Preclinical and Clinical Imaging of the Immune System

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Biomarkers of Response for Radiation and Immuno-Oncology
AAPM Annual Meeting July 12, 2022

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Disclosures

Founder, Board Member, and Consultant to ImaginAb, Inc.
Honorarium, Roche
Consultant, AstraZeneca
Consultant, Novartis Institute for Biomedical Research

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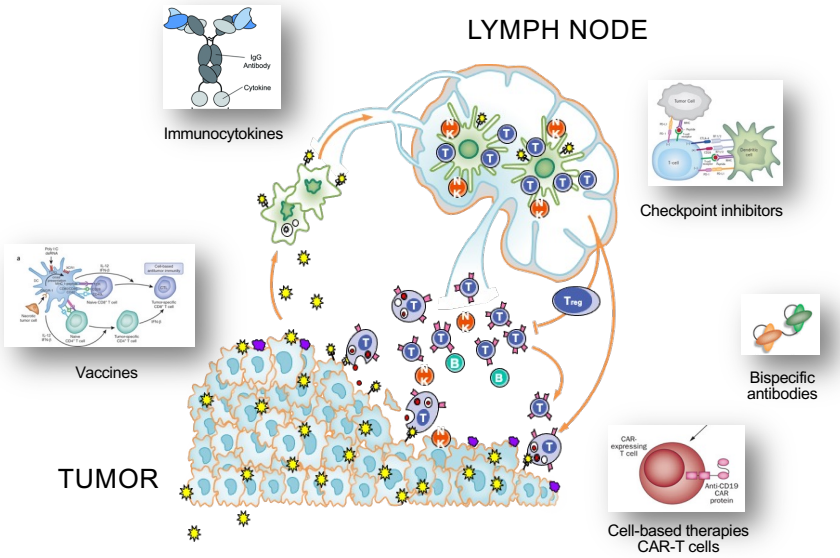
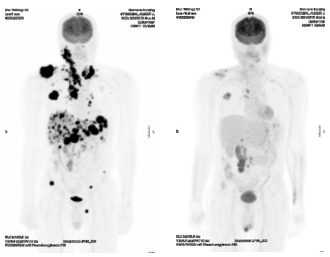
Unlocking the immune system for cancer therapy



Adapted from Mellman, Coukos and Dranoff, Nature 480, 2011

Metastatic Melanoma Response to ipilimumab (anti-CTLA-4)

Before Ipilimumab 04/22/11 | After Ipilimumab 08/05/11



[^{18}F]FDG-PET

Courtesy of Antoni Ribas, UCLA

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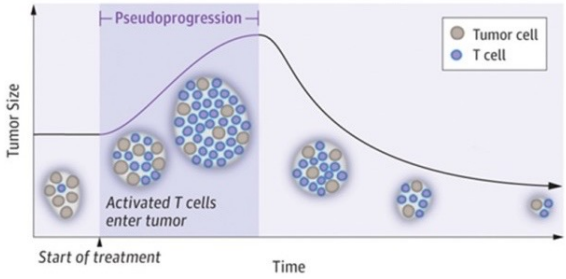
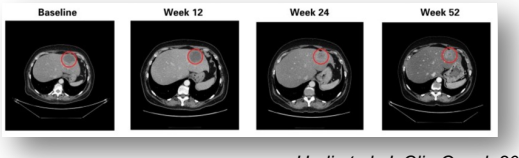
Conventional Imaging and Cancer Immunotherapy: Challenges

Anatomical imaging: CT or MRI



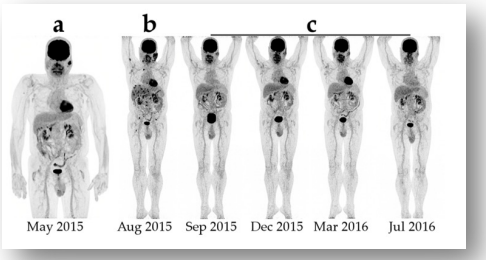
Tumor progression and/or immune responses can look the same using conventional imaging – Conventional imaging is non-specific

