ORIGINAL SCIENTIFIC WORKS | LUCRĂRI ORIGINALE

THE DOG – A GENETIC MODEL FOR THE SPONTANEOUS TUMORS

CÂINELE – UN MODEL GENETIC PENTRU TUMORILE SPONTANE

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ABSTRACT | REZUMAT

The purebred canine population currently provides a unique scientific opportunity in compared oncology for spontaneous tumors study. The study of tumor pathology in this species contributes to global understanding of etiology, pathogenesis, biological behavior and efficiency of cancer therapy.

The aim of this review is to provide to reader an up-dated information regarding the involvement of genetics in canine cancer, highlighting the breed-predisposition for several types of tumors as a reflection of germline/somatic mutations. For those tumors in which the gene-complexes who stand at the basis of the breed-predisposition, as the histiocytic tumorss in Bernese mountain dog, multifocal renal cystadenocarcinoma and nodular dermatofibrosis in German Shepherd or osteosarcomas in Rottweiler, will be discussed.

Keywords: genetics, comparative oncology, spontaneous oncology, dog, human, cancer

Populația canină oferă în prezent o oportunitate științifică unică în oncologia comparată pentru studiul tumorilor spontane. Studierea patologiei tumorale la această specie contribuie major la întelegerea globală a etiologiei, patogenezei, al comportamentului biologic și al eficienței terapiei în cancer.

Scopul acestei analize bibliografice este de a oferi cititorului informații actualizate cu privire la implicarea geneticii în cancerul canin, subliniind predispoziția de rasă pentru mai multe tipuri de tumori ca o reflecție a mutațiilor germinale sau somatice. Pentru acele tumori pentru care genele (sau complexele de gene) care stau la baza predispoziției rasă sunt cunoscute, tumori precum cele histiocitare la Ciobănescul de Berna, chistadenocarcinomul renal și dermatofibroza nodulară multifocală a Ciobănescului german sau osteosarcomul la Rottweiler, etiologia genetică va fi discutată în detaliu.

Cuvinte cheie: genetică, oncologie comparată, tumori spontane, câine, om, cancer

Since the discovery of the first genetic map of an oncogenic virus, published independently by Fiers and Weissman in the late seventies (4; 15), the important progress in cancer genetics and epigenetics had led to the actual concept in oncology resumed by Vogelstein and Kenneth: "*The revolution in cancer research can be summed up in a single sentence: cancer is, in essence, a genetic disease.*" (29). This essential nature of the cancer is highlighted also by its definition as "*a group of lesions characterized by abnormal proliferations of the genetically modified cells*" (4) or, in another version elegantly summarized by Nowell et al. (17) as "*a clonally expansion of cells as a result of somatic mutations*". The type of genetic changes will determine the particular nature of each tumor, nature reflected in its special metabolism, morphology, and finally the degrees by which the oncologic disease affects the general state of the host organism (4). While there are current scientific data which clearly indicate the major role of genetic component in dog cancer, the simultaneous or sequential contribution of multiple genes and particularity of each tumor-type makes difficult the genetic analysis and exact identification of genes complexes involved (24). The aim of this review is to provide to reader the up-dated information regarding the involvement of genetics in canine cancer, highlighting the breed-predisposition for several types of tumors as a reflection of germline/somatic mutations.

The genetics of cancers

The multifactorial etiology of cancer (with interacting genetic, lifestyle, environmental, or/and infectious factors) is an axiomatic truth for most of the tumors. Out of all factors, the genetic component is the component that receives the best attention, the new data from this domain improving the understanding of carcinogenesis, diagnosis and treatment of cancers

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and changing the global optics to tumor disease. The information regarding the genetics of cancers are tremendous and an attempt to completely consume this subject would go beyond the purpose of the paper. Thus, we propose a brief view of the key elements regarding the gene-cancer link, which will be discussed below from known data and principal hypothesis point of view.

