Funding Request for HSIMS

Histiocytic Sarcoma (formerly malignant histiocytosis) is one of the major causes of death in the Bernese Mountain Dogs. It is a cancer of the histiocytes, cells responsible for immune function, which are present in the lymph nodes and a number of organs. Even though it can be diagnosed in several breeds, this cancer affects specifically and with a strong incidence only a few breeds as the Bernese Mountain Dog. Unfortunately, therapeutic possibilities are limited and the evolution of this cancer is fatal in the short or mid-term (Abadie, Hedan et al 2009).

I. State of the art

a. From fundamental research to a selection tool

For over 13 years, the Canine Genetics team of the CNRS in Rennes (France) and its collaborators are leading a genetic study on Histiocytic Sarcoma in the Bernese Mountain Dogs. Thanks to the collect of more than 3000 samples from French Bernese Mountain Dogs and to their clinical follow-ups, the analysis of chromosomal regions of 1000 Bernese Mountain Dog DNA samples has enabled to identify genetic markers associated with risk of developing and transmitting this cancer.

In order to inform breeders and Clubs about these fundamental research results, the Dog Genetics team participates since 2002 in every French National Championship of AFBS and since 2006 in IWG (International Working Group) symposiums. Those exchanges led to a selection tool proposal against this devastating cancer: the Histiocytic Sarcoma test.

This SH test development has been realised thanks to a three-way collaboration between CNRS, Antagene and the French Association of the Swiss Mountain Dog (AFBS) in 2012. This genetic risk test is made to reduce the Histiocytic Sarcoma's impact on the breed. For this purpose, 9 genetic markers have been selected in the implicated chromosomal regions and a genetic index has been calculated based on the alleles distribution of those 9 markers.

This genetic index estimates the risk to develop and transmit the Histiocytic Sarcoma in the Bernese Mountain Dog breed. This index is divided into 3 categories (A/B/C). It has been determined upon a 1000 Bernese Mountain Dogs population, mainly of French origin. Dogs with a A index are 4 times the chance of not developing Histiocytic Sarcoma whereas dogs with a C index are 4 times the risk of developing Histiocytic Sarcoma.

b. SH test results and validation

With the precious participation of European clubs and of the Berner Garde, the SH test has been validated on the European population (144 Bernese Mountain dogs with known clinical status from 11 different countries), and then on the American population (91 Bernese Mountain dogs with known clinical status). In fact, those dogs with a Swiss origin are now spread all over Europe and the United States. Dogs from a large number of European countries are found in every pedigree.

To date, Antagene has tested 1726 dogs with unknown clinical status. Thus, today's distribution of the A, B and C indexes in the Bernese Mountain Dog breed is: 23% A dogs, 45% B dogs and 32% C dogs. These numbers show a large proportion of C and B dogs, underlying the necessity to select those dogs better for the next generations, reasonably and in the long term, using C dogs decently.

c. Research constantly moving forward in the breeder's favour

The study of A, B and C dogs proportions in different litters, led in collaboration by Antagene, the Dog Genetic team and AFBS, included 112 puppies from 18 litters. The SH test realised on the parents and the whole litters demonstrated that two matings with different stud-dogs but with the same indexes (for instance: B male x C female) can produce very different ranges of indexes. This observation shows that compatibility varies between sire/dam.

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In order to answer the questions "Can we predict the compatibility of two stud-dogs?" and "Can we predict the distribution of indexes within a litter based on the mating?" which are relevant questions for Bernese Mountain Dog breeders, we wish to offer a new tool: the HSIMS tool, which allows them to go further in their selection approach against the Histiocytic Sarcoma and to add value to the results of the HS tests realised on the stud-dogs.

II.   What is HSIMS?

HSIMS (Histiocytic Sarcoma Index Mate Selection) is a tool for the mating selection regarding the HS index of the parents. It calculates, for the next generation, in percentages, the distribution of A, B and C indexes for a specific mating, considering all the HS genotypes possible in the next generation (up to 20 000 possibilities per mating).

Thus, the HSIMS test result is strictly specific to each couple considered. Its use requires the individual HS test of the sir and the dam.

a. Utilisation of the HSIMS tool

HSIMS allows the user to:
- select the matings that would statistically produce the best indexes
- choose the best partner for one stud-dog
- find the best mating for its Bernese Mountain Dog with a C index
- avoid "risky" matings

b. Concrete examples of HSIMS utilisation

Warning: The HSIMS result is specific to each considered couple. As a consequence, the examples used and the results shown along this paragraph on the interests of using this HSIMS tool are fictional and do not reflect all the result possibilities.

