Depression is a prevalent mood disorder and can be life-threatening. The currently available antidepressants affect serotonergic, noradrenergic or dopaminergic neurotransmission. One notable issue of the current antidepressant treatment is that it normally requires many weeks of medication to elicit therapeutic response. Additionally, for each drug, up to 80% of the patients only show partial responses. Thus, there is significant need to develop new anti-depression strategies that would benefit a larger patient population and show rapid-acting efficacy. Agents that enhance the action of the available antidepressants would also be desirable.

One emerging approach is to manipulate the metabotropic glutamate type 5 receptor (mGluR5) to treat anxiety and depression. Although some studies suggest using mGluR5 antagonists, others indicate positive modulation of mGluR5 (by positive allosteric modulators or PAMs). You are asked to formulate an NRSA-type proposal to test your favorite hypothesis (i.e. do you favor mGluR5 inhibition or mGluR5 enhancement?). You shall take advantage of the available animal models of depression as well as the known molecular mechanisms underlying depression to develop a feasible approach.

In writing your proposal, you can consult the tips provided by the NIH for writing proposals (http://grants.nih.gov/grants/writing_application.htm). For this exam you only need to consider **significance, innovation and approach**. Remember that the reviewers need to be convinced that you have a grasp of the topic and that you convey your research plan clearly. Even though the research may involve complex relationships you still need to express your ideas as simply as possible.

Your answer, not including references, should be no longer than 7 single-spaced printed pages using a font size of 11 points or larger. The first page should contain the **Specific Aims**; this will be an overview of the problem and your approach. Your research strategy should have the components listed below, with an emphasis on the approach, significance and innovation in that priority. In other words, the reviewers are more interested in how you would approach the problem than lots of “hand-waving” about significance and innovation. Because this question requires that you cover molecular and behavioral approaches to the problem, you should have at least 2 aims, each with a research strategy section.

Specific Aims

State concisely the goals of the proposed research and summarize the expected outcome(s), including the impact that the results of the proposed research will exert on the research field(s) involved.

List succinctly the specific objectives of the research proposed, e.g., to test a stated hypothesis, create a novel design, solve a specific problem, challenge an existing paradigm or clinical practice, address a critical barrier to progress in the field, or develop new technology.

Research Strategy

Organize the Research Strategy in the specified order and using the instructions provided below. Start each section with the appropriate section heading—Significance, Innovation, Approach. Cite published experimental details in the Research Strategy section and provide the full reference in the Bibliography and References Cited section.

Follow the page limits for the Research Strategy in the Table of Page Limits, unless specified otherwise in the FOA.

(a) Significance

- Explain the importance of the problem or critical barrier to progress in the field that the proposed project addresses.
- Explain how the proposed project will improve scientific knowledge, technical capability, and/or clinical practice in one or more broad fields.
- Describe how the concepts, methods, technologies, treatments, services, or preventative interventions that drive this field will be changed if the proposed aims are achieved.

(b) Innovation

- Explain how the application challenges and seeks to shift current research or clinical practice paradigms.
- Describe any novel theoretical concepts, approaches or methodologies, instrumentation or intervention(s) to be developed or used, and any advantage over existing methodologies, instrumentation or intervention(s).
- Explain any refinements, improvements, or new applications of theoretical concepts, approaches or methodologies, instrumentation or interventions.

(c) Approach

- Describe the overall strategy, methodology, and analyses to be used to accomplish the specific aims of the project. Unless addressed separately in the Resource Sharing Plan, include how the data will be collected, analyzed, and interpreted as well as any resource sharing plans as appropriate.
- Discuss potential problems, alternative strategies, and benchmarks for success anticipated to achieve the aims.

Reading list

Palucha A1, Pilc A (2007). Metabotropic glutamate receptor ligands as possible anxiolytic and antidepressant drugs. Pharmacol Ther. 115(1):116-47.

Rodriguez AL1, Grier MD, Jones CK, Herman EJ, Kane AS, Smith RL, Williams R, Zhou Y, Marlo JE, Days EL, Blatt TN, Jadhav S, Menon UN, Vinson PN, Rook JM, Stauffer SR, Niswender CM, Lindsley CW, Weaver CD, Conn PJ. (2010) Discovery of novel allosteric modulators of metabotropic glutamate receptor subtype 5 reveals chemical and functional diversity and in vivo activity in rat behavioral models of anxiolytic and antipsychotic activity. Mol Pharmacol. 78(6):1105-23.

Krishnan V1, Nestler EJ. (2011) Animal models of depression: molecular perspectives. Curr Top Behav Neurosci. 7:121-47.

Masi G, Brovedani P. (2011) The hippocampus, neurotrophic factors and depression: possible implications for the pharmacotherapy of depression. CNS Drugs. 25(11):913-31.

Russo SJ, Murrough JW, Han MH, Charney DS, Nestler EJ. (2012) Neurobiology of resilience. Nat Neurosci. 15(11):1475-84.