SULSA
Scottish Universities Life Sciences Alliance

SULSA, JULY 2017

Scotland's Drug Scene

For many people, if asked about drugs in Scotland, they will think of Euan Macgregor disappearing into the bowl of the "worst toilet in Scotland", in Danny Boyle's film rendition of Irvine Welsh's book "Train Spotting". Drugs, however, represent a critical part of the Scottish economy. Not the damaging recreational kind, but the medicines that save lives. Scotland has been a global pioneer in the discovery of new drugs. Here we outline some of Scotland's landmark contributions to this field.

As early as the middle of the nineteenth century, Scots were leading the way in drug development. Dr Livingstone, the missionary explorer from Blantyre near Glasgow, managed to navigate his way around Africa where others had failed before, through his diligent use of the drug quinine, which killed malaria parasites that had obliterated previous European efforts to explore the African interior. Livingstone had trained as a doctor at Anderson's college in Glasgow and read that quinine prevents the African fever that killed so many of his predecessors. He added rhubarb, jalap and a little opium to produce a mixture that was later marketed by the Burrough's Wellcome phamaceutical Company under the name of "Livingstone's Rousers". Livingstone, born into poverty, was a beneficiary of Scotland's enlightened higher education system. Whilst England, at the beginning of the nineteenth Century, had just the Universities of Oxford and Cambridge, catering primarily for the wealthy, Scotland already had four major Universities plus a range of other establishments, like Anderson's college, that catered for anyone who could pay. Livingstone made enough money working in a mill to sign up and learn medicine at the College, which was later to evolve into University of Strathclyde. Among his favourite books as a youth had been Culpepper's "The Complete Herbal" an inventory of medicinal plants in the UK published in the 17th Century. In Africa Livingstone was always seeking new remedies for the diseases he found there.

Since Livingstone's time, Scotland has maintained an astonishing contribution to the conquest of disease in the tropics. Later this year it is hoped that a new drug to treat a disease called African sleeping sickness will be launched. Sleeping sickness is caused by tiny parasites called trypanosomes that are transmitted between people by blood sucking tsetse flies. The new drug, called fexinidazole, or "fexi" for short, can be taken orally as tablets, rather than injections, as is the case for current sleeping sickness treatments. It has been developed over the last 10 years by a Geneva-based group called the Drugs for Neglected Diseases initiative (DNDi). It was first shown to be active against the parasites by Frank Jennings whilst working at the School of Veterinary Medicine in Glasgow in the 1980s. Alan Fairlamb, working with the Drug Discovery Unit in Dundee, later showed that fexi is also active against another neglected parasitic disease called leishmaniasis. Interest in developing drugs at the Glasgow vet School had reached its pinnacle when James Black, from Uddingston, not far from Livingstone's birthplace in Blantyre, began his research into understanding the effects of adrenaline on the heart.

Figure 1. Sir James Black. Source: www.nms.ac.uk

Black was an alumnus of the University of St Andrews. He later moved to the chemicals giant ICI where his team invented beta blockers like propranolol, which block adrenaline's effects and went on to become the world's bestselling drug. Black was awarded a Nobel prize for his work in 1988. The University of Dundee elected Black as its Chancellor in 1992 and in 2006 opened the £20m Sir James Black Centre. Today the Centre houses one of the world's foremost centres in drug research, targeting some of the world's neglected diseases of the tropics afflicting, as they do, the world's poorest people with no ability to pay for expensive drugs.

"Scottish scientists have blazed a pathway in bringing their inventions to the clinic"

A handful of Pharmaceutical giants, companies like Pfizer, Astra Zeneca, GlaxoSmithKline, Novartis and Merck make huge sums by providing medicines to keep people healthy. But discovering and developing new drugs today is an incredibly costly business. It is estimated that over £1 bn must be invested for each new drug to reach the market place. That cost includes all of the many compounds that make it to different stages of development before being dropped, often because of unexpected side effects. Huge investment is required to check their safety and efficiency against disease and the regulatory authorities look with ever closer scrutiny for clean drugs without side effects. Because of this, remarkably few new medicines make it to the marketplace each year. In the past year (May 2016 – April 2017) just 24 new molecular entities were registered as drugs via the Food and Drugs Administration (FDA) in the United States.

