INDIANA CTSI Clinical and Translational Sciences Institute

Welcome to the Indiana CTSI Notre Dame Retreat

# "DRUG DEVELOPMENT AND TARGET IDENTIFICATION"

**This poster session will begin at 12:15 p.m. EST**

**To view today's agenda or preview the poster sessions, please visit: hwi.nd.edu/CTSIRetreat21**

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# Indiana Clinical and Translational Sciences Institute

# Notre Dame Retreat
# March 10, 2021

## Investigation of a Series of 1,4-diaryl-pyrazolo-pyridinones as Anti-Leishmanial Agents

**Hannah Corman**
**PhD Candidate, Biological Sciences; Indiana CTSI TL1 Predoctoral Trainee**

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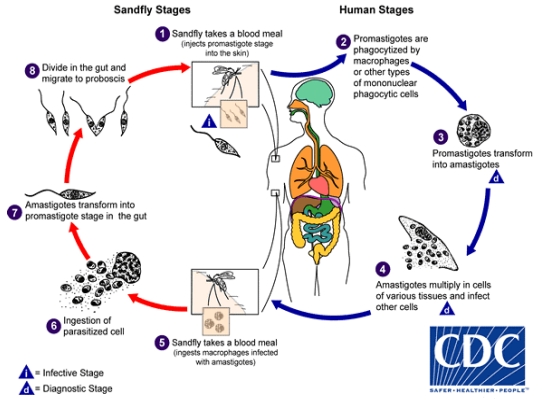
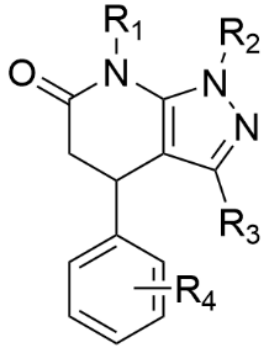
# Here's what we found

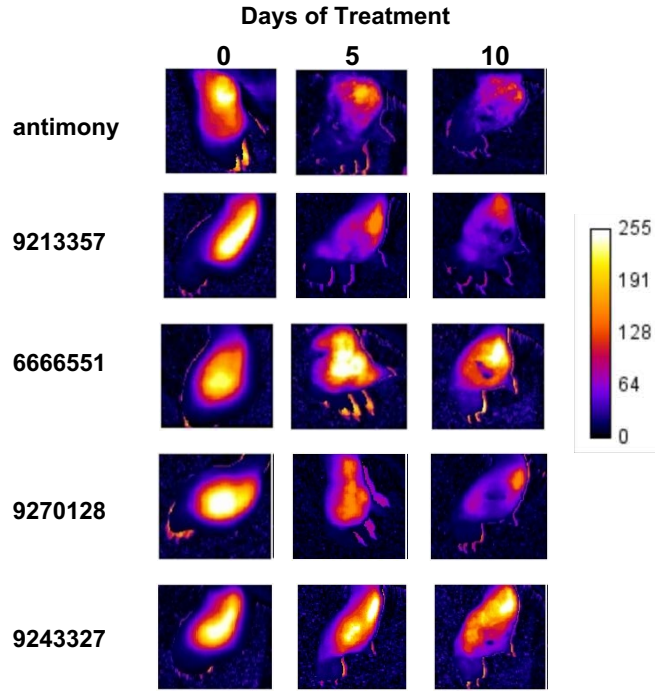
- **We identified and demonstrated a compound class, 1,4-diaryl-pyrazolo-pyridinone, that is effective against Leishmania spp. for the first time.**
- **This discovery is only the beginning of the potential drug development pipeline – new drugs are desperately needed to treat leishmaniasis, especially in low socioeconomic situations.**
- **These findings can be used to make improvements on the current chemotherapy landscape for leishmaniasis, and potentially other parasitic diseases like trypanosomiasis**

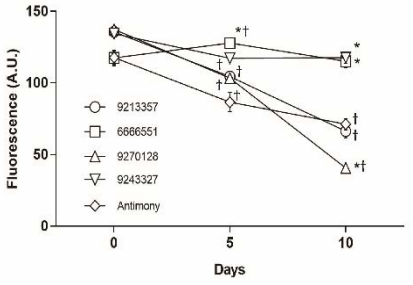


# Here's how we did it

- This study utilized transgenic L. donovani and L. major parasites expressing the fluorescent protein mCherry for real-time quantification in drug screens and in vivo imaging.
- We used in vitro drug screens against parasites and human macrophages to determine efficacy and toxicity.
- Fluorescent parasites allowed us to monitor infection progress and treatment progress in our mouse models.
- We found several compounds that were just as effective against L. donovani as current chemotherapies in vitro – and were significantly less toxic!
- We also found a compound that was nearly as effective against L. major as current chemotherapies in vivo – with substantially less tissue damage.



