

Final summary report EATRIS

Executive Summary

EATRIS is an initiative to create a European, globally competitive infrastructure for biomedical translational research. During its three year Preparatory Phase EATRIS aimed at defining a viable concept for translational research infrastructure, including the setting up of a sustainable financial plan to operate it. The Preparatory Phase of EATRIS has been funded with a budget of € 4.2 million by the European Commission for the years 2008-2010. It will be followed by a Transition Phase foreseen for the years 2011 & 2012, in order to operationalise the EATRIS vision and establish the legal entity.

During the Transition Phase pilot projects will be run to implement the operational configuration and prepare the start of the Operation Phase in 2013. In its Operation Phase EATRIS will offer open access to state-of-the-art infrastructure and expertise for translational research to the biomedical research community. EATRIS will work together with users from academia, the public sector and industry to carry out translational projects of the highest quality standards.

EATRIS will operate through a strong consortium of Translational Centres across Europe that will provide researchers with the necessary means to develop their discoveries into products. This comprises not only broad access to state-of-the-art-facilities, technologies and translational know-how but also training and supporting services. Sharing experience and powerful translational infrastructures will lead to better healthcare provision and provide a bridge between countries of different translational capacity, making Europe more competitive.

Summary description of the project context and the main objectives

The enormous progress made in biomedical research during the last decades bears a tremendous medical and economic potential. However, exploiting this potential has been much more difficult than expected. Translation of basic research discoveries into clinical application has turned out to be a major challenge for the European Research Area.

The translation of discoveries from basic research into commercially viable clinical applications is a complex and lengthy process. Special infrastructure, knowledge and expertise is required which is usually not available to basic researchers. This gap has been recognized worldwide and translational infrastructure is promoted intensively. Way ahead is the USA investing 500 Mio. US \$ annually in the expansion of translation centres until 2012; a similar situation exists in Japan. If Europe wants to maintain or improve its position in biomedical research and in the global pharmaceutical market, it urgently needs to improve the framework conditions to help research to translate results from basic research into clinical application.

Currently, also the pharmaceutical industry is facing challenges in seeking novel means of extracting value in the Research & Development (R&D) process, due to dwindling drug pipelines and the looming patent cliff that many firms face. The current drug testing strategy of the industry involves testing early for safety and toxicity followed by testing for efficacy. This strategy often leads to vast sums of money being spent on testing, only to discover later that the drug is not efficacious. In fact, for every ten drugs that enter clinical testing, only one will make it to market. This is a contributory factor to a R&D process that ends up with a required developmental period up to 15 years and an average price tag of Euro 1.5 billion per novel drug brought to market. Furthermore, despite doubling of R&D expenditures by pharma industry, the output of new molecular entities (NME) in Europe has halved between 1989 and 2008. However, the real innovation crisis for patients and society is not the recent decline in NME, but the small percentage that provide distinguished clinical advantages to patients over existing medications. In 2005 all of the top 10 best-selling drugs on the market were “copycats”, drugs that hit precedented targets and work by the same mechanism of action as other approved drugs. Thus, the pharmaceutical R&D pipeline is in serious need of making drug development and testing more efficient and effective, as well as finding new innovative targets that meet real medical needs.

In addition with increasing life expectancy, the rise of chronic conditions and growing pressures on health care budgets, we are likely to see a growing need for innovative, cost-effective solutions to current health care problems. This can only be achieved if academia, governments, research centres and industry work together to create the right climate and conditions to foster innovation for the benefit of public health throughout Europe.

It is against this background that European governments and centres of excellence in translational biomedical research have gathered to create EATRIS and take concerted new actions for improving translational research from bench to bedside.

EATRIS is one of the biomedical projects initiated by the European Strategy Forum on Research Infrastructure (ESFRI) funded by the 7th Framework Programme of the European Union from 2008-2010.

