Resumen de la línea de investigación.

Tubulina es una proteína constitutiva de gran abundancia en las células y, mediante su ensamblaje en microtúbulos, es responsable de funciones celulares cruciales. Estos filamentos gobiernan y permiten la segregación cromosómica durante la división celular, el andamiaje interfásico, el transporte intracelular de partículas y sustancias y la plasticidad neural a través de funciones estáticas o dinámicas, ya sea actuando como carreteras o ejerciendo fuerzas mecánicas. Ya que tubulina ejerce estas funciones esenciales en cada uno de los tipos de células eucarióticas se convirtió en una diana ideal para envenenar a los predadores en la naturaleza, de manera que muchos organismos han evolucionado para producir compuestos capaces de bloquear el interruptor de activación/desactivación de tubulina. Esto ha resultado en una plétora de productos que, uniéndose a distintos bolsillos de la proteína, pueden modular el ensamblaje en microtúbulos de tubulina. Algunos de estos moduladores se incluyen en la lista WHO de medicinas esenciales, como el mebendazol, paclitaxel, y los derivativos de Vinca, que han salvado millones de vidas tanto en el primer mundo como en los países en desarrollo.

Entre los retos globales de salud hay tres en los que la modulación de tubulina puede ofrecer una aproximación productiva al desarrollo de fármacos: **A)** Enfermedades neurodegenerativas (estabilizar químicamente los microtúbulos para el tratamiento de taupatías), **B)** Cáncer (nuevos moduladores microtubulares libres del efecto colateral de la neurotoxicidad periférica, que frenen la división celular y/o produzcan el colapso vascular en tumores) y **C)** Infecciones víricas (los microtúbulos son transportadores esenciales para el desarrollo del ciclo viral). Aunque, por naturaleza, los compuestos contra tubulina son tóxicos, es posible encontrar ventanas terapeúticas para estas aplicaciones explotando las diferencias en las escalas temporales de los procesos implicados, así como en las concentraciones de tubulina en las neuronas.

En el pasado, hemos contribuido al desarrollo de herramientas bioquímicas, biofísicas y celulares, esenciales en la caracterización de cada modulador de tubulina. En la actualidad estamos explotando estas técnicas e implementando nuevas, así como emprendiendo aproximaciones novedosas, incorporándolas a nuestro arsenal de cara a comprender el mecanismo de acción de estos moduladores. Nuestras líneas de investigación presentes y futuras persiguen obtener conocimiento en:

- Los mecanismos moleculares y celulares de la regulación del citoesqueleto de tubulina, de forma que podamos obtener mejores y más seguras formas de modularlo.
- Los mecanismos moleculares y celulares de acción de agentes moduladores de microtúbulos para desvelar cómo y por qué: (1) ejercen sus efectos y (2) inducen efectos secundarios no deseados, de forma que podamos diseñar, sintetizar y testear mejores drogas.
- La implicación de los microtúbulos y otras proteínas citoesqueléticas en los procesos infecciosos virales, de manera que puedan ser diana farmacológica para su tratamiento. Estos fármacos serían antivirales de amplio espectro capaces de evitar los principales mecanismos de resistencia virales frente a la toxicidad de químicos (mutaciones genéticas).

En la actualidad nuestra investigación se enfoca en los siguientes objetivos específicos:

A) Desvelar el mecanismo molecular implicado en la neurotoxicidad periférica inducida por agentes estabilizantes de microtúbulos, lo que permitirá el diseño y síntesis

de nuevas drogas con leves o ningún efecto secundario sobre el sistema nervioso. H2020-MSCA-ITN-2019 (2019-2023), PID2022-136765OB-I00 (2023-2026)

B) Comprender el mecanismo implicado en la muerte celular en presencia de moduladores de tubulina, el cual es desconocido pero clave para el desarrollo de drogas más seguras contra rutas específicas. PID2022-136765OB-I00 (2023-2026)

C) Explotar la sobreutilización de los microtúbulos por parte de un amplio rango de virus eucarióticos durante las infecciones virales para contribuir a la búsqueda de antivirales de amplio espectro. PID2021-123399OB-I00 (2022-2026).

Últimas Publicaciones del grupo (desde 2020)

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Understand Microtubule Cap Morphology and Function *ACS Omega* (2023), 8, 4, 3540–3550 https://doi.org/10.1021/acsomega.2c06926

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IMPORTANT** – **The Curriculum Vitae cannot exceed 4 pages. Instructions to fill this document are available in the website.

