



Collectis announces the publication of a key article in the *Journal of Biological Chemistry*

This publication illustrates Collectis' ongoing efforts to extend the potential of its Meganuclease Recombination Systems

Biocitech, France, December 6th, 2007 - Collectis SA, the rational genome engineering company, today announced the publication of a new article in the high profile *Journal of Biological Chemistry* (JBC), as a result of its collaborative research effort with the Centro Nacional de Investigaciones Oncológicas (CNIO), a world-class research institute located in Madrid (Spain). This paper is due to appear in the February paper issue of JBC and can already be freely downloaded from the journal's web site (Prieto et al., Generation and analysis of mesophilic variants of the thermostable archaeal I-Dmol homing endonuclease. *J. Biol. Chem.* 2007 Nov 12; [Epub ahead of print]; <http://www.jbc.org/cgi/doi/10.1074/jbc.M706323200>).

Over the last decade, meganucleases have emerged as powerful tools for efficient and precise genome engineering. This technology is a world standard in gene targeting and is used to precisely substitute, delete, add or correct genetic sequences at a chosen location in any given genome. Meganuclease Recombination Systems address a wide range of applications spanning the fields of agricultural biotechnology, protein production and genomic research tools. However, meganucleases also provide new hope for novel therapeutic agents for curing monogenic inherited diseases and viral infections. The meganuclease technology as such and some of the main uses of homologous recombination were discovered at the Institut Pasteur, which then granted Collectis worldwide exclusive rights in 2000. Since then, Collectis has expanded the potential of this technology by developing meganucleases with tailored specificities, which are thus able to target selected genes in any given organism. This achievement was the result of a sustained long-term R&D effort with the development of a dedicated high-throughput screening (HTS) platform. Another key factor was the acquisition of specific knowledge of the intrinsic biochemical and biophysical properties of meganucleases, resulting either from in-house research at Collectis or via collaboration with academic institutions.

Collectis' recent achievements in meganuclease manufacturing have mostly been based on engineering of I-Crel meganuclease, a homodimeric endonuclease from *Chlamydomonas reinhardtii*. I-Dmol (a monomeric meganuclease from *Desulfurococcus mobilis*, a thermophilic microorganism) could represent an advantageous scaffold, especially in terms of specificity. However, the protein is active only at high temperatures. A collaborative research effort between Collectis and the laboratories of Dr Francisco J. Blanco and Dr Guillermo Montoya at CNIO resulted in the identification of I-Dmol variants with improved activity at 37°C. These variants qualify as novel scaffolds for Collectis' protein engineering platform, and significant research efforts are now being made with a view to deriving artificial meganucleases with tailored specificities from I-Dmol-derived scaffolds. These developments should increase the number of sequences that can be cleaved by engineered meganucleases.

The publication of these recent results in JBC - a journal with very high scientific standards - acknowledges the quality of the work performed. "Our collaboration with the laboratories of Dr. Francisco J. Blanco and Dr Guillermo Montoya at CNIO is increasingly productive", stated Dr Frédéric Pâques, Collectis' Chief Scientific Officer. Dr Francisco J. Blanco added that "combining the powerful *in vivo* selection strategies developed by Collectis with our experience in biochemical and biophysical analysis has provided us with unique opportunities for creating novel meganucleases with increasingly useful properties".



About Collectis

Collectis SA (www.collectis.com) is a world-leading company in genome engineering and genome surgery. The company is focused on developing and producing custom meganucleases for *in vivo* DNA surgery and also provides new tools for rational reverse genetics and targeted recombination. Collectis' products induce unique, site-directed, double-strand DNA breaks in a living cell and can be used in a wide range of biotechnological and therapeutic applications. To date, Collectis has entered into more than 48 deals on its genome engineering technologies with major players in the pharma, biotech and agrobiotech industries. Collectis is listed on the NYSE Euronext Alternext market (ticker code: ALCLS). For more information on Collectis, visit our web site: www.collectis.com

About Collectis' technology

A meganuclease is a molecule (protein) that cuts DNA at a highly precise site on a chromosome. Once DNA is broken, it has to be repaired by the cell's natural endogenous maintenance systems. By providing a specifically engineered DNA molecule (called a repair matrix) which will be used as a template to repair the break, one can channel the repair pathway into an insertion, deletion or correction process. Thus, meganucleases can be used to trigger precise modification of specific genes in a variety of cells and organisms. By combining the meganuclease's capacity to cut DNA and the latter's ability to undergo repair, Collectis is creating new generations of products for a wide spectrum of applications.

