SUMMARY KEYWORDS

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00:02

This year, we're delighted to celebrate the 87th Paget lecture, adding Professor Robin Lovell-Badge to our long and eminent list of lecturers. Robin is a principal group leader and head of the laboratory of stem cell biology and developmental genetics here at the Francis Crick Institute. Robin's research in the fields of embryology, stem cell biology and mouse genetics has contributed to groundbreaking discoveries. These began with contributions to the development of embryonic stem cells from mouse embryos and to transgenic mice, both of which proved ways to derive genetically altered animals that were widely adopted. He then went on to discover Sry, the Y chromosome gene responsible for initiating testicular development in mammals, and to characterise how it functions. At the same time, his group found the SOX gene family, including SOX2, which they showed was important for pluripotent cell types in the early embryo, for embryonic stem cells and for embryonic progenitors in stem cells in several systems in both embryos and adults. Because of his research, Robin has a long history of talking to the media about animals and research. He's also very active in both public engagement and policy work around stem cells, genetics, human embryo and the animal research and in the way science is regulated and disseminated. He has always been a strong advocate for openness in the Concordat, and is a former council member of Understanding Animal Research. In 2018 Robin was awarded a CBE for outstanding contributions to science. Tonight, I'm delighted to introduce Professor Robin Lovell-Badge and his lecture, navigating the complexities of working with and talking about animals and research. Thank you Robin.

01:57

Well, of course, I'm greatly honoured to be giving this talk. I feel obviously very passionate about the whole openness issue, as I will mention towards the end of my talk, not just about animals and research, but more generally. But just to say, you know, thinking about all these issues already, it brings back so many memories of the bad and the good. The bad being you know, when I was working at the what was MRC National Institute of Medical Research at Mill Hill, the weekly demonstrations we used to have outside. I have been twice since president of the Institute of Animal Technology for 19 years, coming up to 20, far too long.

02:50

I remember when I first used to go to their annual meetings, there was always a big police presence and worry that there was going to be quite violent demonstrations and things. After a few years, basically, that all went and it was the Concordat that had a big role in that. I'm very honoured to say that I was actually both on an advisory group for the Science Media Center, and on the Council of UAR when the Concordat was developed, so I made a small contribution to that, which I'm very proud. I'm going to tell you a little bit about my research and a little bit about other things, sort of extracurricular activities, so you get a flavour of the sort of animal research we do, as well as other things I've been interested in. I just wanted to point out this on the website - first of all, I have a beard, and I don't know why the photo wasn't of me with a beard. But also with I am not the mysterious animal behind the COVID-19 pandemic.

04:14

Last year's Paget lecturer talked about sex as well, so you're going to get a bit of sex this time. So maybe it's a common theme, and you've got reproductive organs on your awards, so it's a major thing that UAR thinks about. Okay, so just a little bit of my history. I'm going to talk mostly about the sex determination work that we've done, but just to point out, as was briefly mentioned in the introduction to me. Also, in other things, at the same time, we cloned the SOI, the gene on the Y chromosome that triggers male development, we also found the soft gene family, and that included. I should say I worked as a PhD student, as a postdoc with Martin Evans, working initially on embryo carcinoma stem cells, and then towards the end embryonic stem cells, which Martin derived in the lab. These became a very important route to making genetic altered animals.

05:18

And I should just point out, where are we… Martin Evans got a Nobel Prize for this. Very proud that he got a Nobel Prize for it. He got that in collaboration with others for gene targeting. So when we cloned SRY, in1990 we founded other family of genes, including SOX2. We showed that SOX2 was involved in early development in the mouse, critical for pluripotent cells, including embryonic stem cells, which is interesting as I sort of backtracked to what I started with. Shinya Yamanaka won a Nobel Prize for showing you could use SOX2 and other genes to reprogram somatic cells to give induced pluripotent protein stem cells, which, of course, another very important development I've missed out, but I never expected it. Both Martin and Shinya deserve their prizes. We've gone on over the years to look at other aspects of stem cell biology, and not just the early embryo. We looked at the role of these genes, in particular the SOX gene family in central nervous system development in neural stem cells, where SOX2 and unrelated gene SOX9 are very important, also pituitary development and stem cells and pituitary system and that's occupying quite a lot of our time at the moment, besides actually doing a lot of research on this.

