ERA PerMed

2017/2023

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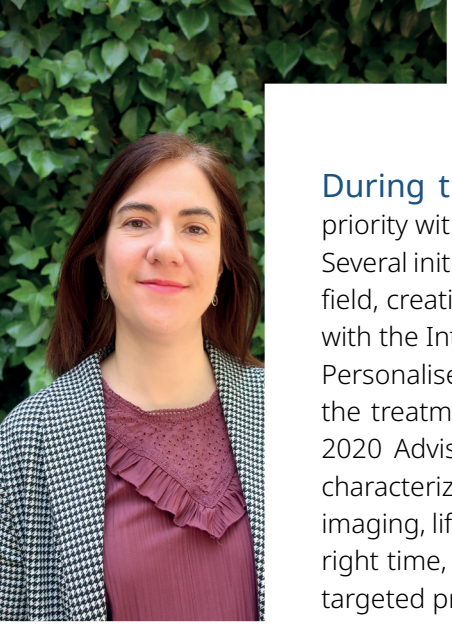


FOREWORD FROM ERA PERMED COORDINATOR

During the last years Personalised Medicine has been set up as a prime research priority within the framework of H2020 and Horizon Europe by the European Commission. Several initiatives have been launched at European level to foster the Personalised Medicine field, creating an inclusive Personalised Medicine Family of initiatives, in close cooperation with the International Consortium of Personalised Medicine (ICPerMed).
Personalised Medicine represents a paradigm shift from a "one size fits all" approach to the treatment and care of patients with a particular condition, as stated by the Horizon 2020 Advisory Group, which defined Personalised Medicine as "a medical model using characterization of individuals´ phenotypes and genotypes (e.g. molecular profiling, medical imaging, lifestyle data) 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".

To better support patients' health and to target emerging therapies, new strategies will be developed using approaches in areas such as diagnostic tests, functional genomic therapies, molecular pathways, data analytics and real time monitoring of conditions. This is a step towards optimized outcome in the management of a patient´s disease or/and the predisposition to diseases, as well as to make health systems more sustainable by reducing costs.

The European Research Area Network (ERA-NET) in the field of Personalised Medicine (ERA PerMed) has been the European instrument to coordinate and align research and innovation funding strategies among the different national and regional funding agencies from the European Union, associated countries and third countries to support personalised medicine multidisciplinary transnational research projects.

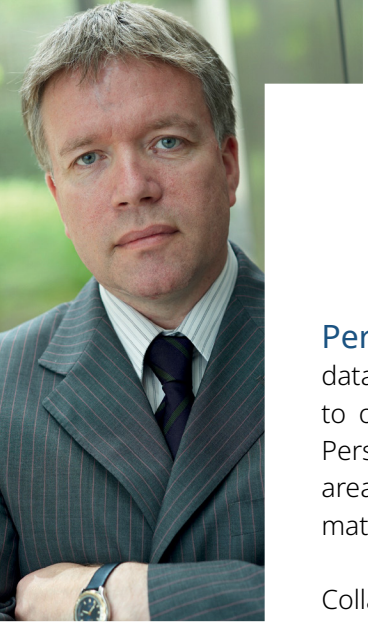
Since its establishment in December 2017, until November 30, 2023, the ERA PerMed consortium has included 32 partners from 23 countries and was co-funded by the European Commission. Moreover, more than 10 additional funding partners have joined the ERA Permed Joint Transnational Calls.

ERA PerMed has enhanced the European collaboration with non-EU countries to successfully support multidisciplinary and translational research and innovation projects in the field of Personalised Medicine. A total of 5 Joint Transnational Calls (with the European Commission co-funding support for the co-funded JTC2018), have been launched, covering the whole value chain, to successfully bring the personalised medicine approach to patients and citizens. More than 130 M€ have been invested in ERA PerMed Calls to fund 111 transnational research consortia including close to 600 partners all over the world.

I am proud of having been given the chance to coordinate ERA PerMed, on behalf of my Institution (the Institute of Health Carlos III from Spain) during these years, leading a high committed consortium of funding organisations that have made enormous funding efforts in order to reach this significant progress in the personalised medicine field.

Currently, we look forward to the new European Partnership of Personalised Medicine that will provide sustainability in the created funding opportunities by ERA PerMed for the personalised medicine research and innovation.

***Maria Cristina Nieto Garcia**, ERA PerMed Programme Coordinator*



A WORD FROM THE EUROPEAN COMMISSION

Personalised Medicine has its roots in genomics but increasingly other data sources are being included to cover all aspects of human variability. This helps to optimise prevention, diagnosis and treatment of diseases for each individual. Personalised medicine approaches have already been used successfully in many areas of oncology and rare diseases. We think that the field has reached sufficient maturity to be introduced at a wide scale in healthcare.

Collaboration across borders, within Europe and internationally, is an important factor helping the harmonisation of approaches and advancing the uptake of personalised medicine in healthcare. Networks such as the ERA PerMed co-fund are crucial in this process. We are delighted to see, that with the help of seed funding from the Commission the partners of ERA PerMed have managed to gather so much investment into collaborative research projects over the past years.

Personalised medicine approaches open up the possibility to personalise prevention measures. Identifying the people at higher risk of developing particular disease before the disease strikes, gives us the opportunity to optimise advice, monitoring and early intervention where needed. Apart from improving the quality of life for the affected citizens, it can also rationalise healthcare expenditure.

