1. **Overweight/obesity and female fertility**
   Background: Overweight and obesity are becoming more and more a serious health problem, not only in humans but also in pet animals. Beside to direct effects on health, obesity in females is also an important cause of fertility problems. In the past few years it has become apparent that the adipokine leptin plays an important role in the initiation of puberty and in adult fertility through its stimulating effects on the kisspeptins. Due to the fact that the kisspeptin neurons are also influenced by sex steroids and project to the GnRH neurons in the hypothalamus, they are thought to play a key role in the regulation of male and female fertility.
   Aim: To determine why fertility in many overweight/obese subjects is affected, despite the fact that they have elevated leptin levels.
   - What is the role of the kisspeptin system in overweight/obesity induced fertility problems in females
   - Why are the effects of overweight/obesity on fertility more severe in females compared to males

2. **Role of the IGF-system in male/female reproduction**
   Background: The insulin-like growth factors (IGF) have in the past been shown to be important for normal fertility. It is however not clear whether it is the locally (in the gonad) produced IGF is essential for normal fertility or whether systemic IGF (produced by the liver) is also involved, and whether locally produced and systemic IGF make use of the same signal transduction pathway when influencing follicle development in the ovary or Leydig cell/Sertoli cell function and thus germ cell formation in the testis.
   Aim: To analyse the pathway(s) along which IGF can influence either ovarian follicle development o or the formation of germ cells in the testis, and whether there exist differences in the effects of locally and peripherally produced IGF.

3. **Thyroid hormones and fat tissue distribution**
   Background: When thyroid hormone levels are too low during fetal and postnatal life, metabolism is severely affected. Our experiments have shown that as a consequence of hypothyroidism fat tissue distribution is severely changed, without influencing total body fat content. This immediately raises the question about what the mechanism is behind this change in adipose tissue distribution and the possible consequences for energy metabolism/homeostasis.
   Aim: To prepare a thorough overview of the present knowledge about the role of thyroid hormone in fat tissue distribution. What is the mechanism behind this change and how does this influence metabolism.

4. **Subjects related to the themes in course HAP30806 Integrated Neuroendocrinology**
   Themes: Sleep, emotions, stress, ingestive behaviour, reproductive behaviour, learning and memory, psychopharmacology and drug abuse, neuronal disorders.
   Aim: To make a literature overview of the physiology of the selected topic.
   For this thesis subject it is strongly advised that you take or have taken the course HAP30806 (Integrated Neuroendocrinology)

5. **Evaluation of infertility in Witrik cattle**
   Background: Homozygous Witrik cattle are usually infertile. This infertility in Witrik cattle could be due to problems with germ cell migration and/or degeneration of the germ cells after they have reached the testes or ovaries. White spotting variant mice ($W^v$) have a similar phenotype, so these mice are a good model to study causes of infertility in Witrik cattle.
   Aim: Perform a literature study to find out the possible cause of infertily in Witrik cattle, including studies of infertile $W^v$ mice.

6. **Physical activity and energy metabolism**
   Background: Physical activity/exercise and energy metabolism are essentially interrelated. Regular physical activity requires adaptations of energy metabolism, and adequate regulation of energy metabolism is crucial for optimal exercise performance.

Aim: To provide a literature overview on specific aspects of the interrelationship of physical activity and (cellular) energy metabolism. This could also include effects of nutritional compounds. A more detailed aim is depending on the students' interest and will be discussed with the supervisor.

7. **Hypoxia and energy metabolism**
   Background: Oxygen is essential for aerobic metabolism of our nutrients, and therefore an important factor in energy metabolism. When subjects are exposed to low oxygen tension (hypoxia), for instance during a stay at high altitude, a loss of body weight is frequently observed. On the other hand, hypoxia is sometimes used to enhance exercise performance, and recent studies suggest that hypoxia may have the potency to treat specific forms of mitochondrial disease. These studies indicate that hypoxia affects energy balance and energy metabolism.
   Aim: To provide a literature overview on the physiological effects of hypoxia on energy metabolism. A more detailed aim is depending on the students' interest and will be discussed with the supervisor.

8. **Communication between adipose tissue and another organ**
   Background: Adipocytes secrete a huge number of signalling molecules, the so called adipokines. These can have a function on e.g. muscle, brain, or liver. It is evident that this kind of communication is going back and forth.
   Questions: What are these adipokines and how do they signal? And what does the alternative organ, e.g. liver, signal to adipocytes? Is this similar in mice and men?
   Aims: To provide a literature review about one or more questions related to communication to and from adipose tissue (the exact topic will be determined together with the supervisor).

