particles such as carbon ions, which transfer large amounts of energy, probably has a greater impact on some solid tumours in part because the ions damage DNA directly, rather than relying on the production of free radicals.

Delivering more oxygen to the tumour cells can thus reduce the impact of hypoxia on the effectiveness of radiotherapy. For example, if patients inhale carbogen—a mixture of 95% oxygen and 5% carbon dioxide—before treatment, their cells become oxygenated because the carbon dioxide elicits a suffocation response that increases heartbeat and breathing rates. This effect can be amplified further by administering nicotinamide, a drug that dilates blood vessels and increases oxygen delivery to cells. A clinical trial to improve radiotherapy against advanced cases of laryngeal cancer is already under way in the USA, testing a technique known as ARCON (accelerated radiotherapy with carbogen and nicotinamide).

In addition, molecular methods can also increase the sensitivity of tumour cells to radiation, in particular by targeting the oncogenes whose mutations transform normal cells into cancer cells in the first place. H-Ras, for example, is a growth factor that, when mutated, can cause cells to become cancerous; accordingly, there is potential for combining drugs that target this gene with radiotherapy, Brunner explained. "On the preclinical side our lab has shown that inhibition of H-Ras is sufficient to sensitise pancreatic cancer to radiation," he said. "This is of critical importance as the predominant mutation of pancreatic carcinoma is in K-Ras [90%]." According to Brunner, H-Ras, a membrane protein that transmits growth signals, is easier to inhibit than K-Ras because it requires blocking the activity of only one enzyme, farnesyl transferase, compared with two enzymes for K-Ras—although it will require more work to elucidate the exact mechanism.

The emerging radiotherapy techniques and technologies raise hope for patients with advanced or intractable cancers that have poor prognoses. Yet, these new weapons will not replace effective screening and early diagnosis, which can often render the more sophisticated treatments unnecessary in the first place. In practice, of course, early diagnosis is difficult to achieve, especially for less common cancers that present few if any symptoms until they have reached an advanced stage. It is for these that better and non-invasive therapies can make a difference for many cancer patients and their relatives.

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Lost in translation

The current focus on translating research into applications might be part of the natural cycle of research funding, but at what cost?

Kristen Minogue & Howard Wolinsky

Canadian biochemist Dennis Vance has always known that his research on phosphatidylcholine biosynthesis is relevant to human health because it focuses on low-density lipoprotein, the transporter of so-called 'bad' cholesterol and the 'culprit' behind heart disease and stroke. Now, Vance says, work in his field is also proving to be unexpectedly relevant to obesity, type-2 diabetes, muscular dystrophy and bone disease. This ought to be good news for him, as his laboratory at the University of Alberta (Edmonton, AB, Canada) might attract more funding for clinically relevant research. Yet, the growing emphasis on translational research—the *nom de jour* for taking basic research towards applications—in North America and Europe is making Vance uneasy. "I am not opposed to Translational Research but I am getting tired of hearing that phrase," he wrote in an editorial for *Biochimica et Biophysica Acta*, of which he is Editor-in-Chief. "[A]ll this discussion about translational research often fails to recognize that it is the basic, curiosity-driven research on which eventual translational research depends. If there is no innovative fundamental research, there will be nothing to translate" (Vance, 2009).

According to Vance, the reason for the emphasis on translation is simple: "The politicians who set the priorities [are] not happy with the rate of cure of disease" he said. In this regard, Francis Collins, Director of the National Institutes of Health (NIH) since August 2009, has said that he plans to make translational research a priority for the NIH in the coming years. It has already been a part of the NIH roadmap since 2003, when former Director Elias Zerhouni brought it to the forefront of the organization's agenda. The creation of the Clinical and Translational Sciences Award (CTSA) programme in 2006, to take "discoveries in the laboratory and turn them into treatments and strategies for patients in the clinic," turned his vision into reality. The programme, which has an annual budget of US$500 million, currently includes 46 member institutions with plans to expand the network to 60 centres nationwide in 2012; although it only accounts for just over 1% of the total NIH budget—approximately US$442 million of the US$30 billion proposed for 2010. It helps institutions to set up their own centres for translational research and to train students for careers in this burgeoning field. Grants usually last five years and can range from US$20 million to US$100 million.

