Defining the Role of Focal Adhesion Kinase in Melanoma

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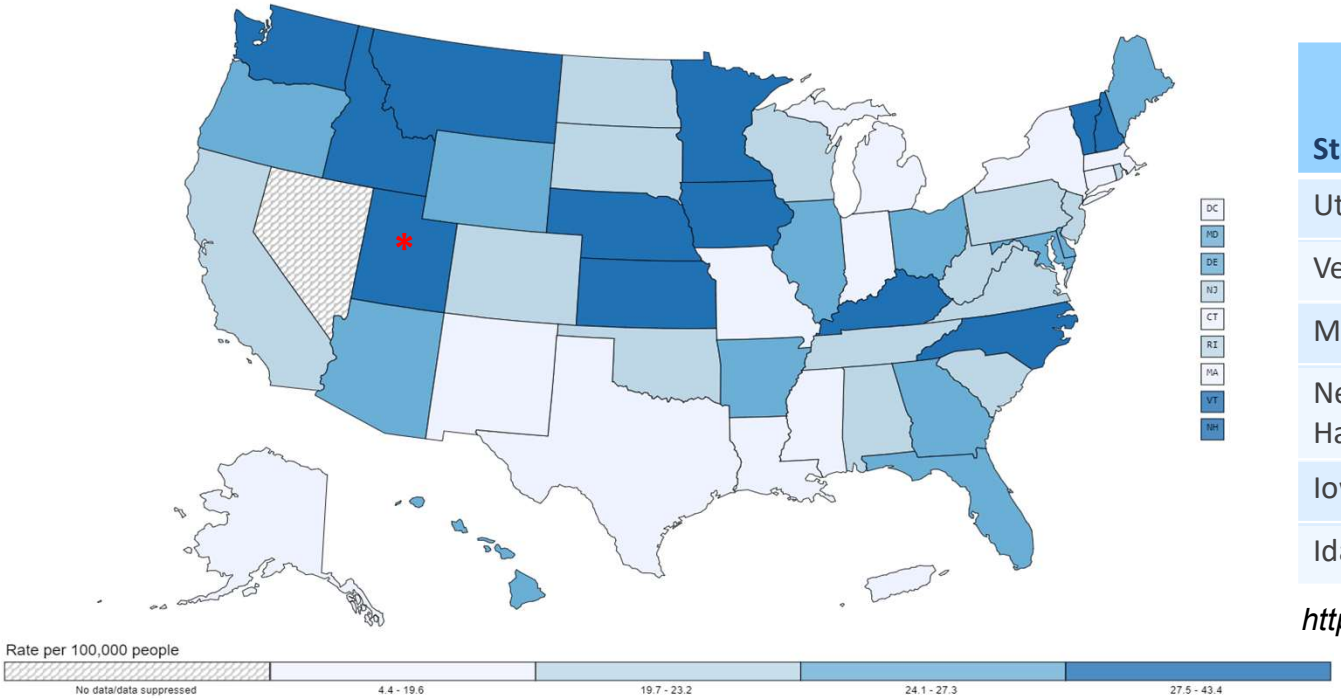
Utah has the highest incidence of new melanoma cases per capita in the US



State	Melanoma cases/100k	% change in cases since 2013-2017	Melanoma related deaths
Utah	41	8%	367
Vermont	37	1%	98
Minnesota	35	13%	713
New Hampshire	32	4%	234
Iowa	30	11%	499
Idaho	30	11%	276

https://quotewizard.com/news/skin-cancer-rates-by-state

The rate of new melanoma diagnoses is ~37% higher in Utah than the national average

https://gis.cdc.gov/Cancer/USCS/#/AtAGlance/

Source - U.S. Cancer Statistics Working Group. U.S. Cancer Statistics Data Visualizations Tool, based on 2021 submission data (1999-2019): U.S. Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute; https://www.cdc.gov/cancer/dataviz, released in November 2022.

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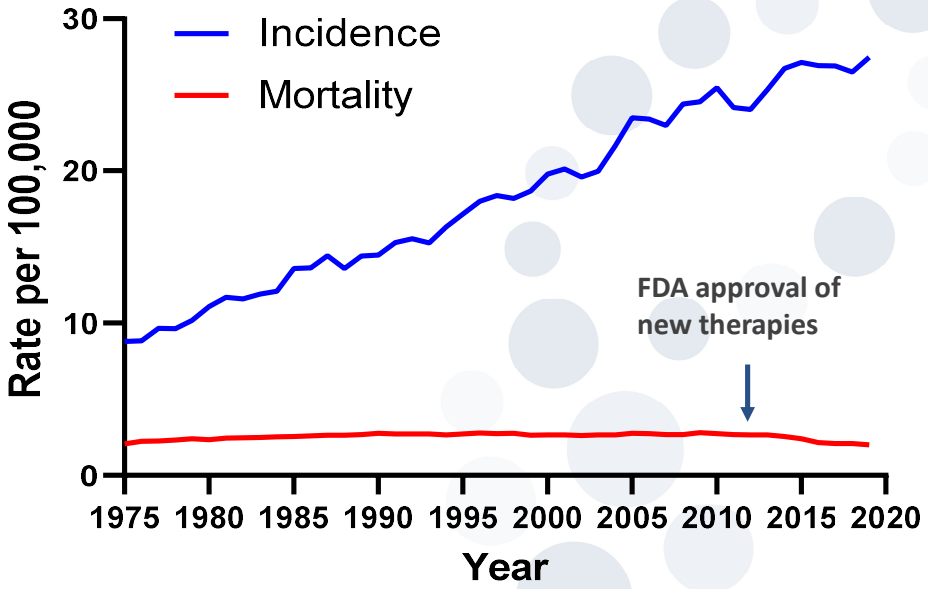
Melanoma
Increasing incidence but decreasing mortality

