

# Research and Development of the Influenza Vaccine

羅筱芳、楊博文

E-mail: 9707272@mail.dyu.edu.tw

## ABSTRACT

Today's influenza vaccines are prepared in fertilized chicken eggs, a traditional method that has been used for nearly 50 years. The chicken egg-based system is still considered the most reliance and well-established production process so far. However, this production cannot provide immediately supply of vaccines, as a new strain of influenza virus is break out. Thus, many researchers have studied in the relevant field to increase the vaccine production in terms of effectiveness, safety and an acceptance of medical/pharmaceutical market. The current production of flu vaccine approach is the use of influenza viruses that are injected into the chicken embryo and replicated. The infected embryo is then go through the process of incubation, concentration, purification, inactivation and formulation, and finally the bulk of vaccines are produced. The method has demonstrated both matured vaccine-production process and cost-effective. However, egg protein allergy, availability of embryo supply, time-consuming production and limitation of biotechnology development are its disadvantages. In recent years, there are some improvement and development in vaccine manufacturing, including cell culture, DNA vaccine, and an immune adjuvant. They all have common characteristics such as shortening of preparation time, suitable against widespread viruses and more flexible schedule of production. However, it still remains some technical difficulties that needed to be overcome when mass productions of vaccines are scale up into manufacture. In the future, there are some concepts in manufacturing technique of influenza vaccine, including reverse genetic techniques, universal vaccine, food-based vaccine and the vaccine mired in tape, which are expected that will improve the method of vaccination, pared-down and shortening of manufacturing process, and increase the protency after vaccination. Hopes of the influenza vaccine will be applied more economically, widely and safely in the countries that need the vaccination. Key Words: Influenza vaccine, Embryo egg, Cell culture.

Keywords : Influenza vaccine, Embryo egg, Cell culture.

## Table of Contents

封面內頁 簽名頁 授權書iii 中文摘要iv 英文摘要V 誌謝vi 目錄vii 圖目錄xi 表目錄xii 1. 緒言1 2. 免疫系統簡介4 2.1 非特異性免疫系統5 2.1.1 防禦組織5 2.1.2 巨噬細胞及顆粒細胞的殺菌作用6 2.2 特異性免疫系統6 2.2.1 B細胞7 2.2.2 T細胞8 2.2.3 NK細胞9 2.2.4 抗原加工呈現細胞12 2.2.4.1 巨噬細胞12 2.2.4.2 樹突細胞13 2.2.4.3 B細胞14 2.2.5 體液性免疫14 2.2.6 細胞性免疫17 2.2.7 抗原19 2.2.8 抗體20 2.2.9 主要組織相容性複合體27 2.2.10 動物免疫的防禦機制28 2.2.10.1 被動免疫29 2.2.10.2 主動免疫30 2.3 疫苗引發之免疫反應31 3. 疫苗之介紹33 3.1 疫苗之發展史33 3.2 疫苗的分類37 3.2.1 細菌或病毒之整個致病病原體37 3.2.1.1 減毒疫苗37 3.2.1.2 不活化疫苗38 3.2.2 純化的次單位抗原42 3.2.3 基因重組表現的抗原42 3.2.4 合成肽?43 3.2.5 基因重組載體44 3.2.6 基因疫苗45 3.3 疫苗的安全性49 4. 流行性感冒疫苗之歷史背景及功能機制50 4.1 流行性感冒的歷史背景50 4.1.1 1918年50 4.1.2 1957年52 4.1.3 1968年52 4.2 流行性感冒的流行病學56 4.2.1 流行性感冒之季節性56 4.2.2 流行病和大流行病傳播56 4.3 流行性感冒病毒之分類及命名58 4.4 流行性感冒病毒之結構59 4.4.1 紅血球凝集素62 4.4.2 神經胺酸酵素65 4.4.3 間質蛋白65 4.4.4 非結構性蛋白66 4.5 流行性感冒病毒致病與免疫機制67 4.6 流行性感冒疫苗之製作68 5. 結論73 5.1 現階段流感疫苗製造技術73 5.1.1 細胞培養73 5.1.2 DNA疫苗74 5.1.3 佐劑75 5.1.4 Virosome疫苗75 5.1.5 鼻腔噴霧疫苗76 5.2 未來流感疫苗製造技術之展望76 5.2.1 反向遺傳技術76 5.2.2 通用型疫苗77 5.2.3 食物疫苗77 5.2.4 貼布疫苗77 5.3 建議78 參考文獻79 圖目錄 圖1. NK細胞之作用機制11 圖2. 體液性免疫反應16 圖3. 流感病毒感染所引發之體液及細胞性免疫反應18 圖4. Ig的五種抗體結構22 圖5. 抗體分子結構24 圖6. A型流行性感冒病毒之結構61 圖7. 流感病毒的抗原飄變64 圖8. 流感疫苗製造流程圖72 表目錄 表1. 人用疫苗的發展史36 表2. 不活化疫苗與減毒疫苗特性比較表40 表3. 減毒疫苗與不活化疫苗的優點表41 表4. 不同疫苗的比較48 表5. 主要的流感大流行54 表6. 西班牙流行性感冒期間死亡人數統計55 表7. 上市流感疫苗種類69

