MUHAMMED MURTAZA, M.B.B.S., PH.D.

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EDUCATION

2014 — Ph.D. (Doctor of Philosophy), Medical Science
Cancer Research UK Cambridge Institute,
Trinity College, University of Cambridge, United Kingdom

2010 — M.B.B.S. (Bachelor of Medicine and Bachelor of Surgery)
Aga Khan University Medical College, Karachi, Pakistan
*equivalent to Doctor of Medicine (MD) in the United States

PROFESSIONAL APPOINTMENTS

2015-present — Assistant Professor, Cancer and Cell Biology Division
Co-Director, Center for Noninvasive Diagnostics
Translational Genomics Research Institute, Phoenix, AZ, USA

2016-present — Assistant Professor of Medicine, Mayo Clinic, Scottsdale, AZ, USA

2014-2015 — Research Assistant Professor, Cancer and Cell Biology Division
Translational Genomics Research Institute, Phoenix, AZ, USA

2011-2014 — Graduate Researcher, Cancer Research UK Cambridge Institute, Cambridge, United Kingdom

AWARDS AND HONORS

2016 — Phil A. Sharp Innovation in Collaboration Award, Stand Up To Cancer

2015 — V Scholar Award, The V Foundation for Cancer Research

2014 — Bisgrove Scholar Award, Science Foundation Arizona

2011 — Graduate Studentship, Cancer Research UK

PUBLICATIONS

Latest pre-prints (In Press/In Review/In Revision)

1. Markus H[+], Zhao J[+], Contente-Cuomo T[+], Raupach E, Odenheimer-Bergman A[+], Connor S[+], McDonald BR[+], Hutchins E, McGilvery M, de la Maza MC, Van Keuren-Jensen K, Pirrotte P, Goel A, Becerra C, Von Hoff DD, Celinski SA, Hingorani P, **Murtaza M**[*]. Sub-nucleosomal organization in urine cell-free DNA. (In Review, pre-print online on bioRxiv doi: 10.1101/696633) [+]lab member, [*]corresponding author

Published manuscripts

2. Lorch G, Sivaprakasam K, Zismann V, Perdigones N, Contente-Cuomo T[+], Nazareno A[+], Facista S, Wong S, Drenner K, Liang WS, Amman JM, Sinicropi-Yao SL, Koenig MJ, Perle KL, Whitsett TG, **Murtaza M**, Trent J, Carbone DP, Hendricks WPD. Identification of recurrent activating HER2 mutations in primary canine pulmonary adenocarcinoma. Clinical Cancer Research (2019 Aug, doi: 10.1158/1078-0432.CCR-19-1145) [+]lab member

3. McDonald BR[+], Contente-Cuomo T[+], Sammut SJ, Odenheimer-Bergman A[+], Ernst B, Perdigones N[+], Chin SF, Farooq M[+], Mejia R, Cronin PA, Anderson KS, Kosiorek HE, Northfelt DW, McCullough AE, Patel BK, Weitzel JN, Slavin TP, Caldas C, Pockaj BA[*], **Murtaza M**[*]. Personalized circulating tumor DNA analysis to detect residual disease after neoadjuvant therapy in breast cancer. Science Translational Medicine (2019 Aug, PMID: 31391323) [+]lab member, [*]co-corresponding author

Highlighted in Nature Reviews Clinical Oncology in August 2019: Personalized MRD assays and therapy? (doi: 10.1038/s41571-019-0269-2)

4. Farooq M[+], **Murtaza M**[*]. Circulating tumor DNA analysis and opportunities for personalized cancer medicine. Companion and Complementary Diagnostics: From Biomarker Discovery to Clinical Implementation (Book Chapter, 2019 May, doi: 10.1016/B978-0-12-813539-6.00011-0) [+]lab member, [*]corresponding author

5. De Mattos-Arruda L, Sammut SJ, Ross E, Bashford-Rogers R, Greenstein E, Markus H[+], Morganella S, Teng Y, Maruvka Y, Pereira B, Rueda O, Chin SF, Ali R, Cope W, Tiezzi D, Contente-Cuomo T[+], Mayor R, Arias A, Reshef D, Martinez E, Peg V, Ramon y Cajal S, Cortes J, Vassiliou G, Getz G, Nik-Zainal S, **Murtaza M**, Friedman N, Markowetz F, Seoane J, Caldas C. The genomic and immune landscapes of lethal metastatic breast cancer. Cell Reports (2019 May, PMID: 31141692) [+]lab member

6. Hurth C, Contente-Cuomo T[+], **Murtaza M**, Zenhausern F. Influence of a single nucleotide polymorphism and DNA hybridization on the drying patterns of micro droplets. Journal of Nanomedicine (2018 Jun) [+]lab member

7. Tsui DWY[*], **Murtaza M**[*], Wong ASC, Rueda OM, Smith CG, Chandrananda D, Soo RA, Lim HL, Goh BC, Caldas C, Forshew T, Gale D, Liu W, Morris J, Marass F, Eisen T, Chin TM, Rosenfeld N. Dynamics of multiple resistance mechanisms in plasma DNA during EGFR-

targeted therapies in non-small cell lung cancer. EMBO Molecular Medicine (2018 Jun, PMID: 29848757) *equal authorship

8. Markus H+, Contente-Cuomo T+, Farooq M+, Liang WS, Board MJ, Sivakumar S, Gollins S, Tran NL, Dhruv HD, Berens ME, Bryce A, Sekulic A, Ribas A, Trent JM, LoRusso PM, **Murtaza M***. Evaluation of pre-analytical factors affecting plasma DNA analysis. Scientific Reports (2018 May, PMID: 29743667) +lab member, *corresponding author

9. Perdigones N+, **Murtaza M***. Capturing tumor heterogeneity and clonal evolution in solid cancers using circulating tumor DNA analysis. Pharmacology & Therapeutics (Review, 2017 Feb, PMID: 28167216) +lab member, *corresponding author

10. Hendricks WPD, Sekulic A, Bryce AH, **Murtaza M**, Ramos P, Trent JM. Cancer Genomics and Evolution. Holland-Frei Cancer Medicine (Book Chapter, 2017 Feb, ISBN: 9781118934692)

11. Tsui DWY, **Murtaza M**. Applications of Circulating DNA analysis in personalized medicine. Cancer Genetics and Genomics for Personalized Medicine (Book Chapter, 2016 Nov, ISBN: 9789814669870)

12. **Murtaza M***, Caldas C*. Nucleosome mapping in plasma DNA predicts cancer gene expression. Nature Genetics (News and Views, 2016 Sep, PMID: 27681289) *co-corresponding authors

13. **Murtaza M***, Dawson SJ*, Provenzano E, Grant J, Chin SF, Tsui DWY, Marass F, Gale D, Ali HR, Shah P+, Contente-Cuomo T+, Farahani H, Shumansky K, Kingsbury Z, Humphray S, Bentley D, Shah SP, Wallis M, Rosenfeld N, Caldas C. Multifocal clonal evolution characterized using circulating tumor DNA in a case of metastatic breast cancer. Nature Communications (2015 Nov, PMID: 26530965) +lab member, *equal authorship

