Hindawi
Mathematical Problems in Engineering
Volume 2021, Article ID 6630419, 6 pages
https://doi.org/10.1155/2021/6630419

Review Article

Emerging Patent Landscape for Gene Therapy as a Potential Cure for COVID-19

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Received 13 November 2020; Revised 15 December 2020; Accepted 28 December 2020; Published 8 January 2021

Academic Editor: Chenxi Huang

There is still a lack of effective therapies for treating SARS-CoV-2-infected patients, as doubts remain whether antibodies provide sufficient immunity for COVID-19, and the safety of vaccines under development needs further study. The treatment of coronavirus from the perspective of RNA interference-based gene therapy offers a more direct approach to combating viral genes in addition to traditional drugs and vaccines and is likely to have a promising future. In this paper, an analysis of the emerging patent landscape was given on gene therapies for coronavirus under development, highlighting patent applications' basic status, geographical distribution, time-series analysis of new inventors, and ranking of patent applicants. Relevant patents were also reviewed and summarized to provide ideas for the control of the current COVID-19 pandemic.

1. Introduction

Efforts to develop drugs and vaccines for COVID-19 have mostly targeted important targets early in the viral life cycle and have been hampered by limited knowledge of the molecular details of SARS-CoV-2 [1]. There are still many unknowns with this new virus as research studies deepen, including the extent to which the presence of antibodies offers protection against future infections [2]. Effective vaccines have been developed, but too late to affect the first wave of this pandemic [3]. Many scientists believe that therapies are still needed regardless of vaccine as they argue that vaccines rarely provide full protection from disease [4]. Border restrictions and internal travel restrictions are unlikely to delay spread unless more than 99% effective [5].

So, antibodies and therapies would be valuable for the suffering patients, especially the elderly. However, there is still a lack of effective therapies for treating SARS-CoV-2-infected patients [6]. Furthermore, predicting drug performance in COVID-19 is difficult, and many therapeutic candidates may fail to demonstrate efficacy or have safety problems [7]. The field of gene therapy has made a quantum leap forward in recent years, while research studies focused on treating genetically defective diseases [8, 9]. Gene therapy uses vector-based siRNAs or dsRNAs targeting different genes of coronaviruses to inhibit virus gene expression and thereafter to inhibit replication of the virus [10]. RNA interference (RNAi) therapeutics have demonstrated a broad potential with numerous proof-of-concept studies in animal models and multiple clinical trials [11, 12]. Currently, there are six RNA-based treatments in clinical and preclinical trials among 319 treatments and 237 vaccines according to FasterCures, Milken Institute (Table 1), while no literature systematically discusses the treatment of coronavirus from the perspective of gene therapy. There is a strong positive relationship between science quality and patents [13], and the patent system has been regarded as a critical factor in promoting innovation in clinical medicine. This paper analyzes the global patent situation of gene therapy for coronavirus based on the Reporting Items for Patent Landscapes (RIPL) to provide ideas for future research on the treatment of SARS-CoV-2 [14].

2. Subjects and Methods

Section 1 of this paper introduces the technical background and novelty of this study, Section 2 describes the subjects and methods, Section 3 gives a review of the existing literature,

Table 1: RNAi-based treatments for COVID-19 in clinical and preclinical trials.

Developer/researcher	Product description	Phase	Anticipated next steps
Mateon Therapeutics	Ot-101, a TGF-beta antisense drug candidate	Clinical	Phase II study IND submitted to FDA on April 27, 2020; phase II trials approved in Peru, Nov 2020
AIM Immunotech/National Institute of Infectious Diseases in Japan/Roswell Park Comprehensive Cancer Center	Ampligen (rintatolimod)	Preclinical	Phase I/II trial in combination with interferon alfa-2b, in cancer patients with COVID-19 not yet recruiting July 2020; phase I/II clinical trials for COVID-19 NCT04379518
Neurimmune/Ethris	Inhaled mRNA	Preclinical	Phase I to start Q4 2020
Sarepta Therapeutics/US Army Medical Research Institute of Infectious Diseases (USAMRIID)	Antisense oligonucleotides, peptide conjugated	Preclinical	Clinical trials for COVID-19
Sirnaomics	RNAi, TESTING 150 RNAiS	Preclinical	Clinical trials for COVID-19
VIR Biotech/Alnylam Pharmaceuticals	VIR-2703 (ALN-COV) siRNA candidate	Preclinical	Clinical trials for COVID-19; phase I to start by the end of 2020

Section 4 presents the results, and Section 5 summarizes the paper and provides an outlook.

