Záverečná karta projektu

Názov projektu

In vitro hodnotenie bio-kompatibility zdravotníckych pomôcok (ZP) a innovatívnych bio-materiálov pre ZP

Evidenčné číslo projektu **APVV-19-0591**

Zodpovedný riešiteľ **Ing. Helena Kanďárová, PhD.**

Príjemca **Centrum experimentálnej medicíny SAV, v. v. i. - Ústav experimentálnej farmakológie a toxikológie**

Názov pracoviska, na ktorom bol projekt riešený

Ústav Experimentálnej Farmakológie a Toxikológie,
Centrum Experimentálnej Medicíny SAV
Dúbravská cesta 9
841 04 Bratislava

Názov a štát zahraničného pracoviska, ktoré spolupracovalo pri riešení

1. Austrian Institute of Technology, Viedeň, Rakúsko
2. Státní Zdravotní Ústav, Praha, Česká Republika
3. Biosurfaces, Ashland MA, USA
4. Medtronic, USA
5. Syngene International, India
6. React4Life, Genova, Taliansko
7. InnoCure, Česká republika
8. Straumann, Rakúsko
9. Bonyf, Vaduz, Lichtenštainsko.

Udelené patenty/podané patentové prihlášky, vynálezy alebo úžitkové vzory, ktoré sú výsledkami projektu

V rámci riešenia práce vznikli nasledovné štandardné pracovné postupy v súlade s princípmi OECD GLP a GIVIMP:
UEFT, ŠPP: In Vitro Eye Irritation Testing of Medical Devices: Reconstructed Human Cornea-like 3D Model (Compliant with ISO 10993-23). 2024
UEFT, ŠPP: In Vitro Photo-Irritation Testing of Medical Devices: Reconstructed Human Cornea-like 3D Model (Compliant with ISO 10993-23). 2024
UEFT, ŠPP: In Vitro Oral and Gingival Irritation Testing of Medical Devices: Reconstructed Human 3D Models of Oral Cavity (Compliant with ISO 10993-23). 2024
UEFT, ŠPP: Histology sample preparation and analysis: Reconstructed Human 3D Tissue Models. 2024
Databázy vytvorené v procese tvorby protokolu foto-iritacie boli použité pre overenie a tréning QSAR softwarerov ML-TOX a Derek-Nexus.

Najvýznamnejšie publikácie (knihy, články, prednášky, správy a pod.) zhrňujúce výsledky projektu – uveďte aj publikácie prijaté do tlače

