

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

SHANGHAI HONGENE BIOTECH CORPORATION,
Petitioner

v.

CHEMGENES CORPORATION,
Patent Owner

Case IPR2023-00862
U.S. Patent No. 8,541,569

PETITION FOR *INTER PARTES* REVIEW OF

U.S. PATENT NO. 8,541,569

CLAIMS 1-2

UNDER 35 U.S.C. §§ 311-319 & 37 C.F.R. §§ 42.1-42.80, 42.100-42.123

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EXHIBIT LIST

Exhibit (Ex.) No.	Title	Abbreviation
1001	U.S. Patent No. 8,541,569	the '569 Patent
1002	File History of U.S. Patent Appl. No. 12/708,827 (which issued as the '569 Patent)	the '569 File History
1003	Declaration of Phil S. Baran, Ph.D. in support of Petition for <i>Inter Partes</i> Review of the '569 Patent	Baran Decl.
1004	Arthur Van Aerschot, Piet Herdewijn, Jan Balzarini, Rudi Pauwels, and Erik De Clerq, 3'-Fluoro-2',3'- dideoxy-5-chlorouridine: Most Selective Anti-HIV- 1 Agent among a Series of New 2'- and 3'- Fluorinated 2',3'-Dideoxynucleoside Analogues, J. Med. Chem. 1989, Vol. 32, No. 8, 1742-1749.	Aerschot

37 C.F.R. § 42.8 MANDATORY NOTICES

Pursuant to 37 C.F.R. § 42.8(b), Petitioner states as follows:

1. **Real Party-in-Interest (37 C.F.R. § 42.8(b)(1)).** Petitioner Shanghai Hongene Biotech Corporation is the real party-in-interest.

2. **Related Matters (37 C.F.R. § 42.8(b)(2)).** On February 18, 2022, Patent Owner ChemGenes Corporation (“ChemGenes”) filed a complaint asserting infringement of U.S. Patent No. 8,541,569 against “Hongene Biotechnology Ltd.” in the U.S. District Court for the District of Massachusetts, case no. 1:22-cv-10290-PBS. On March 30, 2022, ChemGenes filed a first amended complaint against “Hongene Biotechnology Ltd.” Neither complaint was served on Petitioner. On May 27, 2022, ChemGenes filed a second amended complaint against “Hongene Biotech Corporation (of Shanghai, China).” Service of the second amended complaint was accepted on behalf of Petitioner. On July 7, 2022, ChemGenes filed a notice of voluntary dismissal to dismiss the district court case. As of the date of this petition, Petitioner is not aware of any further district court proceedings being initiated regarding U.S. Patent No. 8,541,569.

3. Lead and Back-Up Counsel, and Service Information (37 C.F.R.

§§ 42.8(b)(3)-(4)). Petitioner identifies its counsel as follows:

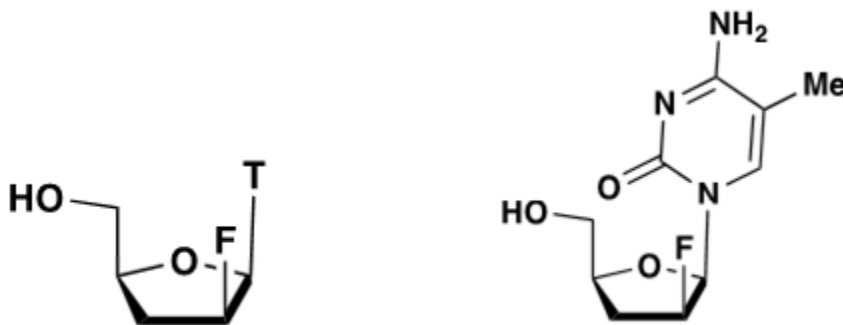
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I. INTRODUCTION

Petitioner Shanghai Hongene Biotech Corporation (“Petitioner”) requests *inter partes* review of Claims 1-2 of U.S. Patent No. 8,541,569 (“the ’569 Patent”), which claims an earliest priority date of September 6, 2008. This Petition is supported by the accompanying Expert Declaration of Professor Phil S. Baran, Ph.D. (Ex. 1003).

Claims 1 and 2 of the ’569 Patent are invalid as anticipated by a single prior art reference called Aerschot.

The following two species each fall within the scope of both Claim 1 and Claim 2:



Aerschot expressly discloses each of these species, depicting each structure, reciting each chemical name, and providing detailed information about how to synthesize each. Aerschot was published in 1989, nearly 20 years before the earliest claimed priority date of the ’569 Patent. Accordingly, as explained further below and supported by the accompanying exhibits, anticipation here is cut-and-dry.

II. GROUNDS FOR STANDING

Pursuant to 37 C.F.R. § 42.104(a), Petitioner certifies that the '569 Patent is available *for inter partes* review, and that Petitioner is not barred or estopped from requesting an *inter partes* review to challenge the patent claims on the grounds identified in this Petition. The Office is authorized to charge all fees due in connection with this proceeding to Deposit Account No. 50-2075.

III. IDENTIFICATION OF CHALLENGE

Pursuant to 37 C.F.R. § 42.104(b), Petitioner requests review and cancellation of Claims 1 and 2 of the '569 Patent pursuant to the following statement of precise relief requested:

Ground	Claim	Basis	Prior Art Reference*
I	1	§ 102(b)	Aerschot (Ex. 1004)
II	2	§ 102(b)	Aerschot (Ex. 1004)

* Full title in Exhibit List.

