A black and white dog with brown patches is lying on a grassy field, looking up towards the camera. The dog's mouth is slightly open, and it appears to be in a relaxed state. The background is a soft-focus green field.

EVALUATION OF THE EFFICACY OF A NUCLEOTIDE AND LACTOFERRIN PRODUCT IN MAINTAINING STABLE/IMPROVING THE CLINICAL PICTURE AND LABORATORY FINDINGS IN LEISHMANIOTIC DOGS: A RANDOMIZED CONTROLLED STUDY

CAVALERA M.A.^{*}, Uva A., Gernone F., Gusatoia O.,
Donghia R., Zatelli A.

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Department of Veterinary Medicine,
University of Bari

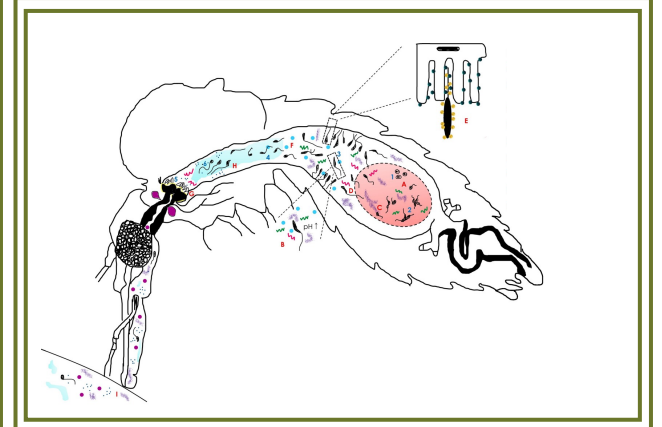
Canine leishmaniasis (CanL)

- Sand fly-borne disease
- *Leishmania infantum*
- Worldwide distribution
- Wide range of clinical forms

