AI Health Innovation Cluster

- an initiative of the Innovation Campus Heidelberg Mannheim Health & Life Sciences

Project Proposals Call 2022

PostDoc Positions (& potentially Staff Scientists)

These positions have been submitted for PostDoctoral fellows. Nevertheless, also interested Staff Scientists can indicate their interest and PIs will make the final decision.

AIH1: COmorbidity modeling IN spinal Cord Injury and DEpression (**COINCIDE**)

Abstract: Depression is a highly frequent and severely disabling condition affecting approximately 40% to 60% of patients with traumatic spinal cord injury (SCI). It has serious consequences for the short- and long-term rehabilitation of individuals with SCI, and is associated with an increased suicide risk. However, the biology of depression in SCI is poorly understood and no biological tools exist that could aid in identifying at-risk patients. COINCIDE, an interdisciplinary project focusing the development and application of artificial intelligence methods to characterize the mechanisms underlying depression in SCI, aims to address this and provide the basis for the development of novel diagnostic and predictive tools. The project will develop and apply multi-task machine learning approaches to characterize the link between neurological SCI deficits and depression-relevant brain function. The project builds on already available data from SCI patients, as well as large-scale brain-functional data acquired in healthy controls, as well as patients with major depressive disorders. COINCIDE will then determine genetic and epigenetic associations in the same individuals, to characterize the biology of depression in SCI, and provide the basis for the development of novel diagnostic and predictive tools.

	Coordinator	Partner 1
PI	Emanuel Schwarz, PhD	Prof. Dr. Norbert Weidner
Institution	Central Institute of Mental Health (CIMH) Department of Psychiatry and Psychotherapy Mannheim	Heidelberg University Hospital (HD) Spinal Cord Injury Center Heidelberg

AIH3: Model Based AI for Zero-Shot/Rater-Independent Tumour Segmentation

Abstract: Supervised deep learning is the most promising technology for medical image segmentation, yet it requires a huge number of manual annotations. In addition, the segmentation quality highly varies depending on experience, subjective interpretation of tumour boundary. Recent publications refer to correct potentially false contours where the correction methodology hints that there is a tumour-specific texture relative to healthy tissue that allows to identify it. Recently, indicate that tumour segmentation might be possible without manual delineation, i.e. where the texture is really the dominant factor. For example, suggests an explicit feature extraction step combined with tumour growth model to find the contour, suggests generating synthetic tumour examples from random masks and tumour features.
This project clarifies by how far a tumour growth model information plus texture information allow to achieve comparable tumour segmentation results towards the state of the art.

Tumour regions are modelled as mixture of healthy tissue and tumour texture and from tumour growth models prior distributions of the shape are given. The goal is to find both the posterior distribution of the tumour shape, and in particular the MAP estimator. Annotation corrected data from brain and lung tumour using including nnU-net is taken as gold standard for comparison.

	Coordinator	Partner 1
PI	Jürgen Hesser	Klaus Maier-Hein
Institution	UMM	DKFZ

AIH4: Never split the difference – Machine Learning approaches to full-length transcript isoforms (ONT-SPLiT-seq) deconvolution.

Abstract: Mutations in the cardiac splice factor *RBM20* cause severe dilated cardiomyopathy (DCM) however, due to technological limitations, its regulatory network is only partially understood. SPLiT-seq is one of the few single-cell sequencing methods for the analysis of cardiomyocytes. In several split-pool rounds, fixed cells are randomly distributed into wells and transcripts are labelled with well-specific barcodes. The Steinmetz Lab (EMBL/Stanford) and Dieterich Lab (U. Heidelberg) combine their expertise on Bioinformatics, long-read Nanopore sequencing, RNA splicing and systems cardiology to rethink SPLiT-seq completely new. While conventional SPLiT-seq uses short Illumina sequencing, we will propel SPLiT-seq into the era of long-read, single-molecule Nanopore sequencing without compromising on accuracy and speed. We have recently established a combined protocol for SPLiT-seq and long-read sequencing (ONT-SPLiT-seq), which we propose to employ for the generation of a single cell isoform atlas of the murine heart. Next, we will identify cell populations that are prone to mis-splicing in mice with patient-relevant mutations in *RBM20*. Finally, we will integrate for the first time CRISPR-mediated perturbations with single-cell long read analysis to associate gene function to splicing in a high-throughput fashion. Combined, this approach will provide crucial insights into the *RBM20*-mediated splice network and its perturbation in DCM.

	Coordinator	Partner 1
PI	Prof. Dr. Christoph Dieterich	Prof. Dr. Lars Steinmetz
Institution	Bioinformatics and System Cardiology, Klaus Tschira Institute for Integrative Computational Cardiology and Department of Internal Medicine III, Medical Faculty Heidelberg, Universität Heidelberg	Genome Biology Unit - Steinmetz Group European Molecular Biology Laboratory (EMBL)

AIH6: Computational models of social interactions as a basis for adaptive gamified treatment approaches

Abstract: Social interactions form a key aspect of our everyday life. Through cooperative exchanges with our fellow human beings, we obtain behaviorally relevant information, as well as emotional support and protection. Disturbed or altered interaction behavior is a core feature in multiple psychiatric disorders, and is perceived as extremely burdensome and stressful, both by the affected individuals as well as by those in their immediate surroundings. Here, we propose to adopt modern Machine Learning (ML) algorithms from the reinforcement learning (RL) domain to model and emulate (alterations in) social interaction behavior in healthy and diseased individuals. Highly predictive models will then be applied to develop model-based adaptive gamified treatment approaches to modify individuals' behavior, as well as to gain mechanistic insights into the pathogenic processes that underlie maladaptive social interactions and their neural substrates. By encouraging positive social learning experiences, the proposed approach is hypothesized to promote learning of more advantageous interaction strategies, enhance cooperation, and strengthen core social competences. We expect that the development and validation of this ML approach will have strong clinical implications and could be integrated into treatment approaches for psychiatric disorders.