To provide a patent landscape and to identify technologies that use gene therapy to coronavirus diseases, we performed a search in the Derwent Innovation (DI) database. The search strategy is based on the combination of International Patent Classification (IPC), DWPI Manual Codes (MC), and keywords. The topics of "gene therapy" and "coronavirus" were searched in "classification number, title, abstract, and claims." The classification numbers for gene therapy were IPC (A61K 48/00), MC (B14-S03A or B14-S03B or B14-S03C or B14-S03D or C14-S03 or C14-S03 or C14-S03A or C14-S03B or C14-S03C), and keywords ("gene therapy" or "gene therapeu*"). The classification numbers for coronaviruses were IPC (A61K 39/215 or C07K 141/165 or C12N 151/50), MC (B14-A02B5 or C14-A02B5), and keywords (coronavir* or "corona virus" or "COVID-19" or "SARS-CoV*" or "MERS-CoV" or "nCoV" or HcoV or "atypical pneumonia" or "severe acute respiratory syndrome").

3. Review of Current Literature

After the SARS outbreak in 2003, researchers applied for a large number of RNAi vaccine-related patents, in which the design of siRNAs mainly targeted PI4KB, N protein gene, M protein gene, RdRp, ORF3a gene, and M, N, and E genes. Gene delivery vectors were also the focus of research, including plasmid, adenovirus vector, AAV vectors, recombinant RV vector, polymeric nanoparticle, lipid nanoparticle (LNP), eukaryotic expression vector pCMV-Myc, cationic polymers, peptides, hyaluronic acid conjugates, and multiblock copolymers (Table 2).

Researchers are also developing gene therapy drugs based on the RNAi mechanism in the wake of the MERS outbreak. Four miRNA and five siRNA molecules targeting the ORF1ab gene of MERS-CoV were confirmed to cause a decrease in viral activity [15]. In addition to SARS-CoV and MERS-CoV, lipid nanoparticle-encapsulated siRNAs were used to treat the Makona outbreak strain of Ebola virus-infected animals, resulting in milder clinical features and full recovery, which successfully demonstrated the efficacy of siRNA against the Ebola virus in a nonhuman primate [16]. These studies demonstrate the potential of gene therapy in antiviral therapy.

Although there have been many articles and patents reporting on RNAi-based gene therapy for SARS, only a few studies have explored its application to SARS-CoV-2. N protein and nucleocapsid protein of SARS-CoV-2 may play an important role in suppressing RNAi to overcome the host defense in cells [17, 18]. Two patents reported COVID-19 antisense RNA multivalent vaccine and dsRNA vaccine targeting SARS-CoV-2 ORF1ab, 3′ UTR, and S, E, M, or N genome region (CN111330003A and CN111321142A). Two new siRNAs aiming at the conserved regions of the SARS-CoV-2 gene were developed, and both had a noticeable inhibition effect on the SARS-CoV-2 gene (CN111139241A and CN111139242A). Hangzhou Yongchengrui Biotechnology reported an siRNA that interferes with expression of the COVID-19 gene and comprises the dsRNA sequence with silencing S gene or RDRP gene function (CN111518809A). ProQR Therapeutics reported a viral vector expressing an antisense oligonucleotide, which modulates the function of programmed death-ligand 1 (PD-L1), allowing the skip of at least exon 3 from the CD274 pre-mRNA that encodes the PD-L1 protein (WO2020201144A1).

4. Results and Discussion

4.1. Global Patent Status. As of August 12, 2020, a total of 192 INPADOC patent families were retrieved. Derwent Data Analyzer (DDA) was used to analyze patent data from 1993 to 2019 to provide comparative information on coronavirus gene therapy patents, focusing on annual trends in the field, geographical distribution, and major applicants. As there is a time lag of 18 months between the priority date and the date of publication, the 2019–2020 figures are for references only, which include a total of 20 SARS-Cov-2-related gene therapy patents as of November 11, 2020.

Table 2: Gene therapy-related patents for SARS and MERS.

