Small molecule drug screen identifies FDA-approved drugs capable of enhancing neutrophil responses to the invasive human fungal pathogen, *Candida albicans*

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MHSRS
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USU Uniformed Services University

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Disclosures

1. Vericel - *medical advisory board*
2. GenMark/Roche Diagnostics - *medical and scientific advisory board*
3. Neutrophil therapeutics - *patents held*
4. UpToDate - *medical writer*
5. ThermoFisher Scientific – *unrestricted grant*
6. Opinions are my own

The Need

1. Rising antimicrobial resistance across all sectors and global sites

2. Lack of antimicrobial development

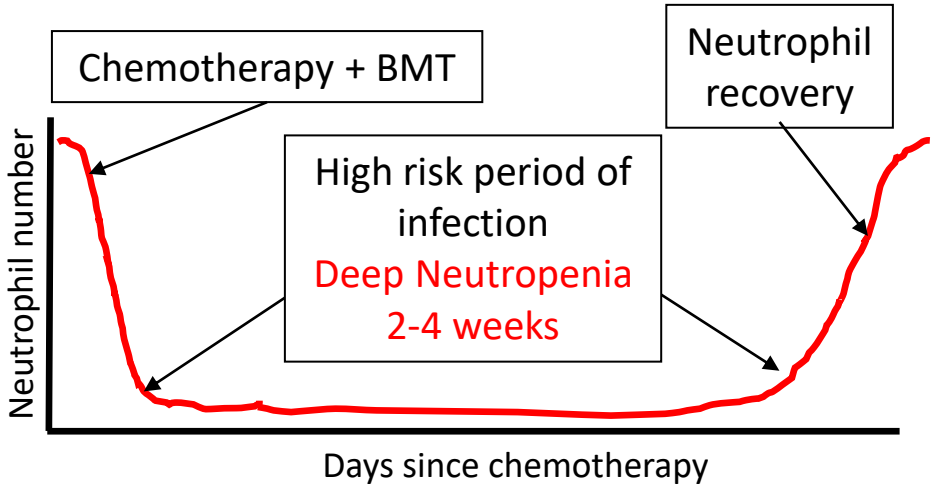
3. Ceiling effect of antimicrobial agents

