Interview of David L Porter, MD

February 10, 2014

DR PORTER: I think the idea of being able to genetically manipulate somebody's own T cells to target their own cancer is not a new idea. In fact, it's been hypothesized that you could do that as early as probably the late 1990s. There have been many preclinical experiments, in fact — several clinical trials — trying to use chimeric antigen receptors to genetically modify somebody's own T cells. In general, they've been very limited. They have shown limited success — the clinical activity has been modest, at best. And I think over the course of a decade there were probably a number of limitations. Initially, the technology wasn't really available to efficiently get genetic material into somebody's cells. I think that is something that was overcome very early on using retroviral vectors or these lentiviral vectors that we're using, [which] has allowed us to efficiently get new genetic material into somebody's own T cells.

The next big hurdle was actually being able to grow these T cells in the laboratory to sufficient numbers where they might be clinically useful, and early on, in the early 2000s or the late 1990s, it was very difficult to grow T cells in the laboratory. I think one of the big advances that has allowed some of this work to move forward has been technology to actually expand T cells ex vivo to numbers that now are clinically meaningful and you can use them in clinical trials.

There was work done by Carl June, who I work with, and Bruce Levine, developing these artificial antigen-presenting cells. They're magnetic beads that are coated with an anti-CD3 and anti-CD28 molecule, and what they do is they stimulate the T cell in culture by engaging the T-cell receptor with appropriate costimulation, and that allows the cells to grow and expand. And in fact you can expand them hundreds of fold in culture over the course of about 2 weeks.

So now you were able to get genetic material into the cells and grow them to levels that were sufficient to use in clinical trials. The trials that were done, I think in the last several years, showed some activity. There was the suggestion that this could be successful, but the 2 biggest limitations at that point was getting the T cells to actually grow in the patient, in vivo. There was very limited expansion and the cells didn't last very long. At best, they lasted a few days or a few weeks, and there was modest clinical activity. And I think we really believe that, for this to be effective, the cells have to grow in the body to higher numbers and they have to persist over some length of time for maximal activity.

One of the things that was really, I think, pioneered by the group at Penn and by Carl June's group, was adding new signaling molecules to the chimeric antigen receptor. That allowed them to signal the T cell to become more active, to proliferate to higher numbers and in fact provide a survival signal to the T cells so they may persist for longer periods of time.

I think some of the most interesting findings that we've had recently is that we see that these genetically modified T cells can go into the body. They can expand thousands of fold, in some cases 3 or 4 logs higher than what we actually administer. And we've now seen them be able to persist over long periods of time. We have some patients who have these cells persisting now beyond 3 years.

DR LOVE: So maybe you can take it to the next step in terms of how this initial research led to clinical trials.

DR PORTER: Sure. I think the initial research really was encouraging. It was really known for a long time that you could redirect the target of an autologous T cell. And so hypothetically I think a lot of people believed this was possible. There was then a lot of preclinical work showing that these genetically modified, redirected T cells could kill cancer cells in the laboratory, could kill acute leukemia cells and other cells with the right target on it.

And then there were some really, really interesting mouse experiments done, again Carl June's group, by Steve Grupp at Children's Hospital, that showed these cells in mice could proliferate to high levels

and could test various iterations of the chimeric antigen receptor and were able to really optimize the signaling domains and the cosignaling domains. And found, in fact, in mice that including a segment of the cosignaling domain 4-1BB, which is a fragment of a CD137 molecule, made the chimeric antigen receptor more potent. The T cells were more active. They could kill leukemia better, and they survive for longer periods of time.

In addition, there has been other work using genetic modification of T cells in humans. There was some work done in HIV by Dr June's group that really showed this kind of technology was safe. There were no untoward complications, and I think, once there was good clinical data that this could be done safely, and really compelling preclinical data, both in culture and in mouse models, the next obvious step was to try and bring this to clinical trials.

DR LOVE: So can you talk about the initial studies that were done?

DR PORTER: We started treating patients in 2010. We treated our first 3 patients who had CLL. Our chimeric antigen receptor targets CD19, and CD19 is on the surface of essentially all B-cell malignancies. I will say initially our intent was to treat any B-cell malignancy, though fortuitously our first 3 patients that were identified for the trial all had CLL. They were treated in 2010. And while we were all very, very confident that this technology could work, we expected to see some activity. I don't think anybody in our group was really prepared for the potency of the therapy.