- Melanoma incidence has increased more than 200% since 1975 in the United States
- Mortality increased ~22% from 1975-2013, then declined by ~30% from 2014-2019



Saginala K et al. Med Sci. 2021
https://seer.cancer.gov/statfacts/html/melan.html

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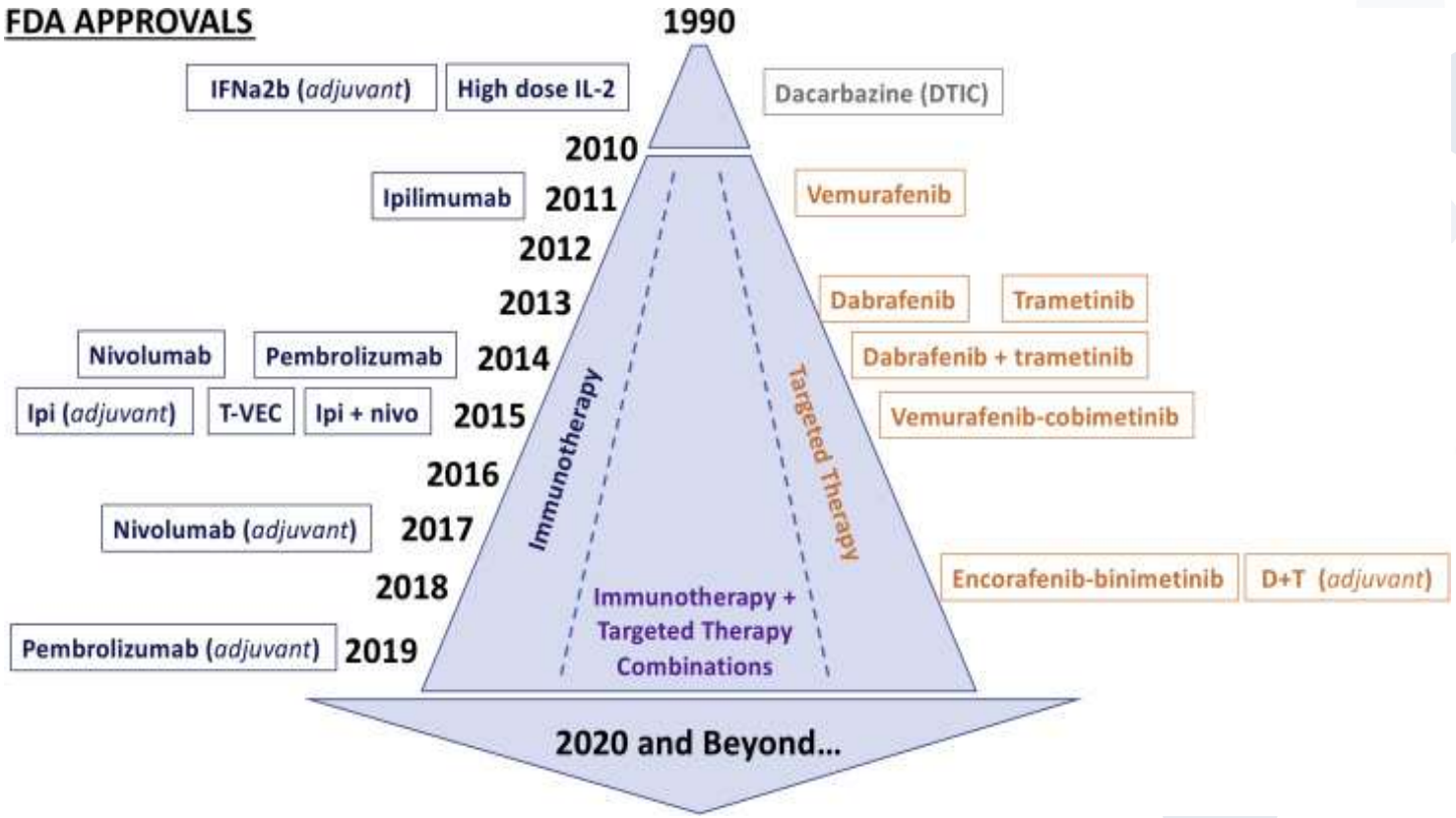
Advances in therapy for metastatic melanoma



2020 Atezolizumab (α-PD-L1) + vemurafenib + cobimetinib
2022 Nivolumab (α-PD-L1) + relatlimab (α-LAG3)
2023 Neo-adjuvant immunotherapy (S1801)

