After half-century's wait, approval paves path for new lupus drugs

On 9 March, Benlysta (belimumab) became the first lupus drug approved by US regulators in over half a century. The event was cause for celebration, not only for Human Genome Sciences, the Rockville, Maryland biotechnology company that originally developed the drug, but also for its many competitors racing to be the next to bring a lupus therapy to market.

Clinical trials in lupus are notoriously difficult because the disease is so variable. For decades, companies have tried to bring a lupus drugs to market only to see their most promising candidates fail. One challenge is that patients frequently take two or three drugs, including steroids and other immunosuppressants, to tame their overactive immune systems, and this can mask the effects of an experimental treatment. Benlysta's approval, however, has given the community hope that such hurdles can be overcome. "This is the path that will give industry the confidence it needs to move forward with other therapies," says Margaret Dowd, president of the Lupus Research Institute in New York.

Benlysta, a human monoclonal antibody drug, is now approved by the US Food and Drug Administration to treat systemic lupus erythematosus, a painful autoimmune disorder that can damage the joints, heart, kidneys and lungs.

In many instances of lupus, unusually high amounts of a protein known as B lymphocyte stimulator (BLyS, pronounced 'bliss') allow overactive immune cells to slip past the body's defenses and into the circulation. Benlysta works by blocking BLyS and thereby allowing B cells to undergo regular programmed cell death instead of going rogue.

Lupus drugs in late-stage clinical trials

Drug	Developed by	Phase	Target
CellCept	Roche	3	Inosine monophosphate dehydrogenase-1
Epratuzumab	UCB SA	3	CD20
LY2127399	Eli Lilly	3	BLyS
Atacicept	Merck KGaA	2/3	BlyS, APRIL
Orencia	Bristol-Myers Squibb	2/3	CD80, CD86
A-623	Anthera Pharmaceuticals	2b	BLyS
Lupuzor	Cephalon	2	T lymphocytes
Laquinimod	Teva	2	T lymphocytes
MEDI-545	AstraZeneca	2	Interferon-alpha
Rontalizumab	Roche	2	Interferon-alpha
IFNalpha-Kinoid	Neovacs	1/2	Interferon-alpha

Source: BioMed Tracker

At least three other companies are developing drugs that target BLyS. One of these experimental medicines, atacicept, developed by Merck KGaA in Darmstadt, Germany and a Seattle biotechnology company called ZymoGenetics, targets both BLyS and a closely related protein called 'a proliferation-inducing ligand' (APRIL). Atacicept is currently in simultaneous phase 2 and phase 3 testing for systemic lupus, but the companies halted trials of the drug in patients with a severe form of the disease owing to an increase in infections.

Several firms are developing antibodies against interferon-alpha, a cytokine molecule upstream of BLyS that can also push the immune system into overdrive. The trick, says Jeff Abbey, president of Argos Therapeutics in Durham, North Carolina, is in finding an antibody that will block as many of the 15 isoforms of interferon-alpha as possible. Argos has one in phase 1 testing that blocks 13 interferon-alpha isoforms, but it lags behind similar drugs from major pharmaceutical companies that are already in phase 2.

Some argue that other cytokines make appealing targets. Amgen, headquartered in Thousand Oaks, California, has an antibody against interferon-gamma in phase 1 clinical testing. Targeting interferon-gamma will not only suppress BLyS, but could also affect immune cell activation and other cytokines, argues James Chung, Amgen's executive medical director. The broader effects of an interferon-gamma–specific antibody could translate to greater efficacy, he says, "though this will need to be balanced by the potential for greater immunosuppression and the attendant risk of infections."

Ultimately, there may be a place for all of these approaches on the market, says Dowd. "Lupus has multiple manifestations," she explains. "We need a ton of treatments for this disease."

Heidi Ledford

Pooled trials drowning in conflict-of-interest oversights

Many influential meta-analyses of clinical trial data may be riddled with buried conflicts of interest. According to a report published last month, even when potential conflicts are disclosed in primary studies, they are almost never included in subsequent pooled analyses. The authors of the report say that more transparency is needed in meta-analyses because clinicians and medical organizations regularly rely on such reviews to inform their decisions.

Clinical trial reporting guidelines have changed tremendously over the last decade, with strict protocols now in place for disclosing potential financial conflicts. Yet the same guidelines do not exist for meta-analyses. For example, the *Cochrane Handbook for Systematic Reviews of Interventions* used to guide the drafting of meta-analyses does not explicitly ask authors to list financial conflicts of interest found in the primary studies used.

In the current analysis, a team led by Brett Thombs, a health services researcher at McGill University in Montreal, parsed 29 carefully chosen meta-analyses selected from the six highest impact general medicine journals and five publications focused on medical specialties, such as oncology and cardiology, that had the top drug sales in 2008. Of the 509 primary clinical trials included in the meta-analyses, more than 40% disclosed some industry funding, but only two of the meta-analyses based on these trials mentioned a potential conflict in any of their primary studies (*J. Am. Med. Assoc.* **305**, 1008–1017, 2011).