

Role of Private Sector, Governments and Charities in Funding Research and Development Related to Tocilizumab

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1. Introduction and Summary

Tocilizumab is one of the drugs that is being tested to treat severe COVID-19 cases. Chugai Pharmaceutical Co., Ltd. - now a subsidiary of Roche - obtained the first regulatory approval for this drug by the Japanese Pharmaceuticals and Medical Devices Agency (PMDA) in 2005 for Castleman's disease. It was registered in the United States in 2010, initially for the treatment of rheumatoid arthritis. Roche markets the drug under the brand names *Actemra* and *RoActemra*. There are no biosimilars on the market, although several candidates are in development.

The funding of the research and development (R&D) for tocilizumab can be described as having three phases. The invention and early development of tocilizumab was supported by the government of Japan. Once the drug entered the market, most, but certainly not all, of the R&D related to tocilizumab was funded by industry, including initially by Roche or companies acquired by Roche. More recently, and certainly as relates the R&D related to tocilizumab and COVID-19, governments have played the leading role in funding R&D, including governments outside the United States.

Tadamitsu Kishimoto, MD, PhD, invented tocilizumab in his laboratory at Osaka University. Dr. Kishimoto first reported the complementary DNA sequence of the interleukin-6 cytokine, cloned the interleukin-6 receptor, patented antibodies to the interleukin-6 receptor, and assigned the rights to these inventions to Chugai Pharmaceuticals. These discoveries, which led to tocilizumab, were funded by the government of Japan through a grant program called Kakenhi.

Following the initial approvals, tocilizumab has received several additional approvals for other indications. One indication recently approved by the U.S. Food and Drug Administration (FDA) is for the management of the cytokine release syndrome in patients receiving cell therapies. The research that pioneered the use of tocilizumab for the cytokine release syndrome was supported with U.S. government grants. The investigation of tocilizumab for COVID-19 is premised on evidence showing it can resolve the cytokine release syndrome.

Over the years, governments around the world and other drug companies have funded additional research related to tocilizumab. It is possible to obtain some data about U.S. government funding, although not all data because not all U.S. federal government grants can be identified through the NIH database RePORTER. Among the grants included in RePORTER are 50 projects that specifically involve research on tocilizumab, directed by 15 principal investigators. Two of these were intramural grants to NIH researchers, and 13 grants were to 11 universities. Collectively, these projects represent \$47 million in funding, all from the NIH.

Although the foundational Kishimoto patents directed to interleukin-6 receptor antibodies have now expired, Chugai and Roche filed additional applications seeking to extend their exclusive

rights over tocilizumab. Some of these applications have been rejected at the European Patent Office (EPO), but were issued by the United States Patent and Trademark Office (USPTO).

Patent applications are typically kept secret for several months before being published by national offices. This limits our understanding of the landscape of pending patent applications relating to tocilizumab specifically for treating the cytokine storm in COVID-19 patients.

The data on clinical trial funding is more illustrative. In 2020, from January 1 through May 19, the NIH registry of clinical trials, ClinicalTrials.gov, listed 54 new trials for tocilizumab. Of these, 44 were related to COVID-19 research, including 43 of the last 46 trials entered into the registry. Of the 44 trials specifically for COVID-19, only eight studies disclose funding by “industry.” Of the clinical trials with any industry funding, three state that they were sponsored by Roche, four state that they were sponsored by Roche and “other”, and one was sponsored by R-Pharma and “other.”

However, at least one trial misidentified the source of funding. Trial NCT04320615, a Phase 3 study for the use of tocilizumab in connection with COVID-19 pneumonia, was funded by a \$25.1 million contract awarded by the Biomedical Advanced Research and Development Authority (BARDA) to Roche/Genentech, but is listed as an industry-funded trial. With this adjustment, the number of trials sponsored by Roche and funded only by industry are just two, rather than three.

For the 2020 COVID-19 tocilizumab trials, the most important funder category is “other,” which represents foreign governments and nonprofit research institutions and charities. There are 34 trials in the “other” funder category alone, and six additional trials that are being co-funded by “other”, including one co-funded with the NIH, four co-funded with Roche and one co-funded with R-Pharma. By enrollment, 89.8 percent of the patients are in trials that are only in the “other” category, and another 5.6 percent are co-funded by “other”; 95.4 percent in total. In contrast, Roche is identified as the funder of 2.2 percent of the enrolled patients, and a co-funder of another 3 percent, or 5.2 percent overall.

2. Tocilizumab is a monoclonal antibody against the interleukin-6 receptor

Interleukin-6 (IL-6) is a cytokine that regulates the inflammatory and immune responses, among other functions. At some levels IL-6 acts as a defense mechanism, but in chronic inflammation it is proinflammatory.¹ Based on its activities, IL-6 is a target for treating several diseases.

Marketed under the brands *Actemra* and *RoActemra*, tocilizumab is a recombinant humanized monoclonal antibody that acts as an IL-6 receptor antagonist.² Tocilizumab recognizes the IL-6 binding site of the human IL-6 receptor and inhibits IL-6 signaling through competitive blockade

¹ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3226076/>

² <https://www.ncbi.nlm.nih.gov/pubmed/19368420>

of the IL-6 binding site.³ Tocilizumab is indicated for several diseases, including rheumatoid arthritis and systemic juvenile idiopathic arthritis. It has been approved by the U.S. Food and Drug Administration (FDA), the European Medicines Agencies (EMA), the Pharmaceuticals and Medical Devices Agency (PMDA) of Japan, and other regulatory agencies worldwide.

3. Discovery of the IL-6 pathway was funded with Kakenhi grants to Kishimoto

Professor Tadimitsu Kishimoto, MD, PhD, is a Japanese immunologist considered to be one of the pioneers in the field of cytokine research. Dr. Kishimoto received his degrees from Osaka University and worked as a postdoctoral fellow in the laboratory of Kimishige Ishizaka at Johns Hopkins University during the early 1970s before returning to Osaka in 1975.⁴ He served as President of Osaka University from 1997 to 2003,⁵ and is now an Emeritus Professor. Dr. Kishimoto has been widely credited with the discovery of the interleukin-6 (IL-6) cytokine and the interleukin-6 receptor (IL-6R),⁶ for which he has received numerous awards. As explained in detail below, he received grants from the Japanese government to fund his research.

Professor Kishimoto cloned the complementary DNA of the human IL-6 gene in 1986.⁷ In 1988 the laboratory of Professor Kishimoto cloned the IL-6 receptor.⁸ The papers respectively reporting the clonation of the IL-6 gene and the IL-6 receptor acknowledged that they were “supported in part by grants from the Ministry of Education, Science and Culture” of Japan.

