HFSP MATTERS

The Newsletter of the Human Frontier Science Program

What a year!

By Guntram Bauer
Director of Scientific Affairs and Communications

Scientifically 2013 was one of the most interesting years. Ground breaking HFSP projects went up on our website, such as the ATRIOS project or the Mind's Eye, to name just two.

Late 2013, however, brought real excitement. Firstly, because the 2013 Balzan Prize and Lasker Award were won by two HFSP alumni. News from Stockholm then left us in awe as five HFSP alumni, one of whom was a member of the Council of Scientists, were among the recipients of the 2013 Nobel Prizes in Physiology and Medicine, and in Chemistry. These awards demonstrate that HFSP's bottom-up curiosity driven programs support researchers that excel in advancing our knowledge. The breadth of research in these award winning laboratories could not be more diverse thus making a strong case for HFSP's unrestricted approach to modern life sciences.

And then there is happenchance. Rarely does an organization supporting basic research have an opportunity to celebrate translational outcome from one of its funded projects. Phil Ingham and his colleagues report in this issue that it takes the right collaborators at the right time to break through. But there is more to 21st century HFSP funded research than just molecular biology, as is evident from the two contributions by Sabine Hauert and Gregory Sutton. High-tech nanoparticle engineering and biophysical analysis of jumping insects occupy the other end of HFSP's exciting scientific spectrum.

We very much look forward to HFSP's 25th anniversary in 2014 and we are highly motivated to further our unique mission to support the brightest minds in the life sciences.

The 2014 HFSP Awardees Meeting

Lugano, Switzerland, 6 - 9 July 2014

The year ahead presents another important milestone for HFSP because in 2014 we will commemorate the 25th anniversary of the Program. For this reason, much thought has gone in to where the Awardees Meeting should be held. Luckily, Isabella Beretta, Swiss member of the HFSP Board of Trustees, came forward with a tempting location that nobody could resist.

Lugano, one of the most scenic places in the alpine region, will be the host city not only for the 2014 Awardees Meeting (6-9 July) but also for a special anniversary event on Saturday, 5 July, preceding our annual get-together.

Preparations for the meeting are well underway. The anniversary event will be held in town and the Awardees Meeting scientific program will take place in the auditorium of the Università della Svizzera italiana (USI).

Participants in the 2013 Strasbourg meeting were happy to use the Strasbourg tram network to get around the city. The city of Lugano, being smaller than Strasbourg, is easy to explore on foot. So, bring your walking shoes for some refreshing morning exercise on your way to the lecture hall.

Further information about the program, meeting registration and accommodation will be published soon in the **Awardees Meeting section** of our website.

We are looking forward to seeing you in Lugano.

In this issue

Impressum

The HFSP Newsletter is issued on behalf of the Human Frontier Science Program by the International Human Frontier Science Program Organization. It contains announcements of HFSP-related matters and other information of interest to the support of young scientists and to interdisciplinary research in general. Please tell your friends, colleagues, students, etc. about this mailing list. They can subscribe via a link on the **HFSP home page**.

Please address any suggestions or comments to: **www.communications.org**

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HFSP alumni reap Nobel Prizes in 2013

James Rothman, Randy Schekman, and Thomas Südhof received the Nobel Prize in Physiology or Medicine "for their discoveries of machinery regulating vesicle traffic, a major transport system in our cells". HFSP alumni Martin Karplus and Michael Levitt received the Nobel Prize in Chemistry jointly with Arieh Warshel "for the development of multiscale models for complex chemical systems".

The five alumni have been supported several times by HFSP. We are very pleased that all five have taken such an active role as HFSP host supervisors in training the next generation of researchers in their laboratories. Below is a summary of their HFSP accolades to date.

James Rothman was a multiple research grant recipient (1990, 1994 and 2005) and has hosted four HFSP fellows in his laboratory (1992, 1993, 1995, and 1998). Randy Schekman was twice a research grant recipient (1991 and 1995) and has hosted seven HFSP fellows (1994, 1996, 2000, 2008, 2009, 2010, and 2012). Randy Schekman was also a member of the HFSP Council of Scientists from 1994 to 1998. Thomas Südhof received a research grant in 1995 and has also hosted seven HFSP fellows in his laboratory (1992, 1995, 1996, 1999, 2006, 2008, and 2009).

Michael Levitt received a research grant in 2008 and is currently hosting an HFSP fellow who was awarded in April this year. Martin Karplus was the principal applicant for a 2005 research grant and has in the past hosted three HFSP fellows in his laboratory (1994, 1995, and 1998).

Japanese honours

Professor Nobutaka Hirokawa

HFSP President Nobutaka Hirokawa and former Council member Toshio Yanagida will be honoured as Persons of Cultural Merit in December 2013. This order is an official Japanese distinction, which recognizes and honours selected people that have made outstanding contributions to advancing the Japanese culture in a variety of fields including academia, science and technology. Being named a Person of Cultural Merit is a highly prestigious status very close to the Order of Culture, which a few years ago was conferred upon former HFSP President Akito Arima.

Other prizes & awards

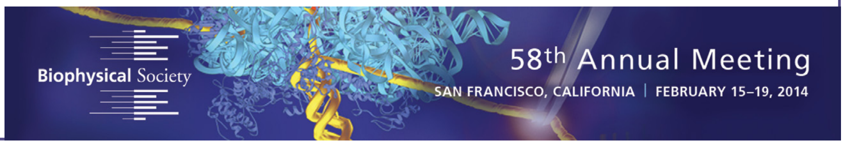
- **Thomas Südhof** received the 2013 Albert Lasker Basic Medical Research Award together with Richard Scheller for discoveries concerning the molecular machinery and regulatory mechanism that underlie the rapid release of neurotransmitters. Prof. Südhof of Stanford University School of Medicine was awarded an HFSP research grant in 1995.

