Of Mice & Men (and Dogs!): Development of a Therapeutic Xenogeneic DNA Vaccine for Spontaneous Canine Melanoma

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Immunotherapy for Cancer

What are we going to cover today?

- Melanoma
  - Treatments & Prognostic Factors
  - The Xenogeneic Concept
  - Xenogeneic DNA Vaccine Program
  - Distill 18 years into 20 mins 😊

- PD-1/PD-L1 studies?
- VCA Clinical Studies review
Disclosure

- Consulting
  - Direct and/or through trial design/implementation
  - Zoetis, BIVI, Merial, Abbott, Elanco, Virbac, Aratana, MBF Therapeutics, Regeneus, AB Science, Bayer, Oasmia, Royal Canin, Ceva, Purina, Kindred Bio, Merck AH

- Research Grants
  - Zoetis, & Merial

- Stock Ownership
  - Aratana, Zoetis, Heska

- Minority Royalty Stream
  - Merial (Oncept® & Xenogeneic DNA Patent)
Canine Malignant Melanoma

- **Disease with two major problems**
  - Local tumor control
    - Partial maxillectomy or mandibulectomy
      - MacEwen et al/Harvey et al
      - Bostock et al/Schwarz et al
    - 3-4 dose RT >>>>> regular fractionation
      - Blackwood et al, JAVMA 1996
      - Bateman et al, JVIM 1994
  - Propensity for metastasis is HIGH
  - Chemotherapy is not helpful
  - Stage II/III MST = 3-8 months
Xenogeneic DNA Immunization Concept

1 Naftzger et al. 1996. PNAS 93:14809
Xenogeneic DNA Vaccination

- Plasmid DNA
  - pING plasmid
  - FDA points to consider
    - Kanamycin selection
    - CMV promoter
  - CpG islands
    - Internal adjuvant
  - Easy to produce & store
  - Safe & Immunogenic
- Insert:
  - Human Tyrosinase
  - Murine Tyrosinase
  - Others
DNA vaccine for melanoma

- Routine Pre-Vaccine Staging
  - PE, bloods, 3 view Chest XR’s, LN FNA/Cyto
- Vaccinate q 2 weeks X 4
  - HuTyr or MuGP75
    - 100 ug, 500 ug, 1500 ug; 3 dogs each dose level
  - MuTyr
    - 100 ug or 500 ug; 5 dogs each dose level
- MuTyr + HuGM-CSF (3 arm seq. accrual; 27 dogs)
  - MuTyr 50 ug; 9 dogs
  - MuTyr (50ug) & HuGM-CSF (100/400/800ug)
  - Pre-Vacc & 6-hr post-vacc serum samples
- MuTyr (50ug) Vitajet “Off Study”
  - Feb 2004 – Apr 2007 = ~ 320 dogs!
  - Allow inclusion of stage I
Canine Malignant Melanoma

Advances in Brief

Long-Term Survival of Dogs with Advanced Malignant Melanoma after DNA Vaccination with Xenogeneic Human Tyrosinase: A Phase I Trial

Philip J. Bergman, Joanne McKnight, Andrew Novosad, Sarah Charney, John Farrelly, Diane Craft, Michelle Wulderk, Yusuf Jeffers, Michel Sadelain, Ann E. Hohenhaus, Neil Segal, Polly Gregor, Manuel Engelhorn, Isabelle Riviere, Alan N. Houghton, and Jedd D. Wolchok


IV disease had long-term survivals (421 and 588+ days) in the face of significant bulky metastatic disease, and two other dogs with locally controlled stage II/III disease had long-term survivals (501 and 496 days) with no evidence of melanoma on necropsy. Four other dogs were euthanized because of progression of the primary tumor. The Kaplan-Meier median survival time for all nine dogs was 389 days.

Conclusions: The results of this trial demonstrate that xenogeneic DNA vaccination of dogs with advanced malignant melanoma is a safe and potentially therapeutic modality. On the basis of these results, additional evaluation of this novel therapeutic is warranted in locally controlled CMM and advanced human melanoma.
Results
Stage Dependent KM Median Survival

- **Stage I > 939 days**
  - 92.8% survival

- **Stage II > 908 days**
  - 79% alive @ 1 year
  - 63% alive @ 2 years

- **Stage III > 1646 days**
  - 77% alive @ 1 year
  - 65% alive @ 2 years
  - 57% alive @ 3 years

- **Stage IV = 239 days**
  - 40.5% alive @ 1 year
  - 18.8% alive at 2 years

- $P < .0001$ (log-rank)
Immunoassay Results

Antigen specific immune responses

- **Humoral**
  - 3 out of 9 dogs, each with ST > 300 days
  - Ab titers: 1:160 (n=1), 1:320 (n=1), > 1:1280 (n=1)
  - 2 out of 3 dogs HuTyr Ab+ cross-react with K9 Tyr
    - Suggests breaking of immune tolerance/ignorance
    - Liao et al, Cancer Immunity 2006
  - **Response most prominent in later post-vaccinate sera**
    - Responses continue to increase over time

- **Cell-Mediated**
  - Goubier et al, Vaccine 2008
    - 100% vaccinates formed HuTyr-specific IFN-γ T cells
DNA Melanoma Vaccine Summary

