PALLADIA®: How it Works and its Many Uses in Dogs

Giovanna Coto, DVM
Oncology Resident, Iowa State University

Wednesday, April 3, 2019, 1:00 - 2:00 PM
What you can expect today...

• Review Palladia (toceranib phosphate) data
  - Mechanism of action
  - Canine MCT pivotal trial data
  - Known and potential side effects
  - Current chemodectoma study

• Understand potential roles and clinical utility for Palladia in oncology case management
  - Mast cell tumors (MCTs)
  - Non-MCT solid tumors
CURRENT TRENDS IN ONCOLOGY
THERAPEUTIC DEVELOPMENT
## Progression of cancer treatment modalities

Moving toward greater specificity

<table>
<thead>
<tr>
<th>APPROACH</th>
<th>SURGERY</th>
<th>RADIATION</th>
<th>CHEMOTHERAPY</th>
<th>TARGETED DRUGS</th>
<th>IMMUNOTHERAPY</th>
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<tbody>
<tr>
<td>SINCE</td>
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Palladia development began in late 1990s/early 2000s during focus on targeted therapies
Personalized medicine: tailored treatments
## Canine Oncology Therapeutics

*Commercially Available (2018)*

<table>
<thead>
<tr>
<th>Trade Name</th>
<th>Compound Name</th>
<th>Company</th>
<th>Indication</th>
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<td>Merial/BI</td>
<td>B-cell lymphoma</td>
<td>USDA Conditional License (2015)</td>
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<td>Aratana</td>
<td>Osteosarcoma</td>
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<td>NovaVive</td>
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<td>Canine melanoma vaccine, DNA</td>
<td>Merial</td>
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<td>Toceranib phosphate</td>
<td>Zoetis</td>
<td>Grade II/III mast cell tumor</td>
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<td>Tanovea®- CA1</td>
<td>Rabacfosadine for injection</td>
<td>VetDC</td>
<td>Lymphoma</td>
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PALLADIA...HOW IT WORKS
PALLADIA: Inhibiting Multiple Tyrosine Kinase Receptors to Disrupt Angiogenesis and Cell Proliferation in Mast Cell Tumors

- VEGFR (vascular endothelial growth factor receptor)
- PDGFR (platelet-derived growth factor receptor)
- KIT
RTKs Regulate Normal Cellular Growth and Differentiation

- RTKs consist of extracellular, transmembrane, and intracellular domains\(^1\)
- RTKs are activated in response to growth factors that bind their extracellular domain\(^2\)
- RTKs catalyze the transfer of phosphate from ATP to other proteins\(^2\)
- Downstream intracellular signaling ensues (signal transduction), which elicits various cellular responses\(^1,2\):
  - Gene activation/inhibition
  - Proliferation
  - Apoptosis
  - Survival
  - Migration

KIT Dysfunction Plays a Role in Canine MCT Proliferation

- Prevalence of KIT mutations is approximately 25% in grade 2/3 canine MCT\(^1\)
  - Internal tandem duplications (ITD) in exons 11 and 12 (juxtamembrane domain) lead to constitutive phosphorylation of KIT in the absence of SCF binding\(^2\)
  - c-KIT ITD mutations are associated with an increased rate of recurrent disease and mortality in dogs with MCT\(^2\)
  - Mutations at exons 8 and 9 have been identified and are constitutively activating\(^1\)
- One study has demonstrated that blocking either wild-type or mutated KIT inhibited MCT growth, leading to cell apoptosis in cultured tumor cells\(^3\)

PALLADIA - Mechanism

• Toceranib phosphate (PALLADIA, Zoetis)
• Tyrosine kinase inhibitor (TKI)
  – KIT
  – VEGFR (vascular endothelial growth factor receptor)
  – PDGFR (platelet-derived growth factor receptor)
• FDA-approved for use in dogs with MCT (2009)
• Potential anti-angiogenic effects
  – Used in several other tumor types in dogs and

Most common signs: GI (inappetence, vomiting, diarrhea, ulceration)
Less common effects: Neutropenia, muscle pain/lameness, change in coat color
CLINICAL FIELD STUDY: SINGLE-AGENT PALLADIA IN DOGS WITH MCT
Clinical Field Study Design

Dogs with recurrent, cutaneous MCTZ

Randomization

4

Blinded phase

6-week blinded PALLADIA 3.25 mg/kg oral EOD (n=86)

3

6-week blinded assessment

Open-label phase

PALLADIA open-label

6-week blinded placebo* (n=63)

Blinded + open-label assessment

* Dogs with progressive disease on placebo during the blinded phase could enter the open-label phase at any time. The primary endpoint was objective response rate (CRR).