Pseudoprogression in melanoma patient treated with pembrolizumab (anti-PD-1)



Hodi et al. J. Clin.Oncol. 2016

FDG flare in melanoma patient treated with ipilimumab (anti-CTLA-4)



Guldbrandson et al. Diagnostics 2017

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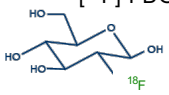
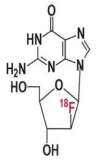
Beyond conventional imaging: Non-invasive molecular imaging of immune responses

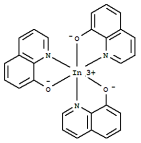
1. Imaging **altered cellular metabolism** (*e.g,* [^{18}F]-fluorodeoxyglucose, FDG; [^{18}F] fluoro-thymidine FLT; [^{18}F]-Clofarabine, [^{18}F]-AraG and analogs)
2. ***Ex vivo* labeling** of cells, followed by re-infusion (^{111}In-oxine; ^{89}Zr-oxine; magnetic nanoparticles, ^{19}F nanoparticles)
3. Engineering cells with **reporter genes/tags** (optical, SPECT, PET; e.g., SSTR2, EGFRt, HSV-tk)
4. Imaging **activation markers** (Granzyme B, IFN-γ)
5. Direct imaging of **cell surface biomarkers** using antibodies, nanobodies, etc. Includes lineage as well as functional markers of activation/exhaustion

[^{18}F]-FDG

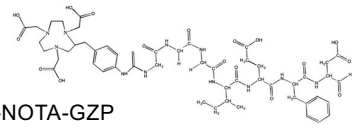




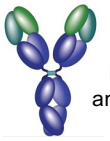
[^{18}F]F-AraG



[^{111}In/^{89}Zr]-oxine



[^{68}Ga]-NOTA-GZP



PD-1 antibody

CD8 diabody minibody

McCracken et al. Adv. In Immunol. 2016

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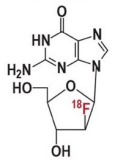
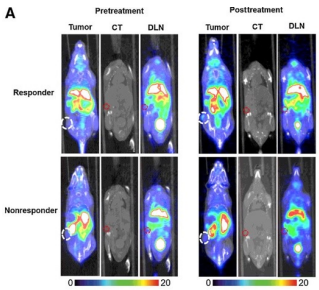
Imaging immune cells *in vivo:* Examples

1. Imaging nucleoside metabolism



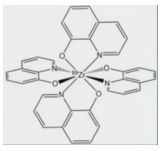
[^{18}F]F-AraG

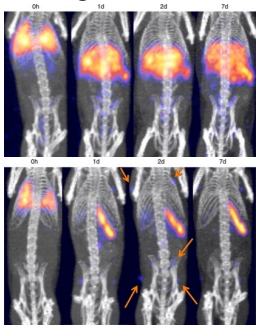


- [^{18}F]F-AraG is selectively taken up by activated CD8 T cells by phosphorylation by mitochondrial dGK
- MC38 tumors treated with α-PD-1
- PET imaging using [^{18}F]F-AraG shows increased uptake in tumor and draining lymph nodes in responders as early as 48 h
- *Currently in clinical evaluation*

Levi et al. Ca. Res. 2019

2. *Ex vivo* cell labeling





- ^{89}Zr-oxine labeling optimized for DC, naïve and activated CTL, OT-1
- Viability and functionality assessed
- DCs track to spleen and liver (upper panels)
- Naïve CTL home to spleen and LN (lower panels)
- *First-in-human ^{89}Zr PET imaging of WBC (Lapi et al.)*