9. **Metabolic programming**
   Background: nutritional interventions in specific windows of opportunity during early life development can have beneficial effects on metabolic health in adulthood.
   Questions: what is the role of a specific macronutrient (fat, carbohydrate) and can we modulate in this way beneficial health effects by nutrition? Is the effective period during development different for macronutrients?
   Aims: To provide a literature review about one or more questions related to metabolic programming on a macronutrient of choice (to be determined in consultation with supervisor).
   Aims: To provide a literature review about one or more questions related to lactate dehydrogenase (the exact topic will be determined together with the supervisor).

10. **Should we put cloths on mice for the study of energy metabolism?**
    Background: Environmental temperatures ($T_a$) affect thermoregulation in mammalian species including humans. Maintaining the body temperature ($T_b$) at a relative constant value requires energy. These energy requirements depend on $T_a$. The energy spend on thermoregulation also affects energy balance and thereby body weight regulation. With the major epidemic proportions of obesity and associated health problems many studies focus on the regulation of body weight, in order to find solutions to the health problems of obesity. Animal models are frequently used, but are mostly performed at standard $T_a$ of around 22 ˚C.
    Questions: What is the role of $T_a$ on energy metabolism? Is this role the same in humans and in animal models for (disturbed) energy metabolism?
    Aim: Integrate results from research papers to create a state-of-the art overview answering one or more questions related to this topic (the exact topic will be determined together with the supervisor).

11. **The role of inflammation in metabolic complications**
    Background: Inflammation has been recognized to influence the development of many metabolic complications. Stimuli such as overnutrition, physical inactivity, and aging may result in cytokine hypersecretion and eventually lead to insulin resistance and diabetes. Similarly, a difference in carbohydrate composition, not quantity, in early life can have similar effects.
    Questions: What is the precise role of inflammation in metabolic complications? Is this role influenced

by nutritional status? Is there a general mechanism involved or are specific pathways more predominantly activated? Are inflammatory mediators interesting targets for nutritional and therapeutic intervention strategies?
Aims: Integrate results from research papers to create an overview about one or more questions related to this topic (exact topic to be determined in consultation with supervisor).

12. **The role of dietary branched chain amino acids in health and disease**
Background: A healthy diet likely prevents the development of diseases. Although the composition of a healthy diet is under intense research, particular macronutrients, micronutrients and the balance between different macronutrients seem to be essential. Dietary protein content and its derived amino acids have been proposed to play a role in a number of diseases. Branched chain amino acids (BCAAs) are of particular interest because they are highly elevated in Type II diabetic patients and on a molecular level activate the cellular master-regulator mTOR.
Aim: Provide a literature overview of the relation between BCAA intake and disease, as well as elucidate molecular mechanisms how BCAA contribute to disease pathology.

13. **Optimizing immune function via the diet**
Background: It has been recently discovered that metabolism of immune cells is a critical regulator of inflammatory diseases. This opens up novel opportunities to design nutritional intervention that impact inflammatory diseases.
Aim: Provide a literature overview of novel cellular and physiological metabolic processes that impact immune function and design nutritional interventions to strengthen the immune function.

14. **Targeting energy metabolism of cancer cells**
Background: Cancer cells use glycolysis for energy production, rather than oxidative metabolism which occurs in mitochondria. Mitochondrial metabolism of cancer cells is reprogrammed for biosynthesis rather than energy production. Mitochondria are thus a target for anti-cancer interventions. AMP-kinase is a cellular energy sensor that targets mitochondria and can stimulate oxidative metabolism. AMP-kinase is activated by exercise.
Aim: Provide a literature overview of exercise as an anti-cancer therapy. Focus on interventions in model animals and humans, including evidence for the underlying mechanisms that are targeted.

15. **Aging, a disease of mitochondrial damage**
Background: Mitochondria have a number of essential cellular functions. Mitochondrial quality is constantly monitored and damaged mitochondria, showing reduced membrane potential, are removed by mitophagy. It is postulated that aging is caused by accumulation of defective mitochondria either because of increased damage or because of problems with monitoring mitochondrial quality.
Questions: What is the role of mitochondria in the aging process? Which processes regulating mitochondrial functions are affected by aging?
Aim: Investigate the evidence for accumulation of damaged mitochondria with aging and describe which markers can be used to assess this in vivo.

16. **The link between redox balance, (mitochondrial) energy metabolism and neuromuscular junctions**
    Background: ATP is generated through cellular respiration in mitochondria, making these cell organelles important for cellular metabolism. Mitochondria are the main source of reactive oxygen species (ROS) as unpaired electrons are generated in the process of oxidative phosphorylation. As a consequence, mitochondria are well equipped with antioxidant defences. High levels of ROS are strongly related to metabolic complications but also to skeletal muscle innervation? One protein, the NNT will have a central role in this topic
    Questions: What is the metabolic consequence of redox balance versus imbalance on Neuromuscular Junctions? Is redox state an interesting target for nutritional or therapeutic intervention strategies?
    Aims: Integrate results from research papers to create an overview about one or more questions related to this topic (exact topic to be determined with supervisor). The aim is to go into depth by describing molecular pathways or the involvement of specific protein(s).