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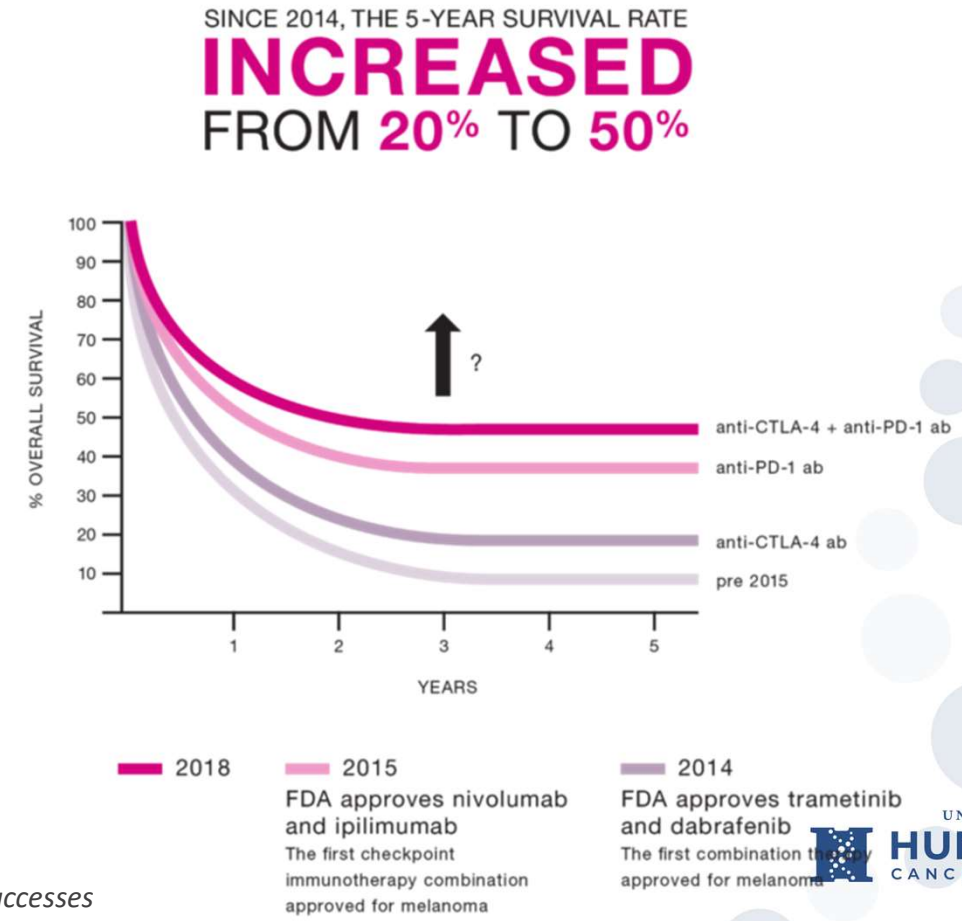
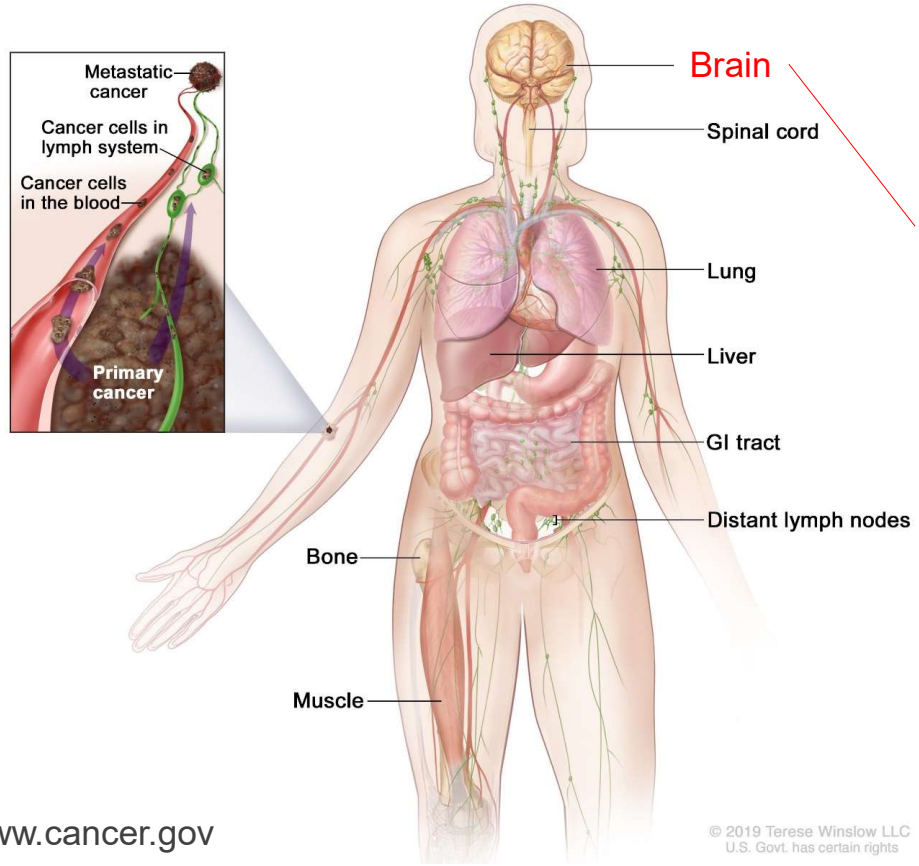
Jenkins and Fisher. 2021 Treatment of Advanced Melanoma in 2020 and Beyond. JID 141: 23-31