- **Pascale Cossart** (Pasteur Institute, Paris), a 2013 HFSP research grant awardee, was awarded the 2013 Balzan Prize for her seminal discoveries on the molecular biology of pathogenic bacteria and their interaction with host cells. Pascale was a member of the HFSP Council of Scientists (2008-2011) and is currently hosting an HFSP fellow in her laboratory. For more information on the Balzan Prize go to **http://www.balzan.org/en**.

Opportunities to meet HFSP in 2014

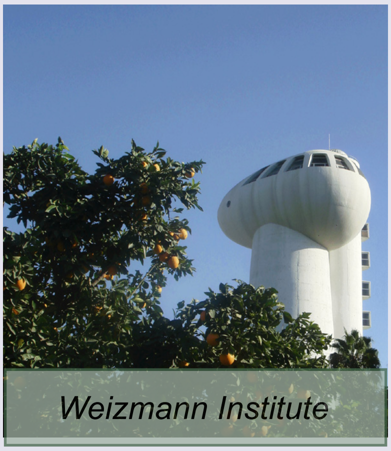
In 2014, there will be plenty of opportunities to meet HFSP in person if you are not able to attend the Lugano Awardees Meeting in July. For the first time, we will have a booth at the exhibition of the Annual Meeting of the Biophysical Society in San Francisco (February 15-19), where you will have the chance to meet Rosalyn Huie and Guntram Bauer. Later in the year HFSP will be present at the EMBO Meeting in Paris, France.

After some absence and thanks to the support of the Japanese Ministry of Education, Culture, Sports, Science and Technology (MEXT), we are looking forward to organizing HFSP talks at two meetings in 2014. HFSP sessions with special talks by awardees and alumni will take place during the annual meetings of the Biophysical Society and the Molecular Biology Society.



The HFSP alumni network keeps buzzing – scheduled meetings for early 2014

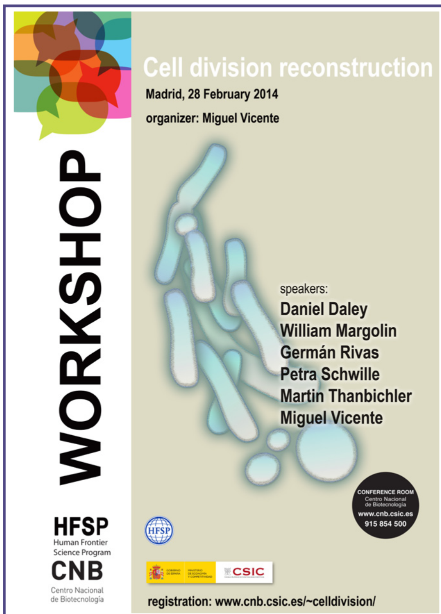
Firstly, we will invite HFSP alumni and current awardees to Genentech Hall where HFSP alumna Katja Brückner will be our local host for the San Francisco Bay Area meeting at UCSF on 19th February 2014. All awardees, past and present, are welcome to attend and can register via the HFSP website **Alumni section** once signed-up as an alumnus. Prior to the Alumni meeting, HFSP will exhibit at the 2014 Annual Meeting of the Biophysical Society in San Francisco (15 - 19 February).



Weizmann Institute

We are very excited about our second stop, which will take HFSP for the very first time to Israel. The second alumni meeting in 2014 will take place on March 27th at the Weizmann Institute in Rehovot thanks to the enthusiastic efforts of Benjamin Born, a current HFSP fellow.

All alumni for whom we have contact addresses in Israel will be invited. Check the **Alumni section** on the HFSP website for more information.



HFSP grant team organizes an open workshop on Cell Division Reconstruction

Miguel Vicente, the PI on a 2010 HFSP Program Grant, together with team members German Rivas, Petra Schwille and William Margolin and colleagues, is organizing an open workshop in Madrid on 28 February 2014, which ends their international HFSP funded collaboration on a high note.

Packing bacterial components in unusual containers allows us to explore how complex machineries work without the limitations imposed when using the whole cell. This approach, central to their HFSP grant, has produced valuable information on the cell division machinery, the divisome. New interactions between elements of the machinery have been revealed and functional assemblies have been reconstructed in the test tube.

During this one day meeting at the CSIC National Biotechnology Center in Madrid, the team will use the workshop not only to summarize the results of the project but also to discuss future Synthetic Biology developments in this field. For more information and registration for the workshop please visit: **http://www.cnb.csic.es/~celldivision/**.

Happenchance and Hedgehogs

By Philip Ingham

Earlier this year, the European Medicines Agency approved the use of a new anti-cancer drug, Erivedge, developed by Genentech in collaboration with the Cambridge (Mass) based biotech company Curis Inc, for the treatment of Basal Cell Carcinoma (BCC), the most common cancer amongst Caucasians. This decision followed similar approval for its clinical use in the USA by the FDA in 2012. The drug works by targeting a transmembrane protein called Smoothened that is a pivotal component of the intracellular pathway that transduces the activity of a secreted signaling protein known as Sonic hedgehog (Shh; Ref. 1).

