Webinar Q&A Report:
Rodent Models of Pharmacotherapy & Chronotherapy for Obesity & Cardiometabolic Disease

1. Were there any gender differences observed?

   C. Axelrod: Male mice were used exclusively for the obesity and glycemia trials shown today. However, we have soon-to-be published data in a different mouse model that demonstrates similar efficacy in female mice. We are highly interested in pursuing this further as sexual dimorphic phenotypes are commonly present with obesity drugs.

2. Does sexual dimorphism also exist in human shift workers?

   S. Kooijman: This is a difficult question to answer because studies in shift workers are often limited to a certain profession. Studies involving females shift workers often look at nurses, while male shift workers are often factory workers. Sexual dimorphism does exist with respect to the acute effects of shift work, the circadian system in under tight control of the sex hormones, but whether this is also relevant for the long term cardiometabolic disease risk is understudied.

3. Have you thought about doing this work in vitro with human cells?

   C. Axelrod: We are certainly interested in carrying out more extensive investigation in primary human cells. This would be particularly interesting in primary human adipocytes or stem cells to see how differentiation and expansion processes are affected. I am open to discussing further if you have further insight into the matter.

4. Do you plan to take this into humans either in vitro or in vivo?

   C. Axelrod: We are in discussions currently to carry out formal pre-clinical trials that would be required to receive investigational drug approval by the FDA. More likely than not, structural modification will be required to optimize the drug for human metabolism.

5. Has your team investigated whether BAM15 alters differential mobilization of different fatty acids? In short, might BAM15 treatment alter the fatty acid composition of the body?

   C. Axelrod: Yes, to an extent. Our published data evaluated effects of BAM15 on free fatty acids, total triglycerides, and medium chain triglycerides. Both free fatty acids and total triglycerides were substantially lowered by BAM15 whereas medium chain were relatively unaltered. I agree that this would be interesting to investigate, particularly as an acute function of BAM15 exposure.

6. Do you have any breath testing data that show the rates at which the animals are oxidizing endogenous lipids?

   S. Kooijman: No, we are planning to perform a pilot study using 13C-labeled triglycerides packages in the lipoprotein-like particles and measure oxidation rates in mice using indirect calorimetry in control and stimulated conditions (e.g. beta3-adrenergic receptor agonist).

7. Is there any possibility that BAM15 causes lipodystrophy? By diverting fats to skeletal muscle, for example?

   C. Axelrod: This is an interesting question. In many ways the adipose tissue phenotype we observe presents similar to lipodystrophy in the sense that the adipocytes do not expand or mature. What is highly dissimilar phenotypically is that the animals are markedly healthier both on the tissue level (inflammation etc.) and whole body. As such, I speculate that what makes this phenotype favorable is the high demand for substrate in highly active tissues, unlike clinical lipodystrophy.

8. Have you measured the energy expenditure at thermoneutral conditions?

   S. Kooijman: Yes, we did. Certain circadian aspect in BAT are actually more pronounced under thermoneutral conditions because you're eliminating the dominant sympathetic driver of thermogenesis.

   C. Axelrod: The studies shown today were all conducted at human thermoneutrality. However, we have ongoing studies at mouse thermoneutrality. Interestingly, the effects appear to be exacerbated at mouse thermoneutrality.

9. Does sleeping with the lights on have effects on the formation of fat tissues?

   S. Kooijman: A large observational study in the UK suggests that the amount of light in bedroom correlates with BMI and other measures of obesity. See this article here: https://academic.oup.com/aje/article/180/3/245/2739112

10. Do you have genotoxicity, carcinogenicity, and immunogenicity data for BAM15?

    C. Axelrod: We do not have genotoxicity or immunogenicity data, but do have some carcinogenicity data that will be published in the upcoming months.

11. Was UCP1 induced by BAM15?

    C. Axelrod: We did not observe any induction of UCP1 in white or brown adipose tissue.

12. Do you think that endocrine disruptors will aggravate the pathophysiological symptoms of these models?

    C. Axelrod: I would argue that our model of uncoupling is reversing pathophysiology induced by over feeding. I certainly agree that endocrine disrupters would aggravate metabolic function, but do not think this would have any interaction with our treatment model.

13. What further questions were inspired by listening to the other speakers' presentation?

    C. Axelrod: Given the relatively short half-life and efficacy, possibly uncoupling therapy could be used to reset clock disruption as is observed with shift-work paradigms or genetics models of circadian rhythm dysfunction.

    S. Kooijman: Would be nice to investigate the effects of BAM15 on the prevention of atherosclerosis development in APOE*3-Leiden.CETP mice

14. What is the role of sex steroids?

    S. Kooijman: For example, estrogen has been suggested to protect females from circadian disruption, but also testosterone has been implicated in the circadian regulation of metabolic processes.

15. Are female shift workers more susceptible to cardiovascular disease when compared to male shift workers?

    S. Kooijman: This is a difficult question to answer because studies in shift workers are often limited to a certain profession. Studies involving females shift workers often look at nurses, while male shift workers are often factory workers. Sexual dimorphism does exist with respect to the acute effects of shift work, the circadian system in under tight control of the sex hormones, but whether this is also relevant for the long term cardiometabolic disease risk is understudied.

16. Did BAM15 alter brown adipose tissue function or thermogenesis? Did you observe UCP1 activation in white or brown adipose tissue?

    C. Axelrod: No, it does not. Neither white or brown adipose tissue displayed any UCP-mediated thermogenesis in response to BAM15 treatment. If anything, UCP-mediated processes were down regulated, a function I would presume to be related to the mitochondria attempting to sustain ATP synthesis.

17. Have studies been conducted to determine the long-term safety and efficacy of BAM15?

    C. Axelrod: Not by our group, no. We do have some preliminary data of longer-term treatment (12-15 weeks) and the effects appear to be similar with no pathophysiological symptoms.

18. Would you recommend going for cold dips/cold plunges in the morning?

    S. Kooijman: Based on the increase in energy expenditure yes, but cold exposure has many more health beneficial effects, for example on the immune system, and we don't know whether timing is also an important determinant for that. Anyhow, I would say that a bit of cold exposure throughout the day gives you health benefits.

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