From Scotland to China: Understanding Energy Balance for Three Decades and On

By XIN Ling (Staff Reporter)

Dr. John Roger Speakman at his Molecular Energetics Lab of the CAS Institute of Genetics and Developmental Biology in Beijing. (Photo: XIN Ling)

Beijing's March was still chilly, but near the Olympic Green, the cherry blossoms at the Institute of Genetics and Developmental Biology (IGDB), Chinese Academy of Sciences had grown quietly into their peak bloom. Swaying in the gentle breeze of spring, the endless tiny pink flowers along the campus' main road were extending the warmest welcome to the visitors here.

As two students walked into a laboratory on the fourth floor of the research building, each holding a big ice box with labeled tissue samples preserved in it, their supervisor John Speakman was working in his white lab coat in front of the microscope. "These are ready for analysis," they told him. "Great job!" John came over and patted on their shoulders, his face breaking into a wide smile.

Greeting me into his lab with a firm handshake, John took some time off to show me around. "This is for measuring the body composition of a mouse without killing it," he pointed to a machine beside the door – "Just put the mouse in the tube and click the button, and it will tell you how fat the mouse is." On the other side of the room, there was a cage in which some small, black mice were jumping up and down joyfully.

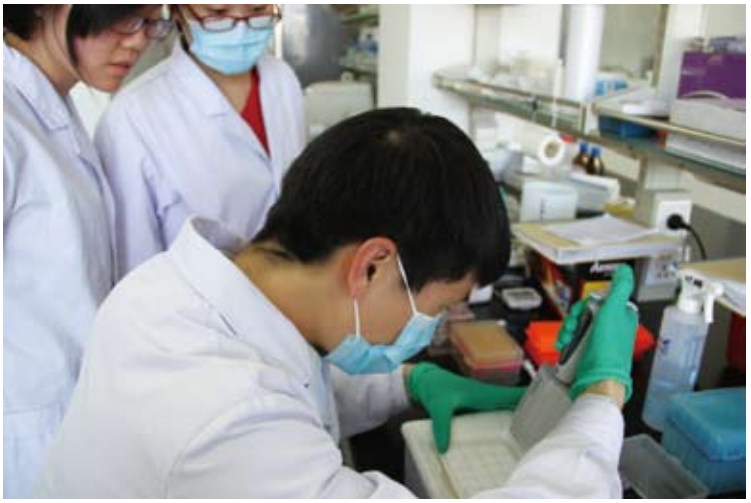
John carefully took one out and put it on his right forearm. "We use them to study the causes of obesity," he explained. Then he noticed the naughty guy had an accident on him. "Can't stop them," his laughter was infective.

Where Has All the Energy Gone?

This was just an ordinary workday for John, after he shifted research focus from the University of Aberdeen in Scotland to Beijing more than four years ago. As a foreign expert who spends nine months in China each year, he joined IGDB in 2011 through the "One-thousand Talent Program", a top-level global talent recruitment program sponsored by the Chinese government.

And he named his lab at IGDB "The Molecular Energetics Lab". Though largely a continuation of his past work on energetics, which means the study of energy balance and all related subjects, the lab is designed somewhat different from the one at Aberdeen "to do a bit more mechanistic work related to the molecular level".

Energy balance, a field in which John has been engaged for over three decades, plays an important role



A PhD student from John's group is pipetting samples. (Photo: XIN Ling)

in our daily life, he said. For example, it is a key part in obesity and ageing, and it has considerable impacts on diseases like diabetes. Also, the study of energy balance offers a fundamental way to understand how animals evolve. "If you hear any story about the way animals evolve, at some point it involves energy – like the animals are trying to save energy, get energy, or do something with energy. So understanding energy is the key to all sorts of things."

His interest in energetics was first inspired by his undergraduate teacher David Bryant, who later became his PhD supervisor and introduced to him one of the most useful skills throughout his research career—the Doubly Labeled Water (DLW) technique, a method invented in the 1950s by researchers at the University of Minnesota to actually measure energy expenditure. It turned out that John not only well mastered DLW, but further developed it to maturity by using it to study various animals in various contexts.

From his bookshelf, John pulled out a blue hardcover and passed it to me. It was a monograph he authored on DLW back in the 1990s.

