major functions of DDM include the following: (1) Serving as the entry point for citizen petitions, comments, hearing requests, and other documents related to FDA's rulemaking and administrative activities; (2) maintaining a public reading room, in which documents are available for public inspections; (3) providing copies of official records maintained in accordance with the Freedom of Information Act; and (4) providing advice and guidance regarding filing requirements pertaining to FDA's rulemaking or administrative activities.

Dated: September 2, 2004.

William K. Hubbard,

Associate Commissioner for Policy and Planning.

[FR Doc. 04–20394 Filed 9–3–04; 11:49 am]

BILLING CODE 4160–01–S

DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

Opportunities for Cooperative Research and Development Agreements (CRADAs) To Undertake Research and Development of Compounds From Specific Categories for the Treatment of Drug Dependence

AGENCY: National Institutes of Health, PHS, DHHS.

ACTION: Notice.

SUMMARY: The National Institute on Drug Abuse (NIDA), a component of the National Institutes of Health, is seeking proposals from potential collaborators for one or more Cooperative Research and Development Agreements (CRADAs) to test, by scientific means meeting U.S. Food and Drug Administration (FDA) standards, the hypothesis that compounds representative of the following classes (numbered 1–8 below) may be useful in the treatment of drug dependence:

1. CRF–1 antagonists.
2. Cannabinoid-1 antagonists.
3. MGluR5 antagonists.
4. AMPA antagonists.
5. Selective, high affinity dopamine D3 agonists and antagonists.
6. Selective, high affinity dopamine D1 full or partial agonists.
7. Kappa opioid antagonists.
8. Compounds from classes not named in 1–7 above, but for which compelling rationales are provided by potential collaborators.

DATES: NIDA will consider all proposals received within 60 days of the date of the publication of this notice. This notice is active until November 8, 2004.

ADDRESSES: Questions and expressions of interest concerning this notice may be addressed to Dr. Frank Vocci (301–443–2711; e-mail: *fv6k@nih.gov*) or Mr. Lee Cummings (301–443–1143; e-mail: *lc65i@nih.gov*) or at the following address: Division of Pharmacotherapies and Medical Consequences of Drug Abuse, National Institute on Drug Abuse, 6001 Executive Boulevard, MSC 955, Room 4123, Bethesda, Maryland 20892–9551.

SUPPLEMENTARY INFORMATION:

Rationale for CRF–1 Antagonists

Evidence suggests that withdrawal syndromes associated with chronic use of drugs of abuse results in elevations of CRF levels. Stress has been shown to modify the intake of drugs of abuse in preclinical studies of drug self-administration. The effects of stress can increase drug intake and can be mimicked by CRF administration. CRF antagonists have a robust inhibitory effect on stress-induced increases in drug taking behavior.

Rationale for Cannabinoid-1 Antagonists

Cannabinoid-1 antagonists (CB–1) block the cell surface receptors activated by marijuana, but have been reported to be involved in effects of other abused substances. A CB–1 receptor antagonist has been shown to reduce nicotine self-administration and nicotine-induced dopamine release in the nucleus accumbens, reduce heroin self-administration in rats, and reduce amphetamine self-administration in rats. Further, CB–1 antagonists may also prevent relapse to cocaine or heroin by blocking rats' responses to both cocaine and heroin priming, and to cues associated with cocaine. Finally, mice lacking the CB–1 receptor do not show stress-induced increases in alcohol consumption, suggesting that the receptor may also contribute to stress-induced drinking. Taken together, results suggest a role for the cannabinoid system in abuse of several classes of drugs.

Rationale for mGluR5 Antagonists

Drugs of abuse increase glutamatergic neurotransmission in the nucleus accumbens, and metabotropic glutamate receptors located there may modulate release of glutamate and dopamine. Since gene knockout studies reported in 2001 showed that mice lacking the mGluR5 receptor show decreased locomotor stimulant effects of cocaine and fail to develop cocaine self-administration behavior, a number of studies have examined the effects of mGluR5 antagonist on behaviors related to drug abuse. Interestingly, mGluR5 antagonists have been reported to decrease cocaine and nicotine self-administration in rodents, decrease amphetamine-stimulated locomotor activity, and to attenuate relapse to alcohol, suggesting a role in abuse of more than one drug.

Rationale for AMPA Antagonists

AMPA antagonists may be useful in the treatment of cocaine addiction because AMPA antagonists have been shown to affect three cocaine-induced processes thought to be important in the development of cocaine addiction for: (1) Prevention of locomotor sensitization, (2) Blockade of cocaine-cue induced drug seeking behavior, and (3) blocking cocaine-primed reinstatement in an animal model of cocaine self-administration.

Rationale for D3 Partial Agonists and Antagonists

Dopamine D3 receptors are localized in areas of the brain that are involved in drug abuse, and have been reported to be up-regulated in the brains of cocaine overdose fatalities. The potency of compounds that activate D3 receptors is related to their ability to decrease cocaine self-administration in rats, suggesting the involvement of these receptor types in cocaine drug-taking. Dopamine D3 partial agonists have been shown to block the behaviorally activating effects of cues that have been paired with cocaine in rats, suggesting potential usefulness in blocking relapse following contact with environmental cues associated with drug use. Dopamine D3 antagonists have recently been reported to block nicotine-primed nicotine seeking behavior in rats as well as cocaine-primed cocaine seeking in rats, suggesting a potential role in preventing relapse. Further, a D3 antagonist has been reported to block both the acquisition and expression of heroin conditioned place preference in rats, suggesting, overall, that both dopamine D3 partial agonists and D3 antagonists may be useful treatments for more than one drug of abuse.

