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Annual Review of Genomics and Human Genetics

The Long Journey from Diagnosis to Therapy

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Annu. Rev. Genom. Hum. Genet. 2020. 21:1–13

First published as a Review in Advance on March 2, 2020

The *Annual Review of Genomics and Human Genetics* is online at genom.annualreviews.org

https://doi.org/10.1146/annurev-genom-112019-083518

Keywords

Duchenne muscular dystrophy, DMD, gene therapy, dystrophin, utrophin, X chromosome, prenatal diagnosis, AAV gene therapy, autobiography

Abstract

I was honored to be asked by the Editorial Committee of the *Annual Review of Genomics and Genetics* to write an autobiographical account of my life in science and in genetics in particular. The field has moved from mapping Mendelian disorders 40 years ago to the delivery of effective therapies for some monogenic disorders today. My 40-year journey from diagnosis to therapy for Duchenne muscular dystrophy has depended on collaborations among basic scientists, clinicians, medical charities, genetic counselors, biotech companies, and affected families. The future of human genetics looks even more exciting, with techniques such as single-cell sequencing and somatic cell CRISPR editing opening up opportunities for precision medicine and accelerating progress.

EARLY LIFE

I was born in a cold, wet April in 1951 in a small town called Stourbridge, the second child of a working-class family living at the edge of what is known in the United Kingdom as the Black Country, the center of the Midlands. During the Industrial Revolution, it became one of the most industrialized parts of the United Kingdom, with coal mines, iron foundries, glass factories, brick works, and steel mills. The Black Country was very working class at that time, and people spoke with a distinctive dialect that was often quite difficult to understand. In Stourbridge, this dialect was not very strong, but the social stigma associated with it meant I needed to disguise it later, during my time as a student at Oxford.

My father was a skilled toolmaker in the car industry, and my mother worked part time providing guided tours around the Stourbridge glass factory. Both were committed to providing the best opportunities for me and my two brothers, and we were very keen on education. My mother was an enthusiastic and obsessional gardener who taught young people gardening in her later years, including one young man who progressed to presenting gardening skills on BBC television. My parents provided much encouragement to succeed at whatever ambitions we had. My brothers and I all went to university, although I am the only scientist.

My early schooling gave me the opportunity to show my skills in mathematics because the headmaster at the junior school (grades 7–11) liked to set puzzles, and I was always ready to meet the challenge. I attended the local state-funded Stourbridge High School for Girls and very much enjoyed the combination of academic pursuits and hockey. Unlike American schools, UK schools require pupils to specialize early. In addition, if you were a potential candidate for Oxford or Cambridge, you needed a Latin qualification for admission, which meant giving up biology because the school timetable did not permit both Latin and biology lessons. When I was 16, I had to choose among sciences, history, geography, and languages, selecting three subjects overall for a two-year period. I opted for courses in mathematics, physics, and chemistry. So unpopular were the sciences for girls in those days that only 6 out of about 150 of us selected physics and chemistry as main subjects. We were fortunate to have Miss Presley, an inspirational teacher in chemistry, challenging and encouraging us throughout the two years of study. She also loved golf, leaving us on some occasions to pursue the practical demonstrations by working them out for ourselves. This in itself made it more fun to explore chemical reactions; it was not as dangerous as it might seem, since we had all gained some experience through vacation jobs in local industry, which had taught us the basics. It is just as well that none of the experiments resulted in an explosion! Miss Presley strongly encouraged me to apply for Oxford and did her best to instill self-confidence in a very shy schoolgirl from a sheltered background.

OXFORD DAYS

In September 1968, I took the entrance exam for Oxford, and although I could not answer many of the questions since I was only halfway through the two-year course, I showed enough aptitude for an interview at Somerville College to study chemistry. Candidates had to wait until December for the final results, and I was fortunate enough to be offered a place subject to my obtaining sufficient marks in the mathematics, physics, and chemistry exams the following June. Oxford awaited me in October 1969, where I was to study chemistry alongside five other Somervillians. That year, the university enrolled about 200 men and only about 25 women to study chemistry. In my first days, I was intimidated by the sheer intelligence and competitive attitude of everyone I met. I soon settled down to college life, although the course was intense because of the time-consuming practical classes. One way to minimize the number of hours spent in the teaching laboratory was to

team up with a more skilled chemist in the class who could help. This was how I met my husband, who was much more adept than I at obtaining high yields in the organic chemistry classes.