***Dr. Indridi Benediktsson**, Policy Officer at the European Commission*

ERA PERMED IN NUMBERS

23
COUNTRIES

32
FUNDING ORGANIZATIONS

111
FUNDED PROJECTS

132.9M
TOTAL BUDGET INVESTED IN RESEARCH

597
RESEARCH GROUPS FUNDED

66
RESEARCH GROUPS FUNDED BY REGIONAL FUNDING AGENCIES

75
CONSORTIA INVOLVE 5 PARTNERS OR MORE

39%
FEMALE COORDINATORS

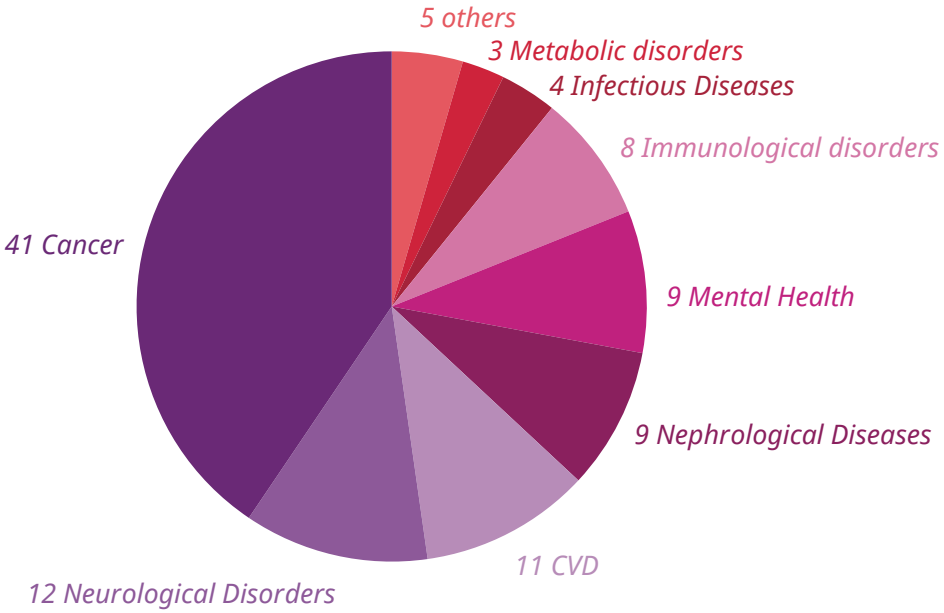
ERA PERMED JOINT TRANSNATIONAL CALLS OVERVIEW

During its runtime, the ERA PerMed programme has carried out 5 Joint Transnational Calls: JTC2018, JTC2019, JTC2020, JTC2021 and JTC2022 on personalised medicine (PM). The first call, JTC2018, was co-funded by the European Commission (EC). The other 4 calls were additional calls carried out by the collaborative efforts of the funding agencies that came together to form and join ERA PerMed.

With the aim to align national and regional research strategies and funding activities, to promote excellence, reinforce the competitiveness of European players, and enhance the collaboration with non-EU countries in the field of personalised medicine, ERA PerMed, as the largest ERA-Net in the health sector, together with the EC, has allocated over 130 million Euros to fund research projects focusing on PM.

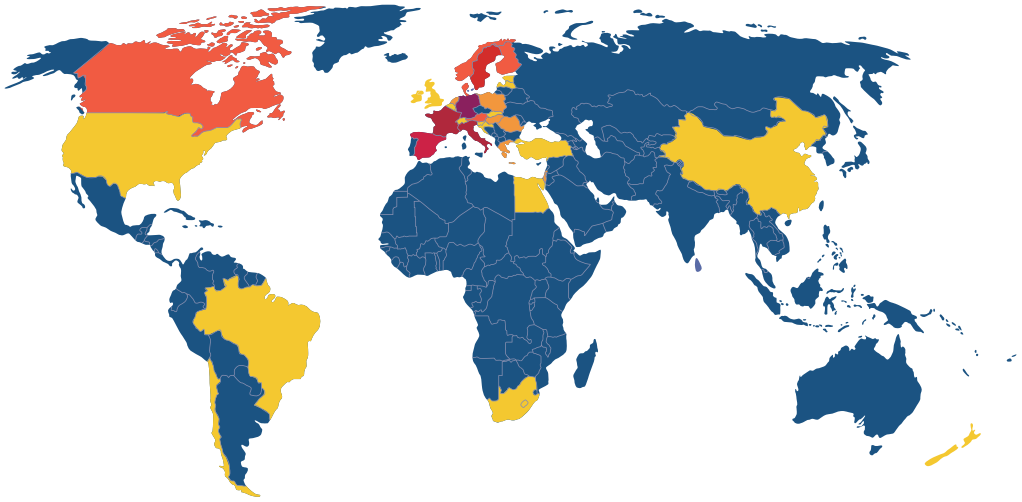
Due to the nature of personalised medicine and its relevance to a broad spectrum of health-related conditions, these funded projects cover various medical domains, including cancer, neurological disorders, cardiovascular diseases (CVD), nephrological diseases, mental health and immunological disorders. Furthermore, they include multi-disciplinary teams from different countries to complement each other's expertise and infrastructures.

