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(12) **United States Patent**
**Ashley**

(10) **Patent No.: US 7,232,572 B2**
(45) **Date of Patent: *Jun. 19, 2007**

(54) **METHODS OF TREATING ROSACEA**

(75) Inventor: **Robert A. Ashley**, Tucson, AZ (US)

(73) Assignee: **CollaGenex Pharmaceuticals, Inc.**, Newtown, PA (US)

( * ) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

This patent is subject to a terminal disclaimer.

(21) Appl. No.: **11/061,866**

(22) Filed: **Feb. 18, 2005**

(65) **Prior Publication Data**

US 2005/0209202 A1 Sep. 22, 2005

**Related U.S. Application Data**

(63) Continuation of application No. 10/272,499, filed on Oct. 15, 2002, now Pat. No. 7,014,858, which is a continuation of application No. 10/117,709, filed on Apr. 5, 2002.

(60) Provisional application No. 60/281,916, filed on Apr. 5, 2001, provisional application No. 60/325,489, filed on Sep. 26, 2001.

(51) **Int. Cl.**

| | |
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| ***A61K 9/20*** | (2006.01) |
| ***A61K 9/48*** | (2006.01) |
| ***A61K 9/68*** | (2006.01) |
| ***A01N 37/18*** | (2006.01) |

(52) **U.S. Cl.** ..... **424/401**; 424/440; 424/451; 424/464; 514/152

(58) **Field of Classification Search** ..... None
See application file for complete search history.

(56) **References Cited**

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| 2003/0139380 | A1 | 7/2003 | Ashley | |

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*Primary Examiner*—Susan Tran
(74) *Attorney, Agent, or Firm*—Hoffmann & Baron, LLP

(57) **ABSTRACT**

A method of treating rosacea in a human in need thereof comprising administering to said human a tetracycline compound in an amount that is effective to treat rosacea, but has substantially no antibiotic activity.

**26 Claims, 1 Drawing S**

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**26 Claims, 1 Drawing Sheet**

