Analysis of and Reflection on Policies of Protecting Nucleic Acid Drug Patents in Europe [1]

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In recent years, cutting-edge scientific technologies such as big data, artificial intelligence and genetic technology have been advancing by leaps and bounds, and innovations have played an increasingly strengthened leading role, which put forward higher requirements for protection of patents in new fields and new formats. Nucleic acid drugs, as a new generation of medicines that have been burgeoning over recent years, are artificially synthesized DNA or RNA segments capable of treating diseases by means of regulating the expression of target protein at the gene and RNA levels, which makes up for the defect of traditional small molecule drugs and antibody drugs that have non-drugable targets, and expands the scope of drugable targets [2]. The nucleic acid drugs mainly comprise antisense oligonucleotides (ASOs), small interfering RNA (siRNA), microRNA (miRNA), small activating RNA (saRNA), messenger RNA (mRNA), etc., among which the siRNA drug is an up-and-coming nucleic acid drug and the most common type on the market and under research.

As a traditional pharmaceutical developed region, Europe has a thorough institutional scheme for protection of drug-related intellectual property rights. Research and analysis of Europe's policies of protecting nucleic acid drug patents cast light on how to strengthen the intellectual property protection of nucleic acid drugs and promote the development of the nucleic acid drug industry in China. Therefore, this article is going to elaborate the examination rationale and basic principles in commonly referenced legal provisions of the European Patent Office (EPO) mainly in consideration of EPO's trial practice of siRNA drug cases in patent grant, opposition and appeal procedures, in hope of providing a reference for China when formulating policies of protecting nucleic acid drug patents.

I. Issues in the examination practice of patent applications related to nucleic acid drugs in China

The importance of patent protection in the field of drug research and development (R&D) is self-evident. After years-long evolution, examination standards suitable for small-molecule drugs and monoclonal antibodies have been formed. The examination of both the small-molecule drugs and monoclonal antibodies is to decide the reasonable scope of the small-molecule drugs or monoclonal antibodies and whether they involve an inventive step based on the kernel structure that is decisive in their main functions and uses, such as the basic core part or basic ring structure of the small-molecule drugs and the CDR sequence of the monoclonal antibodies.

However, as far as a siRNA drug is concerned, the

[12] 歐專局上訴委員會T 0754/11號決定。

[13] 歐專局EP3693463A1審查意見。

[14] 同註10。

[15] 歐專局EP1802644A2審查意見。

[16] 歐專局EP2841443A2審查意見。

[17] 歐專局EP3411480A1審查意見。

[18] 同註5。

[19] 同註9。

[20] 同註15。

[21] 歐專局EP3330378A1審查意見。

[22] 歐專局EP3677679A1審查意見。

structure thereof is a nucleic acid sequence segment, which is like neither a small-molecule drug which has a basic core part or basic ring structure, nor an antibody, the sequence segment of which can decide its function and use. Nor are there clear standards telling us which sequence segment should be selected as the core sequence. Therefore, where the core sequence cannot be determined, it is impossible to simply refer to the examination standards for the small-molecule drugs and monoclonal antibodies for the examination of the siRNA drugs.

As we all know, the siRNA working mechanism is that the antisense strand is fully complementary to and paired with the mRNA, thereby degrading the mRNA to exert its post-transcriptional regulatory function. For this reason, the patent application documents usually recite in-vitro cell experiment so as to clarify the knockdown effect of the siRNA molecule on the target gene. In vitro experiments cost much less than in vivo validation tests and are important means to validate the developability of siRNA. However, the in vivo activity and stability of siRNA drugs are also affected by various factors such as chemical modification and delivery methods. It is impossible to determine that the siRNA molecule can definitely exert the expected efficacy merely according to the in vitro cell experiments. Therefore, as regards a siRNA drug application, further research needs to be conducted on whether in vitro cell experiments alone are sufficient to recognize its efficacy in treating diseases and whether in vivo animal experiments or clinical experiments are in need as further support.

Regarding whether the scope of protection of claims of a drug patent application can be supported by the description, a monoclonal antibody can accept an open-ended limitation by using, e.g., "comprising" based on the CDR sequence defined in a close-ended manner; however, for a siRNA drug, the core sequence that decides its function is not clear and therefore it is unlikely to determine whether the function may be affected if more nucleotides are added at both ends thereof. How to understand and whether to accept the open-ended limitation of siRNA drugs require more research.

In terms of infringement determination, many siRNA drugs are defined by a nucleic acid sequence segment; however, actual siRNA drugs must be nucleic acid products containing chemical modifications, or otherwise they cannot be effectively used for in vivo treatment of patients. In the infringement determination proceedings, more research is also required on how to construe the scope of protection of the claim defined by a base sequence.

