Current Projects

1) Novel inhibitors of the Receptor Tyrosine Kinase like Orphan Receptor 2 (ROR2) enzyme for the treatment of cancer

Elevated expression of receptor-tyrosine-kinase-like orphan receptors 2 (ROR2) is correlated with tumor progression in a variety of solid tumors (1). ROR2 plays a role in carcinogenesis and cancer progression through both WNT canonical and non canonical signalling pathways (2). ROR2 is not expressed in most normal tissues, and thus represents an attractive target for the development of cancer therapeutics (2). The proposed research is significant, because it will lead to the development of lead compounds that target multiple tumor types. Computational approaches combined with molecular biology are used to find novel small molecule inhibitors modulating ROR2 activity during progression in premalignant and malignant phases (3). This will be important to further address the role of the ROR2 as a biomarker and/or a clinical target in multiple human cancers.

References cited

(1) Saji, et al. Critical role of the ROR-family of receptor tyrosine kinases in invasion and proliferation of malignant pleural mesothelioma cells. Genes Cells In Press (2018).
(2) Henry et al. ROR1 and ROR2 play distinct and opposing roles in endometrial cancer. Gynecol Oncol 148, 576–584 (2018).
(3) Rodgers, B, Nishita, M, Bisson WH. Inhibiting the Receptor Tyrosine Kinase-like Orphan Receptor 2 (ROR2) enzyme with small molecules for the treatment of cancer. Poster session, EMT Day, Oregon State University (2016)

2) The Halifax Project and early cancer development

In March 2013, I was selected leader of the Team Validation part of the international Halifax Project in "Assessing the Carcinogenic Potential of Low Dose Exposures to Chemical Mixtures in the Environment". The task force studied the possibility that exposures to mixtures of environmental ubiquitous disruptive chemicals at low doses may be contributing to the high rates of cancer incidence. Drawing on hundreds of laboratory studies, large databases of cancer information, and models that predict cancer development, we compared the environmental chemicals' biological activity patterns to eleven known cancer "hallmarks" - distinctive patterns of cellular and genetic disruption associated with tumor development. The work was published in June 2015 in the journal Carcinogenesis and highlighted on AAAS Science news in July 2015 and by the Environmental Factor, NIEHS in July, September 2015 and September 2016 (1-4).
Colorectal carcinoma remains one of the most frequently diagnosed and deadly cancers in the US. I previously used computational techniques combined with experimental approaches to validate epigenetic allosteric inhibition of HDAC class I (HDAC 1-3) activity by dietary agents in cancerous colon cells (5).
I believe, that a better understanding, of the biology of early cancer development, will be key for the design of novel successful strategies in *precision therapy, prevention* and *early detection*.

References cited

(1) WH. Bisson, A. Amedei, L. Memeo, S. Forte , D. Felsher. Tumor promoting/ associated inflammation and the microenvironment : A state of the science and new horizons. In book : Translational Toxicology and

Therapeutics: Windows of Developmental Susceptibility in Reproduction and Cancer, First Edition. pp 473-510. Edited by M.D. Waters and C.L. Hughes. Published by John Wiley & Sons, Inc. (2018)
(2) Bisson WH. Environmental immune disruptors, inflammation and carcinogenesis: A state of the science and new horizons. Toxicol Lett 280, Suppl1: S9-S10 (2017).
(3) M.F. Miller, W.H. Goodson III, M.H. Manjili, N. Kleinstreuer, W.H. Bisson, L. Lowe. LOW-DOSE MIXTURE HYPOTHESIS OF CARCINOGENESIS WORKSHOP: Scientific Underpinnings and Research Recommendations. Environ. Health Perspect 125, 163-169 (2017)
(4) P.A. Thompson, M. Khatami, C.J. Baglole, J. Sun, S. Harris, E.-Y Moon, F. Al-Mulla, R. Al-Temaimi, D. Brown, A. Colacci, C. Mondello, J. Raju, E. Ryan, J. Woodrick, I. Scovassi, N. Singh, M. Vaccari, R. Roy, S. Forte, L. Memeo, HK. Salem, A. Amedei, R.A. Hamid, L. Lowe, W.H. Bisson. Environmental Immune Disruptors, Inflammation and Cancer Risk. Carcinogenesis 36 Suppl 1:S232-53 (2015).
(5) P. Rajendran, A.I. Kidane, T.-W. Yu, W.-M. Dashwood, W.H. Bisson, C. Löhr, E. Ho, D.E. Williams, R.H. Dashwood. HDAC turnover, CtIP acetylation, and dysregulated DNA damage signaling in colon cancer cells treated with sulforaphane and related dietary isothiocyanates. Epigenetics 8, 612-623 (2013).

3) Aryl Hydrocarbon Receptor PAS-B domain homology models for drug design/discovery in cancer, metabolic disorders and inflammation

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor that regulates the expression of a diverse group of genes. During the last years, I developed computationally successful inter-species ''*ligand-guided optimized*'' homology models of the AHR ligand binding domain for the design and discovery of new ligands. (1-4) In addition, we identified for the first time, through molecular simulations, the structural switch between human AHR agonist and antagonist activity (4). Results obtained from these studies will guide future design and discovery approaches towards new AHR ligands in cancer, metabolic disorders and inflammation.

References cited

(1) Y Zhang, T Yan, D Sun, C Xie, Y Zheng, L Zhang, T Yagai, KW. Krausz, WH. Bisson, X Yang, FJ. Gonzalez.. Structure-activity relationships of the main bioactive constituents of Euodia ruticarpa on aryl hydrocarbon receptor activation and bile acid homeostasis. In Press Drug Metabolism & Disposition (2018).
(2) A.K. Ehrlich, J.M. Pennington, W.H. Bisson, S.K. Kolluri, N.I. Kerkvliet. TCDD, FICZ, and other high affinity AhR ligands dose-dependently determine the fate of CD4+ T cell differentiation. Toxicol. Sci. 161, 310-320 (2018).
(3) TD. Hubbard, W.H. Bisson, AP. Sullivan, A Sebastian, GH. Perry, NG. Jablonski, IA. Murray, GH. Perdew Divergent Ah Receptor Ligand Selectivity during Hominin Evolution. Mol Biol and Evol. 33, 2648-58 (2016)
(4) A Perkins , J. Phillips, N. Kerkvliet, R.L. Tanguay, G. Perdew, S.K. Kolluri, W.H. Bisson. Structural Switch between Agonist and Antagonist Bound Conformations for a Ligand-Optimized Model of the Human Aryl Hydrocarbon Receptor Ligand Binding Domain. Biology 3, 645-669 (2014).