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Datasheet for the decision of 9 June 2016

Case Number: T 1600/12 - 3.3.02

Application Number: 05809080.4

Publication Number: 1815245

IPC: G01N33/50

Language of the proceedings: EN

Title of invention:
PREMATURELY AGEING MOUSE MODELS FOR THE ROLE OF DNA DAMAGE IN AGEING AND INTERVENTION IN AGEING-RELATED PATHOLOGY

Patent Proprietor:
Erasmus MC

Opponent:
KÖNIG SZYNKA TILMANN VON RENESSE

Headword:
Prematurely ageing mouse models/ERASMUS MC

Relevant legal provisions:
EPC Art. 56, 123(2)
RPBA Art. 13

Keyword:
Inventive step - (no)

Decisions cited:

Catchword:

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Case Number: T 1600/12 - 3.3.02

D E C I S I O N
of Technical Board of Appeal 3.3.02
of 9 June 2016

Appellant: (Patent Proprietor)	Erasmus MC Dr. Molewaterplein 40 3015 GD Rotterdam (NL)
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Representative:	König, Gregor Sebastian König-Szynka-Tilmann-von Renesse Patentanwälte Partnerschaft mbB Postfach 11 09 46 40509 Düsseldorf (DE)
Decision under appeal:	**Decision of the Opposition Division of the European Patent Office posted on 9 May 2012 revoking European patent No. 1815245 pursuant to Article 101(3)(b) EPC.**

Composition of the Board:

Chairman	U. Oswald
Members:	K. Giebeler
	L. Bühler

Summary of Facts and Submissions

I. European patent No. 1 815 245, based on European patent application No. 05809080.4, published as WO 2006/052136 (hereafter: the application as filed) and entitled "Prematurely ageing mouse models for the role of DNA damage in ageing and intervention in ageing-related pathology", was granted with six claims.

II. Claims 1 and 3 to 6 as granted read:

"1. A method for the selection of a compound, or a mixture of compounds, said method comprising the steps of:
- providing a genetically altered mouse, wherein said mouse has at least one mutation in a gene encoding a protein of the Nucleotide Excision Repair (NER) pathway, said mutation causing a premature ageing phenotype as compared to a mouse lacking said mutation;
- exposing said genetically altered mouse, or part derived there form [*sic*], to a compound, or a mixture of compounds;
- determining the effect of the compound, or the mixture of compounds, on the premature ageing phenotype of said genetically altered mouse; and
- selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces said premature ageing phenotype in said genetically altered mouse,
wherein said mutation is in a gene selected from the group consisting of: *Xpa, Xpb, Xpc, Xpd, Xpe, Xpf, Xpg, Xpv, Csa, Csb, Ttda, HR23A, HR23B* and *Ercc1*, and
wherein said premature ageing phenotype is a shortened life span, increased osteoporosis and/or increased retinal degeneration as compared to a mouse lacking said mutation."

"3. The method according to claim 1, wherein said mutation is equivalent to or mimics a human Cockayne Syndrome (CS), a Xeroderma pigmentosum (XP), a combined Xeroderma Pigmentosum - Cockayne Syndrome (XPCS), trichothiodystrophy (TTD), a Cerebro-Oculo-Facio-Skeletal syndrome (COFS) or an XPF-ERCCI syndrome causing allele in the *Csa, Csb, Xpb, Xpd, Xpg, Xpf, Ttda* or *Ercc1* genes."

"4. The method according to claim 3, wherein the human Cockayne, COFS or XPCS syndrome causing mutation is selected from the group consisting of CS-associated mutations in: the human *Csa* gene: $Csa^{null/null}$, Y322ter, the human *Csb* gene: Csb^{null}, Q184ter, R453ter, W517ter, R670W, R735ter, G744ter, W851R, Q854ter, R947ter, P1042L, P1095R, R1213G, the human *Xpd* gene: G602D, G675R, 669fs708ter, the human *Xpb* gene: F99S, FS740, and for the human *Xpg* gene: R263ter, 659ter."

"5. The method according to any one of claims 1 to 4, wherein said genetically altered mouse has a mutation in at least two different genes each encoding a protein of the NER pathway."

"6. The method according to claim 5, wherein said genetically altered mouse has a combination of mutations selected from the group consisting of: $Csa^{null/null}/Xpa^{null/null}$, $Csa^{null/null}/Xpc^{null/null}$, $Csb^{G744ter/G744ter}/Xpa^{null/null}$, $Csb^{G744ter/G744ter}/Xpc^{null/null}$, $Xpd^{G602D/G602D}/Xpa^{null/null}$, $Xpd^{R722W/R722W}/Xpa^{null/null}$, and $Xpd^{G602D/R722W}/Xpa^{null/null}$."

III. An opposition was filed against the granted patent, on the grounds of lack of novelty and inventive step (Article 100(a) EPC), insufficiency of disclosure

(Article 100(b) EPC) and added subject-matter (Article 100(c) EPC).

