CROHN'S & COLITIS FOUNDATION OF AMERICA

Breakthroughs in IBD Research: *Helping You Today*

Stephan R. Targan, MD

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Operator: Hello, everyone, and welcome to *Breakthroughs in IBD Research: Helping You Today*, a telephone webcast education program. It is my pleasure to introduce your moderator Kimberly Frederick, Vice President of Patient and Professional Services at the Crohn's and Colitis Foundation of America.

Kimberly Frederick: Thank you. On behalf of the Crohn's and Colitis Foundation of America, I'd like to welcome and thank you all for attending today's program, sponsored by Shire. We chose today's topic based on the large volume of feedback that you all have given us through the years on wanting to hear more about research in IBD. Before we start, though, I wanted to share a little bit about CCFA's research program.

Over the last four decades CCFA has funded $150 million in research worldwide and funded more than 1,100 grants. CCFA has played a role in every major scientific breakthrough in IBD, from generating data that led to new therapies, to the discovery of the first gene for Crohn's. Some of our currently funded grants have played important roles in expanding our understanding in areas such as IBD genetics, the human gut microbiome and the epidemiology of IBD. These breakthroughs are brought about by your support and dedication to CCFA and our signature programs. Without you, we would not have as many breakthroughs as we're lucky to have today.

There will be a lot of information covered in today's program, and we don't expect you to be able to write everything down. That's why we make sure that there will be an archive of the program, along with a written transcript, available on our website shortly after the live event. If you haven't already downloaded the slides, they are already available online.

We want to thank all of you who submitted questions prior to this program. We received close to 1,000 questions, so if your question is not answered in the course of the program, you will have an opportunity to ask your question in the question-and-answer session, or you can also contact our Information Resource Center at 888-MY GUT PAIN after the program.

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Kimberly Frederick: Now, it is my privilege to introduce today's speaker, one of the leading experts in IBD research, Dr. Stephan Targan. Dr. Targan served as the Chair of the CCFA National Scientific Advisory Committee from 1989 to 1993 and is currently Director of the Inflammatory Bowel and Immunobiology Research Institute and the Division of Gastroenterology at Cedars-Sinai Medical Center. Dr. Targan holds the Feintech Family Foundation Chair in IBD and is Professor of Medicine at the University of California, Los Angeles School of Medicine. Dr. Targan received his bachelor's and medical degree from Johns Hopkins University and completed his internship, residency and fellowship in infectious diseases at Harbor-UCLA Medical Center. Dr. Targan has received many investigative grants and contracts and primarily focuses his research on the genetic and immunopathologic mechanisms of inflammatory bowel disease.

Please welcome Dr. Stephan Targan.

Dr. Stephan Targan: Well, it's certainly a pleasure to be here for me this morning, for others early in the afternoon. Why don't we get started?

To give you an overview the goals of research are: clearly and ultimate is a cure, define exactly what the causes are because in these diseases, there will be several, and obviously how to prevent those. But as important, it is to develop new and improved treatments and obviously increase the quality of patients' lives.

If you take a look at the growth of disease occurrence using this map of the world illustrating the countries, pay particular attention to North America and in the United States, Northern Europe particularly with the orange, where IBD was seen between the 1950s and 1970s.

This is what the scene looks like now in the present. It's gone to many other countries, down into Mexico, South America, and particularly there's been a very large rise in the Asian countries and over into Eastern Europe. You'll see areas where it's really absent, such as the African continent, and we get some clues as to where these diseases emerge into the pathophysiology.

If you take a look at the milestones in research and you see this picture, it represents what we need to do. So we don't simply get to the top of that arrow. Research is done in steps and was represented by this. Today, what we're going to present where we actually are on this ladder and highlight the key is this ladder, whatever the angle of the ladder is. If we can tilt it down a little bit, we can get up much more quickly. Right now you'll see that this ladder has been tilted down some, and we're moving very rapidly in the directions that we need to go.

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Dr. Stephan Targan: Back in 1967 there wasn't much available then, and along the lines of cancer treatment and there were really very few medications. Surgery was the only approach. Hospitalizations were common with many early on, even in early disease, where today they're very decreased. Research in 1967 was minimal, particularly due to a lack of recognition of this disease as being a preeminent illness. But secondly, the technologies to really approach the complexities of this illness had not yet emerged.

If we now take a look in 2010 at the issues that we just showed, cancer surveillance is now routine. Treatments have expanded dramatically. The pipeline is enormous with more than 80 or so treatments currently in clinical trials. Surgery has been expanded to be much more creative in maintaining bowel presence, and hospitalizations have dropped particularly because of the advent of novel therapeutics that have come onboard.

If we take a look at research, this has really truly been amazing. Each year, CCFA funds more than 200 current research grants. Since 1967, they have supported training of research fellows and career development awards, which is critical. I would suffice it to say that the CCFA has been involved in almost every single individual in the present day that has focused their research careers on IBD.

The true change in the United States and around the world was in 1989 when the Challenges in IBD, supported by the CCFA, came forth. This transformed the pace and the direction of IBD research—not only the United States in the NIH, but worldwide, and brought in for the first time the interest of the pharmaceutical industry to IBD.

The Clinical Research Alliances were created, the Pediatric Research Network was created to focus on pediatric IBD, a DNA bank was created and, as said by Kimberly, there's been over $150 million gone into research.

Today's goals are really to highlight the past and to understand today's breakthroughs and then to discuss the future of IBD research, which is incredibly robust, exciting and hopefully by the end of this presentation you will understand the fast pace with which we're moving.

