Data science in cell imaging

Lecture 7: deep learning in microscopy

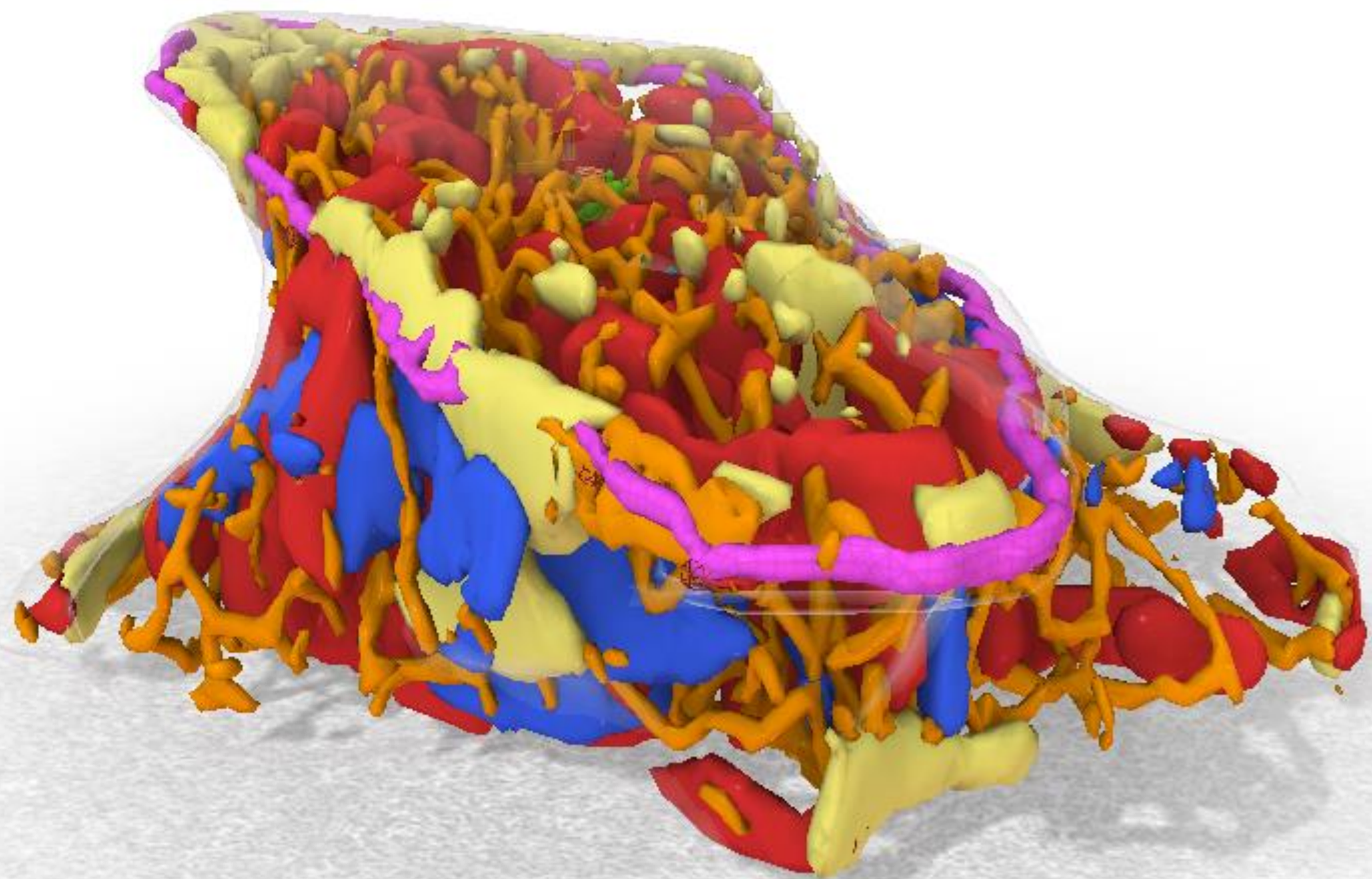
“The Great Wave off Kanagawa”, by Hokusai, ~1830 (Source: Wikipedia)

Last week

- Generative models for cell structure with deep learning
- Classifying cell state with deep learning

Look at a cell and know what it is doing

What it did

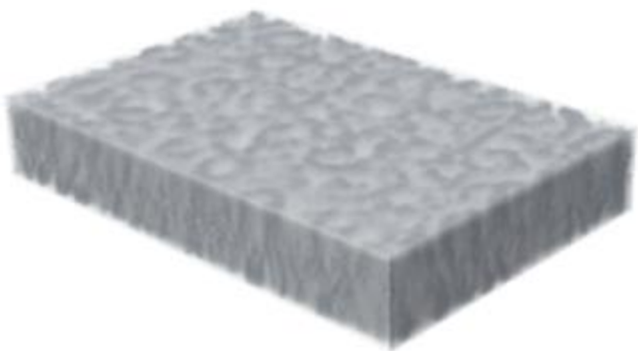


What it will do

Structure ↔ Function

Slide adapted from Susanne Rafelski, Allen Institute of Cell Science

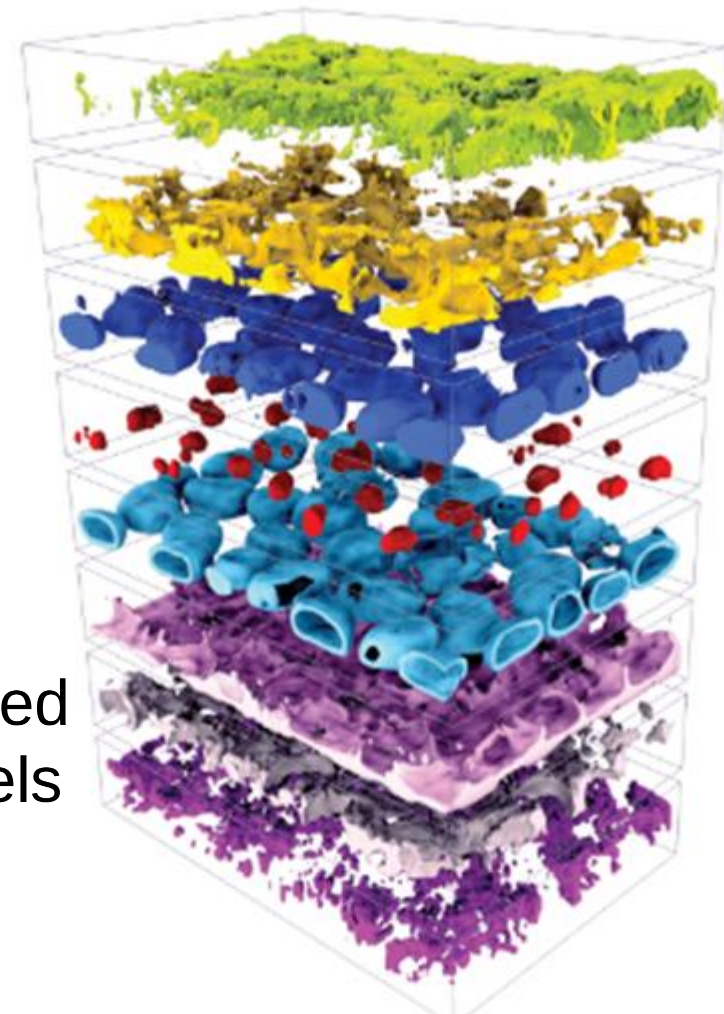
Label-free images contain information on the molecular organization of the cell!



Bright field

Predictive models

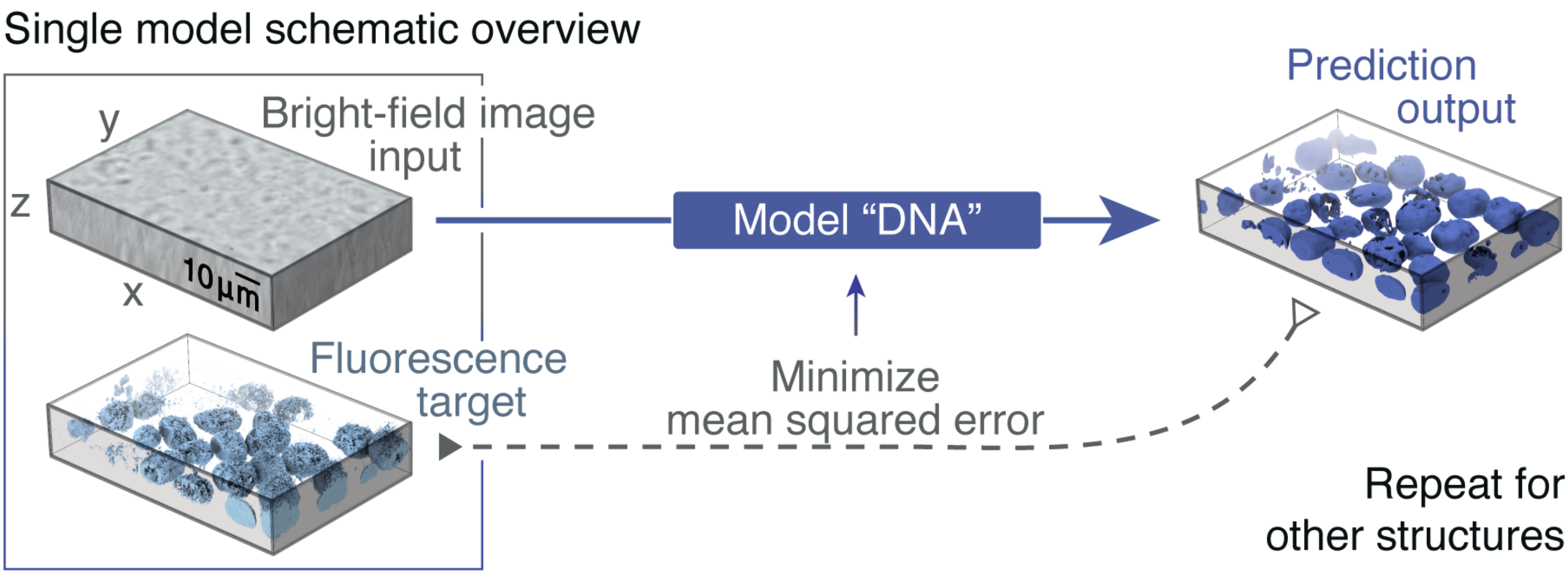
Predicted channels



Ounkomol et al. (2018)

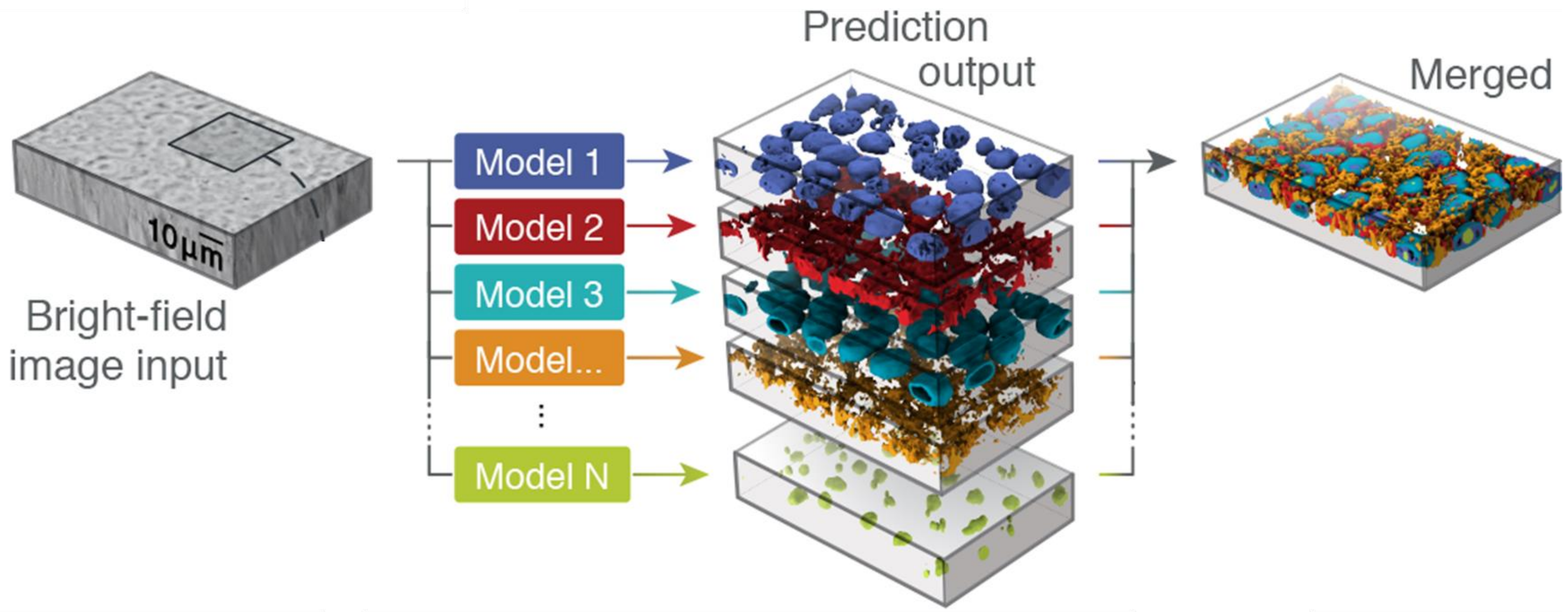
Christiansen et al. (2018)

Unstructured-to-structured information with supervised models



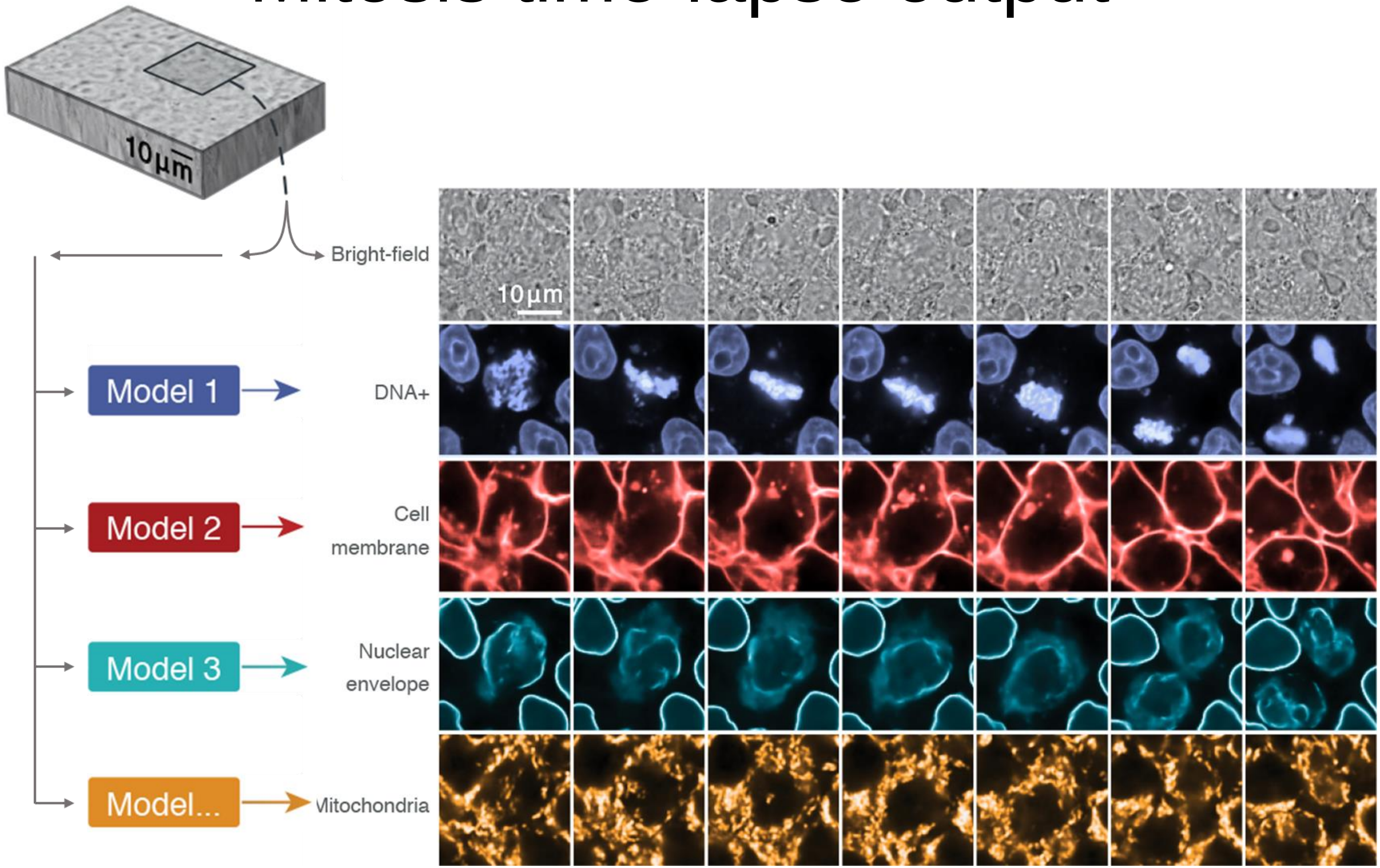
Ounkomol et al. (2018)

Combining multiple models



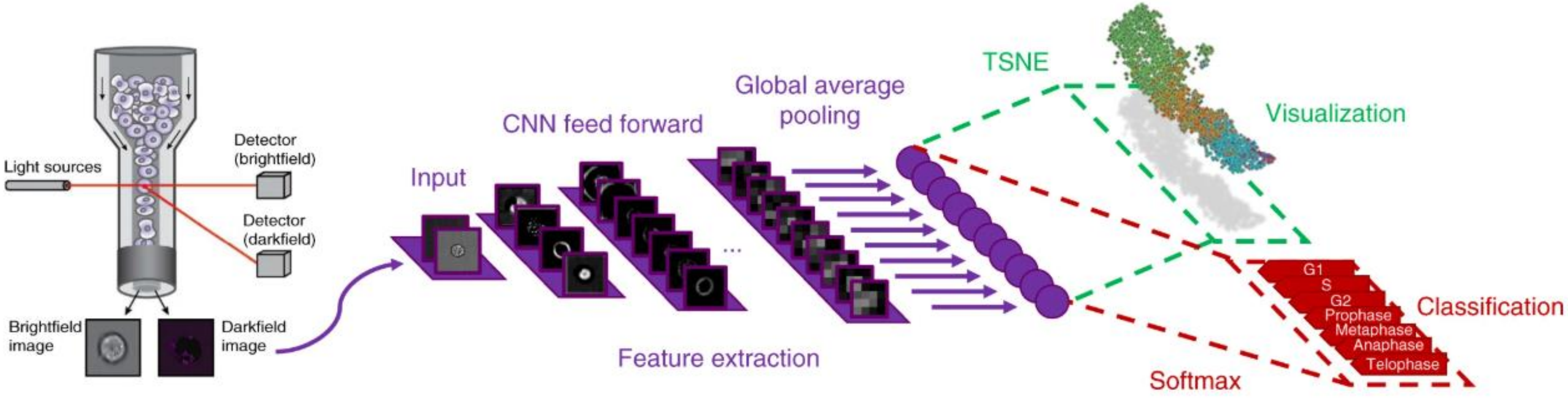
Ounkomol et al. (2018)

Mitosis time-lapse output



Ounkomol et al. (2018)

Predicting cell cycle / disease progression stage ("pseudo time") with deep learning



Eulenberg (2017)

Today

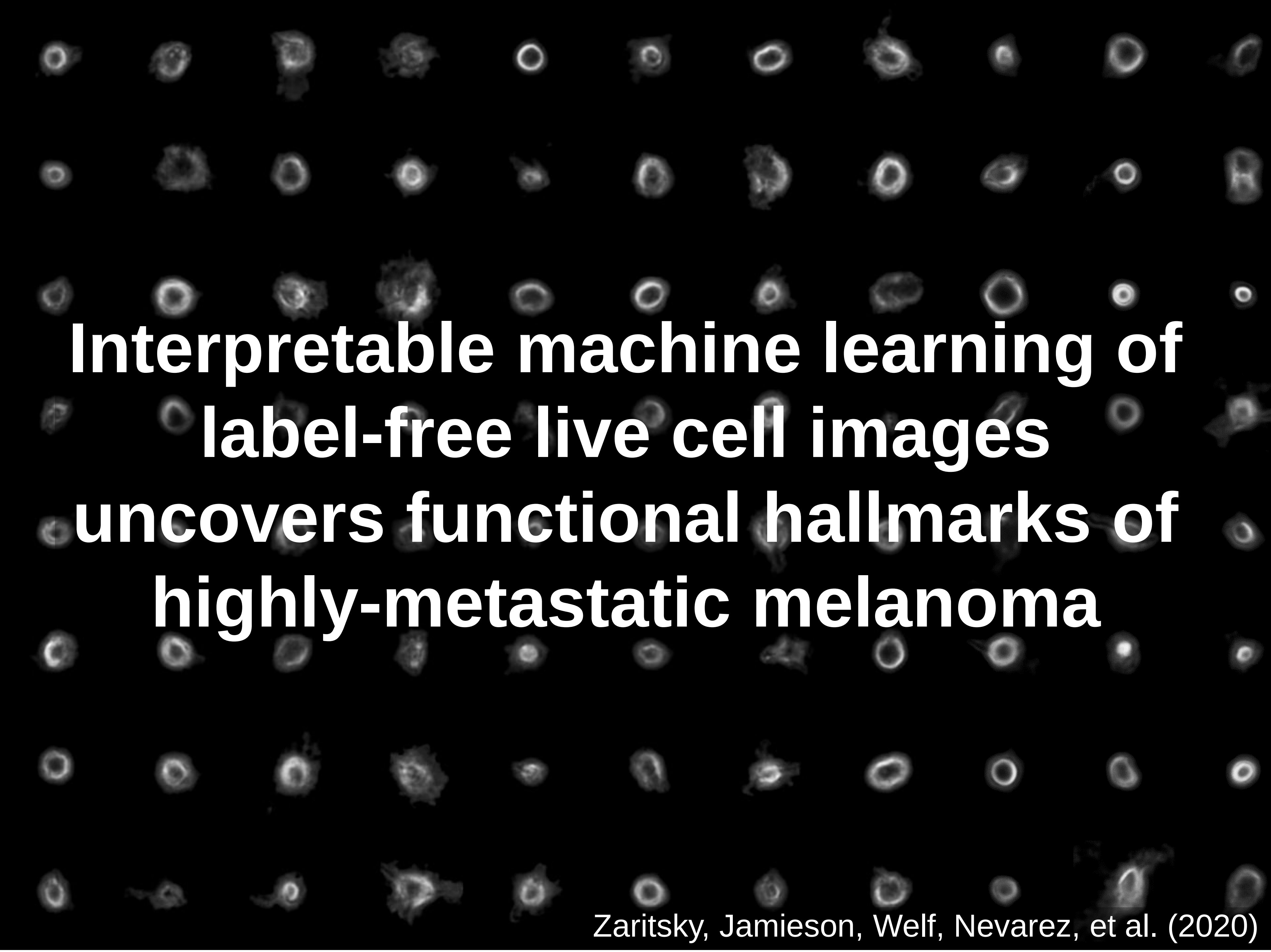
- Guest lecture: Tammy Riklin Raviv, EE, BGU on computer vision in microscopy
- Interpretable deep learning of label-free live cell images uncovers functional hallmarks of highly-metastatic melanoma

Guest lecture

Tammy Riklin-Raviv, EE, BGU

Computer vision in microscopy

(slides not available for public use ☹)



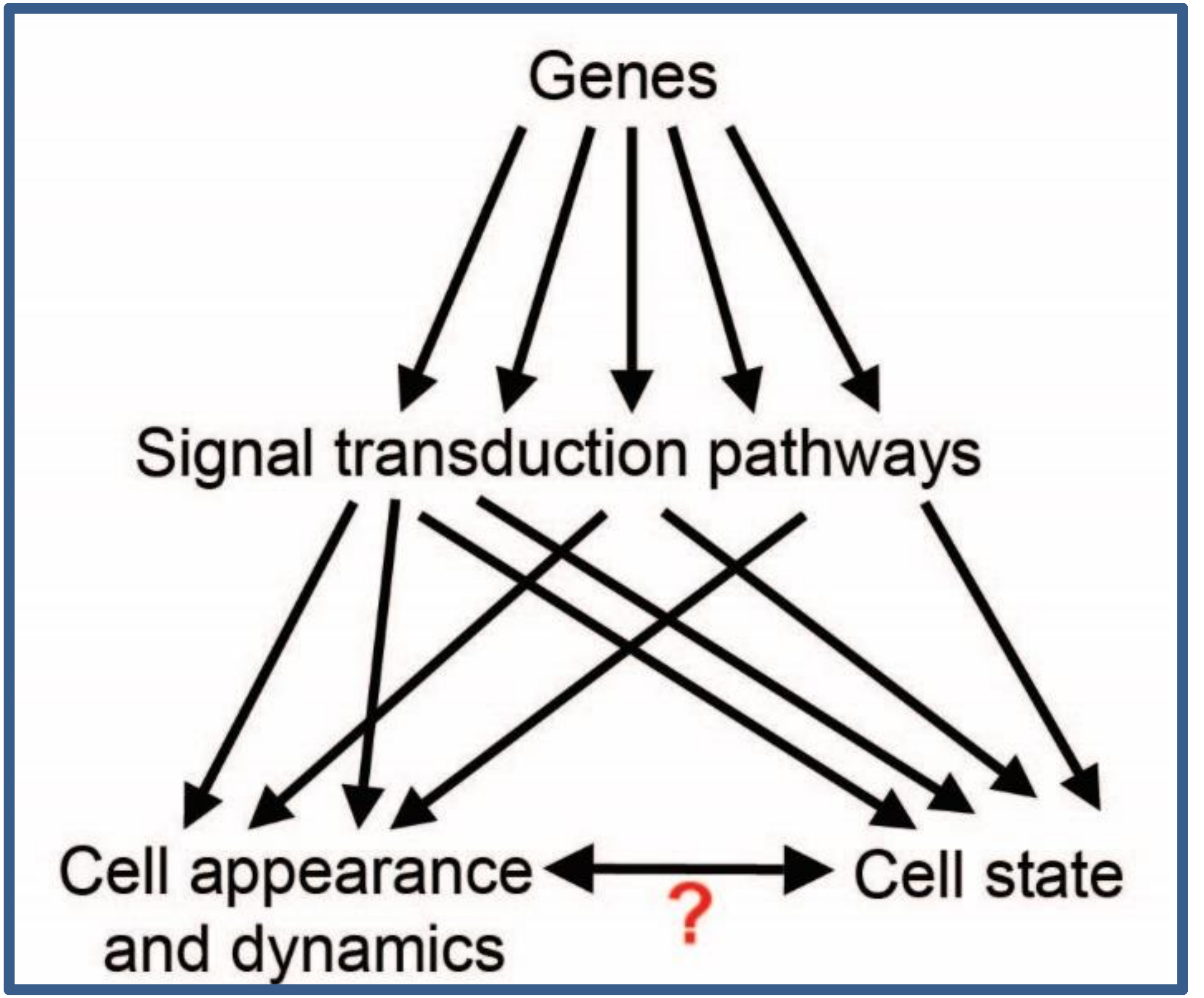
Interpretable machine learning of label-free live cell images uncovers functional hallmarks of highly-metastatic melanoma

Zaritsky, Jamieson, Welf, Nevarez, et al. (2020)

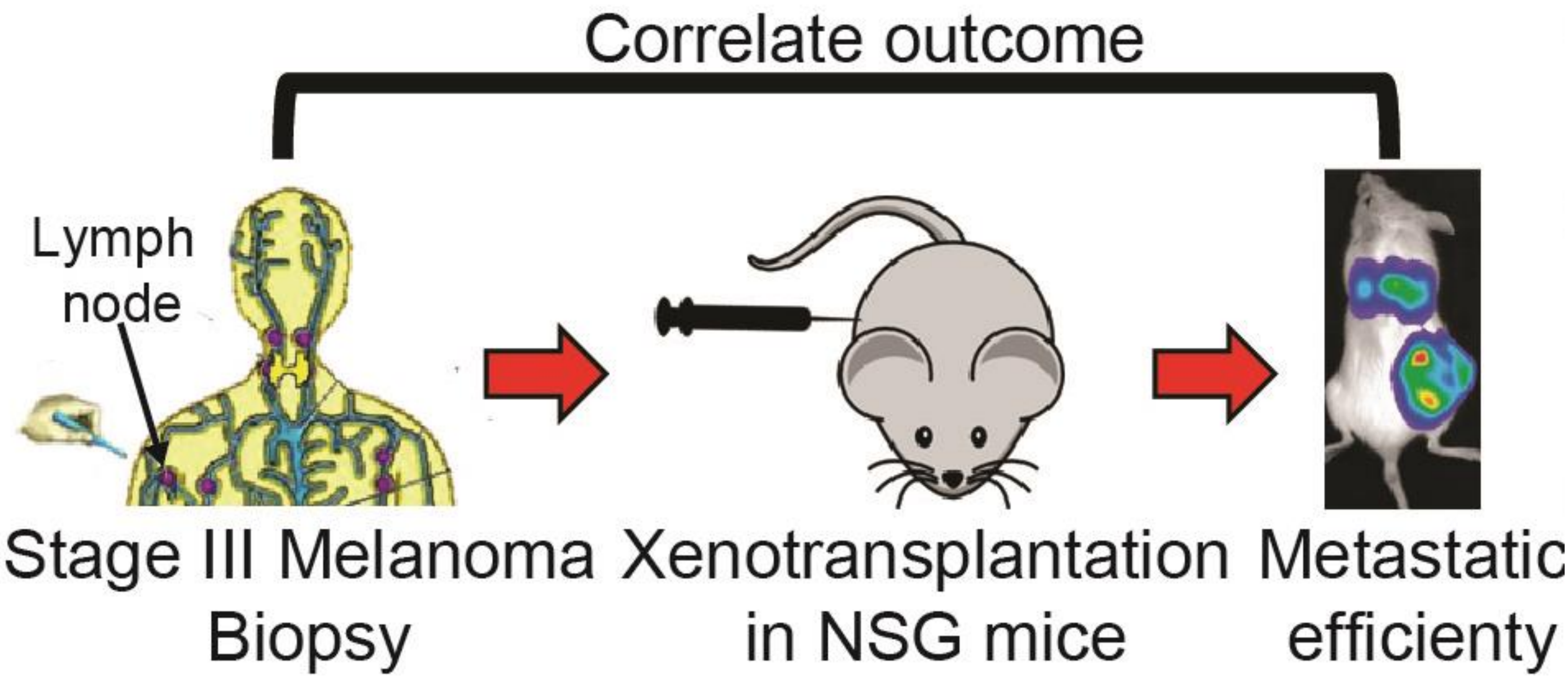
Can we predict cancer cell functional states from live label-free cell images?

