Institution: **University of Sheffield**

Unit of Assessment: **5 - Biological Sciences**

Title of case study: **Design of a New Herbicide to Underpin Programmes of Sustainable Agriculture**

1. Summary of the impact

Herbicides are essential to efficient agriculture to boost crop yield and maintain food supplies in the face of growing demand. However, their use is threatened by a rapid rise in herbicide resistance, a problem that is exacerbated by the limited range of compounds currently in use. In particular, resistance to glyphosate, the compound that currently dominates the market with sales in excess of $4 billion per annum, has emerged far more rapidly than had been predicted. For over twenty years the Sheffield group has worked in collaboration with Syngenta (a world leading agrochemical business) on the development of a novel herbicide targeting IGPD, an enzyme of histidine biosynthesis, to provide an alternative to glyphosate. Over that time Syngenta invested approximately $20M in synthesis and testing of custom chemicals, including conducting worldwide field trials on the lead compound. The Sheffield group determined the structure of IGPD with representative inhibitors which has guided programmes of lead optimisation and greatly informed company decisions on the scope for commercial development. The impact relates to commerce, production and employment, and has significant reach given the vital importance of herbicide development to programmes of sustainable agriculture on a global scale.

2. Underpinning research

The Structural Studies group in Sheffield has extensive expertise in the use of X-ray crystallography to explore systems of fundamental and medical importance in atomic detail. A major programme of protein structure determination led by Professor David Rice concerns the design of novel herbicides which are essential for efficient agriculture to maintain yield. The use of glyphosate as a contact-inactivated herbicide has become important in programmes of sustainable agriculture, allowing the development of no-till farming to reduce soil loss through erosion resulting from ploughing. However, the emergence of glyphosate resistance threatens the current use and further development of this technology with potentially catastrophic results.

In collaboration with Syngenta, in a programme spanning more than twenty years, the Sheffield group has determined multiple structures of imidazoleglycerol-phosphate dehydratase (IGPD), an enzyme of histidine biosynthesis and a validated target for herbicide discovery [**R1-4**]. Importantly, their results showed that IGPD assembles as a 24 subunit protein (a '24mer') in its native state, rather than a three subunit protein (a trimer) as Syngenta scientists had believed, and that this assembly requires metal ions [**R3**,**R4**]. These findings led directly to the company redesigning their IGPD preparation strategy and obtaining improved purity and activity of the enzyme for inhibitor assays. This allowed the Sheffield and Syngenta research teams to work together to develop novel herbicides.

In collaboration with Dr Tim Hawkes, a senior scientist at Syngenta, Rice's team has analysed the structure/function relationships of a family of experimental herbicides targeting IGPD, including potent triazole phosphonates. The research at Sheffield has led to a deep understanding of the enzyme's mechanism and stimulated ideas on the development of new inhibitors as part of a programme of rational design. To complete this programme Syngenta employed and trained a team of synthetic chemists who supplied a panel of over 100 custom synthesised compounds (not publicly available) for Sheffield to test. The results from Sheffield prompted large scale synthesis of the lead compound, and testing in glasshouse and field scale trials for its herbicidal potency and weed specificity The outcome of their experiments have influenced company decisions on its commercial development.

More recently, with co-funding from BBSRC and Syngenta, the joint project has been expanded to include collaborations with Simon Jones (Chemistry, Sheffield) to develop and synthesise, together with Syngenta chemists, a new series of inhibitors, previously not explored, that have been

suggested by novel findings from the crystallography programme. This is designed to produce even more effective herbicides, perhaps with an altered range of weed target specificity.

Due to the commercial sensitivity of the project, the data directly related to the design and mode of binding of the novel compounds are not yet publicly available, although the underpinning research has been published in four research papers in the period 1995-2005 [**R1-R4**].

3. References to the research

R1 Glynn, S.E., Baker, P.J., Sedelnikova, S.E., Davies, C.L., Eadsforth, T.C., Levy, C.W., Rodgers, H.F., Blackburn, G.M., Hawkes, T.R., Viner, R., Rice, D.W. (2005) Structure and mechanism of imidazoleglycerol-phosphate dehydratase. *Structure*, 13: 1809-17. doi: 10.1016/j.str.2005.08.012

R2 Glynn, S.E., Baker, P.J., Sedelnikova, S.E., Levy, C.W., Rodgers, H.F., Blank, J., Hawkes, T.R., Rice, D.W. (2005) Purification, crystallization and preliminary crystallographic analysis of *Arabidopsis thaliana* imidazoleglycerol-phosphate dehydratase. *Acta Crystallogr. Sect. F Struct. Biol. Cryst. Commun*., 61(8): 776-8. doi: 10.1107/S1744309105022451

R3 Wilkinson, K.W., Baker, P.J., Rice, D.W., Rodgers, H.F., Stillman, T.J., Hawkes, T., Thomas, P., Edwards, L. (1995). Crystallization and analysis of the subunit assembly and quaternary structure of imidazoleglycerol phosphate dehydratase from *Saccharomyces cerevisiae*. *Acta Crystallogr. D Biol. Crystallogr*., 51:845-7.

R4 Hawkes, T.R., Thomas, P.G., Edwards, L.S., Rayner, S.J., Wilkinson, K.W., Rice, D.W. (1995). Purification and characterization of the imidazoleglycerol-phosphate dehydratase of *Saccharomyces cerevisiae* from recombinant *Escherichia coli*. *Biochem J.*, 306: 385-97.

