MAX PLANCK RESEARCH GROUP

Mechanoresponsive Molecules as Building Blocks for Smart Materials

Kerstin G. Blank 01.02.1974
1996-2000: Diploma in Biotechnology (University of Applied Sciences, Jena, Germany)
Thesis: Protein engineering of antibody scFv-fragments as ligands for affinity chromatography
2003-2006: Doctoral Thesis in Biophysics (Ludwig-Maximilians Universität, München, Germany)
Thesis: Molecular Force Sensors – Design, Characterization and Applications
2007: FEBS Postdoctoral Fellowship (University of Strasbourg, France)
2008: HFSP Postdoctoral Fellowship (University of Leuven, Belgium)
2009-2014: Assistant Professor (Radboud University Nijmegen, The Netherlands)
Since 07/2014: Max Planck Research Group Leader (Max Planck Institute of Colloids and Interfaces, Potsdam)

Smart materials are designed to display an intrinsically programmed, pre-defined response when exposed to an external stimulus (**Fig. 1**). This unique property makes them attractive for a large range of different applications, ranging from aerospace engineering to regenerative medicine. Our focus is on the development of tuneable materials, which possess a specific response to an externally applied shear or stretching force. In particular, we are interested in materials that change their optical properties or release chemically reactive groups in response to the applied force.

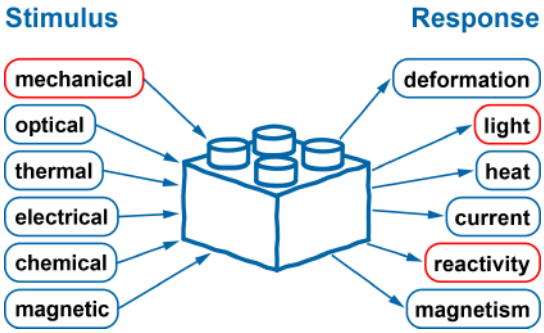

Fig. 1: Smart materials contain specific molecular building blocks that convert an external stimulus into a pre-defined response. For example, a mechanical stimulus may trigger the emission of light or release chemically reactive groups.

Mechanoresponsive materials allow for answering many questions of fundamental interest to the Materials Science community. At the same time, they form the basis for developing highly innovative materials for a range of different applications. Topics of interest for our group are:

- observation of (local) defect formation and propagation inside a material,
- development of soft biomimetic materials that are able to report on the early stages of mechanical damage and/or to self-heal this damage,
- investigation of the molecular mechanisms involved in mechanical cell-material interactions,
- development of synthetic materials that mimic the natural environment of cells or are able to interfere with cellular mechanotransduction pathways.

Towards these goals, we are developing materials as well as methods that allow for a detailed characterization of our newly synthesized materials and their molecular constituents **[1, 2]**.

Mechanoresponsive Molecular Building Blocks

The key components required for the synthesis of functional materials with these applications are self-reporting and/or self-healing mechanoresponsive molecular building blocks (**Fig. 2**). We are specifically interested in the development of self-reporting building blocks that allow for the optical detection of their molecular mechanical state (i.e. molecular force sensors **[1, 2]**). Of further interest are self-healing building blocks. These building blocks undergo a mechanically reversible reaction that involves either covalent or supramolecular bonds, which act as pre-defined mechanical breaking points.

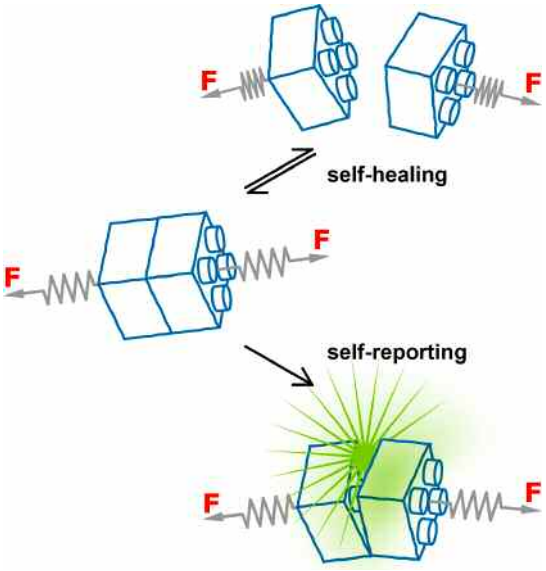

Fig. 2: Mechanoresponsive molecular building blocks possess an intrinsically programmed response to an externally applied force. Self-healing building blocks break into fragments that may subsequently reassemble. Self-reporting building blocks generate an optically detectable signal as soon as the applied force exceeds a threshold value.

Many different molecular structures can serve as mechanoresponsive building blocks. Chemists have developed a number of small molecule mechanophores and integrated them into polymeric materials for the detection of mechanical deformation and damage **[1].** But also biomolecules are used **[2, 3],** e.g. for the synthesis of mechanoresponsive hydrogels for cell culture applications. One drawback of current designs is that only a small number of these structures is calibrated, i.e. it is not known which force is required to obtain the desired molecular response. Our primary goal is, therefore, to develop new mechanically calibrated molecular building blocks that are suitable for both biological and non-biological applications. In the following we will introduce one small molecule mechanophore (example 1) as well as one biomolecular building block (example 2).

