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Canis lupus familiaris as relevant animal model for breast cancer - a comparative oncology review

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Comparative oncology represents an important tool in cancer research and drug development. After the sequencing of the canine genome, many similarities between canine and human tumors have been noticed in what concerns physiological and pathological conditions, including tumorigenesis and many clinical aspects. Breast cancer is a complex and heterogeneous group of mammary neoplastic diseases, thus, it is important to find suitable animal models for new biomarker discovery and therapeutic strategies. From histopathological to molecular level, many similarities between canine and human breast cancers show that dogs can be reliable models for this pathology, and can improve the therapeutic options. In this review, we synthesized the most recent studies that demonstrate the homologies between dogs and humans in terms of mammary cancer development

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and progression. These findings have the potential to bring important contributions to human and veterinary medicine, under the concept of "One Health".

KEYWORDS: animal model / biomarker / breast cancer / comparative oncology / therapy

In the last years, a new global concept was developed in the interdisciplinary collaboration between human, animal and environment health sciences. This strategy called One Health represents a combined effort of multiple disciplines to improve health in humans, animals and plants in the global ecosystem, using an integrated research approach [Lerner and Berg 2015]. Human cancers lack multiple models for experimental research. Respectfully, after the accomplishment of Human Genome Project, other genomes – including canine – were sequenced, and showed common features with the human genome. The Human Genome Project provides us much important information especially in clinical medicine to understanding of human diseases in terms of human biology and pathology. Moreover, canine cancers have certain characteristics among which are a conservatory immune system, specific tumor microenvironment, and a high degree of tumor heterogeneity. Canine spontaneous tumors have additional unique features, some of which are being absent in mouse models, such as maintaining tumor microenvironment conditions necessary for the development and progression of malignancies, including specific oxygen levels in the body and the growth of new blood vessels.

The field of comparative oncology has experienced an exceptional advancement over the past years and has progressively captivated the interest of specialists in cancer research through the development of new study areas such as comparative genomics. This research field could be the key to a better understanding of the relevant challenges involving cancer, starting from epidemiological issues, prevention or novel targeted therapies, to personalized health care [Huminiecki *et al*. 2017, Huminiecki and Horbańczuk 2018, Nunney *et al.* 2015].

Comparative genomics represents an important field of biology which focuses on comparing the genomes of different species. In cancer research, these comparative studies are very significant, since they lay the grounds for finding molecular similarities between species such as human, mouse and dog, and promote them as study models for a better understanding of pathogenesis processes in all species. After the sequencing of the first human genome as a result of the Human Genome Project, researchers started to sequence the genomes of various important animal models, such as the mouse genome sequenced (Mouse Genome Sequencing Consortium) by Waterston [Mouse Genome Sequencing, Waterston *et al*. 2002], and the canine genome sequenced by Linblad-Toh and published in 2005 [Lindblad-Toh *et al*. 2005]. Time and again, sequencing has proven itself to be an important tool for finding similarities between species in terms of DNA, RNA, miRNAs, and lncRNAs sequences, to be used for emerging studies of mutations, common genes and their role in new cancer therapeutic approaches [Pop *et al*. 2014, Irimie *et al*. 2015]. The identification and use of animal models which develop spontaneous tumors with similar molecular profiles to human cancers can provide important information, essential for making advances

in discovering new and improved oncological drugs.

Several murine models have been developed and used to investigate human cancer mechanisms, starting with the identification of factors correlated with malignant transformation, invasion or metastasis, and, more recently, for the evaluation of novel prognostic or diagnostic biomarkers [Richmond and Su 2008, Brown *et al*. 2015]. These models were used to investigate the factors involved in malignant development and progression, as well as to examine the response to therapy. Nowadays, mouse cancer models are used to investigate signaling pathways involved in major mechanisms like carcinogenesis, cancer promotion, progression and metastasis. Many studies demonstrated that several murine models also showed heterogeneity and genomic instability, and did not present any of the key features that define cancer in humans, like long periods of latency, complexity of cancer recurrence and metastases, and the response to new generation therapies [Seok *et al*. 2013, Schiffman and Breen 2015].

Another issue related to mouse models is represented by their incapacity to predict tumor response to therapy, this being translated into lack of success for many phase I or II clinical trials [Seok *et al.* 2013, Mak *et al.* 2014]. The most important aspect influenced by this condition is the fact that a fraction of the patients do not respond to first-line therapy, due to tumor heterogeneity and to the multiclonal development of the disease. Murine models do not develop similar cancer subtypes as humans, and, consequently, only limited drug response tests can be conducted. The newly developed avatar mice are extremely expensive and their use is limited to a few research groups. In this particular situation, more attempts are necessary in order to administer the suitable drugs. Thus, the quality of life of these patients is severely affected, as well as their overall survival [Sparano *et al*. 2004]. Due to this, it is necessary to find other cancer models for an improved, more efficient investigation of the biology of human malignancies. Larger animal species like dogs or cats have higher chances of developing some form of cancer during their lifetime than smaller animals, since each cell division brings a subsequent risk of spontaneous mutations for a tumor lineage, like in the case of humans [Brown *et al*. 2015, Fazekas *et al.* 2016] – Figure 1.

Studies demonstrate that cancers occurring in dogs share many characteristics with human malignancies [Ranieri *et al*. 2013, Gardner *et al.* 2016]. The size of the haploid dog genome is estimated to be 2445 Mb, and the diploid dog genome is organized in 38 pairs of autosomes and two sex chromosomes. Studies show that over ~650 Mb of ancestral dog DNA sequence is common with humans and absent in mice [Alvarez 2014]. A comparative analysis of 13,816 protein-coding genes with 1:1:1 orthology in human, mouse and dog, showed that the numbers of lineage-specific non-synonymous substitutions (i.e., amino acid changing; KA) are 0.017, 0.038, and 0.021 [Lindblad-Toh *et al*. 2005, Rowell *et al.* 2011]. Dogs are susceptible to inherited diseases that are also common in humans, like cancer and other diseases, such as hemophilia and neuropathologies [Sargan 2004, Schiffman and Breen 2015]. Many studies conducted on canine models showed that they are suitable models for human cancer research and translational medicine [Lindblad-Toh *et al*. 2005, Rowell *et al*. 2011, Alvarez 2014].