IV. TECHNOLOGY BACKGROUND

A. Structural Rendering and Nomenclature in Organic Chemistry

Chemists use standardized structures and nomenclature to depict organic molecules in a standardized and concise way. (Ex. 1003 at ¶¶ 32-43.) Structural depictions of organic molecules involves the use of lines and letters to represent atoms and bonds, R groups to represent variation in substitution, ring structures, and

implied carbons and hydrogens. (*Id.* at ¶¶ 33-34.) Lines are used to represent chemical bonds between atoms. A single line (-) represents a single bond, while a double line (=) represents a double bond. Triple lines ($\equiv$) represent a triple bond. (*Id.* at ¶35.) To simplify the rendering of chemical structures, carbons are implied at the intersection of two bond lines. (*Id.* at ¶36.) Further, where all available bonds to a carbon are not depicted, it is implied that the undepicted bonds are bonds to hydrogen atoms. (*Id.*)

To describe a group of compounds having some shared structure but whose members differ with respect to certain substitutions in specific locations, chemists conventionally use the placeholder symbol “R,” and separately identify the different atoms or groups of atoms that R may symbolize. (*Id.* at ¶37.) When it is desired to depict more than one variable location for a given shared structure, chemists may employ superscripts for R, such as R^1 , R^2 , etc. (*Id.*)

Chemists use a systematic, standardized way of naming chemical compounds based on their molecular structure. (*Id.* at ¶39.) Chemical nomenclature uses prefixes and suffixes to describe the substituents present in the compound, the location of substituents on a ring or chain, and the bonding arrangement between atoms. (*Id.*) A numerical prefix indicates the number of carbon atoms in the longest carbon chain. (*Id.*) The substituents present on the chain are then named using appropriate prefixes, with their location on the chain indicated by a number. (*Id.*) The suffix is then added

to indicate the functional group present in the compound. (*Id.*) The International Union of Pure and Applied Chemistry (IUPAC) is responsible for establishing and maintaining the standard naming system for chemical compounds. (*Id.*)

B. Stereochemistry

Stereochemistry is the study of the three-dimensional arrangement of atoms in molecules and how it affects their properties and behavior. (*Id.* at ¶40.) An important concept in stereochemistry is chirality. (*Id.*) A chiral molecule is not superimposable on its mirror image. (*Id.*) This means that a chiral molecule exists in two mirror-image forms, known as enantiomers. (*Id.*)

Stereoisomerism refers to the existence of different isomers that have the same molecular formula and connectivity but differ in their spatial arrangement of atoms. (*Id.* at ¶44.) Stereoisomers can be further classified into enantiomers, which are mirror-image isomers, and diastereomers, which are non-mirror-image stereoisomers. (*Id.*)

41. The structural depiction of stereochemistry involves the use of three-dimensional models, and two-dimensional representations that convey the same information. (*Id.* at ¶¶ 41-42.) These 2D representations include the use of wedges and dashed or squiggly lines (such as §) to indicate the spatial arrangement of atoms in a molecule. (*Id.* at ¶42.) A wedge indicates that the bond projects out of the plane of the paper or screen towards the viewer, while a dashed line indicates that the bond

projects into the plane of the paper or screen, away from the viewer. (*Id.*) A squiggly line indicates that the bond could project toward or away from the viewer. (*Id.*) These 2D representations are commonly used in textbooks, scientific papers, and chemical databases. (*Id.*)

In chemical nomenclature, stereochemistry is often expressed using symbols such as α , β , D, and L. (*Id.* at ¶43.) The α and β symbols are used to indicate the orientation of substituents on a cyclic molecule. (*Id.*) If the substituent is oriented towards the ring's convex side, it is labeled α , while if it is oriented towards the concave side, it is labeled β . (*Id.*) The D and L symbols are used to indicate the absolute configuration of chiral molecules. (*Id.*)

C. Synthetic Organic Chemistry Techniques

Synthetic organic chemistry is the field of chemistry focusing on the preparation of organic compounds through chemical reactions. (*Id.* at ¶45.) Synthetic organic chemists use various techniques to carry out chemical reactions, and analytical techniques to monitor the reactions and purify the products. (*Id.*) As of the priority date there were an array of well-developed synthetic and analytical techniques well-known to and routinely used by a POSA. (*Id.*)

Refluxing is a commonly-used technique in which a reaction mixture is heated to its boiling point under constant stirring, and the resulting vapor is condensed and returned to the reaction vessel. (*Id.* at ¶46.) Refluxing is useful for reactions that

require prolonged heating, as it allows for continuous boiling and prevents the reaction mixture from boiling dry. (*Id.*)

Thin-layer chromatography (TLC) is another commonly used technique and is used to separate the components of a mixture based on their polarity. (*Id.* at ¶47.) A small amount of the mixture is spotted onto a stationary phase, which is a thin layer of an adsorbent material such as silica gel or alumina, and then developed using a mobile phase, which is a solvent that moves up the stationary phase via capillary action. (*Id.*) The components of the mixture are separated based on their different affinities for the stationary and mobile phases, and can be visualized using UV light or a staining agent. (*Id.*)

Column chromatography is a common technique for separating the components of a mixture based on their different affinities for a stationary phase and a mobile phase. (*Id.* at ¶48.) The components of the mixture are separated based on their different affinities for the stationary and mobile phases, and are eluted from the column in order of decreasing polarity. (*Id.*)

In addition, chemists use a variety of analytical techniques to characterize and identify the products of chemical reactions. (*Id.* at ¶49.) These techniques include: melting point analysis to determine the melting point of a compound to help identify and characterize organic solids; ultraviolet (“UV”) analysis, to measure the absorption of UV light by a compound and detect conjugated systems in organic

compounds; and various types of nuclear magnetic resonance (NMR) to determine the structure and purity of organic compounds by analyzing their nuclear magnetic resonance spectra. (*Id.*) Finally, elemental analysis is used to determine the elemental composition of a compound, and can be useful for verifying the purity of a compound or determining its empirical formula. (*Id.*)

D. Nucleotide Chemistry

Nucleotides are the molecular building blocks of deoxyribonucleic acid (“DNA”) and ribonucleic acid (“RNA”). (*Id.* at ¶50.) DNA and RNA are nucleic acids, which are macromolecules that store genetic information and enable protein production. (*Id.*) DNA and RNA are typically made up of millions of nucleotides bound together in a long chain. (*Id.*)

DNA is made up of a complementary pair of nucleotide chains that coil around each other in the famous “double helix” three-dimensional configuration. (*Id.* at ¶51.) The two chains of a DNA macromolecule are connected to one another by bonds between complementary subunits called “nucleobases,” or more simply “bases.” (*Id.*) **Figure 1** (below) is a general depiction of the basic structure of DNA:

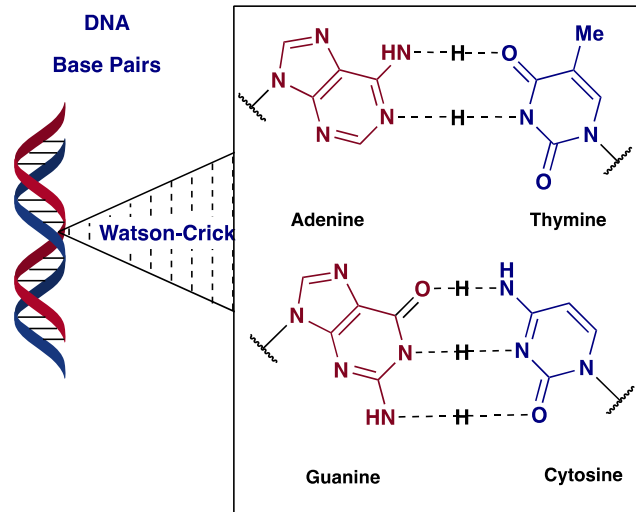


Figure 1: Basic Structure of DNA

(*Id.*)

RNA is a single chain of nucleotides, as opposed to a complementary pair of chains. (*Id.* at ¶52.)

Nucleotides have identifiable substructures. (*Id.* at ¶53.) **Figure 2** below depicts the substructures of a generalized nucleotide, and identifies the chemical bonds between those substructures:

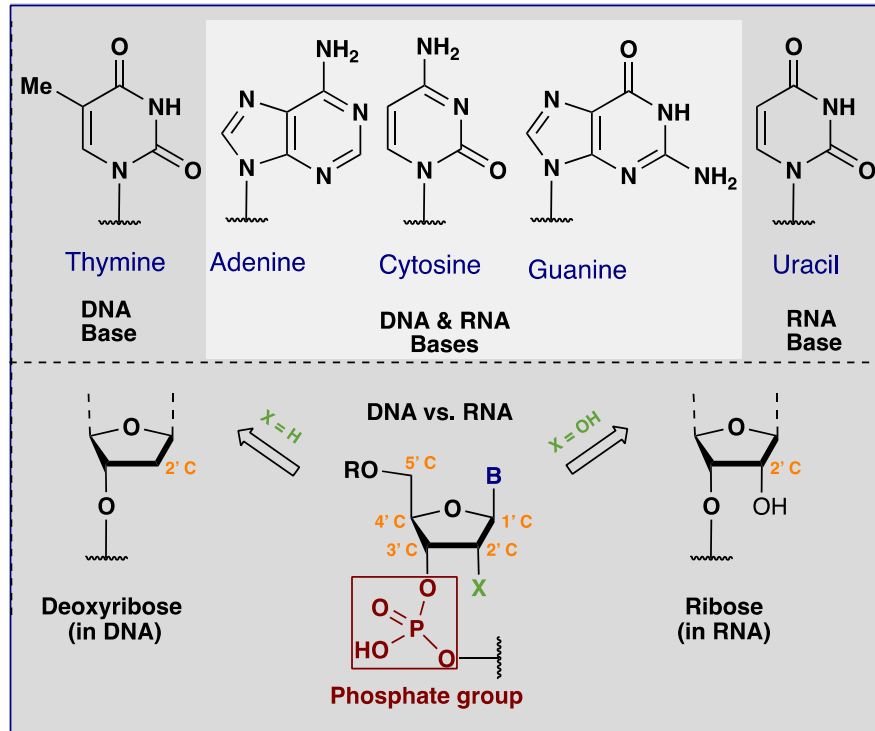


Figure 2: Nucleotide Substructure

(*Id.*)

Nucleotides are made up of three substructures: (1) a five-carbon sugar ring, (“deoxyribose” in DNA and “ribose” in RNA); (2) a “phosphate group,” and (3) one of four major “nucleobases.” (*Id.* at ¶54.)

There are four major nucleobases in DNA: adenine (“A”), thymine (“T”), cytosine (“C”), and guanine (“G”). (*Id.* at ¶55.) RNA contains uracil (“U”) instead of thymine, so the four major nucleobases in RNA are A, C, G, and U. (*Id.*)¹ **Figure**

¹ The four major nucleobases for DNA and RNA, respectively, are often referred to as “canonical” nucleobases. There are other “non-canonical” nucleobases. (*Id.*)

2 (above) depicts the chemical structure of each nucleobase. (*Id.*) Adenine and guanine each has a double ring structure and are “purines.” (*Id.*) Cytosine, thymine, and uracil each has a single ring structure and are “pyrimidines.” (*Id.*)

Chemists use standard numbering to identify positions of each carbon atom (“C”) in the five-carbon sugar ring of a nucleotide. (*Id.* at ¶56.) As shown in **Figure 2** (above), these numbered positions are given prime (“’”) designations to distinguish them from the numbered positions on the ring(s) of the attached nucleobase. (*Id.*) In standard chemical nomenclature, this numbering is employed to identify the locations of bonds between the component parts of the molecule being named. (*Id.*)

Oligonucleotides are relatively short nucleotide chains, generally a few hundred or fewer nucleotides. (*Id.* at ¶57.) “Oligo” is Greek for “few” or “small.” (*Id.*) They have the same general structural features as DNA and RNA discussed above. (*Id.*) Oligonucleotides have many important uses in research, genetic testing, forensics, diagnostics, and therapeutics. (*Id.*)

The sugar rings and nucleobase rings of nucleotides have reactive hydroxyl (-OH) and amine (-NH₂) functional groups, which tend to engage in undesirable side reactions during oligonucleotide synthesis. (*Id.* at ¶58.) Thus, chemists have long found it useful to modify nucleotides by shielding these groups with “protecting groups” during synthesis, and then converting them back into -OH or -NH₂ (*i.e.*,

“deprotecting” these groups) when appropriate, for example, after the formation of the desired oligonucleotide sequence. (*Id.*)

Modern oligonucleotide synthesis employs molecules called nucleoside phosphoramidites (also called nucleoside amidites or simply “phosphoramidites”) to provide longer and better controlled oligonucleotide sequences with higher yields and greater purity. (*Id.* at ¶59.) A nucleoside is a nucleotide without its phosphate group. (*Id.*)

A phosphoramidite is characterized as a phosphorus atom in its P(III)-oxidation state having three substituents: one substituted amine group and two oxygen-containing functional groups. (*Id.* at ¶60.) Of the two oxygen-containing functional groups, one is usually a protecting group and the other is attached to a nucleoside. (*Id.*) Phosphoramidites are highly reactive. Since their discovery, this high reactivity has led to their widespread adoption and optimization as key reagents in oligonucleotide synthesis.