cdc.gov



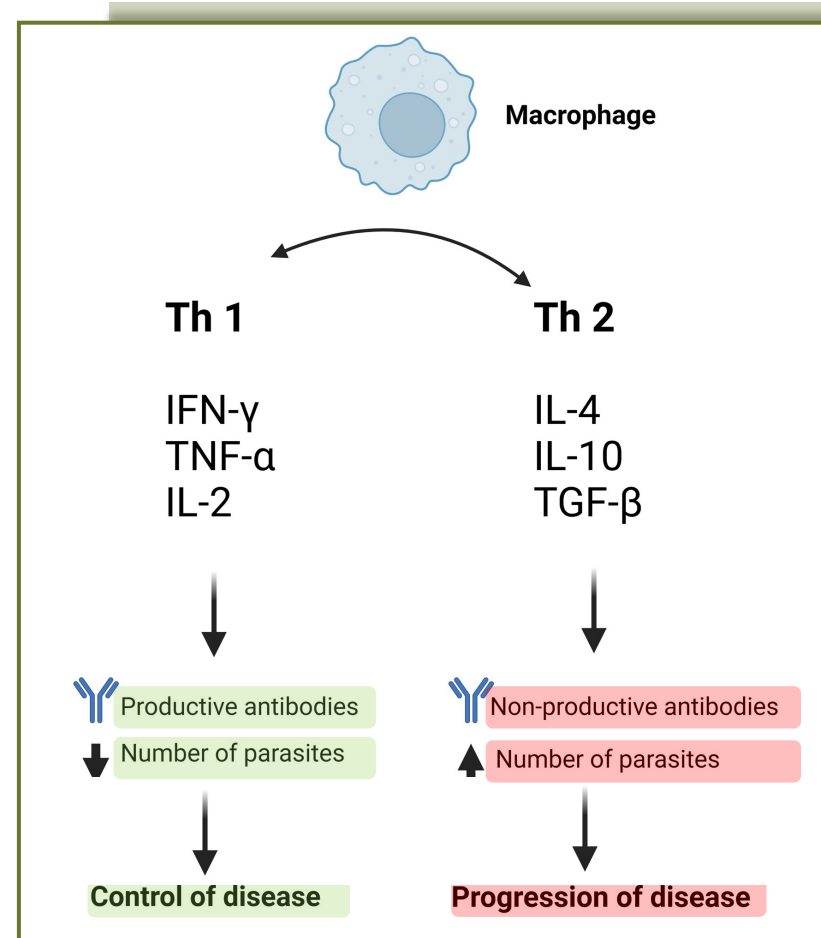
Van Bockstal et al., 2020



Solano-Gallego et al., et al., 2011

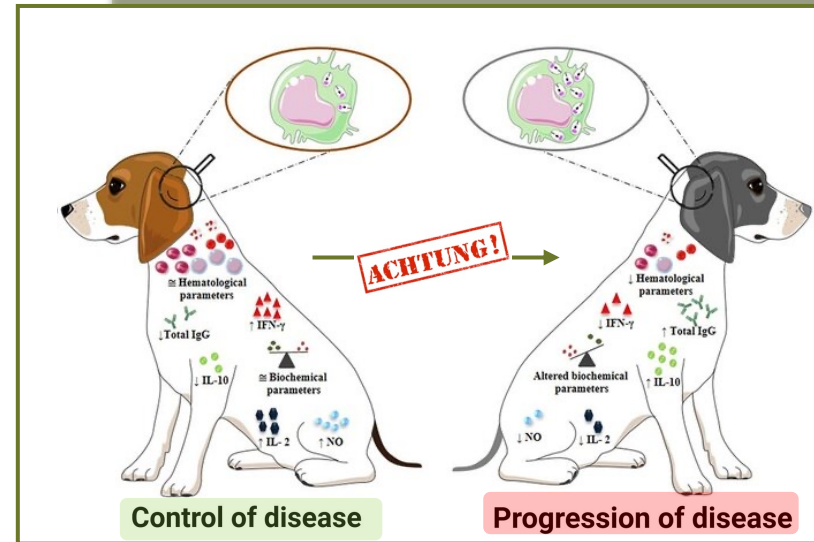
CanL: host immune response

- Host-parasite interaction
- Th1 Vs Th2 responses
- ++ control of disease in endemic areas



CanL: host immune response

- Host-parasite interaction
- Th1 Vs Th2 responses
- ++ control of disease in endemic areas
- Progression of the infection



vanescu et al., 2023 (modified)

CanL: immunotherapy

- Enhance the immune response
- Molecules with immunostimulant activity
- **Nucleotides + AHCC** (Active Hexose Correlated Compound)



microorganisms

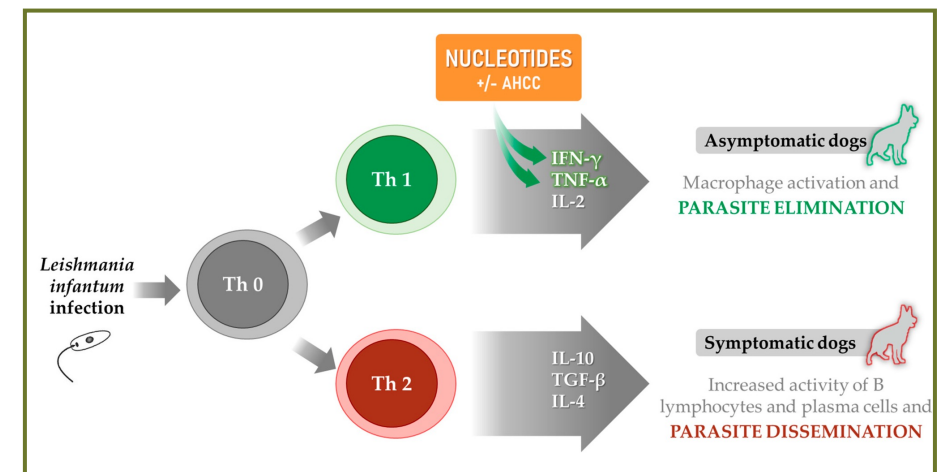


Review

Nutritional Modulation of the Immune Response Mediated by Nucleotides in Canine Leishmaniosis

Sergi Segarra

Animal Species	Main Effects	Reference
Domestic dog, <i>Canis familiaris</i>	Increased antibody titers against parvovirus 14 days post-vaccination, higher unspecific immunoglobulin levels, and improved peripheral blood mononuclear cells test in puppies at weaning.	Romano et al., 2007 [143]
Domestic dog, <i>Canis familiaris</i>	Increased lymphocyte proliferation and higher levels of IgA, IgG, and IgM in dogs receiving chemotherapy treatment (in combination with AHCC).	Evangelio et al., 2008 [144]
Domestic dog, <i>Canis familiaris</i>	Improved leukopenia and neutropenia associated with chemotherapy, increased IgA and IgM levels, and expansion of CD3 and CD4 lymphocytes.	Burkhart et al., 2011 [145]
Domestic dog, <i>Canis familiaris</i>	Clinical and parasitological improvements in two cases of canine demodicosis unresponsive to ivermectin (in combination with AHCC).	Bernal et al., 2014 [146]
Domestic dog, <i>Canis familiaris</i>	In dogs with clinical leishmaniosis receiving an initial course of MGA, clinical superiority vs. allopurinol after 6 months, without producing xanthinuria (in combination with AHCC).	Segarra et al., 2017 [147]
Domestic dog, <i>Canis familiaris</i>	In clinically healthy <i>L. infantum</i> -infected dogs, significant reduction in serology and disease progression rate after 1 year (in combination with AHCC).	Segarra et al., 2018 [148]



