biopharmaceutical proteins totaled $140 billion in 2013, of which $63 billion was accounted for by monoclonal antibodies (mAbs) (Walsh, 2014). General conservation of molecular processes such as transcription, translation, and glycosylation means that systems can be developed from organisms as diverse as microbes, animals, and plants for production of proteins for use in diagnostic, industrial, or therapeutic purposes.

In 2012, Elelyso was approved by the FDA as the first plant-cell-produced, recombinant human protein for therapeutic use. This product, taliglucerase alpha, is a carrot-cell-produced version of human β-glucocerebrosidase used for treatment of Gaucher's disease (Aviezer et al., 2009; Zimran et al., 2011). Although numerous other human enzymes for replacement therapy, such as α-galactosidase-A for Fabry's disease (Kizhner et al., 2015), and serum proteins and hormones, such as erythropoietin for stimulation of red blood cell production (Castilho et al., 2013), are under development at plant-based pharmaceutical companies and academic laboratories, research on mAbs dominates the field.

Typically, mAbs are produced using hybridoma technology pioneered by Kohler and Milstein, in which antibody-secreting B cells from the spleens of mice immunized with an antigen of interest are fused to myeloma cells to produce immortal hybridoma cell lines that continually secrete antibodies with affinity for the antigen of interest (Hansel et al., 2010; Kohler and Milstein, 1975). To date, two plant-produced antibody therapeutics have been approved for clinical trials: (1) anti-HIV mAb 2G12, produced by the Pharma-Planta consortium, was approved for a phase I clinical trial completed in 2011 (Ma et al., 2015); and (2) a cocktail of three anti-Ebola virus (Zaire strain) mAbs, produced by Mapp Biopharmaceutical of San Diego, California, entered a phase I clinical trial in 2015 run by the US National Institute of Allergy and Infectious Diseases (NIAID) in collaboration with the government of Liberia (PREVAIL_II, 2016). A phase I clinical trial involving 27 IgG proteins produced in plants for use as idiotype vaccines for non-Hodgkin's lymphoma has also been completed (Anon, 2014; Bendandi et al., 2010). Although plant-based research on just six biosimilar mAb therapeutics has been published—adalimumab, infliximab, and ustekinumab (Westerhof et al., 2014); palivizumab (Hiatt et al., 2014; Zeitlin et al., 2013); nimotuzumab (Rodriguez et al., 2013); and trastuzumab (Garabagi et al., 2012a,b; Grohs et al., 2010; Komarova et al., 2011; McLean et al., 2012; Zeitlin et al., 2013)—at least 21 companies worldwide use plant-based production technologies with many other mAbs and biologics (McLean and Hall, 2012) against human pathogens, autoimmune disorders, cancers, inflammation, and toxins under development.

17.2 CONVENTIONAL mAb PRODUCTION USING MAMMALIAN CELL CULTURE

Most therapeutic antibodies are produced using either Chinese hamster ovary (CHO) or mouse NS0 (myeloma) cells. Therapeutic mAbs such as trastuzumab are produced using CHO cells that are transfected with the coding sequences of the desired mAb and are grown to multi-thousand-liter cultures using highly engineered, environmentally controlled culture vessels (Bosch et al., 2013; Butler and Meneses-Acosta, 2012). Once the culture is at a proper cell density, the mAb is harvested, purified, and characterized.