

The RccHan[®]:WIST Rat

Supporting advances in science and medicine, one study at a time



The RccHan[®]:WIST rat is a prominent choice for researchers across the globe and a mainstay of toxicological and carcinogenicity studies that are conducted in Europe, Japan, and the US by various multinational companies. These safety studies are typically carried out in the context of seeking regulatory approval of new medicines, industrial chemicals, crop protection products, and food ingredients.

The RccHan[®]:WIST rat is strongly favored because of several attributes that are advantageous to safety assessment studies, including the following:

- + Millions of historical control data (HCD) points, including 104-week survival and growth, spontaneous neoplasm and non-neoplasm at multiple time points, and fetal development
- + Attractive intrinsic factors, such as lower body weight, enhanced survival rates, and lower overall tumor burden relative to some other strains (e.g., CRL:CD[®])

These beneficial features can improve study outcomes, enhance animal welfare, and provide a beneficial economic impact by reducing in-life study costs.

In addition, scientists from a wide array of medical and scientific disciplines commonly turn to the robust RccHan[®]:WIST rat for their research needs.

The RccHan[®]:WIST rat has supported advances in science and medicine across a disparate array of disciplines, including the following:

- + Toxicology
- + Pharmacology
- + Metabolic Syndrome and Obesity
- + Neuroscience

This paper provides a summary of potential cost savings for the in-life component of long-term safety studies that employ the RccHan[®]:WIST rat versus the CRL:CD[®] rat, followed by a selection of research highlights from studies that used the RccHan[®]:WIST rat from these four categories.

The RccHan[®]:WIST rat is a prominent choice for researchers across the globe and a mainstay of toxicological and carcinogenicity studies

In-life cost savings benefit

Based on Envigo's experience, the superior two-year survival rate of the RccHan[®]:WIST rat compared to that of the CRL:CD[®] rat means that fewer animals are required per group.

For instance, to achieve suitable numbers of surviving animals at the end of a two-year treatment period, the group sizes for a long-term study can typically be in the range of 50–55/sex/group for the RccHan[®]:WIST rat, compared to 64–70/sex/group for the CRL:CD[®] rat, which represents a 22-27% reduction in the number of animals required for a typical long-term study.

Based on a sampling of recently completed in-life study costs for two-year carcinogenicity studies, Envigo's data demonstrate a **substantial in-life cost savings of ~15%** for the RccHan[®]:WIST relative to the CRL:CD[®].¹

Research highlights

Each summary of recent research findings from studies that employed the RccHan[®]:WIST rat provides the study rationale and a focus on the *in vivo* rat portion, followed by the study conclusions. Two studies are highlighted for each of the following research areas:

- + Toxicology
- + Pharmacology
- + Metabolic Syndrome and Obesity
- + Neuroscience

To address the unmet medical need for safe and effective obesity treatments, pharmaceutical companies continue to explore new potential drug targets

Toxicology

Safety assessment of a monoclonal antibody being developed as a potential treatment for obesity

To address the unmet medical need for safe and effective obesity treatments, pharmaceutical companies continue to explore new potential drug targets, such as fibroblast growth factors (FGFs) and their receptors (FGFRs).

In this study, the potential toxicity of three anti-FGFR1c monoclonal antibodies (mAbs) were investigated before the clinical development phase. Weekly injections of FGFR1c-specific mAbs (two versions) or a FGFR1c/FGFR4-specific mAb were given to groups of male RccHan[®]:WIST rats for up to four weeks.

All the mAbs caused significant reductions in food intake and an accompanying weight loss. However, microscopic changes were seen in the bones and heart valves of all three groups. Deposition of new bone indicated an osteogenic effect, and the heart's mitral, pulmonary, tricuspid and aortic valves were all adversely affected by all three agents. Targeting the FGF-FGFR1c pathway with anti-FGFR1c mAbs was determined to lead to drug-induced valvulopathy in rats, and the development of these mAbs as potential anti-obesity drugs was terminated (Buss 2018).

Two-year carcinogenicity study of acrylamide with *in utero* exposure

The potential adverse health effects of acrylamide and its ubiquity in the food chain have resulted in heightened scrutiny from researchers and regulatory authorities worldwide.

