# CYTOKINE STORM – A PATENT LANDSCAPE REPORT

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## EXECUTIVE SUMMARY

This sample report is an overview of the patent filing trends and insights from patent literature on cytokine storm (CS) related innovations. The insights presented in the report are as follows:

- Emerging companies
- Companies with M&A
- Analysis of Patent Filing Trends
- Distribution of Patent filings among
    - Academic and Research Institutes
    - Industry/Companies
    - Individual Inventors
- Top priority countries
- Top 10 academic and research institutes
- Top companies

A significant patent filing trend was observed during the years 2001, 2003-2005, 2007, 2009-2010, 2013 and 2020, which correlate with high instances of Avian influenza A (H5N1), SARS, H1N1 influenza, MERS-CoV and COVID-19 infections, respectively, focused studies and a better understanding of the human immune response seemed vital to have better control on patient outcomes.

A preliminary assessment indicates that companies, as patent assignees are leading the patent filings in this area, followed by academic and research institutes, along with a small but significant contribution from individual inventors. Most patent filings originated in the United States (US) with Alder Biopharma, Feinstein Institutes for Medical Research, University of Pittsburgh and University of Kentucky Research Foundation, notable among them.

The findings in this report are indicative and by no means exhaustive. Detailed and customized reports can be prepared based on specific interests of the requesters.

## BACKGROUND

Cytokine storm (CS) is a physiological reaction where the innate immune system causes an uncontrolled release of pro-inflammatory small signalling molecules called cytokines. Scientists, researchers and industries are trying to find effective treatments for CS, owing to its possible role in morbidities associated with SARS, H1N1 influenza, MERS-CoV and recently COVID-19.

## EMERGING COMPANIES (REPRESENTATIVE)

**About:** Enlivex is an Israel-based, venture-funded clinical stage immunotherapy company developing an allogeneic drug pipeline for immune system rebalancing - critical for the treatment of life-

threatening immune and inflammatory conditions involving hyper-expression of cytokines (Cytokine Release Syndrome). On March 26, 2019, pursuant to a Merger Agreement, Enlivex became a wholly owned subsidiary of Bioblast. In addition, upon completion of the Merger, the name of the Company changed to Enlivex Therapeutics Ltd., and the Company has been admitted for continued listing on the Nasdaq Capital Market under the new symbol "ENLV" Bioblast Pharma Ltd. (another Israel based, clinical-stage biotechnology company committed to developing clinically meaningful therapies for patients with rare and ultra-rare genetic diseases [1, 2].

**Headquarters:** Ness Ziona, HaMerkaz, Israel

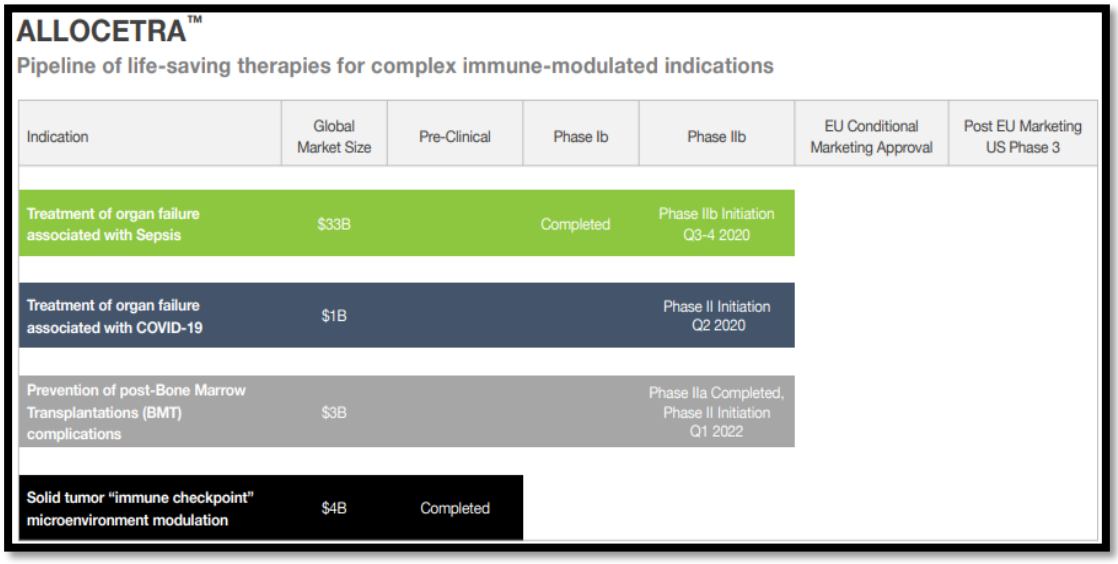
**Founded Date:** Oct 1, 2005

**Founders:** Dror Mevorach

**Website:** www.enlivex.com

**Financial Highlights:** As on Sep 30, 2020, Cash & equivalents is $36 Million. This may be likely due to the fact that the company's innovative immunotherapy candidate is still in clinical phase [3, 4, 7].

