Gert-Jan van Ommen

Personal Details

Name	Gert-Jan van Ommen
Dates	Born 28/09/1947
Place of Birth	Amsterdam
Main work places	Leiden
Principal field of work	Human molecular genetics

Interview

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INTERVIEW WITH GERT-JAN VAN OMMEN, 10 DECEMBER 2010

PH = Interviewer (Peter Harper)

GV = Gert-Jan van Ommen

PH It's Friday, December 10th [2010] and I'm talking with Professor Gert-Jan van Ommen in Leiden. Let's start at the beginning, Gert-Jan: where were you actually born, and when?

GV I was born 28th September 1947 in Amsterdam. I've been living in Amsterdam all my life until now. I have never been living more than 15 minutes by foot from where I was born.

PH That's interesting.

GV Not even a half year or a year of a sabbatical abroad. So I'm pretty rooted. I still know routes of the tramway system in Amsterdam that don't exist anymore, which is sometimes convenient for those that do exist. Yes.

PH Were any of your family medical or scientific in some way? Your parents, others?

GV Yes, my father was an ear, nose and throat surgeon and he was a real old timer; he was from two centuries ago: 1894.

PH Gee.

GV And he died in 1980 at 86 years of age. I was the oldest in his second family. My parents married in 1946. My father and mother got to know each other in the war. My mother was assisting him in his dentist practice, and I was born in September 47, At the time he must have been 53. Yeah. And he has never been willing to tell us his age. We always sort of, he evaded this when we asked him, all our life. My parents divorced when I was 11, then my mother and my brother and sister and me started living somewhere else in Amsterdam, in a floor above my grandparents, and at some time, 2 years after the divorce or so, somebody asked my mother how old is Ben (my father)?. And then she told him that he was 67. And that basically shook me completely for more than a month [laughs] because we always sort of had pegged him at 48 and not aging. That time I was already in my secondary school, from 11 to what is it, 17.

I started doing my study at 17 in the University of Amsterdam, studying chemistry. And then after doing my, that actually, the study started in 1964. Those were the days, you might say, 1964/5/6/7, a lot happened and there were the Beatles and the Stones and the occupations of the university building and so, well, we all participated in a reasonably serious way. And so my study took slightly longer than well, not that was unusual in those days, but definitely than is usual nowadays. My whole study overall took from 64 to 74.

PH What was it that took you into science in the first place?

GV Ah. [pause] I've been always interested in how things really worked. I had walks with my father, in times I can't remember when, when I was really tiny, 6-8, whatever, I wanted to know what one looked at when one looked between two stars. "The back of your head", said my father, "because space is curved".... oh yeah, that's an interesting anecdote: there was a reasonably well known society paediatrician in Amsterdam in those days called Fideldeir Dopp and he was also the paediatrician of my parents. And I had this habit of sucking my thumb, pointing at some machine and asking with all my 3 or 4 or 5 years, "What's that again?" [laughs] So from, well, it's just escaped me, but, and so on. So at some point I pointed to the microscope and asked, "What's that again?" and he explained me that it was a microscope. And then the next visit, or a year later, or something, I just was pointing at the same

thing again and asked, "What's that again?" and he looks and he was busy and not really with his head there, occupied, and he said, "That's a telescope." And then I said, "No, that's a microscope." [laughter]

PH And was it a microscope?

GV It was a microscope because I'd been told a year before. So he just had this kind of 'what now?'

PH Did he let you look at it?

GV Yes… I can't remember because that, so, trying to find out the causes of things and explaining things, but in a sort of technological way, in how things work. And I still do have that when people are coming with complicated schemes with combinations of letters and numbers of genes, and trying to make diagrams of cell signalling and whatever. I always sort of always switch off. I'm far more interested in how to ask the questions than in the actual answers. That's for other people. [laughs]

PH When you'd finished your first degree, then did this continue into a doctorate or did you move departments, or areas?

GV Well, somewhere halfway in my study I focused on biochemistry, and that was, the choices then were more biology oriented or more chemically and physics oriented. I took actually a mix with chemistry, physics and biology. Then in my masters phase I selected biochemistry, and so I rounded up my studies doing biochemistry. And that was, the biochemical lab in Amsterdam had 3 or so departments: one was bioenergetics, Slater, quite a name. I think he still lives but he must be over a hundred. So that was the biochemistry. Then there was a lipid and inborn errors in metabolism group from Joseph Tager, and there was quite a well known group at the time led by Piet Borst, called medical enzymology and they were into DNA. And that was what I found absolutely the most fascinating thing, so that was in, somewhere like 1972 that I started doing DNA and RNA analysis in the section of Piet Borst, studying the yeast mitochondria. That was, say 2 years before the restriction enzymes were coming on. But that sort of got me into molecular biology.

PH You may still remember from the early days also, Ysbrand Portman -

PH Yes.

GV - who is still alive and kicking, and active more internationally nowadays in the patient organisation. So it might be someone you might also want to be in touch with, because he's from the patient community. He's actually with his daughter who was diagn

PH Yes, thank you.

So we'd got really to the end of your, well, to your PhD. Remind me again, well I have it here, the topic of your PhD.

GV Well, in those days it was actually quite early in molecular biology. One of the fields of the biochemistry lab in Amsterdam, was everything with mitochondria. Piet Borst had done his first studies in, amongst others, the mitochondrial DNA of humans and rats and yeast. And in those days just a question was starting to be framed: how does transcription occur? And so the idea was, because that was just then found in mammalian mitochondria, that there was a substantial amount of symmetrical transcription, two ways around; then the RNA that was produced should be self complementary. So I had to look for the self complementary RNA. Those were minute amounts plus that in mitochondria in yeast, well, you first have to unpeel the yeast from its coat with glycoprotein layers and the like, to be able to look at the very short product. You had to give pulse labels, so like, 4 minutes or 10 minutes, or so. How do you give a 4 minute pulse label when you have an organism that you take then for an hour to remove its cell wall?

So we first had to remove the cell wall, make a spheroplast,keep it alive, and then give a pulse label in a big flask, add 20-50 millicuries P32, and then slowly incubate for 4 minutes, and then pour this whole stuff into a yet bigger amount, half a litre or so, and into 2 litres of osmotically stabilised ice so that it was rapidly cooled. So this was juggling with litres of screamingly hot P32 [laughs] stuff, and that was actually still my undergraduate student project. The answer was: we found interesting things but we didn't find symmetrical transcription, at least not in a recognisable way. I think the technologies in those days were sort of so far away from today. Nowadays they actually find, well, unique, genomically unique, noncoding RNA which is complementary to certain genes, and it plays a role in imprinting to silence the genes by going the other way of the promoter. But that was just totally different play. So that was my undergraduate. I graduated and after the graduation I went on to study RNA synthesis in yeast mitochondria. And so, well several chapters and several papers of this and… So first I made a map of the tRNAs on the mitochondrial genome where they all hybridise, and on what part of the map.

