

Institution: EaStCHEM School of Chemistry		
Unit of Assessment: UoA 8: Chemistry		
Title of case study: Expert witness testimony on protein structure and binding in <i>Amgen vs Sandoz</i> leads to a multibillion-dollar verdict that secures the future of <i>Amgen</i> and enhanced protection for biopharmaceutical patents		
Period when the underpinning research was undertaken: 2001 - 2015		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s): James Naismith	Role(s) (e.g. job title): Professor	Period(s) employed by submitting HEI: 01 January 1995 – 30 June 2018
Period when the claimed impact occurred: August 2019 – 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of the impact Key expert testimony by EaStCHEM Professor James Naismith helped to defend patents for <i>Amgen's</i> blockbuster biopharmaceutical <i>Enbrel</i>[®] (etanercept) by demonstrating their validity in a legal challenge from rivals <i>Sandoz</i>. This testimony was based on Naismith's research on protein structure, binding and function, in particular on binding modes of etanercept's target, Tumor Necrosis Factor α (TNFα). As a result of the court judgement, <i>Amgen</i> secured commercial exclusivity in the United States until 2029 and retained approximately USD5,000,000,000 pa in annual sales of <i>Enbrel</i>[®], their major revenue stream, which has helped to secure the jobs of its 22,000 people (employees). On news of the ruling, <i>Amgen's</i> market capitalization grew by over USD10,000,000,000. The verdict, which was upheld by the <i>United States Court of Appeals</i> in 2020, provides a landmark ruling for the protection of intellectual property in the emerging area of biopharmaceuticals in the US. This is both the most important market for medicines and most influential for patent jurisdiction. As a result, global incentivisation of the large up-front investment required to bring new medicines to market is maintained.		
2. Underpinning research Naismith's research credentials as expert witness EaStCHEM Professor James Naismith's research has established him as a world-leading expert in structural biology, blending structural analysis, mechanistic studies and new approaches to biochemistry to answer sophisticated chemical problems in biology. In particular, his research expertise has focussed upon establishing relationships between protein structure, binding and function, as well as probing their interactions with carbohydrates and polysaccharides [R1-R5]. Recognition for this work includes the award of the Colworth Medal, Corday Morgan Medal, Dextra Medal, Jeremy Knowles Medal and Tilden Prize; election to fellowships of the Royal Society of Edinburgh (2005), the Academy of Sciences (2012), the Royal Society (2014) and the American Association for the Advancement of Science (2016); and appointment to his current position as Director of the Rosalind Franklin Institute. These impressive research-based credentials, in addition to specific research expertise on the modes of binding to Tumour Necrosis Factor α (TNFα) [R6], resulted in Naismith being appointed as an expert witness whose testimony the Court could treat with confidence.		

Naismith's research of specific value as an expert witness for Amgen

Naismith's research has illuminated important biological mechanisms, paving ways to target specific disease pathways. Key to the outcome of the court case was Naismith's research expertise on Tumour Necrosis Factor Receptors (TNFR), which bind Tumour Necrosis Factor α (TNF α), a soluble cell signalling protein (cytokine). This binding event starts a signalling pathway that induces fever, apoptotic cell death, cachexia, inflammation and inhibits tumorigenesis and viral replication. Dysregulation of TNF production has been implicated in a variety of human diseases. Therefore, the use of a competitive inhibitor of the formation of the TNF α :TNFR complex has been identified as a viable therapeutic intervention to treat several autoimmune diseases, including rheumatoid arthritis and psoriasis, and other seemingly unrelated ailments, such as Alzheimer's disease, cancer or major depression. Fundamental to these efforts is a detailed structural knowledge of the TNF α :TNFR complex. Crucially, in an influential analysis of TNF α structure-function [R6], Naismith expanded and refined the theory that three plausible, but not equally likely stoichiometry-centred hypotheses could describe TNF α -binding to TNFR, forming a consistent picture of the TNFR superfamily binding capabilities. Therefore, variable lengths of amino acid sequences drive exquisite specificity in recognising their cognate ligands and flexibility of the receptor molecule enables optimisation of ligand interactions through a series of hinging movements. This detailed understanding of the TNF α -TNFR interaction positioned Naismith to be *the expert uniquely positioned* to assess possible binding modes of a chimeric inhibitor molecule, the biopharmaceutical etanercept, marketed by *Amgen* under the name *Enbrel*®.

