NIH BIOGRAPHICAL SKETCH COMMON FORM

Name: Sintim, Herman

Persistent Identifier (PID) of the Senior/Key Person: https://orcid.org/0000-0002-2280-9359

Position Title: Associate Director Harper Cancer Center

Organization and Location: University of Notre Dame, Notre Dame, Indiana, United States

PROFESSIONAL PREPARATION

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of Oxford, Oxford, Not Applicable, N/A, United Kingdom	Doctor of Philosophy (DPHIL)	09/1999	09/2002	Organic Chemistry
University College London, London, Not Applicable, N/A, United Kingdom	Bachelor of Science (BS)	09/1995	05/1999	Medicinal Chemistry

Appointments and Positions

2025 - present	Associate Director Harper Cancer Center, University of Notre Dame, Notre Dame, Indiana, United States
2025 - present	Professor, University of Notre Dame, Notre Dame, Indiana, United States
2016 - 2024	Professor, Purdue University, West Lafayette, Indiana, United States
2015 - 2015	Professor, University of Maryland College Park, College Park, Maryland, United States
2012 - 2015	Associate Professor, University of Maryland College Park, College Park, Maryland, United States
2006 - 2012	Assistant Professor, University of Maryland College Park, College Park, Indiana, United States
2004 - 2006	Postdoctoral Researcher, Stanford University, Palo Alto, California, United States
2002 - 2004	Postdoctoral Researcher, University of Oxford, Oxford, Not Applicable, N/A, United Kingdom

Products

Products Closely Related to the Proposed Project

1. Dayal N, Řezníčková E, Hernandez DE, Peřina M, Bělíček J, Vojáčková V, Krňávková P, Bařina M, Brauer NR, Hunjan MK, Yadav P, Jorda R, Sintim HO. 3H-pyrazolo[4,3-f]quinoline hinge binder, a tunable scaffold for development of novel kinase inhibitors against FLT3-driven leukemia. Eur J Med Chem. 2026 Jan 15;302(Pt 2):118309. PubMed Central PMCID: PMC13070624.
2. Khatri U, Dayal N, Owusu KB, Hunjan MK, Pandey S, Harper HA, McMahan C, Elzey BD, Shen T, Hu X, Evans KW, El-Sheikh A, Jo SJ, Holtsberg FW, Aman MJ, Meric-Bernstam F, Woo S, Sintim HO, Wu J. Identification of alkynyl nicotinamide HSN748 as a RET solvent-front mutant inhibitor with intracranial efficacy. RSC Med Chem. 2025 Aug 13;16(8):3541-3550. PubMed Central PMCID: PMC12147034.
3. Chaudhuri R, Dayal N, Kaiser J, Mohallem R, Brauer NR, Yeboah KS, Aryal UK, Sintim HO. Morpholino nicotinamide analogs of ponatinib, dual MNK, p70S6K inhibitors, display efficacy against lung and breast cancers. Bioorg Chem. 2025 Jun 1;159:108298. PubMed PMID: 40081260.
4. Ramdas B, Dayal N, Pandey R, Larocque E, Kanumuri R, Pasupuleti SK, Liu S, Kanellopoulou C, Chu EFY, Mohallem R, Virani S, Chopra G, Aryal UK, Lapidus R, Wan J, Emadi A, Haneline LS, Holtsberg FW, Aman MJ, Sintim HO, Kapur R. Alkynyl nicotinamides show antileukemic activity in drug-resistant acute myeloid leukemia. J Clin Invest. 2024 Jun 17;134(12) PubMed Central PMCID: PMC11178545.
5. Akwata D, Kempen AL, Lamptey J, Dayal N, Brauer NR, Sintim HO. Discovery of imidazo[1,2-b]pyridazine-containing TAK1 kinase inhibitors with excellent activities against multiple myeloma. RSC Med Chem. 2024 Jan 25;15(1):178-192. PubMed Central PMCID: PMC10809330.

Other Significant Products Highlighting Contributions to Science

1. Dilday T, Abt M, Ramos-Solís N, Dayal N, Larocque E, Oblak AL, Sintim HO, Yeh ES. Identification and characterization of a potent and selective HUNK inhibitor for treatment of HER2+ breast cancer. Cell Chem Biol. 2024 May 16;31(5):989-999.e7.

PubMed Central PMCID: PMC11102337.

