

**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO  
DIRECCIÓN DE NUEVAS CREACIONES**

2020  
Bogotá, D.C.,

Abogado  
JUAN PABLO CADENA SARMIENTO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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| ASUNTO | Radicación | 07 55664 |
|        | Trámite    | 011      |
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|        | Actuación  | 519      |
|        | Oficio     |          |
|        | Folios     | 03       |

**05552**

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|-------------------------|--------------------------|------------------------------------------------------------------|
| Patente de Invención    | <input type="checkbox"/> | Patente de Modelo de Utilidad                                    |
| Vía Nacional            | <input type="checkbox"/> |                                                                  |
| Vía PCT (Fase Nacional) | <input type="checkbox"/> | Cap. I <input type="checkbox"/> Cap. II <input type="checkbox"/> |

No. Solicitud Internacional PCT/US2005/044247  
Fecha de Presentación Internacional 06/Diciembre/2005

Como resultado del Examen de Fondo realizado, con fundamento en el Artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se comunica:

### 1. Documentos estudiados

|                   |                  |                   |
|-------------------|------------------|-------------------|
| Descripción:      | Folios 117 a 185 | 01/Junio/2007     |
| Reivindicaciones: | Folios 186 a 188 | 01/Junio/2007     |
| Dibujos:          | Folios 190 a 208 | 01/Junio/2007     |
| Secuencias:       | Folios 209 a 223 | 01/Junio/2007     |
| Prioridad:        | US 60/633941     | 07/Diciembre/2004 |

### 2. Análisis de la Prioridad

Se acepta la reivindicación de Prioridad porque esta solicitud fue presentada dentro del plazo establecido (Art. 9 D 486), y su contenido técnico corresponde con el de la prioridad reivindicada.

### 3. Objeto de la invención

Título de la solicitud: "Selección de pacientes para una terapia con un inhibidor HER"

El problema planteado en esta solicitud consiste en la necesidad de proporcionar un tratamiento contra el cáncer de ovario, peritoneal, de mama, de pulmón, o de trompas de falopio que consiste en administrar a un paciente un inhibidor para la señalización del receptor del factor de crecimiento epidérmico humano (HER) y que además se administre un agente quimioterapéutico.

Para resolver este problema técnico la solicitud en estudio proporciona un método para seleccionar pacientes que expresan receptores HER y ligandos de HER para ser tratados con inhibidores de HER y un agente quimioterapéutico antimetabólito como gemcitabina. Los receptores HER a determinar en los pacientes son EGFR, HER2 y HER3, mientras los ligandos de HER a determinar son betacelulina y

Expediente 07 55 664 1er Art 45

**REPÚBLICA DE COLOMBIA**  
**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO**

**RESOLUCIÓN**

*Por la cual se otorga una patente de invención*

**CERTIFICADO**

Rad. N° 07-15778

de acuerdo con las razones expuestas en la parte considerativa de la presente Resolución.

**ARTÍCULO SEGUNDO:** Otorgar patente de invención para la creación titulada:

**“ COMPOSICIONES FARMACÉUTICAS SÓLIDAS ESTABLES, LIBRES DE SALES  
BÁSICAS QUE CONTIENEN DESLORATADINA Y UN POLIOL ”**

**Clasificación IPC:** A 61 K 31/454.

**Reivindicaciones:** 1 a 33      **Folios:** 226 a 230.

**Titular:** CIPLA LIMITED.

**Domicilio:** Mumbai, India.

**Inventores:** Amar Lulla, Geena Malhotra y Sankamarayanan Anand.

**Prioridad N°:** 765/MUM/2004    **Fecha:** 16 de julio de 2004    **País:** IN.

**Vigente desde:** 18 de julio de 2005    **Hasta:** 18 de julio de 2025.

**ARTÍCULO TERCERO:** El titular tendrá los derechos y las obligaciones establecidos en la Decisión 486 de la Comisión de la Comunidad Andina y en las demás disposiciones legales vigentes sobre propiedad industrial, precisando que para mantener vigente la patente se deberá cancelar la tasa anual de mantenimiento, conforme lo dispone el artículo 80 de la referida norma comunitaria.