CanL: immunotherapy

- Enhance the immune response
- Molecules with immunostimulant activity
- Nucleotides + AHCC
- Bovine Lactoferrin (bLF) (?)
(antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant activities)

frontiers | Frontiers in Nutrition

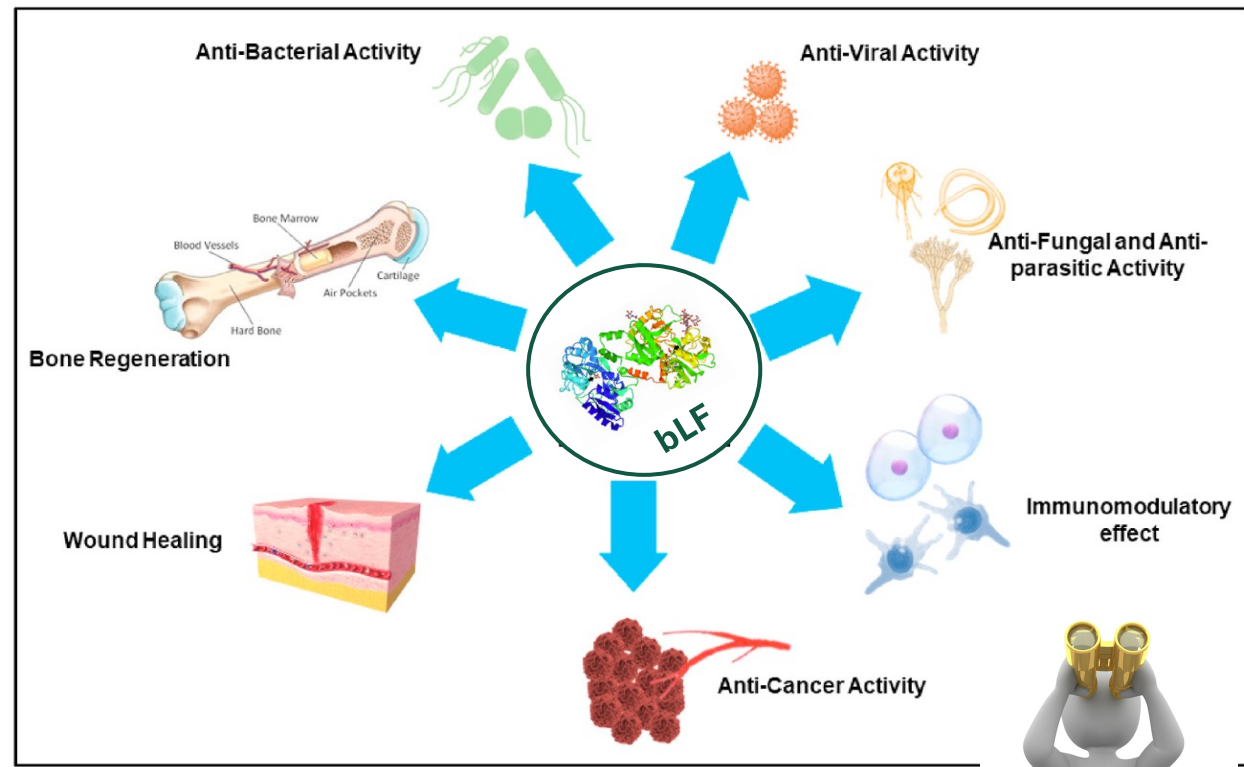
TYPE Review
PUBLISHED 05 January 2023
DOI 10.3389/fnut.2022.1018336

Check for updates

Lactoferrin: A glycoprotein that plays an active role in human health

Xiang Cao¹, Yang Ren¹, Qinyue Lu¹, Kun Wang¹, Yanni Wu¹, YuHao Wang¹, Yihui Zhang¹, Xiang-shun Cui², Zhangping Yang^{1,3} and Zhi Chen^{1,3,4*}

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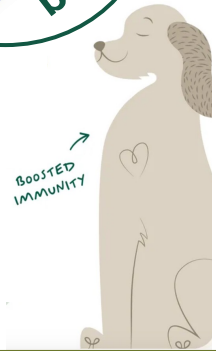
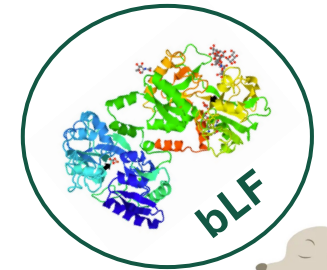


Elzoghby et al., 2020



CanL: immunotherapy

- Enhance the immune response
- Molecules with immunostimulant activity
- Nucleotides + AHCC
- Bovine Lactoferrin (bLF) (?)
(antimicrobial, anti-inflammatory, immunomodulatory, and antioxidant activities)



