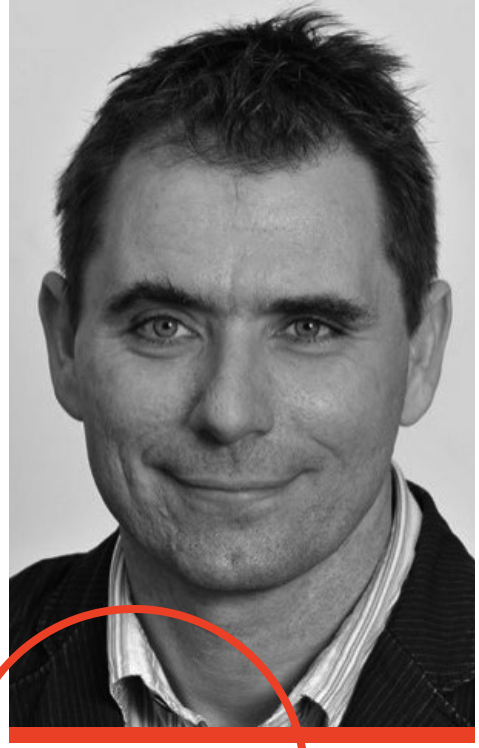


INFERTILITY AND CANCER: INSIGHTS INTO NEW THERAPEUTIC APPROACHES

Steven Conlan is Professor of Molecular and Cell Biology, heading up the vibrant Reproductive Biology and Gynaecological Oncology research group at Swansea University, UK. He has over 20 years of experience in biomedical research and innovation, supporting life science businesses and translating research from his own laboratory. He is currently focusing on developments in several areas of precision medicine including Functional Genomics and AI for drug discovery and disease diagnosis, including future integration into NHS pathology services. A second major element of his work is on the development of Advanced Therapeutics; Antibody Drug Conjugates (patented, and in pre-clinical development), exosomes, and nanoparticle deliver systems.

Polycystic ovary syndrome (PCOS) and endometriosis are conditions related to infertility. PCOS is a multifactorial disease where treatments are currently not well defined, and often carries a psychological burden for patients. Endometriosis is a non-malignant growth in the peritoneum and is associated with a substantial pain burden in many patients. With gynaecological cancers such as endometrial and ovarian, there is significant scope to innovate, developing new therapeutic approaches as well as complementing the current standard of care. We spoke to Professor Steven Conlan to obtain insights into the approaches his group is taking to drive biomarker development for endometriosis and PCOS, as well as the antibody drug conjugates (ADC) being developed for cancer applications. We also discussed the challenges related to the implementation of new therapies into the clinical setting.

Q&A

Tell us a little about your background and the current focus of your research

I've been at Swansea University for 21 years. In 2004, I was asked to join the medical school which is when I started to work more in the preclinical space. We were working in gynaecological areas initially, particularly infertility in women where the problem seemed to be implantation of the embryos. We weren't looking at sperm or egg defects, but at what could be the underlying causes of failed implantation and potential links to PCOS and endometriosis.

We also started working directly with clinicians, supported initially by the fact our university is adjacent to a hospital. Many clinicians really wanted to be involved in research and through them, many of their patients wanted the same thing. One of our philosophies for biomarker discovery is therefore to evaluate using patient tissues in the first instance.

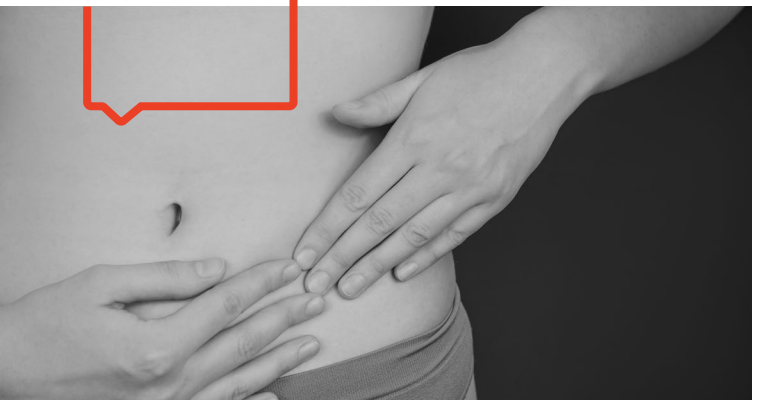
With our biomarker studies, we started asking 'is that biomarker relevant in the disease of interest?', and we recruited patients working closely with pathology. From those pathologies linked to infertility, we then shifted some of our efforts into oncology research. Partially because of the increased risks some PCOS patients appear to face in developing endometrial cancer.