CV date	06/06/2023

Part A. PERSONAL INFORMATION

First name	Díaz Pereira		
Family name	José Fernando		
Gender (*)	Male	Birth date (dd/mm/yyyy)	09/09/1965
Social Security, Passport, ID number	fer@cib.csic-es	URL Web https://cib.csic.es/research/structural-and-chemical-biology/structure-function-and-pharmacology-cytoskeleton	
e-mail	fer@cib.csic.es		
Open Researcher and Contributor ID (ORCID) (*)	000-0003-2743-3319		

A.1. Current position

Position	Senior Staff Scientist/Investigador Científico de OPIS IP:Structure and function cytoskeleton: Pharmacology and Vaccines Head of: Interdepartamental unit for the development of new biologic, immunological and chemical therapeutics for global health		
Initial date	June 2008 as Staff Scientist Dec 2021 as Director of Head of Unit		
Institution	Consejo Superior de Investigaciones Científicas		
Department/Center	Centro de Investigaciones Biológicas Margarita Salas.		
Country	Spain	Teleph. number	
Key words	Tubulin, Cancer, Antitumourals, Microtubules, Alzheimer		

A.2. Previous positions (research activity interuptions, indicate total months)

Period	Position/Institution/Country/Interruption cause
01/1989-12/1993	PhD Candidate, CSIC
01/1994-12/1995	Postdoctoral, Catholic University Leuven, Belgium
01/1996-03/1998	Associated Researcher, Catholic University Leuven, Belgium
04/1998-06/2001	Hired Researcher, CSIC
07/2001-06/2008	Staff Scientist, CSIC
07/2008-	Senior Staff Scientist, CSIC.

A.3. Education

PhD, Licensed, Graduate	University/Country	Year
Graduate Chemistry	Complutense Madrid	1988
Master Chemistry	Complutense Madrid	1989
PhD Chemistry	Complutense Madrid	1993

(Include all the necessary rows)

Part B. CV SUMMARY *(max. 5000 characters, including spaces)*

1.- Seek and discovery of new pharmacological targets.

The regulation of the activity of biomolecules using chemical compounds is the basis of pharmacology. Chemical compounds interact with the biomolecules regulatory sites either activating or deactivating it to produce the desired effect. My career has been focused in one essential system for the eukariotic cells. Tubulin and its assembly product, microtubules, are among the most successful targets in cancer chemotherapy. However, treatment of tumours with tubulin targeting agents is severely hampered by the development of resistance. An obvious way to address resistance is the seek for new binding sites in the same protein with different function and structural properties. When I started my scientific career in 1988 only three binding sites had been discovered in tubulin. Since then, four new binding sites have been discovered, (maytansine, gatorbulin, laulimalide/peloruside and pironetin), all of them

had been discovered and characterized by my group, either alone or in collaboration with other groups.

2.- Structural mechanisms of activation/deactivation of biological molecules.
Having identified the regulatory sites, it is needed to understand at atomic level the mechanisms of regulation in order to be able of optimize their utility. Tubulin is labile and very difficult to crystallize which implied that the determination of its structure and the functional implications of its modulation by antitumoural drugs was a complex problem which was only fully solved in the last years. In coordination with a drug discovery group from Victoria University (New Zealand), a natural product synthesis group from the Swiss Institute of Technology and a crystallography group from the Paul Scherrer Institute (Switzerland), we provided the biochemical techniques needed to optimize the formation of drug/protein complexes allowing us to determine the structure of tubulin in complex with drugs and providing essential structural information about the interaction of these compounds with their binding site and the structural mechanism of activation of tubulin.

3.- Develop of methods for the in vitro evaluation of drugs and of strategies able to predict their effectivity.
Another important problem that has occupied an important part of my scientific career is the search of methods that allow the in vitro evaluation of the potency of a drug in different tumoural cells. We have developed a method for the high throughput evaluation of the binding affinity of taxane binding site microtubule stabilizing agents which is now a standard for evaluating microtubule stabilizing agents. Later we have proof that the binding affinity of a given compound is a good predictive value for their toxicity, allowing the development of highly cytotoxic compounds using quick evaluations of the effect of chemical modifications in the drug structure. The methods are widely used for the evaluation of novel synthesized or discovered tubulin targeting agents.