Contents lists available at ScienceDirect

Veterinary Immunology and Immunopathology

ELSEVIER journal homepage: www.elsevier.com/locate/vetimm

Short communication

Oral administration of bovine lactoferrin upregulates neutrophil functions in a dog with familial β 2-integrin-related neutrophil dysfunction

Saori Kobayashi^a, Yuya Abe^a, Osamu Inanami^b, Shinichi Oda^c, Koii Yamauchi^d, Careen Hankanga^a, Jun Yasuda^a, Reeko SATO^{1)*}

NOTE Internal Medicine

Clinical Effects of Bovine Lactoferrin on Two Canine Cases with Familial Neutrophil Dysfunction

Archives of Animal Nutrition
Vol. 62, No. 2, April 2008, Reeko SATO^{1)*}, Saori KOBAYASHI¹⁾, Yuya ABE¹⁾, Hiroaki KAMISHINA¹⁾, Shinichi ODA²⁾, Jun YASUDA¹⁾ and Juso SASAKI¹⁾

Effects of bovine lactoferrin on the immune system and the intestinal microflora of adult dogs

Petra Hellweg^{a)*}, Stephanie Krammer-Lukas^b, Alois Strasser^c and Jürgen Zentek^a

Aims

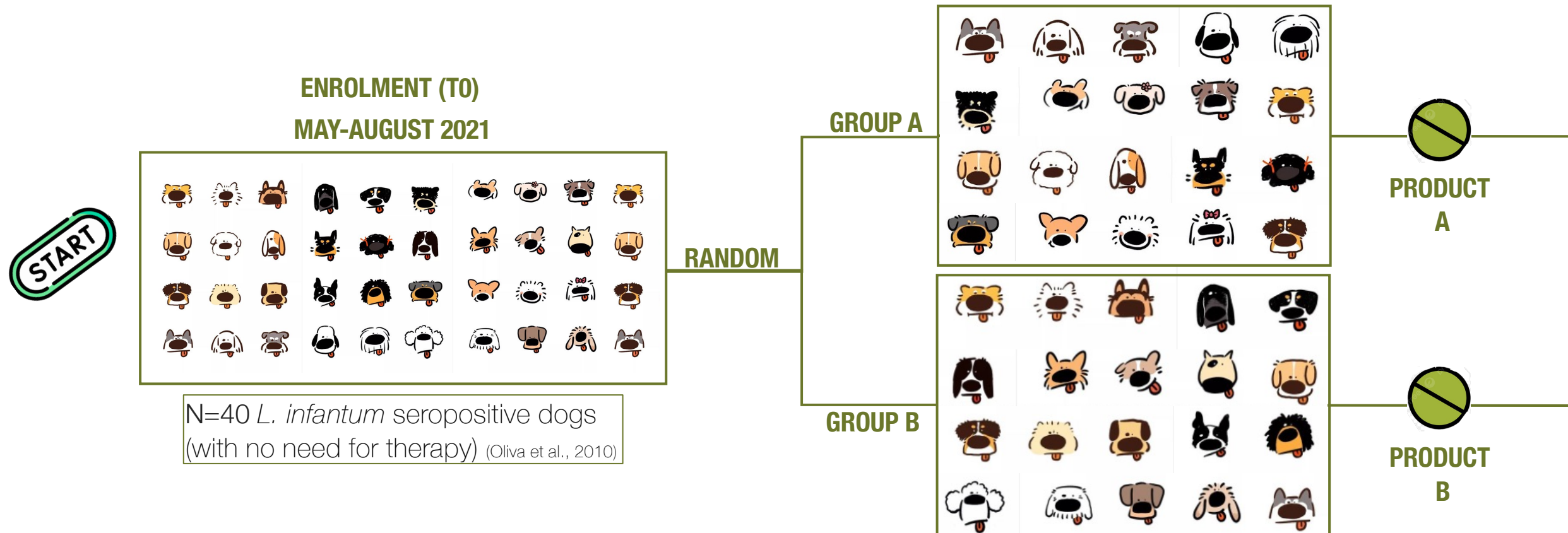
This study aims to evaluate the efficacy of a product containing **nucleotide and lactoferrin** in :

- maintaining stable/improving the clinical picture of CanL
- maintaining stable/improving the laboratory findings of CanL
- Evaluation of the safety and tolerance of the combination NT/bLF



Methods: Study design

- Clinical therapeutic prospective randomised and controlled study (Prot. UNIBA 26-2021)