From my perspective, I've chosen the following important breakthroughs. One of the major things that has occurred in the last five years or so is the unraveling of the IBD-related genetics. In fact, the inflammatory bowel diseases lead all of the diseases that are complex diseases, such as rheumatoid arthritis and psoriasis, in this discovery. Within this discovery of genetics, the importance of a particular pathway in Crohn's disease and ulcerative colitis has really been one of the major breakthroughs that has now led to the here and now with a multitude of different trials ongoing targeting this pathway to treat patients with inflammatory bowel disease.

Dr. Stephan Targan: Then finally, the third breakthrough has been the advent of understanding the relationship of all these genetic abnormalities in the bacteria that exists in all of our guts and how they coexist and the interactions of these will be critical pieces to understand for novel therapies and really truly unraveling the causes of these diseases, and how—importantly—we'll be able to manipulate our environment to actually prevent their onset in years to come.

Just to give you a sense of this explosion of genetics, these are the IBD-related genetics in 2010. If you go to the left slide in white, just nine years ago was the first discovery of the gene *NOD2*. Then as you go across the slide over the years and look at the explosion in 2008, 2009, and now in 2010, there's at least 80 different genes that have been discovered in Crohn's disease and ulcerative colitis. As important in these discoveries we have found that where we thought these were distinctly different diseases, the genetic discoveries have actually shown that there's going to be some overlap in how the inflammation that occurs in the gut is caused. So the purple that you see in this slide are the genes that overlap. Therefore, what you see in Crohn's disease are a spectrum of inflammatory diseases with different causes and biology. This was a huge discovery in these genetics.

The importance of unraveling the genetics in fact will impact our leap forward in understanding inflammatory bowel disease. So what we need to do, as you saw the stacks of these genes, what we need to be doing, and are already doing is understanding how these genes have gone awry, which genes, and therefore the proteins of these genes, interact and in which patients. Not every patient has every one of these abnormalities, and the so-called genetic heterogeneity of this disease will be unraveled. I believe in the next several years we will understand what I call the IBD genome, which is understanding which pathways cluster in which patients and, in fact, don't cluster in other patients.

The importance of this is going to be the second bullet on this slide, which is rapid discovery of new therapeutic targets, and the first of which I will describe here.

The IL-23 pathway is another important breakthrough. I'm not going to get into all the details, there are a lot of words and a lot of symbols on this particular slide, but in each of those symbols and words, there appears to be a variation in a gene of these particular proteins. So there's an enormous focus on this pathway as a very important cause of inflammatory bowel disease, of both ulcerative colitis and Crohn's disease. These are some of the genes that actually overlap in both of the diseases as we know now.

The importance of this is shown in the impact of this breakthrough. There's at least 10 to 15 clinical trials right now that focus on this pathway taking patients, trying to determine who responds, how long they're going to respond, and those that are resistant to other kinds of medications. The important thing is that these treatments can be targeted specifically to those kinds of structures. That way, we limit short of using a sledgehammer to try to treat the disease and use more of a laser focus.

Dr. Stephan Targan: The different variants of the pathway may be able in fact to predict response or non-response to particular therapeutics. That is, before one goes on, one would have a profile and determine if in fact they are a patient that would do well with the particular therapeutic, or could be spared going on and having the disappointment of not actually responding to a particular medication, but indeed could be focused on a different kind of medication. This is called personalized medicine. The approach of it is here and now, and these particular trials, I believe, are going to be the first examples of such attempts to do just that.

The third breakthrough, understanding the relationship of bacteria and genetics is really, really very exciting.

The first gene ever discovered, which happens to be *NOD2*—and those of you that have followed this and are curious, was the first gene ever discovered using different kinds of technology. It told us for the first time that one of the major problems in patients that have these illnesses is their inability to have an appropriate relationship with the normal bacteria and flora and microbiota, as we call it, in their own intestines. We now have discovered that the genetic abnormalities we just showed you actually impact the type of bacteria that are present in the host intestine. But now, importantly, we have discovered that the bacteria themselves impact the host metabolically, and likely the genetic makeup of the host is what determines which bacteria survive and which bacteria impact the host. So this complex relationship is very clear and is going to play a major role in inflammatory bowel disease—even in common conditions, such as obesity and other immune-mediated diseases like diabetes. So the impact of understanding this is going to be specialized treatments and therapies to manipulate an individual's vast array of bacteria. But not globally, by just everyone taking probiotics or everybody taking broad spectrum antibiotics. We must understand which manipulation of which bacteria in which patients are going to have the best impact. Therefore going from a vast blanket of information and research supporting whether or not probiotics work and actually move to be able to understand how they can be used and in which patients.

The current areas of study in research are, as we talked about, genetics, immunology, which is the makeup of the host and how it protects itself against the environment, and is the process that goes awry if it's not protecting itself against environment and overreacting to it, and therefore causes damage and injury to organs. Obviously the ones of us on the phone, we're interested in the gut.

Dr. Stephan Targan: We talked about the microbiology of the environment, which is really critical. What in the environment is actually impacting and setting these things off? The real beauty of putting these all together is going to be for us to understand what particular part of the environment affects which patients with which kind of genetic abnormalities and which bacteria. So just studying the whole disease will make it very confusing.

Then of course, improving diagnosis, treatment and understanding the unique aspects of pediatric inflammatory bowel disease.

The causation factors we've talked about, the coming together of the immune system, the genetic predisposed host, the immune system and how the environment affects the genetically determined immune abnormalities.