IV. The opposition division decided to revoke the patent. It held that the main request complied with Articles 123(2), 54 and 83 EPC, but that neither the main request nor any of auxiliary requests 1 to 3 fulfilled the requirements of Article 56 EPC.

V. The proprietor (hereafter: appellant) filed an appeal against the decision of the opposition division and requested that the decision under appeal be set aside and that the patent be maintained as granted or, alternatively, on the basis of any of auxiliary requests 1 to 3 filed before the opposition division with letter of 13 February 2012 or the newly submitted auxiliary requests 4 and 5.

Claim 1 of **auxiliary request 1** reads:

"A method for the selection of a compound, or a mixture of compounds, said method comprising the steps of:
- providing a genetically altered mouse, wherein said mouse has at least one mutation in a gene encoding a protein of the Nucleotide Excision Repair (NER) pathway, said mutation causing a premature ageing phenotype as compared to a mouse lacking said mutation;
- exposing said genetically altered mouse, or part derived there from, to a compound, or a mixture of compounds;
- determining the effect of the compound, or the mixture of compounds, on the premature ageing phenotype of said genetically altered mouse; and
- selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces said

premature ageing phenotype in said genetically altered mouse,
wherein said mutation is in a gene selected from the group consisting of: *Xpa, Xpb, Xpc, Xpd, Xpe, Xpf, Xpg, Xpv, Csa, Csb, Ttda, HR23A, HR23B* and *Ercc1*, wherein said premature ageing phenotype is a shortened life span, increased osteoporosis and/or increased retinal degeneration as compared to a mouse lacking said mutation,
and wherein said mutation is equivalent to or mimics a human Cockayne Syndrome (CS), a Xeroderma pigmentosum (XP), a combined Xeroderma Pigmentosum - Cockayne Syndrome (XPCS), trichothiodystrophy (TTD), a Cerebro-Oculo-Facio-Skeletal syndrome (COFS) or an XPF-ERCC1 syndrome causing allele in the *Csa, Csb, Xpb, Xpd, Xpg, Xpf, Ttda* or *Ercc1* genes."

Claim 1 of **auxiliary request 2** reads:

"A method for the selection of a compound, or a mixture of compounds, said method comprising the steps of:
- providing a genetically altered mouse, wherein said mouse has at least one mutation in a gene encoding a protein of the Nucleotide Excision Repair (NER) pathway, said mutation causing a premature ageing phenotype as compared to a mouse lacking said mutation;
- exposing said genetically altered mouse, or part derived there from, to a compound, or a mixture of compounds;
- determining the effect of the compound, or the mixture of compounds, on the premature ageing phenotype of said genetically altered mouse; and
- selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces said premature ageing phenotype in said genetically altered mouse,

wherein said mutation is in a gene selected from the group consisting of: *Xpa, Xpb, Xpc, Xpd, Xpe, Xpf, Xpg, Xpv, Csa, Csb, Ttda, HR23A, HR23B* and *Ercc1*, wherein said premature ageing phenotype is a shortened life span, increased osteoporosis and/or increased retinal degeneration as compared to a mouse lacking said mutation,
wherein said mutation is equivalent to or mimics a human Cockayne Syndrome (CS), a Xeroderma pigmentosum (XP), a combined Xeroderma Pigmentosum - Cockayne Syndrome (XPCS), trichothiodystrophy (TTD), a Cerebro-Oculo-Facio-Skeletal syndrome (COFS) or an XPF-ERCC1 syndrome causing allele in the *Csa, Csb, Xpb, Xpd, Xpg, Xpf, Ttda* or *Ercc1* genes, and
wherein the human Cockayne, COFS or XPCS syndrome causing mutation is selected from the group consisting of CS-associated mutations in: the human *Csa* gene: $Csa^{null/null}$, Y322ter, the human *Csb* gene: Csb^{null}, Q184ter, R453ter, W517ter, R670W, R735ter, G744ter, W851R, Q854ter, R947ter, P1042L, P1095R, R1213G, the human *Xpd* gene: G602D, G675R, 669fs708ter, the human *Xpb* gene: F99S, FS740, and for the human *Xpg* gene: R263ter, 659ter."

Claim 1 of **auxiliary request 3** reads:

"A method for the selection of a compound, or a mixture of compounds, said method comprising the steps of:
- providing a genetically altered mouse, wherein said mouse has at least one mutation in a gene encoding a protein of the Nucleotide Excision Repair (NER) pathway, said mutation causing a premature ageing phenotype as compared to a mouse lacking said mutation;
- exposing said genetically altered mouse, or part derived there from, to a compound, or a mixture of compounds;

