

Institution: University College London		
Unit of Assessment: UoA5 Biological Sciences		
Title of case study: AbYsis: Tools and resources accelerating development of antibody-based drugs		
Period when the underpinning research was undertaken: 2004 - 2020		
Details of staff conducting the underpinning research from the submitting unit:		
Name(s):	Role(s) (e.g. job title):	Period(s) employed by submitting HEI:
Andrew C.R. Martin	Professor of Bioinformatics & Computational Biology	2004 - Present
Period when the claimed impact occurred: 1 August 2013 to 31 December 2020		
Is this case study continued from a case study submitted in 2014? N		
1. Summary of Impact (indicative maximum 100 words)		
<p>Novel antibodies represent approximately a third of all drugs in development. Research at UCL has led to creation of free, web-based computational tools to help pharmaceutical companies develop antibody-based drugs. Since 2013, 'abYsis' which allows investigators to analyze the features of novel antibodies has been accessed by more than 44,000 unique users, resulting in over 200 patent applications. Commercial licences, bought by large pharmaceutical companies and small biotechnology companies, generated revenues over GBP325,000 in 2019/20. The software is being used to settle patent disputes at the European Patent Commission and in one case, Professor Martin's expert testimony saved Genentech over GBP600,000. His expertise also informs naming and annotation of antibody-based drugs for the World Health Organisation.</p>		
2. Underpinning research (indicative maximum 500 words)		
<p>Antibodies form a critical part of the body's immune responses to infection. Scientists are exploiting their unique properties to develop new medicines. Antibodies are 'Y' shaped proteins whose function depends on their complex 3-D structure determined by their amino-acid sequence. They 'lock-on' to short peptide sequences or 'antigens' that the immune system targets as 'foreign'. A third of all new medicines under development involve an antibody therapy, with ~100 licensed treatments for cancer, autoimmune disease and blood clotting, amongst others and over 200 in development for Covid-19 alone.</p> <p>Professor Martin's research has led to numerous widely used computational tools and databases to allow the analysis and prediction of antibody sequence and structure. His work has also helped model predicted antibodies and understand how the VH and VL domains (the most important regions of an antibody) pack together. His computational tools also allow investigators to assess how similar a particular antibody would be to a human antibody. The research has enabled pharmaceutical companies to develop antibody-based drugs.</p> <p>In 2008 Martin's team at UCL developed the first automated method for applying standard numbering schemes to antibody sequences. Applying these schemes to antibody sequences and structures is fundamental to analysing their properties [R1] and hence to abYsis. The VH and VL domains of an antibody contain six complementarity determining region (CDR) loops that interact with antigen. Understanding what dictates how the two domains pack together and being able to predict the packing is critical when engineering and modelling antibodies. The UCL team went on to develop a machine learning method to</p>		

predict the packing angle that helps predict the antibodies' 3-D structure and allows key residues to be highlighted in abYsis that affect the packing, critical when engineering antibody-based drugs [R2].

One issue with antibody-based medicines can be that the patient's immune system recognises the new antibody proteins as 'foreign' and they are 'rejected'. To address this, the UCL team developed methods for assessing the 'humanness' of antibodies by evaluating how similar they are to the expressed human repertoire [R3]. This is integrated into abYsis and allows companies to recognize unusual sequences that may lead to rejection.

In 2009, building on the automated numbering system and tools the UCL team had developed, Martin released the first version of the abYsis antibody database; an integrated resource based around a relational database of sequence and structure data together with a set of tools for analysing new sequences. Since then, abYsis has undergone substantial development, including a new interface released in 2017 [R4]. With support from BBSRC for commercialisation (2013-2014) the team developed software that allows investigators, for the first time, to view sequence alignments on a web page and to sort sequences based on regions such as the CDR loops that form the combining site of an antibody [R5]. This software, and other computational tools [R6] developed by the UCL team have undergone continuous development and are now integral to abYsis.

