Alan R. Tall

The Downs and (Mostly) Ups of a Life in Science

Susan Ince

Alan Tall has evidence of his first successful experiment—an image of his aunt pulling glass shards out of the backside of his cousin, hit when fleeing the explosion. Just 11 years old, that brought an end to Tall's bomb-making efforts, and he did not fully rediscover his youthful love of scientific experimentation until his medical residency.

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After completing medical school at the University of Sydney, Tall did a general internship at the Royal Prince Albert Hospital in Sydney and then relocated to the United States, where he was the senior resident and then chief resident in internal medicine at Boston City Hospital. Tall gained a post-doctoral fellowship in gastroenterology with Donald Small, MD, who had recently discovered the role of cholesterol in gallstone formation and was turning his focus to atherosclerosis. Together, they examined the structural organization of lipids in lipoproteins, and Tall's interest and focus on atherosclerosis has continued ever since.

After becoming a junior faculty member at Boston University, Tall was recruited to Columbia University in 1978 to establish an independent laboratory in the Department of Medicine, where he founded the Division of Molecular Medicine in 1990. He currently heads that division and is the Tilden Weger Bieler Professor of Medicine. In the Tall Laboratory, researchers use human genetic information as a starting point to identify genes and processes related to atherosclerosis that can be studied in cells and animal models to expose the underlying mechanisms and when possible to translate that knowledge back into potential therapy for humans.

For example, Tall and colleagues purified the CETP (cholesteryl ester transfer protein) and described the structure of the *CETP* gene, leading to the identification of a human genetic deficiency state of CETP, which is associated with markedly elevated HDL (high-density lipoprotein) and reduced LDL (low-density lipoprotein). As early as 1990, Tall suggested that therapeutic inhibition of CETP might be a treatment for atherosclerosis,[1] but CETP inhibitors failed to show efficacy in several clinical trials. More than a quarter century later, however, the phase III REVEAL trial (Randomized Evaluation of the Effects of Anacetrapib Through Lipid Modification) of the CETP inhibitor anacetrapib showed a benefit in reducing coronary death, myocardial infarction, and the need for coronary revascularization procedures.[2]

Starting with the mutation that causes Tangier disease, a rare inherited error of metabolism that results in low levels of HDL and ApoA-1 (apolipoprotein A-1; leading to the accumulation of cholesterol-filled macrophages in various organs and a heightened risk of atherosclerosis), Tall's Laboratory helped delineate the process of cholesterol efflux. The team demonstrated that the ATP-binding cassette transporter ABCA1, which is mutated in Tangier disease, directly binds and promotes cholesterol transport out of cells where it attaches to ApoA-1 in the bloodstream. The team also learned that the *ABCA1* gene promoter is directly targeted by LXR (liver X receptor) transcription factors, providing early evidence that LXRs control an overall process of cholesterol efflux and reverse cholesterol transport.[3] They then discovered a second transporter, ABCG1 (ATP-binding cassette subfamily G member 1), that promotes cellular cholesterol efflux to HDL particles but not to lipid-poor ApoA-1.[4] Together, ABCA1 and ABCG1 promote cholesterol efflux from macrophages and endothelial cells and suppress atherosclerosis.

Using ABCA1 and ABCG1 knockout mice, the team revealed that mice deficient in both develop leukocytosis and a dramatic expansion of hematopoietic stem and progenitor cell populations in the bone marrow. The findings indicated that ABCA1, ABCG1, and HDL inhibit the proliferation of hematopoietic stem and multipotential progenitor cells, driving the production of leukocytes, which promote atherosclerosis.[5] This revealed a new role for HDL and cholesterol in regulating hematopoietic stem cell proliferation in bone marrow and raised the possibility that targeting

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this process therapeutically might treat disorders characterized by the proliferation of white blood cells.

In recent studies, the human starting points for Tall's research have been genes associated with lipid levels that were identified in genome-wide association studies. Currently they are focused on the T39 (tetratricopeptide repeat domain protein 39B). Using knockout mice, they found that T39 promotes the degradation and ubiquitination of LXR and that, unexpectedly, its deficiency is associated with both an antiatherogenic phenotype and marked protection from steatohepatitis, raising the possibility that inhibiting T39 might be an effective strategy for reducing steatohepatitis and atherosclerosis.[6]

Since 2002, Tall has published regularly in *Circulation Research*. He serves on the editorial board of the *Journal of Clinical Investigation* and as an associate editor of *Circulation Research.* Tall received the Irvine Page Award from the Atherosclerosis, Thrombosis, and Vascular Biology Council of the American Heart Association in 1999, the American Heart Association's Distinguished Scientist Award in 2013, and the European Atherosclerosis Society's Anitschkow Prize in Atherosclerosis Research in 2017.

What Was Your Childhood Like?

