Development of a nanobody anti-mGluR2 as a therapeutic agent for the treatment of schizophrenia

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Project description:

The G protein coupled receptor (GPCR) activated by glutamate mGluR2 is a potential therapeutic target for the treatment of schizophrenia, a major chronic psychotic disease. Most drugs targeting mGluR2 are small molecules and many of them are hydrophobic then resulting in side effects when tested in animals thus halting clinical trials.

Therapeutic antibodies against GPCRs constitute a new class of drugs to treat brain diseases. We have recently developed single domain antibodies from llamas, called nanobodies, to target mGluR2. Among them, DN13 has a therapeutic potential for schizophrenia as it activates mGluR2 i) in heterologous system, ii) in native tissues (hippocampal slices) and iii) in living animals (mice).

The objective of this thesis project is to optimize the nanobody DN13 and to test it in animal models of schizophrenia. Accordingly, the following three specific aims were defined:

1- **Increasing the affinity of the nanobody** in order to limit the amount of DN13 required for injection, either by oligomerization of DN13 and by developing bi-specific nanobodies.

2- **Engineering the nanobody for a better brain penetration.** DN13 in vivo half-life will be enhanced either by increasing its molecular weight, or by fusion to a nanobody like an anti-serum albumin nanobody. To promote its brain penetration, DN13 will be coupled to proteins that cross the blood brain barrier.

3- **Evaluation of the benefit of the optimized nanobody in mouse models of schizophrenia.** Optimized DN13 will be administrated to the animals either by intra-venous or intra-peritoneal injection, and its effects will be evaluated by measuring social interaction and locomotion of mice treated with phencyclidine during adolescence.