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New Directions in CFTR Modification

After participating in this activity, the participant will demonstrate the ability to:

- Summarize the concept of theratyping
- Describe our understanding of the molecular mechanisms of rare CFTR mutation.
- Explain how improved understanding of molecular mechanisms can influence therapeutic approaches to CFTR mutation.

Guest Faculty Disclosure

Dr. George Solomon has disclosed that he served as a consultant for Electromed Inc. and Bayer Pharmaceuticals, and has received grant funding from Vertex Pharmaceuticals, Nivalis Therapeutics, and ProQR Therapeutics.

Unlabeled/Unapproved Uses

He has indicated that there will be no references to the unlabeled or unapproved use of any drugs or products in today's discussion.

MEET THE AUTHOR



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Podcast Transcript

BOB BUSKER: Welcome to this eCysticFibrosis Review podcast.

I'm Bob Busker, managing editor of the program. Our guest today is Dr. George Solomon, Assistant Professor of Medicine at the University of Alabama at Birmingham. And we're here to talk about New Directions in CFTR Modification, Theratyping, and the Future of Individualized Cystic Fibrosis Therapy.

eCysticFibrosis Review is jointly presented by the Johns Hopkins University School of Medicine and the Institute for Johns Hopkins Nursing. This program is supported by educational grants from Gilead Sciences Inc, Vertex Pharmaceuticals Incorporated, AbbVie Inc, and Chiesi USA Inc.

Learning objectives for today's audio program include:

- Summarize the concept of theratyping
- Describe our understanding of the molecular mechanisms of rare CFTR mutation.
- Explain how improved understanding of molecular mechanisms can influence therapeutic approaches to CFTR mutation.

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Dr. Solomon, thank you for joining us today.

SOLOMON: Bob, thank you for this opportunity and invitation to discuss this topic today.

Q1. BUSKER: Individualizing therapy for people with cystic fibrosis — your newsletter issue reviewed some of the ongoing research aimed at achieving that goal, and one of the important concepts you addressed was “theratyping”. So before we do anything else, doctor, let me ask you to start us out with a basic definition: what is “theratyping”?

SOLOMON: Theratyping is a relatively new concept, especially in diseases like cystic fibrosis. In this concept we take knowledge learned about prior studied medications, like modulators for CFTR, and apply the use to new mutations in cystic fibrosis using the data learned from individual biomarkers.

SOLOMON: The idea really is that the drug has a known response in a group — will the same response happen to a different group? And can you predict if that will happen using some kind of biomarker? So the concept of theratyping is pairing known responses in one particular mutation class, comparing that with new responses in a new mutation class using biomarkers.

Q2. BUSKER: Thank you, Doctor. So now, with that as background, please bring us a patient scenario.

SOLOMON: The first case is a case of a 33 year old patient with CF who is homozygous for the F508del CFTR mutation. And the patient comes and asks about current and future treatments for the disease at hand.

Q3. BUSKER: So we know that ivacaftor alone has not been proven effective in homozygous F508del. But what about the use of a corrector/potentiator combination? What would you tell this patient about that?

SOLOMON: We've had the benefit in the last year of beginning to prescribe for patients lumacaftor/ivacaftor combination therapy for F508del homozygous patients. So this patient would be a good candidate for that therapy. What we learned in two main studies, two principal studies led by Wainwright and colleagues is that there were modest improvements in lung function, BMI and frequency of exacerbation with this combination therapy. Those recent landmark studies which are reviewed in this newsletter issue, demonstrate the combination therapy of ivacaftor and lumacaftor is potent enough to improve the key clinical endpoints; however, the response as we're observing both in follow-up and in clinical observation is not as potent as what we'd see with ivacaftor for G551D or other mutations in a response that did that modulator alone.

As you alluded to, previous negative studies, including monotherapy with lumacaftor and ivacaftor point to the need for better ways to theratype these mutations. And, in general, we hope there will be better responses if we better study this mutation and new combination therapies in the future for this patient. So I think the patient should be counseled that there

are new studies ongoing which would look at more advanced combination therapies as well as other approaches treating the F508del mutation which may bring a greater clinical improvement than what's currently available with lumacaftor and ivacaftor alone.

Q4. BUSKER: Doctor Solomon, let's get a little deeper on this. A patient's pulmonary phenotype severity — how might that affect response to therapy?

SOLOMON: Bob, that's a great question. Stuart Elbourne (phonetic) and and colleagues, as reviewed in this newsletter issue, began a study looking at a post hoc analysis to answer that very question. And the short answer is no, it appears that patients across the disease spectrum have some improvements in both lung function, although to a lesser extent in patients with more severe lung function defect than was originally studied by Wainwright and colleagues. However, when we look across the spectrum, there are improvements in rate of exacerbation, patient reported outcome measures including health related quality of life, and some improvements in lung function.

