NuClass: An Ontology-Driven Vision–Language Foundation Model for Zero-Shot Nuclei Classification

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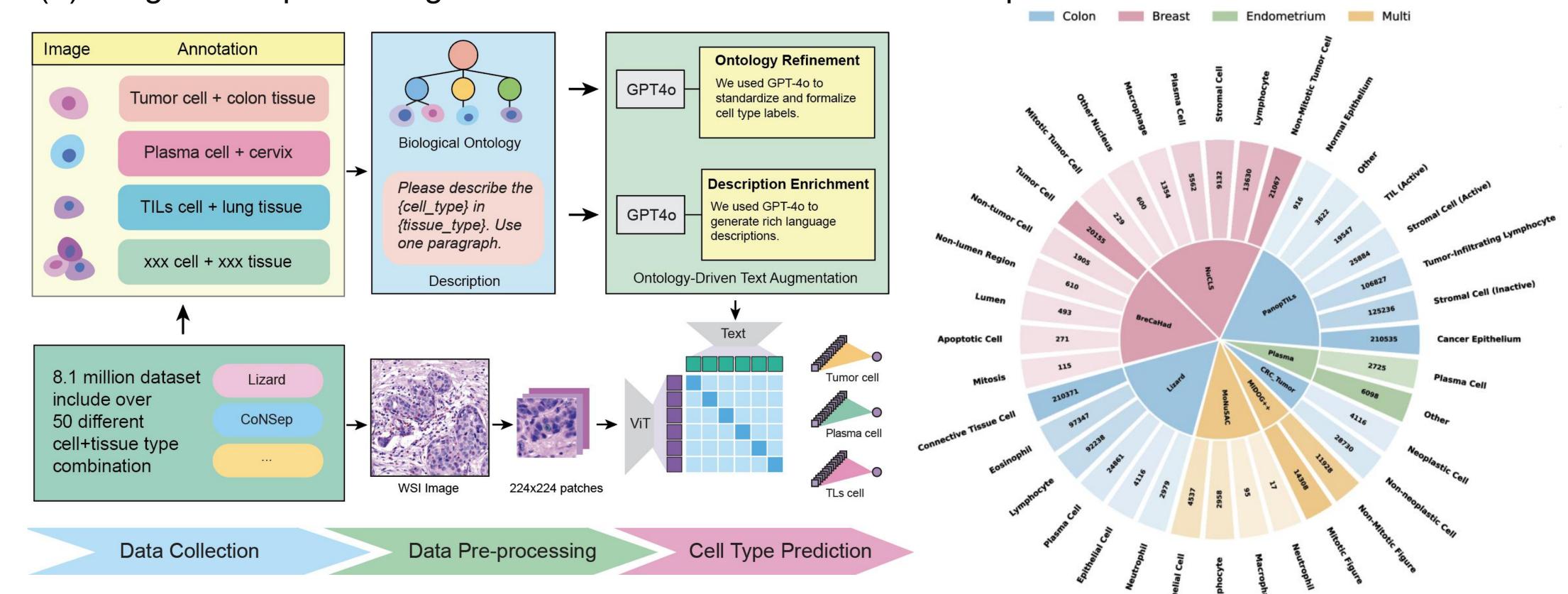[3] Department of Bioengineering, School of Engineering and Applied Science, University of Pennsylvania

What is Nuclass?

NuClass is a **zero-shot, ontology-aware model** that can classify diverse cell types across tissues **without requiring per-class supervision**.

NuClass's three key components:

(1) Biologically grounded hierarchical text embeddings constructed from large language models;

(2) A nucleus-centered patch design that naturally induces ViT attention to focus on nuclear regions;

(3) Large-scale pretraining on over 8.3 million nuclei annotation patches from 11 diverse datasets.
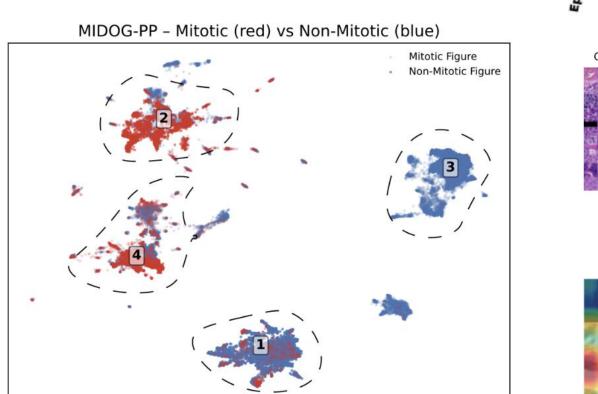