Melanoma as model

Genetic heterogeneity → functional readout to discriminate cell type

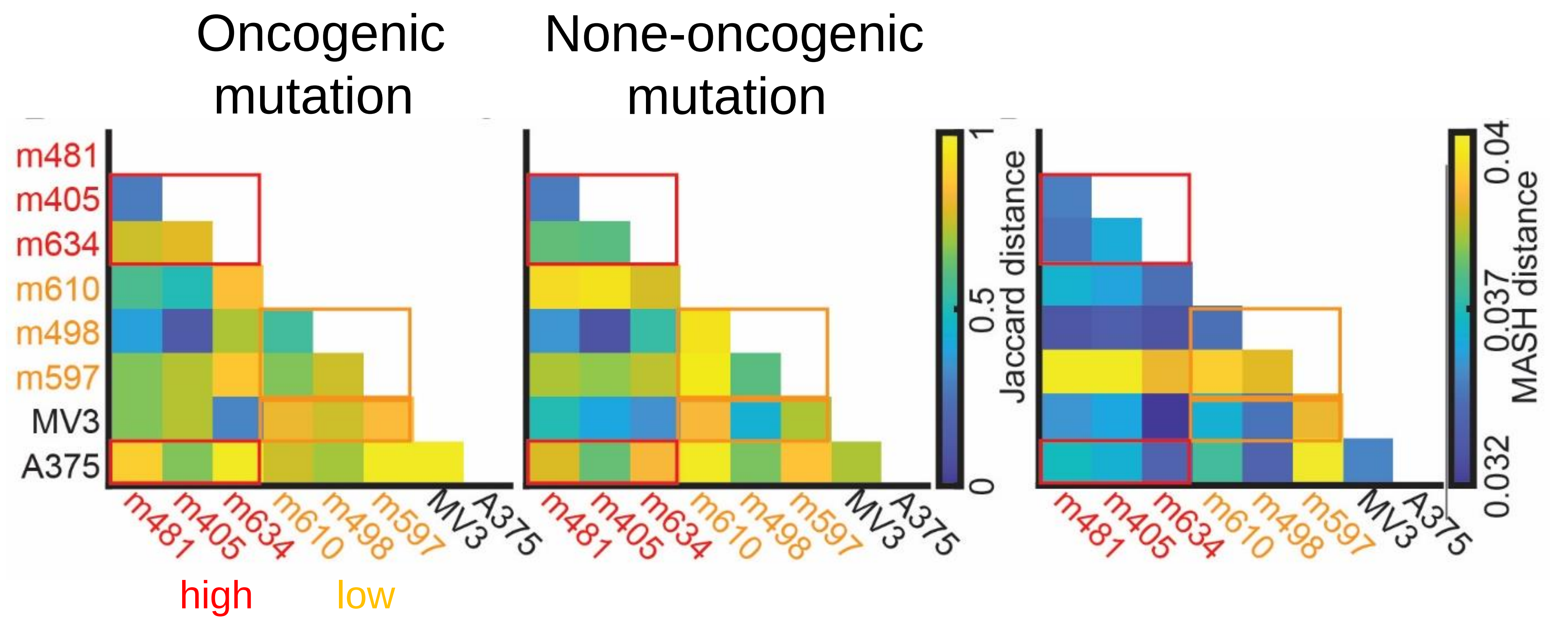


Low versus high metastatic efficiency in patient-derived melanoma

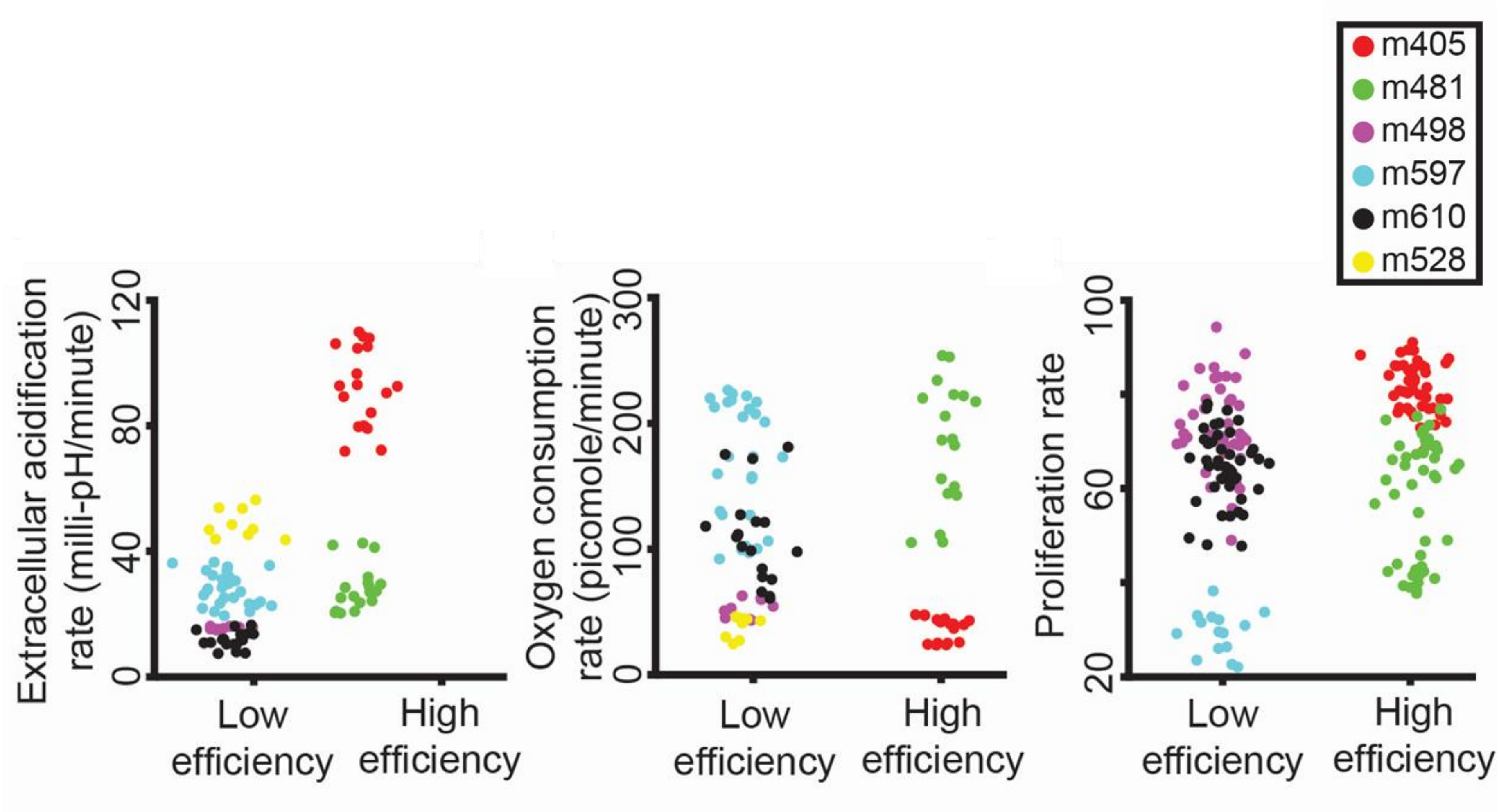


Morrison lab, UTSW
Quintana et al. (2012)

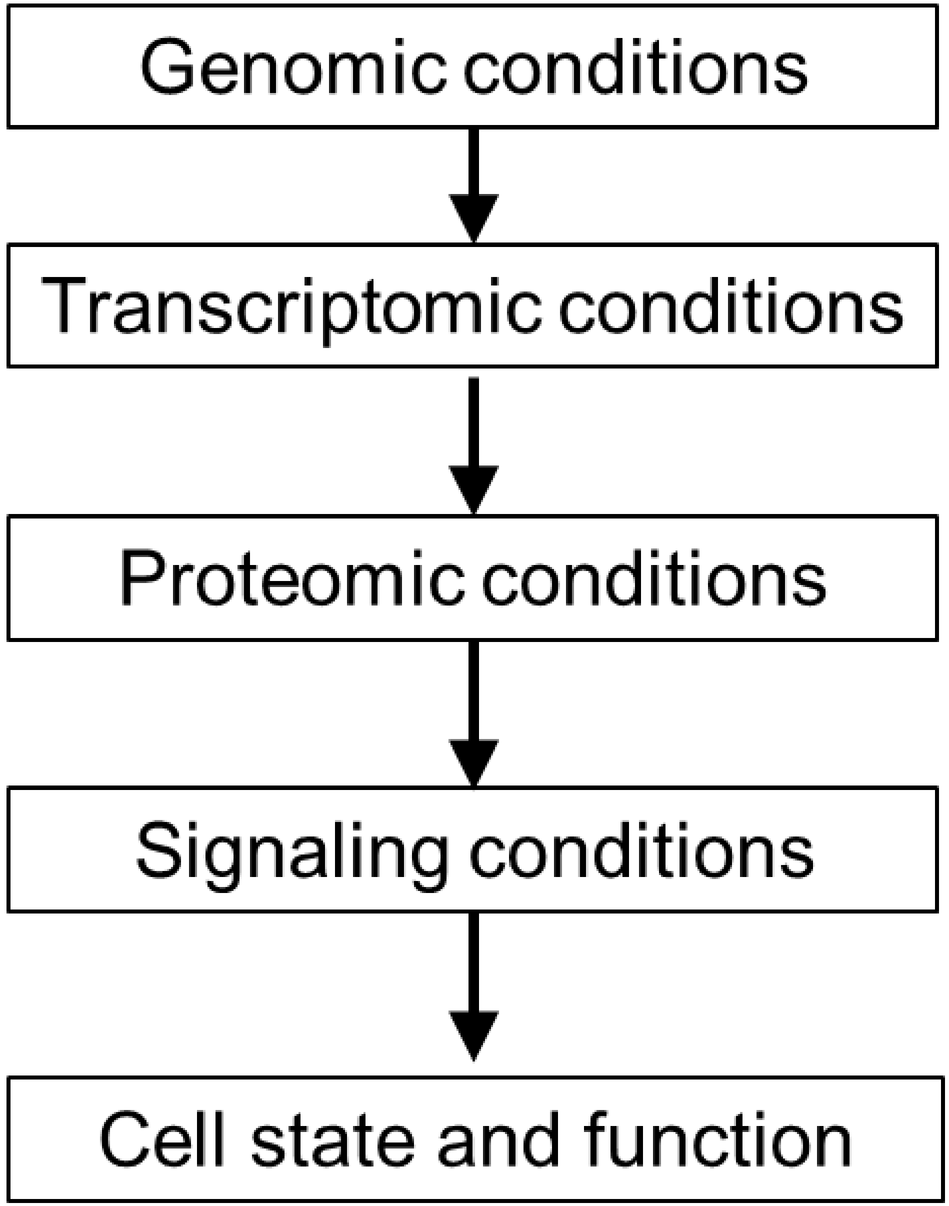
Genomics failed to predict melanoma metastasis efficiency



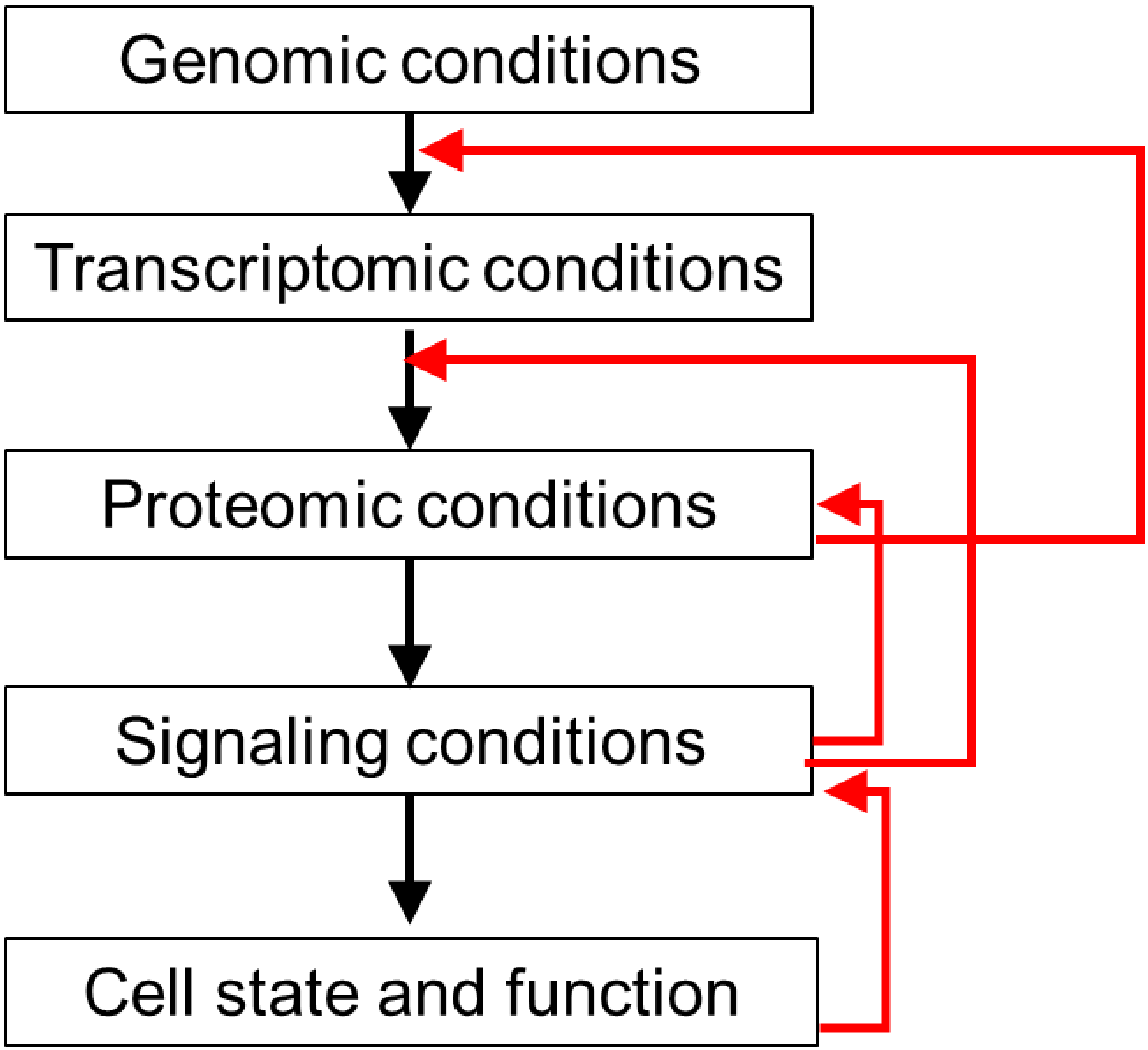
Standard cell biology assays failed to classify melanoma metastasis



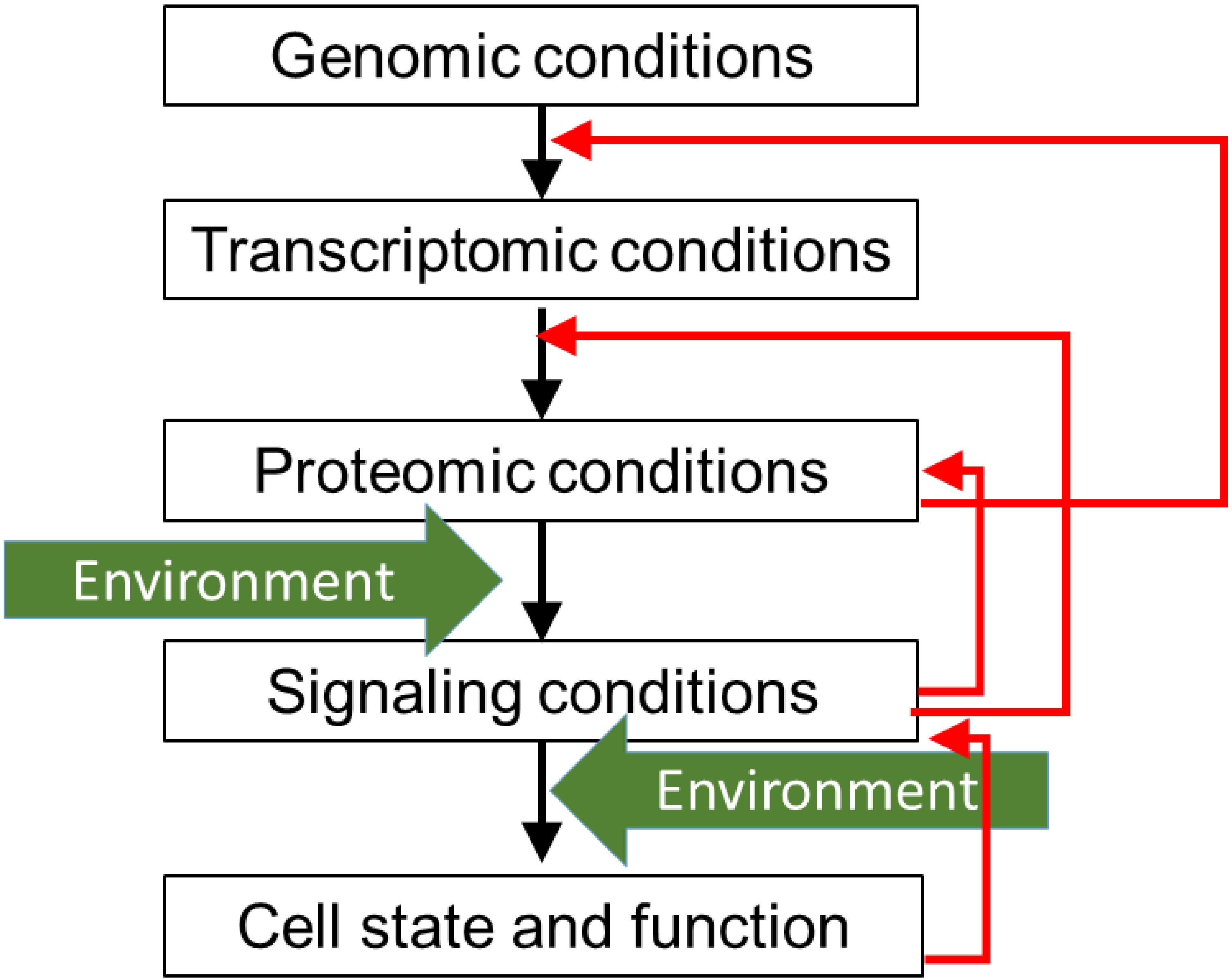
The central dogma of biology



But in reality…



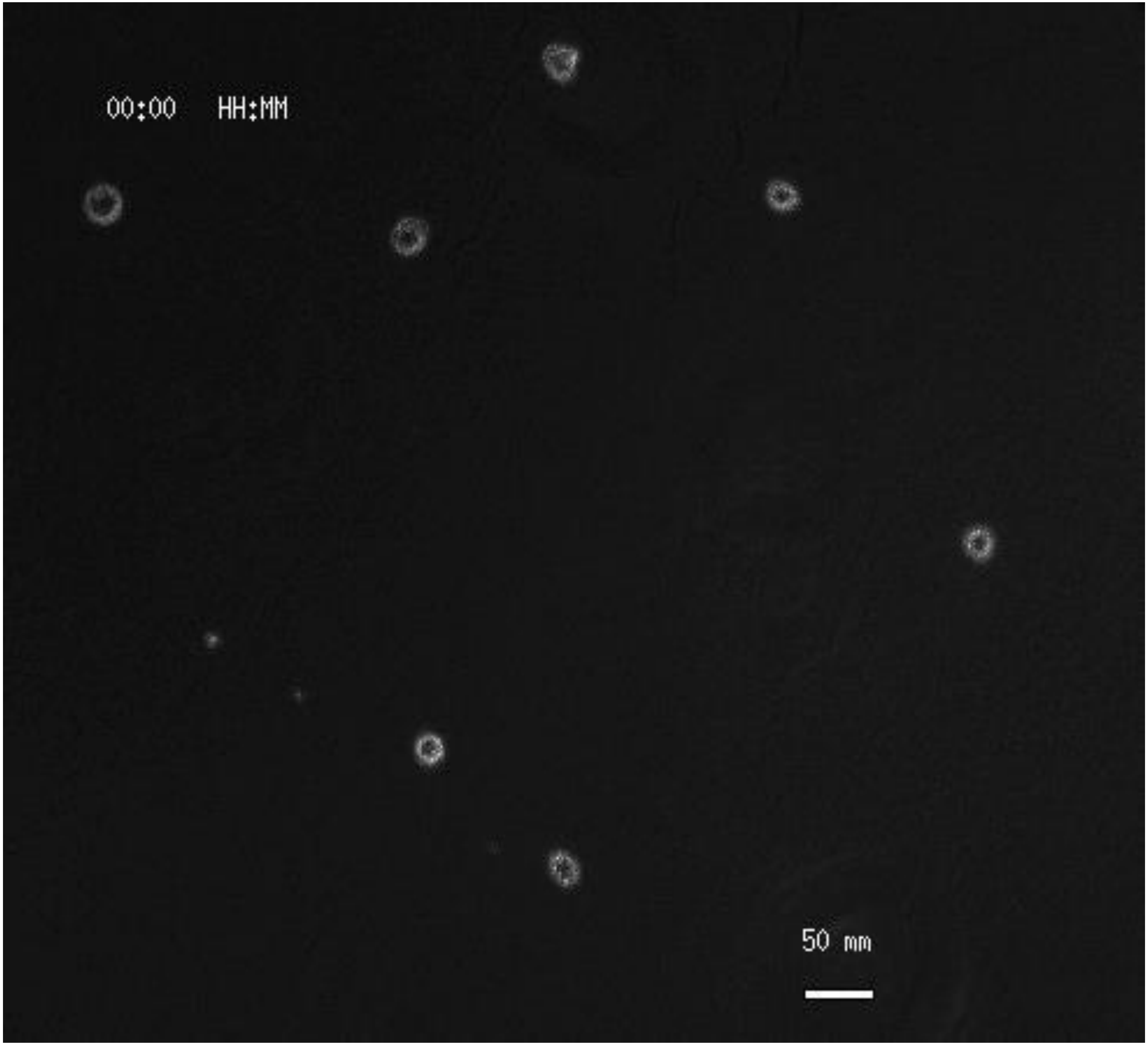
But in reality…



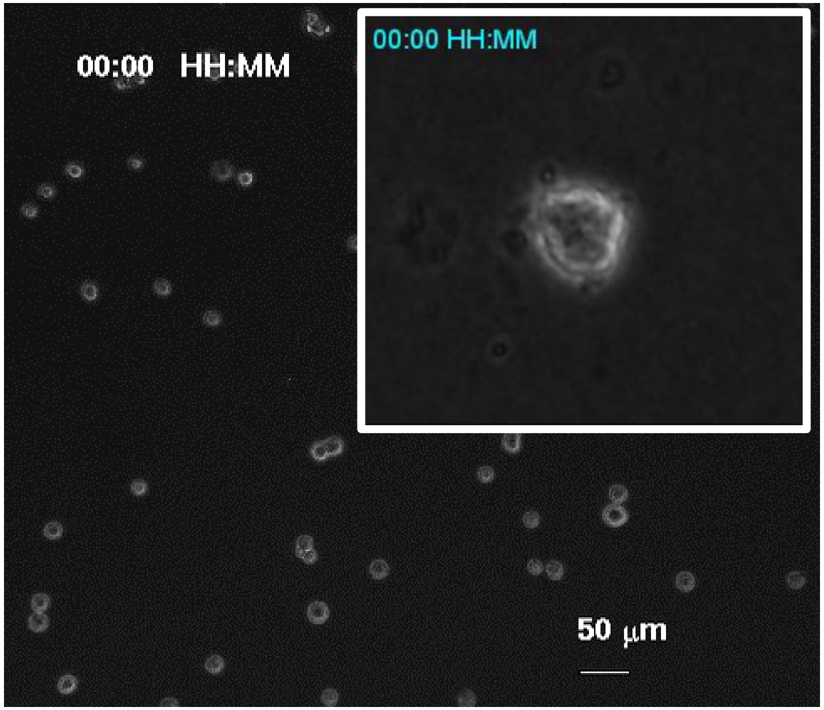
We need functional readouts to stratify melanoma!

