The future of drug discovery for healthy ageing Q&A

The UK SPINE online event took place on 19.06.2020.

The panel consisted of:

Dr Ghada Alsaleh; Postdoctoral researcher in immunology and autophagy in the lab of Katja Simon at the University of Oxford. She leads on a UK SPINE funded project that aims to develop medications which influence TFEB expression to promote effective autophagy and have a positive impact on age-related morbidities.

Dr Graeme Wilkinson; Head of virtual R&D at the Medicines Discovery Catapult and leads on a UK SPINE funded project aimed at the development of a translational roadmap for developing drugs for aging. This document will provide guidance of the route from early stage translation to commercialisation and clinical implementation and will be a key resource for the UK ageing translational landscape.

Alexander Masters; Journalist, biographer, and cofounder of iCancer; a £2million crowdfunded clinical trial for cancer treatment. Together with **Heather Draper** (professor of Medical and Bioethics at the University of Warwick who has a specific interest in research ethics), he leads the UK SPINE funded project on assessing the feasibility of rolling out the funding model of committed philanthropy in the UK. This is a funding model where a clinical trial is funded by wealthy donors, who wish to be part of the trial themselves and in return agree to pay for the other spots on the trial. By doing this, they make the trial accessible for individuals that do not have the same financial power as them.

The Session was moderated by **Dr Beverley Vaughan**; UK SPINE programme director.

These are the questions & answers to all questions posed, some of which could not be answered during the live session in the interest of time.

Questions for Panel

Q1: Hello. I would like to ask a general question to the speakers, please. I agree on developing drugs for age-related diseases although I think sometimes were are curing things that could be potentially avoided changing habits or regulations on food quality. That would probably avoid the disease rather than curing it.

Answer Ghada Alsaleh: This is an excellent point. Indeed, the calorie restriction, fasting and different diet showed a significant impact in health span. However, these are a prevention method more than a cure method. Developing a drug target that helps to cure the disease is essential when the condition is established and can't be controlled by the lifestyle any more.

Answer Graeme Wilkinson: This applies to many non-infectious or non-inherited diseases, whereby adoption of better eating and exercise habits could have a positive effect on all of us; this is probably an issue for public health policy. However, once a disease has taken hold it needs to be managed to prevent further progression and the resultant and this is where drugs play a part. Another area where drug treatments are essential is for degenerative conditions.

Q2: Since ageing is not classified as a disease indication, why would pharma become interested in drugs that deal with ageing rather than specific diseases?

Answer Ghada Alsaleh: Though ageing is not a disease, ageing is the main risk for many diseases. Increasing the ageing research area to understand the link between the process of ageing and the disease and identify new targets in the process of ageing that cause the onset and the development of the disease, will increase pharma interest in dealing with ageing. On the other hand, considering the increasing number in the elderly, the pharma industry can reach a high number of customers, which is regarded as one of the critical factors in the industry.

Answer Graeme Wilkinson: Understanding the link between age-associated changes in biology, how these are affected by the environment or genetics and the role this then has in the progression of disease will allow the development of new therapeutics

What was the biggest obstacle you've experienced in clinical research?

Answer Graeme Wilkinson: Convincing the owner of a compound to consider its use in a new clinical setting

Questions for Ghada Alsaleh

Q1: Great talk. Based on your introduction, what are the prospects of increasing TFEB using nutritional supplements that increase spermidine levels?

Answer: Thank you, our data show that Spermidine and TFEB levels decline with age in peripheral mononuclear cells, and spermidine supplementing in cell culture medium increase TFEB expression and improve B and T cell function in old donors. However, spermidine does not increase TFEB in young donors as they have a sufficient amount of spermidine produced by their cells. From these data, we suggest that taking spermidine or nutrition that increase spermidine can increase TFEB expression in the elderly but not in the young. A clinical trial is needed to confirm this suggestion.

