DANNY LENNON: Here we are. Alun, thank you so much for taking the time to join me on the podcast today.

ALUN WILLIAMS: No problem, thanks for asking me on.

DANNY LENNON: So we have a lot to get through and before we jump into any of those specifics, I think a good way to lay some context for that is to run people through your background and the area you've been involved in academia and your research up to this point.

ALUN WILLIAMS: So I trained I guess, you know, trained in sports science and then a PhD in muscle physiology and there was a bit of nutrition in there and a bit of endocrinology. But while I was completing my PhD, I did some collaboration with some genetics researchers and that really lit my fire as it were. So that's sort of 20 plus years ago, and since then I've increasingly focused more and more on the genetics but not forgetting my original training in exercise physiology, muscle physiology, and nutrition.

DANNY LENNON: The thing I wanted to lead off with, because it's just a completely probably historic moment I guess in sports, and it's probably not too be give a way to phrase that, has been the recent

Caster Semenya IAAF hearing that's taken place recently, and you have obviously had some involvement in which we can get to that. So before we get into any of the specifics of that actual case, first, what was your part and where did your expertise come into getting yourself involved in that landmark case?

ALUN WILLIAMS: Yeah, I think it is, as you say, a landmark case. So I was approached by the legal team working on behalf of Caster Semenya challenging the IAAF regulations, the regulations about the eligibility of DSD, so that's Differences in Sexual Development, DSD athletes in athletics specifically, because it's the IAAF. But obviously I think a lot of other sports are watching this and will basically follow the decision of Caster of the court. So I was asked to get involved because of my research in genetics of sport performance, because DSD athletes, it's sort of a broad category really and there are various individual conditions I suppose that fall within that category, but ultimately they are driven by genetic changes. And given that we're talking about sport performance, then that's the link, so conceptually it's how do genetic changes in DSD athletes compare to other genetic changes that we know of that aren't subject to any regulations, that give some people advantages or disadvantages over other people in the way that we all recognize.

DANNY LENNON: This case is particularly interesting because there is a lot to this, and so maybe a good way to start is outlining what was that IAAF policy that they had proposed to try and address what they deemed as this issue, what was that policy they put in place that was being challenged by Ms. Semenya?

ALUN WILLIAMS: It was in April 2018 that the regulations were announced and expected to come into force by October 2018, so the end of last year. But that has been delayed because of the challenge to those regulations. So the regulations were brought in to address what the IAAF sees as a

problem or it's only an issue about DSD athletes competing in the female category, some of whom have testosterone levels that usually you would find in males, whereas usually female athletes have significantly lower testosterone levels. So in terms of actual levels, total testosterone usually in females would be sort of less than two nanomoles per liter, so a range of 0.1 to 2; whereas again usually in males, you're talking about something like 8 to 30 nanomoles per liter. And in some of these DSD athletes competing in the female category, they do have testosterone levels and natural occurring testosterone levels that are comparable to normal male levels.

DANNY LENNON: Right, and I think there's one immediate thing that probably will jump out at people and we will probably circle back to this later on, because there's obviously in other areas right now a lot of conversations going on about transgender athletes and the implications in sport there. But what is quite clear about what we're discussing here with DSD athletes, these high levels of testosterone that we may be seeing are completely naturally occurring, they're not due to any exogenous sources that are being taken there; that athlete's just natural level of testosterone is just that it's different to what we typically see in female athletes.

ALUN WILLIAMS: Absolutely right, yes. It is important to say that, yes, these are not athletes that have administered testosterone or other substances exogenously. So the regulations are directed at those athletes who were born as female, assigned female gender at birth and have always lived as females and always competed as females in sporting events as well. So yes, that is, in that respect, it's obviously related but it is certainly different from the issue of transgender athletes.

DANNY LENNON: Just to recap, I know you mentioned some of the ranges there – for some of the proposed policy changes to address this issue, what type of ranges or cutoffs were talked about in that

policy of what the IAAF essentially wants to do?

ALUN WILLIAMS: So what they want to do, as you put it, is ensure that anybody competing in the female category in athletics has a testosterone level of less than 5 nanomoles per liter. So if someone is a DSD athlete and has, for example, testosterone level of 20 nanomoles per liter, then they need to undergo treatment, usually hormonal treatment but actually sort of surgery is another option, but they need to undergo that treatment to lower the testosterone levels and it needs to be below that level of 5, and to maintain that level and have evidence that it's maintained at that lower level for at least six months before competition, in an attempt, in the IAAF's words, to level the playing field and make the female category as I said, a level playing field for all athletes competing in there. I think the complexity arises because that assumes that testosterone is the driver of all differences between male and female athletes, and that is highly debatable.

