Journal Review

International Journal Harvest: interesting topics

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Dear readers,

The journal harvest in this issue includes a variety of topics that discuss scientific progress in stem cell research, screening for breast cancer in Sudan, stress ulcer prophylaxis, bariatric surgery for obesity, new anticoagulants & gastrointestinal bleeding, treatment of severe asthma in children, and evidence-based management of hyperkalaemia. Hope you enjoy reading and learning from it.

Generation of tumor-targeted human T lymphocytes from induced pluripotent stem cells for cancer therapy

Published online 11 August 2013

Abstract:
Progress in adoptive T-cell therapy for cancer and infectious diseases is hampered by the lack of readily available, antigen-specific, human T lymphocytes. Pluripotent stem cells could provide an unlimited source of T lymphocytes, but the therapeutic potential of human pluripotent stem cell–derived lymphoid cells generated to date remains uncertain.

In this study, authors combined induced pluripotent stem cell (iPSC) and chimeric antigen receptor (CAR) technologies to generate human T cells targeted to CD19, an antigen expressed by malignant B cells, in tissue culture. These iPSC-derived, CAR-expressing T cells display a phenotype resembling that of innate γδ T cells. Similar to CAR-transduced, peripheral blood γδ T cells, the iPSC-derived T cells potently inhibit tumor growth in a xenograft model. This approach of generating therapeutic human T cells ‘in the dish’ may be useful for cancer immunotherapy and other medical applications.

Comments:
Scientists have combined the ability to reprogram stem cells into T cells with a recently developed strategy for genetically modifying patients’ own T cells to seek and destroy tumors. The result is the capacity to mass-produce in the laboratory an unlimited quantity of cancer-fighting cells that resemble natural T cells. Earlier this year, a team led by cancer specialist Michel Sadelain at the Memorial Sloan-Kettering Cancer Center reported Phase 1 clinical trial results showing that treatment with genetically manipulated T cells could quickly eradicate tumors in patients with acute lymphoblastic leukemia, a tenacious cancer that kills more than 60 percent of those afflicted. However, the immunotherapy—one of a number of treatments in which the immune system is trained to attack cancer—requires the extraction, processing, and reintroduction of T cells from each individual patient’s own blood, making the procedure laborious and expensive.

Now, Sadelain’s team has used cell reprogramming technology to grow in a dish large quantities of precursor T cells that can be can be genetically modified to identify and eliminate tumors, potentially making immunotherapies for certain types of cancer more widely available.

“This is the first proof of principle that it is feasible to use a differentiated-directed process to generate lymphoid T cells endowed with therapeutic properties in vitro”.

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Sudan Med J 2013 December;49(3)
Breast-cancer screening with trained volunteers in a rural area of Sudan: a pilot study
The Lancet Oncology Published online January 31, 2013.doi.org/10.1016/S1470-2045(12)70583-1

Summary
Background: Breast cancer has a low cure rate in low-income and middle-income countries because patients often present with late-stage disease that has metastasised to other organs. We assessed whether the implementation of a cancer awareness and breast examination programme that uses local, volunteer women could increase the early detection of breast cancer in a rural area of sub-Saharan Africa.

Methods: We did this pilot study in two counties in Gezira State, Sudan. We chose Keremet (56 villages) as the experimental county and Abugota (79 villages) as the control county. Female volunteers from villages in Keremet were trained in the detection of breast abnormalities. When trained, volunteers visited households in their village and screened women aged 18 years or older for breast abnormalities, referring women with suspected breast cancer for medical diagnosis and, if necessary, treatment at the district hospital. We also ran a cancer awareness programme for both men and women in study villages. Villages in the control population received no intervention. This study is ongoing.

Findings: Between Jan 1, 2010, and Oct 10, 2012, 10 309 (70%) of 14 788 women in Keremet were screened. 138 women were identified as having breast abnormalities and were referred to the district hospital for diagnosis and treatment. 20 of these women did not report to the hospital. Of the 118 women who did report, 101 were diagnosed with benign lesions, eight with carcinoma in situ, and nine had malignant disease. After treatment, 12 of the 17 women with either carcinoma in situ or malignant disease (four had early breast cancer and eight had ductal carcinoma in situ) were disease-free and had a good prognosis. In the control villages, only four women reported to the centre: one was found to have a benign lesion while three were diagnosed with advanced disease.