> *"The significance of these findings for the fledgling field of Regenerative Medicine was not lost on the three collaborators and a patent application covering the use of Hh proteins in directing the differentiation of stem or progenitor cells for therapeutic use was filed by their respective institutions."*

Shh plays a key role in initiating the development of hair follicles, being the signal by which epidermal cells of the hair placode induce the dermal papilla in the underlying mesenchyme. BCCs arise when the Shh signaling pathway is inappropriately activated in the basal progenitor cells of the interfollicular epidermis, causing them to behave like constitutively stimulated hair follicle progenitors.

The role of Shh in hair development was originally reported in one of a steady stream of papers that followed the discovery of the SHH gene in the labs of Philip Ingham, Andrew McMahon and Cliff Tabin, the result of a three way transatlantic collaboration funded by HFSP in 1993. The original motivation for the research that led to this discovery could not have been further removed from its ultimate application: Ingham and McMahon had been studying the expression of two other genes Engrailed, which encodes a transcription factor, and Wnt-1, a proto-oncogene that encodes another secreted signaling protein, in the embryos of *Drosophila* and mice respectively.

Struck by the similar spatial relationships between the domains of expression of the two genes in each species, McMahon speculated that they might form part of a regulatory loop that maintains the midbrain-hindbrain boundary in the vertebrate brain, by analogy with their well established role in maintaining segmental boundaries in the *Drosophila* embryo. Ingham's work had already shown that the *Drosophila hedgehog (hh)* gene was another key component of this regulatory loop in the fly embryo (Ref. 1) – so the pair agreed to collaborate in the search for vertebrate homologues of the *Drosophila* gene to test McMahon's idea. Aware of Tabin's interest in identifying vertebrate homologues of *hh* that might function in the vertebrate limb, McMahon approached his Harvard-based colleague with an invitation to join the team: the motivation for this invitation was not entirely scientific – though based in the US, McMahon like Ingham was a UK citizen so a non-Brit had to be included to comply with HFSP rules[1] ! This bureaucratic expedient proved highly fortuitous: working with the sequence of the first mouse *hh* homologue isolated in the McMahon lab (Ref. 2), the Tabin lab revealed the presence of not one but three distinct *hh*-like genes through PCR amplification of chicken DNA (Ref. 3). At the same time the Ingham lab identified a full-length version of one of the Tabin PCR fragments in the zebrafish, and examined its expression by the still relatively novel technique of non-radioactive in situ hybridization.

The results were spectacular: while not expressed where Ingham and McMahon had anticipated at the mid-hindbrain boundary, the Sonic hedgehog gene (as it would become known) was expressed along the length of the notochord (Ref. 4), a structure

[1]*Currently HFSP grant applications only require that participating laboratories are located in different countries. The nationality of team members is no longer relevant.*

underlying the neural tube and known to be the source of a mysterious and elusive signal that specifies the identity of different neuronal progenitors. Intriguingly, it was known from experimental manipulation in the chick embryo that transplantation of pieces of notochord into the developing limb bud could also mimic the effects of transplantation of a region of the limb bud known as the Zone of Polarising Activity or ZPA, causing duplications of digits in the manipulated limb. Within a matter of days, the Tabin lab had repeated the expression analysis of Shh, this time in the chick embryo – the limb buds of which are an order of magnitude bigger than the zebrafish's rather puny fin buds – and found that its expression corresponds precisely to the location of the ZPA. And within a few more weeks they had shown that misexpression of *Shh* in the anterior limb bud mimics the effects of ZPA grafts (Ref. 3).

At the same time, the McMahon and Ingham labs had misexpressed *Shh* in the neural tubes of mouse and fish embryos to uncover its ability to specify ventral identity on naïve neural progenitors (Refs. 2, 4). The significance of these findings for the fledgling field of Regenerative Medicine was not lost on the three collaborators and a patent application covering the use of Hh proteins in directing the differentiation of stem or progenitor cells for therapeutic use was filed by their respective institutions. This and a number of other follow-up patents helped facilitate the establishment of a biotech start-up company named Ontogeny that would ultimately merge into Curis Inc. And it was at Curis Inc. that a simple high-throughput screen for Hh pathway agonists and antagonists paved the way for the development of Erivedge in partnership with Genentech.

In the two decades since the landmark discovery of *Shh*, there has been an explosion of interest in the Hh pathway – hedgehog is now recognized as one of the half dozen or so key signaling pathways underlying animal development. Hh signaling plays pivotal roles in a plethora of developmental and regenerative processes and has been implicated in many cancers besides BCC. The discoveries catalyzed by the outcome of the initial HFSP funded curiosity driven research program have thus had profound effects on the understanding of human development and disease and hold great promise for a range of therapeutic applications in the not too distant future.

Philip Ingham is Professor of Developmental Biology at the Lee Kong Chian School of Medicine, Nanyang Technological University, Singapore and at Imperial College, London and is also a Research Director at the A*STAR Institute of Molecular and Cell Biology, Singapore. You can read his full biosketch at **http://www.hfsp.org/node/778**

http://www.imcb.a-star.edu.sg/php/philipingham.php

Andrew McMahon is Director of the Eli and Edythe Broad Center for Regenerative Medicine and Stem Cell Research at the University of Southern California. He is a Provost Professor and W. M. Keck Professor of Stem Cell Biology and Regenerative Medicine. In addition, he chairs the newly created Department of Stem Cell Biology and Regenerative Medicine at the USC Keck School of Medicine and holds an appointment in the Department of Biological Sciences in the USC Dornsife College of Letters, Arts, and Sciences.
http://mcmahonlab.usc.edu/

Cliff Tabin is Professor and Chair of the Department of Genetics at Harvard Medical School. His full biosketch is available at **http://www.hfsp.org/node/777**

http://genepath.med.harvard.edu/~tabin

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For the full list of publications refer to article on the HFSP website (**http://www.hfsp.org/frontier-science/hfsp-success-stories/happenchance-and-hedgehogs**).

