belonging to academic and industrial entities of the Auvergne-Rhône-Alpes region. It will discuss the most appropriate study protocols to meet the scientific and biosafety challenges posed by this project.

Partners of the COVIBIOSE project

The translational research program carried out by Cynbiose and the academic laboratory Virpath will begin in June and will be implemented by a consortium of actors of CYNBIOME™, the 1st European preclinical excellence network on microbiome and infectious diseases based on the NHP model[5]. The COVIBIOSE project is coordinated by Lyonbiopole.

"We are working with the different parties in this project, both within the Lyonbiopôle network of which they are members and within the framework of the HPV Health Hub, which was launched in January of this year. It is therefore only natural that we have partnered to fight the Covid-19 outbreak. Since the beginning of the latter, Lyonbiopôle has mobilized to support its entire network with strong skills to bring out ambitious issues and participate in the understanding of the viral mechanisms involved, as well as the disease. The preclinical model developed by Cynbiose and VirPath, if demonstrated in the coming months, will save time in the fight against the virus. The regional ecosystem is once again present through this innovative health project and demonstrates the ability of academic and industrial actors to mobilize quickly and work together," said Florence Agostino-Etchetto, Managing Director of Lyonbiopôle.

The COVIBIOSE project also involves VetAgro Sup, a higher education and research institution under the supervision of the Ministry of Agriculture and Food. Vetagro Sup will play a leading role in providing expertise in infectious diseases, biosecurity and ethics.

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[5] Patent FR 2002351

[5] Pizzorno A. *et al.* Characterization and treatment of SARS-CoV-2 in nasal and bronchial human airway epithelia. bioRxiv 2020.03.31.017889

[5] Terrier O. *et al.* Broad-spectrum antiviral activity of naproxen: from Influenza A to SARS-CoV-2 Coronavirus. bioRxiv 2020.04.30.069922

[5] CYNBIOME™ was established early 2020. For more information on the sector: https://cynbiose.com/en/innovation-preclinical-research/cynbiome/

Finally, the Auvergne-Rhône-Alpes Region has been heavily involved in the fight against the Covid-19 outbreak by supporting projects such as COVIBIOSE.

"The Auvergne-Rhône-Alpes Region has mobilized extensively since the beginning of the crisis in order to best support its territory in the fight against the Covid-19 *and its consequences. Among its many areas of intervention, research and innovation is particularly important, especially when initiatives are able to quickly provide solutions at the scientific and medical levels. The COVIBIOSE project convinced us of its strategic interest in the fight against* Covid-19 *at the regional, national and international level, and demonstrated the capacity of our territory's actors to urgently set up an effective consortium to innovate. It is therefore with pride that the Region supports this project and sends its encouragement and wishes to the members of this collaboration,"* said Yannick Neuder, Vice-President of the Auvergne-Rhône-Alpes Region in charge of higher education, research, innovation and European funds.

"We are very grateful to the Auvergne-Rhône-Alpes Region, which was able to respond to the urgency of the situation by supporting the project with exceptional funding. We are looking forward to continuing our collaborations with members of the CYNBIOME™ network, such as the academic laboratory Virpath, with whom we will pool complementary expertise in order to develop a strategy for the pre-clinical evaluation of drugs and/or vaccines that are urgently needed to fight this outbreak", said Hugues Contamin, CEO of Cynbiose.

About Cynbiose

Cynbiose is the only Contract Research Organization (CRO) of its kind in Europe and is AAALAC accredited. The company specializes in the development and commercialization of innovative non-human primate models to accelerate the preclinical development phases of drug candidates. It works on exploratory pharmacokinetics and toxicology studies, as well as proof of concept studies in different human pathologies, such as infectious diseases and respiratory conditions, the central nervous system and inflammatory, musculoskeletal disorders and cardiovascular/neurovascular diseases. The company provides its services in line with quality guidelines that meet industry requirements.
Cynbiose has expertise in every stage and technique required to manipulate these preclinical models. It boasts an extensive network of experts and partners in the academic and private domains, allowing complex studies to be conducted with dedicated project teams. Cynbiose is committed, responsible and proud to contribute to advancing healthcare research by participating in numerous preclinical development programs for new therapies.
The SME Cynbiose was founded in 2008 by CEO Dr Hugues Contamin (DVM, PhD) and is based in Marcy l'Etoile near Lyon, France. It currently has 13 staff. In 2017, Cynbiose established the subsidiary Cynbiose Respiratory (based in Tours), with expertise covering infectious and non-infectious respiratory diseases, studies on drugs nebulization and drug deposition in the lungs. Cynbiose is a founding member of the French Association of Service and Innovation Companies for the Life Sciences (AFSSI).
www.cynbiose.com