DANNY LENNON: Yeah. I think this is where it starts getting a bit interesting, because on one end, just the idea of, as they put it, trying to level the playing field, almost seems like a strange one to start off with. Because just what we know about elite athletes by nature and their genetics compared to – the very elite compared to just decent athletes and worse, there's going to be genetic differences, that's what makes it human sport. So trying to think that we're going to try and level out differences in something like a circulating hormone starts to get a bit of a strange issue, particularly because in this case it's just a natural difference that some athletes have and we know that some athletes have more testosterone than others and more or less of other things and other different changes, so it starts to get a bit interesting. In this particular case, like you just alluded to, where I suppose the debate really crops up is the tie between testosterone and the inherence performance differences. So it's not that we're

probably saying that there's no impact of testosterone but it's, are these differences that we would see with a DSD athlete compared to other female athletes, is the differences in performance solely down to testosterone and kind of our best kind of bet might be comparing male athletes with similar testosterone levels to female athletes within the normal range. And we know there's differences there but now we're kind of trying to correlate between the two. So I know you've alluded to it's maybe an iffy premise to build this case on. So from your perspective on the current literature, when it comes down to the various differences between men and women that may explain differences in average athletic performance, where should we stand on the idea of testosterone, be that sole driver versus potential other factors if there are any and where do we start to piece all this together I guess?

ALUN WILLIAMS: So an important fact is that when we say DSD athletes, actually we're talking about a variety of genetic mutations, so we would use that word because these are rare genetic changes, so it's a variety of different mutations that each individual athlete typically will have one of them. It's possible they would have more than one but typically we would expect them to have one of these rare mutations that affects the – depending on the mutation, affects their biology in terms of testosterone production and the response of the body to testosterone. So I think the best way for me to talk about is to give a specific example of one of those conditions. So the IAAF in its regulations lists several categories of athletes that are relevant to the regulations, and the top one in the list, and apparently, I mean the data aren't very comprehensive – but apparently, it's one of the more common ones in terms of the DSD athletes. So there were lots of DSD conditions but many DSD women, many other particular types of DSD are probably not compatible with sport. In fact, they are probably pathological in some way. But probably the most common one

that is relevant to sport is, so the athlete would be called a 5-ARD, so it's a mutation in a gene that affects 5-alpha-reductase 2 production. So this is an enzyme that converts testosterone to dihydrotestosterone, so DHT. And DHT, as opposed to testosterone, has particular effects in the developing fetus in terms of development of genitalia. And then again later during puberty, it has influences on secondary sexual characteristics as well.

So if a person has a mutation in this particular gene that affects the production of that enzyme and the mutation depending the type of mutation it is, it can either completely stop the production of that enzyme or it can maybe just partially limit the production of that enzyme. Then the "usual" conversion of testosterone to DHT is affected. It's either reduced or stopped completely. So testosterone levels themselves aren't reduced but DHT is reduced. So that you can follow through then and would affect the development of genitalia in the developing fetus and would affect some of the secondary sexual characteristics that develop in puberty. So an individual, what's relevant here is that an individual is XY chromosome, so what's usually categorized as male sex chromosomes, but has a mutation in that gene, then in terms of external genitalia then they're typically, I mean there are variabilities, but typically they are born appearing as a girl or sometimes even ambiguous in terms of genitalia, but typically born as a girl. And if assigned the female sex at birth and then continue to live in that way and become involved in sport and compete at a high level in sport, then we have an individual who has naturally occurring high testosterone levels with XY sex chromosomes but is born as a female and has lived as a female, and socially has lived as a female and has been treated as a female all her life. And then these regulations would affect that individual by saying that that they have to undergo treatment to lower their naturally occurring levels of testosterone or basically not compete in the relevant events.

DANNY LENNON: And so if the IAAF case is based on that premise that testosterone is this primary driver of these differences, what evidence are they pointing to in support of that or evidence to essentially explain that position?

ALUN WILLIAMS: I think it's a combination of evidence, so you can sort of move out of sport research and just look at sort of almost sort of textbook understanding of the effect of testosterone on physiology including muscle mass and so on, and also hemoglobin level. And again there's little argument about that. But in terms of specifically in performance, then it gets less clear-cut I would say. So the slight history here is that there was a previous set of the regulations that were applied a few years ago and then they were overturned by a previous case at the Court at Caster with a requirement for greater evidence to be produced that testosterone was directly influencing performance in athletic events. So you're probably aware that there are a couple of papers published, commissioned by the IAAF effectively that provided some evidence for that, but the evidence was not particularly strong, has been very sort of forensically analyzed and written about in the journals by researchers like Ross Tucker and others for example. And even if you took it at face value, the original research has only been applied to the athletic events, only running events and only those events between 400 meters and up to a mile for IAAF. So an athlete with DSD conditions that we're talking about is allowed to compete at 200 meters or 100 meters or sprint hurdles or distance events and all field events which seems incongruous really.

