Type Ia supernovae are not only important astrophysical objects in their own right; they also provide the most precise means of measuring distances to remote galaxies. The calibration of their luminosities in the early 1990s through the Calán/Tololo project[7] allowed two groups of astronomers, headed by Brian Schmidt and Saul Perlmutter, to discover in 1998–99 that, contrary to expectation, the Universe is undergoing an accelerated expansion owing to a mysterious dark energy that constitutes 70% of the Universe's content[8,9]. This amazing discovery has been recognized with this year's Nobel Prize in Physics. Not knowing the exact nature of type Ia supernovae, which have such a crucial place in cosmology, is an embarrassing situation. Although the studies of Nugent *et al.*[2] and Li *et al.*[3] on SN 2011fe do not yet provide a definitive answer to this question, they are a reassuring step forward — one that lends support to our ideas about the nature of type Ia supernovae.

A conclusive answer to this fascinating question will have to await the discovery of other type Ia supernovae in galaxies closer to Earth than Messier 101. Because such supernovae are rare events — they occur once every two centuries in a typical galaxy such as our own[10] — and because there are only a handful of galaxies closer than Messier 101, we might have to wait 30 years for another such event. With patience and luck, we might even be rewarded in our lifetimes with a supernova in the Milky Way. ■

Mario Hamuy *is in the Department of Astronomy, Universidad de Chile, Casilla 36-D, Santiago, Chile.*
e-mail: mhamuy@das.uchile.cl

1. Nugent, P. E. *et al. Astron. Telegr.* **3581,** 1 (2011).
2. Nugent, P. E. *et al. Nature* **480,** 344–347 (2011).
3. Li, W. *et al. Nature* **480,** 348–350 (2011).
4. Rau, A. *et al. Publ. Astron. Soc. Pacif.* **121,** 1334–1351 (2009).
5. Folatelli, G. *et al.* Preprint at http://arxiv.org/abs/1110.3789 (2011).
6. Parrent, J. T. *et al. Astrophys. J.* **732,** 30 (2011).
7. Hamuy, M. *et al. Astron. J.* **112,** 2398–2407 (1996).
8. Riess, A. *et al. Astron. J.* **116,** 1009–1038 (1998).
9. Perlmutter, S. *et al. Astrophys. J.* **517,** 565–586 (1999).
10. Li, W. *et al. Mon. Not. R. Astron. Soc.* **412,** 1473–1507 (2011).

CANCER

A drug-resistant duo

The efficacy of the anticancer drug vemurafenib, which is used to treat metastatic melanoma, is plagued by acquired resistance. A picture of how such resistance develops is emerging. SEE LETTER P.387

HUGO LAVOIE & MARC THERRIEN

Vemurafenib (also known as PLX4032) is a promising drug. Newly approved by the US Food and Drug Administration, it is currently the best prospect against metastatic melanoma, the deadliest form of skin cancer[1,2]. The drug selectively inhibits an oncogenic form of B-RAF, a protein that drives cell proliferation. Unfortunately, most patients acquire resistance to vemurafenib within a year of treatment[3]. All modes of resistance discovered so far involve circumvention of this mutant B-RAF. But on page 387 of this issue, Poulikakos and colleagues[4] report a new mechanism of resistance — enhanced dimerization of the kinase domain of mutant B-RAF. Dimerization normally activates the wild-type protein.

'Gain-of-function' mutations in the *B-RAF* gene are found in about 50% of human melanomas, and its sustained expression is required for tumour-cell proliferation and survival[5]. Therefore, extensive efforts have been devoted to developing selective B-RAF inhibitors, especially those that, like vemurafenib, target its most prevalent oncogenic variant, B-RAF^{V600E}.

In normal cells, B-RAF functions in the RAS/ERK molecular signalling pathway, which has a prominent role in regulating proliferation and survival[6]. The minimum components of this pathway are a cell-membrane-associated protein, RAS, and three protein kinases — a RAF family member (such as B-RAF), MEK and ERK — which convey RAS signals along the pathway (Fig. 1a). On association with signal-activated RAS, the kinase domains of two RAF proteins form a dimer, resulting in their activation[7].

When activated by a gain-of-function mutation, B-RAF induces ERK activity independently of the normal signals, leading to the development of multiple cancers (Fig. 1b)[5]. In melanoma, inhibition of the mutant molecule B-RAF^{V600E} by vemurafenib shuts down ERK activity and rapidly leads to tumour regression[1–3]. However, acquired resistance to vemurafenib is a serious limitation, and several laboratories are hard at work investigating the underlying causes.

Previous efforts have uncovered four mechanisms that counteract vemurafenib effectiveness, all of which bypass B-RAF^{V600E}. In three cases, ERK signalling is reactivated through alternative entry points in the pathway, whereas the fourth mechanism involves

50 Years Ago

For more than one hundred years, the Royal Greenwich Observatory has been responsible for providing exact time signals for a wide variety of users both in Britain and abroad. In recent years this service has become increasingly important in various fields of scientific research where extreme accuracy is essential. In order to provide the various users with more frequent opportunities for checking the time, the present twice-daily transmissions from Rugby were increased to four as from December 1 … As long ago as 1833, the Royal Greenwich Observatory provided hourly time signals for the operation of 'time balls', which were devices consisting of a large ball secured to the top of a mast and released by a special catch at a precise time. One such ball is still in use in the grounds of the old Observatory at Greenwich.
From *Nature* 16 December 1961

100 Years Ago

In the volume on mammals in the "Fauna of British India," the late Dr. W. T. Blanford stated that the black-buck (*Antilope cervicapra*) living on a spit of sand between the Chilka Salt Lake, in Orissa, and the sea, never drank, as there is no water on the spit except in deep wells. The statement has been strongly controverted by various writers, one at least of whom has suggested that the antelopes obtain water from sheep-troughs. Of late years it has, however, been conclusively shown that giraffes, kudu, and gemsbok live for a considerable portion of the year in the Kalahari Desert without drinking, obtaining such moisture as they require from the succulent roots of certain plants … The case of the Chilka black-buck accordingly requires reinvestigation in order to ascertain whether they too may be able to obtain moisture from plants.
From *Nature* 14 December 1911