- determining the effect of the compound, or the mixture of compounds, on the premature ageing phenotype of said genetically altered mouse; and
- selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces said premature ageing phenotype in said genetically altered mouse,

wherein said mutation is in a gene selected from the group consisting of: *Xpa, Xpb, Xpc, Xpd, Xpe, Xpf, Xpg, Xpv, Csa, Csb, Ttda, HR23A, HR23B* and *Ercc1*, wherein said premature ageing phenotype is a shortened life span, increased osteoporosis and/or increased retinal degeneration as compared to a mouse lacking said mutation,

wherein said mutation is equivalent to or mimics a human Cockayne Syndrome (CS), a Xeroderma pigmentosum (XP), a combined Xeroderma Pigmentosum - Cockayne Syndrome (XPCS), trichothiodystrophy (TTD), a Cerebro-Oculo-Facio-Skeletal syndrome (COFS) or an XPF-ERCC1 syndrome causing allele in the *Csa, Csb, Xpb, Xpd, Xpg, Xpf, Ttda* or *Ercc1* genes,

wherein the human Cockayne, COFS or XPCS syndrome causing mutation is selected from the group consisting of CS-associated mutations in: the human *Csa* gene: $Csa^{null/null}$, Y322ter, the human *Csb* gene: Csb^{null}, Q184ter, R453ter, W517ter, R670W, R735ter, G744ter, W851R, Q854ter, R947ter, P1042L, P1095R, R1213G, the human *Xpd* gene: G602D, G675R, 669fs708ter, the human *Xpb* gene: F99S, FS740, and for the human *Xpg* gene: R263ter, 659ter, and

wherein said genetically altered mouse has a mutation in at least two different genes each encoding a protein of the NER pathway and said genetically altered mouse has a combination of mutations selected from the group consisting of: $Csa^{null/null}/Xpa^{null/null}$, $Csa^{null/null}/Xpc^{null/null}$, $Csb^{G744ter/G744ter}/Xpa^{null/null}$, $Csb^{G744ter/}$

G744ter/*Xpc*$^{null/null}$, *Xpd*$^{G602D/G602D}$/*Xpa*$^{null/null}$, *Xpd*$^{R722W/R722W}$/*Xpa*$^{null/null}$, and *Xpd*$^{G602D/R722W}$/*Xpa*$^{null/null}$."

Claim 1 of **auxiliary request 4** reads:

"A method for the selection of a compound, or a mixture of compounds, said method comprising the steps of:
- providing a genetically altered mouse, wherein said mouse has at least one mutation in a gene encoding a protein of the Nucleotide Excision Repair (NER) pathway, said mutation causing a premature ageing phenotype as compared to a mouse lacking said mutation;
- exposing said genetically altered mouse, or part derived there from, to a compound, or a mixture of compounds;
- determining the effect of the compound, or the mixture of compounds, on the premature ageing phenotype of said genetically altered mouse; and
- selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces said premature ageing phenotype in said genetically altered mouse,
wherein said mutation is in a gene selected from the group consisting of: *Xpa, Xpb, Xpc, Xpd, Xpe, Xpf, Xpg, Xpv, Csa, Csb, Ttda, HR23A, HR23B* and *Ercc1*, and
wherein said premature ageing phenotype is increased osteoporosis and/or increased retinal degeneration as compared to a mouse lacking said mutation."

Claim 1 of **auxiliary request 5** reads:

"A method for the selection of a compound, or a mixture of compounds, said method comprising the steps of:
- providing a genetically altered mouse, wherein said mouse has at least one mutation in a gene encoding a protein of the Nucleotide Excision Repair (NER)

pathway, said mutation causing a premature ageing phenotype as compared to a mouse lacking said mutation;
- exposing said genetically altered mouse, or part derived there from, to a compound, or a mixture of compounds;
- determining the effect of the compound, or the mixture of compounds, on the premature ageing phenotype of said genetically altered mouse; and
- selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces said premature ageing phenotype in said genetically altered mouse,
wherein said mutation is in a gene selected from the group consisting of: *Xpa, Xpb, Xpc, Xpd, Xpe, Xpf, Xpg, Xpv, Csa, Csb, Ttda, HR23A, HR23B* and *Ercc1*, and
wherein said premature ageing phenotype is a shortened life span and/or increased retinal degeneration as compared to a mouse lacking said mutation."

VI. The opponent (hereafter: respondent) filed counter-arguments to the appeal.

VII. The board issued a communication as an annex to the summons to oral proceedings, expressing its preliminary opinion, and stating *inter alia* that since claim 1 of the main request did not concern a method for selecting compounds or mixtures of compounds which affect normal ageing, document D8 appeared to represent the closest prior art for the claimed subject-matter.

