Native languages of the Americas are characterized for a great diversity of linguistic affiliations and complex linguistic structures. Mesoamerica (defined as Mexico, Guatemala, El Salvador, Honduras, Nicaragua, Costa Rica, Belize and Panama) are home to no less than 336 attested indigenous languages, of which 26 are already extinct (Glottolog 2.2). Each one of these languages is a unique instance of the most important piece in the cognitive evolution of our species. The systematic study of these extant languages is essential to document the range of diversity present in our days and to try to understand them as a complex biological/cultural system in constant change across time and space. Ultimately, our understanding of what makes us human starts by keeping the record of the diversity of human languages. In this talk I will put forward the research agenda of a “Substance-based Phonological Typology” discussing three typological studies of targeted phenomena for which languages spoken in Mexico and the Americas make crucial contributions: (i) Glottalized consonants, (ii) Partially nasalized segments, and (iii) Laryngeal dynamics. The findings are discussed in the broader context of linguistic typology and their implications for phonological theory.