The weekly tutorials were highly informative because we were taught in pairs, and there was great opportunity to be challenged and to challenge. My tutors were very supportive and encouraged me to be more confident in my own abilities. It was clear to me early on that I could complete the chemistry course, but I was not passionate about the subject and could not see myself pursuing it as a future career. I was fortunate that my tutor, Jo Peach, realized this and encouraged me to select a biological research project for my final year. I moved to biochemistry to work with the late Ian Walker on chromatin structure and transcriptional control. It is hard to believe that this was before we knew that DNA was wrapped around nucleosomes, rather than histones coating the outside of the DNA. We used the slime mold *Physarum polycephalum* as a model system for study because this yellow organism could be made to divide synchronously through the cell cycle. I had to learn a lot of biology quickly but was fascinated by transcriptional control. Not only did I complete my final year's dissertation in Ian's lab, but I also went on to complete my doctoral studies under his mentorship. This was a great time in the Department of Biochemistry at Oxford, which had two Nobel Prize winners: Sir Hans Krebs was still coming into the library on Saturday mornings to review the literature, and Sir Rodney Porter was the head of the department. It was at this time that George Brownlee arrived in Oxford from Cambridge to pursue his molecular analysis of hemophilia B and the cloning of the factor IX gene. There was a constant buzz of activity in all groups with the recognition that gene cloning would transform biological research.

I was funded by a Guy Newton Junior Research Fellowship at Wolfson College at this time and still working with Ian Walker. My husband had taken an opportunity to work with the Nobel Prize–winning chemist Sir Derek Barton and had moved to Gif-sur-Yvette, just outside Paris, to continue his career in synthetic organic chemistry, and I wanted to join him. We both commuted between Paris and Oxford for long weekends by car, which was the best way to travel in the late 1970s, but this was not sustainable long term. After a year, I successfully applied for a Royal Society postdoctoral fellowship to work in André Sentenac's laboratory, which was south of Paris and close to Gif-sur-Yvette, and joined a team attempting to clone yeast RNA polymerase genes. I wished to extend my expertise and to learn firsthand how to clone genes and prepare antibodies, and this was an ideal and interesting project. Those were the days when we had to purify our own restriction enzymes and carefully prepare our own DNA ligases for the cloning experiments.

This period of my life was a very happy one, as the French knew how to work hard and play hard. For example, in winter we would leave the lab at 5 p.m. on a Friday, take a coach overnight to the ski slopes of Chamonix, and return over Sunday night to be back in the lab on Monday morning. We debated many scientific questions on the slopes. On Friday nights in the summer months, the English postdoctoral workers in the region would meet up in the local Café du Sport and teach the French how to play cricket. Up to this point, I had been very much a focused individual, with science as my only objective. The skiing trips and Paris, with its art galleries and restaurants, transformed my life and made me much more outgoing and less risk averse.

LONDON DAYS: DUCHENNE MUSCULAR DYSTROPHY AS A MODEL FOR CYSTIC FIBROSIS

The first gene relevant to human disease to be analyzed by taking advantage of the ability to clone genes was the rabbit beta-globin gene, so it is not surprising that this was swiftly followed by cloning of human genes and an important paper from Y.W. Kan's laboratory in 1978 that described using DNA for the prenatal diagnosis of sickle cell anemia (15). Then a landmark paper by Botstein and colleagues (2) was published proposing the general applicability of restriction fragment length

polymorphisms (RFLPs) for mapping the whole human genome, which would allow not only the prenatal diagnosis of disease but also the identification of the genetic mutation responsible. The human geneticist Professor Bob Williamson was on sabbatical in Paris at this time and had also realized the potential of this new genetics. He invited me to join his team in London to apply RFLPs to localize and eventually identify the gene responsible for cystic fibrosis (CF). I therefore moved back to the United Kingdom to work at St Mary's Hospital Medical School in Paddington, London, in 1980. We began by visiting and collecting blood samples from CF families in the United Kingdom. However, there was still little evidence of whether the RFLPs were randomly distributed across the genome, and there were no clues as to the location of the CF gene. We decided that it would be better to obtain proof of principle for this approach by mapping the gene responsible for Duchenne muscular dystrophy (DMD), an X-linked recessive disease.