Created a delta gap to cure

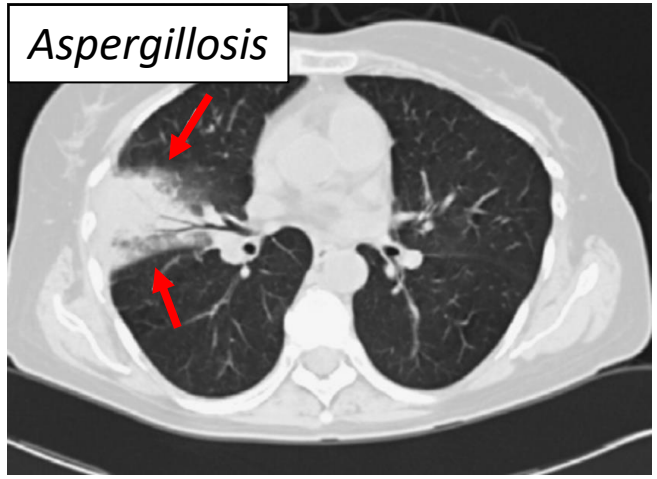
Solution is HOST HARDENING

Devastating consequences of neutropenia

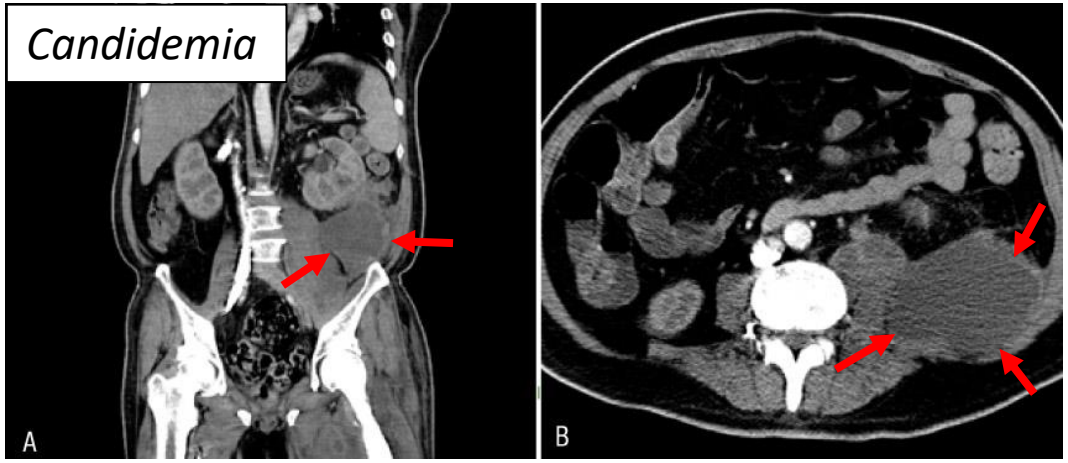
Diagnosis Admission:
Acute Leukemia



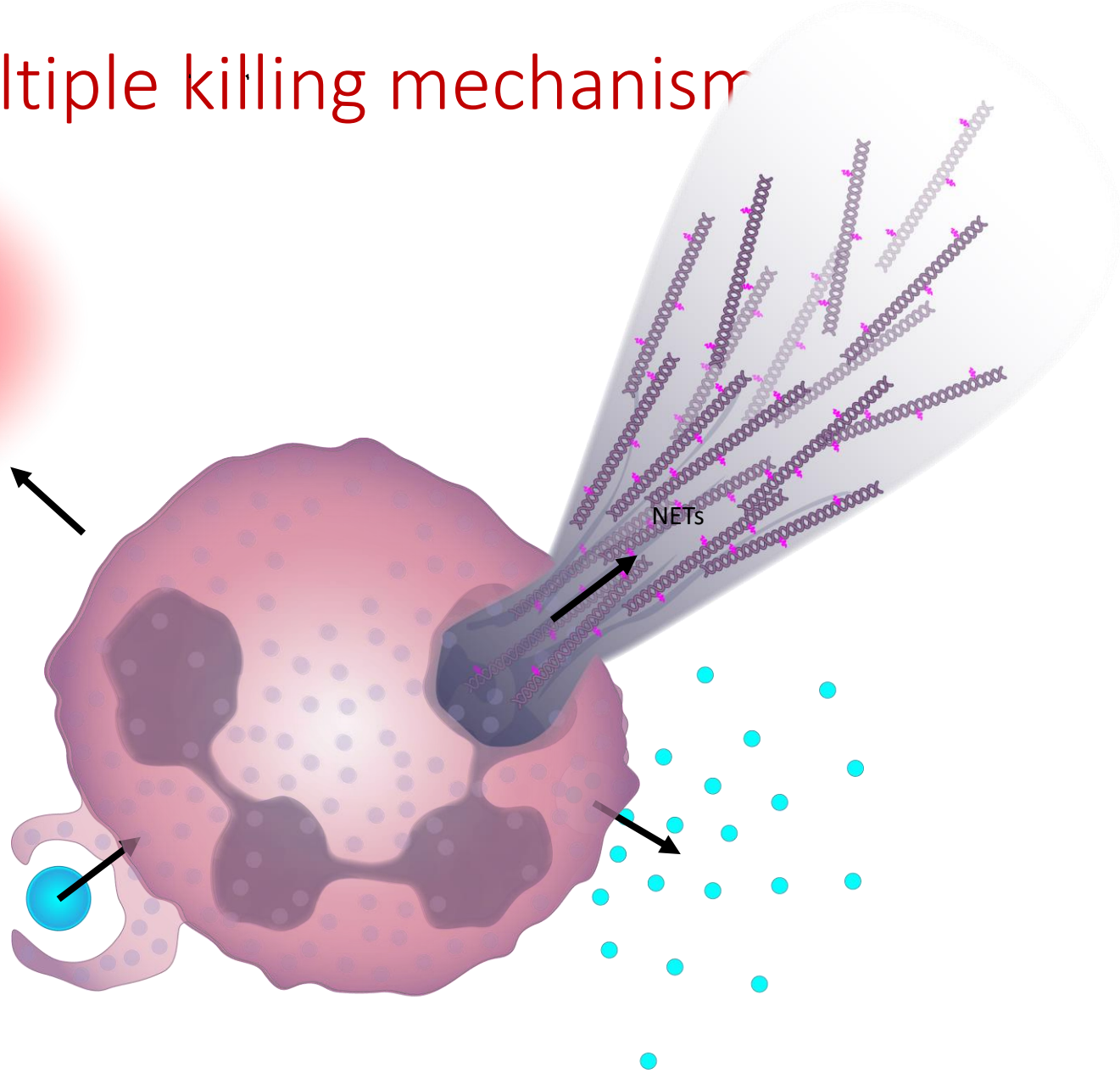
Aspergillosis



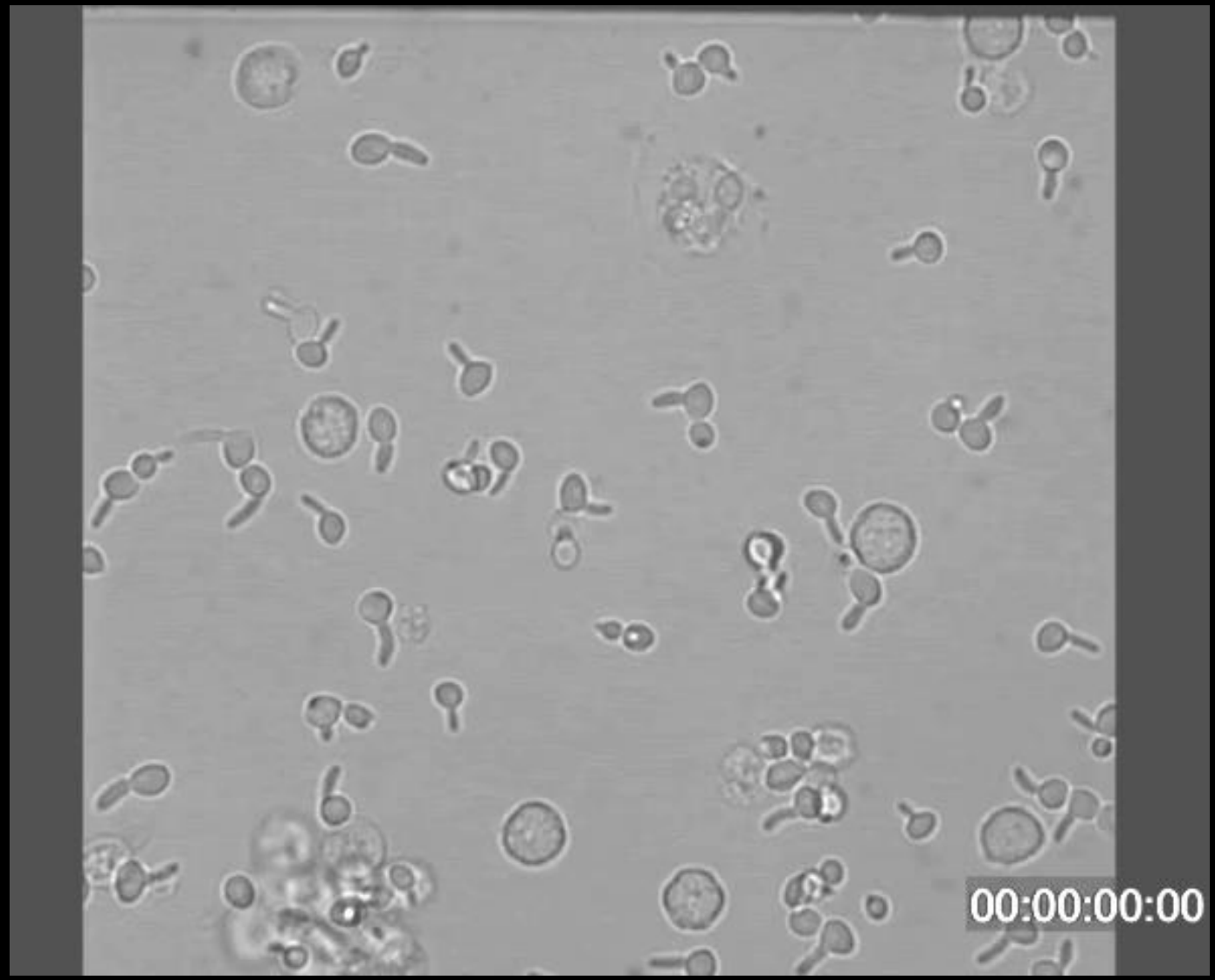
Candidemia



Neutrophils have multiple killing mechanism

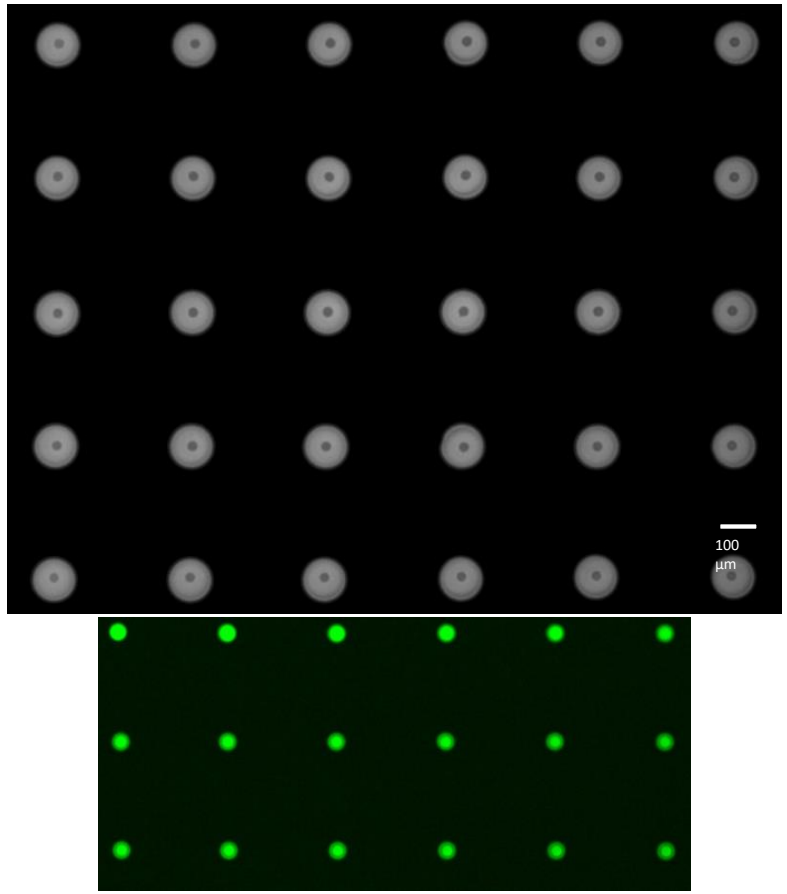


Clues that Neutrophils have preferential recognition

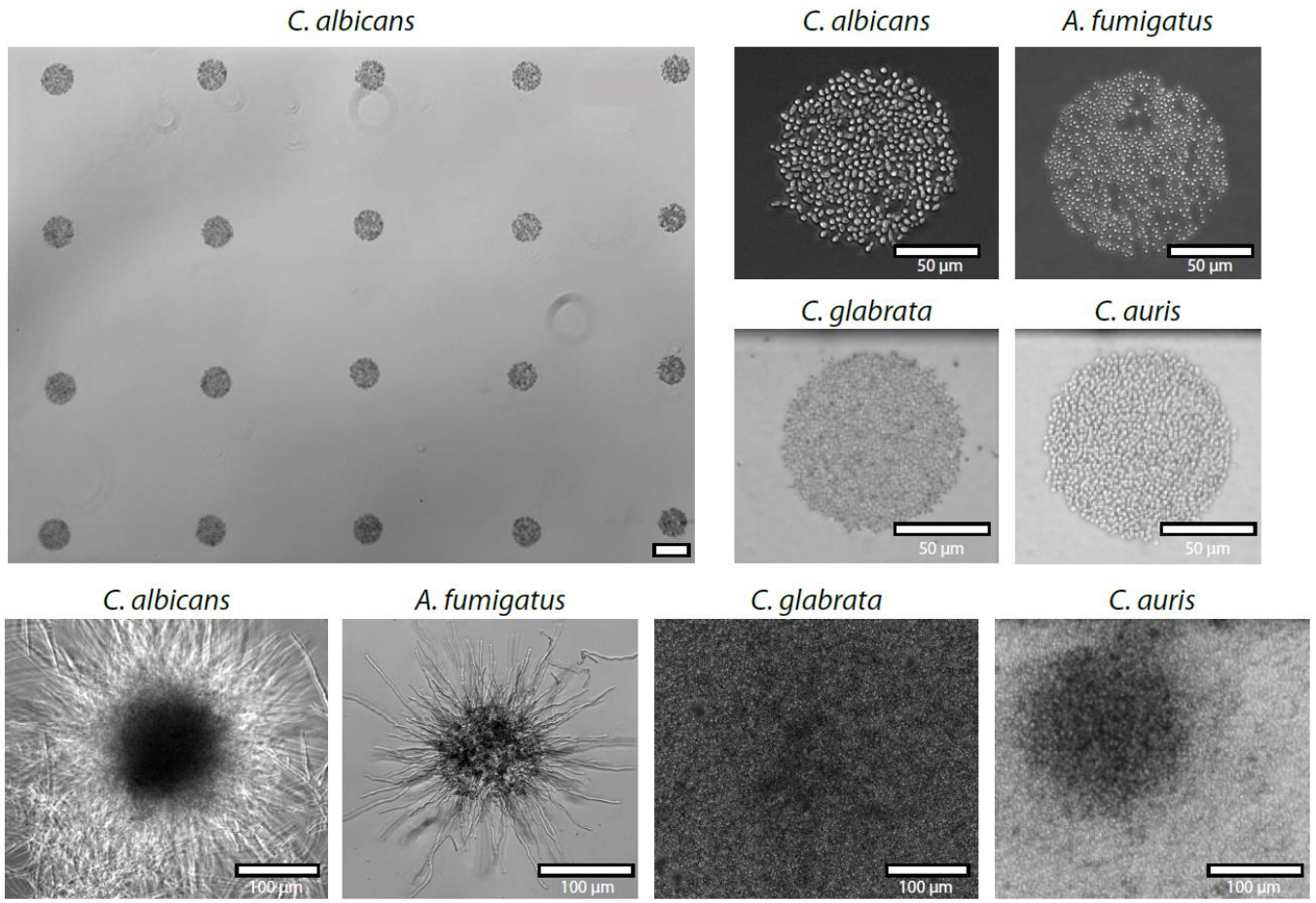


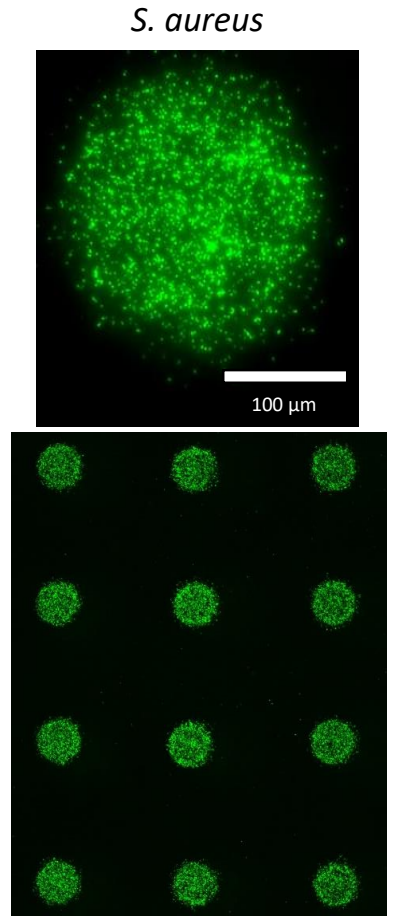
Swarming

Poly-l-lysine/Zetag



Printing large scale arrays of live pathogen targets





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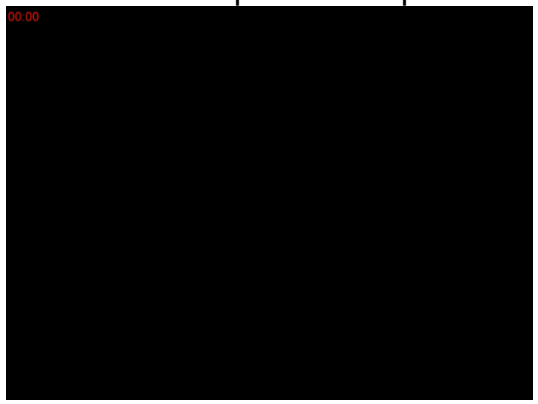
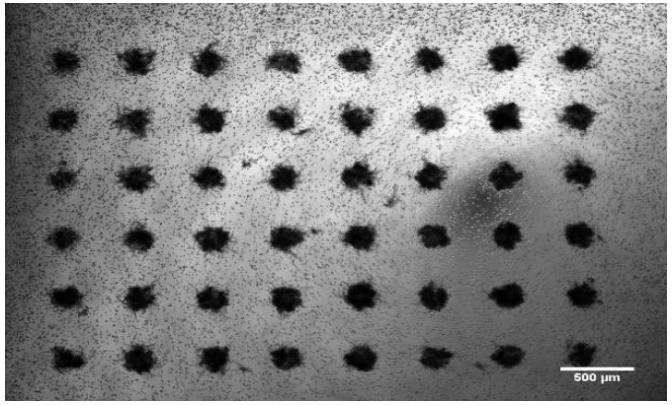
Neutrophil swarming restricts *C. albicans* growth