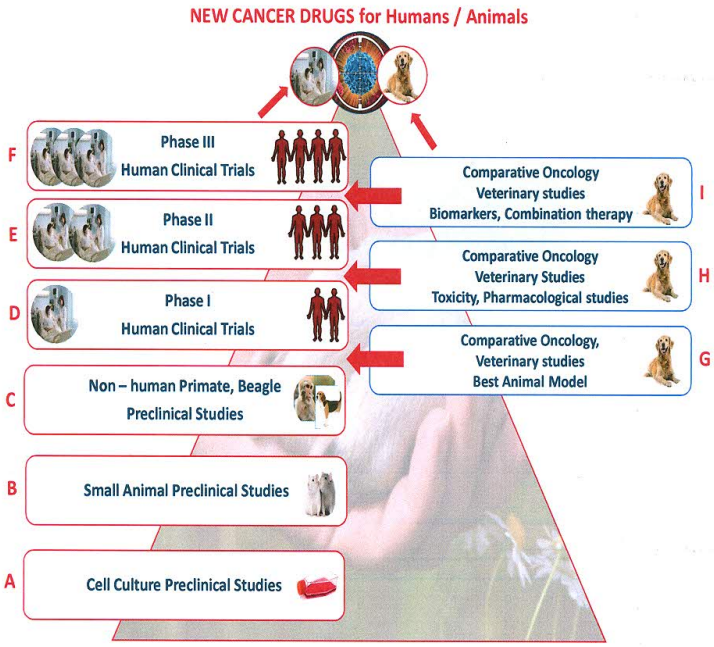

Fig. 1. Advantages of Canine models for New Cancer Therapy development. A) In vitro preclinical studies in cell cultures. B) and C) Preclinical in vivo studies in murine or small animal and human primate and Beagle dog models. D) Phase I human clinical trials: medication safety studies in 20-80 cases – several weeks and months. E) Phase II human clinical trials: safety and efficacy studies, side effect identifying in 100-300 cases – up to two years F) Phase III human clinical trials: safety, efficacy, dosing studies, side effect monitoring 1000-3000 cases – one to four years G) Preclinical comparative oncology studies, better animal model for drug discovery. H) Comparative oncology studies in dogs can eliminate drugs with an unfavorable therapeutic index and can focus in pharmacokinetics, pharmacodynamics in Phase I and II clinical trials. I) Comparative studies can optimize the design of the clinical trials and help to identify most effective drugs in Phase III clinical trials.

Canine as models for breast cancer research

Recent studies demonstrated high similarities between human breast cancer (HBC) and canine mammary tumors (CMT), from histopathological to molecular level. At the same time, the same course of the disease was described in both species [Grosse *et al*. 2014, Rasotto *et al*. 2014]. In female dogs, like in women, there can be found similar shared characteristics of breast cancer, such as spontaneous tumors, hormonal etiology, identical course of the disease, and age of onset. Tumor size evolution, clinical staging and lymph node metastases represent clinical similarities between HBC and CMT which are encountered both at macroscopic and at molecular level [Klopfleisch *et al*. 2011]. These similarities include the overexpression of estrogen and progesterone receptors, similar proliferation markers, epidermal growth factor resemblance, TP53 mutations, comparable features of metalloproteinases and

cyclooxygenases [Queiroga *et al*. 2011, Queiroga *et al*. 2015, Spoerri *et al*. 2015, Hegde *et al*. 2016].

With the common purpose of increasing survival rates in patients with mammary neoplasms, these studies can help the development of new therapeutic strategies in both human and veterinary medicine. CMT can represent a good model to study HBC, from the epidemiological studies to the histopathological patterns of the tumor [Vascellari *et al*. 2016].

Incidence and risk factors

Breast cancer represents one of the most frequent cancer in both women and female dogs, with incidence levels growing more and more in the last years. Globally, in 2012, human breast cancer (HBC) represented 25% of all cancers in the female population. After skin cancer, canine mammary tumors (CMT) are the second most common cancers in female dogs. According to statistical studies from different countries, the incidence of CMT in the last years is 25-47.5% [Gupta *et al*. 2012, Salas *et al*. 2015]. According to Dobson's studies (2013), in the UK 27% of all deaths in pure-bred dogs were caused by cancer. Statistical data show that HBC, similar to CMT, represents approximately 50% of malignant tumors in human and dog patients [Queiroga *et al*. 2011, Dobson 2013].

As companion pets, dogs live in the same environment as their owners and they are exposed to similar carcinogenic factors. These factors, as well as age and obesity, and shared genomes, bring mammary cancer development pattern in dogs closer to the human breast cancer than the murine models [Lim *et al.* 2015]. Annual incidence of CMT estimated at 198/100,000, is comparable to the rate of 125/100,000 for HBC. A risk for malignant tumor development of approximately 26% in spayed or non-spayed dogs after the second estrus was observed [Radha *et al*. 2014, Salas *et al*. 2015]. These studies revealed similar hormonal etiology between CMT and HBC. Several clinical and histopathological similarities between CMT and HBC were observed for the same molecular types and subtypes of mammary cancer. Canine mammary simple carcinomas histologically match human breast carcinomas, presenting large genomic aberrations and showing corresponding key features of human breast cancer [Liu *et al.* 2014]. In humans, associated risks involve the relation between obesity and mammary tumors, and the influence of hormone-related variables, such as puberty onset, existence and number of pregnancies, history of lactation, and menopause debut. Moreover in canines, studies observed a lower age for the development of CMT in overweight or obese dogs (9.0 years) than in normal bodyweight dogs (10.2 years). At the same time, lymphatic invasion of carcinoma cells was found to be more frequent in overweight dogs than in optimal weight dogs [Liu *et al*. 2014, Lim *et al*. 2015].

