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European Biotech Case Law

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Speakers

Simon O’Brien
Partner, Patent Attorney
swo@dyoung.com

Tom Pagdin
Partner, Patent Attorney
twp@dyoung.com

Summary

- T 2036/21: Standard for credible effect/free evaluation of evidence
- T 1989/19: Allowability of post-published data to support inventive step
- T 0835/21: Enablement of functionally defined antibody claims

T 2036/21 (N.V. Nutricia)
Standard for credible effect
& Free evaluation of evidence

T 2036/21: background

- First Board of Appeal decision on the same case (T 694/16):
  - set aside OD decision to revoke the patent for **lack of sufficiency**
  - remitted case to the OD for further prosecution on the basis of Auxiliary Request 4, which was decided by BoA to be novel and sufficiently disclosed.
- The OD further confirmed that Auxiliary Request 4 met all the requirements of the EPC.

T 2036/21: AR4

- Claim 1 of AR4:

  A composition comprising

  (a) one or more ω-3 fatty acids selected from DHA, DPA and EPA,

  (b) uridine selected from the group of uridine, deoxyuridine, uridine phosphates, uracil and acylated uridine derivatives, and

  (c) choline and/or phosphatidylcholine,

  wherein the composition further includes **vitamin B12 and folate**, **for use in the prevention or delay of the onset of dementia in a person having characteristics of a prodromal dementia patient**, wherein said characteristics comprise at least: a level of more than 350 ng Total-tau per litre cerebrospinal fluid (CSF); and a weight ratio of abeta-42/Phospho-tau-181 of less than 6.5 in CSF.

T 2036/21: appellant’s arguments

- The OD had not properly taken into account the teachings of D31 and D47 - these documents showed the claimed composition was not suitable for the claimed purpose:
- The appellant argued:
  - D31 and D47 relate to the clinical trial "LipiDiDiet“ which investigated the effect of composition according to claim 1, on patients affected by prodromal Alzheimer's disease expressing the biomarkers of claim 1.
  - D31 and D47 explicitly stated the claimed treatment was not effective for preventing or delaying the onset of dementia.
  - D31 and D47 further provided evidence that no therapeutic effect was achieved in prodromal patients.

T 2036/21: respondent's arguments

- The BoA in T 694/16 already decided that the claimed composition was suitable for inducing the claimed effect and the **requirement for sufficiency** was fulfilled.
  - Whether the claimed composition was suitable for inducing the claimed effect is relevant to assessment of sufficiency of disclosure (G 1/03)
  - Sufficiency was already settled by the board (T 694/16), the issue could not be reopened.
- In any case, the appellant was misinterpreting the teaching of D31, and D47, picking passages which did not **truly represent** the outcome of the clinical trials described therein.

T 2036/21: considerations of the Board (1)

Reopening issue of whether claimed effect had been achieved

- The Board disagreed with the patent proprietor on their ability to decide on whether the claimed effect had been achieved. The previous Board In T 614/16 remitted the case to the opposition division for further prosecution.
- The EPC, and Article 111(2) do **not preclude** the OD from taking into account facts which were **not at the disposal of the Board remitting the case**. Furthermore, the issue of the effect specified in the claim is achieved is relevant for both sufficiency and **has an impact on the formulation of the problem for assessing inventive step**.

T 2036/21: considerations of the Board (2)

Free evaluation of evidence before the EPO

- The appellant drew attention to the following passages in D31 and D47:
  - “During the 24-month trial period **59 (37%)** participants in the control group and **62 (41%)** in the active group were **diagnosed with dementia** (p=0.642, Fisher's exact test)”
  - “**No significant difference** was found between groups for the [neuropsychological test battery] NTB **primary endpoint** in the mITT analysis or on conversion to dementia”.
  - “During the trial, **no overall difference** was observed between active and control groups in the number of participants **diagnosed with dementia** over 36 months (66 [43.1%] and 70 [44.3%], respectively) or in the time to dementia using Kaplan-Meier analysis (Figure S2B)”
- The appellant argued these passages provided clear-cut evidence that the claimed composition was **not suitable** for inducing the claimed therapeutic effect.

