Proposition Secretary General continuation, 2022-2024: Michael Spedding.

IUPHAR governance brings in new procedures and new ways of working, and the President and Secretary General proposed/were asked to stay on for two years in their current positions to ensure continuity, and that the new structure works.

I was nominated by CNPHARS to stand as President-elect - but will not, after my extended Secretary General duties (10 years) – as I have worked a very long time for IUPHAR (see below) and am currently 72/3 years old. I would quite happily help IUPHAR in an honorary capacity but a President of 75/76 years old would not present the right image, and I have many other things to do in my life. Nevertheless, I underline the necessity of electing the member at large who has a two year position to be a 'trainee' secretary general, this is very important for future viability.

My qualifications for staying on rests on what I have achieved with IUPHAR and what I propose to prioritise until 2025. My history with IUPHAR and receptor classification:

1. I have always been involved in receptor nomenclature, finding the first ATP antagonist in 1974 (pyridylisatogen, now classed as a selective P2Y1 allosteric antagonist in GTP), allowing the first clear differentiation of ATP/adenosine receptors (named P2/P1 in 1985 by Geoff Burnstock).
2. Differentiating four different classes of 'calcium-antagonist' from 1980, with different binding sites, allosteric interactions, functional effects and therapeutic profiles. I was therefore recruited by Paul Vanhoutte to be Secretary to the WHO classification of calcium-antagonists in 1983, which went to become one of the original NC-IUPHAR subcommittees, publishing the first classification document 1992, leading me to be Secretary of NC-IUPHAR.
3. As Secretary NC, I organised the meetings, speakers, minutes, with Paul, then Bob Ruffolo as chair; I became chair from 2000-2015 to be succeeded by Steve Alexander. During this period we made the IUPHAR database (now guidetopharmacology, with Tony Harmar, starting the Edinburgh database group), three receptor compendia (classifying chemokine receptors (with Phil Murphy), nuclear receptors (with Vincent Laudet), voltage-gated and ligand-gated ion channels (with Bill Catterall), also of all P1/P2 receptors, multiple receptor classifications, and raised <1.5M£ with two meetings/year in Paris. This activity structured modern pharmacology.
   At the same time:
4. In terms of my own research, after differentiating ATP/Adenosine receptors, I moved to Merrell Dow in Strasbourg as a scientist eventually building an 8 person research team in John Fozards department, working on enzyme-activated irreversible inhibitors (eg DFMO, first drug

for sleeping sickness), the demonstration that amrinone was a PDE inhibitor (1978), then developing MDL143 a long-acting dihydropyridine, 3 years ahead of amlodipine (but a fake patent, stolen by an East German spy, preceded us by 3 weeks), and MDL72567, a bradycardic dihydropyridine. I was offered to take over the pharmacology department of Syntex Scotland (22 staff) where we developed the metabolic modulator ranolazine (1bn$ sales in US), the highly potent and selective alpha2-antagonist delequamine (male sexual dysfunction) and lifarizine (sodium/calcium channel antagonist for stroke) from discovery to end phase II; lifarizine showed the best results in phase II of any compound to date, but was still stopped by Roche when they bought Syntex, a year after I had left for Servier, to set up their new research centre at Croissy (130 staff, chemistry and biology): in 4 years (1992-6) we built the centre and put 4 compounds into phase 1, S15535, a presynaptic 5-HT1A agonist, S16924 an atypical antipsychotic, a post-proline converting enzyme inhibitor for cognition, and S18986 an 'AMPAkine' (in 1993!) showing it increased BDNF. I reasoned that we needed a completely new approach for CNS drug discovery based on phenotypical effects on brain circuits at risk, researching the hippocampal-prefrontal circuit (H-PFC) at risk for stress (from 1995!) with opposite effects on amygdala outputs (this was all validated 15 years later by the IMI-Newmeds consortium). In 1996, Servier bought EGIS a Hungarian generics company with 120 staff working in a new research centre and I accepted a position in HQ with scientific responsibility for Hungarian research putting several compounds into preclinical research, and using H-PFC targeting we found very novel antipsychotics, AMPA modulators and a GABAα5 antagonist. I was also in charge of building a new medicinal chemistry research centre in Budapest (on time and budget). On 'retiring' I set up my own little research company and using metabolomics found new ways of treating ALS and COVID-19, using metabolomics and generic drug, ambroxol. We have now shown that glucosylceramidase is a critical node for several envelope viruses (coronoviruses, and Dengue)

5. As Secretary General from 2014, I have worked on supporting regions: African research (PharfA; All Africa congresses), made a big difference in Indian research, created a Latin American pharmacology group, supported CNPHARS. I insisted on the creation of an ECR group for IUPHAR. A major objective has been evidence-based medicine for natural products with nine meetings organised, and a reinforced role for metabolomics in product identification. I was behind the MMV-link for the medicines for malaria website (future sites on zika, dengue?), and also for the links with immunopharmacology. I organised a consolidated response of the world's pharmacology societies for advice on the COVID epidemic. Unfortunately, we are now on the 4th IUPHAR-contact person in Parthenon since Kyoto, which has been a major strain. I

have very actively supported NC-IUPHAR and the websites and PEP – these are critical for the future.

Key issues for the future.

- Obtaining finance.
- Consolidation of the regions (PharfA, Latin America, Australasia, India, EPHAR).
- Consolidation of the NC-IUPHAR and PEP websites, with an emphasis on viral diseases, and new antobiotics.
- Consolidation of evidence-based medicine for natural products.
- Expansion of pharmacology (immunopharmacology, clinical pharmacology into biotechs etc)
- Clinical pharmacology (pandemics, ensuring generics can be developed in RLCs, ensuring academic clinical trials are safe, but also feasible from a regulatory point of view); We need to find ways where RLCs can do safe clinical trials but without the impossible regulatory framework as seen in Europe. One small example: generics which are safely given to millions of people must be manufactured to GCP rather than GMP, an impossible barrier for such cheap compounds.

All the best

Michael Spedding, Secretary General IUPHAR & President, Spedding Research Solutions SAS