BIOGRAPHICAL SKETCH

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NAME: George Blanck

eRA COMMONS USER NAME (credential, e.g., agency login): gblanck

POSITION TITLE: Professor

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
University of Pennsylvania	B.A.	5/1978	Biology
Columbia University	Ph.D.	1/1984	Molecular Biology
Harvard University	Postdoctoral	1/1989	HLA molecular genetics
University of Paris VI	Postdoctoral	1/1990	HLA molecular genetics

A. Personal Statement

Applicant is well suited to conduct this project for the following reasons: (a) Applicant has an extensive background in cancer biology, having been among the first to understand the connection between cell cycle signaling pathways and tumor cell immune functions, detailed below; and the first to make a peptidome connection with a protease expression level regulated by an HDAC inhibitor. (b) Applicant has more recently pioneered the use of genomics in immunoscoring with analyses of RNASeq for cancer resident T-cell and antigen presenting cell functions. This work may have represented the very first effort to use cancer specimen genomics data for understanding cells resident in the cancer microenvironment, other than the cancer cells themselves. (c) Applicant has more recently pioneered adaptive immune receptor genomics, identifying immune receptor re-arrangements and V(D)J usage in cancer and Alzheimer's specimens. Two other groups published similar work for RNASeq data, rather than exome data, around the same time as applicant's first work in this area, but applicant's work provides distinct opportunities in several manners. This work emphasizes applicant's success and comfort level with "big data" approaches and has been greatly extended in the published literature. (d) Applicant's recent cytoskeleton and ECM research has breathed new life into understanding the potential impact of cytoskeletal aberrations in cancer development, most importantly by appreciating the inevitability of mutation for these large coding regions and in development of algorithms for identifying cytoskeletal and ECM related driver mutations. (e) Applicant has long-standing, close connections with the Moffitt Cancer Center allowing translational opportunities. (f) Applicant has recently pioneered the role of proteases in making antigen available, particularly from mutant cytoskeleton and ECM proteins, allowing for important interdisciplinary questions regarding the impact of the immune system due to mutant cytoskeleton and ECM proteins, in normal and cancerous cells. (g) Finally, applicant's publication record indicates the very high level rapport with students, in conducting research projects, that facilitates successful outcomes.

B. Positions, Scientific Appointments, and Honors

2002-present Professor (tenured), Molecular Medicine, University of South Florida, Morsani College of Medicine, Tampa, Florida

1995-2002 Associate Professor (tenured), Molecular Medicine, (formerly Department of Biochemistry and Molecular Biology), University of South Florida, Morsani College of Medicine, Tampa, Florida

1990-1995 Assistant Professor, Molecular Medicine, (formerly Department of Biochemistry and Molecular Biology), University of South Florida, Morsani College of Medicine, Tampa, Florida

Other Experience and Professional Memberships

Service as a manuscript reviewer for many scientific journals, reviewer for numerous grant agencies; and as job-applicant reviewer for faculty hiring, promotion and tenure processes in the US and internationally; recent service as Associate Editor for Gene and Cancer Cell International.

Member, Immunology Program, H. Lee Moffitt Cancer Center and Research Institute on the campus of USF, Tampa, Florida

Elected to membership in ASBMB and AII

Honors and Awards

Applicant has been the subject of numerous “acknowledgements of success” and has provided service as a result of large numbers of requests, ranging from manuscript reviews, to grant reviews and to faculty appointment reviews, for institutions and organizations in the U.S. and around the world. The vast majority of applicant coauthors on articles are students who have moved on in science or medicine; or colleagues who have had positive scientific experiences in conducting collaborative projects. These students and colleagues are applicant’s primary record of “honors and awards”, in addition to the publications themselves, which represent the highest possible standards in terms of responsible, honest presentation and vetting of data, at a time when overly rapidly published work can substitute for accuracy and careful treatment of material.

C. Contributions to Science

1. Early contributions as a postdoctoral fellow to molecular organization of the MHCII regions, prior to large scale cloning and massively parallel sequencing, particularly including development of a novel chromosome walking technology that led to breakthroughs in the discovery of important genes, e.g., the TAP and LMP genes in the MHC regions.
    a. Blanck G, Strominger JL. Molecular organization of the DQ subregion (DO-DX-DV-DQ) of the human MHC and its evolutionary implications. Journal of immunology. 1988;141(5):1734-7. PubMed PMID: 3411129.
    b. Spies T, Blanck G, Bresnahan M, Sands J, Strominger JL. A new cluster of genes within the human major histocompatibility complex. Science. 1989;243(4888):214-7. PubMed PMID: 2911734.
    c. Spies T, Bresnahan M, Bahram S, Arnold D, Blanck G, Mellins E, Pious D, DeMars R. A gene in the human major histocompatibility complex class II region controlling the class I antigen presentation pathway. Nature. 1990;348(6303):744-7. doi: 10.1038/348744a0. PubMed PMID: 2259384.