In the present, there are three classes of genes whose alterations are involved in tumor genesis and cancer evolution: 1 - oncogenes, 2 - stability genes ("caretaker genes") and 3 - antioncogenes (tumor-suppressor genes) (29). If mutations in these three groups of genes occur in the germline results an hereditary predispositions to cancer (most often with a familial character, e.g. MTAP and part of CDKN2A in histiocytic sarcoma of the Bernese mountain dog) or in single somatic cells, resulting sporadic tumors (e.g. mutation in p53 gene in spontaneous benign and malignant mammary tumors or lymphomas in dog) (16, 29; 2; 25). A single gene mutation is associated with a predisposition to a certain tumor (a "second hit" being typically required), the cancers being the result of mutations affecting several genes (members of one or more types). Because of large number of genes involved in the tumor genesis (primary or secondary) and for a more "biological accurate" approach, the actual studies focus mainly on pathways (e.g. p53 or Rb) rather than individual genes (29).

Cancer in dogs - a spontaneous animal model of human tumorigenesis

The importance of research in the genetic basis of cancer in dogs resides from the epidemiology of oncologic disease in this species and the recent direction of studying dogs as naturally occurring models of human cancers (23; 7). A brief analysis o epidemiology of cancer in dogs shows that, similar with humans, the oncologic diseases are one of the most important causes of both morbidity and mortality (6). We can observe in canine patients, in the last decades, a significant increasing of number of oncologic cases. Similar to humans, the cancer has become a major cause of death. Thus, in UK, malignant tumors were caused of 27% of the deaths in purebred dogs (6).

The use of canine population represents a solution for lack of animal models for spontaneous cancers, the models that are used as elements for comparison with human tumors. High phenotypic diversity combined with the common environment with humans, makes dogs a convenient model in oncology (23; 24). In addition, the comparative analysis of protein-coding genes in humans, dogs and mice proved that, with a well understood limitation, the canine model is more biologically-relevant because than rodents models (10). This conclusion is sustained also by the recent release of the entire genome sequence of dog, that proves a close resemblance with the human genome (Kirkness, 2003). Also from a population perspective, the dog represents a more natural outbred group compared with inbred laboratory rodents (28).

The dogs have a relatively similar tumor biology and incidence for several tumors (19); mammary tumors are commonly found in bitches (6) and breast cancer is the most frequently type of cancer found in women (23). In addition with epidemiologic, population and genetic data, there are also several arguments for dogs using as spontaneous animal model of human carcinogenesis like: morphological resemblance (the same World Health Organization histopathological classification system of tumors for dogs and humans), similar response to conventional therapies (20) and comparable biologic behavior (4).

Although, there are clear similarities between cancers in dogs and humans, there are still several limitations in this study model, including epidemiological differences in several type of cancer (e.g. high incidence of lung and prostate neoplasia in humans) and incomplete characterization of genetic involvement in canine cancer. However, the last impediment is quickly dissipating by the sequencing of the entire genome in dog and the availability of new genomic tools that represents the starting point of many recent studies concerning the genetic basis of diseases in dogs (28; 10).

Breed-Specific Cancer Susceptibility in Dogs

The first element suggests that a tumor could be inherited is based on high frequency of the same types of cancer in a group of animals (in our case a breed) (6) (Table 1). In order to distinguish between an inherited type of cancer and a breed predisposition, there are 3 major rules that must be followed: identification of the presence of a pattern that can be observed in a pedigree regarding the cases of cancer; the frequency number increases with inbreeding; and a relatively high number in a breed (8). Then, the complex of predisposing genes for a type of tumor must be characterized.

Recent studies supports the paradigm that several dog breeds (or families) carry certain germline mutations (as c-MET/hepatocyte growth factor receptor proto-oncogene in Rottweiler or BHD/Birt–Hogg–

Table 1

Breed-related cancers in dogs (8; 21; 6; 19; 25)

