Correspondence

# To improve outcomes of gallbladder cancer we need to better understand it!

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The famous and most revered Chinese Philosopher, Lao Tzu once said, '*A journey of a thousand miles begins with a single step*'. The words of this wise man hold true for every sphere of life, and certainly medicine is not excluded.

Long-term survival in gallbladder cancer remains poor and there is much to be achieved in terms of improving survival (1) in addition to surgery (2). However, following the advice of Lao Tzu, the search for an overall improvement in survival of gallbladder cancer requires that we take small, but definite steps forward in our quest to understand this disease in its totality before we consider novel therapies. One such path to achieving this dream has been the concerted efforts of oncologists to delve deeper into the genetic changes that accompany the process of carcinogenesis from normal epithelium (3). A couple of years ago, while reviewing the published evidence on the genetic landscape in the progression of gallbladder cancer, we developed a carcinogenesis model for tumours evolving by the dysplasia—carcinoma cascade (3). The reason for choosing the dysplasia—carcinoma cascade was the simple fact that it is the predominant pathway involved in gallbladder carcinogenesis the world over (4).

We thank Dr. Kai for his interest in our work (5). We agree with him that in order to achieve the eventual dream of completely understanding gallbladder cancer so as to develop treatments for it would require us to consider every pathway involved in its pathogenesis, including the adenoma-carcinoma cascade (6) and possibly even xanthogranulomatous cholecystitis as suggested by him (5).

Recently, Yoshida and colleagues (7) attempted to investigate the expression of human epidermal growth factor receptor 2 (HER-2) in an unselected population of gallbladder cancer patients to clarify if anti HER-2 therapy can be justified in gallbladder cancer. Based on a combination of immunohistochemistry and fluorescence in situ hybridisation (FISH) the authors identified a 17% HER-2 positive expression in their cohort.

Based on the available literature coming from studies using only immunohistochemistry, we realised that there was a lack of concurrence between studies from the Far East and from India and the West in terms of HER-2 expression. The study from the Far East (8) suggested an increased expression in advanced cancer while those from India and the West indicated the maximal expression of HER-2 in the premalignant and carcinoma *in situ* stages. In fact, the study by Kim and colleagues (8) further demonstrated a correlation between HER-2 expression and survival (HER-2 positive tumours had a significantly poorer survival). The study by Yoshida and colleagues (7) while supporting the previous findings of increased HER-2 expression (though not reaching statistical significance $P<0.055$) in advanced cancers based on a thoroughly conducted analysis likely provide the 'missing link' between the aforementioned divergent findings namely, tumour heterogeneity. They found HER-2 positive cells in mucosal lesions rather than invasive areas. This aspect certainly warrants further investigation.

In the past we have been unsuccessful in our attempts to extrapolate the role of estrogen and progesterone receptors in gallbladder cancer from breast cancer (9). However, this study serves as an important benchmark for future studies looking to analyse the expression of HER-2 in gallbladder

cancer and certainly provides an impetus to further explore the role of anti HER-2 therapy in gallbladder cancer.

We have often relied on extrapolating ideas from one cancer to another owing to the success achieved in the former thereby overlooking the sheer complexity of carcinogenesis at its very core (10). In the present context, it is likely the female predilection of gallbladder cancer and breast cancer that has driven the exploration of the expression and therapeutic role of HER-2. Although expressed in barely 20% of women with breast cancer, monoclonal antibodies targeting HER-2 have become the standard of care in patients expressing this protein (11). Considering the use of monoclonal antibodies targeting HER-2 in gallbladder cancer represents a promising therapeutic strategy.

In our proposed carcinogenesis model (3), there remained one important lacuna that need to be clarified. This deficiency in our understanding was termed 'inflammatory stimulus' by us given that it appeared to drives the initial cascade of an upregulation of inflammatory markers characterised by an increase in protective mucins as well as a strange divergence of inflammatory markers thereafter from the stage of *in situ* to invasive cancer. While there previously existed epidemiological evidence to support the association of typhoidal *Salmonella typhi* and *S. paratyphi* with the risk of gallbladder cancer (12-15), we have now uncovered the first evidence to support the association of even non-typhoidal *Salmonella* with gallbladder cancer (16). Owing to the ability of *Salmonella* infection to stimulate a host response and non typhoidal species (*S. typhimurium*, *S choleraesuis*) to elicit an even stronger host immune response compared to the typhoidal species, it is likely that these bacteria are able to provide the continued 'inflammatory stimulus' necessary for carcinogenesis. *Salmonella* isolates in the chronic carrier state thus fits the role of the 'inflammatory stimulus' in the genetic model for gallbladder carcinogenesis and its dissemination cascade, which may trigger transformation through chronic inflammation, but not for maintenance of tumourigenesis (3).

The importance of this finding (16) cannot be understated. The current focus of treatment in typhoid-endemic countries has traditionally been to eliminate typhoidal *Salmonella* species often underestimating the contribution of the non-typhoidal isolates that show an inherent higher resistance to the standard antibiotics (17) resulting in their ability to lead to chronic carrier state in humans. The finding of non-typhoidal *Salmonella* species in our study (16) brings to light the fact that in typhoid-, as well as gallbladder cancer-endemic countries, efforts must be directed not only at treating typhoid fever, but also diagnosing and appropriately managing non-typhoidal *Salmonella* species. Such an approach may help reduce the chronic carrier state of these species in humans, and the resultant chronic inflammatory stimulus driving gallbladder carcinogenesis hypothesized by us. Thus, such a simple, yet effective, strategy may help reduce in the incidence of gallbladder cancer.

Thus, in conclusion, we concur with Dr. Kai that every effort must be made to completely understand gallbladder carcinogenesis taking into account every known precursor lesion (18,19). Knowledge gained through such an exercise will only help us develop better and more effective treatment strategies for gallbladder cancer.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

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