Previous studies assessed the carcinogenic potential of acrylamide in Fischer 344 rats and found an increased number of tumor types, including tunica vaginalis mesotheliomas, which was an end point that contributed to classifying acrylamide as a probable human carcinogen. The authors of this study assessed the carcinogenic potential of acrylamide in a different rat strain (i.e., RccHan[®]:WIST) to determine whether the Fischer 344 rat findings might be strain specific.

¹Please note that this analysis is intended to provide a general cost savings estimate from using the RccHan[®]:WIST rat versus the CRL:CD[®] Sprague Dawley in a two-year carcinogenicity study. Envigo cannot guarantee that the same or similar results will be achieved for future studies because there are a multitude of variables that can impact in-life study costs.

Maronpot et al. conducted a lifetime acrylamide exposure study, beginning *in utero* and continuing into adulthood. From gestation day 6, pregnant rats were provided with 0, 0.5, 1.5, or 3.0 mg acrylamide/kg body weight/day in their drinking water until weaning, while male and female F1 rats were exposed for an additional 104 weeks.

For the tumor end points after two years, the authors found an increased rate of mammary gland fibroadenomas and thyroid follicular cell tumors in both sexes for the acrylamide-exposed rats. Notably, tunica vaginalis mesotheliomas were not found to be elevated, and therefore it was concluded that the tunica vaginalis mesotheliomas are rat strain specific and likely not of genotoxic origin (Maronpot 2015).

Pharmacology

Intranasal delivery of levofloxacin is effective

The direct delivery of a drug to the site of infection can be superior to an indirect administration.

Sousa et al. evaluated the efficacy of the intranasal administration of levofloxacin (an antibiotic) as a potentially more effective and safer approach to treat local infections, such as chronic rhinosinusitis. Intranasal administration was achieved in RccHan[®]:WIST rats using a thermoreversible formulated in-situ gel. Drug concentrations were measured in plasma, the olfactory bulb, and nasal mucosa after intranasal and intravenous administration, and pharmacokinetic parameters were compared between routes.

Plasma and olfactory bulb exposure to levofloxacin was minimal following the intranasal dose, and the levofloxacin concentration-time profile in nasal mucosa revealed higher concentrations during the first 60 minutes after intranasal administration.

The higher dose-normalized concentrations and pharmacokinetic exposure parameters of levofloxacin in nasal mucosa after intranasal administration demonstrate that the intranasal method is advantageous for delivering levofloxacin, rendering it a promising approach for the management of conditions such as chronic rhinosinusitis (Sousa 2017).

Inhaled investigational pulmonary vasodilator is longer acting than infused comparator drug

Pulmonary arterial hypertension (PAH) is a debilitating condition that can lead to right heart failure and death. INS1009 is an investigational pulmonary vasodilator prodrug of treprostinil (TRE) in development for PAH.

This study assessed the ability of INS1009 to inhibit vasoconstriction in the pulmonary vasculature and the extent to which local activity within the lung contributes to the activity of INS1009. Male RccHan[®]:WIST rats received a single dose of INS1009 by nose-only inhalation or a continuous intravenous (IV) infusion of TRE. This was followed by an IV challenge of a pulmonary vasoconstrictor and measurement of pulmonary arterial pressure (PAP).

Exposure to inhaled INS1009 inhibited the induced increase in PAP at all three tested doses for up to six hours, with statistically significant inhibition up to 24 hours with the pooled dose-response data. The concentration of TRE in the plasma at which PAP was reduced by 50% was approximately sixtyfold lower for INS1009 compared to IV TRE. These data suggest that inhaled INS1009 is a long-acting vasodilator and that the local activity within the lung contributes to this response. Thus, INS1009 may be able to achieve effective pulmonary vasodilation for long periods with substantially lower systemic exposure than infused TRE (Chapman 2018).

The direct delivery of a drug to the site of infection can be superior to an indirect administration.

Metabolic Syndrome and Obesity

Development of a novel diet-induced obesity model

Novel models of diet-induced obesity (DIO) are needed to help advance the discovery and development of anti-obesity compounds.

