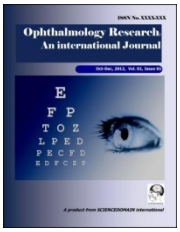

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Aldose Reductase Inhibitors for Diabetic Cataract: A Study of Disclosure Patterns in Patents and Peer Review Papers

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Authors' contributions

This work was carried out in collaboration between all authors. Author MHAM designed the study, performed the analysis, and drafted the manuscript. Authors EM and PMM performed data curation and iterative information retrieval. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To investigate, for 13 aldose reductase inhibitors that had been in development for diabetic cataract, whether patent documents could provide earlier dissemination of knowledge to the ophthalmology community than peer review papers.
Methodology: Searches for intellectual property disclosures were conducted in our internal database of ophthalmology patent documents, and were supplemented by online searches in the public Espacenet and Google Patents databases. Searches for peer review papers were performed in Pub Med and Google Scholar, and in our internal database of machine-readable ophthalmology publications.
Results: For sorbinil, tolrestat, fidarestat and GP-1447 patent documents clearly preempted the peer review literature in terms of data-supported information on potential effectiveness in diabetic cataract, typically by 7-17 months. For alrestatin, zenarestat, zopolrestat, indomethacin, and quercitrin academic journals were clearly first to properly report this therapeutic utility, preempting the corresponding patents by 6 months to several years. For ponalrestat, risarestat, epalrestat, and lidorestat claims of utility in diabetic cataract were first made in patent documents, but with insufficient or incomplete support.
Conclusion: Our results suggest that including patent documents in the routine monitoring of newly disclosed knowledge could significantly improve the

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comprehensiveness of the literature base in ocular pharmacology, and has the potential to alert researchers to emerging drug candidates earlier than reports in the peer review literature.

Keywords: Cataract; diabetes complications; diabetes mellitus, experimental; aldose reductase; patents as topic; peer review; databases, bibliographic; information storage and retrieval.

1. INTRODUCTION

Although patent documents are freely available on the internet in full text, academic research has traditionally shown a strong tendency to disregard them as a source of scientific information. The most frequently named reasons include: the semantics of patents, which tend to use legalistic, redundant and convoluted language; the incompatibility of ontologies and search logic with systems universally used for peer review literature search; superficial disclosures that are often marginal compared to the broad claims being made; and a general perception that, given the continuing proliferation of peer review journals, information published only in patent documents can at best be of minor relevance to academic research. The field of ophthalmology is no exception to this general attitude.

What contribution patent documents can make to the dissemination of emergent knowledge in the field of eye medicine is not a question for which a single answer exists. However, several relatively straightforward approaches can be conceived to investigate key aspects of the issue. One such method is to evaluate whether insights with practical medical applications first become publicly available through peer review journals or patent documents. If the information eventually appears in both, the sequence and the delays between the two routes can be determined. We have undertaken such an exemplary study for the pharmacological treatment and prevention of diabetic cataracts with aldose reductase inhibitors (ARIs).

The investigation we report here traces the patent and peer review disclosures for thirteen ARIs that became drug candidates for diabetic complications, including cataracts. The particular field was chosen because ARIs were developed over a long time, and originated in all regions of the world conducting significant drug discovery and development.

The realization of the role played by polyol formation in the cataractous lens of chronically galactose-fed rats dates back to the late 1950s [1], and six years later the presence of aldose reductase, the enzyme that is ultimately responsible for diabetic complications resulting from protein glycation, was demonstrated in the bovine lens [2]. The peer review literature recorded the first mention of a beneficial effect of an ARI in explanted cataractous lenses in June 1968 [3]. The agent was 3,3'-tetramethylene glutaric acid (1,1-cyclopentanediacetic acid), a lead compound which was later proven ineffective in vivo [4].

These findings triggered a sequence of peer review papers investigating ARIs as potential cataract treatments that is continuing even today, and in parallel developers made corresponding claims in patent documents. The following sections describe how these disclosures were identified and investigated for relevance.

2. METHODOLOGY

For the patent document side of the project, we searched the comprehensive ophthalmology module of our annotated patent database, THIRDSPACE which provides fully corrected text and, to a limited extent, machine-searchable chemistry information [5]. Supplemental text-based patent searches, intended to capture any information that is only tangential to ophthalmology but relevant to the purpose of this analysis, were performed in the public databases Espacenet and Google Patents. Details of the patent landscape for cataract pharmacology that emerged from a previous search have been described elsewhere [6].