	Coordinator	Partner 1
PI	Dr. Georgia Koppe	Jun.-Prof. Dr. Christoph Korn
Institution	ZI	University Hospital Heidelberg

AIH7: Learning algorithms of neurofeedback success

Abstract: Neurofeedback enables people to self-modulate their brains: via a brain-computer interface, they observe their brain activation in real-time and deploy mental strategies to control brain activation. The technique can be used to non-invasively modulate brain activation in the treatment of mental disorders. Learning to self-control brain activation empowers disordered individuals with a skill to ameliorate the emergence of symptomatic behaviour at the brain level. In this project, reinforcement learning (RL) algorithms will be applied to predict how subjects choose mental strategies for brain self-regulation, and to describe how they evaluate the outcome of regulation. Parametrization of these two critical aspects of neurofeedback – choice and action – can equip neurofeedback software with RL algorithms to predict outcomes, based on the individual learning course. The vision of this research proposal is to develop AI approaches for neurofeedback that personalize treatments and that reduce failures of learning brain self-control via neurofeedback. We aim to increase treatment efficiency by providing an AI software implementation for monitoring neurofeedback success. The project leverages recent achievements in neurofeedback and learning algorithm development lead by research groups located at the Central Institute of Mental Health in Mannheim and the University Hospital Heidelberg to advance personalized treatment of psychiatric populations.

	Coordinator	Partner 1
PI	Christian Paret	Jun.-Prof. Dr. Christoph Korn
Institution	Central Institute of Mental Health	University Hospital Heidelberg

AIH8: Post-operative tissue fragment puzzle – How to improve patient care by solving a tissue-piece puzzle?

Abstract: Thinking of puzzles, you probably quickly think of a straightforward child's play? For computers, puzzling is well-known as a complex task, especially when it comes to irregularly shaped human tissue fragments with artifacts and sometimes missing pieces in between, as in our case.
In this project, surgical specimens from head and neck surgery will be reconstructed based on histological sections at the end of a complex work-up process. Determining exact anatomical situations is difficult and error-prone. Therefore, the aim is to determine the tumor size and location more correctly, in particular, to provide more reliable safety margins because patients with positive resection margins have a 2.5-fold increased risk of dying.
First, the specimen or puzzle fragment borders are determined using unsupervised CNN-based segmentation. Second, the borders are compared by sequence comparison (in analogy to Stanco et al.), and a graph-based approach determines the best puzzle piece combination. Third, the tissue cross-sections reconstructed in this way are reconstructed in 3D.
Finally, a 3D histological data set of a surgical specimen with additional resection specimens will be created, allowing to navigate and measure as in a radiological image data set.

	Coordinator	Partner 1	Partner 2
PI	PD Dr. med. Cleo-Aron Weis	PD Dr. med. Claudia Scherl	PD Dr. Karl Rohr
Institution	Institute of Pathology, Heidelberg	Department of Otorhinolaryngology, Head and Neck Surgery, Mannheim	Heidelberg University BioQuant Center, IPMB, Biomedical Computer Vision Group

AIH9: Estimating the health and economic burden induced by heatwaves in Germany using machine learning methods

Abstract: Climate change represents a major threat to human health, for instance due to heatwaves and other extreme weather events. In 2003 alone, about 70.000 excess deaths were attributed to heat within few weeks in Europe. The Lancet Countdown on health and climate change estimates the economic burden of heat induced excess mortality to correspond to 0.28% of the gross world product, with the greatest economic burden occurring in Europe. However, these costs are likely underestimated since very limited evidence is available as to what costs heat imposes on the health system, due to increased health service utilisation, and on society at large, due to reduced productivity and premature mortality. Our study addresses this knowledge gap by combining economic evaluation methods with machine learning methods, to estimate the societal cost of heatwaves in Germany for 2011-2021. To achieve our objective, we examine how machine learning approaches perform compared to the state-of-the-art time series regression approaches to estimate the impact and predict costs by linking nationally representative insurance data with historic temperature data. This represents a unique attempt to reconcile different disciplinary approaches to produce more valid and credible results than those derived by standard approaches and to promote methodological advances.

	Coordinator	Partner 1	Partner 2
PI	Prof. Dr. Manuela De Allegri	Prof. Dr. Joacim Rocklöv	Dr. Alina Hermann
Institution	Heidelberg Institute of Global Health, UKHD, Health Economic and Financing Unit, Hosting institution	Interdisciplinary Center for Scientific Computing, Heidelberg University	Heidelberg Institute of Global Health, UKHD, Climate Change, Nutrition, and Health Group

AIH10: Bias-aware machine learning for sepsis diagnosis with hyperspectral imaging

Abstract: Sepsis is one of the leading causes of death and critical illness, accounting for approximately 19.7 % of all global deaths in 2017. Early sepsis detection is a key factor in patient recovery because the mortality rate increases with every hour the antimicrobial intervention is delayed. Despite decades of clinical research, sepsis detection is limited to few (usually unreliable) biomarkers. Although a recent study found characteristic spectral signatures for septic and non-septic patients, automated machine learning-based diagnosis of sepsis from HSI data was hampered due to confounding factors being present in the data. Similarly, an increasing number of recent papers have revealed severe flaws in study design that lead to confounded algorithms. To address the issue of confounding biases in sepsis diagnosis based on HSI, we propose to develop a method capable of transforming confounded HSI measurements into a so-called confounder-invariant space, where the influence of confounding variables on sepsis diagnosis is minimized. Based on our expertise in the analysis of confounders in HSI data, we will build an extensive database comprising HSI and digital patient data of septic and non-septic patients. This will serve as the basis for our approach to confounder-invariant representation of HSI data for sepsis diagnosis.

