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In This Issue

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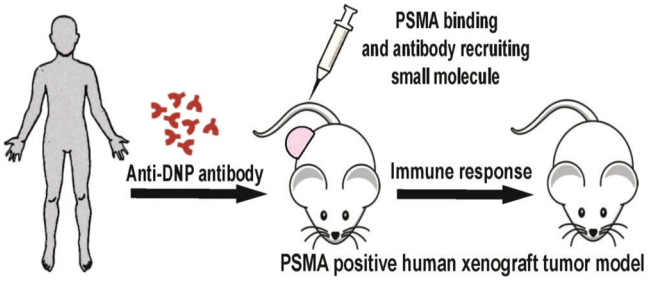
APPROACH FOR PROSTATE CANCER VACCINE DEVELOPMENT

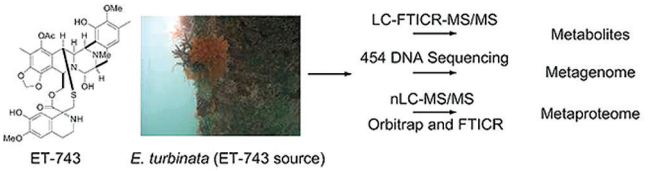
Prostate cancer is a leading cause of cancer-related death among men, which has led to the search for effective therapies. A recent line of research is the development of cancer vaccines that target tumor-associated antigens. In the current issue, Dubrovska *et al.* (DOI: 10.1021/cb200222s) report the development of a vaccine strategy that exploits a ligand with high affinity to a tumor-associated antigen.



The redirection of the immune system to attack tumors is an attractive approach for cancer treatment. The authors used bifunctional ligands comprising a ligand that targets a prostate cancer related antigen, prostate specific membrane antigen (PMSA), conjugated to a dinitrophenyl hapten for antibody recruitment. Importantly, this bifunctional conjugate showed significant antitumor response against human prostate cancer cell lines when studied in relevant murine xenograft model.

BIOSYNTHESIS OF AN ANTICANCER NATURAL PRODUCT

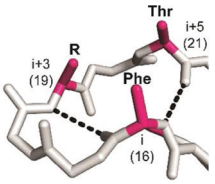
Identifying the source of clinically relevant natural products is important to the drug industry. With this information, large amounts of economically relevant product can be made. ET-743, a compound with antitumor properties isolated from the marine tunicate *Ecteinascidia turbinate*, is one such natural product. In a compelling study, Rath *et al.* (DOI: 10.1021/cb200244t) map out the gene cluster involved in its biosynthesis and show that ET-743 is in fact produced by a symbiont microorganism associated with *E. turbinate*.

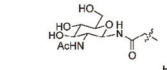
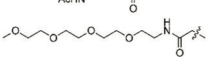


Using a powerful combination of metagenomic sequencing of total DNA from *E. turbinate* and associated microbial symbionts, the authors identified the gene cluster associated with ET-743 biosynthesis. *Candidatus Endoecteinascidia frumen-rumentensis* was found to be the producer of this natural product. Further biochemical characterization confirmed the enzyme function of three ET-743 associated biosynthetic proteins. Keeping in mind the ultimate goal of generating clinically relevant compounds, this study provides an important framework for establishing the source of natural products.

DESTABILIZING THE DENATURED

Proteins as therapeutic agents are an important class of drugs, exemplified by the glycoprotein hormone erythropoietin for treatment of anemia and the monoclonal antibody trastuzumab for treatment of breast cancer. A key strategy both for boosting the stability of such agents and minimizing their propensity to trigger an immune response is to modify their surface with poly(ethylene glycol) (PEG) oligomers. However, it is difficult to predict *a priori* whether PEGylation of a protein at a given site will result in thermodynamic benefit. Price *et al.* (DOI: 10.1021/cb200277u) now report a systematic analysis of the energetic consequences of protein PEGylation.

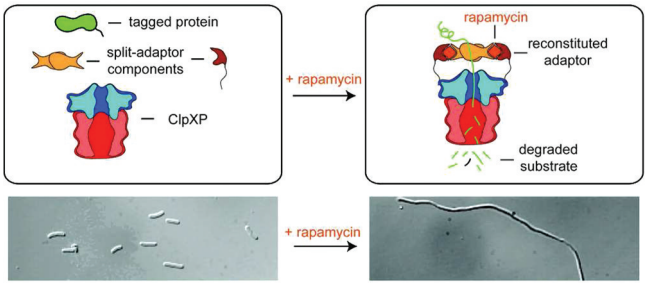


Protein	R =	T_m (°C)
6-F,T		47.4 ± 0.4
6g-F,T		55.0 ± 0.3
6PEG-F,T		55.9 ± 0.3

The "WW" domain of the protein Pin 1 was used as a model protein system, wherein key residues surrounding a PEGylated asparagine were varied in the chemical synthesis of several WW variants. The thermodynamic properties of the variants were evaluated using circular dichroism and by comparison with similar N-glycosylated proteins. The data suggested that PEGylation stabilizes proteins by destabilizing their denatured state, in contrast to N-glycosylation which stabilizes proteins through interactions between the glycan and the protein.

NEW SYSTEM FOR PROTEIN DEGRADATION

Approaches to degrading proteins *in vivo* are an important part of the chemical biologist toolkit. Although there are several methodologies developed for targeting proteins for degradation in mammalian systems, there is a relative lack of robust techniques for bacteria. Now, David *et al.* (10.1021/cb2001389) provide an important new system for the controlled degradation of bacterial proteins.



Escherichia coli and other bacteria utilize energy-dependent proteases, *e.g.*, ClpXP, for proteolysis. The authors in the current study utilize a small molecule, rapamycin, to control the assembly of a split adaptor that enables high affinity binding of suitably tagged proteins to ClpXP and prompting subsequent degradation. This system was applied to efficiently and

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specifically degrade tagged variants of the LacI repressor and cell-division protein, FtsA, *in vivo* in a rapamycin-dependent manner. This study provides a powerful new system for the targeted protein degradation in bacteria.

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