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OPINION

Killing time for cancer cells

Shoshana Klein, Frank McCormick and Alexander Levitzki

Abstract | As the signalling pathways that control cellular proliferation and death are unravelled, a range of targets have emerged as candidates for molecular cancer therapy. For their survival, cancer cells depend on a few highly activated signalling pathways; inhibition of these pathways has a strong apoptotic effect and can lead to tumour regression. But drugs that exploit this weakness, such as imatinib, have not cured patients: withdrawal of the drug leads to disease recurrence, and sustained treatment leads to the emergence of drug-resistant clones. Can cancer be cured, or will it have to be controlled as a chronic disease?

Cancer is a disease of miscommunication. The uncontrolled proliferation of cancer cells is one side of the coin. Impaired signalling for apoptosis (programmed cell death) is the other. Paradoxically, cancer cells are less robust than normal cells. The traditional regimens for treating cancer, chemotherapy and radiotherapy, take advantage of the increased sensitivity of cancer cells to DNA or microtubule damage. In recent years, specific molecular targets have been identified as selective treatments for cancer cells.

In healthy cells, a myriad of interacting signalling pathways provide redundancy, spreading out the cost of damage to a single pathway. Cancer cells accumulate assorted mutations in oncogenes and tumour-suppressor genes, rendering a few signalling pathways overactive. Other mutations lead to the elimination of redundant signalling pathways. Cancer cells can be particularly sensitive to inhibition of the remaining hyperactive pathways (REF. 1 and T. Geiger and A.L., unpublished observations; FIG. 1). Many components of these signalling pathways are kinases, frequently tyrosine kinases. Specific tyrosine-kinase inhibitors have been developed, which arrest the proliferation of cancer cells[2]. Therefore, the strategy that has been developed over the past 15 years is to pinpoint the survival factors of a tumour and, by inhibiting those factors, specifically arrest proliferation and/or induce apoptosis of the cancer cells[3].

This approach of 'signal-transduction therapy'[4] has been validated in the clinic. The spectacular success in the treatment of early chronic myelogenous leukaemia (CML) with imatinib (Glivec) was greeted with euphoria. But is imatinib actually the exception that proves the concept, but not the rule? Early CML is unusual in that it has a single survival factor — BCR–ABL — and, in the chronic phase, the disease is relatively homogeneous. Most tumours, especially solid tumours, are dependent on several pathways and are heterogeneous. It is therefore unlikely that a single therapeutic medium will eliminate a cancerous growth. It will be necessary to develop appropriate combinations of treatment. Other signal-transduction inhibitors have also found their way into the clinic, and many more are in preclinical studies (FIG. 2). By assessing to what degree these drugs are fulfilling their promise, we can redirect strategies for combating cancer. Experience has shown that cancer can be eradicated only if it is caught early. The new drugs might allow us to 'tame' more advanced cancer into a controlled, quiescent state.

Targets for signal-transduction therapy

Even though each cancer is expected to have its own spectrum of signature mutations, some aberrations in signalling appear in a broad range of cancers. These are attractive targets for drug development, because they should be widely applicable. We shall highlight a few pertinent cases.

Targeting cell-division pathways to arrest tumour growth. The canonical growth-factor-mediated signalling pathway is well known (FIG. 2). The pathway can be hyperactivated by mutation at several

