Candidate's Statement

CAREER PROGRESS SINCE LAST PROMOTION

I was appointed as Assistant Professor at the University of Toronto, in the Department of Medicine, Division of Medical Oncology and Hematology in October 2006. Prior to this I was an Assistant Professor in the Department of Medicine at McMaster University for a period of nine months. Although my clinical and research interests were initially in both breast cancer and genitourinary cancers, over the course of my Assistant Professorship my research has become much more focused in the area of genitourinary cancers and in particular in bladder/urothelial cancer. This is the setting in which the majority of my clinical, research and educational activities occur. The overarching goal of my career is to improve clinical outcomes for patients with genitourinary cancers both in Canada but also in the world. To achieve this goal, I have taken a collaborative, multidisciplinary approach that encompasses the three key areas of Research, Education and Creative Professional Activities as detailed below:

-Designing and leading clinical trials of novel therapies at both the national and international level (Research)

-Multilevel teaching, research supervision and mentorship (Education)

-Developing and publishing national consensus guidelines on the management of genitourinary malignancies; advising government organizations on the approval or disapproval of new drugs used to treat genitourinary malignancies (CPA)

Using this approach I have been able to establish a national and international profile in genitourinary oncology. I am the Study Chair of an investigator-initiated, peer-reviewed, international (Canada and Australia) National Cancer Institute of Canada Clinical Trials Group (NCIC-CTG) led randomized trial in second-line bladder cancer. Over the last three years I have co-led the Standardization of Care Working Group as part of the medical advisory board for the Bladder Cancer Advocacy Network US (BCAN). BCAN is an American organization founded in 2005 and is the only national advocacy organization devoted to advancing bladder cancer research and supporting those impacted by the disease. At the national level I sit on both the Executive Council of the Canadian Association of Genitourinary Medical Oncologists (CAGMO), and on the Medical Advisory board of Bladder Cancer Canada.

RESEARCH STATEMENT

A. Designing and Leading Clinical Trials

Bladder cancer is the sixth most common cancer overall and will account for approximately 15,700 deaths each year in North America. For patients with metastatic disease, treatment options beyond first line are limited and life expectancy is a dismal 14-18 months, underscoring the need for novel treatment approaches. I have placed a significant amount of research efforts in developing novel therapeutic approaches for the treatment of advanced bladder cancer, and in efforts towards standardizing the care of this disease.

1. **Sridhar SS,** Winquist E, Eisen A, Hotte SJ, McWhirter E, Tannock IF, Mukherjee SD, Wang L, Blattler C, Wright JJ, Moore MJ. A phase II trial of sorafenib in first-line metastatic urothelial cancer: A study of the PMH Phase II Consortium. Invest New Drugs. 2011. 29(5):1045-9.

   One of the first trials that I conceived, developed, conducted, analyzed and published was a Phase II clinical trial of the antiangiogenic drug, sorafenib in advanced bladder cancer. This study was competitively funded by the National Cancer Institute (NCI) in the United States. This was a negative study, but added to the body of knowledge suggesting that angiogenesis inhibitors have limited efficacy in bladder cancer and further evaluation may not be warranted. I was first author on this publication which appeared in the journal Investigational New Drugs.

2. Ko YJ, Canil CM, Mukherjee SD, Winquist E, Elser C, Eisen A, Reaume MN, Zhang L, **Sridhar SS**. Nanoparticle albumin-bound paclitaxel for second-line treatment of metastatic urothelial carcinoma: a single group, multicentre, phase 2 study. Lancet Oncol. 2013 Jul 1;14(8):769-76.

   Since bladder cancer is a very chemosensitive disease, I then focused on evaluating the efficacy of nab-paclitaxel, a novel taxane chemotherapy in second line metastatic bladder cancer. This is a setting where there is currently no standard treatments anywhere in the world. As co-principal author and co-lead of this trial with oncologists from two other centers, the Odette (Sunnybrook) Cancer Center and the Ottawa Regional Cancer Center, we conducted this Ontario-wide study. I was the lead accruer to this study in which we showed that nab-paclitaxel had the highest tumor response rates (28%), longest progression-free survival (6 months) and longest overall survival (10.6 months) compared to any other single agent chemotherapy tested in this setting. I presented these results in an oral presentation at the American Society of Clinical Oncology Genitourinary Cancers Symposium in 2011. There was also a press release regarding these results. I was co-principal and last author on the 2013 publication appearing in the Lancet Oncology with an accompanying editorial.