**ARTÍCULO CUARTO:** Entregar al titular copia auténtica de esta resolución y el certificado de patente, previas las anotaciones en los libros de registro.

**ARTÍCULO QUINTO:** Notificar personalmente el contenido de la presente resolución a la doctora Luz Clemencia de Páez, en su calidad de apoderada de Cipla Limited y al doctor José Luis Reyes Villamizar, apoderado de Tecnoquímicas S.A., sociedad opositora, o a quienes hagan sus veces, entregándoles copia de la misma y advirtiéndoles que contra ella procede el recurso de reposición, ante el Superintendente de Industria y Comercio, el cual

anfirregulina. Los inhibidores de HER empleados son anticuerpos contra HER, contra HER2 o un fragmento del anticuerpo HER2 que inhiben la dimerización o heterodimerización de HER.

El objeto de la presente Solicitud se relaciona con la Clasificación Internacional de Patentes (CIP): C12Q1/68

#### 4. Excepción a la Patentabilidad (Art 20 D 486 literal (d))

Debido a que se está reclamando un método de tratamiento con un inhibidor HER para tratar el cáncer en pacientes, las reivindicaciones 1, 28 – 34, 40 – 41 no son patentables de acuerdo con el artículo citado.

Debido a que se está reclamando un método de diagnóstico basado en la determinación de los receptores HER como EGFR, HER2 y HER3, y también en la determinación de los ligandos de HER como betacelulina y anfirregulina, las reivindicaciones 1 a 27 y 35 a 39 no son patentables de acuerdo con el artículo citado.

Adicionalmente en el estado de la técnica se encuentran métodos de tratamiento que involucran la detección de receptores HER y ligandos de HER.

| Item | Documento                                                                          | Título                                                                                                                                                                      | Fecha de Publicación |
|------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------|
| D1   | British Journal of Urology International<br>Vol 89, 583–590,<br>2002               | Possible autocrine loop of the epidermal growth factor system in patients with benign prostatic hyperplasia treated with finasteride: a placebo-controlled randomized study | 9/Abril/2002         |
| D2   | The Journal of Biological Chemistry,<br>Vol. 278, No. 26, pp.<br>23343–23351, 2003 | Quantitative Analysis of HER2-mediated Effects on HER2 and Epidermal Growth Factor Receptor Endocytosis                                                                     | 27/Junio/2003        |

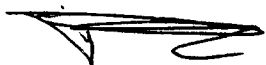
D1 <http://onlinelibrary.wiley.com/doi/10.1046/j.1464-410X.2002.02665.x/pdf> divulga (abstract) la detección de receptores y ligandos del sistema factor de crecimiento epitelial mediante inmunohistoquímica y ELISA y adicionalmente divulga (página 585, tabla 1) las concentraciones de ligandos y receptores en tejido de la próstata en pacientes tratados con finasterida. Tales ligandos y receptores comprenden EGF, HB\_EGF, betacelulina, anfirregulina, HER1, HER2 y TGF-alfa.

D2 <http://www.jbc.org/content/278/26/23343.full.pdf+html> divulga (página 2334, sección procedimiento experimental) el uso de anticuerpos radio-etiquetados contra receptores EGFR y HER2 con el fin de determinar la formación de homo y heterodímeros por parte de los receptores en la señalización del sistema EGF.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta (60) días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Se invita al solicitante se sirva indicar, si así lo considera, su renuncia al término faltante para sesenta (60) días y presentarla por escrito

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No. 10 de 2001.