VIII. With letter of 20 April 2016, the appellant responded to the board's communication and submitted **auxiliary request 6**. Claim 1 of this request reads:

"A method for the selection of a compound, or a mixture of compounds, which prevents, inhibits, delays, or

reduces premature and normal ageing-related conditions in animals and in humans, said method comprising the steps of:
- providing a genetically altered mouse, wherein said mouse has at least one mutation in a gene encoding a protein of the Nucleotide Excision Repair (NER) pathway, said mutation causing a premature ageing phenotype as compared to a mouse lacking said mutation;
- exposing said genetically altered mouse, or part derived there from, to a compound, or a mixture of compounds;
- determining the effect of the compound, or the mixture of compounds, on the premature ageing phenotype of said genetically altered mouse; and
- selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces said premature ageing phenotype in said genetically altered mouse,
wherein said mutation is in a gene selected from the group consisting of: *Xpa, Xpb, Xpc, Xpd, Xpe, Xpf, Xpg, Xpv, Csa, Csb, Ttda, HR23A, HR23B* and *Ercc1*, and
wherein said premature ageing phenotype is a shortened life span, increased osteoporosis and/or increased retinal degeneration as compared to a mouse lacking said mutation;
- wherein said selected compound, or the mixture of compounds, prevents, inhibits, delays, or reduces premature and normal ageing-related conditions in animals and in humans."

IX. With letter of 28 May 2016, the respondent filed further submissions, raising objections against the admission of auxiliary request 6 into the proceedings as well as objections under Articles 123(2), 84 and 83 EPC with respect to this request.

X. With letter of 2 June 2016, the respondent informed the board that it would not be attending the scheduled oral proceedings.

XI. During the oral proceedings before the board, which were held on 9 June 2016 in the absence of the duly summoned respondent, the appellant filed **auxiliary request 7**. Claim 1 of this request reads:

"A method for the selection of a compound, or a mixture of compounds that inhibit, reduce or prevent ageing-related symptoms and conditions in mammals, said method comprising the steps of:
- providing a genetically altered mouse, wherein said mouse has at least one mutation in a gene encoding a protein of the Nucleotide Excision Repair (NER) pathway, said mutation causing a premature ageing phenotype as compared to a mouse lacking said mutation;
- exposing said genetically altered mouse, or part derived there from, to a compound, or a mixture of compounds;
- determining the effect of the compound, or the mixture of compounds, on the premature ageing phenotype of said genetically altered mouse; and
- selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces said premature ageing phenotype in said genetically altered mouse,
wherein said mutation is in a gene selected from the group consisting of: *Xpa, Xpb, Xpc, Xpd, Xpe, Xpf, Xpg, Xpv, Csa, Csb, Ttda, HR23A, HR23B* and *Ercc1*, and
wherein said premature ageing phenotype is a shortened life span, increased osteoporosis and/or increased retinal degeneration as compared to a mouse lacking said mutation;

- wherein said compound inhibits, reduces or prevents ageing-related symptoms and conditions in mammals."

XII. The following documents are mentioned in this decision:

D5: Hasty et al., SCIENCE (2003) 299: 1355
D6: Hasty et al., AGING CELL (2004) 3: 55
D8: US 6,333,153 B1
D9: Miller, AGING CELL (2004) 3: 47
D21: Massie et al., GERONTOLOGY (1984) 30: 371

XIII. The appellant's arguments, insofar as they are relevant for the present decision, can be summarised as follows:

Main request and auxiliary requests 1 to 5 - Article 56 EPC

The method of claim 1 of the main request involved an inventive step. The claimed invention was based on research with mouse models which had mutations similar to those occurring in human patients with progeria disorders and which showed the same kind of accelerated ageing phenotypes. The inventors had identified parallels between these progeroid mice having defects in genome maintenance and aged mice, and had thus found that accelerated ageing and normal ageing had the same single cause: they were the result of damage. At the priority date of the patent in suit, there was a prejudice in the art against this finding, and even today some experts did not accept that premature ageing and normal ageing were related.

The closest prior art was represented by document D21, which related to ageing research and to a compound that delayed ageing. The document described that Vitamin C was tested for its effect on the survival of mice. The

teaching of document D21 differed from the claimed method in that it concerned the testing, not the screening, of compounds and in that it used normal mice, not transgenic mice, as the model system.

Document D8 did not represent the closest prior art, because it related to cancer, not to ageing. The transgenic mice of document D8 had defects in the Msh2 gene, which was involved in mismatch repair, not in nucleotide excision repair (NER) like the mice in claim 1. This defect in the Msh2 gene induced cancer, and the transgenic mice died of cancer, not of old age. Moreover, when referring to symptoms of ageing in column 30, line 37, document D8 did not disclose any of the phenotypes specified in claim 1.

The difference between the disclosure of document D8 and the method of claim 1 was that different mice, a different disease and a different phenotype were used.

If starting from document D8 as the closest prior art, then the technical problem to be solved was how to provide for an improved method to select compounds that affect normal and premature ageing and are relevant to real human diseases other than cancer that are associated with ageing.

It was not obvious for the skilled person that the mice of document D5 would solve this problem, because nowhere in the prior art was it disclosed that any compound could affect the phenotype of prematurely ageing mice. A skilled person would thus not have had a reasonable expectation of success that a method of screening for compounds that prevent, inhibit, delay or reduce age-related symptoms could be based on the mouse models of document D5. It was the finding of the

inventors of the patent in suit that the phenotypes of these model animals were susceptible to compound intervention. Document D8 related to cancer diseases only and expressed merely a prophetic wish to screen for compounds affecting ageing. The last paragraph on page 1359 of document D5 referring to pharmaceutical interventions was also no pointer to use the mouse models for screening purposes. Additionally, the limitation of claim 1 to the phenotypes of a shortened life span, increased osteoporosis and/or increased retinal degeneration rendered the claimed method inventive. Consequently, claim 1 of the main request was allowable under Article 56 EPC.

