



Factor Nine News

The Coalition for Hemophilia B Fall 2009

Topics in Hemophilia

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- Save the Date! CHB Dinner and Symposium



Factor Nine Family Meeting held in conjunction with the National Hemophilia Foundation's 61st Annual Meeting in San Francisco, California - October 31, 2009



Even dogs wear sunglasses in California!

Mystery: Where did the Sea Lions Go?

I am sure that many of you who attended the NHF in San Francisco at the end of October took a little time to see the Sea Lions at Pier 39. For two decades, hundreds of sea lions have made their home at San Francisco's Pier 39. They have provided hours of entertainment to onlookers from all over the world. Around Thanksgiving they disappeared and no one knows why.

The Marine Mammal Center counted more than 1700 sea lions on October 23rd. On December 29th, only about a dozen were found and these were attempting to climb on docks other than the ones reserved for them.

Currently, biologists have no idea as to why the sea lions are leaving. There is no apparent change in the food supply and the increasing ocean temperatures should actually cause a rise in the number of animals.

Joe Cordero is a biologist at National Marine Fisheries Service, he shares with us, "It's hard to say why they've departed. As to when and if they come back, no one can say. It's puzzling."

Hopefully they will come back in the spring - we will keep you posted.

Information obtained from www.examiner.com



A Sense of Community...

by Kirstin A. Duggan

Being involved in the hemophilia community has always been an important part of my life. The community is more than a group of people that share a common need - it is a group that has become my family. With no history in our family, being a female with mild hemophilia and having a brother with severe hemophilia, it was hard to understand and grasp the concept at first. However, the support of those around us helped us get through it every step of the way.

When my brother was initially diagnosed, there was a huge learning period for my entire family. We were introduced to our local chapter and they not only provided support, but also the education that we needed to fully understand. A few years later during a genetic study, I found out that not only was I a carrier, but that my levels were low enough to be an affected member of the community. Until then, I had only known hemophilia as a “male” genetic disorder. Through the resources within our community, my mom was able to find another female with hemophilia that I could talk and relate to. Although I have factor IX and she has factor VIII, there was plenty for us to discuss and to learn from one another. My interest in becoming involved in the community at a higher level was sparked!

My family and I then began to attend national conferences to continue in our education. We learned about the different kinds of bleeding disorders, about advocacy, about the history of hemophilia, and all the things that are important and make this community so unique. I had the opportunity to meet other females with both factor VIII and IX deficiencies. I also

became very involved in the teen group with one of the national organizations and it made me feel great to know that I was a part of a group that could relate to me in so many ways. It allowed us to learn each other’s stories and understand the importance of being involved on so many levels. I developed a strong sense of family, especially within the factor IX community. Years later, I look at most of these individuals as some of my best friends, those that will always understand and those that will always support the needs of the hemophilia community.

Today, I serve as president of my local chapter, continuing to feel strongly about being involved in the hemophilia community. My hope is to assist others in seeing how important it is to stay involved so that our community can stay strong and so that we can continue to succeed in our advocacy, education, and continuous support of our members.



YOU ASKED FOR IT!

“Share your Story”

is now available on our website www.coalitionforhemophiliab.org

We encourage you to submit your articles that will appear in upcoming issues of our newsletter

Factor Nine News

Another Approach to Increasing the Half-Life of Factor IX

by Dr. David Clark

Prophylaxis is the preferred treatment method for severe hemophilia B. Infusions are given every two to three days to keep the patient's Factor IX (FIX) level above about 1%, the level at which most bleeding events can be prevented. However, even twice-a-week infusions are inconvenient and affect compliance with prophylactic protocols. The frequency of infusions could be reduced if the half-life of FIX could be increased.