You can read more HFSP success stories on the HFSP website at: **www.hfsp.org/frontier-science/hfsp-success-stories**

Insect Jumping, an Ancient Question

The acrobatic leaps of insects have fascinated both storytellers and scientists for the scope of human history. Aristophanes wrote in amazement about how far fleas could jump, suggesting that their jump distance be measured in 'flea feet', and compared to the 'human feet' of man's leaps. Hans Christian Anderson likewise marvelled at jumping insects, writing a cautionary tale of a contest between a flea, a grasshopper, and a tuna. In his tale, both the flea and the grasshopper lose the contest, not because they jumped insufficiently high, but because the judge unfairly preferred the tuna's manners over the much greater jumping distances of the two insect contestants. In any fair contest, however, it would be hard to argue that insects are not the most incredible jumpers of the natural world – with fleas able to launch themselves through the air at speeds of over 2 meters per second, grasshoppers reaching speeds as fast as 4 meters per second, and the champion jumpers, planthoppers, reaching speeds as fast as 6 meters per second. The times to reach these speeds are breath-takingly short, with grasshoppers able to reach this speed in less than 20 milliseconds, and fleas and planthoppers able to achieve this feat in less than one millisecond. This is far from easy, as these jumps require the insect to navigate three extremely difficult biomechanical challenges: 1) generating the necessary power, 2) directing the power through the legs to generate a controlled jump, and 3) synchronizing the two legs so that differential leg extension does not cause the animal to spin out of control. To solve these problems, evolution has developed biological structures that are strikingly similar to the man-made devices: composite bows, mechanical linkages, and most surprisingly, gears.

Energy storage and release (composite bows)

The first of these problems is a question of power. Muscles simply cannot generate mechanical work quickly enough to accelerate an insect: muscle can generate power at a maximum rate of 150 Watts per kilogram of muscle. Jumping planthoppers, however, manage to generate 30,000 Watts per kilogram of their muscles, two orders of magnitude higher than what muscles can do alone (Fig. 1). To do this, they use 'cuticular springs' as power amplifiers, which the insect uses in the same way a human being uses a bow to shoot an arrow. The bow generates no energy itself but as we pull back the string, all of the mechanical energy is slowly generated by muscles and stored in the deformation of the wood. When the string is released, recoil of the wood releases the energy extremely quickly, acting as a power amplifier. Insects act similarly using a 'bow' made of their cuticle. Prior to a jump, the muscles slowly load this 'bow', and then, recoil of the cuticular bow shoots the animal through the air, amplifying the muscle power by orders of magnitude.

Until recently, it was thought that insects used two kinds of bow-like energy storage structures: one in the leg of the grasshopper, called the 'semi-lunar process', which was made of hardened insect cuticle, and one in the body of the flea, called the 'pleural arch', which was made of an extremely energy efficient springy protein called 'resilin'. Each structure was thought to store energy in a different material. This left the open question of 'which design is better', i.e. does the planthopper, the fastest of the insect jumpers, use a 'grasshopper' design made of hardened cuticle, or does it use a 'flea' design made of springy protein? As is often the case in science, the answer to this question was 'both'. Planthoppers have an inner layer of springy protein and an outer layer of hardened cuticle (Fig.2). The layering of hardened cuticle with springy protein, in the same way that a composite bow takes advantage of the mechanical properties of wood and horn, creates a combination that is superior to both.

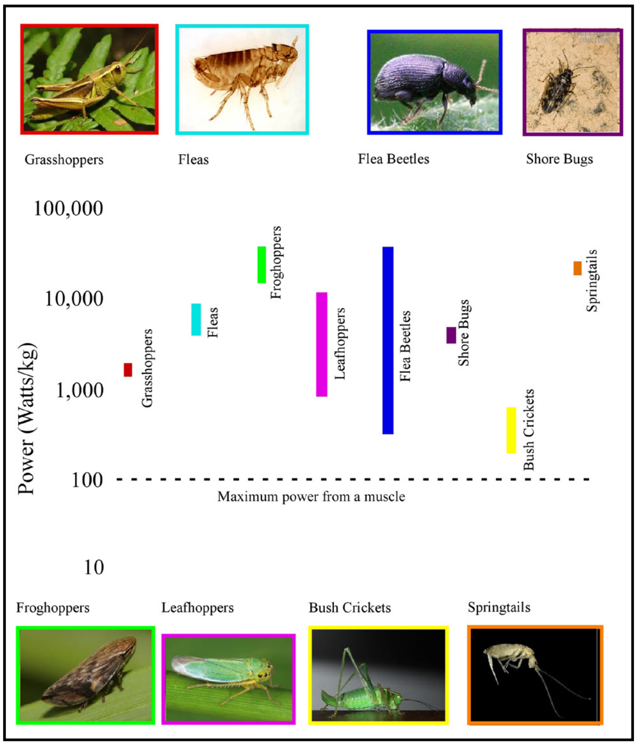


Fig 1: The power requirements for the jumps of various insects. The vast majority of jumping insects require an order of magnitude more powerful to jump than can be generated by muscle alone. Consequently, the insect jump requires a system to amplify power.