Highlighted in JAMA in January 2016: Circulating Tumor DNA Helps Track Cancer (doi: 10.1001/jama.2015.17482)

14. Schwarz RF, Ng CK, Cooke SL, Newman S, Temple J, Piskorz AM, Gale D, Sayal K, **Murtaza M**, Baldwin PJ, Rosenfeld N, Earl HM, Sala E, Jimenez-Linan M, Parkinson CA, Markowetz F, Brenton JD. Spatial and temporal heterogeneity in high-grade serous ovarian cancer: a phylogenetic analysis. PLoS Medicine (2015 Feb, PMID: 25710373)

15. Beaufort CM, Helmijr JCA, Piskorz AM, Hoogstraat M, Ruigrok-Ritstier K, Besselink N, **Murtaza M**, van IJcken WFJ, Heine AAJ, Smid M, Koudijs MJ, Brenton JD, Berns EMJJ, Helleman J. Ovarian Cancer Cell line Panel (OCCP): clinical importance of in vitro morphological subtypes. PLoS ONE (2014 Sep, PMID: 25230021)

16. Weaver JMJ, Ross-Innes CS, Shannon N, Lynch AG, Barbera M, **Murtaza M**, Ong CA, Lao-Sirieix P, Dunning MJ, Smith L, Smith ML, Anderson CL, Carvalho B, O'Donovan M, Underwood TJ, May AP, Grehan N, Hardwick R, Davies J, Oloumi A, Aparicio S, Caldas C, Eldridge MD, Edwards PA, Rosenfeld N, Tavare S, Fitzgerald R and the OCCAM Consortium.

Ordering of mutations in preinvasive disease stages of esophageal carcinogenesis. Nature Genetics (2014 Aug, PMID: 24952744)

17. Gossage L, **Murtaza M**, Slatter AF, Lichtenstein CP, Warren A, Haynes B, Marass F, Roberts I, Shanahan SJ, Claas A, Dunham A, May AP, Rosenfeld N, Forshew T, Eisen T. Clinical and pathological impact of VHL, PBRM1, BAP1, SETD2, KDM6A, and JARID1c in clear cell renal cell carcinoma. Genes, Chromosomes and Cancer (2014 Jan, PMID: 24166983)

18. **Murtaza M**[*], Dawson SJ[*], Tsui DWY[*], Gale D, Forshew T, Piskorz AM, Parkinson C, Chin SF, Kingsbury Z, Wong ASC, Marass F, Humphray S, Hadfield J, Bentley D, Chin TM, Brenton JD, Caldas C, Rosenfeld N. Noninvasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. Nature (2013 May, PMID: 23563269) [*]equal authorship

Featured review in Nature Medicine in June 2013: Tracking tumor resistance using 'liquid biopsies' (PMID: 23744147)

19. Dawson SJ, Tsui D, **Murtaza M**, Biggs H, Rueda OM, Chin SF, Dunning MJ, Gale D, Forshew T, Mahler-Araujo B, Rajan S, Humphray S, Becq J, Halsall D, Wallis M, Bentley D, Caldas C, Rosenfeld N. Circulating Tumor DNA to Monitor Metastatic Breast Cancer. New England Journal of Medicine (2013 Mar, PMID: 23484797)

20. Forshew T[*], **Murtaza M**[*], Parkinson C[*], Gale D[*], Tsui DWY[*], Kaper F, Dawson SJ, Piskorz AM, Jimenez-Linan M, Bentley D, Hadfield J, May AP, Caldas C, Brenton JD, Rosenfeld N. Noninvasive identification and monitoring of cancer mutations by targeted deep sequencing of plasma DNA. Science Translational Medicine (2012 May, PMID: 22649089) [*]equal authorship

21. Tahir MZ, Sobani ZA, **Murtaza M**, Enam SA. Long-tunneled versus short-tunneled external ventricular drainage: prospective experience from a developing country. Asian Journal of Neurosurgery (2016 Apr, PMID: 27057216)

22. Kamal AK, Rasheed A, Mehmood K, **Murtaza M**, Zaidi M, Khan M, Shah N, Samuel M, Ahmed B, Raza E, Ahmed N, Ara J, Ahsan T, Munir SM, Ali S, Maki KU, Ahmed MM, Memon AR, Saleheen D. Frequency and determinants of intracranial atherosclerotic stroke in urban Pakistan. Journal of Stroke and Cerebrovascular Diseases (2014 Sep, PMID: 25088165)

23. Khan M, Rasheed A, Hashmi S, Zaidi M, **Murtaza M**, Akhtar S, Bansari L, Shah N, Samuel M, Raza S, Khan UR, Ahmed B, Ahmed B, Ahmed N, Ara J, Ahsan T, Munir SM, Ali S, Mehmood K, Makki KU, Ahmed MM, Sheikh N, Memon AR, Frossard PM, Kamal AK. Stroke radiology and distinguishing characteristics of intracranial atherosclerotic disease in native South Asian Pakistanis. International Journal of Stroke (2013 Oct, PMID: 23013556)

24. Itrat A, Ahmed B, Khan M, **Murtaza M**, Thaver D, Khowaja Z, Ali S, Bawa Z, Rahat M, Kamal AK. Risk factor profiles of South Asians with cerebrovascular disease. International Journal of Stroke (2011 Aug, PMID: 21745346)

25. Coronary Artery Disease (C4D) Genetics Consortium. A genome-wide association study in Europeans and South Asians reveals five novel loci for coronary artery disease. Nature Genetics (2011 Mar, PMID: 21378988)

