The Terry Fox New Frontiers Program Project Grant in Targeting the Adaptive Molecular Landscape in Castrate-Resistant Prostate Cancer

Progression of prostate cancer to castration resistant prostate cancer (CRPC) following treatment with androgen receptor (AR) pathway inhibitors is the main obstacle to controlling the disease and the central focus of the Vancouver Prostate Centre's *Terry Fox New Frontiers Program Project Grant in Targeting the Adaptive Molecular Landscape in Castrate-Resistant Prostate Cancer*. Our prior studies under the *TF NF Program Project on Prostate Cancer Progression* created first-in-field tumour models, defined key mechanisms driving CRPC, and developed novel drugs and biomarkers. Our current program builds on this momentum, evolving our central hypothesis that selective pressures of AR pathway inhibitors induce adaptive survival pathways that support clonal evolution by reprogramming pro-survival transcriptional, signalling and metabolic networks to reactivate AR signaling or induce stem-like and developmental pathways and collectively drive treatment resistance.

Our overall objective is to elucidate genomic and molecular mechanisms driving CRPC, and use this knowledge to develop new therapies targeting biologically relevant pathways and prolong disease control. We work towards establishing a mechanism-based framework to underpin discovery of novel genes and pathways supporting resistance, in parallel with development of biomarkers and new combinatorial treatments for AR- and non-AR driven CRPC. Our current *TF NF program* comprises 23 multidisciplinary clinical and lab scientists who have clearly demonstrated the synergy and benefits of working as a team towards these common objectives. Our 6 highly integrated projects span the research spectrum from discovery to treatment science.

Project 1 investigates how stress adaptor proteins (YB-1, CLU, Hsp27) activated by AR pathway inhibitors help re-program the translatome and metabolome to enable tumor cell adaptation, survival, and treatment resistance.

Projects 2 and 3 investigate genomic (ERG) alterations and developmental signaling (GLI) pathways that facilitate AR reactivation after treatment with AR pathway inhibitors.

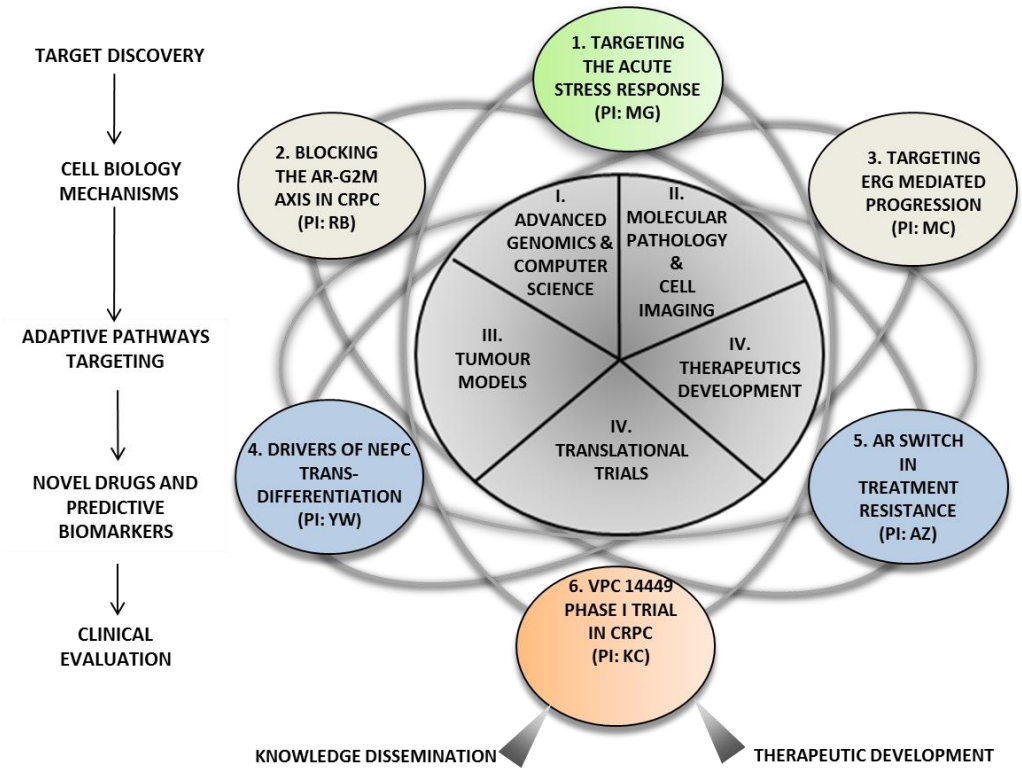
Projects 4 and 5 investigate mechanisms enabling emergence of non-AR-driven CRPC and neuroendocrine prostate cancer.