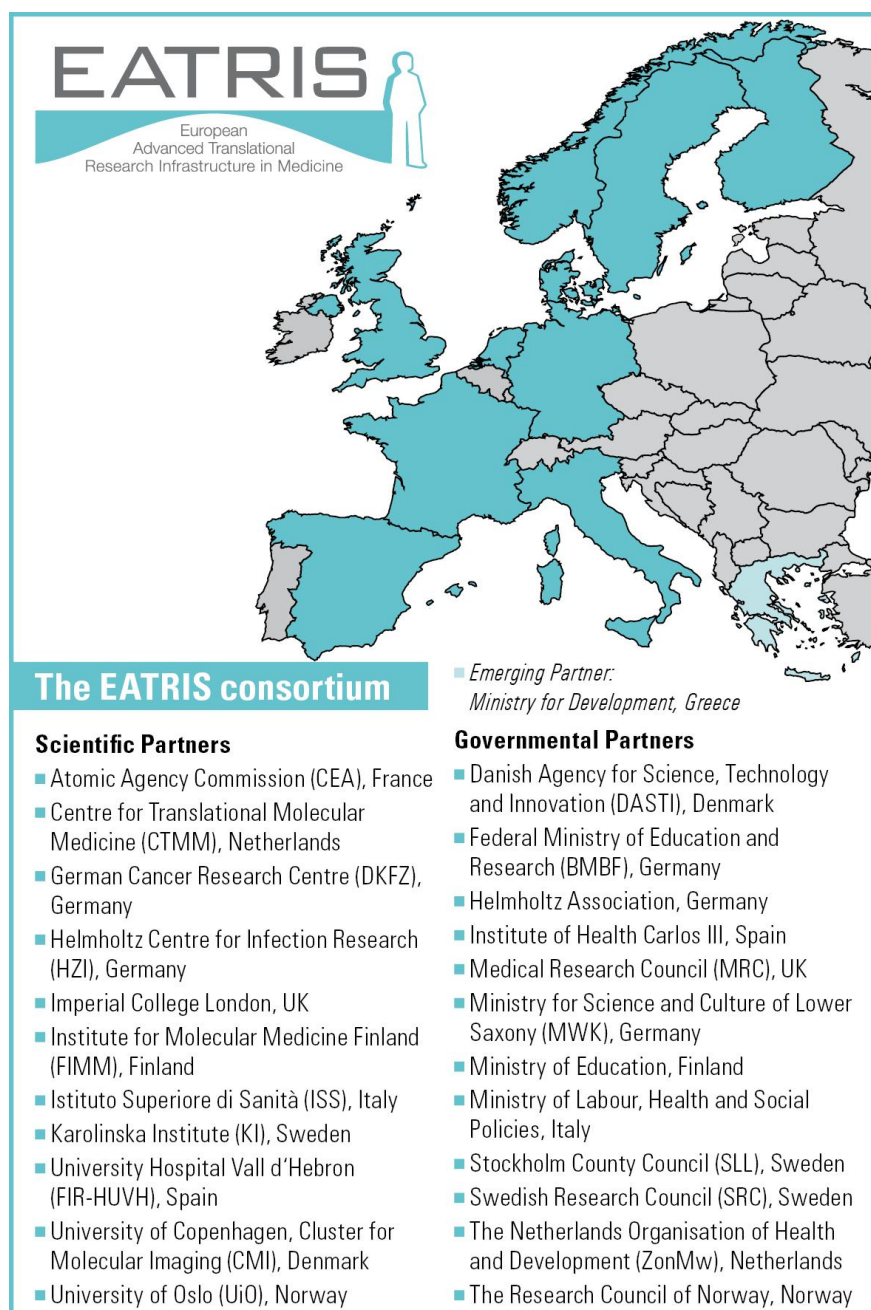


Figure 1: Ten European countries were involved in planning the EATRIS research infrastructure (turquoise)

Objectives of EATRIS: Advance Translational Research

To improve human health, scientific discoveries at the level of basic biomedical research have to be “translated” into practical, clinical applications. At the same time, novel observations about the nature or progression of a disease made by clinical researchers can be passed back to inspire new approaches in basic research. This two-way process of developing new tools or treatments for use in patients is called “translational research” or “translational medicine”.

