

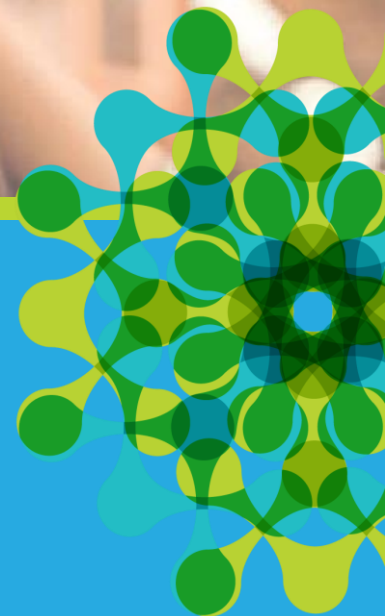
Clinical and safety evaluation of multiple intravenous administrations of Immunocidin® in cats and dogs with malignancies

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FINAL DISCLOSURE:

Dr. Jeannette Kelly : *No relevant financial exists*

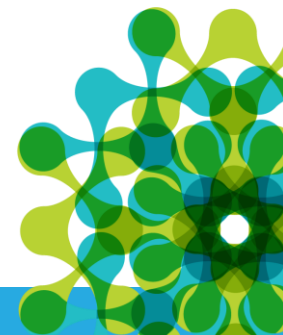
Megan Padget: *No relevant financial exists*

Chad Johannes : *Consulting Engagement –NovaVive Inc*

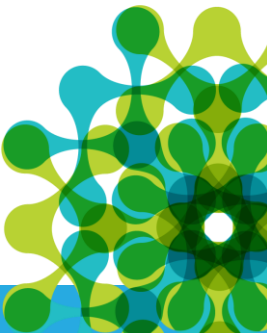
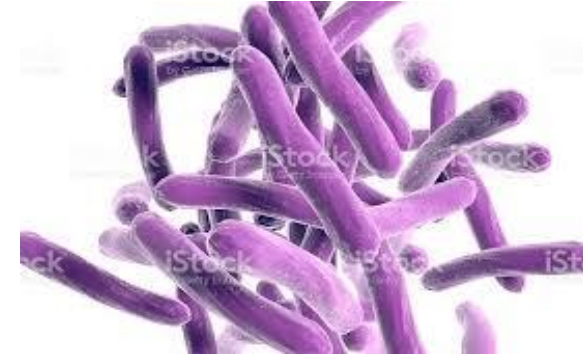
Aleksandar Masic : *Employee of the NovaVive Inc*

UNLABELED/UNAPPROVED USES DISCLOSURE:

I will discuss the results of a pilot clinical trial for the following agent that are currently NOT approved for use in animals intravenously.

