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NEWS AND OPINIONS

Nanomedicine metaphors: From war to care. Emergence of an oecological approach

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Summary Images such as 'therapeutic missile' are commonly used to present targeted drug delivery devices. The ballistic metaphor, reminiscent of Paul Ehrlich's 'magic bullet', has raised great expectations. Accordingly, chemists, physicists and engineers have worked hard to design smart 'missiles' delivering their load of drug to the target. While paying attention to the equipment of the nanodevice for the transport and molecular recognition for the delivery, they have to face the challenges posed by the messy environment of the body. We question the relevance of the missile metaphor, and suggest that an alternative oecological metaphor would be more appropriate. Such an approach, focused on interactions between the nanovehicle and the complex, versatile, heterogeneous biological milieu, seems more heuristic and promising.

Introduction

Nanocarriers for drug delivery and targeted therapy is a hot research topic, generating hundreds of articles every year. Although this approach to therapeutics is often presented as a 'renaissance' or as a 'revolution' it has been framed in a very traditional way, using the old and conventional image of the 'war on cancer', as a strategy for shooting a target [1]. In popular journals such as *American Scientist* or *New Scientist* and even scientific journals nice phrases such as 'therapeutic missiles', 'nano bullets', 'nano-weapons', 'smart bombs', 'stealth kill', and 'targeted strike' are often used.[1]

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[1] Sample of nanomedicine-related paper titles and quotes roughly ranked from more general to more specialized journals, with warfare metaphors highlighted in bold: New **attack** on cancer with nano-**weapon**, *The Times*; Nanoparticle ''**smart bomb**'' formed by bee venom may harbor cancer cure, *Asian News International*; ''**Smart Bomb**'' Nanoparticle **Strategy Impacts** Metastasis, *San Diego Univ. Newsletter*; A new **tiny but deadly** nano-**weapon** against cancer, *Surrey University Newsletter*; Nano **weapons**

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Targeting, shooting, destroying, is it really what it is all about?

These expressions are reminiscent of the famous image of a 'magic bullet' popularized by a 1940 movie on Paul Ehrlich [2]. This 'microbe hunter' of the early 20th century used Emil Fischer's lock-and-key model of molecular recognition for staining infectious bacilli with dyes having specific affinity with the cell's 'side-chain receptors'. By randomly shooting hundreds of dyes on various infected animals, in 1910 he obtained an effective drug against syphilis, Salvarsan. The magic bullet became a kind of ideal-type driving research efforts and encouraged to move beyond the random shooting approach by selecting well identified targets and designing suitable carriers [3]. The ideal almost turned real in the 1970s, first with the production of monoclonal antibodies, and then by the concept of 'microspheres' [4] and 'Nanokapsul' [5,6] penetrating into specific cells for drug, gene or protein delivery. More recently, nanotechnology revived the dream of a specific bullet for each disease [7]. And the promise is all the more attractive that the quest for new miracle therapeutic molecules gives way to the search for more efficient ways of administering pharmaceutical products. If we cannot find better molecules, let's take advantage of what we have and deliver the existing molecules more efficiently.

Metaphors are more than just linguistic ornaments. They belong to the realm of what John L. Austin called 'performative utterances' [8]. More than describing reality, they inform and transform it. As the source domain shapes the 'target domain', metaphors have effects, on overall views of science with publics and sponsors of science, and occasionally on research choices of scientists [9]. As they reflect dominant views and may reinforce them, metaphors also carry tacit meanings and values, which permeate and impregnate our minds to such a point that they become almost natural [10,11].

An offensive and promising strategy

The magic bullet metaphor has actually framed the nanomedicine research field in terms of ballistics. A glimpse on the articles published in scientific journals over the past decade suggests that the challenge was to carry the drug in a controlled manner from the site of administration to its therapeutic target. It is divided up in three basic unit operations: encapsulating, addressing, and releasing the active therapeutic agent.

