Prof. John Thompson
Syd Cancer Conference
DAYMAR COMMUNICATIONS

PROF. JOHN THOMPSON: When given this topic some months ago, it was difficult to decide what would be best to talk about. And what I'm going to talk about, there's little relation, really, to what's in the abstract, so ignore that, if you've seen it. It's a field that is expanding on many fronts. It's a disease which is frustrating in many ways, because we don't have good drug therapy for people with advanced disease. Still we are struggling with simple surgical treatments for people with primarily melanoma, and very much for people with secondary disease, as well, and we'll touch on some of that.

I was thinking of talking about some of the more complex surgical techniques we've developed, but decided that for a general audience, that was probably inappropriate. (Background Conversation) So I thought I'd just home in on three subjects, and in particular, I wanted to spend a little time talking about a new technique for the management of recurrent disease, which seems to have caught the attention of the media and others. And which I think is very interesting and may lead the way to other developments.

I want to mention briefly the successes and failures of vaccines in the treatment of melanoma. One of the things we know about melanoma is that it's immunologically controlled. Just this week, I saw a patient who had a melanoma on his back treated 32 years ago, and he turned up with a recurrence. Now in the intervening 32 years,

his body, his immune system has somehow been controlling that disease, but there's no doubt that this is a recurrent (Inaudible) melanoma treated 32 years ago. So for many years now, our clinical immunology colleagues have been telling us that they will be very shortly curing melanoma with immunological therapies. Sadly, that's not quite true yet, but they continue to remain enthusiastic. And I want to mention that briefly. And in the course of a couple of these recent vaccine trials, I think we've learned some new things that we didn't know before about the role of surgery not for primary melanoma treatment, but for the treatment of metastatic disease.

What I'd like to begin with is to talk about a substance called Rose Bengal. Rose Bengal has been around since the late 19th century. It was originally developed as a dye for dyeing fabrics, wool in particular. And it's called Rose Bengal, not because it has anything to do with roses, but because it's rose-colored. And apparently the name comes from the little spot that Indian ladies put on their foreheads. And this substance, quite how, I'm still not sure, was discovered to be a powerful cytotoxic agent when administered locally to tumors. And an agent that had a profound effect on tumor cells, but almost no effect on adjacent normal tissues. And we've recently been involved in a trial with this agent in people with recurrent melanoma, particularly those with recurrences on or immediately under the skin.

This is what it is. It's a thick, oily, red dye that comes these days in a bottle. And we'll come back to this. It has already been used in some Phase I and Phase II clinical trials for melanoma, for breast cancer and for liver tumors. And the other interesting thing that's been observed, and we'll come back to that, is that when you treat tumors with this agent, quite frequently, in about 25 percent of cases, adjacent

bystander lesions, non-injected lesions, undergo regression as well, which is interesting.

The history of it. It was found by a man in Germany who was working for a pharmaceutical company, because that's what they were called in those days. And it's just a fluorescein dye, essentially. It was used early in the 20th century for medical diagnostic purposes, in particular for liver function testing. It was simply injected intravenously, and if you cleared Rose Bengal, your liver was working well; if you didn't clear the Rose Bengal, your liver was not working well. It was as simple as that. It was used as a food dye, as a dye in fabrics, and also as an ink in felt pens and highlights in more recent times. And most recently, of course, as an active ingredient in this ten percent solution of it, which is known as PV-10, which is what has been used in the clinical trials in melanoma patients.

All this experience, over 50 years or so, has demonstrated that Rose Bengal is not metabolized in the body. It's excreted rapidly and it has minimal toxicity in healthy tissues. The other place it's been used is by the ophthalmologist for testing for corneal injuries and abnormalities. Having found that it was toxic to tumors, of course people rushed off to the laboratory and tried to find out if it worked in animal models. And these are just some of the xenograft models that have been used to assess its efficacy. It's also been used quite widely in spontaneous tumors in animals, in the veterinary field. And animals get a range of tumors, and something that works by injection is of course much better than a course of chemotherapy for animals. And so it's been tried in all sorts of animal tumors, and found to be quite effective.

How does it work? That's the question everyone asks. And the short answer is we're not completely sure. What is clear is that it does something to the membrane of malignant cells, and gets into those cells. And it looks as though the nature of the substance makes it into cancer cells, and not normal cells, much more readily. Once it's inside the cells, and this does seem to have some evidence to support it, the substance accumulates in liposomes, those little sort of intracellular suicide bombers that float around inside cells, which are part of the normal process of apoptosis. And once it gets into these liposomes, it disrupts them and sort of releases the contents of the liposome and produces cell death. And because of its selective uptake, it affects the malignant cells and not the normal cells.

You can therefore use it to selectively destroy tumors whilst producing little effect on surrounding tissues. And it looks as though liberation of tumor antigens from the cells that are destroyed is what promotes the involution of bystander lesions. It's clearly another immunological effect. So this then is what we're talking about: thick, red, oily dye that comes these days in a bottle. And if we have, as we often do, patients with recurrent melanoma, often elderly patients, often confined to a limb, we can treat large numbers of these tumors by direct injection. This is preparations for a patient about to have a Rose Bengal treatment. It's a bit fearsome but it's just a fraction of a ml into each one. Then the tumor is simply injected with this, and as with other intratumoral injections, it usually diffuses quite readily through the tumor, just with a single puncture site. For bigger tumors, you have to inject it at multiple sites.