The map was, at the time, made because those were the early days of the restriction analysis. I can remember, and I still have somewhere a sort of thin carbon copy of a letter of Piet Borst who had a guy called Roberts visit him, and giving a batch of Eco R1, restriction enzyme, to solve for them then an important question and that was whether the mitochondrial DNA of Tetrahymena pyriformis was circularly permutated or was just linear, because it was always found as linear. And they said, "You can resolve that by cutting it up with restriction enzymes." And then I went to Piet and I said, "I don't think you can, because if you have a circularly permutated piece of DNA and you cut it up with a restriction enzyme, you'll never see a modest amount of breaks everywhere. So you will see as if it is circular map with no ends. And so that's not the way to distinguish whether there's an end or not." Actually , Piet noted that and he sent it around to everybody, and I got a copy of it and I was extremely proud that I made a remark that made sense. That actually led to making the restriction map of the yeast mitochondrial DNA in precisely that way, by a colleague of mine in the lab, Johan Sanders. And then I used that restriction map to actually map the messenger RNAs on it.

Slonimsky, in France, had made a genetic map, and what I did was label, but then stable label with P32, the total mitochondrial RNA. I was quite good… I would say 'world known in a very tiny community' for making extremely pure mitochondria without cytoplasmic contamination. And then I ran the RNA through a gel and cut up 40 fractions, from approximately 50S to 10S RNA, eluted all the fractions, made a restriction digest of the whole of mitochondrial DNA and made something what you might call a 'first whole-genome map', because I did the southern blot of 40 parallel lanes of mitochondrial DNA. We knew how that map was, and hybridised each of those with one of the 40 fractions of the mitochondrial RNA, glued all these little strips of Southern blots next to each other and thus made a real 2-D map of the mitochondrial DNA versus the size fractionated P32 labelled RNA. That was an experiment that the first time took me about half a year sitting at home to actually work it out, because it was this, I can pick it up from my thesis [walks away]… I must have it. All things being well, it should be under 'O'. [pause]

PH Don't worry Gert -

GV Ah, yes, here we are. So that's the title, and one of the things is that, also together with the electron microscopist in Groningen, Anika Arnberg, we for the first time, found circular RNAs, and then the printer of my thesis actually managed to actually cut open all the circles in the whole of the cover… [laughter] But It's… here we are… so this is the type of pattern. So the ribosomal RNAs of course hybridise from this moment that their length comes up all the way down, because you always have a little bit of degradation. And it's a large excess so that here you, well this is a complicated story on tracer and driver. If you would have hybridised 220 times lower core value, you would have been seeing something like the other bands you see. Those are the minor messenger RNAs. Nobody ever in the beginning would believe that all these tiny bands here were visible messenger RNAs, but that's of course what happens if you have a genome with only like say, 14 or 15 genes. And I thought it was, and

so cutting it up you would see the whole of the ribosomal RNAs in a proper ratio, and then you hybridise, and these are where the fractions counted; then you'd hybridise those fractions and get this pattern. And in the beginning nobody understood, well at least my bosses didn't, why this would hybridise as if it was degraded, but this is just sort of a ratio of RNA over DNA, as I just said.

There is like a hundred times too much over here, but even 1% would produce a signal like this. Now working this out, in fact, I cross hybridised 2 different strains: one strain with inserts in the mitochondrial DNA that turned out to be sort of mobile introns and there the RNA of the Saccharomyces carlsbergensis, against S. cerevisiae and the other way round, and straight. So there were like 4 patterns, and that allowed me to sort of lay out this whole thing. And the first time I was at the conference somewhere; this was the first experiment I did. I showed that on the conference. It basically explained the complete genetic map, because it was precisely as people had predicted: here were the oligomycin, the cytochrome oxidase genes; this was cytochrome B. And what's interesting in the yeast mitochondrial genome is: thousand base pairs is approximately infinite in terms of recombination fraction. You never get higher than 25% recombination because it's circular, and that means that there were parts of the same, say thousand base pair RNA which turned out to be consecutive exons of something like a 5KB gene that, in terms of recombination, was infinity.

PH My…

GV So that was what my thesis was about and then later I went into Northern blots of all those specific components and studied with the Northern blots and did the same hybridisation to just see how these things were spliced. And finding out that actually, which is still an argument even in the Duchenne gene, where, let me see because I must have it somewhere here… So I was into mapping quite early. I'm sure it must be in here. It was, I set up something like a schema to, ah, here we are… that's a schema of the splicing. So this is a precursor and then it basically has 3 choices of introns being spliced out first, it can take all 3 directions, and I could actually find the compositions of all 3 of these routings. This was the final component, but you could either first splice out this axon, or splice intron, or that, or that; and then the next one would go here, and so then you get something like a cube to visualise how you have 3 different choices and then ultimately the last intron was spliced out. And for those days, still talking 1980, this was where we stood at the time.

PH That's fascinating. So when then did you join Peter Pearson and get involved at the beginning of the human molecular and Duchenne work?

GV Okay. After my thesis, and in fact already before I passed my thesis… I passed my thesis in 1980. In 1979 I went into the Amsterdam Academic Hospital, the Binnengasthuis, which at the day was in the midst of the red light area actually, in the centre of Amsterdam. Later we moved to the Academic Medical Centre in Amsterdam. The Binnengasthuis was like 5 minutes by bike from where I lived. I started working in the paediatrics, in the laboratory of paediatrics with Jan de Vijlder, on thyroid disease: congenital hypothyroidism. That's what I did from 1979 to early 1983. I started doing that because I had quite some sort of reputation working with very long RNA and keeping it keeping it intact, which wasn't very easy, and doing electron microscopy with it. In those days they had an inkling that the thyroglobulin protein had a huge messenger RNA. The protein itself was already 3400 kilodalton so that we required something like a 9KB messenger RNA. My former promoter, Piet Borst actually was an advisor to the professor of paediatrics at the time, Tegelaers, and he told Tegelaers, "you should hire Gert-Jan because he's good with long RNAs and long genes and so". What we then did was beginning to clone the human thyroglobulin gene.