To monitor the trajectory of the capsule through the body a variety of techniques are mobilized such as chemical activators or physical forces. To address the target, a popular strategy is to attach target-specific 'homing' ligands to the vehicle. The release of the drug on the site is triggered either from inside by controlling the stability and degradation time-lapse of the carrier, or from outside by external stimuli, such as ultrasound [12]. Moreover the feeling of control and surveillance is enhanced by efforts to 'track' both the carrier trajectory and the drug delivery by 'non invasive' imaging methods [13]. As nanomedicines have to be both detectable and activable deep into the body by external means (for instance with remotely controlled nanoparticles embedded with iron oxide), the image of the nanorobot sometimes comes to mind, and refers to an enslaved machinery rather than to a free automaton capable of running amok. While most descriptions of nanomedicine emphasize control and precision, the major advantages of nanovectors are listed in terms similar to those used to describe the performances of drones: Scale convergence of nanovectors with living constituents improves penetration through biological barriers, recognition and accuracy in targeting, diminishes collateral damages such as oxidative injury to normal tissues (heart, brain, kidney, liver, etc.) [14] and increases the efficiency of the therapy at the targeted site. Nanocarriers are often named 'nanoplatforms' because they are endowed with multiple functionalities, combining detection with different modalities (*e.g.* optical, ultrasound or magnetic resonance imaging), targeting agents (peptides, antibodies, etc.), therapeutic tools (chemotherapy, hyperthermia, etc.) and stimuli-responsive agents that activate those functions [15]. Thus the magic bullet becomes a device made of a sum of discrete functions that can be monitored and actuated on demand in a pre-programmed manner. Moreover the device is engineered to warrant both safety and therapeutic efficacy.

The military art of ballistic is certainly a source of suggestive metaphors, however it provides no more than a superficial and somewhat misleading description of the actual functioning of drug delivery techniques. The missile metaphor conveys the view of a projectile traveling through a homogenous and inert space. It considers the nanoplatform as an independent multifunctional entity that can recognize its target and be activated by internal or external triggers. This might be how the chemist, the physicist or the engineer views the device while they design the nanoparticles,

join the fight against cancer, *Technology Review MIT*; **Stealthy** nanoparticles **attack** cancer cells, *Technology Review MIT*; New nano**weapon** against cancer — Gold nanoparticles with branching polymers could **attack** tumors in multiple ways, *Technology Review MIT*; Nanoparticle Carrying **Payload** of Chemotherapy **Homes in** on Metastasis, *Azonano*; Brain-penetrating nanoparticle **attacks** deadly tumors, *Nanowerk*; Magic Nano-**Bullets**: Advances in nano-technology could make drug delivery far more accurate and effective, *Scientific American*; Gold ''Nano-**bullets**'' **shoot down** tumors, *New Scientist*; 'Doctor' particle decides when to release drug **payload**, *New Scientist*; Cancer Therapeutics: nanotumor**killer**, *Nature*; Tuning **payload delivery** in tumor cylindroids using gold nanoparticles, *Nature*; Quantum Dots: **nano-tin soldiers**, *Nature Materials Asia*; Micelles **on target**, *Nature Nanotechnology*; Nanomedicine: **Silence the target**, *Nature Nanotechnology*; Magnetic nano-particles **hit the target**, *Nature Nanotechnology*; **Sizing up target** with nanoparticles, *Nature Nanotechnology*; Nanomedicine-based cancer-targeting: a new **weapon** in an old **war**, *Nanomedicine*; Nano **Delivers Big**: Designing **Molecular Missiles** for Cancer Therapeutics, *Pharmaceutics*; **Guided** Molecular **Missiles** for Tumor-Targeting Chemotherapy — Case Studies Using the Second-Generation Taxoids as **Warheads**, *Accounts of Chemical Research*; **Stealth** liposomes and tumor targeting: one step further in the quest for the magic **bullet**, *Clinical Cancer Research*; Engineered cell **homing**, *Blood*; The alpha v beta 3 integrin as a tumor **homing** ligand for lymphocytes, *European Journal of immunology*; Targeting Anti-Epileptic Drug Therapy **Without Collateral Damage**: Nanocarrier-Based Drug Delivery, *Epilepsy Currents*; **Battling** with environments: drug delivery to target tissues with particles and functional biomaterials, *Therapeutic Delivery*.