And so the short answer is, is that the pulmonary disease phenotype does not tell us which patients will have a better response, that there is a response across the spectrum, however, it is variable. In addition, what is of concern though, is that there is a safety, there's a tolerability issue of lumacaftor/ivacaftor therapy. The most common reaction that happens in patients is a chest tightness and shortness of breath reaction which as been observed in both initial studies by Wainwright and colleagues and in this post hoc analysis by Elbourne. And this was corroborated. Unfortunately, the level of severity of this intolerability was greater in patients with more severe lung function disease as measured by FEV₁.

So therefore, clinicians, when prescribing this therapy, would need to counsel patients that have a lower lung function, they have a greater risk of intolerability, especially from a pulmonary standpoint, compared to patients with milder or more moderate lung function defects.

Q5. BUSKER: The biomarkers that were used in developing these data — are they considered adequate enough to predict how a patient would respond to the therapy?

SOLOMON: Bob, that's a ~~great~~ question, ~~it's one~~ that we've struggled with a lot in the CF clinical research community for the past few years. It's no question that the response in aggregate of lumacaftor/ivacaftor in patients that are F508del homozygous CFTR patients, is significantly less compared to patients that got ivacaftor for G551D and other ivacaftor responsive mutations.

So the improvement in sweat chloride was definitely significantly reduced by about 50 percent, and that correlates in aggregate across the patients to a more modest improvement in FEV₁ and other clinical endpoints.

In addition, the FDA demands hard endpoints in a lot of circumstances to approve therapies, especially new classes of therapies. So we have to know what those biomarkers are telling us about the disease. And in addition, we know the individual responses of patients receiving CFTR modulators do not correlate well to clinical response.

One example of that is when you plot the individual improvement in sweat chloride response to a modulator, even in the case of ivacaftor, that does not well correlate to that individual patient's response to, for instance, FEV₁ or clinical improvements like a health related quality of life. Therefore, at present, sweat chloride, which has been a key phase 2-type biomarker, is not adequate to supplant clinical response in mutations like the F508del CFTR. And in addition, would not be an adequate surrogate marker for clinical response in new class therapies or new modulators which are being studied with ongoing modulator therapies.

So, therefore, I think we have to look for better biomarkers which may have a more sensitive prediction of response, the clinical outcomes, than what we have currently.

Q6. BUSKER: So to go back to the patient you presented — 33 years old, homozygous for F508del, and he wants to know about current and future treatments. What would you tell him?

SOLOMON: Bob, this is a great questions we get from patients a lot in our clinical arena, and I would say that the future, first of all, is bright for treatment of patients with F508del CFTR. First we have a first pass at a better, more tolerable corrector potentiator combo, pairing the drug known as VX661, or tezacaftor, with ivacaftor. And this molecule has made it through phase 3 and we know that in a recent press release that there were strong improvements in FEV₁ and other clinical endpoints. So this drug will be put up for seeking of FDA approval in the near future, hopefully in 2018. That's the next first step.

In addition, we're testing two and maybe the potential of up to four next generation corrector molecules. And what they do is they're additions to the first generation corrector molecules like lumacaftor and tezacaftor and they would be entering as triple combination and we're currently in phase 2 studies for those. And we don't know the results yet, we do have a lot of hope they will be effective based on our preclinical modeling of the disease and this mutation.

In addition, there's a strong emphasis across the research arena to look at genetic type based therapies to target specific mutations, including F508del, and there have been some recent results reported which were highlighted in the issue about genetic based therapies which may correct specific mutations in new and novel ways.

And finally, as we learn more about modulation of F508del CFTR, we think that there will be the potential to study patients earlier in the disease process, i.e. earlier in their life, and hopefully be able to better ameliorate the development of lung disease as a real potential for more curative therapy at this time. Therefore, there's a lot of hope for this patient and that should be conveyed, and there's a lot of work in the next few years in the research arena to address these matters.

Q7. MR. BUSKER: Thank you, doctor. And we'll return — with Dr. George Solomon from the University of Alabama at Birmingham — in just a moment.

MR. BUSKER: This is Bob Busker; I'm the managing editor of eCysticFibrosis Review. eCysticFibrosis Review is a combination newsletter and podcast program delivered via email to subscribers. Newsletters are published every other month. Each issue reviews the current literature in areas of importance to pulmonologists, gastroenterologists, infectious disease specialists, pediatricians, respiratory therapists, dietitians, nutritionists, nurses, and physical therapists. Bimonthly podcasts are also available as downloadable transcripts, providing case-based scenarios to help bring that new information into practice in the clinic.

