PEN MET WITH PROFESSOR CARLO VENTURA AT ICCAD 2015 TO DISCUSS HIS WORK ON HOW STEM CELLS ARE EXTREMELY SENSITIVE TO ACOUSTIC VIBRATIONAL SIGNATURES

Sounding out stem cells

Professor Carlo Ventura has devoted his studies to the molecular dissection of myocardial cell growth and differentiation, discovering nuclear endorphin receptors and signalling responsible for stem cell cardiogenesis. He has developed new molecules with differentiating and paracrine logics for cardiovascular regenerative medicine; discovered the ability of extremely low frequency (ELF) magnetic fields and radioelectric fields to enhance stem cell pluripotency, affording the direct reprogramming of human dermal skin fibroblasts to myocardial, neuronal and skeletal muscle lineages.

Ventura provided evidence that shown how properly conveyed electromagnetic fields were able to revert stem cell senescence, disclosing novel perspectives in stem cell-based therapies, and has found that stem cells are extremely sensitive to acoustic vibrational signatures. These findings paved the way for the use of physical energy in stem cell science.

To discuss some of these areas, Pan European Networks met with Professor Ventura at the 11th International Congress on Coronary Artery Disease (ICCAD 2015) in Bologna in November 2015, where he delivered a presentation on 'seeing stem cell biology in the light of physical energies: Mutant vibrations for regenerative medicine'.

How do you feel that the use of physical energies to modulate cell dynamics has come to challenge the more traditional method of using chemicals and tools to affect cell behaviour?

We have become immersed in today's 'physical age'; we are a part of it – we play a part in the Universe's electromagnetic vibrations and sounds and so on – and that is something we not only need to realise, but something that we also need to embrace.

Indeed, it is becoming increasingly evident that, generally speaking, our cells produce energies such as magnetic fields, and they do produce mechanical stimulations. While these things may fall within the audible or subsonic range, that is essentially irrelevant; what is important is the realisation that they are constantly oscillating. As such, the question must be asked as to what is the meaning of this oscillation.

Any fundamental features or traits in our cells are regulated in something of a rhythmic fashion. To take calcium waves (which are very important as a signalling mechanism) as an example: the calcium oscillation is rhythmic, and this can be likened to an input that provides information to itself.

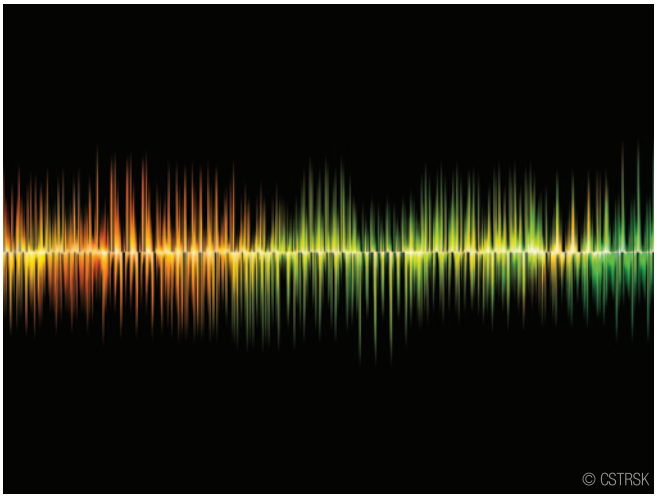
Professor Carlo Ventura

Another critical issue is how the signal molecules recognise each other. The conventional view here is that they have to interact like a key in a lock to trigger an event. This may certainly be the case, but there is also evidence to suggest that the cellular reactions in any kind of environment – especially at the tissue organ level – are too fast to be explained based upon the simple diffusion of the water soluble molecules.

It is, of course, true that water molecules account for around 99% of the number of molecules inside cells, but here you have to imagine that these water molecules that attach to the surface in the subcellular structures in the cells are in motion, like ballet dancers, dancing together. As such, it is extremely difficult for any given protein to freely diffuse because they will crash against the 'dancing' microtubules, the cytoskeleton and nucleoskeleton, the endoplasmic reticulum, the mitochondria and so on.

If we think of proteins as aggregational entities, when you look at the protein it is possible to see its alpha-helices as being like springs and the turns between them as connectors, making the system in a single protein vibrate in a kind of phase resonance. This oscillator (the entire protein) is like a metronome, moving along the

Professor Ventura has found that stem cells are extremely sensitive to acoustic vibrational signatures



microtubules in the cytonucleoskeleton together with other metronomes (the other signalling proteins), with the microtubules acting as elastic entities which dissipate the major rhythmic differences in these oscillators.

