Lat me start by saying how honored I am to have been selected to receive the 2018 Pezcoller Foundation-AACR International Award for Extraordinary Achievement in Cancer Research, particularly on the 21st anniversary of the award. I feel humbled to join the distinguished list of previous awardees.

My life story began in 1943 in the middle of World War II in Ashford, a small market town in the southeast corner of England near Canterbury, and only 10 miles from the English Channel (Slide 1 and 2). My father was a surgeon in the local hospital, while my mother kept house for myself, my sister, who is three years younger than me, and my father, who worked long hours and was on often "on call" at the hospital. I had a very comfortable upbringing, and my parents made sure we had everything, including private schooling. From the age of six, I went to a local private day school called Friars School (Slide 3 - MSD). There I received a thorough grounding in mathematics and languages, including Latin and Greek, but there were no formal science classes. At the age of 13, I was "sent away" to Felsted School, a boarding school in Essex that was founded in 1564 - Felsted is one of the older so-called "public" (i.e. private) schools in the UK. I won a scholarship to attend Felsted, and because of this I was immediately put into the second year class, where subject specialization was already required (Slide 4 - Felsted 1956). After a conversation between my father and the headmaster in the first two weeks I was there, they decided that I should specialize in the sciences, I suspect largely because of my father's medical training. I had some aptitude for science (although my maths was not strong), and so this was probably a good decision. Although I didn't know it at the time, my career as a scientist had now begun.

There are no notable scientists or academics in my family, but my paternal grandfather was a dentist, and my father was an MD, getting his degree at the University of Cambridge, and training as a surgeon at the London Hospital. Through telling me about his medical experiences, my father sparked my interest in science and how the body works. He was very good with his hands and he taught me how to make things, which helped me in my career as an experimental scientist. When I was 16, I took "A" (= Advanced) level exams in Physics, Chemistry and Biology, which are the final national exams taken before entry into college. I stayed on at Felsted for another year concentrating on biology. I liked science and found it relatively easy, apart from the more mathematical aspects, a failing I still have. I was influenced by several teachers at Felsted, with the most notable being my biology teacher, **David Sturdy**, who instilled in me a passion for biology. During my final two years at Felsted, he gave me one-on-one tuition, and introduced me to the subject of biochemistry, teaching me the basics of glycolysis and the mitochondrial tricarboxylic acid cycle. He also encouraged me to do my first field experiments most of which turned out to be notable failures. It was really his influence that led me to "read" (i.e. specialize in) biochemistry at Cambridge - at the time, it was a vibrant area of science bringing together the wonders of biology with the rigor of chemistry. You have to realize that when I started as a graduate student in 1965, the genetic code was still being worked out and molecular biology was in its infancy!

My father was a University of Cambridge alumnus, and so it was natural that I should apply to Cambridge, and in fall of 1960 I took the University of Cambridge entrance exam and won a scholarship at Gonville and Caius College my father's college, apparently on the strength of my answers in the biological sciences sections of the exam. After leaving Felsted at the end of 1961, I had a "gap year". For the first three months of 1962, I was an exchange student in a doctor's family in a small village in southern Germany with goal of learning German. When I got back, I worked in an organic chemistry laboratory at Wye College (part of the University of London), which is five miles from my home in Ashford, before starting at Cambridge in October 1962. I took a Natural Sciences degree - for the first two years I did courses in Biochemistry, Organic and Inorganic Chemistry, Invertebrate Zoology and Experimental Psychology. Biochemistry was the most exciting (and popular) subject, and for my final year I did Biochemistry honors (Part II), and ended up with a first class degree (BA) in June 1965. We had excellent lecturers, but the most exciting were the guest lectures by Fred Sanger, Max Perutz, and Sydney Brenner. My 1965 Part II class of 40 students included Bruce Ponder and Andrew McMichael, both of whom were subsequently elected to the Royal Society.

I hadn't really thought about what I would do after getting my BA degree, but towards the end of my final year in the Department of Biochemistry, one of the lecturers suggested that I should apply to join the department graduate program indicating that I would be admitted if I got a first class final degree. New graduate students had to select a thesis advisor before they started, and I chose to work with Asher Korner, who had given us

some of the most interesting Part II lectures, and who was the only faculty member in the department who was doing any sort of molecular biology. He was trying to understand how growth hormone increases the rate of protein synthesis in the liver. In October 1965, after a 10-week road trip from London through Turkey, Syria, Lebanon, Jordan, Iraq, Kuwait, Iran and back (Slide 5 - Petra Canyon), I joined Asher's lab, which had 8 other graduate students – these included Tim Hunt (future Nobel Prize winner and Fellow of the Royal Society), Brigid Hogan (future FRS), and Richard Jackson (future FRS), all of whom were working on different aspects of protein synthesis - it was a great intellectual environment in which to begin my scientific career.