In the oncology space, we now work directly with gynae-oncologist surgeons, medical oncologist, radiologists and pathologists. It's a privilege to

have their expertise and medical inputs roll back into the lab, and this collaborative environment also helps accelerate our research programmes.

We've now worked across a large number of areas focussing on biomarker development, primarily looking at tissue samples. What's really interesting, is we started by looking at single markers using immunohistochemistry and now it is all being integrated with genomics, proteomics and pathology. I was talking to a pharmaceutical company recently, and they defined three areas that they wanted to work in – bringing together all the informatics, genomics and pathology. At Swansea we already tackle two and a half of those areas.

In terms of other important collaborations, we are engaged in two major research programmes – CEAT and RISE that bring together clusters of companies providing technological capabilities in advanced therapies including exosome development, ADCs, and epigenetic drug development. I chair a research and innovation group for a government entity called Genomes Partnership Wales, where we look at how to integrate genomics across the board, from pre-clinical research and innovation to driving genomics into the healthcare providers.



In the gynaecological field, what are the different disease states and treatment limitations where your research could potentially fill gaps?

PCOS it's a multifactorial disease characterised by hyperandrogenaemia in women. There's a psychological element to it as well as a medical element. Patients can be infertile and some of the women don't ovulate at all. Current treatments are generally not well defined, and patients often pursue IVF programmes. We are looking at how we can better understand the infertility in these women and therefore, how we may better intervene.

With endometriosis, it manifests as non-malignant growth within the peritoneal cavity and is associated with chronic pain. The lesions can be removed surgically and often are. It's a debilitating disease that's been under recognised – only now, there's a drive towards increased awareness through increased press coverage and charities being more active. Here, as well as looking firstly to understand the infertility component of the disease, we are also taking the approach with genomics to gain an enhanced understanding which may help in disease management.

What are the different therapeutic or diagnostic approaches you're investigating?

We're pushing on the therapeutic side of things in endometrial and ovarian cancers. Endometrial cancer prevalence is increasing, and it is associated with PCOS and with obesity. Historically, it was considered a cancer that developed in post-menopausal women. What you see now, is an increase in endometrial cancer in younger women that are more likely to want to try and become pregnant. We've therefore been looking at antibody drug conjugates (ADCs) and exosomes therapies. We're also starting to look at the use of nanoparticles to deliver more classical drugs.

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Ovarian cancer is slightly different from the endometrial one, it is often diagnosed late, already metastatic and has expanded into the peritoneal cavity and beyond. There's significant treatment development but the standard of care treatments are the drugs from the 1950s that are systemic, and where patients often develop resistance quite quickly. Again, we are looking at therapeutics developing ADCs and particle delivery to the site of the disease, which in this case is the peritoneum.

From a diagnostic point of view, we are focussed on whether the environment in which cancer develops is signalling in some way. Ultimately, we want to be able to detect the disease earlier – if you can detect early, you can guide the surgeon early and you can potentially cure the disease.

To summarise, I would say the therapeutic strategies are more geared towards oncology and our diagnostic strategies are geared across the board.

What is your view on the current limitations of bringing these types of new assets into the clinic?

ADCs are rapidly coming online, with approximately 10 being FDA approved. They are very effective when you have the targets to the antibodies overexpressed uniquely on the tumour. The target has to be present, and in that sense, it is only limited by the proportion of the population whose cancers overexpress those targets.

ADCs are a relatively new generation of antibody targeted technologies that work very effectively as seen with Adcetris which targets CD30 in blood cancers. Kadcyla, which targets the HER2 receptor in breasts, is also very effective and it's now being developed for ovarian cancer. However, if you look at HER2 profile and where it is expressed, it is both on healthy and non-healthy tissues which is not at all ideal.

