Video Transcript: Excellence in Hypertension Award Winner Edwin M. Jackson, PhD  
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**Robert M. Carey, MD, FAHA** - The Excellence Award for Hypertension Research is the highest award offered by the Hypertension Council of the American Heart Association. It is an extremely valued honor to receive this award. And it is my pleasure and honor to introduce you to this year's award winner, Dr. Edwin K. Jackson, from the University of Pittsburgh who has won the 2022 Excellence Award for Hypertension Research. Ed, it's a pleasure to be with you today and to ask you a little bit about your career, about the directions that you've taken in research, and the meaning of the research discoveries that you've made.

**Edwin K. Jackson, PhD, FAHA** - Thank you very much, Bob.

**Dr. Carey** - I am indeed impressed and overwhelmed with the contributions that you've made both scientifically and also in mentorship of many, many post-doctoral students, fellows and students at the University of Pittsburgh who've gone into academic medicine and made their own contributions. You've had a very high impact in the field. So I'd like to begin by asking you how you became interested in the role of purines in cardiovascular disease and specifically adenosine.

**Dr. Jackson** - Okay, well, as you may know purines are naturally occurring molecules that have a common structure that's similar to caffeine. And I've always been intrigued by the fact that caffeine is such a ubiquitous, some would say drug, and was curious as to how caffeine elicits its effects. And the way it does elicit its effects is by blocking the receptors that adenosine acts on. So that then stimulated me to start thinking about the physiological roles of adenosine because caffeine has such powerful effects.

You know, Starbucks has picked up on this. The coffee our parents drank, Maxwell House, and those kind of canned coffees maybe had 100 milligrams of caffeine in a normal cup, whereas even a Grande cup of coffee at Starbucks is more like 325 milligrams. The first thing we do is, and here in the hotels, we rush down to Starbucks and get a cup of coffee for a good reason. It blocks adenosine receptors.

So looking at the pharmacology of adenosine it really was striking the experiment that that drove my interest home were some done with my colleague, Mervin Foreman, back at Vanderbilt where we were looking at the, studying the pharmacology of adenosine and we noticed that all the things that adenosine does is what you would want in a drug to protect the heart from injury during a heart attack.

So when you have a heart attack, the treatment of choice is to open up the coronary artery as soon as you can. A heart attack is caused by occlusion of a coronary artery. And that works, that does reduce infarct size but there's something about introducing blood to the heart after it's been ischemic for a time, that is blood flow's been cut off for a time, that causes a, what's called a perfusion injury. So we started studying this in large animals and we found that giving adenosine during the time after reperfusing the heart would reduce reperfusion injury very substantially.

We also knew that one of the problems with percutaneous interventions in cardiology is that when you put the hardware that you need to insert into a diseased artery to open it up, that even if you fix the lesion that you're trying to open up, say, by example, using a balloon to do balloon angioplasty or and usually adding a stent to that, you can fix that region.

But then in some patients,' in those with anterior infarcts, it's probably around 30% develop what's called the no reflow phenomenon. Now the no reflow phenomenon is due to microvascular occlusion. And so we also found that adenosine would reverse microvascular occlusion and prevent it. And in fact, along with my colleague, Mervin Foreman, and some investigators at Rowan University we are trying to capitalize on this knowledge by developing a cardiac guide wire that goes into the coronary circulation, it's a first piece of hardware that does and we have developed a method to put a polymer on the end of the guide wire that is treated or contains adenosine so that when the interventionist inserts this guide wire into one's coronary circulation, the adenosine is released. It causes downstream blood vessels to open up. It protects against reperfusion injury, protects against a no reflow phenomenon, and we hope we'll reduce infarct size, heart failure, hospitalization time, et cetera. So that's one of the things that got is going on adenosine.

The other is that adenosine acts on blood vessels to do a number of good things. For example, if you have an injury to a blood vessel, let's say, due to a stent in your carotid artery or a stent in your coronary artery, the smooth muscle cells can start proliferating, and this is called neointimal hyperplasia. This can occlude the artery. And so we found in preclinical studies that adenosine, through a particular kind of receptor, would prevent smooth muscle cells from proliferating and would cause the good cells, the endothelial cells that line the blood vessel and provide a barrier to factors that should not be getting to the wall of a blood vessel, causes them to grow. So adenosine does all these good things.

