**Transcription of Podcast file: *Nature* Press Conference with Dr. Eran Elinav and Prof. Eran Segal**

**Courtney**: Hello, ladies and gentlemen, and welcome to the *Nature* press briefing call. My name is Courtney and I will be your coordinator for today's event. For the duration of the call you will be on listen only. However, after the call you will have the opportunity to ask questions. If you need assistance at any time please press star zero on your telephone keypad and you will be connected to an operator. I am now handing over to your host, Rebecca Walton, to begin today's conference. Thank you.

**Rebecca Walton:** Hello everyone and welcome to today's *Nature* press briefing for the paper entitled *"Persistent microbiome alterations modulate the rate of post-dieting weight regain",* which will be published online in *Nature* this week.

Before we begin, I would like to remind you all that the paper and this briefing are subject to an embargo of 4PM London time, 11AM US Eastern Time, on Thursday the 24th of November and please note this atypical embargo time.

First, we are going to hear from two of the authors on the paper: Dr Eran Elinav, from the Weizmann Institute of Science and Dr Eran Segal, also from the Weizmann Institute of Science. There will be time for questions after we have heard from our speakers.

So, I would now like to hand over to the first speaker, Dr Eran Elinav.

**Eran Elinav**: Hi there, hi everybody. So, this is Eran Elinav and I will be briefly telling you about the main findings of our story. In this study we focused on a relapse in obesity, which is commonly also called yo-yo obesity, which is a common feature of overweight and obese individuals all over the world and manifested in cycles of obesity in successful dieting which gradually result from the cycle in increased weight gain in obesity over time.

Now, while we, and many others, are attempting to make progress in understanding obesity, the concept of relapsing obesity remains largely obscured.

In this study we utilised three different models over relapse obesity in mice, that involved different diets, different durations of dieting and medical interventions assisting in dieting. And in all of these models we could notice that recurrent episodes of obesity followed by successful dieting were associated with gradually worsening weight gain, diabetes, and hypercholesterolemia, which is very similar to what is observed in recurrently obese humans. We discovered that – following their successful diet and full return to the original weight – all the physiological and metabolic parameters also returned to full normality, except a single set of parameters: which is the gut microbiome composition, function and metabolism which remains severely altered for a prolonged period of time that exceeds in mice by five-fold the period that it took them to actually diet.

Now, what was important in this study is that we found the altered microbiome to contribute to exaggerated weight regain upon re-exposure to obesity promoting conditions. And this was very important and we took a lot of effort to prove this in several ways, including the administration of a wide spectrum of antibiotics during the dieting period which wiped out the microbiomes, or transfer of these post-dieting microbiomes which features – if you may – a memory of previous obesity episodes into drug-free mice, which developed upon transfer the same exaggerated obesity and metabolic disturbances as the original mice. Of course, this by no means implies that we think antibiotics should be added as a component of dieting efforts, but this was a very elegant way – in our opinion – to prove the involvement of the microbiome in this recurring obesity process.

Given the fact that we found the microbiomes to be so important in promoting this persistence or memory of past obesity episodes, and the risk to develop more obesity in following episodes, we produced a machine learning algorithm, which is based on the microbiome, which enabled not only to predict who would get exaggerated obesity in following cycles of obesity, but it enabled us to actually predict the actual amount of weight which each mouse would gain based only on the microbiome. And if this would be applicable in humans, it would mean that based on the microbes one could tell a person who has successfully dieted, how much he or she would regain if they would go back to their obesogenic dietary habits.

And finally, in this study we developed two proof-of-concept approaches that may be used in the future of potential treatments of relapsing obesity.

The first was faecal microbiome transplantation which was performed during the post-dieting period in which the mice were already back to their original weight. And in this period we replaced this persistent microbiome with a naïve microbiome by faecal microbiome transplantation and completely reversed the tendency to develop exaggerated obesity in following cycles of obesity.