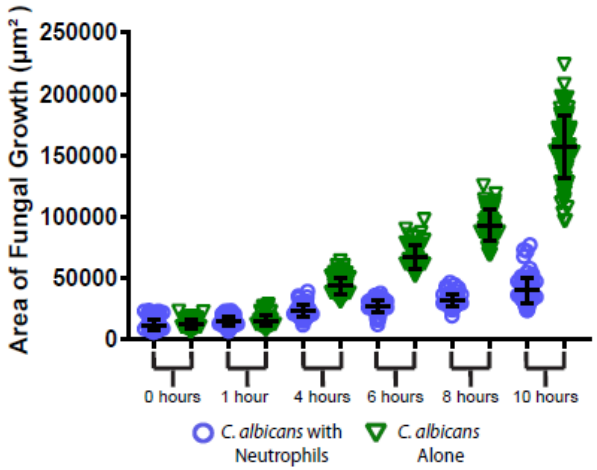
C. albicans plus neutrophils

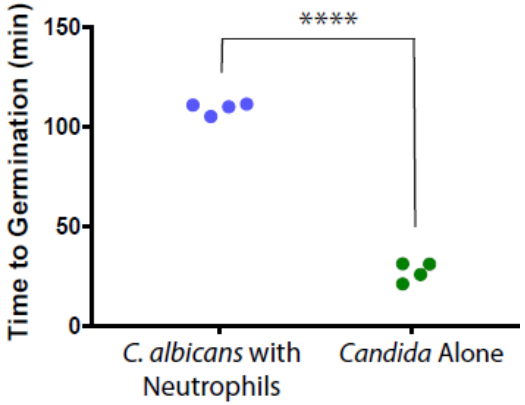


C. albicans Alone

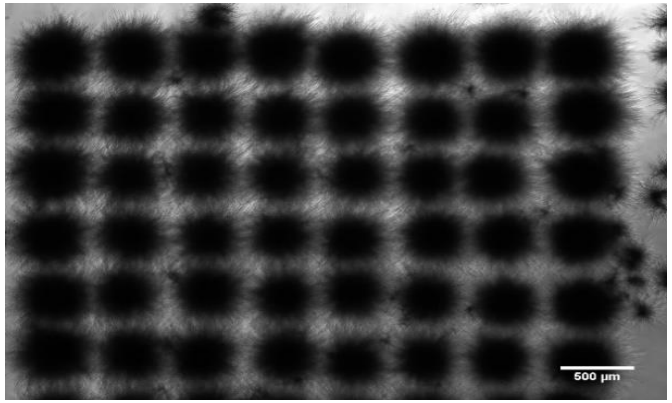
Neutrophil Swarming







C. albicans Alone



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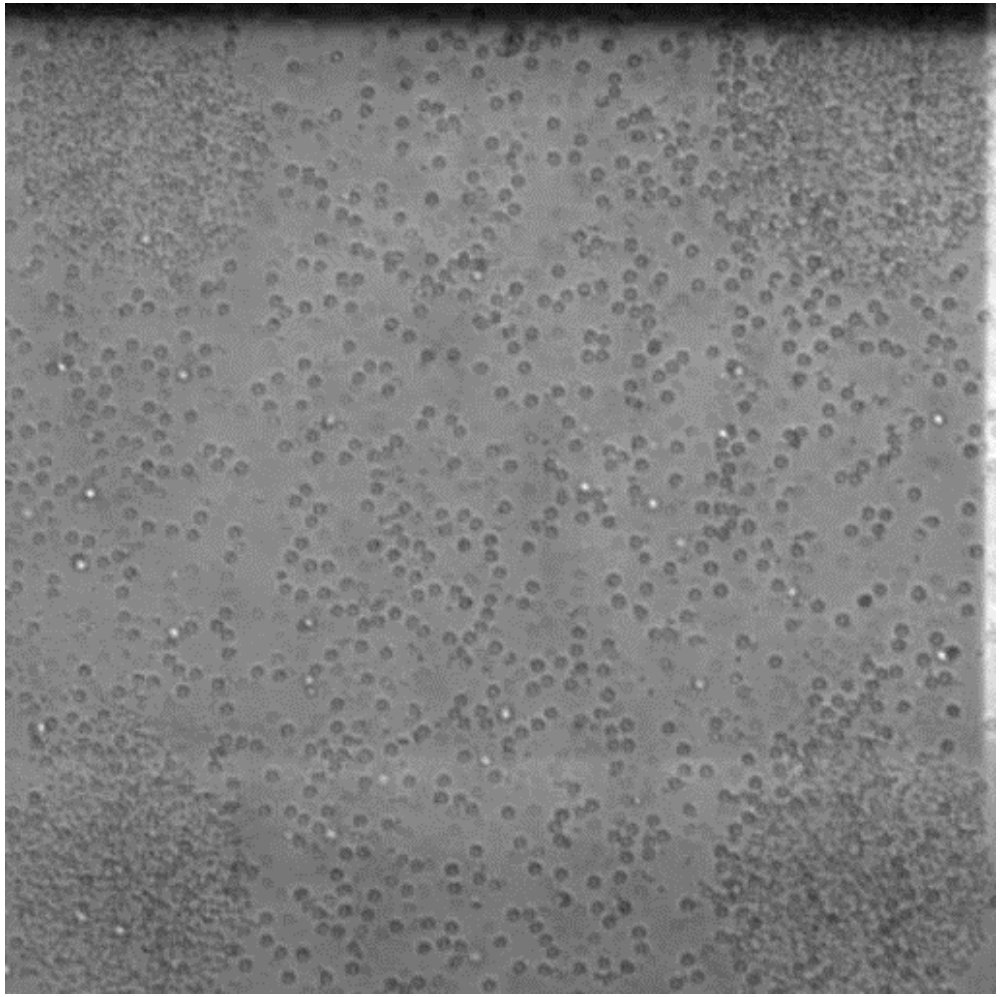
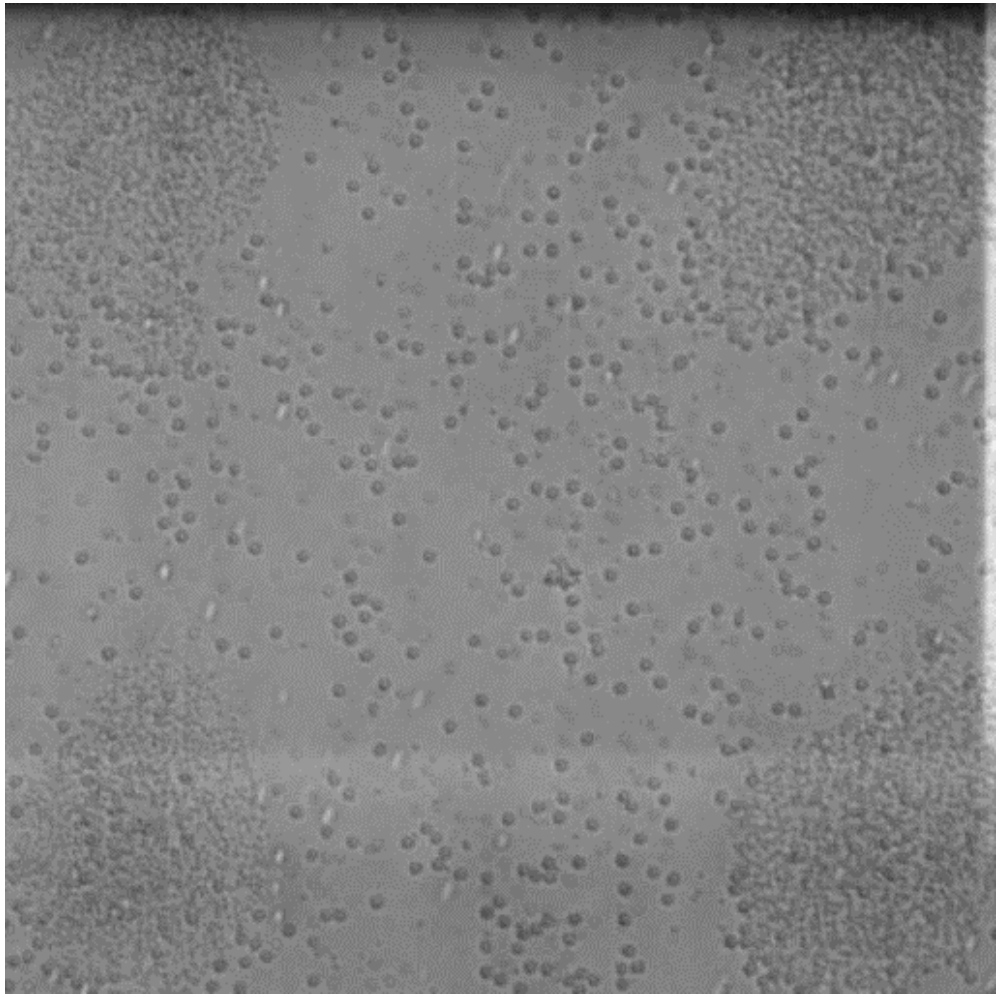
Neutrophil swarming in the presence of inhibitors



Healthy neutrophils



Healthy neutrophils + inhibitors

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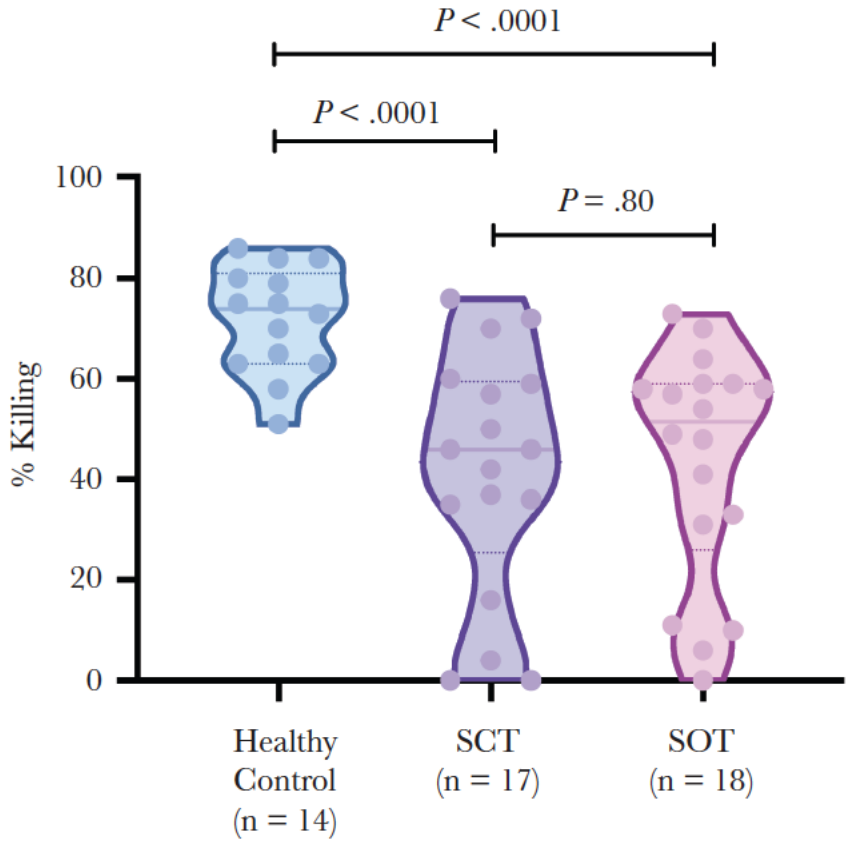
Pilot study - *demographics*

- Transplants:
  1. Renal
  2. Liver
  3. HSCT
- Presenting for outpatient visit 2 months after surgery or BMT
- Feeling well
- Immunosuppression tapered down

