BBGuy Essentials 079:
Pioneering Pathogen Reduction with Ray Goodrich
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Ray: Hi, this is Dr. Ray Goodrich, and this is the Blood Bank Guy Essentials Podcast.

Joe: Hi everyone. This is episode 079 of Blood Bank Guy Essentials, the podcast where my goal is just to teach YOU the essentials of Transfusion Medicine. My name is Joe Chaffin, and I am your host. I have an interview for you today that I'm very excited about. It's with one of the developers, one of the original developers of modern pathogen reduction technology. His name is Dr. Ray Goodrich, and I'm going to tell you more about him in a minute.

But first, you should know that this is NOT a continuing education episode. You can find other episodes where physicians and laboratorians can get those free continuing education credits at BBGuy.org/podcast. Just look for episodes there that end with the letters "CE" (no big deal, right?). You can find those continuing education episodes also at wileyhealthlearning.com/transfusionnews. I should tell you that the continuing education episodes at Wiley Health Learning are brought to you by transfusionnews.com and Transfusion News is brought to you by Bio-Rad, who has no editorial input into this podcast.

So you've heard me talk before on the podcast about the FDA Final Guidance that was issued in late 2019, that guidance that I talked about with Dr. Pat Kopko on BBGuy.org/076 (and you should listen to that if you have not already), I think will finally open the door to very widespread use or potentially widespread use of pathogen reduction technology, or "PRT," as we like to call it. There was a time, though, that the modern versions of pathogen reduction really just existed in the minds of some super smart people, and I'm so lucky today that Dr. Ray Goodrich, who was one of those really smart people, is my guest here on the Blood Bank Guy Essentials Podcast.

Let me tell you a little bit about Ray. Ray is currently the Executive Director of the Infectious Disease Research Center at Colorado State University in Ft. Collins, CO. Ray received his PhD from the California Institute of Technology and his Bachelor of Science from Ohio State (which I'm not going to rag on because I'm from Michigan, but I'll just leave that alone). That's what Ray has done with virtually his whole career. He is most famous for the work that he did at the company that is now known as Terumo BCT, where Ray and his team developed the riboflavin and ultraviolet A combination treatment that is widely known as "Mirasol." Now, Mirasol is used in many, many countries around the world (not yet in the United States though), and Ray and his team's development of Mirasol is a fascinating story. In fact, Ray's been involved in one way or another in most of what we now know as modern pathogen reduction technology and his stories are fascinating and I'm really excited for you to hear them along with Ray's thoughts at the end on where we're going with all of this.

But there's a couple of things I need to tell you. First, while Ray obviously developed one method, as I already said, this is not a commercial for Mirasol. This is not a commercial for anybody. Just like when I talked about the Intercept technology with Dr. Kopko in that previous episode, it was not a commercial for that as well. This is an educational podcast. That is my intent, and I'm just trying to let you know all the things that are out there. And I think Ray does a really good job of just describing what's going on without getting into the competitive stuff.

And second, this episode was recorded just before the FDA Final Guidance that I mentioned was released. So Ray and I don't really discuss that. However, I'm going to give you my thoughts on it a little bit at the end of this episode, so stick around after the interview.

Alright, let us roll! Here is my interview with Dr. Ray Goodrich on “Pioneering Pathogen Reduction.”

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Joe: Hi Ray. Welcome to the Blood Bank Guy Essentials Podcast.

Ray: Hi Joe. Good to be here.

Joe: I think that it probably would behoove us, Ray, to just set the stage a little bit and make sure that everyone is on the same page with us. Certainly, the phrase, "pathogen reduction" is one that people hear all the time in blood banking. Quite frankly, I've heard it for a lot of years, and I know so have you for some really good reasons that we're about to hear about, but why don't we just, for those of us listening to this podcast that are just learning. What does that mean? What exactly is "pathogen reduction?"

Ray: Well, basically it's the application of techniques to reduce the level of infectious agents that are present in blood products. The idea is to utilize methods that either remove the pathogens from blood or inactivate them, prevent them from replicating so that their potential for transmitting disease once they're transfused is reduced or hopefully reduced to the level where they're potentially eliminated, completely eliminated.

Joe: I know that there has been sometimes some confusion with the terms that we use in this, and sometimes you'll hear people say, "pathogen reduction," other times you'll hear people say, "pathogen inactivation," (less so in recent years, I think). Is it important, the distinction between those terms?

Ray: Well, I think, I remember very distinctly where the original comments came up. It was during a meeting that was sponsored by the FDA in the early 2000s, talking about these new technologies as groups were developing the processes and the FDA, I think expressed a concern. It was a presentation, I believe that Jaro Vostal did at that meeting.

They expressed a concern that they wanted groups to talk about the technologies in terms of their ability to “reduce” the likelihood of disease

transmission and not convey a sense that these were “absolute” in terms of their effectiveness by talking about “inactivation” or “eradication.” These were some of the terminologies that were being used at the time.

