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"Whenever a new facility opens, it is immediately swamped," said Lester Peters, M.D., chair of radiation oncology at Peter MacCallum Cancer Institute in East Melbourne, Victoria, Australia, who was not involved in the report. He attributed the lack of adequate facilities to the absence of a cohesive plan between federal and state government, with inadequacy of resources extending to staffing and training.

The report also asserts that there is an unmet need for radiation therapists, physicists, and radiation oncologists and a dearth of training programs nationally. The analysis links the numbers of staff needed to the population. High numbers of unfilled positions for physicists and therapists mean that staffing is inadequate to meet current needs, according to the report.


Dr. Lester Peters

Burton pointed out that Australia does not have a national cancer control program akin to what the World Health Organization recommends. He also noted that searches for qualified personnel in the United Kingdom and Canada will make it even more difficult to fill vacancies in Australia.

Separate Government Inquiry

A second, separate government inquiry also has infuriated some in the radiation oncology profession. It is [illegible] the same issues that the profes-

ing to Burton, "the terms of reference of the second inquiry" are to review and make recommendations concerning workforce, training, funding, patient access, and national standards for services and facility accreditation.

The second panel will also be charged with making recommendations on how the Commonwealth, the states, and private industry can collaborate and implement a nationwide strategic plan. The inquiry will begin next month and report its findings and recommendations to the federal government, probably in mid-to-late 2002.

'A Very Clear Problem'

Burton commended the reach of the profession's strategic plan, acknowledging that it put forward "a lot of evidence, predictions, useful lifespans of equipment, and it pressed the training issue." He too maintained that there is "a very clear problem in manpower planning." One weakness is that the profession's report "did not include health economists or research analysts, nor it spell out priorities or timelines."


Dr. Liz Kenny

He was not surprised that the new government inquiries have eclipsed the profession's report. The government could not move on the profession's report, observed Burton, because "they are inside the box."

Rapamycin's Resurrection: A New Way to Target the Cancer Cell Cycle

CCI-779, a close analogue of rapamycin, has shown activity against a wide range of cancers in preclinical models and in phase I trials, and seven different phase II trials are under way. Some suggest that it may be one of the most promising drugs in the anticancer pipeline.

"I'm excited," said Charles Sawyers, M.D., of the University of California at Los Angeles Jonsson Comprehensive Cancer Center. "It's a safe drug, it's very precise in its action, it's definitely a targeted therapy."

The cancer research community is only now becoming aware of CCI-779. But it is hardly new. The parent drug, rapamycin, was discovered 30 years ago, and its activity against cancer was revealed back in the mid-1970s. All of the research on rapamycin, the very first "cytostatic" agent, nearly fell by the wayside, but it was resurrected by a single determined individual.

Rapamycin is a natural compound produced by bacteria that were found in an Easter Island soil sample around 1970. ("Rapamycin" comes from Rapa Nui, the native name for Easter Island.) "We had the notion we were dealing with something novel," recalled Suren Sehgal, Ph.D., then senior scientist at Ayerst Research Laboratories in Montreal, where rapamycin was isolated in 1972.

Ayerst began developing rapamycin as an antifungal drug, but soon realized it also suppressed the immune system. That killed it as an antifungal, but

National Cancer Institute for testing. "They found absolutely fantastic activity of the drug against almost all solid tumors," said Sehgal. In combination with chemotherapy, "the anticancer effect was absolutely astonishing."

Rapamycin was quickly designated a priority drug by the NCI. "It was a totally new class of anticancer agents we were looking at—cytostatic," said Sehgal. "To that point they were all cytotoxic agents."

But disaster soon struck. As Ayerst researchers (and academic scientists) were struggling to develop an intravenous formulation for use in clinical trials, company management made a fateful decision. To consolidate research facilities, in 1982 it shut down the Montreal laboratories, laid off 95% of the workforce, and sent the remnants to Princeton, N.J. The rapamycin program was aborted. At the time, the notion of blocking signal transduction was completely novel and untested.


Dr. Suren Sehgal

"For all practical purposes, rapamycin was a lost cause," recalled Sehgal. "It was abandoned by Ayerst as a drug candidate." NCI, without a source for the drug, was helpless to proceed. All work halted.

For 6 years, rapamycin was forgotten. But Sehgal never gave up hope. In 1987 American Home Products merged its two drug subsidiaries, Wyeth and Ayerst, and new management took over. In May 1988, Sehgal sent a memo about drug out for animal testing. Outstanding results convinced Wyeth-Ayerst to resurrect the drug as an immunosuppressant. Sehgal contacted the NCI, and anticancer work resumed.

Rapamycin gradually regained momentum. Wyeth-Ayerst synthesized and tested hundreds of rapamycin analogues, both to stay ahead of competitors and to extend patent life. The best one was CCI-779. When it was run through the NCI's standard 60-cell line screen, "we found that it was broadly active against a wide variety of tumor types," said Jay Gibbons, Ph.D., assistant vice president for oncology research for Wyeth-Ayerst.

More importantly, it seemed to work by a completely novel mechanism. "It didn't really look like any other drug in the cell line screen," said Janet Dancey, M.D., a senior clinical investigator in the NCI's investigational drug branch. "Its pattern of activity was unique."