06:55

So back to the main topic. A couple of definitions, when I refer to sex determination, I mean the decision to develop as male or female and how that switch operates. Then you can talk about sex differentiation or gonadal differentiation, which is how that decision is translated, initially into making a result testis and then all the differences between sexes, or most of the differences. Why do research on this, so pure interest, of course, have been theories of how you have males and females being around for, actually, 1000s of years. One of the ancient Greek philosophers by name of Anaxagoras proposed that semen from the left testis gave rise to girls and from the right testis to boys.

07:40

That's a theory that can be tested quite easily. That's not true. It's obviously socially important, and, you know, often in the news these days, differences between males and females. So I'm not going to go into all of that. It's a paradigm of how decisions of cell fate are taken in the during embryo development. Often, cells during development have to choose whether they can be type of cell or this type of cell. For the gonad, you've got these bi-potential cell types, so it's a beautiful system in which to study that. It's also paradigm how you make organs. The gonads are relatively simple organs. So it's a very good topic to look at. Clinically important because there are, in fact, many cases where the whole process goes wrong, generally referred to as disorders of sex differentiation, that can be complete sex reversal where the individual develops the wrong sex compared with their chromosomal makeup.

08:49

For example, XX males or XY females, you can have a mixture, intersex cases, inevitably, these lead to infertility. So, these are of great concern to the individual who have them and their families and the doctors who have to look after them. They're very difficult to deal with. And while many of them are rare, when you sum up all the different causes, it's quite a lot. It's something like 2% of birth. It's really a lot of cases of DSDs, some are relatively mild, but many not. I'm not going to talk about issues about gender dysphoria, although it may be relevant. There's obviously many conditions, including cancer, with differences between males and females, and I guess last year's talk was a lot about that I believe. I’m afraid I missed it. So, knowledge of the genes and processes involved allows better diagnosis, counselling, appropriate choices of treatment, and perhaps development of novel clinical options. And that's what we always panel out on that.

09:58

So for biology lesson - many different mechanisms have evolved as the switch to trigger male versus female development, and we can divide these broadly into two classes, those environmental switches, where all individuals within a species have the same genetic makeup generally, but it's the environment which influences which sex develops. And you see this in many species of fish and reptiles. And reptiles, as many of you probably know it's temperature at which the egg is incubated, the embryo is incubated at a critical point in its development that turns between male or female. I'm not going to that. My ex post doc of mine, still a colleague working in the US, has worked out the mechanism for turtles, and it's beautiful science if you are interested, Blanche Capel is her name. Okay, differences between the sectors must depend on either the environmental trigger and or hormones made by the ovaries or testis.

10:59

And then you've got chromosome or genetic based mechanisms where males are females differ in one or more genes, or in whole chromosomes or sets of chromosomes. So I'm not going to talk about birds, but birds the females are ZW , the males are ZZ. Mammals generally are XY male, and XX female. So it follows almost all species, we know that the Y chromosome acts as a dominant male determinant. So it doesn't matter if you have multiple X chromosomes. If you don't have a Y you're female. If you have a Y chromosome, irrespective of normal X chromosomes, you develop as a male, apart from the ones on your right. I assume they're normal, XXXY, male and female. There's something slightly different with each of those animal species illustrated, which is not quite consistent. So marsupials, it is true whether you make testis or ovaries depends on whether you are XX or XY, but whether you make a pouch or a scrotum depends on the number of X chromosomes you have.

12:13

Moles, the females have a period where they have a high level of testosterone made and part of their gonad looks much more like a testis. I guess you have to be fairly aggressive if you're running around a dark panel and you don’t know who you're going to meet. Wood Lemmings actually are different. There are 3 different types of Wood Lemmings that are being studied and they don't have a Y chromosome necessarily. Some of them have lost a Y chromosome, we don't know yet how sex determination works in those. And then hyenas, they have an XXY system, which makes the aerial testis, but the females have external genitalia that's very masculine. I don't know how they would be treated in debates about which toilets you should use, they all have phalluses. So if the females want to start wincing now, of course, they have to not only have sex through the phallus, they have to give birth through this, so it's a complicated story. I don't recommend being hyena and female.

