



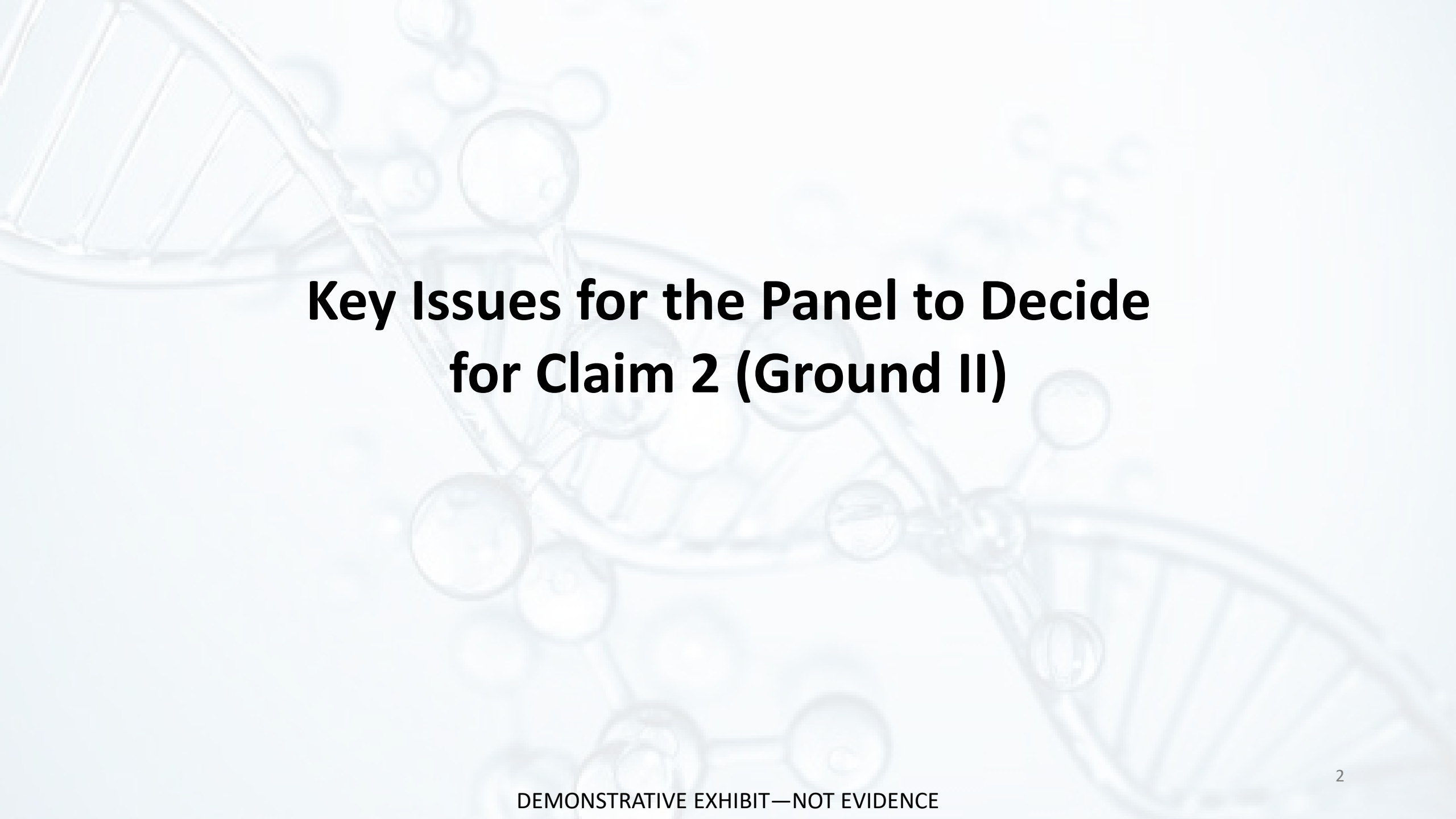
IPR2023-00490
U.S. Patent No. 9,884,885 B2

Oral Argument
Patent Owner Demonstrative Exhibit

April 23, 2024

CHEMGENES DEMONSTRATIVE EXHIBIT 2043
Shanghai Hongene v. ChemGenes
Case IPR2023-00490

DEMONSTRATIVE EXHIBIT—NOT EVIDENCE

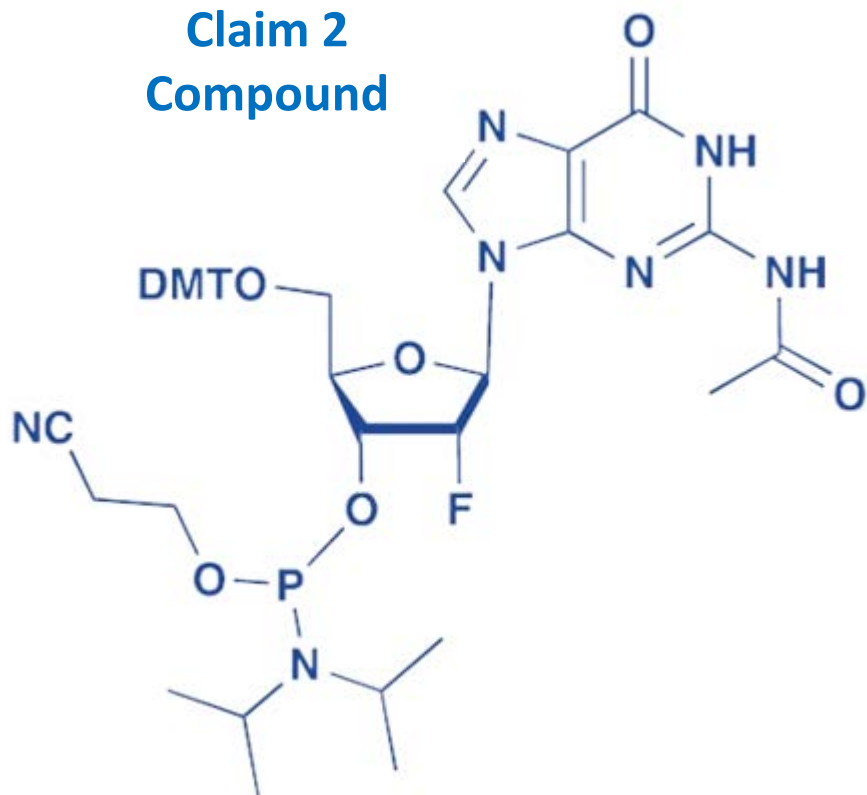


Key Issues for the Panel to Decide for Claim 2 (Ground II)

Key Issues: Claim 2 (Ground II)

✓ Key Issues Before the Panel

Claim 2
Compound



1. Whether the **Lead Compound Analysis (“LCA”)** applies and, if so, whether Hongene has carried its burden to show a POSA **would have selected Compound x** as a lead, or a starting point, for further development efforts. [See slides 52-63](#)
2. Whether Hongene has carried its burden to show a POSA would have been **motivated to modify Compound x** to use acetyl instead of isobutyryl to protect the N2-position of guanine based on Pitsch and Fan. [See slides 64-80](#)
3. Whether Hongene has carried its burden to show a POSA would have had a **reasonable expectation of success** in synthesizing the subject Claim 2 compound. [See slides 81-87](#)
4. Whether the **evidence of unexpected results** and satisfaction of long-felt need further demonstrate the non-obviousness of the subject Claim 2 compound. [See slides 88-93](#)
5. The **weight of expert testimony** submitted. [See slides 40-50](#)

1. Whether LCA applies and has been satisfied.



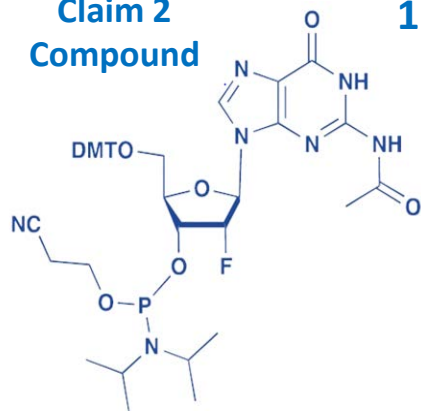
Why ChemGenes Prevails

1. LCA applies to the new Claim 2 compound at bar and Hongene did not apply or satisfy LCA.

- Hongene erroneously **chose not to apply LCA** on the basis the compounds are “**reagents**” and failed to satisfy this well-established standard that protects against hindsight. [See slides 52-55](#)
- A POSA **would not have selected** Compound x as a lead, or starting point, for further development efforts.
 - Compound x was **among thousands** of potential nucleosides in the prior art. [See slides 56-57](#)
 - “**Utility**” of Compound x for use in SPOS “**alone**” does not satisfy LCA. [See slide 58](#)
 - Compound x was **not identified as a lead** in its own disclosure. [See slides 59-60](#)
 - Compound x had known **degradation problems** and would not have been chosen as a lead or starting point.

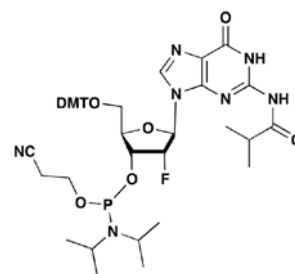
[See slides 61-62](#)

Claim 2
Compound



1.

Compound x
'031 Patent



Hindsight

Pitsch

Compound 20

Fan

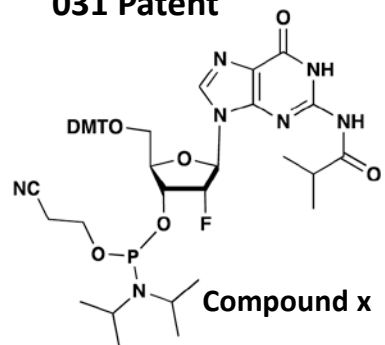
Compound 6a

2. Whether Pitsch and Fan would have motivated a POSA to modify Compound x.

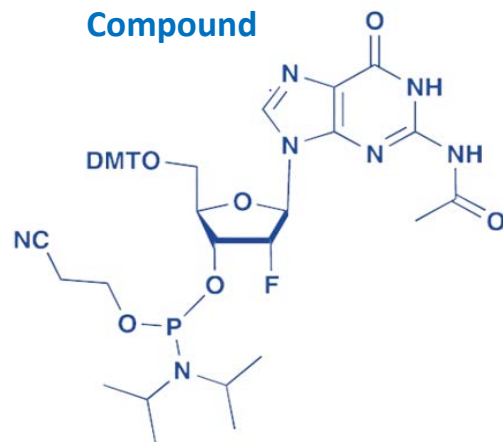


Why ChemGenes Prevails

'031 Patent



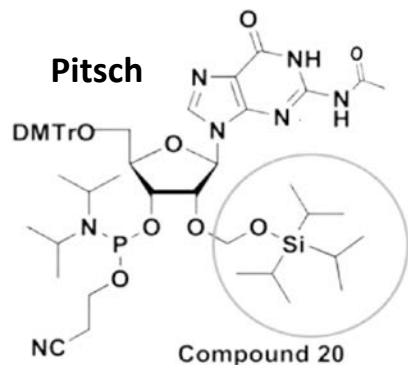
Claim 2
Compound



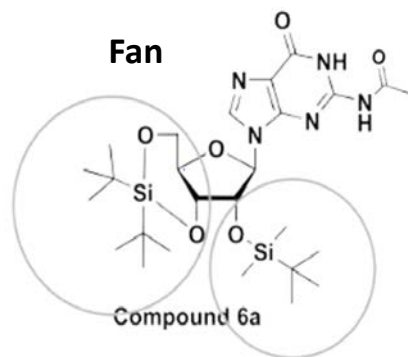
2. A POSA would not have been motivated to modify Compound x based on Pitsch and Fan.

- Pitsch's teachings regarding acetyl applied to the **TOM-protected RNA** it studied and **not "universally"** to all nucleosides. Fan was similarly limited to RNA derivatives (that could not even be used during SPOS). [See slides 65-66](#)
- Khorana **taught away** from using acetyl to protect the N2-position of guanine and the subsequent breadth of literature followed suit. [See slides 68-74](#)
- Guanosine had **known solubility issues** and using acetyl on Compound x would have made it **less soluble in organic solvents**. [See slides 75-77](#)
- Compound x had **known degradation problems** and a POSA would not have been motivated to modify it based on Pitsch, Fan or otherwise. [See slides 61-62, 78-80](#)

Pitsch

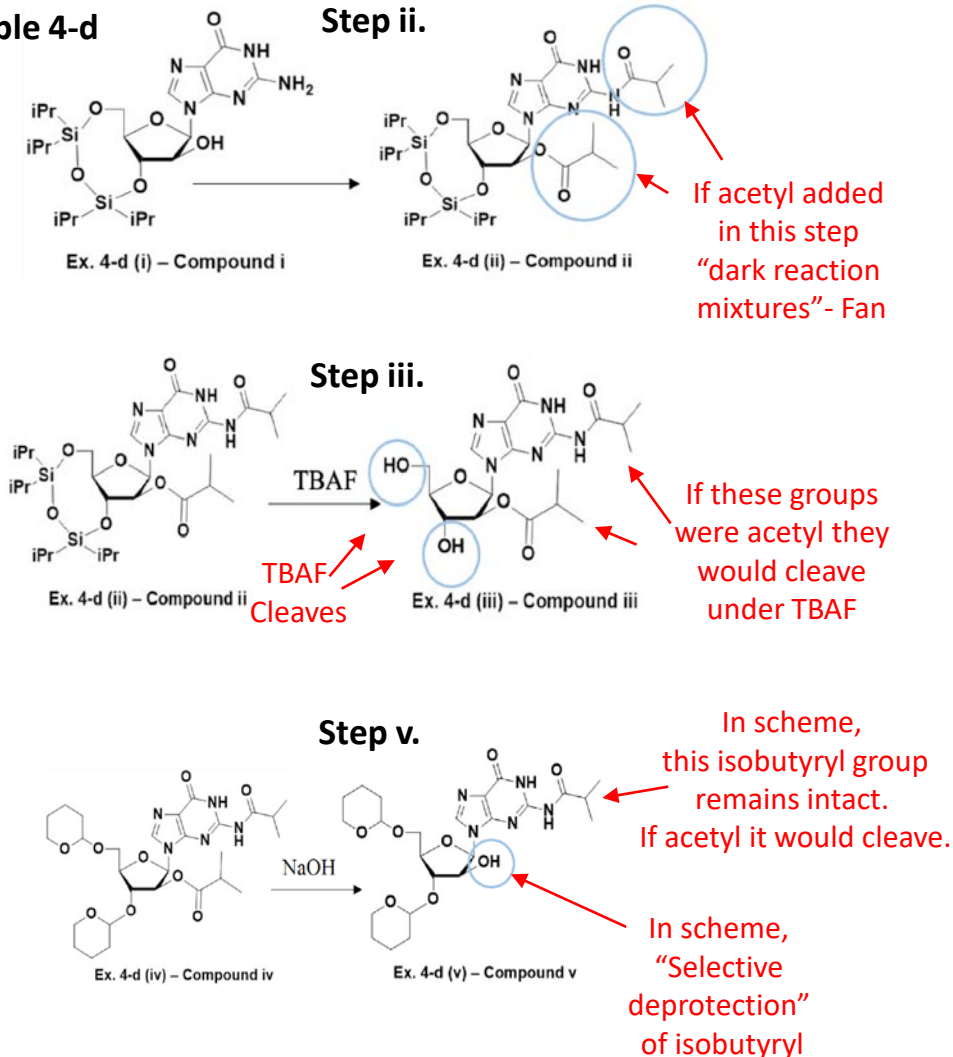


Fan



3. Whether a POSA would have had a reasonable expectation of success in synthesizing the claimed compound.

'031 Patent Example 4-d

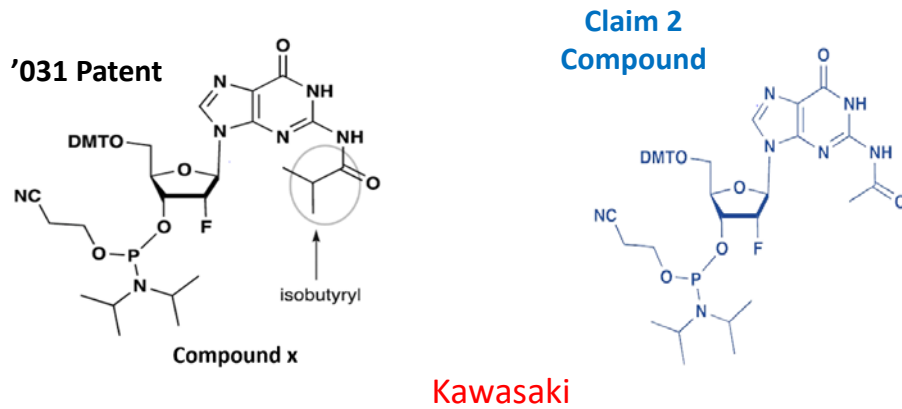


Why ChemGenes Prevails

3. Hongene failed to meet its burden to show reasonable expectation of success.

- Substituting acetic anhydride in Step ii. of Example 4-d of the '031 Patent **would have failed for multiple independent reasons**. [See slide 82](#)
- Acetylation of guanosine in Step ii. **would have failed** (as in Fan). [See slide 83](#)
- Removing 5'-and 3'-groups in Step iii. using **TBAF would have cleaved** O2'- and/or N2-acetyl groups. [See slide 83](#)
- Hongene's compound (with acetyl) resulting from Step iii. would have been **less soluble** in organic solvents. [See slide 84](#)
- Use of sodium hydroxide in Step v. would have **cleaved both acetyl groups** including the N2-acetyl group. [See slide 85](#)

4. Whether secondary considerations further establish non-obviousness.



N²-Isobutyryl-2'-deoxy-2'-fluoro-5'-O-(4,4'-dimethoxytrityl)guanosine. The reaction conditions utilized were similar to those used for the synthesis of 6. Thus compound 16 (0.92 g, 2.60 mmol) was reacted to yield a crude product which was purified by column chromatography using EtOAc-NEt₃ (99:1), followed by EtOAc-MeOH-NEt₃ (94:5:1) to give the title compound as a foam (1.49 g, 87%). ¹H NMR (200 MHz, Me₂SO-d₆): δ 12.11 (br s, 1, NH), 11.61 (br s, 1, NH), 8.12 (s, 1, H8), 7.4–6.7 (m, 13, H-Ar), 6.20 (d, 1, H1', J_{1',F} = 18.3 Hz), 5.65 (d, 1, 3'-OH), 5.42 (dd, 1, H2', J_{2',F} = 52.3 Hz), 4.59 (m, 1, H3'), 4.11 (m, 1, H4'), 3.71 (s, 6, OCH₃), 2.76 (m, 1, HCMe₂), 1.10 (d, 6, CH₃). FAB-MS: 658 [M + H]⁺.

Under the usual oligonucleotide deprotection conditions (concentrated NH₄OH, 55 °C), we in fact **observed significant degradation of the 2'-deoxy-2'-fluoropyrimidine nucleosides** while the nucleosides were stable to methanolic ammonia at room temperature.

Ex. 2025 at 833, 839

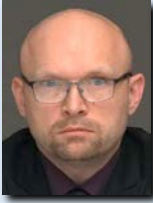


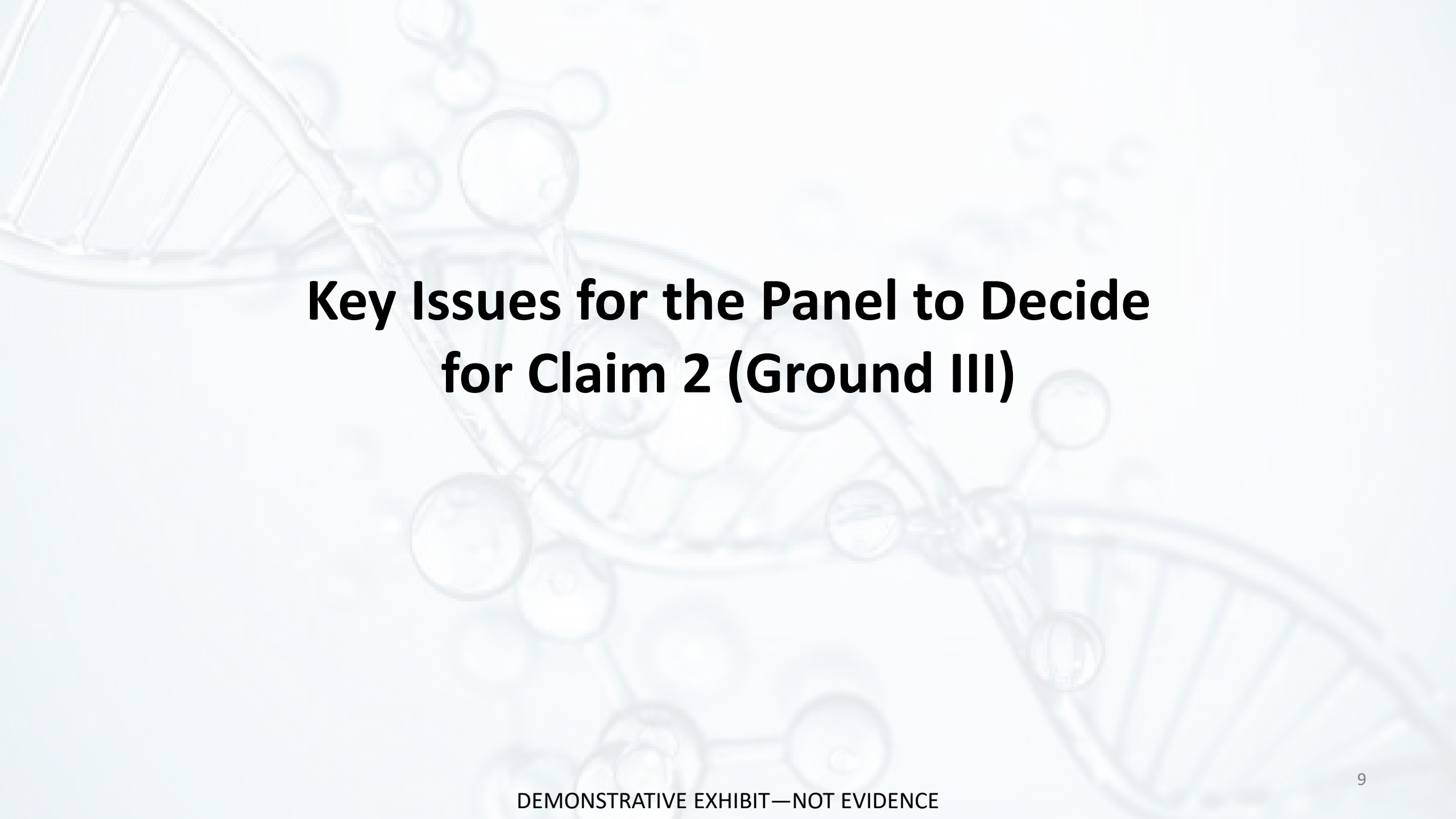
Why ChemGenes Prevails

4. Secondary considerations further demonstrate the non-obviousness of the challenged compound.
- Claimed **N²-acetyl-2'-fluoro-2'-deoxyguanosine** nucleoside **fixed the degradation** problem without the need to resort to limited deprotection conditions. [See slides 89-90](#)
 - This was **unexpected** as compared to the next closest prior art, Compound x, which had known degradation problems. [See slides 90-92](#)
 - This addressed **a long-felt need** of obtaining pure chimeric oligos without needing to resort to limited deprotection conditions. [See slides 90-92](#)
 - “Legally and factually” **significant connection between novel compound and evidence** which is a “direct result of the unique characteristics of the claimed invention.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373-74 (Fed. Cir. 2019). [See slide 93](#)

5. The weight of expert testimony submitted.

✓ Hrdlicka's Testimony Should be Given More Weight

Item	 Hrdlicka	 Baran
P(III) building block design and synthesis experience?	Yes, significant , including since 2009.	No significant demonstrated experience in 2009 or otherwise.
Oligonucleotide design and synthesis experience?	Yes , significant, including since 2009.	Yes , recent. First article relating to P(V) (not P(III)) reagents for use in oligos published in 2018.
POSA in 2009?	Yes (and now) under either definition.	No (and not to date) under ChemGenes' definition.
Financial and business relationship with represented Party?	No .	Yes, significant .
Concealed financial and business relationships with represented Party?	No .	Yes .

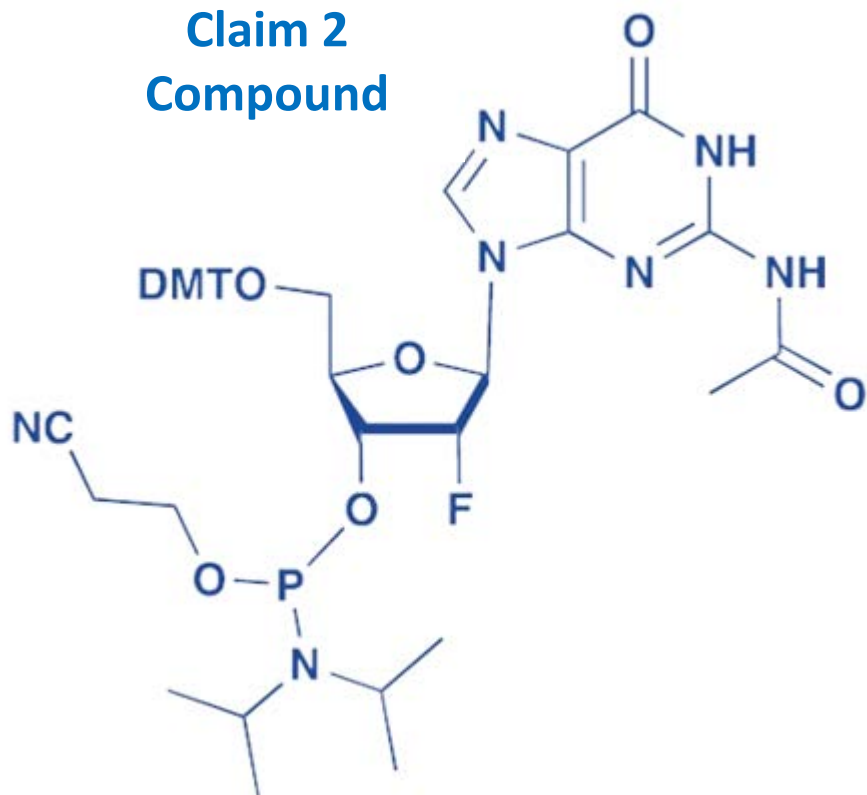


Key Issues for the Panel to Decide for Claim 2 (Ground III)

Key Issues: Claim 2 (Ground III)

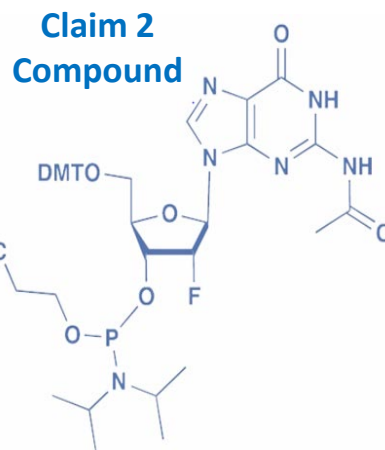
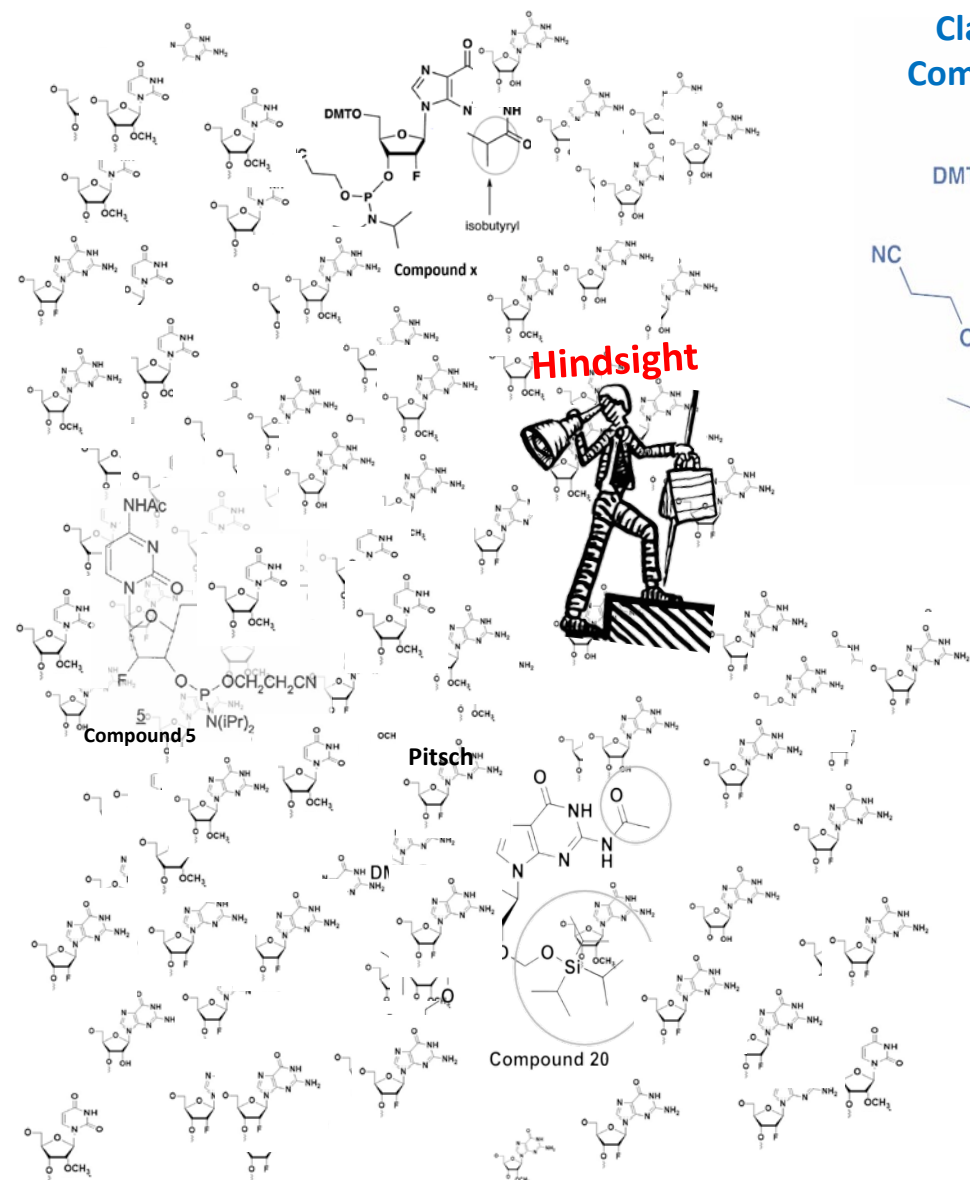
✓ Key Issues Before the Panel

Claim 2
Compound

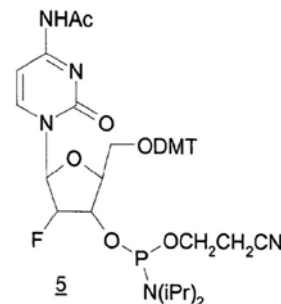


1. Whether **LCA applies** and, if so, whether Hongene has carried its burden to show a POSA **would have selected Compound 5** as a lead, or a starting point, for further development efforts. [See slides 95-96](#)
2. Whether Hongene has carried its burden to show a POSA would have been **motivated to modify Compound 5** in view of Pitsch. [See slides 97-99](#)
3. Whether Hongene has carried its burden to show a POSA would have had a **reasonable expectation of success** in synthesizing the subject Claim 2 compound. [See slide 100](#)
4. Whether the **evidence of unexpected results and satisfaction of long-felt need** further demonstrate the non-obviousness of the subject Claim 2 compound. [See slide 101](#)
5. The **weight of expert testimony** submitted. [See slides 40-50](#)

