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Y a-t-il encore de la place en bas ?

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The Role of “Missile” and “Targeting” Metaphors in Nanomedicine

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Résumé : Dans cet article, je soutiens que les métaphores « missile » et « ciblage » dans la recherche sur les médicaments à base de nanoparticules jouent différents rôles. Je soutiens que le « missile » joue un rôle scientifique marginal et un rôle plus central dans la communication, tandis que le « ciblage » est devenu une métaphore organisatrice dans le domaine de la recherche. La raison, je le suggère, est que le ciblage est l'*explanandum* principal du domaine et que cette métaphore continue d'être pertinente même lorsque la nanomédecine mûrit pour s'attaquer à des problèmes plus complexes. Enfin, je discute des suggestions récentes de nouvelles métaphores axées sur la complexité, et je suggère que le rôle significatif des modèles simplificateurs et le besoin réel de tels modèles peuvent expliquer pourquoi les métaphores de complexité n'ont pas retenu l'attention des chercheurs.

Abstract: In this paper I suggest that the “missile” and the “targeting” metaphors in research on nanoparticle-based drug delivery play different roles. I argue that the “missile” plays a marginal scientific role and a more important role in communication, while “targeting” has become an organizing metaphor for the research field. The reason, I suggest, is that targeting is the main *explanandum* of the field and that this metaphor continues to be relevant even as nanomedicine matures towards tackling more complex problems. Finally, I discuss recent suggestions of new complexity-oriented metaphors, and I suggest that the significant role of simplifying models and the genuine need for such models may explain why complexity metaphors have not caught on among researchers.

1 Introduction

If a nanocarrier is a ship in your body, it is a ship far out at sea, caught in a powerful storm. Objects are floating and flying around everywhere, constantly hitting it, and pushing it off course. What are the chances of arriving at the planned destination? Rather slim, it would seem.

A nanocarrier is a nanoparticle developed to transport and deliver a substance, such as a drug, to specific sites in the body [Peer, Karp *et al.* 2007], [Pérez-Herrero & Fernández-Medarde 2015]. Many a carried substance, however, goes down with its carrier or is stranded somewhere along the way. One goal of targeted nanomedicine is to construct nanoparticles that do reach their target and release the drug they are carrying at that site, typically in cancerous tissues, so that the cancer can be treated without there being severe systemic side-effects [Singh & Lillard 2009]. Nanoparticle-based drug delivery has the potential of increasing the dose and targeted toxicity of drugs reaching the cancer while protecting healthy cells from their toxic effects [Landesman-Milo, Qassem *et al.* 2016].

We often imagine what is going on inside our bodies at the nanoscale as a shrunk version of the world as we experience it (at least approximately). The nanoworld is, however, much messier and more chaotic than the macroworld. Extracellular space and cells are packed with rapidly moving proteins and other molecules constantly bumping into each other, ready for interaction [Morelli, Allen *et al.* 2011]. The order produced is underwritten by random and chaotic processes [Elowitz, Levine *et al.* 2002], [Balázs, van Oudenaarden *et al.* 2011].

Despite the messiness of the nanoscale, nanomedicine literature and communications are dominated by precision metaphors, typically in terms of war and weapons [Bensaude-Vincent & Loeve 2014], [Loeve, Bensaude-Vincent *et al.* 2013]. Nano-carriers have been conceptualized as “therapeutic missiles” armed with poison that will seek out and strike the enemy in the war against disease [McCarron & Faheem 2010], [Yan, Liao *et al.* 2015]. This use of the missile metaphor has some similarities to P. Ehrlich’s vision in the early 20th century of a “magic bullet” drug that would be able to kill specific pathogens with chemical precision and without harming the human body [Strebhardt & Ullrich 2008].

The image of nanoparticles as precision weapons shooting through the space of our bodies to reach and destroy their cancerous targets has been criticized in recent literature [Bensaude-Vincent & Loeve 2014], [Loeve, Bensaude-Vincent *et al.* 2013]. The precision, control and efficiency suggested by these metaphors are a far cry from what is going on in nanoenvironments, where nanoparticles continuously interact with innumerable other substances. Bensaude-Vincent & Loeve suggest that the metaphors of missiles and targets do not provide a constructive framework for nanomedicine and that we should search for new metaphors that better portray the significant complexity of living organisms [Bensaude-Vincent & Loeve 2014]. According to these

authors, nanomedicine needs to take better into account the interactive environment of the body in which the nanocarriers find themselves, and we need a switch of metaphors from those of precision missiles to those of an *oikos*, where we are to work *with* complexity, rather than fighting disease in a one-dimensional war [Bensaude-Vincent & Loeve 2014, 13].