4.- Strategies of optimization of drugs able to overcome resistance/avoid toxicity.
The development of a safe chemical modulators able to overcome resistance to chemotherapy and to minimize the undesired secondary effects are the final objective of my research. The technology developed to evaluate the binding affinity of paclitaxel site ligands have been employed to develop a super taxane, with more than 500 times the binding affinity of the parent compound paclitaxel, the compound is highly effective in all kind of tumoural cells resistant to paclitaxel chemotherapy. The same kind of approach has been used with the company Pharmamar S.A. to select a compound with high affinity targeting the newly discovered Maytansine site. The compound is effective in tumours resistant to chemotherapy and has entered clinical Phase II in Spain and USA. We are now developing drugs able to stabilize microtubules without altering their structure and chemical transport properties, therefore with the potential to show less peripheral neurotoxicity (the main toxical secondary effect), with possible use to stabilize microtubules in neurodegenerative taupaties.

Part C. RELEVANT MERITS *(sorted by typology)*
C.1. Publications *(see instructions)*
Sexenials: 6, last one 2014-2020.
ISI WOK, **h-index: 46** (8 August 2023)
GOOGLE **h-index 53** (8 August 2023)
https://scholar.google.com/citations?user=GW3WUf0AAAAJ
Scope Author ID: Author ID: 56244961600
Orcid ID: http://orcid.org/0000-0003-2743-3319
ResearcherID: U-3532-2017
Thesis supervised: 8

Publications since 2016
-Canela, M.D. et al. RSC Advances. (2016) 6, 19492–19506 http://dx.doi.org/10.1039/c5ra26807a
-Chaaban, I. et al. Arch. Pharm. Chem. Life Sci. (2016), 349 , 9, 749-761 http://dx.doi.org/10.1002/ardp.201600134
-Prota, A.E. et al J. Mol. Biol. (2016) 428, 2981–2988 http://dx.doi.org/10.1016/j.jmb.2016.06.023
-Jantsch, A. et al. Molecules (2016) 21, 1010; http://dx.doi.org/10.3390/molecules21081010
-Cortes Cabrera, A. et al. Aggregated compound biological signatures facilitate phenotypic drug discovery and

target elucidation ACS Chem. Biol., (2016) 11, 3024−3034 http://dx.doi.org/10.1021/acschembio.6b00358
-Antúnez-Mojica, M. et al. J. Nat. Prod., (2016), 79 (8), pp 2113–212. http://dx.doi.org/10.1021/acs.jnatprod.6b00428
-Trigili, C. et al ACS Omega (2016) 1 (6), 1192-1204 http://dx.doi.org/10.1021/acsomega.6b00317
-Canela, M.D. et al Oncotarget (2017) 8 14325-14342, http://dx.doi.org/10.18632/oncotarget.9527
-Kellogg, E.H et al. J. Mol. Biol. (2017) 429, (5) 633–646 http://dx.doi.org/10.1016/j.jmb.2017.01.001
-Bohnacker, T. et al Nature Communications. (2017) Article number:14683 http://dx.doi.org/10.1038/ncomms14683
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-Gilson, P. et al. Scientific Reports (2017) 7, 10209 https://doi.org/10.1038/s41598-017-09491-9
-Field, J.J. et al. J. Nat. Prod. (2018) 81, 3, 494-505. http://dx.doi.org/10.1021/acs.jnatprod.7b00704
-Clara-Rahola, J. et al.- J. Colloid Interface Sci. (2018) 514, 704–714. https://doi.org/10.1016/j.jcis.2017.12.072
-Bueno, O. et al.- European Journal of Medicinal Chemistry. (2018) 148 337-348 https://doi.org/10.1016/j.ejmech.2018.02.019.
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-Bueno, O. et al. Scientific Reports. (2018) 8, 4242 https://doi.org/10138/s41598-018-22382-x
-Menchon, G. et al NATURE COMMUNICATIONS. (2018) 9, 2016. https://doi.org/10.1038/s41467-018-04535-8
-Brindisi, M. et al. European Journal of Medicinal Chemistry (2019) 162 290-320 https://doi.org/10.1016/j.ejmech.2018.11.004
-Gaugaz, F.Z. et al. Int. J. Mol. Sci. (2019), 20, 1113; https://doi.org/10.3390/ijms20051113
-Bonandi, E. et al. ChemPlusChem (2019) 84, 98–102 https://doi.org/10.1002/cplu.201800497
-Unterhauser, K. et al. PNAS (2019) 116 (9) 3774-3783 https://doi.org/10.1073/pnas.1819154116
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C.5. Research projects since 2016, indicating your personal contribution. In the case of young researchers, indicate lines of research for which they have been responsible.

