

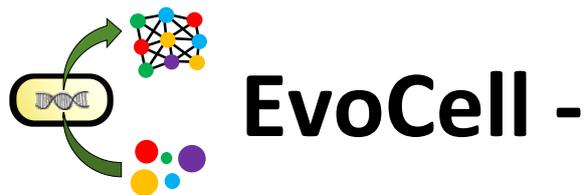
Information for applicants

for the

6 PhD positions

that are available within the

International research training group



Cellular mechanisms of evolutionary innovation

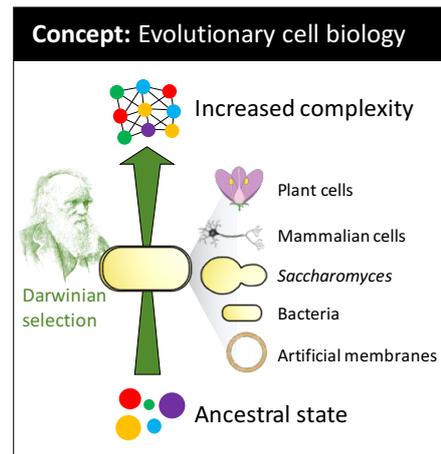
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1. General information about *EvoCell*

1.1 What is Evolutionary Cell Biology?

All evolutionary change causing biological diversification involved modifications at the cellular level. Consequently, a mechanistic understanding of evolutionary processes requires fundamental knowledge of the biochemical and biophysical rules that determine the structure and functioning of cellular features. However, cell biology and evolutionary biology are generally treated as disparate scientific fields that are analysed by two different research communities with very little conceptual overlap. The newly emerging field evolutionary cell biology aims at bridging this gap.



1.2 What is *EvoCell*?

EvoCell is an international research training group that is funded by the University of Osnabrück. The consortium of groups participating in *EvoCell* currently consists of six funded and two associated research groups of three different faculties (School of Biology, School of Physics, and the Institute of Environmental Systems Research) with complementary expertise in organismic-, cell-, theoretical-, and computational biology. The overarching research focus of *EvoCell* is to identify the molecular events, which caused evolutionary innovations that subsequently increased the complexity of a given biological system.

1.3 The curriculum of *EvoCell*

All doctoral students participating in *EvoCell* will prepare for their PhD exam in a 3-year structured program that includes lectures, practical courses, outreach activities, and participation in national and international conferences. This program aims at training the scientific and transferable skills of doctoral students. Moreover, a structured mentoring program will ensure that the students successfully complete their doctoral studies. Afterwards, graduates will be perfectly trained to compete on an international level for jobs in academia or industry.

Main objectives of a doctoral training within *EvoCell*:

- **Interdisciplinary research** projects in an innovative field of life sciences.
- **Comprehensive training** in scientific knowledge and state-of-the-art methodologies.
- **Development of a strong personal career profile** by defining professional goals and obtaining a broad range of transferable skills.
- **Promotion of research stays** abroad as well as of participation in national and international conferences to provide doctoral researchers with international experience and to improve their networking skills.
- **Close supervision** by a team of mentors to ensure that the doctoral researchers achieve the goals of their PhD projects within three years.
- Participation in an **international and interdisciplinary network** of evolutionary cell biologists to enhance communication, collaboration, and coordination of research and fund raising.

1.4 Scientific environment

The University of Osnabrück provides a vibrant and highly collaborative research environment, from which the doctoral researchers of *EvoCell* will greatly benefit. In addition, the University of Osnabrück offers a very well-developed scientific infrastructure that includes for example the newly established Center of Cellular Nanoanalytics Osnabrück (CellNanOs) – a central technology platform that provides access to state-of-the-art analytic equipment. This involves the integrated Bioimaging Facility Osnabrück (iBiOs) that features electron- and super-resolution light microscopes, as well as the central mass spectrometry facility that operates a range of cutting-edge mass spectrometers to identify and quantify proteins, lipids, and other molecules. Finally, due to its focus on computational approaches, the Institute of Environmental Systems Research provides access to a dedicated computer cluster that can be used for time- and computation-intensive calculations. All doctoral students of *EvoCell* will have unrestricted access to these facilities.

