NEW HOT PAPERS - 2008

September 2008

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Edward A. McKenzie talks with *ScienceWatch.com* and answers a few questions about this month's New Hot Paper in the field of Pharmacology & Toxicology. The author has also sent along images of their work.

+enlarge

Article Title: Heparanase: a target for drug discovery in cancer and inflammation
Authors: McKenzie, EA
Journal: BRIT J PHARMACOL
Volume: 151
Issue: 1
Page: 1-14
Year: MAY 2007
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SW: Why do you think your paper is highly cited?

I think this is probably a reflection of the tremendous interest shown by both big pharma and the biotech industry in this enzyme as an anti-angiogenic/metastatic therapeutic target in cancer drug discovery. As there is only one extracellular enzyme that has this role, it is recognized as a key control point in this biological pathway, in contrast to the case of matrix metalloproteinases, for example, where many enzymes can perform a similar role.

Heparanase is elevated in almost every tumor type studied and as such, is heavily implicated as one of the important players in disease progression. Outside of cancer biology, the enzyme also has a role in inflammation and wound healing and so crosses over many disciplines to attract a wider audience. The recent availability of reagent tools (recombinant protein, specific protein antibodies, assay kits, heparan sulphate substrate antibodies, etc.) has also made research into heparanase that much more accessible than before.

Figure 1: +details

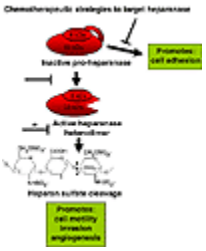


Figure 2:

SW: Does it describe a new discovery, methodology, or synthesis of knowledge?

This review brings together the key publications over recent years since the cloning of the gene in 1999 and synthesizes the knowledge of heparanase biology and pathology which has lead to the current diverse array of inhibitors of heparanase activity. Looking to the future, more focus now needs to be put on the discovery of *in vivo* clinical biomarkers of this enzyme as the validation of

heparanase as a drug candidate becomes even more compelling.

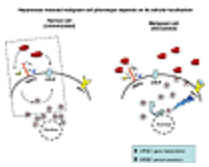
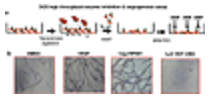


Figure 3:



SW: Would you summarize the significance of your paper in layman's terms?

Tumor cells require a number of essential proteins that allow them to proliferate and spread—a process known as metastasis—throughout the body. To keep ahead in the battle against cancer there is an increasing need for drugs that block these proteins and so neutralize their action. Blocking the action of heparanase with inhibitors, as highlighted in this paper, has been shown to significantly reduce both tumor spread and restrict the growth of new blood vessels (angiogenesis) that feed the tumor.

Many different types of inhibitors have now been developed and are in the exciting transition phase of going from laboratory testing to the clinic. The flagship drug PI-88, which includes a heparanase inhibitory action, is leading the way by showing great promise in clinical trials. New screening tests to examine how well these drugs perform in cancer patients are also being created. Only time will tell, however, whether these drugs live up to the many expectations; hopes are high within the heparanase community.

SW: How did you become involved in this research, and where there any problems along the way?

My involvement in heparanase (HPSE1) and carbohydrate processing enzymes in general first began in June 1999 when I joined Oxford GlycoSciences (OGS), a small biotech company based in Abingdon, south of Oxford. Working in a close-knit drug discovery team, my primary aim was to take a potential oncology therapeutic target protein and help design and implement from basics all the particular protein expression strategies, HTS assay, primary and secondary assays required to screen and test for novel inhibitors.

"Many different types of inhibitors have now been developed and are in the exciting transition phase of going from laboratory testing to the clinic."

An exciting part of this work was the freedom to carry out basic research and to publish my work. This led to the discovery of a novel heparanase enzyme (HPSE2) and work describing for the first time a route to producing large amounts of active HPSE1 enzyme. A series of potent inhibitors were discovered that led to some encouraging preliminary efficacy data on animal models.

Unfortunately OGS fell victim to a hostile takeover in 2003 by Celltech (now part of UCB-Celltech) which led to closure of the program and a large number of redundancies. I subsequently moved back into academia and concentrated on re-building my heparanase career through a number of collaborations. Forging these strong links with academic groups during my OGS days meant, luckily, that I could rely on these to re-establish myself in the field again outside of industry.

SW: Where do you see your research leading in the future?

One of my current research interests is to obtain a high resolution X-ray structural model of the active enzyme. This will facilitate a rational drug design strategy for discovering new inhibitors in addition to improving on current drugs. It is very exciting to see that heparanase 2, which has remained in the shadow for too long, is now attracting attention from a number of groups studying its role in cancer. The challenge now is to determine the individual role of the various heparanase 2 splice forms and examine their precise role in extracellular matrix remodelling.

SW: Do you foresee any social or political implications for your research?

Any therapy (small molecule, antibody, antisense RNA, etc.) for down-regulating the elevated levels of heparanase enzyme observed in cancer and inflammation has tremendous potential for both single or combination therapy. Since cancer biology involves so many different mechanisms, a drug target such as heparanase, which is involved in more than one mechanism (in this case, angiogenesis and invasion), provides a double-hit approach. Expanding our basic knowledge of how this protein functions will only help to further drive the drug discovery process.

The true success of anti-heparanase drugs however can of course only be judged from their success in clinical trial studies. Like others in the field, I am confident that these drugs will pass this test and go on to make a significant contribution to the treatment and quality of life for cancer patients. Anti-heparanase therapy could help to convert cancer from being the killer disease that people fear to a chronic condition that is contained and more manageable.

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Keywords: heparanase, anti-angiogenic/metastatic therapeutic target, cancer drug discovery, cancer biology, extracellular enzyme, matrix metalloproteinases, recombinant protein, specific protein antibodies, assay kits, heparan sulphate substrate antibodies, angiogenesis, tumor cells, metastasis, oncology, therapeutic target protein, heparanase enzyme.

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