R&D MALAYSIA

Cure for animals, hope for humans

A locally made antiviral drug has created a stir in animal welfare circles for its high rate of efficacy. ***Najua Ismail*** traces the development of the drug from its surprising origins to its commercialisation.

ORANGE was a friendly stray cat who roamed the streets of Taipan in Subang Jaya, Selangor. One day, he went missing and the kind lady who had been feeding him assumed he had died or moved away. When he emerged again after a few months, she was shocked to see him covered from head to tail in ulcers, some the size of a 20 cent coin. Orange was taken to a veterinary clinic where he was diagnosed as having sporotrichosis, an infection caused by fungus found in soil and vegetation.

"He was bleeding badly and even when he shed, you could see blood all over the wall," says Dr Benny Tan at his clinic in Puchong, Selangor. "It was a bit gory for people not used to it."

When he first heard of Orange's condition though, Dr Tan was unconcerned as he knew how to treat the infection. "I said, 'oh, sporo, easy to treat, give him medication,'" he laughs. "To me, you don't have to do anything bombastic, you know what it is, you get the medication, mix it in the food and feed it to the cat."

Unfortunately, things were not as simple as they appeared to be. Despite undergoing the standard treatment, which consisted of antibiotics and anti-fungal medication, Orange showed only the slightest sign of improvement: he was not bleeding as much and his ulcers had shrunk a little bit. "He got better but the improvement was just 20 per cent," maintains Dr Tan. "There was also a concern because anti-fungal medication will have an effect on the liver the longer the animal is on it. And Orange was already on it for three months."

Dr Tan suspected that Orange might also have a life-threatening condition. A blood test confirmed his suspicions: Orange had feline immunodeficiency virus or FIV. FIV is the feline equivalent of Human Immunodeficiency Virus (HIV). However, FIV cannot be transmitted to humans and cats cannot contract HIV. Both viruses attack the immune systems of their hosts who will exhibit symptoms of flu-like illness including fever and lethargy during the initial stage.

Then the virus retreats into submission as the host's immune system builds up its resistance. Like the Greeks in the wooden horse though, the virus has only gone into hiding where it is chipping away at the immune system's defenses in preparation for a more severe attack.

> "I thought okay, if we cannot test on HIV-1, then we will test on the virus nearest to HIV-1, which is FIV."
> ***Ung Eng Huan***

When this happens, the compromised immune system will have trouble keeping the virus at bay. As a result, the host will become susceptible to opportunistic infections that take advantage of its weakened immune system. Eventually, this will escalate to full-blown Acquired Immune Deficiency Syndrome (AIDS) in humans and Feline AIDS (FAIDS) in cats.

The silver lining in the FIV positive diagnosis was that Dr Tan now knew why Orange was not responding to treatment, but it came with a very dark cloud, which was the knowledge that the cat was on a downward spiral with no hope of recovery.

Until he heard about a scientist who was looking for cats and dogs to test a new drug on.

HIV AS THE MODEL: In 2008, Ung Eng Huan was working in an aquaculture company in Tawau, Sabah. He was asked to come up with a solution to a problem that was the bane of the aquaculture industry. "At that time, as it is today, viruses are very destructive in aquaculture. For example, the White Spot Syndrome Virus (WSSV), which kills prawns, has cost the aquaculture industry US$10 billion (RM30 billion) globally in the last decade," says Huan during a busy morning at his office in Petaling Jaya, Selangor where we were constantly interrupted by the buzz of his mobile phone.

As a marine biologist, Huan had no experience in drug development. Neither did his colleague, Awang Muhd Sagaf, a molecular biologist who was involved in disease detection. But the two put their heads together and decided to start by looking at the most studied virus in human history – the HIV-1 virus.

"HIV-1 became the model virus and we began to see what others have done so far. When we last did the review back in 2008, I think there were 26 HIV drugs approved by the US Food and Drug Administration (FDA)," explains Huan. And we looked at the mode of action for each one of these drugs and they were all monofunctional. So, we thought, what if we made a drug that could attack HIV-1 from four different locations instead of one?"

Awang Muhd Sagaf (left) and Ung Eng Huan.

They decided to find a way to string up gene sequences from the genomes of various species whereby each gene would attack one viral pathway. "If we could string them together into a Chimeric AntiMicrobial Peptide (ChAMP), then we could hit many pathways simultaneously," he elaborates.

Aside from stringing up genes, producing the antiviral drug involves a complicated process known as protein refolding. Huan likens protein refolding to kung-fu by physically demonstrating now by moving his hands in front of his face as part of a kung fu move, he ends up blocking his mouth. "Let's say my mouth is the active side, I can accidently block the active side and then it won't be functional."

Similarly, a protein can be folded in a million different ways. However, depending on how it is folded, it may block an active side. "In our protein, we have actually identified four different active sides," he elaborates. "If we fold it wrongly at any one time, one or more of the active sites will be blocked and that will interfere with the functionality of our protein as an antiviral."

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