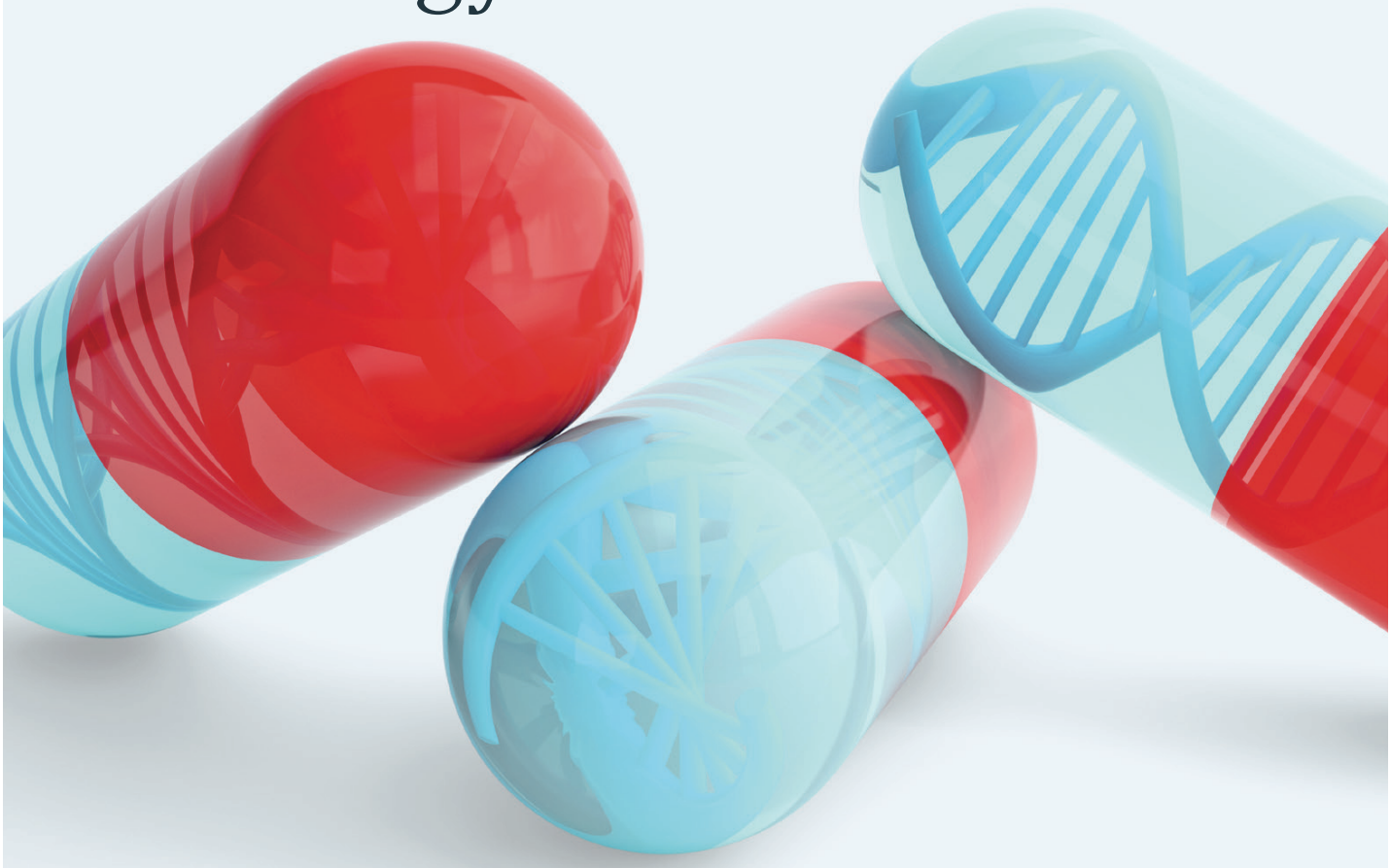
University of Basel

Faculty of Medicine

Certificate of Advanced Studies in Personalized Molecular Oncology



Universitätsspital Basel

SIB

CHUV

ADVANCED STUDIES

Detailed module program

Edition 4: 2022-2023

Document version 3 – 22 February 2023

CAS Personalized Molecular Oncology | 10 ECTS | Duration: approx. 10 months		
	Module title	Module coordination
Module 1	Tumor biology and genetics	CHUV Cancer Genetic
Module 2	Molecular pathology	USB Pathology
Module 3	Clinical bioinformatics	SIB Clinical Bioinformatics
Module 4	Clinical oncology	USB Oncology
Mini-thesis	Planned in small groups	Program Board

Module 1
Tumor biology & genetics

Dates

- 4, 5; 25, 26 November 2022 (28h presential teaching).

Location

- Lausanne, CHUV University Hospital.

Main topics

- Basic cytogenetics and molecular genetics
- Hereditary vs. acquired genetics
- Genetic recombination, DNA damage and repair
- Solid tumors and hematological malignancies
- Genetic predisposition to cancer
- Diagnostic genetic testing
- Clonal evolution & tumor heterogeneity
- Clonal hematopoiesis of indeterminate potential (CHIP) and aging
- Genetic risk stratification of hematological neoplasia

Learning objectives for participants

- Describe the mechanisms yielding to genetic variation, and be familiar with the various types of genetic variants.
- Distinguish hereditary genetic anomalies from acquired genetic anomalies.
- Discuss the advantages and limitations of different genetic laboratory methodologies for diagnostic testing.
- Demonstrate how to interpret non-hotspot mutations using public databases and taking into account overall genomic aberrations and clonal evolution.
- Be aware of ethical implications of incidental genetic findings.
- Have basic knowledge of hematological neoplasia, genetic drivers and treatment options

