

Importance of live melanoma biobanking when developing new therapies for metastatic melanoma

Jonas Nilsson, PhD

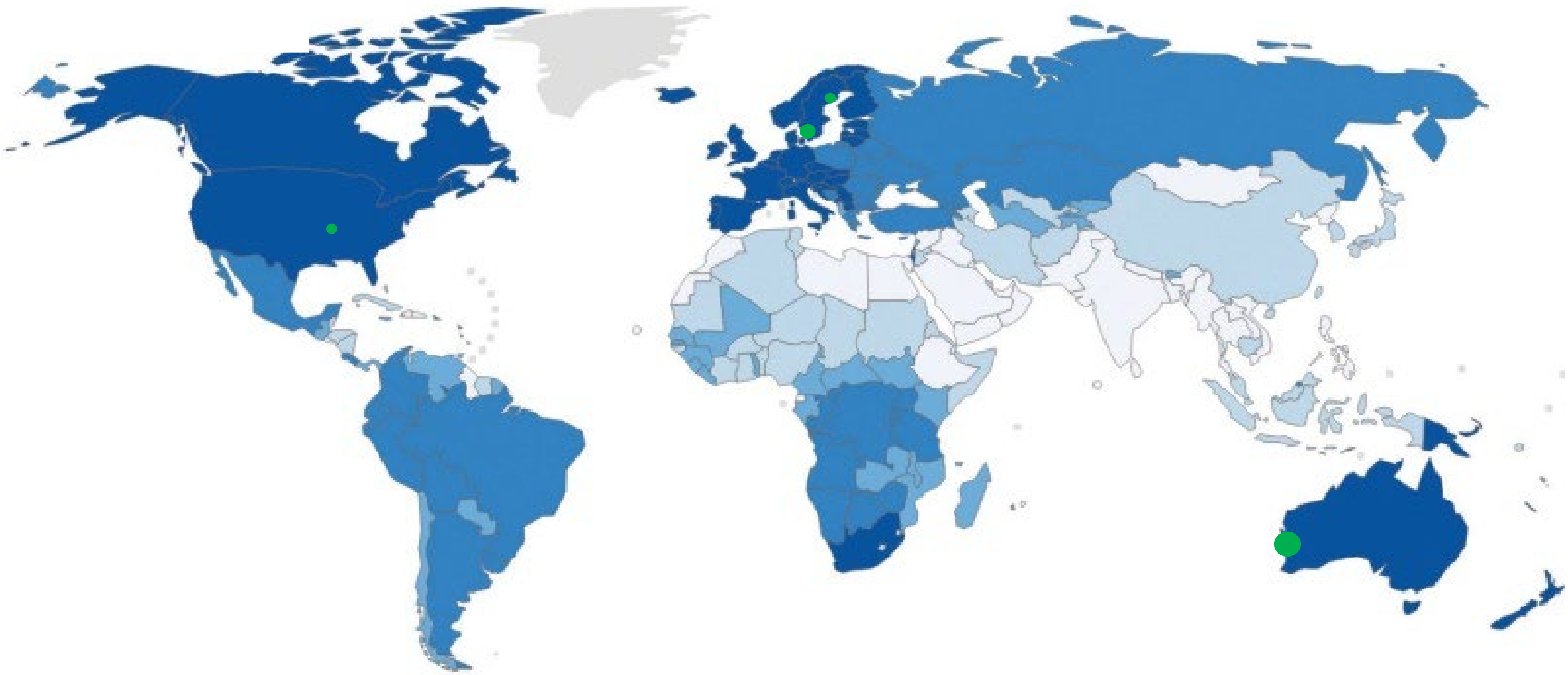
Professor and Chair in Melanoma Discovery



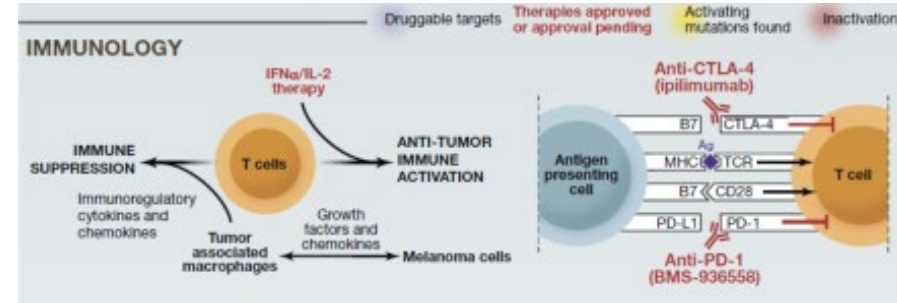
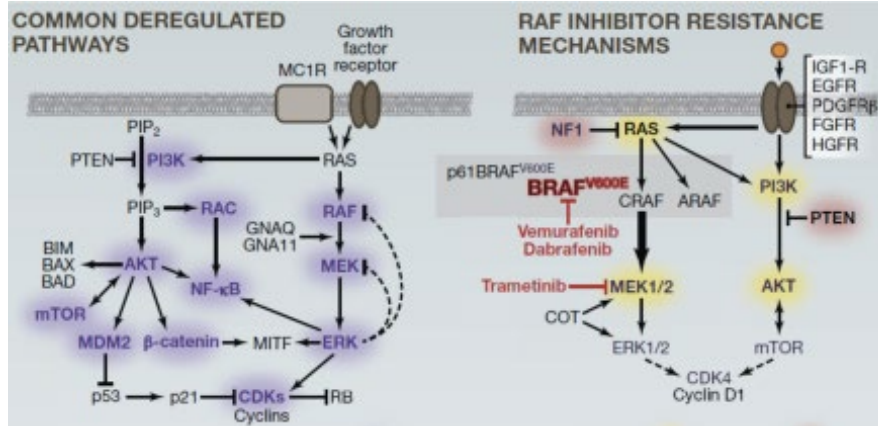
HARRY PERKINS INSTITUTE
OF MEDICAL RESEARCH