DISEASE CATEGORIES OF ALL FUNDED PROJECTS



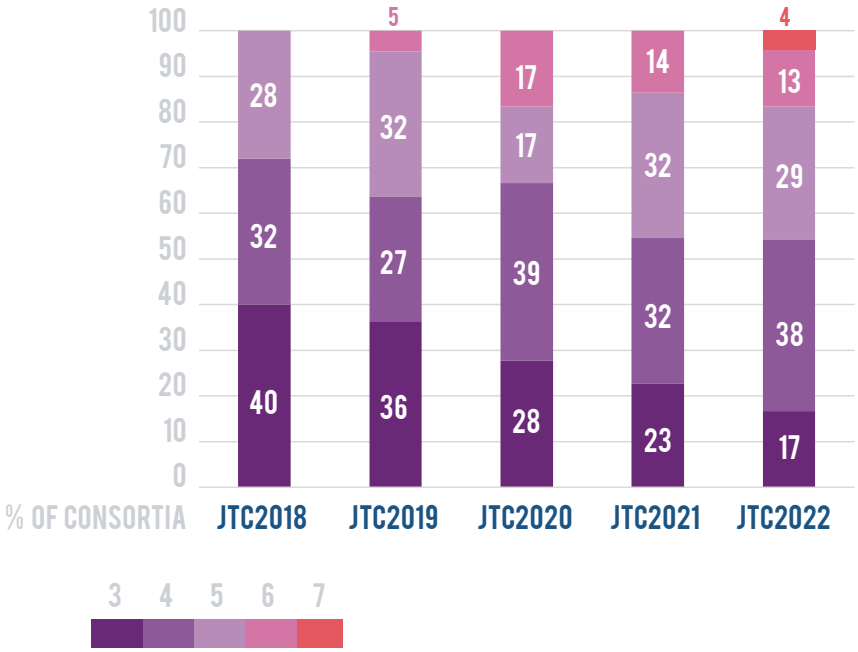
depicted are % of consortia

GEOGRAPHICAL
DISTRIBUTION OF FUNDED RESEARCHERS

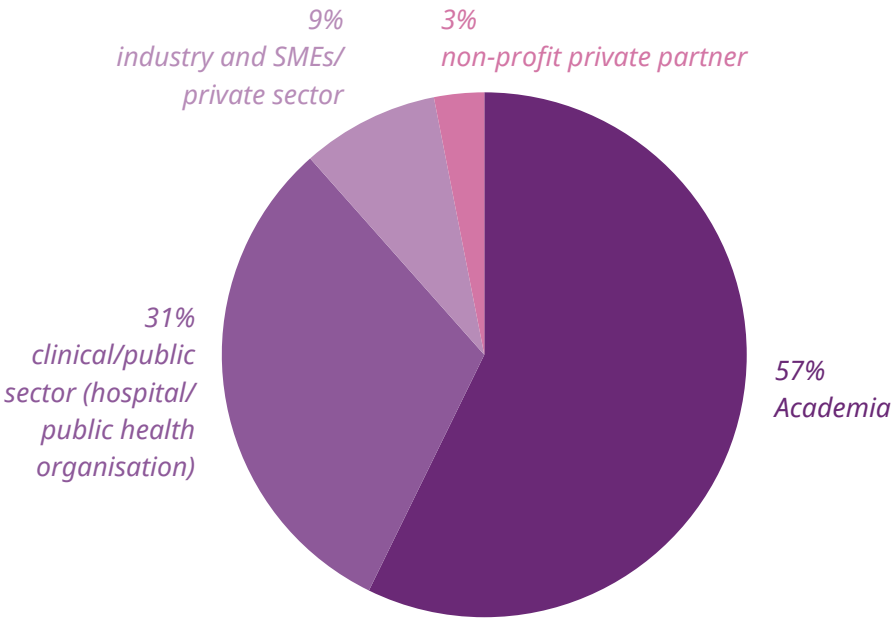


1 South Africa | Brazil | China | Switzerland
2 Chile | Estonia | New Zealand | UK | USA
3 Croatia | Egypt
4 Ireland | Latvia
5 Slovenia
6 Belgium
7 Türkiye
8 Luxembourg
12 Romania
13 Greece | Israel | Hungary
14 Poland
15 The Netherlands
19 Canada
21 Finland | Austria
22 Denmark | Norway
31 Sweden
59 Spain
71 France
72 Italy
128 Germany

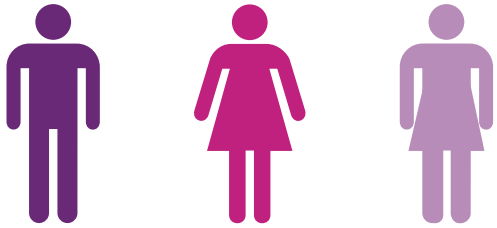
NUMBER OF PARTICIPATING COUNTRIES PER CONSORTIUM



TYPES OF PARTNERS JTC2018–2022

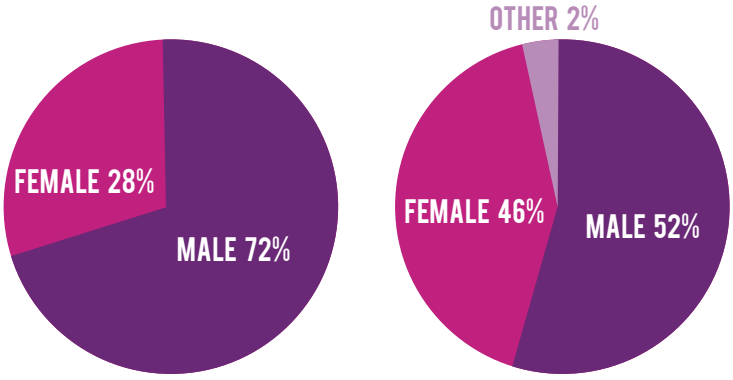


MEAN PERCENTAGE OF ALL PIs IN ALL CALLS



MALE 63% FEMALE 35% OTHER 2%

PERCENTAGE OF PIs



JTC2018 JTC2022

ERA PERMED CALLS IN NUMBERS

	JTC2018	JTC2019	JTC2020	JTC2021	JTC2022
FUNDED CONSORTIA	25	22	18	22	24
TOTAL NUMBER OF RESEARCH GROUPS	130	113	97	116	141
TOTAL INVESTMENT (IN MIO.EUR)	28	25	23	27	30
COUNTRIES IN FUNDED CONSORTIA	18	21	21	21	23
FEMALE PIs(%)	28	35	31	34	46

ERA PERMED ACTIVITIES

The winner of the competition, Ester Aguado from project RADprecise presented her work in the final symposium and shared how participation in this collaborative project contributed to her research career.

FINAL SYMPOSIUM

Dates: February 28th-March 1st, 2023 | Location: Cluj-Napoca, Romania
Number of participants: 67 onsite (including researchers from the JTC2018 consortia, the ERA PerMed EC policy officer, representatives from funding organisations and scientific experts); ~30 online

The symposium aimed at providing the JTC2018 project coordinators with the opportunity to present and discuss their work and results, and promote interactions between the various stakeholders attending the meeting. It provided an excellent opportunity to learn about the outstanding results and outcomes of the JTC2018 EC co-funded projects, who managed to make admirable progress despite being greatly impacted in their work by the Covid-19 pandemic.

Young researchers from the funded consortia were invited to communicate their research through a poster presentation and ten posters have been shown. ERA PerMed's support and encouragement of young researchers was also demonstrated in the awards given to the winners of the best video competition and the best poster. This event also served as an opportunity to discuss the importance of patient and citizen involvement in PM research. A dedicated patient involvement panel was organised, presenting perspectives of the patients/citizens, the researchers and the funders.

Finally, this event served as a great opportunity for networking and fostering new ideas and collaborations, as well as presenting to the researchers the potential funding opportunities in PM field that can be fostered by the future European Partnership on Personalised Medicine (EP PerMed).

The story behind our personalised medicine research project – video competition
This competition was launched by ERA PerMed to provide a platform for the young researchers participating in the JTC2018 ERA PerMed co-funded call to showcase the fascinating cutting-edge research that they are performing on prominent topics in personalised medicine, while collaborating with multi-national research groups.

VIDEOS CAN BE VIEWED HERE>

PATIENT ENGAGEMENT IN PERSONALISED MEDICINE

MEASURES CARRIED OUT IN THE FRAMEWORK OF ERA PERMED:

1 Evaluation Pilot study: Patients as reviewers to select projects for funding

2 Inclusion of patient experts in the midterm evaluation

3 Inclusion of patient experts in the Advisory Board / annual call

4 Relations with EUPATI, EPF (European Patient Forum), EATRIS_Plus and FT3 project

5 Active involvement in research projects encouraged through:

5.1 Evaluation criteria:
5.1.1 Involvement of pertinent patient organisations (if available/ applicable);
5.1.2 Interdisciplinary collaboration: Coherent integration of all kinds of project partners (e.g patient organisations) needed to successfully accomplish the proposed work.
5.2 Detailed description of patient involvement in the proposal template

UNDERWAY:

ERA PerMed Guidelines for Successful Patient Engagement in PM research: with the main objective of identifying the main strategies to include patients in the PM research process, including clinical studies in PM and the subsequent elaboration of guidelines for researchers and funders, to foster the broader and more active implementation of patient engagement in future PM Research Programmes.

KEY NEEDS AND OBSTACLES FROM THE RESEARCHERS' PERSPECTIVE

- Identification of representative and appropriate patients - uniqueness of PM research
- Level of scientific knowledge and diverse expertise of patients/citizens
- Uncertainty about the scope of the patients' roles
- Time, human and economic resources
- Evidence for added value/impact
- Trust
- Step-by-step recommendations, including metrics of economic compensations

PRIORITIZING PATIENT ENGAGEMENT IN RESEARCH – FUNDING AGENCIES' PERSPECTIVE:

- Encourage partnerships between researchers and patient organisations: ensures that patients are involved in the research process from the early stages of project development and can provide valuable insights into the needs and priorities of patients.

- Require patient engagement as a condition for funding: helps ensure that patient engagement is a core component of the research project and that patients are involved in meaningful ways.

- Encourage and prioritize patient-centred research: prioritize funding for research projects that actively engage patients throughout the research process and incorporate patient perspectives and input into the study design, implementation, and dissemination.

- Provide and support training and education for researchers and patients: enhance skills and knowledge related to patient engagement in research. This can include workshops, webinars, or online resources on topics such as effective communication, ethics, and research methods.

- Develop guidelines and standards: including best practices for engaging patients, ethical considerations, and evaluation of the impact of patient engagement on research outcomes.

- Allocate specific funds:

    - For patient engagement activities in the calls for proposals process: patient engagement activities such as patient advisory boards, focus groups, and patient peer review process of research projects.

    - To support patient engagement activities as partner patient co-investigators.

ERA PERMED 1ST TRANSNATIONAL CALL

JTC 2018

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

CO-FUNDED BY THE EUROPEAN COMMISSION (EC)	25 PROJECTS FUNDED	~28 M€ TOTAL BUDGET	133 RESEARCH GROUPS	18 COUNTRIES	>155 PEOPLE HIRED/TRAINED	~280 SCIENTIFIC PUBLICATIONS

The overall aim of the call was to fund projects showing clinical feasibility of personalised medicine in various types of diseases ranging from complex/multifactorial diseases to monogenic diseases, including cancer, rare diseases, psychiatric disorders and more. Clinical feasibility was defined in this call as the demonstration of significant and clinically relevant improvement of current diagnostics and/or therapeutics, based on improved understanding of underlying molecular mechanisms. The outcomes of these projects include novel discoveries, such as new biomarkers, new products and techniques and new guidelines.

IMPRESSIONS FROM JTC2018
FUNDED PROJECTS

AML_PM
Improved treatments of Acute Myeloid Leukaemias by Personalised Medicine

"Through our project we were able to take important steps forward towards using machine learning and mathematical modelling methods to improve the mechanistic understanding of important subtypes of leukemia and use this to select drug treatment. The project crucially depended on collaboration between research groups with leading expertise within different disciplines and having access to patient material from multiple countries. In particular we looked at one cancer subtype (PEL) well suited to develop our approach but with too few samples within each country to enable proper investigation. The approaches developed can be extended and utilized to other cancer types and together with many other efforts contribute to precision medicine helping many more patient groups over the coming years."

Coordinator:
Inge Jonassen

Partners:
Bjørn Tore Gjertsen

Jan Jacob Schuringa

Ursula Klingmüller

Jens Timmer

Mels Hoogendoorn

Aaron Schimmer

BATMAN

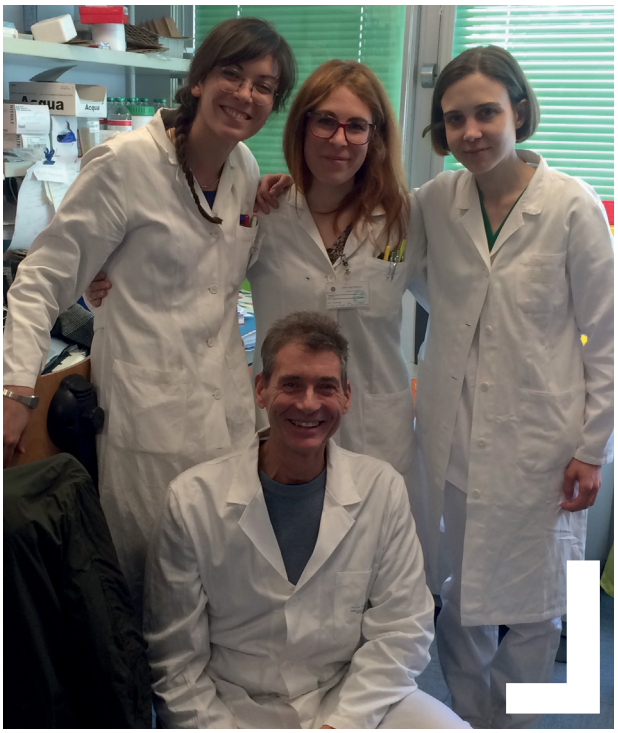
Biomolecular Analyses for Tailored Medicine in Acne iNversa

The multinational collaboration within our consortium, comprising diverse disciplines and sectors, significantly benefited our research in understanding Acne Inversa (AI) susceptibility, severity, and treatment response. Patient recruitment and clinical analysis (involved 310 AI patients, revealing novel genetic variants in genes such as NCSTN, PSENEN, and GJB2. Despite challenges, including the exclusion of familial samples, this work lays the foundation for personalised medicine in AI.