13:30

Genetic sex has established at fertilisation with the inheritance of an Y chromosome from the father is not the whole Y chromosome that determines maleness. It is this gene we found on the Y chromosome termed SRY. I'm not going to that all the history. There's a little bit of history. It's actually only it's in1959 that the Y chromosome was shown to be sex determining in mouse and man, same year. There was a theory for a long time which suggested that it was an antigen that could be detected on the surface of cells from XY individuals but not XX individuals, called HY. But that was disproved by Ann McLaren and Elizabeth Simpson who showed that it can't because they found male mice that didn't have HY. There was no gene proposed to be the sex determining gene on the Y, called ZFY, proposed by a lab in US, led by David Page, everyone believed that for a couple of years, I didn't. I was very persistent with a collaborator.

14:39

First of all, we started looking at what this gene was doing in mice, and it clearly was not responsible for sex determination for a number of reasons. And then with Peter Goodfellows lab, we found the gene on the Y of that was a very, very good candidate, we call that SRY. That was 1990. In 1991 we did some transgenic mouse experiments that proved that it was the gene, and the only gene from the Y required to trigger testis development, mostly male development. So, an XX male mouse carrying copies of a mouse SRY gene as a trans gene.

15:25

His name was Randy. This triggered a lot of interest from the media. So this was really my initiation into talking to journalists in the media. We had basically for weeks and weeks, we couldn't do any work in the lab because we had journalists there it was crazy. I got very used to how they work and what the issues are. And this was in 1991, and so since then I’ve not been frightened of talking to the media. Some headlines are rather weird, by the way. There was, I should point out there was only one bad headline here, which you might be able to see, of mice and mingling that was in the Evening Standard. And luckily, I didn't have to anything about this. Someone else very involved in public engagement science, called up the editor and the next day, they published an apology. Lewis Walter. A little bit about sex determination and gonad differentiation. This is in the mouse at about 11, 11 and a half days where you can't see any visible difference between male and female gonads. In humans, that would be around about 6 weeks involvement.

17:02

If you are XY or particularly, you have SRY gene that leads to the formation of testis, and you can see distinct differences already. This is one day later, between the ovary and the testis here. There is this prominent blood vessel. But the most important part is that you have this sort of stripe appearance, which is due to differentiation and alignment of supporting cells because of into sertoli cells. Sertoli cells are characteristic of a testis, so these organise around the other germ cells. You have a layer of sertoli cells around these. You have a thin layer peritubular myoid cells, which help make this sort of testis chord structure, which is again going to go on to form the seminiferous tubules much, much later, and then in the interstitial memorising cell types, but particularly you have the leydig cells, which make testosterone.

17:59

In the ovary not a lot is happening in terms of organisation, you basically, have germ cells surrounded by granulosa cells, roughly at random beginning, but we actually know the molecular changes have already initiated on the pathway to making an ovary. SRY is active for actually a very brief period. It looks sort of extended here and it peaks at around 11 and a half days and then goes off. So, the first time you start to see overt differences SRY is no longer active. If you look on a cell by cell basis, SRY is only active for about 3 or 4 hours. It is only present for about 3 or 4 hours. It acts very rapidly, and its role is basically to flick a switch. That's all it's doing. The whole process is a balance on a very fine knife edge. And it just requires a little bit of SRY activity to trigger things to go the testicular pathway. And if SRY is not there, it follows the ovarian pathway. SRY diverts the ovary pathway to make a testis.

19:10

Once you start making a testis, this produces number of factors, like testosterone, but then masculinise the rest of the embryo. So this is that decision, basically, you're supporting cell precursors which in the ovaries would give you granulosa cells, and in the testis the sertoli cells. And then once they start making sertoli cells, they influence all the other cells in the gonad to follow the testicular pathway that includes the germ cells, steroid cells, etc. That's the initial decision is taken there. What does SRY do? Well, all the evidence is suggesting that the only critical gene it regulates is a related gene called SOX9. The SOX9 is actually involved in many systems during development and in the adult, and I mentioned it is expressed in a number of stem cells and other cells. But it's particularly important in sex determination because it's a critical gene for making sertoli cells. We know this from human mutations and from mutations in the mouse. Loss of function mutations can give you XY females.