Publication number	Application date	Organization	Virus/mechanism	Gene targets/vectors
WO2017044507A2	2016/9/7	Sirnaomics Inc.	MERS-CoV; siRNA	PLpro, RdRp, S protein; polymeric nanoparticle, liposomal nanoparticle
CN102453712A	2010/10/19	Chinese Academy of Medical Sciences	SARS-CoV; siRNA	PI4KB; adenovirus; VeroE6 cell
CN101597607A	2005/3/25	Chinese Academy of Medical Sciences	SARS-CoV; siRNA	N protein; pCMV-Myc
CN101173275A	2006/10/31	Chinese Academy of Medical Sciences	SARS-CoV; siRNA	M protein
CN101113158A	2006/12/18	Sichuan University	SARS-CoV; siRNA	RdRp; plasmid
CN101085986A	2006/6/8	Shanghai Institutes for Biological Sciences, CAS	SARS-CoV; siRNA	ORF3a
WO2006130855A2	2006/6/1	California Institute of Technology	SARS-CoV	Recombinant retrovirus
CN1704123A	2004/6/1	Guangzhou Tuopu Genetech Ltd.	SARS-CoV; siRNA	Cationic polymers, peptides
CN1648249A	2004/1/19	Shanghai Institutes for Biological Sciences, CAS	SARS-CoV; siRNA	19–25 consecutive nucleic acids on the M, N, and E genes
US20050095618A1	2004/7/28	Chinese University of Hong Kong	SARS-CoV; siRNA	S protein
WO2005019410A2	2004/4/26	Intradigm Corporation	SARS-CoV; dsRNA	nsp1, nsp9, S; aqueous glucose solution
WO2004092383A2	2004/4/13	Sirna Therapeutics, Inc.	siRNA, dsRNA, miRNA, shRNA	Chemically synthesized, modulate the expression of SARS virus RNA
US20140294752A1	2014/4/1	Research & Business FDN Sungkyunkwan Univ.	Hyaluronic acid conjugate	To deliver RNA, DNA, siRNA, aptamer, antisense oligodeoxynucleotide, antisense RNA, ribozyme, DNAzyme
WO2014144486A2	2014/3/14	Children's Hospital of Philadelphia	Recombinant vector plasmid	Cell, viral particle, and AAV particle comprising the recombinant vector plasmid
WO2013123503A1	2013/2/19	Children's Hospital of Philadelphia	AAV-Rh74 vector for gene transfer	AAV vector comprising a heterologous polynucleotide
WO2010111522A2	2010/3/25	University of California	Mesenchymal stem cell	For delivery of siRNA, miRNA, or dsRNA polynucleotide into a target cell
WO2010054266A2	2009/11/6	University of Washington	Multiblock copolymers	For delivery of siRNA, antisense oligonucleotide, dicer substrate, miRNA, aiRNA, shRNA, or siRNA

Note. Listing items include the virus and the targeting gene, mechanism, and gene delivery vectors.

4.2. Patent Application Trends. Research and patenting activities on coronaviruses have been closely linked to related outbreaks. The annual distribution of global patent applications shows that there were very few patent applications before 2002. In 2003, the outbreak of SARS triggered a rapid increase in global patent applications. However, the number gradually declined after 2005 due to the eradication of SARS epidemic by conventional medicine. From 2013 to 2015, the MERS epidemic stimulated global research with a small increase in patent applications (Figure 1).

The time-series analysis of new inventors gives an idea of the activity and market importance of the field of technology. The grey and blue bars in Figure 1 indicate the number of new and existing inventors, respectively, in a given year. The figure shows that there was an explosion of new inventors entering coronavirus gene therapy in 2003–2005. After 2005, the patenting activities were more active than before 2003, but the activity of existing inventors was rarely sustained. This lack of sustainability of technology development activities for coronavirus gene therapy is consistent with disease outbreaks and demise.

4.3. Patent Country/Location Distribution. In terms of geographical distribution, the patents are mainly from the US, China, Japan, and Korea, accounting for 84% of the world's total patents. The US ranks first in the world in terms of the number of patents, far ahead of other countries, accounting for 50% of the world's total patents, which matches the position of the US as a major gene therapy country. As epidemic-stricken countries, China and the Republic of Korea have relatively muscular scientific research strength, so they follow the US in terms of patent application volume. Japan, as a neighboring country of China and the Republic of Korea, also has a larger patent application volume (Figure 2).