17. **Mechanistic role of mitochondria in Alzheimer's disease**
    Background: Alzheimer's disease (AD) is a progressive neurodegenerative disease. Brains of AD patients contain amyloid beta (Aβ) plaques and tau tangles. Mitochondria play a large role in neuronal function by constantly providing energy, particularly at synapses. Mitochondrial function is decreased in AD patients. Decreased mitochondrial functioning impacts on synaps function, which could lead to neuronal damage and ultimately to memory loss and cognitive impairment in patients with AD. Ameloid beta, phosphorylated tau and mitochondrial function affect each other, but the sequence of cause and affect are not clear.
    Relevant questions: What is the evidence that ameloid beta affects various mitochondrial functions and how? What is the evidence that phosphorylated tau affects mitochondrial function and how? What is the evidence that mitochndrial dysfunction can lead to plaque and tangle formation and how? How do ameloid beta and phosphorylated tau affect mitochondrial dynamics and how can this lead to AD? How can dysfunction of mitochondria increase plaque and tangle formation and how can this lead to AD? Ameloid beta, phosphorylated tau and mitochondrial function affect each other, but what is cause and consequence? How is metabolic health (or specific aspects of metabolic health such as insulin resistance) linked to AD? Which mechanisms underlie sex differences in AD susceptibility
    Aim: Define a specific research question related to one or more of the questions above. Write a logically structured report based on literature research question, focusing on specific proteins/mechanisms involved. Conclude and propose an experiment that brings this research on step further.

18. **Effects of statins on mitochondrial energy metabolism**
    Background: Statins are a class of cholesterol-lowering medication that are very effective in reducing serum cholesterol levels and are known to reduce cardiovascular events with 30%. Myopathy is the most important adverse drug reaction of statin therapy with rates up to 26%. The mechanism underlying the muscle side effects remains enigmatic, but it is suggested that statins disturb mitochondrial energy metabolism via various routes.
    Relevant questions: What is the evidence that mitochondrial function is disturbed in myopathic statin users? Is the disturbance in mitochondrial function causally related to the muscle complaints patients experience, or is there also evidence that asymptomatic statin users (statins users without muscle complaints) show a diminished mitochondrial function? What are the different mechanisms discussed in literature via which statins disturb mitochondrial function?
    Aim: Define a specific research question related to one or more of the questions above. Write a logically structured report based on literature research question, focusing mechanisms involved. Conclude and propose an experiment that brings this research on step further.

**19. Effects of statins on exercise performance**

Background: Cholesterol-lowering statins are prescribed to patients with high cholesterol levels and are known to reduce the cardiovascular events with 30%. Besides statins, physical exercise is advised for dyslipidemic patients. In fact, it is suggested that statin treatment along with a moderate to high physical fitness level provides additional protection against premature cardiovascular death. However, adopting or maintaining a physically active lifestyle is often not feasible for statin users, as 26% experiences muscle toxicity as adverse effect of statins. The practice of physical exercise on top of statin treatment is even thought to blunt the aerobic training response, and exacerbate the muscle complaints.

Relevant questions: What is the evidence for a diminished exercise performance and aerobic training response in myopathic statin users? Is there a relationship between exercise performance and muscle complaints in myopathic statin users? What are possible mechanisms that are likely to contribute to the lack of a training response?

Aim: Define a specific research question related to one or more of the questions above. Write a logically structured report based on literature research question, focusing mechanisms involved. Conclude and propose an experiment that brings this research on step further.

**20. Effects of ketones on muscle performance and health**

Background: Ketone bodies are an alternative fuel source for tissues like skeletal muscle, brain and heart, being endogenously produced from fatty acids when glucose supply is limited. Starvation, low carb diets, and intense physical exercise are the most common causes for the body to turn toward ketone bodies for energy. However, researchers are now discovering that even when glucose is available, ketones still may exert a positive influence on these tissues.

Skeletal muscle has been shown to have a high affinity for ketone bodies and is able to metabolize a majority of the available ketone bodies in plasma while in a resting state. Under normal conditions, the availability of ketone bodies is low, forcing skeletal muscle to utilize glucose or free fatty acids. However, when the quantity is raised – either endogenously from dietary manipulation or extreme exercise, or via exogenous ketones – the potential for skeletal muscle to exploit the benefits of ketones is also greater.

Relevant questions: So how do ketone bodies help rebuild and maintain skeletal muscle? How do they intervene in the muscle energy generating processes? Do they speed up muscle recovery? Do they support muscle protein synthesis and muscle regeneration?

