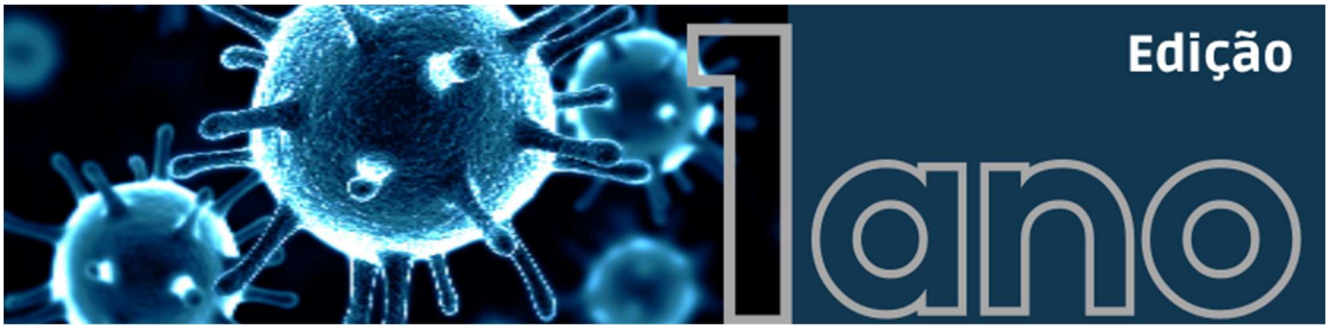

April 9, 2021

Observatory of Technologies Related to COVID-19 – 1 YEAR

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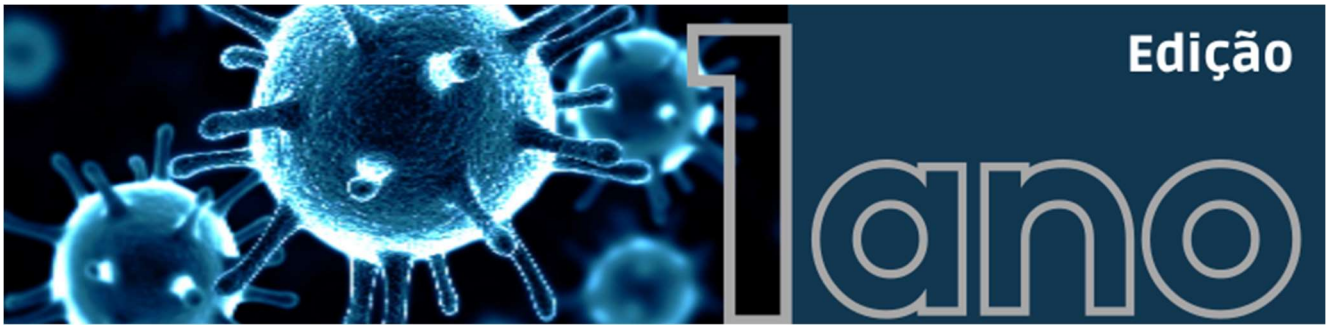
Since the initial reports of a group of pneumonia cases of unidentified origin in Wuhan, China, in December 2019, the new coronavirus (SARS-CoV-2), which causes severe acute respiratory syndrome, spread throughout the world, causing the COVID-19 pandemic. Over the last 12 months, an astonishing range of information was generated by researchers all over the world, covering different fields concerning the supposed origin of SARS-CoV-2 and the development of vaccines, which became the hope for the solution of the pandemic in a time markedly shorter than usual.

The genetic sequencing of the virus that causes the disease was obtained and made available in public databases in mid-January 2020, which enabled the development of diagnostic tests for SARS-CoV-2 and drug repurposing, along with the beginning of the race for the development of vaccines for the prevention of COVID-19. In March 2020, the World Health Organization (WHO) declared that COVID-19 represented a pandemic.

Many immunologists quickly switched their prior researches with similar pathogens to focus on the several aspects involved in COVID-19, and due to that unprecedented convergence of efforts to unravel and define, prevent and treat a viral infection, a remarkable amount of work was produced and disseminated, either by articles published in renowned journals, preprints or postprints, in addition to dissemination by the general media.



ObTec COVID-19

The Observatory of Technologies Related to COVID-19 (ObTec COVID-19) of the Brazilian Patent and Trademark Office – INPI was created in March 2020 in order to identify and spread information about the technologies that could be useful for global and local actions and capable of contributing to the solution of this problem, so that the players of the Brazilian Innovation System had tools to fulfill their role with excellence.

In this context, relevant information provided in scientific papers, news, and patent documents related to COVID-19 is being made available. The scientific papers and news were monitored on a daily basis until December 2020, when the issue started to be published 3 times a week.

The patent documents are under analysis in studies addressing the following topics: medicines, vaccines, protection masks, lung ventilators, and diagnostic methods. Such studies aim to present the different technologies related to controlling the pandemic, including those protected by industrial property and those already expired.

Additionally, information on financings and incentives to R&D, information on the priority processing for COVID-19 patents applications, and a link to other studies and websites about patents in the scope of COVID-19 are available.

Such information is available at https://www.gov.br/inpi/pt-br/servicos/patentes/tecnologias-para-covid-19/. The page is divided into two segments. The top portion includes links to information produced by INPI; attention is called to the link to the technological monitoring studies in the scope of COVID-19 (**Erro! Fonte de referência não encontrada.**).

Figure 1: Links available on the ObTec COVID-19 website.

Information on monitored scientific papers and news is organized by topics and available in the bottom portion of the page, with the daily highlights (**Erro! Fonte de referência não encontrada.**).

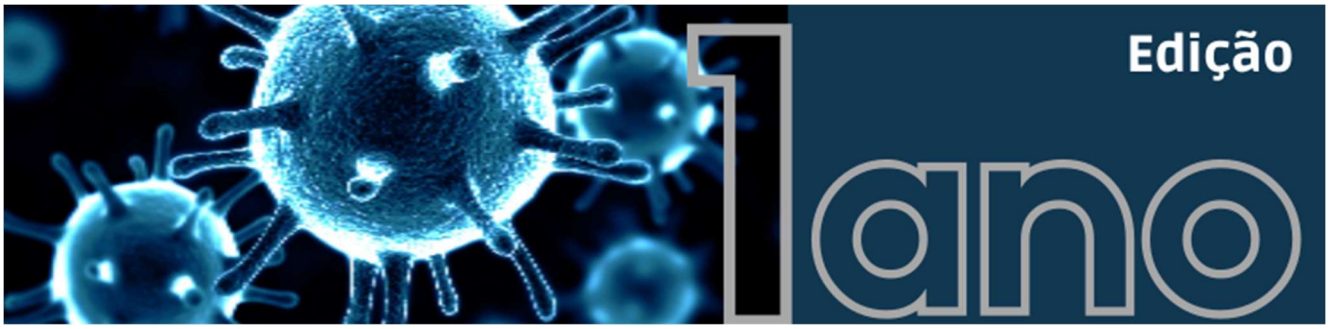


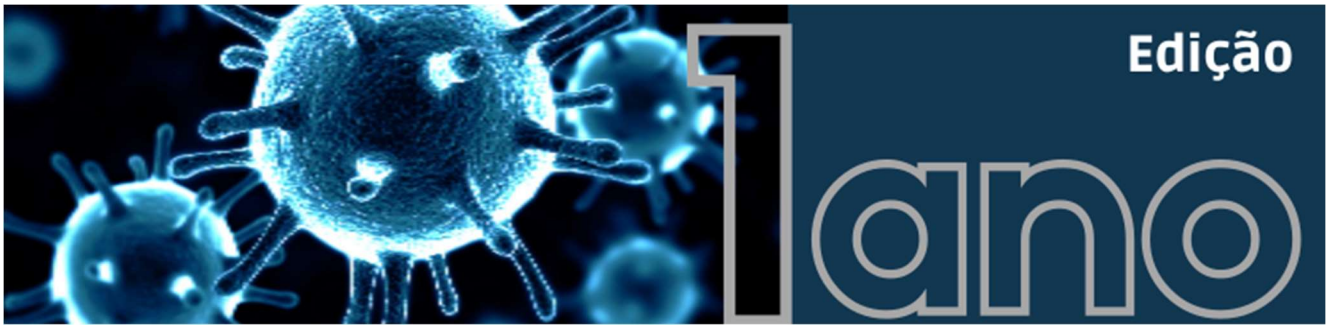
Figure 2: Topics of the scientific papers and news made available by INPI