Professor of Experimental Cancer Surgery

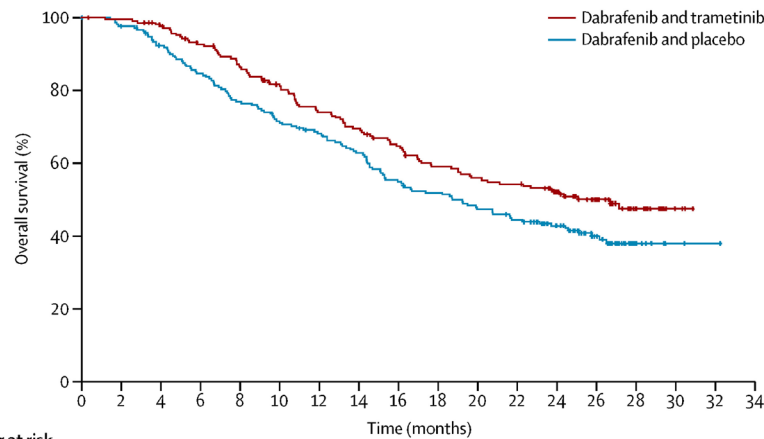
University of Gothenburg, Sweden



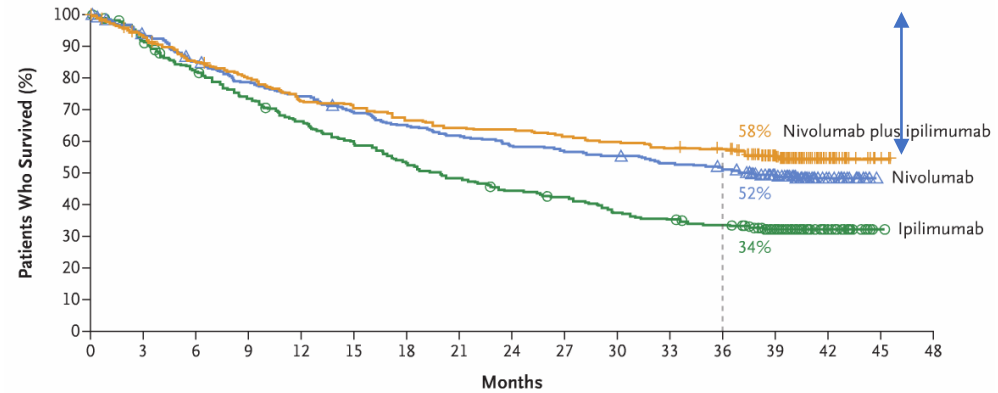
Treatment of metastatic melanoma



A



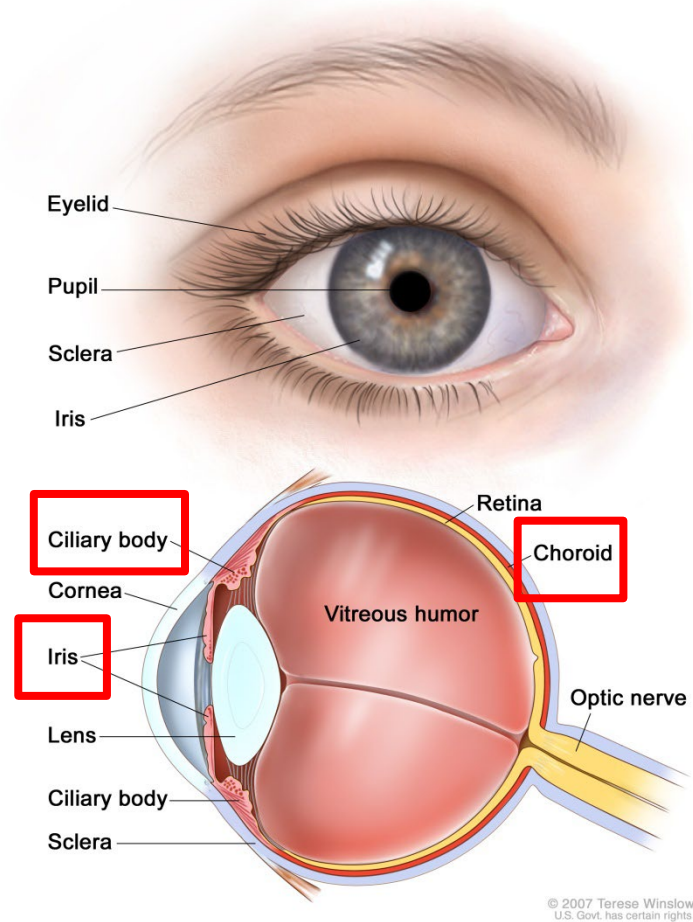
Long et al., 2015, Lancet



Wolchok et al., 2017, NEJM

How can we make the durable responses last and convert non-responders to responders?

Uveal melanoma (UM)



National Cancer Institute: <https://www.cancer.gov/>

- 2% of all melanomas
- Primary tumor in the eye is treated with enucleation or irradiation with good local control
- Metastatic disease will develop later in 50% of patients, mainly to the liver
- Metastatic disease lacks efficient treatments
 - Targeted therapy
 - Immunotherapy (0-5% ORR PD-1 inhibitors)

How is biobanking for research done?

Diagnosis is known
(history, FNA)
Disease is bulky
(excess material)
Patient is operable or
multiple core biopsies


MDT or physicians

YES

Communication about
surgery/biopsy with lab
(Hospital, surgeon, Date
and time)

Lab and physicians

YES

 **Harry Perkins Institute of Medical Research**

Participant Information Sheet/Consent Form

Non-interventional Study - Adult providing own consent

Sir Charles Gairdner Hospital

Title	Perkins Biobank for Translational Cancer Medicine
Short Title	Perkins Cancer Biobank
Coordinating Principal Investigator/ Principal Investigator	Dr Louise Winteringham
Associate Investigator(s)	Professor Peter Leedman Professor Ruth Ganss Dr Bastiaan De Boer A/Professor Evan Ingley Professor Ryan Lister Professor Pilar Blancafort Professor George Yeoh Professor Alistair Forrest A/Professor Andrew Redfern Professor Michael Millward Dr Gabriel Lee
Location	Sir Charles Gairdner Hospital

Part 1 → What does my participation involve?

Introduction

This Participant Information Sheet and Consent Form tells you about the Biobank you are being asked to contribute to.

We are requesting your participation because you will soon undergo a surgical procedure to biopsy or remove your cancer. The pathologist will use part of the cancer removed to perform routine pathology tests to guide diagnosis and the best treatment. We are asking that you consider donating the remaining surplus tissue to the Perkins Cancer Biobank to facilitate research into better cancer treatments. We may also ask if we can take a little extra blood when you have your routine blood sample taken.