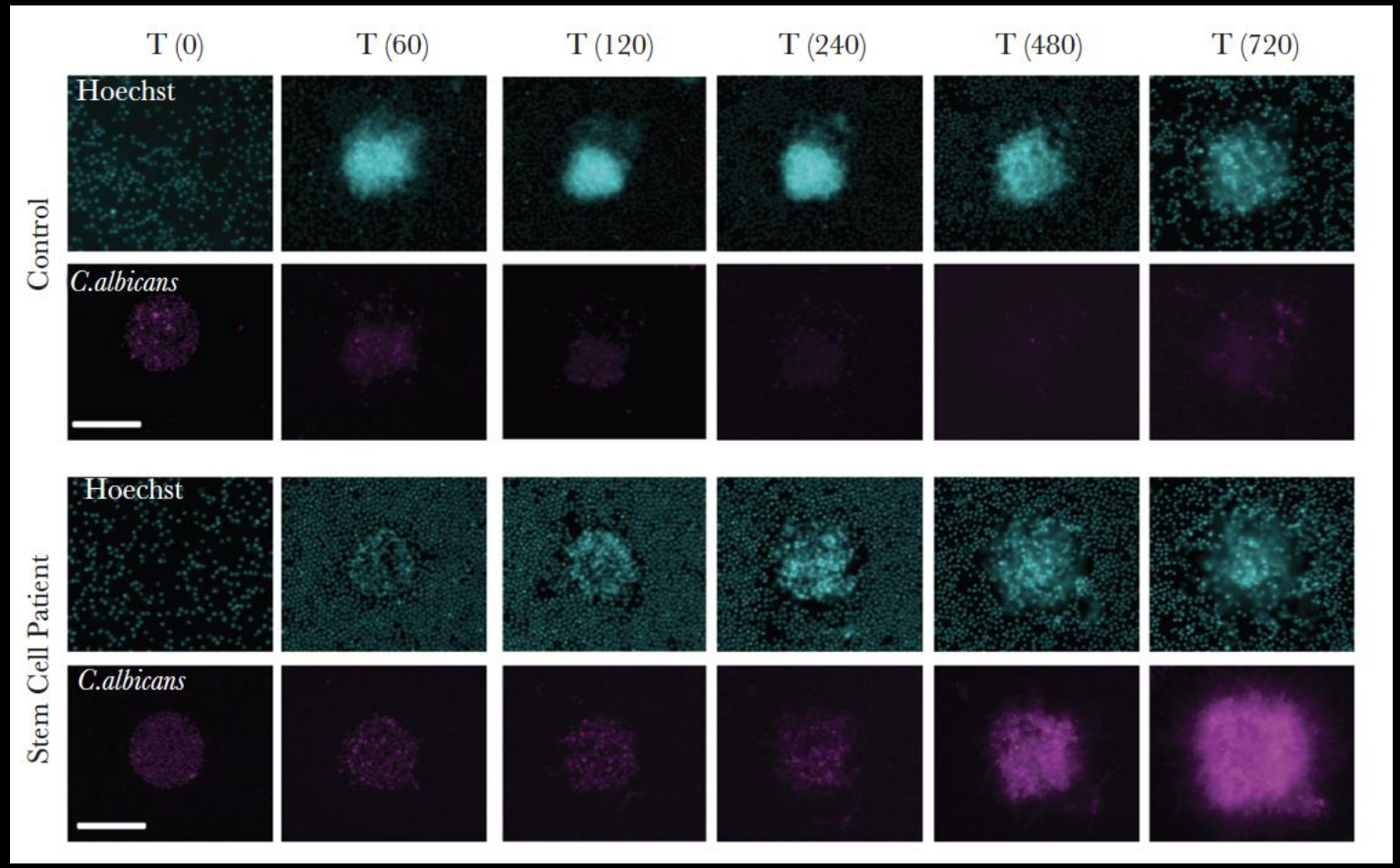
Natalie Alexander

Nico Barros



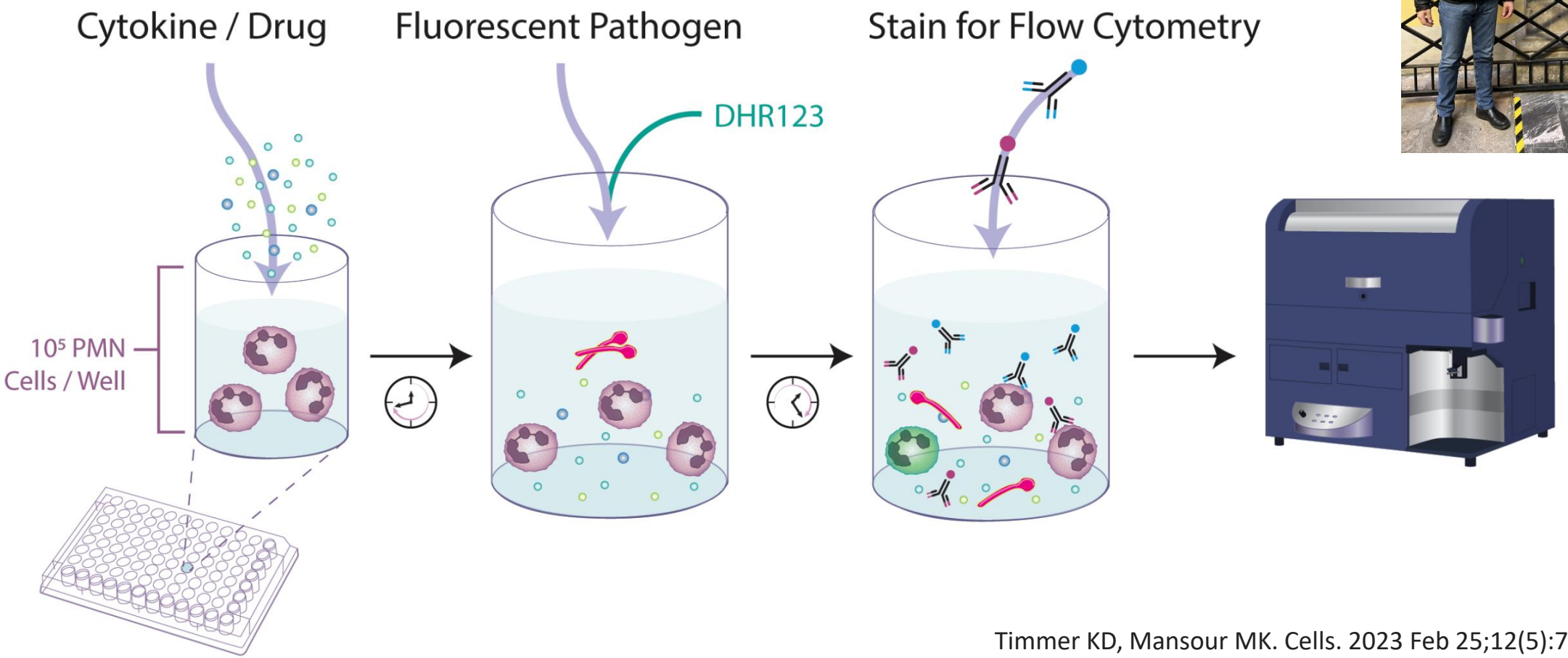
Large spread of responses

Transplant PMN have swarming dysfunction



Rapid multiparametric neutrophil profiling

MultiParametric Assay (MPA)



Timmer KD, Mansour MK. Cells. 2023 Feb 25;12(5):743

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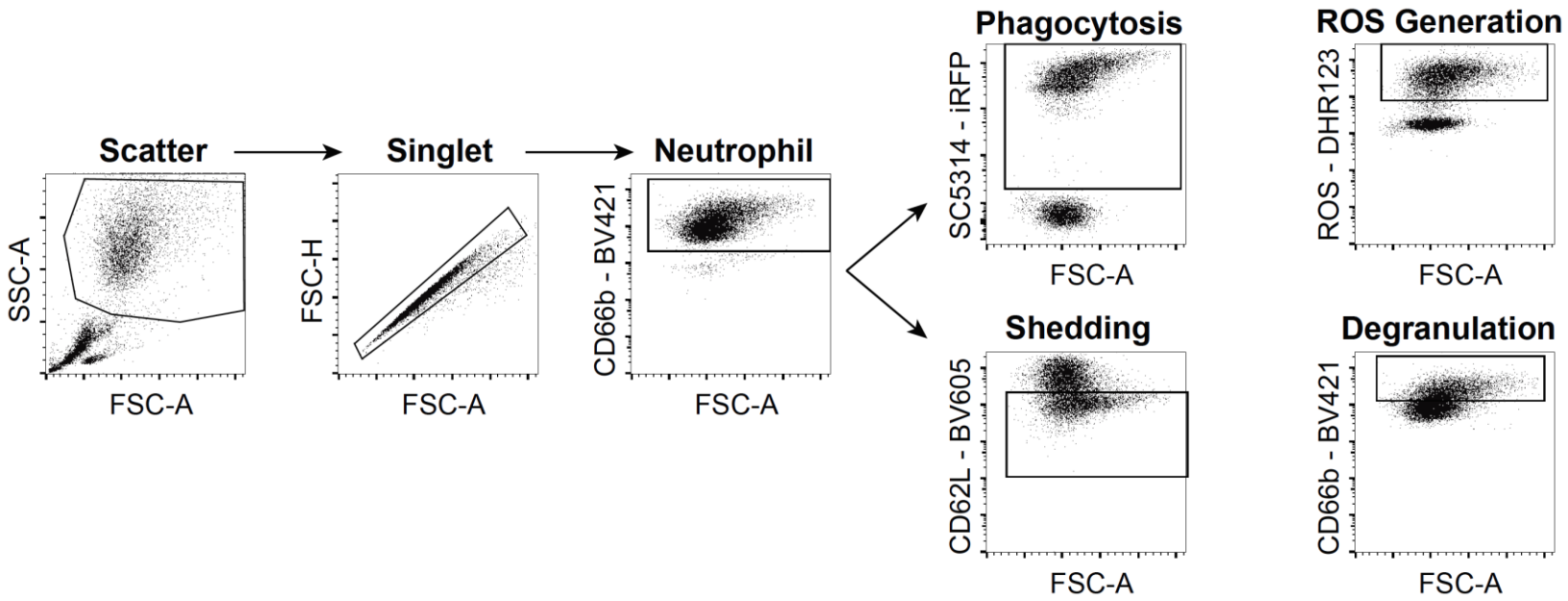

Rapid multiparametric neutrophil profiling

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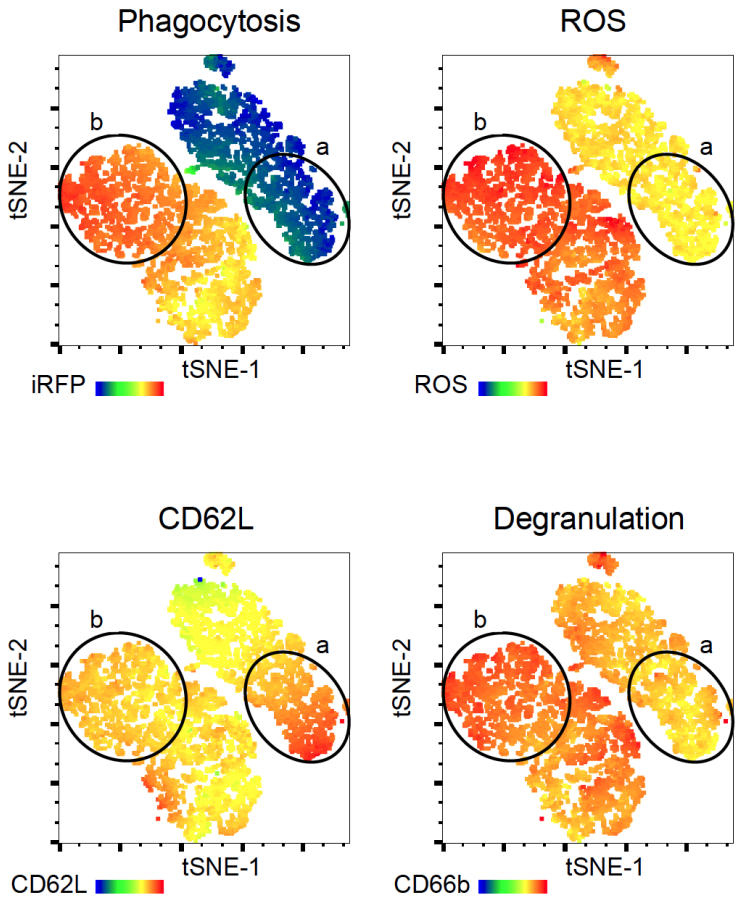

