HealthManagement.org
The Journal
LEADERSHIP • CROSS-COLLABORATION • WINNING PRACTICES
VOLUME 19 • ISSUE 4 • 2019 • € 22
ISSN = 1377-7629

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The Future of Cardiovascular Disease Treatment and Management

Arthur M. Feldman, MD, PhD, Laura H. Carnell Professor of Medicine at the Lewis Katz School of Medicine at Temple University, has been recognised with the 2019 Distinguished Scientist Award-Basic Domain by the American College of Cardiology. Prof. Feldman has received this honour due to his contribution towards improving cardiovascular health and enhancing patient care. His research has focused primarily on the molecular biology of dilated cardiomyopathy and heart failure. HealthManagement.org spoke to Prof. Feldman about his many contributions in the field of cardiology.

You will be receiving the 2019 Distinguished Scientist Award-Basic Domain by the American College of Cardiology (ACC) in honour of contributions to the cardiovascular profession. Can you highlight your key achievements which resulted in this honour?

The major contribution I've made is that I've trained a large number of graduate students, medical students, and particularly cardiology fellows – both in my lab and when I was either a Chief of Cardiology or a Chair of Medicine, and I've also had the opportunity to mentor some superb young scientists over the past 30 years. I think that their success has been my most important achievement. In terms of work, I've focused on understanding the molecular and cellular biology of dilated cardiomyopathy and heart failure using the human heart as the model to identify potential targets and then moving to mice and cells to understand the molecular and cellular pathways. As a result, we were one of the early cardiology labs to use transgenic mice to understand the biology of heart failure. One example occurred around 1989 or 1990 when we discovered that the hearts of patients with dilated cardiomyopathy expressed abnormal amounts of the pro-inflammatory cytokine TNFa. When we over-expressed TNFa in mice, we found that the mice developed heart failure. Unfortunately, when we tried to treat patients with heart failure with a medication to diminish circulating levels of TNFa it worked in Phase 1 and Phase 2 trials but failed in Phase 3 trials – so we had to go back to the drawing board. Although there is some evidence that the TNFa story is reigniting.

Your area of focus has been the molecular biology of dilated cardiomyopathy and heart failure. Can you

highlight the areas where you have already made a difference and where you plan to make a difference in future with your research?

I think that what we are working on right now – and have been working on for the past eight years is one of the most exciting things that I've done and has the best chance of improving the health of patients with heart failure. It's a pretty incredible story that really evolved over time. In 1983 I was the resident in the cardiac care unit at the Johns Hopkins Hospital when we admitted a young woman from PA who had a markedly dilated cardiomyopathy and was only 22 years old. She sadly passed away because it was two or three years before we had heart transplantation at Hopkins when they recruited two superb surgeons from Stanford – Bruce Reitz and William Baumgartner. Move forward to 2002 when I received a call from one of my colleagues at Jefferson. He had seen a patient with a dilated cardiomyopathy who had two children with heart failure, a sister with heart failure and a niece who had heart failure but was deceased. I worked her up, and clearly, she had a familial dilated cardiomyopathy. So I met with as many of her relatives as I could find, drew blood to extract the DNA. It took us almost 10 years, for a variety of reasons, but mostly we didn't have enough affected family members to perform traditional linkage analysis. But in 2012-2013, a colleague in Colorado named Matt Taylor had received funding from the NIH to perform whole exome sequencing, and actually, the cardiologists at Denver were caring for one of the family members. We sent all of our DNA and all the information we had to Matt, and he sequenced the DNA and found a mutation in a gene called BAG3. We were then able to show that the mutation resulted in the levels of BAG3 to be about half of normal – what we call haploinsufficiency.

But here is where the story gets interesting. I was writing the paper to report our finding, and I wanted to make sure that the young woman who was deceased had, in fact, a dilated cardiomyopathy and not some other form of heart disease. To make a long story short – the family helped me to get her chart. She had been hospitalised at Hopkins – and when I got the chart, I realised that she was the young woman who had led me to go into heart failure in the first place.

We were not the first group to identify mutations in BAG3 as causing dilated cardiomyopathy. In fact, the first was Ray Hershberger, a colleague at the University of Miami who had spent a few months in my lab when he was a cardiology fellow. But we were the first to show that the disease-causing mutations caused haploinsufficiency and we were the first to make a mouse model with a heterozygous knock out (haploinsufficiency) and show that it resulted in a dilated cardiomyopathy. But perhaps the most important finding was that patients without a BAG3 mutation – but with heart failure – also had 50% reductions in the levels of their BAG3. Because if BAG3 levels were decreased, we could possibly treat these patients by using gene therapy to increase BAG3 levels. In fact, we have demonstrated in four different mouse models of heart failure that we can cure the mice by over-expressing BAG3 in the heart. In addition, we are now working to move this technology into patients – first performing efficacy and toxicity measures in a large animal model of heart failure.

> "GENE THERAPY IS THE TREATMENT STRATEGY OF THE FUTURE"

What role do you think gene therapy can play in tackling cardiovascular disease?

