[MUSIC PLAYING]

ROBERT ANDERSON: We have a huge disconnect between myself and the molecular biologists regarding what happens with development of the coronary arteries. There's been a colossal amount written by molecular biologists over the past 10 or 15 years, with one particular lady, Kristy Red-Horse working in Stanford producing some exquisite molecular biological work. But I am not convinced she is fully aware of the morphologic issues.

So what she is doing, and [INAUDIBLE] many such as her, is to seek to establish the origin of the arteries. And they're particularly interested in the genes that are involved as they develop. What I would like to do is to take that information that has come forward from the molecular biologists and interpret it on the base of what I see in the episcopic data sets that I shared with you yesterday, which Bill Devine also has access to.

And to see if we can take that information and help us to explain why. But Judy showed us more this morning. Why is it that, on occasion, the right coronary artery takes origin from the left coronary aortic sinus, whilst the left coronary artery takes origin from the right coronary aortic sinus. And we can then extend that to see perhaps why we also got so many malformations in terms of sinusal origin in the setting of a transposition.

So the vascular biologist gets down to the nitty gritty and asks whether the coronary artery is formed by a process of angiogenesis as opposed to vascular genesis. And they take apart the components of the coronary arteries. So much of their work is focused on the origin of the endothelial lining of the coronary arteries as they are. Or the coronary vasculature even, because they also look at the veins. And they argue that there is changing in programming of these vessels as they may be changed from veins to arteries.

And they're doing this on the basis of marking the endothelial lining. And then they look again when the coronary arteries achieve their walls. And they establish the genes that are involved in producing these vascular trees.

For me as a morphologist, I think it's more important to look how the epicardial coronary arteries, which are formed within the surface lining of the heart. And we know that that is where they appear. The big question to me remains, how do those coronary arteries achieve their origin and their connection with the aortic root. And that is obviously key to determine what Julie told us, how is it that the right coronary artery can take its origin from the left coronary sinus?

So the other question, can we then explain why there is such variability in the course that the stems of the coronary arteries take relative to the vascular pedicle as they move up, form the epicardial surface, and achieve their origin from the aortic root.

There's another matter that is then important. Since we know that the intramural circulation, as opposed to the epicardial circulation, the vessels develop first within the epicardial lining. But then they also have to connect, not only with the aortic root but also with the vessels developing within the compact component of the ventricular walls.

Because as I will show you, initially the ventricular walls in the developing heart are a trabecular mesh work and only subsequently is there the development of the compact myocardium. And that occurs after the epicardial coronary arteries achieve their origin from the aortic root.

So this to me focuses again on the need, as you see here, to establish how and when the stems of the main coronary arteries achieve that connection with the aortic root. So let's look at the change in the architecture of the ventricular walls.

So here's a relatively early stage-- as my mouse working now? Can you see my mouse? OK.

So you see, we've got a four-chamber cut showing us the arrangement of the heart at 11.5, quite early in development. You see here the atrial ventricular canal, right atrium, right ventricle, left atrium, left ventricle. You'll recognize now, I hope, that here is the growing primary atrial septum, with its mesenchymal cap.

So you see now that the tricuspid orifice has already achieved its connection with the right ventricle. But if you look at the ventricular wall, you'll see that the larger part of the thickness of the ventricular wall is made up of a mesh work of trabeculations. And only a tiny part is made of compact myocardium.

If we then continue to embryonic third day, 13.5, and the mesenchymal cap has nearly fused now with the inferior atrial ventricular cushion. You see the cushions have now developed properly in both the right and left atrial ventricular junctions. But still, when you look at the ventricular wall itself, the trabecular layer has continued to grow. The compact layer is still very thin.

Now there is a lesion that is also called non-compaction. And I believe that is also a mistake, because there is no evidence to show that these trabeculations compact together to form the compact part of the ventricular wall. This very thin compact layer that you see at this stage proliferates under its own speed, and the trabeculations stop proliferating.

So the notion that there is non-compaction, I think, is a mistake. It is better to talk of excessive trabeculation. But there is a remarkable change between day 13.5 and day 14.5. So here is a four-chamber section through the ventricular mask just one day later.