2. Head of lab and research group, thereby representing one of three research groups, to recognize and describe in high profile publications the degeneracy of cancer signaling pathways, particularly the role of what was considered exclusively a tumor suppressor, cell cycle regulatory protein, RB1, in the regulation of immune function genes. The other two groups were headed by Drs. Stark (E1A and interferon) and Taniguchi (IRF proteins and growth control). This work included the initial use of HDAC inhibitors to regulate immune function genes, now a high priority for the clinic.
    a. Lu Y, Ussery GD, Muncaster MM, Gallie BL, Blanck G. Evidence for retinoblastoma protein (RB) dependent and independent IFN-gamma responses: RB coordinately rescues IFN-gamma induction of MHC class II gene transcription in noninducible breast carcinoma cells. Oncogene. 1994;9(4):1015-9. PubMed PMID: 8134104.

b. Berry DE, Lu Y, Schmidt B, Fallon PG, O'Connell C, Hu SX, Xu HJ, Blanck G. Retinoblastoma protein inhibits IFN-gamma induced apoptosis. Oncogene. 1996;12(8):1809-19. PubMed PMID: 8622902.

c. Osborne A, Zhang H, Yang WM, Seto E, Blanck G. Histone deacetylase activity represses gamma interferon-inducible HLA-DR gene expression following the establishment of a DNase I-hypersensitive chromatin conformation. Molecular and cellular biology. 2001;21(19):6495-506. PubMed PMID: 11533238; PubMed Central PMCID: PMC99796.

d. Osborne AR, Zhang H, Fejer G, Palubin KM, Niesen MI, Blanck G. Oct-1 maintains an intermediate, stable state of HLA-DRA promoter repression in Rb-defective cells: an Oct-1-containing repressosome that prevents NF-Y binding to the HLA-DRA promoter. The Journal of biological chemistry. 2004;279(28):28911-9. doi: 10.1074/jbc.M403118200. PubMed PMID: 15105429.

3. Head of lab and research group to first and essentially solely appreciate that sequential mutations in cancer, rather than exclusively following an "acquisition of function" pathway as proposed by others, are largely due to probabilistic aspects of the chance of larger genes being "hit" by mutation or rearrangements as opposed to smaller genes. Thus, despite continuing misunderstandings to the contrary, the largest factor in sequential mutations is gene or coding region size. Large genes are generally mutated and inactivated first, smaller genes and smaller targets, such as particular codons in oncoproteins, are mutated later. This line of understanding of cancer biology has shed new light on cytoskeletal and extra-cellular matrix (ECM) structural protein coding region mutations, due to the commonly large size of these coding regions and due to the historical, though often not fully appreciated (or resolved) role of the cytoskeleton and ECM in cancer development. This realization has also led our group to extensively, though not solely, develop ideas related to signaling pathway degeneracy in cancer, thereby furthering the understanding of rapid pathways to designer drug resistance in cancer. And, the roles of probability and gene size are likely to have implications for "watchful waiting" versus treat aggressively, in the sense that, if the small, less probable target, such as an oncoprotein codon, has been hit, the (other required) larger target will follow with high frequency.

   a. Narsing S, Jelsovsky Z, Mbah A, Blanck G. Genes that contribute to cancer fusion genes are large and evolutionarily conserved. Cancer genetics and cytogenetics. 2009;191(2):78-84. doi: 10.1016/j.cancergencyto.2009.02.004. PubMed PMID: 19446742.

   b. Long K, Abuelenen T, Pava L, Bastille M, Blanck G. Size matters: sequential mutations in tumorigenesis may reflect the stochastic effect of mutagen target sizes. Genes & cancer. 2011;2(10):927-31. doi: 10.1177/1947601911436200. PubMed PMID: 22701759; PubMed Central PMCID: PMC3374629.

   c. Parry ML, Ramsamooj M, Blanck G. Big genes are big mutagen targets: A connection to cancerous, spherical cells? Cancer letters. 2015;356(2 Pt B):479-82. doi: 10.1016/j.canlet.2014.09.044. PubMed PMID: 25451318.

   d. Ford SA, Blanck G. Signal persistence and amplification in cancer development and possible, related opportunities for novel therapies. Biochimica et biophysica acta. 2014;1855(1):18-23. doi: 10.1016/j.bbcan.2014.11.001. PubMed PMID: 25450826.