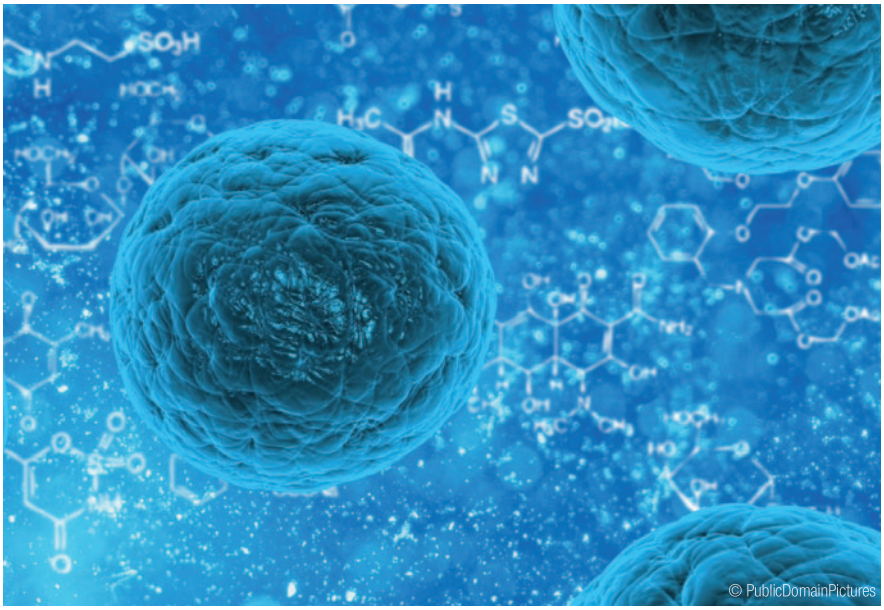
This means that it is easier for them to achieve a synchronous state, and while they will remain individual, each element of the system will become aware of what is occurring in the system as a whole because of its interconnectivity.

This entire approach uses tenets from nanomechanics and quantum field theory because the major challenge is not looking at the single event *per se,* but in investigating how multiple advances can share information.

The message is that, as a part of the Universe, human beings are created from this type of energy and are always resonating, and we can therefore use this energy, which is also produced by our cells, to modulate the fate of these cells – whether they be 'normal' or 'diseased cells', somatic or stem cells.

Indeed, specific devices emitting weak mechanical vibrations or electromagnetic fields have been developed and used to re-programme *in vitro* stem cells to a pluripotent state, which is characterised by enhanced ability to differentiate along multiple fates and produce factors that repair a damaged tissue. Due to the diffusive nature of these physical energies (sounds and even more magnetic fields) we can use them to directly target the stem cells where they are *in vivo,* in any tissue of our body (tissue-resident stem cells). This novel approach may allow us to re-programme the stem cells *in situ,* paving the way for a regenerative medicine that can be afforded without the needs of stem cell transplantation and based upon a gentle stimulation of the natural ability of tissues for self-healing.

Indeed, by using, for instance, mechanical vibrations fashioned around specific frequencies, wave form, amplitude, and/or pause interval(s), research has shown in animal models and *in vivo* in humans that by tuning these vibrations it is possible to decrease adipogenesis and increase osteogenesis, and that this switch mainly results from the ability of mechanical signals to influence mesenchymal stem cell fate, promoting bone and suppressing the fat phenotype.



Studies have shown that electromagnetic fields can be used to drive cell fate at the level of both embryonic and adult human stem cells and to reverse stem cell ageing

In our studies, we have provided evidence that electromagnetic fields can be used to drive cell fate at the level of both embryonic and adult human stem cells and to reverse stem cell ageing. We also succeeded in the use of electromagnetic fields to reprogram human somatic cells, like skin fibroblasts, into lineages in which these cells would never otherwise appear, including myocardial, skeletal muscle and neuronal lineages. We also showed that cellular mechanical vibrations may serve as a signature for the characterisation of cell health, and as a tool to drive stem cell commitment.

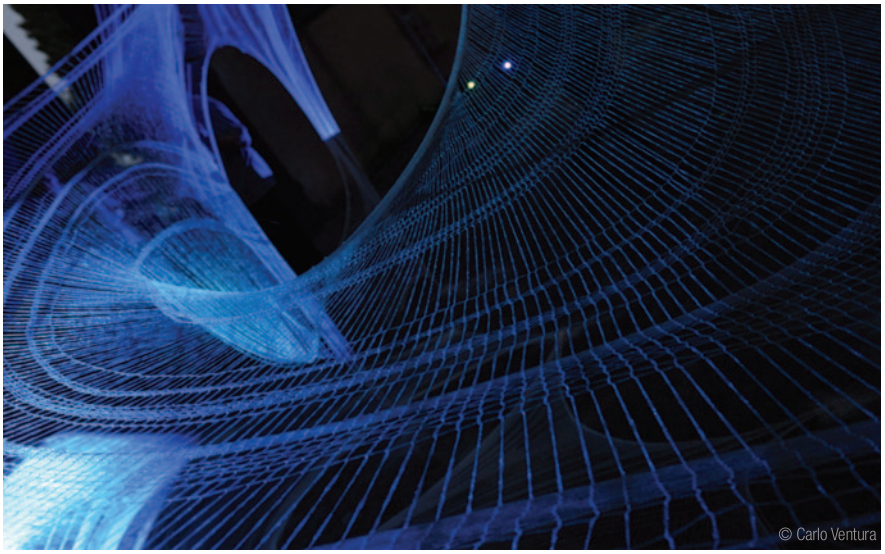
Furthermore, due to the fact that the amount of energy transmitted is so low, these technologies are not classed as medical devices, which will help them through the regulatory and legislative processes. They will instead be classed as 'wellbeing devices', a term which covers a wide variety of areas that are not regulated, meaning that we have to be very careful to try to understand what the wellbeing counterpart for a cell can be at the molecular level.