Purpose

Considering the significant amount of information that we inserted into the ObTec COVID-19 website during the last year, this issue aims to present a history of the main topics addressed in our issues, in order to show the evolution of technology and science related to COVID-19 during this period. The studies published in the scope of ObTec are also presented, noting that these studies were prepared according to the most targeted technologies at the moment, evidencing the progress in the understanding of the immunological response to SARS-CoV-2 and highlighting the knowledge gaps, as well as the fields for further investigation.

Evolution of scientific knowledge and technologies related to COVID-19

During this year, more than 2900 papers and news, distributed according to the previously defined themes (**Erro! Fonte de referência não encontrada.**), were systematically analyzed, as shown in the chart of **Erro! Fonte de referência não encontrada.**, in which it is possible to note that the publications were concentrated in the fields of medicines, science, and vaccines.



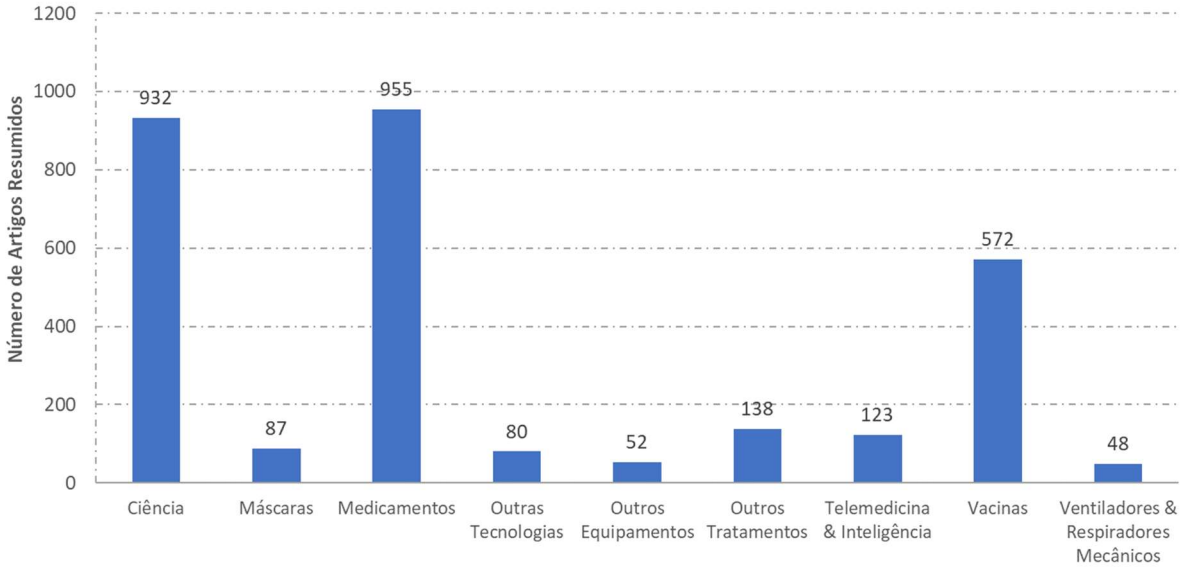
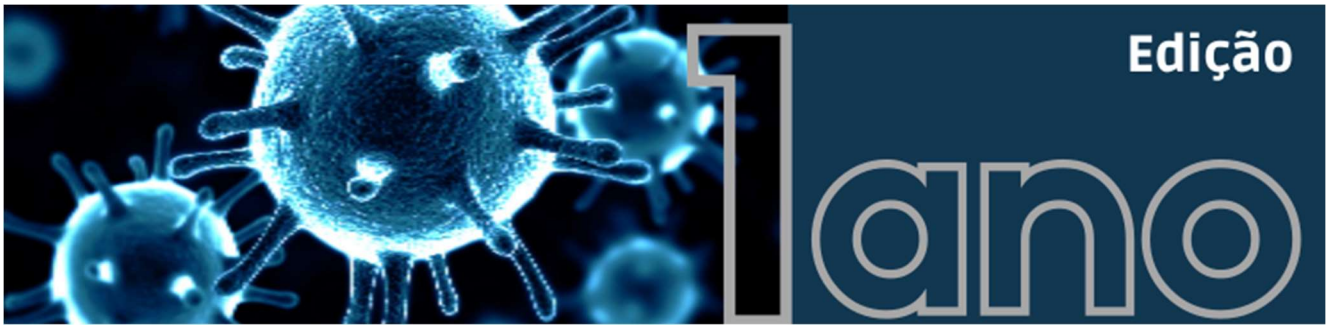


Figure 3: Number of publications disseminated by the Observatory over 12 months, divided into the previously defined themes. Source: INPI-Obtec-Covid-19

. Between April 2020 and the end of February 2021, a set of publications was included in the INPI's ObTec COVID-19 website inside the following "theme areas": medicines, science, vaccines, other treatments, telemedicine and artificial intelligence, and masks. **Erro! Fonte de referência não encontrada.** shows the number of publications available on each of them. Although this is a new disease, several of the medicines, devices, equipment, and processes that were already in use in the fight against other diseases similar to COVID-19 and to its symptoms were initially investigated, aiming at determining their possible application in the fight against SARS-CoV-2.In **Erro! Fonte de referência não encontrada.**, it is possible to note that in the first months of the pandemic, publications were focused on medicines that could be repurposed to contribute to the treatment of the symptoms or even to prevent the replication of the SARS-CoV-2 virus inside the infected individuals.

The other two theme areas with the most publications in the first months of the pandemic were "science" and "vaccines", which indicates the global efforts to understand the cellular and immunological mechanisms involved in the disease, in addition to the search for knowledge related to the origin of the virus and its modes of transmission. It is highlighted that the development of several vaccines in a reduced time was only possible due to ongoing studies on viruses similar to SARS-CoV-2, such as SARS-CoV and MERS-CoV.