Additional research relating to the IL-6 pathway published by Dr. Kishimoto and others in his laboratory were also supported with grants from the government of Japan. For example, a paper published in 1993 about soluble forms of the IL-6 receptor co-authored by Dr. Kishimoto acknowledged support from the Ministry of Education, Science and Culture of Japan.⁹ Professor Kishimoto co-authored a paper published in 1998 at the Proceedings of the National Academy of Sciences, which concluded that “blockade of IL-6 is possibly beneficial in the treatment of rheumatoid arthritis.”¹⁰ That 1998 paper acknowledges that the research was supported in part by grants from the Ministry of Education, Science, and Culture, but also mentions funding from the Osaka Foundation for Promotion of Clinical Immunology and Ono Pharmaceutical.

In a short essay published in 2018, Professor Kishimoto explained that his research has been supported “for 40 years” by the Kakenhi Grants-in-Aid for Scientific Research Program.¹¹ The Kakenhi is a government program in Japan that funds all types of scientific research, from basic

³ <https://www.sciencedirect.com/topics/neuroscience/tocilizumab>

⁴ <https://www.sciencedirect.com/science/article/pii/S2589909019300309> Several scientific papers co-authored by Kimishige Ishizaka around these years acknowledge funding from U.S. government grants.

⁵ <http://www.dma.jim.osaka-u.ac.jp/view?l=en&u=1737>

⁶ <https://rupress.org/jem/article/217/5/e20190347/151633/Historical-overview-of-the-interleukin-6-family>

⁷ <https://www.nature.com/articles/324073a0>

⁸ <https://science.sciencemag.org/content/241/4867/825>

⁹ <https://ashpublications.org/blood/article/82/4/1120/170673/Soluble-forms-of-the-interleukin-6-signal>

¹⁰ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC20957/>

¹¹ https://www.jsps.go.jp/english/e-grants/kakenhi_essay/grants11_112.html

to applied.¹² His first Grant-in-Aid for Specially Promoted Research ran from 1985 to 2003, the years where he made critical discoveries related to the IL-6 receptor. He received “50 million yen a year under the Grant-in-Aid for Specially Promoted Research category.” Dr. Kishimoto acknowledged in his essay that the research funded with these grants led to tocilizumab.¹³

4. Kishimoto assigned key IL-6R antibodies patents, now expired, to Chugai

In addition to his Kakenhi grants, Dr. Kishimoto received funding from Chugai Pharmaceuticals. Chugai is a pharmaceutical company based in Japan, now a subsidiary controlled by Roche as explained in more detail below. In 1986 Chugai and Osaka University, where Dr. Kishimoto is affiliated, signed a research collaboration agreement.¹⁴ Under this collaboration agreement Osaka and Chugai created a drug discovery program targeting the IL-6 receptor. There does not appear to be publicly available information about how much resources Chugai committed to support the program.

According to a book titled *Drug Discovery in Japan: Investigating the Sources of Innovation*,¹⁵ the main points of the collaboration agreement were that Chugai would fund some of the expenses of Tadimitsu Kishimoto; any patent related to the IL-6 receptor would be licensed to Chugai for commercialization; and Chugai had to pay royalties to Professor Kishimoto.

Table 1. U.S. patents by Kishimoto et al. relating to the interleukin-6 receptor

Patent ID	Earliest Priority	Issue Date	Assignee or Applicant	Expected Expiration	Legal Status
8,617,550	12/19/2003	12/31/2013	Chugai	9/11/2025	active
8,802,092	10/17/2003	8/12/2014	Chugai	10/15/2024	active
8,597,644	10/25/2000	12/3/2013	Chugai	12/7/2022	active
8,562,990	10/25/2000	10/22/2021	Chugai	10/25/2021	active
7,320,792	10/25/2000	1/22/2008	Chugai	11/6/2022	expired
6,555,555	4/1/1998	4/29/2003	Ono Pharmaceutical	3/31/2019	expired
7,824,674	3/17/1998	11/2/2010	Chugai	3/16/2019	expired
6,723,319	3/17/1998	4/20/2004	Chugai and Kishimoto	3/16/2019	expired
5,888,510	7/21/1993	3/30/1999	Chugai and Kishimoto	3/30/2016	expired
5,866,689	4/28/1992	2/2/1999	Tosoh and Kishimoto	4/27/2013	expired
5,470,824	5/31/1991	11/28/1995	University of California	11/28/2012	expired
5,360,894	12/25/1989	11/1/1994	Kishimoto	10/22/2010	expired
5,215,892	12/25/1989	6/1/1993	Kishimoto	10/22/2010	expired
5,223,611	8/3/1989	6/29/1993	Kishimoto	8/2/2010	expired

¹² <https://www.jsps.go.jp/english/e-grants/data/handbook.pdf>

¹³ https://www.jsps.go.jp/english/e-grants/kakenhi_essay/grants11_112.html

¹⁴ <https://www.chugai-pharm.co.jp/english/ir/history/history04.html>

¹⁵ <https://link.springer.com/book/10.1007%2F978-981-13-8906-1>

5.132.403	8/3/1989	7/21/1992	Kishimoto	8/2/2010	expired
5.670.373	1/22/1988	9/23/1997	Kishimoto	9/23/2014	expired

Table 1 above reflects all 16 patents issued in the U.S. where Tadamitsu Kishimoto is named as an inventor, and at least one of the claims mentions “interleukin-6” or “IL-6.” Information in this table is updated as of May 2020. The two key patents out of those listed below are U.S. patents 5,670,373 (the ‘373 patent) and 5,888,510 (the ‘510 patent). The ‘373 patent, which has a priority date of January 22, 1988, is directed to an isolated antibody to the human interleukin-6 receptor. Because of its scope, the ‘373 can be considered one of the foundational Kishimoto patents. The ‘510 patent was directed to several methods of treatment, including for chronic rheumatoid arthritis, by administering an antibody against an interleukin-6 receptor.

The ‘373 and the ‘510 patents were clearly related to tocilizumab. In February 2010, Professor Kishimoto and Chugai Pharmaceuticals sought a term extension at the U.S Patent and Trademark Office (USPTO) for these patents in connection to the approval of Actemra. Kishimoto and Chugai stated in their request that these patents were directed to tocilizumab, which is a requirement of these types of term extensions. Both term extensions were granted in September 2013. The USPTO granted a third term extension in connection to the approval of Actemra to U.S. patent 5,795,965 (the ‘965 patent), which does not list Professor Kishimoto as one of the co-inventors. All three of these patents have now expired in the United States.

U.S. patent 5,470,824 (the ‘824 patent) lists Dr. Kishimoto as one of the co-inventors, jointly with other scientists based in the United States. That patent is assigned to the Regents of the University of California, and discloses multiple U.S. federal grants. However, the ‘824 patent is not related to tocilizumab since it was directed to a method of treating Kaposi's sarcoma by administering an amount of interleukin-4. Its sole claim mentions “IL-6” but not an antibody against the interleukin-6 receptor. The ‘824 patent has now expired in the United States.

