



Herceptin, the first marketed personalized medicine, was approved using a coordinated drug/diagnostic approval process that will become more common.

the firm to perform fewer and smaller trials for Iressa, its nonsmall cell lung cancer therapeutic, than the 2,000-person phase 3 trials, which cost hundreds of millions of dollars. "We know Iressa works in some patients [specifically females and nonsmokers] better than others, but we need help understanding the pathway," says Arbutk.

Still, an easy strategy for validating biomarkers has yet to be established. After-the-fact demographic analyses are currently the most common for identifying biomarkers, but this strategy is crude and inefficient and there is often no science to back up the resulting correlation. Preclinical validation of biomarkers would be ideal, but this is often unrealistic considering the infancy of pharmacogenomics.

Although there are various biomarker identification projects taking place in academia and with the support of the FDA and the National Cancer Institute (Bethesda, MD, USA; *Nat. Biotechnol.* 21, 718, 2003), skeptics say the only way to truly validate a biomarker is during large clinical trials. For example, Genentech's (S. San Francisco, CA, USA) Avastin showed promise in phase 2

trials for at least four types of cancer, but the drug failed to reach its primary endpoint in at least one phase 3 trial for breast cancer.

If determining the proper indication for Avastin, which has a known target in a

validated pathway (see page 15), is problematic until phase 3 clinical trials, then how reliable can other cancer biomarkers be? Spiros Rombotis, CEO for Cyclacel (Dundee, UK), believes the key is tailoring techniques that measure cell death to match the drug's mechanism and molecular effects. For example, inducing apoptosis is different from directly killing cells via radiotherapies or starving a cell with angiogenesis inhibitors. One of the methods used by Cyclacel is an ELISA-based biomarker to measure caspase 3-dependent apoptosis induction in solid tumors, and this allows the firm to confirm that tumor cell death is due to apoptosis induced by its drugs.

Rombotis also says pharmacodynamic biomarker validation in phase 1 will help clinical researchers design phase 2 trials by allowing more confidence in giving appropriate doses to ensure the death of tumor cells without causing unnecessary toxicity. "Modern mechanism-based cancer drugs often fail because of toxicity in high doses, whereas lower doses might be sufficient for them to be effective in certain populations," explains Rombotis.

The FDA seems ready and willing to work with the increasing number of firms that generate pharmacogenomic data, based on its recent pharmacogenomics guidance and decisions concerning molecular diagnostics (*Nat. Biotechnol.* 21, 1423, 2003). As Richard Pazdur, director of oncology drug products at the FDA, says: "It's not about drug approval; it's about drug development."

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Chile launches policy to boost biotech

Alvaro Díaz, Chile's deputy economy minister, presented the country's national policy, called "Biotechnology as a tool for development and wellbeing," in a ceremony attended by President Ricardo Lagos on November 18. Although the proposal presents a rational approach to using biotechnology to make more competitive the existing strong sectors of Chile's economy, critics say scientists, many of whom are against the commercialization of scientific research, need to change their attitudes, and bureaucracy must be reduced before the policy can be successful.

The policy sets out four main objectives: updating laws that concern biotechnological activities, creating an overarching regulatory body, developing scientific and technological capacity, and promoting entrepreneurial inno-

vation in biotechnology. To achieve these goals, the government will introduce a biotechnology framework law to parliament in May 2004.

If the law passes, a coordinating Public Biotechnology Regulations Committee will define the role of public institutions responsible for the impact of biotechnology. For example, the Health Ministry, Agriculture and Livestock Service and Environment Commission will have increased enforcement powers for the oversight of genetically modified products. Meanwhile, the proposal suggests the creation of a permanent and independent Biotechnology Forum to be consulted on any proposed biotechnology norms and charged with promoting public debate.