Publikácie zahrňujúce riešenú problematiku výsledky výskumu vrátane publikácií v tlači
[1.] KANĎÁROVÁ, Helena- HAYDEN, Patrick J. Standardised Reconstructed Skin Models in Toxicology and Pharmacology: State of the Art and Future Development. In Handbook of Experimental Pharmacology. - Springer Nature, 2021, 2021, vol. 265, p. 57-71. (2020: 1.605 - SJR, Q1 - SJR. ISSN 0171-2004. Dostupné na: https://doi.org/10.1007/164_2020_417 Typ: ADMB (7 citácií).
[2.] KANĎÁROVÁ, Helena - PÔBIŠ, Peter. The "Big Three" in biocompatibility testing of medical devices: implementation of alternatives to animal experimentation- are we there yet? In Frontiers in Toxicology, 2024, vol. 5, art. no. 1337468. (2023: 3.6 - IF, Q2 - JCR, 0.769 - SJR, Q1 - SJR). ISSN 2673-3080. Dostupné na: https://doi.org/10.3389/ftox.2023.1337468 Typ: BDMA (1 citácia)
[3.] PÔBIŠ, Peter – KUBALCOVÁ, Júlia – MILASOVÁ, Tatiana - KANĎÁROVÁ, Helena. In Alternatives to Laboratory Animals (ATLA), 2024, vol.52, iss.5. ISSN 2673-3080. Development of sensitive in vitro protocols for biocompatibility testing of medical devices and pharmaceuticals intended for contact with eyes: acute irritation and phototoxicity assessment. In press. (2023: 2.4 - IF, Q3 - JCR, 0.397 - SJR, Q2 - SJR). Dostupné na: https://journals.sagepub.com/toc/ATL/0/0. Typ: ADCA.
[4.] AHUJA, Varun - ADIGA PERDUR, Gowrav - AJ, Zabiullah - KRISHNAPPA, Mohan - KANĎÁROVÁ, Helena. In Silico Phototoxicity Prediction of Drugs and Chemicals by using Derek Nexus and QSAR Toolbox. In Alternatives to Laboratory Animals (ATLA) : Fund for the Replacement of Animals in Medical Experiments, 2024, vol.52, iss.4, pp. (2023: 2.4 - IF, Q3 - JCR, 0.397 - SJR, Q2 - SJR). ISSN 0261-1929. Dostupné na: https://doi.org/10.1177/02611929241256040,Typ: ADCA (1 citácia)
[5.] PÔBIŠ, Peter - MILASOVÁ, Tatiana - KANĎÁROVÁ, Helena. Exploring the potential of reconstructed human epithelial tissue models for safety assessment of Intraoral Medical Devices. In Toxicology in Vitro. Submitted as Invited article (29.06.2024). (2023: 2.6 - IF, Q3 - JCR, 0.656 - SJR, Q2 - SJR). Typ: ADCA
[6.] KANĎÁROVÁ, Helena - PÔBIŠ, Peter - SÁKOVÁ, Oľga – JAKUBOVSKÁ, Alena. Assessment of cytotoxicity, skin and oral irritation of medical devices with hydrating properties: A case study. In Interdisciplinary Toxicology, Accepted for publication (10.2.2024) . (2023: Q1 - JCR, 1,583 - SJR, Q1 – SJR). Typ: ADNB
Kapitoly v knihách vydavatelstiev Elsevier a Springer (3):
[1.] KANĎÁROVÁ, Helena. Alternative methods to animal experimentation and their role in modern toxicology. In Toxicological Risk Assessment and Multi-System Health Impacts from Exposure. - Elsevier Inc., Academic Press, 2021, part 1, chapter 2, P. 13-22. ISBN 978-0-323-85215-9. Typ: AECA
[2.] SPIELMANN, Horst - KANĎÁROVÁ, Helena. International Regulation of Toxicological Test Procedures. In Regulatory Toxicology. 2nd edition. - Cham: Springer Nature Switzerland AG, 2021, p. 843-852. ISBN 978-3-030-57498-7. Dostupné na: https://doi.org/10.1007/978-3-030-57499- 4_41 Typ: AECA
[3.] SPIELMANN, Horst - KANĎÁROVÁ, Helena. Integration of Advanced Technologies into Regulatory Toxicology. In Regulatory Toxicology. 2nd edition. - Cham: Springer Nature Switzerland AG, 2021, p. 149-161. ISBN 978-3-030-57498-7. Dostupné na: https://doi.org/10.1007/978-3-030- 57499-4_34 Typ: AECA
Kapitoly v Toxikologickej Encyklopédii Elsevier, 4 vydanie (2):
[1.] KANĎÁROVÁ, Helena. Organ-on-a-chip as novel tox testing tools. In Encyclopedia of Toxicology : Fourth edition. Vol. 1-9. - Elsevier-Academic Press, 2024, vol. 7., p. 173-176. ISBN 978-0-323-85434-4. Dostupné na: https://doi.org/10.1016/B978-0-12-824315-2.01037-X Typ: ABC
[2.] KANĎÁROVÁ, Helena. New approach methods (NAMs) for multiple non-animal based test methods. In Encyclopedia of Toxicology : Fourth edition. Vol. 1-9. - Elsevier-Academic Press, 2024, vol. 6, p. 741-746. ISBN 978-0-323-85434-4. Dostupné na: https://doi.org/10.1016/B978-0-12-824315-2.01036-8 Typ: ABC
Tréningové aktivity:
Lake Como Summer Schools 2020-2024, Online, Taliansko
ESTIV 2020 Applied Training Course - Brusel, Belgicko
ESTIV 2022 Applied Training Couse - LIST, Luxemburgsko
ESTIV 2023 Applied Training Course - CEM SAV Bratislava, Slovenska republika
IMPROVE 2024 Training School - 3D cell models for 3Rs research. Kaunas, Lithuania