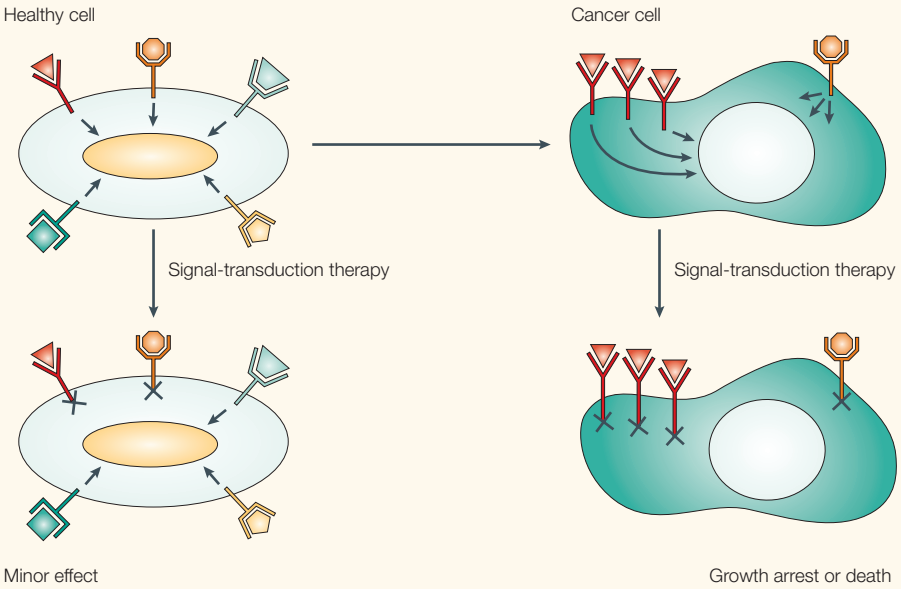

Figure 1 | **Cancer cells are more sensitive to signal-transduction inhibitors than normal cells.** Normal cells respond to a range of signals, and cell proliferation is subject to many checks and balances. Cancer cells have fewer signalling pathways, some of which are overly active. By identifying the nature of the modified, reduced network on which the cancer cell depends, one can devise a strategy to deprive the cell of its survival signals, without harming the normal cells, which retain their more elaborate and robust signalling network.

stages: the excessive production of growth factors by the cells themselves (autocrine activation), growth-factor-independent activation of receptors, constitutive activation of the signal transducers or activation of the cell-cycle effectors. Signal-transduction therapies that show promise include the use of antibodies to deplete the tumour of growth factors or to block growth-factor-receptor interactions, and low-molecular-weight inhibitors that target various stages in the transduction of the growth signal and its execution (FIG. 2). These strategies are designed to arrest the growth of the tumour.

One example is BAY 43-9006, a low-molecular-weight RAF-kinase inhibitor. The small GTPase RAS transmits signals from receptor tyrosine kinases to the serine/threonine kinase RAF, which then signals through MEK (mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) kinase) and ERK, members of the MAPK cascade. Oncogenic mutations in RAS and RAF have been identified in a large spectrum of cancers. BRAF is mutated in many cancers, including over 65% of melanomas. Most of the mutant forms of BRAF have a specific mutation of residue Val599 that constitutively activates the kinase[5]. BAY 43-9006 is an effective inhibitor of BRAF and of the vascular endothelial growth factor receptors (VEGFRs), and so potentially affects both the MAPK pathway and angiogenesis[6].

The extrapolation from preclinical studies to clinical success is not direct. Although BAY 43-9006 inhibited growth of melanoma cell lines and delayed growth of melanoma xenografts[7], it had little impact, if any, on melanoma when used as a single agent in clinical trials, even though RAF kinase activity was inhibited. It is possible that activated BRAF is not necessary for sustained growth and survival of late-stage disease. A more likely explanation for the poor response of melanoma to BAY 43-9006 is that BRAF is necessary for continued proliferation, but is not a major survival factor in metastatic melanoma. Reduced rates of cell proliferation might not translate easily into clinical outcomes, as any evidence of disease progression over a period of months is considered a failure. By contrast, combining BAY 43-9006 with conventional chemotherapy agents has produced more encouraging results. This could be because blocking RAF kinase increases levels of p53 and so sensitizes cells to p53-dependent apoptosis[8].

A second example of a small-molecule inhibitor that targets the cell cycle is flavopiridol, an ATP-competitive inhibitor of multiple cyclin-dependent kinases (CDKs). Flavopiridol arrests tumour cell lines in G1 (before DNA synthesis), owing to inhibition of CDK2 and CDK4 (FIG. 2), and in G2 (before mitosis), owing to inhibition of CDK1. Flavopiridol achieved prolonged stable disease in some patients with non-small-cell lung carcinoma and provides a good example of the importance of scheduling of treatment regimens. When non-cytotoxic doses of DNA-damaging agents, such as gemcitabine or cisplatin, are first administered to cause S-phase delay, subsequent treatment with flavopiridol is synergistic and kills the cells. Inhibition of CDKs during S phase leads to persistent E2F activation, leading to apoptosis of transformed (but not normal) cells. Similarly, when taxanes, which destabilize microtubules, are first administered, they induce mitotic block, and subsequent administration of flavopiridol inhibits the cyclin-B–CDK1 complex and enhances apoptosis. On the other hand, treatment first with flavopiridol leads to G1 arrest and reduces the cytotoxic effect of taxanes that are administered afterwards[9].

These studies have shown that preclinical experiments, including the use of mouse models for cancer, can validate a target, but might be poor predictors of drug efficacy in human patients. Because cell-cycle arrest is intimately associated with apoptosis, cell-cycle inhibitors sometimes act synergistically with inducers of apoptosis, leading to tumour shrinkage.

Targeting cell-survival pathways to induce apoptosis. Traditional cancer treatments kill cancer cells through a range of mechanisms, including mitotic catastrophe, necrosis, autophagy, premature senescence and apoptosis. Defects in the apoptotic pathway can, in some cancer cells, cause resistance[10].

