

COMMENTARY

Lack of efficacy of mono-mode of action therapeutics in COVID-19 therapy - How the lack of predictive power of preclinical cell and animal studies leads developments astray

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Abstract

The diverse experiences regarding the failure of tested drugs in the fight against COVID-19 made it clear that one should at least question the requirement to apply classical preclinical development strategies that demand cell and animal efficacy models to be tested before going into clinical trials. Most animals are not susceptible to infection with SARS-CoV-2, and so this led to one-sided virus replication experiments in cells and the use of animal models that have little in common with the complex pathogenesis of COVID-19 in humans. Therefore, non-clinical development strategies were designed to meet regulatory requirements, but they did not truly reflect the situation in the clinic. This has led the search for effective agents astray in many cases. As proof of this statement, we now bring together the results of such required preclinical experiments and compare with the results in clinical trials. Two clear conclusions that can be drawn from the experience to date: The required preclinical models are unsuitable for the development of innovative treatments medical devices in the case of COVID-19 and mono-action strategies (e.g. direct antivirals) are of very little or no benefit to patients under randomized, blinded conditions. Our hypothesis is that the complex situation of COVID-19 may benefit from multi-mode drugs. Here, the molecular class of aptamers could be a solution.

KEYWORDS

aptamer, COVID-19, COVID-19 animal experiments, innovative thinking, mode of action, predictive value, SARS-CoV-2 cell assays

1 | INTRODUCTION

During the first wave of the COVID-19 pandemic no drugs existed, and doctors and healthcare workers had limited treatment options available, which resulted in high

mortality rates. The World Health Organization (WHO) made, therefore, a call in early Spring 2020, for a search for readily accessible drugs. Fast accessibility would only apply to a re-purposing of existing approved drugs or to candidate drugs in advanced stages of development (phase

Abbreviations: EMA, European Medicines Agency; FDA, Food and Drug Agency; IL-6, interleukin-6.

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2). The development of new anti-SARS-CoV-2-specific drugs would take months or years until reaching the point of being able to test for efficacy in patients.

With respect to re-purposing, it made perfect sense in this emergency situation to check for (i) existing antiviral drugs and drug candidates for possible effectiveness (Chopra et al., 2020; Wang, Cao, et al., 2020).

It was reasonable to also check (ii) for all available options to treat the inflammatory stage of the COVID-19 disease given the different stages of its pathogenesis (Ferro et al., 2020; Galani et al., 2021; Pascarella et al., 2020; Rivellesse & Prediletto, 2020; Rohilla, 2021) and taking into account the differences observed with respect to the severity of the disease (Galani et al., 2021; Lopez et al., 2020). This resulted in the suggestion to check the impact of, for example IL-6 inhibitors in those with hyperinflammation.

A different strategy would be (iii) to support the defence against the virus via, for example the application of the type-III interferon IFN- λ (Lopez et al., 2020).

Then, (iv) direct attack on the virus by application of convalescent serum, especially in severe cases, seemed to be a lifeline (Rajendran et al., 2020). Derived from the principle of convalescent serum containing anti-SARS-CoV-2 antibodies, the development of therapeutic monoclonal anti-SARS-CoV-2 antibodies was a next logical step (Chan et al., 2021; Haagmans et al., 2021; Kreer et al., 2020; Yang et al., 2020), with several players in at the start (DeFrancesco, 2020).

Later, the horizon was widened to (v) include *in silico* methods to check for any approved drugs that may bind onto SARS-CoV-2 proteins (Ke et al., 2020; Singh, Kushwaha, et al., 2020; Watashi, 2021; Wu et al., 2020), checking up to more than 10 million registered molecules (Kowalewski & Ray, 2020) in order to find molecules with the potential to be helpful in fighting the virus.

The strategies were logical and scientifically convincing. Many early attempts seemed to be promising – success was reported for cell and animal experiments and for single strategies when tested in very low numbers of selected cases. This also held true for treatment including hydroxychloroquine (Puyo et al., 2020). But, as soon as these strategies and drugs were tested in the clinic under randomized-blinded conditions, in many cases the failure to demonstrate statistically significant benefit, became obvious (Table 1). Table 2 lists the substances that have already passed non-clinical tests but for which the result of the clinical tests is still pending.

