CRE-Luc GPCR Reporter Mouse Portfolio

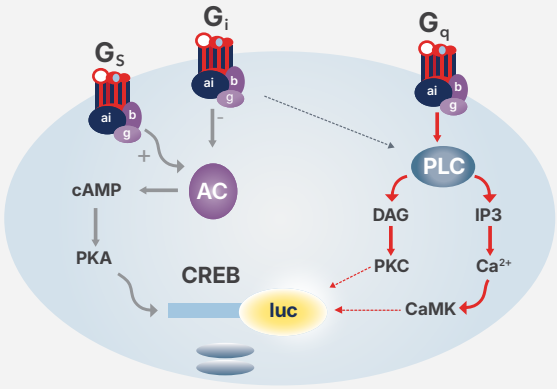
An *in vitro*/*in vivo* Platform for Profiling Leads in GPCR Drug Development

A PANEL OF LUCIFERASE REPORTER MICE ARE AVAILABLE

- Monitor GPCR pathway activation (via the two main GPCR classes, Gs and Gi) in various tissues, to better profile leads in GPCR drug development.
- Rapid *in vivo* PK/PD profiling of compounds with quantitative data to compare pharmacological action.
- The central nervous system CRE-Luc reporter has specified expression in brain and spinal cord, and can be leveraged in a variety of assays including *in vitro* (primary neuronal cultures), *in vivo*, and *ex vivo* (brain slices).

HOW THE CRE-LUC GPCR REPORTER PLATFORM WORKS

- CRE-Luc transgenic models contain a luciferase reporter under the control of a synthetic promoter CRE, which supports real-time bioimaging of GPCR ligand activity in whole animals, tissues, or primary cells.
- GPCR signaling, via the cAMP pathway, can be detected from the target GPCR in its native cellular environment with the full complement of associated receptors and membrane constituents.
- Accelerate transition from high throughput screening (HTS) to *in vivo* profiling of GPCR small molecule leads, while defining the mode of action of GPCR drugs.



For more information on the CRE-Luc reporter platform, visit: **www.taconic.com/CRE-Luc**

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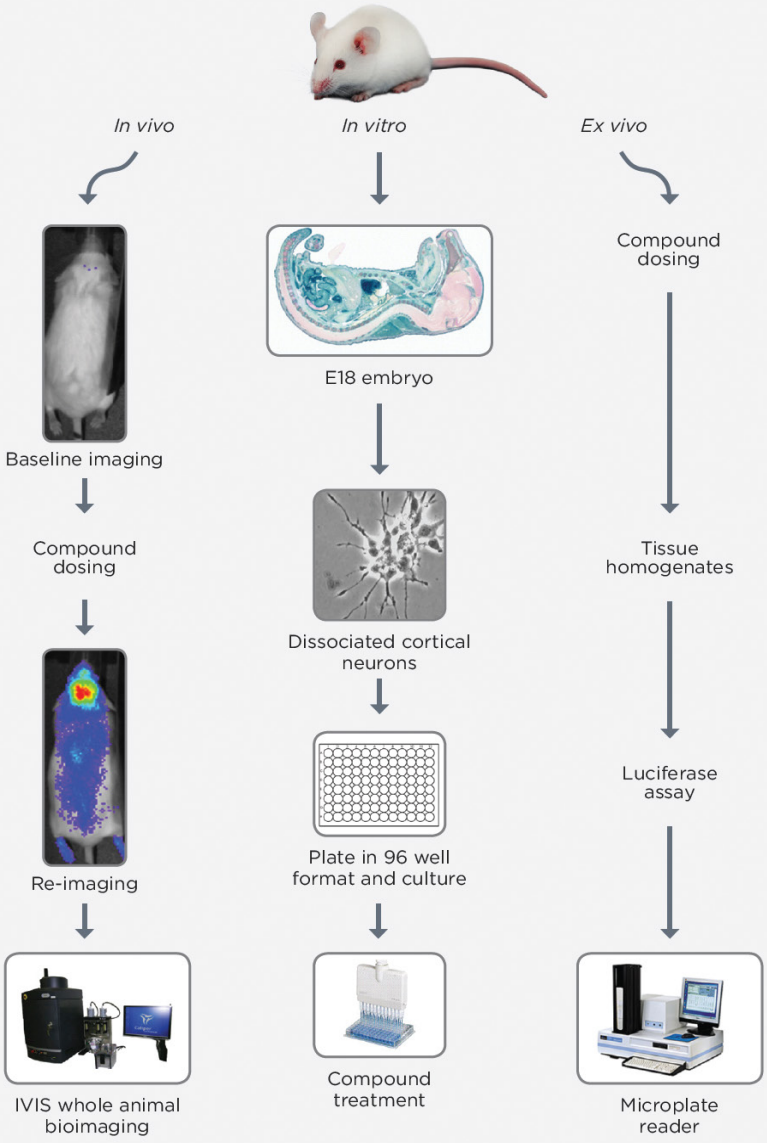
CRE-Luc Mouse Platform Supports Multiple Assay Systems



