“We are living in the most exciting time in the history of the treatment of hemophilia.” This opinion was shared by many of the 100 physicians and researchers attending National Hemophilia Foundation’s (NHF) 11th biennial workshop, Novel Technologies and Gene Transfer for Hemophilia, held in March in Philadelphia.

Why the optimism? World-renowned pioneer in hemophilia treatment Dr. Edward Tuddenham says we are in the midst of a “Renaissance of product development.” More than 30 biosimilar (generic) factor products, extended half-life products, or enhanced-activity factors are in development. Novel treatments are being tested, including ways to eliminate the need for factors VIII or IX. Research into the immune system may show us ways to reduce the risk of inhibitors. Of course, we’ve also made steady advancements in our knowledge of gene therapy.

New products hitting the market in the next few years will offer you more treatment choices. Will you switch to a new product even when your current product is safe and effective? Are there risks in switching? Should you participate in a clinical trial for a new product or for gene therapy?

The goal of this special feature article is first, to outline the major areas of research in hemophilia treatment, and second, to help you be a better-informed consumer. When new products and treatments become an option, you’ll know what questions to ask.
I was sorting through a pile of photos recently from my 24 years in the hemophilia community, preparing them for the scanner in an attempt to go completely digital. I enjoyed the nostalgic feelings I had looking at them, recalling a particular NHF meeting or a certain hemophilia summer camp, smiling at how young we all looked, and marveling at the little boys I know who are now men. I’ve been sending the original photos, once I’ve scanned them, out to colleagues and friends to enjoy and remember.

One photo really caught my eye before I popped it into the envelope: a mom from Massachusetts and me, posing together at an NHF meeting. Behind us hung a big sign: “Campaign for the Cure.”

Remember the campaign? In the mid-1990s, there was a concerted effort to raise money to fund a cure for hemophilia. Sadly, the campaign fell by the wayside when a young man with a chronic disorder died while in a clinical gene therapy trial in 1999. Many researchers became skittish and fearful of liabilities, and gene therapy began to disappear, even though this case was not related to hemophilia.

It seemed then that gene therapy would never become a reality for our community. But there’s still hope. In this issue, Paul Clement reviews not only the quest for gene therapy, but the progress of current technologies that improve quality of life for people with bleeding disorders. From gene therapy to longer-acting factor, you can stay hopeful that a better life is always coming for our loved ones.

I look forward to the day when I take no more photos of my hemophilia days, when I close the doors to my business, when hemophilia becomes history.

PEN is a newsletter for families and patients affected by bleeding disorders. PEN is published by LA Kelley Communications, Inc., a worldwide provider of groundbreaking educational resources for the bleeding disorder community since 1990.

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Thank you for the package [of books] you sent us. We received it just before Christmas, and it was one of the best gifts we received. We just recently had a port put in our seven-month-old son. He did great; bounced right back to his normal happy self! I want to let you know how much we appreciated your reaching out to us. When we first found out about our son, we were so scared. But thanks to the support from people like you, we feel so much better about our situation and count our blessings every day!

Armida McDowell
California
Day and Night: Hemophilia the Second Time Around

My boys are like day and night. My 15-year-old, Julian, is a free spirit: creative, artistic, with a great sense of humor, and a gifted musician. His idea of a perfect day is to be in New York City watching Broadway shows. My 5-year-old, Caeleb, adores choo-choo trains and playing in the dirt, can’t get enough chocolate ice cream, and embraces life with all his heart. They have a bond as brothers, and they also share the bond of severe hemophilia A.

Julian was almost 10 when Caeleb was born. When my husband Joe and I broke the news to Julian that his little brother also had hemophilia, he clapped and jumped for joy! We were stunned. Why was he so excited? “When I am in leadership training at camp,” Julian replied, “he will be a camper!” My sweet son saw only the commonalities and blessings of hemophilia. He would share one of his most exciting summer activities with his baby brother.

But my boys don’t share everything. Caeleb wants to go to a monster truck rally, and Julian loves watching live theater. Caeleb is a social butterfly, while Julian keeps to himself. And as for hemophilia, they can’t even begin to compare adventures.

Julian’s hemophilia has been pretty easy so far. No major bleeds or target joints, and a port that lasted five years without infection. Caeleb, on the other hand, has a target joint and suffers from extremely painful bleeds. He is on his fourth port, fights a high-titer inhibitor, and has been hospitalized often. With ten years’ difference between my boys, at times I still feel like a “newly diagnosed” parent.

During one of Caeleb’s hospital stays, the nurses were having a tough time starting an IV. Poke after poke, nurse after nurse, and my Julian, 12 at the time, was standing outside the room crying silent tears for his brother. His knowledge of empathy and compassion will always be with him. He loves deeply. As for Caeleb, when he has an infusion or blood draw peripherally, despite his fear, he tries his hardest not to “cry and wiggle,” so he can “be like his big bro.”

My sons and their hemophilia differ significantly—you’d almost think they have different severity levels and even different bleeding disorders. But a medical condition may manifest in its own way in each person: what is day to one becomes night to another. Over the past five years, our family has spent immense time and energy learning to live with Caeleb’s hemophilia. It’s been challenging, compared to the ten years before Caeleb’s birth, but one thing’s for sure: my boys struggle with their bleeding disorder in different ways, and it has bonded them together.

In 2010, while I was out of town, Caeleb’s port was not working and my husband had to access him peripherally. Caeleb was having an active bleed, and infusing him was an emergency; we live two hours from the hemophilia treatment center. Instead of letting his little brother be uncomfortable and scared, Julian sat with him, explained what was going to happen, and never stopped holding his hand. His encouragement helped my husband focus on the actual infusion instead of having to keep Caeleb calm. My husband never prompted Julian to help. Julian just rose to the occasion and did what brothers do.

