

## BRIEF REVIEW ΒΡΑΧΕΙΑ ΑΝΑΣΚΟΠΗΣΗ

# Patents on new respiratory viruses

ARCHIVES OF HELLENIC MEDICINE 2010, 27(5):783–786  
ΑΡΧΕΙΑ ΕΛΛΗΝΙΚΗΣ ΙΑΤΡΙΚΗΣ 2010, 27(5):783–786

V. Wiwanitkit

Wiwanitkit House, Bangkhuae, Bangkok,  
Thailand

Διπλώματα ευρεσιτεχνίας  
για τους νέους αναπνευστικούς  
ιούς

Περίληψη στο τέλος του άρθρου

### Key words

Gene sequence  
Patent  
Respiratory virus

Submitted 20.2.2010  
Accepted 4.3.2010

## 1. INTRODUCTION

The respiratory viruses comprise an important group of viruses that can cause respiratory tract infection. In the past few years, many new respiratory viruses have emerged and some of these new pathogens have become public health threats. Severe acute respiratory syndrome (SARS), avian flu (H5N1 influenza) and swine flu (novel H1N1 influenza) are three well-known examples of new respiratory virus infections. Several research projects have been designed to improve the knowledge on these new emerging respiratory virus infections, with a view to designing new diagnostic, preventive and therapeutic tools. This article is a review and discussion of gene sequence related patents on new respiratory viruses, with special focus on these three new respiratory viruses.

## 2. PATENTS RELATING TO THE GENE SEQUENCE OF SARS

SARS is a new respiratory infection with a very high mortality rate,<sup>1,2</sup> caused by a type of coronavirus infection.<sup>1–3</sup> The gene sequence of this virus was successfully detected in 2005 and patented by Peiris et al.<sup>4</sup> Patients who are infected usually develop severe respiratory tract infections, often resulting in death. One unique feature of SARS is the induction of respiratory distress, and patients commonly die of respiratory failure. The pathological mechanisms underlying the respiratory distress include direct injury caused by the virus, and indirect injury resulting from immune responses, circulatory dysfunction, and hypoxia.<sup>5</sup> The famous outbreak of SARS in China is considered

to be a warning of the need for preparation to combat this newly emerging respiratory virus infection.<sup>6</sup> After emergence of this disease, many patents relating to SARS have been registered, some of which are gene sequence related patents.

Many gene sequence related patents for SARS have been developed for diagnostic purposes. For example, the new methods for detecting SARS-associated coronavirus are registered by Briese et al.<sup>7</sup> A synthetic nucleic acid sequence comprising 10–30 nucleotides of the N gene region and the 3' non-coding region of the SARS-associated coronavirus genome, and a synthetic nucleic acid sequence comprising 10–30 nucleotides of a nucleic acid sequence that is complementary to at least one of those regions are used.<sup>7</sup> Another well-known piece of work is the oligonucleotide primer, patented by Minekawa et al,<sup>8</sup> that can specifically hybridize with any nucleotide sequence constructed based on the nucleotide sequence of RNA polymerase of the SARS coronavirus. In addition, the high throughput assay based on the nucleotide sequences of the N (nucleocapsid)-gene of the virus was recently patented by Peiris et al.<sup>9</sup> Nucleic acid sequences that can be used as primers and probes in the amplification and detection of SARS coronavirus were firstly patented by Sillekens.<sup>10</sup> Further primers and probes using molecular based techniques for diagnosis of SARS were proposed by Leijon et al<sup>11</sup> and Lou et al,<sup>12</sup> and new primers and probes were subsequently produced and used successfully for the development of diagnostic tools for SARS.<sup>11,12</sup> Leijon et al noted that their new patent using novel primers and probes for the detection of SARS nucleic acid had high diagnostic sensitivity.<sup>11</sup> In addition to the simple diagnostic tool, the new intervention providing

arrays and probes for re-sequencing SARS virus using an array of probes that are complementary to a SARS reference sequence was recently patented by Mittman et al.<sup>13</sup>