About VirPath

The VirPath laboratory is an academic research laboratory (Claude Bernard Lyon University 1, INSERM, CNRS, ENS lyon) specializing in virology and human respiratory pathologies. VirPath is associated with the World Health Organization and houses the National Respiratory Virus Reference Centre. To contribute to a better control of emerging and re-emerging respiratory viruses, the laboratory conducts multidisciplinary research incorporating complementary approaches to basic, clinical and technological research. In particular, Virpath has developed methodological tools (reverse genetics, models of in vitro infection, ex-vivo and translational) and technologies tools (vaccine antigen production processes, transcriptomic and metagenomic analysis pipeline) and is equiped with BSL-2 and BSL-3 infrastructures. VirPath is a coordinator or partner in many collaborative academic or industrial projects labelled by several national and international competitiveness clusters. Its proactive policy of promoting academic research through technology transfer to the clinic and industry has, in recent years, resulted in the implementation of four phase 2 clinical trials (antiviral evaluation), the constitution of a portfolio of 17 patent families and the creation of a technology research platform (VirNext), a service company specializing in microbiological disinfection (VirHealth) and two startups (Signia Therapeutics and Vaxxel), winners of the French i-Lab competition in 2017 and 2019 and labeled FrenchTech in 2019.
https://www.virpath.com

About Lyonbiopôle

As a French cluster, Lyonbiopole is the gateway to healthcare innovation in Auvergne-Rhône-Alpes. It aims at supporting ambitious projects and innovative companies in the healthcare & life sciences' sector. It encourages innovators to develop new technologies, products and services toward a more personalized medicine and better treatments for patients. The cluster's strategic missions are focused around: - promoting the emergence of innovative R&D collaborative projects; - supporting SME in areas such as strategic partnerships, access to private investors, expertise and training; - fostering SME Internationalization and the cluster's position at the European and International levels; - offering access to high-level facilities dedicated to life sciences companies; - promoting members and healthcare ecosystem. Lyonbiopole currently has more than 240 members, including 6 funders (Sanofi Pasteur, bioMérieux, Boehringer Ingelheim Animal Health, Becton Dickinson, CEA, Fondation Mérieux), 12 subsidiaries of major groups and ETI, 207 SMEs and 18 competence centers (CHU, Universities, Foundations, etc.). Lyonbiopole received the European cluster excellence "Gold Label" by ECEI for 2nd time in 2017. The cluster is part of different European initiaitives such as bioXclusters, MAGIA, S3martMed and EIT Health.
lyonbiopole.com

About the Auvergne-Rhône-Alpes Region

A leader in innovation, research and higher education, the Auvergne-Rhône-Alpes Region, France's largest industrial region and France's 2nd largest region in the field of ESRI, has made the training, research and innovation continuum one of the priorities of its action, with the

aim of creating more sustainable and skilled jobs in more and more competitive companies. It is producing, under the leadership of Vice-President Yannick Neuder, an unprecedented effort to support all territories and develop university sites. Since 2016, the Region has invested more than 441 million euros in the field of ESRI through structuring devices, which also benefit from the leverage of the FEDER funds for research and innovation up to 153 million euros. Our Region is finally the public community whose 3 university sites are labelled "Initiatives of Excellence - Idex" (Lyon and Grenoble) or "Science / Innovation / Territories / Economics Initiatives - I-Site" (Clermont-Ferrand) as part of the Future Investment Plan (PIA).

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