This discovery prompted a re-evaluation of the springs within the flea and the grasshopper – were they really that different? Re-evaluation of the energy storage 'bows' within the flea and the grasshopper revealed that the two structures were not that different at all. Both of them used a composite structure made of an inner layer of resilin and an outer layer of hard cuticle. Thus, there is a general principle that the energy storage mechanism of jumping insects mimics a composite bow.

For full article with references see: **http://www.hfsp.org/frontier-science/frontier-science-matters/insect-jumping-ancient-question**

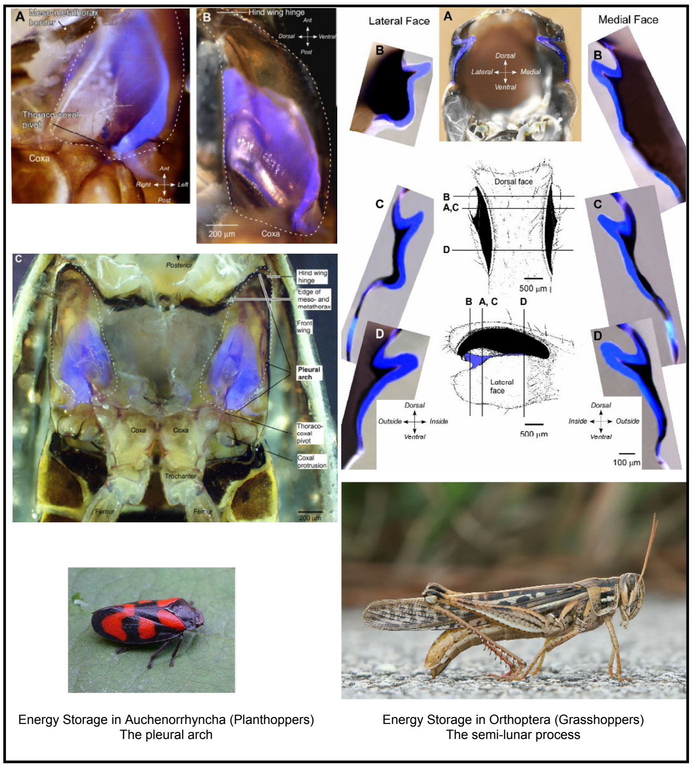


Fig 2: The energy storage 'bows' of planthoppers (left) and grasshoppers (right). Both energy storage structures are arches with an outside layer of hardened cuticle (black) with an inside layer of resilin (blue). The composite structure of these energy storage systems allows the insect to take advantage of the different material properties of both materials.

Directing the energy (mechanical linkages)

Stored energy must be precisely released. Jumping insects do this by having their legs act as mechanical linkage systems which direct the force from the recoiling 'bow' to the ground. Depending on the location of the energy storage device, this is done differently. Grasshoppers, which have their energy storage devices in their legs, use their 'hip' (also known as the coxa/body joint) to direct jumps. Rotations of the coxa/body joint change the direction of force, allowing the grasshopper to quickly and easily direct a jump or a kick. The ease of this directional change allows grasshoppers to change the direction of their jump even in the milliseconds just prior to the recoil of the spring, making it difficult for predators to predict which way the insect will go.

Planthoppers, which have their energy storage device in their body, use a different part of their leg to direct a jump: small muscles in their 'knee' (also known as the femur/tibia joint). These muscles can direct the forces from the recoil to the left or the right, similar to the way the grasshoppers use the coxa/body joint to direct the forces when they jump; i.e. both insects use one leg joint as a 'powered' joint, and another as a 'directional' joint.

Fleas, in contrast, have a jumping mechanism that combines the leg geometry of the grasshopper with the mechanical energy storage device of the planthopper - with the combined system being extremely difficult to control. Strangely, fleas handle this by always jumping in the same direction, with very little variation in the trajectory between individual jumps.

Synchronizing the legs (gears)

Of the three most famous jumping insects, planthoppers have a problem fleas and grasshoppers do not: to generate a controlled jump planthoppers require legs which extend almost perfectly synchronously. If planthopper legs do not extend at exactly the same time, the insect will spin wildly out of control. Adult planthoppers solve this problem quite simply, by having a frictional contact between their two 'hips' which ensures simultaneous extension of the two legs. The nymphs, however, have a different and much more spectacular solution. The nymphs have bumps and grooves on each leg, which interlock like a set of modern gears. Prior to a jump, engaging these gears ensures that each leg extends perfectly synchronously (Fig. 3). These gears represent the very first intermeshing rotating gears that have been discovered in nature, and thus are an evolutionary prototype of high speed - high precision gears for modern machinery.

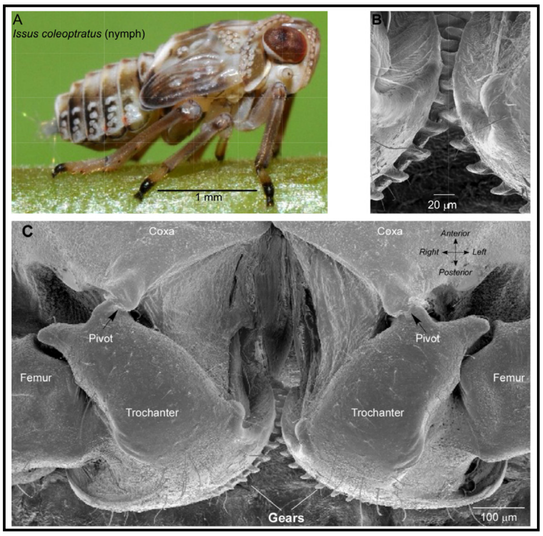


Fig 3: The leg synchronization mechanism of the nymph planthopper 'issus'. The nymph has intermeshing gears on the left and right hind legs. Prior to the jump, the insect engages these gears, which ensure that both legs extend at exactly the same time.