Now I'm a cardiovascular renal pharmacologist interested in adenosine but the reality is adenosine does many things around the body. And I have colleagues at the University of Pittsburgh who are interested in many different disease states. So adenosine has caused me to go to other organ systems and make contributions there. For example, in the area of cancer, one of the areas I'm most proud of is that, in collaboration with some colleagues at Northeastern, Dr. SIHV-KAHV-SKEE, we have discovered that when tumors grow too quickly, they outgrow their blood vessels supply. And when they do, they will start making adenosine. And the adenosine then inhibits the immune cells that are trying to attack the tumor. So adenosine acts as a sort of Enterprise ship shields that prevent the immune system from coming in and killing the tumor cells. So this observation that we've published in PNAS has caused pharmaceutical industry to spend a certain amount of money to try to develop ways to tame this system and make, for example, immunotherapy more successful. So that's another example of the adenosine system that can be tweaked. And I think there are a number of drugs coming down, that will come down the pipe to utilize this information and help humans along.

**Dr. Carey** - Those are major discoveries, and the applications are amazing, not only with the drugs that you just mentioned but also with the profusion injury prevention with an acute administration during catheterization. So Ed, regarding high blood pressure research you've been involved for a long, long time and you've discovered a lot of things about adenosine that apply to high blood pressure. For example, you've described effects of adenosine on juxtaglomerular cells in the kidney and also on sodium reabsorption in the proximal tubal cells I believe mediated by sympathetic neuro transmission. So can you tell us something about those findings?

**Dr. Jackson** - Sure, I'll launch into two findings that relate to what you're asking Bob. One is that we, we're one of the first labs to show that blocking a particular subtype of adenosine receptor population called the A1 receptor has a powerful effect to increase sodium secretion without increasing potassium secretion. And what this means is that blocking the A1 receptor is a viable diuretic. Now we have been working with purines in general and adenosine is a type of purine, so I'm going to change the subject a little bit away from adenosine to adenosine’s poor cousin, and less-studied cousin guanosine.

Guanosine is also a purine like adenosine, but unlike adenosine, that hasn't received a lot of attention, we were intrigued by guanosine, and I'm going to bring this back to hypertension very quickly here, we were attracted to a guanosine also because there was some information that the one position and that molecule could undergo various substitutions, and this seemed to occur naturally. So we realized there was probably a family of naturally occurring guanosine derivatives, and guanosine can be converted to another compound called guanine.

So there are guanosine and guanine derivative that might behave a lot like adenosine. And we started screening these compounds and for, most of our work was negative, but we kept at it, and we finally hit a couple of compounds. One is 8-aminoguanosine, and the other is 8-aminoguanine that turned out to have amazing activity.

We were screening these drugs for, as diuretics, because blocking adenosine receptors causes, is the diuretic. And what we saw was this amazing increase in urine flow. A twentyfold increase in sodium aspiration. Glucose secretion increased by over tenfold, and amazingly, potassium secretion decreased by about 60%. So this was a really unique diuretic and we decided to examine this very closely.

And what we, the first thing we found is that 8-aminoguanosine is actually a pro-drug. It gets converted to 8-aminoguanine very rapidly in the body and it's 8-aminoguanine that has these effects. So then we decided to examine how the 8-aminoguanine is causing these amazing effects on the kidney. And what we discovered was that this small molecule which is orally available and has a fairly long recess time in the body, we discovered that the way it works is it inhibits a particular enzyme that raises the levels of another purine that's similar to adenosine called inosine.

And then inosine causes the small blood vessels in the kidney, the inner part of the kidney, medulla, to dilate and this then causes the effects on renal expiratory function to increase the accretion of salt, glucose and decrease potassium, but increase urine volume. So the next question we ask is, well, what is this good for?

And we found out it was really astonishing the effects of these compounds on hypertension. So the first model we looked at is called the DOKE assault model. And in that model, you remove one kidney of a rat and give the animal a steroid that will call sodium retention, and you also put little salt in the drinking water. And you then measure blood pressure by a technique called radiotelemetry over the course of weeks and weeks. And we found that in that model that 8-aminoguanine and 8-aminoguanosine would actually lower blood pressure quite substantially.

