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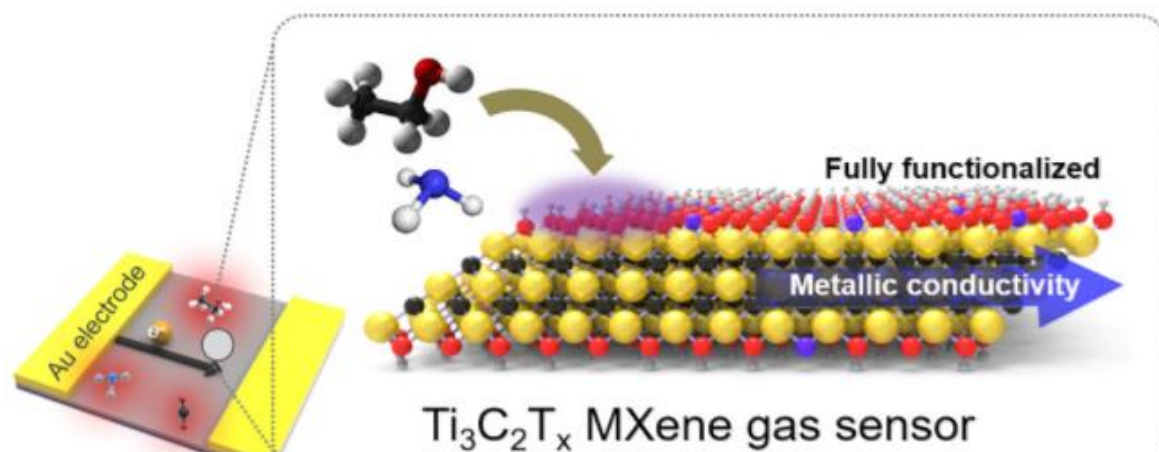
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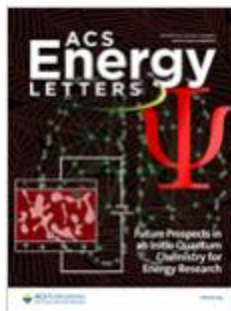
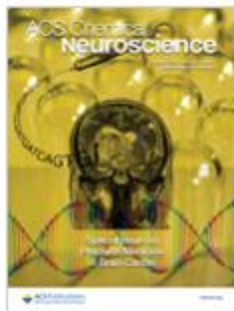
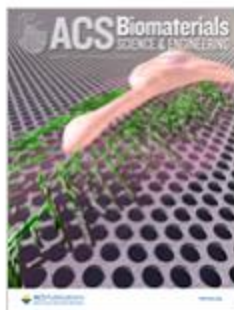
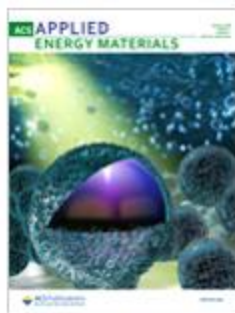
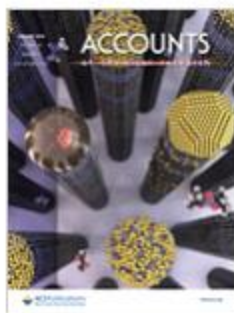
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Chongming Wang, Jose Martin Herreros, Changzhao Jiang, Sahu, and Hongming Xu
Publication Date (Web): January 16, 2018 (Article)
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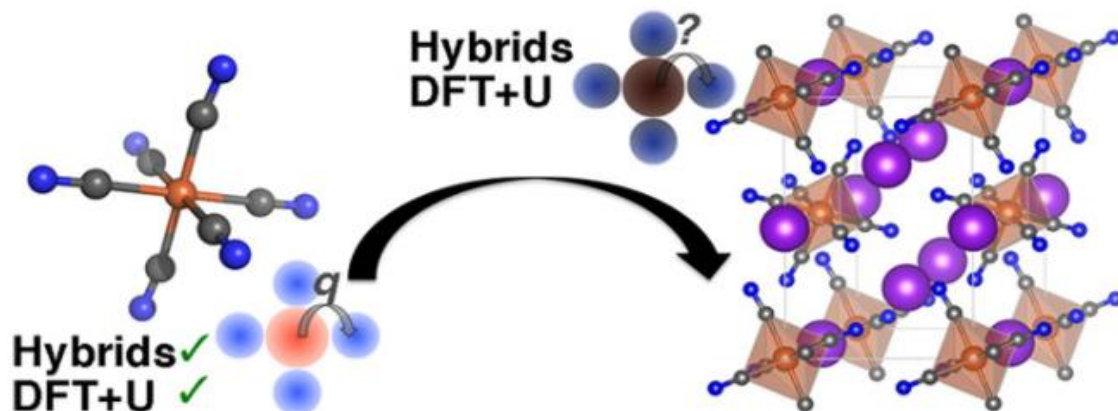
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Qing Zhao and Heather J. Kulik