37.2% ORR in PALLADIA-treated dogs during the 6-week blinded phase and 42.8% ORR in all PALLADIA-treated dogs in the blinded plus the open-label phase.

Among dogs with an objective response, median time to tumor progression or death was 18.1 weeks and median duration of response was 12.0 weeks (n=62).
PALLADIA Exhibited Significant Biological Activity Against Canine MCT in the Blinded and Open-Label Phases

- Biological response rate (SD ≥10 weeks or PR or CR) was 59.5% for all treated dogs in the blinded plus the open-label populations.
- Among all dogs receiving PALLADIA, the biological response for dogs with the KIT ITD mutation was 82.1% and 54.5% for dogs without the mutation.
- KIT mutation testing is not required prior to administering PALLADIA.

GI Side Effects Are the Most Common AEs With PALLADIA

<table>
<thead>
<tr>
<th>Adverse event (AE)</th>
<th>PALLADIA (n=87)</th>
<th>Placebo (n=64)</th>
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<tbody>
<tr>
<td></td>
<td>Any grade</td>
<td>Grade 3 or 4</td>
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<tr>
<td>Diarrhea*</td>
<td>46.0%</td>
<td>6.9%</td>
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<tr>
<td>Anorexia (includes decreased appetite)</td>
<td>39.1%</td>
<td>6.9%</td>
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<tr>
<td>Lethargy</td>
<td>35.6%</td>
<td>4.6%</td>
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<tr>
<td>Vomiting</td>
<td>32.2%</td>
<td>9.2%</td>
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<tr>
<td>Lameness</td>
<td>17.2%</td>
<td>0.0%</td>
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<tr>
<td>Weight loss*</td>
<td>14.9%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Musculoskeletal disorder</td>
<td>11.5%</td>
<td>1.1%</td>
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<tr>
<td>Blood in stool/GI bleed/hemorrhagic diarrhea*</td>
<td>12.6%</td>
<td>2.3%</td>
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</tbody>
</table>

- Dogs treated with PALLADIA in the blinded phase had 34% more days at risk to develop AEs vs placebo-treated dogs

*Any grade AEs that occurred statistically more frequently with PALLADIA than with placebo; there was no difference in grade 3 or 4 AEs between the two groups.

CLINICAL USE IN DOGS
Evaluation of Palladia administered to dogs with solid tumors at doses below the MTD

- Approved dose in dogs = 3.25 mg/kg PO q48h
  - Dose reductions to 2.25 mg/kg PO q48h
- Palladia administered between 2.4-2.9 mg/kg PO q48h
  - Average 6-8 hr plasma concentration: 100-120 ng/ml
  - Well above 40 ng/ml associated with target inhibition
- Lower doses associated with substantially reduced adverse event profile

Lower doses clinically associated with reduced adverse event profile while maintaining biologic activity.

Many faces of MCTs
MCT Prognostic Factors

- Histologic grade
- Clinical stage (metastasis)
- Anatomic location
- Cell proliferation rate (mitotic index, others)
- Growth rate (clinical)
- Recurrence
- Systemic signs
- Breed
- Tumor size
- C-KIT mutation
MCT Chemotherapy - Indications

- High-grade MCT
- Metastatic MCT
- Non-resectable MCT
- Visceral MCT
  - Spleen/liver, bone marrow, internal LN
Chemotherapy - My Approach

• First-line chemotherapy protocol(s)
  ▪ Vinblastine + prednisone
  ▪ Vinblastine + CCNU + prednisone
  ▪ PALLADIA + prednisone

• PALLADIA use still not uniformly defined
  ▪ One High grade MCT approach:
    ✓ Vinb + Pred x 4 w → KIT neg = 4 more Vinb then CCNU x 4
    ✓ Vinb + Pred x 4 w → KIT pos = PALLADIA x 6 mo (minimum)

Cost, logistics, client = all key factors driving protocol choice
Palladia + Prednisone + Hypofractionated Radiation Therapy (RT) for Canine MCT

- **17 dogs** with measurable (unresectable) MCT
- Palladia administered for 1 week before initiating RT
  - 24 Gy delivered in 3 or 4 fractions
- **Overall response rate = 76.4%**
  - 58.8% complete response
  - 17.6% partial response
- **Overall median survival time not reached**
  - Median follow-up of **374 days**
- **Most common toxicoses were GI and hepatic**

Viable option for dogs with unresectable MCT

Pulse-dosed Palladia + lomustine for nonresectable canine mast cell tumor (MCT)