According to Globocan 2012, human breast cancer presented a high incidence and a lower survival rate in patients above the age of 50, while for the age-wise distribution of CMT, the highest incidence was observed in the age group of 10-12,

taking into account the relation between human and canine ages [Gupta *et al.* 2012, Radha *et al.* 2014, Ferlay *et al.* 2015, Salas *et al.* 2015] – Figure 2. High incidence of CMT was reported in purebreds like German Shepherds, Labradors and Spitz [Gupta *et al.* 2012]. Other studies confirmed that, when looking at CMT frequency according to the breed, it presents a higher percentage among purebred animals in comparison to mixed-breed animals (80% *vs*. 20%, respectively). The frequency of CMT is also higher in small breeds than in larger breed female dogs. According to size, larger breeds like German Shepherd or Labradors present an incidence of 23%, medium size breeds such as mixed breeds, Boxers or Beagles have 29%, while smaller breeds like Cocker, Maltese, or Schnauzer present a 48.8% incidence of CMT [Salas *et al*. 2015] – Figure 3. Another study described overall median survival time in 126 dogs to be 1113 days. According to Cox regression analysis, some variables such as histological grade (p=0.029, HR 4.31, 95% CI 1.3-14.31) and age (p=0.009, HR 1.31, 95% CI 1.1-1.62) are important factors in defining the overall survival (OS) [Betz *et al*. 2012]. Another study showed a ±SD survival time for dogs with recurrence/distant metastases of 11.96±7.58 (range 2-24 months) and the mean time for the detection of recurrence/metastasis of 5.29±5.68 (range 1-21 months), the animals presenting a 48% overall 2-years survival. Large tumors (≥3 cm) and invasive tumors were associated

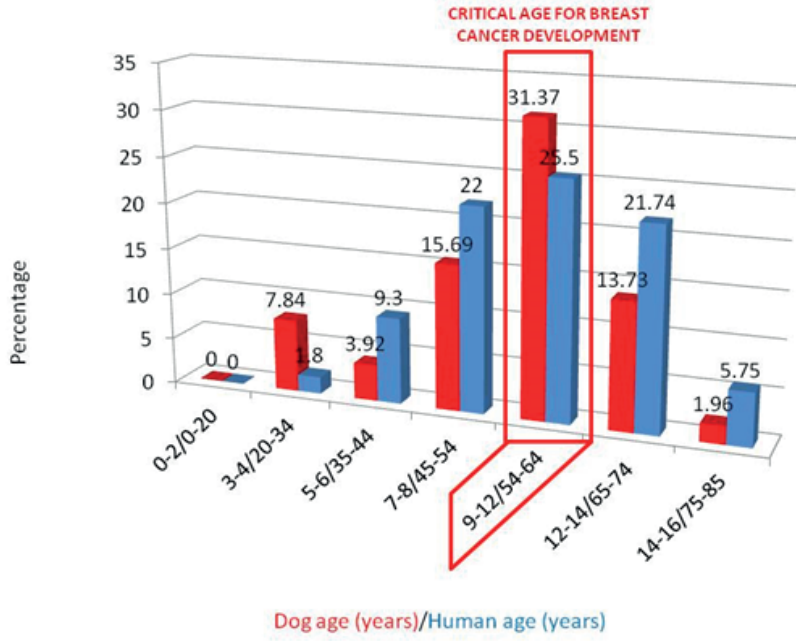

Fig. 2. Comparative incidence of CMT and HBC according to age distribution for humans and dogs emphasizes the relevance of dog as suitable animal models for studying breast cancer. CMT development is mostly reported between 8 and 12 years correlated with the 54-64 year in women.

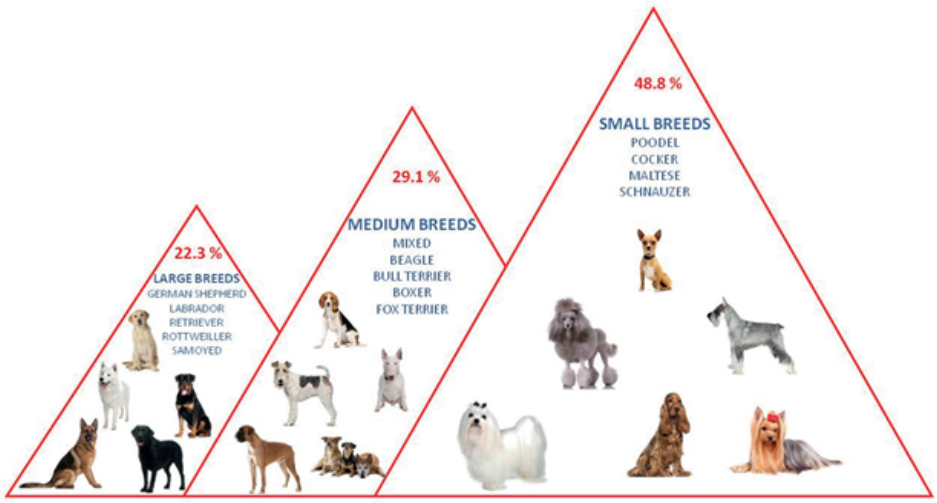

Fig. 3. Incidence of CMT in different types of dog breeds, highlighting the breeds with a high risk of mammary tumors.

with shorter disease-free survival (DFS) and overall survival (OS), and presented an increased risk of recurrences or developing distant metastases [Santos *et al.* 2013].

Clinical and histological similarities

One of the most important prognostic factors in the diagnosis of HBC is the presence of regional lymph node metastases [Hong *et al*. 2015]. In CMT, the existence of lymph node metastases also represents an important prognostic factor [de Araujo, *et al*. 2015]. Studies demonstrate a high correlation between lymph node metastasis of HBC and CMT with gene expression profile specific for increased cell proliferation, altered cell differentiation and increased growth factor signaling [Beha *et al.* 2014, Weishaar *et al.* 2014]. Studies show an up-regulation of genes associated with cell cycle regulation, matrix modulation and proteasomal degradation, in contrast with the down-regulation of differentiation genes, growth factor pathway genes, and actin organization regulatory genes (like p53, p21, RXFP1, MMP-2, p27, VEGF) [Klopfleisch and Gruber 2009, Lamp *et al*. 2013, Raposo-Ferreira *et al.* 2016]. These studies indicate the role of several differentially expressed genes in the induction and maintenance of the metastatic progression in CMT [Chiorean *et al*. 2013, Braicu *et al.* 2016]. Mutations in BRCA1 and BRCA2 genes were associated with increased mammary tumor risk in breeds with high prevalence of breast tumors, conferring an approximately 4-fold increase in the risk for CMT [Egenvall *et al*. 2005, Rivera *et al.* 2009, Melin *et al.* 2016]. A correlation has been observed between the over-expression of EGFR and increased angiogenesis, aggression and metastasis in malignant CMT

[Carvalho *et al*. 2013]. Taking all these into account, it is foreseeable that CMT has the potential to become a useful and more commonly used translational model for further studies of HBC [Klopfleisch *et al*. 2011, Weishaar *et al*. 2014].