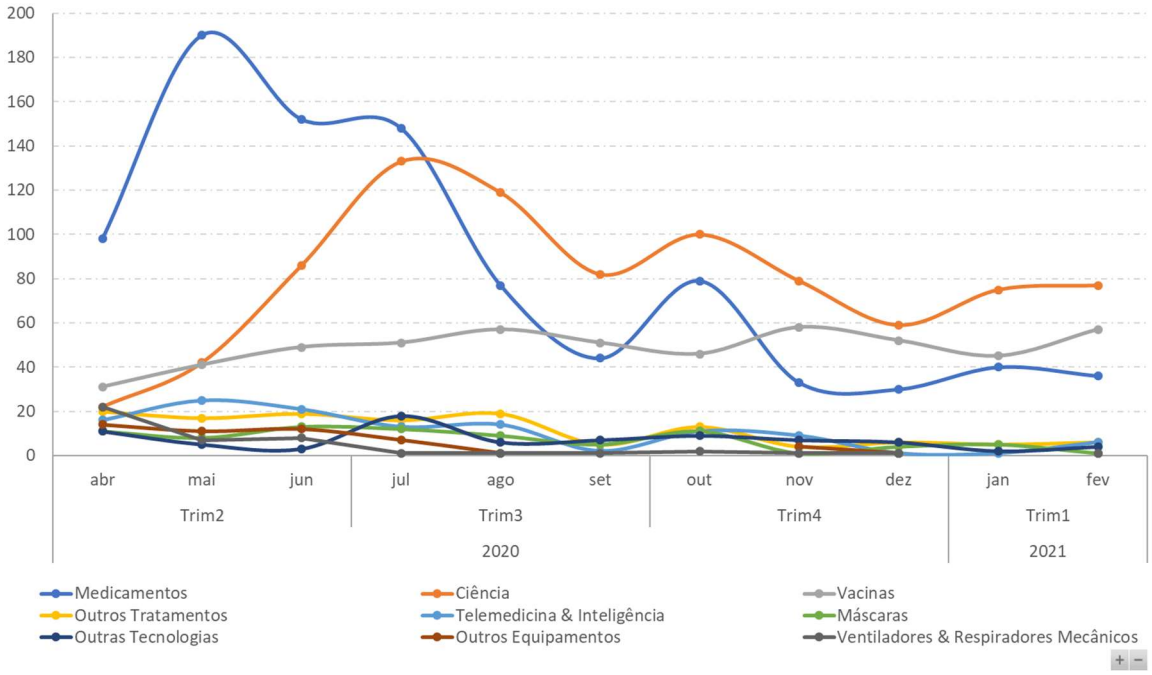


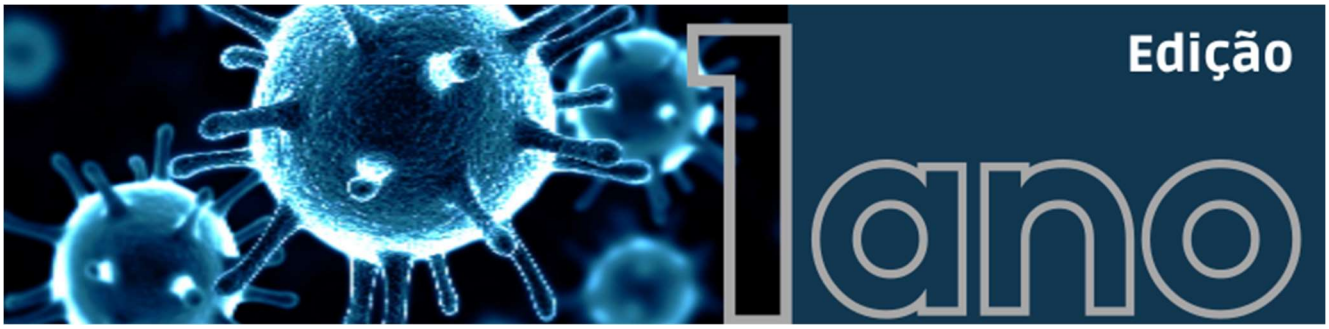
Figure 4: Number of publications by topic from March 2020 to March 2021. Source: INPI-ObTec-COVID-19

, During one year of development of the project, INPI's ObTec COVID-19 also published 9 studies on patent applications related to the pandemic, and there is an outlook for new publications in the next weeks of at least another three studies on vaccines and one on patent applications involving nanotechnology applied to the treatment, prevention, or diagnosis of COVID-19. Additionally, the funding projects and patent program initiatives have also been disseminated.

Highlights of March and April 2020

One of the first assumptions was that, as is the case for the majority of acute respiratory infections caused by viruses, the infection by SARS-CoV-2 would induce an immune response by producing neutralizing antibodies. Therefore, reagents and protocols to better characterize these responses by antibodies were quickly developed and shared around the world.

On March 18, 2020, the WHO and its partners launched a program known as "Solidarity", which consists in international clinical trials to contribute to finding an effective treatment for COVID-19. It is one of the biggest international randomized clinical trials for COVID-19 treatments, registering almost 12,000 patients in 500 hospitals in more than 30 countries. Among the medicines tested, the entity focused on four that seem to be more promising at that moment: Remdesivir, which was used to treat Ebola; Chloroquine, which was used to treat malaria; Ritonavir or lopinavir, which were part of the HIV treatment cocktail; and Interferon-beta, a molecule involved in the regulation of body inflammation that, in previous trials, had shown an effect in marmoset species of monkeys infected by MERS.



In the context of the Solidarity program, on March 27, 2020, the Brazilian Health Surveillance Agency – ANVISA published a research on hydroxychloroquine for the treatment of COVID-19 in the Hospital Israelita Albert Einstein, while Fiocruz initiated studies in a partnership with the WHO. During that period, the repurposing of the drugs lopinavir, ritonavir, and favipiravir to inhibit viral replication was also being studied in Brazil.

On March 26, 2020, two potential vaccines against SARS-CoV-2 started to be disclosed: one mRNA-based vaccine that encodes the SARS-CoV-2 spike protein (S), developed by the Vaccine Research Center of the National Institutes of Health – NIH, USA, and by the North-American pharmaceutical and biotechnology company Moderna, and another one based on an adenovirus vector developed by CanSino Biological Inc. and the Beijing Institute of Biotechnology (China). It is important to highlight that some researchers believe that the development of RNA-based vaccines represents one of the biggest technological advances of mankind in the 21st century.

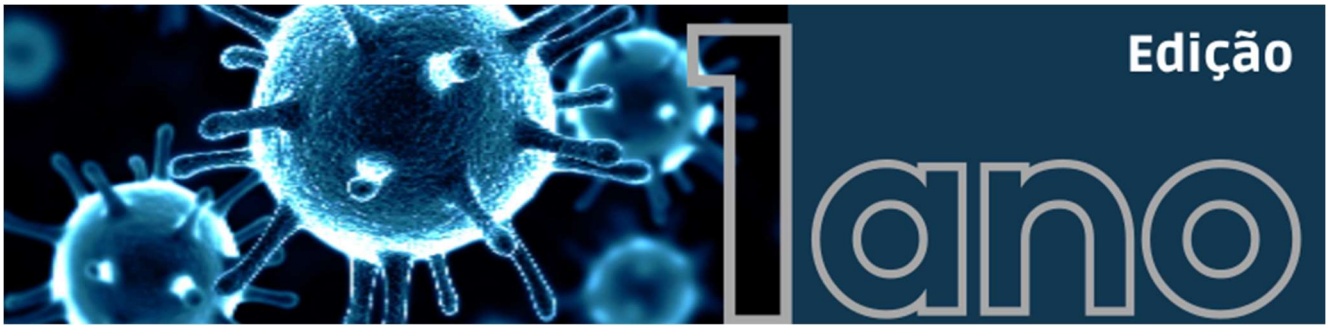
In the field of science, the papers brought important information about the COVID-19 pathogenesis and compared the transcriptional responses to SARS-CoV-2 using cell lineages, ferrets, and patients' serum samples, and discovered that, compared to other respiratory viruses, the host's immune response to SARS-CoV-2 is not able to generate a response of type I and type III interferon. On the other hand, it induces high levels of pro-inflammatory chemokines and cytokines. The ability of the SARS-CoV-2 spike protein, particularly of the receptor binding domain (RBD), to induce responses of neutralizing antibodies makes it the main target for the development of vaccines.