20:29

We also know that if you deliberately mis express SOX9 during mouse gonad development, then you can get XX male development, so no SRY there, you get male development. And there are rare duplications of SOX9, or as I mentioned in a specific enhancer region you could also find in XX males. So, you just need a little bit more SOX9 and that's sufficient to trigger male development. It turns out that many of these disorders of sex development or sex differentiation are due to altered SOX9 gene regulation. Not all them, but certainly many of them are. We spent a while looking at how SOX9 is regulated. And I’m going to cut a long story very, very short and just say that we found one specific enhancer which we called Enhancer 13. It was basically the 13th one we found, which is just 557 base pairs long, located a long way from the transcriptional start site of SOX9. And if we deleted this, a 100% of homozygous deletions, a 100% of XY animals develop as females instead of males: XY female sex versal. And this is just showing some of the gory details.

21:53

So this is a normal male control with testis. This is a normal female control with ovaries, and this is our homozygous mutant for the enhancer, where you have structure a bit smaller than normal, but they look much more like ovaries. So, this little region of DNA controlling the activity of SOX9 is critical to make testis. That fits with human data suggesting that deletions of the region where an equivalent to this enhancer is located are associated with XY female sex reversal, and with duplications of the same region has been found in some XX males. So, it's a critical little enhancer. And unpublished data, but Gonen, who did this work in my lab, has gone on to study this in a lot more detail, and she's shown, in fact, that just altering one or two base pairs within this enhancer can be sufficient to give you sex reversal. It's incredibly amazing that just tiny bit of DNA, and this is non coding region, a tiny little bit of coding region is so specific.

23:09

So, there's the mice. Well, one is a control, one is an XY female. I don't know which is the control actually, they both look female. And the reason for this is basically you've reduced the level of SOX9 expression. So again, this is our normal male, this is the level of SOX9 expression, you have a high expression here. This is our control female, low level of SOX9. And when you mutate the enhancer, you have the same low level of SOX9 as you do in the control female. And the opposite, if you look at markers of varied development and Foxt2 is a few critical one I'll talk bit more about later. That's high now in our in our XY females. And we can also show you molecularly that SRY is banned to enhancer 13 at the right time and place \*\*\*\*\*\*\*. So again, not going to bore you all these technical details, just to say that we can physically show that the two interact.

24:17

So SRY interacts with enhancer 13 just to boost the expression of SOX9 enough that it reaches a critical threshold that it then drives the sertoli cell differentiation. This is what I immediately have. This everything balanced very finely to begin with. And we know from looking at gene expression, gene activity, that in different gonads or these early stages of the formation of the gonads, there is very little difference between an XY and an XX early gonad. In fact, no difference. But all you need is this little bit of SRY expression to boost the expression of SOX9. SOX9 is expressed here but at very low level. You boost the expression of SOX9, and then it triggers these sort of feed forward loops, these pathways that are going to initiate to Sertoli cell differentiation and then maintain it through testis development in the embryo.

25:14

In the absence of SRY, these low levels of SOX9 goes off, and it goes off quickly. This are molecular changes going on in here. And we know of a number of genes that are involved in this active process of making an ovary. WT1 is involved Wnt signalling pathways and machine FOXL2, but they act in a redundant way. So, making mutations in any one of these doesn't necessarily give you a dramatic phenotype. FOXL2 is an interesting gene, and we've been devoting a lot of time for looking at this because over the years, my lab and many other labs now have generated a lot of understanding of the genes involved in making a testis. We wanted to push what makes an ovary, and I mentioned a few of the genes involved. And this one, FOXL2, caught our eyes because it's the beautiful marker of early ovary development. So, you can see staining foot. This is a trans gene reporter, and you can see this expression very clearly in the XX, not the XY gonad. And it's the earliest marker, clear marker we have of these pregranulosa cells in the early ovary.