A high histological similarity between human and dog mammary tumors was described in several studies. According to Radmehr Shafiee [2013], the Elston and Ellis method of histological grading used in human medicine can be a reliable prognostic factor in veterinary medicine as well [Shafiee *et al.* 2013]. The most common tumor types that affect canine mammary glands are complex carcinomas and simple carcinomas. Anaplastic carcinoma subtypes were associated with grade III tumors and carcinoma-tubular subtypes, while carcinoma arising in a complex adenoma/ mixed-tumor subtype is associated with grade I tumors. Invasion into the lymphatic system was observed in comedocarcinoma, anaplastic carcinoma, and inflammatory carcinoma subtype of CMT. In addition, the most frequently occurring molecular subtype was luminal A, while the basal-like subtype was the most malignant form associated with grade III tumors and lymphatic invasion [Goldschmidt *et al*. 2011, Im *et al*. 2014]. Morphology and immunohistochemical studies demonstrate that canine invasive micropapillary carcinoma features are similar with the ones in humans and present a poor prognosis, aggressive development and high degree of metastases to regional lymph nodes [Goldschmidt *et al*. 2011, Gamba *et al*. 2013, Alvarez 2014, Beha *et al*. 2014] – Table 1. These similarities between the histopathological

Tabel 1. Common histopathological subtypes of canine and human mammary tumors

Canine mammary tumor histopathological classification [Goldschmidt *et al*. 2011]			Human breast cancer histopathological classification [Malhotra *et al*. 2010]		
In situ carcinoma	ductal	comedo cribriform micropapillary papillary solid anaplastic	*In situ* carcinoma	ductal	comedo cribriform micropapillary papillary solid anaplastic
Invasiv carcinoma	tubular, tubulopapillary ductal		Invasiv carcinoma	tubular ductal lobular	

characteristics of CMT and HBC sustain the possibility of using the same grading method in canine mammary tumors [Pinho *et al*. 2012, Cassali 2013, Shafiee *et al*. 2013, Im *et al*. 2014].

Molecular similarities

Hormones

Steroid hormones have an important role in mammogenesis. HBC is well classified according to the levels of estrogen and progesterone receptors in two positive (Luminal-A/Luminal-B) and three negative molecular subtypes ($HER2^{+}$,

Triple Negative and Basal Like). The same classification form was described in the CMT [Gama *et al*. 2008, Sassi *et al*. 2010]. In HBC, steroid hormones (estrogen and progesterone) and their receptors, (estrogen receptor – ER, and progesterone receptor – PR), both have predictive and prognostic significance. A lower hormone receptor expression was associated with worse prognosis in both HBC and CMT. In HBC, the main estrogen receptor is represented by the ERα isoform. Studies on the ERβ expression in both species demonstrated that the ERβ-positive tumors are usually benign, rather than malignant [Mainenti *et al.* 2014]. HER2/neu (human epidermal growth factor receptor) has a regulatory role in breast cell growth, maintaining the normal status of mammary tissue [Chiorean *et al.* 2013, Braicu *et al*. 2016]. Studies demonstrated that over-expression of the HER2 induced by carcinogenic factors leads to breast cancer development [English *et al*. 2013]. Dog carcinomas show a significantly higher level of HER2 mRNA expression compared to the one observed in normal mammary tissue [Burrai *et al*. 2015]. Expression of ER1, PR and c-*erb*B-2 in CMT cell lines shows similarities with human breast cancer phenotypes for a selection of canine mammary tumor-derived cell lines. A profiling study on the expression of EGFr family genes c-*erb*B-3 and c-*erb*B-4 in CMT also provided an improved classification of canine breast cancer identifying new phenotypes beyond the conventional luminal-basal characterization used in human breast cancers [Kabir *et al*. 2016].

The progesterone receptor (PR) negative status in HBC is directly correlated with a reduced survival rate, particularly in HER2 negative breast cancer subgroup [Sun *et al*. 2016]. Other studies present PR as an independent prognostic marker [Purdie *et al.* 2014]. The worst survival status in relation with PR and estrogen ER is represented by ER^-/PR^-, followed by ER^-/PR^+, ER^+/PR^-, ER^+/PR^+ and HER-2 over-expression, and $ER^+/HER\text{-}2^-$ [Im *et al.* 2014]. In CMT, the $ER\alpha^-/PR^+$ status was found to be the most common in malignant tumors. During the progression of the disease toward metastases at different levels, tumors have a tendency to lose their steroid hormone dependency, and the worse prognosis is indicated by the ER^-/PR^- in both HBC and CMT [Queiroga *et al*. 2011, Braicu *et al*. 2014] – Figure 4.