The rationale of such a technique, however, sounds not too complicated, which takes advantage of the different metabolic rates of in vivo hydrogen and oxygen isotopes. According to John, if an isotope of hydrogen is put into the human body, it would go in and then slowly get washed out through urination, feces and evaporation. Similarly, if an oxygen isotope is injected, the same thing would happen but the oxygen comes out

John explains the operation of a Soxhlet apparatus. (Photo: XIN Ling)

faster: it is washed out not only by all the water, but also by respiration. As a result, as the two isotopes slowly disappear from our system, their concentrations diverge with time, telling us the energy expenditure.

"The really beautiful thing about this technique is that you only need two points, one at the beginning when (the concentrations of) the isotopes are close together, and one at the end when they are far apart, to tell how much they spread out," John said.

Using DLW, his groups are responsible for at least 20% of the papers ever published to measure the energy expenditure of mammals. Most of them are through collaboration, including the giant panda research which made the headlines after being reported by the journal Science last July.

"People have always speculated that the giant panda must have a really low metabolic rate, because its bamboo diet is so rubbish that it just can't get enough energy," John explained. "It couldn't be an Olympic sprinter or something like that because it can't get enough food to support that life style. If you look at the life style of a panda, he basically just sits down all day eating, moves around a little bit, eats a bit more and doesn't really do anything at all."

But nobody had managed to measure exactly how much energy they consume until John and coworkers from the CAS Institute of Zoology used DLW to figure that out: their subjects included five pandas at the Beijing Zoo and three living in the Foping nature reserve in central China's Shaanxi Province.

It turned out that these carnivore-turned-vegetarians with a mean body weight of 92 kg have incredibly low daily energy expenditure—only 5.2 megajoules, or 1250 calories on average—compared to, say, a 90 kg human living in modern society who burns about 3000 calories per day.

"For its body weight it's almost the lowest metabolism that's ever been measured in a mammal", John revealed, "I guess that's why our paper was in Science."

To find out why the panda has such a low level of metabolism, the scientists went on to look into its genome, as metabolism is generally related to certain physiological systems such as the thyroid system: people with low levels of thyroid hormone put on weight easily and tend to be slow, while those with high levels of thyroid hormone are often thin and hyper.

"It seems that there is something wrong with the

panda's thyroid system—not really something wrong, but something evolved by the thyroid system. There is a gene in the panda called 'DUOX2' that has a panda-specific mutation in it. DUOX2 is involved in the last step in the in the production of thyroid hormone, and is considered to regulate the synthesis of the hormone."

But still, why was that selected—why did evolution favor the panda that had the low metabolic rate?

"It's because it's eating the rubbish food," John went on to explain. "If it has the low metabolic rate and it doesn't have to eat as much food, then it's easier for that panda to survive compared to the one with the normal thyroid hormone levels which has to eat much more food."

In other words, though it is usually disadvantageous to have a low level of thyroid hormone, it could be an advantage in certain situations, just as the panda found itself in that situation eating the bamboo.

Stephen Simpson, a physiologist and nutrition modelling expert at the University of Sydney, spoke highly of John's work on DLW. "His doubly labelled water technique remains the gold standard for measuring energy expenditure," Stephen said.

WANG Wen from the Kunming Institute of Zoology also applauded the unique technique. "DLW laid the foundation for many of John's world-level achievements."

WANG Lu, one of John's PhD students at IGDB, still remembered her supervisor showing off a special "souvenir" from the Beijing Zoo. It was his expensive leather jacket torn by one of the pandas, who was trying to reach through the bars and grab the bamboo as John was feeding him. John proudly pointed out the damage to everyone and declared that he was going to wear the jacket more often, because "if someone asks how I got this, I could say in all honesty, 'I got it in a close encounter with a giant panda!' And there's no cooler answer!"

The "Rule Breaker"

For John, the study of energetics is not only a way to understand the energy balance in different animals, but more importantly, it offers unique insights into some fundamental issues in evolution.

For instance, in traditional ecological theories, the main limiting factor for animal survival and reproduction is the food supply in the environment. It is almost "engrained" in the whole of ecology that the supply of food is limited.

But his view is a little different. What is really limited, he suggested, is not the external supply but animals' physiology—their intrinsic ability to expend the energy.

