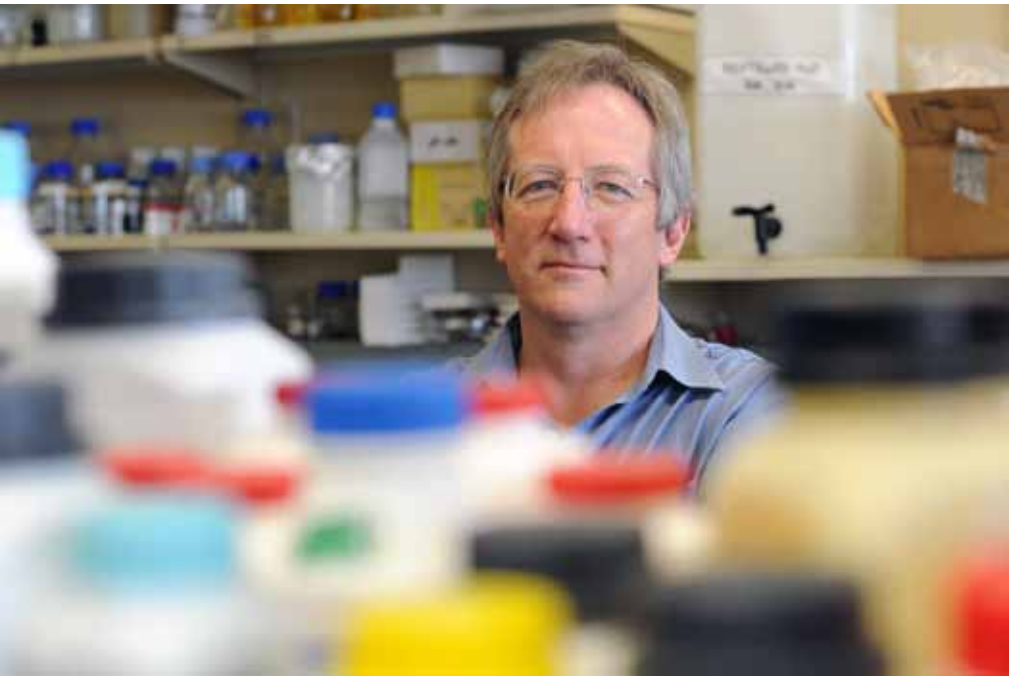
Leading SA Virologist has Commercialisation in Sights



Prolific inventor and one of the country's most cited researchers, Professor Ed Rybicki is an international authority on the creation of human and animal vaccine candidates – including trial vaccines for HIV and Human papillomaviruses (HPV).

As top UCT inventor, Rybicki has 44 granted patents in territories including South Africa, Namibia, China, India, USA and Europe and numerous ongoing applications from the 11 patent families on which he appears as a co-inventor. He is now also seeing the commercialisation of his intellectual property bear fruit, with significant royalties beginning to flow from 2010. Importantly one licensing deal has brought further research and development work into his laboratory as well as in-bound technology transfer. Another exciting collaboration with a commercial partner is finally moving an animal vaccine, which has floundered in the innovation funding chasm for a number of years, well into the development and commercialisation phase.

Based in the Department of Molecular and Cell Biology, but also working in the Institute of Infectious Disease and Molecular Medicine (IIDMM), Rybicki concentrates on the expression of antigens from human and animal viruses in both plants and insect cells for use as human and animal vaccines, and also investigates the genetic diversity and molecular biology of single-stranded DNA viruses.

Aside from advances in the creation of vaccines for mucosal Human Papilloma Virus (HPV) (which is responsible for cancers of the cervix) and Human immunodeficiency virus type 1 (HIV-1) subtype C, made in conjunction with his wife and colleague Professor Anna-Lise Williamson's research group at the IIDMM (see page 21), Rybicki and his researchers have made progress on the characterisation and molecular biology of the parrot Beak and feather disease virus (BFDV).

Rybicki also remains committed to the work on the maize streak virus and other southern African Mastreviruses which he embarked upon 25 years ago. An important part of this is an ongoing project on genetically engineering maize for resistance to maize streak virus, initially done in collaboration with Professor Jennifer Thompson, and more recently with Dr Dionne Shepherd.

In addition to HIV, HPV, BFDV and maize streak virus research, the group are also applying established plant expression technology to quickly produce multiple structural proteins for the distantly related reoviruses, human rotavirus and bluetongue orbivirus 7, and have also recently generated a patent application for a candidate plant-made vaccine for H5N1 avian flu.