So it turned out that this drug is very effective in salt induced hypertension, and, Bob, as you know, salt is a major issue in the pathophysiology of hypertension worldwide. Where salt diets are elevated, hypertension is not far behind. We also tried the drug in another model of salt induced hypertension, a genetic model called the Dahl salt-sensitive graph. And we found that this 8-aminoguanine and 8-aminoguanosine would lower blood pressure in these animals but the blood pressure response was not so much as to explain some other things that we saw that were quite amazing. What we saw was that in the animals that didn't receive 8-aminoguanine that were on a high salt diet, they all expired due to strokes.

We saw zero strokes in the animals that were treated with 8-aminoguanine. So this drug actually reduces, or at least in this animal model, eliminates strokes. We've looked at 8-aminoguanine in the metabolic syndrome, two different models of the metabolic syndrome. CVSD rats is one of them. The CSF1 rat is the other. And we observe that these drugs not only lower blood pressure in these animals, but they also, because of their, the fact that they promote glucose excretion, they've lowered their, improved their diabetic status. They also improve their renal function and their heart function. So it has some amazing effects. We've also looked at 8-aminoguanine and 8-aminoguanosine in models of pulmonary hypertension.

So as you know, Bob, pulmonary hypertension is a very severe disease that carries a bad prognosis in the long term but we have found that treating animals with with this new purine lowers the pressure in the lungs and improves the function of the right side of the heart. So this may seem all to good, to be true. We decided to look at the situation in age related diseases, and this came about because of a personal story. I was in in Maine, coming back from a vacation, and when I got to the airport, I noticed I couldn't see out of one eye. And so I did a quick visual field test and realized I was having a retinal detachment. I called the emergency room in Pittsburgh. I said, I'm coming home, get an ophthalmologist in the ER. So I went to the ER in Pittsburgh and the ophthalmologist taking care of me was a delightful man who asked me what I did. And I told him, and he asked me, if I had any ideas for treating retinal degeneration. Yeah, I have one We started collaboration, looking at the effects of 8-aminoguanine on the retina of really, really old rats. So if you look at a young rat that's about three months old, the area of the retina where the receptor cells reside is very thick. And if you look at the retina in a rat that's about ready for the nursing home, little over 25 months old, the retina, the outer nuclear layer where these photo receptor cells reside has stemmed about 50%. But we put these animals on our drug for about two months, we restore at least half of that. So we're now collaborating with one of the most prominent ophthalmologists in the world on developing this drug for retinal degeneration.

**Dr. Carey** - I think what's amazing is that you've taken purines and particularly adenosine, guanosine and taken them all the way through. After years and years and years of study you can come up with these incredible applications, and lo and behold, they come true.

**Dr. Jackson** - Well, right now, we're looking at these compounds, treatment for systemic and pulmonary hypertension, metabolic syndrome, strokes and premature cardiovascular death, renal diseases. I didn't mention the fact that if we take red blood cells from patients with sickle cell disease and expose them to epoxy, of course, they sickle. If we pretreat them with our drug and then expose them we can reduce sickling by 35%.

**Dr. Carey** - Wow, that's an amazing result.

**Dr. Jackson** - Very important finding. We're very excited about that. So we have a number of cardiovascular renal applications for these purines that are called guanines and guanosines and we also think that we have stumbled upon what we'd like to call an anti, or reverse aging drug for folks like me. You know, antiaging drugs, well, that boat has already left the dock. So anti-aging won't help. We need reverse aging. We think that we have a drug that may be useful along those lines, and we're very excited about that. But going back to adenosine, I think there's a lot of possibilities for the application of adenosine for treatment of heart attacks and for treatment of atherosclerosis and neointimal hyperplasia, and I believe that there's a role for adenosine related drugs in so many areas, including cancer, which is I think is going to be a major application of drugs that interfere with the adenosine system.

**Dr. Carey** - So, Ed, I know you had some very key mentors in your career especially when you were a trainee and young faculty member. Could you very briefly talk about a couple of the mentors and what they meant to you?

