

SURF'S UP

For Academic Drug Discovery
at UC Santa Cruz

Beverley M. Rabbitts, PhD
Director of Operations
UCSC Chemical Screening Center

RRID SCR_021114

13 October 2023



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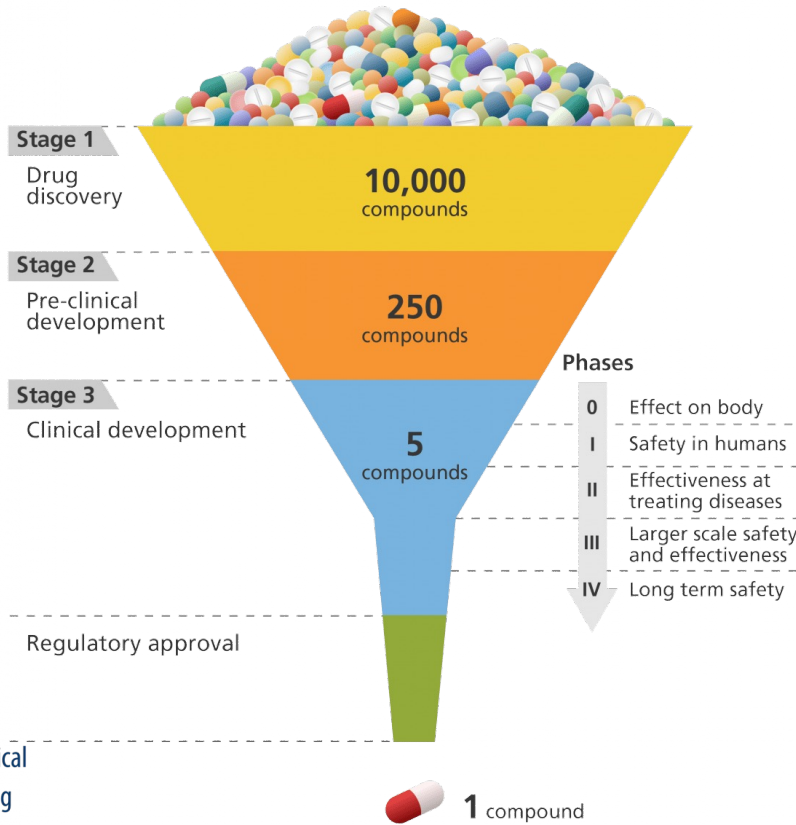
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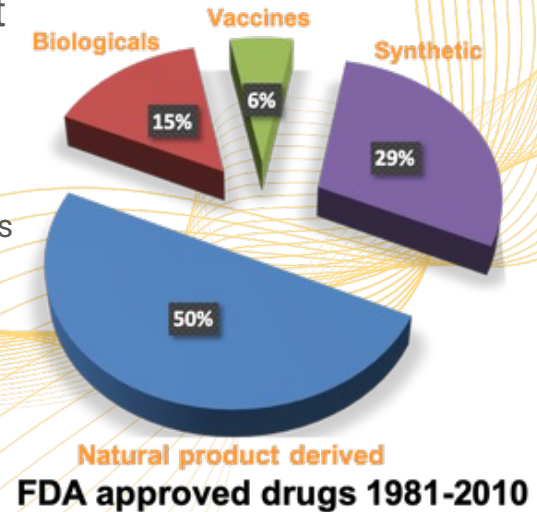
Can universities realistically discover new drugs?

<https://alzheimers.med.umich.edu/>



The opportunity lies in focusing on areas where:

- the university has expert biologists
 - engaged in designing custom assays
 - motivated to pursue follow-up studies on hits
 - ...but how do the biologists know when their project could use our resources?
- the drugs are not expected to be highly profitable
 - rare diseases
 - natural products

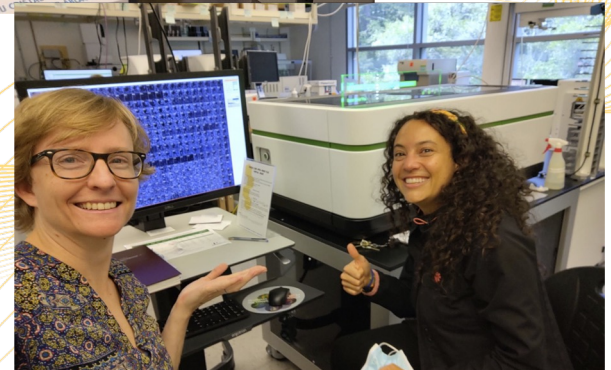


Source: Vinayak Agarwal @ Georgia Tech

High content screening and machine learning for identifying immune-modulating natural products

