BIOGRAPHICAL SKETCH

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NAME: Paul Leonard, PhD

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

POSITION TITLE: Senior Institute Research Scientist

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 Bristol, Bristol, UK	BSc	06/2001	Biochemistry
University College London, London, UK	PhD	03/2008	Biochemistry
University of Medicine and Dentistry of New Jersey, Piscataway, NJ, USA	Post-Doctoral Research Fellow	04/2008 - 08/2012	Structural Biology

A. Personal Statement

During my research career I have gained a wealth of experience in structural biology and biophysical methods for characterizing small molecule binding interactions with a range of macromolecules. I am currently the lead X-ray crystallographer on four drug discovery projects within the Institute for Applied Cancer Science providing essential insights to the medicinal chemistry team to guide the development of more potent and specific compounds that have an excellent safety profile for progression into clinical development. I have a proven track record in developing small molecule inhibitors that have efficacy against a range of oncology targets in *in vivo* models and am the co-inventor on two published patents as well as three further filed patent applications.

In addition, as Director of the Biomolecular Structure and Function (BSF) at MD Anderson Cancer Center (MDACC), I manage a team of researchers that provide protein production, structural biology and biophysics expertise to the MD Anderson research community. I have collaborated on a wide variety of research programs using my expertise in binding studies and structural biology to accelerate the development of small molecule inhibitors and published a number of peer-reviewed articles in leading journals.

- Leonard P.G., Satani N., Maxwell D., Lin Y.H., Hammoudi N., Peng Z., Pisaneschi F., Link T.M., Lee G.R. 4th, Sun D., Prasad B.A.B., Di Francesco M.E., Czako B., Asara J.M., Wang Y.A., Bornmann W., DePinho R.A., Muller F.L. Nature chemical biology. (2016) 12(12) 1053-1058.
  SF2312 is a natural phosphonate inhibitor of enolase.

- Petrocchi A., Leo E., Reyna N.J., Hamilton M.M., Shi X., Parker C.A., Mseeh F., Bardenhagen J.P., Leonard P.G., Cross J.B., Huang S., Jiang Y., Cardozo M., Draetta G., Marszalek J.R., Toniatti C., Jones P., Lewis R.T. Bioorg Med Chem Lett. (2016) 26(6):1503-7
  Identification of potent and selective MTH1 inhibitors.

- Du Y., Yamaguchi H., Wei Y., Hsu J.L., Wang H.L., Hsu Y.H., Lin W.C., Yu W.H., Leonard P.G., Lee G.R., Chen M.K., Nakai K., Hsu M.C., Chen C.T., Sun Y., Wu Y., Chang W.C., Huang W.C., Liu C.L., Chang Y.C., Chen C.H., Park M., Jones P., Hortobagyi G.N., Hung M.C. Nat Med. (2016) 22(2):194-201.
  Blocking c-Met-mediated PARP1 phosphorylation enhances anti-tumor effects of PARP inhibitors.

B. Positions and Honors

Positions and Employment

- 02/2007 – 04/2008 Research Assistant, Department of Biochemistry, University College London, London, UK
- 05/2008 – 09/2012 Post-Doctoral Research Fellow, Center for Advanced Biotechnology and Medicine, UMDNJ, Piscataway, NJ, USA
- 09/2012 – 09/2014 Instructor, Department of Biochemistry, MD Anderson Cancer Center, Houston, TX, USA
- 10/2014 – 08/2016 Instructor, Department of Genomic Medicine, MD Anderson Cancer Center, Houston, TX, USA
- 09/2016 – 12/2019 Institute Research Scientist and Director for the Biomolecular Structure and Function Core, Institute for Applied Cancer Science, MD Anderson Cancer Center, Houston, TX, USA
- 12/2019 – present Senior Institute Research Scientist and Director for the Biomolecular Structure and Function Core, Institute for Applied Cancer Science, MD Anderson Cancer Center, Houston, TX, USA

Memberships

- American Crystallographic Society
- American Society for Biochemistry and Molecular Biology

International Conference Co-organiser

- Industrial Biostructures America 2018

Journal Article Reviewer

- Peer-review journal article reviewer for the Journal of Bacteriology
- Peer-review journal article reviewer for the Toxicology and Applied Pharmacology Journal
- Peer-review journal article reviewer for the Computational Biology and Chemistry Journal

State Funding Grant Reviewer

- Invited expert reviewer for the Institutional Development Grant Program of the North Carolina Biotechnology Center
  Nov 2016 and Dec 2017

C. Contributions to Science

1. I currently hold the position of Institute Research Scientist within the Institute for Applied Cancer Science (IACS) at MD Anderson Cancer Center (MDACC), where I am the lead structural biologist for four small molecule drug discovery programs. IACS is a multi-disciplinary team of researchers within the Therapeutic Development Division of MDACC that is tasked with developing novel small molecules oncology drugs for a variety of metabolic and epigenetic proteins, targeting specific underserved patient populations. My role within this the IACS team is to use macromolecular X-ray crystallography and biophysical techniques to determine the structure, affinity, thermodynamics and kinetics of small molecule interactions with the target protein and provide guidance to the medicinal chemistry team to make changes to the small molecule to improve the potency and specificity of the molecule under development.

One highlight of my research career has been the development of a novel inhibitor of the Shp2 phosphatase. Shp2 is a tyrosine phosphatase that positively regulates the activity of a number of key receptor tyrosine kinases such as EGFR, FGFR and PDGFR among others. I was able to determine the crystal structure of the Shp2 phosphatase with multiple small molecule inhibitors synthesized by the IACS medicinal chemistry team and use these structures, along with thermodynamic data from isothermal titration calorimetry measurements to guide the development of a highly potent, cell permeable inhibitor that has an excellent pharmacokinetic profile for potential clinical development. The inhibitors that I helped to develop are covered by two published patent applications.