Experimental settings

Requirement	**Implementation**
Melanoma cells	**Six** cell lines, **nine** stage III patient-derived tumors
Minimal cell intervention	Label-free
Physiologically relevant microenvironment	Cells on top of collagen
Cell dynamics	Live cell imaging
Sufficient N	High-content imaging


00:00 HH:MM
50 mm

Live cell histology: label-free live imaging of individual melanoma cells



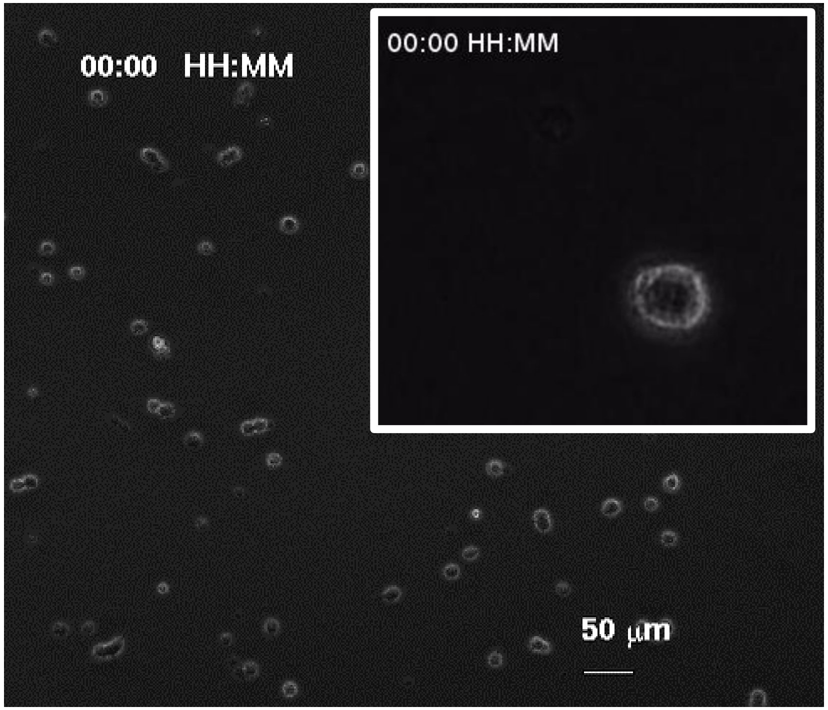
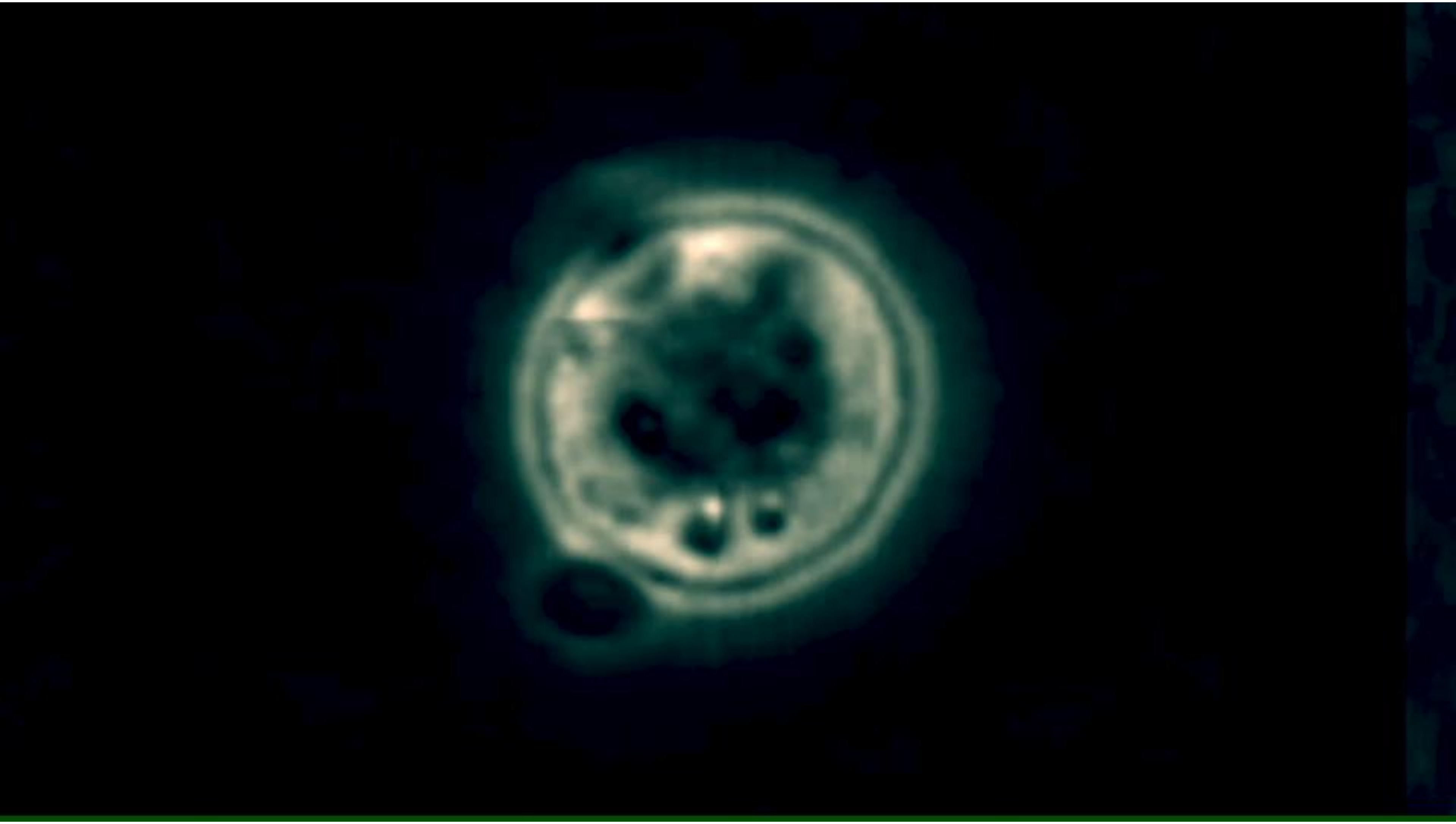
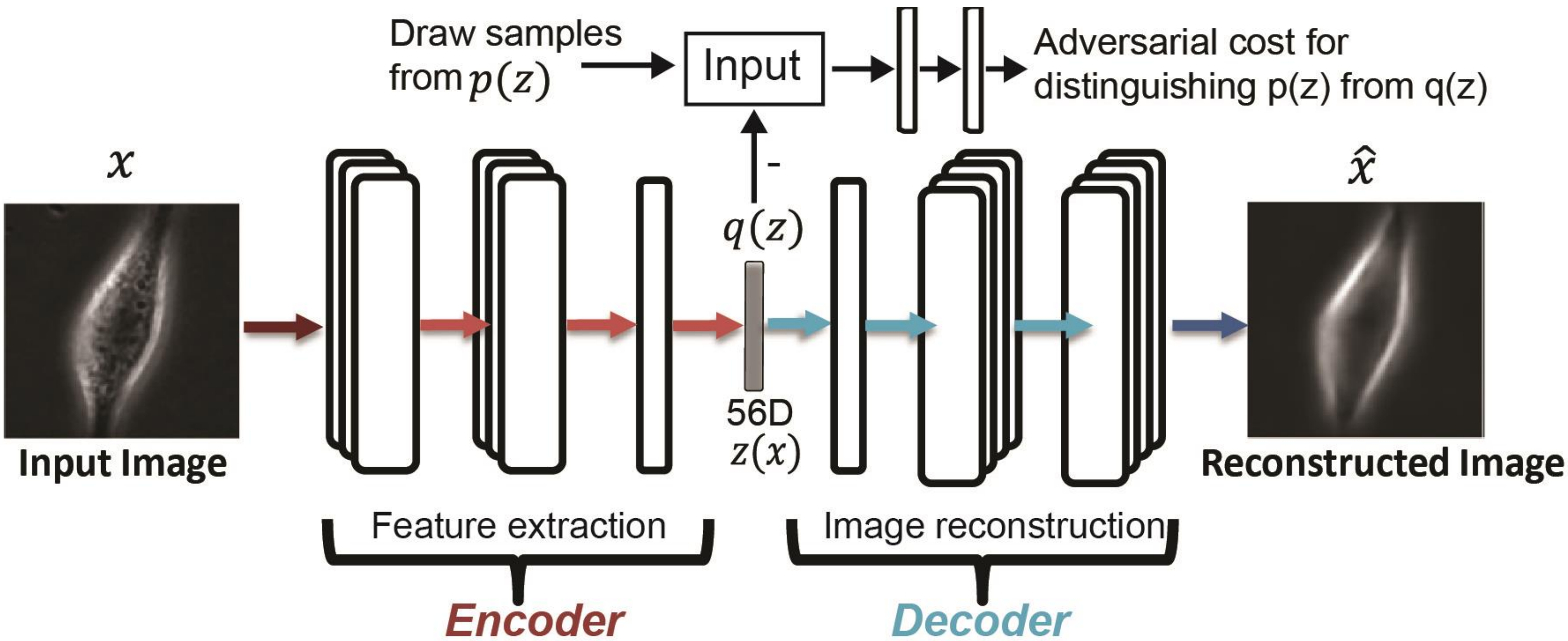


Image analysis pipeline



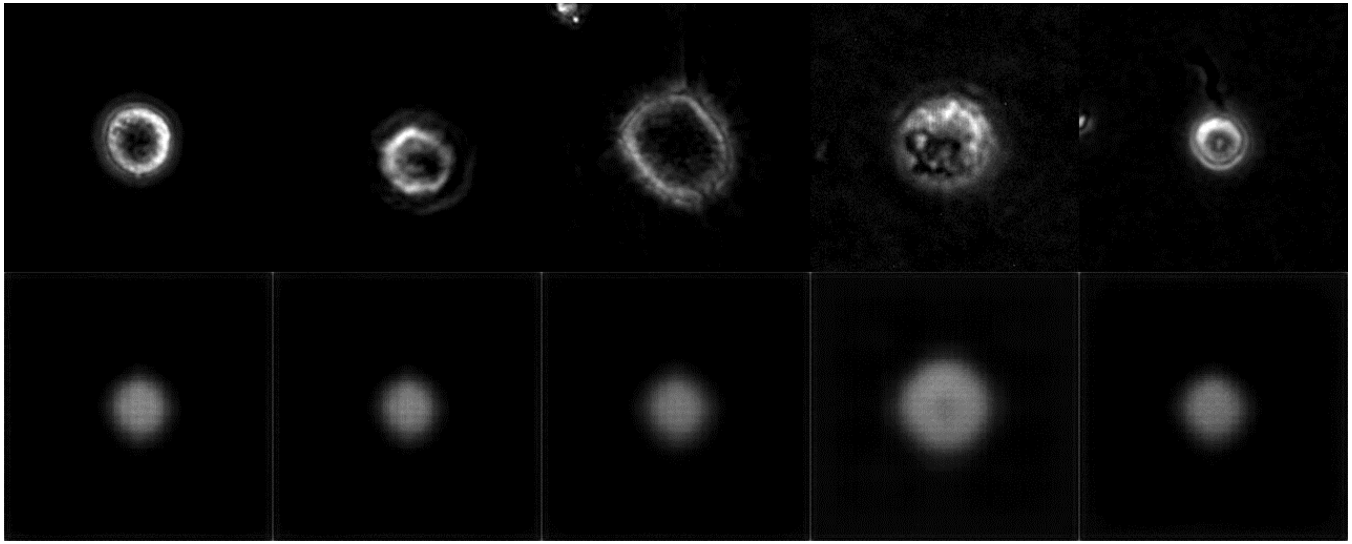
Adversarial autoencoder for unsupervised feature extraction



Training to reconstruct a melanoma cell

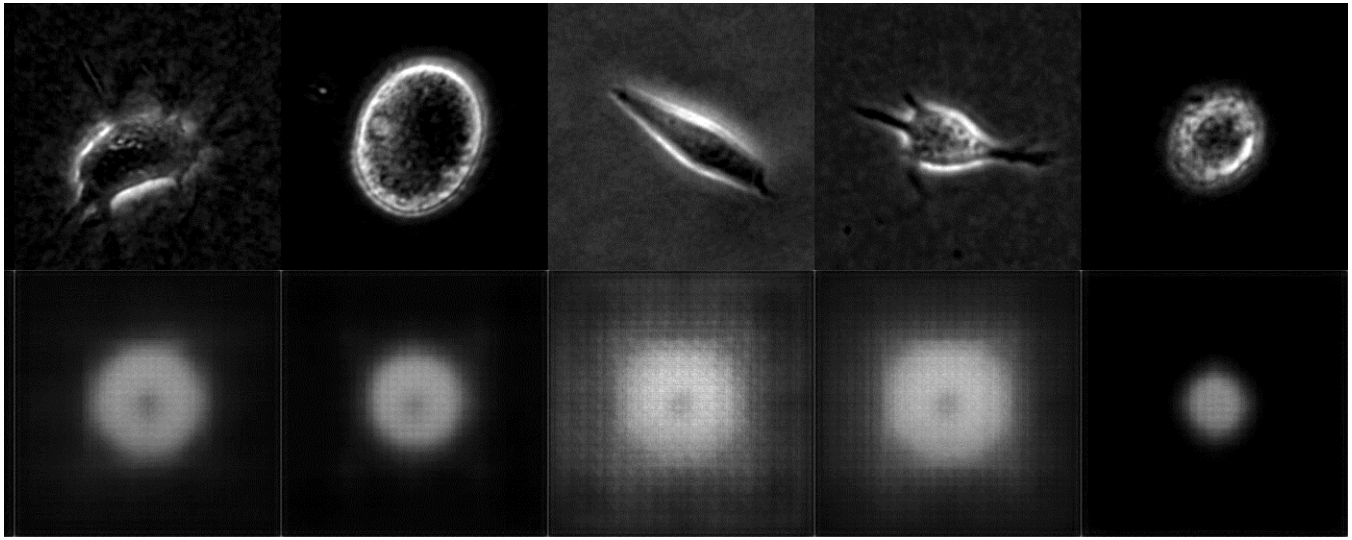
Input

Reconstructed

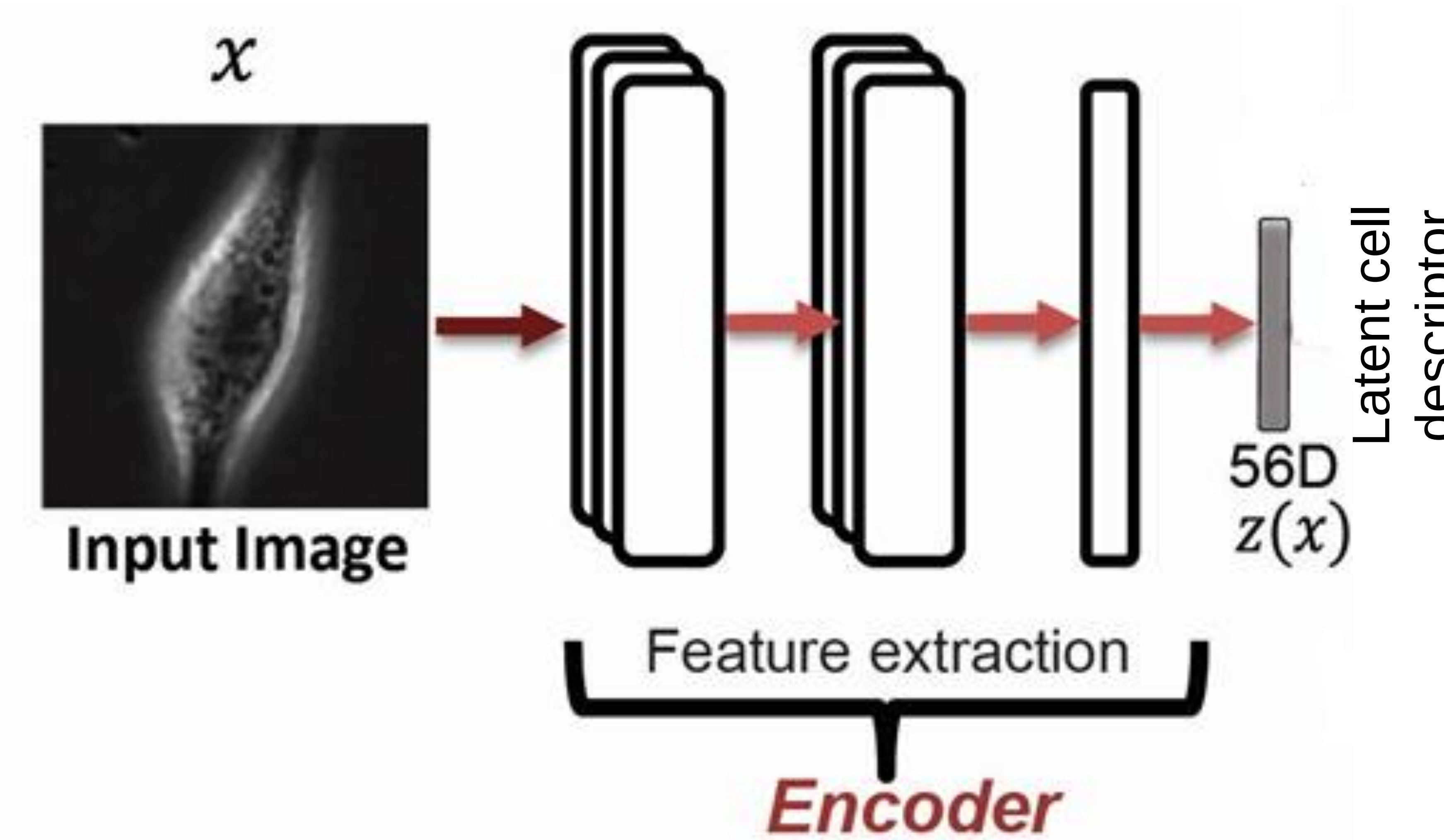


Input

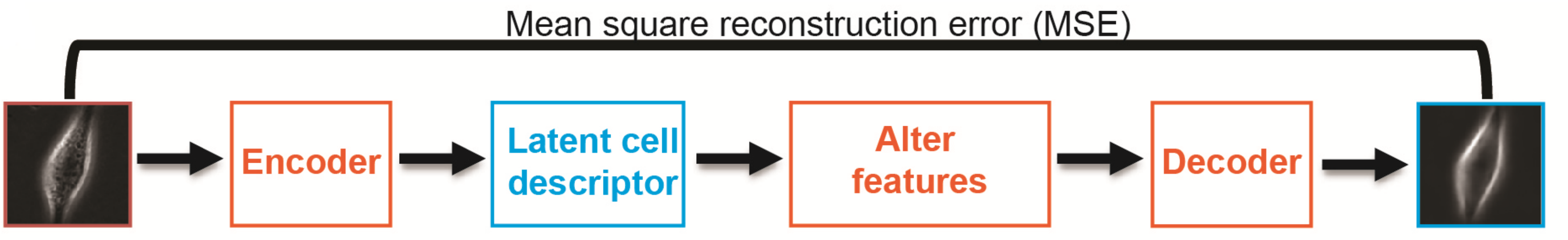
Reconstructed



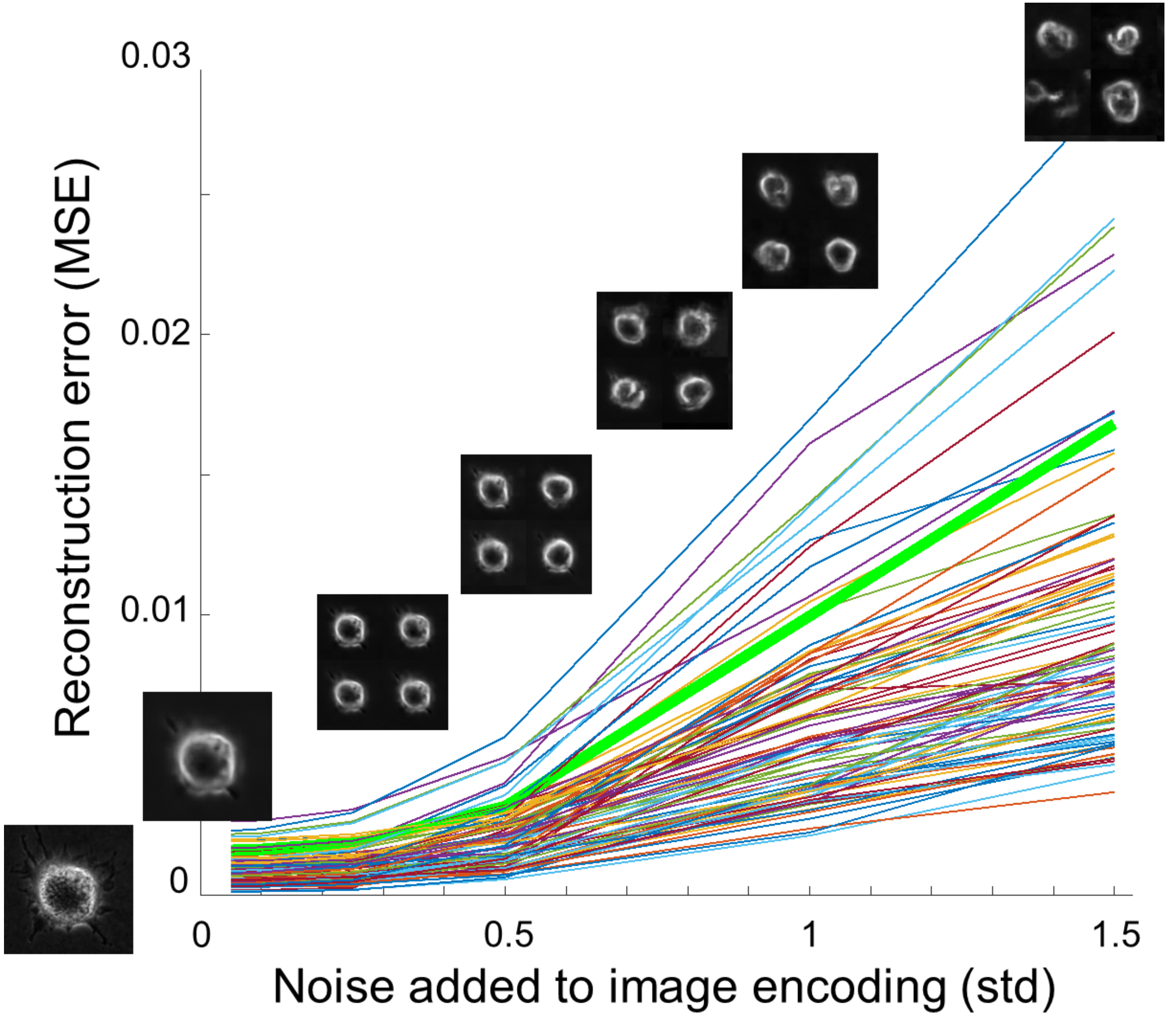
Using adversarial autoencoders for **unsupervised** feature extraction



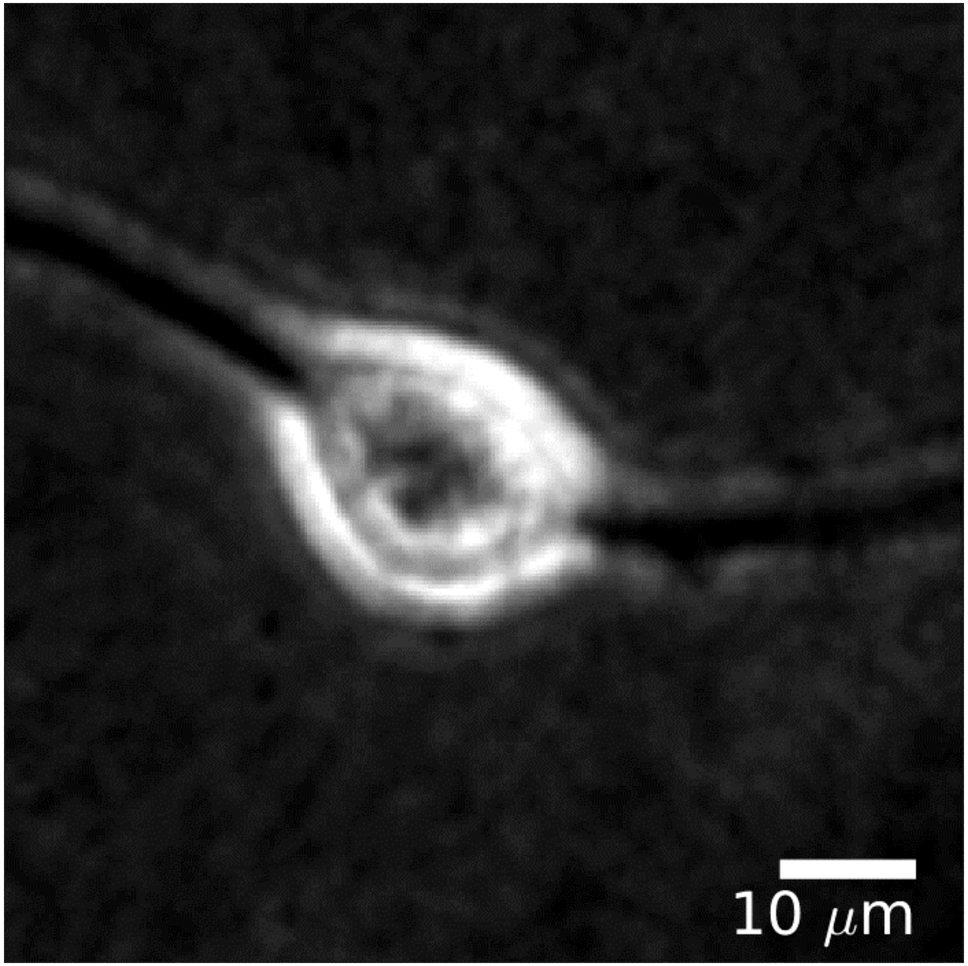
The adversarial autoencoder latent vector is a quantitative measure for cell appearance