	Coordinator	Partner 1
PI	Prof. Dr.-Ing. Lena Maier-Hein	Univ. Prof. Dr. med. Markus A. Weigand
Institution	Computer Assisted Medical Interventions German Cancer Research Center - Deutsches Krebsforschungszentrum DKFZ	Department of Anesthesiology University Hospital Heidelberg

AIH11: Combined **E**pigenomic and **R**ad**I**omics analysis of lung-**CA**ncer biopsies to evaluate tumor risk and to study the role of the tumor microenvironment **(ERICA).**

Abstract: Lung cancer is the leading cause of cancer-death worldwide, partly because of late diagnosis. The most prevalent type, non–small cell lung cancer (NSCLC) accounts for 85% of all lung tumors. Gold standard in lung cancer prognosis and therapy decision is based on tumor stage classification (TNM). Using radiological examinations such as CT and MRI, TNM is determined based on tumor size and extension. Very often patients grouped by TNM stage undergoing the same therapy present different outcome. Tumour heterogeneity, especially epigenetic alterations, including DNA methylation, histone modifications, and noncoding RNA expression play a crucial role in cancer development and response to therapy. To gain a holistic understanding of the patient and its tumor we should integrate the analysis of all clinical, molecular and imaging features in one setting. In this proposal we hypothesize that radiomic features of tumor regions, detected on CT scans, could be correlated with tumor epigenomes reflecting diverse microenvironmental stimuli. To achieve this, DNA methylation profiles of tumor biopsies will be correlated with radiomic features extracted from the same tumor. Integrating precise molecular information able to stratify diverse tumors with imaging features should allow improving tumor diagnosis, classification, patient stratification and support treatment optimization.

	Coordinator	Partner 1	Partner 2
PI	Prof. Christoph Plass	Prof. Hans-Ulrich Kauczor	Dr. Thomas Muley
Institution	*Division of Cancer Epigenomics* DKFZ	*Clinic for Diagnostic and Interventional Radiology* University Hospital Heidelberg (UKHD)	*Lung Biobank* University Hospital Heidelberg (UKHD-Thoraxklinik)

AIH12: Deep Learning-Based Spatial Alignment of High-Resolution 3D Microscopy Images of the Brain

Abstract: Understanding brain function and pathology requires quantitatively analyzing different brain regions as well as studying multiple subjects. In recent years, remarkable progress in 3D imaging technologies has been achieved, which allows investigating the brain at high resolution. In particular, light-sheet fluorescence microscopy enables fast acquisition of whole-brain images at cellular resolution without tissue cutting. A central task is the spatial alignment of the 3D image data with an atlas to map relevant brain regions and transform images of different subjects into a common space. While previous work considered microscopy images of healthy brains, the focus of this project is on images with pathologies, which are much more challenging to cope with. The aims of this project are (1) to develop a novel deep learning method for spatial alignment of high-resolution 3D light-sheet fluorescence microscopy images with brain tumors, (2) to apply the method for 3D image - atlas registration of the mouse brain and for mapping relevant brain regions, and (3) to extend and apply the method to spatially align 3D light-sheet fluorescence microscopy images with 3D MRI data so that complementary image information can be exploited.

	Coordinator	Partner 1
PI	PD Dr. Karl Rohr	Dr. Sevin Turcan
Institution	Heidelberg University BioQuant Center, IPMB Biomedical Computer Vision Group	University Hospital Heidelberg (UKHD) AG Neuro-Oncology of Lower Grade Gliomas

AIH13: Diagnostic molecular profiling of undifferentiated small round cell sarcomas by AI-guided morphology inspection

Abstract: Undifferentiated small round cell sarcomas (SRCSs) are a dynamic and growing group of highly aggressive mesenchymal cancers mainly affecting children, adolescents, and young adults. They are overall characterized by their histomorphological similarities and poor prognosis. In past years, several distinct SRCS entities emerged in reference to Ewing sarcoma as the prototype of a highly undifferentiated small-round cell tumor, which is driven by pathognomonic *FET::ETS* fusions (in 85% *EWSR1::FLI1*). Indeed, the advent of modern high throughput technologies had a transformative effect on the discovery and reclassification of SRCSs. Accumulating genetic, epigenetic, and transcriptomic data in integration with emerging clinicopathological information and experimental models culminated in the inclusion of the new chapter ‘undifferentiated SRCSs of bone and soft tissue tumors’ in the 2020 WHO classification of tumors of soft tissues and bone. The most prevalent fusion-driven morphological mimics of Ewing sarcoma, include *EWSR1/FUS::nonETS* round cell sarcoma (mainly *EWSR1/FUS::NFATC2*), *CIC*–rearranged sarcomas (mainly *CIC::DUX4*) and sarcomas with *BCOR* genetic alterations (mainly *BCOR::CCNB3*). Recent data show that although these SCRCs share a strikingly similar morphology, they are clinically distinct and should be treated differently. Hence, rapid and precise diagnosis is of utmost importance to assign the ‘correct’ patient to adequate treatment regimens. However, due to the rarity of these diseases, limited biopsy material, and the unavailability of sophisticated molecular pathology techniques in most diagnostic centers worldwide, misdiagnoses are common in SRCSs.