Prerequisites to attend the module

- Basic notions of biology.

Module coordinator

- Prof. Jacqueline Schoumans (CHUV)

Course format

- Lectures, exercises, group discussions and lab visit.

Day 1 – Introduction to hematological and hereditary cancers in adults/children and molecular genetics

- [0h30] Welcome
  - Introduction to the CAS (Prof. Dr. Christian Ruiz, Unibas /Miriam Tesfai, SIB)
  - Introduction to module 1 (Prof. Jacqueline Schoumans, CHUV)
    - All participants introduce themselves and their background
    - Brief introduction of clinical utility of somatic genetic testing with overview of organization of laboratories performing genetic testing at the CHUV

- [1h15] Introduction to molecular genetics (Dr Ilaria Scarpelli, CHUV**)**
  - Definition of genomics (whole genome, whole exome, panel), transcriptomics, proteomics, metabolomics
  - DNA structure: chromosomes, nucleotides, genes, introns, exons, regulatory elements
  - From DNA to proteins: transcription, translation, post-translational modifications
  - Roles of proteins in cells (regulatory/signaling networks), importance of 3D structure
  - Genetic modifications
  - Definitions of allele, genotype, haplotype, phenotype
  - Types of mutations: SNVs, SNPs, insertions, deletions
  - Effect of the mutations: synonymous, non-synonymous mutations; nonsense, missense mutations; frameshifts
  - Variant nomenclature

- [1h75] Hereditary cancer in adults (Dr Benno Röthlisberger, Genetica AG, Zurich)
  - Hereditary breast cancer
  - Genetic testing
  - Genetic counseling
  - Ethical aspects

- [1h15] The role of a genetic counsellor (Marie Met-Domestici, CHUV)

- [2h30] Hereditary cancer in children (Dr Raffaele Renella, CHUV)
  - Predisposition to cancer by inherited genomic instability
  - Patient demonstration

Day 2 – Introduction to next generation sequencing data analysis and interpretation