Sato et al. Radiology 2015

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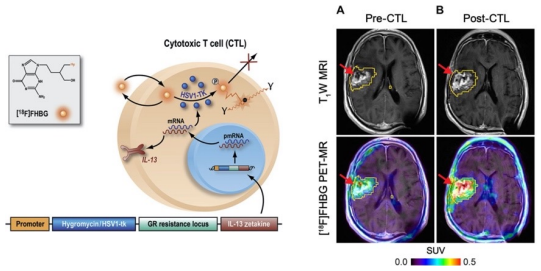
Imaging immune cells *in vivo:* Examples

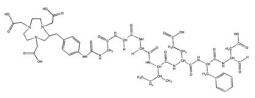
3. Reporter gene imaging

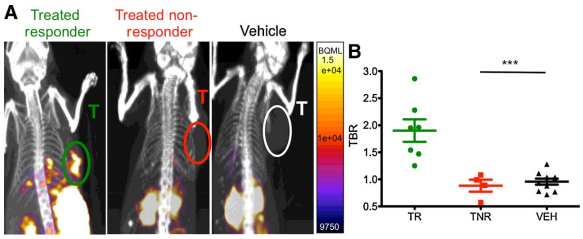


- IL-13 zetakine cytotoxic T cells infused intratumorally in patients with GBM
- HSV1-tk reporter gene detected using [^{18}F]FHBG
- 7 patients imaged (6 pre- and post-treatment)

Keu et al. Sci Trans Med 2017

4. Immune cell activation





- Release of Granzyme B is a major mechanism of cellular cytotoxicity
- Tetrapeptide substrate analog of Granzyme B
- Treated with α-PD-1/α-CTLA-4
- Responding tumor show high GZP signal, indicating presence and activity of cytotoxic T cells
- *Currently in clinical evaluation*

Larimer et al. Cancer Res 2017

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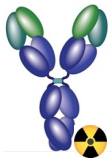
5. Imaging cell surface biomarkers: ImmunoPET



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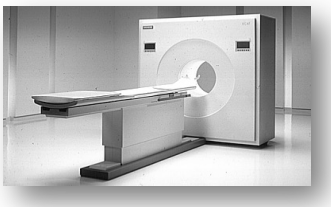
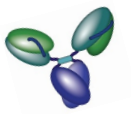


Antibodies: *Specificity*

PET: *Sensitivity, resolution, quantitation*

ImmunoPET research is accelerating due to advances in:

- ✓ Availability of approved therapeutic antibodies; manufacturing infrastructure
- ✓ Positron-emitting radionuclides with longer physical half-lives (Cu-64, Zr-89, I-124) to match antibody circulating half-lives (days)
- ✓ Antibody engineering to optimize for clinical imaging – accelerated clearance



minibody

diabody

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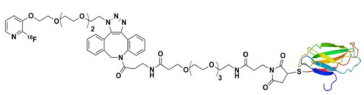
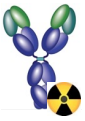
5. Imaging Checkpoint Biomarkers

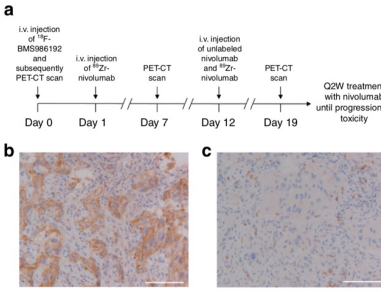


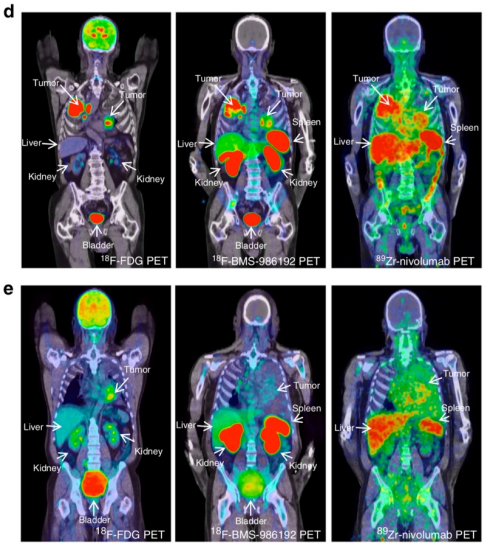
PD-L1 tracer:
[^{18}F]-BMS-986192
(adnectin)