In practice, controversies surround the examination standards for the inventive step of the siRNA drugs. A prevailing view is that the inhibitory effects of siRNA molecules at different target sites of the same target gene on gene expression are not exactly the same, and sometimes even a difference in a few bases will have a great impact on the inhibitory effect on the target genes [3]. If an application proves that the siRNA molecule has a certain inhibitory effect, the siRNA molecule possesses an inventive step in comprehensive consideration of the structural difference and technical effect. In contrast, there is also a different view on this matter. A suitable siRNA molecule of the known gene sequence to be inhibited can be easily devised through logical analyses, reasoning or finite experiments, and the inhibitory effect thereof recited in the application documents is equivalent to that in the prior art. Thus, the siRNA molecule lacks an inventive step. Therefore, more research shall be done on the assessment of inventive step of siRNA pharmaceutical molecules.

II. Summary of relevant patent examination practice in Europe

Based on patent data from Patsnap, we conducted a search on patent applications using both Chinese and English keywords and patent classification numbers. There are 1,796 patent applications filed in Europe. By analyzing the classification numbers of them, it is found that the IPC classification numbers of siRNA drug patents mainly fall into the following categories: (1) nucleic acid sequences, and compounds and compositions comprising nucleic acids, which mainly include C12N15 and C07H21; (2) medical preparations, which mainly include A61K31, A61K48, A61K38 and A61K39; and (3) drug indications, which include A61P35. Among them, C12N15, A61K31, A61K48 and A61P35 are the four most critical patented technologies. It can be seen that the siRNA drug patent applications mainly focus on three aspects, i.e., nucleic acid sequences, corresponding medical preparations and indications, wherein the nucleic acid sequences and modifications thereof are the most crucial technology in the development of the siRNA drugs.

The authors analyzed the drafting formats of the claims of 280 patent applications accepted by the EPO (See Fig.1), finding that 49% of these patent applications in rela-

tion to siRNA drugs are drafted to include a specific sequence. It means that siRNA is mainly limited by a specific sequence in these applications, and only 1% of the applications limit their sequences in a close-ended manner, while the sequences are limited in an open-ended manner in the rest applications, for example, "a siRNA molecule with a sense region and an antisense region each ranging from 18 to 30 nucleotides in length, comprising the following antisense sequence: 5'-AAC ACC ACG GCG GTC ATG TGC-3'." In addition, it is noteworthy that in terms of drafting formats, a great number of patent applications involve functional limitations, wherein only 26% of them define siRNA by function, for example, "a siRNA capable of reducing the expression of gene A".

Furthermore, by analyzing the EPO's written opinions, we found that the articles most frequently referred to by the EPO when examining patent applications for siRNA drugs are Article 54 (novelty), Article 56 (inventive step) and Article 84 (claims should be clear and concise and be supported by the description) of the European Patent Convention (EPC). The controversies in the assessment of inventive step mainly focus on whether the target of the siRNA molecule is disclosed in the prior art, the inhibitory effect of siRNA, whether the modification of the siRNA molecule is conventional, etc.

For the above reasons, it is necessary to conduct research on how the EPO understands the scope of protection of the siRNA drug product claims limited by a sequence in an open-ended manner and how it judges the inventive step of siRNA molecules, so as to clarify the criteria for judging whether the claim in relation to the siRNA product is clear and supported by the description, and involves an inventive step.

1. Understanding of the scope of claim defined by words like "comprising" in an open-ended manner

A siRNA drug molecule is an artificially synthesized short double-stranded RNA molecule ranging from 19 to 25 nucleotides in length, with a core region of around 19 base pairs. If the length exceeds 30 nucleotides, it will trigger an immune response and activate Toll-like receptors, resulting in side effects. If the length is too short, it will lead to specificity reduction. Different parts of the sequence vary in terms of the role in activity. For instance, the "TT" overhangs at both ends are considered to make no contribution to target recognition. Therefore, the scope of protection of the siRNA molecule defined in an open-ended manner shall be defined in combination with its technical characteristics.