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Q8. MR. BUSKER: Welcome back to this eCysticFibrosis Review podcast. Our guest today is Dr. George Solomon from the University of Alabama at Birmingham. And we've been talking about how Theratyping, and understanding the molecular mechanisms of CFTR mutations, can influence the Future of Individualized CF Therapy. So let's continue, if you would, please doctor, with another patient scenario.

SOLOMON: Well thanks, Bob. The next case we'll discuss is a case of a 45 years old white male with CF who has pancreatic sufficiency, who is heterozygous for the R117H CFTR mutation, and has mild lung disease, his FEV₁ is 91 percent or predicted.

He presents to your clinic for counseling about future therapies and what we might know about his disease progression.

Q9. BUSKER: Correct me if I'm wrong, Dr. Solomon, but the R117H mutation — that's a CFTR mutation that ivacaftor has already been approved to treat. So what more do we need to know about it?

SOLOMON: R117H is a relatively newly described CFTR causing mutation. There's a lot of interesting things that have been learned by looking at mutations like this. The short answer about that is that R117H represents an example of studying the concept of splicing portions of the gene. We know that the splicing of this gene is affected by the length of a non-coding portion of the CFTR gene known as the poly T-tract. And so in short, it confers greater risk of the disease and a more severe phenotype if that poly T-tract is shorter.

So patients that have the R117H with what's called the 5T or the short T-tract, have true cystic fibrosis because they have CFTR dysfunction due to abnormalities of the protein as a result of that shorter poly T-tract.

Patients that have a longer T-tract, either 7T, 9T or greater, have a much greater residual function of their CFTR and thus may be called not cystic fibrosis or CFTR-like syndrome, or have at least have a milder phenotype in general than patients that have the 5T poly-T tract. And so this type of mutation brings up a concept that we really have to understand more advanced sequencing techniques, because without advanced sequencing of the non-coding portions of a gene which are being done more readily now, we would never have understood this discrepancy and never begun to understand that the non-coding portions of the gene can affect the splicing of the genetic material together and affect whether or not you have a functional CFTR protein being made inside the cells.

And so, therefore, advanced sequencing techniques are essential for us understanding more about mutations which may have responses to modulators in the future by this type of technique and understanding.

Q10. BUSKER: Doctor, the molecular mechanism of the R117H mutation. Talk to us little bit about what's currently known, if you would please.

SOLOMON: The current understanding is that R117H CFTR exhibits both a reduced gating. And what that means is that the pore does not open appropriately to allow the flow of anions like chloride, which is the common anion that CFTR conducts. In addition, it has a component of delayed conductance to the pore. What conductance means is not only does it not open

properly, which is gating, but it also, once open, does not properly move the anions down their concentration gradients. And so this discrepancy is made by the fact that splicing occurs to put together inappropriate portions of the protein, and, thus, results in the inadequate splicing of this mutation. And so with more inappropriate splicing of this R117H from a non-coding sequence of the gene, it results in an addition of a part of the protein that does not gate or conduct anions properly.

And so the molecular mechanism has sparked interest because one of the molecular mechanisms is gating which is very well treated by a mutation like ivacaftor. So this was an early first pass at a mutation that was not G551D, but had characteristics of the G551D gating mutation. So, therefore, it's thought that ivacaftor might be an effective therapy for this type of mutation, albeit it's a different type of mutation than G551D, itself.

Q11. BUSKER: So that's our understanding of the molecular effect of the R117H CFTR mutation. How does that connect to the clinical trial results testing treatment of R117H?

SOLOMON: Recently trials led by Moss and colleagues, which are reviewed in this newsletter, studied 69 patients with this mutation. They were tested for clinical response, including lung function and sweat chloride response to ivacaftor. In aggregate, the clinical trial was negative for the primary endpoint which was increase in percent predicted FEV₁; however the patients did have a large decrease in sweat chloride of about 20 to 25 millimoles per liter. And a subgroup analysis found the key portions that we had suspected before, that patients that had the 5-T tract on the same mutation as the R117H, demonstrated clinically significant responses. So, therefore, this led to the FDA labeling of patients having treatment with ivacaftor on the basis of their poly T status, and necessitated a next generation sequencing which is done now to treat this mutation.

Q12. BUSKER: So progress has definitely been made in treating this type of mutation. What are the next steps?

