Government funding related to the cobas Liat Analyzer PCR testing device.
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Introduction

Roche Diagnostics has several U.S. patents claiming methods and devices relating to testing that declare government funding. These patents are directed to components of their cobas Liat Analyzer, a point-of-care (POC) polymerase chain reaction (PCR) device that has not yet been authorized by the US Food and Drug Administration (FDA) for SARS-CoV-2 testing .

The cobas Liat Analyzer is similar to other POC devices manufactured by companies like Abbot and Cepheid, which are also based on the PCR diagnosis technique, but have been authorized for SARS-CoV-2 testing by the FDA.

Polymerase chain reaction (PCR) testing technique

PCR is a well-known testing technique that is currently being used by many laboratories to diagnose SARS-CoV-2. This testing technique was first conceived and patented by Dr. Kary Mullis while he was working for Cetus Corp during the 1980s.[1] In 1991 Roche acquired Cetus Corp, including rights to the foundational Mullis patents.[2] The Mullis patents have now expired.

[1] https://www.ncbi.nlm.nih.gov/pubmed/3472723
[2] https://www.nature.com/articles/35003722

A number of companies and laboratories around the world are capable of performing PCR testing. Since mid-March the FDA has given emergency use authorization to more than 20 companies and laboratories that are marketing SARS-CoV-2 testing products based on PCR.[3]

Automatization of the PCR testing technique

A trained scientist is capable of performing PCRs mostly manually.[4] However, performing PCR manually is labor-intensive, time-consuming and prone to errors. Due to this, most innovative efforts now relate to technologies that automatize and scale up the analyses of PCR samples.

Roche Diagnostics has two key instruments for PCR automatization, the cobas 6800/8800 systems and the cobas Liat Analyzer. This company also manufactures several other products that automatize parts of the PCR process, such as the cobas 4800 system which are used for sample preparation. The cobas 6800/8800 systems are fully automated modular analyzers that can run 1056 tests in an 8-hour shift.[5] The cobas 6800/8800 systems are about the size of a small vehicle and are generally used in laboratories that are authorized for performing moderate and high complexity testing. The cobas Liat Analyzer is a point-of-care device that is easy to use and is capable of processing one PCR test in 15 to 20 minutes.[6] The cobas Liat Analyzer is about the size of a shoe box and is generally used in laboratories or patient care settings. The cobas Liat Analyzer was cleared in 2011 by the FDA for diagnosing influenza.[7]

Other companies have developed similar devices. In the point-of-care field, the ID NOW by Abbott[8] and the Xpert Xpress by Cepheid performs similar PCR tests as the cobas Liat.[9]

SARS-Cov-2 emergency use authorizations for PCR point-of-care devices

On March 20 and March 27, 2020 (respectively), the Xpert Xpress[10] and ID NOW[11] point-of-care instruments received emergency use authorization from the FDA for testing SARS-CoV-2. Both of these devices were authorized for use “in patient care settings outside of the clinical laboratory environment.” These seem to be the only two point-of-care PCR devices approved in the U.S. for SARS-CoV-2.

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[3] https://www.fda.gov/emergency-preparedness-and-response/mcm-legal-regulatory-and-policy-framework/emergency-use-authorization#covidinvitrodev
[4] https://www.youtube.com/watch?v=jFl6HmcGw9Q
[5] https://diagnostics.roche.com/us/en/products/systems/cobas-8800-system.html
[6] https://diagnostics.roche.com/us/en/products/systems/cobas-liat-system.html
[7] https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K111387
[8] https://www.alere.com/en/home/product-details/id-now-covid-19.html
[9] https://www.cepheid.com/coronavirus
[10] https://www.fda.gov/media/136316/download
[11] https://www.fda.gov/media/136522/download

As of today, the cobas Liat Analyzer has not received FDA authorization for SARS-CoV-2 testing.

There does not appear to be public information available on whether Roche is currently seeking authorization to use their cobas Liat Analyzer for SARS-CoV-2 testing. Several articles have considered point-of-care devices based on PCR as one critical component of broad testing deployment,[12] and the cobas Liat Analyzer has been mentioned among the brands that could be used for such purpose.[13] For example, the cobas Liat was mentioned, among other point-of-care devices, in a recent narrative review about SARS-CoV-2 testing featured in the Annals of Internal Medicine.[14] Since the cobas Liat platform is premised on the same PCR technique as other point-of-care instruments that have already been authorized by the FDA, it seems at least feasible to leverage the cobas Liat Analyzer device for SARS-CoV-2 testing as well.