DANNY LENNON: Yeah, it's an interesting one. And a few things, as you were going through that, that jumped to mind, one is we obviously know that testosterone has some role in aiding performance and that's why, for example, in a completely different area, but if we're talking about doping and someone using exogenous testosterone that they may see a performance

benefit in certain areas potentially depending on the sport we're talking about. But from this perspective, I think it's probably interesting to consider the acute versus kind of chronic effects. And so if acutely someone who has had, let's say, we take a female athlete who's had typical female testosterone levels throughout her life and then were to start doping and elevate testosterone to higher levels what that potentially could do for performance. But I think what maybe some people might point to in a case of a DSD athlete is they not only have higher testosterone at the time of competing but they've had these kind of key developmental years with a higher testosterone level that's allowed them to build a, let's say, a degree of muscle mass and potentially strength from that they otherwise wouldn't. And even if we were to now reduce those levels, they could potentially still have benefits to that it. Is that another kind of weird aspect to this? Has this been something that you've heard in some discussions around this or how could we even start to view that kind of differences I suppose acutely versus chronically?

ALUN WILLIAMS: I think you're right again, and this is part of the whole complex issue. So the kind of DSD athlete that we're talking about, will have been exposed to those high levels of testosterone from even before birth. And so I don't think it's entirely established how that could affect muscle development, for example, and the number of muscle fibers that might develop at that under that early exposure to testosterone that might provide a benefit later in life when sort of heavy training is conducted whether it's sort of the hypertrophic potential of that muscle because of a larger number of muscle fibers is greater or not. So I think that would make some sense, but I don't think there's clear data on that. And then bring it back to the regulations, the idea that six months of lower testosterone would equate the situation, that now therefore is debatable about whether six months, just the last six months of someone's life at a lower testosterone level below that

level of five, then if the intention is to provide a "level playing field" then it's probably a question about whether that really does that because that individual would have been exposed to high levels of testosterone for the, well, who knows, 15, 20, 25 years before that.

So yes you can look at these things in all different directions and I think there isn't a consensus about many of these things, and that's partly the problem for the IAAF in terms of regulations I think that they were trying to bring in – and of course, we're speaking at the moment, and I don't know the outcome of the case yet but their regulations are based on the premise that these things are all clear-cut and they really are not.

DANNY LENNON: And I think there's definitely something we haven't touched on yet as kind of the ethics around this, and I certainly want to touch on that. But just to round out this piece on performance, because again, I think a lot of this discussion centers around just being accurate in understanding that relationship between these potentially elevated testosterone levels and athletic performance in these certain events at a risk of losing some of the nuance of this super complex issue, what would be your overview that you would want people to come away with to at least understand what your current understanding of the literature tells us of this kind of relationship between testosterone and athletic performance in these particular types of cases?

ALUN WILLIAMS: That very last thing you said in these particular types of cases, that is, you know, there's extremely limited data on that. So really we are inferring from other studies of testosterone almost completely. I think that's almost part of the problem of the regulations because they are presented or they were presented as if there is little question about the advantage that these athletes would have and it's not as clear-cut from that. So the data on those particular type of athletes themselves is very limited, there was

a little bit of data presented as a figure – I forget the precise reference but I can direct you to it later – in a figure, in a review article but they were sort of original data if that makes sense. So not previously published but sort of added into a review article which is fine but means they haven't really been properly peer-reviewed which showed an apparent relationship in DSD athletes between reducing their testosterone levels and a reduction in competitive performance. But it was on an extremely low number of athletes, and no methods presented that you can critically analyze and a whole load of confounding factors in there in athletes that have been required to lower their testosterone levels. And there are other things that can be affecting their performance, most obviously training, diet, any possible side effects of the treatment that they went through, all those things are likely to change those things and likely to reduce performance. So it's just an example of the very limited proper data on this topic.

DANNY LENNON: And I think it probably circles back to what you highlighted right at the start of this conversation of the risk of putting way too much stock into testosterone alone, as opposed to realizing even when we do observe differences between, let's say, male and female athletes, that there's a lot of other things that are very different. Obviously they're not only just testosterone and then indirectly things like muscle mass but also their bone structure or their frame or anthropometrics and probably several other genetic things going on as well that I'm sure you could talk about as well, that there's a lot of differences genetically and physiologically going on that can impact performance in some way.

