Topics on drugs, medication and their effects:

1. **Vitamin A or retinoic acid, is an essential component for animal growth** together with other retinoids like retinol, retinal, and is well known for improving optical function. However, retinoic acid does not function to relieve nyetalopia but works like a steroid hormone with an intranuclear receptor, called retinoic acid receptor protein, through transcriptional regulation. It has been demonstrated that retinoic acid is critical for the lattre steps in heart development, including terminal myocardial differentiation, cardiac looping and ventricular maturation and growth. A recent paper in *Science* by Keegan et al. presented evidence that **retinoic acid functions also in early cardiac specification** and that retinoic acid signaling is involved in selecting the number of cardiac progenitors within multipotentially different cells, also that organ size is controlled by retinoic acid-mediated restriction of the early cardiac progenitor pool. This research was carried out on zebrafish and the transcription and translation of genes which regulate to retinoic acid signaling has been identified; this may make a contribution toward the cure and repair of genetically and physiologically dysfunctional heart muscle. From *Science* vol.**307**: 247-249 (2005).
2. **Anticonvulsant medications extend life span** of *Caenorhabitis elegans* (a small experimental worm); this has been reported in Science by Kornfeld's group. Aging is a universa concern and scientists have been trying to understand it's mechanisms for many years from various perspectives. Approaches based on rational design require information about the aging process, but little information is currently available. *C. elegns* ages rapidly and the process can be studied using various methods. One of these is to test the extension of life span in the presence of various chemicals. Kornfeld et al. found that ethosuximide, trimethadione, and 3,3-diethyl-2-pyrrolidinone increases the mean and maximum life-span of *Caenorhabditis elegans* and delays age-related decline in physiological processes, indicating that these compounds retard the aging process. They assayed 19 drugs that were known to have effects on human physiology and applied these to groups of 50 animals, from the fourth larval stage to death, focusing on their aging. Ethosuximide had the greatest effect on adult life span, extending the mean adult life-span by 17%. The effect was temperature dependent: 35% at 15℃ , 17% at 20℃ and significant at 25℃.

Various genetic and environmental manipulations can extend *C. elegans* life-span. Worms cultured on nonpathogenic *Bacillus subtilis* or ultra-violet ray-irradiated *E.coli* display an extended life-span. Nutritional limitation extends life-span and can be caused by a mutation of the *eat*-2 gene that is important for pharyngeal pumping (42% increase) but this does not mean that limitation of food supply is more effective in increasing life span. Since two wild type animals, treated with ethosuximide or trimethadione, but not nutient limited showed 17% and 47% Increases respectively. These displayed normal pharyngeal pumping, food ingestion and body morphology.

An insulin-like signaling pathway regulates *C. elecans* life. This requires the function of sensory neurons that release an insulin-like ligand, the daf-2 insulin-like growth factor (IGF), a receptor gene and a signal transduction cascade that regulates the daf-16 transcription factor gene. Loss-of-function def-16 mutations reduce life-span (i.e. -16%). Treatment of these with ethosuximide or trimethadione increased life-spun beyond the wild type

controls, meaning a remarkable extension. These compounds, both which are approved for human use in the U.S., are anticonvulsants that modulate neural activity and regulate neuromuscular activity in nematodes. This finding should be incorporated in considering the implication of human neural activities and the regulation of aging. From *Science* vol.**307**: 258-262.(2005)

3. **Diarylquinoline is a drug which kills *Mycobacterium tuberculosis* by attacking the proton pump of adenosine triphosphate (ATP) synthetase.** The outbreak of multidrug-resistant tuberculosis (MDR-TB) which afflicted New York City in the 1990s was relatively minor when compared to the burden of global tuberculosis, but in Asia, it's presence should not be ignored. The current treatment for TB recommended by WHO, known as directly observed therapy short course (DOTS), requires patients to adhere to a three or four drug regimen comprising isoniazid, refampin, pyrazinamide and /or ethambutol for a minimum of 6 months. All of these drugs are old and unattractive by today's standards. Many patients fail to complete therapy because of drug's side effects, resulting in relapse, often in the form of MDR-TB. New drug(s) against MDR-TB are indispensable and one has been found using a new screening method, "medium-through out screening approach" using live *Mycobacteria*. This avoids the problems of drug permeability (which always affect the target-based screens at a later stage) by identifying active compounds that freely enter the mycobacteria. The drugs identified as having such activity are R207910 and related chemicals which block the function of membrane bound ATP synthetase. ATP synthetase has subunits, some of which are exposed externally, some which are intra-membrane and the remaining of which are internal. R207910 binds to the outer portion of ATP synthetase and thus inhibits its function. It is bacterial in origin and exquisitely active against a broad range of mycobacteria, displaying little or no activity against other microorganisms tested. R207910 is active against both the drug-sensitive and drug-resistant forms of M. tuberculosis.

In mice, R207910 exceeded the bactericidal activities of isoniazid and rifampin by at least 1 log unit. A substitution of drugs included in the WHO7s first-line tuberclosis treatment regimen (rifampin, isoniazid and pyazinamide) with R207910 accerelated bactericidal activity, leading to complete culture conversion after 2 months of treatment in some combinations. A single dose of R207910 inhibits mycobacterial growth for 1 week. Plasma levels associated with efficiency in mice were well tolerated in healthy human volunteers. Localization of at least one of the ATP synthetases through cellular membrane and the blocking of enzyme function which kills microorganisms and the discovery of such drugs are significant contribution to molecular biology and medicin. (*Science* vol. **307**: 214,223-227 (2005)).