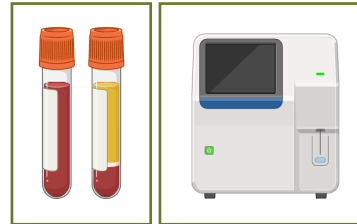


Methods: Study design

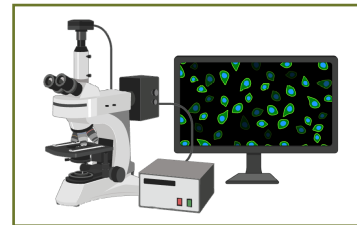
- Follow-up and procedures



- Physical examination
- 19-point scale clinical score (Cavalera et al., 2022)



- CBC
- Biochemical panel (including APP)
- SPEP



- IFAT for *L. infantum* (T0, T180)
- IFAT for *E. canis*, *A. phagocytophilum* (T0, T90, T180)



- Product intake
- Side effects

Methods: Study design

- Endpoints

PRIMARY ENDPOINTS

- Maintenance/reduction CS
- Maintenance/reduction anti-*L. infantum* Abs
- Maintenance/improvement CanL-consistent lab parameters
- Development CanL active forms: Yes or Not?

SECONDARY ENDPOINTS

- Safety and tolerability of NT/bLF

Methods: Study design


- Endpoints

PRIMARY ENDPOINTS

- Maintenance/reduction CS
- Maintenance/reduction anti-*L. infantum* Abs
- Maintenance/improvement CanL-consistent lab parameters
- Development CanL active forms: Yes or Not?

SECONDARY ENDPOINTS

- Safety and tolerability of N/L

- 
- Increased Abs titre (medium-high),
 - Increased globulins +/- reduced albumin, +/- reduced A/G
 - Increased APPs (CRP and/or ferritin)

Results

- Enrolment

GROUP A
=
TREATMENT
(GROUP T)



- N=2 lost-to-follow up at T90
- N=18 completed the study

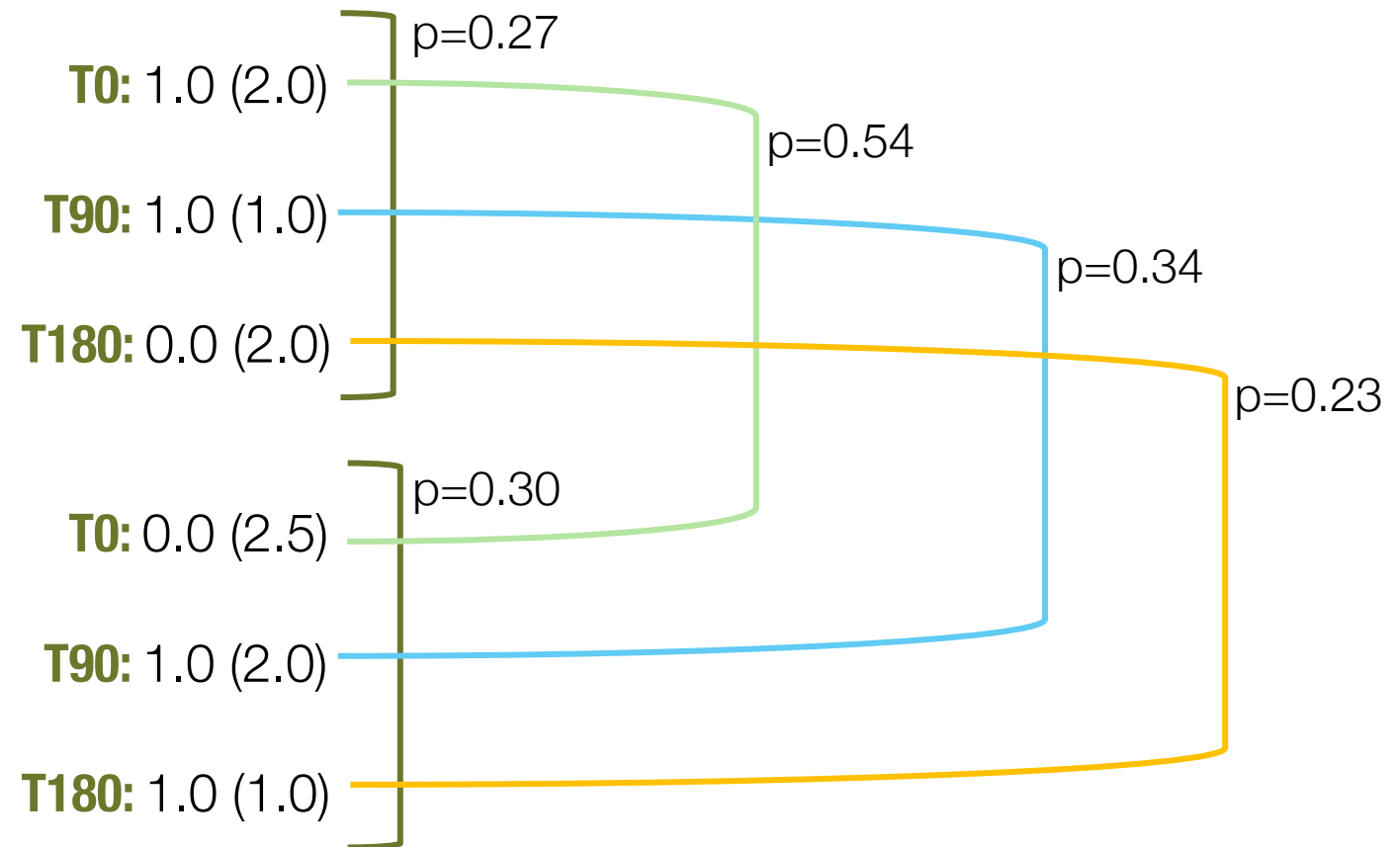
GROUP B
=
CONTROL
(GROUP C)