Talk outline:

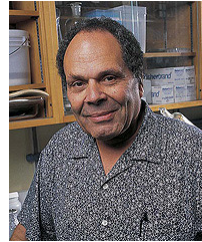
- Introduction
 - natural products research at UCSC
- Methods
 - Types of screening assays
 - High content screening with macrophages
 - Compound libraries
 - Instrumentation
 - Machine learning
- Results
 - Kinase inhibitor hit validation with cytokines



UC Santa Cruz is a hub for experts on natural products



news.ucsc.edu

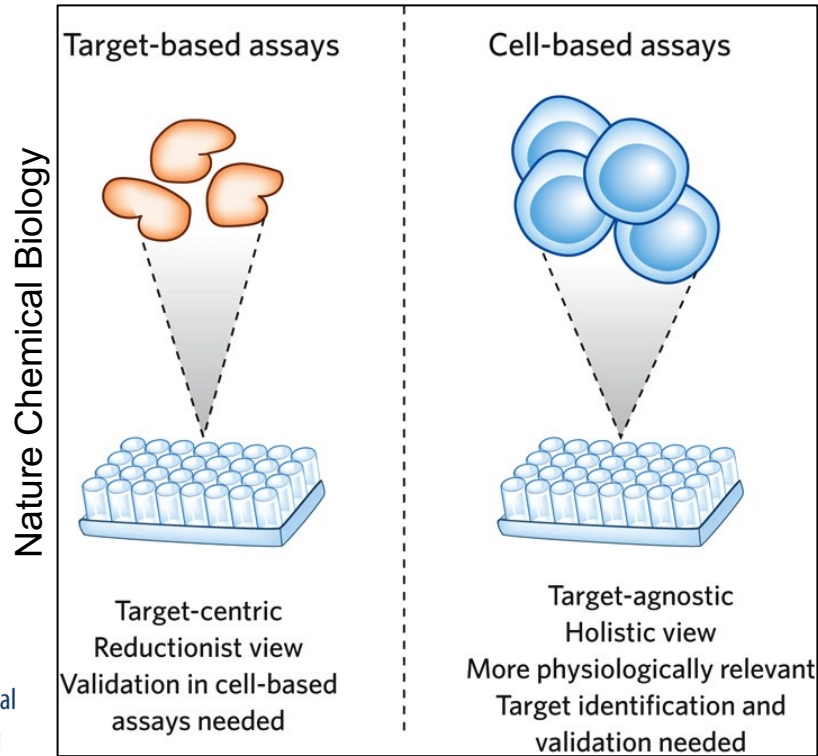


The HiFAN group is funded by the NIH to address these roadblocks in natural product research:



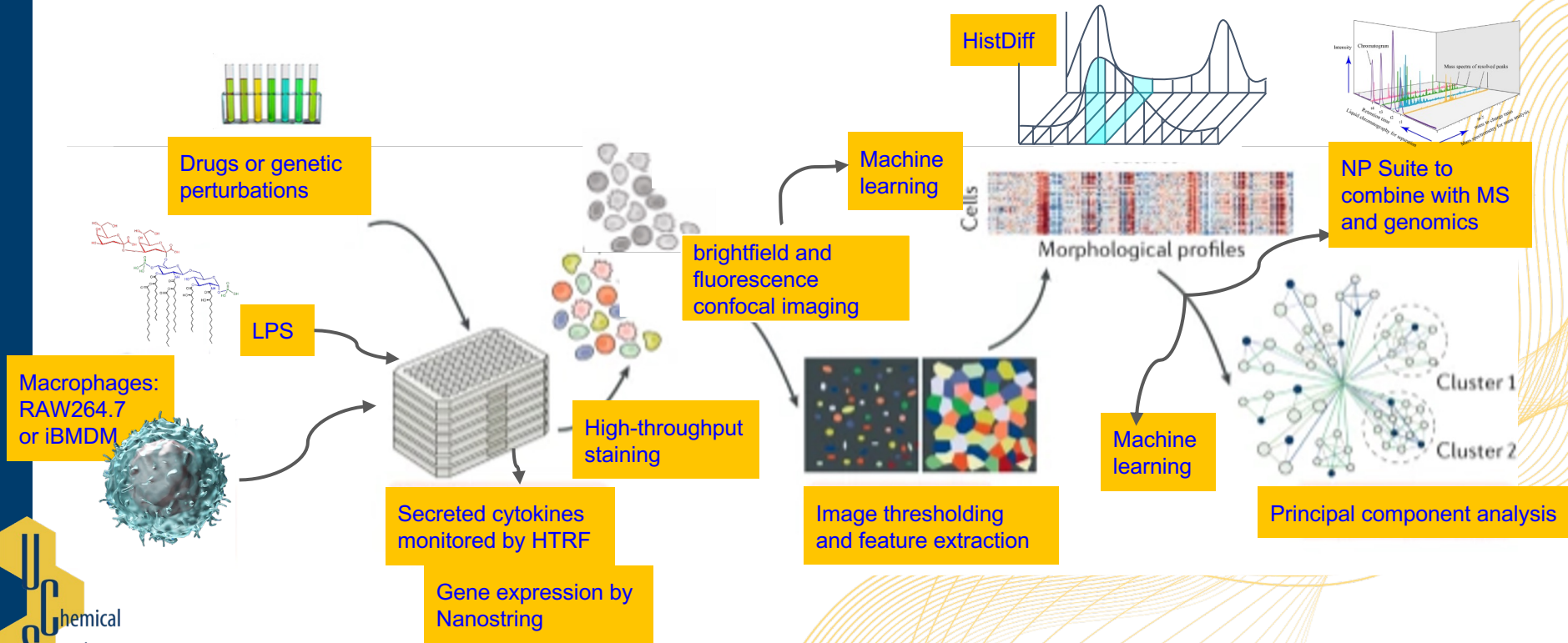
- obtaining a complete chemical makeup of botanical extracts.
- deconvoluting which constituents are sufficient for medicinal effects.
- identifying the mechanism of action of the active ingredients (CP, NanoString, antivirals).

Two approaches to drug discovery



- For this project, we were interested in discovering mechanism of action, especially related to immune modulation, so we used **cultured macrophages**.
- We took advantage of heterogeneous phenotypes by doing **single-cell high content screening**.
- This was done with or without **immune stimulation by lipopolysaccharide**, to highlight anti- and pro-inflammatory compounds.

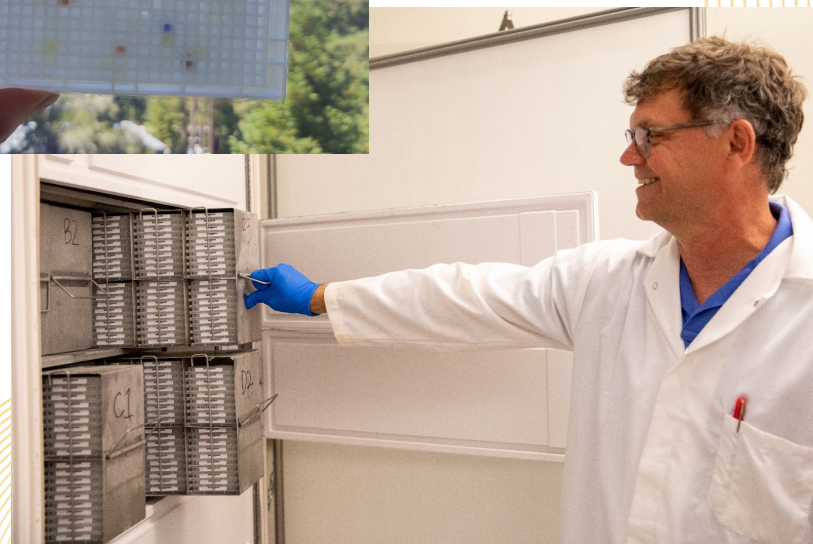
Macrophage high content screening at the CSC