In T 1271/09 [4], the EPO Boards of Appeal stated that a double-stranded oligoribonucleotide with 15 to 49 base pairs shall be interpreted to be capable of connecting other elements on the left and right sides in such a double-stranded structure, but such elements are not base pairs. In other words, even if the claim adopts an open-ended limitation using "comprising" or "having", it cannot be understood as expandable endlessly to have more base pairs. A series of siRNAs derived from shifting the siRNA sequence by a few base pairs up or down relative to the target gene sequence may exhibit potent activity. The shared sequence segments among these siRNAs can be regarded as forming the "core sequence". Therefore, with sufficient examples provided in the description, a short nucleic acid sequence can be used to define the siRNA, such as the granted claim in the patent No.EP2723758B1, which reads "A double-stranded ribonucleic the patent No. acid (dsRNA) for inhibiting expression

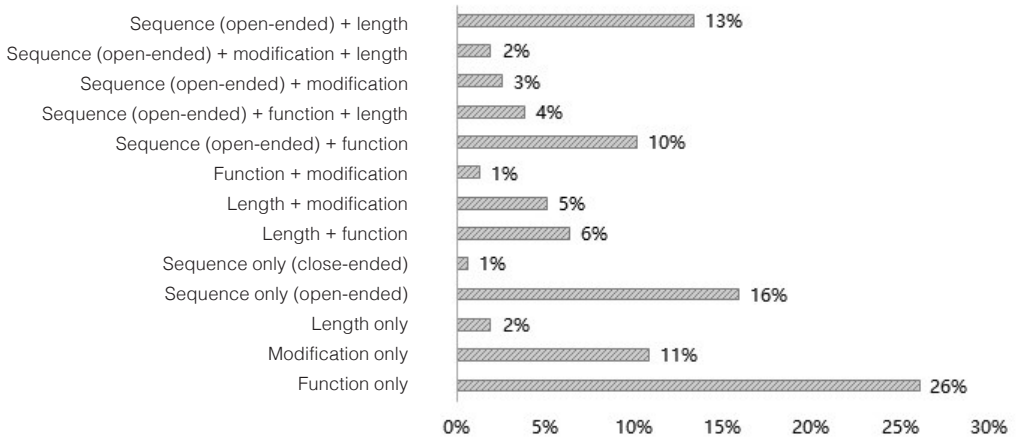

Fig. 1 Analysis of claim drafting formats of patent applications received by EPO

of ANGPTL3, wherein said dsRNA comprises a sense strand and an antisense strand, wherein (a) the antisense strand comprises a region of complementarity which comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from any one of the following antisense sequences: (a1) UAAAAAGACUGAUCAAAUA (a2) ……"

2. Issues concerning ambiguity and lack of support for nucleic acid drug claims

(1) RNAi-based drugs defined by "target gene + length"

For RNAi-based drugs defined only by "target gene + length", the structural feature of a claim for such a product usually contains the length of the sequence complementary to the target gene only. Since the target gene is usually long, the claim may cover tens of thousands of siRNA molecules under such circumstances. The EPO held that such a claim is ambiguous. For instance, the patent No. EP3411481A1 seeks to protect an RNA complex comprising an antisense strand of at least 19 nucleotides (nt) in length having sequence complementarity to a PDGFB mRNA sequence and a sense strand of 15 to 17 nt in length having sequence complementarity to the antisense strand. In this case, the EPO held that the limitation of "complementarity to mRNA of gene A" is of no actual significance, thereby rendering the scope of protection of said claim unclear or not supported by the description. Although the description of this case tests the silencing efficiency of a large number of siRNAs that target PDGFB, the EPO still insisted that the expression of "having sequence complementarity" in claim 1 is ambiguous and there is no definition of complementarity level, which may be quite low. Hence, said claim fails to clearly define that the RNA complex with an antisense strand capable of binding to PDGFB mRNA, let alone the RNA complex capable of inhibiting gene expression PDGFB [5].

(2) RNAi-based drugs defined by "sequence + length"

The drafting format of "sequence + length" specifically defines a segment of the siRNA sequence, and the scope of protection thereof is largely narrowed down as compared with that of the definition by "target gene + length". A typical drafting format is like this: "a siRNA comprising a sense region and an anti-sense region, wherein said sense region and said anti-sense region form a duplex region, and wherein said sense region and said anti-sense region are each no more than 30 nucleotides, and wherein the siRNA comprises the following sense and anti-sense sequences: 5'-AAG CAC ATG ACC GCC GTG GTG-3' and 5'-AAC ACC ACG GCG GTC ATG TGC-3'".

As for the length of siRNA, the EPO sets requirements for the nucleotide with the smallest length of the sense strand and the antisense strand. For the patent No. EP2619309A1, the EPO pointed out that since a siRNA cannot be shorter than 21 nucleotides, it is ambiguous that the sense region and the anti-sense region are each 18-30 nucleotides in length [6]. For the patent No. EP3105331A1, the EPO held that the sense strand and the anti-sense strand are at least 18 nt and 20 nt in length respectively, so the claim which comprises any strand less than the above length is not in line with Article 84 EPC [7]. Although the EPO's understandings of the minimum length of siRNA are not consistent, it can still be seen from the above two opinions that the EPO sets requirements for the minimum length of nucleotides in the sense strand and the antisense strand, but is not inclined to expand the length of nucleotide sequences departing from the prior art.

