Today’s Agenda

• Part I - Introduction to Cancer Immunology
  – Mechanisms of anti-cancer immunity
  – Immune evasion by cancer cells
  – Why can’t we get rid of it?

• Part II - Review of Veterinary Immunotherapeutics
  – Available products
  – Mechanisms of action
  – Evidence (if any) for use
  – What are we going to do about it?
Part I - Introduction to Cancer Immunology

Why can’t we just get rid of it?
The immune system is programmed to recognize “non-self”

- **Two** major divisions of the immune system:
  - Innate immunity
  - Adaptive immunity
The immune system is programmed to recognize “non-self”

- The innate immune system specializes in foreign invaders and distressed cells
  - Pathogen-associated molecular patterns
  - Damage-associated molecular patterns

- Natural killer (NK) cells look for distressed or cancerous cells
  - Destroy cells expressing “stress” molecules, or those without “self” identification
The immune system is programmed to recognize “non-self”

- The **adaptive** immune system is highly specific and tightly regulated
  - **B cells** produce antigen-specific antibodies
  - **T cells** come in several flavors:
    - Helper T cells (CD4+) assist B cells
    - Cytotoxic T cells (CD8+) kill infected cells
    - T-regulatory cells modify and dampen immune responses
The immune system is programmed to recognize “non-self”

- T cells depend on major histocompatibility complex (MHC) proteins to interact with antigen and antigen-presenting cells

- Two classes of MHC:
  - MHC class I - expressed by all “self” cells; interacts with CD8 T cells
  - MHC class II - expressed on antigen-presenting cells; interacts with CD4 T cells
How are cancer cells different from other threats?

- **Microbes** are “easy” to recognize
  - Express antigens not found in tissue
  - Structurally separate from “self”
  - Cell wall, unusual genetic material
- **Tumor cells** are difficult to recognize
  - Express normal tissue antigens
  - HER2, Kit
  - Structurally similar to “self”
How can the immune system recognize cancer cells?

- Cancer cells might “forget” how to identify themselves as “self”
  - Lose expression of MHC class I

- They may express mutated receptors which are structurally different from “self”
How can the immune system recognize cancer cells?

- They may express receptors not present in differentiated tissue
  - “Embryonic” receptors
- Pathways tumor cells exploit may make them more sensitive to death signals from immune cells
Cancer represents a failure of the immune system

- Cancer cells that cannot evade the immune system are killed and cannot cause disease

So why does cancer develop?

Because cancer can evade the body’s defenses!
Cancer has many ways to evade the immune system

- **B cells** are unlikely to make antibodies to proteins so similar to “self”
  - Humoral immunity to tumors is generally poor

- Tumors can **stop expressing** MHC class I
  - Avoids stimulation of **CD8 T cells**
Cancer has many ways to evade the immune system

• Tumors influence their microenvironment
  – Express cytokines that encourage development of Treg cells

• Tumors can express inhibitory receptors
  – Cancer cells “turn off” T cells that encounter them

• Tumors can directly kill immune cells
  – T cells express a “kill switch” that protects the body
  – Cancer cells may activate the switch and cause the death of the T cell
*Immunoediting* results in a tumor able to evade the immune system

- 3 step process results in the *selection* of cancer cells that have the ability to **evade** the body’s defenses
Immunoediting results in a tumor able to evade the immune system

- Phase 1 - Elimination
Immunoediting results in a tumor able to evade the immune system

- Phase 2 - Equilibrium
Immunoediting results in a tumor able to evade the immune system

- Phase 3 - Escape
Part 2: Review of Veterinary Immunotherapeutics

What are we going to do about it?
Why does immunotherapy matter?

• We have reached a **therapeutic plateau** for most veterinary cancers

• Many variations of CHOP (and other alphabet soup) chemotherapy for **canine B cell lymphoma** have been attempted
  – No significant improvement over the expected average survival of **12 months** noted

• Despite surgical (limb-sparing) and radiotherapy (sterotactic radiation therapy) advances, survival for **canine osteosarcoma** remains static
  – Survival with primary tumor control and chemotherapy remains approximately **12 months**
Why does immunotherapy matter?
Immunootherapeutics for Veterinary Use
### Selected recently developed veterinary immunotherapeutics and their regulatory status.

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Compound Name</th>
<th>Company</th>
<th>Indication</th>
<th>Regulatory Status (US)</th>
<th>Available?</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blontress®</td>
<td>Canine lymphoma MAb, B-cell</td>
<td>Aratana</td>
<td>B-cell lymphoma</td>
<td>USDA Licensed (2015)</td>
<td>No</td>
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<td>N/A</td>
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<td>N/A</td>
<td>Immunomodulator</td>
<td>NovaVive</td>
<td>Sarcoma</td>
<td>USDA Conditional License (2015)</td>
<td>Yes</td>
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<tr>
<td>Immunocidin®</td>
<td>Mycobacterium cell wall fraction</td>
<td>NovaVive</td>
<td>Mammary tumors</td>
<td>USDA Licensed (2015)</td>
<td>Yes</td>
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<tr>
<td>Oncept®</td>
<td>Canine melanoma vaccine, DNA</td>
<td>Merial</td>
<td>Melanoma</td>
<td>USDA Licensed (2010)</td>
<td>Yes</td>
</tr>
</tbody>
</table>