The failure to demonstrate clinical efficacy even when non-clinical models were promising held true for antivirals such lopinavir and ritonavir (Paul & Biswas, 2021), the use of which in the WHO Solidarity trial programme was discontinued before its end (<https://www.who.int/news/>

[item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19](https://www.who.int/news/item/04-07-2020-who-discontinues-hydroxychloroquine-and-lopinavir-ritonavir-treatment-arms-for-covid-19)).

Even remdesivir, an inhibitor of the viral RNA-dependent RNA polymerase and originally developed against Ebola, failed to show an effect when tested under ‘field conditions’(WHO Solidarity Trial Consortium et al., 2021), putting the minor effect seen in the single clinical trial in a different perspective (Beigel et al., 2020; Goldman et al., 2020).

Studies with convalescent serum, where more than 100,000 patients were enrolled (Estcourt & Roberts, 2020), failed to demonstrate efficacy when tested under blinded conditions (Simonovich et al., 2021; Wang et al., 2021). As a consequence, unfortunately the first report about the failure of a therapeutic monoclonal antibody followed soon (ACTIV-3/TICO LY-CoV555 Study Group et al., 2021). A different antibody combination is still not the solution to the problem (Weinreich et al., 2021). This study revealed that the antibody is of benefit only when given at a very small time window after infection with SARS-CoV-2. When patients already have developed their own antibodies the cocktail did not show an effect. This is a situation that does not often match the clinical situation of the COVID-19 medical routine (especially not in clinics). For seriously ill COVID patients either hospitalized or requiring oxygen therapy the FDA even issued a warning that the drug might actually make their situation worse (<https://www.fda.gov/media/143892/download>).

Although the safety and effectiveness of the REGN-COV2 cocktail in the treatment of COVID-19 continues to be evaluated, it is remarkable that a novel cocktail of therapeutic antibodies got into the clinic in less than one year after initiation of development.

Tocilizumab, an inhibitor of IL-6 following a different therapeutic strategy of interfering in later phases of the COVID-19 pathogenesis, also failed (Stone et al., 2020). The well-known anti-inflammatory drug hydroxychloroquine (Floris et al., 2018) was discontinued in the WHO guided Solidarity trial and a failure in the RECOVERY trial (<https://www.recoverytrial.net/results/hydroxychloroquine-results>).

These reports into the failures in randomized studies raise a number of questions:

2 | WHAT DOES AN IN-VITRO SARS-COV-2 GROWTH INHIBITION CELL EXPERIMENT TELL US?

Most of these drugs, now failing to show a significant benefit in COVID-19 patients, showed good-to-excellent SARS-CoV-2 growth inhibition in cell experiments, as

TABLE 1 Comparison of outcomes of corresponding preclinical cell and animal experiments to outcome of clinical trials of therapeutic COVID-19 drugs

Drug	Cell-experiments			Animal-experiments			Human outcome (randomized/blinded when available)			
	Moa	EC50 =	eff. yes/no	Ref	Eff. yes/no	Ref	eff. yes/no	Ref	eff. yes/no	
<i>Direct anti-virals</i>										
Remdesivir	RdRp inhibitor	EC50 = 0.77 μ M	y	[2]	y	[21]	Mice, infected with SARS-CoV-1 encoding SARS-CoV-2 RdRP	Failed (Recovery trial)	[22]	n
		EC50 = 1.65 μ M	y	[21]			Decreased viral loads 1 day post infection			
							rhesus macaque, decreased viral load (Gilead EMA/357513/2020, (dated 25 June 2020) – 12 hours post infection)			
Lopinavir and Ritonavir	3CLpro	EC50 = 11.41 μ M	y	[23]	y	[23]		Failed (SOLIDARITY trial discontinued)	[24]	n
		EC50 = 8.8 μ M (MRC5 cells)	y	[23]						
Lopinavir	3CLpro	EC50 = 9.12 μ M	y	[25]	y	[25]		Failed (SOLIDARITY trial discontinued)	[24]	n
Favipiravir	RdRp inhibitor (pro-drug)	EC50 = 61.88 μ M	y	[2]			Hamster, anti-viral activity 1 hour before infection + 3 times/days afterwards	NCT04351295 Open-label – unclear, no significant effect, to second arm: Hydroxychloroquine	[27]	(n) Study Design not optimal
Ribavirin	RdRp	EC50 = 109.50 μ M	y	[2]				Retrospective “Adverse effects were similar between the two groups. In conclusion, in patients with severe COVID-19, ribavirin therapy is not associated with improved negative conversion time for SARS-CoV-2 test and is not associated with an improved mortality rate” NCT04276688 Triple therapy (interferon beta-1b, lopinavir-ritonavir, and ribavirin)	[28] [29]	(n) (y)

