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Custom Oligos: Is Screening for Bioterrorist Threats Possible?

by Richard McDonald, J.D., PH.D.

At first glance, the idea of commercial suppliers screening custom oligonucleotide orders for potential biosecurity threats seems like a great idea, as one can develop complex algorithms (i.e., bioagent screening algorithmic software) to determine biosecurity threats. However, what seems good on paper (i.e., an academic answer), in the real world is too narrow and misguided to work.

Like DNA sequences, music notes have a wide range of possibilities. Depending on how those notes are expressed and articulated, the notes can be part of classical, rock & roll, hip-hop, country, or religious music. While the notes can mean something spiritual to one group, those same notes can signify "rock and roll all day and party all night" to others depending on how the notes are played. Similar to music notes, DNA sequences have a wide range of possibilities depending on how they are used. Although it is true we can develop the best complex algorithms in order to determine biosecurity threats, this proposal has four inherent flaws that cannot be solved.

The first fundamental flaw in suppliers screening custom oligonucleotides is the inability to fix false-positives and false-negatives stemming from its sequence fragment analyses. For example, it is possible for an oligonucleotide supplier to issue a bioalert to the appropriate government agency from a short biological benign sequence requested by a diabetes type I or a *C. elegans* researcher because its profile "fits" a bioagent profile. In this situation, the issue of a false-positive arises. Invariably, that bioalert could be leaked to the press, and that is usually enough (*Just Cause*) for some to destroy the career of the diabetes type I/*C. elegans* researcher. Similarly, an inherently benign microbial sequence can be modified post-oligonucleotide supplier synthesis (e.g., by site-directed mutagenesis) to a bioagent on the government's list. In this situation, the issue of a false-negative arises. Would the supplier screening custom oligonucleotides then be held liable for failing to detect that bioagent threat? These scenarios are real, to include the more complex issue of altering benign microbial genetics post-oligonucleotide supplier synthesis that causes symptoms related to another biological agent (i.e., genetic mimicry) or that causes symptoms to appear later than usual (i.e., genetic masking) (1). No reliable bioagent screening algorithmic software can be developed that has sufficient safeguards to prevent such false-positive and false-negative scenarios.

Second, the idea of commercial suppliers screening custom oligonucleotide orders for potential biosecurity threats implies that the algorithms developed will be based on researchers not cross-talking with others in unrelated fields. For example, the possibility of the government investigating a researcher when the researcher requests custom oligonucleotides for diabetes type I research purposes, but the sequence requested is for the coxsackie virus is likely. In this theoretical example, this type of cross-field fertilization would seem appropriate for the researcher; but for the government investigators it may not be considered appropriate. Taking solutions from one field of study and applying it to another is not unusual. Developing a useful one-round PCR program in the development of a full-length HIV-1gp160 clone from a sea urchin gene PCR protocol (2) may trigger an alert with any algorithmic software program. Insight, experience, gut feeling, or whatever one calls it, gives an edge to some, as innovative science [and medicine] begins where textbooks end. The problem then is explaining to authorities the kind of scientific logic without having data. How does one convince authorities that an unusual PCR protocol loosely based sea urchin gene may work on HIV-1 isolates without any direct, or at least applicable, data?

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TV Shows Featuring Science

What are your thoughts about TV shows that feature characters conducting some type of science? (e.g. House, Breaking Bad, Bones, etc.)

- TV shows about science are quite enjoyable to me.
- TV shows about science make a lot of errors with regards to the scientific information in them.
- I don't like to watch anything about science when I'm not at work.
- TV shows about science make science seem more glamorous than it really is.
- Most of the time, TV shows about science portray scientific concepts accurately.

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Lack of applicable data is also one reason, of twenty-one, why good ideas on grant applications are not funded. Science is not an exact science, and sometimes ideas (and solutions) are developed or found in other fields of study. Without real data, criticism of any idea is easy to do, just as it is easy from a legal viewpoint to second-guess any medical outcome. No reliable bioagent screening algorithmic software can be developed that takes into account the types of cross-field fertilization existing among scientists.