T 2036/21: considerations of the Board (3)

Free evaluation of evidence before the EPO (2)

- The Board was not convinced by the appellants arguments, the Board was of the opinion that:
  - D31 and D47 also explicitly state that the LipiDiDiet study was **not designed** to allow conclusions to be drawn on these discrete endpoints.
  - D47 also explains that the cognitive decline in the control group was much lower than expected, rendering the **primary endpoint inadequately powered**.
  - D47 furthermore explains that the tests to diagnose dementia were only clustered at major study visits.
- This means that D31 and D47 do not convey to the skilled person the message that "the tested composition is unsuitable for preventing or delaying the onset of dementia in a prodromal patient",
- Rather that "this **effect was not detected**, possibly because the clinical trial was **not designed** and **adequately powered** to do so".

T 2036/21: considerations of the Board (4)

Free evaluation of evidence before the EPO (3)

- The Board was of the opinion that:
  - "The crucial point which has to be decided is whether further evidence is available which makes it **credible** that the claimed composition is suitable for preventing or delaying the onset of dementia in a prodromal patient."
  - "… Even if the tests aimed at assessing an endpoint of a clinical trial do not yield a statistically significant outcome, **other results may still be taken into account** to evaluate the efficacy of a treatment."
  - "… Proceedings before the EPO are conducted with application of the principle of **free evaluation of evidence**. According to this principle, the competent EPO body decides in the light of its conviction arrived at freely, taking into account the evidence available in the proceedings and on the footing that **one set of facts is more likely to be true than the other.**"
  - "In proceedings before the EPO it is **not a prerequisite to perform a statistical analysis** of the results and to determine a **specific confidence interval**, as is most often required in biomedical research" – following **G 3/97.**

T 2036/21: considerations of the Board (5)

Free evaluation of evidence before the EPO (4)

The Board was of the opinion that:

- D47 showed the administration of Fortasyn Connect to prodromal dementia patients induces a **significant improvement** of the NTB 5-item and the NTB memory domain scores, the scores of CDR-SB, and a reduction of brain atrophy.
- D47's conclusion stated that: "the present study provides evidence for potentially altered disease trajectories supporting the positive effects of long-term multinutrient intervention in prodromal AD. Over 3 years, **significant benefits were observed** on cognition, function, and brain atrophy, with clinically relevant effect sizes demonstrated."
- "For these reasons, the board concludes that **the results described in D47 make it credible that the claimed composition prevents or delays the onset of dementia in the patient identified in claim 1**. Furthermore, that patients at the earliest stage of prodromal disease benefit the most from the treatment. These conclusions confirm the earlier finding in decision T 694/16, which was based inter alia on example 4 of the opposed patent and on D29."

T 2036/21: conclusions

- The standard to be applied for a claimed effect to be considered achievable is **not the same standard** required in biomedical research or by health authorities granting market authorisations
  - the effect need only be **credible** (G 2/21, previously “plausible”).
  - Proceedings before the EPO are conducted with application of the principle of **free evaluation of evidence**

T 1989/19
Allowability of post-published data to support inventive step

Claim 1 as granted

“Crystalline micronisate of tiotopium bromide [sic] of formula (I)

FORMULA/TABLE/GRAPH

characterised by a particle size X50 of between 1.0 µm and 3.5 µm with a value Q(5.8) greater than 60 %, by a specific surface value in the range between 2 m**(2)/g and 5 m**(2)/g, by a specific heat of solution greater than 65 Ws/g and by a **water content of 1 % to 4.0 %**”

Appellant’s arguments

- Certain objections on grounds of novelty
  - However, statement of grounds of appeal only indicated that they maintained all objection raised in opposition proceedings.
  - Therefore board did not admit these objections which had been “raised merely by reference to the opposition proceedings”.
- Inventive step
  - The appellant argued that the claims lacked IS in view of D9: WO 00/47200 A1.

D9 disclosure

- D9 discloses:
  - Use of tiotropium bromide
  - Ground to a particle size of 1 μm to 5 μm
  - Water content of 1 to 4.0 %?
- D23 and D65 were test reports submitted by the respondent (patentee) that compared the water content and relative stability of the prior art micronised tiotropium bromide with the micronised tiotropium bromide of the patent in question.
- D23 and D65 confirmed that the prior art tiotropium bromide does not have a water content of between 1-4.0%.

