

Next Class in: **FVIIIa MIMETICS** and the Future of **HEMOPHILIA**



Julia Sandrin Gauer: Hello, and welcome to today's episode of the ISTH Pulse Podcast, where we'll be discussing next-generation factor mimetics. So, looking back, the approval of emicizumab revolutionized care for patients with hemophilia A. For the first time, these patients had the opportunity to switch from factor prophylaxis to a factor mimetics.

But developers are pursuing even longer-acting agents, such as Mim8 and NXT007, as well as oral agents like Inno8. So Mim8 and NXT007 are currently being studied with dosing intervals intended to extend beyond emicizumab current schedules, which will be of particular relevance for children, for example, or patients with difficult injection schedules, or really just anyone for whom adherence is an issue.

So, joining me to break down the latest research and discuss how new factor mimetics may address current unmet needs for patients are two experts in this topic. Our first guest is Dr. Sanjay Ahuja, who's a pediatric hematologist. Serving as the medical director and CEO of Innovative Hematology and the Indiana Hemophilia and Thrombosis Center in the United States.

And our second guest is Dr. Allison Wheeler, who's a hematologist and serves as Clinical Research Program Director at the CU Hemophilia and Thrombosis Center, and who's also a visiting professor in the Department of Medicine at the University of Colorado in the United States.

And I'm really excited to have both of our experts with us here today. They bring a wealth of experience in both the patient and clinical perspectives. So welcome both and thank you very much for joining us today.

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Sanjay Ahuja: Thank you, Julia. Thanks, nice to be here.

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Allison Wheeler (she/her): Excited to be here.

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Julia Sandrin Gauer: So, before we get started, we'd like to note that this podcast episode today was supported by independent medical education grants from Novo Nordisk and Roche, and the supporters have had no influence on the content.

Okay, so let's jump straight into our discussion. So, to set the stage for our listeners who may not be as familiar with factor mimetics. Could you please share with us, Sanjay, a little bit about how these agents work, and who they are indicated for?

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Sanjay Ahuja: Sure.

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Sanjay Ahuja: So, Factor VIII mimetics are actually a really elegant example of how our understanding of coagulation biology has really moved or translated into a completely different way of treating hemophilia. So, normally, if you go back to the biology of coagulation, normally, activated factor VIII acts as a cofactor that brings activity at factor IX and factor X together. And this happens on a phospholipid surface. And that markedly accelerates, activation of factor X. And ultimately, that leads to thrombin generation.

Now, in hemophilia A specifically, factor VIII deficiency, that cofactor function is missing, or it's deficient, and that's the biology of the disease. Now, the factor VIII mimetics essentially recreate that function without replacing factor VIII.

So, these are bispecific antibodies, with one arm binding activated factor IX, and the other arm, binding factor X. By bringing these two proteins into the appropriate spatial relationship, they facilitate the activation of factor X. And then, therefore, restore thrombin generation. Now, the distinction is that they mimic the cofactor function of activator factor VIII, but they're not factor VIII.

So, they don't require activation by thrombin, for example. And the most important fact here is that they're not neutralized by factor VIII inhibitors, which positions them in a novel way to be used for patients who develop these inhibitors at an alarming rate in hemophilia. So that's how factor VIII mimetics work, and it found a place in our therapeutic armamentarium.

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Julia Sandrin Gauer: Very good, thank you so much for that introduction. It's really helpful to hear the biology and how it actually is working. So, as really briefly introduced at the start of the episode, emicizumab has already addressed some of the challenges that are associated with the factor prophylaxis.

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Julia Sandrin Gauer: What would you say, in your experience, Alison, are some of the unmet needs that still remain for patients who are currently receiving a factor replacement therapy or emicuzimab?

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Allison Wheeler : So...I think, you know, you made a really important point that we've completely changed in hemophilia therapy, and when I think about the gaps that still exist, in the emicizumab era, you can think about it in the context of patients with inhibitors and also, sort of, patients without inhibitors or putting those two groups together with and without inhibitors. I think for patients with inhibitors, emicizumab was, without question, a life-changing medication. But there are still questions that we talk about with our patients, and we talk about with each other when we're trying to discuss what the best thing to do is clinically for our patients.

