

BIOGRAPHICAL SKETCH

PERSONAL INFORMATION

Name: Heinrich Kovar
Born: 05.03.1959
Address: Children's Cancer Research Institute (CCRI)
Zimmermannplatz 10, 1090 Vienna, Austria
Webpage: <http://science.ccri.at/>

MAIN RESEARCH AREAS

Molecular biology, molecular oncology, pediatric sarcoma

HIGHER EDUCATION

1984 Doctor of philosophy (Zoology/Chemistry) at University of Vienna

ACADEMIC CAREER

2010 Full professor
1997 Habilitation in Molecular Biology at Medical University of Vienna

POSITIONS

2001-2017 Scientific Director of Children's Cancer Research Institute (CCRI), Vienna
1988-present Head of Molecular Biology Lab, CCRI, Vienna
1984-1988 Assistant Professor, Institute of Molecular Biology, Medical University, Vienna
1981-1984 Research Assistant, Institute of Molecular Biology, Medical University, Vienna

INVITATIONS TO PRESENT AT ACADEMIC CONFERENCES

2018 Dwek Workshop on Children and Cancer, Weizmann Institute, Rehovot
2018 From Receptors and Kinases to Transcriptional Regulators: Cancer Genome Landscapes and their Therapeutic Targets, Seggau
2017 Faris D. Virani International Ewing Sarcoma Symposium, Houston
2016 Int. Academy of Pathology / European Society of Pathology, Colgne
2014 American Association for Cancer Research (AACR) Think Tank on the Future of Pediatric Cancer Research and Treatment, Philadelphia
2013 European Cancer Congress (ECCO), Amsterdam
2012 Int. Conference on Systems Medicine SYSMED, Dublin

PRIZES/AWARDS RECEIVED

2009 Grand Middle European Prize for Interdisciplinary Cancer Research
2011, 2006, 1999 Science Award of the Austrian Pediatric Society
2002 Nöllenburg Prize for bone tumor research
1995 Fasanelli Prize for bone tumor research

PEER REVIEW ACTIVITIES

Cancer Cell, Nature, Nature Medicine, Nature Genetics, Cancer Research

MEMBERSHIPS IN ACADEMIC ORGANIZATIONS

Forschungsinstitut, Kinderkrebs Zentrum Hamburg; Lille Cancer Research Institute; ITCC Biology; Comprehensive Cancer Center Vienna-MST.

FUNDED PROJECTS

2017-2022	H2020 IMI2 "ITCC Pediatric Preclinical Proof of Concept Platform (ITCC-P4; #116064, €163.253)
2017-2020	"Role of stress granules in Ewing sarcoma susceptibility". FWF P-29773-B28, €364.795,20
2013-2017	ERA-NET TRANSCAN "Prospective Validation of Biomarkers in Ewing Sarcoma for Personalized Translational Medicine" (PROVABES). FWF I1225-B19, € 241.888,5
2012-2015	"The role of microRNAs in the EWS-FLI1 gene regulatory network of Ewing sarcoma". FWF P24708-B12, € 349.245,75
2010-2016	"Analysing and Striking the Sensitivities of Embryonal Tumours" (ASSET). EU-FP7 #259348, € 822.392
2010-2013	"Mechanisms of Transcriptional Control by EWS-FLI1". FWF P22328-B09, € 284.521,65

KEY INTERNATIONAL COLLABORATION PARTNERS

O. Delattre (Inst. Curie), P. Meltzer (NCI, NIH), B. Lawlor (Children's Hospital Los Angeles), J. Toretsky (Georgetown University, Washington), K. Scotlandi (Rizzoli Inst. Bologna), members of EC funded program grants ("ASSET", "ENCCA", "PROVABES", "EEC") and the European Ewing's Sarcoma Studies (Ewing2008, EWING2012).

PUBLICATIONS LAST 5 YEARS

a) Peer-reviewed publications

1. Srivastava, S., Nataraj, N.B., Sekar, A., Bornstein-Ovits, C., Ghosh, S., Drago, D., Roth, L., Romaniello, D., Marrocco, I., Gilad, Y., Lauriolla, M., Rotkopf, R., Kimchi, A., Mirabeau, O., Surdez, D., Zinovyev, A., Dellattre, O., **Kovar, H.**, Amit, I., and Yarden, Y. (2019). ETS proteins bind with glucocorticoid receptors: relevance for treatment of Ewing sarcoma. *Cell Reports* in press.
2. Selvanathan, S.P., Graham, G.T., Grego, A.R., Baker, T.M., Hogg, J.R., Simpson, M., Batish, M., Crompton, B., Stegmaier, K., Tomazou, E.M., **Kovar, H.**, Üren A, and Toretsky J.A. (2019). EWS-FLI1 modulated alternative splicing of ARID1A reveals novel oncogenic function through the BAF complex. *Nucleic Acids Res.* 2019 Aug 8. [Epub ahead of print].
3. Tsafou, K., Katschnig, A.M., Radic-Sarikas, B., Mutz, C.N., Iljin, K., Schwentner, R., Kauer, M.O., Muhlbacher, K., Aryee, D.N.T., Westergaard, D., Haapa-Paananen, S., Fey, V., Superti-Furga, G., Toretsky, J., Brunak, S., and **Kovar, H.** (2018). Identifying the druggable interactome of EWS-FLI1 reveals MCL-1 dependent differential sensitivities of Ewing sarcoma cells to apoptosis inducers. *Oncotarget* 9, 31018-31031.
4. Machiela, M.J., Grunewald, T.G.P., Surdez, D., Reynaud, S., Mirabeau, O., Karlins, E., Rubio, R.A., Zaidi, S., Grossetete-Lalami, S., Ballet, S., Lapouble, E., Laurence, V., Michon, J., Pierron, G., **Kovar, H.**, et al. (2018). Genome-wide association study identifies multiple new loci associated with Ewing sarcoma susceptibility. *Nat Commun* 9, 3184.
5. **Kovar, H.** (2018). Selective enhancer changes in osteosarcoma lung metastasis. *Nat Med* 24, 126-127.
6. Grunewald, T.G.P., Cidre-Aranaz, F., Surdez, D., Tomazou, E.M., de Alava, E., **Kovar, H.**, Sorensen, P.H., Delattre, O., and Dirksen, U. (2018). Ewing sarcoma. *Nat Rev Dis Primers* 4, 5.

7. van der Lelij, P., Lieb, S., Jude, J., Wutz, G., Santos, C.P., Falkenberg, K., Schlattl, A., Ban, J., Schwentner, R., Hoffmann, T., **Kovar, H.**, Real, F.X., Waldman, T., Pearson, M.A., Kraut, N., Peters, J.M., Zuber, J., and Petronczki, M. (2017). Synthetic lethality between the cohesin subunits STAG1 and STAG2 in diverse cancer contexts. *Elife* 6.
8. Sheffield, N.C., Pierron, G., Klughammer, J., Datlinger, P., Schonegger, A., Schuster, M., Hadler, J., Surdez, D., Guillemot, D., Lapouble, E., Freneaux, P., Champigneulle, J., Bouvier, R., Walder, D., Ambros, I.M., Hutter, C., Sorz, E., Amaral, A.T., de Alava, E., Schallmoser, K., Strunk, D., Rinner, B., Liegl-Atzwanger, B., Huppertz, B., Leithner, A., de Pinieux, G., Terrier, P., Laurence, V., Michon, J., Ladenstein, R., Holter, W., Windhager, R., Dirksen, U., Ambros, P.F., Delattre, O., **Kovar, H.**, Bock, C., and Tomazou, E.M. (2017). DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma. *Nat Med* 23, 386-395.
9. Schwentner, R., Herrero-Martin, D., Kauer, M.O., Mutz, C.N., Katschnig, A.M., Sienski, G., Alonso, J., Aryee, D.N., and **Kovar, H.** (2017). The role of miR-17-92 in the miRegulatory landscape of Ewing sarcoma. *Oncotarget* 8, 10980-10993.
10. Radic-Sarikas, B., Tsafo, K.P., Emdal, K.B., Papamarkou, T., Huber, K.V., Mutz, C., Toretsky, J.A., Bennett, K.L., Olsen, J.V., Brunak, S., **Kovar, H.**, and Superti-Furga, G. (2017). Combinatorial Drug Screening Identifies Ewing Sarcoma-specific Sensitivities. *Mol Cancer Ther* 16, 88-101.
11. Mutz, C.N., Schwentner, R., Aryee, D.N.T., Bouchard, E.D.J., Mejia, E.M., Hatch, G.M., Kauer, M.O., Katschnig, A.M., Ban, J., Garten, A., Alonso, J., Banerji, V., and **Kovar, H.** (2017). EWS-FLI1 confers exquisite sensitivity to NAMPT inhibition in Ewing sarcoma cells. *Oncotarget* 8, 24679-24693.
12. Minas, T.Z., Surdez, D., Javaheri, T., Tanaka, M., Howarth, M., Kang, H.J., Han, J., Han, Z.Y., Sax, B., Kream, B.E., Hong, S.H., Celik, H., Tirode, F., Tuckermann, J., Toretsky, J.A., Kenner, L., **Kovar, H.**, Lee, S., Sweet-Cordero, E.A., Nakamura, T., Moriggl, R., Delattre, O., and Uren, A. (2017). Combined experience of six independent laboratories attempting to create an Ewing sarcoma mouse model. *Oncotarget* 8, 34141-34163.
13. Katschnig, A.M., Kauer, M.O., Schwentner, R., Tomazou, E.M., Mutz, C.N., Linder, M., Sibilja, M., Alonso, J., Aryee, D.N.T., and **Kovar, H.** (2017). EWS-FLI1 perturbs MRTFB/YAP-1/TEAD target gene regulation inhibiting cytoskeletal autoregulatory feedback in Ewing sarcoma. *Oncogene* 36, 5995-6005.
14. He, T., Surdez, D., Rantala, J.K., Haapa-Paananen, S., Ban, J., Kauer, M., Tomazou, E., Fey, V., Alonso, J., **Kovar, H.**, Delattre, O., and Iljin, K. (2017). High-throughput RNAi screen in Ewing sarcoma cells identifies leucine rich repeats and WD repeat domain containing 1 (LRWD1) as a regulator of EWS-FLI1 driven cell viability. *Gene* 596, 137-146.
15. Gardiner, J.D., Abegglen, L.M., Huang, X., Carter, B.E., Schackmann, E.A., Stucki, M., Paxton, C.N., Lor Randall, R., Amatruda, J.F., Putnam, A.R., **Kovar, H.**, Lessnick, S.L., and Schiffman, J.D. (2017). C/EBPbeta-1 promotes transformation and chemoresistance in Ewing sarcoma cells. *Oncotarget* 8, 26013-26026.
16. Ventura, S., Aryee, D.N., Felicetti, F., De Feo, A., Mancarella, C., Manara, M.C., Picci, P., Colombo, M.P., **Kovar, H.**, Care, A., and Scotlandi, K. (2016). CD99 regulates neural differentiation of Ewing sarcoma cells through miR-34a-Notch-mediated control of NF-kappaB signaling. *Oncogene* 35, 3944-3954.
17. Valent, P., Groner, B., Schumacher, U., Superti-Furga, G., Buslinger, M., Kralovics, R., Zielinski, C., Penninger, J.M., Kerjaschki, D., Stingl, G., Smolen, J.S., Valenta, R., Lassmann, H., **Kovar, H.**, Jager, U., Kornek, G., Muller, M., and Sorgel, F. (2016). Paul Ehrlich (1854-1915) and His Contributions to the Foundation and Birth of Translational Medicine. *J Innate Immun* 8, 111-120.
18. Ruiz-Pinto, S., Pita, G., Patino-Garcia, A., Garcia-Miguel, P., Alonso, J., Perez-Martinez, A., Sastre, A., Gomez-Mariano, G., Lissat, A., Scotlandi, K., Serra, M., Ladenstein, R., Lapouble, E., Pierron, G., Kontny, U., Picci, P., **Kovar, H.**, Delattre, O., and Gonzalez-Neira, A. (2016). Identification of genetic variants in pharmacokinetic genes associated with Ewing Sarcoma treatment outcome. *Ann Oncol* 27, 1788-1793.
19. Mutz, C.N., Schwentner, R., Kauer, M.O., Katschnig, A.M., Kromp, F., Aryee, D.N., Erhardt, S., Goiny, M., Alonso, J., Fuchs, D., and **Kovar, H.** (2016). EWS-FLI1 impairs aryl hydrocarbon

receptor activation by blocking tryptophan breakdown via the kynurenine pathway. *FEBS Lett* 590, 2063-2075.

20. **Kovar, H.**, Amatruda, J., Brunet, E., Burdach, S., Cidre-Aranaz, F., de Alava, E., Dirksen, U., van der Ent, W., Grohar, P., Grunewald, T.G., Helman, L., Houghton, P., Iljin, K., Korsching, E., Ladanyi, M., Lawlor, E., Lessnick, S., Ludwig, J., Meltzer, P., Metzler, M., Mora, J., Moriggl, R., Nakamura, T., Papamarkou, T., Radic Sarikas, B. et al. (2016). The second European interdisciplinary Ewing sarcoma research summit--A joint effort to deconstructing the multiple layers of a complex disease. *Oncotarget* 7, 8613-8624.
21. Kager, L., Whelan, J., Dirksen, U., Hassan, B., Anninga, J., Bennister, L., Bovee, J., Brennan, B., Broto, J.M., Brugieres, L., Cleton-Jansen, A.M., Copland, C., Dutour, A., Fagioli, F., Ferrari, S., Fiocco, M., Fleuren, E., Gaspar, N., Gelderblom, H., Gerrand, C., Gerss, J., Gonzato, O., van der Graaf, W., Hecker-Nolting, S., Herrero-Martin, D., Klco-Brosius, S., **Kovar, H.** et al. (2016). The ENCCA-WP7/EuroSarc/EEC/PROVABES/EURAMOS 3rd European Bone Sarcoma Networking Meeting/Joint Workshop of EU Bone Sarcoma Translational Research Networks; Vienna, Austria, September 24-25, 2015. Workshop Report. *Clin Sarcoma Res* 6, 3.
22. Tomazou, E.M., Sheffield, N.C., Schmidl, C., Schuster, M., Schonegger, A., Datlinger, P., Kubicek, S., Bock, C., and **Kovar, H.** (2015). Epigenome mapping reveals distinct modes of gene regulation and widespread enhancer reprogramming by the oncogenic fusion protein EWS-FLI1. *Cell reports* 10, 1082-1095.
23. Schwentner, R., Papamarkou, T., Kauer, M.O., Stathopoulos, V., Yang, F., Bilke, S., Meltzer, P.S., Girolami, M., and **Kovar, H.** (2015). EWS-FLI1 employs an E2F switch to drive target gene expression. *Nucleic Acids Res* 43, 2780-2789.
24. Minas, T.Z., Han, J., Javaheri, T., Hong, S.H., Schleder, M., Saygideger-Kont, Y., Celik, H., Mueller, K.M., Temel, I., Ozdemirli, M., **Kovar, H.**, Erkizan, H.V., Toretzky, J., Kenner, L., Moriggl, R., and Uren, A. (2015). YK-4-279 effectively antagonizes EWS-FLI1 induced leukemia in a transgenic mouse model. *Oncotarget* 6, 37678-37694.
25. **Kovar, H.** (2015). SLFN11: Achilles' Heel or Troublemaker. *Clin Cancer Res* 21, 4033-4034.
26. Gaspar, N., Hawkins, D.S., Dirksen, U., Lewis, I.J., Ferrari, S., Le Deley, M.C., **Kovar, H.**, Grimer, R., Whelan, J., Claude, L., Delattre, O. et al. (2015). Ewing Sarcoma: Current Management and Future Approaches Through Collaboration. *J Clin Oncol* 33, 3036-3046.
27. Bolling, T., Braun-Munzinger, G., Burdach, S., Calaminus, G., Craft, A., Delattre, O., Deley, M.C., Dirksen, U., Dockhorn-Dworniczak, B., Dunst, J., Engel, S., Faldum, A., Frohlich, B., Gadner, H., Gobel, U., Gosheger, G., Harges, J., Hawkins, D.S., Hjorth, L., Hoffmann, C., **Kovar, H.** et al. (2015). Development of curative therapies for Ewing sarcomas by interdisciplinary cooperative groups in Europe. *Klin Padiatr* 227, 108-115.
28. Niedan, S., Kauer, M., Aryee, D.N., Kofler, R., Schwentner, R., Meier, A., Potschger, U., Kontny, U., and **Kovar, H.** (2014). Suppression of FOXO1 is responsible for a growth regulatory repressive transcriptional sub-signature of EWS-FLI1 in Ewing sarcoma. *Oncogene* 33, 3927-3938.
29. **Kovar, H.** (2014). Blocking the road, stopping the engine or killing the driver? Advances in targeting EWS/FLI-1 fusion in Ewing sarcoma as novel therapy. *Expert Opin Ther Targets* 18, 1315-1328.
30. Ban, J., Aryee, D.N., Fourtouna, A., van der Ent, W., Kauer, M., Niedan, S., Machado, I., Rodriguez-Galindo, C., Tirado, O.M., Schwentner, R., Picci, P., Flanagan, A.M., Berg, V., Strauss, S.J., Scotlandi, K., Lawlor, E.R., Snaar-Jagalska, E., Llombart-Bosch, A., and **Kovar, H.** (2014). Suppression of deacetylase SIRT1 mediates tumor-suppressive NOTCH response and offers a novel treatment option in metastatic Ewing sarcoma. *Cancer Res* 74, 6578-6588.

TOP 10 SELECTED PEER-REVIEWED PUBLICATIONS

1. Sheffield, N.C., G. Pierron, J. Klughammer, P. Datlinger, A. Schonegger, M. Schuster, J. Hadler, D. Surdez, D. Guillemot, E. Lapouble, P. Freneaux, J. Champigneulle, R. Bouvier, D. Walder, I.M. Ambros, C. Hutter, E. Sorz, A.T. Amaral, E. de Alava, K. Schallmoser, D. Strunk, B. Rinner, B. Liegl-

- Atzwanger, B. Huppertz, A. Leithner, G. de Pinieux, P. Terrier, V. Laurence, J. Michon, R. Ladenstein, W. Holter, R. Windhager, U. Dirksen, P.F. Ambros, O. Delattre, **H. Kovar**, C. Bock, and E.M. Tomazou. *DNA methylation heterogeneity defines a disease spectrum in Ewing sarcoma*. *Nat Med*, 2017. 23(3): p. 386-395.DOI: 10.1038/nm.4273.
2. Katschnig, A.M., M.O. Kauer, R. Schwentner, E.M. Tomazou, C.N. Mutz, M. Linder, M. Sibia, J. Alonso, D.N.T. Aryee, and **H. Kovar**. *EWS-FLI1 perturbs MRTFB/YAP-1/TEAD target gene regulation inhibiting cytoskeletal autoregulatory feedback in Ewing sarcoma*. *Oncogene*, 2017. 36(43): p. 5995-6005.DOI: 10.1038/onc.2017.202.
 3. Tomazou, E.M., N.C. Sheffield, C. Schmidl, M. Schuster, A. Schonegger, P. Datlinger, S. Kubicek, C. Bock, and **H. Kovar**. *Epigenome mapping reveals distinct modes of gene regulation and widespread enhancer reprogramming by the oncogenic fusion protein EWS-FLI1*. *Cell Rep*, 2015. 10(7): p. 1082-95.DOI: 10.1016/j.celrep.2015.01.042.
 4. Ban, J., D.N. Aryee, A. Fourtouna, W. van der Ent, M. Kauer, S. Niedan, I. Machado, C. Rodriguez-Galindo, O.M. Tirado, R. Schwentner, P. Picci, A.M. Flanagan, V. Berg, S.J. Strauss, K. Scotlandi, E.R. Lawlor, E. Snaar-Jagalska, A. Llombart-Bosch, and **H. Kovar**. *Suppression of deacetylase SIRT1 mediates tumor-suppressive NOTCH response and offers a novel treatment option in metastatic Ewing sarcoma*. *Cancer Res*, 2014. 74(22): p. 6578-88.DOI: 10.1158/0008-5472.CAN-14-1736.
 5. Bilke, S., R. Schwentner, F. Yang, M. Kauer, G. Jug, R.L. Walker, S. Davis, Y.J. Zhu, M. Pineda, P.S. Meltzer, and **H. Kovar**. *Oncogenic ETS fusions deregulate E2F3 target genes in Ewing sarcoma and prostate cancer*. *Genome Res*, 2013. 23(11): p. 1797-809.DOI: 10.1101/gr.151340.112.
 6. Le Deley, M.C., O. Delattre, K.L. Schaefer, S.A. Burchill, G. Koehler, P.C. Hogendoorn, T. Lion, C. Poremba, J. Marandet, S. Ballet, G. Pierron, S.C. Brownhill, M. Nessler, A. Ranft, U. Dirksen, O. Oberlin, I.J. Lewis, A.W. Craft, H. Jurgens, and **H. Kovar**. *Impact of EWS-ETS fusion type on disease progression in Ewing's sarcoma/peripheral primitive neuroectodermal tumor: prospective results from the cooperative Euro-E.W.I.N.G. 99 trial*. *J Clin Oncol*, 2010. 28(12): p. 1982-8.DOI: 10.1200/JCO.2009.23.3585.
 7. Bachmaier, R., D.N. Aryee, G. Jug, M. Kauer, M. Kreppel, K.A. Lee, and **H. Kovar**. *O-GlcNAcylation is involved in the transcriptional activity of EWS-FLI1 in Ewing's sarcoma*. *Oncogene*, 2009. 28(9): p. 1280-4.DOI: 10.1038/onc.2008.484.
 8. Ban, J., I.M. Bennani-Baiti, M. Kauer, K.L. Schaefer, C. Poremba, G. Jug, R. Schwentner, O. Smrzka, K. Muehlbacher, D.N. Aryee, and **H. Kovar**. *EWS-FLI1 suppresses NOTCH-activated p53 in Ewing's sarcoma*. *Cancer Res*, 2008. 68(17): p. 7100-9.DOI: 10.1158/0008-5472.CAN-07-6145.
 9. Siligan, C., J. Ban, R. Bachmaier, L. Spahn, M. Kreppel, K.L. Schaefer, C. Poremba, D.N. Aryee, and **H. Kovar**. *EWS-FLI1 target genes recovered from Ewing's sarcoma chromatin*. *Oncogene*, 2005. 24(15): p. 2512-24.DOI: 10.1038/sj.onc.1208455.
 10. Spahn, L., R. Petermann, C. Siligan, J.A. Schmid, D.N. Aryee, and **H. Kovar**. *Interaction of the EWS NH2 terminus with BARD1 links the Ewing's sarcoma gene to a common tumor suppressor pathway*. *Cancer Res*, 2002. 62(16): p. 4583-7.