Technical effect

- The patentee referred to D23 and D65 as evidence of the technical effect
- The patentee argued that the specific water content of the micronised tiotropium bromide results in improved storage stability
- Prior art samples and samples from the patent in question were subjected to a three-day stress storage at 40°C and 75 % relative humidity and finally re-characterized.
- The results (D23, page 1, second table) show that during this stress test, less stable samples undergo a particle size shift as the particles become larger. The medium shift is less in the micronisate of the patent in question versus the micronisate of the prior art. As such, the micronisate of the patent in question demonstrates a higher stability

Appellant's arguments

- The opponent did not contest that D23 & D65 provide evidence of an improvement of storage stability.
- However, amongst other arguments, they did argue that because the experimental data in D23 and D65 had been post-published and the application as filed did not contain any reference to the technical effect of improved storage stability, such a technical effect could not be taken into account in the context of inventive step.

G 2/21

- Point 2: "An applicant or proprietor of a patent may rely on a technical effect to prove inventive step if, on the basis of **common general knowledge** and on the basis of the application as filed, the **skilled person** would conclude that **that effect is encompassed by technical teaching and embodied by the same invention originally disclosed**."

Is an improved storage stability encompassed by technical teaching and embodied by the same invention originally disclosed?

- Technical effect: improved storage stability.
- Technical teaching / invention originally disclosed: Use of inhalation powders of micronised tiotropium bromide with a preferred particle size of, e.g., 1.5 µm to 5 µm.
- BoA: “Since a certain amount of time necessarily elapses between the manufacture of a medicinal product and its administration, it can be inferred from the application as originally filed that particle size stability (corresponding to the storage stability demonstrated in D23 and D65) is an essential prerequisite for the administration of the medicinal product in accordance with the application”.
- BoA: “It was generally known to the skilled person before the priority date of the application that the stability of the particle size is of crucial importance for the administration of a medicinal product by inhalation. As proof of common general knowledge, the respondent referred to documents D1, D16a, D16b and D17”.

Continued…

- BoA: “On the basis of this above-mentioned specialist knowledge regarding the necessary particle sizes/particle size distribution in the use of inhalation powders for medical administration, the skilled person would recognise on the basis of the application as originally filed that the tiotropium bromide also has an adequate stability of particle sizes due to the disclosed particle sizes and its use.”

Continued…

- “In the Board's view, once the above-mentioned criterion of derivability of a technical effect is met, the same applies to the improvement of that effect.
- **If a particular technical effect, such as storage stability in the present case, can be deduced by the skilled person within the meaning of the operative part of decision G 2/21, point 2 of decision G 2/21, its improvement must also be regarded as implicitly derivable**.”

Inventive step

- The BoA concluded that there was a technical effect.
- The problem to solved was formulated as the provision of a tiotropium inhalation powder with improved storage stability.
- The BoA indicated that neither D9 (or D14) indicate that such a problem can be solved by the crystalline micronisate of claim 1.
- Claim 1 therefore involves an inventive step.

The BoA found the following passages of the specification in question relevant:

- Page 1, line 22 to page 2, line 2: Indicates the **application of tiotropium bromide** is preferably carried out by **inhalation** and that with regard to the inhalation of tiotropium bromide, it is **necessary to provide the active ingredient in micronized form**. Preferably, the active ingredient has an average particle size of 0.5 µm to 10 µm, preferably from 1 µm to 6 µm, especially **preferably from 1.5 µm to 5 µm**.
- Page 2, lines 14 to 18: "... The object of the present invention is to **provide a method which makes micronized tiotropium bromide available in a form which satisfies the high requirements to be met by an inhaled active ingredient** and takes into account the specific properties of the tiotropium bromide."
- Page 6, lines 28 to 30: "**Inhalation powder** characterized by a content of tiotropium bromide micronisate according to the invention."

Conclusions

- Standard of the **“effect is encompassed by technical teaching and embodied by the same invention originally disclosed”** is being applied.
- It is sufficient that a technical effect may be deduced from the application as filed by the skilled person – any improvement of said technical effect is as such implicitly derivable.