Please read this information carefully. It will describe what we intend to do with your tissue sample. Knowing this will help you decide if you want to contribute to this Biobank.

Ask questions about anything that you don't understand or want to know more about. There are several people you can ask, depending on your question - they are listed at the end of the document.

Participation in this Biobank is voluntary. You don't have to take part if you don't want to. You will receive the best possible care whether or not you take part.

SCGH Participant Information Sheet/Consent Form v1.0/26/08/19; based on Master Participant Information Sheet v3.0/05/09/18
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Nurses or physicians

YES

Surgeons

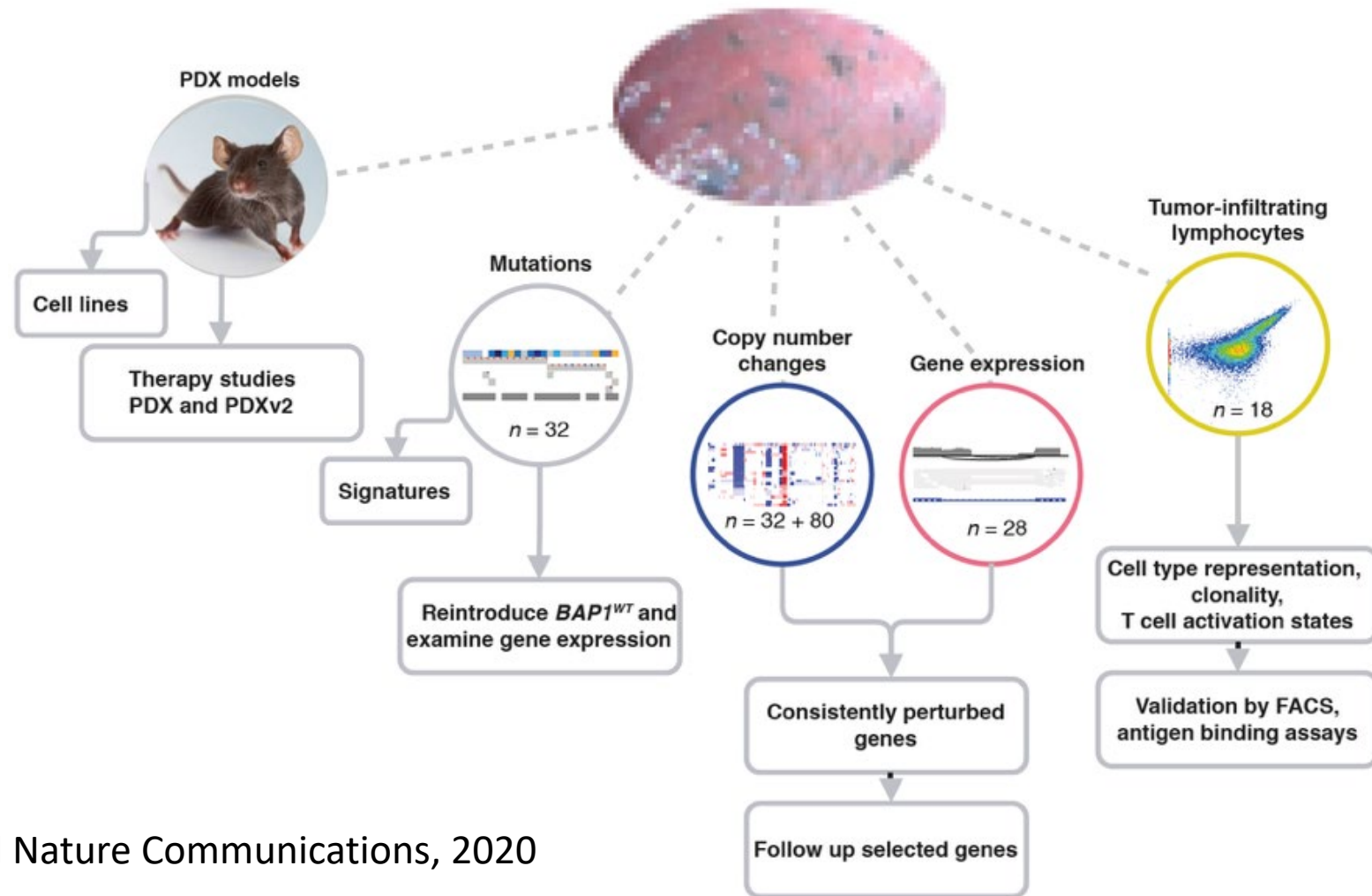
Resection (fresh, no
formalin)
& blood sample

YES

Collection
(pathology->lab)

