BIOGRAPHICAL SKETCH

NAME: Zacharioudaki, Evanthia

POSITION TITLE: Postdoctoral Fellow

EDUCATION/TRAINING:

INSTITUTION AND LOCATION	DEGREE	Start Date	Completion Date	FIELD OF STUDY
University of Crete, Biology Dept.	BS	09/2002	09/2006	Molecular Biology and Biotechnology
University of Crete, Biology Dept.	MSc	10/2006	12/2008	Molecular Biology and Biomedicine
University of Crete, Biology Dept.	PhD	12/2008	07/2013	Developmental Biology and Neuroscience
University of Cambridge, PDN Dept.	Postdoctoral Fellow	03/2013	07/2018	Developmental Biology and Cancer
FORTH-IMBB	Postdoctoral Fellow	12/2018	pending	Developmental Biology and Cancer

A. Personal Statement

Solid neural tumours (e.g. glioblastomas, neuroblastomas) are amongst the deadliest cancers. These tumours are heterogeneous and their growth is sustained by Cancer Stem Cells (CSCs) which exploit self-renewing programs that normal Stem Cells (SCs) use for tissue development and repair. Furthermore, CSCs constantly interact with their microenvironment (e.g immune cells such as Tumour Associated Macrophages or TAMs) and this interaction could either sustain or impede tumor growth and metastasis. I am interested in how intrinsic and extrinsic cues make stem cells go rogue and how these rogue cells orchestrate the demise of other organs and eventually the whole organism. The past 15 years, I was involved in establishing a **Drosophila Central Nervous System (CNS) tumour model** by over activating Notch signaling in larval neural stem cells (NSCs) and their progeny. We are now using this model to study **how genetic and epigenetic changes as well as local and systemic interactions** with other tissues **affect tumour initiation and progression.**

My academic training and research experience have provided me with an excellent background in multiple biological disciplines including genetics, molecular biology, biochemistry, genomics and imaging. As an undergraduate student, I conducted research with Prof. C.hristos Delidakis on characterizing molecular interactions between bHLH-O/HES transcriptional repressors and

bHLH transcription activators in Drosophila melanogaster. In my master thesis, I continued studying the role of bHLH-O/HES proteins in larval CNS development in D.melanogaster.

As a pre-doctoral student with Prof Christos Delidakis, I was involved in studying how perturbations like **excess of Notch (N) signaling** (Zacharioudaki et al., 2012) result in **aberrant NSC proliferation** and CNS **hyperplasia** similar to early stages of tumorigenesis. Using genomic approaches during my PhD (C. Delidakis lab, IMBB) and my early post-doctoral studies (S. Bray's lab, Uni. Cambridge), I showed that N hyperplasia is achieved by upregulation of stemness and growth and suppression of differentiation (Zacharioudaki et al., 2016). While in Cambridge, I also studied the role of genes that were identified as frequently mutated in human pediatric tumours (neuroblastoma, medulloblastoma, glioblastoma) in propagating NSC derived tumours. This work lead to two publications (Zacharioudaki et al., 2019; Feng et al., 2020).

In 2018, I rejoined IMBB as an HFRI post doc fellow hosted by C.Delidakis lab. We showed that **N or HES NSC hyperplasias** can also **progress to malignancy** (Magadi et al., 2020; Voutyraki et al., 2022). Our transcriptomic analysis of Notch and HES primary vs malignant (allograft) tumours revealed that both Notch and HES allograft tumours shut down neural identity processes and upregulate immunity, stress and metabolism processes as they advance to malignancy (Voutyraki et al., 2022), (Voutyraki et al, under revision PNAS). We discovered that haemocytes, the Drosophila macrophages, play a tumour suppressive role in this context by phagocytosing tumour cells. Recently, we have also discerned a possible tumour-enabling role of haemocytes via the production of reactive oxygen species (Voutyraki et al, under revision PNAS).

In parallel, we exploited our Drosophila brain tumour model to study how intrinsic cues might affect neural tumour growth, focusing on epigenetic regulators. While in Cambridge, I observed that loss of either E(z) (PRC2 epigenetic silencing complex) or Mi-2 (NURD chromatin remodeling complex) accelerated N primary hyperplasias in the larval CNS (we abbreviate these as NE and NM tumours respectively (Zacharioudaki et al., 2019). We recently asked whether loss of E(z) or Mi-2 could also modulate allograft N tumour growth. We observed that, *NM* allograft tumours are more aggressive than *N* tumours. Strikingly, NE allografts acquire an epithelial appearance and are less aggressive. Animals bearing NE tumours live longer but they have a worse quality of life as they are cachectic. To uncover gene networks regulated by these epigenetic factors to modulate tumour growth, we obtained bulk transcriptomic profiles of epigenetically compromised (NE and NM) primary and allograft tumours. We have secured funding from i) Worldwide Cancer Research (WWCR: 2022-2025) to analyse these profiles and ii) from Hellenic Foundation for Research and Innovation (HFRI: 2022-2025) to characterize the epigenome of Notch vs epigenetically compromised Notch NSC tumours.

