Dr. Eric Kmiec

Introduction

Dr. Kmiec began his DSU tenure on Oct. 15, 2011 as Chairman of the Chemistry department. Prior to his arrival, Dr. Kmiec was the director of the Marshall Institute for Interdisciplinary Research at Marshall University from 2009-2011, where pioneering biotechnology advances were made under his leadership. Dr. Kmiec is a renowned expert in gene editing – a technique that employs synthetic DNA molecules to repair mutations in human chromosomes. His research aims to identify therapies for diseases including Huntington's disease, Muscular Dystrophy, and Spinal Muscular Atrophy. A recipient of many research and community service awards, Kmiec holds upwards of 60 patents.

He also established several biotechnology companies including OrphageniX Inc. of which he is co-founder. Prior to his arrival to Marshall University in 2009, he was a professor of biology at the University of Delaware and director of the Delaware Biotechnology Institute.

Lab Summary

For over twenty years, the Kmiec laboratory has studied the reaction mechanics, biochemistry and molecular genetics of gene editing in human cells. During the late 90s, this laboratory began a long-term investigation centered on understanding the mechanism and regulation of gene editing using single-stranded DNA oligonucleotides (ODNs). The lab was a pioneering force in developing the use of these specialized ODNs for the treatment of inherited disorders. Building largely on early genetic studies in lower eukaryotes, we were able to define a reaction protocol that can achieve a sustainable level of correction of genetic mutations in human cells. Development of clinical application is underway with a particular focus on utilizing nanofiber scaffolds as patches for implantation of gene edited cells into human tissues. For example, Phenylketonuria (PKU) is an amenable target for which nanofiber patches containing genetically modified cells can be implanted and the mutant phenotype reversed. These nanofiber scaffolds are constructed from natural biodegradable composite fibers, such as chitosan/PCC, created by electrospinning in both aligned and random configurations. Importantly, these patches enable robust proliferation of genetically modified cells. Since the nanofiber constructs are biodegradable, the 3D patchwork is slowly dissolved as the modified or gene corrected cells effectively implant in the target tissue. A major part of this effort centers on identifying chemical compositions of nanofibers that enable the greatest degree of expansion of cells that have been altered by the gene editing protocol. The laboratory is also investigating related reaction barriers including a reduced growth potential and the frequency at which gene editing activity takes place. The ultimate goal of all of this translational research is to develop a feasible protocol for the delivery of genetically modified cells into human tissues using biodegradable nanofiber patches.

Selected Publications

· Bonner M, Strouse B, Applegate M, Livingston P, Kmiec EB DNA Damage Response Pathway and Replication Fork Stress During Oligonucleotide Directed Gene Editing [1]. Molecular Therapy – Nucleic Acids. 2012 1, e18.

· DiMatteo D, Callahan S, Kmiec EB. Genetic conversion of an SMN2 gene to SMN1: a novel approach to the treatment of spinal muscular atrophy. [2] Exp Cell Res. 2008;314(4):878–886.

· Engstrom JU, Kmiec EB. DNA replication, cell cycle progression and the targeted gene repair reaction. [3] Cell Cycle. 2008;7(10):1402–1414.

· Schwartz TR, Vasta CA, Bauer TL, Parekh-Olmedo H, Kmiec EB. G-rich oligonucleotides alter cell cycle progression and

induce apoptosis specifically in OE19 esophageal tumor cells. [4] Oligonucleotides. 2008;18(1):51–63.

· Engstrom JU, Kmiec EB. Manipulation of cell cycle progression can counteract the apparent loss of correction frequency following oligonucleotide-directed gene repair. [5] BMC Mol Biol. 2007;8:9.

· Ferrara L, Engstrom JU, Schwartz T, Parekh-Olmedo H, Kmiec EB. Recovery of cell cycle delay following targeted gene repair by oligonucleotides. [6] DNA Repair (Amst). 2007;6(10):1529–1535.

· Maguire KK, Kmiec EB. Multiple roles for MSH2 in the repair of a deletion mutation directed by modified single-stranded oligonucleotides. [7] Gene. 2007;386(1-2):107–114.

· Parekh-Olmedo H, Kmiec EB. Progress and prospects: targeted gene alteration (TGA). [8] Gene Ther. 2007;14(24):1675–1680.

· Schwartz TR, Kmiec EB. Reduction of gene repair by selenomethionine with the use of single-stranded oligonucleotides. [9]BMC Mol Biol. 2007;8:7.

· Ferrara L, Kmiec EB. Targeted gene repair activates Chk1 and Chk2 and stalls replication in corrected cells. [10] DNA Repair (Amst). 2006;5(4):422–431.

· Skogen M, Roth J, Yerkes S, Parekh-Olmedo H, Kmiec E. Short G-rich oligonucleotides as a potential therapeutic for Huntington's Disease. [11] BMC Neurosci. 2006;7:65.

· Brachman EE, Kmiec EB. Gene repair in mammalian cells is stimulated by the elongation of S phase and transient stalling of replication forks. [12] DNA Repair (Amst). 2005;4(4):445–457.

· Drury MD, Skogen MJ, Kmiec EB. A tolerance of DNA heterology in the mammalian targeted gene repair reaction. [13] Oligonucleotides. 2005;15(3):155–171.

· Engstrom J, Kmiec EB. Caffeine elevates and stabilizes gene repair efficiencies in mammalian cells. Gene Ther Mol Biol. 2005;9:445–456.

· Hu Y, Parekh-Olmedo H, Drury M, Skogen M, Kmiec EB. Reaction parameters of targeted gene repair in mammalian cells. [14] Mol Biotechnol. 2005;29(3):197–210.

· Parekh-Olmedo H, Ferrara L, Brachman E, Kmiec EB. Gene therapy progress and prospects: targeted gene repair. [15]Gene Ther. 2005;12(8):639–646.

· Schwartz T, Kmiec EB. Using methyl methanesulfonate (MMS) to stimulate targeted gene repair activity in mammalian cells. Gene Ther Mol Biol. 2005;9:193–202.

· Brachman EE, Kmiec EB. DNA replication and transcription direct a DNA strand bias in the process of targeted gene repair in mammalian cells. [16] J Cell Sci. 2004;117(Pt 17):3867–3874.

· Drury MD, Kmiec EB. Double displacement loops (double d-loops) are templates for oligonucleotide-directed mutagenesis and gene repair. [17] Oligonucleotides. 2004;14(4):274–286.

· Ferrara L, Kmiec EB. Camptothecin enhances the frequency of oligonucleotide-directed gene repair in mammalian cells by inducing DNA damage and activating homologous recombination. [18] Nucleic Acids Res. 2004;32(17):5239–5248.

· Ferrara L, Parekh-Olmedo H, Kmiec EB. Enhanced oligonucleotide-directed gene targeting in mammalian cells following treatment with DNA damaging agents. [19] Exp Cell Res. 2004;300(1):170–179.

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Links
[1] http://www.nature.com/mtna/journal/v1/n4/full/mtna20129a.html
[2] http://dx.doi.org/10.1016/j.yexcr.2007.10.012
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[4] http://dx.doi.org/10.1089/oli.2007.0109
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