Alopecia - Hair Loss

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Rationale

- “Medication for men plagued by hair loss has become a topic of interest in Japan since a drug company began marketing it at the end of last year.” March 5th, 2006 - Source
- “An increasing number of companies are apparently turning the Chinese fear of a bald spot into big bucks with some doing so well they are branching out into other countries.” February 16, 2006 - Source
- “There is something in the air, or should we say in the hair, these days. Scientific research into hair loss remedies has never been more active or more exciting.” June 7, 2006 - Source

Introduction

Hair basics

- Hair is a complex and delicate part of the body.
- Keeping it healthy and beautiful is a challenge.
- Hair grows everywhere on the body with the exception of lips, eyelids, palms of the hands and soles of the feet.
- Hair is basically a form of skin.
- Hair is made of a protein called keratin.
- Each shaft of hair is made of two or three inter-twined layers of keratin which grow from a follicle beneath the skin.
- Hair Structure - Source
- Hair Cycle - Source

What causes hair loss?

- Decrease in growth of hair
- Increase in shedding of hair
- Breakage of hair
- Conversion of thick terminal hairs to thin vellus hairs

Survey results from Japan
Both men and women lose hair for similar reasons. Hair loss in men is often more dramatic, and follows a specific pattern of loss, one of which has been termed ?Male Pattern Baldness" or "Androgenetic Alopecia".

Types of alopecia

- Alopecia Areata (AA): Hair loss occurring in patches anywhere on the body.
- Alopecia Totalis (AT): Total loss of the hair on the scalp.
- Alopecia Universalis (AU): Total loss of all hair on the body.
- Alopecia Barbae: Loss of facial hair (for a man) especially in the beard area.
- Alopecia Mucinosa: A type of alopecia which results in scaley patches.
- Androgenetic Alopecia (AGA): Also known as male pattern baldness. It is a thinning of the hair to an almost transparent state, in both men or women. It is thought to be a hereditary form of hair loss.
- Traction Alopecia: Traction alopecia is usually due to excessive pulling or tension on hair shafts as a result of certain hair styles. It is seen more often in women, particularly those of East Indian and Afro-Caribbean origin. Hair loss depends on the way the hair is being pulled. Prolonged traction alopecia can stop new hair follicles from developing and leads to permanent hair loss.
- Anagen Effluvium: This hair loss is generally caused by chemicals such as those used to treat cancer. Initially it causes patchy hair loss, which often then leads to total hair loss. The good news is that when you stop using these chemicals the hair normally grows back (usually about 6 months later). Other drugs also can cause hair loss. Many medicines used to treat even common diseases can cause hair loss.
- Scarring Alopecia: A form of alopecia which leaves scarring on the area of hair loss.
- Telogen Effluvium: A form of hair loss where more than normal numbers of hair fall out. There is a general 'thinning' of the hair. Unlike some other hair and scalp conditions, it is temporary and the hair growth usually recovers. (Source)
Androgenetic alopecia

- Gradual onset
- Transition from large, thick, pigmented terminal hairs to thinner, shorter, indeterminate hairs and finally to short, wispy, non-pigmented vellus hairs in the involved areas
- Characterized by a receding hairline and/or hair loss on the top of the head

Main causes

- Genetic predisposition
- Hormonal effect of androgen
- Reduction of blood circulation around hair follicle
- Deactivation of hair matrix cells

Some facts from Japan

- Market size: ¥ 30 Billion
- Number of products: more than 100

(IP activity over the years

The graph indicates:

- Number of patents filed every 5 years (except for first 7 years).
- First solution proposed in 1973
- Filing trend indicates steep rise in activity recently.

Assignees with more than 20 patents
Assignees with fewer than 20 patents

- **Active assignees**

  Assignees currently active with more than 5 patents to their credit during 2000-2005.

  - Warner with 9 patents,
  - Bristol with 6 and
  - Abbott with 5.

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**Active Assignees**

**Taxonomy**
Interactive Taxonomy

Use the mouse (click and drag/scroll up or down/click on nodes) to explore nodes in the detailed taxonomy. Click on the red arrow on the side of a node name to view the content for that particular node in the dashboard.

Flash plugin or Javascript are turned off. Activate both and reload to view the mindmap.

Treatment Approaches

Composition of treatment for causes are identified and categorized as follows:

- Anti-androgens (Finasteride) source
- Vasodilators (Minoxidil) source
- Double action (Anti-androgen + Vasodilator)
- Hair matrix cells activator

<table>
<thead>
<tr>
<th>Cause</th>
<th>Treatment approach</th>
<th>Pathways affected</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hormonal effect of androgen</td>
<td>Anti-androgens</td>
<td>Testosterone pathway</td>
</tr>
<tr>
<td>Reduction of blood circulation around hair follicle</td>
<td>Vasodilators (e.g., Minoxidil)</td>
<td>NO/cGMP Pathway</td>
</tr>
<tr>
<td>Deactivation of hair matrix cells</td>
<td>Hair matrix cells activator</td>
<td></td>
</tr>
</tbody>
</table>

- Wnt pathway
- STAT pathway
- TGF beta/BMP Pathway
- FGF Pathway
Anti-androgens

- Anti-androgens are used in hormone therapy.
- Anti-androgens are designed to affect the hormones made in the adrenal glands. They don't stop the hormones from being made, but they stop them from having an effect leading to hair loss.

What causes hair loss?

- Testosterone is reduced to its active metabolite, Dihydrotestosterone (DHT) by the enzyme 5 alpha reductase.
- DHT attaches to androgen receptor sites at the hair follicle.
- DHT causes gradual miniaturization of the follicle, which eventually results in hair loss.

