Institution: EaStCHEM School of Chemistry

Unit of Assessment: UoA 8: Chemistry

Title of case study: Development, scale-up and formulation of porous materials leading to commercialisation, and the implementation of innovation investment policy in Sweden.

Period when the underpinning research was undertaken: 2006 - 2016

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:
Russell Morris	Bishop Wardlaw Professor	01 October 1995 – present
Alexandra Slawin	Professor	01 July 1999 – present

Period when the claimed impact occurred: August 2013 - 31 December 2020

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

1. Summary of the impact

Researchers within EaStCHEM have translated high-quality research in porous materials to wide-reaching impact via creation of spin-out companies and influencing international innovation policy.

Research from EaStCHEM Professor Russell Morris has demonstrated controlled release of nitric oxide (NO) from porous materials. This has led to the formation of two spin-out companies, *Zeomedix LLC* and *MOFGen*, which developed new medical products that incorporate NO-loaded porous materials. These two companies have attracted significant initial investment of GBP500,000 and generated revenues of approximately GBP200,000. The IP generated by EaStCHEM and these two companies has been optioned by manufacturing giant *PQ Silicas*. Another spin-out company, *PanaceaNano*, has commercialised controlled time-release of agents using biodegradable porous materials co-developed by EaStCHEM Professor Alexandra Slawin. *PanaceaNano* began in 2015, supported by USD5,500,000 in initial investment, and has launched its first product, a line of anti-aging skincare products under the brand *NOBLE*™.

Based on his expertise in the scale-up and formulation of porous materials for use in biomedical applications, Morris was requested to chair a policy committee of the Swedish government's innovation agency, *Vinnova*. Implementation of *Vinnova*'s policy recommendations has resulted in Swedish government investment of [text removed for publication] between August 2013 and 31 December 2020 into healthcare consortia that involve [text removed for publication], resulting in wide-ranging economic and healthcare benefits in Sweden.

2. Underpinning research

EaStCHEM researchers (Professors Ashbrook, McKeown, Morris, Slawin, Wright) have a longstanding track record of innovative research in porous materials, such as zeolites, polymers and metal-organic frameworks (MOFs). This includes investigating their synthesis, structure and properties, as well as employing these materials in downstream applications.

The challenge: controlling the release of guest molecules from porous materials

Porous materials, such as zeolites and metal-organic frameworks (MOFs), are prepared as microcrystalline powders and it is a major challenge to scale-up and formulate these materials for medical or commercial use.

Controlled release of biologically relevant molecules

The Morris research group patented **[WO2005003032A1]** and published research in 2006 **[R1]** demonstrating that porous materials (zeolites) could be used to adsorb, store and deliver biologically active and therapeutic gases such as nitric oxide (NO) in medically relevant quantities at controllable rates. The key advance was the use of toxicologically acceptable formulations of polymer/zeolite composites that provide shelf-stable products, either as self-

supporting composites or as coatings on polymer-based devices. Importantly, the formulation was further extended in 2008 to include a non-aqueous ointment formulation that was demonstrated to be safely used on human skin **[R2]**. The types of porous materials used were expanded to metal-organic frameworks (MOFs) in 2008 **[R3]**. Extremely high-capacity MOF/polymer composites were then developed that can deliver not only NO but also other medically active gases (such as carbon monoxide and hydrogen sulfide) and/or other agents such as antibiotics **[patent #: WO2012020214A2 based on R4]**. The Morris group has also developed polyurethane/MOF, silicone/MOF and PVC/MOF composites that are bioactive in their own right, without the need for any guest molecules. These composites can be fabricated on a large scale using only water as a solvent **[R5]**. In addition to the 36 papers linked to this body of work, the research generated a portfolio of 8 patents that are owned by the University of St Andrews. This translational research illustrates the lifecycle of invention from the genesis of the material and structural elucidation within the chemistry laboratory, through scale-up, to formulation in industry.

Toxicologically benign and biodegradable MOFs based on cyclodextrins (CDs), naturally occurring and biodegradable oligosaccharides, are another class of materials that permit the controlled release of guest compounds. These were co-developed by Slawin, who successfully elucidated the highly complex structure of these MOFs using single crystal X-ray diffraction, despite the challenges posed by both data collection and analysis, which had previously thwarted attempts by other crystallographers **[R6]**. The use of cyclodextrin components endows these MOFs with enhanced aqueous solubility, low toxicity and a high concentration of binding sites for the encapsulation of organic compounds such as drug molecules. This work has been patented, with Slawin as a co-inventor **[patent #: US20150322174A1]**.

3. References to the research

The underpinning research listed was supported by peer-reviewed grants (EP/I028080/1 and GR/T09705/01). All publications are peer-reviewed and published by well-regarded academic journals.

R1. P.S. Wheatley, A.R. Butler, M.S. Crane, S. Fox, B. Xiao, A.G. Rossi, I.L. Megson, **R.E. Morris**, "NO-releasing zeolites and their antithrombotic properties". *J. Am. Chem. Soc.*, **2006,** *128*, 502-509. DOI: 10.1021/ja0503579.

R2. M. Mowbray, X. Tan, P.S. Wheatley, **R.E. Morris**, R.B. Weller, "Topically applied nitric oxide induces T-Lymphocyte infiltration in human skin, but minimal inflammation". *J. Invest. Dermatol.*, **2008,** *128*, 352-360. DOI: 10.1038/sj.jid.5701096.

R3. A.C. McKinlay, B. Xiao, D.S. Wragg, P.S. Wheatley, I.L. Megson, **R.E. Morris**, "Exceptional behavior over the whole adsorption-storage-delivery cycle for NO in porous metal organic frameworks". *J. Am. Chem. Soc.*, **2008**, *130*, 10440-10444. DOI: 10.1021/ja801997r.

R4. A.C. McKinlay, P.K. Allan, C.L. Renouf, M.J. Duncan, P.S. Wheatley, S.J. Warrender, **D.** Dawson, S.E. Ashbrook, B. Gil, B. Marszalek, T. Düren, J.J. Williams, C. Charrier, D.K. Mercer, S.J. Teat, **R.E. Morris**, "Multirate delivery of multiple therapeutic agents from metal organic frameworks". *APL Materials*, **2014**, *2*, 124108, DOI: 10.1063/1.4903290.

R5. D.C. Catteneo, S.J. Warrender, M.J. Duncan, R. Castledine, N. Parkinson, I. Hayley, **R.E. Morris**, "Water based scale-up of CPO-27 synthesis for nitric oxide delivery". *Dalton Trans.* **2016**, *45*, 618-629. DOI: 10.1039/c5dt03955j.

R6. R.A. Smaldone, R.S. Forgan, H. Furukawa, J.J. Gassensmith, **A.M.Z. Slawin**, O.M. Yaghi, J.F. Stoddart, "Metal–Organic Frameworks from Edible Natural Products". *Angew. Chemie Int. Ed.*, **2010**, *49*, 8630-8634. DOI: 10.1002/anie.201002343.

4. Details of the impact

The impact underpinned by the research takes on two distinct forms.

i) The commercialisation of porous materials for medical and cosmetic applications through spin-out companies, *MOFGen*, *Zeomedix* and *PanaceaNano*, each of which received significant investment funding to help bring products to market.

ii) Morris was invited to participate (from 2014) and then chair (from 2016) committees for *Vinnova*, an agency that advises the Swedish government on innovation policy. The

Swedish government's adoption of these policy recommendations has led directly to investments in consortia focussing on healthcare delivery with a total value of EUR15,400,000 since August 2013 (calculated in November 2019 by *Vinnova*).

The research to impact timeline is described in Figure 1.

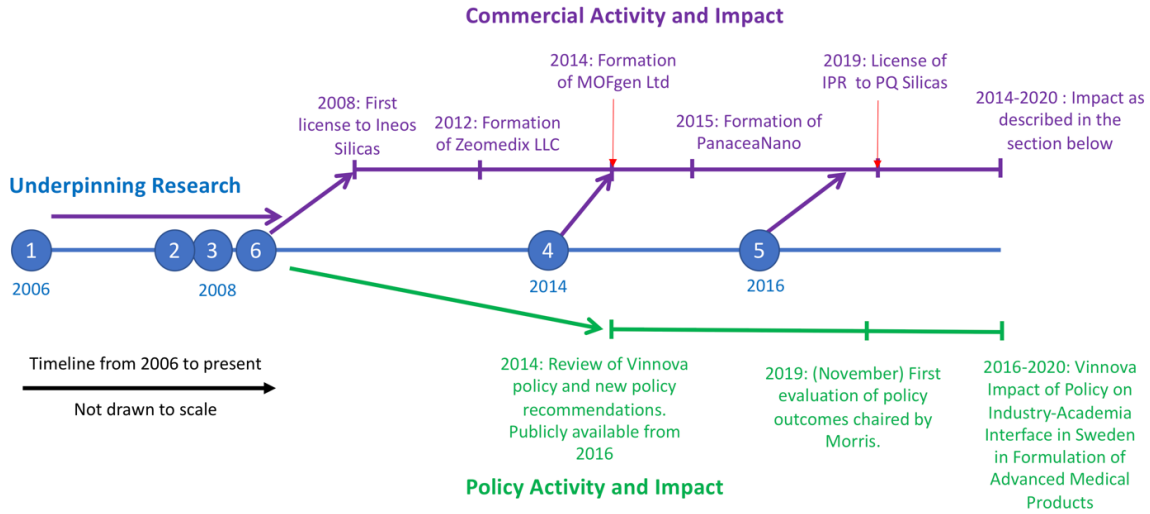

***Figure 1**. Timeline showing the development of impact from the primary underpinning research described in Section 2 (blue line and blue circles refer to publications referenced in Section 3).*

i) Economic and commercial impact from spin-out companies

Since 2014, concerted activity to translate the underpinning research on porous materials into the development and commercialisation of medical products has occurred as follows.

1. The commercial activity of two start-up companies, *Zeomedix LLC* and *MOFGen Ltd.*, which have exploited the EaStCHEM zeolite and MOF technology, respectively, for wound healing formulations and medical device coatings **[S1-S2]**. *MOFGen* **won the RSC's Emerging Technologies Prize in 2016.**
2. The investment provided by *PQ Silicas*, a global materials manufacturer, into *Zeomedix* and their joint development projects for the production of ointments for wound healing (Figure 2a) **[S1]**. *PQ Silicas* has taken an option on the IP from *MOFGen* (12-2019) for GBP80,000.
3. The investment of over GBP300,000 provided by Mercia Fund Management and the Scottish Investment Bank into *MOFGen Ltd* was supplemented by a GBP200,000 investment of public funding into the start-up (10-2016) **[S2]**.
4. The following companies have partnered with *MOFGen Ltd* through joint development (JD) projects across the healthcare sector to develop technology/products, generating revenue for the partner companies **[S2]**:
   a. *Fine Industries Ltd* (UK) for the water-based scale-up of MOFs (Figure 2a) **[R5]**. Fine Industries are a Good Manufacturing Practice-accredited manufacturer of active pharmaceutical ingredients. This JD (2014-2016) provided the necessary capability for GMP manufacture of the MOFs for medical applications and included revenue to *Fine Industries Ltd* of GBP40,000.
   b. *Scott and Fyfe Ltd* (UK) for the large-scale formulation of MOF-coated non-woven fabrics. This JD (2015) demonstrated a roll-to-roll technology for the production of 100 metres of MOF-coated wound-healing gauze fabric (Figure 2b) and was funded by *MOFGen Ltd* and *Scott & Fyfe Ltd* jointly.
   c. T*eleflex Inc* (USA), one of the world's largest medical device manufacturers, for the coated introducer sheaths used in cardiovascular interventions. This JD resulted in the manufacture of MOF/polyurethane coated devices including for cardiac catheterisation. Between 2016 and 2019, this provided sales of MOF/polyurethane coating formulations of more than USD110,000 for *MOFGen Ltd*. Figure 2c shows one of the coated introducer sheaths prepared by *Teleflex Ltd*.

d. *5D Ltd* (UK) for the development of antibacterial assays specifically designed to establish that the MOF/polymer formulations do not leach toxic metals in significant amounts provided revenue to *5D Ltd* of GBP50,000 between 2017 and 2019.
e. *Charles River Ltd* (UK) for animal model safety testing of *MOFGen* polymer/MOF composites provided revenue of GBP50,000 to Charles River between 02-2016 and 11-2016.
f. *Lubrizol Life Sciences* (USA) for the manufacture of MOF/polymer films and testing for bacterial cell adherence reduction, funded by *MOFGen* and *Lubrizol*. Due to COVID-19, this work has been affected and is presently ongoing. A programme of technical development, costing GBP955,000, aimed at manufacturing medical devices was secured (10-2020) in collaboration with *Lubrizol*, *5D Ltd* and the *Manufacturing Technologies Catapult*.

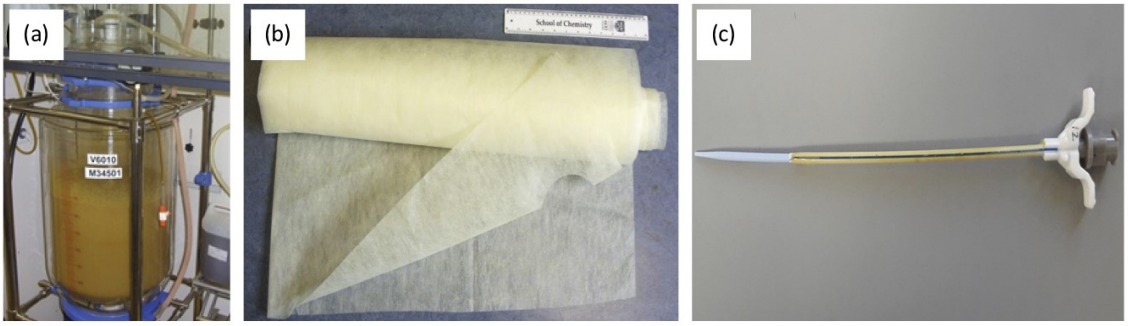

***Figure 2**. (a) The GMP-accredited scale up of MOF manufacture to 100 L by* Fine Industries Ltd. *(b) A roll of MOF/polyester composite coated non-woven fabric manufactured by* Scott and Fyfe Ltd. *(c) A MOF/polyurethane coated introducer sheath for cardiovascular interventions, manufactured by* Teleflex Inc.

5. Creation of *PanaceaNano*, a nanotechnology company co-founded by Sir Fraser Stoddart, co-author of **[R4]** and co-inventor with Slawin of the IP **[S3]** underpinning the company. The company was founded in 2015 based on IP derived from the research contained within **[R4]**, and currently employs 10 people. Initial funding of USD5,500,000 from *Taqnia International*, a California technology investment and development company, has underwritten company formation **[S4]**. In 2018, *PanaceaNano* launched a line of anti-aging skincare products under the brand NOBLE. The technology, which relies on CD-MOFs, is ground-breaking: these materials can be loaded with active ingredients and are engineered to release them at a precise rate over time. The company's first commercialised products are cosmetics, including anti-aging eye cream, anti-wrinkle night cream and skin rejuvenation serum **[S5]**. The launch was accomplished using a multimillion-dollar multi-media advertising campaign (Figure 3), with the product being sold internationally.

***Figure 3**. Advert with actress Jodie Comer (Killing Eve) as* spokesperson.

ii) Public policy impact for innovation in Sweden

Recognizing his contributions to research on porous materials and their translation to medical products, the Swedish Government Innovation agency *Vinnova* in 2014 invited Morris to join/lead a team of five international researchers **[S6]**. This committee would develop policy recommendations for the investment activities of *Vinnova* to enhance the industrial innovation landscape in Sweden **[S7, p7-8]**. Based on the resulting recommendations, *Vinnova* chose the scale-up and formulation for the manufacturing of advanced medical products, as specifically recommended by Morris, to be the focus for the first so-called *Vinnova Competence Centres* launched in early 2016.

To highlight the direct link from Morris' research to *Vinnova* policy and to its subsequent impact, the *Vinnova* Director of Centres wrote **[S5]**:

"Russell Morris' published research into the scale up and formulation of materials for medical applications (especially his work on medical gas delivery for humans) was therefore key in Vinnova choosing him to lead both the policy recommendations and an evaluation of the impact of this policy on the Swedish innovation landscape."

Morris currently chairs the committee of three international experts that evaluates the impact of the centres; the first impact evaluations were completed in 11-2019. On the basis of these evaluations, investment of: (**1**) [text removed for publication]between August 2013 and 31 December 2020; (**2**) SEK14,400,000/EUR1,350,000 from all seven of Sweden's healthcare regions; (**3**) SEK86,400,000 (EUR8,100,000) from the Swedish Government, to the centres has been secured.

The impact of the policy and the subsequent combined investment from companies, the Swedish Healthcare regions and the national government, has led to the evolution of an ecosystem devoted to the development and commercialisation of advanced medical products in Sweden. The impact is wide-ranging, from the development of manufacturing processes and specific new products to Sweden-wide collaborations for the elaboration of novel routes to therapeutics. Specific impacts from the development work are, as the *Vinnova* Director of Centres describes **[S6, p3]**, as follows:

"The impact [of the policy] to date has been wide-ranging and is developing very quickly. As well as the initiation of major projects based on the industry investment, cross cutting themes have developed scale-up and formulation, Standard Operating Practices that have been shared with all industrial and public partners – giving outstanding benefits in terms of know how. However, there are more tangible impacts. Most notable is the library of scaled up human protein therapeutics, completed in the CellNova Center, that is now worth an estimated [text removed for publication]. This library is being exploited by the industrial partners."

5. Sources to corroborate the impact

S1. M. Neidrauer, U.K. Ercan, A. Bhattacharyya, J. Samuels, J. Sedlak, R. Trikha, K. A. Barbee, M. S. Weingarten, S.G. Joshi, "Antimicrobial efficacy and wound healing property of a topical ointment containing nitric-oxide-loaded zeolites", *Journal of Medical Microbiology*, **2014**, *63*, 203-209. DOI: 10.1099/jmm.0.067322-0. *Zeomedix* publication corroborating use of St Andrews technology.

S2. Letter from *MOFgen Ltd* - Supports the claim that spun out the company, levels of investment and funding secured.

S3. US Patent US 2015/0322174 A1. Confirms that Professor Slawin was a co-inventor of the IP underpinning *PanaceaNano*.

S4. "Meet the Nobel Prize winner who can help you look younger". Article from Crain's Chicago Business, 31-01-2019. Article documenting investment by *Taqnia International*. Supports the claim of the investment of USD5,500,000 by *Taqnia International*. https://www.chicagobusiness.com/innovators/meet-nobel-prize-winner-who-can-help-you-look-younger

S5. "Company co-founded by Nobel Prize winner launches nanotechnology based cosmetics". Article from The Daily Northwestern, 16-01-2018. Article documenting *PanaceaNano*'s commercial products. Supports the claim that *PanaceaNano* has developed and is marketing beauty products for the consumer. https://dailynorthwestern.com/2018/01/16/lateststories/company-co-founded-nobel-prize-winner-launches-nanotechnology-based-cosmetics/

S6. Letter from *Vinnova*. Supports the claim that Professor Morris was involved in developing innovation policy in Sweden.

S7. Evaluation Report and Policy Recommendations of *Vinnova* VINN Excellence Centres (R Morris is an author and named in the introduction). Supports the claim that Professor Morris authored the report that guided policy in Sweden.