At first I was by myself and after a year or two I got another person to work with me: Frank Baas, who still is at AMC in Amsterdam, as a professor. He was actually my first PhD student. In those days we were quite closely connected with Dick Flavell and Frank Grosveld. Dick had before been passing through the laboratory of Piet Borst, the Jeffreys and Flavell splicing papers were when Dick was in our

laboratory, so I knew Dick well. And I knew Alec well, and there was a close connection between the lab of Dick Flavell in Mill Hill and our laboratory. Frank Grosveld was in our laboratory and in Mill Hill. And so then the cloning of large genes started, first lambda cloning, but especially cosmid cloning, in those days, that was around 1980. And this cosmid work attracted us for this thyroglobulin. Mind you, the thyroid is a very, very weird cell type: if you run the RNA of a thyroid preparation on a gel, you can actually see the thyroglobulin RNA by the bare eye, just like these ones, as a messenger RNA but is twice as long as the large ribosomal RNA; close to 10KB! And you can see this Tg mRNA higher up in the gel because there's such an enormous amount of it, and such an enormous amount of thyroglobulin to be made. So that was the next excursion, let's say.

What I also learned was to communicate with clinicians. And maybe also a little bit how to dress in that environment.. When you're in laboratories, people just go in short pants in the summer and when you're in a hospital you more often have a shirt and a tie and so on. So that was maybe what ultimately made somewhat of a bifurcation between me and classical molecular biologists like Ron Plasterk and Rene Bernards and so on, that I was a little bit more comfortable in the clinical surroundings. So that's the background of it. Then we had been successful so what we did, in competition and collaboration with a group in Belgium, Gilbert Vassart, we cloned pieces of the thyroglobulin RNA. We were studying actually a goat strain in the Netherlands that had congenital goitre; huge, huge goitres that mostly suffocated the animals when they were born, so big were they. And so the goat was one end, and the human was the other end, and that was what we were studying. When we got the first cosmids out from the human cosmid library: I went to Mill Hill in those days to fish cosmids with the cDNA probes.

I also went to the 'Maniatis course' that was well known at the time. Even before there was a book: our course in a way helped writing the book because we had all sorts of loose-leaved stuff with notes on it. In fact the two people there in my own group, myself and Stephen Goodburn, were the only ones that were sort of familiar with cosmids, so it was just mutual. Maniatis' people were much more familiar with lambda, so… Again getting those cosmids and reviving my contacts with the electron microscopy in Groningen, we actually found for the first time some sort of hybrid between the Tg cDNA and the cosmid that suggested that in the tail of the thyroglobulin gene there was an intron of no less than 17 kilobases! The yeast and globin introns and other introns known at the time were much, much smaller. And I'll never forget that evening; I phoned up Piet Borst and said, "Piet, we've got an intron that is so big that your whole human mitochondrial DNA could fit in it." And he said, "You better repeat that experiment because nature doesn't work that way". And then we started fitting in the rest of the gene and we actually got two cosmids that barely overlapped , and were having the adjacent parts of the cDNA on their other, outer ends, implying an intron of 65.000 base pairs!

And so the whole gene turned out to be 340 kilobases, and that was in the days where others still looked at whole gene clusters, like globin, on just one cosmid. We had big difficulty getting this published. In those days, just the Factor 8 gene was found and there was an enormous furore over Factor 8 gene being 'the biggest gene in the whole genome with180Kb'. And here we were, this group at the AMC in Amsterdam, with claimed to have this kind of mega-gene, come on, Factor 8 it would just fit twice in this thyroglobulin gene of theirs? So that, well, was an interesting time. it was somewhere like 1981/82 or around. That was when, late 1982, I got a phone call from Piet Borst who said, "I think you should get contact with this guy Pearson in Leiden, working on Duchenne. He manages quite well to get in front of any caboose" were more or less his precise words. Sort of slightly admiring, slightly jealous and slightly sort of derogative at the same time. Peter Pearson, who is studying the Duchenne muscular dystrophy gene that might be a big gene. You have quite some experience in big genes.

He of course was aware at the time how it had gone with the thyroglobulin gene. So that was actually how I ended up in Leiden. I must say that in those days I felt absolutely awful to have to leave Amsterdam for my job. At the time I still expressed my sort of GPS position in how many steps from Dam Square in Amsterdam near where I was living. It was actually even due to somebody we know

jointly, Martin Bobrow, that this all happened, because Peter and Martin, who then was professor in Amsterdam, together helped Ysbrand Poortman, to write a grant to the Dutch Prevention Fund, and so they had a post-doc position for studying Duchenne. I also had solicited on a job in Human Genetics in Amsterdam, with Bobrow then, but there were 2 competing solicitations from people in Piet Borst's lab, one of which had older rights, and Piet has always been extremely fair. And so he advised Martin to take the other, which was Christa Heyting. I was very disappointed, because that meant for me to leave Amsterdam. And Christa, while she became a very good geneticist in the plant field, she hasn't made it long in Martin's department. So that was how in April 1983, I started here in Leiden, with Pearson.

That was just after Bert Bakker and Peter Pearson had, in January or February, this course here with Ray White and Web Cavenee, and others, on RFLPs. And Bert has in 1982 also gone to Dick Flavell to generate this first library with human RFLP clones, and so that basically when I came in. At this point L1.28 was just found and busy being described, and Bert can probably tell you or confirm how that precisely went. I don't think he'll have the letters between Peter and Bob Williamson but the way that went was sort of reasonably like Bob Williamson: they planned to write something together on these probes, both of which were linked to the Duchenne gene. And then suddenly Peter got a letter saying, "Well, you know, there were still people that couldn't confirm L1.28" and they had decided to publish their RC8 probe ahead in Nature. So that was somewhat of a trap sprung on Peter and Bert. I think it would have been a lot nicer had this been done together. But that was what made the Murray et al paper being only on RC8, because between Peter and Bob, L1.28 was clearly already being studied at the time, and in terms of heterozygosity and signal it was much more useful and informative. But I mean, well, past history.

So that was when I started working on Duchenne and the first thing was, getting this 4X cell line, making a cosmid library from it, pulling out cosmids with human repeat probes; there was a human 4X library but we actually isolated the X chromosome cosmids from a cell line called Clone 2D, if I'm not entirely wrong, and we picked them out by human repetitive DNA because that was actually an X hamster cellline.It had only one X, but it had the advantage that if you would get out something human, it would be on the X chromosome. And well, then we got all those probes; Marten Hofker generated a whole series of probes with increasing density, and some of those probes we then mapped, now we're talking early 1984. Let me think what happened… we had those cosmid sub clones and by deletion cell line mapping we had the idea that 754 and 782 actually were quite close to the gene. Then Lou Kunkel was not in the Baarn Hooge Vuursche DMD meeting in spring 1984, but Uta Franke was, and Peter then had this 754 sent to Uta, and the message came back that it was in the deletion of the BB patient. And that was in the summer of 1984.