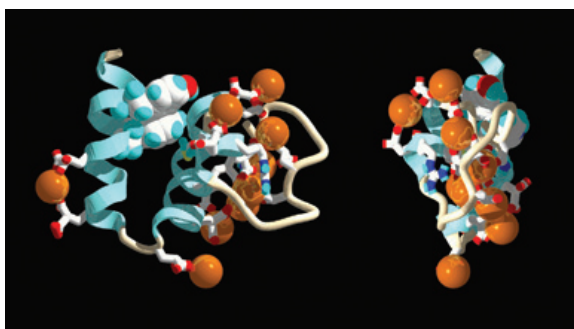
The half-life of a molecule in the body is the amount of time that it takes for half of it to disappear. Molecules in the body have a certain lifespan because they degrade over time. They get banged up physically and they react with various things like oxygen. There are clearance mechanisms to remove older molecules from the bloodstream to keep everything in good working order. Normally, the cleared molecules are replaced continuously by new ones, except in cases like hemophilia where the body can't replace the molecules properly. The rate at which different types of molecules are replaced ("turned over") varies. It depends on many different factors like size, stability and how critical their function is.

The half-life of FIX is 18 - 34 hours—it varies from person to person. That means that if a severe hemophilia B patient, who produces none of his own FIX, is given enough FIX concentrate to raise his level to 2%, after 18 - 34 hours he will be down to 1% and need another infusion. It's all proportional - if his level is raised to 40%, he will be down to 20% after 18 - 34 hours and then down to 10% 18 - 34 hours after that, a total of 36 - 68 hours after the infusion. The time between infusions could be prolonged by raising the

factor levels even higher, but that quickly becomes very expensive because of the large amount of FIX concentrate needed. A better way to reduce the number of infusions needed for prophylaxis would be to increase the half-life of FIX.

With the ability to customize protein molecules via genetic engineering, researchers have tried a number of ways to increase half-life. The half-life of FIX and many other proteins is influenced by the carbohydrate side chains that are attached at various places on the molecule. The carbohydrate side chains degrade along with the rest of the molecule, and a degraded side chain signals the body's scavenging mechanisms to remove the molecule. Scientists have modified the side chains to make them last longer or have added large bulky molecules like PEG that tend to hide the side chains. Another approach is to attach the FIX molecule to another

protein that already has a longer half-life. In the Autumn 2008 issue, we described a product under development by Syntonix (now Biogen Idec) in which FIX was attached to part of an antibody molecule, which increased the half-life three to seven times in animals.



A recent publication by CSL Behring¹ reports another method to modify FIX in which the FIX molecule is attached (fused) to albumin. This was a "concept" study to see what would happen. It may or may not lead to development of a new FIX product. Albumin is the most common blood protein, comprising 50 - 65% of all the proteins in the blood. Albumin thickens the blood and maintains the electrolyte (salt) balance of the blood. It is also a "sticky" protein that carries many other molecules around

continued on page 4

the bloodstream. It has a half-life of about 20 days, much longer than FIX.

The novel aspect of the CSL work is that they created a gene that attaches recombinant albumin to recombinant FIX with a connector that can be broken to remove the albumin when the FIX is activated. The connector is called a cleavable linker. It is a peptide, a short piece of protein, that can be cut by activated factor VII (FVIIa) or activated factor XI (FXIa), the same factors that activate FIX. In fact, they used the same naturally occurring peptide that is cut in the FIX molecule when it becomes activated. Activated FIX is an enzyme, a protein that causes a chemical reaction. Activated FIX causes one of the reactions that leads to clotting. Since we want enzymes to cause their reactions only when necessary, most of them actually circulate in the blood as inactive molecules called proenzymes or zymogens. They are activated to become enzymes only when necessary.

The coagulation cascade, which leads to the formation of a blood clot, is the complex series of reactions that is set off by an injury. Triggering the cascade leads to activation of factors VII and XI, which activate FIX, which activates factor X, which activates factor II, which changes fibrinogen to fibrin, which sticks together to form a clot. That's the simple version; the actual cascade is much more complicated with other factors and proteins interacting to regulate the process so the clot is formed in the right way, in the right place, and only to the extent needed.