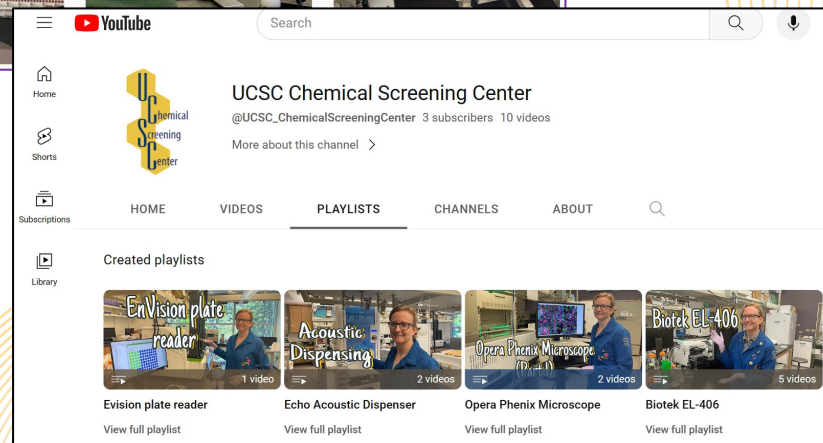
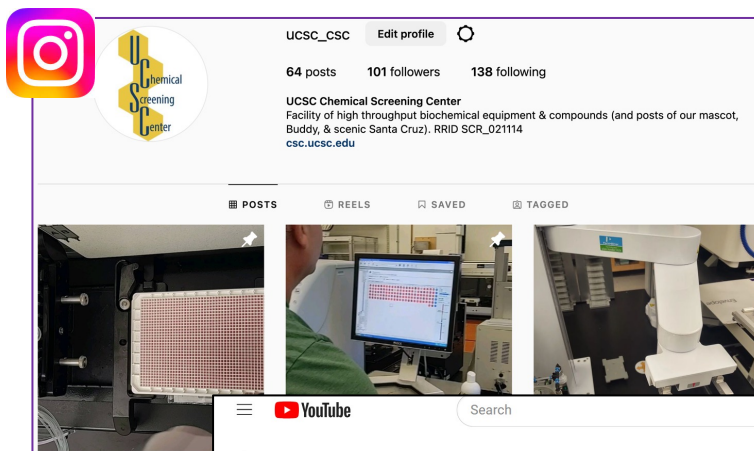
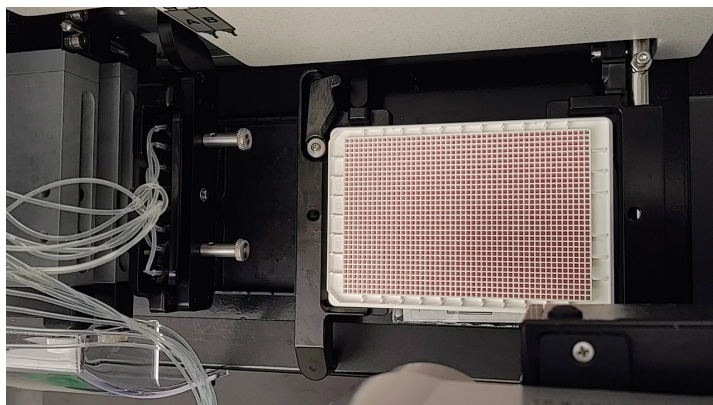
Mechanism of action assignment by CP is limited to the phenotypic space covered by your reference dataset.

CSC compound libraries:

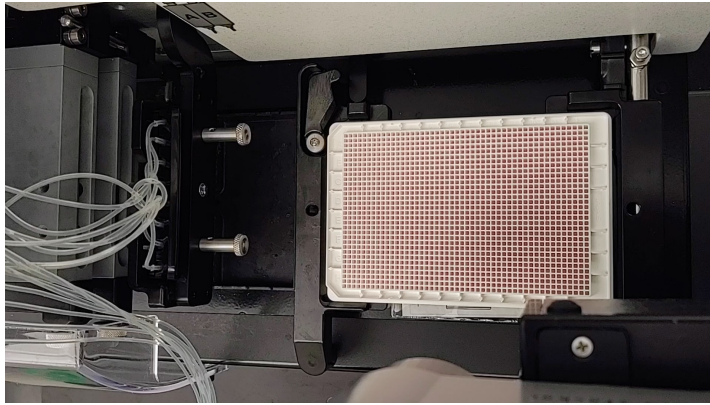
- **known bioactives** (8,387)
- UCSC natural products (~10,000)
- NCI natural products (100,000)
- cyclic peptides (~100,000)
- synthetic fragments (1,262)
- diversity compounds (87,000)