## REFERENCES

1.王金和等。2005。疫苗發展技術與實驗。教育部。 2.王蓉君。朱夢麟。陳恆德。2007。新疫苗法規科學現況之簡介。台灣醫界50(6)。 3.江瑞坤。陳世琦。陳欣欣。2008。流行性感冒與H5N1禽流感。基層醫學23(3):66-69。 4.行政院衛生署疾病管制局:我國因應流感大流行之準備計畫。2005年9月23日公布。 5.李忠明主編。2003。發行當代新疫苗。五南圖書。台北,台灣。 6.呂思潔 譯。2007。基

礎免疫學。文光圖書。台北，台灣。7.林天送。2008。為何?流行性感冒多發生在冬天?健康世界(265):48-49。8.林明泉編。1997。臨床血清免疫學。藝軒圖書出版社。9.林倩?。蕭靜怡。吳宗樹。朱育增。高全良。廖宜真。張勁聿。江百善。朱韻瑾。金傳春。2007。人類流行性感冒的流行病學與偵測系統。疫情報導23(5):254-272。10.吳彰哲。2007。疫苗。食品工業(2)。國立臺灣海洋大學生命科學院電子報。11.孫幸筠。陳世英。2005。漫談流行性感冒及流感疫苗。健康世界229:8-14。12.莊榮輝。2004。細胞融合與單株抗體。13.楊曜旭。江伯倫。2007。疫苗佐劑臺灣醫學11(6):620-625。14.謝顯森。2006。流行性感冒與禽流感-歷史與現況。感染控制雜誌16(2):77-84。15.Abbas, A., Pober, J., Lichtman, A., and W B Saunders. 2000. Cellular and Molecular Immunology (4th ed.) . 16.Ada, G. 1991. Strategies for exploiting the immune system in the design of vaccines. Molecular Immunology 28:225-230. 17.Ada, G. and A. Ramsay. 1996. Past and future needs. In: Vaccines, Vaccination and the Immune Response. Lippincott-Raven Publishers. Philadelphia, U. S. A. 18.Alessandra Desogus, Roberto Burioni, Angela Ingianni, Francesca Bugli, Raffaello Pompei, and Giovanni Fadda. 2003. Production and Characterization of a Human Recombinant Monoclonal Fab Fragment Specific for Influenza A Viruses. Clin. Diagn. Lab. Immunol 10: 680-685. 19.Anthony L. DeFranco, Richard M. Locksley, and Miranda Robertson. 2007. Immunity: The Immune Response in Infectious and Inflammatory Disease. 20.Arvin, A. M. 2000. Vaccines, viral. In: Encyclopedia of microbiology. (2nd ed.) . vol. 4. J. Lederberg, editor-in chief. p. 779-787. Academic Press, San Diego. 21.Belshe, R. B., F. K. Newman, J. Cannon, C. Duane, J. Treanor, C. Van Hoecke, B. J. Howe, and G. Dubin. 2004. Serum antibody responses after intradermal vaccination against influenza. N. Engl. J. Med 351:2286 – 2294. 22.Bernd Sebastian Kamps, Christian Hoffmann, Wolfgang Preiser. 2006. Influenza Report. 23.Beyer WEP, Palache AM, Baljet M, Masurel N.1989. Antibody induction by influenza vaccines in the elderly: a review of the literature. Vaccine 7: 385-94. 24.Brydak LB, Machala M, Mysliwska J, Mysliwski A, Trzonkowski P. 2003. Immune response to influenza vaccination in an elderly population. J Clin Immunol.23:214-22. 25.Cusi, M.G., Terrosi, C., Savellini, G.G., Di Genova, G., Zurbriggen, R., Correale, P. 2004. Efficient delivery of DNA to dendritic cells mediated by influenza virosomes. Vaccine. 26; 22(5-6):735-9. 26.Dowdle WR. 1999. Influenza A virus recycling revisited. Bull World Health Organ 77: 820-828. 27.Fearon, D.T. and Locksley, R.M. 1996. The instructive role of innate immunity in the acquired immune response. Science 272:50-54. 28.Fedson, DS. 2005. Preparing for pandemic vaccination: an international policy agenda for vaccine development. J Public Health Policy 26: 4-29. 29.Fouchier RA, Munster V, Wallensten A, et al. 2005. Characterization of a novel influenza A virus hemagglutinin subtype (H16) obtained from black-headed gulls. J Virol 79: 2814-22. 30.Galli Stephen J., Michele Grimbaldston and Mindy Tsai. 2008. Immunomodulatory mast cells: negative, as well as positive, regulators of immunity. Nature Reviews Immunology 8:478 -486. 31.Geraci JR, St. Auban DJ, Barker IK, et al. 1982. Mass mortality of harbor seals: pneumonia associated with influenza A virus. Science. 215:1129-31. 32.Gross PA, RA Levandowski, C Russo, M Weksler, J Bonelli, S Dran, G Munk, S Deichmiller, R Hilsen, and RF Panush. 1994. Vaccine immune response and side effects with the use of acetaminophen with influenza vaccine. Clin. Diagn. Lab. Immunol 1: 134-138. 33.Gu"rtler L. 2006. Virology of Human Influenza. In: Influenza Report. Kamps BS, Hoffmann C, Preiser W. Flying Publisher, Wuppertal. 