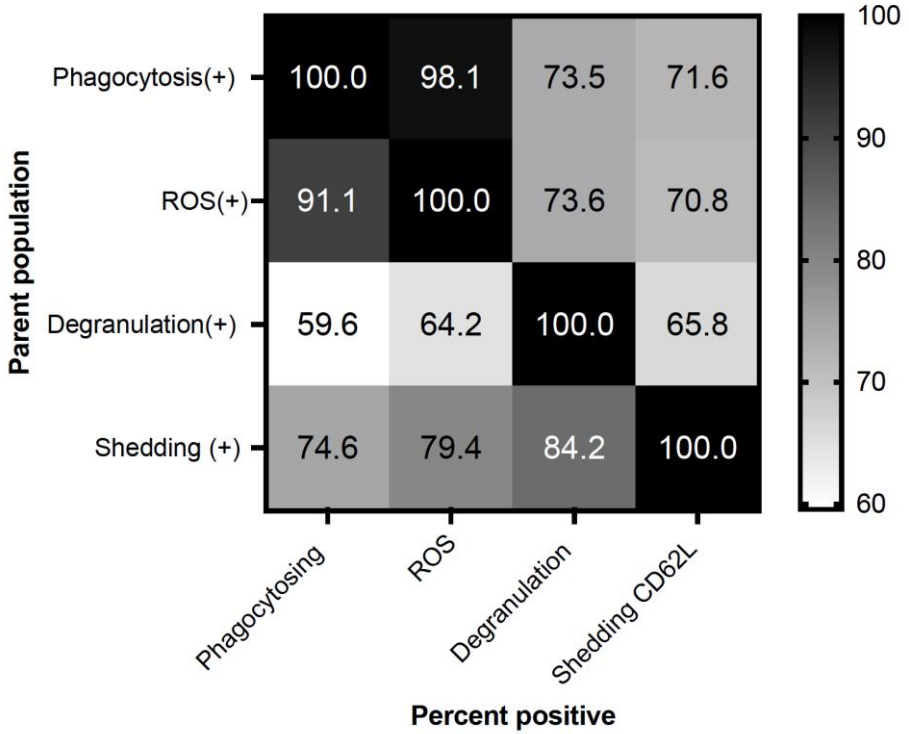

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High-Throughput Screening of Small Molecules for Modulators of the Neutrophil Response

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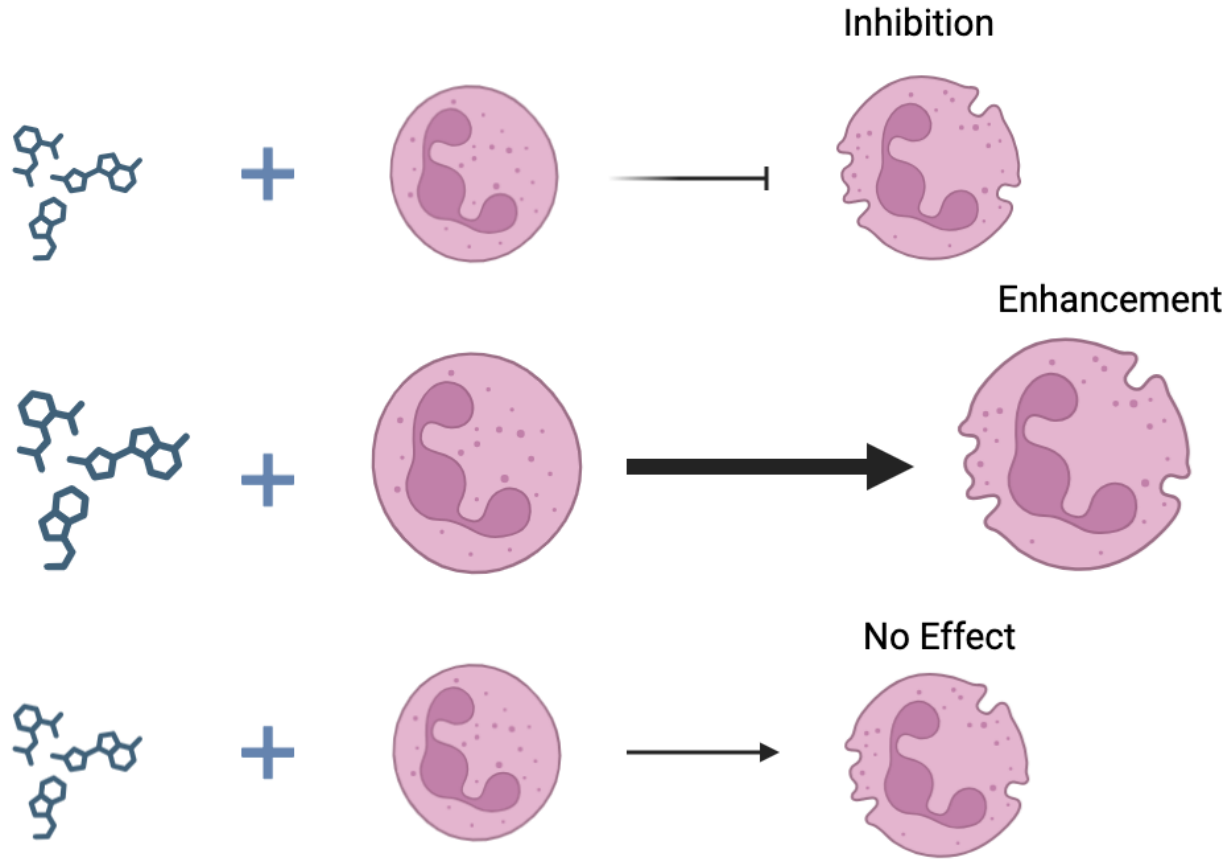
The Screen

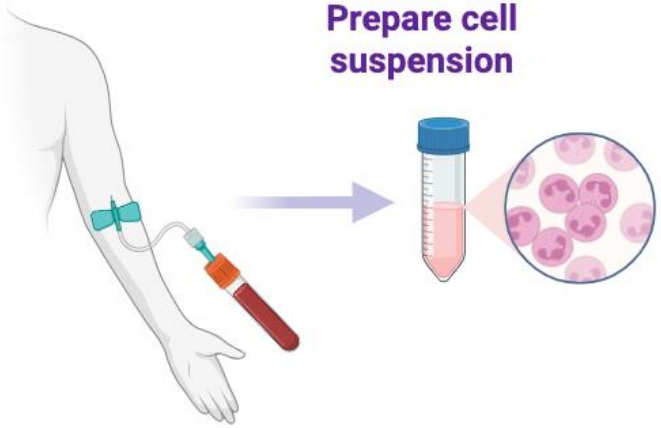
- We conducted a high-throughput, cell-based screen of 2,816 small molecules on healthy donor neutrophils
- We tested a library approved by governing agencies (FDA, EMA, HMA, etc.) or pharmacopoeia (USP, BP, EP, etc.)
- Approximately 3,000 compounds
- Bioactivity and safety have been confirmed in clinical trials.



Workflow

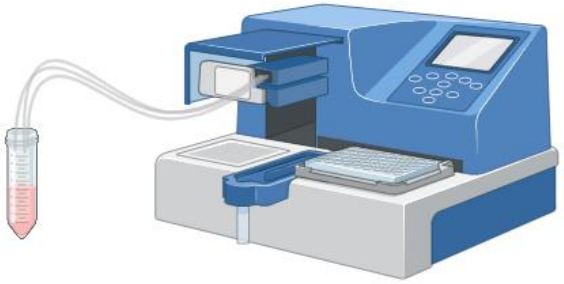
1 Isolate healthy donor primary neutrophils

