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Editorial

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Oral Cancer Biomarkers: Is it a Meaningless Game?

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There are forever new biomarkers discovered every now and then, claiming for their clinical diagnostic and prognostic potentials. When is it going to end or would it ever ends at all? During the pre-omics era, it used to be only a handful of protein markers with well-studied in-depth mechanism of actions. Then came an explosive big data era: genomics, transcriptomics, proteomics, epigenomics, metabolomics, etc., generating huge amount of biomolecular data beyond researchers' ability to handle let alone understand their significance in health and disease.[1,2] It was akin to a child walking into a candy shop overwhelmed by the choices. Researchers are currently busy trying to make sense of these data and slowly attempting to translate them into clinical benefits.[2] Just within the field of oral cancer, omics data are being generated from all sorts of host samples types, including saliva, buccal swaps, tissue biopsies, serum, plasma, lymphatic fluids, etc. Within each sample type, one has choices of investigating Deoxyribonucleic acid (DNA), Ribonucleic acid (RNA), protein, metabolites, small molecules, etc, originating from various cellular compartments such as nuclei, cytoplasm, membranes, mitochondria, microvesicles (exosomes),[3] extracellular fluids (serum, plasma, lymphatic fluids, etc) and etc. Disease and healthy samples are being compared in the aim to identify key driver 'cancer biomarkers' with clinical potentials. As cancer is now perceived as a disease due to 'molecular reprogramming',[4] hence, biomarker researchers are trying to identify global molecular events that induce normal cell to reprogram itself into cancer. Given the complexity and heterogeneity of cancers, predictably, huge numbers of molecular differences exist between normal and cancer samples, and can vary from individual to individual.

There is another dimension of added complexity in the oral compartment the microbiome and its interaction with the host. There have been reports showing microbiome signatures could be used as cancer biomarkers,[5] generating even more potential cancer biomarkers (probably surrogate) based on microbial-host interactions. Recently, human host cell secreted extracellular vesicles (including microvesicles and exomes) have been found to carry potential surrogate cancer biomarkers either on the membranes or within the vesicles to modulate tumor micro-environments[3,6,7] or seeding fertile ground for primary tumor cells to establish organ-specific distant metastasis.[8-11]

Whilst system biology (the 'omics') are slowly unravelling the complex biology of cancer, new and supposedly better biomarkers/drug targets (each claiming to be representing a major oncogenic mechanism) than previous ones, are emerging daily, thus, painting a rosy picture of victory against cancer in the near future. Does this mean that all previously discovered biomarkers are suddenly being rendered obsolete? Are we now better at diagnosing oral cancers as a result of all these novel research? The key question is: Are we translating these fantastic discoveries into clinical use? Unfortunately, a short answer is not (yet)! Big data research is expensive therefore there is a bottleneck in translating big data into cost-effective clinical benefits.[2]

The evidence for the lack of improvements in oral cancer burden is indisputable. Global disease burden for many cancer types are decreasing,[12] unfortunately, head and neck cancer includ-

ing oral cancer incidence and death rates are increasing especially in females and in developing countries.[13-15] A worldwide consensus opinion appears to be that of inability to identify and treat early malignancy that resulting in no improvement in survival rates over the last 3 decades.[16-18] In China, evidence gathered from oral cancer incidence between rural and urban areas[19] indicated that there was no improvement in urban survival rates despite increased detection rates. This could be due to the lack of effective diagnostic test that could identify high-risk patients at early stages when treatment is most effective. Such data is neither surprising nor exclusive to China.[15] The 5-yr survival for early localised oral cancer can exceed 80% but falls to less than 20% in late stage tumors that involve regional lymph nodes.[20] It is well documented that improved diagnostic and prognostic accuracy to inform the most appropriate intervention could significantly improve patient outcome, reduce mortality and alleviate healthcare costs.[21] Hence, clinicians desperately need a cost-effective, practical, objective method for diagnosing and quantifying patients' risks[22-24] for early oral malignancy so that patients could be treated at early stages of the disease when it is most effective. Research strategies and science funding should be focusing on encouraging the translation of the large number of new biomarkers emerged from big data research into cost-effective practical clinical tools to benefit patients. Efforts should be geared towards setting up infrastructures (e.g., clinical bio-bank, clinical databases, etc.) for enabling translational research linking basic scientists to clinicians who have excess to patients. It would certainly be meaningless to discover huge numbers of new potential cancer biomarkers but not translating them into clinical use.

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