Translational research needs a certain critical mass to allow for sufficient quality of procedures. As biomedical translation is multidisciplinary by nature, critical mass is important not only at the individual company /institutional level but also at the cluster level. Many academic users suffer from the limited availability of platform technologies and testing facilities such as compound screening, labs and tools for validation and optimisation of therapeutic approaches. EATRIS will help secure the critical mass needed for successful translational research by creating European wide clusters for translational research. In essence, all aspects of the clinical environment and technology platforms necessary to achieve successful product development will be brought together under the EATRIS roof and be made available to all EATRIS users. These comprehensive research facilities will benefit from strong regional mobilisation.

Another bottleneck in bringing promising research finding into (pre-)clinical development is the fragmented nature of science along the development chain. There is a lack of exchange between various disciplines due to a separation of daily routine and often even the physical separation of clinical and basic research. At the start of a research project awareness of the requirements of later stages of development rarely exists since academic research is often focused on a particular aspect. Furthermore the education and training of scientists is often too narrow and rarely bridges across the biological, medical and technical sciences. However, capacities are fragmented and collaboration with third parties is not uniformly executed. This presents a major opportunity for optimisation, as there is increasing awareness that a multidisciplinary approach is a critical factor for developing new medicinal or preventive products.

The EATRIS translational research infrastructure will overcome fragmentation by establishing multidisciplinary teams to accompany translational projects run within EATRIS. These teams will bring together all clinical, scientific, regulatory and product development related aspects needed over the course of the project. This helps to ensure that all steps of the development process are considered from the start. EATRIS will foster a philosophy of multidisciplinary exchange in its training and education of future translational research scientists. Dedicated training programmes and teaching tools will be made available in all EATRIS Centres.

Access to high quality clinical data as well as to well-defined patient cohorts is fundamental for successful translation. Access is usually limited to the research hospitals that initiated those cohorts as well as to their collaborating partners. Furthermore there is lack of knowledge of the comprehensive regulatory requirements that have to be fulfilled for the successful transition from bench to clinical application.

Exchange of information and knowledge between researchers is currently often restricted to conference papers, publications and e-mail between authors. More effective collaboration during the course of research may be achieved by establishing more sophisticated exchange mechanisms. Another challenge for knowledge exchange is the overwhelming volume of data, the diversity of data and the multitude of data sources. And finally each research community or discipline has its own scientific jargon. EATRIS will help facilitate the technical, semantic and process interoperability between research sites.

The collaboration between academia and industry is limited in Europe, too. The traditionally strict separation of both creates hurdles in the development pathway and often means that the translation from scientific discovery to marketable product and revenue generation is more time-consuming than necessary. EATRIS will encourage public-private cooperation by facilitating the integration of industry with academia and fostering a two-way exchange of resources and expertise. By offering common projects and exchange platforms to researchers in academia and industry alike, it will support closer collaboration.

In summary EATRIS will improve the conditions for and the performance of translational research by

- providing easier access to state-of-the-art research & development facilities and translational knowhow for all scientists and researchers
- overcoming fragmentation along the translational research pathway
- fostering knowledge exchange and standardisation
- providing training programmes for the next generation of translational researchers
- facilitating and encouraging cooperation between academia and industry

Objectives of Preparatory Phase

In this context the objectives of the preparatory phase of EATRIS were to work out a master plan describing in detail the establishment and mode of operation of the planned pan-European infrastructure during a later construction phase: This includes an agreement on the key legal, governance, strategic and financial issues as well as a concept to train and educate the next generation of biomedical translation researchers

Main results

The main result of the EATRIS preparatory phase project is the elaboration of the EATRIS open infrastructure strategy described below.