The role of the growth hormone (GH) and insulin-like growth factor-I (IGF-1) in tumorigenesis was observed in both HBC and CMT. High levels of the GH mRNA, GH receptor and IGF-I expression was described in these cancers [Queiroga *et al.* 2011, Brahmkhatri *et al.* 2015]. The Insulin Like Growth Factor 1 (IGF-1) system has a significant role in human physiology, particularly in the development and function of tissues, including the mammary gland, mammary terminal end bud, and ductal formation. Breast cancer may aberrantly express each component of the IGF-1 system [Christopoulos *et al*. 2015]. Reduced concentration levels of serum IGF-I showed an inhibitory effect on cell proliferation [Hornen *et al*. 2016]. The use of GH receptor antagonists as anti-tumorigenic agents can represent an additional therapy approach in cancer treatments [Felice *et al.* 2013]. The prognostic value of GH and IGF-I concentrations in serum and tumor tissue can become a basis for endocrine

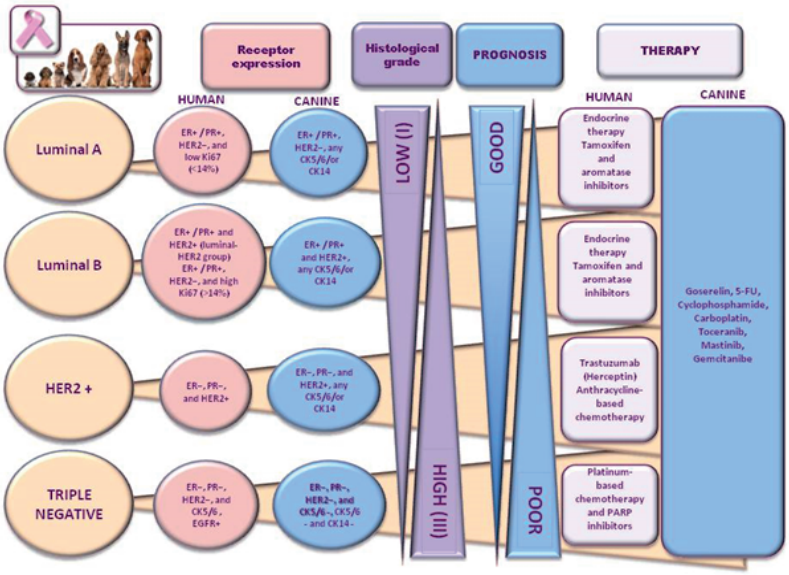

Fig. 4. Breast cancer molecular subtypes/histological grade/prognosis and therapy similarities for HBC and CMT.

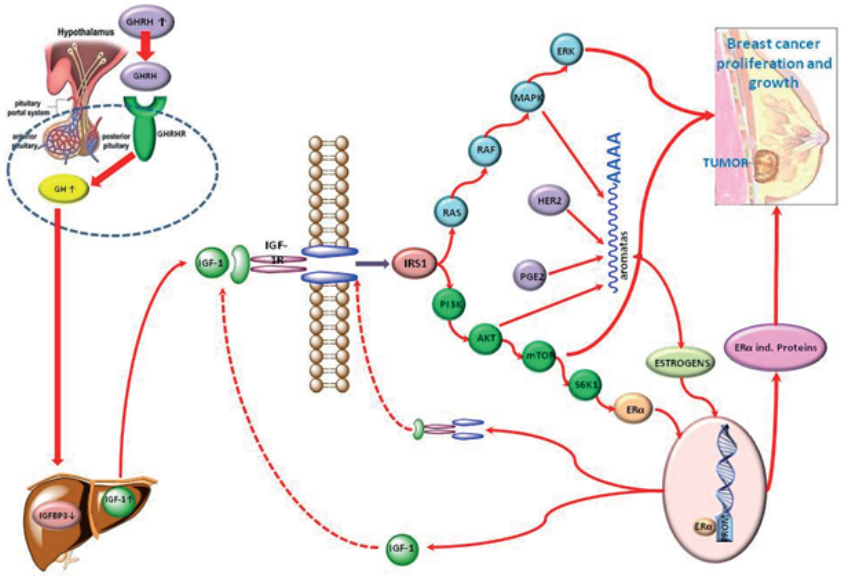

Fig. 5. Schematic GH/IGF axis in breast cancer.

therapies development [Christopoulos *et al*. 2015, Horne *et al*. 2016]. In addition, a high association was observed between increased IGF-I tumor tissue levels and clinical follow-up of the cancer patients, such as rate of growth, tumor size, skin ulcerations and adherence of tumor cells [Christopoulos *et al*. 2015, Horne *et al.* 2016]. This positive correlation between tumorigenesis, malignancy and the GH and IGF-I increased level in malignant tissues can be an indication that this GH/IGF-I axis could have prognostic value [Queiroga *et al*. 2011, Felice *et al*. 2013, Christopoulos *et al.* 2015, Matos and Santos 2015] – Figure 5.

The role of prolactin (PRL) in the development and progression of malignant tumors was described by many recent studies [Wennbo and Tornell 2000, Zemmoura *et al*. 2013, Shemanko 2016]. The prolactin hormone, which is synthesized by the anterior pituitary gland, has multiple biological actions [Queiroga *et al.* 2005]. The first role of PRL is the lactogenic action, but in recent years many studies demonstrated that PRL might also act as a growth factor [Michel *et al*. 2012, Shemanko 2016]. PRL has an important role in mammary epithelial development, and studies show that PRL uptake can increase mammary tumor development. Some studies demonstrate a strong correlation between PRL and sex steroid hormones, especially between progesterone and PRL on the one hand, and the development of the mammary tissue, on the other [Huang *et al.* 2015, Spoerri *et al.* 2015]. The malignant phenotype of CMT was associated with loss of *ERα* (*ESR1*), *PGR*, *GHR,* and prolactin receptor (*PRLR)* gene expressions [Spoerri *et al.* 2015, Mohr *et al.* 2016]. High levels of serum PRL were associated with a decrease in the gene expression of the respective receptors only in malignant mammary neoplasms. Studies show that an increased level of prolactin correlated with steroid hormone levels can represent a prognostic factor in mammary neoplasms [Queiroga *et al.* 2005, Spoerri *et al.* 2015].

Molecular markers

Recent studies in human and veterinary medicine are focused on the discovery of prognostic factors that could lead to the identification of therapeutic targets, and on the development of new methods to increase the survival rate in cancer. There is a high similarity between HBC and CMT molecular prognostic markers, with potential impact on comparative oncology [Schiffman and Breen 2015].