Researchers in academia and industry, in the meantime, were deciphering rapamycin's effect on the cell. Working in yeast, Michael Hall, Ph.D., of the University of Basel in Switzerland, cloned rapamycin's molecular target, dubbing it TOR ("target of rapamycin."). "A beautiful series of experiments," commented Sawyers. Others found its mammalian homologue, mTOR. Meanwhile, Jon Clardy, Ph.D., of Cornell University, Ithaca, N.Y., described how rapamycin inhibits mTOR and blocks its phosphorylation of downstream proteins that control translation of key cell-cycle mRNAs.

Then the last, crucial piece fell into place. In 1997, Ramon Parsons, M.D., Ph.D., of Columbia University cloned PTEN—a new tumor suppressor gene. PTEN, which is mutated (and presum-

cancers and endometrial cancers and in perhaps 20% of metastatic prostate cancers, regulates a critical cell signaling pathway involving a versatile protein called Akt.

In the last few years, Sawyers, Parsons, and others have placed mTOR downstream of Akt, suggesting mTOR's central importance and providing a convincing rationale for the activity of CCI-779 against so many tumors. Finally, three groups showed last summer that mutations in PTEN make tumors especially vulnerable to CCI-779.


Dr. Charles Sawyers

The PTEN link is a clear invitation to apply pharmacogenetics, the much-talked-about but seldom practiced tailoring of cancer therapy to patients' individual tumor genetics. Though tamoxifen is given to estrogen receptor-positive breast cancer patients and Herceptin to those with breast tumors overexpressing the erbB2 receptor, no drug is yet linked to a gene that is mutated in many cancers.

"You want to at least test the hypothesis that cancers that are 'PTEN null' should be the ones that respond the best," said Sawyers. "That's the next step." In most of the phase II trials, patients' tumors will be analyzed for PTEN mutations. It is possible that phase III might include only these patients. "If we see a strong predictive pattern, we could design phase III to limit enrollment," said Dancey. "It re-

Molecular profiling downstream is also crucial. In several trials, mTOR's two chief targets are being checked for phosphorylation status—the hallmark of biological activity—in patients' tumors. "If we just enroll 50 patients with whatever cancer, I would not be surprised if we see a response rate of maybe 10% or 20%," said Sawyers, who argues for the widest possible molecular profiling to learn how to improve that percentage.

Sawyers is planning a CCI-779 prostate cancer trial monitoring Akt. "If your patient's tumor has a high level of Akt phosphorylation, then that [patient is] the perfect candidate for this kind of treatment, if the model is right," he said.

Although labor-intensive and expensive, this work is necessary to later select patients and dose, agreed Manuel Hidalgo, M.D., Ph.D., assistant professor at the University of Texas Health Science Center in San Antonio. "We need to be able to profile who is who in that mass of tumors," he said.

In a phase I study of CCI-779, Hidalgo reported several cases of tumor regression. "It was a surprise to everybody," he commented. "We were expecting cytostasis."

Dr. Jay Gibbons

But combination therapy seems to be the best use for CCI-779, as for other cytostatics. "It's probably a little unrealistic to expect a drug with this mechanism of action to result in out-and-out cures or outright regression of tumors," said Gibbons. The main side effect, immunosuppression, is mostly avoided through intermittent dosing.

Given the importance of the mTOR signaling pathway, why does CCI-779 have so few other side effects? Perhaps normal cells find alternate signaling pathways, while cancer cells rely on this one. "There must be some redundancy of signaling [in a normal cell] that allows it to tolerate no mTOR activity," speculated Sawyers. But in cancer cells, "when you add the rapamycin, there's no backup. And—Boom!—You get a therapeutic effect."

CCI-779's uniqueness is its biggest advantage. "To date, there has not been another drug that attacks this pathway," said Gibbons. Now, after 30 years, that's changing. "Novartis is trying to develop mTOR inhibitors," said Sawyers. "Every major pharma and a lot of biotechs are going after Akt [and] PI3 kinase… Everyone thinks this pathway is important."

—Ken Garber

Rapamycin May Prevent Post-Transplant Lymphoma

Non-Hodgkin's lymphoma is a dreaded complication of organ transplantation. For kidney transplant patients, the risk of lymphoma is 37 times higher than for the general population in the first year after surgery, and for heart transplant patients, it is 155 times higher. Lymphoma is so common after transplants that a new disease term, Post-Transplant Lymphoproliferative Disorder (PTLD), was coined to describe these virulent cancers, of which about 70% prove fatal despite treatment—most within 1 year of diagnosis.

The cause of PTLD is thought to be drug-induced immunosuppression, which allows activation of latent Epstein-Barr virus, which immortalizes infected B cells and sets the stage for malignancy. The widely used immunosuppressants cyclosporine and FK506 are especially dangerous. But rapamycin, an immunosuppressant approved in 1999 by the FDA for kidney transplantation, might help reverse the PTLD scourge.

At the joint annual meeting of the American Society of Surgeons last May, Manikkam Suthanthiran, M.D., of Cornell University, reported that cyclosporine and FK506 increased the number of metastases in several mouse models of organ transplantation, but that rapamycin blocked metastases. "If that observation holds up statistically, I think it will argue very much in favor of more broad use of rapamycin in the transplant setting," said Jay Gibbons, Ph.D., assistant vice president for oncology research for Wyeth-Ayerst, which markets rapamycin. "That's a clear-cut advantage."

Rapamycin is newly approved, so it will be many years before the drug's PTLD-preventive effect (if any) becomes clear. But the National Cancer Institute is sponsoring a phase II lymphoma treatment trial of the rapamycin analogue *CCI-779* (see main story). Success would imply that rapamycin indeed can prevent the devastation of PTLD.