December 15, 2015

To:       WSAVA Board

From:     David Polzin and Larry Cowgill
          Co-Chairs, WSAVA Renal Standardization Project

Re:       2015 End-of-Year Project Progress Report - WSAVA Renal Standardization Study

Summary of Progress of the WSAVA Renal Standardization Project to Date

This report will include 3 Sections: 1) Achievements as linked to the specific aims of the project, 2) key successes of 2015, and 3) 2016-2017 Budget Proposal.

Aim 1: Establish two Diagnostic Renal Pathology Centers linked by a robust communication infrastructure that will provide participating pathologists and nephrologists with shared access to high-resolution digital micrographic images suitable for the diagnosis of glomerular diseases.

Current status: Pathology centers currently active include those at The Ohio State University and Utrecht University. As noted in last year’s report, online collaboration on light microscopy is not generally used since we no longer own the scanner. (2014 summary included in Appendix to this report).

There is ongoing collaboration between the active renal pathology service at The Ohio State University and clinical members of the WSAVA Clinical members. The clinical support involves recommendations for treatment based on the pathologic findings. We are actively working to expand and enhance this system with the goal of making the diagnostic pathology more useful to veterinary practitioners.

Aim 2: Perform comprehensive pathologic evaluations (including immunopathologic and electron microscopic, as well as light microscopic examinations) of renal biopsy specimens obtained from proteinuric dogs in which the clinical and clinicopathologic features of the disorder have been characterized. The results of an initial subset of these comprehensive pathologic and baseline clinical evaluations will be used to establish a semi-quantitative, lesion-based “prototype classification system” for canine glomerular disease. This “prototype classification system” will be subjected to additional prospective testing to include detailed clinicopathologic, therapeutic, and outcome criteria as Aim 3.
Current status: The prototype classification system has been completed and the associated manuscript has been published in Veterinary Pathology. A pdf of this manuscript is sent with this report (World Small Animal Veterinary Association Renal Pathology Initiative Classification of Glomerular Diseases in Dogs).

Aim 3: Correlate pathologic diagnoses with clinical and clinicopathologic data to identify particular patterns of findings that identify distinct canine glomerular disease entities that might be expected to have foreseeable outcomes or predictable responses to treatment. These correlations will be used to render a finalized (validated) morphologic and clinicopathologic classification scheme for canine glomerular disease that can be uniformly applied among veterinary pathologists and nephropathologists.
Current status: The prototype classification system is being applied to all complete cases enrolled in the WSAVA RSP as well as an additional 41 cases with full pathology evaluations and clinical data. These cases will have complete evaluation and scoring of their clinical characteristics (1) at the first sign of disease as well as (2) at the time of renal biopsy. The goal is to determine if any clinical characteristics help define or clarify the pathologic diagnosis. This part of the study will continue through 2016. A manuscript reporting the clinical-pathologic characteristics of canine glomerular diseases will be prepared (timeline goal: late 2016). The pathologic evaluations will be performed in the same manner as the cases reported in the submitted manuscript.

We are somewhat behind our target for scoring cases because the pace of the scoring has slowed for some members (i.e. some members were having difficulty in completing their scoring assignments due to other obligations – the “every-two-week” scoring sessions became overwhelming for some members). Because of this, we have taken a hiatus in scoring and are making the following modifications to our work plan: 1) we have invited a small number of new clinical specialists to join the group to supplement current members who have had difficulty in meeting scoring targets, 2) we will assign teams of 2 clinicians to score cases independently, and 3) the two-clinicians will meet after scoring the cases to resolve inconsistencies in the scoring. We believe these changes will allow us to complete the remaining clinical scorings by mid-2016. The pathologists will be scoring the same cases using the renal pathology scheme they have developed. We anticipate pathology scoring will require much of 2016. We anticipate a manuscript to be completed by late 2016 to early 2017.

Aim 4: Prospectively gather information about the clinical course and outcome of disease in dogs with well-defined glomerular disorders. At the beginning of this study, we anticipated that most or all dogs would receive standard care (i.e., be fed a “renal” diet and given an angiotensin converting enzyme inhibitor); however, intervention with immunosuppressive disease has become common. Nonetheless, all cases with well documented clinical follow-up will be evaluation in terms of the clinical course of their disease. This study will allow us to report the relationship between diagnosis and outcome and, possibly, relationships between therapy and outcome.

Current status: Because of the breadth of sources for the cases submitted, collection of complete follow-up (for any length of time) has proven to be difficult. Often multiple veterinary clinics were involved in management of the cases following biopsy and obtaining reliable follow-up data has been difficult. As a consequence, we intend to limit inclusion to cases submitted through committee members’ clinics where follow-up is available and reliable. This goal will be the final phase of the study. An anticipated date for completion of
this goal will be proposed once the manuscript reporting the clinical-pathologic characteristics of canine glomerular diseases has been completed.