There are two main pathways of apoptosis — the extrinsic and intrinsic pathways. In the extrinsic pathway, ligand binding to death receptors of the tumour-necrosis factor family leads to receptor multimerization. The adaptor molecule FADD binds to the cytoplasmic entity of the receptor multimer, and recruits initiator caspases (caspase-8 and -10), which activate effector caspases (caspase-3, -6 and -7), which cause cell death. In the intrinsic pathway, mitochondrial damage triggers cytochrome *c* release, leading to formation of the apoptosome complex, which includes cytochrome *c*, APAF1 and pro-caspase-9. Caspase-9 activation leads to activation of caspase-3, -6 and -7, and consequent cell death. A bevy of pro-apoptotic and anti-apoptotic proteins regulates the balance between cell growth and cell death.

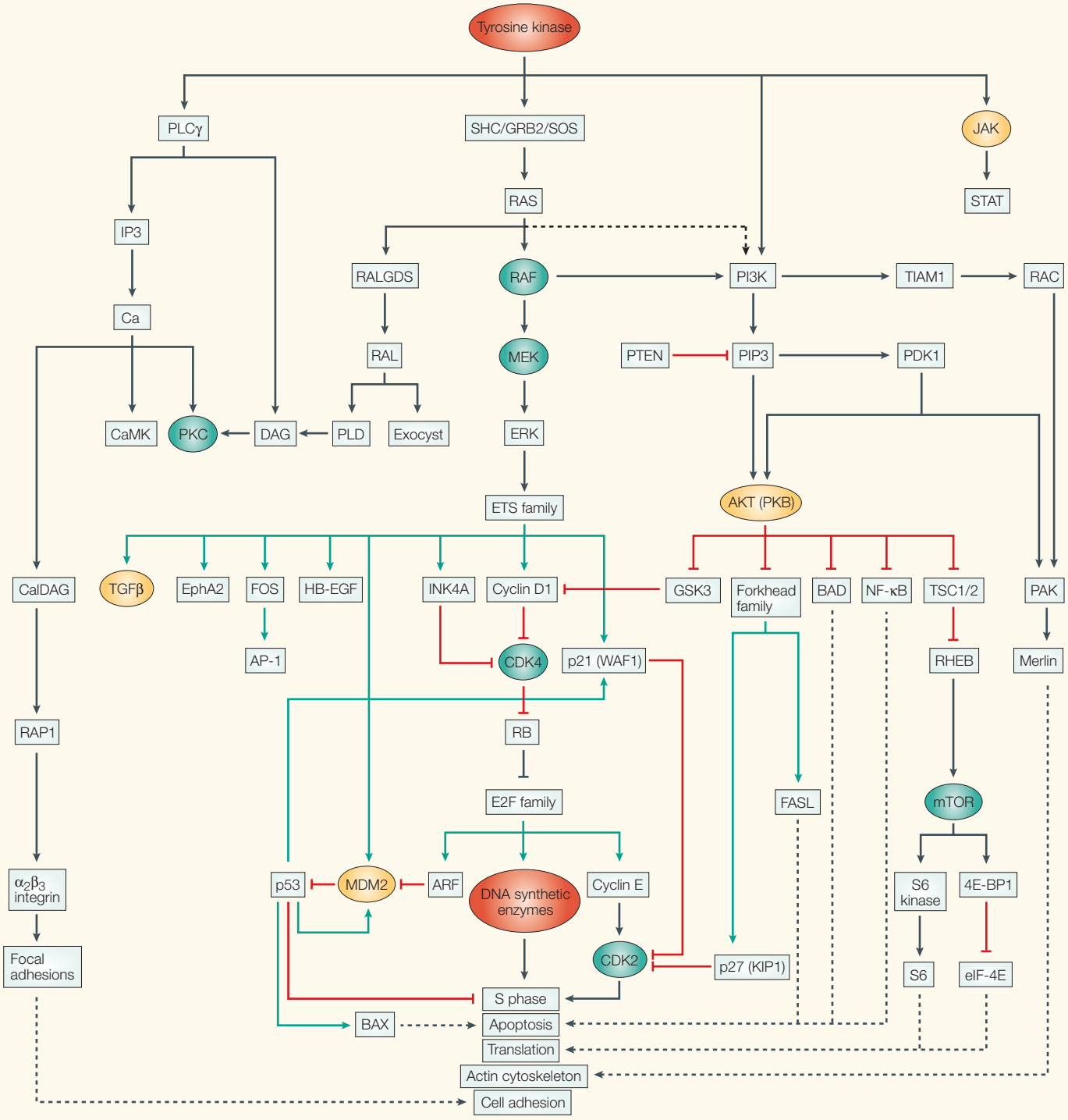

Figure 2 | **Protein tyrosine and serine/threonine kinases.** Activation of cell signalling by a selected repertoire of protein tyrosine and serine/threonine kinases is the hallmark of many cancers. Certain tyrosine kinases and serine/threonine kinases, placed in key positions in the network, have become targets for signal-transduction inhibitors. These are marked by colours according to their current status of development: approved drugs (red); drugs in the clinical trials (green); and drugs in preclinical trials (yellow). Green arrows denote direct transcriptional targets. Red lines show direct inhibitory pathways. Black arrows show direct activation events, and dashed arrows show events that are either indirect or questionable. 4E-BP1, eukaryotic translation initiation factor 4E (eIF4E)-binding protein 1; Ca, calcium; CalDAG, calcium- and diacylglycerol-regulated guanine nucleotide exchange factor; CaMK, calcium/calmodulin-dependent protein kinase; CDK, cyclin-dependent kinase; DAG, diacylglycerol; EphA2, ephrin receptor A2; ERK, extracellular signal-regulated kinase; FASL, FAS ligand; GRB2, growth-factor-receptor-bound protein 2; GSK3, glycogen synthase kinase 3; HB-EGF, heparin-binding epidermal growth factor; IP3, inositol 3,4,5 triphosphate; JAK, Janus kinase; MEK, mitogen-activated protein kinase/ERK kinase; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor-κB; PAK, p21-activated kinase; PDK1, 3-phosphoinositide-dependent protein kinase 1; PI3K, phosphatidylinositol 3-kinase; PIP3, phosphatidylinositol 3,4,5-triphosphate; PKB, protein kinase B; PKC, protein kinase C; PLCγ, phospholipase Cγ; PLD, phospholipase D; RAL, RAS-related protein; RALGDS, RAL guanine nucleotide dissociation stimulator; RB, retinoblastoma; RHEB, RAS homolog enriched in brain; STAT, signal transducer and activator of transcription; TGFβ, transforming growth factor-β; TIAM1, T-cell lymphoma invasion and metastasis 1; TSC, tuberous sclerosis complex.

