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Comment on "Drug discovery: Turning the Titanic"

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The pathobiology-based approach to R&D has been the dominant paradigm for successful drug discovery over the last decades. We propose that the molecular and cellular events that govern a resolving, rather than an evolving, disease may reveal new druggable pathways.

In his Editorial, Turning the Titanic, Elias Zerhouni describes how the research and development (R&D) engines of academia and the pharmaceutical industry that have been so successful at developing treatments for acute diseases are failing to generate effective new compounds for chronic diseases (*1*). He expresses the view that more effort should be directed toward deciphering the natural histories of diseases and that this knowledge could be used to effectively select translatable therapeutic targets. The paper emphasizes the need to use robust technologies to obtain genetic data from patients to "illuminate the genetic underpinning of molecular changes associated with human pathophysiology."

This is the prevailing strategy of pathobiology-based drug discovery. The tacit assumption underlying the approach is that processes that contribute to the development and progression of a disease, will, if it is negated, arrest and reverse the disease process. The consequent research question is "what are the events that cause the disease?" And the implication is that, if we find drugs that target these events, we will be able to effectively treat the disease.

By phrasing a question in a particular manner, the answer is inevitably steered in a specific direction; the question itself limits the landscape of possible answers. In this case, the question "what causes a disease to develop?" inevitably implies that therapeutic strategies lurk in the answers. However, new therapies also may reveal themselves in responses to the question "what causes a disease to resolve?"

In our own field of cancer research, key events in the evolution of tumors are often referred to as the hallmarks of cancer (*2*), and the unchallenged paradigm is that blocking the molecular pathways associated with tumor initiation and progression will lead to disease resolution even when the cancer has matured into full-blown metastatic disease. The last decade has shown us that only in selected cases has this approach led to the development of effective drugs; overall, the success rate of new oncological drugs is at an all-time low (*3*). It has become clear that in the majority of cancers, therapeutic inhibition of tumor-promoting pathways leads only temporarily to disease regression, which often is followed by rapid disease progression. This is often because alternate molecular pathways that are not inhibited by the therapy can take over, allowing cancer cells to escape killing (*4*).

What, then, if the assumptions underlying the research question "what causes a disease to develop?" were not the whole picture? What if the cellular and molecular events that cause a cancer to

regress are different from those that cause it to arise? The low success rate of the pathobiology-based approach to drug discovery can at least partially be explained by the notion that robustness to perturbations is a fundamental property of complex evolvable systems (*5*). So rather than focus on the mechanisms that underpin disease development and persistence, we think that there should be an increased focus on understanding the mechanisms that govern state transitions, such as during disease resolution or remission. This view would radically affect the way we set up our laboratory experiments and clinical trials. As Zerhouni describes in his editorial, many new exciting technologies have allowed us to analyze patient tissues in exquisite detail. However, the knowledge we obtain by using these techniques will be crucially determined by how we use them: Which tissues will be analysed from which patients at which point in their diseases and their treatments?

The everyday clinical reality for doctors treating cancer patients is that some patients respond to treatment while others do not. In esophageal cancer for example, patients with cancers that present identically may respond differently, with complete regression after chemo-radiotherapy on the one hand or with no response on the other (*6*). This also holds true for many other cancer types and treatment modalities, such as in lung cancer or melanoma patients treated with immunotherapy (*7*). In this light, it seems surprising that, even though some of the most successful cancer chemotherapeutics have been around for many decades, their mechanisms of action are still not fully understood, and it is not known what discriminates a responding from a nonresponding cancer. The relatively few studies that have investigated tumor tissues during effective chemotherapy found completely unanticipated effects (*8, 9*). It is equally unknown what happens in the small, but unique group of tumors that regress without any therapy (*10*).

We do not contest the validity of the pathobiology-based drug discovery approach as described in Zerhouni's Editorial, and we fully acknowledge the fact that there is a plethora of data supporting the legitimacy of this approach and that several effective drugs have been discovered in this manner. However, we feel that it is time to add the exploration of a new landscape—that of the resolving disease. By focusing on what we do right as clinicians and medical scientists and investigating the molecular and cellular events associated with disease resolution, we may be able to reinforce or mimic those events to increase the response rates to current treatments. We anticipate that this pathoresolution approach will be relevant to various diseases that display a dichotomous response to treatment, such as cancer and chemotherapy, sepsis and antibiotics, and organ rejection and immune suppressants.

Furthermore, we agree with Zerhouni that improving the pipeline for drug development will necessitate a comprehensive approach by academia, pharmaceutical companies, and patients, but we also think that pursuing distinct approaches with diverse underlying assumptions will increase our chances of finding effective drugs. A resolving disease–based approach will require rethinking in the design of preclinical experiments and selection of animal models. In clinical studies, it will require frequent sampling of relevant tissues during treatment and a comprehensive and detailed assessment of the events that occur in those tissues using cutting-edge technologies. Last, it will require some boldness from funding agencies, allowing us to explore the Rumsfeldian landscape—the things we don't know that we don't know. If we continue to focus only on pathobiology, we may fail to recognize mechanisms associated with disease resolution that could lead to the development of effective drugs.

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