

RIFT VALLEY FEVER THERAPEUTICS

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CLINICAL SYMPTOMS RVF



Icterus and Conjunctivitis: Managil, Gezira State, Sudan 2007. Source: Pierre Formenty

Disease

Majority self-limiting – uncomplicated febrile illness

Severe complications:

- **Ocular complications** (vision reduction, blind spots, photophobia, retro-orbital pain, uveitis, retinitis)
- **Haemorrhagic complications** (jaundice, blood in urine/faeces, vomiting blood, purple rash, gingival bleeding)
- **Encephalitis** - delayed onset - (severe headache, hallucination, disorientation, vertigo, excessive salivation, weakness, partial paralysis)
- **Miscarriage** - Association between RVFV infection and miscarriage
- **No specific treatment**



Bilateral Blindness. Ijara district, Kenya, 2006 Source: Pierre Formenty,



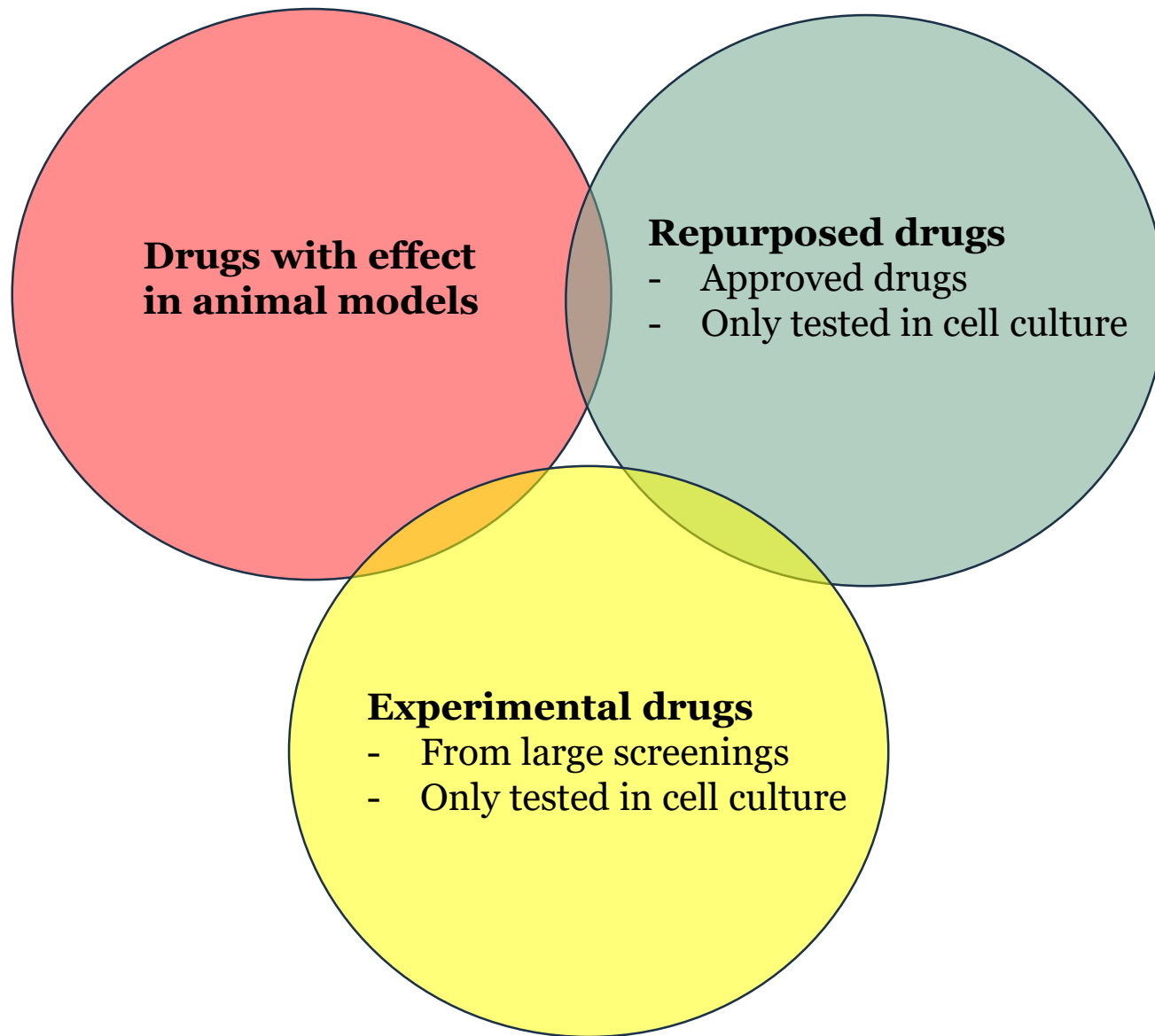
Bleeding from the nose and gum: Sudan 2007. Source: Pierre Formenty