Oligonucleotide synthesis takes advantage of the directionality of oligonucleotides, to build nucleotides in the 3'→5' direction traditionally, but also in the “reverse” 5'→3' direction, as in the '569 patent. (*Id.* at ¶61.)

Reverse oligonucleotide synthesis refers to the process of synthesizing oligonucleotides in the 5' → 3' direction, which is opposite to the traditional 3' → 5' direction. (*Id.* at ¶62.) While the traditional 3' → 5' direction has been the standard

in oligonucleotide synthesis for many years, there are several advantages to using reverse oligonucleotide synthesis.

V. CLAIM CONSTRUCTION AND THE “POSA”

Petitioner does not propose any special construction of any term of Claims 1 or 2, and instead applies the ordinary and customary meaning of the relevant claim language as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent. 37 C.F.R. § 42.100.

As of September 8, 2008, a person of ordinary skill in the art (“POSA”) would have had a Ph.D. (or equivalent degree) in organic or medicinal chemistry, and 2-3 years of post-graduate work experience in medicinal chemistry, synthetic organic chemistry, and nucleic acid chemistry, including the development of oligonucleotide therapeutics, diagnostics, or building blocks. (Ex. 1003 at ¶¶18-21.)

Alternatively, someone who had at least three years of work experience in these fields, and who had gained a thorough understanding of the development of nucleic acid-based materials, would also have qualified as a POSA with a Bachelor’s or Master’s degree in organic chemistry or medicinal chemistry. (*Id.*)

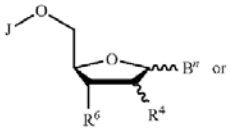
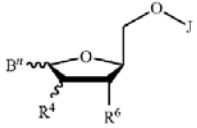
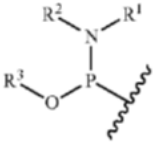
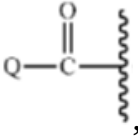
VI. THE CHALLENGED CLAIMS ARE UNPATENTABLE

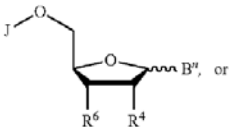
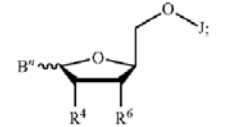
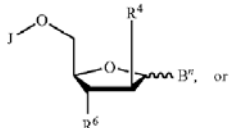
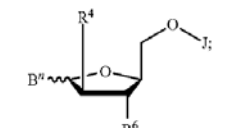
A. Ground I: Claim 1 of the ’569 Patent is Anticipated Under 35 U.S.C. § 102(b) by Aerschot.

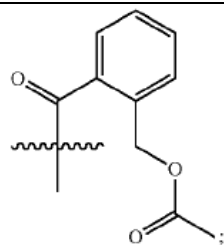
Aerschot anticipates at least two species that fall within the scope of Claim 1 of the ’569 Patent. (Ex. 1003 at ¶¶ 74-124.) The disclosure of these two compounds

in Aerschot is express and unambiguous. (Ex. 1004 at 1744 (compounds 12a and 15a); Ex. 1003 at ¶¶77, 88-92, 108-110.) And although Aerschot is presumed enabling and Petitioner does not need to demonstrate enablement in the first instance in its Petition, Aerschot is clearly enabling as to both anticipatory species. (Ex. 1003 at ¶¶ 93-105, 112-124.)

Claim 1 of the '569 Patent is lengthy, but the below table recites the most pertinent parts of Claim 1, with the portions most germane to the anticipation analysis emphasized in bold, and truncations explained in bracketed italics:

A compound of Formula Ia or 1b:	
 (Ia)	
 (Ib)	
or salt thereof,	
	
wherein J is H ,	
wherein  indicates where J is attached to the O atom;	
[R ¹ , R ² , R ³ , and Q limitations not applicable when J is H]	
R⁴ is a -halo , —R ⁵ , —NR ⁷ R ⁸ , —OR ⁹ , —SR ¹⁰ , or 2'-blocking group; or when Structural Formula Ia or Ib is:	

	(II)  (III) 
wherein R^4 is further selected from $O-Si(R^{11})_3$ or $O-CH_2-Si(R^{11})_3$; or when Structural Formula Ia or Ib is:	
	(IV)  (V) 
R^4 is further selected from $-OC(=O)R^{12}$;	
$[R^5 \text{ limitation not applicable when } R^4 \text{ is a -halo}]$	
R^6 is $-H$ or $-O-Z$;	
$[R^7, R^8, R^9, R^{10}, R^{11}, R^{12} \text{ and } Z \text{ limitations not applicable when } J \text{ is } H, R^4 \text{ is a -halo, and } R^6 \text{ is } -H]$	
B^n is hydrogen or an optionally substituted nucleobase optionally functionalized at each exocyclic amine with an amine protecting group, wherein the nucleobase is selected from...thymine...[and]...5-methylcytosine...;	
wherein any substitutable nitrogen atom within the nucleobase or on the exocyclic amine is optionally substituted with <i>[list of groups]</i>; and	



wherein any substitutable oxygen atom within the nucleobase is optionally substituted with $\text{—C(=O)N(C}_1\text{–C}_6\text{alkyl)}_2$ or —C(=O)N(phenyl)_2 .

(Ex. 1001 at 111:20-114:34; Ex. 1003 at ¶78.)