1. Whether LCA applies and has been satisfied.



Compound 5
'991 Patent

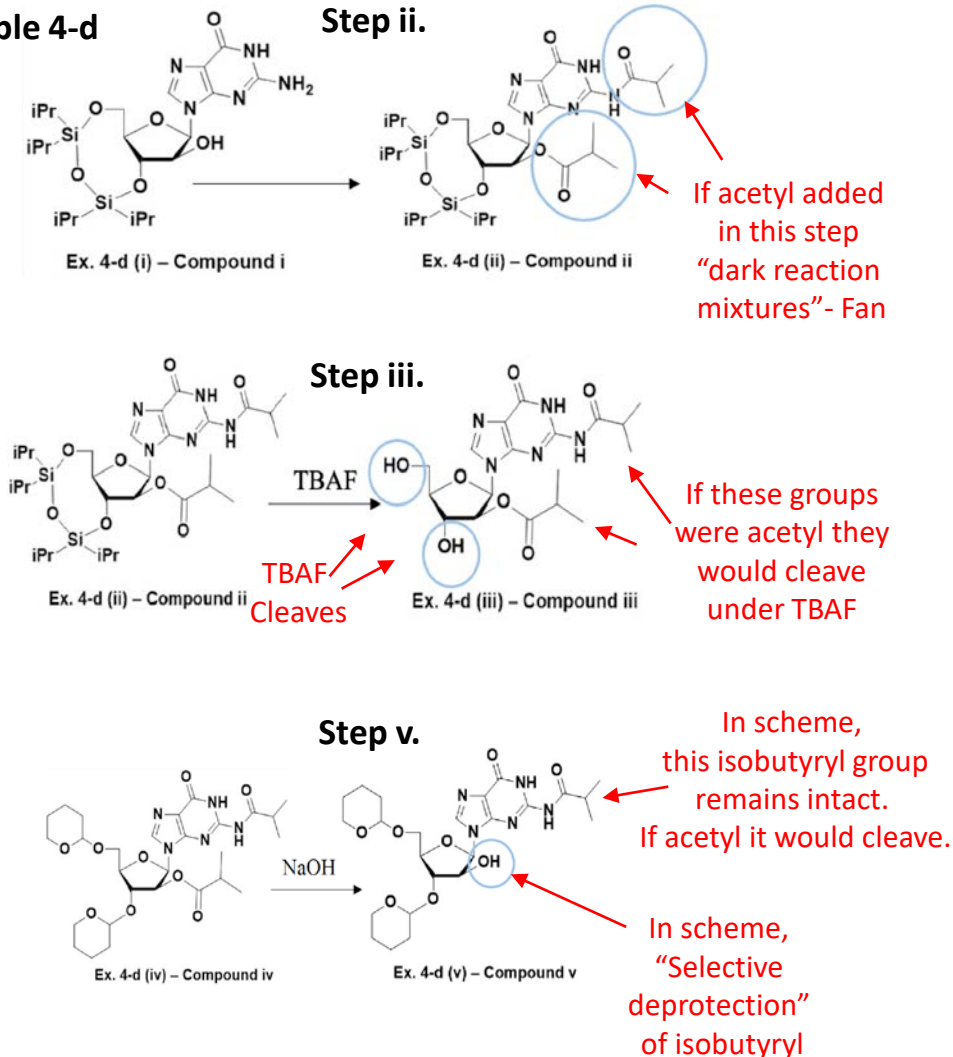


Why ChemGenes Prevails

1. LCA applies to the new Claim 2 compound at bar and Hongene did not apply or satisfy LCA.
 - a. Hongene erroneously **chose not to apply LCA** on the basis the compounds are “**reagents**” and failed to satisfy this well-established standard that protects against hindsight. [See slides 52-55, 95](#)
 - b. A POSA **would not have selected** Compound 5 (cytosine) as a lead, or starting point, for further development efforts. [See slides 96-99](#)
 - i. Compound 5 was **among thousands** of potential nucleosides in the prior art. [See slide 96](#)
 - ii. “**Utility**” of Compound 5 for use in SPOS “**alone**” does not satisfy LCA. [See slide 96](#)
 - iii. Compound 5 was **not identified as a lead** in its own disclosure. [See slide 98](#)

3. Whether a POSA would have had a reasonable expectation of success in synthesizing the claimed compound.

'031 Patent Example 4-d

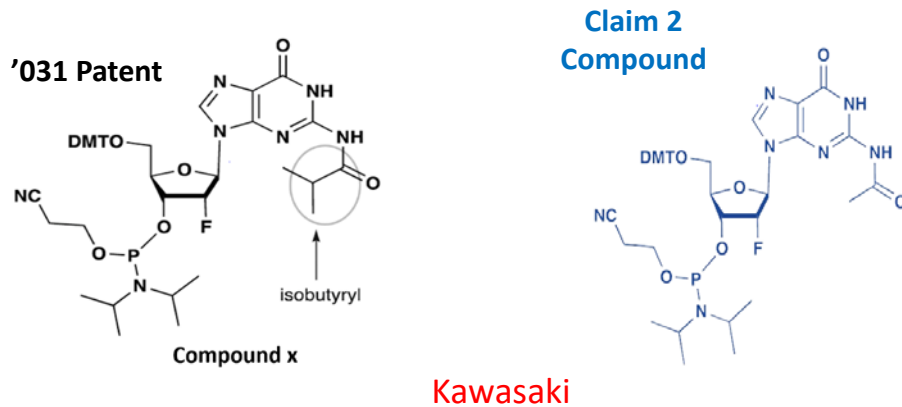


Why ChemGenes Prevails

3. Hongene failed to meet its burden to show reasonable expectation of success.

- Substituting acetic anhydride in Step ii. of Example 4-d of the '031 Patent **would have failed for multiple independent reasons**. See slides 82, 100
- Acetylation of guanosine in Step ii. **would have failed** (as in Fan). See slides 83, 100
- Removing 5'-and 3'-groups in Step iii. using **TBAF would have cleaved** O2'- and/or N2-acetyl groups. See slides 83, 100
- Hongene's compound (with acetyl) resulting from Step iii. would have been **less soluble** in organic solvents. See slides 84, 100
- Use of sodium hydroxide in Step v. would have **cleaved both acetyl groups** including the N2-acetyl group. See slides 85, 100

4. Whether secondary considerations further establish non-obviousness.



N²-Isobutyryl-2'-deoxy-2'-fluoro-5'-O-(4,4'-dimethoxytrityl)guanosine. The reaction conditions utilized were similar to those used for the synthesis of 6. Thus compound 16 (0.92 g, 2.60 mmol) was reacted to yield a crude product which was purified by column chromatography using EtOAc-NEt₃ (99:1), followed by EtOAc-MeOH-NEt₃ (94:5:1) to give the title compound as a foam (1.49 g, 87%). ¹H NMR (200 MHz, Me₂SO-d₆): δ 12.11 (br s, 1, NH), 11.61 (br s, 1, NH), 8.12 (s, 1, H8), 7.4-6.7 (m, 13, H-Ar), 6.20 (d, 1, H1', J_{1',F} = 18.3 Hz), 5.65 (d, 1, 3'-OH), 5.42 (dd, 1, H2', J_{2',F} = 52.3 Hz), 4.59 (m, 1, H3'), 4.11 (m, 1, H4'), 3.71 (s, 6, OCH₃), 2.76 (m, 1, HCMe₂), 1.10 (d, 6, CH₃). FAB-MS: 658 [M + H]⁺.

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Ex. 2025 at 833, 839

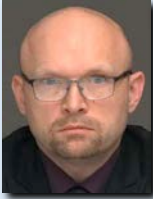


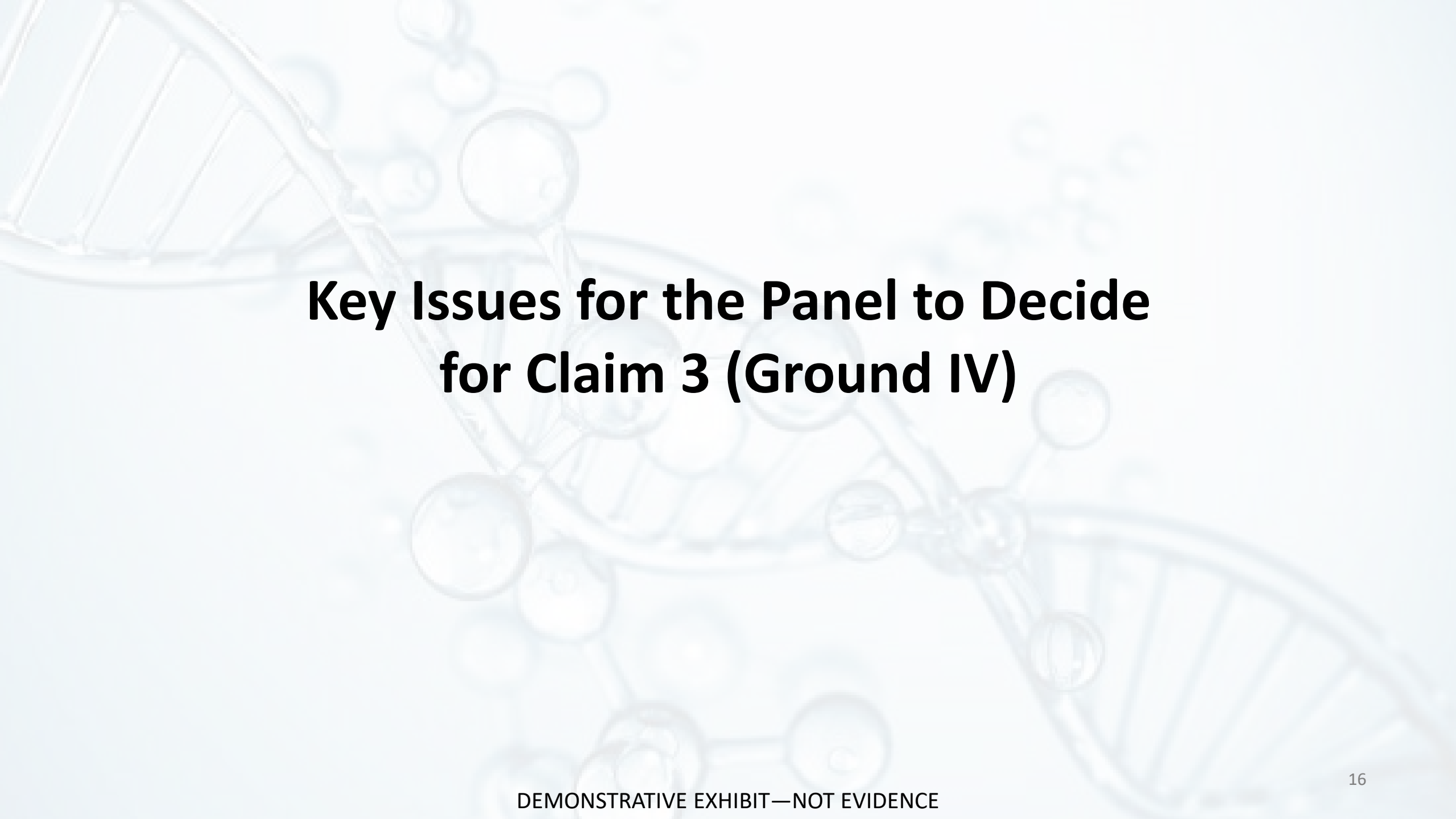
Why ChemGenes Prevails

4. Secondary considerations further demonstrate the non-obviousness of the challenged compound.
- Claimed **N²-acetyl-2'-fluoro-2'-deoxyguanosine** nucleoside **fixed the degradation** problem without the need to resort to limited deprotection conditions. [See slides 89-90, 101](#)
 - This was **unexpected** as compared to the next closest prior art, Compound x, which had known degradation problems. [See slides 90-92, 101](#)
 - This addressed **a long-felt need** of obtaining pure chimeric oligos without needing to resort to limited deprotection conditions. [See slides 90-92, 101](#)
 - "Legally and factually" **significant connection between novel compound and evidence** which is a "direct result of the unique characteristics of the claimed invention." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373-74 (Fed. Cir. 2019). [See slides 93, 101](#)

5. The weight of expert testimony submitted.

✓ Hrdlicka's Testimony Should be Given More Weight

Item	 Hrdlicka	 Baran
P(III) building block design and synthesis experience?	Yes, significant , including since 2009.	No significant demonstrated experience in 2009 or otherwise.
Oligonucleotide design and synthesis experience?	Yes , significant, including since 2009.	Yes , recent. First article relating to P(V) (not P(III)) reagents for use in oligos published in 2018.
POSA in 2009?	Yes (and now) under either definition.	No (and not to date) under ChemGenes' definition.
Financial and business relationship with represented Party?	No .	Yes, significant .
Concealed financial and business relationships with represented Party?	No .	Yes .

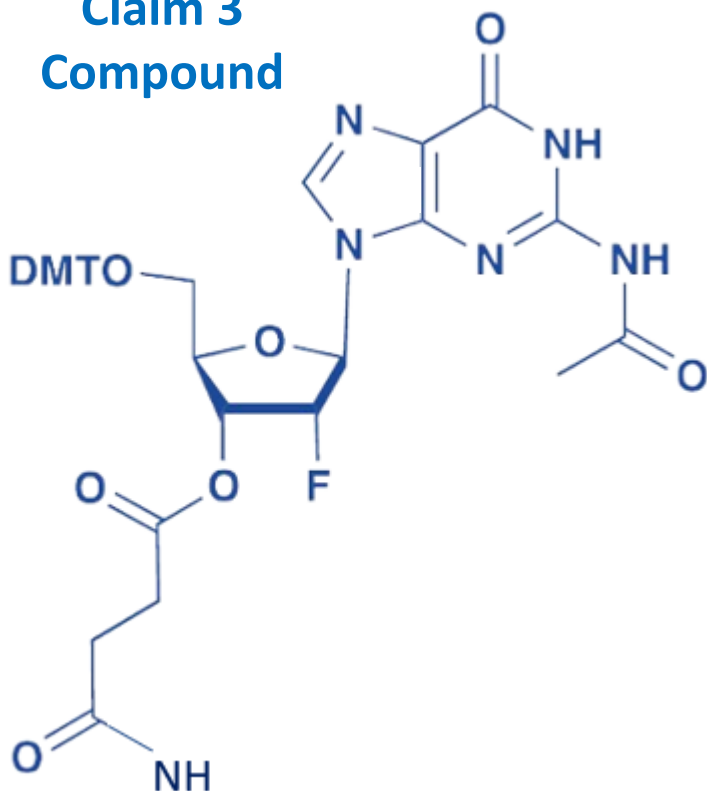


Key Issues for the Panel to Decide for Claim 3 (Ground IV)

Key Issues: Claim 3 (Ground IV)

✓ Key Issues Before the Panel

Claim 3
Compound

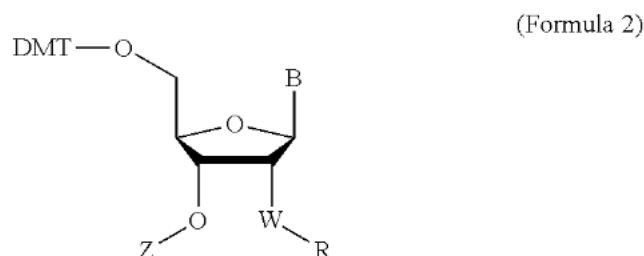


1. Whether **Claim 3 should be construed** as the Parties have proposed. [See slide 103](#)
2. **Whether LCA applies** and, if so, whether Hongene has carried its burden to show a POSA would have **selected Compound x** as a lead, or a starting point, for further development efforts. [See slides 52-63, 104](#)
3. Whether Hongene has carried its burden to show a POSA would have been **motivated to modify Compound x** to use acetyl instead of isobutyryl to protect the N2-position of guanine based on Pitsch and Fan, and in further view of Scaringe. [See slides 64-80, 104-105](#)
4. Whether Hongene has carried its burden to show a POSA would have had a **reasonable expectation of success** in synthesizing the subject Claim 3 compound. [See slides 81-87, 104, 106](#)
5. Whether the **evidence of unexpected results and satisfaction of long-felt need** further demonstrate the non-obviousness of the subject Claim 3 compound. [See slides 88-93, 104, 106](#)
6. The **weight of expert testimony** submitted. [See slides 40-50](#)

1. Whether Claim 3 should be construed as the Parties have proposed.

Proposed Construction for Claim 3 (Not in Dispute)

3. Derivatized nucleosides, succinates and solid supports of general formula 2,



where B is Guanine-N-acetyl, or adenine-N-acetyl;

W=ribo fluoro or ara fluoro, and R is absent;

Z is C(O)-M-C(O)—NH, where M is selected from the group consisting of [succinyl ethyl](#), oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

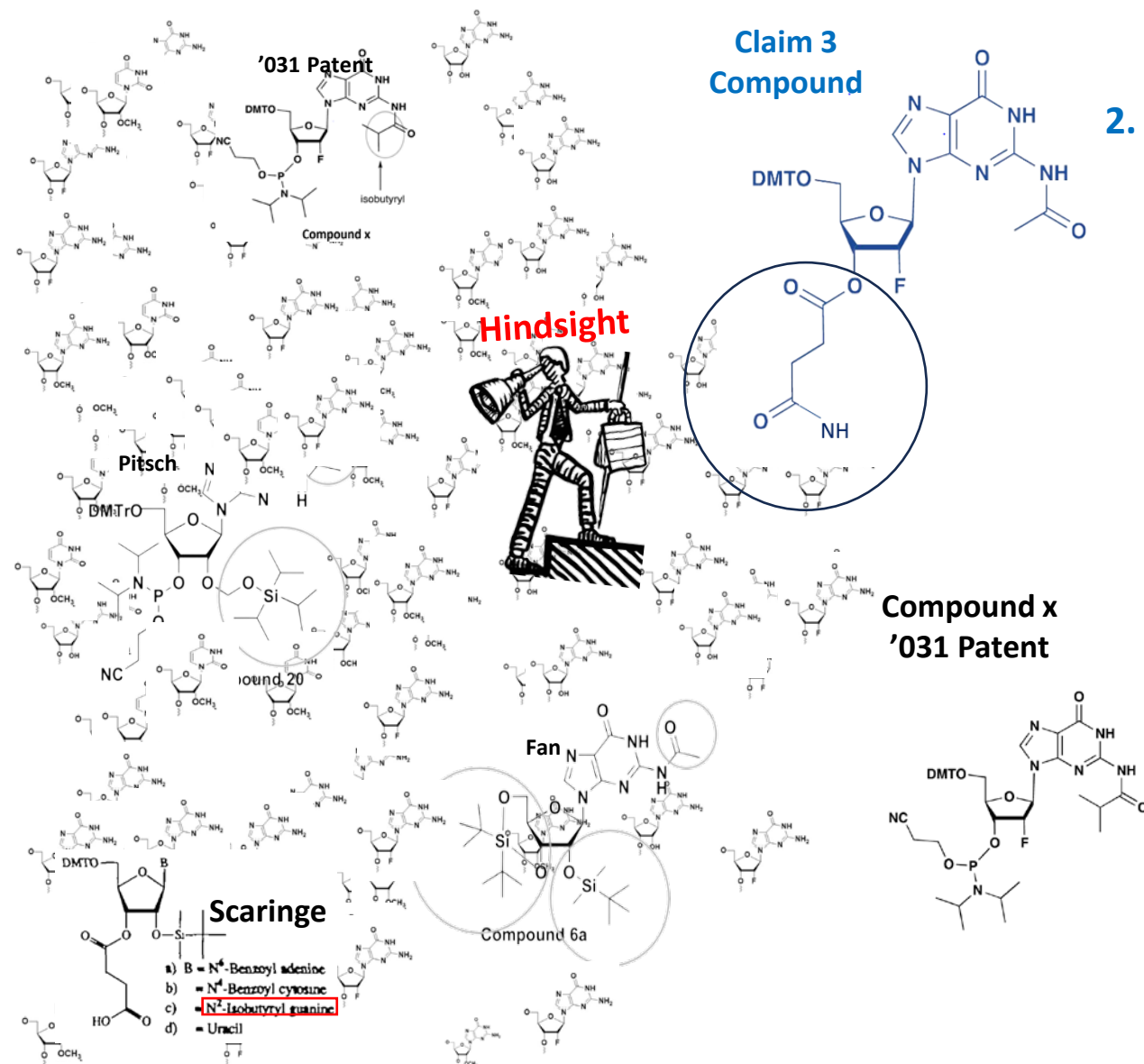


Why ChemGenes Prevails

1. ChemGenes prevails under either construction.

- Hongene proposed this construction and ChemGenes **agrees** with it. [See slide 103](#)
- ChemGenes **prevails** under this construction for the reasons stated in the ChemGenes Response, Sur-Reply and record of this case.
- Should the Panel not construe **Claim 3** in this manner, then **Ground IV necessarily fails** because all of the limitations in **Claim 3** are not taught by the prior art under this interpretation. Hongene did not dispute this. [See slide 103](#)

2. Whether LCA applies and has been satisfied.



Why ChemGenes Prevails

2. LCA applies to the new Claim 3 compound at bar and Hongene did not apply or satisfy LCA.

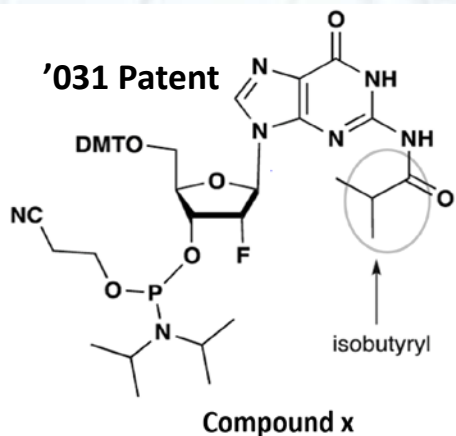
- Hongene erroneously **chose not to apply LCA** on the basis the compounds are “**reagents**” and failed to satisfy this well-established standard that protects against hindsight. [See slides 52-55, 104](#)
- A POSA **would not have selected** Compound x as a lead, or starting point, for further development efforts.
 - Compound x was **among thousands** of potential nucleosides in the prior art. [See slides 56-57, 104](#)
 - “**Utility**” of Compound x for use in SPOS “**alone**” does not satisfy LCA. [See slides 58, 104](#)
 - Compound x was **not identified as a lead** in its own disclosure. [See slides 59-60, 104](#)
 - Compound x had known **degradation problems** and would not have been chosen as a lead or starting point. [See slides 61-62, 104](#)

3. Whether Pitsch and Fan would have motivated a POSA to modify Compound x, further in view of Scaringe.

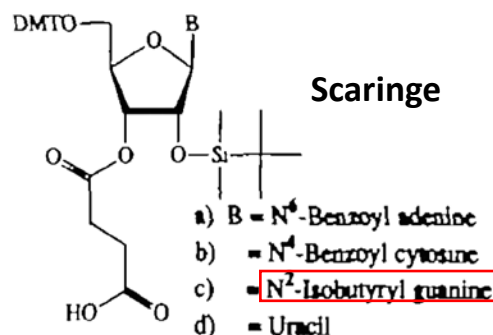
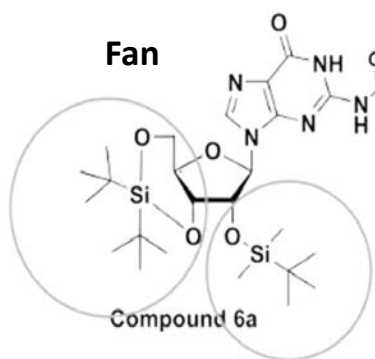
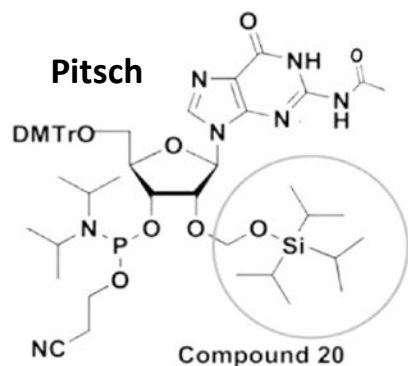
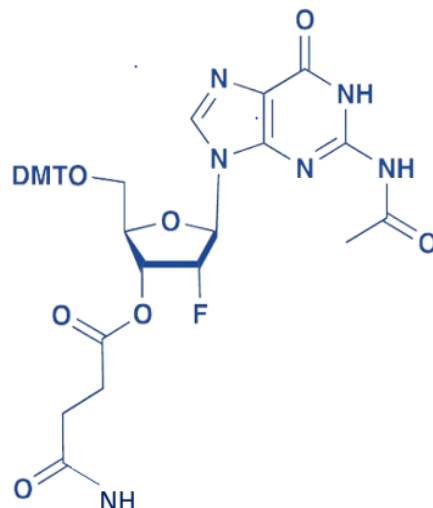


Why ChemGenes Prevails

3. A POSA would not have been motivated to modify Compound x based on Pitsch and Fan in further view of Scaringe.



Claim 3 Compound



a. Pitsch's teachings regarding acetyl applied to the specific **TOM-protected RNA** it studied and **not "universally"** to all nucleosides. Fan was similarly limited to RNA derivatives (that could not even be used during SPOS).

[See slides 65-66, 104](#)

b. Khorana **taught away** from using acetyl to protect the N2-position of guanine and the subsequent breadth of literature followed suit.

[See slides 68-74, 104](#)

c. Guanosine had **known solubility issues** and using acetyl on Compound x would have made it **less soluble in organic solvents**.

[See slides 75-77, 104](#)

d. Compound x had **known degradation problems** and a POSA would not have been motivated to modify it based on Pitsch, Fan, Scaringe or otherwise.

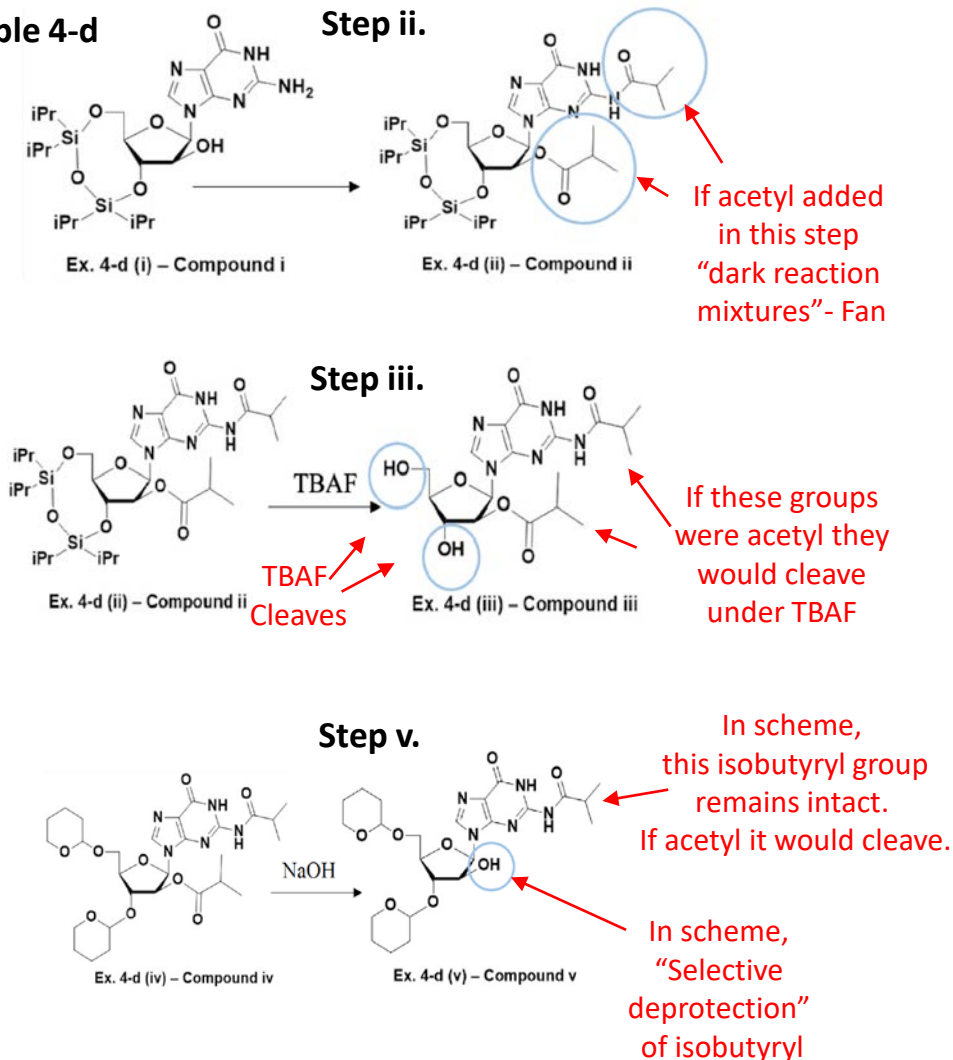
[See slides 61-62, 78-80, 104](#)

e. Scaringe does **not** disclose 2'-F groups, does **not** teach use of acetyl to protect the guanosine nucleobase, and **does not disclose deprotection rates**.

[See slide 105](#)

4. Whether a POSA would have had a reasonable expectation of success in synthesizing the claimed compound.

'031 Patent Example 4-d

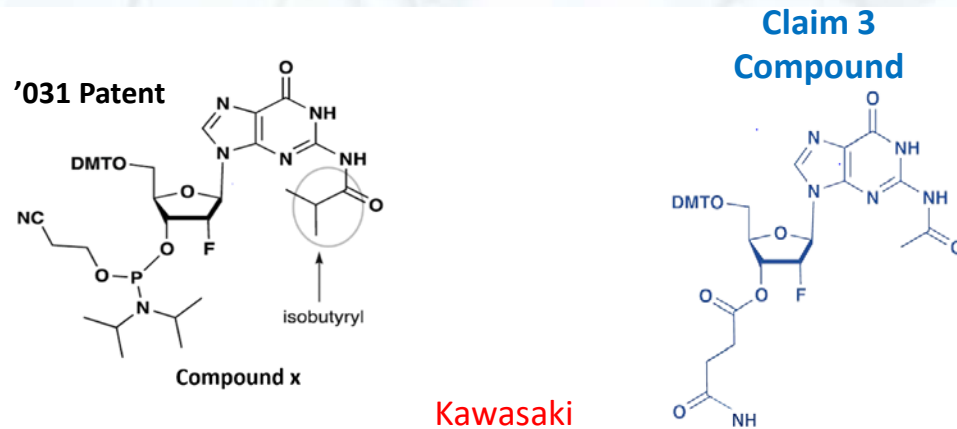


Why ChemGenes Prevails

3. Hongene failed to meet its burden to show reasonable expectation of success.

- Substituting acetic anhydride in Step ii. of Example 4-d of the '031 Patent **would have failed for multiple independent reasons**. [See slides 82, 106](#)
- Acetylation of guanosine in Step ii. **would have failed** (as in Fan). [See slides 83, 106](#)
- Removing 5'-and 3'-groups in Step iii. using **TBAF would have cleaved** O2'- and/or N2-acetyl groups. [See slides 83, 106](#)
- Hongene's compound (with acetyl) resulting from Step iii. would have been **less soluble** in organic solvents. [See slides 84, 106](#)
- Use of sodium hydroxide in Step v. would have **cleaved both acetyl groups** including the N2-acetyl group. [See slides 85, 106](#)

5. Whether secondary considerations further establish non-obviousness.



N²-Isobutyryl-2'-deoxy-2'-fluoro-5'-O-(4,4'-dimethoxytrityl)guanosine. The reaction conditions utilized were similar to those used for the synthesis of 6. Thus compound 16 (0.92 g, 2.60 mmol) was reacted to yield a crude product which was purified by column chromatography using EtOAc-NEt₃ (99:1), followed by EtOAc-MeOH-NEt₃ (94:5:1) to give the title compound as a foam (1.49 g, 87%). ¹H NMR (200 MHz, Me₂SO-d₆): δ 12.11 (br s, 1, NH), 11.61 (br s, 1, NH), 8.12 (s, 1, H8), 7.4–6.7 (m, 13, H-Ar), 6.20 (d, 1, H1', J_{1',F} = 18.3 Hz), 5.65 (d, 1, 3'-OH), 5.42 (dd, 1, H2', J_{2',F} = 52.3 Hz), 4.59 (m, 1, H3'), 4.11 (m, 1, H4'), 3.71 (s, 6, OCH₃), 2.76 (m, 1, HCMe₂), 1.10 (d, 6, CH₃). FAB-MS: 658 [M + H]⁺.

