The Paradigm Shift: Imaging each Individual Patient’s Cancer At the Molecular Level
Precision Oncology

= 

Personalized Molecular Analysis

+ 

Basic Science Discovery

+ 

Interdisciplinary Clinical Development of Targeted & Novel Therapies & Prevention
NCT MASTER Workflow

**Enrollment**
- Patient
- Patient
- Patient
- Clinical Data

**Diagnosis**
- Imaging
- Sampling
- Sample Processing

**OMICS**
- Gen
- Prot
- Immun
- Metabol
  
**Bioinformatics Clinical Report**
- Bioinformatics
- Clinical Report

**Molecular Tumor Board**
- Mol. Tumor Board

**Individualized Therapy**
- Treatment
- RadioOnc
- Trial

**Response, Resistance & Prevention**
- Imaging
- Sampling
- Prevention

**NCT Data There House (SAP HANA)**
NCT MASTER Workflow

Enrollment:
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NCT DataThereHouse (SAP HANA)
NCT MASTER Protocol – Molecularly Aided Stratification for Tumor ERadication

Umbrella protocol for Implementing Personalized Oncology at NCT Consents Every Patient for:

- Questionnaires – Health & Behavior
- Molecular Analysis
- Data Storage
- Clinical Data Analysis
- Re-Contact for Clinical Trials
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SOP-guided Extraction of Analytes

Tasks
- Sample Registration and Barcoding
- Sample Preparation
- Nucleic Acid Extraction
- Quality Assessment and Identity Check
- Sample Submission to Core Facility - 14 HiSeq 2000, 2 HiSeq 2500
- Documentation
- Method Development and Optimization (Robotics)
- Sample Management & Storage

Staff - 1 Laboratory Manager and 4 Technicians

3002 Submissions (~170 Samples/Month)

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<th>Type</th>
<th>Exome</th>
<th>Whole Genome</th>
<th>Transcriptome</th>
<th>SNP</th>
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<td>&gt;1936</td>
<td>&gt;355</td>
<td>&gt;570</td>
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Heidelberg Center for Personalized Oncology
DKFZ-HIPO

Heidelberg Center for Personalized Oncology

Hipo\textsuperscript{gen}
Genome Analysis Program

hipo\textsuperscript{sys}
Systems Biology Bioinformatics Synthetic Biology Program

Hipo\textsuperscript{med}
NCT Precision Oncology Program

Clinical Development

Genome Sequencing
Bioinformatics
Applied Bioinformatics
Proteomics
Next Generation Imaging
DKFZ-HIPO & NCT POP

Innovation Program

• > 50 Hypothesis-driven Projects
• >20 Different Tumor Entities
  Myeloid Leukemia, Colorectal Cancer, Multiple Myeloma, Lung Cancer, CLL, Glioblastoma, Gastric Cancer, Prostate Cancer, HCC, SCC, Panreatic Cancer, Sarcoma, Breast Cancer
• Establishing Standards for Dataflow and Storage & Validation of Sequencing Results

HIPO_015: Subtype Specific Stratification and Targeting of Pancreatic Adenocarcinoma

Rienk Offringa, Roland Eils, Andreas Trumpp
Analysis: 360 Exomes, 260 Transcriptomes

• Develop a Preclinical Model that Preserves all Clinical Subtypes
• Determination of Predictive Therapeutic and Diagnostic Markers
• Evaluation of novel Subtype Specific Drugs
• Initiation of Clinical Trials
Significant Accomplishments

• X Chromosome Hypermutation in the inactice X Chromosome of Tumor Cells – Jäger et al. *Cell* 2013
• Dissecting the Genomic Complexity Underlying Medulloblastoma - Jones et al. *Nature Genet* 2013
• Hotspot Mutations in H3F3A and IDH1 Define Distinct Epigenetic and Biological Subgroups of Glioblastoma - Sturm D,….., Pfister S. *Cancer Cell* 2012
• Genome sequencing of Pediatric Medulloblastoma Links Catastrophic DNA Rearrangements with TP53 Mutations – Rausch T,….., Korbel JO. *Cell* 2012
• Recurrent Mutation of the ID3 Gene in Burkitt Lymphoma Identified by Integrated Genome, Exome and Transcriptome Sequencing – Richter J,….., Siebert R. *Nat Genet* 2012

