BIOGRAPHICAL SKETCH

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NAME: NICOLA ALESI

eRA COMMONS USER NAME (credential, e.g., agency login): Nalesi

POSITION TITLE: Instructor of Medicine

EDUCATION/TRAINING *(Begin with baccalaureate or other initial professional education, such as nursing, include postdoctoral training and residency training if applicable. Add/delete rows as necessary.)*

INSTITUTION AND LOCATION	DEGREE *(if applicable)*	Completion Date MM/YYYY	FIELD OF STUDY
Universita' Politecnica Delle Marche, Ancona-Italy	MD *summa cum laude*	10/2012	Medicine
Universita' Politecnica Delle Marche, Ancona-Italy	PhD	03/2017	Human Science
Brigham and Women's Hospital, Harvard Medical School	Predoctoral Fellow	02/2015	Stem Cell biology
Brigham and Women's Hospital, Harvard Medical School	Postdoctoral Fellow	02/2021	Tuberous Sclerosis Complex
Brigham and Women's Hospital, Harvard Medical School	Instructor in Medicine (Harvard Medical School faculty appointment)	03/2021	Tuberous Sclerosis Complex

A. Personal Statement

I am a fully-trained physician from Italy (certified by the European Board). I obtained my PhD in 2017, working in the Henske Laboratory. My clinical interests include pediatric oncology, child neurology and genetics. During medical school, I spent one year in the Department of Child Neurology at G. Salesi Children's Hospital in Ancona (Italy), studying epilepsy in children with genetic disorders. I have attended three International TSC Research Conferences and received travel awards for two of them.

This project is focused on CTHRC1 (collagen triple helix repeat containing 1), a protein that we have found is highly upregulated in TSC-associated tumors. CTHRC1 has not been previously investigated in TSC. In other diseases, CTHRC1 expression is associated with a poor prognosis and enhanced tumor cell invasiveness. In TSC2-deficient cells, we have discovered that downregulation of CTHRC1 inhibits both proliferation and colony formation, suggesting that it may inhibit tumor progression in vivo, which we will test in this project. Interestingly, CTHRC1 expression is not affected by Rapamycin, suggesting that therapies that target CTHRC1 could ultimately be combined with Rapamycin, with the potential for therapeutic synergy.

B. Positions, Scientific Appointments, and Honors
Positions and Scientific Appointments

2021 – Present Instructor, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School
2017 – 2021 Postdoctoral Research, Department of Medicine, Brigham and Women's Hospital,Harvard Medical School
2015 - 2017 Predoctoral Research, Department of Medicine Brigham and Women's Hospital, Harvard Medical School
2013 – 2015 Predoctoral Research, Stem Cell Biology, Brigham and Women's Hospital, Harvard Medical School

Honors

2014 Travel Award, American Heart Association Annual Meeting, Chicago IL
2016 Research Excellence Award, Brigham Research Day, Brigham and Women's Hospital
2017 Vicky Whittemore Travel Award, 2017 International Research Conference on TSC & LAM, Washington DC
2017 Best Poster Award, 2017 Skeletal Research Symposium, Boston MA
2017 Travel Award, American Society for Bone and Mineral Research Annual Meeting, Denver CO
2019 Vicky Whittemore Travel Award, 2019 International Research Conference on TSC & LAM, Toronto, ON

C. Contribution to Science

1. **Regulation of Lysosome biogenesis in Tuberous Sclerosis via RAGC and TFEB.**

a-TSC2 regulates lysosome biogenesis via a non-canonical RAGC and TFEB-dependent mechanism.
***Alesi N**, Akl EW, Khabibullin D, Liu HJ, Nidhiry AS, Garner ER, Filippakis H, Lam HC, Shi W, Viswanathan SR, Morroni M, Ferguson SM, Henske EP. Nature Communications, 2021.*

b- Keeping up with the Rag GTPases.
***Alesi N**, Henske EP. Nature Cell Biology, 2022.*

I have found that that lysosomal biogenesis is increased in TSC-associated renal angiomyolipomas and renal cell carcinomas, pulmonary lymphangioleiomyomatosis, kidneys from $Tsc2^{+/-}$ mice, and *TSC1/2*-deficient cells, via a TFEB-dependent mechanism. Interestingly, in *TSC1/2*-deficient cells, TFEB is hypo-phosphorylated at mTORC1-dependent sites, indicating that mTORC1 is unable to phosphorylate TFEB in the absence of the TSC1/2 complex. This inability of mTORC1 to phosphorylate TFEB in TSC-null cells appears to be linked to deficient activity of the RAG GTPases, since overexpression of constitutively active RAGA-C but not wild-type RAGA-C is sufficient to relocalize TFEB to the cytoplasm.

2. **Role of Osteoclasts in the Pathogenesis of TSC.**

a- Basic Aspects of Osteoclast Differentiation and Function.
***Alesi N,** Charles JF, Nakamura MC. Basic Aspects of Osteoclast Differentiation and Function. Leder B., Wein M. (eds) Osteoporosis. Contemporary Endocrinology. Humana, Cham, 2021.*

b- Osteoclast-specific TSC2 deletion increases bone mass via a consequent up regulation of osteoblast activity.
***Alesi N,** Henske EP, Charles JF, in preparation.*

Working in collaboration with Julia Charles, MD PhD (Rheumatology Division, Brigham and Women's Hospital), I have discovered that osteoclasts are responsible for the pathogenesis and functional consequences of sclerotic bone lesions in TSC, acting via osteoblasts to increase bone formation. This work has led to travel awards from the TS Alliance (Washington DC, 2017 and Toronto ON 2019) and the Bone and Mineral Research Annual Meeting (2017).

3. **Identification that a second hit mutation in TSC1/TSC2 is necessary for the development of angiomyolipomas.**

Whole Exome Sequencing Identifies TSC1/TSC2 Biallelic Loss as the Primary and Sufficient Driver Event for Renal Angiomyolipoma Development.
*Giannikou K, Malinowska IA, Pugh TJ, Yan R, Tseng YY, Oh C, Kim J, Tyburczy ME, Chekaluk Y, Liu Y, **Alesi N**, Finlay GA, Wu CL, Signoretti S, Meyerson M, Getz G, Boehm JS, Henske EP, Kwiatkowski DJ. PLoS Genetics, 2016.*

In this project, we performed whole exome sequencing in 32 resected tumors samples from 15 subjects. These results indicate that TSC2 and less commonly TSC1 alterations are the primary essential driver event in angiomyolipoma/LAM, whereas other somatic mutations are rare. For this project, I contributed by harvesting angiomyolipoma tissue and processing it to extract DNA, as well as isolating tumorigenic cells for cell culture analyses.

4. **Lysosomal regulation of cholesterol homeostasis in tuberous sclerosis complex.**

Lysosomal regulation of cholesterol homeostasis in tuberous sclerosis complex is mediated via NPC1 and LDL-R. *Filippakis H, **Alesi N**, Ogorek B, Nijmeh J, Khabibullin D, Gutierrez C, Valvezan AJ, Cunningham J, Priolo C, Henske EP. Oncotarget, 2017.*

The major finding of this project is that simultaneous inhibition of the lysosome and endosomal trafficking blocks the proliferation of TSC2-deficient cells, providing a novel potential therapeutic avenue for the treatment of TSC and other diseases associated with mTORC1 hyperactivation, including lymphangioleiomyomatosis (LAM) and the majority of human malignancies. In this project, as second author, I took part on the design, performance and analysis of experiments that included RT-PCR, cell culture, drug treatments and immunoblotting.

5. **p62/SQSTM1 Cooperates with Hyperactive mTORC1 to Promote Tumorigenesis in TSC.**

p62/SQSTM1 Cooperates with Hyperactive mTORC1 to Regulate Glutathione Production, Maintain Mitochondrial Integrity, and Promote Tumorigenesis.
*Lam HC, Baglini CV, Lope AL, Parkhitko AA, Liu HJ, **Alesi N**, Malinowska IA, Ebrahimi-Fakhari D, Saffari A, Yu JJ, Pereira A, Khabibullin D, Ogorek B, Nijmeh J, Kavanagh T, Handen A, Chan SY, Asara JM, Oldham WM, Diaz-Meco MT, Moscat J, Sahin M, Priolo C, Henske EP. Cancer Research, 2017.*

The major finding of this paper is that depletion of p62 in Tsc2-null cells decreases intracellular glutamine, glutamate, and glutathione (GSH). Therefore, p62 helps maintain intracellular pools of GSH in tumor cells with elevated mTORC1, highlighting p62 and redox homeostasis as vulnerabilities for therapeutic targeting. In this project, my major contribution was the performance of immunohistochemistry and analysis of the impact of p62 on renal cysts and tumors in $Tsc2^{+/-}$ mice.

Complete List of Published Work from PubMed:

https://www-ncbi-nlm-nih-gov.ezp-prod1.hul.harvard.edu/myncbi/nicola.alesi.1/bibliography/public/