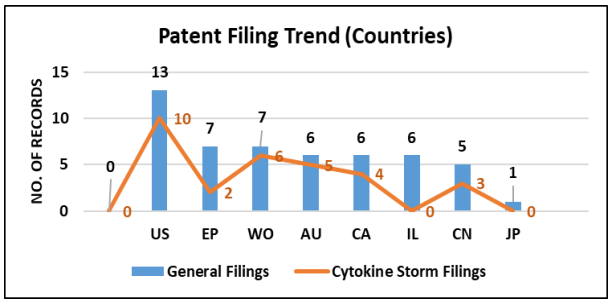
**Key Product:** Allocetra™ is an innovative immunotherapy that is being developed to rebalance life-threatening hyperactivity of the immune system, using the immune system's own natural regulation mechanisms. By intelligently engaging macrophages and dendritic cells, Allocetra™ is designed to avert cytokine storms and restores safe immune balance – without suppressing the immune system [5, 7]. Allocetra™ has received FDA & EU orphan drug designations for Graft-versus-Host Disease (GvHD) [2, 4, 6, 8].

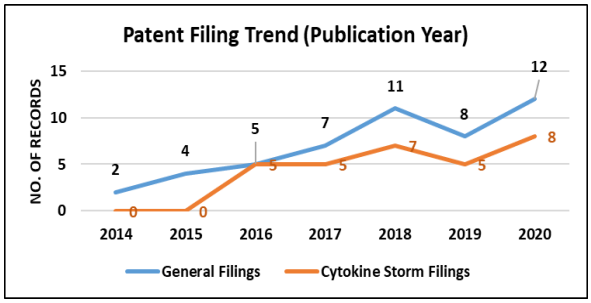



**Patent Filing Trends:** Enlivex is actively working on apoptotic monocytes useful for treating inflammation-associated diseases.

The company has filings on the compositions and methods for inhibiting or reducing the incidence of cytokine release syndrome (CRS) or a cytokine storm in a subject undergoing CAR T-cell cancer therapy. The graphs below depict Enlivex's general patent filing trends (in blue) in addition to the specific trends pertaining to cytokine storm (in orange) based on the following criteria:

- Filing Country (inclusive of all family members)
- Publication year



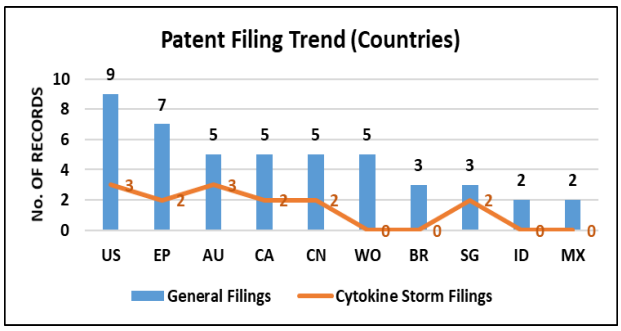

**About:** Defensin Therapeutics ApS is a Danish biopharmaceutical company spun out from Novozymes A/S in 2013. Defensin Therapeutics is based on defensin production know-how from Novozymes and more than two decades of defensin research from Prof. Wehkamp's group at the University of Tübingen. Defensin Therapeutics focuses on the development and commercialization of novel products for the treatment of diseases and conditions associated with dysregulation of the human microbiota. In April 2016, the company signed a license and R&D agreement with Dr. Falk Pharma GMBH regarding the rights to develop, manufacture and market human beta defensin-2 (Hbd 2) in Europe and Australia [9, 10].
**Headquarters:** Copenhagen N, Denmark
**Founded Date:** Oct 6, 2013
**Founders:** Peter Nordkild
**Website:** www.defensintherapeutics.com/
**Financial Highlights:** The Company's revenue amounted to DKK 11,142,900, in 2016. Current revenue figures are not available [10].
**Key Product:** Defensin Therapeutics has generated preclinical data with both oral, intranasal and subcutaneous administration of two different defensins - human beta defensin-2 (hBD-2) and Human Defensin 5 (HD5), in animal models of both IBD, asthma and metabolic syndrome. In the spring of 2016, Defensin Therapeutics entered into a clinical and marketing agreement for Europe for hBD-2 for IBD with Dr Falk Pharma in Germany. Dr Falk is establishing a defensin production technology with Lonza in Switzerland. First in human studies should commence in Q1 2019 [9, 10, 11].
**Patent Filing Trends:** The company has an impressive portfolio on modulating the intestinal microbiota by administering one or more defensins and/or GLP-1/GLP-1 analogs and methods for prevention or treatment of gut inflammation and inflammatory bowel disease.
Defensin Therapeutics has several filings on the methods for maturing the mucosal defense and rebalancing the immune system for