I was born in Australia in Wollongong, a pretty gritty industrial area. As a boy, I loved doing experiments. I had a homemade chemistry set, and my goal was to make poisonous gasses and bombs. In the first goal, I succeeded in giving myself a few headaches. After lots of unsuccessful attempts, such as putting nitroglycerin in a container and throwing bricks at it from the roof to see if it would blow up, when I was 11 I finally succeeded in making a bomb. In those days, you could buy chemicals at the local pharmacy, and the bomb was made from potassium perchlorate, iron filings, and a wick in a glass jar. I blew myself and my cousins up. Fortunately, the shattered glass didn't hit my eye but lodged beneath it as I backed away from the explosion. My cousin turned and ran, and I have a vivid mental picture of my auntie fishing pieces of glass out of his backside. Nobody was seriously hurt, and I regard that as my first successful experiment.

Was Anyone Else in Your Family Interested in Science?

After my father came back from World War II, he did metallurgy at night. He worked for a big company and in his early 40s started his own business involving scrap metal and other things. He never had a bad year. I have a younger half sister who is a physician, but her work is pretty different from what I'm doing. She set up a health spa in Brisbane with a pool, gym, meditation, and other services, and she does the cosmetic part of it.

Tell Me About Your Early Education

The options for public school in our area weren't that great, so my parents made the unusual decision to send me away to Sydney at age 11, so I could get a good secondary education.

I was pretty young, so the first semester I was homesick and a little at sea, but after that, I thrived. I was interested in languages and science. I learned to speak and read French there, and I still read novels in French. It was a rigorous education.

How Did You Pick Your College and Major?

When I finished high school, I didn't really know what I wanted to do. I was 16, and my parents had a big role in pointing me towards medical school at the University of Sydney. I won the university poetry prize in my second year, and throughout the 6-year program, I thought I would end up as a writer. I also spent a year as an exchange student in California, and that was very important in later decisions.

How Did You End Up Coming to the United States?

I made the move after my general internship. My primary motivation was that the research opportunities were outstanding, better than at that time in Australia. Culturally, from my exchange year, I knew I would be comfortable living in America permanently.

How Did You Get Interested in Atherosclerosis?

Within a month or 2 of arriving in Boston for my internal medicine residency, I had to look for a fellowship for my next step. I was fascinated with Donald Small. He had discovered that the cause of gallstones was bile becoming supersaturated with cholesterol, and I thought that was the coolest discovery (I still think so). I was very attracted to his style of science and him as an individual, and I was very lucky to get a job with him. At that time, he was moving his lab into lipoprotein cholesterol research. He was interested in atherosclerosis and that's where my interest in atherosclerosis began.

Were You Doing Mostly Research?

Mostly, I did a modest amount of clinical work in gastroenterology. "Enough to get a job," as Small used to say. He was interested in physical chemistry, and we were doing experiments to deduce information about how the lipids in lipoproteins were organized. Working with him, the funny thing was that my first papers were Tall and Small, so that was good because it gave me some name recognition.

How Did You End Up at Columbia?

I was recruited by Bob Glickman, MD, who was the head of gastroenterology. We had been collaborating while I was still in Boston. I wanted an independent tenure-track assistant professor position, and I thought it would be good to move away from my mentor and set up an independent laboratory. I also really liked the idea of living in New York City. I was recruited to Columbia in the gastroenterology division, and then eventually, I developed my own division in molecular medicine, which is a research division in the Department of Medicine.

What Have Been Your Biggest Challenges or Low Moments in Being a Physician Researcher?

The low moments are related to having papers rejected and grants not funded, but one develops a certain amount of equanimity about such things and learns not to take it personally and move on. But you can't help being disappointed by rejection, and you see other people around you who are geniuses, and you realize your own limitations. I know some people who are very talented, successful scientists who could have had full careers but who just couldn't stand the uncertainty of having to write grants and not knowing for sure that the next year there would be sustenance. You have to be able to deal with uncertainty and rejection. But, as I know from my son starting out as a musician, in that world, rejection is orders of magnitude higher than in the world of research and science. In the end, the biggest challenge is your own intellect, perspective, and training. In the United States, there is great opportunity, but ultimately you have to be able to fulfill your potential.

Have You Tried Being a Creative Artist?

I truly enjoy writing, and some of that now is channeled into writing papers. I think many scientists enjoy writing as a way of explaining to the world what you've done. At the point, when the work is ready to be written up, it's quite pleasurable.

Genetic Variation and Deficiency Syndromes Have Been Important in Your Research. Where Did You Get Your Genetics Training/Knowledge?

Most of it is self-training. I'm not really a geneticist, but I'm attracted to the insights that can come from genetic approaches. In 1978, I decided to do a sabbatical with Jan Breslow, MD, at Rockefeller University. Jan was at the forefront of genetic research in atherosclerosis, and even though I didn't achieve much during that year, I learned the approaches, and that allowed to me to change direction. Looking back, it was a very important decision to take that year.

