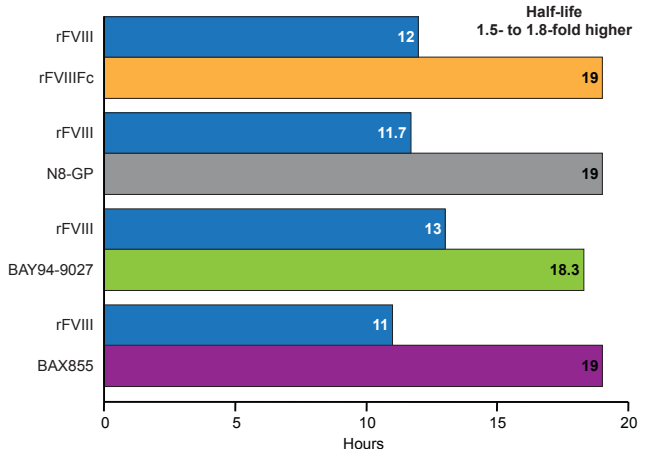
durable knockdown of antithrombin with an up to 4-fold increase in peak thrombin generation. Clinical trial using this novel drug will start at the end of this years.

Figure 2. Half-Life Extension of Long Acting rFVIII



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Another approach is a humanized bispecific antibody to Factors IXa and X, termed hBS23 (ACE910), which is able to restore Factor VIII hemostatic activity. It is delivered via intravenous injection and has a 2-week half-life. Subcutaneous bioavailability of ACE910 is 84%. A clinical trial using this product has already started in Japan [JapicCTI-121934; http//www.clinicaltrials.jp].

Complement Inactive in *E. coli* Shiga Toxin-Producing Diseases

Written by Rita Buckley

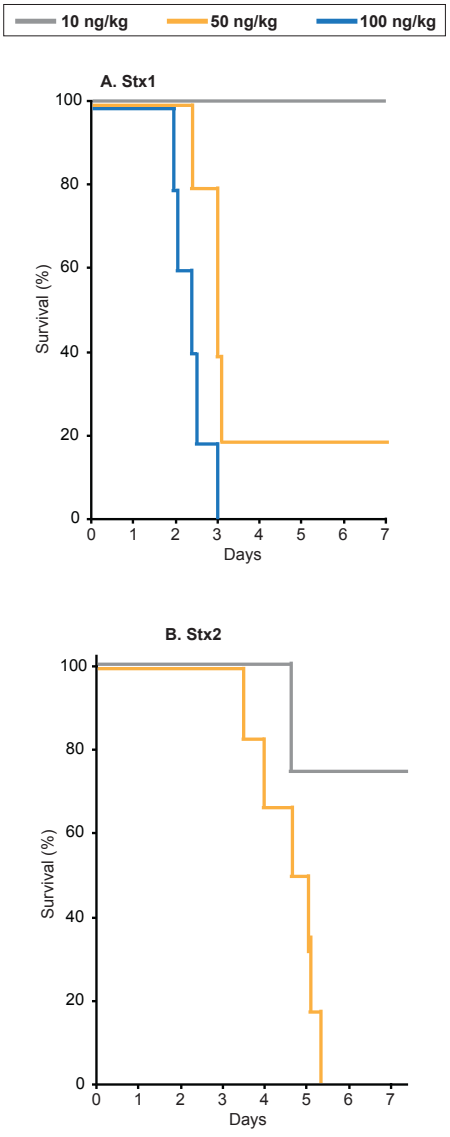
In a nonhuman primate model of hemolytic uremic syndrome (HUS), complement was not activated despite clear microvascular thrombosis and cellular injury. Complement is an important immune defense mechanism. Shinichiro Kurosawa, MD, PhD, Boston University School of Medicine, Boston, Massachusetts, USA, presented outcomes from a study on the role of complement in HUS and thrombotic microangiography induced by *Escherichia coli* (*E. coli*) Shiga toxins.