Významnesie prednášky (Keynotes, Award/Awarded and Invited Lectures) – Výber 20 najhodnotenších
1. KANĎÁROVÁ, Helena. Invited Keynote lecture.: Using NAMs to Improve Clinical Relevance of Biological Tests. The Biocompatibility Insights Conference, Kodaň, Dánsko, Október 15th – 17th, 2024.https://veranex.com/biocompatibility-insights-2024/
2. PÔBIŠ, Peter – MILASOVÁ, Tatiana - KANĎÁROVÁ, Helena. Invited Lecture – Early career students session. Development Of Protocol For Evaluation of Safety of Medical Devices Intended for Oral Cavity. In ESTIV2024: Abstract book. - 2024, p. 74. Invited for publication in VSI ESTIV 2024
3. KANĎÁROVÁ, Helena. Invited lecture. Challenges and complexities in medical device testing in vitro from 2D to 3D. Fifth Virtual Summer School 2024 Lake Como School - Non Animal Models: complexity for interactions..... connecting Science, May 15-16, 2024, Lake Como, Italy
4. KANĎÁROVÁ, Helena. Keynote lecture. Assessment of product safety without animal testing – are we there yet or returning back to the 20th century? DGK/IKW Seminar for Safety Assessors in Warsaw 2023.ttps://www.hpci-events.com/central-and-eastern-europe/
5. KANĎÁROVÁ, Helena. Keynote lecture - Society for Alternatives to Animal Testing in Sri Lanka (SAAT-SL) on 31st January and 1st February 2023.
6. KANĎÁROVÁ, Helena. Plenary Lecture - Reconstructed human 3D tissue models in toxicology: from initial idea to the regulatory acceptance. 3rd Asian Congress for Alternatives to Animal Experiments Alternaives to Animal Experiments: From Asia to the World. 14th-16th December 2022/ICC Jeju - Korea
https://acaae2022.org:477/board02/list.asp
7. KANĎÁROVÁ, Helena - JÍROVÁ, Dagmar - NEUHAUS, Winfried - KEJLOVÁ, Kristína - PÔBIŠ, Peter - DVOŘÁKOVÁ, Markéta - ŠPILAK, Ana - DVOŘÁKOVÁ, Markéta, ml. - SVOBODOVÁ, Lada - MOULISOVÁ, Alena. Invited Keynote lecture. International TraiN-SafeMD project: collaboration towards improved safety assessment of medical devices. In Military medical science letters: 2022, vol. 91, suppl. 1, p. 38. ISSN 0372-7025. Toxcon 2022: Interdisciplinary Toxicological Conference
8. KANĎÁROVÁ, Helena. EUROTOX award lecture. Reconstructed human 3D tissue models in toxicology: from initial idea to regulatory acceptance: meeting abstract PL02-01:. In Toxicology Letters: official journal of EUROTOX, 2022, vol. 368, supplement S, p. S10-S11. (2021: 4.271 - IF, Q2 - JCR, 0.804 - SJR, Q1 - SJR). ISSN 0378-4274. Dostupné na: https://doi.org/10.1016/j.toxlet.2022.07.042. International Congress of Toxicology (ICT 2022): Uniting in Toxicology.
9. PÔBIŠ, Peter - KANĎÁROVÁ, Helena. 3D reconstructed human cornea-like tissue model for in vitro biocompatibility and phototoxicity testing of medical devices. In XI. Miniconference of PhD. students of Centre of Experimental Medicine. Book of Abstracts. 7th of July 2022. - Bratislava : Centre of Experimental Medicine SAS, 2022, p. non. ISBN 978-80-89991-08-2. Miniconference of PhD. students of Centre of Experimental Medicine 2022 Typ: AFH – 1 miesto v súťaži o najlepšiu študentskú prednášku,
10. KANĎÁROVÁ, Helena. BEMA award Lecture. Development and validation of 3D tissue models-based assays for topical toxicity testing -: abstract #414. In ESTIV 2022. 21st International Congress. Barcelona 2022, 21-25 November: abstract book. - Bratislava : Setox (for ESTIV), 2022, p. 208- 209. ISBN 978-80-969474-7-8. (ESTIV 2022. International Congress of the European Society of Toxicology In Vitro).
11. KANĎÁROVÁ, Helena. Invited Keynote lecture The use of reconstructed human tissue models in toxicology, pharmacology and medical safety testing in the regulatory context of the OECD guidelines and ISO standards. The meeting of the scientific cluster Omics4Health. October 8-9, Bratislava, 2021 Slovakia.
https://www.medicaldevicessafety.com/activities-and-news
12. KANĎÁROVÁ, Helena . Alternative Methods and 3D tissue models: The role of reconstructed 3D tissues in the implementation of 3Rs into the regulations worldwide. November 19, 2021, India, virtual meeting
https://www.3radvances.com/speakers/
13. KANĎÁROVÁ, Helena. Invited Keynote lectrureWhat has changed in the implementation of new approach methodologies in 21st century: obstacles, challenges and opportunities. 23rd Conference of SVLZ, Olomouc, Hotel Flora 29. 9.-1.10.2021
14. KANĎÁROVÁ, Helena. Doerenkamp-Zbinden Foundation Awardee 2021 Lecture:

Alternatives in the 21st century: what has changed in 20 years. TOXCON 2021, Stara Lesna September 15, 2021
http://konferencia.uef.sav.sk/?page_id=475
15. KANĎÁROVÁ, Helena. In vitro topical toxicity testing of medical devices in line with the new ISO 10993-23 ISOPS-13, Ankara Turkey, 2021
16. KANĎÁROVÁ, Helena. Invited Webinar Lecture. Alternative Methods and 3D tissue models: Fifth Webinar of the ToxGurukul Foundation Representing Indian Toxicology Community. 7.11. 2020 https://toxgurukul.org/webinars
17. KANĎÁROVÁ, Helena. Invited Keynote lecture Alternative Methods in Modern Toxicology. Event: Alternatives to animal experiments in biology, medicine, toxicology. September 24-25, 2020 Minsk, Belarus. Organizers: Belarusian Medical Academy of Postgraduate Education, Centre for Ethical Attitude Towards Nature, The republican centre of Bioethics.
18. KANĎÁROVÁ, Helena. Invited Keynote lecture Medical Devices Biocompatibility Testing in Vitro - Are We There Yet? ACTC Conference 2020. Cardiff September 30- October 1., 2020.
19. KANĎÁROVÁ, Helena. Invited Keynote lecture Can we rely on the predictions derived from in vitro reconstructed human tissue models? ACTC Conference 2019, June 4-5, 2019, Cardiff, UK
20. KANĎÁROVÁ, Helena. Invited Keynote lecture In Vitro Skin Models for testing of Cosmetics, Chemicals and Medical Devices. VZET Symposium. March 28-29, 2019, Hannover, Germany

Uplatnenie výsledkov projektu

Tri protokoly vyvinuté v tomto projekte (protokol pre hodnotenie očnej a intra-orálnej biokompatibility zdravotníckych pomôcok ako aj protokol očnej fototoxicity) sú okamžite použiteľné v predklinickom hodnotení biokompatibility ZP, inovatívnych biomaterialov a vybraných liečiv, ktoré prichádzajú do kontaktu s okom a tkanivami ústnej dutiny.
Štúdia poukázala na problematickú a nedostatočne popísanú prax prípravy extraktov zo ZP, ktoré absorbujú extrahovadlo.
Dáta, ktoré boli generované počas riešenia projektu významne prispejú k implementácii in vitro modelov do predklinického hodnotenia podľa ISO 10993:23 ako aj v hodnotení fototoxiciy podľa OECD TG 498