5-year survival rate for advanced melanoma has increased significantly since 2014



https://taramillerfoundation.org/funding-successes

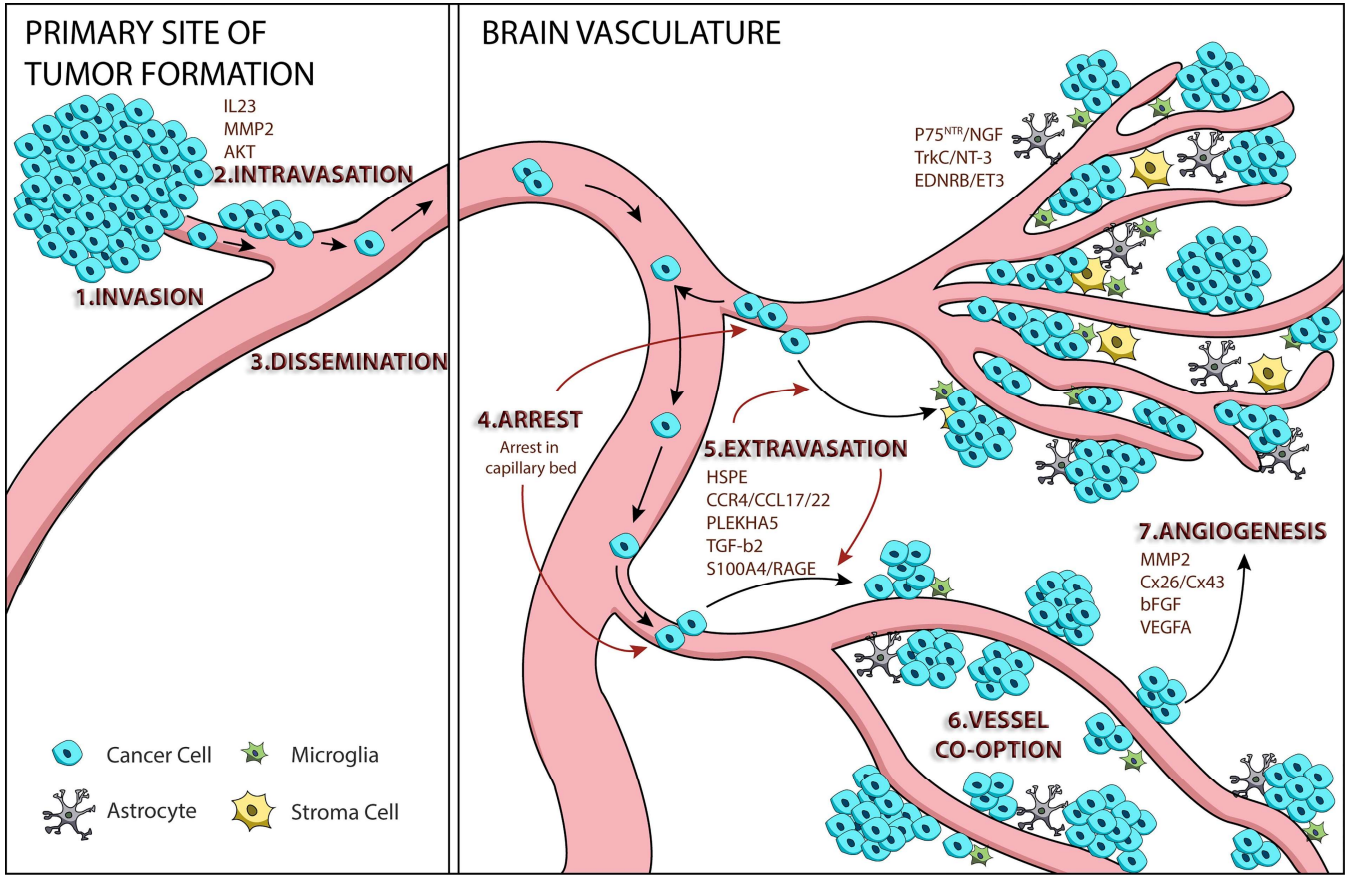
Melanoma brain metastases remain a significant clinical challenge



www.cancer.gov

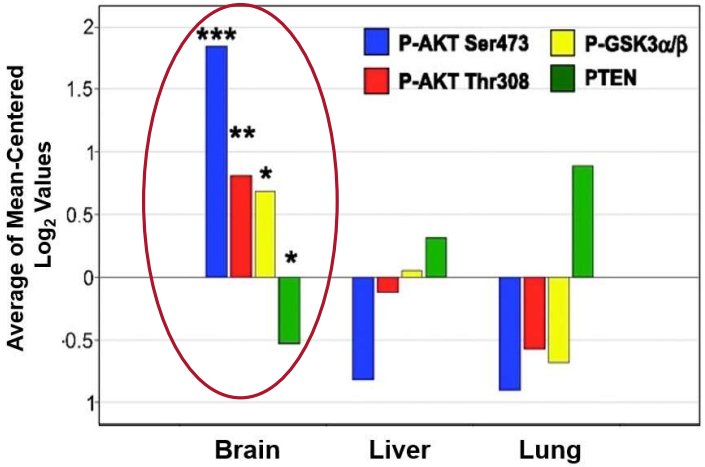
- Among all adult malignancies, melanoma has the highest propensity to metastasize to the brain
  Sandru et al., *J Med Life*. 2014
- 20-30% of stage IV patients have brain metastases at diagnosis
  Rieth et al., *Cancers*. 2021
- Autopsy reports indicate CNS involvement in 50-75% of stage IV melanoma cases
  Shapiro et al., *J Skin Cancer*. 2011
  Rieth et al., *Cancers*. 2021
- With new therapies, the median overall survival for patients with melanoma brain metastases has improved from 7 months (prior to 2015) to 13 months today; however, this is still a poor prognosis for these patients.
  Bander et al. *Cancer* 2021

Mechanisms that drive melanoma brain metastasis



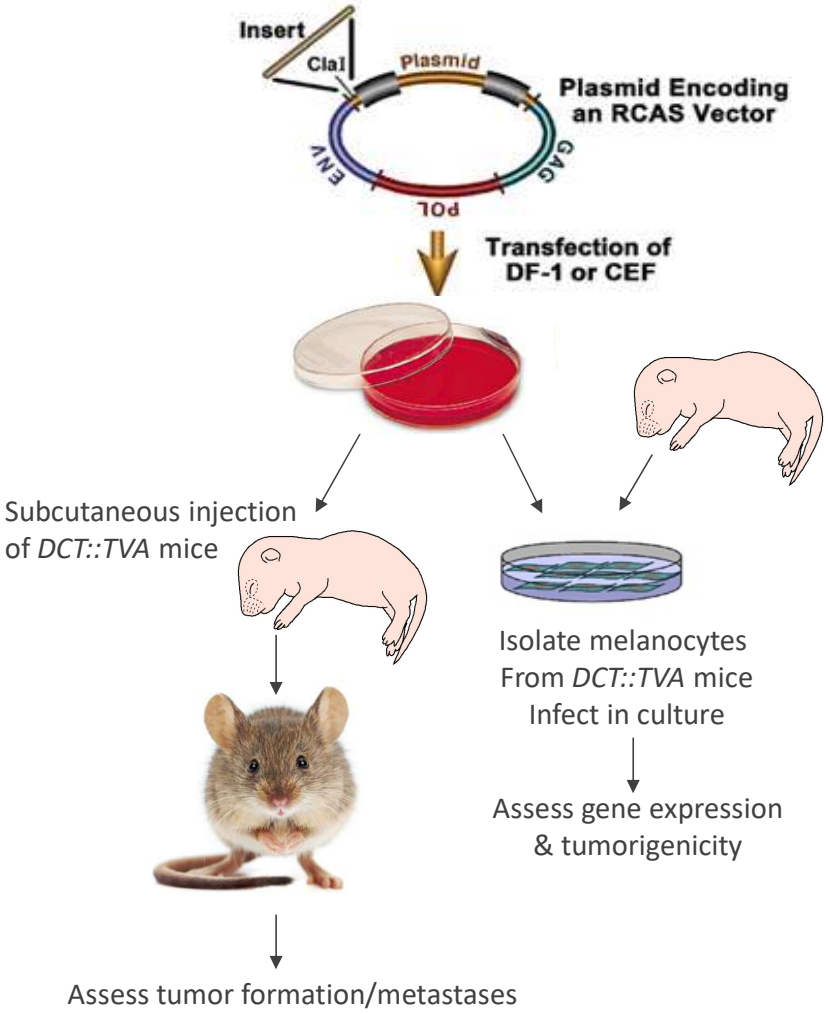
Reviewed in: *Kircher et al.,* Int. J. Mol. Sci. **2016**, 17, 1468

Melanoma brain metastases have higher levels of activate AKT and decreased PTEN compared with other metastatic sites



Davies et al., *Clinical Cancer Res*. 2009

RCAS/TVA Avian Retroviral Vector System

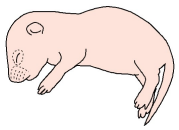


- **Based on well-studied avian retroviruses**
  - ALV/RSV
  - Many tools/vectors available
- **Replication competent in avian cells**
  - No packaging lines or helper virus required
  - High titer virus is produced
- **Stable transfer of genes**
  - Long-term expression
- **Replication defective in mammalian cells**
  - Infection by multiple viruses is possible
- **Virus is targeted to TVA-expressing cells and does not spread in the animals**
  - Two levels of targeting *in vivo*
  - Surrounding micro-environment is normal
- **New viruses can be made and evaluated quickly**
  - Safe to use
- **Can be crossed to existing strains**

Reviewed in: McKinney and Holmen, *CJC* 2011

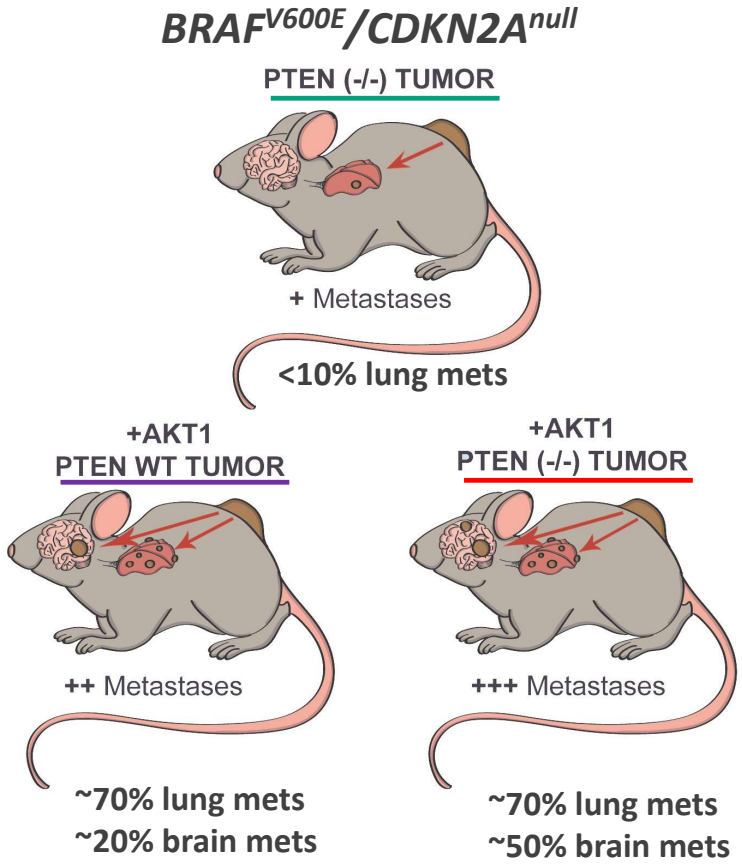
AKT1 activation promotes the development of melanoma brain metastases