The selective approach to cancer treatment targets the specific aberrations that suppress apoptosis. These aberrations are selected for during tumour evolution to suppress the pro-apoptotic effects of mis-regulated signal transduction. With gene expression and proteomics arrays, it is likely that in the not-too-distant future it will be possible to target the particular anti-apoptotic pathways on which an individual tumour is dependent. In the meantime, however, a few prospective targets are emerging that have roles in a broad range of cancers.

The inhibitor of apoptosis (IAP) family includes c-IAP1, c-IAP2, XIAP (X-chromosome-linked IAP) and survivin. Some of these proteins block mitochondrial-dependent and -independent apoptosis, mainly by inhibiting the activity of caspases. Small-molecule inhibitors of XIAP have been shown to sensitize cancer cells to chemotherapy and to suppress tumour growth in xenograft models[11].

DIABLO (also known as SMAC) promotes apoptosis by preventing the IAPs from binding and inhibiting caspases. Studies using human acute leukaemia Jurkat T cells indicate that DIABLO peptides can be used to block IAPs, and enhance sensitivity to apoptosis[12].

Further upstream are the BCL2 proteins, which prevent apoptosis by blocking the release of cytochrome *c* from mitochondria. Although an antisense inhibitor of BCL2 (Genasense) showed no significant improvement in survival in melanoma trials, a small-molecule inhibitor (GX15-070) has just entered Phase I clinical trials to evaluate its safety as a possible treatment for solid tumours.

Another preferential target, p53, transactivates genes involved in both cell-cycle arrest and apoptosis, and also promotes apoptosis in a transcription-independent manner. p53 is mutated in at least 50% of human tumours, and its inactivation could have a role in all solid tumours. Most of the mutations affect specific DNA binding, decreasing the ability of p53 to promote growth arrest and apoptosis. Some tumours in which p53 is competent might be more responsive to chemotherapy, but others, in which p53 causes growth arrest, could be spared from the lethal effects of chemotherapy. The correlation between p53 status and sensitivity to killing is therefore unclear, and might depend on the precise assay that is used to measure these effects[10].