**JOSÉ LUIS SALAZAR LÓPEZ**  
Director de Nuevas Creaciones (C)

El anterior requerimiento fue notificado por fijación en lista, de fecha

17 ABR. 2012

Elaborado por: Jorge Eduardo Cortázar Gómez  
Revisado por: Ana Delia Pinzón García  
Aprobado por: Jose Luis Salazar López

## Possible autocrine loop of the epidermal growth factor system in patients with benign prostatic hyperplasia treated with finasteride: a placebo-controlled randomized study

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**Objective** To analyse the expression of the epidermal growth factor (EGF) system in prostate tissue and secretions obtained from patients with benign prostatic hyperplasia (BPH) treated with or without finasteride (which primarily targets the androgen-sensitive secretory epithelial cells in the prostate, with little effect on basal epithelial and stromal cells).

**Patients and methods** The expression of the EGF system was evaluated by enzyme-linked immunosorbent assay and immunohistochemistry in samples of prostate tissue and secretions from patients with BPH randomized for treatment with finasteride or placebo for 3 months before surgery.

**Results** Prostate tissue expressed the EGF receptor (HER1) and HER2, and the ligands EGF, transforming growth factor  $\alpha$  (TGF $\alpha$ ), heparin-binding (HB) EGF, betacellulin and amphiregulin. Treatment with finasteride produced greater concentrations of amphiregulin ( $P < 0.05$ ) than did placebo, did not change

the level of TGF $\alpha$ , HER1 and HER2, and tended to decrease the concentration of EGF, betacellulin and HB-EGF in prostate tissue. Using immunohistochemistry, HER1 and TGF $\alpha$  were both localized to the basal epithelial cells, and there was a strong positive correlation among the tissue concentrations of HER1, HER2 and TGF $\alpha$ . Amphiregulin localized to the luminal secretory epithelium. Prostate secretions contained only EGF, which was at levels  $\approx 150$  times higher than in prostate tissue; treatment with finasteride did not affect the concentration of EGF in prostate secretion.

**Conclusions** There were only minor changes in the expression of TGF $\alpha$ , HER1 and HER2 after finasteride treatment. This may represent an important system for the continuous growth and homeostasis of the androgen-independent basal epithelial cells in the prostate.

**Keywords** amphiregulin, betacellulin, EGF, TGF $\alpha$ , HER1, HER2, prostate, BPH, finasteride

### Introduction

BPH is the most common neoplastic condition in men and constitutes a major factor affecting the health of adult men [1]. BPH develops from microscopic hyperplasia but progresses to macroscopic hyperplasia and may eventually lead to clinical BPH, characterized by obstructive and irritative voiding symptoms [2,3]. An intact androgen metabolism is a prerequisite for developing BPH; nevertheless, it develops during a period when the level of circulating androgen decreases, suggesting that other factors are involved in the cause of the disease. In the prostate testosterone is converted into DHT, which is about eight times more active as an androgen [4]. Finasteride inhibits the conversion of testosterone to DHT in the prostate and leads to a

decreased volume of the inner gland epithelium, caused by atrophy and apoptosis [5], with little effect on the stroma [6]. The decrease in prostate volume is 20–25% after 6 months of treatment [7] with no further reduction in the volume of the prostate after prolonged treatment [8,9]. While the secretory epithelium requires androgen for its continuous maintenance, the basal epithelial cells, which comprise the proliferative compartment of the hyperplastic epithelium, are androgen-independent [10]. Androgen insensitive cells of the prostate may depend on locally synthesized factors for their continuous growth.

To find candidates for the maintenance of androgen-independent growth and homeostasis of the prostate after prolonged finasteride treatment, we focused on the EGF system in the prostate. EGF ligands are potent inducers of proliferation in prostate epithelial [11] and stromal cell cultures [12], and we recently showed that