1.5 The faculty of *EvoCell*

Project	Principal investigator	Institute (Department/ research group)	Research area
P1	Dr. Armen Mulkidjanian	School of Physics (<i>Experimental Physics</i>)	Molecular biophysics, molecular bioenergetics, evolutionary biophysics
P2	Prof. Dr. Christian Kost	School of Biology/ Chemistry (<i>Ecology</i>)	Evolutionary biology, ecology, microbiology, cell biology
P3	Prof. Dr. Karin Frank	Institute of Environmental Systems Research & Helmholtz Centre for Environmental Research – UFZ Leipzig (<i>Ecological Modeling</i>)	Theoretical biology, ecological modelling, microbial ecology
P4	Dr. Florian Fröhlich	School of Biology/ Chemistry (<i>Molecular Membrane Biology</i>)	Cell biology, membrane biochemistry, mass spectrometry
P5	Prof. Dr. Sabine Zachgo	School of Biology/ Chemistry (<i>Botany</i>)	Developmental biology, comparative genetics, cell biology, evolutionary biology
P6	Prof. Dr. Roland Brandt	School of Biology/ Chemistry (<i>Neurobiology</i>)	Neurobiology, cell biology
A1	Prof. Dr. Joost Holthuis	School of Biology/ Chemistry (<i>Molecular Cell Biology</i>)	Cell biology, membrane biochemistry
A2	Prof. Dr. Jürgen Heinisch	School of Biology/ Chemistry (<i>Genetics</i>)	Genetics, cell biology

(P = Project funded by the University of Osnabrück, A = associated member of *EvoCell*)

2. Detailed descriptions of individual projects

Project 1: Evolution of cell membrane complexity

Project leader: PD Dr. Armen Mulkidjanian (Department of Experimental Physics, School of Physics)
Co-supervisor: Prof. Dr. Christian Kost (Department of Ecology, School of Biology)

1. Background

Cell membranes are of key importance for the cell. On one hand, membranes prevent the loss of cellular components to the environment. On the other hand, membranes contain a plethora of translocators that mediate exchange of ions and molecules with the environment. Therefore, understanding the evolution of membranes is of key importance for clarifying the evolution of the cells. During last years, we, in collaboration with the group of Eugene Koonin of the National Center for Biotechnology Information, NIH, US, have reconstructed the evolution of many membrane energy-converting complexes, as well as of membrane bioenergetics as a whole. It became clear that evolution of membrane bioenergetics followed the evolution of membrane permeability.

2. Project description

We would like to reconstruct the evolution of membrane permeability by means of bioinformatics and put the results on experimental test. We plan, by means of comparative genomics, to specify particular lipid species tentatively present in the Last Universal Cellular Ancestor (LUCA). As next, we plan to produce membrane vesicles made of primordial lipids and study their permeability as function of lipid composition by combining fluorescence spectrophotometry with microscopy and DLS measurements. We hope to assess the contribution of different types of lipids to the stability and permeability of primordial membranes. The experience obtained could be further applied upon clarifying the relation between the complex compositions of modern membranes and their physico-chemical properties.

3. Candidate profile

Candidates must have a M. Sc. degree from a recognized, accredited college or university in biology, chemistry, biochemistry, bioengineering or one of related biological disciplines. A minimum GPA of 3.0 (on a 4.0 scale) is required. Also, candidates should demonstrate their interest in applying evolutionary approaches to biological problems.

4. Key references

- Mulkidjanian, AY, Galperin, MY, Koonin, EV (2009) Co-evolution of primordial membranes and membrane proteins, *Trends Biochem Sci*, 34: 206-215
- Mulkidjanian, AY, Bychkov, AY, Dibrova, DV, Galperin, MY, Koonin, EV (2012) Origin of first cells at terrestrial, anoxic geothermal fields, *Proc Natl Acad Sci USA*, 109: E821-830.
- Koonin, EV, Mulkidjanian, AY (2013) Evolution of cell division: from shear mechanics to complex molecular machineries, *Cell*, 152: 942-944.
- Dibrova, DV, Galperin, MY, Mulkidjanian, AY (2014) Phylogenomic reconstruction of archaeal fatty acid metabolism, *Environ Microbiol*, 16: 907-918.
- Shalaeva, DN, Galperin, MY, Mulkidjanian, AY (2015) Eukaryotic G protein-coupled receptors as descendants of prokaryotic sodium-translocating rhodopsins, *Biol Direct*, 10: 63.
- Lokhmatikov, AV, Voskoboinikova, N., Cherepanov, DA, Skulachev, MV, Steinhoff, HJ, Skulachev, VP, Mulkidjanian, AY (2016) Impact of antioxidants on cardiolipin oxidation in liposomes: Why mitochondrial cardiolipin serves as an apoptotic signal?, *Oxid Med Cell Longev* 2016: 8679469.