So, I remember Jaro going through a list of different terms or words that they thought, conveyed more of an absolute, which they wanted commercial organizations to avoid using, and made a suggestion that “pathogen reduction technology” made a lot more sense, because again, a recognition that although we would likely be able to significantly *reduce*, the levels of disease transmission, it was very unlikely that the technologies would be *complete* in their action. Likelihood that there could be a disease transmission event. There's no stipulation of what terminology is used, but different groups took it and interpreted it and ran with it in different ways. Some groups continued to use the term, “pathogen inactivation” technology. Some groups adopted the terminology pathogen reduction, in order to describe it. I personally feel that pathogen reduction technology is a more appropriate term to be used for all of these types of approaches. And it makes a better acronym than “PIT!”

Joe: [LAUGHS] As people are spelling it in their head…"Oh, yeah. Yeah, that's true. PRT much better!" I like it. So, before we get to the part that you played in this story, Ray, which is fascinating, and I want to hear about that, I wonder if, again, just to set the stage, we can answer, kind of, it might be the "elephant in the room" question, and that's simply this: Why the heck do we need this, Ray? Why the impetus to have an additional technology to deactivate organisms that aren't really likely to be in blood products anyway?

Ray: Well, I think the answer to that today is probably the same as the answer that was given before HIV entered into the blood supply. There is always the potential for new and emerging pathogens to enter into human populations, hence, to have those blood products become an additional conduit for the transmission of disease.

It really was the HIV epidemic that taught us a lot of lessons, and also served as a call, a “clarion call” on the need to be able to address blood safety in a way that perhaps different than what we had been doing up until the point before the disease had emerged into human populations.

And I think that story remains the same even today. It's easy and I think we have the tendency to declare victory based on our successes. And it's easy to forget, you know, situations that have arisen in the past, and I think we do that at the peril that we may not be prepared for the next event.

HIV was a horrible example of a disease entering human populations affecting blood supply safety, had dire consequences broadly within the health care community, among patients, providers, etc. But there are other stories. There's a West Nile Virus story. There's a Zika story. There's a

Chikungunya story. There's a Dengue story that have all occurred after that particular event. And I think the one thing that we can be fairly certain of is that there will be additional chapters in that story.

I think another aspect is, too, that we tend to look at this from the standpoint of high income or high-end income index nations, where a lot of technologies, a lot of different approaches have been put in place over the years to have improved blood safety. That's not the case universally. That's not the case globally. And there are parts of the world today where blood safety is still an issue, and the ability to be able to address those diseases by implementing screening, by implementing donor questionnaires, by implementing other techniques that have been utilized in Western Europe, the United States, Japan, simply aren't practical or possible.

Joe: That's fantastic. That's a wonderful answer. And I completely agree with that. It's very easy… I loved what you said, Ray, it's very easy to declare victory and that is not only premature, it's a little bit arrogant, I think, in a way...

Ray: Well there there was a commercial, I remember years ago, it may have been IBM, where they talked about, you know, they showed famous quotes or phrases over time. “Man will never fly.” “We will never go to the moon.” And then of course, all of those things did happen.

So just when people were either ready to declare victory or admit defeat, there were these developments where it actually happened. And I think the end line on that commercial was, “Many things can happen in the span of a ‘never.’”

Joe: Absolutely. Well that actually I think is a wonderful segue, Ray, to actually me allowing you to tell your story a little bit. I mentioned to everyone in the introduction that you've played a very significant part in the development of not just one type of pathogen reduction technology.

Ray, I would love to just give you the floor and hear a little bit about how you got involved in all this and what part you've played in all of it.

Ray: Well, the story really starts back in the mid to late 1980s. I was a graduate student at Cal Tech, and I was, working on methods to understand stabilization of membranes during freezing and drying. And, I had an opportunity, because it was being funded through an NHLBI training grant that was offered through NIH. And part of that allowed you to go to conferences and to visit with groups on different topics with the idea of stimulating research interests that might ultimately be something that would allow you to go into a field of specialization. And I got an invitation, during that time, I think it was around 87, 88 timeframe, from folks at the American Red Cross, and it was for a small meeting that was being organized at their Rockville, MD site. Gary Moroff, Len Friedman, Bob

Stromberg were heading it. And the topic was, “Methods or developing methods or concepts for treating blood products to prevent transfusion transmitted disease.”

And we were still in the midst of issues that were relating to or were a direct consequence of the emergence of HIV into human populations and ultimately introduction into the blood supply. And people were beginning to think that we needed a new way of being able to address blood safety, that we couldn't rely on a retroactive type of “wait till the disease emerges,” identify it, develop a test, screening methods, and then screen it out.

