# *Curriculum vitae*

## Benjamin P. Brown, MD, PhD

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### Education

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| 2024 - Present | Assistant Professor<br>Department of Pharmacology<br>Center for Applied AI in Protein Dynamics<br>Vanderbilt University School of Medicine Basic Sciences |
| 2022 – 2024 | Research Assistant Professor of Chemistry<br>Vanderbilt University |
| 2017 – 2022 | PhD in Chemical and Physical Biology<br>Vanderbilt University<br>Thesis Advisor: Jens Meiler, Ph.D.<br>Dissertation defended: 03/28/2022 |
| 2015 – 2023 | MD – PhD Candidate<br>Medical Scientist Training Program<br>Vanderbilt University School of Medicine |
| 2011 – 2015 | BSc in Chemistry (ACS), Neuroscience (3.98 GPA)<br>Graduated with Honors: Summa Cum Laude<br>Baldwin Wallace University, Berea, OH |

### Statement of Research Interests

I am developing a research program that integrates emerging techniques in artificial intelligence (AI) with traditional methods in informatics and biophysics for small molecule computer-aided drug discovery (CADD) and biomolecular design. In particular, we are interested in modeling, designing, and pharmacologically controlling protein dynamics using computer simulation. We apply our own methods in combination with other computational tools and in collaboration with experimental scientists to address fundamental biological problems in substance abuse and precision oncology. Specifically, we are working to develop mu-opioid receptor (μOR) partial agonists with selective recruitment of G-protein subtypes and to delineate the structural and dynamical basis of μOR engagement with different G-protein isoforms. Further, we perform simulations to understand and predict the effects of EGFR oncogenic mutations on conformational dynamics and measure how these changes alter intermolecular interactions with signaling partners and therapeutic agents. With respect to the development of methods, we are highly interested in developing and deploying AI for small molecule hit identification, pharmacokinetic liability predictions, and protein conformational sampling.

**Research and Technical Experience**

Computer-aided drug discovery (CADD)

- Software platforms: BioChemical Library (BCL), Rosetta, MOE
- Python packages: PyTorch, RDKit, EquiBind, DiffDock (and related packages)
- Methods: quantitative structure activity relationship (QSAR) modeling, protein-ligand docking, *in silico* small molecule drug design, *in silico* peptide design, MD simulations (see below)

Programming and Scripting

- Languages: C++, Python, Shell script
- BCL Commons core developer
    - Contributed ~40K lines of C++ code
    - Designed the pseudo-reaction and alchemical small molecule design framework
    - Extended reaction drug design framework to include multi-component reactions
    - QSAR ligand- and structure-based feature engineering and machine learning (ML) / deep learning (DL) model training
    - Maintenance and as-needed improvements for the cheminformatics toolkit
- Rosetta Commons PI and developer
    - Integrated BCL with Rosetta to enable small molecule drug design within Rosetta
    - Actively developing small molecule drug discovery tools
    - Actively co-leading and contributing to the RosettaQM project
    - Actively improving C++ and Python code for non-canonical amino acid parameter generation
    - Expanding ParmEd crosstalk with PyRosetta data structures

Molecular dynamics simulations

- MD Engines: Amber, OpenMM
- Sample projects:
    - Mapping conformational free energy landscapes of proteins
    - Measuring protein-ligand pose stability and binding affinity
        - Thermodynamic integration, free energy perturbation, MM-PBSA/GBSA
    - Predicting configurational stability of cyclic peptides
    - Estimating thermodynamic observables for structural water in proteins

**Industry Collaborations and Experience**

2022 Consultant for Rosetta Design Group – Non-canonical amino acids in Rosetta and MD simulations

2021 Consultant for MentenAI – peptide design and non-canonical amino acids in Rosetta and MD simulations

2017 – 2019 Vanderbilt University – Bayer Alliance https://news.vumc.org/2017/09/11/vanderbilt-bayer-collaborate-to-develop-new-therapies-against-kidney-diseases/

