Intellectual Property Rights Series 12

Some Intellectual Property Issues Related to H5N1 Influenza Viruses, Research and Vaccines

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Third World Network

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CONTENTS

NOTE

This paper was first prepared in July 2007 and updated in September 2008.

Country Codes

AT – Austria
AU – Australia
BE – Belgium
CA – Canada
CH – Switzerland
CN – China
CZ – Czech Republic
DE – Germany
FI – Finland
FR – France
GB – Great Britain
HU – Hungary
IL – Israel
IT – Italy
JP – Japan
KR – Republic of Korea
NL – Netherlands
SE – Sweden
SG – Singapore
UK – United Kingdom
US – United States of America

1 Introduction

A DRAMATIC rise in international patent applications related to influenza is underway. This includes patent applications covering the virus itself, vaccines, treatments, and diagnostics. As recently as 1993, years passed with little or no such patent activity. In 2007, however, 54 international (Patent Cooperation Treaty) patent applications were filed on influenza vaccines alone, making it the largest year on record. World Intellectual Property Organisation (WIPO) data indicates that influenza vaccine patent applications in 2008 are on track to meet or exceed those in 2007.

Some patent applications cover genes and smaller pieces (sequences) of H5N1 and other influenza virus strains and techniques for their use. Some key new technologies that are in use or possibly destined for use in future vaccines, such as reverse genetics, are under patent control. Some other influenza vaccine technologies, such as adjuvants and cell culture methods, are highly proprietary. These are used in both seasonal and pandemic vaccine production.

The most important patent claims related to pandemic influenza probably haven't been published, or even filed, yet. What are most important are the worrying trends and kinds of claims being lodged. These indicate a near-term (and long-term) future in which H5N1 strains and all manner of technologies related to using them in vaccines will be patented, making it more difficult for governments to prepare for a pandemic.

The ultimate value of the currently claimed sequences and technologies is uncertain, but if any prove critical to combat a pandemic, it may be enormous. If a particular sequence, vaccine construction, adjuvant or cell culture process is uniquely advantageous to producing an effective pandemic vaccine, then access to that technology may be mandatory for protection of public health. With the dramatic upswing in patent activity, these concerns will steadily increase.

The recent rate of growth of flu vaccine patent applications that make claims specifically on H5N1-type influenza has surpassed that of influenza vaccine claims in general. Some of these have been under provisional claim for some years; but are only coming to light now. Some increase in patents is arguably to be expected given rising concern about H5N1 and renewed interest in vaccines from major pharmaceutical companies, not only for influenza, but for 'biodefence' and (often only from the North's view) emerging infectious diseases.

There are, however, additional explanations. There are practical difficulties and uncertainties around producing H5N1 vaccine with reassortment techniques and egg-based technologies in use for decades. These include, for example, difficulty growing avian strains in eggs as well as concern about the availability of eggs in the event of a pandemic. These issues are contributing to the emergence of new techniques that are vying to replace older ones. Not all of these new technologies are proven and certainly not all are widely available.

Thus, while egg-based flu vaccines are not likely to disappear soon, the business of influenza vaccine production is well into a technological transformation. Many patent claims are accompanying this transformation as companies seek to position themselves to profit in a changing technological environment. Related to these new proprietary technologies, such as reverse genetics and cell culture systems, there has been a wave of influenza-related corporate takeovers and technology deals inked in the last three years.

In addition, as concern about H5N1 grows, increasing amounts of public funds in the North are being funnelled into a biomedical research and development (R&D) system that is predicated upon and incapable of functioning without patents. Thus some key government players in the World Health Organisation's Global Influenza Surveillance Network (WHO GISN) are fuelling the patent surge and, in fact, are politically and legally obligated to encourage such claims because they are an integral component of their health systems.

Together, these developments are resulting in a much more complex and limiting field of intellectual property claims than has ever before existed for influenza vaccine. And it is rapidly getting worse.

2 Trends in International Patent Application Activity Related to Influenza Vaccines, Treatments, and Diagnostics

TO view overall trends, we conducted searches of the World Intellectual Property Organisation (WIPO) international patent application database in September 2008. We searched for patent applications with the international classification A61K 39/145, the designation for human and animal vaccines for influenza viruses (Orthomyxoviridae). Among those applications, we also searched for those that specifically mention H5N1 in one or more patent claims. Finally, we searched for H5N1 claims in seven different patent classifications - those for medicines, vaccines, microbes, peptides, nucleic acids, and immunoassays.

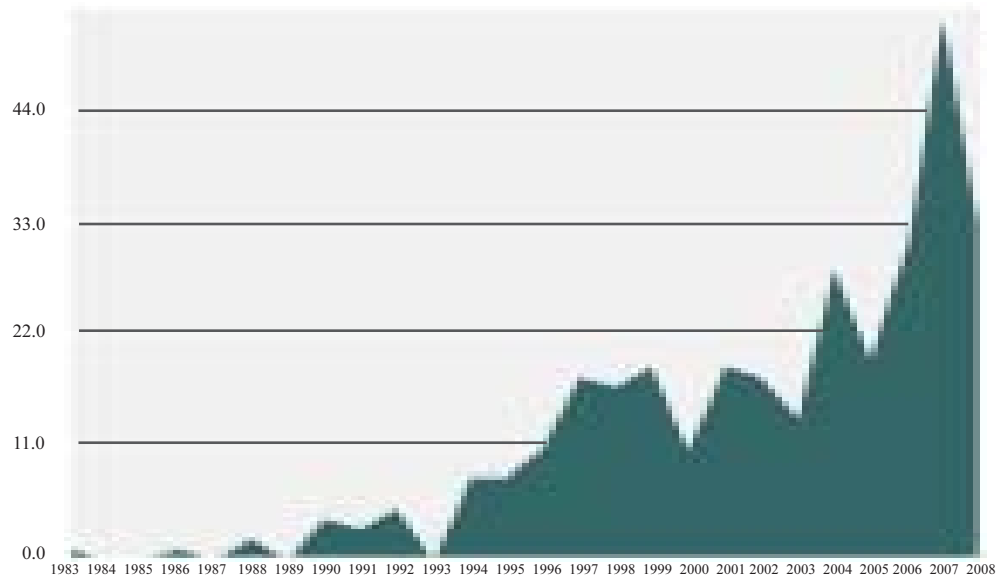
We excluded patent applications for items such as 'functional foods' and related quasi-medicinal products of types that are unlikely to be relied upon by public health authorities in the event of a pandemic.

The following pages of this chapter provide graphical representations of the results.

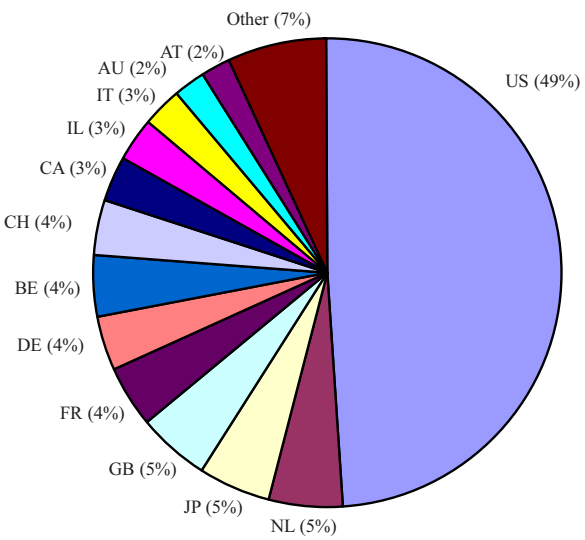
PCT PATENT APPLICATIONS FOR INFLUENZA VACCINES (1983-Sept. 2008)

PCT Classification A61K 39/145 (Orthomyxoviridae). Source: WIPO/PatentScope

Number of Applications by Year (326 total)



Patent Applicants by Country



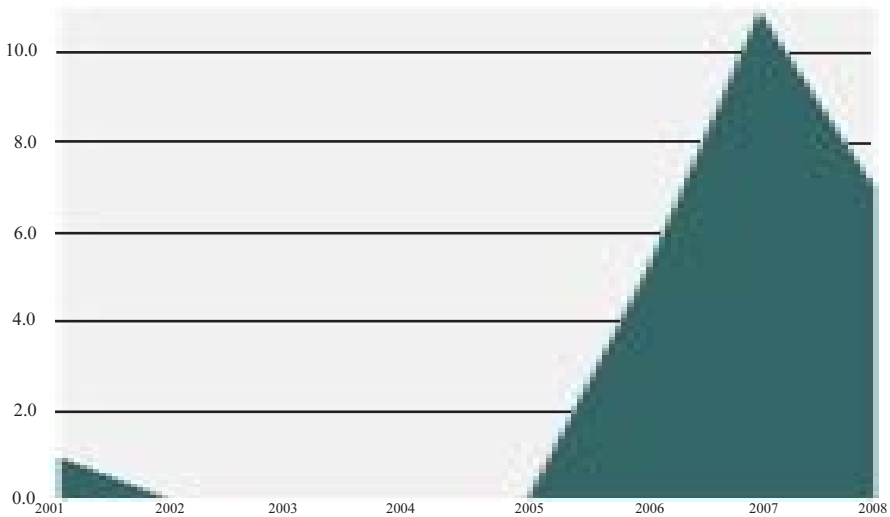
- Patents in this category claim influenza A, B, and C vaccines for animals or humans. Claims may relate to adjuvants or other formulation technology, sequences, production, or a combination thereof.
- In 2007, there were 54 patent applications filed on influenza vaccines.
- In 2008, to date, 33 new patent applications have been filed.

