Additional information on the research programs in the EB House 03_2023

Epidermolysis Bullosa (EB) is a group of rare inherited disorders where mutated genes lead to missing or faulty proteins crucial for connecting cells and tissues together. EB is classified into four main types with disease severity correlating with the plane at which blistering occurs within the tissue, the affected gene, the mutation, and its mode of inheritance. Junctional and dystrophic EB (JEB, DEB) represent the more severe forms, with blisters developing within the lamina lucida and below the lamina densa, respectively. Despite the most obvious clinical manifestation of repeated blistering and chronic wounding, both JEB and DEB are systemic conditions, with patients also suffering from a range of extracutaneous complications, including cardiac, esophageal, intestinal, oral, psychological, renal, respiratory, and urinary sequelae. These impose a heavy burden on patients and significantly reduce their quality of life. Patients and caregivers rank the recessive subtype of DEB (RDEB) with the highest disease severity rating among EB subtypes. DEB is caused by mutations in the collagen 7 gene (*COL7A1)*. Based on patient registries, the estimated incidence and prevalence of DEB is 0.2-6.65 per million live births and 3.5-20.4 per million people, respectively, with patients of all ethnicities reported. By early adulthood, regular monitoring for cutaneous squamous cell carcinoma (SCC) is a necessity, as the cumulative risk for tumor development rises sharply to 68% by age 35. However, early detection of tumors is difficult as these arise in visually complex areas of chronic wounds and fibrosis. Notably, chronic inflammation is an underlying common denominator linking and driving all three. The developing tumors are aggressive and fast-growing, with high recurrence rates despite therapy with multiple treatment modalities, and most patients die within 4-5 years of first cancer diagnosis.

Because the underlying genetic cause differs from one type of EB to another, with resulting differences in symptoms, severity and prognosis, a variety of treatment strategies are being developed. These span from gene, cell, and protein therapy approaches, to specialized wound dressings and drug treatments. These approaches generally aim to tackle at least one of the following unmet needs: **chronic inflammation & fibrosis, pain, itch, and SCC**. Although there is now one approved therapy for EB and a few clinical programs are in Phase 3, there are still no life-changing treatments available. Clinical efforts mainly focus on providing palliative care to repair the skin, heal wounds and control infection.

These facts underscore the need to increase the armamentarium of curative-, wound healing-, and cancer therapies for RDEB. In line with DEBRA Austria's mission to bring such treatment options to EB patients, the EB House Research Unit is re-focusing a significant part of its efforts towards **the development of a translational pipeline**. As such, 6 research programs have been

submitted for review (see Table below). The programs focus on the development of CRISPR/Cas-based gene therapies that are expected to improve wound healing and achieve local permanent cure, as well as cancer therapies that target different tumor-relevant signaling cascades and the tumor microenvironment. Notably, these **programs have been developed together with pharmaceutical industry advisors** to merge EB House's current scientific portfolio and expertise with optimized strategies for the translational development of therapeutic product candidates.

Program	Title	Description
P01	In vivo gene editing for epidermolysis bullosa	CRISPR molecules that induce efficient gene reframing will be evaluated for safety, efficacy and durability of outcomes in disease-relevant *in vitro* and *in vivo* models
P02	Drugs targeting EB-SCC biology	Drug candidates identified via transcriptome-guided *in silico* approaches are tested in disease-relevant *in vitro* and *in vivo* models.
P03	Repurposing anti-viral immunity for cancer therapy by intratumoral injection with COVID-19 vaccines (COVAX-IT)	The COVID-19 mRNA vaccine is leveraged to boost current and promising cancer immunotherapy approaches
P04	Preclinical study: Neutralizing IL-17A to treat SCC in EB patients	IL-17A modulation is validated and tested as a therapeutic target in RDEB-SCC
P05	Development of an antisense oligonucleotide (ASO) therapy for RDEB	Development of a topical ASO therapy to partially correct aberrant RNA splicing in COL7A1 that affects ~13% of RDEB patients in Central Europe.
P06	miRNAs as therapeutics for EB-SCC	Testing previously identified miRNAs mimics or anti-miRs, in vitro and in murine models, for their capability to impair tumor growth or metastasis.