The question was, what do you do in that interim time? While all of that is going on and people still need transfusions, and the consequences of that, kind of like playing Russian roulette, unfortunately led to a lot of incidents of disease transmission and huge issues for patients, their families, the transfusion medicine community, the blood banking community, and people wanted to explore new methods. So, I remember going to this conference in Rockville and listening to a couple of different ideas that people presented and walking away from that thinking, “What could we do? What could we utilize as an approach to be able to address this?”

So, went back to Pasadena, California, and sat with some colleagues and called in a few colleagues from around the country that I'd worked with previously, my mentor at THE Ohio State University, Dr Matt Platz, who's a photochemist, someone that I had worked in in his lab as an undergraduate, and was just incredible in terms of his science knowledge and in the field of photochemistry and photobiology. Gave him a call and we sat down and we thought through the process and we were really intrigued with the idea. We came up with the list. I remember of what we called, “The Properties of an Ideal Photosensitizer or Sensitizer That Could be Used for Treating Blood Products.” And, we went through that list and came up with compounds that we thought might be interesting to take a look at.

And one class of compounds that we were very interested in were “psoralens,” and that interest stemmed from what we knew at the time about the chemistry of those molecules, that they had the ability to intercalate or associate with DNA and RNA, that they would carry out very specific chemistry with those molecules that would lead to a prevention of replication of those agents.

And so, in our criteria, what we were looking for is a way to be able to distinguish the “bad actors” that might be present in a blood product from the cellular and protein components that are necessary for therapeutic efficacy. And, we thought that a way of targeting those agents, the pathogens in blood, was to utilize the fact that despite the differences in structure and function, in some cases of viruses, you could have enveloped or non-enveloped, you could have gram-positive or gram-

negative bacteria, you could have the intracellular pathogens, but one of the characteristics that they all had was that they relied on nucleic acids for replication and ultimately for disease transmission. So, the thought was, if we could use compounds that would associate with nucleic acids and blood products…Of course, plasma proteins don't have nucleic acids, red cells don't have nucleic acids. Platelets have some mitochondrial DNA, but not really associated with the function of the mitochondria. We thought that this would be a way to be able to target, in a broad sense, pathogens which have these nucleic acids and require replication and the therapeutic components of blood that do not. White blood cells, of course do have nucleic acids, but from a donor-to-recipient standpoint, those actually could represent a contaminant that you don't want to have present or don't want to have functionally active when you transfuse them into a recipient.

So, we thought psoralens were an interesting class of compounds to explore, and we had some ideas about improving on the technique that had been described by people like Frank Gasparro and Edelson at Yale, using this for photodynamic therapy.

And so, based on the fact that we knew there was an NIH interest, and actually there was an entity, which I was a cofounder of, coming out of Cal Tech called CryoPharm Corporation, we decided to pursue an NIH SBIR (Small business innovation research) grant, and we put in the proposal, in I think 1988, 1989, October of that year, I believe it was indicated that we were awarded the funding. I remember the amount, to this day: It was $49,700. I remember it because we had asked for $50,000, and we got $49,700.

And I think at the time, we were convinced that's all we would need, that and six months, in order to figure this whole thing out. And, we went on, we received additional funding under the SBIR program as a Phase II grant to continue the development of the technology. Needless to say, it took a little bit more money and a little bit more time to work through the development issues, look at things like toxicology, compatibility with blood products, functional aspects of the products that were being treated, and from about 1989 to 1996, that's the type of work that we were engaged in.

Around that time, based on the preliminary data that we had generated, we pretty much came to the conclusion that, from our standpoint, it was not going to work. We were running into issues with some of the initial toxicology data that we had generated, some issues with immunogenicity that we had seen. And, we decided that there were routes that we could take. We toyed with the ideas of adsorption columns and removal devices, none of which seemed to work completely. They reduced some of the toxicity issues, but they didn't completely eliminate them. And, we decided that it was unlikely that we would be able to continue. It was a small company, didn't have the resources to be able to invest the kind of

development dollars that would be required to overcome some of these problems.

And I remember very distinctly having the conversation with our board of directors at the time saying, "You know, we have learned a lot about the chemistry and biology of these approaches. I don't believe that this approach is going to work, but from what we've learned, I think we could apply that knowledge towards developing new approaches, new methods, that have the potential to work. I just can't tell you what those are today." And they said, "Thank you very much. We don't want to continue investing, find a buyer for the technology, and move on."

So, that's essentially what we did. We went out and talked to a number of different groups, basically shopping the IP and shopping the notebooks of the work that we had developed. And, in 1996, there was a deal that was done between CryoPharm and Baxter International. At that time, Baxter had a relationship with a company that had started in Concord, CA around the same time that CryoPharm had initiated its projects with the blood treatment processes, the psoralen-based chemistry. The company was called “Steritech,” which was spun out of UC Berkeley, and had been developing their own class of psoralen compounds, initially based on a compound called 8-methoxypsoralen, and, ultimately based on derivatives of a compound called “AMT,” or aminomethyltrimethyl psoralen.

