Expression of epidermal growth factor receptor and human epidermal growth factor receptor 2 in periocular squamous cell carcinomas of horses

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Objective—To determine whether epidermal growth factor receptor (EGFR) and human epidermal growth factor receptor 2 (HER2) are expressed in periocular squamous cell carcinomas (SCCs) of horses.

Sample—Biopsy specimens of SCCs from 46 horses.

Procedures—Pathology records were searched retrospectively for biopsy specimens of periocular SCCs obtained from horses. Slides of the specimens were reviewed histologically to confirm the SCC diagnosis and stained for EGFR and HER2 by immunohistochemical methods. For both EGFR and HER2, the immunohistochemical staining intensity and percentage of stain-positive cells on the slides were determined.

Results—43 of 46 (93%) SCCs were immunoreactive for EGFR. The median score for EGFR staining intensity was 4 (range, 2 to 12), and the median number of mitotic figures was 8 mitotic figures/10 hpfs (range, 0 to 34 mitotic figures/10 hpfs). Mitotic index was not correlated with the percentage of EGFR stain-positive cells or staining intensity. Of the 43 EGFR-immunoreactive SCCs, 38 had stain present primarily in the cytoplasm and 5 had stain equally distributed between the cytoplasm and cell membranes. Thirty-five of 46 (76%) SCCs were immunoreactive for HER2. Mitotic index was not correlated with the percentage of HER2 stain-positive cells or staining intensity. Of the 35 HER2-immunoreactive SCCs, the stain was present primarily in the cytoplasm and 7 had stain equally distributed between the cytoplasm and cell membranes.

Conclusions and Clinical Relevance—Results indicated that most periocular SCCs of horses expressed EGFR and HER2, which suggested that equine periocular SCCs might respond to treatment with EGFR inhibitors. (Am J Vet Res 2014;75:912–917)

Squamous cell carcinomas are the most common tumors of the eyes and adnexa of horses and commonly affect the eyelids, third eyelid (nictitating membrane), conjunctiva, and limbus. Breeds most frequently affected by SCC include Appaloosa, American Paint Horse, and draft breeds, and the prevalence of SCC is positively associated with age. In horses, development of SCC is thought to be related to an increased susceptibility to ultraviolet radiation carcinogenesis because all periocular SCCs express p53, lightly pigmented horses are predisposed to the development of periocular SCC, and the prevalence of SCCs is positively associated with altitude, longitude, and mean annual solar radiation.

When left untreated, periocular SCC can invade the local soft tissues, bony orbit, sinuses, and brain and metastasize to regional lymph nodes, salivary glands, and thorax. Following treatment, SCC recurrence most commonly involves the eyelid or orbit. Treatment of periocular SCC in horses is dependent on tumor location, tumor size, extent of tissue invasion, vision status, intended purpose of the affected horse, equipment availability, and financial constraints. Generally, the treatment of choice is surgical excision of the tumor followed by adjunctive treatment such as cryotherapy, iridium-192, strontium-90, intralesional cisplatin, or 5-fluorouracil. Although many treatment modalities are used for the treatment of periocular SCCs in horses, few of them are available to general practitioners, and most are associated with some risk for the personnel administering the treatment.

In human medicine, there has been a tremendous amount of preclinical and clinical research to evaluate the role of EGFRs in tumor growth and targeted cancer treatment. Four types of EGFRs (EGFR, HER2, HER3,
and HER2) have been identified, of which EGFR and HER2 have been most frequently studied in human tumors of humans.10,11 Human epidermal growth factor receptor 2 has been most commonly studied in human patients with breast or colorectal cancer, and testing for HER2 immunoreactivity has been used extensively for targeted treatment with EGFR-inhibiting drugs.12–15 Because healthy epithelial cells also have EGFRs, use of EGFR inhibitors is commonly associated with the development of rashes and occasional adverse effects associated with ocular tissues such as dysfunctional tear syndrome, blepharitis, and eyelash changes.16,17 The detection of EGFR or HER2 expression in periocular SCCs of horses would indicate that preclinical trials to investigate the effectiveness of EGFR inhibitors for targeted treatment of such tumors are warranted. Although EGFR inhibitors are generally administered IV in human patients because of concerns about actual or potential metastatic disease, it might be possible to administer EGFR inhibitors intrareinjectionally in periocular SCCs of horses because of their low rate of metastasis. Epidermal growth factor receptor inhibitors are expensive. Theoretically, for horses with periocular SCCs, intrareinjectional injection of EGFR inhibitors would greatly decrease the cost of treatment and prevent the adverse systemic effects associated with those drugs. Of course, investigation of EGFR inhibitors in cell cultures would be necessary to determine the optimal drug concentration for cytoxicity. However, because of the targeted nature of EGFR inhibitors, it is first necessary to determine whether periocular SCCs of horses express EGFR or HER2 before preclinical or clinical trials are initiated. Also, elucidation of whether the target EGFR proteins are located on the cell membrane or in the cytoplasm will assist investigators in choosing the drug most likely to be effective for those trials. The purpose of the study reported here was to determine whether EGFR and HER2 are expressed by periocular SCCs of horses.