The subject-matter of the claims of auxiliary requests 1 to 5 involved an inventive step for the same reasons as set out for the main request.

Auxiliary request 6 - Article 123(2) EPC

Claim 1 of auxiliary request 6 was allowable under Article 123(2) EPC, since it was based on the application as filed, notably on page 1, lines 13-28, page 25, lines 6-16, page 26, lines 1-4, and page 7, line 26 to page 8, line 28.

Auxiliary request 7 - Admission

Auxiliary request 7 should be admitted into the proceedings, because it addressed the board's objections under Article 123(2) EPC with respect to auxiliary request 6 and did not raise new issues. The newly introduced feature "ageing-related symptoms and conditions" would be understood by the skilled person in the context of the patent and was thus clear under Article 84 EPC.

XIV. The respondent's arguments submitted in writing, insofar as they are relevant for the present decision, can be summarised as follows:

Main request and auxiliary requests 1 to 5 - Article 56 EPC

The claimed methods were obvious from the prior art. The findings of the opposition division concerning a lack of an inventive step based on document D5 as the closest prior art in combination with document D8 were correct. Moreover, if document D21 was used as the closest prior art instead, then the skilled person would still arrive at the claimed subject-matter by combining this document with document D5.

Furthermore, there was no prejudice in the prior art that mouse models of accelerated ageing were unsuitable as models for age-related symptoms or for ageing research. Neither of the two opposing opinions as expressed in documents D9 and D6 represented a prejudice in the art.

Auxiliary request 6 - Admission

Auxiliary request 6 was late-filed and should not be admitted into the proceedings, because it could have been presented in the first instance proceedings. Moreover, this request raised new issues under Articles 123(2), 84 and 83 EPC.

Auxiliary request 6 - Article 123(2) EPC

Claim 1 of auxiliary request 6 did not comply with Article 123(2) EPC, because the application as filed

related only to compounds preventing, inhibiting, delaying or reducing certain disorders in mammals, not in animals in the wider sense. Moreover, there was no original disclosure of the combination of the newly introduced features with the remaining features of claim 1.

XV. The final requests of the parties were:

The appellant requested that the decision under appeal be set aside and that the patent be maintained as granted (main request), or, alternatively, that the patent be maintained on the basis of one of the following auxiliary requests:

- auxiliary requests 1 to 3 filed before the opposition division with letter of 13 February 2012, or
- auxiliary requests 4 and 5 filed with the statement of grounds of appeal, or
- auxiliary request 6 filed with letter dated 20 April 2016, or
- auxiliary request 7 filed during the oral proceedings of 9 June 2016.

The respondent had requested in writing that the appeal be dismissed.

Reasons for the Decision

1. The appeal is admissible.

Admission of document D21 into the proceedings

2. The appellant filed document D21 with the statement of grounds of appeal and submitted that this document -

not document D5, which had been used by the opposition division as the starting point for its analysis of inventive step - represented the closest prior art.

The board acknowledges that document D21 was filed as a reaction to the reasoning on a lack of inventive step in the opposition division's written decision and was thus filed as early as possible. Moreover, the respondent did not object to the introduction of document D21 into the proceedings.

Therefore, the board decided to admit the document into the proceedings.

Main request (claims as granted) - Article 56 EPC

Subject-matter claimed

3. Claim 1 relates to a method for the selection of a compound or a mixture of compounds, said method comprising *inter alia* the steps of
- exposing a genetically altered mouse having a specified type of mutation, which mutation causes a premature ageing phenotype, to a compound or a mixture of compounds,
- determining the effect of the compound or mixture of compounds on the premature ageing phenotype of said mouse, and
- selecting the compound or the mixture of compounds that prevents, inhibits, delays or reduces said premature ageing phenotype in said mouse,
wherein said premature ageing phenotype is a shortened life span, increased osteoporosis and/or increased retinal degeneration as compared to a mouse lacking said mutation.

Claim 1 thus concerns a method for the selection of a compound or a mixture of compounds, whereby a compound or a mixture of compounds is selected that prevents, inhibits, delays or reduces the premature ageing phenotype of a specified type of genetically altered mouse.

3.1 The appellant submitted that in the light of the description of the application as filed, claim 1 had to be understood as concerning a method for the selection of a compound or mixture of compounds which prevents, inhibits, delays or reduces not only premature ageing phenotypes but also normal ageing-related conditions in wild-type animals and in humans.

The board cannot follow this line of argument, because claim 1 does not state that the selected compound or mixture of compounds prevents, inhibits, delays or reduces the normal ageing of a wild-type animal or of humans.