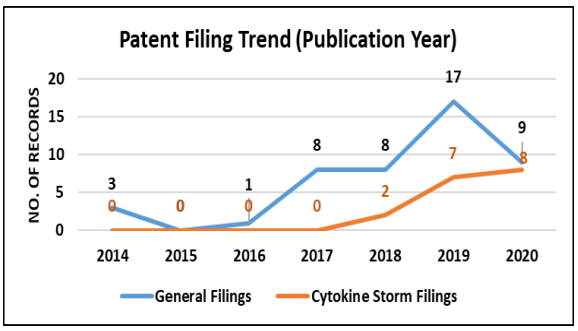
- treatment and/or prevention of acute as well as chronic graft-versus-host-disease (GVHD)
- inflammatory conditions of the lungs
- maturation of mucosal defense and gut/lung function in the preterm infant;

by preventing a cytokine storm through administration of α-defensins, β-defensins, etc.
The graphs below depict Defensin Therapeutics's general patent filing trends (in blue) in addition to the specific trends pertaining to cytokine storm (in orange) based on the following criteria:

- Filing Country (inclusive of all family members)

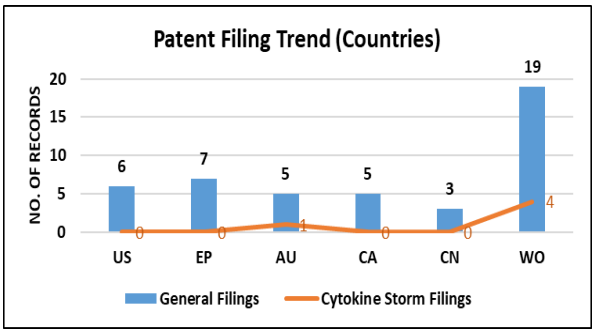
- Publication year

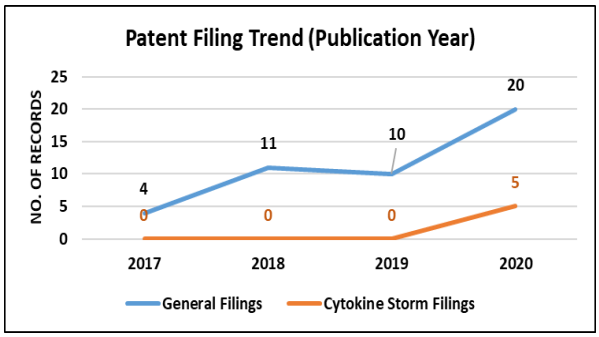



**About:** Elstar Therapeutics (venture capital-backed) brings a powerful new approach to generating multi-functional therapeutics with the potential to fulfil the promise of precision cancer immunotherapy and chart new directions in fighting immunological diseases. Armed with a platform that enables rapid production of multi-functional molecules effective in modulating a broad range of immunological processes, Elstar's goal is to develop new medicines for life-threatening cancers and serious inflammatory diseases.
**Founded Date:** 2015
**Founders:** Andreas Loew, Steve Arkinstall
**Website:** https://www.elstartherapeutics.com/
**Financial Highlights:** The company's revenue details are not available on the website.
**Key Product:** Elstar's T-cell Surface Protein (TSP) Engager avoids release of cytokines associated with cytokine release syndrome [12, 13, 14].
**Patent Filing Trends:** Key filing aspect includes multispecific molecules (e.g., multispecific or multifunctional antibody molecules) for treating autoimmune, inflammatory, and infectious diseases. Elstar Therapeutics is actively working on anti-TCR antibodies that result in lesser, minimal, or no production of cytokines associated with cytokine release syndrome (CRS).
The graphs below depict Elstar Therapeutics' general patent filing trends (in blue) in addition to the specific trends pertaining to cytokine storm (in orange) based on the following criteria:

- Filing Country (inclusive of all family members)
- Publication year



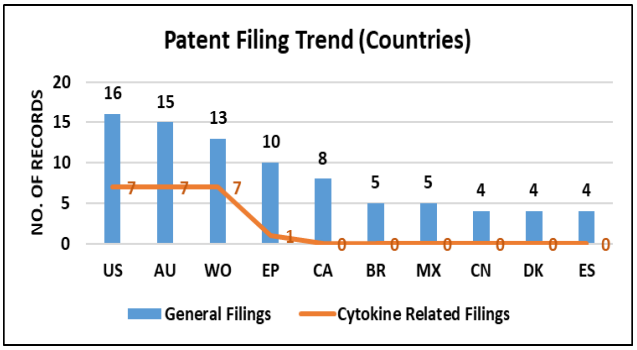



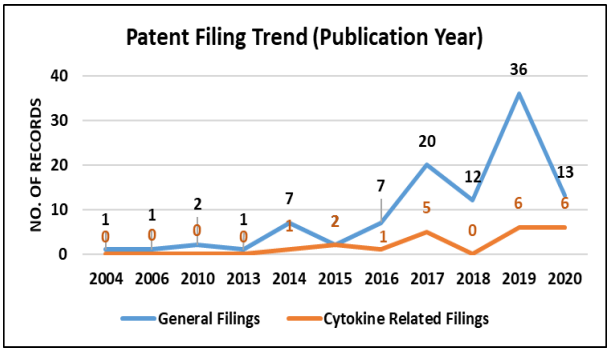
## COMPANIES WITH M&A (REPRESENTATIVE)

**Previously: OncoMed Pharmaceuticals**

**About:** Mereo BioPharma Group plc is a clinical stage, UK-based, biopharmaceutical company focused on rare diseases. On April 23, 2019, the group completed the acquisition of OncoMed, a California-based and Nasdaq-listed company, at which time OncoMed became an unlisted U.S. subsidiary of Mereo [15].
**Headquarters:** London, United Kingdom
**Founded Date:** Mar 2015 (OncoMed in 2004)
**Founders:** Denise Scots-Knight
**Website:** http://mereobiopharma.com/
**Financial Highlights:** Cash resources £56.8 million as at June 30, 2020 [15].
**Key Product:** Mereo's lead oncology product candidate, Etigilimab (Anti-TIGIT), has completed a Phase 1a dose escalation clinical trial in patients with advanced solid tumors and has been evaluated in a Phase 1b study in combination with Nivolumab in select tumor types. Mereo's rare disease product portfolio consists of Setrusumab, which has completed a Phase 2b dose-ranging study in adults with osteogenesis imperfecta (OI), as well as Alvelestat, which is being investigated in a Phase 2 proof-of-concept clinical trial in patients with alpha-1 antitrypsin deficiency (AATD) and in a Phase 1b/2 clinical trial in COVID-19 respiratory disease [16, 17, 18, 19, 20].
**Patent Filing Trends:** Mereo BioPharma is actively filing in the field of osteogenesis imperfect.
The company has several filings on compositions and methods to inhibit excessive cytokine production, with emphasis on treatment of acute exacerbations of chronic obstructive pulmonary disease (AECOPD and cancer.
The graphs below depict Mereo BioPharma's general patent filing trends (in blue) in addition to the specific trends pertaining to cytokine related filings (in orange) based on the following criteria:

- Filing Country (inclusive of all family members): The statistics is based on 10 countries
- Publication year: The statistics is based on 10 years