No one chooses to have a chronic illness. It just happens. Hemophilia has changed my family—it has brought out the best in us all. My husband and I are closer than ever in our 22 years together. The reality of hemophilia can damage and destroy relationships, but luckily, we have made it through stronger than before. Of course, if I could banish hemophilia, I would in a second! And yet, I have so many blessings in my life that if I could give them away, it would...
“I would love to see a longer-lasting VIIa.”
“A medicine that would eliminate an inhibitor.”
“Products that don’t cause inhibitors in the first place.”

Are any of these on your wish list for new or improved inhibitor products?

Wouldn’t it be great to have a fairy godmother (or a genie in a magic lamp) who could grant any wish? How about an inhibitor product that would last days or weeks instead of just a few hours? Maybe even one that didn’t have to be given intravenously?

In our real world, we don’t have fairy godmothers or genies (oh well), but there are scientists, doctors, and researchers who are working on some of the items on our wish lists.

Wishes for... Faster-acting or longer-lasting factor

Factor products that last longer in the bloodstream are at the top of many inhibitor family wish lists. Advances in biotechnology are raising hopes that faster-acting or longer-lasting therapies and treatments for inhibitors will be available in the next few years.

Debbie Porter of California is one mother who’d like to see products last longer. “I mean long lasting,” she explains, “not just an hour or two more—I’m talking days or weeks.” Medically, inhibitor bleeds can mean days in the hospital coping with pain. And bleeds are often more frequent in inhibitor patients because of multiple target joints. A longer-lasting product would possibly reduce the frequency and help preserve the joints.

A bleed also means a child misses many days of school, or an adult misses many days of work. Dosing frequently for several days to heal a bleed can be tough, especially in children, who have trouble sitting still in the best of circumstances. Cicely, who has a son with inhibitors, would also like to see products that last longer than the ones currently available. “Longer-acting VIIa would be wonderful, especially for the inhibitor patients, like my son, who have joint bleeds every day.” She notes, “The hardest thing we face is keeping a very active boy immobile while healing, to prevent re-bleeding.”

Yes, life can be tough for inhibitor patients. The good news is that several companies are now working on longer-lasting recombinant factor VIIa. CSL Behring is testing a new recombinant product, rVIIa-FP, which has a longer half-life than the only factor rVIIa product currently on the market: Novo Nordisk’s NovoSeven®RT. A product with a longer half-life means that patients would need fewer doses of factor to stop bleeds, and the doses could be spread farther apart. Inspiration Biopharmaceuticals is also working on a recombinant factor VIIa, which is now in preclinical trials (not yet tested in humans).

Novo Nordisk is in phase III clinical trial of a faster-acting rVIIa product. It’s designed to produce a stronger clot so a bleed can be stopped with fewer infusions.

Wishes for... New types of products

How about a brand-new type of product—one that hasn’t been on the market yet? Maybe one that works in an entirely different way from the products that are now available?

“T would like to see a new product that would be more...
When gene therapy was first proposed as a treatment for hemophilia, it sounded just like science fiction. We had to use our imaginations to understand this innovative technique because it was so different from today’s standards of treatment with factor concentrates.

But science fiction can be used as an inspiration for learning in the classroom, just as teacher Harry Clement Stubbs (1922–2003) did with his students. Stubbs taught high school science for 40 years at Milton Academy in Milton, Massachusetts, and used science fiction as a teaching tool to motivate his students.

Before his teaching career began, Stubbs had trained as an astronomer at Harvard University, and then had flown combat missions in a bomber during World War II. But what his students may not have known about their teacher was that he was also a writer of science fiction. Stubbs considered himself a teacher more than a writer, and he used the pseudonym Hal Clement when he wrote hard science fiction, a genre grounded in scientific principles. He wrote over 40 short stories and 12 novels, always with a scientific basis. Even in his fiction, Stubbs wanted to be a teacher and provide factual material for readers.

In The Best of Hal Clement, editor Lester del Ray collected 10 of Clement’s science fiction stories. One of these, “A Question of Guilt,” originally published in 1976, included a character with hemophilia. The story takes place sometime around the second century AD. Marc of Bistrita, a diplomat living near the Adriatic, travels to Rome to seek the advice of healers, even Galen of Pergamum (not a fictional character, but a renowned Greek physician who lived in what is now Turkey). Marc’s four sons have been cursed with bleeding that does not stop, and three have already died. His remaining son, Kyros, a young boy of six, bruises easily and shows some lameness.

To stop his son’s bleeding finger cut, Marc applies his own blood, yet he believes that a better treatment would be to replace Kyros’s lost blood: possibly, he thinks, Kyros should drink some blood, or perhaps new blood could be put directly into his veins. Then, after Kyros suffers a right bicep puncture wound from a sharp stick, Marc attempts a blood transfusion. Unfortunately, Kyros dies. His mother, unable to bear the grief of losing four sons to bleeding, commits suicide.

In the afterword to del Ray’s volume, Stubbs explains that “A Question of Guilt” was originally written for an anthology of vampire stories that was never published; the story was subsequently published in an anthology of horror stories, even though Stubbs considered it science fiction. The character Marc was never identified as a vampire in the story, though there were allusions to his strange late-night behavior in search of blood from local villagers.

As a memorial to author Hal Clement, accolades from 26 notable science fiction writers have been collected by Shane Tourtellotte in the book Hal’s Worlds. In an interview, Stubbs comments, “I wrote the story, and when it was done it was hard science fiction. My vampire was a retired Roman army surgeon of about the time of Galen, who had the misfortune to sire four [hemophilic] sons, of whom one was still alive at the time of the story. He got his unpopular reputation with the neighbors by his attempts to solve the problem of blood transfusion a couple of thousand years before we knew enough to have any chance of doing so.” Regrettably, Stubbs’s story contains some medical misinformation: Marc identifies arteries and veins that are needed for the continuous circulation of blood within the body; but in the second century, the Galen theory of blood flow was only one-way from the stomach, where food was converted to blood, and then to the heart where it was burned for energy.