In conclusion

Composite bows, mechanical linkage systems, and gear trains are all critical to the behavioural success of jumping insects. These biological systems are not just metaphorically similar to the mechanical devices used in modern engineering; they represent designs for precise, targeted, and amazingly fast-moving devices. They are beautiful examples of biomechanics providing elegant solutions for problems that have fascinated mankind for thousands of years.

Gregory Sutton received his education at Case Western Reserve University in Cleveland, Ohio. After completing his Ph.D. in 2006, he started post-doctoral work at the University of Cambridge studying the biomechanics and neural control of invertebrates. His corpus of work extends from the extremely slow movements of the feeding motions of gastropods to the extremely fast motions of jumping insects. Regardless of the speed of the motion, he has found that analysis of the musculature is a critical tool for understanding how an animal's behaviour is controlled. He combines classical mechanics with neurophysiological techniques to determine how interactions between the nervous system, the skeleton, and the musculature result in the wide variety of behaviours we see around us. He is currently at the University of Bristol studying how bees detect and react to electric fields.

Crowdsourcing the Design of Swarming Nanoparticles for Cancer Applications

The treatment of cancer is undergoing what could be called a revolution. The field has attracted the attention of bioengineers trying to design nanoparticles that can deliver drugs and therapeutics directly to tumors. Their size, typically 10 nm to 500 nm, is ideal to leak out of porous vessels deep in tumors while remaining in the blood stream throughout the rest of the body. This allows nanoparticles to passively accumulate in tumors while reducing side effects on healthy tissue. With this article we launch a new chapter in HFSP Matters that will present work in progress. The author, HFSP Cross-Disciplinary Fellow Sabine Hauert, has already contributed an initial description of her studies for the Awardees' Articles section of the HFSP website (**http://www.hfsp.org/frontier-science/awardees-articles/gamers-design-swarms-nanoparticles-cancer-research-video**) and gave an inspiring well-received talk at the 2013 Awardees Meeting in Strasbourg. This work was done in the laboratory of Sangeeta Bhatia at MIT.

Nanoparticles come in different sizes, shapes and materials. They can be loaded with drugs that are released in a controlled fashion, or coated with molecules that allow them to interact with their environment. Certain molecules can serve as a signature to uniquely identify and internalize in cancer cells. Nanoparticles can also be made of energy-receptive materials that heat up upon magnetic or laser excitation.

There are many ways to design a nanoparticle. Depending on the design, the nanoparticle will move, sense and act in different ways in the tumor environment (Fig. 1). Control is embedded in the design of the nanoparticles and their interactions with the environment rather than their computational capabilities. In other words, changing the body of the nanoparticle will change its behavior: we call this embodied intelligence. The challenge is to understand which nanoparticle designs will improve treatment outcome. This is a difficult problem because trillions of nanoparticles typically interact in a tumor with millions of cells. Predicting and optimizing the emergent behavior of all these nanoparticles is guess work at best.

Sabine Hauert is a Human Frontier Science Program Cross-Disciplinary Fellow at the Koch Institute for Integrative Cancer Research at MIT. As a swarm engineer she aims to design large collective systems that self-organize. Swarm strategies are either inspired from nature (ant colonies and bird flocks) or are automatically designed in simulation using machine learning and crowdsourcing. Demonstrated applications include designing swarming nanoparticles for cancer treatment and deploying large aerial swarms for communication relay. Underlying her work is a strong involvement in science communication and online learning as demonstrated by her widely recognized blogs, tweets and podcasts. **http://sabinehauert.com**

Sangeeta Bhatia is the John J. and Dorothy Wilson Professor of Health Sciences and Technology and Electrical Engineering and Computer Science at MIT and a Howard Hughes Medical Investigator. Her lab combines engineering and biology to develop micro- and nanoscale platforms for understanding and treating human disease. Dr. Bhatia received her B.S. from Brown University, M.S. and Ph.D. from MIT, M.D. from Harvard and completed graduate and post-doctoral training at MGH. Prior to MIT, Dr. Bhatia held a faculty position at UCSD, and worked at Pfizer, Genetics Institute, ICI Pharmaceuticals, and Organogenesis. Dr. Bhatia has published >100 manuscripts and over 40 issued or pending patents, and has co-founded two biotechnology start-ups, consults for industry, government and academic organizations, and advocates for diversity in science and engineering. **http://ki.mit.edu/people/faculty/bhatia**

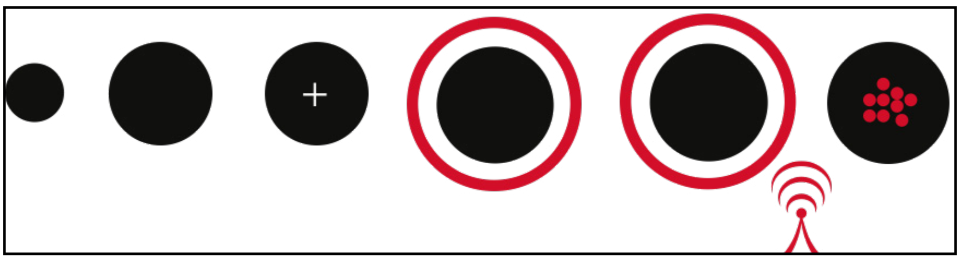


Fig 1: Changing nanoparticle size, charge, coating, materials or cargos changes their behavior in the tumor environment.