How do anti-androgens treat hair loss?

- Anti-androgens compete with DHT to bind to the androgen receptor.
- Upon binding of anti-androgen in place of DHT, follicle miniaturization is lowered and hair loss prevented.

Functions of Anti-androgen

<table>
<thead>
<tr>
<th>Pat/Pub#</th>
<th>Nature</th>
<th>Composition</th>
<th>Composition action</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20060009430</td>
<td>Natural extracts</td>
<td>Palmetto berry extract (fatty acids &amp; sterols), Pumpkin seed extract (Vitamins-B, alpha-linolenic acid, amino acids and phytoesters), Quercetin (Flavonoids) and Beta-sitosterol (Rice bran, wheat germ, corn oils and soybeans)</td>
<td>Fatty acids ? Inhibit testosterone Sterols - Mechanism of action unknown. Quercetin results in cell growth cycle. Beta-sitosterol reduce inflammation on scalp</td>
</tr>
<tr>
<td>BLOTECH (2004)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US20060009427</td>
<td>Organic compound</td>
<td>New class of 4-cycloalkoxy benzonitrile derivatives and salts</td>
<td>Acts as androgen receptor modulator and blocks formation of DHT.</td>
</tr>
<tr>
<td>WARNER LAMBERT (2004)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US20050085467</td>
<td>Organic compound</td>
<td>New class of 6-sulfonamido-quinolin-2-one and 6-sulfonamido-2-oxo-chromene derivatives.</td>
<td>The compounds inhibit, or decrease, activation of androgen receptor by androgens.</td>
</tr>
<tr>
<td>WARNER LAMBERT (2004)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US20050118282</td>
<td>Natural extracts</td>
<td>Supercritical fluid isolate of Saw Palmetto and Sperol (Serenoa repens berry) and their analogs or derivatives.</td>
<td>Modulates androgenic activity by inhibiting 5.alpha.-reductase activity.</td>
</tr>
<tr>
<td>APHIOS Corp (2003)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US20060009429</td>
<td>Nucleotide</td>
<td>Pharmacobologically active oligonucleotides (encompass both DNA and S-DNA bond)</td>
<td>Oligonucleotides inhibit androgen receptor (AR) expression at very low concentrations in skin and hair follicle</td>
</tr>
<tr>
<td>Fundacion Pablo Cassara (2003)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US20030007941</td>
<td>Organic compound</td>
<td>Thyromimetic compounds (structurally similar to thyronine) with finasteride, or cyproterone acetate</td>
<td>Activates thyroid hormone receptors in hair follicle which in turn promote elastisisation of follicle walls and hair follicle</td>
</tr>
<tr>
<td>PFIZER INC (2001)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US20030073616</td>
<td>Peptides/nucleic acid</td>
<td>Bradykinin antagonist (peptide of plasma origin from kinogen precursor-kallikrein)</td>
<td>Inhibits synthesis of bradykinin receptors or compounds by binding to B2 receptor</td>
</tr>
<tr>
<td>N/A (1995)</td>
<td></td>
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</tr>
<tr>
<td>US200279010</td>
<td>Natural extracts</td>
<td>Walnut extract (leaves/pericarps) with an organic solvent</td>
<td>Blocks formation of DHT</td>
</tr>
<tr>
<td>KAO Corp (1987)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Minoxidil (Vasodilators)

- Minoxidil is a “potassium channel opener” that leads to vasodilation.
- The drug is available in two forms. Oral minoxidil is used to treat high blood pressure and the topical solution form is used to treat hair loss and baldness.

What causes hair loss?

- A thick network of tiny veins and arteries line the outer wall of the follicle. Blood pumps through the bulb and hair via this network.
- DHT accumulates in the hair follicles and roots, constricting the blood supply of oxygen and nutrients to the hair roots; which is also seen to possibly contribute towards hair loss.

How does Minoxidil treat hair loss?

- Minoxidil is applied to the scalp topically, where it dilates blood vessels in the scalp and sustains the hair follicles for longer period of time.
- Minoxidil is thought to have a direct mitogenic effect on epidermal cells, as has been observed both in vitro and in vivo. Though the mechanism of its action for causing cell proliferation is not very clear, minoxidil is thought to prevent intracellular calcium entry. Calcium normally enhances epidermal growth factors to inhibit hair growth, and Minoxidil by getting converted to minoxidil sulfate acts as a potassium channel agonist and enhances potassium ion permeability to prevent calcium ions from entering into cells. (Source)
- Minoxidil sulfate (MS) appears to be the active metabolite responsible for hair growth stimulation.