Hereditary

BRCA1, *BRCA2* and *RAD51* genes are expressed normally in breast tissue cells and have important roles in DNA damage repair. *BRCA1* and *BRCA2* gene mutations can affect the DNA damage repair process and can contribute to an increased tumorigenic potential. HBC displays a high correlation between the aggressive tumor phenotype and low expression of the *BRCA1, BRCA2* and *RAD51* complex. The protein encoded by the *RAD51* gene has an important role in the repair of DNA double strand breaks. In CMT, as in HBC, the role of *RAD51* in DNA repair processes was demonstrated.

Studies showed the importance of these gene mutations in the development of the aggressive phenotypes of both HBC and CMT, and their role as potential prognostic biomarkers [Im *et al.* 2013]. The ER negative (P=0.004), PR negative (P=0.046), and triple negative (ER, PR, and HER-2 negative; P=0.016) phenotypes, as well as the basal-like molecular subtype (P=0.019) in Shih Tzu dogs were directly correlated with cytoplasmic and membranous expression of BRCA1 [Im *et al.* 2013]. Germline mutations in BRCA1/2 were associated with increased risk in mammary cancer development in some breeds with known high prevalence of CMT [Rivera *et al*. 2009].

Somatic-genetic

Some genes, like *Ki-67, PCNA, P53, P63, HER2, EGFR, BRCA* etc., involved in human breast cancer, are also active players is CMT carcinogenesis.

Encoded by the *MKI-67* gene, antigen Ki-67 is a nuclear protein necessary for cellular proliferation. Ki-67 was identified in many human and dog malignant tissues, and has a role in ribosomal RNA transcription. Antigen Ki-67 inactivation leads to ribosomal RNA (rRNA) synthesis inhibition [Perez *et al*. 2015, Rossi *et al.* 2015, Sun *et al*. 2015]. PCNA, which has a role in the replication process, is a DNA clamp acting as a processor factor for DNA polymerase δ. Antigens Ki-67 and PCNA represent markers to determine cell proliferation, and their expression in human and canine malignant tissues was associated with metastases and poor prognosis [Inwald *et al.* 2013, Carvalho *et al*. 2016].

P53 is a protein, also named the guardian of the genome, encoded by the *TP53* gene with a controller role in the cell cycle. It has both a DNA repair and tumor suppressor role. Studies demonstrated that mutations in the TP53 gene produce an immunohistochemical expression of accumulated p53 nuclear protein, deregulate cell proliferation and induce or sustain tumorigenesis. This over-expression of the mutant p53 genes in HBC and CMT was correlated with poor survival rates and can represent an important prognostic tool in both species [Queiroga *et al.* 2011, Dolka *et al.* 2016]. A positive correlation was described between cleaved caspase-3 (CC3) and Bcl-2 expression; CC3 and higher mitotic index (MI), ERα and p53 expression. In the longer-survival group (>18 months), CC3 expression was negatively correlated with ERα, whereas p53 expression was positively correlated with reduced tumor differentiation, higher mitotic index, invasive growth, and necrosis [Dolka *et al.* 2016]. There is a high similarity between the organization of the canine p53 coding exons and gene products, and the human p53 gene, and it is a promising therapy target in both human and canine breast cancers [Klopfleisch and Gruber 2009, Dobes *et al.* 2014, Silwal-Pandit *et al*. 2014].

Epidermal growth factor receptor (*EGFR*; ErbB-1; *HER1* in humans) and HER-2/neu are members of the ErbB family of receptors, and subfamily of four closely related tyrosine kinases. The overexpression of these receptors has an important role in the development and progression of both HBC and CMT. Comparative studies at biological and molecular levels showed a high degree of homology between HBC

and CMT associated antigens ErbB-1 (91%) and ErbB-2 (92%) [Singer *et al*. 2012]. Immunohistochemistry studies revealed ErbB-1 over-expression in 3/10 and ErbB-2 in 4/10 patients with CMT. This demonstrates the role in canine tumorigenesis of ErbB-1 and ErbB-2, similar to human carcinomas. The homology of human and canine ErbB-1 and ErbB-2 tumor associated antigens also shows that they can serve as targets for anti-ErbB-1 and anti-ErbB-2 drugs, and can help the further development of new targeted therapies for both species [Singer *et al*. 2012, Burrai *et al.* 2015].

Extracellular proteins

Matrix metalloproteinases (MMPs) are part of the zinc-dependent endopeptidases from the metzincin superfamily [Klopfleisch *et a*l. 2011]. They are involved in processes like cleavage of cell surface receptors, as well as in apoptotic processes, playing a major role in cell proliferation, cell migration, differentiation, and angiogenesis. In HBC, studies showed a correlation between MMP-2, MMP-9 and the lymph node metastatic processes [Aresu *et al.* 2011]. Also, in the aggressive phenotype of CMT, a high MMP-9 expression was observed [Santos *et al.* 2013]. These studies suggest that MMPs may be target molecules for the switch mechanism that leads to the progression of carcinomas from adenomas [Aresu *et al*. 2011, Santos *et al*. 2013].

Phosphatase and tensin homolog (PTEN) protein is encoded by the *PTEN* gene. With a regulatory activity in cell cycle, the *PTEN* gene has an important tumor suppressor role. In HBC, studies demonstrated a high correlation between the low expression of the PTEN protein and the aggressive ER^-/PR^- tumor phenotype, metastasis and low survival rates [Lebok *et al*. 2015]. Also, a low expression of the PTEN protein in CMT was observed [Qiu *et al*. 2008, Ressel *et al.* 2013].