To address this challenge, and following a systems approach, we designed a simulator that models how nanoparticles interact with each other and the tumor environment. The simulator generates reaction diffusion networks for the different nanoparticle designs based on realistic parameters from the literature and uses the stochastic simulation compiler designed at MIT (**http://web.mit.edu/irc/ssc/**). We focus on a representative area of the tumor instead of modeling the entire system. The hope is that if we chose the tumor scenario wisely, we will be able to generalize the results to the rest of the tumor. We've successfully used this computational framework in the past to discover guidelines to improve the penetration of nanoparticles deep in tumor tissue in a generalizable manner (Hauert et al. 2013, under review).

Like our nanoparticles, flocks of birds, ant colonies, cells and robot collectives can exhibit seemingly complex swarm behaviors when large numbers of simple agents react to local information. By design, swarms are efficient, robust and scalable. Emergent swarm behaviors useful for real-world applications include amplification, optimization, mapping, structure assembly, collective motion, synchronization and decision making. Our goal is to explore how nanoparticles can cooperate, or swarm, to synergistically improve their therapeutic effect.

Recent work in our laboratory, which uses nanoparticles that communicate in vivo to amplify tumor-homing, shows promise in this direction (von Maltzahn et al., Nature Materials, 2011). In this work, a near-infrared laser was used to heat gold nanoparticles that had passively accumulated in a tumor, thereby causing damage to the tissue. A second wave of nanoparticles were engineered to bind to the damaged tissue, and would therefore accumulate at higher numbers there. Similar to ants forming trails to a picnic table by depositing pheromones in the environment, these nanoparticles work by depositing and interacting with information in the tumor.

There are many such tumor scenarios and swarm strategies. Each one takes time to explore and requires large amounts of trial and error and human intuition. Furthermore, each problem is different, making it difficult to program a computer that can automatically design the nanoparticles. Instead, we've decided to make our simulator available through Nanodoc (**http://nanodoc.org**): an online game we developed to crowdsource the design of nanomedicine. Crowdsourcing has been shown in the past to bring unthought-of solutions to complex scientific problems such as protein folding (**http://fold.it**). As shown in Fig. 2, bioengineers can design their own tumor scenarios (right side) and submit them to the crowd. Players can then design different nanoparticle strategies (left side), and test them using our scientific simulator. The first levels of the game are used to train new NanoDocs; licensed NanoDocs are then given challenges to solve.

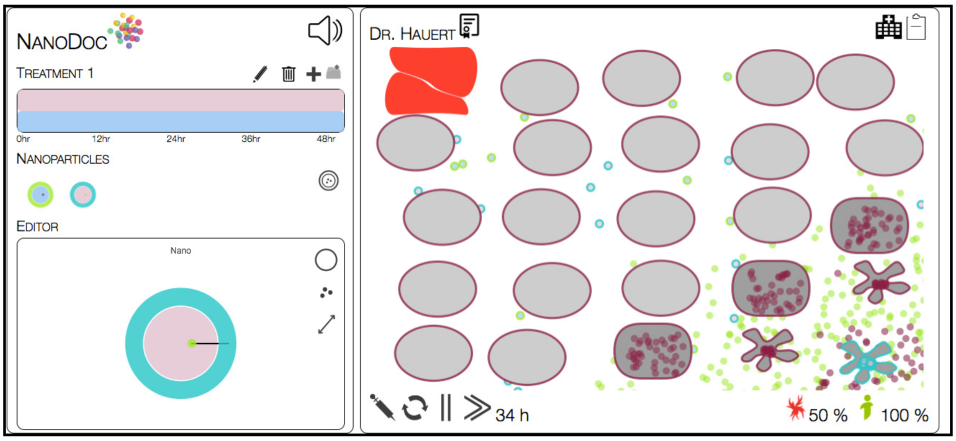


Fig 2: Screenshot of the online game NanoDoc to crowdsource the design of nanomedicine.

During the first two months of being online, NanoDoc attracted nearly 15,000 visitors and was featured in mainstream media including Scientific American, New Scientist and The Guardian. Over 2600 players have now performed over 50,000 simulations with many earning a NanoDoc license that can be posted to social media. This demonstrates the desire of the crowd to learn about nanomedicine and help in the fight against cancer. The crowd was able to solve a first challenge aimed at detecting a rare event in a tumor environment (e.g. mutation, stem cell) and amplifying the signal using a cooperative two-nanoparticle strategy. Interestingly, this challenge required players to design treatments that were beyond what had been taught during training, thereby showing the ability of the crowd to think outside the box and adapt to new challenges.

In parallel to NanoDoc, we've been working on ways to validate nanoparticle designs in reality. This will require expert bioengineers to implement the actual nanoparticles. Selected nano-treatments discovered using NanoDoc will be validated using:
1) in vitro tumor-on-a-chip constructs that we have designed to emulate the extravasation of functionalized nanoparticles from artificial vessels into a compartment containing tumor cells and 2) robotic swarm systems (kilobots) in collaboration with Radhika Nagpal's lab at the Wyss Institute at Harvard University.

