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Strategic paper "Biology of Molecules, Cells and Tissues"

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Strategic paper NWO research community

“The Biology of Molecules, Cells, and Tissues”

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1. Scope of the life science research community “The Biology of Molecules, Cells, and Tissues”

The cell is the basic unit of life and in multicellular organisms, various cell types are organized into complex tissues. Molecules provide cells and tissues with structure and serve functions in the storage of energy and information. Dynamics in structure, activity, and interactions of molecules underlies metabolism and signalling allowing cells and tissues to adapt to chemical and mechanical cues. The Dutch life science community “Molecules, Cells, and Tissues” studies these processes from the molecular scale, using structural and biophysical approaches, to the level of individual cells and tissues using diverse model systems.

2. Current scientific strengths/themes/challenges and (inter-)national position

Recent technological breakthroughs have revolutionized the life sciences. These developments, ranging from advanced structural biology and microscopy methods to high-throughput ‘omics’ analyses and sophisticated in vitro cell/ tissue culture systems, now make it possible to study proteins, metabolites, cells, tissues and organisms with unprecedented detail. NL has a leading role in some of these research areas.

Molecules: Organic molecules are studied at the interface between chemistry and biology and physics. NL has a leading position in the study of DNA damage repair in the context of cancer and ageing. This research includes biochemistry and cell biology methods and also incorporates physics approaches to study mechanical aspects of DNA. NL also has a strong tradition in protein chemistry, molecular, and cell biology approaches to investigate RNA and protein biogenesis, turnover and subcellular localization at high spatiotemporal resolution in living cells. These experiments provide fundamental insights regarding cellular functioning in health and disease. NL has a strong tradition in electron microscopy (EM) to study proteins at high magnification in cells and tissues. NL also plays a leading role in technological advances to measure metabolites, thus informing on the metabolic processes in healthy and diseased cells and tissues.

Cells: Cells adapt and respond to developmental and environmental cues through signal transduction pathways, which eventually result in altered gene expression programs. Gene expression regulation is a complex process, which involves cell-type specific transcription factors and chromatin associated proteins that are regulated by epigenetic processes. NL has a strong foundation of fundamental and applied research dedicated to regulation of gene expression at the level of signalling, genetics and epigenetics in healthy and diseased cells. Nowadays, the majority of research in this area contains a strong ‘omics’ component, made possible by recent technological breakthroughs, which facilitate comprehensive genome, transcriptome, (phospho)proteome and metabolome profiling at unprecedented detail. For signal transduction, the ability to unravel protein complex assemblies and their dynamics is critical for a molecular understanding of cellular behaviour. NL is strong in such cell biology, evidenced by a strong tradition in advanced light microscopy to study signal transduction in real time in live cells at ever-increasing resolution. NL also plays an important role in synthetic biology, which integrates chemistry and biology to understand and deduce the fundamental principles of the cell as the basic unit of life.

Microbiology – single cells and cell communities: Microorganisms compose a wide array of acellular, unicellular, and multicellular structures that cover viruses, archaea, eubacteria and eukaryotes. Often, the organisms are able to live as individual cells but they tend to occur in nature in multicellular structures where small organic molecules allow for communication and hence organization of the community. NL is internationally strong in several areas of microbiology, including virology, anaerobic microbiology, bacterial physiology, fungal biology, yeast biotechnology, and host-microbe interactions in plants and humans within the fields of food and medical microbiology.

Animal and plant tissues: Tissues can be studied in model organisms to unravel guiding principles of tissue formation and homeostasis. Universities and institutes in NL make use of genetically engineered animals such as drosophila, zebrafish and mice to study cells and tissues to unravel molecular mechanisms of disease. Moreover, NL has a world-leading position in the plant sciences combining a strong focus on the fundamental mechanisms underlying the regulation of growth, development and immunity in plants, with effective translation to plant breeding programs. The versatility of the evolution of multicellular life offers tremendous opportunities to discover the logic of multicellularity, including its evolution, and the functioning of complex multicellular organs. One such organ is the brain, which is the physical substrate of human cognition. NL is internationally strong in neurobiology and studying the molecular mechanisms underlying neurological diseases. The recent development of omics approaches that can be used to study such processes at single cell and even molecular level provides unprecedented insight into the complexity and cellular heterogeneity of tissues in health and disease and NL plays an important role in this research area,