During a normal cell cycle, heat-shock proteins (HSPs) have roles in stabilizing and assisting the trafficking of proteins. Several stress conditions induce an increased expression of the HSPs to protect cells via stabilization of the unfolded or misfolded proteins and restore the balance after the activation of signaling pathways in the event of acute or chronic stress factors. It was demonstrated that HSPs play a double role [Seigneuric *et al*. 2011]. First, in the cancer cell they contribute to tumor survival, and second, they have an extracellular immunological function to induce an anti-tumor response [Queiroga *et al.* 2011]. Extracellular heat shock proteins have a cytostimulatory role, inducing immune responses to control microbial infection and eliminate transformed cells [Asea 2006]. Recent studies showed that the expression levels of several HSP in human and canine tumor tissues have a prognostic value [Kumaraguruparan *et al*. 2006, Romanucci *et al.* 2008, Santagata *et al.* 2011]. HSP27 and HSP110 level were increased in human breast cancer, with poor prognostic value present also in other pathologies, like uterine, cervical, and bladder carcinomas [Ciocca *et al.* 2013]. Studies showed an increased expression of Bcl-2, Bcl-XL, HSP70 and HSP90 in apoptotic processes in both HBC and CMT [Kumaraguruparan *et al.* 2006]. Other studies revealed the implication of HSP70 and HSP27 in resistance to chemotherapy in HBC [Ma *et al*. 2013, Nadin *et al.* 2014, Davidson *et al*. 2016].

These similarities of HSPs in HBC and CMT and their implication in carcinogenesis, deregulations of apoptotic processes and response to therapy, could have a promising target therapy value, on the one hand by inducing pharmacological modification of HSPs expression or activity, or by using the HSPs in anticancer vaccines, on the other [Kumaraguruparan *et al*. 2006].

Mucins are transmembrane proteins which are glycosylated at the level of proline, threonine, and serine domains, with a role as physical barriers [Zelasko-Leon *et al.* 2015]. In stress conditions, a mucous barrier formed by secreted and transmembrane mucins protects the epithelium. These types of proteins have important roles in inflammatory processes and cancer [Nicolini *et al.* 2015, Zelasko-Leon *et al.* 2015]. Mucins are also active in tumor progression, being present not only as non-invasive markers for HBC, but also as possible therapeutic targets [Nicolini *et al*. 2015]. In HBC, an important correlation was described between mucin1 (MUC1) over-expression and well-differentiated tumors. MUC1 expression in malignant CMT was also observed. Over-expression of MUC1 was correlated with distant metastasis in mammary tumors in both dogs and humans. This over-expression of mucins in malignant HBC and CMT tissues offers them a good biomarker value, with the potential of representing a molecular marker for prognostic in these malignancies [de Oliveira *et al.* 2009]. Maspin is a serine proteinase inhibitor with suppressor activity in tumor invasion and metastasis in HBC and CMT. Studies showed that Maspin can represent a very sensitive marker for normal and neoplastic myoepithelium in mammary neoplasia, and can be correlated with the aggressiveness of HBC and CMT [Espinosa de los Monteros *et al.* 2005]. The tetrasaccharide carbohydrate Sialyl Lewis x (sL^x) antigen is usually attached to O-glycans on the cell surface and has an important role in cell-to-cell recognition processes. In HBC and CMT, the sL^x antigen facilitates the adhesion of carcinomas to the endothelium, with role in the activation of the metastatic cascade. In both HBC and CMT, studies demonstrated a high correlation between the expression of sL^x and local lymph node metastasis [Pinho *et al*. 2007, Sozzani *et al.* 2008]. Prostaglandin endoperoxid synthase (PTGS) – is an enzyme with an important role in the formation of prostanoid biological mediators like prostaglandin, prostacyclin and thromboxane. COX-2 is a controlling enzyme with an important role in the conversion of the AA/ARA arachidonic acid to prostaglandin PGH_2. It was observed that there is a high correlation between increased levels of COX-2 in HBC [Park *et al.* 2016] and CMT malignant tissues and biological processes, such as tumorigenesis, low tumor apoptosis, high metastatic processes, tumor angiogenesis, and tumor related inflammation [Park *et al.* 2014, Park *et al.* 2016]. Studies also showed an increased level of COX-2 in inflammatory breast cancers, a very rare type of breast cancer [Belevych *et al*. 2013, Esbona *et al.* 2016, Park *et al.* 2016]. These studies show that these COX enzymes are potential targets of non-steroidal anti-inflammatory drugs, which could increase the survival rates in these aggressive diseases [Guimaraes *et al.* 2014, Park *et al.* 2014, Park *et al*. 2016].

