



## **Horizon Joins UK Cancer Initiative; Will Supply Cell Lines to Study Senescence**

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**By Charlotte LoBuono**

Horizon Discovery this week announced that it will become the first corporate member of a consortium launched by Cancer Research UK to form teams of academic and pharmaceutical scientists to study emerging areas of cancer research, and translate basic science into new cancer drugs and diagnostics.

Alongside Horizon, the consortium, called VIMCAD, comprises Cancer Research UK's Cambridge Research Institute, St. George's University of London, the University of Glasgow, and the University of Liverpool.

Cancer Research UK will fund the consortium with £500,000 (\$987,000) over two years, Simon Youlton, the group's business manager, told CBA News this week.

VIMCAD members will look at cellular senescence. "Cell senescence was the expertise of two members of this consortium, and the managers at CRT who assembled it had the idea of focusing on finding agonists of cellular senescence in mind for this project," said Chris Torrance, CEO of Horizon Discovery.

For instance, the principal investigator of VIMCAD, Nicol Keith from the University of Glasgow's Beatson Laboratories, is an expert in assay development and telomerase biology. Another researcher, St. George's University's Dorothy Bennett, is an expert on melanoma, of which senescence is an important aspect.

Since about 2004, senescence has begun to garner more attention among oncology researchers, said Youlton. Senescence was originally noted more as an artifact of cell culture; cells were not believed to senesce so much in vivo, he said.

"People began to see [senescence] in moles, and loss of this function leading to the progression of melanoma," Youlton said. Mainly, cells present in benign moles are senescing — "that is how you keep your moles in check." The pathways that are involved have much to do with the upregulation of the p16 and CDK4 genes, which VIMCAD plans to study.

A lot is now known about the proteins and pathways involved in senescence, which "makes it a very good thing to bring into a focused translational program with the idea that you if can induce senescence, you can put a stop to tumor development," said Youlton.

"Melanoma is being used as a model to better understand senescence in other types of cancer," Horizon's Torrance told CBA News this week. He said that for VIMCAD, Horizon will develop genetically defined human isogenic cancer cell lines that can be used for the high-content screening of potential drug candidates.

Isogenic cell lines are normal immortalized epithelial cells that are paired with identical epithelial cells except for the presence or absence of one or two mutations that are relevant for a particular cancer.

In theory, investigators can take known mutations that occur in patients whose cells have lost the ability to senesce and replace the native genes with a mutated gene in one of those cell lines. By interrogating the normal versus mutant cell lines with a putative compound, researchers can see if the compound is acting on those proteins and/or the senescence pathways they control.

“The real drawback in cell screening is that you are looking for cancer cells to respond to a putative drug,” Youlton said. “If you use a cancer cell line, then you have no idea why that drug caused that cell to die.”

He said that when investigators study a drug candidate they have no way to develop structure-activity relationships because they do not know how the chemistry of a drug relates to the biology of the protein with which it will likely interact.

“You have much more opportunity, if you have these paired cell lines, to deconvolute, or determine, how a putative drug is working,” said Youlton.

In addition to cell-based assays and senescence, which is something that “has not really been studied by pharma before,” Torrance said that the third component of the VIMCAD project is the technologies required to look at something like that, “which involves a cell-imaging approach.”

He added that some cell-based assays that have a surrogate readout are chemical based, and just change color, so “they do not really give you a good sense of what the cell is actually doing” as it ages and dies, or once it has been exposed to a putative drug.

In the field of senescence, one would really need to have “a very good visual image of the cell to get the best markers of what the cell is doing in the senescent period,” Youlton added.

One member of the project, Mike White at Liverpool University, is an expert in cell-imaging technology, Torrance said. The development lab at CRT will also be providing high-throughput screening platforms that it already has in-house. Cambridge Research Institute’s Masashi Narita, another project member, has developed novel biomarkers of cellular senescence that will be applied to these imaging/screening technologies.

“Melanoma is being used as a model to better understand senescence in other types of cancer.” Although VIMCAD was initially designed to be a two-year project, it is “certainly intended to run longer if the objective of getting a pharmaceutical partner involved is met,” said Torrance.

He added that one of the unique features of the project is that, rather than doing a lot of work and “maybe getting some IP at the end that you patent and take to pharma companies — which can actually take a long time” — Cancer Research UK’s aim is to get pharma companies involved early to become part of the process.

Said Torrance: “One of the quickest ways to have a vehicle that a pharma company would be interested in becoming involved with early on is to create something that would be a legal entity unto itself.”

He said that one such entity would be a holding company that owns all the IP and has a seat available for a pharma company to come in early, and ultimately, when the project concludes in two to four years, can get more funding from the pharma partner. “It could even decide to buy the company at some stage,” Torrance said.

Youlton is "very keen to get this advertised to pharma," and it is his intention to get a pharmaceutical partner in early, Torrance said. "He is not going to hold out for the best deal financially, but will also look at what other factors the pharma company brings to the collaboration to make the best fit."

Youlton agreed, saying that "these are very concentrated two-year programs with deliverables and milestones." The programs are geared toward industry rather than academia, "where we give them funding for two or three years, and at the end they submit a report."

Now one week into the program's launch, Youlton said that he "can officially advertise and go out and visit my contacts and colleagues in pharma. I am already targeting the top 30 pharmas, and two of the top 10 pharmas have already contacted us."

Cancer Research UK has two additional programs planned for 2009 and 2010 that will focus on cancer stem cells and the histone code, respectively. Each project has been allotted £500,000.

"Hopefully, we can accelerate from there if the programs are successful, because if they are, then while they are running, industry can add to the funding from Cancer Research UK," Youlton said.

If an industrial partner comes in, they will be urged to support the program by bringing in more postdocs to accelerate the program and its research.

"We may be bringing in some of [the pharmaceutical partners'] compound libraries. In return, they will have the exclusive option to all of the output from the program if they want to take it up commercially and drive it to the clinic," Youlton said.