RECAMO – ...through Cancer Research towards Applied Molecular Oncology; Where, Why and How

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...WHERE – Past Achievements And Current Ambitions

The MMCI RECAMO project was established by the Masaryk Memorial Cancer Institute (MMCI), a long-term full member of the Organization of European Cancer Institutes (OECI). Masaryk Memorial Cancer Institute has been a leading institution in comprehensive cancer treatment and research for about five decades. Nowadays, it represents the largest comprehensive cancer centre in the Czech Republic. Based on the long and unique expertise accumulated at MMCI, the institution was awarded Associate Membership status of the European ESFRI infrastructure designated BBMRI in 2010. The fundamental role of this infrastructure is to assist biomedical scientists in providing high quality biological material that can be utilised for basic and applied and translational cancer research activities. At present, the MMCI actively participates in the preparatory period of BBMRI-ERIC (European Research Infrastructure Consortium) consortium.

At RECAMO, our objective is to establish a multi-disciplinary group of researchers, we intend to focus on the clinical applicability of information derived from studies of defined areas of cancer research in which members of the collaborating consortium have individual expertise, including p53 cell signalling pathways, the role of cancer stem cells, the ubiquitin-chaperone system and angiogenesis in cancer patients. We will use our own experience in genomic and proteomic technologies to identify and evaluate new cancer biomarkers using highly characterised clinical samples and we will assess the applicability of novel imaging technologies in cancer patients. A key aspect of the overall strategy is to enhance the rapid translational research aspects of the gained knowledge through the early inclusion of commercial companies. Thus, our overall objective is to translate basic science knowledge into clinically utilisable markers that can be applied to enhance patient care.

Limitations and Weaknesses of Current Cancer Research Strategies

The recent advances in DNA sequencing and microarray technologies are rapidly defining the genomic landscape of cancer. These genomic approaches provide a wealth of data into the mutational spectra of tumours, including copy-number changes, point mutations, chromosomal translocations, epigenetic changes and the role of regulatory non-coding RNAs. On the contrary, proteomic technologies, although less advanced, have also begun to identify alterations at the levels of individual proteins in cancers. Besides helping us to understand the origins and nature of cancers, these data can provide information of potential clinical relevance for cancer patients, for example by the identification of novel oncogenic changes to "druggable" targets. In addition, the search for proteins that are present in the blood or other fluids such as urine in cancer patients may reveal new markers that can be measured using non-invasive or minimally invasive techniques for cancer screening and to monitor cancer progression and response to therapy. At the current time, numerous potential cancer biomarkers have been identified and new markers are being proposed weekly. However, a major challenge for the cancer research community is to turn this wealth of new information into clinically useful tests that will enhance patient care. Major drawbacks to achieving this necessary aim are the availability of suitable patient material and the relevant expertise involved with its' use for marker evaluation, resources that are often not an integral component of research laboratories. Another major drawback is the ability to produce the necessary reagents required to develop and commercialise assays for use in the clinical setting. Thus, although there are many individual laboratories that are attempting to identify novel cancer biomarkers, there are very few groups in a position to evaluate their applicability or with the experience, expertise and commercial connections to develop and commercialise assays that would lead to widespread clinical use.

The activities at RECAMO are designed to bring together scientists with proven track records in cancer research and clinicians with experience and expertise of the clinical problems involved in applying new information to the clinical setting. The projects are linked and "flowcharted" through defined research, clinical and potentially commercial activities (Fig. 1). At the centre of our project are clinical and basic research collaborators who will collect primary cancer tissues, define key genetic alterations in the tumours based on current knowledge and acquire a database of patient prognosis, drug-response and overall outcome. The "Cancer Research Programme" will define: A) the proteome/transcriptome/genome in the collected cancer samples to identify sub-components (i) responsible for metastasis and therapy resistance (ii) being part of the ubiquitin-chaperone system, and to further evaluate and validate these sub-components as potential anti-

