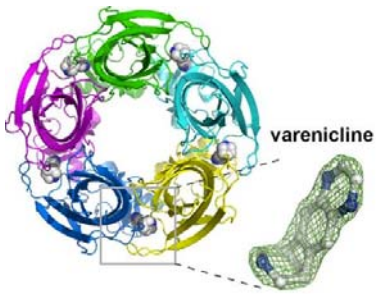
## Neurotransmitter Cys-loop receptors: structure, function and disease

Neurocypres consortium members are devoted to study structural and functional aspects of Cys-loop receptors, a superfamily of ligand-gated ion channels that is crucial to the function of the peripheral and central nervous system. Cys-loop receptors (CLRs) share a generic protein architecture consisting of five subunits with an integral ion-channel that can open and close depending on ligand binding. CLRs comprise of nicotinic acetylcholine-, GABAA-, 5HT3-, and Glycine receptors. Dysfunction of CLRs is linked to muscle disorders (e.g. myasthenic syndromes), hyperexcitabiliy of the brain (e.g. epilepsy) and spinal cord (e.g. hyperekplexia / stiff baby syndrome) as well as nicotine addiction, while CLR subunit genes serve as candidates for frequent psychiatric diseases (e.g. schizophrenia). CLRs are molecular targets for clinically important drugs. Novel drugs are on the horizon, mediating highly selective therapeutic effects and providing new avenues for therapeutic use. Today, the quality of crystallographic data and the general knowledge of structure-function relationships have progressed to the extent that the rational design of ligands has become a feasible objective. Coordinated approaches, such as Neurocypres, are required to increase our knowledge of ligand-gated ion channel structure at high-resolution.

In 2008, Neurocypres brought together 20 groups of researchers in a large-scale integrated effort to capture high-resolution structural information encompassing either the entire structure of selected receptors, or of specific functional domains in these receptors. Since then, new discovery projects in the fields of nAChRs, GABAA and 5HT3 receptors have been established. Various projects were dedicated to understand the fundamentals of receptor structure, e.g, structural data of the acetylcholine binding proteins (AChBPs), co-crystalized with various ligands, was obtained. For various different CLR ligands, in-depth knowledge was gathered on ligand binding to the AChBPs, e.g., various toxins, as well as small molecules important for drug design. Compounds relevant for medicinal use, for instance the anti-smoking compound varenicline, were studied. In addition AChBPs were engineered that can act as new tools for drug development for CLR receptors, for instance of the 5HT3R class. Another important area of the Neurocypres program was to advance new technologies for drug design and screening. New technologies were established with promising results on small molecules targeting the different members of the LGIC family. These included high-throughput electrophysiological analyses of receptor expression in oocytes, fluorescence based assays, and affinity measurements using surface plasmon resonance. Also the use of CLRs to probe neuronal function, as biosensors, has progressed to studies in neurons. Moreover, efforts to produce whole subunits and receptors were initiated. Already in its first year Neurocypres celebrated the first structure solved of an entire cys-loop receptor by one of its partners (P-J Corringer, Pasteur, Paris). A combined genomic search, functional expression and X-ray crystallography yielded the discovery and atomic structural resolution of bacterial homologs of LGICs. The homolog from the cyanobacterium Gloeobacter violaceus (GLIC) revealed that it functions as a proton-gated ion channel. Its X-ray structure was solved at 2.9 Å resolution in an apparently open conformation. Work on the bacterial receptors yielded various new insights. For instance, now having the transmembrane domains available in the structure allowed to discover novel binding sites for substances long known to act as modulators of CLRs. Crystallization studies revealed new insights in compounds normally acting on the GABAA receptors, e.g., acting at the benzodiazepine binding site. In addition, the sites to which the binding of general anesthetics (used in the clinic during surgery) occurs were revealed.

Taken together, the Neurocypres project generated many new insights in receptor structure and function. In four productive years, with 111 publications, the consortium pushed the frontiers of knowledge on CLRs, opening new avenues for drug design at these receptors.

Read more about the discoveries of Neurocypres researchers at : www.neurocypres.eu




The smoking-cessation compound Varenicline binding to AChBP. For details see: Brahms et al., Proc Natl Acad Sci U S A. 2012 109(23): 9173–9178.