Genome Sequencing of Pediatric Medulloblastoma Links Catastrophic DNA Rearrangements with TP53 Mutations

*Rausch, Jones, Zapatka et al.*

*Cell* 2012
Display Data from Various Sources for a Comprehensive Overview of Information Relevant for Personalized Treatment

- Unstructured Data
- Doctor's Letters
- Clinical Pathways
- Array Data
- Patient
- Structured Data
- Researcher
- Sequencing Data
- Molecular Tumor Board
- Doctor
- Process accompanied by Medical Case Manager
- Individualized Treatment Plan
- Comprehensive Information

NCT Goes SAP Hana – NCT DataThereHouse
Clinical Process – Current

*) SOP = Standard Operating Procedure, LOI = Letter of intent, POP = Personalisiertes Onkologie Programm
NCT Clinical Development Strategy

Vision

IS-H, PUBMED, UPTODATE, BIOBANK, INTRANET, IS-H, PACS

Monitoring

In HANA organisiert

Patent

Therapie am NCT

Klinische Studien

Publikation

In HANA organisiert

IS-H, PUBMED, UPTODATE, BIOBANK, INTRANET, IS-H, PACS
### NCT MASTER Workflow

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**DKFZ-HIPO & NCT POP**

**The Individual Patient**

- **Day 1**
  - **Diagnosis**
  - **MASTER ICF Biopsy**

- **Day 5-28**
  - **Sample Processing & Molecular Profiling**
  - **Bioinformatics & Interpretation of Mol. Data**
  - **Validation**

- **Day 35**
  - **Molecular Tumor Board**

- **Day 42**
  - **Second Validation**
  - **Stratification & Targeted Therapy/Clinical Trial**

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**Clinical Sequencing of Individual Patients with Unmet Medical Need**
- Currently >220 Patients Enrolled
- Material from >200 Patients Received
- >150 Patients Discussed in Mol. Tumor Board

**DKFZ-HIPO & NCT POP**

**The Individual Patient**

- **Diagnosis**
  - **Patient**
  - **Clinical Data**

- **MASTER ICF Biopsy**
  - **MASTER ICF**
  - **Sampling**

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- **Molecular Tumor Board**
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  - **Clinical Data**
  - **Mol. Data**

- **Second Validation**
  - **Stratification & Targeted Therapy/Clinical Trial**

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**Fröhling, Glimm et al.**
DKFZ-HIPO & NCT POP

Functional Genomics

Applied Functional Genetics to Translate High-Throughput Molecular Patient Stratification Data into Innovative, Individualized Molecular Interventions

Functional Genomics

Structural Genomics

Genomics
Transcriptomics
Epigenomics

Functional Genomics

Functional annotation of molecular lesions
Tumor models
Primary patient samples
Unbiased identification of functional dependencies

Target validation
Target characterization
Development as therapeutic target
Clinical translation

Krás mutant cancer cells require STK33

Scholl, Fröhling et al. Cell 2009

STK33 as novel HSP90 client

Azoitei, ... Fröhling, Scholl et al. JEM 2012
Molecular Therapy & Immunotherapy

Tumor-initiating Cell Heterogeneity and Chronic Inflammation in Colon Cancer

Detect & Treat

EMT

MET

Glimm

Cell Stem Cell 2011

Primary tumor

Metastasis

LT-TIC

mTIC

Initiation

T-TAC

T-TAC

Tumor cell amplification

Bulk cells

Tumor bulk cells

Self-Renewal

Glimm

Cell Stem Cell 2011
Strategy

Parallel molecular and functional characterization

**Functional profiling**
- Pathway inhibition screen
- Cell seeding
- 48h
- ATP-levels
- Compound libraries

**Molecular profiling**
- Genome (Exome + CNV)
- Transcriptome
- Epigenome

Understand disease biology
Understand drug sensitivity
Rapid clinical translation