Additionally, commercial trials to identify specific antibodies to SARS-CoV-2 started to be disclosed, enabling the performance of serologic tests to determine the dissemination of the virus and the mortality rates caused by the infection. There are also publications mentioning potential treatments with serums of convalescent patients.

At the end of March and the beginning of April 2020, studies reported the loss of taste or smell in about 64% of the patients with mild COVID-19 symptoms. Additionally, several researches and partnerships between universities and private companies were announced to enable the project and production of 3D masks and other Personal Protective Equipment (PPE), as well as the use of nanoparticles to enable medicines, vaccines, and disinfection processes.

Around the same time, observational and retrospective studies reported the beneficial effects of the tocilizumab monoclonal antibody (inhibitor of IL-6) in patients with COVID-19.

In order to restrain the dissemination of the pandemic in the Country, access to reliable tests to identify contaminated individuals became necessary. In this regard, on April 6, 2020, INPI's ObTec COVID-19 published its first study, **"Panorama das patentes depositadas no INPI descrevendo métodos de diagnóstico para coronavírus e outras viroses respiratórias" ("Overview of the patents applications in INPI describing diagnostic methods for coronavirus and other respiratory viruses")**, which analyzed the patent applications that



mentioned the possibility to detect the coronavirus, presenting the documents obtained from INPI's database.

The pandemic created an urgent need for new lung ventilators worldwide. Given the shortage of this equipment and the difficulty to import it, on April 13, 2020, INPI's ObTec COVID-19 published its study **"Pedidos de patente de ventiladores pulmonares" ("Patent applications for lung ventilators")**, which aimed at identifying the patent applications related to lung ventilators in Brazil, presenting an overview of the applicants and technologies present in these documents, in addition to presenting the status of the corresponding patent applications, enabling the identification of those whose technical examare still pending in INPI, as well as the current granted patents in Brazil.

In order to encourage the dissemination and development of technologies that may be useful for the approach to prophylaxis and treatment of COVID-19, INPI created a type of priority processing for patent applications related to "*pharmaceutical products and processes and equipment and/or materials for use in health care, diagnosis, prophylaxis, and treatment of* COVID-19".

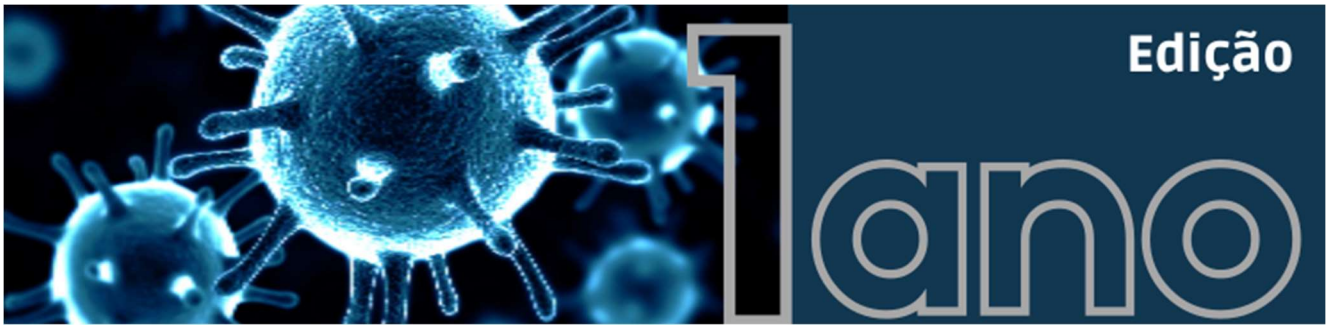
Highlights of May and June 2020

In May 2020, the Chinese vaccine company *CanSino Biologics* reported the first results of clinical trials of its vaccine against COVID-19 – a vector based on a type 5 adenovirus (Ad5) that expresses the SARS-CoV-2's spike glycoprotein. The vaccine proved to be safe, with no reports of severe adverse reactions, and induced specific antibodies and T cell responses in most of the participants.

Also in May 2020, the pharmaceutical company Moderna announced that its RNA-based vaccine, mRNA-1273, was safe and immunogenic. At the beginning of the month, the companies Pfizer and BioNTech also announced, through a press release, that they were performing clinical tests of phase I / II of four COVID-19 vaccines based on mRNA.

Researchers searched for a treatment for COVID-19 in this period, and articles said that dexamethasone could be effective as a therapy for COVID-19, as well as the antivirals (such as remdesivir, favipiravir, and hydroxychloroquine), convalescent plasma, anti-inflammatory agents, including tocilizumab, and steroids in high doses. Several randomized clinical trials of drug repurposing for COVID-19 were published. However, few studies showed significant benefits in the reduction of the severity of the disease, hospitalization time, or mortality rate.

Hydroxychloroquine, which was widely used at the beginning of the pandemic, proved, in randomized clinical trials, not to have any significant benefits as pre-exposure prophylaxis or as



post-exposure prophylaxis in patients with mild disease that were not hospitalized, in mild to moderate disease, or in patients hospitalized with moderate or severe disease.

In contrast, a double-blind, randomized and controlled trial testing intravenous remdesivir in adults hospitalized with COVID-19, infection of the lower respiratory tract, showed that the mortality rates were 6.7% using remdesivir and 11.9% using placebo within 15 days after treatment, and 11.4% using remdesivir and 15.2% using placebo on day 29. Nonetheless, the WHO's Solidarity Trial could not find any significant changes in the mortality rate or the hospitalization time for patients treated with remdesivir.

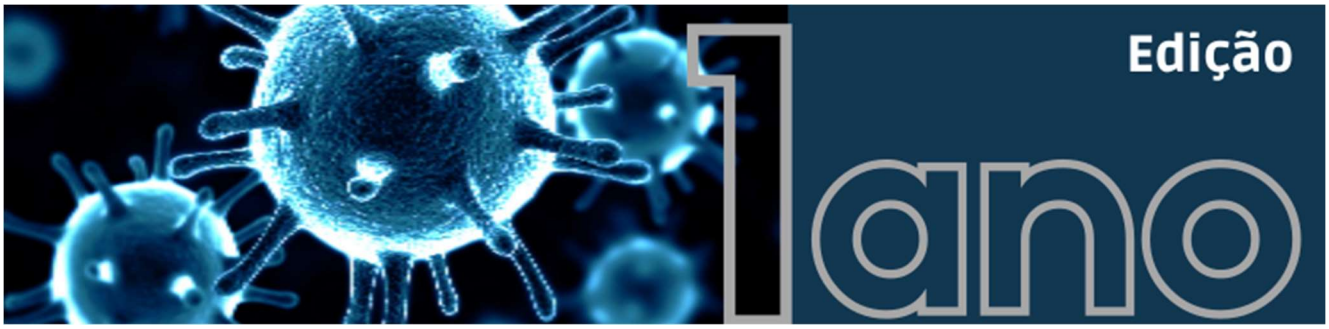
June 2020 brought important progress for the therapy using monoclonal antibodies that were in progress and highlight the potential of viral escape that these monoclonal antibodies could lead to. At that time, the study of the American company Regeneron was mentioned, which had two major implications: firstly, its monoclonal antibodies cocktail received emergency use authorization from the American regulatory agency (*Food and Drug Administration*, FDA); and secondly, the detailed mutagenesis that was conducted helped scientists to quickly understand the natural variants that emerged later, B.1.351 and Y453F.