SOLOMON: The sweat chloride improvements, especially in patients with the 5-T status, is very encouraging. It tells us that targeting patients with specific sequence variants down to the level of non-coding regions is going to be important for rarer mutations like this R117H and point to the fact that we have to continue doing this type of research to understand the real molecular mechanisms of disease in this condition.

We think that combination therapies, including patients with F508del and R117H-5-T may be effective because you would have ivacaftor in combination with the corrector molecule, especially a next generation corrector. So, therefore, it may offer a greater response clinically for patients in combination, like patients with G551D have for ivacaftor. And so we're very encouraged that next generation potentiators also may come around which will reduce sweat chloride sufficiently to carry the load of just a single R117H mutation or other mutations like this in the future.

Q13. BUSKER: Thank you for that case and discussion, Doctor. Now, if you would, please, bring us one more scenario.

SOLOMON: The next case is a 37 year old white female with CF who's pancreatic sufficient, who has a complex genotype of F508del and P67L CFTR mutations. And she comes to your office for counseling about future therapies. She's had recent worsening of her lung function and sinus disease and is hoping for something new to help her.

Q14. BUSKER: That's a rare mutation, P67L. What's our current understanding of treatment modalities for these patients?

SOLOMON: At present, some mutations like the P67L mutation are being investigated when they're in what's called trans or on the opposite gene to the F508del mutation and some gating mutations. Recently the development process for patients with F508del and residual function mutations like P67L, have shown some promise on a recent press release with treatment of both tezacaftor and ivacaftor. And so, therefore, we're hoping there will be an efficacy to reach FDA approval. However, the residual function mutations like P67L can have significant response to tezacaftor/ivacaftor as F508del homozygous patients did.

Probably that has to do with the fact that these mutations are not as well understood except they cause an overall milder reduction in CFTR function. We often have a milder phenotype and we don't quite understand the molecular mechanism of these, as well. And so the later onset of disease and pancreatic sufficiency is related to milder CFTR function, but the cause of having some preserved CFTR function in these types of mutations is still under investigation and has probably been misunderstood for some years. And therefore, leads us to being less precise with theratyping of modulators towards this type of mutation class.

Q15. BUSKER: P67L: where does this rare mutation fit, or does it fit at all, in the commonly used mutation classification scheme?

SOLOMON: Bob, that's a great question, and understanding rare mutations and how they function is really important for this concept of theratyping as one of the themes for this podcast. P67L is a rare mutation, it was thought to be and described to be a conductance mutation, signifying basically reduced pore capacity. However, new evidence reviewed in this newsletter sheds light on the conductance of P67L CFTR as actually normal, but there is new evidence that it hasn't impaired gating

and protein maturation.

Now that's really good for patients with this mutation because that may point to why ivacaftor therapy, as in combination with tezacaftor or other combination therapies, may help these patients, because then you have a drug that improves the gating abnormality of P67L. And so a better understanding of the molecular mechanism helps us to better theratype patients that may respond to drugs that have no response characteristics like ivacaftor in this circumstance.

Q16. BUSKER: So sum it up for us, Doctor Solomon: the new evidence into mutations like P67L — what does it tell us about therotyping and potential future treatments in cystic fibrosis?

SOLOMON: I think the concept of therotyping is we may be seeing, with early evidence of efficacy in mutations like P67L with this combination therapy, is a key for these types of mutations. Understanding the basic defect of the mutation, paired with known clinical responses and biomarkers that predict that clinical response, will allow us to extend the labeling or extend the use of modulator classes more rapidly and tell us how a roadmap for treating a broader array of rare mutations in CF, and hopefully other genetic conditions down the line as a more general roadmap, but for sure in CF in patients with rare mutations.

Q17. BUSKER: “Biomarkers that predict clinical response” — talk to us a little bit more about the importance of those, if you would please.

SOLOMON: Improved biomarkers is really, really a key for better understanding rare mutations. We aren't going to be able to do classic randomized controlled trials for labeling of every rare mutation, because assembling that patient population would be nearly impossible to do that for a study. We present some information by Deckers and others in this newsletter that shows the capacity of one biomarker known as rectal organ weights that adequately predicts a clinical response across two different distinct molecular mechanisms and mutations. And so more studies like this that would help us to determine if biomarkers could do this in a broader sense and be able to take a biomarker from a disparate group of patients, run that in the lab, and say, all right, this patient has this type of molecular mechanism rare mutation, they will respond to this class of modulators, would be awesome, because we could skip the possibility of having to do a traditional randomized control trial to get FDA labeling.