My **long term goal** is to decipher how cell intrinsic and extrinsic mechanisms modulate CSC behaviour at early and progressed stages of tumorigenesis. Our simple Drosophila brain tumour model, our already obtained transcriptomic data along with my expertise in genetics, genomics and live imaging will form the pillar for my future studies. Some of my future plans are i) exploiting live imaging techniques to study the dynamics of chromatin compaction/openness and transcription of stemness and pro-differentiation factors in NSC tumours; ii) Multi-platform (bulk, single cell epigenome and RNA seq, spatial transcriptomics) analysis of epigenetically modified N tumours,); iii) The interaction of CSCs with their microenvironment (haemocytes, glia , trachea)

during N NSC tumour initiation and progression; iv) the effect of the macro-environment (nutrition, oxidative stress, pathogen challenge, drugs) on N NSC tumour progression.

- Chrysanthi Voutyraki, Alexandros Choromidis, Anastasia Meligkounaki, Nikolaos Andreas Vlachopoulos, Vasiliki Theodorou, Sofia Grammenoudi, Emmanouil Athanasiadis, Angela Giangrande, Christos Delidakis*, **Evanthia Zacharioudaki*.** Growth deregulation and interaction with host haemocytes contribute to tumour progression in a Drosophila brain tumour model. *Under revision in PNAS. *co-corresponding authors.*
- Voutyraki C, Choromidis A, Theodorou V, Efraimoglou C, Anagnostopoulos G, Magadi SS, Grammenoudi S, **Zacharioudaki E*,** Delidakis C*. **(2021)** Repression of differentiation genes by Hes transcription factors fuels neural tumour growth in Drosophila. *Int J Dev Biol.* 2022;66(1-2-3):211-222. doi: 10.1387/ijdb.210187cd. **co-corresponding authors.*
- Srivathsa S. Magadi, Chrysanthi Voutyraki, Gerasimos Anagnostopoulos, **Evanthia Zacharioudaki**, Ioanna K. Poutakidou, Christina Efraimoglou, Margarita Stapountzi, Vasiliki Theodorou, Christoforos Nikolaou, Christos Delidakis (**2020**). *Development.* 2020 Nov 23;147(22): dev191544. doi: 10.1242/dev.191544.
- Feng S, **Zacharioudaki E,** Millen K, Bray SJ. (**2020**) The SLC36 transporter Pathetic is required for neural stem cell proliferation and for brain growth under nutrition restriction. *Neural Dev.* 2020 Aug 2;15(1):10. doi: 10.1186/s13064-020-00148-4.
- **Zacharioudaki E,** Falo Sanjuan J, Bray S. (**2019**) Mi-2/NuRD complex protects stem cell progeny from mitogenic Notch signaling. *Elife.* 2019 Jan 29;8. pii: e41637. doi: 10.7554/eLife.41637.
- **Zacharioudaki E**, Housden BE, Garinis G, Stojnic R, Delidakis C, Bray SJ. (**2016**) Genes implicated in stem cell identity and temporal programme are directly targeted by Notch in neuroblast tumours. *Development* 143(2):219-31
- **Zacharioudaki E,** Magadi S.S., Delidakis C. **(2012)** Basic-helix-loop-helix-Orange proteins are crucial for Drosophila neuroblast self-renewal and mediate Notch-induced overproliferation. *Development* 139(7):1258-69.

B. Positions, Scientific Appointments, and Honors

Positions and Scientific Appointments

2018 – Present **Postdoctoral Fellow, FORTH-IMBB**
2013 – 2018 **Postdoctoral Researcher, University of Cambridge, PDN Dept.**
2008 – 2013 **Pre-doctoral Researcher, FORTH-IMBB2012**
2007– Present **Member of the *Hellenic Society of Biochemistry & Molecular Biology***
2014 – Present **Member of the *British Society for Developmental Biology* (BSDB)**
2015 – Present **Member of the *British Genetics Society***

Fellowships/prizes/awards

2008-2010 **T hanassis & Marina Martinos Fellowship**. Owners of "Eastern Mediterranean Maritime ltd.", 69 Grigoriou Lampraki, Glyfada, Athens – Greece.

2010 **EMBO Short Term Travel Fellowship** to visit Prof. Sarah Bray's lab at Uni. Of Cambridge

2010-2013 **Hellenic Ministry of Education and National Strategic Reference Framework 2007-2013, Basic Research Fellowship "Hrakleitos II".**

2018 – 2022 **Hellenic Ministry of Education, Hellenic Foundation for Research and Innovation,** Research grant (€180000) for senior postdocs building towards independence.