Project 2: The evolution of multicellular clusters in bacteria: causes and consequences

Project leader: Prof. Dr. Christian Kost (Department of Ecology, School of Biology)
Co-supervisor: Prof. Dr. Karin Frank (Research Group of Ecological Modeling, Institute of Environmental Systems Research & Department of Ecological Modeling, Helmholtz Centre for Environmental Research – UFZ Leipzig)

1. Background

Bacteria mainly exist within surface-bound or free-floating biofilm communities rather than as isolated, planktonic cells (Tolker-Nielsen and Molin, 2000). The strong propensity of bacterial cells to form multicellular aggregates suggests a strong adaptive advantage drives this pattern. However, despite intensive efforts to understand the molecular basis of biofilm formation, a thorough understanding of both the selective causes and evolutionary consequences is currently lacking. This is because in the past, research has mainly focussed on single bacterial species, rather than performing systematic studies, in which monospecific populations and polymicrobial communities are compared with each other. However, such comparative approaches are urgently required to understand the significance of bacterial aggregates for medically- and biotechnologically-relevant processes such as chronic diseases, antibiotic tolerance, waste-water treatment, and industrial fermentation.

2. Project description

The three main goals of the project are:

(i) to identify the key selective forces driving the aggregation of multiple bacterial cells.

In evolution experiments, populations of single species or polymicrobial consortia will be exposed to different selection pressures. The propensity of cells to aggregate will be quantified using a laser diffraction particle size analyser and by fluorescence microscopy.

(ii) to elucidate the molecular and cell biological causes of cluster formation.

The regulatory and structural genes causing cluster formation will be identified by whole-genome resequencing of derived genotypes and analysing the identified mutations.

(iii) to unravel the evolutionary consequences resulting from a group-living lifestyle.

In a more detailed analysis of derived consortia, it will be verified whether cluster formation is permanent or transient, whether genotypes within clusters evolved metabolic interactions, and how group-living facilitates or impairs the ability of cells to adapt to new environments.

These analyses will be complemented by theoretical models developed in the group of Prof. Dr. Karin Frank (Project 3).

3. Candidate profile

We are searching for a highly-motivated candidate with a Master's degree or equivalent and a strong interest in interdisciplinary research questions, a scientific and critical attitude, and a strong background in evolutionary biology, microbiology, or related fields. Experience in the analysis of large sequence datasets or advanced microscopy techniques is a plus. Good communication skills and proficiency in written and spoken English is required.

4. Key references

- Pande, S, Kost, C (2017) Bacterial unculturability and the formation of intercellular metabolic networks. *Trends in Microbiol*, 25(5), 349-361.
- Pande S, Shitut S, Freund L, Westermann M, Bertels F, Colesie C, Bischofs IB, Kost C (2015) Metabolic cross-feeding via intercellular nanotubes among bacteria. *Nat Commun*, 6: 6238.
- Tolker-Nielsen T, Molin S. (2000) Spatial organization of microbial biofilm communities. *Microb Ecol* 40: 75–84.

Project 3:

The interplay between metabolic evolution on a cell-level and community dynamics in microbial systems

Project leader: Prof. Dr. Karin Frank (Research Group of Ecological Modeling, Institute of Environmental Systems Research & Department of Ecological Modeling, Helmholtz Centre for Environmental Research – UFZ Leipzig)

Co-supervisor: Prof. Dr. Christian Kost (Department of Ecology, School of Biology)

1. Background

In microbial systems, evolutionary dynamics and intracellular processes are closely linked. In particular, the formation of bacterial clusters is common and thought to be driven by bacterial interactions. The evolution of these clusters, however, is mechanistically not fully understood. The so-called Dynamic Energy Budget Theory (DEB) indicates that the activities of a cell are constrained by both its energy budget and its energy allocation strategy. This underpins the importance of intracellular metabolic processes, but also of nutrient availability and bacterial abundance (competition) in the vicinity of a bacterium. Their combined effects have to be analyzed in a theoretically sound way. This can be supported by dynamic modeling.

