

Review Article

EATRIS, a European initiative to boost translational biomedical research

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Abstract: Recent advances in molecular and cellular biology have facilitated the discovery of the key molecular drivers of major diseases. This knowledge raised some optimism in the beginning of this century, yet its impact on disease prevention, diagnosis and targeted intervention remains low. At the same time the pharmaceutical industry is facing the dual challenges of a dwindling drug pipeline and ever increasing cost of drug development. It is against this background that a number of European countries decided to establish EATRIS, the European Advanced Translational Research InfraStructure in Medicine. EATRIS aims for faster and more efficient translation of basic research into innovative products, by providing academia and industry access to the state-of-the-art expertise and highly capital-intensive facilities residing in Europe's top translational research centers and hospitals. To this end, EATRIS formed product groups that provide translational services in the fields of development and supply of (1) molecular imaging and tracing, (2) vaccines, (3) biomarkers, (4) small molecules and (5) advanced therapeutic medicinal products. Herein we describe the background, goals, functions and structure of EATRIS. As an example, it will be described how EATRIS centers involved in imaging and tracing might contribute to more efficient drug development and personalized medicine.

Keywords: Drug development, european advanced translational research infrastructure (EATRIS), immuno-positron emission tomography, molecular imaging, personalized medicine, tyrosine kinase inhibitor-positron emission tomography, translational research

Introduction

Analyses at molecular level, genomics, proteomics and metabolomics, as well as advances in high throughput technologies and systems biology, have led to an exponential increase in information about - and insight into - the underlying mechanisms of disease. However, contrary to expectations, this has not resulted in a concomitant increase in output of new, high impact diagnostics and therapeutics. Academic centers continue to struggle with the process of transferring research findings from applied basic sciences to healthcare products and services. This "translational gap" has been recognized and is awaiting effective solutions. At the same time, the pharmaceutical industry is facing its own challenges. While the global pharmaceutical market has grown during the

last decade to a level of \$875 billion US dollars (USD), with yearly sales growth of 5-10% (especially due to the fast-growing emerging markets such as China, Brazil, Russia and India), question marks surround the efficiency and impact of new drug development by the pharmaceutical industry [1]. Public-private partnerships, in which industry and academia work together in a multidisciplinary and open manner, have been widely proposed as an instrument to accelerate innovations in the life sciences and health sector [2]. As described herein, EATRIS will boost this concept by providing academia as well as industry easy and broad access to preclinical and clinical translational research infrastructure, to facilitate the development of new products and services in medicine along the entire research and development (R&D) process up to the clinic (**Figure 1**).

