Meeting in Bristol 21st April 2012

Presentation by Professor David Lomas

This is a verbatim report of the meeting. The slides used during the presentation are not shown here. Comments and notes are shown in show in square brackets [so]. The symbol -> is at a point where Professor Lomas is highlighting a picture or text on the screen.

You suffer from a very important disease it is a disease that I have worked on for 22 years I did my PhD on your disease where we described the fundamental mechanisms and my ambition is that by the time I retire is to give a talk which says:

- this is mechanism that I described when I was a graduate student in Cambridge,
- this is the pathway of the disease our understanding of the liver and lung disease,
- this is the cure and
- this is the patient that we've cured.
- Thank you and Goodnight.

That is my career plan. That is my goal and I suspect that it is aligned with your goal as well so I think we're on the same page here.

Recently as many of you will have seen we've had a big breakthrough in alpha-1. Alpha-1 has been mentioned on the Press wires and at the top of the publicity – even being on the Today Programme and in the Telegraph, the Times, the Guardian – all the big ones. Your disease was up there and to all those people who say *I've never heard of it* – just say *it's on the News*. You disease is a model for a variety of other diseases and it's first up there for a cure by genetic processes.

What I want to do this morning is to have an interactive session. I don't want to stand and give you a lecture for an hour – I can do that to my medical students at any time.

I really want you to understand what I've done and what I'm trying to do. So the questions and answers are really important in all this and what I'll do is break my talk into a series of chunks. So I'll do liver disease, lung disease, why you are so important and why carrying this mutation actually helped you a few hundred years ago. Then I'll talk about various strategies for a cure. I'll stop after each and take questions. Please, please have questions! If you think *Gosh I don't want to ask that it may make me seem a bit stupid* – it doesn't matter: I'll turn it into something sensible. So please, please engage.

I want you to leave here with a few snippets of information whereby you really understand this disease and I understand where he's going and what he's trying to do.

A special welcome to the people who see me in clinic and have been involved in some of this research – some of your blood – some of your **type** of blood. Those of you who come to the clinic on Wednesday know that the question is *'. . . and now can we take some blood for research?*' And you'll see why.

[INTERJECTION] You do get a free cup of tea! [laughter]

Whenever I give a medical talk I start off with full disclosure and I'll do that for you today: so that you'll all know where I'm coming from and so I disclose my conflict of interests. It's the sort of thing in medicine so that if I say something you can say '*well hold on a bit . . maybe he's giving me a biased picture.*' It is very important.

For many years I've worked for GSK, GlaxoSmithKline, which is a major pharmaceutical company. I've been a consultant with them. I've received grants from them and three years ago they asked me to join the Board that controls the whole of drug discovery for respiratory [indistinct]. And this week they have asked me to be the chair of the board that controls the whole of the discovery pipeline for GSK.

So that's my disclosure of interest, I'm a university professor at Cambridge and I work for GSK and as you'll see I've rather used my position to help you.

I've been at Cambridge for 22 years – I've been there as a graduate student – many of you will know Cambridge.

This -> is my house. Actually it's King's College Chapel seen from The Backs – the centre of communist activities in the 1930s.

This -> is the college where I'm a Fellow – St John's College; a beautiful 500 year-old college. Last year was our quincentenary anniversary and the Queen came to our garden party. We baked her a big cake. The icing was so thick that she made no headway with it at all. The Duke of Edinburgh stepped in with a dagger and broke the icing.

This -> is the famous Bridge of Sighs – you may have heard of one in Venice but this is the original. Well we think that it's the original and it's over the river Cam. And that separates the 500 year-old bit of the college from the 180 year-old bits of the college.

And as you look out of my window in college you can see people punting past under the overhanging willow. This is what we do when we're thinking wonderful thoughts about anything.

This -> where I work – Addenbrookes Hospital – a university teaching hospital associated with Cambridge.

This i-> s my cycle path into work in the morning. I'm a typical Cambridge professor on a sit-up-and-beg bike – overtaken by the lycra-clad brigade. And as you can see; beautiful fields, poppies, blue skies – I won't show you the concrete jungle which is actually the reality.

This -> is the Institute where we do our work. I'm Deputy Director of this building and because I work on Alpha-1 we have our research group set up here -> I have worked on Alpha-1 for 22 years. I am a professor in Cambrigde because of your disease. Alpha-1 has been my research career for 22 years. And that is why you are so important to me.

You are not alone. This -> is a portrait of Frédéric Chopin. You may have seen it before. It hangs in the Louvre. It was painted by his friend Eugene Delacroix. Chopin was, as you know, a pianist, a composer and a [indistinct]. He died young – at the age of 39. If you go to the textbooks or Wikipedia its bound to say that Chopin died of tuberculosis. If you look at the biographies of Chopin you will see that he was a sickly man with recurrent chest infections. His piano was pushed to the south of France to help him recuperate. If you go to Mallorca on your holidays there's a little chapel in Mallorca with lock of Chopin's hair from the time he spent there recuperating. So this I think could be your patron. Lots of people claim Chopin, lots of diseases claim Chopin but I think we have a claim because:

Here's Chopin's family history. Here is Frédéric Chopin -> – he had severe lung diseases as we know. His father -> had recurrent chest infections. His sister -> had recurrent chest infections. And his younger sister -> died vomiting blood. In my world this looks very much like -> emphysema, -> emphysema, -> emphysema and -> liver disease. Plausible, plausible and admittedly I cannot prove this and no-one will ever prove me wrong – so it's a good argument. When Chopin died he had no faith in his doctors – some of you may feel the same. So he left his body for a post-mortem. The post-mortem was carried out by Professor Jean Cruveilhier who was an anatomist at the University of Paris. Cruveilhier was a world expert on tuberculosis. He did Chopin's post-mortem. The post-mortem itself was lost in the Great Fire of Paris in 1879. But, putting the bits together, Chopin's autopsy did nothing to disclose the cause of death. Nevertheless he could not have survived with diverse pathologies, an enlarged heart, but it did not disclose pulmonary consumption (the old term for tuberculosis), lung {indistinct] for many years duration – a disease not previously encountered. And I think that we can say that it was alpha-1 antitrypsin deficiency and it wasn't encountered into 1963.

So next year will be a big celebration of the discovery of alpha-1 antitrypsin deficiency. It was discovered by two people; a clinical chemist Carl-Bertil Laurell and a student Sten Eriksson.

What he did was – he took lots of blood samples from patients, just random patients, and they separated out the proteins. You take a blood sample, put it on a gel and separate out the proteins.

Here -> is the albumen band – it's the major protein in the lung. Here's -> the alpha-1 band. They then received this sample from an individual with lung disease. They ran this on a gel and they found there is no antitrypsin here ->.

So if I did the same experiment for most of you in this room we would find that you lack this -> band. They called this, in Swedish, hypo-alpha1-antitrypsinemia. This was the first case back in 1963. Some 40, 50 years later we know that the disease is a genetic abnormality which is characterised by the substitution of one amino acid, this one here ->, by this one ->. This one -> has a negative charge and this one here -> a positive charge.

I want you think of proteins as beads on a string- like a big necklace. Each bead on that necklace and each bead on the necklace is an amino acid. In this case one of these beads has been changed – it's changed colour, it's gone from being negative to positive. And in doing so it causes the disease.

It's a genetic abnormality – you get one abnormal copy from your mum and one abnormal copy from your dad. You have two abnormal copies which is why you become alphas – it's very common – up to 1 in 1700 north European Caucasians have two abnormal copies of this bead. They are homozygotes. Heterozygotes have one abnormal copy. Alpha-1 antitrypsin levels are low because the protein stays in the liver.

So you've got two problems here. You've got protein stuck in the liver and you don't have enough in the circulation – this should look familiar to you.

When I started 22 years ago it struck me that the lung disease is quite difficult – you've got a lot of factors going on. So in order to understand the disease I, as a chest physician, needed to understand the liver – this was outside my comfort zone.

This -> is the liver disease of alpha-1 antitrypsin deficiency. This is the liver of a 4 year-old boy transplanted at Addenbrookes. It was one of the one of the first liver transplants ever done. It was done by Professor Sir Roy Calne in Cambridge.

In those days this would just be a bit of dead liver – of no use because a new liver was going in – it was of no use to anyone – it was heading for the bin. I collected it just before it hit the bin and took it back to the lab.

