

## Harren Jhoti

President, Master, Graduates and Graduands, Guests, and Colleagues

Today it is my great honour to welcome Dr Harren Jhoti to a Fellowship at Birkbeck, University of London.

“A man needs a little madness or else he never dares to cut the rope and be free”

(Zorba the Greek)

This is the aphorism that Jhoti quoted at the start of his 1989 Birkbeck PhD thesis, entitled “X-Ray Structural Studies on Transferrins”, (transferrin is a protein that carries iron around in the blood). Dr Jhoti is famous for applying crystallography to drug design. He is a man who has cut many ropes and, in the process, freed not only himself but many others suffering from certain forms of cancer.

Anyone in this room can call that thesis up in our library and, along with studying his analysis of the X-ray structure of serum transferrins, can read a tribute to his Birkbeck supervisors, Peter Lindley and Beatrice Gorinsky, his mentor Tom Blundell, and those he calls his “friends at Birkbeck, especially the ‘EB10 crowd’” (that is, the Extension Building, room 10, crowd). He then dedicates his thesis to his mother, who had died of ovarian cancer when he was a young man.

In the 1980s, though, Jhoti was like many in this room: he was studying at University. There was a BSc (hons) at Queen Mary College, before he came to Birkbeck to work in our world-

renowned crystallography department. In 1986, he completed his MSc in X-ray Crystallography at Birkbeck, followed just three years later with his PhD. The PhD honed in on the crystal structures of the full-length rabbit transferrin and a single-domain duck protein. This helped us understand the molecular basis of iron uptake and transport.

After a Wellcome Trust-funded postdoctoral fellowship at the University of Oxford, working in the laboratory of the formidable Professor David Stuart, he was appointed by Glaxo in Greenford (then GlaxoWellcome and now GlaxoSmithKline) as a research scientist, became Head of Structural Biology and UK Bioinformatics there, and, within five years, had established one of the largest and fully integrated structure-based drug design groups within the pharmaceutical industry. Jhoti was responsible for managing a vast array of activities, including molecular biology, protein expression, protein crystallography, NMR, Computer-aided Drug Design, protein informatics, pathway analysis and systems biology. He applied structure-based drug design, seeking to target HIV protease, Thrombin, and multiple kinases. This was where he developed novel methodologies for protein informatics and applied to target validation, pathway analysis and chemogenomics.

Although it was formidable and impressive work, it was not enough. In 1999, Jhoti dared even more “to cut the rope and be free”. He left his safe and secure job at GlaxoWellcome, gave up the company car (much to his father’s dismay), and reinvented himself as a science entrepreneur. He was one of three scientific founders of Astex. The other two were Sir Tom Blundell (the famous structural biochemist who had had taught Jhoti at Birkbeck, but had subsequently left to go to Cambridge) and Chris Abell, who is now Professor of Biological Chemistry and pro-vice chancellor for research at the University of Cambridge. Roberto Solari, a colleague from Glaxo who had moved to the investment firm Abingworth Management, was also instrumental in founding Astex. Abingworth, together with Oxford Biosciences, provided £800,000, the initial seed funding for the company. This was followed, in 2001, with a larger investment of £28.4m. From two rooms (complete with a couple of office chairs from Argos) above an accountancy firm in Wellington Street, Cambridge, they moved to the Cambridge Science Park.

As Chief Scientific Officer and then President and CEO, Jhoti built up Astex from nothing to become one of the world's leading drug discovery and development companies. This needed large sums of money. Jhoti raised over £80M from venture capitalists and big pharma companies. In 2013, as a leader in the field of Fragment-based drug discovery, Astex was sold to Otsuka Pharmaceuticals for \$886m, one of the largest global deals in the biotech/pharma sector. Astex has discovered and then developed four novel cancer drugs.

Their wild success was due to new practices and technologies. Astex set about using high-throughput X-ray crystallography to develop fragment-based drug discovery. Using new technologies and methods, they developed clinical-stage drugs. Initially, their fragment-based drug discovery was not welcomed by the pharmaceutical industry: it is now an approach used throughout the industry and in academia. Indeed, his 'Rule-of-Three – that is, defining “molecular characteristics of useful fragments in terms of molecular weight, hydrogen bond donors and acceptors, numbers of rotatable bonds and lipophilicity” – is now widely accepted. In the words of Nature Reviews Drug Discovery, “the fundamental concept of fragment screening is to use simpler molecules so that the chemical space can be sampled much more efficiently than is possible when using molecules of greater complexity”. Fragment-based drug discovery has revealed “drug candidates with better physico-chemical properties than those generated from conventional screening strategies”.