26. Lanktree BL, Guo Y, **Murtaza M**, Glessner JT, Bailey SD, Onland-Moret NC, Lettre G, Ongen H, Rajagopalan R, Johnson T, Shen H, Nelson CP, Klopp N, Baumert J, Padmanabhan S, Pankratz N, Pankow JS, Shah S, Taylor K, Barnard J, Peters BJ, Maloney CM, Lobmeyer MT, Stanton A, Zafarmand MH, Romaine SP, Mehta A, van Iperen EP, Gong Y, Price TS, Smith EN, Kim CE, Li YR, Asselbergs FW, Atwood LD, Bailey KM, Bhatt D, Bauer F, Behr ER, Bhangale T, Boer JM, Boehm BO, Bradfield JP, Brown M, Braund PS, Burton PR, Carty C, Chandrupatla HR, Chen W, Connell J, Dalgeorgou C, Boer Ad, Drenos F, Elbers CC, Fang JC, Fox CS, Frackelton EC, Fuchs B, Furlong CE, Gibson Q, Gieger C, Goel A, Grobbee DE, Hastie C, Howard PJ, Huang GH, Johnson WC, Li Q, Kleber ME, Klein BE, Klein R, Kooperberg C, Ky B, Lacroix A, Lanken P, Lathrop M, Li M, Marshall V, Melander O, Mentch FD, Meyer NJ, Monda KL, Montpetit A, Murugesan G, Nakayama K, Nondahl D, Onipinla A, Rafelt S, Newhouse SJ, Otieno FG, Patel SR, Putt ME, Rodriguez S, Safa RN, Sawyer DB, Schreiner PJ, Simpson C, Sivapalaratnam S, Srinivasan SR, Suver C, Swergold G, Sweitzer NK, Thomas KA, Thorand B, Timpson NJ, Tischfield S, Tobin M, Tomaszewski M, Verschuren WM, Wallace C, Winkelmann B, Zhang H, Zheng D, Zhang L, Zmuda JM, Clarke R, Balmforth AJ, Danesh J, Day IN, Schork NJ, de Bakker PI, Delles C, Duggan D, Hingorani AD, Hirschhorn JN, Hofker MH, Humphries SE, Kivimaki M, Lawlor DA, Kottke-Marchant K, Mega JL, Mitchell BD, Morrow DA, Palmen J, Redline S, Shields DC, Shuldiner AR, Sleiman PM, Smith GD, Farrall M, Jamshidi Y, Christiani DC, Casas JP, Hall AS, Doevendans PA, Christie JD, Berenson GS, Murray SS, Illig T, Dorn GW 2nd, Cappola TP, Boerwinkle E, Sever P, Rader DJ, Reilly MP, Caulfield M, Talmud PJ, Topol E, Engert JC, Wang K, Dominiczak A, Hamsten A, Curtis SP, Silverstein RL, Lange LA, Sabatine MS, Trip M, Saleheen D, Peden JF, Cruickshanks KJ, März W, O'Connell JR, Klungel OH, Wijmenga C, Maitland-van der Zee AH, Schadt EE, Johnson JA, Jarvik GP, Papanicolaou GJ; Hugh Watkins on behalf of PROCARDIS, Grant SF, Munroe PB, North KE, Samani NJ, Koenig W, Gaunt TR, Anand SS, van der Schouw YT; Meena Kumari on behalf of the Whitehall II Study and the WHII 50K Group, Soranzo N, Fitzgerald GA, Reiner A, Hegele RA, Hakonarson H, Keating BJ. Meta-analysis of Dense Gene-centric Association Studies Reveals Common and Uncommon Variants Associated with Height. American Journal of Human Genetics (2011 Jan, PMID: 21194676)

27. Saleheen D, Hashmi SK, Zaidi M, Rasheed A, **Murtaza M**, Abbas A, Nasim S, Hameed MQ, Shuja F, Sethi MJ, Hussain I, Shahid K, Khalid H, Ahmad U, Frossard PM, Ishaq M. Evaluation of therapeutic control in a Pakistani population with hypertension. Journal of Evaluation in Clinical Practice (2010 Dec, PMID: 20629998)

28. Naqvi I, **Murtaza M**, Nazir MR, Naqvi HA. Gender difference in age at onset in Schizophrenia: a cross sectional study from Pakistan. Journal of Pakistan Medical Association (2010 Oct, PMID: 21381632)

29. Saleheen D, Soranzo N, Rasheed A, Scharnagl H, Gwilliam R, Alexander M, Inouye M, Zaidi M, Potter S, Haycock P, Bumpstead S, Kaptoge S, Di Angelantonio E, Sarwar N, Hunt SE, Sheikh N, Shah N, Samuel M, Haider SR, **Murtaza M**, Thompson A, Gobin R, Butterworth A,

Ahmad U, Hakeem A, Zaman KS, Kundi A, Yaqoob Z, Cheema LA, Qamar N, Faruqui A, Mallick NH, Azhar M, Samad A, Ishaq M, Rasheed SZ, Jooma R, Niazi JH, Gardezi AR, Memon NA, Ghaffar A, Rehman FU, Hoffmann MM, Renner W, Kleber ME, Grammer TB, Stephens J, Attwood A, Koch K, Hussain M, Kumar K, Saleem A, Kumar K, Daood MS, Gul AA, Abbas S, Zafar J, Shahid F, Bhatti SM, Ali SS, Muhammad F, Sagoo G, Bray S, McGinnis R, Dudbridge F, Winkelmann BR, Böehm B, Thompson S, Ouwehand W, März W, Frossard PM, Danesh J, Deloukas P. Genetic determinants of major blood lipids in Pakistanis compared to Europeans. Circulation Cardiovascular Genetics. (2010 Aug, PMID: 20570915)

30. Saleheen D, Alexander M, Rasheed A, Wormser D, Soranzo N, Hammond N, Butterworth A, Zaidi M, Haycock P, Bumpstead S, Potter S, Blackburn H, Gray E, Di Angelantonio E, Kaptoge S, Shah N, Samuel M, Janjua A, Sheikh N, Haider SR, **Murtaza M**, Ahmad U, Hakeem A, Memon MA, Mallick NH, Azhar M, Samad A, Rasheed SZ, Gardezi AR, Memon NA, Ghaffar A, Memon FU, Zaman KS, Kundi A, Yaqoob Z, Cheema LA, Qamar N, Faruqui A, Jooma R, Niazi JH, Hussain M, Kumar K, Saleem A, Kumar K, Daood MS, Memon F, Gul AA, Abbas S, Zafar J, Shahid F, Memon Z, Bhatti SM, Kayani W, Ali SS, Fahim M, Ishaq M, Frossard PM, Deloukas P, Danesh J. Association of the 9p21 locus with risk of first-ever myocardial infarction in Pakistan. Arteriosclerosis, Thrombosis, and Vascular Biology. (2010 Jul, PMID: 20395598)

31. Taj F, Zahid R, Syed UR, **Murtaza M**, Ahmed S, Kamal AK. Risk factors of stroke in Pakistan: a dedicated stroke clinic experience. Canadian Journal of Neurological Sciences. (2010 Mar, PMID: 20437938)

32. Kamal AK, Itrat A, **Murtaza M**, Khan M, Rasheed A, Ali A, Akber A, Akber Z, Iqbal N, Shoukat S, Majeed F, Saleheen D. The burden of cerebrovascular diseases in Pakistan: a community based cross-sectional study. BMC Neurology (2009 Dec, PMID: 19948076)

33. Kamal AK, Taj F, Junaidi B, Rasheed A, Zaidi M, **Murtaza M**, Iqbal N, Hashmat F, Alam SV, Saleem U, Waheed S, Bansari L, Shah N, Samuel M, Yameen M, Naz S, Khan FS, Ahmed N, Mahmood K, Sheikh N, Makki KU, Ahmed MM, Memon AR, Wasay M, Syed NA, Khealani B, Frossard PM, Saleheen D. The Karachi Intracranial Stenosis Study (KISS) protocol: an urban multicenter case-control investigation reporting clinical, biochemical and radiological associations. BMC Neurology (2009 Jul, PMID: 19604359)

34. **Murtaza M**, Kisat M, Daniel H, Sonawalla A. Classification and clinical features of headache disorders in Pakistan: a retrospective review of clinical data. PLoS ONE (2009 Jun, PMID: 19503794)