Twenty-two years ago I could do that. Twenty-two years ago there was no problem at all: it was just a bit of dead liver that no-one wanted. Now, to do that, I would have to complete a 65 page ethics application and give you a 15 page booklet and you would have to give me consent to do it. You can decide if that's a better world or not – but that's the world we live in now.

This -> is an adult liver for comparison. This -> liver is pretty grotty - you can see the nodules here ->. It's lumpy and you can see bits of fibrosis. It's a fibrotic, scarred, cirrhotic liver. It's a young lad with and end-stage liver from alpha-1 antitrypsin deficiency.

So then I chopped this liver up. You can see the proteins, the abnormal beads on the string, accumulating in the liver cells – and here's -> the abnormal protein in the cell. It's enlarging the cell. The cell gets larger and larger and then dies because of all the protein accumulated in it. This was known.

What I did as a graduate student was to purify the protein from a liver and show that it wasn't just random material (which it was thought to be) but it was made of polymers. This was really important because the thing which defines your disease is polymers. This was my PhD – I showed that in your disease this genetic abnormality caused the protein to form chains of polymers.

I've explained that in science terms now I'll explain it in simple terms – because you need to understand this – this is a disease of polymers.

If you go back to 1992 I published that paper in Nature. Until recently the only way we could detect these polymers was by taking liver and isolating them out and showing that they were there. More recently we have a marker – we have an antibody – it is a very specific marker – it works beautifully – we can see these polymers in cells.

This -> is a normal liver and this -> is a liver like most of you in this room. It is stained to show the polymers – the liver will go brown and that shows that that polymers are in your livers. So we have a

beautiful tool, a beautiful resource to be able to detect the abnormal polymers. So now on to the next level – we need to know how these polymers form.

So then we then solved the crystal structure of what the protein looked like – we worked out what the single bead on the string looked like. And then, as the beads formed we showed that they linked together to form chains of polymers.

So we have crystal structure of chains of polymers that get stuck in your liver – it doesn't get out of the liver and you get the deficiency and emphysema. We now know how all these molecules link together to for this chain or necklace of polymers that stuck in the liver cells. I'll show you a little video.

Here -> are the molecules – you see them linking together – one onto the next. And this is happening in every one of your livers, causing the protein accumulation and the deficiency. OK, so that's hard core science as in the high profile journals.

Let me give you an analogy. Alpha-1 antitrypsin functions like a mousetrap and its job is to snap up toxic enzymes that are in the body. That's how it normally functions. The mutation changes this residue here -> from a negative to a positive – so your mousetrap is unstable. When you have unstable mousetraps forming in the liver they all fire at once – and that's the process. Very simplistically what's happening in your liver is the formation of polymers because the mousetraps fire and form the chains. We now know that these mousetraps map onto the chains of polymers.

I'm going to pause there and see if any of you have any questions.

[Question] What is the percentage of people with alpha-1 that have to have liver transplants?

It is the second commonest cause of liver transplants in children in this country.

[Question] How about adults?

It is less common but you've got alcohol – children don't drink – adults do drink a bit more. Alcohol is a major factor.

[Question] Could we not now test Chopin's hair?

Yes, Good question. That depends on if you have a root. You need the root of the hair to get the DNA. If you just have the end bit that the barbers takes off, no. You need the root. His heart is actually buried in Paris so if we could get an act of parliament from the French government . . . [AHJ. Can I come in on that one? I have heard that the real reason that no genetic studies have been done is that the are squabbling over who gets the money for it.] There you go. It's a better story and it's probably better that we don't know – if we do know we might be wrong.

[Question] Some people get liver disease and some people don't. If it originates in the liver have you any idea why some people get the liver disease and some people get the lung problems?

Everybody gets this accumulation – everybody with two abnormal copies of the gene gets these polymers and there will be a second factor which brings on the risk of liver disease. In children it will be secondary

Genetic factors – things that they are born with – these we don't altogether understand. In adults it will be alcohol, being overweight and having abnormal genes. So it's a mixture of things.

[Question] My brother was tested for nephritis at just 8. I was diagnosed at 13 with alpha1. Neither of us had any liver issues.

Most people will show abnormal blood tests but have no liver problems. Very few of those with abnormal blood tests will progress to liver disease – and this is quite common.

[Question] You're talking about polymers accumulating in the liver – is this progressive as you get older.

That's a really good question and the answer is we don't know. To answer that we'd have to take biopsies sequentially – and ethically that's a bit tricky. But it's a really good question. Simplistically, I think kids livers aren't as good at metabolising polymers so kids are more at risk of getting liver disease. There are other factors later on – fat and alcohol, things like that.

[Question] Is there any possibility of the gall bladder being affected by changes in the liver? My sister had her gall bladder removed at a very young age.

No. Not that I'm aware of. Gall stones are common – being young is strange I'll agree with you there but gall stones are quite common.

[Question] My son was quite ill as a baby but now he's well. Is there any evidence to say that he's more likely to get liver disease than other adults?

Good question there. No – not really. They get through it in childhood and then seem to be OK. One of the problems is that we don't have enough evidence. There are 129 people being followed up in Sweden – that's the best epidemiological study that we have. I can't really answer the question but my feeling is 'probably not'.

Now for the lung disease.

Many of you will have seen this -> type of x-ray. I'll show you what emphysema is. This -> is the heart, this -> is the right lung and this -> is the left lung. When you see this it is often back to front – so heart, right lung , left lung -> -> ->. In alpha-1 antitrypsin deficiency the emphysema targets the bottom of the lungs. So normally people who smoke get emphysema at the top of the lungs. If you've got alpha-1 antitrypsin deficiency it tends to be the bottom of the lungs – not exclusively but it tends to be the bottom of the lungs. What I want to show you on the x-ray is this -> is grey and this -> is black. This is because the bottom of the lungs is destroyed by emphysema.

Many of you will have had CT scans. I'll show you what emphysema looks like on a CT scan. This is from someone without alpha-1 antitrypsin deficiency, this is a normal smoker. CT scans are a very good way of getting details of what goes on inside the lungs. We start at the top of the lungs – this is the windpipe, the trochea, you will see it dividing as we go further down – there's -> the heart, this -> is the spine. What I want to show you is that the bottom of the lungs are fairly grey – black at the top and it becomes more and more grey – grey is normal the black is emphysema.

Now for people with alpha-1 it tends to be worse at the bottom rather than at the top – that is one of the signatures of alpha-1 antitrypsin deficiency and that makes doctors say, when they look at an x-ray 'Oh I wonder if that's alpha-1 antitrypsin deficiency? – the emphysema is in the wrong place – bottom rather than top'.

What I've done there is to slice you from top to bottom – salami'd you that way. Now I'll salami you this way – from front to back. You'll see on this -> image that the top of the lungs are black and the bottom of the lungs are grey. This is not alpha-1 this is you bog-standard emphysema that smokers get. You are very special when you get emphysema at the bottom rather than at the top. As a chest doctor that's what we recognise.

This is a normal lung here but in alpha-1, because you don't have an important inhibitor in the lungs (those mousetraps) that mop up all the toxins in the lung – then the lung is destroyed – you get emphysema. As you can see with this lung here -> compared to that lung there ->.

In my clinical practice I explain this to my patient . . . do you remember bars or Aero? I say that the lung is like a bar of Aero with lots of bubbles in. What happens with emphysema is the bubbles get bigger and bigger until they all join together – and that's pretty hopeless for getting oxygen in and getting carbon dioxide out. That's my normal way of describing emphysema.

Let me give you another analogy. The job of this protein – the job of this mousetrap – is to protect the lungs. Here is the map of the lungs – or the United States. It just happens to look like the United States – it wasn't designed like that. And the United States as we know is under attack – these -> are neutrophils, these are white cells which carry enzymes into the lung. But the United States has Homeland Security. Homeland Security is antitrypsin. The white cells that carry enzymes come into the lungs and the protection against the protection against the enzymes that are released are the mousetraps. Very simply for people in this room there is not enough homeland security. There are rather too many cells that release enzymes and the lungs dissolve to give emphysema. Very simply that's what it looks like.