DMD is a devastating muscle-wasting disease where boys go into a wheelchair at age 12 or slightly later and now live into their 20s or 30s with good clinical management (10). When our work began, there was neither prenatal diagnosis of the disease nor reliable carrier detection. However, there was a clue that the gene might lie in Xp21 since there were affected females with the disease and breakpoints in this region of the X chromosome. Our first objective was to construct a library of DNA sequences enriched for X-linked sequences. We were fortunate that Dr. Bryan Young in Glasgow was optimizing chromosome-sorting approaches for his studies of the Philadelphia chromosome, which is caused by a balanced translocation involving chromosome 22. He had screened cell lines to find one that gave him better resolution according to size between chromosomes 21 and 22. The cell line that he finally selected turned out to be a 48,XXXX line that gave a large peak for the X chromosome, offering us the opportunity to sort a population enriched for the X chromosome without too much contamination with the similarly sized chromosomes 7 and 8 (6).

We cloned the library from nanograms of material before the days of amplification by PCR, which was quite challenging. We then used this library to isolate a series of probes, which we localized along the chromosome length using somatic cell hybrids containing different segments of the X chromosome. Somatic cell hybrids, developed by Stephen Goss and Henry Harris, transformed human genetics at this time, and Huntington Willard and colleagues used this methodology to set up a mapping resource for the X chromosome (24). Probes from our enriched library were used to characterize RFLPs along the entire chromosome, and together with collaborators, we constructed the first linkage map of the X chromosome, allowing the localization of many other X-linked disorders (8).

This was a highly collaborative time in human genetics, as cytogeneticists, molecular biologists, and clinical geneticists came together to construct a map of each human chromosome in order to locate single-gene disorders. There were annual international Human Gene Mapping Workshops with subcommittees for each chromosome. Working together was the key, and we labored long and hard to integrate data from many different labs to generate a linkage map. Those were the days when we drew up an initial map on sheets of A4 paper joined together and then cut and pasted them to eventually arrive at a consensus. There were many debates late into the night! The significant localizations reported at this time were Huntington's disease to chromosome 4 (14) and CF to chromosome 7 (4). These observations laid the groundwork for the eventual identification of the causative genes.

Of course, without well-characterized DMD families, we would be unable to test them for linkage with the DMD locus. Professor Peter Harper in Cardiff was a leading clinical geneticist who had had the foresight to collect such families, and we set up what was to become a key collaboration. Peter played an important role here, as large families with the correct diagnosis were essential for success. Our first probe that identified a RFLP lay 10 cM away from the DMD locus—too

Figure 1

Participants of the European Alliance of Muscular Dystrophy Associations workshop held in 1984 to discuss progress in the identification of the gene responsible for Duchenne muscular dystrophy. Peter Pearson is in the back row, sixth from right, and Ron Worton and Gert-Jan van Ommen are in the next row down, fifth and seventh from right, respectively. Louis Kunkel is shown in an inset in the top right-hand corner; although he did not attend this particular meeting, he was there in spirit.

distant to allow accurate prenatal diagnosis or carrier detection (20). However, this confirmed what was suspected from the translocations in the females, that the gene lay in Xp21. We were able to incorporate another X chromosome marker from collaborators Peter Pearson and Gert-Jan van Ommen in Leiden, so that we had two RFLPs that bridged the translocation breakpoint region, making carrier detection possible. Peter Harper's group went on to show that Becker muscular dystrophy (BMD) was also inherited with these RFLPs in a similar manner, suggesting for the first time that DMD and BMD were caused by mutations in the same gene (16).

Advances in this field were greatly facilitated not only by the annual X chromosome workshops but also the annual DMD workshops set up by the Muscular Dystrophy Association in the United States and the Muscular Dystrophy Campaign in the United Kingdom. They organized these workshops to promote collaborations among the groups working to find the DMD gene (see **Figure 1**). The idea was to prevent duplication of effort and promote collaboration wherever possible to enhance the pace at which we could achieve the goal of identifying the DMD gene. In Europe, these workshops were funded initially by the European Alliance of Muscular Dystrophy Associations. The competitive atmosphere was intense but friendly, and resources and ideas were freely shared prior to publication in order to enhance the rate of progress. The first prenatal diagnosis of the disease used RFLPs from various laboratories and came out of one of these workshops (1).