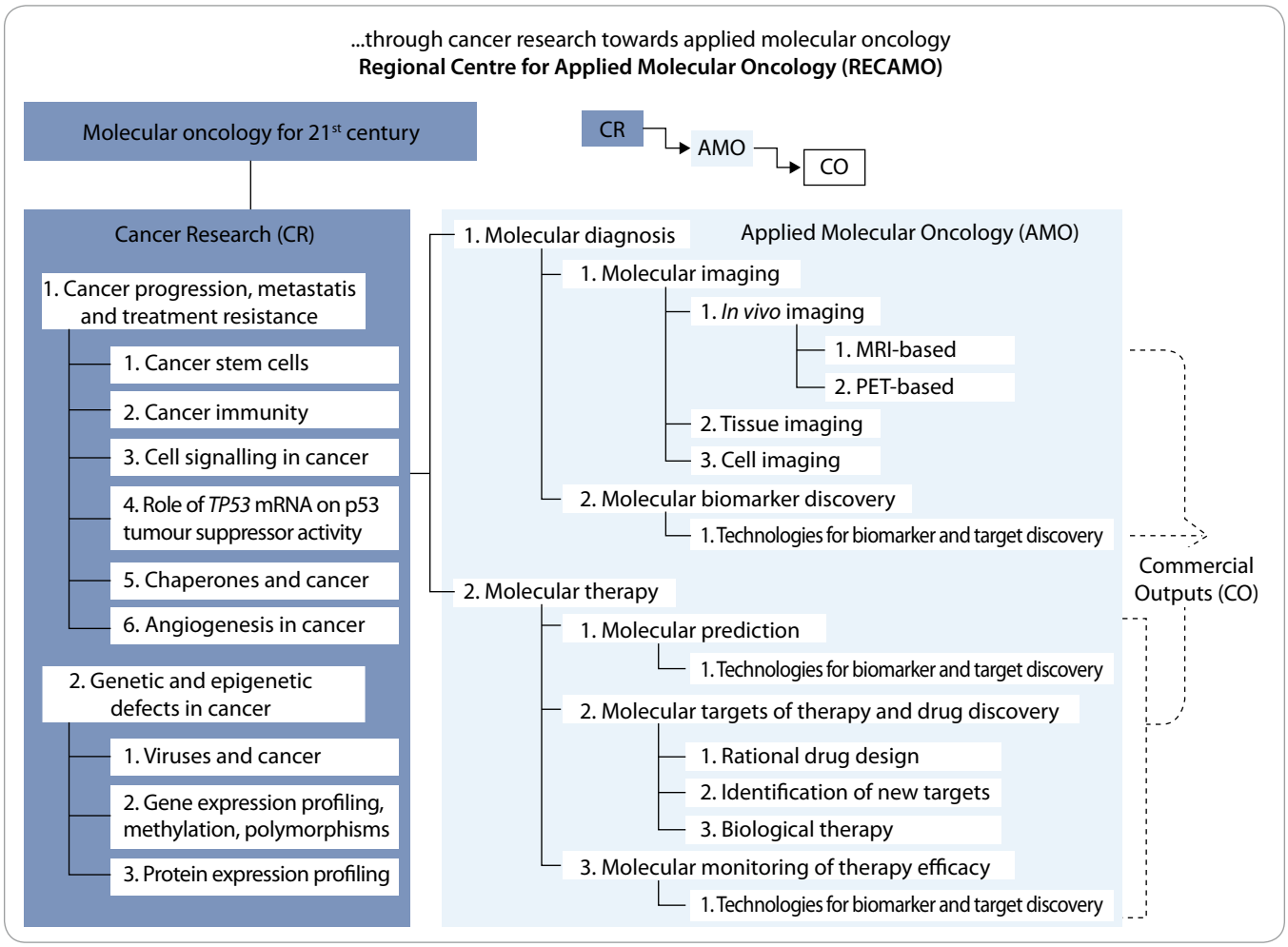

Fig. 1. A conceptual roadmap of the RECAMO operational system that is "flowcharted" to three arms: the **CR arm** structuring the specific research objectives, the **AMO arm** utilising results of the CR arm either within RECAMO or at the partner infrastructures such as CEITEC and **CO arm** melting the achieved results into commercialisable entities such as therapeutics or diagnostic kits.

cancer targets; B) the strategy for evaluation of novel biomarkers for diagnosis, including their potential application in molecular imaging related to cancer detection, grading and assessing therapy response; C) the use of innovative technologies to identify new key biomarkers, including proteins responsible for malignant transformation, metastasis and therapy resistance including molecular ubiquitin-chaperone system in order to enrich the "proteome" from a complex clinical mixture; D) strategy for validation of novel biomarkers and therapy targets; E) strategies for development of immunoreagents for commercialisation, including the development of diagnostic kits and screening assays for testing the potential therapeutic reagents and for potential application as image-enhancing diagnostics. Thus, this multi-disciplinary approach aims to define novel protein biomarkers for the metastasis and resistance of human cancers from experimental models and clinical material, as well as provide diagnostic biomarkers to improve imaging techniques for disease staging and therapeutic response. These proteins will be further evaluated and validated as novel anti-cancer drug leads for future development.

