### Fabrication of poly(γ-glutamic acid)-based biopolymer as the targeted drug delivery system with enhanced cytotoxicity to APN/CD13 over-expressed cells

**Title:** Fabrication of poly(γ-glutamic acid)-based biopolymer as the targeted drug delivery system with enhanced cytotoxicity to APN/CD13 over-expressed cells

**Author:** Li Zhang, Xu Geng, Jie Zhou, Ying Wang, Hongliang Gao, Yue Zhou, and Jing Huang

**Journal:** Journal of Drug Targeting: Early Online, Posted online on February 4, 2015.

**Abstract:** Poly(γ-glutamic acid)-based targeted drug delivery system (PAMCN) targeting transmembrane metalloprotease aminopeptidase aminopeptidase-N (APN/CD13) was fabricated and evaluated for the enhancement of targeting efficiency and cytotoxicity. The cisplatin (CDDP) loading content of PAMCN was about 36 ± 5% and PAMCN showed a sustainable release profile with a half-maximal release time ($t_{1/2}$) of 23 h. The average size of PAMCN was 132 ± 18 nm determined by light scattering (LS) and 158 ± 67 nm by atomic force microscopy (AFM). Flow cytometry and fluorescence microscope analysis showed that the drug carrier (PAMN) could specifically bind to human umbilical vein endothelial cells (HUVEC). PAMCN enhanced the efficacy of CDDP to HUVEC cells with the half maximal inhibitory concentration (IC$_{50}$) value decreased to 90.83 ± 33.00 μg/ml comparing with free CDDP treatment and showed less tube formation amounts ($p < 0.01$) than free CDDP in matrigel angiogenesis inhibition assay in vitro. In vivo toxicity experiment indicated that the survival rate of KM mice in PAMCN group was 100% and PAMCN reduced the hepatic and renal toxicity significantly compared to free CDDP group. Therefore, this novel drug delivery system presents a promising potential for antiangiogenic chemotherapy.

**Database:** Informa Healthcare

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### Atoh1 gene therapy in the cochlea for hair cell regeneration

**Title:** Atoh1 gene therapy in the cochlea for hair cell regeneration

**Author:** Rachael T Richardson, and Patrick J Atkinson
**Introduction:** The sensory epithelium of the cochlea is a complex structure containing hair cells, supporting cells and auditory nerve endings, all of which degenerate after hearing loss in mammals. Biological approaches are being considered to preserve and restore the sensory epithelium after hearing loss. Of particular note is the ectopic expression of the Atoh1 gene, which has been shown to convert residual supporting cells into hair cells with restoration of function in some cases.

**Areas covered:** In this review, hair cell development, spontaneous regeneration and hair cell regeneration mediated by Atoh1 gene therapy in the cochlea are discussed.

**Expert opinion:** Gene therapy can be safely delivered locally to the inner ear and can be targeted to the sensory epithelium of the cochlea. Expression of the Atoh1 gene in supporting cells results in their transformation into cells with the appearance and function of immature hair cells but with the resulting loss of the original supporting cell. While the feasibility of Atoh1 gene therapy in the cochlea is largely dependent on the severity of the hearing loss, hearing restoration can be achieved in some situations. With further advances in Atoh1 gene therapy, hearing loss may not be as permanent as once thought.

**Title:** ERCC1 SNPs as Potential Predictive Biomarkers in Non-Small Cell Lung Cancer Patients Treated With Platinum-Based Chemotherapy

**Author:** Aristea Kalikaki, Alexandra Voutsina, Anastasios Koutsopoulos, Chara Papadaki, Maria Sfakianaki, Emmanouel Yachnakis, Alexandros Xyrafas, Athanasios Kotsakis, Sofia Agelaki, John Souglakos, Dimitrios Mavroudis, and Vassilis Georgoulas

**Journal:** Cancer Investigation: Posted online on February 3, 2015.

**Abstract:** Polymorphisms in ERCC1, XPD, and XRCC1 were examined for (a) association with the clinical outcome of 107 non-small cell lung cancer patients receiving front-line platinum-based chemotherapy, and (b) correlation with the ERCC1 mRNA levels of 176 chemo-naive primary tumors. The ERCC1-C8092 allele and the number of
ERCC1 polymorphic variants (C8092A and Asn118Asn) were associated with progression-free survival. In non-squamous histology, tumoral ERCC1 mRNA levels were lower in patients homozygous for ERCC1-C8092 as compared with the patients carrying the A allele ($p = .024$). These findings merit investigation in larger cohorts of patients treated with uniform regimens.

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**Title:** Genetically modified chondrocytes expressing TGF-$\beta$1: a revolutionary treatment for articular cartilage damage?