A voluntary joint action of physicians, engineers, researchers, and businessmen enabled the University of São Paulo – USP to carry out countless projects of medical application to fight against the new coronavirus. One of such projects involved the manufacturing of anatomic devices ("*coxins*") – a kind of "cushion" – to accommodate seriously-ill patients with COVID-19 that remain hospitalized for long periods in Intensive Care Units (ICUs).

Considering the repurposing of drugs for the treatment of COVID-19, in May, ObTec COVID-19's team published 3 studies related to patents on medicines for the treatment of COVID-19.

On May 1, 2020, the same day of the emergency approval of the drug in the United States, INPI's ObTec COVID-19 published the first study related to medicines, **"REMDESIVIR: Mecanismo de ação, ensaios clínicos e pedidos de patentes depositados no INPI" ("REMDESIVIR: Mechanism of action, clinical trials, and patent applications filed with INPI")**. The paper aimed at presenting the mechanism of action and a summary of the studies and clinical trials under development worldwide using this drug, in addition to appointing the patent applications related to Remdesivir currently filed with INPI, which are, therefore, under industrial protection in the country.

On May 24, 2020, INPI's ObTec COVID-19 published its second study related to medicines, **"RITONAVIR/LOPINAVIR/INTERFERON: Mecanismo de ação, ensaios clínicos, pedidos de patentes e patentes concedidas no Brasil" ("RITONAVIR/LOPINAVIR/INTERFERON: Mechanism of action, clinical trials, patent applications, and patents granted in Brazil")**, which are considered as potential tools for the treatment of COVID-19. The purpose of the paper was to provide a current landscape of the knowledge related to the antivirals lopinavir (LPV) and ritonavir (RTV), used in therapy for patients with HIV (Human Immunodeficiency Virus), known



as HAART therapy (Highly Active Anti-Retroviral Therapy) in the literature. Notably, a survey on patent applications and patents granted in Brazil related to such medicines was presented.

On May 28, 2020, INPI's ObTec COVID-19 published another study related to medicines, the paper **"FAVIPIRAVIR: Tratamento da COVID-19 e Pedidos de Patentes Depositados no INPI" ("FAVIPIRAVIR: Treatment of COVID-19 and Patent Applications Filed with INPI")**. The purpose of this paper was to provide a current landscape of the knowledge related to favipiravir. Notably, a survey on patent applications and patents granted in Brazil related to such drug was conducted.

In July and August 2020

Studies carried out in July and August 2020 correlated high serum levels of cytokines IL-6, IL-8, and Tumor Necrosis Factor (TNF) in patients with COVID-19 at the moment of hospitalization as strong and independent predictors of such patients' mortality. The patients with weaker activation of T or B cells developed a milder disease, while those with hyperactivation of T CD4+ and T CD8+ cells showed greater severity of the disease.

The study of a vaccine based on lipidic nanoparticles containing mRNA-lipid that encodes the SARS-CoV-2's spike protein in mice showed a very efficient induction of germinal centers and the production of T Follicular Helper (TFH) cells specific to the antigen, suggesting that the vaccination may exceed natural immunization in some cases.

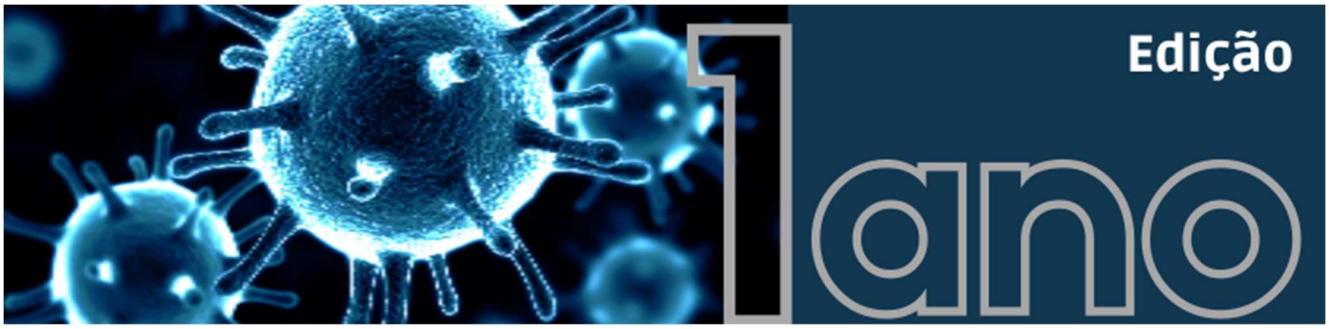
The plasma of convalescent patients, which was one of the first treatments to be given through compassionate use, received emergency use authorization from the FDA in the United States.

A Brazilian study reports and contextualizes the epidemiologic, demographic, and clinical findings of the COVID-19 cases during the first 3 months of the epidemic in Brazil. Until May 31, 2020, 514,200 COVID-19 cases, including 29,314 deaths, were reported in 75.3% (4,196 out of 5,570) of the cities throughout all five Brazilian regions.

Studies demonstrated the participation of the universities in the development and performance of molecular and serologic diagnostic tests for the identification of the coronavirus.

The Brazilian Health Regulatory Agency (ANVISA) published the approval for clinical trials to evaluate the performance of two COVID-19 vaccine candidates: BNT162b1 and BNT162b2, developed by the companies BioNTech and Pfizer (Wyeth).

Novavax presents results of phase 1 clinical trials, a randomized trial controlled by a placebo of its COVID-19 vaccine, based on a protein subunit, with and without the Matrix-M™ adjuvant, in healthy 18- to 59-year-old adults.



A preclinical study published in the Nature Journal has shown positive initial data regarding the immune response against SARS-CoV-2 by Johnson & Johnson's experimental vaccine (Ad26.COV2.S).

Papers report the four main advances in the treatment given to hospitalized patients that reduced the risk of death by COVID-19: positioning the patient in prone position, proper use of medicines (e.g., use of dexamethasone), proper use of lung ventilators, and improvement in the quality of the hospital staff.

On July 20, 2020, INPI's ObTec COVID-19 published a new study related to medicines. The paper **"Tocilizumabe e Sarilumabe: anticorpos inibidores de IL-6, seu papel no tratamento da COVID-19 e pedidos de patentes depositados no INPI" ("Tocilizumab and Sarilumab: antibodies that inhibit IL-6, their role in the treatment of COVID-19, and patent applications filed with INPI")**. The objective of this study was to know the set of patents for the anti-IL-6 receptor monoclonal antibodies, specifically the medicines tocilizumab and sarilumab, applied for in Brazil.

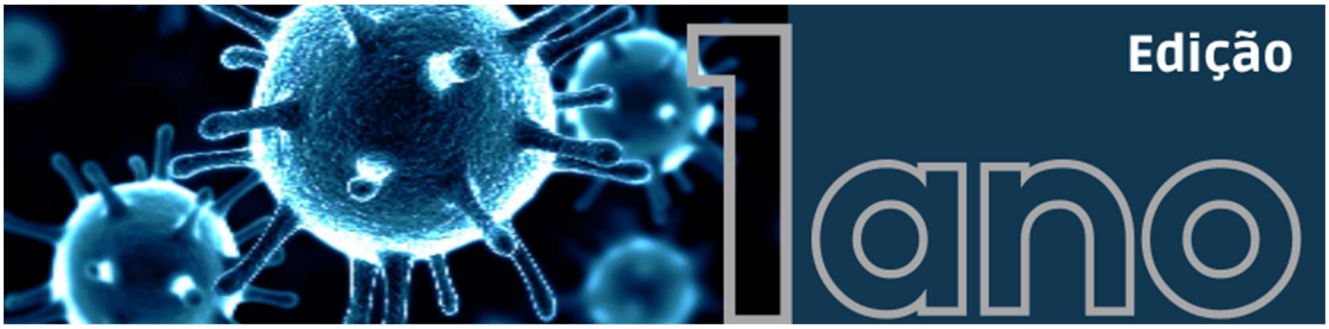
In September and October 2020

Researchers identified that, persons with long-term COVID-19 symptoms (long COVID), months after severe infection, present a wide range of antibody-driven autoantigens (such as cytokines, interferons, chemokines, and leukocytes, which may directly affect the nature of the antiviral immunity), as well as antibodies for tissue-specific antigens expressed in the central nervous system, the vasculature, connective tissues, heart tissue, liver tissue, and the intestinal tract, which could cause damage to the organs mediated by autoantibodies.