4. Head of lab and research group which first indicated the role of small molecules that regulate protease expression and activity, in the regulation of the HLA-DR peptidome. More importantly, this regulation occurs in a predictable manner, i.e., based on the specificity of the protease being up-regulated by the small molecule. The small molecules include chemotherapy drugs that may affect immunotherapy, particularly with regard to protease sensitivity to particular vaccines. Recent follow up with new cancer immunoscoring strategies based on MHCII and TcR expression; and based on detection of rearranged VJ segments in conventional exome files, with such rearrangements representing tumor infiltrating lymphocytes (TILs).

   a. Callahan BM, Yavorski JM, Tu YN, Tong WL, Kinskey JC, Clark KR, Fawcett TJ, Blanck G. T-cell receptor-beta V and J usage, in combination with particular HLA class I and class II alleles, correlates with cancer survival patterns. Cancer immunology, immunotherapy : CII. 2018;67(6):885-92. doi: 10.1007/s00262-018-2139-7. PubMed PMID: 29508024.

   b. Tong WL, Callahan BM, Tu YN, Zaman S, Chobrutskiy BI, Blanck G. Immune receptor recombinations from breast cancer exome files, independently and in combination with specific HLA alleles, correlate with better survival rates. Breast cancer research and treatment. 2018. doi: 10.1007/s10549-018-4961-1. PubMed PMID: 30229447.

   c. B.I. Chobrutskiy, M. Yeagley, P. Tipping, S. Zaman, A. Diviney, D.N. Patel, S. Falasiri, V.N.

Uversky and G. Blanck, Chemical complementarity between immune receptor CDR3s and IDH1 mutants correlates with increased survival for lower grade glioma, Oncogene (2019).

d. B.I. Chobrutskiy, M. Yeagley, A. Diviney, S. Zaman, E.C. Gozlan, P. Tipping, D.M. Koohestani, A.M. Roca and G. Blanck, A scoring system for the electrostatic complementarities of T-cell receptors and cancer-mutant amino acids: Multi-cancer analyses of associated survival rates, Immunology (2019).

5. Head of lab and research group specifically addressing mutant cytoskeletal and ECM proteins in cancer, with the following basic hypotheses and discoveries: (a) Due to polymeric nature of cytoskeletal and ECM structures, mutant subunits have a high probability of corrupting these structures in a dominant negative fashion, as is the case on a macroscopic scale with osteogenesis imperfecta. (b) Cytoskeletal and ECM mutations are candidate cancer drivers, based on statistical algorithms, a result needing more confirmation in the lab. (c) Specific sets of mutant cytoskeketal and ECM proteins correlate with a poor outcome in melanoma. (d) Certain cytoskeletal and ECM proteins are protected from mutagenesis, likely consistent with previously described roles for both a disrupted and functioning (in cell motility) cytoskeleton in cancer. (e) The cytoskelelatal and ECM set commonly mutated in cancer datasets is also commonly mutated in gametogenesis, not surprizing due to the large coding regions.

   a. Segarra DT, Yavorski JM, Blanck G. Protected cytoskeletal-related proteins: Towards a resolution of contradictions regarding the role of the cytoskeleton in cancer. Biomed Rep. 2017;7(2):163-8. doi: 10.3892/br.2017.940. PubMed PMID: 28804630; PubMed Central PMCID: PMCPMC5526129.

   b. Fawcett TJ, Parry ML, Blanck G. A Novel Approach to Evaluating Cancer Driver Gene Mutation Densities: Cytoskeleton-related Gene Candidates. Cancer genomics & proteomics. 2015;12(6):283-90. PubMed PMID: 26543077.

   c. Callahan BM, Patel JS, Fawcett TJ, Blanck G. Cytoskeleton and ECM tumor mutant peptides: Increased protease sensitivities and potential consequences for the HLA class I mutant epitope reservoir. International journal of cancer Journal international du cancer. 2018;142(5):988-98. doi: 10.1002/ijc.31111. PubMed PMID: 29047110.

   d. Falasiri S, Rahman T, Tu YN, Fawcett TJ, Blanck G. Germline cytoskeletal and extra-cellular matrix-related single nucleotide variations associated with distinct cancer survival rates. Gene. 2018;669:91-8. doi: 10.1016/j.gene.2018.05.037. PubMed PMID: 29778426.

Complete List of Published Work, including many more recent articles, My Bibliography:
http://www.ncbi.nlm.nih.gov/pubmed?term=blanck+g&cmd=DetailsSearch

(Note: a small number of early publications represent a different “blanck g” in pubmed, a psychologist; and one 2020 “Blanck G” publication represents a French scientist, not this applicant.)