And here is a lady with quite a large tumor on her leg. This is a close-up of it. It's about four centimeters across, and about two-

and-a-half centimeters thick, so great, big tumor. Injected with Rose Bengal. Slightly messy business, but that's what it looks like after injection. There was a second bystander lesion here with that circle over it and another lesion here that was injected. And this was immediately post-injection. We'll come back to that lady in a minute.

Here's another patient. He'd had an attempt to burn off one of his tumors, but all these other tumors had cropped up. And this is on the day of injection. And here just by day one you'll see already there's substantial involution of this injected tumor. About day seven, the tumor is virtually(?) necrotic, as are the other tumors that were injected at the same time. And by week four, there's just a hole there with some black eschar on the bottom, and eventually that healed right up.

Here's another patient, day one. Already the tumor looking very unhappy. And here is that same person on day seven. Week four, the great big mound of tumor is now just an ulcer with a rim of residual tumor. And by week eight, most of this was actually necrotic when biopsied. Final example here, a man with disease on his arm. It all came up quite rapidly, and this is on day one. Already the tumor deposits are looking unhappy. There he is there. And I'll show you some results in a minute.

The first trial we undertook involved 20 patients, a very cautious Phase I study. And I'll show you the results of those in a minute. Single intralesion injection of up to 20 target lesions and observations of bystander lesions, and then follow-up for a period of 24 weeks. And the objective of this was to confirm the safety of the material and to work out the objective response rate. There were no serious systemic adverse events, but there was one quite significant

photosensitivity reaction. And that was a little unexpected. It occurred in that patient I showed you with the big tumor on her leg, who got the biggest dose of Rose Bengal, and was actually on a thiazide diuretic, which may well have precipitated this. Since this incident, we are very strict about keeping patients out of light for 24 hours, and we've had no further problems. It's a little bit painful for an hour or two afterwards.

This is that lady who had the injection on her leg. And this was just one hour after treatment. And as you can see, she was fine. When she came back in 24 hours, she was not fine. Everywhere she had been exposed to light, she had swelling and erythema and edema. And was not feeling very well. Her hands and her chest ... this is what convinced us it was in fact photosensitivity and not a true allergic reaction. If you look carefully, you can see the V where her dress was, and the white band where her watch was. And in fact what happened was that she had the injection and she was driven home into the setting western sun in late afternoon, and had about an hour of really intense light exposure, which in retrospect was not the best thing.

Day two, she was better, but certainly not recovered. By day four, she was almost recovered, and her two tumors injected were necrotic. Day seven, much better again. And then day 14, she was actually smiling again, and you can see the tumor was actually being lifted off here. It had become completely necrotic, and that was that huge tumor on her leg.

I went bully with all these others, but these are just examples of injected lesions, which go from that to that over a period of 12 weeks. From that to that. Here we are, more tumors. Start off with quite a big, nodular fleshy lesion. By week 12, completely gone. Another big nodule lesion by week 12, gone. These are a couple of

untreated bystander lesions, and over a 12-week period ... sorry, this big one here remained absolutely static. It did not progress. Whereas up to that point, it had been progressing very rapidly. This one here disappeared completely. And this, as I say, occurred in about 25 percent of the patients treated. The bystander lesions disappeared without injection.

Final example is a man ... we didn't know what to do with this man. He was treated by Professor Herzy(?) Newcastle. He had had recurrences in his head and neck region. Very difficult to treat. He had had surgery on several occasions, he had had radiotherapy, and I think he had also had chemotherapy, all to no effect. And he was left with this very large lump here. And this was injected. This is what happened by day 14. And week four, the tumor had become necrotic. Week eight, it had dropped out. And by week 18, it was completely gone. That's the tumor size. And he remains well and disease-free.

So just to summarize all this, in about 75 percent of the patients, we got very satisfactory disease control. Not all of them got complete remission by any means, and these were doses lower than we are currently using, so we were encouraged to proceed with the next phase of the trial, which is 80 patients. And that trial is currently underway.

A few words about vaccine therapy, and I need to stop very shortly. Stage III melanoma, surgical resection is the current standard treatment. Only about 50 percent five-year survival. Stage IV melanoma, miserable responses to systemic chemotherapy, with the greatest respect to Rick Cafford(?) and his colleagues. It's just an unsatisfactory disease. And it really hasn't changed much in the last

20 or 30 years. Look at these median survivals, they're just awful. You know, if you have it in brain or liver, it's just three or four months.

A vaccine trial showed that the vaccine actually didn't do very much, but the overall results in people with resected disease were quite dramatic. And we think this is all a matter of patient selection. These were all patients with completely resected disease checked by PET scans and CT scans and every other scan we could think of. And for patients with Stage III disease, five-year survival of 63 percent, and resected Stage IV disease, 40 percent. And that's quite remarkable. Probably, however, all due to careful selection, but shows that with appropriate selection, surgery can work in these patients.

