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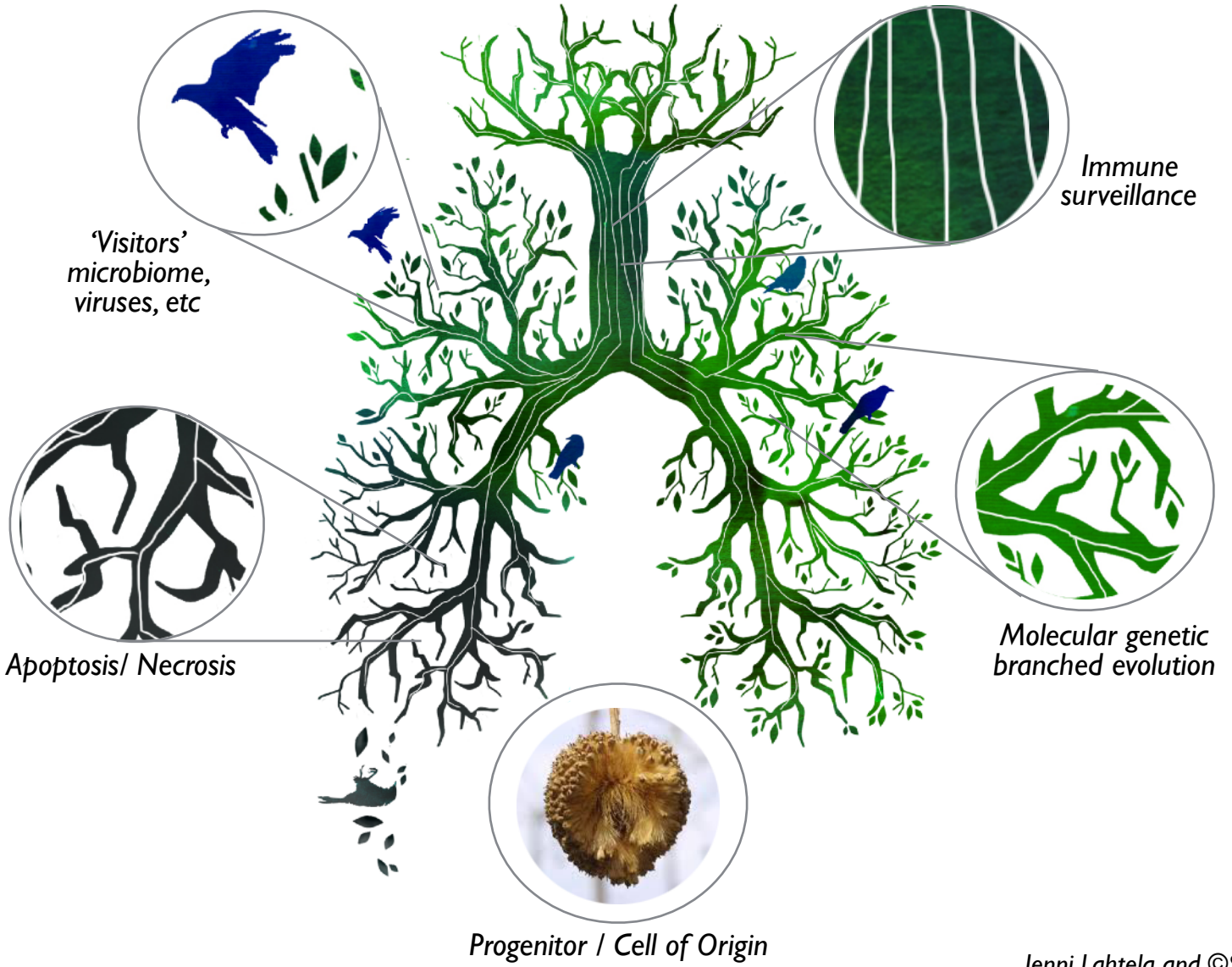
Personalised Phenotypic Diagnostics to Benefit Lung Cancer Patients

Emmy W. Verschuren, PhD
Academy of Finland R'Life Kick-off meeting
November 27 2020

Cancers are Ecosystems that Evolve via a Sequence of Dynamically Changing Environments

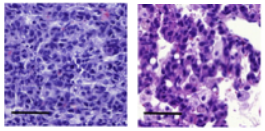


Jenni Lahtela and ©Susanna Tuononen

Questions in Translational Cancer Research

Tissue context ?
Passenger vs driver mutation ?
Intra-tumour heterogeneity ?
Lifetime mutagenic load ?