Functions of Vasodilators

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<table>
<thead>
<tr>
<th>Pat/Pub#</th>
<th>Nature</th>
<th>Composition</th>
<th>Composition action</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20040157856</td>
<td>Organic compound</td>
<td>Benzopyran compounds</td>
<td>Rapidly metabolizes, and causes reduced cardiovascular effects compared to other known potassium channel openers</td>
</tr>
<tr>
<td>WARNER LAMBERT(2002)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US20050053572</td>
<td>Natural extracts</td>
<td>Sophora flavescens extract (alkaloids &amp; flavonoids, luteolin-7-glucose and cytosine) Hinokitiol (Taiwan hinoki oil, Aomori, Western Red Cedar oil) and Nicotinamide (Vitamin B complex)</td>
<td>Promotes function of cell activity and dilates blood vessels</td>
</tr>
<tr>
<td>LG HOUSEHOLD &amp; HEALTH CARE(2001)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
```

Double action (Anti-androgen + Vasodilator)

- Combination of Vasodilator + Anti-androgen (double action) composition for effective treatment of Male-Pattern Baldness.

What is the problem with using only Anti-androgen therapy?

- Anti-androgen is not effective in addressing the issue of vasoconstriction around hair follicles due to sebum oil build up.
- Anti-androgen only prevents binding of DHT to androgen receptors. However, the effects of improper oxygen and nutrient supply to the brain due to vasoconstriction still remains and gradually causes hair loss.

What is the problem with using only Vasodilator (or Minoxidil only) therapy?

- Vasodilator or Minoxidil-based products are generally not effective in stopping hair loss as vasodilators (or Minoxidil) do not block the harmful effects of DHT in the scalp and hair follicles.
- Vasodilators or Minoxidil simply dilate blood vessels in the scalp. However, the harmful DHT still gets produced in the body, enters the scalp and hair follicles causing hair loss.

How is the combination of Anti-androgens and Vasodilator (or Minoxidil) effective?

- Anti-androgens target the problem of DHT binding to androgen receptors and prevents follicle miniaturization.
- Vasodilators like Minoxidil cause vasodilation and therefore improve supply of oxygen and nutrients to the hair follicle and roots.
- Combination therapy therefore proves to be much more effective than individual therapy.

Functions of (Anti-androgen + Vasodilators)

Anti-androgen and Minoxidil
Functions of (Anti-androgen + Vasodilators)

IP Map for (Anti-androgen + Vasodilators)

<table>
<thead>
<tr>
<th>Pat/Pub#</th>
<th>Nature</th>
<th>Composition</th>
<th>Composition action</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20060052405</td>
<td>Peptides</td>
<td>Testosterone blocker or vascular toner (Flutamide, cyproterone acetate, spironolactone, progesterone, or analogs or derivatives) and minoxidil mixed along with non-retinoid penetration enhancer and sunscreen</td>
<td>Inhibits 5.alpha.-reductase activity (block DHT) and increase blood flow on the scalp</td>
</tr>
<tr>
<td>US20050123577</td>
<td>Peptides</td>
<td>Prostaglandin (polyunsaturated fatty acids) EP-2, EP-3 EP-4 receptor agonist with Minoxidil, 2,4-diaminopyrimidine 3-oxide, and Aminexil, cyclic AMP</td>
<td>Minoxidil (designed to mimic nitric oxide’s effects) grows hair via prostaglandin-H synthase stimulation. EP-3 and EP-4 are expressed in anagen hair follicles which induce a reduction in the level of cAMP</td>
</tr>
<tr>
<td>US6447762</td>
<td>Natural extract</td>
<td>Hop extract (oil contains terpenes and humulene), Rosemary extract (hydroalcohol), Swertia extract (glycol with a swertiamarin), Silanodiol salicylate (biologically active silicon compound)</td>
<td>Inhibits activity of 5-alpha-reductase, protects follicular cell membranes by neutralizing action of oxidation reaction in tissues, stimulates hair follicles and blood circulation to the hair root, supplies oxygen and nutrients to base of follicle, retains humidity, avoids dehydration of scalp</td>
</tr>
</tbody>
</table>

Hair matrix cell activator

Hair matrix cell activator is a substance that acts at the matrix cells in the hair follicle preventing their degradation.

What causes hair loss?

- Stem cells are interspersed within the basal layer of the outer root sheath and in an area called the bulge.
- Stem cells migrate to hair matrix where they start to divide and differentiate, under the influence of substances produced by cells of the dermal papilla.
- Perifollicular matrix cells undergo slow degradation which prevents follicle stimulation.
- Hair follicle activation is required for hair growth and thus inhibition of follicle activation eventually leads to hair loss.

How does hair cell matrix activator treat hair loss?

- Hair cell matrix activator slows down and inhibits degradation of the perifollicular matrix.
- This leads to an increase in hair follicle matrix cells that differentiate from progenitor stem cells.
- Matrix activator allows activation of hair matrix cells and therefore follicle stimulation leading to hair growth.

Functions of Hair matrix cell activator

Hair matrix cell activator
### IP Map for Hair matrix cell activator

<table>
<thead>
<tr>
<th>Pat/Pub#</th>
<th>Nature</th>
<th>Composition</th>
<th>Composition action</th>
</tr>
</thead>
<tbody>
<tr>
<td>US20020052498</td>
<td>Organic compound</td>
<td>(2-substituted oxyphenyl) alkanamide derivative and its salt</td>
<td>Mechanism of action has not been made clear, having excellent hair follicle activating action and regrowth promoting effect</td>