Neurological complications: Tanzania. Source: Pierre Formenty

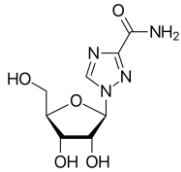


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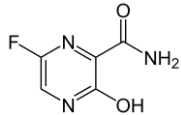
DRUGS WITH EFFECT AGAINST RVFV IN ANIMAL MODELS

Ribavirin



- Nucleoside analog, approved for treatment of selected HFIs.
- Mouse model liposome-encapsulated ribavirin – increased survival (Kende et al., 1985)
- In hamster model – inhibited hepatic infection, but not encephalitis (Scharton et al., 2014)
- Intravenous administration of ribavirin to patients during the 2000 outbreak in Saudi Arabia was quickly stopped due to the finding that it may increase the likelihood of neurological disease (Bird et al., 2012)
- (WHO list of Essential Medicines)

Favipiravir



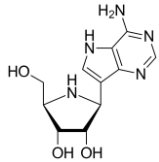
- Inhibition of Influenza virus RNA polymerase (Furuta et al, 2002)
- Approved in Japan against Influenza virus, Phase III clinical trials in USA against Influenza virus
- Hamster, 80% protection against RVFV (Scharton et al., 2014).
- Therapeutic window in hamsters – 6 hours post-infection (60% survival) (Scharton et al., 2014)
- Synergy effect with Ribavirin, 24 hpi 40% survival (Scharton et al., 2014)
- Rats – 92% survival at 48 hpi (Caroline et al., 2014)

2'-Fluoro-2'-deoxycytidine (2'FdC)

- In mice, delayed mortality by approximately 6 days compared to placebo. Low effect on encephalitis (Smee et al., 2018)



DRUGS WITH EFFECT AGAINST RVFV IN ANIMAL MODELS



Galidesivir (BCX4430)

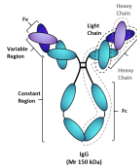
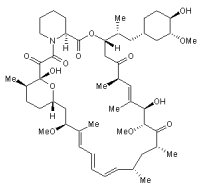
- Broad-acting nucleoside analog, effect against RVFV in vitro (Warren et al., 2014)
- Hamster model RVFV infected - 70% increased survival (Westover et al., 2018)
- In Phase I safety trials against YFV

