Interview: Dr. Georgy Koentges

Grant Winner, Discusses His Research

January 31, 2007 -- In November, we spoke with Dr. Marcus Stoodley, one of the Conquer Chiari/Column Of Hope Research Grant winners. This month, we took the opportunity to talk with the other grant winner, Dr. Georgy Koentges, to learn more about his past work and his research goals moving forward.

Georgy Koentges, PhD, is a Senior Lecturer and Group leader in Developmental Systems Biology at the Wolfson Institute of Biomedical Research, at the University College of London. He is a prolific researcher and his work has been featured on the cover of Nature, one of the most prestigious journals of the scientific community.

We put Dr. Koentges In The Spotlight...

Most Chiari research is undertaken by neurosurgeons, neurologists, and radiologists. Could you talk about your background and how you think it helps you look at a disease like Chiari?
K: I was trained as a developmental biologist and molecular biologist and have been studying the cellular and molecular basis of key vertebrate structures for many years. Chiari's diseases are developmental defects that are likely to occur in the very early embryo and with novel technologies to look at all genes active in specific cell populations (using microarrays) we are making fast progress in understanding the decision making processes in these embryonic cells.

You recently had a publication on the cover of Nature (quite an honor for a researcher), what was the focus of that work?
K: Using a novel genetic lineage labeling strategy we recently discovered novel populations of stem cells that are specifically located in structures affected in patients with Chiari as well as Klippel-Feil. We were not looking for them as we were studying a different phenomenon: we wanted to know which cells formed the neck and shoulder region in ancestral vertebrates. The distribution of these cells is highly unusual, which is the reason why syndromes such as Chiari as well as Klippel-Feil have never been classed together as epiphenomena of one and the same cell population.

What are the implications of what you found for Chiari?
K: Now that we have a clearer idea of which embryonic cell population is the prime suspect in search of the primary defect, we can look at all of the genes these cells turn on during early embryonic stages of mouse development. The decision making processes within cells on whether to form bone, cartilage or muscle connective tissues are highly conserved through evolution and the anatomical structures affected in Chiari's are shared among all vertebrates. We can therefore use this knowledge of gene activity patterns to prioritize the future search for human candidate genes with a higher resolution than was presently possible.

Does what you found go beyond Chiari to other diseases as well?
K: A larger group of syndromes such as Klippel-Feil syndrome (KFS), OHS syndrome, Trisomy 17, a subset of the SIDS (sudden infant death syndrome) and probably even Dandy-Walker syndrome might be caused by defects in neural crest cell populations that we described.

What will you be doing with the Conquer Chiari Research Grant and what do you hope to accomplish?
K: We will isolate these cells from specific locations and at specific stages of mouse development, using a so-called laser-capture microscope. We will amplify their RNA/cDNA and profile this on microarrrays, a technique that I was involved in pioneering while being a postdoc at Harvard. This will allow us to say which master control genes are used by these cells when they make key fate decisions: to become bone, cartilage or connective tissue (and how much of each), as we believe that several of the human syndromes have their origin in 'wrong choices' of these cells: instead of making bone, they make connective tissues at certain places (Chiari). Instead of making connective tissues they form bones (KFS, Chiari).

I hope that we can use our toolkit of analyzing the gene-regulatory networks active in single cells to learn some first lessons about this disease. Once we know some of the key genes, they serve as targets for clinical geneticists with whom we intend to collaborate closely.

If your theory of Chiari proves to be correct, at what age of development does the problem actually occur in humans?

K: At about 2 months after conception.

Do you think it is likely that environmental factors, such as maternal diet or exposure to chemicals, may play a role in this type of developmental error?
K: Unlikely to be a primary component. Our working hypothesis is that of a genetic defect, in particular, that either key genes or they regulatory regions in the genomic DNA of the patients are defective, which would explain why defects are so precisely localized to specific body areas. This is significant, as genes are used as a 'toolkit' over and over again in different cells at different times during our life. If this were a simple defect it would be hard to explain the precision of the time window that we appear to be able to determine. The question when and where a particularly significant gene is upregulated is solved in the genome by virtue of so-called cis-regulatory regions. These are places of DNA where so-called 'transcription factors' would bind. To use a musical metaphor, transcription factors would correspond to your fingers, cis-regulatory regions would correspond to the keys on a piano and obviously the sequence of tones to appear and disappear that constitute the melody corresponds to a genetic programme. It matters when a tone appears in a sequence and how long it stays

around. Biological systems use similar ways of encoding information. If some keys are broken (like on an old piano), something is missing and the chords you are playing are broken. We can now look at these elements and see them function in live cells. Obviously, cells send and receive signals which activate these transcription factors, ie. make a musician play his music. If there are noxious stimuli around, this information encoding and decoding might be perturbed during embryonic development: the musician might be indisposed and miss his part in the concert because he has to sneeze..... However, as we expect some permanent and inheritable causes of this disease such spontaneous 'hick-ups' are not the primary focus of our attention.

What would be the next step(s) for research along this path?

K: Once we know key parts (genes) and their patterns of occurrence in specific cells, 'leitmotifs of these genetic melodies', we can share this information with clinical geneticists, we provide them with information about 'fingers', genetic 'piano keys' i.e. transcription factors as well as their likely binding regions in the genome. Clinical geneticists can then test in larger groups of patients which one of these are mutated. The significance of these human mutations can in the future then be tested in mice by 'recreating' them in the mouse genome. If we see that the resulting mice do show the same phenotype as the affected patients, we know we have found the cause of the illness. We are immensely grateful to ConquerChiari for giving us the opportunity to take the first steps along this path and scout the genetic territory, where we can reasonably expect to find key answers.