But one of the key measures is designed to strengthen entrepreneurial spirit among

Table 1 Examples of consortia between exporting industries and the biotechnology sector in Chile

Members of consortium	Investment	Focus
BioSigma (Santiago): a biomining consortium built by Codelco (Santiago) and Nippon Mining (Tokyo)	\$ 2 million	Genetic engineering of lixiviating bacteria, which allow biological extraction of low-grade reserves of copper.
A genomics consortium that involves the following Santiago-based organizations: the National Commission for Science and Technology, the National Institute of Agricultural Research, the Chilean Exporters Association, Chile Foundation, Fruit Development Foundation, Life Science Foundation, and five Universities: Chile, Santiago, Catholic of Chile (all in Santiago), Talca University (Talca), and Federico Santa María Technical University (in Valparaíso)	\$ 3.5 million	Plant genomics projects to combat fungal rot, improve quality and delay ripening in varieties of grape and nectarine.
A silviculture consortium with Fondo de Desarrollo e Innovación (Santiago), Instituto Forestal (Santiago) and Austral University of Chile (Valdivia)	\$190 million	Cloning technology is now used to improve the productivity of forest plantations, in particular the 'raul' tree.
A fish farming consortium involving Bioschile (Santiago)	*	Production of vaccines against <i>Piscirickettsia salmonis</i> , a bacteria that affects salmon, and diagnostic kits for fish farming.

* unavailable

Chile's biotechnology researchers. Specifically, the policy plans to boost the use of biotech processes in industries that depend on natural resources—principally mining, forestry, fisheries and fruit production—which account for 75% of Chile's exports. "This is where the country's scientific capacity has developed most and this is where the greatest potential for biotechnological R&D lies," says Díaz.

The government believes Chile can attract foreign investment by setting up consortia between firms in Chile's most profitable export sectors and biotechnology companies. For example, Biosigma is a \$2 million alliance between Chile's state copper mining company CODELCO (Santiago) and the Japanese company Nippon Mining (Tokyo) to invest in biological extraction of metal using genetically modified bacteria—a process called bioleaching (see Table 1).

Alfredo de Ioannes, director of the immunological drug discovery company Biosonda (Santiago), says the existing scientific capacity in Chile is so small that the government is obliged to try and attract foreign investment and scientists. But "the fostering of entrepreneurship depends more on the existence of a market than on government incentives, which corroborates Chilean authorities' decision to concentrate on the industries [at which] they excel," says João Paes de Carvalho, executive director of the Brazilian Biotech Enterprises Association (Rio de Janeiro).

Although the government has not yet defined the criteria of the new policy, companies can expect state funding if they are prepared to invest in R&D themselves. Mario Roseblatt, director of the nonprofit organization Life Science Foundation (Santiago) and who has been involved in setting up the policy,

says the favored formula would require the state to match private investment in biotech R&D spending, as it did for Biosigma. He believes the proposed consortia present a realistic way forward: "Given the backward state of biotechnology in Chile, any attempt to develop it needs to be very well focused."



Chilean President Ricardo Lagos and Eric Goles, president of the National Commission for Science and Technology, at the launch of the new biotech policy in the laboratories of the company BioSigma.

However, some are concerned that the concentration of large consortia threatens to marginalize emerging small and medium companies. "The concerns of local biotech companies are insufficiently reflected in this document," says Mónica Acuña founder of DNA analysis company Genética y Tecnología (Santiago). "They are looking for innovation, but the young researchers most likely to provide it will be excluded by the bureaucratic requirements for evidence of capital and [of] previous profits," she argues.

And de Ioannes thinks there is a cultural reticence behind the failure to embrace biotechnology wholeheartedly. "Twenty years ago

biotechnology was seen as the prostitution of science and the universities traditionally had a poor relationship with the commercial sector. So we simply imported technology and exported raw materials."

Yet, as part of the new policy, the government is planning to increase recruitment in biotechnology R&D, which should help change people's attitude towards the sector. "By 2006, the government plans to reach at least 1% of [Gross Domestic Product] in science and technology spending and especially in biotechnology funding," says Díaz. This represents an increase of 25% on current investment in biotechnology R&D, which is about \$380 million. However, the policy document is unclear about how to achieve this goal and delegates the task to a commission, suggesting they consider increasing taxes.

But further changes will be needed. "Our tradition is as good administrators. Now we need to add innovation and creativity," de Ioannes adds. To foster innovation, the government's policy recognizes the need to improve the protection of intellectual property rights. Patenting procedures will be introduced into science education, scientists will benefit from financial incentives to apply for patents, and successful patent applications will be recognized for academic promotions.

That the Chilean government has made biotechnology a national priority is a fundamental step forward. "As in many countries, the grand design of these kinds of 'national policies' is hindered by petty bureaucracy and conflicting regulations," says Carvalho. "If Chilean biotech policy can escape these pitfalls, it has a good opportunity to impact the country's competitiveness."

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