THE WEDNESDAY INTERVIEW | HELEN HOBBS

'Cholesterol-lowering interventions, whether diet or statins, should start early'

The geneticist on her work on coronary heart disease, and why studying different races is critical

PRIYANKA PULLA

Geneticist Helen Hobbs' work on coronary heart disease (CAD) led to the development of PCSK9 inhibitors - the most powerful cholesterol-lowering drugs to hit the market since statins. These drugs fight the PCSK9 protein, which prevents "bad" low density lipoprotein (LDL) cholesterol from being removed from blood. In the mid-2000s, Dr. Hobbs, director of the Eugene McDermott Center for Human Growth and Development at Dallas' UT Southwestern Medical Center, found that a mutation in the PCSK9 gene, present mainly in African Americans, suppressed LDL levels. Consequently, it protected carriers from CAD. Importantly, people with two copies of this mutation had no side-effects of very low LDL, such as loss of adrenal function. A key innovation in Dr. Hobbs' approach was to look for a rare gene variation with a large impact on cholesterol. Most scientists then were carrying out genome-wide association studies (GWAS), which look for common gene variants. Unfortunately, this strategy had mainly identified gene variants with a small impact on CAD risk. Dr. Hobbs' approach bore fruit. Through research on the 3500-strong Dallas Heart Study cohort, she and colleague Jonathan Cohen discovered rare mutations in the PCSK9 gene. Eventually, drugmakers Amgen and Regeneron developed the PCSK9 inhibitors Evolocumab and Alirocumab, respectively, which mimic this mutation's effects. In an interview in Hyderabad, where she spoke at the TNQ Distinguished Lectures in the Life Sciences, Dr. Hobbs discussed the way ahead. Excerpts:

K.V.S. GIRI

How did the Dallas Heart Study begin?

■ The question we were trying to answer was if elevated LDL is necessary for heart disease. You can't ask that question by looking at Mendelian disorders (in which defects in a single gene trigger heart disease), because everyone who has these disorders is sick. We were looking for mutations that would protect people from heart disease. Such healthy people wouldn't be in the clinic. So, we developed the Dallas Heart Study. One of the premises was that there were going to be low-frequency or rare variations associated with major changes in lipids.

Our population was designed to maximise the probability of finding such rare variations. It was a multi-ethnic cohort, in which half the individuals were of African descent, while 15% were Hispanic, and the rest were of European ancestry. Africans, being the most ancient population, are the most genetically diverse. Our approach of looking for rare variations was really key to our findings. As a scientist, you are always looking for things that have large effects, since they are easier to study.

If looking for rare gene variants with large effects could be such a powerful approach, why was everyone else doing the opposite at that time?

■ Honestly, I couldn't figure it out. Maybe my approach had something to do with my medical background. Maybe it was because I had worked on Mendelian disorders. In some ways, I benefited from being in Texas, away from the epicentre where everyone was doing the same thing. With our approach, everywhere we went, we found things. PCSK9 is the biggest story. But that's not the only one. We also found variants in a gene called ANGPTL4, which lowered plasma triglycerides. Mutations in ANGPTL3 were found to lower levels of both cholesterol and triglycerides, and antibodies to this protein are now being developed into a drug as well. What people hadn't known until then was how riddled healthy individuals are with rare mutations that have major effects. What we did then has now become routine. Companies do it all the time today.

One of the problems in genetics is "missing heritability". GWAS that look for common gene variants to explain disease risk have only been able to explain a small part of disease inheritance. Do you think rare-gene variants explain this gap in heritability?

■ There are definitely many more common variants than there are rare. But for an individual who has a rare variant, the rare variant can mean everything. That's the problem.

In our first experiment, we found that people with low HDL ("good" cholesterol) have a major gene defect which is contributing to it.

Statins are not a cure; it's not like giving antibiotics for an infection. You have to start young.