An analysis of the global patent layout shows that patents were basically filed in their own countries. The reason is simple: under PCT Article 21, the international publication of the international application by the International Bureau shall be effected promptly after the expiration of 18 months from the priority date of that application. After the outbreaks were quickly brought under control, most PCT applications did not see a market.

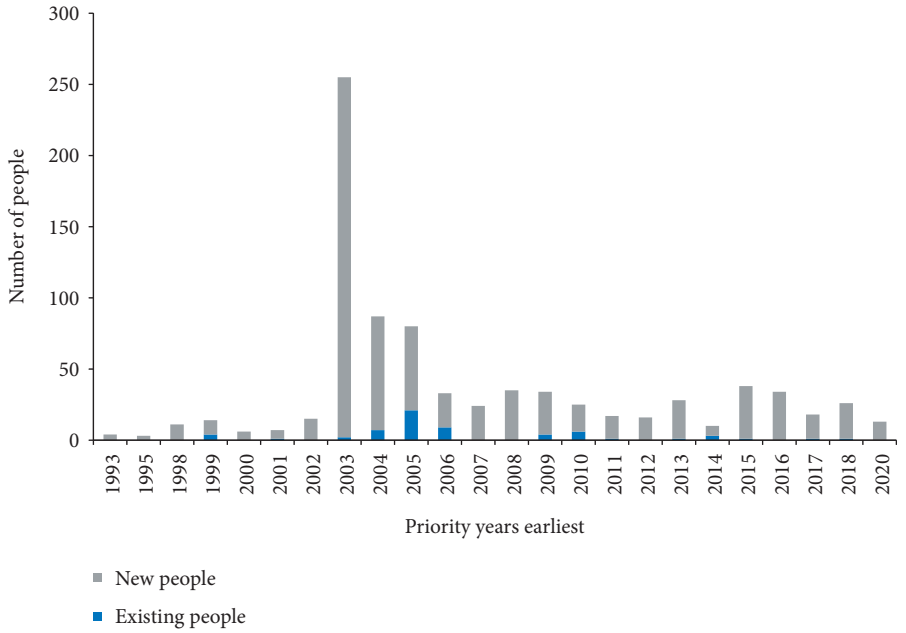

Figure 1: Trends in patent applications and old and new inventors.

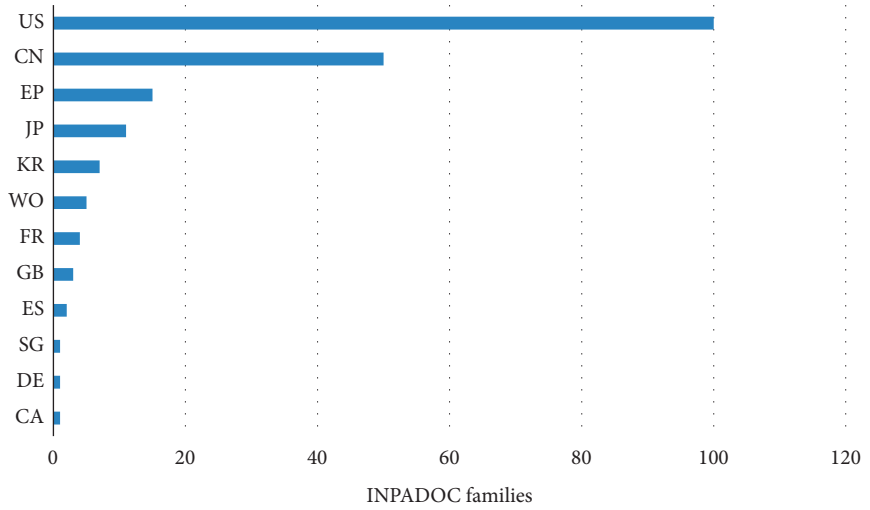

Figure 2: Ranking of patent filings in the earliest priority countries.

Further, a legal status analysis revealed that among the 192 INPADOC families retrieved, only 33 were live, 5 indeterminate, while 154 dead, implicating that innovation in the field is rapid, with new technologies rapidly phasing out old ones that have lost their value.

