Alan E. Smith - Selected Publications

Genetic Code and Initiation of Protein Synthesis

Smith, A.E. and Marcker, K.A. (1970). Cytoplasmic methionine tRNAs in eukaryotes. Nature, 226, 607-610.

Brown, J.C. and Smith, A.E. (1970). Initiator codons in eukaryotes. Nature, 226, 610-612.

Following my earlier demonstration that mitochondria, like all prokaryotes, utilise fMet-tRNA, these papers characterise for the first time, the initiation codons of eukaryotic organisms, a result that reversed contemporary conventional thinking, and was rapidly confirmed in a wide variety of systems.

Viral Protein Synthesis

Smith, A.E., Marcker, K.A. and Mathews, M.B. (1970). Translation of RNA from encephalo-myocarditis virus in a mammalian cell-free system. Nature, 225, 184-187.

This paper describes for the first time the translation of an exogenous eukaryotic mRNA in a mammalian cell-free system.

Identification and Genetics of Tumour Antigens

Crawford, L.V., Cole, C.N., Smith, A.E., Paucha, E., Tegtmeyer, P., Rundell, K. and Berg, P. (1978). The organisation and expression of early genes of Simian Virus 40. Proc. Nat. Acad. Sci. USA., 75, 117-121.

Paucha, E., Mellor, A., Harvey, R., Smith, A.E., Hewick, R. and Waterfield, M.D. (1978). SV40 large and small T-antigens have identical amino termini mapping at 0.65 map units. Proc. Nat. Acad. Sci. USA., 75, 2165-2169.

Paucha, E. and Smith, A.E. (1978). The sequences between 0.59 and 0.54 map units on Simian Virus 40 DNA code for the unique region of small-t antigen. Cell, 15, 1011-1

These papers formally established the organisation of the early region of the SV40 genome, and provided definitive, functional evidence of one of the first models of mRNA splicing and the first example of one sequence of DNA encoding two distinct proteins.

Function of Tumour Antigens

Polyoma Virus Middle-T

Courtneidge, S.A. and Smith, A.E. (1983). Middle-T antigen, the Polyoma virus transforming protein associated with the product of the c-src cellular gene. Nature, 303, 435-439.

This paper is the first to describe a protein:protein interaction between an oncogene and a tyrosine kinase involved in cellular regulation; the first example of an association now known to be based on SH-2 interactions and to be almost universal in regulating normal and oncogenic cell proliferation.

Nuclear Localisation

Kalderon, D., Richardson, W.E., Markham, A.F. and Smith, A.E. (1984). Sequence requirements for nuclear location of Simian Virus 40 Large-T. Nature, 311, 33- 38

Kalderon, D., Roberts, B.L., Richardson, W.D. and Smith, A.E. (1984). A short amino acid sequence able to specify nuclear location. Cell, 39, 499-509

These two papers were the first to describe the now prototypical nuclear localisation signal of SV40 Large-T; related sequences are commonly utilised by nucleated cells and have since been identified in hundreds of other proteins.

Cystic Fibrosis

Gregory, R.J., Cheng, S.H., Rich D.P., Marshall, J., Paul S., Hehir, K., Ostedgaard, L., Klinger, K.W., Welsh, M.J. and Smith A.E. (1990). Expression and characterisation of the cystic fibrosis transmembrane conductance regulator. Nature, 347, 382-386.

Rich, D.P., Anderson, M.P., Gregory R.J., Cheng, S.H., Paul. S., Jefferson D.M., McCann, J.D., Klinger, K.W., Smith, A.E. and Welsh, M.J. (1990). Expression of cystic fibrosis transmembrane conductance regulator corrects defective chloride channel regulation in cystic fibrosis airway epithelial cells. Nature, 347, 358-363.

Cheng, S.H., Gregory, R.J., Marshall, J., Paul, S., Souza, D.W., White G.A., O'Riordan, C.R. and Smith, A.E. (1990). Defective intracellular transport and processing of CFTR is the molecular basis of most cystic fibrosis. Cell, 63, 827-83

Anderson, M.P., Rich, D.P., Gregory, R.J., Smith A.E. and Welsh, M.J. (1991). Generation of cAMP-activated chloride currents by expression of CFTR. Science, 251, 679-682.

Anderson, M.P., Gregory, R.J., Thompson, S., Souza, D.W., Paul, S., Mulligan, R.C., Smith, A.E. and Welsh, M.J. (1991). Demonstration that CFTR is a chloride channel by alteration of its anion selectivity. Science, 253, 202-205.

Denning, G.M., Anderson, M.P., Amara, J., Marshall, J., Smith, A.E. and Welsh, M.J. (1992) Processing of mutant CFTR (ΔF508) is temperature-sensitive. Nature, 358, 761-764.

Welsh, M.J. and Smith, A.E., (1993). Molecular Mechanisms of CFTR Chloride Channel Dysfunction in Cystic Fibrosis. Cell, 73, 1251-1254.

Welsh M.J. and Smith A.E. (1995). Cystic Fibrosis. Scientific American, 273, 52-61

This series of papers describe: the first isolation of the complete CFTR cDNA, the first isolation of the CFTR protein, an antibody and a monoclonal to the protein, the first evidence that CFTR is a chloride channel, the first molecular dissection of the molecule, and a first classification of CF mutations.

Gene Transfer

Zabner, J., Couture, L.A., Gregory, R.J., Graham, S.M., Smith, A.E. and Welsh, M.J., (1993). Adenovirus-Mediated Gene Transfer Corrects the Chloride Transport Defect in Patients With Cystic Fibrosis. Cell, 75, 207-216.

Zabner, J., Ramsey, B.W., Aitkin, M., Gibson, R., Launspach, J., Meeker, D.P., Moscicki, R.A., Richards, S.M., Smith, A.E., Standert, T., Wadsworth, S.C., Williams-Warren, J. and Welsh, M.J. (1996). Repeat Administration of an Adenovirus Vector Encoding CFTR to the Nasal Epithelium of Patients with Cystic Fibrosis. J. Clin. Invest., 97:1504-1511.

Alton, E.W.F.W., Stern, M., Farley, R., Jaffe, A., Chadwick, S.L., Phillips, J., Davies, J., Smith S.N., Browning, J., Hodson, M.E., Durham, S.R., Li, D., Jeffery, P.K., Scallan, M., Balfour, R., Eastman, S.J., Cheng, S.H., Smith, A.E., Meeker, D. and Geddes, D.M., (1998). A Double-blind Placebo-controlled Trial of Cationic Lipid-mediated CFTR Gene Transfer to the Lungs and Nose of CF Subjects. Lancet. 353: 947-954.

Smith, A. E. (1999). Gene therapy – where are we? Lancet. 354 (suppl 1): 1-4.

Early clinical studies of gene therapy as a treatment for Cystic Fibrosis using both viral and non-viral vectors and a review describing the barriers to gene transfer that require further work before gene therapy becomes a clinical reality.