While this was going on, a woman in France had identified families that had very high cholesterol due to a new gene PCSK9. She found two missense mutations in this gene (missense mutations alter the make-up of a protein coded for by a gene; in contrast, nonsense mutations stop the production of the protein). Individuals with the missense mutations had high plasma levels of LDL. To figure out what the PCSK9 mutations did, three groups over-expressed the mutant forms of the PCSK9 gene in the livers of mice. And in those mice, the LDL receptor, which removes LDL from the blood, disappeared. The mice became hypercholesterolemic (developed high cholesterol). We thought, if you didn't have PCSK9, you would have a lot of LDL receptors on the cell's surface, and low LDL. So, we went to the blacks and the whites in the Dallas Heart Study, and we sequenced the individuals who had LDL less than the 5th percentile. We found three sequence variations. One missense mutation was in whites, associated with a modest reduction in LDL. But there were two nonsense mutations, which introduced stop codons in individuals of African descent. Those stop codons are a gift to geneticists, because they are almost invariably a loss-of-function mutation. This means that they kill the (PCSK9) protein.

These two nonsense mutations were only seen in black people. And they were associated with about a 40% reduction in LDL cholesterol. We wanted to know what it meant to be born with such a mutation, and to have low LDL throughout one's life. If LDL is an important factor in heart disease, this mutation should really change one's risk of developing heart disease. So, we went to the only biracial study in the world – the ARIC (Atherosclerosis Risk in Communities) Study – and asked a simple question. Did people who hadn't had a heart attack and were not on lipid-lowering agents have the mutations we found? Among black people in this study, we found that the mutation lowered the risk of heart disease by almost 90% – higher than what we had found in the Dallas Heart Study.

We knew that we had made a significant observation. If you have low LDL for years, you are not going to get heart disease. Atherosclerosis starts early and develops gradually.

You have talked previously about the need to lower cholesterol earlier in life. Should people start taking statins earlier then?

■ The best way to lower cholesterol is through diet, but it must start at an early age.

In 2015, the U.S.'s Dietary Guidelines Advisory Committee said dietary cholesterol may not be a "nutrient of concern for overconsumption", given that there wasn't enough evidence to show its impact on LDL. What did you think of this?

■ I don't believe it. Of course, cholesterol is a nutrient of concern, and its effects are compounded by saturated fat. The benefits of lowering your cholesterol are indisputable now. We have so many studies. But the problem is that you cannot take 50-year-olds, who have had high cholesterol their whole life, lower it, and eliminate risk of heart disease. Atherosclerosis is already in their arteries.

If you look at the statin trials, a large percentage of those who get treated still have a cardiac event. Statins are not a cure; it's not like giving antibiotics for an infection. You have to start young. Either you have to consume a different diet, which gets you on a different trajectory, or you have to start statins at a younger age. What age that should be is still disputed, because there haven't been clinical trials. It's hard to start people on a drug and follow them for 30-40 years.

PCSK9 inhibitors are very promising, but their use is greatly limited by their high cost. Do you think the cost will come down in the future?

■ It can only come down. It already has. When they first came out in the market, they were priced too high at $14,000 per year. It really was a mistake. Then they did a cost benefit analysis, and brought the price down to about $5,000 a year. Now, a lot more people are getting the drugs. The hope is that competition will eventually bring down the price even further.

One reason for the high cost of Evolocumab and Alirocumab is that they are monoclonal antibodies. Are there any alternative strategies that target the PCSK9 protein, but are less expensive or easier to use?

■ There is Inclisiran, a small interfering RNA, which is being tested in humans. Because PCSK9 is made in the liver, you can inhibit it at the level of messenger RNA. Inclisiran, which does this, requires an injection every six months. This is terrific because one of the major problems with statins is compliance; people stop taking them. An injection every six months is much easier to adhere to. People are also thinking about CRISPR-Cas9 strategies, but as everyone knows, that's not going to happen tomorrow.

In your ongoing work, you have identified genetic mutations (in PNPLA3 and TM6SF2) for fatty liver disease (FLD). Is there scope for therapeutics here?

■ I think it's pretty clear that there is.

Again, this disease is burgeoning in frequency, and is huge in India. When we started, almost nothing was known about its pathogenesis, except that when people are obese or have diabetes, they have a higher incidence of fatty liver disease.