Types of Cancer	Predisposed Breed
Adrenocortical tumor	Dachshund, German Shepherd Dog, Poodle
Anal Sac Adenocarcinoma	Alaskan Malamute, Cocker spaniel, Dachshund, German Shepherds
Basal Cell Tumor	Bichon, Cocker Spaniel, Poodle, Siberian Husky
Brain Tumor	Boston Terrier, Boxer, English Bulldog, Doberman, French Bulldog, Golden Retriever, Scottish Terrier (nervous tissue) Labrador, Golden Retriever, Collie
Chemodectoma	Boston Terrier, Boxer
Chondrosarcoma	Boxer, Great Dane, Rottweiler, St Bernard
Cutaneous Papillomas (nonviral)	Cocker Spaniel
Fibroma/Fibrosarcoma	Boston Terrier, Boxer, Golden Retriever, Cocker Spaniel, Doberman, Fox Terrier
Gastric Carcinoma	Collie
Haemangioma/ Haemangiosarcoma	Airedale Terrier, American Staffordshire Terrier, Bloodhound, Boxer, Dalmatian, German Shepherd Dog, Golden Retriever, Pointers
Haemangiopericytoma	Boxer, Collie, Fox Terrier, German Shepherd Dog, Irish Setter, Siberian Husky
Histiocytoma	American Staffordshire terrier, Boxer, Cocker Spaniel, Dachshund West Highland White Terrier, Doberman, Golden Retriever, Great Dane, Rottweiler, Scottish Terrier, Shar Pei
Histiocytic sarcoma	Bernese Mountain Dogs, Flat-coated retriever, Golden Retrievers, Rottweiler
Insulinoma	Boxer, Fox Terrier, German Shepherd Dog, Golden Retriever, Irish Setter, Poodle
Keratoacanthoma	Collie, German Shepherd Dog, Yorkshire Terrier
Lymphoma	Airedale Terrier, Golden Retriever, Boxer, English Bulldog, Bull Mastiff, Chow Chow, Cocker Spaniel, Doberman, German Shepherd Dog, Golden Retriever, Irish Setter, Poodle, St Bernard, Schnauzer, Scottish Terrier
Lipoma/Liposarcoma	Cocker Spaniel, Dachshund, Schnauzer
Mammary Carcinoma	Beagle, English springer spaniels
Mast Cell Tumors	American Staffordshire Terrier, Basset Hound, Golden Retriever, Boston Terrier, Boxer, English Bulldog, Bull Terrier, Dachshund, Golden Retriever, Pekingese, Pointers, Pug, Setter, Shar-Pei, Staffordshire bull terrier, Vizsla, Weimaraner
Melanoma	Airedale Terrier, Boston Terrier, Boxer, Chihuahua, Chow Chow, Cocker Spaniel, Dachshund, Doberman, German Shepherd Dog (uveal), Irish Setter, Poodle, Pug, Schnauzer, Scottish Terrier
Myxoma/Myxosarcoma	Doberman, German Shepherd Dog
Nasal Cavity Tumors	Airedale Terrier, Golden Retriever, Collie, German Shepherd Dog, Golden Retriever, Pointers
Oropharyngeal Neoplasia	Boxer, Pointers
Osteosarcoma	Afghan hound, Borzoi, Boxer, Bullmastiff, Great Dane, Great Pyrenees dog, Irish wolfhound, Rottweiler, Newfoundland, Scottish deerhound, St Bernard
Hepatoid Gland tumors	Cocker Spaniel, Samoyed, Shih Tzu
Paraganglioma	Boxer, Boston terrier, English bulldog
Pituitary Tumors	Dachshund, German Shepherd Dog, Jack Russell Terrier, Poodle,
Plasmacytoma (cutaneous)	Airedale Terrier, Cocker Spaniel, Poodle, Scottish Terrier
Prostatic carcinoma	Doberman pinscher, Shetland sheepdog, Scottish terrier, Beagle, Airedale terrier, Norwegian elkhound
Renal tumors	German Shepherd Dog (renal cystadenocarcinomas)
Schwannoma	Fox Terrier
Sebaceous Gland Tumors	Alaskan Malamute, Cocker Spaniel, Irish Setter, Schnauzer, Shih Tzu,
Squamous Cell Carcinoma	Boxer, Dachshund (digit), Pekingese, Poodle-standard (digit), Rottweiler, Schnauzer (digit), Scottish Terrier
Sweat Gland Carcinoma	Golden Retriever, Collie, Golden Retriever
Testicular Neoplasia	Boxer, Chihuahua, Collie, German Shepherd Dog, Norwegian elkhound, Pomeranian, Poodle, Schnauzer, Shetland sheepdog , Siberian Husky, Yorkshire Terrier
Thyroid Neoplasia	Alaskan Malamute, Beagle, Boxer, Golden Retriever, Siberian Husky
Thymoma	German Shepherd Dog
Transitional carcinoma-bladder	Beagle, Scottish Terriers, West Highland White Terrier, Shetland Sheep Dogs
Trichoepithelioma	Basset Hound, Cocker Spaniel, German Shepherd Dog, Golden Retriever, Irish Setter, Poodle, Schnauzer

Dube tumor suppressor gene mutation in the Multifocal renal cystadenocarcinoma and nodular dermatofibrosis in German Shepherd) that may contribute to high rates of cancer in a similar manner to heritable, cancer-associated mutations in humans (13; 12).

