

Transcription Video 101087

Introductions:

Prof. Peter Beverley Summarizes:

Some time ago we put out a call for research papers.

PB Chair of the SRB at that time

Vigorous peer review process.

SRB selected this project for funding.

This is the project that Artemis and the Leventis Foundation are contributing to.

Reason selected from 12 or more received is that a mutation had been found in LCH by Prof. Barrett Rawlins in Boston that suggested that this might be a cancer like disease.

Most cancers as you are aware have mutations in them and we thought that this was something that should be followed up and finding a mutation does not solve the problems especially finding the mutation in about 50% of the patients so the other half of the patients do not have the mutation which BR found.

Although finding the mutation is suggestive of cancer it raises many questions in this disease in particular.

The 1st is that LCH is a disease found in bone, skin and other organs and yet the cell that is found in these lesions the Langerhans Cell has been thought to originate in the bone marrow.

The 1st question is the mutation found in other tissues as well as the actual lesion.

Half of the Project Prof. Collin deals with asking that question.

So he gets patients with the disease, he gets blood samples & bone marrow so he can ask the question.

In a patient that has the mutation do we also find the mutation in the blood & the bone marrow where the Langerhans Cells are thought to have originated and he will tell you what data he has so far. I think the question is not entirely resolved although it does seem that some patients at least the blood may have the mutation and if it was found in the blood and the bone marrow it would make the disease more like a Leukemia. Most Leukemia's originate in stem cells the cells which produce the red and white cells and of course that has implication for treatment, you cannot just treat the lesions if the bone marrow stem cells have the mutation you would have to treat the disease much more like Leukemia, so it's a very important question also finding the mutation in blood might have useful prognostic implications it might tell you that this is a patient that might do badly or well so it's very important to know where the lesion is and whether this is a systemic disease a Leukemia like disease or a more localized disease of the tissues.

And the other half of the project is actually happening here at King's run by Prof. Geissmann and we thought that this was equally important and it seeks to ask similar questions but using a mouse model to really ask what does the mutation do if it is expressed in the peripheral tissue like the skin or bone marrow. What does it do if you make the mutation in bone marrow stem cells, you can ask questions about the biology of the disease and in the long term those answers will be very important if you do always find it in the stem cells and only if you put the mutation into the stem cells and the bone marrow you get Histiocytosis like disease again it would suggest that this is a Leukemia like disease.

If you find that switching it on in Langerhans Cells again which you can do in a mouse a transgenic mouse again this would have important implications.

Secondly in the mouse you can investigate how things occur

This disease obviously causes brain damage and it also causes holes in the bone, in the mouse model unlike the human you can really begin to ask how are these lesions caused what actually makes the holes in the bone and even more puzzling, what is it that causes the long term brain damage that patients suffer from poor Nikolas being a very good example of that.

And you cannot really answer those questions in humans so we felt that putting these two together was a synergistic interaction. The two principles talk a lot and have a vigorous debate about how the disease is caused and what the mutation does and we think that's extremely helpful.

So they will both tell you a little about what they are actually doing.

Just to say something about our visit here.

We went around the labs which was very useful particularly for Dora and Lynn who raise money & see patients and are not laboratory scientists and I must say that I as a laboratory scientist was very impressed by the equipment that is available here to study the biology of these cells so I think our choice of this laboratory and certainly suggests that we made a good decision because they have the techniques, the mice and they actually work on flies which have the advantages of genetics they have many technologies and very good equipment to study what B600E the mutation that BR found actually does in those species and again that will be translated into humans by experiments that Prof Matt Collin does, his patients material in Newcastle tissue he gets.

Hands over to Matt.

Matt thanks Leventis for support it is difficult to raise money to take LCH research forward and the small amount enable us

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Prof. Matt Collin

Our specialty is to fractionate the blood into all the different types of white cells and also bone marrow compartment.

ENDS

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Prof. Matt Collin

Which point did I get to before it cut off?

