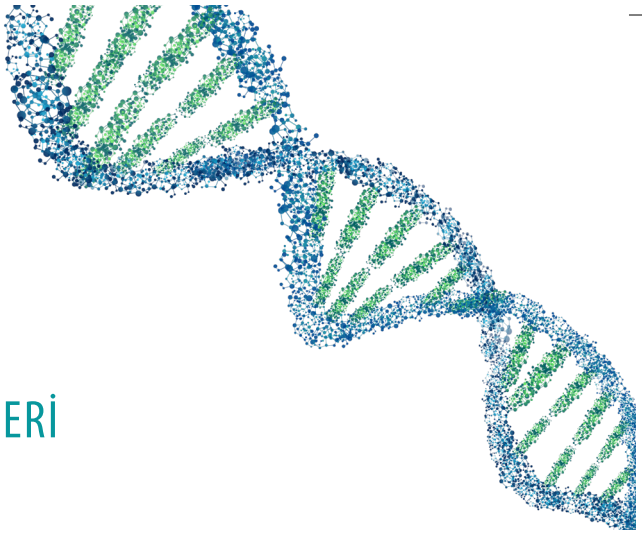

BÖLÜM 13

GEÇMİŞTEN GÜNÜMÜZE AŞI TEKNOLOJİLERİ

Aykut ÖZDARENDELİ[1]

Giriş

Aşı, bir patojene maruz kalındığında enfeksiyona ve/veya hastalığa karşı koruma sağlayan bağışıklık tepkisini güvenli bir şekilde başlatmak için kullanılan biyolojik bir üründür. Bu amaçla aşı ya patojenden türetilen ya da patojenin bileşenlerini temsil etmek üzere sentetik olarak üretilen antijenler içermelidir. Bağışıklık yanıtı ile aşının koruyuculuğu arasındaki ilişki yeni aşıların geliştirilmesindeki temeli oluşturmaktadır [1].

Aşılama, bulaşıcı hastalıkları önlemenin en etkili yoludur. Küresel ölçekte ölüm oranındaki düşüşe rağmen, gelişmemiş ülkelerdeki ilk 10 ölüm nedeninden altısını bulaşıcı hastalıklar oluşturmaktadır [2].

Aşılar, ulusal bağışıklama programlarının ilk kez 1960'larda koordine edilmesinden beri halk sağlığına katkı sağlamaktadır. Dünya Sağlık Örgütü (DSÖ) verilerine göre, mevcut bağışıklama programlarıyla her yıl en az 2 milyon hayatın kurtarıldığı tahmin edilmektedir. Bu sayede dünya çapında 5 yaşından küçük çocuklarda 1990 yılında %9,3 olan ölüm oranının, 2018 yılında %3,9'a düşmesinin sağladığı düşünülmektedir [3,4].

Aşılar, aktif ve pasif olmak üzere iki geniş kategoriye ayrılabilirler. Aktif aşılar, humoral ya da hücresel bağışıklık sisteminin birini veya her ikisini aktive ederek bir hastalığı önlemesi, iyileştirmesi veya neden olan patojeni ortadan kaldırması için uyarır. Pasif aşılar, bir patojene veya hastalığa potansiyel maruziyetten önce veya maruziyet sırasında uygulanan, hastalığa karşı koruyucu olan veya koruyucu olduğu bilinen antikor preparatlarıdır [5]. Aktif aşılar sırasıyla canlı attenüe aşılar, inaktif/ölü aşılar, alt ünite aşıları, virüs benzeri partikül aşıları, vektör temelli aşılar ve nükleik asit temelli aşılar olmak üzere beş ana kategoriye ayrılabilir [6]. Bu bölümde aşılar; alt ünite aşıları, virüs benzeri partiküller, vektör temelli aşılar, DNA aşıları ve mRNA aşıları olmak üzere 5 ana başlık altında incelenecektir.

