Chapter 1: Introduction

May, 8, 2020, marks 40 years since the World Health Organization certified smallpox as globally eradicated (Kutzler, Ugen and Weiner, n.d.). Smallpox was a disease prevalent all around the world. In areas with susceptible populations capable of maintaining reservoirs it existed in the form of an endemic infection. In these areas, with no animal reservoir, the main reservoir of the disease was children. In order for the virus to have survived, it needed to constantly spread from human to human, spreading throughout the world through travelers causing epidemics (Kutzler, Ugen and Weiner, n.d.). Despite the only known reservoir of the smallpox virus being humans, there have been theories tracking the virus back to rodents. It is thought that this virus first began as a rodent-borne poxvirus many years ago. Since its emergence, there have been various epidemics observed throughout human history with an estimate of around 300 million deaths due to smallpox during the 20th century (Chertow & Kindrachuk, 2020; Fenner et al., 1988; Riedel, 2005).

Smallpox caused by the variola virus (VARV) was a devastating disease. While there is no Latin or even Greek word for smallpox, the name variola does have Latin origins. In the 10th century the term “smallpox” was used to distinguish variola from syphilis which was at the time known as the “great pox” (Kutzler, Ugen and Weiner, n.d.). The first reported emergence of smallpox can be traced back to around the first human agricultural settlements which was close to 10,000 B.C.. The first scientific evidence of the disease was isolated and identified from mummified remains dating back to the 18th Egyptian dynasty. Literature for the description of smallpox was not found until the 4th century A.D. in China and 10th century in southwestern Asia. However, rare descriptions do appear as early as 430 B.C.. One of the first descriptions of smallpox in South Africa was in the year 1904 and in the United States in the year 1914 after which it became prevalent all through the United States and some parts of South America, Europe and even Southern and Easten Africa (Kutzler, Ugen and Weiner, n.d.).

The variola and vaccinia viruses are both members of the Poxviridae family, a successful family of viruses consisting of the causative agent of smallpox, variola virus, as the most well known member (Buller & Palumbo, 1991). Poxviruses are oval-to-brick-shaped double stranded DNA viruses. There are several viruses within this genus that are capable of causing human disease including: monkeypox virus (MPXV), cowpox virus (CPXV), variola virus (VARV) and vaccinia virus (VACV) (Chertow & Kindrachuk, 2020; Diven, 2001).

The discovery of vaccinations was a dramatic turning point not only in the story of smallpox but in all of medical history. Since its beginning, in the form of a procedure known as variolation to the development of the vaccination we know today, things have come a long way. Variolation involved the deliberate infection of an individual for a more controlled disease and immunity against future smallpox infections. The use of a similar virus, cowpox, to protect against smallpox was first tested by Dr Edward Jenner followed by the discovery of the vaccinia virus for use as a vaccination (Fenner et al., 1988; Henderson & Preston, 2009). Smallpox was eventually eradicated through the Smallpox Eradication Program launched by the World Health Organization through the years 1966 to 1980 (Chertow & Kindrachuk, 2020; Fenner et al., 1988).

In the case of vaccinations, the modulation of the immune system is the key component to be understood. There is no question regarding the crucial role of humoral and cellular immunity in the case of any infection and vaccination (Munier et al., 2016). The primary response to vaccines comprises the synthesis and release of substances from cells of the innate immune system such as macrophages, dendritic cells and keratinocytes as well as the involvement of the adaptive immune system. The balance between T helper cells (Th) - 1 and T helper -2 cells has been found to be a key determinant of the course as well as the outcome of the disease (Bray, 2003).

There are very few diseases we have been able to declare eradicated globally. Behind a success story of this disease lies a well-designed vaccination and vaccine administration plan. While smallpox has been eradicated it has begun to pose a threat in the form of bioweapons. With the smallpox vaccination no longer being a required immunization, there are a large number of unvaccinated people

around the world with no immunity to this disease, the lack of proper treatment and the large number of immunocompromised people indicates that the variola virus has immense potential for rapid and extensive spread (Kutzler, Ugen and Weiner, n.d; Vermeer et al., 2007). This has led to a growing interest in the development of new vaccines and therapeutic agents (Kutzler, Ugen and Weiner, n.d.). Understanding how our body accepts this vaccine and what happens during the primary immune response to this vaccine may aid in the design of future vaccinations.

To uncover what happens in the body after vaccination, the Affymetrix DNA Microarray platform will be used to analyze numerous genes simultaneously (Liu et al., 2010). Participants of the study were vaccinated and have blood draws prior to vaccination, when the lymph node is inflamed, as well as days 10 to 21. This will be done to map out the body's response to the most successful vaccine in the world. The data analyzed in this study is from Day 13 which is the peak of the effector or activated CD4 and CD8 response.