</tr>
<tr>
<td>SHISEIDO(1999)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>US20040071647</td>
<td>Peptides</td>
<td>Metalloprotease (MMP-9 inhibitor (thiol or a hydroxamate) other than chelating calcium ions</td>
<td>Reducing the expression of MMPs (Metalloproteases) in the scalp - slows down or inhibits the degradation of the perifollicular matrix (extracellular matrix surrounding the hair follicle)</td>
</tr>
<tr>
<td>L’OREAL(1998)</td>
<td></td>
<td></td>
<td></td>
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### Technology mapping based on patents analyzed

#### IPMap: Composition nature matrix

<table>
<thead>
<tr>
<th>Year</th>
<th>Organic Compound</th>
<th>Natural extracts</th>
<th>Peptides</th>
<th>Nucleotides</th>
<th>Natural extract + Organic comp</th>
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</thead>
<tbody>
<tr>
<td>2005</td>
<td>....</td>
<td>....</td>
<td>....</td>
<td>....</td>
<td>UNILEVER (1)</td>
</tr>
<tr>
<td>2004</td>
<td>WARNER (1)</td>
<td>BLOTECH (1)</td>
<td>....</td>
<td>FUNDACION (1)</td>
<td>KAO (1)</td>
</tr>
<tr>
<td>2003</td>
<td>WARNER (1)</td>
<td>APHIOS (1)</td>
<td>....</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2002</td>
<td>WARNER (1)</td>
<td>....</td>
<td>....</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2001</td>
<td>PFIZER (1)</td>
<td>LG HEALTH-CARE (1)</td>
<td>....</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2000</td>
<td>....</td>
<td>....</td>
<td>L’OREAL (1)/N/A (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1999</td>
<td>SHISEDIO (1)</td>
<td>COLOMER (1)</td>
<td>....</td>
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<td></td>
</tr>
<tr>
<td>1998</td>
<td>....</td>
<td>....</td>
<td>L’OREAL (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1995</td>
<td>....</td>
<td>....</td>
<td>N/A (1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1987</td>
<td>....</td>
<td>KAO (1)</td>
<td>....</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1982</td>
<td>UNILEVER (1)</td>
<td>....</td>
<td>....</td>
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</table>

#### Focus of patents

<table>
<thead>
<tr>
<th>Focus of patents</th>
<th>Patent no.</th>
<th>Rec. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-substituted oxyphenyl alkanamide derivative having excellent hair growth effect.</td>
<td>US20020052498</td>
<td>1</td>
</tr>
<tr>
<td>Thyromimetic compounds, and its role in treating hair loss.</td>
<td>US20030007941</td>
<td>2</td>
</tr>
<tr>
<td>Saw Palmetto berry extract, pumpkin seed extract, sitosterol and quercetin for the treatment and prevention of the biologically detrimental effects of DHT</td>
<td>US20060009430</td>
<td>3</td>
</tr>
<tr>
<td>4-cycloalkoxy benzonitriles and its use as androgen receptor modulators</td>
<td>US20060009427</td>
<td>4</td>
</tr>
<tr>
<td>Supercritical fluid isolate of Saw Palmetto, Sperol for inhibition of 5-alpha-reductase activity</td>
<td>US20050118282</td>
<td>5</td>
</tr>
<tr>
<td>New class of quinolin-2-ones and chromen-2-ones and their use as androgen receptor antagonists</td>
<td>US20050085467</td>
<td>6</td>
</tr>
<tr>
<td>Antiandrogen oligonucleotides usable for the treatment of dermatological androgen-related disorders</td>
<td>US20060009429</td>
<td>7</td>
</tr>
<tr>
<td>Bradykinin antagonists for stimulating or inducing hair growth and/or arresting hair loss</td>
<td>US20030073616</td>
<td>8</td>
</tr>
<tr>
<td>Extract from walnut leaves and/or pericarps as 5 alpha-reductase inhibitor</td>
<td>EP0279010</td>
<td>9</td>
</tr>
<tr>
<td>Stimulating hair growth using benzopyrans</td>
<td>US20040157856</td>
<td>10</td>
</tr>
<tr>
<td>Sophora flavescens extract, Coicis semen extract, clove extract, etc for promoting hair growth, function of cell activity and dilating peripheral blood vessels.</td>
<td>US20050053572</td>
<td>11</td>
</tr>
<tr>
<td>Compositions to prevent or reduce hair loss</td>
<td>US20060052405</td>
<td>12</td>
</tr>
<tr>
<td>Prostaglandin EP-3 receptor antagonists for reducing hair loss</td>
<td>US20050123577</td>
<td>13</td>
</tr>
<tr>
<td>Synergic effect arising from the interaction of active ingredients, consisting of three plant extracts and a synthetic organosilicic compound for prevent hair loss and stimulate hair growth</td>
<td>US6447762</td>
<td>14</td>
</tr>
<tr>
<td>Metalloprotease inhibitors to induce and/or stimulate the growth</td>
<td>US20040071647</td>
<td>15</td>
</tr>
<tr>
<td>Method of decreasing sebum production and pore size</td>
<td>US20050277699</td>
<td>16</td>
</tr>
<tr>
<td>Method for reducing sebum on the hair and skin</td>
<td>US4529587</td>
<td>17</td>
</tr>
</tbody>
</table>
Technology focus

Distribution of patents

By patent types

Distribution based on patent types
By key ingredients

**Herbal extract**
(8, 9, 10, 11, 12, 13, 15)
- Saw palmetto berry extract; Pumpkin seed extract; Beta-sitosterol; Sperol; Walnut leaves and/or pericaps extract;
- Sophora flavescens extract, hinokitiol, nicotinamide; Hop extract, Rosemary extract; Swertia extract; Silanodiol salicylate; 5-alpha-avoceta; and minoxidil

**Peptides/Oligonucleotide**
(2, 5, 15, 16, 17)
- Thyromimetic compounds; Antiandrogen oligonucleotide; 5-alpha-reductase inhibitor and minoxidil;
- Prostaglandin EP-3 receptor antagonist; Metalloprotease inhibitor

**Chemical Compounds**
(1, 3, 4, 6, 7, 11)
- (2-substituted oxyphenyl) alkanamide derivative; 4-cycloalkoxy benzonitriles; 6-sulfonamido-quinolin-2-one and 6-sulfonamido-2-oxochromene derivatives;
