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Expert Opinion



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Glycogen synthase kinase-3 – a promising therapeutic target: interview with Hagit Eldar-Finkelman

Dr Hagit Eldar-Finkelman (Sackler School of Medicine, Israel) was interviewed by Emma Quigley (Commissioning Editor, *Expert Opinion on Therapeutic Targets*) on 16th February 2006.

Born in Jerusalem, Dr Eldar-Finkelman received her BSc in Chemistry in 1984 and both her MSc in Physical Chemistry (1986) and PhD in Life Science (1993) from the Weizmann Institute of Science. She was a recipient of the British Council Award, which allowed her to conduct research in biological nuclear magnetic resonance at the University of Oxford in the laboratory of Professor George K Radda. Following postdoctoral work at the School of Medicine of the University of Washington with Nobel Laureate Professor Edwin G Krebs, she became an Assistant Professor in the Department of Medicine at Harvard Medical School. Dr Eldar-Finkelman joined the Sackler School of Medicine at Tel Aviv University in 1999. Dr Eldar-Finkelman's research focuses on the molecular mechanisms regulating the protein kinase glycogen synthase kinase-3 (GSK-3), and their implications in negative regulation of signalling pathways. In particular, her work aims to develop specific inhibitors for GSK-3 and to test their functions *in vitro* and *in vivo*, considering the concept that such inhibitors may be useful in insulin resistance and Type 2 diabetes. These studies provide a conceptual basis for development of GSK-3 inhibitors and may lead to design of small molecules for treatment of diabetes and or neurodegenerative disorders.

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1. What are you currently working on?

We actually focus on development of specific GSK-3 inhibitors. GSK-3 is a serine/threonine kinase, which is involved in several pathological disorders, including diabetes as well as neurodegenerative diseases. Our approach is actually different to that of other groups and companies because we are trying to develop compounds that target the substrate binding site of the kinase. Our approach is rational drug design. We are not trying to find a molecule; we are trying to design a molecule that will bind specifically to the GSK-3 substrate binding site rather than the ATP binding site. We believe this will result in a more specific inhibitor.

2. Who are you working with?

We work with an organic chemist. We design a pharmacophore and then he synthesises several variants for us to test. It is a very nice collaboration between a chemist and the biologists in the lab.

3. How did you come to research this?

I started off working on targets downstream of MAPK (mitogen-activated protein kinase). That was very popular at the time; everybody was working on ERK. I found that GSK-3, which at the time not many people looked at, was a downstream target of the MAPK pathway. I started trying to learn more about the enzyme, but what really directed me to diabetes was the finding that one of the

substrates for GSK-3 is insulin receptor substrate-1 (IRS-1). We could show that GSK-3 phosphorylates IRS-1 on serine which, in turn, converts IRS-1 to an inhibitor of insulin signalling. This was the first link between GSK-3 and insulin resistance. This is how I started researching GSK-3. I didn't plan it, I just followed GSK.

4. What are the clinical applications of this research?

It seems that elevated activity of GSK-3 is involved in diabetes and insulin resistance, as well as bipolar disorder, Alzheimer's disease and Parkinson's disease. Therefore, inhibiting GSK-3 may be a therapeutic tool to improve those conditions.

5. Is this target already being used in any type of therapy?

Lithium is a well known drug for bipolar disorder. It was discovered to be a GSK-3 inhibitor and so GSK-3 is a target for mood-stabilising drugs. GSK-3 is also involved in apoptosis, so degenerative diseases such as Alzheimer's disease, Parkinson's disease and perhaps even stroke could be improved by therapy with a GSK-3 inhibitor. As far as I know, there are no current drugs for neurodegenerative diseases with GSK-3 as the target, but I believe there will be in future.

6. Why is GSK-3 such a good drug target for diabetes treatment?

With GSK-3, we do know that it plays a negative role in insulin signalling, namely that its activity inhibits insulin action. In diabetic conditions, GSK-3 is hyperactive; therefore, inhibition of GSK-3 may produce an antidiabetic effect. I think there are other targets being considered, but they have not been shown to be physiologically upregulated in the disease state.