- Do phenotypes converge as targetable disease vulnerabilities - *histopathology*



  - What can we learn from primary cell & tissue analysis *ex vivo* - *IMI-PREDECT*
    - How can preclinical models inform on clinical diagnostic advances - *Ac. of Finland*

Meilahti University of Helsinki Medical Campus

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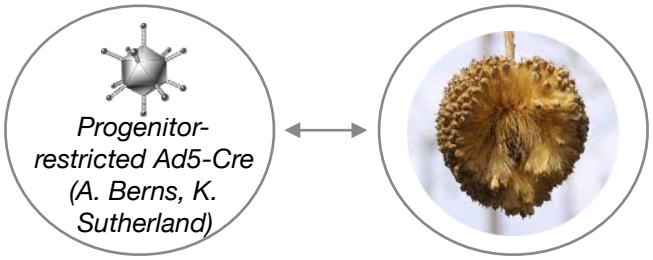
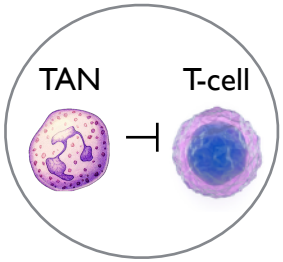
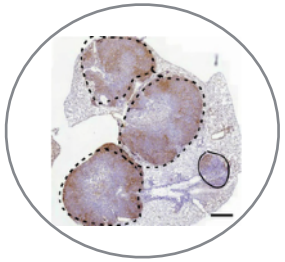


Progenitor cell *and* ***genetic drivers*** *cooperatively define NSCLC histopathology spectrum*



Histopathology-selective phenotypes:
immune suppression, signalling, metastatic propensity



Signalling activities align more with histopathology than genotype, and show significant ***spatial heterogeneity***

$Kras^{G12D}$; $Lkb1^{fl}$
Drivers in appr. 30% human NSCLC
Wide histopathology spectrum

Take home messages preclinical studies

Translational studies to consider histopathology-selective phenotypes in addition to driver mutations

Nagaraj & Lahtela et al, Cell Rep '17
Närhi et al, J Path '18
Bao et al, Sci Rep '19

www.predect.eu
2011-2016

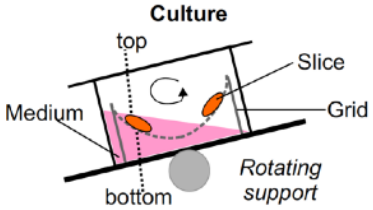
predect
NOVEL COMPLEX MODELS FOR CANCER TARGET VALIDATION

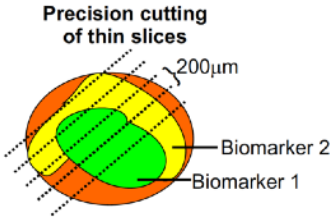
IMI-PREDECT
Public-Private Partnership

Robust Complex *Ex Vivo* Models For Cancer Target Validation

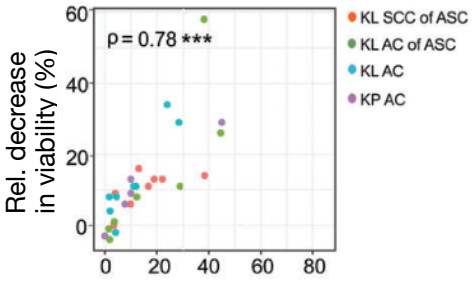
'Can we do better than xenografts or cells grown on plastic ?'

Leica VT1200S



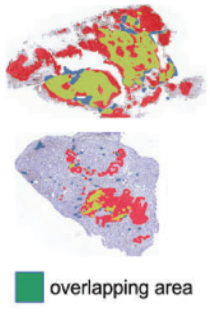


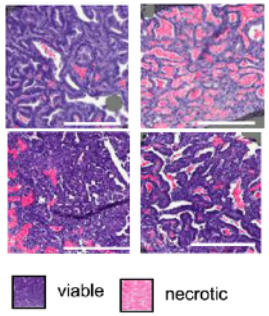
Combination selumetinib (MEKi) + dactolisib (PI3K/mTORCi) treatment



Overlapping expression area (%) of pERK and p4EBP1

Overlay pERK and p4EBP1





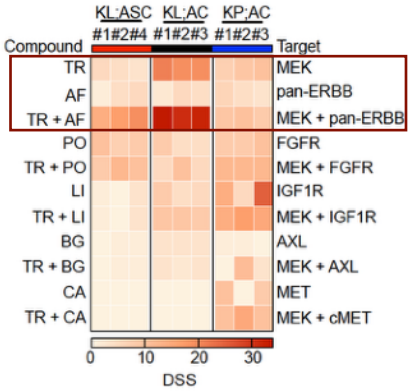
Take home messages organotypic tissue slice studies