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Ex. 2025 at 833, 839



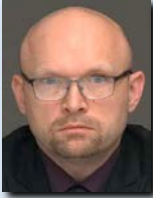
Why ChemGenes Prevails

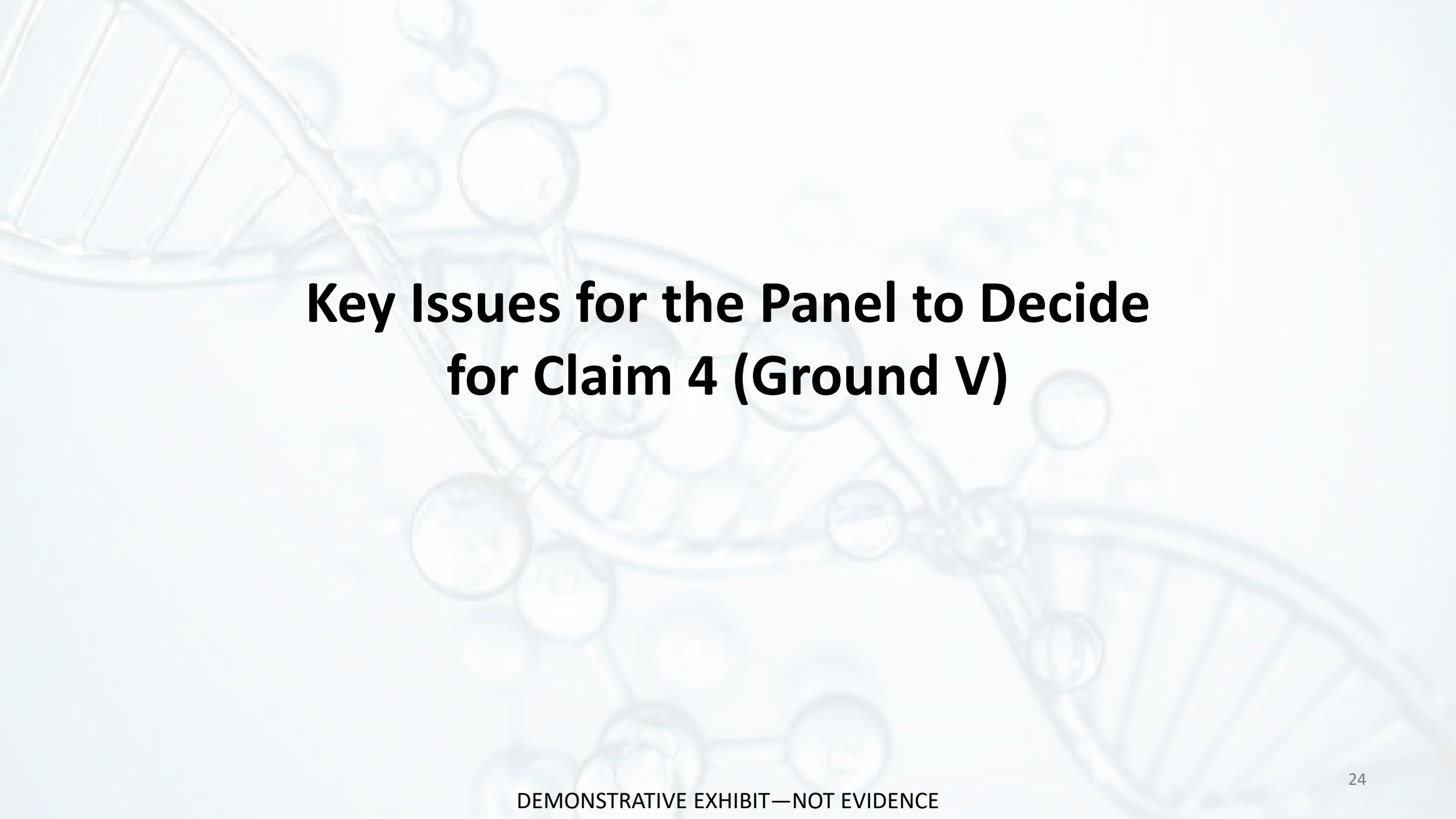
4. Secondary considerations further demonstrate the non-obviousness of the challenged compound.

- Claimed **N²-acetyl-2'-fluoro-2'-deoxyguanosine** nucleoside **fixed the degradation** problem without the need to resort to limited deprotection conditions. [See slides 89-90, 104](#)
- This was **unexpected** as compared to the next closest prior art, Compound x, which had known degradation problems. [See slides 90-92, 104](#)
- This addressed **a long-felt need** of obtaining pure chimeric oligos without needing to resort to limited deprotection conditions. [See slides 90-92, 104](#)
- "Legally and factually" **significant connection between novel compound and evidence** which is a "direct result of the unique characteristics of the claimed invention." *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373-74 (Fed. Cir. 2019). [See slides 93, 104](#)

6. The weight of expert testimony submitted.

✓ Hrdlicka's Testimony Should be Given More Weight

Item	 Hrdlicka	 Baran
P(III) building block design and synthesis experience?	Yes, significant , including since 2009.	No significant demonstrated experience in 2009 or otherwise.
Oligonucleotide design and synthesis experience?	Yes , significant, including since 2009.	Yes , recent. First article relating to P(V) (not P(III)) reagents for use in oligos published in 2018.
POSA in 2009?	Yes (and now) under either definition.	No (and not to date) under ChemGenes' definition.
Financial and business relationship with represented Party?	No .	Yes, significant .
Concealed financial and business relationships with represented Party?	No .	Yes .

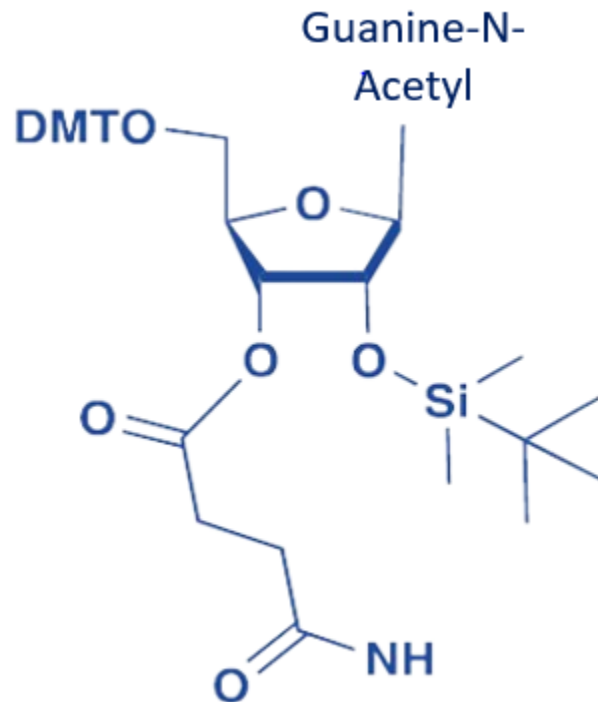


Key Issues for the Panel to Decide for Claim 4 (Ground V)

Key Issues: Claim 4 (Ground V)

✓ Key Issues Before the Panel

Claim 4 Compound

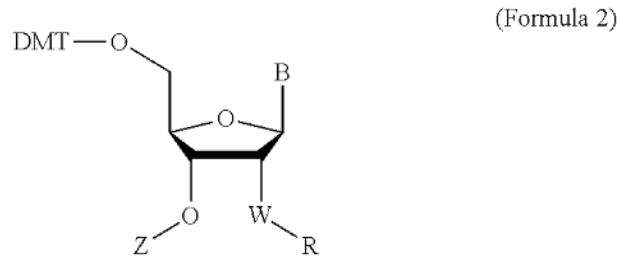


1. Whether **Claim 4 should be construed** as the Parties have proposed. [See slide 108](#)
2. **Whether LCA applies** and, if so, whether Hongene has carried its burden to show a POSA **would have selected Compound 5(c)** as a lead, or a starting point, for further development efforts. [See slides 52-55, 109-110](#)
3. Whether Hongene has carried its burden to show a POSA would have **been motivated to modify Compound 5(c)** to use acetyl instead of isobutyryl to protect the N2-position of guanine based on Pitsch and Fan. [See slide 111](#)
4. Whether Hongene has carried its burden to show a POSA would have had a **reasonable expectation of success** in synthesizing the subject Claim 4 compound. [See slide 112](#)
5. The **weight of expert testimony** submitted. [See slides 40-50](#)

1. Whether Claim 4 should be construed as the Parties have proposed.

Proposed Construction for Claim 3 (Not in Dispute)

4. Derivatized nucleosides, succinates and solid supports of general formula 2,



wherein, B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;

W is Oxygen and R is selected from the group consisting of t-Butyldimethyl silyl, acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and

Z is C(O)-M-C(O)—NH, where M is selected from the group consisting of [succinyl](#) [ethyl](#), oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy



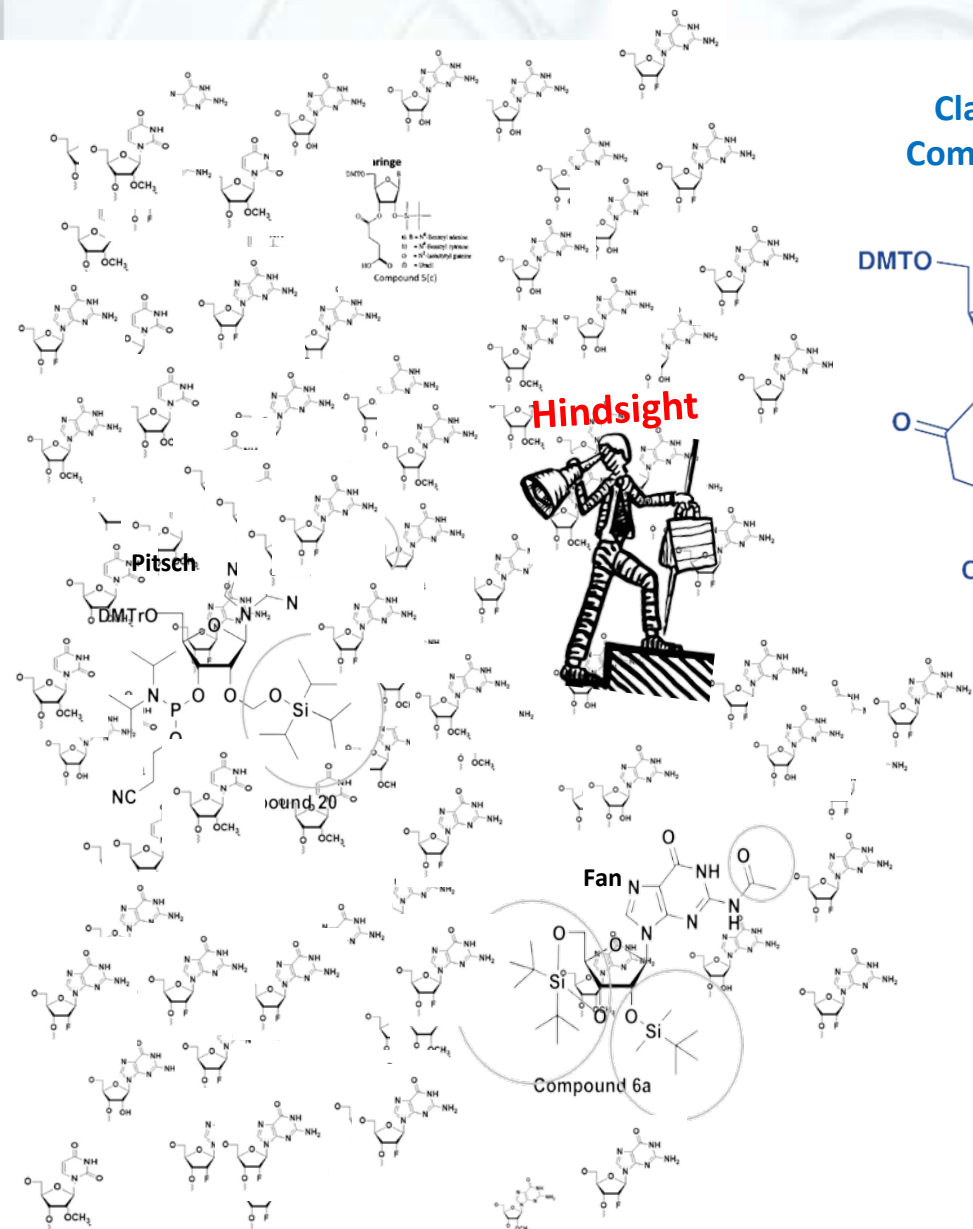
Why ChemGenes Prevails

1. ChemGenes prevails under either construction.

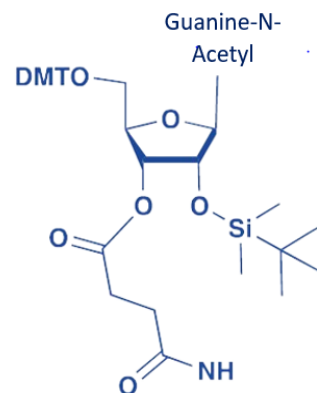
- Hongene proposed this construction and ChemGenes **agrees** with it. [See slide 108](#)
- ChemGenes **prevails** under this construction for the reasons stated in the ChemGenes Response, Sur-Reply and record of this case.
- Should the Panel not construe **Claim 4** in this manner, then **Ground V necessarily fails** because all of the limitations in **Claim 4** are not taught by the prior art under this interpretation. Hongene did not dispute this.

[See slide 108](#)

2. Whether LCA applies and has been satisfied.



Claim 4
Compound

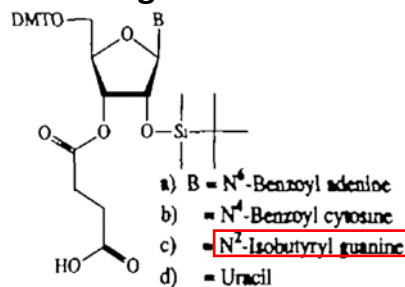


✓ Why ChemGenes Prevails

2. LCA applies to the new Claim 4 compound at bar and Hongene did not apply or satisfy LCA.

- Hongene erroneously **chose not to apply LCA** on the basis the compounds are “**reagents**” and failed to satisfy this well-established standard that protects against hindsight. [See slides 52-55](#)
- A POSA **would not have selected** Compound 5(c) as a lead, or starting point, for further development efforts.
 - Compound 5(c) was **among thousands** of potential nucleosides in the prior art. [See slide 109](#)
 - “**Utility**” of Compound 5(c) for use in SPOS “**alone**” does not satisfy LCA. [See slide 109](#)
 - Compound 5(c) was **not identified as a lead** in its own disclosure. [See slide 110](#)

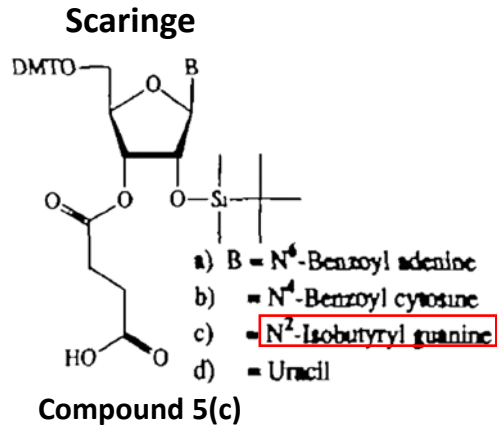
Scaringe



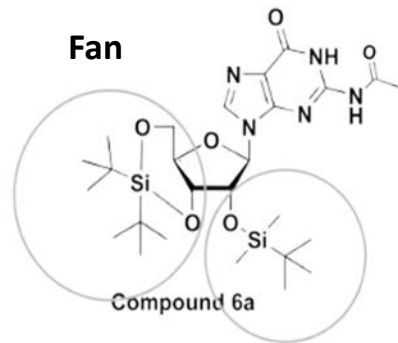
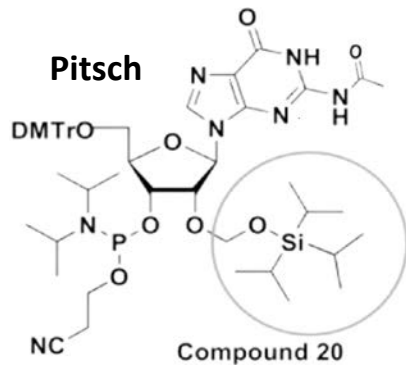
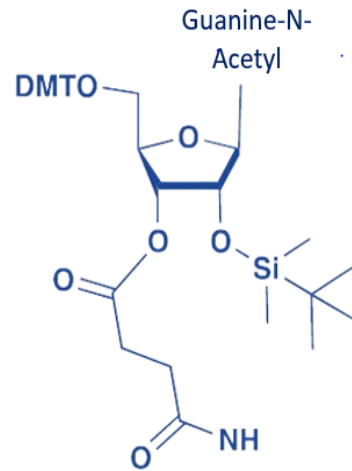
Compound 5(c)

- B = N⁶-Benzoyl adenine
- = N⁴-Benzoyl cytosine
- = **N²-Isobutyryl guanine**
- = Uracil

3. Whether a POSA would have been motivated to modify Compound 5(c) in view of Pitsch and Fan.



**Claim 4
Compound**



✓ Why ChemGenes Prevails

3. A POSA would not have been motivated to modify Compound 5(c) based on Pitsch and Fan.

- Pitsch's teachings regarding acetyl applied to the specific **TOM-protected RNA** it studied and **not "universally"** to all nucleosides. Fan was similarly limited to RNA derivatives (that could not even be used during SPOS).
See slides 65-66, 111
- Khorana **taught away** from using acetyl to protect the N2-position of guanine and the subsequent breadth of literature followed suit. See slides 68-74, 111
- Guanosine had **known solubility issues** and using acetyl on Compound x would have made it **less soluble in organic solvents**. See slides 75-77, 111
- Scaringe does **not** show G on the 3' ends, so **a POSA would view compounds 5(a) and 5(b) as leads**. See slide 110

4. Whether a POSA would have had a reasonable expectation of success to synthesize the claimed compound.

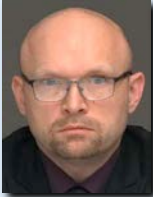


Why ChemGenes Prevails

Hongene provided **no rationale** as to how a POSA would have synthesized the subject Claim 4 compound and therefore fails to carry its burden. [See slide 112](#)

5. The weight of expert testimony submitted.

✓ Hrdlicka's Testimony Should be Given More Weight

Item	 Hrdlicka	 Baran
P(III) building block design and synthesis experience?	Yes, significant , including since 2009.	No significant demonstrated experience in 2009 or otherwise.
Oligonucleotide design and synthesis experience?	Yes , significant, including since 2009.	Yes , recent. First article relating to P(V) (not P(III)) reagents for use in oligos published in 2018.
POSA in 2009?	Yes (and now) under either definition.	No (and not to date) under ChemGenes definition.
Financial and business relationship with represented Party?	No .	Yes, significant .
Concealed financial and business relationships with represented Party?	No .	Yes .



The Parties

ChemGenes Corporation

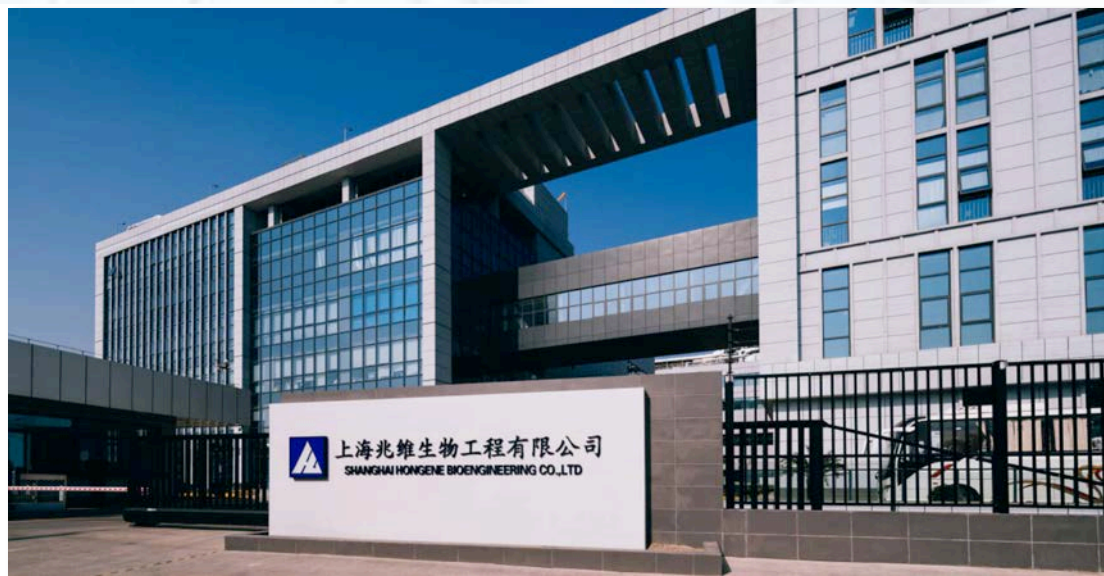
- Headquartered in Billerica, Massachusetts
- Family-founded & operated > 40 years
- Longstanding nucleoside / building block innovator for the industry
- Invested in the patent system and awarded numerous patents including the novel and non-obvious compounds claimed in Claims 2-4 of the '885 Patent



DISPROLATE PHOSPHORAMIDITE RIBONUCLEOSIDES



Hongene Shanghai Biotech Corporation

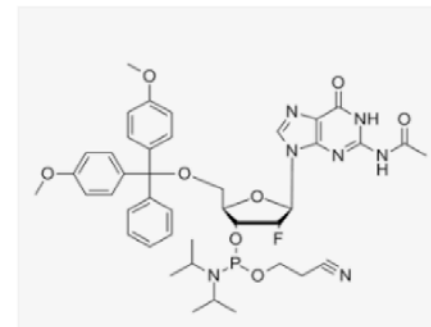


- Headquartered in Shanghai, China
- Direct competitor to ChemGenes
- Has sold/offered for sale at least N2-Acetyl-2'-F-2'-deoxyG phosphoramidite covered by Claim 2 of the '885 Patent

HONGENE PRODUCT A-1

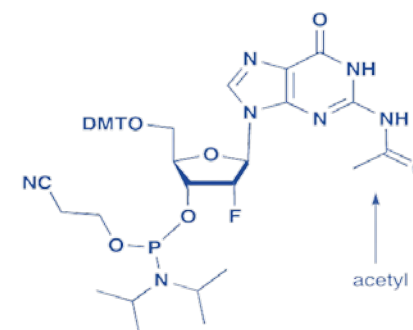
38. Hongene's website refers to Hongene Product A-1 by Catalog No. PD2-013, long product name N2-acetyl -5'-O-(4, 4'-dimethoxytrityl)-2'-fluoro-2'-deoxyguanosine-3'-cyanoethyl Phosphoramidite and abbreviated product name DMT-2'-F-dG(Ac)-CE-

39. Hongene's website provides a structural formula for Hongene Product A-1. The structural formula for Hongene Product A-1 appearing on Hongene's website is:



Ex. 2007, ¶¶38-39

Novel Claim 2 Compound '885 Patent

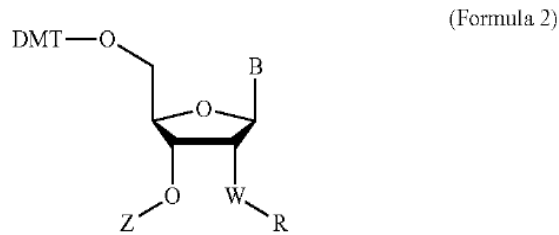




Technology at Issue

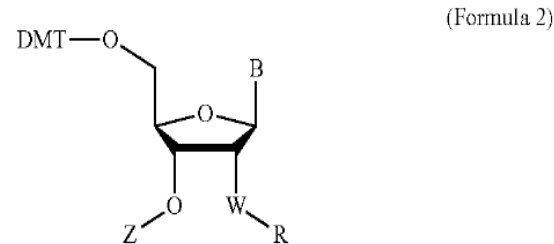
Claims Directed to P(III) Nucleosides not Oligonucleotides

2. Derivatized nucleoside and phosphoramidite of general formula 1,



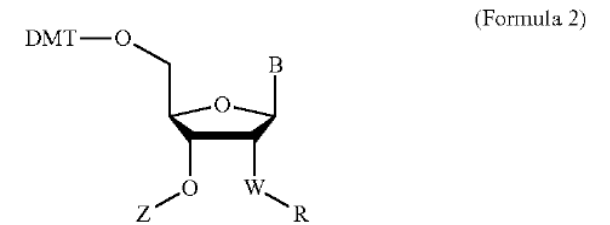
where B is Guanine-N-acetyl, or adenine-N-acetyl;
W=ribo fluoro or ara fluoro, and R is absent;
Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

3. Derivatized nucleosides, succinates and solid supports of general formula 2,



where B is Guanine-N-acetyl, or adenine-N-acetyl;
W=ribo fluoro or ara fluoro, and R is absent;
Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

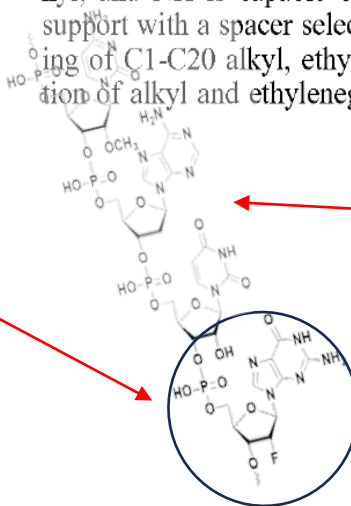
4. Derivatized nucleosides, succinates and solid supports of general formula 2,



wherein, B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;
W is Oxygen and R is selected from the group consisting of t-Butyldimethyl silyl, acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and
Z is C(O)-M-C(O)-NH, where M is selected from the group consisting of succinyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy.

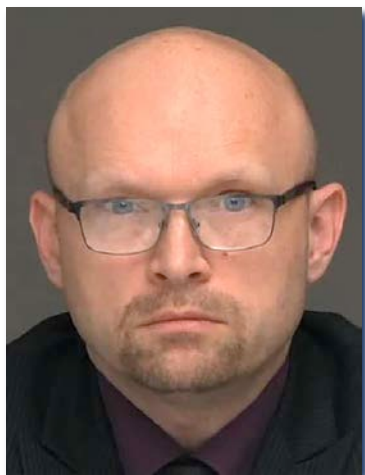
Claims 2-4 are directed to P(III) nucleoside building blocks

Not oligonucleotides



P(III) Building Block Chemistry Was (in 2009) and Remains Highly Complex and Unpredictable

Dr. Patrick J. Hrdlicka – ChemGenes' expert



Then, and now, the syntheses of such structures and related oligonucleotides involve meticulous development, planning and execution of complex, multi-step synthetic routes, all subject to unpredictable outcomes and risk of failure, designed to produce high-quality, stable nucleoside phosphoramidite reagents for use in SPOS to produce oligonucleotides of correct identity with high purity and optimum yield. Ex. 2008, ¶167

68. In my opinion, synthetic routes for phosphoramidites, e.g., often include introduction of a diverse array of chemical reagents designed to transform a starting compound into a new compound (also called a synthetic intermediate), and in succeeding steps, a different array of chemical reagents are added to transform the newly created compound in the prior step into yet another new compound and so on. Phosphoramidite synthesis can involve in the range of 5, 10, 20 or more synthetic steps to attempt to reach the desired compound, and each step, requires carefully selected and controlled reaction conditions to successfully produce the desired product. High levels of unpredictability exist at many of these stages, and even minor changes in either the molecular structure of a substrate or reagent, or in the reaction conditions, can trigger undesirable and unforeseen reactions and cause the planned synthetic transformations to fail. Ex. 2008, ¶168

Baran: P(III) Building Block Chemistry is “Simple” and “Pedestrian”

Dr. Phil S. Baran – Hongene’s expert

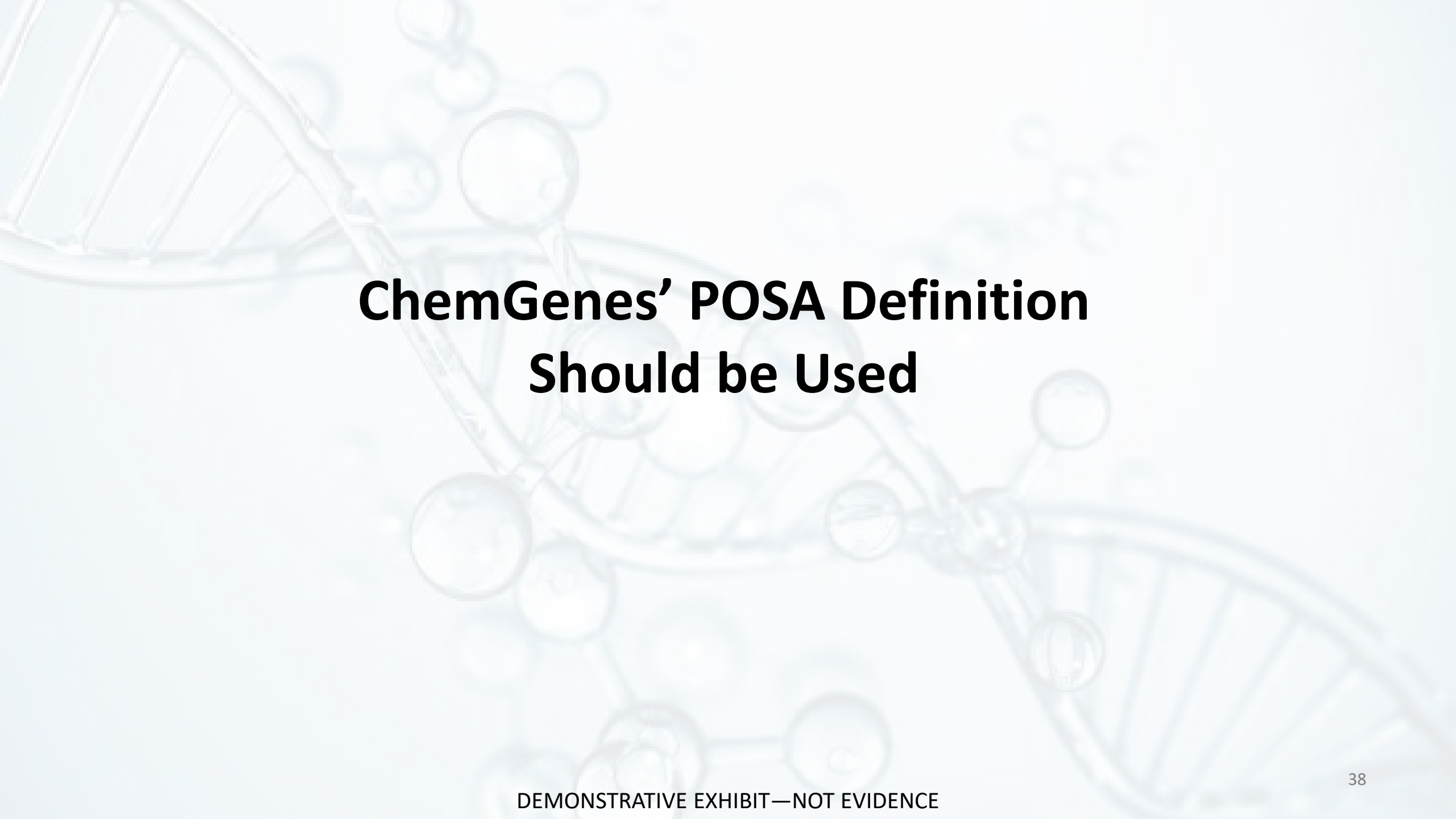


This chemistry is quite simple and beneath the skills of our group. It's pedestrian science, to be honest. Ex. 2032 at 185:17-19

A. No, because this is undergraduate level chemistry, so there would be no need to even contemplate doing something like that. So the answer is no. Ex. 2009 at 161:9-12

N.B. Baran refers to SPOS here, not P(III) nucleoside synthesis

While I agree that SPOS was complex and involved some degree of unpredictability, a POSA in 2009 would have been well-equipped to manage that, and I disagree that I have understated or downplayed any aspect of it in my analysis. Ex.1033, ¶9



ChemGenes' POSA Definition Should be Used

POSA: ChemGenes' Proposed Definition

As of May 18, 2009, a person of ordinary skill in the art ("POSA") would have had a Ph.D. (or equivalent degree) in organic ~~or medicinal~~ chemistry, and at least 2 to 3 years of post-graduate work experience in the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through solid phase oligonucleotide synthesis ("SPOS") pursuant to P(III) chemistry. ~~medicinal chemistry, synthetic organic chemistry, and nucleic acid chemistry, including the development of oligonucleotide therapeutics, diagnostics, or building blocks.~~

Alternatively, someone with a Ph.D. (or equivalent degree) in organic chemistry, and who focused on the development and syntheses of nucleosides, nucleotides, and nucleic acids, including, but not limited to, the syntheses of oligonucleotides through SPOS pursuant to P(III) chemistry during his or her Ph.D. studies.