But, one might ask, why should we consider introducing any new metaphors? If metaphors can become problematic for science, why not minimize the use of metaphors or try to eliminate them altogether? Many philosophers, myself included, hold that a minimization strategy would not serve science at all. Since the 1960s, philosophers of science have argued that many scientific metaphors cannot be substituted by literal language without significant loss of scientific understanding [Black 1962], [Hesse 1966, 1988], [Brown 2003], [Levy 2011]. Metaphors can play important epistemological roles by allowing the meaning of scientific concepts to be formed in the light of concepts drawn from different areas. In addition to conveying understanding, metaphors may also inspire scientific ideas and serve as the basis for developing scientific models [Stegmann 2016]. Because of the vital roles metaphors can play in science, we should instead investigate metaphors of nanomedicine further. The following discussion will, however, not hinge on a view of the indispensability of metaphors in nanomedicine. The “missile” and “targeting” metaphors have played interesting roles in this field of research independently of whether they could have been dispensed with or not.

In this paper, I will be taking a step back and looking at the role that these metaphors have played in nanomedicine. Have they contributed to scientific development, or have they trapped nanomedicine in an unconstructive language of precision warfare? Indeed, the biological nanoscale provides great complexity, but simplifying concepts and models can still prove very useful [Sober 2015]. I will take stock regarding the role of “missile” and “targeting” metaphors in the development of nanomedicine and ask whether conceptualizing nanoparticle-based drug delivery in terms of these metaphors has been useful. More specifically, *how* have they contributed to guiding this research? And last but not least, do metaphors of missiles and targets have any role in the future developments of nanomedicine?

The paper is organized as follows. I first differentiate the roles of “the missile” and “the target” metaphors, arguing that these two metaphors have played different roles in nanomedicine: the first more as a rhetorical device in science communication and the other as an effectively epistemologically useful metaphor guiding nanomedical research and models. In the light of relevant discussions in the philosophy of science, I then suggest how the “target” and “targeting” metaphors have played vital roles in nanoparticle-based drug delivery development, as well as suggesting a marginal role for “the missile” in the trial-and-error process of this research. Towards the end I will argue that the need for simple models partly explains how metaphors can play useful roles in research even though they present simplistic pictures of the processes under investigation.

2 The missile and the target

In the scientific literature on nanomedicine, nanoparticles used in drug delivery are sometimes likened to missiles. For example, according to Yan, Liao *et al.* “just like an active radar guides a missile to its target, nanocarriers equipped with homing devices as a specific recognition mechanism for malignant cells have been studied in various cancers [...]” [Yan, Liao *et al.* 2015, 56]. Similarly, and more pronounced, the “missile” figures in science communication. For instance, nanoparticles are pictured as “smart missiles” (internetmedicine.com 2016), and headlines from internet popular science pieces proclaim that “targeted ‘nano-missiles’ in your bloodstream make you tumor-proof” (io9.gizmodo.com 2008) and that a “nano-missile fights cancer with green tea” (healthcareasia.org 2014).

I will ultimately argue that the missile metaphor has played only a marginal scientific role in nanomedicine compared to the targeting metaphor, but I do nevertheless recognize that the missile has played a role, at least as a motivation as well as being a powerful tool for communication. I will also discuss a possible heuristic role for “the missile” in the design of both simpler and more complex nanoparticles.

A simple google scholar search gives an indication of the difference in significance between the “missile” and the “targeting” metaphor. A search for “nanomedicine and missile” brought up 335 hits, while a search for “nanomedicine and targeting” received 97 500 hits. What can we make of these numbers? Although they are crude measures, they seem to reflect a central role of the “target” and “targeting” metaphors and a rather marginal role of the missile metaphor in the nanomedicine literature. Doing the same search with the general google search engine, however, gave the numbers 143 000 and 540 000, respectively. Thus, in all searchable internet documents, there is still an overrepresentation of “targeting” compared to “missile”, but the difference is not that pronounced. And there is no doubt that talking about missiles in the same breath as nanoparticles is much more common in non-academic documents than in academic ones.