Interpretation: Our findings show that a screening programme using local volunteers can increase the detection of breast cancer in asymptomatic women in low-income rural communities. These findings can inform policymakers’ decisions in the design of cancer control programmes in Sudan and other similar areas in sub-Saharan Africa.

Comments: A good community based study by Sudanese authors dealing with an important subject and published in a high class journal.

Type of stress ulcer prophylaxis and risk of nosocomial pneumonia in cardiac surgical patients: cohort study
Brian T Bateman, et al
BMJ 2013;347:f5416

Abstract
Objective To examine the relation between the type of stress ulcer prophylaxis administered and the risk of postoperative pneumonia in patients undergoing coronary artery bypass grafting.

Design Retrospective cohort study.

Setting Premier Research Database.

Participants: 21,214 patients undergoing coronary artery bypass graft surgery between 2004 and 2010; 9830 (46.3%) started proton pump inhibitors and 11 384 (53.7%) started H₂ receptor antagonists in the immediate postoperative period.
Main outcome measure Occurrence of postoperative pneumonia, assessed using appropriate diagnostic codes.

Results Overall, 492 (5.0%) of the 9830 patients receiving a proton pump inhibitor and 487 (4.3%) of the 11384 patients receiving an H2 receptor antagonist developed postoperative pneumonia during the index hospital admission. After propensity score adjustment, an elevated risk of pneumonia associated with treatment with proton pump inhibitors compared with H2 receptor antagonists remained (relative risk 1.19, 95% confidence interval 1.03 to 1.38). In the instrumental variable analysis, use of a proton pump inhibitor (compared with an H2 receptor antagonist) was associated with an increased risk of pneumonia of 8.2 (95% confidence interval 0.5 to 15.9) cases per 1000 patients.

Conclusions Patients treated with proton pump inhibitors for stress ulcer had a small increase in the risk of postoperative pneumonia compared with patients treated with H2 receptor antagonists; this risk remained after confounding was accounted for using multiple analytic approaches.

Bariatric surgery versus non-surgical treatment for obesity: a systematic review and meta-analysis of randomised controlled trials
Viktoria L Gloy, et al
BMJ 2013;347:f5934

Abstract
Objective To quantify the overall effects of bariatric surgery compared with non-surgical treatment for obesity.
Design Systematic review and meta-analysis based on a random effects model.
Data sources Searches of Medline, Embase, and the Cochrane Library from their inception to December 2012 regardless of language or publication status.
Eligibility criteria Eligible studies were randomised controlled trials with ≥6 months of follow-up that included individuals with a body mass index ≥30, compared current bariatric surgery techniques with non-surgical treatment, and reported on body weight, cardiovascular risk factors, quality of life, or adverse events.

Results The meta-analysis included 11 studies with 796 individuals (range of mean body mass index at baseline 30-52). Individuals allocated to bariatric surgery lost more body weight (mean difference –26 kg (95% confidence interval –31 to –21)) compared with non-surgical treatment, had a higher remission rate of type 2 diabetes (relative risk 22.1 (3.2 to 154.3) in a complete case analysis; 5.3 (1.8 to 15.8) in a conservative analysis assuming diabetes remission in all non-surgically treated individuals with missing data) and metabolic syndrome (relative risk 2.4 (1.6 to 3.6) in complete case analysis; 1.5 (0.9 to 2.3) in conservative analysis), greater improvements in quality of life and reductions in medicine use (no pooled data). Plasma triglyceride concentrations decreased more (mean difference –0.7 mmol/L (–1.0 to –0.4) and high density lipoprotein cholesterol concentrations increased more (mean difference 0.21 mmol/L (0.1 to 0.3)). Changes in blood pressure and total or low density lipoprotein cholesterol concentrations were not significantly different. There were no cardiovascular events or deaths reported after bariatric surgery. The most common adverse events after bariatric surgery were iron deficiency anaemia (15% of individuals undergoing malabsorptive bariatric surgery) and reoperations (8%).

Conclusions Compared with non-surgical treatment of obesity, bariatric surgery leads to greater body weight loss and higher remission rates of type 2 diabetes and metabolic syndrome. However, results are limited to two years of follow-up and based on a small number of studies and individuals.