In addition to diagnostic purposes, there are also many new sequence-based patents designed for therapeutic purposes. Basically, the immunogenic study of the SARS sequence facilitates the design of specific therapeutic agents. Firstly, potentially antigenic, conserved and specific SARS coronavirus peptides were disclosed and patented by Altmeyer et al.<sup>14</sup> and Beadenkopf.<sup>15</sup> For further development, specific compositions of binding molecules specifically binding to a coronavirus such as SARS coronavirus and capable of neutralizing an infection were patented by Ter Meulen et al.<sup>16</sup> and Guoliang.<sup>17</sup> Currently, a more advanced siRNA based therapy for SARS is also available. The idea was primarily described and patented by Tang et al.<sup>18</sup> Tang et al also further patented the specific RNA based therapeutic approach for SARS in 2007.<sup>19</sup>

The patents for SARS prevention should also be mentioned. The vaccine for SARS is the current hope for prevention of this new virus infection, and there are some recent patents on SARS vaccines. The epitope-based SARS vaccine was patented by Gou et al.<sup>20</sup> For this vaccine the immunodominants are short peptide fragments distributed on various viral proteins, including the spike protein, the nucleocapsid protein, the replicase 1a, and the unknown proteins 3a and 9b.<sup>20</sup> For the DNA vaccine, specific sequences from SARS that are required in preparing DNA vaccine are patented by Zhou.<sup>21</sup> In addition, a recently patented attenuated SARS vaccine technique registered by Álvarez et al is considered to be a great success in the development of SARS vaccine;<sup>22</sup> specific nucleic acids encoding attenuated SARS coronavirus, which are capable of producing a maximum viral titer in cell culture and are useful for further vaccine preparation.<sup>22</sup> It is of note that several of these patents are from Asia, where the SARS is registered as a disease in the surveillance program.

### **3. PATENTS RELATING TO THE GENE SEQUENCE OF AVIAN FLU**

Avian flu or bird flu is a new respiratory virus infection in human beings caused by the H5N1 influenza virus.<sup>23</sup> The avian flu is a bird borne infection which surfaced in the past few years and has persisted up until the present time. Millions of birds and chickens were infected, and there were also some sporadic cases of human infection. In human beings, this infection is considered fatal. The common signs and symptoms of influenza can be seen in this viral infection, along with other unusual manifesta-

tions, such as diarrhea.<sup>24</sup> The avian flu receptor in human beings lies in lower respiratory tract; hence it is not easy for them to become infected, but once the infection starts, the consequences are serious.

Many recent patents relating to bird flu infection cover the aspects of diagnosis and treatment for both avian species and human beings.<sup>25</sup> Based on the sequence of swine flu, patents on avian pandemic hemagglutinin and neuraminidase that can be further used for the development of diagnostic tools and vaccines were patented by Yang et al.<sup>26</sup> The kit for detecting non-pathogenic, or pathogenic influenza, a subtype H5 virus, that could give a rapid result within one day, had already been patented much earlier by Yu et al.<sup>27</sup> However, this patent<sup>27</sup> is not specific for avian flu. Focusing on diagnostic primers and probes for avian flu, there are also some patents on this topic.<sup>28,29</sup> In addition, a new DNA array for the diagnosis of avian flu and other types of influenza was patented in 2009.<sup>30</sup> More details can be seen in an earlier paper in this journal.<sup>25</sup>

The new therapeutic and preventive approaches towards avian flu are considered major medical advances. There are several recent patents based on the avian flu sequence that can be applied in treatment and prevention. The avian flu vaccine is at present the biggest hope. Liao et al used a reverse genetic engineering platform to produce protein vaccines for avian influenza virus and patented this concept.<sup>31</sup> Novel sequences to protect a host against avian flu, involving codon-optimized sequences encoding for hemagglutinin and neuraminidase antigenic viral proteins, were designed by Kendigri et al in 2008.<sup>32</sup> These sequences are useful for DNA vaccine development.<sup>32</sup> In 2008, also, the new recombinant vaccine for avian flu was patented by Süzer et al.<sup>33</sup> This specific patent describes an Ankara virus-based recombinant avian flu vaccine.<sup>33</sup> In addition to vaccine design, a new RNA based therapeutic approach for avian flu was reported by Brahmachari et al;<sup>34</sup> targets for human microRNAs in the avian flu genome and specific miRNA targets against avian flu virus were described which can be of use for development of RNA based treatment.<sup>34</sup>

### **4. PATENTS RELATING TO THE GENE SEQUENCE OF SWINE FLU**

Swine flu is at present a global issue. This infection is caused by the novel H1N1 influenza virus. The infection is classified as an upper respiratory tract infection. Acute febrile illness with respiratory manifestations is the most common clinical presentation.<sup>35-37</sup> This newest respiratory virus was firstly detected in Mexico in early 2009, passing

thorough the infectious control barriers and causing a worldwide pandemic.<sup>38</sup> Although antiviral drug for classical influenza can be useful in the treatment of swine flu,<sup>39</sup> the transmission of disease is not yet controllable. Several deaths due to severe lower respiratory tract infections can be seen in the course of an epidemic.