**Author:** Randa K Elmallah, Jeffrey J Cherian, Julio J Jauregui, Todd P Pierce, Walter B Beaver, and Michael A Mont

**Journal:** Expert Opinion on Biological Therapy: Posted online on February 3, 2015.

**Abstract:**

*Introduction:* Currently, joint arthroplasty remains the only definitive management of osteoarthritis, while other treatment modalities only provide temporary and symptomatic relief. The use of genetically engineered chondrocytes is currently undergoing clinical trials. Specifically, it has been designed to induce cartilage growth and differentiation in patients with degenerative arthritis, with the aim to play a curative role in the disease process.

*Areas covered:* This treatment involves the incorporation of TGF-$\beta$1, which has been determined to play an influential role in chondrogenesis and extracellular matrix synthesis. Using genetic manipulation and viral transduction, TGF-$\beta$1 is incorporated into human chondrocytes and administered in a minimally invasive fashion directly to the affected joint. Following a database literature search, we evaluated the current evidence on this product and its outcomes. Furthermore, we also briefly reviewed other treatments developed for chondrogenesis and cartilage regeneration for comparison.

*Expert opinion:* This treatment method has sustained positive effects on functional outcomes and cartilage growth in initial trials. It allows administration in a minimally invasive manner that does not require extended recovery time. Although several treatment modalities are currently under investigation and appear promising, we hope that these effects can be sustained in further studies. Ultimately, we anticipate
that the results may be reproducible in many clinical settings and allow us to effectively treat cartilage damage in patients with degenerative arthritis.

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| Title | Emerging drugs for functional dyspepsia |
| Author | Alkesh V Zala, Marjorie M Walker, and Nicholas J Talley |
| Abstract | **Introduction:** Functional dyspepsia (FD) is a relatively common gastrointestinal clinical condition that remains poorly understood. Controversies remain regarding the definition, pathophysiology and optimum treatment. The current treatment of FD is limited and no established regimen is available.  
**Areas covered:** Recent advances have improved our understanding of the pathophysiology of the disease and have led to the development of newer tailored therapies. Novel agents such as the motilin receptor agonist camicinal and the muscarinic M1 and M2 receptor antagonist acotiamide appear promising; however, the need for a safe and efficacious treatment remains largely unmet. This review describes the currently available management options for FD and critically evaluates emerging therapies.  
**Expert opinion:** The optimal treatment for FD is yet to be determined. A proton pump inhibitor or a prokinetic agent constitutes primary treatment. *Helicobacter pylori* testing and eradication is recommended. Based on currently available data, acotiamide appears promising, particularly in postprandial distress syndrome. Further large-scale multicentered trials are required to define the duration of treatment and the side-effect profile. |
| Database | Informa Healthcare |

| Title | Emerging oral drugs for psoriasis |
| Author | Tahmina Mahmood, Daniel Zaghi, and Alan Menter |
| Abstract | **Introduction:** Psoriasis is a chronic, immune-mediated inflammatory disease that classically presents with well-demarcated, scaly, erythematous plaques on the |
extensor surfaces of the extremities, scalp, and trunk. Nails and joints are frequently affected as well. Whereas a significant number of patients maintain adequate control with topical therapy, up to 25% of patients will require phototherapy, oral systemic medication, or biologic therapy.

Areas covered: The majority of recent advances in therapeutic options for moderate-to-severe psoriasis have been in biologic therapies whereas development of new oral agents has lagged behind. Currently, oral agents are largely confined to methotrexate, acitretin, cyclosporine and most recently apremilast. This article reviews emerging oral treatments for moderate-to-severe psoriasis.

Expert opinion: Despite the recent FDA approval of apremilast, the development of new oral treatments for moderate-to-severe psoriasis has not kept pace with biologic therapies. There continues to be a need for safe and effective long-term oral therapies.

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Title: Synthesis and Evaluation of Bile Acid–Ribavirin Conjugates as Prodrugs to Target the Liver

Author: Zhongqi Dong, Qing Li, Dong Guo, Yan Shu and James E. Polli

Journal: Journal of Pharmaceutical Sciences: Article first published online, 2 FEB 2015 | DOI: 10.1002/jps.24375

Abstract: Ribavirin is used to treat hepatitis C but causes serious hemolytic anemia. The objective of the study was to develop a ribavirin prodrug to achieve liver-specific drug delivery and to reduce its off-target effect in red blood cells (RBCs). The approach aimed to target the human sodium taurocholate cotransporting polypeptide (NTCP), which is a bile acid transporter predominately expressed in the liver. Six prodrugs with ribavirin conjugation at C-3 or C-24 of the bile acids were synthesized. In vitro uptake studies indicated that all six prodrugs were NTCP substrates. Metabolic studies in vitro indicated that ribavirin–I-Val–glycochenodeoxycholic acid (GCDCA) was able to release ribavirin in the mouse liver S9 fraction. Additionally, in vitro studies showed that ribavirin in RBC was reduced by 16.7-fold from prodrug compared with parent drug incubation. Moreover, almost no prodrug was present in RBC. In vivo study in mice also showed
that ribavirin–l-Val–GCDCA could provide almost the same ribavirin exposure in the liver as ribavirin administration, but with about 1.8-fold less exposure of ribavirin in RBC, plasma, and kidney. Overall, the study suggested that ribavirin–l-Val–GCDCA has the potential to achieve ribavirin-specific liver delivery.