Functional investigations on AI-related biological pathways showcased achievements in animal models, with gamma-secretase inhibition impairing autophagy in hair follicles. In vitro studies generated iPSCs lines from AI families, providing valuable resources for future research. Although challenges were encountered, such as mutated HaCaT cell integration issues, significant progress was made in developing a smartphone application for patient data collection.

Looking ahead, the impact of our project on personalised healthcare is profound. With identified genetic variants and pathway insights, we envision tailoring AI treatment based on individual profiles. In 5 years, personalised medicine for AI could involve targeted therapies and interventions, leveraging genetic information for improved patient outcomes. The integration of diverse data sources and ongoing AI analysis further positions our work at the forefront of advancing personalised healthcare for AI patients.

Website: batman-project.eu/en



Coordinator:
Sergio Crovella

Partners:
Esther von Stebut-Borschitz

Matthias Schmuth

Michele Boniotto

Vincent Flacher

Matjaž Gams

Angelo Valerio Marzano

FindingMS

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

The FindingMS project led to two main outcomes in the field of multiple sclerosis. First, we identified biomarkers of disease activity, favoring a more comprehensive understanding of the mechanisms underlying the disease. Moreover, a predictive model of disease activity was developed to potentially help in the classification of patients since the beginning of the disease. This is particularly relevant in the context of multiple sclerosis, for which we foreseen that personalised intervention will gain relevance in the near future given the huge number of drugs that are available and will soon be approved. If properly validated and tested in larger cohorts, our results could have a positive impact on patient management, favorably impacting long-term clinical outcomes and optimizing treatment choices, contributing to improve quality of life and to slow disability accumulation of patients.

The multinational collaboration and integration of different disciplines represented an added value of the project, including the possibility to share data on a large set of sample, and to combine the different expertise in a multiset of fields (such as clinics, molecular biology, systems biology). The integrative approach across different layers of information was a relevant part of the project, allowing us to disentangle the complexity of the topic.

Website: findingms.com

Coordinator:
Federica Eva Esposito

Partners:
David Brassat
Ettore Mosca
Alexander Kel

GATA2-HuMo

Human disease modelling of GATA2-related Myelodysplastic Syndromes and Acute Myeloid Leukemia

"HuMO-GATA2 consortium by this study has unveiled crucial insights into GATA2 deficiency, a rare genetic disease that predisposes individuals to myelodysplastic syndromes and acute myeloid leukemia. Through in-depth genetic analysis, we've pinpointed the specific mutations and genetic factors that contribute to disease progression. These results advance our understanding of this rare genetic disorder, enabling early and accurate diagnosis and the development of personalised treatments tailored to each patient's genetic profile. We are moving toward a future where individuals with these predisposing hematological disorders will receive care that is tailored to their unique genetic characteristics, fostering improved overall well-being and quality of life."

Coordinator:
Alessandra Giorgetti

Partners:
Anna Bigas

Marcin Wlodarski

Csaba Bödör

GEPARD

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

Photo: Tampere University/Jonne Renvall

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer, with approximately 4,000 new cases diagnosed annually in Europe. Our project focused on patients with a suboptimal early therapy response who are at risk of relapse. We identified several genomic alterations and biological processes that can improve diagnostics and developed bioinformatic tools for bulk and single cell analysis of somatic mutations and gene expression changes in leukemia. Animal models provided novel insights into the early steps of leukemia development before the onset of full-blown disease and revealed phenotypes that contribute to drug treatment resistance in different tissue environments. While the worldwide COVID epidemic prohibited planned on-site meetings and researcher exchange, our project connected online experts across various disciplines. Together, we tackled challenges in the ethical application process, clinical data collection, animal modeling, laboratory experimentation, and computational data analyses. We envision that the continuation of this type of interdisciplinary collaboration is not only necessary but will also provide more individualized treatment options for children and young persons with leukemia in the near future.

Coordinator:
Olli Lohi

Partners:
Merja Heinäniemi

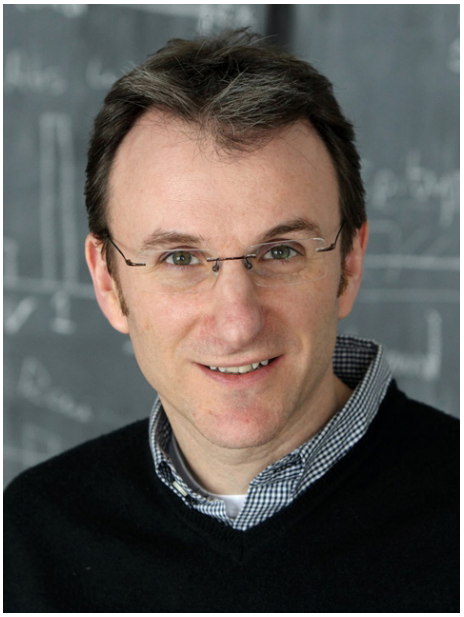
Valtteri Wirta

Jesus Duque-Afonso

Julia Hauer

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. Although antidepressants are the most common treatment and have demonstrated effectiveness, on average, 30-40% of patients do not respond. Personalised treatment is currently impossible due to a lack of objective predictors of antidepressant response.

Our project's goal was to develop a clinically useful biomarker panel to increase the precision of MDD treatment. Using AI-based approaches, we studied existing clinical trial datasets (>40,000 samples) to generate machine learning models of response using clinical and demographic features, and identified key features and patient subgroups that predict differential antidepressant response. In parallel, we investigated biological markers in blood samples (>500 samples) from MDD patients treated with antidepressants. Using next-generation sequencing, we studied small noncoding RNA biological markers and identified a specific microRNA found in blood plasma that was associated with response.