For example, if somebody has an inhibitor, should we still try to tolerize that inhibitor? Try to eliminate that inhibitor? What's the best way to do that? What's the practical way to do it, and what's the

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scientifically best way to do it? Should we allow patients to have inhibitors, and continue on emicizumab as their prophylaxis, and then treat their bleeds when we need to treat their bleeds? So I think there's a lot of questions, surrounding this concept of inhibitor development and inhibitor tolerization. The nice thing is we actually get to ask these questions. Historically, our patients with inhibitors bled so dramatically that tolerizing was really a very critical part of care. And so, I would actually say that we're very privileged to be asking these questions and to be wondering about how to treat these patients.

If we take a step to the other series of questions, which I would say, are relevant to patients with and without inhibitors, we sort of get into this context of "how good is emicizumab at providing prophylaxis for patients with hemophilia?" And I actually think that the better way to ask that question is, "how good is emicizumab at providing prophylaxis for each individual patient?" Because this is a place where individualization of care becomes so critical.

But for example, is emicizumab the optimal prophylaxis for patients who want to participate in sports? What sports can we let our patients with hemophilia participate in? Are we worried about microbleeds or subclinical joint damage, because of increased activity, on emicizumab prophylaxis? And again, these are questions that I think about a lot as a pediatrician, and I think my adult colleagues think about them as well, but sort of optimization of care and optimization of long-term joint health, like, what can emicizumab do for an individual patient, and how far can we sort of let them go in terms of activity?

I'm sure there's a bunch of other questions that I haven't addressed. In fact, I know there are, and I'd love to hear if there's any on the top of Sanjay's mind, but activity becomes a really, really critical question for me when thinking about this drug. And how to think about my patients.

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Julia Sandrin Gauer: Yeah, it's a really interesting point that you make about optimization and how everyone's so different, right? And some people may have inhibitors, some don't, and this idea that you presented about the lifestyle that they will be leading as well and having that in consideration is really interesting. So, if we continue on this train of thought, if you will, about some of the unmet needs that patients may have. And thinking about the next generation of factor mimetics.

What characteristics would you say, Sanjay, that developers are trying to hopefully improve beyond emicizumab, or factor replacement therapies currently available?

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Sanjay Ahuja: That's a great question, Julia. So, as Allison correctly pointed out, you know, emicizumab has a lot of strengths, but there are some gaps as well. So, the next generation is trying to preserve what, first preserve what emicizumab got right. So, what it got right was subcutaneous therapy. It was not possible before that. We all had intravenous therapy only. Durability... so consistent coverage, inhibitor-independent prophylaxis, right? So, prophylaxis for inhibitor patients was a large gap before emicizumab. So, emicizumab got that right.

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The next generation of Factor VIII Mimetics are trying to build on this success, so this is not enough. We need more, right? So, emicizumab established that you can mimic the cofactor function of factor VIII with this framework of bispecific antibody.

But now, question is, can we make that protection even better? And that's where the focus is. So, the first goal, or the, you know, a major goal, would be a greater hemostatic potency. So, as we just talked about it, emicizumab does not completely reproduce the activity of regulation of native factor VIII, and breakthrough bleed can still occur.

So, next-generation molecules are being engineered to bring these two, bring FIXa and FXa together more efficiently. Enhancing that factor VIII, factor X activation, and enhancing that thrombin generation.

So, the aspiration there is provide a level of protection that gets us closer to normal? Or can we do that? Or at least in the mild hemophilia range, almost always consistently.

The second goal. What the developers are trying to do is to have a more consistent protection across a variety of different hemostatic challenges. You know, Allison just mentioned about we worry about children playing sports, or adults going on activities that put them at risk. Can the second-generation mimetics, or future generations, actually overcome this barrier as well?

It's one thing to prevent spontaneous bleeding during everyday life, you know, that's a great goal to have, but it's another to provide sufficient hemostasis during, you know, vigorous physical activity, trauma, or even procedures, for that matter.

So that's another goal that the developers are trying to bridge that gap. The third area is convenience and the treatment burden, right? So emicizumab already made huge strides in this area right? With subcutaneous therapy, very small volume, greater frequency of administration. So, Mim8 is another generation of factor mimetics. It has been studied with both once weekly, but also once monthly. But in addition to that it's an auto-injector pen device. So, it's taking that next level of leap into the burden, treatment burden, and making it more convenient for patients to deliver that medication.