4.4. Top Organizations and Inventors Worldwide. To understand who was in the coronavirus gene therapy industry, we analyzed main organizations in patent applications (Figure 3). The top 10 patent holders are mainly from China, the US, and France. The main organizations in the field are the French National Centre for Scientific Research, Chinese Academy of Medical Sciences, and Pasteur Institute, followed by the US Department of Health and Human Services. The overall few patent applications, which occurred to top inventors too (Figure 4), reflect the relatively low level of technical activity in the field.

4.5. Gene Delivery Vectors. Gene therapy works by introducing a new or modified gene into the body to help treat a disease. Several gene delivery vectors were used in gene therapy, including plasmid transfection, electroporation, liposomes, cationic polymer nanoparticles, and viral vectors, which can be divided into adenovirus (AV), adeno-associated virus (AAV), lentivirus (LV), herpes simplex virus (HSV), and retrovirus (RV) [9]. An analysis of the number of vector-related applications in coronavirus gene therapy patents revealed that plasmid, AV, and RV vectors had the most significant number of applications.

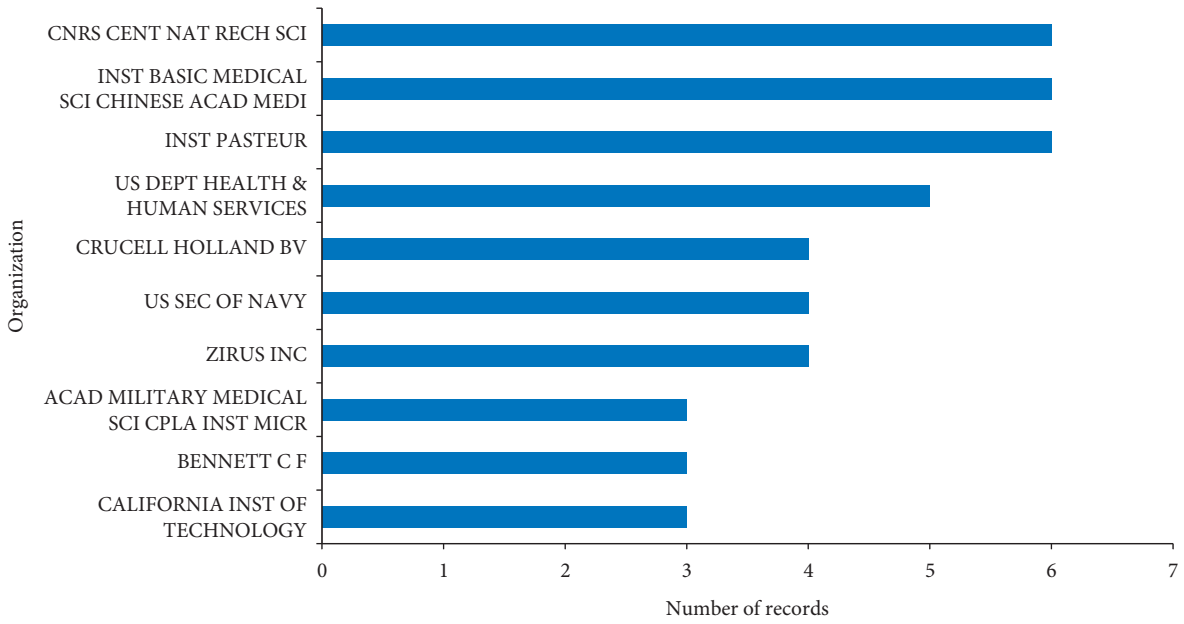

Figure 3: Global ranking of patent applicants.