Advanced tissue culture models: NL is internationally strong in advanced tissue culture models ranging from slices of real tissue to combinations of different cell types, to study communication between cells and their microenvironment (including neighbouring cells, other cell types, and extracellular matrix) to achieve a fundamental understanding of development and homeostasis of tissues as well as advancing models for tissue engineering, drug discovery, and chemical safety testing. The design of sophisticated (stem) cell culture models is pivotal for this. NL is at the forefront of stem cell biology (e.g. IPSC) and leads the development of organoid cultures and organ-on-chip (OoC) models where mechanical engineering and cell biology disciplines are integrated. Another important development where NL plays a strong role is the field of mechanobiology, in which physics and biology are combined to understand functions of cells and tissues in health and disease.

3. Focus areas for the next ten years

The theme of this research community is conceptually united by the evolutionary principles that drive interactions in collections of molecules, collections of cells, and collections of tissues resulting in synergy and eventually “life”. This research community is at the heart of solving key scientific problems in the circular economy (element cycles), building synthetic cells and communities, and health (e.g. microbe-host interactions and effects on the immune system, problems to be solved with organoids and genome editing). Clear trends that have emerged in the past decade and that will further propagate in the next decade are **i)** the increasing focus on single cell analyses of tissues using omics and imaging, **ii)** more focus on quantitative and physics-based approaches to study molecular and cellular biology, and **iii)** the integration of molecular and cellular biology with computational sciences, including artificial intelligence (AI). These shifts have major consequences for the education and training of the next generation of life scientists and it is here that major investments in science and education will be needed.

As outlined in section 2, NL has a leading role in several areas of the life sciences. To maintain this leading position in the coming decade, further knowledge from fundamental research must be obtained and these insights must be translated and applied to benefit society. For this to occur, continued innovations are needed, which are briefly outlined below:

At the level of the single cell, a major challenge that needs to be addressed is the integration of information from various high-resolution imaging approaches (i.e cryo-EM, quantitative mass spec imaging, super-resolution microscopy) with single cell (multi)omics data. With its strong expertise in structural protein chemistry, including “difficult” membrane receptors, as well as in EM and light microscopy, the NL plays a leading role in correlative light-electron microscopy (CLEM) and should build on this. This will provide unprecedented insight in cell biology by integrating information from the nano- to the microscale. Moreover, further investment in real time microscopy using innovative probes based on FRET technology, optogenetics, and activity-based enzyme probes will have to be made. These investments will further our understanding of the complex molecular structures in the cell, the processing of intracellular signals, the dynamic connections between organelles, and the spatiotemporal regulation of proteins, lipids, and metabolites in cells. In addition to such fundamental understanding of the biology of the cell, this will impact on our understanding of a range of pathologies including infectious diseases, neurodegenerative diseases such as dementias and Alzheimer’s, and cancer, which has a significant societal impact, given the world-wide spread of antibiotic resistance and the increasing longevity of our population. Likewise, strengthening our research in building synthetic cells and designing microorganisms, can lead to production of new antibiotics and other drugs, as well as new forms of waste removal and energy production, thus impacting on the environment.

We have gained momentum in unravelling how cells work together to form communities and tissues, but this should be further developed. Further understanding of cellular communication mechanisms involving direct contact, signalling molecules, and nanosized extracellular vesicles will impact on our understanding and combating of disease. Much remains to be learned about the way in which neuronal networks are formed, function, and dysfunction in disease and how microbes talk to each other and to their environment, be that soil, plant, animal or human. The microbiome with its associated microbiota is a field that is in rapid development and here NL can expand its leading role with investments in omics and real time microscopy approaches. Understanding the key factors that regulate formation and stability of the oral and gut microbiome and its impact on oral (dental) health, autoimmune disorders and neurological health and disease in an ageing population should be focus areas. Likewise, the Dutch plant sciences can take full advantage of the many technological advances that allow quantitative and dynamic descriptions of living systems from the molecular to the cellular and tissue scale. The deep evolutionary history and diversity of plant species should be harnessed to understand the molecular and cellular mechanisms that underlie critical processes such as the transition from water to land and adaptation of photosynthesis and growth under extreme and diverse environmental conditions. In general, continued efforts are needed to develop CRISPR/Cas9 and other gene-editing tools as well as large scale- and single-cell genomics, proteomics, metabolomics, and imaging methodologies to unravel mechanisms that regulate cells and tissues ranging from microbes, plant systems, and animals.

