Cancer stem cells

Changing the way we treat cancer

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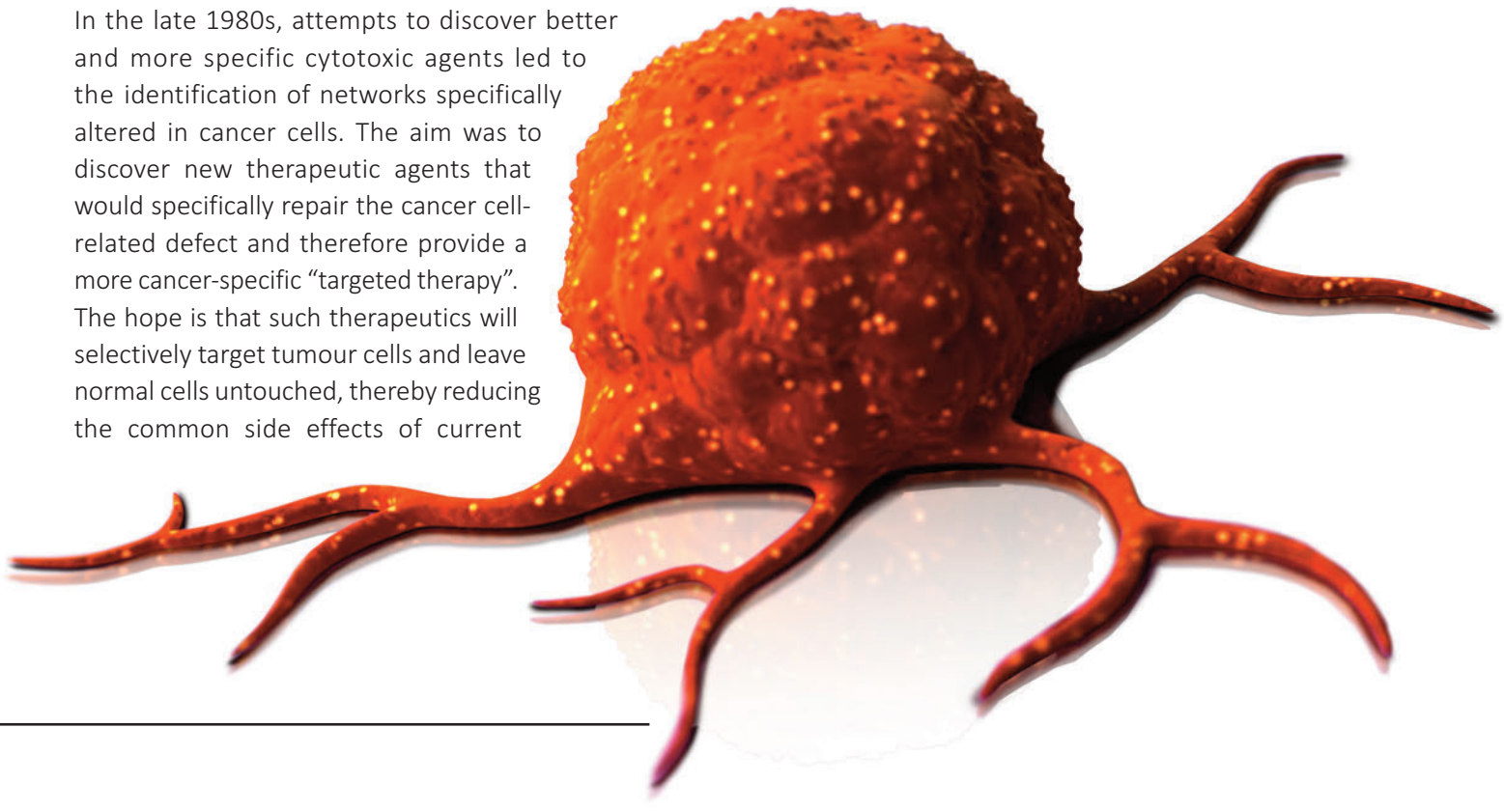
Introduction