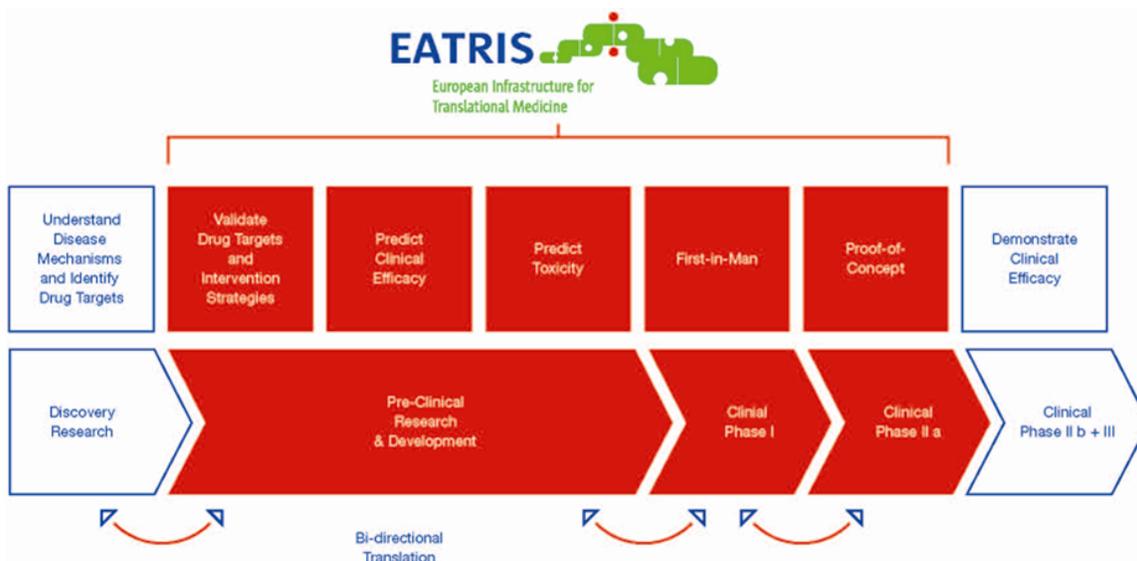


Figure 1. The development chain is the sequence of consecutive R&D steps for product development of clinical application in diagnosis, therapy or prevention. EATRIS will cover the steps highlighted in blue and offer translational support and continuity along the entire process.

Challenges in translational research: the needs of academia

Many of society's important biopharmaceutical breakthroughs originate from ideas and discoveries in academia, and these centers are more and more interested in the application of their research findings towards the development of novel medical products themselves [3, 4]. But advancing ideas from basic research to clinical application is often hampered within such research-focused organizations. A main obstacle lies in the culture of academic centers and biomedical research itself. In general, there is a lack of exchange among the various disciplines, for instance basic researchers such as molecular biologists are physically separated from the physicians and seem to speak different scientific languages. Publications and citations are traditionally valued more highly than patents, and in many countries patents do not constitute a part of scientists' performance metrics at all. Moreover, academics are generally not sufficiently aware of the regulatory and economic hurdles that have to be overcome when bringing a product to the clinic, while only a few centers have the financial resources, infrastructure and expertise to embark on this risky journey. For this reason, development of medical products is primarily the domain of industry. Nonetheless, activities of universities and public research centers in the development of clinical products are increasing, despite facing

many challenges. Simultaneously, funding and patient organizations are increasing the priority of translational and applied research, as only via this route can there be any benefit for patients. It is against this background that EATRIS was initiated [5].

Challenges in translational research: needs of industry

At the moment, the pharmaceutical industry is facing worrying challenges in the pursuit of economic value and medical impact in the R&D process. The current industry strategy involves drug testing in early phase clinical trials for safety and toxicity, and then only at a later phase testing for efficacy and added value using more expansive clinical trials. This strategy often leads to vast sums of money being spent during these development phases, only to discover very late that the drug is not efficacious. Despite a constant trickle of opportunities arising from new insights in the underlying mechanisms of disease, and the introduction of novel, powerful technologies, it can be questioned whether the pharmaceutical industry has been innovative and efficient enough during the last decade. This can be illustrated by some general figures and observations, which impact not only the pharmaceutical industry but also patients and society as a whole: (1) of every ten drugs that enter clinical testing, only one will make it to the market, (2) most of the

Imaging makes 'personalized medicine' possible

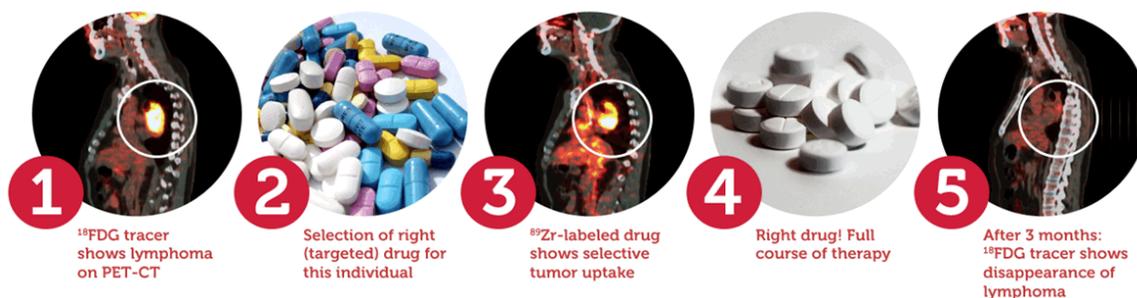


Figure 2. PET tracers can be used for tumor detection (step 1), for confirmation of selective tumor targeting by a specific targeted drug (step 3) and for the early assessment of therapy response (step 5): "The right treatment, at the right time, for the right patient." (PET images of zirconium-89-labeled rituximab in non-Hodgkin lymphoma patient obtained from Dr K Muylle and Prof P Flamen, Jules Bordet Institute, Brussels).

