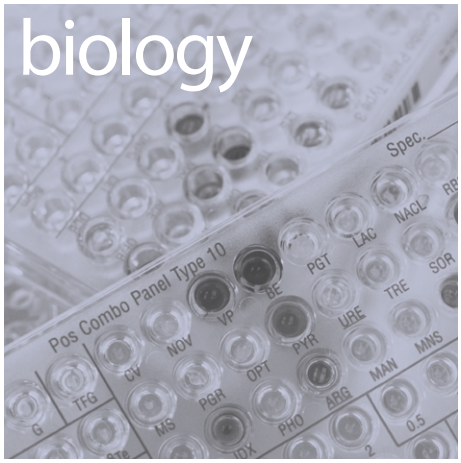


## MICROBIOLOGY

### Fighting pneumonia with siRNA

Respiratory syncytial virus (RSV) is a major pathogen that is responsible for causing bronchiolitis and pneumonia. In the USA alone, RSV is associated with an estimated 17,000 annual deaths. Also, RSV bronchiolitis in infants is considered a predisposing factor for the development of wheezing and asthma later in life. Currently, there is no effective vaccine for RSV. Short interfering RNA (siRNA) was found to be efficient in silencing a number of genes in different viruses, including RSV in cell culture. Hence, the potential therapeutic value of the siRNA approach has justifiably attracted the attention of investigators.

Bitko *et al.* [1] and Zhang *et al.* [2] now report the inhibition of RSV infection by administering siRNA nasally. The P protein is an essential subunit of the viral RNA-dependent RNA polymerase, and the *NS1* gene is an important antagonist to the type-1 interferon-mediated antiviral response. It is therefore reasoned that the ability of RSV to replicate would be compromized if these genes are targeted and downregulated by siRNAs. Tellingly, mice treated intranasally with either of these siRNAs before or after infection with RSV showed substantially decreased virus titers in the lung, and a significant attenuation of pulmonary pathology such as inflammation, airway mucus secretion and bronchoconstriction.

These exciting results suggest that the siRNA approach might be a valuable antiviral regimen against RSV infection in humans. However, this promising approach still requires further validations. It is becoming increasingly apparent that siRNAs in general might produce off-target effects by downregulating genes that are not the intended targets. Moreover, the selection of siRNA-resistant viruses is another possible caveat. Therefore, the potential short and long term adverse effects of siRNAs must first be addressed before they become safely administrable. Nonetheless, these studies have made significant contributions in the search for effective new agents against respiratory viral diseases.

1 Bitko, V. *et al.* (2005) Inhibition of respiratory viruses by nasally administered siRNA. *Nat. Med.* 11, 50–55
2 Zhang, W. *et al.* (2005) Inhibition of respiratory syncytial virus infection with intranasal siRNA nanoparticles targeting the viral *NS1* gene. *Nat. Med.* 11, 56–62

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## NEUROBIOLOGY

### Anti-seizure drugs make a roundworm live longer

Anti-epileptic drugs are thought to control seizures in humans by acting on several neuronal calcium channels. Kornfeld and his colleagues have found that these drugs increase the roundworm *Caenorhabiditis elegans* longevity. With its lifespan of few weeks, this nematode is an excellent model for studying the mechanisms governing aging. Researchers have previously identified mutations that affect its lifespan in several genes. Kornfeld and his colleagues bet that one of the many classes of medications available in the market might extend or shorten the life of the worm by acting on these gene targets [3,4]. After many unsuccessful attempts feeding the worm all classes of drugs, ranging from steroids to diuretics, they tested the anticonvulsant ethosuximide, commercialized under the name of Zarontin. A moderate dose of this drug extended the worm's life by 17 %, when lower doses did not have an effect and higher doses were toxic.

The researchers found that other anti-epileptic drugs with a similar cyclic structure also lengthen the animal lifespan. Trimethadone, a drug approved for human use, almost doubles it. As a compound with a very similar structure but with no anti-convulsant properties did not promote longevity, these effects seem to be related to the anti-seizure characteristics of the drugs. The researchers then show that these

## CELL BIOLOGY

### Towards the total synthesis of a cell

Biologists are notorious for taking apart cells and then not being able to put them back together again. Yet, if we understood how a cell functions, we should be able to reassemble one from its basic components. An important step in resolving this problem has been proposed by Vincent Noireaux and Albert Libchaber at The Rockefeller University. The results described in their report [5] have major implications not only in understanding how cells are made, but suggest new ways to make proteins, possibly without entering the issues surrounding genetically modified organisms.