ALUN WILLIAMS: Yes, again, you're right. It's kind of slightly lazy, I would say, to attribute everything to testosterone. So in layman's terms sort of non-specialists would talk about testosterone as being a "male hormone" and the inference is that everything that distinguishes a male from

a female is down to testosterone. But yeah, it's a significant factor, but it is not the only factor.

DANNY LENNON: I know we've tried to kind of piece through the genetics and obviously your expertise of looking through that has been highly important here, but we can't completely detach that from, I guess, the ethics around a case like this and that's intrinsically tied to sport when we're discussing genetics. And particularly with a proposed policy like this that is not only – it's kind of unprecedented in the sense that is requiring certain athletes who have done nothing wrong to actually say you can't compete unless you undergo medical intervention to change your hormones, it's kind of crazy to kind of think of that when you lay out on paper. But when it comes to the kind of ethics around this we've now got a case where we have an athlete, and if we give the example of Caster Semenya and other athletes in that position that an elevated testosterone level, as we've discussed, is a natural occurrence for these athletes, they have not done anything wrong, they haven't cheated, they are not doping, it's a difference that's just purely down to genetics.

And so even if it was established that there's a performance benefit from that elevated testosterone, it now becomes a dicey issue of saying, well, because you have that advantage we have to eradicate that. And at what point then does that end because pretty much every elite athlete probably has better genetics for something going on than a lot of people, and there are going to be these differences that's what makes them elite to some degree? And now, we're essentially punishing people because they won the genetic lottery, and not that one of these DSD athletes has one genetic lottery in every sense, but specifically at one type of athletic performance, let's say, even if it does work out to have that performance benefit, they're being punished for not cheating or doing anything wrong. And so I'm just wondering for your thoughts on this case from

a kind of ethics of sport issue of how we should think about these, and at least even on a personal note, what is your a framework for thinking around the ethics around questions like this?

ALUN WILLIAMS: If I can I'll start by just addressing the genetics and then talk about the ethics. So the whole field of genetics of sport performance, I mean, it gets a lot of interest or at least it seems like it to me sometimes to work in it. But the reality is that there is so much more that we don't know than we do at the moment, so I need to just lay that out there. But we do know some bits. So if I give just a couple of examples, if people have heard of anything about genetics, one thing they might have heard of in terms of sometimes called a sprint gene or something with gene as abbreviation ACTN3, that's for alpha actinin 3, and there's a variation in that, and it's a common variation. So you're not talking about just a fraction of the population, there's a common variation in that. So we all have a version of the gene but some of us have the version that does its job in terms of making a particular protein that is expressed in fast-twitch muscle fibers only, and some of us don't make that protein because of that genetic difference. And if you are lacking that protein due to this genetic difference, due to this polymorphism, then it seems to affect sprinting performance, perhaps just about 1 or 2%, something like that. So not a great deal, but obviously at the elite level, where you want as many things in your favor as possible to succeed, then that 1 or 2% can make a significant difference. And the data are remarkably consistent that at elite sprint events, if you're one of the people that's not that unusual, but one of the people that cannot produce the protein due to that athletic change, then it is extremely difficult, I won't say impossible, but extremely difficult for you to be truly elite at sprinting, much harder for you than if you have a different version of that gene which means that you do express the protein.

So that's one example, but that's very commonly found ONE, and then you can go to another extreme of a very rare mutation. So there's one in the EPOR genes so the erythropoietin receptor gene that quite famously there was a skier, Eero Antero Mäntyranta from Finland, who in the 1960s won several gold medals and other medals in cross-country skiing. And the effect of that mutation in him and other members of his family actually was to change the structure of the receptor protein that responds to EPO. So he had normal levels of EPO, but the change in the structure of the receptor meant that it was extremely responsive to those normal levels of EPO. So in response, he was pumping out red blood cells continually and had a hematocrit significantly above 60%. And there are other genetic mutations that have a similar kind of effect, but often they maybe come with some pathological problems and therefore people can't compete in elite sport. But for this cross-country skier, he didn't suffer from any other problems, so effectively he had that advantage, that benefit of huge oxygen carrying capacity, and I would lay money that that assisted his sport performance.