The dog still represents a genetic and a scientific curiosity due to the fact that there is a very large variability along the breeds (each breed with a specific pool of genes), facilitating the identification of tumor-susceptibility alleles compared to genetically heterogeneous human population (6). Because of this large variability in the species, there are certain diseases and cancers that are more frequently find in some breeds (Table 1). The high rate of occurrence of a tumor in a breed may be due the breed predisposition regarding the phenotypic aspects or it may be an inherited genetic type of cancer (8). For example, in large breeds like the Saint Bernards there is a high incidence of osteosarcomas, but it is possible that, due to the size of the breed and the faster cells growth, to appear DNA mutations that will lead to bone neoplasia (8). Osteosarcomas are 200 times more often seen in large breeds, than in medium and small breeds (19). In this case, the initiation of tumor process has somatic mutations as causes, and the genetic information is not transmitted to the offspring (8), however this being recently challenged by several genetic studies which proves a heritable transmission of the risk for osteosarcomas in Rottweiler, Greyhounds and Scottish Deerhounds (22; 9; 2). Recently, it was found a mutation in the proto-oncogene mesenchymal-epithelial factor (MET) in 70% of Rottweiler, a breed that is known to be predisposed to several types of tumors suggesting that the high incidence has a strong genetic background (12). Recently described, AKT-2 gene mutation confirms the susceptibility of this breed to osteosarcomas (9; 2).

A more detailed analysis for some of most important tumors with a well-characterized genetics of will be discussed below.

Mammary carcinoma is the most common tumor type in female dogs, representing between 50 and 70% of all tumor types (6). The genesis of mammary tumors have a proven origin: hormonal influences (4), but in some breeds, high incidence suggests that at least some of the tumors are inherited. Germ-line mutations in BRCA1 /BRCA2 are believed to account between 5% and 10% of all breast cancer in women (18). Similarly, in Cocker Spaniel (where the incidence of these tumors reaches 36% of the total population), germ line mutations in BRCA1/BRCA2 (mainly BRCA1) genes are recently shown to be involved in the development of mammary tumors (23). But even if the involvement of the two genes is proven, the presence and degree to which their mutation influences the overall population of dogs is not known. In addition to that, the role of the gene in breast tumors is far from being completely understood. Recently Borge et al. (5) found mutations in 11 genes associated with breast cancer in dogs, additional studies being needed to determine the risk given by these mutated genes in canine mammary tumors.

Mastocytoma or mast cell tumor is the most common cutaneous tumors in dogs, with an overall incidence between 6 and 8% of all tumors (4). Several breeds are susceptible to mastocytoma, including: Boxer (4) and other Bulldog ancestry breads, Golden Retrievers, Labrador, Weimaraner, etc. (19) (for more complete list see Table 1), suggesting a predisposing genetic factors.

Although somatic mutations in the proto-oncogene C-KIT are well-known to be involved in mast cell tumorigenesis, a recent study on the European and US population of Golden retrievers (Arendt, 2015) found the involvement of *GNAI2* and hyaluronidase genes (*HYAL1*, *HYAL2* and *HYAL3* on cfa20 and *HYAL4*, *SPAM1* and *HYALP1*) as risk factors for the appearance of mast cell tumors in this breed.

Osteosarcomas are the most common primary malignant tumor of bones, representing 5–6% of all tumors of dog (4). Large breeds are known to be in high-risk for osteosarcoma (see Table 1), together these breeds accounting more than 80% of all canine osteosarcomas (22). A traumatic etiology is often suspected in both skeletal and extraskeletal osteosarcomas (Liptak, 2004).