PD-1 tracer:
[^{89}Zr]-nivolumab

- 13 patients with NSCLC
- Heterogenous uptake of both tracers
- Correlated with IHC
- Some accumulation in brain metastases





Niemeijer et al Nat Comm 2018

FDG PD-L1 PD-1

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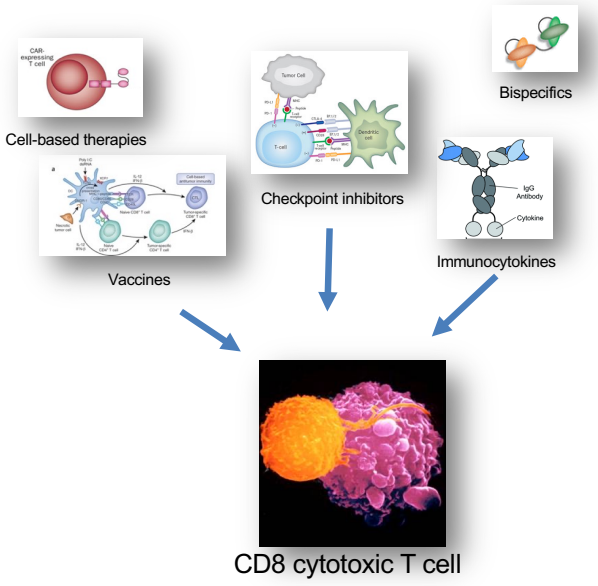
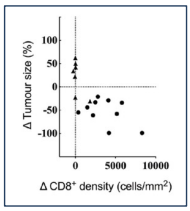
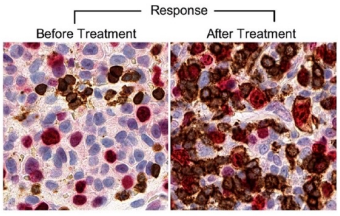
5. Imaging CD8 cytotoxic T Cells:
An early marker of response to immunotherapy







- Many cancer immunotherapies converge on the CD8 cytotoxic T lymphocyte as the key effector cell
- Several on-treatment biopsy studies have shown that infiltration of CD8+ cells soon after initiation of checkpoint inhibitor therapy correlates with outcome

PD-1 blockade; Tumeh, Ribas et al. Nature 2014

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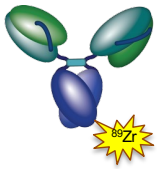
Preclinical applications – CD8 immunoPET

Murine-specific

^{89}Zr-DFO-169 anti-mouse CD8 cys-diabody

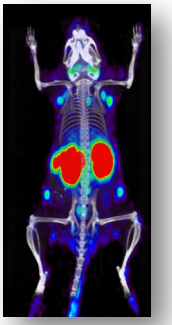
- Pan-specific (all strains)
- Rapid renal clearance



Human-specific

^{89}Zr-crefmirlimab berdoxam (IAB22M2C)
Fully humanized anti-human CD8 minibody

- High affinity (0.4 nM)
- Non-immunogenic, biologically inert
- Rapid hepatic clearance

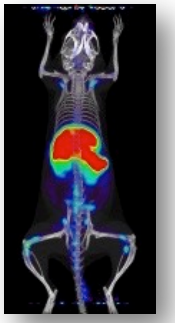


Wild-type mouse

Cancer immunotherapy:

- Checkpoint inhibitor therapy and combinations
- Adoptive cell therapy
- Oncolytic viruses

- Graft vs host disease
- Infectious disease (COVID-19)



Humanized mouse

Tavaré, R. et al., J. Nucl. Med. 2015

T. Olafsen et al. abstract AACR 2016

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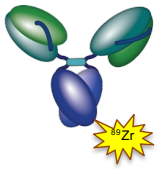
Phase I Clinical imaging of CD8 T lymphocytes using ^{89}Zr-IAB22M2C (crefmirlimab berdoxam)



