

## Cardiometabolic Disease Models

Göttingen Minipigs are very prone to obesity, and even chow feeding results in gross obesity if the minipigs are not kept on a restricted diet.<sup>1</sup> In a recent Newsletter, the experiences running studies with very obese animals are described in two articles.<sup>2</sup> Male animals are much less prone to develop obesity compared to the females but will do so if they are castrated.<sup>3</sup> The fat is stored mostly as subcutaneous fat, but substantial amounts are also stored as visceral fat.<sup>4,5</sup> Brown adipose tissue is not found, as the UCP-1 gene is a pseudogene in pigs.<sup>6</sup> In studies with different anti-obesity compounds, DEXA- and MR-scanning have been used to monitor the effects on the body composition.<sup>7-9</sup>

It is not possible to induce overt diabetes in large animal models (except from non-human primates) by means of diet feeding. Chemical destruction of the beta cells by streptozotocin (STZ) or a similar compound can be used to produce a type 1-like diabetes, and a simple and reliable protocol for this was described recently.<sup>10</sup> As described in the same article, type 2 diabetes is more difficult to model, but several groups find it useful to combine diet-induced obesity, that causes insulin resistance, with low dose STZ treatment.

It is possible to obtain marked obesity, insulin resistance, low grade inflammation and dyslipidemia in small Göttingen Minipigs by feeding them with a high fat diet for a few months.<sup>5</sup> Therapeutic effects on food-intake and body composition, and on the metabolism of glucose and lipids, can thus be studied in a much quicker and easier way. However, the absolute weight loss that can be obtained in adult, very obese animals will more likely be a reduced weight gain in the smaller, moderately obese ones. The degree of insulin resistance can be assessed by performing an IVGTT, using an index based on measurements of insulin and glucose.<sup>11</sup> It is important to notice that Hb1Ac cannot be used in pigs, as porcine erythrocytes are practically impermeable to glucose.<sup>12</sup> Fructosamine can be used instead.<sup>13</sup>

Moderate to severe human-like atherosclerosis develops in approximately 6-9 months in castrated male Göttingen Minipigs fed atherogenic diet high in fat and cholesterol.<sup>13</sup> The plaque lesions show high resemblance to those found in humans and are located the same places, i.e. in both the coronary arteries and the abdominal aorta.<sup>13</sup> The potential to study the lesions by imaging such as PET-MR scanning further provides a basis for performing studies with high translatability to clinical studies.<sup>14</sup> To that end, animals with the most severe lesions can be pre-selected based on a simple 2D ultrasound scan of the abdominal aorta. In addition, Göttingen Minipigs are often used to model infarcts and infarct-based heart failure.<sup>15</sup>

Recent, unpublished studies have shown us that severe non-alcoholic steatohepatitis (NASH) can be induced in Göttingen Minipigs by using a choline-deficient high fat diet. Severe steatosis drives the inflammation and fibrosis in the model. On a more "regular" high fat diet, it is practically impossible to induce marked steatosis in a porcine liver, possibly because the liver in the pig is not the primary site for de novo lipogenesis, and pigs have a high potential for storing fat in peripheral adipose depots.<sup>16</sup> The disease progression can be followed in the same way as in the clinic - including by imaging and ultrasound-guided biopsies.



*"I find it fascinating to work with metabolic diseases in Göttingen Minipigs and have done so for many years. It is important to acknowledge that it is not an area where one model fits all - typically it needs to be adapted to the specific aim of the study."*

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