ERAPerMed

NEWSLETTER 1

January 2019

ERA PerMed Results of the Cofunded Joint Translational Call 2018

"Research Projects on Personalised Medicine – Smart Combination of Pre-Clinical and Clinical Research with Data and ICT Solutions"

25 Successful consortia are funded with a total investment of about 25 million Euro for three years

ERAPerMed is funded under the ERA-NET Cofund scheme of the Horizon 2020 Research and Innovation Framework Programme of the European Commission Research Directorate-General, Grant Agreement No. 779282.

According to the new EU General Data Protection Regulation (GDPR) the ERAPerMed webpage informs on respective policies.

PERSONALIZED MEDICINE

refers to a medical model using characterization of individuals' phenotypes and genotypes for tailoring the right therapeutic strategy for the right person at the right time, and/or to determine the predisposition to disease and/or to deliver timely and targeted prevention. (Horizon 2020 and EC Conclusions (2015/C 421/03).

ERA-NET ON PERSONALISED MEDICINE (ERA PerMed)

ERA PerMed is a new ERA-Net Co-fund, supported by 32 partners from 23 countries and co-funded by the European Commission. To align national research strategies, promote excellence, reinforce the competitiveness of European players in the field of personalized medicine, and enhance the collaboration between European and non-EU countries, national funding organizations have agreed to launch Joint Transnational Calls for collaborative innovative research projects focused on personalized medicine.
50 consortia were selected to submit full proposals (first call 2018 and cofunded by the EC), which were reviewed by 23 evaluators from institutions affiliated with 15 countries. Following the Scientific Board Meeting in Madrid, **25** consortia were chosen to be funded with a total of about **25** million Euro for three years. These projects involve **133** research groups from **18** countries all together.

ERA PerMed 2nd Joint Translational Call is open for submission of pre-proposals. Deadline: March 7th, 2019
More details at: www.erapermed.eu/joint-transnational-call-2019

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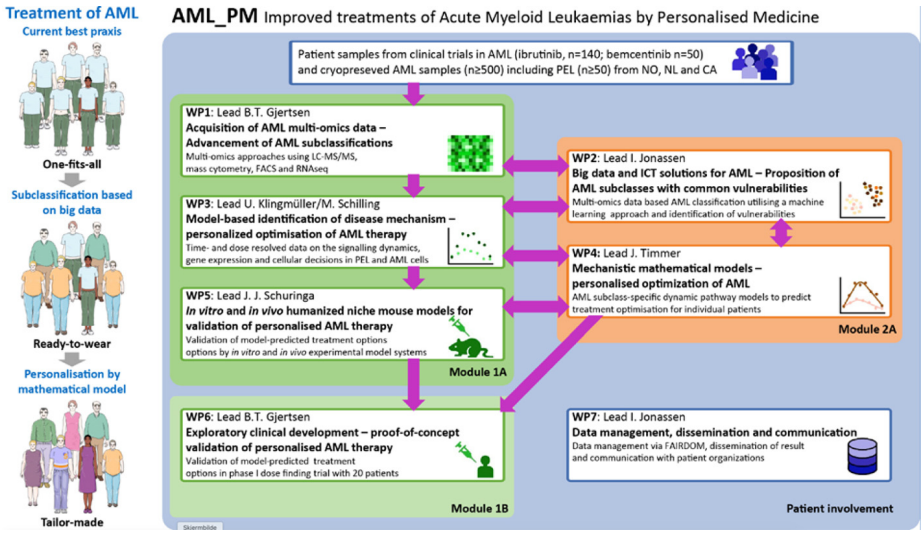
AML_PM
Improved treatments of Acute Myeloid Leukaemias by Personalized Medicine

In the AML_PM project we will develop a novel approach to classify patients by their genetic profile and the status of internal cell signalling associated with the disease to help tailor treatment for the individual patient. In the project we will combine use of mathematical models of signalling pathways with detailed data on gene expression, abundance and forms of proteins in individual cells and patients and relate these to treatment response and prognosis. Model building will proceed in parallel with experimental work on model systems. Machine learning will be utilized to predict disease subtype and to help tailor treatment. The project will initially focus on a small subset of AML, pure erythroleukaemia (PEL), to develop a feasible pipeline to gain insights into disease mechanisms and propose personalised treatment options. This strategy is applied to other AML cases and utilised to optimise therapy for the individual patient. Proof-of-concept validation in patients will be performed when possible.



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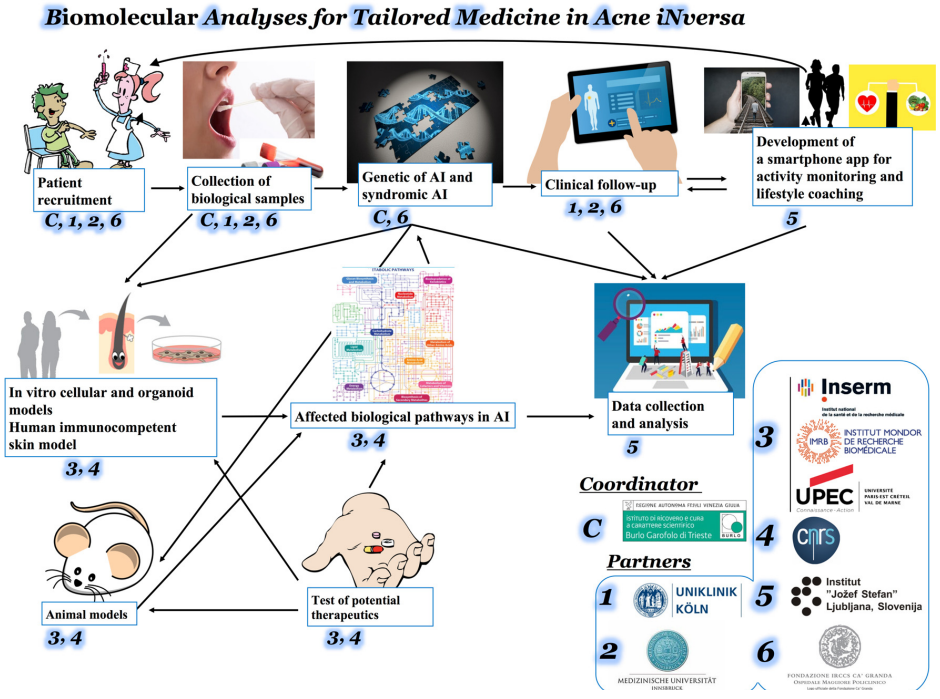
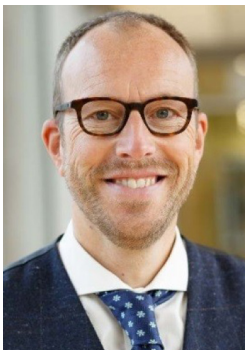
BATMAN

Biomolecular Analyses for Tailored Medicine in Acne iNversa

Acne Inversa (AI) is a chronic inflammatory disease involving hair follicles that presents with painful nodules that release pus.
AI severely impairs the quality of life of patients and its high frequency (1% in Europe) causes significant costs for health systems. Our proposal aims at bringing together medical, genetic, experimental and lifestyle data to build a truly personalized model of each patient in order to tailor specific treatments.
Expected outcomes:

- identify genetic variants associated with AI susceptibility, severity and treatment
- design in vivo and in vitro models to investigate the impact of genetic variants on immune and cutaneous cell biology
- develop a smartphone application to remotely monitor the physical and psychological wellbeing of patients and to advise them on lifestyle adjustments based on their clinical and genetic data
- propose novel stratification and artificial intelligence methods that clinicians can use to assess severity, choose therapy regimen and follow the outcome.

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COMPASS

Clinical implementation Of Multidimensional PhenotypicAl drug SenSitivities in paediatric precision oncology (COMPASS)

Paediatric precision oncology platforms (INFORM, MAPPYACTS, iTHER) have prospectively analyzed over 1.000 relapsed paediatric cancers by next generation sequencing and microarray-based technologies. While targets can be identified in 50% of cases, the remaining patients lack actionable alterations. This occurs particularly in brain tumors, sarcomas and neuroblastoma, indicating significant, currently unmet needs in precision medicine. The COMPASS consortium proposes that direct functional high-content 3D drug response profiling of patient-derived cancer cells will provide additional key information for precision paediatric oncology. We address four main aims: I) establish a standardized ex vivo drug response profiling platform, II) discover new biomarkers and molecular mechanisms for the drug efficacies seen, III) generate a large-scale open-access online data resource of drug efficacies with integrated omics data and IV) clinical translation by using the platform as a basis for clinical trials and future precision clinical cancer care.

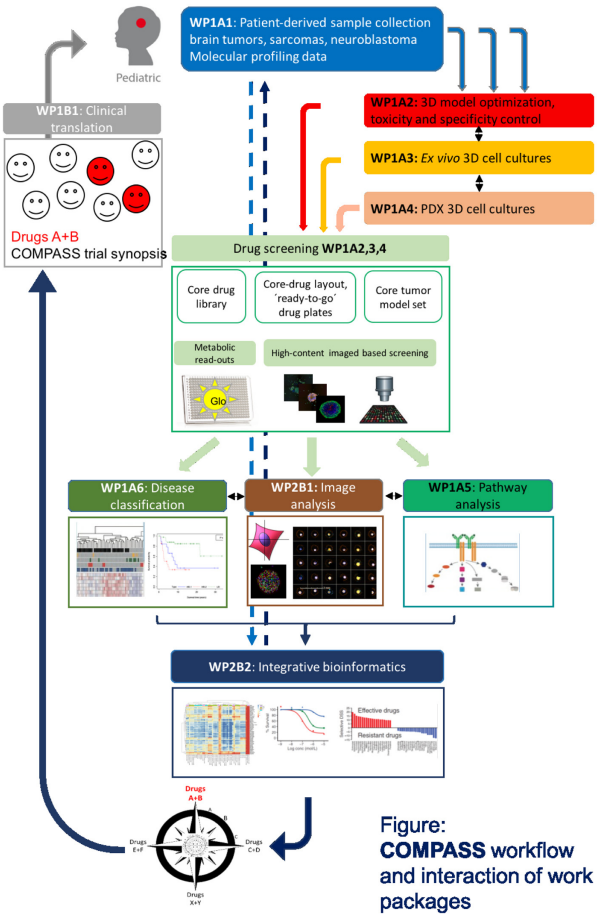

Figure: **COMPASS** workflow and interaction of work packages

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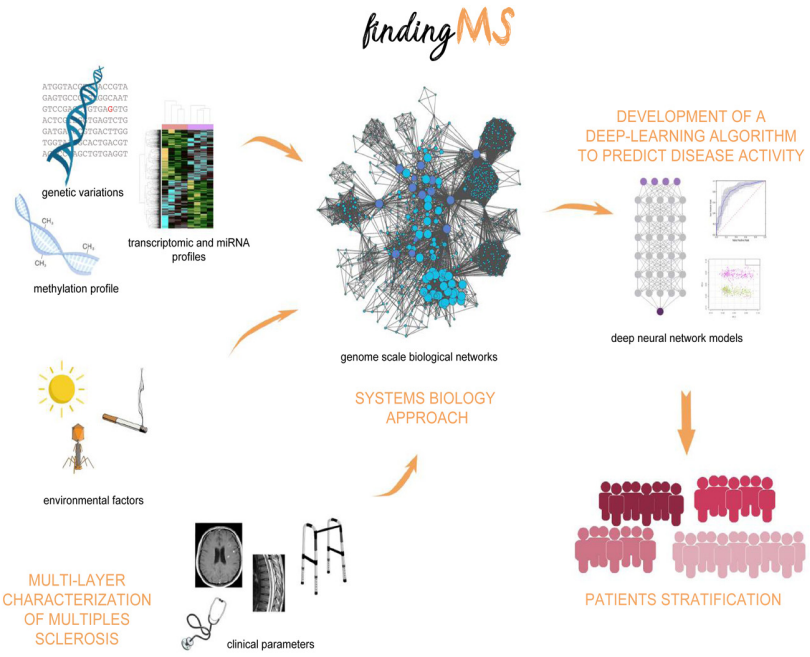
FindingMS

An integrated approach to predict disease activity in the early phases of Multiple Sclerosis

Multiple Sclerosis (MS) is a chronic, autoimmune disorder of the central nervous system, a leading cause of non-traumatic disability in young adults. It is a very heterogeneous disease, with high variability in both clinical manifestations and individual response to treatments, suggesting that specific individual characteristics could play a role and be implicated in disease expression. Starting an effective treatment as early as possible is extremely important, to reduce inflammatory activity and to limit disability progression. This aspect is even more relevant in the present era, characterized by a dramatic increase in the range of treatment options currently available for MS patients.

We plan to study a large cohort of Italian and French patients, combining together clinical, molecular (e.g. genetics, gene expression, methylation) and life-style data. This composite information will be used to stratify patients in subgroups, using advanced bioinformatics tools. These approaches, together with artificial intelligence models, will be used to identify biomarkers able to predict disease activity, with the final aim of supporting treatment choice in the early phases of the disease. Overall we estimate that this project is clinically relevant and could have a positive impact in MS patient's management, towards a more tailored use of available treatment options. We expect that this project will contribute to produce personalized medicine tools, potentially applicable in the future in the clinical setting.



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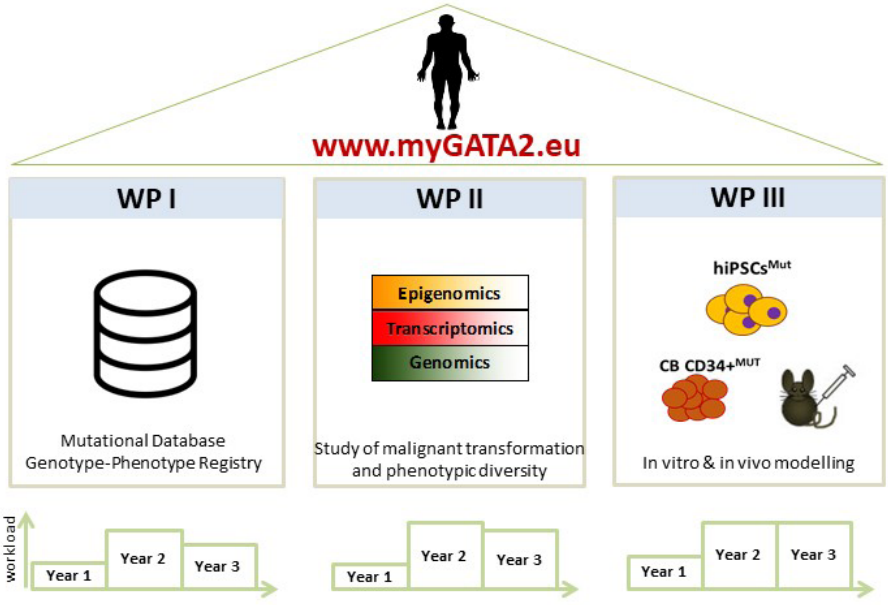
GATA2-HuMo

Human Disease Modeling of GATA2-related Myelodysplastic Syndromes and Acute Myeloid Leukemia

Germline heterozygous GATA2 mutations underlie a complex disorder characterized by bone marrow failure, immunodeficiency and high risk to develop myelodysplastic syndrome (MDS) and acute myeloid leukemia (AML). GATA2 deficiency has been established as the most common hereditary cause of MDS in children and adolescents. Hematopoietic Stem Cell transplantation is the only cure. Since its discovery in 2011, important questions pertaining to mechanism of GATA2 deficiency remain unanswered: (i) Can GATA2 mutation itself promote MDS/AML development? (ii) Is there a genotype-phenotype association? (iii) What factors control disease penetrance? (iv) Which genetic or epigenetic lesions are essential for MDS/AML development? (v) Is there a GATA2-specific clonal architecture in patients' bone marrow? (vi) What is the role of microenvironment? Answering these questions has been hampered by the absence of robust disease models and by decentralized efforts. Here we propose to unravel the mechanisms of malignant progression of GATA2 deficiency by combining centralized registry with multi-OMICs approaches, and in vitro and in vivo modelling. The overarching vision is to build an international consortium of GATA2 experts that through integrative approaches will acquire a precise understanding on the origins, and biological significance of initiating driver events thus allowing for personalized therapeutic decisions.



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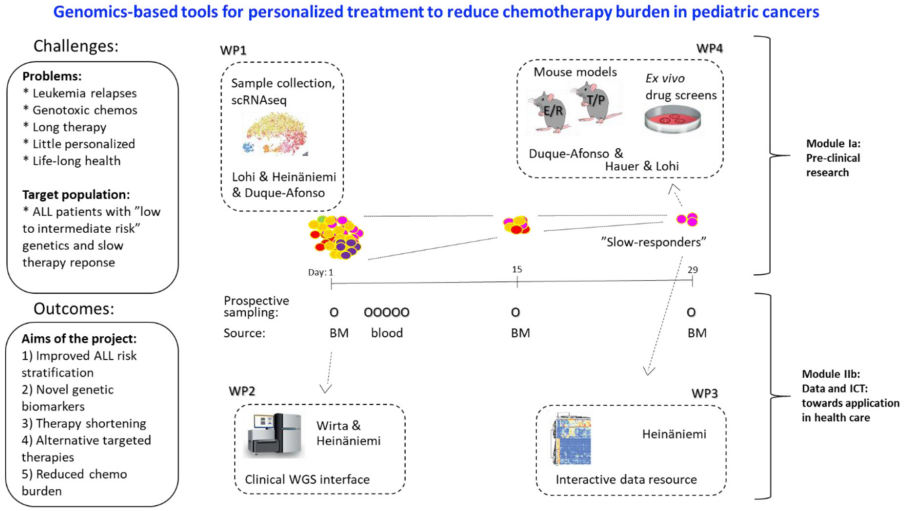
GEPARD

Genomics-based tools for personalized treatment to reduce chemotherapy burden in pediatric cancer

Acute lymphoblastic leukemia (ALL) is the most common cancer in childhood with approximately 4000 new diagnoses every year in Europe. The prognosis of ALL has greatly improved during the past decades but significant problems still exist. Firstly, some patients are undertreated as indicated by disease relapse which occurs surprisingly often in patients originally classified as ”low-to-intermediate risk” cases. Typically, relapse in these cases is associated with slow early therapy response. On the other hand, many patients are overtreated as previous studies suggest that approximately half of “standard-risk” cases could be cured with markedly shorter chemotherapy. We plan to comprehensively compare this patient group stratified by their early therapy response. We expect that our approach will allow shortening of the chemotherapy of ”true” low-risk patients, and target more specifically the deranged biology causing slow response in others. The study will be a transnational and multidisciplinary effort, combining multi-omics studies in patient samples and preclinical models with development of novel clinical bioinformatics interfaces and innovative high-throughput drug screens. Building on strong expertise in ALL biology, genetics, disease models and data analysis, our consortium will pioneer efforts towards personalized treatment strategies. The developed analysis workflows have applicability across a wide range of diseases beyond pediatric cancer studied here.

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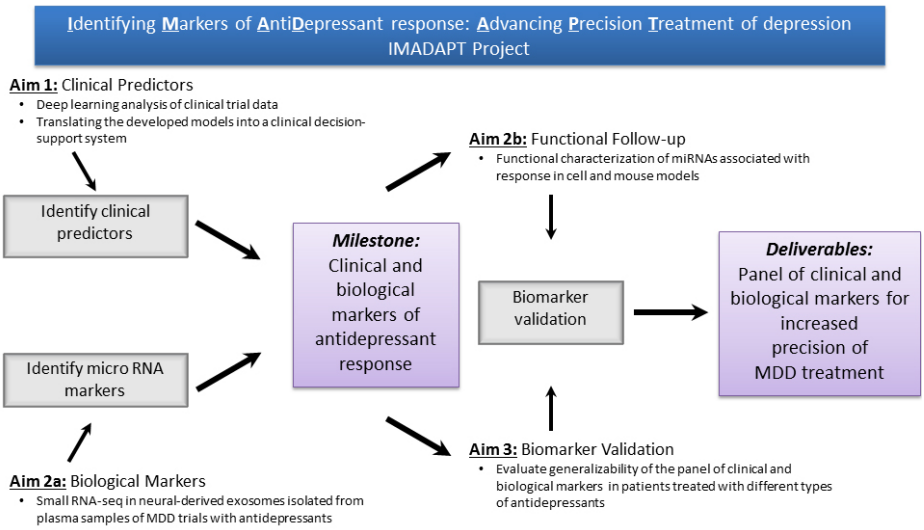
IMADAPT

Identifying Markers of AntiDepressant response: Advancing Precision Treatment of depression

Major depressive disorder (MDD) is highly prevalent in the general population and is associated with grave consequences, including excessive mortality, disability and secondary morbidity. Antidepressants are the most common treatment for MDD and are among the most prescribed medications. While they have demonstrated effectiveness, on average, 30-40% of patients do not achieve response even following multiple adequate trials over several months. In contrast to drug treatment for other medical disorders, and despite a clear biological basis to MDD, personalized treatment planning is not currently possible due to a lack of objective biological predictors of antidepressant response.

The primary goal of this proposal is to develop a clinically useful biomarker panel to increase the precision of MDD treatment. We will expand on our previous work on identifying biological markers, focusing on micro RNAs, using samples from a clinical trial of depression operated across 6 academic institutions across Canada initiated by the Canadian Biomarker Integration Network in Depression (CAN-BIND) and led by Dr. Sidney Kennedy (Canada Team Co-Applicant). Biological marker information will be combined with clinical markers defined by a deep learning-based investigation of clinical trial data, guided by Aifred Health (www.aifredhealth.com), an international award-winning health technology start-up company based in Montreal. This multidisciplinary approach to investigating both clinical and biological markers will further advance biomarker research in MDD for more personalized approach to treatment.

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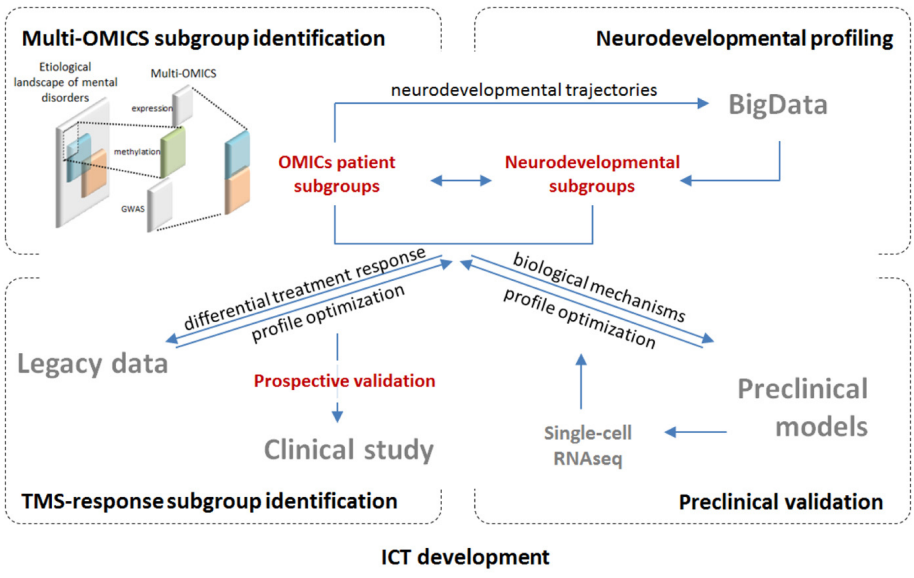
IMPLEMENT

IMproved Personalized medicine through deep LEarning in MENTal disorders

Psychotic disorders are severe mental illnesses with early onset, frequently chronic course and often lifelong impairment. As a consequence, they cause an enormous healthcare burden, costing close to €100 billion annually in Europe alone. The biology of these illnesses is insufficiently understood and no objective tools exist to aid in diagnosis or treatment selection. This leads to long periods of inadequate and ineffective treatment, significantly limiting the opportunity for achieving more optimal clinical outcomes. To address this, IMPLEMENT will develop a translational research framework that uses advanced machine learning to identify biomarkers for treatment-relevant stratification of schizophrenia. The IMPLEMENT framework will incorporate preclinical validation to leverage neurobiological understanding and optimize biological subgroup profiles. The clinical utility of these profiles will be validated in independent clinical samples and prospectively recruited subjects. IMPLEMENT will integrate these efforts with ICT development, to optimize the use of high-dimensional datasets across diverse repositories, to optimally harmonize data for personalized medicine investigations and safeguard patient privacy. Overall, IMPLEMENT will provide the basis for biologically-informed personalized medicine approaches in schizophrenia, addressing an enormous unmet medical need in an area of medicine in which currently no robust clinical stratification tools exist.

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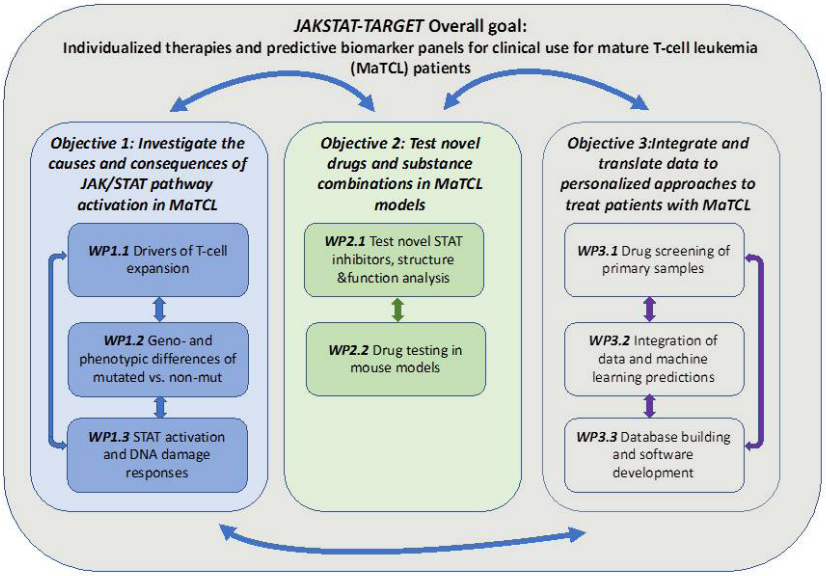
JAKSTAT-TARGET

Novel individualized therapies in JAK/STAT driven T-cell malignancies

Mature T-cell leukemias/lymphomas (MaTCL) are rare blood cancers for which there are not many effective treatments available. Recent research by our consortium members and others have revealed new information on the genetics of these diseases. Particularly, mutations in genes from an important cell growth and survival pathway, called JAK/STAT, are found to be very common in these types of blood cancers. In the JAKSTAT-TARGET project our aim is to investigate the causes and consequences of JAK/STAT mutations, and understand how different mutations in individual patients may impact their treatment. We also aim to test new treatment options and drug combinations in relevant in vivo models and patient samples. Finally, we will combine all of our research data and translate it to personalized treatment options for patients. Our consortium consists of international experts in various fields such as in hematology (blood diseases), immunology, clinical medicine, computational science and chemistry. Together with our unique resources, our project will create individualized therapy options and strategies to predict treatment response for MaTCL patients.

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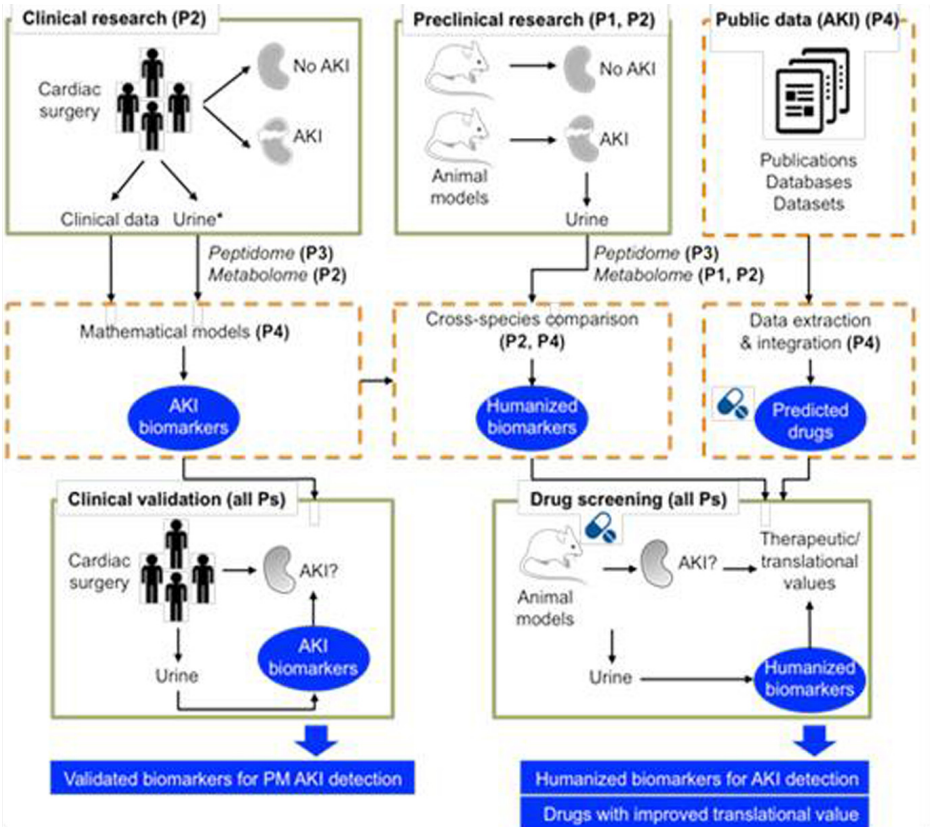
Kidney Attack

Multidimensional stratification for treatment of acute kidney injury

Acute kidney injury (AKI) kills 2 million people every year. In AKI, kidney function fails suddenly and may later recover spontaneously. However there is no treatment that accelerates recovery and patients may require replacement of renal function by dialysis.
Kidney Attack aims to change this status quo by innovative and smart combination of scientific literature, preclinical and clinical studies that explore multiple markers (i.e. systems biology, omics) to propose early personalized detection of AKI and novel treatments.
For this:
i) We will move from a single marker of early AKI to multiple markers that better capture the complexity of human disease
ii) We will develop a humanized version of this multiple marker panel
iii) We will use the humanized version of the multiple marker panel to search for new treatments that may be personalized based on the multiple markers

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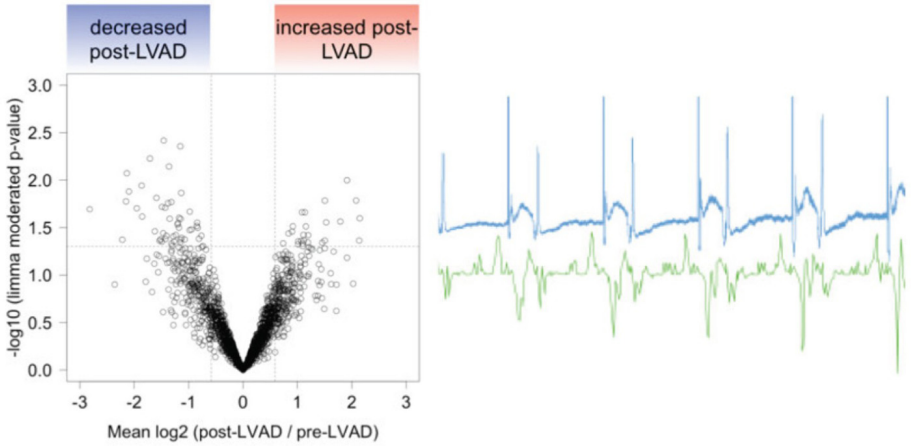
LVAD-Strat

Startification of heart failure patients for cardiac recovery upon cardiac unloading by Left Ventricular Assist Device therapy: Addressing the molecular, epigenetic, and proteomic changes associated with reverse cardiac remodeling

For heart failure, heart transplantation or Left Ventricular Assist Device (LVAD) implantation are the only available treatment options. LVADs typically serve as a bridge-to-transplant or destination therapy. In some patients, LVADs may serve as a bridge to recovery (BTR), where cardiac unloading and recovery of heart function enable LVAD explantation. Biomarkers are needed for the upfront identification of patients that are BTR candidates. We will perform epigenetic, transcriptomic, and proteomic analyses in a cohort of LVAD patients to address this shortcoming. Moreover, we will characterize a mouse model of cardiac unloading to understand its mechanistic foundations. Further, we will optimize a non-invasive imaging technique of cardiac contraction during open-chest cardiac surgery to improve outcomes. Lastly, we will study long non-coding RNAs that are dysregulated in HF and normalized after unloading, to determine whether they may represent targets for therapies, which alone or in conjunction with LVAD-support can promote cardiac recovery.

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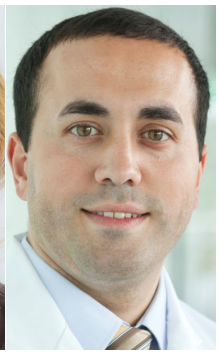
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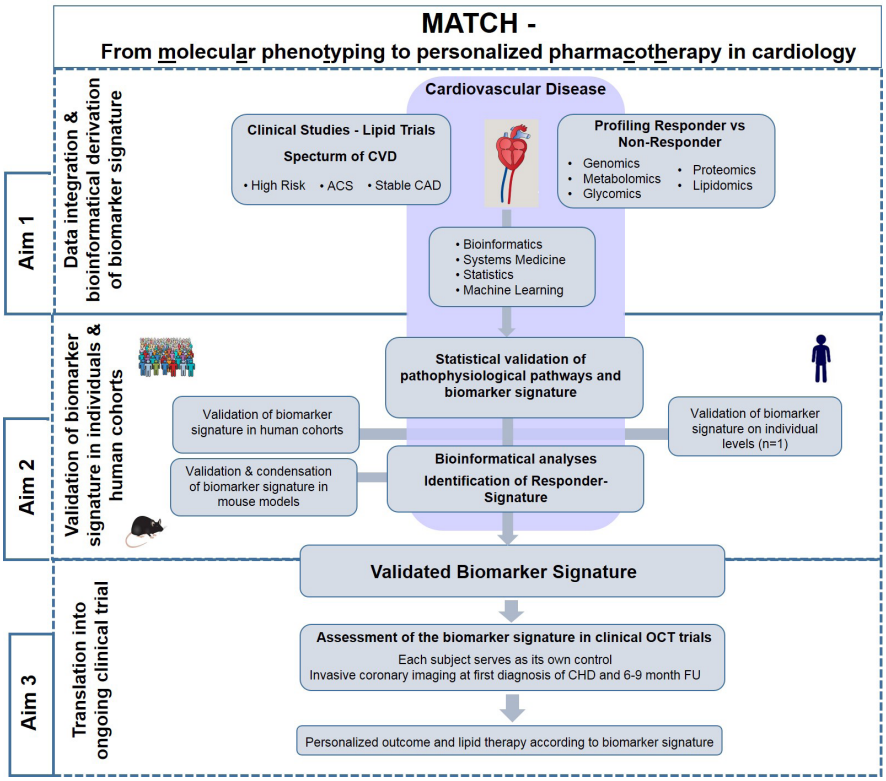
MATCH

From molecular phenotyping to personalized pharmacotherapy in cardiology - an interdisciplinary and translational approach towards precise pharmacotherapy in coronary heart disease

Evidence-based medicine has considerably advanced the treatment of coronary heart disease (CHD), and its implementation was driven by multicenter interventional trials. However, most large-scale clinical trials and therapies did not relevantly reduce the residual risk. Therefore, innovative approaches to foster individualized pharmacotherapy in CHD are urgently needed. The objective of MATCH is the identification of a biomarker signature, which associates with beneficial outcome on specific lipid therapy using an interdisciplinary approach. Bioinformatics analyses will generate a molecular biomarker signature of responders (subjects with no clinical events during follow-up) versus non-responders (subjects with multiple events during follow-up) across cardiovascular lipid trials. This signature will be optimized in human cohorts and atherosclerosis-prone mouse models and validated in a second subset of patients. Finally, the signature shall be translated in an imaging-based OCT (optical coherence tomography) trial longitudinally assessing the progress of coronary atherosclerosis in subjects with CHD.

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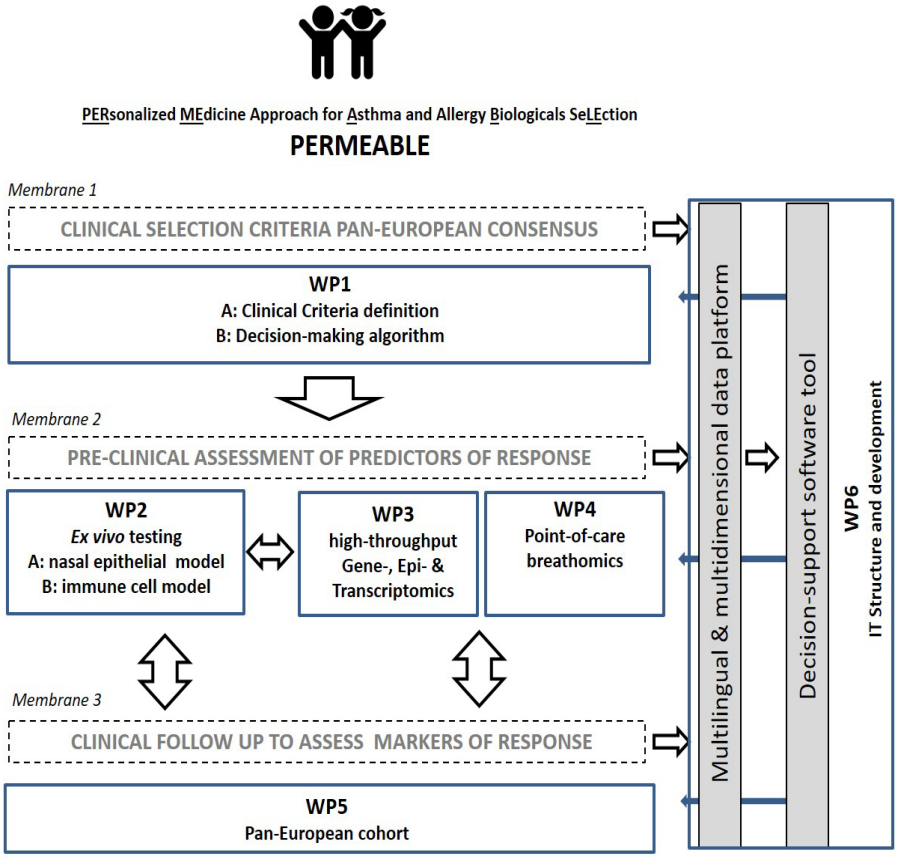
PERMEABLE

PERsonalized MEdicine Approach for asthma and allergy Biologicals seLEction

In total, 50 million Europeans are affected by allergic diseases such as asthma and atopic dermatitis. Approximately 10% of these patients suffer from uncontrolled disease despite high dosages of treatment. Some patients might benefit from novel targeted, yet expensive and burdensome treatments. However, it remains unclear which patient will benefit from which type of treatment. Clinical tools to guide treatment based on individual profiles are lacking and studies including young patients are scarce. The PERMEABLE consortium aims to develop the urgently needed personalized medicine approach to tailor treatment in allergy and asthma in young patients, by combining preclinical and clinical research approaches, as well as applying innovative ICT solutions.



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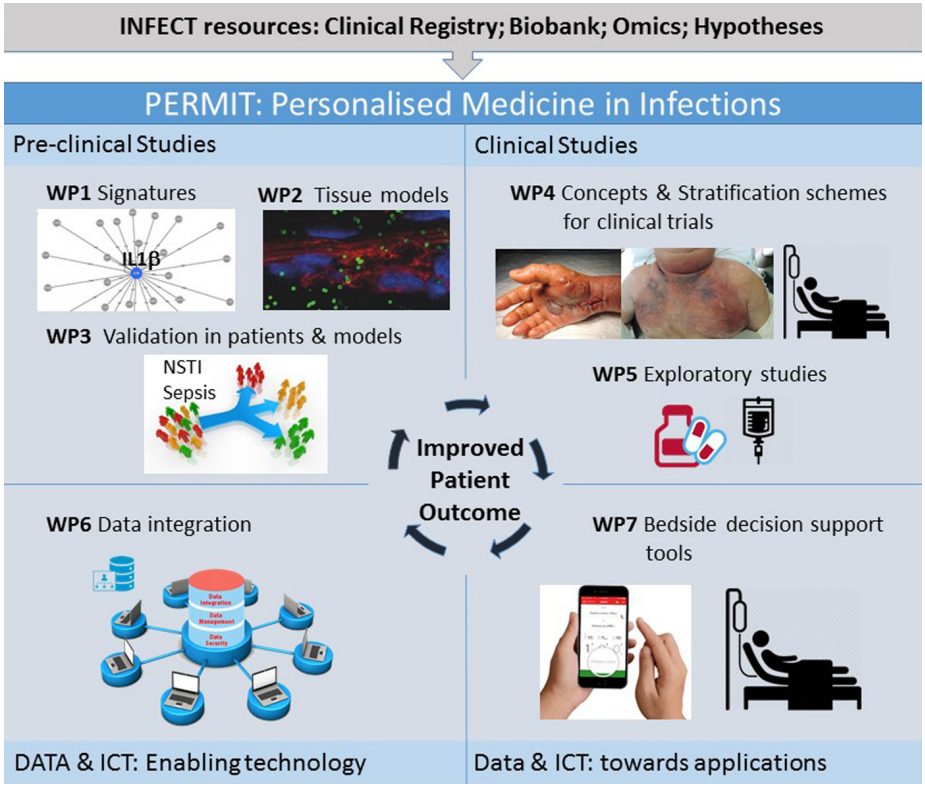
PERMIT

Personalized Medicine in Infections: from Systems Biomedicine and Immunometabolism to Precision Diagnosis and Startification Permitting Individualized Therapies

The PERMIT project focuses on life-threatening infectious diseases, including the destructive necrotizing soft tissue infections (NSTI) and the large group of sepsis patients. The severity of these infections is dictated by the individual's response to the pathogen and greatly depends on subject-specific host-pathogen interactions. For this reason, personalized therapeutic strategies targeting both the pathogen and host response are needed. To achieve this, PERMIT builds on the knowledge and resources created in the EU FP7-project INFECT including the world's largest multicenter, prospectively enrolled patient cohort on NSTI, a biobank, multi-omics data, strategic data stewardship and pathophysiologic models. PERMIT will move towards preclinical validation of disease signatures, underlying mechanisms and biomarkers with the aim of translating these findings into improved or novel diagnostics, and to demonstrate the clinical feasibility and potential benefit of a personalized medicine approach to the treatment of NSTI and sepsis.



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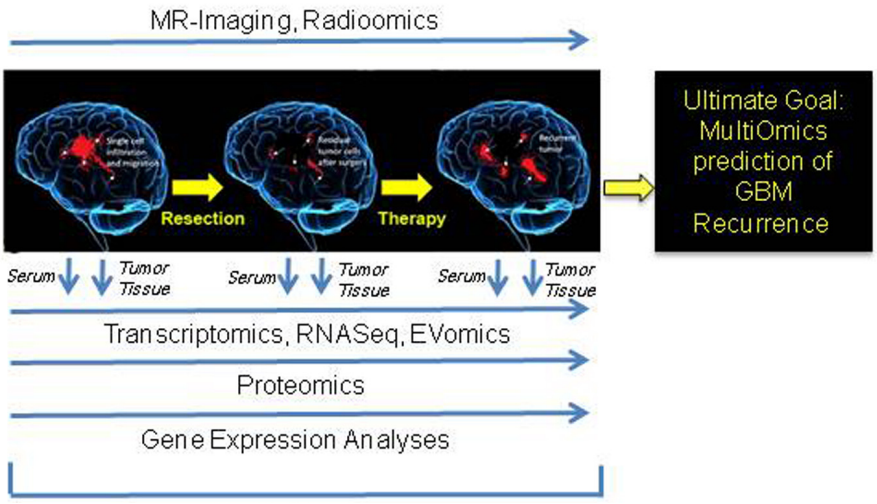
PerProGlio

Integrative Personal Omics Profiles in Glioblastoma Recurrence and Therapy Resistance

Glioblastoma (GBM) is the most common aggressive brain tumor with a poor prognosis and a median survival time of <15 months. Despite multimodal therapy, including surgical resection and radiochemotherapy, recurrence is common. Until now, recurrence monitoring is based on radiologic imaging but suffers from limited sensitivity. Therefore, circulating “liquid biopsy” markers predicting the time window of recurrence are highly desirable. Abundance-based biomarkers associated with time-to-recurrence will be obtained by analyzing the content of serum-derived extracellular vesicles (EVs) with respect to proteolytic fragments, protease activities, and small RNAs (microRNAs). In addition, a full genomic analysis will be performed to characterize recurrence in individual patients and combine multi-Omics with clinical and imaging data. From these analyses, we aim to identify personalized easy-to-access biopsy markers. With these markers, investigation of pre- and post-surgery serum samples (at time of initial surgery) allows to faithfully discern tumor-originating molecules through their altered abundance in post-surgery samples.

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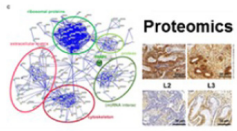
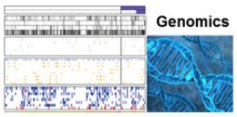
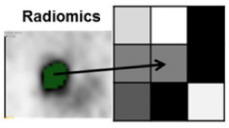
PersoProCaRisk

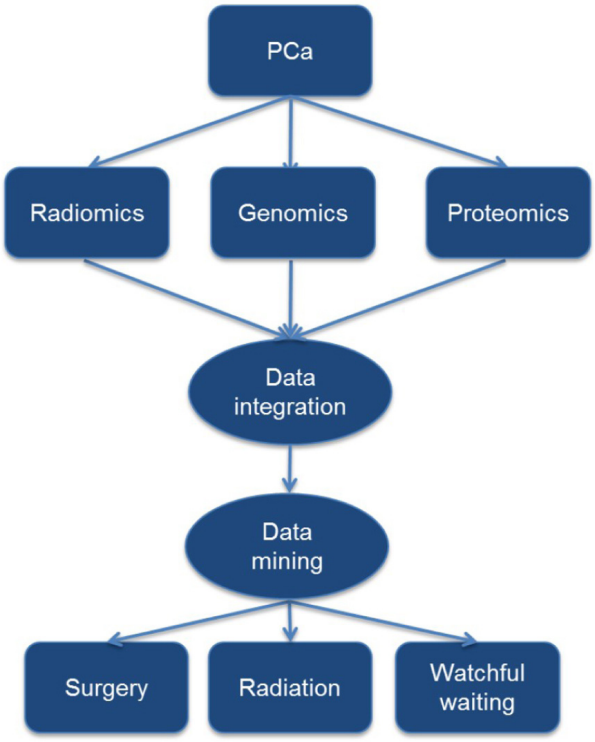
Integrative Personalized Risk and Therapy Stratification of Localized Prostate Cancer

Preventive examination for Prostate cancer (PCa) via prostate specific antigen, needle biopsy and histopathological examination has increased the detected number of localized PCa and provided a first model for risk stratification. However, this model has an imminent need to be rectified in order to a) stratify patient's treatment (surveillance vs. surgery vs. radiation therapy), b) identify patients with high-risk tumors and c) improve disease progression monitoring. The presented consortium concatenates routine clinical course with state of the art omics and bioinformatics analyses derived at primary diagnosis; employing a) deep proteomics of tissue specimens, b) Next Generation Sequencing of seminal vesicle plasma and matched tissue; and c) imaging techniques (PSMA PET, and MRI) as a radiomics. These high dimensional data will be integrated into statistical learning models. The deep and potentially unbiased feature extraction will pave the way for personalized therapy predicting models and risk-profiles; with a strong emphasis on non-invasive approaches.







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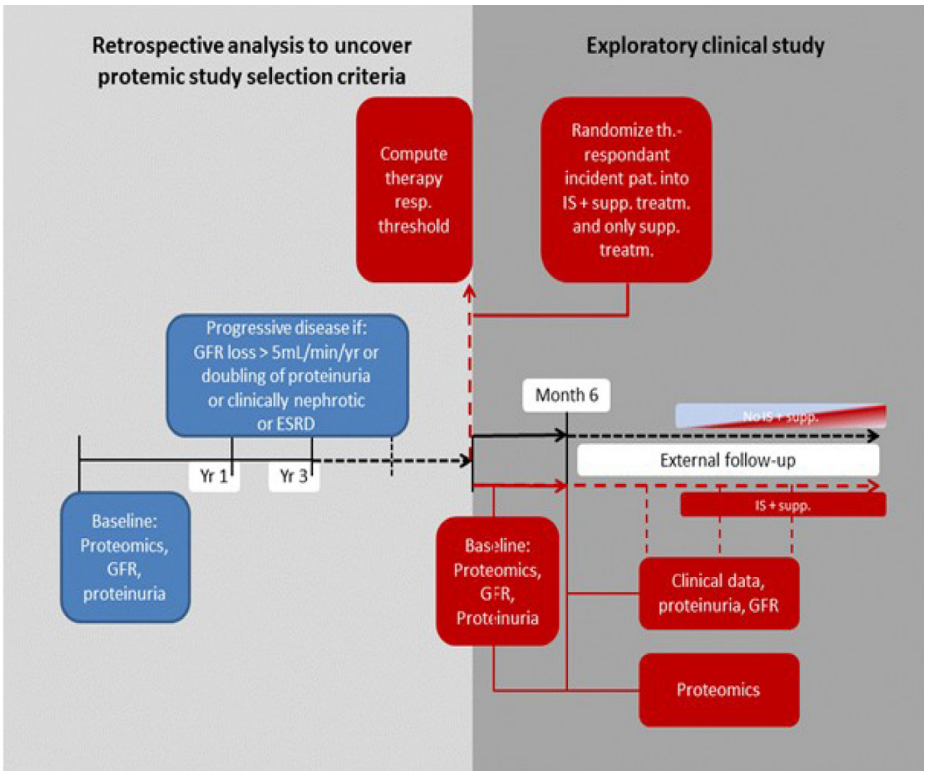
PersTIgAN
Personal Treatment in IgA Nephropathy

IgA Nephropathy (IgAN) is a major cause of end stage renal disease necessitating maintenance dialysis treatment but guidance predicting therapy response is currently lacking. Therefore the project aims at developing a biomarker-based algorithm that predicts drug response in IgAN, personalizing intervention and significantly improving patient management. The ability of urinary peptides to display drug response could be demonstrated in recent studies by capillary electrophoresis coupled mass spectrometry (CE-MS). Using samples from patients with known outcome from multiple clinical centres, urinary peptides significantly associated with response to specific treatment will be identified. An algorithm to predict response based on the urinary peptides and, if applicable, on other relevant variables, will be developed and tested in an independent sample. If the algorithm enabling personalized intervention in IgAN shows significant benefit, a well powered clinical trial will be designed to support implementation in routine care.



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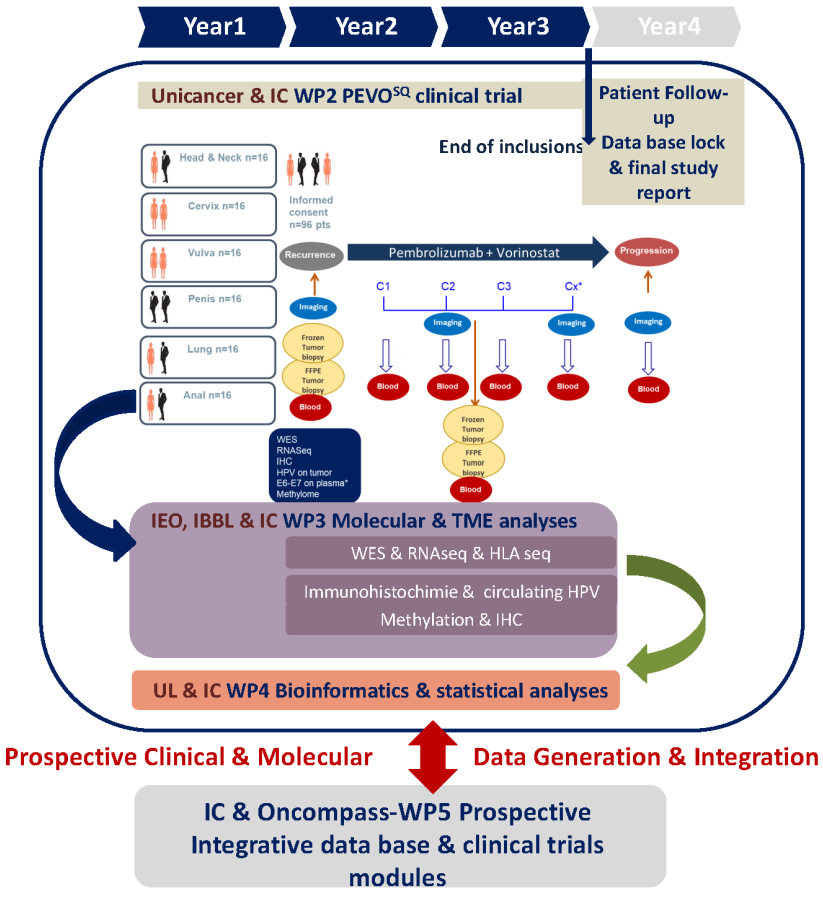
PEVOdata

Data solutions based on a basket prospective trial with pembrolizumab and Vorinostat in patients with late stage squamous cell carcinoma

So far, we have infrequently been able to cure late stage cancers with medical treatments. Late stage cancers acquire multiple drug resistance mechanisms and thus a combination of drugs may be needed for treatment, making the discovery of a cure for late stage disease extremely challenging. Integration of multiple molecular data with patients' clinical history is today crucial to apprehend new mechanisms related to drug efficacy or resistance. Via the PEVOdata project, with its core the PEVOSQ basket trial in patients with late stage squamous cell carcinomas treated with pembrolizumab in combination with vorinostat, we aim to: 1) explore the modifications of immune-related and molecular-epigenetic biomarkers; 2) build a database integrating molecular and clinical profiles for treatment decision; 3) develop long-term standards alongside other strategies for data collection and management, and 4) set a module for patients inclusion in clinical trials.



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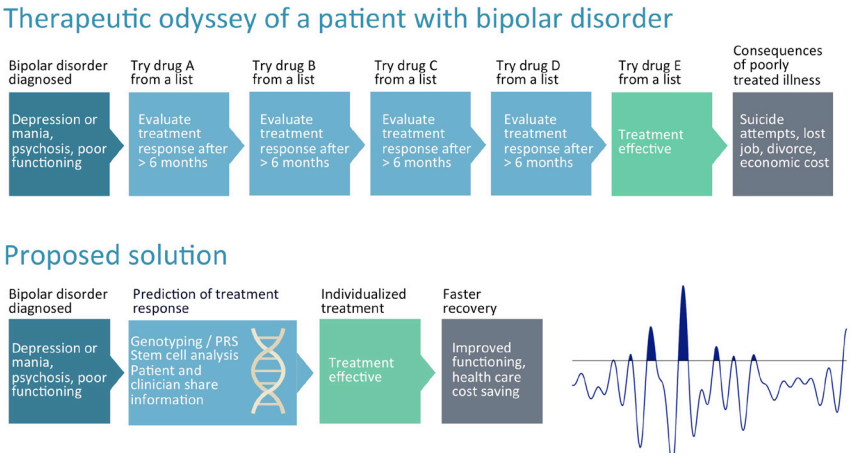
PLOT-BD

Personalization of LOng term Treatment of Bipolar Disorder

The PLOT-BD project aims to improve the long-term treatment of bipolar disorder. Bipolar disorder affects young people in their teens or early 20s and follows a lifelong recurrent course. In many, but not all, patients the episodes of mania and depression can be prevented by suitable medication treatment. To date, long term treatments are commonly chosen by trial-and-error, often taking months or even years. However, our earlier work suggests that clinical and molecular genetic markers can guide the treatment selection on an individual basis. To this end, the collaborating partners will analyze data from existing, as well as newly collected clinical observations of patients treated with lithium. They will combine patients' clinical data with three molecular genetic modalities: genetic polymorphisms, epigenetic modifications, and the properties of neurons derived from induced pluripotent stem cells, to derive a set of variables associated with positive treatment outcome. Personalized treatment selection will shorten time to remission and effective mood stabilization, ultimately reducing the impact of the illness on the lives of patients and their families.



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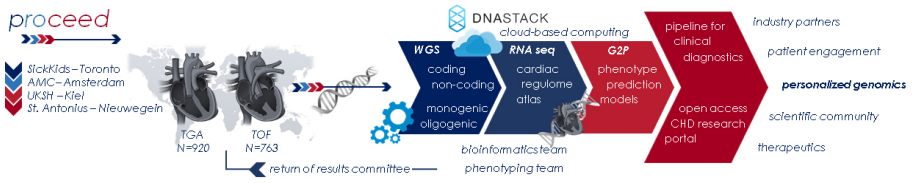
PROCEED

PeRsOnalized Genomics for CongEnital HEart Disease

Congenital heart disease (CHD) affects 1 in 100 live births and is the leading cause of neonatal deaths related to birth defects. The genetic cause is known in less than 10% cases. The PROCEED project will use whole genome sequencing that can search the entire genome to identify the genetic basis of two rare disorders that cause “blue” babies - tetralogy of Fallot (TOF) and transposition of the great arteries (TGA). We will determine how genetic differences help in predicting the severity of disease. Canadian, Dutch and German partners will share patient samples for this study and jointly develop bioinformatics analysis tools that will help to identify the gene defects. These tools will be shared with the broader scientific community internationally. The findings will be leveraged to develop genomic diagnostics for CHD that will predict whether a fetus will have a simple or a complex defect, will help with more accurate counselling of pregnant women, and allow pre-implantation genetic diagnosis to facilitate a subsequent healthy pregnancy. In the future, it may inform which patients may benefit from fetal interventions that can slow disease progression. Together, this will help to reduce the burden of complex CHD and to improve outcomes in this vulnerable population.

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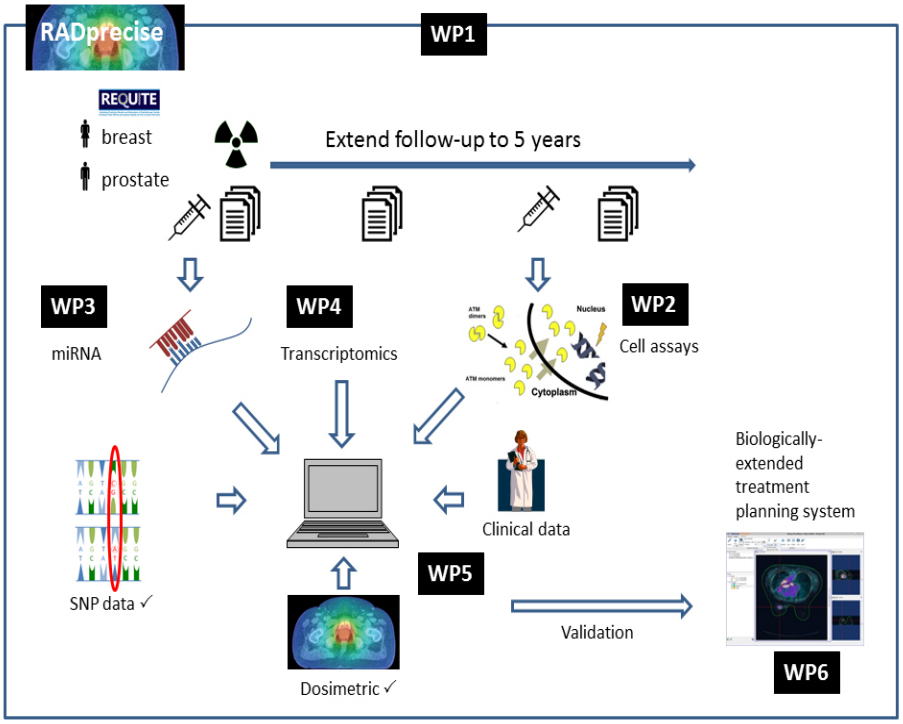
RADprecise

Personalized radiotherapy: incorporating cellular response to irradiation in personalized treatment planning to minimize radiation toxicity

The RADprecise collaborative project aims to personalize radiotherapy treatment for cancer patients. We plan to improve the prediction of the risk for side effects after radiotherapy using multiple biomarkers from blood and tissue in addition to clinical and personal factors. Information from the prediction models will be incorporated into radiotherapy treatment planning systems. With this "biologically extended treatment planning system", radiotherapy can be adapted to each individual patient's sensitivity to radiation to minimize side effects while still effectively eliminate the tumour. This shall provide more effective treatment and benefits for the patient such as improving quality of life.
We will use data from a large established cohort of breast and prostate cancer patients from the REQUITE project (www.requite.eu). Follow-up of patients in Germany, Italy, Spain and the UK will be extended to determine long-term side effects up to five years. New biomarkers from blood and tissue will be tested, including a cell-based assay and gene-expression. Scientists as well as two companies in France together with patient advocates will collaborate in this project to take biological optimisation into the clinic.



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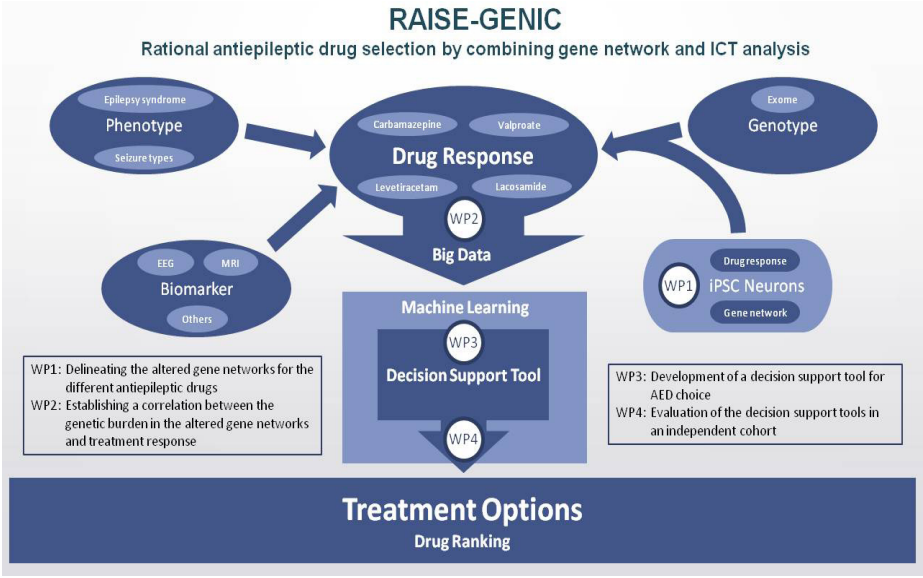
RAISE-GENIC

Rational antiepileptic drug selection by combining gene network and ICT analysis

Epilepsy is treated with anti-seizure drugs with the aim to stop the seizures. Although many anti-seizure drugs are available, we are currently unable to predict which drug works best in a particular patient. Therefore, we must select the drugs based on trial and error which results in less than one in two patients becoming seizure free with the first drug. We aim to predict the anti-seizure drug with the highest likelihood of success in an individual patient (personalized medicine) by combining two strategies. The first strategy examines human brain cells which are generated from skin cells of adult donors. These cells are treated with four different anti-seizure drugs (carbamazepine, valproate, lacosamide, levetiracetam) and we will investigate how specific genes respond to exposure to these drugs. We will then look at available genetic data from 1382 patients with epilepsy and examine if changes in these genes correlate with a drug's ability to stop seizures. The second approach consists of a "big data analysis" incorporating details on the patient's epilepsy, genetic data, brain wave signals (electroencephalography or EEG) and brain imaging to predict treatment effect. Using these large sources of complementary data, we will develop tools to help doctors and patients predict the effect of the different anti-seizure drugs. Subsequently, we will test in an independent cohort of 100 patients if the tool correctly predicts the best anti-seizure drug.



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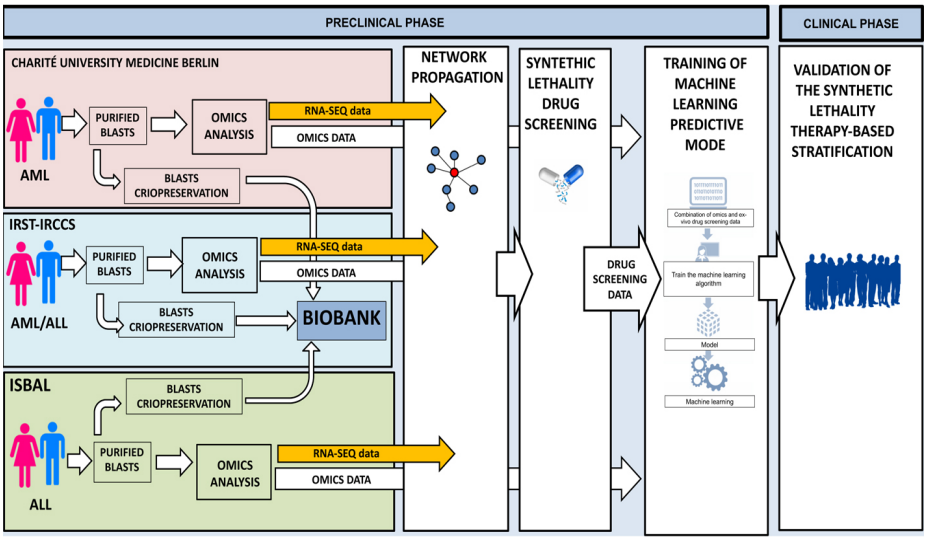
SYNtherapy

Synthetic Lethality for Personalized Therapy-based Startification in Acute Leukemia

Our aim is to develop a machine learning-based model to predict personalized treatment for relapsed or refractory Acute Leukemia. We will exploit two new and promising Synthetic Lethality approaches by multilayer analysis of omics data. Differential expression analysis of RNA-Seq data will provide primary molecular markers that will be propagated in protein-protein interaction networks, to identify secondary not altered candidates genes of Synthetic Lethality. The identified markers will be reduced by selecting DNA Damage Response (DDR)-related genes for which a drug inhibitor is available. The selected drugs will be screened ex-vivo on primary leukemic cells. Combination of omics and ex-vivo drug screening data will be used as training dataset for the predictive model. A multi-centric investigator-initiated clinical trial will test the performance of the predictive model as well as the practical feasibility of the whole procedure. Our ambition is to precisely match leukemia patients with the most effective targeted therapy, thereby increasing chances of successful treatment.

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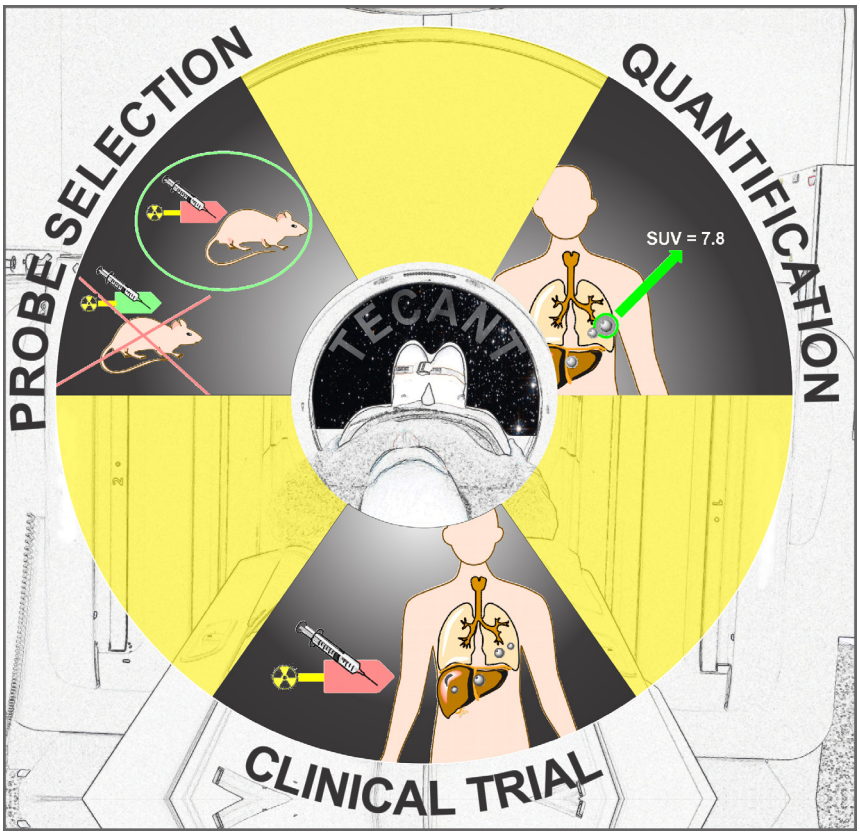
TECANT

Novel 99mTc-labeled somatostatin receptor antagonists in the diagnostic algorithm of neuroendocrine neoplasms – a feasibility study

Detection of neuroendocrine neoplasms (NENs) and monitoring of response to therapy is still challenging due to their cellular heterogeneity. Initial preclinical studies suggest that NENs imaging with the use of somatostatin receptor (SSTR) antagonist may be advantageous in comparison to the widely used SSTR agonists.
The project aims to select the most promising SSTR antagonist (LM-3 vs p-Cl-BASS) for clinical translation and develop a kit-formulation for NEN imaging (WP1), to initiate a clinical feasibility study (WP2) including development of a robust, reproducible quantitative imaging method (WP3). Within phase I clinical study ten patients with proven SSTR expression on agonist imaging will be treated with 99mTc-labelled SSTR antagonist. The safety, tolerability, human pharmacology, dosimetry and NEN targeting properties will be assessed applying the concurrently developed quantitative imaging protocol.
99mTc-labelled SSTR antagonist is expected to be an effective, widely available method for quantitative assessment of SSTR NENs status, allowing a personalized therapeutic approach.

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TREAT-Essential

Personalized decision support system for antimicrobial stewardship

Bacterial resistance to antimicrobials is recognised by the WHO as a major health threat of the 21st century and as the third largest threat to humanity. Antimicrobial Stewardship (AS) promotes rational use of antimicrobials as a way to control the spread of antimicrobial resistance. Our aim is to build a decision support module for AS by targeting its application at point-of-care. We will develop, integrate, test and implement an optimized version of the decision support module (DSM) TREAT, to improve individualized infectious disease diagnosis, rational treatment and management of ongoing therapy in the hospital setting. The outcome of the project involving partners in Denmark, Sweden and Israel is a fully integrated DSM ready for implementation in other centres allowing for a personalized medicine approach, lowering the total usage of prescribed antimicrobials, while prescribing appropriate therapy to those who need it.

Phase I Construction of Decision Support Module	Phase II Integration and Implementation	Phase III Testing and Validation
Patient-specific physiological model	Integration with hospital information systems	Functional testing
Decision model to perform a cost-benefit analysis of possible therapies	Local calibration and customizing the decision engine	Clinical study
	Graphical user interface	
Project management		
Development in compliance with Medical Device Regulation (MDR)		