(3) RNAi-based drugs defined by "function + structure"

For RNAi-based drugs defined only by "function + structure", if the embodiments of the description cover a reasonable number of modes for realizing the nucleic acid agents in the specific functional claim, the agents in these embodiments can accurately express the common functional features of all nucleic acid agents included in the claim, and those skilled in the art can carry them out through a reasonable number of experiments without making excessive efforts, the functional claim may be recognized. In T 1094/10 [8], claim 1 is related to a ribonucleic acid consisting of a double stranded structure, wherein the length of the first strand and of the second strand is 15 to 25 bases and wherein the ribonucleic acid mediates RNA interference. All siRNAs in the embodiments have the length of more than 18 bases, and the description mentions that the double-stranded siRNA molecule can demonstrate activity only when it is more than 17 bases in length. In response to the challenge that the ribonucleic acid having less than 18 bases in the claim cannot mediate RNA interference, the EPO Boards of Appeal held that Example 1 relates to a commercial product and a standard scheme for conducting RNAi experiments. These experimental methods shall also be followed when RNAi research is conducted. Although the biological RNAi route has not been fully determined before the filing date, those skilled in the art can make use of tools and

means to determine whether the ribonucleic acid consisting of a double stranded structure as defined in claim 1 mediates RNAi.

3. Understanding of the scope of protection of product claims for RNAi-based drugs defined by naked sequences

As for siRNA drugs, in absence of sufficient understanding of the structure-activity relationship between biomolecule structure and function, further in-depth research is still needed on the specific working mechanism and influencing factors thereof, so that the predictability of the siRNA drugs is usually much lower than that in other fields. As seen from the grant standards in China, a relatively more prudent attitude is adopted, severe requirements are set for the application of related laws and regulations, and the scope of protection of a granted patent is usually confined to a specific nucleotide sequence. As we all know, the siRNA sequence once determined still needs to be chemically modified in a bid to effectively enhance its resistance to nucleases and prolong the half-life of siRNA drugs. Thus, a prepared siRNA drug usually includes a specific modification, and a relevant patent application is usually drafted by defining a naked sequence in an independent claim and the modification of siRNA in a dependent claim.

In the patent No. EP2223692A1, claim 1 relates to a composition comprising an iRNA agent including a sense strand and an antisense strand, wherein the sense strand and the antisense strand each comprise at least 15 contiguous nucleotides from a specific nucleic acid sequence segment, wherein the sequence comprises bases partially modified by 2'-O-methyl or phosphorothioate. Dependent claims 5 to 7 define that the iRNA agent comprises a phosphorothioate or a 2'-modified nucleotide, as well as specific modifications. The EPO held that dependent claims 5 to 7 render the subject matter of claim 1 unclear on the grounds that claim 1 should be understood as including an unmodified naked sequence according to dependent claims 5 to 7, but claim 1 does not involve an unmodified naked sequence [9]. Judging from the EPO's opinion, it can be seen that the EPO tended to think that the scope of protection of siRNA defined by the naked sequence includes the modified siRNA on the sequence, and it is appropriate that the independent claim defines siRNA by the naked sequence and its dependent claims further define the modifications on said basis.

4. Sufficiency of disclosure and requirements for experimental data in inventive step assessment

Take siRNA drugs for example. The experimental data for effect as recited in the description can be a computer software design level, an in vitro activity experiment level, an in vivo animal experiment level or a result verifying the effect of clinical experiment. The development of nucleic acid drugs requires a long time period and high cost, and needs to undergo multiple steps such as nucleic acid drug molecule screening, in vitro experiments and clinical trials. The verified pharmaceutical application of siRNA and its corresponding dsRNA for direct use in specific indications can undoubtedly confirm the direct industrial application of the nucleic acid drug. Nevertheless, it does not mean that the pharmaceutical use of nucleic acid drugs must be verified by the clinical data on indications. This explains why the EPO generally requires the in vitro experimental data in the examination of sufficiency of disclosure of the description. For instance, in the patent No. EP2004240A2 [10], the EPO did not require clinical or in vivo data, but some in vitro data, as a support for efficacy validation, holding that although actual clinical data are not required to support pharmaceutical use claims, some technical support, such as proving that the interfering RNA inhibits keratitis in vitro, is essential.

On account of the unpredictability of siRNA gene silencing effect, the EPO always bears in mind the technical effects verified by the application documents and reference documents in the three steps of the "problem-solution approach" for assessing inventive step, i.e., in the step of selecting the closest prior art, managing to select the sequence, the effect of which has been verified, as the basis for improvement; in the step of determining the "objective technical problem" to be solved, judging whether a certain effect is realized within the entire scope of the protection of the claim based on the comparison of technical effects between the application documents and the closest prior art; and in the step of assessing the obviousness of the claimed technical solution, fully considering whether the experimental data confirms that the claimed technical solution solves the corresponding technical problem, and whether the claimed technical solution achieves an unexpected technical effect as compared with the reference documents.