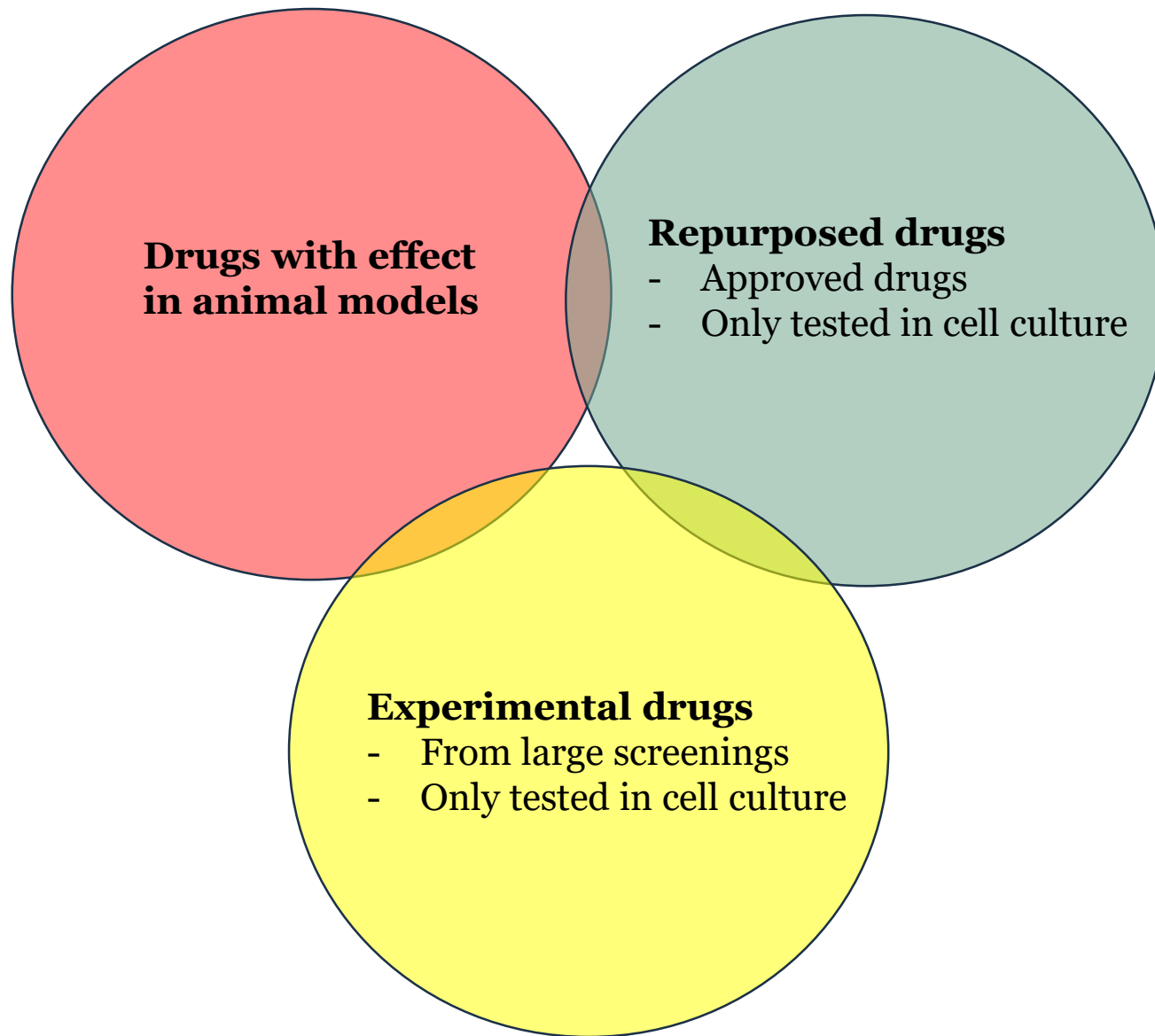
Rapamycin

- Macrolid, used for prevention of organ transplant rejection
- FDA approved treatment
- Mice - 50% increased survival (Bell et al 2017)

RVFV monoclonal antibodies (Mabs)

- Passive transfer of equine immunoglobulin F(ab')₂ fragments against RVFV resulted in reduced mortality in RVFV infected mice (Zhao et al., 2018).
- Gn-MAbs pre-exposure in a mouse model, 100% survival (Allen et al., 2018)
- Gn-MAbs added 1 day after virus challenge – almost 100% protection (32 of 33 mice protected), pre-exposure, all survived (34/34 mice) (Wang et al., 2019)





EXAMPLES OF REPURPOSED DRUGS WITH IN VITRO EFFECT AGAINST RVFV

Cancer drugs

- Sorafanib - a kinase inhibitor drug approved for the treatment of advanced kidney, liver cancer AML and thyroid carcinoma. No inhibition in a mouse model (Benedict et al., 2015)
- Bortezomib, a proteasome inhibitor (treatment of multiple myeloma) (Keck et al., 2015)
- Azacitidine - treatment of myelodysplastic syndrome, sometimes for treatment of acute myeloid leukemia (Ianevski et al., 2018)
- Obatoclox - an experimental drug for the treatment of various types of cancer (Andersen et al., 2019).

