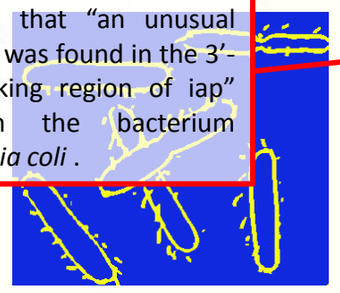
# Timeline of CRISPR Research

## *from* exploration *to* explosion

V1.1 *(update 22 December 2013)*

**1987**

Ishino, Nakata and colleagues describes that "an unusual structure was found in the 3'-end flanking region of iap" gene in the bacterium *Escherichia coli* .



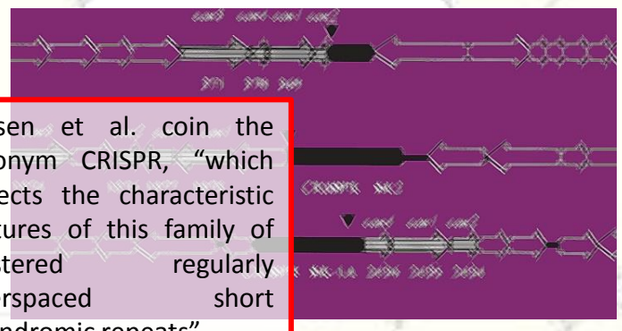
**1989-99**

Similar repeats are found in a number of bacteria and archaea.

**2000**

Short Regularly Spaced Repeats (SRSRs) is proposed to summarize a family of repeats in prokaryotes.

**2002**



Jansen et al. coin the acronym CRISPR, "which reflects the characteristic features of this family of clustered regularly interspaced short palindromic repeats".

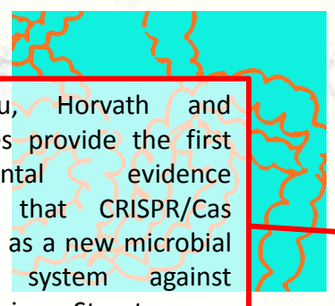
**2005**

Sequences matched between CRISPR spacers and phage or plasmid sequences are documented.

**2006**

Based on *in silico* analysis, Makarova et al. propose that CRISPR/Cas systems might be an adaptive immune system.

**2007**



Barrangou, Horvath and colleagues provide the first experimental evidence showing that CRISPR/Cas functions as a new microbial immune system against viruses in *Streptococcus thermophilus*.

**2008**

DNA not RNA is found to be the molecular target of most CRISPR/Cas systems.

Deveau et al. coin the term protospacer indicating viral sequence that corresponds to a spacer.

**2009**

Protospacer adjacent motif (PAM) is coined to recognize its universality in CRISPR systems.

RNA-guided RNA cleavage by Type III-B CMR complex is characterized biochemically.

Brouns et al. and Carte et al. characterize the crRNA processing pathway.

**2010**

The mechanism for distinguishing self from non-self during crRNA-directed immunity is identified.

Classification of the CRISPR/Cas system is proposed.

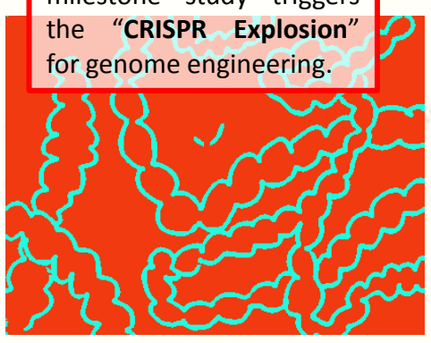
**2011**

Garneau et al. show that CRISPRs can acquire new spacers upon plasmid challenge.

A trans-activating CRISPR RNA (tracrRNA) is found to be involved in pre-crRNA processing in Type II CRISPR/Cas system.

**2012**

Doudna, Charpentier and colleagues apply Cas9 in gene targeting. This milestone study triggers the "**CRISPR Explosion**" for genome engineering.



**2013**

CRISPR/Cas is applied to rat genome engineering.

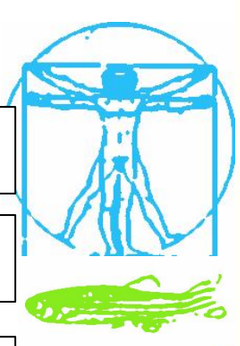
CRISPR/Cas is applied to genome engineering in plants including rice, wheat, *Arabidopsis*, tobacco, *Sorghum*.

High specificity is achieved by double nicking with CRISPR Cas nickase mutant.

**Jan**

CRISPR/Cas is applied to human genome engineering.

CRISPR/Cas is applied to zebrafish genome engineering.



**Feb**

CRISPR/Cas is applied to program repression and activation of gene transcription.

**Mar**

CRISPR/Cas is applied to budding yeast *Saccharomyces cerevisiae* genome engineering.

**Apr**

Weiss and colleages show that CRISPR/Cas-mediated gene regulation also contributes to the regulation of endogenous bacterial genes.

**May**

One-step generation of multiple genes by CRISPR/Cas is possible in mice.

CRISPR/Cas is applied to the fruitfly *Drosophila* genome engineering.

**Jun**

High-frequency off-target mutagenesis induced by CRISPR/Cas is reported.

**Jul**

CRISPR/Cas is applied to the worm *Caenorhabditis elegans* genome engineering.

**Aug**

CRISPR/Cas is applied to genome engineering in livestock.

CRISPR/Cas is applied to the frog *Xenopus tropicalis* genome engineering.

CRISPR/Cas is applied to the silkworm *Bombyx mori* genome engineering.

**Sep**

Structures of type III CRISPR-Cas effect complex are described.

**Oct**

Target sequences, guide RNA and Cas9 contribute to the avoidance of off-target effects.

**Nov**

CRISPR/cas9 is used for correction of genetic disease.

**Dec**

Genome-wide CRISPR/cas9 screening is applied in human cells.

## Abbreviations

**Cas**: CRISPR-associated
**CRISPRs**: clustered regularly interspaced short palindromic repeats
**crRNA**: CRISPR RNA
**PAM**: protospacer adjacent motif
**sgRNA:** single synthetic guide RNA
**SRSRs**: short regularly spaced repeats
**tracrRNA**: trans-activating CRISPR RNA

Background drawings courtesy of Aaron H. Tan.

*details see*
Bassett AR and Liu JL. CRISPR/Cas9 and genome editing in *Drosophila.* ***Journal of Genetics and Genomics*** 41(1) January 2014.
http://dx.doi.org/10.1016/j.jgg.2013.12.004

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