PROJECT TITLE

Circulating multi-molecule signatures for early detection of osteosarcoma recurrence

PRINCIPAL INVESTIGATOR
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SCIENTIFIC SUMMARY

Osteosarcoma (OS) is the most common primary malignancy of bone, with a peak incidence in adolescents and young adults that results in the loss of many years of life and negative long-term sequelae in survivors. Treatment involves aggressive chemotherapy and surgery; however, 30% of patients will relapse with metastasis, and 80% of patients with metastases will die within 5 years. This survival rate has not substantively changed in over 30 years. There are no clinically useful biomarkers that can accurately predict survival at diagnosis and no way to detect metastases until they are already apparent by imaging. Conventional research methods to improve OS prognostication have proved ineffective. The approach our team is taking is radically different. Instead of relying on cell lines or mouse models, we have discovered sets of circulating microRNAs and extracellular vesicle (EV) proteins in pet dogs with naturally occurring OS that correlate with clinical outcome. Canine OS is widely regarded as highly analogous to human OS but is more common and much more deadly with a median survival time of only 1 year after surgery and chemotherapy. Unlike mouse models, canine OS arises spontaneously, is treated similar to the human disease, and metastasizes spontaneously to lungs. We aim to leverage our success in measuring clinically relevant circulating biomarkers in canine OS and apply this approach to human OS. Our Specific Aims are:

1. Evaluate plasma biomarkers for prognostic significance in human osteosarcoma patients retrospectively.
2. Develop a "made in Ontario" lab-on-a-chip system to measure key molecules in human osteosarcoma patient plasma in a highly reproducible assay.
3. Determine if these molecules predict early osteosarcoma metastasis in serially collected plasma samples from post-treatment dogs.

MicroRNAs and EV proteins associated with disease free interval (DFI) in dogs provide proof of principle that this approach can succeed in human OS. Through our collaboration with the Children's Oncology Group, we have access to human plasma samples linked to clinical outcome. Plasma EV proteins and microRNA will be isolated and interrogated with proteomic and whole miRnome array techniques in pooled samples from patients in each quintile of DFI.

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This will provide a set of ~10 EV proteins and microRNAs that will be incorporated into lab-on-a-chip systems validated and manufactured in Aim 2. Individual patient plasma samples will then be run on these chips and correlations to DFI will be assessed for each potential biomarker and combinations. In Aim 3, plasma samples serially collected from dogs after OS treatment will likewise be run on these chips to inform and guide the design of future human OS studies aiming to predict relapse earlier than expensive and inconvenient serial CT imaging.

Our research aims to provide an easy-to-implement tool for accurate prognostication and early detection of progression, and thus potential early intervention, with a simple blood test. In the long term, accurate prognostication at diagnosis could lead to a new paradigm of treatment for osteosarcoma patients with stratification of treatment intensity based on risk rather than "one size fits all" aggressive chemotherapy.