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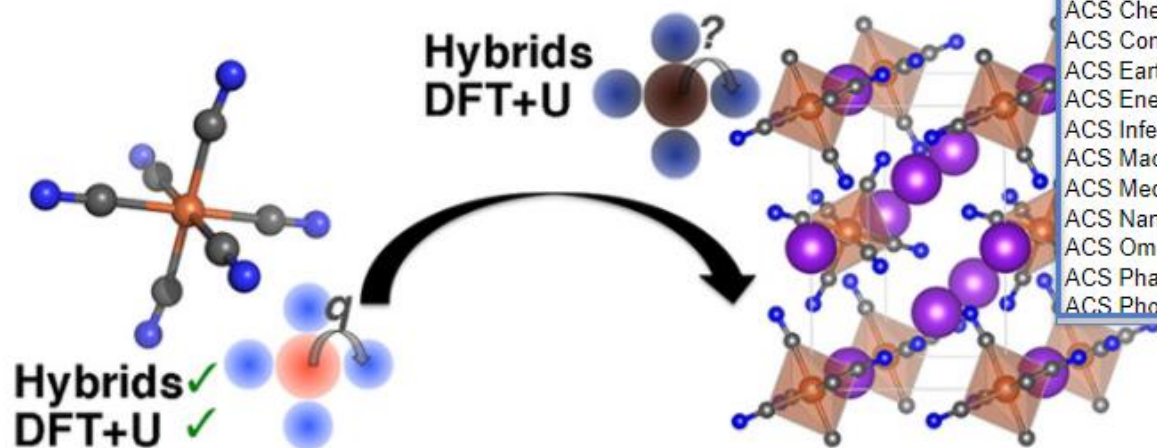


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Publication Date (Web): November 14, 2007 (Review)
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Recombinant Receptor-Binding Domain of Diphtheria Toxin Increases the Potency of **Curcumin** by Enhancing Cellular Uptake

Ashok Kumar[†], Gopal I.
[†]Department of Biotechnology
India

Mol. Pharmaceutics, 2014,
DOI: 10.1021/mp400378x
Publication Date (Web): No
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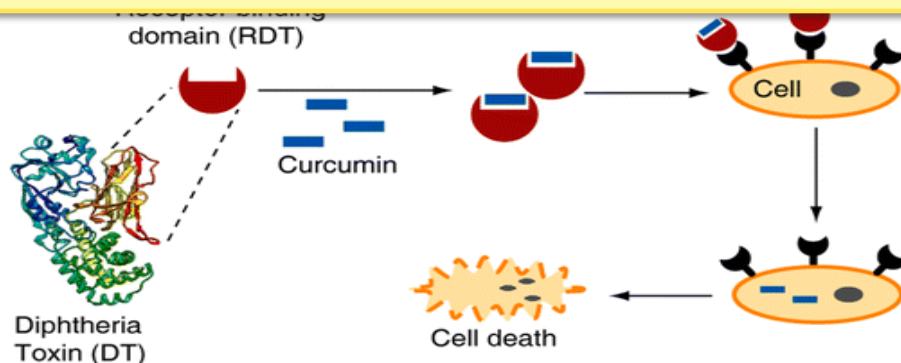
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Diphtheria toxin (DT) binds to a specific cell surface receptor, gets internalized, and causes cytotoxicity through its catalytic domain. The toxicity of DT is used in several therapeutic molecules. Here, we have exploited the receptor-binding ability of DT to increase cellular uptake of **curcumin**, a hydrophobic molecule with low bioavailability and cellular uptake. We have expressed only the receptor-binding domain of DT (RDT) in *Escherichia coli*. Purified RDT binds to the receptor with an affinity equivalent to that of full-length DT. It also binds to **curcumin**, forming a



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Ashok Kumar[†], Gopal Das[‡], and Biplab Bose^{*†}

[†]Department of Biotechnology and [‡]Department of Chemistry, Indian Institute of Technology Guwahati, Guwahati, 781039 India