> **"If there is no innovative fundamental research, there will be nothing to translate"**

In Europe, the situation is different; there is no centralized federal government to distribute funds. Nevertheless, there has long been an emphasis on funding translational research by the European

Commission (EC), although funding from the EC only complements the national science budgets of European Union member states. The EC money represents about 5% of the total funding available for research in Europe, which Manuel Hallen, head of medical and public health research at the European Commission's Directorate for Health Research (Brussels, Belgium), described as "the icing on the cake." He said that about half of the €6.1 billion EC science budget that came into effect in 2007 was targeted to translational research, 30% into basic research and the remainder to public health. As he pointed out, "The European Parliament has a very strong say in where to put the money, and people want to see an outcome [so] it has an impact on the current discussion for the health services."

Philip Greenland, Senior Associate Dean for clinical and translational research at Northwestern University (Chicago, IL, USA)—which received a five-year US$30 million grant under the CTSA programme—also noted that the public and politicians have become increasingly dissatisfied with the pace of science. "Certainly lots and lots of research is going on, but possibly legitimate questions are being raised as to what is the payoff of all of this interesting research," he said. He pointed to the frustrating, nearly 40-year "War on Cancer" declared by US President Richard Nixon, which has left the public wondering "about all of the money that [has] been spent over many, many years on cancer research and still [there are] many, many cancers for which it's not really apparent there have been major advances."

…many European scientists still question whether the current emphasis on translational research is a prudent strategy…

He said that the CTSA has enabled Northwestern to take an interdisciplinary approach to research to foster translation of results. Instead of leaving scientists conducting basic research isolated in their own fields, the university encourages interaction across disciplines. As Greenland pointed out, "the tendency within a given discipline is to keep going in deeper and deeper and deeper to the basic understanding of the problem […] It's only when you start [to] look across, outside of your discipline, that it starts to occur to you that there might be an application of your work beyond the kinds of things that you worry about all the time."

A CTSA grant is also helping Melina Kibbe, a vascular surgeon at Northwestern Memorial Hospital (Chicago, IL, USA), to create an artificial artery graft for patients with vascular health issues. Kibbe said that receiving the grant was crucial to her research. "[The programmes] are absolutely beneficial to young investigators, because it's the young investigators who don't have the grants yet and don't have the money to be able to get their projects off the ground," she said. "So young investigators need seed money programs like this."

For Vanderbilt University (Nashville, TN, USA), a US$40 million CTSA meant that the institution could smooth out often-paralysing snags in its review system, which tied up researchers for months in red tape. Principal investigator Gordon Brown said that investigators at the university might have to get approval from as many as 18 different groups before they can begin their studies. "[I]n some cases it's downright the destruction of somebody's research career," he said. "Because if it takes too long to go through this process, they have no time to actually go and recruit patients and conduct their studies."

The award has allowed Vanderbilt to set up a Research Support Services office, with a staff of six people whose sole job is to answer questions from researchers about how to start their projects. The team has developed software that allows investigators to enter their project proposals, receive a list of departments with which they will most likely need to interact, and obtain copies of the forms that they will probably need to complete. Although it does not remove the red tape, it makes navigating the proposal process faster and more efficient.

Although some researchers fear that support for translational research might inevitably come at the expense of basic science funded by the NIH, the evidence suggests that the CTSA programme is actually competing with General Clinical Research Centers (GCRCs), which focus on producing new medical applications, health studies or other research that might not lead directly to cures. Indeed, a few institutions that formerly received GCRC grants from the NIH are now converting to CTSA grants.

As Anthony Hayward, NIH Director of the Division of Clinical Research Resources, who oversees the CTSA programme, commented: "We decided in 2005 that our GCRCs were not really providing resourceful research that was needed, and we also felt that there wasn't enough interaction between the NIH and what GCRCs did." In order to finance a US$20 million increase for the CTSA programme in this year's proposed NIH budget, the National Center for Research Resources—a part of the NIH that directs funding for laboratory scientists—had to divert more money away from general clinical research, which has seen steadily decreasing funds since CTSA came into existence.