Non-ovariectomized, virgin female RccHan[®]:WIST rats were evaluated for their potential as a model for DIO. Briefly, three-week-old rats were allowed *ad libitum* access to either a high fat (HF) or control (CON) diet for a period of 30 weeks. A third cohort was started on the same HF diet at eight weeks of age for a period of 22 weeks.

The authors noted that body weight was significantly greater at 33 weeks in the HF group compared to the CON group but not between HF groups. In addition, percent body fat was significantly greater in rats maintained on HF compared to the CON group, and leptin levels were significantly elevated in obese rats, consistent with the increased proportion of body fat. All other measured clinical chemistry and hormone levels were within the normal range for the RccHan[®]:WIST rat. Additionally, it was observed that HF rats were approximately 20% less active than the CON animals during the dark cycle.

In this study, RccHan[®]:WIST rats became obese with increased energy intake and reduced activity in the absence of surgical or genetic modification. Thus, this model may be useful to study the interplay between leptin and estrogen on energy-regulating pathways and as an additional tool for testing anti-obesity compounds to evaluate the potential effects of gender-specific hormonal differences on weight change (Flowers 2017).

Maternal nicotine exposure induces oxidative stress and inflammation in fat tissue of female mice

The potential adverse effects of *in utero* nicotine exposure remain poorly characterized, but some recent studies have indicated, for instance, that maternal-nicotine-exposed (MNE) rat offspring exhibit high triglyceride levels due to increased fat production by the liver.

In this study, investigators sought to determine the underlying mechanisms of these high triglyceride levels by evaluating six-month-old female RccHan[®]:WIST rats that were exposed to nicotine during gestation and lactation. Relative to control animals, the nicotine-exposed animals exhibited significantly decreased visceral adipocyte cell area, which was partly attributed to an increase in adipose triglyceride lipase (ATGL) protein expression. At both three weeks and six months, MNE offspring also showed signs of increased oxidative stress and inflammation in white adipose tissue. According to the authors, these data suggest that the expression of ATGL may be induced to counter MNE-induced oxidative stress and inflammation. Consequently, higher levels of ATGL may promote lipolysis and high triglyceride levels (Barra 2018).

Neuroscience

The neurotrophic factor MANF elevates stimulus-evoked release of dopamine

Neurotrophic factors (NTFs) have been characterized as potential disease-modifying therapies for neurodegenerative disorders. NTFs such as glial-cell-line-derived neurotrophic factor (GDNF), cerebral dopamine neurotrophic factor (CDNF), and mesencephalic-astrocyte-derived neurotrophic factor (MANF) have shown neuroprotective and restorative effects on dopaminergic neurons in various animal models of Parkinson's disease. However, the effects of these NTFs on brain neurochemistry have not been compared *in vivo*.

The authors of this study evaluated the biological effects of exogenously administered NTFs in intact RccHan[®]:WIST rat brains. NTFs were unilaterally injected into the striatum, and microdialysis experiments were performed one and three weeks post-injection in freely moving animals. The authors found enhanced stimulus-evoked release of dopamine in the striatum of MANF-treated rats one week post-injection but not in rats treated with GDNF or CDFN. Further, after one week, GDNF treatment significantly modulated the activity of several enzymes responsible for the production or degradation of catecholamines, such as dopamine.

Overall, these data suggest that the NTFs—GDNF, CDFN, and MANF—have divergent effects on dopaminergic neurotransmission and differentially influence the activity of dopamine synthesizing and metabolizing enzymes. These findings may further support the development of new treatments for various brain diseases (Renko 2018).

The monoamine stabilizer compound OSU6162 improves motor impulsive behavior in rats

The rewarding properties of alcohol and the regulation of impulsive behavior are mediated by the dopamine system. OSU6162 is a dopamine stabilizer that has been shown to counteract both hyper- and hypo-dopaminergic states and to attenuate voluntary alcohol consumption, alcohol withdrawal symptoms, and cue-induced reinstatement of alcohol seeking in rats.