approved drugs are directed against common diseases, however, not for all common diseases have effective drugs become available, while rare diseases are mostly neglected, (3) many new drugs are developed against validated targets and are "copies" of registered drugs, while their clinical advantages are minimal (so-called 'me too products') [6], (4) only a small proportion of the indicated patients have objective benefit of treatment with the registered products, varying between 20 and 50% for different disease areas (e.g. 20% for cancer), while benefit is sometimes minimal, (5) drug development is time consuming and costly, with an average development period of 10-15 years and an average price tag of 1.5 billion USD per novel drug brought to the market. Together with the high failure rate of drug development, this results in price settings of approved drug that are excessive (up to 100 kUSD a year for therapy with targeted drugs), and this issue has triggered national discussions regarding access to care [7], (6) without a dramatic paradigm shift, new drug development will further stagnate. There are simply not enough patients to test all the newly designed drugs, while there is a tendency that patients become more critical with respect to participation in clinical trials with experimental drugs, (7) insight into the mechanism of action of approved drugs is mostly lacking, and this makes further improvement of efficacy difficult, (8) the patent position of many current blockbusters will expire shortly (the so-called 'patent cliff'), and (9) despite a doubling of R&D expenditures by the pharmaceutical industry, the output of new molecular entities (NME) in Europe has halved between 1989 and 2008 [8].

Thus, the pharmaceutical R&D pipeline is in serious need of making new drug development more efficient and effective, as well as of finding new, innovative targets that meet real medical needs. The pharmaceutical industry has started to realize that they cannot perform efficient drug development on their own any longer, and 20-30% of R&D expenditures are nowadays outsourced to small- and medium-sized enterprises (SMEs) and academic centers.

The origin of EATRIS

Society is facing a growing number of "Grand Challenges" such as global warming, tightening supplies of energy, water and food, and ensuring quality of life and care for the ageing population. Progress in all these areas strongly depends upon innovation capabilities that require access to the highest quality research infrastructures. Research infrastructures are a key instrument in attracting and bringing together researchers, industry, funding agencies, politicians, and patient advocacy groups to act together as an innovation hub and tackle the cross-disciplinary scientific and technical issues of critical importance for our continued prosperity and quality of life. The European Strategic Forum on Research Infrastructures (ESFRI) was launched in April 2002 and was aimed at exactly these challenges. The field of biomedical and life sciences is one of the ESFRI-fields with very high societal impact, of which EATRIS is one of the prioritized research infrastructures. EATRIS lays emphasis on translating research for human health to maintain Europe's competitiveness in biomedical research and in the healthcare industry.

To establish such a pan-European research infrastructure, it is important to have a clear view on the actual situation of translational research. To this end, during its preparatory phase EATRIS conducted surveys in which 54 academic non-profit institutions from 14 countries participated as well as several SMEs and larger industry parties [5]. The surveys provided clear insight into the status of translational research in Europe and the needs to be achieved, including: (1) provision of comprehensive high-end infrastructure and services which are scarce within both academia and industry, such as facilities for Good Manufacturing Practice (GMP) compliant development and production of medicinal products, patient cohorts and clinical phase I/II units, (2) integration of basic research and clinic to create a multidisciplinary environment, (3) consultation in research project management, product development, quality assurance and quality control, intellectual property and regulatory issues, and clinical phase trials, (4) substantiation of funding concepts, since the traditional model of government support does not meet the costs, diversity and complexity of translational research, and (5) provision of concepts for training and education.