5. Assessment of novelty and inventive step

Novelty and inventive step are requirements essential for the grant of patent for nucleic acid drugs. If an invention does not belong to the prior art, it possesses novelty; and if the solution provided by the invention is non-obvious with respect to the prior art to those skilled in the art, it involves

an inventive step. The EPO's examination criteria for the siRNA drugs can be summarized in the following table [11].

Is the target gene known?	Is there at least one oligonucleotide against this target gene in the prior art?	Novelty?	Inventive step?
No	No	Yes, because the target gene is new (functional definition possible).	Yes, because the target gene is new.
Yes	No	Yes, because it is the first oligonucleotide used in therapy.	Yes, if the oligonucleotide has a better technical effect.
Yes	Yes	Yes, if the oligonucleotide has a different sequence/structure (e.g., with modifications) than oligonucleotides of the prior art.	Yes, if the oligonucleotide has a better technical effect (surprising technical effect if the regions targeted overlap).

The EPO often assesses inventive step by the "problem-solution approach", which includes three steps: (i) determining the closest prior art, (ii) establishing the objective technical problem to be solved, and (iii) considering whether or not the claimed invention, starting from the closest prior art and the objective technical problem, would have been obvious to the skilled person.

(1) Selecting the closest prior art

For a siRNA drug product, in selecting the closest prior art, the first consideration is that it must be directed to a similar purpose as the invention or solves the same or similar technical problem as the claimed invention, i.e., whether it is against the same target gene. If there is not at least one siRNA against this target gene in the prior art, the known target gene can be taken as the closest prior art; and if the claim contains information on sequence, consideration shall also be given to whether the reference document discloses the corresponding target gene, gene region, as well as structural features such as terminal protrusion and chemical modification, and then the closest prior art is selected in view of the number of disclosed features.

In addition, during the R&D process of siRNA drugs, a huge number of siRNAs are usually designed and screened, and these siRNA sequences may be recited in the patent application documents and become the prior art of subsequent patent applications. When a prior-art document recites various siRNA sequences whose effects have not been verified, those skilled in the art still have to conduct the screening process and have no strong motivation to improve any one of said siRNA sequences due to the unpredictability of the siRNA gene silencing effect. In T 0754/11, when determining the closest prior art, the EPO Boards of Appeal gave consideration to both the technical solution *per se*, but also the specific technical effect thereof, holding in the decision that "since both, documents D1 and D11, describe structurally closely related dsRNA molecules but, whilst document D1 merely predicts a possible role of 21- to 25-mer dsRNAs in the induction of target specific RNAi, document D11 actually demonstrates said induction, the board considers document D11 to represent the closest state of the art" [12].

(2) Establishing the objective technical problem to be solved

As for siRNA drugs, the experimental data presented in the application documents usually include in vitro or in vivo data concerning the inhibition rate of target genes, and possibly qualitative or quantitative data obtained through animal or clinical experiments. Therefore, in the determination of establishing the "objective technical problem" to be solved, it is necessary to compare the technical effect of the application documents with that of the closest prior art document. Because of the diversity of claim drafting and the potential differences in distinguishing features between the claims and the closest prior art, the establishment of the "objective technical problem" is quite complicated, which usually includes the following situations:

First, the technical problem is deemed as not having been solved. Where some technical solutions are slightly different from the closest prior art, or there are no experimental data, or the specific effect cannot be determined according to the experimental data based on the knowledge of those skilled in the art, it can be deemed that the technical problem has not been resolved and the claim does not involve an inventive step. A plurality of siRNAs in the patent No. EP3693463A1 is different from the closest prior art only in one nucleotide or modification, so the EPO held that at least some compounds in the claims cannot resolve any meaningful technical problem [13].

Second, the objective technical problem to be solved could be to seek an alternative solution to the known problem. Where the gene inhibitory effect of siRNA is worse than or difficult to compare with the closest prior art, it may also be deemed to provide an alternative solution to the known issue. The claim of the patent No. EP3411481A1 relates to a

siRNA molecule of a target PDGFB gene. According to the data in the description, the inhibition rate of the siRNA against the PDGFB gene in the claim is less than 20%. The closest prior art discloses the siRNA that inhibits 50% of PDGFB gene expression in vitro, which is different from the claimed siRNA molecule sequence. Hence, the established objective technical problem to be solved is to provide more siRNAs targeting PDGFB gene.