- Czako, B., Jones, P., Cross J., Leonard P., Patent No. WO 2017/156397 Heterocyclic Inhibitors of PTPN11. Published 09/14/2017
- Jones, P., Czako, B., Cross J., Leonard P., Mseeh F., Parker C.A., Patent No. US 2017/0342078 Heterocyclic Inhibitors of PTPN11. Published 11/30/2017

2. In recent years, as Director for the Core for Biomolecular Structure and Function, I have established several collaboration projects using biophysical techniques to directly study protein-protein interactions, small molecule-protein interactions, nucleic acid-protein interaction and peptide-protein interactions. My core facility uses analytical ultracentrifugation, microscale thermophoresis, biolayer interferometry, fluorescence assay or isothermal titration calorimetry to characterize the stoichiometries, affinities, kinetics or thermodynamics of these interactions, tailoring the technique to the interaction being studied.

- Liu Z, Chen H, Wang P, Li Y, Wold EA, Leonard PG, Joseph S, Brasier AR, Tian B, Zhou J. J Med Chem. (2020) [Epub ahead of print]. https://doi.org/10.1021/acs.jmedchem.0c00035.
  Discovery of Orally Bioavailable Chromone Derivatives as Potent and Selective BRD4 Inhibitors: Scaffold Hopping, Optimization, and Pharmacological Evaluation.
- Davlieva M., Tovar-Yanez A., DeBruler K., Leonard P.G., Zianni M.R., Arias C.A., Shamoo Y. J. Mol. Biol. (2016) 428(22) 4503-4519
  An Adaptive Mutation in Enterococcus faecium LiaR Associated with Antimicrobial Peptide Resistance Mimics Phosphorylation and Stabilizes LiaR in an Activated State.
- Petrocchi A., Leo E., Reyna N.J., Hamilton M.M., Shi X., Parker C.A., Mseeh F., Bardenhagen J.P., Leonard P.G., Cross J.B., Huang S., Jiang Y., Cardozo M., Draetta G., Marszalek J.R., Toniatti C., Jones P., Lewis R.T. Bioorg Med Chem Lett. (2016) 26(6):1503-7
  Identification of potent and selective MTH1 inhibitors.
- Du Y., Yamaguchi H., Wei Y., Hsu J.L., Wang H.L., Hsu Y.H., Lin W.C., Yu W.H., Leonard P.G., Lee G.R., Chen M.K., Nakai K., Hsu M.C., Chen C.T., Sun Y., Wu Y., Chang W.C., Huang W.C., Liu C.L., Chang Y.C., Chen C.H., Park M., Jones P., Hortobagyi G.N., Hung M.C. Nat Med. (2016) 22(2):194-201.
  Blocking c-Met-mediated PARP1 phosphorylation enhances anti-tumor effects of PARP inhibitors.
- Vohidov F., Knudsen S.E., Leonard P.G., Ohata J., Wheadon M.J., Popp B.V., Ladbury J.E., Ball Z.T.,. Chemical Science (2015) 6(8):4778-4783.
  Potent and selective inhibition of SH3 domains with dirhodium metalloinhibitors.
- Davlieva M., Shi Y, Leonard P.G., Johnson T.A., Zianni M.R., Arias C.A., Ladbury J.E., Shamoo Y.A. Nucleic Acids Res (2015) 43(9):4758-73.
  A variable DNA recognition site organization establishes the LiaR-mediated cell envelope stress response of enterococci *to daptomycin.*

3. Another research project where I have played a critical role in the development of a novel small molecule inhibitor is the development of a potent and highly selective inhibitor of the CSF1R tyrosine kinase. CSF1R or Macrophage colony-stimulating factor 1 receptor is a cell-surface receptor for the CSF1 ligand as is a key regulator of survival, proliferation and differentiation of hematopoietic precursor cells such as

macrophages and monocytes. CSF1R is therefore a potential target for an immunotherapy drug to treat a broad spectrum of cancers as inhibiting CSF1R has been shown to suppress macrophage proliferation, thereby reducing the protective role of macrophages in preventing T-cells from attacking the tumor. I was able to identify a very specific amino acid change within the ATP binding site of the CSF1R kinase that is not observed in other PDGFR kinase family proteins and guide the medicinal chemistry team within IACS to introduce a small chemical group extension at a specific site on the compound core scaffold, such that this chemical extension would sterically clash with the other PDGFR kinases, but would still be able to bind to CSF1R. This modification to the compound resulted in a 100-fold improvement in the specificity of the inhibitor for CSF1R relative to the other PDGFR family kinases, improving the safety profile of the inhibitor. I am a co-inventor on two patent applications describing these inhibitors that were filed in 2017.

- Jones P., Czako B., Burke J., Cross J., Leonard P.G., Tremblay M., Mandal P., *Preparation of benzothiazoles as CSF-1R inhibitors for the treatment of cancer and other diseases.* Patent No. WO/2018/119387, Published on 06/28/2018
- Jones P., Czako B., Burke J., Cross J., Leonard P.G., *Preparation of benzo[d]thiazol-2-ylamine compounds as CSF-1R inhibitors for treatment of cancer and inflammatory disorders.* Patent No. WO2018/081276. Published on 05/03/2018

Complete List of Published Work in My Bibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1vARFNFbggAko/bibliography/public/

D. Additional Information: Research Support

None