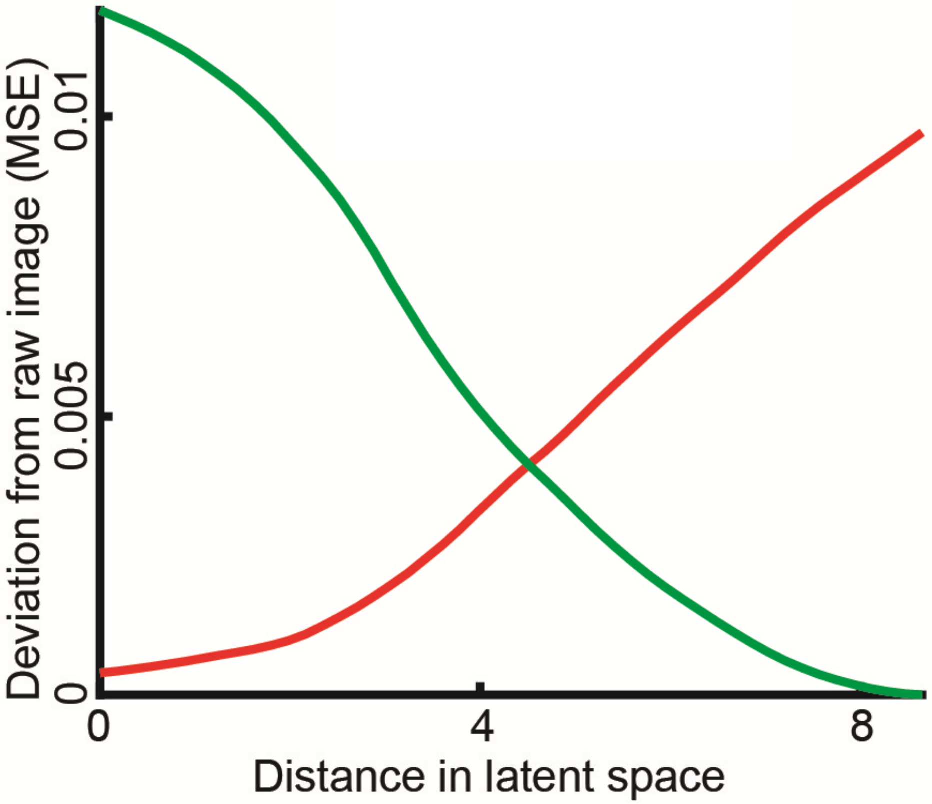


Deviation from encoding associates to deviation from reconstructed image

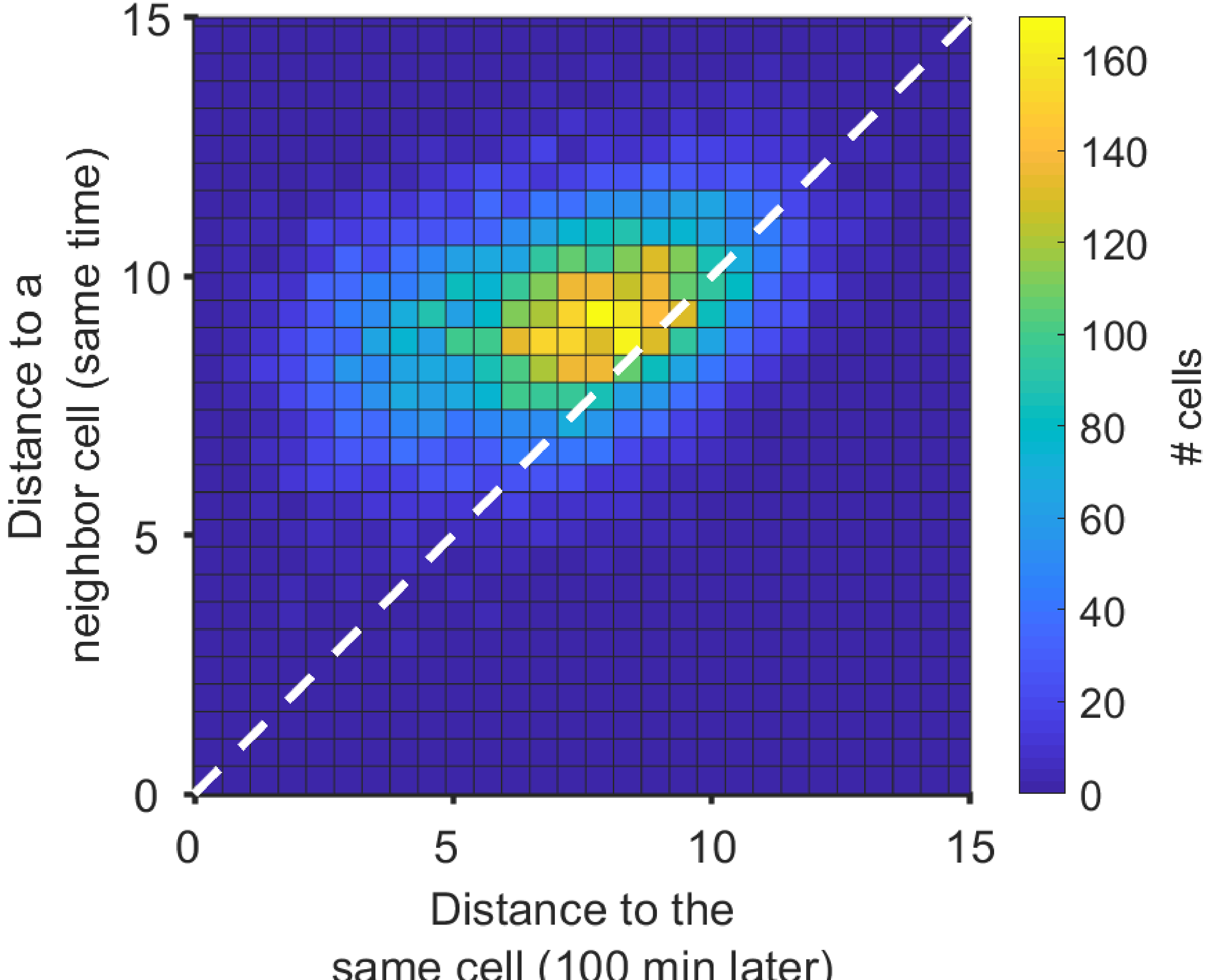


Cell "morphing": gradually transforming one cell to another



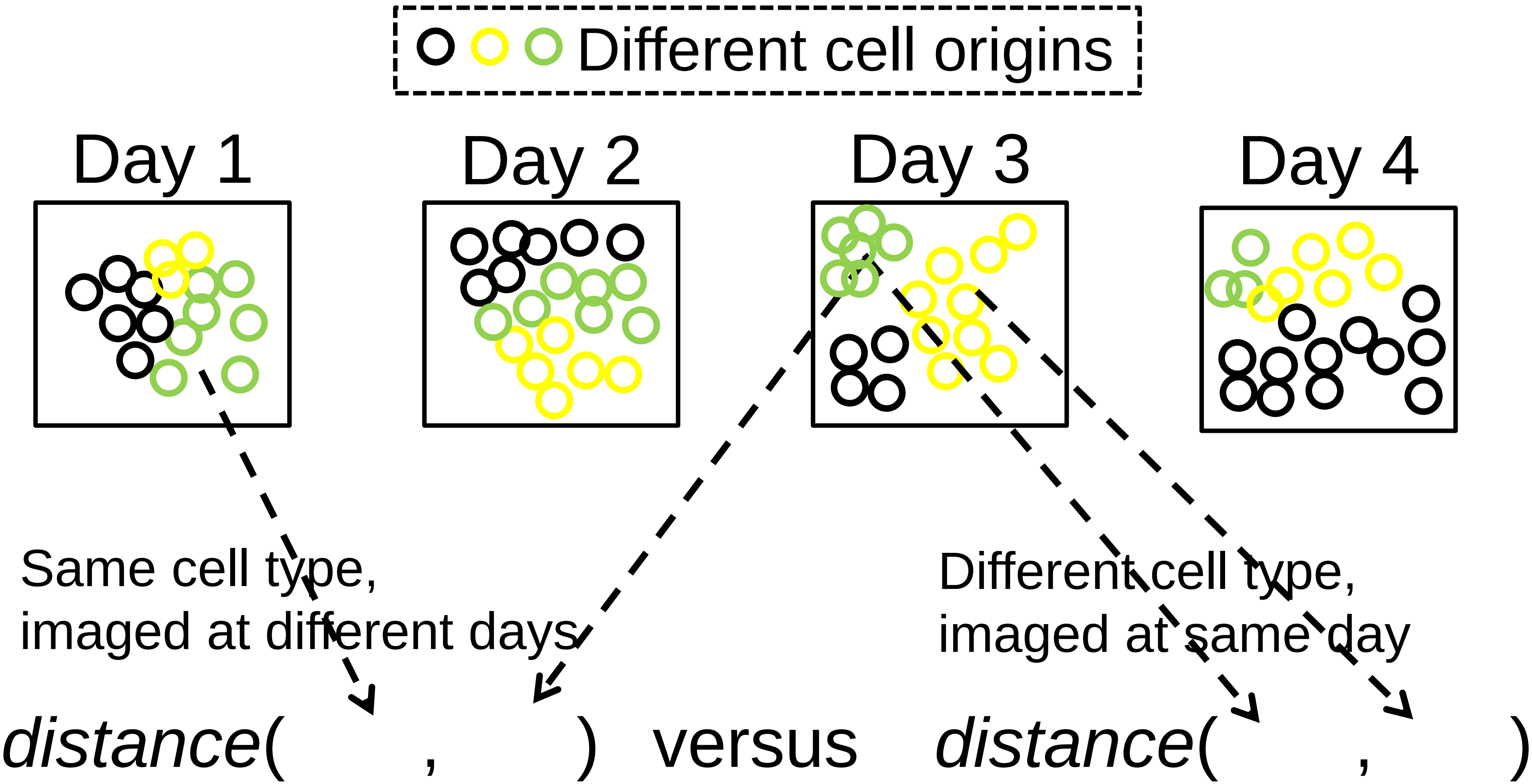


Cells are more self-similar over time than two neighboring cells at the same time

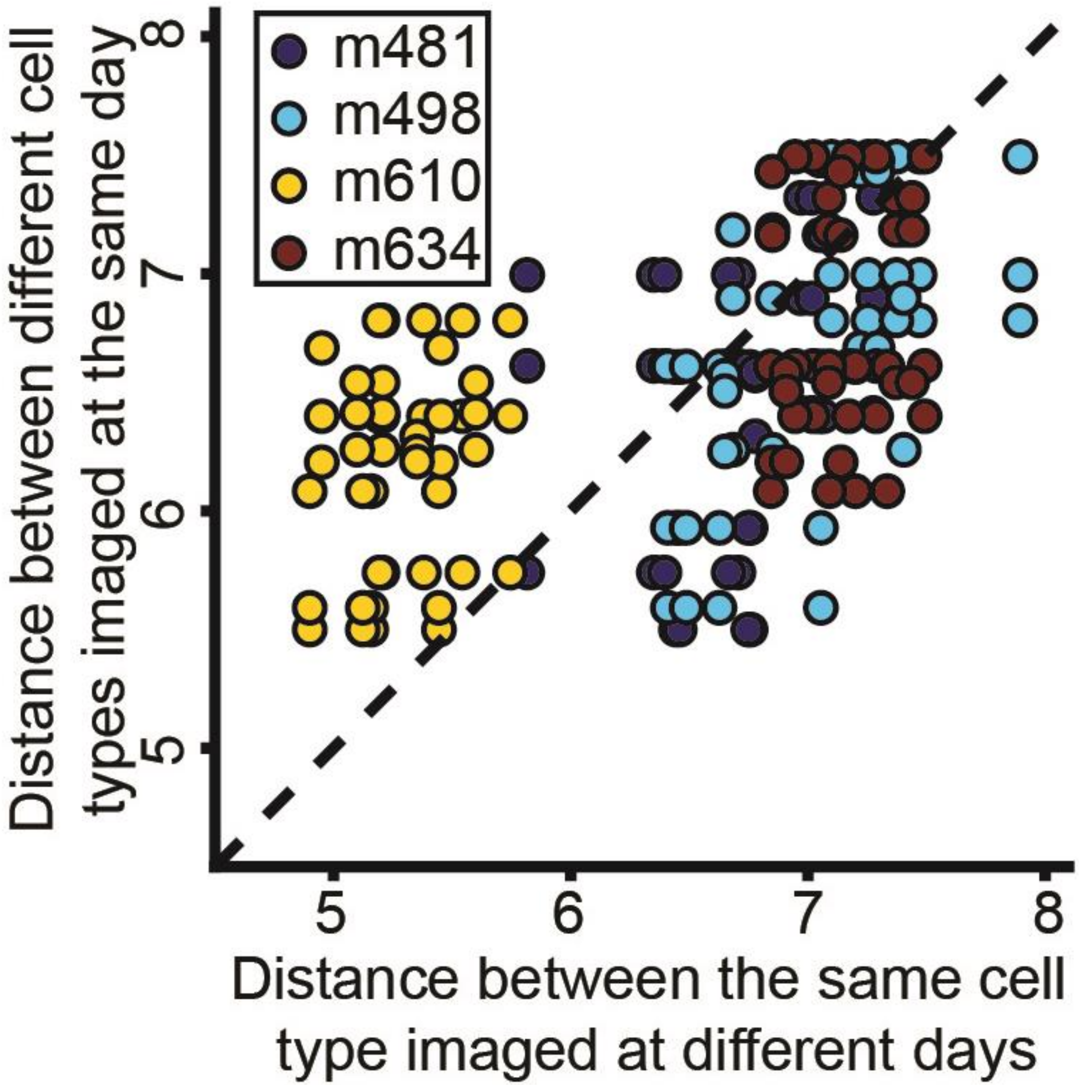


Batch effects (inter-day variability) mask the functional cell state

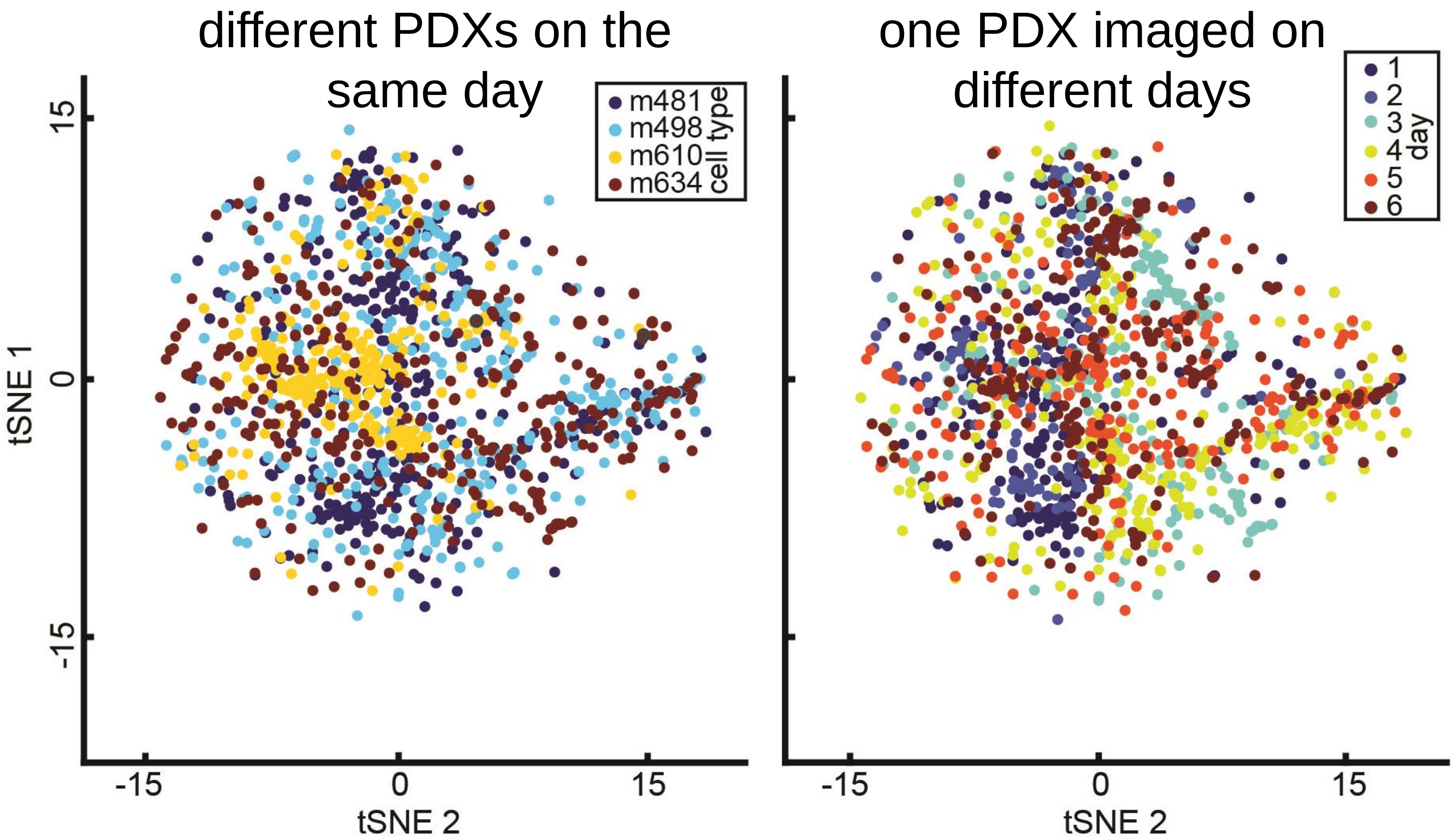
Assessing day-to-day variability in feature representations



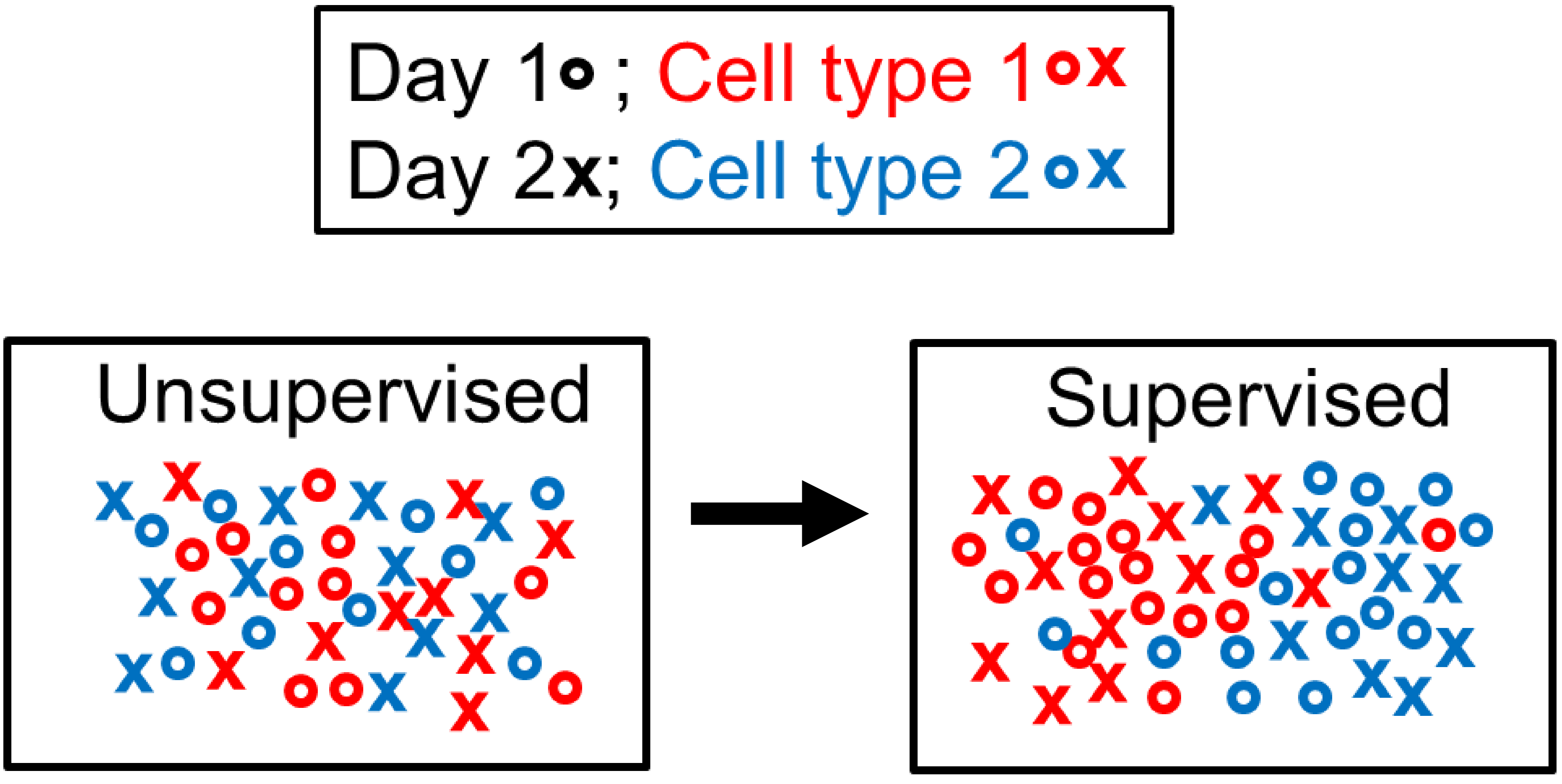
Intra-PDX/inter-day distance (x-axis) versus intra-day/inter-PDX distance



Latent space cell descriptors are significantly distorted by batch effects or lack information on distinct functional states between PDXs

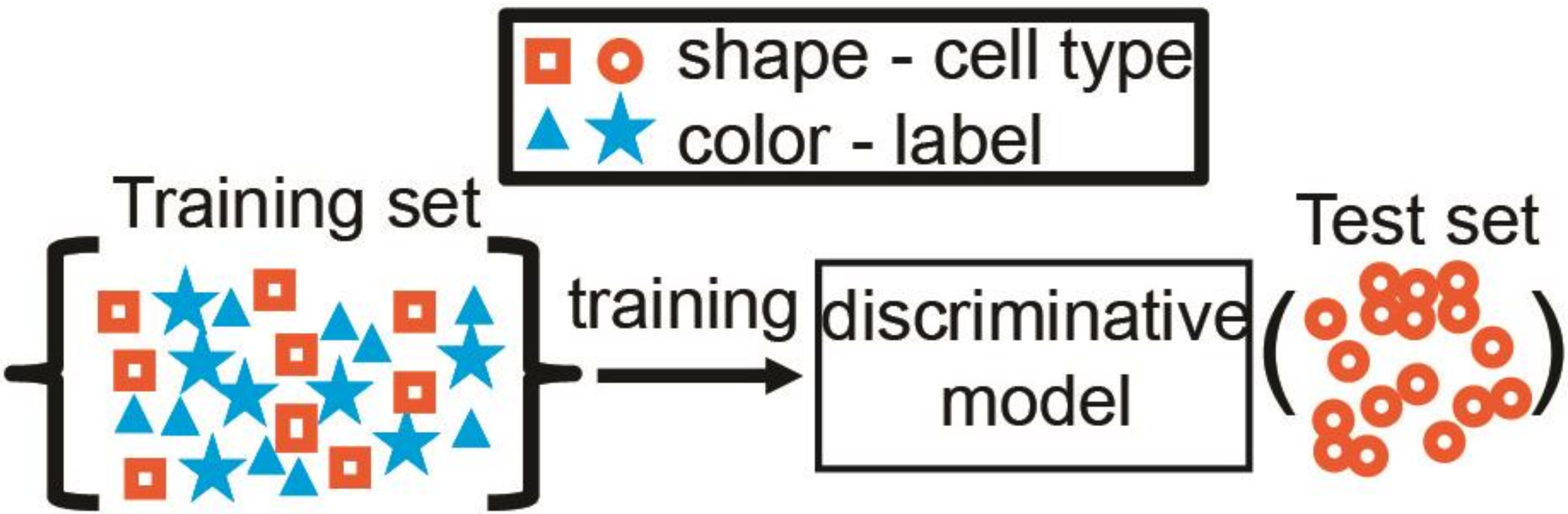


Supervised machine learning for classification

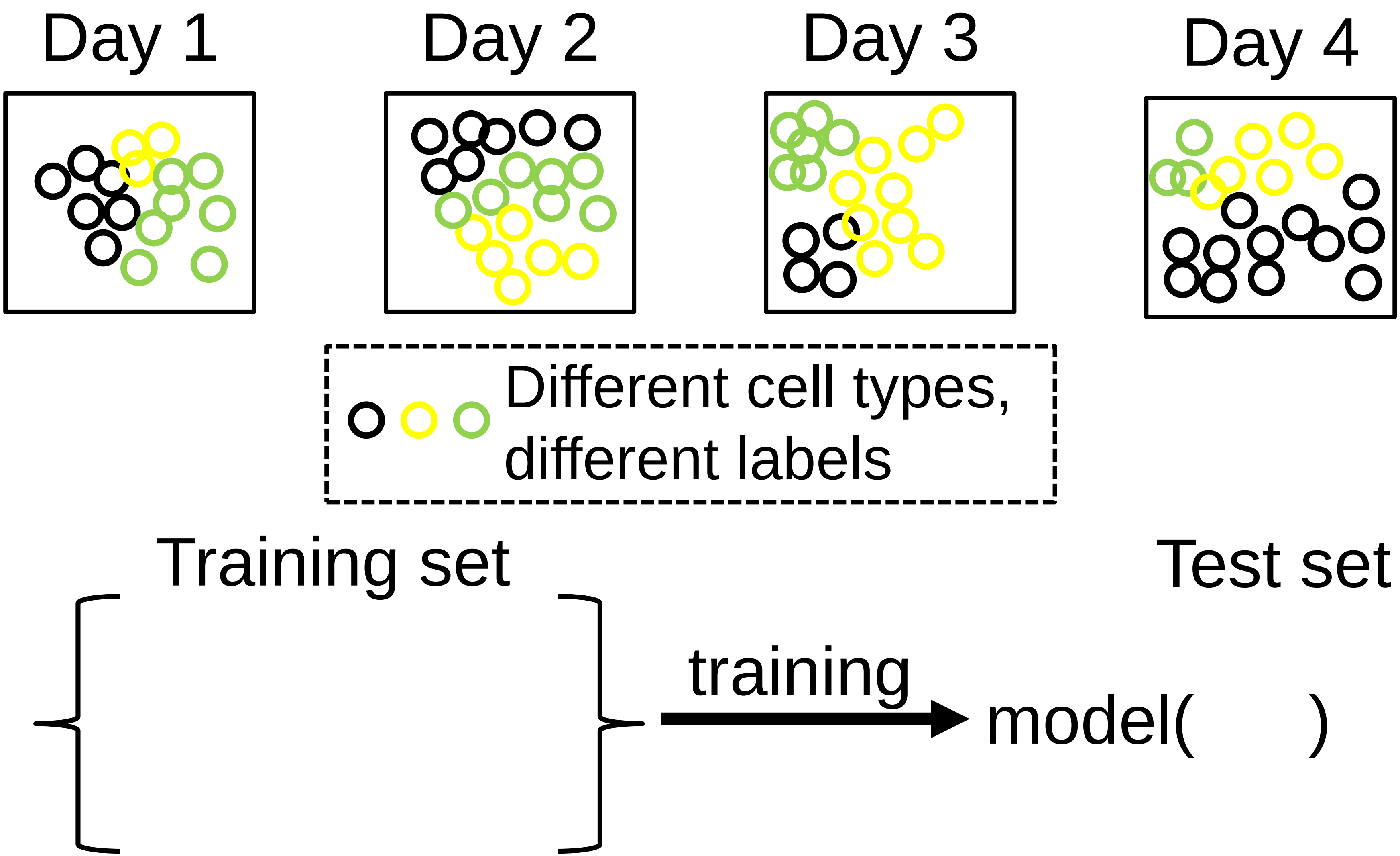


Supervised machine learning for classification

(careful statistical assessment to avoid over-fitting!)

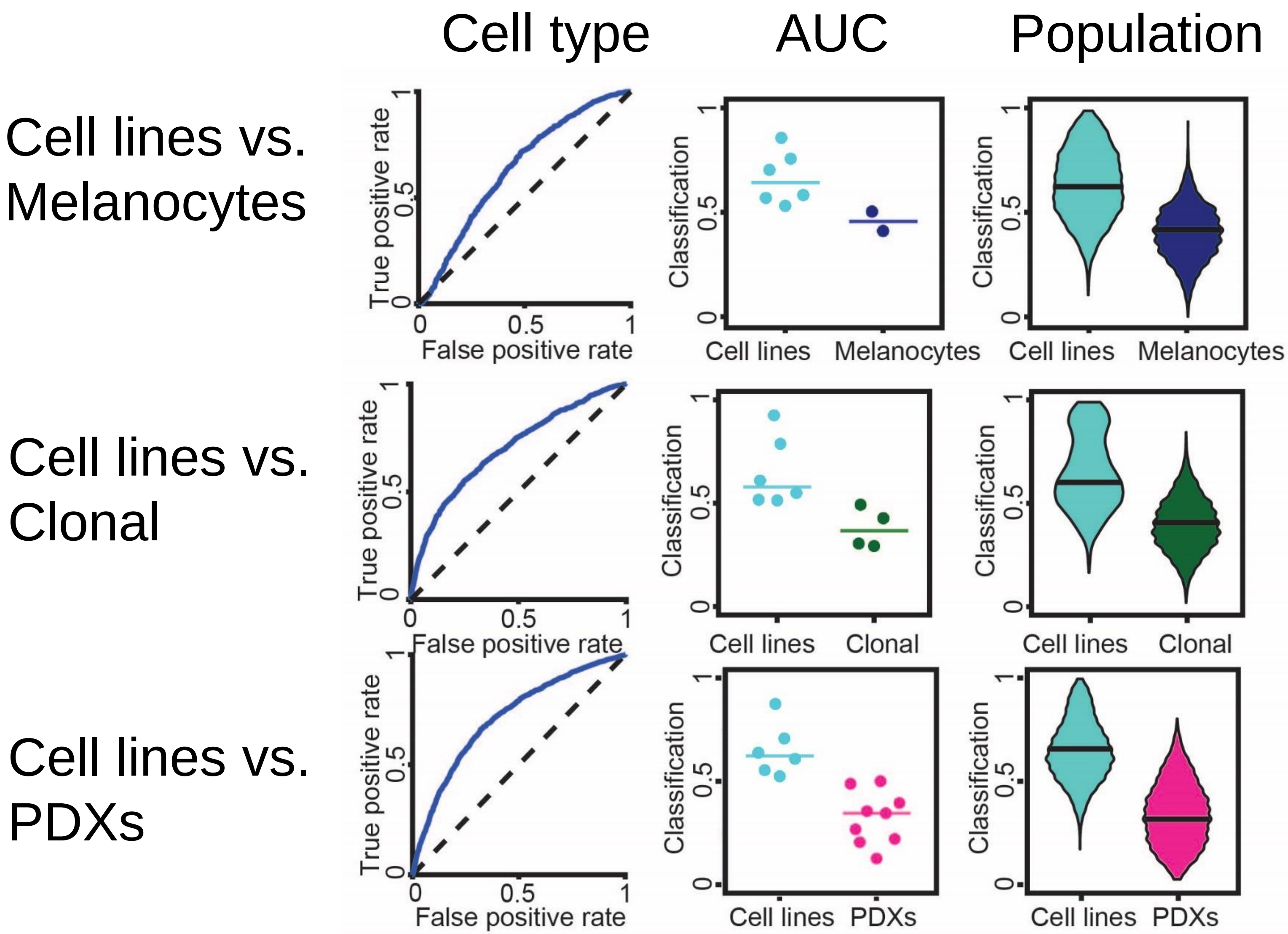


Careful statistical assessment to avoid over-fitting (day + cell type)!