In the first 3 patients we treated, all 3 had just incredible rapid antitumor responses. The second patient we treated actually had tumor lysis syndrome 3 weeks after getting the T cells.

DR LOVE: These were heavily pretreated patients?

DR PORTER: All of these patients were heavily pretreated. They had had somewhere between 4 and 8 prior therapies. None of these patients had achieved a remission with any of their prior therapies, at least in the last several years, and all had extensive and bulky disease. We defined our inclusion criteria to try and estimate that these patients have a limited survival over the course of about 2 years.

DR LOVE: Any comments on the method of administration, side effects, toxicities, and how you modified over time the way the treatment was given?

DR PORTER: The cells are collected by leukapheresis of the patient. They're infected with this lentivirus and then they're cultured in the laboratory where they're expanded. That process takes about 2 to 2 and a half weeks. Cells are frozen, and the patients then come in as an outpatient to get the infusion. When we first started the clinical trials, we were somewhat concerned about infusional toxicities, and we designed the trial where we would give the total dose over 3 days. We gave 10% on the first day, 30% on the second day, and 60% on the third day. We really had no significant infusional toxicity. The infusion was very straightforward. We had a couple of patients with low-grade fevers, but really no major reaction.

All of the patients that we treated went on to have a major reaction several days later. Between about 4 and 20 days later they have what we referred to as a cytokine release syndrome, but that was a delayed phenomenon. And I think we've learned over time that the infusion itself is quite straightforward, and in fact in our current clinical trials we are doing a single-day infusion of the entire dose.

DR LOVE: Now are you still continuing to see these delayed cytokine release syndromes, and what do you actually see clinically and how do you prevent and manage it?

DR PORTER: We do see these delayed cytokine release syndromes. Just about every patient who responds develops this cytokine reaction. The cytokine release syndrome is like a very, very severe flu-like syndrome, though saying a flu-like syndrome somewhat trivializes it. It usually starts with a prelude of fevers. There's usually several days of febrile episodes. Patients are evaluated very carefully to make sure they're not infected, but in most cases it lasts for 2, 3, 4 days, and the fevers escalate and can become quite high. We've had patients with fevers as high as 104, 105 and even higher. It's associated with nausea, anorexia, and some cases of quite severe myalgias and arthralgias.

As it progresses over time, we've had patients even become hypotensive and develop a capillary leak and develop hypoxia, and it really can be quite severe to the point of having to be cared for in an ICU setting.

One of the things that we learned very early on was that the cytokine release syndrome was somewhat unexpectedly associated with very high levels of interleukin-6. IL-6 is an inflammatory cytokine. It's seen in certain other disease processes and in fact tends to be important and elevated in patients with rheumatoid arthritis.

In one of the first pediatric patients that was treated at Children's Hospital with ALL — she had become very critically ill, was hypotensive, was hypoxic, was on maximal life support, and this was the first time we had noted these interleukin-6 levels come back extraordinarily elevated. We reasoned that we would treat the cytokine release syndrome with steroids, but I will say, at least over the first few hours, steroids had little impact on this clinical course.

There are medications that are clinically available — they're FDA approved — to block action of interleukin-6. And so we have been using a medication called tocilizumab, which blocks IL-6 receptor activity — and found absolutely rapid improvement.

The medication just rapidly reverses the side effects of the cytokine release syndrome within the matter of an hour or 2. Patients who are having 105-degree fevers all of a sudden become afebrile. Hypotensive patients normalize their blood pressure and may be on vasopressors, and the vasopressors start coming off. And so we've seen really rapid improvement.

DR LOVE: Now is this an approved drug?

DR PORTER: It is an approved drug.

DR LOVE: Where is it used?

DR PORTER: It's approved for juvenile arthritis and rheumatoid arthritis in adults.

DR LOVE: Wow. And it's effective there?

DR PORTER: It is effective. For arthritis it's given repetitively, usually every 2 weeks. When we have used it, we've used it as a one-time dose in the vast majority of cases. We've had a couple of patients where we've re-treated them a second time with the drug, but in almost all cases we just see rapid resolution of these cytokine symptoms.

DR LOVE: Now what about the tumor lysis syndrome. How often do you see it? Does this monoclonal antibody affect that?