With the costs involved in bringing a new drug to market, University laboratories simply can't take their inventions forward. New models to help innovation in academic science have, however, emerged. Scottish scientists have blazed a pathway in bringing their inventions to the clinic. Perhaps the greatest Scottish achievement in pharmaceuticals was that of a mild-mannered doctor from Darvel in Ayrshire, Alexander Fleming. Whilst working at St Mary's Hospital in London in 1928, Fleming discovered that particular fungal cells that had landed on a Petri dish, a classical way of propagating microbes, killed the bacteria he was growing there. Fleming had already spent years seeking antimicrobial agents before this discovery of "penicillin". It was a decade later, prompted by the threat of World War II that scientists in Oxford managed to take Fleming's discovery further. The importance of penicillin and subsequent growth of the whole area of antibiotics cannot be over-emphasised. Before their discovery nearly a half of all deaths were due to bacterial infections, a number that today has fallen to almost negligible levels, at least in the developed world where antibiotics are readily available. Fleming shared the Nobel prize for his work in 1945.

Medical innovation stemming from Scottish Universities has continued apace. Take Colin Suckling, a chemist at the University of Strathclyde. Along with Hamish Wood, Suckling developed new chemistry for the large-scale synthesis of a compound called leucovorin, which is given in conjunction with chemotherapy drugs used to kill some types of cancers by interfering with a pathway known as the folate pathway. Leucovorin helps healthy cells recover from the side effects of such anticancer drugs like methotrexate. The University of Strathclyde earned around £6 m in royalties from the discovery. It was at Strathclyde too, in the 1970s that George Dewar, working with John Stenlake synthesised a drug called atracurium, a muscle relaxant they licensed to Burroughs Wellcome and is today used to help surgeons access body tissues when they operate. The University raised around £30m in royalties from that drug. Suckling has continued to invent new compounds, including another class of molecule, the so-called "minor groove binders" (MGBs), which kill a range of cells including some bacteria, cancer cells, viruses and parasites by binding to their DNA. The range of conditions that the MGBs might treat is astounding. Strathclyde licenced representative MGBs to a Glasgow based Biotech company called MGB-Biopharma and they have steered one compound through the first steps of clinical development against bacteria that are resistant to other antibiotics. Suckling believes that a wide network of collaborators is essential if new chemicals are to be pursued as drugs, and linking to an industrial partner imperative to take things forward. Currently, Strathclyde compounds are being actively evaluated in five continents around the world. The development of these Scottish exports is, however, a slow process moving from the laboratory to the clinic and will take decades before fruits of discovery may be reaped.

Pioneering research at the University of Dundee led by Professor Sir Philip Cohen since the early 1970's has led to major breakthroughs in the understanding of signalling pathways in cells in health and disease by the regulation of enzmes called protein kinases. Abnormalities in these signalling pathways contribute to many diseases, such as arthritis, cancer, hypertension and Parkinson's disease. Over the past 20 years protein kinases have become one of the pharmaceutical industry's most important class of drug target for cancer and inflammatory diseases. Some 20 drugs that target kinases have now been approved for clinical use, with many more undergoing clinical trials.

Figure 2. Sir Alexander Fleming with his Petri dish. Source www.uk.businessinsider.com

"The most fruitful basis for the discovery of a new drug is to start with an old drug"

- James Black

A key drug used in some cancer therapies today, as well as a number of viral diseases, is interferon, a natural product made by cells of our own immune system when infected by viruses. Interferon can signal to cells to prevent virus replication and therefore become a hostile environment to invading viruses. It can also trigger the immune system to attack cancer cells. The son of Jews who had fled Lithuania, Alick Isaacs studied medicine in Glasgow before moving to the National Institute of Medical Research where he discovered interferon with Jean Lindenmann in 1957. Therapeutic interferon makes billions of dollars today and was the first of the growing number of "biologics" which are natural products rather than chemically synthesised compounds and make up an ever increasing share of the total therapeutics marketplace (over $200 bn a year).