Roche said in a recent update about the pandemic that the demand for the cobas Liat Analyzer has increased "dramati[cally]," but suggests this is due to the "seasonal influenza testing."[15]

While their cobas Liat Analyzer has not been authorized for SARS-CoV-2 testing yet, on March 12, 2020 Roche received emergency authorization for a "cobas SARS-CoV-2 test for use on the cobas 6800/8800 Systems for the qualitative detection of nucleic acid from SARS-CoV-2."[16] In other words, Roche received authorization for a SARS-CoV-2 testing kit that is compatible with their large automated module also based on the PCR technique. According to the FDA authorization, this test is to be used "in laboratories certified under the Clinical Laboratory Improvement Amendments of 1988 (CLIA), 42 U.S.C. § 263a, to perform moderate complexity tests and in U.S. laboratories certified under CLIA to perform high complexity tests, by clinical laboratory personnel who have received specific training on the use of the cobas 6800/8800 Systems."[17] The SARS-CoV-2 testing services that Roche is providing appear to be based on these kits.

Research leading to the cobas Liat Analyzer was supported with federal funds

IQuum, Inc, was a diagnostics company based in Massachusetts that manufactured and commercialized lab-in-a-tube technology. It was founded in 1998 by Dr. Shuqi Chen and Keith Greenfield. IQuum stated in their old website, which is not longer available online but was captured by the WayBack Machine Internet Archive, that their "research and development has

[12] https://www.hindawi.com/journals/ijmicro/2020/8135724/
[13] https://www.labpulse.com/index.aspx?sec=sup&sub=laba&pag=dis&ItemID=800847
[14] https://annals.org/aim/fullarticle/2764737/diagnostic-testing-severe-acute-respiratory-syndrome-related-coronavirus-2-narrative
[15] https://diagnostics.roche.com/us/en/landing-pages/roche-covid-19-updates.html
[16] https://www.fda.gov/media/136046/download
[17] https://www.fda.gov/media/136046/download

been supported by Small Business Innovation Research (SBIR) - National Institutes of Health (NIH) grants."[18]

According to the NIH RePORTER database, between 2000 and 2012, IQuum received funding for 41 research projects totaling $28,952,500 in costs. All of these projects were directed to diagnostics technologies, and some specifically focused on point-of-care devices. Most of these projects name Dr. Shuqi Chen as their principal investigator. Drs. Tian Yu, Jork Nolling, David Dolinger, Martin Zillmann, Bertrand Lemieux, Zihua Wang, and Kevin Kopczynski are also listed as principal investigators in grants received by IQuum, according to NIH RePORTER.

In addition to these grants, IQuum benefited from other federal funds to develop their technology. For example, in September 2003 they were awarded a $2.46 million contract from the U.S. Army Research, Development and Engineering Command (RDECOM) at the Edgewood Chemical Biological Center (ECBC) for the development of a field-portable nucleic acid detection system.[19] In a press release IQuum stated that under this contract they "will develop the Liat Molecular Analyzer and Liat Tube, as well as specialized manufacturing devices and bioassays."[20] In July 2004 the company was awarded a $3.5 million contract by the U.S. Department of Homeland Security Advanced Research Project Agency (HSARPA) to develop a bioaerosol monitoring system for bio-defense applications.[21] IQuum explained that they were going to "apply its lab-in-a-tube platform technology to the development of the Bioagent Autonomous Networked Detectors (BAND), a 'detect-to-treat' system for round-the-clock, distributed monitoring of outdoor urban areas for bacteria, viruses and toxins."[22] In January 2005 they were awarded a $1.96 million contract from the US Army Medical Research and Material Command (USAMRMC) "to develop, test and field a system capable of bringing IQuum's proprietary lab-in-a-tube technology to bear on the diagnosis of cutaneous leishmaniasis in forward-deployed troops."[23] In March 2006 they announced two contracts with the U.S. Department of Homeland Security Advanced Research Project Agency (HSARPA) "to continue development of its sophisticated bioaerosol monitoring system for bio-defense applications," but the contract amount was not disclosed in the press release.[24] That same year the Center for Disease Control (CDC) awarded IQuum a $3.8 million contract to develop a rapid test for avian influenza.[25] Without accounting for the amounts that were not disclosed, these contracts add over $11.7 million in federal funds in addition to the $28.9 million received in NIH grants.

Table 1 below provides a list of U.S. patents in which IQuum's founder is named as an inventor. A sheet with more information about these patents is available here. Most of these patents are

[18] https://web.archive.org/web/20071219060015/http://www.iquum.com/about/partnerships.shtml
[19] https://web.archive.org/web/20050413195504/http://iquum.com/news/09_30_03_dod.shtml
[20] https://web.archive.org/web/20050413195504/http://iquum.com/news/09_30_03_dod.shtml
[21] https://web.archive.org/web/20050403234137/http://iquum.com/news/07_14_04_bd.shtml
[22] https://web.archive.org/web/20050403234137/http://iquum.com/news/07_14_04_bd.shtml
[23] https://web.archive.org/web/20050403233707/http://iquum.com/news/01_11_05_lei.shtml
[24] https://web.archive.org/web/20060617013401/http://iquum.com/news/03_29_06_band2.shtml
[25] https://www.cdc.gov/media/pressrel/r061204.htm

under their statutory term of protection, including adjustments. The last of these to expire will be U.S. patent 10,443,050, which has a 2014 priority date and is expected to live until 2034.