(Continues)

TABLE 1 (Continued)

Drug	MoA	Cell-experiments		Animal-experiments		Human outcome (randomized/blinded when available)	
		Vero E6 cells	Calu3 cells	Ref	Eff. yes/no	Ref	eff. yes/no
Camostat mesylate	Serin-Protease inhibitor (TMPRSS2)	EC50 >50 μ M	EC50 = 0.187 μ M	[25]	y	[25]	Failed (NCT04321096) "Under this protocol, camostat mesilate treatment was not associated with increased adverse events during hospitalization for Covid-19 and did not affect time to clinical improvement, progression to ICU admission or mortality"
<i>Anti-protozoal and anti-leprosy</i>							
Nitazoxanide (NTZ)		EC50 = 2.12 μ M,		[2]	y	[31] [32]	[31] [32]
<p>Interpretation: Compared to placebo in clinical and virologic outcomes and improvement of inflammatory outcomes, the superiority of NTZ warrants further investigation of this drug for moderate COVID-19 in larger clinical trials. A higher incidence of adverse events in the placebo arm might be attributed to COVID-19 related symptoms." but: "no statistically significant difference between treatments in the number of death" and "the number of participants who required invasive mechanical ventilation, although not statistically significant, was higher in the placebo group"</p> <p>Conclusions: In patients with mild COVID-19, symptom resolution did not differ between nitazoxanide and placebo groups after 5 days of therapy. However, early nitazoxanide therapy was safe and reduced viral load significantly."</p>							

(Continues)

TABLE 1 (Continued)

Drug	MoA	Cell-experiments		Ref	eff. yes/no	Ref	Eff. yes/no	Animal-experiments		Ref	eff. yes/no	Human outcome (randomized/blinded when available)			
		Vero E6 cells	Calu3 cells					Animal-experiments	Human outcome (randomized/blinded when available)						
<i>Direct virus attac</i>															
Convalescent serum								K18-hACE2 mice, effective 12 hours before infection or African green monkey Effective 10 hours post infection		[33] [34]	Y y	Failed (NCT04383535) Failed RECOVERY trial	[35] [36]	n n	
Therapeutic antibody	LY-CoV555 (Bamlanivimab)			[37]	y			rhesus macaque 1 day before infection		[37]	y	Blaze-1 slightly Mild COVID only Failed (NCT04501978) Revoked emerg. authoriz. (virus mutations not recognized)	[38] [39]	(y) n	
	Cocktail: LY-CoV555 LY-CoV016 (Etesevimab or JS016) Regn-COV2							Hamster 2 days before infection or 1 day post infection rhesus macaque 3 days before infection or 1 day post infection		[41] [41]	Y y	NCT04425629 If early applied or high viral load	[42]	(y)	
<i>Antiinflammatory</i>															
Chloroquine		EC50 = 1.13 μM		[2]	y								Failed (SOLIDARITY trial discontinued)	[24]	n
		EC50 = 7.28 μM		[25]	y	EC50 = 69.2 μM	y								
Hydroxychloroquine		EC50 = 0.72 μM		[43]	y			Hamster, no effect		[26]	n	Failed (SOLIDARITY trial discontinued)	[24]	(y)	
Tocilizumab	IL-6 inhibitor							Approved – principle seemed logical			n [†]	Failed NCT04356937	[44]	n [†]	

Eff. = effective; y = yes; n = no; (y) tendency towards yes; (n) = tendency towards no; (y/n) no clear result of yes or no; MoA = mode of action; RdRp = RNA-dependent RNA polymerase, n[†] = between submission of the manuscript May 05 and its approval Aug16 tocilizumab received emergency use authorization by the FDA for COVID-19 therapy based on the outcome of different clinical trials (June 25th, 2021; <https://www.fda.gov/news-events/press-announcements/coronavirus-covid-19-update-fda-authorizes-drug-treatment-covid-19>).