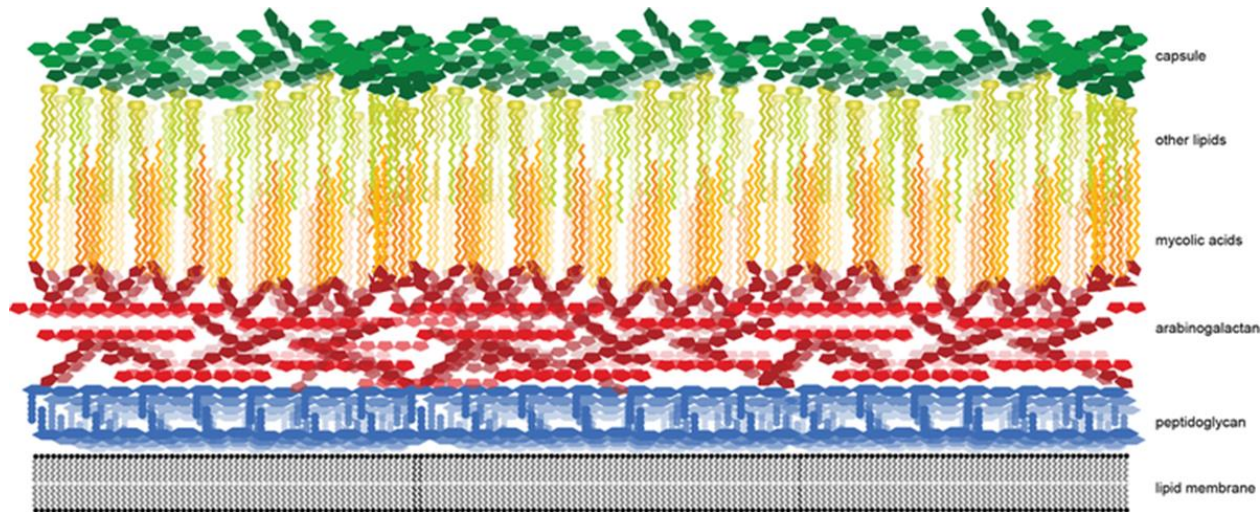


- MCWF - mycobacterial cell wall fraction; composition derived from *Mycobacterium phlei* (*M. phlei*).
- *M. phlei* is a **non-pathogenic**, gram-positive, ubiquitous bacteria commonly found in the environment, soil, dust and on the leaves of plants.
- MCWF contains mycobacterial cell wall complexed with bacterial nucleic acid (DNA and RNA)



MCWF composition

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Elemental Analysis

Carbon	58.0 %
Hydrogen	8.0 %
Nitrogen	7.3 %

Lipid Content

Non polar lipids	53.0 %
Polar lipids	7.9 %

Mycolic Acid Content

α -mycolate	1.5 %
Ketomycolate	0.5 %
Carboxymycolate	18.3 %

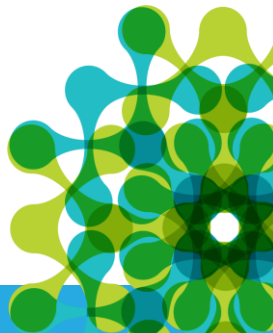
Muramyl Dipeptide Content

.....	4.0 %
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Carbohydrate Content

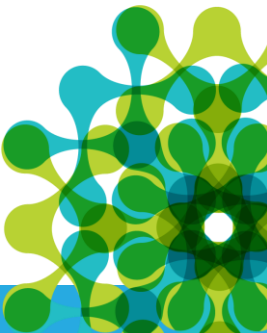
Arabinose	2.9 %
Galactose	1.4 %
Glucosamine	0.5 %
Muramic acid	1.9 %

Major
immunodominant
components



➤ MCWF - induces:

- ❖ Activation of immune system receptors (TLR-2, NOD-2)
- ❖ Cytokine production by immune system cells (monocytes, macrophages, dendritic cells)
- ❖ Colony stimulating factor production (G-CSF, GM-CSF etc.)
- ❖ In general, induction of innate immune responses and cell-mediated immunity.