Claim 1 thus covers a group of compounds, and the members of that group differ with respect to the identity of certain variable substituents. (Ex. 1003 at ¶79.) For compound Ia, there are four primary variable substituents, identified as “J,” “R⁴,” “R⁶,” and “Bⁿ”, respectively. (*Id.* at ¶80.) The wavy lines representing the bonds between the ribose ring structure on the one hand, and either the R⁴ group or the Bⁿ group, on the other hand, indicate either the 2’-functionality or relevant nucleobase, respectively, with all possible stereochemical permutations. (*Id.*) This is confirmed by the specification, which indicates that the structure of compound Ia covers several different stereochemical permutations. (Ex. 1001 at 33:5-67; Ex. 1003 at ¶80.)

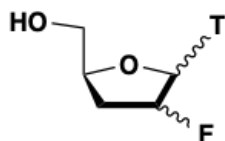
A claim to a genus of compounds is anticipated if the prior art discloses a single species in that genus. *See, e.g., Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985); *Brown v. 3M*, 265 F.3d 1349, 1351 (Fed. Cir. 2001). Here,

as explained below, Aerschot expressly discloses at least two species that fall within the scope of claim 1. Each of those disclosed species independently anticipates Claim 1.

1. Aerschot Compound 12a Expressly Anticipates Claim 1.

One compound that falls within the scope of Claim 1 is Formula Ia in which J is H (hydrogen), R⁴ is the -halo atom fluorine, R⁶ is —H (hydrogen), and Bⁿ is thymine (“T”).² (Ex. 1003 at ¶¶ 81-83, 85.) That compound has the following structure:

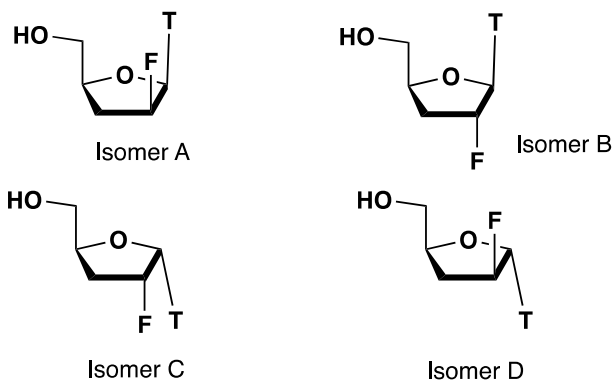
² Thymine satisfies the Bⁿ limitation as a nucleobase because thymine is a nucleobase and is expressly listed in the claim as an option for Bⁿ. (Ex. 1001 at 113:57; Ex. 1003 at ¶83.) The claim does not require the nucleobase of Bⁿ to be substituted or functionalized with an amine protecting group. (Ex. 1003 at ¶84.) According to the claim language itself, substitution and functionalization of the Bⁿ nucleobase are both merely optional. (See Ex. 1001 at 113:42-43 (“an **optionally substituted** nucleobase **optionally functionalized** at each exocyclic amine with an amine protecting group.”) (emphases added); see also Ex. 1003 at ¶84.) This confirmed by the recitation of thymine as one of the available nucleobases, because thymine is not substituted and does not have an exocyclic amine, let alone an amine protecting group. (Ex. 1003 at ¶84.) To be anticipatory, the prior art need not disclose optional



(Ex. 1003 at ¶86.)

The above structure covers the following four different potential stereoisomeric configurations of that compound, in which the positions of fluorine and thymine vary relative to the plane of the ring structure and each other (both “up” (A), both “down” (C), fluorine up while thymine down (D), and fluorine down while thymine up (B)):

features of a claim. *In re Johnston*, 435 F.3d 1381, 1384 (Fed. Cir. 2006) (“optional elements do not narrow the claim because they can always be omitted”); *Butamax Advanced Biofuels LLC v. Gevo, Inc.*, IPR2014-00250, 2014 WL 2187772 at *8 (PTAB May 22, 2014) (instituting IPR based on anticipation, finding that the prior art did not need to disclose optional claim limitations to be anticipatory); *In re OxyContin Antitrust Litigation*, 994 F.Supp.2d 367, 381, 425 (S.D.N.Y. 2014) (“Whether a device includes or excludes the optional element does not determine whether it is an embodiment of the claimed invention, [] so optional elements do not affect an anticipation analysis.”).

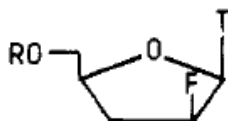


(*Id.* at ¶87.)

Aerschot is a journal article that on its face indicates that it was published in 1989 in the Journal of Medicinal Chemistry. (Ex. 1004 at *passim*; Ex. 1003 at ¶75.) Its 1989 date of publication appears in the citation header on each page. (Ex. 1004 at *passim*; Ex. 1003 at ¶75.) It also bears a 1989 copyright date on the first page. (Ex. 1004 at 1743; Ex. 1003 at ¶75.) As also indicated on the face of Aerschot, the Journal of Medicinal Chemistry in 1989 was a publication by the American Chemical Society (“ACS”). (Ex. 1004 at 1743; Ex. 1003 at ¶75.) The Journal of Medicinal Chemistry in 1989 was a well-established, well-known, and reputable publication that routinely published scientific papers. (Ex. 1003 at ¶75.) ACS was a well-known and reputable professional society. (*Id.*) Aerschot indicates on its face to a POSA that the Aerschot article was publicly available and accessible no later than 1989. (*Id.*) Aerschot is therefore prior art to the ’569 Patent under 35 U.S.C. §102(b) (pre-AIA).

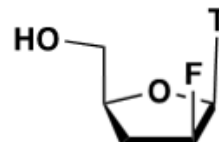
Aerschot expressly disclosed Isomer A of claim 1. (Ex. 1003 at ¶¶ 88-92.) Aerschot referred to that isomer as compound 12a. (Ex. 1004 at 1744; Ex. 1003 at ¶88.) Below is the image from Aerschot, side-by-side with Isomer A of claim 1:

Aerschot compound 12a:



12 a R = H
 b R = MMTr

Isomer A Species of Claim 1



(Ex. 1004 at 1744; Ex. 1003 at ¶¶ 87-88.)