- Over 36% of all applications since 1983 for influenza vaccines (118 of 326) have been filed since 1 January 2006.
- Nearly half (49%) originate in the United States.

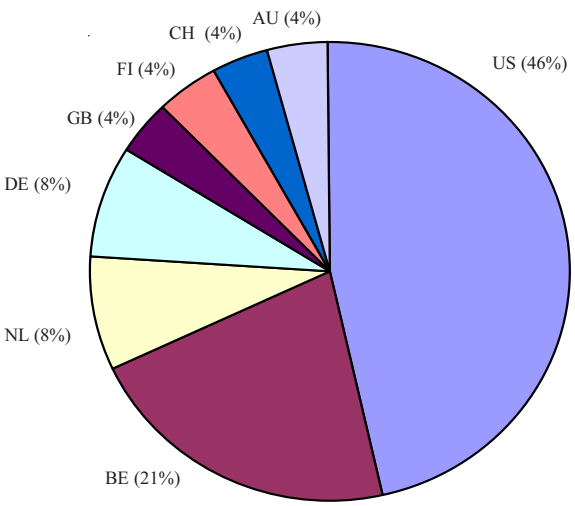
PCT PATENT APPLICATIONS FOR INFLUENZA VACCINES WITH THE TERM 'H5N1' APPEARING IN THE PATENT CLAIMS (1983-Sept. 2008)

PCT Classification A61K 39/145 / Source: WIPO/PatentScope

Number of Applications by Year (24 total)



Patent Applicants by Country

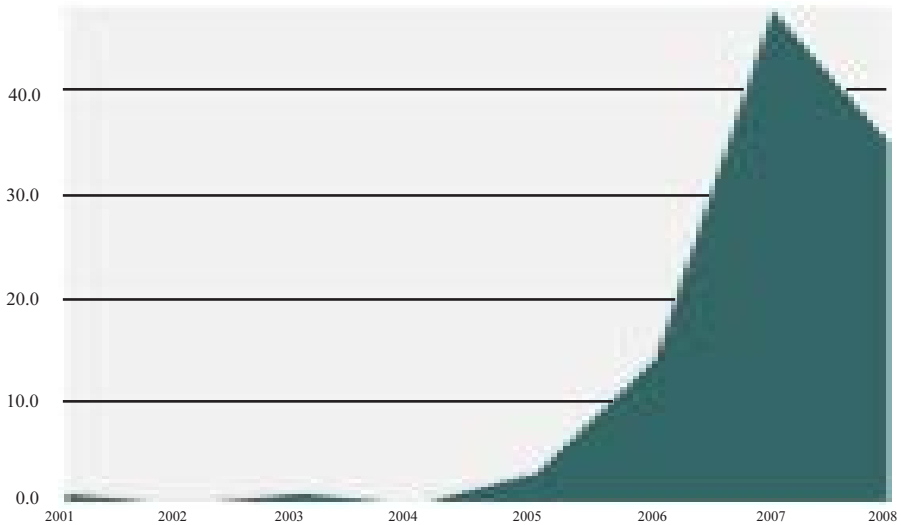


- Before 2006, only one international patent application for an influenza vaccine had ever been filed with the term 'H5N1' in the claims.
- Over a decade passed from the 1997 Hong Kong outbreak until 2006, yet with the exception of a single application in 2001, there were no claims until 2006.
- There is recent dramatic growth in H5N1-related claims. In 2006 there were five claims, followed by 11 in 2007, and seven in 2008 to date.
- US and EU companies account for nearly all applications.

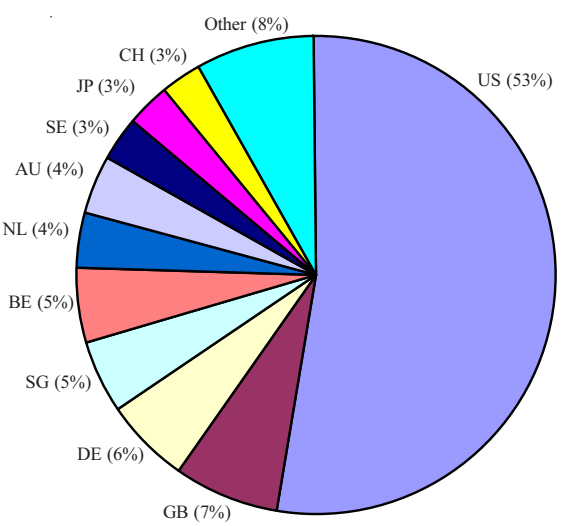
PCT PATENT APPLICATIONS FOR MEDICINES, VACCINES, MICROBES, PEPTIDES, NUCLEIC ACIDS, AND IMMUNOASSAYS WITH THE TERM 'H5N1' IN THE CLAIMS (1983-Sept. 2008)

PCT Classifications A61K/P, C07H/K, C12N/Q, G01N. Source: WIPO/PatentScope

Number of Applications by Year (102 total, of which 83 were filed after 1 Jan 2007)



Patent Applicants by Country



- This broader picture includes patent applications on diagnostics, detection technologies, sequences, etc.
- Excludes some patent claims (e.g. 'functional foods'/ herbals) unlikely to be depended upon in the event of a pandemic.
- 81% (83/102) of applications have been published since 1 January 2007.
- Over half the applications originate in the United States.

3 International Patent Applications Including Claims on H5N1 Genetic Material and Variations Thereof

INTRODUCTION: A number of patent applications that claim H5N1 genes, gene sequences, and/or their use have been identified. Patent applications that specifically claim H5N1 genetic materials and their uses are not the only patents that are relevant for the production of H5N1 vaccines. For instance, it is possible that a general patent on a technique for influenza vaccine manufacture, such as a cell culture technology, may be critical, even if the patent does not mention H5N1 specifically. This section does, however, identify a number of cases in which large and small companies and other institutions have made proprietary claims over viruses and their parts from developing countries, including viruses shared with the WHO GISN and used in its candidate vaccine strains.

First, it is important to note that, unlike many other infectious diseases that can be controlled by vaccines, influenza presents a fast-moving target. Flu is a small, single stranded, negative sense RNA virus[1] that quickly changes. This includes the HA and NA genes (sequences) used in current vaccines. For vaccine makers, this necessitates changes – typically annual – in seasonal influenza vaccines, meaning customers must submit to frequent revaccination to maintain their immunity.

The exact form of the next naturally emerging pandemic strain(s) remains unknown and is not predictable with confidence. Even though it is possible to generate examples of such strains in a laboratory, lab strains are unlikely to be the same as those generated by nature.

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[1] That is, the genetic material of the influenza virus consists of RNA molecules, rather than DNA. Influenza is 'negative sense' because its genes are 'written' backwards, also called 'antisense', in comparison to the direction RNA is usually found and functions in the higher organisms that viruses infect. Influenza virus is 'single stranded' because its RNA does not consist of paired molecules that form a 'double helix' or other helical forms. Single stranded RNA is sometimes abbreviated as 'ssRNA'. There are other negative sense ssRNA viruses that are dangerous to humans, including Ebola, Nipah, and Lassa, as well as measles, mumps, and rabies viruses.

Those observations have implications for intellectual property claims. Influenza HA and NA genes are far less stable over time than, for example, essentially static human gene sequences coding for susceptibility to a disease. This may limit the value of a patent claim on a particular sequence, because that sequence's similarity (homology) to potentially pandemic strains in circulation is likely to diminish fairly quickly over time.