Focusing on patents for swine flu, there were already some patents on animal specific swine flu, but there is no specific patent on the present problematic infection. A new vaccine for protecting swine against influenza virus by administration of an attenuated recombinant vaccinia virus containing inserts of the hemagglutinin (HA) and nucleoprotein (NP) genes of influenza virus, which express the hemagglutinin and nucleoprotein proteins was registered by Foley et al in 1997.<sup>40</sup> However, this vaccine is not specific for novel swine flu H1N1 influenza virus.

Since novel H1N1 influenza virus infection is a very new infection, it still lacks specific gene sequence based patents. However, there are some efforts under way to register for new patents on swine flu, especially on new swine flu vaccines.<sup>41</sup> The application for US 20090047353 for a "Split Influenza Vaccine with Adjuvants" by a vaccine manufacturer is the best example.

## 5. CONCLUSION

Currently, there are many new emerging respiratory virus infections, including SARS, avian flu and swine flu. In parallel, there are many new gene sequence related patents on these new respiratory viruses which can be of use for fighting the new emerging respiratory virus infections, with preventive, diagnostic and therapeutic applications.

## ΠΕΡΙΛΗΨΗ

### Διπλώματα ευρεσιτεχνίας για τους νέους αναπνευστικούς ιούς

V. WIWANITKIT

*Wiwanitkit House, Bangkhae, Bangkok, Ταϊλάνδη*

*Αρχεία Ελληνικής Ιατρικής 2010, 27(5):783–786*

Οι αναπνευστικοί ιοί αποτελούν μια σημαντική ομάδα ιών, οι οποίοι μπορεί να προκαλέσουν λοιμώξεις των αναπνευστικών οδών. Τα τελευταία έτη ανακαλύφθηκαν αρκετοί νέοι ιοί που έχουν γίνει απειλητικοί για τη δημόσια υγεία. Σημαντικές έρευνες για την καλύτερη κατανόηση των συγκεκριμένων λοιμώξεων του αναπνευστικού έχουν διεξαχθεί. Η παρούσα εργασία στόχο έχει την ανασκόπηση και τη συζήτηση για τα διπλώματα ευρεσιτεχνίας που σχετίζονται με τη γονιδιακή αλληλουχία των νέων αναπνευστικών ιών.

**Λέξεις ευρητηρίου:** Αναπνευστικοί ιοί, Γονιδιακή αλληλουχία, Δίπλωμα ευρεσιτεχνίας

## References\*

1. KULJIĆ-KAPULICA N. SARS corona virus – a new dilemma. *Med Pregl* 2005, 58:43–46
2. CHENG VC, LAU SK, WOO PC, YUEN KY. Severe acute respiratory syndrome coronavirus as an agent of emerging and reemerging infection. *Clin Microbiol Rev* 2007, 20:660–694
3. POKROVSKAIA AV. Severe acute respiratory syndrome. *Ter Arkh* 2007, 79:66–70
4. PEIRIS JSM, YUEN KW, POON LM, GUAN Y, CHAN KH, NICHOLLS JM ET AL. 2003, US0224353
5. ZHONG NS, ZENG GQ. Pandemic planning in China: Applying lessons from severe acute respiratory syndrome. *Respirology* 2008, 13(Suppl 1):S33–S35
6. GUO Y, KORTEWEG C, McNUTT MA, GU J. Pathogenetic mechanisms of severe acute respiratory syndrome. *Virus Res* 2008, 133:4–12
7. BRIESE T, LIPKIN WI, PALACIOS G, JABADO O. 2001, US0053519
8. MINEKAWA H, WATANABE K, KOJIY S. 2004, JP008355
9. PEIRIS JSM, YUEN KW, POON LM, GUAN Y, CHAN KH, NICHOLLS JM ET AL. 2004, US0265796
10. SILLEKENS PTG. 2008, EP1911853A2
11. LEIJO M, MOUSAVI-JAZI M. 2006, WO025791A1
12. LOU J, PRICE JRJ, YURISIS D, WOLFE D, KELLER L, HELLYER T. 2009, US0258340
13. MITTMANN M, SCHELL E. 2005, US0136395
14. ALTMAYER R, NAL-ROGIER B, CHAN C, KIEN F, KAM YW, SIU YL ET AL. 2005, WO118813A2