And they were developing in parallel. We were sort of “in the race” at the same time, and they had better success because of some of the changes that they made to the structures of the molecules, which we had only learned about through the work that we had done, that reduced some of the toxicity, reduced some of the immunogenicity issues, and had the resources of a large partner at the time, Baxter international, to help them further develop the disposables and the equipment to make this into a commercial process. And then I think shortly after that, in the around the 96-97 timeframe, Steritech went out as a public company under the name of “Cerus.”

I had spent nine years of my life, I would tell people, living on the "six month plan," and it was, I was getting kind of tired of that approach. And I really wanted to see what the world looked like on the other side of the table. Not just be developing these technologies but seeing what it was like to take them down the next steps of development, commercialization, the regulatory process, the marketing process. I was very interested in learning that, so I had a call, I think I was at an AABB meeting, shortly after, or while, the technology sale was going on for the psoralen technology out of CryoPharm. I had a call from Ed Wood, who was president of Cobe BCT at the time. And I knew Ed, and I knew many of the people in the BCT organization. I knew they were a very vibrant organization. They were doing some terrific work in the development of apheresis technologies. They clearly had all the elements of a commercial operation, marketing, sales, regulatory, clinical, etc. And so, Ed saw me at

this meeting, and he said, “I hear that you guys may be shutting down shop out in California. Would you be interested in coming to join us in Lakewood, Colorado?” He said, “I have no idea what your title would be. I have no idea what you would be working on. I have no idea what area of focus you would be in, but we'd very much like to have you come here and be a part of our organization.” And I said to myself, “How in the world could I turn down an offer like that?”

And it really was an opportunity to come and engage, again, learn all these things. And I thought that I would come and spend two years, learn all that I could, and go off. And I ended up being there for 20 years.

And in about 1998, 1999 timeframe, Ed Wood and Frank Corbin, the VP of R&D at the time, and really one of the people help recruit me to the BCT organization, came to me and said, “You know, we're hearing a lot in the field about ‘pathogen inactivation’ technology, and we were wondering, do you know anything about this? What do you know about psoralens?” And I said, “Well, you know, I know a little bit about that.” And so they said, “Well, we would like to, we're interested in developing, you know, some technology in this area to be a feature to enhance some of the products that we have in apheresis collections and, competitively, obviously, not be in a position to be at a disadvantage if this is the trend or the direction that the field is taking. So, what do you have as an idea, or would you be willing to go out and identify different technologies that we can license?”

And so I did that for…I went out, I looked at a number of different technologies, different companies that were developing technologies, and I kept coming back from these visits and writing up reports and saying, “I don't think this is an approach that will work. I don't think that's an approach that will work.” And finally, Ed and Frank came to me and said, “Well, you keep telling us what WON’T work. Do you have any ideas about what might?” And I said, “You know, oddly enough, I do.”

And, although I was, up till that time from 96 to about 98-99, I was actually working on stem cell collection protocols and processing protocols totally unrelated to pathogen reduction technology, I kept an interest in the field. And so, I was reading a book, a real barnburner called “Bio-organic Photochemistry,” by Harry Morrison, who's a professor, head of the Department of Chemistry at Purdue University. In fact, I'm staring at a copy of it on my bookshelf right now. And in that book, he was talking about different photochemicals and the mode of action that was known about them. And, there was a small couple of paragraphs in that book about riboflavin or vitamin B2, and some of its properties: That it was known to associate with nucleic acids, that it was known to carry out electron transfer chemistry, that it was known to, from a toxicology standpoint, to be a very innocuous compound.

There were references that were in that section, those couple of paragraphs. I went and got them. More references were listed in those; I

went and got those. So, I had a stack of papers and books on my desk about riboflavin and photochemistry and what was known. And it just really struck me that here was a molecule that we essentially were trying to synthesize. And being a chemist, you know, the goal is always make a compound that does better than nature. We were trying to synthesize molecules that would have these very properties that this naturally occurring and rather ubiquitous and very innocuous chemical already had.

And so, the thought was, and armed with the knowledge of where we didn't succeed in the original approach that we were taking…and there's an old saying, I think it's attributed to a Japanese saying, that “Defeat teaches better than victory.” True to that story and that, that adage, we learned a lot. We did learn a lot from the things that we found didn't work and understanding why they didn't work. So, when I saw this, I thought, “This has some potential.” So, I literally wrote a two-page white paper. And I said, "This is what I think might work." And I gave that two-page white paper to Frank Corbin and Ed Wood. And they said, "This is interesting. Go do it!"