The pronounced use of “targeting” in scientific articles I take to indicate that this metaphor is allowed to play a significant conceptual role in nanomedicine. The fact that the “missile” is not mentioned a lot in scientific papers, however, does not exclude the possibility that it plays a role in the conceptual apparatus of scientists. Still, the difference in frequency of use in scientific documents is quite striking and suggests a more prominent role for “the target” than for “the missile”.

Why is the missile metaphor so common in popular science and yet marginalized in scientific literature? The missile is a powerful image capturing a simplistic version of the aim and process of nanoparticle-based drug delivery, probably considered simple enough for scientists and journalists to use as a tool for communication in order to explain the bare basics of nanomedicine

to the lay person. Bensaude-Vincent & Loeve significantly argue that the “therapeutic missile” does not offer much for researchers to work with when approaching the complexities of the nanoparticles’ journey inside the body [Bensaude-Vincent & Loeve 2014]. Most current work on nanoparticles and drug delivery typically addresses the complexities of interactions between nanoparticles and their environment, and for this work the missile may not reflect relevant questions and hypotheses.

As a tool for communication, “the missile” also carries considerable rhetorical power. Similar to many political metaphors, it evokes emotions and may be effective in persuading the public and policymakers that nanomedicine is worth funding as it provides a way to “win the war against cancer” with increasingly smarter and precise weapons. In M. Black’s seminal work on models and metaphors [Black 1962], he suggested how describing war in terms of the metaphor of a game of chess may change people’s attitudes: “[...] to describe a battle as it were a game of chess is accordingly to exclude, by the choice of language, all the more emotionally disturbing aspects of warfare” [Black 1962, 42]. In nanomedicine, the opposite strategy seems to have been adopted. By introducing war metaphors, emotions linked to harsh conflicts may be triggered and could have a motivating effect for allocating resources to this area of research. This is not necessarily problematic, but in the cases where metaphors communicate simple and clear-cut solutions when researchers know there is a long road ahead, this mode of science communication may need to be reconsidered.

3 Metaphors as filters: How to connect nanoparticles and missiles

Several authors have contributed accounts of the role of metaphors in science [Black 1962], [Hesse 1966, 1988], [Harré 1970], [Van Fraassen 1980], [Lakoff & Johnson 1980], [Searle 1993], [Keller 2002], [Brown 2003], [Levy 2011]. The logical positivists were very much against the use of scientific metaphors [Carnap 1959], [Hempel 1965]. “[L]ogical generalizations, laws, and literal deductive relations” [Hoffman 1980, 394] were supposed to secure the objectivity of scientific theories and explanations, leaving no room for the ambiguities of metaphors. The positivist campaign against metaphors in science was opposed by M. Black’s [Black 1962] interaction perspective, challenging the reductive view that metaphors could be substituted by literal language. Black argued that metaphors provide new, modulated meanings by emphasizing some details and downplaying others.

According to this interaction view, metaphors can give new insights not conveyed by literal language. A metaphor delivers a new meaning in the given context “which is not quite its meaning in literal use, nor quite the meaning which any literal substitution would have” [Black 1962]. A suitable

example in our context is “a nanoparticle is a missile”. Here the meaning of the missile metaphor is, in the light of Black’s view [Black 1962, 39] extended via the connection between two ideas, the nanoparticle and the missile. The metaphor, however, “selects, emphasizes, suppresses, and organizes features of the principal subject by implying statements about it that normally apply to the subsidiary subject” [Black 1962, 44]. Thus, the metaphor works like a filter that emphasizes certain selected features.