That summer I went to travel with my wife through the US. This was partly instigated by Peter but also I had done it once before, 5 years earlier, so I planned with my wife, this is 5 years ago when we travelled through the US, let's just sort of go there on holidays and also visit some scientific colleagues. And then, of course, I knew Uta. I was going to Uta Franke; I was also visiting somebody from the old days, Alec Tzagoloff, in New York. And then Peter said, "The person that you should also go and visit is Sam Latt in Boston, where Kunkel works." So that some agreements were made. We also visited Ron Worton in Toronto. At the time Uta had a house in New Haven or so where we were going to stay, and that was at the time that we just had heard that 754 was mapping in the BB deletion. So that was the message with which I came to Lou Kunkel. I was picked up by them, my wife going shopping in Boston and me going to the Children's Hospital. And I was taken to the library by Lou, and Sam was coming but not yet there. And then Lou, who at the time, and I didn't know that, had done this PERT, the phenol enhanced renaturation technique experiment, and had a couple of clones, and they already knew that they had a few probes Pert 84 and Pert 87, which mapped in the BB deletion, but they hadn't come out with that to the rest of the world. They had obtained the BB cells directly from the originator, Hans Occhs, because Uta hadn't wanted to give these out.

And then I told them about 754. When Sam entered the library, which was tiny, smaller than this room, Lou turned around and said, "Sam, they've got a probe in the BB deletion." And the first thing said Sam said, honest as he was, [laughs], he was a really big man and he actually sort of deflated and said, "Well, that's most unfortunate." [laughs]. Okay, so I gave a seminar there on the work we did and so on, went onto to Uta also giving a seminar there.

This was the state of the field. People were generating probes from the X chromosome, mapping them in the deletion, with Uta having the smallest deletion. Then there were some skirmishes with several people whether 754 was or wasn't close to the gene. I can remember that we really had a run in with Cardiff, in our view, because in your results at the time, 754 showed 19% recombination, I'll never forget. And it later turned put to be germline mosaicism that explained this [two affected sons of a non-carrier mother carrying a low percentage of mutant X-chromosomes in her oocytes, an these were scored as two recombinants] boys. At the time we couldn't understand how this was possible, because the other people all had 3%-2% recombination and so on. And then things went really fast: Helen Kingston from Cardiff finding that the same locus might be responsible for Becker muscular dystrophy, as it was also mapping in there, and then later Tony Monaco with this DMD meeting in Versailles near Paris where Marcus Pembrey and Kay and Tony were; and Tony proposing the reading frame theory.

Wait, I think that was 1987; I'm skipping some things. Yes. Because then, yeah, what I skip is that we did have a patient called DL66.6. And that patient had actually quite a large deletion, at least later turned out to have quite a large deletion, and then what was, yeah… what I'm skipping actually in those days, 85ish, there were new technologies coming on. Hans Lehrach and other groups, including our group started to be interested in pulse field electrophoresis that would sort of allow you to look millions of base pairs away. That in fact, once again, was a technology that came through my previous contacts with the lab of Piet Borst because Piet had contacts with Charles Cantor and David Schwartz, and they were setting up this technology and to map the chromosomes of the trypanosomes. Because there you had the maxi circle and the mini circles in trypanosomes and these variable antigen genes that were hopping from one chromosome to another chromosome. When they were expressed it turned out to be one specific expression site where then, this new gene as a cassette was moved into, and they were using this as mapping for that.

I went back to Piet's lab and thought that this pulse field work was one of the best ways to look at large genes, and so then we used all those probes that were spread around by Lou Kunkel and generated by us, and by Kay Davies, and so we made something of a map of the whole of Xp21 and then got closer and closer and closer.

At the time, in fact even Cell was interested in this long range mapping for humans, and the paper in which we were mapping the Duchenne gene with those probes actually managed to get in Cell in about 1986 or so. We'd been doing that work, starting from 1984-5 to begin, and we were really in the development of that field for the applications in humans. And so the next thing to do was called 'chromosome jumping': couldn't we, by starting out from a known position in deletion in a patient, getting to the other end of the patient's deletion? And then there was one patient called DL66.6 where we actually managed to do so. We called that clone Jump 66, getting us to the distal end of this DL66.6 deletion. The interesting thing of that clone was, on the pulse field map, which by that time was sort of more or less closed, something like 2½, 3, 4, million base pairs; on this pulse field map … No I'm historically converting it again… The map was not yet closed.

This new J-66 clone turned out to map proximal to the deletion of another Duchenne patient! So that, almost by necessity, implied that the Duchenne gene wasn't over yet at the other end of this jump. And the distance that was jumped, we could map that distance to be 1.2 or 1.3 million base pairs. And given the extent to which the other patients had gaps, it turned out that the Duchenne gene had to be bigger than what have you, 2 million base pairs. At the time, in 1985 or so, Michel Koenig started working in Kunkel's lab, or at least was working in Kunkel's lab, I can't remember start and end and so on. He was

also doing this cloning; cloning end points of patients, so there were lots of parallel activities. We actually, by random cloning again, found this probe P20 that we sent all around the world, and this was the most effective probe in detecting DMD deletions because it was sort of right in the middle of the deletion hotspot of those days, and that was before this jump 66 got on. And we sent this J-66 clone to Lou Kunkel for the map.

And then Lou found, I can't remember precisely, but in the fall there was a meeting here in Amsterdam, an International Human Genetics meeting or something else, or Gene Therapy, can't remember. Tom Caskey was at that meeting and Peter had introduced me to Caskey, and I was showing Tom and his wife, it was her birthday I think, around the evening that he had delivered the talk in Amsterdam. And then they thought it to be wonderful to look at an Amsterdam canal house, so I actually ended up having the famous C. Thomas Caskey on our own couch in our own house, having a drink at night with his wife. And I told him the story of this jump clone and that we wanted to go on doing these things, and that Lou wouldn't allow it. And then Tom, typical Tom, said, "Oh come on, you shouldn't back down; you should just step in a plane, get to Kunkel, smoke four big cigars, and tell him that this is what you are going to do." Ultimately, as it turned out, we were the ones presenting for the first time, the DMD map to be 2½ million base pairs. I presented that on the ASHG in San Diego in the fall of 1987. Tony Monaco had in the International Congress, in 1986, he found the first parts of the cDNA, of the actual cDNA. Michel Koenig was in '85.

