Institution: University of Leeds

Unit of Assessment: UoA 8 Chemistry

Title of case study: Critical contribution to a small-molecule screening collection that has changed European drug discovery practices

Period when the underpinning research was undertaken: 2007-date

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:
Professor Adam Nelson	Professor, Chemical Biology	01/02/1998-date
Professor Steve Marsden	Professor, Organic Chemistry	01/08/2001-date

Period when the claimed impact occurred: 2013-date

Is this case study continued from a case study submitted in 2014? N

1. Summary of the impact (indicative maximum 100 words)

The European Lead Factory (ELF) drives European drug discovery innovation. The ELF is based on high throughput screening of a high-quality library of 500,000 compounds, over 200,000 of which are novel and distinctive compounds in ELF's Public Compound Collection (PCC). Leeds had a critical impact in the realisation of the PCC through sustained leadership of the ELF's library selection committee, and developing chemistry that led to 21,119 of the PCC compounds, the largest from a single source. The ELF has already changed the strategies and practices of European drug discovery organisations of all sizes, with impacts including patents, licensing deals and spin-outs.

2. Underpinning research (indicative maximum 500 words)

A major research programme has developed unified synthetic approaches to diverse and novel molecular scaffolds with properties suitable for drug discovery applications. The pharmaceutical sector faces challenges to increase both innovation and productivity: an analysis of sector productivity revealed that only 5% of target-to-hit activities result in a launched drug, contributing to a cost per launched drug of around USD2,000,000,000 (*Nat. Rev. Drug Discov.* **2010**, *9*, 203). The molecular properties of hits, leads and drug candidates are now widely recognised to determine attrition rates (particularly lipophilicity, molecular weight and aromatic ring count; *Angew. Chem. Int. Ed.* **2012**, *5*, 1114).

Nelson and Marsden have collaborated since 2007 to develop synthetic methods that align with drug discovery needs. Initially funded by EPSRC and GlaxoSmithKline (EP/E020712/1; GBP593,934; 2007-11), they developed novel catalytic technologies for preparing diverse heterocycles and amines in array format. Screening compounds and drug molecules typically contain multiple Lewis basic sites and display poor solubility in non-polar media: more frequent failure of polar substrates in array synthesis is common, contributing to undesired 'logP drift' towards more lipophilic compounds. Nelson and Marsden therefore developed methods that are tolerant of polar functionality and solvents (for example, an Ir-catalysed asymmetric allylic amination **[1]**).

They developed a platform for the efficient 'lead-oriented' synthesis of diverse, sp^3-rich, 3D molecular scaffolds, again funded by EPSRC (EP/J00894X/1; GBP533,045; 2012-15) and pharmaceutical companies. They developed computational tools to guide unified approaches to diverse and novel scaffolds that, on decoration, would yield lead-like screening compounds. **[2-6]** The platform harnessed chemistries such as their functional group-tolerant allylic substitution **[1]** to generate polyfunctional intermediates. These could then be converted into alternative scaffolds by functional group-selective transformations such as Pd- **[2,3]**, Au- **[4]** and electrophilic **[2,3]**

cyclisations. Two such unified approaches were effective in synthesising multiple scaffolds (52 and 22 respectively) that were shown to have high novelty, diversity and lead-likeness. **[2,3]** A third unified approach based on complexity-generating [4+3] cycloadditions yielded over 50 diverse/novel natural product-like fragments and, via high-throughput X-ray crystallography, hits against three protein targets (collaboration with Structural Genomics Consortium/Diamond). **[5]**

The computational tools were integrated into LLAMA (Lead-Likeness And Molecular Analysis, www.llama.leeds.ac.uk), an open-access, web-based platform that helps synthetic chemists to develop new lead-oriented methods. **[6]** LLAMA allows users to input/upload scaffolds; select/upload transformations for scaffold decoration; and analyse the resulting virtual libraries. A novel 'traffic light' score enables lead-likeness to be assessed easily, and information on three-dimensionality and novelty is also provided. LLAMA has attracted >950 users from academia and industry (>20 countries; >115 universities and >30 drug discovery organisations); it has generated >2600 libraries, and >40 papers (outwith the Leeds team) explicitly cite its use.