Materials and Methods

Specimens—University of Tennessee Veterinary Medical Center pathology records from 2001 through 2011 were searched for biopsy specimens of periocular SCCs obtained from horses. Specimens were selected for the study on the basis of the reported histologic diagnosis, tumor location, and availability of archived tumor specimens for further evaluation. The search resulted in the identification of 46 periocular SCCs that were eligible for the study, of which 14 involved the eyelid, 12 involved the nictitating membrane, 11 involved the cornea and limbus, and 9 involved the conjunctiva. Histologic slides of the SCCs were reviewed by a board-certified anatomic pathologist (KMN) to confirm the diagnosis. For horses that were treated at the University of Tennessee Veterinary Medical Center, medical records were reviewed to obtain information about the patient’s response to treatment, and referring veterinarians or owners were contacted by telephone to obtain follow-up information for horses that were not treated at the university.

Additionally, an eyelid, conjunctiva, nictitating membrane, and cornea were harvested from 1 eye of each of 3 adult horses with clinically normal eyes that were euthanized for reasons unrelated to the study for use as control specimens. This study did not require oversight or approval from an institutional animal care and use committee because all SCC specimens were obtained from the pathology laboratory’s tissue archives and the control specimens were obtained after the horses were euthanized.

Immunohistochemical staining—All biopsy specimens were stored in blocks of paraffin. Each specimen was sectioned into slices that were 5 µm thick, and each slice was placed on a charged microscope slide, air-dried, and then heated at 60°C for 15 minutes. The tissue specimens on each slide were deparaffinized with xylene and rehydrated through graded ethanol to deionized water in a routine manner. Two slides (1 for EGFR and 1 for HER2) from each biopsy specimen were prepared for immunohistochemical staining. For the immunohistochemical staining procedure for EGFR, the slides were rinsed with deionized water and soaked in TBST for 10 minutes. Slides were then loaded on an autostainer, where all procedures were performed at room temperature (22°C), and slides were rinsed with TBST between each step. The slides were then exposed to a 3% hydrogen peroxide solution to block endogenous peroxidase for 5 minutes, a serum-free protein blocking solution for 10 minutes, mouse anti-EGFr clone:31G7c at a dilution of 1:40 for 30 minutes, the secondary reagents in a horseradish peroxidase–labeled polymer system for 30 minutes, and chromagen for 10 minutes. The slides were then washed with chromagen for 5 seconds with hematoxylin. Then, the slides were blued in ammonia water, dehydrated through ethanol, and cleared with xylene, and a coverslip was placed over the tissue specimen.

For the immunohistochemical staining procedure for HER2, slides were heated with EDTA buffer (pH, 9) in a steamer at 95°C for 20 minutes, then cooled for 20 minutes for heat-induced epitope retrieval. After epitope retrieval, all slides were rinsed in deionized water and soaked in TBST for 10 minutes. Slides were then loaded on the autostainer and subsequently processed in the same manner as those that were stained with EGFR, except that the primary antibody used was mouse anti-HER2 clone:CB11d at a dilution of 1:40 for 30 minutes.
Slide evaluation—For each slide, the staining intensity, location of the stain within the cells, and percentage of stain-positive cells were scored as described for EGFR and HER2. Briefly, for both EGFR and HER2, the staining intensity was scored on a 4-point scale (0 = no staining, 1 = low intensity, 2 = moderate intensity, or 3 = high intensity). The location of the stain within the cells was categorized as cytoplasm, cell membrane, or both. For EGFR, the percentage of stain-positive cells was classified into 1 of 4 categories (1 = ≤10%, 2 = >10% to 30%, 3 = >30% to 60%, or 4 = >60%). The EGFR reactivity score was defined as the product of the intensity score and the category for the percentage of stain-positive cells, and an EGFR reactivity score ≥2 was considered positive. For HER2, the percentage of stain-positive cells was classified into 1 of 3 categories (1 = ≤40%, 2 = >40% to 70%, or 3 = >70%) and no reactivity score was calculated.