KEY STRENGTHS OF THE PLATFORM

- Accelerate transition from *in vitro* to *in vivo* assays in GPCR pharmaceutical programs.
- Multiple assay formats enhances lead optimization.
- Monitor all GPCR signaling through the cAMP pathway in a native environment where the critical membrane interfaces are interacting with the targeted GPCR.

Model Number	Reporter Expression
11515	Pancreas
11516	Intestine, liver, pancreas, lungs
11517	Kidney, liver
11518	Spleen, kidney, liver
11520	Brain, spinal cord
11521	Kidney, brain, pancreas, lungs

GPCR Signaling in the CNS

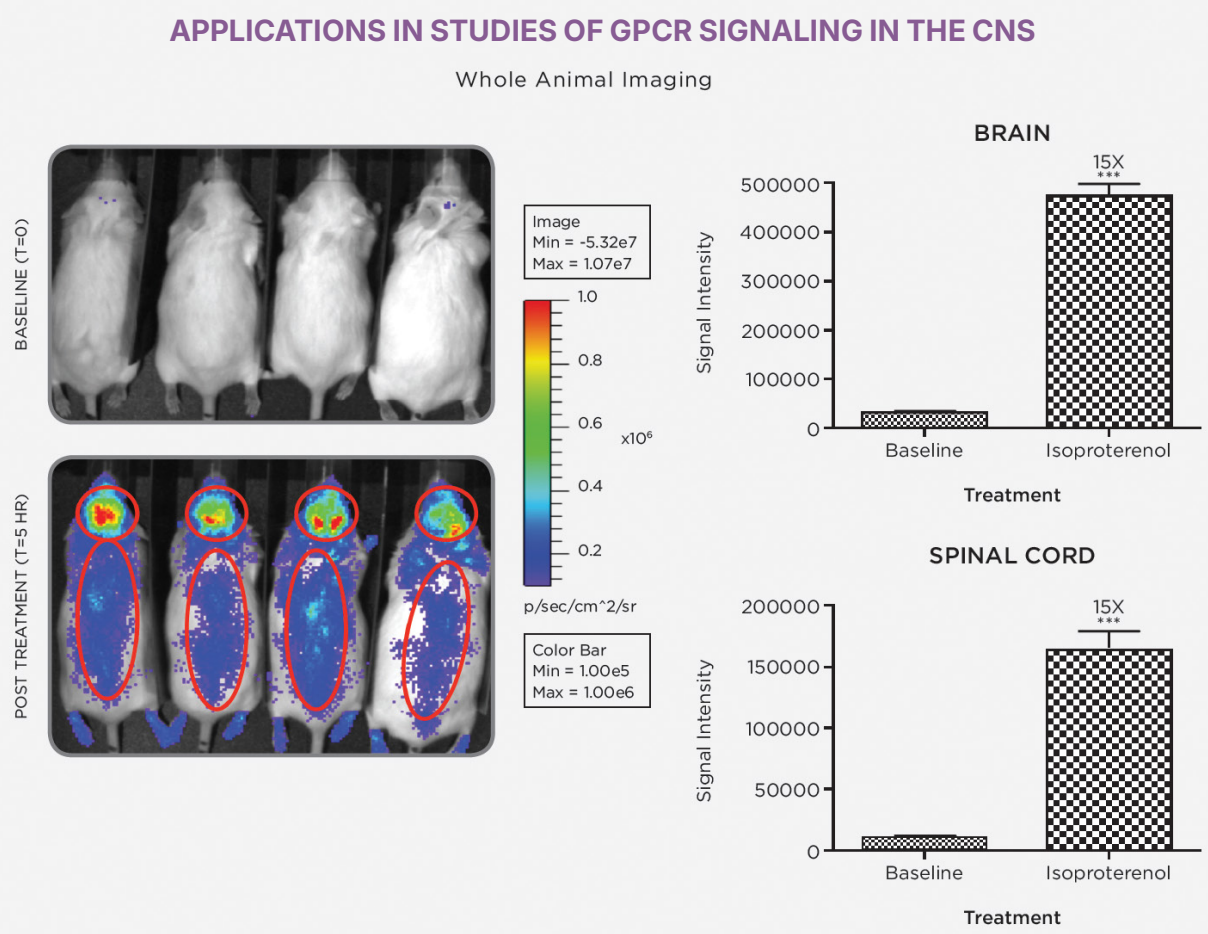


Figure 1. Treatment of mice (Model #11520) with Isoproterenol (β–adrenergic receptor agonist) shows CNS response.

CRE-Luc GPCR Reporter Mouse Platform

CRE-Luc lines serve as a source of primary cells with the GPCR reporter in its native environment allowing for *in vitro* and *in vivo* studies.

IN VITRO STUDIES (PRIMARY CELLS)

Primary cell cultures derived from CRE-Luc models can be used to confirm ligand activation. These assays are an important validation step since it is possible that any receptor (or combination of receptors) can be activated by a single ligand.

