TWN Third World Network
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Briefing Paper 81

December 2015

Synthetic biopiracy gets real with Inovio's deceptive influenza patent claim

by Edward Hammond

US biotech firm Inovio Pharmaceuticals and its partner the University of Pennsylvania ("Penn") have laid patent claim to a key vaccine-making piece of H7N9 influenza virus, an emerging kind of influenza that is thought to be deadly in about 20% of cases, and which is considered to be a pandemic threat.

While it remains to be seen if the recently published patent application will be approved, the way in which Inovio and Penn have made their claim confirms fears that companies will use synthetic biology as a means of committing biopiracy.

The patent application (WO2015023461, published 3 September 2015) covers a specific variant of an influenza gene called HA, which codes for the protein hemagglutinin. It claims the genes as a sequence and in its physical form, i.e., as a nucleic acid. The patent application goes to lengths not to divulge that the HA gene it claims is, in fact, the same as that of an H7N9 virus that was collected from a human victim in China in 2013.

Instead of explaining that they are claiming a gene of Chinese origin, Inovio and Penn present a sequence and a synthesized version of that sequence, which they label as "synthetic". By claiming that the sequence and gene are synthetic, rather than copies of a natural isolate, Inovio and Penn appear to be trying to avoid obtaining prior informed consent from China and sharing benefits they derive from the gene's use.

The case shows how real the fears are that gene synthesis and synthetic biology will be put to the purpose of biopiracy. For years, critics have raised the concern that companies would use synthesis of gene sequence data

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(GSD) to copy valuable genes from nature, and then try to evade access and benefit-sharing obligations by claiming that the copies are not subject to the benefit-sharing rules found in the Convention on Biological Diversity and its Nagoya Protocol. And, as may be particularly relevant in this case, the WHO Pandemic Influenza Preparedness Framework or, for certain agricultural genetic resources, the International Treaty on Plant Genetic Resources for Food and Agriculture (ITPGRFA).

If patent claims like Inovio and Penn's are allowed to stand, then synthetic biology could undermine decades of development of the access and benefit-sharing approach for biodiversity, a paradigm that first took treaty form in the Convention on Biological Diversity, signed at the 1992 Rio Earth Summit.

With costs of gene sequencing dropping dramatically, ambitious projects such as the Diversity Seek ("DivSeek") initiative are springing up worldwide to sequence and database the world's microbial, plant and animal genes. These genes have uses in a myriad of food, pharmaceutical and industrial products. If access to this gene sequence data is not governed by agreements that implement benefit-sharing obligations, then biodiverse developing countries will miss out on benefits due to them, and the access and benefit-sharing (ABS) system could be undermined, destroying incentives for biodiversity conservation and sustainable use.

Inovio's deceptive failure to properly identify its copy of the influenza gene from China in its patent application was uncovered in an unlikely way. While the US Patent and Trademark Office (USPTO) and other Northern patent offices have become notorious for permitting biopiracy, leading to demands from developing countries for mandatory disclosure of origin for genetic resources claimed in patent applications, in this case a USPTO patent examiner took the step of comparing the allegedly synthetic gene sequence claimed by Inovio and Penn against sequences found in online databases.

The patent examiner found that Inovio's "invention" (SEQ ID:40 in the application) is a copy of the HA gene of a virus called A/Zejiang/DTID-ZJU01/2013 (Written Opinion of the International Searching Authority, 7 July 2015).

The Zejiang virus was collected from a male H7N9 victim in China on 3 April 2013. As all researchers are encouraged to do with novel human influenza viruses, Chinese scientists shared the virus' sequence in an international database eight days later (Genbank: KC885956). Shortly after posting the sequence, the same Chinese researchers described the virus in a publication in the British medical journal *Lancet* (2013 Jun 1;381(9881):1916-25).

On 6 August 2013, less than four months after the sequence was posted, Inovio claimed it and the gene it encodes in its patent application for an influenza vaccine, describing the gene as "synthetic" and without identifying its Chinese origin.

Pennsylvania-based Inovio is funded by the US military and the US health ministry, and has a market capitalization of nearly $500 million. Inovio has other vaccines in development, including for Ebola and MERS. It has research collaborations with Roche, GeneOne (Korea), Penn and others. Some other Inovio patent applications appear to use the same tactic as the influenza application, labelling gene sequences of pathogen strains from nature as "synthetic" without disclosing their specific origin.

Synthetic biopiracy is an issue that is rising on the international agenda. Separate committees of the Convention on Biological Diversity, World Health Organization and ITPGRFA[1] are all currently considering the access and benefit-sharing implications of gene sequence data and its synthesis.

In each case, experts envision a future in which the need for physical access to biodiversity is at least partially replaced by synthetic biology, specifically, the ability to sequence, digitally

transmit, synthesize and claim proprietary rights over valuable genes. These capabilities are comparatively well-developed for small organisms, such as many viruses, that have short genomes.

The increasingly easy process of gene synthesis from gene sequence data poses challenges to ABS because use of this data is hard to track without proper data access agreements, and because ABS obligations are typically implemented through the use of material transfer agreements that are linked to physical – not digital – movement of biodiversity samples.

In a related development, the General Assembly of the World Intellectual Property Organization has recently approved a renewal of negotiations aimed at making it mandatory for patent applicants to disclose the origin of genetic resources they claim. This effort to address broader biopiracy issues should also be very relevant to solving the problem of synthetic biopiracy, and clarify that the origin of genetic resources claimed in patent applications must be divulged, including when the resources are generated from sequence data.

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Endnote

1. These are the CBD Ad Hoc Technical Expert Group on Synthetic Biology, the Advisory Group of the WHO Pandemic Influenza Preparedness Framework, and the ITPGRFA Working Group to Enhance the Functioning of the Multilateral System.