3. References to the research

The underpinning research listed was supported by peer-reviewed grants (The Wellcome Trust 081862/Z/06/Z & 100209/Z/12/Z). All publications are peer-reviewed and published by well-regarded academic journals.

- R1.** C. Dong, K. Beis, J. Nesper, A.L. Brunkan-LaMontagne, B.R. Clarke, C. Whitfield, **J.H. Naismith** "Wza the translocon for E. coli capsular polysaccharides defines a new class of membrane protein". *Nature*, **2006**, 444, 226-229. DOI: [10.1038/nature05267](https://doi.org/10.1038/nature05267).
- R2.** W. Wang, S.S. Black, M.D. Edwards, S. Miller, E.L. Morrison, W. Bartlett, C. Dong, **J.H. Naismith**, I.R. Booth "The structure of an open form of an E. coli mechanosensitive channel at 3.45 Å resolution" *Science*, **2008**, 321, 1179-1183. DOI: [10.1126/science.1159262](https://doi.org/10.1126/science.1159262).
- R3.** R.A. Bryce, I.H. Hillier, **J.H. Naismith** "Carbohydrate-protein recognition: molecular dynamics simulations and free energy analysis of oligosaccharide binding to concanavalin A" *Biophys. J.*, **2001**, 81, 1373-1388. DOI: [10.1016/S0006-3495\(01\)75793-1](https://doi.org/10.1016/S0006-3495(01)75793-1).
- R4.** G. Hagelueken, B.R. Clarke, H. Huang, A. Tuukkanen, I. Danciu, D.I. Svergun, R. Hussain, H. Liu, C. Whitfield, **J.H. Naismith** "A coiled-coil domain acts as a molecular ruler to regulate O-antigen chain length in lipopolysaccharide" *Nat. Struct. Mol. Biol.*, **2015**, 22, 50-56. DOI: [10.1038/nsmb.2935](https://doi.org/10.1038/nsmb.2935).
- R5.** A. Plechanovová, E.G. Jaffray, M.H. Tatham, **J.H. Naismith**, R.T. Hay "Structure of a RING E3 ligase and ubiquitin-loaded E2 primed for catalysis" *Nature*, **2012**, 489, 115-120. DOI: [10.1038/nature11376](https://doi.org/10.1038/nature11376).
- R6.** H.T. Idriss, **J.H. Naismith** "TNF α and the TNF receptor superfamily: Structure-function relationship(s)." *Microsc. Res. Tech.*, **2000**, 50, 184-195. DOI: [10.1002/1097-0029\(20000801\)50:3<184::AID-JEMT2>3.0.CO;2-H](https://doi.org/10.1002/1097-0029(20000801)50:3<184::AID-JEMT2>3.0.CO;2-H).

4. Details of the impact

Following a hearing on 09-08-2019, District Judge Claire Cecchi of the District of New Jersey entered a permanent injunction against *Sandoz Inc.* [S1], denying its challenge to launch a copycat version of *Amgen's* drug *Enbrel*® (etanercept) and upholding the two patents that protect etanercept's active ingredient, thereby protecting *Amgen's* return on investment and fostering continuing research and development at the company. As a result of the ruling, *Amgen* has retained the ca. USD5,000,000,000 per year in annual sales of *Enbrel*®, and subsequently saw its market capitalization grow by over USD10,000,000,000, helping to secure the jobs of its

22,000 people (employees). The original judgement has since been upheld (01-07-2020) in *Amgen's* favour by the United States Court of Appeals [S2].

Patent challenge relating to the leading arthritis drug Enbrel in *Amgen vs Sandoz*

In 2018 U.S. pharmaceutical company *Amgen* brought a patent infringement action against *Sandoz Inc.* to protect their anti-inflammatory drug *Enbrel*[®], which is the leading prescription medication to combat rheumatoid arthritis and the second best-selling immunology drug in the U.S. The drug works by binding with and inhibiting Tumor Necrosis Factor α (TNF α), the “master regulator” of inflammatory immune response, which causes many autoimmune diseases through overactive response. The fusion protein, etanercept, is the first ever to be approved by the US FDA, generated by combining a Tumor Necrosis Factor receptor (TNFR) with a portion of a human antibody. *Enbrel*[®] is *Amgen's* top-selling product, with annual sales in the U.S. of approximately USD5,000,000,000 [S3].

