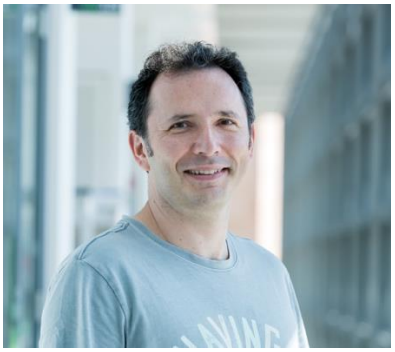
Name	NIC TAPON
Position	Senior Group Leader
Year joined *(Crick or founder institute)*	2003



Career History

1993- 1997: PhD in molecular cell biology, University College London
1998- 2001: Post-doctoral fellow, Massachusetts General Hospital Cancer Center, USA
2002- 2003: Staff Scientist (CNRS), University of Nice, France

Major Awards, Honours and Prizes

2001: Ranked 1st out of 100 by CNRS (France) Commission 25 (Cellular Interactions)
2007: EMBO Young Investigator
2015- present: Wellcome Trust Investigator
2018: Elected to EMBO Membership

Membership of external committees, editorial boards, review panels, SABs etc

Committees:
2020-2023 Member of EMBO Courses and Workshops committee
2020 Tenure panel member for Dr Bjoern von Eyss, Leibniz Institute on Ageing, Jena, Germany
2018 Chair of Institute review committee (HCERES) for Institut Jacques Monod Paris, France
2018 Panel member, Wellcome Expert Review Group (Investigator awards and senior fellowships)
2017 Panel member, Wellcome Trust Seeds Advisory Panel
2013-16 Panel member on Agence National pour la Recherche Cell and Developmental Biology grant panel
2016 Panel member, Wellcome Trust Sir Henry Dale fellowships
2015 Tenure panel for Dr Irene Miguel-Aliaga, MRC Clinical Science Centre

Editorial boards:
Open Biology (2012-present)
Journal of Cell Science (2014-present)
PLoS Biology (2016-present)

Lab Name	***Apoptosis and proliferation control laboratory***

Research programme and achievements

Lab interests
How do cells in a developing organism stop growing and dividing when the correct body size and shape have been reached? How is tissue size maintained in an adult organism? These fundamental biological questions have clear implications for cancer, where cells lose the ability to respond to tissue size boundaries, and for regenerative medicine, where the proliferative potential of quiescent cells must be unleashed in a controlled manner. Our long-term goal is to unravel how a diverse set of cues acting at the local, tissue autonomous level (e.g. mechanical forces, tissue architecture, developmental signalling pathways) are integrated with systemic signals (e.g. nutrient availability, hormones) to determine final animal size. Many of these signals modulate the activity of the Hippo signalling pathway. Thus, much of our work is focused on studying how the Hippo pathway senses growth-regulatory signals.

We use a multidisciplinary set of approaches, including *Drosophila* and mouse genetics, quantitative *in vivo* imaging, biophysics, mathematical modelling and proteomics, as well as structural biology.

Past work
In the past quinquennium, our major contributions have defined some of the key signals that tune Hippo pathway activity *in vivo*:

(I) We identified the energy sensor AMPK as an upstream input that scales the Hippo pathway growth-regulatory signal with energy availability. This work also demonstrated remarkable differences in the wiring of the Hippo pathway in different neural stem cell populations, suggesting that targeting Hippo signalling for therapeutic benefit will entail a better understanding of context-dependent signalling.

(II) Cell-cell junctions are a key site of Hippo pathway regulation, particularly by mechanical forces. Our work elucidated the mechanism through which the mechanosensitive protein Zyxin modulates junctional Hippo signalling. Zyxin antagonises the function of the key Hippo pathway upstream component Expanded via its ability to promote Enabled-dependent actin assembly. Furthermore, we elucidated a mechanism through which rapid ubiquitin-dependent turnover of Expanded at the apical membrane allows the Hippo pathway to be poised to rapidly respond to upstream signals.

(III) Finally, our interest in Hippo pathway phosphatases led us to structurally define a new PP1 recognition motif and to identify a novel coupling mechanism between different types of cell polarity.

Future work
During the past quinquennium, we have devoted substantial effort to establishing genetic, *in vivo* imaging and quantitative biology tools to exploit the *Drosophila* abdomen as a powerful system to study growth dynamics and growth termination during development. This includes the creation of machine-learning and mathematical modelling approaches in collaboration with the Salbreux lab at the Crick which are providing us with unprecedented access to the dynamics of a growing epithelium. We will use this system to understand how tissue size is defined in a developing organism. In particular, we will unravel how diverse outputs such as mechanical forces, circulating hormones/growth factor and nutrients are integrated through the Hippo pathway and other signalling networks in order to precisely tune growth rates, growth termination and differentiation to yield highly reproducible organ size. We are also in the process of generating genetic tools in non-*melanogaster* species of different sizes. This cross-species approach will allow us to define which size control mechanisms are conserved across species, and

which underpin the wide variety in tissue size and shape that is a striking characteristic of the animal kingdom.