Crucially, the new methods and technologies have dramatically cut the amount of time required to determine the three-dimensional structure of a target protein. In the 1980s, Jhoti and Andrew Leach (from Glaxo) later recalled,

it could take several years to determine the crystal structure of a key drug target; obtaining structures of bound inhibitors could consume several more months. [But] Today, protein crystal structures may be obtained in months rather than years and subsequent protein/inhibitor complexes often only take weeks (if not days) to solve.

Closest of all to his heart is his drug discovery programme in oncology. His beloved mother, to whom he dedicated his PhD so many years previously, had died of ovarian cancer. Today, Astex has two approved cancer drugs to its name. KISQALI was developed after using X-ray crystallography to determine, for the first time, the three-dimensional structure of a protein called CDK4 that is involved in the initiation and progression of breast tumours. The drug works by inhibiting the protein. In 2017, KISQALI was approved for Astex's partner Novartis by the US Food and Drug Administration (FDA) and also by NICE in the UK. Just this year, ERDAFITINIB (which is marketed as BALVERSA), was approved by the FDA to treat certain cases of advanced urothelial cancers. These drugs have real effects on real lives.

He has published in Nature and Science. His list of publications in other high-rated journals goes on and on. In 2005, he was named a "Technology Pioneer" by the World Economic Forum. He was named by the Royal Society of Chemistry as "Chemistry World Entrepreneur of the Year" in 2007. In 2012, he received the Prous Institute-Overton and Meyer Award for New Technologies in Drug Discovery from the European Federation for Medicinal Chemistry. Fellow of the Academy of Medical Sciences in 2015. Fellow of the Royal Society of Chemistry in 2016. In 2018, he was honoured with a Lifetime Achievement Award from the UK BioIndustry Association (BIA). He was elected a Fellow of the Royal Society in 2018, the highest accolade in UK science and recognises individuals for their scientific excellence and substantial contributions to research endeavours. He serves and has served on numerous Boards, including the UK BioIndustry Association and consults for life science venture capital firms.

Jhoti is also a Birkbeckian. All those years ago, he was a student like all of you here today. For him, our College's commitment to diversity and inclusiveness is important, as is the way

the College nurtures entrepreneurial spirits. Dr Jhoti supports Birkbeck's mission to provide access to university to forced migrants and, as such, has made a major donation to the Compass Project.

But what about the man? He was born in India, but his Sikh parents brought him to Swindon when he was two years old. His parents had a one-third share in a shop on a council estate which they ran. Jhoti attended a comprehensive school at a time when there were very few Indian faces to identify with. Education was important to his family: they were proud when he was the first in his family to go to university.

His love of science had been nurtured from an early age. His father enjoyed giving him presents of chemistry sets and microscopes. A Chemistry teacher who told him that he "shouldn't take chemistry as I was really poor at it", simply made him grasp the challenge. As he told one interviewer, his "Eureka moment" occurred when he was at junior school. "It was a very sunny day", he observed "and it struck me what a beautiful blue colour the sky was". But when he asked his teacher "why it was blue" she was stumped. It was, after all, "a very complex question."

This anecdote is, I think, typical of The Man. Jhoti is a complex man – alert to beauty and music. While an undergraduate at Queen Mary, he (as bass-player) and some friends formed a band, Emperor's Clothes. They took a year off to try to "make it big" and, when that dream didn't work out, returned to his first love, structural biology. Being knocked back by record companies taught him one important lesson: "don't take 'no' for an answer.

He is a people's person: superior at attracting and retaining staff.

Here are just a few of the things that friends and colleagues said about him:

He is single-minded but accessible; a father-figure to everyone, even those who are much older than him. He has absolute integrity; is very personable: a genuinely nice guy and very

popular. He is also driven and tenacious. He is brilliant at building teams which, in his business, is essential. He is a David Bowie fan: collects his music, has a painting by him, and is working his way through Bowie's reading list of 100 top books.

Jhoti is also a feminist. He is keen to encourage women in science. He is married to Kate Hilyard, also a scientist, whom he met while at Oxford and married in 1993. He dotes on his two daughters, Elisha and Anya, both highly talented in astrophysics and international relations.

In July this year, Astex celebrated their 20<sup>th</sup> anniversary. They did it in style – with a contortionist, magician, jugglers, and strongmen, at Longstowe Hall, Cambridgeshire. Jhoti said: "I don't think in any moment of madness I imagined I would be standing here 20 years later with the company still going." It was a repeat of that Zorba the Greek's comment on the front of his PhD: "A man needs a little madness or else he never dares to cut the rope and be free".

It is a great pleasure to formally welcome Harren Jhoti to a College Fellowship at Birkbeck.