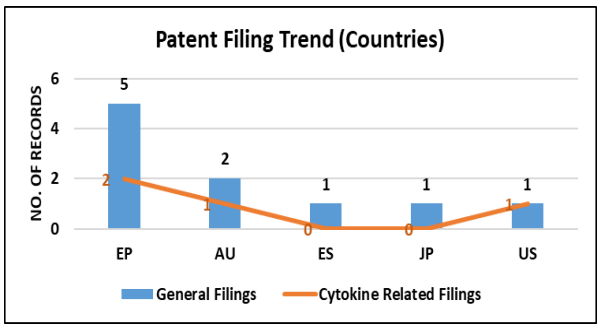


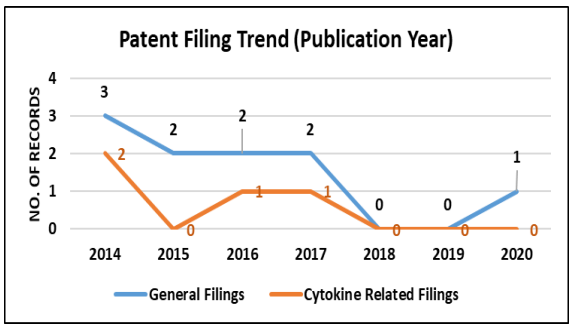



**Previously: Amorcyte**

**About:** Amorcyte was acquired by Caladrius Biosciences in 2011. Caladrius Biosciences, Inc., a cell therapy leader with a late-stage clinical program for immuno-oncology, announced the finalization of its corporate name change from NeoStem, Inc. to Caladrius in 2015 [21, 22].
**Headquarters:** New Jersey, United States
**Founded Date:** 1980 (Amorcyte Inc. in 2005)
**Founders:** Catherine Vaczy
**Website:** http://www.caladrius.com/
**Financial Highlights:** As of December 31, 2018, Caladrius had cash, cash equivalents and marketable securities of $43.1 million. Based on existing programs and projections, the company remains confident that its cash balances will allow it to fund its current business plan through mid-2020 [21].
**Key Product:** CLBS119 is Caladrius' CD34+ cell therapy product candidate targeting repair of COVID-19 induced lung damage. The FDA has authorized administration of CLBS119 under its Expanded Access IND Guidelines to evaluate the safety and efficacy of autologous, peripheral-blood-derived CD34+ cells for repair of COVID-19 induced lung damage in patients who have suffered respiratory failure [23, 24].
**Patent Filing Trends:** Several filings have been done by Caladrius Biosciences on compositions and methods using stem/progenitor cells in a therapeutic approach for treatment of acute and chronic wounds, myocardial injury, ocular diseases and cancer.
The company is focussed on approaches to regulate inflammatory cytokine cascade.
The graphs below depict Caladrius's general patent filing trends (in blue) in addition to the specific trends pertaining to cytokine related filings (in orange) based on the following criteria:

- Filing Country (inclusive of all family members)
- Publication year




**Previously: Critical Therapeutics, Inc.**

**About:** Critical Therapeutics, Inc. and Cornerstone BioPharma Holdings, Inc., a privately-held company, announced the signing of a definitive merger agreement, in 2008. Cornerstone is a specialty pharmaceutical company focused on developing and commercializing prescription medications for respiratory disorders. Cornerstone Therapeutics Inc., a specialty pharmaceutical company focused on

commercializing products for the U.S. hospital and adjacent specialty markets. In July 2003, Critical Therapeutics entered into an exclusive license and collaboration agreement with MedImmune for the discovery and development of novel drugs for the treatment of acute and chronic inflammatory diseases associated with high mobility group protein B1 (HMGB1). Chiesi is funding research on cytokine storm [25, 26, 27]. In 2014, it announced an official name change to Chiesi USA, Inc., following the completion of its acquisition by Chiesi Farmaceutici S.p.A. Critical Therapeutics, Inc. developed and discovered drug candidates with novel mechanisms of action based upon our understanding of the cytokine cascade and its role in critical care diseases.

**Headquarters:** Parma, Italy

**Founded Date:** 1935 (Critical Therapeutics, Inc. in 2000)

**Founders:** Mitchell Fink (Critical Therapeutics)

**Website:** https://www.chiesi.com/en/

**Financial Highlights:** 2019 saw overall revenues totalling €1,992.81 million, of which, €1,376.4 million were generated in Europe, €340.3 million in the Emerging Countries and €273.1 million in the United States [25].

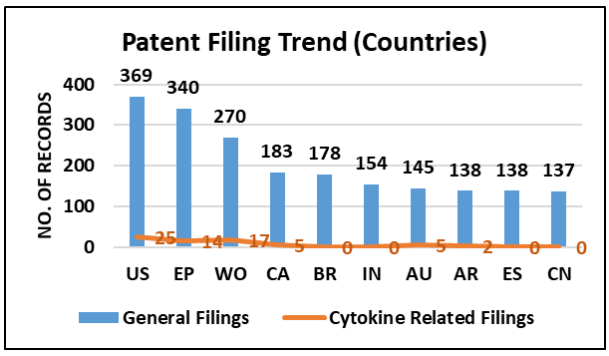
**Key Product:** Critical's asthma drug Zyflo® (FDA-approved), and Cornerstone's product Spectracef® (Spectracef is owned by Meiji and licensed to Cornerstone for sales and marketing purposes in the United States), a treatment for pathogens linked to respiratory diseases [28, 29, 30].