Strategies for reactivating p53 include low-molecular-weight agents or peptides that restore specific DNA binding[13]. Small molecules, such as nutlin-3, prevent p53 degradation by MDM2 in tumours that retain wild-type p53 (REF. 14). Adenoviral vectors that express wild-type p53 are currently being tested to treat head and neck cancer, with and without chemotherapy, in clinical trials. This approach might be selective because p53-negative tumours lack MDM2, allowing p53 to accumulate in these cells, whereas normal cells actively degrade p53. Another strategy is to use adenoviral vectors to overexpress the pro-apoptotic protein BAX, which acts downstream of p53 to cause apoptosis[15].

AKT (also known as protein kinase B) another anti-apoptotic protein, is overexpressed or activated in a range of cancers. AKT activation requires phosphatidylinositol 3,4,5-triphosphate (PIP3), which is produced by phosphatidylinositol 3-kinase (PI3K) in response to several growth factors. Among the many substrates inhibited by AKT are the pro-apoptotic proteins BAD, caspase-9 and tuberin, a repressor of mammalian target of rapamycin (mTOR). AKT activation not only inhibits apoptosis, it also enhances cellular proliferation, through activation of nuclear factor-κB (NF-κB). Furthermore, PTEN, a phosphatase that dephosphorylates PIP3, and so negatively regulates AKT, is deleted in a broad range of cancers[16]. Therefore, AKT is an attractive target for cancer therapy, and several small-molecule inhibitors are being evaluated in preclinical studies[17].

mTOR coordinates nutrient response and cell growth and regulates translation, in response to amino acid and energy levels in the cell[18]. The mTOR inhibitor rapamycin sensitizes tumour cells to pro-apoptotic agents. Combinations of mTOR inhibitors (rapamycin and its analogues) and chemotherapeutic agents are therefore being examined in several solid tumours[19,20]. As mentioned above, mTOR is also regulated by the AKT pathway. The effectiveness of rapamycin might depend on the PTEN/AKT status of the tumour[21].

There is a great deal of crosstalk between the pathways controlling cell proliferation and apoptosis, and elements such as MYC and RAS can either promote or arrest growth and/or apoptosis, depending on the cellular milieu in which they are found[22]. Therefore, oncogenes such as *MYC* or *RAS* might be poor targets for cancer therapy, as the outcome of their inhibition is difficult to predict.

Inducing apoptosis remains the most attractive strategy for killing cancer cells. As inhibitors like those described above move into the clinic, it will be possible to target the cancer cells more specifically, reducing toxic side effects.

Starving the tumour

Starving the tumour of its blood supply is a strategy that could be relevant to any solid tumour. One way to starve the tumour is to inhibit the generation of new blood vessels that are produced in response to angiogenic factors, such as VEGF. Bevacizumab (Avastin), an antibody to VEGF, has recently been approved for the treatment of colon cancer when combined with chemotherapy[23]. Bevacizumab is now also being tested in combination with erlotinib (Tarceva), a low-molecular-weight kinase inhibitor of the epidermal growth factor receptor (EGFR), for the treatment of renal carcinoma and lung carcinoma. It is likely that inhibitors of the VEGFR that induce cytostasis will also sensitize starved tumour cells to apoptosis. One example is BAY43-9006, which is in late-stage clinical trials for the treatment of renal-cell carcinoma. The potential clinical benefit from this agent probably relates to its ability to inhibit VEGFR2 in a disease that depends heavily on neovascularization.

Angiogenesis inhibitors were not effective in trials to treat advanced breast cancer. This might have been expected: advanced breast tumours are very hypoxic, and therefore dependent on glucose fermentation, a phenomenon known as the 'Warburg effect'. The transcription factor hypoxia-inducible factor-1α (HIF1α) is essential for this switch to anaerobic metabolism, and inhibitors of HIF1α are being tested in preclinical studies, with promising results[24,25].

Lessons from imatinib

The paradigm of signal-transduction therapy is the inhibition of BCR–ABL by imatinib in the treatment of CML[26]. Insights gained from the experiences with imatinib and other signal-transduction inhibitors should help to foresee, and hopefully to forestall, difficulties that might be expected to arise when using future targeted molecular therapies.

Mutations that cause resistance. Over 90% of CML patients carry the Philadelphia chromosome, a translocation between chromosomes 9 and 22 that leads to formation of the *BCR–ABL* oncogene. The constitutively active BCR–ABL kinase activates the RAS–MAPK and Janus kinase (JAK)–STAT (signal tranducer and activator of transcription) pathways, leading to

growth-factor independence. BCR–ABL also activates the strongly anti-apoptotic PI3K–AKT pathway, and increases the expression of BCL2 (REF. 27). BCR–ABL appears to be the major survival factor for these cells. Therefore, inhibiting BCR–ABL reinstates apoptosis and leads to the demise of the leukaemia.