2. Yeboah SK, Meher S, Harper HA, McMahan C, Elzey BD, Sintim HO. 5'-Phosphorothioester Linked Cyclic Dinucleotides, Endo-S-CDNs, Displaying Impressive Antitumor Activities In Vivo when Dosed Subcutaneously. ACS Bio Med Chem Au. 2025 Aug 20;5(4):665-693. PubMed Central PMCID: PMC12371493.
3. Brauer NR, Kempen AL, Hernandez D, Sintim HO. Non-kinase off-target inhibitory activities of clinically-relevant kinase inhibitors. Eur J Med Chem. 2024 Sep 5;275:116540. PubMed Central PMCID: PMC11243610.
4. Kempen AL, Brauer NR, Sintim HO. Dual FLT3/haspin kinase inhibitor based on 3H-pyrazolo[4,3-f]quinoline scaffold with activities against acute myeloid leukemia. RSC Med Chem. 2023 Sep 19;14(9):1743-1754. PubMed Central PMCID: PMC10507812.
5. Khatri U, Dayal N, Hu X, Larocque E, Naganna N, Shen T, Liu X, Holtsberg FW, Aman MJ, Sintim HO, Wu J. Targeting RET Solvent-Front Mutants with Alkynyl Nicotinamide-Based Inhibitors. Mol Cancer Ther. 2023 Jun 1;22(6):717-725. PubMed Central PMCID: PMC10239345.

Certification:

I certify that the information provided is current, accurate, and complete. This includes, but is not limited to, information related to current, pending, and other support (both foreign and domestic) as defined in 42 U.S.C. § 6605.

In accordance with Section 10632 of the CHIPS and Science Act of 2022 (42 U.S.C. § 19232), each individual identified as a senior/key person must certify that they are not a party to a malign foreign talent recruitment program.

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Misrepresentations and/or omissions may be subject to prosecution and liability pursuant to, but not limited to, 18 U.S.C. §§287, 1001, 1031 and 31 U.S.C. §§3729-3733 and 3802.

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NIH BIOGRAPHICAL SKETCH SUPPLEMENT

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Position Title: Associate Director Harper Cancer Center

Organization and Location: University of Notre Dame, Notre Dame, Indiana, United States

Personal Statement

My current group consists of 12 graduate students, 1 postdoc, 1 research assistant professor and one staff member who conducts our in vivo efficacy experiments. We have expertise in drug synthesis, drug characterization and in vivo investigations of drugs, using rodent models (rats and mice).
My group has developed several potent inhibitors of enzymes. We have developed inhibitors of protein kinases and STING, which are orally bioavailable and have the potential to be translated into anti-cancer and anti-inflammatory agents. With Gravekamp, we were the first to show that cyclic dinucleotide based STING agonists, c-di-GMP in our example, activated immune system in mice to reduce tumor size (PMID: 24913717). This work has been cited 268 times since 2014. I am a co-founder of a start-up, KinaRx Inc. I am a consultant for AN2 Therapeutics, a publicly listed company.
I am passionate about mentorship. I have graduated 21 PhD and 3 master's students. Nine graduate students and two postdoctoral researchers are currently doing research in my group. In addition 26 postdoctoral researchers have worked in my group in the past. Previous graduate students and postdocs in my group have or now work at the NIH (3), FDA (1), universities (assistant, associate and full professors in US, Slovenia, China, India and Turkey) and industries. Some of my former graduate students have proceeded to careers at R1, R2 universities and small colleges. For example, my first graduate student cohorts, Jingxin Wang and Jacqueline Smith are now Assistant Professor at the University of Chicago Medical School and Associate Professor at Howard University, respectively. Recent graduate students from my group, Kenneth Oyendibe (PhD 2021) and Allison Kempen (PhD 2024), are on the faculty of Morehouse School of Medicine and Loras College respectively. Caroline Karanja (PhD 2019) is a staff member (scientific) at Columbia University Irving Medical Center and George Naclerio (PhD 2021) is a principal scientist at Novartis. These examples highlight that students I mentor are playing significant roles in academia and industry.
My students regularly win department or university fellowships. For example, Riddhi Chaudhuri, a previous student in my group, was supported by a SIRG Grad Research Assistantship from the Purdue Institute of Cancer Research. Riddhi won this Assistantship after writing a competitive proposal, which aimed to characterize a novel MNK inhibitor for the potential treatment of breast cancer. One of my former students, Jie Zhou, was awarded American Heart Association fellowship for her PhD work. One of my proudest moments is when Clement Opoku-Temeng won the prestigious Charles A. Caramello Distinguished Dissertation Award in 2019 (for his 2018 PhD thesis), which recognizes original work that makes an unusually significant contribution to the discipline, at the University of Maryland, College Park. Clement Opoku-Temeng was the College of Science recipient, and he is now a scientist at Arcus Bioscience.
I am the lead PI for the TP53 mutant AML grant. Previously, as CSO at the startup KinaRx and also as the academic lead PI, I had led a team that developed pre-IND experiments for a FLT3 inhibitor, which is being developed for potential treatment of FLT3 mutated AML with F691L mutation, which does not respond to gilteritinib (PMID: 38950330). Thus I have the track to lead a multidisciplinary team of scientists and clinicians to nominate a clinical candidate.