TABLE 2 List of substances that have already succeeded in non-clinical tests but for which the result of the clinical tests is still pending

Drug	MoA	Cell-experiments			Animal-experiments			Human outcome (randomized/blinded when available)	Expected EOS
		Vero E6 cells	Calu3 cells	Ref	Ref	Ref	Ref		
<i>Direct anti-virals</i>									
Nafamostat	Serin-Protease inhibitor (TMPRSS2)	EC50 = 22.50 μM	[2]	y				NCT04390594 (Senegal) NCT04352400 (Padova,Zurich), posted April 2021 NCT04418128 (Gyeongsang), posted June 2020, not jet recruiting NCT04628143 (Chong Kun Dang Pharm.), posted Nov 20; completed, no results posted yet NCT04623021 (Chong Kun Dang Pharm.), completed, no results posted yet NCT04473053 University of Edinburgh UK, posted July 2020, recruiting NCT04483960 (University of Melbourne), posted July 2020, recruiting	Aug 2021 Dec 2021 Apr 2021 April 2021 Dec 2020 Dec 2021 Dec 2022
<i>Anti-Protozoal and anti-leprosy</i>									
Clofazimine	Anti-leprosy (anti-uptake and anti-inflammatory)	EC50 = 13.88 μM	[25]	y	EC50 = 0.0022μM	[25]	y		
		EC50 = 0.31 μM	[45]	y					
		Human embryonic stem cells	[46]						
					Hamster 3, 2 and 1 day before infection (prophylactic) or 1, 2 and 3 day post infection (therapeutic)		y	NCT04465695 (The University of Hong Kong), posted July 2020,	Sep 2021

(Continues)



TABLE 1 (Continued)

Drug	MoA	Cell-experiments			Animal-experiments			Human outcome (randomized/blinded when available)		
		Vero E6 cells	Calu3 cells	eff. yes/no	Ref	Eff. yes/no	Ref	eff. yes/no	Study	Expected EOS
<i>Direct virus attack</i> Therapeutic antibody	SC31	EC50 = 1.85 nM	[10]	y	Syrian Hamster (SC31), very effective, 4 hours post infection	[10]	y	not yet identified		
					K18-human ACE transgenic mice, effective 6 hours post infection	[10]	y			
					Syrian hamster, effective 24 hours before infection	[11]	y	not yet identified		
MAB 47D11		EC50 = 0.57 µg/ml (about 3.8 µM)	[47]	y	Syrian hamster, effective 24 hours before infection	[48]	y	not yet identified		
CV07-209		4.1 ng/mL (about 0.027 µM)	[48]	y	Syrian hamster, effective 24 hours before infection or 2 hours post infection	[48]	y	not yet identified		

Eff. = effective; y = yes; n = no; (y) tendency towards yes; (n) = tendency towards no; (y/n) no clear result of yes or no; MoA = mode of action; RdRp = RNA-dependent RNA polymerase, EOS = End of study

seen with remdesivir (Pruijssers et al., 2020; Wang, Cao, et al., 2020) and many other antivirals such as lopinavir, favipiravir, penciclovir (Wang, Cao, et al., 2020); for an overview see (Ko et al., 2021) (and see Table 1).

Are these cell experiments too removed from reality – monitoring virus growth only in a very few cancer cell lines (<https://web.expasy.org/cellosaurus/sars-cov-2.html#A>) and special cell media, often serum free – which do not reflect the viral growth *in-vivo*, in the patient?

Why do we observe a good viral growth inhibition when the virus is cultivated in one cell line, but not when cultivated in another, or vice versa (Ko et al., 2021)?

And a second question that has to be answered in the light of the outcome of clinical studies is the question:

3 | WHAT DOES AN IN-VIVO SARS-COV-2 ANIMAL EXPERIMENT TELL US, WHEN COMPARING THE ANIMAL EXPERIMENT WITH THE CLINICAL OUTCOME?

Preclinical animal effectiveness experiments required by the majority of the regulatory authorities before drug developers can move forward to the clinics to check for COVID-19 effectiveness, even when testing approved and advanced clinical development drugs. This is a challenge because (i) strictly speaking, no adequate animal models exist and (ii) on top of that, only very few institutes and companies worldwide are able to conduct such experiments under the necessary strict safety measures.