End-to-end workflows with lab automation



End-to-end workflows with lab automation



Imagers



Acoustic dispenser

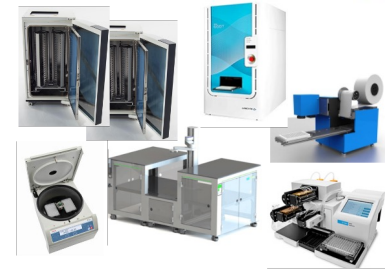
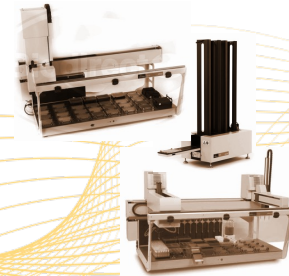


Plate readers



Pipetting and pinning robots



Bulk dispensers & plate washers

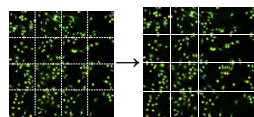


...and more

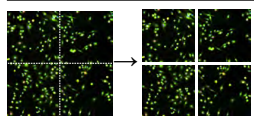


Comparing different machine learning methods

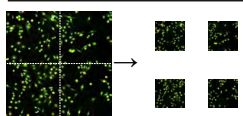
A. Crop 270px → 270px (c270)



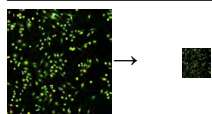
Crop 540px → 540px (c540)



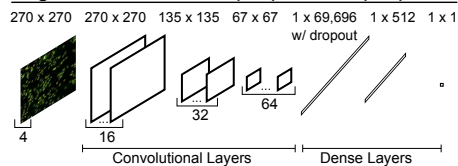
Crop 540px → Resize 270px (cr540)



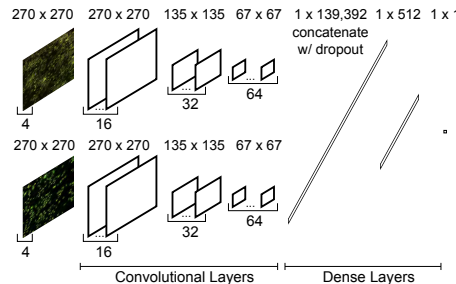
1080px → Resize 270px (r1080)



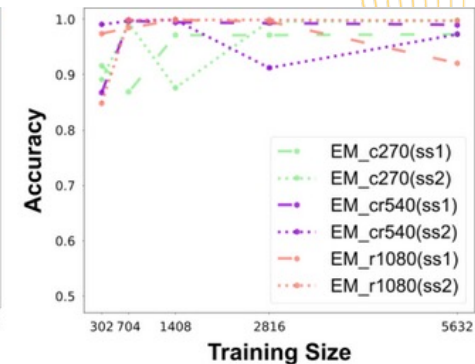
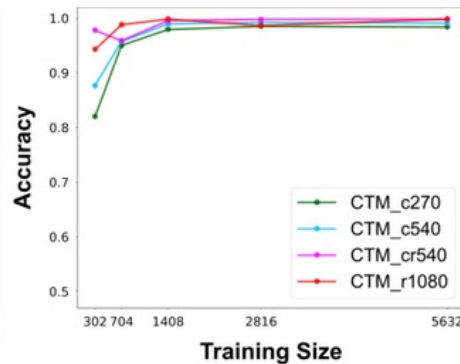
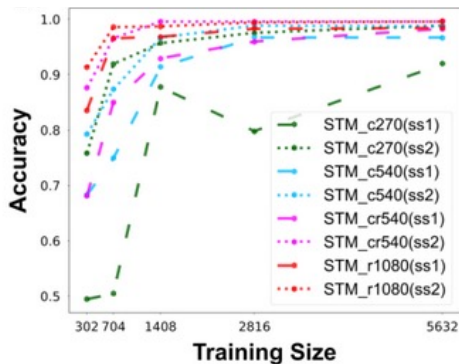
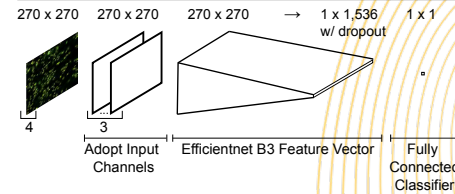
B. Single Tower Model: STM(ss1) and STM(ss2)