The gene was eventually identified by the laboratories of Louis Kunkel and Ron Worton by isolating sequences lying in a deletion in a patient with DMD, chronic granulomatous diseases, and retinitis pigmentosa and by cloning a breakpoint on the X chromosome from one of the affected females, respectively (12). With the gene in hand, further progress was rapid, particularly because of the generosity of the Kunkel and Worton groups in sharing probes from the gene itself. There was a flurry of papers on prenatal diagnosis and carrier detection, and the gene was shown to cover more than 2 Mb of genomic sequence. Kunkel named the gene product dystrophin because

the lack of it caused muscular dystrophy. The molecular analysis of the locus and the biochemical analysis of the protein followed, and again the workshops facilitated progress by enhancing exchange of knowledge prior to publication (3). This was very important in the nondigital age of publication, where data might take a year or more to appear in print.

The progress in molecular genetics was also matched by progress in obstetrics, where chorionic villus sampling at 12 weeks had been developed. Dr. Charles Rodeck at St Thomas' Hospital in London collaborated with us on a prenatal diagnosis in a DMD family who had previously made the difficult decision to abort males because of the risk of having an affected child. The new pregnancy turned out to be twins, and the RFLP alleles showed them to have an identical genotype. The question of whether the same twin had been sampled twice or whether they had the same genotype was fortunately resolved because one was male and one was female, a scenario easily demonstrated using a Y-specific DNA probe. Two healthy babies were born. The time from our receiving the chorionic villus samples to the diagnosis was about three weeks. Today, with PCR, this can be done in a few hours, making it much less stressful for the families and providing more time for genetic counseling.

To work with Bob Williamson, I commuted on the train from Oxford to London, as my husband had been appointed to a faculty position at the University of Oxford. This was an hour and a half's journey each way and meant that I had to be very organized with my experiments in order to get them all done in a day. If I missed a train, I had to wait for an hour for the next one. There was a lot of energy in the laboratory at this time, and with Bob, nothing was impossible; he always knew someone in the field who would be able to help whenever we needed a new technique or vector for cloning. He taught me how much more successful you could be as a scientist if you were collaborative and had an extensive network of basic and clinical scientists.

When I joined the lab, I was funded by a research fellowship from the Cystic Fibrosis Research Trust, which was sensible enough to recognize that work on DMD could help develop the methods to identify the CF gene. Two years later and encouraged by Bob, I realized that I needed my own independent funding. Bob remained dedicated to CF and the development of therapy, and I continued the DMD program. I turned up for an interview for a five-year Medical Research Council (MRC) Senior Research Fellowship with Sydney Brenner in the chair. This was to be a turning point. Not only did Sydney ask probing questions about the science, but he also recognized that I needed a post back in Oxford to further my development as an independent scientist. He arranged for me to meet Professor David Weatherall at the John Radcliffe Hospital, who was working on the molecular analysis of thalassemia. David offered me a small laboratory in which to start my own research group and a shared office with Professor Nick White, an infectious disease specialist who spent much of his time in Bangkok. I was very fortunate to be plunged into an environment of academic clinicians who were supportive and also interested in understanding disease mechanisms and working out approaches to therapy.

The lesson learned from this period of my career in London is that it is hugely beneficial to work with an ambitious and generous leader whose passion for science is infectious. Bob Williamson showed me the real advantages of working with the right collaborators and patient groups, and the importance of public engagement. And having as a mentor such an eminent academic clinician as David Weatherall—who attracted many bright young scientists working at the interface of basic science and medicine—had a huge influence on me.

THE WEATHERALL INSTITUTE OF MOLECULAR MEDICINE, OXFORD

My work in Oxford initially focused on DMD. Analysis of the mutations in the dystrophin gene revealed that about 65% of them were deletions, varying in length from a few kilobases to a megabase