Three versions of NuClass

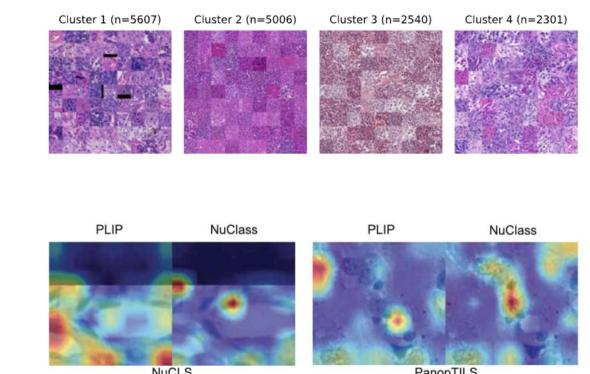To explore the effect of structured and descriptive textual supervision, we define three model variants:

NuClass_Base: Simple rule-based templates.
NuClass_Hier: Ontology hierarchical structure.
NuClass_Natural: LLM enhanced descriptions.

Dataset	NuClass$_{Base}$	NuClass$_{Hier}$	NuClass$_{Natural}$
Lizard	68.57	**82.28**	72.63
MIDOG++	77.30	**80.52**	78.75
BreCaHad	89.24	**95.69**	93.06
CoNSeP	71.79	**73.97**	73.77
CRC_Tumor	93.82	89.26	**94.11**
NuCLS-Single	55.47	**66.00**	63.75
Plasma	92.85	**95.83**	93.64
MoNuSAC	**92.03**	91.12	89.11
PanopTILS	52.16	**79.28**	62.03

Validation accuracy of CellViT++ and NuClass_Hier

Dataset	CellViT++	NuClass$_{Hier}$	Improvement
Plasma	90.27	**97.07**	+6.80
CRC_Tumor	98.01	**98.26**	+0.30
MoNuSAC	87.14	**92.17**	+5.00

Experiment Results

Validation accuracy of zero-shot PLIP vs. Nuclass

Dataset	PLIP (zero-shot)	NuClass$_{Hier}$ (fine-tuned)	Improvement
CoNSeP [10]	10.32 (±2.59)	65.13 (±2.59)	+54.80
Plasma [12]	43.79 (±5.29)	87.28 (±3.55)	+43.50
NuCLS-Single [2]	23.55 (±1.23)	66.48 (±1.23)	+42.90
CRC_Tumor [13]	89.84 (±0.48)	86.26 (±0.54)	−3.60
Lizard [11]	53.06 (±0.48)	71.02 (±0.44)	+18.00
MIDOG++ [3]	47.04 (±1.42)	80.23 (±1.42)	+33.20
BreCaHad [1]	10.25 (±1.25)	95.19 (±0.88)	+84.90
MoNuSAC [22]	34.47 (±2.75)	89.53 (±1.77)	+55.06
PanopTILS [17]	1.29 (±0.45)	72.79 (±1.45)	+71.50

Zero-shot performance of PLIP and NuClass on three datasets

Dataset	Model	Accuracy	Balanced Acc.	Avg. Precision
MoNuSAC [22]	PLIP	15.88	29.88	**41.45**
	NuClass$_{Natural}$	**34.47**	**52.84**	40.94
ATYPIA [19]	PLIP	23.89	52.22	86.98
	NuClass$_{Natural}$	**47.79**	**63.99**	**90.41**
BreaKHis [20]	PLIP	9.60	12.50	13.59
	NuClass$_{Natural}$	**17.73**	**12.63**	**23.56**

Our Outlook:

• Expand annotated H&E datasets from diverse tissues and organs
• Integrate spatial omics to connect morphology with molecular context
• Enable accurate, zero-shot cell typing across unseen classes
• Support scalable annotation and expert validation through AI assistance
• Empower downstream tasks such as spatial analysis, diagnostics, and biomarker discovery