Imatinib does not actually eradicate CML. Complete molecular remission occurs in only 5% of cases, and even in these cases *BCR–ABL* cells might be present, below the detection level. Therefore, patients are kept on imatinib until their disease progresses under treatment. This occurs when drug-resistant clones emerge, probably from pre-existing pools of variants, as discussed below. Currently, the only cure for CML is allogeneic stem cell transplantation.

Some patients develop resistance to imatinib, and others are resistant to start with. Occasionally, resistance is due to amplification of the *BCR–ABL* gene[28]. More often, patients harbour particular mutations in the *ABL* tyrosine-kinase domain. Most of these mutations seem to affect the conformation of the kinase domain, preventing binding to imatinib. In restrospect, it has been found that these mutations can be present in a small population of the cancer cells, before the administration of imatinib[29,30]. Therefore, with sensitive tests, it should be possible to screen patients before beginning treatment. We might have anticipated that imatinib, by its very success, would exert strong selective pressure that would bring the resistant cells to the fore. Combination therapy is the best approach to avoid selection for cancer cells that are resistant to therapy, and combinations of imatinib with interferon or cytarabine are being investigated[31]. The approach of reducing tumour load by means of a targeted inhibitor (imatinib, in this case) combined with interferon treatment or other immunotherapies, to stimulate the immune response against the tumour, might succeed in controlling the disease for longer periods.

Tumour stem cells. When patients stop taking imatinib they relapse. The re-emergent disease is not due to mutation, as it can be controlled by resuming treatment with imatinib[32,33]. The recurrence of the disease could be due to CML stem cells. There is evidence that BCR–ABL is present in different haematopoietic lineages. Recent evidence indicates that the putative cancer stem cells that cause blast-crisis CML might actually be progenitor cells (an early stage following commitment to differentiation) that have regained the ability to self-renew, by activating the WNT–β-catenin pathway[34].

The existence of cancer stem cells was first conclusively demonstrated for acute myeloid leukaemia (AML)[35,36]. Recently, it has been shown that there is a hierarchy of AML leukaemia stem cells, just as there is a hierarchy of normal stem cells[37].

Cancer stem cells are not a peculiarity of leukaemia. They have already been demonstrated for breast and brain tumours[38,39]. This could be the basis for the finding that tamoxifen, an oestrogen antagonist, is most effective in preventing recurrence of breast cancer when it is administered for long periods (up to 5 years)[40]. The experience with imatinib indicates that CML stem cells can be kept at bay by continuous treatment with the drug.

Cancer stem cells are refractory to treatment with most, if not all, cytotoxic drugs. They appear to be quiescent, enabling them to survive and cause relapses[37]. Are there targets that can be exploited to eradicate cancer stem cells that will not kill healthy stem cells? Several groups are studying expression profiles of stem cells, in the hope that these data will eventually provide targets for cancer stem cells[41]. NF-κB is active in AML cells, including the 'quiescent' stem cells. NF-κB activity can be blocked by proteasome inhibition, although this is not a targeted therapy. *In vitro*, combining proteasome inhibition and anthracycline treatment led to apoptosis of AML stem cells, but not of normal haematopoietic stem cells[42]. Therefore, in the future it might be possible to rid a patient of all his or her cancer cells, including the cancer stem cells.

Selectivity and efficacy

In principle, signal-transduction therapy should have minimal side effects, because it targets kinases that are persistently active and have key roles in proliferation and survival of cancer cells, but not of normal cells. For this approach to succeed, the susceptible tumours must be identified. CML is exceptional in that all patients carry the *BCR–ABL* oncogene, so treatment with imatinib is effective. Other cancers are heterogeneous, so only a sub-group of a particular type of cancer is responsive to a given signal-transduction inhibitor.

Breast cancer is a case in point. The best-established case of tumour-tailored therapy is the use of tamoxifen, an oestrogen antagonist, to prevent recurrence of oestrogen-receptor-positive breast cancer. Tamoxifen has no effect on the occurrence of oestrogen-receptor-negative tumours[43]. About 30% of breast cancers overexpress the type 2 human EGF receptor ERBB2 (also known as HER2/neu). Trastuzumab (Herceptin), an antibody that targets ERBB2, is effective for some patients with ERBB2-overexpressing tumours, particularly when combined with chemotherapy. The additional factors that determine whether or not a given ERBB2-overexpressing cancer will respond to trastuzumab remain to be identified.