If we take a look at the current genetic research, I've shared some of what's going on, but we've begun to learn the roles of these genes in IBD. We are mapping the IBD genome. I think we'll know the genome in a couple short years. We have been able to determine or begin to determine, which genes are related to risk, which genes are related to a disease that seems to progress—or progress rapidly in severity. As importantly, to put together what we call profiles of genes that are going to tell us who's going to react to particular medical therapy and in fact who will respond.

So if we take a look at what's occurred, these were the Dark Ages of genetic revolution. I've been in those Dark Ages—not back in the 40s or 50s, I'm not quite that old—but certainly in the early 90s and how things have come to the explosion that occurred in the first decade of this millennium. Now with the advancement in technology of genetics, where we've gone from gene-by-gene discovery to discovering two or three genes at a time, to discovering 20, 13, 80 genes, and now the challenge, which must be done and will be done over the next couple of years, is to understand this vast amount of information, organize it, and again, not only to understand the genome but understand how it impacts the natural history of disease, biology, and all this research going on at the present time.

In fact, if we talk now about immunology, which is particularly important in the study of the immune system, which is all over the body, and certain organs such as the spleen—as it turns out, the gut is the largest immune organ in the body. It is one immune organ that has direct contact with the environment constantly, with the food you're eating and its proximity to the lung, and its surrounding environment.

Immunologic biomarkers that have been discovered, and markers in the blood and stool and other biomarkers, actually can identify subsets of patients with inflammatory bowel disease, and can determine certain disease characteristics in children.

Dr. Stephan Targan: If we take a look at some of these antibody biomarkers, it's a proof of concept where IBD patients have antibodies to normal bacteria that exist in the normal intestine where normal people do not. Actually, patients' family members also have these antibodies. What these represent is the certain types of inflammation that are associated with certain inflammatory response. They actually do not cause inflammation themselves but actually mark the kinds of abnormalities in the system, and in the gut, that allows an abnormal interface and interaction with the host. The result of which are those patients that have reactivity to these. So the presence of these in inflammatory bowel disease patients may increase risks for early onset of disease and are particularly associated with aggressive forms of inflammatory bowel disease, particularly Crohn's disease.

If we now take a shift to the study of microbiology—this what we call the microbiome. You'll hear about this, you'll hear about things in the press of the metabolome. These include not just bacteria, but viruses and certain parasites. There are certain beneficial bacteria. We talked about probiotics. They promote intestinal cell healing. They certainly will inhibit pro-inflammatory production. But as I told you, they don't do it on a global basis. Certain patients will respond to probiotics or may not, and it all depends on what the makeup of their bacteria is.

If we talk about harmful bacteria that causes these diseases, or may cause inflammation, we're not clear, as these are not bacteria that we would think about, that patients do. It's not salmonella, it's not shigella, it's not *turistas*, for those of us on the West Coast that might go to Mexico.

If we take a look at the probiotics, they're listed here on the slide, such as probiotics with lactobacillus, saccharomyces and bifidobacterium. It shows you where they're located. However, as I talked about previously—and I do want to stress this—probiotics and prebiotics studies do continue. You really need to consult your doctor when using individually, or ideally, look for a clinical trial. There is much written about these, commenting on these in the lay press, without having the backup of research. What this talk is about here today is good clinical research which is really going to tell us what works and for whom and that's really important.

One thing I want to stress, and you'll hear about is *Mycobacterium avium paratuberculosis*. It happens to be found in milk, as one of the sources. You'll hear a lot in the press and in the lay press that has been going on for 35 years about this. But at this point in time, in reviewing all the data to date, it does not appear to play a role in the etiology of Crohn's disease, at least as a global disease. So I think that's very, very important and you have to understand and you need to know is why and for what reason you're getting put on something.

Dr. Stephan Targan: There are many environmental triggers, as I talked about—certain things like infections similar to a family going to Mexico, everybody gets *turista*, then one member comes home and never stops their diarrhea. Certainly they could have, as an example, gotten their first episode of inflammatory bowel disease.

The manipulation of bacteria can certainly set it off. Diet is certainly being studied but it's not clear. Smoking can certainly increase the severity of Crohn's disease and may set it off. Stopping smoking may in fact, on some patients make it worse. Stress can be involved. The use of NSAIDs, things that are on the market like Aleve, et cetera, certainly can cause an onset on IBD.

The key here, though, as I told you in the complexity of IBD is not everybody has their IBD started or reactivated by all of these. So what we're going to do is understand the entire genetic makeup and then go back and understand for which patients, which abnormalities, is affected by what environment. Then we're going to be able to manipulate patients' environment in an individual patient basis.

We take a look at diagnosis then and now. Diagnosis was very rudimentary in 1967. In 2010, it's extremely robust. Not only colonoscopy, but the onset of capsule endoscopy has made us to diagnose disease we never thought existed in parts of the small bowel. CT and MRI have helped us get to detail. Serologic panels have helped us, as I talked about, to make the diagnosis and to try to predict severity, and virtual colonoscopy at this time is emerging but not quite ready for prime time.

This is the history of IBD treatments timeline that you can see, goes through 2004, when we had our second generation of biologics. You can take a look at how it's accelerated. From 2004 and now in 2010 having 80 biologics that are in trial or drugs that are in trial. You can see that this is continuing to accelerate. With what I've just shown you in genetics and immunobiology and bacteria, this will accelerate dramatically.