Interestingly, a recent genome-wide association study carried by Karlsson et al. (9) found that the breed-related risk for canine osteosarcomas is largely heritable, strong candidates being AKT2 gene in Rottweiler and CDKN2A/B in Greyhounds (9; 2). Another study carried in Scottish Deerhounds using a whole genome mapping approach found a significant linkage between markers from the CFA34 (34 chromosome) and the osteosarcoma, establishing an heritable risk in this breed (Phillips, 2010). Other good candidates for predisposing to osteosarcomas such as BCL2, AKT2 PPM1L and MECOM are under study for other large breeds as Leonberg, Mastiff, Great Dane, Labrador or Golden Retrievers (9; 2).

Histiocytic sarcoma (previously known as malignant histiocytosis) represents a breed specific,

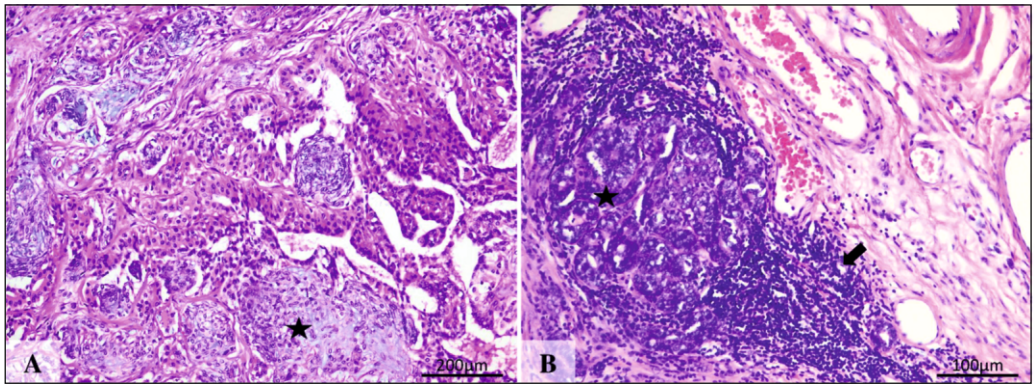

Fig. 1. Histopathological images of a complex mammary carcinoma.
Image A: the ductal/pseudoductal arrangement of the malignant epithelial component (with discrete product secretion) and the differentiated myoepithelial component (indicated by the star) are observed, ob. 20X.
Image B: the infiltrative character of the carcinoma (indicated by the star) and the perivascular invasion. At the same time, the lymphohistiocytic reaction is observed (indicated by the arrow); Hematoxylin-eosin, ob. 40

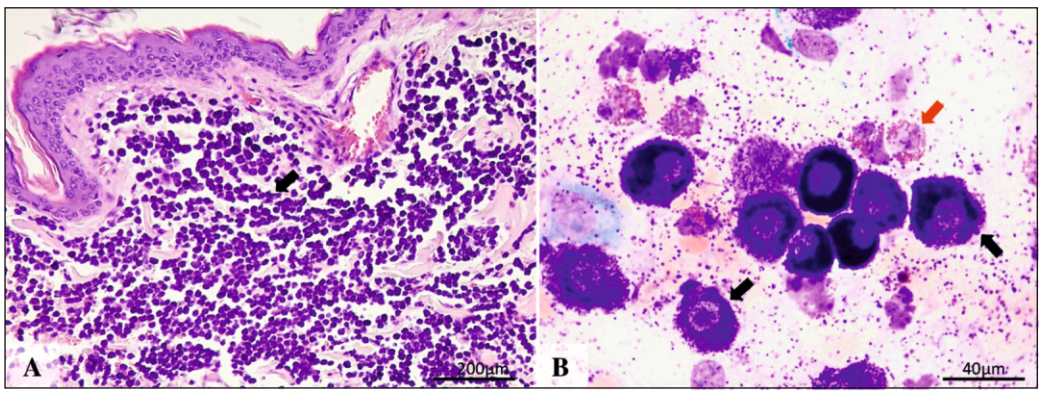

Fig. 2. Histopathological *(image A)* and cytological *(image B)* micrographs of canine cutaneous mast cell tumors.
Image A: the intense cellularity and the row-like arrangement of mast cells (indicated by arrow) in dermis, respectively hypodermis can be observed, hematoxylin-eosin, ob. 20X.
Image B: the presence of well-differentiated mast cells (indicated by the black arrows), with centrally or paracentrally located round nucleus and abundant metachromatic granules is noticed. Also the tumor-associated eosinophils (indicated by the red arrow) are present. Both tumors are well differentiated, corresponding to a low grade Mastocytoma (Kiupel scale); ob. 100 X, Diff-Quick