Another Scot, Sir David Jack, from Fife, is credited for turning GlaxoSmithKline into the pharmaceutical giant it is today. Jack studied Pharmacy and Pharmacology at the University of Glasgow and Royal Technical College (Livingstone's alma mater, now Strathclyde University). His first major product was salbutamol, or Ventolin as it is better known, the drug that opens up the bronchioles in the lungs allowing asthmatics to breathe freely. Jack joined a race against his compatriot James Black to seek inhibitors of the H2 receptors in the intestine to reduce gastric acidification and cure ulcers. Although Black's team came up with the first useful inhibitors, Jack could tinker with structures - arriving in 1981 at the compound now known as ranitidine, better known under its trade name Zantac, one of the highest selling drugs of all time. Tinkering with effective chemical structures to improve drugs in this way is standard. Black famously stated that "The most fruitful basis for the discovery of a new drug is to start with an old drug."

Scotland's pharmaceutical prowess also has knock on effects in its education. Graeme Milligan, who is Dean of research at the University of Glasgow, has seen many of his students pursue highly successful careers in the pharmaceutical industry. Take Derek Charmers, who studied with Milligan in the 1990s before founding Arena Pharmaceuticals and then Cara Therapeutics, a US based company specialising in new ways to treat pain. Arena Pharmaceuticals now have a drug licensed to treat obesity in the USA. Milligan serves as an advisor to both companies and technology invented in his lab has underpinned their success. Glasgow University has managed to earn hundreds of thousands of pounds on royalties from that technology and also made a significant profit as a shareholder in Cara as they floated on the US stock exchange in anticipation of success with their new drug against pain.

The global market in pharmaceutical sales is fast approaching a trillion dollars per year. But it is becoming increasingly difficult to develop new drugs. Some believe the "low hanging fruit" has been picked. Others worry that increasing regulation makes it almost impossible to develop new agents that can treat disease without causing any side effects. Neither aspirin, nor paracetamol, for example, would pass the regulatory hurdles needed to prove a drug's safety if introduced today. However, the potential rewards, both financial and in terms of ameliorating human health and well-being, continue to drive a pathway. To surpass some of the hurdles it has become necessary to build large, interdisciplinary teams to bring drugs forward. Major drugs companies, of course, have many thousands of employees, appointed across the globe. Pfizer, for example, employs 96,500 people and Astra Zeneca 50,000. They are also turning increasingly to academic research to refresh some of their thinking in Drug discovery. Astra Zenca have established a research base looking into new ways to treat Inflammatory diseases of the lung at the University of Glasgow, through their so called GLAZgo Discovery Centre.