Third, the effects that cannot be achieved in the entire scope of the claims should not be used as the basis for establishing the objective technical problem to be solved. When a claim contains a generalized expression, a judgment shall be made on what technical effect can be achieved in the entire scope of the claims, and the technical effect achieved by the embodiment shall not be directly identified as the technical effect achieved by the claims. In the patent No. EP2004240A2, the EPO stated that "two separate issues have to be addressed in the discussion of the inventive merit of the claimed subject matter. The first issue is to assess, whether the claimed subject matter really provides a solution over the entire scope claimed. The second issues is to evaluate, whether the claimed subject matter is a solution that would not have been obvious to the person skilled in the art." [14] In the patent No. EP1802644A2, the applicant argued that the siRNA agent 1 demonstrates the highest activity among all the measured compounds, and such an exceptionally potent effect is unpredictable by the skilled person in view of any of the cited prior art document. The EPO held that the claims cover agents in Table 8 of the description that cannot inhibit ApoB mRNA relative to controls, and the exceptionally potent effect of the siRNA agent 1 cannot be deemed as achievable by all the agents defined by the claims [15].

(3) Common situations in the assessment of inventive step

When a target gene is disclosed, a siRNA defined by the target gene is usually deemed as non-inventive. There are various siRNA design principles for siRNA sequence selection, and it is not difficult to obtain siRNAs having the gene knockout function through further screening experiments. For instance, the patent No. EP2841443A2 relates to "a double-stranded ribonucleic acid (dsRNA) for inhibiting expression of Serpinc1, wherein said dsRNA comprises a sense strand and an antisense strand, wherein said sense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 1 and said antisense strand comprises at least 15 contiguous nucleotides differing by no more than 3 nucleotides from the nucleotide sequence of SEQ ID NO: 5". The sequences of SEQ ID NO: 1 and SEQ ID NO: 5 correspond to the full-length sequences of Serpinc1. The prior art discloses siRNA molecules used as the inhibiting agent of a series of genes, which includes Serpinc1. The EPO held that "siRNA molecules against known genes are gene-validation tools well known to the person skilled in the art and well established in the technical field. In fact, the disclosure of D1 points already at the use of siRNA molecules, among other compounds, for inhibiting the expression of a series of genes among which Serpinc1 is included. The disclosure of D1 is to be considered as a suggestion that the person skilled would take as an incentive to develop siRNA molecules targeting Serpinc1. By doing so, the person skilled in the art would arrive without intervention of any inventive skill to a result falling within the terms of present claim 1." [16]

On the other hand, however, the rules for designing siRNA sequences are mostly derived from statistical analysis of a great number of sequences, and the conclusions drawn are too general and lack relevance. In order to obtain more accurate active sequences, it is also necessary to make a pertinent optimization design. But the design rules can only elevate the predictability of active sequences to some extent, and it is impossible to form an effective screening method merely based on analysis of sequences, thereby failing to provide clear technical guidance. Hence, when the claimed siRNA has a good technical effect, the inventive step thereof can usually be recognized. For instance, in the case related to the patent No. EP3411480A1, the EPO held that "it is generally admitted that the skilled person can obtain (by trial and error using common methods of siRNA design) siRNA agents that can inhibit the expression of virtually any target gene by 50% to 70%, with a reasonable expectation of success". Although the prior art discloses other siRNAs against F2RL1 gene, the target region which the claimed specific siRNA is against differs from that in the prior art and the siRNA can inhibit F2RL1 by more than 70%, which are deemed as non-obvious [17]. In contrast, in the cases related to patents Nos. EP3411481A1 and EP2008274A2, the inhibition rates of 20% and 40% are considered to be derivable by the skilled person in the art by conventional processes [18].

The inhibition rate of siRNA is mainly associated with

the selection of target regions. For instance, in the case related to the patent No. EP2223692A1, the EPO pointed out that "the inhibition efficiency of a siRNA is often unpredictable because of multiple factors such as target sequence, targeting sequence and the chemical structure. In fact, all the evidence in the application suggests that the high level inhibition is due to target sequences and not due to nature of the modifications" [19]. For this reason, siRNA defined by a naked sequence has clearly defined the target region that is most important for inhibition rate. It is generally construed that the scope of protection of such a claim also covers a siRNA with modifications or ligands.

If the claimed siRNA overlaps with the siRNA target region disclosed in the closest prior art, the claimed siRNA is deemed to be inventive only when experiments verify that the siRNA of the present application has an unexpected technical effect. In the case related to the patent No. EP1802644A2, the EPO indicated that the iRNA agent 1 targeting the sequence starting from position 1296 of apoB can be considered to be inventive only when it exhibits a surprising effect or characteristics compared to other iRNA agents used to inhibit apoB gene expression, especially the iRNA agent targeting the sequence starting from position 1293 of apoB disclosed in D2 [20].

