CNIPA offers guidance on validity assessments of siRNA patents

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Ribonucleic acid interference (RNAi) refers to the biological mechanism wherein messenger RNA degradation is triggered by double-stranded small interfering RNAs (siRNA) with complementary sequences, leading to the suppression of target gene expression. Since abnormally overactive genes contribute to certain human diseases and RNAi could be utilised to silence such activity, RNAi represents one of the most promising and rapidly advancing frontiers in biology and drug development today. As a result, patent examination standards surrounding siRNA-related inventions have come under the spotlight in recent years.

The China National Intellectual Property Administration (CNIPA) offered a compelling case study on the validity assessment of siRNA patents in invalidation decision No. 561449, which was rendered on September 5 2023.

The invalidation decision relates to invention patent ZL201380063930.5, titled 'PCSK9 iRNA compositions and methods of use thereof'. The patent is owned by leading RNAi therapeutics company Alnylam Pharmaceuticals and is pivotal to inclisiran (marketed as Leqvio), a proprotein convertase subtilisin/kexin type 9 (PCSK9)-targeted RNAi drug used for lowering low-density lipoprotein cholesterol in heterozygous familial hypercholesterolemia or atherosclerotic cardiovascular disease.

The double-stranded RNAi agent outlined in claims 1 and 2 of the patent share an essentially identical siRNA sequence but differ in terms of chemical modification, with the sense strand being conjugated to at least one ligand. Both have been demonstrated by embodiments to be capable of effectively suppressing the expression of PCSK9 within a cellular context. Claims 3 to 5 of the patent further define the ligand structure and the mode of connection for delivering the double-stranded RNAi agent to a target tissue.

On November 21 2022, the petitioner filed an invalidation request, mainly challenging the support issue of the claims. The petitioner contended that Annex 1 suggests a close correlation between the structure of the ligand and its functionality, and all the efficacy screening and in vivo inhibition experiments in this patent rely on specific RNAi agents. The specification, however, failed to provide any experimental evidence demonstrating that RNAi agents formed by the conjugation of ligands other than L96 with siRNA can effectively silence the PCSK9 gene in cellular contexts.

The petitioner therefore concluded that the specification does not provide a clear and comprehensive description of the technical solution, leaving those skilled in the art unable to anticipate that molecules formed by the connection of alternative ligands with the aforesaid siRNA can achieve the desired effect of silencing the PCSK9 gene in cells. Consequently, the petitioner asserted that claims 1 to 4 lack support from the specification.

In ascertaining whether the claims are supported by the specification, the CNIPA underlined the need to consider, in combination with the common technical know-how of those skilled in the art, the specification in its entirety, rather than focusing solely on the specific embodiments described therein. In cases where a claim defines a component of a product rather than the complete product, the technical solution shall be recognised as supported by the specification, provided that the invention makes improvements to the component relative to the prior art and that those skilled in the art meet the following criteria:

- They could anticipate that this component could independently achieve certain functions of the complete product; and
- They should also be aware that when the component is combined with other elements to form the complete product, the resulting complete product could effectively address the technical issues intended to be solved by the invention and produce the corresponding technical effects.

The CNIPA opined that the disclosed embodiments unravel the inventive concept of the patent as follows:

- A substantial number of siRNA sequences characterised by distinct sequences and various modification forms need to be prepared;
- These sequences are then individually conjugated with L96 to function as RNAi agents for testing purposes;
- Effective double-stranded sequences are identified through in vivo and in vitro screening and subsequently modified; and
- The inhibitory activities of the modified siRNA are verified to ensure the generation of effective RNAi agents specifically targeting PCSK9.

In essence, the invention aims to provide an RNAi agent with the capability to inhibit the expression of PCSK9 and the primary technical problem solved by the invention pertains to the screening and modification of the siRNA sequence in the RNAi agent.

Although only L96 is used as a ligand in the embodiments, those skilled in the art should be able to perceive that the patent employs L96 as an illustrative example, without implying a limitation on the mere utilisation of this ligand to achieve the inventive objective. The ligand's primary function is to facilitate the delivery of siRNA to target cells, while siRNA's role is to silence the target gene. These two functions are relatively independent, allowing for potential combinations and substitutions. In fact, those skilled in the art, based on the known prior art related to ligands and the technical content of ligand selection documented in the application, could easily select alternative ligands (other than L96) to conjugate with the aforesaid siRNA sequence, achieving similar effects.

Comment

In principle, the technical roadmap for the development of RNAi drugs involves identifying target genes, designing siRNA sequences, obtaining siRNA products, conducting siRNA transfection, and assessing RNAi effects. As naked and unmodified siRNA could give rise to poor stability, unfavourable pharmacokinetic behaviour, and the potential to induce off-target effects, developing a safe and effective delivery system is key to realising siRNA technology.

In practice, patents pertaining to RNAi drugs mainly focus on sequence design, chemical modification, and delivery systems. In addressing the support issues often raised in the patentability and invalidity related to RNAi technology, the panel in this case, based on the characteristics of RNAi technology, emphasises the functional independence of siRNA and ligands, and further demonstrates the correlation between each component and the complete product, thereby accurately identifying the practical technical contributions of the patent. Following this methodology, the CNIPA offers a valuable roadmap in approaching the support issues for the RNAi invention in the invalidity decision.

Due to the scarcity of patent prosecution cases in the siRNA field in China, practitioners have been struggling to grasp the CNIPA's examination criteria surrounding the patentability and validity assessments of siRNA-related patents. This case could help to shed light on the drafting approach, examination parameter, and validity assessment methodology of siRNA patents.