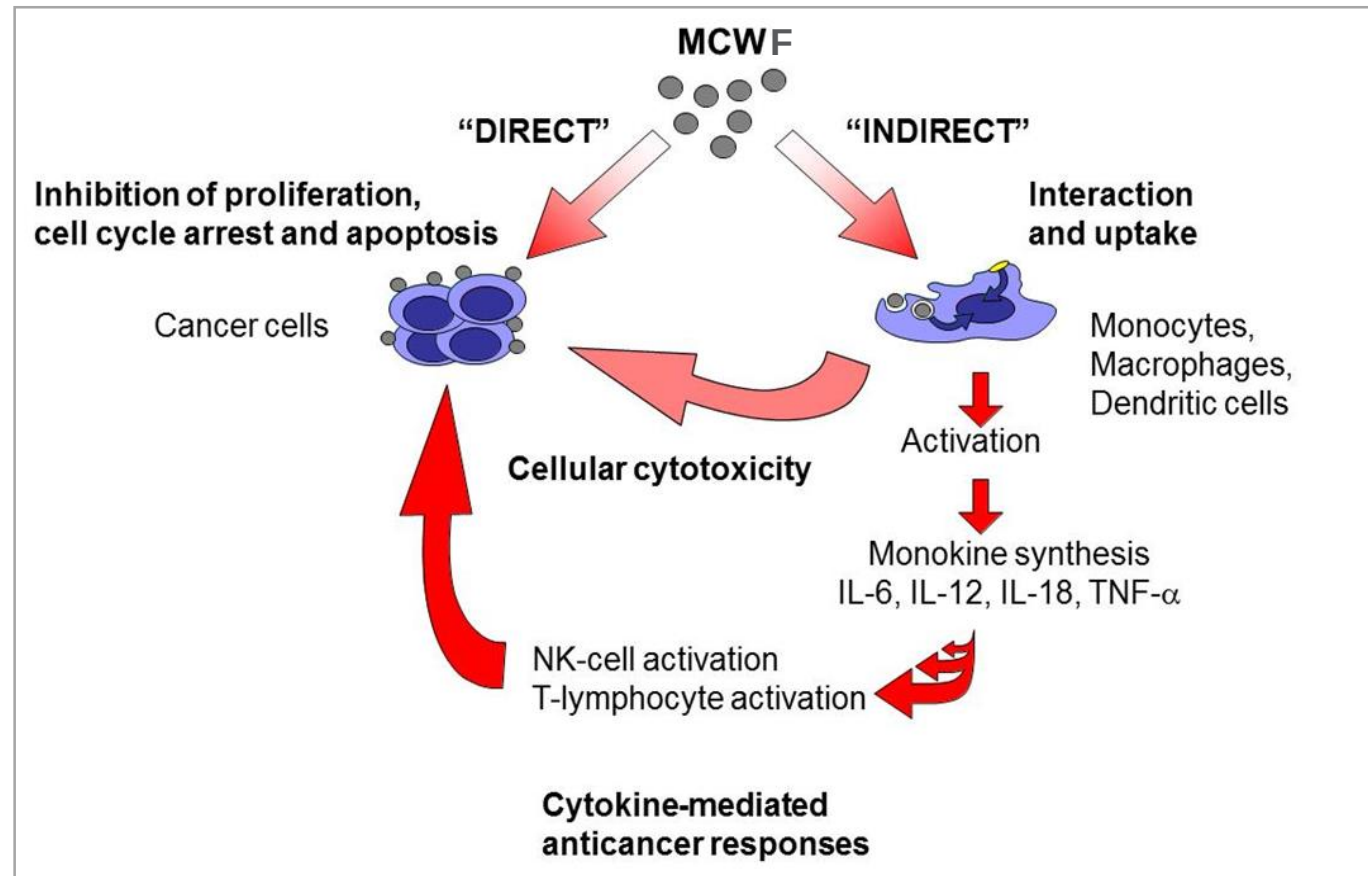
MCWF Immunomodulatory and Anti-Cancer Activity

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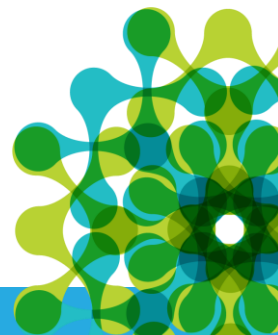
Biological
Modulator

Induces cytokine
production

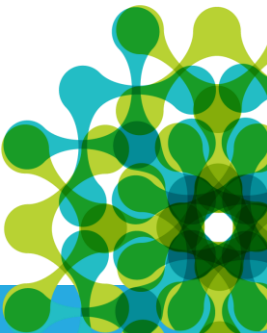
Induces
apoptosis



Filion et al., 1999; Morales et al., 2015
N.C. Phillips Expert Opin Investig Drugs. 2001 Dec;10(12):2157-65
NC Phillips Br J Cancer. 1999 Jan;79(2):229-35.

