

BIOGRAPHICAL SKETCH

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NAME: Nathan I. Nicely

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

POSITION TITLE: Research Assistant 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 Virginia, Charlottesville, VA	B.A.	05/1995	Environmental Sciences
North Carolina State University, Raleigh, NC	B.S.	05/2000	Molecular & Structural Biochemistry
North Carolina State University, Raleigh, NC	Ph.D.	May 2005	Molecular & Structural Biochemistry
Wake Forest University, Winston-Salem, NC	Postdoc	Oct 2006	Biochemistry

A. Personal Statement

I am the Director of the University of North Carolina at Chapel Hill Protein Expression & Purification (PEP) and Macromolecular Crystallography (MX) core facilities. I have over 11 years professional experience producing a variety of proteins not just for structural biology aims, but also for immunology, enzymology, molecular biology, and other purposes. The PEP core at UNC-CH is a vital campus resource, supporting PIs in several different departments. We also have national recognition and generate over half our annual revenue from external clients. I believe my education, training, and work experience demonstrate the relevant expertise and leadership necessary to successfully guide the protein production support needs that are proposed as a part of this grant. I actively participate in providing services to users and participating as needed in specific research aims. I point to several high-impact publications that used materials generated in my core facility as well as other works that demonstrate my engagement in science and my productivity:

1. Bushey R, Moody MA, et al. (2016) A therapeutic antibody for cancer, derived from single human B cells. *Cell Reports*, 15(7): 1505-1513. PMID 27160908. PMCID PMC4871760.
2. Shwab E, Juvvadi P, Waitt G, Soderblom E, Moseley M, **Nicely NI**, and Steinbach WJ (2017) Phosphorylation of *Aspergillus fumigatus* PkaR Impacts Growth and Cell Wall Integrity by Mechanisms Divergent from Yeasts. *FEBS Letters* 591(22): 3730-3744. PMID 29067690. PMCID PMC5705279.
3. Hong L, Chen Y, et al. (2018) CD30-Redirected Chimeric Antigen Receptor T Cells Target CD30(+) and CD30(-) Embryonal Carcinoma via Antigen-Dependent and Fas/FasL Interactions. *Cancer Immunol Res*. 6(10):1274-1287. PMID: 30087115. PMCID TBD.
4. Martinez D, Tu J, et al. (2019) Maternal broadly neutralizing antibodies select for neutralization-resistant infant transmitted/founder HIV variants. *mBio* 11(2):e00176-20. PMID 32156815. PMCID PMC7064758.
5. Hou YJ, Okuda K, et al. (2020) SARS-CoV-2 reverse genetics reveals a variable infection gradient in the respiratory tract. *Cell* S0092-8674(20)30675-9. PMID 32526206. PMCID PMC7250779.

B. Positions and HonorsPositions and Employment

Activity/Occupation	Start Date	End Date	Field	Institution/Company
Research Asst Prof	07/2018	Present	Structural Biochemistry	University of North Carolina
Assistant Professor	07/2017	07/2018	Structural Biochemistry	Duke Human Vaccine Institute

Scientific Research Laboratory Manager	12/2008	06/2017	Structural Biochemistry	Duke Human Vaccine Institute
Research Scientist I	2/2008	11/2008	Structural Biochemistry	Duke Human Vaccine Institute
Senior Research Software Developer	11/2006	12/2007	Scientific Research Computing	Renaissance Computing Institute (UNC)

Academic and Professional Honors

1998-2000 John B. Steele Scholarship, two consecutive years.
1999 Phi Beta Kappa NC State Chapter.
1999 Gamma Sigma Delta NC State Chapter.
1999 Summer research award at NIEHS Summers of Discovery.
2000 J. Fulton Lutz Senior Academic Achievement Award.
2000 Phi Kappa Phi Graduating Senior Award.
2000-2003 Graduate Assistantship in Areas of National Need (GAANN) fellowship.
2001 NCSU Professional Development Workshop, Chapel Hill, NC.
2000-2001 Preparing the Professoriate Program, NCSU, Raleigh, NC.
2001 Tove award for outstanding teaching.
2001 GAANN Minigrant competition in the amount of \$4000.
2001 Quantitative Structure Activity Relationships Gordon Conference, Tilton, NH.
2002 Oak Ridge Associated Universities Award - the 52nd Annual Meeting of the Nobel Laureates, Lindau, Germany.