Oxygen *and* ***culture supports*** *are required for tissue survival*

Combination drug sensitivity in tissue slices relates to ***spatial signalling activities*** *of targeted pathways*

Tissue slice studies/protocols:

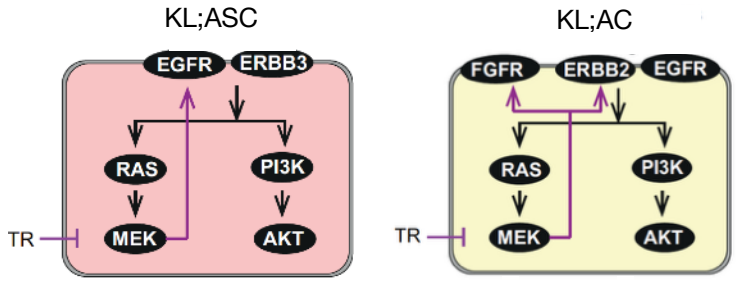
Davies et al., Sci. Rep. '15
De Hoogt et al., Sci. Data '17
Nagaraj et al, J Vis Exp '18
Närhi et al, J. Path '18



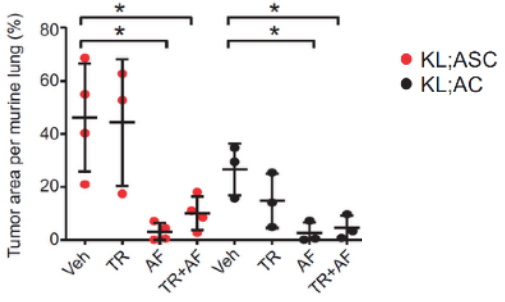
Trametinib (MEKi) + afatinib (pan-ERBBi) combination treatment selective for Kras;Lkb1 NSCLC

Combination drug sensitivity

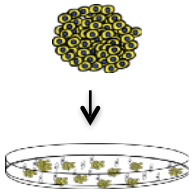
- *Relates to **signalling networks selective for NSCLC histotypes***



- *Is **validated in vivo**, where increased single pan-ERBBi response corresponds with increased ERBB biomarker activity*



Can primary cultures be used to identify and predict drug sensitivities reflective of the native *in vivo* tumour tissue?



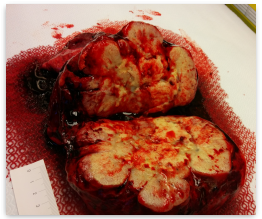
Early passage primary epithelial cultures (conditionally reprogrammed cells; CRC/PDC; Schlegel et al)

Talwelkar & Nagaraj et al, Mol Canc Ther '19

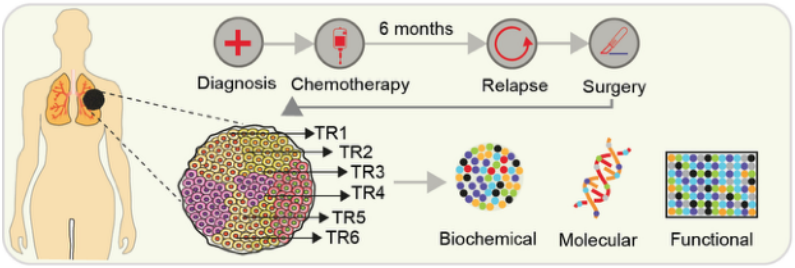
Towards research translation

Challenges of functional diagnostic modelling with clinical samples

- Only half of all resected clinical NSCLC tumours are sliceable, yielding limited numbers of short-lived already necrotic tissue slices, compromising robust study
- Primary epithelial cultures are established at low success rates (10%), and this takes 2-3 months, possibly leading to genetic and phenotypic drift
- Surgically resected tissue is not the disease entity to treat; the majority (>70%) of patients are diagnosed with metastatic stage disease -> assays to be adapted to biopsies or pleural effusions



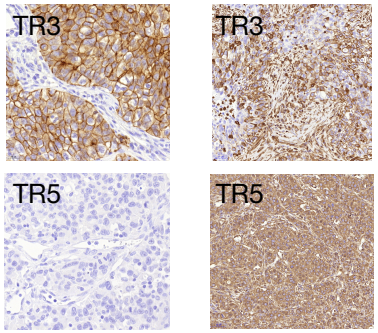
NSCLC - adenocarcinoma
EML4-ALKv3 fusion (driver in 4-7% NSCLC); TP53 mutation (R175H)
chemoresistant (cisplatin + pemetrexed)
Female never smoker