Enterohemorrhagic Shiga toxin-producing *E. coli* (EHEC), the leading cause of acute renal failure in otherwise healthy children, is associated with the potentially lethal complication of HUS. EHEC are food- and water-borne bacteria, contributing to the estimated 76 million illnesses, 325,000 hospitalizations, and 5200 deaths each year in the United States attributable to foodborne outbreaks, with a total annual cost of $10 to $83 billion [Bavaro MF. *Curr Gastroenterol Rep* 2012]. Toxins from these bacteria cause kidney, intestinal, and neurologic damage.

A 2011 outbreak of an *E. coli* strain secreting Shiga toxin type-2 in Germany infected 3842 individuals, many after consuming contaminated fenugreek sprouts. More than 50% of them required hospitalization; 855 developed HUS; and 54 died [Werber D et al. *BMC Med* 2012].

In order to develop a clinically-relevant animal model of HUS, Stearns-Kurosawa and colleagues [*Infect Immun* 2010] studied the effects of Shiga toxin types 1 and 2 (Stx1, Stx2) in nonhuman primates, comparing the *in vivo* consequences of the toxins in a parallel and reproducible manner. They found that the time course, pathology, and cytokine profiles differed between Stx1 and Stx 2, but that both induced HUS (Figure 1).

Figure 1. Time Course, Pathology, and Cytokine Profiles Differ Between Stx1 and Stx2



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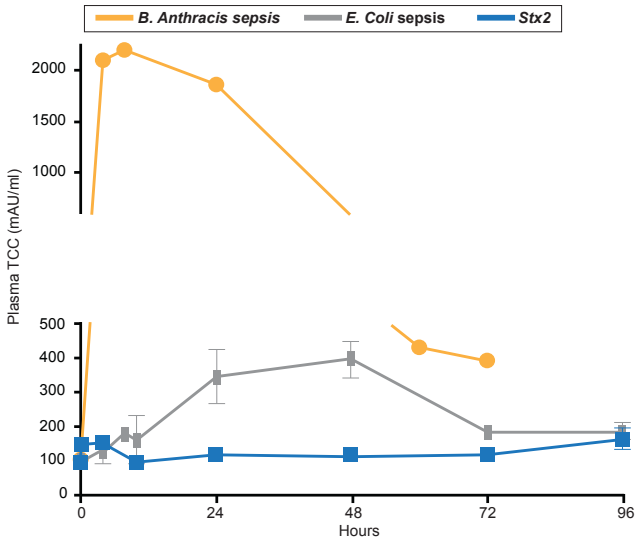
In a subsequent study, Lee and colleagues [*Blood* 2013] asked whether complement activation is a major pathway for HUS development in this animal model. Some patients show evidence of complement activation during EHEC infection, raising the possibility of therapeutic targeting of complement for relief. Nonhuman primate models indicate otherwise. They found that platelet levels declined in a dose-dependent manner after Stx1 and Stx2 (thrombocytopenia). Evidence of coagulation and full HUS development was clear. D-dimer was elevated, indicating that both coagulation and fibrinolysis took place. Damage-associated molecular patterns (DAMPs; HMGB1 and histones) were also elevated, indicating tissue damage. However, complement was not activated. There were no significant increases in soluble terminal complement complex (C5b-9) levels after challenge with lethal Stx1 (n=6) or Stx2 (n=5) in plasma samples from T0 to euthanasia at 49.5 to 128 hours post challenge (Figure 2). This contrasts with robust complement activation in bacteria sepsis models (*Bacillus anthracis*, nontoxin *E. coli*), which have disseminated intravascular coagulation, rather than HUS.

These studies found that in preclinical models, complement activation is not required for the development of thrombotic microangiopathy and HUS induced by EHEC Shiga toxins. The global nature of food processing and distribution raises the stakes in the study of EHEC, heightening the imperative to recognize, treat, and report it. To date, no specific treatment is available.

Figure 2. Complement Activation Is Not the Major Pathway for HUS Development.



Quiescent complement in nonhuman primates during *E.coli* Shiga toxin-induced hemolytic uremic syndrome and thrombotic microangiopathy.

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