PATENTWATCH

Vaccines give written description guidance

In a recent patent interference relating to vaccine technology, the US Court of Appeals provided some guidelines for the written description of biomedical inventions. The Court stated that examples are not required to support written description, that the written description standard is met even if the inventors have not yet reduced their invention to practice, and that there is no requirement for the recitation of a known biological structure within the written description.

The interference was between Falkner *et al.* (US patent 5,770,212) and Inglis *et al.* (US application 08/459,040) who both claim methods for producing vaccines against viruses that consist of a virus particle with an essential gene deleted that renders viral propagation dependent on the host-cell expression of the missing essential gene. The technology is an improvement over existing methods of producing attenuated vaccines because the modified viruses do not carry the risk of reverting back to wild-type in the host cell by recombination with host DNA.

Inglis was judged as the senior party (that is, given priority) based on several earlier filed applications that described the application of the above vaccine technology using herpesviruses as an example. The '040 patent also included passages of description dedicated to poxviruses — the subject of Falkner's patent. Falkner appealed against Inglis being awarded priority on three counts that mostly claimed that the Inglis patent lacked detailed written description and examples of the invention specifically applied to poxviruses.

The US Court of Appeals disagreed with Falkner's arguments, stating that because the differences between poxviruses and herpesviruses were well known and described in the literature the patent would have enabled a person of ordinary skill in the art to apply the invention, as described for herpesvirus, to poxvirus vaccine development. As such, the Court ruled that no detailed description of the structure of the poxvirus genes, their deletion or inactivation was required as part of the written description. Moreover, because the herpesvirus methodology can be readily applied to other viruses, there was no need for a specific poxvirus example in the Inglis patent. Regarding the reduction to practice claim, the Court pointed out that written description requires "a showing of possession of the invention" and that prior legislation has set a precedent that an invention can still be complete even if reduction to practice is absent.

Falkner, F. G. *et al.* versus Inglis, S. C. *et al.* No. 05-1324 (Interference No. 105, 187) (26 May 2006): http://www.fedcir.gov.opinions/05-1179

Merck misses its mark

Merck has lost out in an infringement case against Mediplan Health Consulting in a ruling that has wider, and potentially damaging, implications for the US pharmaceutical industry. A US court held that the FDA's Orange Book, which lists patents that protect approved drugs, did not constitute 'effective public notice' under a statute that requires companies to 'mark' their relevant patents prior to filing an infringement lawsuit. The ruling means that Merck is only awarded damages from the date after which the infringement lawsuit was filed.

Mediplan had been offering generic simvastatin (Zocor) to US customers via an online Canadian pharmacy even though Merck's patents for the drug have not yet expired and Mediplan had not filed an Abbreviated New Drug Application (ANDA) in the US. When Merck sued Mediplan for infringement of its method and composition of matter patent (US4,444,784), Mediplan argued that Merck had failed to 'mark' simvastatin. Merck counter-argued that 'marking' was not required for a method of use patent, because no physical item exists to be marked.

With no previous cases to use as legal precedent, the court decided that the Orange Book serves as "merely a catalog that informs the public of the patent's existence" and does not constitute adequate 'public notice'. The result of this case leaves US drug companies lacking protection against non-US generic manufacturers who work outside US generic drug approval legislation.

Meanwhile, the FDA is to challenge the district court ruling that it must re-list two of Merck's simvastatin patents in the Orange Book and must allow Ranbaxy and Ivax 6-month exclusivity for their generic versions of the drug (see Patent Watch, June 2006). In its letter to the court, the FDA argues that the District Court's decision would decrease competition in the generics market and will lead to industry confusion over the agency's 'statutory authority' relating to drug patents. However, if the FDA moves towards removing the exclusivity provision that came into force under the Hatch–Waxman Act this could put generics firms off filing ANDAs because they would have to go through the costly and laborious process of a patent infringement suit with more competition when it finally reaches the market.

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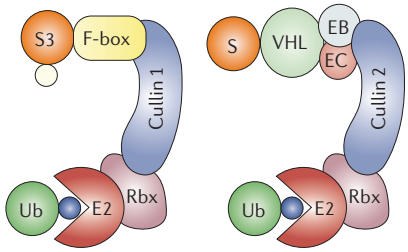

Ubiquitin–proteasome system modulation

On page 596 of this issue, Nalepa and colleagues review drug discovery in the ubiquitin–proteasome system (UPS), which is of interest for cancer, inflammation and neurodegenerative diseases. The table below details patent applications filed in the past year related to the therapeutic potential of the UPS. Data were kindly researched by Cora Sevilla at Thomson Scientific. ▸

Table 1 | **Recent patent applications related to modulation of the ubiquitin–proteasome pathway**