Do You Think It's Possible These Days to be a Successful Cardiac Researcher Without a Firm Grounding in Genetics?

I think there are plenty of other approaches in epidemiology and biochemistry that don't require a knowledge of genetics. Clearly, there are huge discoveries being made in genetics and a deluge of new information that is at the forefront of the understanding of atherosclerosis. So I think genetics is something that has to be reckoned with, but I don't think it's the only way to go.

How Hard Do You Work, and How Is Your Work Time Divided?

I don't think I put in as many hours as I used to, probably 50 when I used to work 60 plus. I still work fairly hard. You can't be a successful researcher on a part-time basis; you have to be pretty absorbed and devoted to it. I no longer do hands-on work in the lab, but my office is in the lab, and I'm talking to people and looking directly at data all day long. In the lab, I'm teaching graduate students, postdoctoral fellows, and MD/PhD students. I do some formal teaching, running a course for graduate students and giving lectures. Every year I see patients on the general medical service for a limited time period. This is mainly a teaching assignment, but I'm responsible for the patients. So I do a moderate amount of teaching, but altogether, teaching and administration take up less than 15% of my workload.

What Do You Like to Do When You Aren't Working?

I like to spend time with my family. I'm very interested in the arts, classical music, in particular, so we go to lots of operas, concerts, plays, and art galleries.

What Advice Do You Give to Young Scientists About Establishing a Research Career? What Qualities Does It Take to Be Successful?

It's obvious that it takes hard work, intelligence, ambition, and drive to become a successful independent researcher, but there also has to be a certain amount of sociability—the ability to get along with colleagues and work in a network of people.

When you establish an independent lab, it's very important at the beginning to focus on an area in which you can become recognized and established and create a niche for yourself. Later it's possible to have several projects and diversify, but at the beginning, resources and time are limited, so focusing on one aspect is important.

Did You Follow That Advice?

I eventually got around to it after getting that advice from others, reading, and participating in the grant review process. I recognized that one had to almost have a brand. Mine was cholesterol ester transfer protein. I decided for about a decade that CETP was all the lab was going to work on. In my case, the focus was a molecule, but it could also be an important process in biology or disease. But it doesn't pay off to move from one subject to another at the beginning, at least not for most people.

Were There Things You Saw the Potential in But Decided Not to Work on in Order to Keep That Focus?

Looking at my own character, I recognize that I actually don't like working in areas where a whole lot of other people are already working. The ability to make a unique contribution under those conditions is pretty tough. I'm still like that. Half of my lab now is working on a pretty obscure unique topic with great potential, but I don't think anybody else in the world is working on it. We're working on a molecule, nicknamed T39, that came out of human genome-wide association studies. We're intensively trying to understand its function and application in different diseases, and it's taking us into a lot of different directions. It's very rewarding and brain-teasing, and you have to keep reading very actively to try to understand the different areas you're being pulled into by the research. It may have potential as a therapeutic for both nonalcoholic steatohepatitis and atherosclerosis.

Some of Your Earlier Work Also Identified Potential Therapeutic Targets. Were You Active in the Translational Research?

Yes. Along with Japanese collaborators, we discovered a human deficiency state of CETP in 1989 to 1990 that was characterized by elevated HDL and reduced LDL. This led to drug companies trying to make inhibitors, which has been a huge effort with several failures. The most recent trial involved 30 000 people and 4 years, and Merck actually succeeded in showing that the CETP inhibitor anacetrapib benefited the patients. This has been a major translation effort, moderately successful and still ongoing, and I have been involved in various aspects of the clinical work along the way providing advice and guidance. Merck did a great clinical trial and got a 9% difference in the primary end point, but they made a decision not to apply for approval of the drug. There are others still being evaluated as therapeutics, and CETP inhibitors may still find a place in therapy.

Other molecules that seemed to have potential as drugs to reverse atherogenesis, the LXR agonists, got into advanced clinical trials but caused side effects that made it impossible to develop further. But there is still considerable interest in using LXR agonists as anti-inflammatory drugs, and there may be ways to get around some of the side effects.

Any Other Current Work You're Excited About?

We didn't discover this area, but we've been trying to understand the relationship between clonal hematopoiesis and atherosclerosis. This is important because clonal hematopoiesis is commoner the older you get. It's present in 10% of people over 70, but it

can also occur in your 40s and is a potent risk factor for coronary disease.

Are There Things I Haven't Asked About That You'd Like to Say About a Career in Research?

Although you asked about some of the downsides, I'd like to emphasize the upside, which is the freedom that comes with being a researcher. You have the ability to come to work and dream up some ideas and talk to some really smart people and do experiments to test your ideas. I think that's pretty unique. I guess being a successful creative artist might be on the same level, but I think in this world being a successful artist or scientist are the most fulfilling things you can do as a person. That's the way I view the world. I am incredibly lucky to be able to have this particular job.

Disclosures

None.

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