The first case of COVID-19 reinfection in a 33-year-old man from Hong Kong was reported by researchers of the University of Hong Kong, who discovered that the patient was infected by virus strains with different genome sequences on each occasion.

Studies unequivocally showed that the type I interferon induction and signaling have important roles in the prevention of lethal COVID-19. The researchers found that innate mutations related to interferon induction and signaling or type I interferon neutralizing antibodies predisposes the body to the worsening of COVID-19 with a higher risk to these patients' lives. Additionally, although the interferons are highly potent in blocking the replication of SARS-CoV-2, the virus has an arsenal of evasion mechanisms to block the induction of endogenous interferons and the signaling of the interferon receptor.

Researchers presented the result of a double-blind, placebo-controlled study carried out in the United Kingdom that assessed the inhaled IFNβ1a (once a day for up to 14 days) in non-ventilated patients hospitalized with COVID-19. Compared to the patients who received a placebo, the patients who received the inhaled IFNβ1 had better chances of recuperation and recovered more quickly from the infection by SARS-CoV-2.



Researchers from the Federal University of Minas Gerais – UFMG developed a niobium-metal-based chemical composition that protects hands and surfaces against the new coronavirus for up to 24 hours.

An open letter to the authors of the study about the Russian vaccine Sputnik V, who published the results of the trial in the journal *The Lancet*, highlighted amounts that seemed to be doubled and alerted them that the paper presented its results only as "boxplots", without providing detailed analysis of the data on which it was based.

Johnson & Johnson announced the large-scale phase 3 clinical tests, the ENSEMBLE study, for its COVID-19 vaccine candidate, JNJ-78436735, under development in its pharmaceutical company Janssen.

The results of a research with 50,027 volunteers in China demonstrated that the Coronavac vaccine, developed by the Chinese pharmaceutical company Sinovac Life Science in a partnership with the Butantan Institute , was safe and did not show significant adverse reactions.

The Brazilian National Service for Industrial Training – SENAI of Rio Grande do Sul developed, together with the company Novus, a new technology that uses artificial intelligence to assist in the diagnosis of COVID-19.

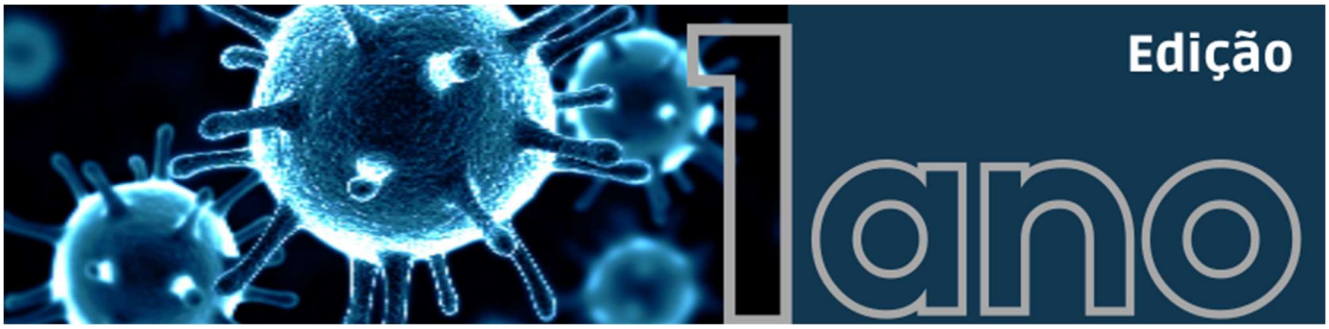
ANVISA initiated the analysis of the first emergency use authorization application for a vaccine against COVID-19 in Brazil, filed by the company Astrazeneca, which developed the vaccine in collaboration with the University of Oxford, in the United Kingdom.

A study demonstrated that the drug REGN-COV-2 can significantly reduce the viral load in the upper and lower airways and decrease the pathological sequelae when administered prophylactically or therapeutically to rhesus monkeys.

At the end of October, the FDA approved the drug remdesivir for antiviral therapy, making it the first drug to obtain formal authorization for the treatment of COVID-19.

Brazilian researchers of different groups from the University of Campinas, São Paulo – Unicamp, USP, the Brazilian Biosciences National Laboratory – LNBio, the D'Or Institute for Research and Education – IDOR, and the Federal University of Rio de Janeiro – UFRJ described how SARS-CoV-2 installs itself in the brain. According to the researchers, the entrance routes seemed to be the olfactory nerve or the capillary barrier that irrigates the brain, through which the virus would be catapulted into the nerve cells by proteins that recognized the viral spikes.

On September 29, 2020, INPI's ObTec COVID-19 published the study **"Máscaras, respiradores e variações: um panorama dos pedidos de patentes (PI e MU) e dos registros de desenho industrial (DI) no Brasil" ("Masks, respirators, and variations: an overview of the patent applications (invention patents (IP) and utility models (UM)) and registrations**



of industrial design (ID) in Brazil"). The objective of this study was to identify the patent and industrial design applications related to masks (and their variations) filed in Brazil, presenting an overview of the types of masks, the countries and regions of origin, the main applicants, and the technologies and settings present in these documents. The study also presented the legal status of the patent and industrial design applications, enabling the identification of those whose analysis are still pending in INPI, as well as the current patents and registrations in Brazil.

In November and December 2020

During this period, it was verified that the virus seemed to have potentially adapted to minks, introducing a Y453F mutation in the receptor binding domain (RBD) of the SARS-CoV-2's spike protein, in addition to other mutations. This led to mass slaughtering of minks in Denmark, and as a result, more attention started to be devoted to the variants of the virus, including the Cluster 5 variants in Europe, which carry the N439K mutation in the RBD. It was evidenced that both Y453F and N439K affected the neutralization by some specific monoclonal antibodies against SARS-CoV-2, although other antibodies were not affected, which would make it unlikely for these two mutations individually to impair the efficacy of the vaccine.

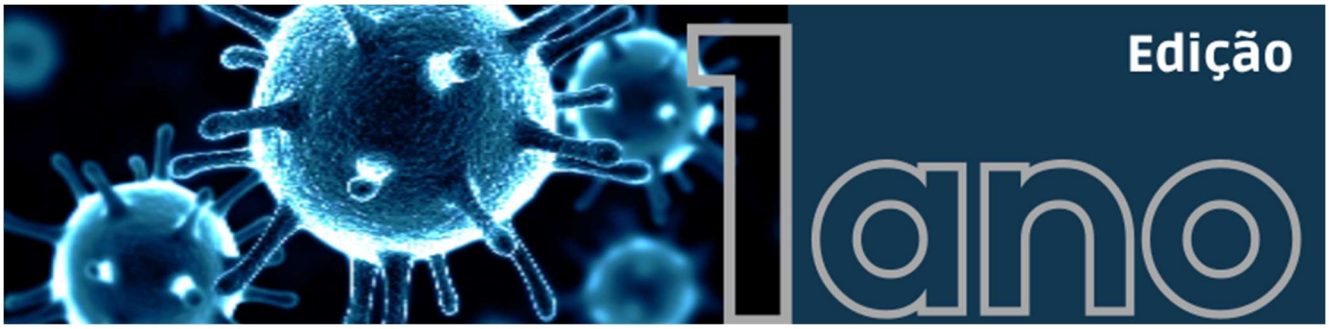
Other concerning variants were described, such as the variant identified in the United Kingdom (B.1.1.7), which carried several mutations, including N501Y in the RBD and truncation of the open reading frame 8 (ORF8).