Comment:
Note the small number of the studies and the risk of surgery. Is it worth it?
New oral anticoagulants increase risk for gastrointestinal bleeding: a systematic review and meta-analysis

Background & Aims: A new generation of oral anticoagulants (nOAC), which includes thrombin and factor Xa inhibitors, has been shown to be effective, but little is known about whether these drugs increase patients’ risk for gastrointestinal bleeding (GIB). Patients who require OAC therapy frequently have significant comorbidities and may also take aspirin and/or thienopyridines. We performed a systematic review and meta-analysis of the risk of GIB and clinically relevant bleeding in patients taking nOAC.

Methods: We queried MEDLINE, EMBase, and the Cochrane library (through July 2012) without language restrictions. We analyzed data from 43 randomized controlled trials (151,578 patients) that compared nOAC (regardless of indication) with standard care for risk of bleeding (19 trials on GIB). Odds ratios (ORs) were estimated using a random-effects model. Heterogeneity was assessed with the Cochran Q test and the Higgins I(2) test.

Results: The overall OR for GIB among patients taking nOAC was 1.45 (95% confidence interval [CI], 1.07-1.97), but there was substantial heterogeneity among studies (I2, 61%). Subgroup analyses showed that the OR for atrial fibrillation was 1.21 (95% CI, 0.91-1.61), for thromboprophylaxis after orthopedic surgery the OR was 0.78 (95% CI, 0.31-1.96), for treatment of venous thrombosis the OR was 1.59 (95% CI, 1.03-2.44), and for acute coronary syndrome the OR was 5.21 (95% CI, 2.58-10.53). Among the drugs studied, the OR for apixaban was 1.23 (95% CI, 0.56-2.73), the OR for dabigatran was 1.58 (95% CI, 1.29-1.93), the OR for edoxaban was 0.31 (95% CI, 0.01-7.69), and the OR for rivaroxaban was 1.48 (95% CI, 1.21-1.82). The overall OR for clinically relevant bleeding in patients taking nOAC was 1.16 (95% CI, 1.00-1.34), with similar trends among subgroups.

Conclusions: Studies on treatment of venous thrombosis or acute coronary syndrome have shown that patients treated with nOAC have an increased risk of GIB, compared with those who receive standard care. Better reporting of GIB events in future trials could allow stratification of patients for therapy with gastroprotective agents.

Comments: The two major limitations of this meta-analysis are: 1) all of the novel oral anticoagulants are lumped together. These agents have differing side-effect profiles and mechanisms of action, greatly limiting the utility of meta-analysis; and 2) it is well known that several of these agents may increase the likelihood of GI bleeding. They, however, may also decrease the likelihood of intracranial hemorrhage, a far more catastrophic clinical event.

Holding chambers (spacers) versus nebulisers for beta-agonist treatment of acute asthma.

Background: In acute asthma inhaled beta(2)-agonists are often administered by nebuliser to relieve bronchospasm, but some have argued that metered-dose inhalers with a holding chamber (spacer) can be equally effective. Nebulisers require a power source and need regular maintenance, and are more expensive in the community setting.

Objectives: To assess the effects of holding chambers (spacers) compared to nebulisers for the delivery of beta(2)-agonists for acute asthma.
**Search Methods:** We searched the Cochrane Airways Group Trial Register and reference lists of articles. We contacted the authors of studies to identify additional trials. Date of last search: February 2013.

**Selection Criteria:** Randomised trials in adults and children (from two years of age) with asthma, where spacer beta(2)-agonist delivery was compared with wet nebulisation.

**Data Collection and Analysis:** Two review authors independently applied study inclusion criteria (one review author for the first version of the review), extracted the data and assessed risks of bias. Missing data were obtained from the authors or estimated. Results are reported with 95% confidence intervals (CIs).

