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SPIRU HARET UNIVERSITY BUCHAREST, ROMANIA

ROMANIAN ACADEMY OF MEDICAL SCIENCES

ONE HEALTH – NEW MEDICAL CONCEPT ASSOCIATION, ROMANIA

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The importance of comparative oncology in translational medicine

Studying naturally occurring cancers in dogs to improve both dogs and people therapy

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Past

« Up to the end of 18 th Century Cancer in Animals was considered as questionable by scientists »

*Professor **Charles Lombard ,** 1956*
Ecole nationale vétérinaire , Toulouse

Les statistiques établies à Zurich (35 cancers sur 805 chiens) placent, par ordre d'importance décroissante, les cancers mammaires, puis les cancers de la thyroïde et de la peau (H. STÜNZI - 1949).

Sarcome fuso-cellulaire mammaire (R. LASSERRE et Ch. LOMBARD)
Chienne cocker, 9 ans, à ostéo-périostite diffuse.

Today

Cancer has increased in the pet animal population in recent years, as have others age-related diseases.

For example , the prevalence of pet dogs that are diagnosed and managed with cancer is estimated over 1 million per year in USA !

Dogs develop a broad spectrum of naturally occuring cancers that share strong similarities with human cancers.

Le Blanc Amy K, 2016

In addition,

Companion animals are exposed to the same cancerogenic threats: pollution, pesticides, asbest,

passive tobaco smokers, … and stress!

Pinello K C, 2019 (N W, Portugal)

Veterinary Cancerology today

A public expectation of Veterinary Care to Cancerous Animals equivalent to this one provided in human medicine …

Pet owners (« parents ») are highly motivated to seek out new options for the management of cancer in their pet.

Veterinary Cancerology today

Recent improvements

- *Diagnostic and Prognostic*

- *Treatment*

- *Biology*

Diagnostic and Prognostic Improvements

- ***Histopathology***

In addition to technical avancements in microscopy, the most valuable tools came from perfecting cytological specific markers:

Immunohistochemistry

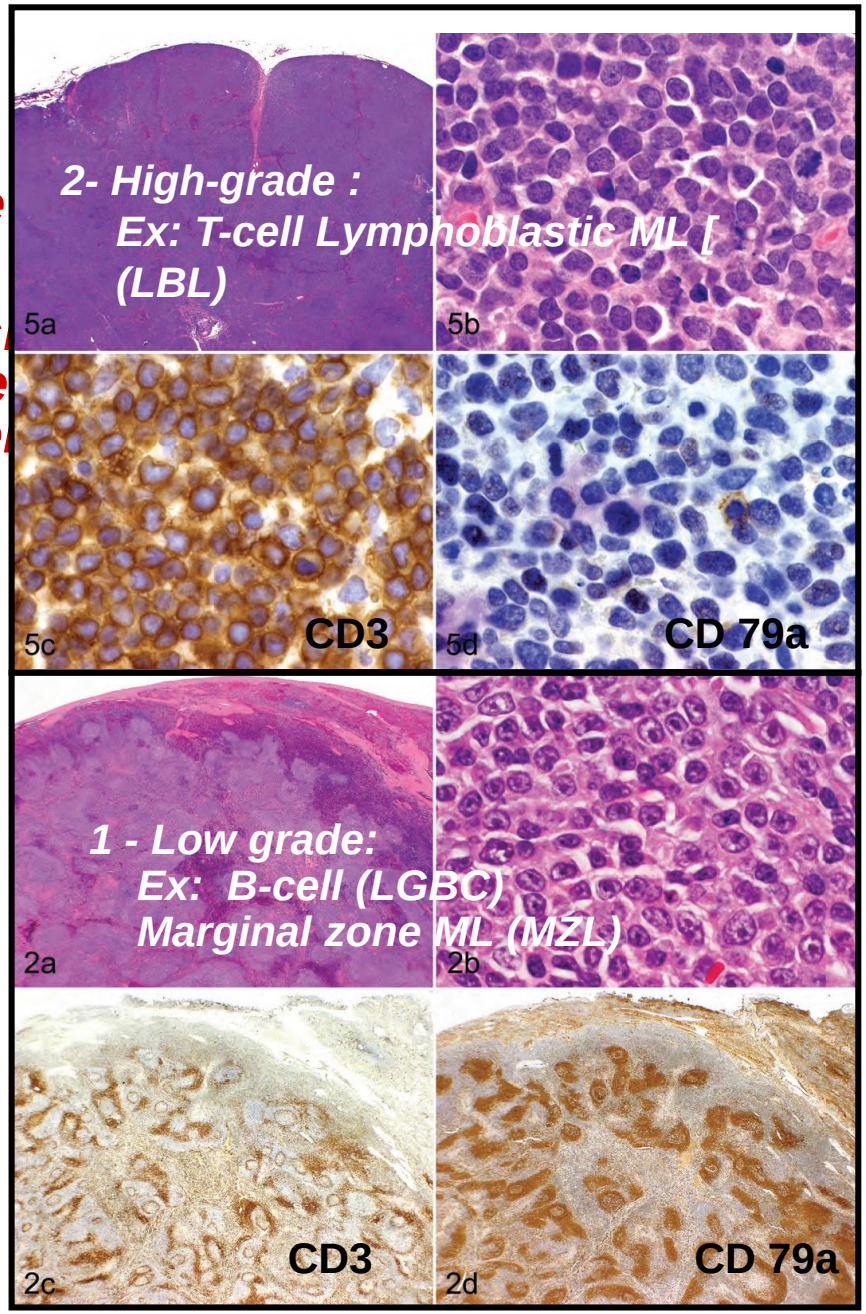
An example

- Canine ML are an important issue

Application of NH Human ML class
classification) to Canine ML has de
Human ML types have their counte

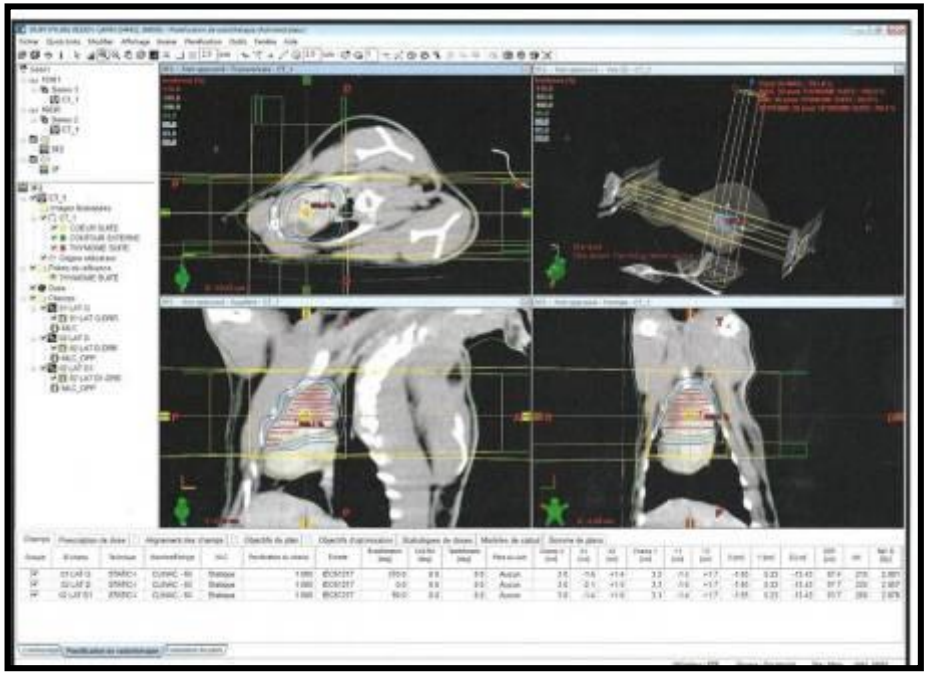
Recent studies indicate that
– as for Human Oncology -
phenotype of the Tumour
(Disease stage, Histological grade
based on mitotic rate,
Histologic/Cytologic type)
is essential for predicting
the evolution of the disease.

➢***Neoplasms are identified***
as various diseases and
not as cell types!



Diagnostic and Pronostic Improvement (cont)

- ***Sophisticated diagnostic imaging facilities:***
  - ***Computerized Tomography (CT)***
  - ***Magnetic resonance imaging (MRI)***
  - ***Positon-emission tomography (PET)***



Treatment

- ***Surgery:***

better surgical process with better imaging.

Treatment (cont)

- ***Radiation therapy:***

  - megavoltage radiation therapy (linear accelerator)
  - intensity–modulated radiation therapy *
  - Tomotherapy *
  - Gamma knife Radiation
  - Stereotactic radiation

**** Assessed in Pet Dogs with Cancer in advance of its wide-spread in Human patients.***

Paoloni, M et al, 2008.