3. A Multicenter Randomized Phase II Trial Comparing Nab-Paclitaxel to Paclitaxel in Patients with Advanced Urothelial Cancer Progressing on or after a Platinum Containing Regimen [ClinicalTrials.gov Identifier: NCT02033993] Study Chair: **Sridhar, SS**

   To confirm the results from the single arm Phase II study above I initiated, designed, developed, and am leading an International, Randomized Phase II trial through the National Cancer Institute of Canada (NCIC) Clinical Trials Group, which will compare nab-paclitaxel to paclitaxel as second-line therapy in metastatic bladder cancer. This trial with a target accrual of 200 patients is open across Canada, and will open in Australia and New Zealand in September 2014. If positive, nab-paclitaxel will likely be adopted worldwide and this would be a global practice changing trial.

Collaborative Efforts

4. In addition to the key trials noted above, I have demonstrated a collaborative approach by being the local site principal investigator, or site co-investigator on over 20 clinical trials. Although the majority of these trials have been in genitourinary cancers, some have also been in the area of breast cancer.

B. Evaluation of Practice Patterns and Knowledge Translation Efforts

Bladder cancer therapy should be evidence-based. Assessment of practice patterns, providing knowledge translational tools, promoting knowledge dissemination, and developing guidelines are different approaches to improve patient care through knowledge translation.

5. Hsu T, Black PC, Chi KN, Canil CM, Eigl BJ, Kulkarni G, North S, Wood L, Zlotta A, Lau A, Panzarella T, **Sridhar SS**. Treatment of Muscle Invasive Bladder Cancer in Canada – A Survey of Genitourinary Medical Oncologists and Urologists. Canadian Urol Assoc Journal. 2014 Jul 21. In Press. Senior Responsible Author.

   One of the key issues recognized in the field of bladder cancer is the low use of neoadjuvant chemotherapy (chemotherapy before definitive surgery) for patients with potentially curable muscle invasive bladder cancer despite the fact that there is Level 1 evidence supporting its use. To address this issue, I led a Canadian national survey in collaboration with my medical oncology and urology colleagues to better understand attitudes towards the use of neoadjuvant chemotherapy. Our study showed that medical oncologists were willing to offer neoadjuvant

chemotherapy, but were not being referred patients. However, when patients were managed in a multidisciplinary setting, they were more likely to receive neoadjuvant chemotherapy. These findings, presented at the ASCO GU cancers symposium show the importance of a multidisciplinary approach when managing patients with muscle invasive bladder cancer. Taking this approach may help to standardize practice and increase the uptake of neoadjuvant chemotherapy, ultimately translating into better outcomes.

6. Apolo AB, Kim JW, Bochner BH, Steinberg SM, Bajorin DF, Kevin Kelly W, Agarwal PK, Koppie TM, Kaag MG, Quinn DI, Vogelzang NJ, **Sridhar SS**. Examining the management of muscle-invasive bladder cancer by medical oncologists in the United States. Urol Oncol. 2014 Jul 1;32(5):637-44. Senior Responsible Author

   Based on my expertise, knowledge and experience in evaluating the use of neoadjuvant chemotherapy for bladder cancer in Canada, I was invited by the head of the Bladder Cancer Advocacy Network (BCAN) in the US to lead a survey directed at US medical oncologists. This work showed similar findings to the Canadian study and has now resulted in a publication in Urologic Oncology, further highlighting that low uptake of neoadjuvant chemotherapy in muscle invasive bladder cancer is a widespread problem that needs urgent attention.

7. Seah JA, Blais N, North S, Rahim Y, Ruether D, Black PC, Zlotta AR, Wood L, **Sridhar SS**. Neoadjuvant chemotherapy (NC) should be administered to fit patients with newly diagnosed, potentially resectable muscle-invasive urothelial cancer (MIUC) of the bladder – A 2013 CAGMO Consensus Statement and Call for a Streamlined Referral Process. CUAJ. 2013 Sep 4;7(9-10):312-318.