My thesis project was to investigate the mechanisms through which mammalian cells make proteins, and a major part of my research was done together with my fellow student Tim Hunt working on rabbit reticulocytes as a simplified model system – reticulocytes are immature red cells whose job is to make hemoglobin, the oxygen carrier protein of red cells. Tim and I published several papers together. Towards the end of my graduate research in 1968, I was encouraged to apply for a Research Fellowship at my own college (Gonville and Caius) and at Christ's College (at the suggestion of Alan Munro, who had become my surrogate adviser when Asher Korner left Cambridge in my second year as a student to become Chair of Biology at the newly founded University of Sussex - I didn't follow him). I was lucky enough to be awarded a four-year research fellowship at Christ's College, which enabled me to live in college, and to continue independent research in the Department of Biochemistry for the next four years, running my own (small) lab. (Slide 5 –chromatography and Slide 6 - passport picture)

The formative step in my career was when I took a two-year break from my college fellowship to join Walter Eckhart's lab at the Salk Institute in La Jolla as a Research Associate in 1971. My first wife, Pippa Marrack, a graduate student in Alan Munro's lab, had arranged to do a postdoc with Dick Dutton, an immunologist in the Department of Biology at UCSD across the street from the Salk, and Alan, who had done a one year sabbatical at the then brand new Salk Institute in 1966, had suggested that I join Walter's lab. Walter was using polyoma virus, a small DNA tumor virus that causes cancer in rodents, as a cancer model in the hope it might give insights into how normal cells become cancer cells. Once I arrived at the Salk, I began to inveatigate how polyoma virus replicates its DNA genome with another postdoc on the lab. It was a great experience, and my first entrée into cancer biology, although I must admit that moving from Cambridge with all its history to freewheeling California in the 1970's was something of a culture shock, but I soon adapted (and grew my hair and beard long) (Slide 7 - long hair/beard). By the end of my two years, Pippa and I had split up, and I returned to Cambridge alone for the final year of my fellowship, while she stayed in the US (she also became an FRS!). Once back in Cambridge in 1973, I started working on protein synthesis again and began applying for faculty jobs. Both the Department of Biochemistry and the Imperial Cancer Research Fund (ICRF) in London turned me down (even though I had published three *Nature* papers and two *JMB* papers, among others), but luckily the Salk Institute, which was only 7 years old at the time, had just begun to appoint its first group of Assistant Professors. I had been offered one of these positions (without any interview!) before I left, and in the end with no job in the UK in sight I returned to California, where I started as an Assistant Professor in 1975, and started working on tumor viruses again (Slide 8 - green card). I have been at the Salk Institute ever since, and don't for one minute regret leaving the UK!

When I rejoined the Salk in 1975, I became a member of the newly formed Tumor Virology Laboratory (TVL), which included Rudolf Jaenisch, Inder Verma, Hung Fan and Bart Sefton, as the other newly appointed Assistant Professors, all working on different RNA and DNA tumor viruses. The TVL was an amazing and vibrant scientific environment, and there were a lot collaborations, because each of us only had a few people in the lab. It was natural for me to continue to work on polyoma virus, and I began using in vitro translation methods that I had learned when back in Cambridge to try to identify the virally encoded transforming proteins, called tumor or T antigens that convert normal cells into cancer cells. Together, with Walter Eckhart, and Ted Friedmann at UCSD, who had just completed the nucleotide sequence of the small polyoma virus genome, we found that polyoma virus uses alternative splicing of a single viral RNA to make three overlapping T antigens - large, middle and small T antigens. The most important for transforming normal cells into tumor cells turned out to be middle T. (Slide 9 – Baja trip)

Karen Beemon joined the lab in 1976 as my first postdoc from the University of California, Berkeley, where she had recently completed her Ph.D. on the structure of the genomic RNA of Rous sarcoma virus (RSV), another animal tumor virus. Karen brought her RSV stocks with her when she came, and this proved to be a lucky happenstance. Karen and I set out to try and identify the transforming protein of RSV by in vitro translation of virion genomic RNA in a reticulocyte lysate protein synthesis system. We succeeded in identifying truncated forms of the *src* gene product, but we were pipped at the post in the discovery of the v-Src protein by Joan Brugge and Ray Erikson in Denver. Nevertheless, my laboratory was now firmly established in the RSV field and over the next two years, largely in collaboration with Bart Sefton, another new Assistant Professor in the TVL, we characterized the v-Src protein.

In 1978, Marc Collett and Ray Erikson made the seminal discovery that v-Src had protein kinase activity, which adds phosphate to proteins. This finding implied that malignant transformation of cells by RSV involves aberrant protein phosphorylation. This was such a provocative discovery that almost immediately every group in the world working with viral transforming proteins tested their own protein to see whether it had protein kinase activity. We were no exception, and examined whether any of the polyoma virus T antigens had protein kinase activity. Early in 1979, Walter Eckhart and I found that the polyoma middle T became phosphorylated in the immune complex protein kinase assay that had been used to show that v-Src had protein kinase activity. This suggested that middle T might also be a protein kinase (although we now know that this is not an intrinsic activity of middle T but rather due to its association with the cellular Src kinase). It was in the course of determining which amino acid residue was phosphorylated in middle T that I made the unexpected finding that the phosphate incorporated in middle T is linked not to the conventional serine or threonine, but rather to tyrosine. As some of you know, this discovery was entirely serendipitous, and resulted from me being too lazy to make up fresh electrophoresis buffer for separation of phosphoamino acids, and using and old buffer instead. In the critical experiment where I analyzed which amino acid was phosphorylated in middle T, an unexpected radioactive spot appeared (Slide 10 – new spot), and my biochemical training led me to guess that this might be phosphorylated tyrosine, which turned out to be the case - as they say chance favors the prepared mind. (Slide 11 - river)

