CELEBRATES SCIENCE

APRIL 2017

THE SOUTH AFRICAN MEDICAL RESEARCH COUNCIL
INFORMATION SERVICES DIVISION
Chronic infection with Hepatitis B Virus (HBV) remains a problem of global significance and improving available treatment is important to prevent life-threatening complications arising in persistently infected individuals. HBV is susceptible to silencing by exogenous artificial intermediates of the RNA interference (RNAi) pathway. However, toxicity of Pol III cassettes and short duration of silencing by effectors of the RNAi pathway may limit anti-HBV therapeutic utility. To advance RNAi-based HBV gene silencing, mono- and trimeric artificial primary microRNAs (pri-miRs) derived from pri-miR-31 were placed under control of the liver-specific modified murine transthyretin promoter. The sequences, which target the X sequence of HBV, were incorporated into recombinant hepatotropic self-complementary Adeno-Associated Viruses (scAAVs). Systemic intravenous injection of the vectors into HBV transgenic mice at a dose of $1 \times 10^{11}$ per animal effected significant suppression of markers of HBV replication for at least 32 weeks. The pri-miRs were processed according to the intended design, and intrahepatic antiviral guide sequences were detectable for 40 weeks after the injection. There was no evidence of toxicity, and innate immunostimulation was not detectable following the injections. This efficacy is an improvement on previously reported RNAi-based inhibition of HBV replication and is important to clinical translation of the technology.
Article:

DOI: 10.1080/14760584.2017.1321990
Impact Factor: 3.555

Summary:

Background: Limited clinical data exists to assess differences between various infant pneumococcal conjugate vaccine schedules. In this trial, we evaluated immunogenicity of the 10-valent pneumococcal non-typeable Haemophilus influenzae protein D conjugate vaccine (PHiD-CV) administered using 3 different immunization schedules in HIV unexposed-uninfected infants in South Africa.

Methods: In this phase III, open, single-center, controlled study (clinicaltrials.gov: NCT00829010), 300 infants were randomized (1:1:1) to 1 of 3 PHiD-CV schedules: 3-dose priming and booster (3 + 1); 3-dose priming without booster (3 + 0); or 2-dose priming and booster (2 + 1). The booster was administered at 9-10 months of age. immune responses were assessed up to 21 months after primary vaccination.

Results: Post-priming antibody levels tended to be lower in the 2 + 1 group. At 6 months post-priming, antibody concentrations and opsonophagocytic activity titers were within similar ranges after 2- or 3-dose priming. Robust increases were observed pre- to post-booster in the 3 + 1 and 2 + 1 groups.

Conclusions: PHiD-CV was immunogenic when administered in different schedules. Post-booster responses suggest effective immunological priming with both 2- and 3-dose primary series and support administration of the booster dose at 9-10 months of age.
Director: Prof Michael Pepper

Article:

Jackson CS, Durandt C, Janse van Rensburg I, Praloran V, Brunet de la Grange P, Pepper MS. Targeting the aryl hydrocarbon receptor nuclear translocator complex with DMOG and Stemregenin 1 improves primitive hematopoietic stem cell expansion. Stem Cell Research. 2017 Apr 20.
DOI: 10.1016/j.scr.2017.04.007
Impact Factor: 3.494

Summary:
Culture conditions used for the expansion of hematopoietic stem and progenitor cells (HSCs and HPCs, collectively HSPCs) should ideally favor the self-renewal of long-term HSCs. At 20% O2, the synthesis of HIF-1α is balanced by its hydroxylation and proteasomal degradation. This favors HSPC differentiation, but can be prevented by culturing CD34+ cord blood cells in the presence of dimethylloxaloylglycine (DMOG). This differentiation may also be reduced by culturing the cells in the presence of Stemregenin 1, an antagonist of the Aryl hydrocarbon Receptor (AhR). The objective of this study was to investigate how hypoxia, DMOG and Stemregenin 1 might affect the expansion of HSPCs with the aim of identifying optimal conditions for expansion in culture. It was found that DMOG decreased proliferation but was effective in preserving the number of cells in the primitive hematopoietic sub-populations in vitro. The effect of DMOG was similar to hypoxia, although differences were observed with regard to the side population and CD34+ sub-populations. Stemregenin 1 on the other hand increased the size of the primitive as well as the other HSC sub-populations. The use of Stemregenin 1 with DMOG increased the proportion of primitive HSCs to 3.54% compared to 2.61% for Stemregenin 1 alone. In vivo engraftment studies confirmed these findings and showed that fewer cells (3710) are required for long-term engraftment when HSCs are grown in Stemregenin 1 together with hypoxia than in Stemregenin 1 under conditions of normoxia (13430).
Summary
Diabetic cardiomyopathy (DCM) is a disease of heart muscle that remains one of the leading causes of death in diabetic individuals. Shifts in substrate preference resulting in aberrant serum lipid content and enlarged left ventricular wall thickness are well-established characteristics associated with the development of DCM. As underlying mechanisms driving the onset of the DCM remain relatively unclear, this study sought to characterize age-dependent development of left ventricular (LV) wall thickness in diabetic (db/db) mice. Such data were compared with low-density lipoprotein (LDL) and triglyceride serum levels to assess whether any correlation exists between the parameters here investigated. For methods, db/db mice together with nondiabetic controls (n = six per group) were monitored from the age of 6-16 weeks. Mice were terminated each week to measure body weights, heart weights, liver weights, tibia length, and fasting plasma glucose levels. Heart tissues were stained with haematoxylin and eosin to measure LV wall and interventricular septum thickness together with an assessment of myocardial remodeling. Serum was collected weekly and used to measure LDL and triglyceride levels. Results showed that db/db mice presented significantly increased body weights, liver/body weight, and fasting plasma glucose levels from the age of 6-16 weeks. They further displayed a marked enlargement of LV wall and interventricular septum thickness from the age of 11 weeks, while increased heart weight/tibia length was recorded only from week 16. From week 11, the LV wall and interventricular septum thickness results corresponded with cardiac remodeling and raised LDL and triglyceride serum levels. In summary, age-dependent development of LV wall thickness in db/db mice is partially associated with increased LDL and triglyceride levels, elucidating a potential pathophysiological mechanism.
Summary

