Q&A WITH PROFESSOR DENIS NOBLE

Q. Please introduce yourself and what are your current ongoing projects?

I am currently Emeritus Professor of Cardiovascular Physiology in the Department of Physiology, Anatomy and Genetics at Oxford University. I am leading an international team (UK and USA) investigating the physiological mechanisms of compounds derived from traditional medication. Also, I am the author of two books (The Music of Life, OUP 2006; Dance to the Tune of Life, CUP 2016) on my principle of biological relativity: no privileged level of causation.

Q. What is your opinion on "where do we stand in drug development" for precision medicine?

Drug development for precision medicine finds itself in a difficult situation. Research investment has increased, while drug pipelines have fallen. We need to be able to move forward urgently, to serve ageing populations, and to deal with major threats, e.g. from drug resistant bacteria and viruses.

Q. What is the greatest challenge at the moment in precision medicine?

I am perfectly happy with the idea of personalised medicine. If it means that treatment will be designed to use whatever information is available, to optimise individual patient needs and susceptibilities. This will only work if we prioritise relevant research to reveal why the correlations with genomics alone are usually disappointing. The reason, of course, is that much more is inherited than the genome. This issue is fully discussed in my recent book, *Dance to the Tune of Life*, published by Cambridge University[1].

Q. What is the next step needed in precision medicine for us to actualise its potential?

We need to use genomics, certainly, but in combination with the kinds of successful physiological and pharmacological methods used by some of the greatest drug discoverers. It means a return to higher level systems approaches. My favourite example is the work of Sir James Black.[2]

Q. How can academia and industry work together to drive forward this next step?

It would help to create the environment in which progress could be made if industry could reconnect with integrative physiological scientists, who have the skills needed to

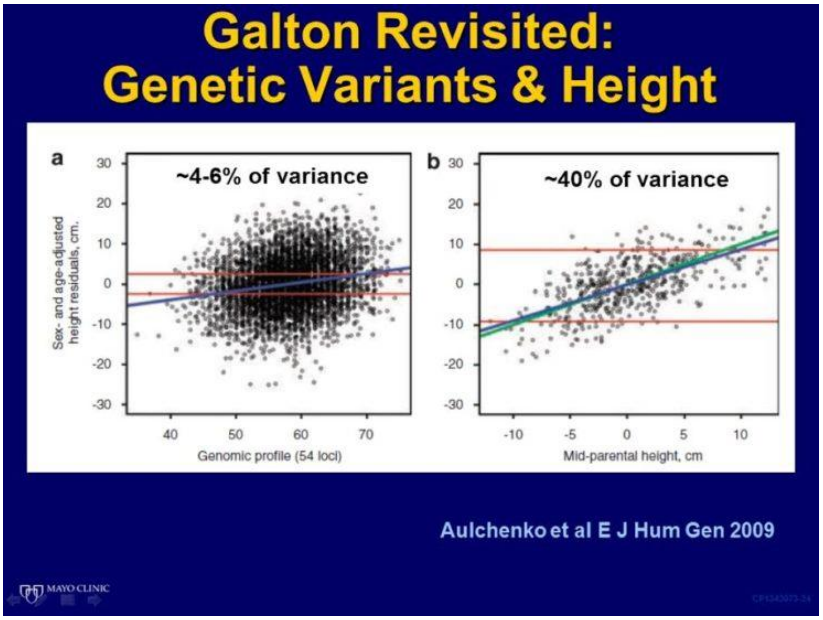
[1] Read about the book here: http://www.musicoflife.website/Dance.html

[2] Sir Black was awarded the Nobel Prize for Medicine in 1988 for work leading to the development of propranolol, a beta blocker and cimetidine, which is used to treat stomach ulcers.

interpret sequence data and proteomics data in functional ways. Organizations like IUPS (www.iups.org) and the larger constituent national societies could help here.

Q. What will you speak about at the Summit? And why is this controversial?

My talk will focus on the fact that GWAS have produced disappointingly small correlations with physiological or pathological states.[3] This problem has been acknowledged even by the leaders of the Human Genome Project, and has been known for a long time. For example, the correlations with a simple physiological parameter like height, are weak from a genome viewpoint. The same parameter is strong when one looks at family history. Yes, inheritance matters but it is not all in the genome.[4] The correlation with the genome is 4-6%. The correlation with parental statistics is 40%, a difference of an order of magnitude.[5]



Much of my work has been on why and how we solve the problem. My team found that we could simulate the block of a protein involved in heart rhythm, that normally contributes about 80% of the functionality. This particular block leads to only a 10% change in frequency. The reason is that the physiological regulatory networks adjust to the knockout and use alternative pathways.

[3] Example: http://rsif.royalsocietypublishing.org/content/11/94/20131017
[4] https://thebestschools.org/dialogues/evolution-denis-noble-major-statement/
[5] Source: https://thebestschools.org/dialogues/evolution-denis-noble-major-statement/

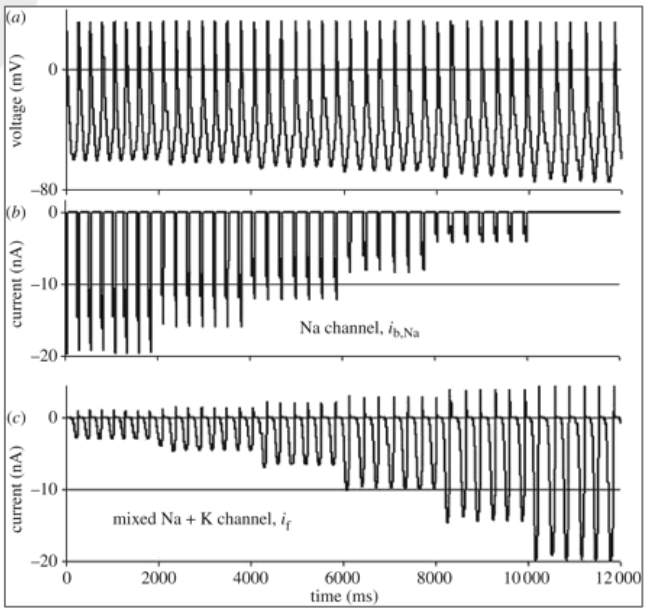


Figure 3 Source: http://rsfs.royalsocietypublishing.org/content/1/1/7.figures-only

This problem is widespread. A study of 6000 genes in yeast showed that 80% show no effect in normal physiological conditions.[6] The organism needs to be stressed metabolically to reveal the functions.

Sequencing companies like 23andme acknowledge this problem, at least implicitly. Prompted by the FDA, they now advise people to take sequencing data together with other indictors to arrive at a sensible idea of their chances of various disease states. I debated this problem with 23andme in Dublin a year or two ago – you can watch it here.

Q. What are you looking forward to at Controversies in Precision Medicine in Berlin?

I like the format of this summit and I believe there could be some very constructive discussion on the ways forward to help both industry and academia. We need this kind of dialogue.

Join Professor Noble with Richard Fitzgerald (Director, Clinical Research Unit, RLUH, Liverpool, UK) for the opening debate, where they will explore whether a genetic-driven approach just needs more time to produce results or whether we need to first invest more in a regulatory filtering of genetic variations.

Be part of 150+ senior level attendees from leading industry companies, academia and government institutions who are ready to address the challenges to ignite solutions.

Join Us 13-15 November 2017 in Berlin!
http://PrecisionMedicine.kenes.com

[6] https://www.ncbi.nlm.nih.gov/pubmed/18420932