- **Human health:** meganucleases that target a gene responsible for a genetic disease are transferred into human cells, together with a DNA repair matrix which includes the correct sequence for the mutated gene. After the DNA break occurs (which takes just a few minutes), the right sequence is copied into the genome of the patients' cells and the gene is thus repaired. This process - termed "genome surgery" - has a defined time-frame of action with permanent effects. All other transferred material is degraded by natural mechanisms.
- **Agrobiotech:** the same process used in human healthcare can be applied to plants, with the objective of replacing one gene by another, modifying the gene or shutting it down. The applications developed using Collectis' technology are essentially focused on improving agronomic features of crops, producing new generations of biofuels and developing better biofibers.
- **Biomanufacturing:** biomanufacturing is the production of therapeutic proteins and antibodies using bacteria, yeasts or mammalian cells (mainly mouse, hamster and human cells). This multibillion market has an annual growth rate of over 15%. Collectis has developed meganucleases that can cut the DNA of the main production cell lines used in biomanufacturing, thus enabling end users (contract manufacturing organizations and biopharmaceutical companies) to shorten their cell line engineering processes, stabilize production yields and thus improve the quality and features of the final product.
- **Research tools:** Collectis' technology is particularly useful for studying the function of a gene or set of genes, stably and reproducibly modifying cell lines for screening active compounds, and, more generally, obtaining research results in a controlled, well-defined cellular, molecular and genetic environment.

About Collectis' R&D and publication policy

To deliver efficient genome engineering tools, Collectis has focused its R&D activity on two major axes. First, Collectis develops custom meganucleases with tailored specificity, capable of cleaving an *a priori* selected gene. This protein engineering process is based on the latest HTS methods, Collectis' in-depth knowledge of the meganucleases' properties (how they bind and cleave DNA, their intrinsic plasticity, etc.) and our ability to potentially modify these properties. The second axis corresponds to optimization of the repair process, which largely depends on the design of the repair matrix.

Collectis' policy is to foster research excellence in order to offer new solutions for genome engineering. To date, the major outcome of this effort has been the production of custom meganucleases that



cleave genes of interest; this capability vastly expands the range of potential applications and is a prerequisite for therapeutic use. While the core activity (i.e. the protein engineering itself) is usually conducted solely by Collectis, upstream studies are often performed in collaboration with major players in the field.

This effort has resulted in a growing body of know-how, of which part has been disclosed (after IP protection) in peer-reviewed journals in order to disseminate the company's achievements to a broad scientific audience. The publications listed below testify to Collectis' technical progress and its recognition by the scientific community.

Arnould S. et al. (2007) Engineered I-CreI Derivatives Cleaving Sequences from the Human XPC Gene can Induce Highly Efficient Gene Correction in Mammalian Cells. *J. Mol. Biol.* 371:49-65

Prieto J. et al. (2007) The C-terminal loop of the homing endonuclease I-CreI is essential for site recognition, DNA binding and cleavage. *Nucleic Acids Res.* 35:3262-45

Paques F. and Duchateau P. (2007). Meganucleases and DNA double-strand break-induced recombination: perspectives for gene therapy. *Curr. Gene Ther.* 7:49-66 (Review).

Smith J., et al. (2006). A combinatorial approach to create artificial homing endonucleases cleaving chosen sequences. *Nucleic Acids Res.* 34: e149.

Gouble A. et al. (2006) Efficient in toto targeted recombination in mouse liver by meganuclease-induced double-strand break. *J. Gene Med.* 8: 616-622.

Arnould S. et al. (2006) Engineering of large numbers of highly specific homing endonucleases that induce recombination on novel DNA targets. *J. Mol. Biol.* 355:443-58

Chames P. et al. (2005) In vivo selection of engineered homing endonucleases using double-strand break induced homologous recombination. *Nucleic Acids Res.* 33:e178.

Perez C. et al. (2005) Factors affecting double-strand break-induced homologous recombination in mammalian cells. *Biotechniques.* 39:109-15.

Epinat J.-C. et al. (2003) A novel engineered meganuclease induces homologous recombination in yeast and mammalian cells. *Nucleic Acids Res.* 31:2952-62.

Collectis' Forward-Looking Statements

This communication expressly or implicitly contains certain forward-looking statements concerning Collectis SA and its business. Such statements involve certain known and unknown risks, uncertainties and other factors, which could cause the actual results, financial condition, performance or achievements of Collectis SA to be materially different from any future results, performance or achievements expressed or implied by such forward-looking statements. Collectis SA is providing this communication as of this date and does not undertake to update any forward-looking statements contained herein as a result of new information, future events or otherwise.

For a discussion of risks and uncertainties which could cause actual results, financial condition, performance or achievements of Collectis SA to differ from those contained in the forward-looking statements please refer to the Risk Factors (Facteurs de Risque) section of the prospectus approved by the French Autorité des Marchés Financiers ("AMF") on January 22nd, 2007 under visa number 07-023, available on the websites of the AMF (<http://www.amf-france.org>) and Collectis (<http://www.collectis.com>).

For further information, please contact:

Collectis SA
Frédéric Pâques, PhD.
Chief Scientific Officer
sciences@collectis.com
+33 (0)1 41 83 99 00

Alize RP
Caroline Carmagnol
caroline@alizerp.com
+33 (0) 6 64 18 99 59