Professor Nelson was awarded the 2018 UBC-Ehrlich award of the European Federation of Medicinal Chemistry, a biennial international award recognising outstanding research in medicinal chemistry. It explicitly recognises "*his ground breaking work to explore novel chemical space*", and that he "*implemented his vision that chemical synthesis should align with drug discovery needs, and introduced methods that have been taken up by the medicinal chemistry community to profile synthetic targets for lead-likeness and chemical novelty*." **[E]**

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

[1] "Iridium-Catalyzed Asymmetric Allylic Amination with Polar Amines: Access to Building Blocks with Lead-Like Molecular Properties", P. Tosatti, J. Horn, A. J. Campbell, D. House, A. Nelson, S. P. Marsden, *Adv. Synth. Cat.,* **2010**, *352*, 3152-3157. DOI: 10.1002/adsc.201000721 (31 citations)
Describes the successful optimisation of catalysts to operate upon substrates containing typical medicinal chemistry functionality that fail using standard catalysts.

[2] "A unified lead-oriented synthesis of over fifty molecular scaffolds" R. G. Doveston, P. Tosatti, M. Dow, D. J. Foley, H.-Y. Li, A. J. Campbell, D. House, I. Churcher, S. P. Marsden, A. Nelson, *Org. Biomol. Chem.*, **2015**, *13*, 859-865. DOI: 10.1039/c4ob02287d (35 citations)
[3] "A systematic approach to diverse, lead-like scaffolds from α,α-disubstituted amino acids" D. J. Foley, R. G. Doveston, I. Churcher, A. Nelson, S. P. Marsden, *Chem. Commun.*, **2015**, *51*, 11174-11177. DOI: 10.1039/c5cc03002a (38 citations)
[4] "Modular, Gold-Catalyzed Approach to the Synthesis of Lead-like Piperazine Scaffolds" T. James, I. Simpson, J. A. Grant, V. Sridharan, A. Nelson, *Org. Lett.*, **2013**, *15*, 6094-6097. DOI: 10.1021/ol402988s (31 citations)
[5] "Synthesis and Demonstration of the Biological Relevance of sp^3-rich Scaffolds Distantly Related to Natural Product Frameworks" D. J. Foley, P. G. E. Craven, P. M. Collins, R. G. Doveston, A. Aimon, R. Talon, I. Churcher, F. von Delft, S. P. Marsden, A. Nelson, *Chem. Eur. J.*, **2017**, *23*, 15227-15232. DOI: 10.1002/chem.201704169 (26 citations)
Papers [2-5] describe the design and execution of synthetic strategies and methods to deliver novel sp^3-rich scaffolds with lead-like properties that were all subsequently exploited within ELF – see section 4.

[6] "A divergent synthetic approach to diverse molecular scaffolds: assessment of lead-likeness using LLAMA, an open-access computational tool" I. Colomer, C. J. Empson, P. Craven, Z. Owen, R. G. Doveston, I. Churcher, S. P. Marsden, A. Nelson, *Chem. Commun.*, **2016**, *52*, 7209-7212. DOI: 10.1039/c6cc03244c (49 citations)
Describes the development and application of an open-access tool for library enumeration/evaluation; the principles informed the library design criteria and tools used in ELF.

The quality of the underpinning research is evidenced by (a) outputs [1]-[6] being published in international peer-reviewed journals and (b) the citations (Web of Science, 13/1/21) of each output that support their influence and scientific impact within the community.