Whereas several passages of the description do indeed express the hope or intention that ultimately some of the selected compounds would have an effect on normal ageing of wild-type animals or humans (see for instance page 8, lines 22-25, the paragraph bridging pages 25 and 26, or page 67, lines 20-22 of the application as filed), none of the examples shows such an effect for compounds or mixtures of compounds selected by using the claimed method. On the basis of the evidence provided by the patent in suit, the board considers that it is not plausible that all compounds or mixtures of compounds selected by performing the claimed method, for instance as described in Example 4, will necessarily prevent, inhibit, delay or reduce the normal ageing of a wild-type animal or of humans.

It is thus not an implicit feature of claim 1 that the claimed method is for selecting compounds or mixtures of compounds which affect normal ageing, i.e. the ageing process of wild-type animals and humans.

Closest prior art

4. Document D8 is considered to represent the closest prior art. It states that "The field of the invention is DNA mismatch protein binding, including animals useful as models for tumorigenesis, apoptosis, and aging" (column 1, lines 22-24) and describes a nullizygous mouse model ($Msh2^{-/-}p53^{-/-}$) useful for identifying compositions which affect the onset of a disease or disorder state caused by said mutations, in particular tumorigenesis (Example 2, column 47, lines 37-45).

Furthermore, in the section "background of the invention", the document notes that "Transgenic animals frequently serve as model systems for the study of various disease states and also provide an experimental system in which to test compounds for their ability to regulate disease. Nullizygous animals are similarly useful as experimental systems for the testing of compounds useful for diagnosis, treatment, or both, of disease" (column 3, lines 30-36).

Both document D8 and claim 1 thus concern methods for the selection of compounds or compositions which affect the phenotype of a genetically altered mouse model having a specified type of mutation.

4.1 The appellant submitted that document D21 rather than document D8 represented the closest prior art, because

it concerned the same purpose as the invention of the patent in suit, namely testing whether a compound can prevent, inhibit, delay or reduce ageing-related symptoms and conditions in mammals, whereas document D8 related to cancer, not to ageing, and did not refer to any of the phenotypes specified in claim 1.

The board cannot follow this line of argument. Document D21 relates to testing the effect of a well-known, pre-selected compound, namely Vitamin C, on the life span of normal, wild-type mice, and not to a method for the selection of a compound which affects the phenotype of a genetically altered mouse. As set out in points 3 and 3.1 above, the method according to claim 1 does not relate to testing compounds which affect the normal ageing of wild-type animals. Therefore, document D8 is considered to come closer to the claimed invention than document D21.

Problem to be solved and its solution

5. The methods disclosed in document D8 differ from the method of claim 1 in that a different type of genetically altered mice having a different phenotype is used.

6. Starting from document D8 as the closest prior art, the technical problem to be solved is the provision of a further method for the selection of compounds or compositions which affect the phenotype of a genetically altered mouse model.

In view of the disclosure in the patent in suit, in particular Example 4, the board is satisfied that the method of claim 1 provides a solution to this problem.

6.1 The board cannot follow the appellant's argument that the problem was to provide an improved method for the selection of compounds that affect normal and premature ageing and are relevant to real human diseases other than cancer that are associated with ageing. This is because the claimed method is not a method for the selection of compounds that affect normal ageing (see points 3 and 3.1 above), and no improvement over the methods of the closest prior art can thus be acknowledged for the claimed method.

Obviousness

7. The question to be answered by the board is therefore whether or not the skilled person, starting from the disclosure of document D8 and seeking a solution to the technical problem formulated in point 6 above, would have arrived at the claimed method without inventive effort.

8. Document D5 is a review article which relates to mouse models with defects in genome maintenance and to their use for understanding the molecular basis of ageing in humans (see abstract). In humans, several heritable mutations accelerate the onset of multiple ageing phenotypes, and many so-called progeroid disorders are linked to defects in genome maintenance (page 1355, column 3, paragraph 2). Mouse mutants defective in genome maintenance are available that display segmental progeria, like their human counterparts (page 1355, column 3, last paragraph).

The document further reports that deficiencies in nucleotide excision repair (NER) "are associated with three human hereditary disorders: xeroderma pigmentosum (XP), trichothiodystrophy (TTD), and Cockayne syndrome

(CS)" (page 1356, column 1, last four lines). "TTD is caused by point mutations in the XPD gene, different mutations in which can give rise to XP, CS, or TTD. (...) To model the XPD mutation that causes TTD, de Boer *et al.* (*13*) generated an analogous mutation in mice (*14*). (...) TTD mice prematurely show age-related phenotypes, including osteoporosis, osteosclerosis, gray hair, cachexia, and reduced life-span" (page 1356, paragraph bridging columns 2 and 3). "CS is caused by mutations in either CSA or CSB (...). CS mouse models are not as severely affected as humans, but as they age, they develop neurological abnormalities, including tremors, limb ataxia, and inner ear defects. They also show cachexia and retinal degeneration" (page 1357, column 1, second full paragraph).

Table 2 lists ageing-related phenotypes in mouse models with genome maintenance defects, *inter alia* mice with a genetic alteration in the Xpd gene (resulting in a reduced life span and in early osteopenia), the Ercc1 gene (resulting in a reduced life span) and the CSB gene (resulting in early retinal degradation).

Document D5 thus describes mice with a premature ageing phenotype which fall under the definition of the genetically altered mouse in claim 1.

9. The board considers that in view of the fact that the mouse models of document D5 display segmental progeria, like humans with hereditable segmental progeroid syndromes carrying the same mutations, the skilled person would have been motivated to use these mouse models as experimental systems to identify compounds that prevent, inhibit, delay or reduce said premature ageing phenotype.

10. The appellant has submitted that the skilled person would not have used the mice of document D5 in order to solve the problem posed, because he/she would not have reasonably expected from the prior art that any compound could affect the phenotype of prematurely ageing mice; this had been shown by the patent in suit for the first time.

The board cannot follow this line of argument, because the problem posed is merely the provision of a further method for the selection of compounds or compositions which affect the phenotype of a genetically altered mouse model, and there is nothing in document D5 that suggests that the described mouse models would not be suitable for use in such a method. The board is thus convinced that the skilled person faced with the problem posed would have applied the mouse models of document D5 in a method for the selection of compounds or compositions which affect their phenotype.

11. The appellant further submitted that claim 1 was non-obvious in view of the ageing phenotypes specified in the claim, i.e. a shortened life span, increased osteoporosis and/or increased retinal degeneration. The board cannot agree, because said phenotypes are explicitly mentioned in document D5 (see page 1356, column 3, line 7 for osteoporosis; page 1357, column 1, line 32 and Table 2 for retinal degeneration; page 1356, column 3, line 8 and Table 2 for a shortened/reduced life span) and would thus have been applied by a skilled person faced with the problem posed.

12. The board further observes that the question whether or not, at the priority date, a prejudice existed in the art against the use of prematurely ageing mouse models

in research into normal ageing is not relevant with respect to the issue of an inventive step of the claimed method, which does not concern normal ageing (cf. points 3 and 3.1 above).

13. In view of the above considerations, the board concludes that the skilled person would have arrived at the subject-matter of claim 1 in an obvious manner.

Therefore, the main request fails to meet the requirements of Article 56 EPC.

Auxiliary requests 1 to 5 - Article 56 EPC

14. Claims 1 of auxiliary requests 1 to 3 differ from claim 1 of the main request in that the mutation present in the genetically altered mouse is defined more specifically (see section V above).

Mutations as referred to in claims 1 of auxiliary requests 1 to 3 were however also known from document D5: with respect to claim 1 of auxiliary request 1, see page 1356, the paragraph bridging columns 2 and 3 referring to TTD mice with a mutation in the *Xpd* gene, with respect to claim 1 of auxiliary request 2, see page 1357, column 1, second full paragraph and Table 2 referring to *Csb* knock-out mice, and with respect to claim 1 of auxiliary request 3, see page 1356, column 2, penultimate line to column 3, line 26, referring to the crossing of $Xpd^{R722W/R722W}$ mice of reference (*14*) to $Xpa^{null/null}$ mice.

Therefore, claims 1 of auxiliary requests 1 to 3 lack inventive step for the same reasons as set out above for claim 1 of the main request.

15. Claim 1 of auxiliary request 4 differs from claim 1 of the main request in that the premature ageing phenotype is limited to increased osteoporosis and/or increased retinal degeneration, and claim 1 of auxiliary request 5 differs from claim 1 of the main request in that the premature ageing phenotype is limited to a shortened life span and/or increased retinal degeneration. However, each of the premature ageing phenotypes referred to in claims 1 of auxiliary requests 4 and 5 was known from document D5 to occur in NER-mutated mice (see point 11 above).

Therefore, claims 1 of auxiliary requests 4 and 5 lack inventive step for the same reasons as set out above for claim 1 of the main request.

16. It follows that auxiliary requests 1 to 5 fail to meet the requirements of Article 56 EPC.

Auxiliary request 6 - Admission and Article 123(2) EPC

17. Auxiliary request 6 was submitted by the appellant seven weeks before the oral proceedings, in response to the board's communication accompanying the summons. The board considered that this request addressed issues raised in its communication and could be dealt with without adjournment of the oral proceedings. Therefore, the board decided to admit auxiliary request 6 into the proceedings.

18. Claim 1 of auxiliary request 6 differs from claim 1 of the main request in that it states that the method is for the selection of a compound or mixture of compounds "which prevents, inhibits, delays, or reduces premature and normal ageing-related conditions in animals and in humans" and that the selected compound or mixture of

compounds "prevents, inhibits, delays, or reduces premature and normal ageing-related conditions in animals and in humans".

