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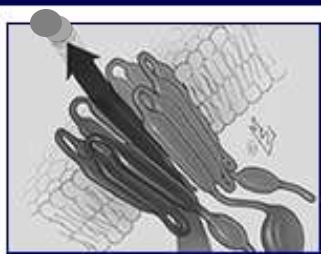
EMERGING CF THERAPIES 2009



Transcript: Pathophysiology & Therapeutic Targets – Richard B. Moss, MD

I would like to welcome you all and thank the Hopkins CME folks for helping to organize this hopefully good learning experience.

Here are some disclosures about my activities as an investigator and a consultant to several pharmaceutical and biotech companies.

Okay, so let's begin then by starting where everyone usually starts, which is the pathogenesis diagram. And the talks today will really be aimed at certain segments of this pathway, but we don't have time to really cover them all. And my job as sort of the overview introducer is to back off and try and cover the whole thing but from a very high altitude, so it is going to be kind of general. And then hopefully situate the talks by JP Clancy and Pam Zeitlin, and then Chris Goss is going to get up and put that information into some context for you as clinicians and investigators, some of the dilemmas that you'll be facing with these new approaches.

So we have the gene product, defective CFTR leading to defective ion transport. Through work primarily at UNC we now pretty much now accept this idea of airway surface liquid depletion as a central driver of pathogenesis, very tightly linked to defective mucociliary clearance. And then the creation of obstruction in airways.

We know there is the presence of infection and inflammation, and this cyclical diagram here indicates to some degree a lack of knowledge about the actual temporal sequence, which probably is going to have therapeutic significance as we understand this better. In other words, which agents are we doing to start with and when do we start them.

And diagrammatically we can see here on this panel up here that this depleted airway surface liquid results in dehydration and accretion of mucous above it creating the typical lesion that we're used to seeing in cystic fibrosis with occlusion of bronchioles and a very inflamed airways, these plugs containing both mucous, but

also a large number of neutrophils and bacteria. And then the interesting feature of CF, the relative sparing of the actual gas exchange parenchyma.

Now when we talk about drug discovery in CF, to put the discussion tonight into a bit broader context, let's remember that there are really three different approaches that we can take to drug discovery. And the first one is to actually try and find agents to replace or treat the underlying defective protein. And that is going to be JP's task tonight is to just review where we're at with that and where we're going.

Closely related, but quite distinct, is the discovery of new therapies that treat secondary consequences of that dysfunctional protein. And among those would be alteration of the fluid and ion transport characteristics, and that is really going to be Pam Zeitlin's bailiwick.

We are really not going to have much time to go into inflammation and infection. Luckily, most of you I think were probably at the plenary this morning and head Jim Chmiel (Case Western Reserve) beautiful fill-in for Michael Konstan (Case Western Reserve) on that area. And let's not forget, although we'll be focusing on investigational drugs tonight, the importance of identifying approved medical therapies that can benefit our patients.

So we have this low hanging fruit approach where the development of new drugs is accompanied in many cases by bringing other approved drugs to our patients, and we all know about those examples with ibuprofen, azithromycin and hypertonic saline all being well accepted and recommended for treatment with specific indications in patients for CF.

It is clear that we have these advantages that this is a much faster and cheaper way to go than to have to bring drugs through the pipeline which can cost up to a billion dollars, and take 15 years to bring from bench to bedside. Nevertheless, we do have to turn to investigational drugs because so far we don't have anything off the shelf that is really a powerful disease modifying agent for cystic fibrosis.

So here is the familiar pipeline slide. You've seen a number of versions of this in recent days and we're really going to be focusing in this area in terms of the subsequent talks. But it is important to just keep in mind that all these things represent opportunities.

And in thinking about the respiratory disease, in particular, and about what our approach should be, keep in mind a paradigm where the measurement that we are primarily using is FEV1. And let's recall that the reason we're doing that is because

of some very robust epidemiology that's been done over the last 20, 30 years, tightly linking FEV1 with survival in cystic fibrosis. So that the actual FEV1 level is predictive of ultimate survival.