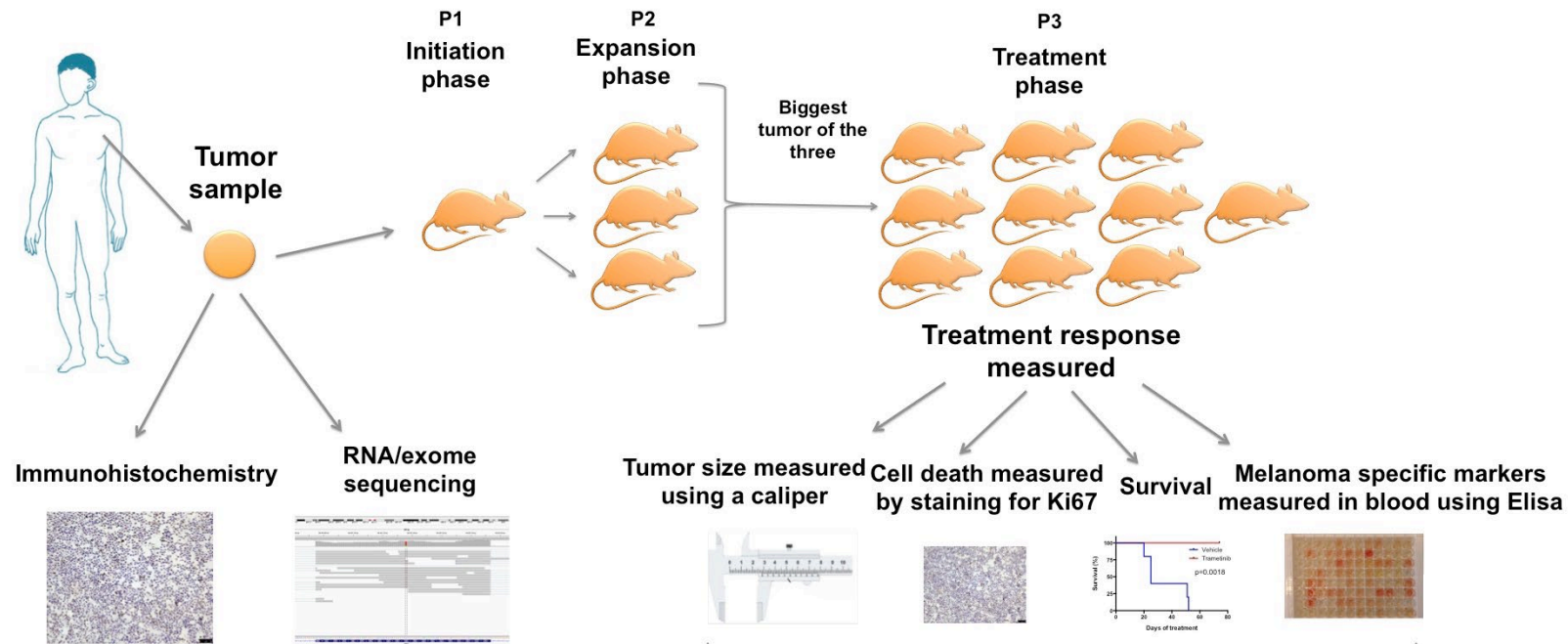
Lab

Why is biobanking done?



Karlsson et al Nature Communications, 2020

Patient Derived Xenografts

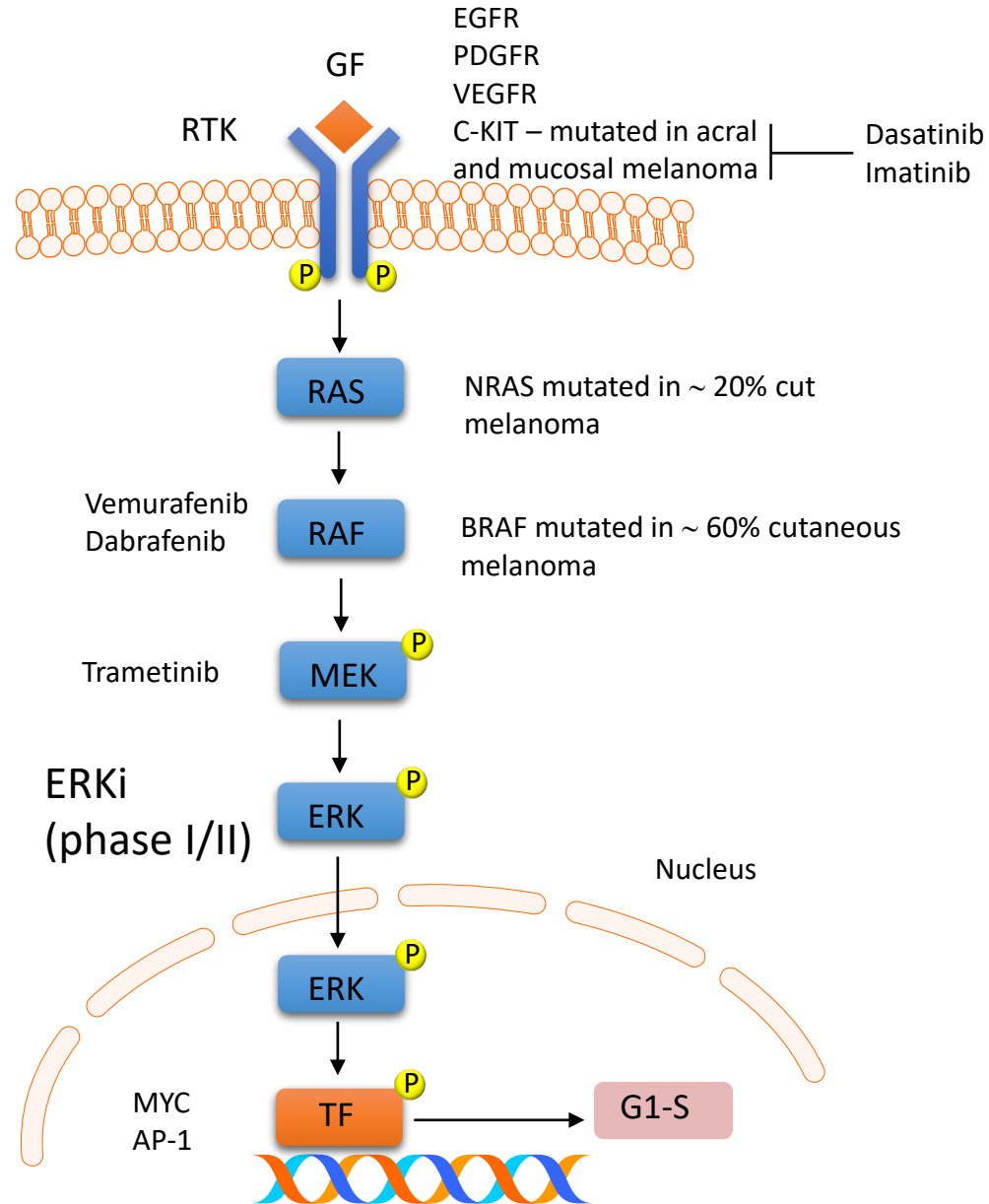
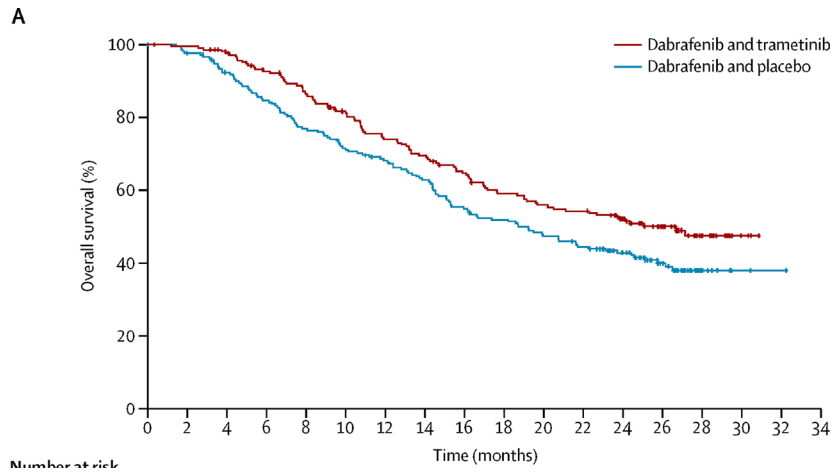


