

IN brief

Four rebuffs for Cabilly

The saga over the validity of Genentech's widely licensed recombinant antibody patent, Cabilly 2, inched forward in late February when the US Patent and Trademark Office (USPTO) rejected it officially for the fourth time (though two were partially withdrawn). The patent covers a fundamental method of using host cell culture to make therapeutic antibodies; in 2007, it generated \$133 million for Genentech, of San Francisco. Genentech can respond to the rejection, then appeal the decision to the patent office's board of appeals and later to the courts. Cabilly 2 remains valid until the end of the proceedings, which could take up to a decade. The legal costs are trivial compared with the licensing revenue, so the company has every reason to continue fighting. The rejection may be the USPTO's most thorough response to Cabilly 2 since the start of its re-examination in 2005, meaning that "Genentech has some work to do here to overcome this," says Ivor Elrifi, co-chair of intellectual property at Mintz Levin in Boston. The USPTO argues that Cabilly 2 is a variation of the art described in a number of earlier patents, including Genentech's Cabilly 1. While there are some in the industry who perceive Genentech as having an unfair monopoly with its Cabilly patents, others suggest the ruling is a sign that the patent office is increasingly rejecting patents based on prior art. (*Nat. Biotechnol.*, **25**, 699–700, 2007.) For example, Alice Martin, a partner at Barnes & Thornburg in Chicago, says the decision could "backfire on biotech companies."

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India's IP snub

The Indian government is challenging the patent legitimacy of two more big-selling biotech drugs. On February 28, the Indian patent office began reviewing a plea from Natco Pharma of Hyderabad, India to produce generic versions of two patent-protected oncology drugs under compulsory license (CL)—Tarceva (erlotinib) owned by Roche, of Basel, and partners OSI, of New York, and Sutent (sunitinib), produced by New York-based Pfizer. This has happened before, as authorities refused in 2006 to uphold the patent on leukemia drug Glivec, held by Novartis, also of Basel, on the grounds that small tweaks should not extend patent life. Roche has now lost its case against Cipla, of Mumbai, India: on March 19, the Delhi High Court ruled Cipla could continue to sell its generic version of Tarceva. "Being a tweaked version [-] Tarceva's patent is invalid and at \$120 per tablet it is unaffordable. I can sell it for \$20," says Cipla managing director Yusuf Hamied. The Natco case invokes recently introduced CL rules, granted for use in urgent or emergency situations, and Natco wants to produce the drugs for export to Nepal. If permission is granted, it may trigger a slew of CL applications from other companies, says Mohan Nair, Chennai-based patent consultant to pharmaceutical companies. This will surely make multinational drug companies "think twice" before investing in India in research and development, he says.

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Table 1 Marketed osteoporosis drugs

Marketer	Product	Class	Indications	2007 sales (\$)
Eli Lilly	Evista (raloxifene)	Selective estrogen receptor modulator (SERM)	Osteoporosis, breast cancer prevention	1.09 billion
Eli Lilly	Forteo (teriparatide)	Recombinant parathyroid hormone	Osteoporosis	709 million
Merck	Fosamax (alendronate)	Bisphosphonate	Osteoporosis, Paget's disease	3 billion
Novartis	Reclast (zoledronate)	Bisphosphonate	Osteoporosis, Paget's disease/	41 million ^a
	Zometa (zoledronate)	Bisphosphonate	Oncology	1.3 billion
Procter & Gamble, Sanofi-Aventis	Actonel (risedronate)	Bisphosphonate	Osteoporosis, Paget's disease	NA
Roche, Glaxo-SmithKline	Boniva (ibandronate)	Bisphosphonate	Osteoporosis	1.1 billion
Servier	Protelos ^b	Strontium malonate	Osteoporosis	€99 (\$152) million

^aLaunched in the US in September 2007; limited European launch in October 2007. ^bNot approved in US figures for 2005/2006 fiscal year. NA, not available.

Most osteoporosis therapies act by inhibiting osteoclast-mediated bone resorption (Table 1). Although they prevent further bone loss, they also inhibit new bone formation, as osteoblasts fail to receive the correct activation signals (Box 1; Table 2). Denosumab has the same shortcoming, as it also works by reducing osteoclast activity. The therapeutic rationale, however, is that because in elderly patients new bone formation is minimal, it is less important than stopping excessive bone loss.

Pitted against the dominant bisphosphonate class—and its latest generation of long-acting agents, such as Basel-based Roche's Boniva (ibandronate) and Basel-based Novartis' Zometa (zoledronate)—denosumab, produced using XenoMouse transgenic mice technology licensed from Fremont, California-based Abgenix, has a more precisely targeted mechanism of action. The mAb binds a soluble protein produced by osteoclasts, the receptor activator of nuclear factor kappa B ligand (RANKL), normally responsible for triggering osteoclast differentiation, activation and survival. Preliminary evidence suggests this mechanism may have the upper hand over

bisphosphonate therapy.

"It's relatively easy to prevent vertebral fracture," says Javier San Martin, Amgen's executive director of global development for denosumab. The most potent bisphosphonate, Zometa, reduces risk of vertebral fracture by around 70%. "It's going to be very difficult to go above that level," he says. However, bisphosphonate therapy leads to reductions in nonvertebral fractures, ranging from around 20–25%, he says, whereas Amgen hopes that denosumab will achieve reductions of 25–40%. "We do have good reasons to believe that will be the case," he says.

Even so, Eric Schmidt, analyst at SG Cowen in New York, says that Fosamax, due to come off patent in the coming weeks, will continue to take "the lion's share" of the osteoporosis market, and Amgen will initially position denosumab as a second-line therapy and as an alternative option for patients who are unable to take bisphosphonates, which can cause gastrointestinal side effects and severe musculoskeletal pain. Although the oncology patient population is smaller than that affected by osteoporosis, the opportunity for

SELECTED research collaborations

Partner 1	Partner 2	\$ (millions)
Abbott (Abbott Park, Illinois)/ Genentech (S. San Francisco, California)	The Walter and Eliza Hall Institute of Medical Research (Melbourne, Australia)	*
Amgen (Thousand Oaks, California)	Kyowa Hakko Kogyo (Tokyo)	520
Genmab (Copenhagen)	Pepscan (Lelystad, The Netherlands)	*

*Financial details not disclosed.