The *chakragati (ckr)* mouse is a unique disease model of psychosis – the best model available for screening antipsychotic compounds.

The ckr model is a US-patented transgenic mouse model of dopamine dysfunction. Chakra Biotech Sdn Bhd has an exclusive license for compound screening.

The *chakragati (ckr)* mouse was the result of insertional mutagenesis discovered during the course of making transgenics with the mouse renin gene. Of the 19 founders with the transgene, only one did not express the transgene and when this was bred to homozygosity, it exhibited an abnormal circling behavior in response to environmental stress cues such as cage banging. The heterozygous littermates did not exhibit this circling phenotype, which has co-segregated with the transgene insertion site since its discovery in 1988. A US Patent was granted for the *chakragati* mouse (USPTO5,723,719).

Extensive research has been carried out on the ckr mouse since its discovery. The following table lists the endophenotypes reported in published literature for the ckr mouse and its mapping to clinical manifestations of psychotic disorders in humans. A full list of published research is given at the end of this document.

<table>
<thead>
<tr>
<th><em>ckr</em> Endophenotypes</th>
<th>Human Clinical Manifestations</th>
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<tbody>
<tr>
<td>Asymmetric Up-regulation of Dopaminergic Tone</td>
<td>Left hemi-spatial preference may be linked to asymmetric striatal dopaminergic activity common to all psychoses. Subgroup of schizophrenia patients has underlying right striatal hyper-dopaminergia. Greater pathological involvement of dominant hemisphere in schizophrenia and of non-dominant hemisphere in bipolar disorder. (Lyon et al 1992; Bracha 1989; Lohr &amp; Caliguri 1995)</td>
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<td>(Fitzgerald et. al. 1992)</td>
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<td>Circling</td>
<td>Left-prone circling behavior (neglect of right-sided turning) was found in unmedicated schizophrenic patients. A tendency was noted for circling to occur more frequently among paranoid than nonparanoid schizophrenics. (Bracha 1987; Marder &amp; Woods 1987)</td>
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<td>(Ratty et. al. 1990)</td>
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<td>Hyperactivity</td>
<td>Hyperactivation (reduced task-related suppression) of default regions and hyperconnectivity of the default network may contribute to disturbances of thought in schizophrenia and risk for the illness. (Whitfield-Gabrelli et al 2009)</td>
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<td>(Fitzgerald et. al. 1991)</td>
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<td>Prepulse Inhibition</td>
<td>Impairment in pre-pulse inhibition generally seen as sensorimotor deficits. PPI disruption occurs in the prodromal stage of schizophrenia and in patients with schizotypical personality disorder. (Quednow et al 2009; Kumari et al 2008; Kunugi et al 2007)</td>
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<td>(Verma et. al. 2007)</td>
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<td>Latent Inhibition</td>
<td>Absence of LI in acute phase of schizophrenia. LI found to be correlated to the duration of the disease. (Rascle et al 2001; Gray &amp; Snowden 2005; Vaitl D et al 2002)</td>
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<td>(Verma et. al. 2007)</td>
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<td>(Torres et. al. 2004)</td>
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<tr>
<td>Lateral Ventricular Enlargement</td>
<td>Ventricular enlargement represents a morphometric endophenotype for schizophrenia. Significant correlation between size of the lateral ventricles and underestimation of the metabolic activity of the caudate. (McDonald et al 2006; Berkataki et al 2006; Reig et al 2007)</td>
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<td>(Torres et. al. 2008; Torres et. al. 2005)</td>
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<tr>
<td>Agenesis of the Corpus Callosum</td>
<td>Reductions in the thickness of the anterior callosum differentiate between high-risk individuals who transition to psychosis and those who do not, and is highly predictive of transition. (Walterfang et al 2008)</td>
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<tr>
<td>(Torres et. al. 2004)</td>
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<tr>
<td>Reduction of Myelinated Neurons in Striatum</td>
<td>Myelin impairment is a key factor in the pathogenic loop of psychiatric diseases and drug addiction. (Feng 2008)</td>
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<td>(Torres et. al. 2004)</td>
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</table>
The *ckr* mouse has been shown to have predictive validity in psychosis and cognition.

The following antipsychotic compounds attenuated hyperactivity in the *ckr* mice in a dose-dependent manner at the range of doses used clinically:

- Haloperidol
- Clozapine
- Olanzapine
- Aripiprazole
- Pimozide
- Ziprasidone
- Quetapine
- Risperidone

The *ckr* mouse exhibits deficits in pre-pulse inhibition and latent inhibition that were reversed by clozapine but not haloperidol or risperidone.

Chakra Biotech offers the following protocols for screening and assessment of compounds with potential utility in the broad spectrum of psychotic illness:

1. **ckrRapidScreen**: Effect of drug on open field behavior (hyperactivity and circling) for prediction of antipsychotic efficacy, dose dependency and catalepsy.

2. **Pre-Pulse Inhibition**: Effect of compounds on PPI reversal to screen compounds for potential for cognitive enhancement. Shown to differentiate antipsychotics aiding cognition (clozapine) from antipsychotics not aiding cognition (haloperidol).

3. **Home activity monitoring**: Effects of drugs on home cage activity (24-hr) after 2-day habituation. Behaviors monitored include sleep/wake cycle, locomotion, climbing, eating, drinking and circling.

4. **Anxiety**: Effect of chronic treatment (7-day or 14-day) on anxiety in *ckr* mice using a T-maze.

5. **Memory**: Effect of compound on working memory, spatial and temporal memory and learning using the Barnes maze.

The *ckr* mouse offers numerous advantages over the commonly use pharmacologically induced models used for the majority of antipsychotic screening:

- Disease model with several endophenotypes relevant to psychosis allowing simple, clear and sensitive **translational** outputs
- Not hypothesis biased – results independent of mechanism of action of compound
- Not confounded by the pharmacological kinetics of the inducing agent and can differentiate behavioural kinetics of comparative compounds.

The *ckr* model gives the best translational insights into the clinical features of your antipsychotic compounds.
The chakragati (ckr) mouse
A translational disease model of psychosis

State-of-the-art Test Platforms

Improved objectivity, higher throughput, reduced animal usage

Chakra Biotech’s lab in Malaysia has automated our neurobehavioural screening using state-of-the-art testing platforms to give greater levels of confidence to our customers.

- **Laboras Home Activity Monitoring**: neurobehavioural assays with increased efficiency, quality (objectivity) and throughput.
- **Noldus Ethovision® XT system**: automated multi-arena tracking and data analysis of neurobehavioural assays.
- **Metris SonoTrack®**: recording and analysis of ultra vocalizations to test stress, anxiety, pain and social interactions.

Chakra Biotech works closely with customers to develop protocols to increase confidence turning HITS into LEADS.

For more information on our services please contact us through our website:

**www.chakrabiotech.com.my**

Helping our customers to improve the lives of psychiatric patients by offering the most predictive *in-vivo* screens to discover the next generation of therapeutic compounds.
The *chakragati (ckr)* mouse

*Published papers on the *ckr* mouse:*