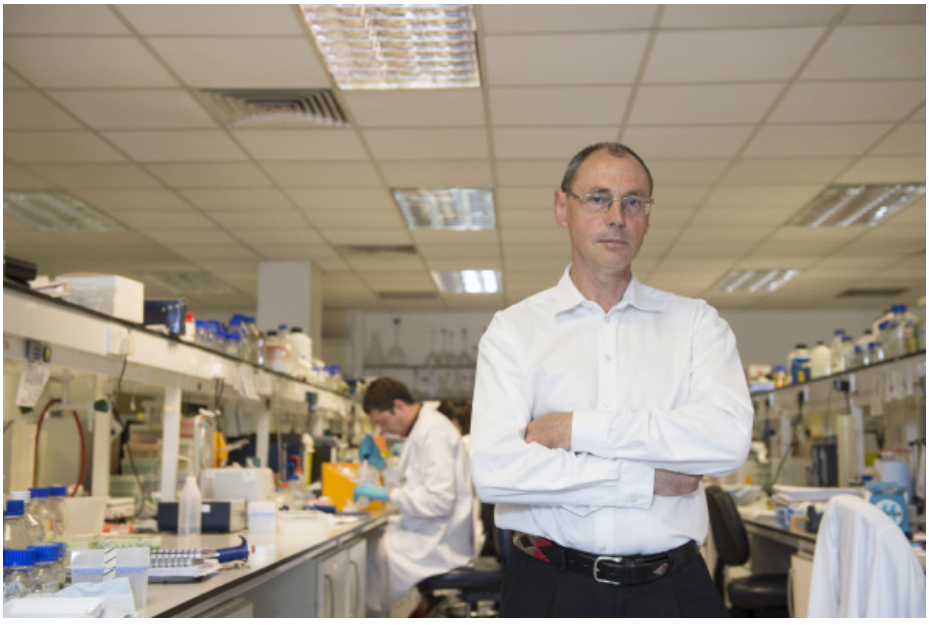

Figure 3. Professor Graeme Milligan. Source: Univeristy of Glasgow

Scottish Universities continue to play a very significant role in Drug discovery. Mainly through smart innovations, discovering molecules to pass on to others to take through development. At The University of Edinburgh, for example, Professor Neil Carragher is co-director of the Edinburgh Cancer Discovery Unit and the Edinburgh Phenotypic Assay Centre as well as being chief scientific officer of the Phenomics Discovery initiative, one of the public private partnerships associated with the National Phenotypic Screening Centre (NPSC). The NPSC, centred at the University of Dundee, was founded with an £8m grant from the Scottish Funding Council through the Scottish Universities Life Sciences Alliance (SULSA) and centred at the University of Dundee. Phenotypic screening involves seeing how compounds work on whole cells rather than individual target molecules. It has become increasingly popular since the complexity of cells, the tiny units from which all living organisms are made, is such that it remains incredibly difficult to predict how individual chemicals, like drugs, will behave when exposed to that complexity. Phenotypic screening has become possible with improvements in automated microscopy, supported by massive computing power, making it possible to image the impact of many thousands of drugs at the same time against cellular systems. It is then possible to find out retrospectively what those drugs actually do to kill the cells. The NPSC was the brain-child of Professor Andrew Hopkins, who had been one of the brightest scientists at Pfizer before coming to the University of Dundee, attracted by the Drug Discovery Unit (DDU, www.drugdiscovery.dundee.ac.uk/home) that was offering a new paradigm in academic drug discovery. Hopkins also runs his own Company, Exscientia, who use artificial intelligence to seek chemical features that make drugs perfect for use in people. Exscientia has recently signed contracts running into hundreds of millions of pounds with Pharmaceutical giants GSK and Sanofi.

The DDU was founded, in 2006, with investment from the Wellcome Trust by two investigators, Professors Alan Fairlamb and Mike Ferguson, who have devoted their careers to follow the laudable Scottish tradition of seeking drugs for tropical diseases, which afflict the world's poorest people and are largely ignored by the Pharmaceutical industry. Since its inception the DDU now employs more than 95 people and has candidates progressing to treat malaria, leishmaniasis and trypanosome infections of animals. Housed initially in the James Black building, the DDU has undergone a continual programme of expansion; now additionally occupying two floors of the new Wellcome Trust Centre for Anti-infective research (CAIR) furnished with state of the art equipment and funded through a £13.6 m grant from the Wellcome Trust.

The DDU is directed by Prof Paul Wyatt who was enticed to Dundee from Cambridge where he had been a leading scientist at Astex a drug discovery company that was acquired by Japanese Pharma giant for nearly $1bn in 2013.

The DDU, although working at a scale previously unimaginable in an academic setting also uses a broad partnering model to help take drugs forward. A major link with GSK is helping bring forward new drugs for leishmaniasis, and other companies such as the Edinburgh based innovative pharmaceuticals company IOmet Pharma have partnered with Dundee to bring forward a new series of potential anti-cancer agents. A collaboration with Medicines for Malaria Venture based in Geneva has delivered a remarkable new compound with the potential to cure malaria with a single dose. The drug is now under development by the Pharmaceutical company Merck KGaA.

The DDU in Dundee is one of two jewels currently sitting in Scottish Universities' pharmaceutical crown. The other, also administered from the University of Dundee, is the European Screening Centre (ESC, www.lifesci.dundee.ac.uk/research/esc) based at Newhouse just east of Glasgow. The ESC is part of a pan-European network, the European Lead Factory (ELF) www.europeanleadfactory.eu, that was founded to stimulate innovation of pharmaceutical design, and established with £100m from the European Commission's Innovative Medicines Initiative. Many companies have assembled chemical libraries of hundreds of thousands, or even millions of compounds. Of course not all work against the particular targets under study in any one disease type. But what if they have activity against other targets? In an extraordinary effort, a 500,000 compound library was assembled, with contributions from seven Big Pharma companies several small companies and academic chemists. The library was then open to anyone who had a viable screen for a potential drug target that would, if successful, offer routes to useful new drugs. The infrastructure was put in place to perform the required high throughput screens and provide expertise to follow-up the output. Since its inception in 2013 the ELF has initiated more than 80 collaborative drug discovery projects from across Europe with 10 originating from Scottish Universities.