And finally, all of this has to be achieved while maintaining safety. So, emicizumab has proven to be a pretty safe drug. With increasingly potent mimetics, can we maintain that? So, the idea is to generate sufficient thrombin to overcome the gaps that I just mentioned, but can that be done without having an increased risk of thrombosis or having that therapeutic window the same as for emicizumab. So, to me, the next generation is really about moving from excellent bleed prevention towards more predictable and physiologic hemostatic protection, if you will, right? With the hope of fewer breakthrough bleeds, greater freedom for physical activity, less need for supplemental factor, and even, very low treatment burden.

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Julia Sandrin Gauer: Thank you very much. And yeah, you sort of already touched upon my next question, as well, in terms of the second generation of mimetic agents. So, for agents like Mim8 and

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NXT007, they are currently being studied at dosing intervals, like you said, that would extend beyond those currently being used for emicizumab.

What do we know so far, Allison, about the safety and the efficacy of these agents? I know Sanjay's already touched upon them briefly, but what else is out there in terms of how effective they are and how safe they are?

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Allison Wheeler : Yeah, so I think it's important to note that these two drugs, these next-generation mimetics, are at very different points in the clinical trial pipeline. Mim8, we have seen, you know, Phase 1, 2, and 3 data, whereas for NXT007, we've really just seen Phase 1 data at this point. So, it's a really different answer between both of those drugs. But I will also point out that both of those drugs had an advantage over emicizumab, which is they came you know, second and third, or however you want to think about it. And there was some safety concern during the emicizumab clinical trial programs when emicizumab was combined with a drug called FEIBA which is used as a bypassing agent for patients who have inhibitors.

In the clinical trial program, there, were episodes of thrombosis and thrombotic microangiopathy when those two drugs were combined in very specific circumstances. And so, the safety profile, when we look at the Mim8, and so far, the NXT clinical trial programs have been really excellent. They have, benefited from the fact that they used the risk mitigation strategies that we learned about because of the emicizumab experience. And so, the fact that those events didn't happen in those clinical trial programs is predictable because we didn't give FEIBA in those clinical scenarios, those very specific clinical scenarios.

So, when we look at the safety of these two drugs, it looks really lovely, and you know, we talk about injection site reactions. These are things that are always going to happen whenever we're giving a subcutaneous injection. They're occurring at very small numbers.

Obviously, we have more experience with Mim8 than with NXT, but we're seeing, you know, really very minimal, especially minimal persistent injection site reactions in the patients who are on those clinical trials. We're not seeing thrombotic events, which is really critically important, and something that, as Sanjay pointed out, we pay extremely close attention to, and we really need to, to maintain that, that level of safety. So overall, I think, I'm extremely happy with the safety profile that we're seeing, from these drugs.

In terms of efficacy, again, we have so much more information about the Mim8, and we are seeing really nice efficacy, really similar ABRs, or annualized bleeding rates to what we see with the emicizumab drug, especially over time, as we have patients on emicizumab long-term.

And, and as I said, the NXT, we're really just looking at very early data. So, in terms of what we're going to get in terms of efficacy when patients are on that drug longer term, I think that's still to be determined, but the initial data is looking, is looking really nice. I think in some ways, as a lot of us would have predicted, knowing sort of how, how that drug was developed.

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But I think to say that we're looking towards continued excellent efficacy and continued safety is a reasonable thing to say. And I think the big question that sort of comes up in some of our conversations is, are we going to get to the point with one of these next-generation mimetics when we have zero bleeds and zero factor use? So similar to what I was discussing and what Sanjay mentioned, like, what happens when people have trauma, what happens when people play sports, and our patients are still using factor when they have injuries. They are still using factor during surgical procedures, and so are we going to find a drug that is optimized to the point that we don't need to do that, while, very importantly, maintaining that safety profile?

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Julia Sandrin Gauer: That's really exciting. Sounds like loads of work to be done. Maybe you will get there, that would be, that would be fantastic. I'm curious, though, for a patient who's happy and satisfied with their current treatment strategy, what would you say, Sanjay, are some of the factors that may make them consider, or I guess perhaps their care team, propose that they consider switching to a newer factor mimetic?