**Publications (by topic)**

***Identification of structural mechanisms of activation and inhibitor sensitivity in cancer-associated kinases*.**

2023 Marin, A.*, Mamun, A.*, Akamatsu, H., Ye, D., Sudhan, D.R., , Eli, L., Marcelain, K., **Brown, B.P.,** Meiler, J. †, Arteaga, C.L. †, Hanker, A.B. †. (2023). Acquired secondary HER2 mutations enhance HER2/MAPK signaling and promote resistance to HER2 kinase inhibition in HER2-mutant breast cancer. *Cancer Research*.
*Equally contributing co-first authors; †Co-corresponding authors

2022 **Brown, B.P.*** †, Zhang, Y.*, Kim, S.*, Finneran, P., Du, Z., Yan, Y., Smith, A.W. †, Lovly, C.M. †, Meiler, J. † (2022). Allele-specific activation, enzyme kinetics, and inhibitor sensitivities among

EGFR exon 19 deletions in lung adenocarcinoma. *Proceedings of the National Academy of Sciences of the United States of America*.
*Equally contributing co-first authors †Co-corresponding authors

2021 Hanker, A.B.*, **Brown, B.P.***, Meiler, J.*, Marín, A., Harikrishna, S., Ye, D., Lin, C., Akamatsu, H., Lee, K., Chatterjee, S., Sudhan, D.R., Servetto, A., Red-Brewer, M., Koch, J.P., Sheehan, J.H., He, J., Lalani, A.S., Arteaga, C.L. Co-occurring gain-of-function mutations in HER2 and HER3 modulate HER2/HER3 activation, oncogenesis, and HER2 inhibitor sensitivity. *Cancer Cell.*
*Equally contributing co-first authors

2021 Du, Z.*, **Brown, B.P.***, Kim, S, Ferguson, D., Pavlick, D.C, Jayakumaran, G., Benayed, R., Gallant, J.N., Zhang, Y., Yan, Y., Red-Brewer, M., Ali, S.M., Schrock, A.B., Zehir, A., Ladanyi, M., Smith, A.W., Meiler, J., Lovly, C.M. (2020). Structure-function analysis of oncogenic EGFR Kinase Domain Duplication reveals insights into activation and a potential approach for therapeutic targeting. *Nature Communications*.
*Equally contributing co-first authors

2019 **Brown, B.P.***, Zhang, Y.*, Westover, D., Yan, Y., Qiao, H., Huang, V., Du, Z., Smith, J.A., Ross, J.S., Miller, V.A., Ali, S., Bazhenova, L., Schrock, A.B., Meiler, J.†, Lovly, C.M†. (2019). On-target resistance to the mutant-selective EGFR inhibitor osimertinib can develop in an allele specific manner dependent on the original EGFR activating mutation. *Clinical Cancer Research*.
*Equally contributing co-first authors

### *Development of software for molecular modeling*

2024 **Brown, B.P.** †, Stein, R.A., Meiler, J. †, Mchaourab, H†. (2024). Approximating conformational Boltzmann distributions with AlphaFold2 predictions. *Journal of Chemical Theory and Computation*.
†Co-corresponding authors

2022 **Brown, B.P.** †, Vu, O., Kothiwale, S., Geanes, A.R., Butkiewicz, M., Lowe, E.W., Mueller, R., Mendenhall, J., Meiler, J†. (2022). Introduction to the BioChemical Library (BCL): An application-based open-source toolkit for integrated cheminformatics and machine learning in computer-aided drug discovery. *Frontiers in Pharmacology.*
†Co-corresponding authors

2021 **Brown, B.P.** †, Mendenhall, J., Geanes, A.R., Meiler, J†. (2021). General purpose structure-based drug discovery neural network score functions with human interpretable pharmacophore maps. *Journal of Chemical Information and Modeling.*
†Co-corresponding authors

2020 Mendenhall, J., **Brown, B.P.**, Sandeep Kothiwale, Meiler, J. (2020). BCL::Conf – Improved Open-Source Knowledge-Based Conformation Sampling using the Crystallography Open Database. *Journal of Chemical Information and Modeling*.