Immune suppressor drugs

- Cyclosporine - an immunosuppressor used for prevention of rejections in transplantations. Also against RA, psoriasis, Crohn's disease, nephrotic syndrome, keratoconjunctivitis (WHO list of Essential Medicines). (Ianevski et al., 2018)

Antibacterial drugs

- Minocycline – tetracycline antibiotic against bacteria, anti-inflammatory, neuroprotective (Ianevski et al., 2018)
- Oritavancin – glycopeptide antibiotic for the treatment of bacterial infections (Ianevski et al., 2018)

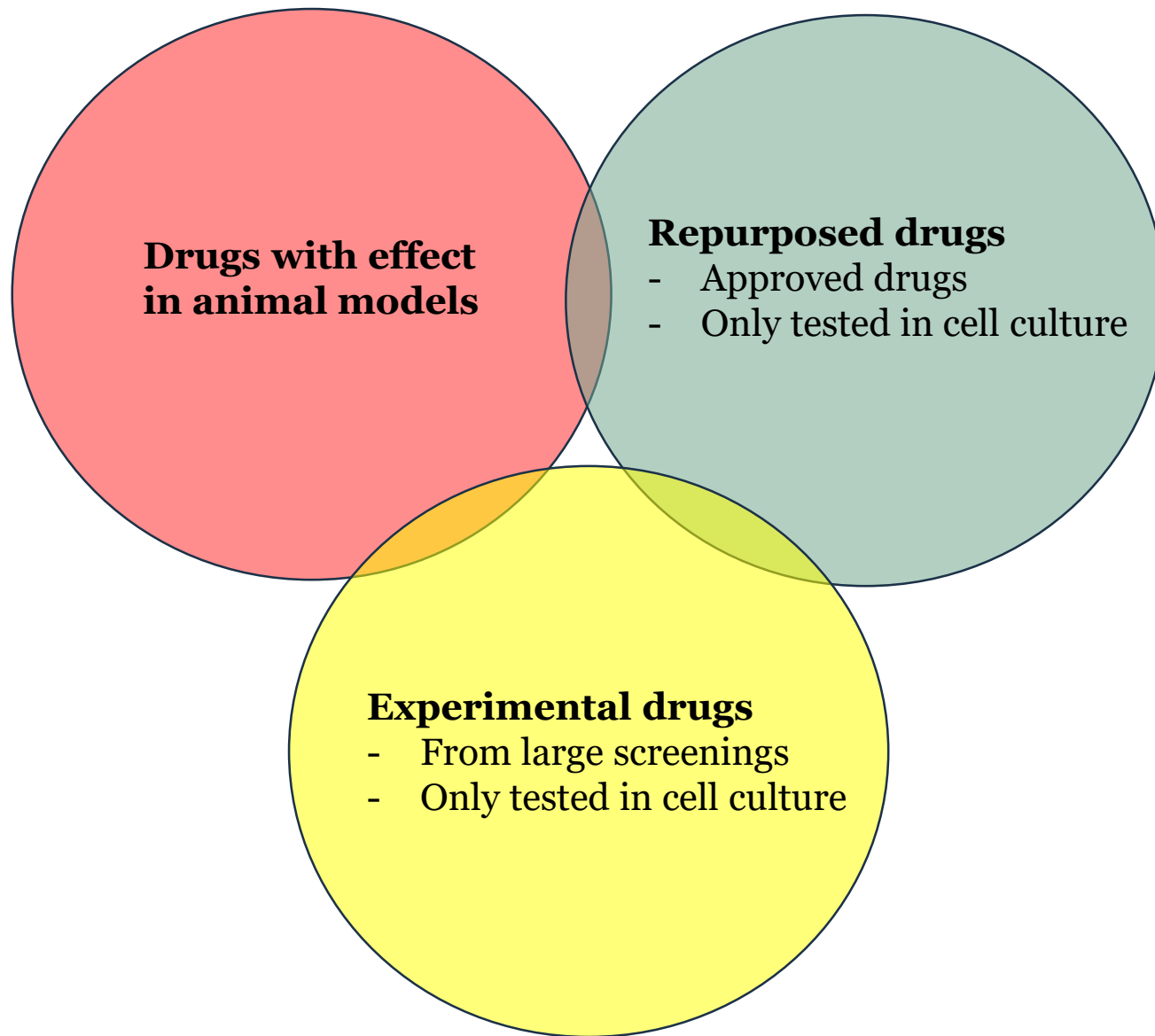
Anti protozoal/worm drugs

- Emetine – anti-protozoal and to induce vomiting (Andersen et al., 2019).
- Suramin – treatment for sleeping sickness and river blindness (WHO list of Essential Medicines) (Ellenbecker et al., 2014)

Antiviral drugs

- Ritonavir - HIV protease inhibitor, booster of other protease inhibitors (inhibit a particular liver enzyme that normally metabolizes protease inhibitors). (WHO list of Essential Medicines) (Ianevski et al., 2018)