"Just think about your running performance," he said. "Your performance to run is not decided by how much food you can eat to sustain the energy for the running, but by the fact that you can't dissipate enough heat to avoid getting overheated or hyperthermic—that's the true big constraint on how much you could do in running."

Therefore, the main limit for an animal is not how much food it can get, but "how much heat it can get rid of", John argued in one of his papers published in 2010 with a colleague in the Journal of Animal Ecology. That is, what really matters is not the energy supply but the energy expenditure. And it doesn't matter how much food is available, because the animal's physiology already restricts how much food it can utilize.

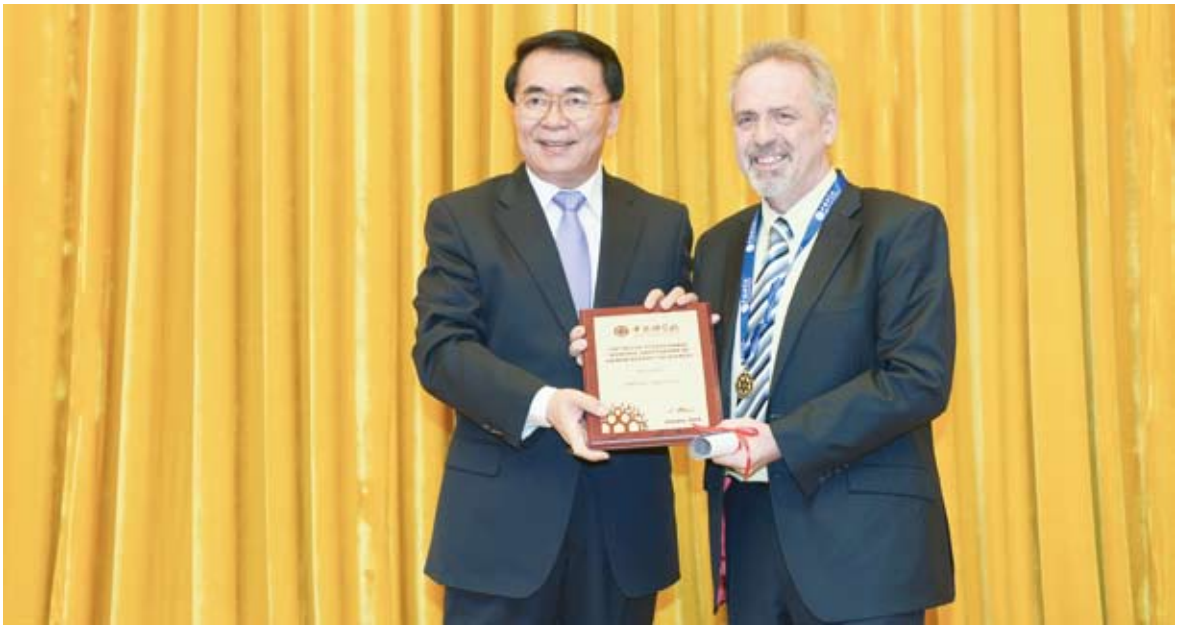
Based on such a theory, John and his collaborators have made many interesting predictions. For example, what sets a limit on how big an animal can be on earth? From the perspective of energetics, as all body tissues are generating heat, our metabolism is determined by our volume, while our ability to get rid of that heat depends on our surface. However, it is also known that as animals become bigger, their volume increases much faster than their surface. "At some point, an animal would become so big that it couldn't get rid of even its basal metabolism", he said, and that would finally put an end to growth in size.

The theory also readily answers another question: why the biggest animal on earth is much bigger in the water than on the land? The blue whale lives with a tongue the size of an elephant—probably because the water conducts heat much better than the air does, and is thus more conducive to heat dissipation.

"This is an example of how, by understanding energetics, it can tell you something about the structure of life on earth, the way things are that isn't immediately obvious," John believed. "Otherwise, those questions could be really difficult to answer."

This unconventional perspective led him to question another classical theory in energy and obesity research: something called the "thrifty gene hypothesis".

Obesity is a really strange phenomenon. Scientists have long ago discovered that there is a very high genetic contribution to obesity: it's about 65% genetic. But since it is so disadvantageous and increases all kinds of disease risks from diabetes, cancers to heart diseases, how come



Dr. John Speakman was conferred on the Award for International Scientific Cooperation of the Chinese Academy of Sciences by CAS President BAI Chunli on January 14, 2016. (Photo: IGDB)

evolution favored obesity?