   Considering the findings of both the Canadian and American surveys, showing the importance of a multidisciplinary approach in managing bladder cancer patients, I led an initiative through the Canadian Association of GU Medical Oncologists to develop a national consensus statement . This statement incorporated a suggestion for a streamlined referral process to help overcome the challenges and barriers to the use of neoadjuvant chemotherapy identified in the surveys. This paper is the first of its kind to be published on the subject, and will be highlighted on the website UroToday.com. This website publishes articles relevant to the wider urology community. We will evaluate through surveys and pharmacy records whether the uptake of neoadjuvant chemotherapy has increased and the impact that this publication has had on clinical practice, approximately one year from the date of publication.

TEACHING STATEMENT

Improved patient care can only take place if we train future clinicians and clinician-researchers properly. To be an effective teacher either in the classroom or in the clinic, my priorities are to develop an enthusiastic, approachable, and student-centered approach.

A. Clinic Teaching: Training Future Clinicians

In all of my clinics, I have taken the initiative to spend the first or last 15 minutes of the clinic providing trainees with a clear and concise approach to the management of a patient with either a genitourinary malignancy or breast cancer. These mini-teaching sessions are a mix of didactic teaching and discussion where together we review presentation, diagnosis, and management including current areas of research and ongoing clinical trials. I present topics in a way that stimulates interest, and always try to put knowledge into context so that its relevance is readily apparent. By tailoring the teaching session to the knowledge and interest level of the trainee, I find that I can actively engage the trainee to maximize their learning. These mini-teaching

sessions have been extremely well received, and I have received positive feedback not only for these sessions but also for the overall clinic experience. I have also been asked by the head of my division, to share my teaching approach with new staff members in my tumor site group.

B. Research Supervision: Training Future Clinician-Researchers

From a research standpoint, I have supervised internal medicine residents, oncology residents, and oncology fellows both from Canada and from other countries, in several different research projects. Some of these projects developed as a direct result of the mini-teaching sessions discussed above, while others have been initiated by the trainees. My philosophy is that trainees should ask questions continuously and take ownership of their research projects. Two of the internal medicine residents I have supervised have won Merit Awards at the ASCO and ASCO GU international meetings, and the majority have presented their work at international meetings and published in peer reviewed journals (See section on Publications). Many of the residents and fellows I have supervised have gone on to develop independent careers in oncology, both in the academic and community settings, and we continue to collaborate.

C. Mentoring: Training Balanced Clinicians and Clinician-Researchers

All trainees benefit from mentorship, in order to be successful individuals, clinicians, researchers, and colleagues. I have developed an approachable, available style of mentorship for trainees at all levels to discuss career choices, and issues around balancing family and career. In some cases the mentoring relationship has continued even after the trainee has started working in other institutions. In addition to informal mentoring, I was invited to participate in a session entitled “Doc Talks” through the Wightman Berris Academy, University of Toronto. This is a series of interactive sessions where faculty meets with second year medical students to discuss career choices and challenges.

D. Teaching Summary

Overall I am a very good teacher, supervisor and mentor, and strive to continue my development in these areas. I have had very good to excellent teaching scores consistently, and have been cited as an excellent teacher within the Department of Medicine. In 2011, I was awarded a Wightman Berris Academy, University of Toronto Teaching award, in the Postgraduate Category. I was also recognized as one of the top 10 teachers in the Division of Medical Oncology and Hematology according to teaching effectiveness scores from 2013.

CREATIVE PROFESSIONAL ACTIVITY STATEMENT AND LONG TERM VISION

I am applying for promotion to Associate Professor on the basis of Research, and not CPA. The purpose of this CPA statement is solely to support my application, and show my contributions to the development of my professional practice. It is also presented as a means of explaining my long-term vision of my future academic contribution on the national and international stage. Two main initiatives are detailed below.

A. Increase the Uptake of Neoadjuvant Chemotherapy in Bladder Cancer in Canada

In the field of genitourinary cancers (prostate, kidney, bladder), bladder cancer has significantly lagged behind other cancers in terms of progress. This is partly due to a lack of new treatments, but also because of the low uptake of neoadjuvant (before surgery) chemotherapy for patients with muscle invasive bladder cancer. By improving the uptake of neoadjuvant chemotherapy (for which there is Level 1 evidence), outcomes in this disease and overall survival can be improved.

Aim 1: To understand why neoadjuvant chemotherapy is underutilized in Canada I led a national survey of medical oncologists and a separate survey of urologists to further explore this issue. I supervised an oncology resident in this initiative and engaged medical oncologists and urologists across Canada. Together, we demonstrated that although medical oncologists were willing to offer NC, they were not being referred cases. However, when patients were managed in a multidisciplinary setting, rates of neoadjuvant chemotherapy use increased. These findings were presented at the American Society of Clinical Oncology international meeting, and have been submitted for publication.

Aim 2: Based on my expertise and knowledge in this area, I was then invited to lead a similar survey of medical oncologists across the US. Again we showed low uptake of neoadjuvant chemotherapy, variable practice patterns and a lack of standardization. These results were also presented at the American Society of Oncology meeting, and the paper has now been published in the journal Urologic Oncology.

Aim 3: The next step in this project was to try and standardize practice and increase the uptake of neoadjuvant chemotherapy by developing a national consensus guideline. I led this guideline initiative through the Canadian Association of GU Medical Oncologists. It was the first guideline of its kind, and was written by one of my oncology fellows and published this year in the Canadian Urological Association Journal. Its impact on practice and uptake of neoadjuvant chemotherapy will be evaluated by using surveys and evaluating pharmacy databases for use of neoadjuvant chemotherapy approximately one year from publication. This will allow us to understand if there are any ongoing challenges to the use of neoadjuvant chemotherapy and attempt to address them. This publication has was also profiled in the publication Uro-Today that is a broadly directed publication to everyone in the urologic oncology field.

Future Vision: Over the next five years, I would envision that as a result of our efforts a greater proportion of patients would receive neoadjuvant chemotherapy. This will not only improve individual patient outcomes but may also facilitate new drug development, because the neoadjuvant setting is particularly conducive to evaluating new drugs. This is largely because tumor tissue is available before and after treatment to perform correlative studies to better understand molecular features predicting response or resistance to new treatments. Designing a neoadjuvant clinical trial with a novel treatment, incorporating both correlative studies and potentially novel imaging approaches would be one of my next initiatives. This platform and approach could be used to evaluate many new agents in the future.

B. Regulatory Efforts: Ensuring Appropriate Use and Access to Important Systemic Therapies across Canada.

I am a member of the following committees: Oncology Subcommittee of the University Health Network Pharmacy and Therapeutics Committee, Ontario Steering Committee for Cancer Drug Programs, and the Pan Canadian Oncology Drug Review Committee. Recent advances in the field of oncology have led to the development of several new molecularly targeted anticancer agents. In order for these agents to be made available to our patients, they first need to be carefully evaluated for efficacy, toxicity, and cost effectiveness.

Medical oncologists must be involved in these drug use review processes. In this regard I have taken an increasingly broader role in this area from my initial involvement on our hospital

subcommittee, to a provincial committee, and finally to a national committee. I am also a reviewer for the Case-by-Case reviewer program that evaluates requests for unfunded drugs.

Over the course of the next 5-7 years, I would be interested in taking on a long-term goal of advocacy in the regulatory sector – ensuring that governments and government agencies (e.g. Cancer Care Ontario) properly evaluate and fund cost-effective therapies, not only in the genitourinary setting, but across all cancer sites. I would see myself leading some of these committees and guiding policy-makers and regulatory officials to make appropriate funding decisions.

SUMMARY

Since my appointment, I feel I have been able to build a national and growing international reputation in the field of genitourinary oncology, by taking a collaborative multidisciplinary approach, and becoming actively involved in leading and participating in clinical trials; establishing consensus guidelines; and mentoring students, residents and fellows. Over the next 5-7 years, my long-term vision is to improve the care of all cancer patients but particularly genitourinary cancer patients by: (i) continuing to test novel therapies and approaches to care; (ii) perform assessment of knowledge translation of the best practices and evidence-based medicine in genitourinary oncology across North America and beyond; and (iii) ensure proper regulatory oversight that aligns with the evidence-based practice providing access to effective new drugs in oncology. The ultimate goal of my research, teaching, and creative professional activities is to improve clinical outcomes (increased survival, quality of life, decrease symptoms, treatment toxicities) for patients with genitourinary cancers in the loco-regional, provincial, national, and international setting.