- [1h30] Usefulness of cytogenetics in hematological neoplasia (Prof Jacqueline Schoumans CHUV)
  - Confirmation and WHO classification of disease
  - Prognostication with scoring systems and risk stratification
  - Interactive interpretive exercises with chromosome anomalies

- [2h] Next generation sequencing data analysis and interpretation (Dr Ilaria Scarpelli)
  - Frequency of mutation in a tumor (VAF) and in population (MAF)
  - Impact of the mutations: variant of uncertain significance, benign variant vs. pathogenic prediction, variant databases
  - Molecular risk stratification in hematological neoplasia

- [2h] Interactive workshop of genomic variant interpretation focusing on hematological malignancies (practical exercises performed in small groups using Seqpilot software package (laptops will be provided). (Dr Ilaria Scarpelli CHUV)

- [2h] Continued interactive workshop & discussion of results of practical exercises (Dr Ilaria Scarpelli CHUV)

Day 3 – Cell biology and tumor genetics focusing on hematological malignancies

- [2h30] Tumor genetics in the lab (Prof Jacqueline Schoumans, CHUV) part 1
  - Hereditary cancer genetics vs. acquired genetics
  - Meiosis, mitosis, genetic mechanisms (e.g DNA repair, homologous recombination, double hit chromothripsis)
  - Solid tumor vs. blood cancers
  - Overview of laboratory technologies and their capabilities and limitations for detecting various types of genomic aberrations in cancer

- [1h15] Clonal hematopoiesis and aging (Dr Abhishek Niroula, Lund University, Sweden)
  - Clonal hematopoiesis and aging
  - (CHIP) mutations in myeloide and lymphoide neoplasia

- [1h30] Precision medicine in hematological malignancies (Dr Sabine Blum, CHUV)
  - History of first targeted therapy (precision medicine) in chronic myeloid leukemia (CML)
  - Development of Tyrosine kinase inhibitors (TKI)

- Acquired resistant mutations
- Monitoring of treatment response by Minimal Residual Disease measurements (MRD

- [1h45] Tumor genetics in the lab (Prof Jacqueline Schoumans, CHUV) part 2
  - Introduction to group exercises genomic testing strategies in onco-hematology (Prof Jacqueline Schoumans, CHUV)
  - Practical exercises concerning genetic testing strategies and interpretation of results will be solved in small groups and discussed at the end of the session in the entire group

Day 4 – Diagnostic applications of tumor genetics focusing on hematological malignancies

- [1h30] Introduction to hematological neoplasia (Prof Caroline Arber, CHUV)
  - Introduction to hematopoiesis
  - Classification of hematopoietic neoplasms (WHO)
  - Overview of technologies needed for classification
  - Overview of treatment options

- [1h30] Cellular therapies in hematologic malignancies (Prof Caroline Arber, CHUV)
  - Hematopoietic stem cell transplantation
  - Chimeric antigen receptor T cell therapy

- [0h30] Introduction to demonstrations and practical exercises of genomic methodologies in the oncogenomic laboratory BH19 (Prof Jacqueline Schoumans, CHUV

- [3h30] Practical demonstration of genetic methodologies and automation at the oncogenomic hematology laboratory, CHUV (demo organized)
  - Conventional karyotyping (Laure Barman, CHUV)
  - FISH (Franziska Steffen, CHUV)
  - SNP-array (Kilian Bühler CHUV)
  - NGS gene panels and complementary molecular tests (Marion Rebeaud, CHUV

- [0h15] Summary and end of module in lunch room BH18 (Prof Jacqueline Schoumans, CHUV)

Module 2
Molecular pathology

Dates

- 20, 21 January; 3, 4 February 2023 (28h presential teaching).

Location

- Basel, Basel University Hospital.