- N=2 lost-to-follow up at T180
- N=18 completed the study

Results

- Clinical Score



Results

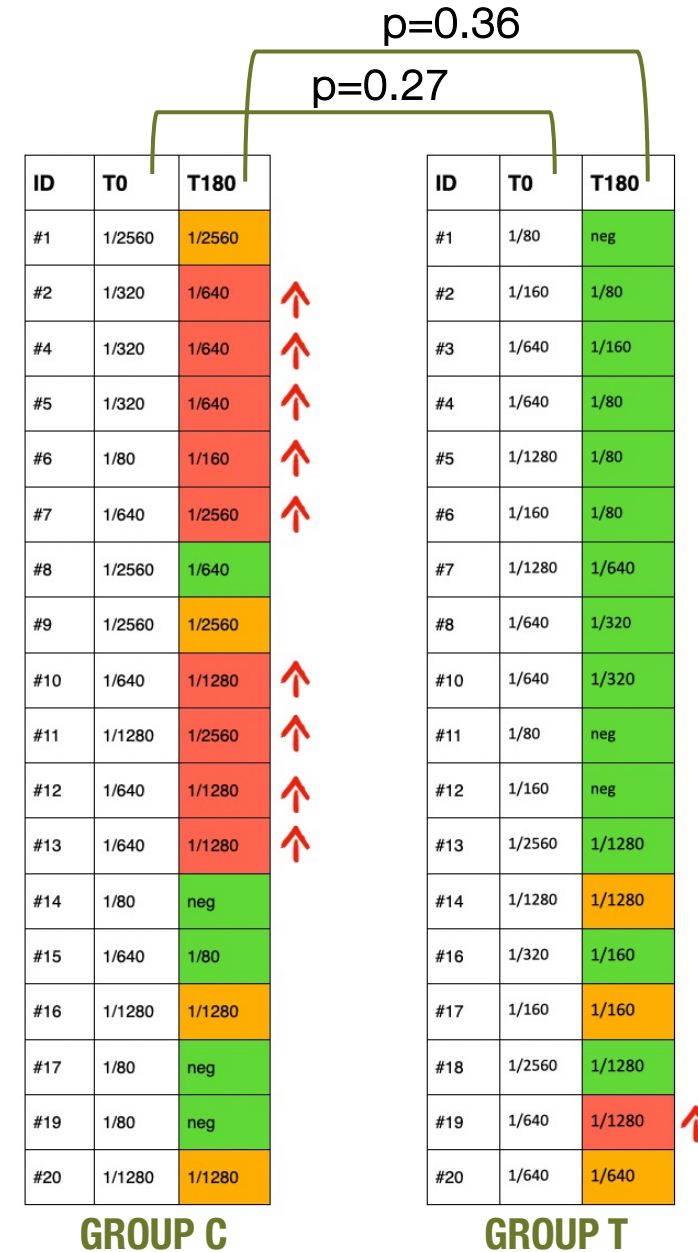
- Anti *L. infantum* antibody titres

GROUP T

- $p=0.0001$
- 14/18 (77.8%) reduced Abs titre
- 1/18 (5.5%) increased Abs titre
- 3/18 (16.7%) maintained stable Abs titre

GROUP C

- $p=0.004$
- 5/18 (27.8%) reduced Abs titre
- 9/18 (50.0%) increased Abs titre
- 4/18 (22.2%) maintained stable Abs titre



Results

- Lab parameters + CanL active forms

GROUP T

- Stable CRP ($p=0.34$) and ferritin ($p=0.96$) values
- 1/18 (5.6%) CanL active form

PARAMETERS	T0	T90	T180	p
CRP (0.00-0.45 mg/dL)	0.05 (0.36)	0.16 (0.30)	0.12 (0.26)	0.34
FERRITIN (80-270 ng/dL)	228.5 (207.5)	144 (91)	226 (95)	0.96

GROUP C

- Increased CRP ($p=0.04$) and ferritin ($p=0.03$) values
- 9/18 (50.0%) CanL active form