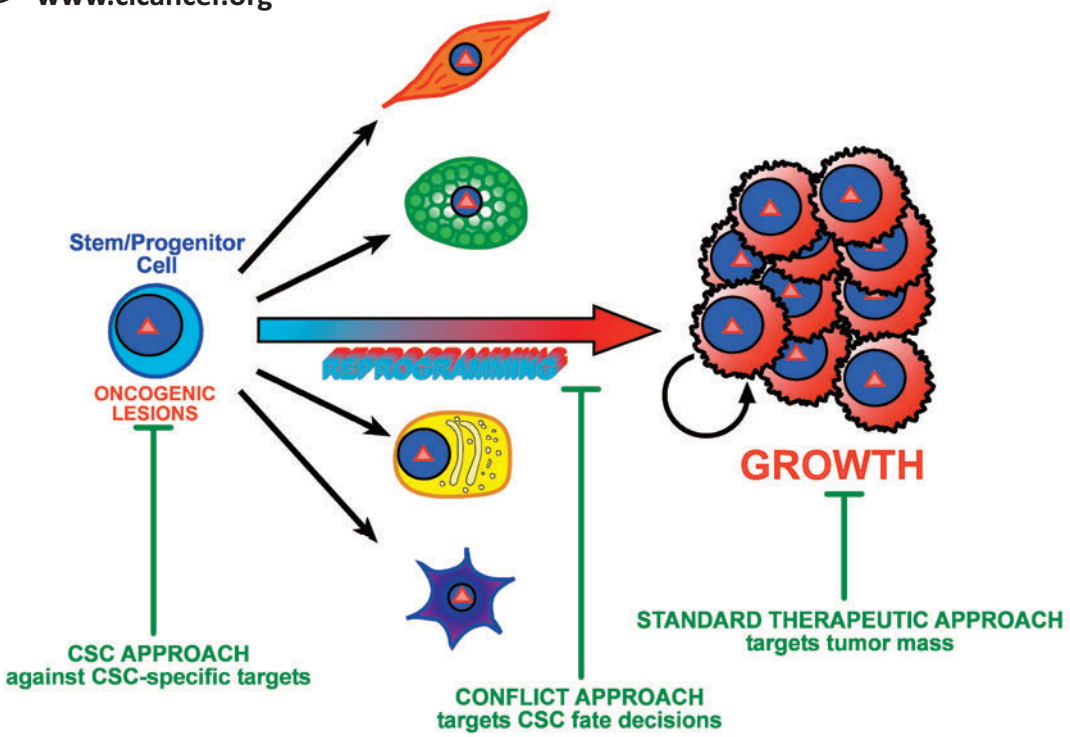
All available data shows that, despite a better understanding of the biology of tumour cells, the treatment of most cancers has not significantly changed for the past three decades. For the main types of cancer, survival rates for people diagnosed when their tumours were in an advanced stage has changed very little in the last 20 years. In contrast, survival is relatively good with early diagnosis. So the current observed decrease in global cancer mortality is mostly the result of early detection and prevention rather than the consequence of effective therapeutics once the cancer has reached a certain stage. So the question that inevitably arises is: are current cancer drugs targeted at the wrong kind of cells? An emerging theme in the field of cancer biology has been the existence of a “cancer stem cell” (CSC) which drives and maintains tumour development. Evidence for this hypothesis has been obtained for a variety of cancers, including leukaemias and solid tumours. Under this new paradigm this cell type is solely responsible for maintaining tumour growth. Thus, tumour formation and maintenance are a consequence of altered differentiation of CSCs and not cellular proliferation, as assumed until recently. Under the light of these facts our view of cancer development has to be re-interpreted, especially in what refers to the early stages of carcinogenesis. Shifting the maintenance of human cancers to the stem cell compartment has serious implications for its treatment. Conventional therapy targets the proliferating cells, largely leaving the cancer stem cells unaffected. The initial therapeutic success would then be followed by relapse of the patient as the cancer stem cells repopulate the tumour. Novel therapies, specifically designed to target the CSC, must be designed to remove this cellular source of the tumours and, when combined with traditional anti-proliferative therapies, will most likely be able of curing the cancer. The purpose of this review is to discuss the current status of the field, pointing out the new experimental avenues that the CSC concept has opened and to serve as a starting point for future studies.