So if we take a look at treatments and we take a look particularly at the newer treatments of the biologics, these are therapies that target specific proteins and enzymes in the immune system that relate to the body's inflammatory response. That is, the body is overactive and these treatments— tamp down the body back into the normal activity. The target outcome is sustained remission and is to get people off steroids, and to actually find and heal their mucosa because the healing of mucosa tells us they'll stay in remission. To reduce severity of this, as determined by decreasing hospitalizations and surgery, and obviously to immediately improve quality of life.

Dr. Stephan Targan: Pediatrics is very important, has always been, but the CCFA now has really accelerated its focus on this. It has the CCFA Pediatric Network. It has preventing growth issues that are being addressed by the Pediatric Network. It's got biologic agents now that hold promise for growth enhancement, convincing the pharmacologic industry to do trials and include kids—because obviously they're one of the most of our population that's affected—and to avoid surgeries.

So what does this all mean to the people on the line? In the next five minutes or so, I'm going to really take all of what I've been talking to and really take it to the people online. So what does this mean to you all, and what can you do to get involved in supporting the research as well as participating in the research?

Let's discuss the future of the IBD research, particularly the next steps, and what are going on. I alluded to several of these, but the next slide, really, I think, summarizes both the beauty and excitement of where we are but brings up something that you all certainly can help us to overcome.

The problem in 2010, and it was a problem in 2001, but as I told you about all these drugs that are being developed, we just simply have too many targets in drugs. And right now not enough patients. And so the key is it's marvelous, but for each of these trials we need 100 to 200 to 300 to 400 patients. We need as many people to participate in them, where it's appropriate, obviously when you talk with your own physician, so that we can find out all the good things that we just talked about as quickly as possible.

Because I will tell you, going to the next slide, and this is what clinical trials are about, you can take a look at this, you can see that study, the treatment prevention, diagnostics and screening and quality of life, and the clinical trials are done in phases, from phase I through phase IV trials. From having a good idea and understanding that a particular protein or target needs to be manipulated, all the way to when this actually gets accepted by the FDA—and right now, in the way we do this, it takes years. Right now, in the way we do this, it takes hundreds and hundreds of patients to take this.

What we can do to accelerate these trials is to take advantage of our genetics, which we will do in many of these trials, to target and bring in patients that we think will benefit from the target in a more directed fashion—but also to try to be able to enroll patients in these trials more quickly.

People say, 'What is a placebo?' 'Am I not going to get a drug?' But many of these trials, even if you're on a placebo or don't respond, are being designed where they have an open label. Meaning, if you go through the trial and you don't seem to respond, you get an opportunity to get an open-label drug, just to see if you're going to do or not. So it doesn't mean that if you go into a trial, you may not get a drug and you get concerned about it.

Dr. Stephan Targan: But this is one of the major, major things that we need to correct.

A clinical trial has its risks and its benefits. You know the risks, you know it may not be effective. We talked about that. You may get placebo. But remember some are designed so you can minimize—you'll get a placebo, but how you might be able to get the drug. It may require your time. But obviously, this is critically important to know whether it works. Not all costs may be covered, but there's huge benefits. You participate, you gain access to new treatments, you obtain expert medical care. Not only are you potentially helping yourself but the thousands of other people where this may be beneficial, you're certainly helping those patients.

You need to, however, talk to your doctor about clinical trials as a treatment option. Obviously, if you're doing well, you don't get off your medication to go into a trial. You stay on your medication. If you need to find a clinical trial, again, you must consult your doctor regarding this as far as I'm concerned, and see what's out there. You can call CCFA's Information Resource Center. You can visit the websites that are shown on this particular slide, and I encourage everybody that's on here to do that because you get an opportunity and also see what trials are out there and find a site maybe near you that you could go to and participate.

In closing, why do we need more research? If we've made so many significant advances at this point in time, and I want to reiterate, we have. I've been in this game a long time, and I've never been as excited as I am now. In my own personal research, I've never been as productive, as with many of my IBD focused colleagues not only because of the explosion of technology, but where we can see the goal. We can see the end of it and want to be part of it and to accelerate the next period.

There's many forms of these disease, like I talked about, and I don't believe there's going to be one cure. We need to now understand and organize the information in each of these forms. We need to develop innovative treatments to induce remission, relapse, prevent complications. As we unravel the pathogenesis, these novel treatments are there, new and those in the pipelines. It's incredibly exciting.

Science and technology are poised to make rapid progress, and that progress will depend on the amount of support and funding available. I cannot re-stress that. When we started out in 1989 and came away from what we thought was going to be important—the ability to act on that maybe there were going to be four or five laboratories, and we were going to try to get that going.

Dr. Stephan Targan: But right now, the excitement in this disease, we hear what's going on, and the number of labs that have been brought into this, the number of incredibly high-quality scientists around the world have been brought in to focus on the scientific processes that are going to impact these new treatments and ultimately the cure, is unbelievable.

Now, the problem is obviously with economics and everything, is that I would love to fund it all, as an advocate for this. But we do need that as well. So with that, I will take any questions and try to provide good answers.

Kimberly Frederick: Thank you, Dr. Targan, for that thorough and informative presentation. It was just so excellent.

We're now going to begin the question-and-answer session with the audience. We know that many of you have questions, and we're going to address as many questions as we possibly can in the next 30 or so minutes.

Operator: Our first caller comes from Jennifer in Indiana.

Kimberly Frederick: Hi, Jennifer.