- Benzopyran compounds; Polyamine derivatives; nicotinamide

**Antagonists**
(14, 18)
- Bradykinin antagonists; Biotin antagonist

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**Distribution of key ingredients**

**By target disease**

- Alopecia areata, 3
- Acan, 3
- Prostatic hyperplasia, 3
- Androgeno-genetic alopecia, 2
- Hirsutism, 2
- Oily skin, 2
- Alopecia, 4
- Other, 6
- Androgenic alopecia, 13
- Alopecia pityriodes, 1
- Alopecia seborrheica, 1
- Greasy hair or scalp, 1
- Scalp related problems, 1
- Scarring alopecia, 1
- Seborrhoea, 1

*NOTE: Record no. 16 (US20050277699) has not disclosed the target disease or disorder.*

**Distribution based on target diseases**
### Key ingredients vs. Target disease

<table>
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<tr>
<th>Rec. no.</th>
<th>Source of Key ingredient</th>
<th>Key ingredient</th>
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<th>Alopecia areata</th>
<th>Alopecia areata</th>
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<th>Alopecia universalis</th>
<th>Prostate hyperplasia</th>
<th>Acne.</th>
<th>Hirsutism.</th>
<th>Oiliness</th>
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<tr>
<td>17</td>
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<td>Prostaglandin EP3 receptor antagonist</td>
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<td>Biotin antagonist</td>
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</table>

### Target species

- **Human:** 1, 3, 7, 8, 12, 13, 14, 15, 16, 18
- **Animal:** 2, 4, 5, 6, 9, 10, 11

- **Dog (2), Cat (3), Cattle (2) and Horses, Swine, Pig, Chicken, Mice, Rat, Gerbils, Rabbit, Monkey and Chimpanzee (1 each)**

**NOTE:** Record no 15 (US20050244362) has not disclosed the target species.

### Target species

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<td>US20050123577</td>
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<tr>
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<td>EP0279010</td>
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</tbody>
</table>

**Target species**

- **Human:** 1, 3, 7, 8, 12, 13, 14, 15, 16, 18
- **Animal:** 2, 4, 5, 6, 9, 10, 11

**NOTE:** Record no 15 (US20050244362) has not disclosed the target species.
**Mode of administration**

![Mode of administration diagram]

**Product type vs. Product form**

![Product type vs. Product form diagram]

---

**NOTE:** Record no 15 (US20050524886) have not disclosed the mode of administration

**NOTE:** In cosmetics product form was not disclosed in record no. 11 (US2005052572); and in pharmaceutical or cosmetics, product form was not disclosed in records 7 (US20060009429), 13 (US20051235777), 14 (US6447762), 18 (US4529587) for pharmaceuticals and in record no. 12 (US200600052405) for cosmetics.
<table>
<thead>
<tr>
<th>Target disease/ disorder</th>
<th>Patent no.</th>
<th>Rec. no.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alopecia areata, alopecia pityrodes or alopecia seborrhoeica, or androgenic alopecia (i.e. male pattern baldness)</td>
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<td>Inappropriate activation of the androgen receptor, acne, oily skin, alopecia</td>
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<tr>
<td>Prostatic hyperplasia, prostatic cancer, hirsutism, acne, male pattern baldness, seborrhea, and other diseases related to androgen hyperactivity</td>
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<td>Alopecia, acne, oily skin, prostrate cancer, hirsutism, and benign prostrate hyperplasia</td>
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<tr>
<td>Androgen-associated hair loss and androgen-skin related disorders.</td>
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<td>Androgenetic or androgenic alopecia or androgeno-genetic alopecia</td>
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<tr>
<td>Diseases caused by testosterone (male-pattern alopecia)</td>
<td>EP0279010</td>
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<tr>
<td>Alopecia areata, female pattern hair loss, hair loss secondary to chemotherapy or radiation treatment, stress-related hair loss, self-induced hair loss, scarring alopecia, and alopecia in non-human mammal</td>
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<td>Hair loss</td>
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<td>Androgenetic, androgenic or androgenogenetic alopecia</td>
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<tr>
<td>Curing other scalp related problems</td>
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</table>

**List of patents**

**Pathways and linkages**

**Pathways associated with hair matrix cell activation**

Molecular mediators of hair follicle embryogenesis: Identification of the molecular pathways controlling differentiation and proliferation in mammalian hair follicles provides the crucial link to understanding the regulation of normal hair growth, the basis of hereditary hair loss diseases, and the origin of follicle-based tumors. Homeobox (hox), hedgehog (hh), patched (ptc), wingless (wg)/wnt, disheveled (dsh), engrailed (en), Notch 1 and armadillo/B-catenin genes are all critical for hair follicle.

- **Wnt pathway:** Maintains hair-inducing activity of the dermal papilla.
- **Hedgehog pathway:** Sonic hedgehog (SHH) signaling plays a critical role in hair follicle development. Sonic hedgehog gene. Sonic hedgehog, SHH for short, helps guide hair follicles from a resting stage into growth activity. SHH is particularly important in the embryonic formation of hair follicles.