C. Contributions to Science

1. My postdoctoral research focused on sporulation and virulence factors of *Bacillus anthracis*. The ability of anthrax to rapidly emerge from its spore state to a live bacteria is triggered by a few key processes, one of which includes the conversion of coenzyme A to coA-SH via a pathway spearheaded by a novel pantothenate kinase type III enzyme compared to that borne by other microbes. My research into the structure of the *Bacillus anthracis* pantothenate kinase type III (BaPanKIII) protein and studies of its activity explained how the type III enzyme was insensitive to feedback inhibition unlike type I and II enzymes. I showed that BaPanKIII was structurally and functionally different from other pantothenate kinase variants, thus could be exploited for inhibition by chemically synthesized compounds. With additional mentoring by a collaborator from the UK, we screened the enzyme against a library of such compounds and discovered a sugar-triazole-nucleoside compound that acted as an ATP mimetic for and inhibitor of BaPanKIII.

- a. Nicely NI, Parsonage D, et al. (2007) Structure of the type III pantothenate kinase from *Bacillus anthracis* at 2.0 Å resolution: implications for coenzyme A-dependent redox biology. *Biochemistry* 46(11): 3234-45. PMID 17323930. PMID PMC2613803.
- b. Rowan AS, Nicely NI, et al. (2009) Nucleoside triphosphate mimicry: A sugar triazolyl nucleoside as an ATP-competitive inhibitor of *B. anthracis* pantothenate kinase. *Org Biomol Chem*. 7(19): 4029-36. PMID 19763307. PMID PMC6074028.

2. In the field of HIV research, the RV144 vaccine trial established a beachhead in the challenge to develop a viable HIV-1 immunization strategy by showing a modest but measureable protective effect. We found that in RV144 responses, the human immune system preferred a germline precursor antibody with an L2 bearing a specific Asp-Glu motif prime for interaction with Lys169 on the HIV-1 gp120 V2 region, a noted site of immune pressure. Moreover we showed with that the maturation process then focuses the immune response by decreasing polyreactivity, decreasing flexibility, and increasing affinity for specific antigens. The trend is that antibody structure does not change significantly in going from germline precursor to mature antibody, rather that maturation improves local structural elements to be pre-configured for antigen recognition as well as increasing the number of specific antibody-antigen interactions. I showed this specifically to be the case with CH58, an antibody found in an RV144 vaccinee, by determining the crystal structure of its inferred, unmutated ancestor. The aforementioned Asp-Glu motif occurred on an L2 pre-conformed for germline for optimal interaction with the gp120 V2 region; in contrast, a secondary contact between V2 Lys169 and a residue from HCDR3 was a result of conformational selection (pre-configuration) with maturation. Moreover, we have shown that specific antibody-antigen contacts can be exploited to develop better-binding antigens for precursor antibodies.