The second proof-of-concept approach is based on molecular understanding which we gain on how the microbiomes <un xx 00:05:35> this tendency for exaggerated weight regain and we found two key metabolites which are normally metabolised by the microbiomes by mixing in these post-dieting microbiomes – and these are molecules of the isoflavonoid family – and we found that normally they affect the host and its fat tissue and its ability to extract energy from fat. So, in the absence of these two molecules in mice they develop a tendency to be more obese because their brown adipose tissue spent much less energy in creating heat therefore creating more fat. And in treatment we replenished these missing metabolites and this corrected the defect and abolished the exaggerated weight regain in following cycles of obesity. And this <un xx 00:06:25> treatment, which we term post-biotic intervention <un xx 00:6:29> therapy is now being researched by us in humans and may potentially complement other microbiome-targeting approaches such as prebiotics and probiotics.

**Rebecca Walton**: Thank you. So, will we now hear from Eran Segal?

**Eran Segal**: Yeah, so, hi everybody. So, I would like to add our joint thoughts on the higher-level meanings and implications of the study and bring out a few points that we think would be interesting to discuss.

So, the first one is, obviously, obesity is a world wide epidemic these days and it is heavily researched. It is very common in humans and I think one of the novel aspects that we examined here, is we looked at the phenomenon of relapsing of obesity which is also very common and much less well understood. So, it is also very well-known, and published, that diets generally fail and do not work and it is typically not because they do not work initially. Initially— and there are many different strategies – initially, they work, but the problem is with the weight regain. And then people go on diets over and over again and we keep failing in that. And so, just first of all, investigating and looking into this question is one novel aspect of this work and obviously a very common problem that we see in humans. We would also like to point out that this study obviously was performed in mice. So definitely needs to be checked in humans. However, we believe that this will, a similar phenomenon and similar involvement of the microbiome in humans would also persist and we are also basing this, even in mice, we observed this in three different dietary regimes that we gave the mice and observed this enhanced weight regain effect.

Another interesting discussion point is, when we think about the involvement of the microbiome with us, and when we think about us together with the microbiome being a super organism – if you will – that really acts together, and in this respect I think this work adds some insight on how the microbiome acts as a buffer to changes in our diet. So, what we showed here is that upon a change in the diet – in this case a high fat diet that the mice go onto – in this case the microbiome exhibits a persisted state that remains for a very long period of time, even after we suddenly switched to a normal chow diet in this case for the mice. And while in many cases perhaps the microbiome during our evolution has evolved to buffer us and protect us, in this case it is now acting against us with this persistence, or – if you will – this memory encoded by the altered configuration of the microbiome which acts against us, in this case, to persist in the state of the previous high-fat diet and then exhibit the, in this case, adverse effect of enhanced weight regain upon a secondary exposure to the high-fat diet.

Another finding in this study, which also has much relevance, is that when we transferred the microbiome into germ-free mice we saw the enhanced weight regain effect only when these mice were also on a high-fat diet and not when these mice were on a normal chow diet and so that indicates that the microbiome, by itself, may not be sufficient to induce this effect, but it is in fact the combination of the microbiome and the diet which is what we want to understand of how they exhibit this effect. And in that respect, I will even go a step further and say that it's really down to a personalised microbiome, because as Eran Elinav mentioned before, the computational predictor that we developed as part of this work was able to take only the microbiome configuration and, from it, be able to predict what the weight regain – what the exact weight regain – would be of individual mice when they now are put on the same diet.

So, it is not just that there were two groups of mice in that prediction, because every mouse, when we measure, every mouse exhibits a different amount of weight that it gains and we were able, only looking at the microbiome, to not just separate the two different groups, but to each individual mouse be able to predict the amount of weight that it will gain. And so, if we think of potentially doing that in humans – and this is ongoing studies that we are now engaged in – then one promise would be that we might be able to look at the personal and unique microbiome configuration that each of us host and use that unique microbiome configuration in order to be able to say, and predict, which types of diets would induce which types of changes in weight.