[1] Prof. Dr., Erciyes Üniversitesi Tıp Fakültesi Tıbbi Mikrobiyoloji AD.,
Erciyes Üniversitesi Aşı Araştırma ve Geliştirme Uygulama ve Araştırma Merkezi (ERAGEM), aozdarendeli@erciyes.edu.tr

nanokompleks oluşumunu etkiler. Katyonik bir peptit olan ve sıklıkla kullanılan protamin, çözeltide mRNA ile NaCl konsantrasyonuna bağlı olarak kendiliğinden bir kompleks oluşturur [89]. Protamin ile formüle edilen mRNA, RNaz bozunmasına karşı daha dirençlidir ve *in vivo* olarak daha iyi stabilite gösterir [90].

6.7. Katyonik nanoemülsiyon

Katyonik nanoemülsiyon (CNE), katyonik lipidlerin mRNA iletimi için kullanıldığı bir yöntemdir. Nanoemülsiyonda, sulu fazda yağ damlacığını stabilize etmek için hidrofobik ve hidrofilik yüzey aktif maddeler kullanılarak partiküller oluşturulur [81]. Bunun en bilinen örneği olan MF59, inaktif grip aşısı ile kullanılan FDA onaylı bir nanoemülsiyon adjuvanıdır [91].

6.8. Dendritik hücre temelli mRNA aşıları

Terapötik aşılamada, adaptif bağışıklığın etkin bir şekilde aktivasyonu gerekir. Bunun için, ASH'ler antijenleri alır, işler ve fonksiyonel lenfositlere sunar. DC'ler, yakalanan mikroorganizmalar, virüsla enfekte hücreler ve tümör hücreleri gibi çeşitli kaynaklardan işlenen antijenleri sunabilir [92]. mRNA'ların DC'lere iletimi için elektroporasyon ve LNP gibi çeşitli stratejiler kullanılır. Bunlardan en sık kullanılan yöntem elektroporasyondur.

6.9. mRNA aşılarının güncel durumları

Kuduz ve grip gibi viral ajanlara ve kansere karşı geliştirilen mRNA aşıları, sağlıklı gönüllülerde ve hastalarda humoral ve hücresel bağışıklık yanıtı oluşturmuştur [83]. BNT162b2 aşısının Faz III klinik çalışmasında 40.000'den fazla kişi yer almış ve COVID-19'u engellemede %95 etkili olduğu tespit edilmiştir. mRNA-1273 aşısı ise, Faz III aşamasında 30.000'den fazla katılımcıda COVID-19'u engellemede %94 etkinlik sağlamıştır [93]. CureVac tarafından geliştirilen aşı adayı (CVnCoV) ise ilk aşamalarda başarılı olsa da Faz III aşamasında %47 etkinlik göstererek başarısız olmuştur [29]. Bazı mRNA aşı adaylarının güncel durumları Tablo 7'de verilmiştir.

Tablo 7. Bazı mRNA aşı adaylarının güncel durumları [94].

Hedef	Taşıyıcı	Kurum Adı	Durum
Zika	LNP	Moderna	Faz I
Kuduz	Protamin	Curevac	Faz I
Influenza A - Influenza B		Moderna	Faz I/II
İnsan Sitomegalovirüs	LNP	Moderna	Faz II
Influenza (H3N2)		Translate Bio, Sanofi	Faz I