This transnational collaboration brought researchers from Canada, Germany, and Israel, each possessing unique expertise and background, to work collaboratively to carry out a large-scale and comprehensive study. The ERA PerMed funding provided a unique opportunity to apply a multidisciplinary approach to investigate both clinical and biological markers, and further advanced biomarker research in MDD for a more personalised approach to treatment.

Coordinator:
Gustavo Turecki

Partners:
Alon Chen
Bart Rutten
Ariel Rosenfeld
Sidney Kennedy

JAKSTAT-TARGET

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

JAK STAT TARGET CONSORTIUM

In the Era-PerMed JAKSTAT-Target project, our focus was on studying mature T-cell leukemias/lymphomas (MaTCL), a group of blood cancers typically associated with a poor prognosis. Conventional therapies, such as chemotherapy, have shown limited effectiveness against MaTCL. Despite the diverse nature of MaTCLs as distinct cancer types, they exhibit common features, including mutations in the JAK/STAT pathway genes.

Our consortium comprised partners with varied expertise encompassing clinical hematology, immunology, computer science, and chemistry. Each specialized area contributed significantly to uncovering novel mechanisms associated with the disease's biology. Moreover, these findings were instrumental in advancing novel drug development efforts. Alongside the development and testing of new chemical compounds, we identified synergies among existing cancer drugs capable of targeting multiple pathways driving this form of leukemia. These drug combinations are earmarked for future clinical trials.

In essence, our research offers innovative personalised medicine approaches, facilitating improved individualized diagnostic tools and treatment decisions. Furthermore, it contributes to the formulation of more informative trials aimed at benefitting MaTCL patients.

Consortium website: jak-stat.org

Coordinator:
Satu Mustjoki

Partners:
Marco Herling
Heidi Neubauer
Patrick Gunning
Tero Aittokallio
Benjamin Haibe-Kains

Kidney Attack

Multidimensional stratification for treatment of acute kidney injury

Kidney disease is one of the fastest growing global causes of death, projected to become the fifth global cause of death by 2040. Unlike for other diseases, such as cardiovascular disease, the concept of primary prevention of kidney disease does not exist. Primary prevention involves identifying patients a high risk of a condition (cardiovascular or kidney disease) and provide preventive intervention so as the condition never develops. For kidney disease, identification of at-risk individuals is especially important, as current diagnostic criteria for either acute or chronic kidney disease only identify patients at an advanced stage of the disease: therapeutic intervention may be less effective or not effective at all. KIDNEY ATTACK focuses of acute kidney injury and used systems biology (the simultaneous assessment of thousands of molecules) to characterize molecular signatures in urine that allows to predict who will develop acute kidney injury following cardiac surgery or in intensive care units. Moreover, different molecular signatures were characterized for men and women. This tool will help select high risk participants for clinical trials of novel treatments that prevent acute kidney injury. Eventually, this will lead to the availability of novel interventions in daily clinical practice that contribute to maintain kidney health.

Coordinator:
Alberto Ortiz

Partners:
Stanislas Faguer

Jochen Metzger

Stéphane Gazut

PERMEABLE

PERsonalised MEdicine Approach for asthma and allergy Biologicals seLEction

"Asthma is a prevalent chronic condition, particularly among children. Severe asthma has a large burden on the lives of patients and their families. The outcomes of the PERMEABLE consortium have contributed to a joint European roadmap to address the unmet needs and priorities of children with severe asthma on biological therapy. The project's findings on molecular signatures of treatment response, contribute to empowering patients and their families with information about the likelihood of treatment response, enabling shared decision-making and facilitating a more personalised and patient-centred approach to care.
The multidisciplinary and multinational aspect of our PERMEABLE consortium made it possible to apply novel techniques in samples obtained in an international setting that are scarce on a national level. Furthermore, the transnational collaboration facilitated access to other European consortia and networks, bringing multiple stakeholders together for a common goal."

Coordinator:
Susanne Vijverberg

Partners:
Michael Kabesch
Uroš Potočnik
Erik Melén
Jakob Niggel
Susanne Reinartz

PERMIT

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

The PerMIT project focused on life-threatening infectious diseases, including the destructive necrotizing soft tissue infections (NSTI) and the large heterogenous group of sepsis patients. The severity of these infections is dictated by the patients' response to the infection. For this reason, personalised therapeutic strategies targeting both the pathogen and the host response are needed. PerMIT built on the resources created in the EU FP7-project INFECT including the world's largest multicenter, prospectively enrolled patient cohort on NSTI, patient samples, multi-omics data, strategic data stewardship and pathophysiologic models. The work in PerMIT pinpointed predictive metabolites, protein biomarker profiles, immune profiles, and genetic polymorphism underlying specific host responses in specific subgroups of sepsis or NSTI patients. Furthermore, our studies have provided insight into adjunctive therapies in NSTI linked to microbiologic aetiology. The significant advances achieved in PerMIT were enabled by the strong collaboration between clinicians, experimentalists, bioinformaticians and computational biologists; all part of the PerMIT transnational and interdisciplinary consortium. The project has demonstrated the clinical feasibility and prospects for personalised medicine approaches to the management of severe acute infectious diseases. Clinical trials are in the planning, as is also diagnostic tool development to enable patient stratification in the field.

Other info: permedinfect.com

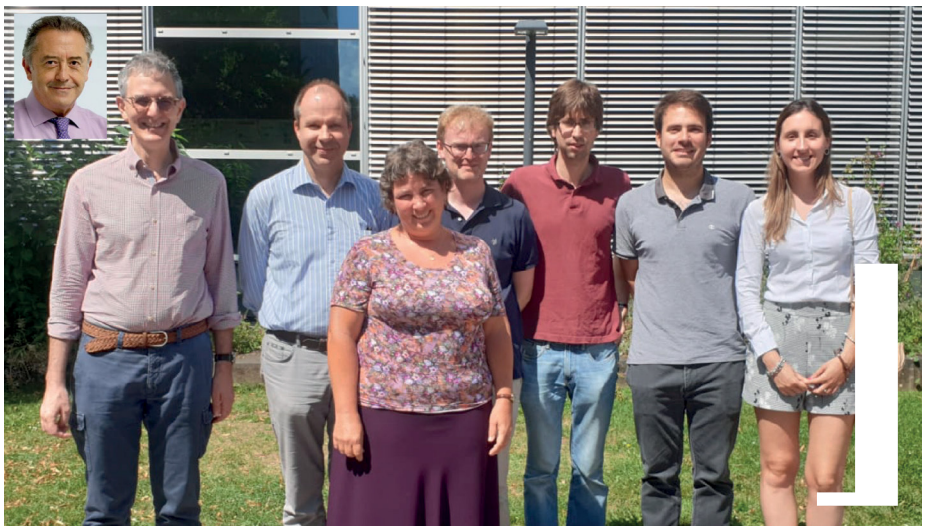
Coordinator:
Anna Norrby-Teglund

Partners:
Ole Hyldegaard
Steinar Skrede
Vitor Martin dos Santos
Edoardo Saccenti
Annebeth De Vries

