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Targeted Anticoagulants Move From Lab to Patient Trials

ALTERNATIVES TO HEPARIN

Anticoagulants like heparin have been around for decades, but the drug has some drawbacks causing the biotech industry to look into more specific targeted therapies. Welcome to The Clinician's Roundtable on ReachMD, The Channel for Medical Professionals. I am Bruce Japsen the Healthcare Reporter with The Chicago Tribune and with me today is Dr. Ted Love. Dr. Love is the Chief Executive Officer of the San Francisco Biotech Company, Nuvelo. He was appointed to this position in 2001 after previously holding several senior management positions in medical affairs and product development at the well-known biotech company, Genentech, where he oversaw many drugs in development including the breast cancer treatment Herceptin. Dr. Love earned his Bachelor's Degree in Molecular Biology from Haverford College and his medical degree at Yale Medical School. He completed his residency and fellowship training in internal medicine and cardiology at Massachusetts General Hospital and the Harvard Medical School and I am so happy that he joins us today from Nuvelo's offices in beautiful San Francisco, California.

BRUCE JAPSEN:

Dr. Ted Love welcome to ReachMD XM157, The Channel for Medical Professionals.

DR. TED LOVE:

Thank you Bruce it's a pleasure to be with you.

BRUCE JAPSEN:

So anticoagulants such as heparin and warfarin have existed for half a century, but there is need for more targeted, more specific therapies, tell us about why that is and what we can see from yours and other companies going forward?

DR. TED LOVE:

You know, I do think its remarkable that the requirement to anticoagulate blood is an important topic in medicine, but essentially the majority of indications for treatment of patients in those situations today still use drugs, as you said they have been around for a long time, heparin and warfarin, but I think we are on the brink of that changing dramatically. You probably have read and probably even written about the fact that several of the major companies like Bayer and like Pfizer are making pills that inhibit Xa, which is an element

in our blood coagulation cascade, those drugs look very exciting and recently Bayer actually gained approval for their drug in Europe, so those drugs are coming and will I think be a major improvement in terms of our capacity to anticoagulate blood chronically in patients that need over a long period of time. Our company has actually been focused on the acute anticoagulation of blood particularly for medical procedures. One of the medical procedures that I have been involved in taking many patients through is coronary artery bypass surgery and in that procedure we actually replace the work being done by your heart and your lungs with a machine, but unfortunately when the blood is in that machine it would clot if it were not anticoagulated. Historically, we have used heparin to produce that anticoagulant effect at the end of the operation because you are at great risk of bleeding due to the surgical procedure; we try to correct that bleeding problem by giving you another animal-derived product called protamine. So we are working on a DNA-based product, fully synthetic, very specific and very potent at anticoagulating your blood that goes away spontaneously, very rapidly, so there is no reason to correct and we have actually complete 2 phase-I trials already and hopefully later this year or the beginning of next year, we will actually start to take patients through bypass surgery, so on the chronic front and on the acute front, I foresee big changes in anticoagulation.

BRUCE JAPSEN:

And given your role as not only just a seasoned industry executive, but as a former practicing cardiologist, could you tell us a little bit about, I mean, are physicians looking for this, are they looking for new anticoagulant products and perhaps what specifically are they interested in?

DR. TED LOVE:

Without a doubt, I mean, we have really managed through the limitations of heparin and warfarin over and over and over again, but these drugs actually have efficacy, they work well. The real issues is that the drugs are difficult to use and require a lot of titration and also the drugs have some significant side effects associated with them and when you think about drugs that are used so commonly, so broadly even a very rare side effect becomes a major health issue because you are exposing your drug to millions and millions of people. So we now are focussed on drugs which are very specific, synthetically derived, hit one specific target in the coagulation cascade and because of the specificity of what the drug does, but also the quality of the clean manufacture. We don't the issues of contamination and we also don't have many of the off-target side effects that you get with such heterogeneously derived products such as heparin.

BRUCE JAPSEN:

Well if you are just joining us or even if you are new to our channel, you are listening to the Clinician's Roundtable on ReachMD, The Channel for Medical Professionals. I am Bruce Japsen of the Chicago Tribune, I am your host and with me today is Dr. Ted Love, he is the President and CEO of Nuvelo, which is a biotech company based in San Francisco and one of the products they are developing are some synthetic alternatives to products like heparin and anticoagulants like heparin have been around for half a century, we were just talking about.

Dr. Love if you could elaborate a little bit on the side effects, these products are used so often, maybe people forget about the side effects, if you could talk a little bit about those side effects and perhaps how these products would avoid them?

DR. TED LOVE:

Absolutely. When we use heparin over a prolonged period, most patients actually develop thrombocytopenia that is their platelet counts begin to fall. About 1% to 2% people actually develop a very severe allergic reaction to heparin that we call heparin-induced

thrombocytopenia and that may not sound like much, but when you think about the millions and millions of exposure to heparin that actually amounts to a significant health concern.

BRUCE JAPSEN:

Probably tens of thousands of people?