34.Hannoun C, Megas F, Piercy J. 2004. Immunogenicity and protective efficacy of influenza vaccination. Virus Res.103:133 – 8. 35.Hilleman MR. 2002. Realities and enigmas of human viral influenza: pathogenesis, epidemiology and control. Vaccine 20: 3068-87. 36.Hilleman MR. 2000. Vaccines in historic evolution and perspective: a narrative of vaccine discoveries. Vaccine 18: 1436-47. 37.Holmes EC, Ghedin E, Miller N, et al. 2005. Whole-genome analysis of human influenza A virus reveals multiple persistent lineages and reassortment among recent H3N2 viruses. PLoS Biol. 38.Huang, KC, Jan CF, Kao CL, et al. 1999. A pilot study of immune response after influenza vaccination. Formosan J Med 3: 661-6. 39.Janeway CA, Travers P, Walport M, et al. 2001. Immunobiology: The Immune System in Health and Disease. (5th ed) . New York, Garland Publishing. 40.John J. Donnelly, Arthur Friedman, Douglas Martinez, Donna L. Montgomery, John W. Shiver, Sherri L. Motzel, Jeffrey B. Ulmer, Margaret A. Liu. 1995. Preclinical efficacy of a prototype DNA vaccine: Enhanced protection against antigenic drift in influenza virus. Nature Medicine 1:583-587. 41.John M. Barry. 2004. The Great Influenza: The Epic Story of the 1918 Pandemic. Viking. USA. 42. Joseph Kutza, Peter Gross, Donald Kaye, and Donna M. Murasko. 1996. Natural killer cell cytotoxicity in elderly humans after influenza immunization. Clin. Diagn. Lab. Immunol 3: 105-108. 43.Keren G, Segev S, Morag A, Zakay-Rones Z, Barzilai A, Rubenstein E. 1988. Failure of influenza vaccination in the aged. J Med Virol 25: 85-9. 44.Kilbourne ED, Couch RB, Kasel JA, et al. 1995. Purified influenza A virus N2neuraminidase vaccine is immunogenic and non-toxic in humans. Vaccine 13:1799-1803. 45.Langley JM, Halperin SA, McNeil S, et al. 2005. Safety and immunogenicity of a Proteosometrade mark-trivalent inactivated influenza vaccine, given nasally to healthy adults. Vaccine. 46.Lazzari S, Stohr K. 2004. Avian influenza and influenza pandemics. Bull World Health Organ 82: 242. 47.Lee CW, Dennis A. Senne, and David L. Suarez. 2006. Development and Application of Reference Antisera against 15 Hemagglutinin Subtypes of Influenza Virus by DNA Vaccination of Chickens. Clin. Vaccine Immunol. 13: 395-402. 48.Louria DB, Blumenfeld HL, Ellis JT, Kilbourne ED, Rogers DE. 1959. Studies on influenza in the pandemic of 1957-1958. II. Pulmonary complications of influenza. J Clin Invest 38: 213-65. 49.Mastrobattista, E., Schoen, P., Wilschut, J., Crommelin, D.J.A., Storm, G. 2001. Targeting influenza virosomes to ovarian carcinoma cells. FEBS Letters:50971-76 . 50.Matriano, J. A., M. Cormier, J. Johnson, W. A. Young, M. BATTERY, K. Nyam, and P. E. Daddona. 2002. Macroflux microprojection array patch technology: a new and efficient approach for intracutaneous immunization. Pharm. Res 19: 63 – 70. 51.Marion D. Kendall. 1998. Dying to Live: How our Bodies Fight Disease. Cambridge University Press, New York. 52.McDonnell, W.M., Askari, F.K. 1996. DNA vaccines. N. Engl. J. Med 334:42-45. 53.Medzhitov, R., and Janeway, C.A. 1998. An ancient system of host defense. Current Opinion in Immunology 10: 12-15. 54.Niall Johnson. 2006. Britain and the 1918-19 Influenza Pandemic: A Dark Epilogue. Routledge. London and New York. 55.Nichol KL. 2003. The efficacy, effectiveness and cost-effectiveness of inactivated influenza virus vaccines. Vaccine 21:1769-75. 56.Nicholson KG, Wood JM, Zambon M. 2003. Influenza. Lancet 362:1733-45. 57.Noda T, Sagara H, Yen A, et al. 2006. Architecture of