Remember that for me this disease is a disease of polymers. You have polymers in your liver and what we showed was that you also get polymers in your lungs. As well as having not enough material you've got polymers in these lungs. There's -> the white cells – the boulders attacking the United States – the brown staining in the background are polymers. This is you lung, the lining of

your lung, you can see the meteors next to the polymers ->. You can see that they may interact. It's not a bad analogy – they look a bit like meteors. When you put polymers with them they get angry; they get activated and they release all the toxic enzymes.

If you do washings from your lungs – and some people will have contributed to these studies – if we take washings from people with antitrypsin deficiency – you have more of these inflammatory meteors in your lungs, cells called neutrophils than people with normal emphysema.

So. Here's my model, it's all about models. This is not to scale. This -> is your blood, here's -> a white cell and this here -> represents that -> [indistinct]. There's a bit of a scale problem here.

If you smoke – and it's usually smoking, not always, but usually smoking – then you set up inflammation in the lung. This is the lung surface here -> and the blood cells have to go from the circulation throught into the lung space. And as they march though, normally in response to cigarette smoke (in alpha-1 people – you lot) the polymers in the lung, the white cells are trapped in the lungs and they release their enzymes and cause tissue damage.

This is a new idea. You will have all been familiar with the idea that there's not enough protein and therefore you get emphysema – that's what you'll read about and that's true. But I'm giving you a second idea here base on the fact that you have polymers.

So this is our model of your lung disease – it's different from what you'll read. It's growing in status – we presented this in about 2005 and now, 6 – 7 years on it's gaining in popularity. I.e. other people now agree with us. In science you put an idea forward, but it's only when other people reproduce it that the community will believe it.

So antitrypsin is stuck in your liver as polymers; there's a deficiency; not enough of this key protein and hence emphysema. But the protein in the lung, the alpha-1 antitrypsin , the mousetrap, can also polymerise – probably driven by smoking. When the mousetraps fire they don't work properly. They're also inflammatory so they recruit more of the meteors into the lungs. This makes it worse.

You've got two signals. One, not enough protein and, Two, these inflammatory mousetraps. And of course if you add smoking into all of this it gets worse.

Now let me give you another analogy. Normally when you smoke the antitrypsin is there as the extinguisher – it normally puts out the fire caused by cigarette smoke. If you have antitrypsin deficiency that antitrypsin that does rush in can change shape and form these polymers. These polymers cause more inflammation. SO you are pouring lighter fuel onto the fire. That's why when **you** smoke you get more disease and more emphysema than someone who doesn't have this condition.

You can use whichever of these analogies that you want to take home. Mousetraps, pictures of devils, lighter fuel . . . The idea is that the lung disease is just more than a deficiency. We came up with this idea – it's not entirely accepted but it's growing in popularity – that the polymers themselves cause part of the lung damage.

I'm going to pause there and ask about the emphysema.

[Question] How does this affect the lungs of non-smokers.

If you don't smoke:-

What I'' see in my clinical practice is someone in theie 50s or 60s for the first time being slightly breathless – more than someone of their own age group. When I do the x-ray it will be essentially normal, I may see a bit of emphysema. When I do lung function test it'll show that the diffusion of how much air gets in is down. That is my classic presentation of a non-smoking Alpha.

Now that's not always the case because there are examples . . . I stood in front of an American group and said 'largely smoking related' and someone put up his hand and said 'I've got emphysema at 40 and I've never smoked.' So I have to be slightly cautious – but that's the general picture. Other than that it usually has something to do with smoking or occupational disease.

[Question] Does infection have a part to play in that – bringing on the inflammatory response?

A really good question and the answer is, we don't know, because not enough of you have been followed up for a long time. There's not the evidence for that. But, intuitively, you are right. If you get more infections, you get more inflammation, more polymers and therefore you get more

destruction. Certainly, my Alphas say 'I've had an infection but I've not got back to where I was before.' That sort of fits. But if you say to me 'where's the data' – then I'm hand-waving. I do a lot of hand-waving!

[Question] Is that something to do with the antibiotics that are available? They never quite get rid of of the infection as a short course rather than one designed to eliminate it.

Good question. Let me alter that slightly and say that antibiotics are probably quite good at killing off the infections in most people but what they don't do is dampen down the inflammation. So I'm going to separate the infection from the inflammation.

What you may do is dampen down the infection but the inflammation is still there which is why you still feel rough, cough up sputum and why you go back again.

[Question] That's why it affects you for month after month.

Well it may not be. You're absolutely right there are times when it takes ages to get rid of an infection. But often we can get rid of the infection but it's the ongoing background inflammation that causes the problem. I'm going to separate the two out.

The infection we can treat with antibiotics and we can eradicate in many people but what we don't do is dampen down the inflammation. You may get cycles of this. Infection is usually driven by an organism: inflammation is the sort of thing you get when you put a chemical on your hand – if you spill bleach on your hand you'd get inflammation – a hot, red, swollen area.

[Question] Is that when steroids would come in – to handle the inflammation?

Possibly, possibly. They're not great but that is exactly right. Steroids may dampen down the inflammation.

[Question] My doctor put me on steroid in order that when the antibiotics started working . . .

Exactly right – we would often use steroids and antibiotics together.

[Question] Can the steroids affect the polymers?

Good question. Not so far as we are aware, but we don't have enough data to answer the question.

[Question] The diagrams and the metaphors that you've been using to explain the neutrophils and the attackes etc . . . how does that fit in with the inflammation?

They are the inflammation. The neutrophils is/are the inflammation.

[Question] [cont'd] So the neutrophil is both the infection and the inflammation.

No. The infection is an organism, a bug, but the neutrophil is the inflammation.

[Question] [cont'd] So the neutrophil is reacting to the bug and the neutrophil is causing the inflammation.

[Question] You mentioned at the beginning the difference between how COPD exhibits and how alpha emphysema exhibits. Are there any practical differences in the way our COPD works compared to a smoker's COPD? Likewise are there any treatments that can target the bottom of the lungs?

Let me answer a different question then I'll answer a different one if I may. In the world of Lomas this is a disease of polymers and the polymers in the lung may be inflammatory. We know that in any individual the bottom of the lung gets more blood than the top of the lung. So if the polymers are really and truly driving this, and this is a big if, we're in a different world here – there may be more polymers at the bottom and more disease. I vote everything about your disease on polymers.

Are the diseases different? Yes they are. If we do gene studies on your lungs compared with a smoker's with emphysema they look very different. So there's a different process going on in the two cases. There are shared features, yes, but there are differences between the two. Can we target the bottom of the lung? No – we can target the process.

[Question] What are your views on long term antibiotics? I was on a course for three months then a different one for the next three months . . .

That's what I do when I'm desperate. We do that because we're drawn into it. What will happen is that you'll put popel on a course of antibiotics to treat the infection then they come back with more infections and then . . . actually we're stuck. I don't want to give you lots of steroids so what I do is

put you on long-term antibiotics. I use doxycycline, tetracycline, sometimes amoxicillin, and I put them on it for long terms. And I normally explain it's a look and see. We'll see whether it makes any difference or not. The idea is that you dampen down the infection and the inflammation – some antibiotics have an affect on inflammation. I guess that your doctor is trying to dampen down the inflammation.

[Question] Is there any relationship between asthma and bronchiectasis in children?

No. I said that with great confidence didn't I. I don't think so. Asthma is common remember. In some people with asthma they can progress to small airway disease, this is definitely true. Most asthmatics don't. Most asthmatics just get better and the asthma burns out. Sometimes it can come back in adolescence. We can't pick the people that will progress and those that won't. No relation with alpha-1 – it's a different process.

I used to chair the Asthma UK Grants Committee for four years and that is one of the big research questions – and it's a nightmare!

[Question] Why is there no place for inhaled steroids in alpha-1 if you need to damp down the inflammation.

How about if the inflammation is resistant to steroids? Steroid-resistant inflammation. In the big studies it's difficult to prove that they work. In reality we don't have very much to say, that what we do will be of benefit. What we end up doing is being pragmatic and that's why you'll see chopping and changing – let's try this – let's try that. And there's no real guidelines, because inr elaity we don't have things that clearly work. They work for some people and not for others.

[Question] Could MZs have liver problems?

Yes they do. The MZs get liver disease if there are other factors – there are usually other factors. My liver colleagues in Cambridge – there's a big transplant centre there – believe that its a risk factor but there are other factors as well.

And I can tell you from our big genetic studies that if you are a heterozygote, ie MZ, and you smoke you are more likely to get emphysema than an MM. Buts it's nowhere near as bad as if you're a ZZ.