The concept and status of EATRIS: open access to knowledge and infrastructure

On the basis of aforementioned inventories EATRIS was designed. EATRIS aims to support academia, SME's and large industry in translating results from bench to bedside. This will be achieved by establishing consortia of translational "EATRIS centers", each consortium representing a "product group" involved in the development and supply of either molecular imaging and tracing, or vaccines, or biomarkers, or small molecules or advanced therapeutic medicinal products. Each product group comprises top existing European translational research centers and hospitals that have state-of-the-art expertise and highly capital-intensive facilities for efficient development of a particular product. These centers dedicate part of their R&D capacities to EATRIS, and collectively cover the entire product development chain up to the clinic (**Figure 1**). The goal is to have all necessary disciplines (basic and clinical research) operating closely together as a strong innovation core, to bring new products efficiently to the clinic. Breakthroughs are expected in

the form of better understanding of high impact diseases and disease-specific molecular targets, more efficient development and use of diagnostic and (expensive) targeted therapy/drugs, and better understanding of inter-patient variability. These achievements will result in reduced costs of drug development, while bringing better quality of life for patients and a reduction of healthcare costs.

After a preparatory phase and a transition phase, in 2012 EATRIS entered its construction phase. A legal framework was chosen for EATRIS, and an agreement made by the participating countries. In the mean time 9 countries committed themselves to EATRIS, while several countries are intending to do so in the near future. In 2011 the EATRIS headquarters (EATRIS Coordination and Support; info@eatris.eu, www.eatris.eu) were opened in Amsterdam. These headquarters will function as a broker office matching clients and translational service providers. First pilot projects are planned to be started in 2013.

Added value of EATRIS: greater than the sum of the parts

The EATRIS consortium provides the support required along the entire value chain for 5 inter-related and highly specialized product types, collectively offering a vastly superior research structure than would be possible with individual institutions. Several advantages of using the strengths of the network can be identified: (1) The entire spectrum of cutting edge translational research infrastructure and patient cohorts, all available at high capacity through one portal: "one-stop-shop", (2) High-speed management procedures with clear contact points, efficient project planning, and quick time to contract based on standard contracts, (3) Access to the latest discoveries and technology/equipment developments coming from the EATRIS centers, (4) Wide range of expert knowledge, from biological mechanisms to regulatory aspects to clinical experience, efficiently integrated with professional project team management into multi-disciplinary management teams, (5) Access to the top quality assurance/quality control level within each project, by virtue of best practices and procedures dissemination among the EATRIS centers. Quality sharing will facilitate the conduct of high-speed, harmonized, multi-center trials across

European countries, and will avoid learning curve risk, (6) Translational focus – maximizing product output potential, with support from discovery to clinical trial (Phase I/IIa), and (7) The benefit of the foresight of experienced professionals in translational research, from day one of the project.

EATRIS imaging and tracing centers: what do they offer?

The potential of EATRIS is illustrated here by its offerings in the field of imaging and tracing. One of the most obvious unmet needs in the development and use of new drugs are new in vitro and in vivo biomarkers that can be used for prediction of therapy efficacy or as (surrogate) endpoint to assess therapeutic effects. Imaging, combining high resolution spatial information with specific functional and molecular information, is making rapid progress in providing valuable in vivo biomarkers. Molecular imaging is of value for sensitive visualization and quantification of critical disease targets and targeting molecules – either drug candidates or diagnostic agents – at high resolution [9-12]. As such, molecular imaging is of high utility for initial diagnosis and prognosis, treatment selection and guidance, outcome monitoring, and especially for new drug development. Key in molecular imaging is the exploitation of critical biomarkers involved in pathogenic processes, and the development of ‘disease-specific contrast agents’, herein collectively called ‘tracers’. Some biomarkers need association with a tracer for visualization, while others do not (e.g. oxy/deoxyhaemoglobin using functional magnetic resonance imaging (fMRI), or changes in phospholipid metabolism in ^{31}P magnetic resonance spectroscopy (MRS)). In addition, validated methods are needed to visualize the biomarkers (semi)quantitatively by an imaging modality and to process and interpret images. Tracers, which can be used in nuclear (e.g. positron emission tomography (PET)), radiological (MRI & ultrasound (US)) and/or optical procedures, enable visualization and quantification of critical disease targets and molecular processes, or serve to track (targeted) drugs (e.g. monoclonal antibodies, peptides, small molecules etc.), carrier systems (e.g. liposomes) or cells in vivo. In addition, molecular imaging can be used to assess the effect of (unlabeled) pharmaceuticals on critical disease processes, which are imaged with