Hence, to overcome this barrier, this project will leverage AI-based classification of conventional histology (H&E) sections to reliably diagnose EwS and other SRCSs without the need of expensive molecular work-up. In addition to classification of tumor type, our large cohort of specimen with various fusion partners will allow exact subtyping for specific genetic events. As a result, we will provide a validated algorithm that allows to perform rapid and robust state-of-the-art diagnostics of SCRCs with minimal resources, which will be of great advantage especially for developing countries.

	Coordinator	Partner 1
PI	Prof. Dr. Dr. Thomas Grünewald	Prof. Dr. Dr. Felix Sahm
Institution	Division Head (W3, tenured) Division of Translational Pediatric Sarcoma Research (B410) Hopp-Children's Cancer Center (KiTZ) & German Cancer Research Center (DKFZ)	Dept. of Neuropathology University Hospital Heidelberg

AIH14: Identification of plasma proteins causally linked to cancer development through integrated deep and machine learning

Abstract: Establishing causal relationships between plasma protein levels and cancer development is essential for understanding disease aetiology and improving current cancer prevention. Problematically, differences in plasma protein levels between cases and healthy controls may anticipate disease (protein→cancer) or arise as a consequence of the tumour (cancer→protein). Single nucleotide polymorphisms (SNPs) associated with plasma protein levels can be used to infer directionality, distinguishing proteins that precede disease and thus inform risk prediction and precision prevention. We aim to apply deep and machine learning to a unique collection of prospective plasma samples from 104 gallbladder cancer case-control pairs with extensive epidemiological and SNP data. After generating mass-spectrometry (MS) proteomics data for this cohort, we will use deep neural networks for differential plasma proteome profiling based on MS features. We will then apply advanced machine learning techniques (robust LASSO) to predict plasma protein levels based on individual SNP data, finally leading to novel "protein→cancer" associations. Collectively, the sequential application of two AI tools (deep and machine learning) to newly generated proteomics data for a unique collection of prospective plasma samples, and to large existing genetic-proteomic cancer data, will provide a blueprint towards risk prediction for other disease entities using different types of molecular data.

	Coordinator	Partner 1
PI	Jeroen Krijgsveld	Justo Lorenzo Bermejo
Institution	Division of Proteomics of Stem Cells and Cancer, DKFZ	Statistical Genetics Research Group, UKHD

AIH15: Increased knowledge on AI-based diagnostics: conducive to user acceptance?

Abstract: Deep learning image analysis algorithms have shown their potential to improve skin cancer screening in numerous studies. However, these studies have largely been conducted in artificial settings, and real clinical implementation of such algorithms in clinical practice is mostly lacking. One prerequisite for a successful translation into the clinic is user acceptance, which may be correlated with a better, if still basic, understanding of the way these algorithms work. In addition, the introduction of AI into medical diagnostics significantly increases the complexity of physician consultations. It is challenging for physicians to comprehensively address AI methods, statistical implications and individual consequences in conversation.
We therefore propose to generate modular information on the function, potential uses and pitfalls of deep learning-based image analysis algorithms in Dermatology in the form of short movie sequences. Different combinations of the information modules will then be shown to potential users (both dermatologists as direct users and skin cancer screening participants as indirect users).
Their impact on the users' willingness to employ/accept them as an integral part of skin cancer screening, as well as the direct and indirect users' psychobiological stress responses during their interaction will be assessed as outcomes.

	Coordinator	Partner 1
PI	Prof. Dr. B. Ditzen	Dr. T. Brinker
Institution	UKHD	DKFZ

AIH16: AI-based study of imaging biomarkers in pediatric brain tumors

Abstract: Since the publication of the 2016 WHO CNS Tumor Classification, and especially with the recent 2021 5th Edition, brain tumors have been increasingly stratified in molecularly defined subclasses with improved prognostic and predictive value over the traditional histological classification. Previous studies on small data samples have demonstrated the potential of MR-based radiomics and imaging features to enable a non-invasive classification of pediatric brain tumors. However, as opposed to adult brain tumors, no large-scale studies have been performed in this field, and deep learning techniques so far have never been investigated. With our project, we aim to bridge the gap in the current imaging research knowledge between adult and pediatric brain tumors, and namely to apply radiomics- and deep learning-based methods to study novel biomarkers for prognostic and predictive modeling of pediatric CNS tumors, as well as to identify specific imaging phenotypes that correlate to molecularly defined tumor subtypes.

	Coordinator	Partner 1	Partner 2
PI	PD Dr. med. Philipp Vollmuth	Dr. David Jones	PD Dr. med. Felix Sahm
Institution	Heidelberg University Hospital	DKFZ Heidelberg	Heidelberg University Hospital

AIH17: Leveraging surrogate modelling with machine learning to predict microbiota contribution to the host metabolism of medical drugs

Abstract: Recent studies have demonstrated that gut microbes can substantially contribute to the host metabolism of medical drugs *in vivo*, thus potentially changing drug pharmacokinetics and contributing to interpersonal differences in drug response. Physiology-based pharmacokinetic models (PBPK) that explicitly include microbiota drug metabolism in the gut were able to quantify bacterial contribution to drug metabolite levels in systemic circulation. However, this approach requires time-resolved quantitative measurements of drug and metabolite concentrations in different tissues, which are hard and expensive to obtain in animal models, and practically impossible to obtain in humans.
The goal of this project is to leverage surrogate modelling based on PBPK and machine learning together with data from *in vitro* experiments with gut microbes and *in vivo* animal models, to predict drug pharmacokinetic profiles in the host and assess microbiota contribution to the drug metabolism for a given drug. This project will result in development of predictive models to assess microbiota contribution to the host drug metabolism, which will help to reduce animal experiments, to extend this approach to human studies, and to identify drugs for which microbiota contribution should be investigated further to inform drug development and personalized treatment strategies.

