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This is to confirm that Dr Mohammad Mahdi Ghahramani Seno presented orally his abstract entitled *„Potent RNAi-mediated Dystrophin knock-down in vitro and in vivo and transcriptomic evaluation dystrophin deficiency"* at the 13th Annual Congress of the European Society of Gene Therapy, Prague, 2005.

Sincerely,

David Klatzmann, ESGT President

for the programme committee

ESGT 2005 - oral

vector-control MSC (p= 0.007), while recombinant IFNb protein (50,000 IU qod) was ineffective (p=0.14). IV injected IFNb-MSC prolonged the survival of mice bearing metastatic breast carcinomas (p=0.001) IP injections of IFNb-MSC into mice carrying ovarian carcinomas resulted in doubling of survival in SKOV-3, and cures in 70% of mice carrying OVCAR-3 tumors, suggesting that incorporation of gene modified MSC in the tumor was responsible for controlling tumor growth.

Or 36

PRODRUG ACTIVATION GENE THERAPY USING AN ADENOVIRUS EXPRESSING NITROREDUCTASE (NTR) AND PRODRUG CB1954 IN PATIENTS WITH LOCALIZED PROSTATE CANCER (PCa)

Peter F. Searle, P. Patel, V. Mautner, J.G. Young, D. Hull, D. Jackson, A. Mountain, J. Ellis, D.M.A. Wallace, H.Y. Leung, L.S. Young, N.D. James

CR UK Institute for Cancer Studies, University of Birmingham, UK

We report a phase I/II clinical trial in Prostate Cancer (PCa), using intraprostatic injection of a replication defective adenovirus encoding NTR (CTL102) +/- iv prodrug CB1954. NTR converts CB1954 into a highly cytotoxic, bifunctional alkylating agent effective in replicating and quiescent cells.Patients underwent trans-rectal ultrasound (TRUS)-guided, intraprostatic injection of CTL102 in escalating doses from 10^10 to 10^12 particles, with subsequent prostatectomy (gene expression study) or iv CB1954 24mg/m2 (therapeutic group) 48-72h post injection. Primary endpoints were safety and tolerability; secondary endpoints were gene expression (operable patients), or efficacy (inoperable, therapeutic group) by TRUS, repeat biopsies and PSA measurement. NTR expression in resected tissue was assessed by immunohistochemistry.20 patients have been treated with virus alone (particle dose 10^10 n=3, 5x10^10 n=7, 10^11 n=4, 5x10^11 n=3, 10^12 n=3) with no virus-related serious adverse events. NTR staining was seen in tumour, glandular epithelium and stroma. Increasing the injection volume achieved more widespread NTR expression as measured by colour deconvolution on immunohistochemistry images. In the therapeutic arm of the trial, 12 patients with inoperable, biopsy-confirmed, locally relapsed PCa were treated with virus plus prodrug (virus particle dose 5x10^10 n=3, 10^11 n=3, 5x10^11 n=3, 10^12 n=3), and a further 11 are being recruited for an expanded phase I/II study at 5x10^11. Repeat administration has been performed on 9 patients. Both virus and prodrug injections were well tolerated with no significant toxicity apart from a transient transaminitis at day 8 in 11/15 patients. At 6 months 3/10 patients had stable disease and 2/10 patients showed a partial response.Direct intraprostatic injection of CTL102 is feasible and safe, with evidence of dose related NTR expression. Dose-limiting toxicity has not been observed up to 10^12 virus particles, and there are encouraging indications of antitumour activity.

Or 37

"TRANSCRIPTION FACTOR THERAPY" WITH ENGINEERED ZINC FINGER PROTEINS

Philip D. Gregory, H. Steve Zhang, Sally A. Price[1], Lei Zhang, Reed Hickey[2], Dingang Liu[2], Yan Huang[2], Dmitry Guschin, Danny Xia, Xiaohong Zhong, Casey C. Case, Dale Ando, Edward J. Rebar, S. Kaye Spratt, Frank Giordano[2], David R. Tomlinson