And that was the start of the technology that in around 1998, 1999, ultimately became the "Mirasol" technology. And we grew that over time, and we carried out the preclinical and clinical work that was required from around the timeframe of about 2000 to about 2007. And in 2007, got approval in Europe under a CE Mark for the Mirasol technology and introduced the technology right at the end of 2007, beginning of 2008, and it has been in commercial use, various parts of the world, ever since that time, applied to plasma, platelets, most recently, applications related to the treatment of whole blood with the technology.

In the same timeframe, there are similar developments, by other groups. There's been the "Intercept" technology, which was introduced by Cerus earlier than the Mirasol technology in Europe, now approved in the United States as of a couple of years ago.

So, there's been a wealth of new technology platforms and existing technology platforms that have actually gone into routine use over time. And that's sort of the “long version” of the story, that, you know, has brought us to the point today where these technologies are actively being used in the field.

Joe: That is quite a story, my friend! To say that you've been "involved" is a massive understatement. I mean, you’ve been responsible for some, for some groundbreaking stuff, and things that are being used all over.

Ray: You know, Joe, the one, the one thing that I have learned over the years is that it really never is an individual. It really has taken, not only, many people to be involved in this, but also many functions, even within an organization. Success is not just determined by an individual's effort, but

by how that individual works within a group of people within an organization.

Joe: Completely agree. A couple of things that I want to discuss quickly before we get to the specific technologies, and I think that people struggle with this a little bit, so maybe you can help us out with a little bit of a clearer picture of this. People have asked me, "What is the basic assumption underlying pathogen reduction technology?" In other words, how much reduction is *enough*? Do we have anything that's been written or discussed about that previously?

Ray: Well, I think we have written some articles, I've been involved in a couple of publications, there have been others that have published, concepts about what is an "adequate" or "effective" level of pathogen reduction that you need to attain, in order to achieve efficacy. And I think that question has come about for a number of reasons.

First of all, you have to have some target that you're aiming for, in order to, have an idea about if it's worthwhile to take the next step. Ultimately, however, what really matters is, have you brought the level of pathogens that might be present in a blood product down to a point where disease transmission is either reduced significantly or eliminated completely?

Obviously, you target the latter, but you must at least achieve the former, a reduction in the level of disease transmission, in order to say that you have an efficacious product. And I think that there have been struggles, because it is a very complex issue. We don't really have defined levels of how much virus do you have to have or how much bacteria do you have to have in a product (or parasite) before you actually see a disease transmission event?

It varies broadly. In some cases, a single organism that might be present might be sufficient in order to cause disease transmission, albeit at a relatively low probability, but theoretically possible that it could. In other cases, there have to be certain levels of agents that are present in order to cause infection because of the nature by which infection occurs in-vivo. And the question that comes about is, can you apply a set rule that says, "If I achieve this, 'X' amount of reduction in infectivity, I will have an efficacious product." I personally don't believe that that is possible. I think certainly higher is better, but higher also comes at a price.

What I've seen in my own experience is that it's a balance between how much weight you put on the scale of pathogen reduction and how much weight you put on the scale of the side effects that come as a result of that. I used to make the joke, "Pathogen inactivation in blood products is not problematic. You just add bleach!" And you can kill everything that's there, but if you destroy the quality and the integrity of the product that you're treating, is that victory? I don't think so.

And so, I think there's a balance that has to be made. So, we're really talking about infectivity and how that correlates from an in-vitro standpoint to an in-vivo one or a clinically relevant one. That isn't clear. I would suggest that a way to be able to address that is actually look at the ability of these techniques to reduce the amount of disease transmission that occurs in practical clinical settings.

I was a part of one that was done several years ago, published in the Lancet, looking at disease transmission in patients who received transfusions of whole blood that was treated with the Mirasol technology, the riboflavin and UV technology, and looked specifically for the reduction in the transmission of malaria, transfusion-transmitted malaria, and was able to show efficacy, in preventing the transmission, over a control group, which received standard products that were not treated with the pathogen reduction technology. Was it complete? Was it 100%? No. Did it significantly reduce the amount of disease transmission that occurred? Yes, it did.

Aaron Tobian at Johns Hopkins is actually going to be launching a program, looking at the ability to prevent transfusion-transmitted disease in Uganda, looking at eight, I believe, different markers for disease: HIV, HBV, HCV, HEV, bacterial infections, malaria, and to do that on a large scale in Uganda. It's a program under the title "MERIT study," I believe it's listed on clinical trials.gov [NOTE: See clinicaltrials.gov/ct2/show/NCT03737669]. And that will be kicking off here within the coming year. And I think it's that kind of analysis that you would do in a region where disease transmission today is relatively high. and you can actually get some practical measurements of what impact that technologies like this are having on disease transmission in the actual clinical setting.