	Coordinator	Partner 1
PI	Dr. Maria Zimmermann-Kogadeeva	Prof. Dr. med. David Czock
Institution	EMBL	Universitäts Klinikum Heidelberg

AIH18: Machine-learning enhanced deep-tissue imaging for decoding neuron-glia interactions

Abstract: Our brain consists of an equal proportion of broadly classified groups of cells called neurons and glia. Although glial cells constitute 50% of the brain, the mechanisms by which glia connect and communicate with the neurons in health and disease remain unknown. To understand neuron-glia interactions, we require novel non-invasive optophysiological technologies, which enable investigation of the structure and function of glial cells in intact brains. We have recently developed intravital deep-tissue multiphoton microscopy with adaptive optics which can deliver volumetric images at sufficiently high speed and resolution. The bottleneck in the analysis of complex cellular communication *in vivo* now lies with the image analysis part of the pipeline which needs to extract the signals from large, noisy image volumes, at a high throughput rate. The aim of our proposal is to bring together AI-based computer vision techniques and methods of computational neuroscience to reconstruct the cell morphology and calcium signals in an accurate and reliable manner. Furthermore, we will make the resulting tools accessible to a wider neuroscience community. AI-driven computational analysis methods will play a key role in our multidisciplinary approach to study physiology and pathophysiology of the neurons and glia in the intact brain.

	Coordinator	Partner 1	Partner 2
PI	Amit Agarwal	Robert Prevedel	Anna Kreshuk
Institution	HU/UKHD	EMBL	EMBL

AIH19: Combining Multiplexed Imaging and Computational Frameworks to Reveal Cellular Metabolic Interactions in the Human Tumor Microenvironment

Abstract: Significant transition points in human cancer span tumor initiation, expansion, metastasis, and therapeutic resistance. Importantly, these transitions involve complex interactions between cells within the tumor microenvironment (TME). Novel spatial-omics technologies now provide an opportunity to interrogate this complexity at unprecedented resolution. In this project, we will combine a novel proteomic imaging platform (multiplexed ion beam imaging: MIBI) with machine learning frameworks to extract clinically significant cellular interactions from human melanoma tissue. MIBI visualizes the expression and spatial distributions of up to 40 proteins and thus enables deep analysis of the TME. Extracting knowledge from multiplexed spatial data requires the development of scalable computational methods that can leverage the availability of the spatial context. We have recently developed such approaches, with an emphasis on leveraging prior biological knowledge to extract mechanistic insights. Bringing together this novel cutting-edge imaging technology with AI-supported data analysis frameworks will advance our understanding of cellular interactions and their functional consequences and may thus lead to novel biomarkers and potential therapeutic targets for human cancer.

	Coordinator	Partner 1
PI	Dr. Felix J. Hartmann	Prof. Dr. Julio Saez-Rodriguez
Institution	German Cancer Research Center (DKFZ)	University of Heidelberg

AIH20: Deep learning analysis of rat facial expressions in oxytocinmodulated emotional states

Abstract: We aim to create an AI-based analysis tool for automatized assessment of facial expression in rats. The rats will display different emotional states under the modulation of specific oxytocin circuits in brain areas linked to key emotional states. A fear grimace which head fixed rats display when subjected to a fearful stimulus will be “neutralized” by stimulating the oxytocin system in the central nucleus of the amygdala. To pay tribute to the range of emotions we will also investigate positive emotional states upon social interaction. Therefore, we intend to recreate the facial expression of affection occurring when animals are subjected to a sibling, by stimulating oxytocin receptor cells in the nucleus accumbens. The ground breaking new approach of looking into facial expressions will allow us to gain a first level readout of the rats’ emotional state and thus understand for the first time what the animal actually feels. This method will not only be helpful in oxytocin research but could change the whole rodent research field dedicated to investigate various emotional states, including aversive and rewarding stimuli.

	Coordinator	Partner 1
PI	Prof. Dr. Valery Grinevich	Prof. Dr. Klaus Maier-Hein
Institution	CIMH/ZI	DKFZ

AIH21: Automated detection and molecular characterization of micronuclei in cancer cell lines and tumor tissues.

Abstract: Chromosomal instability (CIN) is a hallmark of cancer and manifests as structural or numerical alterations in the chromosomes. CIN is associated with widespread therapeutic resistance, immune evasion, and metastasis. Despite its prominent role, no druggable molecular targets are currently known. To enable a systematic assessment of CIN, we will leverage genetic constructs of members of the kinesin family to generate various levels of chromosomally unstable cell lines. The most common way to assess CIN is by micronucleus scoring, which is usually performed manually by counting micronuclei or abnormalities under a microscope. Here we propose to (i) create a computational approach to automatically count micronuclei and associated abnormalities in immunofluorescence images. Next, (ii) we will perform spatial omics analysis on those cell lines to create a molecular profile of CIN. Finally, (iii) we will apply the here developed computational methods to human tissue samples (connected to clinical information) to uncover potential druggable molecular targets for CIN. The spatial omics technologies and single cell analysis pipelines created by AG Schapiro combined with the image analysis and machine learning capabilities by AG Hamprecht provide a unique setup for this interdisciplinary project.