T 0835/21
Enablement of functionally defined antibody claims

Patenting antibodies at the EPO

- EPO Guidelines for Examination: G.II.5.6
- Case study: T 0835/21
  Consideration of enablement for ‘functionally’ defined antibody claims
- Differences in EPO approach v other jurisdictions (for example, USPTO)

Types of antibody claims at the EPO

- In general, antibodies can be defined by (but are not limited to):

(a) **their own structure (amino acid sequences)**;

(b) nucleic acid sequences encoding the antibody;

(c) reference to the target antigen;

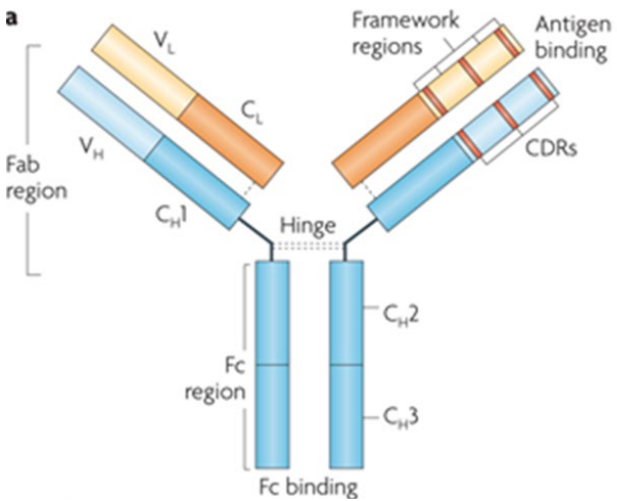
(d) target antigen and further functional features;

(e) functional and structural features;

(f) the production process;

(g) the epitope;

(h) the hybridoma producing the antibody.



Types of antibody claims at the EPO

- Antibody structure
- Clarity: CDRs required for binding to the antigen
- Unless it is experimentally shown that one or more of the six CDRs do not interact with the antigen
- CDRs defined by reference to a larger heavy or light chain sequence: numbering scheme must be indicated (for example, Kabat, Chothia or IMGT)

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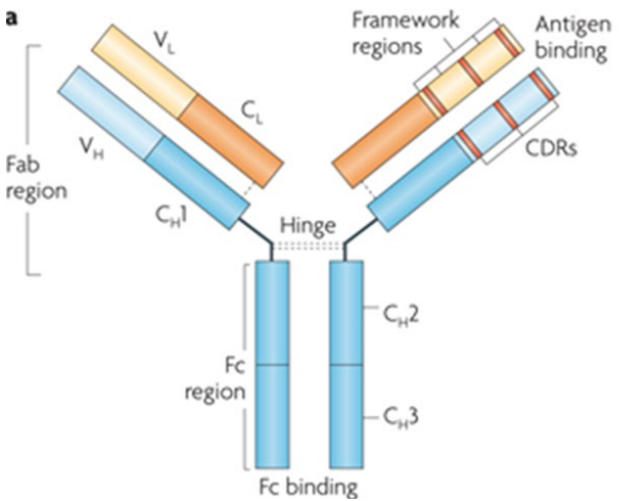
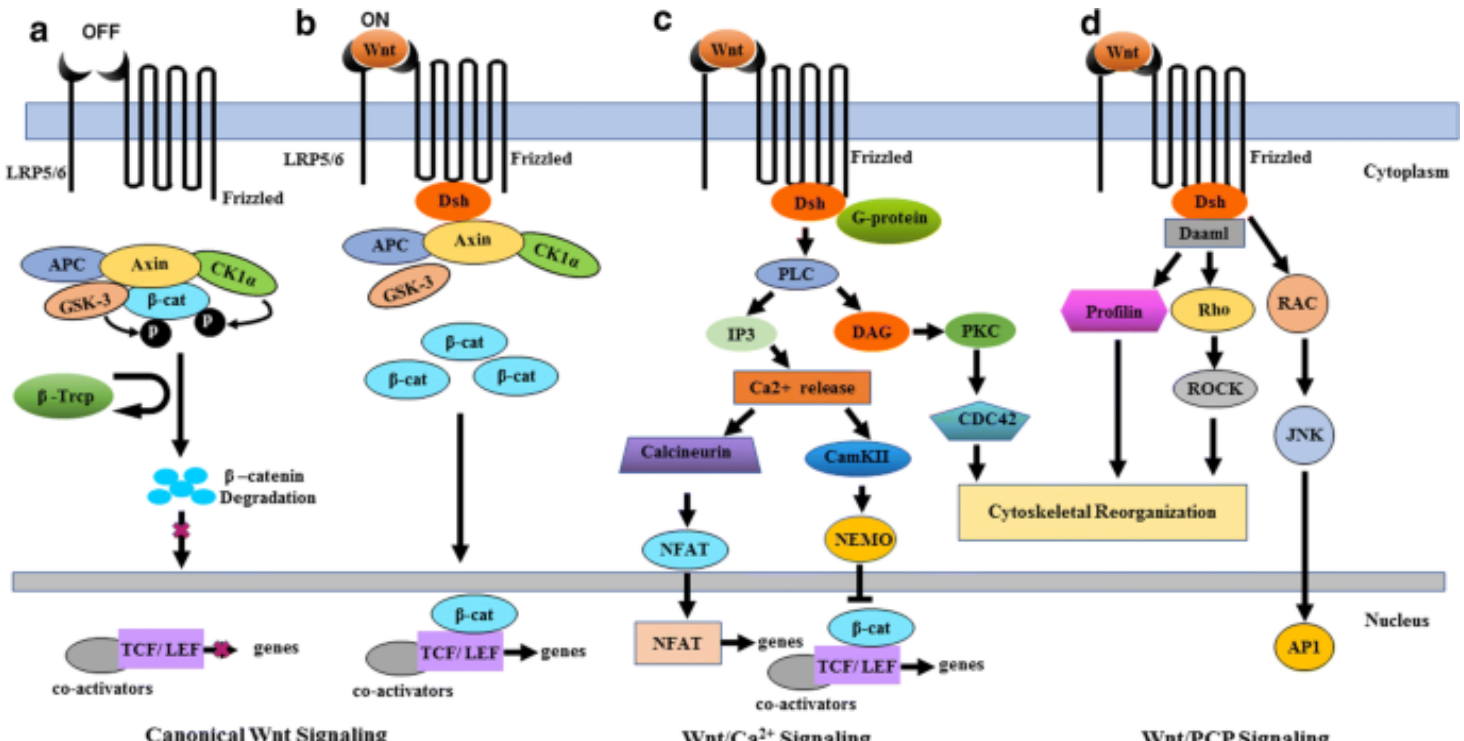