Tony was in Boston around Pert87 doing things, and Tony was the first to actually get his hands on cDNA and do a Northern blot. I won't forget that because he, a reasonably reticent quiet-spoken, very nice guy, our age, was really the boy with the blue eyes in this 1986 International Human Genetics meeting in Berlin, where he presented the first Duchenne cDNA. And right after that, in France. Because actually I took the plane to Amsterdam and then flew on to France because there was a meeting of the French Muscular Dystrophy Association in Tours, in this sort of historical centre with these timber-frame houses. Tony and Bert and I were there drinking Calvadoses on a mellow square. Tony had the paper in press, and it would come out the day after or something. And Tony spoke about this at that meeting and then it turned out that the AFM in fact managed to more or less upstage the MDA in America by presenting this as big news: "DMD gene discovered, Tony Monaco interviewed in Tours" and so on. So there were some blows exchanged between the MDA and the AFM for having the news that the Duchenne gene was found coming out of France while it was discovered in the US.

And so you feel quite, well, humble to be on-site at the time, because these were really historic discoveries of course, and the only thing that we were sort of making of fun of sitting in this town square with our glasses of Calvados in front of us. That was a real nice time. And so then, so the mapping, I'm going back and forth a little bit: 1987 was the mapping year. 86 was the first map in the Cell paper; 87 was with the Jump 66 clone and the pulse field map getting so far beyond.

What was a bit of a pity was that Lou and Tony wrote a review, in, well I can't remember what journal but it was a high end journal, and they asked me if they could quote me for the Duchenne gene being over 2 million base pairs in their review, and I said, "Yes." Well of course, I mean, that's what it was, and so on. And then it turned out that actually I couldn't get my map published in a, I did but not in the high end journal that I thought, because one of the reviewers, or two or so, say, "Well, everybody knows now that it's 2½ million because that's in the review of Monaco and Kunkel. Events have passed these people by." So really, in those days, you could have a flu and miss your point.

PH Yes. It was an amazing period really, to be around in. Fantastic. I've not really heard the full story before, at least not from this perspective.

GV From the inside.

PH Not from the inside, no.

GV And then the other thing was, and I can't remember… it must have been something like 85 or 86, there was a meeting in Oxford that, where Art Buller from the Muscular Dystrophy Group in England, I was there, Peter was there, Lou was there, Kay… it was chaired by Peter [pause]… a rather affectionate speaking person… can't remember. Now and Lou gave his talk and came with the Pert probes. But he did it in an extremely presenting way: just imagine that you would do this or that; just imagine that you would be able to this or that; just imagine that you would, and so… I can't… I still have his slide in my mind with this sort of funnel-shaped things over a map, with black and white lines and so on. And then near the end, he says, "Well, you don't have to imagine. This has happened, and here are the probes, and these probes are gone in only a few patients, but those probes are gone in many more patients." That was actually quite an historic moment when he came about with his probes.

And probably the timing of this meeting would be somewhere in beginning of 1985, would be my guess, with the thing. And then one other memorable thing is there was the meeting at Versailles where Tony actually came with his reading framerule, where Bert Bakker came with the germline mosaicism: a mother with two children with the same deletion and the mother being unaffected. And we also came with our pulse field map showing, because at the time, the Pert probes together only saw 15% deletions, and we saw, with our pulse field map, we saw 65% altered fragments with pulse field. And so my argument was, well, okay, with restriction fragments you can only look 5KB away. If your watchtower is like 10 times as high, you can cover 10 times the horizon. That meeting was also visited by Miranda Robertson from Nature and Lou and Miranda and me sat on, well, on these sort of sitting tombs in the bar, and Lou wouldn't believe it. He was just sort of absolutely convinced that it was impossible to have so many deletions and so on. And Miranda actually was very interested in this sort of, the technology, but also this argument that if you just could look around in a wider range and still have the precision, you could actually see many more things happening.

So that, after that, I contacted her and asked, "Would Nature be interested in getting this manuscript?" So that was how, I think 1987 October, or round about, was the paper showing that, and of course that was diagnostically quite useful . That was why, in the beginning, we would do diagnosis making agarose plugs from patients just to look, look further around. I think that was also the time of the jump 66.

I could try to put this in an actual timeframe because now they come as tidbits, you know, you just give, and you probably have this experience with many other people that you spoke. As they speak, I think it's just some sort of reticular activation in your brain when you just hit a certain register then suddenly all the things around it come up and become quite clear again. If I would have had to write this down, it wouldn't have happened.

PH Yes.

Gert-Jan, it's a fascinating story. We must come to a close fairly soon, but, and there's not time really to go in detail to everything that happened after the Duchenne time. But is there anything you'd especially like to say about the following years that stands out, and the wider work, you know -

GV In the human genome?

PH Well, yes.

GV That whole thing is probably just worth another half an hour, or hour and a half, because that was… Because of Peter's involvement with Bob Williamson and so, we got into this probe business, and because we got into this probe business and got into this long range cloning, we got into the YAC cloning in the early days of 1987. I visited David Cox and Rick Myers who were then toying around with....

[break for telephone call]

PH So this is the second part of the recording with Professor Gert-Jan van Ommen on 10th December 2010.
Gert-Jan, we've gone through your early career and the period of research on Duchenne, but we haven't really said anything yet about the wider development of your institute in relation to molecular genetics and genomics. So can I start by asking what year was is that you were appointed as head here?

GV That was 1990, I think. I'm not entirely sure, it could be 1991, but it was in the books from 1989 onwards when Peter decided to move on to GDB/OMIM in Baltimore and the very early inkling was after the New Orleans ASHG meeting in 1988 when we flew back together. We sat in the Trans World terminal in New York and he said, "People have been approaching me for a job in the US. It's about the moment when I have to decide whether I will grow 65 years in the Library Committee in Leiden, or do something challenging still." And then he said, "I think that you should be the one who would take over" and then I explained to him that I felt that I needed to be a bit longer in the oven to get a bit browner crust. And then Peter said, "Well, it's your choice. Looking at the Netherlands, either you become your own boss or Charles Buys may have a good chance of becoming your boss." And while I like Charles and admire him a lot, it just wouldn't change a lot for me then, so that basically, there and then I started thinking and decided, well, everybody's always called too early. It's better to just step up to the plate. So that was one. Then because of all this toying around with long range techniques, CCR cloning with pulse field and so on, there was a very small genomics community in those days.