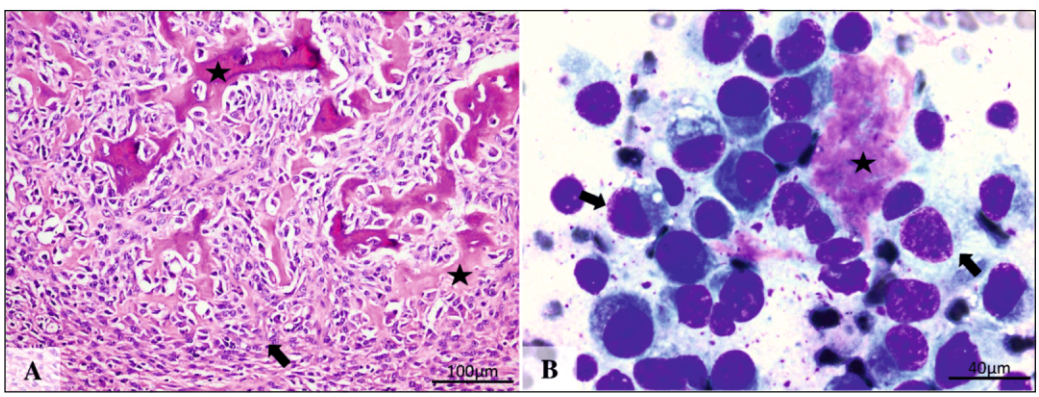

Fig. 3. Histopathological *(image A)* and cytological *(image B)* micrographs of osteosarcoma in dogs.
Image A: the pleomorphism of tumoral cells (indicated by arrow) and deposition of a partially mineralized osteoid under an irregular woven pattern (indicated by two stars) can be observed, hematoxylin-eosin, ob. x40.
Image B: the anisocytosis and anisokaryosis of the tumoral cells (indicated by arrows) and production of the non-mineralized osteoid (indicated by the star); ob. 100 X, Diff-Quick

highly aggressive and lethal histiocytic proliferative disorders (1). This highly breed-specific disorder occurs in 15% to 25% of Bernese Mountain Dogs (27), being also frequently observed in Flat-coated retriever, Golden Retrievers, Rottweiler (see Table 1). In a genome-wide association study Shearin et al. (2012) found that the susceptibility of Bernese Mountain Dogs for Histiocytic sarcoma may be primary associated with expression of the CDKN2A and CDKN2B genes (cyclin-dependent kinase inhibitors),opening the perspective for new approaches in this particular tumor.

Multifocal renal cystadenocarcinoma and nodular dermatofibrosis is a kidney cancer syndrome that was first described in German Shepherds. It is characterized by bilateral, often multifocal tumors in the kidneys, uterine leiomyomas and nodules in the skin consisting of densely packed collagen fibers (13). The analysis of extended pedigrees of dogs with RCND strongly indicates an autosomal dominant pattern of inheritance that needed to be proved at the gene level. A simple mutation in the Folliculin gene (FLCN) consisting of a substitution of a single nucletotide modifies the aminoacid sequence by changing the Histidine by Arginine in a highly conserved region of the protein. The mutation was present in all the dogs clinical diagnosed with the syndrome (13). For humans, the germline mutations in the FLCN gene, initially named BHD after the Birt-Hogg-Dubé syndrome (BHD) are responsible for the appearance of multiple fibrofolliculomas (hamartomas of the hair follicle). The individuals carrying the mutations are predisposed to an increased risk of developing renal neoplasms and spontaneous pneumothorax. The majority of BHD described for humans have mutations in different parts of the encoding region of the gene which were predicted to truncate the BHD protein, folliculin (26).

Other well characterised tumors in dogs include Anal sac carcinoma in English Cocker Spaniels (DLA-DQB1* 00701 type harbouring animals being at higher risk) and Squamous cell carcinoma of the digits in Poodle, Schnauzer (Genes implicated - KITLG, MC1R).

CONCLUSIONS

The recently studies in domain of tumor genetics conducted to increasing of knowledge level of the genetic role in the origins and evolution of cancer.

Dogs, especially the purebred population, are currently providing a unique scientific opportunity as models for human tumors causes, behavior and further platform for translational oncologic therapeutics.

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