The authors have created tiny (20 μm) vesicles in which cell extracts are enclosed by a phospholipid bilayer. These bioreactors have transcriptional and translational activity that comes from the extract, and they can be programmed with cDNAs such as plasmids encoding Green Fluorescent Protein (GFP). When the bioreactors are programmed to co-synthesize a-hemolysin, a bacterial pore protein that has a molecular mass cut-off of 3 kDa, they are able to exchange nutrients with a feeding solution while retaining synthesized proteins. Under these conditions, proteins can be synthesized for periods up to four days, reaching a concentration of 30 μM. This is well beyond the duration and concentration reached by current continuous flow *in vitro* translation mixtures. Presumably, this system will synthesize any protein for which it is programmed. In one example, artificial cells were programmed with cDNAs encoding a membrane targeted derivative of GFP, and thereby produced GFP that was localized at the membrane.

The potential uses of these artificial cells take off in several directions. In one sense these cells are a controlled system in which to study the physical parameters of cell biology. In another, they can be used to synthesize proteins of medicinal and industrial importance. As public perception of genetically modified organisms becomes an issue, artificial cells might replace the current living protein synthesis systems such as recombinant bacteria, yeast and cultured insect or mammalian cells. To borrow an adage from chemists, when one is capable of a total synthesis of a natural product it opens the way to nearly unlimited modification and improvement. Maybe the same will apply one day to cells.

5 Noireaux, V. and Libchaber, A. (2004) A vesicle bioreactor as a step toward an artificial cell assembly. *Proc. Natl. Acad. Sci. U. S. A.* 101, 17669–17674

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1359-6446/04/$ – see front matter  PII: S1359-6446(04)03388-X

drugs act on the worm neuromuscular system, as they do in humans. They demonstrate that they can stimulate the neurons responsible for egg-laying as well as some of the ones controlling body movements.

As these drugs still have an effect on worms carrying mutations in the insulin signalling pathway, identified previously as governing the worm aging processes, they also reveal a new role the nervous system in controlling worm longevity. The next step will be to test their anti-aging effects in higher organisms such as mice in order to find out if they could also help us live longer.

3 Evason, K. *et al.* (2004) Anticonvulsant medication extend worm life span. *Science* 307, 258–262
4 Wickelgren, K. (2004) As the worm ages: epilepsy drugs lengthen nematode life span. *Science*, 307, 193

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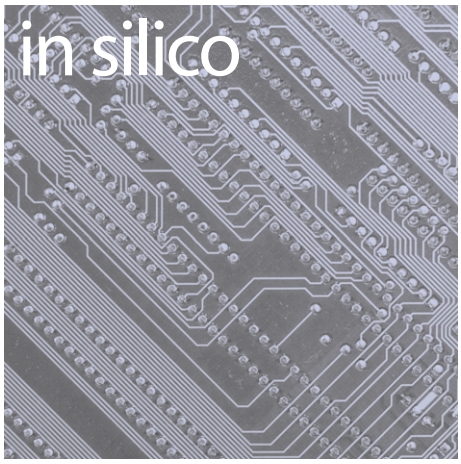


## A tool for automated structure-based 3D-pharmacophore generation and its application to virtual screening

Virtual screening has established itself as a valuable *in silico* technique alongside the traditional HTS for new active compounds in the pharmaceutical industry. Pharmacophore modeling is the approach generally taken in presence of a set of known ligands, which are analysed for common functional groups responsible for specific drug–receptor interactions and their spatial alignment in 3D. The so-called pharmacophore comprizes chemical features such as hydrogen bonding, charge transfer, electrostatic and hydrophobic interactions. Alternatively, a resolved ligand–receptor complex can be analyzed in a structure-based approach typically linked to docking, where small molecules are fitted flexibly into the receptor and scored based on most favourable interactions. However, virtual screening of large databases via docking is expensive in CPU-time; thus, protein-based pharmacophore models provide an interesting, fast and powerful alternative.

Wolber and Langer now report LigandScout [1], which represents the first software tool with an automated method for pharmacophore model generation from structural protein-ligand data. Thereby, small organic molecules are extracted from high quality protein structures deposited in the Protein Data Bank (PDB) or any other databases containing protein-ligand complexes. The PDB is a repository optimized for protein structures with little regard of the correct description of small molecules, resulting in incomplete data. Thus, much attention is given to ligand perception and interpretation in terms of topology, hybridization states and bond types. In the final step, the pharmacophore is generated based on a set of rules for hydrogen bonding, charge and lipophilic interactions. This pharmacophore represents a model that is universal and comparable but still specific to reflect a certain mode of action as demonstrated and validated by application examples.

The resulting, automatically generated, pharmacophore model can be further analyzed, adapted and used for rapid database screening with any common screening platform. An example is Catalyst, a widely used pharmacophore modeling software package compatible with the above presented software tool making LigandScout a valuable contribution to virtual screening.

1 Wolber, G. and Langer, T. (2005) LigandScout: 3-D pharmacophores derived from protein-bound ligands and their use as virtual screening filters. *J. Chem. Inf. Comput. Sci.* 45, 160–169

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1359-6446/04/$ – see front matter  PII: S1359-6446(04)03397-0