Project 6 will lead a first-in-man clinical trial evaluating a novel AR DNA-binding domain inhibitor discovered at the Vancouver Prostate Centre.

All projects are supported by 5 cores (*Advanced Genomics and Computer Science*, *Pathology & Molecular Imaging, Tumour Models*, *Therapeutics Development*, *Translational Trials),* all uniquely managed as a collective within a single organization focused on understanding and controlling treatment resistance.

In summary, our *TF NF PPG* is an ideal example of how team science helps define the adaptive molecular landscape in CRPC, supports discovery of underlying mechanisms of resistance, leads to development of new therapies, and translates lab research into clinical practice.

TF NF PPG in Targeting the Adaptive Molecular Landscape in CRPC



Recent key publications

Optimal sequencing of enzalutamide and abiraterone acetate plus prednisone in metastatic castration-resistant prostate cancer: a multicentre, randomised, open-label, phase 2, crossover trial**.** Khalaf DJ, Annala M, Taavitsainen S, Finch DL, Oja C, Vergidis J, Zulfiqar M, Sunderland K, Azad AA, Kollmannsberger CK, Eigl BJ, Noonan K, Wadhwa D, Attwell A, Keith B, Ellard SL, Le L, Gleave ME, Wyatt AW, Chi KN. ***Lancet Oncol.*** 2019 Dec;20(12):1730-1739. Epub 2019 Nov 11. PMID: 31727538

Ivermectin inhibits HSP27 and potentiates efficacy of oncogene targeting in tumor models. Nappi L, Aguda AH, Nakouzi NA, Lelj-Garolla B, Beraldi E, Lallous N, Thi M, Moore S, Fazli L, Battsogt D, Stoffeliene S, Ban F, Nguyen NT, Saxena N, Dueva E, Zhang F, Yamazaki T, Zoubeidi A, Cherkasov A, Brayer GD, Gleave M. ***J Clin Invest.*** 2019 Dec 17. [Epub ahead of print] PMID: 31845908

Inhibition of GLI2 with antisense-oligonucleotides: A potential therapy for the treatment of bladder cancer**.** Raven PA, Lysakowski S, Tan Z, D'Costa NM, Moskalev I, Frees S, Struss W, Matsui Y, Narita S, Buttyan R, Chavez-Munoz C, So AI. ***J Cell Physiol.*** 2019 Nov;234(11):20634-20647. Epub 2019 Apr 22. PMID: 31012113

RNA Splicing of the BHC80 Gene Contributes to Neuroendocrine Prostate Cancer Progression. Li Y, Xie N, Chen R, Lee AR, Lovnicki J, Morrison EA, Fazli L, Zhang Q, Musselman CA, Wang Y, Huang J, Gleave ME, Collins C, Dong X. ***Eur Urol.*** 2019 Aug;76(2):157-166. Epub 2019 Mar 23. PMID: 30910347