Searches for peer review papers were performed online in PubMed and Google Scholar by combining the MeSH terms ["aldose reductase" OR "aldehyde reductase"] with "cataract." Supplemental searches were carried out in our internal database of machine-readable ophthalmology publications. For each compound the earliest patent and peer review document pertaining to cataract was identified.

Table 1 summarizes the search terms for two additional, independent cross-database searches that were based on (a) the names and research codes for each of the 13 ARI compounds, and (b) a bipartite chemical search that used meaningful fragments of various versions of the chemical names and (for the THIRDSPACE ophthalmology database only) the abbreviated form of the IUPAC International Chemical Identifier which encodes the unique chemical structure of a compound in string format.

Results from each of the three searches were winnowed for content relevant to our investigation (i.e., utility of specific ARIs for diabetic cataract had to be explicitly stated), then merged into a data pool, and curated into a working database.

Table 1. Search terms used to identify information concerning aldose reductase inhibitors applied to treatment and/or prevention of diabetic cataract

Names and research codes	Chemical designations	InChIkey
Alrestatin AY-22,284 HIC 016G NSC 299132	(1,3-Dioxo-1H-benzo[de]isoquinolin-2(3H)-yl)acetic acid (IUPAC) 1,3-Dioxo-1H-benz[de]isoquinoline-2(3H)-acetic acid	GCUCIFQCGJIRNT-UHFFFAOYSA-N
Sorbinil CP-45,634	(4S)-6-Fluorospiro[2,3-dihydrochromene-4,5'-imidazolidine]-2',4'-dione (IUPAC) (S)-6-Fluorospiro(chroman-4,4'-imidazolidine)-2',5'-dione (4S)-6-Fluorospiro[2H-1-benzopyran-4(3H),4'-imidazolidine]-2',5'-dione (S)-6-Fluoro-2,3-dihydrospiro[4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione (4S)-6-Fluoro-2,3-dihydrospiro[4H-1-benzopyran-4,4'-imidazolidine]-2',5'-dione (4S)-6'-Fluoro-2',3'-dihydrospiro[imidazolidine-4,4'-[4H][1]benzopyran]-2,5-dione	LXANPKRCLVQAOG-NSHDSACASA-N