And that is why the FDA accepts this as a valid surrogate endpoint for clinical trials. The FDA is very focused on outcomes that affect patient performance, survival, or subjective feeling. And the FEV1 is one of those, but it's a valid surrogate because it predicts survival outcome.

So in thinking about what we can do with FEV1, there is a couple of different ways to conceive of how a drug may impact it. The more traditional approach, and this is exemplified by some of the drugs that we're using today, is to start, initiate therapy, and then notice that there is an improvement in lung function. But when we track it over time we find that that initial improvement in lung function doesn't seem to change the overall slope of decline of the disease. So this is an effective therapy but it is not really disease modification.

If think of what we could conceive of as the cure, we would have an intervention that whenever we started it would basically arrest the disease. Now if we started it sooner after birth with a newborn screening process, you might actually preserve lung function as well as structure, completely intact that would be as close to a cure as you could conceive of.

More likely you are going to be instituting this a little bit later in life, at least initially, and arresting the disease and having no decline, other than what's a normal decline as we all age. There is some decline in lung function normally.

But what we are really looking for in terms of what is achievable right now is to slow that decline, change that slope, and that is what we really mean by disease modification. And what we're really hoping to do with these agents that are going to be talked about in the subsequent talks is to achieve disease modification.

Let's consider how we actually might be able to do that. This is a conceptual diagram taking a patient from birth through time and you will notice that there's a series of observations that can be made. If we consider how we're looking at new drugs, we're using FEV1 to validate them. Think about the Pulmozyme trial or the TOBI trial, azithromycin, hypertonic saline, they all were winners on improving lung function. And the way you improve lung function is to move that FEV1 up. But if you think about it, these patients often don't have normal lung function. So the validation is occurring late in a conceptual process that is preceded by other things.

Actually, as clinicians, we're acting earlier than that in our actual care of the patient and instituting therapies, especially when we use the low hanging fruit approach. In this case, we're looking at patients who have persistent symptoms and/or pulmonary exacerbations and initiating practice here. So we are actually doing something that is a step ahead of what we're doing in clinical trials, and what the FDA will say is okay.

If we think about starting even earlier, we can consider the possibility of achieving better outcomes by starting earlier, using some other markers, or outcomes, that have not been linked to survival, and therefore are not accepted as actual surrogates for drug approval, but which can be considered helpful. So these biomarkers can include, for example, the early occurrence of bacterial infection. And as we will all hear about tomorrow morning, the EPIC trial is really aimed at an intervention that is based upon, if you will, a biomarker, the occurrence of *Pseudomonas* in a throat culture specimen. So that is a biomarker driven clinical intervention, and it is very doubtful the FDA would ever approve a drug, let's say we had a new antibiotic, on that basis, but it is something that we, as clinicians, can do because we feel comfortable that that information is useful in helping the patient.

In the future, we may also be able to use some other markers like cytokines or cells in the BAL or induced sputum. You heard a little bit about that this morning in terms of how we can evaluate anti-inflammatories, and also what hasn't been talked about much is the interest in serologies and looking at the immune response as indication, for example, of when infection is occurring. We know that this can be a signal that appears even before we can do a culture detection of the bacterium.

I will mention a little bit about structural changes, because I think that is rapidly emerging as an outcome measure that is going to be useful in future trials. But these all really are predicated upon the fact that we may be able to get better outcomes by targeting upstream, relying on emerging biomarkers.

So the targeting interventions, as I mentioned has really started with evidence of disease based on loss of lung function. And the cystic fibrosis consensus pulmonary guidelines are really based on evidence, and so are the Cochrane guidelines. And if you think about it, those are based on evidence, and evidence is based upon patients who already have loss of lung function.

So all these six drugs that are recommended for the treatment of cystic fibrosis are occurring in the presence of established disease with noticeable loss of lung

function.

There is another level which is the use of risk factors, and there is some literature that has come out of ESCF and other databases that can identify for us risk factors which can precede the loss of lung function. And one can easily conceive of the use of these approved drugs, approved by our peers, really, not the government, for use in the disease based on risk factors.