Kaynaklar

1. Plotkin SA. Updates on immunologic correlates of vaccine-induced protection. Vaccine 2020;38(9): 2250-2257.
2. https://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death. Erişim Tarihi: 4 Nisan 2022.
3. https://www.who.int/teams/immunization-vaccines-and-biologicals/strategies/global-vaccine-action-plan.Erişim Tarihi: 4 Nisan 2022.
4. https://www.who.int/gho/child_health/mortality/mortality_under_five_text/en/. Erişim Tarihi: 4 Nisan 2022.
5. Ellis RW, Rappuoli R, Ahmed S. Technologies for making new vaccines, pp: 1283-1304. In: Plotkin SA, Offit PA, Orenstein WA, Edwards KM. Plotkin's Vaccines, 2018, 7th ed. Elsevier.
6. Hansson M, Nygren PA, Stahl S. Design and production of recombinant subunit vaccines. Biotechnology and Applied Biochemistry 2000;32(2): 95-107.
7. Edwards KM, Decker MD. Pertussis vaccines, pp: 467-517. In: Plotkin SA, Orenstein WA, Offit PA, editors. Vaccines, 2008, Saunders/Elsevier. Philadelphia.
8. Sato Y, Kimura M, Fukumi H. Development of a pertussis component vaccine in Japan. Lancet 1984;1(8369): 122–126.
9. https://www.cdc.gov/vaccines/vpd/mening/public/index.html. Erişim Tarihi: 6 Nisan 2022.
10. Frasch CE. Preparation of bacterial polysaccharide-protein conjugates: analytical and manufacturing challenges. Vaccine 2009;27(46): 6468-70.
11. Zhaoa J, Hud G, Huange Y, Huangc Y, Wei X, Shia J. Polysaccharide conjugate vaccine: A kind of vaccine with great development potential, pp: 1331-1340. In: Qian X. Chinese Chemical Letters. 2021, Elsevier.
12. Shirley M, Dhillon S. Bivalent rLP2086 vaccine (Trumenba(®)): a review in active immunization against invasive meningococcal group b disease in individuals aged 10-25 years. BioDrugs 2015;29(5): 353-61.
13. Toneatto D, Pizza M, Masignani V, Rappuoli R. Emerging experience with meningococcal serogroup B protein vaccines. Expert Rev. Vaccines 2017;16(5): 433-451.
14. Babiuk LA. Broadening the approaches to developing more effective vaccines. Vaccine 1999;17(13-14): 1587–1595.
15. Plotkin SA. Vaccination in the 21st century. The Journal of Infectious Diseases 1993;168(1): 29-37.