The ADC space is complex – you have the targeting antibody which can form one element of IP for a company. The conjugation part of ADC development is based on complex chemistry – there are companies that are just focused on developed linker technology. You've got an IP space, you've got complex chemistry and then you've got the drug element. Here you can use super potent chemicals that you can't possibly use systemically because of their side effects, so you bury them in an antibody and can get them to the site of the disease.

Saying all that, we've reached more than 10 approvals against different diseases and different targets to the same disease, and now we're starting to see the development of bivalent/bispecific antibodies. So rather than just targeting one protein which is overexpressed on the cancer, you target two using the same engineered antibody – then you start to get an even more specific response.

From the different aspects you've mentioned, which do you think will need the most work in terms of speeding up the process for the transition to clinic and what types of innovation may help?

There's so much preclinical work out there on ADCs and there needs to be a filtering process on what is taken into phase 1. The preclinical work in in vivo models is where you'll see most of that filtering.

I think that the main gateway is the linker drug conjugate technologies. There's the stability of the drug element to be considered, and there are the limitations in the numbers of linkers and drugs available, so I think those areas will push the research forward. A good example would be the German company Heidelberg Pharma – they've been working for a very long time on a drug called alpha-amanitin which is a well-known mushroom-derived drug. It's always been known to be lethal, but they've made a synthetic version and they've got a lot of interest from those companies needing novel payloads.

What we're also seeing is people starting to develop ADCs outside of oncology because you will always have overexpressed proteins and they're the basis of any biomarker in immunohistochemistry. To develop outside of oncology where you don't particularly want to kill the cell but might want to change its metabolism or as I like to say, "tickle the cell", new classes of payloads will be needed.

How do you think ADCs compare to the implementation of other tailored approaches, such as genomics?

With the ADCs you need to know the targets that are expressed. You've got a single protein being targeted, two at most, so the screening is quite simple. Similarly, it's the case for small molecule kinase inhibitors where you've got a fixed number of targets. Mutational screening is important to determine whether certain kinase inhibitors will function effectively.

Whilst I don't think it's necessary, I can see the possibility that everybody's going to get their genome sequenced at some stage as the cost keeps driving down. From this, you'll know what an individual's mutational burden is, and from

this, how an individual might respond to certain treatments. Take the case of the kinase inhibitors – this is going to speed up decisions around what treatments could be given.

Currently there are many large genome projects across the globe. In the UK you've got the 100,000 Genome Project which is evolving into the 500,000 Genome Project. Pharmaceutical companies are also building their own genome databases. With this information, you can build a better understanding of single gene mutations at a population level and then potentially go down a gene therapy route using oligonucleotide-based therapies to correct the effects of the mutations.

For drug development a good example is with the Cancer Research UK and AstraZeneca collaboration around the CRISPR technologies. Using CRISPR allows the effects of test compounds to be evaluated in cell models that have been engineered to contain mutations. It's also worth noting that with the mutations from the whole genome sequencing, you will have the clinical records of all those patients allowing you to do the association studies, and that's been done as part of the Genomes UK programs.

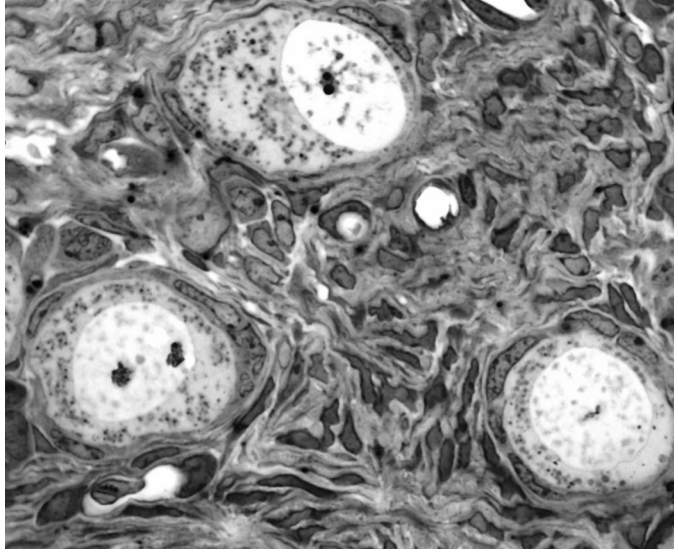
> **"There are other areas of functional genomics looking at gene profiling – which genes are being expressed and which aren't. These will allow genomics to really come into play, leading to better and early diagnosis, and finding applications in areas such as oncology and haematology."**