Main topics

- Sample classification and preparation
- Principles of nucleic acids extraction
- Sequencing platforms and setup
- Understanding gene panels
- Internal / external quality controls
- Laboratory accreditation
- Reporting clinically relevant genomic variants
- Interpreting a molecular profile

Learning objectives for participants

- Gain knowledge about the different types of specimens (e.g. tissue biopsy, cytology, resections, blood samples).
- Get an overview about the currently used technological platforms in molecular diagnostics (comparison with the research setting).
- Get familiar with all the steps that lead from sample collection to final molecular report generation along with all possible bottlenecks.
- Algorithms for appropriate gene panel selection.
- Understand the basics (procedures and rules) of an accredited clinical laboratory, including internal and external quality controls.
- Get familiar with the most common clinically relevant variants along with their interpretation and classification system.

Prerequisites to attend the module

- Module 1 or equivalent knowledge.

Module coordinators

- PD Dr. Christian Ruiz (University of Basel), Dr. Salvatore Piscuoglio (USB), PD Dr. Matthias Matter (USB)

Course format

- Lectures, exercises, group discussions and lab visit.

Day 1 – General Introduction into Pathology and Molecular Pathology

- [0h30] Welcome and Introduction to the Institute of Pathology in Basel (PD Dr. Matthias Matter, USB, Dr. Salvatore Piscuoglio, USB, Prof. Dr. Christian Ruiz, Unibas)

- [0h30] Different types of samples and requirements for molecular analysis (Prof. Dr. Christian Ruiz, Unibas)

- [1h] Introduction into general pathology: general concepts of neoplasia (PD Dr. Matthias Matter, USB)

- [1h] Overview of the techniques used in molecular pathology (PD Dr. Matthias Matter, USB)

- [1h30] Lab visits:
    - I: General pathology laboratory (45 min) (Prof. Dr. Alexandar Tzankov, USB)
    - II: Molecular pathology (45 min) (Dr. Ivana Bratic, USB)

- [1h] Practical/Hands-on microscope: real-life cases of clinical pathology (PD Dr. Matthias Matter, USB)

- [0h45] Wrap up of the day, questions & answers

Day 2 – Intro into genomics; Tumor specific molecular pathology; Accreditation; Molecular Pathology: Analysis of different tumor types

- [1h] Introduction into Genomics & NGS (Dr. Philip Jermann, Thermo Fisher Scientific)

- [1h] NGS panels for genomic analyses, BRCAness, TMB, genomic biomarkers (Dr. Philip Jermann, Thermo Fisher Scientific)

- [0h45] Digital Pathology (Prof. Dr. Viktor Közer, University Hospital Zürich)

- [0h45] Organoids for Diagnostics (Dr. Clémentine Le Magnen, USB)

- [0h45] Laboratory Accreditation (Prof. Dr. Alexandar Tzankov, USB)

- [0h45] Molecular Pathology of the Lung (PD Dr. Spasenija Savic, USB)

- [0h45] Molecular Pathology of Urothelial Carcinomas (PD Dr. Tatjana Vlajnic, USB)

- [0h45] Practical/Hands-on: real-life cases, Part 1 (Dr. Ilaria Alborelli, USB, Dr. Ivana Bratic, USB, Valeria Perrina, USB)

- [1h]Practical/Hands-on: real-life cases, Part 2 (Dr. Ilaria Alborelli, USB, Dr. Ivana Bratic, USB, Valeria Perrina, USB)

Day 3 – New cutting-edge Technologies in Molecular Pathology

- [1h] Advances in liquid biopsies (CTCs) (Prof. Dr. Nicola Aceto, ETH Zürich)
- [1h] Single cell sequencing (Dr. Guglielmo Roma, GSK, Italy; VIRTUAL)
- [0h45] Molecular Pathology of Breast and Endometrium Carcinoma (PD Dr. Simone Münst, USB)
- [14h15-15h00] Molecular Pathology of Soft Tissue and Bone Tumors (Prof. Dr. Daniel Baumhoer)
- [1h] BRCAness, HRD etc. (Prof. Dr. Tom McKee, HUG)
- [0h45] Molecular Pathology of Gastrointestinal Tumors (PD Dr. Matthias Matter, USB, Prof. Dr. Luigi Terracciano, University of Basel)
- [1h] Guidelines for diagnostic reporting (PD Dr. Matthias Matter, USB)

Day 4 – Results, Data Interpretation, data usage, etc.