Jennifer: Hi. My question is, I'm know I'm not supposed to do individual cases, but myself, I'm on Imuran®, and how long is it safe to be on that because of the low white blood count?

Dr. Stephan Targan: Well, I think it's a drug that can be safe over a long period of time and many—just to give in a broader context of these medications, with proper not only management of it, but follow-up with your physician, can be quite safe. Monitoring, for instance, blood counts—obviously monitoring blood levels of all of these are really a way of keeping it quite safe. I'm not going to answer individually with low white counts. A lot of that depends on how low, et cetera, but those are the kinds of things you need to directly address with your own physician.

Kimberly Frederick: Okay, great, thank you. I'm going to take a web question. Dr. Targan, this is asked from David, and his question is, "I noticed on the growth of IBD slide from 1970 to present that it was most prevalent among modernized countries. Race did not seem to play an issue as both Latin America, China and Japan were all affected. Do you think that the treatment and processing of food could be part of the causes for IBD?"

Dr. Stephan Targan: That's a very good question. So, why in the developing countries, in countries that didn't have it before, do they now have it developing? One of the things certainly could be the type of diet. Again, the sort of quote-unquote industrialization of those particular countries, with a multitude of different potential environmental factors that can occur certainly could play a role as well during these developing countries.

Dr. Stephan Targan: The lack that we see of it, as an example, in most of the African continent tells us that part of why the improvement of water supplies and everything else can play a role.

The problem is going to be the complexities of the makeup of this disease, and it turns out, the genetic impact on the Asian population is somewhat different than the Caucasian, so it could also relate to genetic makeup of individuals and what may be different in each of the countries.

Kimberly Frederick: Okay, thank you. We'll take another question from the web. This is asked by Elliott, and his question is, "Dr. Targan, thank you for your time today. Your chart illustrated a significant number of genes related to UC and Crohn's disease. In a typical case, would a patient show abnormalities on a single gene or multiple of the genes indicated? Thank you."

Dr. Stephan Targan: That's a very good question. We don't think that these diseases are a single-gene disease, and it's very likely that a given patient will have a profile of genes. Both the number and the types of genes that an individual has will likely differ. That will impact the kind of disease they have, how it manifests itself, what will make it responsive or not in the context of that. So unlikely—there may be a single gene that relates to how severe their disease is, but there's going to be more than one per individual.

Kimberly Frederick: Thanks. We'll take a question from the phone audience.

Operator: The next question comes from Mike in New York.

Mike: I was wondering, how does acidophilus help someone with ulcerative colitis?

Kimberly Frederick: Okay, a question about acidophilus.

Dr. Stephan Targan: Yes. So, acidophilus is one of the forms we were talking about that contain a bacterium that is known to be what they call a probiotic. It's not bad to take those, but how it would affect the actual inflammation of the disease is really not known. So although there have been trials of these—not this particular one, but of the probiotics in inflammatory bowel disease, that particular milk and acidophilus doesn't seem to have an effect.

If, obviously, you've been on antibiotics for some reason or not and need to replenish your flora and make it come back, probiotics can certainly help with the replenishment and changing of the microbiome back.

Kimberly Frederick: Great. We're going to take a web question from Cheryl. "Clinical trials seem to be geared toward medications. What about just getting genetic information and history, et cetera, from patients to focus more on the variations in genetics?"

Dr. Stephan Targan: That's a superb question. And there are—we don't call them clinical trials, but we certainly call—certain main sites, you know, centers, IBD centers around the country, around the world. When their patients come in for appropriate care, they are asked to participate in such studies, where they would be able to donate a blood sample, for instance, to get their DNA, get certain information about them and put that information into a database. The more people we can get to participate in those kinds of studies and the more we understand that we're trying to divide this disease up into anywhere from five to ten different kinds, this is going to be extremely helpful. So if you're doing well, you don't need a novel therapeutic to do it, participating in these kinds of research is very important.

Kimberly Frederick: Great. We'll take a question from the phone audience.

Operator: The next question comes from Rita in Florida.

Rita: Hi, Dr. Targan, a question for you. If a person is over 65, they test positive for PPD, does that mean they're excluded from taking the anti-TNF meds? And part two of the question is, are there any new meds coming along that are not anti-TNF?

Dr. Stephan Targan: Two good questions, I think it's very important to know. Having a positive PPD does not preclude you from getting an anti-TNF, but it does say that you need to be treated for being exposed to tuberculosis prior to getting on the anti-TNF. How long that treatment needs to be—it seems to be individualized from place to place and very much dependent upon the thought processes of specialists in this area called infectious disease doctors, on how long they can be treated. But we treat many patients that have the positive PPD. We just need to delay it to make sure that they're taken care of.

Your second part of the question—yes, the vast majority, if not all of the new therapeutics being tried are independent of TNF as a target. So, as an example, the 10 or 15 I showed you on the talk, regarding to one pathway—lots of agents that are looking to prevent bad cells and things from getting into the tissues to cause the inflammation, and many, many, many others that are independent of TNF.

Kimberly Frederick: Okay, I'm going to take a web question from Jenny. "What options are there for people who have failed or exhausted every medication, including Tysabri®?"

Dr. Stephan Targan: That's a good question. It can be a frustrating question. My feeling would be, in these kinds of patients, if it's very reasonable, is to really get aggressive, and what I suggested—going online, talking with your doctor of where there can be trials that you may be able to get on. Maybe looking at trials that have as part of their—how they've designed the trials, have an open label.