The current paradigm in cancer treatment

The modern use of chemotherapy as a main tool for cancer treatment traces back to the 1940s. Since then, cancer drug development has grown into a multi-billion dollar industry. For many years the main basis behind chemotherapy of cancer relied on the fact that, from the macroscopic point of view, the majority of the cells in the tumour are actively proliferating, more than the average cells in the body. From this starting point, it is clear that cytotoxic chemotherapy (or radiotherapy) of cancer is limited by the serious, sometimes life-threatening, side effects that arise from toxicities to sensitive normal cells, because in spite of their different behaviour, cancer cells share many features with the normal host cells from which they derive. All cancer chemotherapeutics that are in common use at present owe their very limited selectivity to the higher proliferation rates of cancer cells. This leads to high toxicities against normal tissues that also show enhanced proliferation rates, such as the bone marrow, gastrointestinal tract and hair follicles. These problems, which are often accompanied by the development of drug resistance and metastatic disease, result in the eventual failure of the therapy.

In the late 1980s, attempts to discover better and more specific cytotoxic agents led to the identification of networks specifically altered in cancer cells. The aim was to discover new therapeutic agents that would specifically repair the cancer cell-related defect and therefore provide a more cancer-specific “targeted therapy”. The hope is that such therapeutics will selectively target tumour cells and leave normal cells untouched, thereby reducing the common side effects of current anticancer therapies. This transition represents an important advance, but the basic principles of cancer treatment and drug resistance, as developed in the period from 1950 to 1980, remain the same. All therapeutics, either targeted or non-targeted, aim at reducing proliferation of cancer cells. With this approach, in spite of the enormous amounts of public and private money invested, in the last 35 years the improvement of the average 5-year-survival for cancers in general has been only of a modest 17% (NCI – SEER Cancer Statistics Review 1975- 2003). The challenge therefore remains: how to design and develop novel cancer treatments? Or, in other words, can cancer be cured?