Pfizer and BioNTech announced a provisional efficacy of more than 90% for their mRNA-based vaccine candidate, BNT162b2, whose trade name is COMIRNATY. After meeting all primary endpoints, it was evidenced that the vaccine has a general efficacy of 95% and 94% in the high-risk group of 65- to 85-year-olds.

Afterward, there was Moderna's announcement, which stated a 94.5% efficacy for its vaccine candidate: mRNA-1273. In addition, AstraZeneca's provisional results for its vaccine ChAdOx1 with a viral vector showed a general efficacy of 70.4% in two cohorts.

Therefore, Pfizer's and Moderna's vaccines received an emergency use authorization in the USA, and Pfizer/BioNtech's, Moderna's, and AstraZeneca's vaccines received an emergency use authorization in the United Kingdom.

A study assessed a variant of SARS-CoV-2 containing the D614G substitution and identified that the variant has a more efficient ability of infection, replication, and competitive fitness in primary epithelial cells of the human airways, but it has similar characteristics related to morphology and neutralization *in vitro*, as compared to the ancient wild-type virus.



ANVISA provided a guide on the minimum requirements for requesting emergency use authorization for experimental use of vaccines against COVID-19.

The University of São Paulo – USP developed a low-cost mask based on 3D modeling and printing. The mask also has an integrated oxygenation measuring system.

A study assessing the safety and efficacy of the ChAdOx1 nCoV-19 vaccine in a grouped provisional analysis with four trials including data from four blind, randomized, controlled studies in progress throughout the United Kingdom, Brazil, and South Africa was published with positive results.

Researchers from Unicamp developed a spray that, when applied to cotton masks, creates a protective barrier that kills SARS-CoV-2 in a single minute. Named SprayCov, 99.99% of its efficacy lasts 48 hours after application.

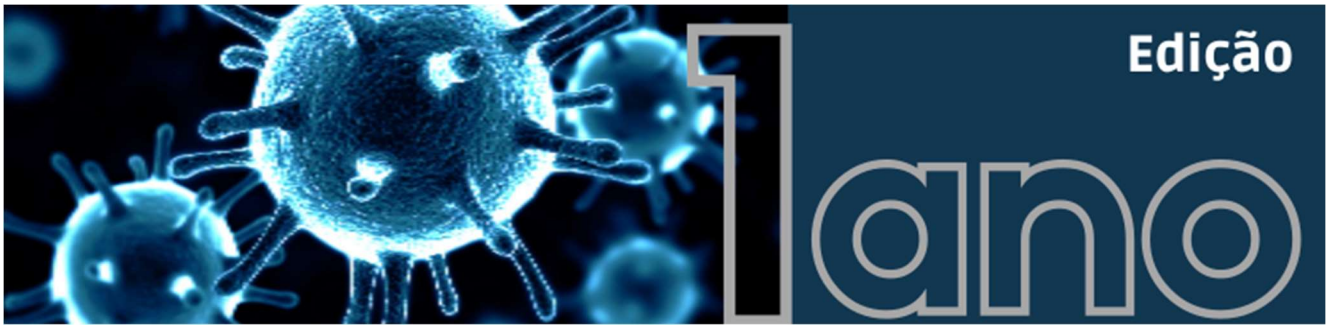
Several studies showed the decline in levels of antibodies specific to SARS-CoV-2 over time after infection, causing concern about a lack of durability of the humoral immunity against the virus. However, other studies showed that the memory B cells (MBC) could provide durable humoral immunity, even if the titers of neutralizing antibodies of the serum decrease.

Novavax's vaccine received accelerated approval status from the FDA, which should help speed up the development of the immunizing agent, which is in phase 3 of the clinical trials in the United Kingdom.

In November and December, 2020, INPI's ObTec COVID-19 published another two studies about technologies related to treatments of COVID-19, beginning a series of studies on vaccines in more advanced clinical trials. The publication of these studies coincided with the approval of the first vaccine against COVID-19, granted by the United Kingdom, whose population started to be vaccinated in December with the mRNA-based vaccine developed by Pfizer/BioNtech.

On November 18, 2020, INPI's ObTec COVID-19 published the first paper related to COVID-19 vaccines, entitled **"Vacinas baseadas em DNA para prevenção da COVID-19: Mecanismo de ação, ensaios clínicos e pedidos de patentes" ("DNA-based vaccines for prevention of COVID-19: Mechanism of action, clinical trials, and patent applications")**. The study addressed DNA-based vaccines, the state-of-the-art or know-how arising from the developing institutions, and analyzed the patent applications related to such vaccines that are closer to the technology of the vaccine under development.

On December 14, 2020, INPI's ObTec COVID-19 published the paper **"Panorama dos documentos de patente relacionados às vacinas de RNA em testes clínicos para a prevenção da COVID-19" ("Overview of the patent documents related to RNA-based vaccines in clinical trials for prevention of COVID-19")**. The purpose of this study was to provide a current landscape of the knowledge related to RNA-based vaccines in the most advanced clinical stage to



date for the prevention of SARS-CoV-2, based on patent documents related to these technologies. Moreover, it aimed at identifying patent applications and their status in INPI and around the world.

From January to March, 2021

The results of the phase-III trial for Novavax's vaccine demonstrated 89.3% of efficacy in the United Kingdom, while the single-dose vaccine developed by Janssen, from Johnson & Johnson, presented 66% of efficacy.

Although no safety problem has been detected during the phase-III trials, anaphylactic reactions were observed during the launching of Pfizer's and Moderna's vaccines, first in the United Kingdom and then in other countries. These severe allergic reactions seem to occur at a rate of 11 for every 1 million vaccinations (Pfizer) and 2.5 for every 1 million vaccinations (Moderna), according to the US Centers for Disease Control and Prevention – CDC, and are frequently associated with a known history of anaphylaxis.

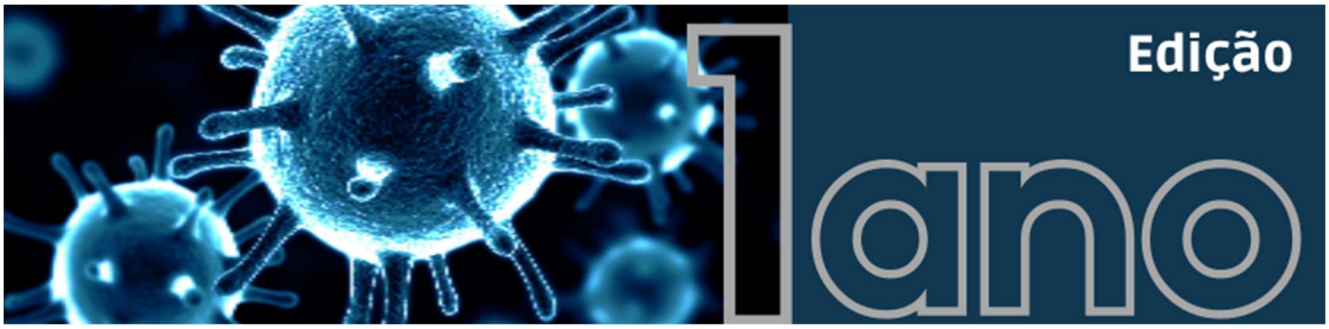
Based on the results for non-human primate models, although the majority of the vaccines under development are able to prevent the disease, they still allow the replication of the virus in the upper respiratory tract. The replication of the virus was generally lower and had a shorter duration in vaccinated animals than in control animals, but the replication occurred.