- **STAT pathway**
- **TGF beta/BMP Pathway:** Bone morphogenetic protein (BMP) signaling have been implicated in the regulation of both proliferation and differentiation in the hair follicle. BMP2 is expressed in the embryonic ectoderm, but then localizes to the early hair follicle placode and underlying mesenchyme. BMP4 is expressed in the early dermal condensate. Research results show that BMPs are a key component of the signaling network controlling hair development and are required to induce the genetic program regulating hair shaft differentiation in the anagen hair follicle. Transforming growth factor beta (TGF-beta), inhibits mitogen - induced dermal papilla cell proliferation
- **FGF Pathway:** Fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF) potentiate the growth of dermal papilla cells. It is proposed that these proteins increase the synthesis of stromelysin (an enzyme, matrix metalloproteinase) which acts on the papilla cells and accelerates their growth.
- **MAPK Pathway:** Mitogen-activated protein kinase (MAPK) activation, increases keratinocyte turnover.
- **NOTCH Pathway:** Notch-1 is expressed in ectodermal-derived cells of the follicle, in the inner cells of the embryonic placode and the follicle bulb, and is also expressed in the suprabasal cells of the mature outer root sheath. Delta-1, one of the three ligands is only expressed during embryonic follicle development and is exclusive to the mesenchymal cells of the pre-papilla located beneath the follicle placode, and appears to promote and accelerate placode formation, while suppressing placode formation in surrounding cells. Other ligands, Serrate 1 and Serrate 2, are expressed in matrix cells destined to form the inner root sheath and hair shaft.

**Pathways associated with Anti Androgen**
Integrative Signaling Pathways-Major players

**Input signal**
- Wnt
- Frz/LRP5/6
- Shh
- IL-2, IL-4, IL-7, IL-9, and IL-15
- TGFβ/BMP
- FGF2
- LPS
- Testosterone

**Mediator signal**
- Dvl
- Ptc1
- Smo
- JAK
- TAB1/2
- ALK2/3/6
- Grb2/SOS
- CD14
- NADPH
- 5-α-reductase
- DHT

**Effectors**
- Axin/GSK3β-catenin(P)
- Restricted activation
- Smad1/5/8
- RasGTP/Raf/MAPK/ERK
- TAK1
- NLK
- AR

**Wnt pathway**
**Hedgehog pathway**
**STAT pathway**
**TGFβ/BMP pathway**
**FGF pathway**
**MAPK Pathway**
**Testosterone Pathway**

Players of WNT inhibition Pathway

**Alopecia**

Controls hair follicle morphogenesis
<table>
<thead>
<tr>
<th>Patent no.</th>
<th>Key compound</th>
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<tr>
<td>US6664247</td>
<td>Pyrazole compounds</td>
<td>GSK3</td>
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Role of Pyrazole compounds in Wnt Pathway

**Pyrazole**

- **Pyrazole** (C3H4N2) refers both to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5-membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions and to the unsubstituted parent compound. Being so composed and having pharmacological effects on humans, they are classified as alkaloids although they are not known to occur in nature.
- **Pyrazoles** are produced synthetically through the reaction of α, β-unsaturated aldehydes with hydrazine and subsequent dehydrogenation.
Pyrazole (C3H4N2)

- Pyrazoles are used for their analgesic, anti-inflammatory, antipyretic, antiarrhythmic, tranquilizing, muscle relaxing, psychoanaleptic, anticonvulsant, monoamineoxidase inhibiting, antidiabetic and antibacterial activities.
- Structurally related compounds are pyrazoline and pyrazolidine.

Structurally related compounds

GSK3 inhibition by pyrazole compounds

Pyrazole compounds (CAS NUMBER : 288-13-1)

Inhibition by amine derivatives

**Patent Number:** US6989385  **Applicant:** Vertex Pharmaceuticals Incorporated  **Title:** Pyrazole compounds useful as protein kinase inhibitors

**Basic Structure:**
Derivatives of pyrimidine-pyrazole amine disclosed in US6989385 patent

**Patent Number:** US7008948  **Applicant:** Vertex Pharmaceuticals Incorporated  **Title:** Fused pyrimidyl pyrazole compounds useful as protein kinase inhibitors

**Basic Structure:**

---

Derivatives of pyrimidine-pyrazole amine disclosed in US7008948 patent

**Patent Number:** US6977262  **Assignee:** Mitsubishi Pharma Corporation  **Title:** Dihydropyrazolopyridine compounds and pharmaceutical use thereof

**Basic Structure:**

---

Derivatives of pyrimidine-pyrazole amine disclosed in US6977262 patent

**Patent Number:** US6664247  **Assignee:** Vertex Pharmaceuticals Incorporated  **Title:** Pyrazole compounds useful as protein kinase inhibitors

**Basic Structure:**
Derivatives of pyrimidine-pyrazole amine disclosed in US6664247 patent

Patent Number: US2004224944
Assignee: VERTEX PHARMACEUTICALS INC
Title: Pyrazole compounds useful as protein kinase inhibitors

Basic Structure:

Derivatives of pyrimidine-pyrazole amine disclosed in US2004224944 patent

Other derivatives for alopecia

GSK-3 Inhibition Mechanism - Phosphorylation

- GSK-3 inhibition targets treatment of chemotherapy-induced alopecia [source]
- In the canonical Wnt signaling cascade, adenomatous polyposis coli (APC), axin, and GSK3 constitute the so-called destruction complex, which controls the stability of beta-catenin. It is generally believed that four conserved Ser/Thr residues in the N terminus of beta-catenin are the pivotal targets for the constitutively active serine kinase GSK3. GSK3 covalently modifies beta-catenin by attaching phosphate groups (from ATP) to serine, and threonine residues. In so doing, the functional properties of the protein kinase’s substrate (beta-catenin) are modified.