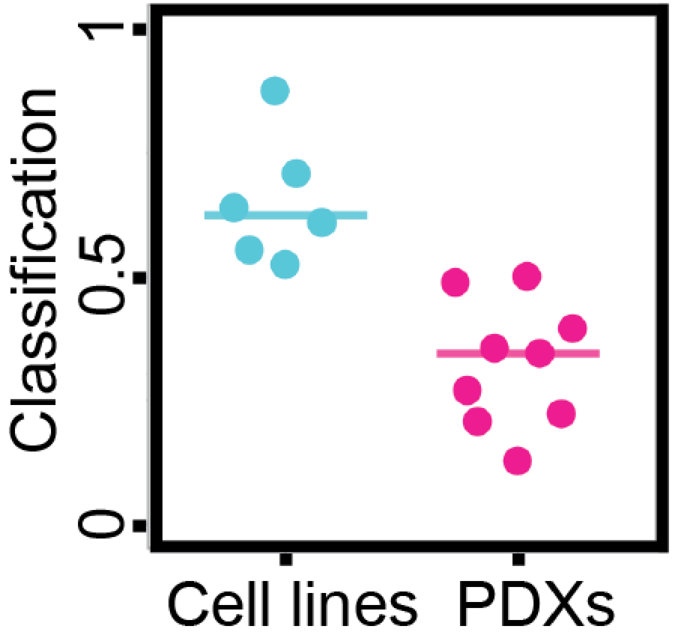
Discrimination of different melanoma cell types

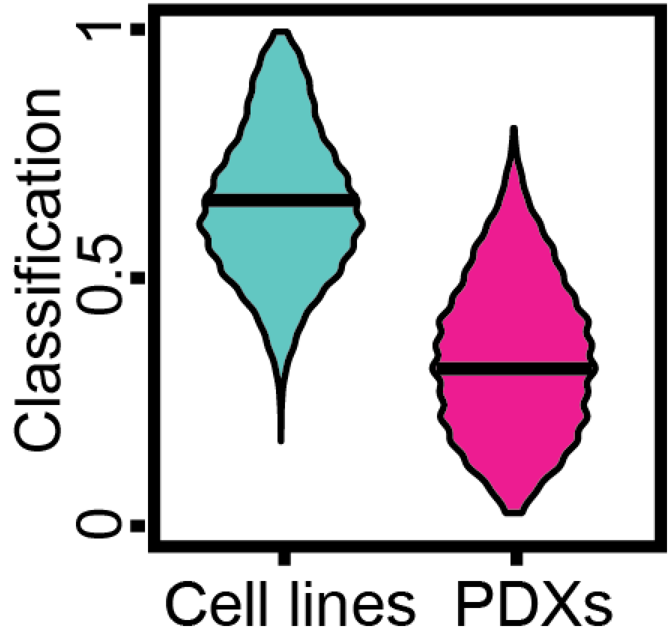
(classifier blind to the cell system)



Focus on cell lines versus PDXs…

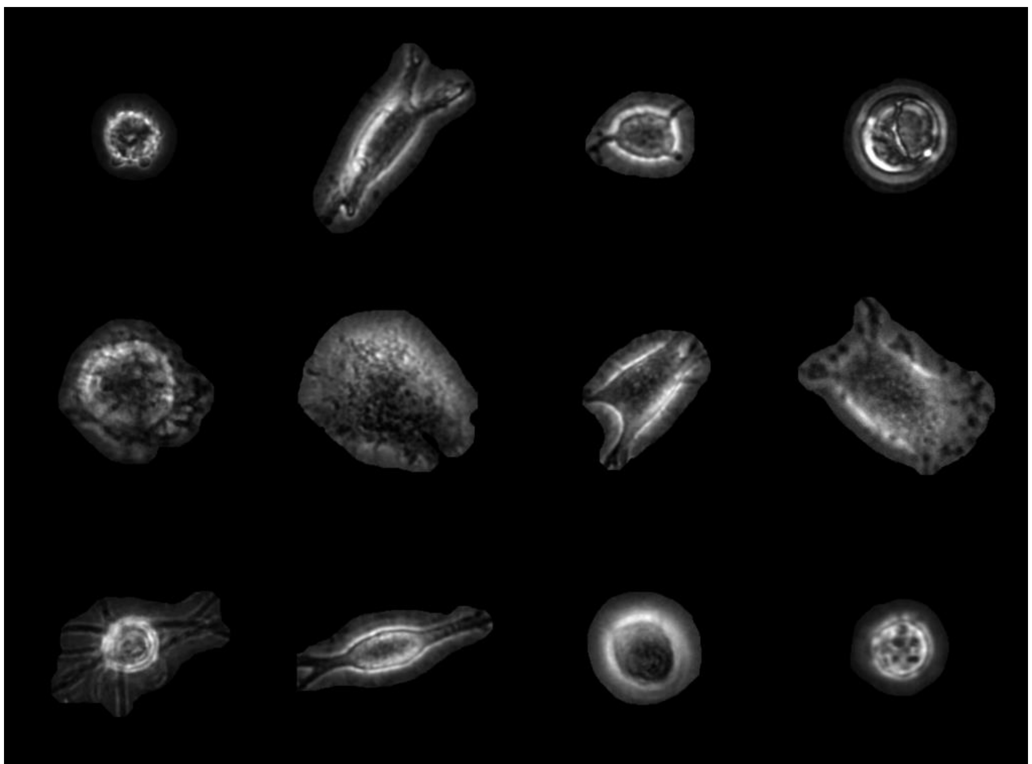
Classifier blind to the cell system



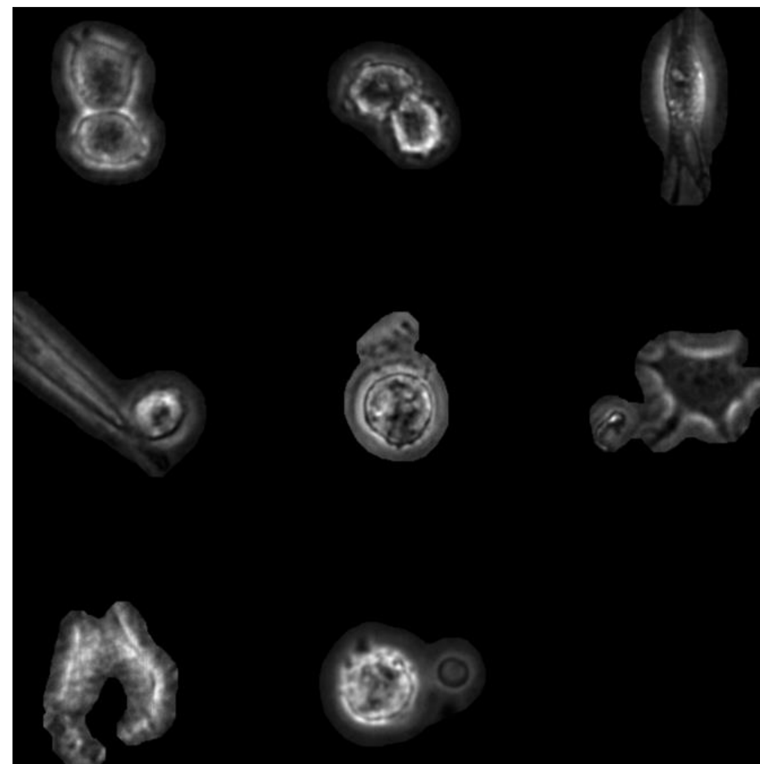


Alternative descriptors - shape: single cell segmentation in phase-contrast images by LEVER

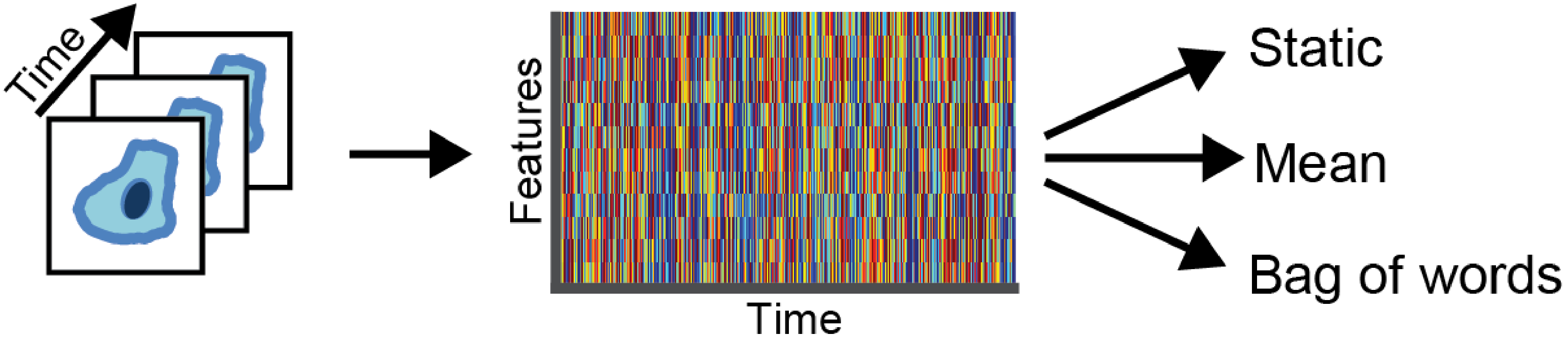
Successful



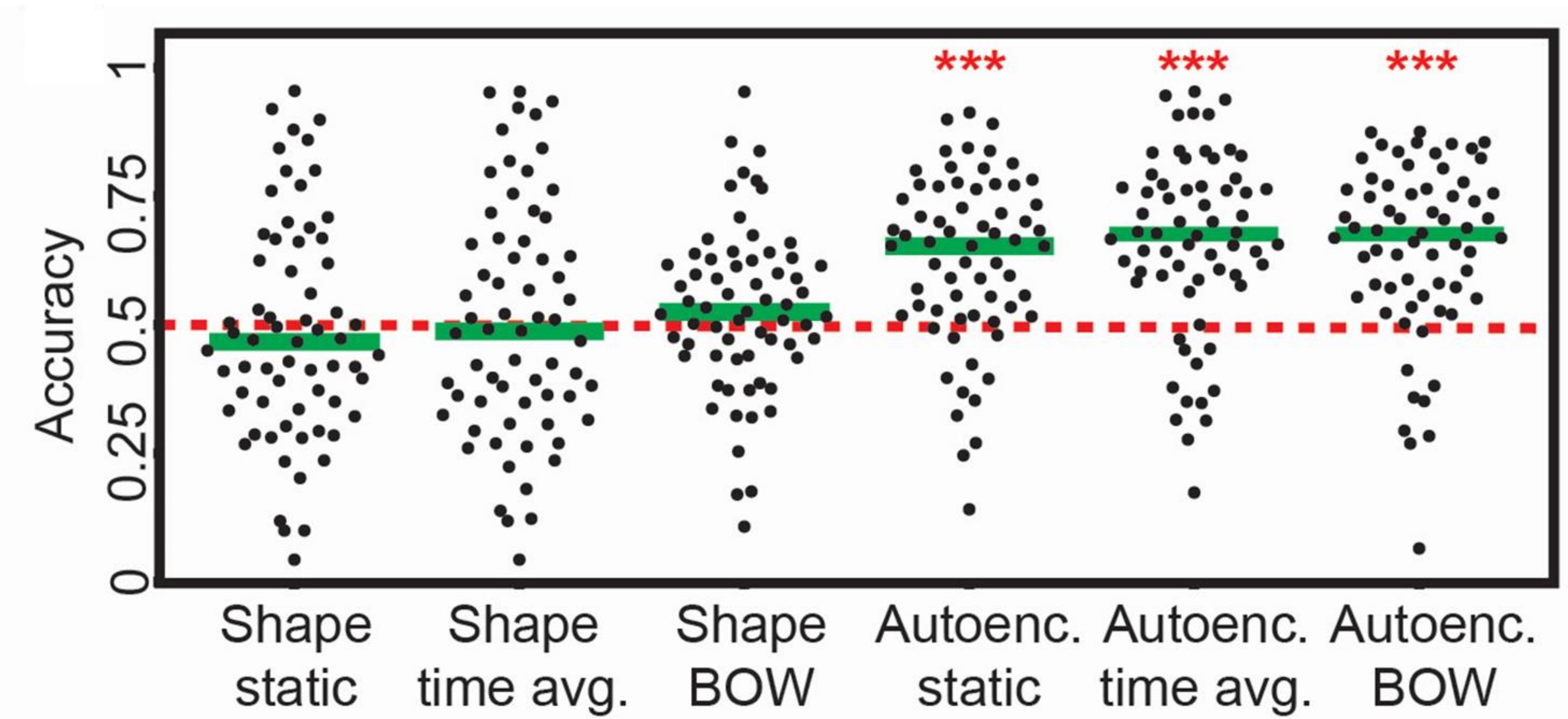
Failed



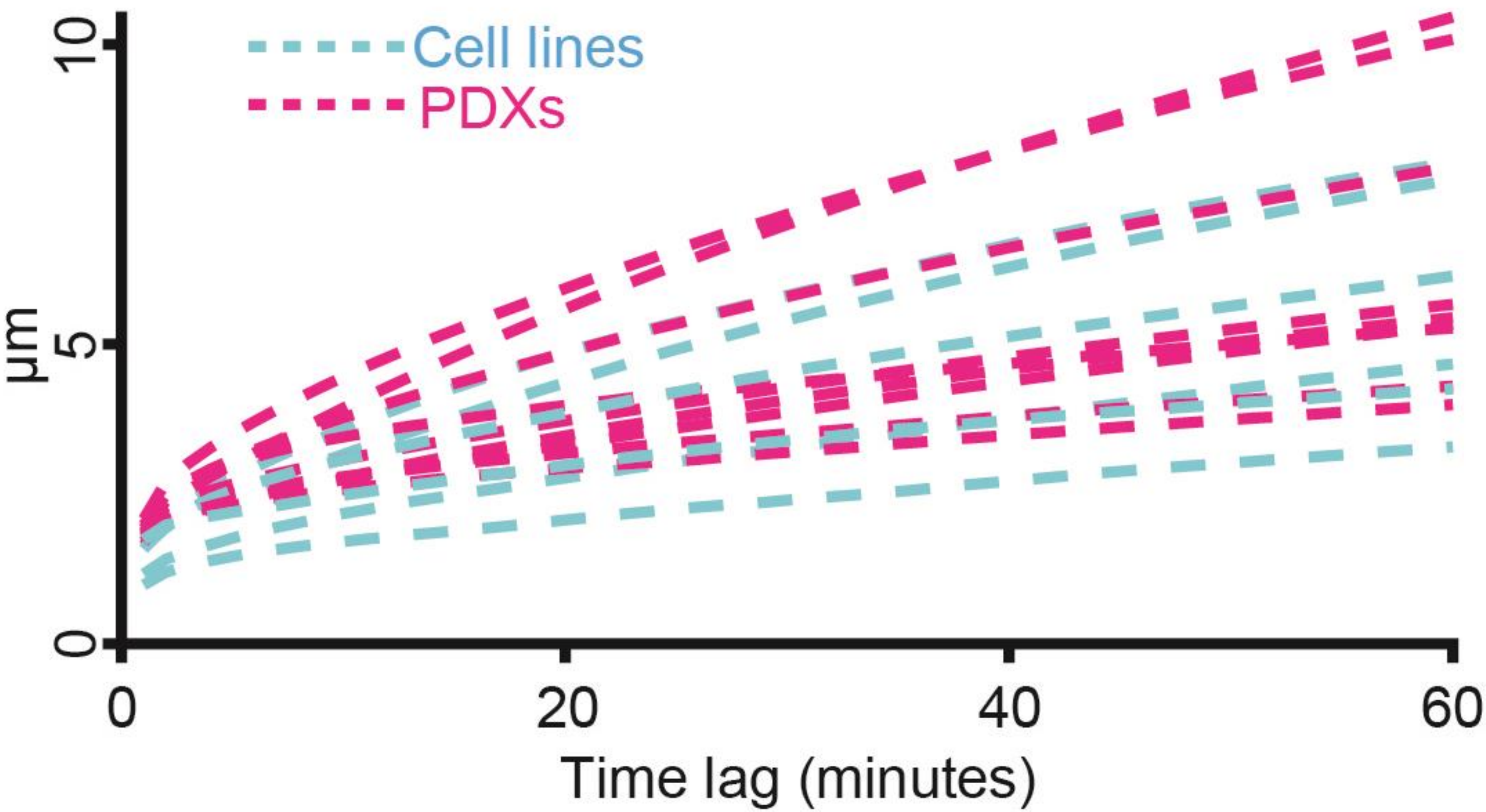
Alternative descriptors



Classification comparison using cell shape and temporal information to distinguish cell lines from PDXs

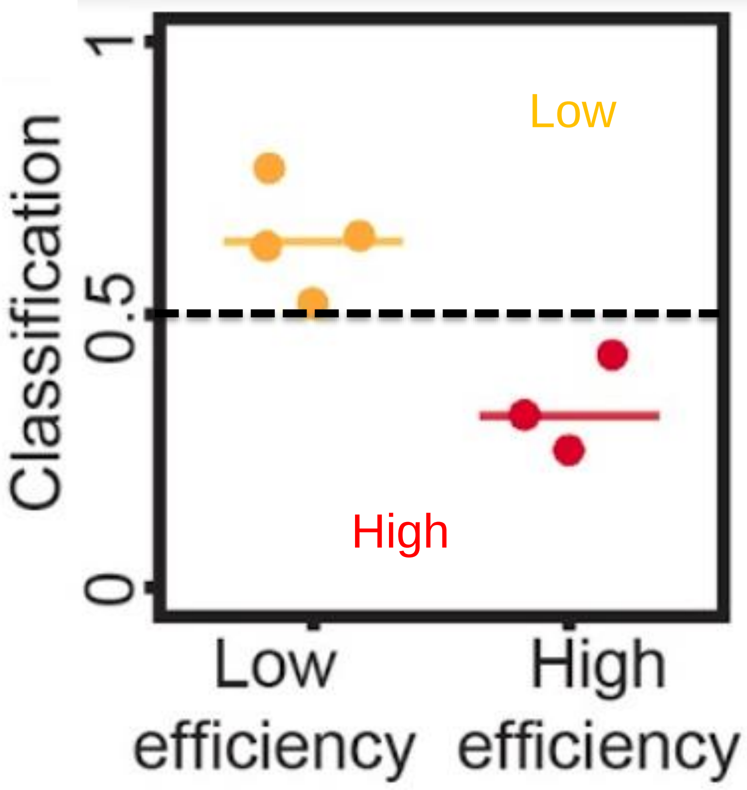


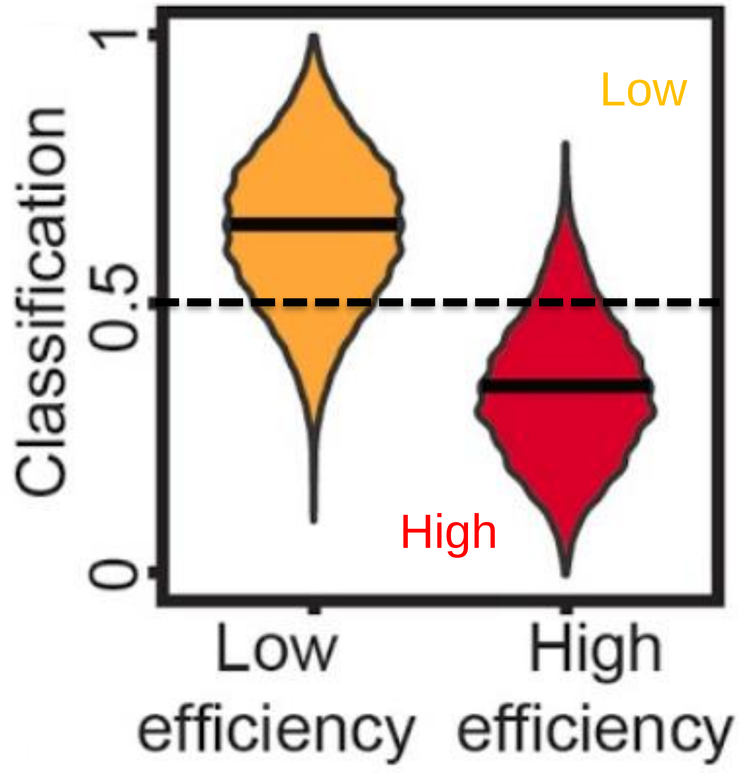
Mean squared displacement analysis of single cell trajectories



Live cell histology for classification of melanoma metastatic efficiency

Classifier blind to the patient

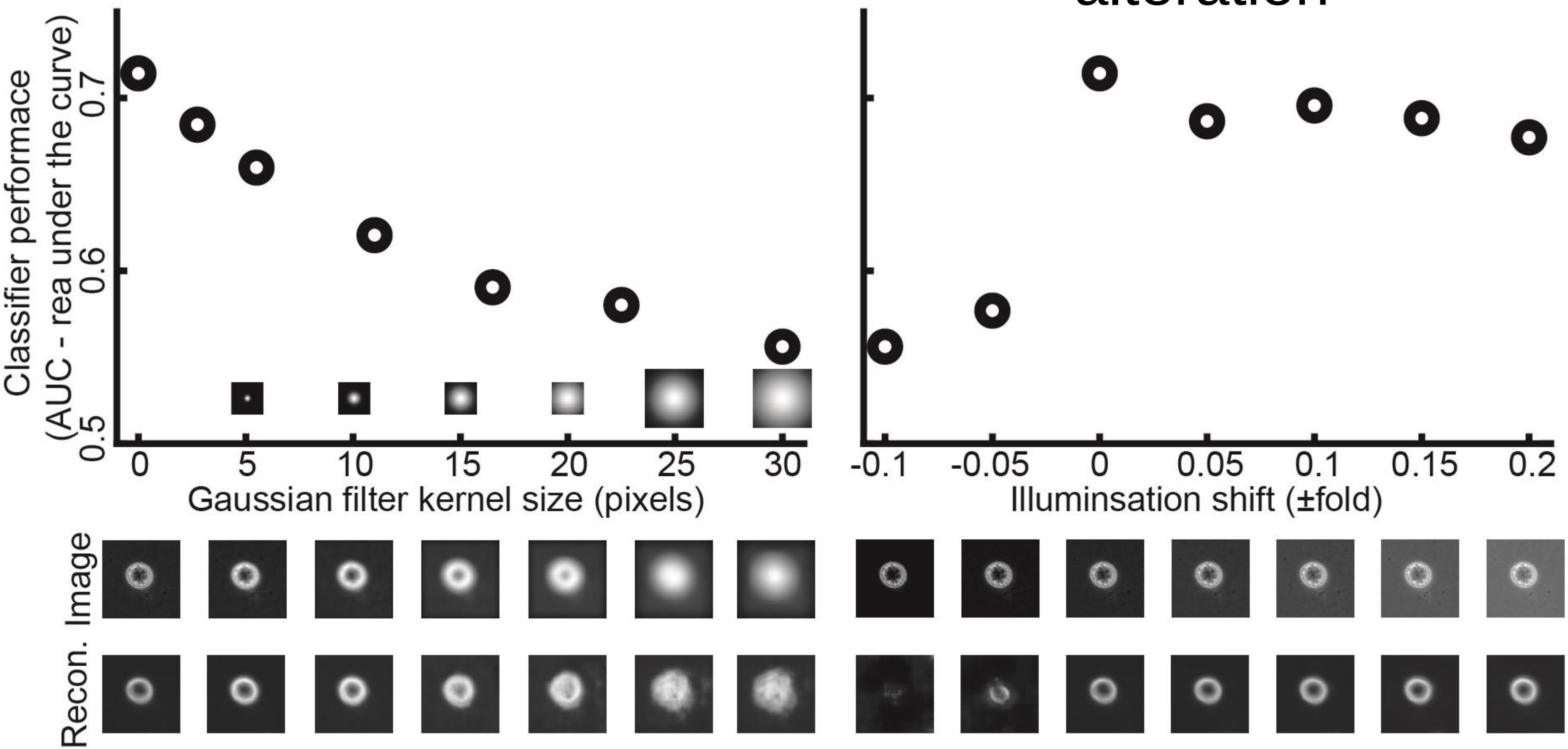




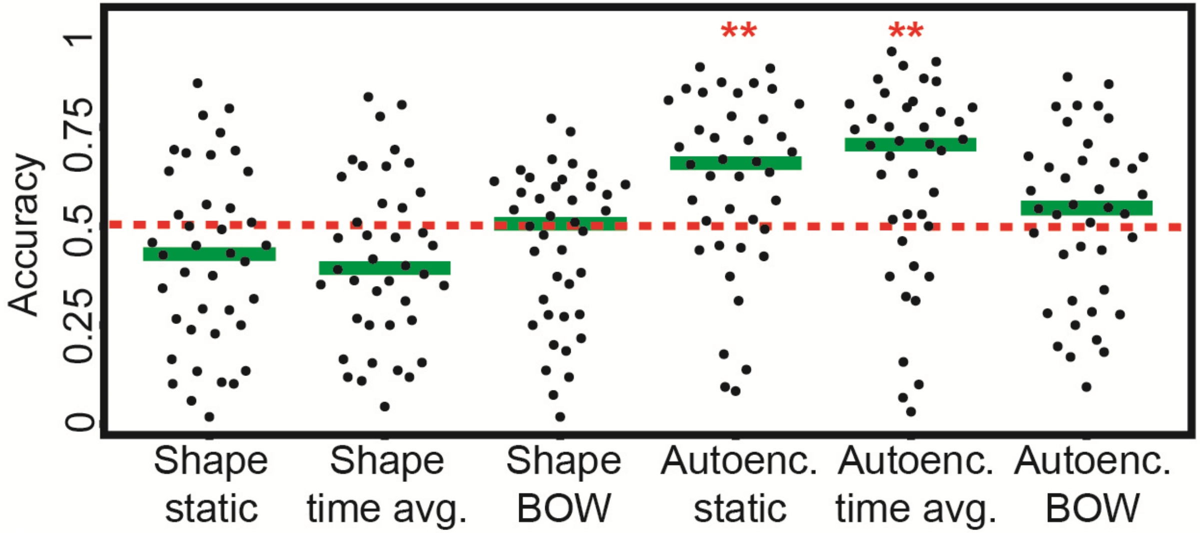
Robustness analysis

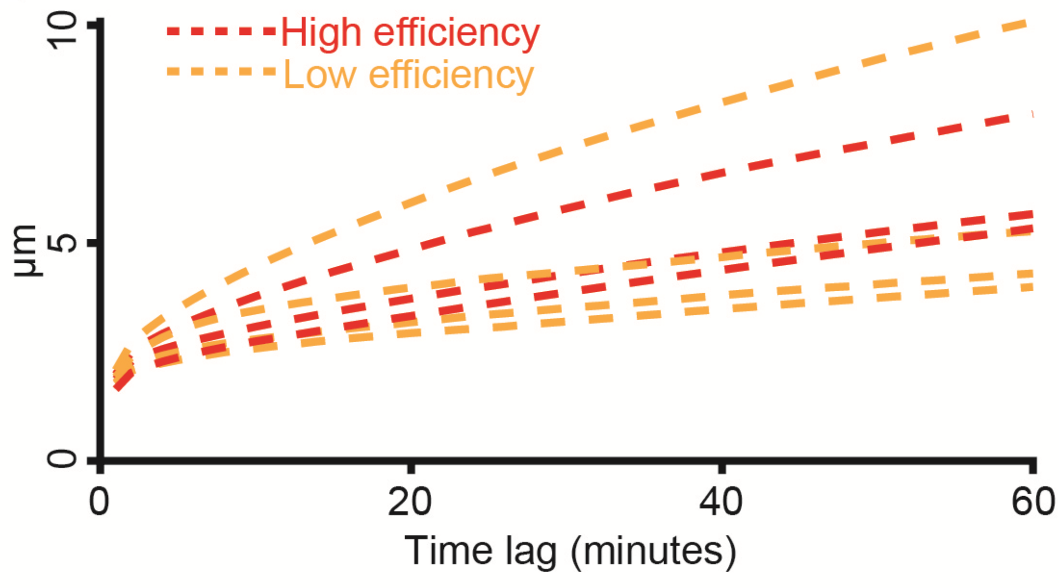
Gaussian blur

Simulated illumination alteration

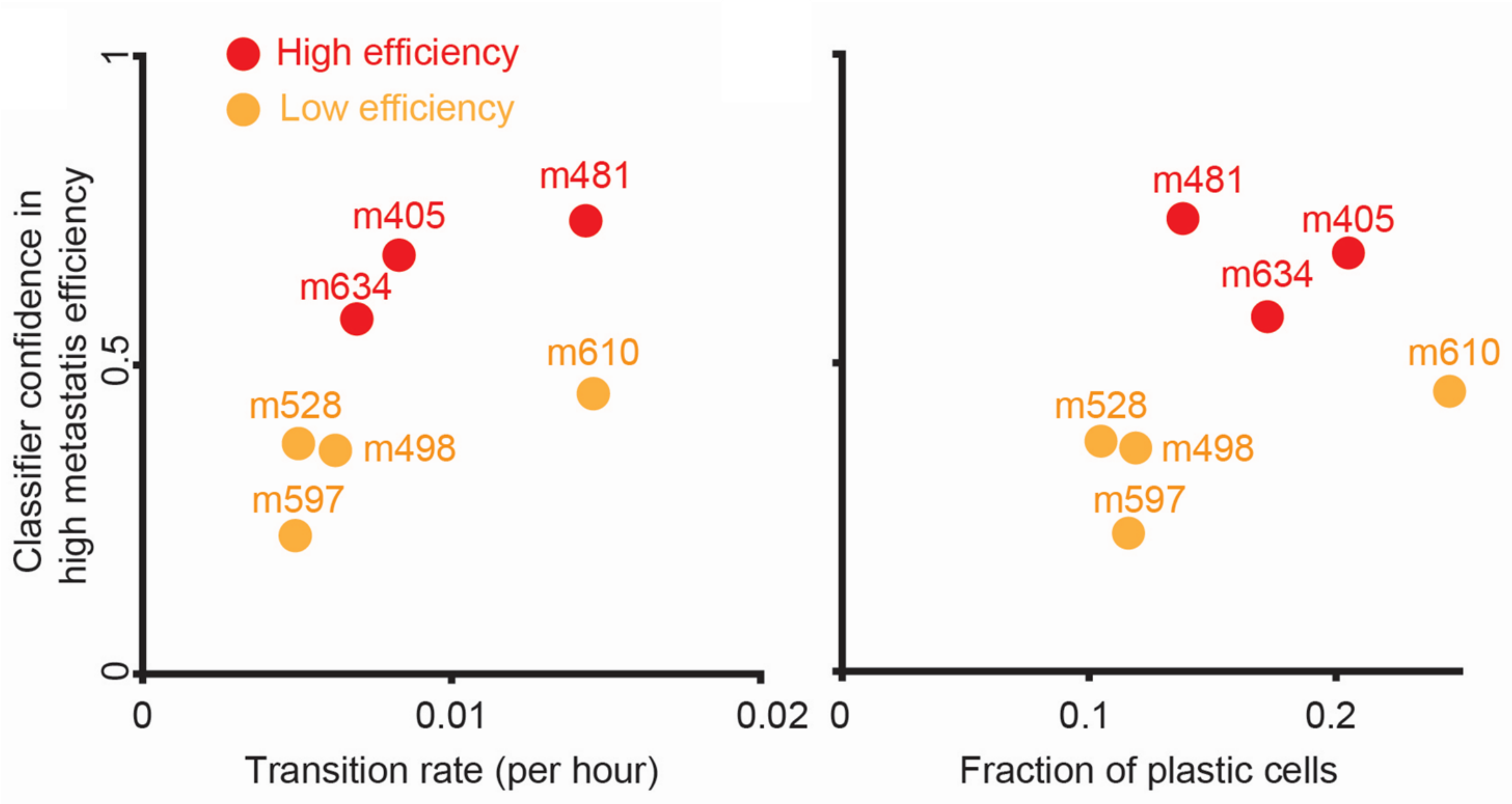


Shape and motility can not distinguish metastatic efficiency



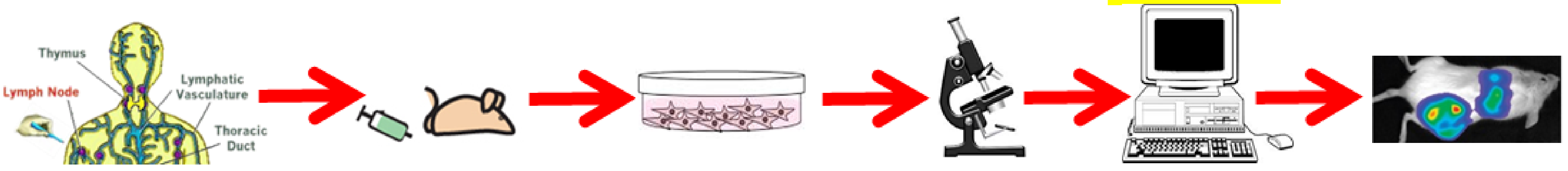


Cell plasticity

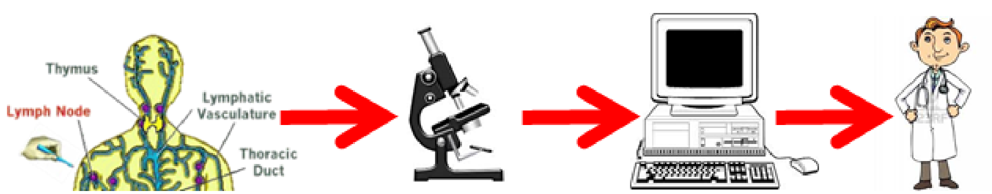


The dream: live cell histology (LCH) of fresh biopsies to predict metastatic potential