Title: Systematic Screening of Different Surface Modifiers for the Production of Physically Stable Nanosuspensions

Author: Maria L. A. D. Lestari, Rainer H. Müller and Jan P. Möschwitzer


Abstract: The role of a surface modifier is important in the formation of stable nanosuspensions. In this study, a simple and systematic screening method for selecting optimum surface modifiers was performed by utilizing a low-energy wet ball milling method. Nine surface modifiers from different classes with different stabilization mechanisms were applied on six different models of active pharmaceutical ingredients (API). Particle size analysis showed that at concentration five times higher than the critical micelle concentration, SDS and sodium cholate (anionic surfactant) showed the highest percent success to produce stable nanosuspensions with particle size smaller than 250 nm. Similar findings were also shown by poloxamer 188 (nonionic surfactant) and hydroxypropylmethylcellulose E5 (polymeric stabilizer) at concentration 1% (w/v) and 0.8% (w/v), respectively. In addition, combinations of anionic surfactant and nonionic surfactant as well as combinations of anionic surfactant and polymeric stabilizer showed high percent success in the formation of stable nanosuspensions. In general, no correlation can be found between the physicochemical characteristics of the model API (molecular weight, melting point, log P, pKa, and crystallinity) with its feasibility to be nanosized. The concentration and the principle of stabilization of surface modifier determine the formation of stable nanosuspensions.
**Title:** Reducing unacceptable missed doses: pharmacy assistant-supported medicine administration

**Author:** Wasim Baqir, Kate Jones, William Horsley, Scott Barrett, David Fisher, Richard Copeland, David Campbell and Rosemary Stephenson

**Journal:** International Journal of Pharmacy Practice: Article first published online, 28 JAN 2015 DOI: 10.1111/ijpp.12172

**Abstract**

**Objectives**

The potential harm from omitted and delayed medicines for hospital inpatients was highlighted by the National Patient Safety Agency (NPSA). Despite evidence of omitted doses, few interventional studies have been reported on preventing the problem. This study aimed to assess the impact on omitted doses when medicine administration was supported by pharmacy assistants (PAs).

**Methods**

PAs were trained to support nurses on medicine administration rounds. Using stratified random sampling, two intervention and control wards were selected. Three study groups were defined: (A) intervention group (PA-supported medicine administration); (B) intra-ward control group; and (C) inter-ward control group. Primary outcome measure was number of patients with unacceptable omitted doses (UODs) in group A versus C. Secondary outcome measures were patients with critical UOD (cUOD), as defined by the NPSA, in groups A, B and C and UODs in group B versus A and C. Data were collected over 2 weeks (December 2011 and February 2012).

**Key findings**

Using aggregated data over 2 weeks, 778 patients were assessed; 308 were male (40%). The overall proportion of patients with ≥1 UOD was 12.4% (n = 96). The proportion of patients with ≥1 UOD was 1.1% (n = 2) in group A (intervention) and 18.5% (n = 68) in group C (control). There were significantly fewer patients with cUOD in group A (1.1%; n = 2) compared with group C (7.4%; n = 27).

**Conclusion**

PA-supported medication rounds can significantly reduce the rate of omitted doses. This study provides evidence for a potential solution to the problem of omitted doses for hospital inpatients.
Objectives
Vaccination is considered the most successful health intervention; yet incomplete immunisation coverage continues to risk outbreaks of vaccine preventable diseases worldwide. Vaccination coverage improvement through a single-dose prime-boost technology would revolutionise modern vaccinology, impacting on disease prevalence, significantly benefiting health care and lowering economic burden of disease.

Key findings
Over the past 30 years, there have been efforts to develop a single-dose delayed release vaccine technology that could replace the repeated prime-boost immunisations required for many current vaccines. Biocompatible polymers have been employed to encapsulate model vaccines for delayed delivery in vivo, using either continuous or pulsed release. Biomaterial considerations, safety aspects, particle characteristics and immunological aspects of this approach are discussed in detail.

Summary
Despite many studies showing the feasibility of vaccine encapsulation for single-dose prime-boost administration, none have been translated into convincing utility in animal models or human trials. Further development of the encapsulation technology, through optimising the particle composition, formulation, antigen loading efficacy and stability, could lead to the application of this important approach in vaccine deployment. If successful, this would provide a solution to better global vaccination coverage through a reduction in the number of immunisations needed to achieve protection against infectious diseases. This review provides an overview of single-dose vaccination in the context of today's vaccine
needs and is derived from a body of literature that has not been reviewed for over a decade.

Database: Wiley Online Library