The changeable nature of influenza has led some research groups, including at least one major company (Merck), to seek new influenza vaccines that do not rely on particular HA or NA sequences. Others have laid claim to sequences **and** any other sequence that is similar, for example, 90% or more the same. At least one other has responded by attempting to patent large numbers of varying HA and NA genes. The various types of claims that have been filed are discussed in more detail later in this report.

Key genes and sequences of a pandemic strain certainly can be patented if the applicant acquires them and recognises their significance early enough. Scientists may correctly predict the strains that will best confer immunity to an actual pandemic strain (e.g. a good case scenario prepandemic vaccine). Alternatively, it is possible that a vaccine approach involving a conserved sequence(s) may be developed and the critical sequence may be patented.

Patent Search Results: We reviewed recently published US and international patent data and identified applications that specifically claim H5N1 genes, sequences, and variations thereof. Because of the 'moving target' nature of influenza, however, it may be assumed that further claims on recent isolates exist but are not yet available due to delays in submission of applications and publication of patent claims.

Despite the limitations of available patent data in such a time-sensitive situation, patent claims have been identified on HA and NA sequences of all (8/8) H5N1 strains used in WHO-recommended vaccine seed strains announced since February 2005. In some cases, the patent applications claim the entire gene per se. In others, the gene or a modified gene sequence is claimed when used in a specific manner.

The following chart lists the virus strains used in WHO GISN prototype vaccine strains and matches them with patent claims found in the WIPO database:

WHO GISN Prototype Vaccine Strains and Patent Claims
(Searches performed of the WIPO PatentScope Database, through August 2008)

Date of WHO Notice	WHO Vaccine Strain includes gene(s) from:	Company/Institution Patent Application No. (indicative – more claims exist for some strains)	Patent Claim
February 2005	A/Vietnam/1194/04	Remedal WO2007065967	The HA gene used in any H5N2 vaccine
	A/Vietnam/1203/04	MedImmune (AstraZeneca) WO2006098901	Entire HA and NA gene sequences
		St. Jude's (WHO CC) WO2007019094	Modified HA sequence
		Univ. of Pittsburgh WO2006063101	HA gene used in adenovirus-based vaccine
	A/Hong Kong/213/03	MedImmune (AstraZeneca) WO2006098901	Entire HA and NA sequences
March 2006	A/Indonesia/5/2005	Hawaii Biotech Inc. WO2007022425	Partial HA sequence in cell culture vaccine
		Novavax WO2007047831	HA + NA genes in VLP vaccines in cell culture
May 2006	A/Bar-headed goose/Qinghai/1A/2005	Novavax WO2007047831	HA + NA genes in VLP vaccines in cell culture
	A/Whooping swan/Mongolia/244/05	Paul Ehrlich Institut WO2008061939	HA gene in modified vaccinia virus (Ankara MVA) vaccine
June 2006	A/turkey/Turkey/1/2005	Paul Ehrlich Institut WO2008061939	HA gene in MVA vaccine
December 2006	A/Anhui/1/2005	Novavax WO2007047831	HA + NA genes in VLP vaccines in cell culture

The following summaries provide specific information on the specific patent applications mentioned in the chart above as well as other patent claims that were identified in searches of the WIPO database.

PCT Application WO2007100584 (7 September 2007)

Title: **Antiviral agents and vaccines against influenza**
Owner: US National Institutes of Health and Centers for Disease Control

What is it? This patent application relates to a new kind of influenza vaccine called a DNA vaccine. The DNA vaccines are composed of loops of DNA, called plasmids, that cause an immune response when injected into humans. Many of these plasmids contain genetic material from H5N1 strains including full genes and shorter sequences. The patent application claims the genetic sequences contained in the plasmids by themselves (in Claim 1) and as used in the DNA vaccine.

The illustrative example of invention, of which a plasmid diagram is included on the front page, utilises the HA gene from A/Indonesia/5/05 (see image from the patent application).

In addition to A/Indonesia/5/05, the patent application also claims parts of flu strains from Thailand (A/Thailand/1(KAN-1)/04) and A/Ck/Thailand/1/04), Hong Kong (A/Hong Kong/156/97) and South Korea (A/Ck/Korea/ES/03).

According to the international patent application, the US government will advance this patent claim in more than 100 countries.

WHO Centre Link: The US Centers for Disease Control (CDC) is a WHO Collaborating Centre (CC). Both the CDC and the US National Institutes of Health (NIH) are part of the US Department of Health and Human Services (the health ministry). Thus this patent application on WHO materials comes from US institutions that host the US WHO CC. This patent application contradicts reports that the US CDC has stated that it has no interest in patenting WHO GISN materials.[2]

PCT Application WO2006098901 (21 September 2006) and family, including WO2005116258 and WO2005116260 and related national applications

Title: **Influenza hemagglutinin and neuraminidase variants**
Owner: MedImmune (now AstraZeneca) and the US Government

What is it? This complicated set of overlapping claims has been evolving in successive patent applications for several years. MedImmune's claims currently cover sequences from at least 29 influenza strains, in many cases the entire HA and/or NA genes. The applications cover producing influenza vaccines from them by placing the genes, or variants, onto a 'backbone' of a lab-adapted influenza strain.

WO2005116260 claims the entire HA and NA sequences of a number of influenza viruses, including those of A/Vietnam/1203/04, A/Hong Kong/213/03, A/Hong Kong/486/97, and A/Hong Kong/491/97.

The claims of **WO2005116258** cover a series of 20 different H5N1 and H9N2 HA and NA genes and sequences from Vietnam and China (Hong Kong). The patent application also claims the proteins encoded by those genes, antibodies, use of the genes and proteins in a vaccine, and variants of those genes and proteins, both in isolated form and used in a product.

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[2] For a lengthier description of this important patent application, please see Hammond, E. 'WHO-linked centre lays patent claim on bird flu virus' in *SUNS* #6539 Friday 15 August 2008.

The image below is from page 78 of US patent publication number 60/657,554, which was submitted as the priority document for the international patent applications. All sequences ('nucleotides') and proteins ('Amino Acids') listed in the image at right are claimed in their entirety.

In October 2006, a WIPO search report on the patent application questioned the novelty of MedImmune's claims. WIPO cited three main 'prior art' items to question the patent claims, each of them ironic in a slightly different way. The first was one of MedImmune's own reverse genetics patents, one which it acquired when it bought the US company Aviron. The second was reverse genetics technology invented by St. Jude's, a WHO CC. The third was a publication by Kanta Subbarao, a US government flu researcher. Due to MedImmune and the US government's cooperation, Subbarao is one of the inventors of the instant patent application.

Notably, the WIPO search report, which may or may not influence the US Patent and Trademark Office in the domestic US application, fundamentally posits questions that relate to the novelty and inventiveness of using these H5N1 sequences in conjunction with the underlying vaccine technologies that MedImmune and others

26-004110US

SUMMARY OF SEQ ID NO DESIGNATIONS

SEQ ID NO	HA or NA	STRAIN NAME	Amino Acid or Nucleotide
SEQ ID NO: 1	HA (H5)	A/Vietnam/1203/04	Nucleotide
SEQ ID NO: 2	NA (N1)	A/Vietnam/1203/04	Nucleotide
SEQ ID NO: 3	HA (H5)	A/Hong Kong/213/03	Nucleotide
SEQ ID NO: 4	NA (N1)	A/Hong Kong/213/03	Nucleotide
SEQ ID NO: 5	HA (H5)	A/Hong Kong/491/97	Nucleotide
SEQ ID NO: 6	NA (N1)	A/Hong Kong/486/97	Nucleotide
SEQ ID NO: 7	HA (H5)	A/Hong Kong/491/97 (Ser211)	Nucleotide
SEQ ID NO: 8	NA (N1)	A/Hong Kong/486/97	Nucleotide
SEQ ID NO: 9	HA (H9)	ca A/ck/Hong Kong/G9/97	Nucleotide
SEQ ID NO: 10	NA (N2)	ca A/ck/Hong Kong/G9/97	Nucleotide
SEQ ID NO: 11	HA (H5)	A/Vietnam/1203/04	Amino Acid
SEQ ID NO: 12	NA (N1)	A/Vietnam/1203/04	Amino Acid
SEQ ID NO: 13	HA (H5)	A/Hong Kong/213/03	Amino Acid
SEQ ID NO: 14	NA (N1)	A/Hong Kong/213/03	Amino Acid
SEQ ID NO: 15	HA (H5)	A/Hong Kong/491/97	Amino Acid
SEQ ID NO: 16	NA (N1)	A/Hong Kong/486/97	Amino Acid
SEQ ID NO: 17	HA (H5)	A/Hong Kong/491/97 (Ser211)	Amino Acid
SEQ ID NO: 18	NA (N1)	A/Hong Kong/486/97	Amino Acid
SEQ ID NO: 19	HA (H9)	ca A/ck/Hong Kong/G9/97	Amino Acid
SEQ ID NO: 20	NA (N2)	ca A/ck/Hong Kong/G9/97	Amino Acid

already own, and not MedImmune's claim of the H5N1 genes and sequences in principle. The next move is MedImmune's.