- a. Martinez D, Vandergrift N, et al. (2017) Maternal binding and neutralizing IgG responses targeting the C terminal region of the V3 loop are predictive of reduced peripartum HIV-1 transmission risk. *Journal of Virology* 91(9):e02422-16. PMID 28202762. PMCID PMC5391478.
- b. Wiehe K, Nicely NI (equally contributing authors), et al. (2017) Immunodominance of antibody recognition of the HIV envelope V2 region in Ig-humanized mice (RE505-22). *The Journal of Immunology*, 198(3):1047-55. PMID 28011932. PMCID PMC5262538.
- c. Nicely NI, Wiehe K, et al. (2015) Structural analysis of the unmutated ancestor of the HIV-1 envelope V2 region antibody CH58 isolated from an RV144 vaccine efficacy trial vaccinee. *EBioMedicine* 2(7): 713-22 PMID 26288844. PMCID PMC4534707.
- d. Wiehe K, Easterhoff D, et al. (2014) Antibody light-chain-restricted recognition of the site of immune pressure in the RV144 HIV-1 vaccine trial is phylogenetically conserved. *Immunity* 41(6): 909-18. PMID 25526306 PMCID PMC4324565.
- e. Liao HX, Bonsignori M, et al. (2013) Vaccine induction of antibodies against a structurally heterogeneous site of immune pressure within HIV-1 envelope protein variable regions 1 and 2. *Immunity* 38(1):176-86. PMID 23313589. PMCID PMC3569735.
- f. Alam SM, Liao HX, et al. (2011) Differential reactivity of germ line allelic variants of a broadly neutralizing HIV-1 antibody to a gp41 fusion intermediate conformation. *J Virol.* 85(22):11725-31. PMID 21917975. PMCID PMC3209283.

3. Prior to my initiation into HIV research, the field had well established that the pre-fusion fold of the HIV-1 coat protein spike was a trimer of gp120-gp41 dimers embedded in the lipid membrane coating the virion. Even though the structural details were not known at the time, it was known that the protein retained its overall multimeric structure until triggered by association with CD4 on host cell surfaces to undergo a series of massive conformational changes resulting in loss of its head gp120 head grouping, then refolding of the gp41 proteins. The post-fusion conformation of the resulting gp41 trimer was well-characterized; however, folding of the protein mid-fusion was not (and still is not) well understood. Amid this landscape, it was also known that the majority of immune responses to vaccination with various HIV spike protein constructs yielded non-neutralizing antibodies. I determined the structure of one such non-neutralizing antibody, 13H11, which was isolated from a mouse immunized with a gp120-gp41 fusion protein construct. I also determined the structure of 13H11 in complex with a peptide bearing the antibody's epitope in the gp41 membrane-proximal external region (MPER). The structures clearly showed that 13H11 and antibodies like it bound the post-fusion conformation of gp41. Moreover 13H11 lacked a long, hydrophobic CDR like that of the known neutralizing antibodies 2F5 and 4E10, belying its inability to associate with viral membrane. Recent structural investigation of a Rhesus macaque clonal lineage producing anti-MPER antibodies showed that antibodies can exhibit neutralizing capability and bind a helical conformation of MPER only if they bear sufficient lipid reactivity. Additional work investigated an anti-gp41 antibody that bound to the gp41 immunodominant loop and showed this loop to be functionally conserved yet difficult to characterize among retroviruses.

- a. Nicely NI, Dennison SM, et al. (2010) Crystal structure of a non-neutralizing antibody to the HIV-1 gp41 membrane-proximal external region. *Nat Struct Mol Biol.* 17(12):1492-4. PMID 21076400. PMCID PMC6081738.
- b. Santra S, Tomaras GD, et al. (2015) Human Non-neutralizing HIV-1 Envelope Monoclonal Antibodies Limit the Number of Founder Viruses during SHIV Mucosal Infection in Rhesus Macaques. *PLoS Pathog.* 3;11(8):e1005042. PMID 26237403. PMCID PMC4523205.
- c. Zhang R, Verkoczy L, et al. (2016) Initiation of HIV envelope gp41 neutralizing B cell lineages. *Science Translational Medicine* 8(336):336ra62. PMID 27122615. PMCID PMC5006673.
- d. Williams L, Ofek G, et al. (2016) Potent and Broad HIV Neutralizing Antibodies in Memory B Cells and Plasma. *Science Immunology* 2(7): eaa2200. PMID 28783671. PMCID PMC5905719.