- [1h] How are variants classified? What is considered clinically significant? (Dr. Ilaria Alborelli, USB)
- [1h] Data handling and IT regulations (Dr. Thierry Sengstag, University of Basel, sciCORE)
- [1h] Computational Analysis (Dr. Charlotte Ng, DBMR University of Bern)
- [1h] Analysis of real-life cases using –omics technologies (Dr. Salvatore Piscuoglio, USB)
- [1h] Cell-Free DNA (Prof. Dr. Davide Rossi, IOSI, Bellinzona)
- [0h45] Methylome Analysis (Dr. Jürgen Hench, USB)
- [0h45] Nanopore Sequencing (Dr. Jürgen Hench, USB)
- [1h] Guidelines for diagnostic reporting (PD Dr. Matthias Matter, USB)
- [0h45] Wrap up of the day, questions & answers

Module 3
Clinical bioinformatics

Dates

- 17, 18 March; 31 March, 1 April 2023 (28h presential teaching).

Location

- Lausanne, University of Lausanne, campus UNIL-Sorge, building Amphipôle.

Main topics

- Data pre-processing
- Read mapping
- Variant calling
- Quality control
- Variant annotation
- Hardware, security, privacy
- Artificial intelligence (AI) basics
- AI current and future applications

Learning objectives for participants

- Communicate efficiently with bioinformaticians.
- Describe a bioinformatics analysis pipeline to call mutations from NGS data.
- Perform quality control at the run, read and variant levels.
- Use off-the-shelf bioinformatics tools to annotate and support the interpretation of variants.
- Consider hardware, security and privacy issues when managing omics data.
- Understand how artificial intelligence contributes to and will further impact personalized oncology.

Prerequisites to attend the module

- Modules 1 and 2, or equivalent knowledge.

Module coordinators

- Dr. Aitana Neves (SIB), Valérie Barbié (SIB)

Course format

- Lectures, hands-on, exercises and group discussions.

Day 1 – Somatic and germline variant calling

- [0h45] Introduction and general overview (Dr. Aitana Neves, SIB)
- [1h45] Pre-processing and quality control (Dr. Aitana Neves, SIB)
  - HANDS-ON: Reads pre-processing.
- [1h] Sequence alignment and read mapping (Dr. Aitana Neves, SIB)
- [1h30] Bioinformatics for RNA-seq and CHIP-seq (Agnieszka Kraft, ETHZ)
- [1h30] HANDS-ON: Exploring BAM files (Dr. Yann Christinat, HUG/SIB; Dr. Aitana Neves, SIB)
- [0h30] Sequencing depth, genome and gene coverage, variant frequency (Dr. Aitana Neves, SIB)
- [1h] Variant calling (Dr. Edoardo Missiaglia, CHUV)

Day 2 – Variant quality control and annotation

I. QC at the variant-level

- [0h30] Example case (Dr. Yann Christinat, HUG/SIB).
- [1h15] HANDS-ON: Technical artifacts (Dr. Yann Christinat, HUG/SIB)
- [0h30] Copy number variants (CNVs) and other structural variants (SVs) (Dr. Yann Christinat, HUG/SIB)
- [0h30] HANDS-ON on SVs in IGV (Dr. Yann Christinat, HUG/SIB)

II. Variant annotation

- [0h45] Effect and functional impact (Dr. Aitana Neves, SIB)
- [1h30] HANDS-ON (Dr. Yann Christinat, HUG/SIB)
  - Genes, transcripts and HGVS nomenclature.
  - Spotting germline variants and assessing clonality.
  - Annotation using bioinformatics tools.
- [0h15] DISCUSSION: Beyond gene panels (Dr. Yann Christinat, HUG/SIB; Dr. Aitana Neves, SIB)

III. IT infrastructure and data management for NGS analysis

- [1h30] All you need is IT: a study case on all that's hidden (Florent Tassy and Valérie Barbié, SIB)

Day 3 – What next?