Background: Health interventions fall along a spectrum from simple to more complex. There is wide interest in methods for reviewing 'complex interventions', but few transparent approaches for assessing intervention complexity in systematic reviews. Such assessments may assist review authors in, for example, systematically describing interventions and developing logic models. This paper describes the development and application of the intervention Complexity Assessment Tool for Systematic Reviews (iCAT_SR), a new tool to assess and categorise levels of intervention complexity in systematic reviews.

Methods: We developed the iCAT_SR by adapting and extending an existing complexity assessment tool for randomized trials. We undertook this adaptation using a consensus approach in which possible complexity dimensions were circulated for feedback to a panel of methodologists with expertise in complex interventions and systematic reviews. Based on these inputs, we developed a draft version of the tool. We then invited a second round of feedback from the panel and a wider group of systematic reviewers. This informed further refinement of the tool.

Results: The tool comprises ten dimensions: (1) the number of active components in the intervention; (2) the number of behaviours of recipients to which the intervention is directed; (3) the range and number of organizational levels targeted by the intervention; (4) the degree of tailoring intended or flexibility permitted across sites or individuals in applying or implementing the intervention; (5) the level of skill required by those delivering the intervention; (6) the level of skill required by those receiving the intervention; (7) the degree of interaction between intervention components; (8) the degree to which the effects of the intervention are context dependent; (9) the degree to which the effects of the interventions are changed by recipient or provider factors; (10) and the nature of the causal pathway between intervention and outcome. Dimensions 1-6 are considered 'core' dimensions. Dimensions 7-10 are optional and may not be useful for all interventions.

Conclusions: The iCAT_SR tool facilitates more in-depth, systematic assessment of the complexity of interventions in systematic reviews and can assist in undertaking reviews and interpreting review findings. Further testing of the tool is now needed.

Director: Prof Catherine Mathews
1. **INTRAMURAL RESEARCH UNITS**

**Alcohol, Tobacco and Other Drug**

   **Impact Factor: 1.731**

**Biomedical Research and Innovation Platform**

1. Dludla PV, Essop MF, Gabuza KB, Muller CJ, Louw J, Johnson R. Age-dependent development of left ventricular wall thickness in type 2 diabetic (db/db) mice is associated with elevated low-density lipoprotein and triglyceride serum levels. Heart and Vessels. 2017 Apr 9. DOI: 10.1007/s00380-017-0978-3
   **Impact Factor: 3.434**

   **Impact Factor: 2.476**

**Biostatistics**

   **Impact Factor: 6.557**

   **Impact Factor: 1.844**

   **Impact Factor: 1.687**

**Centre for Tuberculosis**

   **Impact Factor: 2.885**

   **Impact Factor: 2.806**
   Impact Factor: 1.916

   Impact Factor: None

   Impact Factor: 13.217

**Gender and Health**

   Impact Factor: 17.686

   Impact Factor: 2.806

   Impact Factor: 2.265

   Impact Factor: 2.797

**Health Systems**

   Impact Factor: 3.935
   DOI: 10.7189/jogh.07.010701
   **Impact Factor: 2.707**

   DOI: 10.1186/s12874-017-0349-x
   **Impact Factor: 3.295**

   DOI: 10.1016/j.jclinepi.2017.04.010
   **Impact Factor: 4.978**

**Non-Communicable Disease**

   DOI: 10.1186/s12889-017-4199-6
   **Impact Factor: 2.265**

   DOI: 10.1186/s12879-017-2309-9
   **Impact Factor: 2.768**

   DOI: 10.1016/j.jstrokecerebrovasdis.2017.03.031
   **Impact Factor: 1.517**

   DOI: 10.1681/asn.2016050562
   **Impact Factor: 8.966**
South African Cochrane Centre