DR PORTER: The tumor lysis syndrome happens concurrently when we see the cytokine release syndrome, and I think they're both related to rapid T-cell proliferation. They both happen at the time when we see exponential expansion of the genetically modified T cells. The tumor lysis syndrome we see in many cases. It's of course dependent on the tumor burden of the patient. We do try and prevent complications from the tumor lysis syndrome by treating all patients with a xanthine oxidase inhibitor like allopurinol. We've had several patients where we've had to treat the complications of hyperuricemia, for instance, with the drug rasburicase. It's been effective in all cases. But they do happen concurrently and at the same time.

DR LOVE: But again, this anti-IL-6 antibody does not affect the tumor lysis — or does?

DR PORTER: We don't know. We know that it can rapidly reverse the cytokine reaction. What we don't know is whether or not it will inhibit T-cell activity. So I think we have a very good handle on how to prevent this or how to manage it when it develops, but what we don't know is when to do it. And in fact right now our current approach is to let the reaction continue as long as it seems clinically safe, and we are only intervening at the time that there's hemodynamic instability. And we've actually developed a somewhat detailed grading system to help guide when intervention would be needed. But we don't yet know whether blocking this activity and blocking this reaction actually inhibits the activity of the T cells, and that's something we hope to learn as we move forward.

DR LOVE: You mentioned corticosteroids. How would you envision corticosteroids affecting the therapy itself, assuming you use them?

DR PORTER: Corticosteroids are really good at killing T cells, and I think it is likely to inhibit the activity of the T cells. In fact, we try and avoid them if at all possible, once we've given the infusion.

DR LOVE: I would think so. Again, at this lung cancer conference the issue came up — they had looked at ipilimumab with chemotherapy, and because of the chemotherapy, the patients were getting corticosteroids, and how that interfered with the whole process.

DR PORTER: Yes. And so I think steroids probably are just counteractive to what we're trying to do with the T cells. We did think initially that, should the T cells proliferate really uncontrollably or they did develop a severe reaction, we actually thought steroids were likely to be effective to block the reaction. But at least anecdotally we found the blockade of IL-6 activity to be much more rapid and much more potent.

DR LOVE: Now, along the way since the beginning of the development of this therapy, have you had deaths as a result of it?

DR PORTER: We have not. We have not had any deaths related to the therapy. We've had patients become quite sick and critically ill and, as I mentioned, we've had patients on maximal life support, but in all cases the toxicities that have developed have been reversible, thankfully.

DR LOVE: Can you talk more in terms of how many patients overall have been treated and at this point where we're at in terms of the efficacy of this therapy?

DR PORTER: Our group at Penn has treated just over 70 patients at this point, with a combination of CLL and ALL. The CLL trials are still ongoing. We completed an initial pilot trial of 14 patients where we were really trying to define safety, determine some of the side effects, get a sense of activity. That trial closed a little over a year ago. We reported the updated results at ASH this year. Of those 14 patients, our response rate was just under 60%. About half of those were complete responses and about half partial responses.

In fact, in these CLL patients, even the partial responses we've seen have been quite remarkable. We have a number of patients who get the T cells and have complete clearance of CLL from their blood and from their bone marrow. And we see these patients who start with very bulky adenopathy and see the adenopathy slowly improve over time. That meets all criteria of a partial response because their lymph nodes haven't returned to normal. This is very similar to activity we see, say, in the setting of a bone marrow transplant where patients have a so-called graft versus leukemia effect, but that evolves over the course of several months. So we have patients who have negative bone marrow, who have no CLL in their blood, and have marked reduction in their adenopathy that continues to improve over months. In fact, I have a patient who took 9 months to go into a complete response.

So even these partial responses we think are quite clinically meaningful and clinically important.

DR LOVE: Any explanation for patients who really don't respond?

DR PORTER: We don't. That is one of the, I think, most important questions: Why this works and, in fact, why it doesn't work. We are looking very hard to try and identify where this may or may not be effective. From this initial pilot trial we did, we had patients get a very wide range of cell doses that had to do with the manufacturing. And for the follow-up trial that we did, trying to determine whether cell dose was critical for efficacy, we are in the middle of a randomized Phase II, but a dose-finding study or a dose-optimization study. We're randomly assigning patients to 1 of 2 dose levels. Again, we reported preliminary analysis at ASH this past year, and at least on first look there's no suggestion that there's a dose-response effect. And in fact there's no suggestion that there's a dose-toxicity effect.