- **47 dogs** with measurable MCT
- **Palladia** administered on days 1, 3 and 5 of 21-day cycle
  - Target dosage = 2.75 mg/kg PO
- **Lomustine** administered on day 3 of each cycle
  - Starting dosage = 50 mg/m² PO
- **Objective response rate = 46%**
  - c-kit gene mutation status did not affect outcome
- **Protocol was well-tolerated**
  - Relatively low incidence of adverse GI events

Reasonable option for dogs with unresectable or metastatic MCT

CASE #1: CHLOE
12 Year-Old, F/S, Labrador Retriever
Case #1: Chloe

History and PE

- **March 2016:** Low grade (Patnaik Grade I) MCT excised - right, dorsal antebrachium (complete margins)
  - Mitotic index: <3 / 10 hpf
- **August 5, 2016:** Mass on right shoulder
  - Referral to ISU Oncology
- **11 cm** firm, non-mobile mass in area of right prescapular LN
- **2 cm** firm thickening/mass along prior MCT excision site

~10-15% of low grade MCTs will act aggressively!
Case #1: Chloe
Staging at ISU Oncology

- FNA + Cytology
  - LN, prior surgical site
- CBC + Serum Chem
- Chest Radiographs
- Abdominal Ultrasound
  - Aspirates: Liver & Spleen + Cytology

MCT Prognostic Panel submitted to MSU
MCT Panels: What should you do?

- High/Grade III/High MI = KIT mutation testing
  - **Positive:** Chemotherapy + PALLADIA
  - **Negative:** Chemotherapy alone vs Chemo + PALLADIA

- **When to run a full panel?**
  - Incomplete resection, assess chance of recurrence
  - Biologic behavior does not fit histopathology
    - Tumor growing rapidly, large, etc.
  - “Hot” Anatomic sites = muzzle, mucocutaneous, etc.
  - Low owner risk tolerance
    - ~ 5-15% chance of low grade MCT behaving aggressively
    - Low MI does NOT guarantee excellent prognosis
Case #1: Chloe
Treatment and Progression

8/10/16: 11cm
8/17/16: 7cm
8/25/16: 4.5cm
9/1/16: 1.1cm

- Prednisone alone + supportive
- Eosinophil count 23.96 x10³ cells
- + Vinblastine 3.6 x10³ cells
- + Vinblastine 0.61 x10³ cells
- + Palladia 1.6 x10³ cells

c-Kit mutation positive
CASE #2: FRODO
12 YEAR-OLD, M/N, TOY POODLE
Case #2: Frodo

History
- July 2015: 6-month history mass on left, rostral mandibular lip

Physical Examination
- 2.5 cm firm mass left, rostral mandibular lip
- Left mandibular LN firm and enlarged (2 cm)

Diagnostics
- FNA + Cytology: Mass and LN
- CBC + Serum Chem + UA
- Abdominal Ultrasound
  - Aspirates: Liver & Spleen + Cytology

Muzzle MCTs often act more aggressively!
Case #2: Frodo

Treatment

• Neoadjuvant vinblastine (2 doses) + prednisone
  – ~50% reduction in size of MCT
• Marginal surgical excision: High-grade MCT (MI = 13 / 10 hpf) with mandibular LN metastasis

Additional Diagnostics

• c-kit mutation analysis: exon 11 ITD present

Continued Treatment

• Post-surgery vinblastine x 6 doses
• Palladia initiated 2 weeks following last vinblastine (Nov 2015)
• July 2018: Doing well on Palladia, new MCT noted (1.8 cm)
Evidence for biologic activity of Palladia in solid tumors (non-MCTs)

Clinical benefit (CB) observed in 63/85 (74%) dogs

<table>
<thead>
<tr>
<th>Tumor Treated</th>
<th># Responding</th>
<th>Responses</th>
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</thead>
<tbody>
<tr>
<td>Anal sac carcinoma</td>
<td>28/32</td>
<td>8 PR; 20 SD</td>
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<tr>
<td>Metastatic OSA</td>
<td>11/23</td>
<td>1 PR; 10 SD</td>
</tr>
<tr>
<td>Thyroid carcinoma</td>
<td>12/15</td>
<td>4 PR; 8 SD</td>
</tr>
<tr>
<td>Head &amp; neck carcinoma</td>
<td>7/8</td>
<td>1 CR; 5 PR; 1 SD</td>
</tr>
<tr>
<td>Nasal carcinoma</td>
<td>5/7</td>
<td>1 CR; 4 SD</td>
</tr>
</tbody>
</table>

Median dose = 2.8 mg/kg
36/63 (58.7%) dosed on M/W/F
47/63 (74.6%) treated ≥4 months