or more. Tony Monaco in Kunkel's group showed that the allelic, milder form of the disease, BMD, was explained by in-frame deletions that resulted in truncated but partially functional dystrophin. DMD was caused by out-of-frame deletions that resulted in little or no protein, as a result of nonsense-mediated decay. Clinical geneticists sent us samples from their families in the United Kingdom so that we could confirm their diagnosis as DMD, as opposed to other autosomal forms of muscular dystrophy that present with a similar phenotype. We and others showed that the deletions were not random across the gene but were clustered in two hot spots, which greatly assisted carrier detection and prenatal diagnosis. One patient sample, from Sarah Bundey's clinic in Birmingham, came from a gentleman in his 50s. He showed no symptoms of disease until his 40s, after he left the army, so we expected him to have a small in-frame deletion. We were amazed to find that he had 46% of the coding region of the gene missing (11)! Colleagues suggested that his mild phenotype was probably due to genetic background, perhaps with the upregulation of a compensating gene. Sarah Bundey diligently explored the family tree and found a distant cousin who was a bodybuilder. He had the same large deletion and volunteered for a muscle biopsy so that we could investigate whether he produced a truncated dystrophin in muscle, localized at the muscle membrane. Analysis of his muscle biopsy showed the correct localization of the truncated protein. With collaborators Nick Wells and George Dickson, we reconstructed this dystrophin minigene as a transgene and introduced it into the *mdx* mouse model of the disease to test the hypothesis that it could compensate for full-length dystrophin. Expression of this patient's truncated gene prevented the pathology, showing that the minigene was functional. This gene was the starting point for gene therapy protocols using microdystrophin genes, since the large 14-kb mRNA is not compatible with adeno-associated virus (AAV) vectors (5, 9). Progress toward therapy thus depended on collaboration between the clinical geneticists and basic scientists.

During our attempts to clone the full-length coding sequence of the dystrophin gene, my postdoctoral worker Don Love came across a sequence that mapped not to the X chromosome but to human chromosome 6. We were mystified by this but did not have the sequencing ability to clarify the origin of the sequence. Fortunately, Diane Hill visited from Dunedin to discuss her sequencing projects in sheep. She volunteered to take the chromosome 6–derived clone with her and sequence it over Christmas back in New Zealand, where she had the facilities to do so. On Boxing Day, she emailed us with the results, and she was excited to report that the sequence was very similar to dystrophin's, which was not what we had expected (18). Unlike dystrophin, whose expression is confined to muscle and brain, this gene was ubiquitously expressed, and we called it utrophin for that reason. The homology with dystrophin allowed us and others to explore replacing dystrophin with utrophin as a therapy for DMD patients (12). This may seem quite obvious in retrospect, but few grant reviewers believed that it was possible, and utrophin was already increased in DMD patients. We now know that this is because utrophin is transiently expressed in regenerating fibers rather than being localized long term at the membrane.

This work is an example of how a long-term commitment of funding for at least five years is critical for a successful career. Non-micromanaged program funding from the MRC allowed my group to make transgenic *mdx* mice expressing high levels of utrophin and to show that this prevented the muscle pathology. Few funding agencies today make such a commitment, which permits high-risk experiments and innovation. Transgenic mice were a new approach in those days, and it was difficult to recruit young postdocs who were familiar with the technology. Here I was fortunate that Jon Tinsley was willing to move from Birmingham to join the group and set up the method. One constant thread in my scientific career has been the need to keep up with the latest technologies (or collaborate on having access to them) and to recruit individuals who share a passion for progress toward a therapy for DMD. I have been fortunate in collaborating with so many scientists who could work as a team and had complementary skills.

This was an exciting time in muscular dystrophy research, as many groups were analyzing the detailed function of dystrophin, and others were thinking ahead about therapy. My group also worked on exon skipping, and I had the pleasure of chairing the UK group that was pioneering the approach, first suggested by George Dickson. The MDEX consortium was set up to promote work in experimental therapies for the muscular dystrophies and included basic scientists, clinicians, and patient representatives, with administrative support provided by the Muscular Dystrophy Campaign. This consortium led to one of the first clinical trials of exon skipping for DMD in 2011, which has subsequently led to an approved drug, eteplirsen (22). The gene was identified in 1986, and it seems incredible that only in 2019 is the field within reach of an effective therapy for DMD (5). This long development time is not unique to DMD, of course. Therapy for sickle cell anemia, where the beta globin gene is mutated, is only now being realized thanks to CRISPR gene editing technologies (7). Again this emphasizes that success requires not only long-term funding but also tenacity about the goals.