Humanized anti-human CD8 minibody

- High affinity (0.4 nM)
- Non-immunogenic
- Biologically inert
- Rapid clearing

Objectives:

- Safety, tolerability & whole body distribution (including tumor sites)
- Determine recommended protein dose & scanning parameters for future studies

Design:

- Open-label, non-randomized, 2 stage:
  - Protein dose escalation (6 patients: 3 mCi ^{89}Zr; 0.2-10 mg protein)
  - Expansion (9 patients: 1.0 – 1.5 mg)
- Serial imaging at 1-2 h; 6-8 h; 24 h; 48 h; 96-144 h
- Serial blood draws for pharmacokinetics, cytokines, anti-drug antibody

N. Pandit-Taskar et al. J. Nucl. Med. 61:512-519, 2020
M. Farwell et al., J. Nucl. Med. 63:720-726, 2022

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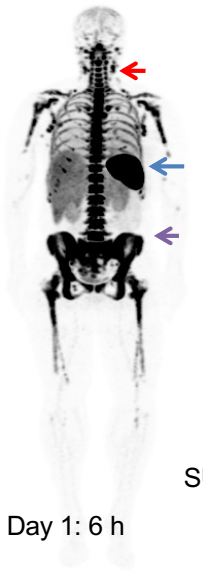
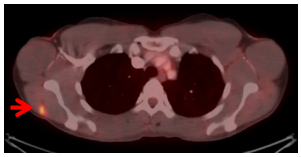
Phase I ^{89}Zr-crefmirlimab PET - CD8 T cells Visualized in Tumor

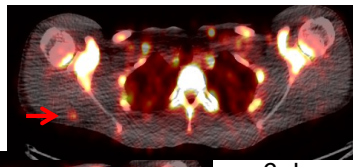




FDG PET/CT

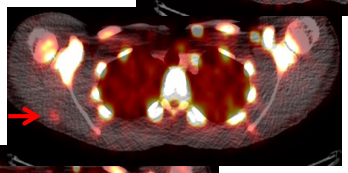
- 37 year old female with metastatic melanoma
- Ipi/Nivo (2 yr); Pembro
- 3 mCi/0.2 mg

1.4



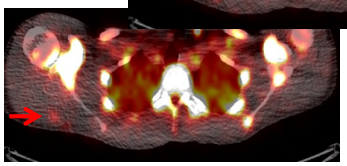
6 days

0.8



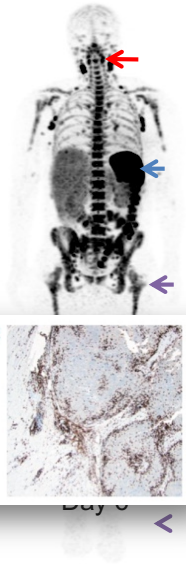
1 day

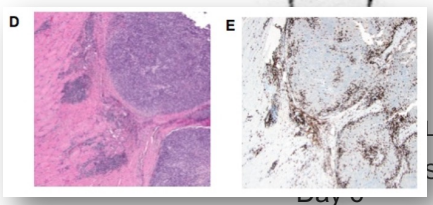
SUV = 0.7



Day 1: 6 h

CD8 immunoPET/CT 6h





LN

Sp

BM

Pandit-Taskar et al., J. Nucl. Med. 2020

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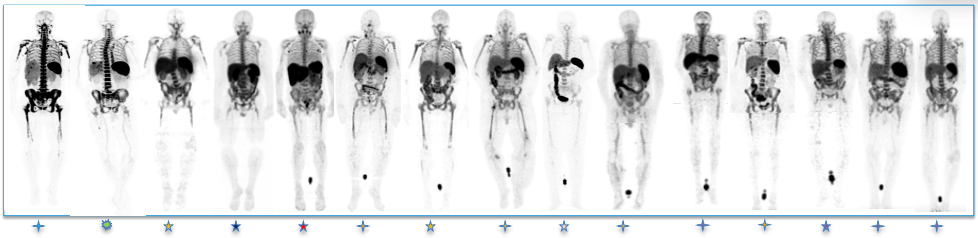
Phase I Summary