Aim: Define a specific research question related to one or more of the questions above. Write a logically structured report based on literature research question, focusing mechanisms involved. Conclude and propose an experiment that brings this research on step further.

**21. Effects of early aging on skeletal muscle energy metabolism**

Background: Around the age of 50, clear decreases in resting and activity energy expenditure can be seen. Also decreases in muscle mass tend to occur from that age onwards. Yet, the decrease in muscle function is far greater than the decrease in muscle mass, and the decreased muscle mass, cannot solely explain the decreased metabolic rate of skeletal muscle from mid-age onwards.

Relevant questions: What is the evidence for decreased muscle function from mid-age onwards? Is there a clear relationship between a diminished skeletal muscle function and muscle mitochondrial energy metabolism in the mid-age? Can skeletal muscle function explain more of the aging phenotype than the mass part of muscle?

Aim: Define a specific research question related to one or more of the questions above. Write a logically structured report based on literature research question, focusing mechanisms involved. Conclude and propose an experiment that brings this research on step further.

22. **Role of mitochondrial oxidative stress in atrial fibrillation**
    Background: Atrial fibrillation (AF) is age-related progressive arrhythmia. Mitochondrial dysfunction and oxidative stress are often observed in AF patients. But is mitochondrial oxidative stress or cause for AF in still unclear.
    Relevant questions: What is the role of mitochondrial oxidative stress in the pathogenesis of AF? What is the potential underlying mechanism?
    Aim: Provide a literature overview of role of mitochondrial oxidative stress in atrial fibrillation and the involved (potential) molecular signalling pathways.

23. **Role of ER (SR) and mitochondrial contacts in cardiac aging and arrhythmia**
    Background: SR (smooth endoplasmic reticulum (ER) found in cardiomyocytes) and mitochondria, the two central organelles involved in Ca2+ and energy (ATP) homeostasis which are both crucial for normal cardiomyocyte contraction and relaxation. SR stores Ca2+ and plays a major role in cardiac excitation-contraction (EC) coupling in close cooperation with mitochondria, which play a vital role in generating ATP and buffering cytosolic Ca2+. During the EC coupling, Ca2+ is released from SR into the cytosol, allowing Ca2+ to bind to the myofilament troponin-tropomyosin complex, which then initiates myofilament contraction. Proper Ca2+-handling and myofilament contraction and relaxation requires ATP. For efficient ATP regeneration during contraction, mitochondria take up part of the SR-released Ca2+ that stimulates key enzymes of the tricarboxylic acid (TCA) cycle to increase the production of substrates (NADH and FADH2) for the electron transport chain. This close cooperations of SR and mitochondria, termed SR-mitochondrial contacts, are achieved by tether proteins including Mitofusion 2. Changes of SR-mitochondrial contacts may cause cardiac arrhythmia and aging.
    Relevant questions: How SR-mitochondrial contacts regulate heart function?
    Aim: Provide a literature overview of role of SR-mitochondrial contacts in the heart with focus on cardiac aging and arrhythmia.

24. **The roles of muscle protein synthesis and breakdown in muscle disuse atrophy**
    Background: Situations such as the recovery from injury and illness can lead to enforced periods of muscle disuse or unloading, e.g. via bedrest or limb immobilization. Such circumstances lead to rapid skeletal muscle atrophy, loss of functional strength and a multitude of related negative health consequences. Any loss of skeletal muscle mass must be underpinned by a chronic imbalance between muscle protein synthesis and breakdown rates.
    Relevant questions: How does a period of muscle disuse affect muscle protein synthesis and breakdown rates? What is the role of changes in muscle protein synthesis and breakdown in disuse atrophy in older individuals, and how does this contribute to sarcopenia? How are different muscle groups affected?
    Aim: Provide a literature overview on the role of muscle protein synthesis and breakdown in muscle disuse atrophy (for instance in different populations, disuse models, muscle groups, etc).

25. **Strategies to prevent muscle mass and metabolic health during periods of physical inactivity**
    Background: Situations such as the recovery from injury and illness can lead to enforced periods of muscle disuse or unloading, e.g. via bedrest or limb immobilization. Such circumstances lead to rapid skeletal muscle atrophy, loss of functional strength and a multitude of related negative health consequences, which requires rehabilitation. Moreover, it is suggested that the accumulation of such periods of inactivity contributes to age-related muscle loss, i.e. sarcopenia. As such, there is an urge for effective interventional strategies to preserve muscle mass and function during periods of disuse.
    Relevant questions: Can muscle disuse atrophy be prevented via nutrition, exercise (mimetics), pharmacological interventions, or a combination thereof?
    Aim: Provide a literature overview on one or multiple different interventional strategies to preserve muscle mass (and/or function and/or metabolic health) during periods of disuse.