T 0835/21: enablement of functionally defined antibody claims

A monoclonal antibody or an antigen-binding fragment thereof that specifically binds to human low-density-lipoprotein receptor-related protein 6 polypeptide (LRP6) having the amino acid sequence of SEQ ID NO:1,

- is **capable of antagonizing the Wnt signaling pathway**,
- and **inhibits Wnt3- and Wnt3a-specific signaling activity**,
- wherein the **antigen binding portion binds to an epitope of human LRP6 within amino acids 631-932 of SEQ ID NO:1 as shown in Table 1**.

T 0835/21: background



Harb, J., Lin, PJ. & Hao, J. Recent Development of Wnt Signaling Pathway Inhibitors for Cancer Therapeutics. *Curr Oncol Rep* **21**, 12 (2019).

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T 0835/21: asserted invention

- Antigen binding portion binds to an epitope of human LRP6 within amino acids 631-932 of SEQ ID NO:1 as shown in table 1 - **propeller domain 3**
- Inhibits Wnt3- and Wnt3a-specific signaling activity

T 0835/21: disclosure of the patent

- No structural information (CDR, VH/VL etc) **for any antibody**
- Internal Fab designation: “Fab002”
- Examples:

  (1) luciferase reporter assays for Wnt signalling, and

  (2) LRP6 sub-domain deletion, broadly defined Ab activity reported (“Wnt3A Antagonist”).
- No corresponding designation between labelling in the examples
- No figures

T 0835/21: disclosure of the patent

	Wnt3
Fab003	2%
Fab004	1%
Fab023	9%
Fab015	83%
Fab016	73%
Fab019	66%
Fab020	68%
FabControl	100%

	Agonist	Wnt1 Antagonist	Wnt3A Antagonist
LRP6 full length	+++	+++	+++
LRP6 del I	+++	--	+++
LRP6 del II	+++	+++	+++
LRP6 del III	--	+++	--
LRP6 del I-II	+++	--	+++
LRP6 del I-III	--	--	--

T 0835/21: disclosure of the patent

- General statement that binding of Fabs (“Fabxxx”) to different propeller domains of LRP6 had different effects on Wnt ligand signalling.
- Fabs binding to propeller 3 of LRP6 (epitope defined in claim 1) had Wnt3/3A specific antagonist activity or general Wnt agonist activity.