26:37

Now it was found as a candidate for gene giving XX male sex reversal in goats. Why were people looking at goats? Goats have horns, farmers quite like their goats not to have horns because they damage things, they damage each other sometimes. There’s been a couple of mutations that occur spontaneously that farmers have been keen about and one of them called polled intersex. When heterozygous, you have all XX females, XY males and they lack horns. But when homozygous, the XX animals develop as males. So, we now know that this is work done in France, that this is definitely the causative gene. They may use genome editing to specifically mutate FOXL2, and indeed you get this early gonadal sex reversal to give you animals with testis like gonads not ovary like.

27:43

ln humans heterozygous mutations in the gene give this syndrome, which I'm not even going to attempt to pronounce, BPES. It's also more dominant. No one's ever found a homozygous mutant, and the chances are pretty much zero that you'd ever do so. If you have eyelid malformations and sort of craniofacial problems in both males and females, but the females almost always show premature ovarian failure. So, the gene has some role in ovaries, it certainly does in goats and it probably does in humans. We really see what happens in mice, and you also have the eyelid defects and things in mice. But if you study mice that are non-mutant for this gene, so never seen FOXL2 protein ever, they have no phenotype in the ovaries. The ovaries develop perfectly ok. No phenotype is seen until about a week after birth when the ovaries begin to become very messy, dysgenic.

28:50

With sporadic up regulation of SOX9, which should only be expressed in the testis post -- and other male pathway genes. So we wanted to know what would happen if you deleted this gene. In the less confusing period, lots of things are happening this week, 2 weeks after birth, you have this period called mini puberty, all sorts of changes and things are happening. So what's happening if we just delete it from an adult female?

29:19

So we need a conditional mutation, an inducible creed driver. This is the result. So we have, this is our control ovary, normal looking follicles, oocyte. If we delete this from, this is from an 8 week old female, we delete the gene, and then we look 3 weeks later just using normal histology techniques, you no longer have something that looks like an ovary. In cross section, this looks a little bit like a testis. In fact, much like a testis, including structures that look very much like seminiferous tubules, including cells that look like sertoli cells, peritubiluar myoid cells, and actually, I'm not going to do the evidence, but there's lady like cells in the interstitium as well, and these gonads made through levels of testosterone that are equivalent to their brothers. There's no germ cells, because the oocytes don't like being surrounded by sertoli cells, so they all die.

30:22

But you've got gonadal sex reversal. This is pretty interesting. It happens very rapidly. So, I'm not going to show you all the data but if you look molecularly, as soon as you lose FOXL2 protein, you now see SOX9 being expressed, and the cells start trans differentiating. So you have a trans differentiation of granulosa cells to sertoli cells, and then everything else follows on. We begin recently to again look a lot more in molecular detail at what is going on, and clearly, FOXL2 early on it is redundant. These other genes are probably helping to lead to ovary differentiation, so if you just delete FOXL2 you still get ovaries. But after birth, there's something different happening. And so we think this is likely that FOXL2 regulates different genes at embryonic stages compared to postnatal stages through the interaction with different factors probably bound to DNA at the same place and same time.

31:35

So Roberta Migale looked at this, this is all recent work, and she used a very clever method which allows you to detect FOXL2 bound to its DNA target sequences, and also to identify the proteins it's interacting with when it's bound to DNA. And this has given a huge amount of data. I'm not going into it but basically it says that the hypothesis is correct: FOXL2 interacts with different things at different times during development of the ovary. In the embryo, it's different compared with postnatally. It interacts with many more things postnatally. So, it's becoming more important we think. If you start looking at some of the factors interacting with, this is now revealing new candidates that are involved in disorders affecting development. So, she found this gene, Usp7, again, not going to get into any of the details, but just to illustrate the fact that this basic data is now giving us a lot of information which might help inform clinical cases. If you delete Usp in granulosa cells, it blocks primordial follicle activation and impairs ovarian development.

