Text box: **The science behind Lemaitre's Toll Discovery**.

To appreciate the state of scientific research before Lemaitre made his discoveries, let's look at a paper by one of the main US labs. In their 1993 Cell paper 'Dif, a dorsal-Related gene that mediates an immune response in Drosophila', Michael Levine's group at UCSD set the scene as follows:

1. Insects have an innate immune response to bacterial infection – they produce peptides that have antimicrobial properties, binding and disrupting the bacterial cell wall.
2. Several groups had cloned the genes for these peptides and discovered regulatory sequences in their promoter regions. In Strasbourg, this research was conducted by JM Reichhart.
3. One of the promoter sequences resembled the binding site for the mammalian transcription factor, NF-kappaB (Nuclear Factor kappa-light-chain-enhancer of activated B cells). In mammals, this protein appeared to regulate the acute phase response of the innate immune system – when we're infected, our livers secrete a variety of proteins with protective roles (e.g. inactivating proteases, promoting wound healing). Many of these proteins are induced by the cytokine, interleukin-1 (IL-1) which activates the IL-1 membrane receptor and then the NF-kappaB transcription factor.
4. In Drosophila, the equivalent of NF-kappaB was thought to be the transcription factor, dorsal, a gene regulating the development of the dorsoventral axis in fly embryos. Furthermore, it emerged that "there are striking parallels between the regulation of gene expression along the dorsoventral axis of Drosophila embryos and lymphoid-restricted expression in the mammalian immune system."
5. This genetic regulation of dorsoventral pattern formation requires the "Toll signalling pathway" (the work of Kathryn Anderson in Tubingen and UC Berkeley). Toll is a transmembrane receptor protein: "activation of the Toll receptor initiates the nuclear transport of dorsal in the Drosophila embryo, while the activation of the IL-1 receptor mediates nuclear transport of NF-kappaB." In addition, notes Levine, "the cytoplasmic domains of the Toll and IL-1 receptors are related."
6. What was the factor regulating the production of antimicrobial peptides in the insect's immune response? Levine's group had just discovered the dorsal-related immunity factor (Dif) which, as its name implied, was similar to the dorsal protein but mediated an immune response in Drosophila embryos. Levine states that "these results suggest that mammalian and insect immunity share a common evolutionary origin."
7. Meanwhile, in Strasbourg, JM Reichhart's group were still convinced that dorsal was the key regulatory factor.
8. Bruno Lemaitre joined Reichhart's group in 1992 (age 27). He had just obtained his PhD in Paris, using genetics to identify the regulatory mechanisms of transposable P elements in Drosophila. He was the first geneticist to join the Strasbourg lab. His initial project was to use genetic analysis to test the hypothesis that dorsal was the immune regulator.
9. His study soon showed that dorsal was not involved in the injury induced expression of diptericin, an antibacterial peptide (Lemaitre et al. EMBO J 1995).
10. At this point, Lemaitre explains, Reichhart decided to continue to look for the regulatory factor using many of the biochemistry and molecular biology techniques his group had already employed. Lemaitre decided to continue his genetic studies.

11. From fly stock centres in the US and Tubingen, Germany, Lemaitre had already obtained many flies with mutations related to the Toll signalling pathway (since it was already known to regulate dorsal). To these he added any fly mutations that might possibly have an effect on the immune response. He was also in direct contact with other fly genetic labs, including Michael Levine's.
12. In 1994, he discovered a new mutation – immune deficiency mutation (imd). Flies with this mutation could not resist bacterial infections (Lemaitre et al. PNAS 1995).
13. Around a year later, he discovered that although mutations for the Toll receptor did not affect their resistance to bacteria, it instead made them vulnerable to fungal infections (Lemaitre et al. Cell 1996).
14. Lemaitre continued his research and confirmed that imd and Toll represented two distinct regulatory pathways – one for the fly's innate immune response to bacteria, the other for fungal infections (Lemaitre et al. 1997 PNAS). Lemaitre presents his personal account of these discoveries in "The Road to Toll" (Nature Review Immunology 2004). This is a researcher's lab bench view of the research, together with key moments when chance, other labs, and good luck aided him.
15. In 1998, Lemaitre set up his own research group near Paris at the CGM (CNRS molecular genetics centre) where he successfully continued his genetics research on fly immunity. In 2006, he was appointed Full Professor of Genetics at Switzerland's Ecole Polytechnique Federale de Lausanne (EPFL).
16. A human Toll-like Receptor homolog, TLR4, was shown to "signal activation of adaptive immunity" (Medzhitov et al. Nature 1997).
17. Genetic evidence for TLR4 function in microbial recognition comes from the Beutler lab (Poltorak et al. Science 1998).