At the core of the EATRIS infrastructure are the EATRIS Translation Centres organised in a pan-European network. Each Centre consists of one or more European biomedical research and development institution(s) with translational knowledge and experience, which dedicate part of their capacities (up-graded or de novo) to EATRIS. The goal is to have all necessary disciplines (basic and clinic research) close together as a strong innovation core. Connecting different disciplines will enhance cross-fertilization and the

creation of new knowledge. According to their core expertise the EATRIS Translation Centres will specialise in products such as diagnostics, small molecule drugs, biologics, vaccines or advanced therapy medicinal products like cell therapies.

The EATRIS Centres comprise research infrastructure required along the entire development chain for prevention, diagnostic and therapy for particular diseases. They combine **high-quality physical resources** (so-called ‘bricks’) and **scientific expertise** as well as **professional translational project management** (‘brains’). EATRIS will use the **unique approach of opening the doors** of its comprehensive Centres to provide access for external users with promising discoveries. This ‘brick and brains’-infrastructure will guide the scientist best through the difficult process of translational medicine.

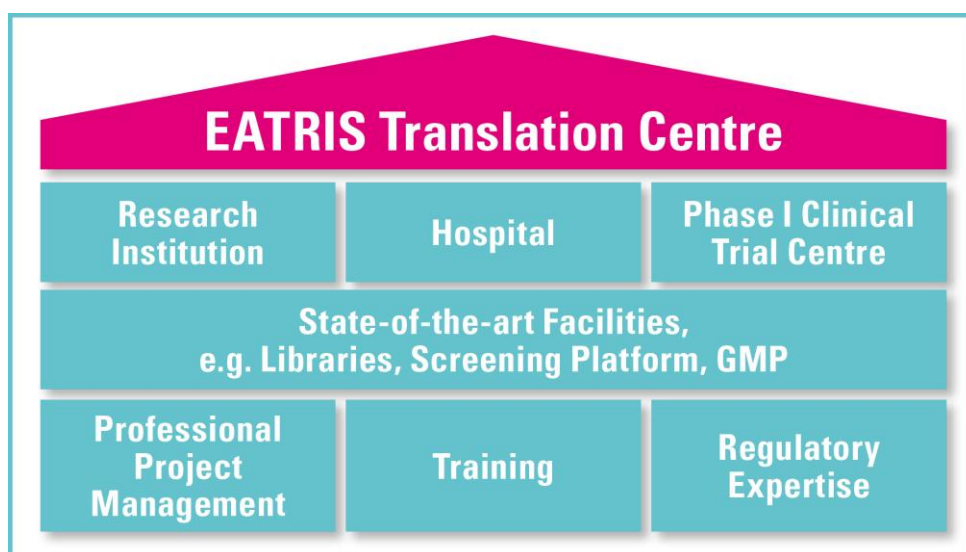


Fig. 2 The comprehensiveness of an EATRIS Translation Centres.

The available infrastructure within an EATRIS Centre will consist of all facilities necessary from a **first validation** of the hypothesis (**proof of principle**) to a **proof of concept** in human (phase I/IIa clinical studies) including physical components such as

- State-of-the-art animal facilities for preclinical validation studies
- Small molecule screening facilities to identify and characterize new drug targets
- Compound libraries
- High-resolution imaging facilities for preclinical and clinical validation
- Cyclotrons to produce tracers for diagnostics and efficient therapy development
- “omics” screening facilities for biomarkers and individualised medicine
- Disease specific patient and population cohorts to develop and validate new hypotheses for innovative diagnostic and therapeutic strategies
- Centralized GMP facilities for bioprocess development and manufacturing
- Facilities to carry out clinical phase I studies.

In the same way, expertise will be part of the infrastructure such as

- Professional product research and development
- Multidisciplinary teams to accompany the development
- Regulatory knowledge
- Training programmes

For improving Europe's translational research **excellent "Brains", meaning highly qualified staff, are as essential as excellent "Bricks"**. Therefore EATRIS will offer **training and education for scientists**, physicians and nurses, technicians and science-oriented clinicians. Along with know-how and experience EATRIS will foster a philosophy of multidisciplinary exchange in its training and education of future translational research scientists. This leads to highly educated, experienced personnel and a better communication through all disciplines and all steps of the drug development chain.

