

# The war on cancer – What is the enemy, and are we winning?

Jo Whelan

Textpharm Ltd, UK

## Correspondence to:

Jo Whelan,  
Textpharm Ltd,  
Oxford, UK  
jo@textpharm.com

## Abstract

The so-called 'war on cancer' is now in its fifth decade. This article presents some facts and figures about cancer and the effort to treat it. It outlines updated thinking on the hallmarks and classification of cancer, and draws together published quotes from experts on the state of play in the fight against this disease.

**Keywords:** War on cancer, Cancer

Alongside the war on terror and the war on drugs, another war is going on. We have been fighting it for 40 years, and although we have made progress, it does not look as though we will win it any time soon. Yes, the 'war on cancer' has just entered its fifth decade. Many of us are involved in this war in some small way, part of the enormous army of medical staff, biological scientists, medicinal chemists, genomics scientists, clinical researchers, and pharmaceutical industry workers who are in a job because of cancer.

A 'war on cancer' was never declared in those exact words, but the term was widely used to describe the signing of America's National Cancer Act by President Nixon in 1971. The fighting gets more intense as the war goes on. According to the Economist (Medco),<sup>1</sup> the world pharmaceutical industry had around 900 cancer drugs in phases I-III development in 2010. The next biggest category, central nervous system, numbered about 350. Cancer accounts for about 13% of deaths worldwide – the same proportion as ischaemic heart disease, with stroke and cerebrovascular disease contributing a further 11% (WHO).<sup>2</sup> Yet, only just under 200 cardiovascular drugs are in pipeline. Cancer is huge business. However, attrition rates for new drugs are high (figures of 74–95% are quoted in the literature I found), with many promising new agents failing to meaningfully alter disease characteristics (phase I or II failures) or patient outcomes (phase III failures).

The explosion in the number of cancer drugs in development is being driven by an enormous growth in our knowledge of cancer biology. The more we know about the behaviour of cancer cells, the more potential drug targets emerge. We have known for

some time that cancer is not one disease but many, but only in the last decade have we begun to realize how many. Take lung cancer. Lung cancer is one of the few diseases that have entered the era of personalized medicine – where treatment is selected according to the genetic makeup of the patient (or in this case, their cancer). There are two main types, small cell and non-small cell lung cancer (NSCLC, which accounts for about 80%).

NSCLC is subdivided into adenocarcinoma and squamous cell carcinoma: the type matters, in terms of both prognosis and treatment selection. Now, even this degree of classification is not enough. Adenocarcinoma of the lung is now analysed to see whether it has an activating mutation of EGFR (epidermal growth factor receptor), because patients with such mutations are much more likely to respond to tyrosine kinase inhibitors that target the receptor. The approval of a second targeted agent, crizotinib, will bring pressure to test for its target mutation also, the EML4-ALK translocation. In the case of advanced lung cancer, which is inoperable, all this information must be gathered from small biopsy samples – access to tissue for testing is a major issue in both clinical practice and clinical trials.

These targeted agents are not for everyone: a paper presented in 2011<sup>3</sup> found that only 17% of lung adenocarcinomas had an EGFR mutation and 7% had the EML4-ALK mutation. Twenty-two per cent had a KRas mutation, for which there is no drug approved yet. And 46% of tumours had none of the mutations known to drive lung cancer, so are not currently treatable with targeted agents. Even when targeted agents work, responses are relatively short-lived, and relapse (in advanced disease) is almost inevitable.<sup>4</sup> This is because of cancer cells' ability to change. When one pathway is blocked, their genetic instability means that it is not long before clones that have circumvented the blockage develop and thrive. This is helped by the fact that the network of signalling pathways in cells is extremely complex and has inbuilt redundancy, so several pathways can lead to the same result. Because of this, there is an increasing recognition that targeted

agents (with rare exceptions) will be most useful as part of combinations, rather than acting as a single magic bullet as was once hoped.

Given that it has so many types and subtypes, and is so changeable, what makes cancer cancer? This question was addressed in an influential paper by Hanahan and Weinberg published in 2000, called *The Hallmarks of Cancer*.<sup>5</sup> They suggested that ‘most if not all cancers have acquired the same set of functional capabilities during their development, albeit through various mechanistic strategies’. They described six hallmarks that set cancer cells apart from other cells: evading apoptosis; self-sufficiency in growth signals; insensitivity to anti-growth signals; sustained angiogenesis; limitless replicative potential (i.e. immortality); and tissue invasion and metastasis. In the years since, much more has been learned about the way in which cancer cells interact with and subvert non-malignant cells to serve their own ends. Tumours are not pure lumps of cancer cells growing in isolation. They are like dirty snowballs, full of white cells, cytokines, blood vessels and scaffold tissue as well as malignant cells. This mix is called the tumour microenvironment. Many researchers now believe that targeting the microenvironment is a promising new line of attack against cancer.

The year 2011 saw the publication of the eagerly awaited *Hallmarks of Cancer – The Next Generation*.<sup>4</sup> In their update to the original paper, Hanahan and Weinberg added two more hallmarks: deregulating cellular energetics (cancer cells can use metabolic pathways in ways that normal cells do not) and avoiding immune destruction (cancer cells can sabotage the immune cells that are sent to attack them). They also described two ‘enabling characteristics’ of cancer: genome instability and mutation, and tumour-promoting inflammation (a characteristic of the tumour microenvironment). They observe that: ‘Given that the number of parallel signalling pathways supporting a given hallmark must be limited, it may become possible to target all of these supporting pathways therapeutically, thereby preventing the development of adaptive resistance’.

The hallmarks of cancer have been tremendously influential, but the emphasis on them was questioned in a 2010 commentary in *Nature Reviews Cancer*.<sup>6</sup> Yuri Lazebnik noted that of the six original hallmarks, five were also characteristic of benign tumours. These

can grow extremely large but do not kill because they do not spread to other parts of the body. Only the capability for tissue invasion and metastasis is unique to malignant cells, he argued, continuing: ‘If five of the proposed hallmarks of cancer are also characteristic of benign tumours, why has it become so widely accepted to consider these features in the same league as tissue invasion and metastasis, which are responsible for most cancer mortalities?’.

Lazebnik suggests that the terms ‘cancer’ and ‘tumour’ are too often used interchangeably. He says: ‘Keeping in mind the difference between tumours and cancers might [also] help us to focus more on mechanisms underlying the key emergent property of cancers, their malignancy. This change might help to correct the situation in which, after producing nearly two million papers on cancer, we are yet to understand when and how cancer cells metastasize, or to learn the underlying mechanisms sufficiently well to have a sizable impact on cancer mortality’. However, Hanahan and Weinberg<sup>4</sup> say that they ‘envision significant advances during the coming decade in our understanding of invasion and metastasis’.

So after 2 million papers and billions spent, where are we in the war against cancer? In an interview for *The Naked Scientist*,<sup>7</sup> Robert Weinberg said: ‘Right now, advanced solid tumours from the colon and the pancreas, and the lungs are really formidable enemies, and we don’t really know how to stop them. It would be nice – I think it’s even realistic, to assume that 10 years from now, some of those tumours will be stopped in their tracks, caused to shrink. They may not be caused to totally disappear, but they will be kept at a small size that will render the patient fully normal in terms of his or her lifestyle, and will create a chronic – albeit, tolerable disease’.

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## Author information

**Jo Whelan** BSc is a medical writer and occasional science journalist specialising in oncology. She is currently studying for an MSc in Cancer Therapeutics at Barts Cancer Institute, Queen Mary University of London.