

# CEREP SERVICES

Cerep offers *in vitro* pharmacology, *in vitro* ADME-Tox and *in vivo* PK services, and provides solutions allowing faster and cost-effective drug discovery by identifying at early stages the most promising drug candidates as well as eliminating those compounds likely to fail in development.

Cerep's services benefit annually to about 500 pharmaceutical and biotechnological companies worldwide including most of the top pharmaceutical firms.

Both standard and custom research solutions are available.

→ Standard research services include:

- ▶ compound management,
- ▶ high-throughput screening,
- ▶ *in vitro* safety profiling,
- ▶ lead optimization (or SAR) profiling,
- ▶ *in vitro* ADME profiling,
- ▶ *in vivo* PK.

→ Custom research services encompass assay development, profile design as well as data interpretation and provide scientist-to-scientist communications to understand and address client's needs.

Over the past 12 years, Cerep has developed BioPrint<sup>®</sup>, a unique database and related IT tools (see page 4), which allows the modeling of clinical effects of drug candidates from their molecular properties. BioPrint<sup>®</sup> may be used to interpret complex profiling data, prioritize lead or drug candidates or design lead optimization profiles.

To ensure the highest quality and provide the most reproducible data, Cerep produces in-house biological material that are used in most Cerep assays and qualifies its suppliers for best quality reagents and plasticware.

In 2010 Cerep has established a laboratory in Shanghai which is now fully operational to effectively support drug discovery projects that are run in Asia by providing the same high quality data that made Cerep's reputation in the market.

The success of this endeavor could only be achieved through the adaptation, set-up and implementation of processes which have proven their superiority in terms of quality, reproducibility, cost effectiveness and reduced timelines.

## ■ BROAD PROFILING/SCREENING SERVICES

Cerep continues to expand and diversify the assay families, with an average of 100 assays added or updated each year. These assays are either integrated in the Cerep catalog, or are exclusively available to sponsor.

The *in vitro* pharmacology and ADME-Tox & PK 2011 catalogs regroup about 1,300 assays, of which 473 GPCRs, including 134 cellular functional targets (agonist and antagonist effects), 255 biochemical kinases and 32 cellular kinase assays (activator and inhibitor effects), 51 ion channels, 61 CYPs (phenotyping, inhibition, induction), 20 epigenetic and DNA-related enzymes, 14 PDEs, 24 phosphatases ...

Cerep's platforms cover a wide range of target classes including ADME-Tox related targets, GPCRs, various enzymes, transporters, nuclear receptors and ion channels; employing methods and assay types such as radioligand binding assays, calcium mobilization and cAMP measurement using TR-FRET, transporter/uptake assays, and bioluminescent and other fluorescent-based assays.

## ■ ASSAY DESIGN AND DEVELOPMENT

The customized assay development services include a full range of assays and technologies adapted to clients' specific projects and needs.

Cerep has an extensive and integrated suite of core competencies valuable to any drug discovery programs. The tool boxes shown below provide information about Cerep's know-how and expertise in assay development. They are extendable to other studies, targets and technologies depending on your needs.