I continued to work closely with clinicians and the patient groups on the identification of disease genes. My other main interest was spinal muscular atrophy (SMA), a childhood-onset motor neuron disease. We collaborated with a leading pediatric neurologist, Professor Victor Dubowitz, who was particularly interested in this disease and had classified patients into three clinical categories depending on their motor milestones. Again teaming up with an expert clinician and receiving support from charities were key. Type 1 SMA patients usually died within two years and were born very floppy, type 2 patients sat but did not walk, and type 3 patients were able to walk but eventually ended up in a wheelchair. Using linkage analysis in families, we and others demonstrated that all three types of SMA were caused by mutations in a gene on chromosome 5. This gene was shown by Judith Melki's group to encode the SMN protein (17). The detailed function of SMN, which is expressed in all tissues, remains elusive, but recent clinical trials of AAV delivery of SMN and exon-skipping strategies to restore functional SMN protein in motor neurons are transforming the lives of the most severely affected SMA patients if delivered very early in the disease course. This story emphasizes the advantage of doing a first-in-man clinical trial as soon as possible when it is safe to do so and when there is an unmet clinical need (19, 21).

The MRC fellowship scheme runs through two five-year cycles, and then the fellow is expected to have a faculty position. Therefore, in 1990, eight years after my first fellowship award, I needed to find a post. There was no possibility of this at the Weatherall Institute of Molecular Medicine, as the rest of the unit was focused on the hemoglobinopathies, and there were no vacancies elsewhere within Oxford. I decided it was time to ask for career advice, this time from the head of the MRC, Sir Dai Rees. I was fortunate because he took an immediate interest in mentoring me and suggested that I look at the directorship of a new institute at the Hammersmith Hospital in London. This was a new challenge and meant that I was back to commuting to and from London at a time when I had a four-year-old son. My husband and I agreed that this time it might be better for him to commute and for the family to move to London. I took the post as the first director of the MRC Clinical Sciences Centre in 1992. The mission was to bring basic science into clinical medicine, and this was the perfect place to do it because of the high academic standing of the academic clinicians there. The first two years were spent doing final designs for the new laboratories and recruiting new staff. My team and I were made to feel very welcome, and several collaborations were initiated, particularly with the Neuromuscular Centre run by Victor Dubowitz.

I learned a lot about leadership and how effective teamwork can have a major impact on progress. Unfortunately, the vision of the Clinical Sciences Centre was greatly hampered by the government of the day deciding to rationalize teaching hospitals, and the Hammersmith Hospital was threatened with closure and a move to another location. The effect on me was the requirement to attend many meetings about the future, and planning blight became an issue at the

institute given its uncertain future. My ability to do scientific research was also being eroded, and I knew that I had to take action if I wanted to continue in research. I was again fortunate because I was mentored by David Weatherall, who was wise enough to realize that the future of London hospitals might become an issue and had allowed me to maintain staff in my research laboratory at Oxford. We had many conversations, and after many tortuous weeks, I decided to resign from the post at the Clinical Sciences Centre. The MRC was generous and agreed to maintain my personal research funding as it was before I moved to London. A year later, the Professor of Genetics chair at Oxford fell vacant on the retirement of Professor John Edwards, and I was fortunate in being appointed to the post. Even though John Edwards and David Weatherall were at Oxford, there was no major genetics activity in the central university, and the Department of Genetics was part of the Department of Biochemistry and had only two tenured staff. This was helpful for me, as it allowed me more time to focus on my own research program. However, with the identification of more and more disease genes, it became imperative to think about efficient ways to determine gene function, and I needed to progress from this small department.

FUNCTIONAL GENOMICS: FROM GENE TO THERAPY

It was at this time that I was appointed as the Dr Lee's Professor of Anatomy and head of the Department of Physiology, Anatomy, and Genetics, for which I had been encouraged to apply. I was welcomed by the staff, who were excellent anatomists and cell biologists. They embraced genetics and were very supportive when I set up the Functional Genomics Unit funded by the MRC. I had discussed my ideas of using model organisms and bioinformatics tools to determine the functions of genes, and the MRC invited to me to bid to set up a small unit of four principal investigators working with fly and worm models (which fit well with my mouse studies of human disease) and a bioinformatics group. The secret of the success of MRC units was their five-year funding, with review every five years. This provided the resources to do long-term and sometimes risky experiments, and without such support, I doubt that I could have managed to move to a phase 2 clinical trial for muscular dystrophy (see below).