POR at 19

Alternatively, someone with a Bachelor's or Master's degree in organic chemistry who had at least 5 years of extensive work experience in these fields, and who had gained a thorough understanding of the syntheses of nucleic acid-based materials pursuant to P(III) chemistry, would also have qualified as a POSA ~~with a Bachelor's or Master's degree in organic chemistry or medicinal chemistry.~~

This definition would not exclude medicinal or other chemists so long as the chemist in question met the above requirements. *Id.*

POR at 19

Background in P(III) chemistry should be required and background in medicinal chemistry **should not** be.



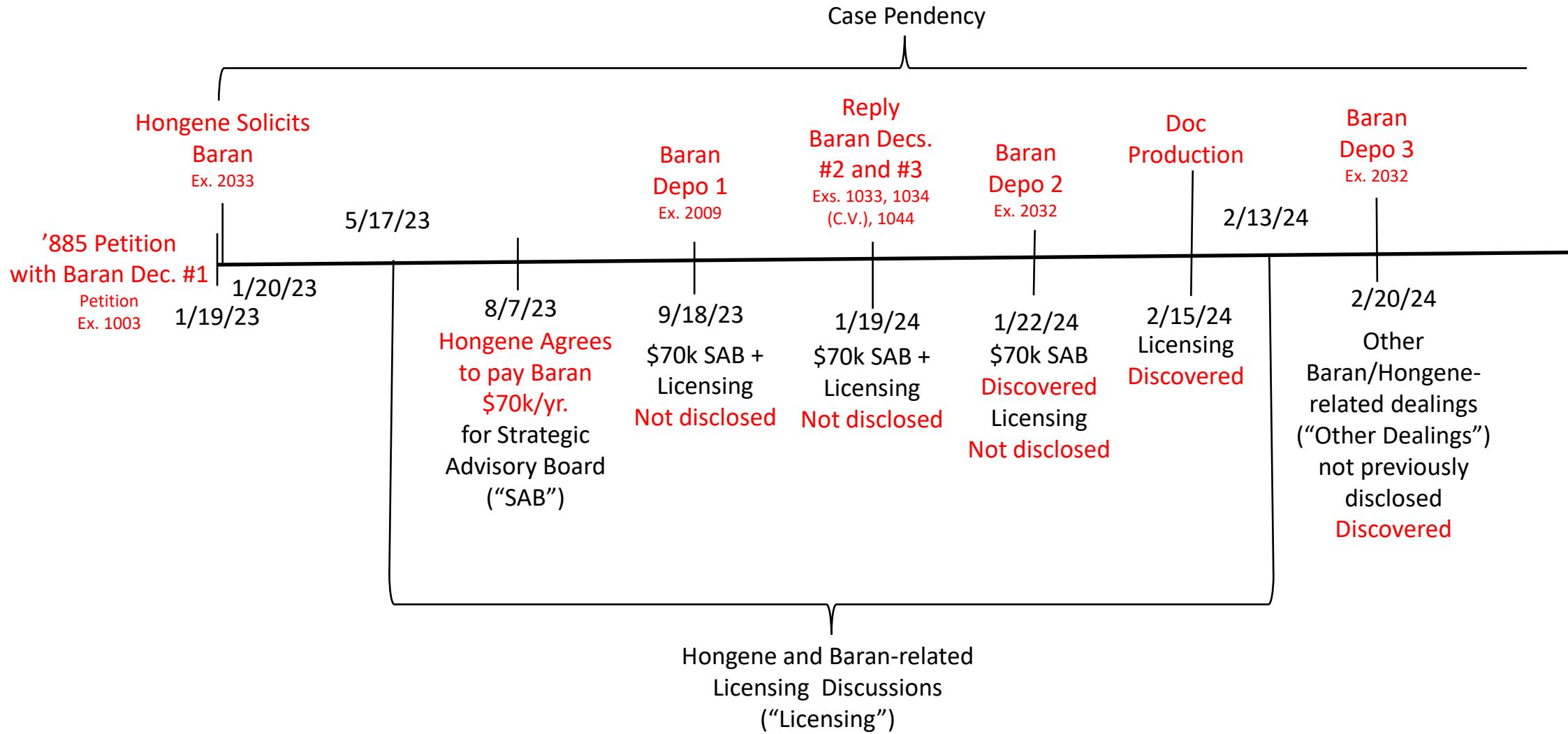
A I mean, I don't want to revise the testimony. It is what's written here. But, sure, there's exceptions to this that -- you know, it's malleable, I believe other definitions were proposed, and I had no problem with them as well.

Ex. 2032 at 177:22-178:1



Baran is Biased and Hrdlicka's Testimony Should be Given More Weight

Concealed Financial and Business Relationships Between Baran and Hongene During the Pendency of this Case



Baran and Hongene Intentionally Concealed Baran's \$70,000 Annual Contract for Baran's Service on Hongene's Strategic Advisory Board ("SAB")



Q But you didn't disclose your \$70,000-per-year contract with Hongene in your January 19th, 2024 declaration, right?

A I didn't think it was relevant. Jeremy knew about the SAB. None of us thought it was relevant to the facts of the case because my obligations to the SAB have nothing to do with this case.

Ex. 2035 at 121:14-20

Baran Testified that He Had No Other Agreements with Hongene Which Was Later Discovered to be False

Baran January 22, 2024 Deposition

Q And do you have any other agreements with Hongene besides the agreement that you referenced earlier that relates to the service on the advisory board?

A No.

Ex. 2032 at 161:16-20



Baran February 20, 2024 Deposition

Q And this email indicates that there was a CDA that was completed between you and Hongene; is that right?

A That's what it says.

Q What was the date of that agreement?

A "Please find attached fully executed CDA."
It is Thursday, February 9th, 2023.

Ex. 2035 at 122:16-19, 24-25, 123:1

Baran Concealed Licensing Discussions with Hongene (see Sur-Reply) Despite Being Asked Questions that Invited its Disclosure

Baran January 22, 2024 Deposition

Would CO. consider licensing P(V)

technology to Hongene?

A I don't think they legally can. I think that needs to be done like a -- for selling

Q So if a company wanted to license P(V) reagents, to your knowledge, they would approach BMS?

A Correct.

Ex. 2032 at 160:22-25, 161:4-7

Baran February 20, 2024 Deposition

So my understanding is, based on your testimony and then these documents, is that CO. and

CO. began discussions of a potential licensing arrangement for CO. starting around May of 2023; is that fair?

A May, yeah, that plus or minus a month, something like that, yeah.

Ex. 2035 at 145:23-146:4



Despite All of This, Baran Argues That He Has “Nothing to Hide”

Baran February 20, 2024 Deposition

Q But your testimony is you didn't feel the need to disclose those -- these discussions that we covered in this -- recently in this deposition, right?

MR. EDWARDS: Object to form. Vague.

A Again, I don't know what discussions you're talking about. What -- I guess my feeling back in January was I was surprised by the number of hours you spent on things which have nothing to do with this case. I mean, I'm getting paid either way so I'll talk all day about whatever you want, give you a lecture on organic chemistry or talk about plastic bottles, whatever you like.

Ex. 2035 at 152:9-20

I state for the record I have absolutely nothing to hide here. So just ask what you want, you'll get whatever you want. I'll show you my emails, I'll screen share whatever you would like, sir. There's nothing to hide.

Ex. 2035 at 153:2-6



Despite All of This, Baran Contemptuously Argues His Financial and Business Interests with Hongene are Not “Relevant” and That He “think[s] it’s all funny.”

Baran February 20, 2024 Deposition

Q Well, you didn't disclose any of these relationships, the discussions between CO. and CO. . You didn't -- you didn't disclose any of that in any of your declarations or in your -- in your deposition.

MR. EDWARDS: Ask a question.

Q Is that correct?

A I also didn't disclose, you know, my favorite color sweater, my kids' sports that they go into.

This is so irrelevant to the case, I think it's sad. I feel sorry for your client that this is what you're doing. It's irrelevant. Why would I put that in the declaration? It's irrelevant. None of this is relevant to the case.

Ex. 2035 at 151:5-19

I'm sorry your client is paying for this. I know you'll strike it from the record. Go ahead.

Ex. 2035 at 151:20-21

But you can depose all the people at CO. This is as relevant as deposing my mortgage broker to find out what my terms are on my mortgage. You can check my DNA, urine samples, whatever you like, sir; it's all irrelevant. But you can depose everybody.

MR. SHORES: Move to strike the witness' answer as nonresponsive.

A I responded. I think it's all funny.

Ex. 2035 at 141:8-15



Bias Standards

4 Weinstein's Federal Evidence § 607.04

Weinstein's Federal Evidence > *Rule 607 Who May Impeach a Witness.* > *CHAPTER 607 Who May Impeach a Witness*

Impeachment by showing the witness to be biased rests on two assumptions: (1) that certain relationships and circumstances impair the impartiality of a witness, and (2) that a witness who is not impartial may, consciously or otherwise, shade his or her testimony in favor of or against a party. Since bias of a witness is always significant in assessing credibility,³ the trier of fact must be sufficiently informed of the underlying relationships, circumstances, and influences operating on the witness to determine whether a modification of testimony reasonably could be expected as a probable human reaction.

[4] Evidence of Bias Demonstrated Circumstantially

The existence of bias usually is demonstrated only circumstantially by proof of relationships, conduct, or utterances. The hearsay problem generally is disregarded when the testimony seeks to impeach for bias, usually on the theory that it is being used to show the witness's state of mind.³³ Although numerous sources of

[5] Relationships Between Witness and Party

Relationships between a party and a witness³⁵ are always relevant to a showing of bias, whether the relationship is based on ties of family, sex³⁶ (whether heterosexual³⁷ or homosexual),³⁸ employment,³⁹ business,⁴⁰ friendship,⁴¹ enmity,⁴² or fear.⁴³

Ferring B.V., v. Barr Labs., Inc. 437 F.3d 1181, 1187 (Fed. Cir. 2006)

The general law of evidence has long recognized that the testimony of any witness may be rendered suspect by a past relationship with a party.⁷

A witness's interest is always pertinent to his credibility and to the weight to be given to his testimony, and relevant interests are not limited to direct financial interests.

⁷ See *United States v. Robinson*, 530 F.2d 1076, 1079–80 (D.C.Cir.1976) (finding a witness's past business transactions with a party significant in assessing the witness's credibility); *Aetna Ins. Co. v. Paddock*, 301 F.2d 807, 812 (5th Cir.1962) (finding a witness's past financial affiliation with a party significant in assessing his credibility); see also 3A Wigmore, Evidence § 949, at 786 (Chadbourn rev. 1983) (“The relation of employment, present or past, by one of the parties, is also usually relevant.”).

Baran Does Not have Significant Experience in P(III) Building Block Chemistry



Q And have you ever published a paper that is related to the synthesis of a phosphoramidite?

A There may be something in the papers. I'm not sure. But for certain, I have consulted on this topic on multiple occasions and taught it in class.

I think looking at papers is just one myopic way of trying to pitch and hold one's expertise. One doesn't reach my level by not having expertise in something as fundamental and foundational to the field of organic chemistry as oligonucleotide synthesis.

So I've consulted on it for years, taught classes on it. Certainly well aware of the area as of the 2008 time frame, regardless of whatever the publications are.

Q Yeah, I'm not trying to pigeonhole you. I'm trying to understand the work that you've conducted in connection with the synthesis of building blocks. So that's the purpose of -- of my

Ex. 2032 at 184:7-25

Other than conclusory statements, the record does not show Baran has significant experience in P(III) nucleoside chemistry and synthesis, as neither Hongene nor Baran identify specific papers, companies, consultancies, awards, patents, or other facts that demonstrate he does. Nonetheless, Baran repeatedly belittles this complex and unpredictable technology.

inquiry here.

Have you ever published a paper that relates to the synthesis of, you know, building blocks that go into the oligonucleotides?

A Generally those are too simple. Our lab is really focused on far more complicated things.

So the synthesis of basal nucleotide building blocks is pedestrian, and honestly, below that of the capabilities of our lab.

And so I think that your intent, though, based on what you've written after the deposition, is indeed to try to invalidate me as a POSA or cast shade in some light, and I understand that's your job; it's wonderful. But it's a -- a tactic which is, while legal, it's probably not morally right.

So I'm stating the fact that, yeah, I'm a POSA of that date. This chemistry is quite simple and beneath the skills of our group. It's pedestrian science, to be honest.

MR. SHORES: Okay. I have no further questions at this time.

Ex. 2032 at 185:1-21

Baran Does Not have Significant Experience in P(III) Building Block Chemistry and Hrdlicka Does

86. Dr. Baran has characterized himself as a professor in organic chemistry and an expert in medicinal chemistry, but testified that only 14 of the over 250 papers he has authored in his career relate to oligonucleotide synthesis, and the earliest of those papers is dated just 5 years ago. Ex. 2009, 75:22-24; 73:21-23; 97:23-98:1; 99:15-100:7 Furthermore, the focus of the most prominent of those papers appears to be on *P(V) chemistry* which, as Dr. Baran acknowledged, is a fundamentally different synthesis platform than the P(III) chemistry at bar. *Id.*, 109:4-6 (“Q. But the focus of this paper [Ex. 2001] is on P(V)? A. the focus of this paper is awakening people to the difference between P(V) and P(III).”); Ex. 2010, 1 (Dr. Baran and the other authors describing “P(V)-based reagent platforms” as “as a fundamentally different approach” as compared to “phosphorus(III) [P(III)]-based reagent systems.”).

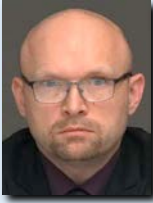
Ex. 2008, ¶186

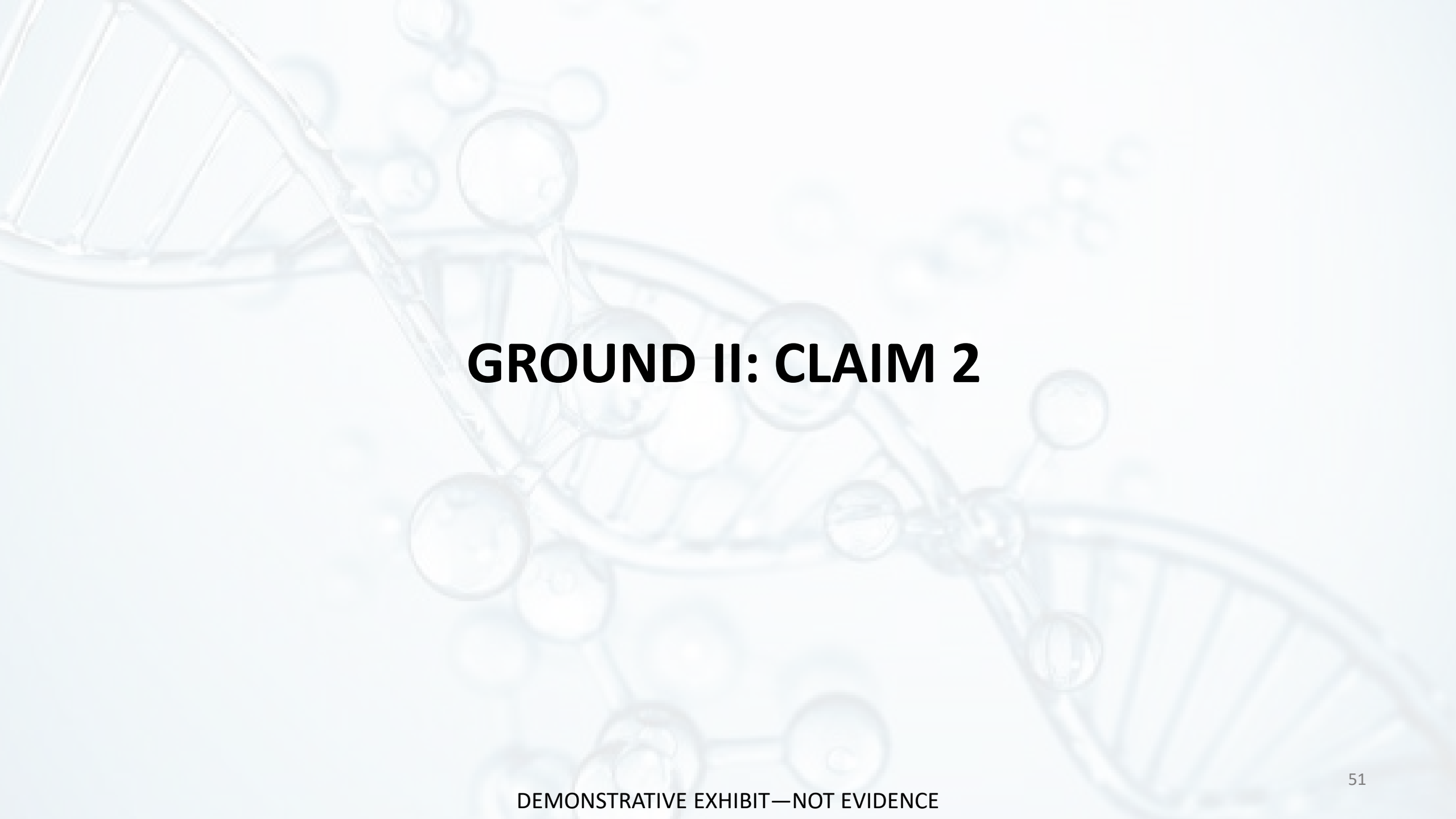
87. I am, and was in the 2009 timeframe, highly skilled in developing synthesis schemes and directing the synthesis of nucleosides, nucleotides, and nucleic acids pursuant to P(III) chemistry, including, but not limited to, the synthesis

Ex. 2008, ¶187



Hrdlicka's Testimony Should be Given More Weight

Item	 Hrdlicka	 Baran
P(III) building block design and synthesis experience?	Yes, significant , including since 2009.	No significant demonstrated experience in 2009 or otherwise.
Oligonucleotide design and synthesis experience?	Yes , significant, including since 2009.	Yes , recent. First article relating to P(V) (not P(III)) reagents for use in oligos published in 2018.
POSA in 2009?	Yes (and now) under either definition.	No (and not to date) under ChemGenes' definition.
Financial and business relationship with represented Party?	No.	Yes, significant.
Concealed financial and business relationships with represented Party?	No.	Yes.



GROUND II: CLAIM 2

**Ground II: Hongene Failed to Apply and
Satisfy the Federal Circuit’s Lead Compound Analysis
(“LCA”)**

Hongene Erroneously Argues that LCA Does Not Apply to “Reagents”

Hongene’s Reply

As in *NOF*, the

claims here are directed to *reagents* used in the production of oligonucleotides, not therapeutic compounds, so the lead compound approach is inapposite.

As explained above (Section VI), the “lead compound” analysis is not appropriate.

Pet. Reply at 4, 28

Hongene proposes the Board adopt a rigid rule that LCA **does not apply to “reagents”**

- There is no such rule
- The Federal Circuit has not held this, neither has PTAB
- *NOF Corp.* does not support this proposition and applied the first prong of LCA

Baran Depo



Q Okay. So is it your testimony that your opinion is that the lead compound framework does not apply to this case?

A Correct.

Q Okay. And, therefore, you did not apply it to this case?

A Correct.

Ex. 2035 at 95:14-20

LCA Should Apply to Claim 2's New Compound

- Claim 2 claims a “**new compound**” (not disputed)
- There is **no rigid rule** that LCA does not apply to “**reagents**”
- The law **protects against hindsight** by determining, for example, whether or not a POSA would have selected Compound x as a “lead compound” and
 - “found it **most promising to modify** in order to improve upon its activity and obtain a compound with better activity,” *Takeda Chem. Indus. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007)
 - “**had reason to select** [Compound x] **from the panoply of known compounds** in the prior art,” *Otsuka Pharm. Co., v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012), and
 - found it “**a natural choice** for further development efforts.” *Altana Pharma AG v. Teva Pharm. USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)

Hongene Contradicts Itself by Arguing Building Blocks are “Not Therapeutic Compounds” While Later Endorsing their Ability to Impart “Significant Biological Activity”

Hongene argues in its **Reply** that building blocks are “**not therapeutic compounds**” and therefore LCA is “inapposite”

As in *NOF*, the claims here are directed to *reagents* used in the production of oligonucleotides, *not* therapeutic compounds, so the lead compound approach is inapposite.

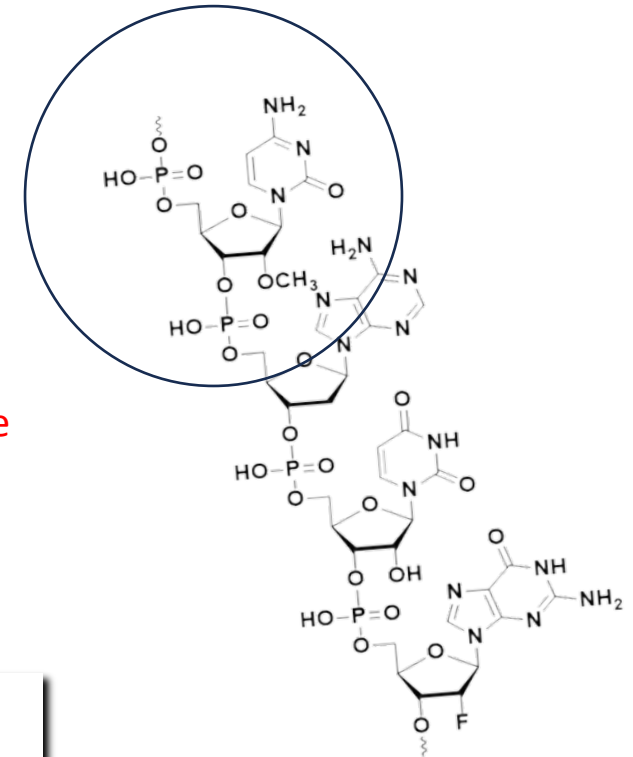
Pet. Reply at 4

But later endorses ChemGenes’ catalog statements that building blocks have “**significant biological activity**” and impart “**many interesting biological properties**” to argue there was “**ample**” reason to select Compound x

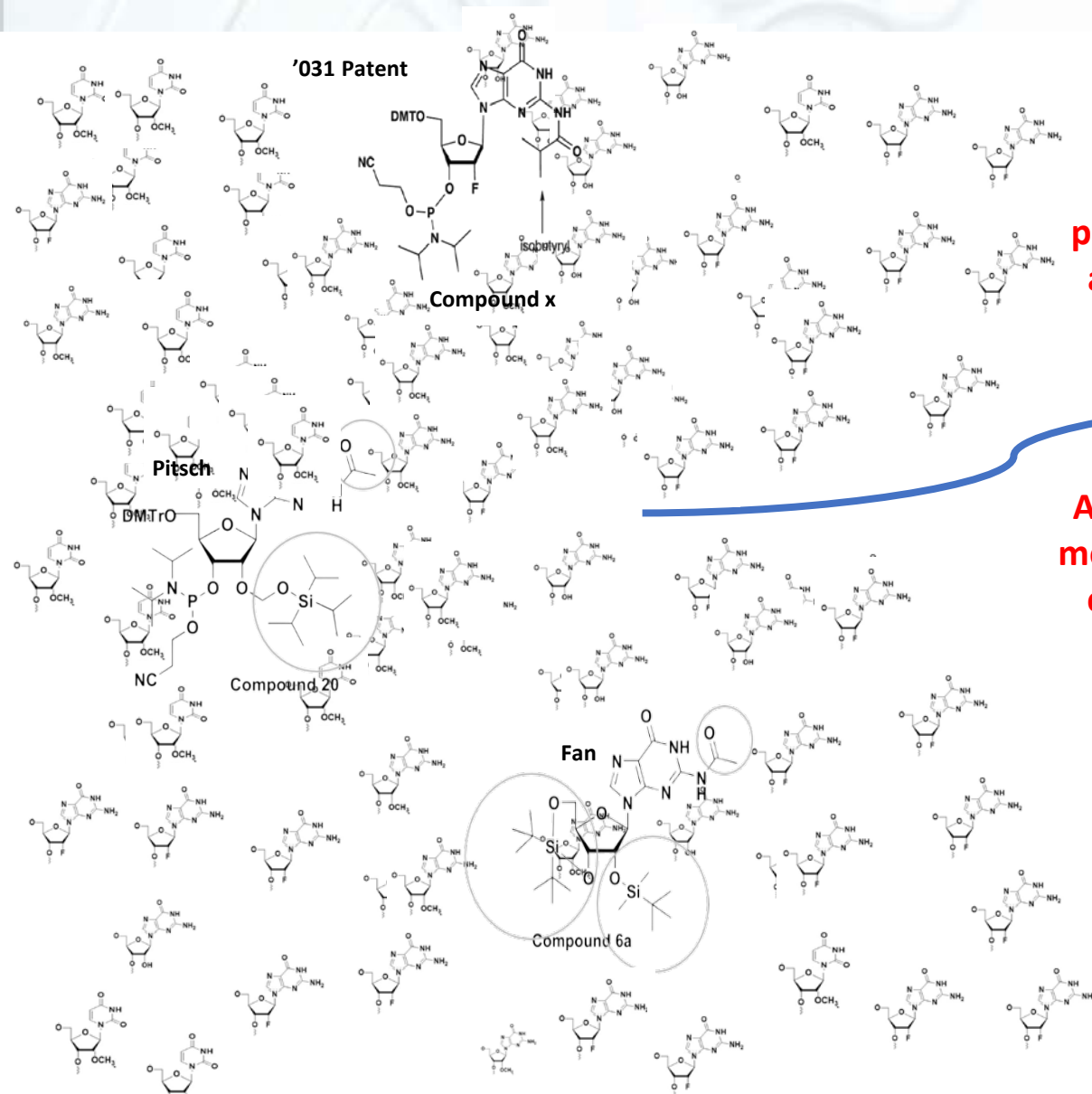
A. There was ample reason to select Compound x.

—citing publications from the 1990’s—touting their “**significant biological activity**,” use as “versatile probes” and that incorporating them into oligonucleotides “**imparts many interesting biological properties**”.

Pet. Reply at 9



Selection of Compound x Was Hindsight-Driven



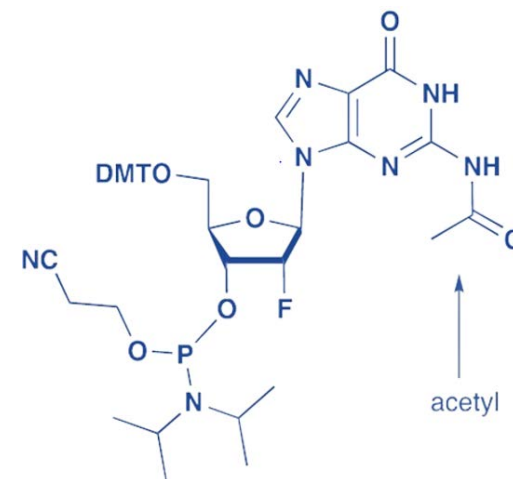
Thousands of
potential
phosphoramidites
and nucleosides
having similar
“utility”

Alleged “myriad”
motivations add to
complexity and
hindsight

Hindsight



Claim 2 Compound
'885 Patent



Hongene provides no selection rationale in its Petition
for Compound x beyond “utility” in SPOS

There Were Thousands of Potential Nucleosides and Nucleotides Available in 2009



78. In my opinion, given the variety of options for protecting groups, and chemically modified sugars and nucleobases, there were thousands of different phosphoramidites and nucleosides available to a POSA in the 2009 timeframe.

Ex. 2008, ¶178



Q. And you agree that there are a large number of different chemically modified phosphoramidites that exist; right?

A. Yes.

Q. And you'd agree that there are a large number of chemically modified phosphoramidites that existed in the 2009 time frame; is that correct?

A. Yes.

Ex. 2009 at 22:15-22

Q. Would you say hundreds of -- hundreds of different chemically modified phosphoramidites?

MR. EDWARDS: Object to form.

THE WITNESS: I mean, it would be conjecture, but certainly one could easily identify hundreds in the literature at that time. Sure.

BY MR. SHORES:

Q. Thousands?

A. Perhaps.

Ex. 2009 at 26:23-27:6

Hongene never disputed Hrdlicka's testimony that there were thousands of different phosphoramidites and nucleosides available to a POSA in 2009 and Baran acknowledged as such

Hongene Selects Compound x Based on “Utility” “Alone”

Reply Brief

Because nucleosides were building blocks for a wide variety of compounds that themselves had a wide variety of uses, this utility of Compound x *alone* was a reason for POSAs to select it.

Pet. Reply at 6

Baran Declaration



In my opinion, as explained above, given the nature of nucleosides as building blocks for a wide variety of compounds that themselves have a wide variety of uses, this clear utility of Compound x alone would have been reason sufficient for a POSA to select Compound x for use and potential improvement.

Ex. 1033, ¶125

The '031 Patent Does Not Disclose Data for Compound x

Q. Figure 1 shows 6 oligos; correct?

A. Correct.

Q. None of this data relates to 2 prime fluoromonomers; correct?

A. The data on this figure, I don't see it explicitly shown with the fluorine.

Ex. 2009 at 137:2-7

H-RAS TARGETED ANTISENSE OLIGOS:

FIGURE 1

FULL 2' methoxy	C C A C A C C G A C G G C G C C C
3 BASE RNA GAP	□ □ □ □ □ □ ● ● □ □ □ □ □ □
5 BASE RNA GAP	□ □ □ □ □ □ ● ● ● ● □ □ □ □ □ □
7 BASE RNA GAP	□ □ □ □ □ ● ● ● ● ● ● □ □ □ □ □ □
9 BASE RNA GAP	□ □ □ □ ● ● ● ● ● ● ● ● □ □ □ □ □ □
FULL RNA	● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ● ●

Ex. 1017 at 2

'031 Patent itself discloses **over 50 nucleosides**
None of the figures in the '031 Patent show
Compound x being used to incorporate 2'-fluoro-2'-
deoxyguanosine monomers into any
oligonucleotides

Example 8 in the '031 patent does not mention or relate to 2'-fluoro monomers



Incorrect

Example 8 **does not** mention or relate to 2'-**fluoro** monomers

Example 8 (a) describes using phosphoramidites to introduce 2'-fluoro monomers in the wing segments of the oligonucleotides, (b) describes introducing guanine monomers, and (c) Compound x is the only 2'-fluoro guanosine phosphoramidite disclosed in the '031 Patent. Ex. 1033, ¶31

Example 12 does not mention Compound x

EXAMPLE 12

Chimeric "end" gapped phosphorothioate oligoribonucleotides

iii. "3'-End" gapped phosphorothioate chimera, e.g. [2'-F]/PS.[2'-OH]/PS oligoribonucleotide

In the manner of Example 8, a chimeric compound having an "open gap" at its 3' terminus, 2'-fluoro nucleosides in its 5' "wing" segment, 2'-OH nucleosides in its open "gap" segment and phosphorothioate linkages through out is prepared. Ex. 1017 at 28

EXAMPLE 8

Chimeric phosphorothioate oligoribonucleotides, e.g. [2'-O-Me]/PS.[2'-OH]/PS oligoribonucleotide

Chimeric oligoribonucleotides having 2'-O-alkyl phosphorothioate and 2'-OH phosphorothioate oligonucleotide segments were synthesized using an Applied Biosystems automated DNA synthesizer Model 380B, as above. Oligoribonucleotides were synthesized using the automated synthesizer and 5'-dimethoxytrityl-2'-tert-butyldimethylsilyl 3'-O-phosphoramidite for the RNA portion and 5'-dimethoxytrityl-2'-O-methyl-3'-O-phosphoramidite for 5' and 3' wings. The protecting groups on the exocyclic amines were, phenoxyacetyl for rA and rG, benzoyl for rC and 2'-O-methyl A and 2'-O-methyl C, and isobutyryl for 2'-O-methyl G. The standard synthesis cycle was modified by increasing the wait step after the delivery of tetrazole and base to 600 s repeated four times for RNA and twice for 2'-O-methyl. The fully protected oligoribonucleotide was cleaved from the support and the phosphate group was deprotected in 3:1 Ammonia/Ethanol at room temperature overnight then lyophilized to dryness. Treatment in methanolic ammonia for 24 hrs at room temperature was then done to deprotect all bases and sample was again lyophilized to dryness. The pellet was resuspended in 1M TBAF in THF for 24 hrs at room temperature to deprotect the 2' positions. The reaction is then quenched with 1M TEAA and the sample is then reduced to ½ volume by rotovac before being desalted on a G25 size exclusion column. The oligo recovered was then analyzed spectrophotometrically for yield and for purity by capillary electrophoresis and by mass spectrometer. Ex. 1017 at 26



Q Yes.