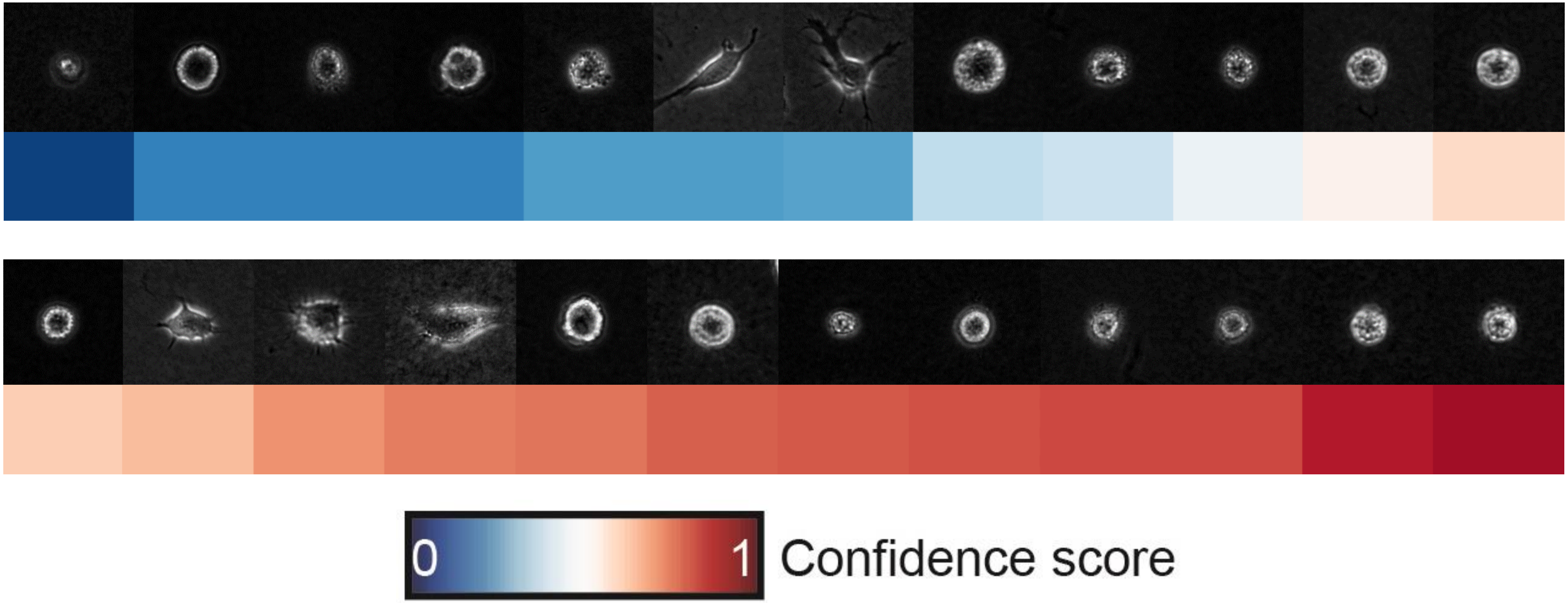
Biopsy Transplant culture Image **LCH** Correlate



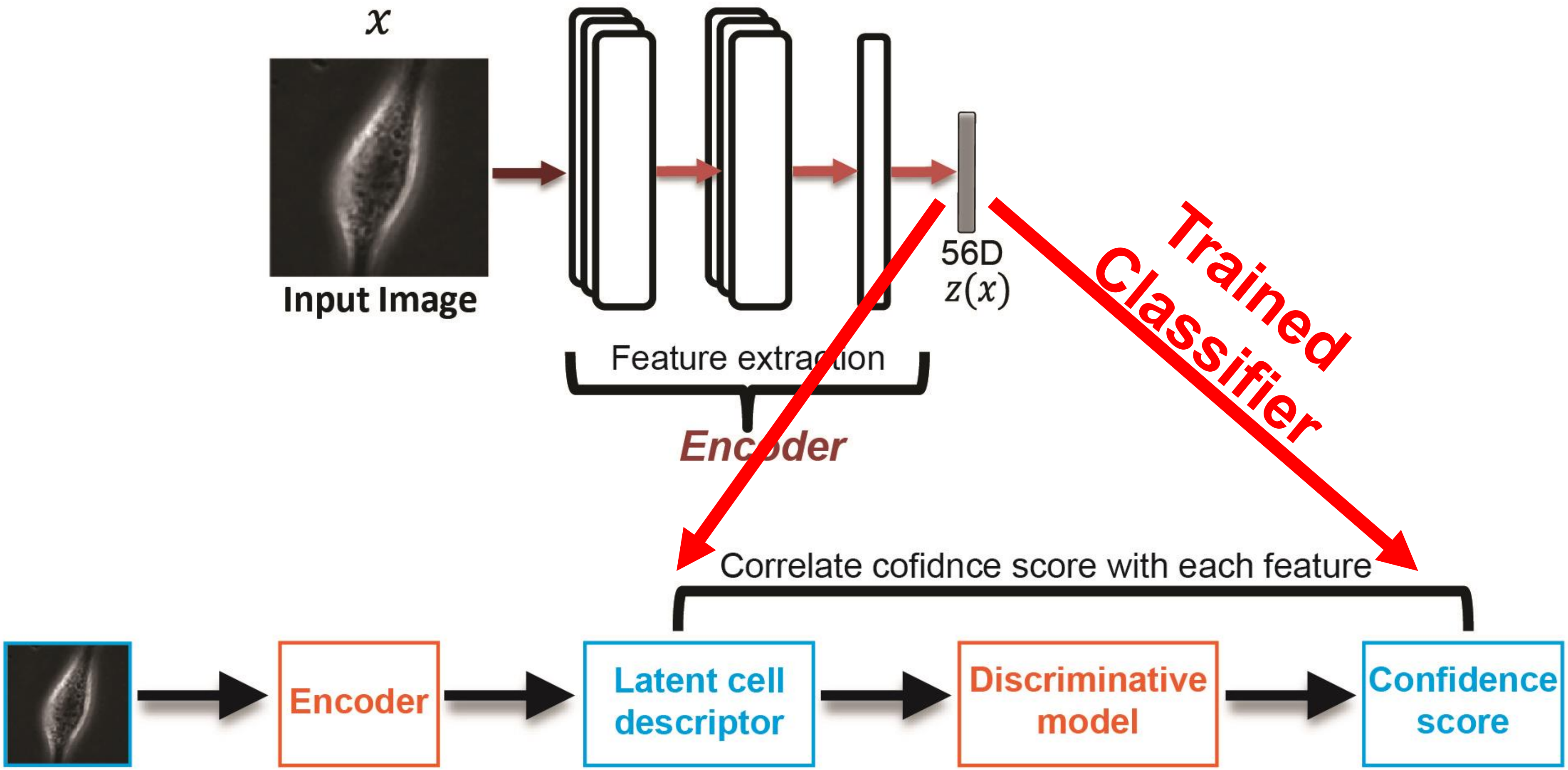
Biopsy Image **LCH** MD



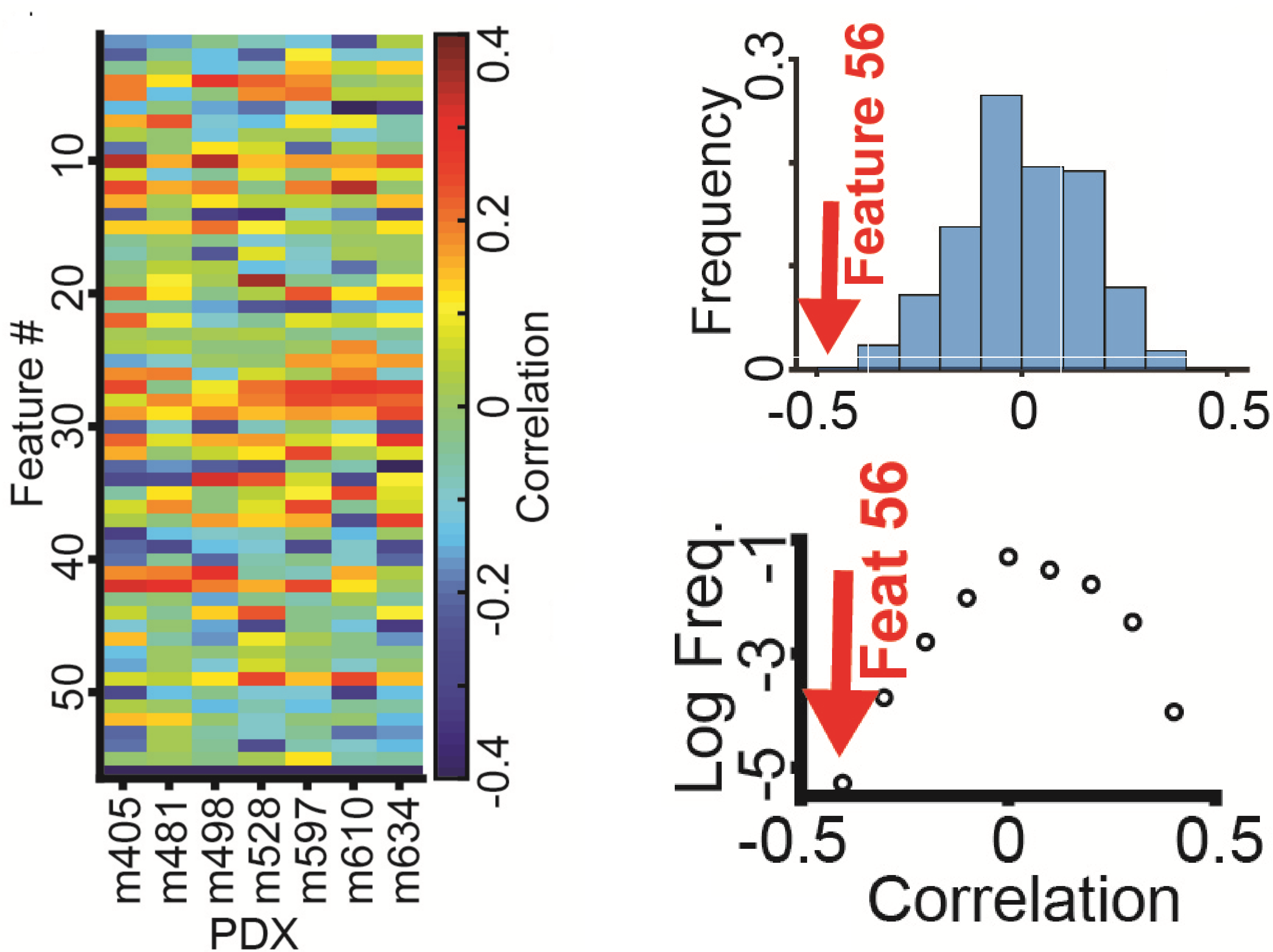
What are the physical attributes that discriminate high from low metastatic efficient cells?



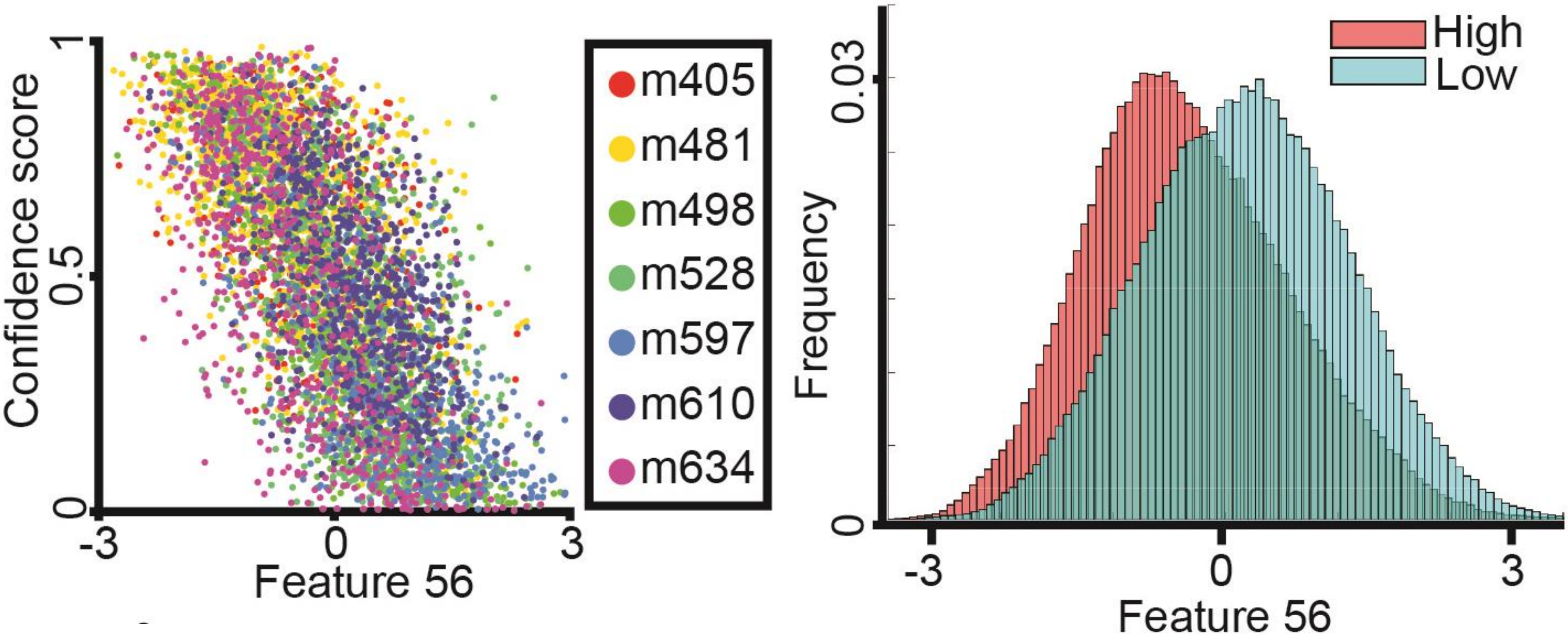
Using the variability within the data to identify key features for the classification



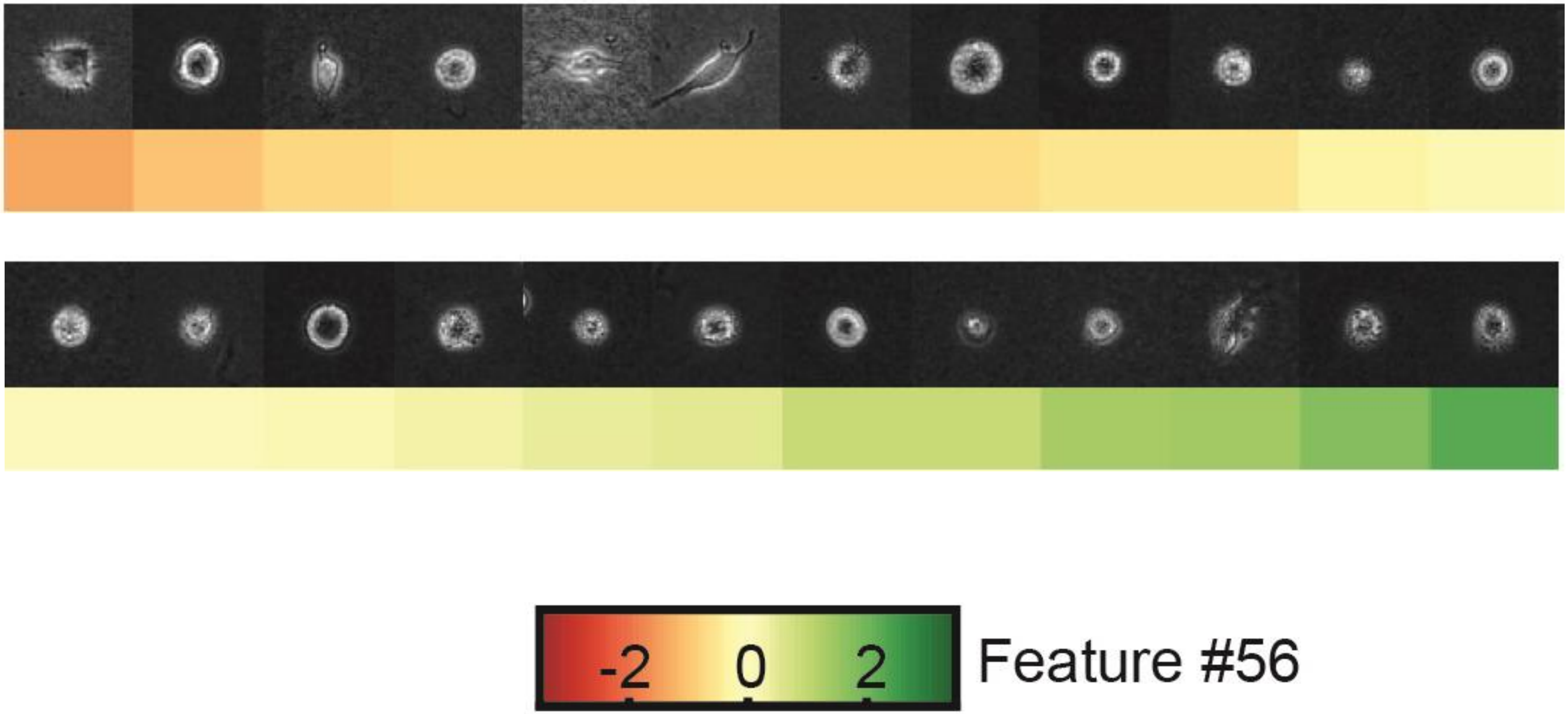
Correlating all features and classifier scores for all PDXs



Feature #56 is negatively correlated with the classifiers' predictions!



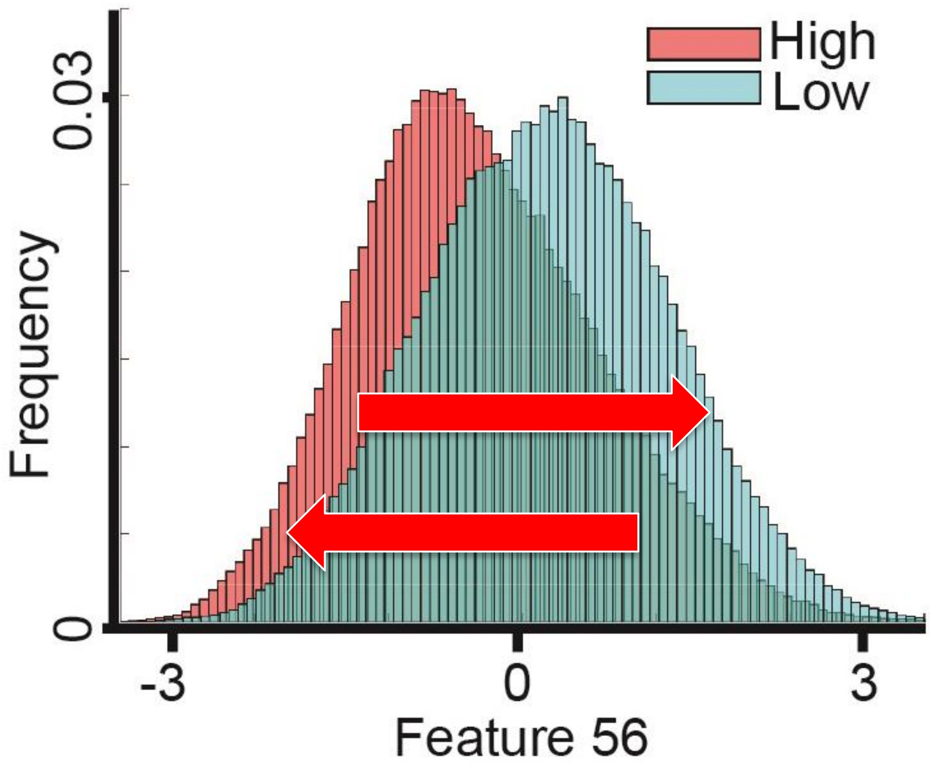
Second try: what physical properties are encoded by feature #56?

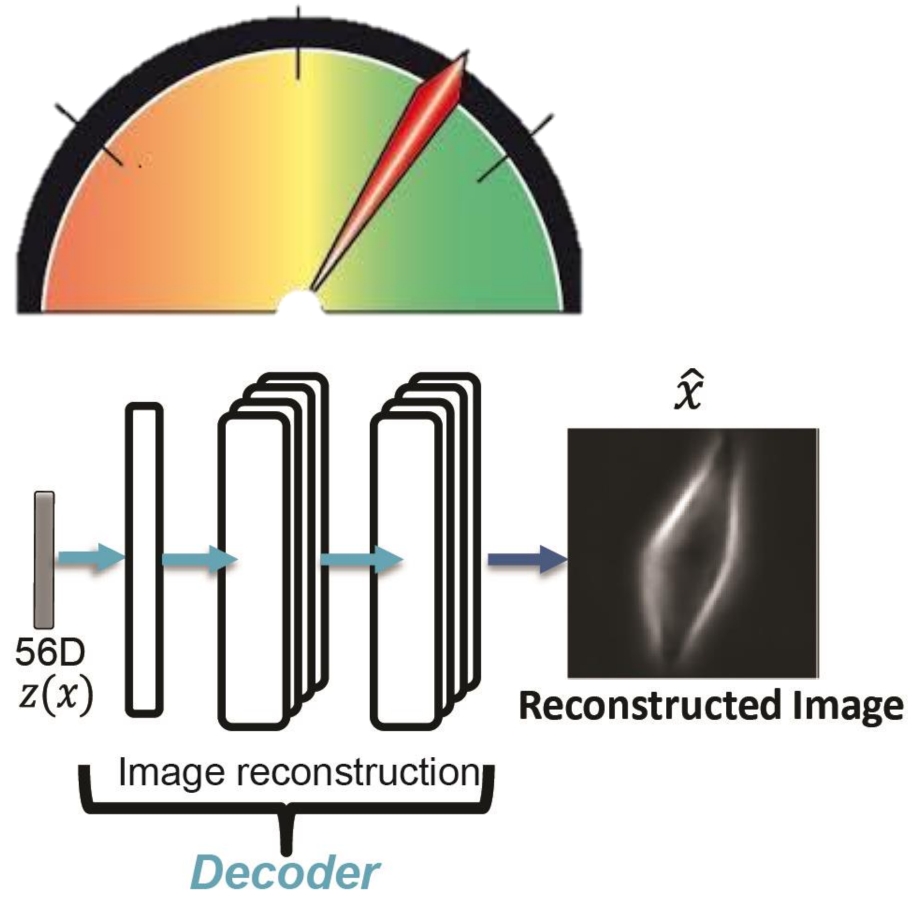


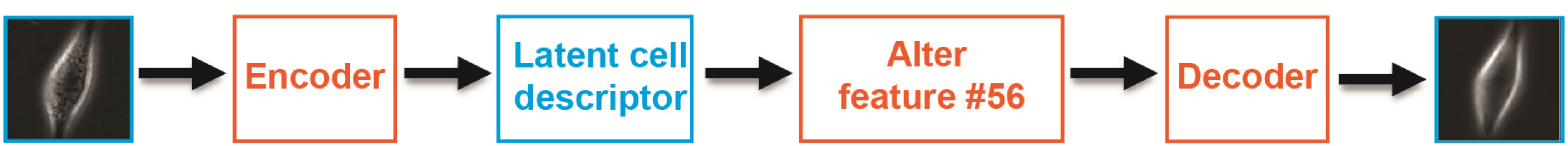
Morphing (celebrity) faces

Source: http://picchore.com/animated-gif-2/rather-mesmerizing-face-morphing-gif-of-assorted-celebrities/

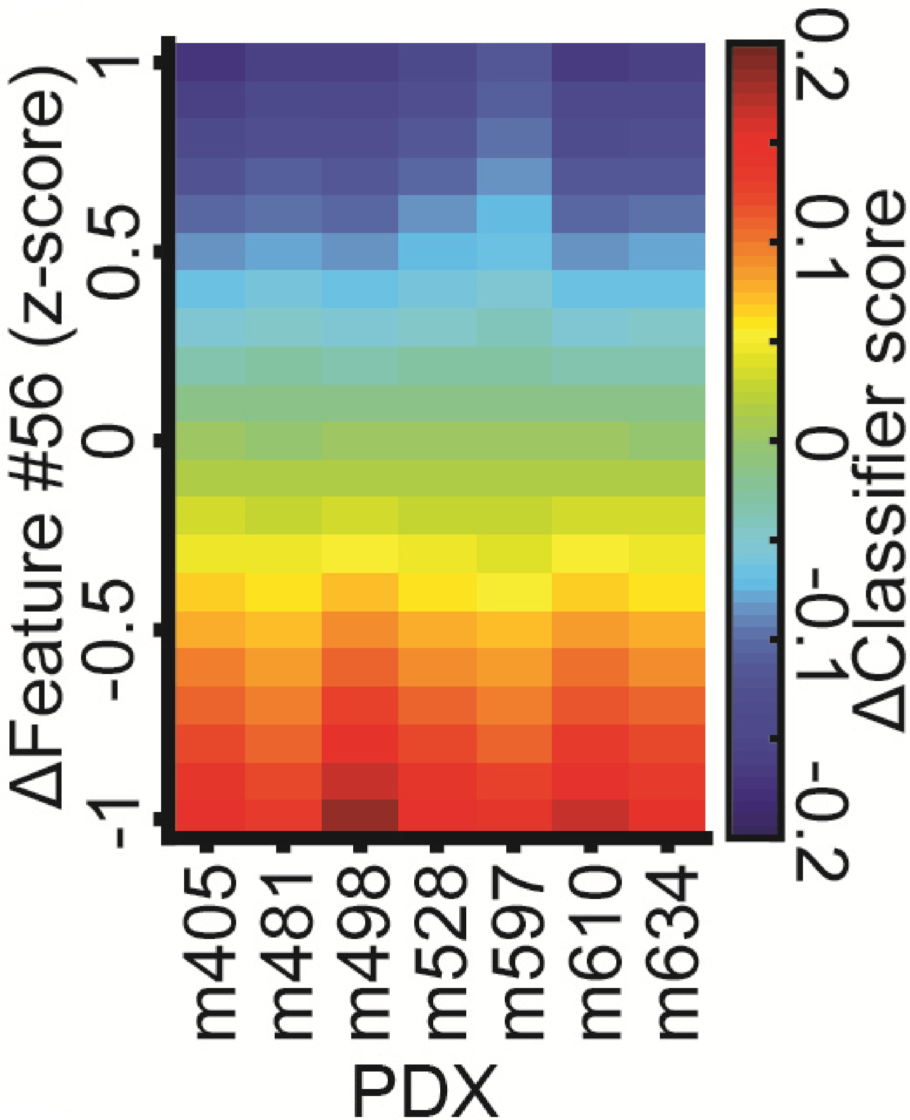
Transforming cells “in silico”