16. Plotkin SA, Plotkin SL. The development of vaccines: how the past led to the future. Nature Reviews Microbiology 2011;9(12): 889-93.
17. Upreti RK, Kumar M, Shankar V. Bacterial glycoproteins: Functions, biosynthesis and applications. Proteomics 2003;3: 363-379.
18. MacLennan CA, Martin LB, Micoli F. Vaccines against invasive salmonella disease. Human Vaccines & Immunotherapeutics 2014;10(6): 1478–1493.
19. Pichichero ME. Protein carriers of conjugate vaccines: characteristics, development, and clinical trials. Human Vaccines & Immunotherapeutics 2013;9(12): 2505–2523.
20. Chellasamy G, Kiriyanthan RM, Govindaraju S, Radha A, Yun K. Recent trends in the development of vaccine technologies to combat pandemic outbreaks and challenges, pp: 235-243. In: Viswanath B. Pandemic Outbreaks in the 21st Century Epidemiology, Pathogenesis, Prevention, and Treatment. 2021, Academic Press, Cambridge, Massachusetts.
21. García A, De Sanctis JB. An overview of adjuvant formulations and delivery systems. APMIS, 2014;122(4): 257-267.
22. Francis MJ. Recent Advances in Vaccine Technologies. Veterinary Clinics of North America: Small Animal Practice 2018;48(2): 231-241.
23. Rosales-Mendoza S, Angulo C, Meza B. Food-grade organisms as vaccine biofactories and oral delivery vehicles. Trends in Biotechnology 2016;34(2):124-136.
24. Cino J. High yield protein production from Pichia pastoris yeast: A protocol for bench top fermentation. American Biotechnology Laboratory 1999;17: 10–13.
25. Cid R, Bolivar J. Platforms for Production of Protein-Based Vaccines: From Classical to Next-Generation Strategies. Biomolecules 2021;21;11(8): 1072.
26. https://www.fda.gov/vaccines-blood-biologics/vaccines/shingrix. Erişim Tarihi: 6 Nisan 2022.
27. Slon-Campos JL, Dejnirattisai W, Jagger BW, López-Camacho C, Wongwiwat W, Durnell LA, et al. A protective Zika virüs E-dimer-based subunit vaccine engineered to abrogate antibody-dependent enhancement of dengue infection. Nature Immunology 2019;20(10): 1291-1298.
28. Waehler R, Russell SJ, Curiel DT. Engineering targeted viral vectors for gene therapy. Nature Reviews Genetics 2007;8(8):573-587.
29. Heinz FX, Stiasny K. Distinguishing features of current COVID-19 vaccines: knowns and unknowns of antigen presentation and modes of action. npj Vaccines 2021;6(1): 1-13.
30. Skwarczynski M. and Toth I. Peptide-based synthetic vaccines. Chemical science 2016;7(2): 842-854.
31. Mosqueda J, Hernandez-Silva DJ, Romero-Maldonado A, Mejia-Lopez S, Mercado-Uriostegui MA. Innovative recombinant protein-based vaccines against SARS-CoV-2, pp: 193-211. In: Rosales-Mendoza S, Comas-Garcia M, Gonzalez-Ortega O. Biomedical Innovations to Combat COVID-19. 2022. Academic Press. Cambridge, Massachusetts.
32. Lua LH, Connors NK, Sainsbur F, Chuan YP, Wibowo N, Middelberg AP. Bioengineering virüs-like particles as vaccines. Biotechnology and bioengineering 2014;111(3): 425-440.
33. Thompson CM, Petiot E, Lennaertz A, Henry O, Kamen A. Analytical technologies for influenza virüs-like particle candidate vaccines: challenges and emerging approaches. Virology journal 2013;10;1: 141.
34. Polla Ravi S, Shamiya Y, Chakraborty A, Elias C, Paul A. Biomaterials, biological molecules, and polymers in developing vaccines. Trends in Pharmacological Sciences 2021;42(10): 813-828.
35. Dai S, Wang H, Deng F. Advances and challenges in enveloped virüs-like particle (VLP)-based vaccines. Journal of Immunological Sciences 2018;2(2).
36. Li TC, Yamakawa Y, Suzuki K, Tatsumi M, Razak MA, Uchida T, Takeda N, et al. Expression and self-assembly of empty virüs-like particles of hepatitis E virüs. Journal of virology 1997;71(10): 7207-7213.
37. Kushnir N, Streatfield SJ, Yusibov V. Virüs-like particles as a highly efficient vaccine platform: diversity of targets and production systems and advances in clinical development. Vaccine 2012;31(1):58-83.
38. Fuenmayor J, Gòdia F, Cervera L. Production of virüs-like particles for vaccines. New Biotechnology 2017;39: 174-180.
39. Mohsen MO, Zha L, Cabral-Miranda G, Bachmann MF. Major findings and recent advances in virüs-like particle (VLP)-based vaccines. Seminars in Immunology 2017;34: 123-132.
40. https://www.who.int/publications/m/item/draftlandscape-of-covid-19-candidate-vaccines. Erişim Tarihi: 11 Nisan 2022.
41. Sasso E, D'Alise AM, Zambrano N, Scarselli E, Folgori A, Nicosia A, et al. New viral vectors for infectious diseases and cancer. Seminars in Immunology 2020;50: 101430.
42. Ghattas M, Dwivedi G, Lavertu M, Alameh MG. Vaccine Technologies and Platforms for Infectious Diseases: Current Progress, Challenges, and Opportunities. Vaccines 2021;16;9(12): 1490.
43. Vrba SM, Kirk NM, Brisse ME, Liang Y, Ly H. Development and Applications of Viral Vectored Vaccines to Combat Zoonotic and Emerging Public Health Threats. Vaccines 2020;13;8(4): 680.
44. Vanaparthy R, Mohan G, Vasireddy D, Atluri P. Review of COVID-19 viral vector-based vaccines and COVID-19 variants. Le Infezioni in Medicina 2021;29(3): 328-338.
45. Baldo A, Leunda A, Willemarck N, Pauwels K. Environmental Risk Assessment of Recombinant Viral Vector Vaccines against SARS-Cov-2. Vaccines 2021;9(5): 453.
46. Hofmeyer KA, Bianchi KM, Wolfe DN. Utilization of viral Vector vaccines in preparing for future pandemics. Vaccines, 2022;12;10(3): 436.
47. Kaynarcalidan O, Moreno Mascaraque S, Drexler I. Vaccinia Virüs: From Crude Smallpox Vaccines to Elaborate Viral Vector Vaccine Design. Biomedicines 2021;9(12): 1780.
48. Verheust C, Goossens M, Pauwels K, Breyer D. Biosafety aspects of modified vaccinia virüs Ankara (MVA)-based vectors used for gene therapy or vaccination. Vaccine 2012;30(16): 2623-32.
49. Callendret B, Vellinga J, Wunderlich K, Rodriguez A, Steigerwald R, Dirmeier U, et al. A prophylactic multivalent vaccine against different filovirüs species is immunogenic and provides protection from lethal infections with Ebolavirüs and Marburgvirüs species in non-human primates. PLoS One 2018;13(2): e0192312.
50. Chiuppesi F, Salazar MD, Contreras H, Nguyen VH, Mar-