Prepare cell suspension

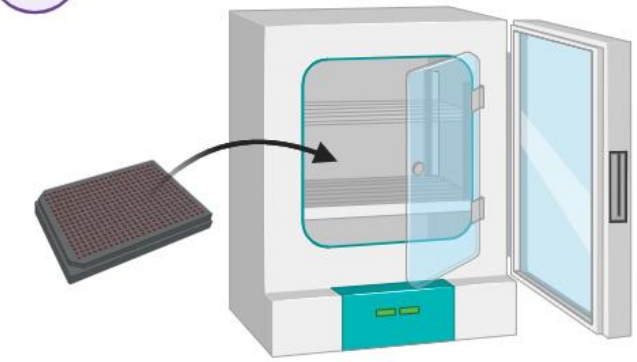


2 Dispense FDA-approved compound library into 384-well plate

3 Dispense neutrophils, ROS dye (DHR123), and stimulus (fMLP or *C. albicans*)



4 Incubate for 60 minutes

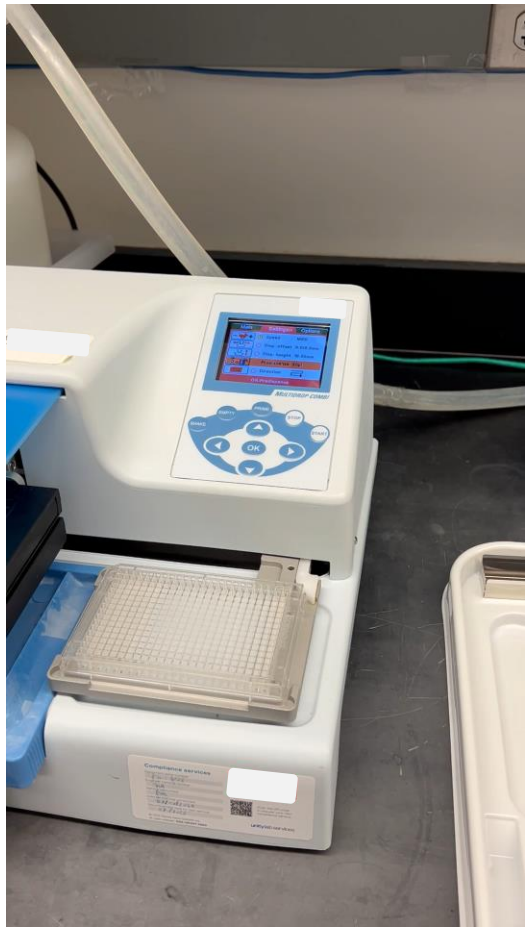


5 Read fluorescence

Equipment

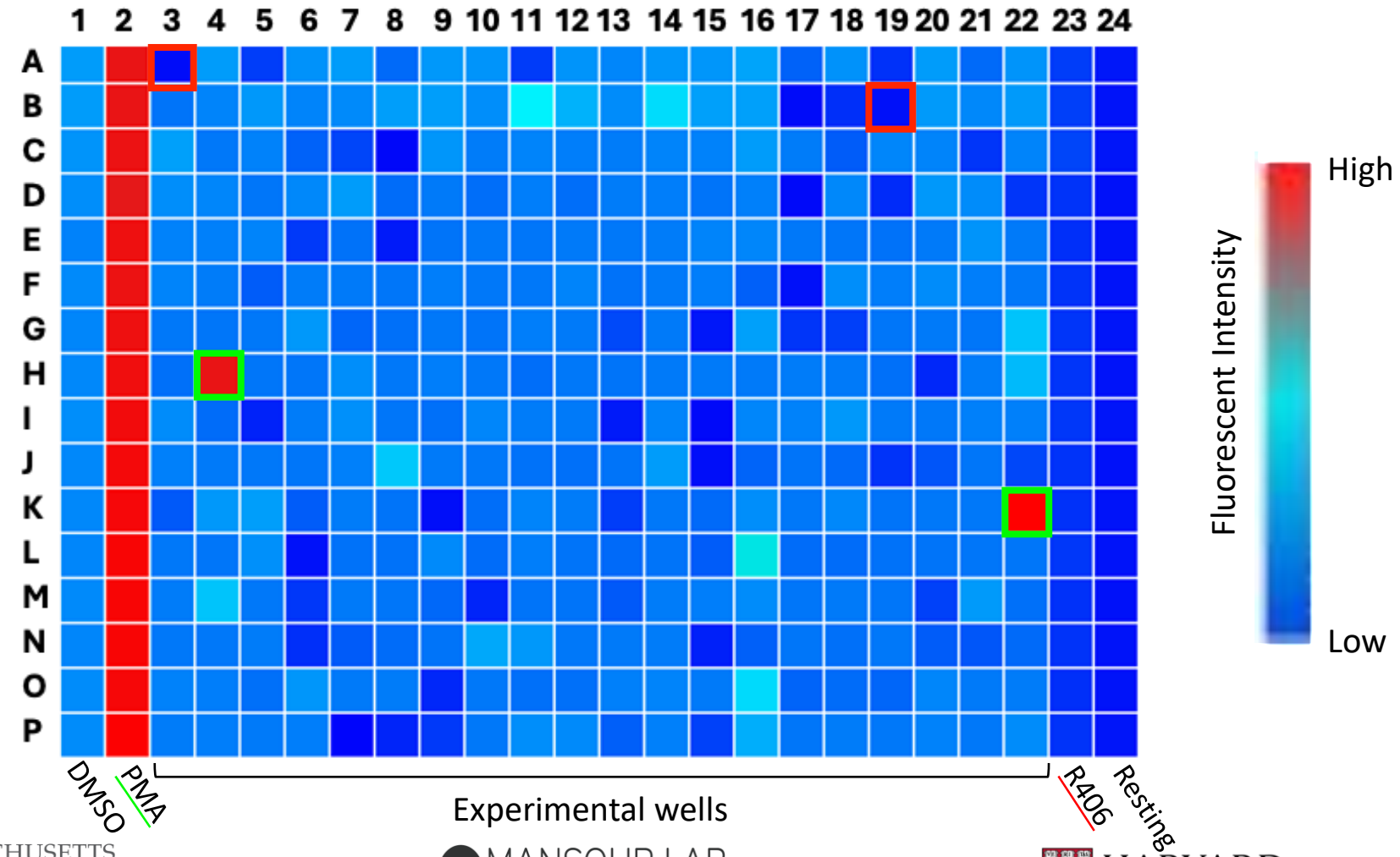
Acoustic Dispenser

Automated Solution Loader



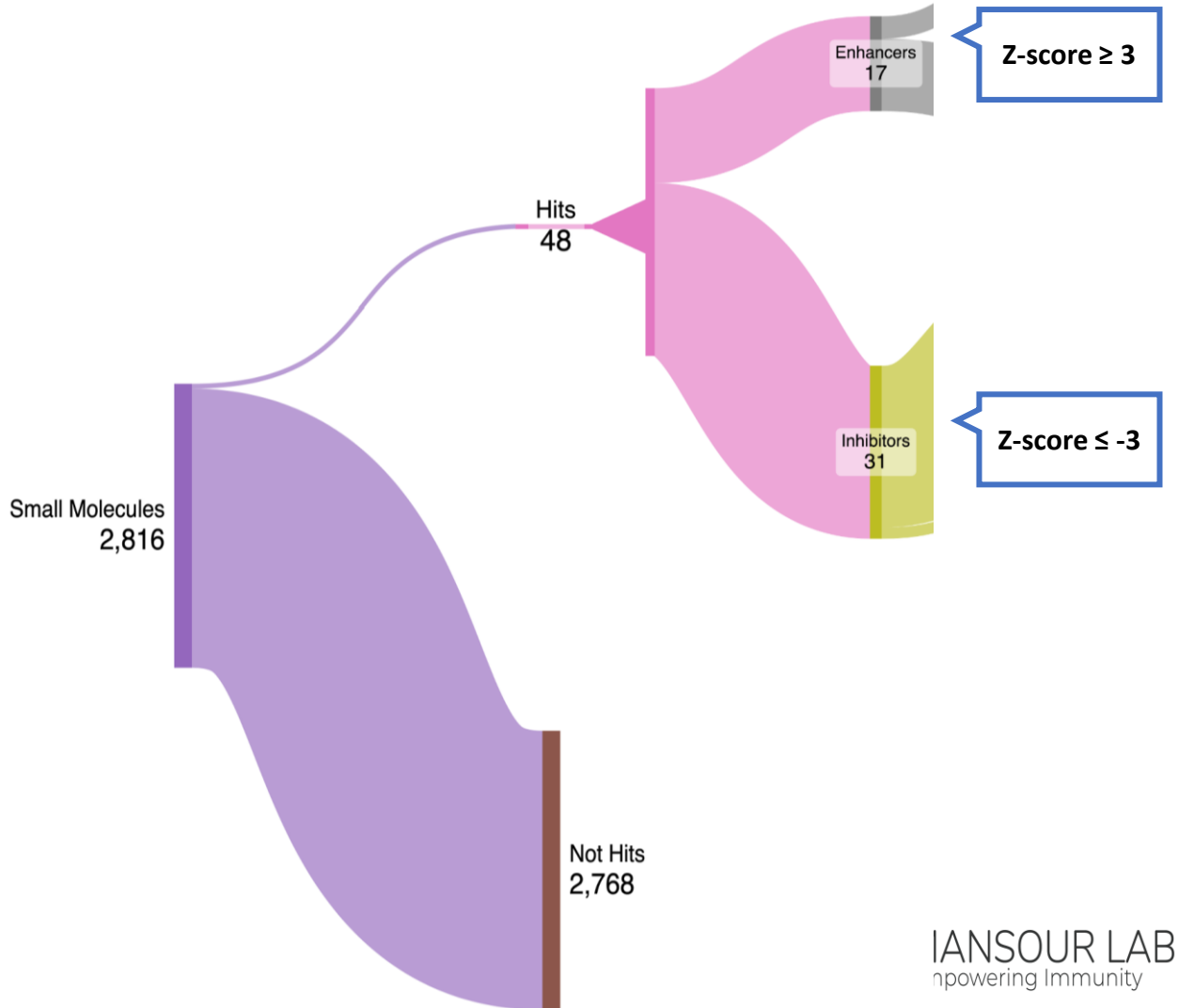
Representative screen plate

- An experimental plate containing potential enhancers and potential inhibitors.



Compound selection

After testing 2,816 compounds in duplicate, 48 compounds had statistically significant z-scores



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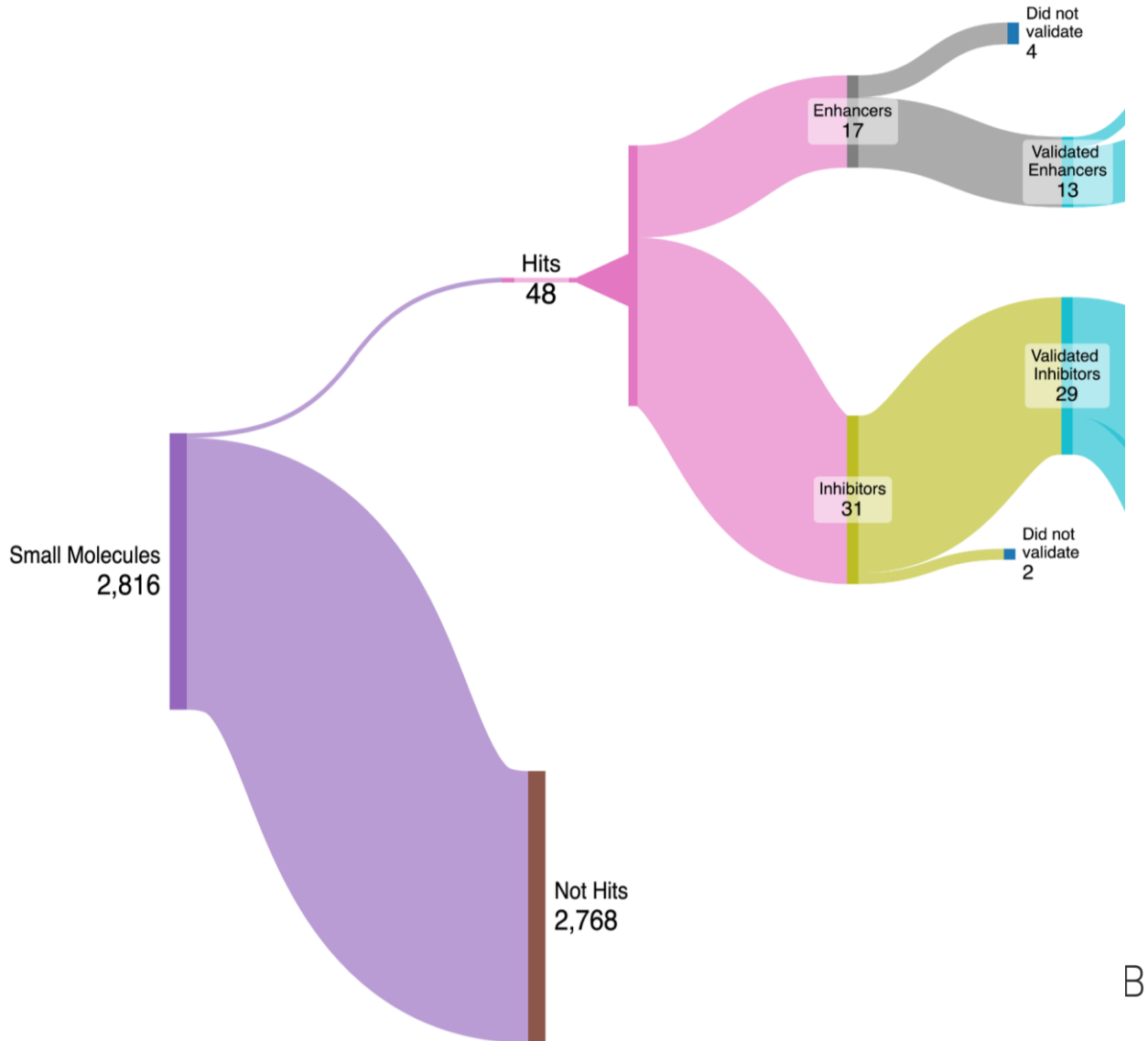
Compound selection