CASE #3: CHLOE
11 YEAR-OLD, F/S, CHIHUAHUA MIX
Case #3: Chloe

History
- **July 2016:** 1-month history of firm ventral cervical mass

Physical Examination
- 6 cm firm, non-mobile ventral cervical mass
- Peripheral lymph nodes wnl

Diagnostics
- FNA + Cytology: Mass and LNs
- CBC + Serum Chem + UA
- Thoracic radiographs

Dx = Thyroid carcinoma
Fixed / non-mobile = poorer prognosis!
Case #3: Chloe

Thoracic Radiographs
Case #3: Chloe

Treatment
• Palladia 2.4 mg/kg PO M/W/F each week
• Piroxicam 0.3 mg/kg PO on non-Palladia days

Response
• Thyroid mass ~33% reduction = PR
• Pulmonary metastatic lesions smaller
• Clinical response to Palladia for ~1 year
• Rescue therapy: Carboplatin, DOX, vinorelbine

Palladia can be utilized for as long as patient is experiencing clinical benefit and tolerating therapy.
Immunomodulatory effects of Palladia + low-dose cyclophosphamide (CYC)

- **Goal:** Determine effects of Palladia and metronomic CYC on regulatory T-cells (Treg) and interferon-gamma (IFN-γ)
- 15 dogs with advanced tumors
- Palladia dose: **2.75 mg/kg PO q48h**
  - After 2 weeks, oral CYC added at 15 mg/m² q24h
- Administration of Palladia significantly decreased the number and percentage of Treg
- Dogs receiving Palladia and CYC demonstrated a significant increase in serum concentrations of IFN-γ

Palladia following doxorubicin for canine splenic hemangiosarcoma (HSA)

- 43 dogs with splenic HSA
- 5 cycles of DOX (30 mg/m² IV) q2w
- No metastatic disease → Palladia 3.25 mg/kg PO q48h
- Median survival time (ST)
  - All dogs enrolled: 169 days
  - Dogs receiving Palladia: 172 days

23% developed disease recurrence within 3 mo

Use of Palladia following DOX does NOT improve outcomes in dogs with splenic HSA compared to previous reports

Impact of Metronomic Chemotherapy +/- Palladia® in Dogs with OSA

- Randomized prospective trial
- Amputation + carboplatin x 4
- Randomized to piroxicam and cyclophosphamide +/- Palladia
- Did not improve overall survival
  ✓ 318 d w/ Palladia vs 242 d control (p=0.08)

Two recent studies in dogs with metastatic OSA show NO clinical benefit for Palladia.
GIST Therapeutic Targets

**Human GIST**

- Inhibition of Kit with TKIs is impactful in high-risk GIST
  - **Imatinib** (Gleevec, Novartis) standard-of-care for high-risk tumors
  - **Sunitinib** (Sutent, Pfizer) approved for imatinib-resistant GIST

**Canine GIST**

- **Toceranib** (Palladia, Zoetis) a TKI approved for use in dogs
  - Activity at Kit, PDGFR, and VEGFR

- Biologic effect of toceranib apparent
  - Retrospective study: 27 cases (ISU)*
  - Clinical benefit in 5/7 dogs with measurable disease

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CASE #4: POGO
9 YEAR-OLD, M/N, LABRADOR RETRIEVER
Case #4: Pogo

History
• Oct 2015: Presented to ISU for evaluation
• 2-month history of weight loss (~10 pounds)

Physical Examination
• Tense, non-painful on abdominal palpation
• Concern for caudal abdominal mass

Diagnostics
• CBC + Serum Chem + UA
• Thoracic radiographs
• Abdominal ultrasound
Case #4: Pogo

Abdominal Ultrasound
FNA of Intestinal Mass

- Malignant neoplasia - either epithelial or mesenchymal origin

Surgery & Histopathology

- October 27, 2015 - exploratory laparotomy
- Mass excision with partial typhlectomy

**Surgical pathology**

Cecal sarcoma - gastrointestinal stromal tumor (GIST) or gastrointestinal leimyosarcoma; **incomplete excision**

**Additional stains**

- cKit - positive immunoreactivity - **consistent with GIST**
- Smooth muscle actin - little to no immunoreactivity
Case #4: Pogo

Treatment

- **November 2015:** Palladia (2.6mg/kg PO q48h) x ~1 year
  - Tolerated therapy relatively well
    - Mild leukopenia → dose frequency reduction to M/W/F
    - 1 week drug withdrawal due to diarrhea
    - Developed proteinuria and mild hypertension
- **May 2017:** No evidence of disease