Dr. Stephan Targan: Or some of the trials are early on that could be what we cause phase I, where there's open-label drug given. I think at that point in time, other than just taking the latest thing that one sees on the web because it helped one person—that can be dangerous and, more importantly, prevent you from immediately getting on something that can help you.

Kimberly Frederick: Okay, we'll take a phone question.

Operator: The next question comes from Christine in Washington.

Christine: Hi. Thank you so much, this has been such a great conference. How do you get involved in some of those medical trials?

Dr. Stephan Targan: That's a very good question. If this is being put up and archived, you can go back to the slide, you can contact the CCFA and we put up some websites as well as where you can call to get on these trials, and I would urge you to do that. Again, I think everyone has to do that in consult with their own primary physician.

Kimberly Frederick: Yes, you can call our Information Resource Center for steps and help and information on how to do that, which is 888-MY GUT PAIN. Dr. Targan, a lot of questions came in over the web on nutrition and diet and so we've summarized it with, "Are there any clinical trials on diet, and are they looking at specific diet since the growth of IBD in the metropolitan areas?"

Dr. Stephan Targan: You know, this is a question, and it's a good broad question, because everybody can think well, it's my gut, I'm taking in these foods, you talked about bacteria and how that—obviously, foods that come down, the food sources for bacteria are also that. The difficulty has been, you know, for me to say as an example—and I don't want anybody to get this wrong—"we know that patients with ulcerative colitis can't eat peanuts." *That's not correct*. So there has not been trials with selected diet manipulations in the global ulcerative colitis/Crohn's disease that have affected the chronic inflammation. You may be able to manipulate your diet and change some things like bloating, et cetera, but when it comes to, are you taking and treating your actual inflammation that's causing you to feel tired, et cetera, there's been really, to date, no trials.

On the other hand, I think we're going to go back to these once we have the IBD genome and know the microbiome interactions, and then we can design them to really test specific dietary things in specific kinds of patients.

Kimberly Frederick: Great. I'm going to take a web question from Darrell. The question is, "How can one have a profile done to know what the genetic markers present and possibly have a more personalized treatment developed?"

Dr. Stephan Targan: I'm really happy somebody asked that question. So—genetics, as trying to determine if my child and what their chances of getting the disease, what is my disease like and what am I going to respond to, is at this moment not ready for prime time. So going on to these sites that claim they can take some of your saliva and tell you you're going to get Crohn's or not and what your percentages are, it's too early. Does that mean that this will never be the case, that it may not be in the next two to four, five years, that we can do this? I think we'll be able to. But in 2010 here, the end of March, you know, these aren't being used for clinical decision-making just yet.

Kimberly Frederick: Okay, great. Can we take a phone question now?

Operator: The next question comes from Donna in Texas.

Donna: Hello. I have a recurring stricture and I was wondering, my doctor says we can control Crohn's, but the stricture comes at the scar tissue and previous surgeries. I was just wondering, is there any study being done on how to prevent strictures or any medication for stricture prevention?

Dr. Stephan Targan: That's a very good question. So these—and I'm going to take them in a global sense—so strictures are one of the complications of Crohn's disease that ultimately will be one of the things that moves patients to having to have surgery for the removal. There are now studies ongoing, and there are no medications that can reverse a stricture. So once it's there, it's there. We can't reverse it from a medical perspective.

On the other hand, if an area is taken out—and studies are now ongoing long-term—we are hoping that medications and biologics, such as the anti-TNFs, will again prevent patients that are known to be stricture-forming people, to slow down or prevent them getting another stricture.

In rheumatoid arthritis, anti-TNFs have been demonstrated to be able to minimize, even reverse or particularly stop the progression of joint erosions. We are just at the beginning of trying to see if that's the case with stricturing in Crohn's disease.

Kimberly Frederick: Okay, I'm going to take a web question. The question is from Susan. "Has there been research on how the disease changes with age?"

Dr. Stephan Targan: That's an outstanding question as well. There have been some research in mice, and mice aren't men, people, where suggesting that over time, when inflammation occurs over time in the same individual, that the nature of the inflammation can certainly change.

Dr. Stephan Targan: We haven't done those kinds of trials, if you will, to take a look at it, but there is no doubt, certainly, in my practice—and many, many other people that observed this—that as patients get into the older decades, where their disease may well have been well-controlled, they may reach a point that all of a sudden the medicines they're on aren't controlling it. We need to understand why that's happening, why the shifts are happening and in whom, because it may be related to their original genetic makeup. So this has been an observation, but no studies as to why that is have yet been initiated.

Kimberly Frederick: Great. Can we take a phone question now?

Operator: The next question comes from Amber in North Carolina.

Amber: Hi. I was wondering, are there any new reversal surgeries that are being studied or that have come out for patients with ostomies?

Dr. Stephan Targan: Okay, let me talk about this. So people with ostomy, it all depends on what the surgery was done for, whether the entire colon was removed, what is the nature of the disease, where the surgery was done. If you talk about reversal to being continent, there are several surgeries that are used to generate that. Let's say somebody had a surgery for ulcerative colitis and the whole colon was taken out, and they have an ostomy and that was their decision, they want to be reversed, yes. There are now abilities to create an internal pouch in two different ways—one where you can defecate the way you used to defecate, called a pouch, both of them pouches. So those things are possible, but it depends on the circumstances of the individual as to what may be available.

Kimberly Frederick: Okay, we'll take another phone question.

Operator: The next question comes from Shauna in California.