32:50

We can't see sex reversal, because the gonads disappear. They don't persist very long. It's such an important gene for ovary development. There are families living with Usp7 mutations, and so it's clearly they have problems with fertility. And then this part of the talk, I just want to end with a little bit about well.. F or some of these experiments, we end up using a lot of mice, particularly when you're having to get small amounts of tissue from embryos to do these molecular studies and genetic studies, we use quite a lot of mice. So of course, we are interested in the 3Rs and trying to reduce animal usage. And so a couple years ago, Nitzan in my lab, started to develop methods for seeing whether we could derive gonadal cell types in culture from pleurotopic stem cells.

33:49

And she started in my lab, and then we ended up collaborating with a group in Paris led by Anu Bashamboo to see whether we could apply this method in human as well. So, clearly it's very difficult to study gonadal development in human embryos because it's all occurring at a time when you can't see anything, it is inaccessible, it’s very difficult. If you want to understand the disorder of sex development due to a problem in the upper gonad, it’s almost impossible. The only way we were doing it was by making mouse mutants and trying to see whether you got the same thing but often it wasn't quite the same. Anyway, again, to rush through the story, we can begin with mouse embryonic stem cells or iPS cells, or human iPS cells or and I'm going to show you a bit of work with human iPS cells, where it's possible to begin with control female iPS cells, control male iPS cells, and also iPS cells derived from XY female individual.

35.00

And go through this process, which takes a couple of weeks, to differentiate the cell types that you'd normally find in the early gonad. You can then change the culture conditions and you can follow various markers, and we can begin to find the markers that we expect to be present in the early gonad. We find that SOX9, which is our marker of the sertoli cells, is in the differentiating XY cell cultures but not the control XX cell cultures. So, this indicates that what we're getting is SRY dependent expression of SOX9, it is the only real difference there.

35:43

So this makes it a useful system, we believe, to look at disorders of sex alone in humans. And just to prove this, we looked at the iPS cells from this DSD patient, this XY female patient, and you could take them through to give gonadal cell types but the cells from the DSD patient, which are the ones in the middle here, would never form tuber like structures in culture, whereas from our control male they would, from the control female they wouldn’t obviously but from the control male they would. From our DSD patient they wouldn't form the tubules. If you then use geno-medicine to correct the mutation in the gene if we knew what the gene was, now they make tubules again. So, we believe that this is a powerful system for studying DSD in humans.

36:40

Lots of people I can thank for work over the years. I'm not going to go into all of these people now. I want to return to other things. I'm involved in Openness. As I mentioned, I was involved a bit in setting up the Concordat at early stages. I mentioned, talking about the sex reverse mouse, Wendy, a lot media and other things came up over the years that were relevant. And of course, Dolly was a very relevant appearance because that was 1997, the paper was published February 1997. And it led to my first interview with Jeremy Paxman on tonight program; I survived. It’s actually relatively easily. I was set up against someone else, and that other person couldn't make the arguments why you wouldn't clone animals very well. So, it was very easy for me, Jeremy was rapidly on my side. It was quite pretty good.

37:55

That led on to other things. And so in part it led me to be asked to help with changes to the human fertilisation and embryology act. The change was being made in 2000, 2001 to permit the derivation of human embryonic stem cells and also therapeutic cloning, so like using the cloning techniques to derive embryonic stem cell lines, allowing that to be permitted in the UK. I was corralled to help with that, partly because I was already talking to the media but also to some policymakers about these sorts of things. Anne McLaren probably who was also my mentor for a while also pushed me into this.

38:45

That was all successful. When it came to updating the HFE act again, so this started earlier than this, basically 2 years of my life were devoted to this, 2006, 2007, 2008, 3 years almost. It became necessarily to update the Act again due to further advances in science, clinical practice, public opinion, etc, and also legal challenges due to ambiguous wording. There many amendments were planned to be made to the original act, several of which were quite contentious.

39:29

I just say that thee punch line is that, again, it was passed by both houses of parliament by a significant majority. But some of the contentious issues were things like pre implantation, genetic diagnosis, save your siblings, research involving in vitro derived gametes, that's still contentious, and then human embryos carrying animal cells or DNA. I was asked to join a working party by the Academy of Medical Sciences to look at the sorts of science that was being done and might be done where you have inter species embryos, so where you might be mixing animal and human.