The fact that we were able to use the microbiome as a read-out – in fact as the only read-out – that persisted after the introduction of the high-fat diet, also indicates that this is now perhaps a marker that we can use in order to understand the length, in terms of time, timewise, the length of the window in which the effect, or the persistence, would remain. And this would be something to profile in order to understand for how long we still see the persistence of the previous diet.

Eran Elinav touched on this before as well, but more-and-more we, and others, are beginning to understand the interaction between the microbiome and the host and how that interaction occurs. And we more-and-more understand that this is going on to a very large extent at the level of molecules that are exchanged between the host and the microbiome. And this work is also an example of specific metabolites that we were able to see; in this case a differential degradability of the microbiome for particular molecules. And by looking at these molecules we were able to identify molecules that could help us in intervention. And so, this could also indicate that, even though many of us have different particular microbiomes species, when we go and look at the level of metabolites this is where we could find common ground across different human individuals and then perhaps use that either as biomarkers or even as molecules that we could intervene as we did in mice, in this study.

And so, the final point is, really, that we believe that this can be promising to do this in humans and see if similar molecules or different molecules, but same type of methodology could also be applied. And if you think about it, in this case, if successful, we would actually be intervening at a very different point in time. Not at the point where the individual is obese, but in fact perhaps after a dietary intervention. Even though the individual has lost weight, there still remains the microbiome to deal with and this type of approach would then go at the more lean state and see if by various means we could intervene and alter the microbiome which may have a causal role in why, upon a secondary introduction, of a— or going back to normal dietary patterns we would see enhanced weight regain.

**Rebecca Walton**: Thanks very much to both of our speakers. We can now take questions from journalists on the line. And during the Q&A if you can please mute your line if you would like to type while the authors answer your questions. Thank you.

**Courtney**: Ladies and gentleman if you would like to ask a question, please press star one on your telephone keypad. If you have changed your mind and you would like to withdraw your question, please press star two. You will be advised when to ask your question.

We currently have no questions coming through, so just a reminder, if you would like to ask a question, please press star one.

**Rebecca Walton**: While we wait to see if anyone has any other questions – this is Rebecca from the *Nature* Press Office – I just wondered if the authors could talk a bit more about some of the ongoing studies looking at what the next steps might be to discern whether or not these findings could be applied to humans eventually.

**Eran Elinav**: Sure, this is Eran Elinav. And of course, the next obvious step is to use humans and to study it in a population of humans that suffer of similar relapse in obesity phenotypes – and, you know, there are many of these – according to different studies up to fifty two percent of all obese individuals featured this type of relapse in obesity pattern in their weight behaviour. And there are many subgroups that are of particular interest: people that undergo bariatric surgery and other groups of people. And we aim to study these populations using the same methodology that we developed here in animal model. We are not sure whether the exact same molecule and the exact same <un xx 00:17:50> would be applicable in humans. But it seems that the general concept may hold true in different species, including in humans. So, the trick here is to understand the mechanisms in humans to identify the relevant molecules that are linked to the microbiome of relapsing obesity in individuals and then to find ways developing, from this proof-of-concept therapeutic approaches that we developed in mice, to intervene as a means of prevention of excessive weight regain or excessive development of blood sugar disturbances in people who have already undergone successful dieting. And if you think about it, this is the population which is the most frustrated population, because most dieting approaches, when you look at them in the first few months, are highly successful. And it does not matter whether it is done based on advice given by your dietician, your family physician or whether you buy them in a book at the airport. However, this overwhelming data that if you look at these individuals for twelve months or longer, the vast majority, ninety five percent, and more of these individuals go back to their original weight, or to higher weight than they started with. And so, it is this period of success in the short term, which is the one that has not been really targeted so far. And we see that the microbiome dictates the future for these individuals with these initial successes. So, we really aim at this window of opportunity in order to understand what we can do in terms of the regulation of the microbiome to optimise the long-term success of these individuals. And I think this lack of long term success is what marks our general inability to control the obesity epidemic worldwide.

