*'What if there was a way to shorten the time between the identification of a compound as promising and the day it becomes available to cancer patients who can benefit from it?'*

# editorial

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## Can single-patient investigational new drug studies hurry slow trains to the fast track?

'The reasonable man adapts himself to the world; the unreasonable one persists in trying to adapt the world to himself. Therefore, all progress depends on the unreasonable man.'
–George Bernard Shaw (1856–1950)

In 1999, cancer surpassed heart disease as the cause of the greatest number of deaths in the USA among those under the age of 85, and it has held that distinction ever since [1]. Responding to various long-standing and growing pressures, the US National Cancer Institute (NCI) has declared its desire to 'eliminate the suffering and death from cancer by the year 2015', an ambitious goal indeed.

Unquestionably, one of the greatest opportunities to achieve the 2015 goal lies in the promise of the emerging molecular-target cancer therapies, which are increasingly augmenting or replacing systemic cytotoxic chemotherapy as the focus of researchers and clinicians. Recently released data on the targeted breast cancer therapy trastuzumab (Herceptin®) give powerful evidence that the hopes for great achievements from the targeted cancer therapies, so often expressed by so many, are not misplaced but have needed only time for hard data to confirm high expectations.

Herceptin® is a monoclonal antibody targeted against the HER2/neu protein that, when overabundant, makes 15–25% of breast cancers particularly fast-growing and poorly responsive to chemotherapy. Herceptin® cuts the rate of recurrence almost in half during the first year, when used following chemotherapy [2]. In combined data from two other studies, ~85% of patients given Herceptin® at the same time as chemotherapy were alive without recurrence at the four-year follow-up, compared to 67% of those getting placebo, a difference so large that study stopped early [3].

When given to the correct patient group, the targeted lung cancer drug gifitinib (Iressa™) shrinks tumors markedly and provides progression-free times with a median length of six to eight months [4], and up to two years [5] for those responding best, a stunning achievement for a drug with relatively few and mild side-effects compared with cytotoxic chemotherapy.

The continuing fulfillment of the promises of targeted therapies, and the better understanding of their principles, has led to large-scale plans to employ them further. The US National Institutes of Health (NIH) plans to sequence 12,500 tumor-cell genomes – 250 samples from each of the 50 most common types of cancer – in an effort to identify the most common causal mutations so that they can be targeted.

Others seek to offer doctors more incentives for molecular diagnostic tests, to have genetic privacy laws passed to protect from insurance discrimination, and to redesign clinical trials to include molecular diagnoses and early intra-trial tests that confirm a match of molecular target with effective inhibitor, and re-calibration if necessary. These valuable projects should be completed, but that will take a long time.

The *HER2/neu* gene was first identified as a potential therapeutic target in 1987, yet it was 1998 before Herceptin® was approved. Most drug candidates take longer than a decade to wind their way through the pipeline from design to market.

What if there was a way to shorten the time between the identification of a compound as promising and the day it becomes available to cancer patients who can benefit from it? History suggests that there is a way and that perhaps we should use it more often.

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The widely-hailed leukemia drug imatinib (Gleevec/Glivec®) is now used for a cancer very different in organ of origin from the chronic myeloid leukemia (CML) for which it was first approved. But that might never have happened without the efforts of an 'unreasonable' man, a Finnish oncologist named Heikki Joensuu. Well, maybe Joensuu was not so unreasonable at all. Maybe like the man George Bernard Shaw jokingly called unreasonable, he really was only unwilling to accept the medical status quo of the time.

The medical status quo of the time was that his patient would soon die. It was 1998 – advanced, metastatic gastrointestinal stromal tumors (GISTs) were then invariably fatal [6] and his patient's GIST was metastatic to the liver and ovary. Aggressive polyagent chemotherapy made no difference, nor did anti-angiogenic or immunostimulatory drugs. Joensuu found nothing in clinical trials for GIST that looked remotely promising.

The reasonable thing to do was to tell his patient, a 50-year-old woman, that he had exhausted the tools available, and that she should go home and put her affairs in order. But Joensuu simply was not reasonable in that particular way. He was unwilling to give up.