I think gene therapy is the treatment strategy of the future. However, it is in its infancy because we have to focus on patients with mutations that cause haploinsufficiency – where large pieces of DNA have been deleted from the gene or truncations where a large piece of the gene has been cleaved off. In both cases, gene therapy is really what we call "gene replacement therapy." In the case of BAG3 mutations, we know that the predominant genetic variant that causes HF, approximately 80% of the time, is a truncation or a deletion leading to haploinsufficiency. Thus we are putting back in something that is missing – one allele of the gene. But like anything else, gene therapy does have some limitations. About a third of the population has antibodies to the viral vectors and therefore can't receive therapy and point mutations can be associated with a dominant negative effect of the transduced gene resulting in an adverse effect. As a result, there is still a lot of work to be done. Nonetheless, for that group of patients that are amenable now to the therapy, we believe gene therapy will have an enormous impact.

Can you give your views on the role of precision medicine in heart failure?

We know that when we give a medication to a patient with heart failure – and the same can be said for many diseases – that many patients – if not most of the patients – will have no response and some may actually have a worse response. One element that causes this differential response is genetic differences. We can see a lot of examples, but the best example in heart failure is the fact that the combination of hydralazine and isosorbide dinitrate is beneficial in individuals of African ancestry but has no effect in individuals of European ancestry because it works in black heart failure patients but not in white heart failure patients. The study that showed the benefits in African ancestry was, of course, the AHeFT study. Dr. Dennis McNamara at the University of Pittsburgh, my second recruit after arriving at Pittsburgh in 1994, has been studying this phenomenon in a study called GRAFH and in GrAFH 2, and we have

participated in those studies. Dennis' lab sequenced the DNA from patients enrolled in AHeFT, and we found that there were unique genetic variants that appeared to be more prevalent in individuals who responded than in patients who didn't respond. One of the most interesting was the beta subunit of the G protein – a protein that I studied back in 1986 when I first went into the lab. Dennis has just led a superb prospective and randomised study to assess prospectively whether we can really use variants in this protein to identify who will and who won't respond to this combination of drugs. Here in Philadelphia, we recently sequenced BAG3 in heart failure patients of African ancestry and found four unique genetic variants that in aggregate predicted a worse outcome – but were not causative of disease. And I think that we will find the same to be true for almost all drugs that we now use for treating patients with heart failure.

We are now the Philadelphia site for an NIH-sponsored study called All of Us – Pennsylvania which is led by Dr. Steven Reis, at the University of Pittsburgh – my first recruit who moved with me from Hopkins in 1994. Participants at centres across the country will be genotyped and will provide access to their medical records. The study is the outcome of the $100 million Precision Medicine Initiative that President Obama announced shortly before leaving office. This study will be a game changer because it will provide both genetic and phenotypic data from one million Americans – creating a resource and investigational infrastructure that will provide investigators with data for much of the rest of this century. Our focus will be on enrolling participants from the largely African Americans and Hispanic communities of North Philadelphia.

The prevalence of cardiovascular disease continues to increase. What measures do you think can be taken to reduce this prevalence?

First, we have to decrease the incidence of socio-economic factors that have been clearly shown to increase the risk of cardiovascular disease. In fact, individuals of African ancestry have a much higher incidence of non-ischaemic heart failure, and socio-economic factors appear to play a role along with potential genetic factors. Second, we have to reduce the many risk factors for cardiovascular disease that are over-represented in urban populations – smoking, obesity, diabetes, untreated hypertension, some recreational drugs, excessive alcohol, high cholesterol, and high-fat diets and inactivity. As part of our All of Us programme, we have partnered with a local church in Philadelphia and a church in Pittsburgh to test the hypothesis that a place of worship can also be a place of healing and that linking that with genetics can be a powerful tool for improving population health. Second, we need to identify individuals at risk earlier in the course of their disease – treating high blood pressure early on, sophisticated care of diabetics and therapy of hypercholesterolaemia. And then, we need to ask every patient whether they have first degree relatives who have the same disease. If they do – they likely have a genetic variant that is causing their disease. We have to recognise that different populations have different aetiologies for their disease in terms of genetics but also in terms of habits, environmental risks, and social risks. In fact, there is strong data showing that the house that a person lives in has a lot to do with their disease risk and what diseases they develop. Temples located in North Philadelphia, is the poorest urban neighborhood amongst the larger U.S. cities. We see lots of patients who can't pay for their medicines, who don't have anyone at home to help them, and can't afford the healthy foods that you and I eat regularly such as fish, fresh vegetables and fresh fruits.

> "ALL OF US IS A PROMISING INITIATIVE THAT CAN MAKE PRECISION MEDICINE A REALITY"

Based on your research, are there any new therapeutic agents and/or advanced treatment strategies that you think can be more effectively used to manage cardiovascular disease and improve patient outcomes? Any preventive strategies that you recommend?

I think that the future is precision medicine – and that the driving force that will change the way we take care of patients will be studies like All of Us that will provide the infrastructure to make precision medicine a reality. By combining genomic data with extensive phenotypic data we will one day soon be able to give the right drug to the right person and avoid giving anyone the wrong drug. In addition, the development of viral vectors that are trophic for a single organ and non-immunogenic will allow doctors to use gene replacement therapy and/or gene editing with CRISPR to cure the many rare diseases and perhaps to lower the risk of common diseases. We have been talking about the prospects for gene therapy for two decades – but its time has finally come. Two great examples – not yet in the area of the heart – but they show the power of gene therapy. Gene therapy for SMA – spinal muscle atrophy or floppy baby syndrome - has shown incredible results – preserving life in infants who had only a 5% chance of survival - AveXis . And Spark Therapeutics here in Philadelphia has developed gene therapy for the treatment of some forms of childhood blindness. In fact, the FDA has recently approved both agents. I think the next decade will be a very exciting time to be in both medicine and science. ■