WO2006098901 is the newest member of the same international patent family to be published (21 September 2006). This application relates to seasonal influenza vaccines and claims 48 entire HA and NA genes from 24 different influenza A and B viruses.

The image on pages 14 and 15 is from pages 49 and 50 of US patent publication number 60/659,832, which was submitted as the priority document for the international patent applications.

The patent claims use a very similar template as those of WO2005116258 (discussed above). All RNA sequences (polynucleotides) indicated in the image at right are claimed in their entirety as well as the proteins (polypeptides) that they encode.

The claims cover many H1N1 and H3N2 type A influenzas as well as influenza B strains, the three types of influenza that are typically used in current seasonal influenza vaccines.

The claims include HA and NA genes that are currently or were recently recommended for use by WHO in both Northern and Southern seasonal influenza vaccines, such as (among others):

- A/New Caledonia/20/99 (H1N1), currently recommended for use in both hemispheres.

- B/Shanghai/361/02, B/Jilin/20/2003 and B/Jiangsu/10/2003, recommended and used in vaccines for both hemispheres (05-06).

- A/Panama/2007/99 (H3N2), like A/Moscow/10/99, recommended North and South (01-04).

The patent application also claims the genes of other viruses from Malaysia, South Africa, China, Australia, New Zealand, and the US. No search report has been published by WIPO.

WHO Centre Link: The US government has legal rights to some MedImmune inventions because the US Department of Health and Human Services, of which the US Centers for Disease Control (WHO CC) is part, has heavily funded MedImmune's research. It is not completely clear if the US government has rights

FIGURE 2		
SEQ ID NO	**HA or NA**	**Strain Name**
SEQ ID NO: 1 and 49	HA	ca A/Shandong/9/93
SEQ ID NO: 2 and 50	NA	ca A/Shandong/9/93
SEQ ID NO: 3 and 51	HA	ca A/Johannesburg/33/94-Like
SEQ ID NO: 4 and 52	NA	ca A/Johannesburg/33/94-Like
SEQ ID NO: 5 and 53	HA (H3)	ca A/Wuhan/395/95
SEQ ID NO: 6 and 54	NA (N2)	ca A/Wuhan/395/95
SEQ ID NO: 7 and 55	HA (H3)	ca A/Sydney/05/97
SEQ ID NO: 8 and 56	NA (N2)	ca A/Sydney/05/97
SEQ ID NO: 9 and 57	HA (H3)	ca A/Panama/2007/99
SEQ ID NO: 10 and 58	NA (N2)	ca A/Panama/2007/99
SEQ ID NO: 11 and 59	HA (H3)	ca A/Wyoming/03/2003
SEQ ID NO: 12 and 60	NA (N2)	ca A/Wyoming/03/2003
SEQ ID NO: 13 and 61	HA (H1)	ca A/Texas/36/91
SEQ ID NO: 14 and 62	NA (N1)	ca A/Texas/36/91
SEQ ID NO: 15 and 63	HA (H1)	ca A/Shenzhen/227/95
SEQ ID NO: 16 and 64	NA (N1)	ca A/Shenzhen/227/95
SEQ ID NO: 17 and 65	HA (H1)	ca A/Beijing/262/95
SEQ ID NO: 18 and 66	NA (N1)	ca A/Beijing/262/95
SEQ ID NO: 19 and 67	HA (H1)	ca/A/New Caledonia/20/99
SEQ ID NO: 20 and 68	NA (N1)	ca A/New Caledonia/20/99
SEQ ID NO: 21 and 69	HA	ca B/Ann Arbor/1/94
SEQ ID NO: 22 and 70	NA	ca B/Ann Arbor/1/94
SEQ ID NO: 23 and 71	HA	ca B/Yamanashi/166/98
SEQ ID NO: 24 and 72	NA	ca B/Yamanashi/166/98
SEQ ID NO: 25 and 73	HA	ca B/Johannesburg/5/99
SEQ ID NO: 26 and 74	NA	ca B/Johannesburg/5/99
SEQ ID NO: 27 and 75	HA	ca B/Victoria/504/2000
SEQ ID NO: 28 and 76	NA	ca B/Victoria/504/2000
SEQ ID NO: 29 and 77	HA	ca B/Hong Kong/330/01
SEQ ID NO: 30 and 78	NA	ca B/Hong Kong/330/01
SEQ ID NO: 31 and 79	HA	ca B/Brisbane/32/2002
SEQ ID NO: 32 and 80	NA	ca B/Brisbane/32/2002
SEQ ID NO: 33 and 81	HA	ca B/Jilin/20/2003
SEQ ID NO: 34 and 82	NA	ca B/Jilin/20/2003
SEQ ID NO: 35 and 83	HA	wt/A/California/7/04
SEQ ID NO: 36 and 84	NA	wt/A/California/7/04
SEQ ID NO: 37 and 85	HA (H3)	ca A/Sandai-H/F4962/02
SEQ ID NO: 38 and 86	NA (N2)	ca A/Sandai-H/F4962/02
SEQ ID NO: 39 and 87	HA (H3)	ca A/Wellington/1/04

SEQ ID NO: 40 and 88	NA (N2)	ca A/Wellington/1/04
SEQ ID NO: 41 and 89	HA (H3)	ca A/Malaysia/1/04_1
SEQ ID NO: 42 and 90	NA (N2)	ca A/Malaysia/1/04_1
SEQ ID NO: 43 and 91	HA (H3)	ca A/Malaysia/1/04_2
SEQ ID NO: 44 and 92	NA (N2)	ca A/Malaysia/1/04_2
SEQ ID NO: 45 and 93	HA	ca B/Jiangshu/10/03
SEQ ID NO: 46 and 94	NA	ca B/Jiangshu/10/03

in these applications since no US patent has yet been issued that states the government interest, if any. The listing of Subbarao and another US government researcher among the inventors of application WO2005116258, however, strongly suggests that it does. If applicable, government rights include the ability to 'march in' on the patent, meaning that if there is a national emergency or if MedImmune fails to work to patent, the government may force the company to issue it a royalty-free, irrevocable licence. Thus, the same US government agency that operates the WHO Collaborating Centre at the Centers for Disease Control is funding MedImmune's flu research and may be acquiring privileged access to its patents.

PCT Application WO2008033105

Title: **Hemagglutinin antibody and uses thereof**

Owner: St. Jude Children's Research Hospital (US)
DSO National Laboratories (SG)

What is it? This patent application claims antibodies to Vietnamese (A/Vietnam/1203/04) and Chinese (A/Hong Kong/213/03) strains of H5N1 as well as any other monoclonal antibody that binds to a particular piece of influenza hemagglutinin. These antibodies may be useful as vaccines or treatments for H5N1 infection.

Pertinent claims: The simple claims of this patent application cover the key part of the genetic sequences necessary to generate monoclonal antibodies against A/Vietnam/1203/04 and A/Hong Kong/213/03. These antibodies bind to a specific part of the hemagglutinin protein encoded by the influenza HA gene, and the patent further claims any antibody that specifically binds to that same site. These antibodies are generated using WHO GISN materials.

PCT Application WO2007047831

Title: **Functional influenza virus-like particles (VLPs)**

Owner: Novavax, Inc. (US)

What is it? Novavax's technique is to place influenza HA, NA, and M1 genes into another virus and to grow the hybrid virus in an insect cell culture. This produces partial influenza viruses ('virus-like particles' - or VLPs). These may be useful for vaccines because they can, like a whole virus, produce an immune reaction. In some cases the influenza genes are changed ('optimised') for use in the insect cell system.

Pertinent claims: The patent application claims any influenza VLPs produced by its cell culture methods as well as specific VLPs. VLPs claimed include those made with: the HA and NA genes of A/Indonesia/5/05, the HA gene from A/Anhui/1/2005, and the NA gene from A/Bar-headed Goose/Qinghai/1A/2005, as well as VLPs made from sequences 90% (or more) homologous to those.