**Dr. Jackson** - Sure. I recently had this flashback when I was thinking about this award, I was walking down the hallway of a research building at UT Southwestern Medical Center in Dallas and I saw this young assistant professor walking toward me. He had a pensive look on his face, I could tell he was immersed in his thoughts about his research. But he had a face that looked like he was approachable, and he was just a nice guy. He had a reputation of being extremely bright and he was a cardiovascular pharmacologist. So I thought, you know I'll go ask William B. Campbell to be my PhD advisor. And I asked him, and I was fortunate that he said, yes, and that was a turning point in my career.

Bill was the perfect mentor. He taught me how to read the literature. He taught me how to think about it and come up with hypotheses, to design and experiment, to test these ideas, to implement the experiment, to interpret the data, to write up the manuscript and to publish. I remember the first manuscript I wrote with Bill. I wrote the first draft. It was, I don't know, catastrophically terrible. It was really bad. That manuscript, I think he left a few of these, hands in it, and he rewrote it and we published it in *American Journal of Physiology* and it's been cited since 1979. So Bill really was a great mentor, and he's still going strong.

**Dr. Carey** - Yeah.

**Dr. Jackson** - So when I left Dallas, I went to Vanderbilt, which was another excellent place to land. I was in the division of clinical pharmacology and the head of that unit was John A. Oates. Dr. Oates was arguably the founding father of clinical pharmacology. He was a soft spoken man but when he said something, it always, you'd better listen because he knew what he was talking about. I learned so much from Dr. Oates. He passed away, unfortunately, just recently, but he won this award, I think it was in 2010 that he won this award. So I was so lucky to have both Bill Campbell and John Oates as mentors in my early days in career development. It at both Dallas and Vanderbilt there were a number of people that I interacted with, I was so lucky to have access to.

**Dr. Carey** - Yes, that's great. So one more question, Ed, and that is, can you remember what your very first research grant was?

**Dr. Jackson** - Absolutely, I wrote a grant called an AHA Established Investigator Grant that made the difference in my career, I have to say, because it gave me the funding to bridge from a junior faculty member into a more secure position. And in those days you had to fly out to a institution where there was a person on the committee who was looking at the grants and have a personal interview. So I went to the University of Iowa and I was told I was to talk to Francois Aboud. And he was the chair, I didn't know Dr. Aboud and I walked into his office and he asked me something. I answered. And then we got into an argument. And we argued the whole time. that was it.

**Dr. Carey** - He must have been impressed with the intellect.

**Dr. Jackson** - So I was shocked when I got back home and a few weeks later found that I was awarded the AHA Established Investigatorship, and then I realized that that Dr. Aboud, that's the way he talked people. He would challenge you. And I think what he probably respected was my stubbornness of not backing down.

**Dr. Carey** - That's right. I have a debt of gratitude I got to know him very well, and he's a great guy and I really appreciate the interaction that we had, looking back.

**Dr. Jackson** - So as a result of that first grant we're now in 2022, looking at over 400 publications, and how many years of grant funding have you had?

**Dr. Jackson** - Oh my gosh, well, let's see, I guess, from the mid-eighties till now.

**Dr. Carey** - That continuous grant funding is amazing

**Dr. Jackson** - Nearly 40 years. And I'm very, very grateful to the American public for supporting both the AHA and the National Institute of Health and allowing folks like you, Bob, and others and myself to try to make a difference in people's lives. And I think that although we are a competitive lot, we compete for, to be the first to discover, we compete for pages and prestigious journals, and we also compete for grant funds to keep our lab going. But what I respect most about the council, Hypertension Council and the AHA in general is that down deep we know that the competition really isn't between ourselves. The competition is between us and disease and us and disability and us and premature death. And I think that that's what makes, the council and AHA is all about, really, really special. I'm proud to be a part of it and proud to walk with my colleagues in lockstep to make whatever contributions we can make.

**Dr. Carey** - Ed, thank you. You are a pioneer in cardiovascular science and certainly one of the world's authorities if not the foremost authority on purine metabolism, physiology, pharmacology, and applications. You've made incredible discoveries which have realized themselves in terms of practical applications to human health. And so we thank you for all the work you've done. And on top of that, for mentoring so many people that have gone into academic medicine. You're a real leader and it's a pleasure to see you around the 2022 Excellence Award for Hypertension Research of the Hypertension Council, American Heart Association.

**Dr. Jackson** - Thank you so much.