- Purifícacion de proteínas de citoesqueleto a partir de diversos organismos y evaluación de compuestos con actividad biológica frente a ellas. 21.000 € Proyecto Intramural CSIC, 201620E051. IP: José Fernando Díaz
-Diseño de antitumorales inhibidores de los procesos metastáticos y eficaces en celulas cancerigenas resistentes a quimioterapia. 160.000 € Ministerio de Economía y Competitividad (2017-2019) BFU2016-75319-R I.P. José Fernando Díaz
- Tuning Tubulin Dynamics and Interactions to Face Neurotoxicity: a Multidisciplinary Approach for Training and Research H2020 MARIE SKLODOWSKA-CURIE ACTIONS UE/TUBINTRAIN (H2020-MSCA-ITN-ETN/0582). 250.904,88 € Main Proposer Daniele Passarella I.P. CSIC. José Fernando Díaz
-Analisis estructural de la interacción de compuestos antitumorales con tubulina y microtubulos. 37484.46 € Proyecto Intramural CSIC, 201920E111 IP: José Fernando Díaz
-Interrupción de los procesos virales de transporte mediados por microtúbulos. 70.000 € COV20/01007 ISCIII, FIS. IP: José Fernando Díaz Pereira. (Marzo 2020 Diciembre 2020)
-Bases estructurales de la neurotoxicidad por antitumorales dirigidos contra tubulina: hacia mejores moduladores de microtubulos contra cancer y enfermedades neurodegenerativas 160.000 € Ministerio de Ciencia e Innovación PID2019-104545RB-I00 (2020-2023) IP: José Fernando Díaz.
-Bases moleculares de la regulación de microtúbulos y sus implicaciones en la neurotoxicidad producida por fármacos: Fundación TATIANA 92.400 € IP: José Fernando Díaz Pereira y Juan Francisco Giménez Abian. (Diciembre 2020 Diciembre 2023)
-Interrupción de los procesos virales de transporte mediados por microtúbulos. 45.000 € 20202020E301 CSIC. IP: José Fernando Díaz Pereira. (Diciembre 2020 Diciembre 2021)
-Estrategias para quimioterapia antiviral de amplio espectro basada en moduladores de microtúbulos WP9 Plataforma de Antivirales. SGL2103051 Proyecto 9.2 Modelos biológicos basados en dianas. Subproyecto 9.2.1. Total: 299141 € Fondos de Recuperación Europeos. (Enero 2021-Diciembre 2022)
- Modulacion quimica del codigo de tubulina como herramienta para el desarrollo y optimizacion de farmacos. 180.000 € Miniestrio de Ciencia e Innovación PID2022-136765OB-I00 (Septiembre 2023- Agosto 2026)

C.4. Contracts, technological or transfer merits, Since 2016

- Technological support Contract Paul Scherrer Institut 2015-2018.Villingen Switzerland 30.500 €
- Contract License / PURSOLUTION LLC Memphis, Tennessee, USA 2016-2023 20.000 €
-Technological support Contract Pharmamar 2018. 15000 €
- Paul Scherrer Institut 2018. Villingen Switzerland 22.000 €
- Technological support Contract. Pharmamar Jan 2019. 13000 €
- Paul Scherrer Institut 2019. Villingen Switzerland 22.000 €
- Technological support Contract. Pharmamar Oct 2019-June 2020. 12000 €
- Technological support Contract. Pharmamar Jan 2021-March 2022. 12000 €
- Paul Scherrer Institut 2021. Villingen Switzerland 22.000 €

C.4. Patents

Andreu, J.M., Díaz J.F., Barasoain I. Método de detección y evaluación de compuestos miméticos de paclitaxel N. de solicitud: 200101710 País de prioridad: ES
Andreu, J.M., Díaz J.F., Barasoain I. Redondo-Horcajo, M. Metodo para la producción y liofilización de tubulina purificada. Secreto Industrial registrado. 2016 Licenciado a PURSOLUTION LLC Memphis, Tennessee, USA.