Honors

2026	Howard Burkett Memorial Lectureship, DePauw University
2025	44th Musselman Visiting Scientist, Gettysburg College
2025	Grace Rupley Professorship, University of Notre Dame
2023	Distinguished Professorship, Purdue University
2022	St. Elmo Brady Lectureship, University of Illinois, Urbana-Champaign
2022	Cancer Research Award, Lafayette Lions Club
2022	NSF Director's Award (as Program Director for Molecular Foundations for Biotechnology), NSF
2022	Richard B. Wetherill Professorship, Purdue University
2018	NOBCChE lectureship , University of Pennsylvania
2017	Outstanding contribution to drug discovery (Open innovation), Elli Lilly
2015	Drug Discovery Professorship, Purdue University

2015	Sigma Xi Distinguished lectureship, Sigma Xi
2011	Camille Dreyfus Teacher-Scholar, Camille Dreyfus
2010	Allen Angerio Award for Excellence in Faculty Mentorship, Georgetown University
2008	NSF career award, NSF

Contributions to Science

1. Protein kinases play important roles in the cell and are targets for anticancer therapy. My group developed novel compounds that inhibit various cancer related kinases.
   We developed compounds that have the potential to treat RET-driven non-small cell lung cancer (NSCLC) and FLT3-driven acute myeloid leukemia via inhibition of protein kinase phosphorylation.

   Two RET inhibitors, Selpercatinib (Loxo-292) and Pralsetinib (Blu-667) were recently approved by the FDA for treatment of RET-driven cancers. Unfortunately RET mutations that are resistant to Selpercatinib and Pralsetinib, solvent front G810S/C/R and L730V/I, have emerged in the clinic and thus there is a need for new generation RET inhibitors that are active against such mutations. We developed a RET inhibitor, which is active against solvent front mutations and also crosses the blood brain barrier (PMID: 40496186).

   Acute myeloid leukemia, AML, is a devastating disease with a 5-year overall survival of about 30%. For elderly patients over 65 years, the 5-year survival rate is less than 10%. Approximately 30% of AML patients harbor activated FLT3 kinase. Although many FLT3 inhibitors have undergone clinical trials, most suffer from drug resistance due to secondary mutations. We have developed new class of FLT3 kinase inhibitors that are active against drug-resistant secondary mutated FLT3 kinase (PMID: 38950330, PMID: 37731695, PMID: 34288692).

   TAK1 is a key stress kinase, that cancers utilize for chemo resistance. We have reported novel TAK1 inhibitors (PMID: 38283221). Our TAK1 inhibitors have displayed potent activities against various solid tumors, the topic of this proposal. Relevant to this proposal, we have reported the development of CLK inhibitors (PMID: 39770502) and Haspin inhibitors (PMID: 29698892; PMID: 37731695) for the potential treatment of cancer.

2. Cyclic dinucleotides were first described as important signaling molecules in bacteria and shown to regulate a variety of processes, including biofilm formation and cell wall synthesis. Cyclic dinucleotides also affect mammalian cells, particularly immune cells, and play important roles related to inflammation, T-cell maturation, and antigen presentation. Due to the essential roles played by these fascinating second molecules, there are now intense research efforts to identify macromolecular targets in the cell that sense these molecules. Recently, the activation of immune response to cyclic dinucleotides (CDNs) via STING has come to the forefront. Many groups have initiated programs aimed at identifying activators or inhibitors of STING as cancer immunotherapy or anti-inflammatory agents respectively. We have illuminated certain aspects of cyclic dinucleotide signaling in bacteria and immune cells. We have also developed activators (PMID: 39344905, PMID: 38784462) and inhibitors (PMID: 37360395) of the cGAS-STING pathway.

3. Antibacterial agents:
   Bacterial resistance to current antibiotics, especially methicillin and vancomycin is a well-known phenomenon that threatens humanity if new and potent inhibitors of antimicrobial resistant bacteria are not found or discovered. There are now concerted efforts by many laboratories to find new chemical entities that kill or retard the growth of methicillin or vancomycin-resistant bacteria. We have developed several small molecules that inhibit the growth of bacteria.
   For example, we reported compounds with remarkable antibacterial activities against C. difficile with ultrapotent activities [MICs as low as 0.003 μg/mL (0.007 μM)], which surpassed the activity of vancomycin against C. difficile clinical isolates (PMID: 32960605).

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