One answer to this question came in 1962 from American geneticist James Neel, who used famine to account for the genetic origin of obesity. According to his thrifty gene hypothesis, people used to deposit fat to survive the next famine. So the genes enabling fat deposition spread in the population and into the modern society where there is no more famine at all.

In John's eye, this interpretation isn't true. On one hand, there is rarely a situation with absolutely no food available; what really makes the difference between survival and not survival is whether the person can get that food or not. On the other, statistics have shown that people who died in recent famines were not lean people, but old people, or young children who didn't differ in obesity.

So John and his students came up with a novel way to test the idea. If obesity was advantageous they argued then it would also be a secondary sexual characteristic: people would see fat people as attractive because they would carry advantageous genes. To test this idea, first, they built an evolutional model to work out the optimum body fatness, by combining two contrasting things: being obese is good when there is a famine, but not good when there is no famine.

"The relationship between physical attraction and obesity should go like this", John drew a parabola on my notebook. The body mass index (BMI) at the bottom of the curve, as his model predicted, was approximately 24. It meant that people with a BMI of 24 should be maximally attractive, if the thrifty hypothesis was right.

He then showed me a piece of paper, on which there were images of women with different levels of fatness (BMIs): the interviewee could not see their faces or any other details, but just how fat they are. The task was to rate the attractiveness of these women, and put them in order from the least to the most attractive.

And over the last few years, such a survey had been conducted among more than 1300 people, male and female, from three Asian populations, three Caucasian countries and four African countries as an international research consortium under John's leadership.

"In Beijing, we had a total of 209 volunteers aged between 18 and 55. Each of them was given ten minutes to rank the attractiveness of 21 women in the pictures: the leftmost being the least attractive and the rightmost the most attractive. The BMI spectrum was from 18 to 40," said WANG Guanlin, John's PhD student at IGDB and lead author of their research paper published later in the journal *PeerJ*.

"It turned out that most people chose to put picture No.6 on the far right, who is obviously one of the thinnest —with only 23% body fat and a BMI of 18," she said.

John and his team at the CAS Olympic S&T Park in north Beijing, March 2015. (Photo: IGDB)

As similar results were reported from the other nine societies, there appeared to be a huge gap between the predicted optimum BMI of 24 and the actual result of only 18 to 19. "There is no famine effect whatsoever", John argued.

An alternative he put forward to explain obesity was not selection-based. "Maybe two million years ago there was a selection, but then the selection stopped. What happened afterwards is people got the mutations in the genes that regulate their body weight, but they are never selected out of the population because there is no selection pressure."

"So these genes change by a process called 'genetic drift', and people have the susceptibility just because of the random chances that happen over that two million years' time," John proposed.