3. References to the research (indicative maximum of six references)

- [R1] Abhinandan, K.R., Martin, A.C.R. (2008) Analysis and improvements to Kabat and structurally correct numbering of antibody variable domains. *Mol Immunol.* **45**:3832-9. doi:10.1016/j.molimm.2008.05.022. [186 citations]
- [R2] Abhinandan, K.R., Martin, A.C.R. (2010) Analysis and prediction of VH/VL packing in antibodies. *Protein Eng Des Sel.* **23**:689-97. doi:10.1093/protein/gzq043. [79 citations]
- [R3] Abhinandan, K.R., Martin, A.C.R. (2007) Analyzing the "degree of humanness" of antibody sequences. *J Mol Biol.* **369**:852-62. doi:10.1016/j.jmb.2007.02.100 [82 citations]
- [R4] Swindells, M.B., Porter, C.T., Couch, M., Hurst, J., Abhinandan, K.R., Nielsen, J.H., Macindoe, G., Hetherington, J. and Martin, A.C.R. (2017) abYsis: integrated antibody sequence and structure – management, analysis and prediction. *J Mol Biol* **429**:356-364. doi:10.1016/j.jmb.2016.08.019 [65 citations]
- [R5] Martin, A.C.R. (2014) Viewing multiple sequence alignments with the Javascript sequence alignment viewer (JSAV). *F1000Research* **3**:249. doi:10.12688/f1000research.5486.1 [10 citations]
- [R6] Porter, C.T. and Martin, A.C.R. (2015) BiopLib and BiopTools – a C programming library and toolset for manipulating protein structure. *Bioinformatics* **31**:4017-4019. doi:10.1093/bioinformatics/btv482 [14 citations]

4. Details of the impact (indicative maximum 750 words)

Antibody-based drugs are a major growth area for pharmaceutical companies. The freely accessible abYsis software, developed at UCL, is a web-based analytical tool that has helped accelerate drug development. [S1]. Over 40 biotech companies have used the software in their drug design work and since 2013, more than 200 patents applications have cited abYsis. In addition, patent lawyers, courts and the WHO are using the evidence and analysis provided by the software and presented by Professor Martin, to resolve patent disputes and standardise naming of antibody-based drugs.

Use of abYsis by biotech companies to accelerate drug development and patent lawyers to resolve patent disputes

AbYsis allows users to compare their antibody sequence data with sequences stored in databases such as Genbank or trEMBL, together with structural data from the Protein Data Bank. Comparing sequences allows researchers to identify unique or unusual features of their antibody sequences. The abYsis web site (www.abysis.org) also allows users to determine how human-like the antibodies appear.

Since 2013 approximately 40 new companies have used the freely available software [S2] and patent lawyers are also making significant use of the web site, including Fenwick, Morrison & Foerster, and Sheridan Ross.

Although abYsis is freely accessible online, commercial users can purchase a licence that allows them to store and analyse proprietary sequence and 3D structure data locally. Since 2013, seven major pharma (Lundbeck, Johnson and Johnson, Pfizer, Bayer, Teva, Boehringer Ingelheim and UCB) have bought commercial licences for the software together with more than 20 smaller biotechnology companies including AbCellera, Alexion Celldex, CytomX, Dragonfly, Eisai/KAN, Gilead, IBio Solutions, Imclone, Incyte Lake Pharma Harpoon, Ohana, Molecular Templates, Shionogi, StemCentrx, Surrozen-Arcus Biosciences, SutroBio, Tizona, Twist Bioscience, Versau. Revenue generated in 2019/20 financial year was over GBP 325,000, with a gross total since 2013 of GBP 534,000. It is the largest grossing software sold by UCL Business [S3].

The software has helped accelerate drug design by enabling companies to identify unusual features in their sequences and to improve strategies for humanisation [S4-S7]. For example, [TEXT REMOVED FOR PUBLICATION] state [S4] that their “entire antibody engineering team uses this software for multiple applications”, that it has “facilitated many programs and is [...] an in-expendable tool” reducing the time for these efforts “by at least 25%”. They have “successfully enhanced or humanized antibody leads that have or are currently entering the clinic”. **Twist Bioscience** state [S5] that they “have used abYsis in the design of antibody libraries for in-house use [for development of drug leads] and for sale to customers”. They estimate the use of the software to result in a “50% saving in time”. They state that they have “employed >10 highly skilled staff to develop antibodies and libraries that all rely on using abYsis.” **SutroBio** have said that it is “a central tool [...] for internal synthetic library designs” used by their “entire Protein Engineering team”. They estimate that they can do their analyses “3-4x faster than using alternative solutions” [S6]. **UCB** have said that abYsis “continues to be an integral component [...] to support the antibody design and development activities”. As a result it has “supported, in part, hundreds of Antibody design campaigns.” [S7]

AbYsis software cited in patents underpinning drug development

The research underpinning the abYsis software has been cited in over 300 patent documents since 2013 [S8] and ‘abYsis’ itself has been cited by more than 200 organisations making patent applications. Companies include Novartis, Immunogen, Kite Pharma Inc, Gilead Sciences Inc, Janssen Biotech Inc, Leucid Bio Ltd, MAB Immune diagnostics, Millenium Pharm Inc, Bristol Myers Squibb, Pfizer and Biogen as well commercial applications by KCL, Harvard College and Massachusetts Institute of Technology [S8].