The FDA is making a first impetus very recently by extending the label of ivacaftor to about 23 additional ivacaftor responsive mutations without doing control trials. So they've told us that this may be a possibility in the future. And by that, individual biomarkers using cells lines, there's either cell lines expressed by a particular mutation, and/or primary human tissue, specifically bronchial epithelial cells grown in culture, it showed that those patients tissues had a similar response that was seen in ivacaftor and other ivacaftor responsive mutations. Pairing that allowed the FDA to extend the label of ivacaftor very recently, and so assuming those patients do have a sustained clinical response as patients with ivacaftor, that will tell us that that concept of using a biomarker without having to have the actual patient study, will be a viable approach in the future to attacking rare mutations.

In addition to that, as we mentioned earlier, we can use genotype agnostic approaches to treat rare mutations. So you could take patients independent of mutation and give them fully functional CFTR protein or CFTR genetic material, and they would have correction of their CFTR function independent of what the molecular mechanism of their defect is. So I think the studies of therotyping, including biomarkers and extending the labeling like we've talked about, as well as the future of genetic genotype agnostic approaches, are going to be the real keys for the future of helping patients, especially with rare mutations.

Q18. BUSKER: We've kind of moved into discussing the future, Dr. Solomon, so let me ask you: personalized therapeutics, individualized treatment for CF — your thoughts on that? SOLOMON: Personalized therapeutics, in short, I think are possible in cystic fibrosis. At present, CF has been one of the model research arenas in which this has been studied and is being advanced. It's no question, as we discussed in this podcast and as reviewed in this newsletter issue, the continued work in biomarkers that are sensitive at the patient level are going to be key to making, advancing this forward.

And in addition, as we get more capable of understanding unpersonalized therapies, in other words, genotype agnostic approaches, we may be able to treat every patient regardless of their molecular mechanism of CFTR dysfunction. However, those techniques are future, we are not there yet with those. And so they require a lot more research in the basic science arena before we're going to get to that point.

And so I think we have to, at this point, because we're not there with those types of unpersonalized types of approaches, we've got to continue to understand the precise molecular nature of mutations until we have a definite gene level treatment for this disease. So I think those two things, current and future, will guide us to therapies that are very effective for all patients with CF.

Q19. BUSKER: Thank you for sharing your insights, Doctor. Let's wrap things up now by reviewing today's discussion in light of our learning objectives. So our first objective: the concept of therotyping.

SOLOMON: We've discussed today in this podcast therotyping is a new approach in CF. This concept pairs understanding

of the molecular mechanism of new and rare CFTR mutations with means to predict the response of known modulator therapies on an individual patient level. This concept is revolutionizing the way we think about rare mutations in CF and we hope will be a concept we can use in the future to advance therapies to more patients.

Q20: BUSKER: And our second objective: understanding the molecular mechanisms of rare CFTR mutations.

SOLOMON: This is important for the concept of theratyping and links in very tightly. We reviewed two cases in this podcast of relatively rare and variable phenotypic severity CFTR mutations, and we found that in reviewing those, that these mutations have unique genetic and functional molecular mechanisms.

In the case of the R117H mutation, variable splicing due to non-coding reasons that surround this mutation, affect the amount of this mutation which is incorporated into the CFTR protein. And, thus, helps us to understand that by variable incorporation of this mutation, we have variable levels of a gating abnormality and a conductance abnormality which can be treated with ivacaftor, a well known and well described modulator therapy, and thus links us in a theratyping approach.

In the case of P67L, another rare CFTR mutation, we found that new understandings of channel function have led us to a better understanding of the molecular mechanism, and a refined and corrected understanding of the molecular mechanism, and inform us why studies, including combination therapy of tezacaftor with ivacaftor, may show response in patients with residual function mutations like P67L because of refined mechanistic understandings.

Q21. BUSKER: And finally: how improved understanding of molecular mechanisms can influence therapeutic approaches to CFTR mutation.

SOLOMON: As we've seen today, there's new therapies being advanced for several rare mutations. The molecular mechanism is key to understanding a theratyping approach. Because in the theratyping approach, if we can predict how a patient's going to respond based on the known characteristics of the drug, in other words how it works on mutant CFTR, like knowing that ivacaftor improves gating of certain gating dysfunction CFTR mutations, that we would be able to predict, if we understand that molecular mechanism, that patients with a similar molecular mechanism but not G551D, might similarly respond to that modulator. And thereby we can test, using individualized type biomarkers, whether or not the patient should have a response and advance therapies to new patients and new mutations.

Q22. BUSKER: Dr. George Solomon from the University of Alabama at Birmingham, thank you for participating in this eCystic Fibrosis Review Podcast.

SOLOMON: Bob, thank you, and to the organizers, this has been a lot of fun and I hope will be informative to the audience.

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