And we also know, of course, the experimental therapies, the potentiators and correctors that will be talked about and ion channel agents, and distantly, perhaps, gene therapy, which might be considered way upstream when the process is silent and the only readout might be a biomarker that has no clinical accompaniment.

We can also conceive of the fact that the drugs currently approved could be used as far upstream as we like to take it based on rationale. So some of us are starting some of these therapies very early in the life of these patients before we have FEV1 loss or before we even do FEV1 testing.

I mentioned structure, so there is another way to look at the progression of CF lung disease than function, and that is to look at structure, and they tell you different things about the disease process. And there is a fair amount of evidence now that structural analysis, as done by a high resolution CT, provides information before changes in lung function, except, perhaps for the most sensitive and experimental measures that we can do in infants.

So according to this paradigm, if you have normal airways, you can consider an intervention that is preventative in nature. So you can imagine a time in the future when patients might be started at diagnosis on, for example, a corrector. That might occur before any onset of disease that is detectable by either structure or function.

There are some subtle changes like air trapping and regional airway thickening, as well as mucous plugging, and then somewhat later, but fairly early on, the occurrence of mild bronchiectasis that then progresses, and various therapies that might be envisioned along the way.

There is some interesting work at this meeting on the early occurrence of bronchiectasis in infants with CF that have otherwise no signals of disease. It's a little bit scary to see bronchiectasis in kids just a few months old.

So turning to the classification of genotype related problems, we're going to hear in JP Clancy's talk about some specific genotype aimed therapies that are a major subject of this year's meeting.

First there is the class one mutations where there is no synthesis or synthesis of truncated CFTR, the so-called nonsense mutations, and a specific approach that's been developed for that that is going into phase III trial. The most common problem, of course, is the processing block with missense mutations like delta-F-508, that affects up to 90 percent of patients. So an approach that would be effective in dealing with this processing block would be a tremendous breakthrough for our patients and we are working on a phase II approach right now.

And then finally, the block in regulation, other kinds of missense mutations where the protein is produced, it's transported normally to its place in the apical membrane, but is dysregulated. And again, we're moving from phase II to phase III with a drug which is aimed at this particular class. So that is going to be the topic of Dr. Clancy's presentation.

Moving beyond the genotype specific approach, we have the more general approach, to go one step down, but still very early in the whole schema, which is to address this issue of volume depletion of the airway surface liquid, as cartooned here in a visualization by Dr. Richard Boucher (UNC-Chapel Hill). Where you have both production of mucous by submucosal glands, as well as goblet cells, and a loss of the periciliary fluid, so you get a hyposecretion and a diminution of mucociliary clearance.

Now to deal in that, there is really quite a robust effort being made by a lot of different people trying to develop therapies that are aimed at that. So let's break this down a little bit more.

When you think about mucociliary clearly, we're dealing with a number of different levels of activity. One is to consider chloride transport, itself. So some approaches are based on alteration of chloride transport that does not involve CFTR. Another might be other ways to modulate ion transport. A third might be to not worry so much about channels, but just worry about the hydration and figure out ways to hydrate the airway that don't rely on channels. And then finally, there might actually be other ways to enhance mucociliary clearance that don't depend on any of the above.

So in terms of how they act, CFTR would be involved in all of these, but alternative chloride channels would also be involved in chloride transport and the rest. Moving a step over, sodium transport would not be involved with chloride but might be an effective treatment for the disease based upon inhibition of absorption of sodium and rehydration through that mechanism.

Moving beyond that, we have osmotic agents that could affect airway hydration without dealing with ion transports of either channel. And then even beyond that, we can conceive of ways of helping mucociliary clearance through other mechanisms such as surfactant or lubricant secretion and alteration of ciliary beat.

And when we look at the pipeline we see that we already have a number of drugs which affect some of these possibilities. So under CFTR there is a number of, this is a gene vector approach, so that is one way to do that, by replacing CFTR, but there is also these drugs that act upon various genotypic problems with CFTR in those classes we talked about.