Other science fiction writers have admired Hal Clement for the high quality of his writing and for his role as their mentor. And I suspect that the students at Milton Academy admired their teacher, Harry Stubbs, because they benefited from his style of science teaching—augmented with science fiction.

Don’t we all wish that our high school science teachers had been as innovative as Stubbs in capturing our attention and stimulating our curiosity? Today, we can also appreciate Hal Clement for including a character with hemophilia in a sci-fi short story.
Pulse on the Road kicked off 2012 with a visit to Hawaii, during the same week that the Supreme Court listened to oral arguments over the Affordable Care Act (ACA).

Pulse on the Road welcomed 35 families of the newly founded Hawaii Hemophilia Foundation, headed by Jennifer Chun. Jenn is the mother of five, including two sons with hemophilia. She’s done a super job of bringing the community together to learn, support one another, and network.

Pulse on the Road’s three-hour insurance symposium began with Laurie Kelley’s look at the history of hemophilia healthcare; how the US healthcare system has treated us in the post-HIV era; and how and why that system has sometimes created roadblocks that prevent access to care. Next, Michelle Rice, director of public policy at National Hemophilia Foundation, shared ideas on comparing and contrasting healthcare plans with an insurer, using the NHF Insurance Toolkit. Jim Romano of Patient Services Inc. (PSI) concluded by reviewing ACA and discussing what Hawaii can expect from healthcare reform. We had great audience interaction with a very informal atmosphere.

Keep an eye on the news in June for the Supreme Court’s decision on the individual mandate and ACA. The court’s decision will affect us all for a long time to come.

Next stop…Hemophilia of North Carolina! To find out more about Pulse on the Road and where we are headed this year, visit our website:

www.kelleycom.com

We are grateful to Baxter Healthcare for supporting this event and all the Pulse on the Road symposia.
Why the Burst in New Products?

It’s no coincidence that every manufacturer of factor concentrates has one or even several new products in the pipeline. This is because the patents or orphan drug “periods of exclusivity” on most current factor concentrates have expired or will soon expire. Patents and periods of exclusivity protect a manufacturer from competition, so that after investing time and research into creating a product, the company has time to recoup its expenses.

Within the last five years, the patents, patent extensions, and periods of exclusivity expired on all major brands of factor VIII, IX, and VII sold in the US. As less expensive generic forms, called biosimilars or follow-on biologics, come to market, the loss of these patents and manufacturer protections will cut into pharma profits. As a result, pharma is looking for new, improved products to patent and sell to maintain market share and profits.

Biosimilars

Almost all the major manufacturers of current factor products (US-based and international) have one or more biosimilar products in phase II or III clinical trials (see sidebar, page 13). Biosimilars are undergoing full clinical trials because, unlike generic forms of chemical compounds that are easily reproduced and cheap to make, biologic drugs such as clotting factor can’t be made identical to the original forms. The proteins in every brand of factor are slightly different. This is because dozens of variables in the manufacturing process can alter a protein; a tiny change in the manufacturing process of a biosimilar might make it more immunogenic or less effective. That’s very important for hemophilia patients—more immunogenic means more likely to produce an immune response and cause inhibitors to form.

immunogenic – likely to produce an immune response

low immunogenicity – unlikely to produce an immune response (read: lower risk of inhibitors!)

Rest assured for now that the US Food and Drug Administration (FDA) will not rush, or fast-track, approvals of biosimilar factor. Several organizations, including NHF and Plasma Protein Therapeutics Association (PPTA), have urged the FDA not to take shortcuts in approving biosimilars, fearing that they would be less effective or more immunogenic. Under the FDA’s current proposal, issued in February, the extent of the clinical work needed for biosimilars to go to market will be determined case-by-case, and researchers believe that for factor products, this will mean full clinical trials.

And what about price? Biosimilar factor will definitely be less expensive, but perhaps not by as much as many of us would like. Unlike chemical generic drugs (such as ibuprofen) that may sell for a fraction of the cost of the brand-name drug (such as Motrin®), biosimilars are expected to sell at only 10% to 30% less than current factor concentrates. This is because manufacturers will still have to recoup their investments in research and development and build additional production facilities, which cost $400 to $500 million each.

Besides biosimilars, what else is on the horizon? A lot.

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generic refers only to chemical drugs, like pills and creams.

biosimilar refers to biologic drugs, which are made from living organisms, or to their products, such as vaccines or factor.

1. A pharmaceutical company can apply for orphan drug status from the FDA for drugs with a potential target population of fewer than 200,000. Orphan drugs are granted a seven-year period of exclusivity, during which the FDA will not accept applications for other similar drugs. 2. NHF letter to FDA on biosimilars: www.hemophilia.org/NHFWeb/Resource/StaticPages/menu0/menu7/menu122/NHF_FDA Biosimilars.pdf. PPTA White Paper on Biosimilars: www.pptaglobal.org/UserFiles/file/White%20Paper-toPPTA6-4-09-withoutPlasSD.pdf.
Extended Half-Life

Extending the half-life of factor concentrates is by far the most intensive area of research—probably because it’s the most easily obtainable goal, with the highest potential to quickly generate new products.

The half-life is the amount of time it takes for one-half of a drug to be removed from the blood. The half-life of factor varies with each product, and also from person to person. For patients with inhibitors, the half-life of factor is short—sometimes measured in minutes instead of hours. For factor VIII deficiency without inhibitors, the half-life is about 8 to 12 hours. For factor IX, it’s about 18 to 24 hours.

Factor with a longer half-life would offer obvious benefits: fewer infusions, fewer bleeds, lower lifetime cost, and better quality of life. Imagine having to infuse only once every five or seven days for prophylaxis!

So how are researchers making factor with longer half-lives? They’re taking some different approaches, which we’ll review in the next few sections.

PEGylation – modifying a molecule by attaching to it long strands of polyethylene glycol, to delay the molecule’s removal from the blood.