My research focus remained with utrophin, and there was a lot of skepticism about whether it really could substitute for dystrophin. We demonstrated the potential of this approach in the *mdx* mouse model of the disease, where increased utrophin levels prevented the pathology. I presented these data at Cold Spring Harbor, and Jim Watson introduced me to a BMD patient who offered to sponsor the development of a utrophin upregulation screen through a biotech company in New York. One of my graduate students went to work in their laboratories to establish the screen, which we eventually brought back to Oxford, as the host company had other priorities. This enabled me to form a collaboration with Steve Davies, the Waynflete Professor of Chemistry at Oxford, to cofound a company, VASTox plc, to continue to screen for molecules that increase utrophin levels. VASTox provided an opportunity to take the DMD program into the clinic. At first, the company did not focus exclusively on DMD, but we were fortunate to recruit Glyn Edwards as CEO, who had the right experience and commitment such that we were able make substantial progress in the development of a drug. We set up a strategic alliance that included the MRC, the university, the Muscular Dystrophy Campaign, and the Muscular Dystrophy Association in addition to the company. The company was later renamed Summit Therapeutics. Running an academic lab alongside a biotech company was hard at times, as the milestones and timelines are very different in the two sectors, but the common commitment to develop an effective therapeutic for all DMD patients bound us together.

Collaborating with chemists led by Angela Russell and Steve Davies, along with Summit Therapeutics, we optimized a molecule (ezutromid) that increased utrophin levels and showed efficacy

in preventing pathology in the *mdx* mouse model of the disease (13). Summit Therapeutics developed biomarkers for assessing the levels of utrophin in human muscle biopsies, and phase 1 trials showed that the drug had a very good safety profile in both normal volunteers and DMD patients. They progressed ezutromid into a phase 2 trial, but unfortunately, although we observed a positive effect at 24 weeks, this was not sustained, and no effect was seen at 48 weeks. We were obviously very disappointed, and Summit Therapeutics decided not to continue the DMD program.

Having observed the apparent positive result at 24 weeks, my group, in collaboration with Angela Russell and Steve Davies, decided to investigate whether there might be a scientific explanation of the trial data that would enable us to find other molecules that could sustain the apparent clinical effect we had seen. We have been able to show that ezutromid is rapidly metabolized, particularly in DMD patients, and that this would have prevented any sustainable clinical effect. We have also determined the target of ezutromid, which is providing us with new pathways to target and new opportunities to find a small molecule to treat DMD (23). The next stage of drug discovery has begun.

We are watching the promising clinical trials on delivering dystrophin minigenes to DMD patients. In the future, it may be that the combination of AAV gene therapy and utrophin upregulation will provide the best solution for patients. What is clear is that an effective therapy is now in sight for this devastating muscle-wasting disease.

PUBLIC OUTREACH AND PUBLIC SERVICE

Throughout my career, I have been conscious about the need for public engagement and communication with government on the importance of science in everyday life and particularly the role of genetics. In 1991, I chaired an expert working group on the Human Genome Project for the UK government's Office of Science and Technology, and I have served on various committees on the ethics of the application of genetics, such as advisory groups on genetic testing, the use of animals in research, and xenotransplantation. This year, I have the privilege of co-chairing, along with Dr. Richard Lifton, president of Rockefeller University, the International Commission on the Clinical Use of Human Germline Genome Editing. There is so much opportunity for genetics as applied to health, but we must maintain public confidence in the science and its ability to deliver better health for all. I am also conscious of the potential impact that genome sequencing has on health and serve on the Board of Genomics England, a company funded by the UK government, which was initially set up to sequence 100,000 genomes and has now embarked on a more ambitious target of five million genomes over the next five years. It was also a pleasure to serve on the Institute Scientific Advisory Board of the Wellcome Sanger Centre when the late John Sulston was director, watching the development of the first draft of the human genome sequence funded by Wellcome, an endeavor that was conducted in partnership with Francis Collins at the US National Institutes of Health. It was wonderful to witness the progress that was made through the international collaborative effort that culminated in the first draft human genome sequence in 2001. I currently serve on the Board of Directors of Genome Research Limited, which oversees the governance of the Sanger Institute and its spectacular genome sequencing programs at scale, which continue to provide novel insights into disease.

From the very early days running my research group, I served on the grant committees of many charities and the MRC. It was hard but very stimulating to work with colleagues who were studying different aspects of human genetics but often used or developed similar tools. It was an ideal opportunity to broaden my scientific knowledge and be challenged about my own work. I also gave talks and did interviews on radio to raise awareness of rare diseases and the need for more research to develop therapy.