An important point that arose in Pfizer's and Moderna's studies is that the vaccines start to offer protection approximately 10 days after the first dose of the vaccination, when the titers of neutralizing antibodies are still low or even undetectable in many receptors, suggesting that high antibody titers may be unnecessary for protection against diseases.

A research carried out at the Leônidas & Maria Deane Institute (ILMD / Fiocruz Amazônia) confirmed the identification of the source of the new variant of SARS-CoV-2, the B.1.1.28 lineage in the state of Amazonas, provisionally named B.1.1.28 (presenting the mutations K417N / E484K / N501Y).

The COVID-19 vaccine developed by Janssen Pharmaceuticals, based on a recombinant viral vector that utilizes a human adenovirus to express the SARS-CoV-2's spike protein proved to be safe and effective for preventing moderate to serious cases of COVID-19 in adults, according to a preliminary analysis of the clinical data of Phase 3. The vaccine, named Ad.26.COV2.S or JNJ-78436725, requires only a single injection and can be stored in a fridge for months.

USP, which assumed the commitment to develop a vaccine for COVID-19, has seven projects in progress in several University campuses: a nasal spray vaccine from the Heart Institute – Incor of the School of Medicine – FMUSP; a nanoparticle vaccine from the Ribeirão Preto Medical School – FMRP; a vectored vaccine from the School of Animal Science and Food Engineering –



FZEA; four vaccine platforms in pre-clinical trials from the Institute of Biomedical Sciences – ICB: a nanovaccine, a subunit vaccine, and the DNA- and RNA-based vaccines.

The COVID-19 nasal spray vaccine under development by USP was able to stimulate a strong local response. Its production is fairly simple and 100% Brazilian. Moreover, the vaccine is extremely adaptable to the different variants and can be kept at room temperature.

On March 26, Butantan presented its Butanvac vaccine, fully produced in Brazil and with the possibility to reduce the dependence on external information about active pharmaceutical ingredients (APIs) to produce COVID-19 vaccines.

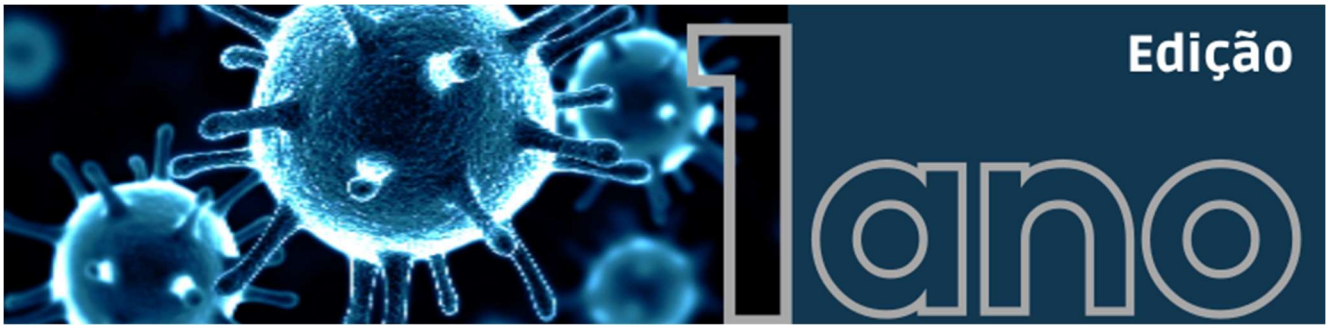
The Versamune®-CoV-2FC vaccine is a COVID-19 vaccine project that combines the platform against COVID-19 developed by the Brazilian company Farmarcore, in a partnership with the American company PDS Biotechnology Corporation. The vaccine aims to provide an immune activation with a recombinant fusion protein (antigen) developed by Farmacore.

In a study supporting CDC's instructions, researchers identified that 20% of the infections by SARS-CoV-2 remain asymptomatic, but contagious – a number rather lower than the 80% announced at the beginning of the pandemic. Most people have symptoms a few days after infection.

It is possible to note that in the first quarter of 2021, several studies from several research groups around the world, including groups from Brazilian universities, developed quick low-cost tests simpler than the RT-PCR that can diagnose the original SARS-CoV-2 and identify its variants without the need for sequencing samples.

Researchers from the Technology Center in Nanomaterials and Graphene of the Federal University of Minas Gerais (CTNano) developed a technology that can perform, in a faster and cheaper way, two of the diagnostic tests for COVID-19, one being serologic and the other molecular.

In March 2021, studies raised awareness of the emergence of new variants of SARS-CoV-2 in different continents, causing great concern for global human health. These variants had in common increased transmissibility, becoming dominant within the populations in a short time, and an accumulation of a large number of S-protein mutations, especially inside the N-terminal domain (NTD) and the receptor binding domain (RBD). There were also already signs of increased virulence, reinfection frequency, and increased resistance to the action of monoclonal and polyclonal antibodies of convalescent serums and in vaccinated individuals in regions in which the variants spread predominantly.



Important research groups publish their results of using monoclonal antibodies (alone or in cocktails) for treating COVID-19. A study found out that one antibody against the coronavirus (VIR-7831), developed by Vir Biotechnology and GSK, reduced the chances of hospitalization or death among the participants by 85%. In another study, a cocktail of two antibodies – bamlanivimab and etesevimab, both created by Eli Lilly – reduced the risk of hospitalization and death by 87%.

The final analysis of a phase-III clinical trial revealed that the vaccine produced by the University of Oxford and AstraZeneca was 79% effective in preventing symptomatic COVID-19 and 100% effective in preventing severe diseases and hospitalization.

An analysis performed by CDC, in the United States, pointed out that Pfizer's and Moderna's vaccines are highly effective in controlling COVID-19 after their 1st dose and that the risk of infection decreased by 80% after the first dose in frontline professionals.

On March 30, 2021, the WHO published a report about the origins of the COVID-19 pandemic, issued by a team of experts from several areas and countries, including China.

Finally, on March 31, 2021, a clinical trial of Pfizer-BioNTech's vaccine demonstrated that the vaccine can be considered very protective in teenagers. The study did not find infections among vaccinated 12- to 15-year-old children, and no severe side effects were identified. The trial involved 2,260 12- to 15-year-old teenagers in the United States. The beginning of clinical tests in children and teenagers of other vaccines already approved worldwide, such as Moderna's, Oxford's, and Janssen's, was also announced.

NEXT STEPS

INPI's ObTec COVID-19 continues to monitor and select the relevant publications related to the pandemic in its different aspects, publishing them on INPI's website 3 times a week. Additionally, three other studies that will present the technologies of viral vector vaccines, protein subunits, and inactivated vaccines against COVID-19 are being finished, in addition to a study that will present the patents involving nanotechnology applied to the treatment, detection, and prevention of COVID-19.

In the near future, ObTec COVID-19 will begin the evaluation of the patent applications continuously in the same way as it evaluates scientific papers; moreover, other studies may be carried out according to the demands of the Brazilian Innovation System.