Súhrn výsledkov riešenia projektu a naplnenia cieľov projektu v slovenskom jazyku (max. 20 riadkov)

Projekt bol zameraný na vývoj dvoch inovatívnych protokolov pre hodnotenie biokompatibility zdravotníckych pomôcok na 3D in vitro rekonštituovaných tkanivových modeloch ľudskej rohovky a nekeratinizujúcich epitelov. Výskumný tím navrhol a experimentálne overil protokol pre očnú dráždivosť extraktov zo zdravotníckych pomôcok, ako aj materiálov testovaných priamym kontaktom. Protokol s použitím rekonštituovaného modelu EpiOcular bol navyše rozšírený o možnosť sledovania fotoiritácie a nežiaducich účinkov látok aplikovaných do oka a očného okolia.
Druhým výstupom projektu bol vývoj a experimentálne overenie nového protokolu pre sledovanie biokompatibility zdravotníckych pomôcok určených pre ústnu dutinu. Za týmto účelom sme použili rekonštituovaný model EpiOral a jeho vhodnosť sme overili na sérii experimentov s eluátmi zo zdravotníckych pomôcok, ako aj priamym kontaktom. V štúdii sa nepotvrdilo, že pôvodne navrhovaný model EpiOcular by mohol byť univerzálnym tkanivom pre štúdium toxicity látok na nekeratinizujúcich epiteloch.
V projekte sme overili aj vhodnosť zavedenia mikrofluidiky do pôvodne statických podmienok kultivácie. Tento dynamický model kultivácie umožňuje sledovanie dlhých expozícií a prípadnej metabolizácie látok, čo môže byť pridanou hodnotou pri overení biokompatibility zdravotníckych materiálov a pri sledovaní vedľajších účinkov zdravotníckych pomôcok, ako aj liečiv.
Oba protokoly, ako aj výsledky získané pre hodnotenie vybraných materiálov, boli zaslané pracovnej skupine ISO, ktorá rieši problematiku biokompatibility (ISO TC194) pre budúce zapracovanie do smerníc ISO. Výsledky z protokolu pre fototoxicitu boli zdieľané s pracovnou skupinou OECD pre zapracovanie do smerníc hodnotenia fototoxického potenciálu chemikálií (OECD Guidance Document on Phototoxicity).

Súhrn výsledkov riešenia projektu a naplnenia cieľov projektu v anglickom jazyku (max. 20 riadkov)

The project focused on developing two innovative protocols for evaluating the biocompatibility of medical devices on 3D in vitro reconstructed tissue models of the human cornea and non-keratinized epithelia. The research team designed and experimentally validated a protocol for ocular irritation of extracts from medical devices and materials tested by direct contact. The protocol using the reconstructed EpiOcular model was further extended to include the monitoring of photo-irritation and adverse effects of substances applied to the eye and periocular area.

The second output of the project was the development and experimental validation of a new protocol for monitoring the biocompatibility of medical devices intended for the oral cavity. For this purpose, we used the reconstructed human 3D tissue model EpiOral and verified its suitability through a series of experiments with eluates from medical devices, as well as direct contact. The study did not confirm that the originally proposed EpiOcular model could be a universal tissue for studying the toxicity of substances on non-keratinized epithelia. We also verified the suitability of introducing microfluidics into the originally static cultivation conditions. This dynamic cultivation model allows for the monitoring of long-term exposures and potential metabolization of substances, which can add value in verifying the biocompatibility of medical materials and monitoring the side effects of medical devices and drugs.

Both protocols, as well as the results obtained for evaluating selected materials, were submitted to the ISO working group dealing with biocompatibility (ISO TC194) for future possible incorporation into ISO guidelines. The results from the phototoxicity protocol were shared with the OECD working group for incorporation into the guidelines for assessing the phototoxic potential of chemicals (OECD Guidance Document on Phototoxicity)