Collectively with Williamson's research group, Rybicki and his team have been highly successful in generating IP, but although some of this is being licensed to major companies, "the lack of any other products than the US- or UK-manufactured HIV candidate vaccines in human trial presently, is a matter for frustration," he says. In part this relates to the significant barrier to entry when establishing a local start-up in the human vaccine sector and the dearth of a variety of local vaccine producers to partner with; there is currently only one in South Africa, the Biovac Institute, with whom they collaborated on certain projects.

Rybicki says that the development of transgenic maize resistant to maize streak virus is highly advanced. "A number of transformed plant lines having been successfully tested in glasshouse trials, and used in experimental breeding

programs to "introgress" the trait into commercially-usable breeding lines," he says

With funding from Pannar Ltd of South Africa, the team is presently developing second- and third-generation transgenic maize lines resistant to maize streak virus, via pathogen-derived resistance. "This involves expressing a mutated virus protein involved in virus replication as a 'dominant negative mutant' to destructively interfere with virus replication in transgenic plants," he explains.

"First generation plants proved the concept for the resistance mechanism in greenhouse trials, but contained antibiotic resistance genes. Second generation plants now no longer have this gene and are resistant to the virus and will be field-trialled soon, while third-generation plants are being developed which will contain a novel inducible gene technology which could be more effective," Rybicki reports.

This work has resulted in one patent and he is confident of success further along the innovation chain. "There's a very real possibility of serious, international commercialisation coming out of this patent," he maintains.

"This is mealies we're talking about and people sell a lot of mealies," he exclaims. "So we're witnessing an undisputed success story in motion, but we haven't seen the financial rewards as the product isn't out in the field yet."

His initial HPV vaccine work began in the mid-1990s, funded by Poliomyelitis Research Foundation, and led on in 1999 to two successive Department of Science and Technology Innovation Fund projects which ended in 2006; these resulted in several major breakthroughs. They were able to produce the L1 capsid protein, which forms the heart of the vaccine, in both plants and insect cells in addition to a chimaeric form that it is hoped will elicit a wider spectrum of cross-neutralising antibodies than standard L1.

"We were among the first – one of three groups publishing simultaneously in 2003 – to demonstrate the feasibility of making a HPV vaccine in plants via transgenic plants, and were the first to demonstrate both that a plant-derived HPV vaccine was protective in an animal model and that transient expression in plants was a very good means of making HPV vaccines," he says proudly.

After the Innovation Fund project ended in 2006, the papillomavirus vaccine development has continued in a consortium composed of several collaborators. The consortium, led by Professor Johann Gorgens of the University of Stellenbosch, comprises Rybicki's (with colleague Dr Inga Hitzeroth an important contributor), as well as researchers from the University of the North West, Medunsa, NICD (JHB) and the University of Limpopo. The project began in 2007 and is financed by the DST and NRF with funds that stem from a South African and Cuban collaboration agreement.

"We are developing novel chimaeric HPV vaccine candidates in plant and in insect cell expression systems as well as exploring the production of a novel subunit South African rotavirus strain vaccine against infant diarrhoea in plants," he says.

"Progress has been very satisfactory, with five different HPV variants all produced in both plants and insect cells, three at very high yield, and tested in mice for immunogenicity. The rotavirus capsid protein expression has also gone well, with several proteins produced at high level."

Rybicki and Hitzeroth are also making breakthroughs in their work on a viral disease responsible for a common malady in parrots and related birds. Beak and feather disease virus (BFDV) causes skewed beaks and feather malformation in affected birds, as well as weight loss in adult birds and often death in juveniles. Since 2002, in work initiated with Prof Anna-Lise Williamson, the researchers have been investigating the possibility of making vaccines and therapeutics for the virus disease.

BFDV causes psittacine beak and feather disease (PBFD) in all psittacine birds (parrots). It is a highly infective and debilitating disease and to date no specific treatment exists to protect against it. It is a contributing factor to the decline of wild populations and especially endangered species such as the South African Cape Parrot. It is also the scourge of a multi-million rand global pet industry in which parrots and related birds are a lucrative trade item.

"We have made candidate subunit protein vaccines against BFDV which have been subjected to preliminary testing in budgies, as well as progress towards establishing a reliable challenge model for infecting vaccinated birds," Rybicki explains.

If successful the vaccine could significantly aid eradication of the disease in South Africa and help ensure infected birds are not traded or exported, it could counter this virulent disease in wild populations of parrots, especially the endangered Cape Parrot, which has been found to have high infection rates in the wild in South Africa.

Rybicki and Hitzeroth are excited about the prospect of its development. "We have comprehensively mapped diversity and made significant progress to both making and testing vaccines and therapeutic antibodies against the virus

which has generated a patent," he says.