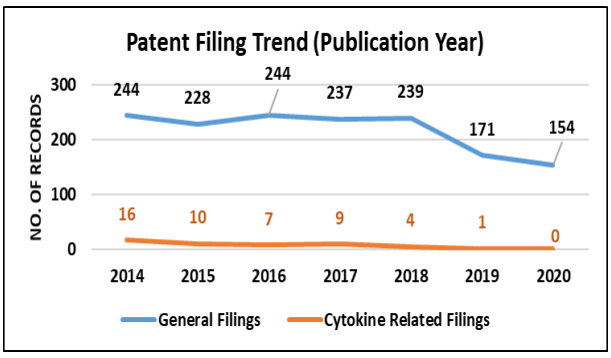
CHF6001, Roflumilast (to date, the current study is out of scope of the Chiesi policy on Clinical Data Sharing) [31, 32, 33].

**Patent Filing Trends:** Chiesi is actively filing patents in the field of management of respiratory diseases. One of the research areas of the company is inhibitors of cytokines.

The graphs below depict Chiesi's general patent filing trends (in blue) in addition to the specific trends pertaining to cytokine related filings (in orange) based on the following criteria:

- Filing Country (inclusive of all family members): The statistics is based on 10 countries
- Publication year: The statistics is based on 10 years

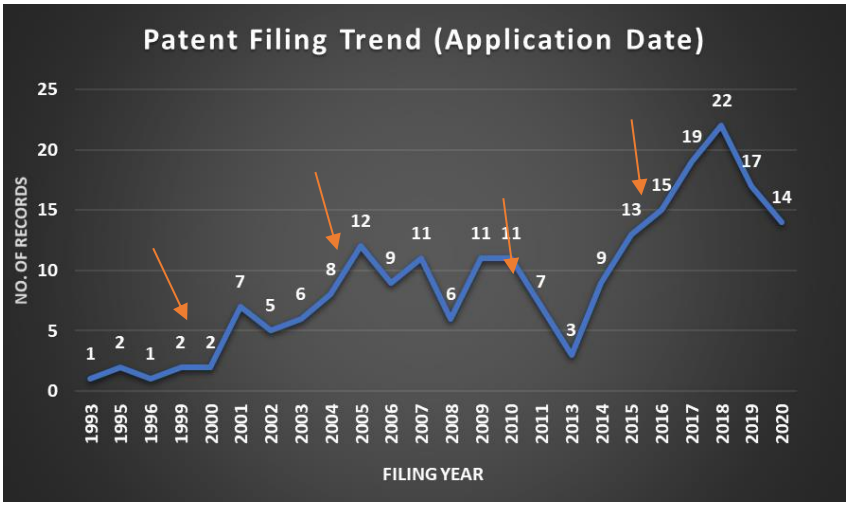



## ANALYSIS OF PATENT FILING TRENDS

We present a snapshot of various analyses performed based on patents and published applications related to "cytokine storm" and "regulation of cytokine cascade and pro-inflammatory cytokines".

The graph below depicts the number of applications filed till date related to the concept.



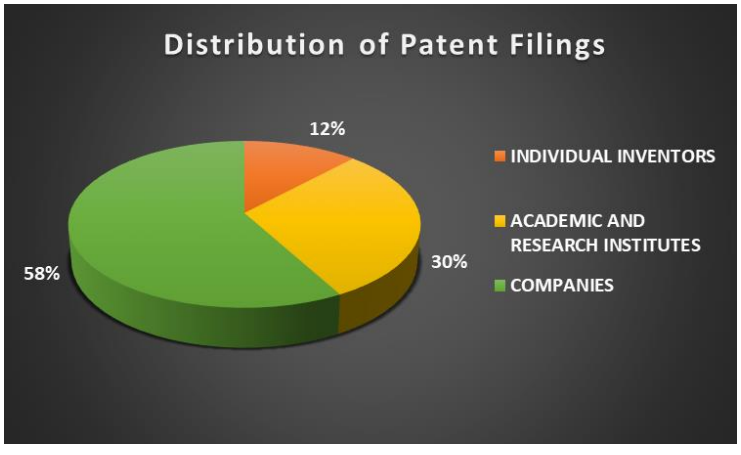

COVID-19 disease displays similarities with other viral diseases (SARS, MERS and influenza), where development of a cytokine storm signals disease escalation. There has been continued research and significant filing activity around the outbreak of these viral diseases (as indicated in the above graph): 2001, 2007 (Avian influenza A (H5N1)), 2003-2005 (SARS), 2009-2010 (H1N1 Pandemic), 2013 onwards (MERS-CoV) and 2020 (ongoing COVID-19) [34, 35]