Lung cancer is another example where identifying the susceptible subgroup of patients can lead to successful therapy. Ten percent of patients harbour specific mutations in EGFR. These patients respond well to the EGFR inhibitor, gefitinib (Iressa/ZD1839). Their mutations, which do not activate cell-growth pathways, do activate the AKT and STAT survival pathways. In cancer cell lines, the mutant EGFR is an essential survival factor, and therefore its inhibition sensitizes the tumours to apoptosis[44–46]. Japanese patients, who had a better overall response to gefitinib in clinical trials, have a higher frequency of the responsive mutations than American patients[44].

A similar story can be told for imatinib. This drug is also used in the treatment of gastrointestinal stromal tumours (GISTs). Ninety percent of GISTs carry activating mutations in *KIT*, which encodes another tyrosine kinase that is inhibited by imatinib. These mutations are usually in exons 9 or 11, but the best clinical responses are obtained in those patients who carry mutations in exon 11 (REFS 47,48). We do not yet understand the molecular basis for this specificity.

Paradoxically, the more virulent the growth of a tumour, the more susceptible it might be to specific inhibition of its aberrant, overactive signalling pathways. Therefore, chemoresistant lung carcinoma cell lines expressing high levels of ERBB2 can be sensitized to chemotherapy by specific inhibition of ERBB2 (REF. 49).

Many kinase inhibitors are ATP-competitive. Given the strong homology between the ATP-binding domains of tyrosine kinases, it is not surprising that these inhibitors target groups of related kinases and are not overly specific. Inhibitors against less conserved regions of a kinase should be more selective. A novel inhibitor, ON012380, targets the substrate-binding domain of BCR–ABL. In preclinical tests, this compound was both more potent and more selective than imatinib, and it inhibited all of the imatinib-resistant versions of BCR–ABL identified to date[50].

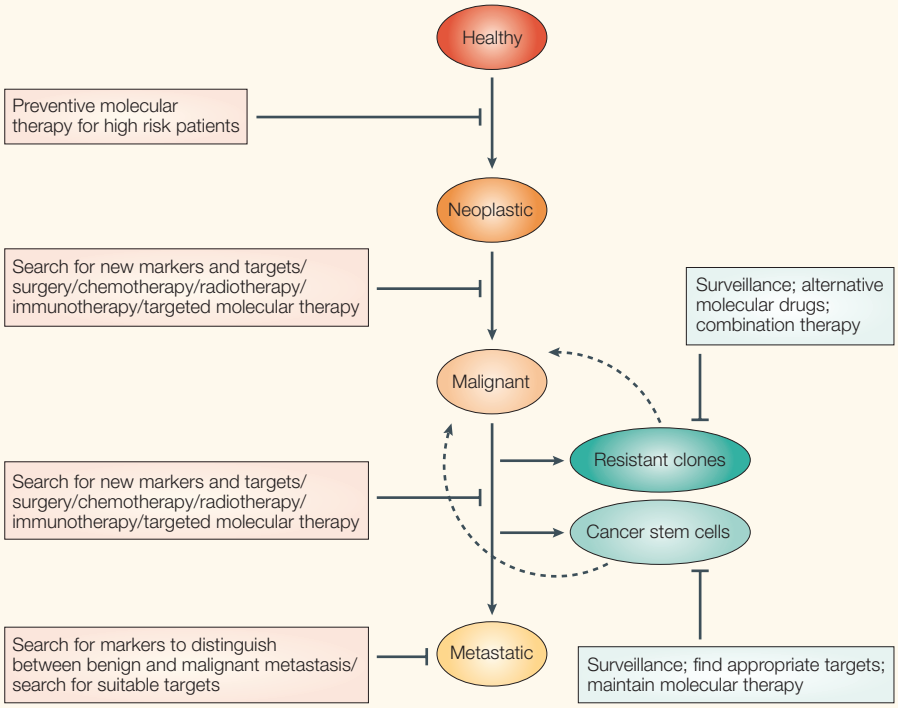

Figure 3 | **Cancer as a chronic disease.** Targeted molecular therapy has roles to play in prevention and treatment of cancer. Long-term treatment and novel drug cocktails should nip cancer stem cells in the bud and prevent the emergence of resistant tumours.

ON012380 acts synergistically with imatinib to inhibit BCR–ABL *in vitro*[50]. Combined therapy using both of these agents should minimize the emergence of resistant versions of BCR–ABL, as these presumably would have to acquire two mutations, in the ATP-binding and substrate-binding domains.

Exquisite sensitivity has been reported for a series of AKT inhibitors. The three isoforms of AKT have practically identical kinase domains and strong homology throughout the proteins, yet these inhibitors can distinguish between the different isoforms. These inhibitors target the PH or hinge domains of AKT, preventing activation or correct folding of the kinase[51,52].