The chemical modification of siRNA is primarily aimed to, among other things, reduce nuclease degradation and enhance half-life. Therefore, when the closest prior art has disclosed siRNA with the same or similar sequence, attention should be drawn to whether the claim has resolved the technical problem in relation to modifications. In the case related to the patent No. EP3330378A1 [21], the claims relate to siRNA defined by a specific sequence, and modifications at a plurality of positions. The EPO held that organic modifications such as 2'-O methylated nucleotides are well known to improve stability of siRNAs. Also there is no evidence showing that the present range of modifications across the whole of the claimed scope would have any improved technical effect. Inventive step is alleged to be based on a surprising combination of nuclease resistance combined with retention of RNAi activity and the claims should be limited to those sequences with the specific modifications which have been shown by way of evidence to have the surprising combination of activities. The siRNA conjugated to GalNAc can achieve a live targeting effect, which has been widely used with more improvements on the chemical connection method. Therefore, more attention shall be paid to the technical effects of and the technical problem solved by the linker as proved in the description. The patent No. EP3677679A1 is directed to a siRNA conjugated to GalNAc, which differs from D1 only by the nature of the linker. The EPO concluded that the claims do not involve an inventive step on the grounds that the linker does not cause any unexpected technical effect and is just one of the many possibilities available to the person skilled in the art to provide an alternative siRNA [22].

III. Summary of European policies for protection of nucleic acid drugs and enlightenment for China

1. Different considerations of requirements for experimental data in examination under different provisions

A siRNA usually has structural features at three levels, i.e., basic short sequence, modification method and ligand selection: its in vitro silencing effect is mainly dependent on its basic short sequence, and its chemical modification is primarily aimed to increase in vivo stability or other favorable characteristics; its functional activity in vivo is mostly decided by the overall effect of the basic short sequence, modification method and ligand selection, which means that the in vivo technical effect verified by the invention usually results from joint work of the basic short sequence, modification method and ligand selection; and meanwhile, the long-term mechanism of siRNA drugs in vivo has a direct bearing on chemical modifications, delivery, dosage, administration and the like.

Therefore, it is recommended that special attention should be paid to the level and degree of effect experiments recorded in the specification of an invention patent application during patent examination in China, and full consideration shall be given to the correspondence between the claimed siRNA in the invention of patent application and the technical effect verified in the specification. If the claimed siRNA is not chemically modified, the data of in vitro tests can meet the requirement of sufficiency of disclosure; and if the claimed siRNA has a modification or ligand, the specification shall provide the data about in vivo tests. For the requirement of inventive step, if the level of innovation of an invention needs to be proved by in vivo experimental data, it is usually required to simultaneously define the technical means in three aspects, namely the basic

short sequence, modification method and ligand selection, in the technical solutions of the claims; and if the siRNA product of the invention is obtained by computer software design in combination with high-throughput screening, but with an ordinary gene inhibition efficiency, the degree of innovation of the invention can be reasonably challenged by the target gene known in the prior art and the conventional siRNA R&D means.

2. Reasonable understanding of the scope of protection of claims defined by naked sequence so as to promote the effective linkage between patent infringement determination procedures and patent grant and invalidation procedures

By analyzing the drafting manners and examination of patent applications for nucleic acid drugs filed with the EPO, the authors noticed that the set of granted claims often consists of a claim defined by a naked sequence and dependent claims defining specific chemical modifications, which are dependent on the claim defined by a naked sequence, and the description of the patent usually makes a clear statement on whether the siRNA defined by the naked sequence contains any chemical modification; and in the infringement determination procedures, if simply based on literal meaning, the nucleic acid drugs which have been put in actual production and use will not fall within the scope of protection of the claim defined by the naked sequence, such nucleic acid drugs are prepared totally by means of chemical synthesis without using the naked sequence as an intermediate, and there will occur great controversy if the use of the patented product is deemed to result in infringement, which is not in conformity with the original intention of patent protection.

Based on such analysis, even if the claim defined by the naked sequence of the nucleic acid drug patent does not contain a technical feature involving a chemical modification, there is a good reason to construe said naked sequence as a nucleic acid molecule including a conventional chemical modification that corresponds to the sequence according to the information definitely recorded in the description and the prior art. In the patent grant and invalidation procedures, the scope of protection of the claim should be determined based on the above understanding so as to judge whether the claim complies with the relevant provision of the patent law. In doing so, the patent infringement determination procedures and the patent grant and invalidation procedures are effectively linked up.