Table 2. Breast cancer biomarkers for diagnostic and prognostic use

Gene symbol	Gene name	Breast cancer type	Expre-ssion	Prognostic	Biological significance	Therapy	Reference
MKI-67	marker of proliferation Ki-67	her-2, ER+, PR, luminal A, luminal B, basal-like and "not classified"	high	poor	encoding Ki-67 nuclear protein, role in cellular proliferation	Taxanes, Fluorouracil, Epirubicin, Cyclophosphamide, Trastuzumab, Docetaxel, Anthracycline	Chen *et al.* 2015, Laurinavicius *et al.* 2015, Perez *et al.* 2015, Rossi *et al.* 2015, Sonnenblick *et al.* 2015, Sun *et al.* 2015, Elkablawy *et al.* 2016, Laurinavicius *et al.* 2016
PCNA	proliferating cell nuclear antigen	ERα mediates proliferation of breast cancer	high	poor	increase the processivity of leading strand synthesis during DNA replication	-	Campbell *et al.* 2013, Yu *et al.* 2013, Liao *et al.* 2014
TP53	tumor protein p53	luminal B, HER2-enriched, normal-like tumors, luminal A, ER, PR	mutation	poor, higher pCR	encode a tumor suppressor protein inducing cell cycle arrest, apoptosis, senescence, DNA repair, or changes in metabolism	Anthracycline, Cyclophosphamide, Paclitaxel, Radiotherapy	Deb *et al.* 2014, Dobes *et al.* 2014, Silwal-Pandit *et al.* 2014, Quigley *et al.* 2015, Vymetalkova *et al.* 2015, Watanabe *et al.* 2015, Wang Xu *et al.* 2016
EGFR	epidermal growth factor receptor	EGFR-/HER2-positive, luminal breast cancer, triple-negative breast cancer	high	poor	receptor for members of the epidermal growth factor family	Taiwan cobra cardiotoxin III, Vandetanib, Trastuzumab, anti-EGFRvIII antibody CH12, KU004, Panitumumab-Modified Gold Nanoparticles Complexed to the β-Particle-Emitter, (177)Lu, Meso-dihydroguaiaretic acid, Neratinib	Choi *et al.* 2015, Tai *et al.* 2015, Tian *et al.* 2015, Xu *et al.* 2015, Yook *et al.* 2015, Alam *et al.* 2016, De Andrade *et al.* 2016, Ki *et al.* 2016, Lim *et al.* 2016, Tsai *et al.* 2016
BRCA1	breast cancer r1	ER(-), PR(-), triple-negative phenotype	low	poor	encodes a nuclear phosphoprotein that plays a role in maintaining genomic stability, and it also acts as a tumor suppressor	Radiotherapy, ruthenium-based compounds	Amin *et al.* 2015, Drooger *et al.* 2015, Qiu *et al.* 2015, Zhang and Long 2015, Hongthong and Ratanaphan 2016
BRCA2	breast cancer r2	Triple negative	low	poor	genome stability, specifically the homologous recombination pathway for double-strand DNA repair		Ataei-Kachouei *et al.* 2015, Hedau *et al.* 2015, Shao *et al.* 2015, Wong-Brown *et al.* 2015, Yoshikawa *et al.* 2015, Meeks *et al.* 2016
PTEN	phosphatase and tensin homolog	Centrally HER2-positive patients, ER+	low/ mutation	poor	negatively regulates intracellular levels of phosphatidylinositol-3,4,5-trisphosphate in cells and functions as a tumor suppressor by negatively regulating AKT/PKB signaling pathway	EC/Trastuzumab, Docetaxel/Trastuzumab, Capecitabine, Lapatinibe, CuO Nanowire fabricated with Folic acid (CuO-Nw-FA)	Burnett *et al.* 2015, Du *et al.* 2015, Lebok *et al.* 2015, Ning *et al.* 2015, Ahir *et al.* 2016, Loibl *et al.* 2016
MUC1	mucin 1 cell surface associated	ER+,luminal A-like tumors, luminal B-like tumors(HER2), MUC1+	high	poor	encodes a membrane-bound protein, role in forming Protective mucous barriers on epithelial surfaces, role in intracellular signaling	MUC1-C inhibitor GO-203, Dinuclear platinum(II) complex (Pt12) used with anti-MUC1 in human breast cancer cells, oxidized mannan-MUC1 (M-FP)	Vassilaros *et al.* 2013, Alam *et al.* 2014, Gornowicz *et al.* 2014, Beatson *et al.* 2015, Haddon and Hugh 2015, Iizuka *et al.* 2015
SERPINA6 SERPINB3	serpin peptidase inhibitor	Her-2 negativ	high	poor	proteinase inhibitor, role in invasion and metastasis inhibition	Doxorubicin, Cyclophosphamide	Collie-Duguid *et al.* 2012, de Ronde *et al.* 2013
COX2	cytochrome C oxidase subunit II	HER-2, ER, PR, luminal A, luminal B, triple negative	high	poor			Chimal-Ramirez *et al.* 2013, Karavitis and Zhang 2013, Aggarwal *et al.* 2014, Chikman *et al.* 2014, Han *et al.* 2014, Serra *et al.* 2016
MMP-9	matrix metalloproteinases-9	human basal-like and triple negative tumors	high	poor	a family of zinc-dependent endopeptidases with important functions in extracellular matrix remodeling during development and in inflammation and wound repair processes	Doxorubicin, Taxanes, Marimastat	Sparano *et al.* 2004, Mehner *et al.* 2014

Treatment of canine mammary cancer

Surgery represents the golden-standard method for breast cancer therapy in CMT. Different types of surgery techniques are applied in CMT according to the tumor type [Tran *et al*. 2016]. These types of surgery techniques are: lumpectomy in the case of small non-invasive tumors; regional mastectomy in grade I and II tumors with resection of associated glands; unilateral mastectomy in multiple tumors; and bilateral mastectomy in sever multiple tumors in both mammary chains [Sleeckx *et al*. 2011, Karayannopoulou 2016]. At the time of surgical intervention, like in HBC, canine patients present metastases of mammary tumors, which conduct to a high relapse rate of the malignancy. In HBC, after the surgical treatment, a well-established postoperative adjuvant therapy is applied for best survival rates (Tab. 2). In canine patients, this post-surgical therapy is not routinely used, and the majority of these treatments are still in experimental phases. Some studies described several chemotherapeutics used in veterinary medicine for mammary cancer treatment. Chemotherapy represents an adjuvant treatment in high grade and metastatic CMT [Simon *et al.* 2006, Karayannopoulou 2016, Tran *et al*. 2016]. Lack of severe side effects and increased survival rate were observed in the case of chemotherapy using Cyclophosphamide, 5-Fluorouracil and combination with Vincristine or Mitoxantrone in CMT [Clemente *et al.* 2009, Karayannopoulou 2016]. Canine mammary tumors treated with a lower dose of Docetaxel also showed good results [Simon *et al.* 2006]. A combination of Gemcitabine and Carboplatin treatment in canine carcinomas showed a moderate toxicity and a 13% response rate [Dominguez *et al*. 2009].

Conclusions and remarks

The One Health Strategy becomes a worldwide, combined effort of multiple disciplines to develop an integrated research approach in human, animal and plant health for a better understanding and management of several pathologies including cancer. The progress in the field of comparative oncology can be sustained by preclinical studies, which implies the use of relevant animal models, and dogs can be a suitable alternative. The spontaneous mammary tumor development in dogs and the similarity in clinical and biological aspects with mammary tumors in humans demonstrate that dogs can be a valid model for future researches in mammary cancer pathologies. Studies on dogs will help identify the safety and activity of new anticancer drugs and the discovery of relevant biomarkers associated with response or exposure to these treatments. Dog clinical trials may be useful for the development of anticancer agents currently in early human clinical trials. Investigations made in CMT can contribute to the development of research directions in HBC focused on finding new therapeutic strategies and identifying new prognostic factors. The field of comparative oncology, particularly the study of mammary cancer, will lead to important benefits in the context of personalized healthcare and an improved quality of life in both humans and their canine companions.

Conflict of interest Statement

The authors certify that they have NO affiliations with or involvement in any organization or entity with any financial interest in the subject matter or materials discussed in this manuscript.

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