We further analysed the records for "Distribution of Patent filings" among the companies vis a vis academia and individual inventors. The records were then categorized as top 10:

- Academic and Research Institutes
- Companies
- Individual Inventors

**DISTRIBUTION OF PATENT FILINGS**

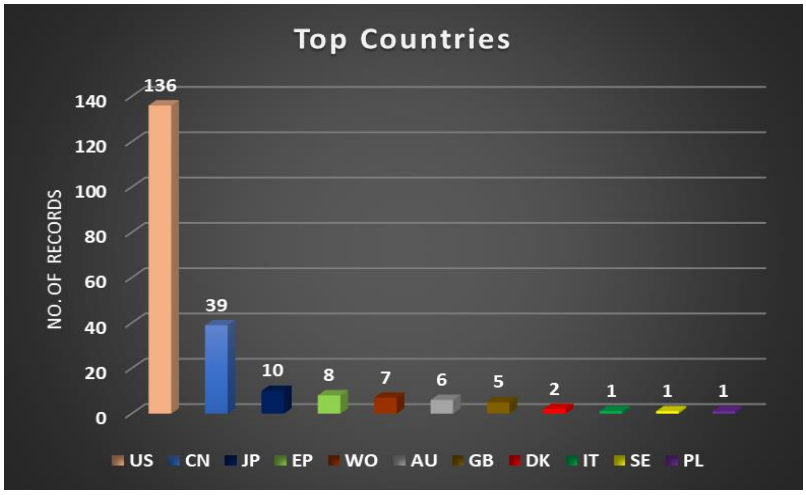
The pie-chart below displays the distribution of patent filings.




It is clear from the graph that research on cytokine storm has already generated commercial interest and many companies as patent assignees are getting involved in developing better methods and compositions to reduce or inhibit the influence of cytokine storm.

**TOP 10 PRIORITY COUNTRIES**

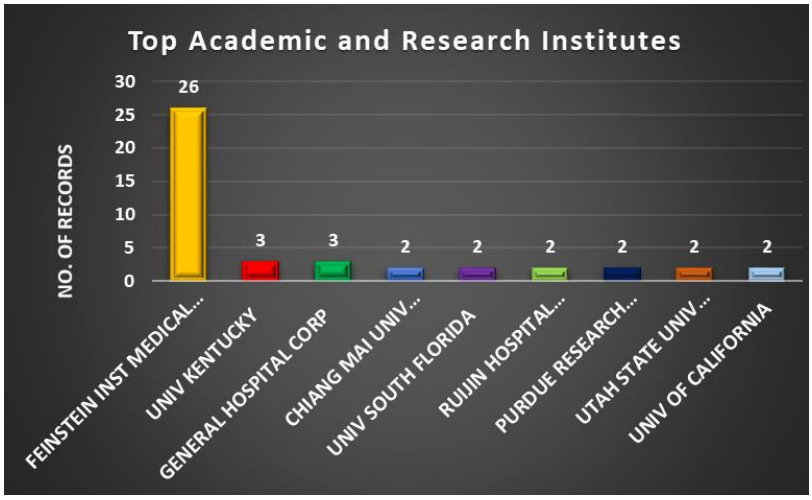
The graph below indicates the top filing countries in the field of cytokine storm.




The largest patent filings are in the US, followed by China and Japan. The most prolific research institutes, companies and inventors are based in the US.

**TOP 10 ACADEMIC AND RESEARCH INSTITUTES**

The graph below represents top assignees from academic and research institutes.



