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Candidate biomarkers in neurooncology: determinants impacting on translation into diagnostic application

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Background: Brain cancer comprises a large spectrum of rare malignancies. In spite of considerable research efforts, candidate biomarkers hardly translate into diagnostic application, and typing of brain tumours remains to be based on conventional light microscopy. Linchpins to accelerate the translational pace would be desirable.
Methods: Based on principles defined by the National Cancer Institute Specialized Programs for Research Excellence (NCI-SPORE) for biomarker development and the cybernetic model of viable systems (VSM, Stafford Beer) we identified in a sequence of critical interdisciplinary discussions systemic determinants impacting on translation of neurooncological biomarkers into diagnostic application. Further, we analysed causes of the slow translational pace of the following candidate biomarkers: Ki-67 index in ependymoma; chromosome 1p status in oligodendroglioma; methylation status of the O6-methylguanine-methyltransferase (MGMT) promotor in glioblastoma; INI1 protein expression in malignant pediatric CNS tumours.
Results: We identified five systemic determinants influencing the translational pace: methodology, communication/cooperation, funding, research strategy, normative component. Further, we detected deficiences linked to these determinants as causes of protracted biomarker translation. For instance, methodology: focus on retrospective studies, insufficient statistical power, use of non-standardized laboratory methods, etc.; communication/cooperation: insufficient interdisciplinary interaction, fragmented research landscape, etc.; funding: insufficient funding of clinical neurooncological research; research strategy: neglect of patient-centered clinical research as distinct field of research; normative component: lack of platforms for implementation of broadly accepted analytical guidelines.
Conclusions: Multiple causes impede the translational pace of candidate biomarkers in neurooncology. These causes are linked to five systemic determinants. Promising initial linchpins to accelerate the translational pace seem to be: promotion of patient-centered research as distinct field of neurooncological research, and reinforcement of lively interdisciplinary scientific interaction between diagnostic and therapeutic neurooncological disciplines.

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Strategic directions for biomarker research: progress toward ensuring clinical relevance

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Background: An overview of the progress made toward implementing the recommendations from NBCCF's Strategic Consensus Conference, Shaping the Future of Biomarker Research in Breast Cancer to Ensure Clinical Relevance.
Methods: In 2005, the National Breast Cancer Coalition Fund (NBCCF) convened a multi-stakeholder, consumer-led conference with the goal of developing consensus on strategies to ensure that biomarker development in breast cancer leads to clinically meaningful applications. Participating consumers, clinicians, basic science researchers, industry representatives, and regulators developed five general principles that serve as the framework for six consensus priorities and 18 specific recommendations.
The following year, the consensus principles, priorities, and recommendations were published in a peer-reviewed journal (Nature Reviews Cancer, April 2007) along with a timeline for implementation.
Since then, NBCCF has monitored and reviewed various new private sector and government initiatives that pertain to biomarker assays. We have identified areas for which there are still no agreed-upon standards or guidelines, and compiled next steps for implementation of the consumer-led consensus panel recommendations.
Results: There has been much activity relevant to eleven of the eighteen consensus recommendations within the six priority areas.
The US federal government has published several new guidance documents, private sector entities have developed guidelines for the standardization of biomarker measurement, and several new collaborative initiatives have been formed among government, academia, and consumer advocates.
NBCCF's "Beyond the Guidelines" Project will address two recommendations by providing consumers with regularly updated information relevant to the level of scientific and clinical evidence and unresolved issues and controversies on specific biomarkers as part of a larger web-based breast cancer diagnosis and treatment information service.
Conclusions: Progress has been made in the past few years but much work is still to be done. NBCCF will collaborate with all stakeholders to ensure that progress continues toward implementing all of the strategic consensus panel recommendations on biomarker research.

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Affibody® molecules for molecular imaging of HER2-positive breast cancer lesions

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Background: Affibody® molecules are a novel class of small, non-immunoglobulin affinity ligands capable of binding to a wide range of protein targets. They are selected from combinatorial libraries based on a 58 amino acid protein A domain scaffold. Their small size holds promise for good penetration properties for in vivo diagnostic and they can be functionally produced both by peptide synthesis and by recombinant expression in E. coli. A HER2-specific Affibody molecule has been used to target HER2 in a mouse xenograft model showing outstanding tumor-to-blood ratio within one hour after injection. The Affibody® molecule was rapidly cleared from the blood via the kidneys leading to very low background and good biodistribution kinetics. Here, we present clinical data where a synthetic, monomeric, DOTA-conjugated Affibody® molecule, (ABY-002) was used to visualize HER2-expression in metastatic lesions in patients with recurrent breast cancer.
Methods: ABY-002 was labeled with 111-Indium or 68-Gallium at the clinic with a simple one step procedure and was injected into patients intravenously. High contrast SPECT and PET/CT images were obtained 2−3 hours post injection. Standard 18FDG-PET/CT images were also available for comparison.
Results: Molecular imaging with 111-In and 68-Ga conjugated ABY-002 showed specific tumor targeting with rapid blood clearance and allowed the detection of small metastatic lesions. No adverse effects were observed. One of the patients had received several cycles of Herceptin treatment; however, this did not preclude ABY-002-mediated imaging.
Conclusions: The ABY-002 Affibody® molecule shows promising imaging properties for both SPECT and PET; and further clinical investigations of this novel molecular imaging agent are warranted.

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Investigation of three founder mutations in BRCA1 and BRCA2 in Iranian breast cancer patients

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Background: Breast cancer (BC) is the most commonly diagnosed cancer in Iranian women, and is the leading cancer cause of death in this population. Mutations in the hereditary breast cancer suppressor gene BRCA1/2 account for almost half of the familial breast cancers (FBC) and the majority of the combined familial mammary and ovarian malignancies. The mutations with the highest number of registrations associated with breast cancer are 185delAG, 5382insC (in BRCA1) and 6174delT (in BRCA2). Mutation analysis of BRCA1/2 genes is helpful in the determination of developmental potential, early diagnosis and gene therapy for breast cancer. In our study, we used multiplex PCR to analyze breast cancer patients for three BRCA mutations in tissue samples using immunohistochemical features as criteria.
Methods: Patient samples were drawn from three medical centers in Iran. We retrieved formalin-fixed, paraffin-embedded tissue blocks from women with breast cancer diagnosed, the age of 25−80 years for the years 2004 and 2005. Eighty-four samples were used for multiplex PCR and immunohistochemical diagnosis. All cases were reviewed using a special questionnaire, which allowed taking into account the presence or absence family history of breast cancer and also other pathology information. CINAGEN Inc.'s DNA Extraction Kit was used to isolate blood and tissue DNA. A simple and rapid method was used to detect the simultaneous detection of 185delAG, 5382insC (in BRCA1) and 6174delT (in BRCA2). Morphological and Immunohistochemical diagnoses of breast cancer were retrieved from their hospital records.
Results: The proportions of cases for women with at least 1 first-degree relative with breast cancer were 32.1% in Iranian breast cancer pateints. One of three BRCA mutations (5382insC) was detected by multiplex PCR in 3 breast cancers samples. Comparison presences of 5382insC mutation in tumor samples with family history and without family history have shown that frequency of 5382insC mutation was higher in familial samples ($P < 0.001$) relatively non-familial breast cancer samples.
Conclusions: The incidence of FBC increases with age, doubling about every 10 years until the menopause, when the rate of increase slows dramatically. The relative risk of breast cancer conferred by a first-degree