I remember the first time I went to the ASHG was in1984 in Salt Lake City, and we came from a long range mapping / chromosome hopping/jumping meeting with Hans Lehrach at EMBL where Francis Collins was too, and basically we all took the same plane, and that was like 20, 30 people that were doing things like this. Then, at least that part of the genomics community wasn't big. There were several people in long range techniques, but in continental Europe was it Hans Lehrach and me. At the same time there were the mapping efforts of Helen Donis-Keller and, what is it, Cohen in Paris from Genethon, who made, in 1992, he made this complete map, or made a YAC map even. I just have these times confused, but those could be sought out, but I guess it's all in these things here; the sheets. Then at some time, I try to think how I ended up in HUGO; by the way, there is actually an intermezzo; at some point there was this, yes, there was this Cold Spring Harbor Genome Mapping meeting going on every year and we would meet each other there: Peter and Michael Morgan and David Cox and all these other genome people. And we were in that community and one person that I, at the time, started knowing quite well was Michael Morgan from the Wellcome Trust.

And at some point, I think in 1992,3,4… it becomes a bit blurred… Michael approached me and said, "The Wellcome Trust wants to make some big decisions and genomics is really not neuroscience, it's not molecular biology, it's a little bit of everything, and so we want to establish a board called the Genetics Interest Group that has 2 people of each of the other boards of the Wellcome Trust, and 2 people from abroad. And one person from the US by the name of Jim Watson, and one guy from continental Europe by the name of Gert-Jan van Ommen." So while I felt like those were far too big shoes to fill, still I thought it fantastic to be as a fly on the wall in that committee. We got together like 3,4 times a year and pretty soon after this started, this was also in the time that the Wellcome Trust actually disinvested all the money from Wellcome that they made with the AZT, because before, I think, Wellcome made quite a fortune with AZT. They disinvested their corporate interest; they wanted to do something new, and so the plans came on the table for the Sanger Centre. So actually, and I won't say that I have made a big impact on that specific thing, but I was there when all these plans were coming around and we had to comment on the plans and listen to the proposed PIs.

So John Sulston and David Bentley came past the Genetics Interest Group to present their plans, and then the decisions were taken. And we were shown Hinxston Hall when it was still an old castle and a bit derelict pond in front of it, and nothing like all the new buildings. On the side of that terrain was the YAC cloning facility or the cosmid library facility, there was already something there. And so I was in

that community. Then, and I can't remember who precisely, someone approached me to become the vice president for Europe, or at least at the time there was a HUGO Europe and a HUGO Americas, and a HUGO Asia. And they asked me whether I would be in the board of HUGO Europe and whether in fact I would want to be president of HUGO Europe, for several reasons, one of which being, and that's always when you are from a small country and there's not entirely flies on you, then it's always easy: the French don't want an Englishman, the English don't want the French; the Germans it seems nobody wants, and so ultimately, well this is maybe a too negative way of phrasing why they came out to me. I was at the time also Chairman, President of the Dutch Society of Human Genetics and quite successful, and I've been that for 8 years, which is actually one of the longest terms.

And after being president of HUGO Europe, at some point, when Tom Caskey was president of HUGO International and then Grant Sutherland, and so then they wanted a European. I can still remember that Charles Cantor at some point just basically materialised in Amsterdam, inviting me out to one of his 6* restaurants that he always goes around having a list of, and told me that many people thought that I would be a very good candidate for the presidency of HUGO. So, well, I'm homozygous for saying no, at least that's what I've noticed in life. I always end up in these chore jobs, and I must say that I like that type of job. What I do like is trying to make people work together and to get across mistrust and transatlantic nausea and all these things because there's a lot of sort of people posturizing against each other for their peers, and it doesn't get a lot of work done. So that I have been president of HUGO 1998-2000.

So, HUGO: well those were of course very fascinating days. In the Cold Spring Harbor meetings in those days, actually a little earlier… more like already in 1995, I would think. John Sulston got up during the Cold Spring Harbor meeting and said, "I think we should just sequence the damn thing. This is about the time. We're all talking about next technologies but we shouldn't wait until next technology, we can do it with the existing technology." And that started the ball rolling, and the rest is history, you might say. And, so in those days, what happened, you were flying all the way around the world because the main thing of the HUGO days, at the time, was actually trying to convey to the public that this was the most fascinating thing to be involved in, and that there might be scary aspects, but it wouldn't be , "Oh I'm only scary." And so I went, it was also a crash course in communicating with the press. I remember being in a press conference in Brisbane with Leena Peltonen and Eric Lander when the whole stuff about Dolly, broke. And then, well, that dominated our opening press conference. And then you see how people like Leena and Eric were fielding journalists' questions. So you learn and learn and learn and learn tosay things in few words and cut the crap, and so that was quite a good schooling. Not only in HUGO, and genomics, which I felt, of course, to be a fascinating development with all this stuff with Venter and NIH, patenting stuff and then going private, and then the discussion about the patented ESTs.

And then later on in 94, there was a genome meeting in Baltimore. That was at the heydays of the debate on gene patenting. Genome Sciences was patentling thousands of ESTs, and Merck, possibly instigated by Tom Caskey, made a sort of counter move by actually having a company pay for offering things to the public domain while NIH, as a public body, started the patenting of it all, with Craig Venter, but it was the boss of NIH, a woman of which I don't remember the name, who decided to go that route. I thought was an interesting sort of opposite way how it went. At the meeting this came to a head in a heavily guarded room. Venter, Bill Hazeltine, Michael Morgan, the Merck people, everybody was there. Randy, was is it, Scott or so from Incyte, and their own patenting of genomes. The Merck position was that they weren't in the business of patenting gene snippets but in that of drug development. Actually the president of HUGO was QQ also a member of the IP Committee and QQ member of the Ethics Committee. The IP Committee was chaired by Joseph Strauss, a leading IP lawyer from Germany and he's really, he was a Max Planck professor; well regarded in the US and Europe for a large amount of things. I got to know him quite closely so that actually even taught me an enormous amount and formed my thoughts about how to deal with patenting: that diagnostic things you might

not want to patent, but therapeutic things you should protect because otherwise nobody would ever develop something. And I actually have been using those arguments in the debate in the Netherlands again. And on the Ethics side, Bartha Knoppers had gotten, like the IP committee, a large grant from Merck, through HUGO to actually develop all those HUGO statements on how to deal with protection of privacy and advancement of genome research.