…one of the reasons for the slight decline in support for basic research is that as little as one per cent of it is developed into licensed applications

Although the EC has always had a strong focus on funding translational research, many European scientists conducting basic research apparently worry about a change in general funding priorities. As Hallen commented, "[basic researchers] are a bit scared that the funds are drifting away from basic research [because there is now] a general note to place more emphasis on translation. [But] at the end of the day [the public] want to see some tangible results." Nevertheless, he pointed out that government funding for basic research is actually something of a new idea. "If we go back to the origins of these European programmes, […] there was hardly [any provision for] basic research in the health sector. They were much more [focused] on epidemiology," he said. "So it goes in waves. A lot [of money] was heavily invested in the days of the human genome sequencing [project] and [for the] sequencing of all sorts of organisms. But now we are in the days of translation. And I'm more than sure that one day we will come back to more investment into basic research."

Yet, many European scientists still question whether the current emphasis on translational research is a prudent strategy, and in particular, if this focus comes at the expense of basic science. Among them is André Goffeau from the

Catholic University of Louvain (Louvain-la-Neuve, Belgium), who made his reputation as a scientist conducting basic research on yeast and sequencing the yeast genome—work that became a model for sequencing the human genome. Goffeau, now retired, said that he was pleased by the recent EC approval of an additional €1 billion funding for basic research, but commented that this sum is still "very minor compared to the biotechnology programme and the biomedical programme."

…proponents of the translational approach say that it creates an important bridge between basic science and clinical therapies

Increased funding for translational research, which could potentially take funds away from basic research, has alarmed Goffeau over the past decade: "I think it's wrong," he said. "It's obvious to me, for instance, that translational research will not cure or speed up the cure of cancer." He explained that the limiting factor in curing cancer and other diseases is that we still do not have a full understanding of the mechanisms that cause the disease, and that science will advance through curiosity-driven research, rather than top-down, short-term applied science. "I think [translational research] should be funded by the companies and those who could make money from it, but not from public funding," he said.

Carol Greider, joint recipient of the 2009 Nobel Prize in Physiology or Medicine—for her work on telomerase—and Director of the Department of Molecular Biology and Genetics at Johns Hopkins University (Baltimore, MD, USA), said that her own research demonstrates the value and unpredictability of basic science because scientists "don't know where the next most interesting findings are going to come from." She added that although basic research is taking a financial hit in the recession, the same is true for translational research. "The NIH has always supported really basic science. And the trouble is that anytime money gets tight, it gets tight [for] everyone," she explained. "When the people [who] are doing disease-targeted research also aren't getting their grants, and the basic scientists aren't getting their grants, of course the basic scientists are going to feel a little bit put upon that they have to go to such [lengths] to justify why they're doing it. So I think it really has to do with the overall stress on the whole system when money gets tight."

Whatever its cause, the current tug-of-war between translational and basic research simply reflects the longer conflict between basic and applied science

Goffeau acknowledged that one of the reasons for the slight decline in support for basic research is that as little as 1% of it is actually developed into licensed applications. "It is true that the output is weak. But is [this] due to the fact that basic research has been insufficiently funded […]?" he asked. "[L]ife is just so complex. But can this be solved by just funding more translational research?" He added that his own basic research on yeast has not yet resulted in medical applications, and that sequencing the human genome has yet to deliver translational results. Nevertheless, he pointed out that drugs and vaccines are likely to come from these projects: "It's just a matter of patience."

Still, proponents of the translational approach say that it creates an important bridge between basic science and clinical therapies. "The number of basic science discoveries is now so huge that it's like an ocean of ideas that have been put

out there in the literature," commented Lars Bo Nielsen, who has undertaken both clinical and basic research at the University of Copenhagen in Denmark and its associated hospital. He pointed out that, "there [are] a lot of good ideas that could be potentially extremely useful for patients, but getting them into the clinic is really the tough part."

In the same vein, Liselotte Højgaard, chair of the European Medical Research Councils, thinks that focusing more attention on clinical research allows basic researchers to learn about the issues facing patients, which can help them to direct their own work. "I think it's important for basic science to get the right ideas so that they know what is relevant for patients, and I think from this […] fruitful intellectual exchange, […] they can get a lot of interesting ideas," she said.

Whatever its cause, the current tug-of-war between translational and basic research simply reflects the longer conflict between basic and applied science. For Gregory Petsko, a biochemist at Brandeis University (Waltham, MA, USA), the use of the terms 'translational' and 'basic' is rather counterproductive—the two are simply different sides of the same coin: "We should stop talking about translational versus basic research and start talking about research," he said. "[We should] make it clear that every type of research is important towards achieving our goals; our goals being happier people and healthier people and a better society […] Why can't we seamlessly move from one set to the other without believing that we're crossing some kind of divide?"

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