Example 1 – Triazole Building Blocks

The number of building blocks that combine self-healing with self-reporting properties is very limited. Triazole rings, formed in so-called 'click chemistry' reactions, are possible candidates, which may integrate both functions in one and the same molecule. Triazoles form in the cycloaddition reac-

tion between alkynes and azides (N_3). If this reaction would be mechanically reversible (cycloreversion), the azide and alkyne starting materials would be released and become available for subsequent reactions (**Fig. 3**). They may either reform material crosslinks (self-healing) or react with fluorogenic reporter molecules, such as azido-coumarin (self-reporting).

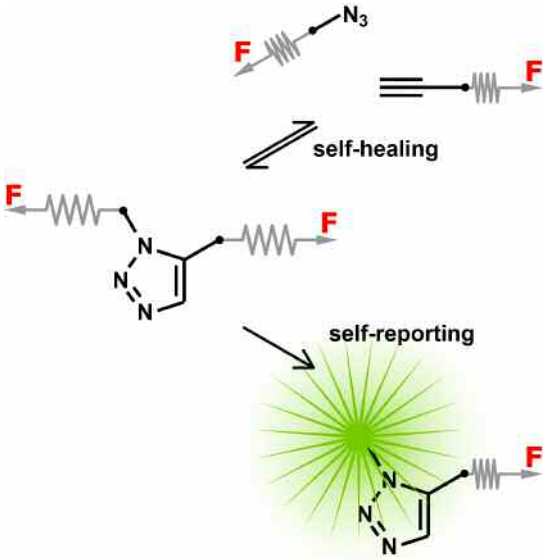

Fig. 3: Possible applications of triazole rings as mechanoresponsive building blocks with self-healing and self-reporting properties.

The envisioned mechanically induced cycloreversion was investigated using density functional theory calculations (in collaboration with Günter Schneider, Oregon State University, Corvallis (OR), USA). To obtain a detailed mechanistic picture, different triazole molecules were investigated and the force was applied to different atoms **[4].** The 1,5 regiosomer, shown in **Fig. 3**, is the product of the ruthenium-catalysed reaction of an azide with a terminal alkyne. For this example, the desired cycloreversion was observed, suggesting that triazoles are indeed highly interesting mechanophores. From an application point-of-view, however, the ruthenium catalyst would have to be added to the material to utilize these properties.

To overcome this limitation, cyclooctynes can be used as an alternative. These ring-shaped alkynes react with azides in the absence of a catalyst and are, therefore, ideally suited as material building blocks. Density functional theory calculations of the triazole formed in the reaction with aza-dibenzocyclooctyne (DIBAC) show that also this molecule undergoes cycloreversion **[4].** DIBAC is currently investigated with single-molecule force spectroscopy to experimentally verify the computer-based predictions.

Example 2 – Peptide-based Building Blocks

The mechanically induced cycloreversion of triazoles requires forces larger than 500 pN, as covalent bonds need to be broken in this reaction. For biological applications, building blocks are needed that react in a force range between 10-200 pN. For this purpose, a library of peptide-based building blocks is currently being developed. The design of these building blocks is inspired by naturally occurring coiled coil structures, which fulfil mechanical function in biological tissues.

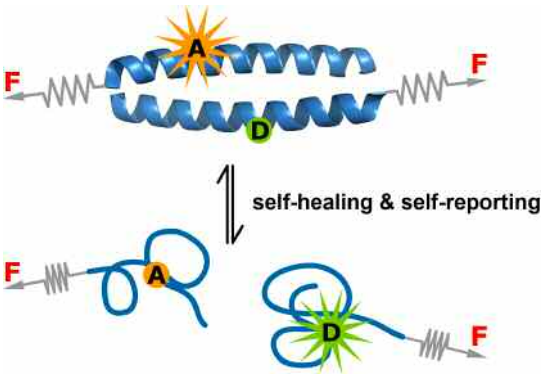

Fig. 4: Possible applications of coiled coil-forming peptides as mechanoresponsive building blocks with self-healing and self-reporting properties.

Coiled coils (CCs) are superhelical structures that are stabilized by hydrophobic and ionic interactions (**Fig. 4**). Using short synthetic CCs, we are currently performing single-molecule force spectroscopy to determine the mechanical stability of different CC structures. Our results show that the force required to break a CC dimer depends on the CC length **[5]** and amino acid sequence, in particular the helix propensity. Molecular dynamics simulations (Ana Vila Verde and Reinhard Lipowsky; Theory & Bio-Systems) as well as metal-stabilized helical structures (Matthew Harrington; Biomaterials) will shed further light on the underlying mechanisms in the future.

Using the obtained knowledge, we have generated a set of CC sequences that break in the range between 20-60 pN. These mechanically calibrated CC building blocks are now being used as crosslinkers for hydrogels. Equipped with a fluorescence-based reporter system (donor and acceptor for Förster resonance energy transfer; FRET), it will become possible to optically read out the mechanical state of every individual CC (**Fig. 4**). This self-reporting hydrogel allows for correlating the mechanical properties of the building blocks with the properties of the bulk material. We anticipate that this new material will serve as a powerful platform for investigating and influencing cellular mechanotransduction mechanisms.

K. G. Blank, R. Dünnebacke, D. Farhadi, M. Göktas, A. Heilig, P. López García, J. L. Ruiz Rodriguez, A. Sanz de León, R. M. A. Sullan, I. Tunn, H. van Kan-Davelaar
kerstin.blank@mpikg.mpg.de

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