PEGylation

PEG stands for the chemical compound polyethylene glycol. PEGylation is the process of attaching long strands of PEG to the factor molecule. Researchers think that the constantly moving, long strands of PEG whir around the factor molecule—keeping away immune cells, antibodies, enzymes, and anything that might attach to the factor and remove it from the blood. This same mechanism might also potentially reduce the formation of inhibitors or reduce the clearance (removal from the bloodstream) of the factor in the presence of inhibitors. Early tests with PEGylation found that it did indeed lengthen the half-life, but it also destroyed up to 70% of the factor’s activity. To avoid this problem, subsequent research has focused on targeting where the PEG attaches to the factor molecule. By finding the right spots, researchers have discovered that the PEGylated factor VIII still works, and its half-life can be at least doubled in animals. Results of a clinical trial with PEGylated factor VIII in humans is expected to be available this summer.

Polysialylation

A similar, but perhaps safer, alternative to PEGylation is polysialylation. Instead of using PEG, this method uses polysialic acids, natural compounds found mainly on the

GlycoPEGylation

A variation of PEGylation is glycoPEGylation, in which PEG is attached to a sugar (glycan) that is attached to the factor. This

PEG Problems?

Although PEGylation has been used successfully in several drugs for short-term treatment, a problem for hemophilia and chronic therapy is the possibility that PEG could build up to toxic levels over time. Other PEGylated drugs use smaller chains of PEG that can be partially metabolized (broken down) and excreted through the kidney. But PEGylated factor uses long chains of PEG; these are not naturally metabolized and are too large to be excreted by the kidney. Because the liver is believed to be the primary site where factor is removed from the bloodstream, the long chains of PEG attached to PEGylated factor might build up over time in the liver, even to toxic levels over a patient’s lifetime.

PEG is Popular!

Bayer is working on a PEGylated recombinant factor VIII (rFVIII) product, Novo Nordisk has a glycoPEGylated rFVIII and rFIX molecule, and Baxter is testing a PEGylated rFVIII product, all in early-to-midstage testing in humans.

3. On the other hand, patients have made antibodies against PEGylated drugs used to treat other conditions.
surfaces of nerve cells and easily metabolized. Not only do these molecules increase the half-life of the factor, but they’re also non-immunogenic, they reduce the immunogenicity of the factor (making inhibitors less likely), and they’re easily degraded, even at large doses. Baxter is in the early stages of testing a polysialic acid rFVIII product in animals.

Fusion Technology
If you subscribe to HemAware or have visited the exhibition hall at an NHF meeting in the past few years, you may have already heard about fusion technology. Fusion involves producing a recombinant factor molecule that has another recombinant molecule attached—fused—to it. The fused molecule extends the half-life of the factor. When in production, both the factor and the fused molecule are expressed by the cell line together as a unit, the same way as recombinant factor is now produced. Two fusion protein prospects are in clinical trials: albumin fusion and Fc fusion.

Albumin Fusion
Albumin is a natural blood plasma protein with a low immunogenicity and a long half-life of about 20 days. One of its jobs is to ferry smaller molecules through the circulatory system. Attaching albumin to factor IX might help extend half-life as albumin ferries the factor. To maintain the factor’s activity, the albumin-fusion factor molecule was designed so that when the factor IX is activated (ready to participate in the clotting process), the albumin will break off—so it won’t interfere with the factor’s function. Early tests of a factor IX albumin fusion molecule by CSL Behring have been shown to triple the half-life of factor IX. Just think: this could allow prophylaxis with once-a-week infusions. This same technology is also being used in a factor VIIa albumin-fusion product that has recently entered clinical trials.

Fc Fusion
Biogen Idec has two fusion products in clinical trials: a recombinant factor VIII and recombinant factor IX. Both use a “recycling” process to extend half-life. Here’s how it works: circulating proteins, including factor, are continually being cleared (removed) from the bloodstream. This happens naturally: one clearance process involves endothelial cells, which line the insides of blood vessels. These cells randomly latch onto proteins—such as factor—circulating in the blood, and then pull them into the cell, where they are digested by enzymes. The body sees the older proteins as “trash” and efficiently removes them, allowing “fresh” proteins to be synthesized.

If we could somehow prevent factor from being digested by the endothelial cells, then it would remain in the bloodstream longer and have a longer half-life. This is the goal of Fc fusion. Scientists have found that some proteins, like certain antibodies produced by the immune system called immunoglobulin G (IgG), have a protein fragment called Fc attached to them that protects them from being digested. When factor with Fc fused to it is pulled in by the endothelial cells, the cells “spit” the factor back out into the bloodstream—recycling the protein! Biogen Idec’s clinical trials show an almost-doubled half-life for factor VIII and a near-tripled half-life for factor IX using Fc fusion.

**cell line** — a group of cells, maintained outside the body, used to produce recombinant proteins

**expression** — the process a cell uses to take information coded in the DNA and then make a finished product, such as clotting factor
XTENylation
A third type of fusion molecule is XTEN. XTENs are long chains of proteins that act similarly to the chemical compound PEG. XTENylation is the fusion of XTEN to proteins, such as factor VIII or IX, to extend their half-life. XTEN fusion has several advantages over PEGylation: unlike PEG, XTEN is readily biodegradable and has little or no immunogenicity, and proteins attached to XTEN maintain their activity. Plus, compared to PEGylation, the manufacturing process is simpler and up to 50% less expensive. Amunix, the company that invented the XTENylation process, is partnering with Biogen Idec to develop XTENylated factors VII, VIII, and IX. Early studies of XTENylated factor are promising: an increase in the half-life of 1.6 times for factor VIII, 2.7 times for factor IX, and 7.6 times for factor VII, all in animals.

What does “1.6 times the half-life” mean, in practical terms?
If the half-life of factor VIII is 12 hours, and if a new product shows an increase of 1.6 times the half-life, the factor product would now have a half-life of 19.2 hours. That’s pretty good. For a factor IX product showing an increase of 2.7 times the half-life, the half-life would now be up to 65 hours—that’s really good! So before you get too excited when you hear about an increase in half-life, be sure to do the math: multiply the increase by the original half-life to see how many more hours or days the new product’s effectiveness is extended.

