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DRUG DELIVERY

# EXPLODING DENDRIMERS

## Single signal would trigger release of large payloads at tumors, other sites

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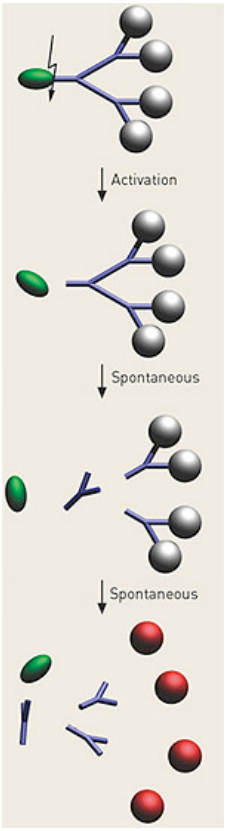
Exploding dendrimers--structures that release multiple payload molecules simultaneously after a single triggering event--were apparently ripe for discovery. Two groups thought of the idea independently, conceived nearly identical solutions, did the requisite experiments, wrote separate papers, and submitted them to the same journal within two days of each other this past May.

As a result, the first single-trigger, multiple-release dendrimers are reported in this week's *Angewandte Chemie International Edition* [**42,** 4490 and 4494 (2003)]. Chief Executive Officer F. M. H. (Vincent) de Groot of Syntarga B.V., Nijmegen, the Netherlands, and colleagues call their structures "cascade-release dendrimers," while senior lecturer Doron Shabat and coworkers at Tel Aviv University call theirs "self-immolative dendrimers." But no matter what you call them, such dendrimers could lead to useful new drug-delivery systems or chemical amplifiers.

VIDEO - CLICK ON IMAGE




**TRIGGER Single activation of dendrimer causes it to release four end groups by a spontaneous two-step route.**


Triggering a single activating reaction at the focal point of either type of dendrimer initiates a spontaneous fragmentation of the structure to its constituent building blocks, releasing all its covalently bound end groups (tail molecules). The triggering event can be chemical bond cleavage, biological (enzymatic) cleavage, or a photochemical reaction.

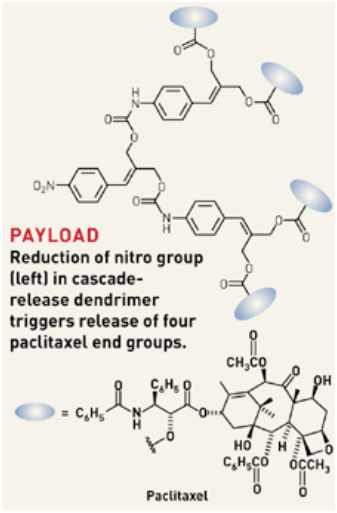
In previous work, several groups have constructed dendrimers with drug end groups, but in those cases each dendrimer-drug bond had to be cleaved separately and individually to release the drug.

In the new structures, a single cleavage reaction in the dendrimer core initiates a spontaneous chain-fragmentation process that releases all end groups virtually simultaneously. The two research teams independently developed similar

spontaneous reaction cascades that begin with a chemical- or photo-induced triggering event and are perpetuated with a sequential series of self-elimination reactions. Both teams have created animations that illustrate the process.

Exploding dendrimers could be useful for amplifying chemical signals (such as in enzyme-linked immunosorbent assays) and delivering payloads of drug molecules to tumors and other target sites. Structures of sufficiently large size have been shown to concentrate selectively in tumors--a phenomenon called the enhanced permeability and retention effect--and dendrimers might act similarly, de Groot says. Fragmented dendrimers would also tend to be cleared from the body easily.

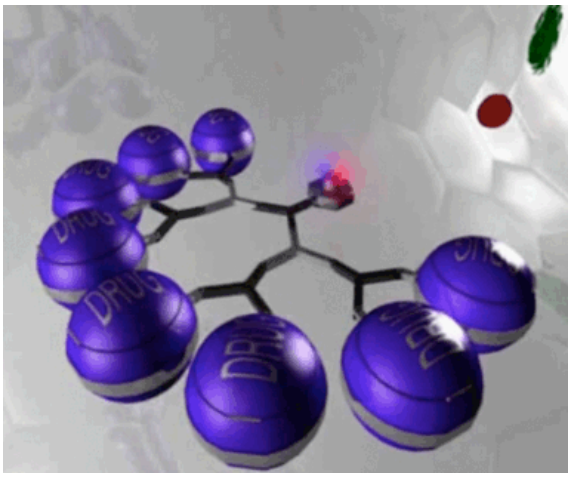
"These are interesting developments--the application of new concepts to dendrimers--although self-immolating linkers are already well known," comments professor Ruth Duncan, director of the Centre for Polymer Therapeutics at the Welsh School of Pharmacy, Cardiff. "To make use of such ideas in a biological setting, it is important to have a biocompatible dendrimer and biocompatible linking chemistry," she notes.






In a preliminary study, Shabat and coworkers have demonstrated that the catalytic antibody 38C2 can induce self-immolative dendrimers to release a prodrug, a drug precursor that can be activated. These released prodrugs "show clear advantage over conventional monomeric prodrugs in cytotoxicity assays," Shabat says.

VIDEO - CLICK ON IMAGE

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