42 out of 48 compounds validated during cherry-pick



B

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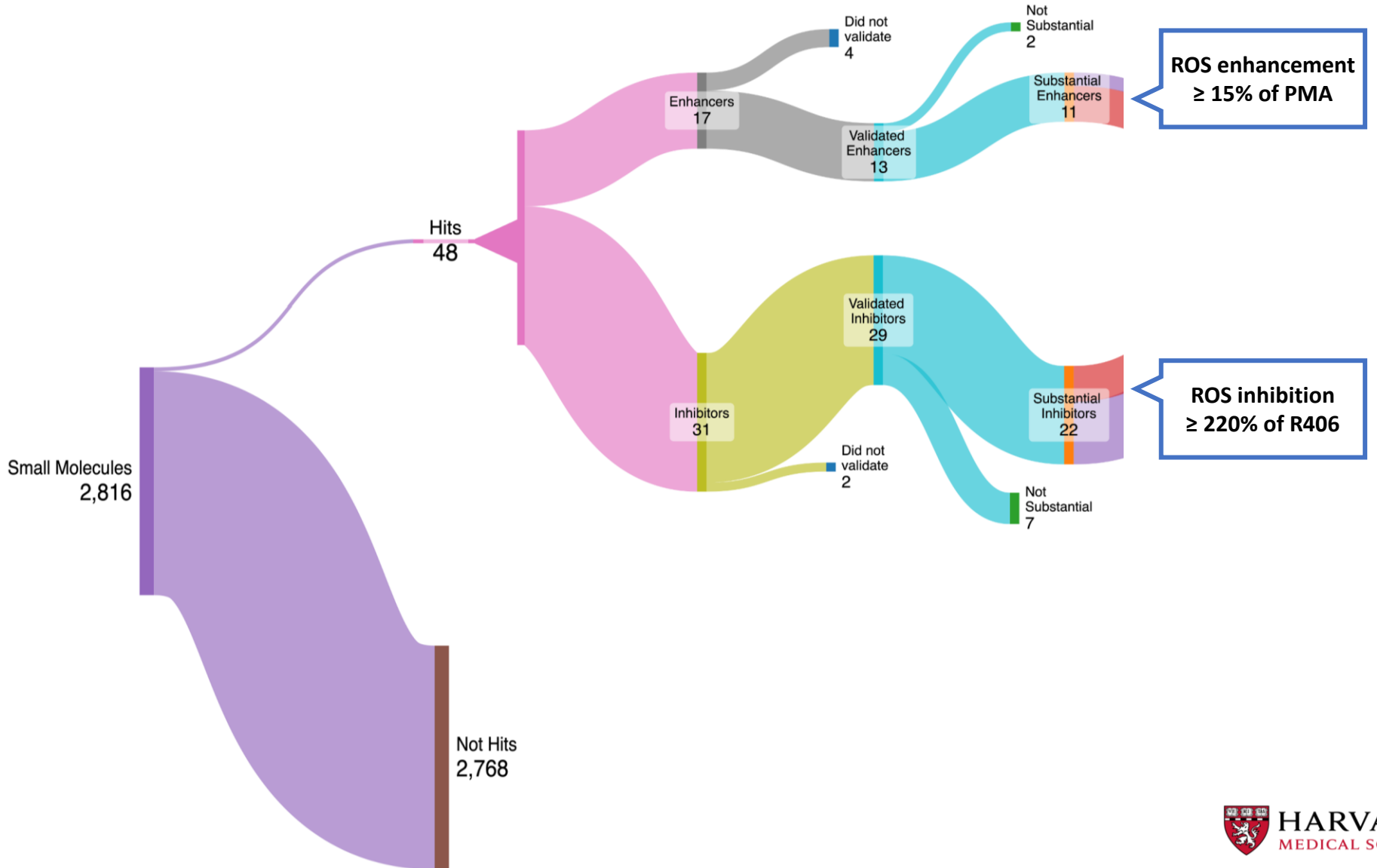
Compound selection

33 compounds had substantial response when normalized to our positive controls



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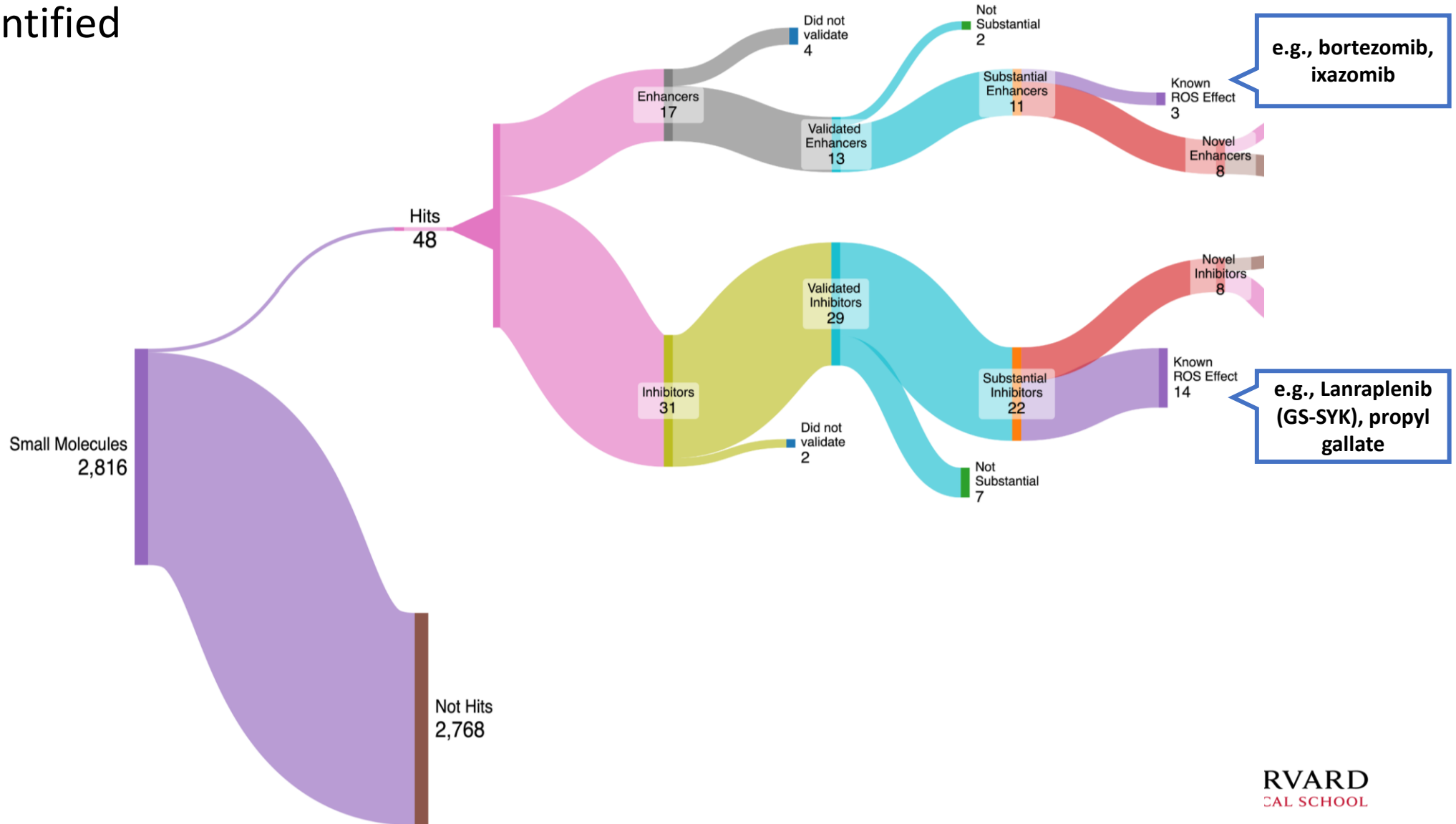
Compound selection

After excluding known augmenters of ROS (i.e., antioxidants), 16 compounds were identified