PCT Application WO2007022425

Title: **Influenza recombinant subunit vaccine**

Owner: Hawaii Biotech Inc. (US)

What is it? This patent application, published on 22 February 2007, claims 12 variations on production of a new type of influenza vaccine made in insect cells and H5N1 vaccines made with the technology.

Pertinent claims: This patent application specifically claims H5N1 genetic sequences from a virus isolated in Indonesia in 2005 (A/Indonesia/5/05) and another isolated in China in 1997 (A/Hong Kong/156/97). It also claims sequences from an H3N2 virus isolated in China in 2002 (A/Fujian/411/02).

PCT Application WO2007019094

Title:	**Modified influenza virus for monitoring and improving vaccine efficiency**
Owner:	St. Jude's Children's Hospital (US) (a WHO Collaborating Centre)
What is it?	This patent application, published on 8 February 2007, claims small changes to influenza HA genes. These changes are intended to strengthen the immune system reaction (boost immunogenicity) to the genetically engineered virus. This might improve possible pandemic influenza vaccines because people vaccinated may exhibit a stronger immune reaction against H5N1.
Pertinent claims:	This patent application claims any influenza HA gene modified in a certain way. It specifically claims the modified HA gene from an influenza virus isolated in Vietnam in 2004 (A/Vietnam/1203/04). This is the same strain whose entire HA and NA sequences have been claimed by MedImmune.
Government interest:	The US government has rights in this patent application (see discussion of this issue under MedImmune's patent applications).

PCT Application WO2006063101

Title:	**Vaccines for the rapid response to pandemic avian influenza**
Owner:	University of Pittsburgh (US)
What is it?	This patent application, published on 4 January 2007, claims new human and animal influenza vaccines based on replication-deficient adenoviruses. These genetically engineered vaccines incorporate genetic sequences from H5N1 viruses.
Pertinent claims:	This patent application claims pieces of any influenza HA gene used in the adenovirus-based vaccine. It specifically claims use of the HA gene of A/Vietnam/1203/04.

PCT Patent Application WO2006104615

Title: **Influenza nucleic acids, polypeptides, and uses thereof**

Owner: University of Massachusetts (US)

What is it? This patent covers adaptation of influenza genes for expression in mammalian cells, for use in recombinant vaccines.

Pertinent claims: Claims include the H1 HA sequence from A/New Caledonia/20/99, and the H3 HA and H2 NA sequences from A/Panama/2007/99.

PCT Patent Application WO2007051036 (Published 3 May 2007)

Title: **Influenza combinatorial antigen vaccine**

Owner: Protelix Inc. (US)

What is it? This patent application covers nucleotide sequences from influenza HA and NA genes, a method for selecting them, and their use in influenza vaccines. An advantage that Protelix claims is that it can tailor vaccine composition to the virus strains from a specific geographic area. Protelix specifically claims HA and NA sequences derived from recent H5N1 isolates from Thailand and Indonesia, as well as slight variations on those sequences, for use in vaccines.

Pertinent claims: Claims include sequences derived from the HA and NA genes of A/Thailand/NK165/2005, A/Thailand/2-SP-33/2004, A/Thailand/Chaiyaphum/622/2004, A/Thailand/SP83/2004, A/Thailand/1-KAN-1/2004, and A/lndonesia/286H/2006.

Discussion of the Protelix Application to Illustrate Issues Raised by Patent Claims

The Protelix patent application illustrates how claims on 'techniques' and 'materials' (e.g. genes, sequences, viruses) can overlap, and why a clear distinction often cannot be made between the two. It can also be used to illustrate how 'smaller' patents (when compared to MedImmune's major grabs) can cause big problems.

The Protelix application describes a technique to take flu virus sequences and to use a complex, calculated method to generate a set of slight variants and to then use those variants, together with natural sequences, in a vaccine. The variants are generated in an attempt to predict future changes (mutations) that may occur in naturally circulating strains. The variants differ from natural RNA by a few bases. The intent is to create a more effective vaccine that provides broader immunity - to both the natural sequences and the slightly altered ones. By (possibly) anticipating mutations that will occur in nature, this may make a prepandemic vaccine more effective in an actual pandemic.

This patent application uses recent Thai and Indonesian sequences as examples of the general approach. Then, the second and third claims of the patent cover vaccine use of the Thai and Indonesian sequences themselves, as well as the set of variants derived from them. The patent application thus claims the Protelix technique as applied to any influenza **and** it claims the application of the technique to Thai and Indonesian sequences and the slight variations generated on them.

These sequences are referred to in the patent application in two groups, called ‘SEQ ID NO:14’ and ‘SEQ ID NO:20’.

Claim number 2 of the patent covers SEQ ID NO:20. This group of sequences includes:

A) Portions of the HA genes from five Thai isolates: A/Thailand/NK165/2005, A/Thailand/2-SP-33/2004, A/Thailand/Chaiyaphum/622/2004, A/Thailand/SP83/2004, and A/Thailand/1-KAN-1/2004; and

B) 16 slight variations on the above sequences (two changed bases in each).

Claim number 3 of the patent covers SEQ ID NO:14. This group of sequences includes:

A) The same Thai partial HA sequences of claim 2; and

B) A portion of the HA sequence of the strain A/Indonesia/286H/2006; and

C) 31 slight variants derived from the sequences of A and B.

In this case, because of the more diverse set of natural source strains (including the genetically more distant Indonesian one), there are 31 instead of 16 variants.

Due to the very high homology of the variants with natural Thai and Indonesian sequences and the fact that they are 100% calculated from the natural types, Indonesia, Thailand (or any other country in the same position) very well may conclude that it has sovereign rights over them.

A defender of the patent application might argue that virus-providing countries should not be concerned because (in this kind of case) the patent application does not claim **all** uses of the sequences. That is, because **other** things can be done with the sequences, then the company's control should not be a worry. This oversimplifies the problem. What if, in fact, the instant patent proves to be particularly useful? Or even critical to pandemic response?

What if, in the real world, influenza strains of concern emerge which have sequences that are like Protelix's variants? Would the company, or another with a similar kind of claim, attempt to assert a right over sequences that did not exist in nature at the time of patent filing, but which it claims to have anticipated? What if a government also wanted to develop a 'combinatorial' H5N1 vaccine approach? Protelix might interfere. Patent litigation is full of expensive and lengthy lawsuits based on the slenderest slice of rationality.

Huge patent claims, like MedImmune's grab for dozens of HA and NA genes, are one way that a microbial resource can be locked up. Another is a 'thicket' of smaller patent bites, in dozens of patents, like Protelix's application, that gradually lead to the commons being carved up into an overlapping and confusing mess of claims. Currently, both types of problem are on their way for H5N1 viruses and vaccines.

The issues raised by this patent application are not unique. Other H5N1-related patent applications can and do apply to both methods (techniques) and materials (sequences). More discussion on the homology issue as it plays out in patent claims follows.

Methodological Problems with the Cambia Influenza Patent Landscape

In cooperation with the World Intellectual Property Organisation (WIPO), the Australian non-profit science research organisation Cambia recently prepared an influenza patent landscape to give an overview of intellectual property claims related to the influenza genome.

Published in April 2008, the Cambia study[3] presents data different than this paper, particularly with respect to patent claims lodged on H5N1 genes. Some of the patents discussed in this paper do not appear in the Cambia study at all. In fact, that study concludes that Cambia could find no claims on H5N1 HA and NA nucleotide sequences.

Put simply, Cambia's conclusions are inaccurate. This is because the patent search methodology used in that study is deeply flawed. Cambia failed to identify many of the patents described in this paper because it only searched for one type of language used by patent attorneys when writing claims covering genes and sequences.

In reality, there are several different ways to write a patent claim so that it extends to genes and sequences. Thus, methodological shortcomings led Cambia to inaccurate conclusions.

The following is a (simplified) illustrative example of the major flaw in Cambia's methodology. While both pairs of the following patent claims could cover an H5N1 gene and sequences like it, only the first would be identified by Cambia's search:

Example A (Identified by the Cambia study):

We claim:

1. The HA gene of A/Vietnam/1204/04 with the sequence SEQ ID #1.
2. An influenza A HA gene 95% or more homologous to SEQ ID #1.

Cambia's search methodology would identify the above application, because it searched for a particular kind of claim construction, primarily used in the United States, that uses the phrase 'SEQ ID'. The next claim language, however, is different:

[3] See URL: http://www.patentlens.net/daisy/influenza/4132.html (accessed 21 September 2008).

