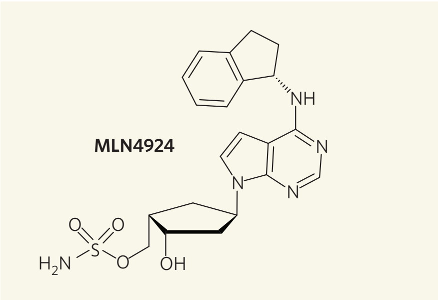

Figure 2 | Structure of an NAE inhibitor. **Soucy *et al.*[2] have discovered MLN4924, an inhibitor of CRL activity that blocks the first step of NEDD8 activation.**

'neddylation', NAE catalyses the reaction of NEDD8 with ATP (a fuel molecule). The active site of NAE that catalyses this process has been well defined by enzymological studies and X-ray crystallography[10], providing invaluable information on targeting the enzyme for drug discovery. Reasoning that this active site might be a prime target for small, drug-like molecules, Soucy *et al.* carried out a high-throughput screen of a chemical library for NAE inhibitors. This identified an AMP analogue as a good starting point for a medicinal-chemistry programme, from which the authors eventually obtained MLN4924 (Fig. 2) as a highly potent and selective inhibitor of NAE.

With MLN4924 in hand, Soucy *et al.*[2] set out to characterize the dynamics of neddylation–deneddylation cycles and the consequences of abrupt inactivation of NAE. They found that CRLs account for a substantial fraction (about 20%) of all proteasome-dependent protein degradation. More startling was their finding that the NEDD8 cycle is extraordinarily fast — MLN4924 induces nearly complete loss of neddylated cullins within five minutes in cells grown in culture. The consequent inactivation of CRLs leads to a large build-up of CRL substrates, as well as over-replication of and damage to DNA. These results demonstrate that MLN4924 will be an awesome tool for cell-biological investigations on the functions of CRLs and their regulation by NEDD8.

Soucy *et al.* took their studies a remarkable step further by asking two key questions. Can neddylation be inhibited so as to cause accumulation of CRL substrates in human tumours that have been transplanted into mice? And if so, does this affect the growth of the tumours? They had good reason to expect such effects, because they had observed that MLN4924 induces cell suicide in proliferating cancer cells *in vitro*, possibly as a result of the deregulation of DNA synthesis. Happily, the answer to both questions is a resounding 'yes'. Most impressively, the authors report nearly complete regression of transplanted human lung-tumour tissue in MLN4924-treated mice, with no obvious side effects. It remains unclear, however, why a drug that inactivates so many different CRLs (presumably also those in healthy cells) should kill only cancer cells.

These are exciting findings[2], but it is prudent to remember that many promising drug candidates have been shown to cure cancer in mice, only to fail spectacularly in humans. Although MLN4924 is sufficiently promising that Millennium is conducting clinical trials in humans, it remains to be seen whether it will become the second marketed drug that deliberately targets components of the ubiquitin system.

What is clear is that research on the UPS — and more specifically, on CRLs and the NEDD8 pathway — has led to a thorough description of neddylation, the identification of NEDD8's cullin targets, and an exploration of the effects of neddylation on the structure and function of CRLs[11,12], all in the short span of about 10 years. This has culminated in the discovery of an exciting drug candidate[2], currently in clinical trials as an anticancer therapy. And it is worth remembering that NAE genes were first uncovered in the mustard weed *Arabidopsis* in a screen for mutants resistant to the plant hormone auxin[13]. Perhaps the seeds of the next breakthrough in cancer therapy will also sprout from some unlikely place. ■

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ASTROPHYSICS

Hidden Universe uncovered

Ian Smail

An experiment flying on a balloon at the edge of the atmosphere offers the deepest far-infrared view of the sky yet achieved, revealing previously unidentified, dust-obscured, star-forming galaxies in the early Universe.

To the human eye, the night sky is a canopy of stars. With the aid of a small telescope it is possible to see our nearest Galactic neighbours, and using sensitive charge-coupled detectors and the world's largest optical telescopes we can go beyond this and peer into the farthest reaches of the Universe. However, even the most sensitive of these visible-light surveys miss much of the light emitted by galaxies over the history of the Universe. This missing light comes from the youngest stars, which are still cocooned in their natal dust clouds. Dust clouds absorb starlight and re-emit it at far-infrared wavelengths. Surveys of the sky in the far-infrared and the longer-wavelength submillimetre wavebands are thus essential if we are to obtain a complete picture of the star-formation history of galaxies, and hence to identify more precisely the epoch at which galaxies such as our own formed.

On page 737 of this issue, Devlin and colleagues[1] present results from an experiment that identifies for the first time the sources of the bulk of this far-infrared and submillimetre emission in the Universe: a population of dust-obscured, star-forming galaxies seen in the first 5 billion years after the Big Bang. The implication of these observations is that the active growth phase of most galaxies that are seen today is well behind them — they are declining into their equivalent of middle age.