**Rebecca Walton**: Thank you.

**Courtney**: We have a question coming in from the line of (Volker Masek). Please go ahead.

(**Volker Masek**): Yes hello, this is (Volker Masek) with the German National Public Radio in Cologne, in Germany. My question would have been the same as Rebecca's. You are planning to have these human trials. Can you give me an idea of when they are going to start, where they are going to start and how long it might take to get an answer – whether this really works in humans as well?

**Eran Segal**: Yes, so this is Eran Segal. So as Eran Elinav mentioned before, we have ongoing trials that we have actually started where we are— what we are doing is we are… And to answer your question we are starting them here in Israel and we are… what we are doing is in the first stages. We are observing the changes in the microbiome that occur between obese individuals and lean and also what happens after dieting. We already know from previous work that we already did that there is an ability, even if you take a snapshot of different human individuals, we have the ability – partly – to distinguish them based on their microbiome because it is— we do find differences between obese and lean individuals. And so, the first step in observing this in humans is to follow also a dietary change, which we know will result in successful dieting in the first period and then observe the changes in the microbiome: do we see, as in mice, after such an observational period that actually the microbiome also would persist in the… to remain… to resemble the obese state as what occurred in the mice set-up. And in parallel to that we are also doing the other Omics profiling, like double Omics, to examine the molecules that are… the state of the metabolites and molecules between human host and microbiome and specifically the flavonoids that we examined, but also unbiased to a very comprehensive way. And after this first stage is completed I believe that we hopefully will be able to identify targets and different ways by which we could perhaps intervene and then design the second stage of such a study where we would intervene possibly with different molecules, possibly in other means, it all depends on what results and what microbiome configurations we see after observing what happens before and after dieting.

**Courtney**: Our next question comes in from the line of Irene Klotz. Please go ahead.

**Irene Klotz**: Hi, thanks very much and thanks for taking the time to do this today. I wanted to know, in the mouse studies, at some point did the microbiomes stay with what was developed under the lean diets, or no matter how much time passed, did it revert back— or did the microbiomes stay as it had been under the obese models? And also, do you have a sense of whether the microbiome is genetically determined, or is it believed to be more a function of what people or animals eat? Thanks.

**Eran Elinav**: This is Eran Elinav. Thank you for those two good questions. As for your first question: what we observed – and this was the heart of the study – was that following successful dieting to a point where no one could distinguish between mice that were once obese and mice that were never obese, in terms of any metabolic parameter, including their weight, the microbiome remained altered and it remained altered for an exceedingly long period of time of up to six months. So, just to give you a flavour: mice in captivity live an average of two years and we observed the microbiome to be persistently altered for six months, which is a very long period and an unexpected period of persistence, or of memory. Importantly, while the point arrived in which the microbiome for six months was no longer different between mice that were previously obese to mice that were never obese. At that point when we reinduced the obesity by administration of high-fat diets, we no longer could see the exaggerated weight gain in these previously obese mice. Which means that once you get rid of the differences in the microbiome, you wait long enough then you close this window of risk and then it might behave just like regular mice. Now what this implies, the period of time in which a similar persistence would hold in dieting humans is an open question. And this is what is at the centre of our big effort to continue the study in humans. And, you know, it could span anything from months to years. And I know this is perhaps a sobering thought, but it may explain some – more than some – of our great failure to maintain weight following dieting.