35. Saleheen D, Zaidi M, Rasheed A, Ahmad U, Hakeem A, **Murtaza M**, Kayani W, Faruqui A, Kundi A, Zaman KS, Yaqoob Z, Cheema LA, Samad A, Rasheed SZ, Mallick NH, Azhar M, Jooma R, Gardezi AR, Memon N, Ghaffar A, Fazal-ur-Rehman, Khan N, Shah N, Ali Shah A, Samuel M, Hanif F, Yameen M, Naz S, Sultana A, Nazir A, Raza S, Shazad M, Nasim S, Javed MA, Ali SS, Jafree M, Nisar MI, Daood MS, Hussain A, Sarwar N, Kamal A, Deloukas P, Ishaq M, Frossard PM, Danesh J. The Pakistan Risk of Myocardial Infarction Study: a resource for the study of genetic, lifestyle and other determinants of myocardial infarction in South Asia. European Journal of Epidemiology (2009 Apr, PMID: 19404752)

PATENTS

2018 **Murtaza M**, Kisat M[+], Odenheimer-Bergman A[+]. Methods for enriching microbial cell-free DNA in plasma. The Translational Genomics Research Institute. US Patent Application US16/197319. [+]lab member

2018 Hendricks W, **Murtaza M**, Lorch G. Identification of HER2 mutations in canine lung cancer and methods of treatment. The Translational Genomics Research Institute. Provisional Patent Application US62/778282.

2017 McDaniel T, **Murtaza M**. Molecular tagging methods and sequencing libraries. The Translational Genomics Research Institute. International Patent Application PCT/US2017/035330.

2017 **Murtaza M**, Perdigones N[+]. Molecular tagging methods and sequencing libraries. The Translational Genomics Research Institute. International Patent Application PCT/US2017/034329. [+]lab member

2016 **Murtaza M**, Contente-Cuomo T[+]. Quality assessment of circulating cell-free DNA using multiplexed droplet digital PCR. The Translational Genomics Research Institute. International Patent Application PCT/US2016/028159. [+]lab member

2015 Rosenfeld N, Forshew T, Marass F, **Murtaza M**. A method for detecting a genetic variant. University of Cambridge. United Kingdom Intellectual Property Office GB application number GB1512626.1 and International Patent Application PCT/GB2015/052086.

GRANTS AND FELLOWSHIPS

Active

1U01-CA243078-01A1: Murtaza (PI) 09/2019-08/2024
NIH/NCI
Pre-analytical factors affecting ctDNA analysis in early and locally advanced breast cancer
Major goal: To evaluate pre-analytical factors affecting ctDNA levels in early stage cancer patients, such as blood processing, plasma DNA extraction and long-term storage.

1R01-CA223481-01: Murtaza (PI) 08/2018-07/2023
NIH/NCI
Individualized monitoring of treatment response and resistance in patients with metastatic melanoma

Major goal: To assess clinical validity of ctDNA analysis for early assessment of treatment response to immune-checkpoint inhibitors, for molecular stratification to immunotherapy and for analysis of disease progression on immune-checkpoint inhibitors.

Project Funding: Murtaza (PI) 11/2015-11/2020
The Ben and Catherine Ivy Foundation
Monitoring a moving target – a project to assess the molecular makeup of residual glioblastoma through the development of liquid biopsies
Major goal: To assess feasibility of liquid biopsies in patients with glioblastoma for tracking treatment response and clonal evolution.

Translational Seed Grant: Murtaza (PI) 11/2019-04/2021
Flinn Foundation
Optimizing treatment of metastatic breast cancer through real-time disease monitoring
Major goal: To develop a blood test for treatment monitoring for metastatic breast cancer using computational analysis of whole genome sequencing.

Pending

1UH2-CA234306-01A1: Murtaza (PI)
NIH/NCI
Treatment monitoring in early and locally advanced breast cancer using circulating tumor DNA analysis
Major goals: To perform analytical validation (UH2 phase) and clinical validation (UH3 phase) for detection of post-neoadjuvant and post-operative minimal residual disease in patients with breast cancer
Impact Score 12, pending funding decision

Completed

BSP 0542-13, Bisgrove Scholar: Murtaza (PI) 12/2014-12/2016
Science Foundation Arizona
Analysis of circulating tumor DNA in canine and human solid cancers
Major goals: To establish ctDNA diagnostics program, develop quality metrics and develop ctDNA as a biomarker in sporadic canine cancer

Phil A. Sharp Innovation in Collaboration Award: Murtaza (PI) 05/2016-05/2018
Stand Up To Cancer
Fingerprinting the systemic microbiome in plasma to predict immunotherapy outcomes in melanoma
Major goals: To establish feasibility of plasma microbiome assessment in patients with melanoma

V2015-017, V Scholar: Murtaza (PI) 11/2015-11/2018
The V Foundation for Cancer Research
Analysis of circulating tumor DNA to guide non-operative management of rectal cancer

Major goals: To explore ctDNA as a biomarker for identification of patients with complete pathological response to pre-operative chemotherapy

INVITED TALKS

2019 Circulating tumor DNA analysis for cancer diagnostics. Pathology and Laboratory Medicine Grand Rounds, Perelman School of Medicine, University of Pennsylvania, Philadelphia, PA, USA. Oct 28.

2019 Circulating tumor DNA analysis for cancer diagnostics. Pathology Grand Rounds, City of Hope, Duarte, CA, USA. Oct 16.

2019 Improving accuracy and precision for liquid biopsies using personalized targeted digital sequencing. Cold Spring Harbor Laboratory Banbury Center, Lloyd Harbor, NY, USA. Sep 9.

2019 Monitoring and optimizing cancer management using circulating tumor DNA analysis. Cancer Center Grand Rounds, Boston University School of Medicine, Boston, MA, USA. Apr 18.

2019 High-accuracy personalized detection of residual disease using circulating tumor DNA analysis. Session Chair and Speaker. American Association for Cancer Research (AACR) Annual Meeting, Atlanta, GA, USA. Mar 30.

2019 Evaluation of reference samples for validation of circulating tumor DNA analysis. Session Chair and Speaker. Molecular Medicine Tri-Conference, San Francisco, CA, USA. Mar 13.

2018 Circulating tumor DNA analysis to monitor breast cancer. Mayo Clinic Breast Cancer Conference, Scottsdale, AZ, USA. Nov 10.

2018 Improving precision in cancer medicine using circulating tumor DNA analysis. Massachusetts General Hospital Cancer Center, Boston, MA, USA. Mar 20.

2018 Personalized treatment monitoring using circulating tumor DNA analysis. City of Hope Phase I Clinical Trials Retreat. Duarte, CA, USA. Jan 5.

2017 Development and use of liquid biopsies for pancreatic cancer. Mayo Clinic Pancreatic and Hepato-Biliary Cancer Symposium. Scottsdale, AZ, USA. Nov 10.