4. Details of the impact

Overview

Scientific research carried out in Sheffield has informed commercial decisions on the research and development of a novel herbicide, making a direct contribution to its identification and potential development by a global commercial agrichemical company. The results from Sheffield persuaded the company to invest in a different research direction to design this novel herbicide, and to conduct in-house glasshouse trials and field trials in Europe and both North and South America. The company involved (Syngenta) has global reach ($9.2 billion sales, employing over 21,000 people in more than 90 countries). Glyphosate, the product that the novel herbicide aims to replace, plays a critical role in maintaining a large percentage of the world's food supply but its use is threatened by the emergence of resistance [**S4-S7**]. Glyphosate currently dominates the world herbicide market with sales in excess of $4 billion per annum and the development of a novel product to replace it would have worldwide implications.

Impact on Commerce

Syngenta has so far invested approximately $20M in the development of a herbicide targeting IGPD to identify a suitable replacement for glyphosate. The work of the Sheffield group has led to the determination of the structure of IGPD and a deep understanding of the structure/activity relationships of different classes of lead compounds that have been developed by Syngenta. The structural data were key to decisions made by the company to continue research in this area.

Over the REF period, and based on results obtained in Sheffield, Syngenta custom synthesised kilograms of the lead compound and recently (2010-12) performed glasshouse trials followed by a series of field trials (in North America, South America and Switzerland) to test the herbicidal efficacy of the lead compound. This is one of the key steps in the commercial and regulatory pathway prior to marketing of the product, and equivalent to the stage of clinical trials in the medical arena. The costs of performing such trials are commercially sensitive but are significant.

The results of these trials against their panel of resistant weed cultivars (which are also commercially sensitive) has had a direct outcome on both the company's decision whether to take

the product through to market and on the direction of future research in this area. Thus, the Sheffield research programme has had a direct influence on the commercial decisions of a major global company. In a supporting letter [**S1**], Dr Tim Hawkes, who leads research into weed control solutions at Syngenta, confirms that work at the University of Sheffield "*exerted a considerable and direct influence on our work here at Syngenta*" and "*helped to lead Syngenta into a programme of chemistry aimed towards new inhibitors*" and that "*over the last few years Syngenta has certainly invested multi-million pounds in the IGPD area*".

As a result of the discoveries by the Sheffield team, over the REF period Syngenta invested considerable expenditure on chemical consumables and the employment and training of several synthetic chemists. Syngenta also co-funded the IGDP structural studies in Sheffield, resulting in the employment and training of a team of research scientists, and co-funded three PhD students at the University [**S2, S3**].

Ongoing Impact on Commercial Research and Development

The research collaboration between Sheffield and Syngenta represented a rational-design approach to the development of novel herbicides in which precise knowledge of enzyme structure/activity relationships is used to model/design/screen potential inhibitors. This approach has influenced on-going work between Sheffield and the commercial partner, and the collaboration continues to influence ideas for further lead compound optimisation in an on-going project funded by BBSRC and Syngenta [**S3**].

5. Sources to corroborate the impact

Although the results of the field trials and the research directly pertaining to the impact are commercially sensitive (and thus not publicly available), documentary evidence is available from Syngenta to corroborate the nature and significance of the work and the impact that it has had on the commercial decisions made by the company.

S1 A **letter from a Senior Syngenta Fellow**, a lead scientist in weed control strategies, outlining the '*considerable and direct influence'* of the work in Sheffield on Syngenta's investment in IGPD research and field trials, is available.

S2 **Research Collaboration Agreement (2009) between Sheffield and Syngenta** setting out details of milestone payments from Syngenta to Sheffield during commercial development, and royalty payments on commercialisation, is available.

S3 **Syngenta and research council co-funding for a team of structural biologists studying IGPD in Sheffield (further details at http://www.bbsrc.ac.uk/pa/grants/).**

- *Towards the exploitation of IGPD as a target for herbicide development* - D W Rice and P J Baker. BBSRC Industrial Partnership award with Syngenta (BB/C518065/1) April 2005 to March 2008. Employed 3 researchers. £233k (Syngenta contribution approx. £50k contribution in kind for provision of equipment/materials).
- *The Development of a Novel Herbicide* - D W Rice, P J Baker and S Jones. BBSRC Industrial Partnership award with Syngenta (BB/I003703/1) Jan 2011 to June 2014. Employs 3 researchers. £717k (Syngenta contribution approx. £111k).
- Three Research Council CASE PhD training grants (Collaborative Awards in Science and Engineering) from 1998-2011: Claudine Bisson (2007 to 2011), Thomas Eadsforth (2004-2008), Kay Grabham (1988-1991). Syngenta contribution approx. £200k (approx. 20k per student per annum).

S4 Duke, S.O., Powles, S.B. (2009) Glyphosate-resistant crops and weeds: now and in the future *AgBioForum*, 12 (3&4), 346-57, http://tinyurl.com/o4h4eod. Describes the threat posed by glyphosate-resistant weeds to agriculture.

S5 Reuters: http://tinyurl.com/3b5zuss. Describes the threat posed by glyphosate-resistant weeds to agriculture

S6 Price, A.J. et al. (2011). Glyphosate-resistant Palmer amaranth: A threat to conservation tillage. *Journal of Soil and Water Conservation*, 66, 265-75

Describes the threat posed by glyphosate-resistant weeds to agriculture

S7 *Glyphosate China Monthly Report,* 4, 01 (20 January 2013). http://tinyurl.com/os8fvxq.
Describes the commercial importance of glyphosate.