I mentioned previously that, you know, when myself and Matt Platz, when we sat down back in the late 80s and put together the list of the ideal sensitizer or the ideal process, we had all these characteristics, and one is, of course, it completely eliminates disease transmission. One of the things I could tell you that has been learned over the years is that that ideal doesn't exist. It's probably like with most human endeavors, impossible to ever have the perfect solution, but that doesn't mean that we can't develop and design and implement systems that significantly impact and reduce the amount of disease transmission that does occur. And because we cannot be *perfect* doesn't mean that we shouldn't do something that's *good*.

Joe: That's a great way to look at it. I think we need to move on and describe a little some of the technologies that are available today, some of which you've mentioned already in your story, but everyone, as I said in the introduction, the point of this is not to endorse or not endorse any of these technologies. It's simply to give you an idea, an educational idea of what's out there right now, what is available right now. So, Ray, are you ready to take a little quick tour?

Ray: Oh, absolutely, yes.

Joe: All right. So, let's start with one of the things that you mentioned in one of the older versions of pathogen reduction that's been around for a while. And I'm speaking of solvent detergent treatment. Currently I believe only available with plasma products. So why don't we talk through that a little bit?

Ray: Well. It was originally approved and used, commercially. Then there was a hiatus for a while, and I think there's been a reintroduction of it. Solvent detergent plasma, really a brilliant idea, and the idea was again, utilize a characteristic of the pathogen that is unique to the pathogen and distinct from the therapeutic component that you're treating.

In this case, what you're doing is, the solvent and the detergent dissolve membranes. They dissolve the membranes that are present on enveloped viruses. HIV, for example, is an enveloped virus. And so, if you dissolve the membrane and you remove the receptors that are present in those membranes by virtue of disrupting them with solvent and detergent, you prevent them from ever infecting a cell.

And you could use this approach clearly with non-cellular components, and that's where it's been applied, because if you put this solvent and detergent in with a platelet or in with a red cell, it doesn't just dissolve the membrane of…membrane envelope.. of a virus or bacteria or a parasite. It would dissolve the membrane of the red cell and the platelet as well.

And so, it's been applied with great success, a lot of history behind it, for plasma or for components derived, factors derived from plasma, and has been in use now, I don't know, maybe close to 30 years or more, with great success.

Joe: Let's move on and talk about one that, that is interesting. It is not approved in the United States, but it is CE-marked and that is the use of methylene blue, specifically for plasma. What comments do you have about that?

Ray: Yes, the methylene blue technology is also one that has been around for a very long period of time. It actually dates back in Germany, to where it was originally developed and utilized for plasma products. In that process, it was all done in centralized facilities. In the more modern versions of it, it's been picked up commercially and has been utilized as a single unit treatment process that can be done in blood centers. It is used in Europe. I know that there's extensive use of it as well going on in China.

It has a disruptive effect when the technology is applied to cellular components like red cells and platelets. And so, it has been used with success in treatment of plasma products on an individual unit basis.

Joe: Also CE-marked in the European Union is the use of straight ultraviolet C treatment of platelets. So that's interesting that the idea is apparently just

to use the ultraviolet C without a previous photosensitizer Ray, is that correct?

Ray: That's correct. And the concept behind it is that again, UV light can have a sterilizing effect of and by itself. UVC is very high energy UV, and it is capable of doing direct alteration of nucleic acid. It can cause strand breaks. It can cause direct oxidation of certain base pairs that are present in nucleic acids.

The challenge has been finding ways to be able to reduce the side effects. As with all of these technologies, all of them have some side effects, because it's a very nonspecific-acting approach. So, methods that are used for platelet treatment of platelet products include reducing the amount of plasma in these products and supplementing with additive solutions that are more transparent to UV light, doing mixing techniques in order to increase the exposure of the products. And I think to this point, it exclusively has been used with platelet products.

Joe: These last two are obviously, for reasons we've already discussed, very near and dear to your heart in terms of your involvement in their development. But let's talk first about the riboflavin or vitamin B2 plus UV light treatment, "Mirasol," as it is known, of course. So, what's the current status on Mirasol?

Ray: It is, in addition to the CE Mark for platelet and for plasma, it has also received a CE Mark for whole blood treatment. So, it is available in those forms for use in places that recognize and accept the CE Mark for commercial activity.

It is in clinical trials in the United States, both for the platelet application as well as for the red cells that are derived from a whole blood treated product. And I believe those trials are ongoing. The platelet trial, as far as I know, which is called "MIPLATE," is also on clinical trials.gov with the details [NOTE: See Clinicaltrials.gov/ct2/show/NCT02964325], is ongoing and currently recruiting, actively recruiting subjects in the United States.

Joe: And then the one that has been approved in the United States is the “Intercept,” or the amotosalen plus UVA light treatment of both plasma and platelets. Any comment on that?