\* Many references are the patents that are listed in patent databases and are cited in the standard format of patent citation according to the Vancouver style [author (2), year of patenting, patent number].

15. BEADENKOPF RJ. 2008, EP0154023
16. TER MEULEN J, VAN DEN BEN, DE KRUIF CA, GOUDSMIT J. 2008, US0014204
17. GUOLIANG YU. 2005, WO007671A2
18. TANG QQ, PATRICK LY, XIE FY, LIU Y, JUN X, WOODLE M. 2005, WO019410A2
19. TANG QQ, PATRICK LY, XIE FY, LIU Y, JUN X, WOODLE M. 2007, US20070203082
20. GUO Z, ZHONG X, GUO Z, YANG H, XIE Y. 2006, WO071896A2
21. ZHOU X, DONG JY. 2008, US0206283
22. ALVAREZ GE, DE LÓPEZ DG, ENJUANES SANCHES L, ALMAZÁN T. 2006, EP1736539A1
23. WONG GW, LEUNG TF. Bird flu: Lessons from SARS. *Paediatr Respir Rev* 2007, 8:171–176
24. WIWANITKIT V. Diarrhoea as a presentation of bird flu infection: A summary on its correlation to outcome in Thai cases. *Gut* 2005, 54:1506
25. WIWANITKIT V. Recent patents relating to bird flu infection. *Recent Pat DNA Gene Seq* 2007, 1:112–115
26. YANG CF, KEMBLE G, SUBBARAO K, MURPHY B. 2005, US133346
27. YU ACH, SO KL, KO LS, LAU LT. 2009, US20060101
28. REN EC, NG LPH, CHIA J. 2008, US 0261198
29. REN EC, NG LPH, CHIA J. 2009, US 0226888
30. ROWLEN KL, KUCHTA R, TOWNSEND M, SMAGALA J, MOORE CL, DAWSON E ET AL. 2009, US0124512
31. LIAO C, CHANG H, HWANG K. 2007, EP0251592
32. KENDIRGI F, CHEN Y. 2008, WO124331A1
33. SÜZER Y, LÖWER J, SUTTER G, OSTERHAUS A, RIMMELZWAAN GF, KREIJTZ J. 2008, WO061939A1
34. BRAHMACHARI SK, HARIHARAN M, SCARIA V, PILLAI B. 2008, US0045472
35. CHANG LY, SHIH SR, SHAO PL, HUANG DT, HUANG LM. Novel swine-origin influenza virus A (H1N1): The first pandemic of the 21st century. *J Formos Med Assoc* 2009, 108:526–532
36. NOVEL SWINE-ORIGIN INFLUENZA A (H1N1) VIRUS INVESTIGATION TEAM, DAWOOD FS, JAIN S, FINELLI L, SHAW MW, LINDSTROM S ET AL. Emergence of a novel swine-origin influenza A (H1N1) virus in humans. *N Engl J Med* 2009, 360:2605–2615
37. SHINDEV, BRIDGES CB, UYEKIM, SHU B, BALISH A, XU X ET AL. Triple-reassortant swine influenza (H1) in humans in the United States, 2005–2009. *N Engl J Med* 2009, 360:2616–2625
38. WIWANITKIT V. Swine flu: The present pandemic infectious disease. *Kulak Burun Bogaz Ihtis Derg* 2009, 19:57–61
39. WIWANITKIT V. Antiviral drug treatment for emerging swine flu. *Clin Ther* 2009, 160:243–245
40. FOLEY FL. 1997, US5676950
41. WIWANITKIT V. Swine flu vaccine: Present status. *Hum Vaccin* 2009, 5:777–778

Corresponding author:

V. Wiwanitkit, Wiwanitkit House, Bangkhae, 10160 Bangkok, Thailand  
e-mail: wwiwoj@yahoo.com

.....