A Example 12, the reference to example 8, a POSA would arrive at example 8 and be very concerned and confused -- confused and concerned because this -- what's written in example 8 is a -- is -- is an outline for how to make the compound of example 8 and does not speak of 2 prime fluoro nucleosides.

Q Okay. So in your view, example 12 little 3 at the bottom of column 43 --

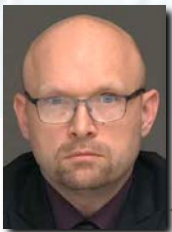
A Uh-huh.

Q -- does not by its own terms reflect the making of oligoribonucleotide with a 2 prime fluoro.

A Example 12 by itself without the reference to example 8?

Q No, with the reference to 8.

A With -- in my opinion, it does not. Ex. 1035 at 67:15-68:10



Compound x Had Known Degradation Problems

121. A POSA would have also known that in the 2009 timeframe a persistent problem existed with at least 2'-fluoro-2'-deoxyribonucleotides where oligonucleotides with those monomers would degrade.

Ex. 2008, ¶121

Kawasaki

temperature. Under the usual oligonucleotide deprotection conditions (concentrated NH_4OH , 55 °C), we in fact observed significant degradation of the 2'-deoxy-2'-fluoropyrimidine nucleosides while the nucleosides were stable to methanolic ammonia at room temperature. It was

Ex. 2025 at 833

Sinha

However, the lability of the 2'-F modification must be taken into consideration when working with mixed sequences consisting of RNA and 2'-F RNA. The 2'-F modification is subject to depyrimidation (especially with methylamine or ammonia/methylamine deprotection) and elimination and hydrolysis as shown in Figures 2.41 and 2.42 respectively. In the case of 2'-F-uridine, shown in Figure 2.41, a postulated mechanism

Ex. 2024 at 83



Sinha (2013) (Ex. 2024) does discuss the potential degradation of 2'-fluoro-2'-deoxyribonucleotides, but does not say it is a “problem,” let alone a “persistent problem.” Instead, Sinha (2013) notes merely that this potential “must be taken into consideration.” (Ex. 2024 at 83.)¹

Ex. 1033, ¶158

Q So you're saying that Kawasaki did identify the degradation problem?

A They identified a problem which is easily rectified by simply changing their deprotection conditions.

Ex. 2035 at 85:4-8

Compound x's Degradation Problems Not Considered by Baran or Asserted in Hongene's Case-in-Chief



Q That's not what I asked, respectfully.

It's a simple question of whether you were aware of the degradation issues relating to using compound X when you submitted your January 2023 declaration?

MR. EDWARDS: Object to form.

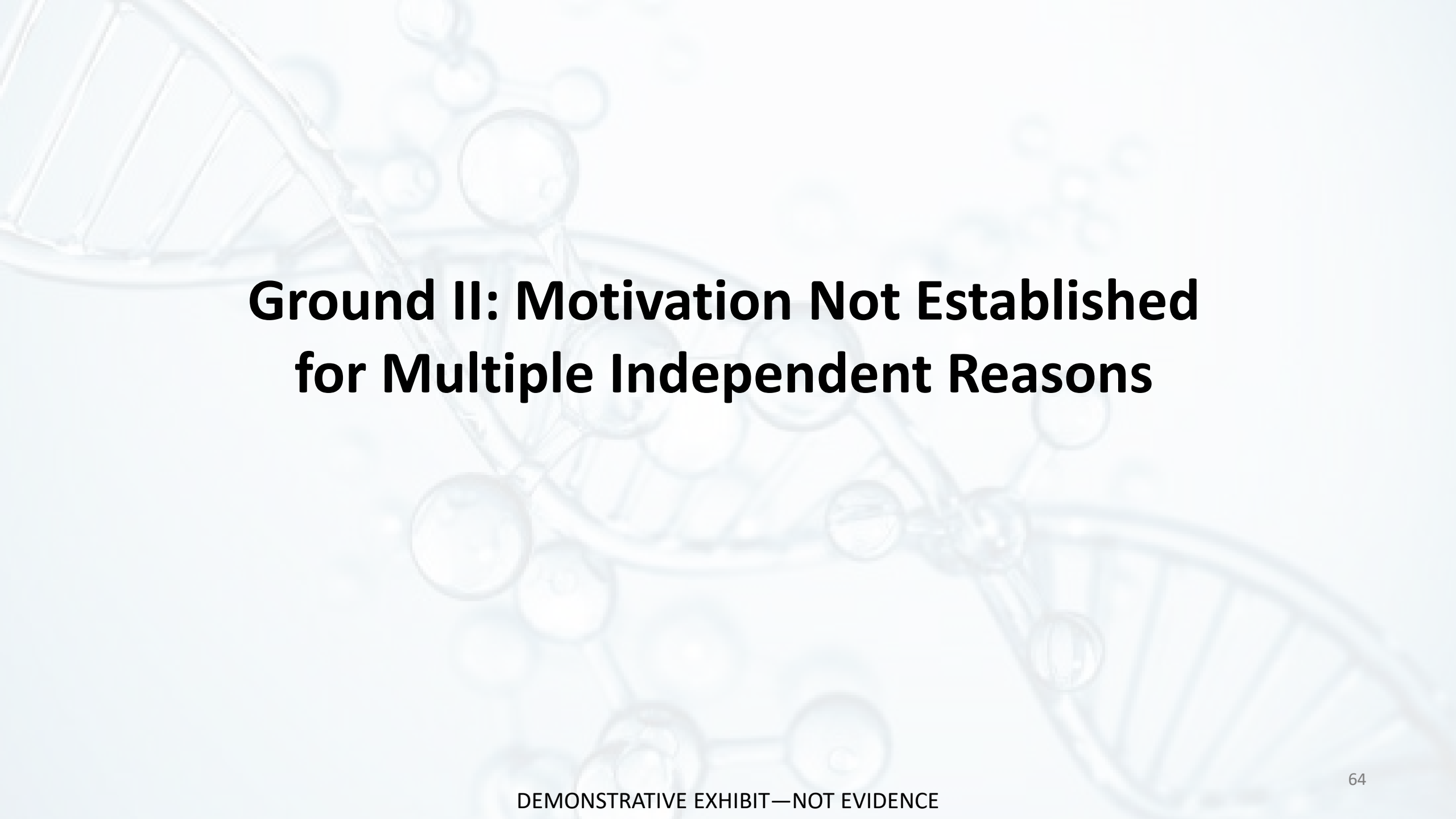
A As I said, I'm aware that it has to be something to look out for in all cases. But as far as it being a specific problem associated with this compound, no.

Ex. 2035 at 60:25-61:9

Compound x (a 2'-fluoro-2'-deoxyribonucleotide phosphoramidite) caused known degradation problems that would have "directed [POSAs] away" from Compound x, issues that Baran admitted he did not consider in his opening declaration. Takeda, 492 F.3d at 1359; (Ex. 2035, 61:1-62:5; see also Ex. 2024, 83; Ex. 2025, 833).

Hongene Did Not Plead its Particular Obviousness Theories in its Petition

- Hongene **did not reveal** its legal grounds for its obviousness theories in its Petition
 - “A party may take several different paths to support obviousness grounds...” *NOF*, at 10-11.
 - Hongene cited to **no case law or standards** for obviousness in its Petition
 - Failed to put ChemGenes on notice of its particular legal grounds and violated 35 U.S.C. §312(a)(3)



Ground II: Motivation Not Established for Multiple Independent Reasons

Pitsch Does not Teach that Acetyl “Universally” Applies to “Virtually Any” Nucleoside



Pitsch

HPLC, we determined half-lives of <2 min for the 2'-O-tom-protected *N*⁴-acetylcytidine and *N*⁶-acetyladenosine derivatives, and a half-life of 4 min for the 2'-O-tom-protected *N*²-acetylguanosine, respectively (*Scheme 3*). These values indicated that complete base-deprotection of oligonucleotide sequences can be achieved within 1 h (equal to 15 half-lives for the acetylated guanosine residues) and demonstrated that the Ac group, in combination with MeNH₂, is indeed suited for a labile universal nucleobase protection. Under the deprotection conditions with MeNH₂, the 2'-O-tom

Ex. 1018 at 6

Q And what is your interpretation of "universal" here?

A Meaning it can be used on virtually any nucleobase, regardless of the sugar substitution or the type of nucleobase.

Q So where in Pitsch does it say that?

Ex. 2035 at 65:20-25

A That's -- well, you asked me what I interpreted universal to mean, and that's what I interpreted universal to mean.

Q So that's based on -- that's not based on any statement that's made in Pitsch other than that one sentence, correct?

A Well, it's based on the Merriam-Webster definition of what universal means.

Q In fact, the data presented in Pitsch only relates to these novel 2-prime-tom RNA nucleosides, correct?

A Yes.

Ex. 2035 at 66:1-8, 67:6-9

Pitsch Does not Teach that Acetyl “Universally” Applies to “Virtually Any” Nucleoside

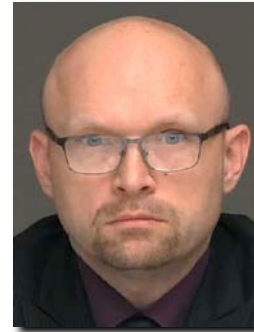
120. Therefore, a POSA would have understood that Pitsch and Fan did not teach 2'-deoxyribonucleotides (i.e., nucleotides lacking an (-OH) group at the 2'-position), yet alone, 2'-fluoro-2'-deoxyribonucleotides (i.e., nucleotides lacking an OH group at the 2'-position but having a 2'-fluoro substituent like Compound x), and instead only taught nucleosides with (-OH) at the 2'-position protected by TOM or TBDMS. Ex. 2008, ¶120

125. A POSA would have readily known that these oligonucleotides—incorporating the Pitsch and Fan monomers—are directed to RNA because of the (-OH) functional groups at their 2'-positions and the related disclosures in Pitsch and Fan that discuss “RNA” synthesis but not modified RNA or DNA or chimeric oligonucleotides. Exs. 1018; 1019. Ex. 1018, 3773; 1019, 2556. Ex. 2008, ¶125.

Ex. 2008, ¶125

127. A POSA would have therefore found the limited teachings of Pitsch and Fan, which only applied to protected ribonucleosides and phosphoramidites for RNA synthesis, and not 2'-fluoro-2'-deoxyribonucleotide phosphoramidites for modified oligonucleotide synthesis, as not relevant (i.e., “apples and oranges”) to efforts in modifying a 2'-fluoro-2'-deoxyribonucleoside phosphoramidite like Compound x. Ex. 2008, ¶127

Ex. 2008, ¶127



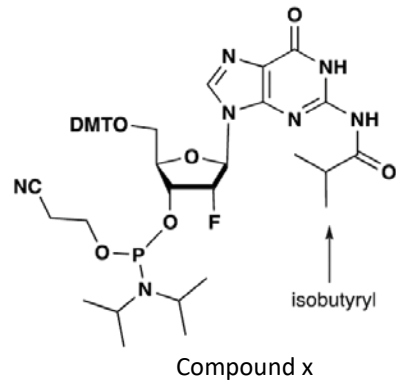
Q Sure. We're reaching the limit of my computer skills here. One second. Does the person of ordinary skill in the art in your opinion take anything from Pitsch as to why the '031 patent compound X should be acetylated?

A I believe I provide very rich testimony to -- to that effect already in my written declaration that a POSA would not have been motivated to switch from an -- switch the isobutyryl group of the '031 compound X to an acetyl group for a variety of reasons. I mean, again, here, Pitsch is a -- first off, Pitsch speaks about TOM-protected -- O2 prime TOM-protected nucleosides and oligonucleotides, whereas Fan -- no, whereas the '031 is -- compound X is of course a 2 prime fluoro, so we're talking very different compound classes here to begin with, yeah.

Ex. 1035 at 139:15-140:10

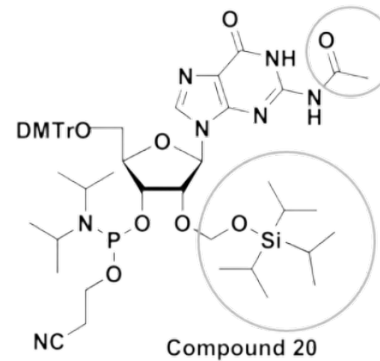
Compounds 20 and 6a Would Not Have Motivated a POSA to Install Acetyl on Compound x for Faster “Deprotection Speed”

'031 Patent



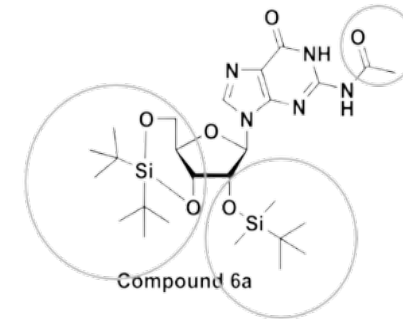
- 2'-fluoro-2'-deoxyguanosine (not disputed)
- Known degradation problems
- Known solubility problems
- Provides no comparison of deprotection rates (not disputed)

Pitsch



- Teaches RNA nucleosides with 2'-OH and not 2'-deoxyguanosine or 2'-fluoro-2'-deoxyguanosine (not disputed)
- Provides no comparison of deprotection rates (not disputed)

Fan



- Teaches RNA nucleosides with 2'-OH and not 2'-deoxyguanosine or 2'-fluoro-2'-deoxyguanosine (not disputed)
- Nucleoside derivative that could not even be used during SPOS (not disputed)
- Deprotection conditions used to remove acetyl would have never been used in SPOS (not disputed)
- PAC listed as **57 times faster** than Acetyl

Khorana Eschewed Using Acetyl to Protect the N-2 Position of Guanine Nucleobases Including 2'-deoxyguanosine and the Field Followed Suit



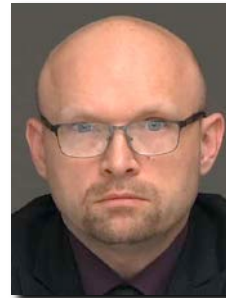
to have been completely satisfactory in the past. The *N*-acetyl group was introduced some years ago (Ralph, Connors, Schaller & Khorana, 1963) and it has been used in all the synthetic work reported so far, but its disappearance to a significant extent during the course of synthetic and isolation procedures has repeatedly been observed (e.g. Kössel, Buchi & Khorana, 1967)‡. In view of the extended nature of the present task, those that were guanine rich) on DEAE-cellulose columns. Further investigation (see the succeeding paper) showed the *N*-isobutyryl group to be considerably more stable than the *N*-acetyl group and this group has been used for the protection of all the deoxyguanosine residues in the present work, except for the first one at the 5'-terminus.

Ex. 2011 at 221

a POSA would have known very well that Nobel Laureate Har Gobind Khorana established that acetyl groups were not suitable to protect the N2-position of the guanine nucleobase in nucleosides and nucleotides due to the demonstrated instability of N2-acetyl groups under basic conditions, and that isobutyryl groups were superior.

108. It is my opinion that based on these findings alone, a POSA in the 2009 timeframe would have been discouraged from using acetyl groups to protect the N2-position of the guanine nucleobase in nucleosides and nucleotides as the reference by Dr. Khorana explicitly taught away from that approach.

Ex. 2008, ¶¶107-108



109. It is my further opinion that following Dr. Khorana's discovery, isobutyryl and a range of other base protecting groups, were used in the field to protect the N2-position of guanine nucleobases, but acetyl was not one of those groups, as evidenced by the breadth of literature spanning the following decades.

Q Acetyl is more labile than isobutyryl.

Ex. 2008, ¶109

A I already provided testimony that Khorana in 1972 observed that on the — on the basic conditions, that acetyl group had a tendency to fall off readily — too readily, whereas the isobutyryl group was — provided more stability.

Ex. 1035 at 137:12-17

Q. Okay. So is it fair to say that the standard protecting group for guanosine in the 2013 time frame was isobutyryl?

A. For most applications, isobutyryl is fine.

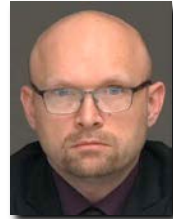


Ex. 2009 at 156:13-16

Khorana “Set the Stage” for the Field not to use Acetyl to Protect the N2-position of Guanine

It's your opinion that the Khorana article taught away from using acetyl protective group?

A It is my opinion that – that Khorana here reports the problems associated within the N2 acetyl group, and speaking to the benefits of an isobutyryl group, and that has been a very foundational paper that – that set the stage for the field using isobutyryl, and therefore, not -- not using acetyl as a protecting group.



Q No implications.

A I don't know how to answer your question in other terms than to say that the teachings of Khorana were taken note of and inspired the field in the subsequent works, the decades that followed.

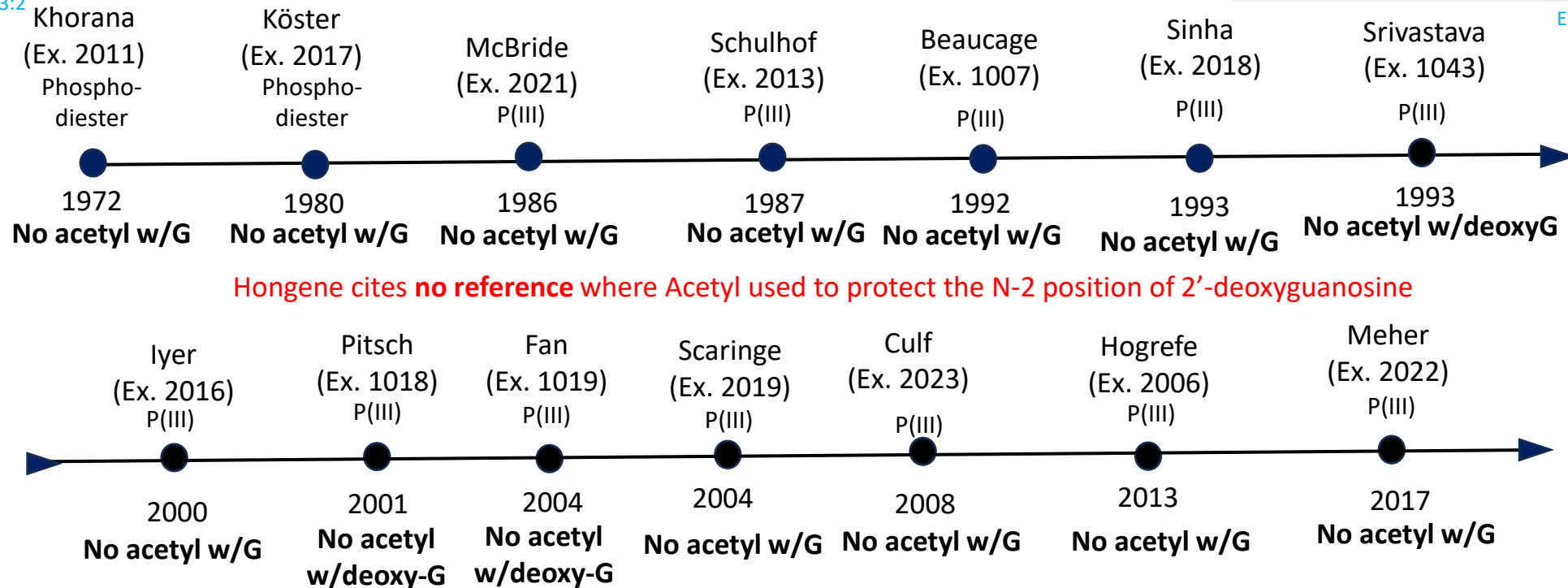
Ex. 1035 at 127:4-8

Q Well, wouldn't you say that Pitsch ended up at the acetyl protecting group?

A The Pitsch paper is very much an outlier in the ocean of literature that pertains to -- to protecting groups for G I would say. The vast majority of papers looked to the isobutyryl group as the protecting group for G, and yes, there was certainly efforts being made to come up with alternative protecting groups, many examples that I cite to that I provide testimony to, but none of them ended up with -- with Pitsch -- with Pitsch -- with Pitsch's acetyl, if you will.



Ex. 1035 at 126:7-18



Contrary to Baran, POSAs Acknowledge the Field Followed Khorana's Teachings Into the P(III) Era



Q And it goes back to Khorana, right?

A Well, invoking that old literature, you know, the problem is science evolves, and if you go back far enough in the literature, you can be convinced that the earth is flat.

So in general, the POSA is going to try to find the most up-to-date, recent, and well-described experimental details for the modern era. So while Khorana is really useful literature in the classroom, that literature is for really a different system all together, phosphate ester-type methods, not phosphoramidite.

So if you put a 1960 Khorana paper next to this paper and ask the POSA which one do you want to use as your guiding reference, no one would pick the Khorana reference for anything other than historical understanding of how the field progressed.

Ex. 2035 at 71:19-72:10

Beaucage (1992)

In the late fifties and early sixties, Khorana and his colleagues succeeded in the preparation of short, defined sequences of deoxyribopolynucleotides which were helpful in deciphering the genetic code.^{4,5}

This "phosphodiester" approach to the synthesis of oligonucleotides became routine for nearly two decades and led to the total synthesis of genes encoding an alanine tRNA from Yeast⁷ and a tyrosine suppressor tRNA from *E. coli*,⁸ respectively. The biologically active genes were constructed from synthetic DNA segments linked together by T4-DNA ligase.⁷⁻⁹ During the course of this colossal achievement, the development of trityl group derivatives for the protection of the 5'-hydroxy function of nucleosides along with the benzoyl and isobutyryl groups for the protection of the exocyclic amino function of adenine and guanine, respectively, became a landmark in the field. These protecting groups are still used in modern oligonucleotide syntheses. One major drawback pertaining to the

Ex. 1007 at 2-3



Hogrefe (2013)

Khorana et al. also developed the oligonucleotide protection/deprotection scheme^[8] that is still used today more or less intact. The 4,4'-dimethoxytrityl (DMT) protecting group for the protection of the 5'-hydroxyl^[8b] group is ubiquitous in oligonucleotide chemistry. Khorana et al. introduced protecting groups for the nucleosidyl exocyclic amines that are known today as standard protecting groups: isobutyryl (iBu) for guanosine, and benzoyl (Bz) for adenosine and cytidine.^[8a,9] Although others exist,^[10] these groups are those most commonly used, with the possible exception of acetyl-protected cytidine, which is more readily and cleanly removed compared with Bz^[11] (Figure 1).

Ex. 2006 at 327

Baran Myopically Focuses on Pitsch and Ignores the Broader “Scope and Content” of the Prior Art Within the Knowledge and Skill of a POSA



Q You didn't identify any papers after Pitsch that used acetyl with guanine on a guanine-based nucleoside, though, correct?

A I didn't need to look for more than Pitsch.

Ex. 2035 at 73:10-13



A POSA Would Have Known Compound x Had Degradation Problems and Not Have Been Motivated by Pitsch and Fan

121. A POSA would have also known that in the 2009 timeframe a persistent problem existed with at least 2'-fluoro-2'-deoxyribonucleotides where oligonucleotides with those monomers would degrade. Ex. 2024, 83 (book chapter by Nanda D. Sinha et. al. stating that the 2'-F modification of chimeric oligonucleotides “is subject to depyrimidation [] especially with methylamine or ammonia/methylamine deprotection...”); Ex. 2025, 833 (observing “significant degradation of the 2'-deoxy-2'-fluorpyrimidine nucleosides” while under “the usual oligonucleotide deprotection conditions (concentrated NH₄OH, 55°C)”). A POSA would have also known that Pitsch discloses using methylamine (in ethanol and water) and Fan uses methylamine (in ethanol and methylene chloride), i.e., the reagents that Ex 2024 identifies as causing damage. Ex., 1018, 3778. Ex. 1019, 2556.

Ex. 2008, ¶121

122. Accordingly, in my opinion, a POSA would have recognized that the unique challenges associated with oligonucleotides with 2'-fluoro nucleotides would not have been resolved by the fundamentally different studies described in Pitsch and Fan, and would therefore not have been motivated by those references.

Ex. 2008, ¶122

Schulhof is Consistent with Khorana's Teachings not to Use Acetyl to Protect N2-position of Guanine

Schulhof features **2'-phenoxyacetyl** (PAC) as an alternative to isobutyryl to protect the N2-position of 2'-deoxyguanosine and lists over a dozen additional protecting groups, **none of which are acetyl**.

Table 1 : Comparison of the N-deacylation time required by the protecting groups by t.l.c. measurements in 29% ammonia/pyridine (80/20) at 20°C.

Compound :	Half time of N-deacylation in 20°C 29% ammonia (t 1/2).
N2-isobutyryl-2'-deoxyguanosine	10 hours .
N6-benzoyl-2'-deoxyadenosine	8 hours .
N4-benzoyl-2'-deoxycytidine	2 hours .
1. N4-isobutyryl-2'-deoxycytidine	30 minutes .
2. N6-phenoxyacetyl-2'-deoxyadenosine	7 minutes .
3. N2-phenoxyacetyl-2'-deoxyguanosine	15 minutes .
4. N2-methoxyacetyl-2'-deoxyguanosine	45 minutes .
N2-chlorophenoxy-acetyl-2'-deoxyguanosine	8 minutes .

Ex. 2013 at 399

In order to suppress these drawbacks, many studies have been carried out in search of new protecting groups. Various substitutions of the benzoyl (3) and butyryl groups (5) have been suggested. Of interest are the p.t.butylphenoxyacetyl, p.t.butyl-phenylacetyl (3,6), phenylacetyl (7), the benzyloxycarbonyl (CBZ) (8) and (9-fluoroenyl)-methoxycarbonyl (FMOC) (9) groups : These five groups exhibit an important lability, far below the classically used benzoyl and isobutyryl groups. Besides, we can also mention among other compounds : the 2-nitrophenylsulfenyl (NPS) (10), isovaleryl, pivaloyl, propionyl (5,11), 2-methylpropanoyl (12), nitrophenylethoxycarbonyl (13), dialkylformamidines (14), succinyl, phthaloyl and substituted (15), and more recently (3-methoxy 4-phenoxy)benzoyl (16).

Ex. 2013 at 398

Khorana Did Not Use “Harsh” Deprotection Conditions

Khorana: Deprotected d-G-Isobutyryl with **Ammonia** which are **Milder Deprotection Conditions** than Pitsch



Baran Dec.

prolonged and harsh deprotection conditions used in phosphodiester synthesis were not used in SPOS using phosphoramidites. As explained below, a POSA in 2009 would have known this, and thus would not have been dissuaded by Khorana from using acetyl to protect the exocyclic amine of a guanosine phosphoramidite.

Ex. 1033, ¶139

Hongene Reply

Unlike the phosphoramidite methods used in 2009, phosphodiester coupling used prolonged and harsh deprotection conditions.

Reply at 10

Baran: Ammonia Less Basic (Milder) than Methylamine

Q And then you've got methylamine.

A Methylamine, which is slightly more basic even than ammonia because you've got that alkyl group on it that adds basicity.

Ex. 2035 at 22:17-20

Pitsch Used Methylamine

Prior to the synthesis of oligonucleotides, we established the conditions required for the removal of the base-protecting Ac groups with MeNH_2 (10M in $\text{H}_2\text{O}/\text{EtOH}$ 1:1, 25°).

Ex. 1018 at 6

Finally, certain observations made during this and the subsequent work on the removal of the protecting groups may be mentioned. Due to the exceptional stability of the benzoyl protecting group on deoxyguanosine residue it proved necessary to give compounds containing this residue a more powerful base treatment than the usual treatment with concentrated ammonia at room temperature; treatment with an anhydrous *n*-butylamine/methanol mixture at room temperature was effective in quantitative removal of the protecting group (paper CVII). Upon such treatment,

The *N*-acyl groups of protected oligonucleotides were removed by one of the following methods. (a) Compounds (usually portions of 20 to 40 o.d. units) containing *N*-benzoyl-deoxyguanosine residues but no *N*-anisoyldeoxycytidine residues were treated, after complete evaporation of the solvent, with a 1 : 1 mixture (v/v) of *n*-butylamine and methanol (1 ml.) at room temp. for 2 days. (b) Compounds containing **no** *N*-benzoyldeoxyguanosine residues were treated with conc. ammonia (1 ml.) at room temp. for 2 days. (c) Compounds containing both *N*-benzoyldeoxyguanosine residues and *N*-anisoyldeoxycytidine residues were treated first with conc. ammonia (1 ml.) at room temp. for 2 days, then, after evaporation of the solvent in a vacuum, with a 1 : 1 mixture (v/v) of *n*-butylamine and methanol (1 ml.) at room temp. for 2 days. During evaporation of the conc.

Ex. 2011 at 236, 240

A POSA Would Have Known that Replacing Isobutyryl with Acetyl Would Have Made Compound x Less Soluble in Organic Solvents



113. A POSA would have readily understood nucleosides with guanine moieties were notoriously insoluble in organic solvents and that lipophilic base protecting groups like isobutyryl or *tert*-butylphenoxyacetyl to protect the N2-position of nucleosides with guanine moieties would have enhanced the nucleoside's solubility. Ex. 2018, 14 ("Problems associated with solubility of deoxyguanosine-phosphoramidites using other labile N-protecting groups are eliminated with the use of the more lipophilic t-butylphenoxyacetyl groups.").

114. My opinion is that a POSA would have known that acetyl groups would have made nucleoside derivatives *less soluble* in organic solvents than isobutyryl groups when used to protect the N2-position of the guanine of nucleosides/nucleotides. That is because acetyl groups are smaller, more polar groups, than isobutyryl groups and therefore less hydrophobic and less apt to solubilize nucleosides with guanine moieties, as Dr. Baran confirmed. Ex. 2009,

Ex. 2008, ¶¶113-114



175:25-176:6 ("Q. And isobutyryl is more hydrophobic—isobutyryl group is more hydrophobic than an acetyl group; right? A. I would expect that to be the case, yes. Q. So an acetyl group is more polar than an isobutyryl group? That would be my expectation, yes.").

POR at 28-29 (citing Ex. 2009 at 175:25-176:6)

115. It is my opinion that a POSA would have understood that the literature demonstrated that adding acetyl to (i.e., acetylation of) 2'-deoxyguanosine caused solubility problems. Ex. 2012, 3822-26 (stating that "[a]cetylation of deoxyguanosine so as to prepare N,3',5'-triacetyldeoxyguanosine did not proceed satisfactorily ... A part of the cause of failure to accomplish N-acetylation could be due to the insolubility of 3',5'-di-O-acetylguanosine which separates from the reaction mixture. ... The lack of N-acetylation was probably due to the insolubility of 3',5'-di-O-acetylguanosine in the solvent. ... In a parallel experiment benzoylation with [more lipophilic] benzoyl chloride did cause N-benzoylation as clearly shown").

Ex. 2008, ¶115



Pitsch Compound 20 “More Lipophilic” and Therefore Less Apt to Fail During Synthesis Due to Insolubility

46. First, Chemgenes’ assertion is squarely **refuted by Pitsch**, which used the acetyl protecting group to synthesize RNA oligonucleotides. As noted above, Pitsch conducted a thorough workup of various reaction conditions and reported a resounding success, and **did not report any solubility problems**. Chemgenes does not acknowledge or address this in making its assertions regarding solubility.

Ex. 1033, ¶46

Q Well, I'm asking it. If they were to think about that, if someone were to pose that question to a POSA, if you switched the 2-prime-OH-tom, switched that -- switched in fluoro, switched out 2-prime-OH-tom, whether the resulting compound with the 2-prime-fluoro would be less soluble in organic solvents?

Ex. 2035 at 78:20-79:1

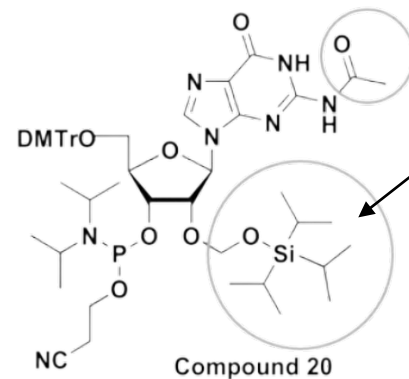
Sur-Reply at 13-14



A I think a POSA would probably say that the compound 20 depicted here is more lipophilic than the compound with the fluorine. But in terms of relative solubility, I'm not sure it would be easy to predict one way or the other.