- In the absence of Wnt signals, glycogen synthase kinase (GSK) is presumed to phosphorylate the N-terminal end of beta-catenin, thus promote degradation of beta-catenin and subsequent ubiquitination and proteasomal targeting.

- Exposure of cells to Wnts leads to inactivation of GSK-3 through an as yet unclear mechanism. The phosphoprotein Dishevelled is required, after receptor-ligand interaction, to transduce the signal that results in the inactivation of GSK-3. As a result, beta-catenin is dephosphorylated and escapes the ubiquitination-dependent destruction machinery.

- Unphosphorylated beta-catenin accumulates in the cytoplasm and translocates to the nucleus, where it can associate with the TCF/LEFs and become a transcriptional transactivator.

More details on GSK-3

Key points

- Beta-catenin phosphorylation at serine 45 (Ser45), threonine 41 (Thr41), Ser37, and Ser33 is critical for beta-catenin degradation. [source]
- Regulation of beta-catenin phosphorylation is a central part of the canonical Wnt signaling pathway. [source]
- Ser-X-X-X-Ser (X is any amino acid) motif is obligatory for beta-catenin phosphorylation by GSK3. [source]
- Beta-catenin phosphorylation/degradation and its regulation by Wnt can occur normally in the absence of Thr41 as long as the Ser-X-X-X-Ser motif/spacing is preserved. [http://pubs.acs.org/cgi-bin/abstract.cgi/bichaw/2006/45/i16/abs/bi0601149.html source]

GK3 Inhibition:

- GSK3 is regulated by phosphorylation.
- Phosphorylation of GSK3 beta on Ser9 (Ser21 in GSK3 alpha) by protein kinase B (PKB) causes its inactivation is the primary mechanism responsible for growth factor inhibition of this kinase. Activation of GSK3 beta is dependent upon the phosphorylation of Tyr216 (Tyr279 in GSK3 alpha). Upon activation, it has been shown to phosphorylate a number of different cellular proteins, including p53, c-Myc, c-Jun, heat shock factor-1 (HSF-1), beta-catenin and cyclin D1. [source]
- GSK3 is inhibited by phosphorylation of serine-9 or serine-21 in GSK3 beta and GSK3 alpha, respectively. [source]
- GSK3?S substrate specificity is unique in that phosphorylation of substrate only occurs if a phosphoserine or phosphotyrosine is present four residues C-terminal to the site of GSK phosphorylation. [source]
- A phosphorylation cascade starts from GSK3 itself and initiates it in beta-catenin. [source]
- Thus our goal is to stop the phosphorylation of the serine and threonine residue of GSK3.
The figure below illustrates the phosphorylation mechanism of serine and threonine by ATP.

- We can't stop conversion of ADP to ATP that releases phosphorous group causing phosphorylation.
- We can only block the oxygen atom on serine and threonine as a result which will in turn stop phosphorylation.
- The two probable ways of blocking the oxygen atom are (a) As oxygen is a Lewis acid with strong electron donating capacity, so usually a strong electron pair acceptor can easily bind to oxygen atom and preventing phosphorylation or (b) breaking of the -OH bond with the carbon atom.

**Serine - pyrazole reaction**

![Serine and Pyrazole reaction](source)

- The T-loop of GSK-3 is tyrosine phosphorylated at Y216 and Y279 in GSK-3b and GSK-3a, respectively, but not threonine phosphorylated. Y216/Y279 phosphorylation could play a role in forcing open the substrate (e.g., beta-catenin)-binding site.
- Thus, T-loop tyrosine might facilitate substrate phosphorylation but is not strictly required for kinase activity.
- Stimulation of cells with pyrazole compounds cause inactivation of GSK-3 through phosphorylation (S9 of GSK-3 beta and S21 of GSK-3 alpha), which inhibits GSK-3 activity. Thus leading to dephosphorylation of substrates (e.g., beta-catenin) resulting in functionalactivation and consequent increased hair follicle morphogenesis.
- Phosphorylation of S9/S21 creates a primed pseudosubstrate that binds intramolecularly to the positively charged pocket of the GSK-3. This folding precludes phosphorylation of substrates (e.g., beta-catenin) because the catalytic groove is occupied. The mechanism of inhibition is competitive.
- A consequence of this is that primed substrates, in high enough concentrations, out-compete the pseudosubstrate and thus become phosphorylated.
- Thus, small molecule inhibitors modeled to fit in the positively charged pocket of the GSK-3 kinase domain could potentially be very effective for selective inhibition of primed substrates.

**Proposed mechanisms to regulate GSK-3**

1. Inactivation of GSK-3 through serine phosphorylation
2. Activation of GSK-3 through tyrosine phosphorylation
3. Inactivation of GSK-3 through tyrosine dephosphorylation
4. Covalent modifications of substrates through priming phosphorylation
5. Inhibition or facilitation of GSK-3 mediated substrate phosphorylation through interaction of GSK-3 with binding or scaffolding proteins
6. Targeting of GSK-3 to different subcellular localizations
7. Differential usage of isoforms or splice variants to alter subcellular localization or substrate specificity
8. Integration of parallel signals conveyed by a signal stimulus.

**Key Finding**

- Pyrazole compounds with inhibition constant (Ki) of <0.1 mM are a good starting point for developing molecules that can inhibit serine/threonine protein kinase (such as GSK-3) and the proteins they help to regulate.
Pathway associated with anti-androgen

- Dihydrotestosterone
  - Formed by peripheral conversion of testosterone by 5-alpha reductase