Ponalrestat (INN) Statil(TM) Statyl(TM) Prodiax(TM) ICI-128436 MK-538	2-[3-[(4-Bromo-2-fluorophenyl)methyl]-4-oxophthalazin-1-yl]acetic acid (IUPAC) 3-(4-bromo-2-fluorobenzyl)-4-oxo-3H-phthalazin-1-ylacetic acid	LKBFFDOJUKLQNY-UHFFFAOYSA-N
Tolrestat (INN) Tolrestatin Alrestin(TM) Alredase(TM) Loredase(TM) AY-27,773	*N*-{[6-Methoxy-5-(trifluoromethyl)-1-naphthyl]carbothioyl}-*N*-methylglycine (IUPAC) *N*-[[5-(Trifluoromethyl)-6-methoxy-1-naphthalenyl]-thioxomethyl]-*N*-methylglycine *N*-[[6-methoxy-5-(trifluoromethyl)-1-naphthalenyl]thioxomethyl]-*N*-methylglycine	LUBHDINQXIHVLS-UHFFFAOYSA-N
Risarestat (INN) CT-112	5-(3-Ethoxy-4-pentoxyphenyl)-1,3-thiazolidine-2,4-dione (IUPAC) 5-(3-ethoxy-4-pentyloxyphenyl)-2,4-thiazolidinedione	CRPGRUONUFDYBG-UHFFFAOYSA-N
Fidarestat (INN) Aldos(TM) SNK-860	(2R,4S)-6-Fluoro-2',5'-dioxo-2,3-dihydrospiro[1-benzopyran-4,4'-imidazolidine]-2-carboxamide (IUPAC) (2S,4S)-6-Fluoro-2',5'-dioxo-2,3-dihydrospiro[chromene-4,4'-imidazolidine]-2-carboxamide (2S,4S)-2-Aminoformyl-6-fluoro-spiro[chroman-4,4'-imidazolidine]-2',5'-dione	WAAPEIZFCHNLKK-UFBFGSQYSA-N
Zenarestat (INN) FR-74366 FK-366 CI-1014	2-[3-[(4-Bromo-2-fluorophenyl)methyl]-7-chloro-2,4-dioxoquinazolin-1-yl]acetic acid (IUPAC) [3-(4-Bromo-2-fluorobenzyl)-7-chloro-2,4-dioxo-1,2,3,4- tetrahydroquinazolin-1-yl] acetic acid [3-(4-Bromo-2-fluorobenzyl)-7-chloro-2,4-dioxo-3,4-dihydro-1(2H)-quinazolinyl]acetic acid 2-(7-Chloro-3-(4-bromo-2-fluorobenzyl)-1,2,3,4-tetrahydro-2,4-dioxoquinazolin)-1-acetic acid	SXONDGSPUVNZLO-UHFFFAOYSA-N
Epalrestat (INN) Kinedak(TM) ONO-2235 ONO-2	2-[(5Z)-5-[(E)-2-Methyl-3-phenylprop-2-enylidene]-4-oxo-2-sulfanylidene-1,3-thiazolidin-3-yl]acetic acid (IUPAC) [5-(2-Methyl-3-phenyl-allylidene)-4-oxo-2-thioxo-thiazolidin-3-yl]-acetic acid (E)-3-Carboxymethyl-5-[(2E)-methyl-3-phenylpropenylidene] rhodanine 5-[(Z,E)-β-Methylcinnamylidene]-4-oxo-2-thioxo-3-thiazolidineacetic acid 5-((1Z,2E)-2-Methyl-3-phenylpropenylidene)-4-oxo-2-thioxo-3-thiazolidineacetic acid	CHNUOJQWGUIOLD-NFZZJPOKSA-N
Zopolrestat (INN) Alond(TM) Xedia(TM) CP-73850	2-[4-Oxo-3-[[5-(trifluoromethyl)-1,3-benzothiazol-2-yl]methyl]phthalazin-1-yl]acetic acid (IUPAC) 3,4-Dihydro-4-oxo-3-[[5-(trifluoromethyl)-2-	BCSVCWVQNOXFGL-UHFFFAOYSA-N

	benzothiazolyl] methyl]-1-phthalazineacetic acid 2-[4-Oxo-3-[5-(trifluoromethyl)benzothiazol-2-ylmethyl]-3,4-dihydrophthalazin-1-yl]acetic acid	
GP-1447	2-[3-Methyl-5-[(4,5,7-trifluoro-1,3-benzothiazol-2-yl)methyl]phenyl]acetic acid (IUPAC) 3-[(4,5,7-Trifluorobenzothiazol-2-yl)methyl]-5-methylphenylacetic acid	BEGJKQPWVJRBPU-UHFFFAOYSA-N
Lidorestat (INN) IDD-676	2-[3-[(4,5,7-Trifluoro-1,3-benzothiazol-2-yl)methyl]indol-1-yl]acetic acid (IUPAC) 3-[(4,5,7-trifluorobenzothiazol-2-yl)methyl]indole-N-acetic acid	KYHVTMFADJNSGS-UHFFFAOYSA-N
Indomethacin	2-[1-(4-Chlorobenzoyl)-5-methoxy-2-methylindol-3-yl]acetic acid	CGIGDMFJXJATDK-UHFFFAOYSA-N
Quercitrin Quercetrine Quercimeline Quercitroside Thujin	2-(3,4-Dihydroxyphenyl)-5,7-dihydroxy-3-[(2S,3R,4R,5R,6S)-3,4,5-Trihydroxy-6-methyloxan-2-yl]oxychromen-4-one (IUPAC) Quercetin 3-O-rhamnoside	OXGUCUVFOIWWQJ-HQBVPOQASA-N

3. RESULTS AND DISCUSSION

3.1 Disclosure Sequence for Aldose Reductase Inhibitors for Diabetic Cataract

3.1.1 Alrestatin

The first ARI to undergo actual early-stage drug development for diabetic cataract was Ayerst Pharmaceuticals' Alrestatin, for which a peer review paper published in December 1973 reported oral doses to markedly decrease the accumulation of polyols in the lenses of rats with streptozotocin-induced diabetes. In addition, treatment of rats on a high-galactose diet with Alrestatin effectively suppressed the formation of cataracts [7].