5. Chugai sought secondary patents claiming IL-6R antibodies and certain uses

Although several Kishimoto patents have now expired, including the ‘373 patent, Chugai sought, and in some countries obtained, additional secondary patents. *Secondary patenting* is a strategy frequently used by pharmaceutical companies to extend the term of their intellectual property monopolies beyond the expiration of the original patents rights. While *primary patents* are directed to active ingredients, *secondary patents* typically claim incremental modifications of known compounds or methods of treating certain diseases based on known compounds.

The Medicines Patent Pool (MPP) recently published a landscape of applications and patents related to tocilizumab in certain developing countries.¹⁶ Drawing from that analysis it is possible to independently identify twin applications filed at the European Patent Office (EPO) or the USPTO. Table 2 provides a list of EPO applications also filed at the USPTO, based on the MPP

¹⁶ <https://www.medspal.org/?keywords=Tocilizumab&page=1>

landscape analysis for tocilizumab. This table is updated as of May 2020. These applications name a number of inventors, most of which appear to be in-house Chugai scientists.

Table 2. EPO applications related to tocilizumab, based on the MPP database

EPO number	Earliest Priority	Assignee	EPO Outcome	USPTO Outcome	Equivalent USPTO Numbers
EP08866971	12/27/2007	Chugai	granted	granted	8568720
EP04807818	12/19/2003	Chugai	revoked	abandoned	20140079695
EP04730090	4/28/2003	Chugai	withdrawn	granted	8709409 , 7521052
EP10180308	4/28/2003	Chugai	filed	granted	8709409 , 7521052
EP16165323	4/28/2003	Chugai	filed	granted	8709409 , 7521052
EP03705165	2/14/2002	Chugai	granted	granted	8921527 , 9051384 , 8840884
EP03705166	2/14/2002	Chugai	granted	granted	8921527 , 9051384 , 8840884
EP10010404	2/14/2002	Chugai	rejected	granted	8921527 , 9051384 , 8840884
EP17155264	2/14/2002	Chugai	withdrawn	granted	8921527 , 9051384 , 8840884
EP19157205	2/14/2002	Chugai	filed	granted	8921527 , 9051384 , 8840884
EP02708772	4/2/2001	Chugai	rejected	granted	9255145 , 7955598
EP08010046	4/2/2001	Chugai	rejected	granted	9255145 , 7955598
EP10011862	4/2/2001	Chugai	withdrawn	granted	9255145 , 7955598

All of the applications in Table 2 were filed long after the foundational '373 patent directed to an isolated antibody to the human interleukin-6 receptor was published. Most of these applications claim methods of treating certain diseases using tocilizumab or other anti IL-6 receptors antibodies. Several of these applications were rejected at the EPO, but issued at the USPTO.

Take, for example, EPO applications EP02708772,¹⁷ EP08010046,¹⁸ and EP10011862.¹⁹ These procedures are all based on two applications filed at the Japanese patent office in April 2001. They claimed methods of treating juvenile rheumatoid arthritis using tocilizumab or other anti IL-6 receptors antibodies. Both EP02708772 and EP08010046 were rejected in decisions respectively confirmed by the Boards of Appeal of the EPO.²⁰ In these cases the Board of Appeal identified prior art explicitly mentioning the treatment of juvenile rheumatoid arthritis by administering humanised anti-IL-6 receptor antibodies. Based on this prior art, the EPO Board of Appeal concluded that the subject matter claimed by Chugai lacked inventive steps. EPO application EP10011862, which claimed similar methods of treatment, was withdrawn.

¹⁷ <https://register.epo.org/application?number=EP02708772>

¹⁸ <https://register.epo.org/application?number=EP08010046>

¹⁹ <https://register.epo.org/application?number=EP10011862>

²⁰ EPO Appeals Board decisions [T 0652/12](#) and [T 0790/12](#) dated December 8, 2016.

In the United States, however, a related application was issued as U.S. patent 9,255,145 (the '145 patent). That patent is directed to methods of treating juvenile rheumatoid arthritis by administering an antibody against the human IL-6 receptor, similar to what was claimed in the EPO applications that were refused. The '145 patent is expected to expire in April 2022.

EPO applications EP04730090,²¹ EP10180308,²² and EP16165323²³ provide another similar example. These applications were generally directed to anti-IL-6R antibodies comprising methotrexate for the treatment of IL-6 related diseases. Applications EP10180308 and EP16165323 were refused by the examining division at the EPO. Application EP04730090 was withdrawn by Chugai. For the two applications that were refused the EPO examining division considered that the claimed inventions lacked inventive steps. These refusals were elevated to the Board of Appeals, where they are currently pending a final decision.

In contrast, the USPTO issued U.S. patents 7,521,052 (the '052 patent) and 8,709,409 (the '409 patent) respectively in 2009 and 2014. These granted U.S. patents benefited from the same priorities in the EPO applications that were rejected and were directed to a similar subject matter, claiming methods of treating rheumatoid arthritis by administering an IL-6 antagonist and an amount of methotrexate. U.S. patents '052 and '409 are expected to expire in 2024.

Furthermore, Chugai or other companies may have already filed secondary patents relating to tocilizumab beyond those reflected in the MPP database. In particular, there could be additional applications claiming methods of treating the cytokine release syndrome. However, pending patent applications typically remain secret for several months before being published. This hinders further research into whether additional secondary applications have been filed.

6. Roche and Chugai formed an alliance, including licenses to IL-6R patents

In December 2001, Chugai announced the creation of a strategic alliance with Roche. In October 2002, the Swiss company acquired a majority of Chugai's stock, making it a member of the Roche Group. In connection with this alliance Chugai licensed part of their patents to Roche, including IL-6R antibodies inventions conceived in the laboratory of Tadimitsu Kishimoto.

Roche had already acquired a majority stake of Genentech in September 1990. In March 2009, Roche acquired the shares it did not already own. Over the years Roche, Genentech, and Chugai have entered into a number of collaborations, including for the marketing of tocilizumab.

²¹ <https://register.epo.org/application?number=EP04730090>

²² <https://register.epo.org/application?number=EP10180308>

²³ <https://register.epo.org/application?number=EP16165323>

7. Tocilizumab has already generated billions of dollars in sales worldwide

Actemra was first approved for the treatment of Castleman's disease in Japan in 2005.²⁴ In 2008, it received additional approvals in Japan for the treatment of rheumatoid arthritis, active juvenile idiopathic arthritis in multiple joints, and systemic juvenile idiopathic arthritis.²⁵

EMA first approved tocilizumab under the brand name RoActemra in 2009, for the treatment of rheumatoid arthritis.²⁶ Since then EMA has granted additional indications for RoActemra, including active systemic juvenile idiopathic arthritis and juvenile idiopathic polyarthritis.