the proper imaging procedures and tracers. For these applications, PET, US, Ultra High Field MRI and even (near infrared) optical imaging methods are considered to be the most powerful.

The EATRIS product group on imaging and tracing provides the highest available level of expertise and infrastructure of the molecular imaging and tracer-related R&D process. Expertise is provided in e.g. the fields of nuclear medicine and radiology, medical physics, (radio)pharmaceutical chemistry, (radio)pharmaceutical kinetic modeling, and in vivo pharmacology. The infrastructure comprises facilities for target revalidation; radionuclide production facilities including cyclotrons and shielded nuclear radiation containment chambers (“hot cells”); licensed GMP labs for tracer production according to the latest European Union (EU) and European Medicines Agency (EMA) guidelines; animal facilities with several models of diseases; labs for metabolite analysis; preclinical imaging centers with the newest devices such as μPET , μCT , μMRI , μSPECT , US, optical imaging as well as hybrid systems; clinical phase I/II trial units; clinical imaging centers, which harbor the latest equipment developments such as PET-MRI and 7T MRI, and allow multimodality imaging (image acquisition, analysis and integration as well as image interpretation) with all kind of tracers in various patient cohorts; data analysis centers to handle, process, integrate and store multimodality data and potentially couple them to other data sets by using information and communication technology (ICT) infrastructure; and large patient cohorts with a broad variety of diseases.

One of the emerging services: PET imaging with radiolabeled anticancer drugs

Recent advances in molecular and cellular biology have resulted in the identification of critical molecular tumor targets involved in proliferation, differentiation, cell death and apoptosis, angiogenesis, immune recognition, invasion and metastasis, and cancer cell stemness. This knowledge has boosted the rational design of cutting-edge pharmaceuticals, with monoclonal antibodies (mAbs) and tyrosine kinase inhibitors (TKIs) forming the most rapidly expanding categories. Presently 12 mAbs, all being intact immunoglobulins, and 12 TKIs