Enhanced Clotting Factors
What if scientists could make factor work better, or faster? We could stop bleeds using less factor, or stop bleeds faster.

Faster-Acting Factor
Several faster-acting products are now in development. Novo Nordisk has bioengineered factor VIIa to make it faster acting when compared with the company’s own NovoSeven®RT recombinant factor VIIa—and with stronger clot formation. This means that a person with inhibitors could control bleeds faster and with fewer infusions. In fact, the company hopes the product will initiate clotting as effectively as an infusion of factor VIII or IX in someone without inhibitors. And because the clots are stronger, there may be less re-bleeding in the days after a bleed. Novo Nordisk initiated the phase III clinical trial of this fast-acting recombinant factor VIIa in summer 2011. Bayer is developing a bioengineered recombinant factor VIIa that is faster acting and longer lasting, and has recently finished an early clinical study.

Hyperfunctional Factor
In 2009 the New England Journal of Medicine reported on a 23-year-old man in Padua, Italy, who was diagnosed with thrombophilia (the tendency to form clots) as a result of a mutated factor IX gene. Although the man had normal levels of factor IX, his factor activity was eight times that of normal factor IX! This mutation, dubbed factor IX Padua, has since been cloned, and through bioengineering, several variants of
factor IX have been developed with high activity. These “hyperfunctional” factor IX variants will be useful not only in gene therapy and in treating factor IX deficiency, but also in treating factor VIII deficiency with inhibitors. When researchers tested different hyperfunctional factor IX variants, they found that high activity could initiate clotting even in the absence of factor VIII! These are not yet in clinical testing, and as the products enter the trials, scientists will need to watch carefully for too much clotting, as happens with the natural Padua mutation.

**Tweaking the Clotting Cascade**

Research on hemophilia treatment isn’t limited to developing better clotting factors; it also includes modifying how coagulation works internally—so that treatment won’t require infusing factor at all!

There are natural checks on coagulation. It works something like this: any injury to a blood vessel instantly activates the clotting cascade to begin clot formation and stop blood loss. At the same time, the body kicks into gear to limit coagulation. Why? So the process won’t spiral out of control and cause excessive clotting (thrombosis). One coagulation check is tissue factor pathway inhibitor, or TFPI. TFPI is a protein that slows or stops factor VII from combining with tissue factor. When factor VII and tissue factor combine, they activate factors IX and X, making them ready to participate in the clotting cascade. When the action of TFPI is blocked, more factor IX and X are activated, increasing clotting. Researchers have found that if TFPI is blocked, then coagulation can proceed—even if the person is missing factor VIII or IX, or has inhibitors!

Two anti-TFPI products are now in early clinical development. Novo Nordisk has developed a monoclonal antibody that blocks the action of TFPI. This product can be infused subcutaneously (under the skin) and is in phase I clinical trial. The specific target population (hemophilia A or B, with or without inhibitors) has yet to be determined. Baxter is studying another anti-TFPI compound derived from brown algae, which can be injected subcutaneously or taken orally.

**Human Cell Culture Lines**

You may know that recombinant clotting factors are produced from genetically engineered baby hamster kidney (BHK) cells or Chinese hamster ovary (CHO) cell lines containing the human gene for factor VIII or IX. These animal cells produce (express) human factor, which is then collected, purified, freeze-dried, and bottled. But human factor VIII is a very large and complex molecule that is hard for these nonhuman cells to express. Although the BHK and CHO cell lines do a good job of expressing factor, it’s hard for nonhuman cells to properly “finish” the factor—meaning they may not properly fold the factor into its final three-dimensional shape, and they may not do a good job of attaching other molecules to the factor’s surface, as human cells do. Improperly finished proteins may not work efficiently or may have increased immunogenicity. On the other hand, if we used human cells to express and finish factor proteins, then the cells may be able to express more factor, and that factor may have lower immunogenicity and may work better. But we’ll have to wait for the results of clinical trials to find out if this is true. Octapharma has an rFVIII product created by a human cell line currently in phase III clinical trial.

**Custom-Designed Clotting Factors**

Not all factor VIII or IX molecules are identical. Factor differs slightly among different human races. This may be why African Americans have a significantly higher rate of
inhibitors: commercial factor may differ slightly from their own factor, making it more immunogenic to them. Bioengineering of the factor molecule may allow for more custom-designed factor for specific populations, reducing the incidence of inhibitors.

Recombinant Porcine Factor VIII
Inspiration Biopharmaceuticals is currently in phase III clinical trial of OBI-1, a new recombinant porcine (pig) factor VIII to treat acquired hemophilia A (an autoimmune disease) and hemophilia A with inhibitors. Porcine factor VIII is different enough from human factor VIII that it usually escapes detection by the immune system (so inhibitors aren’t alerted), but similar enough that it functions to produce a clot.

Besides the drugs and treatments mentioned here, lots of others are being explored. Read the Headlines section in PEN, and subscribe to the electronic NHF eNotes and HemAware Express for news releases on new treatments under development.

Patient Services Inc. is a national nonprofit organization committed to providing a variety of services to patients living with specific chronic illnesses. Call or visit us online today to see if you are eligible for assistance!

www.patientservicesinc.org
1.800.366.7741

What Happened to Gene Therapy?
After raising more than $9 million during a decade of fundraising for research into gene therapy, NHF’s “It’s Time for a Cure” campaign ended in 2008. Yet many people are still asking: Where’s the cure?