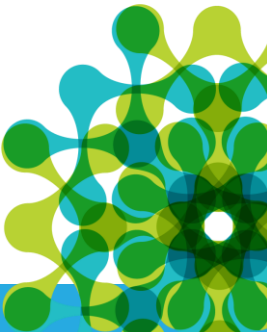


- MCWF formulation used in final phase III clinical trials for the treatment of human bladder cancer (BCG refractory patients)
- **Veterinary use:** MCWF formulations - various licensed products (USA, CAD, AUS, NZ) for different indications in equine, bovine and canine species.
- **Immunocidin®** - MCWF formulation fully licensed for treatment of mixed mammary tumors and mammary adenocarcinoma in dogs.
- **Immunocidin®** has been used for treatment of other malignancies such as osteosarcoma, transitional cell carcinoma, soft tissue sarcoma, hemangiosarcoma and transmissible venereal tumors in dogs

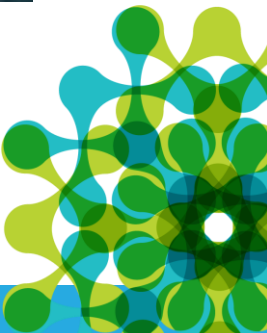
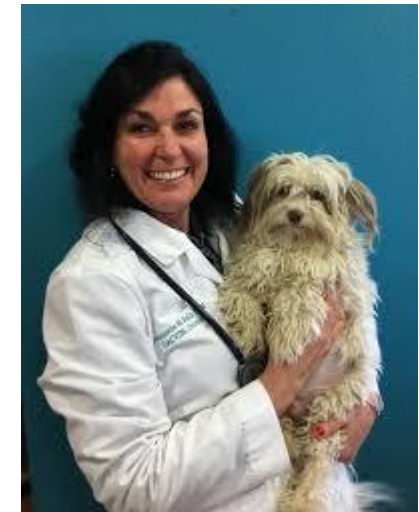


Study Objectives:

- To assess clinical and safety profile of **Immunocidin®** following multiple intravenous administrations in cats and dogs with various malignancies.
- To explore **Immunocidin®** immunomodulatory potential and effectiveness as an adjunct treatment to oncology standard of care protocols for treatment of various histologies in dogs and cats.



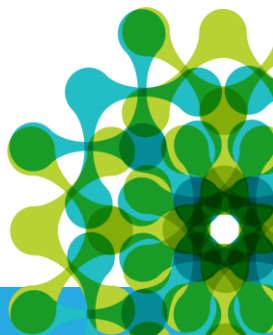
- Study was single site specific (oncology referral clinic Veterinary Cancer Care, Santa Fe, NM, USA).
- Non-blinded
- Clinical, pilot-study
- **Inclusion criteria:**
 - life expectancy of minimum of 6 weeks,
 - confirmed neoplasia by histology or cytology
 - no concurrent radiation or steroid therapy.
- A total of 44 patients were enrolled in the study.
 - 40 Dogs
 - Note: 2 canine patients were each diagnosed with 2 malignancies, but were considered only for the more severe malignancy
 - 4 Cats



➤ Patients enrolled in the study had the following tumor types:

Tumor Type Treated	Number of Canine Patients	Number of Feline Patients
Lymphoma	10	1
Osteosarcoma	5	
Hemangiosarcoma	4	
Anal Gland Adenocarcinoma	2	
High Grade Soft Tissue Sarcoma	2	
Mammary Adenocarcinoma	2	1
Transitional Cell Carcinoma	2	1
Histiocytic Sarcoma	2	
Oral Melanoma	2	
Mast Cell Tumor	1	
Fibrosarcoma	1	
Pulmonary Carcinoma	1	
Multiple Myeloma	1	
Pheochromocytoma	1	
Hepatocellular Carcinoma	1	
Apocrine Adenocarcinoma	1	
Acanthomatous Epulis	1	
Squamous Cell Carcinoma	1	
Injection Site Sarcoma		1

➤ Both canines and felines were treated using the same administration protocol!

