IN brief

One patent for Europe

The European Patent Office might grant the first unitary European patent as early as 2013. Forty years in the making, the European Council pushed through draft regulations governing the unitary patent system in record time under the EU's 'enhanced cooperation' procedure. The last remaining contentious issue—the central court's location—will be decided by June 2012, Member States agreed at a summit held in January 2012.

At present, Europe is a collection of national patent systems—a situation that makes patent litigation expensive, complicated and can lead to different decisions on the same patent. A unitary patent system would solve most of these issues. Patent proprietors will be able to choose a European patent with protection in specific states or a unitary patent with protection in all states participating in the scheme, or a combination of both. Proprietors will also be able to pursue litigation through a single legislative and judicial system made up of central, regional and local courts.

But some critics argue that the draft regulations contain too little detail on the proposed judicial process. The level of technical competency required by judges is not specified, neither is the language of local court proceedings, or how the courts will be financed. These unsettled matters, if not amended, might make the new system "more costly and more uncertain," says Tim Roberts, president of the Chartered Institute of Patent Attorneys in London.

Despite its shortcomings, the progress is welcome. "From a university perspective a unitary patent would be fantastic," says Alexander Weedon, head of business and legal affairs at UCL Business in London. Obtaining a patent valid in most of Europe can cost up to €100,000 ($126,000), the majority spent on validating the patent in each country and translation, he says. The cost of a unitary patent would be €680 ($890) in addition to the roughly €2,000 ($2,600) procedural fee for an initial patent application. "That would be a massive benefit," says Weedon. "We could file another 6 or 7 patents on the savings." Nathalie Moll, Secretary General of EuropaBio, agrees. "For SMEs [small- to medium-sized enterprises], the costs were simply stifling. At no other time, has such a need for simplified and cost-effective procedures to support innovation in Europe been more relevant." *Gunjan Sinha*

IN their words

"People who are knee-deep in genetic diseases say this is one of the most dramatic animal model recoveries they've ever seen." David Blaustein, whose son has achondroplasia, a genetic condition that causes dwarfism, on reaction to Novato, California–based BioMarin's announcement in January that it will be initiating phase 1 trials for a drug for the condition, BMN-11, an analog of C-type natriuretic peptide. (*Bloomberg*, 23 January 2012)

Table 1 Selected Btk inhibitors in development

Company	Molecule	Indications	Clinical stage
Pharmacyclics, Johnson & Johnson	PCI-32765	B-cell lymphoma, chronic lymphocytic leukemia, mantle cell lymphoma, small lymphocytic lymphoma, multiple myeloma, indolent non-Hodgkin's lymphoma	Phase 2
Avila Therapeutics	AVL-292	Chronic lymphocytic leukemia, B-cell non-Hodgkin's lymphoma, Waldenstrom's macroglobulinemia	Phase 1b
Ono Pharmaceutical	ONO-WG-37	B-cell malignancies	Preclinical

in mantle cell lymphoma, although trials in other indications, including diffuse large B-cell lymphoma and multiple myeloma are ongoing. As reported at the American Society of Hematology meeting in San Diego, last December, low-dose PCI-32765 achieved an objective response rate of 67% in patients with R/R CLL or R/R SLL. Patients on a high-dose regimen attained an objective response rate of 68%. Pooled 12-month progression-free survival data (PFS) stands at an estimated 86% for the 61-patient, open-label trial. "What's really striking in the Pharmacyclics data is the PFS curves are flat—the PFS curves are almost like [those of] Gleevec," says Sharman, who has participated in clinical trials of both PCI-32765 and AVL-292. "Patients are not progressing on this drug," he adds. "It just gets better and better with time." According to interim data from a phase 2 trial in mantle cell lymphoma, PCI-32765 induced an objective response in 71% of patients who had not previously received Velcade (bortezomib) and in 65% of patients who had previously taken that drug, which is marketed by the Millennium Pharmaceuticals subsidiary of Osaka, Japan–based Takeda. At the time of that analysis, 89% of patients had ongoing responses to therapy, after a median follow-up time of 3.7 months.

So far, PCI-32765's safety profile also appears promising. Unlike other BCR pathway targets, such as spleen tyrosine kinase (syk) and phosphoinositide 3-kinase delta (PI3Kdelta), Btk is, within the immune system at least, only active in activated B cells. As a result, it does not carry the same risk of myelosuppression, says Buggy. Btk also has activity in osteoclasts, the cells responsible for bone resorption, which raises additional possibilities. "Bone disease is a very important element of metastatic cancer," says Singh. "The opportunity for a Btk inhibitor could be broader than just the B cells."

AVL-292 has yet to deliver any significant efficacy data, although that situation should change quite quickly. "Even [without] the Celgene transaction, we are on track to begin phase 2 studies in a couple of different tumor types later this year," says Avila CEO Katrine Bosley. "The molecule is ready for that kind of broad and deep development." Avila has yet to publish the structure of AVL-292. But it is unconcerned about a recent Pharmacyclics patent grant (US 8088781), which, the latter claims, covers all Btk inhibitors that act by covalently binding the cysteine-481 residue. "We're obviously comfortable with our position in that regard," Bosley says. "They are chemically distinct," says Singh, who also claims that AVL-292 is more selective for Btk than PCI-32765 is.

As yet, Pharmacyclics and Avila are the only firms with Btk inhibitors in the clinic. Osaka, Japan–based Ono has one drug in preclinical development (**Table 1**). Others are at earlier stages of development, among them Aegera Therapeutics, now a subsidiary of Montreal-based generic drug maker Pharmascience. "Our objective is to have a development candidate in 2012," says Mathieu Boudreau, director of business development and strategic planning at Aegera. The company, which is currently in lead optimization, is working on noncovalent inhibitors and has, he says, drawn lessons from the experience of others, including CGI Pharmaceuticals (now part of Foster City, California–based Gilead Sciences), whose Btk inhibitor chemotype CGI1746 stabilizes an inactive conformation of the enzyme. "What we've learned in the noncovalent space is you can achieve potency, you can achieve selectivity," he says. "Some of our predecessors put forward molecules that were not developable for other reasons."

Btk is the fourth "immunokinase" target to get "hot," says Bruce Booth at Cambridge, Massachusetts–based Atlas Venture, one of Avila's investors, after syk, PI3Kdelta and Janus kinase (JAK). "I think we'll see that other immunokinase targets will continue to be of great interest to pharma. At the top of that list are IRAK4 (interleukin-1 receptor-associated kinase 4), which is historically tough to drug, but which is validated through human genetics, and Tyk2 (tyrosine kinase 2) in the JAK family." So far, only one immunokinase inhibitor has completed development, the JAK1 and JAK2 inhibitor Jakafi (ruxolitinib), which recently gained approval in myelofibrosis and other myeloproliferative disorders.

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