[Question] [contd] I've never smoked.

If you're a heterozygote and you've never smoked then you'll probably be absolutely fine.

[Question] I've got asthma and emphysema and I've noticed that I don't get a lot of infections but people with bronchiectasis and emphysema seem to get more.

Yes. That's correct. I can tell you that from Quality of Life surveys that people who produce sputum – people with alpha-1 who produce sputum – tend to have a worse quality of life than people who do not.

[Question] Where does bronchiectasis fit in?

When you have CT scans done we often see that airways are bigger than they should be. I describe the lungs like a tree that's turned upside down. The alveoli are the leaves and the bronchi the twigs. The twigs are dilated and that causes increased sputum and increased infection.

If I give you a label of bronchiectasis I'll often say to your GP 'and can we treat with amoxicillin (assuming not allergic) for two weeks – not 5 or 7 days'. I'll give you a two week course.

[Question] [contd] Can you send a letter out to GPs about this. [laughter]

My wife is a GP and I wouldn't be that brave.

And now the next section and why I think you've got it.

Why does 4% of people in this country have an abnormal alpha gene? Why about 1 in 17000 of this population have two abnormal genes. Why am I special?

Bob Brantly – a friend of mine and some of you may have seen or communicated with him in the United States – used to tell his alpha-1 patients that people who carry the Z gene are more intelligent!. There is no evidence – no evidence at all. Then there is the story that people with the Z gene have more children; they are more fertile. Not much evidence for that either.

So in 2006 I came up with a hypothesis (it's in the big respiratory journals in the United States) and its under the heading 'Hypothesis'. Hypothesis means 'I can make it up!' At the bottom of the paper is 'what I need to do to prove this.' That's normal – we have more questions than we have data. So this is my guess.

This is what I think. Your Z gene arose about 2000 years ago from the Vikings. We can trace it back about 2000 years and it probably arose in northern Germany and was then transferred to Scandinavia where it is particularly prevalent and it came to us via the Vikings. As the Vikings invaded the United Kingdom they brought this genetic disease with them – as they raped, pillaged and plundered the good lady-folk of years gone by. So the gene is a gene that you can map by Viking migration. In our country and northern Europe. Less common in southern Europe and its also prevalent in America – it got to America because of mass migration. You can use the Z gene to track population movements. So why is a gene that arose 2000 years ago in this fearsome group of individuals?

This -> is Sten Eriksson who was the first person who described this – he is Swedish and therefore must be a Viking. [Viking helmet appears – laughter] This -> is John Walsh and must also be a Viking. And if you look closely at John – I've know John for many years – and if you think about the old Viking picture there's a sort of resemblance . . . [Viking helmet appears – laughter]

It means that everyone in this room must have Viking genes – we all have some Viking origin. So why – why have you got this gene. This is my idea – and it's back to polymers. Remember polymers get stuck in the liver, cause disease in the lung. This is the Lomas view – no-one in the world has a more polymer-centric view of this disease than me. But they're catching up – they're slowly catching up!

If you back a hundred years the things that killed people were pneumonia and gastroenteritis and they killed children. If you trace your family tree when you get back a hundred years they are horrible – big families with lots of deaths in childhood. In some parts of Africa they didn't give their children names until they were five because infant mortality was so high. Death in childhood is a major problem and it's usually because of infectious disease.

When you get an infection, say pneumonia, you will know that your temperature goes up and antitrypsin rushes into the lungs. It rushes into the site where the inflammation is. Becasue you have an unstable mousetrap then you form polymers – you form polymers in your lung and you form polymers in your gut – depending on the type of inflammation. I've told you before that polymers cause inflammation, make inflammation worse, and in years gone by that would have been good. If you had pneumonia and you had more inflammation in your lungs to respond to the pneumonia that was probably good. You could clear the pneumonia and you would live. SO my view is that the gene that you have is a protective gene. It's been around for 2000 years probably because people have lived longer after infection. However, a hundred years ago, people started to smoke – and antibiotics started to arrive so we could treat infections very well. So what happened then was very different, the cigarette smoke causes inflammation in the lungs, the polymers form in the lungs and make it an awful lot worse, you get more inflammation and you get emphysema. So what was once good – a good gene to keep you alive – is now bad because we've got antibiotics to treat the infection and smoking drives the inflammation.

I'm going to pause there for my third set of questions.

[Question] My question is a fairly general one. You've got the two main effects of the antitrypsin on the lungs and the liver – is there any other works being done on any other systems?

Yes. Good question. We know that alphas are more at risk of inflammation of the kidneys, inflammation of the skin and maybe increased risk of inflammation of the joints. And to go back to the Lomas view of the world, it's all about polymers, we can find polymers in those tissues. To my mind it's polymers that drive that inflammation and cause the disease. Other people have published on that so I'm no longer on my own in that territory.

[Question] So if I don't smoke and I don't have antibiotics and I don't go into aggressive air environments, dust and so on, am I going to go back a hundred years to my living standards?

Sort of . . . If you don't smoke and you have no dust then, probably, probably you'll be OK . . .

[Question] [contd] – I was talking about the antibiotics . . .

No No. The antibiotics are good. The point was that in the olden days it was the inflammation that kept you alive; nowadays it's the antibiotics that keep you alive. You don't need the inflammation – the excessive inflammation. Now, that inflammation causes disease. So you don't have to go back to mud huts . . .

[Question] How exactly does the inflammation keep you alive?

Let's say that you have pneumonia what you want is a brisk inflammatory response. If you've got these bugs invading your lungs you want the body to mount an aggressive response. It's a bit like if you have a spot – remember when you were a teenager and you had spots. When you had a boil - that's a huge response to a bit of infection that the body mounts. I know that's a bit unsightly but if you imagine that inside the lungs that inflammatory response is really good because it kills the bacteria. And the same happens with the gut and gastroenteritis.

[Question] You lose weight, you don't smoke; what good is exercise to you?

Tremendous. Exercise is great. I've just taken on a new job. I chair an MRC panel, a Government panel, giving out research grants for all topics and one of the key things that has come out of MRC research is that exercise is probably the most important thing. My mother is 75 and when I see her I say 'Mum, mum, you've got to lose weight and exercise'; so the poor old dear is doing yoga and . . [laughter] and she tells me that she's walked an extra ten paces every day. But its exercise and losing weight – they're the two most important things.

[Question] You were talking about antibiotics as if they were bad and now you're saying they're good.

No, antibiotics are good they take over a job that years ago was done by inflammation.

[Question] [contd]Could you not just raise your temperature so that you kills off the bugs?

Yes. A hundred years ago that's exactly what happened. Now that's bad – the antibiotics will do it for you.

[Question] [contd] But surely long-term antibiotics are bad?

Not really. They may be good. They may actually keep the bugs at bay – keep the inflammation down. So the antibiotics are trying to suppress any infection and keep the inflammation down. It's a bit like collateral damage. So you get inflammation which is trying to fight infection and it's the collateral damage that causes damage to the lungs.

[Question] Earlier you mentioned sputum and the worse quality of life – sputum producers versus non-producers.

Ah – not the quantity. AS you know we score them; a teaspoon full, an eggcup full, a teacup full, a bucket full [laughter]

[Question] [contd] When I was younger I did not produce much sputum at all but now I have more lung problems and it has increased. Is that what everybody gets?

Well – it's highly variable actually. So if I ask a patient, and alpha-1 patient, do you produce sputum they will often say 'none at all'. But some will report sputum. It tends to be the sputum producers that report more problems.

[Question] [contd] and what would classify as a sputum producer?

Do you cough up any phlegm?

[Question] [contd] Any at all?

Yes

[Question] [contd] Ever?

Well not ever because you can have a cold. It's normally when it's every day. It's just implying that there's something going on in the background – that there's some ongoing inflammation.

[Question] What is your stand on mucolytics? I'm on Mucidin (acetylcysteine) [name not identified – Professor Lomas changed this to the brand Carbocisteine]

I've just done a little stint on the wards and every time i see a patient the duty doctor has put them on Carbocisteine. Carbocisteine would be a typical mucolytic. And I say that there's no evidence that they work.

[Question] [contd] I don't bring sputum up.

The idea is it's meant to help you bring sputum up – that they make it looser. I say that it doesn't work and all the junior doctors put them on it because it's all we've got.