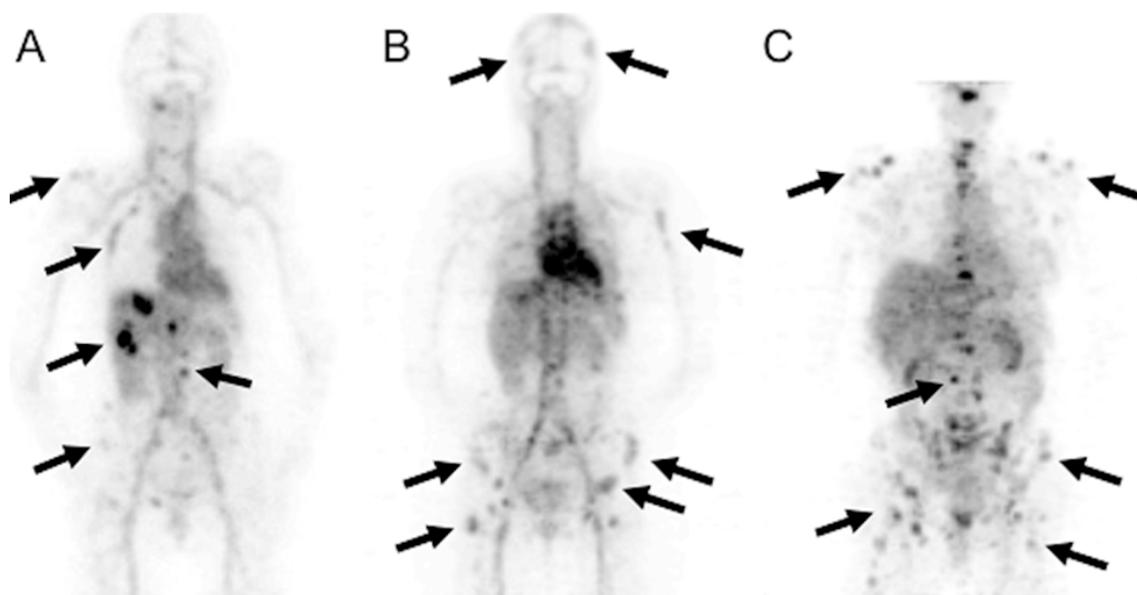


Figure 3. Examples of ^{89}Zr -trastuzumab uptake 5 days p.i. in a patient with liver and bone metastases (A) and two patients with multiple bone metastases (B+C). A number of lesions have been specifically indicated by the arrows (from Dijkers *et al* [20]).

have been approved by the U.S. Food and Drug Administration (FDA) for the systemic treatment of cancer [13]. The total yearly sales of mAbs and TKIs is estimated to be 30 and 16 billion USD respectively, mostly for the treatment of cancer, while hundreds of new mAb and TKI candidates are under clinical development by biotech and pharmaceutical companies [14].

The tremendous pace of development of new targeted drugs might be cause for optimism about future perspectives in the treatment of cancer, but also raises the question of how to test all these drugs in an efficient way, since in current drug development practice it would require numerous clinical trials with large numbers of patients. Since just 10% of all anticancer drugs under clinical development will eventually reach the market, it becomes increasingly important to distinguish drugs with high potential from the ones with low potential at an early stage. This requires better understanding of the behavior and activity of those drugs in the human body. Furthermore, the effectiveness of current targeted therapies in oncology is limited, while their reimbursement costs are excessive. Several questions come to mind: how to improve the resource efficiency of drug development, by which drugs can become less expensive; how to improve the efficacy of thera-

py with targeted drugs; and how to identify the patients with the highest chance of benefit from treatment with these drugs? In other words: when, how, and for whom should targeted therapy be reserved? To answer these questions, better insight in the *in vivo* behavior of therapeutic mAbs and TKIs should be obtained, including their interaction with critical disease targets, mechanism of action, and beneficial effects in individual patients. Nowadays it is possible to radiolabel all mAbs and the majority of TKIs with positron emitters and to visualize them with PET, so called immuno-PET and TKI-PET [13, 15-18]. EATRIS centers are able to radiolabel drugs and to evaluate them preclinically as well as clinically in the appropriate animal models and patient cohorts as will be demonstrated in the next sections by a few typical examples.

The ability of PET to quantitatively image the distribution of radiolabeled drugs within the body makes this technique a valuable tool at several stages of drug development and application. From first-in-man clinical trials with new drugs it is important to learn about the ideal drug dosing for optimal tumor targeting (e.g. saturation of receptors), the uptake in critical normal organs to anticipate toxicity, and the interpatient variation in pharmacokinetics and

tumor targeting. Drug imaging can provide this information in an efficient and safe manner, requiring fewer patients, as well as fewer patients treated at suboptimal doses. Pre-treatment imaging with the drug of interest might also have added value for patient selection, because it can be used to assess target expression and drug accumulation in all tumor lesions and normal tissues, non-invasively, quantitatively, and even over time. This information might be particularly relevant for heterogeneous tumor types, or when targeted drugs are combined with other treatment modalities like chemo- and radiotherapy, to find routes of maximum synergism [19]. Ideally, anatomical information on tumor extension is obtained, as is possible with PET-CT and PET-MRI, to enable assessment of homogeneity of tumor drug accumulation. Imaging during therapy is also attractive in order to show that tumor targeting is effective and indeed results in antitumor effects, as can be assessed by e.g. ^{18}F -fluorodeoxyglucose (^{18}F FDG) PET (**Figure 2**). If a targeted drug is not effective in a particular patient, adaptive treatment can be considered by dose escalation or by choosing targeted drugs that inhibit compensatory pathways. Apart from applications in treatment planning, treatment monitoring and response monitoring, imaging with radiolabeled targeted drugs like mAbs can also be used for diagnostic purposes and for better understanding of *in vivo* biology ('immunohistochemistry *in vivo*').