Patent number(s)	Assignee(s)	Subject
Assay development		
WO 20050032139	Rigel Pharmaceuticals	Fluorescent assay for detecting modulators of ubiquitin ligase; involves tagging ubiquitin with a fluorescent label and incubating with E2 and E3 ligases, and quantifying the amount of tagged ubiquitin bound to E3 ligase
FR 2867783	Cytomics Systems	Method for screening for modulators of ubiquitylation of IκBα by ubiquitin ligase complex incorporating β-TRCP; useful for treating inflammation and autoimmune diseases
FR 2859733	CRNS	Claims a cell-based screen for ubiquitin hydrolase modulators; can identify compounds that affect disorders associated with UPS dysfunction such as cancer and neurodegenerative disorders
WO 200520922	State University of New York	Claims a screening method for identifying compounds that modulate FBP1 ubiquitin ligase by measuring the activity of FBP1 relative to FBP5
WO 200420979	Rigel Pharmaceuticals	Claims the use of ubiquitin ligation pathway components for identifying compounds that modulate cell-cycle activity, and a method for inducing cell-cycle arrest
WO 200388910	Rigel Pharmaceuticals	Claims methods for identifying compounds that modulate cell-cycle arrest by acting on target proteins including ubiquitin-conjugating enzyme E2 variant
WO 200438036	Rigel Pharmaceuticals	Method for identifying a compound that modulates inflammation by affecting the ubiquitylation pathway; useful for the diagnosis, prevention or treatment of UPS-associated disorders
WO 200012679	State University of New York	Claims nucleic-acid sequences for substrate-targeting domains of ubiquitin ligases with F-box motifs; useful for screening for compounds that modulate the UPS
WO 200255665	Pagano, M. *et al.* (State University of New York)	Method for screening compounds for treating cancer, infections or immune disorders by detecting a change in the activity of SKP2
WO 200617855	Geng, Y. & Wassler, M. (University of Texas)	Regulation of a stem cell by causing β1,4-galactosyltransferase-mediated ubiquitylation of cell proteins; useful in cancer, neurodegenerative diseases, heart failure and tissue repair
Modulating the UPS		
WO 200607023	US Department of Health	Nucleic acid that encodes the UbEG2 binding domain from gp78 ubiquitin ligase; useful for gene therapy in ERAD associated disorders such as cancer, diabetes and neurological disorders
US 20050282818	Rigel Pharmaceuticals	Novel diazole ubiquitin ligase inhibitors; useful for a variety of indications including cancer, inflammatory diseases, sepsis and viral infections
WO 200507141	Proteologics	Describes a small-molecule inhibitor of POSH, a protein with ubiquitin ligase activity; useful for neurological disorders including Alzheimer's disease and Huntington's disease
US 20040247586	Abelovich, A. & Staropoli, J. (University of Columbia New York)	Identification of a parkin-associated complex comprising parkin, hFBXW7 and cullin-1; claims a therapeutic composition for modulating parkin activity in neurodegenerative disorders
WO 200498492	Proteologics	Claims a method for modulating the activity or localization of trans-Golgi network-associated protein, which involves altering the activity of POSH, a protein with E3 ligase activity
WO 200294198	Jackson, P. & Reimann, J (Stanford University)	A method of inhibiting anaphase-promoting complex by administering EMI1, which inhibits ubiquitin ligase activity
WO 2003105774	Signal Pharmaceuticals	Covers substituted tetrahydropyran or cyclohexane derivatives of a disclosed formula; useful for inhibiting E3 ubiquitin ligase activity and modulating p27/KIP1 levels
WO 200255536	Ambroggio, X. *et al.* (California Institute of Technology)	Describes the isolation and structural classification of a protein comprising a JAB1-associated metalloenzyme motif (JAMM); includes claims for modulating neddylation and ubiquitylation
WO 200224878	Bayer	Claims novel ubiquitin-ligase-like enzymes; useful for screening for agents that modulate E3 ligase activity to treat neurodegenerative diseases and cancer
EP 1182251	The Hebrew University of Jerusalem	Method for identifying inhibitors of ubiquitylation of NF-κB activation that directly interfere with the E3 ligase receptor subunit (β-TRCP/E3RS)
WO 200058472	University of North Carolina	Identification of novel nucleic acids that encode cullin-regulating zinc-finger proteins (ROCs) that stimulate cullin ubiquitin ligase activity; useful in screening for UPS modulators
WO 2000344447	Signal Pharmaceuticals	Claims a protein that enhances ubiquitylation of phosphorylated IκB; useful for treating disorders associated with NF-κB activation

β-TRCP, β-transducin repeat-containing protein; CNRS, Centre Nationale de la Recherche Scientifique; EMI1, early mitotic inhibitor 1; ERAD, endoplasmic reticulum-associated degradation; FBP, F-box protein; hFBXW7, human F-box and WD40 domain protein 7; IκB, inhibitor of NF-κB; JAB1, Jun activation domain-binding protein 1; NF-κB, nuclear factor-κB; POSH, plenty of SH3 domains; SKP2, S-phase kinase-associated protein 2; UbEG2, ubiquitylation-dependent endocytosis G2 motif; UPS, ubiquitin–proteasome pathway.