**Survival = 36 months; died of an unrelated cause**
Canine Chemodectomas

• Chemodectomas are the most common type of aortic body tumor
  – Locally invasive
  – Low metastatic propensity

• Treatment
  – Subtotal pericardectomy
    • OST 661 days vs 129 days
  – Radiation therapy
    • 30-76% volume reduction

Palladia for Chemodectomas

- Recent retrospective study
- 110 dogs with an aortic body chemodectoma
- Treatments:
  - Monitoring, supportive
  - NSAIDs
  - Chemotherapy
  - Radiation therapy
  - Surgery
  - Palladia
Palladia for Chemodectomas

• Treatment with *Palladia*
  – Most common treatment
    • 40% of all dogs were definitively treated
    • 63% were treated with Palladia
  – Overall clinical benefit of 88%
  – OST of 592 days vs 169 days for all patients
## Other Prognostic Factors

<table>
<thead>
<tr>
<th>Variable names (categorical)</th>
<th>P-value (Log-rank test)</th>
<th>Median point estimate (Median survival time, in days)</th>
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Other Prognostic Factors

- Positive prognostic factors
  - Palladia
    - OST 592 days
  - Pericardiectomy
    - OST 578 days

- Negative prognostic factors
  - Pericardial effusion
  - Metastatic disease
Effects of Palladia on systolic blood pressure and proteinuria in dogs

• Part 1: 26 control and 30 dogs with cancer
• Part 2 (Palladia treatment): 48 dogs (20 control, 28 with cancer)

• Results:
  – Systolic blood pressure significantly (P = 0.0013) higher in previously normotensive dogs after initiation of Palladia
    • 152 mmHg ± 19 compared to baseline (136 mmHg ± 14)
  – 37% of treated dogs developed SBP ≥ 160 mmHg

Recommend baseline BP and UPC prior to starting Palladia along with routine monitoring on therapy.

## Palladia recheck schedule*

<table>
<thead>
<tr>
<th>Visit</th>
<th>CBC</th>
<th>Serum chemistry</th>
<th>UA</th>
<th>UPC</th>
<th>Blood Pressure</th>
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<td>Week 2</td>
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<tr>
<td>Week 4</td>
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<td>✔</td>
<td>✔</td>
<td>As indicated</td>
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<tr>
<td>Week 8</td>
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<td>As indicated</td>
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<tr>
<td>Every 4 to 8 weeks</td>
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<td>✔</td>
<td>✔</td>
<td>As indicated</td>
<td>✔</td>
</tr>
</tbody>
</table>

*Protocol tailored on a case-by-case basis to best match patient needs with client logistics and finances.
Palladia Clinical Considerations

Concomitant Medications

Standard
- Famotidine or omeprazole

Clinical Signs Present (stop Palladia therapy)
- Sucralfate - GI ulceration
- Misoprostol - GI ulceration
- Metronidazole - diarrhea
- Cerenia®, ondansetron - vomiting
- Entyce® - inappetence

Adjust Palladia dose for weight loss if experienced while on therapy
Palladia Clinical Considerations

**Adjuvant Therapies**

**Mast Cell Tumors**
- Prednisone 0.5-1.0 mg/kg PO q24-48h

**Several Solid Tumors**
- Piroxicam 0.3 mg/kg PO q24-48h*

**Cytotoxic Chemotherapeutics**
- Vinblastine, carboplatin, DOX, CCNU evaluated (concurrent)
- Often requires dose reduction/treatment delay
- Consult with Oncologist

Palladia Clinical Considerations

Treatment Breaks

Most Common Reasons

• Gastrointestinal signs
• Neutropenia
• Lameness/muscle cramping

Duration of Break

• Typically ~1 week
• Consider changing frequency (to M/W/F) or reducing dose

Client communication and education is key!
When in doubt, stop drug.
Consult Oncologist as needed.
When do I consider Palladia therapy?

Dogs

- Mast cell tumor (high grade)
- Thyroid carcinoma
- Anal sac carcinoma
- Squamous cell carcinoma
- Other carcinomas (nasal, GI, lung, mammary, TCC)
- GIST
- Chemodectoma
- +/- Histiocytic sarcoma (refractory to CCNU, DOX)
In Review...

- Review Palladia (toceranib phosphate) data
  - Mechanism of action
  - Canine MCT pivotal trial data
  - Known and potential side effects

- Understand potential roles and clinical utility for Palladia in oncology case management
  - Mast cell tumors (MCTs), non-MCT solid tumors

New uses evolving for an established therapeutic option!
Questions?

Chad Johannes, DVM, DACVIM (SAIM, Oncology)

cmj15@iastate.edu