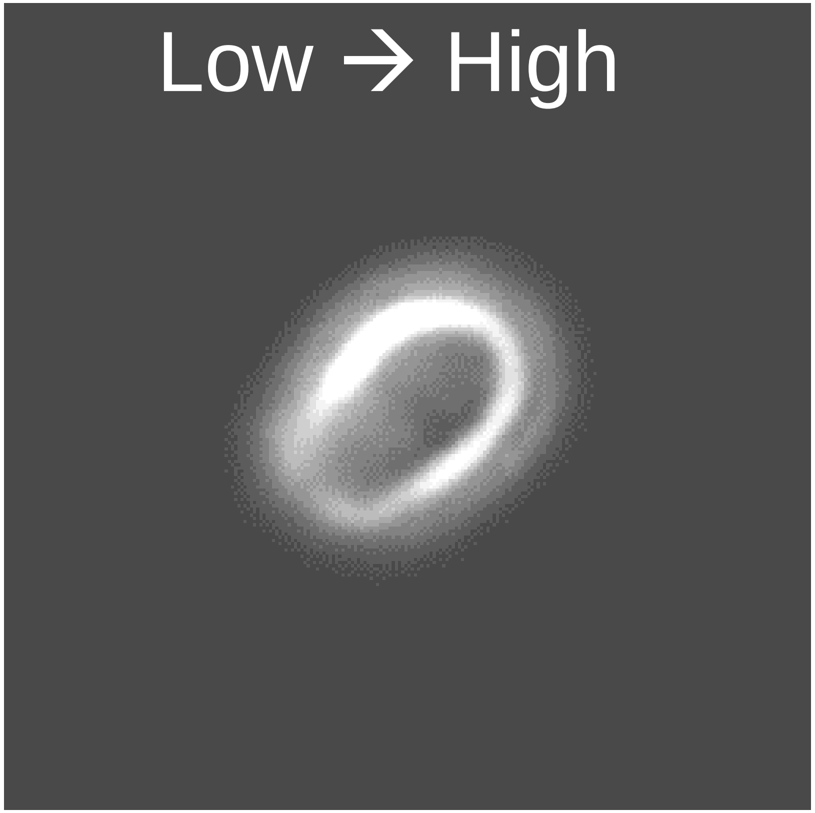


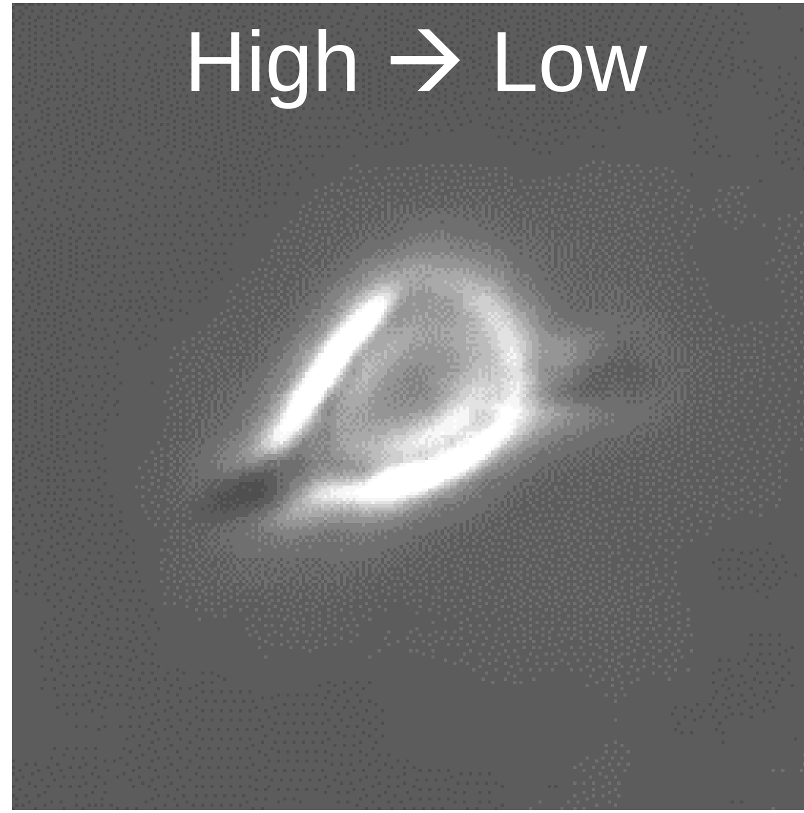


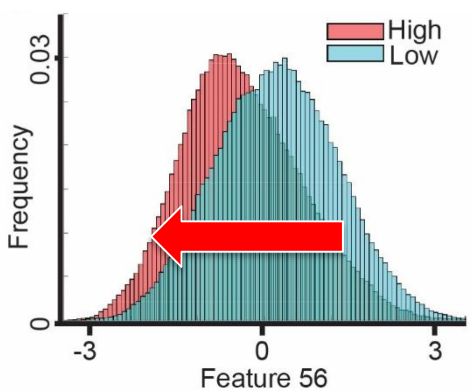
Shifts in feature #56 negatively correlated with variation in the classifier scores

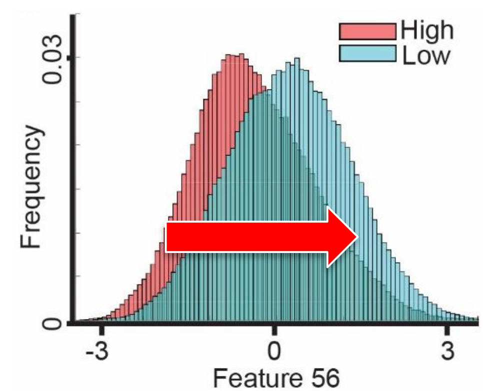


Morphing melanoma *in silico*

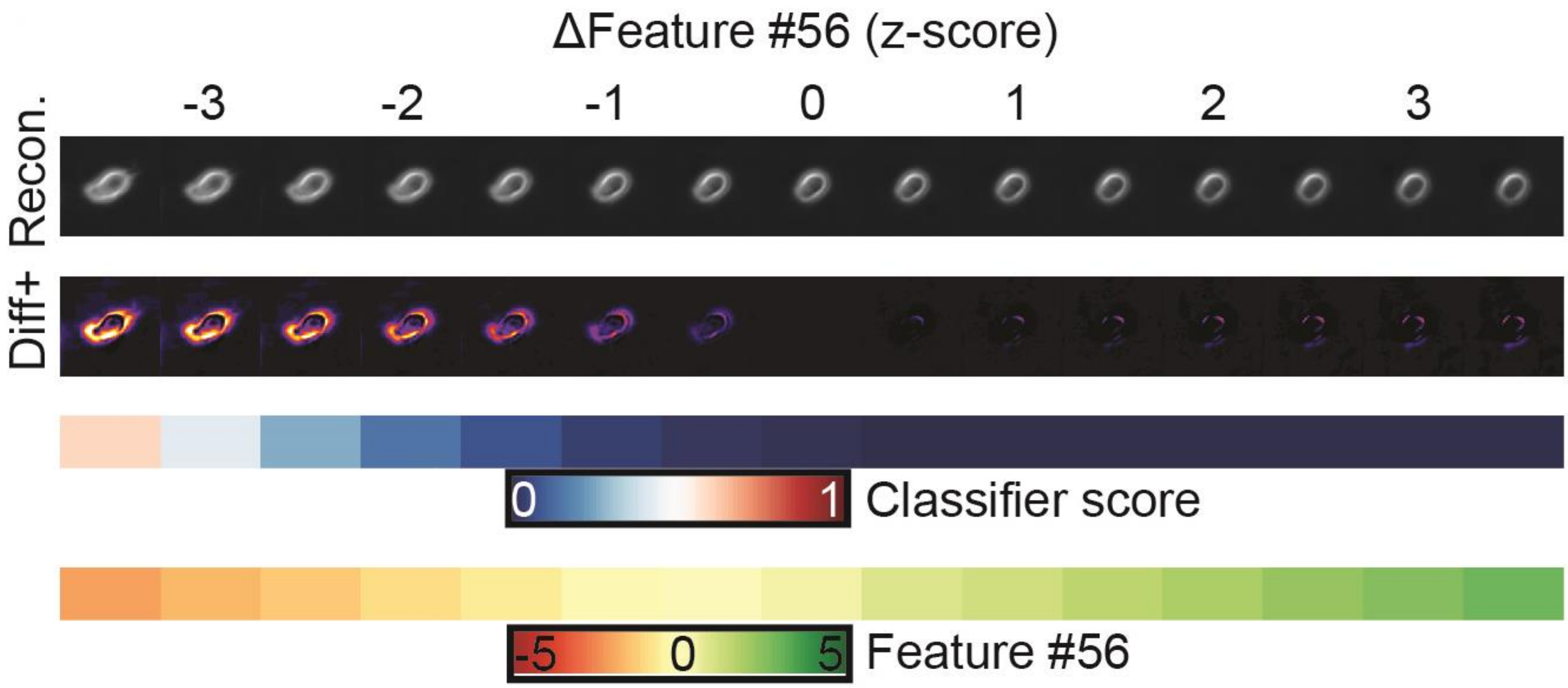




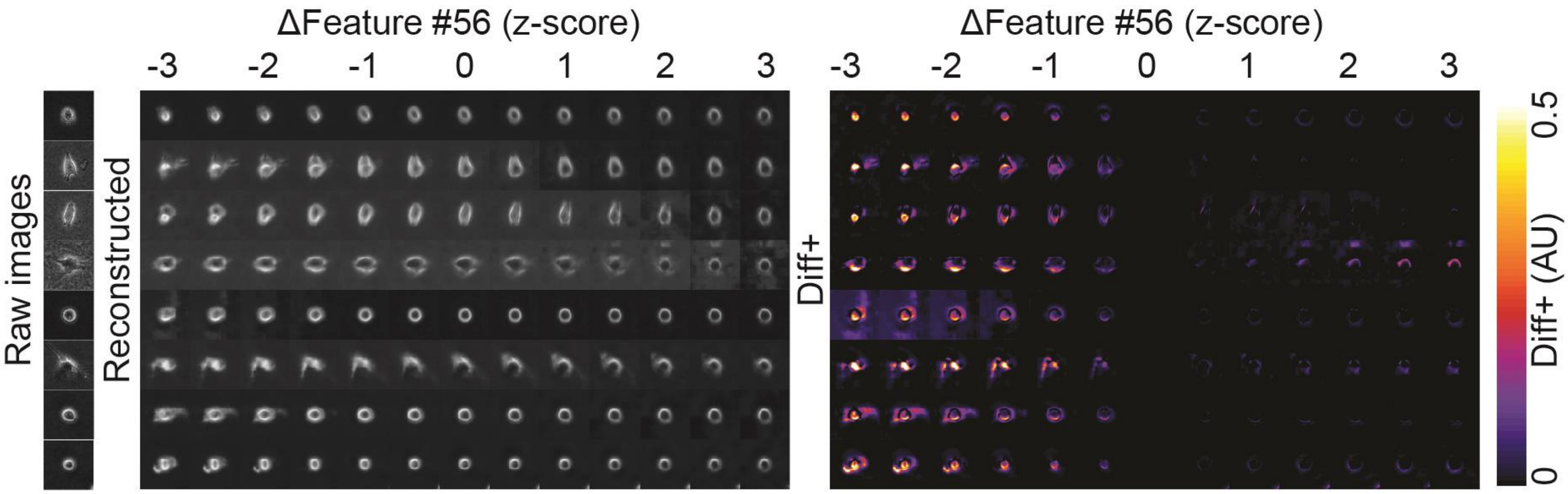




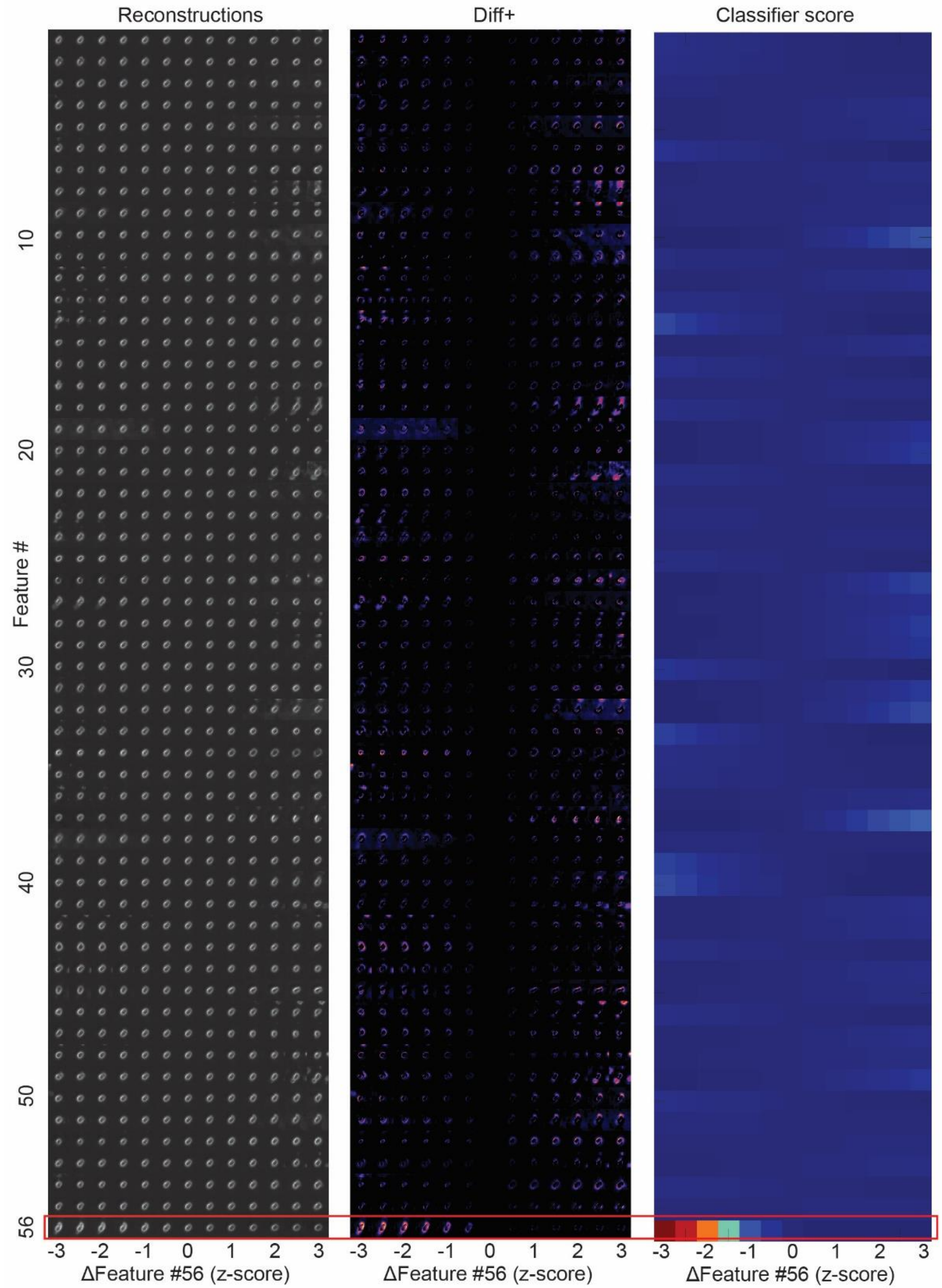
What can we **see**?



Is it replicated?



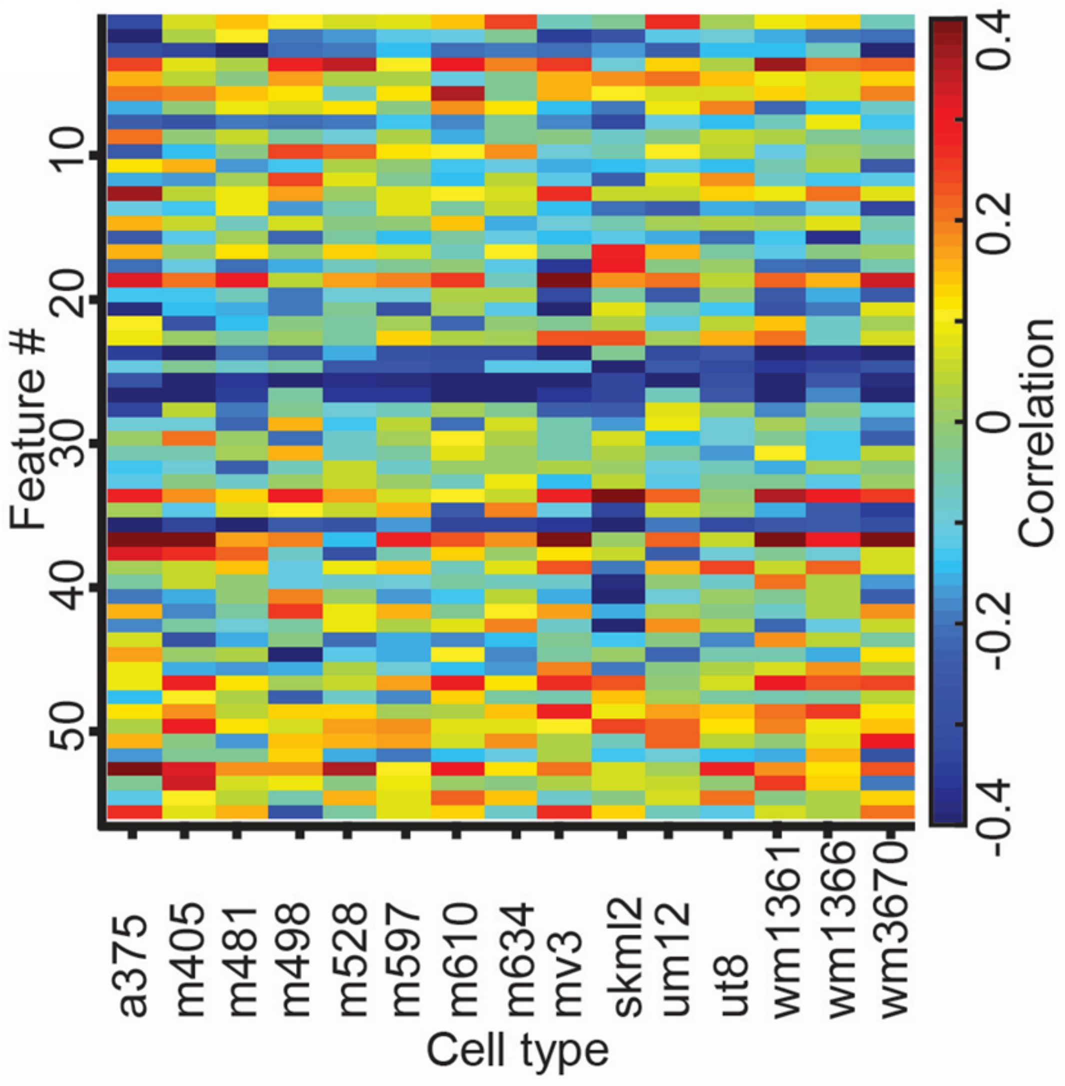
Is it specific?



Hypothesis: feature #56 is associated with a combination of enhanced protrusive activity, and increased light scattering

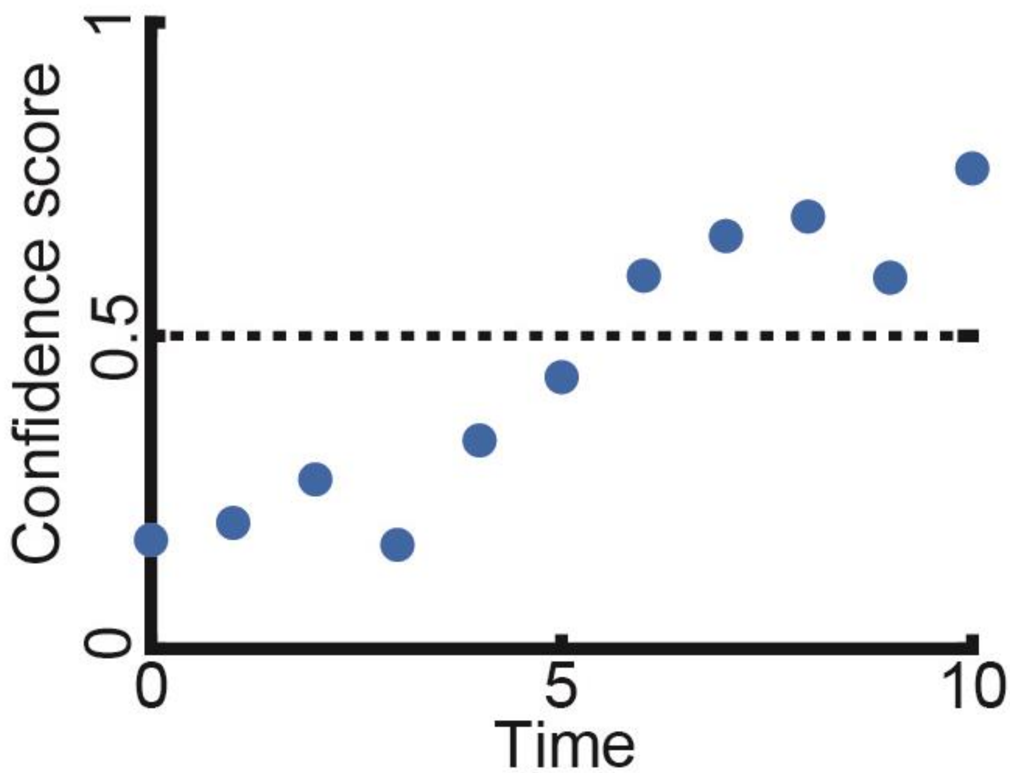
Just one feature? We were lucky!

Multiple features are classification-driving for discriminating cell lines from PDXs

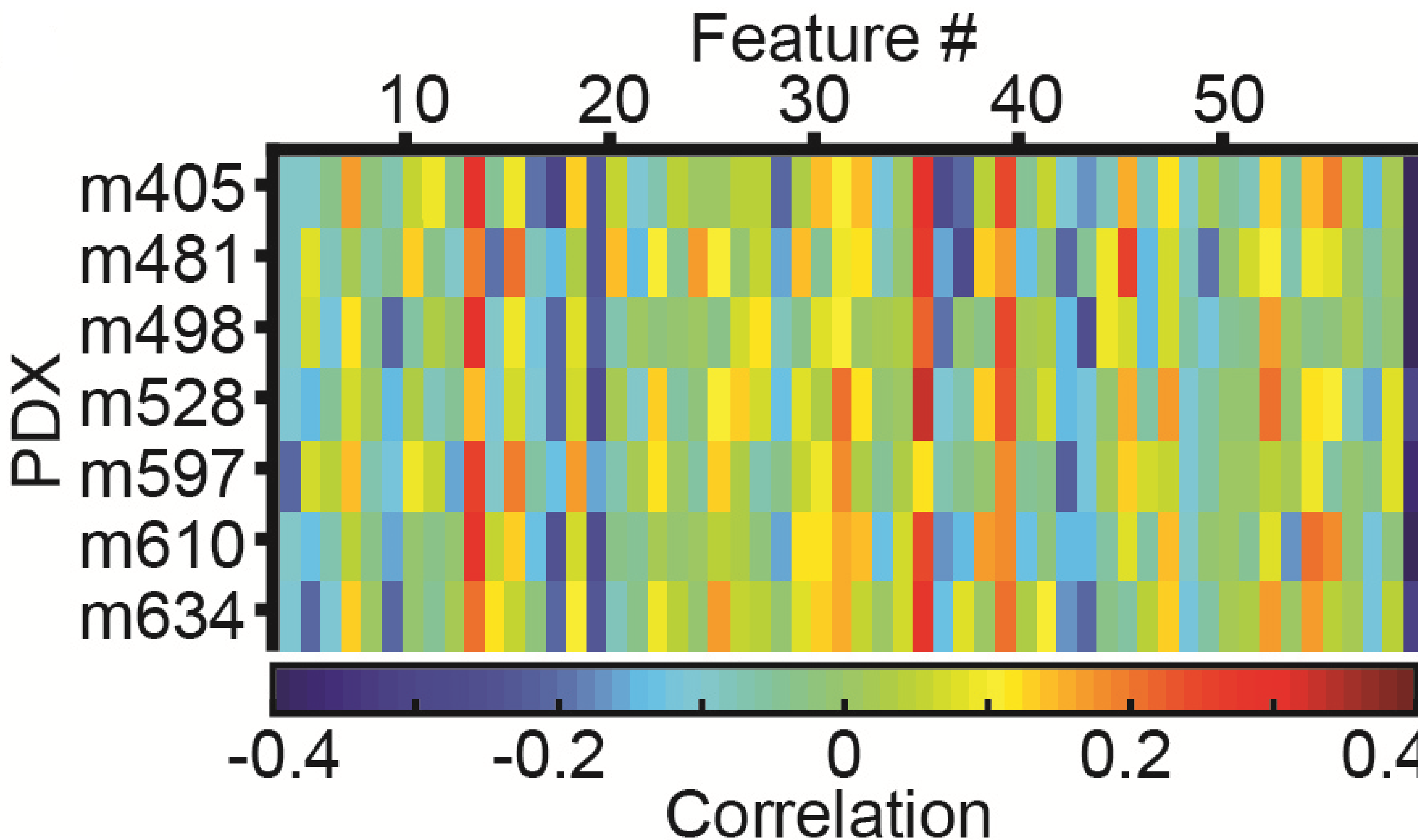


Validation with live cell imaging!