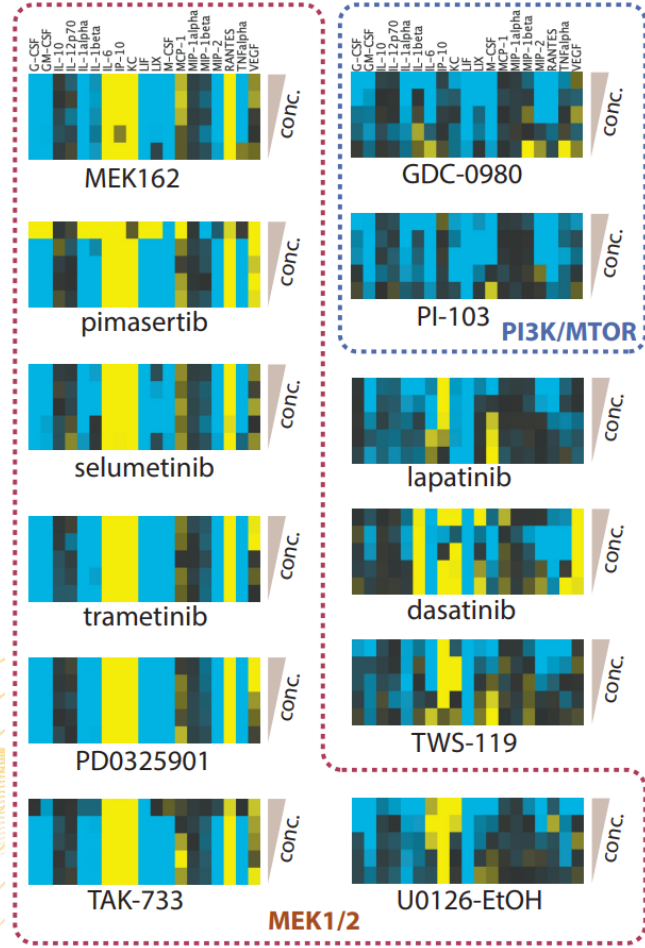
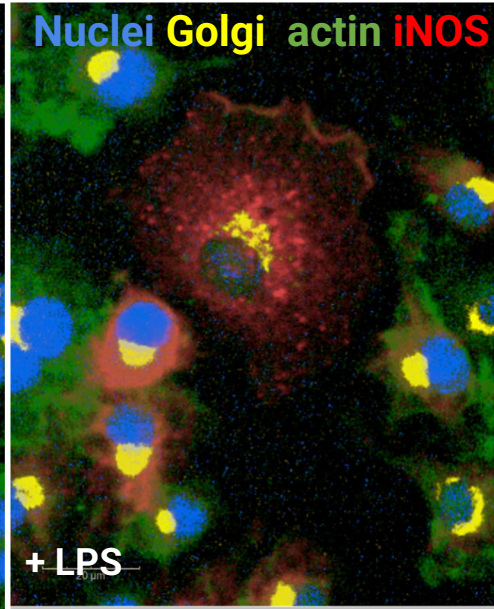
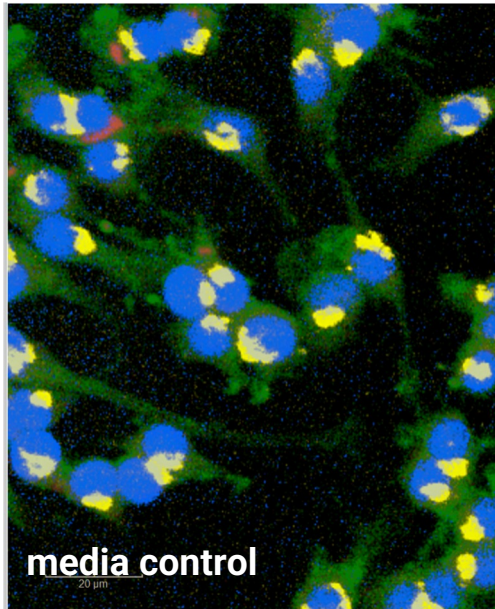
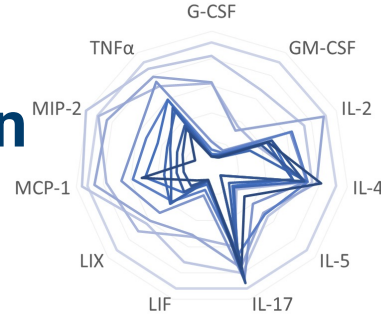
C. Combined Tower Model: CTM(ss1+ss2)



