while solvent-based silk scaffolds with a similar pore size showed significantly less degradation over the same time course, with residual material still present one year after implantation. Throughout the study, the animals showed no visible signs of any adverse response. The low host immune response towards the implant was inferred by comparing mRNA expression of various markers, including interferon-γ, tumour necrosis factor-α and interleukins, from the retrieved scaffolds and control tissues (Wang et al. 2008). The results indicated that the macrophages recruited towards the silk were the main contributors to silk degradation, because only scaffolds that allowed cell infiltration showed any substantial degradation over the study period (Wang et al. 2008). Silk has been reported to induce a transient and mild foreign body response that activates the complement system, but this response typically subsides within 14 days and does not progress to a chronic inflammatory response (Thurber et al. 2015).

All biomaterials derived from a non-autologous source will elicit a foreign body response following implantation *in vivo*, albeit to varying degrees (Altman et al. 2003). Historically, adverse reactions reported for silk sutures can be largely attributed to the use of virgin silk fibres that contained contaminating sericin, as this causes an allergic reaction, or to the use of braided silk fibres that were coated with waxes (commonly referred to as black braided silk) (Altman et al. 2003). Silk fibroin elicits a foreign body response following implantation *in vivo* (Thurber et al. 2015), but this response is comparable to that elicited by the most popular synthetic materials in use today as biomaterials [e.g., poly(lactic-co-glycolic acid), polycaprolactone, polylactic acid].

The intensity of the biological response also depends on the implantation site and the model used for investigation. For example, silk scaffolds, films and hydrogels are commonly implanted subcutaneously (Thurber et al. 2015) and are expected to result in different biological responses when compared to that triggered by their placement into immune privileged sites such as the back of the eye (e.g., vitreous, retina), the testicles and, to some extent, the articular cartilage. A different biological response would be expected yet again following the administration of silk directly into tissues of the immune system, such as the spleen, lymph nodes or liver.

Information is currently limited regarding the tissue response towards silk hydrogels, but the available data are encouraging (Etienne et al. 2009; Critchfield et al. 2014; Hamilton et al. 2015). For example, injection of sonication-induced silk hydrogels into the cervix of pregnant rats (gestational day 13) as a potential therapeutic approach to preterm birth (Critchfield et al. 2014; Brown et al. 2016) resulted in a mild foreign body response similar to that observed with polyglycolic acid and poly(ethylene terephthalate) sutures (Critchfield et al. 2014). These *in vivo* studies assessed the biological response at 4 days post treatment, and they were supplemented by *in vitro* studies with human cervical cells, which showed no up-regulation of inflammatory markers. However, the longer-term effects, such as longitudinal inflammatory responses, biodegradation or impacts on pregnancy (e.g., a shift to a post-term pregnancy), are currently unknown (Critchfield et al. 2014).

One longer-term study compared silk hydrogels to collagen type I hydrogels both *in vitro* and *in vivo* (Etienne et al. 2009). Nude mice, at one and two weeks post implantation of silk hydrogels, showed signs of inflammation in the tissues surrounding the silk hydrogels, as indicated by the presence of eosinophils, neutrophils and macrophages around the hydrogel periphery, but showed no infiltration of these