In parallel to our *in vivo* work, we are developing cell-based systems that enable us to precisely manipulate the mechanical environment of cells through cell-cell junctions and cell-extracellular matrix contacts. We will use these tools to understand how the Hippo signalling pathway is regulated by mechanical forces emanating from the cellular microenvironment, and which upstream molecular pathways mediate these responses. This biophysical and molecular approach will enable us to better understand how the Hippo pathway functions in a complex mechanical environment *in vivo*.

Finally, we will elucidate the role of Hippo pathway-regulating PP1 phosphatase complexes in tissue growth and architecture. To approach this question, we will study the function of the RASSF protein family, many members of which are key regulatory subunits in PP1 complexes, using both *in vivo* mouse genetics and *ex vivo* organoid culture approaches.

Research outputs

Bertran MT, Mouilleron S, Zhou Y, Bajaj R, Uliana F, Kumar GS, van Drogen A, Lee R, Banerjee JJ, Hauri S, O'Reilly N, Gstaiger M, Page R, Peti W, Tapon N (2019) ***ASPP proteins discriminate between PP1 catalytic subunits through their SH3 domain and the PP1 C-tail*****. Nature Communications 10(1):771-771 DOI: 10.1038/s41467-019-08686-0**
Our past work had indicated that the ASSP proteins are key regulators of junctional dynamics during morphogenesis. Here we used a multidisciplinary approach encompassing X-ray crystallography, NMR, biochemistry and genomic engineering in flies to unravel the function of ASPP as a PP1 phosphatase targeting subunit. We identified a novel PP1 rectuitment mode where ASPP uses both a canonical RVxF motif and its SH3 domain to discriminate between PP1 isoforms based on the divergent PP1 C-tail. This new mode of SH3 domain/PP1 interaction vastly increases the scope to discover new substrates and accessory subunits for PP1 holoenzymes.

Fulford AD*, Holder MV*, Frith D, Snijders AP, Tapon N+, Ribeiro PS+ (2019) ***Casein kinase 1 family proteins promote Slimb-dependent Expanded degradation*****. eLife 8 e46592. DOI: 10.7554/eLife.46592**
The Hippo signalling pathway is a central regulators of tissue size during development and adult homeostasis. Although we have a good static picture of how the Hippo pathway functions, its signalling dynamics remain poorly understood. Here we elucidated how the Hippo pathway upstream component Expanded is constantly turned over at its site of activity at the apical membrane. This occurs through its recruitment by the polarity protein Crumbs, followed by Casein Kinase 1-dependent phosphorylation and recruitment of the SCF^{Slimb} ubiquitin ligase complex. This ensures that Hippo signalling is poised to respond to external stimuli such as loss of cell polarity.

Banerjee JJ, Aerne BL, Holder MV, Hauri S, Gstaiger M, Tapon N (2017) ***Meru couples planar cell polarity with apical-basal polarity during asymmetric cell division*****. eLife 6 e25014. DOI: 10.7554/eLife.25014**
Polarity is a shared feature of most cells. From a limited set of core building blocks (e.g. the Par complexes and the Frizzled/Dishevelled Planar Cell Polarity complexes), a vastly

diverse array of polarised cells and tissues is generated. This suggests the existence of little-studied tissue-specific factors that rewire the core polarity modules to the appropriate conformation for each cellular context. We identified the RASSF family protein Meru as such a factor, and showed that it fulfils a key function in bridging apico-basal and planar cell polarity during asymmetric cell division.

Gailite I, Aerne BL, Tapon N (2015) ***Differential control of Yorkie activity by LKB1/AMPK and the Hippo/Warts cascade in the central nervous system*****. Proc Nat Acad Sci USA 112(37):E5169-E5178. DOI: 10.1073/pnas.1505512112**
The Hippo pathway is a highly conserved tumour suppressor network that restricts developmental tissue growth and regulates stem cell proliferation and differentiation. As a growth regulatory pathway, Hippo signalling needs to integrate information about nutrient and energy levels to ensure that growth proceeds only when sufficient resources are available. In this study, we uncovered a key regulatory input from the energy sensor AMP-activated protein kinase (AMPK) in repressing the activity of Yki, the transcription factor target of the Hippo pathway.

Gaspar P, Holder MV, Aerne BL, Janody F, Tapon N (2015) ***Zyxin antagonizes the FERM protein expanded to couple F-actin and Yorkie-dependent organ growth*****. Current Biology 25(6):679-689. DOI: 10.1016/j.cub.2015.01.010**
Coordinated multicellular growth during development is achieved by the sensing of spatial and nutritional boundaries. The conserved Hippo signalling pathway has been proposed to restrict tissue growth by perceiving mechanical constraints through actin cytoskeleton networks. Here, we elucidated the mechanism through which the mechanosensor Zyxin modulate Hippo pathway activity. We showed that Zyxin antagonises the FERM-domain protein Expanded (Ex) to control tissue growth, eye differentiation, and F-actin accumulation and established a link between actin filament polymerisation and Hipppo pathway activity.