2. Project description

This project (P3) focuses on ecological modeling. It aims at the development of a model system, which innovatively combines Dynamic Energy Budget Theory (DEB), Flux Balance Analysis (FBA), and Individual-based Community Modelling (IBCM). This model will be used for systematically analyzing the emergence, determinants, and consequences of bacterial cluster formation in close linkage to the metabolic measurements and evolutionary experiments planned in project P2. Special focus will be on the relationship between nutrient availability, the interplay of intracellular metabolic and spatial community processes, the resulting bacterial energy budget, the evolution of nanotubes inducing cross-feeding as bacterial interaction, and, finally, the likelihood of bacterial cluster formation. The modeling work covers the development of a model concept, its implementation as a computer model through programming, and cutting-edge analyses of simulated and experimental data. The project will be conducted at the Institute of Environmental Systems Research in close cooperation with the Institute of Biology with longer research stays at the Department of Ecological Modeling at the Helmholtz Centre for Environmental Research – UFZ in Leipzig.

3. Candidate profile

A highly-motivated candidate is sought with a Master's degree or equivalent in Applied System Sciences, Computational Sciences, Biology or a related field. Expertise in ecological modeling (broad spectrum of approaches of model building and analysis) and excellent programming skills (e.g. C++, Java, R) are obligate, ideally in combination with basic experience with laboratory experiments in microbiology. The candidate should have a strong interest in research at the interface of cell and evolutionary biology, excellent English skills, and be motivated to engage in interdisciplinary work. She/he should be willing to go out for longer research stays at UFZ.

4. Key references

- Grimm, V, & Berger, U (2016) Structural realism, emergence, and predictions in next-generation ecological modelling: Synthesis from a special issue. *Ecol Model* 326, 177-187.
- König, S. et al. (2018) Functional resistance to recurrent spatially heterogeneous disturbances is facilitated by increased activity of surviving bacteria in a virtual ecosystem. *Frontiers Microbiol.* 9, art. 734
- Kooijman, S. (2010) Dynamic Energy Budget theory. Cambridge University Press.
- Orth, JD, Thiele, I, & Palsson, BO (2010) What is flux balance analysis? *Nat Biotechnol*, 28(3), 245-248.
- Pande, S, & Kost, C (2017) Bacterial unculturability and the formation of intercellular metabolic networks. *Trends Microbiol*, 25(5), 349-361

Project 4: Evolution of TORC1 signaling in the control of serine and sphingolipid homeostasis

Project leader: Dr. Florian Fröhlich (Research Group Molecular Membrane Biology, School of Biology)
Co-supervisor: Prof. Dr. Roland Brandt (Department of Neurobiology, School of Biology)

1. Background

Sphingolipids (SLs) and their metabolites are essential structural components of membranes and act as signaling molecules. Maintaining SL homeostasis is crucial to sustain membrane integrity and trafficking. Accumulation of SL metabolites can cause severe neurodegenerative disorders. How cells sense SL levels and adjust their metabolism accordingly is a long-standing and fundamental problem of biology. Our long-term vision is to define how cells maintain SL homeostasis.

The first and rate limiting step in SL biosynthesis is the condensation of serine and palmitoyl-CoA. Regulation of SL levels occurs by post-translational modifications of key enzymes. The vacuolar TOR complex 1 has been suggested to be involved in the regulation of SL biosynthesis¹. However, the precise role of TORC1 in regulating SL homeostasis remains largely elusive.

2. Project description

Capitalizing on unbiased genetic, proteomic and lipidomic approaches in yeast, we have made progress towards understanding SL homeostasis by identifying key components of regulated serine uptake that are controlled by the TORC1 complex and control the uptake of serine into the cells². However, except TORC1 these components are lost throughout evolution by the development of specific serine transporters. How serine uptake in mammalian cells is regulated is unknown but serine uptake appears to be highly important for mammalian cells. Mutations of the sole serine transporter, SLC1A4, result in a neurodegenerative disorder³ and serine has been shown as essential component for the proliferation of cancer cells⁴. In this project, we will decipher how TORC1 signaling evolved to control serine and SL homeostasis in mammalian cells. First we will test if TORC1 activity in mammalian cells is controlled by the availability of serine and how this affects SL levels. These studies will involve western blots as well as mass spectrometry (MS) based lipidomics. In a second approach we will use mass spectrometry based proteomics to identify the regulatory networks controlling serine uptake via mTORC1 and try to understand how these networks evolved from their yeast ancestors.

3. Candidate profile

The successful candidate (m/f) should be excited about research at the intersection of cell biology and evolutionary biology, and have experience in techniques such as biochemistry, molecular biology, cell biology or related disciplines. Experience in mass spectrometry and using statistical software (R or MATLAB) are advantageous.