- [2h] Risks and probabilities for the interpretation of genetic results (PD Dr. Frédéric Schütz, UNIL/SIB)

- [2h30] Molecular modeling: predicting the impact of variants on proteins (Prof. Dr. Vincent Zoete, UNIL/CHUV/SIB)
    - HANDS-ON: Impact of mutations on proteins 3D structure

- [1h30] Computational Cancer Pharmacogenomics (Dr. Michael Menden, Helmholtz München) VIRTUAL

- [1h30] Personalized cancer immunotherapy: predicting neo-epitopes (Prof. Dr. David Gfeller, UNIL/CHUV/SIB)

Day 4 – Artificial intelligence: basics and applications

- [1h30] Machine learning basics (Dr. Aitana Neves, SIB)

- [1h] Introduction to image analysis (Dr. Andrew Janowczyk, CHUV)

- [1h15] HANDS-ON: Features extraction (Dr. Andrew Janowczyk, CHUV)

- [2h] HANDS-ON: predicting diagnosis from the extracted features (Dr. Andrew Janowczyk, CHUV)

Module 4
Clinical oncology

Dates

- 12, 13 May; 26, 27 May 2023 (28h presential teaching).

Location

- Basel, Basel University Hospital.

Main topics

- Tumor Physiology
- Tumor Immunology
- Cancer Statistics and Epidemiology
- Prognostic and Predictive Markers
- Targeted Therapies in Clinical Oncology
- Risks / probabilities for the interpretation of genetic results and counseling
- Clinical Trials in Molecular Oncology
- Molecular Tumor Board

Learning objectives for participants

- Describe main intracellular signaling pathways in solid tumors and molecular aberrations hampering this signaling.
- Get detailed knowledge of immunological mechanisms and how these may be used to optimize therapeutic approaches.
- Get a basic understanding of the principles underlying the design and analysis of clinical trials in oncology.
- Understand the importance of predictive markers in molecular oncology.
- Get familiar with the most frequent molecular aberrations in solid tumors and routinely used targeted therapies.
- Learn about genetic counseling and its implications for patients and families.

Prerequisites to attend the module

- Modules 1, 2, 3 or equivalent knowledge.

Module coordinators

- Prof. Dr. Dr. Sacha Rothschild (KSB), Prof. Dr. Dr. Andreas Wicki (UZH), PD Dr. Dr. Benjamin Kasenda (USB)

Course format

- Lectures, exercises and group discussions.

Day 1 – Tumor Biology, Epidemiology and Basic Concepts of Cancer Therapy

- [1h] Welcome. Cancer statistics and epidemiology (PD Dr. Dr. Benjamin Kasenda, USB)

- [1h] Familiar cancer, cancer genetics (Prof. Karl Heinimann, USB)

- [2h] Basic concepts of cancer therapy: (Prof Dr. Dr. Sacha Rothschild, KSB)
    - Surgery, radiation therapy, systemic therapy
    - Adjuvant, neoadjuvant, palliative
    - Markers for systemic therapy: prognostic, predictive
    - Definitions: OS, PFS, ORR, etc.