Biopsies

- Bulky in-transit
- Lymph node resections
- SubQ mets
- Liver biopsies or metastases
- Brain metastases
- Intestinal mets

**Melanoma patient-derived xenografts accurately model the disease and develop fast enough to guide treatment decisions
...but lacks an immune system**

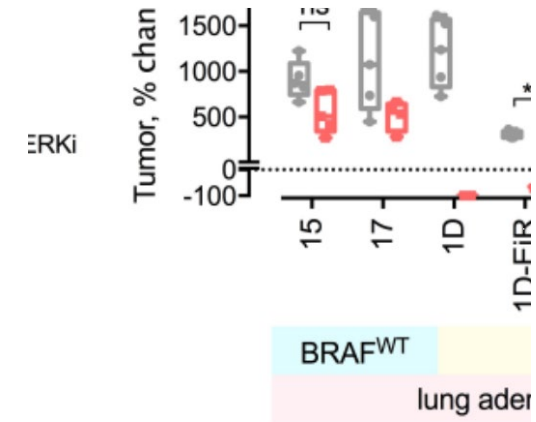
Targeted therapy of cutMM



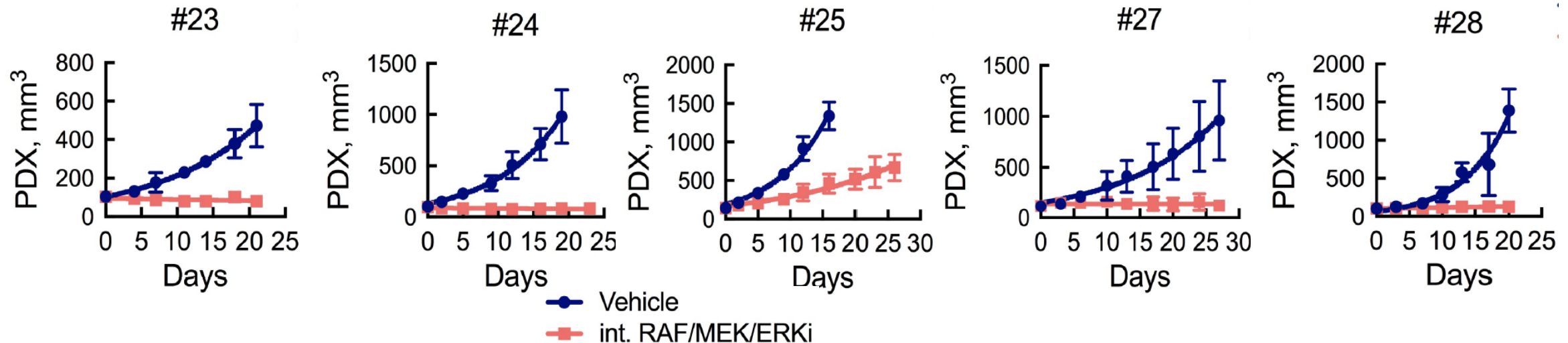
BRAF/MEK/ERK inhibition blocks emergence of BRAFamp

Lung cancer (BRAFV600E)

1D R2



Melanoma (BRAFV600E)