When the NHF campaign was implemented in 1998, our community was optimistic about the future of gene therapy—in hindsight, we were also naïve about the challenges. Gene therapy was slowed by setbacks: in 1999, 18-year-old Jesse Gelsinger, who suffered from a rare metabolic disorder, died after a gene therapy treatment at the University of Pennsylvania. Fearing safety issues and liabilities, researchers put many gene therapy trials on hold after Jesse’s death—some for years—while research protocols were reviewed and patient safeguards strengthened. A few years later, four gene therapy trials were put on hold when a three-year-old boy in France, after having been cured by gene therapy of a fatal immune deficiency disease (“Bubble Boy” disease), developed a cancer similar to leukemia—and his gene therapy treatments were blamed. Within several years, two more boys in the same clinical trial developed the same type of cancer, and in 2007, a woman died after receiving a gene therapy treatment for rheumatoid arthritis. All these incidents occurred in conditions other than hemophilia, using different genes and different viruses to carry the gene into the body than those used in hemophilia gene therapy.

Despite these setbacks, gene therapy has made steady progress since the first trial in 1989. Scientists worldwide are working on individual pieces of the gene therapy puzzle that can eventually be assembled into effective treatments for a variety of diseases, from hemophilia to severe combined immune deficiency.

4. She was later found to have a systemic fungal infection, and the gene therapy treatment is believed to have weakened or stressed her immune system, letting the fungal infection rage unchecked.
Some scientists are working on more effective ways to get the genes for producing factor into the cell of choice. Because viruses are experts at getting genetic material into cells, most of this avenue of research focuses on bioengineering viruses to effectively carry the genes to the cell. These bioengineered viruses, called **viral vectors**, are disabled and can no longer cause disease. They are designed to target only the cells of interest (for hemophilia, mainly liver cells), to make them less immunogenic, safer, and less toxic.

Other scientists are working on **non-viral vectors**, including stem cell transplants that would then produce functional factor. Still others are working on how to target exactly where in the DNA a gene will be inserted—reducing or eliminating the risk of causing cancer that can occur when genes are randomly inserted into the DNA (which is what happened in earlier gene therapy trials). And scientists are also working on bioengineering the genes for factor VIII and IX to make it easier for a cell to produce them, and to make variations of the factor proteins with higher activity—so less factor can do the job.

Scientists who attended NHF’s Novel Technologies and Gene Transfer for Hemophilia workshop believe that the technical details of an effective gene therapy for hemophilia can be worked out within the next five to eight years. Yet they don’t believe that gene therapy will be commercially ready until at least a decade from now. Why? Because no one group (research lab or pharmaceutical company) will hold all the cards to put together an effective gene therapy treatment. The work of many different groups will need to be combined to create safe, effective products that can be marketed. The problem is that each group has patented its own proprietary processes, techniques, and bioengineered molecules. Unless some pharmaceutical company with deep pockets can buy out or make an arrangement with each group that holds a patent, we’ll just have to wait until the patents expire—and most will expire in about a decade.

When gene therapy does become a reality, you’ll most likely see a treatment for factor IX deficiency debut first. Why? Because the gene for factor VIII is so large that it’s hard to package the gene and other necessary genetic material into some viral vectors. The factor VIII protein itself is large too, and difficult for some cells to produce. The factor IX protein and its gene are much smaller, making them easier to work with.

**Clinical Trial Phases**

The FDA requires that new drugs and treatments be tested for safety, and also to demonstrate that they effectively treat the disorder or disease for which they are being developed. Drugs always start with a phase I clinical trial, and then may move to phase II and phase III trials. If a drug is found unsafe or ineffective at any stage, then the clinical trial will be ended, and research on the drug will be either modified or abandoned.

**Phase I:** After a new drug or treatment is initially tested on animals, researchers test it on a small group of people (20–80) to evaluate safety, determine the safe dosage range, and identify side effects.

**Phase II:** If a drug or treatment appears safe at the end of the phase I trial, researchers give it to a larger group of people (100–300) to evaluate its effectiveness in patients, and to further assess safety.

**Phase III:** At this stage, the drug or treatment is given to an even larger group of people (1,000–3,000) to confirm effectiveness over a broad range of patients, monitor side effects, compare to commonly used treatments, and collect information to promote safe use. For rare disorders such as hemophilia, it’s almost impossible to enroll 1,000 patients for a clinical trial. In these cases, the FDA will approve phase II or III trials with much smaller populations.

**Phase IV:** Post-marketing studies provide more information, including the drug or treatment’s risks, benefits, and best use.

*For information: clinicaltrials.gov/ct2/info/understand*
One factor IX gene therapy treatment has shown some promising early clinical results, as published in the *New England Journal of Medicine* in December 2011. Although the treatment caused some mild liver toxicity (which was managed), four of the six patients in the study are now using much less factor or no factor after more than a year, with factor levels after the treatment ranging from 2% to 12%. Although none of the six patients’ factor levels reached 13%—the minimum factor level needed to stop most spontaneous joint bleeds, and the minimum goal of gene therapy—the study showed that the technique could work. More clinical studies are underway using this technology. But because factor VIII is a much larger molecule, it may not work using this same system. Scientists are confident that hemophilia will be cured by gene therapy, but it will take longer than we anticipated. The good news is that just as the Renaissance ushered in a new era of rapid scientific exploration and innovation following the Middle Ages, we are now in a Renaissance of hemophilia product development. Fortunately, we can expect advanced products in the near future that will greatly improve our quality of life.

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5. One drawback of enrolling in early gene therapy clinical trials is that you won’t be able to enroll in another trial—if the “new and improved” version of the therapy—using the same vector because your immune system is now trained to rapidly destroy the viral vector the next time it’s encountered.

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Questions to ask before participating in a clinical trial

Know as much as possible about the clinical trial, and feel comfortable asking your healthcare team about it. Use these questions as a guide:

- What is the purpose of the trial?
- Who is going to be in the trial?
- Why do researchers believe the experimental treatment being tested may be effective?
- Has this treatment been tested before?
- What kinds of tests and experimental treatments are involved?
- How do the possible risks, side effects, and benefits in the trial compare with my current treatment?
- How might this trial affect my daily life?
- How long will the trial last?
- Will hospitalization be required?
- Who will pay for the experimental treatment?
- Will I be reimbursed for other expenses?
- What type of long-term follow-up care is part of this trial?
- How will I know that the experimental treatment is working? Will results of the trial be given to me?
- What happens if I am harmed by the trial?
- Who will be in charge of my care?