tinez J, Park Y, et al. Development of a multi-antigenic SARS-CoV-2 vaccine candidate using a synthetic poxvirüs platform. Nature communications 2020;11(1): 6121.

51. Gilbert SC. Clinical development of Modified Vaccinia virüs Ankara vaccines. Vaccine 2013;31(39): 4241-4246.
52. E Silva DSO da Fonseca FG. The Rise of Vectored Vaccines: A Legacy of the COVID-19 Global Crisis. Vaccines 2021;9(10): 1101.
53. Zuniga A, Wang Z, Liniger M, Hangartner L, Caballero M, Pavlovic J, Wild P, et al. Attenuated measles virüs as a vaccine vector. Vaccine 2007;25(16): 2974-83.
54. Humphreys IR, Sebastian S. Novel viral vectors in infectious diseases. Immunology 2018;153(1): 1-9.
55. Combredet C, Labrousse V, Mollet L, Lorin C, Delebecque F, Hurtrel B, et al. A molecularly cloned Schwarz strain of measles virüs vaccine induces strong immune responses in macaques and transgenic mice. Journal of virology 2003;77(21): 11546-11554.
56. Mateo M, Reynard S, Journeaux A, Germain C, Hortion J, Carnec X, et al. A single-shot Lassa vaccine induces long-term immunity and protects cynomolgus monkeys against heterologous strains. Science Translational Medicine 2021;13(597): eabf6348.
57. CyanVac LLC. Phase 1 Study of Intranasal PIV5-vectored COVID-19 Vaccine Expressing SARS-CoV-2 Spike Protein in Healthy Adults. https://ClinicalTrials.gov/show/NCT04954287. Erişim Tarihi: 22 Temmuz 2022.
58. Institute of Vaccines and Medical Biologicals Vietnam A Phase 1/2 Safety and Immunogenicity Trial of COVID-19 Vaccine COVIVAC. https://ClinicalTrials.gov/show/NCT04830800. Erişim Tarihi: 22 Temmuz 2022.
59. Flotte TR and Lu S. DNA Vaccination in 2018: An Update. Human Gene Therapy 2018;9: 963-965.
60. Saha R, Killian S and Donofrio RS. DNA Vaccines: A Mini Review. Recent Patents on DNA & Gene Sequences 2011;2: 92-96.
61. Atanasiu P, Orth G, Rebiere JP, Boiron M, Paoletti C. Production of tumors in the hamster by inoculation of desoxyribonucleic acid extracted from tissue cultures infected with polyoma virüs. Comptes Rendus Hebdomadaires des Seances de L'academie des Sciences 1962;254: 4228-4230.
62. Hasson SSAA, Al-Busaidi JKZ and Sallam TA. The past, current and future trends in DNA vaccine immunisations. Asian Pacific Journal of Tropical Biomedicine 2015;5;(5): 344-353.
63. Miklavcic D. Handbook of Electroporation, pp: 1933–1952. In: Liu L, Morrow MP and Bagarazzi M. Clinical Use of DNA Vaccines. 2017, 1st ed. Springer.
64. Ulmer JB, Donnelly JJ, Parker SE, Rhodes GH, Felgner PL, Dwarki VJ, et al. Heterologous protection against influenza by injection of DNA encoding a viral protein. Science 1993; 259(5102): 1745-1749.
65. Calarota S, Bratt G, Nordlund S, Hinkula J, Leandersson AC, Sandström E, et al. Cellular cytotoxic response induced by DNA vaccination in HIV-1-infected patients. Lancet 1998;351(9112): 1320-5.
66. Shafaati M, Saidijam M, Soleimani M, Hazrati F, Mirzaei R, Amirheidari R, et al. A brief review on DNA vaccines in the era of COVID-19. Future Virology 2022;17(1): 49-66.
67. Witharana C. DNA Vaccine: An insight. International Journal of Medical Science in Clinical Research and Review 2021;4(06):1-6.