**Main Results:** This review includes a total of 1897 children and 729 adults in 39 trials. Thirty-three trials were conducted in the emergency room and equivalent community settings, and six trials were on inpatients with acute asthma (207 children and 28 adults). The method of delivery of beta(2)-agonist did not show a significant difference in hospital admission rates. In adults, the risk ratio (RR) of admission for spacer versus nebuliser was 0.94 (95% CI 0.61 to 1.43). The risk ratio for children was 0.71 (95% CI 0.47 to 1.08, moderate quality evidence). In children, length of stay in the emergency department was significantly shorter when the spacer was used. The mean duration in the emergency department for children given nebulised treatment was 103 minutes, and for children given treatment via spacers 33 minutes less (95% CI -43 to -24 minutes, moderate quality evidence). Length of stay in the emergency department for adults was similar for the two delivery methods. Peak flow and forced expiratory volume were also similar for the two delivery methods. Pulse rate was lower for spacer in children, mean difference -5% baseline (95% CI -8% to -2%, moderate quality evidence), as was the risk of developing tremor (RR 0.64; 95% CI 0.44 to 0.95, moderate quality evidence).

**Authors’ Conclusions:** Nebuliser delivery produced outcomes that were not significantly better than metered-dose inhalers delivered by spacer in adults or children, in trials where treatments were repeated and titrated to the response of the participant. Spacers may have some advantages compared to nebulisers for children with acute asthma.

This is a good systematic review and meta-analysis that supports the concept that in adults with asthma there are no differences in outcomes using a spacer device compared with an albuterol nebulizer. There were some concerns with the summary of the review because it does not mention whether there were any significant differences in baseline characteristics of the groups assigned to the spacer versus the nebulizer. No limitations of the the review/individual trials were mentioned, and there was also no mention of the quality of the studies and/or bias, other than rating the evidence as "moderate".

**Emergency interventions for hyperkalaemia**

Mahoney BA, et al
Cochrane Database Syst Rev 2005 Apr 18;(2):CD003235

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**Abstract**

**Background:**
Hyperkalaemia occurs in outpatients and in between 1% and 10% of hospitalised patients. When severe, consequences include arrhythmia and death.

**Objectives:**
To review randomised evidence informing the emergency (i.e. acute, rather than chronic) management of hyperkalaemia.

**Search Strategy:**
We searched MEDLINE (1966-2003), EMBASE (1980-2003), The Cochrane Library (issue 4, 2003), and SciSearch using the text words hyperkal* or hyperpotass* (* indicates truncation). We also searched selected journals and abstracts of meetings. The
reference lists of recent review articles, textbooks, and relevant papers were reviewed for additional potentially relevant titles.

**Selection Criteria:**
All selection was performed in duplicate. Articles were considered relevant if they were randomised, quasi-randomised or cross-over randomised studies of pharmacological or other interventions to treat non-neonatal humans with hyperkalaemia, reporting on clinically-important outcomes, or serum potassium levels within the first six hours of administration.

**Data Collection Analysis:**
All data extraction was performed in duplicate. We extracted quality information, and details of the patient population, intervention, baseline and follow-up potassium values. We extracted information about arrhythmias, mortality and adverse effects. Where possible, meta-analysis was performed using random effects models.

**Main Results:**
None of the studies of clinically-relevant hyperkalaemia reported mortality or cardiac arrhythmias. Reports focussed on serum potassium levels. Many studies were small, and not all intervention groups had sufficient data for meta-analysis to be performed. On the basis of small studies, inhaled beta-agonists, nebulised beta-agonists, and intravenous (IV) insulin-and-glucose were all effective, and the combination of nebulised beta agonists with IV insulin-and-glucose was more effective than either alone. Dialysis is effective. Results were equivocal for IV bicarbonate. K-absorbing resin was not effective by four hours, and longer follow up data on this intervention were not available from RCTs.

**Authors’ Conclusions:**
Nebulised or inhaled salbutamol, or IV insulin-and-glucose are the first-line therapies for the management of emergency hyperkalaemia that are best supported by the evidence. Their combination may be more effective than either alone, and should be considered when hyperkalaemia is severe. When arrhythmias are present, a wealth of anecdotal and animal data suggests that IV calcium is effective in treating arrhythmia. Further studies of the optimal use of combination treatments and of the adverse effects of treatments are needed.

**Comments:**
This study looks at evidence-based management of hyperkalaemia, a serious problem that could lead to immediate death due to arrhythmia. However, IV calcium gluconate should be administered from the beginning to guard against the occurrence of arrhythmias.