The corresponding U.S. patent [8], which has a July 1972 priority date, reached the public six months after the peer review paper had been published. Alrestatin is the compound described in Example 1. The patent document specifies the use of sterile buffered solutions (0.5-2.0% w/v) as eye drops.

3.1.2 Sorbinil

A United States patent by Pfizer, Inc. published in September 1978 [9] provided the first disclosure of Sorbinil (Example XXII), its in vitro performance against aldose reductase from calf lenses, and demonstrated its in vivo benefit in a rat cataract prevention study. When given orally to streptozotocinized rats at 2.5 mg/kg twice daily for seven days, 71% reduction in lens sorbitol levels had occurred relative to to the control group. In rats on a high galactose diet sorbinil (10 and 20 mg/kg p.o.) reduced lens galactitol values by 40 and 72 percent, respectively.

Two papers published back-to-back in the April 1979 supplement issue of *Metabolism* reported that Sorbinil effectively delayed cataract formation in galactose-fed rats at oral

doses of 5 mg/kg/day [10], and that the de-epithelialized corneas of diabetic rats regenerated the epithelium much quicker than controls [11].

3.1.3 Ponalrestat

Imperial Chemical Industries had a patent application specifying ponalrestat as the preferred compound published in July 1979 [12]; a Ki value of 20 nM is reported for inhibition of aldose reductase from bovine lenses, but quantitative data for in vivo cataract studies are absent. Only in 1985 a peer review paper [13] reported that ponalrestat completely prevented the development of cataracts in diabetic rats at oral doses of 25 mg/kg/d.

3.1.4 Tolrestat

This compound represented Wyeth-Ayerst's final (and initially successful) attempt to commercialize an orally active ARI (tolrestat was marketed as Alredase and Alrestin in some countries until it was withdrawn because of liver toxicity in 1997), although cataract was not among its approved uses.

A European patent application [14] dating from September 1982 represents the first explicit mention (as Preparation Example 23) of tolrestat in the context of cataract. At oral doses of 11 mg/kg/day given for four days, a 10% reduction of dulcitol content was observed in the lenses of galactosemic rats.

A March 1984 paper in the *Journal of Medicinal Chemistry* [15] presented similar rudimentary information. It was followed up by a paper dedicated to cataract a year later [16]. In rats fed 30% galactose for 31 days, no cataracts were detected at a tolrestat dose of 35 mg/kg/day. In rats given tolrestat with the diet for 14 days, then rendered severely galactosemic, and subjected to continued treatment with tolrestat at 43 mg/kg/day, no lens changes were detected after 207 days.

3.1.5 Risarestat

In its Example 6, a European patent application jointly filed by the Japanese companies Takeda and Senju and published in August 1981 [17] describes the synthesis of this ARI, gives its in vitro inhibition constant against partially purified aldose reductase from human placenta (41.8% at 1 μM), and specifies a phosphate-buffered polyvinylalcohol-based eyedrop formulation specifically for risarestat. An assay demonstrating inhibition of swelling of explanted rat lenses gives data for seven compounds but not for risarestat.

The companion peer review paper [18] which detailed these findings further was published 14 months later. The next identifiable peer review paper discussing risarestat with respect to ophthalmology [19], published in 1986, addresses not cataract but diabetic corneal epitheliopathy which is not explicitly mentioned in the patent application claiming risarestat. Results from a successful clinical trial for this condition were reported almost 20 years later [20].

3.1.6 Fidarestat

For this ARI that originated at Sanwa Kagaku Kenkyusho Co., Ltd. the disclosure is provided by a European patent application published in September 1986 [21]. It defines fidarestat in Example 2 and gives inhibitor data for rat lenses in vitro, but in vivo data from

galactosemicrats are provided only for sciatic nerve. Although cataract is implicitly covered by the umbrella term "diabetic complications," only peripheral neuropathy appears supported by the data. In 1991 Sanwa made up for this with a much more specific patent application [22] which apparently did not go beyond the Japanese national stage. In the eyedrop formulations intended for treating cataract, fidarestat is the preferred ARI, "useful in prevention or treatment for cataract and having good long term stability, cornea permeability and transition to the crystalline lens."