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Improper regulation of gene expression underlies a considerable proportion of human disease, yet the majority of therapeutic interventions only target proteins amenable to "small-molecule" or antibody-based inhibition. This limits the development of new therapeutics to the restricted set of such "druggable" gene products. To extend our therapeutic arsenal to the complete universe of known disease targets requires methodology that can function independently of the nature of the molecular target - a potential promise of tackling disease at the transcriptional level. To this end we have shown that control over human genes implicated in disease can be achieved by using a designed transcription factor (ZFP TF) composed of an engineered zinc finger protein-based DNA binding domain specific for the gene of interest and a relevant functional domain (Jamieson et al., Nat. Rev. Drug Disc. 2: 361). Such designed ZFP TFs exhibit single-gene specificity in the context of the human genome (Tan et al. PNAS 100: 11997), can direct stem cell fate towards a particular cell or tissue type (Bartsevich et al., Stem Cells 21: 632), and function to evoke therapeutic gene control in vivo (Rebar et al., Nature Medicine 8: 1427; Dai et al., Circulation 110:2467). Here we report the successful application of such ZFP TFs in two different cellular and animal models of disease; (i) a ZFP TF repressor of the Phospholamban gene, a critical regulator of myocardium Ca2+ flux, for treatment of congestive heart failure; and (ii) a ZFP TF activator of the endogenous VEGF-A gene for protection of nerve function in the streptozotocin-induced rat model of diabetic neuropathy (DN). A Phase I clinical trial is open to investigate the clinical and laboratory safety of the latter approach in patients with DN. These data highlight the flexibility of a potential "transcription factor therapy" and demonstrate the utility of engineered ZFP TFs in enabling its general application.

Or 38

A NOVEL ANTI-GENE LOCKED NUCLEIC ACID (LNA) CONSTRUCT INDUCES SEQUENCE-SPECIFIC GENE SILENCING

Rongbin Ge, Juhana E. Heinonen, Mathias G. Svahn, Peter E. Nielsen, Abdalla J. Mohamed, Karin E. Lundin, C.I. Edvard Smith

Clinical Research Center, Krolinska Institutet, Karolinska University Hospital Huddinge, SE-14186, Stockholm, Sweden

Locked Nucleic Acids (LNA) are synthetic analogs of nucleic acids, which contain a bridging methylene carbon between the 2' and 4' positions of the ribose ring. In this study, we generated a novel sequence-specific anti-gene LNA construct, which induced effective strand invasion into DNA duplexes and potent inhibition of gene transcription (?90 %). By comparing the novel anti-gene LNA construct with traditional linear LNA as well as a tail-clamp bisPNA (Peptide Nucleic Acid) directed against the same target sites, respectively, we found that the novel LNA construct was unique in arresting gene transcription in mammalian cells. To our knowledge, this is the first time that in mammalian cells, gene transcription was blocked by a nucleic acid analog in a sequence-specific way using low, but saturated binding of a blocking agent. This offers a novel type of anti-gene drug, which is easy to synthesize. In this study, we also suggest that high molar excess of PNA induces inhibition of expression due to the formation of a supramolecular complex restricting access to the transcriptional machinery. We also believe that this phenomenon may well be the reason for the effect on replication observed by other authors. When supramolecular complexes are formed, the specific PNA anchor sequence seems to act as a nucleation site initiating this process.

Or 39

POTENT RNAI-MEDIATED DYSTROPHIN KNOCK-DOWN IN VITRO AND IN VIVO AND TRANSCRIPTOMIC EVALUATION OF DYSTROPHIN DEFICIENCY

Mohammad Mahdi Ghahramani Seno, Ian Graham., Ken Laing, Takis Athanasopoulos., Marita Pohlschmidt, Mark Crompton, George Dickson

Centre for Biomedical Research, School of Biology, Royal Holloway-University of London, Egham, Surrey, TW20 0EX, UK

Duchenne Muscular Dystrophy (DMD) is one of a group of genetically heterogeneous muscular dystrophies that are characterized by progressive weakness and loss of skeletal muscle. Myofibres degeneration occurs due to deficiency of dystrophin, a protein which is believed to be responsible for myofibre maintenance and integrity. Dystrophin forms a physical link between the cytoskeleton and the membrane-spanning dystrophin-associated glycoprotein complex (DAPC), indicative of a structural role for dystrophin. But, molecular biology studies indicate that this may not be

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Dear Mohammad Mahdi Ghahramani Seno,

We are pleased to confirm acceptance of your abstract entitled "*Potent RNAi-mediated Dystrophin Knock-down in vitro and in vivo and transcriptomic evaluation of dystrophin deficiency*" by the Scientific committee of the 13th Annual Congress of the European Society of Gene Therapy, Prague, 29.10-1.11.2005), as an **oral presentation**.

Your presentation will take place on ***Monday, October 31, 2005*** at ***11:00 - 13:00*** in session ***PS 8 / SiRNA, miRNA, Zn Fingers***.

Oral presentations should be 12 minutes long, followed by a 3 minutes discussion.

Please confirm that you (or a co-author) will give this oral presentation.

All presentation will have to be transferred to the congress computer system and should be brought on a CD or a USB memory key.

Looking forward to seeing you in Prague!

Sincerely,

David Klatzmann, ESGT President

for the programme committee