

PRESS RELEASE

**Collectis Announces the Issuance of U.S. Patent 9,458,439  
Following U.S. Patent 8,921,332 Issued in December 2014**

**Two Patents of a Family Claiming the Basic Uses of Chimeric  
Restriction Nucleases for Gene Editing in Any Type of Cells**

**October 4, 2016** – New York (NY) – Collectis (Alternext: ALCLS; Nasdaq: CLLS), a biopharmaceutical company focused on developing immunotherapies based on gene edited CAR T-cells (UCART), today announced the issuance of U.S. patent 9,458,439 – which claims gene inactivation by use of chimeric restriction endonucleases. This patent granted by the USPTO to the Institut Pasteur and Boston Children's Hospital naming Dr. André Choulika and Pr. Richard C. Mulligan as co-inventors, is exclusively licensed to Collectis.

This issued U.S. patent 9,458,439 claims the method of introducing chromosomal modifications at a locus by induction of double-stranded DNA cleavage using a chimeric restriction endonuclease and non-homologous end joining recombination (NHEJ). This pivotal invention is at the basis of current nuclease-based precise gene inactivation techniques using chimeric restriction endonuclease such as Cas9/CRISPR (and related families), Zinc finger Nucleases, TAL-Effector Nucleases, Mega-TALEs, some Meganucleases *i.e.* endonucleases generated by the juxtaposition of specific DNA binding sequences and DNA cleavage domains with a recognition site of at least 12 base pairs. This technology is universal as it can be applied to any types of cells, including human, animal, plant cells or microorganisms.

This new patent follows U.S. patent 8,921,332 issued on December 30<sup>th</sup>, 2014, which claims the use of chimeric restriction endonucleases for directing chromosomal gene editing in cells by homologous recombination.

This new patent complements Collectis' strong portfolio of gene editing technologies that are implemented in its CAR T-cell product candidates, as well as within its Minnesota-based agricultural biotechnology subsidiary, Calyxt, which develops food products with healthier characteristics.

The inventors of this patent are Dr. André Choulika, Chairman & CEO of Collectis and one of the pioneers in the development of nuclease-based genome editing technologies, and Professor Richard C. Mulligan, Mallinckrodt Professor of Genetics, Emeritus, at Harvard Medical School and a Founding Partner of Sarissa Capital Management. Professor Mulligan is a world-renowned scientist and former member of Collectis' Board of Directors whose laboratory has made seminal contributions to the development of fundamental gene transfer and gene therapy technologies.

**Claim 1 of the U.S. patent 9,458,439:**

“A method for attenuating or inactivating an endogenous gene of interest in a cell in vitro comprising:

inducing in the cell double stranded cleavage of chromosomal DNA at a genomic

site of interest in the specific sequence to be modified, wherein the inducing comprises contacting the genomic site of interest with a chimeric restriction endonuclease, said chimeric restriction endonuclease comprising a DNA binding sequence and a DNA cleavage domain, and said restriction endonuclease recognizing a DNA sequence of at least 12 bp, wherein said restriction endonuclease is introduced as a protein or is encoded by a nucleic acid vector that is expressed, thereby inducing a cellular repair mechanism which leads to highly efficient recombinational events at said genomic site of interest, wherein said recombinational events introduce a mutation into said genomic site of interest, thereby modifying the specific sequence in the chromosomal DNA of the cell and thereby attenuating or inactivating an endogenous gene of interest in said cell.”

**Claim 1 of the U.S. patent 8,921,332:**

“A method of modifying a specific sequence in chromosomal DNA of a cell *in vitro* comprising:

inducing in the cell double stranded cleavage of chromosomal DNA at a genomic site of interest in the specific sequence to be modified, wherein the inducing comprises contacting the genomic site of interest with a chimeric restriction endonuclease, said chimeric restriction endonuclease comprising a DNA binding sequence and a DNA cleavage domain, and said restriction endonuclease recognizing a DNA sequence of at least 12 bp, wherein said restriction endonuclease is introduced as a protein or is encoded by a nucleic acid vector that is expressed; and contacting said cell with a targeting DNA or a nucleic acid vector encoding said targeting DNA in an amount sufficient to produce recombination between said targeting DNA and said chromosomal DNA at the site of interest, wherein said targeting DNA comprises (1) DNA homologous to the region surrounding the genomic site of interest and (2) DNA which modifies the specific sequence upon recombination between said targeting DNA and said chromosomal DNA, thereby modifying the specific sequence in the chromosomal DNA of the cell.”

**About Collectis**

Collectis is a biopharmaceutical company focused on developing immunotherapies based on gene edited CAR T-cells (UCART). The company’s mission is to develop a new generation of cancer therapies based on engineered T-cells. Collectis capitalizes on its 16 years of expertise in genome engineering - based on its flagship TALEN® products and meganucleases and pioneering electroporation PulseAgile technology - to create a new generation of immunotherapies. CAR technologies are designed to target surface antigens expressed on cells. Using its life-science-focused, pioneering genome-engineering technologies, Collectis’ goal is to create innovative products in multiple fields and with various target markets. Collectis is listed on the Nasdaq market (ticker: CLLS) and on the NYSE Alternext market (ticker: ALCLS). To find out more about us, visit our website: [www.collectis.com](http://www.collectis.com)

Talking about gene editing? We do it. TALEN® is a registered trademark owned by the Collectis Group.

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