The worrying thing about this trial was that there was a statistically significant worse outcome in those who received the vaccine. So that set us back a little bit in the Stage III patients. I think I probably should stop there in the interest of time, Rick. I'm happy to ...

RICK: (Inaudible) a few more minutes.

PROF. JOHN THOMPSON: A few more minutes? Well, I'll continue on a bit, then. Looking at the disease-free survival and the overall survival in these trials, no significant difference in the Stage IV patients. But this is the overall survival curve. And this intrigues us. Forty percent survival at five years, and just with surgery, we think the vaccine really had no place in that. So we're re-thinking the role of surgery. Traditionally, once someone's diagnosed with Stage IV disease, it's been up to the chemotherapist or the clinical immunologist. But I think it does behoove us on the basis of these results to think very carefully whether it is possible to resect all disease

you can identify in the hope of improving the survival outcome of some of these patients, at least.

One of the things we've been doing in conjunction with Professor Peter Hurzy(?) who works with us and is based up in Newcastle, is to use autologous vaccines. And he's been very interested in this for a number of years. And we recently analyzed our results. And we're a little surprised by the results. We expected yet another negative trial. It wasn't a randomized trial, but we did a very careful matched peer analysis with(?) two(?) cases for each treated patient. And in Stage III disease, no difference.

But the thing that surprised us was the survival in those patients with Stage IV disease. Now remember the figures I showed you before? Median survival, nine to ten months. Here is a median survival much better than that. It's around about 40, 45 percent. And this is with an autologous vaccine, a vaccine created from the patient's own tumor cells, and then re-injected with DNCB(?) augmentation. And so we're encouraged to proceed and perhaps set up a proper randomized trial to take this further.

I will stop there. There are many other things we could discuss, but if there are any that you would like to discuss, I'm happy to do that.

RICK: Thank you very much, John. I'm happy to take questions.

PROF. JOHN THOMPSON: Nicholas?

NICHOLAS: John, you mentioned (Inaudible/Off-Mike)?

PROF. JOHN THOMPSON: Well, I mean, this is a constant finding: that by day one, the tumors are partly necrotic. We see the same thing after isolated limb infusion and isolated limb

perfusion with cytotoxic drugs. So in the case of Rose Bengal, I assume that by then it's done its work and the lysosomes have been disrupted and the tumor cells are beginning to undergo necrosis. But a lot more work needs to be done to define that. We're not sure.

WOMAN: With the Rose Bengal, is there any (Inaudible) used (Inaudible) tumors that are not subcutaneous (Inaudible)?

PROF. JOHN THOMPSON: You remind me that I should have mentioned that. The question is ... what about tumors that are not on the skin or immediately under the skin? And yes, I think that's the tantalizing bit about Rose Bengal. There has been a little bit of work done injecting tumors in the liver, and goodness knows they're difficult enough to treat. So perhaps there might be a role for direct injection, either laparoscopically or open into liver tumors or any other visceral tumors for that matter. And it may even be possible to give it systemically at some stage in doses sufficient to treat tumors wherever they happen to be. That's a long way off, I think. But for the moment, we're sort of progressing slowly along. And I think the next step would be to treat visceral disease by intratumoral injection and that certainly would be possible.

MAN: (Inaudible) interested in the bystander effect. Could you clarify what the tempo(?) of that is? How long after (Inaudible) injection do you see (Inaudible) of that? And I wonder whether if you've done your biopsies on lesions like that to indicate what the mechanism might be?

PROF. JOHN THOMPSON: First question is how long does the bystander effect take. If it's going to occur, it usually occurs within two or three weeks. It's quite rapid. And we've seen this with other intratumoral treatments. When we did a study on

electroporation, for example, when we injected bleomycin and treated the tumor with or without an electrical field, we saw the same thing. And it seems that the tumor is releasing something that has that local effect. And same sort of time-frame. You know, within two or three or four weeks. The biopsies we've done are not all that helpful, because the ones that are still there still look like tumors and the ones that have gone away look like ... things that have gone away. (LAUGHS) Without any particular lymphocytic infiltrate. Maybe we haven't been biopsying at the right time.

MAN: (Inaudible/Off-Mike) suggests (Inaudible) cytokine (Inaudible) tumors rather than (Inaudible).

PROF. JOHN THOMPSON: Yes, it does.

WOMAN: John, can you (Inaudible/Off-Mike)?

PROF. JOHN THOMPSON: We haven't, but the people who have developed Rose Bengal, that's the Provectus company, have got some information on that. Not a lot. This is all new. That's why we're presenting it, and we haven't got to that point yet. But it would be very interesting.

WOMAN: Yes. It's just (Inaudible/Off-Mike) detect (Inaudible).

PROF. JOHN THOMPSON: (Overlap) Tell us what's happening in the lysosomes(?) and things?

WOMAN: Yes, I think so (Inaudible) studies and things like that (Inaudible).

PROF. JOHN THOMPSON: I'll be in touch.

RICK: There are no other questions. John, thanks for sharing with us (Inaudible) and please join me in thanking (Inaudible). (Applause)

(END OF TAPE)