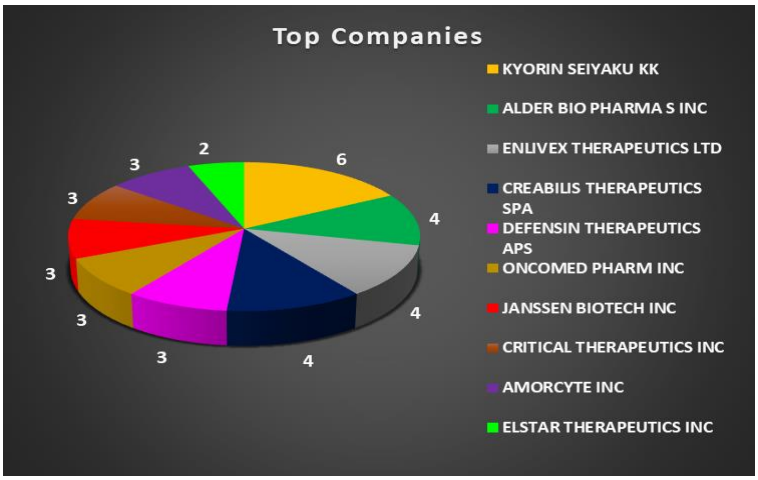

The Feinstein Institutes for Medical Research (US) have many patent applications and granted patents. The researchers have worked extensively on targeting high mobility group-1 (HMG1) to inhibit the release of the proinflammatory cytokine, or to inhibit the inflammatory cytokine cascade. There are several records on collaborative efforts of Feinstein Institutes with General Hospital Corp (US) and University of Pittsburgh (US).

University of Kentucky Research Foundation (US) has patents for use of Deltorphin and other peptides for reducing or preventing cytokine-mediated hepatic injury.

Chiang Mai University, Thailand has worked on phytochemical compositions anti-cytokine storm effect.

**TOP COMPANIES**

The pie-chart below is a snapshot of assignees from key companies involved in developing innovative technologies to combat CS.




Kyorin (Japan) has patents on "Diphenyl Sulfide Derivatives" that were found to be effective therapeutic or prophylactic agents for cytokine storms caused by influenza virus or other respiratory syndrome causing virus.

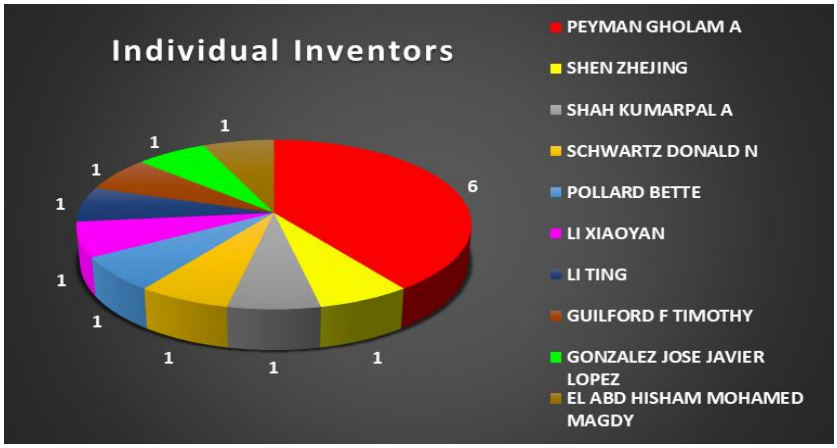
US-based Alder BioPharmaceuticals works extensively on anti-IL-6 antibodies; useful for ameliorating or reducing the symptoms of, or treating, or preventing, diseases and disorders associated with cytokine storm. Danish pharmaceutical company Lundbeck acquired Alder BioPharmaceuticals, in 2019.

Enlivex is an Israeli clinical stage immunotherapy company, which is actively working in the field of cytokine storm, particularly in COVID 19 patients.

Companies such as Defensin Therapeutics (a Danish biopharmaceutical company) and OncoMed Pharmaceuticals, Inc. (US) (now acquired by Mereo BioPharma Group (UK)) are relatively new entrants and have filed applications relating to various agents to increase an effective immune response without causing cytokine release syndrome (CRS) or a cytokine storm.

**INDIVIDUAL INVENTORS**

The pie-chart below displays assignees from individual inventors who filed CS related patent applications.




Dr. Gholam A. Peyman has worked extensively on the combination of thermotherapy and immunotherapy for preventing cytokine storm, particularly during cancer treatment. His recent publications are significant contributions during COVID19 pandemic. The invention relates to biocompatible drugs comprising nanoparticles or microparticles used as a carrier. The biocompatible drug with the semifluorinated alkane and the nanoparticles or microparticles is administered by inhalation to the patient to treat one or more respiratory tract inflammatory diseases.

**DISCLAIMER**: *This is a sample report. The patent filing trends presented in this report have been done using WIPO PATENTSCOPE database and are indicative representations of all publications (patent applications, patent grants and overlaps in some cases) as sourced from this database. The data presented in this report is not to be construed as accurate or deliberately misleading as the report is meant for general illustrative purposes only.*

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