Treatment (cont)

- ***Interstitial Radiotherapy***

Iridium hight flow

Treatment (cont)

- ***Chemothérapy:*** ***all conventional chemo therapeutics used to treat Dogs are human drugs used off-label.***

In addition to recent chemical treatments some improvements as:

Electrochemotherapy

which induces a transient membrane cell permeability thus allowing transport of active molecules into the cell cytoplasm.

Spugnini E P et al , 2014

Treatment (cont)

➢ Immunotherapy

- ***Monoclonal Antibodies (mAb)***

  Ex: Canine Malignant Lymphomas (ML):

  anti CD52 (B and T cell ML)

  anti CD20 (mature B cell ML)

  Canine Mastocytomas:

  Toceranib (Thyrosine kinase receptor inhibitor)

  Masitinib (Id°)

- ***Telomerase Immunotherapy (added to standard therapy)***

  Ex: Canine Malignant Lymphomas (ML)

- ***Innate Immune response Inducer:***

  Ex: Canine Osteosarcoma :

  Listeria monocytogenes as inducer of Tumor specific T-cell mediated Immunity.

Biology

- ***Genetic predisposition***

- ***Immunology***

Genetic predisposition

Preamble:

- ✓ ***Canine Genetic heterogeneity is comparable to the human one.***
- ✓ ***Canine genoma is closer to human genome thane murine genoma.***

Lindblad-Toh et al, 2005.

Genetic predisposition (cont)

Ex : Canine Histiocytic Sarcoma:

is a highly breed-specific disorder ,

mainly diagnosed in the Bernese Mountain Dog (BMD),

Flat Coated retriever (FCR), Rottweiler (ROTTW).

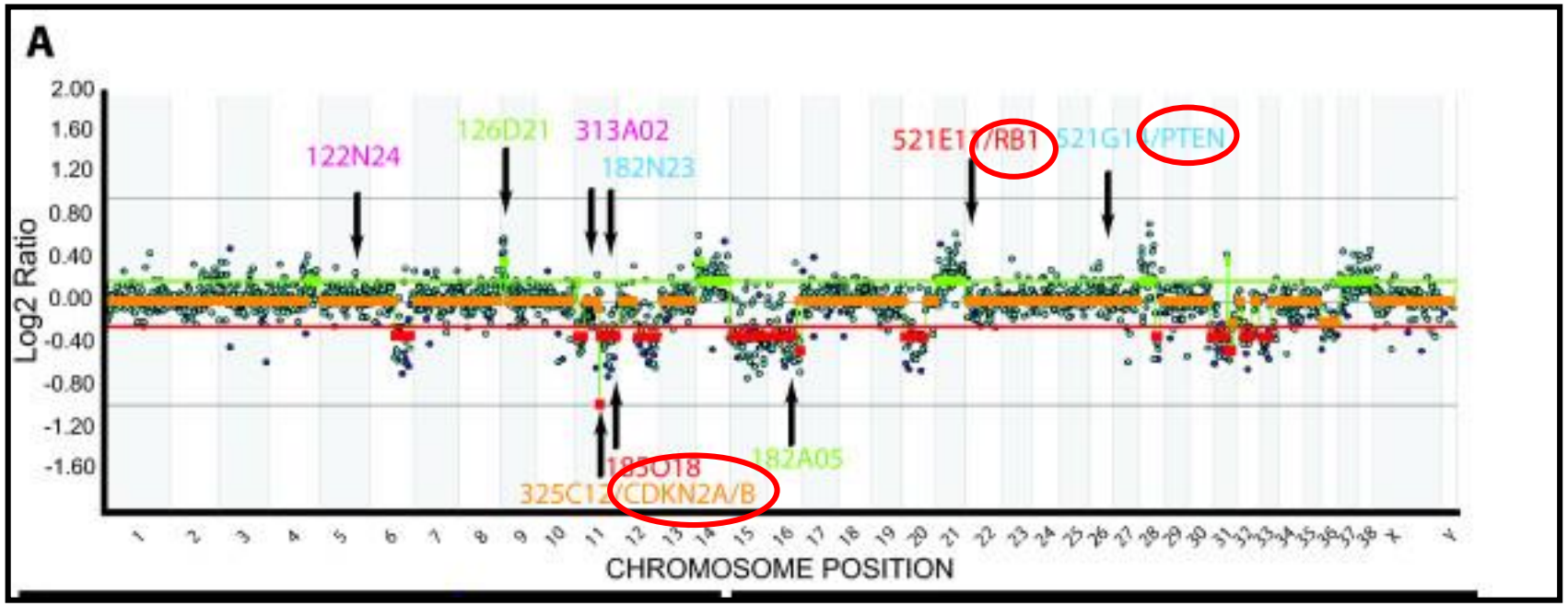
(Padgett et al, 1995).