Statistical analysis—The respective correlations between mitotic indices and staining intensity and percentage of stain-positive cells for both EGFR and HER2 were determined with the Pearson product moment correlation. Statistical software was used for all analyses, and values of \( P \leq 0.05 \) were considered significant.

Results

Specimens—Periocular SCC tissue specimens from 46 horses were evaluated. Breeds represented included American Paint Horse (n = 13), Appaloosa (9), and so on. The table below shows the median and range values for various measures of expression of EGFR and HER2 in periocular SCC (n = 46) and normal (control; 3) tissue specimens obtained from horses.

<table>
<thead>
<tr>
<th>Type of EGFR</th>
<th>Location of lesion</th>
<th>Specimen type</th>
<th>Percentage of stain-positive cells*</th>
<th>Staining intensity†</th>
<th>Reactivity‡</th>
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</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>Cornea</td>
<td>SCC (n = 11)</td>
<td>4 (2–4)</td>
<td>1 (1–3)</td>
<td>4 (2–12)</td>
</tr>
<tr>
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<td>Control (n = 3)</td>
<td>1</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Conjunctiva</td>
<td>SCC (n = 9)</td>
<td>4 (2–4)</td>
<td>1 (1–3)</td>
<td>4 (2–12)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (n = 3)</td>
<td>3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Nictitating membra</td>
<td>SCC (n = 10)</td>
<td>3 (1–4)</td>
<td>1.5 (1–2)</td>
<td>3 (2–8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (n = 3)</td>
<td>2</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Eyelid</td>
<td>SCC (n = 10)</td>
<td>4 (2–4)</td>
<td>2 (1–2)</td>
<td>6 (2–8)</td>
</tr>
<tr>
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<td>3</td>
<td>2</td>
<td>6</td>
</tr>
<tr>
<td>HER2</td>
<td>Cornea</td>
<td>SCC (n = 6)</td>
<td>3</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
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<td>1</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Conjunctiva</td>
<td>SCC (n = 7)</td>
<td>3 (2–3)</td>
<td>2 (1–2)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (n = 3)</td>
<td>3</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Nictitating membra</td>
<td>SCC (n = 8)</td>
<td>3 (2–3)</td>
<td>1.5 (1–3)</td>
<td>—</td>
</tr>
<tr>
<td></td>
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<td>Control (n = 3)</td>
<td>3</td>
<td>2</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td>Eyelid</td>
<td>SCC (n = 14)</td>
<td>3 (2–3)</td>
<td>2 (1–2)</td>
<td>—</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control (n = 3)</td>
<td>3</td>
<td>2</td>
<td>—</td>
</tr>
</tbody>
</table>

Of the 46 SCC specimens, 43 stained positive for EGFR and 35 stained positive for HER2. For all values, the lack of a range in parenthesis indicates that all specimens had the same value for that variable.

*For EGFR, the percentage of stain-positive cells was classified into 1 of 4 categories (1 = ≤10%, 2 = >10% to 30%, 3 = >30% to 60%, or 4 = >60%). For HER2, the percentage of stain-positive cells was classified into 1 of 3 categories (1 = ≤40%, 2 = >40% to 70%, 3 = >70%).

†For both EGFR and HER2, the staining intensity was scored on a 4-point scale (0 = no staining, 1 = low intensity, 2 = moderate intensity, or 3 = high intensity).

‡For EGFR only, the reactivity score was defined as the product of the staining intensity score and the category for the percentage of stain-positive cells, and an EGFR reactivity score ≥2 was considered positive.

— = Not calculated.

Table 2—Distribution of immunohistochemical stains for EGFR and HER2 in periocular SCC (n = 46) and clinically normal (control; 3) tissue specimens obtained from horses.