Example B (Not identified by the Cambia study):

We claim:

1. The HA gene of A/Vietnam/1204/04 with the sequence contained in Table 23.
2. An influenza A HA gene 95% or more homologous to that of claim 1.

Although in this example this latter set of patent claims is functionally identical to the first, it is written differently and would not have been identified by the Cambia study.

In addition to potentially missing the claim on the HA gene itself, the Cambia search method would not capture the significance of claim 2 in the latter example above, the claim to anything 95% or more homologous to the sequence of claim 1, which might include a number of other H5N1 HA genes.[4]

With the very complicated field of patent applications related to H5N1, Cambia cannot be blamed for trying to use a simple search method. Unfortunately, however, there are many ways to write patent claims covering influenza genes and sequences, and no single type of search will yield an accurate picture of the patent landscape.

In short, studies to identify H5N1-related patent claims need to use robust and iterative search methods, and many pertinent patent applications may only be understood through 'claims analysis' – a tedious and more lengthy process that requires reading each claim and interpreting it in the context of the patent applications, and the information it contains.

Thus, whereas the Cambia patent landscape relies on an oversimplified search method that omitted important patent claims, the approach of this paper is to apply the more rigorous process of claims analysis.

[4] The following is a real example (from the US NIH / CDC patent applicationWO2007100584) of a claim on H5N1 gene sequences that was entirely missed by the Cambia search methodology:

WHAT IS CLAIMED IS:

1. A nucleic acid molecule comprising a polynucleotide encoding an influenza protein selected from the group consisting of hemagglutinin A (HA), neuraminidase (NA), M2 Protein, and nucleoprotein (NP), wherein said polynucleotide comprises (a) a plasmid taken from Table 1 (or its insert), or (b) an analog of said plasmid or insert having at least 95% identity thereto.

In this case, the plasmids and inserts of Table 1 and its annexes contain claimed gene sequences from Indonesian, Thai, Korean, and Hong Kong H5N1 strains. In addition, the language claiming any sequences 95% or more the same as those of Table 1 likely includes a number of additional HA, NA, M2, and NP genes, some of which may be identifiable through gene sequence database searches.

4 Some Claims and Strategies Used by Patent Applicants

INFLUENZA keeps changing, especially its all-important HA and NA genes. This is not only a problem for pandemic preparedness, but a headache for patent attorneys. A patent on yesterday's sequence may not be very valuable when a product for today or tomorrow's bird flu strains is needed. Yet it is the patent attorney's job to lay the strongest influenza patent claims they can for their employer.

Corporate intellectual property offices are testing the waters to see what they can get away with. The following section describes some influenza patent strategies used by companies, ranging from the usual (claiming a gene sequence) to the more novel, a practice that here will be called 'homology fishing'.

Claims on Natural Genes and Parts Thereof

Although natural evolution of influenza viruses may limit the usefulness of such claims, many patent applications make them. These include the University of Pittsburg (use of the HA gene of A/Vietnam/1203/04) and MedImmune (HA and NA genes of 29 different strains).

The breadth claims are variable. In the case of Pittsburgh it may be limited to the length of time that A/Vietnam/1203/04 is sufficiently antigenic to natural bird flu strains to merit its inclusion in a vaccine of Pittsburgh's type. In the case of MedImmune, the company is claiming a broader range of diversity, increasing the breadth and possibly the longevity of the usefulness of the patent claims. They may be especially valuable for several years or more, although eventually, they too will be outmoded by changes in the natural virus.

Although simple sequence and gene claims are susceptible to being quickly antiquated by the natural virus, if a sequence or a gene from a pandemic strain, or one that is antigenically very closely related, is successfully patented, then the patent may be quite powerful.

It is important to note some patent applications that make simple gene and sequence claims **also** make claims of the types described below.

Claims on Slight Variations of Natural Genes and Parts Thereof
In addition to naturally occurring sequences, some patents claim natural sequences that have been genetically altered. Such alterations typically only constitute a very small percentage of biological items of interest, usually an HA gene or a part thereof. The sets of variant sequences claimed by Protelix fall into this category and extend to synthesised copies and near-copies of natural viruses.

Taking a different example, St. Jude's patent application (WO2007019094) is on an altered HA gene from the strain A/Vietnam/1203/04. (It also claims any other H5 type influenza modified in the same way.) The change is of a single nucleotide in the HA gene. The entire HA gene sequence of A/Vietnam/1203/04 recorded in the Los Alamos National Laboratory database is 1741 nucleotides. Thus, the difference between the natural HA gene and that being patented is considerably less than $1/10^{th}$ of 1% (0.0574%).

Put differently, the HA gene of the invention is greater than 99.94% identical (homologous) to the natural Vietnam HA gene. Other patent applications may include alterations greater than one nucleotide; but typically still present sequences that are 99% or more homologous relative to the whole gene. Small variations can make big differences.

Homology Fishing
The constant changes in natural influenza virus strains and the desire of some companies to extend their patent controls over them have led some influenza patent claimants to engage in a practice here called homology fishing. While not entirely new, homology fishing may be reaching a new level of importance with influenza-related patents because of the potentially devastating effects of a pandemic.

Much of the value of an influenza virus, from a patent perspective, lies in its particular HA and NA gene sequences. But with sequences changing faster than patent applications can be processed, claim writers are trying to reach forward in time, and are writing claims that, expressed in plain language, are the equivalent of 'we claim this gene and anything like it'.

Practically, the following imaginary, simplified claims illustrate the approach:

Patent Claim 1: We claim influenza virus sequence X [used in Y kind of application].

Patent Claim 2: We claim any influenza sequence 95% or more the same as the sequence of claim 1 [used in Y kind of application].

There are variants on the above, but the concept is the same: The applicant knows that new variability will emerge in nature and is trying to capture it beforehand in a patent claim.

The approach can go to the extreme of the company inviting the patent examiner to assign it a percentage homology to the claims sequence:

For instance, MedImmune's application (WO2005116258) claims HA and NA genes from 20 different strains. Then, it claims all sequences 98%, 98.5%, 99%, 99.2%, 99.4%, 99.6%, 99.8%, and 99.9% identical to those genes. Why all the overlapping numbers? MedImmune is homology fishing, inviting the patent examiner to accept one of the options it presents. The lower the percentage circled, the greater the diversity of influenza strains it will control.

There are other examples of audacious homology fishing. Novavax's patent application claims virus-like particles made from genes 90% or more homologous to the three genes it specifically claims (A/Bar-Headed Goose/Qinghai/1A/2005 NA, A/Indonesia/5/05 HA and NA, and A/Anhui/1/2005 HA). The 10% variation claimed by Novavax is huge and, although a more detailed genetic analysis is required to be precise, it likely would encompass many other recent natural influenza strains from across Asia and beyond, as the difference between natural strains can be quite small – a few nucleotides or even less. Thus, if the patent application's homology fishing is successful, it will impact not only the three strains cited, but many more.

The University of Massachusetts application (WO2006104615) also makes a 90% homology claim.

Claims on Proteins and Pieces Thereof (Polypeptides) for Vaccines

Influenza genes, the physical material that scientists sometimes call 'polynucleotides', encode proteins. These proteins are sometimes termed 'polypeptides'. While polynucleotides are the hereditary material that provides the instructions for how to make influenza polypeptides (proteins), generally speaking,

it is the proteins that do the work. That is, the proteins encoded by the viral genes are what triggers an immune response in humans (and other animals).

Thus, a vaccine may include polynucleotides that become active in the body, producing proteins that trigger the immune response, (and)/or it may contain polynucleotides – the proteins encoded by viral genes – which themselves (if sufficiently biologically active) can trigger immunity.

Therefore, a patent that claims the proteins (polypeptides) encoded by particular viral genes is relevant to vaccines. Polypeptides can be specified in sequences that are similarly constructed as those of DNA and RNA, except using a different 'alphabet' of building blocks.

In practice some patent applicants, such as MedImmune (AstraZeneca), claim both the viral genes and the proteins they encode. For example, the following partial claims from MedImmune (in which the sequence IDs refer to H5N1 genes):

What is claimed is:

1. An isolated or recombinant polypeptide, which polypeptide is selected from the group consisting of: a) a polypeptide encoded by a polynucleotide sequence of one of SEQ ID NO:1 through SEQ ID NO:34; b) a polypeptide encoded by one of SEQ ID NO:35 through SEQ ID NO:68 …

5. A polypeptide comprising a sequence having at least 95% sequence identity to at least one polypeptide of claim 1.

Other claims in the patent application cover the genes (polynucleotides) themselves.