So those two examples, a common variation in the ACTN3 gene that has a small effect on performance and then a rare mutation in EPOR gene that has a substantial effect on performance. I would put the kind of mutations that the DSD athletes have, somewhere in the middle between those two, perhaps a little bit more towards the EPOR and towards the rare end. But these are not totally unique cases, there are a number of individuals with fairly similar mutations. So in that sense, these kind of mutations in the DSD athletes are within the range of other genetic variations we know about that affect poor performance. So in that sense actually then why should they be treated differently? I think the answer is why they could be treated differently. The argument is that those other kind of variations, they are not specific to just females or just males, they are –

it would have a advantageous or disadvantageous effect whether someone is male or female. In terms of the mutations related to DSD athletes, they are only potentially performance-enhancing in female athletes. In male athletes, they would not be performance-enhancing. If anything, they might even be performance reducing, but certainly not performance-enhancing.

So then it broadens out, if it only applies to female athletes, we then have to start looking at a broader question of who is eligible to be in the female category. Because if these athletes are eligible, then it's just another mutation that gives them an advantage and other athletes have other mutations that aren't qualitatively different. But if they are not eligible for the female category, well then the question is irrelevant. So it does broaden out then into a sort of broader thing about almost defining for the purposes of sport, at least what is a female. And then, as you say, this gets a broad sort of ethical debate. So I'm going to refer back to the position of the legal team that was working on behalf of Caster Semenya and others which was released publicly, which is that these kind of DSD athletes that were born as women, reared, brought up, socialize as women, legally recognized as women for their entire lives are comfortable in that female gender as well, have always competed in athletics maybe in that school level and then onwards as women, then to then prevent them from competing as adults seems discriminatory in my opinion. So I agree with that kind of view.

DANNY LENNON: And I think that's where the implications for this further down line for other cases even that our outside of DSD athletes could be big because a lot of them I think will probably start referring back to this. And so that's where it's going to be interesting to see how that ends up getting defined. And, like you say, in this particular case, we have athletes who were born female, raised female, who have not taken any exogenous interventions or hormone

treatment to change anything and have been competing in athletics, and just have happened to have this genetic change that may influence their performance to some degree but it's, I think, probably at least some people will look at, does this open up the option for people who are then transitioning gender in adulthood and maybe who would have gained some advantage from, let's say, previously being male, and if they're now illegally female, and should they be allowed in female classes. And it just gets a lot into even beyond genetics at that point, it's very much a cultural and ethical issue, and I don't know if there's any easy answers right now.

ALUN WILLIAMS: Yeah. I think you're right. So they are obviously related, and yes I'm certain that interested parties are waiting on this decision before addressing the other question about transgender athletes that you mentioned. So yes, heavily related but still separate. This case, yes, it was explicitly about DSD women athletes and not about transgender athletes.

DANNY LENNON: Yes, absolutely. I think that's important that it is people realize there is a very clear distinction, because at least to me, on just a personal level, I think it's two very, very different scenarios that were to acquire two separate lenses to look through to answer some of those questions. For people who are interested to find out more about the work you're doing or to catch you on social media or anything like that where is the best place on the internet that they can track you down and your work and anything that you want to mention?

ALUN WILLIAMS: So I'm not particularly active on Twitter but I have a presence. So my title on there, so it's @RugbyGeneStudy. I tweet some of our work about genetics in rugby, so yeah from that then I think there's a link to ResearchGate from that as well where you can actually see some of the papers that are produced with my collaborators. So yeah, that's probably as good as anything.

DANNY LENNON: I will link up to that in the show notes for everyone listening. And like I said, Alun, we will definitely have to try and arrange a round two because I think all that I've looked into of that particular work that you've got going on is fascinating and I think a lot of the audience would enjoy that as well, so we'll hopefully be able to arrange that. Before I let you go, the very final question I end every podcast on is something that can be to do with anything even completely outside of what we've discussed, and it's simply: if you could advise people to do one thing each day that would have a positive impact on any area of their life, what would that one thing be?

ALUN WILLIAMS: Well, I'd not be particularly original perhaps, I'm going to just say something about physical activity. But the angle I'm going to put on it is just a lot of people are, I'm sure you are as busy as me, we're very busy and it's often a challenge to find the time to do some physical activity whether that's a specific training session or just some other kind of good physical activity. So my comment would be just try to make the time for it, try to prioritize it, it's important for health and for other things. In terms of genetics, you can have all the genetics you like, that might mean you might be a good training responder or something like that, but it's all about gene environment interactions. So if you don't do the exercise as well, then the genetics does nothing. So yeah, that's my thought.

DANNY LENNON: Brilliant, Alun, with that, I want to say thank you for taking so much of your time to come and talk to me, and for the fascinating information you've been able to give, and the insight that you've been able to give into this particular case, and I think people will really find it fascinating.

ALUN WILLIAMS: Thanks Danny, enjoyed it.