However, we saw in the Dallas Heart Study that 50% of people who were obese did not have FLD. This suggests that there might be genes involved in the propensity to deposit fat in liver. In this case, we did a GWAS, and found that the Hispanics had a common sequence variation associated with high triglyceride content.

How big a problem is the under-representation of certain ethnicities in genetic research? Most genome-wide association studies have involved Europeans. What opportunities are we missing because of this?

■ I think the opportunities are huge. We need to study more groups, especially Indians. It is an incredibly genetically diverse population, which has poorly understood susceptibilities to coronary heart disease and to diabetes at a lower body mass index.

Studying different races is very critical. In PCSK9's case, if we had not had blacks in our population, we would never have discovered the gene mutations that led to new cholesterol-lowering therapy. In the FLD study, if we didn't have Hispanics, we would never have discovered PNPLA3, which is currently the most important risk factor for fatty liver disease.

SINGLE FILE

Lessons of 1979

Post the revolution, Iran's staying power as a state in the face of a very hostile international milieu has been remarkable

MOHAMMED AYOOB

AP

This month marks the 40th anniversary of the Iranian revolution. It is time, therefore, to evaluate the fundamental lessons of the revolution. It is true that the takeover of the broad-based revolution against Mohammad Reza Shah Pahlavi by hard-line mullahs distorted the original trajectory of the revolution and stifled the democratic aspirations of the people. At the same time, one should not overlook the fact that the anti-Western thrust of the revolution that played into the hands of the hard-line clergy was in large part a delayed reaction to the British and American role in the coup that overthrew Iran's first elected government in 1953.

The American support to Saddam Hussein's invasion of Iran in 1980 augmented anti-Western sentiments and further helped the clergy-dominated regime to consolidate its power in the country. The bankrolling of Hussein's war to the tune of billions of dollars by Saudi Arabia and allied Gulf regimes solidified the antagonism between revolutionary Iran and the Arab monarchies of the Gulf. It also hardened the division between Shias and Sunnis in West Asia. The Iranian-Saudi rivalry is being played out to this day in Yemen, Syria, Lebanon and other parts of West Asia.

However, the most important lesson of the revolution and its aftermath is the demonstration of Iran's remarkable staying power as a state and a nation in the face of a very hostile international milieu. Iran has confronted unprecedented economic sanctions since the revolution, a process that intensified in the past decade and a half to force Tehran to give up its presumed nuclear aspirations. The Iranian people put up with grave hardship for four decades but did not surrender their national sovereignty. This is because the state of Iran/Persia has been in existence since time immemorial, and in its present contours from the early 16th century, its citizens have developed a sense of innate pride and confidence in the state's staying power against the heaviest odds. The development of Persian nationalism has been a gradual process that, one can argue, culminated in the underlying thrust of the revolution.

Persian nationalism draws upon its glorious pre-Islamic heritage, as described in the *Shahnameh*, Iran's epic par excellence. It is also engendered by the twin marks of distinction that Iranians are very proud of: their ability to preserve their Persian character and language despite their acceptance of Islam, a religion of Arab origin; and the distinctive character of Persian Islam embodied in Shia doctrines that distinguishes it from its predominantly Sunni neighbours. Regardless of the nature of a particular regime, longevity of national memories and people's pride in them can work great miracles when faced by hostile forces bent on emasculating the nation's sovereignty.

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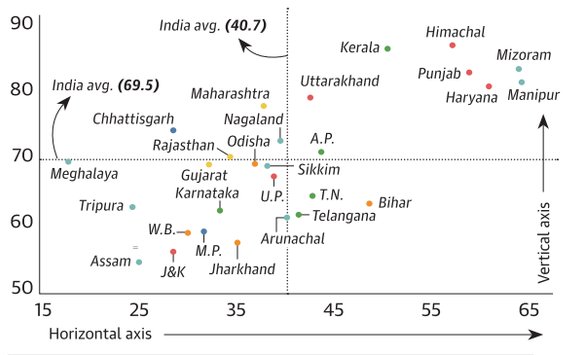
DATA POINT

Abysmal standards

In as many as 443 of 586 rural districts, less than 50% of students in Grades VI-VIII knew how to carry out basic division, ASER-2018* revealed. Learning levels measured by knowledge of division and the ability to read simple texts remained low across India. **By Vignesh R.**