2019 **Brown, B.P.**, Mendenhall, J., Meiler, J. (2019). BCL::MolAlign: Three-Dimensional Small Molecule Alignment for Pharmacophore Mapping. *Journal of Chemical Information and Modeling.*

### *Peptide design*

2023 Watson, P.R., Gupta, S., Hosseinzadeh, P., **Brown, B.P.**, Baker, D., Christianson, D.W. (2023). Macrocyclic Octapeptide Binding and Inferences on Protein Substrate Binding to Histone Deacetylase 6. *ACS Chemical Biology*

2020 Sevy, A.M., Gilchuck, I.M., **Brown, B.P.**, Bozhanova, N.G., Nargi, R., Jensen, M., Meiler, J., Crowe, J.E. Jr. (2020). Computationally designed cyclic peptides derived from an antibody loop increase breadth of binding for influenza variants. *Structure.*

2015 Lang BT, Cregg JM, DePaul MA, Tran A, Xu K, Dyck, SM, Madalena KM, **Brown B.P.**, Weng YL, Li, S, Karimi-Abdolrezaee S, Busch SA , Shen Y and Silver J. (2015). Modulation of the proteoglycan receptor PTPσ promotes recovery after spinal cord injury. *Nature*.

***Other***

2023 Shi, X., Lingerak, R., Herting, C.J., Kim, S., Toth, P., Wang, W., **Brown, B.P.**, Meiler, J., Sossey-Alaoui, K., Buck, M., Himanen, J., Hambardzumyan, D., Nikolov, D.B., Smith, A.W., Wang, B. (2023). Time-resolved live-cell spectroscopy reveals EphA2 multimeric assembly. *Science*.

2022 Bozhanova, N.G., Flyak, A.I., **Brown, B.P.**, Ruiz, S.E., Salas, J., Rho, S., Bombardi, R.G., Myers, L., Soto, C., Bailey, R., Crowe Jr., J.E., Bjorkman, P.J., Meiler, J. (2022). Computational identification of HCV neutralizing antibodies with a common HCDR3 disulfide bond motif in the antibody repertoires of infected individuals. *Nature Communications*.

2021 Zeng, D., **Brown, B.P.**, Voehler, M.W., Cai, S., Reiter, N.J. (2021). Dissecting Monomer-Dimer Equilibrium of an RNase P Protein Provides Insight Into the Synergistic Flexibility of 5'Leader Pre-tRNA Recognition. *Frontiers in Molecular Biosciences*.

2020 Bozhanova, N.G., Calcutt, M.W., Beavers, W.N., **Brown, B.P.**, Skaar, E.P., Meiler, J. (2020). Lipocalin Blc is a heme binding protein? *FEBS Letters*.

2018 Zeng, D., **Brown, B.P.**, Voehler, M.W., Cai, S., Reiter, N.J. (2018). NMR resonance assignments of RNase P protein from Thermotoga maritima. *Biomolecular NMR Assignments*.

2014 **Brown, B.P.**, Kang, S., Gawelek, K., Zacharias, R.A., Anderson, S.R., Turner, C.P., & Morris, J.K. (2014). In vivo and in vitro ketamine exposure exhibits a dose-dependent induction of ADNP in rat neurons. *Neuroscience*.

**Professional Oral Presentations**

2023 8th annual *Chemistry and Pharmacology of Drug Abuse (CPDA) Conference*, invited speaker, "Has artificial intelligence learned protein conformational equilibria? Implications for designing G-protein selective partial agonists of the mu opioid receptor"

2021 *Lung Cancer Oncogenome Group (LCOG) meeting*, "Mechanistic Insights into EGFR Variants of Uncertain Significance"

2021 *Winter RosettaCON*, "Integration of the BCL cheminformatics toolkit with Rosetta for small molecule drug design"

2020 *Summer RosettaCON*, "Improved estimation of protein-ligand binding free energy in Rosetta through Monte Carlo – Metropolis resampling and explicit estimation of gas-phase interaction entropies"