In the United States, Actemra was first approved by the FDA in 2010 for the treatment of adult rheumatoid arthritis.²⁷ That approval was based on seven Phase 3 clinical trials, according to our own analysis of the medical review documents.²⁸ Those clinical trials listed Roche as their sponsor and the papers that describe them acknowledge funding from the Swiss company. Since the first approval, the FDA has greenlit several additional indications for Actemra, including systemic juvenile idiopathic arthritis²⁹ and polyarticular juvenile idiopathic arthritis.³⁰

Actemra has generated billions of dollars in worldwide sales. Between 2010 and 2019 Roche reported 13.644 billion Swiss francs in global sales for Actemra.³¹

For the 20 mg/mL intravenous solution one source has a price in the U.S. of \$491 for 4 milliliters.³² The same source quotes a price of \$1,100.16 for the 162 mg/0.9 mL subcutaneous solution. The Federal Supply Schedule (FSS) price for the 162 mg/0.9 mL subcutaneous solution is \$986.46, and the Big 4 price for the 162 mg/0.9 mL solution is \$754.48.³³

8. Biosimilar development

There are no approved biosimilars of reference to tocilizumab, but there are several candidates currently in the pipeline. A non-exhaustive list of candidates based on publicly-available information follows. Bio-Thera Solutions, a Chinese company, is sponsoring a Phase 3 study of their biosimilar candidate BAT1806 compared to Actemra in subjects with rheumatoid arthritis

²⁴ <https://www.pmda.go.jp/files/000153119.pdf>

²⁵ <https://www.pmda.go.jp/files/000232775.pdf>

²⁶ <https://www.ema.europa.eu/en/medicines/human/EPAR/roactemra>

²⁷ https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2010/125276s000ltr.pdf

²⁸ These trials are available on ClinicalTrials.gov under the ID numbers: NCT00106548, NCT00106535, NCT00109408, NCT00106522, NCT00106574, NCT00721123, NCT00720798

²⁹ https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2011/125276s0022.s0023ltr.pdf

³⁰ https://www.accessdata.fda.gov/drugsatfda_docs/applletter/2013/125276Orig1s064ltr.pdf

³¹ Our own estimates based on: <https://www.roche.com/investors/historic-quarterly-reporting.htm>

³² <https://www.drugs.com/price-guide/actemra>

³³ <https://www.va.gov/opal/nac/fss/pharmPrices.asp>

that is inadequately controlled by methotrexate.³⁴ This trial is expected to conclude during the second half of this year and Bio-Thera says they plan to file for approval in 2021.³⁵

Taiwanese company Mycenax says they have been developing a tocilizumab biosimilar since 2013,³⁶ including with a completed Phase 1 clinical trial of their candidate LusiNEX versus Actemra.³⁷ Mycenax recently announced the sale of their LusiNEX program to Gedeon Richter, a Hungarian company that reportedly plans to start a Phase 3 clinical trial.³⁸ Fresenius Kabi is also developing a biosimilar candidate, MSB11456, which recently concluded a Phase 1 clinical trial.³⁹ Fresenius Kabi says that they expect to launch a tocilizumab biosimilar in 2023.⁴⁰

9. U.S. government has spent millions in further research related to tocilizumab

Following the initial approvals of Actemra, the U.S. government has spent millions of dollars researching tocilizumab for other indications. In fact, research funded by the U.S. government contributed to the approval of at least one additional indication and to the premise upon which tocilizumab is being tested for COVID-19. This section analyzes some U.S. government grants related to tocilizumab in general, and the next section focuses on publicly-funded research that specifically led to treating the cytokine release syndrome with this drug.

We searched the National Institutes of Health (NIH) RePORTER database for projects that mention the term “tocilizumab” in their description. This search returned 64 projects. After reviewing each one of their descriptions, we dropped 14 of the 64 projects from the dataset because they mentioned “tocilizumab” but not in the context of investigating this drug. The remaining projects, which relate to research specifically about tocilizumab, are in Table 3.

The first three letters of a grant number indicate the type of grant. For these, they include:

- “K08” = Mentored Clinical Scientist Research Career Development Award
- “R01” = Used to support a discrete, specified, circumscribed research project
- “R03” = NIH Small Grant Program
- “U01” = Research Project Cooperative Agreement
- “U34” = Planning Cooperative Agreement
- “UG1” = Clinical Research Cooperative Agreements - Single Project
- “Z1A” = Investigator-Initiated Intramural Research Projects

³⁴ <https://clinicaltrials.gov/ct2/show/NCT03830203>

³⁵ <http://www.bio-thera.com/plus/view.php?aid=370>

³⁶ <http://www.mycenax.com.tw/en/news.php?act=view&id=157>

³⁷ <https://clinicaltrials.gov/ct2/show/NCT03522012>

³⁸ <http://www.mycenax.com.tw/en/news.php?act=view&id=157>

³⁹ <https://clinicaltrials.gov/ct2/show/NCT03282851>

⁴⁰

https://annualreport.fresenius.com/wp-content/uploads/sites/4/2020/03/Fresenius_SE_2020_03_00_Company_presentation.pdf

Table 3. Selected NIH REPORTER projects that involve research on “tocilizumab”

Core Grant	Principal Investigator	Affiliation	Projects	Total Costs
U01AI113362	Flavio Vincenti	University of California, San Francisco	6	\$13,166,235
U01AI136816	Joren Madsen	Massachusetts General Hospital	4	\$8,349,795
U01AI105937	Michael Lederman	Case Western Reserve	5	\$5,809,580
ZIAHG200373	Daniel Kastner	NIH Human Genome Research Institute	3	\$4,876,709
U01DK61034	Carla Greenbaum	Benaroya Research Institute	5	\$3,860,833
R01AI132774	Jane Hoyt Buckner	Benaroya Research Institute	3	\$2,904,615
R01HL134691	Chance John Luckey	University of Virginia	4	\$2,076,596
ZIAAR41194	Raphaela Goldbach	NIH Intramural Research Program	4	\$2,053,963
UG1HL139106	John Fahy	University of California, San Francisco	3	\$1,123,378
R01CA211611	Susan Mallery	Ohio State University	3	\$1,068,665
R01AI141710	Miguel Fribourg	Mount Sinai	2	\$847,500
K08DE26500	Alexander Pearson	University of Chicago	4	\$640,266
U34AR66294	Laura Schanberg	Duke University	1	\$377,749
R03CA235200	Todd Hankinson	University of Colorado Denver	2	\$155,500
U01NS113451	Jaroslawn Aronowski	University of Texas	1	\$115,389
Total			50	\$47,426,773

Table 3 illustrates the role of the U.S. government in further researching tocilizumab. For instance, Flavio Vincenti, MD, is a professor of medicine at the University of California, San Francisco. He is the principal investigator in six projects titled *Novel therapies to modulate the inflammatory alloresponse in renal grafts*, representing \$13.1 million in cost to date. A press release about this grant explained that the aim is to study the use of tocilizumab for reducing or eliminating inflammation in kidney transplant recipients.⁴¹ Although the RePORTER database reflects that the cost so far has been \$13.1 million, the 2014 press release indicates that the budget for this project was \$17 million to be disbursed during the course of seven years.⁴²

A group of researchers at the Benaroya Research Institute in Seattle have been investigating the efficacy of tocilizumab in treating new-onset type 1 diabetes.⁴³ Professors Carla Greenbaum and Jane Hoyt Buckner are leading the Phase 2 trial.⁴⁴ Together, they have received \$6,765,448 in grants for multi-year projects by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) and the National Institute of Allergy and Infectious Diseases (NIAID).