[Question] [contd] So I've been taking it for eight years and it's a waste of time. [laughter]

In my view. But some would say . . . [audience discussion] and you could say they've changed my life [laughter] and that would put me in an awful lot of trouble. I would say that the evidence isn't great. But as ever with this disease I would say that if it's of any use to you then that's fine. I can sit on my moral high ground as a scientist but in reality it's patients that matter. Back to the junior doctors – they book it down and I cross it off. [laughter]

[Question] Does physiotherapy be of any assistance?

Ah a really good question. I think breathing exercises can. The way that you breath can help and also with sputum. For some people huffing and puffing exercises can help.

[Question] I suffer from panniculitis and I'm relay interested in the concept of polymers and what actually happens when I have a lesion. [indistinct] I can imagine now that I've got polymers in my fat cells and they're ready to flare up at any time. [indistinct] [requests for the professor to clarify the question]

Sometimes people with alpha-1 antitrypsin deficiency, Alphas, will get painful swollen nodules in their skin, often in the thigh and in the lower leg. Does that sound familiar? And it's usually inflammation in the fat – we call that panniculitis – but if you biopsy that there's lots of these neutrophils, lots of these white cells in the skin. And someone has reported, it wasn't us, that you can find polymers there as well. And the question is are the polymers driving that or is it just the lack of antitrypsin itself may be sufficient. And that is the one condition where there is the clearest evidence for the use of antitrypsin replacement therapy. I wrote the textbook for the country and that's the only time – I wrote that there is good anecdotal evidence that replacement therapy works in that condition.

[Question] I've had it once last year [indistinct]

That's the only time when I say it may be effective. It's anecdotal but I think that the data is quite good.

[Question] I have one of our mums here and she has three ones and one of them has panniculitis. What about augmentation therapy for little ones.

I've got three little ones. Isn't that interesting? Well you can . . .

[Question] [contd by the mother] She was treated last year [Professor Lomas: Did they put her on Dapsone?] They didn't put her on anything.

I don't do p's. I don't do little ones. So maybe I'm out of my depth – may want to take what I say with a pinch of salt because the paediatricians will say you're talking rubbish – and that may be the case. Dapsone is the standard treatment I think. And if fails to respond then – then replacement therapy may be effective. But I'm down to anecdote – when I reviewed the cases there is enough data there – but I suspect they will go for standard treatment first. It's sometimes called Weber-Christian disease – that's a posh name for it. If you want a posh name then Weber-Christian disease sounds a bit better than panniculitis.

[Question] Can an MZ get panniculitis?

Not seen it. Usually it's ZZ's. But there's always someone who says 'I've got it'

We've had a go a livers, we've had a go at livers and we've had a go at Vikings. Now I want to move on to therapy.

This will polarise views. Some people are very pro and some people are very anti. I'm known as a sceptic. And the reason why I'm a sceptic is that in the UK system, which is a managed health care system, in order to get things onto the formulary you have the have clinical trials. You have to show

that giving this is better than giving nothing at all in an outcome that means something to a patient. And so that's never been proven in trials and consequently it's not licensed in the UK.

Before I did soem work for GSK and I used to sit on a Government regulatory authority for new drugs – called the MHRA. We never saw Prolastin but I know that sort of process and that's the sort of thing they're looking for. They're looking for hard evidence.

Now in the US you'll find people on Prolastin, in Europe you'll find people in Prolastin. Overall my view is that it probably does work – but what I can't tell you is who it works in – how often you have to take it. That's because you haven't had a study showing benefit. My view. We can debate that.

[Question] I've been on therapy for nine years and it has saved my life.

Yes people have that view and in the US they'll have that view as well. But what the Government would see, or the regulatory authorities would see – well, they would take a broader view. They would say 'show me the data'.

[Question] Would they take any notice of statistics from countries that are using it now?

You can make various arguments based on registries – but they're always biased. What I mean by bias is that different types of people will have it (treatment) and so you don't have matching populations to see what happens. That's the gold standard that we look for. I sense that we're going into a Prolastin debate which was something that I was hoping to avoid.

[Question] There have been tests done with the tomography scales to show that it does stave off the effects of alpha-1. [Other speakers explain that the reference was to CT scans.]

Yes they have shown that there is a lack of progression – reduced progression. Again it's statistics – what we say is it more likely than flipping a coin 20 times to get that result – that's the way we do it.

I genuinely feel that it has some benefit but I don't know the cost-benefit or the risk-benefit. But I'm known as a sceptic. On the polymer spectrum here's me [gesture] and everyone else [gesture]. On replacement therapy there are the real enthusiasts [hand to the right] who'll tell you that it works and there are the real negatives [hand to the left] and I'm here [middle]. It doesn't mean I'm right.

I chair the American Alpha One grants committee and round that table virtually everyone else is a believer – there are a few sceptics with me.

[Question] My question is more about the process than whether it is good. Am I right in thinking that it is not just a case of the MHRA or the NHS or whoever decides that 'this drug will come in' or 'we don't want it'. It's actually because the drug companies themselves believe 'we can't prove it so we're not going to push it forward for licensing because we haven't got a strong enough case - and we know that we'd lose.'

I don't know. I couldn't possible comment. [laughter] Within your community there will be powerful advocates – but you should also see the negative view. It's not proven – that's where I am,

[Question] [contd] My fear is that everyone thinks that it's down to the MHRA, it's down to the NHS; at the end of the day it's a business decision by the drug companies.

It's down to data. If you come up with a new cancer drug that makes us live another three months or another six weeks – which is nonsense – a huge amount of money for a really trivial effect – it will be licensed because you've shown it in a clinical trial.

[Question] Just a statement rather than a question. One of the things that you said was that we have to show that it's better than nothing at all – but from our perspective, surely, something is better than nothing.

You may be right – except that it's a lot of money and the Government would look at the health economics situation. It's a managed pot of money. Would you rather use the £100,000 or whatever it is for replacement therapy for one year or would you rather use it for 5 hip replacements to get old ladies out of bed. That's the question we're being asked to address. And there is no doubt that hip-replacements have a phenomenal lif-transforming effect.

[Question] [contd] Ask a hip replacement person and she's going to say yes.

No – it's as a community. I'm not trying to be antagonistic but if you put yourself in the place of the Government that's the kind of calculation you're trying to do.

To move on – I want to move on to the exciting bit.

Strategies to stop polymers – because that's what it's all about. Can we stop the polymers forming in the liver. I want to show you three strategies.

Since we describe polymers 20 years ago it has been my plan to block them forming because if we can do that we can treat this disease.

This -> is your protein and I want to show you a little movie here -> here it is nicely folded up and what your mutation does is open it up. And there's another one here -> and they join and these mousetraps extend . . . forming chains of polymers. If you look at the process ther's a lot of movement in this -> part of the molecule. I want to see if I can stop this movement – if I can stop this protein opening I can stop a single bead forming on the necklace. Then we will cure your disease. Very simply that's been my strategy – can I stop this process, can I cure your disease?

Here's -> the big cavity. In 2006-7 I wanted to put a small molecule in the cavity to stop the chains – a drug to stop the protein increasing in size and linking together to form the polymer.

We couldn't see this cavity with any great clarity. We had our crystal structures but we couldn't see the detail. When you were at school you had supersaturated solutions of copper sulphate and you put a bit of fluff in it and the crystals would grow. That's what protein crystals are like. We would take a solution of antitrypsin, supersaturate it and – it's usually men with beards that do this, a bit of fluff breaks of and – and (it's not terribly scientific) around all the fluff the crystals will form.

We couldn't get good crystals because we grow them on Earth and the gravity causes currents, called micro-currents. To overcome this we sent your protein up on the European space shuttle. This was back, oh it must have been ten/fifteen years ago. We got a grant for this from the European Space Agency who wanted to do this because they want to show that doing science in space was good. We got some crystallisation chambers. The astronauts took the containers into Space and they opened the chambers and the protein comes into contact with the fluff (if you like). The crystals form, the astronauts come back to Earth and we collect the crystals and we take them back to Cambridge. Now this was funded by the European Space Agency who were trying to show that doing science in Space was worthwhile. We also left some crystals back here at base station because we wanted to compare the two. The ones that came from Space were sort of OK but nothing special. The ones left behind were fantastic. [laughter] This -> is what they look like. From these we now could really see this cavity with real clarity. We could see the target that we were going after. We wanted to put a small molecule in this cavity.