2017 Finding and counting needles in haystacks: molecular and bioinformatics approaches for measuring circulating tumor DNA. Individualizing Medicine Conference at Mayo Clinic Center for Individualized Medicine. Rochester, MN, USA. Oct 10.

2017 Droplet digital PCR to measure and accommodate pre-analytical variability in cfDNA samples and guide downstream NGS. Next Generation Dx Summit. Washington, DC, USA. Aug 18.

2017 Bridging diagnostic gaps in precision medicine using circulating tumor DNA analysis. Baylor Sammons Cancer Center Oncology Grand Rounds. Dallas, TX, USA. May 2.

2016 Capturing tumor heterogeneity and clonal evolution using ctDNA analysis. NCI Workshop on Circulating Tumor DNA Assay in Clinical Cancer Research. Washington, DC, USA. Sep 29-30.

2016 Analysis of circulating tumor DNA for cancer diagnostics. Next Generation Dx Summit. Washington, DC, USA. Aug 24-25.

2016 Analysis of circulating tumor DNA for cancer diagnostics. Arizona State University Biomedical Informatics Seminar Series. Tempe, AZ, USA. Mar 18.

2016 Quality assessment of cell-free DNA to guide downstream molecular analyses. Molecular Medicine Tri-Conference. San Francisco, CA, USA. Mar 10-11.

2016 Analysis of circulating tumor DNA for cancer diagnostics. Mayo Clinic Center for Individualized Medicine Grand Rounds. Rochester, MN, USA. Feb 11.

2015 Monitoring treatment response and resistance using circulating tumor DNA analysis. Mayo Clinic Cancer Center Thoracic Oncology for the Oncologist. Scottsdale, AZ, USA. Dec 12.

2015 Analysis of circulating tumor DNA to monitor clonal evolution. AACR-NCI-EORTC International Conference on Molecular Targets and Cancer Therapeutics. Boston, MA, USA. Nov 5-9.

2015 Liquid biopsies for monitoring response to therapy in pancreatic cancer. Mayo Clinic Pancreatic Cancer Conference. Scottsdale, AZ, USA. Oct 23.

2015 Analysis of circulating tumor DNA to monitor metastatic cancer. Individualizing Medicine Conference at Mayo Clinic Center for Individualized Medicine. Rochester, MN, USA. Sep 23.

2015 Digital PCR and sequencing for analysis of circulating tumor DNA. qPCR and Digital PCR Congress USA. San Diego, CA, USA. Jun 25-26.

2015 Liquid biopsies: circulating tumor DNA analysis for monitoring cancer. Best Science Breakfast at Baylor Charles A. Sammons Cancer Center. Dallas, TX, USA. Feb 19.

2014 Analysis of Circulating Tumor DNA to Monitor Cancer Burden and Evolution. Leeds Institute of Molecular Medicine. Leeds, United Kingdom. Nov 27.

2014 Analysis of circulating tumor DNA to monitor cancer. Blood Systems Research Institute. San Francisco, CA, USA. Jun 26.

2014 Noninvasive analysis of acquired therapeutic resistance using ctDNA sequencing. Next Generation Dx Summit. Washington, DC, USA. Aug 20.

2014 Analysis of circulating tumor DNA to monitor metastatic cancer. Mayo Clinic Cancer Center Grand Rounds. Scottsdale, AZ, USA. Mar 20.

2013 Analysis of circulating tumor DNA to monitor metastatic cancer. Oncological Biomarkers Symposium organized by Working Group of Oncologic Biomarkers. Utrecht, Netherlands. Nov 14.

2013 Noninvasive analysis of cancer genomes using circulating tumor DNA. Broad Institute and Dana-Farber Cancer Institute, Cambridge, MA, USA. Matthew Meyerson's Lab. Jul 19.

2013 Noninvasive analysis of cancer genomes using circulating tumor DNA. Boston University Medical Campus, Boston, MA, USA. Jul 18.

2013 Noninvasive analysis of cancer genomes using circulating tumor DNA. Memorial Sloan Kettering Cancer Center, New York City, NY, USA. David Solit's Lab. Jul 16.

2013 Noninvasive analysis of cancer genomes using circulating tumor DNA. Translational Genomics Research Institute, Phoenix, AZ, USA. Jul 9.

2013 Noninvasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. European Symposium of Biopathology. Paris, France. Jun 13-14.

CONFERENCE PARTICIPATION

Talks

2019 Kisat M[+], Odenheimer-Bergman A[+], Markus H[+], Joseph B, Srivatsan SN[+], Contente-Cuomo T[+], Khalpey Z, Keim P, O'Keeffe T, Askari R, Salim A, Rhee P, **Murtaza M**. Quantifying bacterial DNA levels in ICU patients suspected of bacterial sepsis using whole genome sequencing of plasma DNA. American Association for Surgery of Trauma Annual Meeting, Dallas, TX, USA. Sep 19. [+]lab member

2017 Markus H[+], Contente-Cuomo T[+], Liang W, Borad M, Sivakumar S, Gollins S, Tran N, Dhruv H, Berens M, Bryce A, Sekulic A, Ribas A, Trent J, LoRusso P, **Murtaza M**. Evaluation of pre-analytical factors affecting plasma DNA analysis. Circulating Nucleic Acids in Plasma and Serum International Symposium, Montpellier, France. Sep 20-22. [+]lab member

2017 Odenheimer-Bergman A[+], Kisat M[+], Joseph B, Srivatsan SN[+], Contente-Cuomo T[+], Khalpey Z, Keim P, Fofanov V, Rhee P, **Murtaza M**. Identification of pathogens in patients with sepsis using whole genome plasma DNA sequencing. Circulating Nucleic Acids in Plasma and Serum International Symposium, Montpellier, France. Sep 20-22. [+]lab member

2016 Kisat M[+], Joseph B, Contente-Cuomo T[+], Khalpey Z, Keim P, **Murtaza M**, Rhee P. Longitudinal analysis of circulating mitochondrial DNA as a biomarker in patients with Systemic Inflammatory Response Syndrome. American Association for Surgery of Trauma Annual Meeting, Waikoloa, HI, USA. Sep 14. [+]lab member

2013 **Murtaza M**, et al. Noninvasive identification and monitoring of cancer mutations by sequencing circulating tumor DNA. EACR Summer Conference on Cancer Genomics. Cambridge, United Kingdom. Jun 25-28.

2013 **Murtaza M**, et al. Noninvasive identification and monitoring of cancer mutations by sequencing circulating tumor DNA. International PhD Student Cancer Conference. London, United Kingdom. Jun 19-21.

2012 **Murtaza M**, et al. Developing blood tests to monitor progress of cancer and to guide chemotherapy. University of Cambridge Clinical Medicine Research Day. Cambridge, United Kingdom. Jun 18.

2011 **Murtaza M**, Lo YMD, Rosenfeld N. Nucleosome positioning can help identify DNA fragments with higher abundance in plasma. Circulating Nucleic Acids in Plasma and Serum Meeting VII. Madrid, Spain. Oct 24-25.

