

# Basic cancer research: why it is essential for the future of cancer therapy

Yosef Yarden and Carlos Caldas recently wrote a position paper on the behalf of the EACR, which was published in the *European Journal of Cancer (EJC)* 2013 49 issue 12. It describes the irreplaceable role of basic research in the future of cancer therapy. This paper is reprinted below.

## Basic cancer research is essential for the success of personalised medicine

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### KEYWORD

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**Abstract** The last decade has witnessed significant progress in cancer understanding and therapy: we can now identify the genetic drivers of individual tumours, and tailor drugs able to specifically intercept the driver mutations. While all agree that personalised cancer medicine is a clear outcome of the resources dedicated to cancer research over the last 50 years, some critics question the necessity for continuous investments in sub-fields other than clinical research and drug development. Herein, scientists from the European Association for Cancer Research (EACR) argue that the new ways to diagnose and treat cancer present important and hitherto unaddressed challenges for fundamental research of cancer. Allocating the resources needed for basic studies will likely fuel the next wave of achievements in the long way to conquer cancer.

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For scientists and clinicians who kept following the field of cancer therapy, the third millennium brought encouraging news: the impervious dam has eventually been breached and a plethora of new revolutionary drugs, like Rituximab, Imatinib, Cetuximab and Trastuzumab, started entering worldwide routine application in clinical wards and new hope was given to patients and their families. In the same vein, the completion of the human genome project and the great strides made by its successors, the world-wide *cancer* genome projects,

have further escalated the euphoria and rightly so: the unprecedented high resolution maps of the genomes of thousands of tumours have taught us that each cancerous lesion is driven by a combination of specific mutations, and at least some of those can be targeted by the novel drugs that keep flowing to the clinic. Moreover, this new level of understanding will likely also instruct the more effective use of conventional, 'old' anti-cancer drugs. This fresh realisation gave birth to a thrilling new concept called *personalised cancer therapy*: specific drugs are being perfectly matched to individual patients on the basis of the genetic alterations carried by their cancers. In the foreseeable future, this will

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undoubtedly also be expanded to include the specific epigenetic alterations of each tumour, which govern the way in which the genetic information is executed. Yet, despite the exciting progress, cancer remains one of the major worldwide killers and one of the fastest growing causes of death.

Naturally, the feeling of victory within reach has evoked careful optimism, but also generated calls demanding reconsideration of the right balance between basic and clinical cancer research. While all agree that the era of personalised cancer medicine is a clear outcome of the resources and skills dedicated by Western societies since 1972 to fundamental cancer research, some critics question the necessity for continuous investments in sub-fields other than clinical research and drug development. However, along with accomplishments, the new understanding of cancer mechanisms unearthed a hitherto unrecognised magnitude of the challenge of fighting cancer: tumours often harbour several dozen mutations, and they are extremely heterogeneous, meaning that several different variants of a given cancer type may co-exist in one patient. Moreover, despite initial response and while under treatment, patients often develop resistance, which prevents long-lasting clinical benefit. To complicate the matter, each patient might develop resistance that differs from other patients, which underscores, once again, the need to individualise cancer treatment. This realisation has sparked in the last few years both basic and clinical research, which is marking a potential solution: by elucidating the molecular mechanisms underlying resistance, it should be possible to identify relatively effective combinations of drugs that simultaneously target both the primary drivers of the tumour and the anticipated secondary resistance mechanisms, thereby reducing the likelihood that the patient will relapse with an untreatable cancer later on.

In summary, we now appreciate that cancer represents a moving target that comes in multiple variants, even within the same patient. Understanding intra-tumour variation as well as the interaction of the tumour cells with the microenvironment, along with the knowledge of the molecular mechanisms underlying resistance, is expected to lead to the identification of powerful drug combinations able to prolong patient response. Hence, nurturing and strengthening the capabilities of cutting-edge basic research are crucial to sustain successful personalised cancer medicine.

Moreover, unlike the development of cancer drugs, which is characteristically the domain of the pharmaceutical sector, the identification of potential drug targets (i.e. specific proteins and biochemical processes) and of mechanisms underlying resistance, remains the mission of academic research. There is no replacement for investigator-initiated, high-risk and exhaustive combing for candidate targets and mechanisms, which is ideally performed in academic environments. Indeed, almost all current drug targets and knowledge concerning resistance mechanisms have emerged from publicly-supported basic cancer research. The distribution of roles is even clearer when it comes to early detection, the ultimate key for successful therapy. Unlike academia, medical and industrial institutions face great difficulties in maintaining the multi-disciplinary virtual incubators that are crucial for the development of innovative cancer diagnosis. This is because the new methodologies incorporate biochemistry and nanochemistry, on the one hand, and sophisticated software and hardware, on the other hand, which are so vital for the increasingly sensitive and accurate early detection of cancer.

Perhaps the most daunting mission confronted by basic research in the post cancer genome era is the identification of the carcinogens underlying the unexpected multiplicity of mutations specific to each tumour type. While the benefits for society are enormous in terms of longevity and health economy, the stakeholders are difficult to identify: due to lack of short-term incentives, the pharmaceutical and even hospital sectors may not be considered natural partners of cancer prevention initiatives. Hence, academia-based gathering of at-risk human cohorts, developing appropriate animal models, along with better understanding of DNA repair mechanisms and the establishment of statistical models, must be regarded of great interest to society and taxpayers in the broadest sense.

Effective cancer prevention programs and population-wide early detection screens, in conjunction with rationalised drug combinations able to overcome tumour resistance, would eliminate the lion's part of current cancer incidence. Basic research plays an irreplaceable leading role in achieving this noble goal of public health.

#### Conflict of interest statement

None declared.