He knew preclinical work with a promising molecular target drug then under development – STI-571 – inhibited not only its main target, but also the gene product of mutant *KIT*, an aberration that had shown up in his patient's tumor in the pathology laboratory. Because KIT is a tyrosine kinase receptor, its mutant form might be constantly sending growth signals to the nucleus and so might be responsible for the growth of his patient's tumors. He decided to try to obtain the drug.

But STI-571 was then an investigational new drug (IND), only in Phase I clinical trials for leukemia, so unobtainable through normal channels – perhaps not available at all. Joensuu pushed ahead anyway, contacting the drug's maker, Novartis, and researchers working with the drug, explaining his thinking and his hope. It was not easy but ultimately, he was successful. With approval of his hospital's review board, he obtained the drug and got his patient's informed consent to participate in a single-patient study of the new drug.

In March of 2000, with her earlier metastases growing and new ones appearing, Joensuu began treating his patient. She received four 100 mg capsules of the drug daily. Within two weeks, her tumors had shrunk 40%. Eight weeks later, another 50% shrinkage had occurred. Eleven months after starting STI-571, a time when she otherwise would likely already have been dead, Joensuu's patient continued to respond to treatment, and was without clinical signs of cancer. The main side effects were mild transient nausea [6].

These results led researchers to approach the NCI in November 2000, and soon clinical trials of STI-571 against GIST were underway, accompanied by a large FDA 'compassionate use' program for those unable to participate in trials. STI-571, by then known as Gleevec®, was approved for use against GIST by the FDA in May 2001, two months after the results of the single-patient study were reported in the New England Journal of Medicine [6].

By that time, Gleevec® had been approved for CML for about a year. Joensuu's quest – and help from the FDA, Novartis and others – had cut huge chunks out of the time it would otherwise have taken for a drug effective against GIST to be identified, and for Phase I, II and III trials to be completed and the results collated.

This 'unreasonable man' – actually a very reasonable man, but a very determined, clear-thinking and bold one – had, with help, changed the course of medical history, prolonging and ultimately saving countless lives.

Recently, a Harvard team seeking the reason for acquired resistance to Iressa™ in non-small-cell lung cancer (NSCLC) cells conducted a study in one patient, resequencing the (epidermal growth factor receptor) *EGFR* gene in a new biopsy taken after resistance developed, and found a new mutation – the T790 mutation – was responsible [7]. A Wyeth compound, known only as CL-387,785, restored sensitivity to Iressa™ and stopped proliferation even when the new mutation was present.

However, a later study showed that some NSCLC cells proliferate independently of any known EGFR mutation, perhaps because of altered receptor trafficking inside the cell. Wyeth researchers tweaked the molecule and came up with a follow-up drug, called HKI-272, that inhibited NSCLC cell proliferation and killed the NSCLC cells regardless of the mechanism driving proliferation. In fact, in an effort to test the efficacy of HKI-272 against any other mechanism of proliferation, the researchers generated multiple clones and could not generate one that was not responsive to the drug [8].

Of course, it is early days, and HKI-272 has not yet been approved for lung cancer. But it is in Phase I testing for another cancer, as STI-571 was at the beginning of Joensuu's trek. That means it could be available through a cooperative compassionate use program allowing single-patient IND studies. The FDA allows such use in some cases, but says it is up to the drug company whether to make available any IND in development.

Wyeth's policy is not to facilitate such efforts until after a compound has shown efficacy in Phase II trials (personal communication). That seems to be a reasonable policy, and in practice it is similar to the policies often cited by other companies with drugs in development. But is it best? In correctly monitored single-patient IND studies, patients would run no greater risks than those in Phase I studies testing the drug for other indications. Efficacy data would be of significant value to the drug's developers And in any instances in which strong benefit became clear earlier than it otherwise would have – as happened with Gleevec® and GIST – the benefit to those patients would in turn become a benefit to the entire cancer community.

Perhaps it is time that drug companies, the NCI and regulatory bodies assisted more actively such patients to help them gain the chance to benefit themselves and others. Is that really so unreasonable, after all?

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