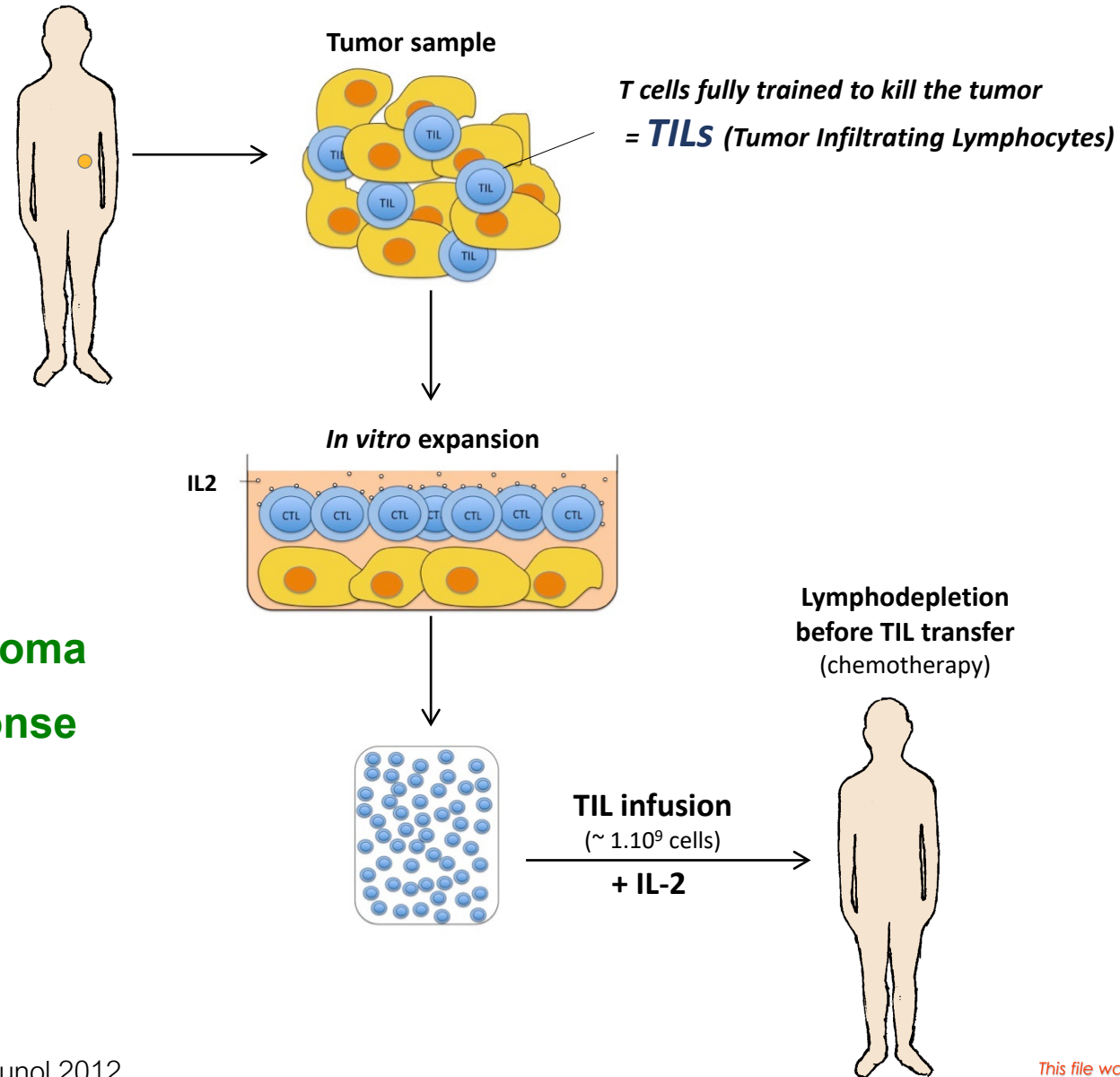


Xue et al., Nature Medicine 2017

Limitations

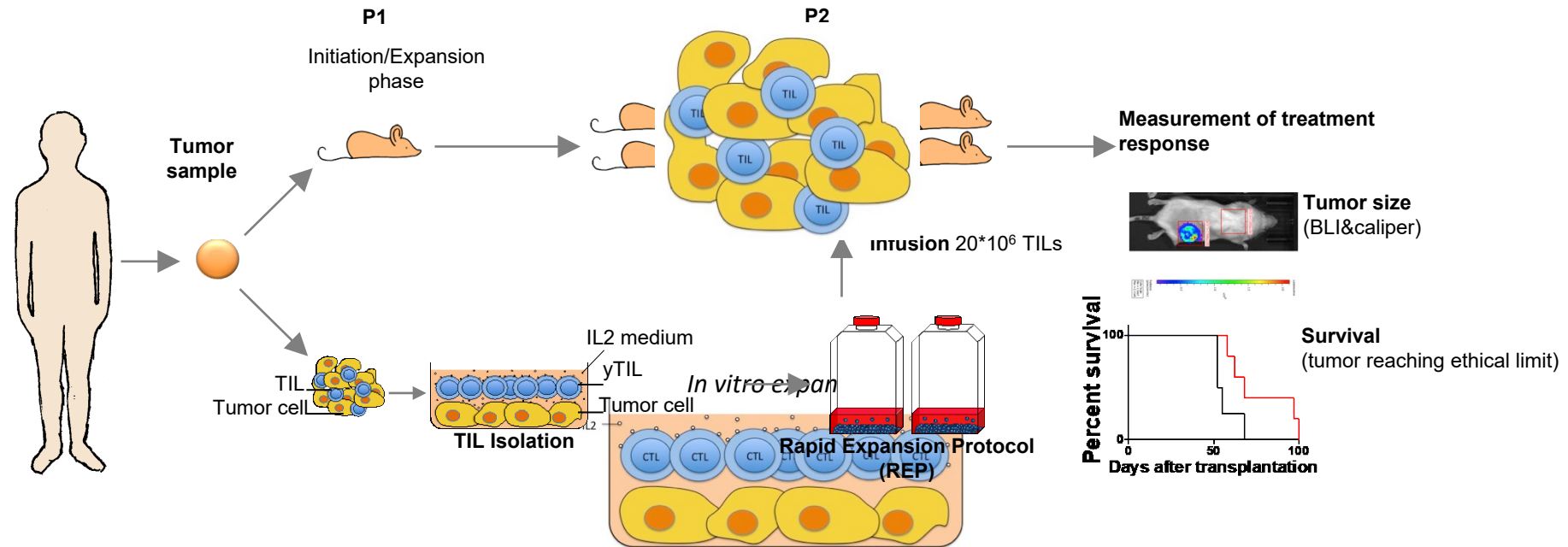
**Melanoma patient-derived xenografts accurately model the disease and develop fast enough to guide treatment decisions
...but lacks an immune system**

Adoptive T-cell transfer (ACT)

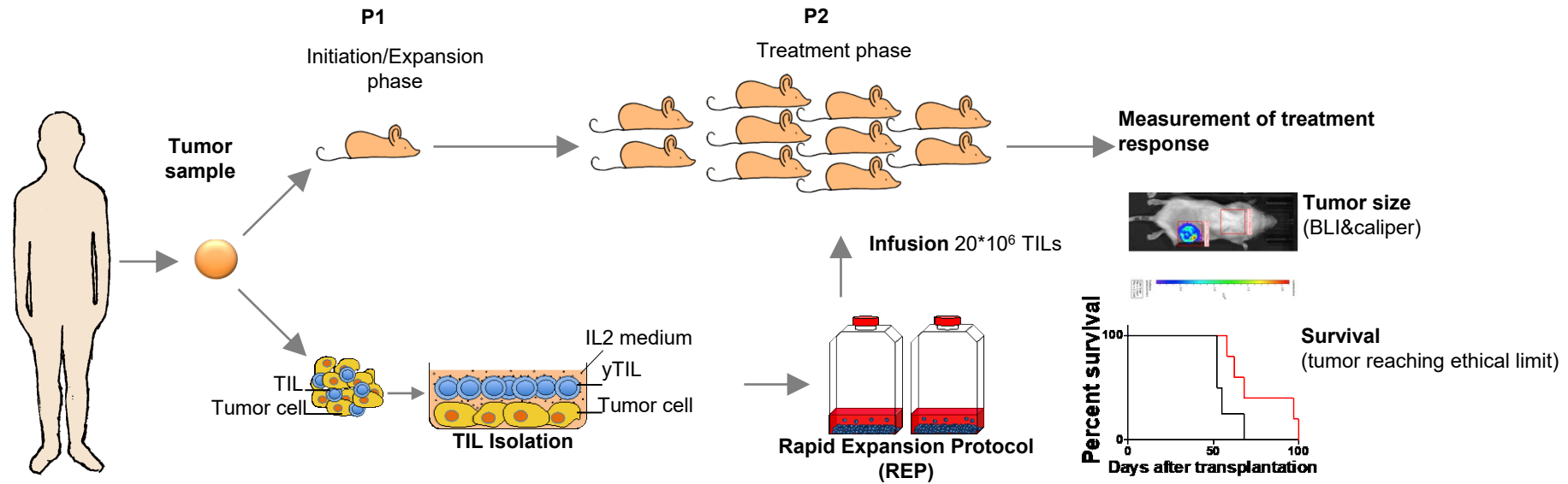


- High response rate in melanoma
- Complete and durable response
- Considerable toxicities
- Labor intensive
- Expensive