Black also suggests *how* this connection between ideas takes place. For words like “missile”, there is a “system of associated commonplaces” [Black 1962, 40], which are what ordinary men and women hold to be true about missiles. This could be, for instance, that missiles are dangerous, they are fast, they are weapons, they can explode, and they are destructive. Imprecise and wrong statements could also be part of the system of associated commonplaces, as long as these mistaken beliefs are held to be true by the man and woman in the street. This system of associations is activated when “missile” is used as a metaphor, but how it is activated depends on the context the metaphor is placed in. When a nanoparticle is referred to as a missile, other associations may be emphasized, compared to when, for example, a hurtful comment is termed a missile. There are, in Black’s view, no general rules for how much *weight* or *emphasis* is to be put on different parts of the system of associations triggered by a metaphor. This is also why a literal substitution constitutes a cognitive loss or a “loss of insight”. A literal substitution would typically be too crude or simply say too much, because the delicate and context-dependent weighing of associations will be lost. Although aware that metaphors can be “dangerous”, Black defends the significance of metaphors in science holding that “[...] a prohibition against their use would be a willful and harmful restriction upon our powers of inquiry” [Black 1962, 47].

As suggested in recent accounts [Bensaude-Vincent & Loeve 2014], [Loeve, Bensaude-Vincent *et al.* 2013], the “missile” metaphor can be dangerous in the sense that it may emphasize associations that are found unfruitful both when it comes to how nanomedicine is perceived by the public (as a game of war rather than an activity of care) and concerning how it may affect the scientific process: the emphasis on precision and control may result in a science that is less focused on complexity and interaction than it should be.

Going through scientific papers on nanoparticle-based drug delivery published in recent years gives the impression that the latter worry is not necessarily warranted. While it is true that many papers focus on the development of more efficient nanoparticles giving increased control over the delivery process, this “increased control” is sought via addressing the complexity of the delivery process and trying to come up with the means to work with this complexity [Hillaireau & Couvreur 2009], [Skotland, Iversen *et al.* 2014], [Shi, Kantoff *et al.* 2016], [Kakkar, Traverso *et al.* 2017], [Liu, Li *et al.* 2017]. There is a worry that the complexity may be just too large, and that research on nanoparticles in drug delivery may not be able to handle this [Leroux 2017]. Many are still optimistic, though, that better drug delivery with

nanoparticles will be achieved in the future. A frequently suggested solution is more complex designs of nanoparticles that can tackle complex environments.

The first generation of particles were typically very simple and did not wear protective molecules to prevent interactions. Soon it was discovered that these particles had a very short lifespan in a living system. A strategy was then developed to add particular chemical compounds, so-called PEGs (polyethylene glycol), to the surface of the particles in order to increase their lifetime. The adding of PEGs to nanoparticles (pegylation) is now the gold standard to reduce unwanted interaction and cellular uptake of nanocarriers [Schöttler, Becker *et al.* 2016]. Yet new generations of nanoparticles are modified in various ways to cope with the challenge of interactions. This process depends on the strategy of trial and error. Because the cellular environment is so complex, it is impossible to predict what will happen when introducing a new nanoparticle into a living system. Thus, the challenges and the way to overcome them are discovered in a trial-and-error fashion along the experimental road.

Accordingly, although first generation nanoparticles were not prepared to travel through a complex environment, the reason for their shortcomings was probably not that the researchers did not foresee that extra- and intracellular environments could interact with these particles. Researchers had to start somewhere and face problems when they appeared. It seems that a frequently used strategy has been to start with a simple picture, and then employ a trial-and-error process to figure out the next steps towards more complex and better performing nanoparticles. In some early research, the “missile” metaphor played such a simplifying role focusing attention on some selected associations of the “missile”: the ability to strike a selected target [Yokoyama, Inoue *et al.* 1989], [Gref, Miralles *et al.* 1999].

What is the extended meaning created when the idea of the missile connects to the idea of the nanoparticle in the way M. Black suggests? Since what experts and lay people know about nanoparticles (and missiles) is generally very different, the interaction between the meaning of nanoparticle and missile could be expected to differ between experts and non-experts. The woman in the street would probably not know a lot about nanoparticles but would have some superficial knowledge about missiles as indicated above. A nanoparticle researcher, on the other hand, who has knowledge about the latest scientific findings on nanocarriers, will put weight on different associations triggered by the missile metaphor in a much more sophisticated manner than the lay person. She would, for instance, know that the nanoparticles are not steered through the body towards the target. The passage through the body is rather random, but if and when the particle reaches cancerous tissues, various mechanisms, such as the EPR effect¹ or active targeting of

1. The EPR effect (Enhanced Permeability and Retention) is when nanoparticles and other molecules of certain sizes end up and stay in tumor tissues more easily than in other tissues due to anatomical differences between diseased and healthy tissues.