⁴¹ <https://www.ucsf.edu/news/2014/08/116471/toward-personalized-medicine-kidney-transplant-recipients>

⁴² <https://www.ucsf.edu/news/2014/08/116471/toward-personalized-medicine-kidney-transplant-recipients>

⁴³ <https://clinicaltrials.gov/ct2/show/record/NCT02293837>

⁴⁴ <https://clinicaltrials.gov/ct2/show/record/NCT02293837>

Jaroslav Aronowski at the University of Texas is investigating the potential of tocilizumab as a new treatment for strokes. He received a \$115,389 grant in 2019 from the National Institute of Neurological Disorders and Stroke (NINDS) for this project, which is expected to run for several years. Chance John Luckey at the University of Virginia is developing a preclinical mouse model system to determine the therapeutic efficacy of targeting the IL-6/IL-6R signaling pathway for the prevention and treatment of red blood cell alloimmunization. This research, which is intended to provide further data on whether tocilizumab should be considered for select, high-risk alloimmunized patients, has benefited from \$2,076,596 in grants so far. A team of scientists working in the laboratory of Daniel Kastner recently discovered a previously unknown autoinflammatory disease and showed evidence that it can be treated with tocilizumab.⁴⁵ His laboratory appears in three projects funded by the NIH with a combined \$4,876,709 cost.

To be precise, Table 3 is merely an illustrative list of publicly-funded projects related to tocilizumab according to a search based on the NIH RePORTER database. There are likely more projects investigating tocilizumab with the support of other federal or state agencies not listed in the NIH RePORTER. Surely there are other grants to investigate this drug that did not mention the term “tocilizumab” in their description. Some of those grants are discussed next.

10. Publicly-funded research led to the approval of tocilizumab for the cytokine storm

Tocilizumab received supplemental approval by the FDA on August 30, 2017 for the treatment of severe or life-threatening cytokine release syndrome induced by chimeric antigen receptor (CAR) T-cells.⁴⁶ The cytokine release syndrome, also referred to here as the *cytokine storm*, is one of the potential side effects of CAR T-cell therapies. The cytokine storm is a systemic inflammatory response that can be triggered by a variety of factors, such as infections or infusion with CAR T-cells.⁴⁷ The reported incidence of the cytokine storm after CAR T-cell infusion ranges from 50% to 100%, with 13% to 48% of patients experiencing the severe or life-threatening form.⁴⁸ Because of its potential for fatal outcomes, the tools to manage severe or life-threatening cytokine storms are important for the development of CAR T-cell therapies.

One of the researchers that first reported the benefits of tocilizumab to manage the cytokine storm induced by infusion with CAR T-cells is Stephan Grupp, MD, PhD. Grupp has several roles at the Children's Hospital of Philadelphia (CHOP), including as Director of the Cancer Immunotherapy Program.⁴⁹ He is also a professor at the University of Pennsylvania (Penn).⁵⁰ Grupp has collaborated with Carl June and others in the development of CAR T therapies.⁵¹

⁴⁵ <https://www.nature.com/articles/s41586-019-1828-5>

⁴⁶ https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/125276Orig1s114Approv.pdf

⁴⁷ <https://jitc.biomedcentral.com/articles/10.1186/s40425-018-0343-9>

⁴⁸ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6156173/>

⁴⁹ <https://www.chop.edu/doctors/grupp-stephan-a>

⁵⁰ <https://www.med.upenn.edu/apps/faculty/index.php/g275/p5251>

⁵¹ <https://www.nejm.org/doi/full/10.1056/NEJMoa1215134>

In a paper published in April 2013 in the New England Journal of Medicine (NEJM), Grupp, June and colleagues reported that interleukin-6 cytokines were elevated following infusion with CAR T-cells.⁵² Next, in a paper published in June 2013 in the Blood Journal, Grupp and others reported clinical evidence from one patient that developed a cytokine release syndrome after being infused with CAR T-cells.⁵³ The patient had severe symptoms including respiratory failure, but they improved after being treated with tocilizumab. Grupp and colleagues further described this approach to CAR T toxicity management in a paper published in Current Opinion in Pediatrics Journal in February 2014, with evidence from four patients treated with tocilizumab.⁵⁴ Their data suggested that tocilizumab was effective in reversing the cytokine storm induced by CAR T. Another paper published in August 2014 in the Cancer Journal reported these findings.

⁵⁵

Stephan Grupp has benefited from millions of dollars in research grants from the NIH. According to the RePORTER database, Grupp is listed as a principal investigator in 24 projects with \$9,427,575 in grants from the National Cancer Institute (NCI) and the NIAID. Two of these grants, R01CA102646 and R01CA116660, are explicitly acknowledged in the papers published in the NEJM, the Current Opinion in Pediatrics, and the Cancer Journal. These two grants lasted for a period of five years each and totaled \$1,556,318 and \$1,488,593, respectively.

A search for patents issued by the USPTO that cite "IL-6" and "cytokine release" in any of the claims currently returns nine results. There are also several pending applications in the U.S., which are described in Box 1 below. One of the U.S. patents issued is 10,603,378 (the '378 patent), co-assigned to CHOP and Penn. The patent names Grupp, June, and two other as co-inventors. The priority date of the '378 patent was March 14, 2013, shortly before the NEJM paper described above was published. The first claim is directed to a method for treating cancer by administering CAR T-cells, resulting in cytokine release syndrome, and further administering an IL-6 inhibitor to treat the syndrome. Ten other claims are directed to methods of treatment that specifically mention tocilizumab as the IL-6 inhibitor. Contrary to several of the academic papers where Grupp and colleagues reported the use of tocilizumab in patients receiving CAR T-cell therapies, the '378 patent does not acknowledge support from NIH grants.⁵⁶

Since Grupp and colleagues first reported the benefits of this drug for the management of the cytokine release syndrome induced by treatment with CAR T-cell therapies, tocilizumab has been increasingly studied for that indication.⁵⁷ U.S. government grants continue to support the

⁵² <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4058440/>

⁵³ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4123427/>

⁵⁴ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4198063/>

⁵⁵ <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4119809/pdf/nihms607703.pdf>

⁵⁶ Based on evidence establishing that Dr. Stephan Grupp received support from the NIH for this research, and the fact that he acknowledged those grants in the papers that described the use of tocilizumab for the cytokine release syndrome induced by infusion with CAR T-cells, we believe that he should have disclose these grants in the '378 patent as required by the Bayh-Dole Act, but failed to.