2009 **Murtaza M**, Kisat M, Daniel H, Sonawalla AB. Classification and clinical features of headache disorders in Pakistan: a retrospective review of clinical data. Pakistan Society of Neurology Annual Meeting. Karachi, Pakistan. Mar 21-23.

Posters

2019 McDonald BR[+], Contente-Cuomo T[+], Stephens M[+], Trent JM, Sekulic A, LoRusso PM, Bryce A, **Murtaza M**. Treatment monitoring using circulating tumor DNA analysis in patients with metastatic melanoma. Mayo Clinic Individualizing Medicine Conference, Scottsdale, AZ, USA. Sep 20. [+]lab member

2019 **Murtaza M**, et al. High-accuracy personalized detection of minimal residual disease after neoadjuvant therapy in patients with breast cancer. Stand Up To Cancer Scientific Summit. Santa Monica, CA, USA. Jan 26-29.

2018 McDonald BR[+], Contente-Cuomo T[+], Sammut SJ, Ernst B, Odenheimer-Bergman A[+], Perdigones N[+], Chin SF, Farooq M[+], Cronin PA, Anderson KS, Kosiorek HE, Northfelt DW, McCullough AE, Patel BK, Caldas C, Pockaj BA, **Murtaza M**.

Detection of residual disease after neoadjuvant therapy in breast cancer using personalized circulating tumor DNA analysis. San Antonio Breast Cancer Symposium, San Antonio, TX, USA. Dec 7. [+]lab member

2018 Farooq M[+], Egan J, McDonald B[+], Markus H[+], Contente-Cuomo T[+], Fernandez-Zapico M, Vasmatzis G, Braggio E, Borad M, **Murtaza M**. Detection of copy number aberrations in cholangiocarcinoma using shallow whole genome sequencing of plasma DNA. Gastrointestinal Cancers Symposium, San Francisco, CA, USA. Jan 18. [+]lab member

2017 Perdigones N[+], Connor S[+], Hartman L, Contente-Cuomo T[+], Reid G, Berens M, Dhruv H, **Murtaza M**. Circulating tumor DNA analysis in patient-derived xenograft models of glioblastoma. Society for Neuro-Oncology, San Francisco, CA, USA. Nov 17.

2017 Perdigones N[+], McDonald B[+], Contente-Cuomo T[+], Ernst B, Odenheimer-Bergman A[+], Aldrich J, Liang WS, Sekulic A, Bryce A, Trent J, LoRusso P, Pockaj B, **Murtaza M**. Personalized treatment monitoring using multiplexed targeted digital sequencing of circulating tumor DNA. Circulating Nucleic Acids in Plasma and Serum International Symposium, Montpellier, France. Sep 20-22. [+]lab member

2017 Markus H[+], Contente-Cuomo T[+], Zhao J[+], **Murtaza M**. Size distribution of urine cell-free DNA is consistent with sub-nucleosomes. Circulating Nucleic Acids in Plasma and Serum International Symposium, Montpellier, France. Sep 20-22. [+]lab member

2017 Kisat M[+], Odenheimer-Bergman A[+], Joseph B, Srivatsan SN[+], Contente-Cuomo T[+], Khalpey Z, Keim P, Fofanov V, **Murtaza M**, Rhee P. Longitudinal analysis of circulating mitochondrial DNA as a biomarker in patients with Systemic Inflammatory Response Syndrome. American Association for Surgery of Trauma Annual Meeting, Waikoloa, HI, USA. Sep 13-16. [+]lab member

2016 **Murtaza M**, et al. Monitoring treatment response and resistance in patients with metastatic melanoma using circulating tumor DNA analysis. Stand Up To Cancer Scientific Summit. Santa Monica, CA, USA. Jan 26-29.

2015 Contente-Cuomo T[+], **Murtaza M**. Quality assessment of circulating cell-free DNA using multiplexed droplet-digital PCR. American Association for Cancer Research Annual Meeting. Philadelphia, PA, USA. Apr 18-22. [+]lab member

2014 **Murtaza M**, et al. Investigating genomic evolution and acquired resistance in solid cancers by sequencing plasma DNA. Molecular Medicine Tri-Conference (MMTC). San Francisco, CA, USA. Feb 13-14.

2013 **Murtaza M**, et al. Noninvasive identification and monitoring of cancer mutations by sequencing circulating tumor DNA. Cancer Research UK PhD Students' Meeting. London, United Kingdom. May.

2012 **Murtaza M**, et al. Sequencing circulating DNA for identification and monitoring of cancer mutations. Cambridge Research Institute Symposium. Cambridge, United Kingdom. Nov 2-3.

TEACHING EXPERIENCE

Post-doctoral Trainees

Bradon McDonald, PhD	Computational Scientist (11/2016 to present)
Karan Budhraja, PhD	Computational Scientist (10/2019 to present)
Patricia Favaro, PhD	Postdoctoral Fellow (10/2019 to present)
Maria Farooq, MD	Postdoctoral Fellow (03/2017 to 05/2019)
Jun Zhao, DO	Clinical Fellow (07/2016 to 07/2018)
Nieves Perdigones, PhD	Senior Postdoctoral Fellow (02/2016 to 01/2018)
Mehreen Kisat, MD	Clinical Fellow (06/2015 – 06/2016) Masters in Science, University of Arizona

Pre-doctoral Trainees

Sridhar N Srivatsan	Masters in Science, Indiana University School of Informatics (Summer 2016)
Pankti Shah	Masters in Biomedical Informatics, Arizona State University (09/2014-05/2016)
Havell Markus, MPhil	Associate Bioinformatician (06/2015 to 05/2019) Previously Undergraduate Intern in the lab

Undergraduate Students

Kaden Brown	Undergraduate Intern (06/2019 to present)
Sasha Celada	Helios Scholar (Summer 2019)
Sydney Connor	Undergraduate Intern (06/2017 to 07/2019)
Anamika Basu	Ivy Scholar (Summer 2018)
Sidney Covarrubias	Helios Scholar (Summer 2018)

Jigar Patel	Helios Scholar (Summer 2016)
Alexandra Nazareno	Undergraduate Intern (Summer 2014 and 06/2015-05/2016)
Christopher Krimbill	Helios Scholar (Summer 2014)

ADDITIONAL TRAINING / CONTINUING EDUCATION

2011 Advanced Sequencing Technologies and Applications, Cold Spring Harbor Laboratory, NY, USA. Nov 8-21.

2011 Variant Calling in Genomic Sequencing Data, European Molecular Biology Laboratory, Heidelberg, Germany. Jul 18-20.

2009 Visiting Researcher, Wellcome Trust Sanger Institute, United Kingdom. Aug-Nov

SERVICE TO PROFESSION

Conference Committees

2019 AACR Annual Meeting Education Committee

Grants Review (ad hoc)

2018 European Research Council

2017 NCI Genetics Branch Intramural Site Visit, Cancer Research UK, Worldwide Cancer Research

2016 PRESTIGE Marie Curie Post-doctoral Fellowship

2015 Mayo Clinic Arizona Center for Individualized Medicine Biomarker Program

2015 Baylor Charles A. Sammons Cancer Center Pilot Projects

Manuscripts Review

2019 Nature, Science Translational Medicine, Proceedings of the National Academy of Science, Nature Communications, Genome Medicine, JCO Precision Oncology, Molecular Oncology

