# CeNeS and Tripos Announce Advances in COMT inhibitor discovery programme

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***Cambridge, U.K. and St. Louis, USA, 13 April 2005***– CeNeS Pharmaceuticals ("CeNeS", AIM:CEN) the Cambridge-based biopharmaceutical company, and Tripos ("Tripos", Nasdaq: TRPS), a leading global provider of drug discovery chemistry and informatics solutions, today announced that they have reached important milestones in their joint research partnership on COMT inhibitors and have consequently entered into a new agreement to continue their collaboration. Terms of the agreements were not disclosed.

*Following on from CeNeS' innovative research programme that commenced in 2003, the two companies have been working together and have identified several series of novel compounds active against the clinically validated target catechol-O*-methyltransferase (COMT). COMT inhibitors are currently used clinically for adjunct therapy in Parkinson's disease since they prolong the effects of the dopamine precursor L-DOPA. CeNeS first identified an opportunity to improve on current drugs in 2002 and has been working with Tripos to design novel COMT inhibitors that may have significant improvements over existing treatments.

As part of the ongoing collaboration, Tripos Discovery Research is using its knowledge-driven chemistry process to facilitate rapid lead identification, follow-up and chemical optimization of candidate molecules. Building on CeNeS' proprietary information coupled with CeNeS' internal chemical design platform, Tripos uses structure-based design tools to investigate the interaction of proposed leads with the validated target. Novel compounds have been selected for synthesis and screened for biological activity. The new project will involve the optimization of these active compounds.

In addition, new genetic data has recently been published implicating a genetic link between the high activity form of the COMT enzyme with a predisposition to develop drug-induced psychosis. Caspi et al.,[1] as noted in The Times (London, UK, Tuesday 12 April 2005), observed that one in four people carries the high activity version of the COMT gene and that possession of this variant gene increases the vulnerability to psychotic illnesses by about 5-fold in adolescents that smoke cannabis.

Continuing the association between COMT and psychosis, recent work[2], most notably from Professor Daniel

Weinberger's group based at the National Institute of Mental Health (NIMH, Bethesda, USA), has provided strong evidence supporting the hypothesis that a COMT inhibitor that acts in the brain would be a useful agent to tackle the profound cognitive deficits in schizophrenia.

"CeNeS' strategy is to develop novel products that reduce the risks inherent in drug development by focusing on known mechanisms and established clinical targets. Two COMT inhibitors are marketed currently. One does not enter the brain effectively and the other is associated with serious liver toxicity. Our goal is to identify compounds without these deficits." said Neil Clark, CeNeS Chief Executive Officer.

"The COMT discovery program is a good example of our strategy in progress," said Dr. Gary Tilbrook, CeNeS Chemistry Director. "CeNeS is excited about this discovery programme's potential to deliver improved drugs for the treatment of Parkinson's disease. The important recent data also shows that our COMT inhibitors may have therapeutic utility in psychotic disorders including schizophrenia."

ENDS

[1] Moderation of the effect of adolescent-onset cannabis use on adult psychosis by a functional polymorphism in the catechol-O-methyl transferase gene: longitudinal evidence of a gene X environment interaction. Caspi et al., Biological Psychiatry. In Press 2005.

[2] Presented at the Society for Neuroscience (San Diego, USA, November 2004) and the American College of NeuroPsychopharmacology (Puerto Rico, December 2004) meetings.

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**About CeNeS**

CeNeS (CEN.L) is a biopharmaceutical company specialising in the development and commercialisation of drugs for pain control, sedation and other CNS disorders such as Parkinson's disease. The company is based in Cambridge, England. For further information visit www.cenes.com.

**About Tripos**

Tripos (Nasdaq: TRPS) combines cutting-edge technology and innovative science to deliver leading chemistry-research products and services for the biotechnology, pharmaceutical and other life science industries. Headquartered in St. Louis, Mo., Tripos spans the world with global research operations and an international client base. www.tripos.com

**About Parkinson's disease**

Parkinson's disease is the second most common neurodegenerative disease after Alzheimer's disease. It affects approximately 2 per cent of the population over the age of 65, representing approximately 4 million patients worldwide.

Parkinson's disease results from a loss of the neurotransmitter dopamine in the brain. Replacement therapy using L-DOPA, the precursor of dopamine, is the main treatment for Parkinson's disease. However, L-DOPA is quickly metabolised in the gut and liver allowing only a small proportion (approximately one per cent) to reach the brain. Therefore, L-DOPA is formulated with agents that inhibit the breakdown of L-DOPA by DOPA-decarboxylase, such as carbidopa and benserazide. The Directors anticipate that L-DOPA therapy will continue to be the 'gold standard' treatment for the foreseeable future.

After prolonged use, the beneficial effects of L-DOPA become reduced and patients develop motor fluctuations and dyskinesias. These probably represent the biggest single problem in the long-term management of a patient with Parkinson's disease.

The enzyme catechol-O-methyl transferase ("COMT") also causes significant depletion of L-DOPA in the brain and periphery, limiting the efficacy of L-DOPA replacement therapy.

The global market for drugs targeting Parkinson's disease was $1.7 billion in 2003 and is forecast to grow substantially over the next decade with an increased prevalence of the disease as a consequence of the ageing population. COMT inhibitors currently have a 10% share of the Parkinson's disease market by value and their usage is growing

**About Schizophrenia**

Schizophrenia is a debilitating mental illness characterized by disturbances such as hallucinations and delusions as well as a range of negative symptoms, including cognitive disturbances. Cognitive disturbances often prevent schizophrenia patients from readjusting to society and require patients to be under medical care for their entire lives. Despite the availability of a variety of current antipsychotic drugs with worldwide sales exceeding USD $12 billion, cognitive disturbances are poorly addressed by existing therapies and represent a large unmet medical need in schizophrenia therapy.

**About Drug-Induced Psychosis**

Use of cannabis or other drugs can cause a condition known as drug-induced psychosis. Symptoms usually appear quickly and last a relatively short time (a few days) until the effects of the cannabis wear off. Disorientation, memory problems and visual hallucinations are the most common symptoms. If someone has a predisposition to a psychotic illness, such as schizophrenia, use of drugs such as cannabis may trigger the first episode in what can be a lifelong, disabling condition.

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