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

The European Lead Factory (ELF) was launched in 2013 to address high attrition in drug discovery and facilitate discovery of new drug classes for unmet medical needs. **[A]** Driven by the European Federation of Pharmaceutical Industries and Associations (EFPIA), and co-funded by the EU Innovative Medicines Initiative (IMI), the EUR196,000,000 project brought together seven major EFPIA companies (Bayer, Merck, UCB, Lundbeck, Janssen, Sanofi, AstraZeneca), 10 SMEs and 13 universities. Leeds was invited to participate in the consortium based on its international reputation in lead-oriented synthesis. **[B]**

ELF consists of a shared Joint European Compound Library (JECL) of >500,000 high-quality screening compounds, and a publicly-accessible high-throughput screening platform. **[A,B]** The JECL comprises 326,846 compounds contributed by EFPIA partners and >200,000 high-quality novel compounds (Public Compound Collection, PCC). The JECL is being screened in >350 high-throughput assays via the original initiative (2013-18) **[A,B]** and an ongoing EUR37,000,000 IMI-co-funded project (2018-23). **[C]**

Underpinning research at Leeds and Nelson's leadership in ELF enabled the effective transfer of innovative chemistry from across Europe, and had a major impact on the realisation of the PCC. The quality and accessibility of ELF's compound collection has enabled strategy and practices in European drug discovery to change.

<u>Maximising the quality of the Public Compound Collection (PCC)</u>
The University of Leeds had a **critical impact** in realising the ELF's PCC. Noting Professor Nelson's relevant research record, **[1-6]** the ELF Executive stated that:
"*On the basis of Professor Adam Nelson's international reputation in the development of computational methods and tools for lead-oriented synthesis, he was invited by the consortium to chair the Library Selection Committee (LSC)…throughout the project (2013-18).*" **[B]**
As LSC Chair, Nelson's research expertise critically impacted on the design, selection and delivery of the PCC, a EUR50,000,000 investment. **[B]** After capturing consortium views, he led the definition of library selection criteria (molecular properties; novelty; diversity potential; structural features; innovation; synthetic tractability), which also guided the design of final libraries produced by SME partners. **[B]** He led the team that developed a web-based tool to enable transfer of innovative chemistry into ELF (design, submission, review and selection of libraries) by both ELF partners and third parties **[B,D]**. Overall, the LSC reviewed 1053 library proposals, of which 312 ultimately contributed to the PCC. **[B]** Nelson's leadership within ELF was cited in his 2018 UBC-Ehrlich award. **[E]** The ELF Executive state:
"*The protocols and criteria implemented under Professor Nelson's leadership were driven by his research expertise and impacted critically on PCC: our published cheminformatic analysis* (**[F]**) *shows that the PCC is of very high quality, and is highly distinctive from the EFPIA-contributed compounds".* **[B]**

<u>Sustained collaboration to enable knowledge transfer of lead-oriented synthesis approaches</u>
Leeds' lead-oriented synthesis approaches were translated into produced libraries through collaboration with Edelris. The workflow for technology transfer **[**described in **H]** had a conspicuously high success rate within ELF. **[B,G]** Researchers at Leeds optimised syntheses of diverse scaffolds, and demonstrated their derivitisation and purification. The scaffolds exploited Leeds's underpinning research including: **[G,H]** electrophilic, **[2,3]** palladium- **[2]** and gold- **[4]** catalysed cyclisations and [4+3] cycloadditions. **[5]** In all, Leeds successfully transferred 34 validated libraries, enabling Edelris to produce 21,119 compounds. **[G,H]** This constitutes 11% of the PCC, the largest contribution from the 8 university partners; based on the total PCC budget, these compounds are valued at around EUR5,500,000. **[B,G]** Beyond ELF, Edelris states:
"*On the basis of Professor Nelson's development of lead-oriented synthesis concepts and tools, such as LLAMA, we have engaged him as a consultant since 2017 to help expand our business based on natural product-like sp^3-rich screening libraries*." **[G]**

