“Implementation of Genome-guided Concepts of Precision Oncology”

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Personalized Medicine

The Role of Genome Analysis
Aims of Cancer Genomics

- Identify changes in the genomes and epigenomes of tumors that drive cancer progression
- Validate **prognostic** potential of changes
- Potential to **predict** response to therapy
- Identify **new targets for therapy**
- Select **drugs based on** the genomic information of the tumor
The Human Genome

2001

~ 23,000 Genes that code for Proteins
The Technological Revolution

Performance per day
→ 24h for one genome is possible today
(“The“ human genome was done in 10 years)

Costs per genome
→ today < 5000 €
(“The“ human genome costed > 1.000.000.000 €)
DNA „Next Generation“ Sequencing:
Data Storage

Storage for 10 Petabyte

Data Analysis

Computer Cluster
International Cancer Genome Consortium

PedBrain Tumor (Pediatric Brain Tumors) WGS, n > 550

=> Pilocytic Astrocytoma, Medulloblastoma, Glioblastoma, Ependymoma

=> Clinical Trial(s) in Oncology, the Heidelberg experience
Pilocytic Astrocytoma

- Novel “actionable” targets
- Alterations in one pathway in 100% of cases
- Pilocytic Astrocytoma: a “single pathway” disease!

=> Therapy options

Jones et al. Nature Genetics 2013
2008, female

- 11/2013: initial diagnosis **Anaplastic Astrocytoma (Grade III)**
  treatment by standard protocol (radiotherapy & temozolomide)
- 11/2014: Tumor progress
- 12/2014: **sequence analysis**: **FAM131B:BRAF fusion**, typical for **Pilocytic Astrocytoma (Grade I)** => MAPK pathway activation
- Patient now treated with a **MEK-inhibitor (Trametinib)** + valproate + low-dose cyclophosphamide + chloroquine
- since 10/2015: **stable disease**

**Patient example**

Chromosome 7
Pediatric Glioblastoma: Recurrent MET fusion gene

Bender, Gronych et al. Nature Medicine 2016

Preclinical model

T1 RARE
*2006, male

- 04/2011: initial diagnosis of a metastasized group 3 Medulloblastoma treatment by standard protocol (incl. craniospinal irradiation)
- 09/2014: massive tumor growth
- 10/2014: sequence analysis: PTPRZ1-MET fusion with amplification and overexpression of MET + TP53 mutation (most likely radiation-induced Glioblastoma)
Patient example: Treatment response .... .... and resistance?

Treatment with a MET-inhibitor (Crizotinib)

baseline post-OP  
2 months Crizotinib  
further 16 days Crizotinib
Survival rates of pediatric cancer patients
INFORM (INdividualized therapy FOr Relapsed Malignancies in childhood)

Genome-based personalized treatment of children with relapsed tumors

- On average ~3 weeks from DNA/RNA preparation to tumor board
- ~60% “actionable” target molecules

n > 300

S. Pfister, O. Witt, P. Lichter, A. Eggert & all of GPOH
Patient stratification based on molecular data

International cooperation

European partners

DKTK + partners

Australia & New Zealand

Own platform for molecular profiling:

IGR = Institut Gustave Roussy, Paris (‘MAPPYACTS’)

... in development:

GOSH = Great Ormond Street Hospital, London (‘SM-Paeds’)

PMC = Prinses Maxima Centrum, Utrecht (‘iTHER’)

Countries that have already joined

Countries that plan to join this year

Countries that are considering participation
European partners on clinical trials
HIPO-H021: The Individual Patient

NCT/DKTK MASTER
Molecular High-throughput Analysis

NCT MASTER Registry Study
- All NCT Patients < 50 Jahre, Rare Tumors
- Molecular Profiling
- Clinical Analysis and Interpretation
- Therapy Recommendation

NCT MASTER Interventional Studies
- Clinical Intervention
- Basket Trials
- Multiple Treatment Arms

Horak et al. Int J Cancer 2017
DKTK MASTER TRIAL
(young adults, rare tumors)

October, 2017
Molecular Tumor Board Management recommendations (Level 1-4) 793 patients
Genome-based clinical management ~75% (05/2016: ~60%)
~30% (05/2016: ~25%)
Genetic Heterogeneity: tumors may consist of subclones

Diagnosis on multiple biopsies

Diagnosis based on single cell sequencing?


Thank you for the attention!