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Therapeutic focus – Tekmira setback a sign of little Ebola progress

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It was unfortunate timing for Tekmira Pharmaceuticals last week when, in the midst of the deadliest Ebola virus outbreak ever documented, it was forced to announce that US regulators had put its phase I antisense project for the condition on clinical hold for safety reasons.

Not only does the announcement represent a setback for research into treating the deadly virus, it also serves to demonstrate how far the sector is from discovering a cure or vaccine – and the most advanced projects so far are in the costly antisense space. Big pharma has no presence whatsoever, and much of the work is being done by acadaemia and biodefence specialists (see table).

From animal to human

Ebola and the related Marburg fever are haemorrhagic diseases caused by a family of viruses known as filoviruses, first identified in 1967. These viruses typically spread from natural hosts in animals, predominantly monkeys and bats, to humans, and once a human is infected it can spread to other humans.

The virus attacks numerous types of cells in the body, and among them are the macrophages of the immune system, which simultaneously spread it throughout the body and generate cytokines in response to the invasion, magnifying the effect of the disease. Diagnosis is complicated by similarities in ebola symptoms with other routine diseases. Treatment, meanwhile, is non-existent other than supportive hospital care; neither are there any preventive vaccines.

This is a particularly deadly virus. In the current outbreak, which arose in March, there have been 750 cases and 445 deaths. Another indication of its lethality is that, as of mid-June, just 117 patients of the 522 cases reported at that time were listed as recovered and discharged.

Thus the developing world is keen to see the launch of a treatment. It might be waiting quite a while, and perhaps even longer if it wants to see an affordable one.

Slow progress in Ebola and Marburg viruses					
	Project	**Company**	**Pharmacology class**	**Proprietary level 2**	**Indication summary**
Ebola haemorrhagic fever					
Phase I	AVI-6002	Sarepta Therapeutics	Ebola virus antisense	NME + proprietary drug delivery	Ebola haemorrhagic fever [Phase I]
	TKM-Ebola	Tekmira Pharmaceuticals	Ebola virus antisense	NME (patented compound)	Ebola haemorrhagic fever [Phase I]; Ebola haemorrhagic fever prophylaxis [Phase I]; Marburg haemorrhagic fever [Preclinical]
Ebola haemorrhagic fever prophylaxis					
Phase I	Ebola vaccine	Uniformed Services University of the Health Sciences	Ebola virus vaccine	NME (patented compound)	Ebola haemorrhagic fever prophylaxis [Phase I]
Marburg haemorrhagic fever					
Phase I	AVI-7288	Sarepta Therapeutics	Marburg virus antisense	NME + proprietary drug delivery	Marburg haemorrhagic fever [Phase I]
Marburg haemorrhagic fever prophylaxis					
Phase I	Marburg vaccine	Uniformed Services University of the Health Sciences	Marburg virus vaccine	NME (patented compound)	Marburg haemorrhagic fever prophylaxis [Phase I]

What will it cost?

Tekmira's setback last week happened during a phase I single ascending dose trial of TKM-Ebola in healthy patients without use of steroid pre-medication. The company said the FDA wanted to see "data related to the mechanism of cytokine release observed at higher doses", something the group said was "well understood". The regulator was seeking a protocol modification to the trial before a multiple ascending dose portion began, to ensure safety.

The Vancouver-based group's shares fell 17% on the announcement last Thursday. TKM-Ebola was the only project in the filovirus space to have a sales forecast attached to it – $89m in 2020, according to *EvaluatePharma*.

Like so many of the candidates in this space, TKM-Ebola was backed by the US government – in 2010, it was the recipient of a $140m contract from the Defense Department's Medical Countermeasure Systems BioDefense Therapeutics joint product management office.

Similarly, Sarepta Therapeutics' AVI-6002 was being advanced under a Defense Department contract, but the Massachusetts-based group received a stop-work notice in 2012 because of budgetary constraints. The group has said little about the project since then, although it continues work in Marburg virus with AVI-7288.

Although numerous vaccines addressing the two filoviruses are listed as being in preclinical stage, only one appears to be in active clinical work – a project from the Uniformed Services University of the Health Sciences, the US military's medical school.

Two other projects had formerly been listed in phase I, from Crucell and Okairos. Acquistion of the former by Johnson & Johnson and of the latter by GlaxoSmithKline has probably put paid to both of those projects, as neither of the big pharma buyers currently list a filovirus vaccine in its pipeline presentation.

It is interesting that the most advanced work is in antisense, a treatment approach that, if successful, would almost certainly present cost concerns for the West African nations so hard hit by the disease. Antisense makes more sense in orphan disorders like Duchenne muscular dystrophy where the cost effects are rather narrow.

Given the involvement of the US military, it is clear that protecting Western nations is a high priority, but whether that mission would lend itself to donating or at least offering the treatment to those poorer nations is an unanswered question.

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