A Q&A with David Galas:
Developing a Test for COVID-19

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You may have seen the recent news about the sudden availability of a new test to determine if one is infected by the coronavirus (COVID-19). This test, which can give a positive result in five minutes or a negative result in twelve minutes, results from work led by my good friend David Galas. Rapid and wide-spread testing for coronavirus will be an essential tool for getting our country and the world back to some sense of normalcy and for mitigating the catastrophic impacts we have experienced during this pandemic when future novel viruses arise. Here are several links to articles addressing the need for testing:

- https://fivethirtyeight.com/features/why-we-still-need-to-test-widely-for-coronavirus
- https://a16z.com/2020/04/02/coronavirus-tests

The following interview with David provides his description of how and why this work began 20 years ago and how research initiated for one purpose often finds diverse application in different fields.

David started his education at the Air Force Academy, finished at UC Berkeley, and in the middle flew fighter jets. David has held many positions during his distinguished career including leading the Department of Energy's contribution to the Human Genome Project from 1990-1993. I think you will find his story of the development of this test fascinating and timely. It illustrates that the progress from an idea, to initial proof of concept, to final deployment, takes many skills.

Quest: How did your involvement in development of this test begin?

DG: Around the year 2000 there was a growing concern in the world, and particularly in our country because of a number of incidents, over infectious agents that could be used by adversaries or terrorists, so-called biothreat agents, bacteria and viruses. Anthrax was the primary agent in the news, but the concern was widespread.

Quest: What motivated the need for a new approach?

DG: At that time the major method for detection of the nucleic acid genomes of infectious agents, DNA or RNA molecules, was the well-known Polymerase Chain Reaction[1] (PCR) method which led

to the 1993 Nobel Prize in Chemistry for its inventor, Kary Mullis. PCR required, among other things, a machine that could rapidly cycle the temperature of the reaction test tube up and down many tens of times. This meant that overall, while PCR was reliable and powerful in being able to amplify these molecules many thousand-folds, it was ill-suited as a means of rapid detection of threat agents, and posed significant problems as a portable and flexible test system.

Quest: How did your involvement in development of this test begin?

DG: At this time my research group at the Keck Graduate Institute (KGI) in Claremont, CA was working on various aspects of nucleic acid analysis. We were initially motivated by other problems, particularly genetic variant analysis, but we recognized the wide range of applications of sequence specific amplification methods.

Quest: Can you describe the scientific process you and your group went through during the course of development?

DG: In the course of that work we had a few ideas about developing a new kind of nucleic acid amplification reaction that could take place at a constant temperature (isothermal amplification). The ideas were appealing for many reasons in that they promised to allow the elimination of the usual temperature cycling machine as part of an analysis system, and possibly several other advantages.

I recognized that if we could make this work there were many potential applications, well beyond genetics and bacteria and virus detection. After some brainstorming and many experiments, we hit upon an entirely new way of amplification, which was isothermal and used known enzymes of a different kind than were used for PCR. The reaction we first devised, which I called EXPAR (Exponential Amplification Reaction) was shown to be able to amplify a specific DNA or RNA sequence 10^6-10^7 -fold within minutes.

Quest: How did this early work proceed after the initial proof-of-principle was demonstrated?

DG: The idea and initial results were promising enough for me to initiate a grant request to Defense Advanced Research Projects Agency (DARPA), which at the time was specifically interested in technologies for detecting biothreat agents. DARPA liked the proposal and funded my laboratory to work on the technology ideas and to see if it could be applied to practical, rapid bacterial detection. Continued work under this grant confirmed more technical characteristics of the reactions and triggered two immediate actions. First, I founded a company to develop and commercialize the technology. This was Ionian Technologies Inc. which licensed the patent applications from KGI, and second, we wrote up the work for publication in the scientific literature.

Quest: What were some of the challenges?

DG: Work continued both in my laboratory and at the company and shortly thereafter an annoying and interesting phenomenon was observed. If the reaction was allowed to continue for long enough the background signal increased and limited the sensitivity of the detection. It is interesting that several other groups around the world have worked directly over the past decade or so on trying to understand this background effect and on reducing or eliminating it. This problem was critical for practical applications, since the tests would need to detect very small numbers of molecules, and with significant background it would be unreliable to try to tell the difference between the signal from small numbers of bacteria or viruses and the background signal which resulted even in the absence of any bacteria or viruses. A modified form of the reaction (EXPAR2) was developed and tested by Ionian Technologies against practical detection problems. These application experiments showed that EXPAR2 worked extremely well and was capable of detecting very small number of specific DNA molecules in a small volume of sample (10 to 100 molecules). This work proceeded and much work was done to develop practical assays for specific test "bugs."

Quest: Can you describe the process that lead to commercialization?

DG: Ionian Technologies worked on a number of commercial applications for the technology including these: disease diagnostics for a range of infectious diseases, detecting GMO genes in corn and other crops, food contamination detection, and environmental applications. While I left KGI in 2005 to move to Seattle and Ionian Technologies moved to San Diego, I remained chairman of the board of the company, and started a new research group in Seattle focused on different topics. The work at Ionian on applications of EXPAR2 was all proceeding well, and in 2009 the company began discussions about possible acquisition with Alere, Inc. which was negotiated and was completed in 2010. At that point Ionian was working on a number of tests including for flu A and B. Alere was very interested in having their newly acquired subsidiary move the flu test forward, and so it was done and was approved both in Europe and by the US Food and Drug Administration. In addition, the Department of Health and Human Services authorized its use in any approved laboratory, hospital or doctor's office. This last step is very important for the commercial success of a test like this, called point-of-care (POC), and also is medically very important. Subsequently two other commercial product tests were likewise approved, a Strep A test, and an RSV test (respiratory virus, common in children and adults), all were based on the EXPAR2 reaction, and the commercial success of the acquisition by Alere was rapidly well validated. I should mention here that experience in the company has showed that once the sequence (DNA or RNA) of the target agent is known the team could usually generate an assay and do clinical trials (given the availability of patients and samples) on a new test within two or three months.

Quest: And finally, how did this work end up leading to Abbott Laboratories producing of rapid coronavirus detection?

DG: Some years later Alere was acquired by Abbott, the large diagnostics and pharmaceutical company, in a legally contentious transaction. Thus, Ionian Technologies became part of Abbott and the technology itself and the three commercial tests were now Abbott's.

It was hardly a surprise to me when it was announced by Abbott that a coronavirus test had been developed and approved a few days ago. Since the sequence has been known for a few months the timing was about right, given that an effort was launched shortly after the sequence became known. While not unexpected, this outcome is, of course, gratifying to all of the people involved, from my original research group at KGI, to the Ionian Technologies team, some of whom surely worked on the coronavirus test.

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1. https://en.wikipedia.org/wiki/Polymerase_chain_reaction