4. References

- Olson, D. K., Fröhlich, F., Farese, R. V. & Walther, T. C. (2015) Taming the sphinx: Mechanisms of cellular sphingolipid homeostasis. *Biochim Biophys Acta Mol. Cell Biol. Lipids* DOI: 10.1016/j.bbalip.2015.12.021
- Fröhlich, F., Olson, D. K., Christiano, R., Farese, R. V. & Walther, T. C. (2016) Proteomic and phosphoproteomic analyses of yeast reveal the global cellular response to sphingolipid depletion. *Proteomics* 16, 2759-2763
- Damseh, N. et al. Mutations in SLC1A4, encoding the brain serine transporter, are associated with developmental delay, microcephaly and hypomyelination (2015) *J. Med. Genet.* 1, 541–547
- Mattaini, K. R., Sullivan, M. R. & Vander Heiden, M. G. (2016) The importance of serine metabolism in cancer. *J. Cell Biol.* 214, 249–57

Project 5: Evolution of regulatory networks controlling development and stress-related processes in land plants

Project leader: Prof. Dr. Sabine Zachgo (Department of Botany, School of Biology)

Co-supervisor: Dr. Florian Fröhlich (Research Group Molecular Membrane Biology, School of Biology)

1 Background and project description

Project P5 aims to analyze the evolution and cellular function of transcription factors that contributed to the development of complex land plant architectures and to the adaptation to novel abiotic and biotic stressors typical for the life of plants on land. Land plants evolved 450 mya from an ancestral charophycean algae and the earliest diverging extant land plant lineages are the mosses. Bryophytes lack real organs such as the vasculature but possess key innovations of land plants such as a multicellular diploid sporophyte and a gametophytic shoot apical meristem producing three-dimensional tissues with diverse cell specializations providing morphological and physiological terrestrial adaptations. The liverwort *Marchantia polymorpha* is a novel bryophyte model organism, which has not experienced polyploidisation events and therefore redundancies of transcription factors are lower than in other bryophytes. Efficient tools for transformation and genome editing have been established enabling the analysis of their function in cellular differentiation processes that contributed to land plant diversification. We aim to investigate the contribution of redox-processes to the regulation of transcription factor activities employing transgenic approaches and high-resolution microscopy, provided by the CellNanOS centre.

2. Candidate profile

Candidates with a Master's degree in biology should have a background in molecular genetics, basal land plant cultivation and genome editing knowledge as well as experience with fluorescence microscopy. Preference is given to applicants with a strong interest to investigate plant evolution by linking analyses of molecular cellular processes with investigations of the morphological and biochemical diversification processes in land plants.

3. Key references

- Gutsche N., Holtmannspötter M., Maß L., O'Donoghue M., Busch A., Lauri A., Schubert V. Zachgo S. (2017) Conserved redox-dependent DNA binding of ROXY glutaredoxins with TGA transcription factors. *Plant Direct*, DOI: 10.1002/pld3.30
- Bowman JL, Kohchi T, Yamato KT, et al., Yotsui I, Zachgo S, Schmutz J. (2017) Insights into land plant evolution garnered from the *Marchantia polymorpha* genome. *Cell* 171, 287-304
- Buschmann H., Zachgo S. (2016) The evolution of cell division: from streptophyte algae to land plants. *Trends in Plant Science*, 21, 872-883

Project 6:

The evolution of cytoskeletal regulation and neuronal complexity

Project leader: Roland Brandt (Department of Neurobiology, School of Biology)

Co-supervisor: Sabine Zachgo (Department of Botany, School of Biology)

1. Background

The cytoskeleton is the major intracellular determinant of neuronal morphology and complexity. This is in particular evident for the microtubule (MT) system, which is required for the development of axons and dendritic branching. The axonal MT-associated protein tau (MAPT) and its dendritic counterpart MAP2 are involved in the compartment-specific regulation of neuronal MT dynamics. They are present in all vertebrate neurons and belong to a family of homologous MT-binding proteins. Bioinformatics analysis revealed that a gene duplication, which led to the evolution of the MAPT gene, occurred before the separation of jawless fishes (cyclostomes) and sets the period of the formation of the MAPT gene around 550 million years ago. It will be very informative to identify motifs in the homologous MT-binding proteins, which led to the compartment-specific distribution and function of the respective MAP and contributed to the increased complexity of axons and the dendritic tree during the development of higher vertebrates. Since tau is involved in the development of neurodegenerative diseases, the results may also shed light on the evolutionary events that led to the generation of a gene product, which contributes to a neurologic disease in higher vertebrates.