Third, the idea of commercial suppliers screening custom oligonucleotide orders for potential biosecurity threats implies that the algorithms developed will be based on the assumption that only certain microbial profiles--those on the government's biothreat list--pose biothreats. Just as it was incorrectly assumed that bioagents, such as *Bacillus anthracis*, could only be delivered by planes or rockets, so is the assumption that only government-restricted microbes are problematic. The anthrax letters showed that bioterrorism can be low-tech, and it showed that a bioagent does not have to cause thousands of deaths to be considered problematic. As with dirty bombs, disease outbreaks with common microbes can result in fear, confusion, and economic problems rather than thousands to millions of deaths. For example, the biodisruption of an industry, such as the milk and cheese industries, is possible from a microbe not listed on the government's bioagent list. The milk and cheese industries could be disrupted (and ultimately destroyed) with *Staphylococcus aureus*, yet it is not a government-listed bioagent. *Staphylococcus aureus* is already a common contaminant source in milk and milk products. In addition, 10% to 40% of people infected with this bacterium are asymptomatic carriers (3,4,5,6). Like *Staphylococcus aureus*, *Salmonella typhimurium* is not considered a bioagent by the government, yet it was sprayed on salad bars making many sick (7). Fear and economic problems stemming from a microbe are real, just as non-vaccinees traveling overseas returning with a microbe creating health-related economic concerns (8). With common, potentially non-lethal microbes, the death rate may be close to zero, but the biodisruption any-sized industry or treatment of the sick does make an economic impact statement. No reliable bioagent screening algorithmic software can be developed that takes into account the threat--medical or economic--from the more than 10,000 microbes that are not on the government's bioagent list.

The fourth and perhaps the most fundamental flaw in the custom oligonucleotide order screening is that it does not take into account the many labs that have in-house oligonucleotide synthesizers, and consequently do not need a commercial supplier for their oligonucleotides. In addition, synthesizers can be purchased easily from primary or secondary markets. In either situation, any gene or DNA fragment can be synthesized and thus bypassing any commercial custom oligonucleotide supplier. Taking it a step further, the idea of then banning the sale of synthesizers and confiscating synthesizers in labs forcing researchers to order only through government-approved commercial suppliers is nonsensical. This creates a very long list of legal issues, from *Probable Cause* to a violation of the Racketeer Influenced and Corrupt Organizations Act (commonly referred to as the RICO Act) (9,10). The Patriot Act, though useful, is not a blanket Act that supersedes all laws in the U.S. [this is testable in courts, but like anything legal, heavily dependant on who does the arguing], paralleling legal arguments with gun, automotive, alcohol, and plane industries for example, on product liability uses in perpetuating crimes or the misuse of them (11,12,13,14,15,16).

Just as musical notes are not inherently unsound, genetic sequences are not inherently biological threats. Bioterrorism by its nature is dynamic, that is, it is a multi-threat weapon that cannot be boxed-in neatly, as theoretical solutions can be in a PowerPoint presentation. However, bioterrorism countermeasures should be multi-tech, both low- and high-tech, but applicable in the real world. The idea of a supplier screening custom oligonucleotide orders for potential biosecurity threats is shortsighted beyond an academic interest, and in no way parallels airport security measures, as qualitative differences exist between the two. This includes the overly simplistic view of "wishful thinking" or "doing something is better than nothing." No compelling justification exists, even in today's environment of heightened public scrutiny, for a supplier to screen custom oligonucleotide orders for potential biosecurity threats because it fails to do what is designed to do...it cannot screen custom oligonucleotides orders for potential biosecurity threats properly in the real world.

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GenoVar Bioscience
22963 California St.
St. Clair Shores, MI 48080-2503 USA

voice mail/fax: 586.776.4616
mcdonald@scientist.com
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