Rationale for D1 Agonists

There is evidence that dopamine D1 receptors are down-regulated in rats and monkeys following exposure to cocaine using in vitro measures. In addition, D1 agonists have been shown to lack priming effects in rats trained to self-administer cocaine, and are able to block the effects of a priming dose of cocaine in this model. Other cocaine-self administration models indicate that D1 agonists can reduce the self-administration of both low and high

doses of cocaine. In a cocaine self-administration reinstatement model in monkeys that may model relapse following a period of abstinence in humans, a D1 agonist can reduce the effect of a priming dose of cocaine that might lead to relapse. In humans, a D1 agonist blunted the subjective effects of cocaine, and reduced craving for cocaine and other drugs.

Rationale for Kappa-Opioid Antagonists

Kappa-opioid antagonists block receptors for the endogenous opioid ligand dynorphin, which is up-regulated by chronic opioid use and has been linked to dysphoric states that can lead to opioid relapse. There is also evidence that kappa antagonists have anti-stress effects, which may make them useful in the prevention of relapse to drugs of abuse like cocaine.

Rationale for Compounds Not Named Above To Be Considered

The possibility exists that compounds that have mechanisms of action other than those described in items 1–7 above may be potentially useful in the treatment of drug dependence. NIDA will consider candidate compounds from other classes if, and only if, scientific evidence exists to support a compelling rationale for testing and/or development.

Potential for Collaborative Development

NIDA does not currently own or have adequate access to compounds representing the referenced classes. To this end, NIDA is seeking to enter into a CRADA collaboration with entities that may qualify as CRADA collaborators. These would include, but not be limited to pharmaceutical companies, academic research institutions with company affiliations, and other commercial entities with adequate capacity to participate in the evaluation and development of candidate compounds from the classes listed for the treatment (reduction in use in drug dependent persons and prevention of relapse in formerly drug dependent individuals). NIDA will consider proposals from all qualified entities and will, subject to negotiation of the details of a mutually agreed upon research plan and CRADA, provide the CRADA collaborator access to services and data generated from its comprehensive preclinical and clinical trials facilities. CRADA Collaborators will be able to utilize data derived from the CRADA to pursue regulatory filings in the U.S. and abroad. Compounds of the representative classes at all stages of development will be considered. NIDA's Medications Development Program possesses the capacity to perform pharmacological and toxicological testing, pharmacokinetics, dosage form development, regulatory management, and clinical testing from Phase I through Phase III testing and is willing to apply these capacities in the assessment of specified compounds as may be warranted.

Following classical drug development schema, decisions to proceed to each subsequent preclinical or clinical study will be based on data derived from previous or ongoing studies. Assuming adequate safety can be demonstrated, it is NIDA's intention to provide clinical trials services sufficient to permit, subject to FDA approval, research and development up to and including Phase II hypothesis testing. Assuming demonstration of safety and efficacy at the conclusion of Phase II trials and subject to negotiation, NIDA will, in some cases, also consider collaborations to undertake Phase III trials sufficient to permit collaborator to seek a U.S. New Drug Approval (NDA).

No funding may be provided to a collaborator under a CRADA: all assistance is provided ''in-kind''. Therefore the collaborator will bear the financial and organizational costs of meeting its obligations under collaborator's portion of any research plan that may be negotiated. Benefits of collaborating with NIDA beyond access to NIDA's clinical and preclinical resources include the option to an exclusive license to any subject inventions made by NIDA scientists during the course of the collaboration, and exclusivity with respect to submitting data from the collaboration for regulatory filings.

Selection Factors and Considerations

Selection factors and considerations of importance of NIDA include:

1. It is mandatory that collaborators possess commercialization rights to the compound sufficient to permit research and commercial development for the intended field of use, *i.e.*, treatment of drug dependence. In the event the collaborator does not own the compound or composition, collaborator must provide appropriate documentation of a license permitting research and commercialization for the field of use sufficient to permit the CRADA to proceed.

2. NIDA will consider the amount of research and development documentation and experience already in the collaborator's possession. NIDA will sign appropriate confidential disclosure agreements in order to review confidential and unpublished data. While NIDA will review all proposals concerning candidate compounds representative of the listed classes, it will give a higher priority to proposals that can document a more advanced level of development with the proposed compound(s).

3. NIDA will consider the amount and type of research and development resources the collaborator proposes to undertake as part of a proposed CRADA.

4. NIDA will consider the background, experience, and expertise in medications development of the proposed collaborator.

Dated: August 27, 2004.

Steven M. Ferguson,

Director, Division of Technology Development and Transfer, Office of Technology Transfer, National Institutes of Health.

[FR Doc. 04–20290 Filed 9–7–04; 8:45 am]

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DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute: Cooperative Research and Development Agreement (''CRADA'') Opportunity and Licensing Opportunity: Scientific and Commercial Drug Development To Exploit Antiangiogenic Activity Targeting Adrenomedullin Gene Products

AGENCY: National Institutes of Health, Public Health Service, DHHS.

ACTION: Notice.

SUMMARY: The National Cancer Institute (NCI) is currently seeking Cooperative Research and Development Agreement (CRADA) collaborator(s) to work with investigators in the Center for Cancer Research (CCR) to explore, for drug development and clinical testing, novel antiangiogenic agents that target adrenomedullin gene products. Research and development may include development of blocking reagents (humanized antibodies, peptide antagonists, small molecules), formulation for systemic and topical application, preclinical animal studies, and clinical trials. Licensing is available for background inventions related to this technology.

DATES: Parties interested in a CRADA collaboration should notify the Technology Transfer Branch of the NCI in writing of their interest no later than October 25, 2004. The written notice should briefly address the selection criteria listed below under Supplementary Information.