To understand tissue function, research using animal models will continue to be crucial and investments in this field cannot be discontinued. Nevertheless, alternatives are becoming increasingly available. To advance the leading position of NL in the fields of organoid biology and OoC models further multidisciplinary research has to be boosted. NL has strong expertise in the chemical design of activity-based enzyme probes, light- or temperature-regulated pharmacological delivery molecules, and extracellular matrix scaffolds whose chemical and mechanical properties can be tuned. The search for pharmacological approaches and new chemically and mechanically tuneable scaffolds, to steer cell fate as well as implementation of IPSCs harbouring genetic mutations, will strongly advance personalized human tissue and organ models. The strong position of NL in the area of mechanobiology warrants further investment at the interface of physics and biology towards a comprehensive understanding of chemical and mechanical signals that govern tissue formation and function. Proper representation of tissue microenvironments in tissue culture models represents an unmet challenge in models that currently still include a small selection of cell types. Other specific challenges that have to be met include the combination of organoids with vasculature and the immune system. The study of such complex 3D tissue models requires further advancement of imaging modalities such as multi-photon imaging, adaptive optics, mesoSPIM, and lattice light-sheet microscopy to visualize (sub)cellular processes at high spatiotemporal resolution in tissues with low phototoxicity. Moreover, dynamics of gene expression, cytoskeletal rearrangements, cellular signalling, metabolism have to be analyzed quantitatively and at the single cell level to shed light on development and homeostasis of tissues. Validation of models against real tissues will also be an essential step to provide a benchmark and move this technology forward. Altogether, these investments will contribute to fundamental understanding of development and homeostasis of tissues and have a major impact on tissue engineering, drug discovery, and chemical safety testing.

Systems biology will become more important and big data from omics experiments will require computational approaches for integration and interpretation. With the ability to simultaneously record activity from hundreds, thousands or even millions of cells (or their cellular constituents) and connect this to information at the tissue level, it becomes necessary to perform dimensionality reduction and apply pattern-recognition algorithms to ease and allow data analysis and interpretation. Investments in computational frameworks are required to facilitate this. Moreover, large-scale simulations and computational/ theoretical modelling will have to complement and guide experimental designs. To make this possible, collaborations between physicists, mathematicians, computer scientists and biologists have to be promoted actively.

4. Impact on society and contribution to topsectors (and related missions), national science agenda-routes and SDG’s

This research community has a broad societal impact that includes biotechnology (e.g. engineering of microorganisms and (stem)cells for food-agro and biomedical purposes), biomedical research (e.g. tissue engineering, in vitro testing for drug development, identifying new strategies for therapeutic intervention), chemical safety testing (improved in vitro testing platforms and reduction of animal use). It drives advances in environment, food, and medicines. It addresses major ageing-related processes including neurodegenerative and inflammatory diseases, and cancer as well as life threatening infectious diseases through advanced understanding and new preventive and therapeutic solutions (e.g. vaccines, antibiotics, drugs). Beyond its applied scientific impact, the economic impact of the community is also profound: every year lots of start-ups and public-private partnerships are being established based on research performed in the community.