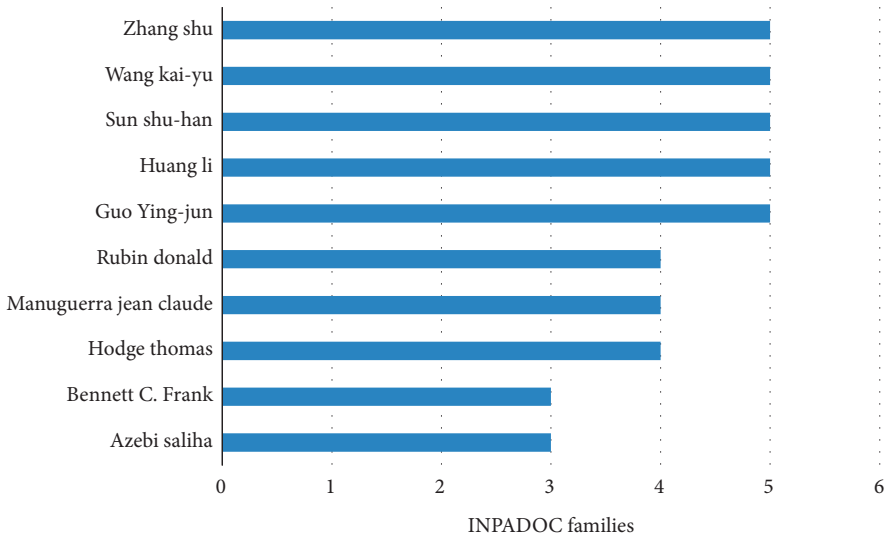

Figure 4: Global ranking of inventors.

On the other hand, recombinant AAVs (rAAVs) are the leading platform for in vivo delivery of gene therapies [7], which was evidenced by the top three most cited patents in this field (Figure 5) being related to a chimpanzee nucleic acid sequence useful for generating chimpanzee adenoviral vectors as vaccine carriers (WO2005071093A2), a recombinant alphavirus particle gene vector (US6376236B1), and an oligonucleotide-core carrier composition (US20090053169A1).

5. Prospective

Due to the time lag between patent filing and publication, many developed medical technologies have not been published and, therefore, could not be included in the scope of this study. However, at present, the global distribution of patents presented in this study shows that the US and China have the leading number of patents and are technologically more advanced and were able to develop novel therapies to curb the pandemic. Research centers and pharmaceutical companies in the US, France, and China should join forces and draw inspiration from past research experiences to accelerate the development of effective therapies.

In summary, with patterns of past patent activities providing lessons for current research, we outline a scenario of the current trends in coronavirus gene therapy through analysis of the patent landscape of the field, demonstrating the potential for gene therapy to be used against COVID-19. We expect that the six existing RNAi therapies will be successful in clinical trials and will soon be available for the

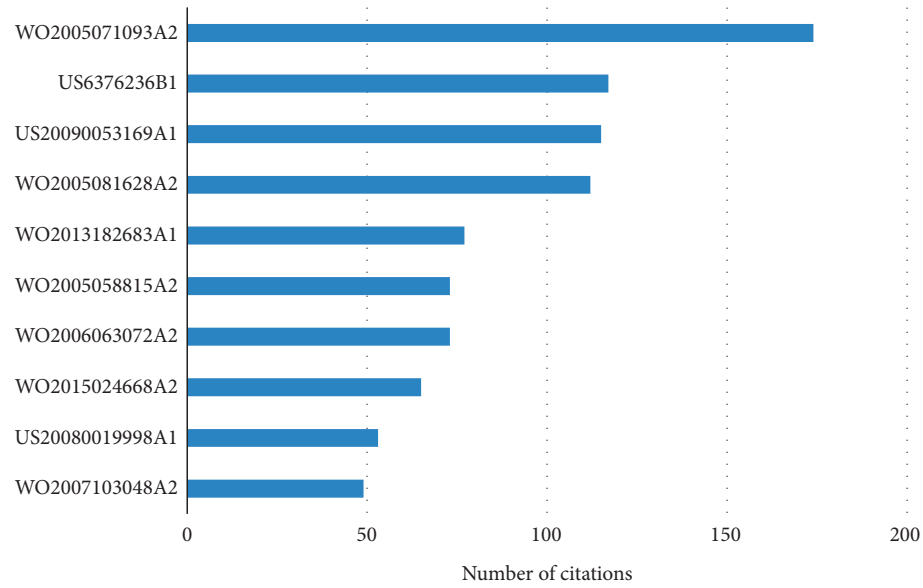

Figure 5: Top ten cited patents related to gene therapy for coronavirus.

effective treatment of SARS-CoV-2, and this patent landscape will help defeat the COVID-19 pandemic. It may also be a great opportunity to promote the development of gene therapy.

Conflicts of Interest

The authors have declared no conflicts of interest.

Acknowledgments

This work was supported by the National Natural Science Foundation of China (grant no. 61976192) and the Zhejiang Soft Science Research Program (2019C35070).

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