3. Selection of suitable protection modes to construct rules for protection of siRNA patents which meet China's actual requirements

The requirements for patent protection vary at different industrial development stages. Excessive or insufficient patent protection will hinder the healthy development of the industry. Thus, it is crucial to formulate intellectual property policies that can evolve as the industry is getting mature. Such policies seek to find a balance between encouraging innovation and safeguarding the public interest in a bid to boost the continuous prosperity of the industry.

Take siRNAs for example. Europe is in a leading position in terms of research and industrial foundation of nucleic acid drugs. R&D and manufacturing of nucleic acid drugs play a vital role in European countries such as Germany, Switzerland and the United Kingdom. In addition, Europe has also attracted many innovative biotechnology companies and research institutes that are concentrated on R&D and commercialization of nucleic acid drugs. In contrast, China is relatively weak in basic research, and siRNA-related basic patents and platform patents account for a small portion. However, China is relatively strong in applied research directed to concentrated R&D fields. Many domestic innovation entities make more efforts on the R&D of differentiated siRNA products with known target genes and targets.

Against the current backdrop, it is extremely vital to encourage inventions with industrial value and stimulate the innovation vitality of market entities by means of intellectual property protection. Meanwhile, it is necessary to ensure that the scope of protection of a patent is commensurate with the technical contributions it made, and a patent with an overbroad scope, such as a siRNA defined by a target gene, should be avoided in order not to impede the overall development of the industry. Such an approach for selecting policies is not only conducive to attracting more innovation entities to participate in the patent protection system, but also ensures that their innovative achievements are under effective protection. Moreover, it can also prevent patents with overbroad scopes from posing unnecessary obstacles to technical innovations, and put R&D, production and selling activities of similar nucleic acid drugs under reasonable protection, thereby ensuring that the people's needs for medication are satisfied.

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[1] This article is based on the 2023 annual research project (GP2314) of the CNIPA's mid- and high-caliber talent development research platform, and the project team consists of Wei Cong, Xiao Jing, Wang Yiran, Zhang Chi, Sun Yanke, Li Xing, Shi Jing, Huang Li, Zhu Huibin, Li Zijia, Zhang Xiaoxia, Zhao Yali and Ma Lu.

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[4] T 1271/09 of the EPO Boards of Appeal.

[5] EPO's opinion for the patent No. EP3411481A1.

[6] EPO's opinion for the patent No. EP2619309A1.

[7] EPO's opinion for the patent No. EP3105331A1.

[8] T 1094/10 of the EPO Boards of Appeal.

[9] EPO's opinion for the patent No. EP2223692A1.

[10] EPO's opinion for the patent No. EP2004240A2.

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[12] T 0754/11 of the EPO Boards of Appeal.

[13] EPO's opinion for the patent No. EP3693463A1.

[14] See supra note 10.

[15] EPO's opinion for the patent No. EP1802644A2.

[16] EPO's opinion for the patent No. EP2841443A2.

[17] EPO's opinion for the patent No. EP3411480A1.

[18] See supra note 5.

[19] See supra note 9.

[20] See supra note 15.

[21] EPO's opinion for the patent No. EP3330378A1.

[22] EPO's opinion for the patent No. EP3677679A1.

Joint Communiqué on Entry into Second Phase in EPO-CNIPA Patent Cooperation Treaty Pilot Project

From 1 December 2024, users of the EPO-CNIPA Patent Cooperation Treaty (PCT) pilot project will pay international search fee directly at the CNIPA in Renminbi.

The European Patent Office (EPO) and the China National Intellectual Property Administration (CNIPA) have jointly announced the next phase in their joint PCT pilot project. This new phase offers greater convenience to Chinese applicants designating the EPO as their International Search Authority (ISA): Starting from 1 December 2024, applicants will be able to pay their search fees through the CNIPA to the EPO in Renminbi.

The first phase of this pilot project began on 1 December 2020. The second phase simplifies the process for Chinese nationals and residents by allowing fee payments in local currency, making it easier to access high-quality international searches and written opinions from the EPO.

By choosing the EPO as their ISA, applicants gain accelerated access to European patent protection. Additionally, phase two maintains key advantages, such as a 75% reduction in the examination fee when requesting international preliminary examination under PCT Chapter II with the EPO. No supplementary European search or translation of the PCT application are required when entering the European phase, saving both time and costs.

The pilot's capacity remains limited to 3,000 applications per year, ensuring that a broad range of applicants can continue to take advantage of these benefits.

CNIPA Commissioner Shen Changyu noted that as an important part of the cooperation between the CNIPA and the EPO, the pilot project has been widely welcomed by Chinese users since it was launched nearly four years ago. More than 440 innovative entities benefited from the pilot.

Source: CNIPA