I think that's somewhat logical because I actually don't think it has to do with the dose of cells we give patients. I think it has to do with the dose of cells they end up with, because these are a biologically living drug, if you will, that grow in the body. And if they can grow, it doesn't matter, within some range, how many cells we actually give at the beginning. So it doesn't seem to be the cell dose. It doesn't appear to be a patient age. We haven't identified any pretreatment characteristics. It's not their prior therapy. It doesn't seem to correlate with their cytogenetic or risk profile or other risk factors of their underlying disease.

We're doing a lot of studies right now trying to look at different factors of their immune system and their T cells, whether their T cells are equally functional going in to the process in patients who respond and who don't respond, but as of yet we've not been able to identify anything to predict why 1 patient may respond and another wouldn't.

DR LOVE: So in terms of these CLL patients, obviously there can't be that much follow-up because you just started using this the last few years, but what's the longest you've seen people [respond], and what's the average duration of responses you're seeing?

DR PORTER: You're right, the trials are somewhat early in development, though we do have 2 of our earliest patients that we initially treated still in remission at about 3 and a half years now. And remarkably they're still in remission and they still have detectable genetically modified T cells in their blood and in their bone marrow.

So the remissions can be sustained. It is true in CLL that a 3, 3-and-a-half-year remission still requires longer follow-up though. In fact, both of these patients were patients who hadn't achieved a complete remission with prior therapy. And then follow-up on our other patients in remission goes anywhere from about 3 months to 18 months at this point.

DR LOVE: So maybe you can talk about the other patient types that have been treated and the data that we have there — and also where else research is going on this treatment.

DR PORTER: In addition to CLL, we've also treated both adults and children with ALL. Again, most B-cell ALLs express CD19. We've treated 6 adults so far with relapsed or refractory ALL. These patients have a dismal prognosis. They really have no effective treatment options. Even allogeneic transplant is ineffective for patients with refractory ALL.

Of our first 5 evaluable patients, all 5 patients have achieved a complete remission. It really was quite dramatic. In addition to that, Steve Grupp has been treating pediatric patients with ALL at Children's Hospital in collaboration, and they've now treated a little over 26 children. The response rates for these kids with relapsed and refractory ALL is somewhat astounding. Over 80% — I think on the evaluable patients there's an 81% complete remission rate. There is really no precedent for this in relapsed and refractory ALL.

In addition, many of these kids have relapsed leukemia after an allogeneic transplant, and as much as I'm explaining how poor prognosis is in relapse, once you relapse after an allogeneic transplant, the options are extraordinarily limited and prognosis terrible.

Of the first 11 children he treated with relapse after allo transplant, 8 go into complete remission. Really quite remarkable. Several of these patients have relapsed. While there's an 81% complete remission rate, a few patients have subsequently relapsed, but still the ongoing complete remission rate is a little over 50% at this point, which we find quite remarkable.

DR LOVE: What other types of cancers have been treated?

DR PORTER: I think one of the really important parts of this technology is that if you can identify a target on a cancer cell and there's an antibody for that target, it can be placed into these chimeric antigen receptor vectors much like a cassette, and so you can target other tumor types, of course. We are just about to open our trials with non-Hodgkin lymphoma, also targeting CD19. Others have treated small numbers of patients around the country with lymphoma, and again, for similar reasons we think there is reason to be optimistic, and they're looking forward to starting to treat these patients.

There are trials being developed trying to target myeloma. We have a very active, though still preclinical, program trying to target AML, for instance. One of the problems with AML is trying to identify a unique target that isn't on a hematopoietic stem cell or, perhaps, on vascular endothelium. But we have a few leads of targets that we think will be clinically useful and hope to have clinical trials, at least in certain clinical scenarios, for AML sometime in the next year.

Trials are being developed for Hodgkin's disease, and I think there are other tumor types. At University of Pennsylvania there's a similar CAR trial for patients with pancreatic cancer, for ovarian cancer.

DR LOVE: Where else is this therapy being given and developed?

DR PORTER: Now there are a number of different centers that are using similar types of approaches, and certainly there's a number of important programs out there. It's being done at Memorial Sloan-Kettering. The NCI has a program. Baylor down in Houston. MD Anderson have their own approach to a very similar type of therapy. It's being done at the Fred Hutchinson Cancer Center in Seattle. And a number of other centers are starting to develop CAR programs with similar types of technology.

