BIOGRAPHICAL SKETCH

Provide the following information for the Senior/key personnel and other significant contributors.
Follow this format for each person. **DO NOT EXCEED FIVE PAGES.**

NAME: Zamboni, William Christopher

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

POSITION TITLE: Associate Professor, UNC Eshelman School of Pharmacy

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 Pittsburgh School of Pharmacy	B.S.	05/1992	Pharmacy
University of Pittsburgh School of Pharmacy	Pharm.D.	05/1994	Pharmacy
National Institute of Health, Bethesda, MD	Residency	07/1995	Pharmacy
St. Jude Children's Res. Hosp., Memphis,TN	Fellowship	12/1997	Pharmaceutical Sci.
University of Pittsburgh School of Pharmacy	Ph.D.	05/2005	Pharmacology / Pharmaceutical Sci.

A. Personal Statement

My research interests focus on the application of pharmacokinetic, pharmacodynamic, and pharmacogenetic principles in the optimization of the chemotherapeutic treatment of cancer. My research focuses on the development and characterization of nanoparticle and carrier-mediated agents (CMAs). I worked in this area for >15 years and have worked on the development of >80 different nanoparticle and CMAs. A focus of my research is evaluating the bi-directional interaction between nanoparticle and carrier-mediated agents and biologics and the mononuclear phagocyte system (MPS) and evaluating the factors affecting the tumor and tissue delivery of these agents. As part of this studies we have developed novel methods and technologies to evaluating MPS function in blood and analytical platforms to evaluate monoclonal antibodies in serum and PBMCs. I have the ideal expertise and motivation necessary to successfully carry out the proposed work and I am excited to collaborate on this grant. These studies will be performed as part of my role as Director of the Analytical Chemistry and Pharmacology Core (ACPC) Labs in the UNC Lineberger Comprehensive Cancer Center (LCCC) and UNC Eshelman School of Pharmacy. The ACPC consists of the Translational Oncology and Nanoparticle Drug Development ($TOND_2I$) Lab. The UNC $TOND_2I$ Lab has all of the expertise and resources to perform the studies outlined in the grant proposal.

The goal of this proposal is to evaluate biomarkers of MPS Fc-gamma-receptors (FcγRs) and chemokines (Aim 1) as predictors of the PBMC PK (Aim 2), standard serum PK of anetumab ravtansine and PD (efficacy and toxicity) as part of three clinical trials of anetumab ravtansine alone and in combination with other antibodies and immune modulators. My experience in drug development, pharmacologic and biomarker studies of CMAs and the MPS, and being a member of the NCI CTEP anetumab ravtansine project team are ideally suited for me to be the PI on this research grant.

B. Positions and Honors

Positions:

1997–1998 Assistant Professor, Dept. of Pharmacy Practice and Science, School of Pharmacy at University of Maryland, Assistant Member, Program of Developmental Therapeutics, University of Maryland Cancer Center

1998–2008 Assistant Member, Molecular Therapeutics Drug Discovery Program, University of Pittsburgh Cancer Institute, University of Pittsburgh Health System, Pittsburgh, PA

1998–2008 Assistant Professor, Dept. of Pharmaceutical Sciences, School of Pharmacy and Assistant Professor, Dept. of Medicine, School of Medicine at University of Pittsburgh; Assistant Member of Program of Molecular Therapeutics, University of Pittsburgh Cancer Institute (UPCI)

2008–present Associate Professor, Division of Pharmacotherapy and Experimental Therapeutics, School of Pharmacy, University of North Carolina, Chapel Hill, NC

2008–present Associate Member, Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, NC

2008–present Director, UNC Translational Oncology and Nanoparticle Drug Development ($TOND_2I$) Lab, School of Pharmacy and UNC Lineberger Comprehensive Cancer Center, Univ. of North Carolina, Chapel Hill, NC

2008–present Member, Institute for Pharmacogenomics and Individualized Therapy, University of North Carolina, Chapel Hill, NC

2008–present Member, Carolina Center of Cancer Nanotechnology Excellence, University of North Carolina, Chapel Hill, NC

Other Experience and Professional Memberships

1998 - present American Society of Clinical Oncology, Active Member

1998 - present American Association for Cancer Research, Active Member

2005 - present Gynecologic Oncology Group, Phase I and Pharmacology Committees, Member