receptors, are employed for the nanoparticles to stay there and release the drug at this site. Thus, the researcher may give more weight to associations of the bombing of a specific target compared to associations of a device with a navigation system. A lay person would probably not know the details about how the nanoparticle travels through the body or how it ends up in cancerous tissues and may give equal weight to associations of the bombing of a specific target and steering via a navigation system. If such differential emphasis of associations exists between experts and non-experts, this means that a rather simplistic metaphor, like the missile, may still contribute to understanding in the conceptualization of nanoparticles. It also means that communicating science via metaphors may be a trickier business than using them as tools for understanding and conceptual change within science.

Recently, the missile metaphor has been invoked anew in the context of nanoparticle-based drug delivery. Petrenko & Gillespie suggest that there is an on-going “paradigm shift in bacterio-phage mediated delivery of anticancer drugs: from targeted ‘magic bullets’ to self-navigated ‘magic missiles’” [Petrenko & Gillespie 2017]. Criticisms of the missile metaphor are partly based on the metaphor’s misrepresentation of precision and navigation; smart missiles have navigation systems, nanoparticles do not. The point in [Petrenko & Gillespie 2017] is, however, that future approaches will develop delivery systems that *do have* navigation systems. Through adding several functional ligands² to the surface of bacterio-phages,³ the particles will navigate toward the cancer cells “by a variety of ligands binding different components of tumor vasculature and its microenvironment” [Petrenko & Gillespie 2017, 379].

Still, even though future nanoparticles may have more controlled journeys, the smart missile metaphor continues to communicate the image that the nanoparticles search for and seek out their target, while the journey of the nanoparticles will still be passive and partial. Nanoparticles will not seek out their target, but by adding several compounds to the surface of particles, they may be able to react with several selected compounds in their environment that will direct a larger number of them towards the cancer cells. So even though future nanoparticles may be “smarter” than before, their journey will still be much less precise compared to a smart missile. The existing criticism of the missile metaphor will thus still be relevant.

As my examples show, even though “the missile” metaphor may have its main role in science communication and not in research, an epistemological role for “the missile” is not excluded. Even though metaphors may only hold to a certain degree before they break down, the way they work in communication and understanding adds to the scientific epistemological apparatus.

For example, tumor tissue tends to have high vascular density and large gaps between endothelial cells in blood vessels [Fang, Nakamura *et al.* 2011].

2. Ligand: a small molecule that may bind to proteins or DNA, often taking part in cell signaling processes.

3. Bacterio-phage: a virus that may infect bacteria and that may be used in constructing nanoparticles for drug delivery.

4 Targeting

Unlike the missile metaphor, “target” and “targeting” metaphors are found in most scientific literature on nanoparticle-based drug delivery. A couple of examples among the thousands of papers that exist are “Active targeting of brain tumors using nanocarriers” [Béduneau, Saulnier *et al.* 2007] and “Diagnostic nanoparticle targeting of the EGF-receptor in complex biological conditions using single-domain antibodies” [Zarschler, Prapainop *et al.* 2014]. In these two, and in the majority of papers on nanoparticle-based drug delivery, “targeting” is a key concept. In what follows, I discuss and suggest why the “targeting” metaphor seems to be more helpful and useful to researchers than the “missile”.

First some thoughts on the military connotations of “target” and “targeting”. When mentioned in the same sentence as missile, “target” is obviously interpreted as what the missile is aimed at; a target for a weapon of war. And “targeting” is the aiming or directing of the missile towards its target. When disconnected from the missile, however, which is the case for most uses of “targeting” in scientific papers on nanomedicine, the “target” metaphor need not trigger strong associations with war. Even though the literal meaning of “target” is “an aim for shooting”, the word “target” is so often used figuratively in different contexts, that this word may well trigger various associations besides “war” or “weapon”. It is for example used a lot in various sports. And if you sell cars, you may have a sales target (or you may be the target of ridicule). More generally, targets can be indicators that orient you in some way or the other. “Targeting” is also so deeply incorporated into the scientific language on nanoparticles that researcher in this field may not even think of it as a metaphor. For some researchers, “targeting” may literally concern what they try to make nanoparticles do.