The screening centre is the major occupant of the BioCity site at Newhouse, a major site of economic regeneration across Scotland's central belt. The site's director Dr Phil Jones says "In just four years we have built up the expertise and capabilities within the ESC and ELF to make a real impact on drug discovery. Output from the group has already led to investments from charities, public-private partnerships and venture funding which has the potential to create new medicines to treat diabetes, anti-microbial resistance and Parkinson's disease."

Since it's inception the DDU in Dundee now employs more than 95 people and has candidates progressing to treat malaria, Leishmaniasis and trypanosome infections of animals.

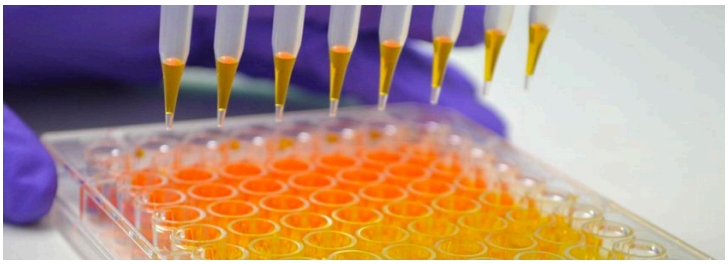

Figure 4. Drug Discovery Unit. Source: www.drugdiscovery.dundee.ac.uk

"Scotland and Scots have been pioneers in drug discovery"

Scotland and Scots have been pioneers in drug discovery, and this looks set to continue as the nation has taken a leading role in a new approach to medicine once called "personalised" but now more widely known as "precision medicine". Not everyone benefits from drug treatments for their particular disease. There can be a number of reasons for this. In cancer, for example, it turns out that even "breast cancer" is actually a series of different diseases, caused by changes to different molecular processes in affected cells. In some instances a drug that targets the faulty molecular process can be useful. However, the same drug won't work where other mechanisms are at play. Other things affect drug response too. Different people for example, are better able to assimilate drugs given orally, or else to modify drugs in ways that can inactivate them. Ultimately, even available medicines will work much more frequently and effectively if given to the right patient at the right time. Improvements in diagnosing diseases, and sub-varieties of those diseases means that we will become better at choosing the right medicine for the right patient at the right time. Precision medicine is also sometimes referred to as "stratified" medicine (since we won't really work on new therapies for each and every individual, instead clustering people and their diseases into groups, or "strata", for therapeutic choice). As part of the Scottish Funding Council's initiative in investing in areas seen as key drivers to economic growth, the Stratified Medicine Scotland Innovation Centre (SMS-IC) was founded in 2014 with £10m of investment, matched by inputs form other industrial partners and now occupies a wing of the new Queen Elizabeth University Hospital in Glasgow, the largest (acute care) hospital in Europe. SMS-IC is leading the way in identifying biological markers that explain the variation between people that underlies their ability to respond to drugs. These markers will indicate the likelihood of response to drugs and then be used to develop tests that help doctors choose just who will benefit from a particular drug and use it only for those who will respond.

There are also other new successes in Scotland, and from truly interdisciplinary approaches. For example the Kosterlitz Therapeutic Centre at the University of Aberdeen is named in honour of Hans Kosterlitz, the father of Michael Kosterlitz who was awarded the Nobel Prize in Physics in 2016. From the University of St Andrews, Pneumagen is a new company based in Biology for the development of new anti-viral drugs; MOFgen based in Chemistry who are developing antibacterial metal organic framework materials; and Ripptide Pharma Ltd formed from a collaboration between chemists both in St Andrews and Aberdeen who are developing new chemical/biological process for the efficient production of useful compounds for drug discovery and development. More ideas are bound to follow.

And so it is, Scotland with its highly educated workforce, pioneering history of enlightened thought and invention continues to lead the world in helping its inhabitants "Choose life".


SULSA
Scottish Universities Life Sciences Alliance