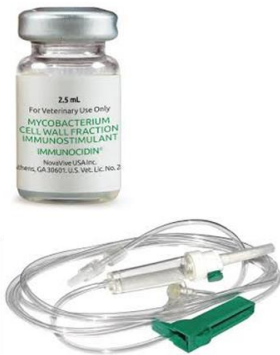


Immunocidin® I.V Protocol

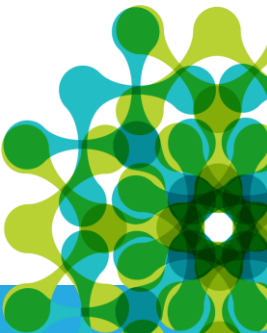
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➤ Dosages range administered :

Body Weight (kg)	Immunocidin® dose (mL)
<5	0.1
5-10	0.2-0.25
10-15	0.3
15-25	0.5
25-35	0.75
>35	1



- Prior to administration, each dose was diluted into 150ml sterile 0.9% NaCl and administered intravenously over 30 minutes
- Each patient was pre-treated with diphenhydramine
- Treatments were performed weekly or every other week depending on standard chemotherapy protocol
- *Anal gland carcinoma* patients were treated every 3 weeks in combination with Carboplatin



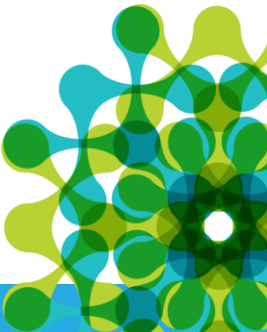
Each administration was performed on the same day following standard chemotherapy dosing of one of the following:

- Vincristine (0.5mg/m²)
- Doxorubicin (25mg/m²)
- Dacarbazine (800mg/m²)
- Carboplatin (225mg/m²)

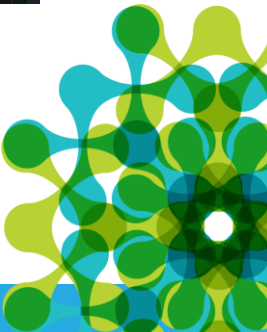


Following administration, all animals were closely monitored for 2h in the clinic

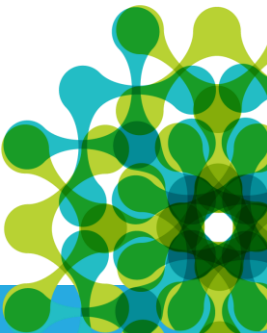
- Temperature, blood pressure, heart, and respiratory rate were assessed every 30-45 min
- Whole blood samples were taken every two to four weeks and complete blood counts and clinical chemistry analysis were performed



- Adverse events were observed in **5 animals** within hours after MCWF administration, and were considered minimal
- ❖ Adverse events included:
 - ❖ Mild lethargy
 - ❖ Mild transient hyperthermia
- ❖ One canine patient with histiocytic sarcoma and high grade soft tissue sarcoma had hyperthermia (104.2 F) and vomiting
 - ❖ Resolved within 12 hours with diphenhydramine and Cerenia® but required prednisone to resolve the fever
- No clinically relevant hematology changes observed
- Total treatments administered:
 - Canines (40 patients): 146 treatments
 - Felines (4 patients): 11 treatments



- MCWF was used in combination with standard chemotherapy protocols in several cases with measurable pulmonary metastasis:
 - Injection site sarcoma (1 feline)
 - Histiocytic sarcoma (1 canine)
 - Osteosarcoma (2 canines)
 - High grade soft tissue sarcoma (1 canine)
 - Mammary adenocarcinoma (1 canine)
 - Pheochromocytoma (1 canine)
 - Squamous cell carcinoma (1 canine)
 - Transitional cell carcinoma (2 canines)
- Pulmonary metastasis remained stable or showed regression radiographically
 - 6 canines/1 feline remained stable or regressed in 11 treatments or less



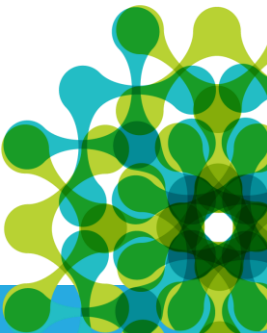
Average Survival Times for Deceased Patients

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- The average survival times from diagnosis were calculated as follows:

Cancer	Average Survival Time (Mths)	Average Number of Treatments
Hemangiosarcoma (3)	7.0	3
High grade soft tissue sarcoma (1)	14.9	3
Histiocytic sarcoma (1)	9.5	4
Injection site sarcoma (1)	21.6	4
Lymphoma (5)	6.7	3
Mammary adenocarcinoma (1)	8.8	2
Mast cell tumor (1)	39.8	1
Oral melanoma (1)	9.1	2
Osteosarcoma (3)	8.2	4
Pheochromocytoma (1)	4.6	3
Pulmonary carcinoma (1)	1.5	4
Transitional cell carcinoma (1)	12.2	6

- Currently, 24 patients are still alive
- Survival times available for 20 deceased patients:
 - 19 of 40 canines
 - 1 of 4 felines

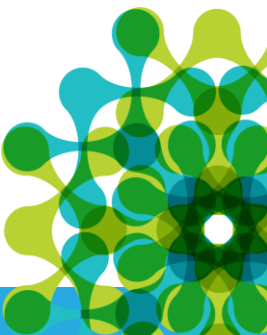


Average Follow Up Times for Active Patients

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Cancer	Average Follow Up Times (Mths)	Average Number of Treatments
Acanthomatous Epulis (1)	83.5	1
Anal Gland Adenocarcinoma (2)	12.1	3
Apocrine Adenocarcinoma (1)	52.1	5
Fibrosarcoma (1)	19.4	1
Hepatocellular Carcinoma (1)	1.73	8
Hemangiosarcoma (1)	8.7	2
High Grade Soft Tissue Sarcoma (1)	42.8	2
Histiocytic Sarcoma (1)	10.7	11
Lymphoma (6)	14.5	3.5
Mammary Adenocarcinoma (2)	5.7	2.5
Multiple Myeloma (1)	14.4	3
Oral Melanoma (1)	10.8	5
Osteosarcoma (2)	5.4	3.5
Squamous Cell Carcinoma (1)	3.1	6
Transitional Cell Carcinoma (2)	5.3	4.5

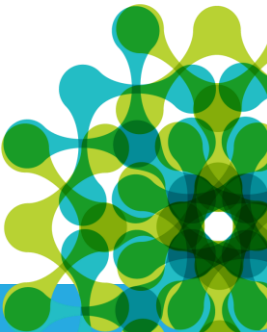
- Follow up times available for 24 active patients:
 - 21 of 40 canines
 - 3 of 4 felines



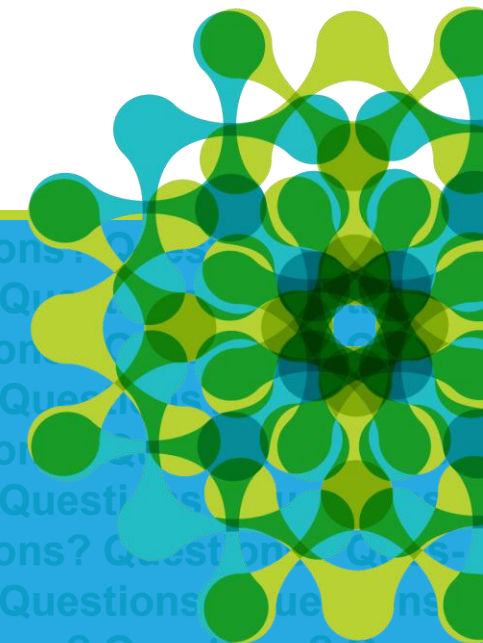
Conclusions

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- Current observations on safety of IV administration of Immunocidin® to cats and dogs with various neoplasms are satisfactory and provide a solid base for future research
- MCWF has immunomodulatory potential that may help treat additional neoplasms beyond mammary tumors as an adjunct treatment in combination with standard protocols
- Additional, controlled clinical studies are planned to demonstrate Immunocidin® efficacy as conjunctive therapy to standard treatment of hemangiosarcoma and soft tissue sarcoma



Questions?





American College of **Veterinary** Internal Medicine

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