“Target” and “targeting” can also be understood as two of many associations with the word “missile”. As suggested in the previous section, the bombing of a specific target may be an association with “missile” that will receive more emphasis from a nanoparticle researcher than for example the association of a device with a navigation system. Thus the “target” and “targeting” metaphors may correspond to those associations of “missile” that fit best with current nanoparticle research. In one respect, the target is a more specific metaphor than the missile as it can be viewed as concerning one aspect of the missile. In another respect, it is a more general metaphor, since the total system of associations connected to “target” is larger than for the “missile”.

“Targeting”, I suggest, is an organizing metaphor for research on nanoparticle-based drug delivery. Importantly, it organizes the research in the sense that it defines the goal of the scientific work. The research on nanocarriers has succeeded when effective targeting is achieved. “Targeting” is more specific than the more general goal of cancer medicine, which is simply

to kill cancer cells and cure or improve the health of affected individuals. “Targeting” embodies the goal of a certain branch of cancer medicine that searches for ways to reach cancer cells more specifically through exploiting knowledge about characteristics specific to cancer cells or cancerous tissues. Research on nanoparticle-based drug delivery is an important part of this branch of cancer medicine.

Although it may not be impossible, explaining the goal of this research without using the “targeting” metaphor is very difficult. As argued by Black, literal translations are typically too crude, either in being too general (to kill cancer cells) or too specific (to use receptors on the surface of cancer cells for nanocarriers to specifically latch on to) [Black 1962]. The use of “targeting” allows for a better understanding of the goal of research without the need for describing specific mechanisms that may be many and diverse (and new ones can still be discovered).

For effective targeting to be achieved, one needs to discover mechanisms through which this is possible and design particles that exploit these mechanisms. Thus, to achieve targeting, targeting needs to be understood and explained. “Targeting” is therefore the *explanandum* and not part of the explanations of how to achieve the goal of research. Since the “targeting” is not found in the models and the explanations, but rather is *what is to be explained*, it plays a somewhat different role compared to many other scientific metaphors. For instance, when computer metaphors are used about the brain, these metaphors often take place in explanations of how the brain works and are then parts of the explanatory framework. The same goes for the “code” metaphor in genetics. “The genetic code” suggests how genes work, how genetic “information” may be “transferred” from genes to RNA and proteins. “Target” or “targeting” in research on nanocarriers, on the other hand, is something one wants to obtain in one way or the other. And this “one way or the other” is the explanatory part of the story.

When we establish “targeting” as the *explanandum*, an implication is that these metaphors remain open to both simple and complex models for how targeting is achieved. “Targeting” is therefore not as simplistic a metaphor as the “missile” can be, and can therefore work as a constructive framework, leaving room for complexity-oriented approaches to nanocarriers. While research is focused on achieving effective targeting, it can simultaneously focus on nanoparticles’ “ability to interact with complex cellular functions in new ways” [Singh & Lillard 2009, 215]. Although what it means to reach the target in many cases is rather well-defined, the processes through which the target is reached can still be intricate and messy. Complexity oriented approaches may be necessary to achieve effective targeting. Since “targeting” says more about the end-goal of research than about the process of reaching it, chances are good that “targeting” will continue to play the role of an organizing metaphor in future nanomedicine.

Still, there are discussions within the field of nanomedicine whether targeting should define the goal of nanocarrier research [Cheng, Tietjen *et al.* 2015], [Lammers, Kiessling *et al.* 2016]. Lammers *et al.* asks “is targeting our target?” [Lammers, Kiessling *et al.* 2016]. Part of this discussion problematizes the fact that targeting efforts in nanomedicine have only led to very small increases in the percentage of a drug ending up in cancerous tissues, and thus we may say that targeting efforts have not really led to effective targeting as understood within the science. Still, small increases in the percentage of a drug reaching tumors seem to have clinically relevant effects, although the actual targeting of the drug is miniscule (0,7 percent on average). The question is therefore asked, whether such a small percentage deserves the label targeting and whether we need to worry too much about targeting when such small increases in drugs reaching tumors still have substantial effects. These are relevant questions, and although it may be argued that such ineffective processes do not deserve the label “targeting” at all, it seems that achieving these small increases in the tumor specificity of drugs may still have depended on a conceptual framework of targeting. These results have been achieved partly because “targeting” has organized the research around certain goals.