Now, as for your second question, this relates to the microbiome field in more general terms and we are engaged in many different aspects of microbiome and host interaction research. The more we probe the more we find the microbiome, if you consider it as a hub that integrates into it many signals that come from many different places, the microbiome is greatly affected by the host genome, the human genome, or the mouse genome, depending on which studies you look at – and there are identical twin studies that are showing this very convincingly – that the microbiome is also affected by our immune system. But what is special about the microbiome is that it is also greatly affected by any form of environmental condition that surrounds us: nutrition, stress, the medications we take and many more factors which affect our health, but up until now we did not really know how, into which channel they impact our body. So, the microbiome perceives all of these different signals coming from inside us and from around us, it integrates them and then it uses them in its communication channelling with the host. And it is this communication between us and our microbes which we believe is the key to understanding many aspects of our physiology and many aspects related to how we develop very important and common diseases such as diabetes, obesity, inflammatory diseases and even cancer. And understanding it may be the alphabet by which we communicate with our microbes, back and forth, is the key to understanding or to developing new interventions targeting the microbiome and metabolites as we highlighted in this study and, in other studies, are part of this alphabet by which we and our microbes communicate with each other.

**Courtney**: Our next question comes in from the line of Hannah Devlin. Please go ahead.

**Hannah Devlin**: Hi there, yes, I have two quick questions. The first, I wanted to make sure that I properly understood, when you talk about the altered microbiome. Is that alteration just from being obese or is it to do with the cycling of the diets. I think I might have missed that at the start. And the second thing, I was wondering if you could tell us a bit about why they put on the weight quicker. So, was the microbiome working against them because it made them more hungry, and sort of eat more? Or was it to do with changes in metabolism? Thanks a lot.

**Eran Segal**: Yeah, so this is Eran Segal. So, as regards to your first question on what actually changed the microbiomes. So, the mice that we started with are actually identical, genetically identical. And what causes the change, in this case, so they are genetically identical and we also checked and actually they start with very similar microbiome configurations, all of the mice. And then what happens – and this has been well documented in the past – is that when we feed them a high-fat diet then the diet actually alters significantly the microbiome configuration. This has also been shown in previous studies. What we show here is than even after you remove the high-fat diet and you put them now on a normal chow diet then their microbiome configuration still remains like that of the high-fat diet and it gradually shifts, but even for a very long period of time the microbiome actually stays similar to its altered state when fed a high-fat diet. So, in this case, it is the diet that actually is causing the alteration to the microbiome.

With regards to your second question, so in this work we also began to explore the mechanism underlying, exactly your question, of what is the mechanism by which this altered microbiome configuration actually leads to enhanced weight regain and, while of course, we do not have the full mechanism we did gain significant insights which we showed in multiple ways, showing basically that the microbiome configuration that is altered actually has a reduced energy expenditure. And so, if you will, then the ability then basically— more of the energy that goes in is actually then converted into fat. And this would be one of the ways, one of the mechanisms by which the altered configuration would lead to the enhanced weight regain.

**Courtney**: Our next question comes in from the line of Kate Kelland. Please go ahead.

**Kate Kelland**: Thank you. Actually, all my questions have been answered now. Thank you, they've all been asked by the previous people.

**Courtney**: We currently have no further questions in the queue. So just a reminder if you would like to ask a question, please press star one now.

Okay, we have no further questions. I shall hand you back to your host to conclude today's conference.

**Rebecca Walton**: I would like to thank you all for dialling into today's briefing and I would also like to thank our speakers for their time. If you would like any more information, please consult the *Nature* Press Site where we will be posting a recording of this briefing shortly. I would also like to remind you once again of the *Nature* embargo for this paper which is 4PM London, 11AM US Eastern Time, on Thursday the 24th of November. Thank you, very much.

**Courtney**: Ladies and gentlemen, thank you for joining today's call. You many now replace your handsets.

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*Transcribers comments:*

Unintelligible speech is placed between < > tags, with x's representing the number of approximate syllables. The time at which the speech utterance was made is also indicated, e.g. <un xx 00:05:35>

Speakers' names which are unclear are placed between brackets (), e.g. (Volker Masek)