- Conditional licensure March ‘07
- FIRST US-Gov’t approved vaccine for treatment of cancer
- Release of vaccine to US-based veterinary oncologists on June 7, 2007
- Canadian & UK/EU veterinary oncologists via compassionate use in August, 2007
- 2007 Animal Pharm Companion Animal Product of the year
DNA Melanoma Vaccine Summary

- **Xenogeneic DNA Vaccine Program Development**
  - Bergman et al, Vaccine 2006
  - Bergman et al, Cancer Therapy 2008

- **Melanoma – Phase II in Minimal Residual Dz**
  - USDA Registration Trial, April, 2006 (support application for full licensure)
    - Accrual across 5 sites completed June, 2007
    - Final results submitted back to USDA – early ’09

- **USDA Full Licensure**
  
  Dec 1, 2009
Xenogeneic Murine Tyrosinase DNA Vaccine for Malignant Melanoma of the Digit of Dogs

C.A. Manley, N.F. Leibman, J.D. Wolchok, I.C. Rivière, S. Bartido, D.M. Craft, and P.J. Bergman
Phillips et al, J Eq Vet Sci 2011

- N = 6 (VitaJet vs. Bioject2000)
  - VitaJet & pectoral = optimal
  - No significant pain responses
  - Dependent edema common 24 hours post-vaccination

- Progressive Ag-specific humoral responses seen in all horses at day 56

- Efficacy studies ongoing
Studies against Oncept efficacy?

- All retrospective and very small #’s of cases
  - Ottnod et al, VCO 2013
    - 30 cases across 2 arms w/ Stage II/III (ie 15 vaccinates)
    - Local tumor control? Death due to local dz progr vs mets??
  - Boston et al, Vet Surg 2014
    - 14 patients receiving Oncept (of 151 total dogs)
    - Stages of disease and level of local tumor control not given
    - Death due to local recurrence vs mets also not given
    - Huge # of variables – what did we learn?
  - Tuohy et al, JAVMA 2014
    - 70 dogs with Sx for oral melanoma – 4 received vaccine!
    - MST (variable Rx’s) = 723d BUT >50% stage I dogs
    - 32 dogs with Sx & Oncept; MST = 335d
    - > 50% euthanized due to local tumor progression = No local tumor control 😞
    - Stage, margins and time to vaccine NOT significant
      - OPPOSITE OF ALL PREVIOUS LARGER STUDIES


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<td>JFMS</td>
<td>Feline Safety Study</td>
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<td>Verganti et al</td>
<td>JSAP</td>
<td>UK Canine Melanoma</td>
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Summary

Dogs with malignant melanoma are an excellent model for advanced human melanoma

- **Spontaneous** syngeneic cancer
- Immuno-competent host
- Similar living environments & cancer-bearing ages
- Tumors are locally aggressive & widely metastatic
  - Similar metastatic sites
- Tumors are chemo & relatively RT resistant
- Veterinary & Human cancer centers can work well together!!

Most faithful model to human malignant melanoma
Acknowledgements

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- **Clients & Pets**
Next Phase of Cancer ImmunoRx?

- Checkpoint Inhibitors
  - Cancer Ag of interest independent
  - CTLA-4/PD-1/PD-L1/STING/etc.
    - Multiple human FDA approved mAb’s
      - CTLA-4 = Yervoy® (2011)
      - PD-1 = Keytruda® (2014), Opdivo® (2014),
      - PD-L1 = Tecentriq® (2016)
  - Next phase at MSK = checkpoint inhib + vaccine

- Status in Veterinary Medicine?
  - Multiple companies active in area – VERY exciting!
Checkpoint Inhibitors

Why so important?
- “Most exciting advance in human oncology” – Science 2013
- Cancer Ag Target Independent
- 30-40% durable response rates
- Combination = 90% ORR
- Generally tolerable side effects

Issues?
- Hard to predict responders in advance!
  - Highly mutagenic = ↑ neoAg’s = better responders
  - Very few biomarkers for response
    - e.g. ICOS+ CD4 T cells for Yervoy
- Expense of mAb’s – worse with combinations!
- Responses take time – not like chemo/TKI’s
Timeline & Infrastructure

- 2013 to date
- WoofWare/Antech/Antech Imaging Databases

Clinical Study Types?

- Sponsored studies
- Internal clinician/house officer/technician studies
- Academic Collaboration studies

> 50 completed studies in ~ 3.5 years

Numerous publications
VCA Clinical Studies

- **Academic Pursuits**
  - **Ross University & Newcastle Collaboration**
    - 2VERY large datasets shared
      - Special thanks to Dr. Dave Aucoin for datasets
  - **University of Missouri Collaboration**
    - Bioinformatics approach
      - 2 datasets handed off (> 12 billion data points)
  - **MidWestern University Collaboration**
    - 1) Pneumonia “one medicine” study
    - 2) Additional studies in preparation
  - **Royal Vet College & VetCompass** – data handed over.....
  - **UWisc & Trepanier LSA study** – just beginning
  - **UMinn & VCA Chicago area sites** – just beginning
VCA/Academic Collaborations

- University of Washington Canine Aging Study
  - VCA VSC of Seattle (#602)
    - VCA PI = Dr. Kline
    - Novel anti-aging compound safety study
      - Kaeberlein et al, Mamm Genome 2016
      - Urfer et al, GeroScience 2017
  - VERY open to academic collaborations in future
    - Philip.Bergman@vca.com
- Many foundations eager to have academia/private practice collaborative grants
Questions?