DR LOVE: You use the word "similar" a lot, and I'm wondering how easy or difficult it is to standardize this. I mean the clinical results you talked about were enough for a lot of people who are listening to this to go, wow, I'd like to get one of my patients on that. What would be involved in FDA approval for this type of therapy?

DR PORTER: Interestingly, I think with the really exciting results there's now interest by pharmaceutical companies. The University of Pennsylvania has entered into a licensing agreement with Novartis, for instance. I know that other pharmaceutical companies have entered into other agreements with other academic centers, and they are starting to develop processes to commercialize something like this — to have this be a drug that could be available all over the country and, in fact, all over the world.

Going into standardizing this across various centers I think is like any other therapy. Many different centers try and optimize how they do it, and I think that's really, really important for the field. And sharing of information, sharing of data, and trying to come up with the best way and the best approach to do this moving forward is going to be really important for everybody.

DR LOVE: I was flashing a little bit on sipuleucel-T and how that evolved as an approved therapy. There is 1 central place everything goes to. Do you think that's the way this is heading?

DR PORTER: I do. I think that it's easy to envision. A patient doesn't have to be at a central location. They can have their cells collected locally and shipped to a central location. In the laboratory they can undergo

genetic modification — they get grown in the laboratory. That's about a 2-week process. The cells that are given are actually frozen and thawed before infusion, so they can be shipped back to a local site, and you can envision how this can be done centrally and, in fact, disseminated to many, many places all over the country and all over the world.

DR LOVE: So again, for somebody who hears this and says, wow, I've got a patient who seems like they would benefit, what do they do? I mean do you accept patients, or are there trials that are ongoing that people can get enrolled in?

DR PORTER: There are indeed. We are actively enrolling patients on to our clinical trials right now with CLL and ALL as well as lymphoma, as are other centers around the country. The ClinicalTrials.gov website is fantastic to try and find out the kind of activity that's around the country, and the way to get involved and get enrolled is often with a phone call or an email. And certainly we have a good mechanism to try and evaluate patients and get them involved as appropriate.

DR LOVE: I want to ask you about the 3 patients that you brought here today, but I guess another question that I'm sure must come up a lot is — it's kind of interesting/ironic that this very, very exciting development would occur at the same time that there's a lot of other stuff going on in B-cell cancer, particularly the small molecules — Bruton tyrosine kinase inhibitors, idelalisib, and PI3 kinase inhibitors, and also the antiapoptotic agents. How do you see this all coming together? Is there any thought about combining, sequencing? How do you see it starting to play out?

DR PORTER: I think this is an exciting time to be studying new therapies for B-cell malignancies, and any time there's so many options — and in fact, options that are proving to be effective — it's only good for patients. There is a lot of thought about combining these different modalities. We have found, for instance, that this T-cell therapy is really quite potent and patients that we have treated that have a complete remission have very, very deep remissions. They have no minimal residual disease on all levels of testing, including deep sequencing of their bone marrow specimens.

One simple way to think about this would be to sequentially treat patients with some of these newer agents and get away from the more toxic chemotherapy approaches using a biological agent for cytoreduction, and patients who have minimal residual disease, perhaps, could then be treated with T-cell therapy. That's particularly attractive as an approach because one of the other things we seem to be finding is that the toxicity that happens with the T cells seems to be related to tumor burden. And while we haven't done these experiments yet, we're hypothesizing that if we treat patients with low tumor burdens they potentially will respond without a lot of the toxicity. So you could easily envision that as a strategy.

What's going to be the best initial therapy and how to sequence and combine these drugs I think is going to be the topic of a lot of clinical trials over the next few years, though I actually think this is a field that is moving quickly and these are trials that will be done over the matter of a few years, not over the matter of a few decades.

DR LOVE: So I guess the other questions is, I've heard people talk about the fact that if you give a therapy, even chemotherapy or maybe one of these other new biologics, how does that affect T-cell therapy? Do you see more release of antigens? Would it make it other than just bulk reduction? And also are there any specific synergies that get you excited in terms of some of these new agents, like would you think an antiapoptotic agent would make more sense, or any of these, in terms of synergy?