I have always been very, very firm on the value and the contribution of HUGO because it was under fire. It was perceived as a sort of gentlemen's club around the Bodmers and Cantors of this world who were accused of flying to exclusive places by expensive flights and condominiums bought by HUGO Americas, and so on. But the latter was, in fact, only an investment and it was given to HUGO. But I really think that what didn't sit well, especially with the funders, was that Wellcome Trust and NIH and a few more, in fact invested amounts like $200 or $400 million in the Human Genome Project, while all of HUGO's budget has never been a lot more than $200,000 or so, this is 0.1%, while, yet, in the public eye, it was HUGO doing the genome project. I have always been trying to explain to people what the difference was between HUGO and HGP, the Human Genome Project, but it was almost a lost battle because HUGO had, one way or the other, was lodged in people's brains and they called it the HUGO project, and that meant that the Collins' and Morgans and others were sort of, well, were in an uneasy relationship later with HUGO. While, indeed, they got it started. Wellcome actually, for a long time, housed us in London. But, well, it took a while and then they just were not so happy with HUGO getting the credit, but no matter we did, we got them anyway.

So the more recent time of HUGO, already 2000 till 2003, I've been senior vice president. I'm still Trustee, together with Sue Povey and Bodmer and Ian Craig, together with the HUGO Americas, I think the big rescue of the organization was when Ed Liu offered to take it over, and set it up in Singapore. He really invigorated HUGO incredibly. But I really think that HUGO has never been 'the building itself', rather the mortar that connected the bricks. We did the ethics aspects, we did the IP aspects, we had the statements, we were a non government organisation; we were sort of connected with companies but never any specific company: we had sponsors that way. And so we could, in a way, operate to the best of our view to just fill in the blanks here and there. And that I really found a very valuable and formative time, which again, got me into new circles.

As of 2000, 2001-2, the Netherlands got wide awake about where the genome went. I remember being asked for the opening of the University in 2000 to deliver the opening lecture at the University. That was at the time when just, in June 26th, the completion of the first human genome sequence was announced. I got in my holidays a telephone from the Rector of the University that at the opening of the academic year could I please present this lecture.

And then I made a slide with a fake composite newspaper front page heading, "The Netherlands is investing 400,000-million- guilders in the Genome Project" and it wasn't even half a year later that this turned out to become reality. In fact the next speaker was our Minister of Finance at the time, Gerrit Zalm, and well, it was the only time that a minister couldn't sneak away and had to sit there in the front row and listen to me. And I used to say that that had some influence. In fact there were several people gearing up to genomics at the time: me, Ron Plasterk, a few other people from the plant genomics and 'white biotech'' and together we were pounding on the government's door. Then they made EURO 400 million available for genomics over a five year period. That started the Netherlands Genomics Initiative (NGI) and then people had to submit plans for genome centres. Ultimately 4 genome centres were selected: one in plant genomics, one in white biotech, one in cancer genomics, and one in the common diseases, That were we: the Center for Medical Systems Biology (CMSB). It was quite technology-oriented and it covered basically the waterfront from say common and rare diseases, and so on. Like Alzheimer, arthritis, depression, metabolic disease, migraine. We did immunity and viral cancer as well. We snuck the rare diseases in through the curtains because the whole name of the game at the time was genomics for cardiovascular and rheumatoid and whatever, while my argument, certainly now, is

that actually common and rare diseases are two ends of a continuum, and that you have modifier genes as well for rare diseases.

In fact most of the common diseases now tend to fall apart in rare subclasses. David Cox has just delivered two lectures in the Netherlands, he's now Vice President Research and Development at Pfizer. And he emphasized that most of big pharma is really back against the wall: at best one in every 35 drugs hit the market, and it gets less and less, and there are too few drugs to buy. Too few small biotech companies with interesting leads. And so the new game is actually that they all are concentrating on rare diseases.

In the beginning of the genome era there was a lot of outcry from the rare disease community that we all were in this big caboose of the genome, and that they were just forgotten. But what you see happening now is that due to this enormous amount of money invested in the genome, (and personally I don't think it's so enormous. If the Americans had left Iraq a week early they could have paid for the whole genome project 10 times over) the first clinical community which is now really benefitting from the genome project, through the advances in Next Generation Sequencing, is actually the rare disease community.

I actually have a slide with the table of contents of the American Journal of July, and about 60-70% of all the papers in there are discoveries of new rare disease mutations in new genes that nobody had thought before, and all of them are using chip technology, next generation sequencing, whole genome sequencing. And in all these cases you suddenly get new diagnostic possibilities. There are already one or two examples of when, after a gene is discovered, they suddenly find out what to do about the disease, because often it's maybe just a shortage or a toxic metabolite or what not. So I really think that the way things have gone is that the rare disease population has been taken on board just as well as the, as the more common diseases. And it will take quite a while before these GWAS studies will actually deliver drugs, clinical benefit and so on. And then you can even then say that the rare diseases may actually track the path to proper therapies. The way I look at rare diseases is that, for example, besides developing a therapy for Duchenne with the antisense, what we're doing, is at the same time also having found how to administer it, what the dosage is, the toxicity, and what the general tendency of genes is when you try to skip exons.

And we're already expanding this in the direction of Huntington's disease, and in the direction of several other diseases, and many of those therapeutic things that are now gradually beginning to take hold in the rare disease field. You can also say that this translational development work is filling your toolbox for intervening in human biology. And many patients, also of common diseases, couldn't care less if you treat their cause: they are interested in treating their symptoms. And while many of the common diseases will be really hard to treat causally, you can treat different aspects of that disease's biology if you know how to put a spanner in the works in those regions. And that's what I think is actually possible much better with rare diseases because at least there you know what you should see when it works. And that's not the case with Alzheimer's. How can you follow therapeutic success there? That they become a little bit less forgetful after 10 years? That's not a way to develop drugs. So that is what links the common to the rare diseases: through the genome, And what now begins to dawn to big pharma is that they are, they shouldn't focus on personal genomics, because that's too expensive: specific drugs for every person. Pie in the sky. But they should focus on precision medicine: which is to try to find that group of people within a clinical end point that is sick in the same way.

And then you can develop medicines for a group which is sick in the same way. Indeed, that is the promise of the biobanking going on nowadays, and getting a lot of power in Europe, that if you manage to get these biobanks in the academic world, but with access to industry in a collaborative fashion, then you can begin determining, within a large biobank, the subsets that are sick in the same way. And so that is what I have been after in our genome centre, from 2003 to now. This is still on-going, the CMSB. And in 2006, I got involved in the biobanking community. Maybe even earlier, in 2002 with the

GenomEUtwin programme led by Leena Peltonen from Finland. In fact the CMSB is, in a way, a way to use biobanks for basic research. In 2006 there was money available in the Netherlands for large research infrastructures and we wrote a plan based on CMSB but nationwide. It didn't make it, but it was a fantastic plan. And then there was a call in Europe, or a plan to make a call in Europe, from what's called ESFRI, the European Strategy for Research Infrastructures, and I was in on of the committees together with John Sulston, Doron Lancet, somebody from the early protein world, and a few more people. And one of the themes that had to be developed in that call was Biobanking.