Imaging conclusions:

- Rapid clearance; excretion primarily hepatobiliary
- Uptake in T-cell rich tissues (spleen, BM, LN)
- No/low uptake in normal organs (muscle, heart, brain, lungs)
- Tumor uptake variable and seen in 2/3 of patients
- Protein dose range with favorable biodistribution: 0.5-1.5 mg
- Most favorable imaging time: 24 hrs, although tumors seen as early as 1-2 hrs



Pandit-Taskar et.al., J. Nucl. Med. 2020; Farwell et al. J. Nucl. Med. 2022

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Phase II Pre-treatment/On-treatment study (NCT03802123, NCT05013099)

- Patients with metastatic solid tumors, initiating checkpoint inhibitor therapy
  - Pre-treatment (baseline) CD8 PET scan and biopsy (3 mCi or 1 mCi/1.5 mg; 24 h)
  - Initiate immunotherapy (ipi/nivo/pembro standard of care)
  - On-treatment CD8 PET scan and biopsy (4-5 weeks after therapy initiation)
- Goals
  - Safety of repeat dosing and imaging
  - Correlation of CD8 PET with CD8 IHC
  - Correlation with RECIST and outcome
- Multi-center Phase IIa trial complete; Phase IIb iPREDICT in progress

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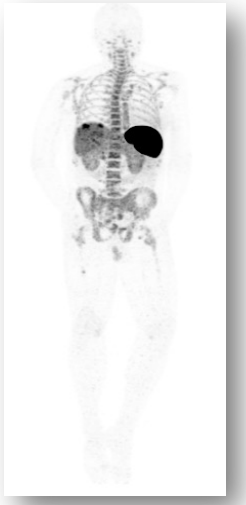
Future: Non-invasive Imaging in Immuno-oncology

- Molecular imaging of immune responses: powerful, specific, whole-body approaches for monitoring immune responses
- Current approaches include metabolic imaging, *ex vivo* immune cell labeling, reporter gene imaging, and activation marker detection
- ImmunoPET for detection of cell surface biomarkers (PD-1/PD-L1 checkpoints, CD8 cytotoxic T cells)
- Many of these approaches show promise in clinical trials
- Potential role in cancer immunotherapy
  - Patient selection
  - Early on-treatment response, ongoing response
  - Optimization of combination therapy
  - Management of toxicities
- Potential role in other immune-mediated conditions and diseases



Clinical immunoPET of CD8 cytotoxic T cells

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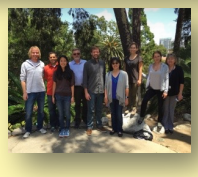
Acknowledgments

Research



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Kirstin Zettlitz

Tove Olafsen

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Richard Tavaré
Scott Knowles
Amanda Freise

UCLA collaborators:
Antoni Ribas
Owen Witte
Arion Chatziioannou

Crump Institute Imaging Facility
Jason Lee
Waldemar Ladno

Clinical

Phase I sites:

MSKCC:
Neeta Pandit-Taskar
Wolfgang Weber
Jedd Wolchok
Michael Postow
Jason Lewis
Serge Lyashchenko
Joseph O'Donoghue

UPenn:
Mike Farwell
David Mankoff

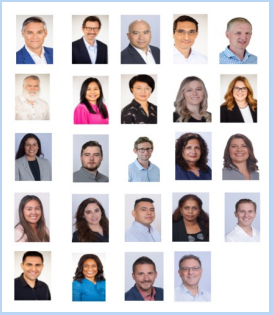
Honor Health
Mike Gordon
Ron Korn

Phase II sites

…and our patients!

Industry

ImaginAb
Ian Wilson
William Le
Alessandro Mascioni
Jean Gudas
Michael Torgov
Tobe Olafsen



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