68. Soltani S, Farahani A, Dastranj M, Momenifar N, Mohajeri P, Emamie AD. DNA vaccine: Methods and mechanisms. Advances in Human Biology 2018;3: 132-9.
69. Porter KR, Raviprakash K. DNA Vaccine Delivery and Improved Immunogenicity. Current issues in molecular biology 2017;1: 129-138.
70. Oyston P, Robinson K. The current challenges for vaccine development. Journal of medical microbiology 2012;61: 889-894.
71. Maruggi G, Zhang C, Li J, Ulmer JB, Yu D. mRNA as a Transformative Technology for Vaccine Development to Control Infectious Diseases. Molecular Therapy 2019;27(4): 757-772.
72. Wolff JA, Malone RW, Williams P, Chong W, Acsadi G, Jani A, et al. Direct gene transfer into mouse muscle in vivo. Science 1990;247: 1465-1468.
73. Jirikowski GF, Sanna PP, Maciejewski-Lenoir D, Bloom FE. Reversal of diabetes insipidus in Brattleboro rats: intrahypothalamic injection of vasopressin mRNA. Science 1992;255: 996-998.
74. Qiu P, Ziegelhoffer P, Sun J, Yang N. Gene gun delivery of mRNA in situ results in efficient transgene expression and genetic immunization. Gene therapy 1996;3: 262-268.
75. Lurie N, Saville M, Hatchett R, Halton J. Developing Covid-19 Vaccines at Pandemic Speed. New England journal of medicine 2020;382(21): 1969-1973.
76. Pollard C, De Koker S, Saelens X, Vanham G, Grooten J. Challenges and advances towards the rational design of mRNA vaccines. Trends in molecular medicine 2013;19(12): 705-713.
77. Sullenger BA, Nair S. From the RNA world to the clinic. Science 2016;352(6292): 1417–1420.
78. Steinle H, Behring A, Schlensak C, Wendel HP, Avci-Adali M. Concise review: application of in vitro transcribed messenger RNA for cellular engineering and reprogramming: progress and challenges. Stem Cells 2017;35(1): 68–79.
79. Pardi N, Hogan MJ, Porter FW, Weissman D. mRNA vaccines- a new era in vaccinology. Nature reviews Drug discovery 2018;17(4): 261-279.
80. Gupta SK, Haigh BJ, Griffin FJ, Wheeler TT. The mammalian secreted RNases: mechanisms of action in host defence. Innate immunity, 2013;19(1): 86-97.
81. Ahmed R, Akira S, Casadevall A, Galan JE, Garcia-Sastre A, Malissen B, et al. Current Topics in Microbiology and Immunology, pp: 1-40. In: Zeng, C., Zhang, C., Walker, P.G., Dong, Y. Formulation and Delivery Technologies for mRNA Vaccines. 2020, 1st ed. Springer, Berlin, Heidelberg.
82. Probst J, Weide B, Scheel B, Pichler BJ, Hoerr I, Rammensee HG, et al. Spontaneous cellular uptake of exogenous messenger RNA in vivo is nucleic acid-specific, saturable and ion dependent. Gene Therapy 2007;14(15): 1175-1180.
83. Sahin U, Derhovanessian E, Miller M, Kloke BP, Simon P, Löwer M, et al. Personalized RNA mutanome vaccines mobilize poly-specific therapeutic immunity against cancer. Nature 2017;547(7662): 222-226.
84. Canton J. Macropinocytosis: New Insights Into Its Underappreciated Role in Innate Immune Cell Surveillance. Frontiers in immunology 2018;9: 2286.
85. Sahay G, Alakhova DY, Kabanov AV. Endocytosis of nanomedicines. Journal of controlled release 2010;145(3): 182-195.