# Future implications for patients or the community/ or next steps

- These findings have implications for further drug development against leishmaniasis, a grouping of Neglected Tropical Diseases that over 300 million people are at risk of infection each year.
- Previous results on a different compound class have been published in a peer-reviewed journal, International Journal of Antimicrobial Agents, and manuscripts are being developed for our results here.
- Techniques used in this study are extremely helpful for drug discovery, not just for parasitic diseases but for infectious diseases as a whole.

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## Determinants of Peptide-MHC Antigenicity for the Development of Personalized/Multiple Peptide Vaccines

**Grant Keller**
**PhD Candidate, TL1 Predoc Scholar**
**Dept. of Chemistry and Biochemistry**
**University of Notre Dame**

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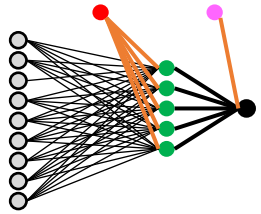
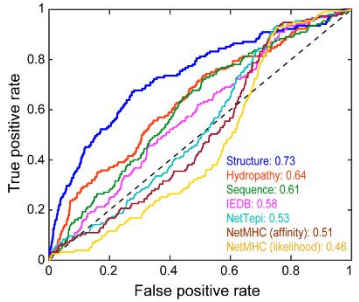
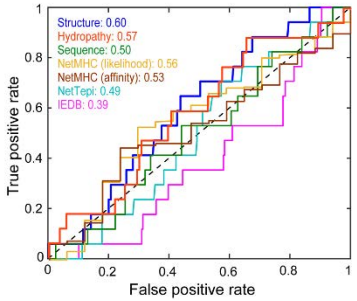
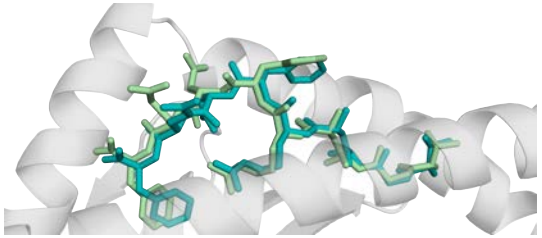
# Improved computational modeling of peptide-MHC structure