State-wise comparison | The scatter diagram shows the wide gulf between the top six States and others in learning levels. On the **horizontal axis**, the % of VI-VIII students who **could carry out simple division** is plotted. On the **vertical axis**, the % of VI-VIII students **who could read Grade II-level text** is plotted. States are coloured based on their geographical location



- Students in Manipur & Mizoram had good learning levels while Meghalaya, Tripura & Assam had the worst
- Students in Bihar fared badly in reading, but had better maths skills. This trend was also seen to an extent in T.N.
- Haryana, Punjab and Himachal were among the best in both aspects. J&K, M.P. and W.B. were among the worst
- In Punjab, none of the districts had worse reading levels or maths skills than the national average (see Table)

Levels across districts | Table shows rural districts in each State with **poor reading skills** (the reading levels of students in these districts was lower than the national avg.) and **poor math skills** (lower than the national avg.)

State	Districts with poor reading skills	Districts with poor maths skills	Total districts
M.P.	39	42	50
U.P.	38	36	70
Bihar	29	4	38
Karnataka	22	23	30
Jharkhand	21	17	24
Assam	18	23	26
T.N.	18	13	31
Rajasthan	17	19	33
Odisha	15	17	30
Gujarat	13	22	26
W.B.	13	13	17
J&K	10	10	14
Telangana	7	5	9
Maharashtra	6	20	33
Chhattisgarh	6	14	16
A.P.	6	6	13
Nagaland	4	7	11
Arunachal	4	2	6
Tripura	3	4	4
Sikkim	3	2	4
Meghalaya	2	7	7
Haryana	1	1	21
Manipur	1	1	8
Mizoram	1	0	8
Uttarakhand	0	5	13
Himachal	0	1	12
Kerala	0	1	12
Punjab	0	0	20

*Source: Annual Status of Education Report, 2018

FROM The Hindu. ARCHIVES

FIFTY YEARS AGO FEBRUARY 13, 1969

United Front swept back to power in West Bengal

The United Front was swept into power in the mid-term poll in West Bengal to-day [February 12]. The 12-party combination registered a series of successes and won an absolute majority in the 280-member Assembly. No single party has been able to win an absolute majority in the 425-member U.P. Assembly. The Congress obtained 208 out of 420 seats for which results have been declared. The picture emerging from the results of 260 seats declared so far to the 318-member Bihar Assembly does not hold out easy prospect for any single party to secure absolute majority though the Congress emerged as the largest single party with 100 seats. With 241 results announced in Bengal the U.F. bagged 181 seats and the Congress 50 seats, the other 10 being shared by other splinter parties and independents.

A HUNDRED YEARS AGO FEBRUARY 13, 1919

Reform Committees.

'The Times' [of London on January 31] says that the Committee appointed to enquire into the organisation of the India Office is strong and representative. Lord Crewe gained intimate experience of the questions at hand when he was Secretary of State for India. It is perhaps a little unfortunate that he has already fathered one scheme for India Office reform, which threatened to undermine the Secretary of State's Council and came to untimely end. Sweeping constitutional changes in India, however, were not then contemplated, and 'The Times' expresses its conviction that the Committee will approach the new conditions with an entirely open mind. The principle involved is really very simple. We cannot offer India self-government progressively and simultaneously keep her bound hand and foot to the India Office. The Montagu-Chelmsford Report recognised this very frankly.

CONCEPTUAL

Ancient astronaut hypothesis

ARCHAEOLOGY

This refers to the proposition that human civilisation is the product of an intelligent alien visiting the earth during prehistoric times and establishing contact with human beings. The origin of various religious beliefs, for instance, has been attributed to alien gods establishing contact with people prior to the age of recorded history. The ancient astronaut hypothesis was first proposed by Swiss writer Erich von Däniken in his 1969 book *Chariots of the Gods*? It has been rejected overwhelmingly by scientists who consider the idea to be pseudoscientific due to the lack of any credible scientific evidence.

MORE ON THE WEB

Nelson Mandela exhibition, with several unseen artifacts, opens in London

http://bit.ly/2XOL8UD