Adapted from clinicaltrials.gov/ct2/info/understand
Wheels for the World

On June 17, cyclist Barry Haarde will launch a coast-to-coast 3,667-mile bike ride from Oregon to New Hampshire to raise funds for the international nonprofit Save One Life. Barry is a 46-year-old Texan living successfully with hemophilia A, HIV and hepatitis. This is the first time someone will bike across America for hemophilia.

Why this matters: The ride will publicize hemophilia, show what people with hemophilia can do, and raise funds for those who are without treatment.

For info: www.SaveOneLife.net

NHF Inhibitor Education Summits

July 19-22 • Miami, Florida
August 2-5 • San Diego, California

Join inhibitor families and patients for a special gathering to learn about treatments and to network. Summits are for inhibitor patients only; travel and accommodations provided.

Why this matters: With only about 1,200 patients with inhibitors in the US, families often feel isolated, and can gain support by meeting each other.

For info: Zuiho Taniguchi, 877-560-5833
ztaniguchi@hemophilia.org

The Time is NOW for VWD Patients

Arizona Hemophilia Association (AHA) hosted the first annual National Outreach for von Willebrand (NOW) conference. AHA executive director Cindy Komar and her team assembled a great cast of speakers and facilitators, and provided entertainment for the kids during the weekend event. At least 25 states were represented. NOW was funded by CSL Behring, makers of Humate-P® for VWD.

Why this matters: Although up to 1% to 2% of Americans are affected by VWD, most patients remain undiagnosed or are not connected with HTCs.

For info: www.hemophiliaaz.org
Bayer HealthCare’s Factor Solutions program now provides the Bayer Reimbursement Helpline to assist Kogenate® FS users with the changes in healthcare reform and insurance, including product reimbursement and claim issues; assessing new insurance and alternate funding sources; understanding Explanation of Benefits; and determining eligibility for assistance programs. **Why this matters:** Some insurance changes may be specific to the brand of factor you use.  
**For info:** 800-288-8374  
The Bayer Reimbursement Helpline does not guarantee reimbursement.

### Try Koate-DVI

Kedrion Biopharma is continuing the Koate®-DVI TRY IT program through December 31, 2012. Koate-DVI is a plasma-derived factor VIII concentrate that is subject to double-viral inactivation with solvent detergent and heated in the final container to 80° C. TRY IT provides up to two weeks’ therapy at no charge for qualified applicants. Applicants must be factor VIII patients who have never used Koate-DVI, who have physician approval, and whose request does not exceed 50,000 IU. **Why this matters:** Hemophilia patients tend to be brand loyal; free trials offer a way to sample new products without commitment.  
**For info:** www.koate-dviusa.com

### Advate’s New Diluent Size

Baxter now has a 2 mL diluent volume for Advate, available for dosage strengths 250, 500, 1000, and 1500 IU. The new package includes a 25-gauge Terumo butterfly infusion set to help accommodate the smaller infusion volume. Advate will continue to be available with a 5 mL diluent for dosage strengths 2000 IU and 3000 IU. **Why this matters:** Smaller diluent size means smaller volume and potentially faster infusions.  
**For info:** www.thereforyou.com

### Meet the World of Hemophilia

**World Federation of Hemophilia Biannual Congress**  
**July 8–12, 2012**  
**Palais des Congrès de Paris**  
**Paris, France**  
Over 4,000 patients, healthcare providers, and industry reps are expected at WFH’s biannual event. **Why this matters:** It’s important for the global community to meet to share new treatments, strategies, and networking opportunities to advance care around the world.  
**For info:** exhibitis2012@wfh.org or www.viparis.com

### Inhibitors: Independent Iran

Iran has launched domestic production of a recombinant factor VIIa concentrate to treat hemophilia patients with inhibitors. The product will be manufactured at the Aryogen Research and Manufacturing complex, which reportedly has also initiated production of recombinant monoclonal antibodies. Currently, Iran imports Novo Nordisk’s NovoSeven®RT. **Why this matters:** Iranian government officials estimate that producing both factor VIIa and monoclonal antibody products will save the country approximately $100 million annually.  
**Source:** IBPN, www.marketingreserachbureau.com
My First Factor series is designed to help young children, ages 18 months to 4 years, understand their bleeding disorder.

My First Factor: HTC
Who does a toddler meet at the HTC? Help your child develop a positive relationship with his or her hemophilia treatment center. By Shannon Brush, mother of a son with hemophilia. Illustrated by Brooke Henson. Published October 2011 by LA Kelley Communications, Inc. Sponsored by Factor Support Network.
To order: www.kelleycom.com

First Hand-Held Device Detects Need for CT Scans
The US FDA approved marketing of the first hand-held device, Infrascanner Model 1000, intended to aid in the detection of intracranial hematomas. A trained healthcare provider can use the device to help determine the likelihood of an intracranial hematoma and the need for further diagnostic procedures, such as a computed tomography (CT) scan. Why this matters: An intracranial hematoma can be life-threatening if it is not treated immediately.
For info: www.fda.gov or 888-INFO-FDA

clarification
In “Private Parts: Is Your Personal Health Information Exposed?” (February 2012), a reference to the HERO study may have given a misleading impression concerning its patient privacy policy.

HERO is the largest-ever, multinational multi-method study exploring the psychosocial impact of hemophilia. It is supported by Novo Nordisk and led by the HERO International Advisory Board. In each of 10 participating countries, patients and caregivers were recruited through hemophilia patient organizations.