PerProGlio

Integrative Personal Omics Profiles in Glioblastoma Recurrence and Therapy Resistance

Glioblastoma is a malignant brain tumor with currently no cure. Clinically relevant therapy options include a "one-fits-all" strategy with chemo- and radiotherapy. Often in glioblastoma patients, the progress of therapy and disease is monitored by Magnetic Resonance Imaging which is costly and normally performed in 6 months intervals. This leaves the patients with uncertainty about the success of therapy. Our project aimed to facilitate the monitoring of therapy response and progress by using blood-based markers which can be either nucleic acids or proteins. Based on our results, we are confident that in the future we can monitor therapy success and tumor progression routinely and more frequently with ease. To identify reliable and specific blood-based markers, we collaborated with experts in their field in Europe (Milan, Freiburg, Marburg, Valencia, Bucharest) and Canada (Toronto). Without ERA PerMed funding, this would never have been possible. Glioblastoma is a perfect example for personalised therapy, since the development of novel drugs is continuing and the personalised strategy allows a better fitted therapy for patients in the future. We are confident that we will have better treatments and monitoring methods in the next 5 years to improve quality of life and survival of patients affected by glioblastoma.



Members of ERAPerMed project „PerProGlio": from left to right: top left inset: Luis Marti Bonmati (HuLaFe), Giovanni Tonon (Milan), Jörg W. Bartsch (Coordinator, Marburg), Anca Gafencu (Bucharest), Oliver Schilling (Freiburg), Hannes Roest (Toronto), Alejandro Rodriguez Ortega, Leonor Cerda Alberich (both HuLaFe).

Coordinator:
Joerg Walter Bartsch

Partners:
Oliver Schilling
Hannes Roest
Giovannni Tonon
Anca Gafencu
Luis Marti-Bonmati

PersoProCaRisk

Integrative Personalised Risk and Therapy Stratification of Localised Prostate Cancer

Prostate cancer is the most common malignancy in males in Europe and treatment personalisation is a main pillar to improve treatment outcomes and maintain a good quality of life after treatment. In the project "Implementation of mobile health tools and artificial intelligence for personalised radiation treatment planning and monitoring in prostate cancer (PersoRad)" a multidisciplinary consortium consisting of physicians, physicist, biologist, computer scientist and psychologist aimed in incorporating the most novel development coming from the health-technology sector for a more personalised treatment approach. The multidisciplinary of the team enabled novel synergisms fostering cutting-edge research. By using a prospectively collected study cohort and state-of-the-art medical imaging like PSMA-PET/CT, the team was able train convolutional neuronal networks (Artificial intelligence) for automatic tumor and organ segmentation as well as non-invasive tumor characterisation in terms of radio-resistance. These findings were translated into radiobiological model systems and might lead to a fully personalised radiation dose prescription in the future. In parallel, the study team performed targeted interviews assessing the demand of a mobile health application for monitoring the patient's quality of life. Taken together, the PersoRad project successfully paved the way towards the implementation of modern health-technology towards a patient-centered and personalised cancer treatment.

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PersTIgAN
Personal Treatment in IgA Nephropathy

The ERAPermed PersTIgAN group developed a biomarker consisting of small protein fragments in urine, which is able to indicate the severity and progression risk of IgA kidney disease. IgA nephropathy is the most frequent of a group of rare inflammatory kidney diseases called glomerulonephritis. IgA nephropathy affects around 1 in 1000 people and causes 10 to 30 % (depending on the global region) of all cases needed to be treated by dialysis. The course of the disease is mostly slow and chronical, but the risk in terms of later onset of dialysis cannot be foreseen precisely. Therefore, appropriate therapy, which carries the potential of side effects, is under debate. PersTIgANś collaborative approach made a access to sufficient patients and samples possible and it was the prerequisite for both the explorative and applicable phases of the project.
The PersTIgAN biomarker, IgAN237, now provides more information on disease progression with an 89% accuracy and augments the decision in favor or against immunosuppressive treatment. It was already used in clinical routine in Sweden and Germany and documented in an accompanying observational clinical study.

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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

PEVOdata project focused on novel therapeutic options for Squamous cell carcinomas (SCC) from different locations. The pillar of PEVOdata was the PEVOSQ basket trial (NCT04357873) evaluating the efficacy of immunotherapy (pembrolizumab) in combination with an epidrug (vorinostat) in patients with late stage SCC of various locations.

PEVOdata objectives were to: 1) explore the modifications of immune-related and molecular-epigenetic biomarkers; 2) build a database integrating molecular and clinical profiles to assess predictive biomarkers of response/resistance to the combination; 3) develop long-term standards for data collection and management with appropriate metadata and provenance for precision oncology research.

Main results were the encouraging antitumor activity of pembrolizumab combined with vorinostat in SCC with unselected PD1/PD-L1 status, especially in HPV-associated cancers. Responses were interestingly higher than previously reported in trials with immunotherapy alone. Integrating clinical with genomic, transcriptomic and epigenetic data will allow identifying biomarkers that will be tested in independent cohorts and will set the ground for future clinical trials.

Open and interoperable standards for data sharing enabling collaborators to exploit complex information to make discoveries which will benefit cancer patients, safeguarding privacy according to European regulations is key for next generation precision medicine trials and health care development in coming years.

