Introduction:
Sarcomas are a rare malignant tumour with less than 15,000 new cases diagnosed each year in the United States. Though rare, sarcomas are highly debilitating malignancies as they are often associated with significant morbidity and mortality. Sarcomas are biologically very heterogeneous as evidenced by the fact that these tumours arise from a plethora of different tissues and cell types. They are classically defined by their tissue of origin and are additionally stratified by their histopathology or patient's age at diagnosis.1 While these classifications have proven useful, modern pathobiological and clinical techniques have the ability to further stratify sarcomas based on their genetic profile.2 Cytogenetic and karyotype analyses have revealed two divergent genetic profiles in sarcomas. The first and most simple genetic profile is the observation of translocation events in sarcomas with an otherwise normal diploid karyotype. On the other hand, most sarcomas display a more complex genetic phenotype, suggesting genomic instability plays an important role in many sarcomas.

Tumour suppressor and oncogenic pathways involved in sarcomagenesis:
Tumour protein 53 (TP53), tumour suppressor pathway is one of the most well characterized pathways in cancers.3 TP53 gene encodes a transcription factor required for the activation of numerous DNA damage-dependent checkpoint response and apoptotic genes, and thus its activities are often ablated in many cancers. In addition to loss of TP53 functions via inherited germline mutations, TP53 pathway is commonly deregulated in many sarcomas. In addition to loss of tumour suppressor pathways, sarcomagenesis is also driven by aberrant oncogenic signal. The RAS signal pathway in particular is thought to be altered during sarcoma development.13 Deregulation of the RAS pathway aberrantly stimulates cellular proliferation, which in and of itself impinges on TP53 and RB pathways, collectively demonstrating the significant cross-talk between these three separate but overlapping pathways.

Oncogenic signalling and Leimyosarcomas:
In addition to loss of tumour suppressor pathways, sarcomagenesis is also driven by aberrant oncogenic signal. The RAS signal pathway in particular is thought to be altered during sarcoma development.13 Deregulation of the RAS pathway aberrantly stimulates cellular proliferation, which in and of itself impinges on TP53 and RB pathways, collectively demonstrating the significant cross-talk between these three separate but overlapping pathways. Given the numerous signal pathways potentially disrupted in sarcomas, there has been a critical need to interrogate how each of these genes and divergent pathways impact sarcomagenesis in a prospective manner. Since these experiments are nearly impossible in human patients, scientists and clinicians are now using mice genetically tailored for such studies. Below, we will highlight several well characterized genetically engineered mouse models harbouring common genetic alterations observed in sarcoma pathobiology.

Given the extreme heterogeneity of sarcomas with regards to tissue of origin, it is obvious that alterations to numerous genes, pathways, and signal complexes play an important role in the pathobiology of sarcomas. While this review does not cover all genetic alterations responsible for sarcoma de-
development, there are numerous additional genes that impact this disease. For example, alterations in expression of tumour suppressor genes, such as NEOUROFIBROMASIS (NF1 and NF2), likewise impact the etiology of some sarcomas. Mouse models that carry genonomic deletions and/or tissue-specific Cre-mediated deletion of NF1 result in neurofibromas. These NF1-dependent phenotypes are further exacerbated when NF1 is concomitantly deleted with other tumour suppressors (TP53 and P14ARF) resulting in more aggressive phenotypes as evidenced by malignant peripheral nerve sheath tumour formation. To further illustrate that loss of a single gene impacts sarcoma formation, mice harbouring an Psmb9 deletion resulted in spontaneous uterine leiomyosarcomas. This provides evidence of its role as a tumour suppressor and a potential biomarker in human uterine leiomyosarcoma. In addition to loss of function alterations, overexpression of teratocarcinoma-derived growth factor 1, also known as Cripto, results in leiomyosarcomas by deregulation of the WNT pathway.

Conclusion:
The vast differences in the cellular origins of sarcomas, the lack of availability of tumour specimens, and the heterogeneity inherent within individual tumours has impeded our ability to fully understand the biology of sarcomas. However, given the availability of numerous genetic knock-outs, knock-ins, and conditional alleles coupled with the bevy of tissue-specific Cre-recombinase expressing mouse lines, we now have the ability to systematically and prospectively interrogate how individual genes and mutations impact sarcomagenesis. Going forward, tumor analysis from multiple murine derived tumour types can be compared and contrasted in order to identify critical changes in specific sarcomas. These mouse models have clearly demonstrated that while there are driver tumour types can be compared and contrasted in order to identify critical changes in specific sarcomas. These mouse models have clearly demonstrated that while there are driver tumour formation, mice harbouring an Psmb9 deletion resulted in spontaneous uterine leiomyosarcomas. This provides evidence of its role as a tumour suppressor and a potential biomarker in human uterine leiomyosarcoma.

References: