Institution: King's College London

Unit of Assessment: UoA5

Title of case study: The development of a 'first-in-class' N-cadherin antagonist for cancer

1. Summary of the impact

The cell adhesion molecule N-cadherin has been shown to be required for the survival of cancer cells, their metastasis and the formation of new blood vessels in solid tumours, however, cell adhesion molecules like N-cadherin were generally not considered to be "druggable." Scientists at King's College London have contributed to the development of a "peptide-pipeline" of novel N-cadherin antagonists, including the cyclic HAV peptide (N-Ac-CHAVC-NH2), also now known as Exherin and/or ADH-1, as a "first-in-class" N-cadherin antagonist. This compound was granted FDA organ drug designation for Melanoma in 2008 and successfully completed a number of phase I and II clinical trials, with an additional clinical trial currently recruiting. The demonstration that N-cadherin peptides can be used to treat cancer has changed the perception of what is possible and opened up new clinical and commercial opportunities.

2. Underpinning research (indicative maximum 500 words)

Cancer continues to kill several million people each year and there is an unmet need for compounds that promote cancer cell death, inhibit cancer cell spread or prevent the formation of the new blood vessels (angiogenesis) required for the growth of solid tumours. The cell adhesion molecule (CAM) N-cadherin, which can promote cancer cell survival and migratory responses as well as angiogenesis, has emerged as a potential therapeutic target for several cancers. However, CAMs were not considered to be good drug targets and therefore largely ignored by major pharmaceutical companies. Work carried out at King's College London (KCL) by Prof Patrick Doherty (1990-present, Head of the Wolfson Centre for Age-Related Diseases at KCL), Dr Emma Williams (1994-present, Senior Research Fellow) and Dr Gareth Williams (1997-present, Wolfson Bioinformatics Lead) has established that small peptides can be developed as specific antagonists for a number of CAMs including N-cadherin.

Early in the 1990's, scientists at KCL developed assays to measure N-cadherin function and provided the first direct evidence that peptides harbouring a histidine-alanine-valine (HAV) motif (important for N-cadherin function) could act as selective N-cadherin antagonists. One way N-cadherin promotes cancer cell invasion is through activation of the fibroblast growth factor receptor (FGFR) via the HAV motif. KCL scientists went on to show that synthetic 'peptidomimetics' from an FGFR domain that contained the HAV motif could inhibit the function of N-cadherin along with the adhesion molecules L1 and N-CAM (Williams E-J, et al. Neuron, 1994). Based on this, they embarked on a number of projects to develop constrained cyclic peptides as selective and specific N-cadherin antagonists that might serve as potential clinical candidates for cancer treatment.

The first cyclic N-cadherin antagonists were developed by KCL scientists in collaboration with Orest Blaschuk and Barbara Gour at McGill University, Montreal, Canada, and a McGill spinout company: Adherex Technologies Inc. This collaboration resulted in the development and characterisation of a family of short cyclic peptidomimetics based around the HAV motif present in the classical cadherins. KCL led on the work that became the first publication to describe the utility and selectivity of a large family of novel N-cadherin antagonists and identified the cyclic HAV peptide (N-Ac-CHAVC-NH2), also now known as ADH-1 or Exherin™, as a selective N-cadherin antagonist (Williams E-J, et al. J Biol Chem, 2000). ADH-1 was shown to fully inhibit N-cadherin function and was claimed as a product in patent application WO-09802452 in 1998 (subsequently granted as US-06031072) with the data from the Williams et al. 1994 paper providing the basis for the claims made in the patent (Figs 4-6 in the US-06031072).

Further studies led to the development of a second family of cyclic peptides based around a distinct N-cadherin binding motif identified in the KCL lab. These peptides are more active and selective than the HAV family (Williams E-J, et al. Mol Cell Neurosci, 2000) and were also granted patent protection with the lead KCL scientist (Prof Doherty) identified as an inventor on the patent (Publication number: EP2438925 A3). In a BBSRC funded program, KCL scientists developed a simple strategy to turn the N-cadherin antagonist peptides into agonist peptides that stimulate

regenerative responses from neurons (Williams G, et al. J Biol Chem 2002). In an ensuing collaboration with GlaxoSmithKline (the largest UK pharmaceutical company) they went on to demonstrate that these N-cadherin agonist peptides can protect a variety of neurons from excitotoxicity (Skaper SD, et al. Mol Cell Neurosci 2004) and as such might have therapeutic potential in neurodegenerative diseases. The demonstration that N-cadherin peptides can be used to treat cancer has changed the perception of what is possible and made possible new clinical and commercial opportunities.

3. References to the research

Williams EJ, Furness J, Walsh FS, Doherty P. Activation of the FGF receptor underlies neurite outgrowth stimulated by L1, NCAM and N-cadherin. Neuron 1994;13(3):583-94. Doi:10.1016/0896-6273(94)90027-2 (428 Scopus citations).

Williams E, Williams G, Gour BJ, Blaschuk OW, Doherty P. A novel family of cyclic peptide antagonists suggests that N-cadherin specificity is determined by amino acids that flank the HAV motif. J Biol Chem 2000;275(6):4007-12. Doi: 10.1074/jbc.275.6.4007 (83 Scopus citations 83)

Williams EJ, Williams G, Gour B, Blaschuk O, Doherty P. INP, a novel N-cadherin antagonist targeted to the amino acids that flank the HAV motif. Mol Cell Neurosci 2000; 15(5):456-64. Doi: 10.1006/mcne.2000.0847 (26 Scopus citations)

Williams G, Williams EJ, Doherty P. Dimeric versions of two short N-cadherin binding motifs (HAVDI and INPISGQ) function as N-cadherin agonists. J Biol Chem 2002; 277:4361-67. Doi: 10.1074/jbc.M109185200 (29 Scopus citations)

Skaper SD, Facci L, Williams G, Williams EJ, Walsh FS, Doherty P. A dimeric version of the short N-cadherin binding motif HAVDI promotes neuronal cell survival by activating an N-cadherin/fibroblast growth factor receptor signalling cascade. Mol Cell Neurosci 2004; 26(1):17-23. doi: 10.1016/j.mcn.2003.12.015 (23 Scopus citations)

Patents

Compounds and methods for modulating adhesion molecule function. Inventors: Patrick Doherty, Orest W. Blaschuk (+1). Applicant: Adherex Technologies Inc (Ca). US6277824B1. Publication date: 21.8.2001: http://www.google.com/patents/US6277824

Cyclic peptides and peptiomimetic compounds that modulate neuronal growth. Inventors: Patrick Doherty and Williams. Applicant: Wyeth Corp (US); Doherty Patrick (GB). EP1663276 A2. Publication date: 7.7.2006: https://www.google.com/patents/EP1663276A2?dq=EP2438925+A3+patent&ei=sihxUqWaNuGv7AaIk4DQBQ&cl=en

Grants

1998-2000. Development of N-cadherin antagonists. Adherex. £80,000 plus peptides. PI: Doherty.

2002-2005. Molecular basis of the formation of an N-cadherin/FGF receptor signalling complex and development of peptide agonists. BBSRC. £256,296. PI: Doherty

4. Details of the impact

Scientists from King's College London (KCL) directly contributed to the development of a highly innovative and novel 'peptide-pipeline' of N-cadherin antagonist and agonist peptides, demonstrating that this class of adhesion molecule is capable of being turned into a clinically-useful pharmaceutical compound. This includes the N-cadherin antagonist Exherin™/ADH-1, manufactured and trialed by Adherex Technologies Inc., which was awarded FDA organ drug designation in Melanoma in 2008 (1). Dr Orest Blaschuk, the co-founder of Adherex Technologies Inc. says of the KCL research detailed above that "*these studies unequivocally demonstrated that*

the cyclic peptide CHAVC (designated as ADH-1) was an N-cadherin antagonist." He goes on to say that "*these findings led to subsequent Phase I and II clinical trials to determine the ability of ADH-1 as an anti-cancer drug"* (2).

Only around one in a thousand compounds discovered in the pre-clinical stage finally gain FDA approval. The vast majority of drugs tested for efficacy in animal models do not make it into human clinical trials as they need to pass a very rigorous evaluation process that scrutinises all aspects of the drug including the logic underpinning its development, the results obtained in animal models of disease, the manufacturing conditions and the clinical trial design (3). The success of ADH-1 is shown in that it has been trialled in five Adherex Technologies Inc. Phase I or Phase IIa studies in patients with either advanced in-transit malignant melanoma, advanced extremity melanoma, advanced solid tumours or N-cadherin-expressing solid tumours. Patients were administered ADH-1 either in conjunction with standard chemotherapy or, in cases refractive to all other therapy, as a single therapy (4). Four publications have reported on the outcomes of trials involving a total of 116 patients during the impact period. This work has definitively shown that this new intervention for cancer is safe and tolerable in man. Importantly, as progression to Phase II indicates a well tolerated treatment in healthy individuals, in the Phase I studies no maximum tolerated dose of ADH-1 was reached (5).

There remains considerable interest in ADH-1 as evidenced by development of an anticancer drug with additional preclinical studies recently showing good efficacy against neuroblastoma (6). The excellent saftey data with ADH-1 is leading to strategies where it is being evaluated as a combination therapy alongside other anti-cancer agents. For example, recruitment has recently opened for a Phase I trial of ADH-1 in combination with gemcitabine hydrochloride and cisplatin in treating patients with metastatic pancreatic or biliary tract cancer that cannot be removed by surgery, sponsored by the University of Nebraska, the National Cancer Institute and Adherex Trechnologies Inc (7).

The identification of ADH-1 has also had a commercial impact underpinning a $10 million public offering that established Adherex as a listed company on the Toronto Stock Exchange. The company to date has invested $70 million in cancer research. Their 'Cadherins in Oncology' brochure detailing 'therapeutic opportunities through cadherin targeting' includes discussion of the development of ADH-1 N-cadherin antagonist, citing Williams E, et al. J Biol Chem, 2000 as well as other work from the KCL lab (8).

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

1) ADH-1/Exherin awarded orphan drug designation: http://adherex.com/adherex-receives-orphan-drug-designation-for-adh-1-in-melanoma

2) Letter of professional corroboration from Dr Orest Blaschuk–Scientific founder of Adherex available on request

3) Fierce Biotech article: FDA Approval Process:
http://www.fiercebiotech.com/topics/fda_approval_process.asp

4) Completed Clinical Trials of ADH-1

- A Study of ADH-1 in Combination With Normothermic Isolated Limb Infusion of Melphalan: http://www.clinicaltrials.gov/ct2/show/NCT00421811?term=Adh-1&rank=6
- A Study of the Safety and Effects of ADH-1 Given Intravenously as a Single Agent: http://www.clinicaltrials.gov/ct2/show/NCT00264433?term=Adh-1&rank=5
- A Study of ADH 1 in Combination With Carboplatin, or Docetaxel or Capecitabine: http://www.clinicaltrials.gov/ct2/show/NCT00390676?term=Adh-1&rank=4
- A Study of the Safety and Effects of ADH-1 Given Daily to Subjects With Solid Tumors: http://www.clinicaltrials.gov/ct2/show/NCT00225550?term=Adh-1&rank=3
- A Study of ADH-1 Given Intravenously to Patients With Solid Tumors: http://www.clinicaltrials.gov/ct2/show/NCT00265057?term=Adh-1&rank=2

5) Publications of ADH-1 Studies

- Phase I
  - Beasley GM, McMahon N, Sanders G, Augustine CK, Selim MA, Peterson B, et al. A phase 1 study of systemic ADH-1 in combination with melphalan via isolated limb infusion in patients with locally advanced in-transit malignant melanoma. Cancer 2009;115(20):4766-74. DOI: 10.1002/cncr.24509

  - Perotti A, Sessa C, Mancuso A, Noberasco C, Cresta S, Locatelli A, et al. Clinical and pharmacological phase I evaluation of Exherin (ADH-1), a selective anti-N-cadherin peptide in patients with N-cadherin-expressing solid tumours. Ann Oncol 2009;20(4):741-5. DOI: 10.1093/annonc/mdn695

  - Yarom N, Stewart D, Malik R, Wells J, Avruch L, Jonker DJ. Phase I clinical trial of Exherin (ADH-1) in patients with advanced solid tumors. Curr Clin Pharmacol 2013;8(1):81-8. DOI: 10.2174/1574884711308010011

- Phase II

  - Beasley GM, Riboh JC, Augustine CK, Zager JS, Hochwald SN, Grobmyer SR, et al. Prospective multicenter phase II trial of systemic ADH-1 in combination with melphalan via isolated limb infusion in patients with advanced extremity melanoma. J Clin Oncol 2011;29(9):1210-15. DOI: 10.1200/JCO.2010.32.1224

6) Lammens T, Swerts K, Derycke L, De Craemer A, De Brouwer S, De Preter K, Van Roy N, Vandesompele J, Speleman F, Philippé J, Benoit Y, Beiske K, Bracke M, Laureys G. N-cadherin in neuroblastoma disease: expression and clinical significance. PLoS One. 2012;7(2):e31206. doi: 10.1371/journal.pone.0031206

7) ADH-1, Gemcitabine Hydrochloride and Cisplatin in Treating Patients With Metastatic Pancreatic or Biliary Tract Cancer That Cannot Be Removed By Surgery: http://clinicaltrials.gov/show/NCT01825603

8) Adherex Technologies Inc. Caherins in Oncology brochure: http://media.corporate-ir.net/media_files/irol/14/144663/final_cadherin_brochure.pdf