Getting back to the CSL work, when FVIIa or FXIa activate the rFIX-albumin fusion protein, they also cut the cleavable linker releasing the albumin molecule from the FIX molecule. One of the problems with sticking something onto FIX is that it can change the ability of the activated FIX molecule to activate factor X. In fact, CSL showed that rFIX-albumin fusion molecules in which the albumin was not removed after activation had much lower clotting activities in laboratory assays than either BeneFIX or Mononine.

This decrease in activity has also been reported in the literature for other coagulation factor fusion proteins. The lower activity can result because the attached

molecule physically just gets in the way (called steric hindrance), or because the presence of the attached molecule changes the electron distribution in the active enzyme, changing its ability to cause a reaction. The idea with the CSL FIX fusion protein, is that when the molecule gets activated, the albumin is also removed leaving a normal activated FIX molecule.

Of course, scientists know that things don't always work the way they "should", especially when their idea seems so simple there's no reason it shouldn't work. Even though the albumin is removed so it doesn't interfere with the activated FIX, it could interfere instead with activation of the FIX in the first place. Or, the FIX molecule could interfere with removal of the albumin by the FVIIa or FXIa. Or, the whole FIX-albumin molecule could have some other effect no one ever dreamed of. Or... That's why we do experiments.

However, CSL has some encouraging results. They tried a number of different FIX-albumin fusion proteins, found some that didn't work and some that worked very well. The fusion proteins that worked the best in laboratory tests were then tested for recovery and half-life in mice, rats and rabbits compared with BeneFIX and Mononine. Not every product was tested in every animal, but using rats as an example, recoveries, the amount of factor activity found in the blood immediately after infusion, were 1.4 - 1.7 times greater than those of BeneFIX and essentially the same as those of Mononine. Half-lives were 3.4 - 4.7 times greater than BeneFIX and 3.9 - 5.4 times greater than Mononine.

The rFIX-albumin fusion proteins also worked to control bleeding. In FIX-deficient mice (hemophilic mice that don't make their own FIX) bleeding times for the best fusion protein were comparable to those for BeneFIX when dosed to the same activity level. Thus, rFIX-albumin proteins with a cleavable linker might be another good approach for increasing the half-life of FIX. If successful, this protein could reduce how often FIX infusions would be needed for effective prophylaxis.

Metzner HJ, Weimer T, Kronthaler U, Lang W, Schulte S, Genetic fusion to albumin improves the pharmacokinetic properties of FIX, *Thromb. Haemost.*, 102(4), 634-644, 2009.

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Case Closed: Famous Royals Suffered From Hemophilia

By Michael Price
ScienceNOW Daily News
8 October 2009

Queen Victoria's male descendants were cursed with poor health. The 19th century British monarch's son Leopold, Duke of Albany, died from blood loss after he slipped and fell. Her grandson Friedrich bled out at age 2; her grandsons Leopold and Maurice, at ages 32 and 23, respectively. The affliction, commonly known as the "Royal disease," spread as Victoria's heirs married into royal families across Europe, decimating the thrones of Britain, Germany, Russia, and Spain. Based on the symptoms, modern researchers concluded that the royals suffered from hemophilia--a genetic disease that prevents blood from clotting--but there was never any concrete evidence. Now, new DNA analysis on the bones of the last Russian royal family, the Romanovs, indicates the Royal disease was indeed hemophilia, a rare subtype known as hemophilia B.

Hemophilia prevents proteins known as fibrins from forming a scab over a cut or forming clots to stop internal bleeding. Even minor injuries can lead to bleeding, which lasts for days or weeks and can be fatal. The disease is recessive and is carried on the X chromosome, meaning that men are more likely to develop it, whereas women usually act as carriers and don't show symptoms.