And now you see how the trabecular layer is becoming far less obvious. There is growth now of the compact layer. But that is due to proliferation of that compact layer. There is, however, compaction of the trabeculations to form the papillary muscles. And we also know that the trabeculations form the ramifications of the ventricular conduction system.

There is also compaction within the septum. But the compact wall itself grows by proliferation. And all this happens after the epicardial coronary arteries achieve their connection from the aortic root. So to summarize what I've told you of the compact myocardium develops from 14.5 onwards in the mouse.

And yesterday I told you 14.5 in the mouse coincides with eight weeks of development in the human, which is when there is closure of the embryonic interventricular communication. And we know from our analysis of data sets in human hearts, that this is parallel, this appearance of the compact myocardium is paralleled in the human heart as in the mouse.

To emphasize again, the compact wall is not the consequence of compaction of pre-existing trabeculations. So I firmly believe that so-called non-compaction is much better described as excessive trabeculation. And Julie will know, also, that in adults who have excessive trabeculation, they too suffer a potential risk of arrhythmic problems and, I think, also sudden death.

So the coronary arteries develop to nourish the compact myocardium. And we can see, at 14.5, well-formed epicardial vessels. There is another point, however, to take in mind.

Because at this stage the arterial roots, which are developing in the middle part of the outflow tract, are themselves still encased in a turret of myocardium. And there are coronary arterial primordial within that turret of myocardium.

And they surround the entirety of the developing arterial roots. So it is this ring of arterial primordiums that gives you the option for abnormal vessels to encircle the route. And I'm sure we're going to see some of those when Diane demonstrates her PowerPoint and when you see it with-- when Bill shows you the specimens.

So to me the burning question, how does the ring make contact with the aortic root? And this has long been a bone of contention. Do the coronary arterial stems grow into the aortic root? Or do the coronary stems grow out of the arterial root?

Well, a long time ago, a man called [INAUDIBLE] a gentleman, I think, investigator suggested there was outgrowth, but he argued that stems grew out, not only from the aortic valve-- developing aortic valve stenosis, but also the pulmonary stenosis.

So the old notion was that you had both pulmonary and aortic stems. And this gave you a nice explanation of why coronary arteries could also appear originating from the pulmonary valval stenosis. Then about 30 years ago, the group from Leiden in Holland headed by [INAUDIBLE] with [INAUDIBLE] contributing suggested that, in fact, there was ingrowth as opposed to outgrowth.

But now the situation has changed yet again. Because another group of workers in Marseilles headed by [INAUDIBLE] and also including Robert Kelly have produced evidence to show that, indeed, stems grow out of the aortic root but only from the aortic valve stenosis.

So we have these two contrasting theories. The one saying it's a matter of an ingrowth, with [INAUDIBLE] now producing evidence that there is outgrowth. And this is the evidence that [INAUDIBLE] has produced. Robert Kelly is her boss. And so he sent me this picture. This is an early outgrowth of one of the coronary arteries. And these blue markers show that this is aortic endothelium that is growing out of the aortic root.

But my own investigation of the episcopic data sets support strongly the notion that there is outgrowth from the aortic root. So here is the developing aortic root in one of the mouse embryos I've looked at at day 13.5. And there you see the root.

There you see the epicardial development of the left coronary artery, which is inert-- which is within the muscular turret, which is enclosing the entirety of the roots. And I believe I can see there an outgrowing stem from the root, which is unifying itself with the epicardial coronary artery.

So it is my belief that the notion of union with the [INAUDIBLE] ring by the outgrowth from the sinuses provides us a good explanation and, arguably, those stems can also go out from the pulmonary root since they are together within this ring of-- this [INAUDIBLE] of myocardium.

The other point is, if I take you back just a moment, this is very distal within the developing aortic root, which as yet has not formed its sinus. So the fact that the coronary arteries are originating while distal within the developing outflow tract, provides a very good explanation of why high origin of the coronary arteries is so common.

So this is not the end. In fact, we're only beginning to scratch the surface. I do believe that increased knowledge of the mechanism of development itself will give us new insights. But I do think we also need to take note of the morphology. Because only combining the two, will we get the final answer. So Diane now will explain to you what are these variations in origin and in course of the coronary arteries relative to the arterial pedicles.