- [2h] Tumor biology: from molecular biology of cancer to targets for anti-cancer drugs (Dr. Nicola Miglino, KSBL)
    - What are the hallmarks of cancer (Weinstein/Hanahan)?
    - What hallmarks are druggable?
    - Clinical data for drugs targeting hallmarks of cancer
    - Clinical data for markers of benefit in targeted therapies
    - Mechanisms of resistance to targeted therapies

- [1h] Questions & Answers, wrap-up of the day

Day 2 – Tumor Immunology, Genomic Reports, Response Prediction

- [2h] Tumor immunology: how to get an immune response against cancer (Prof Dr. Dr. Heinz Läubli, USB)
    - What mechanisms prevent the immune system to attack cancer cells?
    - How can we overcome silencing of the immune system?
    - What are druggable targets for immuno-oncology?
    - Clinical data for drugs targeting the immune system
    - Clinical data for markers of benefit in immune therapies

- [1h] Overview: what markers can predict outcome of therapies? (Prof Dr. Dr. Andreas Wicki, USZ)
    - Clinical parameters
    - Radiology parameters
    - Histology
    - Immunohistochemistry
    - FISH
    - Comparative genomic hybridization
    - Sequencing of DNA, RNA (genomics, transcriptomics)
    - Others

- [2h] Using genetic markers to predict therapy in cancer patients (Prof Dr. Dr. Andreas Wicki, USZ)
    - Bulk sequencing vs single cell sequencing
    - Tissue vs liquid biopsy
    - Targeted/amplicon-based sequencing vs whole exome/genome
    - Issue of interpretation
    - Service providers in Switzerland
    - Clinically relevant turn-around time
    - Integration of genetic data in clinical routine
    - DISCUSSION: ethical issues with genetic data (germline vs tumor DNA)

- [2h] How do you read a genomic report as a clinician? (Prof Dr. Dr. Sacha Rothschild, KSB)
    - Basics: sources of information, databases
    - Tips and tricks
    - HANDS-ON: interpret bulk DNA sequencing report

Day 3 – Clinical Oncology, Drug Development in Oncology

- [2h] Current clinical standard: Interpreting predictive markers (both genomics and others) in the big four: part 1 (colorectal and urogenital) (PD Dr. Arnoud Templeton, Claraspital Basel / Prof Dr. Dr. Andreas Wicki, USZ)

- [2h] Current clinical standard: Interpreting predictive markers (both genomics and others) in the big four: part 2 (breast and lung) (PD Dr. Marcus Vetter, KSBL / Prof Dr. Dr. Sacha Rothschild, KSB)

- [2h] Overview: drug development in oncology (PD Dr. Dr. Benjamin Kasenda, USB)
    - Preclinical
    - Early phase
    - Late phase and approval
    - Post marketing studies
    - Attrition rate
    - Clinical trial protocol, role of ethical committees and Swissmedic, informed consent
    - Primary endpoints vs secondary endpoints vs exploratory endpoints
    - Relevance of endpoints in clinical trials: OS, PFS, TTP, ORR, etc.
    - How to interpret a clinical trial
    - HANDS-ON: detailed analysis of current clinical trial protocols

- [1h] Questions & Answers, wrap-up of the day

- [0h30] CAS mini-thesis: presentation of topics and general explanations (Dr. Aitana Neves, SIB)

Day 4 – Predictive Biomarkers in Clinical Trials, Molecular Tumor Board

- [1h] Reimbursement: how to get a drug after your test predicts utility (Prof. Dr. Dr. Sacha Rothschild, KSB)
    - DISCUSSION: assurance of equal treatment for all patients ("off-label" use)

- [2h] Beyond genetics in therapy prediction (Prof Dr. Dr. Andreas Wicki, USZ)
    - Proteomics
    - Single cell phenotyping
    - Machine-based learning

- [1h30] Algorithm trials: how to transform data in a robust prediction (Prof. Dr. Dr. Andreas Wicki, USZ)

- [1h30] Point of care: decisions at the molecular tumor board (Prof. Dr. Dr. Sacha Rothschild, KSB / PD Dr. Dr. Benjamin Kasenda, USB)
    - How can a molecular board improve care for cancer patients?
    - HANDS ON: simulate molecular board

- [1h] Questions & Answers, wrap-up of the day

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