   Impact Factor: 2.369

   Impact Factor: 3.211
2. EXTRAMURAL RESEARCH UNITS

Antiviral Gene Therapy

   Impact Factor: 6.392

   Impact Factor: 6.688

Bioinformatics Capacity Development

   Impact Factor: 1.698

   Impact Factor: 1.698

Child and Adolescent Lung Health

   Impact Factor: 6.429

   Impact Factor: None

Developmental Pathways for Health

   Impact Factor: 2.265
Drug Discovery and Development

   DOI: 10.1021/acsinfecdis.6b00205
   **Impact Factor:** 3.600

   DOI: 10.1126/scitranslmed.aad9735
   **Impact Factor:** 16.796

Hypertension and Cardiovascular Disease

   DOI: 10.1093/ajh/hpx061
   **Impact Factor:** 3.541

Impact Factor: 47.831

Immunology of Infectious Disease


Impact Factor: 29.886

Maternal and Infant Health Care Strategies


Impact Factor: 1.826
Microbial Water Quality Monitoring
   DOI: 10.1155/2017/5178937
   Impact Factor: 1.300

   DOI: 10.12980/apjtd.7.2017D6-411
   Impact Factor: None

Respiratory and Meningeal Pathogens
   DOI: 10.1017/s0950268817000668
   Impact Factor: 2.075

   DOI: 10.1080/14760584.2017.1321990
   Impact Factor: 3.555

   DOI: 10.1016/s1473-3099(17)30232-3
   Impact Factor: 19.864

Risk and Resilience in Mental Disorders
   DOI: 10.1038/mp.2017.77
   Impact Factor: 13.204

   DOI: 10.1186/s12905-017-0388-9
   Impact Factor: 1.572

   DOI: 10.1590/1516-4446-2016-2079
   Impact Factor: 2.049
   **Impact Factor: 5.230**

   **Impact Factor: 11.412**

**Stem Cell Research and Therapy**

   DOI: 10.1016/j.scr.2017.04.007
   **Impact Factor: 3.494**
3. **GRANT FUNDED RESEARCH**

   **Impact Factor:** 3.550

   **Impact Factor:** 3.348

   DOI: 10.1371/journal.pone.0176006
   **Impact Factor:** 2.806

   DOI: 10.1016/j.ajhg.2017.03.012
   **Impact Factor:** 9.025

   DOI: 10.2989/16085906.2017.1285795
   **Impact Factor:** 0.861

   DOI: 10.1038/s41598-017-01184-7
   **Impact Factor:** 4.259

   DOI: 10.1007/s00737-017-0719-8
   **Impact Factor:** 3.367

   DOI: 10.2174/1871521409666170412124226
   **Impact Factor:** 2.598

DOI: 10.4102/sajpsychiatry.v23i0.1013
**Impact Factor: 0.193**

DOI: 10.1016/j.humimm.2017.04.006
**Impact Factor: 2.311**
4. RESEARCH CENTRES
Soweto Matlosana SAMRC Collaborating Centre for HIV/AIDS and TB

DOI: 10.1016/j.clim.2017.04.006
Impact Factor: 3.990

DOI: 10.1093/jac/dkx112
Impact Factor: 5.071
RESEARCH UNITS WITH NO QUALIFYING PUBLICATIONS

Intramural
- Burden of Disease
- Environment and Health
- HIV Prevention
- Office of AIDS
- Office of Cancer
- Office of Malaria
- Office of Tuberculosis
- Violence, Injury and Peace

Extramural
- Common Epithelial Cancer
- Diarrhoecal Pathogens
- Gynaecological Cancer
- Health Services to Systems
- Herbal Drugs
- HIV/TB Pathogenesis and Treatment
- Human Genetics
- Medical Imaging
- Molecular Mycobacteriology
- Prospective Gastrointestinal Cancer
- Receptor Biology
- Rural Public Health and Health Transition

Research Centres
- Advancing Care and Treatment (ACT) For TB/HIV
- Centre for Basic and Translational Human TB Research
- Centre for Tuberculosis Biomarker-Targeted Intervention
- Clinical and Community HIV-Tuberculosis Research Collaborating Centre
- TB Free through Research and Innovation
- Tuberculosis Collaborating Centre for Child Health (TB-CHILD)
- Tygerberg SAMRC Collaborating centre for HIV Laboratory Research
- UCT Collaborating Centre for Optimising Antimalarial Therapy in South Africa
- UP Centre for Sustainable Malaria Control
- Wits Clinical HIV/TB Research Unit, WITS Health Consortium
- Wits Collaborating Centre for Multi-Disciplinary Research on Malaria
- Wits RHI Collaborating Centre for HIV/AIDS