

Dr. Stephen Hiscox: non-receptor tyrosine kinases as therapeutic targets in metastasis

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Dr. Stephen Hiscox (Figure 1) is currently Senior Lecturer in Cancer Biology within the School of Pharmacy and Pharmaceutical Sciences, Cardiff University, UK. He has a long-standing interest in cancer invasion and metastasis particularly in the context of drug resistance in a broad range of tumor types. His early translational work at the School of Medicine in Cardiff focused on understanding the role of c-Met signaling in GI cancers and his subsequent lab in the School of Pharmacy was one of the first to identify a role for Src family kinases in the acquired drug resistant phenotype in breast cancer.

The long-term goal of their laboratory is to better understand the cellular and molecular pathways underlying metastasis as such studies will assist in identifying prognostic and predictive biomarkers and have the potential to reveal novel therapeutic targets to both prevent the occurrence of, and treat patients with, metastatic cancers.

TGC: *Your speech topic in the 9th National Gastric Cancer Academic conference is “Non-receptor TKs (tyrosine kinases) as therapeutic targets in metastasis”. Could you briefly describe this?*

Dr. Hiscox: Non-receptor tyrosine kinases represent a group of proteins that reside inside the cell and play important roles as regulators of many cellular signalling pathways and gene transcription programmes, a number of which govern the metastatic capacity of the cell.

TGC: *Could you share with us the current progress of your research (interest)?*

Dr. Hiscox: I have a number of interests within the field of tumor metastasis and currently my group is looking at how these cytoplasmic tyrosine kinases can promote metastatic cell behavior particularly by influencing the way tumor cells interact with their microenvironment. We have recently shown that specific non-receptor TKs appear to sensitize



Figure 1 Dr. Stephen Hiscox.

tumour cells to fibroblast-derived signals which in turn can promote a migratory response in the tumour cells. Another, and particularly important, question for metastasis is one of therapy resistance. So my group is looking at the role of cytoplasmic tyrosine kinases, particularly those of the Src family, as mediators of drug sensitivity and resistance.

TGC: *So during your research progress, what challenges have you met?*

Dr. Hiscox: That is a good question. One of the challenges is really identifying which kinases play dominant role because this is a group of 10 broad families representing at least 20 cytoplasmic kinases; within some of these groups there is evidence which suggests some level of redundancy between them. So if you inhibit one kinase, its function may be taken up by another family member to a greater or lesser extent. For example, I showed a lot of data on inhibitors of

the Src family and those inhibitors are not specific for one particular member, they would inhibit multiple members of the Src family because of the high degree of homology between those enzymes. What I am interested in is looking at whether one or more members of these subfamilies (e.g., the Src family, the JAK family, etc.), whether there is a dominance. Should we try to inhibit Src, YES, FYN or FAK selectively, rather than broad families? In fact, some of our research shows that for example, in some context, it might not be Src itself, but it might be a protein called YES that plays a role in resistance to some kind of therapies. It's a challenge because there are a number of proteins to look for. It's important to look at the hierarchy in these families as this may help selective targeting. Alternatively, therapeutic approaches could target all members of a particularly family, though there may well be obvious clinical drawbacks associated with this. We are going to choose a family.

A further challenge is to know how to best select patients ultimately to trial these agents. That is really a challenge for any clinical trial. Whilst we don't conduct clinical trials directly, *in vitro* laboratory studies and preclinical translational data are important to help provide a rationale for the use of targeted therapies, such as ones that inhibit non-receptor TKs, in certain types of cancer. So the real challenge is having the right patients to test these agents. A lot of trials will try small molecular monotherapies in advance stage patients, but they are not selected on any other basis just that they have advanced stage disease. Although this might be helpful in terms of telling you how well these agents are tolerated, sometimes, maybe quite frequently, a lot of these studies are not that encouraging—tumour growth is not suppressed or you don't see disease regression. Perhaps this would be different because these agents were used in selected patient group. For example, patients who have HER-2 over-expressing gastric cancer might be more appropriate for Src inhibitor and trastuzumab combination therapy or Met over expression might direct for Src/FAK kinase inhibition. Of course, study numbers are small in advanced stage trials which are a further challenge to patient selection. Across the board, it is difficult to know which patients are going to benefit the most from each type of treatment. That is really important. I guess it leads to biomarker studies, being able to select those patients that are going to benefit most from various inhibitors.