Ray: As I said, the technology has really now been implemented for many years in Europe and for the past few years in the United States, for platelets and for plasma. The organization, Cerus, which has developed these products, has really done, I think, a very commendable job in clinical trial research with the products, supporting various studies and doing work around the world with the product, including the studies that have been done in the United States with the product that has supported their applications to get approval for commercialization, in the U.S. and in other parts of the world.

Joe: I have seen some previous presentations that you've made, and in the past you have made some fairly bold statements, and I guess I would call them predictions, going back well into the past, and I wonder if we can talk a little bit about some of those things that you've said and whether your "seeing eye" was correct. One of the things that you said, again, as far back as at least 2000 is that you predicted that as part of the pathogen reduction process, there would be a "measurable reduction in cell or protein quality following the treatment."

What data do we have and what concerns, maybe, do we have about some of the impact of these technologies on the normal function of these products that are being transfused?

Ray: Well, I think that, you know, the prediction was based on the experience and the belief that we had to recognize what some of the tradeoffs might be. You know, as I said, I think it's a fallacy to believe that we can be perfect, and we should be straightforward in describing that as well as the shortcomings because that's what leads to, ultimately, improvements or at least clear understanding of how and when to use these approaches.

The evidence that's out there, I think, comes from the clinical trial experience and the actual use experience. Where studies have been done, there is a reduction in the count increments, for example, with platelets, that occurs as a result of a treatment, likely due to changes or indiscriminate damage that occurs to the platelets.

There's increased metabolism that has been observed in platelets that are treated with these approaches. There is some metabolic and other markers in-vitro that predicted, I think, to some degree, the changes that we observe in-vivo, with reductions in count increments. So far, no significant evidence of increases in the likelihood of clinically significant bleeding from large studies that had been done with both the Intercept and the Mirasol product. There are changes in the overall numbers of transfusions that are required. There are changes in, some of the, grade 1 bleeding events, I believe that occur in those subjects, but no evidence of increases, significant increases in grade 3 or grade 4 bleeding.

There are some excellent analyses that have been done, a sort of a retrospective analysis on a number of different studies that have been published as part of the Cochrane database that described some of the findings from those studies.

Very similarly, I think, the story goes with plasma in terms of reduction in some of the factor activities. Also, clinical evidence of the need to increase some of the transfusion frequencies in those cases to compensate. With red cells, again, a very similar story, some reduction in survival and recovery of the red cells after treatment compared to before treatment.

But again, in all of these cases, I think, no significant evidence that the efficacy is compromised to the point where the products are no longer able to support patients.

So I think as long as you go into these products knowing what they can and what they cannot do and what consequences occur as a result of utilizing these approaches to treat these products, it's possible to compensate for the effects that are seen, at least from a cell quality or protein quality standpoint.

Joe: You made some other predictions, including things like, not all pathogens will be eliminated by application of these processes. And of course, that, as we've already discussed, has certainly come true. One quick thing I wonder if you would hit is the concern we're adding these "things" to the blood products, things that aren't necessarily "normal" parts of the human body or normal things that are found in the human body. How do you feel those concerns have been addressed over the years, Ray?

Ray: Well, I think, again, the clinical data is very helpful and very supportive. The in-vitro studies that have been done, which looked at toxicity, looked at the potential for carcinogenicity or mutagenicity, those studies have been performed to address the concerns or at least identify the magnitude of them that is present with the application of these approaches. Ultimately, I think time will tell how these things impact people. Concerns, I think, still remain, and always should remain for any new agent that's introduced into the blood supply, because of the types of patients that it goes to.

Yes, it goes to patients who are suffering from, hematological or other malignancies, but it's also going to patients who are undergoing knee replacement surgery, or a trauma treatment because of an accident, and otherwise might have very long lifespans after treatment or after therapy, and hopefully one which is free of complications and issues.

And so, I think you have to look at these questions, not only from the immediate effects, but the longer-term effects. And I think we have to look at what that data tells us, and then be careful and be sure that we're following what that data tells us when we're looking at this in the longer term as they're implemented with patients.

Joe: Well, the last prediction that you made, Ray, I have to say that the crystal ball probably didn't have to struggle too hard with this one, which is that, doing this, adding pathogen reduction technology would add cost to the process. And that is certainly true in terms of the cost of the product, certainly. In my discussions as medical director of a blood center, anytime I talk to people about pathogen reduction technology, specifically for platelets is the most common discussion, when the topic gets to how much these cost, that's where things tend to get to a grinding halt.

And so, I've seen that as somewhat of a barrier for implementation in the United States, and I'm assuming perhaps in other places as well, but certainly in the United States. Any comments on that and how those value judgements should be made, Ray?

Ray: Well, I think in part it has to be driven by the value that you get for the cost that you expend, what's put into it. And the answer to that question is likely not to be a universal one unless you're facing something that is a universal issue across the board for an entire geographic location, or the globe in its entirety, for example, a major pandemic that affects very large regions. I don't think if we had another disease outbreak like HIV, that people would be sitting around debating whether or not they should spend the money to implement a technology that could eliminate it. That doesn't exist, that scenario doesn't exist in the United States, in Western Europe, in Japan today.

