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Control/Tracking Number: 2017-E-1953-DNADAY
Activity: DNA-Day Essay 2017
Current Date/Time: 4/26/2017 10:18:11 AM

Breath-taking *CRISPR*!

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11 *πᾶσά τε ἐπιστήμη χωριζομένη δικαιοσύνης καὶ τῆς ἄλλης ἀρετῆς πανουργία, οὐ σοφία φαίνεται.* [sections 246e-247a] *Menexenus*, by Plato [English translation of the Ancient Greek quotation in http://www.gutenberg.org/files/1682/1682-h/1682-h.htm]

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Essay:

According to one of the ancient Greek myths with *Epimetheus*[1] as a protagonist and symbol of imprudence, man usually acts without weighing up the consequences of his deeds. This is more than true even for the 21st century man. The startling developments of science have inevitably created the sense of an all-powerful humankind able to solve all sorts of its problems. Especially, during this decade, groundbreaking advances have been attained in genetics offering modern man the opportunity to change even his own genome. One of the latest versatile techniques of successful genome engineering is known as the CRISPR-Cas9 system. The above mentioned technology exploits the endogenous protection mechanism of certain bacteria against invading nucleic acids, mainly DNA from bacteriophages. More precisely, the intruded viral DNA is recognized via base complementarity (usually homology of 20 nucleotides length) by short RNA molecules known as CRISPR-RNAs (crRNAs) synthesized by the prokaryotic host; crRNA molecules are stably complexed with the bacterial DNA endonuclease Cas9, the second component of this antiviral system, which takes drastic action by snipping the viral DNA following target sequence binding mediated by crRNAs. Based on this successful molecular defense mechanism, scientists can design artificial 'guide' RNA molecules (gRNAs) combining the molecular properties of crRNA with the specific base sequence of the gene/genomic target they wish to have edited via Cas9 protein. Then the programmed RNA-guided, DNA-targeting double strand breaks formed by Cas9 trigger DNA repairing via intrinsic cellular mechanisms leading to site-specific sequence mutagenesis and corrections. Despite its versatility and ease of use, this simple approach was shown to have off-target effects, but researchers are already trying to optimize the CRISPR-Cas9 protocols and minimize any

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unwanted interference.[2,3,4] As happens with every newly established and revolutionary achievement, the seeds of ethical issues about CRISPR-Cas9 system applications have already been sown.[5] In the context of agricultural biotechnology, CRISPR-Cas9 has been put into practice successfully.[6] Intervening in genome revision of various plant species with great accuracy via this technique can give them selected or desirable traits. In this way, crops resistant to various parasites or adverse weather conditions can be obtained; their production can be easier, more efficient and of lower cost than the one based on the classical genetic modification, which is necessarily associated with the permanent integration of foreign DNA. Furthermore, the potential offered by the CRISPR-Cas9 tool to modify at the same time various traits of an organism is a real advantage for crop plants with huge genomes. Likewise, production of biofuels has gained advantage from this method on plants. Therefore, by keeping it always under control for likely, long-range outcomes, the use of this technique in the agricultural sector looks appealingly good and lawful. The so far successful implementation of the CRISPR-Cas9 platform to repair dysfunctional genes either in stem cells *ex vivo*, in laboratory mice or even in human embryos opens the outlook for novel gene/genome therapeutics based on several specialized versions of this molecular system. However, more research is needed to surpass some technical barriers posed by the CRISPR-Cas9 system itself (eg. gene delivery *in vivo*, relatively low specificity of Cas9 binding) in relation with target cells' behavior from genome level (risk of oncogenesis, epigenetic regulation) up to the level of organism (cell communities).[7,8] Undoubtedly, before any clinical applications launch in the future, all therapeutic strategies need to be tested thoroughly so that safety and the maximum efficiency are secured for patients. Another matter in hand is whether several potential uses of CRISPR-Cas9 could be considered unacceptable or even unlawful. Could applications of this method in animals for business grounds be beneficial at all? This could lead to the selection of certain genetic traits thus changing the frequencies of the responsible genes (genetic drift) and affecting biodiversity in wild populations, which is crucial for ecosystems' equilibrium and species' evolution.[9] The value of biodiversity, as well as the "rights of future generations" constitute ethical obligations that cannot be assured by genome editing of animals/plants, causing heritable changes in generations to come able to change the gene pool of species.[10] For this reason, genome editing in gametes or embryos should be controllably and exclusively allowed for basic research purposes until the perils of the CRISPR-Cas9 technology have been precisely identified and assessed.For sure, the ground-breaking CRISPR-Cas9 system promises much for our future standard of living, but we should not rest on our laurels disregarding imprudently the yet unseen hazards: "all knowledge, when separated from justice and virtue, is seen to be cunning and not wisdom". [11]

Essay in original language:

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