Up to this point, and apparently until 1999 [23], the peer review literature on fiderestat addressed its utility only for diabetic retinopathy and neuropathy but not for cataract.

3.1.7 Zenarestat

Because Fujisawa's European patent application for zenarestat [24], published in April 1987, discloses only data on sorbitol content in sciatic nerve of diabetic rats, a February 1990 Japanese peer review paper [25] has to be regarded as the first document regarding diabetic cataract. The abstract states that a concentration of 0.075% FR74366 both prevented and reversed cataracts in galactosemic rats, a concentration of 0.025% being less effective.

3.1.8 Epalrestat

Ono Pharmaceuticals' ARI and data supporting its utility in diabetic cataract first became public through a European patent application published in March 1982 [26], but the disclosed data on sorbitol accumulation in explanted rat lenses (50% inhibition at concentrations of 1 - 10 μM) apply to all disclosed ARIs conforming to a general formula. Specific data for epalrestat ("Sorbitol accumulation in the isolated rat lenses were effectively inhibited during incubation with 8-50 mM glucose by ONO-2235 at a concentration of about 1 μM") are given in a peer review paper [27] that was published two years later.

Epalrestat has been approved for the treatment of diabetic neuropathy in Japan and other Asian countries, where it is available as a generic drug.

3.1.9 Zopolrestat

Pfizer's July 1990 U.S. patent [28] mentions zopolrestat in the context of diabetic cataract treatment but without giving data, which the inventors and others disclosed in a peer review paper half a year later [29].

3.1.10 GP-1447

The Japanese company, Grelan Pharmaceuticals had its European patent application for this compound - which apparently never acquired an international non-proprietary name - published in June 1996 [30]. GP-1447 is Example 1(ii), and its data on sorbitol accumulation in lenses of rats with experimentally induced diabetes are given in the patent document's Table 3. The corresponding peer review paper [31] was published seven months later.

3.1.11 Lidorestat

One of the most recent ARIs, lidorestat originated at the privately held Institutes of Pharmaceutical Discovery as a derivative of GP-1447. Its first mention is in an international patent convention treaty application published in 1999 [32]. However, this document reveals

only in vitro IC50 values for human aldose reductase, and merely mentions cataract as one of the diabetic complications for which lidorestat should be suitable as a treatment. Peer reviewed publications were late to publish, stating only in 2005 that lidorestat lowers lens sorbitol levels in the 5-day streptocozin-induced diabetic rat model with an ED50 p.o. dose of 4.5 mg/kg/d and good drug penetration into the anterior chamber of the eye (1.45 µgequiv/g when dosed at 10 mg/kg p.o.) [33].

3.1.12 Indomethacin

A July 1982 paper in *Experimental Eye Research* reported that several of the most popular non-steroidal anti-inflammatory drugs, including indomethacin, are potent ARIs [34]. The publication of a U.S. patent for this application of indomethacin followed in April 1984, claiming a July 1981 priority date. In vitro inhibition is said to be 13% and 52% at 1 µM and 10 µM, respectively. Claim 3, which is for topical application of sterile aqueous solutions of indomethacin to the eye to treat diabetic cataract or retinopathy, is not supported by in vivo data.

3.1.13 Quercitrin

Sarget Laboratories of France stated on the cover page of a U.S. patent that was published in July 1980 [35] that this rhamnoseglycosid of quercetin is "effective in modifying the evolution of diabetic cataracts." This is not reflected in the granted claims. The reason is immediately apparent from the fact that at least two peer review papers had reported this biological activity in June 1975 [36] and January 1977 [37], respectively - well before the earliest French patent application date of May 1977. Remarkably, the utility of quercitringallate in diabetic cataract models was reported again by a Korean group in 2011 [38].

3.2 Discussion

Our analysis of thirteen exemplary aldose reductase inhibitors shows that in four of these cases (sorbinil, tolrestat, fidarestat and GP-1447) patent documents preempted the peer review literature by reporting the utility of these compounds in the treatment and/or prevention of diabetic cataract, with specific experimental data in support. With four additional compounds (ponalrestat, risarestat, epalrestat and lidorestat) the preemption was only by statement of concept, presenting data that were not unequivocally associated with the compound in question, or had only partial relevance for diabetic cataract while later peer review papers provided solid information in this respect. In five cases (alrestatin, zenarestat, zopolrestat, indomethacin, and quercitrin) peer review journals were clearly first in reporting information on utility in diabetic cataract.