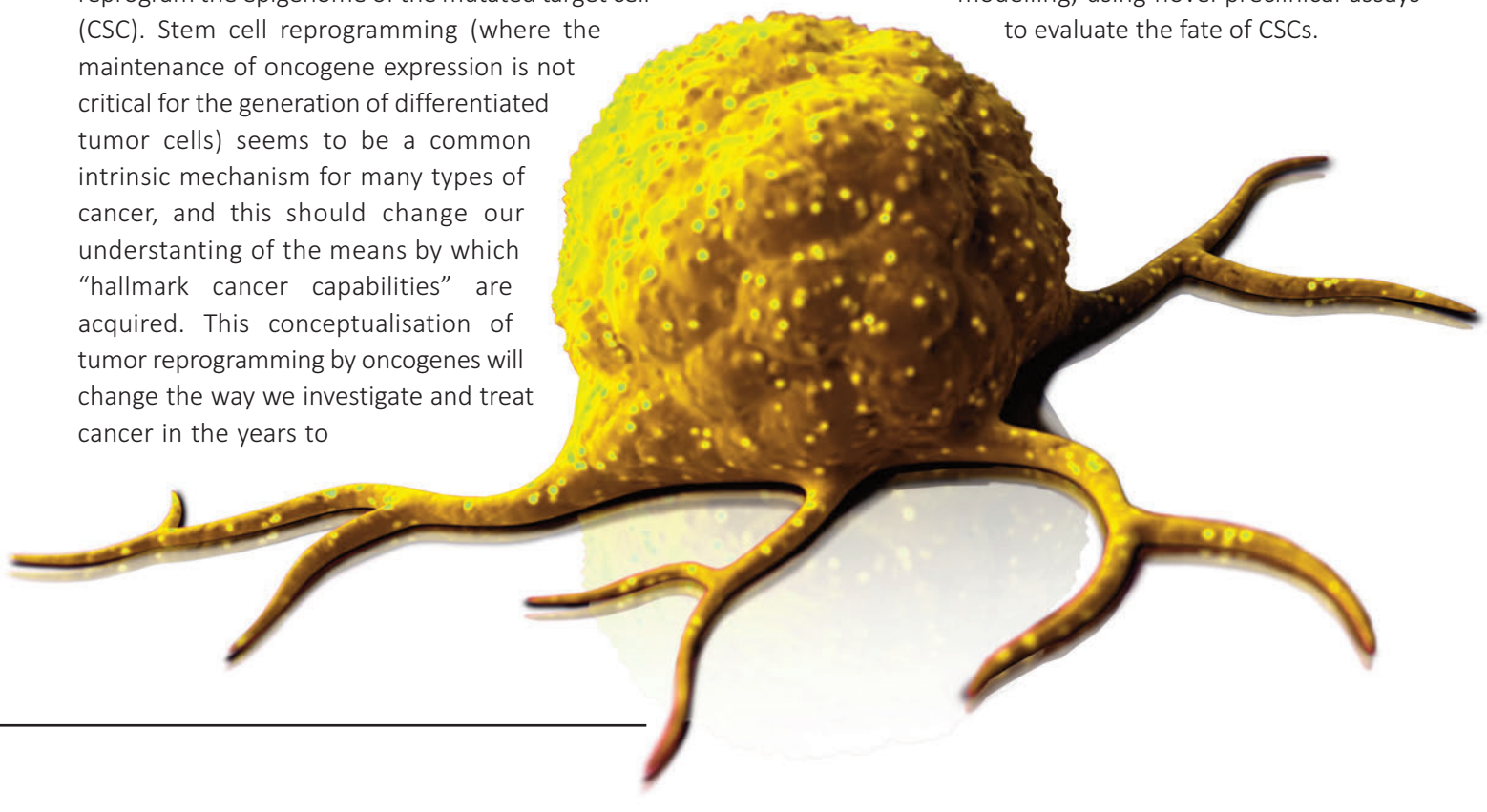


The new paradigm: Cancer Stem Cells (CSCs).

The Cancer Stem Cell (CSC) hypothesis about the origin of cancer is an updated version of the "embryonal rest hypothesis" that was proposed more than 150 years ago to account for the similarities between certain tumours, like teratocarcinomas, and a developing embryo. The failure of conventional therapies in eliminating cancer in a definitive manner can be easily understood when one examines the side effects of current cancer treatments and how they disappear once the treatment is stopped. The tissues that require constant self -renewal, like hair or gut epithelium or the hematopoietic system, are the most damaged during treatment, but they recover quickly once this is finished. So does cancer on the long round. This implies for cancer a level of organisation similar to that of any of these tissues, in which a small population of undifferentiated stem cells, slow-cycling and resistant to therapy, are in charge of generating the main tumour mass of more differentiated cancer cells, more proliferative and responsive to usual treatments. Under the light of the CSC hypothesis, we can consider that it is in the very nature of CSCs to be resistant to chemotherapy because of their stem cell properties. Due to these facts, CSCs can survive the therapy and re-originate the tumour. So, the existence of CSCs implies the presence of a small pool of slow-cycling cells that carry the oncogenic mutation and are apparently insensitive to anti-proliferative treatments, although their cellular descendants are sensitive. However, the aforementioned observations, derived from human targeted-therapy failure, might suggest that oncogenes have a mode of action that is not homogenous throughout the cancer cell population. This would explain the different sensitivity towards anti-oncogene targeted therapies among the different cancer cellular stages. Recent in vivo genetic evidences have shown that human oncogenes are capable of reprogramming early stem/precursor cells towards specific differentiated tumor cell fates, but they are not required within the CSCs. Accordingly, tumoral reprogramming is the process by which an oncogene (or cancer genetic alteration) can "reset" the epigenetic and/or transcriptome status of an initially healthy cell (the cancer cell-of-origin), therefore establishing a new, pathological differentiation program ultimately leading to cancer development. The initiating lesion would be the driving force in the reprogramming process, essential for tumorigenesis. However, once reprogramming has taken place this initiating hit would only be a passenger mutation within the CSC, either without a significant function anymore, or even performing a different role, unrelated to the reprogramming one, in tumor expansion or proliferation. This mode of action explains why well-designed targeted therapies fail in eradicating the CSCs, in spite of their apparent efficacy against the main tumor mass.