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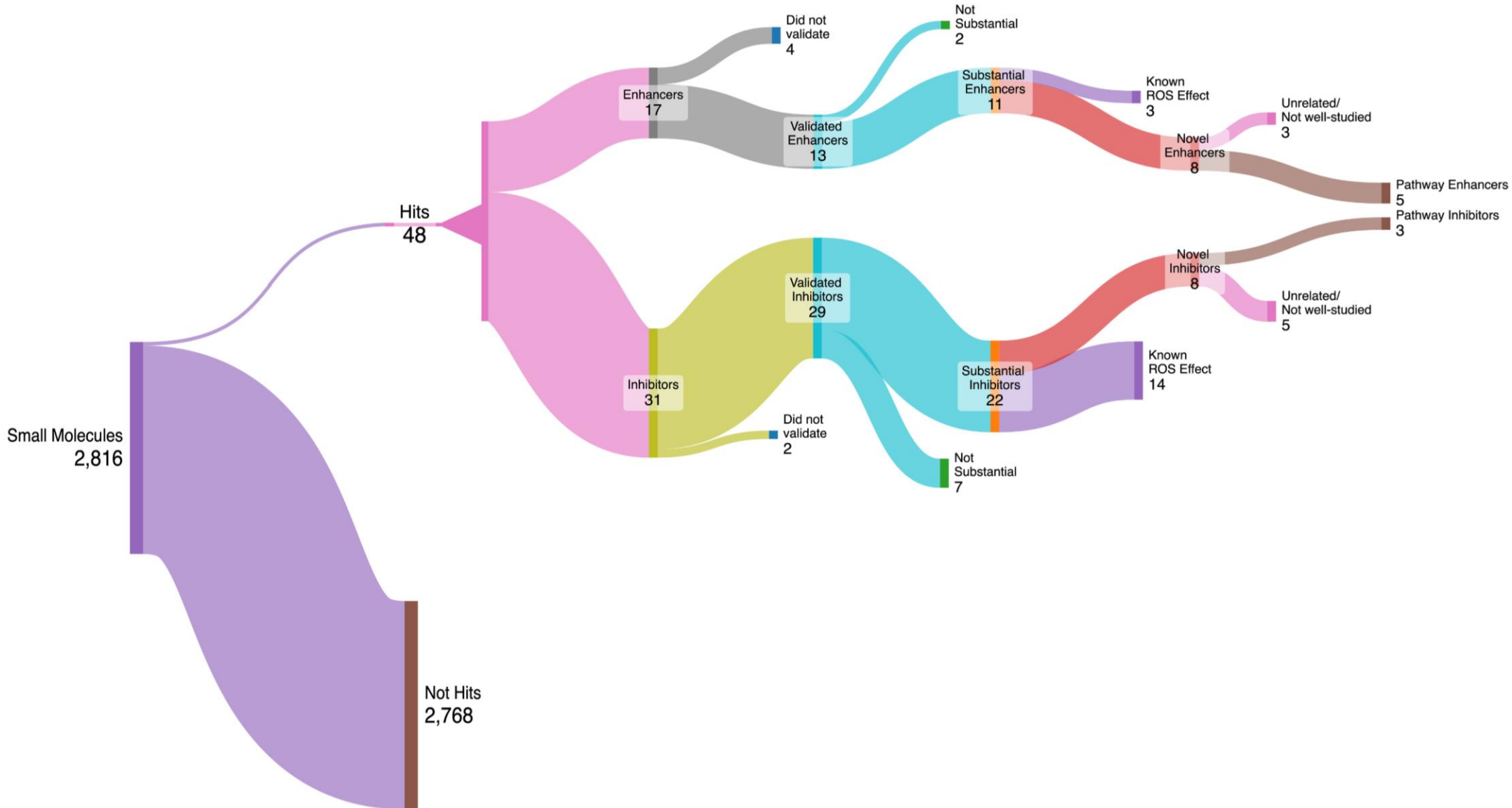
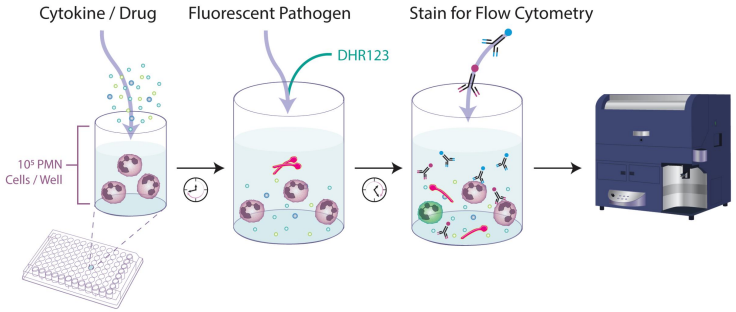
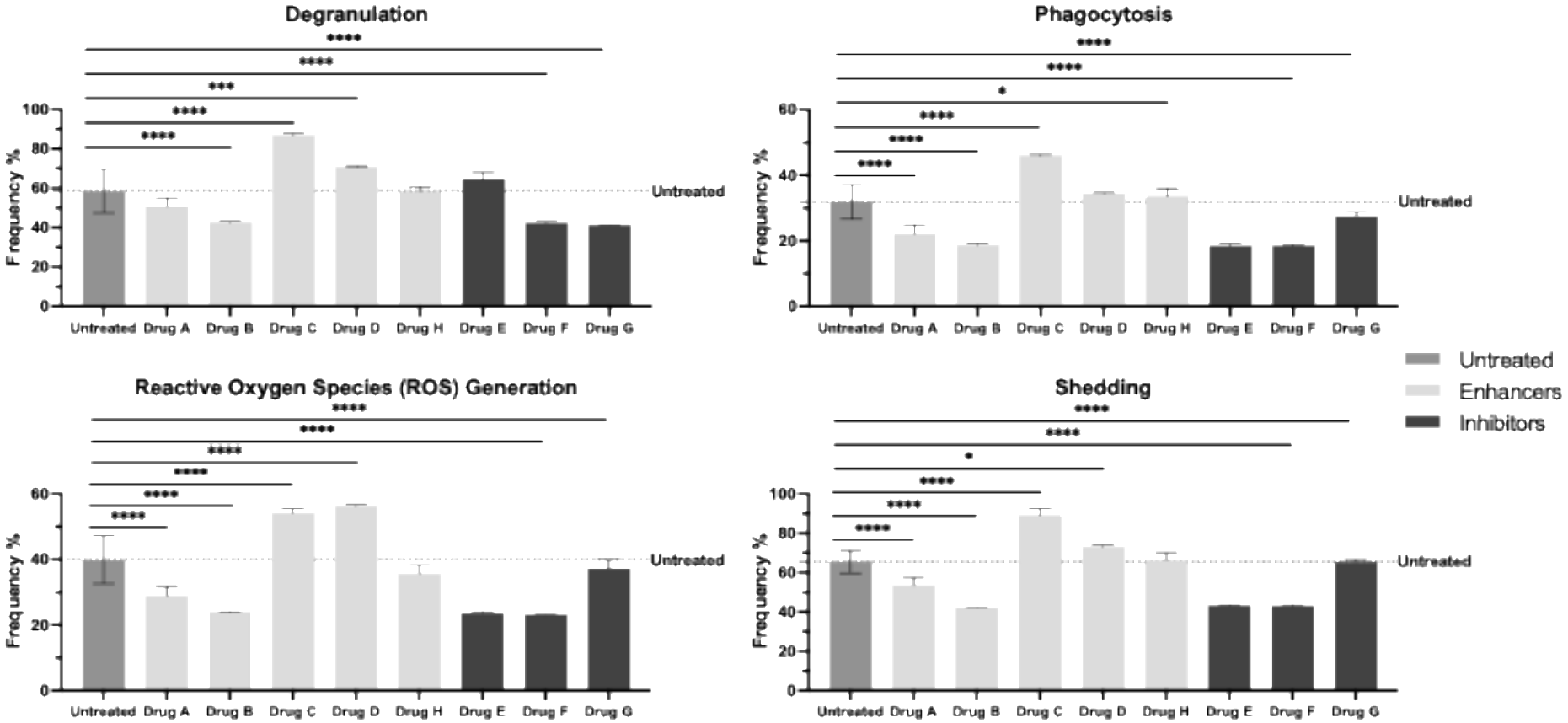
Compound selection

Of these 16 compounds, 8 appear to be working acting on a similar pathway



Validation using multiparametric flow assay





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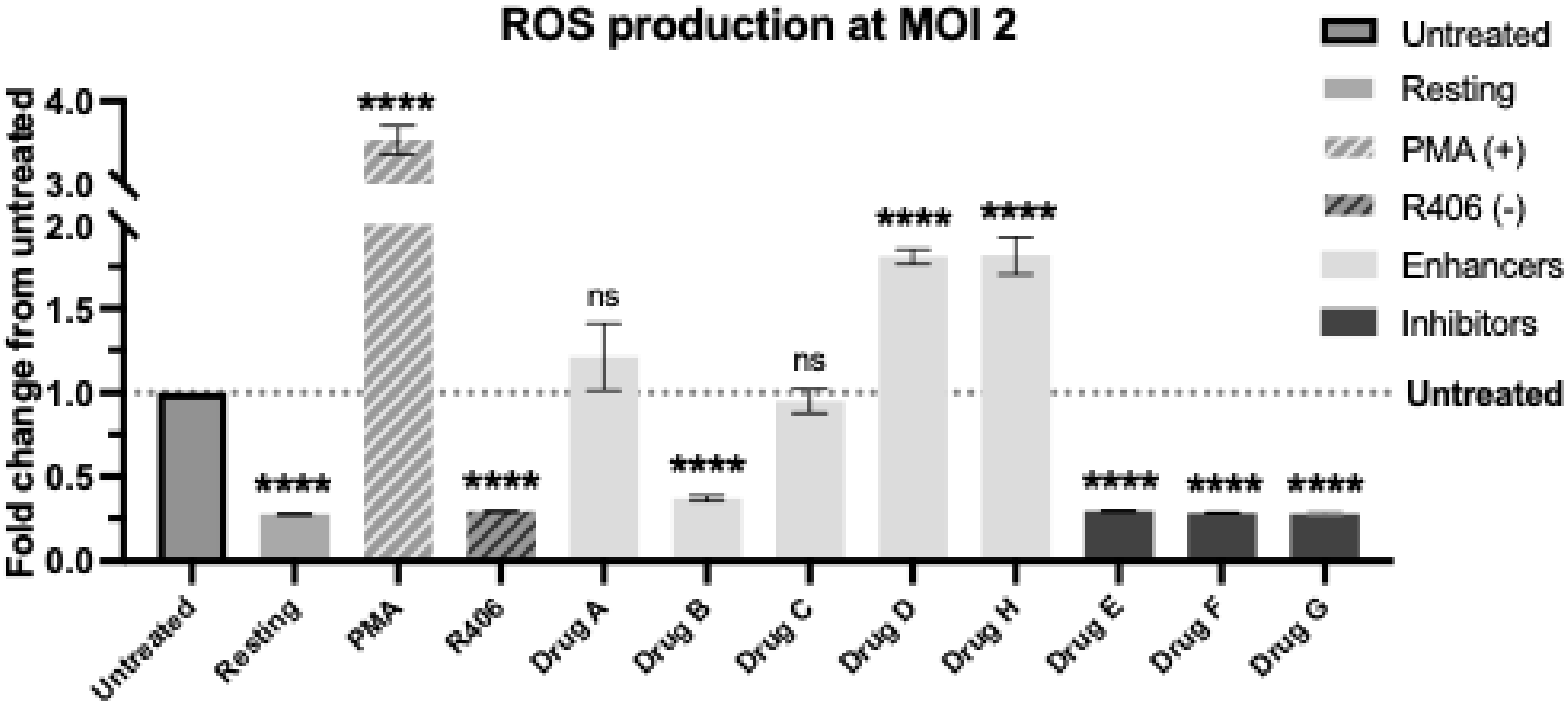
ROS Production



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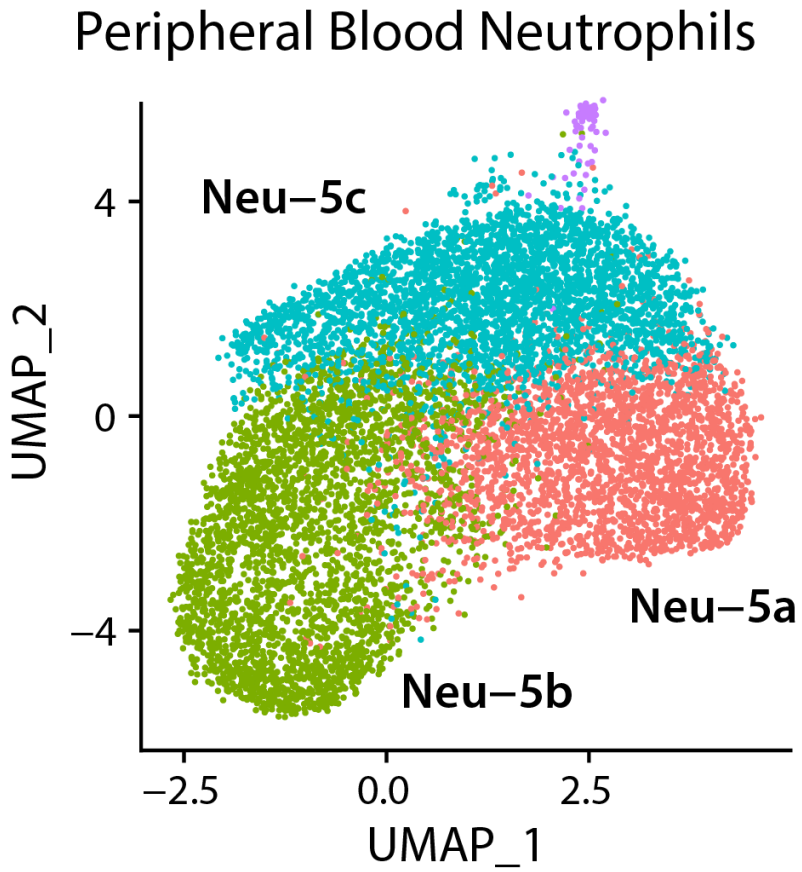
Conclusion

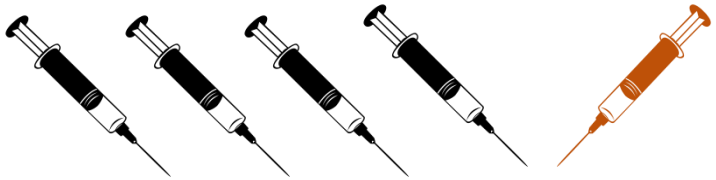
1. Neutrophil dysfunction
   - **Neutrophils are incredibly dynamic cells with multiple functions**
     - **Swarming**
     - **MPA**
     - **In vivo assays**
     - **Heterogeneity**
2. Clinical cohorts
   - **Functional differences exist in multiple patient cohorts**
3. Therapeutic implications
   - **Augmentation – drug screen**
     - **Drug screen identifies several small molecules**
   - **Cytokines**
   - **Cell therapy?**



Cell Therapy for Ionizing Radiation or MDR Infection

C. albicans
+ saline only

C. albicans
+ engineered
neutrophils



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David Sykes
David Scadden

MGH Transplant Center

Broad Institute of
MGH, MIT and Harvard

Wellman Center for Photomedicine
Charles Lin

National Institute of Allergy and Infectious Diseases

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