Therefore, in addition to paying attention to patent claims on viruses, genes, and gene sequences, it is necessary to also address the issues raised by patent claims on H5N1 polypeptides.

5 Further IP Considerations: Reverse Genetics Patents and WHO GISN H5N1 Vaccine Seed Strains

ALL prototype vaccine seed strains made available by WHO GISN have been produced using a patented technology called reverse genetics. Reverse genetics allows researchers to assemble plasmids encoding selected influenza gene segments which, when introduced into cells, will result in production of a specific desired influenza virus, for example, one with an H5 HA gene of interest on a 'backbone' of other genes from a laboratory-adapted strain.

Reverse genetics is used for several reasons. It arguably allows more 'rational' influenza vaccine design by facilitating genetic engineering to, for example, ease production of seed strains that are less pathogenic – often through modification of the HA gene – and easier to grow in eggs. Reverse genetics-produced strains (sometimes denominated 'RG') are genetically modified organisms.

A variety of patents exist on reverse genetics techniques. The majority of this intellectual property (IP) is owned by or licensed to MedImmune, itself recently purchased by the UK's AstraZeneca. MedImmune's reverse genetics IP portfolio includes its own patents, those of Aviron (a company which it purchased), and some technology developed by the WHO Collaborating Centre St. Jude's and Mt. Sinai Medical Center in New York City. One study (Krattiger, 2006)[5] identified 29 influenza-related reverse genetic patents and patent applications, with three primary owners, all of which have at least some interlocking relationships in ownership/licensing of the technology.

MedImmune has allowed royalty-free use of its reverse genetics intellectual property by researchers for the creation of pandemic influenza vaccine seed strains. This

[5] Krattiger, A et al. 'Intellectual Property Management Strategies to Accelerate the Development and Access of Vaccines and Diagnostics: Case Studies of Pandemic Influenza, Malaria, and SARS' pp 67-122 in *Innovation Strategy Today*, v.2 n.2 (2006).

permission, however, does not extend to production of influenza vaccine. Thus, H5N1 prototype seed strains are transferred under a Material Transfer Agreement (MTA) necessitated by MedImmune (and perhaps other) patents. These MTAs have not been made public. Their stipulations presumably include that the recipient of the seed strain must make arrangements with MedImmune before commercial production of vaccine.

MedImmune has stated that it will make its patents available on reasonable terms and that it does not wish to impede production of H5N1 vaccine. Nevertheless, the US government which, ironically, has long-funded the company, is reported to recently have been forced to resort to a threat to use its 'march-in rights' (under the US Bayh-Dole Act) to exact a MedImmune licence to Sanofi for the latter company to produce a quantity of prepandemic H5N1 vaccine. Thus, there is reason to view MedImmune's pledges with considerable caution. Other governments will not enjoy the same leverage over MedImmune as the US does.

On 18 June 2007, London-based AstraZeneca completed a deal to take over control of MedImmune. No public comments by AstraZeneca could be found with respect to the reverse genetics patents.

6 Antisera Research: Emerging Intellectual Property Claims

A COMPLEMENTARY approach to vaccines against H5N1 is the medical use of H5N1 antisera, which may theoretically be used as either a vaccine or a treatment for infected persons.

Antisera are the chemicals produced by the immune system when it tries to fight off an infection. They are typically specific to the particular strain that has infected the body, and sometimes provide cross-protection to other flu strains. Like the old 'gamma globulin' (or 'immune globulin') shots for Hepatitis A (now largely replaced by a vaccine), shots of H5N1 antibodies may theoretically stimulate resistance and help fight off a bird flu infection.

H5N1 antibody research is growing. In September 2007, an international patent application was filed by Singapore's DSO National Laboratories and US-based St. Jude Children's Research Hospital for monoclonal antibodies (MABs – a specific type of antibody) against Vietnamese (A/Vietnam/1203/04) and Chinese (A/Hong Kong/213/03) strains of H5N1, as well as any other MAB that binds to a particular piece of hemagglutinin.[6]

In addition, the US National Institutes of Health is currently conducting human experiments seeking to isolate H5N1 antibodies from human subjects (who are given an experimental vaccine), as possible flu treatments.[7]

Antibody research often involves blood samples from survivors of H5N1 infection. The antibodies contained in the blood of survivors are particularly interesting because H5N1 survivors typically have a stronger immune reaction than those

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[6] See patent application WO2008033105 at URL: http://www.wipo.int/pctdb/en/

[7] See URL: http://clinicaltrials.gov/ct2/show/NCT00383071?term=h5n1+antibody&recr=Open&rank=4 (accessed 21 September 2008).

who are killed by the virus. Presently, the Wellcome Trust (UK) is sponsoring research in Vietnam on H5N1 survivors, and in relation to this research the case of an 11-year-old girl who survived Bird Flu and whose blood is being studied has been featured in the news media.[8]

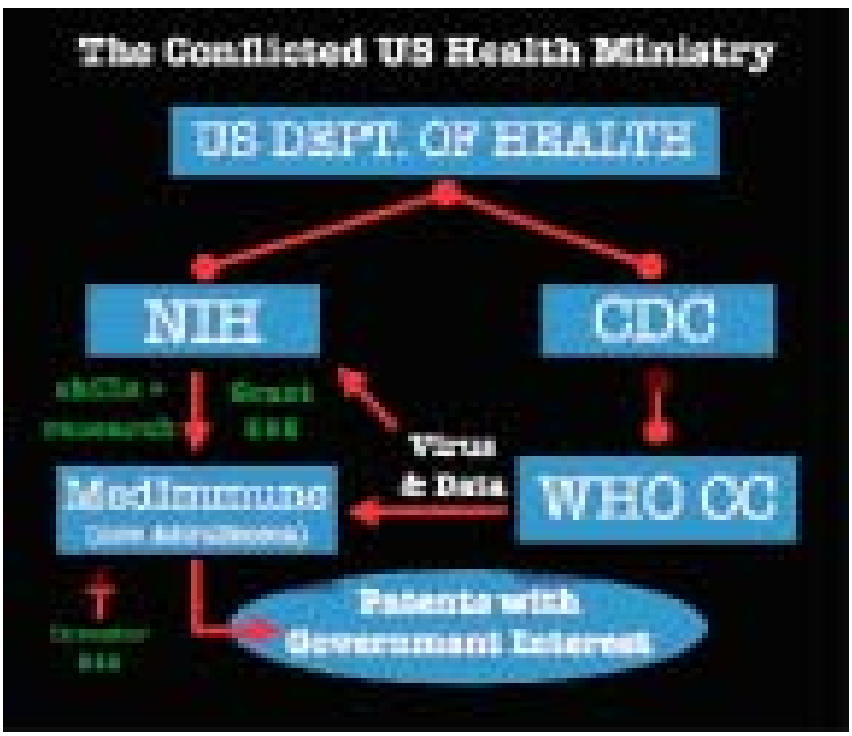
In general, H5N1 antibody research uses antisera generated from WHO GISN materials, without which the antibodies cannot be produced. Therefore, it is important that governments address development of antibody-based treatments and vaccines in the course of reforming the GISN to ensure developing country access to these treatments and equitable sharing of benefits arising from them.

[8] See URL: http://www.wellcome.ac.uk/News/News-archive/Browse-by-date/2007/Features/WTX035290.htm (accessed 21 September 2008).

7 Conflicting Priorities: Public Research and Private Patents, Two Examples

THE competing priorities of WHO Collaborating Centres that serve both WHO and a national government have been pointed out before. The way in which some governments structure their support (and consumption) of biomedical research deepens the competing interests.

For example, the sketch below is a simplified diagram of relationships between elements of the US health ministry and one company it funds, MedImmune. In the United States, the Centers for Disease Control (CDC) and National Institutes of Health (NIH) are both part of the Department of Health and Human Services (HHS).

