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Berridge M J & Irvine R F. Inositol trisphosphate, a novel second messenger in cellular signal transduction. *Nature* 312:315-21, 1984.
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Agonists acting on cell surface receptors release inositol trisphosphate into the cytoplasm where it functions as a second messenger to mobilize calcium as part of a signalling system for controlling secretion, metabolism, contraction, phototransduction, and cell proliferation. [The *SCI*® indicates that this paper has been cited in over 1,850 publications.]

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The inositol lipid field was recently identified as the largest research front in the life sciences.[1] My interest in phosphoinositides began in 1976 when I read Bob Michell's review[2] that for the first time linked the hydrolysis of these lipids to the receptor mechanism for generating calcium signals. Not being a biochemist, I approached the subject of lipids with considerable apprehension and tried to overcome my "lipophobia" by studying the water-soluble products of hydrolysis rather than the lipids. This was a fortunate decision because it soon became apparent that agonists stimulated a very rapid formation of inositol trisphosphate (Ins1,4,5P_3), which led me to propose that it may function to mobilize calcium as it had all the hallmarks of a second messenger.[3]

The next problem was to find an assay to study this putative messenger. At a meeting on intestinal secretion at the Royal Netherlands Academy, I heard from Irene Schulz that she and Hanspeter Streb had set up a permeabilized pancreatic preparation that seemed ideal for studying calcium mobilization if only we had some Ins1,4,5P_3. On returning to Cambridge, I discussed the problem with Robin F. Irvine, who set up his Ins1,4,5P_3 factory that was soon to become the worldwide supplier of this novel messenger. The first samples off the assembly line were sent to the Max Planck Institute in Frankfurt and within a week we received an ecstatic phone call—Ins1,4,5P_3 had released calcium. The paper[4] describing our results was enthusiastically received by *Nature*, and we were fortunate in that it appeared towards the end of 1983 because in the following year confirmations that Ins1,4,5P_3 functioned as a calcium-mobilizing messenger began to appear in considerable numbers.

Perhaps the most remarkable aspect of the events leading up to the discovery of Ins1,4,5P_3 as a second messenger is that they coincided almost exactly with the discovery of the second messenger action of diacylglycerol (DG) by Yasutomi Nishizuka. It soon became apparent to those of us at the centre of these new discoveries that this phosphoinositide system was spawning not one but at least two second messengers, which motivated me to write a review to bring together the idea of a bifurcating signalling system. This review was submitted to *Nature* in March 1983 but was rejected and subsequently found a home elsewhere[5] and has been highly cited. One reason given by *Nature* for not considering my review further was that "in the meantime Nishizuka has submitted a review on protein C-kinase, one of the main topics you dealt with." Since the review by Nishizuka[6] concentrated on the DG/C-kinase limb of the bifurcating signal pathway, I felt that I had a strong case for having a platform to provide equal coverage of the Ins1,4,5P_3/Ca^{2+} pathway. After some gentle pressure, *Nature* agreed but laid down a very tight schedule. As Irvine had played such a central role in developing the evidence that Ins1,4,5P_3 was a messenger, I asked him to collaborate in reviewing this exciting new development.

This review has been so highly cited because it not only summarized the role of Ins1,4,5P_3 in mobilizing intracellular calcium, but it also showed how this Ins1,4,5P_3/Ca^{2+} limb of the signal pathway acted together with the DG/C-kinase limb to regulate so many vital cellular processes. The central role of this signalling system has captured the imagination of everyone and resulted in the publication of over 2,000 papers on this topic in 1985.[1] For my contribution to the unveiling of the second messenger role of Ins1,4,5P_3, I received the Feldberg Award in 1984, and the King Faisal International Prize in Science and the Louis Jeantet Prize in Medicine in 1986.

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3. **Berridge M J.** Rapid accumulation of inositol trisphosphate reveals that agonists hydrolyse polyphosphoinositides instead of phosphatidylinositol. *Biochemical J.* 212:849-58, 1983. (Cited 450 times.)
4. **Streb H, Irvine R F, Berridge M J & Schulz I.** Release of Ca^{2+} from a nonmitochondrial intracellular store in pancreatic acinar cells by inositol-1,4,5-trisphosphate. *Nature* 306:67-9, 1983. (Cited 815 times.)
5. **Berridge M J.** Inositol trisphosphate and diacylglycerol as second messengers. *Biochemical J.* 220:345-60, 1984. (Cited 1,440 times.)
6. **Nishizuka Y.** The role of protein kinase C in cell surface signal transduction and tumour promotion. *Nature* 308:693-8, 1984. (Cited 2,375 times.)

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