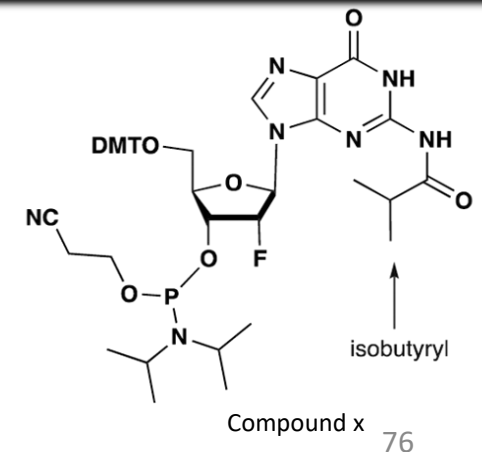
Perhaps some people would say, oh, maybe it will be slightly less soluble. Some people would say it's probably going to be the same for the purposes of making a stock solution for an oligo synthesizer.

Ex. 2035 at 79:2-10



Switch to fluoro =
less “lipophilic”

Switching TOM to
Fluoro removes 10
lipophilic
hydrocarbon groups



DEMONSTRATIVE EXHIBIT—NOT EVIDENCE

Sinha and Schaller Clearly Identify Solubility “Problems” with Deoxyguanosine Nucleosides

Sinha

amidite or H-phosphonate chemistries. Problems associated with solubility of deoxyguanosine-phosphoramidites using other labile N-protecting groups are eliminated with the use of the more lipophilic t-butyl-phenoxyacetyl groups. N-Deacylation is not only faci-

Ex. 2018 at 14

Schaller

Acetylation of deoxyguanosine so as to prepare N,3',5'-triacetyldeoxyguanosine did not proceed satisfactorily,²¹ although in the case of deoxyguanosine-5' phosphate¹⁹ acetylation of the ring occurred readily.²²

(21) A part of the cause of failure to accomplish N-acetylation could be due to the insolubility of 3',5'-di-O-acetylguanosine which separates from the reaction mixture. More recently, using the base tri-n-hexylethylammonium

Ex. 2012 at 3822



Ex. 1033, ¶148

Sinha (1993) alludes only to problems associated with DNA synthesis, not RNA synthesis, because it refers only to “deoxyguanosine-phosphoramidites.” (Ex. 2018 at 14.) Thus, Sinha (1993) does not suggest any problem using base labile N-protecting groups in oligonucleotide synthesis involving 2'-fluoro-substituted monomers (like Compound x) or RNA synthesis (as in Pitsch).

Compound x is a 2'-deoxyguanosine and Baran's other testimony is that it would “react similarly to a ‘regular’ 2'-deoxyguanosine.”

A POSA would have reasonably expected that 2'-fluoro-2'-deoxyguanosine would react similarly to a “regular” 2'-deoxyguanosine (i.e., one with a 2'-H instead of the 2'-F substitution) in connection with the preparation of reagents for SPOS,

Ex. 1003, ¶123

Hongene and Baran's New "RNA Like" Theory is Baseless and Contradicts their Other Meritless Theories



Baran's New Theory

"2'-fluoro-2'-deoxy nucleosides" are "RNA-like"

56. Also contrary to Chemgenes' suggestion that a POSA would not apply teachings of Pitsch and Fan to Compound x, it was well known that 2'-fluoro-2'-deoxy nucleosides were "RNA-like" and had been incorporated into RNA to create "antisense" oligonucleotides with better target affinity. Indeed, the Kawasaki paper (Ex. 2025) cited by Chemgenes illustrates this close relationship, incorporation advantage, and significant utility of resulting antisense oligonucleotides.

It explained that (a) such oligonucleotides may be useful antisense molecules, in part because "2'-deoxy-2'-fluoro homopolymers show characteristics more closely related to RNA than DNA;" and (b) such Ex. 1033, ¶156

Kawasaki's "closely related" comment did not apply to deoxyguanosine

In fact the 2'-deoxy-2'-fluoro-substituted oligonucleotides have been prepared enzymatically as the homopolymers of 2'-deoxy-2'-fluorocytidine,^{16,17} -uridine,¹⁸ -inosine,¹⁷ and -adenosine.¹⁹ These 2'-deoxy-2'-fluoro-substituted homopolymers possess thermal stabilities similar to or higher than those of the corresponding RNA duplexes,^{16,18} and the CD spectra of these 2'-deoxy-2'-fluoro homopolymers show characteristics more closely related to RNA than to DNA.^{16,17} Ex. 2025 at 831-832



Baran's earlier contradictory testimony

2'-fluoro-2'-deoxyguanosine would "react similarly" to "regular" 2-deoxyguanosine (i.e., DNA)

A POSA would have reasonably expected that 2'-fluoro-2'-deoxyguanosine would react similarly to a "regular" 2'-deoxyguanosine (i.e., one with a 2'-H instead of the 2'-F substitution) in connection with the preparation of reagents for SPOS,

Ex. 1003, ¶123

Iyer teaches 2'-deoxyguanosine has greater depurination risk than guanosine and each react differently (and 2'-deoxy-G therefore not "RNA like")

Presence of the 2'-OH has a significant effect on the nucleoside's susceptibility to depurination. For example, guanosine and adenosine are more resistant to depurination compared with deoxyadenosine and deoxyguanosine. Ex. 2016 at 10

Q And then those two compounds, the guanosine and deoxyguanosine compounds react differently under those conditions, correct?

A Yes.

Ex. 2035 at 59:10-13



Hongene and Baran's New "Chemically Distant" Theory is Baseless



55. Indeed, a POSA would have known as a matter of common sense in 2009 that the exocyclic amine of the nucleobase and the 2' position on the sugar ring are, chemically speaking, remote from one another and not expected to affect the reactivities of one another. This is illustrated, for example, by Zhu (2003), et al., which shows that under substantially the same reaction conditions, there were little or no differences in silylation time and benzoylation time of various nucleosides, regardless of which group was attached to the 2' position of the sugar ring. (Ex. 1038 at Table 1.)

Ex. 1033, ¶55

Q Isn't that -- isn't the silylation time of 2 prime-deoxyguanosine monohydrate three times that of guanosine?

A That is correct. But it's the guanosine monohydrate versus the guanosine, so -- but half an hour versus one-half hours is, for a monomer, it's -- that's not a -- not a big difference in time for an organic chemist.

Ex. 2035 at 81:20-82:2



Zhu: 300% increase in silylation and benzoylation time going from guanosine to 2'-deoxyguanosine

Table 1. N-Benzoylation of ribo-, arabino-, 2'-deoxy-ribo nucleosides.

Entry	Substrate	TMSCI (eq.)	Silylation time (h)	Benzoylation time (h)	Yield (%)
1	adenosine	3.3	0.5	2	96
2	cytidine	3.6	0.5	4	95
3	guanosine	3.6	0.5	2	99
4	ara-adenosine	3.6	1.0	2	95
5	ara-cytidine	3.6	1.0	4	98
6	ara-cytidine monohydrochloride	3.6	1.0	4	93
7	2'-deoxycytidine monohydrochloride	2.4	0.5	4	96
8	2'-deoxycytidine monohydrate	2.4	0.5	4	81
		3.6	0.5	4	98
		4.8	0.5	4	95
9	2'-deoxyadenosine monohydrate	3.6	0.5	2	91
10	2'-deoxyguanosine monohydrate	3.6	1.5	6	98

Ex. 1038 at 4

Q So then the benzoylation time for 2 prime-deoxyguanosine monohydrate is three times that of guanosine according to this table, correct?

A Yes.

Ex. 2035 at 82:11-14

Hongene's Sole Motivation Theory is Based on "Deprotection Speed" Which is Undercut by Fan

"Deprotection speed" is the only argument for motivation in Hongene's *prima facie* case

Petition: Thus, a POSA would have been motivated by the respective teachings of Pitsch (2001) and Fan (2004) to synthesize a guanosine phosphoramidite similar to the one made in step "x" of Example 4-d in the '031 Patent — but with an acetyl instead of an isobutyryl protecting group on the exocyclic NH₂ group of the guanine base — to take advantage of the drastic improvement in deprotection speeds. [Pet. at 36](#)

Baran: Thus, a POSA would have been motivated by the respective teachings of Pitsch (2001) and Fan (2004) to synthesize a guanosine phosphoramidite similar to that made in step "x" of Example 4-d in the '031 Patent — but with an acetyl instead of an isobutyryl protecting group on the exocyclic NH₂ group of the guanine base — to take advantage of the drastic improvement in deprotection speeds [Ex. 1003, ¶121](#)

PAC accepted as a viable protecting group for G and is larger and more lipophilic than acetyl. See, e.g., Schulhof

Fan

Table 1. Deprotection of *N*-Acylguanosine Derivatives

<i>N</i> -acyl group	time required for 50% deprotection
isobutyryl	18 h
acetyl	4.5 h
phenoxyacetyl	4.7 min

[Ex. 1019 at 2](#)



Hongene's sole "speed" argument undercut by Fan which teaches that acetyl is much slower than phenoxyacetyl ("PAC"), which Baran and Hongene Ignored

Q I mean, here in this Table 1, it shows phenoxyacetyl as being significantly faster than acetyl, right?

A It is.

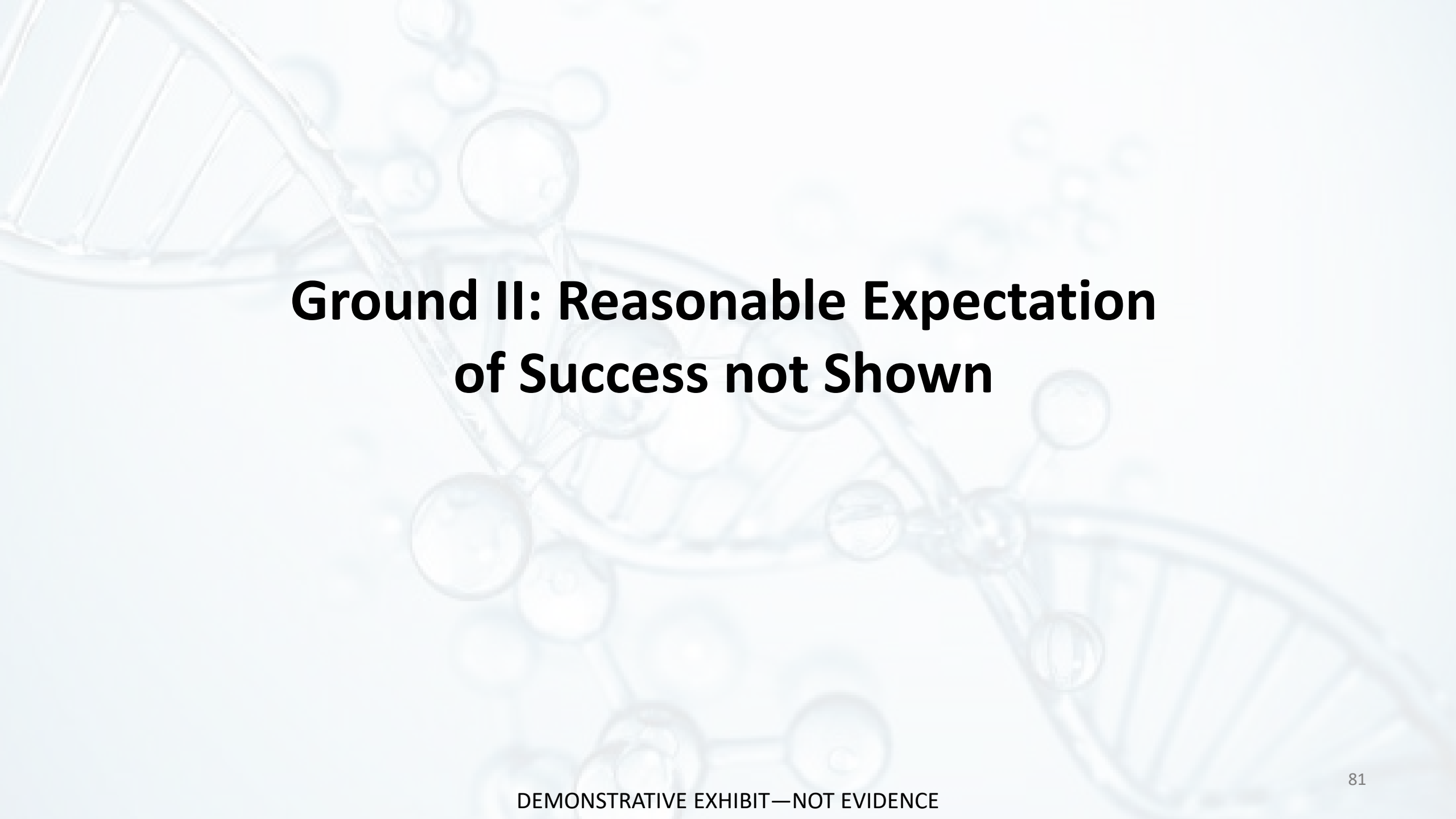
Q Right. In your testimony you just identified, you know, in your declaration, you omitted the phenoxyacetyl group as one of the -- the groups to compare, correct?

A Okay.

Q Do you agree?

A I mean, if that's -- if it's omitted from -- if it's omitted from the declaration, then that's what it is, sure.

[Ex. 2035 at 89:20-90:3, 90:4-7](#)



Ground II: Reasonable Expectation of Success not Shown

Baran's Acetic Anhydride Theory is Baseless and Would Have Resulted in Failure



Baran

Thus, a POSA would have simply substituted acetic anhydride (for isobutyric anhydride) in step “ii” and thereafter performed the remaining steps “iii” through “x” of Example 4-d in the '031 Patent to make the molecule in Claim 2 of the '885 Patent where “B” is guanine-N-acetyl and “Z” is ribo fluoro.

122. A POSA would have had a reasonable expectation of successfully synthesizing the claimed molecule, and would have regarded the conditions and yield for the installation of an acetyl protecting group as trivial and similar to those for an isobutyryl group.

Ex. 1003, ¶122

So that was your testimony. And my question was whether you went into the lab to prove that theory.

A. No, because this is undergraduate level chemistry, so there would be no need to even contemplate doing something like that. So the answer is no.

Ex. 2009 at 161:6-12



Hrdlicka

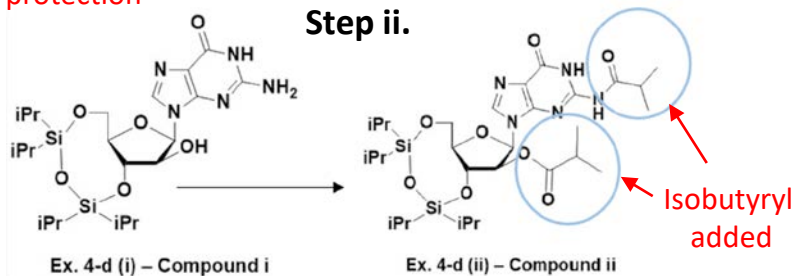
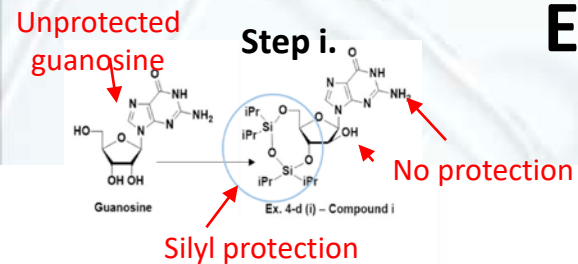
143. Petitioner largely relies on speculation by Dr. Baran in alleging that substituting acetic anhydride in step ii. of the complex 10-step process set forth in Example 4-d of the '031 Patent would have resulted in the claimed invention. *Id.*

145. Petitioner and Dr. Baran do not provide any additional references, data, experimental evidence or technical reasoning to support Dr. Baran's theory that the proffered modification to the Example 4-d scheme would have succeeded in resulting in the claimed compound.

146. Contrary to these unsubstantiated arguments, as supported by literature and my opinions set forth in the following subsections, it is my opinion that a POSA would have instead expected that substituting acetic anhydride for isobutyric anhydride in step ii. of Example 4-d in the '031 patent and executing the subsequent synthetic transformations (steps iii-x) would have resulted in failure.

Ex. 2008, ¶¶143, 145, 146

Example 4-d: Adding Acetic Anhydride in Step ii Would Have Resulted in Failure

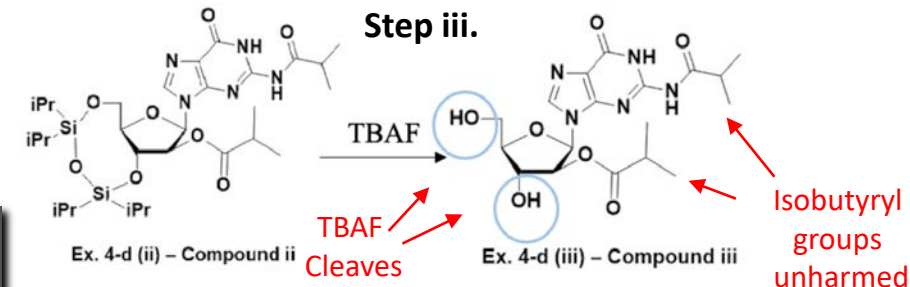


Hongene argues TMSCI treatment would fix but provides no explanation as to result of using it would have on scheme

151. The statements in the Petition and Dr. Baran's Declaration that introducing an acetyl group via acetic anhydride in accordance with this step ii. would be successful is belied by one of Petitioner's primary references, Fan, reporting that isobutyrylation (i.e., addition of isobutyryl groups) of guanosine derivatives (like Compound i) using isobutyryl in its scheme worked well, *but acetylation (i.e., addition of acetyl groups) of guanosine derivatives did not* ("the reaction mixtures were dark and the yields were unsatisfactory."). Ex. 1019, 2555.

152. A POSA would have understood that a failure to attach acetyl groups (instead of isobutyryl groups) to the O2'- and/or N2-positions at this step would have completely derailed the subsequent synthetic transformations towards the N2-acetyl analogue of Compound x purported by Petitioner and Dr. Baran, as the reactive/nucleophilic O2'- and/or N2-positions would have reacted with reagents in some of the subsequent steps, to produce undesirable intermediates that would not have resulted in the synthesis of the N2-acetyl analogue Compound x. Ex. 1017, 25:32-28:19.

Ex. 2008, ¶¶151-152



Hongene argues "different deprotection complex" would fix but provides no explanation as to result of using it would have on scheme

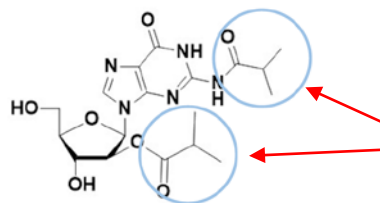
a POSA would have expected, as supported by the literature, that removing the 5'-O,3'-O-silyl protecting groups in step iii. with TBAF also would have seriously risked the undesirable removal of the O2'- and/or N2-acetyl groups, given the basic/nucleophilic conditions disclosed. *See, e.g.,* Ex. 2015, 18144 ("The subsequent deprotection of the TBDMS groups proved to be difficult due to parallel cleavage of the [N2] acetyl protecting group under basic fluoride deprotection conditions such as TBAF in THF."). Literature support

156. It is my opinion that a POSA would have expected that the undesirable removal of the acetyl group(s) at the O2'- and/or N2-positions at this step would have completely derailed the subsequent synthetic transformations towards the N2-acetyl analogue of Compound x, as the presence of a reactive/nucleophilic 2'-OH and/or 2-NH₂ groups would have reacted with reagents in subsequent steps to produce undesirable intermediates that would not have resulted in the synthesis of the N2-acetyl analogue Compound x as Petitioner and Dr. Baran allege. Ex. 1017, 25:32-28:19.

Ex. 2008, ¶¶155-156

Example 4-d: Adding Acetic Anhydride in Step ii Would Have Resulted in Failure

Step iii. (cont'd)



Ex. 4-d (iii) – Compound iii

Hongene and Baran's theory: Acetyl instead of Isobutyryl

159. Therefore, a POSA would have understood that, according to Petitioner's and Dr. Baran's theory, Compound iii, shown [above] would have had two acetyl groups at the O2'- and N2- positions instead of the two isobutyryl groups. Ex. 1017, 25:32-28:19.

160. A POSA would have expected Petitioner's and Dr. Baran's proposed molecule to be less soluble in organic solvents than Compound iii, which a POSA would have expected could have negatively affected purification and caused the synthesis to fail. Additionally, a POSA would have also been concerned that the lower solubility of acetyl groups as compared to isobutyryl groups would have derailed the subsequent synthetic transformations and purifications (steps iv. – x.) of Example 4-d. Ex. 1017, 25:32-28:19.

Ex. 2008, ¶¶159-160

In my opinion, as a general matter, a POSA would have no reason to expect that removing 2 carbon atoms from a large nucleoside monomer (going from isobutyryl to acetyl) would have a solubility effect so profound that it would prevent the molecule from reacting in subsequent chemistry.

Ex. 1033, ¶74

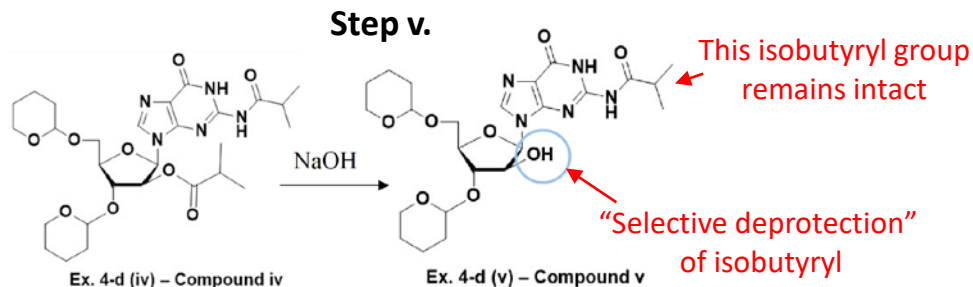
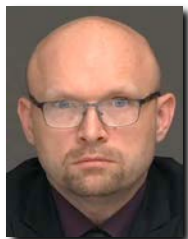
Baran ignores that compound 4-d (iii) has **two** isobutyryl groups and therefore switching to acetyl groups would remove **four**, not two carbon atoms, and thus reduce solubility twice as significantly as Baran argues, which would have had a significant impact on its solubility.

And indeed, Chemgenes' speculation is refuted by literature reporting using acetyl protected nucleosides, including Pitsch, Donga, and Reddy, none of which mention solubility-induced reactivity challenges.

Pet. Reply at 19

Hongene ignores that the subject compounds in Pitsch, Donga and Reddy have large hydrophobic 2'-protecting groups and not the more polar 2'-fluoro-deoxyguanosine compounds at bar or OH- group in Compound iii.

Example 4-d: Adding Acetic Anhydride in Step ii Would Have Resulted in Failure



Pitsch used

sodium hydroxide at the analogous step in its synthesis and obtained a 77% yield, and did not report any problems associated with its use of sodium hydroxide. (Ex. 1018 at 3787.) This alone refutes Chemgenes’ assertion and demonstrates that a POSA would have had a reasonable expectation of success

Ex. 1033, ¶175

164. A POSA would have expected that, had two acetyl groups been present on Compound iv, (as per Petitioner’s and Dr. Baran’s theory), instead of the two isobutyryl groups, and the scheme had not already failed in prior steps (which, as discussed above, a POSA would have expected it would have), the use of sodium hydroxide to remove the O2'-acetyl group in step v. of Example 4-d would have caused concomitant removal of the N2-acetyl group given the basic/nucleophilic conditions disclosed, which include an over 10-fold molar excess of sodium hydroxide (NaOH) relative to the reactant nucleoside. Ex. 2020, 252, 279 (“the N-isobutyryl group showed, as might have been expected, considerably higher stability than the N-acetyl group” when deprotected “in a mixture of pyridine (0.4 ml.) and water (0.6 ml.) at 4°C [and] Sodium hydroxide (1 ml. of 2 M), which had been cooled to 4°C [and] added with vigorous agitation.”).

Ex. 2008, ¶164

Pitsch teaches totally different molecules and 2'-substituents. Per Hrdlicka, POSAs would have expected TBAF to cause **both** acetyl groups to cleave rather than a single acetyl under Example 4-d’s “selective deprotection” protocol. Hongene fails to show how such selective deprotection would have occurred under its theory.

Hongene or Baran could have conducted tests to prove Baran’s theory that the claimed molecule could have been synthesized by “simply” substituting acetic anhydride in Step ii. of Example 4-d, but at least Baran did not do so.



Hongene's Sivets Arguments are Illogical and Baseless

Baran Opening Dec.

123. As another example, a POSA could have also synthesized the molecule claimed in Claim 2 of the '885 Patent (where "B" is guanine-N-acetyl and "Z" is ribo Fluoro) by starting with 2'-fluoro-2'-deoxyguanosine, either acquired from a commercial source or synthesized according to Sivets (2007) (Exh. 1028).²¹ (Exh. 1028 at 1821 (compound 17).) A POSA would have reasonably expected that 2'-fluoro-2'-deoxyguanosine would react similarly to a "regular" 2'-deoxyguanosine (i.e., one with a 2'-H instead of the 2'-F substitution) in connection with the preparation of reagents for SPOS, and thus would have had a reasonable expectation of successfully installing protecting groups onto a 2'-fluoro-2'-deoxyguanosine pursuant to known methods in the art as outlined below. Ex. 1003, ¶123

Baran Reply Dec.

As noted above, a POSA would not expect that the presence of fluorine at the 2' position would have any significant impact on the ability to acetylate the exocyclic amine of the nucleobase. This is supported by Zhu (2003), for example, where multiple different nucleosides were benzoylated at the exocyclic amine of the nucleobase with differing 2'-substituents.

Ex. 1033, ¶81

Evidence of
commercial
source
not provided

Contradicted by
"RNA-like"
theory *supra*

Reliance on Zhu
erroneous
See supra

Hrdlicka

167. In my opinion, Dr. Baran's conclusory statement is not supported by any evidence (e.g., a product or catalogue disclosure) that shows 2'-fluoro-2'-deoxyguanosine was commercially available at the time of invention.

The statements in the Petition rely solely on the conclusory testimony of Dr. Baran and no references, data, or experimental evidence for the proposition that these completely different molecules "would react similarly" are provided. *Id.*

170. When asked about the basis for this testimony during his deposition, Dr. Baran testified that his testimony is based on "[t]ons of experience in the area and doing this chemistry through supervision and seeing it over the years" along with "literature" that he failed to identify in his declaration or during his deposition. Ex. 2009, 167:9-12. This testimony does not appear to be supported by facts or data. benzoyl chloride did cause N-benzoylation as clearly shown") Furthermore, in my opinion, and contrary to these unsupported arguments, a POSA would have also known, at the very least, that the different 2'-substituents of 2'-fluoro-2'-deoxyguanosine and 'regular' 2'-deoxyguanosine (i.e., 2'-F vs. 2'-H) would have had markedly different electronegativities, and would have expected those differences to have had a significant effect on the conformations of the resulting nucleosides and thus their reactivities. Ex. 2016, 1421 (stating "[n]ucleoside conformation[s] are determined by the electronegativity of the sugar substituent...").



Hongene's Sivets Arguments Are Meritless and Illogical



Baran Opening Dec.

124. For example, Pitsch (2001) teaches the installation of an acetyl protecting group on the exocyclic amine of the guanosine. (Exh. 1018 at 3775; Scheme 1, step “c”), molecule 3.) Pitsch (2001) also teaches the installation of a DMT protecting group on the 5'-oxygen of the sugar ring. (*Id.*; Scheme 1, step “d”), molecule 6.²²) In Pitsch #2 (2001) (Exh. 1021),²³ Support Protocol 2 further discloses a step-by-step recipe for preparing N²-acetyl-5'-O-(4,4'-dimethoxytrityl) guanosine. (Exh. 1021, 2.9.8-2.9.10.)

Ex. 1003, ¶124

Baran Reply Dec.

A POSA would have expected the installation of protecting groups on of 2'-deoxy and 2'-fluoro-2'-deoxy monomers to be easier than protection of the more complicated monomers protected in Pitsch, Pitsch #2, and the '031 Patent, because, as I explained my opening declaration, the former do not have a reactive oxygen-bound substituent at the 2' position. Contradicted by “chemically distant” theory See *supra*

Ex. 1033, ¶43

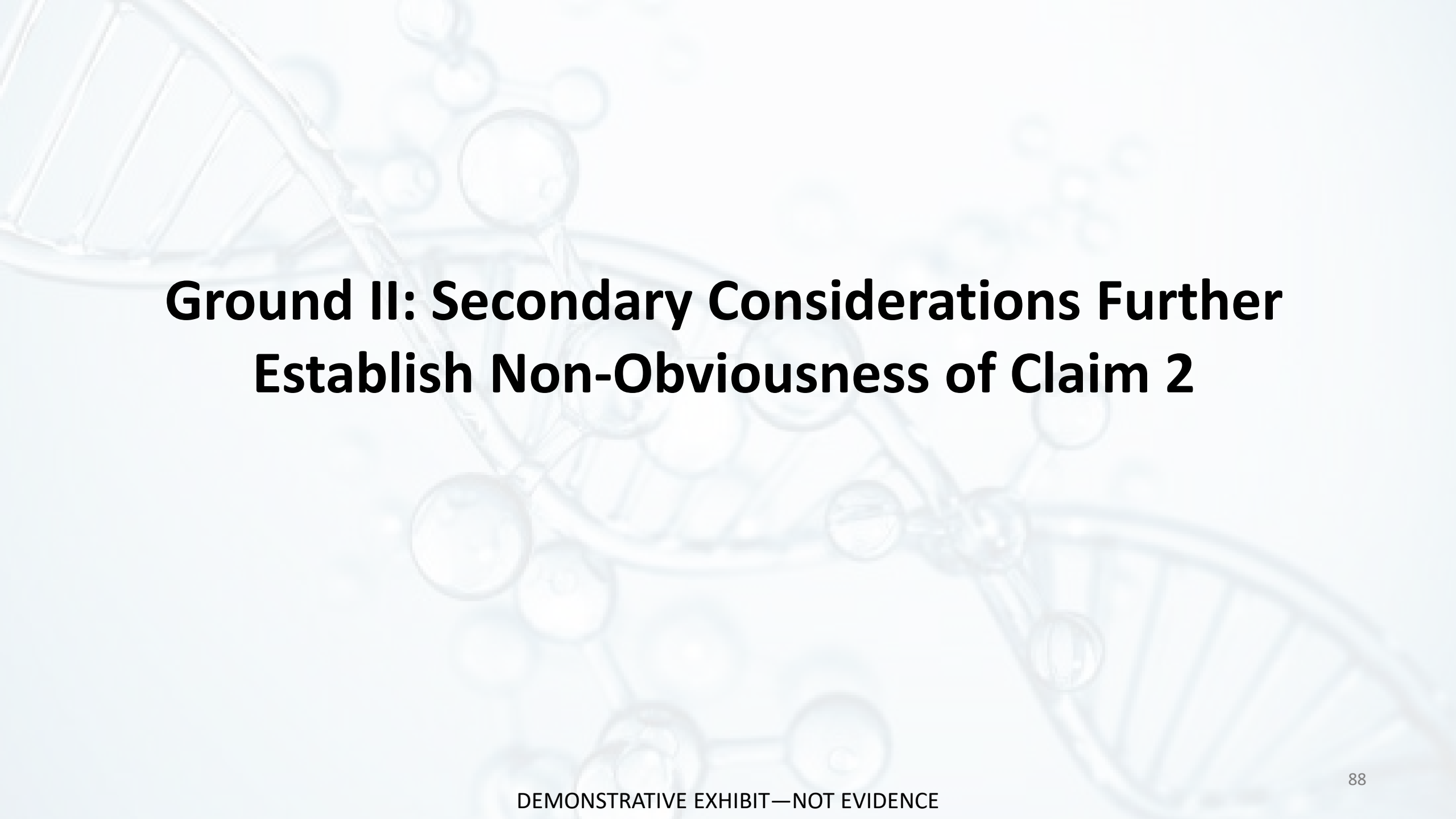


Hrdlicka

172. The rest of the statements in the Petition in Section VI.B.4. are illogical in my opinion. A POSA would have understood that neither Pitsch (Scheme 1, step “c”) molecule 3; step “d”), molecule 6); and Step “f”); Pitsch #2 (2001) (Support Protocol 2); nor the '031 Patent (Example 4-d, Step “x”) (Figure 3) teach the installation of protecting groups on “regular” 2'-deoxyguanosine. Pet., 38. Accordingly, in my opinion, it does not make sense to cite to those protocols as being useful for the synthesis of “regular” 2'-deoxyguanosine (or, for that matter, 2'-fluoro-2'-deoxyguanosine).