I went round the pharma companies and said 'I've got this terrific idea – small molecules are the cure for this disease - - -.' And they said 'Yes, David. Yes, David – great science, great story, lovely models but too difficult for us.'

Undaunted I teamed up with a group at Scripps – the Scripps Institute on the West Coast, a famous research institute. We screened, on a computer, 1.2 million compounds. We went through a computer library (of molecules) and looked to see which ones would fit into this cavity and we found 68 that would potentially fit into the cavity that we were interested in. This is pioneering stuff – no-one had ever used small molecules before. We bought the 68 compounds from a commercial library – this is not high-tech.

We got them back in Cambridge and gave one of my medical fellows the job of naming the compounds and seeing whether they worked. This lad grew up in London, he support Arsenal and he knew nothing about medicinal chemistry, or indeed, science but he was doing his PhD at the time on a Government Training Grant. He named the 68 compounds after the only thing in the World that he was familiar with – a map of the London Underground. So he named each compound after a tube station on the London Underground. He named each derivative after monument next to a tube station on the London Underground. He named each derivative of a derivative after a road next to a monument next to a tube station on the London Underground. This is the Gospel truth. For 18 months my lab meetings featured this wretched map.

When patients come to clinic we take their plasma, we take their blood, and we purify the antitrypsin and it looks like this -> on a gel. This is mutant protein from my patients. We take lots of patients and we pool everything, so I can't tell you who this belongs to.

We then heat it to 37 degrees – body temperature - and it forms these -> polymers. Se that -> ladder – that's polymers. I want to show you that the lead compound turned these polymers into this ->. So we abolished that ladder. CG stands for Covent Garden. When this lad left Cambridge after three years we bought him a picture of Covent Garden - [laughter]

So this is the start of the cure. Ultimately, turning this -> into this -> will be the cure.

These are not molecules we would give to anyone. Scientists would never give drugs to anyone – but we've proved a principle - that it works.

We took Convent Garden and stuck it into the big pocket in antitrypsin. We then rescreened another 1.2 million compounds and came up with other hits. I want to show you some of the other names (this could be a pub quiz) – to help you CG – Covent Garden and the others LA (Long Acre), ENO (English National Opera), MS (Monmouth Street), SD (Seven Dials), TR (Theatre Royal) & WH (Westminster Hall). If you go to our paper, the journal is actually a real journal, you will find all the studies are published and all those -> letters are shown on the structures.. We we got it accepted by the editor, the editor said 'can you change all those letters?' We said 'Noooo'. We'd lived with those letters for 18 months and they're staying in the manuscript. Very few people know that ENO stands for English National Opera – many think that it's a heinously complex name.

This, one day, will be the cure.

What I've done now is to persuade GSK to buy into this. I've shamelessly abused my position – sitting on the board and now chairing the board – to persuade them to buy into this. I now have a major pharmaceutical company backing what I'm trying to do – because one day it will be cured and a small molecule will be involved. It may not be by the company I'm working with – it may be a whole variety of different companies – and the more of us that are doing it the more likely it is to [indistinct]. That's my view and that's always been my view.

My colleagues at GSK say that drug discovery is a bit like walking over alligators. Remamber the old James Bond film? James Bond runs from one bank of the river to the other bank by walking on alligators. He said that's what it's like - if the first alligator doesn't get you the second one will. Which means we start the programme and if the first one works that's terrific but it may fall down at any stage – we have an awful long way to go.

This is what the I think the cure will look like. I'm going to tell you some terrific science in a minute but ultimately my belief is that this will be the cure – and my plan is to get that done before I retire.

[Question] How old are you?

Guess! I am now 50 as of this year – an astonishing age! And in Cambridge professors retire at 67.

[Question] [contd] So we've got 17 years.

I showed the same slides to the Americans last year and they asked the same question. My point is that I don't know if I'll make it because drug discovery is a difficult game and we may not get there – and it may not be us. But what we've done is lay down the platform. We need to engage with major companies. If I were to make a drug you should never take it- I don't do that – I do clinical science. We need to engage with major pharmaceutical companies – and there are other biotech companies as well and other pharma companies that have their own programmes.

So for me alpha-1 which has always been a slightly orphan disease is even now more and more important. There are now different companies who are interested in this disease

[Question] What about GSK?

It is now seen as something which is worth a go.

[Question] Is this because the number of people suffering from alpha-1 are becoming greater.

It's because discovery is getting better – we now have tools. My job is to lower the bar so that the pharma would engage.

The people in the pharmas look at the small molecules and say 'They're horrible, David – they'll cause cancer – you would never give them to anybody – they are poisonous.' They are a starting point – they work in the test tube but after other people work on them.

We've characterised the polymers, we've found the crystal structure, we've found a blocking molecule – all these things mean that we have an opportunity – better than we were ten years ago.

[Question] Why will stopping polymers forming benefit my lungs?

One, by stopping the polymers forming we protect the liver. The second step is if we can stop the polymers and get them out of the liver as normal functioning protein - - -

[Question] [contd] Did you know that it's normal functioning protein?

We didn't know. I'm giving you a dream – I'm presenting you with a vision. It's important to see where it's going. People are now trying to get a small molecule that will get it out of the liver, that will function and that will protect the lungs. If you believe that my idea that polymers in the lungs are important and suddenly there are no polymers the lungs are better. There are a lot of acts of faith here.

[Question] [contd] Because you are stopping the polymers on both the lungs and the liver.

And I'm increasing the level of antitrypsin in the circulation. If it works.

The reason why I've had Government funding for many years is to do the science of alpha-1 – to do the science of alpha-1 – to work out the principles – but drug discovery will be done by industry. I's absolutely critical to work with industry to do that – which is why I put my declaration of interest at the start so that you can see where I'm coming from. But as I said earlier I have rather shamelessly used my position to influence them.

[Question] We're looking for a marble to fit in the hole – how does this compare or is it similar to other research with peptides, s4A strands - - -

Yes. Good lad – you've been reading my papers. Yes we did all of those - we showed that peptides block polymerisation – but it kills the molecule – again terrific science – good science – showing that it works, solving crystal structures – doing all the enabling work – but actually none of these is [indistinct] It has to be a small molecule ultimately.

[Question] Are you suggesting that the polymerisation is actually preventing the alpha-1 getting out of the liver?

I don't want to raise false hopes but, if it works, you block the polymerisation in the liver and if you can cure, or at least contribute to helping with, the lung disease. I've shown you the data but it's a long way from where we are – but I've got 17 years - - - I'd really like to be back here well before that saying 'here it is.'

[Question] You've got something to live up to because my son was told by a consultant in Derby that there will be a cure in ten years. [laughter]

Yes. Yes. But genuinely there is interest in this disease where there wasn't before. The pharma companies are now engaging. There are trials coming out this year where people are trying to switch off the antitrypsin in the liver. Most of the clinical trials are aiming for the liver. Because it's easier than the lungs. They are trying to switch off the polymer production by knocking out the gene. Those trials will happen this year – next year.

[Question] What's your view on inhaled alpha-1.

If I take my scientist's high-ground there's no evidence that it's of benefit – the problem I have with it, scientifically, is that the antitrypsin is quite a big molecule. Back to the tree – you have to get from the top of the (upside-down) tree all the way to the leaf. It's a big molecule: most of it won't get anywhere near – it will get stuck half way down; or you may hope that it will be absorbed into the circulation and then come back to the leaf. My problem is delivery. Can you get enough of it to the right place?

[Question] [contd] Is it an approach that you could see would work?

Delivery – If you can get it there – if you can get it there in sufficiently high concentrations. That's the problem.

[Question] [contd] You're not worried about the liver anymore?

No no. I'm not sure that it would get to the right place. But I'm very happy to look at the data.

Don't know. Absolutely no idea – we are nowhere near. I've no idea what it will look like when we get there. Ultimately, to my mind this [-> small molecules on the slide] is what the cure will look like.

[Question] When the cure is here –

I'll come back - - - and gloat!

[Question] [contd] – will it be available for children.

No idea – we're so far away. I'm delivering you hope rather than reality. For those people in my clinic who've been bled for month after month – that's the reason. That's exactly why I'm doing it. That's why you've given blood – that's why we've purified the protein. There are other people talking about it and now there are more people talking about therapy.

