Professor Angela Russell

Cures from within: can we use chemistry to teach the body to heal itself?

Questions	Response from presenter
Is it possible to use stem cell therapy to generate P53s to reduce the likelihood of an organism getting cancer?	It's possible in principle. I'm not aware of anyone doing this, but stem cells are being explored as 'delivery vehicles' for other biological therapies. The issue is that there are multiple other approaches out there directed to p53, so it may be hard for a cell therapy approach to compete.
Why couldn't you regularly administer the drug?	Assuming this refers to ezutromid, the drug we were testing for Duchenne muscular dystrophy, we did administer this regularly (twice daily over 48 weeks) in the trial. The issue we faced was that when the patients took the drug, their bodies got better at breaking it down and getting rid of it. Ironically it may have worked better if we had not given the drug continually, but given periodic gaps in treatment, to stop the body being 'primed' to break down ezutromid. This approach has worked well in other cases where tolerance to a drug develops over time.
During the analysis stage of the mass spectrometry, were there any measurements that were similar and therefore sapping to decipher?	If we had used conventional mass spectrometry yes, but the approach we used was more advanced which allowed us to distinguish different peptides by their distinctive fragmentation patterns. When you see many, many different peptide fragments enriched following a treatment which are derived from the same protein, it gives much more confidence in your assignment.
Did you have to find mice also with DMD for the testing?	Very often in preclinical research a mouse (or other animal model) has to be created to mimic the human disease. Actually the mouse model of DMD tested arose from a spontaneous mutation in the dystrophin gene and was discovered many years ago.
Where do you get the funding for your research?	As a research scientist you have to be adaptable in seeking funding, and so usually it comes from a variety of sources. We have been fortunate over the years to have received funding for our science from Government sources, the EU, the industry sector and charities including Cancer Research UK, the British Heart Foundation, Muscular Dystrophy UK amongst others.
How hard is it to keep your morale up when a trial fails after so long spent working on it?	It's extremely difficult, but the biggest impact is on the patients and their families who place a great deal of hope in these experimental medicines, especially in diseases where there are no or few other treatment options. This is really what drove us to understand why the trial had failed, especially given how promising the effects looked at the mid-way point. We believe that by understanding the limitations of ezutromid, we can find a path to an effective and lasting therapy.

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What do you think about the potential of bacteriophages in the the treatment of cancers?	Cancer-targeting viruses have been being explored for several years now and some of the data coming out looks very promising. The real hope is that these approaches show remarkable levels of selectivity for cancer cells, including cancer stem-like cells which are more challenging to target with conventional therapies, over healthy cells. However, there are lots of challenges with this sort of approach too which still need to be addressed. Making these types of gene therapy on scale to be given to larger patient groups is a real challenge, and the costs are likely to be very high.
Is there a way for the body to not recognise Utrophin like insulin for type 2 diabetes thus not allowing muscle to be regenerated or developed?	I'm not aware of any such mechanisms or any reports of this.
What ethical barriers did you face while conducting the clinical trials for Ezutromid?	There were lots of aspects that needed careful consideration, particularly as the trial to test whether ezutromid would work was conducted in a relatively small number (40) of young boys (5-10 years old) diagnosed with DMD. Issues such as patient consent and anonymisation has to be carefully considered.
You were detecting the success of this drug by how much muscle cells are regenerating? So no regeneration is good?	This was one of the measurements we took and, yes, if a muscle is not regenerating as much it means there is less damage which is the outcome we were hoping for. We also looked at other measurements like muscle inflammation as we did not want to rely on only one measurement to convince us of whether the drug was working.
Is there any way of reducing the activity of the CYP enzymes to prevent the metabolism of the stilbenes?	A good suggestion! There are inhibitors of CYP enzymes which can be given to a patient at the same time as a drug to block or slow down metabolism by this pathway. This has been used to 'boost' antiretroviral therapy in HIV treatment. Care also needs to be taken as CYPs are responsible for metabolising many drugs and other substances that are ingested. By giving a drug that inhibits the function of CYPs it is also likely to affect the levels of other drugs which may lead to dangerous complications, especially when a patient is taking many other medications.
What would you say the most overwhelming/ challenging aspect of scientific research is?	Science is challenging, but immensely rewarding at the same time. Probably the biggest challenge (for most researchers) is securing funding for research. There are always more good ideas than there is resource to fund them. This is why scientists need to be adaptable in seeking funding for their work.

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As the receptors response to the shape, does that mean the stereoisomers had no effect on the patient?	In our case the drug did not have stereoisomers so we did not need to worry about this. There are however, lots of examples where stereoisomers of a drug can have very different effects. For example levorphanol and dextrorphan are enantiomers (stereoisomers which are non-superimposable mirror images) and yet one acts as a pain killer and the other as a cough suppressant!
How do you deal with failure and delays in such life-saving research?	It can be extremely frustrating! However, successful translational research can only be built on robust basic science. It is therefore always important to do the right basic experiments. In the event of a failure or a set-back, it is important to stand back and ask why, and return to the basic principles in order to move forward again.
Can your lifestyle effect whether or not your child will have Duchenne muscular dystrophy?	There is no evidence to suggest this is the case. DMD arises either where there is already a family history, or as a result of a spontaneous mutation in the DMD gene which means that a functional form of the dystrophin protein cannot be produced.
Can this sort of work be applied to making the body produce its own nutrients that it is lacking?	A very interesting question! In principle, yes. In fact at the moment this is often tackled the other way around. In some diseases such as Gaucher's disease and Pompe disease there is a block in nutrient processing, and the disease symptoms arise from an unwanted build-up of certain nutrients. In these diseases Enzyme Replacement Therapies (ERT) have been (or are being) developed to normalise nutrient processing.