86. Kowalski PS, Rudra A, Miao L, Anderson DG. Delivering the Messenger: Advances in Technologies for Therapeutic mRNA Delivery. Molecular Therapy 2019;27(4): 710-728.
87. Blakney AK, Abdouni Y, Yilmaz G, Liu R, McKay PF, Bouton CR, et al. Mannosylated poly(ethyleneimine) copolymers enhance sarna uptake and expression in human skin explants. Biomacromolecules 2020;21(6): 2482-2492.
88. Chahal JS, Khan OF, Cooper CL, McPartlan JS, Tsosie JK, Tilley LD, et al. Dendrimer-RNA nanoparticles generate protective immunity against lethal Ebola, H1N1 influenza, and Toxoplasma gondii challenges with a single dose. Proceedings of the National Academy of Sciences 2016;113(29): E4133-E4142.
89. Sköld AE, van Beek JJ, Sittig SP, Bakdash G, Tel J, Schreibelt G, et al. Protamine-stabilized RNA as an ex vivo stimulant of primary human dendritic cell subsets. Cancer immunology, immunotherapy 2015;64(11): 1461-1473.
90. Hoerr I, Obst R, Rammensee HG, Jung G. In vivo application of RNA leads to induction of specific cytotoxic T lymphocytes and antibodies. European journal of immunology 2000;30(1):1-7.
91. Vesikari T, Forstén A, Herbinger KH, Cioppa GD, Beygo J, Borkowski A, et al. Safety and immunogenicity of an MF59(®)-adjuvanted A/H5N1 pre-pandemic influenza vaccine in adults and the elderly. Vaccine 2012;30(7): 1388-96.
92. Wculek SK, Cueto FJ, Mujal AM, Melero I, Krummel MF, Sancho D. Dendritic cells in cancer immunology and immunotherapy. Nature Reviews Immunology 2020;20(1):7-24.
93. Choi A, Koch M, Wu K, Chu L, Ma L, Hill A. *et al.* Safety and immunogenicity of SARS-CoV-2 variant mRNA vaccine boosters in healthy adults: an interim analysis. Nature medicine 2021;27(11): 2025-2031.
94. Chaudhary N, Weissman D, Whitehead KA. mRNA vaccines for infectious diseases: Principles, delivery and clinical translation. Nature Reviews Drug Discovery 2021;20(11): 817-838.