**Plans for Atlas development:** We are committed to preparing an atlas of canine renal pathology. It is important to have all scientific publications accepted before completing the atlas; thus, the atlas will be the final publication to come from this group. We do not have a firm date for completion of this atlas at this time. Most likely this will be prepared for publication in 2016-2017.

**Section 2: Key Successes of 2014:**

1. Publication of the primary publication of the WSAVA RSP - World Small Animal Veterinary Association Renal Pathology Initiative: Classification of Glomerular Diseases in Dogs. Cianciolo, Rachel; Mohr, F; Aresu, Luca; Brown, Cathy; James, Clare; Jansen, Johan; Spangler William; van der Lugt, Jaco; Kass, Phil; Brovida, Claudio; Cowgill, Larry; Heiene, Reidun; Polzin, David; Syme, Harriet; Vaden, Shelly; van Dongen, Astrid; Lees, George. This article has been published in the journal Veterinary Pathology.

2. Additional progress has been made on clinical characteristics of glomerular disease in dogs. A preliminary plan for statistical analysis of the clinical data has been developed. The review process for scoring the clinical material has been worked out and approximately 50% of the clinic cases have been scored. This process will be completed in 2016.

3. We have negotiated with the IRIS Board to fund one more year of database access so that we can complete the study.

**Impact of the project:** Canine glomerular disease has been associated with short survival and poor quality of life. The WSAVA Renal Standardization Project and the advanced biopsy pathology this study has made available to practitioners has opened a new dialogue on what the therapeutic approach to this disease should be. One key outcome of our study is the recognition of immune mediated factors that are acting in at least 50% of dogs with glomerular disease. The “International Renal Interest Society Consensus Clinical Practice Guidelines for Glomerular Disease in Dogs” published as a supplement in the Journal of Veterinary Internal Medicine in November of 2013 grew out of the WSAVA RSP. The purpose of this Consensus was to take what we have learned from renal biopsies to practitioners by telling them how to manage canine patients with glomerular disease. By recognizing the role that immune mediated processes play in many dogs with glomerular disease, use of immunosuppressive therapy is being revisited in this disease. In contrast to the relatively short survival recognized
with this disease in the past, increased application of immunotherapy has been recognized to be associated with dramatically longer survival and even resolution of glomerular disease in many dogs.

Members of the WSAVA Renal Standardization Project are committed to the goals of seeking ways of making the findings of this study available and useful to practicing veterinarians. We believe that further studies are indicated to determine the most financially acceptable and effective ways of bringing these important studies to practitioners and pet owners. Further, we believe that therapeutic drug trials linked to renal pathology are needed to confirm the value and proper application of immune therapy for dogs with glomerular disease. Additionally, we firmly believe that the database developed for the WSAVA Renal Standardization Project is an outstanding resource for study management that should be perpetuated for use in renal projects in the future. We are committed to seeking ways to fund this tool. We look forward to engaging with the WSAVA and our sponsors to seek ways of furthering these goals.

**Section 3: 2015-2016 Budget Proposal – WSAVA RSP:**

Unofficial current study balance: $6,436.

The core budgetary priorities for completing the study are: 1) continue access to the study database for a minimum of 12 additional months (January –December, 2016), 2) continue access to the online communication systems (Go-To-Meeting subscriptions), and 3) provide resources for publication costs.

We have negotiated an agreement with IRIS to provide one-year of support for the Electronic Database Management System. This will provide sufficient funds to complete the study.

<table>
<thead>
<tr>
<th>Description</th>
<th>Year</th>
<th>Amount</th>
</tr>
</thead>
<tbody>
<tr>
<td>Electronic Database Management System (Vision – Prelude Dynamics)</td>
<td>(2016)</td>
<td>$12,500.00</td>
</tr>
<tr>
<td>Electronic Database Management System (3 months)</td>
<td>(2017)</td>
<td>$3,215.00</td>
</tr>
<tr>
<td>Communication subscriptions (Go-To-Meeting): (2/year @ $468/yr)</td>
<td>(2016)</td>
<td>$936.00</td>
</tr>
<tr>
<td>Publication costs (unknown at this time – including Atlas)</td>
<td>(2016-2017)</td>
<td>N/A</td>
</tr>
<tr>
<td>Subtotal (2016)</td>
<td></td>
<td>-$10,125.00</td>
</tr>
<tr>
<td>Database support from the IRIS Board</td>
<td></td>
<td>$12,500.00</td>
</tr>
<tr>
<td><strong>Total 2016/2017</strong></td>
<td></td>
<td>$2,375.00</td>
</tr>
</tbody>
</table>