"My vision for these projects is that we can develop novel, low cost vaccines and therapeutics and reagents using both plant and insect cell expression technology, and at the same time train students and technical folk to a high degree of skill in cutting-edge techniques," he adds.

Rybicki's laboratory is also investigating the feasibility of producing emergency response vaccines against highly pathogenic avian influenza viruses - specifically, H5N1 flu - in both plant and insect cells and as a DNA vaccine.

He explains this particular study was initiated in 2006 with extraordinary one-year funding from the local Poliomyelitis Research Foundation (PRF) following warnings by WHO officials that there would be no vaccines available for developing countries if a bird flu pandemic hit. This funding was extended in 2008 with a Major Impact Project Grant from PRF (2008-2010) and progress has been heartening.

"We have been able to produce large amounts of H5 haemagglutinin protein in plants, as well as in insect cells, with the former producing surprisingly large amounts of protein that appeared to fold properly, and to have haemagglutinating ability, and to be immunogenic. A DNA vaccine candidate is also being investigated," elaborates Rybicki.

His research team also obtained EU funds as part of a Europe-Russia-SA consortium called "PlaProVa" for plant-produced vaccines. The funding, which is for the period 2009-2011, is being used by them to develop plant-made vaccine candidates against bluetongue virus of ruminants.

The virus causes bluetongue disease mainly in sheep, but also can also affects cattle, goats and animals in the wild such a buffalo and antelope. The disease is endemic in South Africa and is currently a serious emerging disease problem in Europe. Rybicki believes satisfactory progress has been made in this area, with several of the virus structural proteins expressed and reagents made for detection of proteins.

The fact Rybicki works 'across species' has given him an extremely broad view of virology and biotechnology. "It also gives one unique advantages when it comes to exploiting certain niches of research, and in having unique ideas in the innovation space. However, mostly this is due to my having been a plant virologist, which is a narrow enough field of work that one takes a lot of information from the human and animal virology spheres, which definitely does not work in reverse!" he stresses.

"This allowed a fairly easy transition into working with animal and human viruses, after plant virus research did not attract funding in the 1990s."

It was this reduction in funding that led to Rybicki seeking funding from other sources and which ironically led to his group receiving ten-fold his previous funding amounts. "Thereafter, it has been an interesting tightrope walk over a plant virology-virus biotechnology divide, with the viral biotechnology side gradually becoming predominant in my interest bubble," he reports.

Looking back over his rollercoaster innovation ride Rybicki candidly expresses that despite the ensuing success of many of his projects, innovating was something he "drifted into". He advises others testing the innovation waters to prepare for a serious learning curve with regard to understanding intellectual property, and how to not only develop it, but also how to exploit it.

"Do not divulge things willy-nilly, but rather talk to RCIPS about whether or not something is protectable, and if so,

how to patent, copyright, or protect other rights. Also prepare to visit and revisit things that you thought you'd left behind years ago, as patent disputes, renewals and/or revisions come up at regular intervals," he cautions.

He says part of the recipe for successful innovation is being open-minded enough to shift from established positions. "You've got to be able to change your mind and you've got to shift with imperatives, and that includes funding imperatives. You've got to be able to move fairly fast to keep abreast with, in this country especially, trends in funding."

Despite setbacks he hastens to add that over almost two decades they have collaboratively managed to build up a valuable body of expertise, including a legion of trained students and other scientists, as well as a large body of published work.

As for the immediate future, Rybicki envisages he and his researchers becoming a dedicated animal and emergency response human virus vaccine development group, a technology platform for insect cell and in particular plant expression of high-value proteins, and a centre for the development of transgenic maize for other traits than MSV resistance."

Application in Reference style	Granted Regions	Pending Regions
Rybicki, E.P., Varsani, A.D. Chimaeric Human Papillomavirus 16 L1 Virus Like Particles and a Method for Preparing the Particles.	AU, ZA, US, EP: [LU, IT, MC, RO, PT, DE, SE, SI, TR, NL, CY, SP, AT, FI, CH, IE, CZ, DK, SK, FR, GB, GR, HU, BE, EE, BG]	JP, US Reg.
Rybicki, E.P., Varsani, A.D., Williamson, A-L. Pharmaceutical Compositions and a Method of Preparing and Isolating Said Pharmaceutical Compositions, and Use of Said Compositions for Prophylactic Treatment of Lesions and Carcinomas.	IN, ZA, CN	_
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Mangwende, T., Rybicki, E.P., Shepherd, D.N., Thomson, J.A. An Isolated Nucleotide Sequence and Transgenic Organism Containing Said Sequence.	ZA	_
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Hitzeroth, I.I., Rybicki, E.P. Method for Enhancing the Expression of HPV L1.	Prov	_