A POSA would immediately appreciate and know that these compounds are identical, including that “T” in both represents thymine. (Ex. 1003 at ¶¶ 87-92.) This is further confirmed by the chemical name provided for compound 12a in Aerschot, which corresponds precisely to Isomer A. (*Id.* at ¶¶ 90-91.) Indeed, Aerschot identifies compound 12(a) as “1-(2-Fluoro-2,3-dideoxy-β-D-threo-pentofuranosyl)thymine.” (Ex. 1004 at p.1745 (stating that “1-(2-Fluoro-2,3-dideoxy-β-D-threo-pentofuranosyl)thymine (**12a**) was obtained from 11b in 57% crystalline yield.”) (bold emphasis in original, underlining emphases added); *see also id.* at p.1747, left column, first paragraph (“**1-(2-Fluoro-2,3-dideoxy-β-D-threo-pentofuranosyl)thymine (**12a**)**.” (bold emphasis in original, underlining emphasis added).)

Because Aerschot is anticipatory prior art, it is presumed enabling, and Petitioner does not have to demonstrate herein that Aerschot enables a POSA to make compound 12a. *Apple v. Corephotonics, Ltd.*, 861 Fed. Appx. 443, 450 (Fed. Cir. 2021) (finding that it was error to shift to Petitioner the burden of providing evidence in its petition that the asserted anticipatory art was enabled).

Nevertheless, applying the *Wands* factors, Aerschot clearly is enabling, and would not have required a POSA to engage in undue experimentation to make Aerschot compound 12a. (Ex. 1003 at ¶¶94-105; see *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Aerschot contains robust, detailed, step-by-step instructions for synthesizing compound 12a. (Ex. 1004 at 1744-45, 1747; Ex. 1003 at ¶¶ 96.) First, in the Chemistry section beginning on page 1744, Aerschot provides a method for the synthesis of compound 12a, identifying at least the following: the starting materials and intermediates used; the reagents; reaction media; reaction conditions, including time and temperature; the synthetic organic chemistry techniques employed; the percent yield at each step; and citations to supporting scientific literature. (Ex. 1004 at 1744-45; Ex. 1003 at ¶¶ 96.)

Second, in the “Experimental Section” beginning on page 1747, Aerschot provides even more detailed instructions on how to synthesize compound 12a. (Ex. 1004 at 1747; Ex. 1003 at ¶ 97.) This section also reports various characterization and identification data for compound 12a, including data for melting point (“mp”),

UV absorption (“UV”), mass spectrometry (“MS”), and nuclear magnetic resonance (“NMR”). (*Id.*)

A POSA following the disclosures in Aerschot would not have had to engage in very much, if any, experimentation to make compound 12a. (Ex. 1003 at ¶¶ 99-100.) This supports enablement. Given the advanced education and training of a POSA, making compound 12a would have been well within their technical skill. (*Id.*) Given the extensive disclosure in Aerschot, making compound 12a would have been a routine, predictable endeavor. (*Id.* at ¶104.) This, too, supports enablement.

Also, a POSA would understand from Aerschot that the authors had actually made, characterized, and tested compound 12a. (Ex. 1003 at ¶98.) Thus, Aerschot contains a working example, which further supports enablement. (*Id.* at ¶101.)

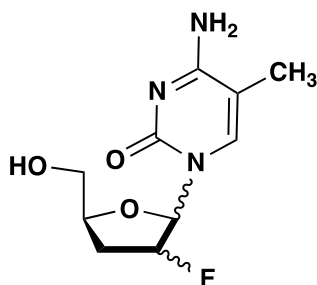
The state of the relevant art was well-developed, which further supports enablement. (*Id.*) Indeed, Aerschot itself demonstrates that the art was well-developed with detailed instructions on how to make compound 12a. (*Id.* at ¶101.) Further, Aerschot cites publications to support its disclosure of various aspects of the synthesis of compound 12a. (Ex. 1003 at ¶102.) This further demonstrates the well-developed state of the art. (*Id.*)

Accordingly, compound 12a of Aerschot anticipates claim 1.

2. Aerschot Compound 15a Expressly Anticipates Claim 1 of the '569 Patent.

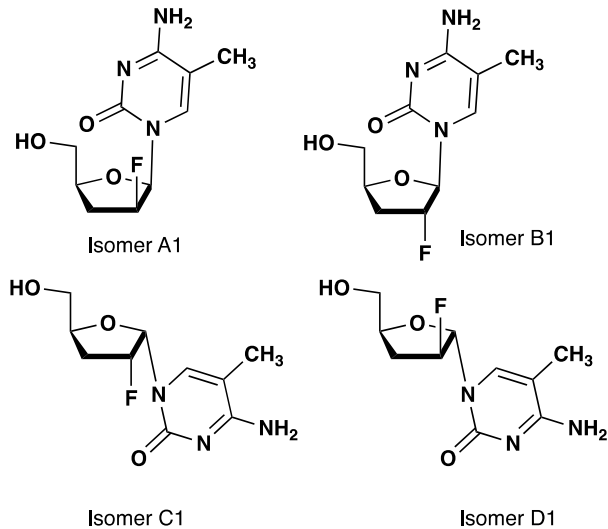
Another species of claim 1 is the compound of Formula Ia wherein J is H, R⁴ is the -halo fluorine, R⁶ is —H, and Bⁿ is 5-methylcytosine. (Ex. 1003 at ¶106.)