Shauna: Thank you, Dr. Targan, for this forum. First off, I want to let you know that I have the infection by the name of pseudomembranous colitis in 2007, whereby it landed me in the hospital for 12 days. My first question is, what are the symptoms, signs that would alert you as a GI doctor that the same course of antibiotics, such as ciprofloxacin, metronidazole, had become ineffective to a Crohn's patient having many infections, whereby you would upgrade an antibiotic to eradicate the same infections that were coming persistently, thus avoiding getting pseudomembranous colitis in the first place?

Dr. Stephan Targan: So, let me take a broad approach to this question. One of the now community-based infections that can exacerbate both ulcerative colitis and Crohn's disease is *Clostridium difficile*. Part of it is, people can get this by getting antibiotics, and this particular bacterium overgrows because you've changed the bacterium that keeps it in check. When that overgrows like that, you get certainly an inflammation in the colon itself, you get colitis. But you also can re-exacerbate Crohn's disease, and any antibiotic can do this. There's a rising incidence of patients that actually come to the hospital, and one of the things that actually makes their disease worse is this infection they got in the community.

The part of the question about antibiotics and Crohn's disease—many people use antibiotics for Crohn's disease for a long time. There are certain patients that do well on them. Globally, just putting antibiotics on patients in IBD altogether, I certainly don't do. And again, I think from what's been presented today, as you hopefully appreciate, is that we need to find the patients where what types, what spectrum, what bacteria we want to manipulate in which patients, so that they can have a positive result and have not a positive result, but get these secondary infections.

Kimberly Frederick: Okay, great. We're going to take a web question from Jane. Her question is, "I have identical twins, only one has been diagnosed with Crohn's disease. What research has been done with twins and what is the prevalence of IBD with twins?"

Dr. Stephan Targan: That's again a very good question. Back in the old days, that was what the observation was, that these diseases were genetic, it was a family association. The reason was that the incidence was higher in monozygotic—that is, identical twins. For fraternal twins—lower in fraternal twins. If one has Crohn's disease, the incidence is higher, definitely, in identical twins. The incidence in Crohn's disease of identical twins versus fraternal twins is higher in Crohn's disease, and the percentage of patients that may get it from twins is lower in the classic ulcerative colitis.

The percentages go up as high as 40%, but I can tell you there are many twins that I've seen, one of which has the disease—and remember, it's genetics and environment—even though they're raised together, there's things that may be setting it off versus not setting it off.

The highest incidence—so if you have a fraternal, a brother or sister, the chances of you getting it lifetime are right at this point in time are probably, you know, 3% to 8%, which means 97% to 94% you're not. The biggest thing is, if you have two parents who have IBD, the chances of an offspring is about 25%. So, again, those are old data. I think they're going to be modified as with the new genetics that we have, but it's the best answer I can give you at this time.

Kimberly Frederick: Okay, I have a question from the web from Cheryl. "Is there any way that patients and families can help speed research for Crohn's disease other than financially? Which is how our family has done it in past."

Dr. Stephan Targan: Yes, I think if you have a family where there are members—to be able to again participate, as another caller had brought up, in studies that are collecting materials, that are collecting blood. Because obviously once we have these families and we begin to get what we call biomarkers that tell us what may be markers that patients and families, if they have these markers, may go on to develop this disease in 5 to 10 years. They've done this, as an example, in type 1 diabetes. These would be extremely helpful to participate in these data collection trials.

Kimberly Frederick: Okay, great. We'll take a phone question now.

Operator: The next question comes from Elsa in New York.

Elsa: Hi, thanks for taking the call. I'm wondering if a child had been on prednisone for a very long time, will it affect the person's growth? And if when they take him off the prednisone, will growth be stimulated again?

Dr. Stephan Targan: That's a very good question. In children, what are the role of prednisone in not only growth, but maturation and going through puberty, and I think this is critically important. The goal is clearly to get a young child into remission, to make sure their nutrition is excellent and to get them off steroids as soon as can be accomplished. With new therapeutics, including immunomodulators, and, again, depending upon the disease, biologics, more and more young people are moving on to these and allowing themselves to take the window of two to three, four, five, six years to get their growth and development occurring. Even at times if there's a very narrow area that doesn't seem to respond to anything, actually having surgery, not having to be on chronic steroids and allowing that child to have a window to both grow and mature, may be important. Again, I think one needs to address how this is done, what needs to be done, with their individual physician.

Kimberly Frederick: We'll take a web question from Jason. The question is, "Are doctors currently using knowledge of the bacterial environment in treatment, or is that coming in the future?"

Dr. Stephan Targan: Excellent question. That is coming in the future. Right now they're not using the emerging knowledge as of yet, but that will come.

Kimberly Frederick: Great. Another question from the web: "How promising does low-dose naltrexone look for treatment?"

Dr. Stephan Targan: Well, there have been very few real controlled trials with this. There have been some anecdotal and open-label trials with this to see how it affects inflammation. So this is very early days, to say whether it does or doesn't. I think the important lesson here is that we've had drugs that looked extremely good, even from major centers, in open label. I can tell you of one of the anti-TNFs from a major center in Europe, which is well respected all over the world—when the control trial was done, it virtually didn't work whatsoever any better than placebo. So I think it's important that if you're considering these kinds of—in global, not just naltrexone—that you first look, as we've been stressing, onto the sites that we've talked about for actual trials, to go into for some novel therapeutic.

Kimberly Frederick: Another web question. We've got a significant amount on stem cell research, and the question is, "What are some of the promising therapies that are on the horizon, like stem cell research?"