  - Binds to androgen receptor on susceptible hair follicles
- Hormone-receptor complex activates genes responsible for gradual transformation of large terminal follicles to miniaturized (progressive diminution of hair shaft diameter and length in response to systemic androgens) follicles
**Pathway associated with Minoxidil (vasodilators)**

Minoxidil is a well-known drug used for the treatment of alopecia. A correlation between Sesquiterpene lactone (Helenalin) produced from Arnica montana and Minoxidil is illustrated in the figure below. Arnica montana, a Vasodilator, acts on the NO/cGMP Pathway through T-cells, B-cells and epithelial cells & abrogates kappa B-driven gene expression.
### Alopecia IPMap
Dolcera IPMap for Alopecia

### Patent activity in China

#### Treatment approaches

<table>
<thead>
<tr>
<th>Treatment approach</th>
<th>Patent number</th>
<th>Priority year</th>
<th>Assignee/Inventor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vasodilators</td>
<td>CN1772105</td>
<td>2005</td>
<td>???</td>
</tr>
<tr>
<td></td>
<td>CN1772139</td>
<td>2005</td>
<td>???</td>
</tr>
<tr>
<td></td>
<td>CN1569080</td>
<td>2003</td>
<td>???</td>
</tr>
<tr>
<td></td>
<td>CN1506103</td>
<td>2002</td>
<td>???</td>
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<tr>
<td></td>
<td>CN1403100</td>
<td>2001</td>
<td>???</td>
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<tr>
<td></td>
<td>CN1165181</td>
<td>1996</td>
<td>???</td>
</tr>
<tr>
<td></td>
<td>CN1031022</td>
<td>1988</td>
<td>???????????????</td>
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## Details of treatment approaches

<table>
<thead>
<tr>
<th>Patent number</th>
<th>Patent title</th>
<th>Treatment approach</th>
<th>Composition nature</th>
<th>Composition</th>
<th>Composition action</th>
</tr>
</thead>
<tbody>
<tr>
<td>CN1772105</td>
<td>YE MINGWEI   (CN)</td>
<td>Chinese herbal medicine decoction for treating blood stasis obstruction type alopecia and its prep</td>
<td>Vasodilators</td>
<td>Astragalus root, prepared rhizome of rehmannia, white peony root, angelica, peach kernel and sufflower</td>
<td>Promote blood circulation</td>
</tr>
<tr>
<td>CN1772139</td>
<td>WANG YAJIE   (CN)</td>
<td>Alopecia areata treating medicine</td>
<td>Vasodilators</td>
<td>Pinellia tuber, fleeceflower root, arborvitae seed, chicken's gizzard membrane, prepared rhizome of rehmannia, Poris cocos, Codonopsis pilosula, etc</td>
<td>Promote blood circulation</td>
</tr>
<tr>
<td>CN1569080</td>
<td>TAN RUBIAO   (CN)</td>
<td>Natural Chinese herb composition for treating alopecia and leucotrichia and its application</td>
<td>Vasodilators</td>
<td>Ginger, Cinnamomum cassia, myrrh, clove, mace nutmeg, Loranthus mulberry mistletoe, rhizoma dioscoreae, ligustrum japonicum, drynaria, fleece-flower root, and black sesame seeds</td>
<td>Enhances the hair growth and healthier hairs</td>
</tr>
<tr>
<td>CN1463693</td>
<td>??? 2002</td>
<td>Hair growing preparation containing compound of Chinese medicine and Western medicine</td>
<td>Hair matrix activator</td>
<td>Persimmon leaf, oriental arbor-vitae leaf, ginseng leaf, yellow qi, fruit of the glossy privet, polygonum multiflorum, Kudzu root, dry ginger; Plus?Minoxidil, Vitamins and derivative, cystine, serine, leucine</td>
<td>Better and faster hair growth</td>
</tr>
<tr>
<td>CN1506103</td>
<td>???2002</td>
<td>Hair follicle activating liquid</td>
<td>Vasodilators</td>
<td>Ginseng, twists the stock blue, the licorice, the Sophora flavescens and hot peppers</td>
<td>Activates the hair-follicle and enhances the hair growth.</td>
</tr>
<tr>
<td>CN1403100</td>
<td>??? 2001</td>
<td>Trichogen and its prep</td>
<td>Vasodilators</td>
<td>Ginseng, ganoderma lucidum, Chinese rhubarb, polygonum multiflorum, Chinese prickly ash, ginger, grass seed</td>
<td>Promote blood circulation and enhance hair growth</td>
</tr>
<tr>
<td>CN1165181</td>
<td>??? 1996</td>
<td>Washing free shampoo for nourishing and growing hair</td>
<td>Vasodilator</td>
<td>Vitamin P (Bioflavonoids), Vitamin B15, Vitamin B2, nicotinic acid, bromo?geramineum</td>
<td>Stimulate hair growth</td>
</tr>
<tr>
<td>CN1150043</td>
<td>??? 1996</td>
<td>Efficient low-side effect external use medicine for curing seborrhoeic baldness</td>
<td>Anti-androgen + Vasodilator</td>
<td>Polygonum multiflorum, Ligusticum lucidum, Morus alba, Rehmannia glutinosa, Eclipta prostrata, Salvia miltiorrhiza, Carthamus tinctorius, Cnidium monieri, Sophora flavescens, Dictamnus dasycarpus, Kochia scoparia, and antioxidants</td>
<td>Inhibit the excess secretion of the sebaceous glands, increase the blood circulation on scalp and enhance the hair growth</td>
</tr>
<tr>
<td>CN1031022</td>
<td>?????????? 1988</td>
<td>Channel-stimulating and hair-growing hair shampoo</td>
<td>Vasodilators</td>
<td>Herbal extract + detergent</td>
<td>Increases the blood circulation under the scalp, reduces the hair los</td>
</tr>
</tbody>
</table>

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<td>Patent Landscape Services</td>
<td>Dolcera Processes</td>
<td>Industry Focus</td>
</tr>
<tr>
<td>Patent Search Services</td>
<td>Patent Alerting Services</td>
<td>Dolcera Tools</td>
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Conclusions

- Hair loss medication is a very active area of research and intellectual property development.
- One of the most promising areas of development is the area of Anti-androgens.
- The top companies are Merck, L’Oreal and Smithkline.

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