Traditionally, it was thought that inhibitors should be as selective as possible, ideally targeting a single survival factor, in order to minimize toxic side effects. Recent studies indicate that this might not be true. Imatinib itself was originally designed as an inhibitor of the platelet-derived growth factor receptor (PDGFR) kinase[53], and was later found to target ABL[54,55] and KIT[56] as well. The small molecule BMS-354825 targets the active conformations of SRC and ABL kinases. BMS-354825 inhibits most but not all of the imatinib-resistant versions of BCR–ABL, and is currently in clinical trials for treatment of imatinib-resistant CML[57]. Although even less selective than imatinib, BMS-354825 appears to be less toxic. Similarly SU11248, which targets PDGFR, VEGFR, KIT and FLT3 (REFS 58–60), is doing so well in clinical trials to treat GISTs that Pfizer announced in early February that it is filing for Food and Drug Administration approval earlier than planned. SU11248 also shows efficacy against several other cancers, in which probably one or more of the kinases it inhibits are persistently active and have key roles in tumour development and survival. Selectivity could be less important for inhibitors that target a kinase in its active conformation, because this is the predominant form in cancer cells, whereas it is transient in normal cells[61].

Future prospects

Tumours are heterogeneous. Furthermore, every cancer is a constantly evolving entity. Therefore, there is unlikely to be a single 'magic bullet'. Combinatorial therapy is more likely to succeed than single agents. A more thorough understanding of the complex interactions between signalling pathways is necessary before we will be able to predict the effects of inhibiting specific targets, individually or in combinations. New drug cocktails that attack a few selected pathways will be developed. The old standbys of chemotherapy and radiotherapy are probably here to stay. Actually, they represent the first molecular approaches to curing cancer by inducing cell death. Combining specific and universal regimens of therapy will take advantage of our ability to inhibit the essential survival factors of a given cancer, thus sensitizing the cancer to lower doses of chemotherapy and reducing side effects.

The major cause of death for cancer patients are metastases. There is considerable evidence that metastases migrate to distant sites early, even before the primary tumour is diagnosed, but not all disseminated cancer cells develop into metastases. The characterization of individual metastatic breast cancer stem cells separated from bone marrow has recently been described[62]. In the future, it might be possible to determine the proliferative potential of disseminated cancer cells, and use this as a basis for choosing active treatment or surveillance. Similarly, it might be possible to predict which precancerous lesions are most likely to develop into malignant cancers, and which will remain benign and are best left untreated.

In 1971, President Nixon declared war on cancer. Despite an improved understanding of cancer development and some impressive advances in treatment, bona fide cures have been elusive. The biggest impact on reducing the cancer burden to public health derives from screening programmes that detect cancer early, or even in the precancerous state[63]. In this regard, it is encouraging that the National Cancer Institute is committed to developing new methods for early detection of cancer, and to discovering drugs that will pre-empt the malignant process[64]. With the advent of genomic and proteomic arrays, it is likely that molecular markers will soon be available for early detection of many cancers. Proteomics profiles of serum that detect ovarian, breast, prostate, and head and neck cancers have been reported[65]. It is important to find suitable markers for precancerous lesions and early, localized cancer and to develop inexpensive, robust technologies that can be used in the clinical setting. Some of these new markers will also be effective targets for signal-transduction therapy.

Molecular targeting has a role in prevention of cancer, as well as in its treatment. Tamoxifen has been shown to cut by half the incidence of breast cancer in women at increased risk for the disease, and is now offered to such women as preventive medicine[43]. Aspirin, a cyclooxygenase inhibitor, apparently reduces the incidence of colorectal cancer[66]. On the other hand, a proposed trial to test whether gefitinib

reduces lung cancer rates in heavy smokers with premalignant lesions has been deferred because of safety concerns[67]. Most of the current drugs cause side effects too harsh to warrant administering them to healthy individuals. Furthermore, a better understanding of which patients will benefit from which agents is needed. In time, better molecular drugs, with minimal side effects, will make their mark on reducing cancer incidence, alongside programmes to promote healthier nutrition and lifestyles. Some day, we shall learn how to eliminate cancer stem cells. Until that day, the best we can do is to remove or kill most of the cancer cells, and to tame the rest. With novel drug cocktails, long-term treatment and careful surveillance, we should be able to turn cancer into a 'chronic' disease that can be lived with (FIG. 3). A diagnosis of cancer will no longer generate the fear that it does today, the treatments will be less arduous, and patients will remain symptom-free longer. Nonetheless, the best investment towards reducing the human, social and financial costs of cancer will be to focus research on prevention and early detection.

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Competing interests statement
The authors declare competing financial interests: see web version for details.

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