CRISPR-Cas9 Reference Model

for MPEG LA's CRISPR-Cas9 Joint Licensing Platform

Version 1.0

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Introduction

The CRISPR-Cas9 Reference Model (the "Reference Model") is authored by MPEG LA for MPEG LA's use in the formation of a CRISPR-Cas9 Joint Licensing Platform to provide one-stop, worldwide licenses to CRISPR-Cas9 patent rights as a convenient alternative to negotiating separate licenses with individual patent owners with the broader purpose of fostering innovation in genome engineering and accelerating the development and deployment of CRISPR-based products, therapies, and services.

The Reference Model describes the components of a generic CRISPR-Cas9 system. It is not based on, nor intended to describe, a particular CRISPR-Cas9 system or component from a particular provider. Neither is the Reference Model limited to a particular technological application or field of use out of the many that may utilize CRISPR-Cas9 systems or components. It is intended only to support the efficiency of including in a single licensing transaction access to as many complementary patents as possible for the benefit of the market consistent with applicable legal requirements.

The Reference Model will be used by MPEG LA as a tool to identify holders of patent assets who are eligible to participate in discussions to be facilitated by MPEG LA regarding the creation of a CRISPR-Cas9 Joint Licensing Platform. Eligible patent assets will consist of issued patents or published patent applications having one or more claims directed to:

- the CRISPR-Cas9 System (as defined below) or any of its elements;
- a composition of matter containing the CRISPR-Cas9 System or any of its elements;
- a composition of matter derived from use of the CRISPR-Cas9 System or any of its elements; or
- a method of use, or a method of manufacture, pertaining to any of the foregoing.

Although published patent applications meeting these criteria may qualify their holders to participate in the facilitation discussions, only issued patents will be included in the actual CRISPR-Cas9 Joint Licensing Platform.

Version 1.0 of the Reference Model may not be fully comprehensive with respect to existing and foreseeable future CRISPR-Cas9 technology. Therefore, it may be augmented or revised by subsequent versions.

CRISPR-Cas9 Reference Model

The CRISPR-Cas9 System as defined in this Reference Model comprises[1] the following elements:

(1) DNA-targeting RNA comprising:

(a) a[2] CRISPR targeting RNA ("crRNA")[3] that hybridizes or is capable of hybridizing with a target DNA sequence in the operative environment, and

(b) a trans-activating crRNA ("tracrRNA")[4] that is associated, associates or is capable of associating with the crRNA to facilitate the formation of a complex, in the operative environment, with the Cas9 protein of element (2) below; and

[1] Throughout the Reference Model, the term "comprises" or "comprising" has the definition provided in the USPTO Manual of Patent Examining Procedure (MPEP) (9th Ed.), Section 2111.03, as follows: The transitional term "comprising", which is synonymous with "including," "containing," or "characterized by," is inclusive or open-ended and does not exclude additional, unrecited elements or method steps."

[2] Throughout the Reference Model, the indefinite article "a" or "an" carries the nonsingular meaning of "one or more" consistent with the "comprising" language used in the preamble. Subsequent use in the Reference Model of definite articles such as "the" or "said" refer back to the same term initially introduced by "a" or "an" and do not change the general plural rule, but simply reinvoke the nonsingular meaning.

[3] In the patents and scientific literature, the crRNA as used herein is sometimes referred to as "targeter-RNA", "guide sequence", "guide" or "spacer." The crRNA as used herein may or may not contain a "tracr mate" sequence, which in the Class 2, Type II CRISPR-Cas9 natural environment is the part of the crRNA hybridizing to the tracrRNA.

[4] In the patents and scientific literature, the tracrRNA is sometimes referred to as "activator-RNA." In the Class 2, Type II CRISPR-Cas9 natural environment, the tracrRNA hybridizes to a sequence within the crRNA known as the "tracr mate" sequence thereby forming a double-stranded RNA duplex protein binding segment recognized by the Cas9 protein.

(2) a Cas9 protein, which may be modified from wild-type provided that the Cas9 retains the ability to form a complex with the DNA-targeting RNA, thereby targeting the Cas9 protein to a target DNA sequence in the operative environment.

The CRISPR-Cas9 Reference Model is intended to encompass the CRISPR-Cas9 System in its entirety as well as the elements (1)(a), (1)(b), and/or (2), individually or in any combination.

The CRISPR-Cas9 Reference Model is further defined by reference to various features, elements, and aspects of the CRISPR-Cas9 System, as follows:

I. Operative Environment

The CRISPR-Cas9 System may operate in any environment, e.g., in prokaryotic cells, eukaryotic cells, or in a cell-free *in vitro* environment.

II. DNA-targeting RNA

The DNA-targeting RNA may take the form of one or more RNA molecules. For example, the crRNA and the tracrRNA may be two separate RNA molecules.[5] Alternatively, the crRNA and the tracrRNA may exist as a single RNA molecule comprising both the crRNA and the tracrRNA features.[6]

Further, the DNA-targeting RNA may be present in the CRISPR-Cas9 System not only as one or more molecules of RNA, but also as one or more nucleic acids (e.g., DNA) comprising a nucleotide sequence encoding said one or more molecules of RNA (e.g., in one or more vectors).

[5] In the patents and scientific literature, the two RNA molecules are sometimes called “dual guide RNA” or “two-molecule guide RNA.”

[6] In the patents and scientific literature, the single molecule DNA-targeting RNA is sometimes referred to as a “single guide RNA” or “sgRNA”, a chimeric RNA or chimeric guide RNA, or a synthetic guide RNA.

III. Cas9 Protein

The Cas9 protein may be present in the CRISPR-Cas9 System as Cas9 protein or as a nucleic acid comprising a nucleotide sequence encoding said protein (e.g., in one or more vectors). The Cas9 protein may be modified from wild-type, e.g., to comprise mutations (e.g., in one or more of its catalytic domains) and/or additional functional domains.

IV. Function

The CRISPR-Cas9 System is unlimited as to function. The following are examples of functions that may be performed by the CRISPR-Cas9 System, but are not meant to be inclusive of all possible functions:

- Cleaving DNA by making a double-stranded break;
- Cleaving DNA by making a single-stranded break, e.g., through use of a "Cas9 nickase," which is a modified version of a wildtype Cas9 that makes a single-stranded break instead of the canonical double-stranded break;
- Editing DNA by, e.g., base pair deletion, insertion, or translocation;
- Knock-out of one or more target genes;
- Epigenetic manipulation, e.g., by altering methylation;
- Targeting DNA without catalytic cleavage, e.g., where a catalytically inactivated, "dead Cas9" ("dCAS9") serves as a base for incorporating a heterologous functional moiety such as a heterologous protein domain for a variety of functions, including, e.g., transcriptional activation and repression, localizing fluorescent protein labels, and recruiting histone-modifying enzymes;
- Purifying regions of DNA;
- Visualization of genomic loci, or DNA labeling;
- DNA detection;
- Genomic screening, e.g., for basic research, drug screening, and/or genome-wide screens