Genetic predisposition (cont)

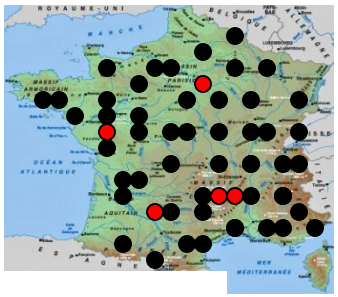
- ***Molecular cytogenetic characterization:***

Ex: Canine Histiocytic Sarcoma in both BMD and FCR :

- ***Recurent copy number variations (CNVs) = DNA copy number aberrations (CNAs) were identified***
- ***A subset of these recurrent CNVs suggests involvement of cancer associated genes in HS pathogenesis including deletion of Tumour suppressor genes : CDKN2A/B, RB1 and PTEN.***



(Hedan B et al, 2011)



Blood,
tissues,

CaniDNA BioBank :
- 10 000 canine DNA
- 2000 tissue samples(RNA)
- 300 breeds
- Healthy / affected
- 100 genetic homologous diseases

Antagene, the 4 French Vet Schools
Practioners, Pathology labs

Quality procedure ISO 9001

Cancer models

Melanoma
Histiocytic sarcoma
M Lymphoma
Osteosarcoma
Glioma

Immunology

- ***Canine adjuvant autologous cancer vaccines:***

  Various undergoing trials (ML, Mastocytomas, …)

  with higher survival rates.

Yannelli J R , 2016.

Weir C , 2018

The Future

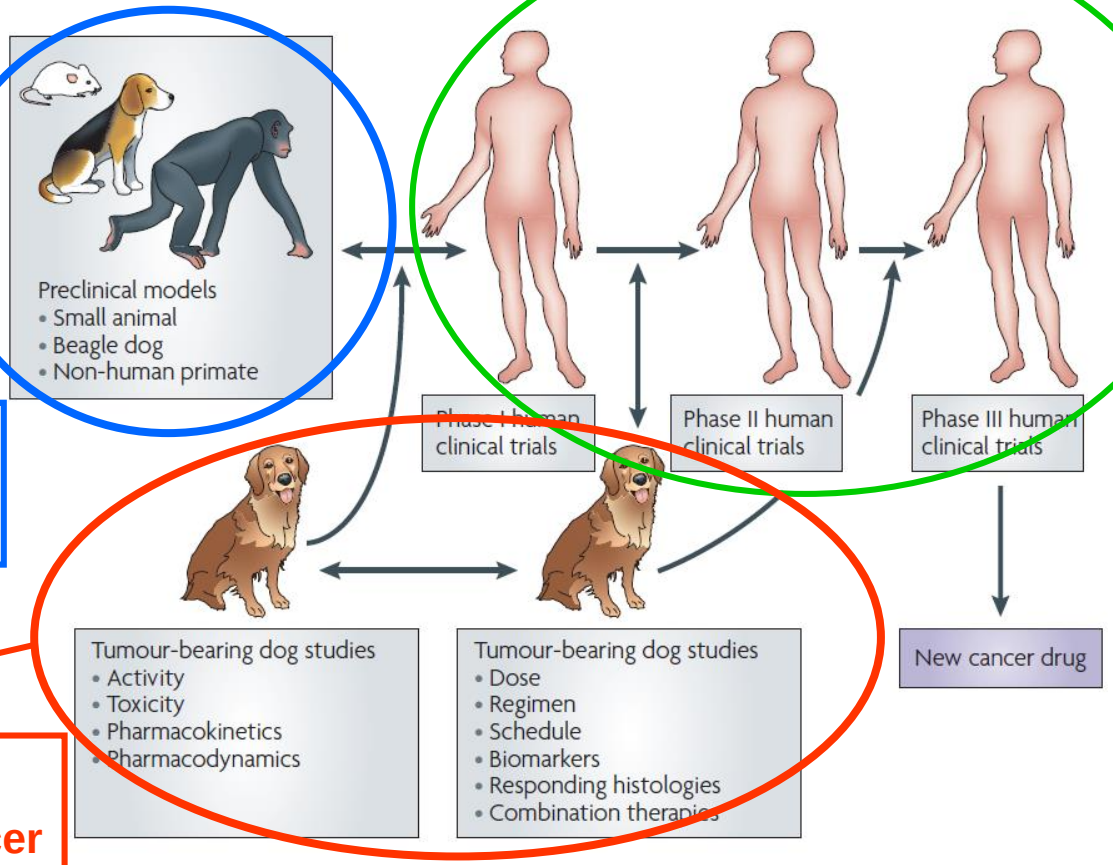
- ***Veterinary Cancerology is in a position to provide valuable support to Human Cancerology investigation.***