7. Have you developed a candidate drug based on this?

Yes, we have two lines of development. One is a peptide, L803-mts, which is patterned after GSK-3 substrate. This peptide behaves as a substrate-competitive inhibitor.

The other line is design and development of small molecules, which we term GS molecules. Not peptidomimetic, but non-peptide small molecules that will mimic the recognition motif of GSK-3, which is very unique. These will also act as substrate-competitive inhibitors.

8. What is the mechanism of action for these drug candidates?

They prevent the phosphorylation of GSK-3 substrate, such as IRS-1 for example. In preventing this phosphorylation, the

inhibitory effect is relieved. The substrate in question could be IRS-1, glycogen synthase or other transcription factors such as CREB.

9. How are you researching this? What techniques are being used?

First, we do the synthesis with our chemists, then we test *in vitro*, then we move onto cells and diabetic animal models. We basically use high-fed diet, induced-diabetic mice and Ob/Ob mice.

10. How will this compound compare with other therapies currently available?

It is difficult to compare efficacies at this stage, but I do believe that they will have less side effects and will be less toxic than other drugs. We do know, for example, that they do not cause weight gain. Whereas some drugs lead to an increase in fat tissue mass, these drugs do not. They do not alter the blood chemistry; for example, they do not increase triglyceride or cholesterol levels in the blood. I do believe they have the advantage of being less toxic.

11. What stage are you currently at with this drug?

We are still in the preclinical phase with these drugs. We are trying to build up a pharmacological profile, looking at pharmacokinetic data and really trying to see how these compounds work as a drug. I have been working on this for about five years now.

12. There are many ways to treat diabetes now. What is the advantage of pharmacological intervention?

I do believe that balanced nutrition and physical exercise are very important as preventative steps. However, there comes a point where the insulin resistance is too severe; it is like the system has lost its balance. Administering the drug can shift the balance back to a better situation allowing the body to cope with the adverse effects. The drug just pushes it back a little bit to a better metabolic point, but it does depend on the stage of the insulin resistance. You get to a point where diet and exercise do not help anymore and that is when you need to interfere with the cellular system; I won't say to repair it, but to help it return to a better steady-state.

13. Who are your main competitors in this area, and how do their compounds compare with yours?

There are many because GSK is so hot! There are several companies but they are all working on ATP-competitive

inhibitors, whereas we are working on substrate-competitive inhibitors. Because the ATP binding site is highly conserved in protein kinases, we expect ATP-competitive inhibitors to be less specific than substrate-competitive inhibitors, so that is an advantage of our compound.

14. What are the current 'hot topics' in diabetes and GSK research, and where do you see the field going in the coming years?

I do believe GSK-3 is a leading target for diabetes treatment, but good treatment is often in combination. I think the GSK-3 inhibitor could be part of a drug cocktail with other inhibitors, such as a PKC β inhibitor, which we also know is involved in diabetes. I definitely think the GSK-3 inhibitor is required.

In terms of other GSK research, the CNS research is becoming very hot. Particularly depression and Alzheimer's disease because, *in vivo*, lithium, a GSK-3 inhibitor, has been shown to improve Alzheimer's-like conditions and we already use lithium for bipolar disorder.

15. Provide your Expert Opinion

GSK-3 is a good target for diabetes. It is interesting to note that increased activity of GSK-3 has harmful effects, but also no activity of GSK-3 has harmful effects. Therefore, GSK is important for both the life and death of the cell and moderate GSK-3 inhibition, rather than total inhibition, is the way to go. Total inhibition may explain why you get toxic effects with other inhibitors. Finding a substrate-competitive inhibitor is a particularly challenging area as the binding site of the kinase is not well defined like the ATP binding site for example.

I hope to get my research to a stage where we have a leading drug with good efficacy *in vivo* and no toxicity. I hope that we can find a company to collaborate with in order to move on with this project.

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