Leventis

You have been able to locate the BRAF in patients at a very advanced stage.

Matt

So we can find it in the blood and also in the bone marrow but it is only in a couple of patients with multi-system LCH so there is another group of patients where the blood is negative for the mutation those ones with the single system disease and particularly isolated bone lesion's.

It is interesting that in principal that it shows that in certain types of the disease that there is potentially a connection with the bone marrow & the blood and it is also interesting practically as it may be that if we do this blood test at diagnosis and we just ask is the blood positive or negative that we will allow quite rapid development of a clinical test that will be useful so it may be that positive blood is an adverse risk factor, and it does correlate with some data that is about to be published in children from a group in the US.

So the way I want to take this forward is to engage with the LCH4 trial and a very simple question will just ask for a blood sample & diagnosis and the patients that enter this trial and are we will do the sensitive test for BRAF and we will see if it has some clinical utility. When we have got the blood test in our hands obviously we will continue to divide up the white cells and see if we can track which components of the white cells that the mutation is found in.

I think it offers a good chance of something that will be useful in the Clinic within a couple of years and also of continuing to make progress into the biological front to find a bit more about whether the disease is present in which compartment of the white cell.

That question is there Langerhans Cell precursor that basically the question.

Leventis – Well that's very important

Matt- So that is where we have got to with that , it is quite good timing in relation to the funding, we have had that we are finished the study and are about to send it for publication.

So I will hand over to Frederic now.

Leventis – Thank you

Prof Frederic Geissmann – Hello

Research mostly doing only research and we are interested in doing macrophage in Histiocytosis

We try to investigate the BRAF mutation is responsible for the development of the disease.
Introducing it in a conditional manner macrophage mice.

The question how does this BRAF involve in generation to bone lesions

Does it cause disease and which features of the disease are caused by the BRAF activation

And if we say no BRAF is not condition of the bone or the brain or other tissue we need to look for an explanation

It is also important if treatment of a BRAF limiter on a scientific basis
BRAF Studies of the disease is found in cancer.

We would want to make sure that a patient potentially receiving toxic drugs so that we can agree a benefit, and this we go from clinical studies but this we also by knowing what the effect of the application in the macrophages is
And what is the effect of muted macrophages in the mutation?
It is a long process because we need to conditionally introduce it to the patients.

We have a very good experience of doing this type of study and we are now doing that.

The other thing we did a clinical study with mostly patient kids and in general the mutation is not found in the blood it can be detected with heightened sensitivity but in general it is not in the blood
and that fits with an idea which is now supported by many data that shows macrophage do not come from the bone marrow and they have locked together with the tissue.

It is a new idea because it's against the text book but the text book will eventually be changed they are actually starting to change already everybody agrees.

And that raises an interesting question cause may be some other patients will actually have a Leukemic disease but may be some other patients will actually have a development of the disease if it's not in the bone marrow but of a tissue macrophage.

Leventis – They will be receiving the wrong treatments

Frederic- Yes they would receive the wrong treatments so that we know that treatments for Histiocytosis disease are not completely optimal they work in some but not in others characterizing better how this develops from which cell has the potential to tell us if what we do is right or wrong.

Leventis-Potential to have drugs that are less toxic when they are not needed

Frederic – Yes

Leventis – Make it easier for patients

Frederic- For patients it will be interesting to know that the disease is not in the bone marrow
But it would be very interesting for a 10 year old kid with an isolated bone lesion to know that it is fine.
And it will be very interesting to know why there is some kind of brain inflammation present in some patients, because the pathology is addressed by the treatment it would be interesting to know if BRAF mutation is causing the type of brain lesion or not which we don't know, but if it was a case we could try to see whether in????BRAFF would have an effect.

It is possible that it is not going to be the case so we really need to know.

Because then we need to inform what we do

So basically we need the mouse model to express the BRAF to get the consequences of the tissue

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Leventis- Rap up

Thank you.