Although the general privacy policies of Kantar Health, the company carrying out the study, may not have been described on the NHF web page that invited patients to participate, the HERO study actually took these extra precautions to protect patients and caregivers:
(1) Independent Research Board (IRB) overseeing conduct of the study by the sponsor and recruitment efforts by NHF;
(2) IRB-approved patient recruitment materials distributed by NHF that include description of how the data will and will not be used and plans to protect patient privacy;
(3) an additional IRB-approved description of the risks/benefits of participation and privacy protection on the online survey itself, including a mandatory consent; and
(4) a toll-free contact number and website for the IRB, and an email contact for the HERO team at Kantar Health where potential participants could direct questions.

Any patient contact information will be used solely by Kantar Health to provide honorarium for participation, and personal information will not be transferred to any third parties.
be by the truckload. I hope that when I share my story or a few words of encouragement, someone may see a positive in what’s often the negative of living with a chronic condition.

Siblings can be like day and night. One is the life of the party, and the other prefers a quiet corner. One is a sports nut, and the other a musician. One is a math whiz, and the other a writer. I had no idea, when hemophilia came into my life a second time, that this journey would be so incredibly different from the first. Ten years after my older son was born, my younger son’s birth has become the biggest surprise and biggest challenge of my life.

But day always follows night, and dawn brings hope. Hope can be the best of things, and it never abandons you.

Inhibitor Insights... from p. 4

effective during an inhibitor [bleed] instead of taking so many days or weeks for a bleed to heal,” says Cazandra MacDonald, mother of two sons with inhibitors.

Inspiration Biopharmaceuticals is currently in the phase III clinical testing stage of a new recombinant porcine (pig) factor VIII, called OBI-1. It’s not a bypassing product but is intended to treat hemophilia A with inhibitors. Porcine factor VIII is close enough to human factor VIII to participate in the coagulation process to form a clot, but different enough that it escapes detection by most inhibitors to human factor VIII.

Novo Nordisk is also working on a new treatment method called Anti-TFPI, which is in phase I clinical trial. TFPI stands for tissue factor pathway inhibitor. It’s a protein that stops or slows the formation of blood clots. Anti-TFPI blocks the action of TFPI, allowing coagulation to proceed even in the absence of factor VIII or factor IX. And best of all, it can be injected subcutaneously!

The new or improved products currently being tested hold much promise, but not everyone may be willing or able to change treatment regimens right away. Cazandra explains, “There would have to be some significant reasons to change...when you find a product that works, why change?”

Wishes for...

Better access to care

Unfortunately, many of the challenges facing families with inhibitors may not be fixed by new and improved products alone.

Your family may live far from a hospital or HTC, or the medical staff near you may have little or no experience with inhibitors. “We have to go to another state to monitor the inhibitor because their doctors have inhibitor experience,” Cazandra explains. More treatment centers with staff trained in inhibitors would ease this burden.

The high cost of inhibitor products is another major concern. As medical costs skyrocket, employers and insurance companies are taking a closer look at their bottom line. They may start limiting access to certain (more expensive) products or discouraging the use of “newer” or what they consider “experimental” products. Employers may cut back on their employees’ insurance coverage. But, says Debbie, “It would sure be nice to have [products] that more people could have access to.”

Wishes for...

Finally, a cure

Of course, a cure for hemophilia or prevention of inhibitors tops everyone’s list. Debbie explains, “Inhibitor patients have more joint damage, more hospitalizations...The top of my wish list would be medicines or therapies that cure hemophilia or eliminate the inhibitor.”

As scientists continue to study the complex genetics of hemophilia, they hope to gain insights into who might be more likely to develop an inhibitor. We may be able to tailor treatments to prevent inhibitors in people who show a high risk of developing them based on their genetics. Or, if inhibitors do develop, specific treatments could be created for individuals based on their particular genetics or biochemistry.

Researchers are working on finding ways to cure or prevent hemophilia altogether. If we could replace the defective genes that are causing hemophilia with properly working genes, patients could eventually produce their own clotting factor. No bleeds, no inhibitors. A wish come true. @

Cazandra lives in Truth or Consequences, New Mexico, with her husband, Joe, and their sons, Julian and Caeleb. She works in the healthcare industry, is active in church ministry, and writes a column for the local newspaper. Follow more of her journey with hemophilia: 2brotherswithhemophilia@blogspot.com
Inbox... from p. 2

Project SHARE

Thank you so much for helping Reniel. We received the factor in time to save his life. In two weeks he will have a follow-up checkup with his doctor. God bless, and thank you for your sincerity in helping us!

Raymund Naños
Blood Brothers Aid, Inc.
Philippines

Thank you for the support given to my son Jovan. I am so grateful for your love and care. It has not been easy for him for the last three weeks because of the bleed, but thank God we have people like you in the world. Be blessed.

Stella Ssewungu
Uganda

Thank you so much for fulfilling my request. I received the FEIBA yesterday. My mom got it from HAPLOS [a local hemophilia organization]. It came in time for the bleed in my right hip. I was very lucky to have the medicine. Thank God I was able to infuse it yesterday. My heartfelt thanks to you.

Robert Jhon Bunag
Philippines

I just received your gift today. You’re really very generous. I didn’t believe my eyes: three vials of factor, each more than 1700 IU. These things I’d seen only in pictures on the Internet. From the deepest bottom of my heart, I appreciate you and your organization. Thank you so much for bringing me such feelings. I hope you are always strong, healthy and happy to go forward on your compassionate way.

Le Huu Hung
Vietnam

“Private Parts: Is Your Personal Health Information Exposed?”

I had a chance to peek at the November issue of PEN and the privacy work you’ve done. Kudos—this is great work. Such an important topic to provide education and provoke thoughtful dialog. We continue to communicate on this as well. Coming from multiple sources can only support learning for our community members!

Kimberly Haugstad
Executive Director
Hemophilia Federation of America

Mother’s Day Parenting Moment

A mother is a person who seeing there are only four pieces of pie for five people, promptly announces she never did care for pie.

—Tenneva Jordan

God could not be everywhere and therefore he made mothers.

—Jewish proverb

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