Shigellosis caused by Shiga toxin (Stx)-producing *Shigella dysenteriae* serotype 1 or Stx-producing *Escherichia coli* (STEC) continues to be a major public health threat and is a particular concern because of the potential to develop life-threatening extra-intestinal complications, such as acute renal failure (hemolytic uremic syndrome; HUS), and CNS complications, such as seizures, paralysis, and death. Once Shiga toxins (Stxs) are internalized following the toxin-receptor binding on host cellular surface, they are trafficked into the Golgi apparatus and to the ER in a retrograde manner to enter the host cell cytosol, leading to various host cellular responses, including protein synthesis inhibition, apoptosis through ER stress, autophagy, and inflammation. Distinct investigations on host cell signaling responses activated by Stxs as multifunctional proteins are necessary to identify novel targets for intervention in pathogenesis. Moreover, many studies present compelling and strong evidence regarding therapeutic applications to target particular diseases, such as tumors, by engineering the toxins.

At the molecular, cellular or clinical level, an improved understanding of the pathogenesis of the diseases' bacillary dysentery and hemorrhagic colitis, and the subsequent development of extra-intestinal/extrarenal complications caused by STEC, will be necessary to develop effective protective and interventional therapies to treat patients infected with the organism.

This Special Issue of *Toxins* will focus on recent advances to consider unexplored mechanisms of STEC-mediated pathogenesis, current therapeutic applications or STEC genetics contributing to pathogenicity.