Accepted for publication 21 December 2001

## Quantitative Analysis of HER2-mediated Effects on HER2 and Epidermal Growth Factor Receptor Endocytosis

DISTRIBUTION OF HOMO- AND HETERODIMERS DEPENDS ON RELATIVE HER2 LEVELS\*<sup>§</sup>

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Endocytic trafficking plays an important role in the regulation of the epidermal growth factor receptor (EGFR) family. Many cell types express multiple EGFR family members (including EGFR, HER2, HER3, and/or HER4) that interact to form an array of homo- and heterodimers. Differential trafficking of these receptors should strongly affect signaling through this system by changing substrate access and heterodimerization efficiency. Because of the complexity of these dynamic processes, we used a quantitative and computational model to understand their integrated operation. Parameters characterizing EGFR and HER2 interactions were determined using experimental data obtained from mammary epithelial cells constructed to express different levels of HER2, enabling us to estimate receptor-specific internalization rate constants and dimer uncoupling rate constants. Significant novel results obtained from this work are as follows: first, that EGFR homodimerization and EGFR/HER2 heterodimerization occur with comparable affinities; second, that EGFR/HER2 heterodimers traffic as single entities. Furthermore, model predictions of the relationship of HER2 expression levels to consequent distribution of EGFR homodimers and EGFR/HER2 heterodimers suggest that the levels of HER2 found on normal cells are barely at the threshold necessary to drive efficient heterodimerization. Thus, altering HER2 concentrations, either overall or local, could provide an effective mechanism for regulating EGFR/HER2 heterodimerization and may explain why HER2 overexpression found in some cancers has such a profound effect on cell physiology.

In the EGFR<sup>1</sup> family, endocytic trafficking processes can strongly influence cell responses to EGF family ligands. Many cell types express multiple EGFR family members that can interact to form an array of homo- and heterodimers (1). Reg-

ulation of the distribution of these receptors among cell compartments can significantly modulate the overall signaling through this system by changing access to heterodimerization partners. Because of the potential complexity of EGFR family interactions associated with concomitant receptor trafficking and signaling, application of quantitative experimental and computational modeling techniques to its analysis should be very useful.

The EGFR family (EGFR/HER1/ErbB-1, HER2/ErbB-2/neu, HER3/ErbB-3, and HER4/ErbB-4) of receptor tyrosine kinases consists of four highly related receptors each with a unique set of functional properties. Following ligand binding, EGFR family receptors interact to form an array of homo- and heterodimers each with a characteristic repertoire of downstream signaling molecules (1). EGFR and HER2 are by far the most studied and have gained particular attention in the process of tumorigenesis. HER2 is commonly postulated to be the “preferred dimerization partner” of all EGFR family receptors (2–4). HER2 behaves much like a receptor subunit, as it binds none of the eight reported EGF family ligands (EGF, transforming growth factor- $\alpha$ , betacellulin, amphiregulin, heparin-binding EGF, epiregulin, and the neuregulins (NRG and NRG-2)) with high affinity (5).

Overexpression of both the EGFR and HER2 has been associated with cell transformation and tumorigenesis. HER2 is overexpressed in 25–30% of all breast and ovarian cancers and is emerging as an important player in many other cancers as well (6). HER2 overexpression correlates with poor prognoses in breast cancer (7), and its effects in the process of tumorigenesis have been fairly well documented. Increased HER2 expression contributes to cell transformation, anchorage-independent cell growth, increased proliferation and mitogenic sensitivity, as well as increased tumor cell migration and invasiveness (8–11).

Receptor overexpression could potentially influence cell behavior in multiple ways. The presence of excess receptors could recruit additional signaling molecules, resulting in an increase in signal amplitude. Alternatively, excess receptors could saturate and interfere with processes involved in receptor down-regulation and signal attenuation (12, 13). This second phenomenon is a receptor trafficking effect that may affect the duration of the signaling by interfering with receptor degradation and ligand dissociation. Studies have shown that trafficking defects in receptors can facilitate cell transformation (14), suggesting that signal duration may be more of a determining factor in mitogenic sensitivity than signal amplitude, particularly at physiological ligand concentrations. It appears likely that receptor expression levels are directly connected to their trafficking behavior which, in turn, affects signaling.

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<sup>§</sup> The on-line version of this article (available at <http://www.jbc.org>) contains the Appendix.

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<sup>1</sup> The abbreviations used are: EGFR, epidermal growth factor receptor; EGF, epidermal growth factor; HER2, human epidermal growth factor receptor 2; mAb, monoclonal antibody.