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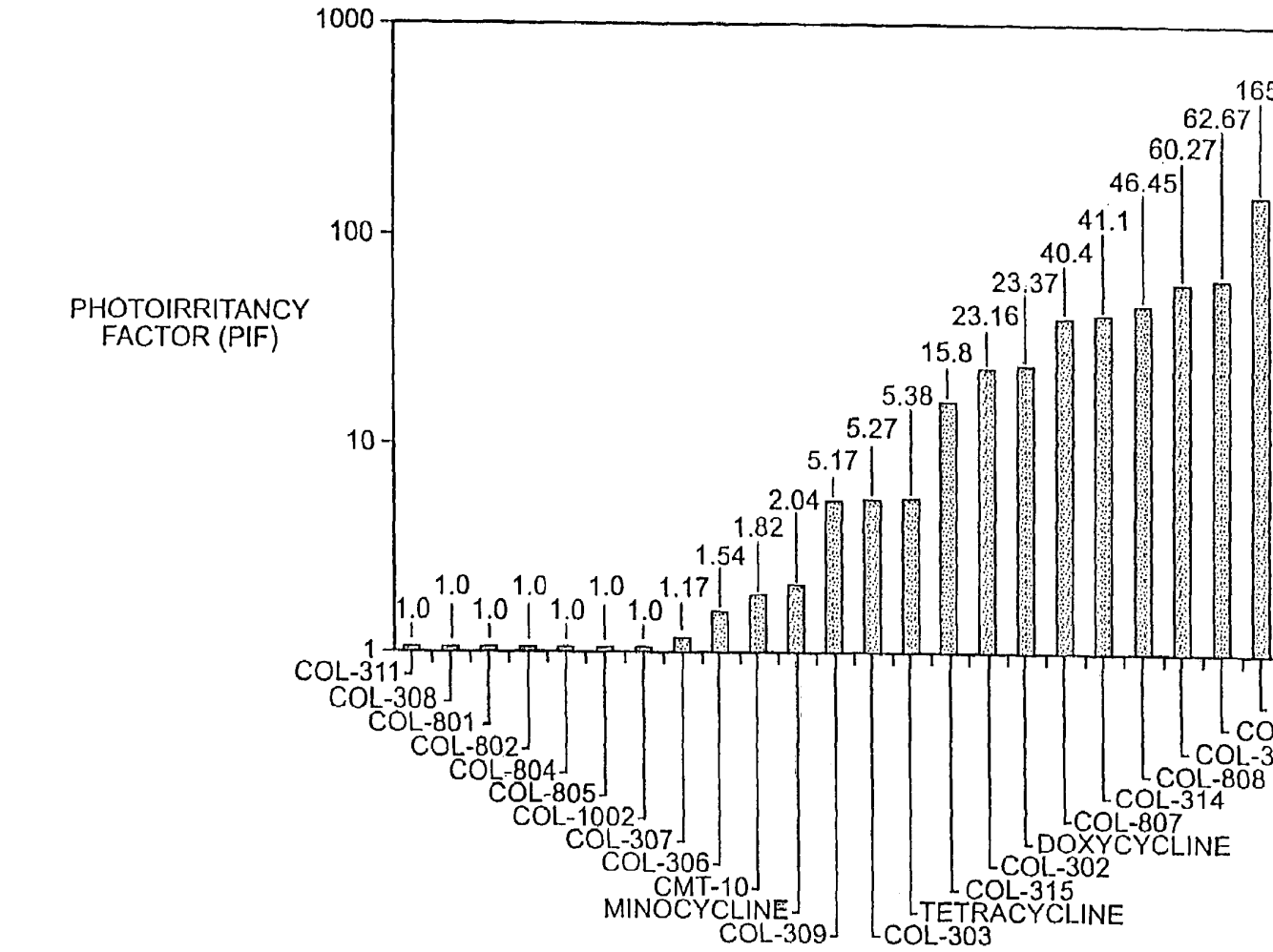
FIG. 1 PHOTOTOXICITY INDEX



# METHODS OF TREATING ROSACEA

## CROSS-REFERENCE TO RELATED APPLICATION

This application is a continuation of U.S. application Ser. No. 10/272,499, filed Oct. 15, 2002 now U.S. Pat. No. 7,014,858, which is a continuation of co-pending U.S. application Ser. No. 10/117,709, filed Apr. 5, 2002. This application claims benefit of U.S. Provisional Application No. 60/281,916, filed Apr. 5, 2001; and U.S. Provisional Application No. 60/325,489, filed Sep. 26, 2001, all of which are incorporated herein by reference.

## BACKGROUND OF THE INVENTION

Acne is a common disease characterized by various types of lesions. The areas affected typically are areas of the skin where sebaceous glands are largest, most numerous, and most active. The lesions associated with acne are usually categorized as either non-inflammatory or inflammatory.

Non-inflammatory lesions include comedones. Comedones appear in two forms, open and closed. Comedones are thought to arise from abnormal follicular differentiation. Instead of undergoing shedding and discharge through the follicular orifice, abnormal desquamated cells (keratinocytes) become unusually cohesive, forming a microcomedo or a microscopic hyperkeratotic plug in the follicular canal. The progressive accumulation of these microcomedones lead to visible comedones.

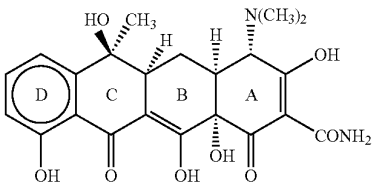
In its mildest form, acne is a more or less superficial disorder characterized by slight, spotty skin irritations. In such cases, ordinary skin hygiene is typically a satisfactory treatment. In the more inflammatory types of acne, however, pustules; infected cysts; and in extreme cases, canalizing, inflamed and infected sacs appear. Without effective treatment, these lesions may become extensive and leave permanent, disfiguring scars.