	Coordinator	Partner 1
PI	Denis Schapiro	Fred Hamprecht
Institution	Institute for Computational Biomedicine and Institute of Pathology, Heidelberg University Hospital	Heidelberg Collaboratory for Image Processing (HCI), Interdisciplinary Center for Scientific Computing (IWR) and Department of Physics and Astronomy, Heidelberg University

AIH22: Deciphering tumor cell networks with artificial intelligence

Abstract: This proposal is based on the recent discovery that the nervous system plays a pivotal role in cancer formation, progression and therapy resistance resulting in the emerging research field ‘Cancer Neuroscience’. This project aims at adapting methods for microscopy image acquisition and analysis using state-of-the-art artificial intelligence algorithms to segment dynamic, multicellular tumor networks and their microenvironment in in-vivo light and ex-vivo electron microscopic datasets. It will require strong interdisciplinary interaction and the development of novel microscopy and subsequent analysis approaches to uncover novel aspects of tumor biology that has the potential to transform oncology research and therapy.

	Coordinator	Partner 1
PI	Anna Kreshuk	Varun Venkataramani
Institution	EMBL	University Hospital Heidelberg

AIH23: Medical Object Detection for Holistic Image Understanding

Abstract: This project will develop cutting-edge deep learning technologies with a focus on recent detection methods that are applicable to 3D medical images. The ultimate goal is achieving strong representations that allow a more holistic image understanding and solving of multiple tasks within one network. Specifically, we will be working on common interfaces for medical object detection, with standardized and sound object centric evaluation, aiming at methods that can either be automatically adapted to various datasets and or that can ultimately learn joint representations for various tasks. We are also interested in establishing a new open benchmark for the public in this direction.

	Coordinator	Partner 1
PI	Klaus Maier-Hein	Jürgen Hesser
Institution	DKFZ	UMM

AIH24: Building a framework for the integrative analysis of clinical parameters and multi-omics data in cancer care

Abstract: The increasing availability of high-dimensional biomedical data creates the opportunity to optimize cancer care towards better individualized treatment, including prevention of complications after surgery. Simultaneous characterization of tumours and patient constitution may help to identify individuals at high risk of severe post-surgical complications, often excluded from prospective studies. While multi-omics data is informative on tumour aggressiveness and evolutionary plasticity, it could be combined with clinical data to improve assessment of patient fragility and prediction of post-surgical complications such as sepsis.

This pilot study will initialize a strategic partnership between the UMM and the DKFZ to integrate these data levels into a holistic approach for patient stratification. Several thousand digital health records and multi-omics datasets of cancer patients will be analysed using supervised and unsupervised machine learning techniques to identify relevant features for short-term and mid-term outcomes. The candidate will address fundamental questions including the integration of longitudinal clinical and laboratory parameters into the training of AI algorithms, the implementation of efficient transfer learning for different cancer entities and feature selection of prospective studies.

The upcoming decade will shape how AI will be integrated into clinical care, and this project is an opportunity to promote this development.

	Coordinator	Partner 1	Partner 2
PI	Feuerbach	Schneider-Lindner	Westermann
Institution	DKFZ	UMM / Medical faculty Mannheim	KITZ/DKFZ

AIH25: Machine learning for subcellular pattern discovery in spatial multi-omic data

Abstract: The wave of single-cell sequencing applications in the last decade gave rise to a highly complex and heterogeneous picture of cellular types and states in biological samples. Despite these advances, the high-dimensional spatial organization within individual cells remains extremely challenging to assay and analyze.
To address this, we here propose an interdisciplinary project that tightly couples multiplex protein and RNA imaging (Saka) and integrative computational modelling (Stegle) to enable high-throughput characterization of subcellular localisation patterns in health and disease. The core aim of the project is to retrieve and characterize the full information content of subcellular resolution multi-omic data, including resolving rich subcellular patterns in single cells.

	Coordinator	Partner 1
PI	Oliver Stegle	Sinem Saka
Institution	Institution Division of Computational Genomics & Systems Genetics, DKFZ	Genome Biology Unit, EMBL Heidelberg

AIH26: AI-guided design of functional RNA origami structures

Abstract: Bottom-up synthetic biology and DNA/RNA nanotechnology are two distinct frontier fields. What unites them is their rational engineering mindset, their common understanding that precise function needs precise components – with the aim to either build a cell or to repurpose nucleic acids for nanoscale construction. Here, we will explore how AI-guided evolutionary approaches can lead to a step change in the functional complexity of DNA/RNA-based nanomachines and synthetic cells alike because they allow us to explore a large design space. In particular we will probe RNA-lipid interactions with AI-accelerated multi-scale simulations. This alone will provide insights on the potential role of RNA-lipid interactions at the origins of life. Moreover the simulations yield design instructions for functional RNA origami structures, in particular (i) RNA nanopores and (ii) vesicle division inducing RNA structures. These structures will be implemented experimentally and tested in lipid vesicles as synthetic cellular compartments. We thereby envision an interdisciplinary contribution to the field of bottom-up synthetic biology as well as applicable RNA origami-based tools for nanopore sensing and as genetically encoded biophysical probes in cell biology.

	Coordinator	Partner 1
PI	Kerstin Göpfrich	Frauke Gräter
Institution	Max Planck Institute for Medical Research	HITS

AIH27: Machine learning vs logistic regression: valid Propensity-Score-estimation for observational studies in a research platform

Abstract: Observational studies evaluating real world treatment effects require identification of appropriate comparator groups. For this, a propensity score (PS)-based method is commonly used. Both logistic regression and machine learning (ML) methods can be applied for PSestimation, with the favourable method dependent on factors like study size and covariate characteristics. This project will support local and federated clinical data analyses by determining the optimal PS-estimation method for a range of common study features from our local research context at UMM, DKFZ and NCT. Pre-existing and the candidate's own simulation study results will also facilitate definition of an algorithm for recommendation of study-specific optimal PS-estimation methods to be integrated in a software application for control selection currently developed jointly with the digital research environment affiliated with Mannheim's data integration centre. This way, advanced epidemiological and ML methods will be made easily accessible supporting valid state-of-the art data analyses for the cluster and beyond.

	Coordinator	Partner 1	Partner 2
PI	PD. Dr. Dr. Verena Schneider-Lindner	Prof. Dr. Martin Lablans	Prof. Dr. Richard F. Schlenk
Institution	Department of Anesthesiology and Surgical Intensive Care Medicine Medical Faculty Mannheim, Heidelberg University	German Cancer Research Center, Federated Information Systems, Heidelberg Complex Data Processing in Medical Informatics, University Medical Center Mannheim	NCT-Trial Center, National Center for Tumor Diseases, Heidelberg University Hospital and German Cancer Research Center, Heidelberg

AIH28: Gut microbiome profile as a diagnostic marker in eating disorders.

Abstract: The gut microbiota is essential in the regulation of appetite and body weight and has been found to be altered in eating disorders. Previous research has identified gut microbiota dysbiosis as a potential pathognomonic aspect of Anorexia Nervosa, Bulimia Nervosa and Binge Eating Disorder. Changes in microbiota composition and production of bioactive metabolites may contribute to the development and/or maintenance of eating disorders. In this project, we plan to longitudinally assess gut microbiota composition and function in patients with eating disorders during in-house treatment to gain a better understanding of microbiome changes associated with progression or remission of eating disorders. In line with similar investigations in obesity, where variations in the gut microbiome allow classification of individuals according to their risk of further weight gain, we aim to establish an AI-based diagnostic procedure for the classification of patients into different profiles of disease progression.

	Coordinator	Partner 1
PI	Prof. Dr. Hans-Christoph Friederich	Dr. Georg Zeller

Institution	Centre for Psychosocial Medicine Department of General Internal Medicine and Psychosomatics, University Hospital Heidelberg.	Structural and Computational Biology Unit, EMBL Heidelberg

AIH29: Invertible Neural Networks in Biomedical Image Analysis

Abstract: Medical image computing and computer-assisted interventions hold great promise for reshaping clinical imaging and interventional healthcare. However, a major bottleneck on the way to clinical translation is that tasks such as image registration or tissue parameter estimation present ill-posed inverse problems for which there are no unambiguous, unique solutions. Invertible Neural Networks (INNs) are a type of normalizing flow architecture that can learn to represent ambiguity in the shape of posterior distributions. This project aims to successfully establish INNs in the domains of medical imaging and computer-assisted interventions by investigating (1) the key methodological issue of automatic mode detection, and (2) the application task of multimodal image registration. For the latter, this includes the design and implementation of a pipeline for clinical use.

	Coordinator	Partner 1
PI	Lena Maier-Hein	Ullrich Köthe
Institution	DKFZ Heidelberg	University of Heidelberg

AIH30: Multiplexed proteomics and transcriptomics to uncover spatial patterns of progressive neuroinflammation

Abstract: Ongoing tissue damage and sustained immune cell activation are hallmarks of chronic neuroinflammation and key features of progressive multiple sclerosis, various inflammatory muscle diseases and brain involvement in COVID19. Despite a relatively good control of peripheral immune activation, the precise mechanisms underlying smoldering tissue inflammation and eventually damage and loss of neurons and muscle cells are unknown.
Various technologies are available to measure the molecular signatures of these inflammations including imaging mass cytometry, high-resolution confocal imaging, RNA in situ hybridization and tissue RNA-sequencing in addition to single-nucleus RNA-sequencing. While the experimental methods are becoming more mature, computational methods to integrate these different readouts are a critical unmet need.
The aim of this project is therefore to create novel machine learning approaches for multi-omics integration to decipher patterns of progressive neuroinflammation and identify new spatially-resolved cues for a better characterization of disease progression and treatment of patients.

	Coordinator	Partner 1
PI	Denis Shapiro	Lucas Schirmer
Institution	Heidelberg University Hospital	University Medical Center Mannheim

Staff Scientist Positions

AIHI: Data science engineer single cell / spatial omics in precision oncology

Abstract: Our overall aim is to understand variable treatment response to modern cancer therapies, improve treatments to increase response rates, and design individualised treatment regimens based on patients' and tumours' molecular properties. We approach this aim using the latest molecular measurement technologies and machine learning. The technologies include transcriptome profiling at single cell resolution, other multi-omics approaches and spatially resolved assays such as highly multiplexed immunohistochemistry imaging. They are applied to investigate patient-derived tumour samples and ex-vivo tumour models. Our work is a highly interdisciplinary and dynamic collaboration between University Hospital Heidelberg and EMBL.

Your role will be to build a performant system for data and metadata management, engage in data curation together with domain scientists, and to engineer and apply data analytical workflows using tools from statistics, interactive visualisation and machine learning. E.g., a recurrent challenge is finding underlying low-dimensional manifolds in the high-dimensional molecular data that predict disease heterogeneity, disease trajectories, and treatment outcomes. We are looking for candidates who are excited to operate in the space spanned by these dimensions: data management, research software engineering, and biomedical discovery research.

The position is embedded in the existing collaboration between the two institutions through the MMPU group "Systems Medicine of Cancer Drugs" led by Dietrich and Huber. This team has a successful track record, an on-going set of grant-funded projects spanning biological discovery as well as method development research, and several joint PhD-students and postdocs.

	Coordinator	Partner 1
PI	Dr. rer. nat. Wolfgang Huber	Prof. Dr. med. Sascha Dietrich
Institution	EMBL MMPU co-director	Heidelberg University Hospital Centre for Internal Medicine, Clinic V

AIHII: Surgical AI platform – a core facility fostering translational research and clinical innovation for decision support in surgical oncology.

Abstract: Our AI innovation is to provide a platform for clinical translation of data driven decision support in surgical oncology. We aim to link data from the medical data integration center at UKHD with novel surgical data science algorithms developed at the DKFZ to be used by surgeon scientists in the labs and operating rooms of the surgical department.

In particular, the requested staff scientist will maintain and further develop the Kaapana platform that has been developed at DKFZ within the NCT-DSDSO-project to meet the crucial need for a platform within the surgical department of UKHD. Firstly, the platform will be used to extract multimodal surgical data from their primary sources and integrate it into the semantic data model of the MEDIC-environment of UKHD in order to obtain semantically enriched

structured data in a standardized format (FHIR, OpenEHR, ODM). Secondly, algorithms developed at DKFZ will be integrated into the real-time environment of the operating rooms within the surgical department. Finally, in order to facilitate surgical AI innovation for a larger community we will establish a core facility within the surgical department to support both, other clinician AI scientists at UKHD and basic scientist inside and outside DKFZ and UKHD.

	Coordinator	Partner 1	Partner 2
PI	Prof. Dr. Dugas	Dr. Wagner	Prof. Dr. L. Maier-Hein
Institution	Heidelberg University Hospital	Heidelberg University Hospital	DKFZ

AIHIII: Machine-learning enhanced deep-tissue imaging for decoding neuron-glia interactions [*also suitable for PostDoc*]

Abstract: Our brain consists of an equal proportion of broadly classified groups of cells called neurons and glia. Although glial cells constitute 50% of the brain, the mechanisms by which glia connect and communicate with the neurons in health and disease remain unknown. To understand neuron-glia interactions, we require novel non-invasive optophysiological technologies, which enable investigation of the structure and function of glial cells in intact brains. We have recently developed intravital deep-tissue multiphoton microscopy with adaptive optics which can deliver volumetric images at sufficiently high speed and resolution. The bottleneck in the analysis of complex cellular communication *in vivo* now lies with the image analysis part of the pipeline which needs to extract the signals from large, noisy image volumes, at a high throughput rate. The aim of our proposal is to bring together **AI-based computer vision techniques and methods of computational neuroscience to reconstruct the cell morphology and calcium signals** in an accurate and reliable manner. Furthermore, we will make the resulting tools accessible to a wider neuroscience community. AI-driven computational analysis methods will play a key role in our multidisciplinary approach to study physiology and pathophysiology of the neurons and glia in the intact brain.

	Coordinator	Partner 1	Partner 2
PI	Amit Agarwal	Robert Prevedel	Anna Kreshuk
Institution	HU/UKHD	EMBL	EMBL

AIHIV: AI for serological analysis of COVID-19 patients using multiplex microscopy assay

Abstract: The emergence of the novel pathogenic coronavirus SARS-CoV-2 and its rapid pandemic spread had dramatic consequences on human society across the globe. Continuous evolution of new viral variants affecting infectivity, disease severity and immune evasion has challenged the society's efforts to contain the virus. Mutations in the viral spike protein are of special interest, as all currently licensed vaccines against SARS-CoV-2 are based on the immune response to the spike. Early in the pandemic, we have established a microscopy-based assay which allowed for studies of population immunity to the original strain of the virus. We will now extend this work to simultaneously measure the levels of patient serum antibodies against different spike mutants and determine the patient's susceptibility to emerging variants. The assay will also detect auto-recognizing antibodies as major determinants of Long COVID. The approach relies heavily on the analysis of very large microscopy images. The aim of this project is to develop an image analysis pipeline based on state-of-the-art AI-based methods for segmentation and classification of complex cellular staining patterns. The pipeline needs to be implemented as a flexible solution to be employed in other clinically relevant projects within the Center for Integrative Infectious Disease Research and beyond.

	Coordinator	Partner 1	Partner 2
PI	Vibor Laketa	Anna Kreshuk	Constantin Pape
Institution	University Hospital Heidelberg	EMBL	University of Göttingen

AIHV: Generation of multiplex data and integration with electronic medical records for dimension reduction towards prediction of complications in critical illness

Abstract: The immune response to severe injury (trauma, infection, cancer…) and its treatment critically determines the risk of acute and difficult-to-predict clinical complications. Among these, sepsis and organ dysfunction predominate. New prognostic and diagnostic classifiers are urgently sought to improve patient outcomes. Electronic medical records (EMRs) in the intensive care unit (ICU) capture clinical courses at high resolution. Their integration with large-scale longitudinal immunophenotyping has potential to significantly advance classifier discovery by AI. To this end, the staff scientist will direct medium-throughput multiplex analyses of blood markers of immunity in 1100 available blood samples collected from 100 ICU patients and leverage expertise in processing EMR data at UMM and in application of AI for nonlinear dimensionality-reduction at DKFZ. Multiplex data will be integrated with EMR data from same patients and time points and analysed by uniform manifold approximation and projection (UMAP). Ground truth labels on sepsis and organ dysfunction will be projected onto resulting UMAP embeddings. We seek clusters associated with the onset of clinical complications and afferent trajectories of patient time for analyses of the clinical features/blood markers that essentially define them. We expect these features/markers to inform future patient stratification strategies and to represent potential classifiers for further investigations.

	Coordinator	Partner 1
PI	Lindner	Feuerbach
Institution	UMM / Medical Faculty Mannheim	DKFZ