Providing expertise to the World Health Organization International Nonproprietary Names committee

In 2016, Professor Martin was invited to be an expert advisor to the WHO International Nonproprietary Names (INN) Committee, providing expertise on nonproprietary names for biologic drugs and antibodies in particular. As stated by the WHO, his “long career in research on antibodies and [his] expertise in the field enabled [him] to research and develop an annotation scheme that is computer-readable”. In 2018 Martin “performed some research on computational linguistics and developed a program that allows a rapid comparison of potential new antibody names against a database of existing names” and

that “[t]his has been invaluable during INN Consultations to allow rapid comparisons as new names are discussed” [S9] (manuscript in preparation).

Acting as an expert witness in court cases relating to patent disputes

The UCL team’s research and resources, including the abYsis tool have been used to provide expert testimony in patent disputes relating to equivalence and obviousness. Professor Martin has acted as an expert witness to provide evidence in written reports in at least 6 court cases. For example, between August 2013 and November 2014, Martin provided written evidence and attended the European Patent Commission for [TEXT REMOVED FOR PUBLICATION] in a dispute with [TEXT REMOVED FOR PUBLICATION] in an opposition to patent EP1725261 (Avidity IP) [S10]. Between September 2017 and August 2018 Martin wrote a report for Genentech to demonstrate infringement of their patent in Brazil by Pró Genericós. This patent relates to Genentech’s blockbuster drug Avastin and resulted in the Brazilian court issuing an injunction against Pró Genericós to stop them producing these drugs. (Williams & Connolly) [S11].

In a related dispute with Amgen in the US, Williams & Connolly stated that Martin “prepared reports related to infringement and patent validity” and “[h]ad it gone to trial, Dr. Martin would have been the primary witness to explain antibody humanization technology to an American jury” [S11]. In a related dispute in Ireland, William Fry state that Martin’s “expertise in this highly complex area and [his] ability to clearly explain the technical issues involved meant that our team was confident [his] affidavit would assist the Court in understanding the background to and the subject matter of the proceedings”. [S12]

In another case (May 2018–Jan 2019) Martin acted as an expert witness in the High Court for Genentech in their dispute with Lilly who were trying to have Genentech’s patent EP1641822B1 declared invalid. Marks & Clark [S13] state that “based on Professor Martin’s evidence, Genentech was successful in overcoming a number of Lilly’s pleaded attacks on the validity of the patent and also in establishing that Lilly’s product fell within the scope of its claims” The judge wholly accepted Prof Martin’s evidence on this issue, the analysis for which was performed using the UCL team’s open source software. The statement also says: “some measure of the importance of [Martin’s] evidence may be gleaned from the deductions from Lilly’s recoverable costs that were ordered by the judge”. The costs payable by Genetech to Lilly were reduced by 11.5% as a result and amounted to GBP690,000.

In 2018, abYsis was selected as an Impact case by the BBSRC [S14].

5. Sources to corroborate the impact (indicative maximum of 10 references)

S1 AbYsis is available from <http://www.e-lucid.com/i/software/bioinformatics/Abysis.html> and through Ebisu (UK) <http://www.chemogenomix.com/chemogenomix/Abysis.html>. The latter website corroborates details of how the software is used.

S2 AC Immune, Aimm Therapeutics, Amgen, Apexigen, Asahi-Kasei, Astellas, Autolus, Benemae, Biomatters, Bio-techno, Biovitrum, Bristol-Myers Squibb, Chemical Computing Group, DrugDesignTech, FujiFilm, Gan & Lee, Genentech, Genm,ab, Genscript, Henlius, Immunogen, Innovent Bio, Innogen Laboratories, Johnson & Johnson, Jounce Therapeutix, Kaneka, Lilly, Lundbeck, Medicilon, Meiji, Merrimack Pharmaceuticals, Morphotek, Roche, Sanofi-Aventis, Shionogi, TX Cell (Sangamo), Xintrum Pharmaceuticals, and Zymeworks

S3 A report on Abysis income from UCL Business is available on request.

S4 Letter of support from Julian Chandler, Research Scientist II, Alexion Pharmaceuticals, Inc.

S5 Letter of support from Aaron Sato, Chief Scientific Officer, Biopharma, Twist Bioscience

Impact case study (REF3)

- S6** Letter of support from Hara Dilley, Associate Director, Scientific Data Management, Sutro Bioscience
- S7** Letter of support from Phil Scordis, Data and Translational Sciences, Innovation Lead, UCB Celltech
- S8** Search on ESPACE patent base (results reported 25.01.2021)
- S9** Testimonials from WHO
- S10** Confirmation by Richard Bisley at Avidity IP available on request
- S11** Testimony from Williams & Connolly
- S12** Testimony from William Fry
- S13** Testimony from Marks & Clark
- S14** <https://bbsrc.ukri.org/research/impact/pharmaceuticals-industry-benefits-from-antibody-sequence-software/>