⁵⁷ <https://www.ncbi.nlm.nih.gov/pubmed/31219357>

researchers doing these studies. Out of the 28 papers published in the PubMed Central database between January 2014 and December 2019 that cite “tocilizumab” and “cytokine release syndrome” in the abstract, 15 acknowledge funding from NIH grants.⁵⁸

Box 1. Pending U.S. patent applications citing “tocilizumab” and “cytokine release”

A search for published USPTO applications that cite “IL-6” and “cytokine release” in any of the claims currently reveal 48 results of which 20 appear to be pending. There are 12 applications that cite “tocilizumab” and “cytokine release” in any of the claims. Pending applications may be rejected, narrowed, abandoned, or otherwise not issued, but they are worth exploring too.

A list of U.S. patent applications based on this search strategy is available in [this link](#).

Some of these applications relate to methods for managing the cytokine storm induced by CAR T-cells infusion or by immunotherapy in general. For illustration, U.S. patent application 2019-0151361 filed by Kite Pharma claims methods of treating certain diseases with CAR T-cells. Claim 29 is directed to a method that includes administering an specific dose of tocilizumab during one hour, and repeating every eight hours, to treat the cytokine release syndrome. U.S. patent application 2019-0336504 filed by Novartis and Penn relates to several methods of treatment based on CAR T-cell infusion. Some of the claims involve administering an IL-6 inhibitor prior to, concurrently with, or after CAR T cells infusion.

A few of these applications have claims related to the cytokine storm where the scope does not appear to be narrowed to methods of treatment with CAR T-cell infusion. For instance, U.S. patent application 2019-0300615 claims formulations of antibodies, one of which is tocilizumab. The first claim describes an anti-interleukin-6 receptor antibody “containing aqueous formulation falling within a pH range of 4.5 to 6.5.” Claim 18 is directed to a “method of treating an interleukin-6-mediated disease” with that antibody, and claim 19 specifically describes that one of those diseases is the cytokine release syndrome. This application was filed by Mycenax and is pending examination at the USPTO. As noted above in Section 8, Mycenax has been developing a biosimilar of reference to tocilizumab since 2013.

Patent applications in the U.S. and other jurisdictions typically remain secret for several months before being published by national intellectual property offices. Considering this, there may be additional pending patent applications related to tocilizumab for treating the cytokine storm in addition to those mentioned here. There may be additional patents or pending applications that are directed to “tocilizumab” and “cytokine release,” but used other keywords in the claims and therefore will not be reflected in the search strategy described here.

Roche did not have to conduct prospective clinical trials to obtain supplementary approval by the FDA of tocilizumab for the management of the cytokine release syndrome induced by CAR T-cell therapies. The efficacy for this indication was assessed based on a retrospective analysis of pooled data from clinical trials of CAR T therapies for hematologic malignancies, submitted in

⁵⁸ Own elaboration based on: <https://www.ncbi.nlm.nih.gov/pmc/>

Biologic License Applications (BLAs) 125646 and 125643.⁵⁹ These BLAs were filed by Novartis for the approval of Kymriah⁶⁰ and Kite Pharma for Yescarta.⁶¹ Along with supplementary approval, the FDA gave tocilizumab an orphan drug designation for this indication.⁶²

11. Clinical trials of tocilizumab prior to 2020

There are 349 studies registered in ClinicalTrials.gov from the beginning through December 2019 which cite research related to tocilizumab, for any indication. ClinicalTrials.gov has a search field that describes, in non-mutually exclusive categories, the type of organization that funded a specific trial. Our review of that field indicates that 243 disclose some industry funding, eight trials disclose some funding by the NIH or other U.S. federal agencies, and 141 disclose funding by “other” types of organizations. Among the studies that disclose funding by “other” types of funding, 47 had at least one location in the United States, and 94 were only abroad.

Table 4. Funders of clinical trials related to tocilizumab, according to CT.gov

Funded Code by in CT.Gov	Trials	Percentage
Funded entirely by industry	205	58.7%
Funded partially by industry	38	10.9%
Funded entirely by the NIH or other federal	3	.9%
Funded partially by NIH or other federal	5	1.4%
Funded entirely by “other”	99	28.4%
Funded partially by “other”	42	12.0%

“Other” is an inclusive category that could mean the trial was funded by non-federal government agencies in the U.S., public bodies outside the U.S., charities inside or outside the U.S., or any “other” types of funders different from industry, the NIH, or U.S. federal agencies. Considering this, 69.6 percent of the trials relating to tocilizumab prior to 2020 were funded partially or entirely by “industry.” The rest disclose some type of funding that is different from “industry.”

Among those trials that are funded “by industry,” in whole or in part, a number of trials, particularly in recent years, involve companies other than Roche or its subsidiaries.

Through 2008, all “industry” trials were sponsored by Roche (or its subsidiaries, Chugai and Genentech). Subsequently, several non-Roche companies sponsored trials, typically when using tocilizumab in combination with other products. In 2018, 64 percent of industry-funded trials were sponsored by the Roche group, and in 2019, half were sponsored by the Roche group.

⁵⁹ https://www.accessdata.fda.gov/drugsatfda_docs/nda/2017/125276Orig1s114MultidisciplineR.pdf

⁶⁰ <https://www.fda.gov/media/106989/download>

⁶¹ <https://www.fda.gov/media/108458/download>

⁶² <https://www.accessdata.fda.gov/scripts/opdlisting/oopd/detailedIndex.cfm?cfgridkey=589317>

Among the industry sponsors or co-sponsors of trials through 2019, other than Roche, were the following companies.

- Ablynx
- Astellas Pharma Korea, Inc.|Astellas Pharma Inc
- Bio-Thera Solutions
- Bristol-Myers Squibb
- Celgene
- Forty Seven Inc.
- Fresenius Kabi SwissBioSim GmbH
- Immunomedics, Inc.
- Incyte
- JW Pharmaceutical
- Heckel Medizintechnik GmbH
- MJM Boten
- Mycenax Biotech Inc.
- Novartis
- Prizer
- Regeneron Pharmaceuticals
- Sanofi
- Seattle Genetics, Inc.
- Tesaro Inc.
- The Emmes Company
- UCB Pharma

Any trials relating to tocilizumab for COVID-19 started in 2020. The trials reported to ClinicalTrials.gov from January 1, 2020 to May 19, 2020, are examined next.

12. Clinical trials of tocilizumab in 2020, for COVID-19 and other indications

Tocilizumab is currently being investigated in clinical trials as one of several drugs to treat severe COVID-19 patients. The premise upon which these studies are based is that tocilizumab can resolve the cytokine storm associated with COVID-19 infections. This premise builds upon previous evidence showing the efficacy of tocilizumab for the management of the cytokine release syndrome induced by CAR T infusions.⁶³ As explained previously, research funded with NIH grants contributed to establishing the efficacy of this drug for the treatment of a cytokine storm.

