In the human body, the coordinated movements and trafficking of cellular components are essential to the cell function, division and survival. Within the cell, the movements of large macromolecules, vesicles and organelles cannot rely upon simple diffusion, but instead biological motor proteins have evolved to enable directed and rapid movements and trafficking. Myosins constitute one of the major families of such cellular motors. Myosin molecules travel on an intracellular railway system made up of actin tracks.

Myosin motors have been the focus of structural and biochemical studies for more than 50 years as a model to better understand how an enzyme can use chemical energy to generate directed forces.

A major goal of our team is to visualize snapshots of the motor at atomic resolution using X-ray crystallography. Trapping of the different structural/biochemical states in different crystals allows to visualize in detail how the motor works. We were for example the first to describe the conformation of the motor when it binds strongly to its track (Fig. 1). Our studies and others’ have led to propose that rather small conformational changes within the motor domain are amplified via the swing of the converter/lever arm region, which amplifies the movement and produce mechanical force.
Using a reverse motor, myosin VI, which walks in opposite direction to the other myosins, we were able to identify the structural element responsible for defining the directionality (Fig. 2). This very unconventional motor has also revealed that the converter can change conformation (Fig. 3) and contribute to further amplify the conformational changes in a motor. Current studies aim at depicting the conformational changes that initiate force production. Our goals are also to better understand how molecular motors are regulated and recruited in the cell and how their action is coordinated to achieve efficient intra-cellular transport and force production.

We are currently focusing efforts on developing modulators of molecular function for molecular motors that are molecular targets in human diseases such as cardiomyopathies and cancer.

Figure 2: The structure of Nucleotide-free Myosin VI is compared to that of Myosin V (left). Note the difference in the position of the lever arm (IQ motif, cyan) due to the specific insert (purple) and its associated-calmodulin.

Figure 3: Four structural states of myosin VI have been visualized depicting the cycle from the end of force production to the initialization of the lever arm swing upon actin binding.
Key publications

Year of publication 2018

Julien Robert-Paganin, Daniel Auguin, Anne Houdusse (2018 Oct 3)
Hypertrophic cardiomyopathy disease results from disparate impairments of cardiac myosin function and auto-inhibition.
Nature communications : 4019 : DOI : 10.1038/s41467-018-06191-4

Florian Blanc, Tatiana Isabet, Hannah Benisty, H Lee Sweeney, Marco Cecchini, Anne Houdusse (2018 May 31)
An intermediate along the recovery stroke of myosin VI revealed by X-ray crystallography and molecular dynamics.
Proceedings of the National Academy of Sciences of the United States of America : 6213-6218 : DOI : 10.1073/pnas.1711512115

Year of publication 2017

Stéphanie Miserey-Lenkei, Hugo Bousquet, Olena Pylypenko, Sabine Bardin, Ariane Dimitrov, Gaëlle Bressanelli, Raja Bonifay, Vincent Fraisier, Catherine Guillou, Cécile Bougeret, Anne Houdusse, Arnaud Echard, Bruno Goud (2017 Nov 3)
Coupling fission and exit of RAB6 vesicles at Golgi hotspots through kinesin-myosin interactions.
Nature communications : 1254 : DOI : 10.1038/s41467-017-01266-0

Vicente J Planelles-Herrero, James J Hartman, Julien Robert-Paganin, Fady I Malik, Anne Houdusse (2017 Aug 5)
Mechanistic and structural basis for activation of cardiac myosin force production by omecamtiv mecarbil.
Nature communications : 190 : DOI : 10.1038/s41467-017-00176-5

Myosin 7 and its adaptors link cadherins to actin.
Nature communications : 15864 : DOI : 10.1038/ncomms15864
Highly selective inhibition of myosin motors provides the basis of potential therapeutic application.

Proceedings of the National Academy of Sciences of the United States of America: 201609342

DOI: 10.1073/pnas.1609342113