(It should benefit both to the doctors and patients).

It is benefit to the doctors because they can better treat patients. They can prevent some patients being over treated.

We can direct the treatment to the patients likely to benefit the most.

TGC: *You have mentioned the opportunities for cytoplasmic TKs in GI cancers in your speech. So what can we expected in the future development about this?*

Dr. Hiscox: Work from my own group along with a number of others have shown the benefits of combining inhibitors of Src family members or FAK family members with agents that target c-Met/HER-2 both in cell models and *in vivo* systems. I would like to see this approach being taken into HER-2 positive gastric cancer, initially with appropriate *in vivo* modeling and, if this looks encouraging, there could be opportunities for clinical investigations, particularly given that HER-2 is known to be over expressed in GI cancer. Additionally, a similar approach could be used for Met amplified cancers and I'm aware that the preclinical data is also encouraging in this respect. We don't know until we do the trials. But based on the preclinical data, that's where I would assume the greatest benefit would be.

TGC: *GI cancer is a big problem in the world? So what are your comments in the GI cancer research in China?*

Dr. Hiscox: The first thing is that you are right about the GI cancers. I think it is the second most commonly diagnosed cancer worldwide. So it's a major problem, particular in the Eastern world. And I think in China it is the major problem compared to the West.

A lot of important research has arisen from Chinese research groups—studies validating the extent of HER-2 overexpression and Met amplification (up to 50%) in GI and colorectal cancers. There have been recent studies, again by the Chinese research community, that have identified that Met amplification can make cells sensitive to Src kinase inhibitors. There have been some really interesting reports recently from Chinese groups for example that have looked at micro RNAs in GI cancers, some of which may regulate FAK, and other studies that look at the role of the microenvironment in colorectal cancers. It really appears to be a very active and productive area for China cancer research—so my comments on Chinese researches are that the international scientific community is getting a lot of important data from Chinese research groups driven in part by the dominance of GI cancers in this geographic location.

However, as is the case for any disease, we cannot afford to be complacent and still need a concerted research

effort in this direction. And what I would like to see is kind of more combination approaches: preclinical data reported on combination treatments. There are a lot of interesting talks at this meeting that are looking at combining different receptor tyrosine kinases inhibitors with chemotherapies for example. But I think the general principle is that combination treatment rather than the monotherapy is the way forward and not exclusively tailored to chemotherapeutics but also combining targeted agents.

My other comment is that although this is just my first time at the NGCAC meeting, I am extremely impressed by the variety of science but also the quality of the science. I think it is a real privilege to take part in this meeting and being amongst other scientists and clinicians, who are doing top quality basic, translational and clinical research. It really is a credit to the Chinese research community.

TGC: What would you like to say to the doctors in China, especially to the young ones?

Dr. Hiscox: Firstly, I would encourage the clinicians to engage in some kind of research, not necessary to do it themselves in the lab (although this is preferable as it is a very good experience) but at least to read about it regularly and have some level of participation in it. In my lab we regularly have clinicians that have taken time out of their medical training to study for a research MD

degree. I think that is very important because it makes you a better doctor—understanding how therapies work at a cellular level can help you understand the treatments that you are giving to the patients. Research is also a key component if you are going to understand and maybe suggest a rationale for effective clinical trials. So what I would say to the clinicians, I would just encourage them to get involved in research in whatever capacity that is. And also I would encourage collaboration between the clinicians and scientists. What is really important in a lot of studies is to get access to the clinical material. What we see in the cell line or animal model does not necessarily mean that it would hold true in the human context. So human material is really important for translational study so we can look at various molecular profiles, various biomarkers in tissue from GI cancers for example. That's why good collaboration between scientists and clinicians is fundamental and really important.

TGC: Thank you very much!

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