2018 New England Journal of Medicine, Science Translational Medicine, Nature Communications, Nucleic Acids Research

2017 Science Translational Medicine, Nature Communications, Molecular Cancer Research, Scientific Reports, PLoS ONE, BioMed Research International, Clinical Cancer Research, Journal of Molecular Medicine

2016 Annals of Human Genetics, PLoS ONE, Scientific Reports, Clinical Chemistry, Clinical Cancer Research, Genome Medicine, Oncotarget, Cancer Research

2015 eLife, PLoS ONE, Oncotarget

2014 Molecular Oncology, Bioinformatics, Nucleic Acids Research, BMC Genomics, PLoS ONE

PROFESSIONAL MEMBERSHIPS

2014 – American Association for Cancer Research

Statement of Research Interests

Pushing the boundaries of personalized cancer medicine using liquid biopsies

Liquid biopsies have captured the imagination of the cancer research and clinical communities for almost a decade. The ability to interrogate tumor-derived analytes in blood or urine and without tissue biopsy is a game changer. Of several different potential biomarkers, circulating tumor DNA (ctDNA) analysis has been particularly promising, primarily due to relatively higher stability of DNA in circulation and reliance on tumor-specific somatic genomic alterations. I started working in the area of circulating tumor DNA (ctDNA) analysis about 10 years ago, first as a graduate student and currently as a principal investigator. ctDNA analysis holds immense potential across the spectrum of diagnostic needs for cancer patients, ranging from early detection in pre-symptomatic patients to treatment monitoring and subclonal tracking in advanced metastatic cancer patients. My research program is focused on pushing the boundaries of precision medicine by developing novel methods and applications for liquid biopsies.

One application of liquid biopsies that has already materialized clinically is blood-based tumor genotyping for metastatic cancer patients. In the first demonstration of noninvasive tumor genotyping (Forshew*, Murtaza* et al. Science Translational Medicine 2012), we developed an assay using sequencing of PCR amplicons to identify and quantify cancer mutations in plasma DNA. Using careful optimization of molecular methods and development of a novel computational informatics pipeline for variant calling, we achieved a limit of detection of 0.1% to 1% tumor fraction. A diagnostics startup company called Inivata has now commercialized this approach and recently received reimbursement coverage from Medicare, highlighting the clinical impact and utility of this approach. In a follow-up study (Murtaza et al. Nature Communications 2015), we evaluated the extent to which ctDNA analysis can capture genetic heterogeneity from multiple distinct metastases. We showed that mutation levels in ctDNA represent the phylogenetic hierarchy of the tumor, such that founder mutations are detectable at much higher levels than subclonal and private mutations. This observation implies that quantitative mutation levels in plasma genotyping data can predict extent of treatment response i.e. if a targeted actionable mutation is higher in plasma relative to non-targeted mutations, the therapeutic response will be deeper. This hypothesis was subsequently confirmed in an external study of patients with non-small cell lung cancer (Oxnard et al. JCO 2016).

Quantitative analysis of plasma DNA using digital PCR or sequencing enables measurement of changes in ctDNA levels during treatment. Plasma levels of founder mutations can represent changes in the overall burden of tumor in a patient. If subclonal mutation levels are measured, it may be possible to track subclonal dynamics and clonal evolution during treatment. I contributed to one of the first demonstrations that changes in ctDNA levels are indeed informative of tumor response to treatment or disease progression (Dawson et al. NEJM 2012). To demonstrate how analysis of plasma DNA at multiple loci can capture clonal evolution in each patient's tumor and aid discovery of mechanisms of acquired therapeutic resistance, we performed whole exome sequencing of plasma (Murtaza et al. Nature 2013). A follow-up study in a larger cohort of patients with non-small cell lung cancer confirmed these observations (Tsui*, Murtaza* et al. EMBO Molecular Medicine 2018).

For most patients with non-metastatic cancers treated with curative intent, there is currently no objective biomarker that establishes end of treatment. An accurate test for minimal residual disease can serve as such a biomarker but current ctDNA analysis technologies are far from reaching required accuracy. We developed a new approach for personalized ctDNA analysis, called targeted digital sequencing (TARDIS), a method capable of simultaneously analyzing up to 115 patient-specific mutations in plasma to achieve sensitivity for ctDNA levels as low as 0.002% (two orders lower than current commercially available tests). Using this method, we have observed that ctDNA levels are detectable in 100% patients with non-metastatic breast cancer at presentation. In addition, we can predict response and outcome for neoadjuvant therapy in locally

advanced breast cancer prior to surgical resection (McDonald et al. Science Translational Medicine 2019; corresponding senior author).

Practical and clinical implementation of ctDNA testing requires thorough understanding of pre-analytical factors than can affect ctDNA measurement. We developed a molecular approach for quality assessment of cell-free DNA samples and evaluated 8 different cell-free DNA extraction methods and 3 blood processing protocols to identify optimal solutions (Markus et al. Scientific Reports 2018; corresponding senior author). These results have been highly regarded by users and assay developers in academia and industry alike, evidenced by 25 citations within 18 months of publication.

Current and future directions

Advancing detection of minimal residual disease to personalize management of patients with non-metastatic cancers treated with curative intent

A key goal of my translational research program is to validate our preliminary findings that MRD detection could enable individualized clinical management in cancer patients. To achieve this goal, across multiple clinical indications and cancer types, we need to execute clinical validation studies followed by clinical utility trials. In on-going work, we are focused on scaling up and automating the TARDIS assay, along with building a logistical and informatics workflow to facilitate large scale studies. One of the first studies on the horizon is a multi-center validation of our findings in ~200 patients with non-metastatic breast cancer. Additional studies include patients with esophageal cancer, pancreatic cancer, rectal cancer and prostate cancer. We anticipate receiving an NCI award that will partially fund analytical and clinical validation of TARDIS for patients with breast cancer in the current fiscal year (a four-year UH2/UH3 grant has received an impact score of 12). In anticipation of challenges associated with practical implementation of such a clinical test, we are also evaluating the impact of pre-analytical factors such as blood collection, processing and transport, plasma DNA extraction, and long-term storage of plasma DNA samples, funded by a separate NCI award (an active five-year U01).