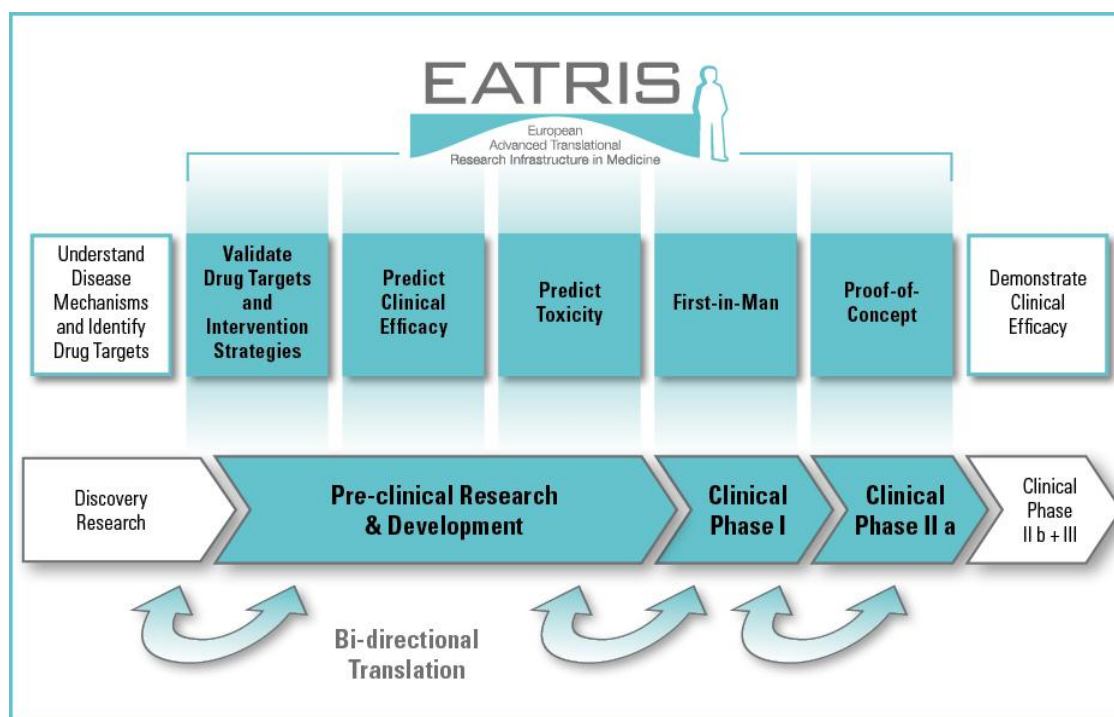


Fig. 3 The developmental chain is the sequence of R&D steps for product development of clinical application in diagnosis, therapy or prevention. EATRIS will cover the steps highlighted in blue.

The users of the EATRIS infrastructure will be basic biomedical researchers and clinical scientists located at universities, research institutions or SMEs and industrial partners that need support in order to overcome specific bottlenecks and to move their research projects from a discovery to the preclinical and clinical stage. EATRIS offers **comprehensive services to help secure the successful and rapid development of new products**. From the beginning, a translational project within EATRIS is accompanied by a multidisciplinary team and a project manager experienced in drug development and regulatory issues will guide the whole process. The guidance and support will include an assessment of the scientific basis, issues related to intellectual property rights, regulatory requirements, benchmarking with regard to existing technologies, potential risks, market

potential, cost, medical need and ethical issues. EATRIS will also support the transfer of results to industry for further development.

