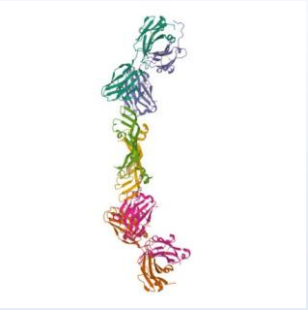

THE HISTORY OF AVASTIN

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1. Formulation and Development

- The development of Bevacizumab (Avastin) was driven by Genentech's pioneering recombinant DNA technology
- Avastin is a recombinant humanized IgG1 monoclonal antibody that binds with high affinity to human vascular endothelial growth factor (VEGF)[1].
- First approved for the treatment of colorectal cancer (2004), it was based on the hypothesis that tumour progression was driven by angiogenesis, with upregulation of VEGF in most human tumours[2,3], including gastrointestinal[4,5]

2. Lucentis Trials

- Ranibizumab (Lucentis) and Avastin are both engineered from the same anti-VEGF antibody
- Lucentis was thought to be more suitable for ophthalmic use due to its smaller size and higher VEGF affinity [Fig 1][6]
- Genentech proposed a intravitreal drug delivery methodology for Lucentis[7]
- Promising phase 1 and 2 trials showed its efficacy in neovascular age-related macular degeneration (AMD) but clinical approval was far behind Avastin

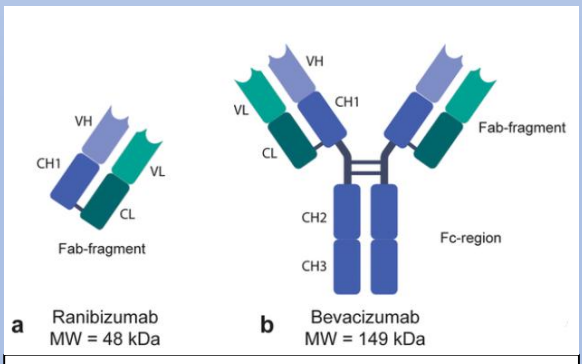

Figure 1. Difference in molecular structure between ranibizumab and bevacizumab

3. Systemic Avastin

- Due to concerns that regular intravitreal injections would be poorly tolerated, their long-term safety, and the earlier approval of Avastin by the FDA the Systemic Avastin for Neovascular AMD (SANA) study was designed and led by Professor J Rosenfeld.[7]
- The study, consisting of 18 participants followed up over 6 months, showed remarkable efficacy in long-term reduction of retinal fluid in neovascular age-related macular degeneration (AMD) [Figure 2][7]
- Despite promising results progress was halted due to concerns of thromboembolic events and haemorrhage associated with systemic therapy

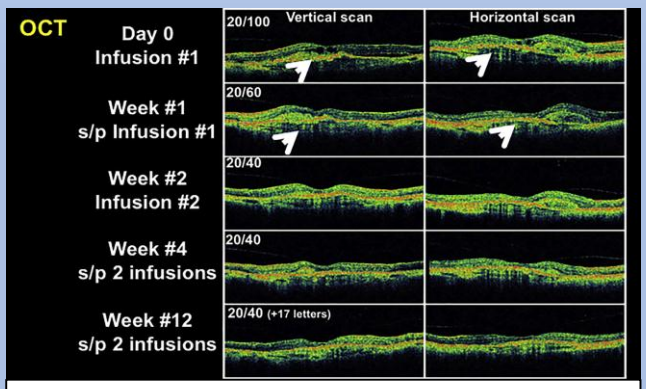

Figure 2. Results of systemic bevacizumab as seen in the SANA trial

4. Eureka

- With the setbacks faced with systemic Avastin, clinicians were faced with waiting for the completion and subsequent approval of phase III Lucentis studies prior to clinical use.
- Professor Rosenfeld had a eureka moment in 2005 in which he realised that both Avastin and Lucentis had similar molar concentrations and were similarly packaged.[7]
- In May 2005 the first individual received intravitreal Avastin with similar results to Lucentis [Figure 3]. This prompted the off-label use of Avastin, with adoption internationally by ophthalmologists.[7]

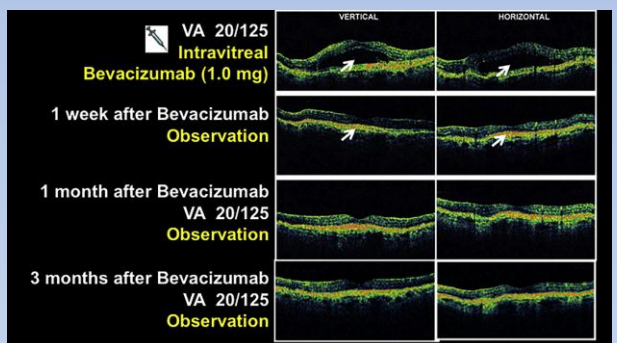

Figure 3. Pilot data of intravitreal Avastin in neovascular AMD

5. Impact

- The development and clinical implementation of Avastin revolutionised the treatment of exudative and neovascular ocular diseases internationally
- The disseminated use of Avastin and subsequent anti-VEGF therapies was critical in encouraging the adoption of OCT into routine clinical practice
- It was estimated that in the US alone, between 2008 and 2018, the use of Avastin saved Medicare approximately $50 billion[7]

6. References

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