<table>
<thead>
<tr>
<th>Type of EGFR</th>
<th>Location of lesion</th>
<th>Specimen type</th>
<th>Cytoplasm only</th>
<th>Cell membrane only</th>
<th>Equally between cytoplasm and cell membrane</th>
<th>Primarily cytoplasm</th>
<th>Primarily cell membrane</th>
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</thead>
<tbody>
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<td>EGFR</td>
<td>Cornea</td>
<td>SCC</td>
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<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Conjunctiva</td>
<td>SCC</td>
<td>2</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Control</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>Nictitating membra</td>
<td>SCC</td>
<td>6</td>
<td>0</td>
<td>0</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td></td>
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<td>0</td>
<td>0</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>Eyelid</td>
<td>SCC</td>
<td>7</td>
<td>0</td>
<td>2</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
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<tr>
<td>HER2</td>
<td>Cornea</td>
<td>SCC</td>
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<td>0</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<tr>
<td></td>
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<td>SCC</td>
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<td>0</td>
<td>4</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td></td>
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<tr>
<td></td>
<td>Nictitating membra</td>
<td>SCC</td>
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<td>0</td>
<td>1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
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<td>0</td>
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</tbody>
</table>

See Table 1 for key.
Quarter Horse (7), Tennessee Walking Horse (7), and 7 other breeds (10). Of the 46 affected horses, 27 were geldings, 15 were mares, and 4 were stallions. The mean ± SD age of horses at the time the biopsy specimens were obtained was 13 ± 3.2 years. Thirty-seven of the SCC specimens were obtained from patients examined at the University of Tennessee Veterinary Medical Center; the remaining 9 specimens were obtained from outside submissions to the pathology laboratory. The clinically normal (control) tissue specimens were obtained from 2 Appaloosas and 1 Mangalarga Marchador.

Immunohistochemical staining—The EGFR staining intensity and percentage of stain-positive cells were consistent among control specimens (Table 1). For the control eyelid skin specimens, the stain was located in the cell membrane to a slightly greater extent than in the cytoplasm, and the stain was most intense in the basal region and decreased in intensity through the superficial layers. For the conjunctival specimens, the stain was located primarily in the cell membranes, and its intensity varied throughout the specimens. For the nictitating membrane specimens, the stain was located in both the cell membranes and cytoplasm of cells in the basal layer, and its intensity was varied throughout the specimens. For corneal specimens, staining was limited to the cell membranes of the basal cells at the limbus (Table 2).

Forty-three of 46 (93%) SCCs had an EGFR reactivity score ≥ 2 (Figure 1). Of the 3 SCCs that had a reactivity score of 0 or 1, 2 were obtained from the nictitating membrane and 1 was obtained from the eyelid. For the 43 EGFR stain-positive SCCs with a reactivity score ≥ 2, the median reactivity score was 4 (range, 2 to 12; Table 1) and the median number of mitotic figures was 8 mitotic figures/10 hpfs (range, 0 to 34 mitotic figures/10 hpfs). The mitotic index was not significantly correlated with the percentage of stain-positive cells (r = 0.03; P = 0.403) or staining intensity (r = 0.04; P = 0.523). The stain was located in the cytoplasm of all 43 EGFR stain-positive SCCs; it was located only in the cytoplasm of 22 tumors, was located primarily in the cytoplasm of 16 tumors, and equally distributed between the cytoplasm and cell membrane of 5 tumors (Table 2).

For the control specimens stained for detection of HER2, the stain was located only in the cytoplasm of all 43 EGFR stain-positive SCCs; it was located only in the cytoplasm of 22 tumors, was located primarily in the cytoplasm of 16 tumors, and equally distributed between the cytoplasm and cell membrane of 5 tumors (Table 2).
low in healthy epithelial cells and is increased from bas-
specimens. In humans, the basal HER2 expression is
ocular tissues, the percentage of HER2 stain–positive
specimens; however, for SCCs that involved the other
percentage of HER2 stain–positive cells in SCCs that
mic staining was not identified. In the present study, the
HER2 expression by human colorectal tumors, mem-
membrane. Immunohistochemical staining of dermal
nasal tumors of dogs generally express EGFR in the cell
expressed EGFR, the stain was generally located in the
cytoplasm, whereas for feline cutaneous SCC that
gets both EGFR and HER2. Promising results have
been achieved in human patients with cutaneous SCCs
treated with cetuximab as monotherapy or as a radia-
tion-sensitizing drug. In a phase II clinical trial, 25
positive results were achieved for most human patients
with aggressive cutaneous SCC that were administered
gefitinib prior to radiation therapy or surgery. Current-
ly, most of the available literature on drug treatment for
SCC involves human patients with aggressive or meta-
static SCC.