The final strategy summarised above is described in more detail in the Business Plan (first draft published in November 2009, final version by the end of the Preparatory phase), which serves as the central basis for the detailed scientific and organisational planning of the operation phase. It describes the vision, scope, guiding principles, operational and financial plan for EATRIS. It is intended as a platform for discussion with potential partners to seek endorsement for the EATRIS concept and secure partnerships and support to make EATRIS operational. The document is divided into 10 sections:

- Section 1 provides the context for EATRIS
- Section 2 describes the Vision and purpose of EATRIS
- Section 3 describes the Mission and benefits of EATRIS
- Section 4 defines the EATRIS landscape
- Section 5 provides a description of the EATRIS Centres
- Section 6 describes EATRIS Coordination & Support and outlines the services it will provide to the Centres and to external users
- Section 7 describes how EATRIS will attract research projects under its umbrella through its User Access unit
- Section 8 describes the governance and legal structure of EATRIS
- Section 9 outlines the Operational plan and defines a timeframe for its execution
- Section 10 provides the Financial plan for EATRIS Centres and Coordination & Support.

In addition to the development of the above described strategy of the EATRIS infrastructure, EATRIS produced further results necessary to achieve the objectives of the EATRIS preparatory phase namely to advance the project to a level of legal and financial maturity to implement the infrastructure.

In order to base the EATRIS strategy on existing best practice examples and to cover the needs of the European researchers two surveys have been performed. In addition, a stakeholder meeting in 2009 and a follow-up in 2010 as well as an EATRIS conference in 2010 provided the forum for a valuable exchange with potential users and industry representatives. Expert interviews were conducted throughout the project to draw in additional expertise outside the academic setting.

As a major success of EATRIS a **Memorandum of Understanding (MoU)** has been signed by seven EATRIS member states in September 2010. The MoU describes the willingness of countries to support the creation of EATRIS as independent legal entity and their efforts to find ways of financing. To bridge the time between the end of the EU project and the creation of a legal entity, a Transition Phase has been set up. The major aim of the Transition Phase is to establish a legal entity for EATRIS within the envisaged two years duration (2011-2012) of the Transition Agreement.

The Transition Agreement has been negotiated and determines

- The conditions under which the Parties will implement the EATRIS Initiative during the Transition Phase;

- The governance structure of the EATRIS initiative during the Transition Phase;
- The financial provisions for EATRIS Coordination and Support as well as the management and daily operations of the EATRIS initiative during the Transition Phase.

Also in preparation of the implementation of EATRIS The Netherlands was voted host country for the future legal entity and for the EATRIS coordination & support office.

As outcome of the work performed in the legal framework, ERIC seems to be an appropriate legal structure for EATRIS. Thus draft statutes have been prepared and the application of establishing ERIC will be finalised during the Transition Phase.

As result of the legal work, relevant criteria for an Intellectual Property-sharing model have been designed to prepare the access of external users to the EATRIS infrastructure. The fundamental objective of this EATRIS model is to provide a framework that is acceptable for all parties that leverages their individual strengths, given their divergent interests and risk profiles.

A **Governance model** was developed that reflects the central role of the EATRIS Translation Centres and that of the central EATRIS unit (EATRIS Coordination & Support) which is responsible for those tasks that cannot be performed effectively on a local level or where the added value is higher when being provided centrally (subsidiary principle). The budget for EATRIS Coordination & Support unit up to the formal establishment of the ERIC has been negotiated. This budget for the Transition phase will be adopted together with the Transition Agreement that the governmental partners are about to sign.

The **infrastructure components**, their design and the expertise that needs to be provided by EATRIS differs for the various product types developed like e.g. Molecular Imaging/Tracers, Biomarkers, Small Molecules, Advanced Therapeutic Medicinal Products (ATMPs) and Vaccines. Therefore an analysis of the different modules along the translational path has been made and a development chain has been designed, identifying all components that are needed from first proof of principle to proof of concept in humans for each of the product types that will be offered in EATRIS. For each product development chain, a position paper was prepared. These “position papers” describe the respective product development along defined milestones; the necessary infrastructure needed, engaged cutting-edge technologies, facilities/platforms and know-how at EATRIS partner centers and moreover, targeted bottlenecks in academia that currently hamper the progress in translational research. Realistic solutions on how to solve these roadblocks by infrastructural means are being described in these papers.

To allow collaboration between EATRIS centres interoperability at syntactical, semantic and process level is needed. This requires standardisation of data models, protocols and messages as well as harmonisation of working procedures. Therefore an action plan for standardisation and harmonisation within translational research has been developed.