This research community yields scientific advances to the topsectors “Life Sciences & Health”, “Agri & Food”, “Horticulture & Starting Materials”, and the related missions ‘’Health and Care’’, and ‘’Agriculture, Water and Food”. It adheres to the NWA routes “Regenerative medicine”, “Health care research, sickness prevention and treatment”, “The quantum/nano-revolution”, “Sustainable production of safe and healthy food”, “NeuroLabNL: the ultimate living lab for brain, cognition and behavioural research” , “Quality of the living environment”, “Personalised medicine: the individual at the centre”, ‘Materials: Made in Holland’, and “Sustainable development goals for inclusive global development”. Finally, it connects to the Sustainable Development Goals: “Zero hunger”, “Good Health and Well-being”, “Life below water”, and ‘’Life on land’’.

5. Infrastructure in national & international perspective

Individual Dutch institutes have continuously invested in large scientific equipment such as advanced microscopes or mass spectrometers. In addition, in recent years, many research facilities, accessible to multiple institutes or even the entire Dutch scientific community, have been established. These infrastructure initiatives include: Accelerator facility KVI-Center for Advanced Radiation Technology (AGOR), Applied Molecular Imaging at Erasmus MC (AMIE), Biomarker Development Center (BDC), CAT-AgroFood Shared Research Facilities Wageningen UR, Core facility Cellular Imaging, European Advanced Translational Research Infrastructure in Medicine (EATRIS ERIC), ELIXIR - A distributed infrastructure for life science information, Else Kooi Laboratory (EKL), Laboratories for Infectious Disease Control (LIDRD), Maastricht MultiModal Molecular Imaging institute (M4I), Metabolomics Facility Leiden, Netherlands Centre for Electron Nanoscopy (NeCEN), Netherlands Electron Microscopy Infrastructure (NEMI), Netherlands BioImaging Advanced Microscopy, A Dutch small molecule screening and hit optimisation facility for the translation of biomedical research findings (NL-OPENSCREEN), Proteins@Work: A large-scale proteomics research facility for the life sciences, Radboud Imaging Center, Leiden University Cell Observatory, Systems Biology Natural Technology Facility (SYMBIONT), An ultra-high field NMR facility for the Netherlands (uNMR-NL), DNA sequencing and analysis (USF), the LUMC human IPSC hotel, NanoLabNL Cluster, and the Mouse Clinic for Cancer and Ageing.

Based on this, The Netherlands has state-of-the-art equipment available, which has been essential for the scientific progress outlined in section 2. It will be important to continuously invest in infrastructure to allow Dutch researchers to get sufficient access to such advanced equipment and to keep up with new technological developments in the field of life science research.

6. Involvement of Dutch organisations in your research community

- All Dutch Universities.
- All Academic Medical Centers, Prinses Maxima Centrum, NKI-AVL.
- AMOLF, NIN, Hubrecht Institute.
- RIVM, TNO, patient and other health organizations such as KWF, Hartstichting, Nierstichting, “virtual institutes” including Oncode, hDMT.
- Wide range of industry: pharmaceutical biotech (Galapagos, Genmab, Mimetas, OcellO, Merus, etc), Philips (healthcare, innovation services, research), cosmetics and chemical industry (safety testing; e.g. Unilever), agro-food (e.g. FrieslandCampina; product testing and development), farming and plant breeding, biotech and microscopy companies.
- Outreach: multiple media, museums (NEMO, Boerhaave, …).

7. Specific challenges for the community

As outlined in detail in sections 2 and 3, chemical, physical and mathematical approaches are becoming increasingly more important in the biological sciences, and there is therefore a strong need for interdisciplinary scientists and interdisciplinary research consortia. This includes chemistry/biology, physics/biology, data science/bioinformatics/biology, and computational modelling/biology. Investment is needed to train multidisciplinary scientists and interactions between biologists, chemists, physicists and mathematicians should be actively stimulated.

Scientific progress requires free exploration and cannot only rely on goal-oriented, applied research. Therefore, basic research should be explicitly fostered and support of basic research has to remain a key pillar in Dutch research funding.

Finally, it is clear that research in the life sciences requires continued investment in high-end research infrastructure and equipment. The opportunity to occasionally invest in high-end equipment (e.g. advanced microscopes) is not further supported by funds that foresee in expensive maintenance contracts that are needed for such equipment. This puts a major financial burden on research groups to maintain their high-end research infrastructure.