5 The need for simple models of a messy world

Bensaude-Vincent & Loeve have suggested that we need the metaphor of an *oikos* in nanomedicine to guide researchers towards approaching complexity and to work *with* complexity rather than seeing it as an obstacle to be overcome [Bensaude-Vincent & Loeve 2014]. Correspondingly, in the field of genetics, D. Noble has suggested viewing the interactions between genes and the environment as a symphony or as an orchestra rather than viewing the genome as a control unit [Noble 2008]. I am very sympathetic to suggestions of introducing metaphors that reflect complexity, but such metaphors do not seem to catch on as organizing metaphors for research. I think an important reason for this is that researchers already appreciate the presence of complexity and that living organisms are extremely messy, but in addressing such intricate systems, simplifications are needed. When a research field matures, however, more and more complexity can be addressed and accounted for in models. A consequence may be that some metaphors may lose their relevance or acquire new meanings within the field. In this light we can see the continued importance of the “targeting” metaphor as evidence for its ability to stay relevant as the field matures, because it does not work against a stronger focus on complexity. It may well be that how researchers approach complexity could have been different and perhaps more constructive within the framework of an *oikos* metaphor, but it does not seem like the field of nanomedicine needs it to address the complexities of nanoparticle-based drug delivery.

A significant point is also that a system does not have to be simple for simple models to help us grasp important aspects of it. A nice example from the field of genetics is the metaphor of the “genetic code”. Although the code metaphor is too simple to give us a full understanding of how genes contribute to protein production, it has had a large influence on models and explanations through the history of genetics. Stegmann shows how the “genetic code” metaphor in the initial phases of research on the gene-protein relation was used to suggest different mechanism schemas providing researchers with hypotheses for the nature of this relationship [Stegmann 2016].

Even in a context where researchers are obtaining more tools and knowledge to be able to work with complexity, they will not stop looking for patterns, principles and causes. The goal is still to find or create some order in the mess. There is not much to work with if systems are generally unpredictable. Thus, researchers look for pockets of tidiness that can be exploited for intervention or they may even create their own pockets like in the synthetic biology approaches [Oftedal & Parkkinen 2013]. Accordingly, there need not be an opposition between the quest for precision and control and a more holistic approach to nanomedicine. Although systems are complex, there is still precision and order that can be exploited. For example, active targeting in nanomedicine can be understood as exploiting biological mechanisms for specificity. Specificity is ubiquitous in living systems and is based on recognition, affinity and chemical interaction between particular substances. Via these mechanisms, certain interactions are excluded while others are enabled and thereby certain outcomes are ensured. In active targeting, knowledge about such mechanisms is used in getting nanoparticles to latch onto certain receptors. Living systems have evolved functionality partly through developing processes that ensure that certain inputs give certain outputs, and when modeling living systems researchers may look for this kind of order to find some handles they can use as a basis for interventions. Metaphors that help researchers in this quest for order in the mess seem to be those that catch on. An *oikos* is not without order but may not provide the desired simplification.

6 Conclusion

Being a nanocarrier in the messy environment of the body is a struggle. The large majority never complete their assignment, and their functionality is effectively hampered by bombardment from interactive molecules.

I have in this paper defended the thesis that, although nanomedicine needs to approach complexity in an appropriate manner, precision metaphors continue to play valuable roles in conceptualizing nanomedicine and organizing the direction of research.

Employing an interaction view of metaphors, I have suggested that even though a “missile” might be a simplistic metaphor for nanoparticle-based

drug delivery, it may still play some epistemological role and be of value in conveying understanding. Nevertheless, the differential weight of the associations of “missile” may differ substantially between researchers and lay persons, making communication of science to the public using this metaphor a difficult task. “Missile” is still a marginal metaphor in nanomedicine compared with “targeting”, which I have argued is an organizing metaphor for nanocarrier research and will continue to be so in the future. “Targeting” is the main *explanandum* and can accommodate the change in focus from simple first generation nanoparticles to more intricate designs and approaches addressing the complex interactions with the biological environment.

In future work on this topic, it would be interesting to address the difference in the role of metaphors as parts of two different toolboxes: the toolbox of research and the toolbox of communication to the public.

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