Reminder of the possible results for the HS test:

A : Dogs have 4 times the chance of not developing Histiocytic Sarcoma

B : Neutral

C : Dogs have 4 times the risk of developing Histiocytic Sarcoma.
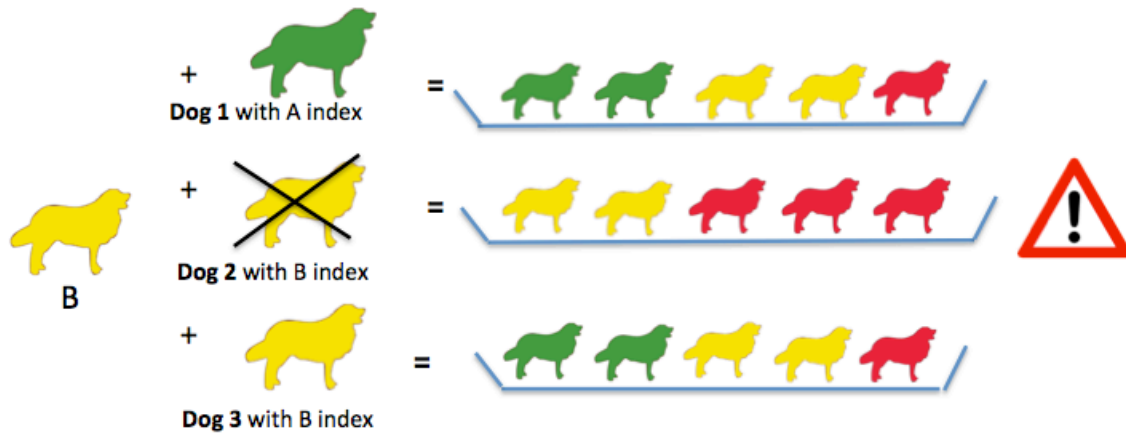The risk of the markers associated with the disease being transmitted to offspring is greatly increased

i. *Selecting matings that would statistically produce the best indexes:*
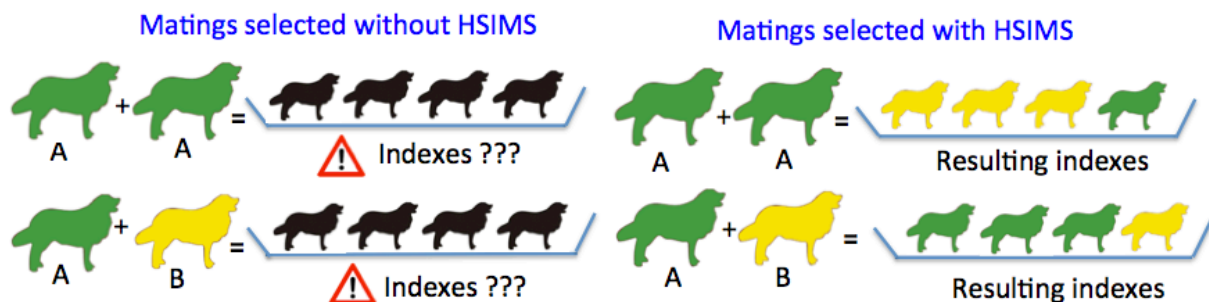
ANTAGENE's suggestion:
For the example above, the results obtained using HSIMS show that the mating between an A Bernese Mountain Dog and a B Bernese Mountain Dog is better than the mating between two A Bernese Mountain Dogs.

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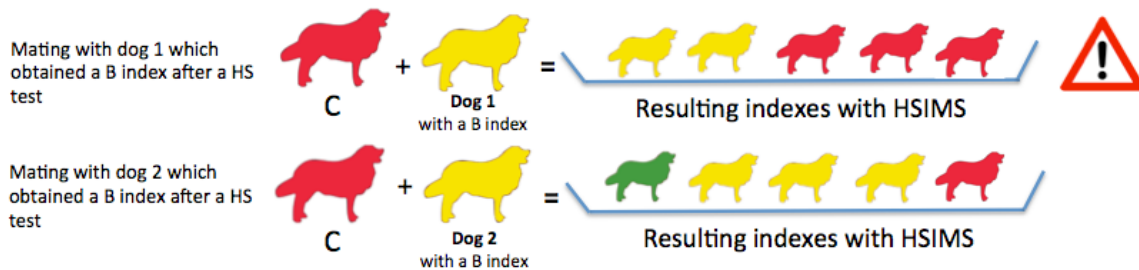
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ii. *Choose the best partner for your stud-dog:*