40:90

This was rather focused on the sort of work that might be done using human embryos with some animal component. And particularly the things like hybrid embryos, where you wanted to do nuclear transfer using a cow egg and replace its nucleus with human nucleus, and that generated a lot of controversy and a lot of fuss. So anyway, we produced this report. It was initially entitled inter species embryos but actually the term that ended up being in the Act was human admixed embryos. It wasn't just about the hybrids nuclear transfer.

40:52

We had two hybrids in there. We've got transgenic human embryos, so where you have modified them in some way with animal DNA. And animal DNA could be interpreted very broadly. So, it could be plant DNA or bacterial DNA. And actually the genome editing that can be done now with human embryos, that was allowed because of these changes in 2008. Of course we didn't know about genome editing back in 2008. So obviously, none of these were going to be permitted embryos that could never be transferred back. I was very much involved in the discussions, not just in Parliament, but with the media. And my view all along, was to be very open and just say: this is what the science is about, this is what the science can tell us, this is what the science how it might benefit us, no promises can be made, this is basic research, we don't know but this is what it's about. It got quite contentious, the debates got quite hot. If Fiona Fox was here, she would tell you all about this.

42:03

The Easter march 2008, the Roman Catholic Church got very active trying to campaign against this. The Cardinal Keith O'Brien condemned plans for the creation of hybrid human-animal embryos as monstrous, and we were likened to all sorts of individuals who were unpleasant. I responded, science progresses by, I'm going to read this out because I believe it: science progresses by refuting falsehood. The bishops of Roman Catholic Church at this time apparently want to promote falsehood. The proposals within the Embryo Bill that the Bishops object to are to permit research which can be done with very sincere and honourable aims, which are to provide understanding of normal processes in life and to develop cures for the debilitating diseases and conditions that occur when these go wrong. Each of these aims informs the other. We are not seeking to make monsters, as the bishops proclaim. If its research is successful in its aims, it will help improve quality of life and give back dignity to those who suffer.

43:09

Anyway, we wondered about it. I wasn't alone by the way that many others doing this, helping. There’s a report that followed up on that, which is perhaps a bit more relevant to understanding my own research. Having done the human embryos containing a little bit of animal stuff, what worked the other way around? How about animals containing human cells? And so we wrote this report animals containing human material. And that included the first time I was involved in a public dialog, so this is not just simply doing public engagement, having consultations and things, opinion polls, but proper dialog sessions with members of the public, which I think were really informative and some great promoter of these. This was published in 2011. The day the report was published, a movie was released called, Rise of the Planets of the Apes, which didn’t help particularly but I guess it helped the debate to some extent.

44:16

And it took a while but the recommendations in the report were eventually adopted into UK law in 2015. And then the other situations where I've been involved in this sort of public dialog, and it's very important so, public consultation methods to avoid mitochondrial disease. The Royal Society conducted a genetic technology program, which I was leading, and we did a public dialog exercise to look at the policy environment for the use of these techniques in plants and animals, as well as possibly in humans. This is again genetic alterations. And then more recently, research involving early human embryos and research involving human stem cell-based embryo models. These are very important ways of being able to… I know I've got to finish.

45:13

Just go back to openness. So Concordat in openness in animal research is so important. I'm a great fan of open access publishing. I think it's really important. And for the scientists who are a bit resistant because they have to pay a little bit more for it, they think open access papers draw far more citations and from a broader readership than description only journals. I am a supporter of open data and sharing of resources. Once published, I always give out everything, including genetically altered animals, I think it’s really important. Openness and clinical trials, of course, is also so important. I'm going to stop there to say, be open to everything.

46:22

I probably should have been looking at what my clock a bit better. I'm Karen Gardner, former
Glaxo consultant of various organisations and worked for the IT for a long time and I now work for BBC. You and I worked together with the IAT and had many long discussions, about what stops people being open, and where the balance was between fear of their professional work being compromised and fear of animal extremism, which you and I both faced directly and I've all said that the psychology around the animal extremism was far too successful, because they were very good at indenting fear, and there wasn't a lot of threat there, and that seems to have changed now, people aren't so scared. What's your comment on that?