...WHY – Concepts and Objectives

It is well known that new and powerful methods in genomics, proteomics and molecular imaging are driving biomedical research and the development of personalised medicines, where drug treatments will be directed to the physiological and genetic background of the patient and their particular cancer "blueprint". The completion of the entire human genome sequence raises the possibility that the genotype of an individual could be obtained and this information employed to predict disease susceptibility. Progress in human cancer medicine has generally been driven by a combination of cytogenetic technologies, the use of gene cloning advances and the use of model organisms to define cancer gene function. The completion of the human genome sequences also facilitated the development of progressive technology such as DNA microarrays. However, while DNA microarrays are powerful research tools, it is unclear whether, due to the complexity of sample preparation and other technical aspects, this technology will ever be adop-

ted to the clinical routine. Moreover, human cancer is proving to be a heterogeneous and tissue-specific disease whose true molecular pathology is not entirely reflected by the use of "model systems". For example, it is now generally recognised that the cancer cell lines used for basic cancer research do not reflect the real blueprint of a human cancer, thus emphasising the need to define the proteome and transcriptome of human clinical samples. The revolution in molecular biology and genomics in the past 10 years has had significant impact in raising the hope of increasing the efficiency of diagnosing and treating various types of cancer. The discovery of novel biomarkers that can aid with diagnosis or predict patient outcomes requires a multi-disciplinary approach involving collaborations between many groups including basic cancer researchers, clinical oncologists and healthcare professionals, technologists and drug companies. Such a network located in one institute is necessary to guarantee that biomarker discovery programmes are formulated to answer key questions and those biomarkers with limited, but significant utility, are confined to specific patient groups.

...HOW – Coaching a Team Approach

A series of multi-disciplinary approaches will be used to discover and validate these novel targets including cell biology, immunochemical, structural biology, chemical biology and medicinal chemistry, peptide-mimetics, mass spectrometry and proteomics, transcriptomics, small molecule drug discovery screening, and clinical science. With such approaches, we aim to expand our basic knowledge of the p53, molecular chaperone and immune system pathways, identify novel drug targets and diagnostic targets, and develop targeted approaches for continued drug development in human cancers. Key recommendations for implementation, relevant to the short-term aims of RECAMO, include: 1) Promote and encourage synergistic collaboration across disciplines for biomarker discovery; 2) Incorporate drug and patient responses with comprehensive biomarker validation; 3) Improve access to prioritised biological specimens with a central registry; and 4) Develop high standards to create a model for clinical methodologies aimed at biomarker discovery. Key recommendations for implementation that will be relevant to the long term aim of RECAMO include: 1) Develop biomarker assays and new drug treatments in tandem; 2) Encourage adoption of guidelines for the publication of biomarker studies; 3) Establish rules for biomarker surveillance; 4) Improve access to information on all biomarker studies; and 5) Educate stakeholders in all aspects of biomarker research.

It is becoming evident that biomarker discovery in cancer research needs leadership that aims to bring together diverse disciplines to bear upon a common goal. Indeed it was implicit in the Research and Development for Innovation call that such an approach is needed for biomarker discovery and anticancer drug development using patient material. Our activities summarised here aim to fill that role by developing an innovative multi-disciplinary institute to define biomarkers relevant for diagnostic or anti-cancer drug development in metastatic and drug resistant cancers. Our key aim is to use knowledge from basic cancer research on cutting edge anti-cancer drug targets, state-of-the-art technology in transcriptomics and mass spectrometry, and well characterised clinical sample groups to identify novel biomarkers in specific cancer types. Although each individual program in RECAMO uses state-of-the-art technologies to address a key goal, each activity also implements an innovative approach that creates a platform that is beyond the current state-of-the-art. Further, by linking these inter-dependent programs together (see Fig. 1), a synergy is created to ensure innovation and success in biomarker discovery.

In RECAMO, we realise that comprehensive support of the career development of young scientists is critical for future success and competitiveness. Therefore, the new research centre will contribute to education of pre- and post-gradual students through innovating current courses and launching new education programmes. The attractive research programme of RECAMO will integrate students in specific research activities. Collaboration with internationally recognised expert teams will help our young scientists obtain relevant professional experience that enhances their competitiveness in basic and translational research, health services, education and pharma and biotech industries.

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