Practical implications of the CSC hypothesis

This new concept of the cancer seen as tissues that are originated from, and maintained by CSCs has far-reaching implications for cancer treatment. Given that CSCs share many functional properties with normal stem cells and that many of the critical pathways involved in maintaining normal stem cell function are also deregulated in cancer, therapies directed against CSCs, targeting such shared pathways might also inadvertently decimate normal resident stem cells. However, we have seen the evidence showing that oncogenes contribute to cancer development not just by inducing proliferation, but rather because of their capacity to developmentally reprogram the epigenome of the mutated target cell (CSC). Stem cell reprogramming (where the maintenance of oncogene expression is not critical for the generation of differentiated tumor cells) seems to be a common intrinsic mechanism for many types of cancer, and this should change our understanting of the means by which "hallmark cancer capabilities" are acquired. This conceptualisation of tumor reprogramming by oncogenes will change the way we investigate and treat cancer in the years to come. The ability to generate tumor stem cells from specific diseases and mutations in vivo has opened prospects for studying how different disease states develop from the start. If we can understand the regulation of the oncogene-target cell interaction, and as a result we learn how to manipulate cellular states experimentally, we could unlock the potential to provide great advances in human cancer medicine. Because of the difficulty of assessing the effects of therapies on the rare CSCs responsible for relapse, the development of such approaches requires new clinical paradigms and methodologies that should rely heavily on preclinical modelling, using novel preclinical assays to evaluate the fate of CSCs.



Challenging the stem cell convention

Professor Alan Clarke, Director of the European Cancer Stem Cell Research Institute gives an overview of how cancer stem cells differ from the conventional stem cell…

Cancer remains one of the major challenges in terms of life expectancy and is recognised as the second largest cause of mortality within the EU, accounting for 28% of all deaths in 2010. Although we are slowly improving 5 year survival rates for many tumour types, we still do not have effective therapies for all tumours and we still do not properly understand the processes that underlie resistance to therapy and tumour relapse. Furthermore, for some tumours (such as those of the pancreas) our understanding of how to treat patients is so woeful that they are currently virtually untreatable. There is therefore a plethora of unmet clinical needs relating to better cancer diagnosis and treatment.

One concept that may aid in tackling these problems is that of the 'cancer stem cell'. Normal stem cells have now been found in many different tissue types and these are responsible for the growth and subsequent maintenance of those tissues, and also for their repair following damage, such as exposure to toxins or irradiation. One way to view this is that the stem cells sit at the top of a hierarchy of cells which are required for correct tissue maintenance and that the stem cells are capable of generating all of that hierarchy. Our understanding of these normal stem cell populations is burgeoning and as it does it opens up radical new prospects for regenerative medicine in diseases such as neurodegeneration and arthritis.

The 'Cancer Stem Cell' notion is that, in a manner parallel to normal tissues, tumorous tissues actually possess a similar hierarchy of cells, with a small proportion of cancer stem cells capable of driving the growth and development of the entire tumour. However, this view clashes with the more conventional notion that all tumours are homogeneous – i.e., that all cells within a tumour have similar tumorigenic capacity. Evidence from many different laboratories is now challenging this conventional view, with clear examples of cancers that are driven by a small population of 'cancer stem cells' which we can identify by the unique profiles of proteins they express on the surface of these cells. The importance of the cancer stem cell concept may also extend beyond implications for the growth and relapse of the primary tumour, as these cells have also been implicated in the spreading of the tumour around the body – a process termed metastasis which is the stage of disease most closely associated with lethality. If the above is correct, it may be possible to treat cancer more effectively by concentrating on the stem cells alone, rather than all the cells in the tumour, as current treatments do.