PARAMETERS	T0	T90	T180	p
CRP (0.00-0.45 mg/dL)	0.27 (0.81)	0.10 (0.43)	0.67 (1.48)	0.04
FERRITIN (80-270 ng/dL)	216 (159.5)	230.5 (209)	316.5 (441)	0.03

Friedman test for repeated measures 

GROUP T Vs GROUP C AT T180

- < albumin % ($p=0.05$) in group C
- > alpha-2 globulins ($p=0.02$) in group C

Results

- Safety and tolerability of the products



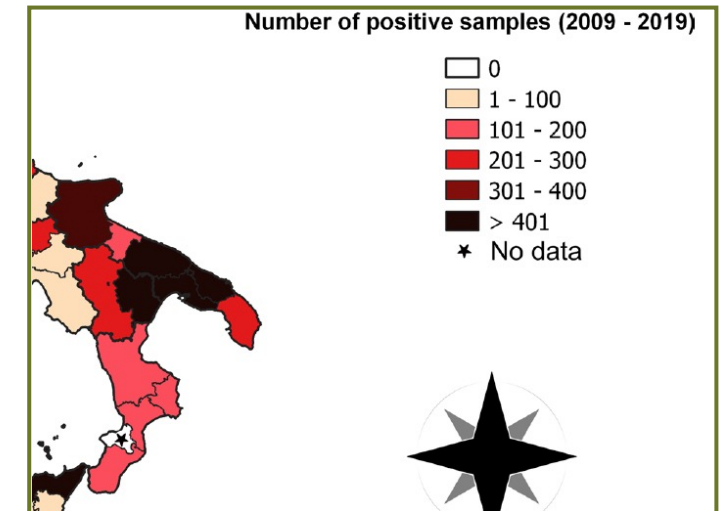
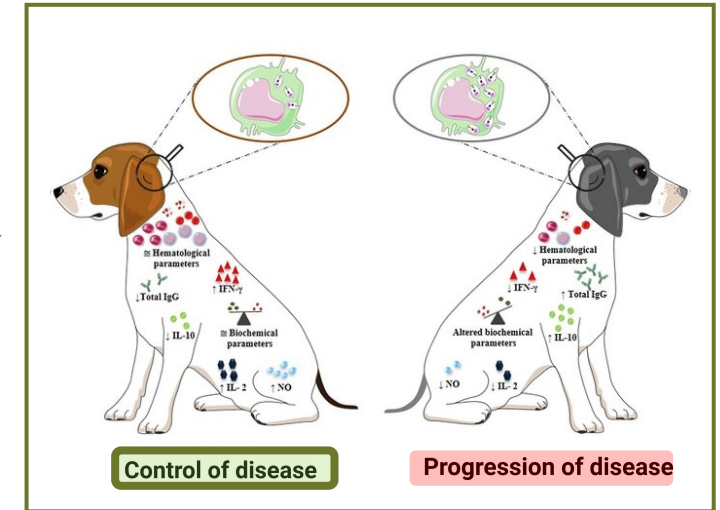
Discussion

- 1° evaluation of the efficacy of a product containing NT/bLT

Discussion

- 1° evaluation of the efficacy of a product containing NT/bLF
- LOW CS regardless of the group

Baneth et al., 2008

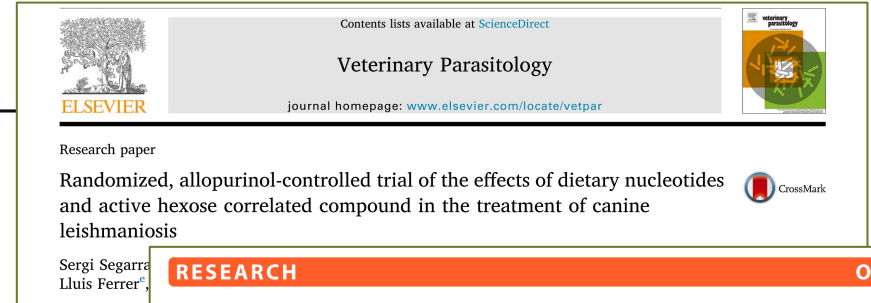


Discussion

- 1° evaluation of the efficacy of a product containing NT/bL
- LOW CS regardless of the group
- Significant variations in the Ab titre