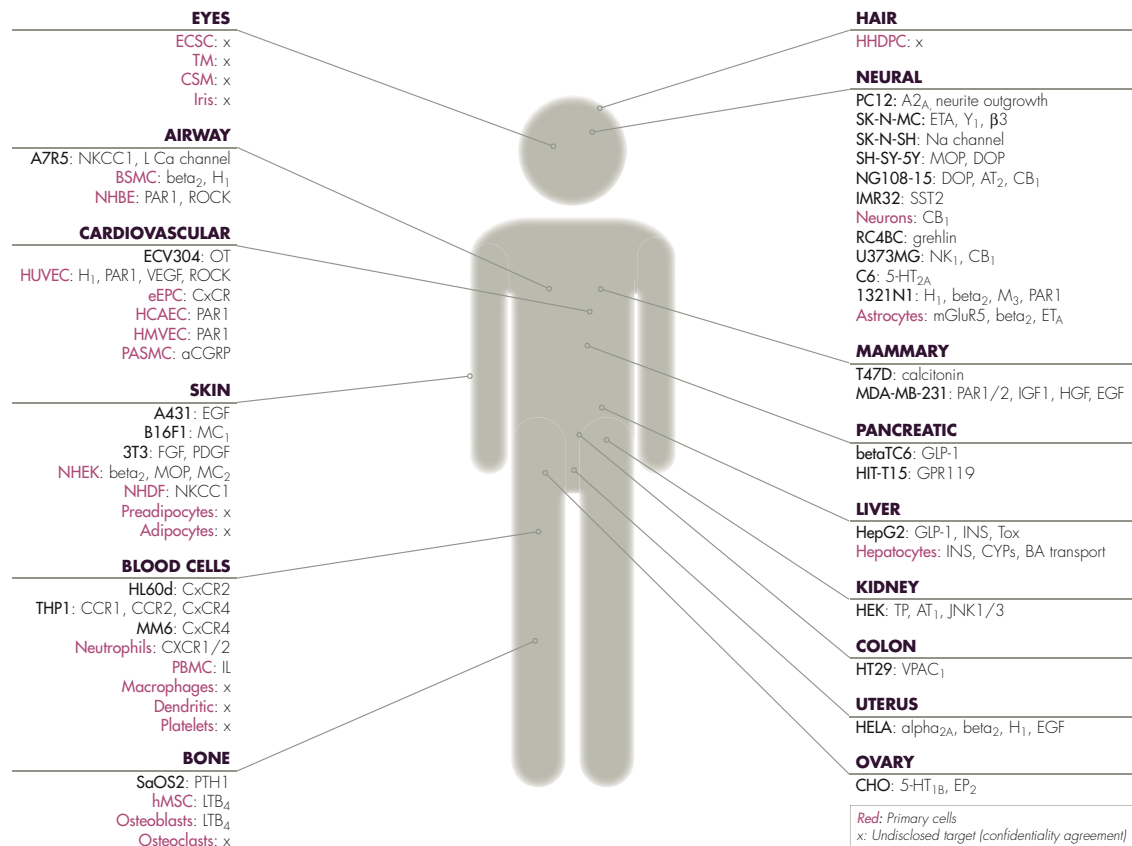
Please contact us for a specific solution adapted to your specific request at: [customresearch@cerep.com](mailto:customresearch@cerep.com).

### ■ TOOL-BOX FOR CELL-BASED ASSAY DEVELOPMENT

In order to study compounds activity in a living cellular background, Cerep can design cellular assays for any target. For this purpose, Cerep offers a broad panel of cell-based assay solutions, for which principal

families are represented here. These assays can be applied either on recombinant models or more physiologically relevant models such as primary cells.

→ Customized cellular assays developed at Cerep on non-recombinant models



■ TOOL-BOX FOR BIOCHEMICAL ASSAYS

In addition to cellular assays, Cerep offers multiple biochemical assays to accurately study the interaction of compounds with the target of interest. These assays can be developed on recombinant material or native tissues.

Targets ↓	Binding assays	Functional assays
GPCR	Radioligand binding	GTPγS
Ion channel	Radioligand binding	–
Kinases	TR-FRET	TR-FRET
Other enzymes	Radioligand binding	Multiple technologies
Growth factor receptors	Radioligand binding	–
Cytokine receptors	Radioligand binding	–
Nuclear receptors	Radioligand binding	AlphaScreen
Transporters	Radioligand binding	–

→ Customized binding assays developed at Cerep on native animal tissues:

- Serotonin 5-HT<sub>1A</sub>, 5-HT<sub>2A</sub> in rat brain, 5-HT<sub>3</sub>, 5-HT<sub>6</sub>, 5-HT<sub>7</sub> in rat cDNA
- Muscarinic M<sub>1</sub>, M<sub>3</sub> in rat brain, M<sub>2</sub> in rat heart
- Endothelin ET<sub>A</sub> in rat A-10 cells, ET<sub>B</sub> in rat cerebellum
- Cholecystokinin CCK<sub>A</sub>, CCK<sub>B</sub> in rodent
- Dopamine D<sub>1</sub>, D<sub>2</sub> in rat striatum
- Transporters choline, dopamine and norepinephrine in rat striatum, 5-HT in rat brain
- ...