The critical distinction between these views (homogeneous versus driving cancer stem cells) means that, if the cancer stem cell concept is correct, current cancer therapies being developed and used may not be being targeted at the correct cell type within the tumour. At the present time, this traditional view could mean an "apparently" successful therapy or treatment in a cancer patient that results in reducing tumour 'bulk' is, in fact, a poor or failed treatment because it still allows the driving cancer stem cell population to survive and therefore the tumour is still able to re-grow. It could also mean that potential cancer treatments and therapies which successfully target the cancer stem cell are currently being disregarded. These are the cutting-edge scientific issues that now need to be addressed. If we can now confirm that the cancer stem cells concept is correct, it offers the possibility of transforming our progress in the fight against cancer.

The cancer stem cell concept has always been vigorously debated, with the field split into two camps – those advocating the existence of cancer stem cells and those opposed to this concept. However, there have been significant changes over the last 12-24 months in that a series of high impact scientific papers have been published that are seen to prove the notion of the cancer stem cell, or at least confirmation of the existence of hierarchy within tumours. Furthermore, there has been rapid technological development in our capacity to extract and indefinitely grow cancer stem cells in a laboratory setting which is revolutionising the utility of these cells. For example, this is now opening up possibilities for the development of tailored therapy per patient (known as 'stratified' or 'personalised' medicine) which is predicted to change the landscape of both research and therapy over the coming years.

The study of cancer stem cells remains in its infancy. There are a number of key objectives within the field that need to be met. The most basic of these is to improve our understanding of cancer stem cells and the roles they play in a range of cancers. For example, we are still unsure if the concept is relevant to all cancers or just to a subset. We also need to identify robust markers of disease that reflect the presence of cancer stem cells; and further we need to use this approach to identify new therapeutic targets. Perhaps most excitingly, it may be possible to repurpose existing drugs against cancer stem cells that have previously not been shown to be effective against bulk cancer cells. This latter approach carries the great twin benefits of reduced cost and reduced time in development. We will also need to develop new platforms based around cancer stem cells which will allow mid-to-high throughput drug screening of both existing and novel agents (including natural agents) to assess their capacity to target the cancer stem cell.

The cancer stem cell concept offers a new approach to the treatment of cancer that has wide ranging implications. From our improved basic knowledge, the aim will be to develop new therapies which can be shown to make a real difference in the clinic. Ultimately, the objective will be to transform the survival rates for patients suffering from a range of cancer types. All of the above of course requires substantial investment from both industrial and academic partners. Currently this is derived from a range of funding streams, none of which is wholly devoted to the cancer stem cell concept. However some institutions do exist, such as the European Cancer Stem Cell Research Institute, based at Cardiff University, which is wholly focussed on this problem. The key challenge must be to coalesce efforts across the EU to truly ascertain the value and usefulness of the cancer stem cell notion.

Statement from the Welcome Trust….

"Stem Cell research continues to be one of the most promising fields of biomedical research that offers the opportunity to greatly improve the health of European citizens. We call on the European Parliament and European Commission to oppose the 'One of Us' Citizens' Initiative that is seeking a ban on all financing of activities that presuppose the destruction of human embryos, including stem cell research. Such a ban would have a negative impact on research involving human embryos for regenerative medicine, reproductive health and genetic disease.

"We ask the Commission and Parliament to maintain the provisions of the current framework for funding stem cell research in Horizon 2020. These provisions were recently approved by the European Parliament after much debate on 13 December 2013. Horizon 2020 allows ground breaking and important research using all forms of stem cells, subject to it meeting fundamental ethical principals.