Questions for Graeme Wilkinson

Q1: What are the main bottlenecks in commercialising drug discovery research in chronic diseases of ageing such as diabetes/cardiovascular disease? How would you make a case to stakeholders that investing in research in this area is potentially worthwhile?

Answer: There is starting to be a lot of interest from US biotech, in particular, with substantial VC funding, however, large pharma investment is not at that level yet. Stakeholders need to see a good rationale for targeting core processes and targets with a clear line-of-sight to the clinic that includes a biomarker strategy, that the RoI that will be needed to take a drug to market is justified. There needs to be a regulatory environment that supports clinical trials in older populations.

Questions for Alexander Masters

Q1: Hi Alexander, Doesn't the US NIH already approve other funding of research that fails to get NIH funding? Can that be used to argue for funding in the UK?

Answer: I'd need to know more about how this to be able to answer your question. Of course, lots of projects fail to get funding from one source and so go to another, and one of the issues to consider with Committed Philanthropy is, what defines a 'neglected' piece of research. Does it have to have been rejected by all other funders but still of course pass the quality test of peer review, or has it just failed to get funding from the main suppliers of cash? And who's to be keeping track of that? Another question: should the idea really be limited only to neglected research? You don't want to let traditional funders off the hook, so that they don't support projects that they should, but at the same time, what about new work? One idea I've discussed with a genomics lab, is that patient donors could pay for new research, specifically designed to target their particular condition. The lab then designs an appropriate molecule. Other suitable patients with the same condition would then also have to be found, and the trial approved by all the usual, appropriate people; but it would clearly not be neglected research except in the broadest sense, ie that the research was not yet even begun when the donor (through a Matching Agency, if this were to be done by Committed Philanthropy) first approached the lab. As far as clinical studies about healthy ageing are concerned (and this really is way beyond my expertise) the funding issue as I understand it is less to do with the neglected nature of the work, and more with the inability of a traditionally-designed trial to study elderly patients with multiple morbidities – ie it is the neglected requirements of the patient group more than the science that's at issue, although it still ends up with the same unhappy result of good work being put aside

Q2: Have you considered crowd funding in terms of many people each contributing small amounts without any expectation of participation?

Answer: Yes, that's how I first got into this. I set up a crowd-funding campaign (iCancer.org.uk) which raised enough money to start a clinical trial in Uppsala. It was done for a friend of mine, and I said I'd do it only if the university agreed to put my friend on the study, should I raise the money in time. It was hard work and, apparently, the first time a trial had been funded this way. By far and away the largest donor in that campaign was a man in Geneva who read about our campaign in the Financial Times and he offered the money on the same condition I had proposed for my friend, i.e. that he would be able to take part in the experiment himself. That was how we moved from pure crowd-funding into a mix of crowd-funding and a nascent version of Committed Philanthropy. As it happened, the potential ethical issues that these promises threatened to stir up never occurred, because both my friend and the wealthy donor died before the trial started. After that, and more careful thought and a lot of asking around, I realised that, to ensure an ethical process – especially one that could guarantee the donor-patient wouldn't be exploited or led up the garden path by quacks, and the research team wouldn't be bullied by wealth – I had to have a mediating agency overseeing the process. Ethically, the scheme is much more straight-forward than I ever suspected when I first dreamed it up. Practically, there's still a lot of work needed, of course.

Q3: Hi Alexander, fantastic idea! Why limit the donors to people who are patients that can participant in the trial rather than allowing other non-patients to donate as well?

Answer: That was my fault in the talk. The idea is open to anyone who wants to pay, you're quite right. Only suitable patients can participate in any funded trial this way, but the patient doesn't have to be the donor. Donors will, of course, also be willing to fund trials that would be to help their child,

their partner, a stranger. I've come across several cases of that last situation: a wealthy donor funding research that has no connection to them or their family – they do it because they've been moved by the plight of someone who's ill. This scheme would be perfect for such acts of generosity.