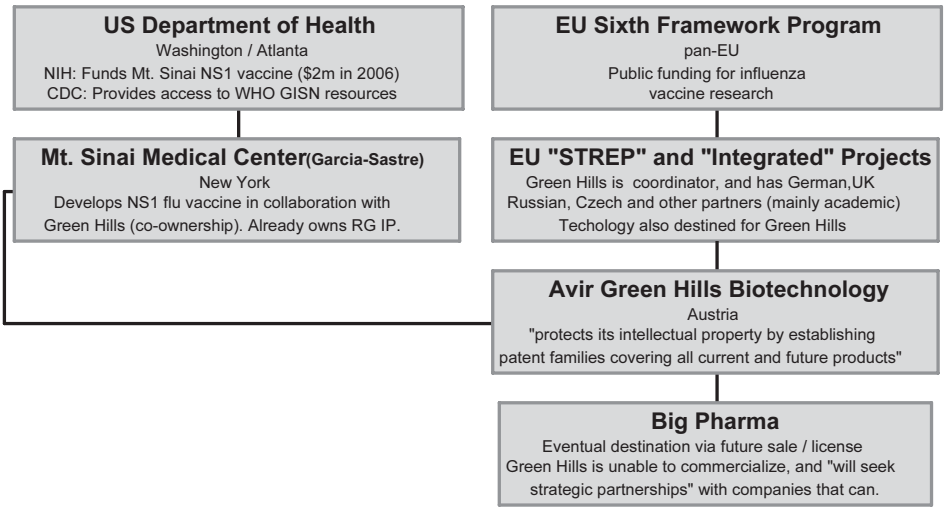


NIH is the primary funder of biomedical research, and it conducts its own research. Flu research is mainly supported through the NIH's National Institute of Allergy and Infectious Disease (NIAID). CDC also has labs in Atlanta and elsewhere. CDC's main charges related to infectious disease include epidemiological investigations, tracking nationally notifiable disease conditions, implementing public health regulations, disease prevention, etc.

In the US there is inadequate public capacity to manufacture and distribute vaccines and no national health care system, making the government even more dependent on the private sector than in many other developed countries. But to a large extent, and especially with infectious diseases, the private sector and collaborating academic researchers are dependent on government grants to fund research and development. With respect to these grants and cooperative agreements, domestic laws (notably the Bayh-Dole Act) encourage, even demand, patenting and commercialising research results. This includes H5N1 research.

The US Department of Health's intimate relationships with MedImmune are certainly not the only case of conflicting priorities brought about by the competing demands of relationships with industry versus service to the public WHO system. The sketch below shows the complex field of public funding and relationships with (mainly) academic researchers that has been developed by the small Austrian

Creating a Proprietary Vaccine with Public Resources:
Case Example: Avir Green Hills Biotechnology (Austria)



company Avir Green Hills Biotechnology. Green Hills currently has a new intranasal pandemic flu vaccine, called FluVacc, in human trials.

Green Hills' own staff virology team working on FluVacc consists of only three persons. But the company has positioned itself as the beneficiary of millions of dollars and euros of publicly funded research at both US and European (mainly academic) labs, for instance, projects at Mt. Sinai Medical Center in New York.

Importantly, Green Hills Biotechnology, like many other small biotech firms, has no significant internal capacity to produce and commercialise an influenza vaccine. The entire effort is conducted with the intent to sell the resulting patents (and perhaps trade secrets) to a larger biotech or pharmaceutical firm. This is openly declared by Green Hills on its website.

Although it's a legitimate question if citizens of the US and EU should tolerate public funding to be allocated in this way, the more important point for this report is that public influenza research and development funding structures in North are often inextricably tied to the intellectual property system. Thus, a restructured WHO GISN must take into account the fact that many North health ministries are politically and legally obligated to encourage patent claims on influenza virus and may be unable to stop such claims, even if they want to.

Appendix: The Fast-changing Landscape of Takeovers and Licensing of Influenza Vaccine Technologies (Tables)

Consolidation: Recent Takeovers

New Owner	Target	Date	Notes
AstraZeneca (UK)	MedImmune (US)	June 2007	MedImmune holds RG IP, patent claims, manufactures FluMist intranasal seasonal vaccine
Novartis (CH)	Chiron (US)	October 2005	Chiron was troubled but major seasonal flu manufacturer, raft of recent flu vaccine patent applications filed.
GlaxoSmithKline (UK)	ID Biomedical (CA)	December 2005	Purchased Canadian flu vaccine maker. Also purchased adjuvant maker Corixa (US) in 2005.

Cell Culture Technology: Alliances and Licensing*

Vaccine Company	Ally / Licensor	Technology / Activity
Sanofi (FR)	Crucell (NL)	Licensed Crucell's PER.C6 cell culture technology
Baxter (US)	DynPort / CSC (US)	Baxter has its own cell culture technology, and also has a cell culture development deal with Dynport (controlled by CSC).
GlaxoSmithKline (UK)	Vivalis (FR)	Licensed Vivalis 'EBx' avian embryonic stem cell culture technology
CSL Biotherapies (AU)	Vivalis (FR)	Licensed Vivalis 'EBx'
Nobilon (NL)	Vivalis (FR)	Nobilon's vaccine subsidiary, Akzo Nobel, licensed Vivalis 'EBx'

* Companies including Solvay (BE) and Novartis (CH) have their own proprietary cell culture technology.

Examples of Proprietary Adjuvants (Source: IFPMA 2006, +)

Company	Name
Novartis (CH)	MF59, IC31 (from Intercell) +
Solvay (BE)	Yes
GlaxoSmithKline (UK)	Yes

COMPANY*	MANUFACTURING BRAND, LOCATION INFO
AstraZeneca (UK)	Acquired MedImmune (US), 18 June 2007 'FluMist' (intranasal spray, uses RG technology as of 2007/08) Makes live, attenuated H5N1 (RG) candidate Locations: UK, US
Sanofi Pasteur (FR)	Major manufacturer Licensed Crucell (NL) 'PER.C6' cell culture technology Locations: FR, US
Novartis (CH)	Recently bought Chiron (US) Chiron: 'Begrivac', 'Fluvirin', 'Fluad', 'Aggripal S1' (seasonal) Novartis: 'Optaflu' (seasonal, cells), 'Focetria' (pandemic, eggs) Developing cell-culture-based pandemic vaccine Locations: IT, UK, DE, US
GlaxoSmithKline (UK)	'Fluarix', 'Fluviral' (seasonal) Licensed Vivalis EBx avian embryonic stem cell technology Purchased ID Biomedical and Corixa in 2005 Locations: DE, CA, US (former Wyeth facility)
Baxter (US)	Cell-culture (Vero), works with DynPort (US, CSC subsidiary), Has BSL-3 production facility, i.e. can work with virulent strains Locations: AT, CZ
Solvay (BE)	'Influvac', 'Invivac' (seasonal) MDCK cell culture technology for pandemic Locations: NL, US (to be built)
CSL Biotherapies (AU)	'Fluvax' (seasonal, south, eggs), licensed Vivalis EBx Locations: AU
Akzo Nobel (NL)	Nobilon is name of vaccine subsidiary, licensed Vivalis EBx Locations: NL

Others

Omnivest (HU)	H5N1 vaccine, not produced with RG, with Hungarian approval
Protein Sciences (US)	Has FlubIØk in late trials.
Sinovac Biotech (CN)	Has split influenza vaccine approved by government
Green Hills Biotech (AT)	Testing intranasal FluVacc product, made in Vero cells
Iomai (US)	Patch that potentiates immune response to vaccine.
Merck (US)	Working on M2-based vaccine, not H or N type specific.

* Excludes Japan-based and other manufacturers. Japanese vaccine makers include Kaketsuken, Kitasato Institute, Biken, and Denka Seiken.

SOME INTELLECTUAL PROPERTY ISSUES RELATED TO H5N1 INFLUENZA VIRUSES, RESEARCH AND VACCINES

Concern about the possibility of a new influenza pandemic has sparked increased scientific interest in influenza viruses, particularly the H5N1 virus that causes Bird Flu. Currently, global vaccine production capacity cannot meet the potential demand of a major Bird Flu outbreak and there are concerns that traditional vaccine production methods are poorly adapted for H5N1 vaccines.

As Bird Flu research increases and vaccine technology changes, a growing number of corporate and government laboratories are laying patent claims to influenza virus genes, gene sequences, treatments, and vaccines. These include proprietary claims on viruses originating in developing countries and that were shared with the international community for public health purposes. These claims threaten the ability of countries to prepare for a pandemic because they potentially restrict access to treatments and may make them too expensive for many countries to afford. In response to these problems, many developing countries are seeking reform of the World Health Organisation's Global Influenza Surveillance Network (GISN), to make sharing of the benefits from influenza research more fair and equitable.

This report reviews recent trends in patenting of influenza viruses and treatments, and provides details on a number of specific patent applications by corporations and government laboratories. It also provides information on corporate concentration in the vaccine industry, with a view to raising awareness of the implications of the wave of influenza patent claims and of the importance of reforming the international system for sharing influenza viruses and research results.

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