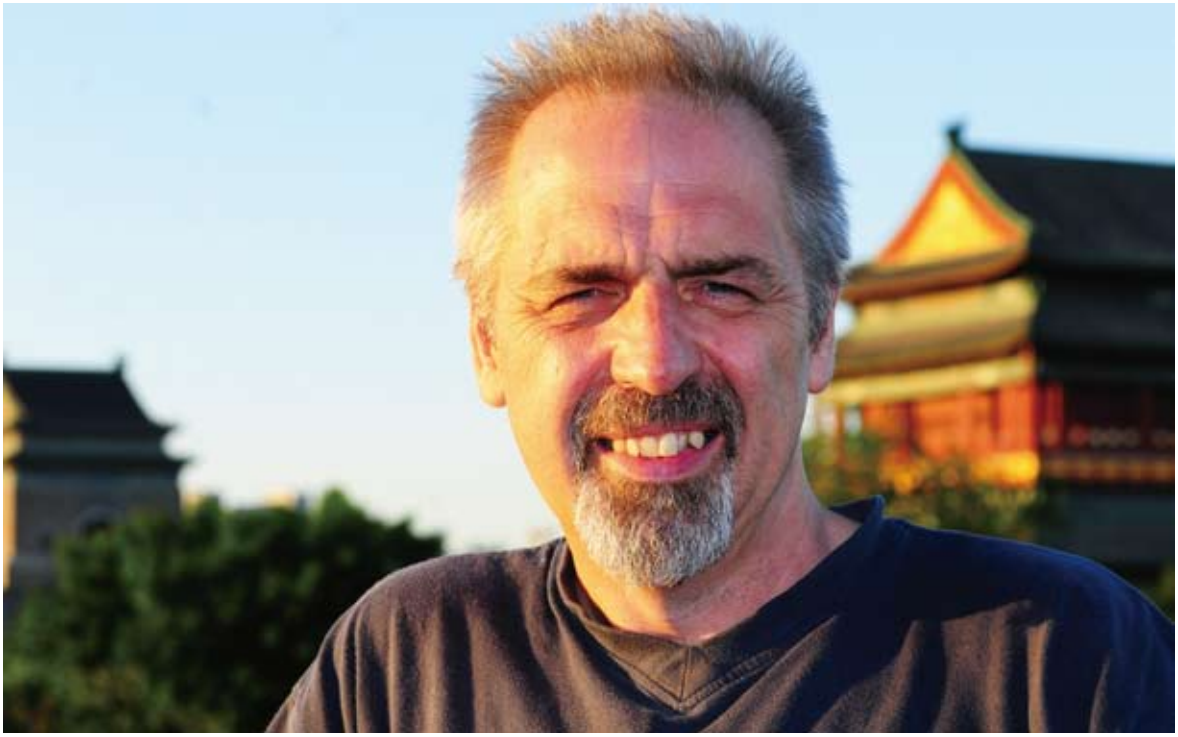
You may not want to believe it but it is plausible: your chance of being fat is just like a lottery, and the one to blame is your ancestors who happen to have accumulated disadvantageous mutations in the control system.

David Allison, a world class obesity expert from the University of Alabama at Birmingham, said that he would rank John as "one of the most innovative and creative scientists". Their academic discussion starting right from John's genetic drift theory, the two successfully applied for a large grant from the National Institutes of Health (10 million USD) and have been working together since then.

"John was always very welcoming of my challenging dialogue," David told BCAS. "I greatly admire his work and especially the depth of his thinking. He is one the rare individuals who has gone from topics as diverse as the methodology of energy expenditure measurements using isotopic techniques, to statistically informative modeling of evolutionary genetic hypotheses, to field observations, to experimental laboratory work, to elucidating the methods of action by which caloric restriction may affect lifespan, and others still. And yet, in each area, his work is marked by a depth of understanding and thought that vastly exceeds what most scientists bring to the table. He is truly one of the great thinkers of our field."

"Obesity Is Coming to China"

With John's guidance, WANG Lu is now using mice with the same genetic background to examine the diet effect on obesity. "The factors leading to obesity can be extremely complicated, and we are looking at one factor —early stage feeding—like the nutrition a fetus gets from the mother, the milk it gets from breastfeeding, and the food given to it immediately after weaning: how would



John says he really enjoys working and living in Beijing, which is now his second home. (Photo: Speakman)

these things change body weight later on, and what is the mechanism in the brain that controls food intake, energy expenditure and the balance between them? I'm really very interested in digging these things out at the molecular level," she said.

The nutritional environment has a main effect on a gene-environment interaction like the development of obesity, John said. "When you are very young, what you experience in that stage sets you up for the rest of your life."

And it takes a long time for a big environment change to show its effect. For instance, when the KFC, McDonald's and other similar fast food places move into a country, there is no impact on obesity because the people were born when their parents were not eating that food. But when they have children, their children are potentially programmed to have bad effects later in their life.

In terms of percent of obesity, China is "about 50 years behind America", estimated John. But like elsewhere in the world, the increase seems to be unstoppable—and exceptionally rapid here. He showed me several graphs of obesity in children in China between 1985 and 2010. It is a stunning eighty-fold increase. In 1985, the obesity in children was just 0.1%; now it's more than 8.1%.

And China just opened up to those companies ten years ago. "Thirty years later, that's when you start to get a real problem."

Although there is still a long way to get to the same obesity level as the Americans now have, by then it will be impossible to reverse the problem, he warned. So it's better to do something now while everybody is mostly thin.

For the two big ideas to deal with obesity—food intake and exercise, "I'm pretty sure there is almost nothing to do with exercise," John said. With colleague Klaas Westerterp from the Netherlands, he had looked at all the DLW data back to the 1980s and found the energy expenditure of people between 1990 and 2008 was completely flat. But the food supply has gone up by 20%.