Can you expand on the merging of different areas such as genomics, transcriptomics and pathology in the clinical practice – do you already see it being applied and if not, how could it be done?

For solid cancers, the genome work happens in the genome service. Samples get sent off and analysed with Illumina gene panels – and then your pathology will be done on tissue sections that get stained for a couple of antibodies. What emerging functional genomics technologies called 'spatial transcriptomics' allow you to do, is to take that tissue sample and spatially resolve what genes are being expressed in different areas of a tissue sample.

With this knowledge, you can potentially develop whole new treatment regimens through understanding and looking to modifying the local environment of a tumour. This is certainly coming, and we're working with pathologists to see how to implement the technology, how to get samples out of theatre to pathology and onto one of these spatial slides, and how we get the data back very quickly to a multi-disciplinary team that manages cancer patients.

For blood-based cancers, you can do single cell sequencing to look at the whole repertoire of cells in the blood of the patient. You can identify the T cells, B cells, dendritic cells among others and you can then look at what's happening in those cells in the snapshot where you draw blood, and that's going to inform diagnosis and treatment. All this is driven by some quite simple and elegant technologies and a lot of bioinformatics. The clinicians can see the power of this, but they don't want to be presented with reams and reams of data. It's therefore important to present them with the analytics that can show the meaningful gene expression profile of a patient to help develop and implement the best treatment plan. Here, data visualisation will be key.



How important is the simplification of the information and messaging that reaches the physicians?

> **"I've talked to so many clinicians over the years that say 'this is incredibly exciting science, but I want you to give me a red or green light. I don't have time to look through a 20-page report. Tell me what it means and tell me how it's going to help manage patients better'."**

That's something we have to work on. We've got electronic patient records – if we integrate all this genomics data into it, yes, the files are going to get bigger, but the treatment process is also going to get better. We must keep refining, and we will get to something that's significantly simplified and is going to lead to better and more effective patient management. I'm currently working with

physicians on a programme of research where we are looking to implement functional genomics into a new pathology initiative that we're setting up in West Wales. Data will need to be integrated into Wales central genomics services, and through this into patient records. These tasks are underway, but there is a tremendous amount of work to be done.

How should we tackle the demographical challenges that come with genomic analysis?

To date most genomics research has been done in western developed countries because of the investment and access to technology. A large proportion of the patients therefore are from a white western demographic. We did a paper on functional genomics recently and it clearly emerged that the numbers of Asian and African patients or volunteers in studies is very low in terms of global population density. We therefore need to understand the differences, certainly at the genome level. We know there are underlying genetic differences – certain Asian populations have prevalence for different diseases compared to western populations and the same happens with African populations in terms of disease susceptibility.

The positive thing I can say, is that the genomic technologies are becoming more distributed and genome centres are being set up across the globe. The challenge then becomes, how to integrate everything globally and how to merge all these enormous data sets. I think it's something we need to be very mindful of. There are rapidly growing companies, for example in China, that are going to serve those very large populations predominantly – we need to make sure the drugs that are developed can benefit as broad a population as possible.

Amongst the different therapeutic approaches being explored in gynaecological cancers (namely endometrial and ovarian), antibody drug conjugates (ADCs) are showing great promise. However, complications related to the different manufacturing processes require a concerted integration of the academic and industry spaces for a smoother transition to the clinical setting. Additionally, merging technologies such as genomics, transcriptomics and pathology offers potential for a more tailored and comprehensive analysis of patient samples and treatment identification, but needs to go through a process of message/content simplification to obtain physicians' endorsement and be implemented into the daily practice. Starting the conversation early with the aid of specific programmes is what will help these new platforms succeed in the long term.

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