ribonucleoprotein complexes in influenza A virus particles. *Nature* 439: 490-492. 58.Palach AM. 1997. Influenza vaccines: a reappraisal of their use. *Drugs* 54: 841-56. 59.Peter Parham. 2005. *The Immune System*. ( 2nd ed. ) . Garland Publishing/Elsevier Science Ltd. 60.Playfair, J. 1996. Vaccination. In ' *Immunology* ' (4th ed.). Edited by I. Roitt, J. Brostoff, and D. Male.p. 19.1-19.10. Mosby. 61.Plotkin, S. A. 1999. Vaccination against the major infectious diseases. *C R Acad. Sci. III*. 322: 943-51. 62.Plotkin SA, Orenstein WA. 1999. *Vaccines*, ( 3rd ed. ) . Philadelphia. W.B. Saunders Company. 63.Potter J, Stott DJ, Roberts MA, et al. 1997. Influenza vaccination of health care workers in long-term-care hospitals reduces the mortality of elderly patients. *J Infect Dis* 175: 1-6. 64.Roitt I, Brostoff J, Male D .2001. *Immunology*. ( 6th ed. ) . Mosby. 65.Reid AH, Fanning TG, Hultin JV, Taubenberger JK. 1999. Origin and evolution of the 1918 "Spanish" influenza virus hemagglutinin gene. *Proc Natl Acad Sci U S A* 96:p.1651-6. 66.Sabine N, Tom Deroo, Xavier Saelens, Peter Vanlandschoot, Willy Min Jou, Walter Fiers. 1999. A universal influenza A vaccine based on the extracellular domain of the M2 protein. *Nature Medicine* 5:1157-1163. 67.Sadava David, H. Craig Heller, Gordon H. Orians, William K. Purves, Emeritus, and David Hillis. 2008. *Life: The Science of Biology*. ( 8th Ed. ) . W. H. Freeman and Company. U.S. 68.State of the world ' s vaccines and immunization. 1996. World Health Organization. United Nations Children ' s Fund. Geneva, Switzerland. 69.Stephenson I., J. M. Wood, K. G. Nicholson, A. Charlett, and M. C. Zambon. 2004. Detection of anti-H5 responses in human sera by HI using horse erythrocytes following MF59-adjuvanted influenza A/Duck/Singapore/97 vaccine. *Virus Res* 103:91 – 95. 70.Strassburg MA, Greenland S, Sorvillo FJ, Lieb LE, Habel LA. 1986. Influenza in the elderly: report of an outbreak and review of vaccine effectiveness reports. *Vaccine* 4: 38-44. 71.Tartaglia, J., M. E. Perkus, J. Taylor, E. K. Norton, J. C. Audonnet, W. I. Cox, S. W. Davis, J. van der Hoeven, B. Meigner, and M. Riviere. 1992. NYVAC: a highly attenuated strain of vaccinia virus. *Virology* 188: 217-232. 72.Taylor, J., C. Trimarchi, R. Weinberg, B. Languet, F. Guillemin, P. Desmettre, and E. Paoletti. 1991. Efficacy studies on canarypox-rabies recombinant virus. *Vaccine*. 9: 190-193. 73.Thomas J. Kindt, Barbara A. Osborne, Richard A. Goldsby. 2007. *Kuby Immunology*. ( 6th ed. ) . U.S. 74.Wareing, M. D. and Tannock, G. A. 2002. Influenza update: vaccine development and clinical trials. *Current Opinion in Pulmonary Medicine* 8:209-213. 75.*Weekly epidemiological record*. 2000. NO. 35:281-288. 76.World Health Organization. 2007. *The world health report : global public health security in the 21st century*. World Health Organization 5: 45-48. 77.Zei T, Neri M, Iorio AM. 1991. Immunogenicity of trivalent subunit and split influenza vaccines (1989-90 winter season) in volunteers of different groups of age. *Vaccine* 9: 613-7.