To overcome the lack of knowledge of **regulatory issues** quickly (a major bottleneck in translational research), a **First-in-Man Manual** (FIM) has been developed to help and guide European researchers to address the most relevant regulatory issues when preparing and performing Phase I clinical studies. This manual also describes the requirements and preclinical testing needed to move a product through development and into the clinic. The regulatory requirements and other constituent components of an effective pipeline have been tailored to each product type.

Training: A successful pilot EATRIS PhD course/workshop was held in Milan in November 2010. It included subjects such as Biomarkers, Molecular Imaging, Clinical Trials, Bioinformatics in Translational medicine or Intellectual Property (IP) rights. There was a strong focus on interactivity to promote the contacts and collaboration between the participants.

Description of the potential impact

Setting up an infrastructure for translation research & development offering expertise and equipment for a wide range of different diseases and a broad spectrum of required treatments cannot be successfully covered by any individual country alone. This undertaking needs a truly European effort, accordingly ten European governments gathered within EATRIS to build up a distributed pan-European infrastructure based on existing biomedical translation research centres or hospitals. The setting up of the EATRIS infrastructure will be a strategic investment to structuring the European Research Area (ERA) by coordinating the existing national efforts in developing translational research infrastructure. EATRIS will use European synergies and the existing translational expertise to satisfy the huge demand for translational infrastructure. This will allow for better use of existing research capacity and avoidance of duplication across Europe through the bridging of complementary research facilities across the EATRIS consortium.

In October 2010 the European Commission has set up the '**Innovation Union**' to put innovations in areas such as healthy aging at the heart of its political agenda. The aim of the Innovation Union is to bring more ideas into innovative products. EATRIS will contribute by implementing an open infrastructure to develop innovative medical products. The **open access** is a crucial aspect to spread scientific excellence through Europe as a whole, as the advantages of the new infrastructure will not be limited to the EATRIS Translational Centres, but will be open to the whole translational research community of Europe. The services will be of special importance to researchers in those countries that are facing special challenges in terms of infrastructure, economic & institutional organisation. The availability of this open infrastructure will substantially increase the attractiveness of the ERA for researchers as it increases their chances of exploiting their basic biomedical research projects. Open Access to the EATRIS infrastructure will give equal chances and thereby **strengthen the ERA**.

The **services offered by EATRIS** in training and consulting will enable EATRIS to reach even more European researchers. By sensitising the European medical researchers e.g. to regulatory issues EATRIS will increase the number of basic research projects that have the potential for commercial application significantly and thereby generate a powerful European research force. Thus it will improve the societal impact of the high-quality fundamental discoveries made in European research institutions, thereby generating higher returns on the public investment in basic and clinical research. Especially as EATRIS Centres have a high potential to become the core of new **innovation clusters** in translational research, thus providing a boost to the national economies of member states that house them. It will help maximise **return on investment in translational research**.

By linking basic research and clinical trials and making the process from "bench to bed" more professional EATRIS will help industry to refill their pipeline with new, innovative

candidates of high quality. EATRIS will “de-risk” targets for industry: Drug candidates from academia will be more advanced on the translational path and developed following high quality standards. This increase in promising academic research projects will not only enhance the **competitiveness of the EU in biomedical research** but will improve its attractiveness for the biomedical and pharmaceutical industry as well. Industry can also benefit for their own research and development from the services as EATRIS will provide state-of-the-art facilities and knowledge usually not available in industry like tracers and cyclotrons. The proximity of research and (process) development will create spin-offs. This will attract further research and business (Small and Medium Enterprises, SMEs, and big industry). The economy will improve as more research and development will be performed in Europe. This opens the chance of more employment and due to the improved economy a higher standard of living.