For a complete list, please contact us at [customresearch@cerep.com](mailto:customresearch@cerep.com).

## TOOL-BOX FOR GPCRs

Depending on the type of target, study and model, Cerep can recommend the most adapted technology.

Studies ↓	Targets →	Gi	Gq	Gs	G12/13
Affinity Kon/Koff		RLB <sup>1</sup> SPA <sup>2</sup>	RLB <sup>1</sup> SPA <sup>2</sup>	RLB <sup>1</sup> SPA <sup>2</sup>	RLB <sup>1</sup> SPA <sup>2</sup>
Agonist Antagonist Allosteric (PAM & NAM)		GTPγS TR-FRET cAMP CDS <sup>3</sup> Aequorin <sup>4</sup>	TR-FRET IP1 Fluorescence CDS <sup>3</sup> Aequorin <sup>4</sup>	TR-FRET cAMP CDS <sup>3</sup> Aequorin <sup>4</sup>	ELISA CDS <sup>3</sup> Aequorin <sup>4</sup>
Inverse agonist		GTPγS TR-FRET cAMP CDS <sup>3</sup>	TR-FRET IP1 CDS <sup>3</sup>	TR-FRET cAMP CDS <sup>3</sup>	CDS <sup>3</sup>
Weak agonist Slow agonist		GTPγS TR-FRET cAMP CDS <sup>3</sup>	TR-FRET IP1 CDS <sup>3</sup>	TR-FRET cAMP CDS <sup>3</sup>	CDS <sup>3</sup>
Deorphanization		CDS <sup>3</sup> Aequorin <sup>4</sup>	CDS <sup>3</sup> Aequorin <sup>4</sup>	CDS <sup>3</sup> Aequorin <sup>4</sup>	CDS <sup>3</sup> Aequorin <sup>4</sup>
Coupling mechanism		CDS <sup>3</sup>	CDS <sup>3</sup>	CDS <sup>3</sup>	CDS <sup>3</sup>
Kinase phosphorylation		AlphaScreen	AlphaScreen	AlphaScreen	AlphaScreen

<sup>1</sup> RLB: Radioligand Binding

<sup>2</sup> SPA: Scintillation Proximity Assay

<sup>3</sup> CDS: Cellular Dielectric Spectroscopy

<sup>4</sup> Expression of chimeric or promiscuous G proteins may be required.

## PROFILE DESIGN

Cerep offers a **profile design service** based on the experience and knowhow of its scientists **for both content and execution of profiles**. Cerep BioPrint® database (see below), various publicly available databases, and the scientific literature are used to design different types of profiles according to your needs.

### TOOL-BOX FOR PROFILE DESIGN

Type	Content	Applications
Disease profile	Targets that are associated to a particular disease	<ul style="list-style-type: none"> <li>- Find a therapeutic indication for a given compound or marketed drug (repositioning)</li> <li>- Find the target(s) responsible for the therapeutic effect (mechanism of action)</li> <li>- Lead optimization</li> </ul>
Side effect profile	Targets that are associated to a particular side effect	<ul style="list-style-type: none"> <li>- Anticipate an unwanted side effect</li> <li>- Find the target(s) responsible for the therapeutic effect (mechanism of action)</li> <li>- Lead optimization</li> </ul>
Predictive profile	Targets that are susceptible to be hit by a given compound	<ul style="list-style-type: none"> <li>- Assess the target selectivity of a given compound</li> <li>- Find a therapeutic indication for a given compound or marketed drug (repositioning)</li> <li>- Find the target(s) responsible for the therapeutic effect (mechanism of action)</li> <li>- Anticipate an unwanted side effect</li> <li>- Find the target(s) responsible for the therapeutic effect (mechanism of action)</li> <li>- Lead optimization</li> </ul>