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Sanjay Ahuja: Sure. So, I think I'll reframe the question in a different way. So, I think the first point is that if a patient is doing well on factor replacement or emicizumab, there is no automatic need to switch, first of all. The question is really whether a newer therapy, a newer mimetic, offers something that matters to that particular person.

Right. So that's where we need to figure out how to, you know, who to switch. So, one consideration would be, obviously, as we have, both Allison and I have pointed out, is residual bleeding, or breakthrough bleeding, as we call it, or a desire for greater hemostatic protection. So, patients may have low annualized bleed rates otherwise, but still experience activity-related bleeds, breakthrough joint bleeds, or feel that their current level of protection limits them from sports or any other activity. So, if a next-generation mimetic can provide more potent and sustained hemostasis, that could be an important reason to consider a change.

A second consideration would be the treatment burden, and we already talked about this as well. So, obviously on factor, intravenous access and infusion frequency was a big burden. Emicizumab came along, and some patients found value in a regimen that was subcutaneous, given less often, even monthly without sacrificing, in a big way, bleed protection. Now, if you look at the data for Mim8 in Frontier 2, patients switching from prior factor prophylaxis to Mim8 reported a meaningful reduction in treatment burden, and in, I think, upwards of 90% expressed a strong preference for Mim8 over their previous treatment, and this was measured around 52 weeks or so.

The third issue is lifestyle and patient goals. So, what do they want, right? So, some patients want to participate in higher intensity physical activity, travel. More often, more easily. Simply think about hemophilia less often. So, you know, I would not make the decision based purely on annualized bleed rate. And we increasingly need to ask whether treatment is allowing that patient to live the life that they want. And of course, there are practical considerations, right? Injection volume, frequency, venous

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access, you know, and so on, surgery planning, laboratory planning, monitoring, insurance coverage, which is very important, obviously, for switching.

So, ultimately, I think switching should be about incremental value, if I were to put a word on it. Is the newer therapy likely to give that individual patient better bleed production, greater freedom to do things, lower the treatment burden? Or a combination, some combination of all of these put together. So, the reason to switch should not simply be that a newer therapy... that a therapy is newer, it should be because it offers a meaningful improvement in protection, convenience, or freedom that the patient actually values.

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Julia Sandrin Gauer: That's an excellent point that you make, and just because it's new doesn't mean it's particularly necessary for everyone to switch, so thank you for that. If we move on now to oral agents, such as Inno8, What role do you see, Allison, these particular agents playing in the future treatment landscape? What would you say are some of the potential advantages that they may have, or even challenges that you see with an oral factor mimetic approach?

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Allison wheeler : Well, I think I mean, I can't even remember how many years ago it was, when one of the parents, one of my patients, asked me, you know, when are we going to get an oral factor? And the truth is, there have been companies that have tried to develop oral factor replacement, and my understanding, albeit minimal, is that we should not consider that to be a part of our future, at least not with our current scientific abilities.

But, you know, an oral medication is an amazing opportunity. You know, again, both myself and Sanjay are pediatricians.

Subcutaneous injections are significantly less burdensome than IV infusions, especially at the frequency that each of those need to happen to provide hemostatic protection for our patients with hemophilia. But the idea that we could give patients prophylaxis without using needles at all, I think is really advantageous to the pediatric patients. You think about a lot of our adult patients, who have difficulty with venous access, either because they've had repeated infusions, or because they were just getting older, and venous access becomes more difficult in the elderly. So, I think that just really simply, for a lot of patients, an oral option is a big game changer and would be a really amazing opportunity.

I think, though, that the really critical thing is we do need to maintain the excellent efficacy that we currently have, and the excellent safety that we currently have. So, you know, it's going to be really important that we watch the data as it comes out from Inno8, just to make sure that we're maintaining those standards, because, I personally would say that an oral agent that isn't as effective is not a great option, but I think, as Sanjay points out, our patients want different things, and our patients have different goals, and so, you know, it'll depend on what happens with the clinical trial data and approvals, but, I also could envision having those conversations about what patients' goals are in terms of their treatment, in terms of their lifestyle, in terms of their convenience, and I think it's our

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obligation to provide this information to our patients and provide them the data and then let them provide to us what their goals are, so we could help shape the best care that would be for them individually. And that's an advantage that we have that we didn't have when I started my career, but for me, it would be great if we could have all three.