Admitting infringement, *Sandoz's* defence challenged the validity of *Amgen's* two patents for etanercept and its method of manufacture. A federal court trial in 09-2018 sought to determine the validity of these patents based on the two legal principles of: (1) written description and enablement and (2) obviousness.

Expert testimony confirming unexpected binding properties and patent validity

Professor Naismith was accepted as an expert by the New Jersey Federal District Court based on his research expertise in protein structure and function and was called to give evidence on the 18-09-2018 [S1, S4]. Naismith was asked about two key issues alleged by *Sandoz* to invalidate the patents: (**issue 1**) the adequacy of the written description of the two key patents, as required to enable the reader to make and use etanercept; and (**issue 2**) whether etanercept had unexpected properties supporting the non-obviousness and therefore validity of the original patents.

In answering (**issue 1**), Naismith relied on his knowledge of biochemistry and carbohydrates [R1-R5] to testify that proteins can gain or lose weight depending on glycosylation. He concluded that TNF receptors with molecular weights of either 65 or 75 kD are the p75 protein used in etanercept, confirming that the patent as written would clearly direct the reader to the correct protein needed to manufacture etanercept. The written description also correctly directed the reader to the required protein in the *GenBank* database.

Judge Cecci noted: “*Naismith credibly testified that there was less than a one-in-a-million chance that the wrong protein would be produced by GenBank if an inquiry was made to retrieve the complete p75 sequence corresponding to one of the sequence identification numbers*” and that there was “*zero chance*” that any other protein would be returned by *GenBank* if the request included both sequence identification numbers noted in the patent [S1, p19]. The judge ruled in light of Naismith's testimony that the written description of the patents was valid [S1].

In answering (**issue 2**), Naismith drew on his specific analysis of the properties of the TNF α :TNFR complex [R6]. He explained that fusion proteins like etanercept can bind to TNF in either one of two ways: (1) Mode 1 binding, which occurs when a bivalent fusion protein binds two TNF cytokines at each of its two separate binding sites; or (2) Mode 2 binding, which occurs when a bivalent fusion protein binds one TNF with both binding sites. Although Mode 2 binding is uncommon in proteins similar to etanercept, because the receptors have to be precisely arranged for Mode 2 binding to work, etanercept surprisingly engages in Mode 2 binding. Naismith testified that etanercept's unexpected ability to bind in Mode 2 has important consequences that underpin its powerful ability to neutralize TNF. With Mode 1 binding, aggregation would result in the body, leading to further inflammation; with Mode 2 binding, in contrast, little to no aggregation occurs. Moreover, Mode 2 binding is more efficient, a result that would not have been expected from the prior art and provides a 1000-fold increase in TNF neutralization.

Judge Cecci found that *“Dr. Naismith credibly explained that a POSA (Person of Skill in the Art) in 1990 would have expected etanercept to bind in Mode 1 because Mode 1 had fewer limitations”*. Since it bound in Mode 2, Judge Cecci concluded that etanercept had *unexpected* properties, rejecting arguments made by Sandoz that the patents covering Enbrel’s active ingredient until 2029 were invalid because of their obviousness [S1].

Economic impact of Amgen vs Sandoz for Amgen

As a result of the ruling, Amgen has retained the approximately USD5,000,000,000 per year in annual sales of *Enbrel®*, its major revenue stream, and has subsequently seen its market capitalization grow by over USD10,000,000,000, both helping to secure the jobs of its 22,000 employees [S3]. Immediately after the ruling, shares of Amgen closed up at approximately 6% at USD196.25 and rose by another 4.5% the following Monday, 12-08-2019 [S5]. Amgen’s stock rose a further 7% to USD252.45 on the news of the Appeals court ruling upholding the verdict in favour of Amgen in 07-2020 [S6]. Analysts have noted that *“The positive ruling helps to de-risk Amgen revenues which relied heavily on Enbrel...”* and *“removes a critical overhang for the company as Enbrel... is a significant component of the base commercial business and a meaningful contributor of revenue, cash flows and dividend capacity”* [S5, S7].