What would you say have been the biggest achievements and advances in this area in recent years?

Advances in areas concerning general issues such as areas which can really provide a major shift in the way we see cell biology as a sort of entanglement of biology with physics are crucial. This concerns, fundamentally, the knowledge that cells produce electromagnetic fields, they oscillate, and they experience coherent phases.

There is now more than ever a need for transdisciplinary efforts rather than the more traditional silo-based approach. This, of course, is often more easily said than done, not least because of the different scientific vocabularies used by different disciplines, which can often remain indecipherable to non-specialists.

Nevertheless, we are quite lucky in this sphere because we are able to bring together areas as diverse as art and science. For instance, in 2011 I founded VID art|science, where VID is the abbreviation of *vide,* Latin imperative singular of *videre,* 'to see'. VID therefore means: see, have a vision!



The image is captured from a textile three-dimensional installation of Julia von Stietencron, Art Director of VID artIscience, entitled "Feeding Networks"

VID artIscience is a common journey of artists and scientists exploring the avant-garde of scientific innovation to unravel how human arts may talk to the innermost dynamics of our biology. At VID artIscience, artists are also evolving towards expressive forms autonomously inspired by a scientific landscape made of novel discoveries and paradigms.

What are your hopes for the regulatory/legislative landscape in Europe when it comes to stem cells?

The differences between the Food and Drug Administration (FDA) in the US and the European Medicines Agency (EMA) here in Europe are becoming smaller and smaller.

We have provided evidence that transplantation of microfractured human adipose tissue, containing the stem cells within their own microenvironment (niche), enhances tissue repair at a remarkably higher level than the transplantation of isolated stem cells, unplugged from their niche and expanded (grown in culture) *ex vivo* prior to injection. This indicates that when stem cells are transplanted within their own microenvironment they can perceive what is needed by the damaged tissue and trigger a self-healing response. Such ability is consistently reduced if you take the stem cells out of their own microenvironment and grow them *in vitro* to increase their number. Their transplantation will adhere more to a pharmacological paradigm, i.e. you need a lot of cells to replace the damaged ones. But most of the cells that are injected will die or migrate to other sites etc. and will not transdifferentiate. If, however, you transplant the tissue that contains the stem cells rather than the cells alone, this can be avoided, and that tissue will act as a 'slow releasing medium' of regenerative factors where they are mostly needed.

It is this situation that is changing the regulatory standpoints. The issue of transplanting a tissue both for the FDA and EMA is totally different as compared with transplanting expanded, cells, because the latter are seen as advanced-therapy medicinal products (ATMPs) and are therefore treated in the same way as drugs, with all the necessary permissions etc. required, which can take many years and may not work properly at the end of the day.

Conversely, if you transplant the tissue containing the stem cells, it is just a tissue transplantation, and this can be done right away in the surgical room, provided you are not inducing a major manipulation of the tissue itself (i.e. by using enzymes etc.), and you have obtained the permission from an ethical committee.

Is enough being done to make sure that the funding is there for this type of research and, indeed the facilities and infrastructure you require?

This is an important point because, of course, while some of the facilities needed for many studies are often the same as those needed for classical stem cell biology, you will also need other devices to deliver the mechanical vibrations, and much of this equipment is still in the early phases – such as some lasers or electromagnetic field generators, as well as proper tools to register and record the outcomes.

It is also important to consider the people required from many different disciplines who will need to come and work together.

Do you think there needs to be more training in this area for young researchers?

Absolutely. We need to make them more open minded. To return to the issue of different scientific vocabularies, we are perhaps lucky in one sense because the experimental results in nanotech and this particular extreme field of micro/nano biology are so complex that there is no conventional language to describe things. As such, we need to find new words and new languages, which is incredibly difficult and so we are borrowing words from the classical languages and poetry to describe what is sensed but not seen.

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