The level of available advanced care through veterinary specialities institutions provides the opportunity to conduct well-organized and advanced clinical trials in pet dogs with cancers.

Translational drug development studies :

Pet Dogs with Cancer would be an intermediary between conventional preclinic models (mouse, research-bred dogs, non-human primates) and the human clinical trials.

Human Clinical trials



Conventional Preclinical models of efficacy and toxicity

Translational drug development Studies in the pet dog with cancer

Figure 3 | **Integrated approach.** Current drug development efforts are largely uni-directional and

Melissa Paoloni and Chand Khanna,, 2008

Translational drug development studies

Benefits:

- ***Study duration: Translational drug development studies in pet dog with cancer may prevent any delays in the conduct or completion of human clinical trials.***
- ***Less expensive costs (including serial biopsies, imaging, necropsy, …) covered by the sponsoring Company.***
- ***More optimal design of Human clinical trials.***
- ***Early identification of liabilities.***
- ***Reduced late attrition or failure of cancer drugs in Human patients.***
- ***Improve care of future Human and Canine cancer patients.***

Translational drug development studies

Limitations:

- ***Cancer prevalence: the most common human cancers (breast, prostate, GIT, lung carcinomas) are less common in canine.***
- ***The gastrointestinal sensisivity of Dog is higher than human patients (oral administration).***
- ***Care of pet animals must be given great consideration and should include institutional Animal Care and use of Ethics Committees approval.***
- ***Regulatory reporting is not still well defined .***
- ***Compliance of complete data reporting and study conduct (adherence to all parts – incuding dog owners - of the study protocols) needs to be better defined.***

Nevertheless …

NIH NATIONAL CANCER INSTITUTE

The NCI's Comparative Oncology Program (NCI-COP)

- ***Provides infrastructure and resources needed to integrate the Canine naturally occuring cancer models into the development of new Human cancer drugs, devices and imaging techniques.***

- ***Ensure compliance with regulations regarding ethical use of companion animals.***

- ***Pet owners are clearly informed as their animals participate in a clinical trial.***

http://ccr.cancer.gov/resources/cop/COTC.asp

Oncovet Clinical Research
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MAIN RESEARCH SERVICES

Comparative medicine

Pets as new predictive models of human diseases.
Clinical trials of Pets with natural diseases making clinical trials in Human more relevant.

Veterinary clinical trials

Veterinary contract research organization.
Clinical trials of Dogs & Cats for new animal drug application.

OTHER RESEARCH SERVICES

Histopathology Lab

Animal histopathology & IHC laboratory

Biobank – Cell lines

Canine & Feline tumor tissues.
In vitro assessment of drug candidates on canine & feline tumor cell lines

Research projects

Immunotherapies in Pets
Melanoma & ICI
Mammary Carcinoma -/-/-

Conclusion

Naturally occurring cancers in companion animals are a great resource, as shown by the remarkable growth that comparative oncology has seen over the last 30 years.

Cancer has become a leading cause of death in companion animals now that more pets are living long enough to develop the disease. Furthermore, more owners are seeking advanced and novel therapies for their pets as they are very much considered family members.

Living in the same environments, pets and humans are often afflicted by the same types of cancer which show similar behavior and, in some species, express the same antigen molecules.

The treatment of pet tumors using novel therapies is of compelling translational significance.

This comparative approach is able to provide benefits both to human beeings and their companion animals.

« Your Dog is able to save lifes ! »

Another component of the «One Health» concept !