Such was the case with Prince Alexei Romanov, son of Tsar Nicholas II, great-grandson of Queen Victoria, and heir to the Russian throne. From an early age, Alexei was prone to prolonged bleeding, and his family feared that he wouldn't make it through his first month of life, says Evgeny Rogaev, a geneticist at the University of Massachusetts Medical School in Worcester. The disease didn't kill Alexei, however: He was murdered at age 13 in 1918 along with the rest of the Russian royal family following the Russian Revolution. Earlier this year, Rogaev and his colleagues reported that, based on DNA analysis, the bodies of two children found near the murder site were indeed those of Alexei and his sister Maria. They further confirmed that the other bodies near the site belonged to the rest of the Romanov family. But Rogaev wanted to solve the final Romanov riddle: Did they really suffer from hemophilia?

He and colleagues analyzed DNA from the royal bone fragments again, this time looking for genetic markers

of hemophilia. The most common type of the disease, hemophilia A, accounts for about 80% of hemophilia cases and is caused by a mutation to a gene called F8, which encodes a protein involved in blood clotting. They didn't find the mutation. So Rogaev moved on to looking for a rarer form of the disease, hemophilia B, which involves another gene, F9. This time, the team found a mutation in F9, which would have inhibited clotting, in bones from Alexei, his sister Anastasia, and their mother Alexandra.



Royal affliction: Prince Alexei bled frequently and for prolonged periods.
Credit: State Archives of the Russian Federation


The findings, published online today in *Science*, indicate that Alexei did indeed have hemophilia B and that his mother and Anastasia were carriers for the disease, bearing out the previous speculation. They also confirm that the other instances of "Royal disease" in the family line were hemophilia, Rogaev says, because they all shared a common genetic heritage. The last carrier of the disease in the royal family was Prince Waldemar of Prussia, who died in 1945.

The disease impacted not only the Romanov family but also probably Russian history, Rogaev adds. Alexei's frail condition encouraged his mother Alexandra to keep close company with the Russian mystic Grigori Rasputin, who claimed to wield healing magic. "There was no medication at that time," Rogaev says. "She tried to do everything possible." According to some historians, when Rasputin used his close relationship with the Romanovs to influence bureaucratic affairs in his favor, the public grew increasingly suspicious of the regime, possibly hastening the revolution.

Katherine High, a hematologist who studies blood coagulation at The Children's Hospital of Philadelphia, says that the mutation found in the Romanov bones fits an established genetic pattern known to cause hemophilia B, further supporting Rogaev's findings. Tracing this pattern back to the royal family and its history of disease is "very interesting and very exciting," she says.

People affected by the disease today should be excited to see hemophilia B step out from under the more common A-type's shadow, says pediatric hematologist Paul Monahan of the University of North Carolina, Chapel Hill. "Now it's clear it's had an enormous impact on Western history."

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The Hemophilia Alliance Foundation announced the culmination of its first grant cycle with the awarding of more than \$250,000 to organizations serving people with bleeding disorders. The funding focused on strengthening the effectiveness of the recipient organizations. The goal was to fund one-time project requests and reward collaboration between two or more organizations. The Foundation approved funding for such projects as board development, technology purchases and upgrades, establishment of a regional advocacy group, educational meetings and educational materials.

“The Hemophilia Society of Colorado is proud to receive a 2009 grant from the Hemophilia Alliance. As a Chapter that has been going through some transitional pains, we are greatly appreciative of the support of our Hemophilia Treatment Centers in helping us better meet the needs of our community. We look forward not only to working collaboratively with our local HTC, but also to demonstrating to other Chapters how a functional Chapter should be modeled – one that is truly accountable to the hemophilia community and capable of focusing and delivering on its Mission Statement and long term goals. Such a level of cooperation is essential to improving life for all persons and families dealing with bleeding disorders, now and in the future.” reported Treasurer, Nathan Wilkes.

Joanne Davis, MD, wrote, *“At the University of Miami, we are committed to ensuring that our patients and families have complete access to all available educational and financial assistance information. This commitment requires us to make sure that all materials are presented in clear, concise and comprehensible language – both English and Spanish. The 340B program represents a significant savings for eligible families, as well as a source of income to improve*

and expand HTC services. However, the concept and mechanism of implementation of this program can be confusing! We are very pleased to be able to make our Spanish language 340B materials available to Alliance members, through the support of a grant from the Alliance.”