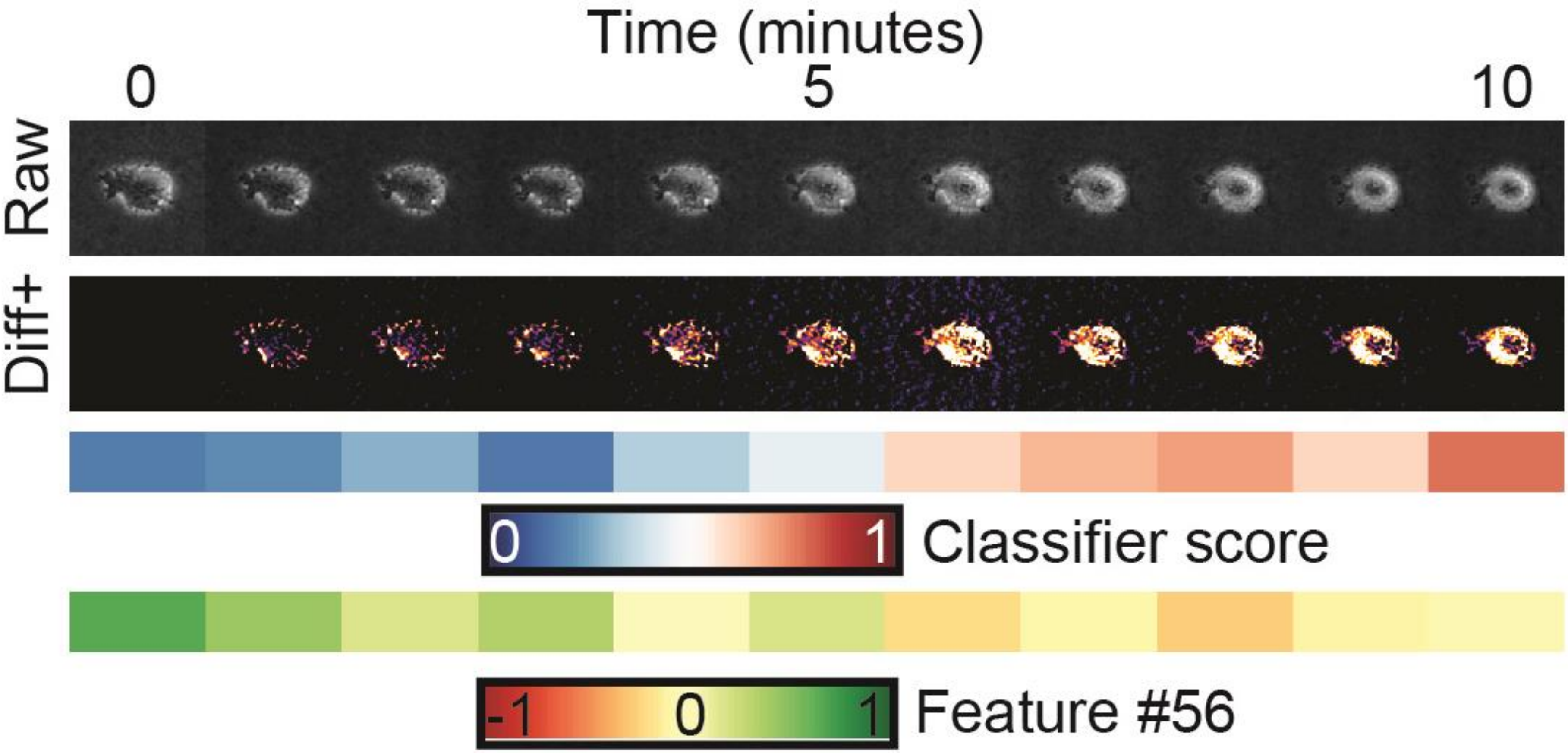
Cell transitioning "in the wild"



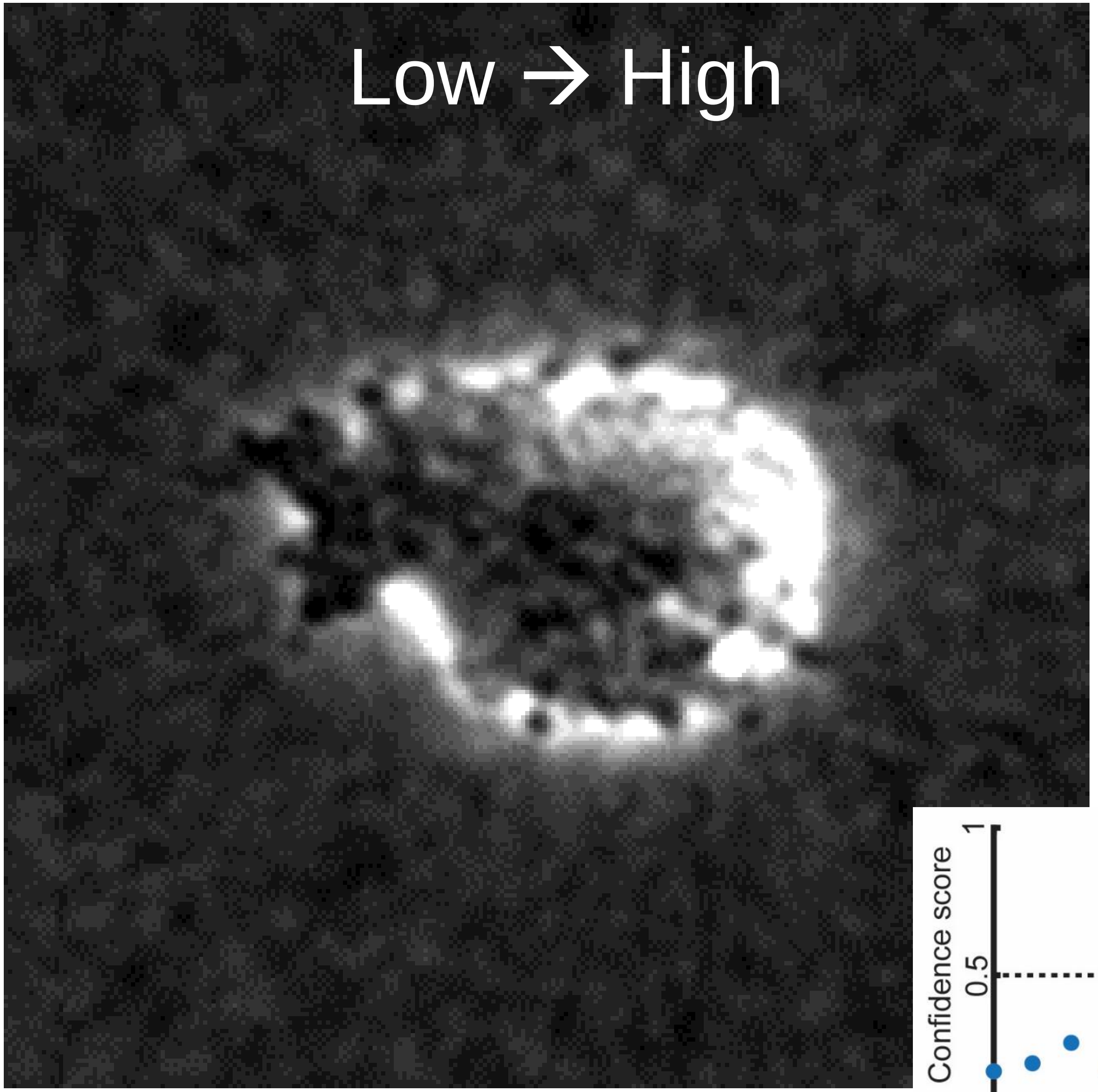
Temporal fluctuations in feature #56 negatively correlated with the temporal fluctuations in the classifier scores

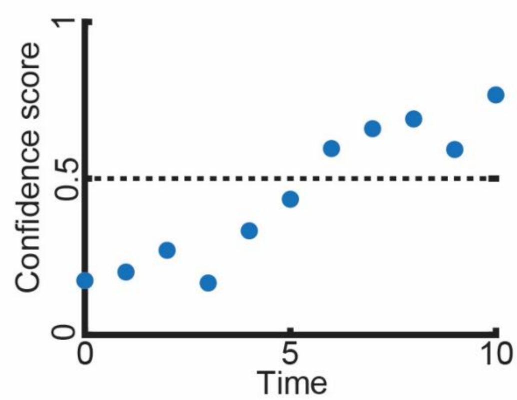


Spontaneously transitioning from a predicted low to high met. efficiency



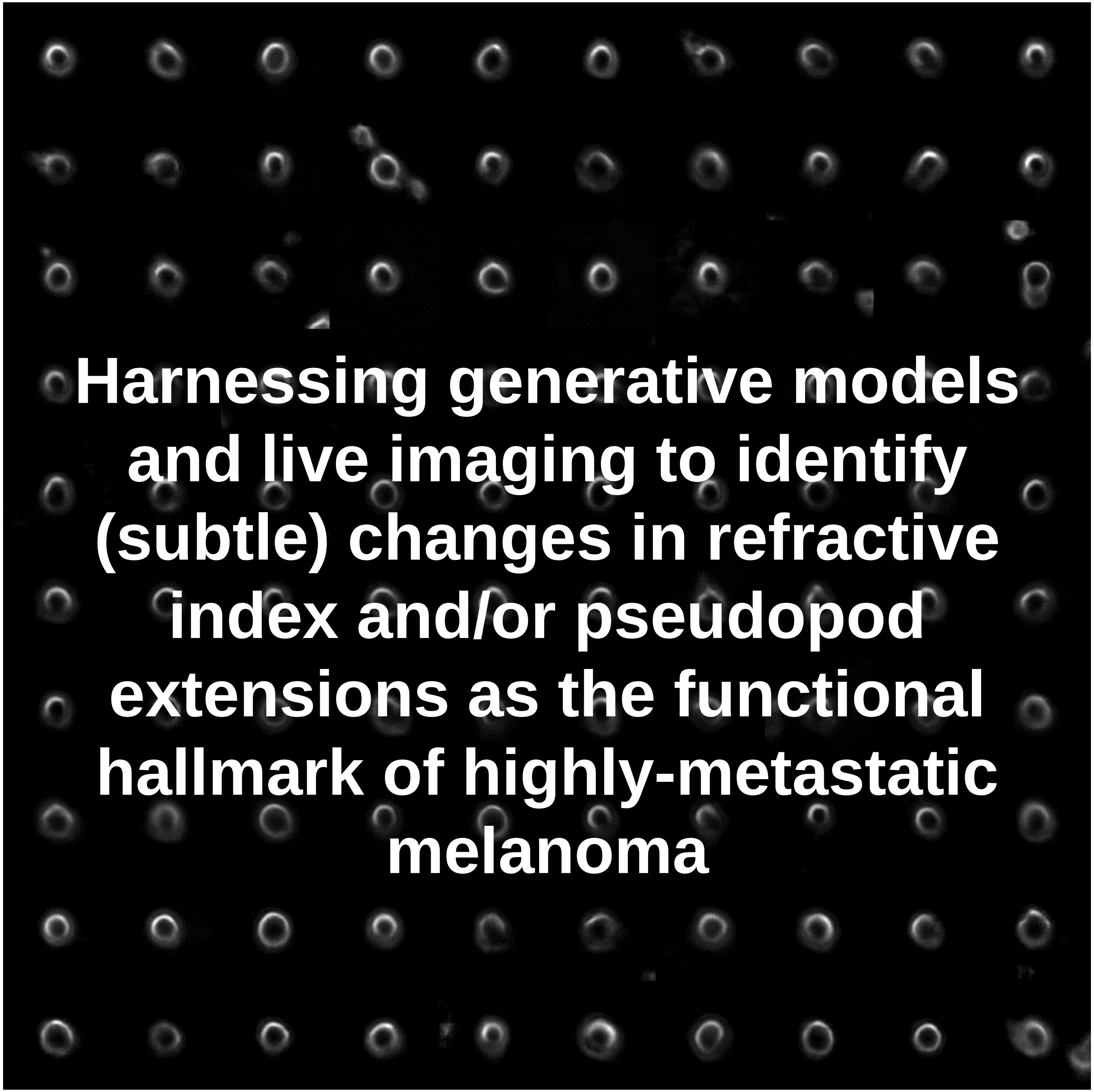
Cell transitioning "in the wild"





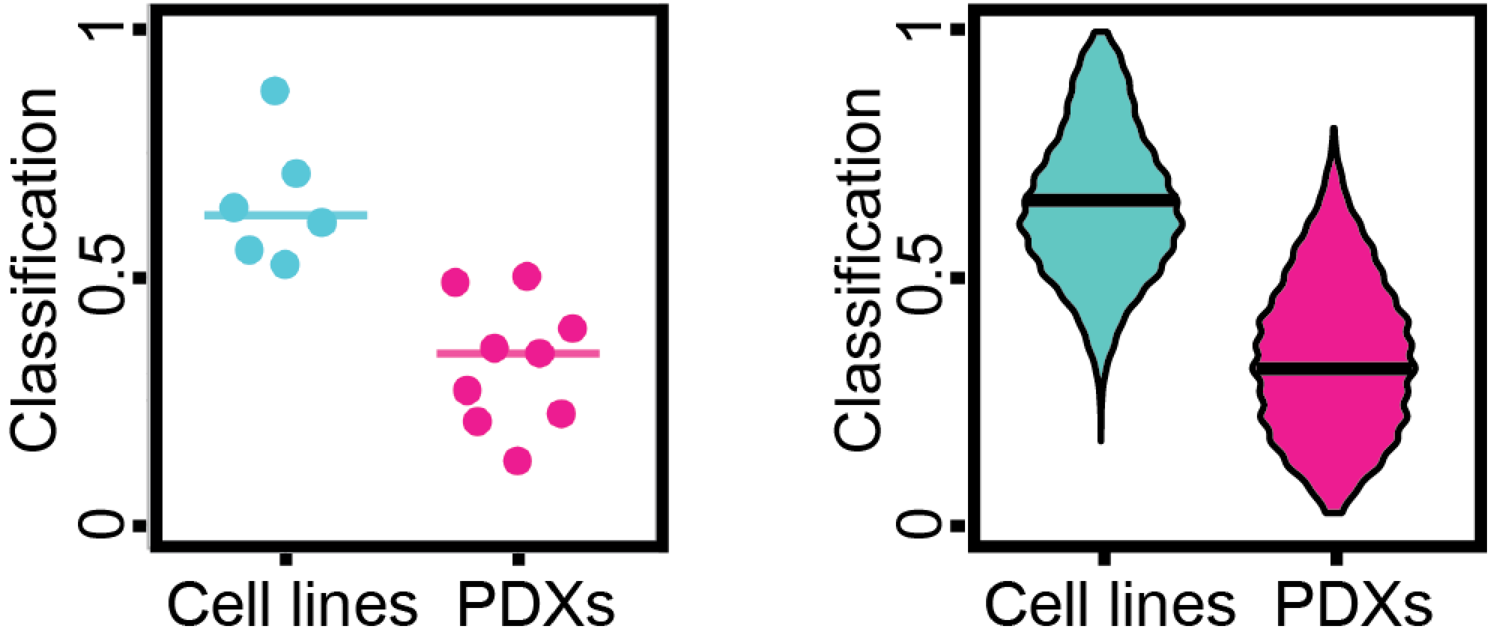
Hypothesis: feature #56 is associated with a combination of enhanced protrusive activity and **increased light scattering**

Increased light scattering must be caused by alteration in the refractive index: fluctuations in organelle/cytoplasm composition? cell stiffness?

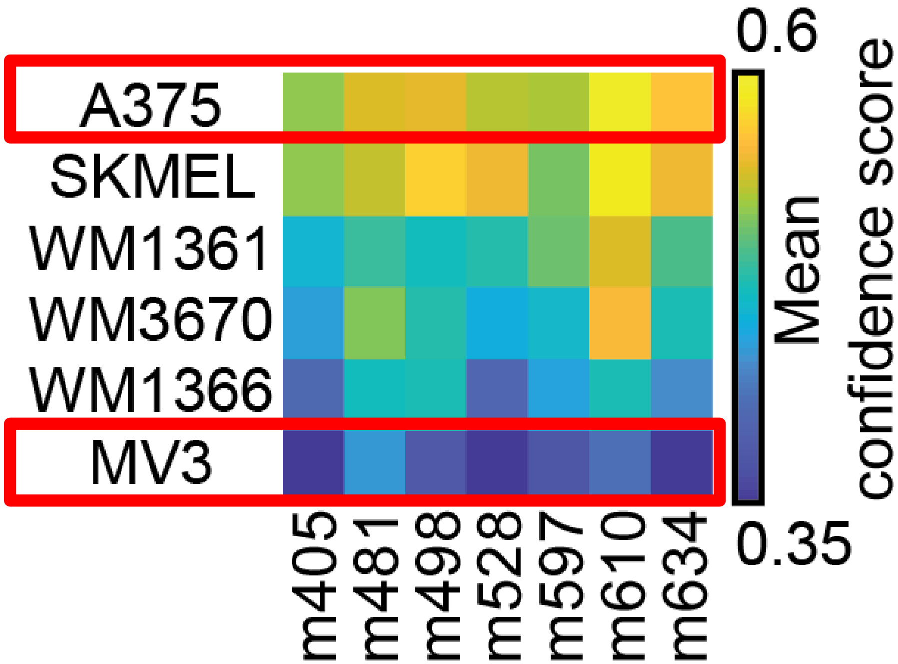

Harnessing generative models
and live imaging to identify
(subtle) changes in refractive
index and/or pseudopod
extensions as the functional
hallmark of highly-metastatic
melanoma

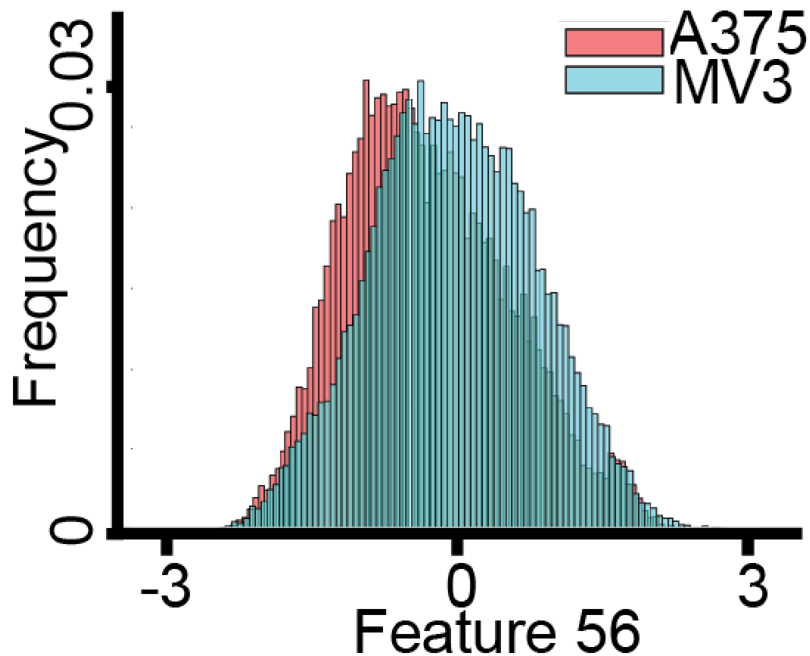
What about melanoma cell lines? Definitely different than PDXs…

Classifier blind to the cell system

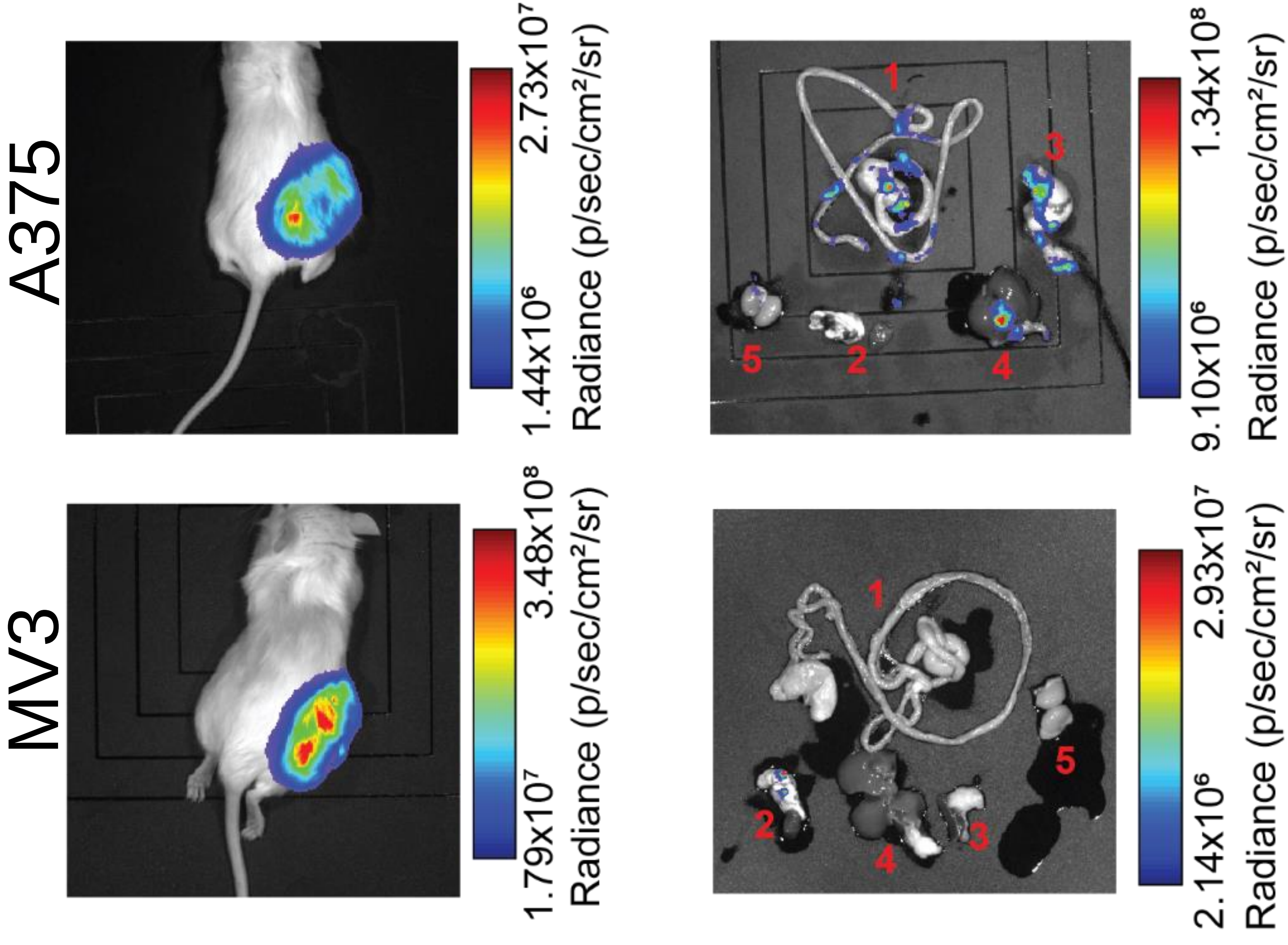


A375 has the highest and MV3 the lowest **predicted** metastatic efficiency





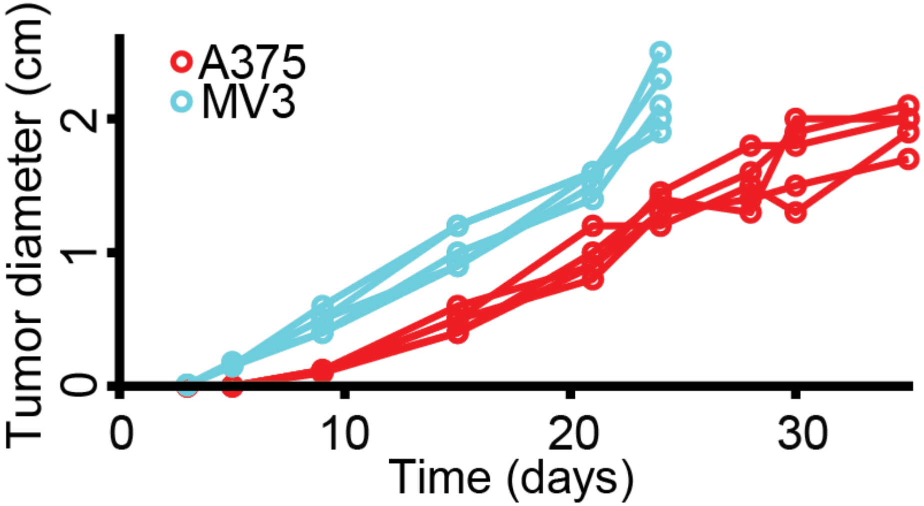
Xenografting A375 and MV3 cells into NSG mice



A375 is more aggressive than MV3

Cell line	BLI Lungs	BLI other organs	Remote macro mets
A375	(4/5)	(4/5)	(5/5)
MV3	(5/5)	(2/5)	(1/5)

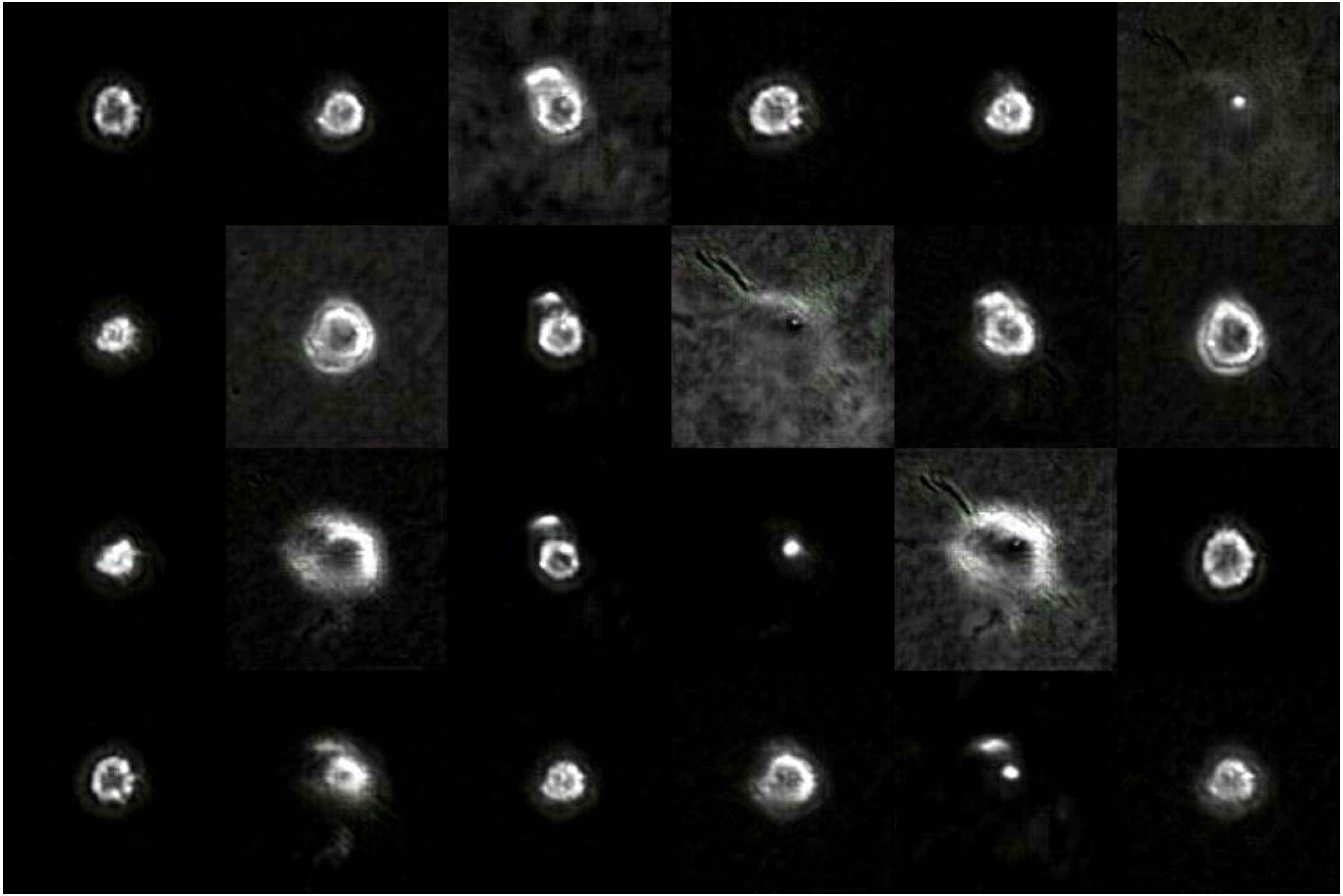
Uncoupled from tumor growth



PDX-trained classifier can predict metastatic potential of melanoma cell lines in mouse xenografts

Capturing a generic predictive property for the metastatic potential of melanoma

Summary



Acknowledgments

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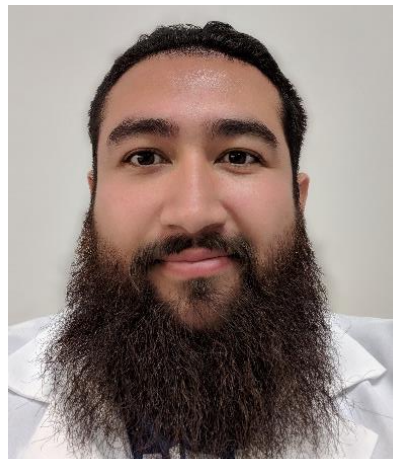
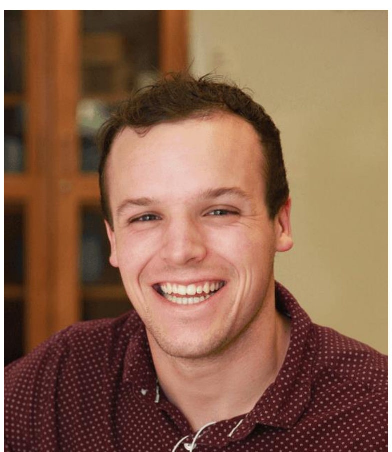


Erik Welf

Justin Cillay



Gaudenz Danuser

Available soon

(next week?) @

bioRxiv

THE PREPRINT SERVER FOR BIOLOGY

Next week 20.5

- Kota Miura, NEUBIAS, on bioimage analysis (English), 17:10!
- Students lectures:
  - Oron Barazani - DL in microscopy
    - Deep learning enables cross-modality super-resolution in fluorescence microscopy. Hongda Wang, Yair Rivenson,..., Aydogan Ozcan (2019)
  - Shani Kleiman - medical imaging
    - Prediction of cardiovascular risk factors from retinal fundus photographs via deep learning. Poplin, Varadarajan,..., Peng, Webster (2018)