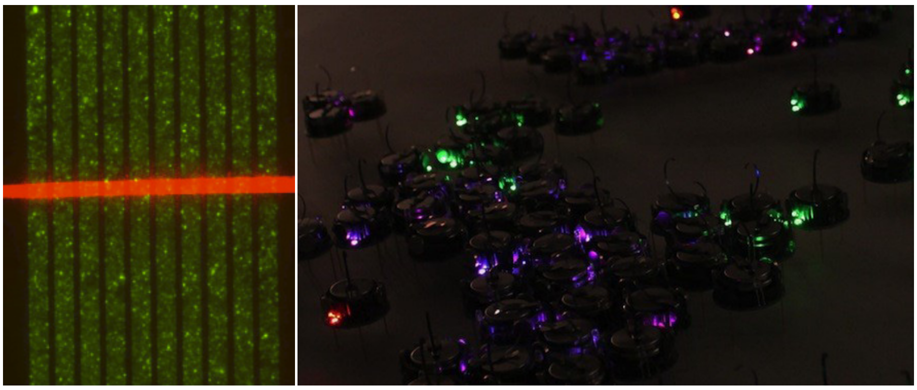
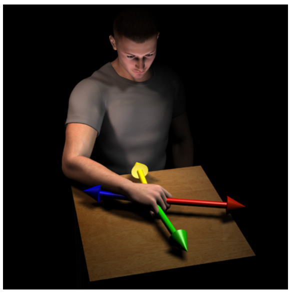


Fig 3: **Left:** *Tissue-on-a-chip construct designed to emulate the extravasation of nanoparticles (red) from artificial vessels into a compartment containing tumor cells (green).* **Right:** *Diffusing nanoparticle robots (green) binding to cell robots (red) within communication range and internalizing within the cell (purple). Experiments were performed using kilobots designed by Mike Rubenstein at the Wyss Institute, Harvard.*

References

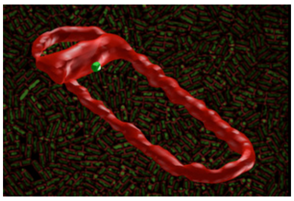
Hauert, S., Berman, S., Nagpal, R., Bhatia, SN. (2013) A computational framework for identifying design guidelines to increase the penetration of targeted nanoparticles into tumors. Submitted.

von Maltzahn, G, Park, J-H, Lin, KY, Singh, N, Schwöppe, C, Mesters,R, Berdel, WE, Ruoslahti, E, Sailor, MJ, Bhatia, SN (2011) Nanoparticles that communicate in vivo to amplify tumour targeting.
Nature Materials, 10: 545-552.



[Virtual surgeries reveal the modular organization of movement](#)
by HFSP Program Grant holders Andrea d'Avella and Dinesh Pai and colleagues

How does the brain control complex motor skills and why are some skills harder to learn than others? Using simulated surgeries during a manipulation task, a new study provides direct evidence that the nervous system groups muscles into modules, or muscle synergies, to simplify movement control. It shows that skills that require new or modified modules are harder to learn than skills that don't.



[Mechanism of an ATP-fueled molecular motor that transports DNA across membranes](#)
by HFSP Career Development Award holder Marcelo Nollmann and colleagues

How is DNA transported across membranes? We investigated the mechanism of DNA segregation by a bacterial DNA motor that uses the energy of ATP hydrolysis to power the movement of chromosomes across membranes during bacterial cell division.

[Novel mechanism for frequency modulation in songbirds](#)
by HFSP Cross-Disciplinary Fellow Ana Amador and colleagues

The underlying similarities in the biomechanical mechanisms of vocalization in songbirds and humans make songbirds an interesting animal model to study learned vocalizations. By developing a novel technique for pressure manipulation during singing, we modified the vocal output in various ways to study mechanisms of vocal control. Results were validated with a physical model for song production that shed light on dynamical mechanisms for frequency control that could be extrapolated to humans.

Read more in the **Awardees' Articles section** of the HFSP website.

HUMAN FRONTIER

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POSITION OF SECRETARY GENERAL

The Board of Trustees of the Human Frontier Science Program (HFSP), representing the member countries*, invites applications and nominations for the position of Secretary General of HFSP. The SG is responsible for the implementation of the Program and is the public voice for HFSP in the world of global science funding. HFSP supports research into the complex mechanisms of living organisms, promoting international collaboration in the spirit of science without borders. It offers funding programs that enable innovative, cutting-edge and high-risk research at the frontiers of the life sciences and actively fosters the financial and intellectual independence of early-career researchers. The SG therefore should be:

• An internationally recognized and respected scientist, preferably with senior-level scientific management experience, who is convinced of the distinctive value of international collaboration and is therefore able to make a compelling case for the support and promotion of frontier research globally, strengthening this prestigious Program and leading it into the next period of its development;

• An innovative researcher, qualified in a field relevant to the scientific priorities of the Program, who understands the importance of novel approaches for the development of life-science research.

The SG will be based in Strasbourg, France for the duration of the appointment, which begins July 2015 for a renewable term of 3 years. Candidates must be citizens of an HFSP member country.

Applications and nominations, accompanied by a CV, should be sent to **SecGen@hfsp.org** by 30 November 2013. Inquiries, nominations, and applications may also be addressed to HFSP's search consultant, Craig Smith, PhD, of Opus Partners: **craig.smith@opuspartners.net**.

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