Sustained impact of the PCC on European drug discovery practice

ELF has enabled **more efficient and effective utilisation** of a screening collection. Rather than being restricted to a single owner, ELF enabled the seven EFPIA partners, plus European SMEs and university teams, to exploit the PCC. **[A]** This shared the high burden of resourcing, sourcing and maintaining a high-quality compound collection. The original consortium generated 161 qualified hit lists (5,649 validated hits) including for neglected tropical disease, neurodegeneration, CNS and oncology targets. **[A,B]**

Hit lists from public screens have resulted directly in: **[A]** five patents (in antibiotics, pain and cancer); two new companies (Scandicure; Keapstone Therapeutics); two partnering deals with major pharmaceutical companies; and a preclinical antibiotic development programme from which two drug candidates emerged. Testimonials **[I]** specifically evidence the impact of the compound collection on drug discovery practice across Europe:

(1) **Improving efficiency in EFPIA companies: [I]** "*ELF's innovative compound collection enabled us to identify chemical matter for two new programmes superior to our internal and superior to commercial screening collections*." (Director Technology Platforms, Sanofi)

(2) **Enabling poorly-druggable targets: [I]** "…*exceeded our expectations, particularly with very low druggable targets*…" (Alliance Manager, Bayer)

(3) **Levering investment for spin-out creation: [I]** "*The hit compounds…were validated to a degree you would expect to see in industry. This gave us confidence to fund the project…with a budget of £1.3 M."* An additional £1M was subsequently invested. **[J]** (Drug Discovery Manager, Parkinson's UK)

The **strategy and practices of European drug discovery organisations of all sizes have been changed**. The high quality of the screening collection, based upon criteria developed by Nelson, has been recognised as critical (*"There are many chemical libraries available but many are not very drug like, in contrast to....the JECL"* (CEO, Cellipse)). **[I]** The PCC continues to impact European drug discovery practice through the expanded ELF (8 EFPIA partners plus Medicines for Malaria Venture). **[C]** The ELF Executive summarises Nelson's role in this impact: **[B]**
"The successful realisation of the €50M PCC, which is highly complementary to the EFPIA-contributed compounds, was possible because of the criteria and tools developed by the LSC under Professor Nelson's leadership, and is central to the ongoing effectiveness of the JECL in driving European drug discovery innovation."

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

[A] https://www.europeanleadfactory.eu/sites/elf/files/Brochure_ELF_executive_summary.pdf
[B] Letter from European Lead Factory Project Executive (3rd December 2020)
[C] https://www.europeanleadfactory.eu/news-events/european-lead-factory-europe%E2%80%99s-largest-collaborative-drug-discovery-platform-continues
[D] C. Kallus, J. Hüser, P. S. Jones and A. Nelson, "The European Lead Factory", in "Small Molecule Medicinal Chemistry: Strategies and Technologies", W. Czechtizky, P. Hamley (eds.), Wiley, 2015.
[E] https://www.efmc.info/ucb-ehrlich-award-excellence-medicinal-chemistry
[F] "Expansion of chemical space for collaborative lead generation and drug discovery: the European Lead Factory Perspective." A Karawajczyk; F Giordanetto; J Benningshof; D Hamza; T Kalliokoski; K Pouwer;, R Morgentin; A Nelson; G Muller; A Piechot; D Tzalis, *Drug Discovery Today*, **2015**, *20*, 1310. DOI: 10.1016/j.drudis.2015.09.009
[G] Letter from Edelris Vice President for Strategic Innovation (9th November 2020)
[H] "Translation of Innovative Chemistry into Screening Libraries: An Exemplar Partnership from the European Lead Factory." R. Morgentin, M. Dow, A. Aimon, G. Karageorgis, T. Kalliokoski, D. Roche, S. Marsden, A. Nelson *Drug Discovery Today*, **2018**, *23*, 1578-1583. DOI: 10.1016/j.drudis.2018.05.007
[I] https://www.europeanleadfactory.eu/results/testimonials
[J] https://www.keapstone.com/news/keapstone-therapeutics-limited-secures-further-1-million-investment-from-parkinsons-uk/