Once ligand activation has been profiled in primary cells, more complex tissue profiles can be assayed for luciferase enzyme levels either *ex vivo* or using tissue homogenates. Although tissue homogenate analyses can be time consuming, it is especially valuable when combined with dosing in whole animals, as it allows investigators to generate tissue-specific, and quantitative ligand activation profiles.

IN VIVO STUDIES (WHOLE ANIMAL)

Once the activation profiles have been established using primary cells, ligand profiles can be probed in whole animals using bioimaging techniques, while incorporating dose-response and time-course assays. Data analysis can occur in the same day as the imaging session allows unknown endpoints or results in the assay to be defined as the study progresses. This feature impacts flexibility in the animal study and can save significant time and money by avoiding repetitive studies to capture overlooked data.

The whole animal bioimaging assay can quantitatively define the site and magnitude of ligand activation, and can support a quantitative comparison of similar compounds which can be useful for selecting optimal lead structures, and SAR.

BRAIN SLICE IMAGING (MODEL #11520)

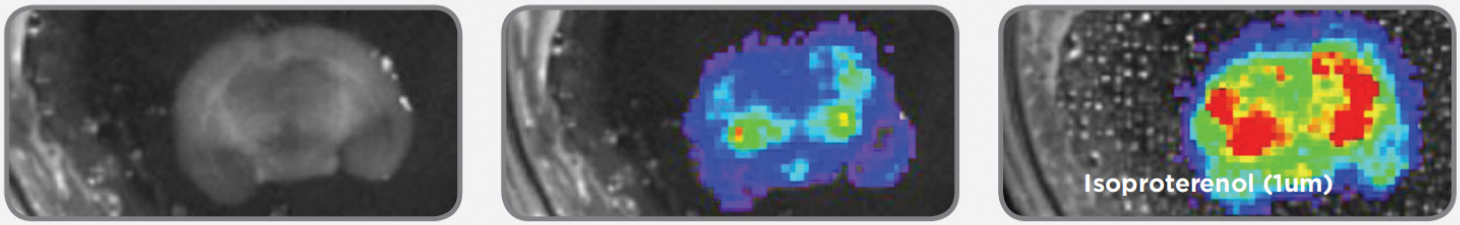


Figure 2. Imaging of compound induced changes in luciferase levels by a β–adrenergic receptor agonist.

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