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50 & 100 YEARS AGO

50 YEARS AGO

Among the numerous well-known scientists who were born in 1857... Ronald Ross is widely known, for the story of his long and patient attempts to identify the carrier of malarial fever has often been written... An outstanding centenary of the present year is that of the birth of Heinrich Rudolf Hertz, the German physicist, who was the first to detect electromagnetic waves in free space and measure their velocity... Elwood Haynes (1857–1925) is another American who should be remembered this year. He discovered several important alloys, including tungsten chrome steel, and in 1919 filed a patent for stainless steel... The question of the inheritance of acquired characteristics has recently received much attention. An early worker in this field of research was the Danish botanist W. L. Johannsen (1857–1927). One of the founders of modern research in heredity, he introduced the terms 'pure line', as well as 'gene', 'genotype' and 'phenotype'.

From *Nature* 5 January 1957.

100 YEARS AGO

In a recent note attention was directed to the recent renewal of experiments with Count Zeppelin's latest airship on the Lake of Constance... The 1906 Zeppelin airship...is 11 metres high, and each of the two cars can hold four persons, besides having a separate motor. The author states that with both motors working simultaneously a speed of 15 metres per second, or 54 kilometres per hour, can be maintained for sixty hours with the quantity of benzene the machine will carry... The advantages of the Zeppelin airship are more or less counterbalanced by the present necessity of using a sheet of water for starting and landing. Apart from the uses of such a machine in warfare, its applications in time of peace to the meteorological survey of the atmosphere are contemplated.

From *Nature* 3 January 1907.

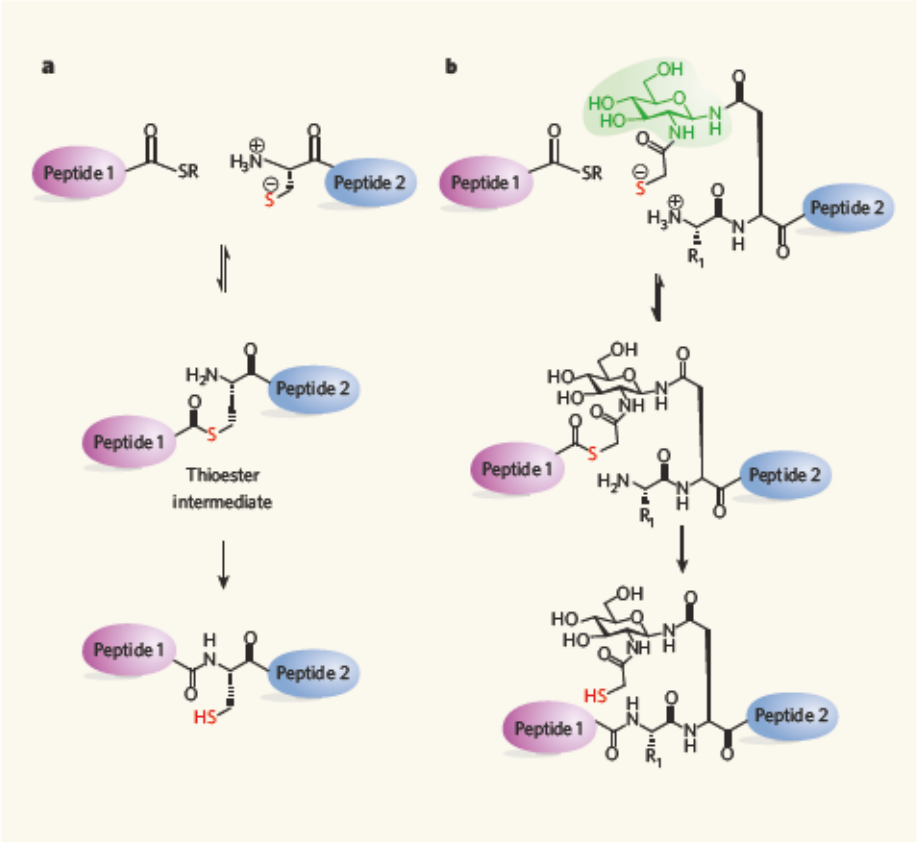

Figure 1 | Glycopeptide synthesis. **a**, Native chemical ligation is a well-established method for preparing peptides. A reactive sulphur atom (red) on the side-chain of a cysteine amino acid attacks another peptide (where R is typically a phenyl ring), producing a thioester intermediate that spontaneously rearranges to yield a peptide bond. **b**, Brik *et al.*[1] have modified this method to prepare glycopeptides, in which sugars are attached to peptide chains. A reactive sulphur atom (red) attached to an appended sugar (green) acts as a surrogate for the cysteine side-chain. Peptide bonds can thus be formed between a greater variety of amino acids. R_1 represents an amino-acid side-chain.

larger polypeptide. Moderately sized proteins have been produced in this way by sequential ligation of several peptide fragments, or through the coupling of a peptide to a larger protein fragment. Crucially, native chemical ligation provides exquisite control over the protein structure being formed, and allows the incorporation of various useful groups — such as synthetic amino acids, biophysical probes or stable isotopes of atoms used for structural studies — into selected sites within proteins[3,4].

Building on this approach, Brik and colleagues[1] attached a reactive sulphur group to a sugar within a peptide (Fig. 1b). In a process similar to the two-step mechanism for native chemical ligation, the authors reacted this sulphur group with a second peptide to form a thioester intermediate. This intermediate subsequently rearranges to give the desired product, in which the two starting materials are linked by a peptide bond. This strategy[1] has several remarkable features. Native chemical ligation requires cysteine — a sulphur-containing amino acid — to be at the reacting end of one of the peptides being joined together. By placing a reactive sulphur group on the sugar of a glycopeptide, rather than in an amino acid, the authors circumvent this requirement, thus allowing bonds to be formed between a broader range of amino acids.

Moreover, a surprisingly wide array of amino acids is tolerated at the reaction site, thus permitting access to glycopeptides that are difficult to synthesize using other methods. Amino acids with small side-chains and those (such as histidine or aspartate) with side-chains that can serve as a base in the ligation pathway are favoured substrates in the reaction. Finally, the sulphur atom on the sugar provides a convenient handle for subsequent chemical manipulation — for example, it can be removed to give a naturally occurring sugar, reacted to append fluorescent dyes or other groups to the glycopeptide, or elaborated to form more complex sugars by using glycosyltransferase enzymes[1].

Further investigations are needed to assess the full scope of Brik and colleagues' reaction[1] and its potential application to glycoprotein synthesis. Nonetheless, the emergence of this and other methods[5–8] for constructing pure peptides and proteins with sugars installed at preselected sites has many implications. For example, such techniques could transform the way therapeutic glycoproteins are discovered, developed and manufactured. Many of these proteins are obtained only as a mixture of glycoforms, just a fraction of which may