Treatment monitoring in patients with advanced metastatic cancers

Despite several earlier proof of principle studies, monitoring of treatment response in metastatic cancer patients has not materialized clinically. There are logistical and technical reasons for this lack of progress. Most studies in literature have relied on tumor-guided digital PCR assays. Patient-specific digital PCR assays are difficult to optimize in a clinical diagnostic setting. In addition, ctDNA levels routinely fall below the limit of detection in mid-treatment plasma samples. An alternative strategy shown in literature is shallow whole genome sequencing (sWGS) of plasma DNA. sWGS integrates signal from across the genome instead of deeply characterizing any single genomic locus. However, current sWGS approaches have a limit of detection of 1% to 3% tumor fraction and remain inadequately sensitive for routine clinical use. We have recently developed a novel computational framework to interpret sWGS data based on deviations from expected nucleosome positions in plasma cfDNA (in revision, preprint online: Markus et al. bioRxiv 2019; corresponding senior author). Our preliminary results suggest this analytical approach is ~10 fold more sensitive than existing informatic frameworks. We are investigating this further for treatment monitoring in patients with metastatic melanoma (supported by an active NCI R01) and in patients with metastatic breast cancer (supported by a newly funded seed grant by Flinn Foundation). A potential application of this approach is guiding intermittent dosage of cytotoxic chemotherapy in patients with metastatic breast cancer, to delay the onset of treatment resistance and prolong progression-free survival. We are evaluating this hypothesis in a clinical trial in collaboration with colleagues at Arizona State University and Mayo Clinic Arizona.

Urine as a source of tumor-derived nucleic acids

Urine is an alternative body fluid with potential utility as a liquid biopsy in cancer patients. Compared to plasma, urine can be obtained in abundance, completely noninvasively and without requiring phlebotomy support.

However, initial efforts to use urine cfDNA described in literature have been variably successful. We have recently described fragmentation profiles in urine cfDNA are consistent with stable intermediates of nucleosome digestion (in revision, preprint online: Markus et al. bioRxiv 2019; corresponding senior author). We inferred genome-wide nucleosome positioning in urine and using these maps as reference, we measured the fraction of cfDNA fragments at unexpected genomic loci (aberrant fraction). In patients with non-metastatic cancers, we showed aberrant fractions were significantly higher compared to healthy volunteers, distinguishing cancer samples with an area under the curve of 0.89. We are now developing this approach further for joint analysis of plasma and urine samples to enable early detection of cancer. This will require further refinement of pre-analytical factors affecting urine cfDNA analysis, development of a healthy individual reference set of urine cfDNA profiles and investigation of changes in urine cfDNA across cancer subtypes and stages. These will be pursued in future NCI grant applications planned for submission in 2020 and beyond.

Analysis of non-human DNA in plasma to interrogate systemic microbiome

In patients with viral and bacterial infections, a fraction of plasma DNA is contributed by pathogens. We recently demonstrated bacterial DNA was measurable in plasma of patients with sepsis and offered quantitative insights into their diagnosis and treatment (in review, Kisat et al. 2019, corresponding senior author). In the course of this project, we have found evidence of bacterial DNA from commensal microbes in plasma. Supported by the Phil Sharp award from Stand Up To Cancer, we are investigating whether the composition of the plasma microbiome in cancer patients differs from healthy volunteers, if it changes during treatment and how it may affect treatment outcomes. These investigations are on-going in patients with metastatic melanoma, advanced cholangiocarcinomas and early stage breast cancer. Preliminary results from this work will be used to pursue an NCI grant further investigating plasma microbiomes in cancer in 2020.

Low-cost accessible liquid biopsies

Nearly three-fourths of cancer-related deaths in the world occur in low and middle income countries, despite a distinctly lower incidence of cancer in this region. Poor clinical outcomes are mainly due to lack of access to diagnostics and treatment. Most patients are diagnosed late and do not have access to clinical management strategies that are standard of care in the US. Lack of access to diagnostics is a significant impediment in the implementation of care. We are pursuing a research theme to improve access to a cutting edge technology in cancer diagnostics (liquid biopsies) for resource-limited settings. In the first project of this theme, we will leverage recent computational advances in our lab for monitoring treatment response and progression in metastatic cancer patients. The goal of this project is to develop a low-cost dried blood spot assay that can objectively monitor treatment response in metastatic cancer patients and be deployed in resource-limited environments. A pilot grant application to fund this project was invited and will be submitted shortly for review to the Mark Foundation.

Summary

I started my independent research program focused improving accuracy of molecular technologies for liquid biopsies, in order to enable novel clinical applications such as residual disease detection. In the next phase of my program, my focus is to develop computational methods coupled with less complex molecular technologies in order to improve access to liquid biopsies. This include expanding our methods to include dried blood spots, urine samples and evaluating the breadth of molecular information found in cell-free circulating DNA, beyond cancer mutations. Together, progress in these areas can improve access to minimally invasive genomics assays, enable more frequent sampling and analysis of patients and resulting in improved outcomes for patients across the world.

Statement of Teaching Interests

My goal as a mentor and teacher is to impart critical skills needed to recognize gaps and solve problems in clinical medicine. During my own training in medical school, I experienced a curriculum largely focused on problem-based learning. Instead of conventional didactics, problem-based learning focuses on mentored discussions of clinical cases, allowing students in small teams to identify learning opportunities. Inevitably and often, these discussions ventured beyond questions one could answer using textbooks. In these cases, we would either need to review recent biomedical literature or admit that some questions in a clinical scenario needed additional research. I credit this experience for my interest and success in interdisciplinary translational research later in my career.

Successful translational scientists recognize gaps and areas of clinical need, translate them into discrete research questions, drawing on prior knowledge, targeted reading and the collective knowhow of colleagues. They form and test hypotheses in collaborative teams from across multiple disciplines and interpret their results in clinical context. To create such opportunities for trainees, I setup a lab that includes members with different educational backgrounds (clinical fellows, molecular biologists and computational biologists are all embedded in our lab). This creates a diversity of perspectives during our project discussions, which is only amplified by the multinational and multicultural workforce in scientific research. Undoubtedly, differences in culture and background often create challenges in communication but learning to navigate these is part of the learning experience. Such differences in life and training experiences often lead to collective insights that any single member cannot achieve.

During the last few years in my cancer diagnostics and genomics research lab, I have coached clinical fellows to convert diagnostic gaps into research questions, set them up as research projects with discrete steps, optimize molecular approaches as needed for each step and then test the overall approach. I have helped molecular biologists look beyond optimization of protocols on the bench as a goal in itself and focus on areas most relevant to the overall diagnostic challenge. I have also encouraged computational scientists to communicate their unique perspective effectively to the team, to draw on the team's collective knowhow to guide their analyses, to evaluate their results against practical expectations from reference data and to focus on problem-solving just as much as if not more than computational efficiency.

I am keen to teach a translational genomics course for graduate and medical students. While a broad base of working knowledge and key concepts is essential, the rate at which new technologies arise and evolve and medical literature expands, focusing too heavily on factual memory and recall is unlikely to benefit the future translational scientist. A course that combines conventional didactic lectures with case-based scenarios will be more useful. Early in this course, such case discussions can be more guided with predefined milestones and transition later to more open-ended challenges.

I believe rapid advances can be made by recognizing gaps on the bedside, converting them into questions you can tackle on the bench and translating the advances back to the bedside. In my research career, I have seen this process work and mentored trainees through such iterations. In my teaching career, I would love to develop and teach a course that imparts necessary skills that prepares future scientists and clinicians to taken on such challenges.