Many animals are almost or completely resistant to SARS-CoV-2, which means they do not develop symptoms of the disease after inoculation (Singh, Singh, et al., 2020). Therefore, new animal models are under development, such as hACE2-receptor-overexpressing mice (Dinnon et al., 2020; Hassan et al., 2020). Given the short time since the beginning of the pandemic, most models are not yet well characterized. Currently, the best model with respect to comparability to humans seems to be the Syrian hamster, which is also one of the best characterized models (Imai et al., 2020; Rosenke et al., 2020; Sia et al., 2020). Here it becomes clear that even with this hamster model, animals start to recover on their own already 5–8 days after virus inoculation. Therefore, the drugs to be tested are given pre-inoculation (prophylactically) of SARS-CoV-2 virus infections (Haagmans et al., 2021; Kreye et al., 2020; Yuan et al., 2020), or almost parallel to the inoculation (Kreye et al., 2020). Very few studies have tested the application at 1, or a maximum 3, days post inoculation in order to still meet the small time window of being able to show an effect compared to controls (Chan et al.,

2021; Yuan et al., 2020) (see also Table 1, column “animal experiments”).

This time frame clearly does not reflect the situation in humans in the clinic. Neither from the point of view of viral load nor the accompanying variable immune response in humans. Here the patient comes in days (typically more than 5 days) after infection, when infection and inflammatory and other processes already overlap.

Is this the reason why we can read about successful animal tests with drugs, which afterwards failed in humans, such as in the case of convalescent serum (Cross et al., 2021; Zheng et al., 2021) or Favipiravir (Kaptein et al., 2020)?

Why are these animal models still demanded, which do not predict the situation in the clinic? This non-comparability was well described by Gilead in their Assessment report for remdesivir EMA/357513/2020, (dated 25 June 2020), on page 77 with respect to the rhesus macaque COVID-19 model:

The rhesus macaque model resembles a moderate COVID-19 disease; thus, conclusions from this animal model might not be transferable to severe disease. The inoculation with SARS-CoV-2 induced a transient, moderate disease in rhesus macaques with signs of infection one day post inoculation (dpi) with disease lasting 8–16 days. ... The duration of disease in rhesus macaques seems to be very short with differences also in incubation times, compared to the disease in humans. In addition, differences observed in pulmonary involvement, duration of viraemia, serological and immunological responses might impact the validity of this animal disease model for SARS-CoV-2 in humans. ... One of the uncertainties includes the relevance of the animal models for human COVID-19, as well as the fact that RDV was administered only 12 hours after viral challenge in the animal model. ... This is not reflective of the currently studied use of remdesivir in COVID-19 patients, where first administration is unusual before day 4 of symptom onset. Thus, animals in this model may not be representative for the clinical status of patients that will receive RDV in clinical practice, as it rather reflects a prophylactic or post-exposure than a therapeutic approach.

This raises the question: wouldn't it be possible with appropriate justification to omit animal experiments in certain situations? Is there not also the option to look at the

development as a whole – safety aspects from previous studies along with the likelihood of having a positive effect and just assess the benefit/risk ratio from previous data and afterwards check in small groups? Would that not be a way to go, in the light of the progress of the disease of the ongoing global crisis which seems to be increasing in complexity despite the availability of vaccines in some regions the world?

This way, the bottleneck of inaccessible animal experiments – which seem not to predict the clinical situation very well anyway – might be circumvented, thereby allowing faster development for this high unmet need.

Even in the case of complete success of vaccination programmes, for which we hope for the sake of humanity, effective medicines will still be very necessary in view of variant escape and waning of immunity or poor response to immunization.

So far, no reliable drugs exist besides dexamethasone, and this only for patients on ventilators in a progressed state of the disease (Gozzo et al., 2020).

Since specific single-mode of action drugs widely failed so far to show any meaningful benefit for COVID-19 patients, we developed the working hypothesis that multi-mode of action drugs need to be searched for.

4 | THE COMPLEXITY OF THE COVID-19 DISEASE DEMANDS NEW CONCEPTS OF TREATMENT

Aptamers, already the focus of interest for antiviral treatment, including for SARS-CoV (Esposito et al., 2020; Jeon et al., 2004; Musafia et al., 2014; Song et al., 2020; Torabi et al., 2020), have at least in some cases the chance to be not only absolutely specific for one epitope but to also show (some) affinity with several oligonucleotide-binding-susceptible sequence sections for different proteins of the virus (Esposito et al., 2020; Tucker et al., 2012; Weisshoff et al., 2020). This way, a cumulative multi-effect might result (multi-mode of action), together increasing the chance of treatment success.

Supporting this demand is the fact that a monotherapeutic anti-SARS antibody has already lost its emergency authorization due to resistance of a viral variant when used alone (Commissioner O of the. Coronavirus (COVID-19), 2021). This can be overcome to some extent using mixtures of anti-SARS antibodies.

In the same light, Brouwer and colleagues have also recently proposed to develop monoclonal antibodies that “define multiple targets of vulnerability” (Brouwer et al., 2020).

Multi-mode of action is important as it has already been shown that less than fully effective treatment could

trigger the formation of viral escape mutations in an immunocompromised patient (Kemp et al., 2021).

Moreover, the drug/aptamer might also show effects occurring from its original indication, as is the case with aptamer BC 007, which is able to neutralize functionally active autoantibodies which target and activate G-protein coupled receptors (GPCR- γ AABs) (Becker et al., 2020; Haberland et al., 2016; Müller, 2019). If able also to neutralize self-reactive SARS-CoV-2-induced antibodies (autoantibodies) which are discussed to be one of the reasons for the severity and persistence of COVID-19 symptoms (Long-COVID) (Bastard et al., 2020; Ehrenfeld et al., 2020; Khamsi, 2021; Novelli et al., 2021; Zhou et al., 2020), an additional positive impact on treatment might be possible. This is especially the case since with Long-COVID patients the occurrence of such GPCR- γ AABs have also already been described (Wallukat et al., 2021). And, a treatment of a Long-COVID patient in a named patient programme has shown that BC 007 neutralizes the autoantibodies and significantly improved the patient's health status (Hohberger et al., 2021).

Such a complexity of effects, however, cannot be tested in existing animal models, as explained above.

So, the chance to adopt completely new methods for combating SARS-CoV-2 might be lost if forced to comply with prescribed regulatory development requirements, not being able to bypass certain requirements such as animal models which would not even reflect the complex clinical situation.

5 | CONCLUSIONS

Established strategies for the research and development of efficient anti-SARS-CoV-2 drugs have so far not been very successful. Completely new innovative strategies have been delayed due to conservative regulatory expectations, since drug developers have to follow prescribed regulatory methods (efficacy tests using animal models that may not even reflect the mode of action, besides that there is no easy access to such experiments given the current situation of many developments being pursued in parallel).

Moreover, at least in Europe, only very little money has been given for drug development (<https://www.faz.net/aktuell/wirtschaft/unternehmen/firmen-brauchen-geld-fuer-forschung-an-corona-medikament-17098254.html>). All resources have gone into vaccine development. This is a strategy that needs to be reconsidered. Given the mutation rate of viruses and other factors, such as not everybody being able to be vaccinated at least at the same time, the focus on vaccines at the expense of treatment development is now becoming evident. There is an urgent need for the medicines regulators, public health organizations

and funding bodies to adapt to this shifting paradigm in view of the global health crisis. For innovative drugs with multiple mechanisms of action relevant to the human disease spectrum with COVID (which cannot be recapitulated in non-clinical disease models) and where little will be gained from non-clinical animal model testing – but doing so will delay clinical development – standard requirements for non-clinical testing should be reconsidered on a case by case basis. While the promise of vaccines has in part been met, the lack of global vaccination, the emergence of new variants of concern and the lack of an immunological correlate of protection (ICP), and waning immunity means that effective new treatment for disease remain a priority. Improved funding opportunities are needed now for innovative approaches to address the unmet need of COVID-19 disease.

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CONFLICTS OF INTEREST

Annekathrin Haberland and Johannes Müller are employed at Berlin Cures GmbH. Annkathrin Haberland and Johannes Müller are shareholders of Berlin Cures Holding AG, the holding company of Berlin Cures.

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