EXPERIMENTAL DRUGS AGAINST RVFV

- Several publications
- Screening of compound libraries
- Strong inhibition of RVFV in vitro
- Not yet analyzed in animal models



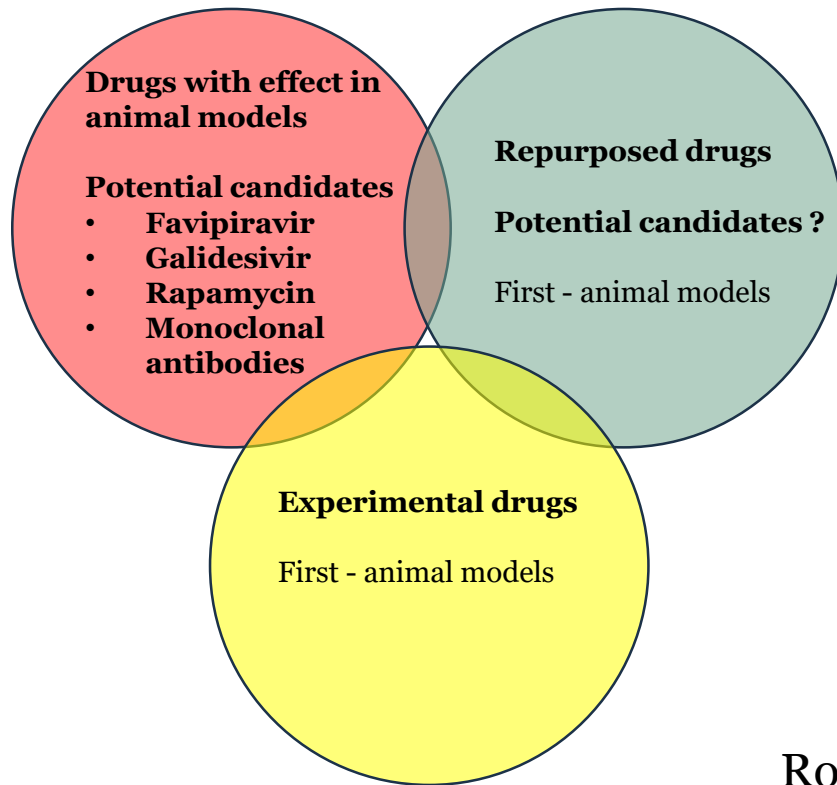


Photo: Magnus Evander

Rodent model? Monkey model?
 Case recognition?
 OCT? RCT?
 Therapeutic window?
 Side effects?



Source: Pierre Formenty



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CLINICAL TRIAL PRE-REQUISITES

- Patient with clinical symptoms that could be RVF attends health clinic/hospital
- **Needed** – a point-of-care test for rapid diagnostics to prove RVFV infection
- Patient can join clinical trial
- Different arms – antiviral, placebo etc
- End point – no severe RVFV disease or less severe RVFV disease in treatment arm
- NOTE: treatment of encephalitis may be impossible (virus is not present anymore and/or the antiviral will not pass BBB)
- NOTE: pregnant women cannot join the clinical trials on antivirals since most antivirals have potential side-effects that could affect the pregnancy