173. In is my further opinion that Petitioner's and Dr. Baran's reliance on Pitsch, Scheme 1, step “c”) is misplaced since Pitsch teaches installing acetyl on a completely different molecule than 2'-fluoro-2'-deoxyguanosine which is not instructive to synthesizing 2'-fluoro-2'-deoxyguanosine, and its teachings would therefore not have provided a POSA with a reasonable expectation of success in synthesizing the claimed compound.

Ex. 2008, ¶¶172-173



Ground II: Secondary Considerations Further Establish Non-Obviousness of Claim 2

Patent Statements Explicitly Report Degradation Problem Experienced by Industry

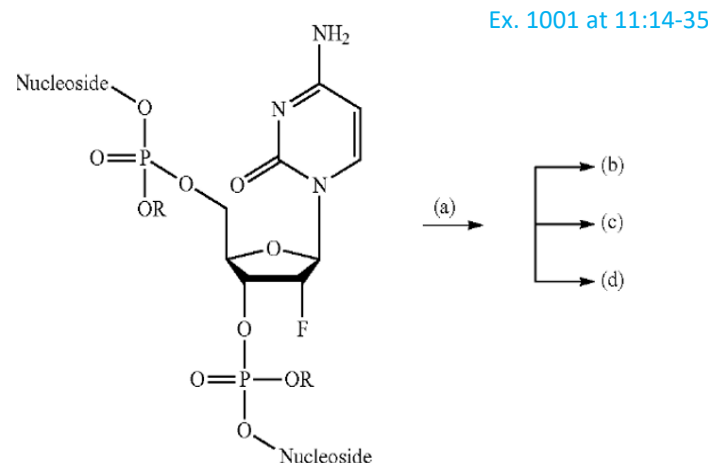
The utility of N-FMOC protected nucleoside was discovered by the present inventors and it was shown to possess additional significance and importance. When oligo ribonucleotide chimeras comprise of mixed bases composed of 2'-fluoro and 2'-ribo bases they present a challenge in obtaining pure chimera oligonucleotides. It has been well documented by several recent reports that oligonucleotide chimeras having 2'-fluoro-2'-deoxy bases along with natural ribo bases present difficulty in obtaining pure oligos. It has been shown that with strongly basic conditions, there is significant loss of fluorine as loss of Hydrogen Fluoride ("HF") is seen as M-20 peak in Mass spectral analysis. Besides it has also been shown that uracil and cytosine are eliminated to a significant extent, when oligo chimeras containing 2'-fluoro-2'-deoxy uridine and 2'-fluoro-2'-deoxy cytidine are part of chimeras (see scheme 3).

The studies as shown in scheme 3 were carried out independently by two groups recently. Ken Hill, Agilent Technologies, Boulder, Colorado; Identification of Process Related Impurities—Understanding Oligonucleotide Production, TIDES 2007, Las Vegas, Nev. The author showed depyrimidation of chimera oligonucleotides carrying 2'-fluoro-2'-deoxy pyrimidine in RNA's; and,

Nanda D. Sinha, Avecia Biotechnologies Inc., Massachusetts—Depyrimidation, as well as loss of HF and chain cleavage in chimeras having 2'-fluoro-2'-deoxy pyrimidines in RNA sequences. Eurotides, 2005, Munich, Germany.

Ex. 1001 at 10:63-11:47

Scheme 3. Graphic Representation of effect on quality of oligonucleotides containing 2'-fluoro nucleosides: (a) deprotection using methyl amine, the usual deprotection condition of protecting groups of bases, (b) loss of fluorine leading to loss of HF, generating significant amount of M-20, (c) loss of cytosine and uracil, the pyrimidine bases is observed quite frequently, d) with the loss of pyrimidine, subsequent cleavage of chain occurs.



Ex. 1001, 11:36-47. These observations are corroborated by publications, including from one of the cited authors, Nanda D. Sinha. Ex. 2024, 83 (book chapter by Nanda D. Sinha et. al. stating that the 2'-fluoro-2'-deoxyribonucleotide of chimeric oligonucleotides "is subject to depyrimidation [] especially with methylamine or ammonia/methylamine deprotection...").

Ex. 2008, ¶187

Patent Statements

- Show **degradation problem existed** at time of application
- Were made at the time of the patent application
- Were submitted **under oath**
- Were **not** made in view of litigation
- Were not "self-serving"
- Were **corroborated** by literature



The Novel N2-acetyl-2'-fluoro-2'-deoxyguanosine Compound Demonstrated Unexpected Results as Compared to Compound x

Hongene ignores Kawasaki arguments

188. It is my further opinion that, in addressing this longstanding industry need, the applicants of the '885 Patent reported the following unexpected results:

Our data shows that by utilizing n-acetyl-guanine protected ribonucleoside phosphoramidites, used in oligo with 2'-fluoro substitution, high quality full length RNA were obtained.

It is therefore imperative to utilize 2'-fluoro-2'-deoxy nucleosides and corresponding phosphoramidites with guanine protecting groups having N-2 acetyl guanine for mild and shorter base deprotection protocol.

Ex. 1001, 11:48-55 (emphasis added). The compounds referenced in this passage— i.e. “2'-fluoro-2'-deoxy nucleosides and corresponding phosphoramidites with guanine protecting groups having N-2 acetyl” — cover the exact N2-Acetyl-2'-F-2'-deoxyG phosphoramidite that Petitioner has challenged.

Ex. 2008, ¶188

189. In my opinion, the cited results were unexpected as compared to the properties of what Petitioner and Dr. Baran have alleged is the closest prior art— Compound x from the '031 Patent. Based on the disclosures in the '885 Patent and other literature (e.g., Exs., 2024 and 2025) referencing oligoribonucleotide chimeras comprised of mixed 2'-fluoro and 2'-ribo bases presenting serious challenges in obtaining pure chimeric oligoribonucleotides, a POSA would have expected that using Compound x would have caused similar purity problems under usual oligonucleotide deprotection conditions. *Id.*

190. In my opinion, this is supported by at least Kawasaki, which observes “significant degradation” of the 2'-deoxy-2'-fluorpyrimidine nucleosides” while under “the usual oligonucleotide deprotection conditions (concentrated NH₄OH, 55°C).” Ex. 2025, 833. Kawasaki shows (in Scheme II) significant overlap with the synthesis schemes of Example 4-d of the '031 Patent and both publications identified as originating from the same company (Isis Pharmaceuticals, Inc.). Ex. 1017, Cover; Ex. 2025, 831.

Ex. 2008, ¶¶189-190

Hongene Ignores ChemGenes' Unexpected Results Arguments Based on Kawasaki

Hongene ignores Kawasaki arguments

191. While Compound x is not shown as synthesized in Kawasaki, its precursors are, and the Compound x structure—"N2-Isobutyryl-2'-deoxy-2'-fluoro-5'-O-(4,4'-dimethoxytrityl)guanosine 3'-[β-Cyanoethyl N,N-diisopropylphosphoramidite]"—is described in the experimental protocols. Ex. 2025, 839. It therefore appears the work disclosed in Kawasaki and the '031 Patent may be related and, in any event, address the same structures including Compound x.

192. Kawasaki also states the authors used methanolic ammonia instead of NH₄OH, but did not modify the N2-protecting group, to address the degradation problem. Ex. 2025, 833. Given that this publication was dated in 1993, the overall degradation problem persisted in the industry for at least over 15 years before the filing of the application that led to the issuance of the '885 Patent.

Ex. 2008, ¶¶191-192

193. Accordingly, the results obtained by the applicants by utilizing N2-acetyl on 2'-fluoro-2'-deoxyguanosine to address this problem using methylamine for deprotection were surprising and unexpected as compared to the prior art which did not disclose using the novel N2-Acetyl-2'-F-2'-deoxyG compound claimed by the '885 Patent to address the longstanding industry need. Ex. 1001, 11:15-17.

Ex. 2008, ¶193

Kawasaki

N²-Isobutyryl-2'-deoxy-2'-fluoro-5'-O-(4,4'-dimethoxytrityl)guanosine. The reaction conditions utilized were similar to those used for the synthesis of 6. Thus compound 16 (0.92 g, 2.60 mmol) was reacted to yield a crude product which was purified by column chromatography using EtOAc-NEt₃ (99:1), followed by EtOAc-MeOH-NEt₃ (94:5:1) to give the title compound as a foam (1.49 g, 87%). ¹H NMR (200 MHz, Me₂SO-*d*₆): δ 12.11 (br s, 1, NH), 11.61 (br s, 1, NH), 8.12 (s, 1, H8), 7.4–6.7 (m, 13, H-Ar), 6.20 (d, 1, H1', *J*_{1',F} = 18.3 Hz), 5.65 (d, 1, 3'-OH), 5.42 (dd, 1, H2', *J*_{2',F} = 52.3 Hz), 4.59 (m, 1, H3'), 4.11 (m, 1, H4'), 3.71 (s, 6, OCH₃), 2.76 (m, 1, HCMe₂), 1.10 (d, 6, CH₃). FAB-MS: 658 [M + H]⁺.

Under the usual oligonucleotide deprotection conditions (concentrated NH₄OH, 55 °C), we in fact observed significant degradation of the 2'-deoxy-2'-fluoropyrimidine nucleosides while the nucleosides were stable to methanolic ammonia at room temperature.

Ex. 2025 at 833, 839 91

Unexpected Results in View of Sinha



Hrdlicka

194. Moreover, POSAs routinely used methylamine to remove protecting groups from guanosine, but Sinha observed problems using methylamine, further demonstrating that the results using N2-Acetyl-2'-F-2'-deoxyG were unexpected. Ex. 2024, 83 (book chapter by Nanda D. Sinha et. al. stating that the 2'-F modification of chimeric oligonucleotides “is subject to depyrimidation [] especially with methylamine or ammonia/methylamine deprotection...”); Ex. 1001, 22:63-23:1 (using methylamine); Ex. 1018, 3778 (using methylamine); Ex. 1019, 2556 (using methylamine).

Ex. 2008, ¶194

Sinha

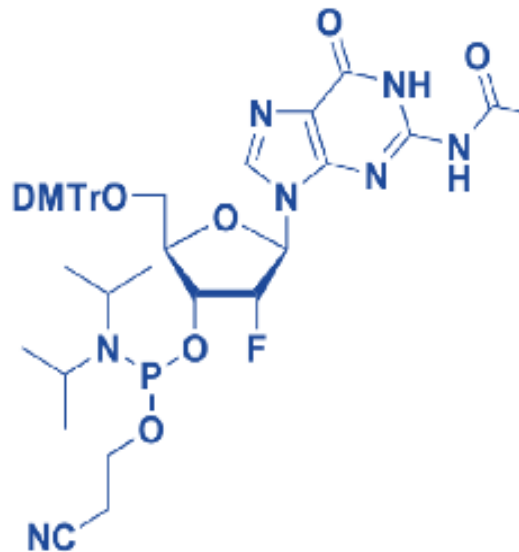
However, the lability of the 2'-F modification must be taken into consideration when working with mixed sequences consisting of RNA and 2'-F RNA. The 2'-F modification is subject to depyrimidation (especially with methylamine or ammonia/methylamine deprotection) and elimination and hydrolysis as shown in Figures 2.41 and 2.42 respectively.

Ex. 2024 at 83

Nexus Between Evidence and N2-acetyl-2'-fluoro-2'-deoxyguanosine

[6] [7] [8] In order to accord substantial weight to secondary considerations in an obviousness analysis, “the evidence of secondary considerations must have a ‘nexus’ to the claims, *i.e.*, there must be ‘a legally and factually sufficient connection’ between the evidence and the patented invention.” *Henny Penny Corp. v. Frymaster LLC*, 938 F.3d

Challenged
Claim 2 Compound

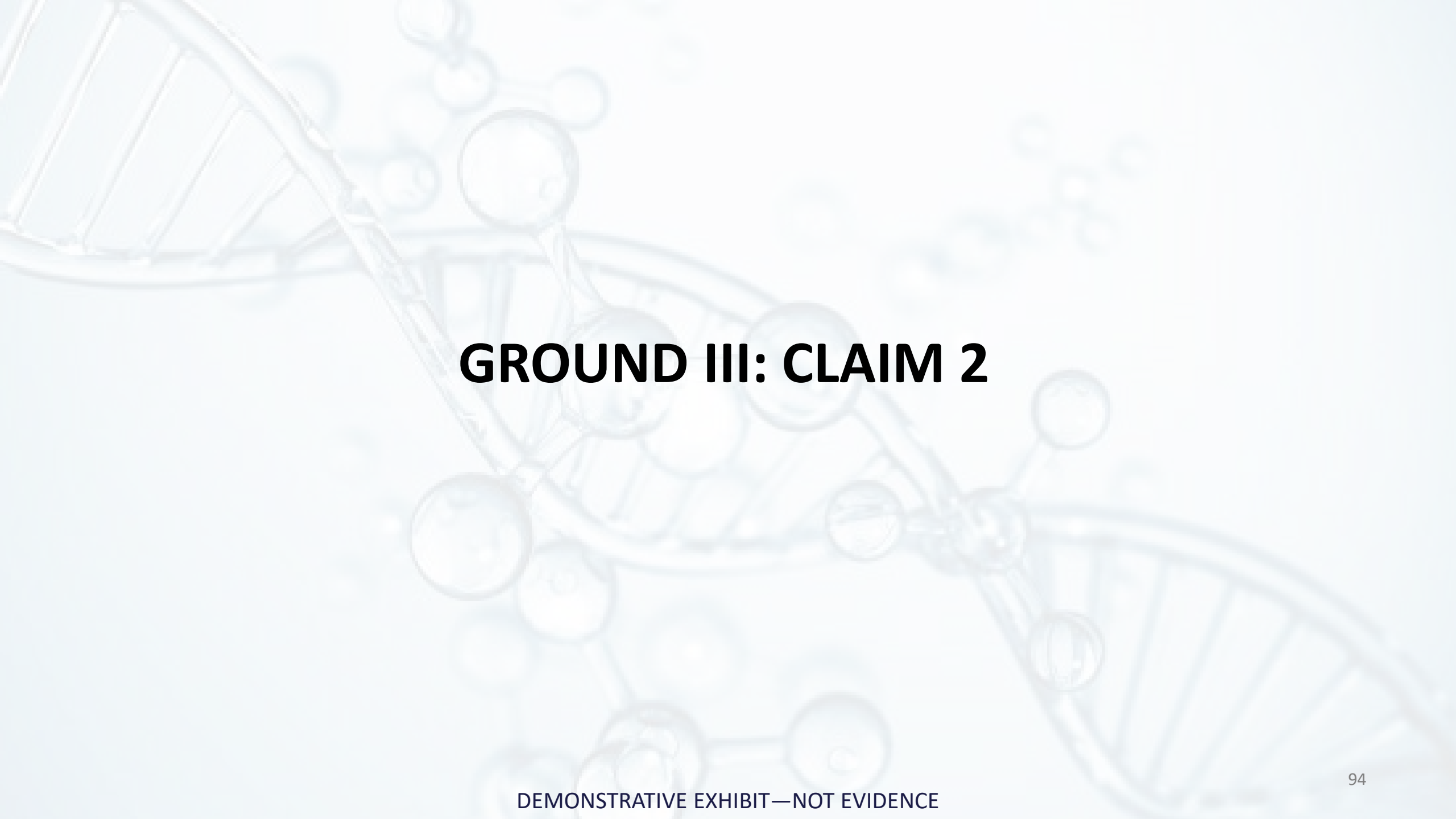


[12] A finding that a presumption of nexus is inappropriate does not end the inquiry into secondary considerations. See *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996). To the contrary, the patent owner is still afforded an opportunity to prove nexus *1374 by showing that the evidence of secondary considerations is the “direct result of the unique characteristics of the claimed invention.” *Id.*

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1373-74 (Fed. Cir. 2019).

N2-acetyl-2'-fluoro-2'-deoxyguanosine is the same compound:

- That is **challenged**
- That is **claimed**
- That **demonstrated unexpected results**
- That **satisfied a longstanding need**



GROUND III: CLAIM 2

Hongene and Baran Disregarded LCA

Hongene Reply

As explained above (Section VI), the “lead compound” analysis is not appropriate here, ...

[Pet. Reply at 28](#)



Q Okay. So is it your testimony that your opinion is that the lead compound framework does not apply to this case?

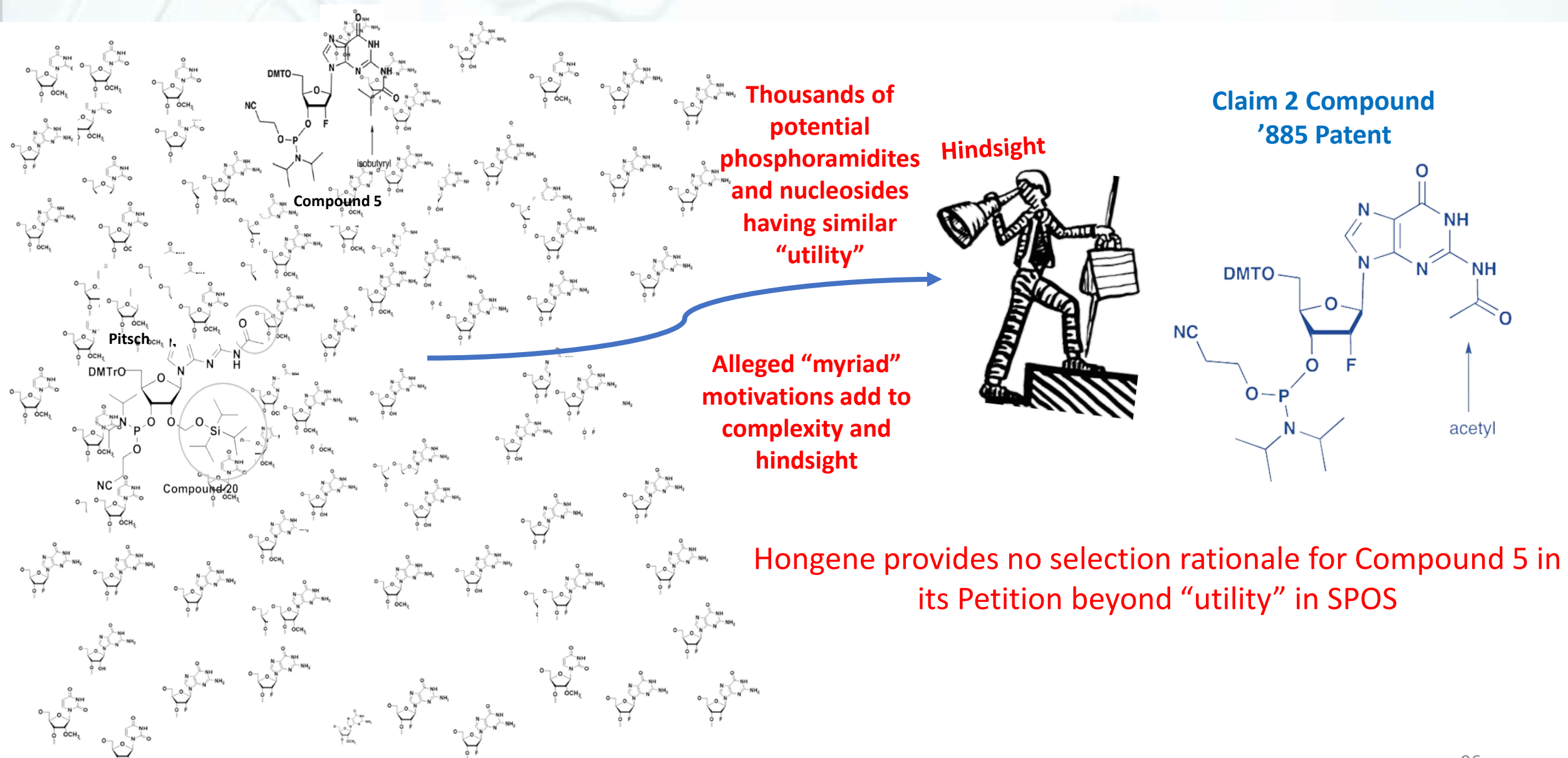
A Correct.

Q Okay. And, therefore, you did not apply it to this case?

A Correct.

[Ex. 2035 at 95:14-20](#)

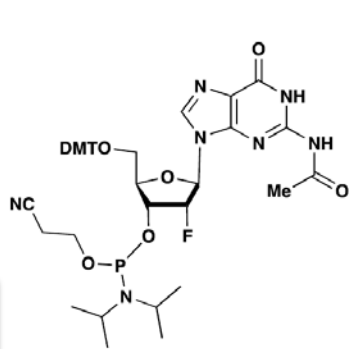
Selection of Compound 5 Was Hindsight-Driven



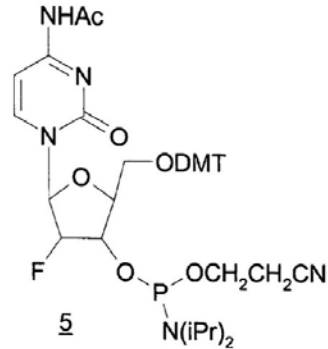
Compound 5 Not “Almost Identical” to Claimed Compound and Would Not Have Motivated a POSA

Petition

2. The '991 Patent Discloses an **Almost Identical** Molecule (where “B” is cytosine-N-acetyl)



The '885 Patent, Claim 2



The '991 Patent, Fig. 16 (#5)

Pet. at 39-40

Reply

Chemgenes' incorrectly suggests that the structural differences between Compound 5 and Claim 2 demonstrates non-obviousness of Claim 2. (POR61-64.)

But the two are closely structurally related. (Ex. 1033¶100.) Both are phosphoramidite building blocks for SPOS that are identical except for the nucleobase they carry and their stereochemistry. Motivation to create homologs can be provided by structural relationships. *In re Deuel*, 51 F.3d 1552, 1558 (Fed. Cir. 1995). Thus, POSAs encountering the cytosine phosphoramidite (Compound

Pet. Reply at 24

Baran does not refer to Compounds 5 and Claimed Compound as “homologs” because they are not homologs

Sur-Reply & Hrdlicka Decl.

⁴ See, e.g., *Brenner v. Manson*, 383 U.S. 519, 522, fn. 3 (1966) (explaining homologs are “related compounds” that “var[y] from member to member by CH(2) (one atom of carbon and two atoms of hydrogen).”

212. The statements in the Petition that Pitsch would have motivated a POSA to make the N2-Acetyl-2'-F-2'-deoxyG compound claimed in Claim 2 are also without merit for at least the reasons set forth above, including that the prior art taught away from using acetyl groups to protect 2'-deoxyguanosine. Ex. 2011, 221.

Sur-Reply at 26 n.4; Ex. 2008, ¶212 97

Q. Would you say that they're substantially identical?

A. I wouldn't use any of that language. would say they're both just 2-fluoro nucleoside derivatives.

Ex. 2009 at 170:21-25

POR at 61-65; Sur-Reply at 26



certainly not “almost identical.”

Ex. 2008, ¶198

DEMONSTRATIVE EXHIBIT—NOT EVIDENCE

Compound 5 is an L-, not D-, Configured Nucleoside and the '991 Patent Would Not Have Motivated a POSA

Baran admits Compound 5 is L- not D- configured

199. Further, a POSA would have also recognized that **Compound 5 is an L-configured nucleoside**, as Dr. Baran admits. Ex. 2008, ¶199

Q. Could you read that into the record?

A. "Figure 16 shows the illustration of 2 prime-fluoro-L-cytidine phosphoramidite based on 2 prime-fluoro-L-uridine."

Q. Right. So does that clarify for you that figure 16 shows L configured cytosine?

A. Yes. Ex. 2009 at 180:14-16

Reply: omits sentence from '991 Patent

"The nucleic acids according to the present invention can either be D nucleic acids or L nucleic acids."

Pet. Reply at 26

The nucleic acids according to the present invention can either be D nucleic acids or L nucleic acids. **The nucleic acids are preferably L nucleic acids.** It is also possible that one or

Ex. 1020 at 11:33-34

'991 Patent teaches preference for nucleosides with pyrimidine not purine bases like guanine

A particularly advantageous modification in connection with the present invention constitutes configuring the inventive nucleic acid(s), in which at least one, preferably more and **most preferably all pyrimidine nucleotides forming the nucleic acid have a 2'-fluoro group at the 2' position of the ribose section of each nucleotide.** Other modifications represent for example those with PEG. Ex. 1020 at 12:33-40

'991 Patent teaches **instability** of D-nucleosides

The L nucleic acids are enantiomers of the naturally occurring nucleic acids. The **D nucleic acids however are not very stable in aqueous solutions** and in particular in biological systems or biological samples as a result of the broad distribution of nucleases. Naturally occurring nucleases, in par-

Ex. 1020 at 12:33-40

The invention claimed is: **'991 Patent claims L-nucleosides**

1. An antagonist of CGRP, wherein the antagonist is an **L-nucleic acid** which binds to CGRP with a K_D of less than 100 nM, wherein said L-nucleic acid comprises SEQ ID NO:246 or an L-nucleic acid at least 85% homologous thereto. Ex. 1020 at 12:33-38

Therefore, a POSA reading the '991 Patent would have been discouraged from pursuing D- over L-configured nucleic acids.

Ex. 2008, ¶1214

Baran's Testimony Regarding Motivation Based on Compound 5 and Pitsch is Conclusory and Lacks Support



Baran

128. As discussed above, since the advent of phosphoramidite chemistry in oligonucleotide synthesis, a POSA would have recognized that the purpose of a phosphoramidite compound was to serve as a **building block** for incorporating the corresponding nucleobase into a growing oligonucleotide chain through automated SPOS. A POSA would also have known that the synthesis of most oligonucleotides would have required the incorporation of all four canonical nucleobases (A, C, G, T or U). **Thus, the 2'-fluoro-L-cytidine phosphoramidite disclosed in Fig. 16 (#5) of the '991 Patent would have motivated a POSA to build the structurally analogous 2'-fluoro-guanosine phosphoramidite claimed in Claim 2 of the '885 Patent,** especially in view of Pitsch (2001), which (as discussed above) informed a POSA about the advantages of using an acetyl protecting group to protect the exocyclic NH₂ group of the guanine nucleobase.

Ex. 1003, ¶128



Hrdlicka

211. The statements in the Petition are illogical and Petitioner provides no support, **other than Dr. Baran's identical conclusory statements** set forth in his declaration, for why Compound 5, a totally different L-configured compound with a cytosine base, would have motivated a POSA to build the **structurally non-analogous** D-configured N2-Acetyl-2'-F-2'-deoxyG claimed in Claim 2.

212. The statements in the Petition that Pitsch would have motivated a POSA to make the N2-Acetyl-2'-F-2'-deoxyG compound claimed in Claim 2 are also without merit for at least the reasons set forth above, including that the prior art taught away from using acetyl groups to protect 2'-deoxyguanosine. Ex. 2011, 221.

Ex. 2008, ¶¶211-212

Reasonable Expectation of Success Not Shown

B. Hongene Fails to Carry its Burden to Show Reasonable Expectation of Success

Hongene relies on the same reasonable expectation of success arguments it made for Ground II (Reply, 26), which are without merit for at least the reasons ChemGenes provided for Ground II and Claim 2.

216. Petitioner relies solely on “Section VI.B.4” of its Petition to show a POSA would have had a reasonable expectation of success in synthesizing the molecule claimed in Claim 2 based on the ’991 Patent or Compound 5. Pet., 41. But, in my opinion, neither Section VI.B.4 of the Petition, nor anywhere else in the Petition or Dr. Baran’s Declaration, do Petitioner or Dr. Baran discuss or address reasonable expectation of success based on the ’991 Patent or Compound 5.

217. Accordingly, in my opinion, Petitioner and Dr. Baran fail to provide any evidence or reasoning for reasonable expectation of success based on the ’991 Patent or Compound 5 – a completely different molecule from Compound x from the ’031 Patent and the molecules disclosed in Pitsch, Fan, Sivets (2007), Pitsch #2 (2001), and McBride (1983).

218. It is also my opinion, of course, that Petitioner’s arguments also fail for at least the reasons stated in Sections I.X.B.]herein for Ground II.

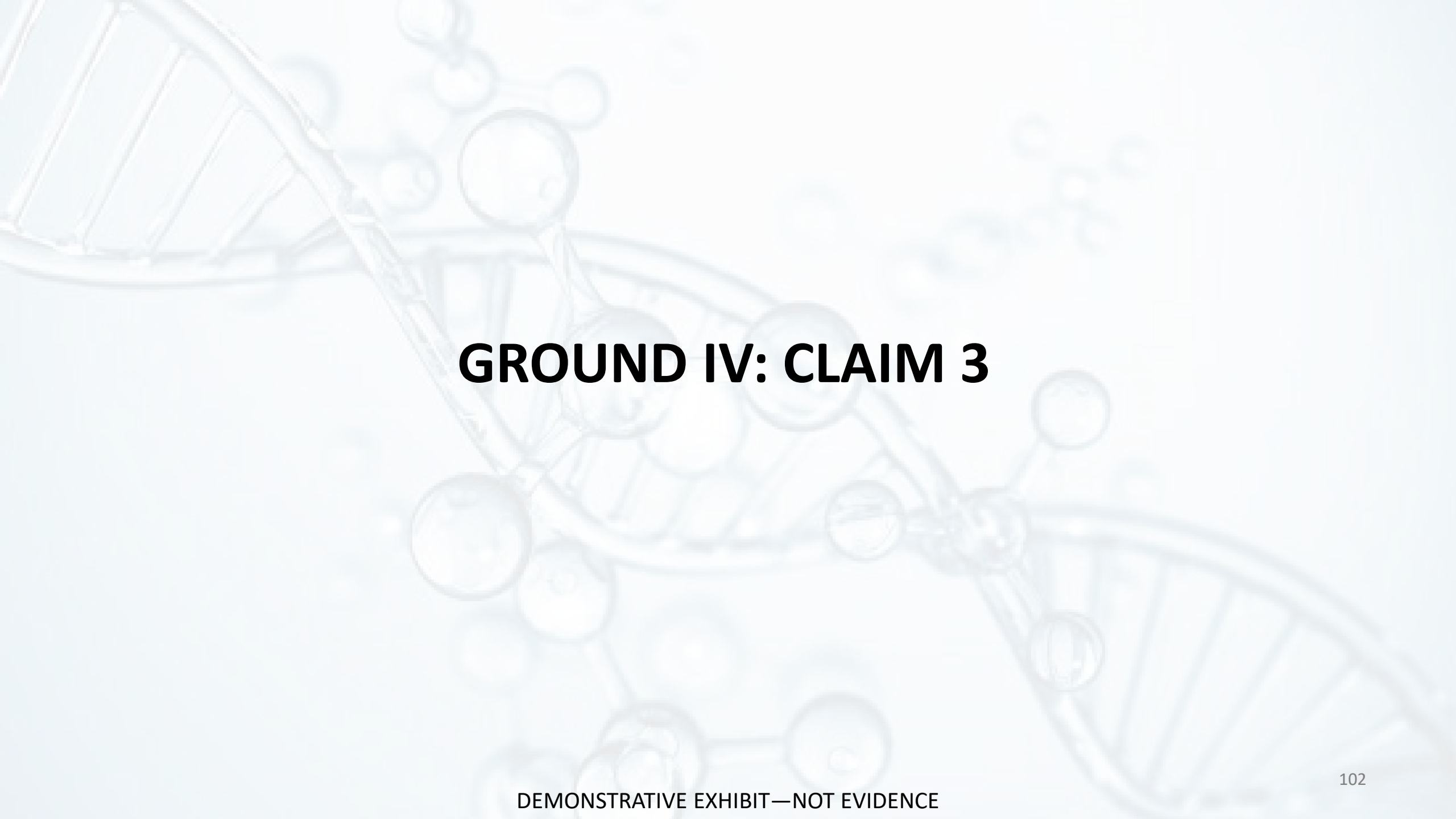


Ex. 2008, ¶¶216-218

Secondary Considerations Further Establish Patentability of Claim 2

C. Secondary Considerations Further Establish Patentability of Claim 2

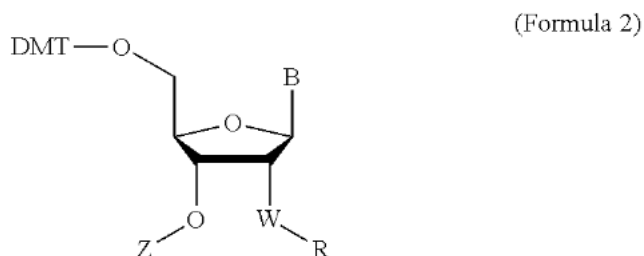
Hongene relies on the same arguments it made for Ground II (Reply, 26), which are without merit for at least the reasons ChemGenes provided for Ground II and Claim 2.