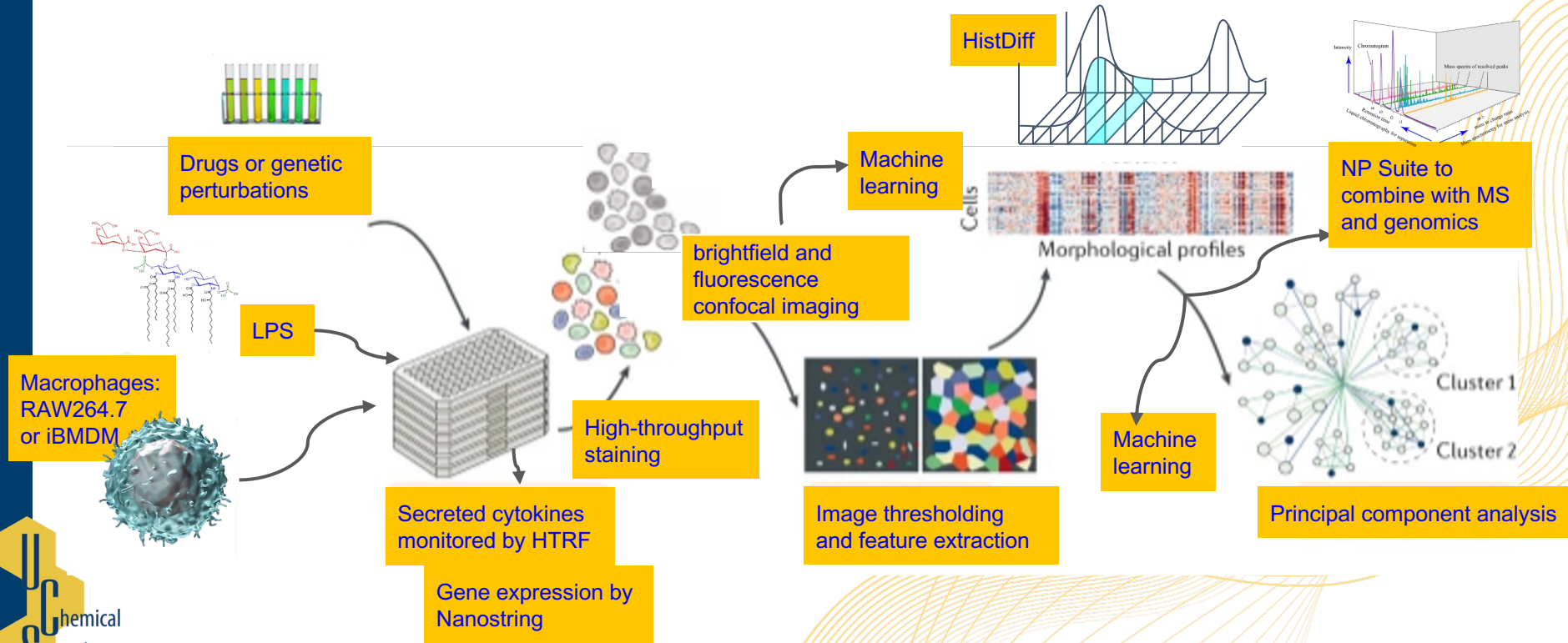
D. Efficientnet Model: EM(ss1) and EM(ss2)



Follow-up experiments profiling iNOS expression and cytokine secretion for kinase inhibitor hits



Ongoing studies with macrophage high content screening



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Email:
brabbitts@ucsc.edu

YouTube:
[UCSC_ChemicalScreeningCenter](https://www.youtube.com/UCSC_ChemicalScreeningCenter)

Instagram:
[UCSC_CSC](https://www.instagram.com/UCSC_CSC)