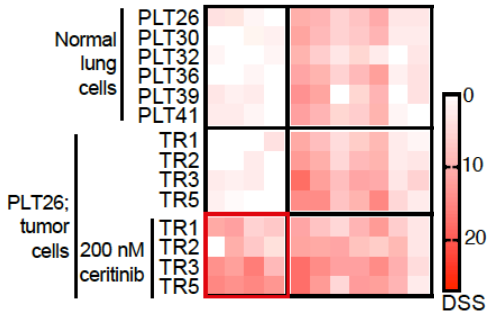


Target inhibition enhances Alki (ceritinib) sensitivity, without affecting normal epithelial cells

TR3: epithelial (E-cadherin)

TR5: EMT/ mesenchymal (CK18)

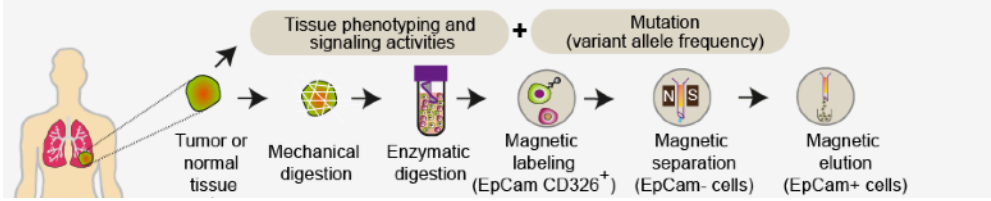




Towards research translation
a case study

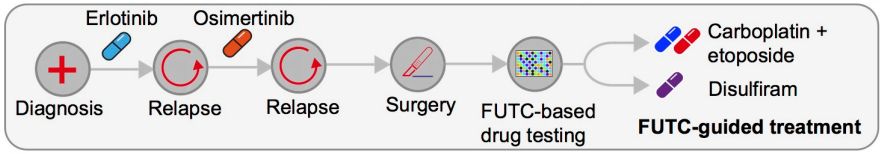
Talwelkar et al, in preparation

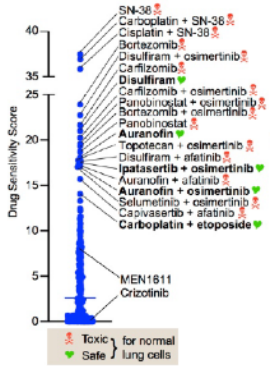
Functional diagnostic profiling using ***Fresh Uncultured Tumour Cells*** *(FUTCs)*

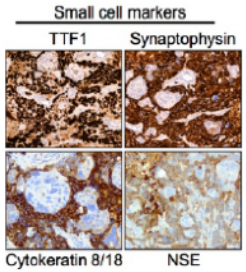


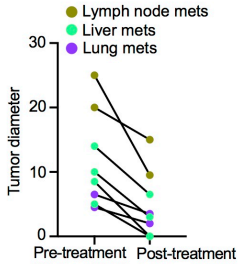
- Normal and tumour **epithelial (EpCam+) and stromal (EpCAM- cells)**
- Drug sensitivity profiling **within three days**
- **Validation:** mimic of pharmacological and adaptive signalling profiles of murine histopathology subtype-matched cultured cells
- **Clinical sample-derived FUTCs show drug response matched to driver mutations** (EGFR, ALK, MET, KRAS) in 18/19 cases

FUTC profiling-guided compassionate treatment of a chemorefractory metastatic EGFRmut NSCLC patient









- Patient was scheduled to receive pemetrexed + carboplatin
- FUTC profiling showed **etoposide + carboplatin** as superior combination
- Treatment was adjusted, **small-cell histotype conversion** was confirmed 2 wks later
- Patient shows response to 4 cycles of treatment over period of one year

Towards research translation
circumventing culture challenges

Talwelkar et al, bioRxiv

Future directions in R'Life

- Develop NSCLC organoid cultures (in collaboration with HUB, Utrecht)
- Compare FUTC responses to those seen in primary organoids
- Functionally interrogate adaptive signalling networks to understand primary/acquired resistance mechanisms
- Extend diagnostic applications to biopsies & pleural effusions


Thanks to the Team !
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Jie Bao, MSc
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Krister Wennerberg - *Drug sensitivities*
Mikko Mäyranpää, HUS - *Pathology*
Kaisa Salmenkivi, HUS - *Pathology*
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Peter Horvath - *Imaging software*

FIMM TC & HTB unit Support

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Swapnil Potdar -*DSRT analysis*
Laura Turunen - *Drug plates*
Jani Saarela - *Assay development*

Preclinical and clinical patients

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Current

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