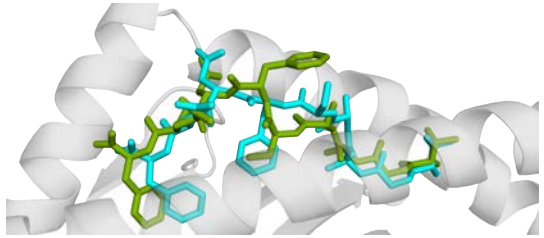




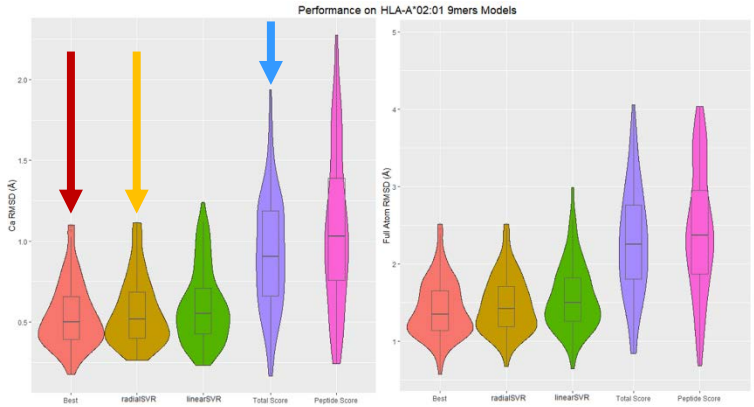



NEO RMSD: Cα 0.46, all 1.7



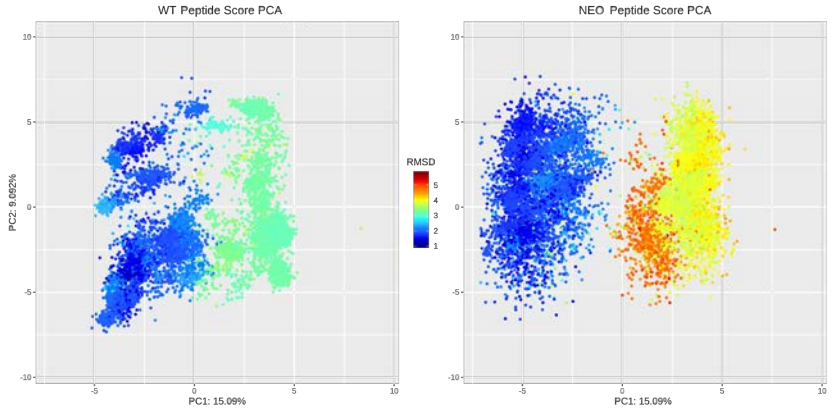
WT RMSD: Cα 1.2, all 3.1



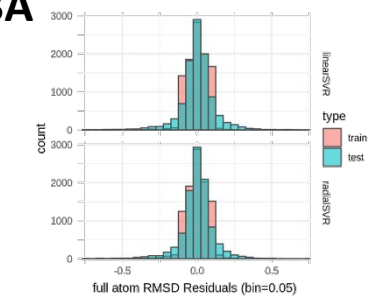

- The topology of potential T cell antigens is useful in predicting whether they induce an immune response. Predicting immunogenicity is limited by the lack of experimental structures, which necessitates modeling structure in silico.
- Modeling structure accurately is possible (left) but standard quality metrics are not well-suited for T cell antigens and may yield incorrect models (right).
- We developed a method to identify T cell antigen structural models in crystal structure-like conformations from an ensemble of distinct conformations.

# From one inaccurate model to generalized, accurate structure prediction

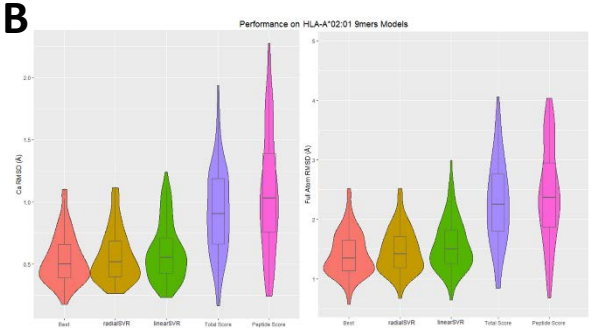
1



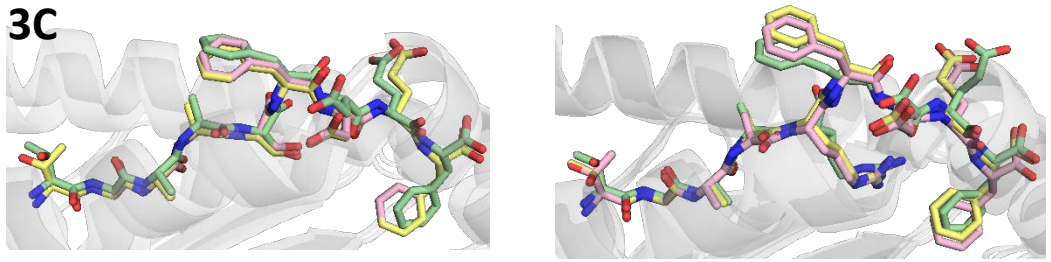

3A




3B




3C



1. In an initial case study, simply recombining energetic descriptions of the antigen interface distinguish near native models from poor representations of structure.

2. We developed linear regression models reweighting per-residue energy terms e.g. vdW, hbond, Coulombic, solvation, etc. to predict structural accuracy.

