

流行性感疫苗之研究與發展 = Research and development of the influenza vaccine

羅筱芳、楊博文

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

摘要

以雞胚胎蛋培養生產流感疫苗已經有50年歷史，是一項成熟穩定的生產技術。然而，此一生產技術在碰到新型流感病毒株出現時會面臨無法緊急供應疫苗之問題，故現今許多學者都在研究探討相關技術來應付新型流感病毒之生產可行性、產品有效性、安全性及醫藥市場的接受性。目前世界各國生產流感疫苗之方式，是利用病原大量在雞胚胎蛋中培養後，經由不活化處理，再將其抗原蛋白萃取純化。此具有技術成熟、生產成本相對較低的特性；不過雞蛋蛋白過敏、胚胎蛋供應負擔、產程耗時與技術發展性低是其使用上的缺點。近年來在疫苗之製作上有一些新的進展及趨勢，包含細胞培養、DNA疫苗、新型免疫佐劑等，其具有製備耗時短、適用病毒廣泛、製備時程富有彈性等特性，但目前於大量生產製備仍有技術上之困難需待克服。未來流感疫苗製造技術概念包括有反向遺傳技術、通用疫苗、食物疫苗及貼布疫苗等，期能改善預防接種的方式、簡化並加速疫苗之生產流程及提升接種後所產生之免疫力時效，讓其能夠更經濟、更廣泛、更安全地應用在需要接種疫苗的國家。

關鍵詞：流感疫苗，雞胚胎，細胞培養

目錄

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 流行性感病毒之分類及命名58 4.4 流行性感病毒之結構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 流行性感病毒致病與免疫機制67 4.6 流行性感疫苗之製作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. 西班牙流行性感期間死亡人數統計55 表7. 上市流感疫苗種類69

參考文獻

- 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。為什麼?流行性感多發生在冬天?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. Buttery, 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.