DR. TED LOVE:

Absolutely. So drugs which would not introduce that kind of side effect profile into the healthcare system would be a huge advantage. So we have actually worked on a product that we call NU-172 which is a very specific DNA-based product that is synthetically produced, so no derivation from animal materials and it very specifically creates an anticoagulant effect that's rapidly reversed when we turn the drug off. So by doing it this way, we actually are able to produce the anticoagulant effect in a much cleaner in a much more predictable way and we are also able to turn off the drug effect simply by turning off the infusion without the use of a reversal agent such as protamine.

BRUCE JAPSEN:

And how far are we away from some of these new products, I mean are there any synthetic anticoagulants out there on the market and how far are we from perhaps seeing some of these new products come through clinical trials and perhaps end up in a hospital surgery suite near you?

DR. TED LOVE:

Well there actually are a few synthetically-derived anticoagulants that are on the market already. Unfortunately all of those products have very long half life and none of them are reversible. So if you try to use a drug like that for a patient going through bypass surgery, at the end of the operation you would predict and in fact we see a high rate of bleeding. The advantage that heparin has over those drugs even with all of its contamination and side effects issues is that you can reverse, largely reverse anyway heparin by giving a second drug called protamine. So the drug that we are developing has a unique advantage relative to heparin and all the other alternatives that are synthetically produced and that our drug is very rapidly self reversed literally within minutes of turning off the infusion. So you could take a person effectively through a bypass operation, at the end of the operation when you are worried about bleeding you simply turn the drug off and we have proven that very elegantly already in 2 phase-1 trials and later this year or early next year we actually expect to begin doing bypass procedures in phase-2.

BRUCE JAPSEN:

And do you have all of your clinical sites lined up, I mean if there are physicians out there listening in, I mean is there anything that they can do or anything that they perhaps would be looking forward to in this regard rather in regard to research.

DR. TED LOVE:

Well we actually are working with The Cleveland Clinic to identify a handful of sites to do a phase-2 trial and then after that we will be looking at doing phase-3 trials which would involve a very large number of centers, so people that are interested in doing clinical trials

with us, there will be, we hope, significant opportunities to do so in the future.

BRUCE JAPSEN:

And where do you think this will all head, I mean what would an ideal anticoagulant look like and perhaps what would the future hold as far as when we would start to see some of these things on the market?

DR. TED LOVE:

Well I think the ideal anticoagulant is exactly what we are working on, which is a drug which is very predictable. You give a certain amount and you get predictably a certain effect. A drug obviously that has potent efficacy, so it does what you want in a strong way, but does not introduce off-target or unanticipated side effects. One of the issues that we have been focused on is a drug which spontaneously goes away quickly because we are specifically focused on situations where we currently use heparin and protamine to reverse because you need the anticoagulant profile of heparin, but at the end of for example a bypass operation, you need the anticoagulant effect to go away. So our drug spontaneously goes away literally within minutes. Finally one additional characteristic that we have been focused on is the spontaneous nature of reversal, specifically no antidote required, so if you do need to reoperate on a patient which we occasionally do, you don't have the complexity of having introduced an antagonist to your anticoagulant.

BRUCE JAPSEN:

Yeah that is a key significant point because especially these days when folks are talking about errors and unfortunately the surgeries do have to be redone, but in your case with the developing a synthetic, there are just so many more things that you can do without worry in harming a patient.

DR. TED LOVE:

That's absolutely correct. And one other thing is that patients that we take to bypass often have limited kidney function or abnormal kidney function and one of the issues with heparin, but also many of the alternatives that we occasionally use when you can't use heparin, patients have abnormal kidney function or renal function. So then it creates additional complexity of using those drugs. So the drug that we are focused on also has no interaction at least based on what we have seen so far in terms of kidney function, so irrespective of patients kidney function, the drug continues to be predictable in terms of its onset and predictable in terms of its rapid offset.

BRUCE JAPSEN:

And could you tell some of our physicians, just in wrapping up, you know, what is the future hold for this type of therapy, I mean do you that there will be some synthetic alternatives on the market that they would need and perhaps why should they be looking forward to those?

DR. TED LOVE:

Well I think the major advantage of heparin quite frankly has been that it's cheap and over time when you are talking about the total cost

of managing a patient including its side effects often the better agent is the cheaper agent, so I think over time there will be a move toward fully synthetic products. One of the other advantage is that heparin has had over all of the synthetic alternatives is that it's reversible. We really have not had an agent that has the anticoagulant capacity that you can reverse just like heparin and that's why our company has focused on developing this product that we call NU-172 that's rapidly self-reversed, potent anticoagulant, as potent as heparin, but rapidly self reversed.

BRUCE JAPSEN:

Well with that I would like to thank Dr. Ted Love who has been our guest. He is the CEO of a San Francisco biotech company, Nuvelo, and we have been talking about the future of anticoagulation. This is Bruce Japsen of the Chicago Tribute, I have been your host and I would like to thank Dr. Love again for being our guest and I would like to thank you today for listening.