47:41

Well, you know, I was never particularly scared, and I never ever had any threat directly to me. Been open about this stuff for all these years. Not a single email. I'm going to invite them now probably. I was told to check for bombs under my cars, all this stuff, and never did, no physical threat. We had these demonstrations outside the NMR but that wasn't personal to me, it was just they knew this was a place where stuff was going on, they didn't know what it was. And I think telling everyone what went on there would have been a solution to stop them doing it because it was pretty much mostly mice and a few ferrets and that was it, not much. So, the fear, I think, is often exaggerated in my view. I know some people did receive threats, did receive nasty things. There were very nasty things happening to some individuals and organisations. And this still goes on, I know that, but I think openness helps. It can't hurt. And I think when people clam up and are not saying what they're doing and why they're doing it, it’s a problem. That's inviting trouble. I've actually had more complaints about the stuff I've talked about, human embryo research, so I have had some nasty, vitriolic emails and letters from that.

49:35

So with regulations the way that they are, does that include some of the science that you might want to do with hybrids or that you can do, or are there some limitations? The current act needs to be updated again, the HFA act needs to be updated again but that's not particularly to do with any animal research. And the animal regulations, I think, are in theory fine. There are some issues. A lot of us were talking about these issues of an IAT meeting the other day, where we miss seeing the inspectors. We miss seeing things like that. I think regulation could be smoother, where you're actually talking to people regulating you in a much better way than that’s carrying on at the moment.

50:32

There are some other issues, which we find frustrating in the lab getting the research done because we care a lot about our animals, but sometimes I think the steps we are forced to do are probably a little bit more stressful and harmful to the animals in the long run because we have to have them under operation for far longer than they really need to be, just as an example. But that's just sort of my personal experience, and what people in my lab complain about. It can be really hard sometimes. Because this is too much for them, they don't have the time to spend doing some of the experiments.

51:13

It was delegated to really great people in our animal facility to do it. But again, what that means is that the PhD students and postdocs in the lab are a lot more hands off, and I think that's such a pity. So, I want them to get back in doing stuff but there's a barrier, because I think some unnecessary barriers are coming up to do this. I may be only one person talking about this. I care very much about our animals but sometimes it gets a little bit silly. If there are any vets in the audience, they can attack me on that one.

51:37

What would be a potential candidate or a sex dependent disorder that you could treat in humans with gene editing in the future. Is there anything that you think may be coming out potentially? Well, there's lots of cancers, which are, you know, some are being targeted already. There is metabolic disorders, there is, you know, all sorts of things. Do you think that it would be quite challenging to find good targeting ways to -- movements?

52:48

Genome editing in humans, I'm going to forget heritable genome editing for the moment, that has whole lots of issues by itself. But gene therapy, the biggest issue is delivery of the genome editing components. So, if you can take cells out of the body, manipulate them, ex vivo, for example, bone marrow stem cells, which is done for beta thalassemia and sickle cell disease, for example, and then put the cells back through bone marrow transplant, that can work. It's comes with quite a lot of costs because you have to get the bone marrow graft to go in properly and take over, which means using nasty drugs to eliminate the resident bone marrow stem cells.

53:49

And that inevitably, almost inevitably, leads to infertility of the individual and stuff. So, really negative consequences but the disease can be cured. And we've seen that now for sickle cell disease and beta thalassemia. The issues there are more to do with cost, equity of access. They're very expensive treatments done that way. If you could simply introduce them into the body so that the genome editing components in a viral vector or liquid nanoparticle find the right cells to target efficiently enough, then that would be much less expensive and it will allow you to hopefully target a greater range of diseases. You can get things into the liver quite easily, and that's proving to be quite successful as well. There's quite a few metabolic disorders and things which you can now treat that way. But getting into muscle, getting into skin, getting into tissues that are difficult to access, the brain, really hard. So, we need people working on delivery methods. Well, thank you, Robin, one more round of applause for...