⁶³ For example, see: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7151347/pdf/main.pdf> “Given the efficacy of tocilizumab in CRS and the pivotal role of IL-6 in COVID-19, we propose to repurpose tocilizumab to treat severe cases of COVID-19.”

A May 19, 2020 search of trials first posted on ClinicalTrials.gov in 2020 identified 54 trials. Of these, 44 note that they are specifically investigating tocilizumab for COVID-19. Only eight of these studies disclose funding by “industry.” Three studies disclose funding by the NIH. Most of them, a total of 34, disclose funding by “other.” Only eight of the 44 trials have at least one location in the United States. The relatively small number of studies with locations in the United States partially explains why so many are labeled as “other,” because trials that are sponsored and funded by foreign governments should appear in that category since they are neither funded by U.S. federal agencies nor by industry. Trials funded by charities or by government agencies at the U.S. state level are probably also categorized as “other.”

A closer look into these trials reflects that several of them were indeed supported by the U.S. government, including at least one that only disclosed “industry” as the funder. For most of these trials we are unable to discern the total cost based on publicly-available information, but for some we can. For instance, on March 18, 2020, Roche and Genentech announced a controlled Phase 3 trial of tocilizumab in hospitalized patients with severe COVID-19 pneumonia.⁶⁴ Roche and Genentech stated that this trial was a collaboration with the Biomedical Advanced Research and Development Authority (BARDA). KEI filed a Freedom of Information Act (FOIA) requesting BARDA to release all contracts in their Novel Coronavirus Medical Countermeasure Portfolio, which includes this trial. Our request is still pending.

Publicly, BARDA has said that they are providing \$25,100,000 towards the trial.⁶⁵ A search for contracts between BARDA and Genentech on the feds.gov website returns a contract identified as 75A50118D00036, which is an existing agreement between both parties modified on March 26, 2020, to provide an additional \$25,100,000 for the “activation of CLIN 0008 for Actemra Phase 3 RCT for COVID-19 [...]” On March 23, 2020, Genentech announced that the FDA approved the launch of their Phase 3 trial of tocilizumab for COVID-19, named COVACTA.⁶⁶ The COVACTA trial seeks to enroll 330 subjects and is expected to conclude at the end of August 2020.⁶⁷ This total cost and enrollment represents a per patient cost of \$76,060, if the additional \$25,100,000 funding provided under the BARDA-Genentech agreement indeed goes to the trial.

Two other trials of tocilizumab for COVID-19 are being sponsored by the NCI. In early May the NCI launched a clinical trial of cancer patients with COVID-19.⁶⁸ During a meeting of the National Cancer Advisory Board held on April 9, 2020, James Doroshow from the NCI said that this is a compassionate use trial, but they also plan to gather some clinical data.⁶⁹ Doroshow

⁶⁴ <https://www.roche.com/media/releases/med-cor-2020-03-19.htm>

⁶⁵ In the press release about the trial BARDA provided a “\$25 million” quote, but the landing page relating to BARDA’s COVID 19 portfolio has the “\$25,100,000” quote, For both quotes, see, respectively, here: <https://www.medicalcountermeasures.gov/newsroom/2020/genetech/> and <https://www.medicalcountermeasures.gov/app/barda/coronavirus/COVID19.aspx>

⁶⁶ www.gene.com/media/press-releases/14843/2020-03-23/genentech-announces-fda-approval-of-clin

⁶⁷ <https://clinicaltrials.gov/ct2/show/record/NCT04320615>

⁶⁸ <https://clinicaltrials.gov/ct2/show/record/NCT04370834>

⁶⁹ <https://nci.rev.vbrick.com/#/videos/6fa7bd32-ff67-4c05-a674-a8372209998f>

said that they are working “in concert” with Genentech and the aim is to enroll 200 subjects. KEI filed a FOIA request, still pending, for records relating to the budget or cost of this trial.

NCI is also funding a clinical trial sponsored by Emory University, which is investigating tocilizumab for the treatment of cytokine release syndrome.⁷⁰ This is a Phase 3 clinical trial that launched in April 2020, and seeks to enroll 180 subjects. This trial acknowledges funding from P30CA138292, an NCI core grant to Emory University that has funded hundreds of projects over several years. Because this is a multi-year core grant that has funded hundreds of projects it is not possible to discern, based on the information that the NIH has made available via their Project RePORTER database, the amount of money that has been allocated specifically towards this trial. KEI filed a FOIA request for records relating to the cost of this trial, and we are still awaiting a response. It seems from the description that this trial is being conducted by the Winship Cancer Institute. In 2020 alone the Winship Cancer Institute has received thus far \$2,574,000 through the P30CA138292 grant to Emory, which likely supports several projects.

Several other trials are being conducted outside of the United States. A number of those trials are being funded by public institutions, but they are coded at ClinicalTrials.gov as funded by “other” since those institutions are neither the NIH nor other U.S. federal agencies. The University of Oxford is sponsoring the RECOVERY trial, a Phase 2/3 randomized study that is investigating several potential treatments for COVID-19.⁷¹ One of the potential treatments being evaluated is tocilizumab. Other drugs investigated in this trial include lopinavir-ritonavir, corticosteroid, hydroxychloroquine, and azithromycin. Professor Peter Horby from the University of Oxford received a £2.1 million grant from the National Institute for Health Research in the United Kingdom for this trial.⁷² A website dedicated to the trial also acknowledges “core funding provided by NIHR Oxford Biomedical Research Centre, Wellcome, the Bill and Melinda Gates Foundation, the Department for International Development, Health Data Research UK, the Medical Research Council Population Health Research Unit, and NIHR Clinical Trials Unit Support Funding.”⁷³ The trial is expected to enroll 12,000 subjects and run until December 2020.

Assistance Publique - Hôpitaux de Paris is sponsoring a randomized trial of tocilizumab that initially aimed to enroll 228 subjects. The primary outcome was need for ventilation or death on day 14. A press release about the trial reports that 129 subjects were randomized, a significantly lower proportion of patients reached the primary outcome in the tocilizumab arm.⁷⁴ The press release acknowledges that this trial received grant support from the Programme Hospitalier de Recherche Clinique of the French Ministry of Health, initiation funding from the

⁷⁰ <https://clinicaltrials.gov/ct2/show/NCT04361552>

⁷¹ <https://clinicaltrials.gov/ct2/show/NCT04381936> For more, see: <https://www.recoverytrial.net/>

⁷²

<https://www.nihr.ac.uk/news/covid-19-vaccine-and-therapies-research-boosted-by-six-new-projects-in-10-5-million-rapid-funding-round/24489>

⁷³ <https://www.recoverytrial.net/>

⁷⁴

www.aphp.fr/contenu/le-tocilizumab-ameliore-significativement-le-pronostic-des-patients-avec-pneumonie-covid

REACTing/INSERM Network via the Fondation pour la Recherche Médicale, Paris, France, and a grant from the Fondation AP-HP pour la recherche, Paris, France.⁷⁵

In Malaysia, the University of Malaya is sponsoring a Phase 3 trial of tocilizumab versus corticosteroids in hospitalised COVID-19 patients.⁷⁶ The study aims to enroll 310 subjects. The University of Malaya raised initial funding of RM450,000 “from a small group of private donors” to conduct this trial.⁷⁷ Professor Adeeba Kamarulzaman, principal investigator of the study, estimates that “a total of RM1.5 million will be needed for the trial which will be run over a period of 6 months at the 4 hospitals.”⁷⁸ Yayasan Sime Darby (YSD), the philanthropic arm of Malaysia-based multinational Sime Darby Berhad, announced in a press release the allocation of RM600,000 to cover “the costs of analyser equipment, monitoring kits and control reagents.”⁷⁹ The Ministry of Health of Malaysia is also collaborating in this clinical trial, according to public reports,⁸⁰ but it is unclear how much funding they are allocating to support the study.