So, I think that in those locations, the questions might be more appropriate to ask, from my perspective, are there specific patient populations who may benefit from this or may see value from this? More specifically, and I know it's difficult to think about, partial implementation, and I know the commercial entities certainly don't want to think about it that way, but maybe that makes sense. Maybe this would have better application.

I wrote an article recently talking about special considerations for use in pediatric patients of these technologies. That might actually be a place where it makes sense. Because you have patients that have higher probability of extended lifetimes.

I think it also depends upon the geography and the need. If you're in an area where a disease is endemic, where the transmission rates are high, or where the concern or risk associated with transmission is high, that might make sense to implement rather than deal with the consequences of an unsafe transfusion and the impact that has on the patient and on the community.

So, a lot of factors are going to go into this, and I think short of an epidemic outbreak that affects very large regions of the country or the world, I think it's going to be difficult to justify, at the cost profiles that exist today, difficult to justify, implementing this broadly and across the board. But it doesn't mean that it can't be done, in special cases or circumstances where the math and the economics of it and the patient value aspects of it make sense. All of those things, I think, have to be factored into the cost as well. And it should be based on what is the benefit that you're going to gain by putting this in place, by implementing it?

Maybe, for example, in some locations (and I've actually seen this happen), the fact that it's not the pathogen inactivation that's the value, it's the white cell activation, because you don't need to use gamma irradiators if you are able to inactivate white cells to the same level or better than

what you get with a gamma irradiation device. And so I think there are a variety of scenarios where the Cost:Benefit could tip in favor of doing this. It may not be as broad as some would hope.

I think, interestingly, as these technologies mature, I believe that there will be manufacturers who will be able to develop these technologies at much lower price points, and therefore offer them at much lower price points, on a global basis.

Joe: Well, Ray, I can't think of a better way to end our discussion than with those points. I think that there's a lot of hope for the future and as you said, we're trying to overcome some significant challenges in the implementation of these products, but ultimately, again, as you said, I think we have to figure out ways to get these, at least to the most vulnerable patients in our societies…

Ray: Well, you know, Joe, there was a sort of prayer that I would say to myself all through this process, which is, you know, if what we are doing is really going to do good in the world, then may all angels fly to our aid. And if not, then they should be delegated to the waste bin of history as something that, that failed.

Joe: Ray, this has been a wonderful discussion, and you are so full of insight and knowledge on this whole process. Thank you for sharing both your story and your perspectives on how things are now and where we're going with pathogen reduction technology. I just really appreciate the time.

Ray: My pleasure, Joe.

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Joe: Hey everybody. It's Joe with just a couple of quick closing thoughts. As I mentioned at the top, this interview was recorded just before the FDA released their final guidance on how to keep patients from getting platelet products that are contaminated with bacteria and offered pathogen reduction technology as one of the options there. I really do think that the guidance changes the dynamics a little bit and changes a little a little bit from what Ray and I were discussing. I think that there is a very good chance that 2020 and 2021 we'll see much more implementation of PRT for platelets especially, and I do believe it's the future really PRT and despite the increase in costs and the decrease in numerical response to platelet transfusion that Ray talked about, I really do think is PRT is where we're going and I'm personally in favor of it.

I want to remind you to go to Apple Podcasts and give this podcast a review and a rating. It's really important. I have to tell you, people really do find the podcast from the things that you write. I'm so grateful for everyone that's already gone and done so, but if you haven't done so, please do that. It will really, as I said, help other people find the podcast. And I do read every one,

by the way, so be nice. No, you don't have to be…Be HONEST! That's what I want.

I also want to mention, while this is not a continuing education episode, if you are a physician or a laboratorian, you can visit wileyhealthlearning.com/transfusionnews and find numerous hours of completely free continuing education. My thanks for that, as always, to Transfusion News, to Bio-Rad who brings you Transfusion News, and to Wiley Health Learning.

I've got so many cool episodes, you guys, coming up, you just wouldn't believe it! The next episode will feature Dr. Mindy Goldman from Canadian Blood Services describing choices she and CBS have made in Canada regarding donor and patient safety, and the bonus is, that episode also comes with free continuing education. I've got a round table discussion with some laboratory science leaders in Transfusion Medicine that I can't wait for you to hear, as well as an update on the most important changes you need to know about in the 32nd edition of the AABB Standards that is becoming effective in April 2020. Both of those episodes, I think, are really interesting, and I think you will enjoy them very much.

But until then, my friends, as always, I hope that you smile, and have fun, and above all, never, EVER stop learning. Thank you so much for listening. I'll catch you next time on the Blood Bank Guy Essentials Podcast.