Mol. Pharmaceutics, 2014, 11 (1), pp 208–217

DOI: 10.1021/mp400378x

Publication Date (Web): November 13, 2013

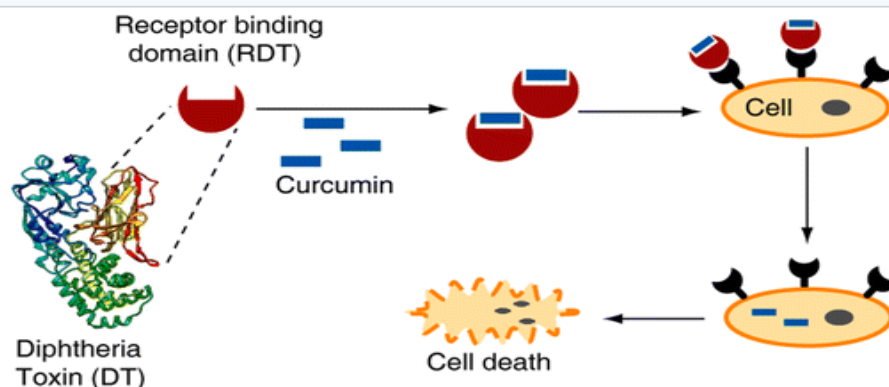
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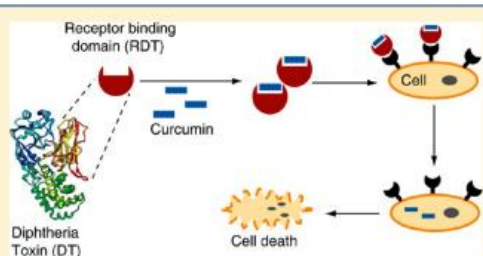
Ashok Kumar,[†] Gopal Das,[‡] and Biplab Bose^{*,†}

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Supporting Information

ABSTRACT: Diphtheria toxin (DT) binds to a specific cell surface receptor, gets internalized, and causes cytotoxicity through its catalytic domain. The toxicity of DT is used in several therapeutic molecules. Here, we have exploited the receptor-binding ability of DT to increase cellular uptake of curcumin, a hydrophobic molecule with low bioavailability and cellular uptake. We have expressed only the receptor-binding domain of DT (RDT) in *Escherichia coli*. Purified RDT binds to the receptor with an affinity equivalent to that of full-length DT. It also binds to curcumin forming a curcumin–RDT complex, and this increases the fluorescence intensity and fluorescence lifetime of curcumin. The curcumin–RDT complex binds to the receptor and associates with human glioblastoma cells (U-87 MG) expressing the receptor. The cellular uptake of curcumin is higher for the curcumin–RDT complex than curcumin alone. This increase in uptake enhances the antiproliferative effect of curcumin and induces apoptosis of these cells even at a lower dose.

KEYWORDS: diphtheria toxin, curcumin, cellular uptake



1. INTRODUCTION

The potency of a drug can be enhanced by the synergistic effect of another drug or by making a formulation that can increase stability/solubility/delivery of the drug to target cells. Various approaches from encapsulation in liposomes¹ to protein-based nanocarriers² have been used to enhance delivery of therapeutic agents. Biomolecules and biomimetic molecules are also used to enhance cellular uptake of drugs. For example, cell-penetrating peptides, derived from natural sequences or designed one, increase the cellular uptake of therapeutic molecules by endocytosis or by passive translocation through plasma

One can exploit ligand–receptor interaction to achieve enhanced cellular delivery of curcumin. Ligands to cell surface receptors overexpressed in disease related cells are usually used for such purpose. Heparin-binding EGF-like growth factor (HB-EGF) is one such cell surface molecule. HB-EGF is overexpressed in several types of cancers and is involved in tumor growth, metastasis, and angiogenesis.¹² HB-EGF is expressed as a membrane anchored molecule, which subsequently gets released through ectodomain shedding.¹³ As a membrane anchored molecule, HB-EGF participates in juxtacrine signaling.¹⁴ Interestingly, HB-EGF is also a cell

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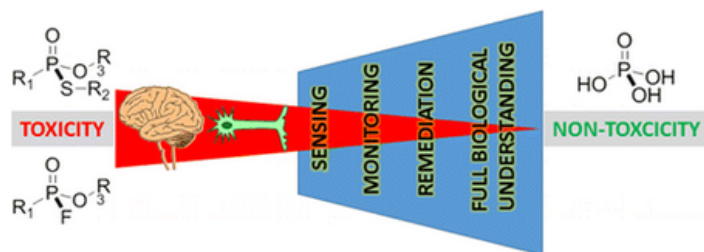


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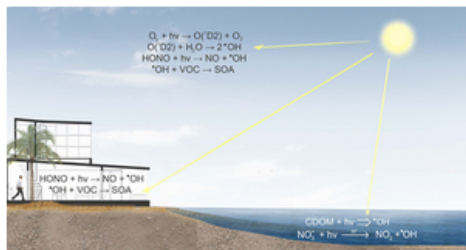


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