Below is the structure of that claimed compound:



(*Id.*)

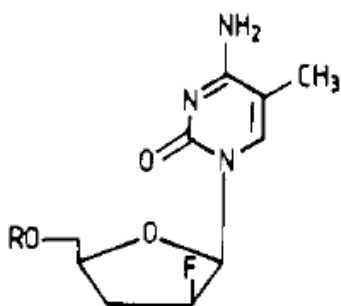
The only difference between this compound and the compound discussed in the preceding section is that in this compound, Bⁿ is 5-methylcytosine instead of thymine. (Ex. 1003 at ¶106, n.3.) The wavy bonds in this structure mean that it encompasses four stereoisomers of the compound, in which the positions of fluorine and 5-methylcytosine vary relative to the plane of the ring structure and each other (both “up”, both “down”, fluorine up while 5-methylcytosine down, and fluorine down while 5-methylcytosine up). (*Id.* at ¶ 107.) These four stereoisomers are depicted below:



(*Id.*)

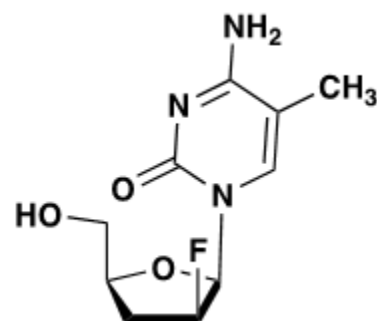
Aerschot expressly disclosed Isomer A1 of this compound, and thus expressly anticipates Claim 1 of the '569 Patent. (*Id.* at ¶108; Ex. 1004 at 1744.) In Aerschot, this isomer was referred to as compound 15a. (*Id.*) For ease of comparison, below is the Aerschot compound 15a structure side-by-side with Isomer A1. The two are chemically identical, because in Aerschot compound 15a, “R” is H:

Aerschot Compound 15a



¹⁵
 a R = H
 b R = MMTr

Isomer A1 of Claim 1



(Ex. 1003 at ¶¶ 107-108.)

Aerschot also identifies the chemical name of compound 15a as “1-(2-Fluoro-2,3-dideoxy- β -D-threo-pentofuranosyl)-5-methylcytidine.” (Ex. 1004 at p.1747, right column, third full paragraph; Ex. 1003 at ¶110.) 5-methylcytidine (as used in Aerschot) and 5-methylcytosine (as used in claim 1 in the list of possible nucleobases that could satisfy the Bⁿ limitation) are merely two different names for the same nucleobase. (*Id.* at ¶111.) Accordingly, another name for compound 15a is 1-(2-Fluoro-2,3-dideoxy- β -D-threo-pentofuranosyl)-5-methylcytosine. (*Id.*)

Because Aerschot is anticipatory prior art, it is presumed enabling, and Petitioner does not have to demonstrate herein that Aerschot enables a POSA to make compound 15a. *Apple v. Corephotonics, Ltd.*, 861 Fed. Appx. 443, 450 (Fed. Cir. 2021).

Nevertheless, applying the *Wands* factors, Aerschot clearly is enabling. (Ex. 1003 at ¶¶ 112-124; see *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Aerschot contains robust, detailed, step-by-step instructions for synthesizing compound 15a. (Ex. 1004 at 1744-45, 1747; Ex. 1003 at ¶¶ 115-116, 120.) First, in the Chemistry section beginning on page 1744, Aerschot provides a method for the synthesis of compound 15a, identifying at least the following: the starting materials and intermediates used; the reagents; reaction media; reaction conditions, including time and temperature; the synthetic organic chemistry techniques employed; the percent

yield at each step; and citations to supporting scientific literature. (Ex. 1004 at 1744-45; Ex. 1003 at ¶115.)

Second, in the “Experimental Section,” beginning on page 1747, Aerschot provides even more detailed instructions on how to synthesize compound 15a. (Ex. 1004 at 1747-48; Ex. 1003 at ¶116.) This section also reports various characterization and identification data for compound 15a, including data for melting point (“mp”), UV absorption (“UV”), mass spectrometry (“MS”), and nuclear magnetic resonance (“NMR”). (*Id.*)

A POSA following the disclosures in Aerschot would not have had to engage in undue experimentation to make compound 15a. (Ex. 1003 at ¶113.) In fact, a POSA would not have had to engage in very much, if any, experimentation to make compound 15a. (*Id.* at ¶118.) This supports enablement. Given the advanced education and training of a POSA, making compound 15a would have been well within their technical skill set. (*Id.* at ¶¶118-119, 122.) Given the extensive disclosure in Aerschot, making compound 15a would have been a routine, predictable endeavor. (*Id.* at ¶123.) All of this, too, supports enablement.

Also, a POSA would understand from Aerschot that the authors had actually made, characterized, and tested compound 15a. (*Id.* at ¶117.) Thus, Aerschot contains a working example, which further supports enablement. (*Id.* at ¶120.)

The state of the relevant art was well-developed, which further supports enablement. (*Id.* at ¶¶ 120-121.) Indeed, Aerschot itself demonstrates that the art was well-developed with detailed instructions on how to make compound 15a. (*Id.* at ¶120.) Further, Aerschot cites publications to support its disclosure of various aspects of the synthesis of compound 15a. (*Id.* at ¶121.) This further demonstrates the well-developed state of the art. (*Id.*)

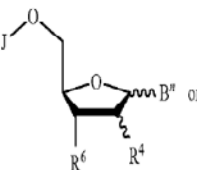
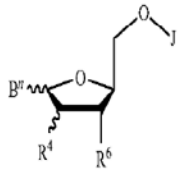
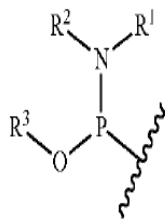
Accordingly, compound 15a of Aerschot anticipates claim 1.

B. Ground 2: Claim 2 of the '569 Patent is Anticipated Under 35 U.S.C. § 102(b) by Aerschot.

Claim 2 overlaps with Claim 1, and encompasses the same two compounds discussed above for Claim 1. (Ex. 1003 at ¶¶ 126-131.) Accordingly, as explained further below and above, Aerschot compounds 12a and 15a also anticipate Claim 2. (*Id.* at ¶132.)