The rapid advances made in the early 1990s prompted Oxford University Press to approach me to found a new journal, *Human Molecular Genetics*, to serve the expanding community of human geneticists. I knew that I could only do this with my collaborator for many years on the X chromosome, Huntington Willard. We founded *Human Molecular Genetics* in 1991, and Anthony Wynshaw-Boris replaced Willard in 2005 as co-editor for molecular papers. I have been fortunate to work with such talented co-editors with the same work ethic as me. Helen Johnson, my personal assistant for more than 30 years, is the editorial manager. The journal continues to serve the researchers in genetics from all over the world, and we convene annually with our editorial board during the annual meeting of the American Society of Human Genetics. Rapid advances are being made in genetics due to the development of technologies such as single-cell sequencing, artificial intelligence, and CRISPR editing. I am delighted to still be part of this evolution, which is beginning to transform human health in many populations globally.

In 2008, I was called by a colleague about applying to serve on the Board of Governors of Wellcome (formerly the Wellcome Trust), a post that had been advertised. I did not think that I would be considered but I was encouraged to apply, if only to experience an interview for a top leadership position. This was a time when many women, including myself, did not apply for such positions because they were male dominated, and we did not consider ourselves able or experienced enough. I could think of many reasons why I might not meet their criteria, rather than considering what skills I could offer. Encouraged by my colleagues, I did apply and was successful. Serving on the board has been an extraordinary privilege because of its broad brief on improving human health instructed by the will of Henry Wellcome. Thanks particularly to the wisdom in investments of Sir Roger Gibbs as the director and Danny Truell as the chief investment officer, Wellcome is now the second-largest charity in the world, with an endowment of about £26 billion. This has enabled it to have a major impact on health research, from basic science to the clinic. For example, Wellcome helped to transform global health in Asia and Africa and made major contributions through the funding of scientists in the United Kingdom. Wellcome also set up the Sanger Institute, which has established an international leading reputation in undertaking genome sequencing programs at scale. I hope that I played a small strategic role and facilitated these activities. I remain co-chair, with Barry Bloom, of the Independent Expert Committee of H3Africa, an initiative to develop genetics and health in Africa that is supported by a partnership with Wellcome and the US National Institutes of Health.

When I was head of the Department of Physiology, Anatomy, and Genetics at Oxford, the vice chancellor nominated me for a leadership course in higher education set up by the Higher Education Funding Council to train potential vice chancellors. I was skeptical at first, but the course changed my perception of myself and gave me much-needed self-confidence. Such management courses are more common now, and the best ones involve interactions with leaders inside and outside science. Such was the impact of this course on my career that I set up a leadership course at Wellcome when I was deputy chair, which has been a great success.

REFLECTIONS

From my initial research days, I have interacted with patient groups, particularly the muscular dystrophy charities. I have attended most of the annual international patients' research meetings that they organize, which continue to stimulate collaboration between groups and inform patients and their families. We have also hosted visits from patients and their families to the lab. We are now in an era when effective therapies for DMD are in clinical trials, and some have been approved. I hope that it will be possible in the not-too-distant future to treat all patients, wherever they are in the world. The end of the journey from diagnosis to therapy in DMD is now within reach.

A huge motivation for me and my group over the years has been the knowledge that we are working toward a specific unmet clinical need for the families with DMD. I have been privileged to work with many committed and talented scientists, some of whom have been tenacious enough to be part of this program for more than 15 years (Arran Babbs, Ben Edwards, and Sarah Squire), and we continue to work with the chemists led by Angela Russell and Steve Davies in the pursuit of a treatment that is accessible to all DMD patients.

David Weatherall advised me very early on that secretarial support was essential for a successful scientist who wished to embrace not only research but also active public service. My personal assistant, Helen Johnson, has been very much part of my team for more than 30 years, enabling me to take on demanding challenges.

Genetics applied to medicine is a very exciting field. I cannot imagine a more rewarding career.

DISCLOSURE STATEMENT

The author is a founder and shareholder of Summit Therapeutics.

ACKNOWLEDGMENTS

My thanks to my family, my mentors, and all the scientists who have worked with me over the years. I am also grateful to all the funders, particularly Action Duchenne, the Association Française Contre les Myopathies, the Duchenne Project France, Duchenne UK, the International Collaborative Effort for Duchenne Muscular Dystrophy, the US Muscular Dystrophy Association, Muscular Dystrophy UK, the Rosetrees Trust, the TREAT-NMD Neuromuscular Network, and the MRC.

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Annual Review of Genomics and Human Genetics

Volume 21, 2020

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