19. Article 123(2) EPC stipulates that a European patent may not be amended in such a way that it contains subject-matter which extends beyond the content of the application as filed. It is the established case law of the boards of appeal that the content of an application comprises the disclosure directly and unambiguously derivable from it.

20. Page 1, lines 13-28 of the application as filed, to which the appellant referred, states that the invention "provides a method for screening for compounds that inhibit, reduce or prevent ageing-related symptoms and conditions in mammals, such as those caused by genome maintenance disorders or those caused by normal, natural ageing processes during the normal life span of a mammal", and that the mouse models used "are particularly suited for testing of compounds, substances and compositions that will prevent, inhibit, reduce or delay an ageing-related parameter or several ageing-related parameters and/or phenotypes in mammals."

The board notes that said passages concern only the effect of compounds on certain conditions, parameters or phenotypes in **mammals**, and cannot thus provide a basis for an effect of compounds in humans and in animals in general, i.e. insofar as the animal is not a mammal.

21. Page 25, lines 13-16 of the application as filed refers to "a method for screening for (mixtures of) compounds that inhibit, prevent, delay or reduce to some extent

ageing-related symptoms and pathology in normally ageing mammals", and page 25, line 32 to page 26, line 2 states that "Hence the identified and/or selected compounds or compositions by the screening method of the current invention will provide new treatments and therapies for both premature and normal ageing-related conditions in animals and in humans".

Said passages thus teach that the method referred to is for screening compounds which affect ageing-related symptoms and pathology in **mammals**, and that the identified compounds will provide new treatments and therapies for ageing-related conditions in **animals** and in humans.

The appellant submitted that the claimed method was disclosed in said passages of the application as filed because in order for therapy to be possible, the compound would have to have the specified effect on animals.

The board cannot follow this argument, because there is no disclosure in the application as filed of actually selecting compounds that affect animals other than mammals. It may well be that some of the compounds selected for their effect on mammals could later turn out to also have an effect on non-mammalian animals, but this does not provide a direct and unambiguous disclosure of selecting the compounds for an effect on non-mammalian animals in the first place.

22. Similarly, page 8, lines 2-4 stating that "The invention provides a method for the selection of compounds or mixtures capable of inhibiting, delaying, preventing or curing premature ageing phenotypes in mammals" and lines 22-25 on the same page stating that

"Some of the above meant compounds/applications will provide novel treatments and therapies for ageing-related conditions, more in particular premature ageing-related conditions caused by defective GM systems, as well as natural ageing symptoms in animals and in humans" cannot provide a direct and unambiguous disclosure of the claimed method for the selection of compounds which affect ageing-related conditions in animals other than mammals.

23. Therefore, claim 1 of auxiliary request 6 does not comply with Article 123(2) EPC.

Auxiliary request 7 - Admission

24. Auxiliary request 7 was filed only at the oral proceedings before the board, as a further attempt to overcome the board's objections with respect to the higher-ranking requests.

25. Under Article 13(1) RPBA, such late-filed requests are considered amendments to a party's case and admissible only at the board's discretion. Said discretion is to be exercised in view of *inter alia* the complexity of the new subject matter submitted, the current state of the proceedings and the need for procedural economy.

26. Claim 1 of auxiliary request 7 differs from claim 1 of the main request in that it states that the method is for the selection of a compound or mixture of compounds "that inhibit, reduce or prevent ageing-related symptoms and conditions in mammals" and that the selected compound or mixture of compounds "inhibits, reduces or prevents ageing-related symptoms and conditions in mammals."

27. With respect to the clarity of these amendments under Article 84 EPC, the following is to be noted.

The method of claim 1 comprises the step of selecting the compound, or the mixture of compounds, that prevents, inhibits, delays or reduces the premature ageing phenotype of the genetically altered mouse, said premature ageing phenotype being a shortened lifespan, increased osteoporosis and/or increased retinal degeneration. The newly introduced feature "inhibit(s), reduce(s) or prevent(s) ageing related symptoms and conditions in mammals" could thus be understood as merely referring to the effect on the premature ageing phenotypes as specified in the claim (i.e. shortened life span, increased osteoporosis and/or increased retinal degeneration) and thus as not having any limiting effect on the claim. The appellant, however, submitted that the newly introduced feature was indeed limiting, which would mean that the selected compound or mixture of compounds had to show an inhibiting, reducing or preventing effect on ageing-related symptoms and conditions other than the specified premature ageing phenotypes of a shortened life span, increased osteoporosis and/or increased retinal degeneration, without any indication in the claim as to what these ageing-related symptoms and conditions might be. This gives rise to doubts as to the clarity of the subject-matter for which protection is sought.

The amendments made in claim 1 of auxiliary request 7 thus raise new issues under Article 84 EPC.

28. Consequently, the board made use of its discretionary power under Article 13 RPBA and decided not to admit auxiliary request 7 into the proceedings.

Order

For these reasons it is decided that:

The appeal is dismissed.

The Registrar: The Chairman:

N. Maslin U. Oswald

Decision electronically authenticated