But the main objective of EATRIS is to **contribute to public health** by ensuring that basic research leads to new innovative medical application which will improve health. EATRIS Translational Centre are predestinated to find cures for diseases with high unmet medical needs by focusing on innovative targets and therapeutics. In addition, advanced diagnostics and clinical studies aiming at patient stratification to identify non-responders will lead to a more individualised medicine, avoiding inefficient prescriptions and thus will allow to safe costs in the healthcare system. As EATRIS will not have the same economic constraints as industry, it can pursue as well rare disease areas that are not of primary interest to industry or highly innovative projects that carry a great promise but are more risky in terms of success. In future the development of new medicines will change fundamentally towards a more personalized medicine. Here, EATRIS is perfectly positioned and will serve as a valuable partner to industry. EATRIS will provide the basis for a better health of the European and global population.

Main dissemination activities

The dissemination activities of EATRIS provide information about translational research and EATRIS for the research community, policy makers, funding agencies, industry and the general public. This section gives an overview of the main dissemination activities and the articles published.

Webpage

The website www.eatris.eu acts as the central information portal of EATRIS. It provides information about the involved partners, the EATRIS concept and the ESFRI process. In order to complement the information according to the achieved progress the external website was updated in 2010. It describes EATRIS as an infrastructure initiative and thus looks beyond the Preparatory Phase by focusing on the future user. Results made towards the objective of the project will be directly included in description of the work, services and added value etc. of EATRIS targeted towards the future users and other stakeholders.

Publications

Media contacts were established and publications about EATRIS initiated in media and newsletters which address the main stakeholders (scientists, policy makers, scientists and

industry representatives), e.g. BIOforum Europe, Public Service Review: European Union, embnet news. Additionally the coordinator has been asked to give interviews on behalf of EATRIS and was quoted in Nature and Nature Review Drug Discovery in the context of translational research and European infrastructures. A peer reviewed article will be published in the Journal of Cardiovascular Translational Research (Springer Science and Business Media) in 2011.

Conferences

EATRIS organised a stakeholder meeting which was held on the 14th October in Basel within the context of the MipTec 2009 - The Leading European Event for Drug Discovery - which had 3'000 attendees from both academia and Industry. The MipTec thus offered the unique opportunity to reach the targeted stakeholders reducing both travel time and travel costs and making the advertisement of such event more targeted. During the Stakeholder Meeting, the EATRIS strategy, as well as the planned infrastructure prototypes were presented. As a follow-up, EATRIS was invited to contribute to the Round Table Discussion "Open Innovation" at the MIP Tec 2010. The round table brought together representatives from large pharma companies, academic institutions and bridging organizations to discuss how to foster innovation in drug discovery by new ways to partner in a more collaborative mode. Various strategies to increase innovation in drug discovery have been introduced.

In January 2010 (11st – 12th) EATRIS was presented at the "Advancing Biologics From The Lab To The Clinic Conference" in Brussels with a speech given by Guus van Dongen. At the Sixth European Conference on Research Infrastructures, ECRI, in Barcelona a poster was presented from 23rd to 24th March.

An EATRIS conference served as launch or "kick-off" event for the forthcoming implementation and to intensify communication with potential funders and future users of the EATRIS's infrastructure. It was titled "From Basic Research to Medical Innovation" and took place from 7th-8th October 2010 in Rome. EATRIS aimed at gathering experts and key players from research, politics and industry to discuss how application-orientated biomedical research and development could best be promoted and how it could be used as a motor for innovation in Europe. As follow-up a conference report was compiled, which was distributed to all participants and other interested stakeholders.

In year 3 EATRIS has become an interested party to the Committee for Advanced Therapies (CAT) at the European Medicine Agency (EMA) in London. The CAT is a multidisciplinary committee who plays a central role in the assessment of quality, safety and efficacy of new advanced therapy medicinal products (ATMPs) for market approval. Being accepted as interested party is thus an important step for the EATRIS initiative in implementing itself as a stakeholder of the translational research community.

Extension of EATRIS

All scientific institutions that expressed interest in joining the EATRIS consortium, were provided with a summary of the project aims. It was communicated that EATRIS is open to new partners and that a country can join EATRIS if the Ministry responsible for funding research infrastructure will also join the EATRIS consortium