2008 - present National Cancer Institute Development Therapeutics Study Section

Honors

2015 Triangle Business Journal - BDO Life Sciences Awards, Outstanding Research University Biotech Company

2001 ACCP / Aventis Oncology Fellowship

1999 ACCP / Rhone-Poulenc Rorer Oncology Research Award

1999 Phi Delta Chi Alumni of the Year

1997&1996 ASCO Merit Award

1994 Summa Cum Laude, Doctor of Pharmacy Program, University of Pittsburgh

C. Contributions to Science

Evaluation of the Bi-directional Interaction between Nanoparticles (NP) and the Mononuclear Phagocyte System.

A commonly held theory was that the mononuclear phagocyte system (MPS), previously called the reticuloendothelial system (RES), was the primary clearance pathway for nanoparticle (NP) and carrier mediated agents (CMA). The MPS consists of phagocytic cells of the immune system such as monocytes, dendritic cells and macrophages. Our research group was one of the first to evaluate mechanisms associated with the interactions between NPs/CMAs and the MPS in animal models and in patients. As part of these studies we developed phenotypic probes of the function of MPS cells in blood (e.g. monocytes) which predicted the clearance of NP in preclinical animal models and patients. We also identified that there is a bi-directional interaction between NPs/CMAs and the MPS, where MPS cells takeup and clear NP which then alters the funcation of the MPS cells and may also result in cytotoxicity to the MPS cells. A few selected publications are provided below which specifically highlight my contribution to this area:

1. Caron WP, Lay JC, Fong AM, La-Beck NM, Kumar P, Newman SE, Zamboni BA, Crona DJ, Clarke-Pearson DL, Brewster WR, Le LV, Bae-Jump V, Gehrig PA, **Zamboni WC**. Translational studies of phenotypic probes of the mononuclear phagocyte system and nanosomal pharmacology. J of Pharmacol Exp Ther. 2013;347(3):599-606. PMID: 24042160.
2. **Zamboni WC**, Maruca L, Edwards RP, Strychor S, Lee S, Ahn SK, Friedland DM, Ramalingam S, Ramanathan RK. Bi-Directional pharmacodynamic interaction between pegylated liposomal CKD-602 (S-

CKD602) and monocytes in patients with refractory solid tumors. J of Liposome Research, 21(2);158-65:2011. PubMed PMID: 20626314

3. Yang Q, Jones SW, Parker CL, **Zamboni WC**, Bear JE, Lai SK. Evading immune cells uptake and clearance requires PEG grafting at densities substantially exceeding the minimum for brush conformation. Mol. Pharmaceutics. 2014; 11(4): 1250-1258. PubMed PMID: 24521246
4. Song G, Tarrant TK, Barrow DA, Santos CM, White TL, Timoschenko RG, Hanna SK, Bae-Jump V, Gehrig P, **Zamboni WC**. Relationship between chemokine ligands and pharmacokinetics and pharmacodynamics of PEGylated liposomal doxorubicin. Nanomedicine: Nanotechnology, Biology and Medicine, In press (July 2015).

Evaluation of the Factors that Affect the Pharmacokinetics (PK) of Nanoparticle (NP) Agents.

The PK of NP is dependent upon the carrier and not the encapsulated drug until the drug is released from the carrier. The drug that remains encapsulated within liposomes or NP is an inactive prodrug, thus the drug must be released from the carrier to be active. The PK of these agents is complex, and detailed studies must be performed to evaluate the disposition of the NP encapsulated and the released forms. We have developed unique methods to evaluate the PK of NP encapsulated and released drug in plasma for several NPs. Our studies suggest that there is a high and clinically relevant interpatient variable in the PK of NPs and that the PK variability is 10-fold greater than reported for small molecule drugs. We performed a meta-analysis comparing the interpatient PK variability of liposomal and small molecule formulations of the same anticancer agents which confirmed the significantly higher PK variability of NPs compared with small molecule drugs. We were also the first group to report that PK variability of NPs and CMAs is related to a patient's age, gender, body composition, type of cancer, location of tumor(s), MPS function, MPS mediators (chemokines and hormones) and other concommitantly administered medications. We have also identified that these factors have significantly impacted the translational development and clinical ultility of thes agents. A few selected publications are provided below which specifically highlight my contribution to this area:

1. Zamboni WC, Maruca L, Strychor S, Zamboni BA, Ramalingam S, Friedland DM, Edwards RP, Stoller RG, Belani CP, Ramanathan RK. Pharmacokinetic study of pegylated liposomal CKD-602 (S-CKD602) in patients with solid tumors. Clinical Pharmacol Ther. 86(5);519-26:2010. PubMed PMCID: PMC3428134.
2. La-Beck NM, Zamboni BA, Gabizon A, Sidone BJ*, Edwards RP, Tzemach D, Schmeeda H, Sapir R, Amantea M, Zamboni WC. Factors affecting the pharmacokinetics of pegylated liposomal doxorubicin in patients. Cancer Chemotherapy Pharmacol. 69;43-50:2012. PubMed PMID: 21590446.
3. Schell RF, Sidone BJ, Caron WP, Walsh MD, White TF, Zamboni BA, Ramanathan RK, Zamboni WC. Meta-analysis of study design issues and pharmacokinetic variability of liposomal and non-liposomal anticancer agents in patients. Nanomedicine. 2014;10(1):109-117. PMID: 23891988.
4. Caron WP, Morgan KP, Zamboni BA, Zamboni WC. A review of study designs and outcomes of phase I clinical studies of nanoparticle agents compared with small molecule anticancer agents. Clinical Cancer Res. 2013;19(12):3309-15. PMID: 23620407.
5. Zamboni WC, Torchilin V, Patri A, Hrkach J, Lee R, Stern S, Nel A, Malghan S, Panaro N, Grodzinski P. Best Practices in Cancer Nanotechnology: Perspectives from NCI Nanotechnology Alliance. Clinical Cancer Research. Clin Cancer Res. 18(12);3229-41:2012. PubMed Central: PMC3916007.

Evaluation of the Factors that Affect the Tumor Delivery of Nanoparticle (NP) and Standard Drugs.

In theory, enhanced permeability of the tumor vasculature allows NPs to enter the tumor interstitial space, while suppressed lymphatic filtration allows them to stay there. This phenomenon, termed the Enhanced Permeability and Retention (EPR) effect, may be exploited by NPs to deliver drugs to tumors. Progress in developing effective NPs using this approach has been hampered by heterogeneity of EPR effect in different tumors, lack of information on factors that influence EPR and limited data from preclinical tumor models and patients on this mechanism. In addition, cancer cells in tumors are surrounded by a complex microenvironment comprised of endothelial cells of the blood and lymphatic circulation, stromal fibroblasts, collagen, cells of the mononuclear phagocyte system (MPS) and other immune cells that may be associated with the variability in EPR and tumor delivery of NPs. We have evaluated these factors in a series of tumor models. Our results suggest that the ability of NPs to enter tumors by EPR or other factors is highly variable across tumor types and thus all solid tumors may not be conducive for NP delivery and treatment. We have also evaluated how these factors affect NPs of different sizes and shapes and how these factors translate from preclinical tumor models

and to tumors in patients. A few selected publications are provided below, which specifically highlight my contribution to this area:

1. **Zamboni WC**, Stewart CF, Thompson J, Santana V, Cheshire PJ, Richmond LB, Lui X, Houghton JA, Houghton PJ. The Relationship between Topotecan Systemic Exposure and Tumor Response in Human Neuroblastoma Xenografts. Journal of National Cancer Institute, 90(7):505-511, 1998. PubMed PMID: 9539245.
2. Song G, Darr DB, Santos CM, Ross M, Valdivia A, Jordan JL, Midkiff BR, Cohen S, Feinberg, Miller CR, Tarrant TK, Rogers AB, Dudley AC, Perou CM, **Zamboni WC**. Effects of tumor microenviroment on nanoparticle disposition and efficacy in triple negative breast cancer. Clinical Cancer Res, 2014;20(23):6083-95. PMID: 25231403.
3. Combest AJ, Roberts PJ, Dillon PJ, Habibi S, Eiseman JL, Strychor s, Hanna SK, Muller M, Brunner M, Ross CM, Sharpless NE, **Zamboni WC**. Genetically engineered cancer models, but not xenografts, faithfully predict anti-cancer drug exposure in melanoma. Oncologist 17(10);1303-16:2012. PubMed PMCID: PMC3481896.
4. **Zamboni WC**, Eiseman JL, Strychor S, Rice PM, Joseph E, Zamboni BA, Donnelly MK, Shurer J, Parise RA, Tonda ME, Yu NY, Engber C, Basse PH. Tumor disposition of pegylated liposomal CKD-602 (S-CKD602) and the reticuloendothelial system in preclinical tumor models. J of Liposome Research 21(1);70-80:2010. PubMed PMID: 20528623.
5. Chu KS, Hasan W, Rawal S, Walsh MD, Enlow EM, Luft JC, Bridges AS, Coleman J, Napier ME, **Zamboni WC**, DeSimone JM. Plasma, tumor and tissue pharmacokinetics of docetaxel delivered via nanoparticles of different sizes and shapes in mice bearing SKOV-3 human ovarian xenograft. Nanomedicine. 2013;9(5):686-93. PMID: 23219874. NIHMSID: NIHMS433583.
6. Prabhakar U, Maeda H, Jain R, Sevick-Muraca E, **Zamboni W**, Barry S, Gabizon A, Grodzinski P, Blakey D. Challenges and key considerations of the enhanced permeability and retention effect (EPR) and nanomedicine drug delivery in oncology. Cancer Research. 2013;73(8):2412-7. PubMed Central: PMC3916009.

Enhanced Delivery of Drugs to the Brain and Brain Tumors via the use of Nanoparticle (NP) Agents.

The development of chemotherapeutic agents to effectively treat solid tumors within or outside of the central nervous system depends, in part, on the ability of these agents to achieve cytotoxic drug exposure within the tumor(s). We were one of the first groups to identify that encapsulating common anti-cancer agents into NP delivery systems, particularly liposomes, provides a promising approach to enhance central nervous system delivery and delivery to intracranial tumors compared with small molecule drugs. In addition, our studies suggest that a wide range of NP and carrier-mediated agents (CMAs) are able to deliver drugs to intracranial tumors and thus these results may have a far reaching impact for all NPs and intracranial tumors. We are currently evaluating the mechanism(s) of enhanced delivery of these agents to intracranial tumors. A few selected publications are provided below, which specifically highlight my contribution to this area:

1. **Zamboni WC**, Gajjar AJ, Houghton PJ, Mandrell TD, Einhaus SL, Danks MK, Rogers WP, Heideman RL, Stewart CF. A topotecan 4-hour intravenous infusion achieves cytotoxic exposure throughout the neuraxis in the nonhuman primate model: implications for the treatment of children with metastatic medulloblastoma. Clinical Cancer Research, 4:2537-2544, 1998. PubMed PMID: 9796988.
2. **Zamboni WC**, Strychor S, Joseph E, Walsh DR, Zamboni BA, Parise RA, Tonda ME, Yu NY, Engbers C, Eiseman JL. Plasma, tumor, and tissue disposition of STEALTH liposomal CKD-602 (S-CKD602) and nonliposomal CKD-602 in mice bearing A375 human melanoma xenografts. Clin Cancer Res. 2007;13(23):7217-23. PubMed PMID: 18056203. PubMed PMID: 18056203.
3. Anders CK, Adamo B, Rawal S, Walsh MD, Karginova O, Darr D, Deal AM, Santos C, Bash R, Hanna SK, Carey, LA, Miller CR, Sharpless N, Perou CM, **Zamboni WC**. Efficacy and pharmacokinetic disposition of PEGylated liposomal doxorubicin compared with non-liposomal doxorubicin in an intracranial breast cancer murine model. PLOS One. 2013;8(5):1-10. PMID: PMC3641071.
4. Walsh MD, Hanna SK, Sen J, Rawal S, Cabral CB, Yurkovetskiy AV, Fram RJ, Lowinger TB, **Zamboni WC**. Pharmacokinetics and antitumor efficacy of XMT-1001, a novel, polymeric topoisomerase I inhibitor, in mice bearing HT-29 human colon carcinoma xenografts. Clin Cancer Res. 2012;18(9):2591-602. PubMed PMID: 22392910. PubMed PMID: 22392910.