PET imaging of radiolabeled monoclonal antibodies: immuno-PET

The potential of immuno-PET was demonstrated by Dijkers *et al* [20] in a study with ^{89}Zr -trastuzumab in breast cancer patients. In this feasibility study with 14 patients, three different dose cohorts were evaluated: 10 or 50 mg for trastuzumab-naïve patients and 10 mg for patients on trastuzumab treatment. It was proven that the latter two performed equally. Although this study was not aiming for the comparison with conventional staging modalities or for assessing specificity and sensitivity, lesions with ^{89}Zr -trastuzumab uptake were generally in good agreement with CT, MRI and bone scans. PET resulted in an image quality unapproachable by previous trastuzumab single photon emission computerized tomography (SPECT) scans. Excellent visualization of mAb uptake in human epidermal growth factor receptor 2

(HER2)-positive lesions as well as in metastatic liver, lung, bone and even brain HER2-positive lesions was observed (**Figure 3**). ^{89}Zr -trastuzumab PET allowed quantification of conjugate uptake in HER2-positive lesions, and it became clear that for some patients with extensive tumor load no HER2 saturation occurred during trastuzumab therapy [21]. This latter observation indicates that some breast cancer patients might be underdosed with current trastuzumab therapy regimens, and it therefore could be considered to use HER2-PET for applying a more patient-tailored trastuzumab dosing schedule. In the mean time, immuno-PET is broadly applied as has been described in some recent reviews [15, 16, 22].

PET imaging of radiolabeled tyrosine kinase inhibitors: TKI-PET

PET imaging can also contribute to better understanding of TKI activity. The most appealing results have been obtained with erlotinib, which competes with adenosine triphosphate (ATP) for the ATP-binding site on the epidermal growth factor receptor (EGFR), thereby preventing signal transduction leading to proliferation. Erlotinib can induce dramatic clinical responses but only in 10-15% of non-small cell lung cancer (NSCLC) patients, when used as a single agent [23]. Expression and mutation status of the EGFR have been associated with increased response [23]. It has been hypothesized that the presence of sensitizing mutations might increase the binding of the drug with its target. This might result in better drug retention within the tumor as well as in a more efficient inhibition of signaling through EGFR. However, for assessment of EGFR expression and mutation status a tumor biopsy has to be taken, which is not always possible like in NSCLC. Even when a biopsy is available, it is questionable whether this is sufficient to obtain a representative overview of the whole (often heterogeneous) tumor. Moreover, it is possible that expression and mutation status differ in primary tumor and metastatic lesions and change during the course of disease, for example upon chemo- or radiotherapy. Taking this into account, it might be that PET imaging with the radiolabeled EGFR TKI inhibitor itself gives a more comprehensive overview of EGFR receptor status, and the interaction of the drug with this receptor. To test this possibility, Memon *et al* [24] evaluated the uptake of ^{11}C -erlotinib in nude mice bearing