Leukemia cells

Zenz et al.
Molecular Therapy & Immunotherapy

Effect of BRAF Inhibition in Hairy-Cell Leukemia and Myeloma

Raab et al. *Cancer Discovery* 2013
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NCT MASTER - Whole Exome Sequencing of every NCT Patient < 50 Years with Advanced Disease

The individual Patient

2013

NCT MASTER Patients <50 years

2014

All Patients

2016

OMICS

Genomics

Metabolomics

Proteomics

Immunomics

• Patient Stratification
• Treatment Response
→ Trial Success
• Surprise Responders
→ Targets / Pathways for Novel Therapies

NCT Clinical Studies (IIT)

e.g.
• Pancreas
• Glioma
• Multiple Myeloma
• Breast
• Lung
• Medullo-blastoma
• Heavy Ion Radiation

National Center for Tumor Diseases
NCT Project of Dietmar Hopp Foundation  
Positioning of National Center for Tumor Diseases Heidelberg as International Center of Excellence for Precision Cancer Medicine

• Partnership of DKFZ, NCT, UKL HD, Dietmar Hopp Foundation, Molecular Health, GATC and SAP
• Funded by Dietmar Hopp Foundation
• Whole Genome Sequencing (DKFZ)
• Panel Analysis of 600 Genes (GATC & MH)
• Piloting Phase 50 Patients / Trial 1000 Patients
• Comparison of different Analysis Strategies
• Implementation in Clinical Routine
INFORM = INdividualized therapy FOrr
Relapsed Malignancies in childhood

Angelika Eggert, Stefan Pfister, Olaf Witt, Peter Lichter & Study Groups of the GPOH

Feasibility-Registry Study (Year 1+2)

- ALL
- AML
- HGG (incl. DIPG)
- Medullo/Ependym. 
- Ewing Sarcoma
- Neuroblastoma
- NHL
- Osteosarcoma
- Rhabdomyosarcoma
- Rhabdoid Tumors

Clinical Trial (Year 3-5)

Enrollment

Phase I/II

- Standard of Care: Backbone Chemotherapy
- Backbone
- Targeted Drug 1
- Targeted Drug 2
NCT 3.0 – Molecular Diagnostics Program

NCT MASTER – Registry & Interventional Trial

Patient Sample Asservation → Sequencing → Bioinformatic Analysis → Clinical Evaluation → Validation → Molecular Tumor Board

*Recommendation: 61%
Treatment: 14%

Unbiased Functional Testing → Focused Functional Testing

Feed Back Results
Adapt Treatment/Functional Testing

Stefan Fröhling, Christoph Heining, Hanno Glimm
Claudia Scholl (Functional Genomics)

DKTK – LMU München, Frankfurt

(1) BAY1125976 ("Allo-AKT"): PI3K/AKTmut
(2) BRF117019 ("ROAR"): BRAFV600E
(3) EORTC 90101 ("CREATE"): ALK/METabn
(4) Palbo-AL-1: MLL rearrangement
Precision Medicine

What Does it Take to Change Practice?

- Unique Sensitivity and Specificity for Stratification
- "Would I be Better off Being Treated as Something Else?" (BRAF V600E; MYD88)
- Exploit the "Gold Rush" in Genetics
- Fast Track Development of New Standards of Care
- Potential to Combine Treatment and to Prevent Disease by Early Intervention

Early Diagnosis and Combination Therapies Require a New (System(s) Wide) Medicine in Every Patient
Fusing High-Throughput Technologies with Hypothesis-driven, Stratification & Intervention towards Personalized Medicine
Thank You