Claim 2 of the '569 Patent is lengthy, but the below table recites the most pertinent parts of Claim 2, with the portions most germane to the anticipation analysis emphasized in bold and truncations explained in bracketed italics:

A compound of Formula Ia or Ib:
--

(Ia)  (Ib)  or a salt thereof,	 wherein J is H or
<i>[R¹, R², and R³ limitations not applicable when J is H]</i>	
R⁴ is a -halo, —R⁵, —NR⁷R⁸, —OR⁹, —SR¹⁰, or 2'-blocking group; <i>or [recites alternatives for R⁴ when Structural Formula Ia or Ib is in recited stereochemical configurations];</i>	
<i>[R⁵ limitation not applicable when R⁴ is -halo]</i>	
R⁶ is —H or —O—Z;	
<i>[R⁷ limitation not applicable when J is H, R¹ is not applicable, R² is not applicable, R⁴ is a -halo, and R⁵ is not applicable]</i>	

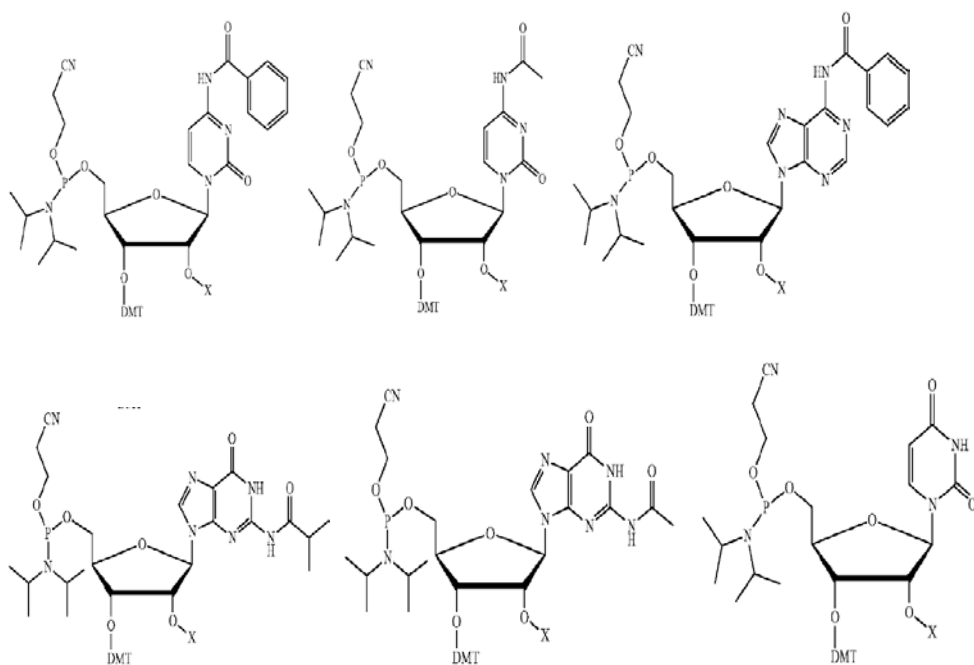
[R^8 limitation not applicable when R^4 is a -halo and R^5 is not applicable and R^7 is not applicable]

[R^9 and R^{10} limitations not applicable when R^4 is a -halo and R^5 is not applicable]

[R^{11} and R^{12} limitations not applicable when R^4 is a -halo]

[Z limitation not applicable when R^6 is —H]

Bⁿ is hydrogen or an optionally substituted **nucleobase** optionally functionalized at each exocyclic amine with an amine protecting group, provided that the compound is not represented by one of the following structural formulas:



wherein X is tert-butyldimethylsilyl or triisopropylsiloxymethyl.

(Ex. 1001 at 114:35-117:52; Ex. 1003 at ¶126.)

In Formula Ia of Claim 2, when J is H (hydrogen), R⁴ is the -halo fluorine, R⁶ is —H (hydrogen), and Bⁿ is either thymine or 5-methylcytosine, those two compounds (hereinafter referred to as “the thymine compound” and the “5-methylcytosine compound,” respectively) are the same ones discussed above for Claim 1. (Ex. 1003 at ¶ 126-131.)³

For the reasons discussed above for Claim 1, Aerschot discloses, enables, and anticipates each of those two species of Claim 2. (Ex. 1003 at ¶132.) Specifically, compound 12a of Aerschot is identical to Formula Ia of Claim 2 wherein J is H (hydrogen), R⁴ is the -halo fluorine, R⁶ is —H (hydrogen), and Bⁿ is thymine. (*Id.*)

³ As is readily apparent from the structures of those compounds, neither is excluded from the scope of claim 2 by the proviso at the end of claim 2. (Ex. 1003 at ¶130.) Neither the thymine compound nor the 5-methylcytosine compound corresponds to any of the six excluded structures. (*Id.*) For example, all of the excluded compounds have a DMT group and a cyanoethyl group (CN-CH₂-CH₂-), whereas neither the thymine compound nor the 5-methylcytosine compound contains either such group. (*Id.*) As a further example, neither the thymine compound nor the 5-methylcytosine compound contains a tert-butyldimethylsilyl or triisopropylsiloxymethyl group. (*Id.*)

Likewise, compound 15a of Aerschot is identical to Formula Ia of Claim 2 wherein J is H (hydrogen), R⁴ is the -halo fluorine, R⁶ is —H (hydrogen), and Bⁿ is 5-methylcytosine. (*Id.*)

VII. CONCLUSION

For the foregoing reasons, Claims 1 and 2 of the '569 Patent are unpatentable. Petitioner requests institution of an *inter partes* review and cancellation of these claims.

Respectfully submitted,
PROCOPIO, CORY, HARGREAVES & SAVITCH LLP

Dated: April 20, 2023

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CERTIFICATE OF COMPLIANCE

I, the undersigned, hereby certify that the above Petition for *Inter Partes* Review complies with the type-volume limitations of 37 C.F.R. § 42.24(a)(1)(i). Exclusive of the portions exempted by 37 C.F.R. § 42.24(a)(1), this Petition, including footnotes, contains 5,885 words as counted by the word count function of Microsoft Word.

Dated: April 20, 2023

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CERTIFICATE OF SERVICE

I, the undersigned, hereby certify that a copy of the above Petition for *Inter Partes* Review of U.S. Patent No. 8,541,569, along with all exhibits supporting and filed with the Petition, were served on April 20, 2023 via FedEx overnight courier delivery directed to counsel of record for U.S. Patent No. 8,541,569 and counsel of record for Patent Owner ChemGenes Corporation in the related district court case at the following addresses:

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