[Question] Could I just ask who's doing the other trials?

There are different biotech companies. There's one that I saw in a press release that is trying to silence the antitrypsin production – gene silencing. It's out ther – it is going on and well ahead on the pathway. The gene silencing is going through and will go to clinical trials.

After 22 years in this field – alpha-1 has been a disaster but now I sense that it's changing – people are trying different things. It's looking better – alot better. We've enable it.

[Question] This isn't what was on the Today programme.

Coming up. Coming up.

[Question] The focus has been on the 85% that doesn't get through rather than the 10-15% that does get through. My question is what's so special about this 10-15%.

It's random – it manages to fold properly and escape. The Great Escape – it gets through the tunnel to the other side. The rest just folds into polymers or is just degraded.

I want to show you an experiment that came out in Science a few years ago and there's a clinical trial already.

Polymers form inside the cells – can you clear them? This si a mouse experiment done by a group in the US.

This -> is what an antirytrpsin mouse looks like – bless – this mouse, or one of its relatives, produces human antitrypsin in its liver. They form polymers in its liver – exactly as advertised. What the group did was to kill the mice after a period of time and they could see the polymers forming in the liver.

This -> is what polymers look like in a mouse liver, or a human liver. These -> red blobs. You treat it with a drug call carbamazepine – carbamazepine is a drug used for epilepsy and it has a secondary property that it can clear proteins in the cell. This group treated the mice with a huge – a humungous – dose of carbamazepine. If you gave that to a person –

[At this point the Professor's computer signalled that it's batteries were low – the power lead was connected but not switched on. Continuing.]

When treated for a couple of weeks with this drug the polymers went away – in a mouse. That's terrific.

Here's -> antitrypsin staining red and witht he aid of something that treats epilepsy – this -> is fibrosis in a mouse, the red staining – and here -> the fibrosis went away. It's terrific science – it's a huge dose of drug – but it's a mouse!

The human liver doesn't regenerate like this. Nevertheless, it hit the wires again – alpha-1 is up there in the scientific community. And the group that did this in Pittsburgh are now running a clinical trial – again trying to reduce the polymers in the liver by using this drug. Will it work? I don't know. But it's a clinical trial – it's hope – it's a prospect of therapy.

And finally, the reason why you all came. But as I had a captive audience I wanted to do all the rest first – just to do a bit of brain-washing before we got to this bit.

This -> is from the 12th of October when we published our paper in Nature. Using cells from a patient of mine with alpha-1 to try and produce liver cells and in doing so try to correct the genetic defect. It caused a huge, huge interest in the press.

It was published in Nature and other journals picked it up. There was an interview on the Today programme – which is very scary. It's still available – it's online – but my mother's got a copy if you ever want it. I went to the BBC Radio Cambridge studio – do you remember The King's Speech? I was sitting in a room with a huge brass microphone – the rest of the room was shrouded – no one else in there. They put headphones on me and said Edwin Davis will be in this ear and you will be in that ear. They don't tell you what they're going to ask. And another thing about the Today programme is that the closer you get to 8 o'clock the more high profile they think your work is.

So I arrived at quarter past seven and they said you've been bumped to 20 to 8 – that's good. SO you listen to the preamble – they got Tom Field in to do the preamble because they thought that he would be able to explain what we'd done to a lay audience. Then it went across to me talking to Edwin Davis. I looked at this microphone and I thought if I make a complete Horlicks of this, this will be the end of my career. All I have to do for the next few minutes is not to say anything stupid – and in the way of medicine get all the caveats in front. That was my plan. I sat there facing the microphone with this strategy. No matter what the first question was going to be I was going to say 'Yes, but the caveats are - - - '. [long pause]

But of course it caused a real stir in the alpha-1 community, here and abroad. It's just been absolutely terrific.

Let me explain – very simply the strategy was a hugely ambitious project. You cannot imagine how scientifically how ambitions this was.

We took skin cells from a biopsy from a person in this room. The biopsy is tiny – a tiniest piece of skin – turn it into normal liver cells and then put it back into a mouse to show it works. That was our plan.

The person who did this – I suggest that at some stage you get him to come and talk to you – he's a liver Fellow. He saw me give a talk on alpha-1 at the Royal College of Physicians. He said he wanted to do a PhD with me and said he wanted to do it with stem cells.

So I said that's great. I said here's your plan. I want you to take a skin biopsy. I want you to turn it into stem cells. I want you to correct the genetic defect. I want you to produce normal liver cells. I want you to put them into mice and I want you to show that they're normal. And because he's a PhD student he said Yes that's OK [tug of forelock].

[Question] All in three years?

Three years. He went to his mates and said they laughed at me. They say it is not possible in that period of time to do that work. He did it.

Actually the real star of this is this PhD student. He now has his PhD and he was the joint first author on the Nature paper. I don't take the credit for this; I want to give the credit to the doctor who actually did the work. He pulled together all the strands that were required.

[Question] How old is he? [laughter]

He's about 28 [laughter] He's the future – he will be an alpha-1 person. He is into metabolic diseases. He will be a liver disease doctor. He's already been offered serious positions in the liver units in the UK – which I've stopped him accepting because I want him to grow a bit more scientifically. He's had a terrific success but scientifically he needs to do a lot more.

[Question] The Sorcerer's Apprentice.

The Sorcerer's Apprentice. He will get there and he's a really likeable bloke and he must come and talk to you. He's a liver doctor, I just make it up but he's the real deal.

This -> is the scientific slide – I'll take you through it.

So on our Wednesday clinic we said 'and can we take a little skin biopsy while you're here?' We had to go through ethics approval – round and round until we got all the leaflets – because we can't do anything without ethics.

So we take the skin biopsy, grab the skin cells, turn them into stem cells that produce all the cells in the body. Then we turn them into liver cells.

We did the skin biopsies, took out the cells and we grew those cells on plates and we turned them into stem cells. Stem cells are the fundamental cells that regenerate – produce all the cells of the body. They are the starting point of all growth.

We know that they are stem cells because these -> different markers light up. They've all got names but they don't matter – if we have all four lit – it's a bit like if you pull the handle of a slot-machine – when all the things come up you've got what you want. You've got a stem cell.

[Question] how long did it take to get to that stage?

They'd already done that when he came to the lab. It was using a reprogramming factor.

We'd got these stem cells and by cooking – you've got a whole series of recipes – bit of this, bit of that, milk, sugar - - -. Then over 25 days the stem cells turn into liver cells. As they go through the process of turning into liver cells the genes get switched on and we recognise them as being liver genes. When you get to about day 20 they produce albumen, albumen is a big protein in the liver and by about this stage they produce antitrypsin – they are now producing your protein.

So from a skin biopsy we have turned it into a liver cell. That's really clever. We've now got liver cells from people with alpha-1 and we've got liver cells from who they're married to (because they came to the clinic at the wrong time) and we use them as controls. A husband and wife will do fine. We'll take the skin biopsy from the alpha and we'll take a skin biopsy from their partner who doesn't have alpha-1.

The liver cells produce antitrypsin -> the red staining. We then need to say are there any polymers in these cells? Remember what I was telling you, it's all about polymers. We have an antibody marker – a way of detecting polymers in cells. We screened 10,000 cell lines to make that antibody, it's very close to my heart that. It was in my prayers every night. It revolutionised the whole field. So there you go!

Here are cells from you lot and we've made liver-like cells and here -> is a big green signal of polymers. We took skin parts from husbands and wives turned them into stem cells, we made liver cells and we produced antitrypsin. Those liver cells look just like those in your liver. Terrific achievement.

We published that in 2010. We used our antibodies to show those polymers were there. We have human lines now that look just like you livers and I can use these in drug screening. I can use those with my small molecules to see if they will work. If you go back to 2010 that caused a big stir as well – that's another press release.

What we've got is a whole load of human cells that produce polymers. Not great – why would you want me to give you back cells that produce an abnormal protein? N You'd be no better off than what you were when you started. We now need to correct the genetic defect.

So I said to him 'very good, very good my boy.' That was the first year of his PhD. Got a very nice paper – we were very impressed. 'Now do it all over again and along the way when you've made the stem cells I want you to correct the genetic defect in the stem cell – I want you to change two base-pairs out of six billion. I don't want you to change anything else – if you change anything else you'll be in trouble. And I want you to show me that it works.' And he said 'Thank you David.' {tug forelock] That's how it works at Cambridge.