In Italy, the Istituto Nazionale Tumori, Naples, a public institution, is sponsoring a Phase 2 trial of tocilizumab for COVID-19 that seeks to enroll 400 patients.⁸¹ Francesco Perrone, MD, PhD, is the principal investigator responsible for the trial. KEI reached Dr. Perrone via email, who kindly explained that the trial was conducted using the existing infrastructure for the web management of multicenter clinical trials that was created and is commonly managed at the Istituto Nazionale Tumori, Naples. Dr. Perrone directed the trial with his staff at the Istituto Nazionale Tumori.

Table 5 reports on the number of trials in 2020 funded entirely or partly by industry, NIH and “other” with correction for the BARDA funding of NCT04320615. Note, as explained above, that several trials funded by “other” received funding from public institutions outside the U.S.

Table 5. Funding of trials involving tocilizumab, Jan 1, 2020 to May 19, 2020, according to ClinicalTrials.gov

“Funded by” for tocilizumab trials registered in 2020, according to Clinicaltrials.gov, on May 19, 2020.*	Number of trials	%
All	54	100%
Funded entirely by industry	5	9.3%

⁷⁵

www.aphp.fr/contenu/le-tocilizumab-ameliore-significativement-le-pronostic-des-patients-avec-pneumonie-covid

⁷⁶ <https://clinicaltrials.gov/ct2/show/NCT04345445>

⁷⁷ <https://www.um.edu.my/news/drug-to-treat-severe-cases-of-covid-19>

⁷⁸ <https://www.um.edu.my/news/drug-to-treat-severe-cases-of-covid-19>

⁷⁹ www.simedarbyplantation.com/media/press-releases/moh-dg-lauds-clinical-trial-severe-covid-19-cases

⁸⁰

www.thestar.com.my/news/nation/2020/04/12/health-dg-trial-on-tocilizumab-to-treat-covid-19-under-way

⁸¹ <https://clinicaltrials.gov/ct2/show/NCT04317092>

Funded partially by industry	7	13.0%
Funded entirely by “other”	39	72.2%
Funded partially by “other”	8	14.8%
Funded entirely by NIH	1	1.9%
Funded partially by NIH funding	2	3.7%
Funded by BARDA	1	1.9%
Funded party or entirely by NIH or BARDA	4	7.4%

*We corrected the one trial funded by BARDA but labelled as funded by “industry.”

Table 6 reports the number of trials in 2020 that were for tocilizumab and COVID-19, and also includes enrollment data, with the correction for NCT04320615, which was funded by BARDA.

Table 6. Funding of trials involving tocilizumab and COVID-19, Jan 1, 2020 to May 19, 2020, according to ClinicalTrials.gov, with correction for NCT04320615.

“Funded by” for tocilizumab trials registered in 2020 for COVID-19, according to Clinicaltrials.gov, on May 19, 2020, with correction for NCT04320615	Number of trials	%	Enrollment	%
All	44	100%	21,740	100%
Funded entirely by industry	2	4.5%	479	2.2%
Funded partially by industry	5	11.4%	1,030	4.7%
Funded entirely by “other”	34	77.3%	19,521	89.8%
Funded partially by “other”	6	13.6%	1,210	5.6%
Any funding by “other”	40	90.9%	20,731	95.4%
Funded entirely by NIH	1	2.3%	200	.9%
Funded partially by NIH funding	1	2.3%	180	.8%
Funded by BARDA (NCT04320615)	1	2.3%	330	1.5%
Any funding by NIH or BARDA	3	6.8%	710	3.3%
Funded entirely by Roche	2	4.5%	479	2.2%
Funded partly by Roche	4	9.9%	658	3.0%
Any funding by Roche	6	13.6%	1,137	5.2%

Calculations available [here](#).

14. Additional notes on exclusivity in the United States

While a number of key patents on tocilizumab have expired, Roche may have certain patents granted or filed on manufacturing processes, as well as patents granted or pending for new indications, including treatment of the cytokine release syndrome. The process patents are challenging to assess given the lack of transparency of patent landscapes for biologic drugs.

In the United States, Roche is entitled to 12 years of exclusive rights in regulatory test data. For the initial registration of Actemra, those rights expire in January 2022. Roche has received 4 Orphan Drug designations for tocilizumab, including three that were approved by the FDA:

1. Treatment of active polyarticular juvenile idiopathic arthritis in patients 2 through 16 years of age. Exclusivity ended April 29, 2020.
2. Treatment of active polyarticular juvenile idiopathic arthritis in patients 2 through 16 years of age. Exclusivity ended April 29, 2020.
3. Treatment of chimeric antigen receptor (CAR) T cell-induced severe or life-threatening cytokine release syndrome (CRS) in adults and pediatric patients 2 years of age and older, exclusivity ends August 30, 2024.

15. Concluding comments and take-away messages

Tocilizumab was invented in Japan on grants from the Japanese government, and has been marketed since 2005 under the brand name *Actemra* and *RoActemra*. Between 2010 to 2019, Roche earned 13.644 CHF billion in Actemra sales, including 2.311 CHF billion in 2019, an increase of 7 percent over 2018.

The invention and early development and nearly all of the research on tocilizumab specifically as a treatment for COVID-19 is being funded by governments or other non-industry institutions.

Roche is currently identified as the sole funder of two COVID-19 related trials, and as a co-funder of four additional trials. In contrast, the NIH lists “other”, a category that includes non-US governments and non-profit research institutes and charities, as the sole funder of 34 trials and the co-funder of another six trials. The U.S. government is funding two trials and co-funding another. To the extent that tocilizumab is found to have utility for the treatment of COVID-19, the public sector, in the United States and elsewhere, have funded the key research.

If its efficacy to treat COVID-19 proves true, in order to ensure access to tocilizumab, governments, including in the United States, may find it necessary to undertake measures to force technology transfer to competitive suppliers, overcome liability from methods of treatment patents, and refuse patent applications relating to methods of treatment for the cytokine storm.⁸²

⁸² <https://dc.law.utah.edu/scholarship/160/>