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Julia Sandrin Gauer: Yeah, thank you for sharing that. It's interesting that you mention about your experience of being a pediatric hematologist. I guess all these newer agents have an impact on the caregivers as well, not only just the patients, but the families and everyone involved with the burden of the disease and the treatment. So, really interesting approach.

My final question for you both is, in your opinion, which patient population, or perhaps clinical scenario, do you think that these next-generation mimetics could have the greatest impact in? So perhaps if we could start with Sanjay.

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Sanjay Ahuja: You know, I think there's several populations, that, if I were to list, who would have the potential value may be particularly compelling for that population. So, first is, obviously, we talked about this, the patients who continue to bleed despite what we currently consider good prophylaxis, whether it's emicizumab, the first-generation mimetic, or it's an ultra-long half-life Factor VIII product such as Efa.

So, there are patients who still experience those breakthrough bleeds or traumatic bleeds, as we call it. Now, fortunately for us, the current Phase 3 data with Mim8 is encouraging in this regard. So, you know, both weekly and monthly prophylaxis substantially reduced the treatment, reduced treated bleeds, including when we compared them with the prior prophylactic regimens, factor prophylaxis for example. So that's one group. The second group would be highly active patients. So, the children and adolescents who are participating in sports, and adults whose work or lifestyle exposes them to greater physical challenges. So, for these individuals, the question increasingly is not simply, are you having spontaneous bleeds, but does your treatment give you enough confidence and hemostatic reserve to participate in the activities you want to [do]. And that word hemostatic reserve is important, because I think we are entering the stage where therapies are actually not only just preventing spontaneous bleeds, but also providing that level of added protection as a reserve for the activities that somebody wants to do. So that's very attractive.

And then the third is, and this is something we haven't talked about, neither Allison nor I have talked about in this podcast, is the patients with established joint disease, right? So, there are a group of patients who have already established joint disease over the number of years, and especially adults.

So, better prophylaxis cannot reverse existing arthropathy, but recurrent bleeding into an already damaged joint can accelerate that process. So, if we move closer to consistently providing joint support and preventing joint bleeding, potentially very small or clinically unrecognizable bleeds, as Allison pointed out, that could be very meaningful over decades of treatments. But we still need clinical evidence in this area, you know, demonstrating that the newer mimetics actually translate

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into better long-term joint outcomes, but I would be certainly very interested in that patient population.

And, of course, another important population is the one with inhibitors. They already are being served pretty well with emicizumab. Can we decrease their treatment burden with a, you know, pen injector? That is going to be available with Mim8. There is a group of patients that we didn't talk about, which is patients for whom the treatment burden itself is a major unmet need, right? So, if you look at all the unmet needs we talked about, treatment burden itself becomes an unmet need for certain people.

Who, you know, have a bad venous access, or really hate needles, and can decrease their frequency of therapies to once a month with a lower treatment burden, such as an auto-injector. So that's a group or population that both Mim8 as well as NXT007 has an ability to fill that unmet need. And finally, as a pediatrician, I think young children may ultimately be one of the most interesting populations for these newer therapies, newer mimetics.

Although we need to be a little bit thoughtful here, because I'll tell you why. So, starting highly effective subcutaneous prophylaxis early on could potentially prevent joint bleeding from happening, and joint damage from happening early on in life. And it could avoid many of the venous access challenges that we talked about associated with factor or with needle phobia for children.

But when we minimize factor VIII exposure early in life, we also create an important unanswered question, which is, when and how do these children develop immune tolerance to factor VIII? And they may still need factor VIII later for major trauma or surgeries. Will that put them at higher risk later on if they're not exposed early? So, you know, there was recent real-world data with emicizumab in previously untreated and minimally treated children that highlight how relevant factor exposure and inhibitor surveillance remain even in this era of non-factor prophylaxis. So, I think the patients with the greatest potential benefit are those with residual bleeding, high physical activity, deferred venous access, high treatment burden, inhibitors, or simply a desire for greater freedom from hemophilia, right? So, the most important point, again, is the value proposition. And that will not be identical for every patient. It'll be different.

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Julia Sandrin Gauer: Thank you very much. And Allison, anything you'd like to add about who you think would benefit most?