4. Broadly neutralizing antibody responses to HIV-1 infection are rare, and their production is subject to tolerance controls. The basis for such auto-immune responses was not well understood. We identified sources of auto-immune recognition by broadly neutralizing HIV antibodies of interest, the most significant case being that the essential enzyme kynureninase presents the same motif as the HIV protein gp41 that 2F5 recognizes as its core epitope (Figure 3). Comparative study of human kynureninase with a variant found in opossums which bears an EKW motif instead of the 2F5-recognized DKW showed definitively that 2F5 recognizes KYNU through the DKW motif shared with HIV-1 gp41. These findings have significant repercussions in that there may be natural, as-yet unidentified human kynureninase variants that retain enzymatic function yet do not present the 2F5 epitope; and that HIV-1 vaccination strategies may be developed to rely on selection of naïve B cells for those that do not react with known self antigens. My role in this body of work was to identify the location of probable interaction for 2F5 with kynureninase and other antibody-ligand pairings, and to develop experiments with the express intent of testing those binding rationales.

- a. Liu M, Yang G, et al. (2015) Polyreactivity and autoreactivity among HIV-1 antibodies. *J Virol.* 89(1):784-98. PMID 25355869. PMCID PMC4301171.
- b. Yang G, Holl TM, et al. (2013) Identification of autoantigens recognized by the 2F5 and 4E10 broadly neutralizing HIV-1 antibodies. *J Exp Med.* 210(2):241-56. PMID 23359068. PMCID PMC3570098.

5. The induction of broadly neutralizing antibody responses to immunization with HIV-1 Env components is the primary goal of the field. The extraordinary structural and chemical diversity of Env isotypes euphemistically and literally makes it a moving target. We have isolated and characterized several neutralizing monoclonal antibodies to infection or vaccination, detailing the ways in which antibodies interact with their protein or oligosaccharide antigens. We have also studied the differential presentation of such antibody epitopes by HIV-1 Env isoforms and glycoforms. My role has been to generate and produce the requisite proteins, glycoproteins, and peptides, and to determine and analyze the crystal structures of antibody-antigen complexes.

- a. Williams WB, Zhang J, Jiang C, **Nicely NI (equally contributing author)**, et al. (2017) Initiation of Neutralizing B Cell Lineages with Sequential Envelope Immunizations. *Nature Communications* 8(1): 1732. PMID 29170366. PMCID PMC5701043.
- b. Go E, Ding H, et al. (2017) Glycosylation benchmark profile for HIV-1 envelope glycoprotein production based on eleven Env trimers. *Journal of Virology* 91(9):e02428-16. PMID 28202756. PMCID PMC5391476.
- c. Saunders K, **Nicely NI**, et al. (2017) Vaccine elicitation of high mannose-dependent neutralizing antibodies against the V3-glycan broadly neutralizing epitope in nonhuman primates. *Cell Reports* 18(9):2175-2188. PMID 28249163. PMCID PMC5408352.
- d. Williams LD, Ofek G, et al. (2017) Potent and Broad HIV Neutralizing Antibodies in Memory B Cells and Plasma. *Science Immunology* 2(7):eaal2200. PMID 28783671. PMCID PMC5905719.
- e. Martinez D, Tu J, et al. (2019) Maternal broadly neutralizing antibodies select for neutralization-resistant infant transmitted/founder HIV variants. *mBio* 11(2):e00176-20. PMID 32156815. PMCID PMC7064758.
- f. Williams WB, Meyerhoff RR, et al. (2020) Fab-dimerized glycan-reactive antibodies neutralize HIV and are prevalent in humans and rhesus macaques. *Science*. In press. PMID TBD. PMCID TBD.

A full list of my published work can be found at [SciENcv*](#) or by searching pubmed.gov for 'Nicely NI [au]' or 'Nicely N [au].'

*<http://www.ncbi.nlm.nih.gov/sites/myncbi/nathan.nicely.1/bibliography/41127621/public/?sort=date&direction=descending>