+PDX



= PDX v2.0

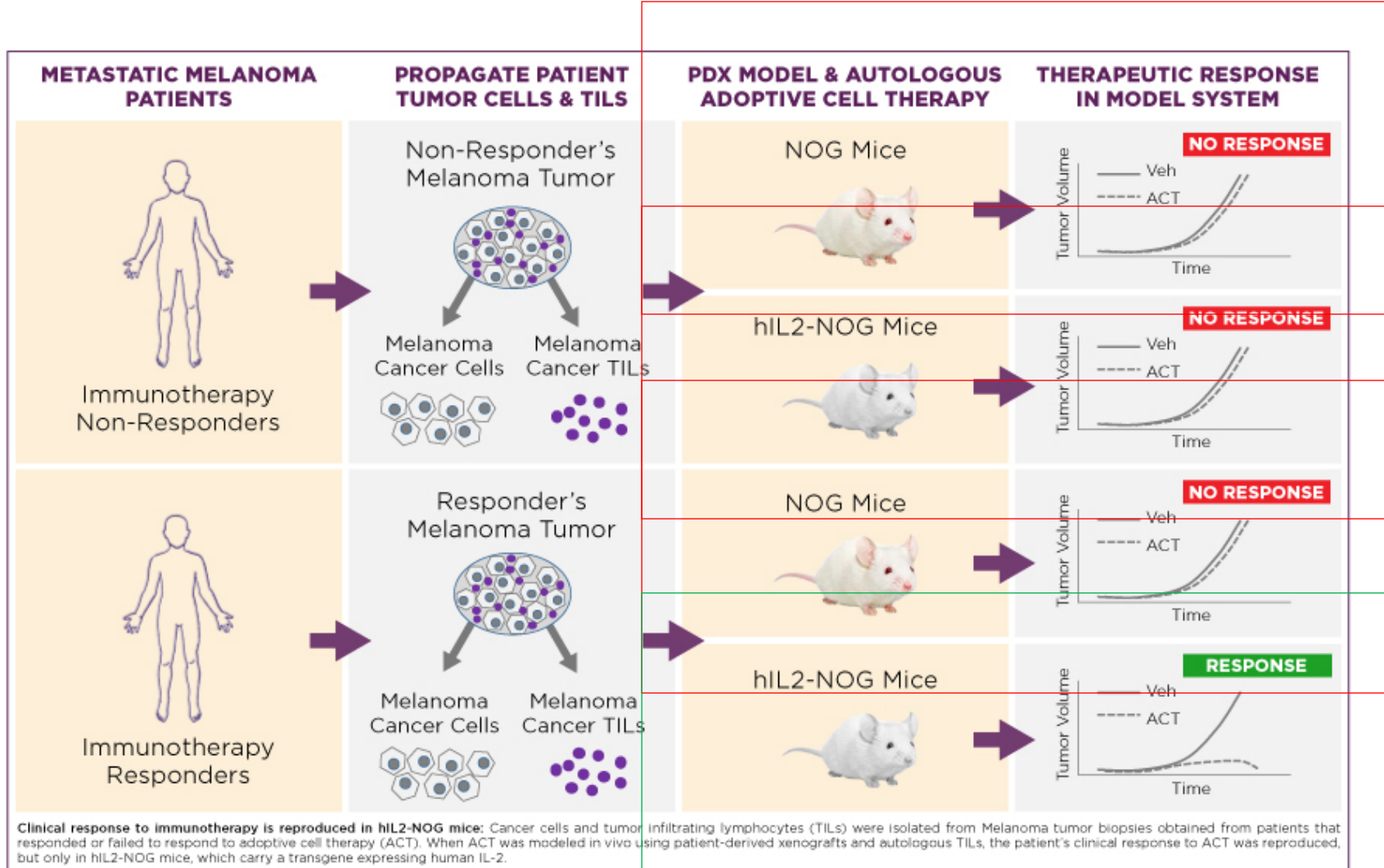


- Correlation to ACT patient data?
- Marker for response?
- Model for combination therapy?
- Model for study of resistance mechanisms?

Clinical responses to adoptive T-cell transfer can be modeled in an autologous immune-humanized mouse model

Henrik Jespersen¹, Mattias F. Lindberg¹, Marco Donia², Elin M.V. Söderberg¹, Rikke Andersen², Ulrich Keller^{3,4}, Lars Ny¹, Inge Marie Svane², Lisa M. Nilsson¹ & Jonas A. Nilsson¹