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Allison Wheeler Yeah, it was an excellent, excellent answer, and Sanjay hit all of the major populations. You know, I'll just add on that final group that he was talking about, the infants who have such excellent protection, they don't have Factor VIII exposure. I think the other circumstance in which factor VIII exposure could play into the conversation is, as we develop newer gene therapy options. At least the gene therapies that were studied, that have been studied already, you needed to have factor exposure and demonstrate that you had not developed an inhibitor, in order to receive the gene therapy. So, factor exposure will also be important, I think, as we start getting our next options for gene therapy, and I say that with optimism and hope that we're going to be seeing new options in that regard.

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The other very, very small population to make note of is patients who have developed inhibitors, or antibodies that make emicizumab ineffective. So, it's a very small population, but it's important if somebody's on emicizumab and their bleeding profile changes, to think about that possibility, and to consider one of these other agents, for that, that group, albeit a very small one.

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Julia Sandrin Gauer: Thank you both so much for sharing your insights. It's been such an insightful conversation. I've certainly learned a lot, so thank you very much for sharing and for being here today. Just before we conclude the episode, we have a bit of a tradition here in the podcast where we like to end the episode by asking our guests more of, like, rapid-fire type questions, if you will, to get to know them at a bit more of at a personal level. And so just please feel free to answer the first thing that comes into your head.

So, my first question is, do you prefer tea or coffee? So, if we could start with, Alison.

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Allison Wheeler : Coffee.

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Julia Sandrin Gauer: Coffee. What about you, Sanjay?

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Sanjay Ahuja: Tea.

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Julia Sandrin Gauer: Very good. And what has been the best career advice that you've ever received? Sanjay, you can go for it.

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Sanjay Ahuja: Well, I think the best career advice I ever got was, you know, it's never too late to start learning something new. Because that's how you make progress. And I've stuck to that, and, you know, continuous learning is something that has really advanced my career in a big way.

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Julia Sandrin Gauer: I like that. Yeah, I guess as scientists and clinicians, we are always learning new things, and it's great to keep that mindset. How about you, Allison?

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Allison Wheeler : I'm gonna go with send the email. Very specifically, this was a piece of advice I got as a fellow when I was heading to some conferences, and I wanted to talk to people in the hemostasis field about their careers. Not about jobs, but just about their career development, and my mentor said, just email them.

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Set up coffee. They're gonna be excited to hear from you. They want to talk to junior faculty, they want to talk to fellows who are interested. And so I did, and I can't tell you how many relationships I still have from those emails I sent 15, 14 years ago, and it was a really great experience for me to do that, and so I tell everyone to do that. I call it the cold call email.

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Julia Sandrin Gauer: I love that. Be brave, just go for it.

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Allison Wheeler : Exactly.

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Julia Sandrin Gauer: I like that. And my final question, this can potentially be a bit controversial. But which is your favorite coagulation factor?

Sanjay?

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Sanjay Ahuja: Actually, my favorite coagulation factor is factor XII. Because it, it's, you know, it has got a very important role, though not the traditional coagulation as we think about it. It has... it's... there is so much left to be... it's like a mystery factor.

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Julia Sandrin Gauer: Yeah.

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Sanjay Ahuja: You know, it doesn't cause bleeding symptoms, but it's important in wound healing, in angiogenesis, and so many other things. So, it's like one of those factors that is hiding in the shadows, waiting to be discovered, and there is some mystery about it that makes it very intriguing. So that's my favorite factor.

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Julia Sandrin Gauer: Nice, thank you. It's a bit mystical, isn't it? Lots to learn still about factor XII. How about you, Allison? Which one's your favorite?

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Allison Wheeler : I'm horrible at favorites, but I will go with 13. In addition to doing clinical hematology, I also work in the laboratory, and anytime I get to help parcel out a difficult case or anytime laboratory folks are sort of squinting their eyes a little bit, I get excited, and I think 13 makes us do that, so...

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Julia Sandrin Gauer: Amazing. Thank you so much for being here today. Dr. Ahuja and Dr. Wheeler, thank you for your insights and for helping us better understand the evolving landscape of factor mimetics for hemophilia A. It's been an absolute pleasure talking to you both.

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Sanjay Ahuja: Thank you for having us.

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Allison Wheeler : Yeah, thank you, it was great.

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Julia Sandrin Gauer: And to all of our listeners, thank you for tuning in. We'll see you next time on the ISTH Pulse Podcast.