

Progress in Human Papillomavirus (HPV) Vaccine Development

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Papillomaviruses are a group of small non-enveloped DNA tumor viruses with a virion size of ~55 nm in diameter. This group of viruses infects various animals from birds to mammals, including humans. Papillomaviruses replicate and assemble exclusively in the nucleus. The viral gene expression and replication proceed in a tightly controlled fashion regulated by keratinocyte differentiation. The viral gene expression leads to the expression of six nonstructural viral regulatory proteins (E1, E2, E4, E5, E6 and E7) from the early region of the viral genome and two structural viral capsid proteins (L1 and L2) from the late region of the [1]. E1 and E2 are involved in viral DNA replication and the regulation of early transcription. L1 and L2 are involved in capsid formation and E6 and E7 are mainly responsible for cancer cells growth [2].

To date, more than one hundred human papillomavirus genotypes (types) have been identified of which HPV 16 and 18 are considered as high-risk type and responsible for 70% of cervical cancers worldwide, and HPV 6 and 11 are the predominant low-risk types that mostly cause genital warts. Human papillomavirus (HPV) is one of the deadliest virus for human which cause the second largest of cancer related death of women all over the world with an estimated 490,000 cases and 270,000 deaths each year [3]. Currently, two prophylactic vaccines, Gardasil (Merck, USA) and Cervarix (GlaxoSmithKline, UK) are available in the market. Both vaccines consist of the immunogenic L1 VLPs (Viral Like Particles) of HPV 16 and 18, with Gardasil containing additional 6 and 11 [4]. The vaccines are administered intramuscularly and require multiple doses. The approximate cost for three doses is 500 dollar.

The vaccines have significant limitations that restrict their applications in the third world countries, the places where they are most needed. The vaccines are expensive, require cold chain storage and trained personnel for administration. Thus it necessitates further development of this vaccine to overcome the drawbacks. The most feasible way to achieve this goal is to develop an oral formulation using nano or micron-sized particle of biodegradable polymer. Nano or micro-particulate oral formulation of vaccines is able to address all of these limitations as they are stable at room temperature, inexpensive to produce and can be administered orally [5,6]. Examples of nanoparticle based vaccines/drugs include oral biodegradable microspheres with recombinant anthrax vaccine for anthrax infection, poly (DL-lactide-co-glycolide) (DL-PLG) microspheres encapsulating phosphorylcholine against *Salmonella typhimurium*, and albumin-chitosan mixed matrix microsphere-filled coated capsule formulation of typhoid vaccine [7-9]. One of the major advantages of using nanoparticle as vaccine is that no adjuvant is required in the formulation. In general, the performance of particulate carriers as vaccine adjuvant is attributed to a number of functions such as particulate carriers can serve as an effective antigen delivery system and facilitate the uptake of antigens by antigen-presenting cells, particle-based antigen carriers may serve as a depot for controlled release of antigen, particle-based formulation may possess the ability to modulate the type of immune responses induced when used alone or in combination with other immunostimulatory compounds, and particulates have the ability to protect the integrity of antigens against degradation until delivered to the immune cells [10,11]. Several technologies for the oral administration of drugs/vaccine using nanoparticles and microparticles and several biodegradable polymer based vaccine microparticle formulations

have been studied as effective vaccine delivery systems [12]. Also the vaccines are not therapeutic vaccines. Therefore another goal is to develop a therapeutic HPV vaccine. Thus the nano or micro-particulate formulation of HPV vaccine will be able to provide the opportunity to combine both prophylactic and therapeutic vaccines in the same formulation. In summary, the current HPV vaccine research mostly focused on developing a formulation that will be able to address the drawbacks of marketed vaccines and will also be able to contain both prophylactic and therapeutic vaccines.

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