Table 1. U.S. patents with Dr. Shuqi Chen as an inventor, according to USPTO databases

Patent ID	Filed	Govt Rights	Title
10,443,050	6/15/2017	declared	Sample processing methods
10,022,722	4/1/2015	declared	Sample vessels
9,708,599	12/17/2014	declared	Sample processing methods
9,662,652	4/3/2012	-	Sample processing device for pretreatment and thermal cycling
9,005,551	2/7/2011	declared	Sample vessels
8,936,933	5/18/2010	declared	Sample processing methods
8,414,845	8/30/2010	-	Sample multiprocessing
8,148,116	5/2/2011	-	Sample processing device for pretreatment and thermal cycling
7,935,504	11/15/2005	-	Thermal cycling methods
7,833,489	2/25/2008	-	Fluid sample testing system
7,799,521	9/11/2002	declared	Thermal cycling
7,785,535	6/7/2005	-	Sample multiprocessing
7,718,421	2/5/2004	declared	Sample processing
7,337,072	6/8/2004	-	Fluid sample testing system
6,964,862	8/16/2004	-	Sample processing device and method
6,896,519	8/27/2002	-	Method of oral transmucosal delivery of a therapeutic agent
6,780,617	2/13/2001	-	Sample processing device and method
6,748,332	7/20/2001	-	Fluid sample testing system
6,439,889	1/19/2001	-	Teeth crevice cleaning apparatus and method of using the same
6,318,191	6/23/1999	-	Fluid sample testing system
5,656,501	6/6/1995	-	Flow cell device for monitoring blood or other cell suspension under flow

Nearly all of these 21 patents are directed to methods or devices used in diagnostics, with a couple of exceptions. Seven of them declared government funding. The grants listed in the patents that declared government funding are: R44HL067568, R43HL067568, R43AI055079, R43HL074689, R43HL065867. These grants were awarded to IQuum and named Shuqi Chen or Bertrand Lemieux as principal investigator. The government interest statements for some of these patents also disclose contract number DAAD13-03-C-0086, awarded by the Department of Defense.

In August 2011 IQuum received regulatory clearance for its point-of-care diagnostics device to detect and discriminate between influenza A and B, then branded as *Lab-in-a-tube* or *Liat*.[26] IQuum described this device as an "automated sample-to-result multiplex real-time RT-PCR assay."[27] In a press release announcing this regulatory clearance IQuum acknowledged that "[t]he development of the Liat Influenza A/B Assay was partially funded and supported by grants from the National Institute of Allergy and Infectious Diseases, National Institute of Health."[28] In 2015, the cobas Liat System was Clinical Laboratory Improvement Amendment (CLIA) waived by the FDA as a moderate complexity test for use outside traditional laboratory facilities.

Roche acquired IQuum, including rights to the Chen et al. patents

In April 2014, Roche announced the acquisition of IQuum for $450 million.[29] At the time of this transaction the Liat was the main product commercialized by IQuum. The press release suggests that Roche's key motive was to acquire "access to IQuum's Laboratory-in-a-tube (Liat) System, which enables healthcare workers to perform rapid molecular diagnostic testing in a point of care setting, closer to patients and with minimal training."[30] With this acquisition Roche obtained rights to patents assigned to IQuum, including those that name Chen as an inventor.

Roche Diagnostics has a website listing patents that relate to products they currently market.[31] It appears that this website was last updated in 2015. Several of these patents are related to the Liat instrument, according to the website. Four of the cobas Liat patents listed there, U.S. patents 7,718,421, 7,799,521, 8,936,933, and 9,005,551, disclosed government funding.

[26] https://www.accessdata.fda.gov/scripts/cdrh/devicesatfda/index.cfm?db=pmn&id=K111387
[27] https://web.archive.org/web/20121129052259/http://www.iquum.com/news/11_08_23_faba.shtml
[28] https://web.archive.org/web/20121129052259/http://www.iquum.com/news/11_08_23_faba.shtml
[29] https://www.roche.com/media/releases/med-cor-2014-04-07.htm
[30] https://www.roche.com/media/releases/med-cor-2014-04-07.htm
[31] https://web.archive.org/web/20200414012052/https://diagnostics.roche.com/us/en/about-us/patents.html