2. Project description

The main objective is to identify functionally relevant sequence motifs, which developed during evolution and which are associated with increased neuronal complexity, a prerequisite for the development of the remarkable cognitive abilities of higher vertebrates. This involves reconstructing the common evolutionary precursor of MAP2 and tau by bioinformatics analysis. As a next step, synthetic genes with the reconstructed sequence as well as MAPT sequences from selected species, where major steps in the development of neuronal complexity occurred will be prepared. The constructs will be functionally analyzed after expression in neuronal cells to determine effects on MT dynamics, compartment-specific distribution and influence on dendritic arborisation using quantitative live cell imaging and algorithm-based image reconstruction.

3. Candidate profile

Qualified master degree in biology, bioinformatics or related subjects; good English language skills; background or some experiences in bioinformatics and cell culture; willingness to work in an international team; high motivation.

4. Key references

- Bakota L, Ussif A, Jeserich G, and Brandt R (2017) Systemic and network functions of the microtubule-associated protein tau: Implications for tau-based therapies. *Mol. Cell. Neuroscience* 84:132-141
- Gauthier-Kemper A*, Suárez Alonso M*, Sündermann F, Niewidok B, Fernandez MP, Bakota L, Heinisch JJ, Brandt R (2018) Annexins A2 and A6 interact with the extreme N-terminus of tau and thereby contribute to tau's axonal localization. (*joint first authors) *J. Biol. Chem.*, DOI: 10.1074/jbc.RA117.000490
- Janning D*, Igaev M*, Sündermann F, Brühmann J, Beutel O, Heinisch JJ, Bakota L, Piehler J, Junge W, and Brandt R (2014) Single molecule tracking of tau reveals fast kiss-and-hop interaction with microtubules in living neurons. (*joint first authors) *Mol. Biol. Cell* 25:3541-3551
- Niewidok B, Igaev M, Sündermann F, Janning D, Bakota L, and Brandt R (2016) Presence of a carboxyterminal pseudo-repeat and disease-like pseudohyperphosphorylation critically influence tau's interaction with microtubules in axon-like processes. *Mol. Biol. Cell* 27:3537-3549

3. How to join *EvoCell*?

Doctoral positions are awarded following a competitive, worldwide call for applications.

3.1 Required documents

The following documents are required for the application:

- **curriculum vitae**
- **list of publications**
- **certificates of academic qualifications** (Last relevant academic certificate (usually M.Sc.) and transcript of study (study record))
- **names and addresses of two referees**, who are able to evaluate your personality, academic experience, and intellectual merit.
- a short statement describing your **research interest and motivation** to join the research training group
- **name the project(s)** you are applying for
- **statement of proficiency in English** for non-native speakers

Application documents should be sent via email **as one single PDF** (not bigger than 5 MB) to:

bewerbung@biologie.uni-osnabrueck.de

Deadline for application is **June 16th, 2018**.

Any incomplete application or applications reaching the *EvoCell* coordination office after the deadline cannot be taken into consideration.

3.2 Application procedure

Step 1: Online-submission of your application documents

Please follow the above-mentioned instructions to apply.

Step 2: Pre-selection of suitable candidates

All applications will be evaluated by the *EvoCell* Faculty based on the qualifications and the applicant's research interests and motivation. It is important that applicants link their interest to the research themes of the school and the projects on offer in the application call. After screening all completed applications, the committee will come up with a short list of candidates to be interviewed by phone. This process will take 2-3 weeks.

Step 3: Phone interviews

Short-listed candidates will be interviewed by phone to select those that will be invited to participate at a recruitment symposium in Osnabrück. This takes about 2-3 weeks.

Step 4: Recruitment event for short-listed candidates

Short-listed candidates will be invited to the recruitment, which takes place about 3-4 weeks

after the interviews. At the recruitment, candidates will have to give a talk and will be interviewed by several *EvoCell* faculty members. Selected applicants from abroad will present a short talk and be interviewed via Skype.

Offers of admission to *EvoCell* will be made two weeks after the group recruitment. The preferred starting time for the PhD program is as soon as possible, but not later than October 2018. However, other arrangements are possible.