An attorney at Richards Patent Law PC, not involved in the case, noted the great impact of this ruling for Amgen, stating [S8]: *“A win for Amgen strengthens its patent portfolio by further solidifying its granted monopoly for the life of its remaining patents, including licensed patents.”*

Broader impact of Amgen vs Sandoz: incentivising research in biopharmaceutical development

The verdict in favour of Amgen has major implications for the commercial development of biopharmaceuticals, which is of growing importance to the pharmaceutical industry. It sets a clear precedent in protecting a company’s return on its very significant investment into the development of a biopharmaceutical, and therefore incentivises continuing research and development. Amgen’s CEO and chairman declared of the verdict [S9]: *“We are pleased with today’s decision recognizing the validity of these patents. Protecting intellectual property is critical to incentivize innovation and the large investments in research and development that are required to bring new medicines to patients and fully develop their therapeutic potential for patients.”*

IP analysts have noted that, against a *“scarcity of biologics (biopharmaceuticals) patent case rulings”*, the case provides *“an interesting precedent for how future decisions may treat biologics patent issues”* [S10]. With respect to the role of scientific evidence in deciding written description legal arguments in particular, the case is seen as *“a good example for patent owners of the types of evidence that can overcome those sorts of arguments”* [S10].

5. Sources to corroborate the impact

- S1.** Court judgement: *Immunex Corp et al. vs. Sandoz Inc. et al.* including quotes from the judge’s assessment of the impact of Naismith’s testimony.
- S2.** Court of Appeals judgement. Supports that the original judgement in [S1] was upheld.
- S3.** “Amgen Has 10 Billion Reasons to Cheer Patent Validity Ruling”. Article from the New Jersey law journal, 14-08-2019. This article summarizes the salient points of the court ruling. <https://www.law.com/njlawjournal/2019/08/14/amgen-has-10-billion-reasons-to-cheer-patent-validity-ruling/>
- S4.** Report by IPD Analytics, engaged by Amgen, to assess the progression of the trial. Supports the claim that Professor Naismith was accepted as an expert witness based on his research expertise in protein structure and function
- S5.** “Amgen stock gets boost from Friday ruling on Enbrel”. Marketwatch article detailing the continuing financial impact into the following week of the ruling on Amgen’s market capitalization, 12-08-2019. Supports the claim of positive financial impact that the ruling had for Amgen. <https://www.marketwatch.com/story/amgen-stock-gets-boost-from-friday-ruling-on-enbrel-2019-08-12>.

- S6.** “Amgen Wins Appeals Court Ruling Upholding Patents on Enbrel (3)”. Article from Bloomberg, 01-07-2020. This article provides analysis of the economic impact of the Court of Appeals ruling. <https://news.bloomberglaw.com/health-law-and-business/amgen-wins-appeals-court-ruling-upholding-patents-on-enbrel-1>.
- S7.** “The Biggest Biotech Stock Is Approaching A Breakout — Here's Why”. Article from investors.com, 12-08-2019. Corroborates the quote from Credit Suisse analyst reporting on the wider impact that patent protection affords companies like *Amgen* in terms of de-risking investment in these companies. <https://www.investors.com/news/technology/amgen-stock-buy-point-judge-upholds-enbrel-patents/>.
- S8.** “Battle for Enbrel: Ruling on patent lawsuit could transform US biosimilar marketplace”. Article from healio.com, 10-06-2019. Corroborates the quote from a patent lawyer not involved in the case, on her assessment of the impact of the court ruling. <https://www.healio.com/news/rheumatology/20190610/battle-for-enbrel-ruling-on-patent-lawsuit-could-transform-us-biosimilar-marketplace>.
- S9.** Amgen press release. Corroborates the quote from *Amgen*’s CEO on his assessment of the positive impact of the court ruling.
- S10.** “Breaking Down Amgen's Win In The Biosimilar Enbrel Patent Fight”. Article on biosimilar.com, 17-09-2019. Article authored by IP expert that provides an independent opinion on the positive IP implications from the court’s decision. <https://www.biosimilardevelopment.com/doc/breaking-down-amgen-s-win-in-the-biosimilar-enbrel-patent-fight-0001>.