For more than a decade, astronomers have known that the birth of many of the stars that formed in young galaxies in the early Universe is hidden from direct view by dust and finally emerges at far-infrared wavelengths. Because of the subsequent expansion of the Universe, this far-infrared radiation is redshifted (its wavelength is stretched to longer wavelengths), and appears in the submillimetre waveband today. Unfortunately, Earth's atmosphere is relatively opaque to submillimetre wavelengths. Hence, to identify these young, dust-obscured galaxies, astronomers need to get their experiments above the atmosphere, either by sending them into space or by flying them at high altitude.

As its name suggests, the Balloon-borne Large-Aperture Submillimeter Telescope (BLAST) uses a high-altitude balloon to fly a telescope with a 2-metre mirror and a sensitive submillimetre detector at altitudes of up to 40 kilometres to undertake surveys of the cosmos (Fig. 1). Devlin *et al.*[1] report the results of BLAST's most recent flight, an 11-day voyage

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Figure 1 | Ready to launch. The BLAST (Balloon-borne Large-Aperture Submillimeter Telescope) is prepared for lift-off from Antarctica. BLAST's observations[1] indicate that most of the far-infrared cosmic radiation comes from previously undetected galaxies that formed stars at impressive rates during the first 5 billion years after the Big Bang.

from McMurdo Station in Antarctica in late 2006. This highly successful flight provided our first representative maps of the extragalactic sky at wavelengths of 250, 350 and 500 micrometres, identifying hundreds of individual emission sources.

The sources detected by BLAST are likely to range from relatively nearby galaxies whose star formation has been enhanced by minor disturbances, such as mergers with small galaxies; through massive, gas-rich disk galaxies, which are either gravitationally disturbed by interactions with other galaxies or become inherently unstable and collapse in a burst of star formation; to the most extreme and most distant events, 'cosmic collisions'. These collisions represent the mergers of two (or more) 10^{32}-kilogram galaxies that plough into each other at relative velocities of a million kilometres per hour. The resulting impact triggers a burst of star formation that consumes all the gas in the system and that at its peak has a luminosity 1,000 times that of the Milky Way, equivalent to 10^{13} Suns. These bursts are capable of forming all the stars in our Galaxy in less than 100 million years — an instant in astronomical terms — and they are the most powerful Galactic-scale events known.

The mix of these different populations is reflected in the way the number of sources changes as a function of their brightness, or flux — the number counts — in the BLAST maps. If the population being observed was dominated by nearby low-luminosity, star-forming galaxies, the number counts would depend on flux (S) as $S^{-2.5}$, the Euclidean model. Number counts that rise more steeply at fainter fluxes than the Euclidean model predicts would mean a larger contribution from the more distant and luminous, merger-triggered starbursts — galaxies forming stars at extremely high rates.

The number counts in the BLAST maps are steeper than the Euclidean model (see Fig. 2 on page 738), showing that most sources are likely to be distant starbursts seen at a time when the Universe was 5 billion years old. Moreover, the counts are steeper in the submillimetre than in the far-infrared waveband, demonstrating that these starbursts are an increasingly important galaxy population in the submillimetre waveband. Devlin *et al.*[1] confirm this trend by looking at how submillimetre emission from the whole population of galaxies changes with their distances from Earth.

The authors[1] show that the most distant starburst galaxies contribute an increasing fraction of the total flux detected in their maps as one moves to longer wavelengths. This conclusion is consistent with earlier ground-based observations at wavelengths around 1,000 micrometres (to which the atmosphere is transparent), where almost all of the sources detected are extremely luminous and very distant starbursts[2], potentially representing the formation of massive galaxies in a single burst of star formation. After their youthful phase of activity, these galaxies are expected to evolve more sedately. As seen today, their light will be dominated by older, redder stars and their characteristics will match those of the more massive galaxies in the local Universe.

Studies of these extreme galaxy-forming events in the early Universe will be aided by three major advances due over the next year or so. First, the submillimetre camera on BLAST is actually a copy of one to be launched on the ESA/NASA Herschel Space Observatory[3] later this year. The larger, 3.5-metre-diameter mirror on Herschel and the even darker skies in space mean that Herschel should be able to see beyond the galaxy population identified by BLAST. Herschel will map larger areas of sky, and hence identify many thousands of submillimetre galaxies, compared with the 450 sources seen by BLAST. This advance should greatly improve the statistics of the analysis and allow more detailed studies of individual classes of submillimetre sources.

Second, the development of large-format detectors working at submillimetre wavelengths (the first example of which is the new SCUBA-2 submillimetre camera[4] mounted on the James Clerk Maxwell Telescope) will facilitate surveys of even more distant and luminous galaxies. Such surveys are needed if we are to understand the physics involved in the youngest phases of formation of galaxies such as our own.

Finally, the commissioning of the first phase of the Atacama Large Millimeter Array (ALMA)[5] will provide a 100-fold improvement in both the spatial resolution and the sensitivity of submillimetre maps. Such observations will allow astronomers to study the distribution of gas and star formation within these early galaxies, which in turn will help to identify the physical process that triggers these ultraluminous bursts of star formation and their role in the formation of the galaxies we see in the Universe today. ■

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