Dr. Stephan Targan: Well, okay, there have been—stem cells are certainly in the news, certainly some very dramatic things are being done with stem cells. There's actually been a trial with certain forms of stem cells in Crohn's disease that wasn't positive at this point in time. Other kinds of cell-based therapies are being tried, and these are all early days for those. So the failure of that trial doesn't mean anything in my mind about the failure of that approach in patients.

I mean, the novel therapies that are coming out, the range that are being tested, range from antibodies to important inflammatory proteins, antibodies to important molecules that prevent cells from getting into the tissues. Actually, things as potential as some herbal extracts that seem to have some potent anti-inflammatory ways of going about it. Small molecules are being tested, even looking at certain kinds of manipulation of the system by certain vaccine-type approaches that are in earlier phases. So it's virtually unlimited, the kinds of approaches at this point in time.

Kimberly Frederick: Great. We'll take a phone question.

Operator: The next question comes from Sarah in Virginia.

Sarah: Hi, thank you. In the past year or two, it seems that there's been a proliferation of the probiotics and prebiotics on the market. I'm aware generally of some clinical trials involving Sigma-Tau's #3, but I'm curious whether you have any opinion on the efficacy of the other ones that are on the market.

Dr. Stephan Targan: Well, I won't give any specifics, but I think I stated, but I will briefly restate my opinion. I think there's much more written about rather than scientifically proven about the use and efficacy of probiotics in various forms and situations in inflammatory bowel disease. And as I said previously, as we unravel the IBD genome and the microbiome in combination, I think the trials that will be designed will be likely more specific and perhaps will yield better efficacy outcomes. But until that, there's no downside in using some probiotics, but again, there's no proof that they work.

Kimberly Frederick: Okay, great. The next question I'll take from the web. "Have the recent legislative and regulatory changes in stem cell research led to any new promising lines of IBD research?"

Dr. Stephan Targan: Well, there's a lot of very promising lines of IBD research. I think the whole idea of new stem cells and trying to understand the transition and how one process could change to another or another process can become overactive by manipulating certain parts of a cell's machinery, will no doubt have an impact on not only our understanding but also on our treatment of these diseases.

But without getting too redundant here, the amount of research going on now, having been there in the Dark Ages, is just incredible to me—to the point that I'm not a young pup anymore but I don't ever plan to retire because it's too exciting with things going on now.

Kimberly Frederick: I have another web question. "Will the new healthcare bill put a damper on research for Crohn's disease and UC?"

Dr. Stephan Targan: As with all of us, that bill is so hard to interpret simply on the basis of how it's going to affect our healthcare, it's very difficult for us to really have any knowledge how it might impact certainly research. We as investigators, however, are incredibly concerned about how cuts in funding or things are going to the NIH and particularly into studies of inflammatory bowel disease—because it's not like we're at the end of understanding everything, we're at the beginning of having to accelerate it. So we need much more, many more studies, a lot more resources put into this. But I'm not sure there will be a one-to-one relationship with the healthcare bill versus that.

Kimberly Frederick: Okay, we're going to take a phone question.

Operator: The next question comes from the location of Darlene in California.

Darlene: I wanted to know if hormones play a part in the inflammation part getting started.

Dr. Stephan Targan: That's another very excellent question, I'll answer in a global set. There is no doubt that we as clinicians observe, as an example, varying activity of inflammatory bowel disease during pregnancy, where some patients, when they become pregnant, go into remission. We like to have patients in remission before they go into pregnancy. During pregnancy, they do fine and when they deliver—important fact—their disease will flare. It can be that when they go in and they become pregnant, it may be their first onset of their disease.

So we know that hormones may play a role in some patients. We're not advocating any kind of hormonal therapy on patients at this point in time. But again, as we unravel the genes and find patients where clearly hormonal things may be targeted by these gene variations, studies will begin to go, to look at that in these specific kinds of patients.

Kimberly Frederick: Okay, I'm going to take a web question from Randall. "Of the immunological biomarkers you spoke of, how specifically will these biomarkers guide the treatment of IBD?"

Dr. Stephan Targan: That again is an excellent question. "Biomarker" is a pretty broad term, and certain biomarkers are used to understand the degree of how much inflammation is going on in an individual. Those are biomarkers like CRP or a sedimentation rate or how high people's platelets are, or, as example, taking a stool sample and picking out a protein that can see how much inflammation. The other biomarkers are intended to try to get a handle on the kind of disease and what's the natural history of a particular patient. So, do they have Crohn's or ulcerative colitis, and are they going to be, aggressively go on to have a problem, and therefore does the doctor need to treat them aggressively early on, even though they look like their neighbors and are not any more serious at that point in time. Some of these antibody biomarkers have been shown to indeed be able to be associated with a more aggressive course, and actually, in pediatrics, for sure, have been shown to be able to predict which children will have a more aggressive course. So that is emerging as a use of these. Each individual one, to predict their particular course, research is going on in that, but those are not ready for prime time.

Kimberly Frederick: Great. Thank you again to Dr. Targan for your presentation today, and to all of you for joining us. If you missed out on any information in today's program or would like to listen to it again, it'll be available on the CCFA website, www.ccfa.org, shortly.

If you weren't able to get your question answered in today's program and you would like general information, please contact our Information Resource Center at 888 MY GUT PAIN.

This concludes our program. Thank you, and good-bye.

Operator: Ladies and gentlemen, this concludes today's conference. Thank you for your participation. You may now disconnect. Have a wonderful day.

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