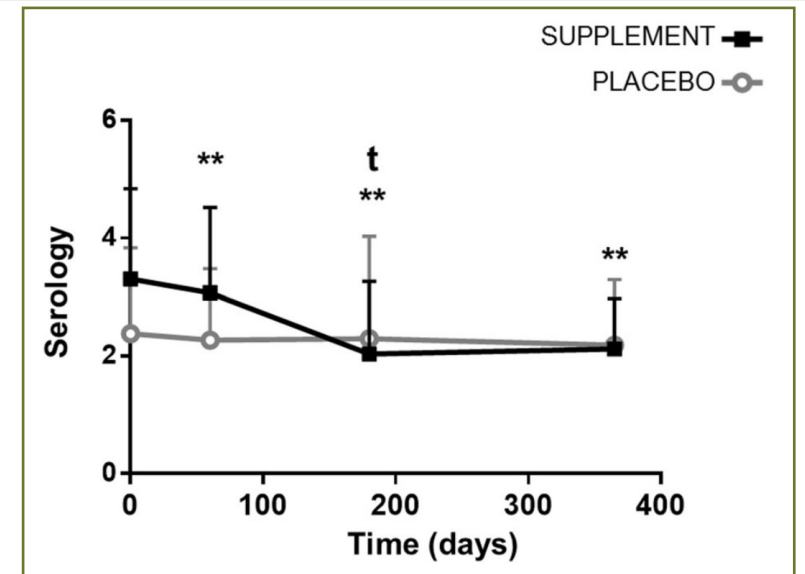
GROUP T: almost 78% of the dogs demonstrated a REDUCTION in Ab titre

GROUP C: approximately half of the animals exhibited an INCREASE in Ab titre



Prevention of disease progression in *Leishmania infantum*-infected dogs with dietary nucleotides and active hexose correlated compound

Sergi Segarra^{1*}, Guadalupe Miró², Ana Montoya², Luis Pardo-Marín³, Joan Teichenné⁴, Lluís Ferrer⁵ and José Joaquín Cerón³



Discussion

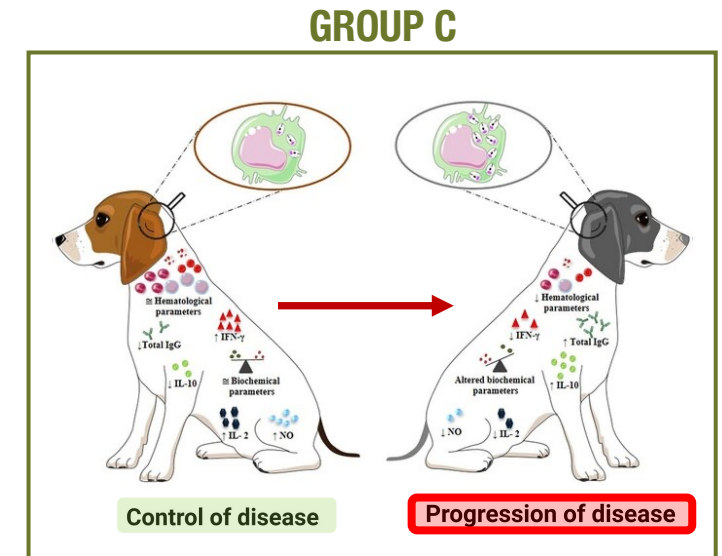
- 1° evaluation of the efficacy of a product containing NT/bLF
- LOW CS regardless of the group
- Significant variations in the Ab titre
- LOW percentage of CanL active forms

Martinez-Subiela et al., 2011, 2014

Ceron et al., 2021

GROUP T: 1/18 (5.6%) CanL active form, stable APP levels

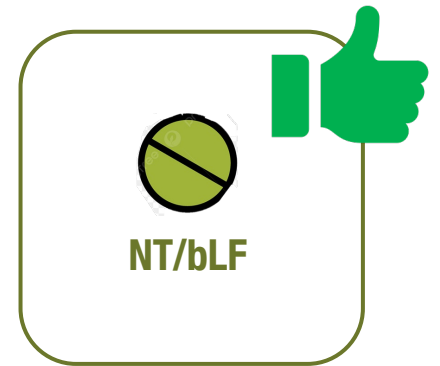
GROUP C: 9/18 (50.0%) CanL active form, increased APP levels



Ivanescu et al., 2023 (modified)

Discussion

- 1° evaluation of the efficacy of a product containing NT/bLF
- LOW CS regardless of the group
- Significant variations in the Ab titre
- LOW percentage of CanL active forms
- Well-tolerated, easy to administer, and free of side effects



Discussion

- 1° evaluation of the efficacy of a product containing NT/bLT
- LOW CS regardless of the group
- Significant variations in the Ab titre
- LOW percentage of CanL active forms
- Well-tolerated, easy to administer, and free of side effects
- **MAIN LIMIT:** SHORT EVALUATION PERIOD!



TO BE CONTINUED...

Conclusions

6-month long oral administration of a supplement containing nucleotides and lactoferrin



effective in maintaining a stable clinical score and improving laboratory parameters in dogs serologically positive for *L. infantum*



potential reduction in the progression
from NON ACTIVE to ACTIVE FORMS of CanL

Thank you for the
attention!!!



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