Fredriksson et al. investigated the effects of OSU6162 on motor impulsivity in male RccHan[®]:WIST rats that had voluntarily consumed alcohol or water for 10 weeks. Motor impulsivity was measured using the five-choice serial reaction time task, and a prolonged waiting period was applied to induce premature responses. The effects of OSU6162 on the alcohol deprivation effect were also evaluated in long-term alcohol-drinking rats.

The authors report that OSU6162 pretreatment was able to significantly improve motor impulsivity in the time task in both alcohol-drinking and alcohol-naïve rats. The pretreatment also prevented the alcohol deprivation effect, which the authors characterize as “relapse-like drinking behavior after a forced period of abstinence in long-term drinking rats.”

The authors suggest that these results provide further support for the potential use of OSU6162 as a treatment for alcohol use disorder and that improvement of motor impulse control might be a mechanism through which OSU6162 attenuates alcohol-mediated behaviors (Fredriksson 2018).

Conclusions

The RccHan[®]:WIST rat continues to be a top choice rat strain for researchers across the globe for a variety of research purposes across many different disciplines of science and medicine.

In addition to the availability of a robust HCD, the RccHan[®]:WIST rat has several attractive intrinsic factors that can improve study outcomes, enhance animal welfare, and provide significant in-life cost savings for long-term studies. Indeed, internal Envigo data suggest that approximately 22-27% fewer animals are required for long-term studies that utilize the RccHan[®]:WIST versus the CRL:CD[®] rat. This can translate to a substantial in-life cost savings. Envigo scientists have extensive knowledge and experience in the utilization of the RccHan[®]:WIST rat across many different study types. Get in touch for a free consultation that can help guide your study to success.

References

- Barra NG, VanDuzer TA, Holloway AC, Hardy DB. Maternal Nicotine Exposure Leads to Augmented Expression of the Antioxidant Adipose Tissue Triglyceride Lipase Long-Term in the White Adipose of Female Rat Offspring. *Toxicol Sci.* 2018 Jul 1; 164(1):72-84.
- Buss N, Lapointe JM, de Haan L, Price S, Ahnmark A, Irving L, Buchanan A, Keyes F, Davidsson P, Dixit R, Lindén D. Monoclonal antibody targeting of fibroblast growth factor receptor 1c causes cardiac valvulopathy in rats. *Toxicol Appl Pharmacol.* 2018 Sep 15; 355:147-155.
- Chapman RW, Li Z, Corboz MR, Gauani H, Plaunt AJ, Konicek DM, Leifer FG, Laurent CE, Yin H, Salvail D, Dziak C, Perkins WR, Malinin V. Inhaled hexadecyl-treprostinil provides pulmonary vasodilator activity at significantly lower plasma concentrations than infused treprostinil. *Pulm Pharmacol Ther.* 2018 Apr; 49:104-111.
- Flowers, J., & Horn, M. J. Female Wistar Han[®] Outbred Rats as a Model of Obesity When Fed High Fat Diets. *The FASEB Journal*, 31(1_supplement). (2017); 797-6.
- Fredriksson I, Wirf M, Steensland P. The monoamine stabilizer (-)-OSU6162 prevents the alcohol deprivation effect and improves motor impulsive behavior in rats. *Addict Biol.* 2018 Feb 26.
- Maronpot RR, Thoolen RJ, Hansen B. Two-year carcinogenicity study of acrylamide in Wistar Han rats with in utero exposure. *Exp Toxicol Pathol.* 2015 Feb; 67(2):189-95.
- Renko JM, Bäck S, Voutilainen MH, Piepponen TP, Reenilä I, Saarma M, Tuominen RK. Mesencephalic Astrocyte-Derived Neurotrophic Factor (MANF) Elevates Stimulus-Evoked Release of Dopamine in Freely-Moving Rats. *Mol Neurobiol.* 2018 Aug; 55 (8):6755-6768.
- Sousa J, Alves G, Fortuna A, Falcão A. Intranasal Delivery of Topically-Acting Levofloxacin to Rats: a Proof-of-Concept Pharmacokinetic Study. *Pharm Res.* 2017 Nov; 34 (11):2260-2269.

The RccHan[®]:WIST rat continues to be a top choice rat strain for researchers across the globe for a variety of research purposes across many different disciplines of science and medicine