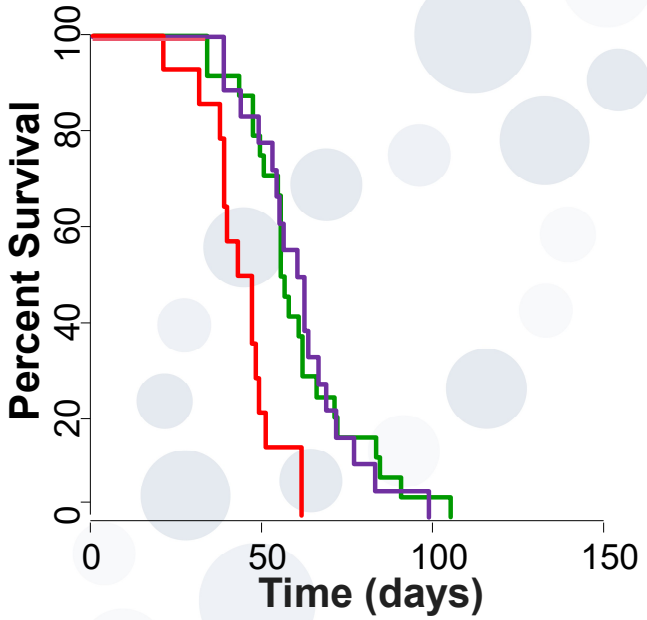
Virus producing DF-1 cells



Subcutaneous injection of RCAS-Cre and RCAS-myrAKT1 into newborn *Dct::Tva*;BRAF^{CA};*Cdkn2a*$^{lox/lox}$ *Pten*$^{lox/lox}$ mice

Assess tumor development and metastasis





Cho et al *Cell Reports* 2015, 13:898-905
Kircher et al *Molecular Cancer Research* 2019, 17:1787-1800

Joseph Cho, MD, PhD

RPPA revealed upregulation of phosphorylated Focal Adhesion Kinase (FAK) in tumors expressing activated AKT1

Lysates from Primary tumors

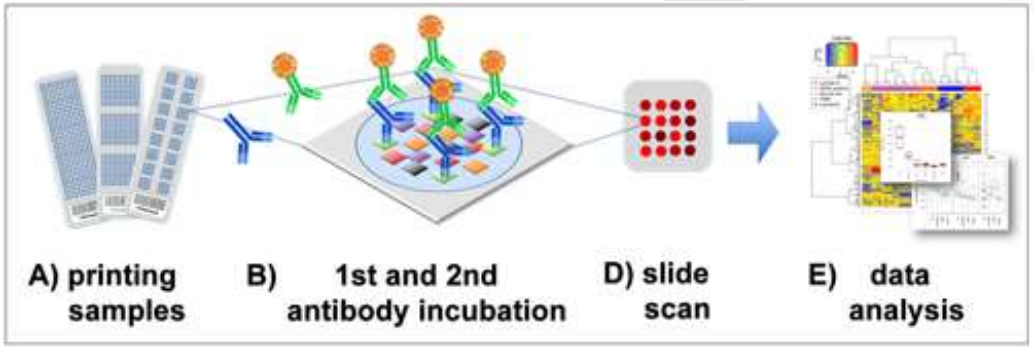
$BRAF^{V600E}$
$Cdkn2a^{-/-};Pten^{-/-}$

Non-metastatic

$AKT1^{E17K}$
$BRAF^{V600E}$
$Cdkn2a^{-/-};Pten^{-/-}$

Metastatic

Reverse Phase Protein Array



Wachter et al., *Microarrays.* 2015

In collaboration with Mike Davies & MDACC RPPA Core

David Kircher, PhD

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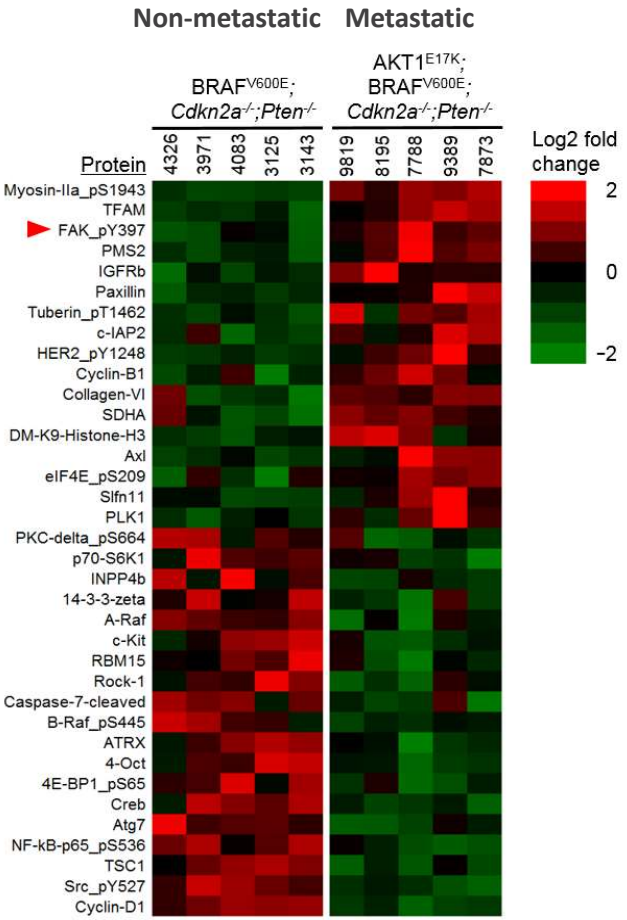