- **Therapeutic vaccines**
- **Monoclonal antibodies**
- **General immune stimulants**
- **Canine Osteosarcoma Vaccine**
Therapeutic DNA Vaccines
Canine melanoma vaccine, DNA (Oncept®)

- **Tyrosinase** is essential in melanin synthesis pathway
- DNA vaccine containing xenogeneic human tyrosinase

Bergman et al, Small Animal Clinical Oncology
Canine melanoma vaccine, DNA (Oncept®)

- **Label use:** stage II or stage II oral malignant melanoma, after local disease control

- Literature surrounding use of Oncept is **mixed**
- **Original studies** showed **significant** differences between treated and untreated dogs
- **Later studies** found no difference between treated groups

- The vaccine is available for use and well tolerated; cost and efficacy concerns may limit use
Canine lymphoma vaccine, DNA

• Xenogeneic murine CD20 DNA vaccine, under conditional USDA licensure since 2015

• There are no published studies to date regarding this product, however it is available to veterinary oncologists
  – Trials using this product both after and concurrent with CHOP chemotherapy are actively enrolling patients
Feline IL-2 Immunomodulator

- Conditional license granted by USDA (March 2015)
  - Delay postsurgical recurrence of ISS in cats
- Commercially available to veterinary oncologists
- Limited data available

- US Field Study for ISS
  - Multi-center randomized controlled trial
  - Initiated April 2015
  - Target accrual n = 75 cats; still enrolling
Monoclonal Antibodies
Blontress®

- Caninized monoclonal antibody designed to target CD20

- Fully licensed by USDA for use as an aid in treating B cell lymphoma
Tactress™

- Caninized monoclonal antibody designed to target CD52

- **Fully licensed** by USDA for use as an aid in treating T cell lymphoma
Blontress® and Tactress™

- **Interim data** from studies showed disappointing results (2015)
  - **Failure** to improve progression-free survival
  - **Poor binding** of intended targets
- Information on these drugs is still available, but...

These products are no longer available commercially
1E4

- **Anti-CD20** monoclonal antibody
- Similar to human anti-CD20 Mab, **Rituxan®** (rituximab)
  
  - **Depletes** B cell levels significantly in healthy Beagles*
  
  - In murine xenograft model, demonstrated **single agent efficacy** against canine B cell lymphoma+

- Current commercial status - **unknown**

*Rue et al, *Vet Immunol Immunopathol* 2015
Generalized Immune Stimulants
Bacillus Calmette-Guérin (BCG)

- Live attenuated vaccine against tuberculosis
  - 1930s: noted that humans who received the vaccine had a lower incidence of cancer
- Several authors noted increased survival times in dogs with osteosarcoma receiving BCG (1974-75, 1977)
- Banned for use in cattle (interferes with tuberculin test) - not widely used
Immunocidin®

- Mycobacterial cell wall fraction
- **Labeled use:** intratumoral injection for treatment of canine mammary tumors
- **Initial clinical evaluation:** safe to administer IV

- **Current trial** in canine hemangiosarcoma, following surgery and concurrent with standard-of-care chemotherapy
Canine Osteosarcoma Vaccine, Live Listeria Vector (COV-LLV)
COV-LLV is an engineered *Listeria* expressing a tumor-associated antigen

Courtesy of Aratana Therapeutics
Longer overall survival in treated dogs (following local control + carboplatin)

All dogs without gross metastatic disease at the time of first dosing
* Some dogs received booster vaccine treatment q4-6 months

**Vaccinated dogs** showed **significant benefit** when compared to **historical controls**

- Longer disease-free interval
  - 615 days vs 257 days
- Longer mean survival time
  - 956 days vs 423 days
- Greater 1, 2, and 3 year survival
Is it too good to be true?

- The data is extremely promising!
- Possible study limitations
  - Small sample size
  - Variable doses used
  - Historical controls

- CAUTIOUS OPTIMISM
Modification of the original vaccine

- Aratana Therapeutics purchased the rights to the vaccine product for animal development.
- Original product stored at -80°C.
- Lyophilization allows storage under refrigerated conditions.
Common adverse events

• Signs of **generalized** immune stimulation
  – Fever
  – Lethargy
  – Nausea and vomiting

• Dogs receive **pretreatment** to minimize the risk of severe signs
  – IV fluids
  – Anti-emetic
  – Antihistamine
  – NSAID
Possible serious adverse events

- Immune stimulation can result in serious systemic effects
  - Hypotension
  - Hemorrhagic diarrhea
  - Renal and/or liver dysfunction
  - Arrhythmias
  - Cytokine storm
  - Death
Canine OSA Vaccine

Extended Field Safety Study

- Initiated early 2018 at ~25 oncology practices
  - Ongoing; enrollment approaching completion
  - Available for off-study use in any reasonable candidate

- Inclusion Criteria
  - > 1 year age; >2 kg body weight
  - Diagnosis of OSA
  - Amputation, followed by chemotherapy
  - ECOG Performance Score 0 or 1

- Exclusion Criteria
  - Pulmonary metastasis
  - Prior immunotherapy for OSA
Expanding our treatment arsenal for dogs with cancer...
Where are we now?
Is there anywhere to go?
What does the future hold for veterinary oncology?
In summary...

- The **immune system** and **cancer** are closely intertwined
- Cancer must **evade** immune attack to survive
- Available **treatment options** may or may not be supported by published evidence
- Knowledge of available **immunotherapy options** leads to better client counseling...

... and hopefully, improved outcomes!
Questions?

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