T 0835/21: arguments for lack of enablement

- Lack of structural information: Examples cannot be reproduced
- No clear link between binding to LRP6 propeller 3 and Wnt3 inhibition
- No selection criteria to determine Abs that inhibit Wnt3 activity
- Undue burden and invitation to conduct a research program

T 0835/21: Board of Appeal's reasoning

- Agreed specific Fabs in Examples could not be reproduced, lack of figures and non-specific labelling
- Lack of structural information doesn't mean lack of enablement: Art. 83 EPC does not require a reproducible example
- The claimed antibody is broadly **functionally** defined by:
  1. Ability to bind to an epitope of human LRP6 within amino acids 631 to 932 of SEQ ID NO:1; and
  2. Preferential inhibition of Wnt3- and Wnt3a-specific signalling activity.

T 0835/21: Board of Appeal's reasoning

- Preparing and screening antibodies is a routine task: relevant assays (luciferase and LRP6 mutants for domain specificity) are provided in the Examples
- No evidence that the teachings of the patent: Abs that bind propeller 3 are either agonists or Wnt3-specific antagonists is incorrect
- Amount of work and potential tedious nature does not mean lack of enablement

T 0835/21 & Amgen v Sanofi

- An isolated monoclonal antibody that binds to PCSK9, wherein the isolated monoclonal antibody binds an epitope on PCSK9 comprising at least one of residues 237 or 238 of SEQ ID NO: 3, and wherein the monoclonal antibody blocks binding of PCSK9 to LDLR.

T 0835/21 & Amgen v Sanofi

T 0835/21	Amgen v Sanofi
The preparation of a monoclonal antibody that binds to an epitope within a defined amino acid sequence, i.e. a known target, for example by immunisation of an animal with a protein or peptide consisting of or contained within the defined amino acid sequence, or by phage display using such a peptide, **is a routine task for the skilled person and does not require any inventive activity**.	In doing so, we do not doubt that **Amgen's specification enables the 26 exemplary antibodies it identifies by their amino acid sequences**. Even Sanofi concedes that description is enough to allow a person skilled in the art to make and use those embodiments. See Tr. of Oral Arg. 68. But the claims before us sweep much broader than those 26 antibodies. And we agree with the lower courts that **Amgen has failed to enable all that it has claimed, even allowing for a reasonable degree of experimentation**.
It may be tedious to screen candidate antibodies binding to the propeller 3 domain of LRP6 for inhibition of Wnt3- and Wnt3a-specific signalling activity, **but this does not necessarily amount to an undue burden** if the screening results in the desired product, i.e. if the information in the patent leads the skilled person "directly towards success through the evaluation of initial failures" (see decision T 544/12; Reasons 4.8).	**These two approaches amount to little more than two research assignments**. The first merely describes step-by-step Amgen's own trial-and-error method for finding functional antibodies—calling on scientists to create a wide range of candidate antibodies and then screen each to see which happen to bind to PCSK9 in the right place and block it from binding to LDL receptors.

EPO: routine task to generate antibodies against a known target

- Enablement v inventive step.
- A claim defining a novel, further antibody binding to a known antigen requires a surprising technical effect or lack of reasonable expectation of success.
- Improved affinity, improved therapeutic activity, reduced toxicity or immunogenicity, unexpected species cross-reactivity or a new type of antibody format with proven binding activity.

T 0835/21: inventive step

“Nothing in the prior art pointed the skilled person towards an antibody that bound to an epitope within the propeller 3 domain of LRP6 as a solution to this technical problem. Indeed, it was **not known in the art that different Wnt ligands bound to different propeller domains** of LRP6, and that therefore antibodies that preferentially inhibited the signalling activity induced by particular Wnt ligands could be prepared by targeting different LRP6 propeller domains. The **link between binding to the propeller 3 domain of LRP6 and preferential inhibition of Wnt3 and Wnt3a signalling activity was therefore not suggested in the prior art and hence was not obvious to the skilled person**.”

Considerations

- EPO considers the provision of antibodies against a known target to be “routine”
- Identification of a novel effect may support a functionally defined claim
- Undue burden ≠ tedium
- Must also be able to establish inventive step

Lexology masterclass webinar invitation

Techbio patents: maximising the impact of wet-lab and ai data

1pm (GMT) Wednesday 13 March 2024

Jennifer O'Farrell and Robbie Berryman discuss strategies for the effective use of AI-derived data in patent applications and question where and how wet-lab data fits into this process.

Key topics include plausibility, inventive step and the roles and risks of negative evidence.

Registration: https://dycip.com/lexology-techbio-patents

Any Questions…?

Simon O’Brien
Partner, Patent Attorney
swo@dyoung.com

Tom Pagdin
Partner, Patent Attorney
twp@dyoung.com