Our discovery that polyoma middle T is associated with a tyrosine kinase activity was quickly followed by our finding that the RSV v-Src protein is also a tyrosine kinase – this discovery was also made quite by accident – I was using v-Src as a control that should have phosphorylated threonine, but to my amazement it also phosphorylated tyrosine. In a very productive collaboration with Bart Sefton, we quickly showed that there is phosphotyrosine in proteins in all mammalian cells, that v-Src itself is phosphorylated on tyrosine in cells, and that RSV-transformed cells have greatly elevated levels of phosphotyrosine in protein. Shortly afterwards, Owen Witte and David Baltimore found that the Abl transforming protein of Abelson murine leukemia virus also has tyrosine kinase activity. This was quickly followed by reports from other groups that several additional viral transforming proteins had a similar tyrosine kinase activity, and that the cellular EGF receptor is also a tyrosine kinase. Within the next few years, human oncogenes that encode tyrosine kinases were discovered, which like v-Src, are constitutively active.

We now know that about half of all the 90 human tyrosine kinases play a role in cancer. Ultimately this led to the development of a new class of cancer drugs, called TKIs, that inhibit oncogenic tyrosine kinases. The first TKI drug approved for human cancer therapy was Gleevec, an inhibitor of the BCR-ABL tyrosine kinase that causes chronic myelogenous leukemia. Gleevec proved to be a wonder drug, and many of the treated CML patients who went into remission in 2001 are still taking Gleevec. This striking success has led pharma to develop many additional TKIs that block other oncogenic tyrosine kinases for the treatment of specific cancers – as of last month 32 TKIs have been approved for cancer therapy (Slide 12 - TKIs). This is a remarkable outcome of discoveries made with two simple tumor viruses, and a strong justification of continuing funding for basic research

The 1979 discovery of tyrosine phosphorylation was the turning point in my career, and has had a major influence on what I have done for the past nearly 40 years. As a result, I became interested not only in the role of tyrosine phosphorylation in regulating cell function and triggering cell transformation, but also in protein phosphorylation in general. We have gone on to study many types of protein kinase and their downstream

targets. We have cloned new tyrosine kinases and phosphotyrosine phosphatases and characterized their functions, and we have expended a lot of effort in identifying substrates for oncogenic and growth factor receptor tyrosine kinases, mapping tyrosines that are phosphorylated in target proteins, and trying to elucidate what these tyrosine phosphorylation events do. Through Jon Pines, a postdoc who came to me from Tim Hunt's group, we made an entrée into the cell cycle, cloning the first human cyclins in 1989. Ironically, this led us straight back into the field of protein phosphorylation when it was discovered that the cyclins are activating subunits of the key regulators of the cell cycle, the cyclin-dependent kinases. Our most recent work is on yet another type of protein kinase that phosphorylates histidine in proteins, and we have just obtained the first evidence that this may also play a role in cancer.

In retrospect, there was no defining moment that led me to be a scientist. My father had interested me in the biomedical sciences, but had dissuaded me from becoming an MD, because he was critical of the National Health Service system in the UK, which he felt did not reward initiative and excellence. As will be apparent from my early career history, my choice to become a researcher was not driven by a burning desire to do research or cure disease, but in many ways it was serendipitous and relied largely on being in the right place at the right time, having some talent, and being lucky enough to have mentors that recommended what steps to take next. Certainly, I would not have become involved in cancer research, unless I had come to the Salk Institute, and this only happened because I followed my first wife to San Diego! Of course, I have no regrets that this is how it all worked out!

Let me finish by thanking all the people who have helped me and mentored me both in life and in science. First, my wife Jenny and our two sons, Sean, a graduate student in Cancer Biology at Stanford, and James for supporting me and putting up with my long hours in the lab and my many absences from home to attend meetings and advisory committees around the world. Then of course Alan Munro and Walter Eckhart who between them influenced me to become a cancer biologist - Alan who served as a surrogate adviser and suggested that I come to the Salk Institute, and Walter who took me on sight unseen as a postdoc, and then gave me my first job. In addition, I am indebted to my many scientific colleagues at the Salk, including Karen Beemon, Walter Eckhart, Bart Sefton, Jon Cooper, Gernot Walter, Inder Verma who all played key roles in my early independent career and the discovery of phosphotyrosine, for which I am being recognized by the 21st Pezcoller-AACR Award.

It seems like a long time since I discovered tyrosine phosphorylation 40 years ago, but an amazing amount has been learned since then about the importance of this process, and the payoff in understanding and treating human disease has been remarkable and gratifying. Let me end by thanking the Pezcoller Foundation again.