Make the stem cells and correct the genetic defect and to do this he needed – and this is why he was brilliant – he needed to phone a company in the US and persuade them to give him the correcting material, free, as opposed to $30,000. He needed to get hold of the Sanger Centre to do all the genome correction stuff, and he needed the patients and he needed the stem cell technology. This is a huge feat of just pulling people together – he's a very engaging chap, he works very well and then reprogrammed they're the skills you need to get people to pull together. He did it.

Back to where we started. Skin biopsies – skin cells – re-programme them into stem cells. Back to the slot machine – all the colours come up – red, green, red, green – the markers we want; these are stem cells. But these stem cells have your genetic abnormality, they have the Z abnormality.

So we said to him 'Fine but now I want you to cut the DNA next to the mutation.' This -> is the DNA all lined up. These are you base pair lined up as a sequence of four different letters. 'I want you to cut only at one point close to the mutation,.'

So he used what is unfortunately known as a FOK 1 enzyme and that cuts the DNA -> breaks it. Then we needed a scaffold to repair it. We got the scaffold from the Sanger Centre. The scaffold lines up next to the break with the correct sequence. So that when the break is repaired the correct sequence is now in there. We choose those cells which have the correct sequence. Five percent of the cells have one gene corrected and point three percent have two corrected. So we could choose the ones which were corrected. Then we said 'fine – that's terrific. Now turn those corrected stem cells into liver cells.' WE went through the recipe – milk, eggs, sugar, - - -. And a month later we look at the cells that we get and we say can you produce antitrypsin and are there any polymers any more?

These -> are the stem cells from the people, like people in this room, and these -> are the stem cells from their partners. And when we corrected the genetic defect there are no polymers ->. We had corrected the genetic defect. We said 'that' fine, that's very clever – but we have to show that we haven't wrecked the genome. If we've wrecked the genome that's not good.'

In Cambridge there's the Sanger Centre and it seems that there's a big button at the Sanger Centre. You put in DNA, push the big red button and out comes the sequence. We sequenced the genome of the cell 30 times and out of the base pairs we looked at there had been 27 changes from start to finish – starting from the skin cell to get to the liver cell and the genetic correction was absolutely clear – beautifully clear. So we had corrected the genetic defect at the stem cell level and we'd produced normal liver cells.

We then said 'that's really clever – but do they work?' You can see it's pretty tough in Cambridge. We had some mice and we put some cells into the livers of the mice and we killed the mice six weeks late. Six weeks later we found cells – can you see that -> that produced human antitrypsin. So the cells that we'd made work. We'd put them in a mouse liver and they function – and the genome is clear. We'd corrected a genetic abnormality.

This can now be done for every genetic disease that involves a single-point mutation. The technology is terrific – it just happens that your disease was the first one through. It's a super way of correcting the abnormality at the genetic level. Technologically terrific but for your disease even more important.

This was published in the New England Journal of Medicine. It's the biggest medical journal in the World. Sandy Sandhaus, who some of you may have met, wrote an editorial to accompany our paper which was published in Nature and once again [new slide} poor old John Walsh ->. The medical fraternity got it – this caused a huge stir in the science community as well as in the patient groups. Scientifically it's a tour-do-force because the graduate student pulled together these different people with different resources to get this done. I can't praise him highly enough as you will have gathered.

In conclusion. The genetic abnormality that you've got forms polymers. This is a disease of polymers. The polymers form in the liver that's why we get liver inclusions and liver disease. Lung disease is largely deficiency – no doubt – and you can also get polymers in the lung. I still think that despite the terrific science that I've just shown you, the cure will be a small molecule. I still believe that and whoever does it good luck to them.

Some drugs may clear polymers in liver cells, at least in mice, and those studies have started. If this works it may negate what we want to do. Good luck to them. Someone has to make progress. This trial is available, it's in the public domain, it's started.

Stem cells may allow the growth of new liver cells. We can put healthy liver cells back into patients.

Finally. People who gave us money; MRC, the Medical Research Council have funded me now for 22 years from when I was a young, spotty graduate student. This is the hardest money to get in the country – they had funded largely on the basic science of your disease.

I'll stop now and just take questions.

[Question] Obviously the first question with stem cells is – when?

Before I retire [laughter]

Let me give you the answer I gave to Evan Davis – has to come with caveats – when you go from stem cell to liver cell I need to be absolutely comfortable that they don't cause harm. You will read in the papers about people doing some very dodgy stem-cell work. In my world this will not get into man until I'm really happy about it. The last thing in the world is for it to go wrong.

Second thing is that the liver cells that we made look relay like liver cells – you will see in the papers I don't call them hepatocytes, we call them hepatocytes-like cells. And that's deliberate because they're not really the finished article. They're like a baby's liver cells and we would hope that if you put them in a liver they would then grow.

Cambridge has just got some money from the Government via the Biomedical Research Centre to set up a big stem-cell initiative. At the end of five years, I, and I will only be peripherally involved in this, will try to get stem cells, liver cells, into man. We have a development plan to be able to do it. The simple way to do it is not to do the genetic correction – the correction adds a whole level of complexity. The first thing is that it will take, probably, primary biliary cirrhosis, with this you get a stable but progressive disease – and I can see a system whereby you can take a skin biopsy from those people, make liver cells, put them into mice – they must be absolutely safe – say for six months and then put them into a patient a couple of years later. Then I would feel comfortable.

[Question] Do the cells have to come from a donor and go back into the same person?

The same person – the beauty of that is that you overcome all the problems of rejection. If I made cells from me and I gave them to you then you'd reject them.

[Question] It'll be very expensive.

Yes. We've answered that for the press – it's actually cheaper than a liver transplant – cheaper than a liver transplant and then long term therapy after transplant. If you have to have a liver transplant, or a lung transplant, you have to be on agents to stop your body rejecting it for years and years. It would be expensive at first and then get cheaper because everything gets cheaper.

[Question] Costs versus augmentation therapy?

One may work.

Do you know when the Guthrie test for all babies at birth will come?

Guthrie test for alpha-1 – Robert Stockley, some of you will know him, when I was a young doctor I worked for Rob. Rob and I worked with Sue Hill to try and get the genetic monitoring group in the UK to have antitrypsin measurement but they threw it out. They said why test now – what's the advantage of testing now when you can wait until people are 12, 13, 14 and make their own decision? Clinically it makes no difference.

[Question] Surely things like cystic fibrosis are tested for?

That's because early intervention makes a difference.

[Question] Are there not cases – children have been lost because doctors did not recognise liver damage?

Good point – but when a baby presents with liver problems then the paediatrician would test for alpha-1.

It's a cost benefit calculation. They screen for under-active thyroid, used to be called cretinism in the old days, because giving babies thyroxine changes their lives. The test for phenylketonuria for leaving the absence of a particular amino acid in your diet allows the brain to develop. The same for CF because early diagnosis may prevent the lungs deteriorating. And so on.

There is a panel for what they screen for. Alpha-1 doesn't make it. Now if we had a small molecule and that has to be implemented early we may get it through. We tried it was an impassioned plea but - - - the logic of science is rather cold.

[Question] The liver cells put back in a patient – is the assumption that they would grow at the expense of the existing liver cells.

That's my idea.

[Question] [contd] Is there any evidence for this?

In mice, yes. The reason for that is that the existing liver cells have a burden which are the polymers. Simplistically, if you put back cells without that burden they should have a survival advantage.

[Question] Going back to screening. Were the panel that you spoke about in favour of a milestone at the age of 12?

It's difficult. If you have a diagnosis of alpha-1 it halves the smoking rate. The Government would say that the smoking rate of 30% is falling (only rising in young girls) – and we tell everybody not to smoke anyway.

[Question] Can we go back to the small molecules?

The vision, the promise, the sunny uplands –

[Question] I've heard that the problem is the degrades.

I see it as more an accumulation and the cell dies – we're in hand waving territory again. Let's assume that you actually reduce polymerisation because you increase degradation – [hand waving]

Ultimately it requires a lot of resources – lost of people.

[Question] Very exciting.

It is very exciting. For me to engage a pharmaceutical company is great. I've been trying for years to do that. With more people engaged we're more likely to get a cure. But we will get one – and before I retire. With that I close.

[prolonged applause]