In those four cases where patent documents provided the earliest availability of relevant information, the timeline advantage offered by inclusion of patent documents ranged from 7 months (sorbinil and GP-1447) to 17 months (tolrestat). We do not consider the 13-year delay for fidarestat to be significant, given the fact that this ARI had been under development for retinal complications of diabetes during much of this time.

For the five ARI compounds which had substantial and unequivocal information on utility in diabetic cataract disclosed by peer review papers first, the advantage ranged from 6 months (alrestatin and zopolrestat) to more than five years (for quercitrin). Indomethacin and

zenarestat were intermediate cases, the academic literature being 22 months and 34 months ahead of the patent disclosures, respectively.

No such clear-cut situation exists for the four ARIs for which the initial disclosure in their patents was implicit or ambiguous. Ponalrestat was evaluated against aldose reductase from bovine lenses, which is a reasonable indicator for potential utility in diabetic cataract. However this in vitro assay does not reveal whether the compound penetrates to its site of action from the bloodstream or through the cornea in experimental animals. A similar situation exists for epalrestat and lidorestat. For risarestat, the disclosure most closely related to use in diabetic cataract is made in the (earlier) patent document; while these data do not provide the hard evidence that would be desirable, the (later) peer review literature never addressed the subject of cataract at all.

4. CONCLUSION

Our analysis shows that, for the particular case of aldose reductase inhibitors as potential therapeutics and/or prophylactics for diabetic cataract, inclusion of published patent documents in a comprehensive literature surveillance algorithm could have provided third-party researchers with a considerable advantage in a significant fraction of cases. Moreover, even if disclosure in an early patent document was incomplete in an academic sense, researchers would have been provided with a valuable alert to a particular compound and its immediate congeners. The fact that no ARI has been approved for the treatment or prevention of diabetic cataract in humans has mostly economic reasons (cataract surgery with intraocular lens insertion is one of the most cost-effective medical interventions worldwide) and cannot, in our opinion, distract from the potential significance of our findings although we are aware of some limitations.

This study was highly longitudinal in nature, with the majority of the disclosures reaching back into times where neither peer review papers nor patent documents were available to the public in near-real time, and were not as easily searchable online, if at all. It is also important to note that our investigation covers a period during which the international patenting system landscape underwent significant changes. This was mostly caused by the increased acceptance of the European and Patent Convention Treaty patent systems which enforce public disclosures of patent applications within 18 months from the filing date, irrespective of the examination status. Before the mid-1990s United States patents emerged into the public only when and if they were granted, after an examination process that could take much longer than 18 months. The publication speed advantage of academic journals therefor diminished over time, although it never disappeared entirely. (Most manuscripts that are finally accepted for publication spend less than 18 months in peer review.)

While the wide time frame allowed us to capture disclosure patterns across an entire pharmacological class in a narrow therapeutic application, we are aware that a more cross-sectional design -- covering a broader ophthalmological field but focusing on the more immediate past -- would complement the present study with valuable insights from which more directly applicable lessons on integrated searching of emergent knowledge could be drawn.

Finally, our study was performed using a highly focused ophthalmology patent database that could draw on fully corrected document texts and searchable chemistry information. Although this database was exclusively assembled from information that is publicly available online, its considerable added value is not available to the public at this time. Public

databases covering peer review journals operate only on abstracts and index terms, and offer little if any directly searchable chemistry information. Although we tried to compensate by doing additional full-text searches in our ophthalmology peer review paper database this might have introduced an identification bias favoring patent documents. We are also aware that the current lack of external access to our high-content patent database complicates independent verification of our results. However, all raw data on which it is being assembled are available by downloading the cited patent documents from the PatentScope and Espacenet databases which are freely accessible at the World Intellectual Property Office and the European Patent Office, respectively.

In summary, our case study demonstrates - within the limits discussed above - that ophthalmology research could realize considerable advantages by including patent documents into the search frame when monitoring the state of science.

CONSENT

Not applicable.

ETHICAL APPROVAL

Not applicable.

COMPETING INTERESTS

The authors declared that no competing interests exist.

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