2020 *Virtual COVID-19 RosettaCON*, "Machine learning-guided automated design of SARS-CoV-2 viral protease small molecule inhibitors"

**Professional Memberships**

2023 Principal Investigator, Rosetta Commons

2023 Editorial Board Member, *Frontiers in Pharmacology*

**Honors & Awards**

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| 2022 | Vanderbilt-Ingram Cancer Center Graduate Student of the Year |
| 2015 | Graduated Summa Cum Laude, Baldwin Wallace University |
| 2015 | Outstanding Senior Award, Baldwin Wallace University |
| 2015 | Chemistry Department Outstanding Senior Award, Baldwin Wallace University |
| 2014 | Norman Wells Chemistry Scholarship, Baldwin Wallace University |
| 2013 – 2014 | Center for Innovation and Growth Student Fellow, Baldwin Wallace University |
| 2013 | Mark Gorman Outstanding Neuroscience Award, Baldwin Wallace University |
| 2013 | Society for Neuroscience Travel Award, Faculty for Undergraduate Neuroscience |
| 2013 | Chemistry Department Memorial Award, Baldwin Wallace University |
| 2013 | Ovation President's Luncheon Speaker, Baldwin Wallace University |
| 2011 – 2015 | STEM Scholarship |
| 2011 – 2015 | Dean's List |
| 2011 – 2015 | Baldwin Wallace University Presidential Scholarship |
| 2011 – 2015 | Baldwin Wallace University Honors Program |

**Research Funding**

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| 2023 – Present | NIH NIDA DP1DA058349 "Developing a computational platform for induced-fit and chemogenetic drug design." May 2023 – April 2028; $300,000 direct annually. |
| 2022 | Rosetta Commons Mini Grant, "Rosetta as a general-purpose computer-aided drug design platform"; Awarded 09/2022; one-time allotment of $33,500. |
| 2018 – 2022 | NIH NIDDK F30DK118774 "Targeting receptor tyrosine kinases with novel methods in computer-aided drug discovery for the treatment of fibrotic renal disease." |

**Mentorship / Trainees**

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| 2023 – Present | Johnathan Ahdout – high school student intern; |
| 2022 – Present | Joseph DeCorte – graduate student; co-mentor with Jens Meiler |
| 2021 – Present | Claiborne Tydings – graduate student; co-mentor with Jens Meiler and Allison Walker |
| 2022 – 2023 | Yingrong Chen – Rosetta undergraduate research intern; Barry Goldwater Scholar |
| 2021 | Hannah Thirman – Meiler Lab graduate rotation student |
| 2021 | Zhengyi Chen – Meiler Lab graduate rotation student |
| 2021 | Furqan Teke – Meiler Lab undergraduate research assistant |
| 2020 | Abdullah Al Mamun – Meiler Lab post-doctoral fellow |
| 2019 | Hari Sharma – Meiler Lab post-doctoral fellow |
| 2019 | Qingchuan Sang – Department of Chemistry at Vanderbilt University graduate student |
| 2019 | Seema Baddam – Department of Chemistry at Vanderbilt University undergraduate capstone |
| 2018 | Aidan Cloonan – School for Science and Math at Vanderbilt (SSMV) research internship |
| 2016 | Stanley Chibueze – Students for a National Medical Association – Minority Association of Pre-Medical Students (SNMA-MAPS) joint mentor-mentee program |

**Organizational Leadership**

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| 2018 – 2020 | Co-chair, Vanderbilt MSTP F30/F31/AHA Mock Study Section |
| 2022 | BioChemical Library (BCL) Workshop: Integrating BCL and Rosetta to enable comprehensive ligand- and structure- based small molecule drug design (Speaker and Chief Organizer) |

- Prepared, validated, and released BCL v4.2 on Windows, Apple, and Linux OS.
- Wrote 8 tutorials (100+ pages) with functional code
- Prepared and presented 6 talks; assisted with 2

- Answered questions for 50+ attendees over a one-week period