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PLOT-BD

Personalisation of LOng term Treatment of Bipolar Disorder

Bipolar disorder, like most severe psychiatric conditions, affects young people and runs a lifetime course. Early intervention and accurate selection of long-term treatment are the cornerstone of its clinical management. However, due to the heterogenous nature of the illness and absence of suitable biomarkers, most clinicians select treatments on the "trial-and-error" basis. This inevitably leads to delays in effective mood stabilization, increased risk of functional impairment and possibly suicide.

Our work funded by ERA PerMed has shown that by combining clinical and genomic information, many people with bipolar disorder can be treated effectively without significant delays. Applying novel technologies based on induced pluripotent stem cells helped us identify novel potential molecular targets for treatment of people who do not respond to prototypical bipolar treatments. Based on these results, we will now proceed to validate our results in a prospective study as well as screen for molecules that modulate the discovered cellular phenotype of bipolar disorder.

The results so far give us confidence that in the next five years, treatment of severe mental illness will become more rational. It will still be based on a comprehensive clinical assessment, but will also make use of genetic, biochemical, and metabolic markers.

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PROCEED
PeRsOnalised Genomics for CongEnital HEart Disease

PeRsOnalized Genomics For CongEniTal HEart Disease

Congenital heart disease (CHD) is a common birth defect affecting 1 in every 100 babies born. The genetic cause is known in fewer than 20% cases. As part of the PROCEED network that includes researchers from Canada, the Netherlands, and Germany, we used "whole genome sequencing" to look at the entire genetic code of over 1500 patients with CHD.

We discovered new causes of CHD which included defects in new genes, defects affecting multiple genes, and trouble in parts of the genetic code that control how genes work. This discovery made it four times more likely to find the cause of CHD compared to regular genetic tests. We further found that some gene defects are related to more severe disease.

These findings were returned to physicians and families to help speed up the diagnosis of the genetic cause of CHD. It also laid the groundwork for personalised care. By knowing the type of gene defect, doctors can predict how severe a person's heart and other health problems might be and can decide the best type and timing of surgery. This information can also give a more accurate idea of the chances of having a similar problem in the family.

In the future, this research could help doctors figure out which babies might benefit from special treatments before they're born. This would reduce the challenges of dealing with complex CHD and improve the chances of successful treatment.

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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. RAISE-GENIC uses artificial intelligence to develop a tool that predicts the anti-seizure drug with the highest likelihood of success in an individual patient. Such a personalised medicine approach would allow patients to start on the best drug immediately thereby reducing the time until patients become seizure free and improving quality of life. The ERA PerMed funding allowed us to merge large international datasets including details on the patients' epilepsy, genetics, raw brain wave signals and brain imaging data and combine this with experimental results in human neuronal cell models to create a multimodal machine learning model. This paves the way for future approaches including even larger datasets which will further advance precision medicine in epilepsy and other diseases by reducing the patients' burden caused by seizures, comorbidities and treatment side effects."

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SYNtherapy

Synthetic Lethality for Personalised Therapy-based Startification in Acute Leukemia

High-throughput technologies have significantly advanced our comprehension of leukemia, unveiling potential targets for personalised therapies. Despite these strides, therapeutic options for relapse/refractory leukemic patients remain limited. The SYNTHERAPY project aimed to unveil novel therapeutic strategies for leukemia patients based on the synthetic lethality (SL) approaches. Through NGS, we efficiently detected various genetic alterations in B-ALL patients, encompassing SNVs/INDELs, fusion genes, CNVs, aneuploidies, and SNPs associated with pharmacogenetics (doi:10.3390/jpm10030137). Several of these genetic vulnerabilities were validated as promising therapeutic targets for SL approaches. Notably, the essential role of the ETV6/RUNX1 (E/R) fusion protein in ALL viability was established (doi:10.3390/cells9010215). Furthermore, a potent synergism between doxorubicin and cell cycle checkpoint inhibitors in ALL cells was identified, highlighting their dependence on the ATR-CHK1 pathway to survive doxorubicin (doi:10.1007/s10565-021-09640-x). ATR kinase also emerged as an ideal target for del(11q)/TP53-mut leukemia treatment. We generated a leukemia cell models that resulted only partially responsive to BCR signaling inhibitors (ibru:nib) but sensitive to the effect of AZD6738, ATR inhibitor (doi:10.1002/ctm2.304). Additionally, novel vulnerabilities in del(11q)/ATM-mut leukemias were uncovered, showcasing the synergistic effect of PARP1 and BCR inhibitors (olaparib and ibrutinib) associated with impaired homologous recombination repair (RAD51 dysregulation) (doi:10.1038/s41375-020-0714-3). Finally, Nanopore sequencing facilitated copy number analysis and fusion gene detec:on in AML samples, identifying HNRNPK haploinsufficiency as a potential synthetic vulnerability.

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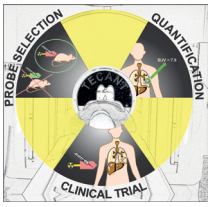
TECANT

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



"A milestone in the diagnosis and treatment of neuroendocrine neoplasms (NEN) was the introduction of radiolabelled somatostatin receptor (SSTR) agonists. However, in some clinical settings, a more sensitive diagnostic tool is needed, and also a better targeted therapy for patients with NEN.

Since the SSTR antagonists recognise more binding sites in tumour tissues and provide higher uptake and better tumour/background contrast even at low SSTR tumour expression, the translational TECANT study was planned. To achieve this goal, five experienced international partners specialized in new radiopharmaceuticals development and in the management of NEN patients joined together.

Two antagonists, N4-LM-3 (TECANT1) and N4-p-Cl-BASS (TECANT2), were compared preclinically for their stability in human serum, affinity for the SSTR and in vivo biodistribution in animal model. Finally, [99mTc]Tc-TECANT1 was selected for the clinical trial as it showed longer tumour residence time and the lower kidney and liver uptake.

A subsequent clinical feasibility study confirmed the safety of [99mTc]Tc-TECANT1 with rapid distribution with predominant renal excretion. [99mTc]Tc-TECANT1 showed a very high detection rate in all examined patients – in most cases with higher contrast in comparison to 68Ga-SSTR agonist, the current gold standard in NENs imaging.

We believe that the [99mTc]Tc-TECANT1 development may be the key to reliable assessment of the SSTR status (primary focus/metastasis) and will be important for improving personalised NEN management, increasing therapeutic efficacy."

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