GROUND IV: CLAIM 3

Proposed Claim Construction

3. Derivatized nucleosides, succinates and solid supports of general formula 2,



where B is Guanine-N-acetyl, or adenine-N-acetyl;

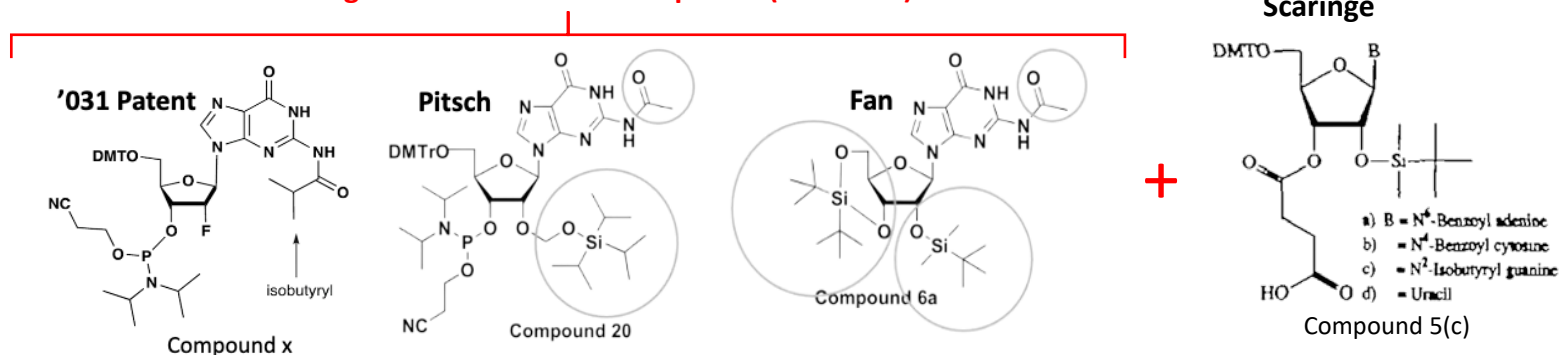
W=ribo fluoro or ara fluoro, and R is absent;

Z is C(O)-M-C(O)—NH, where M is selected from the group consisting of ~~succinyl~~ ethyl, oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethoxyglycol, and a combination of alkyl and ethyleneglycoxy.

- Hongene proposed this construction and ChemGenes agrees with it
- Should the Panel not construe **Claim 3** in this manner, then **Ground IV** necessarily fails because all of the limitations in **Claim 3** are not taught by the prior art under this interpretation. Hongene did not dispute this in its Reply.

Claim 3 Not Obvious For at Least the Reasons Provided for Claim 2

Same arguments for Claim 2 compound (Ground II)

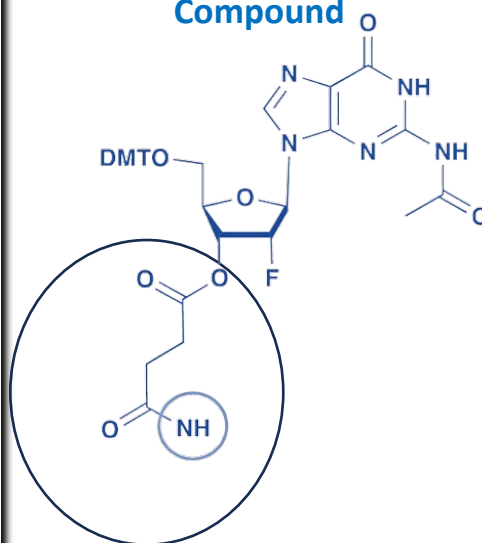


Petition

As discussed above in Section VI.B, (a) the guanosine phosphoramidite made in Example 4-d in the '031 Patent has an isobutyryl protecting group at the exocyclic NH₂ group of the guanine base of that molecule; (b) a POSA would have been motivated by the respective teachings of Pitsch (2001) and Fan (2004) to make and use a similar guanosine phosphoramidite, but with an acetyl instead of an isobutyryl protecting group; and (c) a POSA would have had a reasonable expectation of successfully doing so. This would have resulted in the derivatized nucleoside and phosphoramidite claimed in Claim 2 of the '885 Patent where "B" is guanine-N-acetyl and "Z" is ribo fluoro. (Exh. 1003, ¶ 141.)

The corresponding succinate in Claim 3 (where "B" is guanine-N-acetyl and "Z" is ribo fluoro) would likewise have been obvious. Pet. at 45

Claim 3
Compound



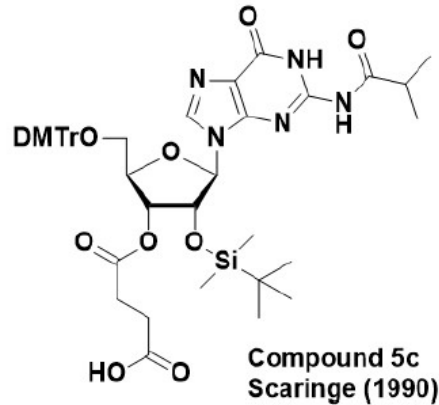
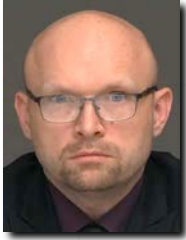
Claim 3 Arguments:
Add succinyl, solid support, and
spacer groups to 3'-position of
Claim 2 compound

Response

Petitioner's argument is therefore without merit for at least the reasons set forth in Section VI.B. (Ground II) above relating to Claim 2, i.e., (a) Petitioner fails to provide a rationale as to why a POSA would have chosen Compound x as a lead compound; (b) neither Pitsch nor Fan would have motivated a POSA to modify Compound x to make the compounds claimed in Claim 2; (c) a POSA would not have had a reasonable expectation of success in synthesizing the compounds claimed in Claim 2; and (d) secondary indicia of non-obviousness further establish that Claim 2 is not unpatentable. Ex. 2008, ¶ 224. Accordingly, because Petitioner fails to establish *prima facie* obviousness for Claim 2, Petitioner also fails to establish a *prima facie* obviousness for Claim 3 (Ground IV).

POR at 69

Scaringe Would Not Have Motivated a POSA to Synthesize the Compound of Claim 3



226. As shown above, Scaringe does not disclose 2'-F groups and instead uses an O2'-TBDMS group and only teaches using an isobutyryl group to protect the N2-position of the above guanine nucleobase, does not teach using an acetyl group, and does not disclose deprotection rates. *See, e.g.*, Ex. 1022, 5434.

- Scaringe does not disclose 2'-F groups (O2'-TBDMS only)
- Scaringe does not teach acetyl groups on N2 position of Guanosine nucleobase (isobutyryl only)
- Scaringe does not disclose deprotection rates

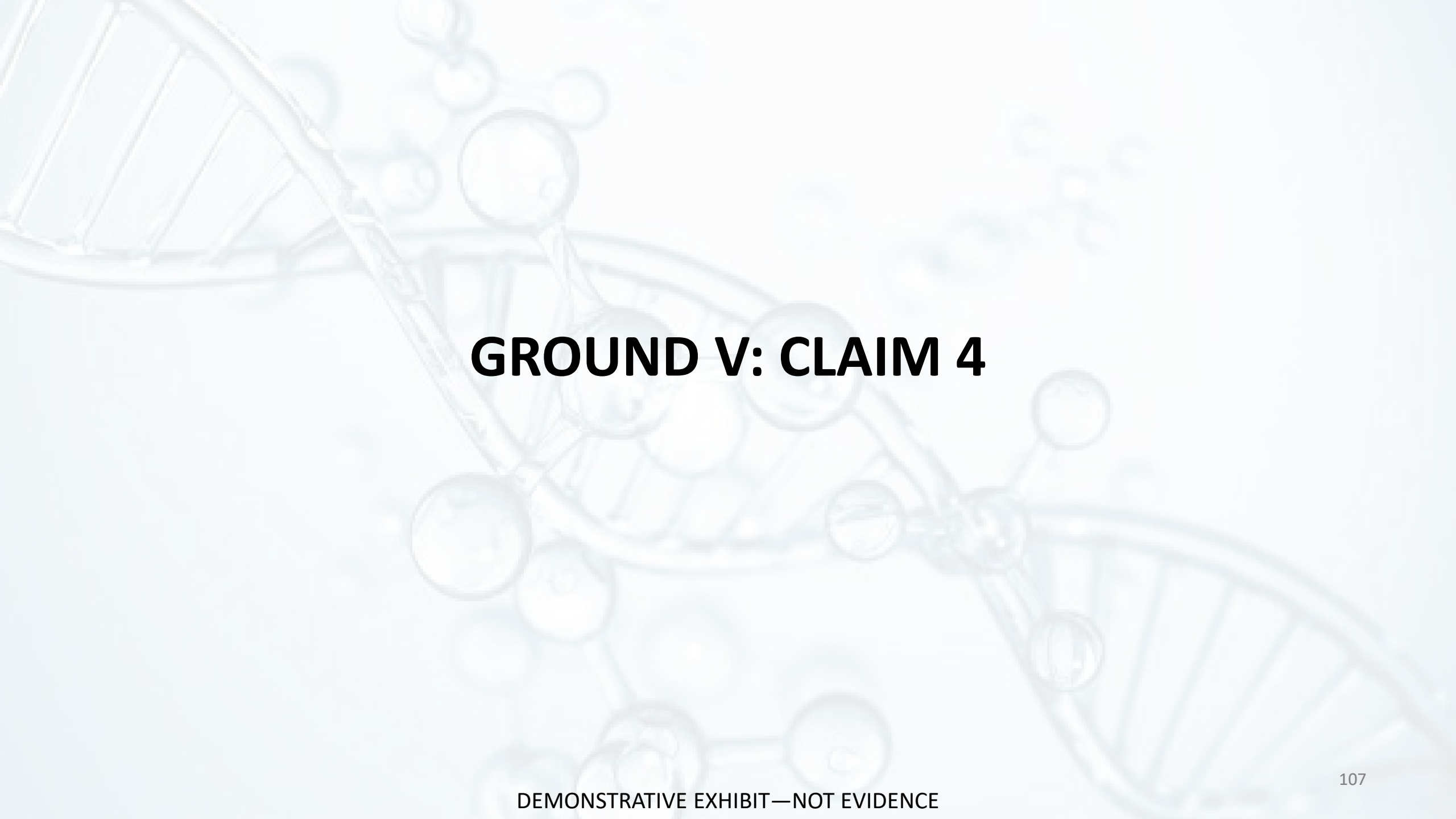
Ex. 2008, ¶1226

Hongene Failed to Establish Reasonable Expectation of Success for Claim 3



224. In my opinion, Petitioner's arguments for this ground fail for at least the reasons set forth in Section[I.X.B.](Ground II) above relating to Claim 2, i.e., (a) Petitioner and Dr. Baran fail to provide a rationale as to why a POSA would have chosen Compound x as a lead compound; (b) neither Pitsch nor Fan would have motivated a POSA to modify Compound x to make the compounds claimed in Claim [3]; (c) a POSA would not have had a reasonable expectation of success in synthesizing the compounds claimed in Claim[3] and (d) secondary indicia of non-obviousness further establish that Claim [3] (further discussed below) is not unpatentable.

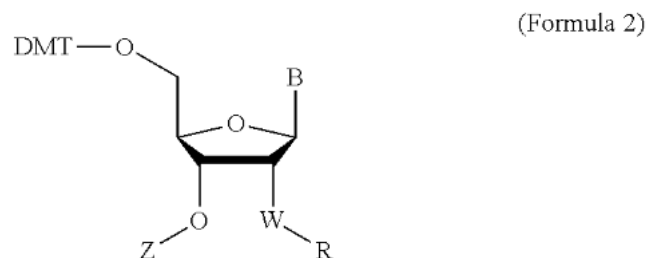
Ex. 2008, ¶ 224



GROUND V: CLAIM 4

Proposed Claim Construction

4. Derivatized nucleosides, succinates and solid supports of general formula 2,



wherein, B is selected from the group consisting of Guanine-N-acetyl, adenine-N-acetyl, cytosine-N-acetyl, cytosine-N-isobutyryl, 5-methyl cytosine-N-acetyl, and 5-methyl cytosine-N-isobutyryl;

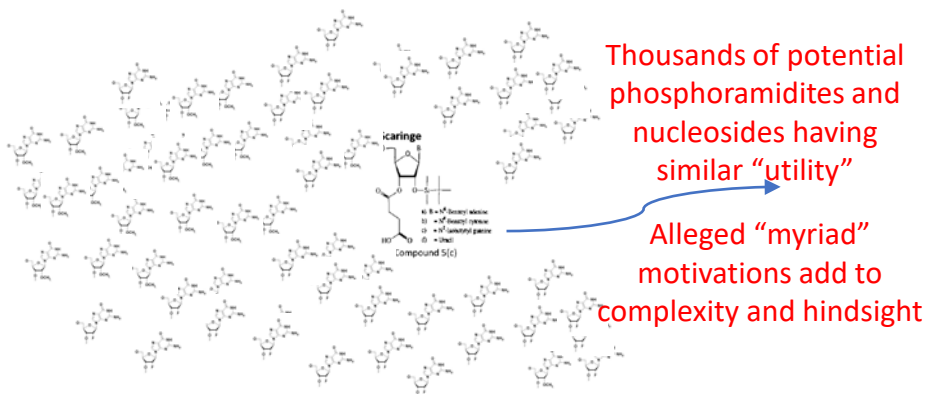
W is Oxygen and R is selected from the group consisting of t-Butyldimethyl silyl, acetal levulinyl ester (ALE), pivaloyloxy, cyanoethylmethylene (CEM), dithiomethylene (DTM)); and

Z is C(O)-M-C(O)—NH, where M is selected from the group consisting of ~~succinyl~~ [ethyl](#), oxalyl, and hydroquinolynyl, and NH is capable of being attached to a solid support with a spacer selected from the group consisting of C1-C20 alkyl, ethyloxyglycol, and a combination of alkyl and ethyleneglycoxy

- Hongene proposed this construction and ChemGenes agrees with it
- Should the Panel not construe **Claim 4** in this manner, then **Ground V** necessarily fails because all of the limitations in **Claim 4** are not taught by the prior art under this interpretation. Hongene did not dispute this in its Reply.

Selection of Compound 5(c) Was Hindsight-Driven

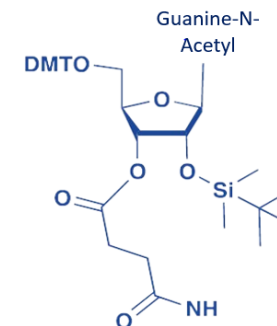
Hongene provides no selection rationale for Compound 5(c) beyond “utility” in SPOS



Hindsight



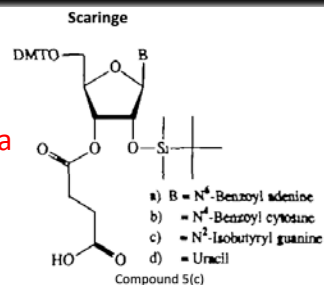
Claim 4
Compound



234. Petitioner makes *no showing* as to *why* a POSA would have selected compound 5(c) as a lead compound as the most promising to modify in order to improve upon its activity and obtain a compound with better activity or why a POSA “would have had a reason to selected Compound 5(c) from the panoply of known nucleoside building blocks in the prior art.

Ex. 2008, ¶1234

Disclosure provides no experimental data



116. In any event, Chemgenes is not correct. As I explained in my opening declaration, Scaringe discloses that Compound 5(c) can be attached to LCAA-CPG to prepare a solid support for SPOS. (Ex. 1003 ¶152, referring to ¶¶144-47 (“[A]s discussed above with respect to Claim 3 of the ’885 Patent, Scaringe (1990) also discloses the coupling of [Compound 5(c)] to LCAA-CPG to prepare the solid support for SPOS.”).) This clear utility alone would have been reason sufficient for a POSA to select Compound 5(c) in Scaringe.

Ex. 1033, ¶116

“Utility” alone does not satisfy LCA

A POSA Would Not Have Selected Compound 5(c) as a Lead Compound



235. It is my opinion that a POSA would not have chosen Compound 5(c) as a lead compound. Scaringe reports the syntheses of oligoribonucleotides (RNA) via SPOS. During SPOS, the synthesis of the RNA strand proceeds in the 3' → 5' direction. A POSA would know that the nucleotide on the 3'-end was bound to a solid support (and thus made via the succinate) and the remaining nucleotides are sequentially added in coupling steps in a 3' → 5' fashion (i.e., added using phosphoramidites).

Ex. 2008, ¶235

- The RNA sequences in Scaringe do **not** show guanosine at the 3'-ends (only cytosine and adenine).
- No evidence of guanosine being bound to a solid support through a succinate or otherwise.
- A POSA would view compounds 5(a) or (b) as leads

Table 4

Name	Sequence 5'-3'	Length
S	GCG CCG AAA CAC CGU GUC UCG AGC	24
R	GGC UCG ACU GAU GAG GCC C	18
μ-Helix	GGG GCU AUA GCU CUA GCU CCA CCA	24
m-Helix	GGG GCU AAG CGG UUC GAU CCC GCU UAG CUC CAC CA	35
1.	TTTTTrATTTT (2% 5'-2')	10
2.	TTTTTrATTTT	10
3.	TTTTTrGTTT	10

Ex. 1022 at 5436

Ex. 1022, 5436. In my opinion, none of those four sequences show a guanosine on the 3'-end, and they all instead show C, C, A, and A at their 3'-ends, and there is therefore no evidence of a solid support bound guanosine (or U) (via a succinate or otherwise) being used for the synthesis of these oligoribonucleotides. Ex. 2022, 5436. Thus, a POSA in reviewing Scaringe, would not have viewed Compound 5(c) as a lead compound and would have instead viewed Compounds 5(a) or 5(b) as leads because they were demonstrated as bound to a solid support used for RNA synthesis.

Ex. 2008, ¶236

Scaringe Would Not Have Motivated a POSA to Synthesize Claim 4

Petition

As discussed above in Section VI.B.3-4, Pitsch (2001) and Fan (2004) taught a POSA that using an acetyl group offers far superior deprotection speeds than an isobutyryl group. A POSA would have been likewise motivated by these references to make a guanosine succinate similar to molecule 5(c) of Scaringe (1990) — but with an acetyl instead of an isobutyryl protecting group on the exocyclic NH₂ group of the guanine base — to take advantage of the drastic improvement in deprotection speeds, and would have had a reasonable expectation of success. (Exh. 1003, ¶ 154.)

A POSA would have recognized that the substitution of the protecting group on the exocyclic NH₂ group of the guanine base would not be affected by the 2'-O-TBDMS protecting group, which had been commonly used to shield the 2'-OH. (*Id.* at ¶ 155.) For example, “... the use of the 2'-O-TBDMS group in conjunction with the phosphoramidite approach may be the method of choice for the synthesis of oligoribonucleotides.” (Exh. 1007 at 2270; *see also* Exh. 1017, 17:30-32, Example 1 (“... 2'-OH (blocked as 2'-t-butyldimethylsilyl derivative) nucleoside amidites are available from Glen Research, Sterling, Va.”).)

Pet. at 51

Hrdlicka

238. In my opinion, a POSA would have also known, as discussed above, that the prior art taught away from using acetyl groups to protect the N2-position of guanosine derivatives based on the demonstrated instability of acetyl group and that acetyl groups would have made guanosine derivatives less soluble in organic solvents than isobutyryl. Ex. 2013, 400. Accordingly, in my opinion, a POSA would not have been motivated by Pitsch and Fan to pursue a course antithetical to established teachings in the art. Pet., 51.

239. Petitioner and Dr. Baran also state that a “POSA would have recognized that the substitution of the protecting group on the exocyclic NH₂ group of the guanine base would not be affected by the O2'-TBDMS protecting group, which had been commonly used to shield the 2'-OH.” Pet., 51 (citing Ex. 1007). But Petitioner’s and Dr. Baran’s reliance on Beaucage (Ex. 1007) is misplaced because that reference does not disclose the use of an acetyl group on the N2-position of guanosine derivatives in conjunction with O2'-TBDMS protecting groups, never mind providing evidence that the substitution “would not be affected by the O2'-TBDMS protecting group.” *Id.*

Ex. 2008, ¶¶ 238-239



Hongene Failed to Show Reasonable Expectation of Success

Petition

A POSA would have recognized that the substitution of the protecting group on the exocyclic NH₂ group of the guanine base would not be affected by the 2'-O-TBDMS protecting group, which had been commonly used to shield the 2'-OH. (*Id.* at ¶ 155.) For example, "... the use of the 2'-O-TBDMS group in conjunction with

The above substitution of the protecting group on the exocyclic NH₂ group of the guanine base would have resulted in a 5'-O-DMT-2'-O-TBDMS N²-acetyl guanosine 3'-O-succinate. (Exh. 1003, ¶ 155.) As discussed above, Scaringe (1990)

Pet. at 51



Hrdlicka

240. Similarly, Petitioner and Dr. Baran fail to provide any rationale as to how a POSA would have synthesized the "5'-O-DMT-2'-O-TBDMS N²-acetyl guanosine 3'-O-succinate" molecule, and fail to provide any evidence or argument for reasonable expectation of success for that molecule. Therefore, The statements in the Petition on these points rely solely on the conclusory testimony of Dr. Baran.

Ex. 2008, ¶240



"Claim 3" argument not in Petition

123. Chemgenes asserts that I did not explain why a POSA would have had a reasonable expectation of success in making the compound of Claim 4. (POR 76; Ex. 2008 ¶240.) Chemgenes is incorrect. I explained in my opening declaration that "as discussed above with respect to Claim 3, a POSA would have (a) known how to couple the resulting succinate to the amine group of [LCAA-CPG] as disclosed in Scaringe (1990)...and (b) regarding a C6 alkyl as a suitable spacer...". (Ex. 1003 ¶156.)

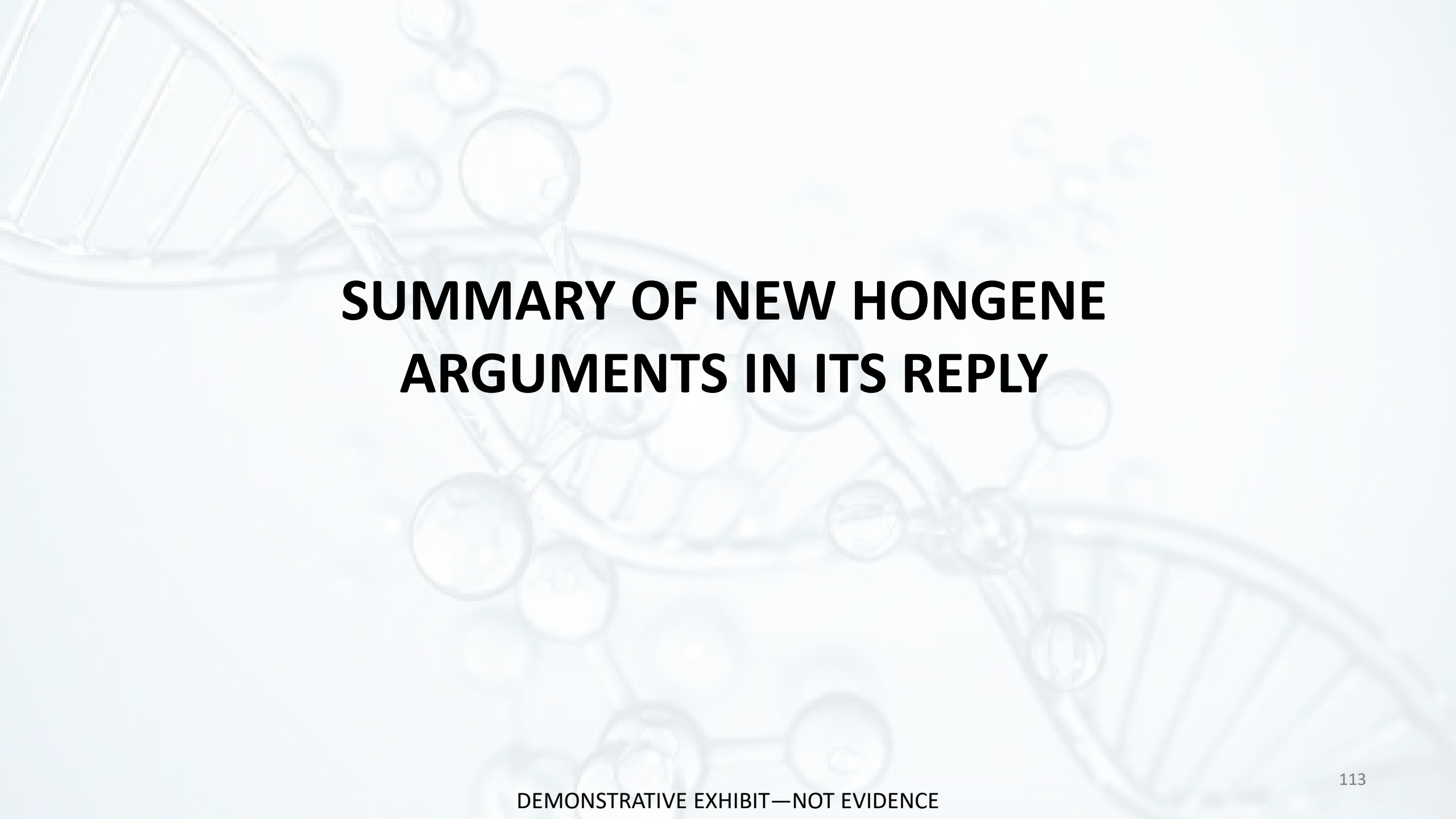
Ex. 1033, ¶123

Sur-Reply

First, Hongene never argued how POSAs would have synthesized the "5'-O-DMT-2'-O-TBDMS N²-acetyl guanosine" in its Petition. (Pet., 51-52). Hongene now relies on its arguments for Claim 3 to allege reasonable expectation of success of Claim 4, a new argument not allowed under T.P.G., 73-75. (Reply, 29).

Moreover, Claim 3 involves a 2'-fluoro-succinate not a 2'-OTBDMS-succinate as in Claim 4, which are different molecules, and Hongene provides no argument accounting for this gap, even in its Reply. If this argument is considered, which it should not be, it also fails for the reasons provided in the POR and above regarding Claim 3.

Sur-Reply at 29



SUMMARY OF NEW HONGENE ARGUMENTS IN ITS REPLY

Hongene Reply: New Arguments That Should Not Be Considered to Support its *Prime Facie* Case

New Hongene / Baran Argument	Cite
Accordingly, there were myriad motivations at play for POSAs in developing and improving upon oligonucleotide building blocks, and which set of motivations might be at play would have depended on the use case and could shift depending on the stage of development and scale of production.	Reply 4-6
'031 invention. (Ex. 1033¶26.) Hongene also noted that the '031 Patent discloses several nucleoside amidites that “had useful properties,” “clearly describes how monomeric phosphoramidites” such as Compound x “can be prepared,” “and the ways these compounds can be used to synthesize oligonucleotides with therapeutic potential.” (Ex. 1033¶27.) Indeed, one of the “useful properties” of nucleoside amidites identified throughout the '031 Patent is that 2'-fluoro substituted nucleosides were preferred and used to make preferred oligomers with enhanced binding affinity. (<i>Id.</i>)	Reply 6-7

Hongene’s new alleged “motivations” were not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene’s new alleged selection criteria based on alleged “useful properties” were not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene Reply: New Arguments That Should Not Be Considered to Support its *Prime Facie* Case

New Hongene / Baran Argument	Cite
And the '031 Patent's use of a 24-hour deprotection period would have prompted POSAs to explore shortening that period, especially in view of the iterative nature of SPOS. (Ex. 1033¶33.)	Reply 8
agriculture.” (Ex. 1033¶56.) Indeed, 2'-fluoro-2'-deoxynucleosides were considered “RNA-like.” (<i>Id.</i>) Thus, POSAs would have applied the teachings of	Reply 14

Hongene's new argument relating to “shortening that period” were not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene's new argument relating to “RNA-like” were not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene Reply: New Arguments That Should Not Be Considered to Support its *Prime Facie* Case

New Hongene / Baran Argument	Cite
The 2' substitution is considered independently from the nucleobase PG, because those sites are chemically distant and not expected to affect each other's reactivities.	Reply 14
Nevertheless, <i>Fan reports successfully acetylating guanosine</i>, “smoothly” and “without generation of dark mixtures” using TMSCl to treat an intermediate similar to the '031 intermediate “Compound i”	Reply 17-18
There is no reason to expect that removing two carbon atoms from a large nucleoside monomer (going from isobutyryl to acetyl) would have a solubility effect profound enough to prevent the molecule from reacting in subsequent chemistry.	Reply 18

Hongene's new argument relating to “chemically distant” was not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene's new argument relating to using TMSCl for intermediate treatment was not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene's new argument relating to “removing two carbon atoms” were not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene Reply: New Arguments That Should Not Be Considered to Support its *Prime Facie* Case

New Hongene / Baran Argument	Cite
But POSAs would have expected the installation of PGs on of 2'-deoxy- and 2'-F-monomers to be easier than on the more complicated monomers protected in Pitsch, Pitsch #2, and the '031 Patent, because the former do not have a reactive oxygen-bound substituent at the 2' position.	Reply 20
1033¶91.) And second, deprotection conditions and PGs go hand-in-hand. (Ex. 1033¶91.) It was known that (a) mild and shorter base deprotection was preferred when synthesizing RNA, (b) using labile protecting groups facilitates RNA synthesis and allows incorporation of modified and base sensitive nucleosides, and (c) acetyl PG was useful in making RNA oligonucleotides because it permitted rapid deprotection under mild conditions. (Id.) POSAs looking to make oligonucleotides containing 2'-F-monomers would naturally have used an acetyl PG along with the mild, short deprotection conditions it facilitated. (Id.)	Reply 22-23

Hongene's new argument relating to installation of protecting groups "to be easier" was not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene's new "hand in hand" arguments was not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene Reply: New Arguments That Should Not Be Considered to Support its *Prime Facie* Case

New Hongene / Baran Argument	Cite
Thus, POSAs encountering the cytosine phosphoramidite (Compound 5) would have been immediately motivated to make its guanosine homolog (Claim 2), so that both nucleosides could be incorporated into an oligonucleotide, which typically requires all four nucleobases. (Ex. 1033¶100.)	Reply 24
This worked for Scaringe with the larger 2'-OTBDMS present, so it would be expected to work better with the 2'-F-substituted species, because fluorine is smaller, providing less steric hindrance, rendering the 3'-OH site more reactive. (<i>Id.</i>)	Reply 27

Hongene's new argument relating to a POSA being "immediately motivated to make its guanosine homolog" was not raised in its Petition (or supported by Baran) and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene's new "expected to work better" and "less steric hindrance" arguments were not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.

Hongene Reply: New Arguments That Should Not Be Considered to Support its *Prime Facie* Case

New Hongene / Baran Argument	Cite
Chemgenes does not argue that POSAs would not have had a reasonable expectation of success in making the compound of Claim 4. Instead, Chemgenes incorrectly asserts that Hongene provided no basis to establish a reasonable expectation of success for Claim 4. (POR76.) But Hongene provided those bases in connection with Claim 3. (Ex. 1033¶¶123-24.)	Reply 29

Hongene's new argument relating to a reasonable expectation of success of Claim 4 based on reasonable expectation of success of Claim 3 was not raised in its Petition and should therefore not be considered to support its *prima facie* case for unpatentability. T.P.G. at 74.



CONCLUSION

Conclusion

X. CONCLUSION

Hongene failed to carry its burden of proving unpatentability by a preponderance of the evidence for at least the reasons in the POR [the Sur-Reply, and record in this case.]



IPR2023-00490

U.S. Patent No. 9,884,885 B2

Patent Owner Oral Argument Demonstratives

April 23, 2024

Respectfully Submitted