Oncogenic functions of Focal Adhesion Kinase:

- Proliferation
- Motility
- Invasion
- Angiogenesis
- Immunosuppression
- Metastasis

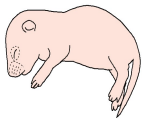
David Kircher, PhD

In collaboration with Mike Davies & MDACC RPPA Core

Is FAK necessary and sufficient for the development of melanoma brain metastases?

Pharmacological inhibition of FAK prevents the development of brain metastases

Virus producing
DF-1 cells



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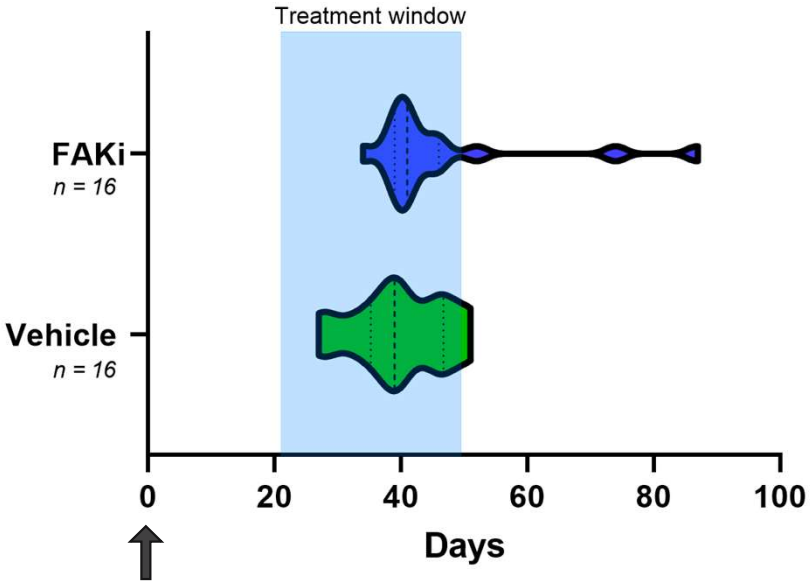
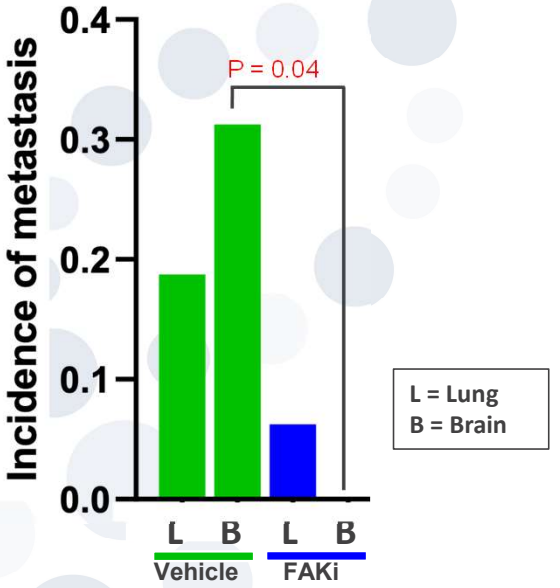
Assess tumor development and metastasis