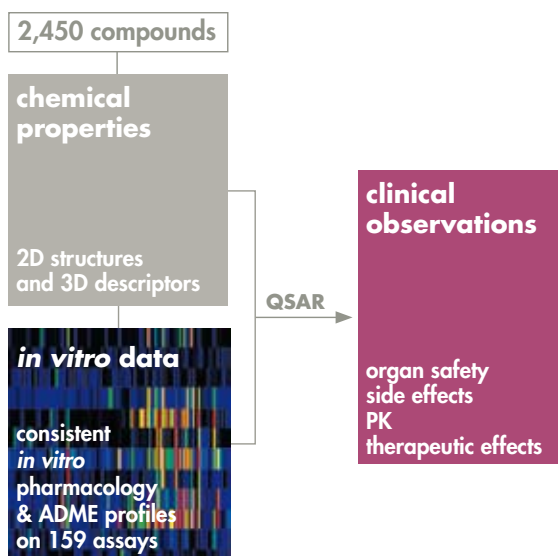
## BIOPRINT® PROFILE & SERVICES

BioPrint® is a large, homogenous pharmacology and ADME database, which provides a unique resource for supporting decision making in drug discovery. The database is composed of three main data sets:

- chemical descriptors (structures and chemical information, 2D and 3D descriptors),
- in-house generated *in vitro* pharmacology and ADME data, also considered as compound descriptors,
- collected and curated *in vivo* effects of drugs.

Chemical and pharmacophoric descriptors together form a data set for QSAR generation supporting organ safety modeling.

BioPrint® positions a new drug candidate in the context of marketed drugs, anticipating potential *in vivo* liabilities, predicting off-target activities, and ADME characteristics (Drug profile interpretation). In another application, BioPrint® serves to identify secondary targets that are not genetically parented to a test target (target profile design). Both these applications are available as custom services.



## ■ BIOPRINT® PROFILE

The BioPrint® profile includes the assays used to explore the properties of about 2,450 BioPrint® compounds (mainly marketed drugs and reference compounds), establishing individual Pharma-ADME fingerprints for each compound.

Offered on a standard basis, this profile is mainly based on target diversity and includes today 105 binding assays (GPCRs, nuclear and other receptors, ion channels and transporters), 34 enzyme assays (including 10 kinases, 10 proteases and 5 phosphodiesterases), as well as 20 ADME-Tox assays (Solubility, Absorption, Metabolism and CYP-mediated drug-drug interaction). More than 70% are human targets. The 159 assays of this profile represent a rationalized panel from a larger assay collection in the database, selected for highest information content.

→ For list of assays included in BioPrint® profile, please go to [www.cerep.com](http://www.cerep.com) **CATALOG ONLINE**

## ■ BIOPRINT® DRUG PROFILE INTERPRETATION

Any compound in drug development, when run as a test compound on the BioPrint® profile, can be placed in the context of already marketed drugs, when similar *in vitro* profiles exist in the database. Hypotheses on clinical behavior of the test compounds can be drawn by comparison with data on BioPrint® compounds that have been collected and analyzed over the last twelve years, including:

- ▶ **Clinical effects of drugs** with a similar profile or sub-profile.
- ▶ **Adverse Drug Reactions (ADRs) correlated with *in vitro* assays:** more than 5,000 significant statistical associations have been identified between the activity of molecules on a specific target and the occurrence of an ADR in man.
- ▶ **Probability of occurrence of clinical effects or ADRs** estimated with multivariate models using the complete *in vitro* profile: today more than 170 ADRs have been modeled.

## ■ BIOPRINT® TARGET PROFILE DESIGN

Any target, run as a test target on the BioPrint® compound library, can be compared to any other target in BioPrint®, based on its pharmacological profile (compounds that interact with a given target). Analysis of cross-reacting compounds between targets (number and intensity of common hits), allows to identify targets that are “pharmacophorically related” to the test target. Interestingly, a profile of pharmacophorically related targets can differ significantly to a list of genetically related targets.

BioPrint® target profile design represents highly valuable information, when setting up secondary screening tests, anticipating secondary targets and effectively supporting lead optimization to monitor potential secondary target related liability issues. If the test target is already part of BioPrint® assays, BioPrint® target profile design is limited to data-analysis and establishment of a profile of secondary targets. If the test target is not part of the BioPrint® assay panel, Cerep can develop the assay and run the BioPrint® compounds on an exclusive or shared data basis.



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■ **QUESTIONS OR CONCERNS?**  
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