"Any roll back on this agreement would be a major step backwards for research across regenerative medicine, reproductive health, and genetic disease and delay the development of much needed treatments for a host of untreatable conditions."

www.wellcome.ac.uk/About-us/Policy/Spotlight-issues/EU-funding-for-stem-cell-research/

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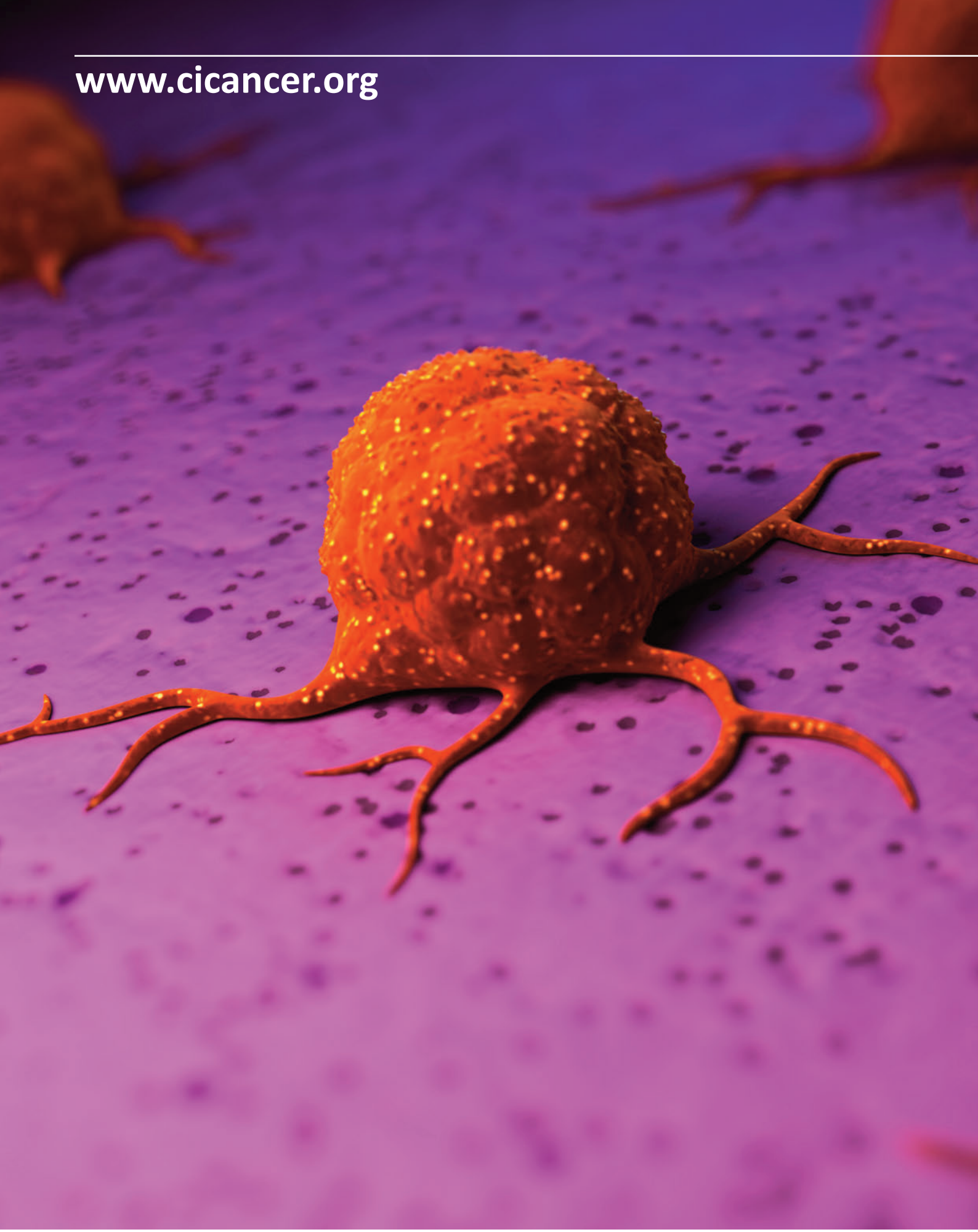

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