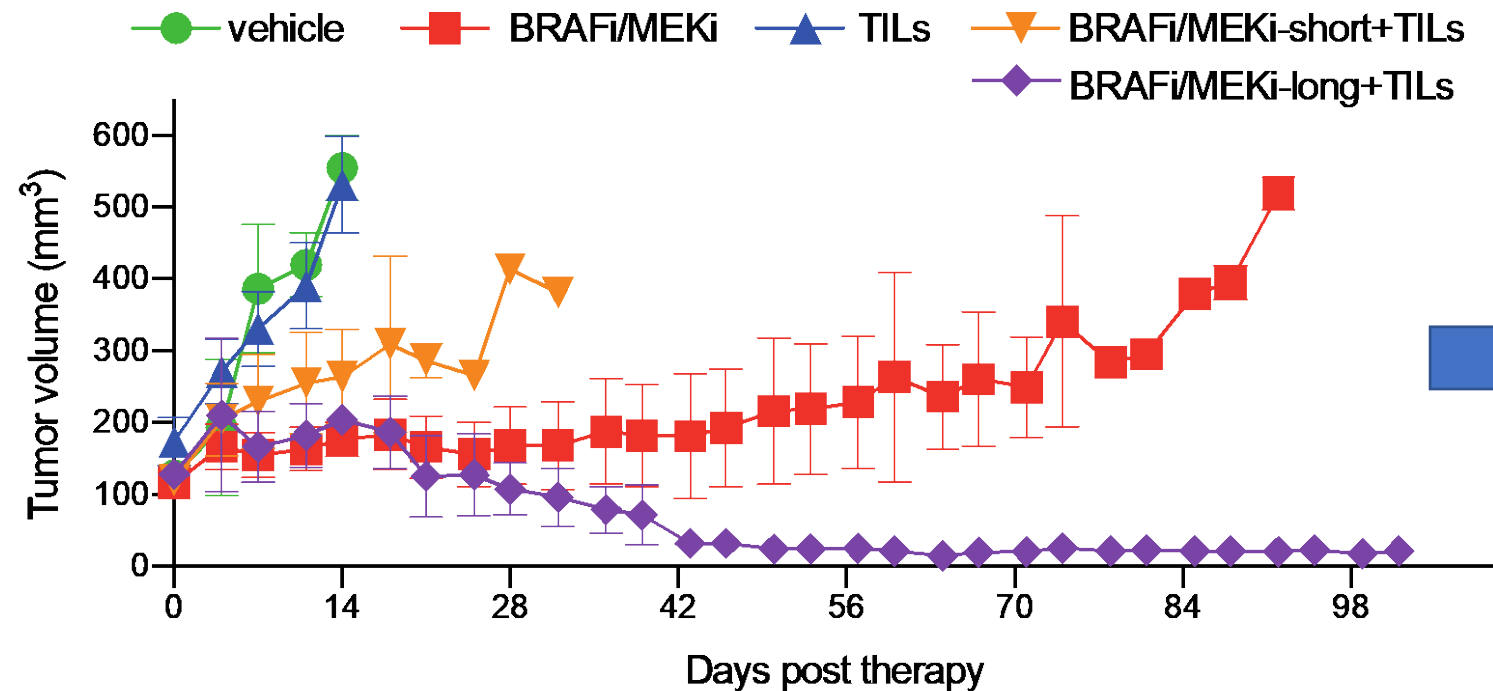
<https://www.taconic.com/taconic-insights/oncology-immuno-oncology/new-humanized-mouse-immunotherapy.html>



ORIGINAL ARTICLE

Supporting clinical decision making in advanced melanoma by preclinical testing in personalized immune-humanized xenograft mouse models

L. Ny^{1,2†}, L. Y. Rizzo^{1,3†}, V. Belgrano^{1,3}, J. Karlsson^{1,3}, H. Jespersen^{1,2}, L. Carstam⁴, R. O. Bagge^{1,3}, L. M. Nilsson^{1,3} & J. A. Nilsson^{1,3*}



Clinical trial

Status and ongoing biobank project

Complete responses to ACT is possible in immune compromised mice

- Defining the optimal cell product (eg phenotype or before/after ICI)
- Combination with targeted therapies
- Genetical engineering of tumor cells and TILs
- Generation of 3D cultures

Limitations: Bulk sequencing, No myeloid cells, stroma or T-cell priming

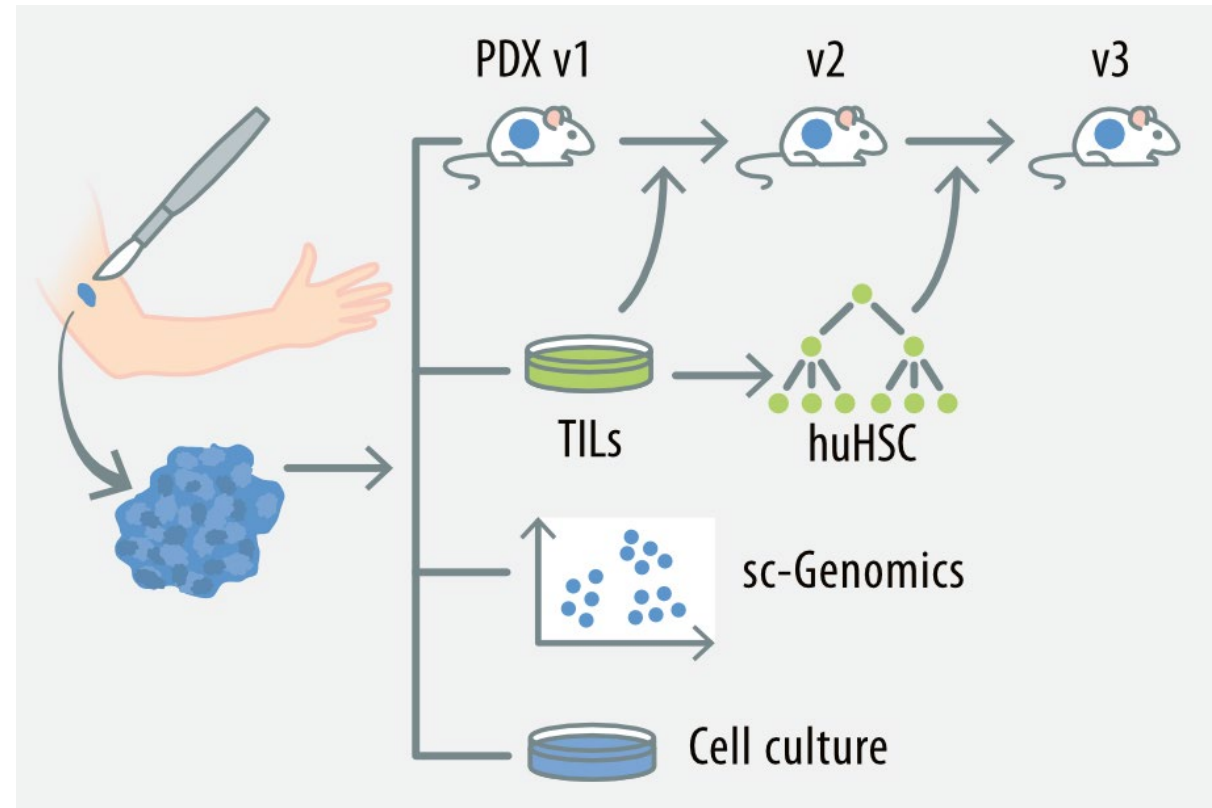
-Analysis of tumor microenvironment by scSeq

Generation of iPSC->HSC

-Generation of PDXv3

Potential clinical outcomes

- Clinical trials on ACT
- Novel engineered T cell products for melanoma
- Biomarkers to predict next line therapies



Acknowledgments



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