So I said, "Well, you know, I do have some experience in that area. Would you mind if I take what I have and adapt it?" So I took what I had from the Netherlands, replaced all the 'the Netherlands' by 'Europe' and they really liked it. That caused this European biobanking infrastructure, that was then submitted to the call by Kurt Zatloukal, Leena Peltonen, and several leading biobank people across Europe. Also people from the UK, but the UK always take a bit of an aloof attitude in this, they're not really part of the continent sometimes. [laughs] BBMRI was led by Kurt Zatloulkal, an Austrian, and even though it only got EURO 4 million for 52 participants so all that could be eastablished was the network, has become a very high profile activity that the EU likes very much, called BBMRI. And then, interestingly, the Dutch government got back in touch with me and asked "would I, with my community, be willing to submit a grant to the Dutch roadmap (because ESFRI was the European roadmap)?". And in this Dutch roadmap they also wanted to give biobanking a very high priority. And so we submitted a biobanking plan for the Dutch roadmap, originally to the tune of Euro 40 million. As they wanted it to be like BBMRI and be connected to it … I took the European application, replaced the "Europe's" for "The Netherlands" again and then they invited us. Clearly that it was scoring very high, but they said, "Well, you asked 40 million and we only have 63 in total."

And then I explained that that, in a way, was more their problem, and that, on the other hand, we had approximately 400,000 well described samples and it would be quite logical to assume that about half of it would be useful, and that spending Euro 200 per sample wasn't unreasonable. So then they said, "Yeah, maybe you're right. Maybe then what we do is we'll allow you the funds but we'll cut it in time. We'll only give you 3 years rather than 5." So we got Euro 22½ million for say, last year, to 2 years from now, and we are in a big consortium with all the Dutch academic people, and it actually is working really nicely. I do have… I had… I'm sure I had it… the first newsletter of this, and we actually have already the first round and a call for [pause]… give me one minute… I'll give you the newsletter [pause] This is the first newsletter announcing us. And this is the second newsletter when we had the kick off meeting just in September where the State Secretary actually came to open the whole thing. And here you -

PH This is very interesting.

GV - this is one of the people that, I mean, this is what I told you, this is out here.

PH Thank you. That is great. Thank you, Gert-Jan. Now I know you have to disappear shortly, but I've been asking everybody I've talked with two questions: the first one is, is there any one particular person...

GV Ah, okay. But still. Some within my field and some outside. One that has been very much an example for me how to explain things in simple terms to lay people is somebody from the nutritional field that was a colleague in the time at Piet Borst and his name is Martijn Katan. He writes columns in a national newspaper, is on the radio and sometimes on TV on explaining things about human nutrition and all the misconceptions there. That's somebody who really taught me, or was an example to me on how to give examples that people could relate to. In my own field somebody like David Cox has been quite influential to me in his views on, well, where the field goes and… but I have a lot of examples around me that each and all…Ysbrand Poortman with the importance of getting the support from the patients. So people like that, one of the patient people that I'm very closely connected to who was in that way

influential is Elizabeth Vroom from the Duchenne Parent Project. Because in the early days of our Duchenne work with the exon skipping, we made the proposal to the Muscular Dystrophy Campaign in 1997; I still have the papers. We proposed two things: that is make a mouse with the human DMD gene, and set up exon skipping for Duchenne. And we got back from them that, yes, we got the money but only for making the mouse because the exon skipping wasn't going to work. Nobody believed that.

And so, that was when we went to the Duchenne Parent Project in the Netherlands and they have been helping us, and much unlike what people think, it is not so that the Patient Organizations help you, modestly, in the beginning and then later you get the big money from other funding. This is definitely not so. They have been continuously supporting us. We have to file competitive grants, but I recently made up the tally with Elizabeth and since then, between then and now, we've been supported by about Euro 2.7 million, and it's rather expanding than decreasing because now the exon skipping is there, you want to just try to make better condition muscle, so there are more things to do. So that so… the patient community is really important for me.

PH The other thing I've been asking everybody is: if you had to choose just one of your pieces of work, what piece of work, or area of work, would you feel is the most important for you? Not necessarily the most important altogether scientifically, but which do you feel most proud of?

GV Duchenne work. No question. I have, because I have, as you have heard and noticed, I have a relatively chaotropic interest, so I do a lot of things and so I tend to do a lot of things not entirely as good as when I would have done them alone. And I realised that from reasonably early on and I have always been that committed to Duchenne that, very early on, I really vowed to myself that Duchenne would be my measure. That every situation where I had to make a choice between not doing something unrelated to Duchene to the benefit of something related to it, or vice versa, I would always have to choose the Duchenne. And that still is the line I go by. If I get an invitation for something and it conflicts with another invitation or another commitment, and even agenda commitments, I now and then I have this little voice on my shoulder saying, "Do you still remember what to measure it by?" And that is easy because you are always torn between many decisions, and it helps if you have something that in a way guides you.

PH I'm sure you're right. Gert-Jan; I'm going to finish there and thank you very much for giving your time and sharing your thoughts. Thank you.

GV Well, you're welcome. Actually, what you may not know, although I may at some point have told you: I do have a reason for that, and that is that my wife lost a brother with Duchenne. So I have seen, that was a family of 9 kids, so they could take care of it, which is different in smaller families nowadays, so you have seen the whole process of a boy deteriorating from 7 years old, and getting in a wheelchair, in bed, out of bed, in bath, out of bath. He got to be 24 and he died in 19… he's from 1960, so he died 1984. And he was as clever as what, so he certainly wasn't one of the mentally retarded. Real nice person. But had lived, in this sense that by the time he died, he didn't want anybody to help him and he told his brother, who wanted him to get out of bed and so on, "You don't have to because I'm an old man." And so you really saw that, in a way, this acceptance comes, which is what makes it for me also possible to understand the hesitations now and then with Duchenne patients. If there were a therapy would I like to erase my personality and become someone that got up from his wheelchair and started playing basketball? Or do I want it to just sort of at least stop deteriorating? And because we tend to phrase all these things from, you have to, well, obliterate disease, but this is sometimes not people's goal. And it's important that you realise what people's goals are, and that yeah, so that's, I'm not only a scientist developing but also a user of this.

PH Many thanks, Gert-Jan.