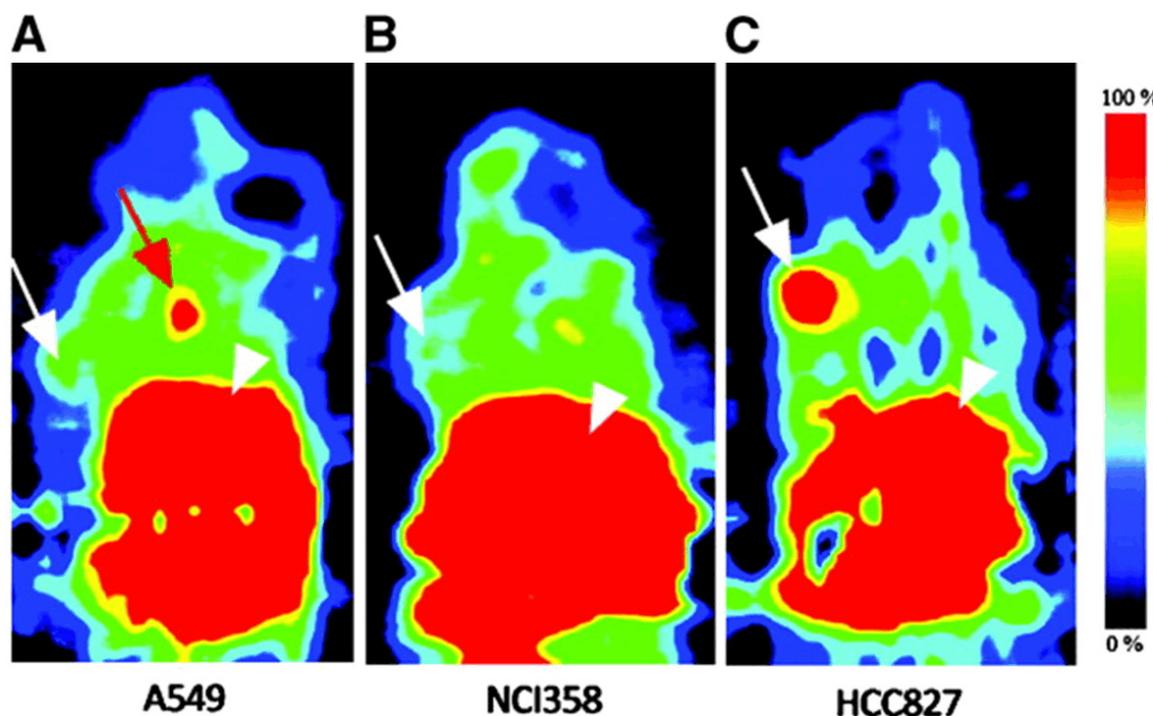


Figure 4. ^{11}C -erlotinib micro-PET imaging of lung cancer xenografts. Coronal micro-PET images of anesthetized athymic nude mice xenografted with A549 (A), NCI358 (B) and HCC827 (C) lung cancer cells at the left shoulder. A549 and NCI358 cell lines are less sensitive to erlotinib than HCC827, while the latter cell line harbors an in-frame deletion mutation in exon 19 of EGFR. White arrows: tumors. It can be concluded that the highest tumor uptake of ^{11}C -erlotinib was found in the most sensitive xenograft line HCC827. The hot spot in A (red arrow) was found in all mice, however, it is not possible to show it in all mice as the tumors are located in different planes. Liver is seen with very high activity with spillover to the surrounding area (arrowheads) (derived from Memon *et al* [23]).

lung cancer xenograft lines with different sensitivity to erlotinib treatment and different mutation status. In mice carrying the most sensitive xenograft line, a xenograft line with an activating mutation in EGFR, tumor uptake of ^{11}C -erlotinib was highest, indicating that ^{11}C -erlotinib PET can indeed identify erlotinib sensitive tumors (**Figure 4**).

Very recently it was demonstrated that these exciting preclinical results are translatable to the clinic [25]. In the mean time, TKI-PET becomes more broadly applied as has been described in some recent reviews [13, 17, 18].

Conclusions

The current drug R&D paradigm is in urgent need of the technology and process innovations that can once again bring R&D spending under control. The translational space is an area ripe for attention, and it is in this space that EATRIS aims to significantly improve the throughput of high potential products arising

from academic efforts. This entails deeper collaboration of the multiple disciplines involved in the translational phase. EATRIS combines the expertise and infrastructure required, integrating technologies, soft skills and know-how to approach academic applied research in a novel, more goal-directed manner. Imaging and tracing is an extremely high potential set of modalities that can increase the speed and reduce the cost and risk of products in development, and at the same time facilitate personalized medicine development and healthcare.

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