Tumor Onset



Tumor Induction
Day 0

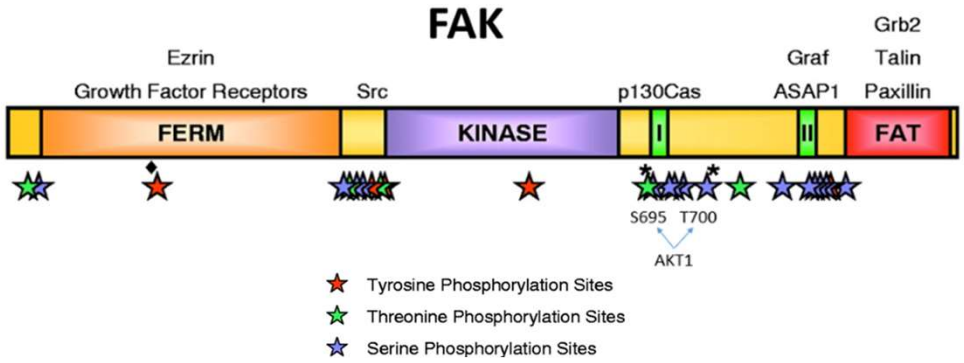
Metastasis



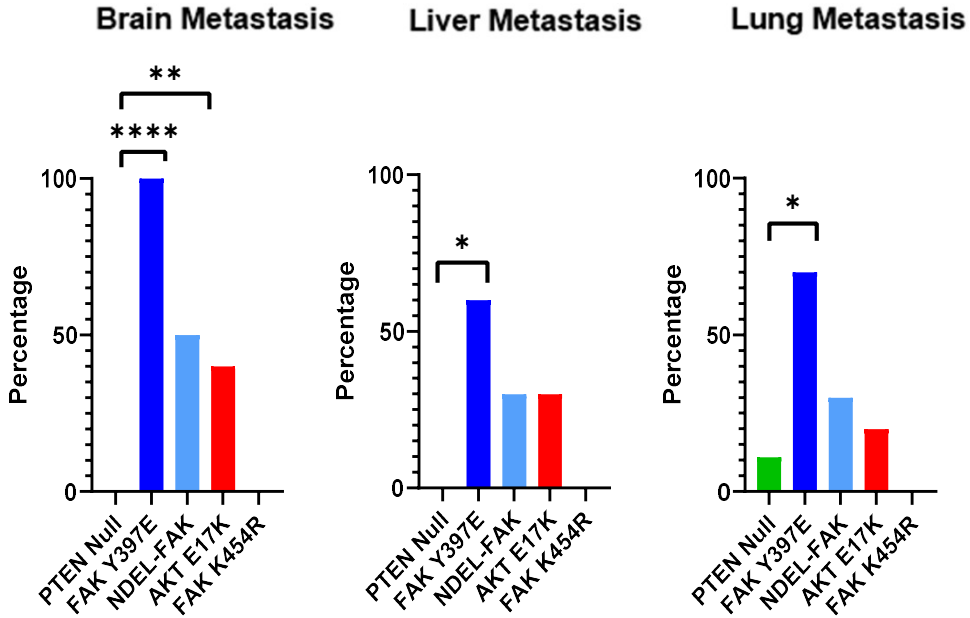
FAK inhibitor (FAKi): PF-573228

David Kircher, PhD

Activated FAK is sufficient to promote melanoma brain metastases



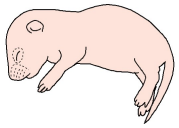
Quispe et al., *Drug Discovery Today.* 2022



FAK Y397E (phospho-mimic)
NDEL-FAK (blocked autoinhibition)
FAK K454R (kinase dead)

FAK-Y397E mirrors the phenotype of activated AKT1 in terms of tumor penetrance and latency

Virus producing DF-1 cells



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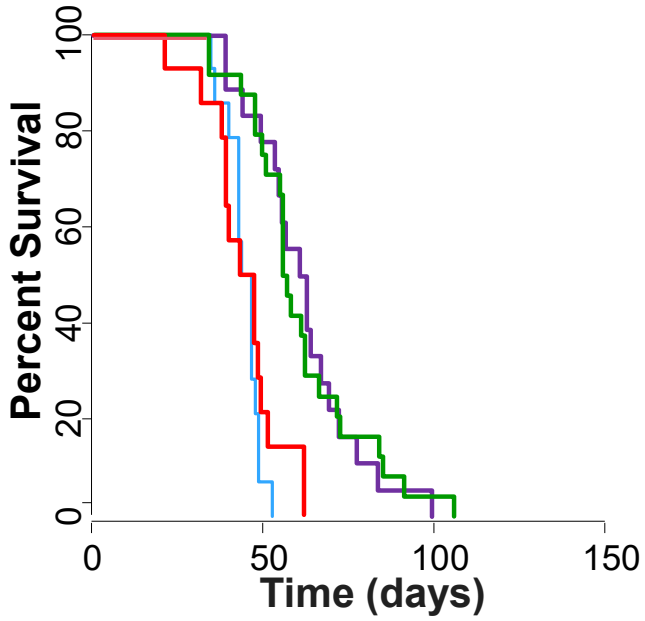

BRaf^{V600E};Cdkn2a-/-;Pten-/-
BRaf^{V600E};Cdkn2a-/-;myrAkt1
BRaf^{V600E};Cdkn2a-/-;Pten-/-;myrAkt1
BRaf^{V600E};Cdkn2a-/-;Pten-/-;FAK^{Y397E}

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MiKaela Field

Future directions

- Assess tumor penetrance and latency in the RCAS/TVA model with other forms of activated FAK.
- Assess the incidence of metastases to distant organs through immunohistochemistry.

Acknowledgements

Lab members
David Kircher, PhD
Gennie Parkman, PhD
Chris Stehn
Katie Culver
MiKaela Field
Karly Stanley
Jared Almazan
Tursun Turapov
Adriene Pavek
Clara Smith
Matthew Wilcox
Savannah Pettey
Mercedes Randhahn
Paulina Medellin
Garrett Otrimski
Steven Stanley

Funding provided by:
Melanoma Center
University of Utah/HCI
USTAR
Melanoma Research Alliance
NIH/NCI: R01CA121118
Melanoma Research Foundation
Stowell Family
Undergraduate Research Opportunities Program at the University of Utah awarded to MiKaela Field

Shared Resources
High-Throughput Genomics & Bioinformatics
Biorepository Molecular Pathology (BMP)
Research Informatics
Preclinical Research Resource
Cancer Biostatistics

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Matt VanBrocklin, PhD, Utah
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Ken Boucher, PhD Utah
Silvio Gutkind, PhD UCSD

Verastem Oncology
Silvia Coma, PhD
Jonathan Pachter, PhD

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