3. These selectors exhibited negligent overfitting (A) and generally selected near native conformation structures (B,C).

# Future implications for patients or the community/ or next steps

- **These results have been incorporated into our existing prediction pipeline:**
  **sequence → structure → (selection) → immunogenicity**

- **In the future, we will investigate how improved structural descriptions of peptide-MHC affect immunogenicity predictions of peptides generated from mutated tumor, viral, and/or intracellular parasite proteins.**
  - **Currently evaluating T cell responses to SARS-CoV-2 antigens identified using our prediction pipeline.**

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## Insights from an in vitro derived T Cell Receptor

**Jesus Alonso**
**Postdoctoral Research Associate**
**University of Notre Dame**

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# Here's what I we found

- **We discovered – for the first time ever – that there's now a scientific way to determine which women will relapse following surgery and chemotherapy for triple negative breast and which will remain disease free for up to at least two years**
- **This discovery stops the fear of the unknown that women with triple negative breast cancer having been living in, by providing them a scientific way to determine whether or not their disease is coming back**
- **These findings are so significant they are now being used in clinical studies beyond triple negative breast cancer, to now include colon and other breast cancer studies.**

# Here's how we did it

- This study analyzed the plasma in the blood of 196 women as part of clinical study BRE-158 using a cutting edge technology known as the " foundation one liquid biopsy device"
- This new technology allowed us to see the presence of circulating tumor DNA or residual tumor DNA in a woman's blood plasma.
- By viewing the presence of circulating tumor DNA in some women with triple negative breast cancer, we were able to determine that meant a high likelihood (approximately 81%) the woman's triple negative breast cancer would return
- When combined with the presence of circulating tumor cells, the likelihood of the woman's triple negative breast cancer returning within 2 years increased to 89%

# Future implications for patients or the community/ or next steps

- These findings, discovered by researchers at Indiana University School of Medicine, have implications for clinical studies around the world, beyond just triple negative breast cancer
- Disseminated as an oral plenary session as part of the prestigious San Antonio Breast Cancer Symposium and the prestigious peer-reviewed international journal, JAMA Oncology, are testaments to the credibility of these scientific findings
- These discoveries form the basis of an upcoming Phase II clinical study named PERSEVERE which will stratify patients based on their risk of recurrence and help find targeted therapies for this high risk group.

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## Interrogating the clinically-relevant T cell receptor TIL 1383i

Aaron Rosenberg[1], Michael Nishimura[2], Brian M. Baker[1]
Department of Chemistry and Biochemistry[1], Harper Cancer Research Institute, University of Notre Dame, Notre Dame, IN
Loyola University Medical Center, Maywood, IL[2]

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# Here's what I found

- Through my studies, I have determined that I can in fact utilize nicking saturation mutagenesis in combination with yeast display to generate libraries of point mutant single chain T cell receptors.
- Interrogation of these libraries via pMHC tetramer staining for FACS coupled with deep sequencing has allowed me to calculate fitness scores for each mutant.
- The positive fitness mutations reside in both the CDR loops as well as the framework region of the single chain TCR. In addition, these fitness scores provide a map of mutagenic beneficial and deleterious mutations of the CDR loops and framework region.

# Here's how I did it

- I generated two libraries of the single chain TCR 868-Z11 via nicking saturation mutagenesis that encompass a total of 1620 point mutants in the CDR loops and the framework region.
- Each library was stained with pMHC tetramers and sorted via FACS.
- The subsequent populations were deep sequenced and analyzed to determine fitness scores for each individual mutation.
- These mutations were then mapped to a crystal structure to determine candidates for further interrogation via SPR and combinatorial peptides libraries.

# Future implications for patients or the community/ or next steps

- These findings are crucial in determining the relationship between affinity enhancing mutation location (CDR loops vs framework region) and cross reactivity profile.
- In order to develop higher efficacy TCR based immunotherapies while maintaining or minimizing cross reactivity profiles, we must understand the aforementioned relationship through these studies.
- Once this workflow is validated with the well characterized 868-Z11 single chain TCR, I plan to apply the same workflow to characterize the clinically relevant TIL 1383i.
- Through these studies, I hope to generate a variant of TIL 1383i that has increased efficacy to be tested in clinical trials for the treatment of melanoma by our collaborators at Loyola University Medical center.

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