Stress-induced tunneling nanotubes support treatment adaptation in prostate cancer. Kretschmer A, Zhang F, Somasekharan SP, Tse C, Leachman L, Gleave A, Li B, Asmaro I, Huang T, Kotula L, Sorensen PH, Gleave ME. ***Sci Rep.*** 2019 May 24;9(1):7826. PMID: 31127190

Circulating Tumor DNA Abundance and Potential Utility in De Novo Metastatic Prostate Cancer. Vandekerkhove G, Struss WJ, Annala M, Kallio HML, Khalaf D, Warner EW, Herberts C, Ritch E, Beja K, Loktionova Y, Hurtado-Coll A, Fazli L, So A, Black PC, Nykter M, Tammela T, Chi KN, Gleave ME, Wyatt AW. ***Eur Urol.*** 2019 Apr;75(4):667-675. doi: 10.1016/j.eururo.2018.12.042. Epub 2019 Jan 10. PubMed PMID: 30638634

BAP1 haploinsufficiency predicts a distinct immunogenic class of malignant peritoneal mesothelioma. Shrestha R, Nabavi N, Lin YY, Mo F, Anderson S, Volik S, Adomat HH, Lin D, Xue H, Dong X, Shukin R, Bell RH, McConeghy B, Haegert A, Brahmbhatt S, Li E, Oo HZ, Hurtado-Coll A, Fazli L, Zhou J, McConnell Y, McCart A, Lowy A, Morin GB, Chen T, Daugaard M, Sahinalp SC, Hach F, Le Bihan S, Gleave ME, Wang Y, Churg A, Collins CC. ***Genome Med.*** 2019 Feb 18;11(1):8. PMID: 30777124

Targeting Semaphorin 3C in Prostate Cancer with Small Molecules. Lee CCW, Munuganti RSN, Peacock JW, Dalal K, Jiao IZF, Shepherd A, Liu L, Tam KJ, Sedgwick CG, Bhasin S, Lee KCK, Gooding L, Vanderkruk B, Tombe T, Gong Y, Gleave ME, Cherkasov A, Ong CJ***. J Endocr Soc.*** 2018 Oct 11;2(12):1381-1394. eCollection 2018 Dec 1. PMID: 30534631

Patient-derived Hormone-naive Prostate Cancer Xenograft Models Reveal Growth Factor Receptor Bound Protein 10 as an Androgen Receptor-repressed Gene Driving the Development of Castration-resistant Prostate Cancer. Hao J, Ci X, Xue H, Wu R, Dong X, Choi SYC, He H, Wang Y, Zhang F, Qu S, Zhang F, Haegert AM, Gout PW, Zoubeidi A, Collins C, Gleave ME, Lin D, Wang Y. ***Eur Urol.*** 2018 Jun;73(6):949-960. Epub 2018 Mar 12. PubMed PMID: 29544736

Heterochromatin protein 1alpha mediates development and aggressiveness of neuroendocrine prostate cancer. Ci X, Hao J, Dong X, Choi SYC, Xue H, Wu R, Qu S, Gout PW, Zhang F, Haegert A, Fazil L, Crea F, Ong CJ, Zoubeidi A, He HH, Gleave ME, Collins CC, Lin D, Wang Y. ***Can. Research***. 2018 May 15;78(10):2691-2704. PMID: 29487201

Stromal Gene Expression is Predictive for Metastatic Primary Prostate Cancer. Mo F, Lin D, Takhar M, Ramnarine VR, Dong X, Bell RH, Volik SV, Wang K, Xue H, Wang Y, Haegert A, Anderson S, Brahmbhatt S, Erho N, Wang X, Gout PW, Morris J, Karnes RJ, Den RB, Klein EA, Schaeffer EM, Ross A, Ren S, Sahinalp SC, Li Y, Xu X, Wang J, Wang J, Gleave ME, Davicioni E, Sun Y, Wang Y, Collins CC. ***Eur Urol.*** 2018 Apr;73(4):524-532. Epub 2017 Mar 19. PubMed PMID: 28330676