DR PORTER: I actually think synergy is going to be very important. For instance, patients with CLL can have defective T-cell function. There are a number of biological activities of the CLL cell itself that result in poor immune function. Some of these biological agents actually have the ability to repair immune function. Whether it be the drugs that result in immune stimulation, there is some data about some of the other biological agents that actually repair some of the specific defects that you find in the T cells in patients with CLL. So it is again interesting to hypothesize that you could lead or combine one of these immune-repairing agents, or immune-stimulating agents, with the T cells, particularly in a setting where they've not been very effective, and get them to be more potent and more effective.

I think, for instance, of lenalidomide as one example that we hope to study. But ibrutinib may also have similar immune-modulating approaches, may be a drug that can induce a minimal disease state and is also another approach that is pretty easy to envision combining with this type of therapy.

DR LOVE: It's funny that you would mention lenalidomide because I just wrote down on my pad "lenalidomide." Because you mentioned myeloma, and I've been asking people for years what their thoughts are about how that drug works. I'm curious what your concept is and, again, how you see it in any way interacting with or synergizing with T-cell therapy.

DR PORTER: I think there's been some exciting new data about how lenalidomide may work at this point. And one of the targets has now been identified. But biologically there's also some very interesting laboratory data showing that lenalidomide can repair the way that a T cell may interact with a target B cell — that it may synapse with the B cell. And lenalidomide has the ability to repair that targeting defect in the T cell. So if you can do that and if that is a mechanism, for instance, [of] why our T-cell therapy may be less effective in some patients, you can envision how this may repair that defect and then allow the T cells to recognize their target and become very active.

DR LOVE: Does that concept tie into what's been seen when lenalidomide has been combined with a monoclonal antibody, the examples being rituximab in lymphoma and elotuzumab in myeloma?

DR PORTER: Yes, I think it might. I think that the way those therapies work and the combinations are probably very complicated, and you probably do need T-cell activity. It's not just direct targeting of the drug, and if you use the antibody and at the same time it's stimulating T-cell activity, you certainly would anticipate a more potent response.

DR LOVE: So, just to take a deep breath, just kind of sitting here thinking about what it's been like to be you the last few years and all the other people working on this therapy, what has it been like? It seems amazing to me.

DR PORTER: Yes. It's been a remarkable few years. I work with an absolutely incredible group of people who are more dedicated than any other group I've ever come across. It has been tremendously exciting. It's been tremendously busy. It's been really an incredible experience and somewhat of an honor to be involved in this kind of therapy that is new, may be paradigm shifting, and in fact is working. I think it's got the potential to change the lives of many, many people, and it's been incredibly exciting. But every once in a while we as a group, and myself included, need to step back and just try and see it from a higher level and try to get a handle on where it's going and what we need to do to make it effective.

DR LOVE: It sounds like it must have been incredibly scary at times. You talk about people being hypotensive in units, et cetera.

DR PORTER: At the beginning we all expected this would have some activity, but nobody expected the potency and the rapidity of the activity, and it was very frightening. It is scary to use a new therapy that's never been given to people, to not know what's going to happen, not know what to expect, and early on didn't really understand some of the biological mechanisms of what was happening. I think one of the remarkable things is the ability to get some of the correlative biological laboratories that we had that really allowed us to manage these people in an incredibly safe way and understand what was happening with them. It has been frightening, but yes, just an absolute joy to be a part of.

DR LOVE: Yes, that IL-6 thing was amazing. I imagine it must have been really incredible the first time you gave that monoclonal antibody.

DR PORTER: It was absolutely dramatic. It was given to this little girl, who has been the subject of a great deal of press, in the middle of the night. And these days — nobody was on the phone, but everybody was on their email and texting. And I think we, as a group, were sharing Dr Grupp's anxieties through the night and getting our hourly updates and just couldn't get over how fast this drug worked, taking somebody from maximal life support to, within 24 hours, being off vasopressors, being off a ventilator and watching television.

DR LOVE: How old was this child, and what is her current status?

DR PORTER: She was 7 years old when she was treated. She's a year and a half out in complete remission and in third grade, and she's a remarkable, remarkable young girl, very matter-of-fact. She's a tremendous spokesperson for this program, as is her family. But she goes off to school every day and on some level in the best possible way is just a normal, I think now probably 9-year-old little girl.