Limitations of the present study include the in-
ability to assess the respective correlations between
standard treatments and EGFR immunoreactivity and
treatment response. Although treatment and follow-
up data were obtained for each horse, the variation in
SCC size, numerous treatment modalities used, lack of
a standardized follow-up protocol for many horses, and
client financial constraints prevented us from evaluat-
ing those correlations. Additionally, antibodies against
EGFR and HER2, which have not been evaluated by
Western blot analysis, were used as the primary anti-
levels in fetal tissues and neoplasms. Expression of
HER2 is localized primarily in the superficial layers of
the ocular surface epithelium of humans, which was
also observed in the control specimens of all equine tis-
ues evaluated in the present study except for the cor-
nea. The finding that HER2 is expressed primarily on
the surfaces of clinically normal tissues suggests that
HER2 is preferentially expressed by differentiated post-
mitotic epithelial cells.

Interpretation of HER2 reactivity in tissues has not
been completely elucidated. Most research into HER2
reactivity has involved breast cancer in human patients.
In human breast tumors, HER2 expression is increased
20% to 30% from that in healthy breast tissue, and
tumors that have an overexpression of HER2 tend to be
more aggressive and are associated with a worse prog-
nosis, compared with HER2-negative tumors. Human
patients treated with trastuzumab, a monoclonal
antibody against the extracellular domain of HER2, af-
after breast cancer surgery had an increased survival rate
and decreased tumor recurrence rate, compared with
similar patients who were not treated with trastuzum-
ab. However, because trastuzumab affects only the
extracellular domain of HER2, it has no effect on HER2
localized in the cytoplasm, a fact that has directed inter-
pretation of HER2 immunoreactivity in breast cancer.21
Investigators of another study report that human pa-
tients with colorectal tumors in which HER2 is local-
ized in the cytoplasm might have a poorer prognosis
than do patients with HER2-negative tumors. Nonethe-
less, the relevance and prognostic value of HER2 im-
munoreactivity patterns in various tumors and species
require further investigation.

Knowledge of the staining pattern and location of
the different types of EGFRs is important when ad-
ministration of anti-EGFR drugs is considered. The 3
types of anti-EGFR drugs include monoclonal antibod-
ies such as cetuximab, which targets the extracellular
portion of the EGFR molecule; small-molecule tyrosine
kinase inhibitors such as erlotinib and gefitinib, which
target the intracellular protein kinase domain; and dual
tyrosine kinase inhibitors such as lapatinib, which tar-
gets both EGFR and HER2. Promising results have
been achieved in human patients with cutaneous SCCs
treated with cetuximab as monotherapy or as a radia-
tion-sensitizing drug. In a phase II clinical trial,25
positive results were achieved for most human patients
with aggressive cutaneous SCC that were administered
gefitinib prior to radiation therapy or surgery. Current-
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ability to assess the respective correlations between
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treatment response. Although treatment and follow-
up data were obtained for each horse, the variation in
SCC size, numerous treatment modalities used, lack of
a standardized follow-up protocol for many horses, and
client financial constraints prevented us from evaluat-
ing those correlations. Additionally, antibodies against
EGFR and HER2, which have not been evaluated by
Western blot analysis, were used as the primary anti-
bodies in the immunohistochemical staining protocols of the present study because equine-specific antibodies against EGFR and HER2 have not been developed. Murine and equine EGFR and HER2 proteins are 91% and 88% homologous, respectively. Given the specificity of the staining distributions in the control eyelid, conjunctiva, and cornea specimens, it appears that the murine antibodies used in the immunohistochemical staining protocols of this study selectively reacted with equine EGFR and HER2. It was difficult to compare the results of the present study with other studies because there is great variation in the expression of EGFR and HER2 among species and studies. Some of this variation is undoubtedly caused by differences among species and between clinically normal and neoplastic tissues, but it could also be caused by tumor stage and variations in tissue fixation and storage (including length of storage), primary antibodies used to identify EGFR expression, antigen retrieval methods, and staining techniques.15

In the present study, most of the periocular SCCs obtained from horses expressed EGFR and HER2, which suggested that administration of EGFR inhibitors might be useful for the treatment of those tumors, assuming that extracellular or intracellular EGFR and HER2 have a pathogenic role in the development of SCC. Variation in immunoreactivity to both EGFR and HER2 among the SCCs of the present study might indicate that each tumor should be immunohistochemically evaluated prior to treatment to determine which EGFR inhibitor is likely to be most effective, as is currently done for human patients with breast cancer. However, some human patients with colorectal tumors that do not have immunoreactivity to EGFR respond favorably to treatment with EGFR inhibitors,26 and if periocular SCCs of horses respond similarly, immunohistochemical evaluation of each tumor may not be necessary. Further research is necessary to determine the efficacy and feasibility of EGFR inhibitors for the treatment of periocular SCC in horses.

References