"It's all driven by food intake."

Good thing is: countries often have a lot of control over the food supply. The government can simply control it by issuing licenses for restaurants to open and operate; or by controlling how easy it is for people to get access to high sugar, high fat food, like putting high taxes to make candy bars "economically unattractive". This could be especially feasible in China, John suggested, where, unlike in the western countries, the big food companies do not exert a lot of power on the government.

Meanwhile, KFC is not necessarily to blame for the

obesity problem, as even the scientists themselves are not sure what really happens. For instance, there is a big debate going on in the US now—whether it is the fat content or sugar content in a diet that is more important. And that is one thing John's team is working on now at IGDB.

"We are changing the dietary component and looking at what impact it has on mice. The question is quite complex and not exactly what people usually think. We have made some small advances, but there is still a long way to go before we fully understand it," he added.

A Scotsman in Beijing

John is extremely happy these days, because three students from his lab have been announced to win the best abstract award of the International Congress of Obesity, which is a premier obesity research event attracting thousands of participants from all over the world.

Each time, the conference gives out five best abstract awards to recognize the work of new investigators. Dick Atkinson, who has been chairman of the committee that administers the award since they were first started, said that it is "completely unprecedented for three students from the same group to be selected, and was a real vindication of John's mentoring skills – the decision of the Chinese government to offer him a position in China and for him to accept it."

John is very proud.

So this coming May, WANG Guanlin, WANG Lu and another student from IGDB will get their travel and accommodation free to attend the meeting in Vancouver, present their work at a special oral session, and have the chance to compete for the overall new investigator prize.

"I have really learned a lot from my teacher. He always inspires me to think deeper and do research with an open-mind," WANG Lu told BCAS.

"John is an amazing mentor to his students, helping them to be the most productive scientists possible, and providing them with exciting scientific opportunities," said Daniel Promislow, an expert in ageing and longevity at the University of Washington. "He also has a fantastic ability to bring together people with different kinds of expertise, to facilitate interactions, and to bring a big complex project with many people and many complex aspects to fruition."

Now, John is having a big group in Beijing—14 people.

"Many people in the West have the view that students in China are very obedient, less creative and they always do what the professor tells them to," John mentioned.

"It's completely rubbish," he went on. "My own experience is that the students here have just as many as ideas as the students in the UK—and sometimes more creative ideas. They seem to read the literature more, and they really have no problem in telling me that what I'm saying is wrong."

For him, CAS is also an ideal place to work at. "There are so many opportunities, and it's just great," he really seemed to enjoy the work and life here.

In fact, before settling down in Beijing, he was already coming to the city every year since 2004. Then one day, his collaborator from the CAS Institute of Zoology WANG Dehua said to him, "you know, John, there is this One-thousand Talent position that you can apply for. You can spend most of the time here and then go back to the UK." So he applied and it was successful.

"Actually what brought me to China was I just really love being here," John confessed. Beijing is a big city, and like most big cities, it has a lot of things to do. For instance, "you can go to a really nice restaurant and a different one each week for a whole year". For those who like ballet or opera, the best companies always come to Beijing because it is a capital city.

And he is definitely planning to stay longer. "With 14 people working in my group and my wife teaching here at an international school, this is where I live now. I've got no reason to go. As long as CAS is keen to have me, I'm keen to stay."

His Thousand Talent contract expires by the end of this year, but the contract with IGDB will go through till the end of 2018.

"It's funny because we started to call this place 'home'," he told me. His daughter gets "annoyed" sometimes because she is confused when John and his wife are talking about going home. "My daughter doesn't know which home we are talking about, the home in the UK or the home in China."

Tight as his schedule always is, John never forgot to relax and have his favorite cup of coffee. At the end of our interview, he grabbed his backpack, walked down with me, and straddled onto his bike. It was 11 am. "I need to leave now for Starbucks for a change of environment. Or it will be packed with people by noon." Sounds like a local Beijinger indeed. Then he waved goodbye and disappeared with his bike into the endless cherry blossoms.

(By the time this article is published, BCAS is happy to hear that John's student WANG Lu had won the overall prize at the XIII International Congress on Obesity in Vancouver in May.)