In the alternative chloride transport area we have at least two drugs that activate that, one that is being looked at and more to come in sodium transport, at least two agents that affect osmotic hydration of the airway, and then another agent which is Denufasol, that works on alternative chloride transport, but also has been shown to have independent activities on sodium transport inhibition, surfactant secretion, and ciliary beat frequency increase. So possible multiple modes of action in this space of increasing mucociliary clearance.

In terms of the pathogenesis of the infection, very briefly, it's important to realize that there's this link between the loss of periciliary fluid, stasis, increase in mucous plaques on the airway that are not mobile, trapping of bacteria, and the ability of some bacteria, or CF pathogen friends, to deal with that situation by being able to grow in an environment that is progressively hypoxic and also lacks other nutrients. So these, particularly *Pseudomonas*, are adaptable to this environment. And *Pseudomonas* undergoes a further change from single cell planktonic life to a biofilm or macro colony mode of living that becomes impermeable to eradication, usually impermeable to eradication, and also is stimulating a great degree of inflammation. And that's the clinical picture we see in our patients, what can we do about this therapeutically.

Well let's not forget that one of the upstream maneuvers that might be successful is to give a vaccine. And the history of vaccines in CF is a long one, but is so far not successful, and I think that's the furthest off of our achievable goals, but ultimately should be achievable.

The second is one that you are all familiar with and that is antibiotics. And Lisa Saiman, MD, MPH (Columbia New York-Presbyterian) gave a beautiful overview this morning of the wide variety of inhaled antibiotics coming onboard that are soon going

to augment our ability to treat the infection through an anti-infective approach.

And then as Jim Chmiel talked about, the anti-inflammatory field, which is more difficult, and I'll close with just a picture of this that comes from a review that came out of a workshop last year, to give you a sense of the number of different possible intervention points, just in the anti-inflammatory field.

So some of the fundamental treatments that will be talked about obviously it's hoped that those changes will translate to a gradual decrease in inflammation downstream. But we don't know that, that's a hypothesis that needs to be proven. So we don't know if starting a 20 year old with moderate lung disease, for example, on a potentiator, is going to allow them to clear their infection and inflammation. That's an experiment that is going to be done and we'll learn about through long-term clinical trials.

But there are all these other pathways that can be involved ranging from antioxidants to manipulation of the lymphocyte response which is importantly driving the neutrophils recruitment through chemokines secreted by TH2 cells, and in particular, TH17 cells that we have learned about recently, to some of the intracellular pro-inflammatory pathways that Jim Chmiel talked about.

So I put this up mainly just to show the very rich field of target opportunities. He went over some of the difficulties in really figuring out how do we fine tune this anti-inflammatory approach so it's not overpowering because patients need a certain degree of inflammation to respond appropriately, we just don't want it to be too mucous.

In CF there is evidence that inflammation is related to infection, there is also evidence that inflammation is excessive for any given degree of infection, and there is also evidence that there is intrinsic inflammation. So it is most likely that all three mechanisms of hyper inflammatory response are present in patients with CF.

So just to close, this is the schema. We have drugs that we currently are able to use in these areas, if you think about the mucous clearance space, that's why we're using DNase and hypertonic saline as well as all kinds of airway clearance. We certainly have a lot of anti-infectives and more to come and we rely on bronchodilators to help assist. Anti-inflammatories, we have one that's recommended, others that we're using, over half of our patients are on inhaled steroids without firm evidence, that reflects an unmet need.

We can replace damaged lungs with transplantation. In the future we hope to

not only have gene therapy but also the ability to manipulate modifier gene effects on CF. And there has been a bit of information, new information about modifier genes at this meeting. We'll talk further tonight about rescue with correction and potentiation and also addressing proper ion transport. And I hope I have just given you a flavor of the issues with infection and inflammation.

More distally we can think about regenerative medicine as we learn more about the progenitor cells and the ability to perhaps repopulate the airways on an ongoing basis with the progenitor cells that are healthy. I think this will be achieved in the future, but, of course, a whole lot of work needs to be done in that area.