Robert Fox, President and CEO of the Mary M Gooley Hemophilia Center, wrote *“These grants enable people with bleeding disorders to participate in educational offerings, advocacy initiatives and a variety of other programs. The Alliance Foundation is one way that HTCs with factor programs support the communities they serve. In New York, the Alliance Foundation is supporting a statewide effort aimed at giving patients access to elected officials and other decision makers.”*

The Foundation also provided \$5,000 in funding to each of the 12 federal hemophilia regions in support of their annual meetings. These meetings provide a forum for hemophilia care providers to exchange information and share best practices.

A second grant cycle is planned for early 2010. Leaders of tax-exempt organizations that serve people with bleeding disorders who are interested in more information should contact Joe Pugliese at the Alliance offices: 1758 Allentown Road #183; Lansdale, PA 19446, 215-439-7173, joe@hemoalliance.org or visit our web site.

*The Alliance is a not-for-profit organization that currently comprises 74 Hemophilia Treatment Centers. The purpose of the Alliance is to assist its members in providing outstanding care for their patients. Our mission The Hemophilia Alliance provides member Hemophilia Treatment Center with resources and services to sustain the Comprehensive Care Model for individuals with bleeding and clotting disorders for more information about the Alliance and how you can help further our mission visit us at www.hemoalliance.org or email us at info@hemoalliance.org

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*Health care professionals are not eligible for the free gift.



Maureen Cook

***April 6, 1961 -
December 2, 2009***

It is with heavy hearts that we inform you of Maureen Cook's passing. After a prolonged battle with cancer, Maureen passed away on December 2, 2009. She leaves behind her son, Wayne, III and his wife Morgan, her daughters, Shannon and Kasie, and her loving husband, Wayne.

Maureen was a warm and genuinely kind-hearted woman. Her family was always her first priority and she devoted her life to them. With her husband at her side, Maureen generously offered countless hours of her time to The Coalition for Hemophilia B. She was the quiet strength behind the Coalition. She gladly offered her assistance in any way possible – whether it was shopping for raffle prizes, staffing the Coalition's exhibit booth, or working at the Fundraising dinners, Maureen was always there ready to offer an easy smile. She was a loving, kind and generous spirit and we will miss her very much.

***When somebody dies, a cloud turns into an angel
And flies up to tell God to put another flower on a pillow.
A bird gives the message back to the world
and sings a silent prayer that makes the rain cry.***

***People disappear, but they never really go away.
The spirits up there put the sun to bed, wake up the grass, and spin the earth in dizzy circles.
Sometimes you can see them dancing in a cloud during the daytime
when they're supposed to be sleeping.***

***They paint the rainbows and also the sunsets and make waves splash and tug at the tide.
They toss shooting stars and listen to wishes.
And when they sing wind songs, they whisper to us,
Don't miss me too much. The view is nice and I am doing just fine.***

Whenever you think of Maureen, we ask that you celebrate the life that was, rather than grieve the loss that her husband and children have endured. That is what she would have wanted. Maureen will be greatly missed by the many whom she touched during her lifetime.

Godspeed Maureen... our memories of you will be forever cherished.

SAVE THE DATE!



The Coalition for Hemophilia B
3rd Annual Fundraising Dinner
Friday, March 26th, 2010
Millennium Broadway Hotel
145 West 44th Street
8th Floor, 5:00 PM
New York City

The Coalition for Hemophilia B
New York Symposium
Saturday, March 27th, 2010
Millennium Broadway Hotel
145 West 44th St.
4th Floor, 9:30 AM
New York City



Daniel Darling (4 1/2) at Diamond Lake, MN. This was his first attempt at water skiing and he was pretty excited when he got up!

***The Coalition for Hemophilia B
wishes everyone a very
Happy and Healthy 2010!***

For back issues of **Factor Nine Newsletter** or for more information on research, please call or write to:
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