Microorganisms, especially *Propionibacterium acnes*, are strongly implicated in the pathogenesis of acne. The microorganisms are thought to release microbial mediators of inflammation into the dermis or trigger the release of cytokines from ductal keratinocytes.

Accordingly, the efficacy of antibiotics in treating acne is thought to be due, in significant part, to the direct inhibitory effect of the antibiotics on the growth and metabolism of these microorganisms. Systemically-administered tetracycline antibiotics, especially minocycline hydrochloride, are particularly effective in treating acne.

The tetracyclines are a class of compounds of which tetracycline is the parent compound. Tetracycline has the following general structure:

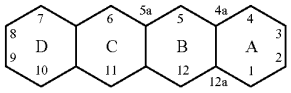
Structure A






The numbering system of the multiple ring nucleus is as follows:

Structure B




Tetracycline, as well as the 5-hydroxy (oxytetracycline, e.g. Terramycin) and 7-chloro (chlorotetracycline, e.g. Aureomycin) derivatives, exist in nature, and are all well known antibiotics. Semisynthetic derivatives such as 7-dimethylaminotetracycline (minocycline) and 6α-deoxy-5-hydroxytetracycline (doxycycline) are also known tetracycline antibiotics. Natural tetracyclines may be modified without losing their antibiotic properties, although certain elements of the structure must be retained to do so.

In addition to the direct antibiotic activity of tetracyclines, further activities of antibiotic tetracyclines have been investigated for possible therapeutic effects on acne. For example, a study by Elewski et al., *J. Amer. Acad. Dermatol.,* 8:807-812 (1983) suggests that acne therapy, consisting of orally-administered tetracycline at a total daily dose of 1000 mg, may have therapeutic anti-inflammatory effects in addition to antibiotic effects. In particular, it was found that the anti-inflammatory effect of tetracycline was, at least in part, due to inhibition of neutrophil chemotaxis induced by bacterial chemotactic factors.

A more recent study, performed by Eady et al., *J. Invest. Dermatol.,* 101:86-91 (1993), evaluated the effects of oral minocycline or tetracycline therapy on the cytokine and microflora content of open comedones in acne patients. The total daily dose of minocycline administered was 100 mg. The total daily dose of tetracycline administered was 1000 mg.

Eady et al. found that the therapies upregulated the production of bioactive IL-1α-like material and immunochemical IL-1β. IL-1 is considered to be a pro-inflammatory cytokine.

Accordingly to Eady et al., no overall decrease in the numbers of propionibacteria/mg of comedonal material was found. It is important to note, however, that the numbers of propionibacteria/mg of comedonal material are not expected to decrease in response to antibiotic therapy. Since the bacteria within comedones are encapsulated by the follicle, they are not susceptible to antibiotic treatment.

Another possible activity of tetracyclines in acne therapy was investigated by Bodokh, I., et al., *Acta. Derm. Venerol.,* 77:255-259 (1997). Their study was designed to evaluate the action of minocycline on sebaceous excretion in acne patients. A 100 mg daily dose of minocycline was administered. A subclinical increase in seborrhoea was reported. The authors propose that minocycline induces an increase in seborrhoea via a reduction in ductal obstruction. The mechanism by which the ductal obstruction is reduced is proposed to be a reduction in ductal irritation. The authors suggest that the reduction of ductal irritation is due to minocycline's direct effect on *P. acnes*, or minocycline's effect on the lipase produced by *P. acnes*.

Bodokh et al. also found that during treatment no correlation exists between seborrhoea intensity and clinical severity of acne. The authors state that the lack of correlation shows that seborrhoea is pathogenic because it is the "culture medium" of *P. acnes*. Thus, it can be concluded that the authors consider the antibiotic activity of minocycline to be therapeutically significant with respect to acne.

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