ANTAGENE's suggestion:
In the example above, the results obtained using HSIMS show that the mating B gives the biggest proportion of C dogs. Then, the choice between mating 1 and mating 3 is up to the breeder depending on morphological and behavioural criteria and/or on the dog's health.
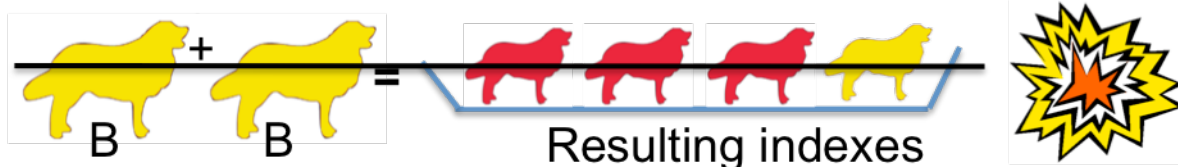
iii. *Find the best mating for a C Bernese Mountain Dog:*

ANTAGENE's suggestion:
In the example above, the results obtained using HSIMS show that the mating with dog 2 is better than the mating with dog 1.

iv. *Avoid "risky" matings :*

ANTAGENE's suggestion:
In the example above, the results obtained using HSIMS are not beneficial for the selection of a future stud-dog. Statistically, this mating produces mainly C dogs. The breeder should favor to choose another mating.

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            c. HSIMS Functionalities

- International database with a direct access for Bernese Mountain Dog's breeders all around the world
- Confidentiality of the HS test index for each dog
- Individual and reversible integration to HSIMS by the owner for each dog
- Results property: the user can simulate a mating only if he owns at least one of the stud-dogs. The second dog of the mating can be another dog from the breeding or a dog from another breeder which has been integrated to HSIMS by its owner
- Instantaneous and automatic online results with a version that can be downloaded in pdf
- Free and unlimited use

III.   <u>Steps of HSIMS development</u>

Through an Internet access, HSIMS will allow breeders to know the repartition of the HS indexes resulting of one mating. The construction of this tool requires several steps:

      a. Index calculation development: creation of a mathematical formula in order to define all the indexes resulting of a mating between two dogs tested for HS.

      b. Validation of the formula: formula validity checking upon real data.

      c. Website specifications: descriptions of the necessary units in order to fill out all the functioning conditions for the HS tested Bernese Mountain Dogs breeders and owners.

      d. Website developing: realised following the website specifications. Requires the intervention of a programmer contractor.

The first two steps (a and b) have already been completed by the Dog Genetics team. The validation has been completed thanks to real data collected during the litters study (cf. part I.c.).
The third step has been completed by Antagene. The estimated cost for developing the website has been asked to the contractor who developed Antagene's database and who does the maintenance. The developing cost offered by the external contractor is 11 220€ all fees included (cf. attached estimate).

IV   <u>Funding request</u>

      In order to guarantee a free use of HSIMS by the breeders, we ask all the Bernese Mountain Dog clubs around the world to support financially the website developing costs (d), and so, allowing the availability of this tool via Internet.

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Antagene
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Libourne, le 19 avril 2017

DEVIS N° 17-04-02

Développement Logiciel HSIMS

Simulation de mariages entre chiens Bouviers bernois sur la base des résultats du test SH (Sarcome Histiocytaire)

Description	Qté et P.U.	Total HT
Module HSIMS dans l'espace client ANTAGENE Partage des reproducteurs dans la communauté HSIMS Simulation de mariages entre chiens de l'élevage et extérieurs à l'élevage Adaptation de l'algorithme de calcul des probabilités des chiots d'indice A, B ou C Affichage des fréquences théoriques de chiots A, B ou C dans la descendance Adaptation de l'interface et des critères de sélection des reproducteurs **Etude, développement et tests : 17 jours** Tarif jour normal : 750€ Tarif jour négocié ANTAGENE : 550€	17 jours x 550 €	9 350,00 €

Modalités de facturation - 30% à la commande - le solde à la mise en place de l'application finale, après validation du client	**Total HT**	**9 350,00 €**
	TVA 20%	1 870,00 €
Pour confirmation de votre acceptation, nous vous prions de renvoyer ce devis daté, cacheté et signé.	**Total TTC**	**11 220,00 €**

Fait à   , le

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